

# The role of sensor data for the prediction of cardiovascular disease



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## Abstract

The early identification of individuals at high risk of cardiovascular disease (CVD) is the cornerstone of effective primary prevention. Current risk stratification tools, such as QRISK3, rely heavily on non-modifiable factors and have limited predictive accuracy. This thesis explores the use of digital sensors to objectively measure physiological and lifestyle risk factors not captured by traditional methods to improve the prediction of incident CVD. In this thesis, I assess the added value of exercise electrocardiogram (ECG) signals and accelerometer-measured physical activity (PA) to QRISK3-Inspired risk scores using established clinical risk factors from the original QRISK3 model.

I first examined the association between ECG measurements and incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE). ECG recordings were available in 41,076 UK Biobank (UKB) participants without a history of MACCE who underwent a submaximal exercise cycle ergometry ECG test, following quality control checks. ECG parameters were obtained across three distinct phases: rest, exercise and recovery. Prospective associations were assessed in a subset of 35,596 participants with extractable ECG parameters. Over a median of 12.5 years follow-up, there were 3,463 MACCE. The association between ECG parameters and risk of incident MACCE was assessed using multivariable-adjusted Cox regression models, following adjustment for multiple testing.

Multivariable ECG risk scores were derived from ECG parameters significantly associated with incident MACCE during rest, exercise, and recovery phases. These multivariable ECG risk scores demonstrated moderate discrimination for incident MACCE, C-index: 0.63 (95% CI: 0.62–0.64) for males, and a C-index of 0.62 (95% CI: 0.62–0.64) in females. Exercise and recovery ECG measurements modestly improved discrimination when added to QRISK3 in males (Exercise  $\Delta$ C-index = 0.006 (0.003–0.009),  $p < 0.001$ ; Recovery  $\Delta$ C-index = 0.004 (0.002–0.006),  $p < 0.001$ ), however no significant effect was observed in females. Despite these modest improvements in predictive performance, no significant changes in risk stratification were seen at currently recommended risk thresholds.

I subsequently developed deep-learning ECG risk models developed from 41,076 participants with high-quality ECG scans from the UK Biobank exercise ECG cohort. Over 12.5 years of follow-up 4,082 MACCE were recorded. Deep learning ECG risk exhibited a significant incremental association with MACCE (hazard ratio: 1.18 per SD increase,  $p < 0.001$ ) but did not outperform conventional ECG parameters. When combined with QRISK3 risk factors, a modest but significant improvement in model discrimination was observed ( $\Delta$ C-index = +0.032, 95% CI: 0.026–0.038,  $p < 0.001$ ). However, no significant changes in risk stratification were observed at current treatment thresholds.

In addition to ECG-based models, I subsequently explored whether objective accelerometer measurements of PA could further enhance MACCE risk prediction beyond conventional clinical risk factors. Accelerometer-measured PA data from 88,422 UKB participants (2013–2015) without prior MACCE were analysed to assess the added value of daily step counts, overall activity, and time spent in moderate-to-vigorous, light, and sedentary behaviours to established clinical risk factors used in QRISK3 and SCORE2. PA-based MACCE risk scores demonstrated moderate levels of discrimination among male (hazard ratio = 1.46 (1.40 - 1.52), C-index= 0.61 (0.60 - 0.62) and female sub cohorts (hazard ratio = 1.60 (1.54 - 1.66), C-index 0.65 (0.63 - 0.66). However, integrating PA data into existing risk scores had minimal impact on risk stratification, with no significant reclassification improvements in males and only a marginal yet significant improvement in females at a 10% risk threshold ( $\Delta$  Net-benefit 0.014 (0.001-0.025),  $p = 0.03$ ;  $\Delta$ NRI = 0.018,  $p < 0.001$ ).

A novel deep-learning risk score was developed using accelerometer time-series features. Deep learned risk models showed superior predictive performance to conventional PA measurements, exceeding the univariate discrimination of all QRISK3 risk factors with the exception of age: Male cohort C-index = 0.63 (0.62–0.64); female cohort = 0.68 (0.67–0.70). When integrated with QRISK3 risk factors, a significant improvement in discrimination was observed with an increase in C-index of  $\Delta$ 0.003 (95% CI 0.001 - 0.005,  $p = 0.003$ ) and  $\Delta$ 0.007 (95% CI 0.004 - 0.01,  $p < 0.001$ ), for males and females respectively.



For females, significant improvements in risk stratification were reported at a 10% risk threshold,  $\Delta$  Net-benefit 0.022 (0.007-0.035,  $p=0.03$ ), NRI = 0.033 (0.019 - 0.046,  $p < 0.01$ ).

This work contributes to the emerging evidence on ECG and accelerometer-based risk prediction for CVD. It supports existing guidance that while exercise ECG tests provide modest improvements in absolute predictive performance, there is little evidence that they enhance risk stratification for asymptomatic individuals. This thesis addresses prior limitations regarding insufficient sample size and lack of integration with existing clinical risk models in prior risk prediction studies investigating ECG and PA measurements. Additionally, this investigation highlights the potential of deep learning-based PA models to enhance MACCE prediction, particularly in females.

## **Contents**

|                                                                                      |               |
|--------------------------------------------------------------------------------------|---------------|
| <b>List of Tables.....</b>                                                           | <b>16</b>     |
| <b>List of Figures.....</b>                                                          | <b>18</b>     |
| <b>Abbreviations .....</b>                                                           | <b>22</b>     |
| <b>Contributions.....</b>                                                            | <b>23</b>     |
| <b>Outputs.....</b>                                                                  | <b>24</b>     |
| <b>Funding and resources .....</b>                                                   | <b>25</b>     |
| <br><b>Chapter 1 – Background &amp; Introduction .....</b>                           | <br><b>26</b> |
| 1.1 Cardiovascular Disease .....                                                     | 26            |
| 1.1.1 Risk factors .....                                                             | 27            |
| 1.2 Primary prevention of Major Adverse Cardiovascular & Cerebrovascular Events..... | 29            |
| 1.2.1 Population-level interventions .....                                           | 29            |
| 1.2.2 Individual-level intervention.....                                             | 30            |
| 1.3 Cardiovascular risk prediction for targeted intervention.....                    | 31            |
| 1.3.1 Risk prediction and prognostic modelling.....                                  | 31            |
| 1.3.2 Risk prediction for primary prevention of cardiovascular disease .....         | 33            |
| 1.3.3 Limitations of Cardiovascular Risk Scores.....                                 | 34            |
| 1.4 Digital Sensors in Cardiovascular Disease Risk Prediction .....                  | 36            |
| 1.4.1 Electrocardiograms .....                                                       | 36            |
| 1.4.2 Accelerometer measured Physical activity.....                                  | 38            |
| 1.4.3 Measuring CVD risk factors in high resolution sensor data .....                | 39            |
| 1.5 Deep Learning for CVD Risk Prediction.....                                       | 40            |
| 1.5.1 Brief introduction to deep learning.....                                       | 40            |

|                                                                                    |           |
|------------------------------------------------------------------------------------|-----------|
| 1.5.2 Background and motivation .....                                              | 41        |
| 1.5.3 Deep Survival Networks .....                                                 | 42        |
| 1.6 Gaps and opportunities.....                                                    | 43        |
| 1.6.1 Phenotyping high resolution sensor data .....                                | 43        |
| 1.6.2 Assessing the predictive value of exercise and recovery ECG.....             | 44        |
| 1.6.3 Assessing the predictive value of device measured Physical activity.....     | 44        |
| 1.6.4 Integration with existing clinical risk models .....                         | 45        |
| 1.7 Thesis aims and objectives .....                                               | 46        |
| <b>Chapter 2 – Literature review: Digital sensors in CVD risk prediction .....</b> | <b>48</b> |
| 2.1 Introduction.....                                                              | 48        |
| 2.2 Evaluating performance.....                                                    | 49        |
| 2.2.1 Discrimination.....                                                          | 50        |
| 2.2.1.1 Area under the receiver operating curve.....                               | 50        |
| 2.2.1.2 Harrell's C-index.....                                                     | 50        |
| 2.2.2 Calibration.....                                                             | 51        |
| 2.2.2.2 Integrated Calibration index .....                                         | 52        |
| 2.2.3 Reclassification .....                                                       | 52        |
| 2.2.3.1 Categorical Net reclassification index.....                                | 52        |
| 2.2.3.2 Continuous Net reclassification index.....                                 | 53        |
| 2.2.3.3 Standardised Net benefit.....                                              | 54        |
| 2.3 Electrocardiogram.....                                                         | 55        |
| 2.3.1 Pathology and electrical activity of the heart.....                          | 55        |
| 2.3.2 Introduction to the Electrocardiogram .....                                  | 56        |

|                                                                                        |            |
|----------------------------------------------------------------------------------------|------------|
| 2.3.3 ECG and cardiovascular disease .....                                             | 58         |
| 2.3.3.1 Association between Resting ECG and incident cardiovascular disease .....      | 58         |
| 2.3.3.2 Resting ECG for cardiovascular disease risk prediction .....                   | 59         |
| 2.3.3.3 Association between exercise ECG and incident cardiovascular disease .....     | 61         |
| 2.3.3.4 Exercise ECG for cardiovascular disease risk prediction .....                  | 62         |
| 2.3.3.5 Deep learning and the ECG for cardiovascular disease risk prediction .....     | 73         |
| 2.3.4 Discussion .....                                                                 | 79         |
| Findings.....                                                                          | 79         |
| Limitations and research gaps.....                                                     | 80         |
| 2.3.5 Summary.....                                                                     | 81         |
| 2.4 Accelerometer measured Physical activity .....                                     | 82         |
| 2.4.1 Physical Activity.....                                                           | 82         |
| 2.4.2 Measuring Physical activity .....                                                | 82         |
| 2.4.3 Physical activity and cardiovascular disease .....                               | 85         |
| 2.4.4 Physical activity and primary prevention .....                                   | 87         |
| 2.4.5 Physical activity and risk prediction of incident cardiovascular disease.....    | 88         |
| 2.4.5.1 Association between Physical activity and incident cardiovascular disease .... | 92         |
| 2.4.5.2 Physical activity and CVD risk scores .....                                    | 97         |
| 2.4.6 Discussion .....                                                                 | 103        |
| Limitations and future research.....                                                   | 103        |
| 2.4.7 Summary.....                                                                     | 104        |
| 2.5 Conclusion and objectives.....                                                     | 105        |
| <b>Chapter 3 – Datasets.....</b>                                                       | <b>106</b> |

|                                                                           |     |
|---------------------------------------------------------------------------|-----|
| 3.1 Background.....                                                       | 106 |
| 3.2 Introduction to UK Biobank .....                                      | 107 |
| 3.2.1 Recruitment.....                                                    | 107 |
| 3.2.2 Baseline assessment .....                                           | 108 |
| 3.2.3 Disease outcomes and health record linkage .....                    | 109 |
| 3.2.4 Ethical approval .....                                              | 110 |
| 3.2.5 Accessing UK Biobank Data .....                                     | 110 |
| 3.2.6 UK Biobank Sub-studies and Resource Enhancement.....                | 111 |
| 3.3 UK Biobank Cardio assessment study and cycle ergometry ECG data ..... | 112 |
| 3.3.1 Recruitment.....                                                    | 112 |
| 3.3.2 Protocol .....                                                      | 112 |
| 3.3.3 Data preparation .....                                              | 114 |
| 3.3.3.1 Participant data .....                                            | 114 |
| 3.3.3.2 ECG data.....                                                     | 115 |
| 3.3.4 Cohort description.....                                             | 115 |
| 3.3.5 Data quality.....                                                   | 116 |
| 3.4 UK Biobank Physical activity monitoring and accelerometry data.....   | 117 |
| 3.4.1 Recruitment.....                                                    | 118 |
| 3.4.2 Protocol .....                                                      | 119 |
| 3.4.3 Data preparation .....                                              | 120 |
| 3.4.3.1 Participant data .....                                            | 120 |
| 3.4.3.2 Accelerometer data.....                                           | 121 |
| 3.4.4 Cohort description.....                                             | 122 |

|                                                                                                                                     |            |
|-------------------------------------------------------------------------------------------------------------------------------------|------------|
| 3.4.5 Data quality.....                                                                                                             | 124        |
| <b>Chapter 4 – Electrocardiogram measurements and the 10-year risk of Major Adverse Cardiovascular/Cerebrovascular Events .....</b> | <b>127</b> |
| 4.1 Introduction.....                                                                                                               | 127        |
| 4.1.1 Background.....                                                                                                               | 127        |
| 4.1.2 Aims .....                                                                                                                    | 129        |
| 4.2 Methods .....                                                                                                                   | 130        |
| 4.2.1 UK Biobank Cardio Assessment Study .....                                                                                      | 130        |
| 4.2.2 Data processing.....                                                                                                          | 131        |
| 4.2.2.1 Ascertainment of risk factors and study endpoint.....                                                                       | 131        |
| 4.2.2.2 Electrocardiogram phenotypes from submaximal exercise tests.....                                                            | 132        |
| 4.2.3 Risk prediction of incident cardiovascular disease .....                                                                      | 136        |
| 4.2.4 Model validation .....                                                                                                        | 137        |
| 4.3 Results.....                                                                                                                    | 140        |
| 4.3.1 Study population .....                                                                                                        | 140        |
| 4.3.2 Association between ECG parameters and MACCE.....                                                                             | 143        |
| 4.3.3 Predictive value of ECG .....                                                                                                 | 148        |
| 4.3.3.1 Univariate Predictive Performance .....                                                                                     | 148        |
| 4.3.4 Added value of ECG to MACCE risk prediction.....                                                                              | 151        |
| 4.3.4.1 Discrimination .....                                                                                                        | 151        |
| 4.3.4.2 Calibration .....                                                                                                           | 154        |
| 4.3.4.3 Reclassification.....                                                                                                       | 157        |
| 4.4 Discussion.....                                                                                                                 | 159        |

|                                                                                                                                                          |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 4.4.1 Overall findings .....                                                                                                                             | 159        |
| 4.4.2 Comparison with previous work in the UK Biobank .....                                                                                              | 162        |
| 4.4.3 Comparison with the wider literature.....                                                                                                          | 162        |
| 4.4.4 Summary.....                                                                                                                                       | 167        |
| <b>Chapter 5 – Deep learning of the Electrocardiogram measurements and the 10-year risk of Major Adverse Events Cardiovascular/Cerebrovascular .....</b> | <b>168</b> |
| 5.1 Introduction.....                                                                                                                                    | 168        |
| 5.1.1 Background.....                                                                                                                                    | 168        |
| 5.1.2 Aims .....                                                                                                                                         | 169        |
| 5.2 Methods .....                                                                                                                                        | 170        |
| 5.2.1 Study population .....                                                                                                                             | 170        |
| 5.2.2 Data processing.....                                                                                                                               | 170        |
| 5.2.2.1 Ascertainment of study endpoint and risk factors.....                                                                                            | 170        |
| 5.2.2.2 Electrocardiogram phenotypes from submaximal exercise tests.....                                                                                 | 171        |
| 5.2.3 ECG-net implementation.....                                                                                                                        | 171        |
| 5.2.4 Model development and evaluation .....                                                                                                             | 175        |
| 5.3 Results.....                                                                                                                                         | 177        |
| 5.3.1 Study population .....                                                                                                                             | 177        |
| 5.3.2 Association between ECG and MACCE.....                                                                                                             | 180        |
| 5.3.3 Predictive value of ECG .....                                                                                                                      | 185        |
| 5.3.3.1 Univariate Predictive Performance of ECG risk scores.....                                                                                        | 185        |
| 5.3.4 Added value of ECG to MACCE risk prediction.....                                                                                                   | 187        |
| 5.3.4.1 Discrimination .....                                                                                                                             | 187        |

|                                                                                                                                              |            |
|----------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 5.3.4.2 Calibration .....                                                                                                                    | 192        |
| 5.3.4.3 Reclassification .....                                                                                                               | 194        |
| 5.3.4.4 Subgroup analysis.....                                                                                                               | 197        |
| 5.4 Discussion.....                                                                                                                          | 199        |
| 5.4.1 Overall findings.....                                                                                                                  | 199        |
| 5.4.2 Comparison with the wider literature.....                                                                                              | 200        |
| 5.4.3 Summary.....                                                                                                                           | 203        |
| <b>Chapter 6 – Accelerometer measured physical activity and the 6-year risk of Major Adverse Cardiovascular/Cerebrovascular Events .....</b> | <b>204</b> |
| 6.1 Introduction.....                                                                                                                        | 204        |
| 6.1.1 Background.....                                                                                                                        | 204        |
| 6.1.2 Aims .....                                                                                                                             | 206        |
| 6.2 Methods.....                                                                                                                             | 207        |
| 6.2.1 UK Biobank activity monitoring study .....                                                                                             | 207        |
| 6.2.2 Data processing.....                                                                                                                   | 207        |
| 6.2.2.1 Ascertainment of study endpoint: cardiovascular disease diagnosis .....                                                              | 207        |
| 6.2.2.2 Processing of raw Accelerometer data .....                                                                                           | 208        |
| 6.2.3 Risk prediction of incident cardiovascular disease.....                                                                                | 209        |
| 6.2.4 Model development and evaluation .....                                                                                                 | 212        |
| 6.3 Results.....                                                                                                                             | 215        |
| 6.3.1 Study population .....                                                                                                                 | 215        |
| 6.3.2 Association between physical activity and MACCE.....                                                                                   | 218        |
| 6.3.3 Predictive value of physical activity .....                                                                                            | 221        |



|                                                                                                                                                                                                                      |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 6.3.3.1 Univariate Predictive Performance .....                                                                                                                                                                      | 221        |
| 6.3.4 Added value of device measured Physical activity to MACCE risk prediction .....                                                                                                                                | 224        |
| 6.3.4.1 Discrimination .....                                                                                                                                                                                         | 224        |
| 6.3.4.2 Calibration .....                                                                                                                                                                                            | 227        |
| 6.3.4.3 Reclassification.....                                                                                                                                                                                        | 230        |
| 6.3.4.4 Subgroup analysis.....                                                                                                                                                                                       | 232        |
| 6.4 Discussion.....                                                                                                                                                                                                  | 234        |
| 6.4.1 Overall findings .....                                                                                                                                                                                         | 234        |
| 6.4.2 Comparison with the wider literature.....                                                                                                                                                                      | 236        |
| 6.4.3 Summary.....                                                                                                                                                                                                   | 241        |
| <b>Chapter 7 – Development and validation of deep neural network risk models using wearable accelerometer data for the prediction of Major Adverse Cardiovascular/Cerebrovascular Events in the UK Biobank .....</b> | <b>242</b> |
| 7.1 Introduction.....                                                                                                                                                                                                | 242        |
| 7.1.1 Background.....                                                                                                                                                                                                | 242        |
| 7.1.2 Aims .....                                                                                                                                                                                                     | 244        |
| 7.2 Methods .....                                                                                                                                                                                                    | 245        |
| 7.2.1 Study population .....                                                                                                                                                                                         | 245        |
| 7.2.2 Data processing.....                                                                                                                                                                                           | 245        |
| 7.2.2.1 Ascertainment of study endpoint: cardiovascular disease diagnosis .....                                                                                                                                      | 245        |
| 7.2.3 Deep Learning for CVD Risk Prediction .....                                                                                                                                                                    | 245        |
| 7.2.3.1 Deep survival of accelerometer data .....                                                                                                                                                                    | 245        |
| 7.2.3.2 Feature engineering.....                                                                                                                                                                                     | 246        |

|                                                                                     |            |
|-------------------------------------------------------------------------------------|------------|
| 7.2.3.3 Network Training.....                                                       | 247        |
| 7.2.3.4 Model development and evaluation for MACCE risk prediction .....            | 248        |
| 7.3 Results .....                                                                   | 252        |
| 7.3.1 Activity Health Score Pre-training- Predicting incident hospitalisation ..... | 252        |
| 7.3.2 Association of Activity Health Scores with MACCE .....                        | 253        |
| 7.3.3 Predictive value of Activity Health Score.....                                | 255        |
| 7.3.3.1 Univariate Predictive Performance of Activity Health Scores .....           | 255        |
| 7.3.4 Added value of Activity Health Scores to MACCE risk prediction .....          | 257        |
| 7.3.4.1 Discrimination .....                                                        | 257        |
| 7.3.4.2 Calibration .....                                                           | 259        |
| 7.3.4.3 Reclassification .....                                                      | 263        |
| 7.3.4.4 Subgroup analysis.....                                                      | 265        |
| 7.3.4.5 Cross validation performance .....                                          | 267        |
| 7.4 Discussion.....                                                                 | 268        |
| 7.4.1 Overall findings.....                                                         | 268        |
| 7.4.2 Comparison with the wider literature.....                                     | 270        |
| 7.4.3 Summary.....                                                                  | 274        |
| <b>Chapter 8- Discussion.....</b>                                                   | <b>275</b> |
| 8.1 Summary of findings .....                                                       | 275        |
| 8.2 Limitations .....                                                               | 280        |
| 8.3 Ethical implications .....                                                      | 284        |
| 8.4 Future work .....                                                               | 286        |
| 8.4.1 Multimodal modelling .....                                                    | 287        |

|                                                                    |            |
|--------------------------------------------------------------------|------------|
| 8.4.2 Explainability and targeted interventions .....              | 288        |
| 8.4.3 Policy relevant deep learning.....                           | 289        |
| 8.4.4 Consumer grade devices .....                                 | 291        |
| 8.5 Conclusion .....                                               | 292        |
| <b>References.....</b>                                             | <b>294</b> |
| <b>Thesis Supplementary material.....</b>                          | <b>330</b> |
| Section A: Model development.....                                  | 337        |
| Section B: Supplementary Figures and Tables.....                   | 347        |
| Section C: Model coefficients, formulas and usage.....             | 475        |
| Section D: Tripod guidelines for predictive model development..... | 543        |

## List of Tables

|                                                                                                                                                                                      |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 2.1 Summary of recent studies on the prognostic value of resting and exercise ECG measurements for incident cardiovascular disease. ....                                       | 64  |
| Table 2.2 Performance of resting and exercise ECG risk scores for incident cardiovascular disease.....                                                                               | 68  |
| Table 2.3 Summary of recent deep learning ECG risk scores studies for incident cardiovascular disease.....                                                                           | 76  |
| Table 2.4 Performance of deep learning derived ECG risk scores for incident cardiovascular disease.....                                                                              | 77  |
| Table 2.5 Summary of recent studies on the predictive value of Physical activity measurements for incident cardiovascular disease.....                                               | 89  |
| Table 2.6 Overview of the association between Physical activity and incident cardiovascular disease.....                                                                             | 95  |
| Table 2.7 Performance of Physical Activity Risk scores for incident cardiovascular disease...                                                                                        | 99  |
| Table 3.1: Baseline comparison of overall UK Biobank cohort and sub-cohorts who underwent submaximal exercise ECG testing and wearable activity monitoring, respectively. ....       | 125 |
| Table 3.2: Stability measurements of selected UK Biobank variables between the initial baseline assessment after recruitment and the first repeat assessment (2-7 years later) ..... | 126 |
| Table 4.1: Baseline characteristics and ECG parameters of 35,597 UK Biobank participants without a history of MACCE who underwent a submaximal cycle ergometry test. ....            | 142 |
| Table 4.2: Performance of sex-stratified age, ECG and QRISK3-Inspired risk scores for 10-year risk of incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) .....   | 150 |
| Table 4.3: Net reclassification and net-benefit improvement following the addition of ECG parameters to QRISK3-Inspired risk scores at a 10% risk threshold. ....                    | 158 |
| Table 5.1: Baseline characteristics of 41,076 UK Biobank participants without a history of MACCE who underwent a submaximal cycle ergometry test. ....                               | 178 |

|                                                                                                                                                                                                                                                                    |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 5.2: Association and predictive performance of ECG risk scores derived from 15-second recordings during rest, peak exercise and late-stage recovery for 10-year incident Major Adverse Cardiovascular & Cerebrovascular Events.....                          | 186 |
| Table 5.3: Changes in Net Reclassification and Net Benefit following the addition of Q-ECG to Age + Sex, QRISK3-Inspired, Cox Clinical, and Clinical DSN risk scores, derived from QRISK3 risk factors.....                                                        | 195 |
| Table 5.4: Performance of Q-ECG Deep survival networks (DSN) versus Age + Sex, risk models and Cox clinical risk scores for stratifying high-risk individuals.....                                                                                                 | 196 |
| Table 6.1: Baseline characteristics of 88,422 UK Biobank participants without a history of Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) who consented to wear a wrist worn accelerometer for 7 days, stratified by overall activity quartile..... | 217 |
| Table 6.2: Performance of sex-stratified age, Physical activity (PA) and QRISK3-Inspired risk scores for 6-year risk of incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) .....                                                               | 223 |
| Table 7.1: Upstream performance of deep survival derived Activity Health Scores (AHS) for predicting incident hospitalisations due to cardiovascular disease, cancers, chronic kidney disease and stroke.....                                                      | 252 |
| Table 7.2: Performance of Univariate Activity Health Scores for 6-year MACCE risk prediction .....                                                                                                                                                                 | 256 |

## List of Figures

|                                                                                                                                                                                                                                                                                                                                           |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 1.1: Key modifiable and non-modifiable risk factors of Major Adverse Cardiovascular& Cerebrovascular Events (MACCE).....                                                                                                                                                                                                           | 28  |
| Figure 1.2 Overview of deep learning vs conventional machine learning methods for disease classification and prediction using ECG data from the work of van de Leur <sup>84</sup> .....                                                                                                                                                   | 40  |
| Figure 2.1: Overview of the cardiac cycle of the heart.....                                                                                                                                                                                                                                                                               | 55  |
| Figure 2.2 Organisation of 3 lead (limb leads) ECG electrodes.....                                                                                                                                                                                                                                                                        | 57  |
| Figure 2.3: Allocation of Sleep, sedentary, Light physical activity and moderate-vigorous physical activity throughout a 24-hour day.....                                                                                                                                                                                                 | 83  |
| Figure 2.4: Benefits of Physical activity for reducing cardiovascular disease risk .....                                                                                                                                                                                                                                                  | 86  |
| Figure 3.1: Timeline of the UK Biobank study .....                                                                                                                                                                                                                                                                                        | 108 |
| Figure 3.2: Cardiorespiratory fitness assessment protocol.....                                                                                                                                                                                                                                                                            | 113 |
| Figure 3.3 Median resting beat (black) and individual beats (grey) from the bottom 5%, median and top 95% Signal-to-noise-ratio from the UK Biobank cycle ergometry exercise test.....                                                                                                                                                    | 117 |
| Figure 3.4 Participant flow chart; the UK Biobank physical activity sub-study 2013–2015 (n = 106,053). .....                                                                                                                                                                                                                              | 118 |
| Figure 3.5 Accelerometer used in the UK Biobank: (a) device orientation (b) sample device wear, with example accelerometer trace elapsed over 30 seconds .....                                                                                                                                                                            | 119 |
| Figure 3.6: Cumulative incidence of (A)Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) and (B) all-cause mortality, 9 years after initial accelerometer wear time for participants who attended physical activity monitoring, those who were invited but did not attend and the remainder of the UK Biobank population..... | 123 |
| Figure 4.1: Processing of raw ECG data for feature extraction.....                                                                                                                                                                                                                                                                        | 134 |

|                                                                                                                                                                                                                                                                                                                                       |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 4.2: Extraction of 15-second ECG windows during (A) Rest, (B) Peak Exercise, and (C) Recovery following a submaximal Cycle Ergometry ECG test and subsequent Morphology and rhythm Feature Analysis.....                                                                                                                       | 136 |
| Figure 4.3: Characteristics of study population: (A) Flowchart illustrating the number of participants included, along with any exclusion criteria and derivation of development/validation sets for MACCE .....                                                                                                                      | 141 |
| Figure 4.4: Association of ECG-derived parameters obtained during (A) 15 seconds of rest; (B) the final 15 seconds of a 6-min period of submaximal exercise, (C) the final 15 seconds of a 1-min recovery period post exercise with the 10-year risk of MACCE. ....                                                                   | 145 |
| Figure 4.5: Forest Plot showing Harrell's C-index for ECG risk scores .....                                                                                                                                                                                                                                                           | 152 |
| Figure 4.6 Smoothed calibration curve: for (A) Age, (B) Age + resting ECG, (C) Age + exercise ECG, and (D) Age + recovery ECG risk scores. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.....                                                                                              | 155 |
| Figure 4.7 Smoothed calibration curve for QRISK3-Inspired and QRISK3-Inspired + ECG risk scores derived for male and female participants. Calibration curves are shown in the order of: (A) QRISK3-Inspired; (B) QRISK3-Inspired+ resting ECG; (C) QRISK3-Inspired+ exercise ECG; (D) QRISK3-Inspired+ recovery ECG risk scores ..... | 156 |
| Figure 5.1: Overview of the derivation of deep survival ECG risk scores .....                                                                                                                                                                                                                                                         | 174 |
| Figure 5.2: Characteristics of study population.....                                                                                                                                                                                                                                                                                  | 179 |
| Figure 5.3: Association between the output of a deep survival network trained on 7-minute 15-second submaximal exercise ECG recordings (Q-ECG) and the 10-year risk of incident Major Adverse Cardiovascular and Cerebrovascular Events (MACCE),.....                                                                                 | 182 |
| Figure 5.4: Association of deep-learned ECG risk scores (Q-ECG) and conventional ECG parameters obtained during (A) 15 seconds of rest, (B) the final 15 seconds of a 6-min period of submaximal exercise, (C) the final 15 seconds of a 1-min recovery period post exercise with the 10-year risk of MACCE. ....                     | 183 |

|                                                                                                                                                                                                                                                                                                                                                                          |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 5.5: Forest Plot showing Harrell's C-index of clinical risk models derived from Age + Sex, QRISK3-Inspired risk modles, and linear Cox model of QRISK3 risk factors combined with ECG risk scores derived from 7-minute15 second submaximal ECG recordings using a Deep neural network (Q-ECG); in 41,076 UKB participants with ECG collected from 2009-2013..... | 189 |
| Figure 5.6: Forest plot of Harrell's C-index for clinical risk scores derived from Age + Sex, QRISK3-Inspired, risk scores and deep survival networks with clinical risk factors and ECG data (Q-ECG). .....                                                                                                                                                             | 191 |
| Figure 5.7 Smoothed calibration curve: for (A) Age + Sex, (B) QRISK3-Inspired, (C) Age + Sex + 7 minute 15 second ECG, and (D) QRISK3-Inspired + 7 minute 15 second ECG risk scores. .                                                                                                                                                                                   | 193 |
| Figure 6.1. Triaxial Accelerometer and Data Processing Workflow for Physical Activity Extraction.....                                                                                                                                                                                                                                                                    | 209 |
| Figure 6.2 Internal validation pipeline to calculate optimism in the presence of multiply imputed data.....                                                                                                                                                                                                                                                              | 212 |
| Figure 6.3: Exclusion of study participants:.....                                                                                                                                                                                                                                                                                                                        | 216 |
| Figure 6.4: Association between accelerometer-derived physical activity and sleep, obtained over 7 days of continuous monitoring in a free-living environment with the 6-year risk of MACCE for males and females, respectively.....                                                                                                                                     | 220 |
| Figure 6.5 Optimism adjusted Harrell's C-index for risk scores derived from Age, Age + Physical activity (PA) and a QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) extended with PA; and QRISK3-Inspired risk scores extend by PA.....                                                                                                 | 226 |
| in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015. After 6 years of follow-up, 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.....                                                                                                                                                     | 226 |
| Figure 6.6 Smoothed calibration curve for (A) Age and (B)Age + physical activity (PA) risk scores derived for male and female participants.....                                                                                                                                                                                                                          | 227 |



|                                                                                                                                                                                                                                                                                                                          |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Figure 6.7 Smoothed calibration curve for (A) QRISK3-Inspired and (B)QRISK3-Inspired + physical activity (PA) risk scores derived for male and female participants .....                                                                                                                                                 | 229 |
| Figure 6.8 Decision curves for Age, Age +Physical activity (PA), QRISK3-Inspired and QRISK3-Inspired +PA risk scores.....                                                                                                                                                                                                | 231 |
| Figure 6.9 Optimism adjusted Harrell's C-index stratified by age and sex for QRISK3-Inspired and QRISK3-Inspired + PA risk scores. ....                                                                                                                                                                                  | 233 |
| Figure 7.1: Overview of derivation (A) and validation (B) of deep survival Activity health scores (AHS) derived from 88,422 participants (4,221, MACCE; 4.8%) and over 600,000 person-days of accelerometer data.....                                                                                                    | 251 |
| Figure 7.2 Association between deep learning-derived Activity Health Scores (AHS) and 6-year incidence of MACCE. ....                                                                                                                                                                                                    | 254 |
| Figure 7.3 Optimism adjusted Harrell's C-index for risk scores derived from Age, Age deep learning derived Activity Health Scores (AHS) and a recalibrated QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) extended with AHS; and full QRISK3-Inspired risk scores extended by AHS..... | 258 |
| Figure 7.4 Smoothed calibration curve for (A) Age and (B)Age + Activity Health Scores (AHS) derived for male and female participants.....                                                                                                                                                                                | 260 |
| Figure 7.5 Smoothed calibration curve for (A) QRISK3-Inspired and (B)QRISK3-Inspired + Activity Health Scores (AHS) risk scores derived for male and female participants. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. ....                                                 | 262 |
| Figure 7.6 Decision curves for Age, Age +Activity Health Scores (AHS), QRISK3-Inspired and QRISK3-Inspired +Activity Health Score (AHS) risk scores .....                                                                                                                                                                | 264 |
| Figure 7.7 Optimism adjusted Harrell's C-index stratified by age and sex for QRISK3-Inspired and QRISK3-Inspired + AHS risk scores.....                                                                                                                                                                                  | 266 |

## Abbreviations

AHS: Activity Health Scores

AF: Atrial fibrillation

AV: Atrioventricular

BMI: Body mass index

CVD: Cardiovascular disease

CAD: Coronary artery disease

CODE: Clinical Outcomes in Digital Electrocardiography

ECG: Electrocardiogram

FHS: Framingham heart study

HR: Hazard ratio

HDL: High-density lipoproteins

LDL: low-density lipoproteins

LA: Left Atrium

LV: Left ventricle

ML: Machine learning

MACCE: Major Adverse Cardiovascular & Cerebrovascular Event

NICE: National Institute for Health and Care Excellence

NHS: National Health Service

NRI: Net reclassification index

NB: Net benefit

PA: Physical Activity

PCE: Pooled cohort equation

RA: Right Atrium

RV: Right ventricle

SA: Sinoatrial

SBP: Systolic blood pressure

TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

UKB: UK Biobank

USPSTF: United States Preventive Services Task Force

## Contributions

The work conducted in this thesis is my own work, and was supervised by Dr Stefan Van Duijvenboden, Professor Aiden Doherty, and Professor Barbara Casadei.

I planned and conducted data preparation, data analysis, interpretation, and writing. Some others contributed to elements of this work:

- Shing Chan assisted with the design and implementation preparation of UK biobank accelerometer data and the design and implementation of the deep survival risk network presented in chapter 7.
- Charlie Harper assisted with the survival analysis of the UK Biobank physical activity monitoring cohort provided in figure 3.6 in addition to critical discussion in both the planning and interpretation of several of the analyses in this thesis.

Figures and tables in the text are my own, except where otherwise indicated.

# Outputs

This work has contributed to the following outputs:

## **First author manuscripts:**

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## **Conference presentations:**

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Sturge et al. Development and validation of an ECG-based 10-year risk prediction model for Major Adverse Cardio/Cerebrovascular Events in UK Biobank, Oral presentation at ***European Society of Cardiology (ESC) Annual Symposium 2024***

Sturge et al. Steps Towards Prevention: Harnessing Wearable Activity Data for Precision Risk Assessment in Primary Cardiovascular Care. Oral presentation at ***International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM) 2024***:

Sturge et al. The added value of deep learning to submaximal exercise electrocardiogram for the 10-year prediction of major adverse cardiovascular and cerebrovascular events. Oral & poster presentation at ***British Cardiovascular Society (BCS) Annual Conference 2024***:

Sturge et al. The added value of device measured physical activity to the prediction of incident cardiovascular disease. Oral & poster presentation at ***British Cardiovascular Society (BCS) Annual Conference 2024***.

Sturge et al. Can wearable devices help improve the prediction of cardiovascular disease? Oral & poster presentation at ***British Heart Foundation Centre for Research Excellence Symposium 2024***:

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## Chapter 1 – Background & Introduction

### 1.1 Cardiovascular Disease

Cardiovascular disease (CVD) encompasses a broad range of conditions affecting the heart and circulatory system<sup>1</sup>, primarily caused by thrombosis or atherosclerosis and is the largest cause of mortality globally<sup>2,3</sup>. Major Adverse Cardiovascular/Cerebrovascular Events (MACCE), defined as (1) ischaemic heart disease, (2) stroke/transient ischaemic attack, or (3) heart failure, are the largest contributors to cardiovascular morbidity and mortality<sup>4,5</sup>. There is currently no gold-standard for the definition of MACCE, and composite endpoints vary widely across studies. This thesis adopts a broad definition of MACCE to capture the full spectrum of clinically significant cardiovascular and cerebrovascular outcomes arising from shared pathophysiological processes, which most contribute to morbidity and mortality. Narrower subtypes of CVD assessed in the literature such as CHD-or stroke-only capture only part of the disease burden and substantially reduce event numbers, limiting relevance for primary prevention. Together, ischaemic heart disease and stroke were the first and second largest contributors to global mortality, and as of 2021, accounting for 9.14 (95% uncertainty interval 8.40, 9.74) million and 6.55 (6.00, 7.02) million deaths, respectively<sup>6</sup>. While heart failure remains a major contributor to CVD morbidity, shares many common risk factors with adverse CVD and is a major risk factor for incident stroke. The prevalence of MACCE continues to rise against the backdrop of an ageing population and declining mortality<sup>3</sup>; from 1990 to 2021, the prevalence of MACCE has over doubled from 285 million in 1990 to 610 million in 2021<sup>7</sup>. This presents a major challenge to healthcare systems and threatens to reverse much of the progress made in recent decades in reduced morbidity and increased overall life expectancy<sup>8</sup>. A large proportion of MACCE mortality is premature (occurring in individuals below the age of 75) and is preventable through early interventions<sup>3,9-11</sup>. Recent improvements in treatments and increasing public awareness of key risk factors have led to a decline in age-adjusted mortality from MACCE across high-income countries. In the UK, age-adjusted mortality fell by 70% from 1979 to 2013.

However, recent rates of decline have begun to stall while MACCE morbidity continues to rise. Reductions in MACCE mortality fell from a 33% improvement in 2005-2012 to just 11% between 2012-2019 and even reversed following the COVID-19 pandemic, with age-adjusted cardiovascular mortality reaching 80 per 100,000 in 2022, the highest mortality rate recorded since 2011<sup>6-8,12</sup>.

As the prevalence of MACCE continues to rise, alongside the increasing cost of long-term medical care and rising mortality, primary prevention is essential to reducing the high burden placed on public health from MACCE. Intervention strategies for MACCE target lifestyle risk factors such as physical activity (PA), smoking, and high-risk conditions, including elevated systolic blood pressure, high LDL cholesterol and cardiac arrhythmia<sup>9,10,13-17</sup>. The increasing burden of MACCE and shifting population demographics highlight the need for a better understanding of key risk factors, to inform more effective interventions and identify high-risk individuals.

### **1.1.1 Risk factors**

Prior to the Framingham heart study (FHS), little was known about the root causes of MACCE. It was thought that conditions such as atherosclerosis and arteriosclerosis (clogging and narrowing of the arteries) were simply a natural part of ageing<sup>15</sup>. Launched in 1949 with the goal of finding a single prevailing cause of MACCE, the FHS marked the first systematic attempt to identify the main risk factors of MACCE. Rather than a single overarching cause, it was soon discovered that MACCE was the result of many interacting factors, giving rise to the concept of “cardiovascular risk factors”. This proved to be an inflexion point in our understanding of the causes and management of MACCE. The establishment of high blood pressure and elevated serum cholesterol as key risk factors would later pave the way for the use of antihypertensive and cholesterol-lowering medication, which play a crucial part in primary prevention strategies across the globe<sup>11,18</sup>. The realisation that risk factors contribute synergistically to the overall risk of MACCE gave rise to the first multivariable risk scores, which combine multiple risk factors into a single overall risk score<sup>19</sup>.

Risk factors for MACCE can be defined as non-modifiable or modifiable. Non-modifiable risk factors, such as age, gender, family history, ethnicity, and genetic predisposition cannot be altered through lifestyle or medical interventions. In contrast, modifiable risk factors can be altered or prevented altogether through changes to behaviour, environment, or therapeutics.

Notable modifiable risk factors include blood pressure, BMI, smoking status, alcohol intake and lipid levels (Figure 1.1)<sup>20,21</sup>. In 2013, the World Health Organisation (WHO) devised the Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2030. This plan established nine targets to tackle non-communicable diseases, with a large focus on modifiable CVD risk factors. The action plan specifically identifies alcohol consumption, PA, salt intake, tobacco usage, blood pressure and diabetes as key risk factors which could be reduced to tackle the large public health burden caused by CVD<sup>22</sup>. According to the latest WHO estimates, up to 80% of CVD mortality is attributed to modifiable risk factors and can be prevented through lifestyle and medical interventions, with similar estimates provided for the UK by the British Heart Foundation<sup>3,6,23</sup>. This creates a large scope for the prevention of incident MACCE.

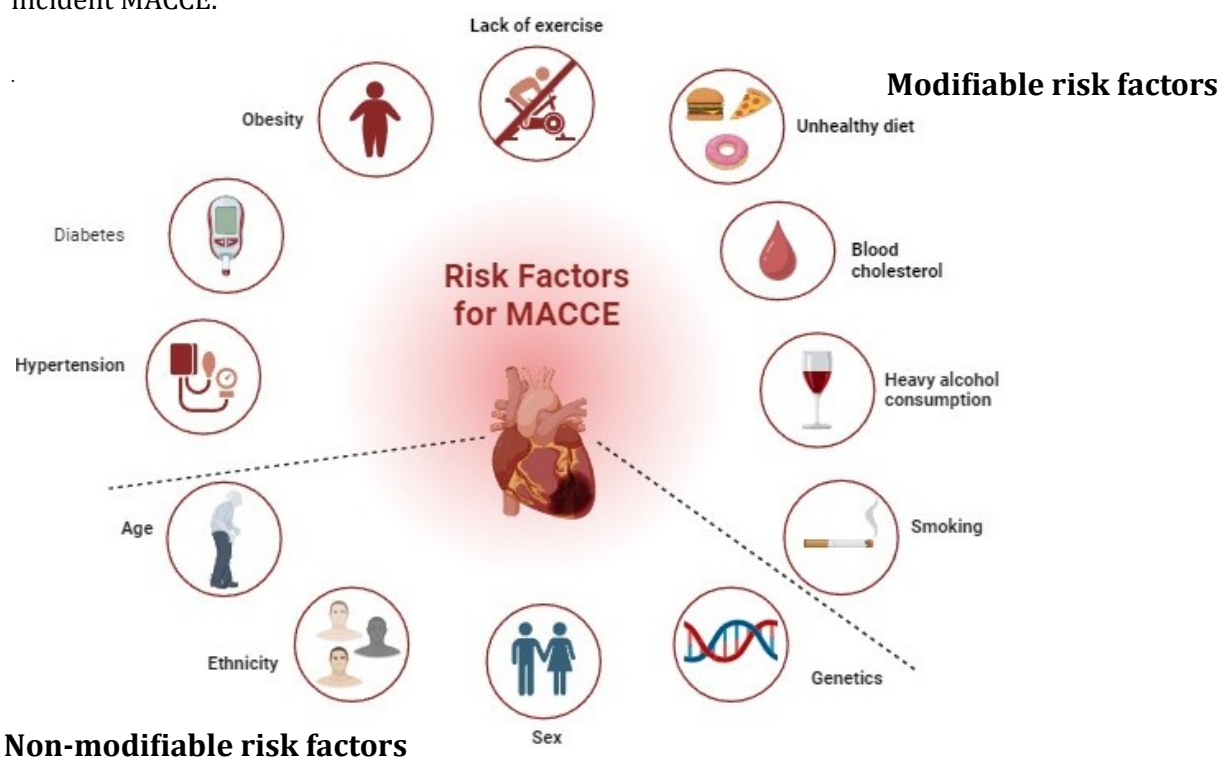


**Figure 1.1: Key modifiable and non-modifiable risk factors of Major Adverse Cardiovascular & Cerebrovascular Events (MACCE)**



## **1.2 Primary prevention of Major Adverse Cardiovascular & Cerebrovascular Events**

The prevention of MACCE is, in large part, achieved through managing key modifiable risk factors, such as poor diet, low PA, and high blood pressure<sup>24–26</sup>. Despite the recent rise in the prevalence and mortality due to MACCE, primary prevention remains an effective and cost-efficient means of tackling the high public health burden caused by MACCE<sup>27–29</sup>. Primary prevention can broadly be divided into two overarching strategies, first introduced by Geoffrey Rose et al. in a landmark paper, “Sick Individuals and Sick Populations”, consisting of population-level and individual-level interventions<sup>30</sup>. Population-based strategies aim to limit exposure and prevalence of key risk factors through social and environmental interventions such as reductions in smoking, dietary salt, and improved access to education and health care<sup>27,30,31</sup>. An individual approach aims to target interventions at high-risk individuals to control for key risk factors through changes to lifestyle and medication<sup>26,30,32,33</sup>. These approaches are often employed in tandem, such as in the UK, where regular health checks are used to identify high-risk individuals and are supported by population-wide policies such as smoke-free legislation<sup>34,35</sup>.

### **1.2.1 Population-level interventions**

Population interventions aim to achieve small shifts in the absolute risk of disease by targeting common risk factors over entire populations. The effectiveness of the intervention depends on both the relative risk (RR) associated with specific risk factors and the prevalence of those factors within the population. If a highly influential risk factor is uncommon, even significant changes to this factor may result in only a modest reduction in the overall risk of disease. Conversely, targeting a less impactful but more prevalent risk factor can substantially decrease disease rates across the population; this was later coined the Geoffrey Rose paradigm<sup>30,32</sup>.

While a population-wide strategy can result in significant reductions in the overall burden of MACCE, their benefit at the individual level is relatively modest<sup>36</sup>.

This is particularly relevant for individuals at the highest risk of MACCE, as much of their risk is attributed to fewer, more impactful risk factors.

Population-level approaches may be insufficient to lower the risk of incident disease enough to benefit such populations<sup>32,36</sup>. Additionally, current evidence suggests that high-risk individuals are less engaged and are unlikely to respond to such measures. Therefore, while population-level approaches offer major advantages in terms of broad public health impact, their effectiveness for high-risk individuals may be limited without additional targeted interventions<sup>31,36</sup>. High-risk individuals stand to benefit more from targeted interventions tailored to their specific risk profiles<sup>32,37</sup>. However, this necessitates the accurate identification of high-risk individuals, which can pose challenges in practice<sup>38,39</sup>.

### **1.2.2 Individual-level intervention**

Those at high risk of MACCE stand to benefit the most from risk factor modification<sup>32,37,40</sup>. Individual level interventions, also referred to as 'high-risk' strategies, centre on personalised care and targeted interventions for those at elevated risk of MACCE<sup>30,32,33</sup>. High-risk strategies have been shown to enhance patient motivation, improve adherence to interventions, increase treatment coverage of cholesterol-lowering medications, and prioritise the use of limited healthcare resources<sup>34,35,41</sup>. International guidelines such as those from the UK<sup>26</sup>, USA<sup>42</sup>, Europe<sup>32,40</sup>, and the WHO<sup>22,43</sup> all recommend routine risk assessments to identify individuals at heightened risk of MACCE.

The latest evidence from the Office of Health Improvement and Disparities has shown that individual health checks are successful in reducing hospitalisation and incidence of MACCE<sup>16,34</sup>. Individualised risk assessment has also been shown to increase the rate of prescription for cholesterol-lowering medication. Such medications, notably statins, accounted for a 14% reduction in mortality related to coronary heart disease, with the overall risk of MACCE decreasing by 25% for every 1 mmol/L reduction in LDL<sup>44,45</sup>.

Current guidelines recommend statin intervention for individuals with high-impact risk factors such as type 1 diabetes or elevated LDL cholesterol<sup>26</sup>.

However, as more recent evidence has highlighted, individual risk factors are often poor predictors of cardiovascular risk<sup>15,19</sup>. This has given rise to the use of multivariable risk scores to assess how multiple risk factors interact and contribute to the overall risk of MACCE.

Clinical guidelines now recommend the use of cardiovascular risk scores to stratify patients into various treatment groups as well as guide the type and intensity of interventions<sup>26,32,40,42</sup>. This shifts prevention away from the management of specific risk factors to instead focusing on the reduction of overall risk.

### **1.3 Cardiovascular risk prediction for targeted intervention**

#### **1.3.1 Risk prediction and prognostic modelling**

Risk prediction, also referred to as prognostic modelling, aims to provide a personalised estimate of the risk for a future disease or outcome. In primary care, risk prediction is often used to help guide lifestyle interventions and therapeutic decisions as well as identify high-risk individuals. This approach is intended to identify those that would most benefit from intervention, supporting the efficient allocation of limited medical resources<sup>46</sup>. Modern prognostic modelling can be traced back to the work of Dr Schnur, in the early 1950s, who developed the first multivariable risk score for patients admitted to the hospital with acute myocardial infarction (AMI)<sup>47</sup>. Dr Schnur demonstrated their MI risk score could successfully identify those at heightened risk of mortality within 1 year of admission, based on their symptoms at admission. Dr. Schnur highlights the potential of their risk score to enhance the assessment of treatment effects across different risk groups and to better stratify patients in randomised controlled trials based on perceived risk rather than relying on simple pair alternation. This would later have important implications for risk prediction studies moving forward. Prediction models are now widely adopted across clinical practice for a range of conditions in both the prevention and management of disease outcomes, well-known risk models include Framingham Risk Score<sup>48</sup>, Nottingham Prognostic Index<sup>49</sup>, EuroScore<sup>50</sup> and QRISK3<sup>51</sup>.

In contrast to associative evidence and population-based approaches, which rely on the overall risk observed across whole populations, risk scores offer an individualized assessment for incident diseases for personalised decision-making. Indeed, overall risk across a population is often a poor prognostic marker at the individual level. Survival times and outcomes can vary significantly within groups sharing similar risk profiles. This was perhaps best highlighted by Dr Stephen Jay Gould in a widely circulated article, “The Median isn’t the Message”<sup>52</sup>, after having survived for 20 years with abdominal mesothelioma following an initial prognosis of eight months based on the median survival time. This notion of individual heterogeneity was more formally described by Hemingway et al. in establishing the Prognosis Research Strategy (PROGRESS) for predictive modelling. They outline the considerable variation in survival times across different medical practices in the USA for acute myocardial infarction and traumatic brain injury, among other conditions. The authors go on to show how these individual variations can be explained in terms of the interactions between multiple risk factors such as education status, socioeconomic position and quality of care across practices<sup>53</sup>.

The need for a multivariable approach to predictive modelling was further explored by Riley et al. who investigated the variation in survival times for individuals stratified based on a single risk factor. The authors present the survival time for patients with node-positive breast cancer treated with tamoxifen. Patients were stratified into three risk groups based on the grade of tumour present. Not only was there a large degree of heterogeneity within each group, but the distribution of survival time overlapped considerably<sup>46</sup>. Currently adopted clinical risk models now utilise multiple risk factors in combination to predict the future risk of disease for individual patients. These multivariable models assess the risk associated with each factor by assigning relative weights to each predictor to obtain a risk or probability of an event. By considering the unique combination of factors for each patient, these models enable healthcare providers to offer more accurate, individualised recommendations for prevention, treatment, and long-term management<sup>54</sup>.

### **1.3.2 Risk prediction for primary prevention of cardiovascular disease**

Cardiovascular risk prediction plays a central role in the primary prevention of MACCE. Risk scores are used to guide clinical decision-making and intervention strategies by quantifying the absolute probability of an event during a fixed period (i.e. 10 years)<sup>55</sup>. This approach is based on the principle that the intensity of intervention should match the risk of the individual<sup>56</sup>.

Under current clinical guidelines, this primarily pertains to the prescription of cholesterol-lowering medication and more intensive lifestyle modifications for individuals with higher absolute risk, where interventions are more likely to outweigh the potential harm<sup>30,57</sup>.

Cardiovascular risk scores were first conceived following the Framingham heart study (FHS), which was pivotal in establishing that CVD resulted from multiple risk factors that contribute synergistically to the overall risk of cardiovascular disease<sup>15,48</sup>. Furthermore, CVD risk factors seldom occur in isolation, and the risk associated with any given risk factor can vary greatly depending on the presence of other risk factors. Patients with a greater accumulation of these risk factors are consistently shown to have a higher risk of CVD, with most incidents occurring in those with more than one risk factor. CVD risk scores were designed to combine information from multiple risk factors to produce a single absolute probability of disease. Since the FHS, cardiovascular risk scores have become a mainstay of primary prevention across the globe and feature prominently in many international guidelines.

Current cardiovascular risk prediction centres on population-tailored algorithms, which consider traditional risk factors, such as age, sex, systolic blood pressure, cholesterol, smoking status and medical history. Risk scores are typically developed from large population cohort studies where multiple risk factors are measured at a baseline date and followed up for a period of time or until the outcome of interest. Established CVD risk scores include QRISK3<sup>51</sup> in the UK, SCORE2<sup>58</sup> in Europe, American Heart Association PREVENT<sup>59</sup> Calculator in the USA and WHO CVD risk charts<sup>60</sup>. Such risk scores have undergone extensive validation for the population of interest and are widely regarded to improve CVD outcomes.

The adoption of cardiovascular risk scores for primary prevention has been shown to prevent hospitalisations, reduce key risk factors, including BMI, smoking, and blood pressure, as well as increase the prescription of cholesterol-lowering medication for high-risk individuals<sup>16,26</sup>.

### **1.3.3 Limitations of Cardiovascular Risk Scores**

Whilst well validated for clinical use on large populations, clinical risk models for MACCE suffer from limited accuracy and large heterogeneity across individuals<sup>38,61,62</sup>. A recent analysis by Grammer et al. evaluated ten cardiovascular risk algorithms used in primary care in the DETECT study. The authors showed that estimates of absolute risk differed substantially between algorithms, with median risk scores ranging from 5% (ESC-HS) to 8.4% (FRS-CVD). Divergence between risk scores was more pronounced as risk levels increased. Furthermore, the authors report at the guideline-recommended 20% 10-year risk threshold, around 50–80% of events were not classified as high risk and would therefore have been excluded from preventive treatment<sup>38</sup>. A large multi-centre observational study from Li et al. demonstrated that accounting for variability between clinical practices substantially altered the absolute risk of individuals. This was found to be particularly severe for those deemed at high risk of incident events, significantly altering treatment recommendations<sup>63</sup>.

The performance of cardiovascular risk scores largely depends on the ability to capture and accurately measure the key risk factors contributing to the risk of disease. However, there is considerable heterogeneity across primary care practices regarding the quality of available data. Li et al. found considerable inter-practice variations across primary care practices for several risk factors, such as mean age and BMI<sup>63</sup>. Missingness of ethnicity ranged from 19% in the bottom 5<sup>th</sup> percentile up to 93.9% in the 95<sup>th</sup> percentile. Recording of BMI also ranged from 18.7% to 60.1%. These findings were further supported by DeLusignan et al. who found large variations in the quality of data across practices, in addition to differing definitions of key clinical concepts and the use of out-of-date READ codes in many practices<sup>64</sup>.

Perhaps the most severe limitation of current risk scores in primary care, such as QRISK3, is a reliance on non-modifiable risk factors such as age, sex and ethnicity. This not only limits one's ability to lower their risk through behavioural interventions but also impacts who will receive potentially lifesaving interventions.

Recent evidence suggests that the provision of routine health assessments is based predominately on one's age, which is often the most heavily weighted risk factor among common CVD risk scores<sup>65</sup>. As a result, CVD risk scores tend to provide low absolute risk scores for younger individuals with high levels of modifiable risk factors<sup>32,65,66</sup>.

In the latest review of the NHS health check programme for CVD, the vast majority of individuals under the age of 55 were classified as having a low 10-year risk of developing CVD, thus not recommended to receive medical or behavioural interventions. However, 50% of these individuals were deemed to be at a high lifetime risk of CVD<sup>16</sup>. As a result, there remains a large opportunity for further prevention of MACCE, which is currently unaddressed by existing clinical risk models. This gap underscores the need to refine risk assessment tools to better identify individuals who most benefit from preventive interventions.

Addressing these challenges will require a standardised approach to data collection, along with the identification and objective measurement of novel risk factors that better reflect the underlying pathology of CVD. A review by Lloyd-Jones et al. (2010) highlighted the addition of new risk factors into existing prediction tools as a critical area of research to enhance predictive performance and better identify high-risk individuals within key subgroups<sup>67</sup>. Similarly, the National Institute for Health and Care Excellence (NICE) in the UK recommends investigating novel risk factors to simplify risk scores, to improve adoption and generalisability<sup>68</sup>.

Digital sensors, such as electrocardiograms (ECG) and wrist-worn accelerometers, offer a promising solution by providing non-invasive, cost-effective measurements of key behavioural and physiological risk factors that can be easily scaled to large populations.

Existing research has already demonstrated strong associations between ECG and accelerometer measurements with MACCE; however, current evidence on their added value in MACCE risk prediction remains unclear.

## **1.4 Digital Sensors in Cardiovascular Disease Risk Prediction**

Digital technologies have emerged as a promising area of research in the management and prevention of CVD. The recent proliferation of widely accessible medical and consumer-grade sensors has attracted significant interest in primary care due to their ability to provide non-invasive, objective measurements of key cardiovascular risk factors.

Digital sensors enable the measurement of physiological and lifestyle risk factors not captured by traditional clinical risk models and can be utilised in both clinical and free-living environments. Such measurements hold significant potential to improve currently adopted CVD risk calculators and tailor intervention strategies to better meet individual needs.

ECG and accelerometers are among the most widely used digital sensors in cardiovascular research. ECG captures the electrical activity of the heart, providing insights into arrhythmias, conduction abnormalities, and repolarization markers that have been linked to increased cardiovascular risk<sup>69–71</sup>. Accelerometers, embedded in wearable devices, provide objective measures of PA patterns, sedentary behaviour, and sleep metrics—factors that are well-established contributors to cardiovascular health and feature prominently in prevention guidelines<sup>72,73</sup>.

### **1.4.1 Electrocardiograms**

The ECG is a low-cost, non-invasive medical test used to describe the electrical activity of the heart, using electrodes placed on the body's surface. Any changes in the normal flow of electricity may indicate damage to the heart. Such damage can result from various pathologies, including arrhythmias, myocardial infarction, or pulmonary embolism, all of which are associated with an increased risk of MACCE<sup>74</sup>.



The ECG has long been used in clinical practice to detect cardiac abnormalities such as arrhythmias and conduction abnormalities, which are established predictors of cardiovascular events. In a recent systematic review, Moshawrab et al. (2023) evaluated the role of digital sensors for CVD assessment across 87 studies. The ECG was the most frequently adopted sensor (79.3%) for CVD while Cardiac arrhythmias were the most common study endpoint (49/87), with atrial fibrillation being the primary focus of 39 studies<sup>75</sup>.

While typically used for disease diagnosis, conventional ECG features, such as prolonged QT interval, ST depression, and heart rate variability, have been increasingly linked to risk of incident MACCE. Recent risk prediction studies have indicated that ECG measurements may improve predictive performance beyond traditional risk factors, however the added value of ECG to established clinical risk models to stratify patients into intervention groups remains unclear.

ECG testing can be conducted in various settings, including resting ECG, exercise ECG, and ambulatory monitoring using Holter monitors or chest-worn ECG patches, each providing distinct insights into cardiac function and CVD risk.

**Resting ECG** is the most commonly used ECG test in primary care, typically performed while the patients in a supine or seated position. Resting ECGs are used to provide a snapshot of the electrical activity of the heart under baseline conditions and is widely used to detect structural abnormalities, conduction disorders, arrhythmias, and ischemic change. Extensive epidemiological evidence, dating back to the Framingham Heart Study, has consistently linked resting ECG parameters including heart rate variability, PR, QRS and QTc intervals to incident MACCE, independent of established clinical risk factors.

**Exercise ECG**, also known as a stress test, evaluates the heart's response to physical exertion, typically using a treadmill or cycle ergometer. Exercise ECG is used to assess how the heart responds to physical stress, revealing any abnormalities that otherwise could not be detected at rest.

The exercise ECG is typically used to diagnose and stratify patients with stable ischemic heart disease (IHD). Physiological changes during an exercise test including ST depression and frequency of premature ventricular contractions have been shown to be associated with risk of incident MACCE. Recent evidence has shown exercise ECG measurements are predictive of incident MACCE however their added value to established clinical risk models remains largely unexplored.

**Ambulatory ECG:** Holter monitors, and wearable ECG patches provide continuous cardiac recordings over extended periods, outside of a traditional, clinical setting, allowing for the detection of abnormalities that were not present during a shorter resting or exercise ECG test. The Apple Heart Study has demonstrated the ability of wearable ECGs using smartwatch technology to detect atrial fibrillation, whilst implantable loop recorders have shown state-of-the-art performance for diagnosing arrhythmia with infrequent symptoms<sup>76</sup>. Despite this early access, more work is needed to validate the use of wearable ECG for detecting and predicting a greater range of arrhythmia and CVDs. This thesis will not consider Ambulatory ECG monitoring owing to a lack of a large-scale Ambulatory ECG dataset with longitudinal health follow-up.

A detailed overview of the ECG, along with the role of resting and exercise ECG in CVD risk prediction is provided in section 2.2.

#### **1.4.2 Accelerometer measured Physical activity**

PA is integral to human life and one of the most powerful interventions to reduce risk of MACCE. Increased PA reduces the risk of various non-communicable diseases and is linked to improved cognitive function and mental well-being<sup>73,77</sup>. Capturing movement behaviours and overall, PA has historically relied on self-reported data via activity questionnaires. However, such self-reported measures of PA are often inaccurate and prone to substantial recall bias. In recent years, accelerometer measured PA has emerged as the gold standard for PA monitoring and activity recognition.

Thanks to recent technological advances, such as increased memory for on-device storage, extended battery life and improved analytic techniques, the use of wearable accelerometers has become increasingly scalable and widely adopted in epidemiological research. Recent evidence has consistently demonstrated a stronger association between accelerometer-measured PA and CVD risk compared to self-reported data<sup>78,79</sup>, indicating a historic underestimation as to the protective effects of PA. Evidence from risk prediction studies has shown that measures of PA such as walking pace and total activity counts, to be among the strongest predictors of CVD, exceeding the predictive value of established clinical risk factors such as diabetes, hypertension and even age. Ever larger accelerometer-based cohort studies, with long term health follow-up, such as the UK Biobank, provide a novel opportunity to assess the predictive value of objectively measured PA for CVD risk prediction.

An in-depth overview of the current literature on PA measurements for CVD risk prediction is provided in section 2.3.

#### **1.4.3 Measuring CVD risk factors in high resolution sensor data**

The integration of high-resolution sensor data into CVD prevention pipelines remains a significant challenge in clinical research. Current CVD risk scores are often limited to a small number of established risk factors and frequently assume a linear relationship among risk factors and the target outcome. In contrast, digital sensors can capture hundreds of readings per second, creating data with complex structural and temporal dependencies. This presents a pressing need for new analytical methods which can better handle complex patterns present in such high frequency data.

There are two predominant approaches to the analysis of such high frequency data;(1) summary statistics, where signals are reduced to aggregate measures like heart rate variability from ECG or total daily steps from accelerometers, and (2) whole-signal analysis, which preserves temporal and structural patterns.

In recent years, there has been growing interest in the use of deep learning to analyse high-resolution sensor data for predicting disease outcomes. Unlike traditional regression-based methods, deep learning excels at capturing complex interactions within high-dimensional data without prior assumptions as to the relationship between risk factors<sup>80</sup>.

## 1.5 Deep Learning for CVD Risk Prediction

### 1.5.1 Brief introduction to deep learning

Deep learning is a subset of machine learning methods that use artificial neural networks with multiple layers to learn complex patterns and features from large datasets. Such methods can automatically model non-linear interactions between risk factors and identify subtle associations between inputs and the outcome of interest. When training a deep neural network model parameters are tuned iteratively by penalising or rewarding the algorithm based on how close model predictions are to the observed training data. Deep learning differs from conventional approaches in its ability to learn directly from raw data, such as ECG waveforms, integrating feature extraction and classification into a single model without manual feature selection (Figure 1.2). Deep learning has demonstrated state-of-the-art performance in the prediction of a range of diseases, often exceeding the performance of conventional risk scores<sup>81-83</sup>.

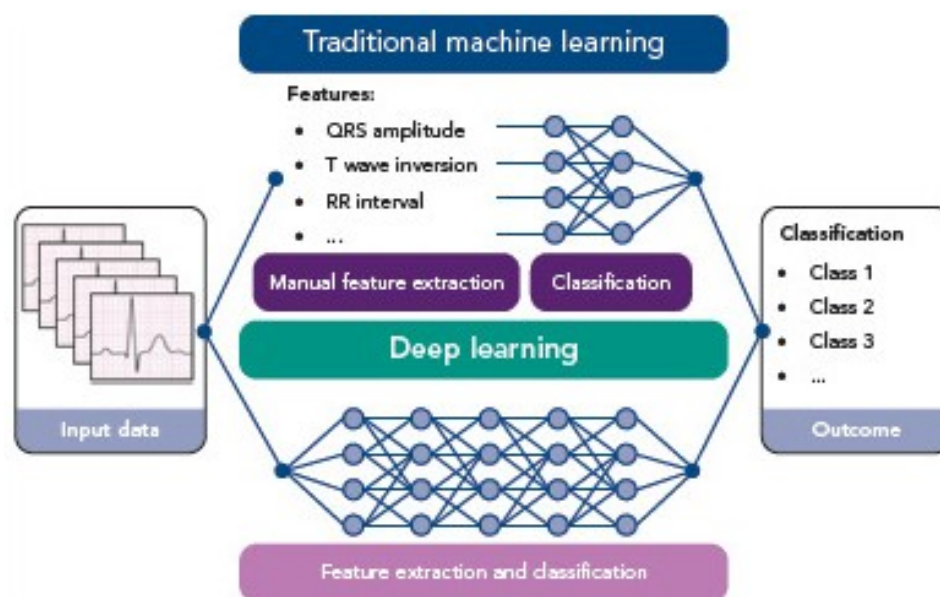


**Figure 1.2 Overview of deep learning vs conventional machine learning methods for disease classification and prediction using ECG data from the work of van de Leur<sup>84</sup>.**

### **1.5.2 Background and motivation**

Traditional risk scores are typically developed using multivariable regression frameworks to estimate the absolute risk of an event based on a combination of risk factors (such as age, sex, smoking, medical history etc). To this end, logistic regression and Cox proportional hazard models are the most frequently used models for both short- and long-term outcomes, respectively<sup>85-88</sup>. These models quickly grew in popularity due to their low computational cost and ease of interpretation, making them well-suited for practical application in clinical settings<sup>19</sup>.

However, regression approaches are not without their limitations. Regression models rely on a set of a priori assumptions as to the model's structure and the relationships between risk factors and outcomes. One of the most fundamental assumptions is that the association between our exposures and outcomes is linear, and any non-linear relationships must be explicitly programmed into the model.

There are many examples in CVD research where this assumption does not hold, including age, where risk rises exponentially for older individuals<sup>89</sup>, and BMI, where both under and overweight individuals are at higher risk.<sup>90-92</sup> Furthermore, any interactions between risk factors must also be explicitly modelled beforehand. For example, a large body of research has consistently shown non-linear interactions between HDL and age, with the risk associated with higher HDL attenuating as one ages<sup>93</sup>. As datasets have grown larger and new risk factors have been identified, the number of potential interactions has grown exponentially.

In response, deep learning has become a popular alternative to traditional regression methods. Rather than choosing the risk factors in advance, deep learning is able to identify which features of the data are important to the outcome without a prior assumption as to the relationship with the outcome or other exposures. This makes deep learning an ideal candidate for risk prediction research when dealing with large-volume and high-dimensional data such as the ECG and free living accelerometry<sup>46,94</sup>.

### 1.5.3 Deep Survival Networks

Deep survival is a subtype of deep neural networks that aims to combine the strengths of deep learning with time-to-event techniques such as Cox regression. Similar to regular neural networks, deep survival can automatically learn complex structures and non-linear interactions between risk factors, making it particularly useful in for high dimensional and complex data such as ECG and accelerometer time series. As a result of data driven and non-linear nature of deep survival models, they are not subject to prior assumptions on the relationships between risk factors, and are more able to capture complex relationships between exposures and time to event outcomes<sup>81</sup>.

A key distinction between deep survival and traditional neural networks is how censoring is handled: in survival data, not all subjects experience the event within the study period. Deep survival models account for censored data by explicitly weighting censored cases in the loss function<sup>81</sup>, while typical deep learning models are generally focused on fully observed outcomes. This allows deep survival models to make better use of incomplete data, an important advantage in medical research where patients may be lost to follow-up, or the event hasn't yet occurred.

In deep survival networks, censoring is handled using a negative log partial likelihood error function, similar to that of a Cox proportional hazard model (1.1). However, in this case, the likelihood estimation is optimised iteratively via backpropagation and repeated exposure to training data, as opposed to the traditional maximum likelihood estimation used in Cox regression.

Deep survival networks estimate the risk of incident events by modelling the hazard function, which represents the instantaneous rate at which events occur. Similar to Cox proportional hazards models, deep survival networks compute the cumulative survival probabilities over time, enabling time-specific predictions such as a 10-year risk score. Instead of using a linear predictor (as in traditional Cox regression), deep survival networks replace the traditional regression terms with a deep neural network.

This allows the model to capture complex, non-linear relationships within the data without prior assumptions as to the relationships between the exposures and outcome of interest.

$$l(\theta) := -\frac{1}{N_{E=1}} \sum_{E_i=1} \left( \hat{h}_\theta(x_i) - \log \sum_{j \in \mathcal{R}(T_i)} e^{\hat{h}_\theta(x_j)} \right) + \lambda \cdot \|\theta\|_2^2 \quad (1.1)$$

Where  $L(\theta)$  is the negative log partial likelihood;  $N_{E=1}$  is the number of observable events,  $\lambda$  the L2 regularisation and  $\hat{h}_\theta$  is the output of the deep-survival network with weights  $\theta$ .

## 1.6 Gaps and opportunities

The growing availability of both ECG and accelerometer recordings in large prospective cohort studies, with long term health follow-up, such as the UK Biobank opens up new opportunities for understanding the clinical utility of common digital sensors for primary prevention of MACCE. This thesis focuses on the integration of resting + exercise ECG and accelerometer measurements comparing both traditional and deep learning methods to enhance established clinical risk models for MACCE risk prediction. However, challenges remain in how to best utilise such measurements for risk prediction.

### 1.6.1 Phenotyping high resolution sensor data

Traditional risk scores for MACCE typically rely on a limited set of relatively simple risk factors, such as age, ethnicity and routine blood measurements. In contrast, common sensor modalities provide a continuous stream of high-resolution physiological and behavioural disease markers. Identifying and interpreting clinically relevant features within these vast data streams remains a significant challenge for integrating high-resolution digital signals into clinical risk prediction frameworks.

Thus, new methods are needed to extract salient features from these large data streams which are associated with the outcome of interest, which may enhance current risk prediction methods. This challenge is particularly acute for dynamic signals such as exercise ECG and free-living accelerometer recordings, where the signal characteristics can vary rapidly.

While some have demonstrated success at automating feature extraction in fixed time windows and aggregating across the signal, there is currently no standardised framework as to which features are of interest or how these should be measured.

Others have demonstrated great success in using deep neural networks to identify relevant features and interactions. However, the added predictive value of such models over traditional risk models is unclear and is an important objective of this thesis.

### **1.6.2 Assessing the predictive value of exercise and recovery ECG**

The predictive value of exercise and recovery ECG measurements for primary prevention remains largely unexplored in the literature. While resting ECG has been extensively studied in cardiovascular risk prediction, relatively few studies have evaluated whether exercise ECG adds value beyond traditional risk factors, with most reporting marginal improvements in predictive performance<sup>95–98</sup>. To date, investigations into the predictive value of exercise ECG have been limited by short follow-up durations, modest sample sizes, and a frequent lack of evaluation of clinical utility in accordance with current guidelines. A recent review by the US Preventive Services Task Force (USPSTF) highlighted these gaps, calling for further investigation into the clinical utility of exercise ECG in asymptomatic populations, particularly in relation to treatment thresholds for cholesterol-lowering interventions. This thesis aims to address these gaps through a comprehensive evaluation of resting, exercise, and recovery ECG measurements, assessing their predictive utility using model discrimination, calibration, and reclassification.

### **1.6.3 Assessing the predictive value of device measured Physical activity**

While there is substantial evidence showing a strong association between PA and incident MACCE, the predictive value of device-measured PA for individual risk assessment remains unclear. Several studies have assessed the predictive value of self-reported PA for incident CVD, reporting modest improvements in predictive performance.



However, these studies are often limited by inherent bias through the use of self-reported PA data and modest sample sizes. Prior evidence has consistently demonstrated that device-measured PA has a far stronger association with incident MACCE than self-reported data while initial evidence from prospective cohort studies demonstrate strong predictive value. For instance, Ledbetter et al. demonstrated that adding device-measured PA to traditional risk factors significantly improved the prediction of cardiovascular mortality, with the univariate performance of PA exceeding that of all conventional risk factors, including age. However, the predictive value of device-measured PA for incident fatal and non-fatal MACCE for primary prevention remains largely unexplored.

#### **1.6.4 Integration with existing clinical risk models**

While there is a large body of evidence associating ECG and accelerometer measurements with incident MACCE, there is little evidence as to whether or not they improve upon existing MACCE risk scores. A number of studies have investigated the predictive value of ECG and accelerometer readings in isolation or combined with a number of hand selected clinical risk factors; however, few have investigated the impact of directly incorporating such measurements into existing risk prediction frameworks.

A handful of studies have shown that ECG and accelerometer measurements may improve the absolute predictive performance beyond clinical risk factors, there remains a lack of evidence as to the clinical utility of such measures. There is limited evidence as to whether ECG or accelerometer measurements can help to reclassify patients into new treatment groups or the impact such measurements have on the calibration in new populations. This leaves a huge gap as to the clinical utility of ECG and accelerometer measurements compared to current clinical practice. Therefore, this thesis seeks to assess the incremental value of ECG and PA to established clinical risk factors for MACCE and their potential impact on patient stratification.

## **1.7 Thesis aims and objectives**

Current clinical risk models for MACCE are constrained by a reliance on non-modifiable risk factors and limitations in accurately measuring key risk factors. Digital sensors enable the objective measurements of key behavioural and physiological risk factors for MACCE, which are currently not accounted for in existing clinical risk tools. Substantial epidemiological evidence has demonstrated a strong association between ECG and accelerometer recordings with incident MACCE. However, despite these associations, no clinically adopted risk scores incorporate ECG or PA for identifying high-risk individuals. This thesis investigates the added value of ECG and accelerometer recordings to existing clinical risk models. To this end, this thesis seeks to satisfy the following objectives:

1. Assess the prospective associations between conventional ECG parameters, derived from submaximal exercise ECG testing, and incident MACCE and to evaluate their added value to existing clinical risk models.
2. Develop deep-learning risk models to predict incident MACCE from raw ECG data and assess their added value to current clinical risk models.
3. Investigate the added value of objective measurements of 24-hour movement behaviours to existing clinical risk models.
4. Develop and integrate a deep-learning risk prediction tool with existing clinical risk models based on large accelerometer time series data.

The outline of the remainder of this thesis is presented below.

## **Thesis outline**

**Chapter 2:** Narrative review on the role of Electrocardiogram and accelerometer measured PA in prediction and prevention of CVD.

**Chapter 3:** Introduces the UK Biobank and subsequent submaximal exercise ECG and wearable accelerometer sub-studies.

**Chapter 4:** Assess the association between manually extracted ECG parameters from time series data and their added value to existing clinical risk models.

**Chapter 5:** Develop a deep-learning risk prediction model using raw ECG recordings measured during a submaximal exercise test and assess their added value to conventional CVD risk scores. Subsequently I will assess the predictive performance of deep-learned risk scores vs those based on conventional ECG parameters.

**Chapter 6:** Investigate the association of device-measured physical activity behaviours, such as daily step count and sleep activity, with incident CVD and evaluate their added value to existing clinical risk models.

**Chapter 7:** Investigates the added value of device-measured accelerometer time-series data to the prediction of incident CVD using deep neural networks and compare their performance to conventional measurements of physical activity.

**Chapter 8:** Summarises the findings presented in the thesis, placing them in the broader context of current knowledge and public health. Discusses the contribution of the thesis to existing evidence and highlight remaining questions, limitations, and future research.

**Appendix A** provides further details and a rationale for the methods used in chapters 4-7 for signal processing and model development.

**Appendix B:** Supplementary tables and figures

**Appendix C:** Risk Score model coefficients

**Appendix D:** Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) Checklist

## Chapter 2 – Literature review: Digital sensors in CVD risk prediction

### 2.1 Introduction

Chapter 1 briefly outlines the limitations of current risk scores for Major Adverse Cardiovascular & Cerebrovascular Events (MACCE), particularly their reliance on non-modifiable risk factors and challenges in accurately measuring key risk factors. It also highlights the opportunities presented by digital sensors such as the ECG and wearable accelerometers in primary prevention of MACCE through more precise measurement of physiological and behavioural risk factors that are not currently accounted for in conventional risk models.

Driven by recent advancements in ubiquitous computing, there has been rapid expansion of medical and consumer-grade digital sensors for population health monitoring, enabling more precise and scalable data collection. In a recent systematic review by Moshawrab et al. (2023) emphasized the rapid growth in the use of digital sensors for CVD research. Among 87 identified studies, 78% were published between 2019 and 2022, with ECG being the most frequently used sensor (79.3%)<sup>75</sup>. In a similar systematic review, Cuevas-Chavez et al. (2023) evaluated the role of digital sensors across 160 studies for detecting and predicting CVD<sup>69</sup>. The review highlights the advanced performance of digital sensors, such as ECG and accelerometers, in predicting a range of CVDs and related risk factors, including atrial fibrillation, systolic blood pressure, and heart failure. However, the authors highlight the lack of clinical validation and limited data availability as a key bottle neck to further advancement in the field. Despite the success of digital sensors in detecting CVD and CVD risk factors such as arrhythmia, their integration into existing clinical risk prediction tools remains underexplored. Following the general overview provided in Chapter 1 it is useful to consider the current evidence on the predictive value of such measurements for incident MACCE. A better understanding of the predictive performance of ECG and accelerometer measurements for incident MACCE may help open the door to further investigations on the clinical value of such measurements in clinically relevant populations.

This chapter reviews the evidence on the use of ECG and PA measurements for predicting incident MACCE. Section 2.2 introduces the evaluation metrics used throughout this thesis to assess the performance of risk prediction models. Section 2.3 introduces the fundamentals of ECG to orient readers unfamiliar with cardiac electrophysiology before evaluating the association and predictive value of both resting and exercise ECG for MACCE. Section 2.4 explores the epidemiology of PA, covering its measurement, relationship with CVD, and the current evidence on its role in risk prediction.

## **2.2 Evaluating performance**

The evaluation of clinical risk models is multifaceted, requiring assessment across multiple metrics to determine their overall utility. A well-performing model should not only distinguish between individuals at higher and lower risk (discrimination) but also accurately align with the true absolute risk, (calibration) and offer meaningful improvements for eligible participants over existing risk models such as classification into appropriate intervention groups (reclassification).

Current reporting guidelines such as the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD), and the Prediction model Risk of Bias Assessment Tool (PROBAST) recommend a range of evaluation metrics assessing discrimination, calibration and reclassification, emphasising that evaluation metrics should not be used in isolation.

The following sections summarise the most commonly used evaluation metrics in the literature and describes their relative advantages, and limitations, including Harrell's C-index for discrimination, calibration curves and the integrated calibration index (ICI) for calibration, in addition to the net reclassification index (NRI) and net benefit (NB) for reclassification and decision-making.

## 2.2.1 Discrimination

### 2.2.1.1 Area under the receiver operating curve

The area under the receiver operating curve (AUC) is a commonly used measure of discrimination in binary outcome models. It quantifies the model's ability to distinguish between individuals who experience the event and those who do not by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) across all possible thresholds. An AUC of 0.5 indicates no discriminative ability (equivalent to random chance), while an AUC of 1.0 represents perfect discrimination.

$$AUC = \int_0^1 TPR(FPR^{-1}(x))dx \quad (2.1)$$

Where  $TPR$  = True positive rate;  $FPR$  = False positive rate;  $x$  = model predictions

### 2.2.1.2 Harrell's C-index

Harrell's C-index<sup>99</sup> measures how often the model correctly predicts a higher risk for the participant who experienced the event earlier in a randomly selected pairing, i.e. the proportion of concordant to discordant pairs. A C-index of 1.0 represents perfect discrimination, whilst a C-index of 0.5 represents the same performance as random chance, i.e. no discrimination. Harrell's C-index is often preferred over the AUC in survival analysis because it accounts for censored data and time-to-event information, providing a more appropriate estimate of discrimination in risk prediction models.

The C-index is summarised in equations 2.2 and 2.3.

$$Cindex = \frac{\sum_{i \neq j} I\{T_i < T_j\} I\{S_i > S_j\} d_j}{1\{T_i > T_j\} d_j} \quad (2.2)$$

Where  $T_i$  &  $T_j$  are the observed survival times of individuals  $i$  and  $j$ ;  $S_i$  &  $S_j$  are the predict risk for individuals  $i$  and  $j$ ;  $I$ : Indicator function equal to 1 if the condition is true

More succinctly this can express as:

$$Cindex = \frac{\# \text{ Concordant pairs}}{\# \text{ Concordant pairs} + \# \text{ discordant pairs}} \quad (2.3)$$

Despite being the most widely reported measure of discrimination for risk prediction models, the C-index has several well-recognised limitations. First, it is insensitive to calibration and therefore cannot detect systematic over- or under-prediction. Second, because it summarises discrimination across all time points, it may obscure clinically important misclassification within specific time horizons. The C-index was nevertheless included due to its widespread use in the risk prediction literature, and consistent with TRIPOD recommendations, should be interpreted alongside calibration assessments and reclassification-analytic measures rather than in isolation<sup>88,100</sup>.

### **2.2.2 Calibration**

Calibration is essential for contextualising model performance, as poor calibration (i.e. systematic under or over-prediction of risk) can inflate other performance metrics such as the net reclassification index. Additionally, a model that discriminates well may still be poorly calibrated and thus not clinically useful. The TRIPOD guidelines recommend reporting calibration graphically, plotting the model prediction against the observed outcome. Such plots are often accompanied by summary statistics seeking to describe the calibration curves slope, intercept and alignment/misalignment with the observed outcomes. The alignment between observed and predicted event outcomes is typically assessed by measuring the distance between the smoothed calibration curve and the line of perfect calibration. Common metrics include the E50 and E95, which represent the median and 95th percentile of the absolute error between predicted and observed risk, respectively, as well as the ICI, which quantifies the average absolute deviation across the full range of predicted probabilities<sup>101</sup>.

#### **2.2.2.1 Continuous calibration curve**

Visual overviews of model calibration are reported in the form of calibration curves, which plot the scatter of predicted and observed risk against the line of perfect fit<sup>102</sup>. In this work the observed risk was estimated for censored individuals using pseudo probabilities obtained via a leave-one out jack-knife approach as outlined by Royston et al. 2014<sup>103</sup> and smoothed using a local polynomial regression smoother (LOESS)<sup>104</sup>.

### 2.2.2.2 Integrated Calibration index

The ICI<sup>101</sup> quantifies model calibration by evaluating how closely the predicted risk aligns with the observed probabilities in the population. The ICI measures the absolute difference between the continuous calibration curve and the diagonal line of perfect calibration. In contrast to other calibration metrics, such as E50 or E95, the ICI calculates a weighted average of the errors across the entire range of observed probabilities, giving a higher weighting to regions where the model makes more predictions. This approach ensures that calibration is evaluated where it is most relevant for the model and event in question, downweighing the contribution of errors towards the extremes of the distribution.

The general formula for the ICI is provided in equation 2.4.

$$ICI = \int_0^1 f(x)\phi(X)dx \quad (2.4)$$

Where:  $f(x) = |x - xc|$ , where  $x$  denotes the predicted probability between 0-1 and  $xc$  denotes the value of the calibration curve at  $x$

$\phi(X)$  represents the density function for the distribution of predicted probabilities.

### 2.2.3 Reclassification

Model classification/reclassification metrics compare a new model to a reference model by assessing the number of participants classified into the appropriate risk. Reclassification enables the assessment of the clinical utility of a new model or risk factor where clinically relevant decision thresholds exist. Common metrics include the categorical net reclassification index (NRI)<sup>105</sup> and net-benefit (NB)<sup>106</sup>.

#### 2.2.3.1 Categorical Net reclassification index

Categorical NRI measures the net change in appropriate reclassification across event and non-event groups. Comparing a baseline and comparator risk score.

A positive NRI suggests that the new model improves risk stratification by correctly moving more events into higher-risk categories and non-events into lower-risk categories. Conversely, a negative NRI indicates increased misclassification, where events are moved to lower-risk categories or non-events are moved to higher-risk categories.



NRI calculations rely on fixed risk thresholds, such as the 10% threshold recommended for stratifying patients into intervention and non-intervention groups for CVD risk scores in UK primary care<sup>26</sup>.

The formula for categorical NRI is provided in equation 2.5.

$$NRI = P(up|event) - P(down|event) + P(down|nonevent) - P(up|non event) \quad (2.5)$$

### 2.2.3.2 Continuous Net reclassification index

In contrast to the categorical NRI, continuous NRI evaluates improvements in predicted risk scores without relying on predefined risk thresholds<sup>105</sup>. Instead, continuous NRI measures the pairwise change in predicted risk. For any pair of models, the continuous NRI evaluates whether the new model assigns higher predicted risk to individuals who experienced the event and lower risk to those who did not. The overall NRI is calculated in the same way as for categorical NRI; however, “upward” and “downward” reclassification are no longer defined by a fixed risk threshold. For any pair of models, the continuous NRI evaluates whether the new model assigns higher predicted risk to individuals who experienced the event and lower risk to those who did not. In other words, the overall continuous NRI is calculated as the net proportion of participants whose predicted risk increased for events and decreased for non-events, indicating better discrimination between cases and non-cases. The formula for continuous NRI is outlined in equation 2.6.

$$NRI_{continuous} = P(higher\ risk|event) - P(lower\ risk|event) + P(lower\ risk|non\ event) - P(higher\ risk|non\ event) \quad (2.6)$$

heavily on arbitrary risk thresholds and is sensitive to miscalibration, which can create the appearance of improvement without genuine gains in predictive accuracy. The continuous NRI, although avoiding thresholds, is numerically unstable, often yields disproportionately large values, and is not a proper scoring rule<sup>107-109</sup>.

Both continuous and categorical NRI may inflate type I error rates and overstate incremental value<sup>108,110</sup> and should therefore be interpreted alongside calibration and decision-analytic measures<sup>51,58</sup>. Despite these limitations, the NRI was included to maintain consistency with contemporary cardiovascular risk-prediction studies, where it remains a widely reported measure of incremental improvement<sup>111</sup>.

### 2.2.3.3 Standardised Net benefit

Finally, the standardised net benefit (NB)<sup>106</sup> is used to evaluate each model's clinical utility by balancing the benefits of correctly identifying individuals at risk against the harms of false positives at a given risk threshold.

NB is expressed as a percentage of the maximum utility, where a value of 1.0 represents perfect decision-making (e.g. treating all cases and no controls), and a value of -1.0 represents maximum harm (e.g. treating only controls). NB has several key advantages over NRI in that it incorporates the relative weight of true positives and false positives, making it more interpretable in clinical decision-making contexts and will never be inflated by poor model calibration. The formula to derive the standardised net benefit is provided in equation 2.7.

$$NB_R = TPR_R - \frac{R}{1-R} \frac{1-P}{P} FPR_R \quad (2.7)$$

*Where: NB = Net benefit; TPR = True positive rate; FPR = False positive Rate; P = prevalence; R = risk threshold*

## 2.3 Electrocardiogram

### 2.3.1 Pathology and electrical activity of the heart

The human heart is a highly specialised muscular organ which works continuously to pump blood throughout the lungs and body, ensuring a constant flow of oxygen. The heart consists of four primary chambers: the left and right atria (LA and RA) and the left and right ventricles (LV and RV). Surrounding these chambers is the myocardium, which consists of specialised and interconnected myocardial cells known as myocytes. These myocytes generate and propagate electrical signals, forming a conductive system that ensures coordinated contraction and relaxation of the heart chambers. (Figure 2.1).

These electrical impulses facilitate the sequential contraction of the atria and ventricles, a process referred to as the cardiac cycle. The cycle begins with atrial contraction, and ventricular contraction, and concludes with ventricular relaxation. The synchronized transmission of these impulses is essential for efficient blood circulation. Any disruption in this electrical activity can lead to abnormal cardiac rhythms, which can be detected and analysed using electrocardiography.

The following narrative review explores the role of the ECG in primary care and its potential to improve the prediction of incident MACCE.

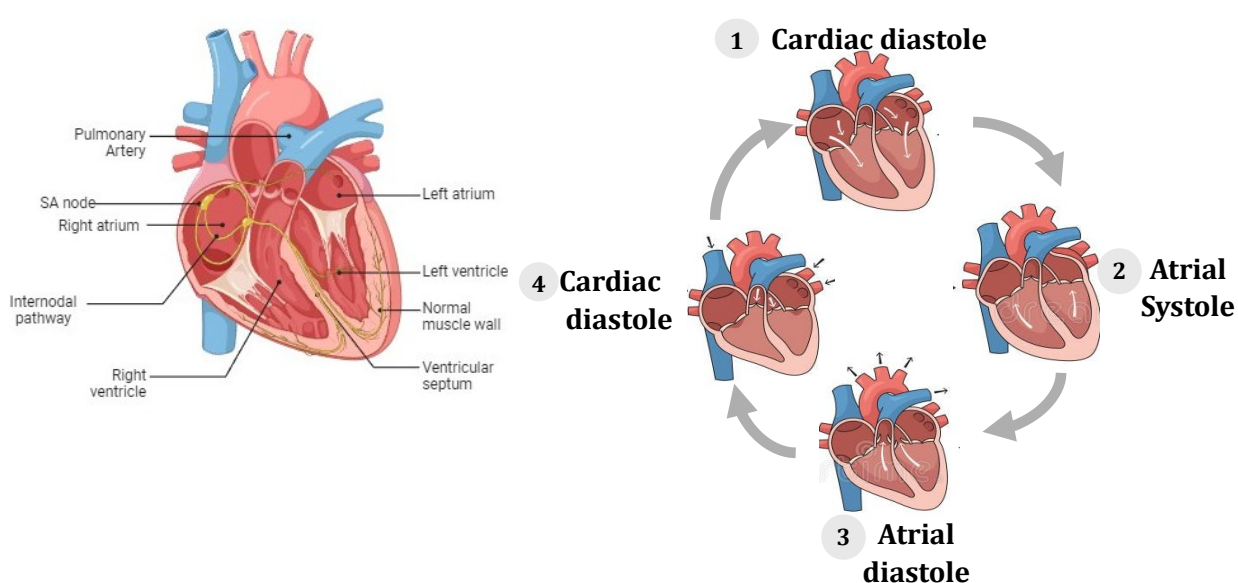


**Figure 2.1: Overview of the cardiac cycle of the heart**

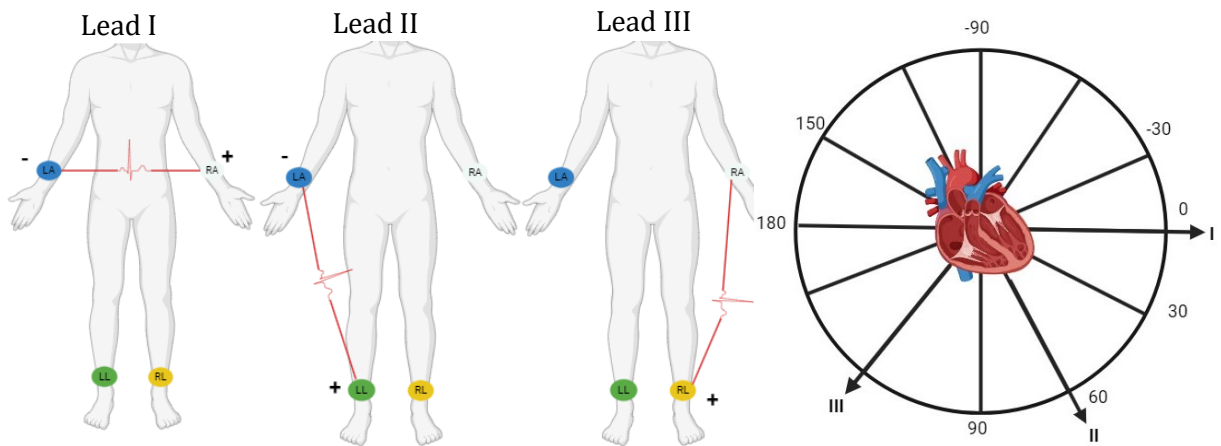
### **2.3.2 Introduction to the Electrocardiogram**

The Electrocardiogram (ECG) is a low-cost, non-invasive, and widely available medical test used to measure the heart's electrical activity. By placing a few electrodes on the body's surface, the electrical signals produced during each stage of the cardiac cycle can be accurately measured<sup>112</sup>. An ECG enables clinicians to assess the conduction and rhythm of the heart. Any changes in the normal flow of electricity may indicate damage to the myocytes and can easily be detected via an ECG. This damage may be due to several disease pathologies, including infarction, pulmonary embolism and arrhythmia, which all contribute to a higher risk of adverse cardiovascular outcomes<sup>74</sup>. As a result, the ECG has become an indispensable tool in both primary and secondary care to diagnose and monitor heart rhythm, treatment effects and a range of cardiac conditions.

#### **ECG leads, waves, and intervals**

ECG recordings are obtained from electrodes placed on the limbs and chest, capturing different perspectives of the heart's electrical activity. The recorded voltage changes between two electrodes form a lead, each offering a unique view of the heart<sup>113</sup>. A standard ECG typically includes three limb leads (Figure 2.2) recorded at rest, but advanced assessments may use a 12-lead ECG for detailed cardiac evaluation, exercise stress testing to assess heart function under exertion, or 24-hour Holter monitoring for continuous rhythm analysis in daily activities.

## A: ECG limb leads



## B: Einthoven's triangle

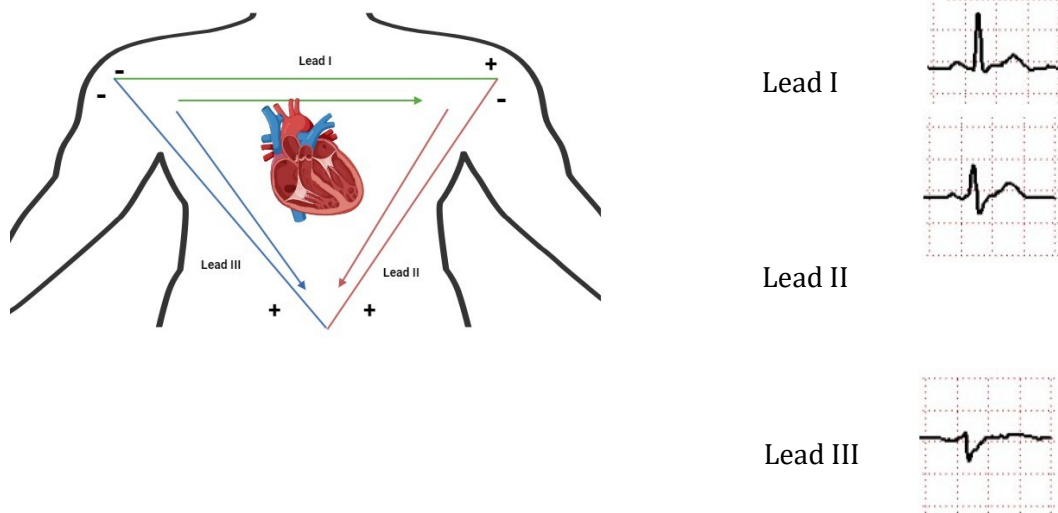


**Figure 2.2 Organisation of 3 lead (limb leads) ECG electrodes**

Abbreviations: RA- Right forearm, LA- Left forearm, LL – Left lower leg, RL – Right lower leg

### **2.3.3 ECG and cardiovascular disease**

The relationship between ECG measurements and the future risk of MACCE has been the focus of numerous studies since the digitisation of ECG analysis<sup>114,115</sup>. While initial studies focused on the association between ECG measurements and MACCE, more recently, there has been an increase in the use of the ECG for screening high-risk individuals<sup>116–118</sup> (Table 2.1). By capturing real-time, patient-specific information on myocardial structure, perfusion and electrical activity, it is hoped that the ECG can provide useful insights into the impact of clinical and subclinical risk factors on the heart.

#### **2.3.3.1 Association between Resting ECG and incident cardiovascular disease**

A large body of epidemiological evidence dating back to the Framingham heart study has consistently shown strong associations between resting ECG parameters and incident MACCE, independent of established clinical risk factors<sup>70,95,119,120</sup>. In 1969, Kannel, Gordon, and Offutt demonstrated that ventricular hypertrophy, diagnosed via an ECG, is highly predictive of incident MACCE in asymptomatic adults<sup>121</sup>. Since then, a plethora of ECG abnormalities have been identified which are associated with a higher risk of MACCE (Table 2.1). A growing body of evidence from prospective cohort studies has indicated the presence of a dose-response relationship between the number of ECG abnormalities and MACCE<sup>122–124</sup>. Krittayaphong et al. (2019.) assessed the prevalence of ECG abnormalities in high-risk individuals with existing atherosclerotic disease. They found that an increased prevalence of ECG abnormalities was independently associated with the risk of MACCE following adjustments for established clinical risk factors<sup>125</sup>. Significant positive associations were reported for ECG diagnosed Atrial fibrillation Hazard ratio (HR) = 2.78 (1.53–5.05); Q/QS: HR = 2.78 (1.53–5.05) and intraventricular conduction delay: HR = 3.71 (2.22–6.23). Their findings were supported by a subsequent observational analysis conducted by Niu et al. (2020), which investigated the prevalence of several ECG abnormalities, including changes in ST-T waves, major Q/QS changes and atrial fibrillation, amongst those with incident CVD.

They found the presence of ECG abnormalities to be independently associated with CVD risk in patients at high risk of atherosclerotic CVD (ASCVD) and a consistent increase in the prevalence of abnormal ECG findings for those with incident CVD<sup>71</sup>.

Beyond these findings, additional research has explored the strength and shape of associations between specific ECG abnormalities and incident MACCE. Shah et al. (2016) observed a U-shaped association between P-axis, R-axis, frontal QRS-T angle, and T-axis deflection with incident MACCE, indicating a non-linear relationship between these ECG markers and MACCE risk. Additionally, they reported statistically significant improvements in MACCE prediction when combining associated ECG risk factors with clinical risk factors from the Framingham risk score (FRS) and Pooled Cohort Equation (PCE)<sup>70</sup>.

### **2.3.3.2 Resting ECG for cardiovascular disease risk prediction**

In 1996, the US Preventive Services Task Force (USPSTF) conducted its first review on the role of ECG screening for primary prevention of coronary artery disease (CAD), concluding that there was insufficient evidence to recommend for or against the use of ECG in primary prevention of CAD<sup>126</sup>. Since then, substantial research efforts have been undertaken to address this gap in the evidence and establish the prognostic value of resting ECG measurements in the primary prevention of CVD.

In one of the largest studies since the initial USPSTF review, Shah et al. (2016) evaluated the added value of ECG measurements to the Framingham risk Score (FRS) and pooled cohort equation (PCE)<sup>127</sup>. The author reported significant improvement in the classification of high-risk individuals following the addition of ECG risk factors to FRS and PCE with a Net reclassification index of 25% for each score, respectively. Similar findings have been reported across diverse cohorts in a range of studies. In 2012, Auer et al.<sup>128</sup> assessed the added value of ECG abnormalities (see Table 2.1) to traditional CVD risk factors in older adults in the USA. The authors report a 7.4% improvement in Net reclassification index (NRI) over 4-years of follow-up. However, the authors note that the magnitude of the improvement was highly dependent on the baseline clinical risk factors selected for assessment.

Jørgensen et al. (2014) evaluated the added value of ECG measurements alongside clinical risk factors from the European Heart Score, Framingham and Global Risk Score in individuals over 65. Significant associations were found between fatal and non-fatal CVD with ECG morphology measurements such as PR, QRS, and QTc intervals, in addition to left ventricular hypertrophy (LVH).

Combining these ECG parameters with clinical risk factors significantly improved predictive performance for incident CVD<sup>119</sup>. Deo et al. (2016) further investigated the added value of ECG parameters in predicting CVD risk in individuals with chronic kidney disease. They reported strong positive associations between ST depression, LVH, and changes in Q and T waves, noting significant improvements in identifying high-risk individuals when combining ECG morphology parameters with clinical risk factors<sup>120</sup>.

The magnitude of improvement in CVD risk prediction provided by ECG readings varied widely across studies, owing to differences in study populations and choice of ECG parameters. In many of the previously mentioned studies, participants were either over the age of 65, as in Auer et al.<sup>128</sup> and Jørgensen et al.<sup>119</sup>, or had preexisting comorbidities, as in Deo et al. 2016<sup>120</sup>, both of which predispose participants to higher baseline CVD risk. In a 2015 prospective cohort study, Groot et al. reported no significant improvements in predictive performance after incorporating resting ECG parameters with SCORE<sup>58</sup> in 2,370 participants aged 38–74 eligible for CVD risk assessment. Similarly, Niu et al. (2020) reported marginal improvement in CVD risk prediction in adults at high-risk NRI = 0.060 (–0.022, 0.132) and no improvements for low-risk or asymptomatic adults<sup>129</sup>.

In 2018, the USPSTF published its latest review on ECG screening for CVD prevention in primary care, summarising the available evidence up to this point. The review highlights a great deal of heterogeneity between study findings owing to inconsistencies in prediction models, risk thresholds, types of ECG abnormalities assessed, and study endpoints.



Across nine cohort studies involving 66,407 participants, combining resting ECG measurements with traditional risk factors led to minor improvements in risk discrimination ranging from 0.001 to 0.05. Reclassification results varied greatly from study to study, ranging from a 3.6% to 30% improvement in NRI. The review concludes that there is insufficient evidence to recommend resting ECG for routine CVD risk assessment in asymptomatic adults<sup>118</sup>.

Table 2.2 summarises the results across these different studies.

### **2.3.3.3 Association between exercise ECG and incident cardiovascular disease**

Exercise ECG testing poses a dynamic physiological stress on the heart that may unmask underlying cardiac anomalies not evident at rest. An exercise ECG is typically used to diagnose and stratify patients with stable ischemic heart disease (IHD). Current clinical guidelines, including those from NICE and the US Preventive Services Task Force (USPSTF), advise against the use of exercise ECG for low-risk and asymptomatic individuals for screening individuals for future CVD events, citing a lack of evidence for low-risk CVD groups<sup>118,130,131</sup>.

Numerous studies have sought to quantify the prognostic value of exercise ECGs across a diverse range of cohorts to address this gap in the current literature. An observational study conducted by Duijvenboden et al. 2023, demonstrated that the frequency of PVCs measured during an exercise ECG test among asymptomatic individuals showed a strong incremental association with future MACCE<sup>132</sup>. Research from the multiple risk factor intervention trial identified a significant positive association between abnormal ST waves and heart rate during exercise with incident CHD mortality<sup>133</sup>. Building on this finding, a subsequent analysis by Peter M. Okin et al. found that measurement of abnormal heart rate and induced ST depression during exercise could successfully identify individuals who would benefit from therapy aimed at reducing key cardiovascular risk factors, Relative risk (RR) = 4.1, (95% CI 2.7 to 6.0,  $p < 0.0001$ ), hinting at the value of exercise ECG screening in primary prevention<sup>96</sup>.

In a systematic review Chou et al. (2011), reported a strong association between abnormal exercise ECG tests, particularly ST-segment abnormalities, and incident CVD (Pooled HR = 2.1 (95% CI: 1.6–2.9), following adjustments for clinical risk factors. However, there was insufficient evidence to determine the accuracy of exercise ECG for classifying high-risk individuals to guide preventive treatment<sup>134</sup>.

#### **2.3.3.4 Exercise ECG for cardiovascular disease risk prediction**

In a 2018 systematic review investigating the use of resting and exercise ECG for screening individuals for CVD, Jones et al. evaluated five prospective cohort studies (N = 9,582 participants), assessing the predictive value of exercise ECGs to established clinical risk factors<sup>97,117</sup>. They found that the addition of exercise ECG to clinical risk factors marginally improved predictive performance for incident CVD with changes in C-index ranging from 0.02–0.03; however, improvements in risk stratification remain uncertain<sup>95</sup>. Only one study identified in the review evaluated changes in risk stratification (Chang et al.<sup>135</sup>) using nonstandard risk thresholds of n 6%, 6% to 20%, and more than 20%. The authors reported an overall NRI of 9.6%.

Jones also identified two RCTs (1,151), DADDY-D and DYNAMIT trials, which assessed the predictive value of exercise ECG in older individuals with diabetes. They found no significant improvements in predictive performance in this high-risk group with DADDY-D: RR = 0.84(0.40-1.79) and DYNAMIT: RR = 1.07 (0.64-1.79) between screening and control groups. However, it should be noted that both studies were limited by modest sample sizes and failed to reach their initial recruitment goals. Additionally, both studies lacked sufficient follow-up time to assess their added value to established clinical risk models in line with established guidelines. While CVD risk is typically assessed on a 10-year time frame, each study only had 3.5 and 3.6 years of follow-up at the time of publication<sup>97,117</sup>.

Since the publication of this review, numerous studies have sought to build on these findings by assessing the predictive value of exercise ECG for a range of CVDs such as ischemic heart disease (IHD)<sup>136,137</sup>, coronary artery disease (CAD)<sup>138,139</sup> and MACE<sup>140</sup> (Table 2.1). Zhang et al. (2024) reported a significant association between the QRS duration (odds ratio 1.032,  $p = 0.024$ ), number of leads with high-frequency QRS complex (HFQRS) (odds ratio 1.188),  $p = 0.007$  and post-exercise recovery heart rate (Odds ratio: 0.973 (95% CI 0.960 - 0.986) for CAD. In a similar investigation, Schaerli et al. evaluated the prognostic value of HFQRS during exercise tests for MACE after 2 years of follow-up. HFQRS was independently associated with MACE following adjusted for CVD risk factors 2.76 (95% CI 1.73–4.42). When combining HFQRS and ST-segment abnormalities from an exercise ECGs, the authors were able to predict incident IHD with an AUC of 0.64 (95% CI 0.59–0.70); no comparisons were made to a baseline clinical risk score.

None of the previously highlighted studies evaluated the clinical utility of exercise ECG tests for primary prevention. All participants were recruited from cardiology or hospital-based prevention centres. As a result, there is a lack of evidence regarding the use of exercise ECG in asymptomatic individuals who would typically be eligible for CVD screening in the general population. Furthermore, no evaluation of model calibration or reclassification was provided, making it unclear whether exercise ECG improves risk stratification or clinical decision-making in routine preventive care. While these studies help to further demonstrate the association of exercise ECG with MACCE, the utility of exercise ECGs as a means of improving stratification for CVD prevention remains unclear.

An overview of the study findings is shown in Table 2.2.

**Table 2.1 Summary of recent studies on the prognostic value of resting and exercise ECG measurements for incident cardiovascular disease.**

| Cohort                                                              | Study reference              | Study design                   | Population                                             | N     | Outcome                                           | Base model                                | ECG phenotypes                                                                                                     | ECG Hardware and lead configuration | Study type      |
|---------------------------------------------------------------------|------------------------------|--------------------------------|--------------------------------------------------------|-------|---------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------|
| <b>Resting ECG</b>                                                  |                              |                                |                                                        |       |                                                   |                                           |                                                                                                                    |                                     |                 |
| Health, Aging, and Body Composition Study (Health ABC Study)        | Auer et al. <sup>128</sup>   | Prospective cohort study       | Older black and white adults aged 70 to 79             | 351   | 7.5-year coronary heart disease                   | FRS                                       | Major and minor ECG abnormalities:                                                                                 | 12-lead ECG                         | Risk prediction |
| University of Pittsburgh Medical Centre patients                    | Maanja et.al. <sup>141</sup> | Cross sectional                | Patients undergoing CMR with QRS < 120 ms              | 783   | 1-year Mortality<br>Heart failure hospitalisation | Cardiovascular magnetic resonance imaging | Frontal QRS-T angle, QTc interval                                                                                  | 12 leads ECG                        | Risk prediction |
| National Health and Nutrition Examination Survey                    | Shah et al. <sup>70</sup>    | Prospective cohort study       | Representative sample of US adults aged 40-74years     | 9,969 | MACE                                              | FRS & PCE                                 | Frontal P, R, and T axes; heart rate; and PR, QRS, and QT intervals                                                | 12 lead ECG (Digicorders; Beckman)  | Risk prediction |
| Netherlands primary care patients (Utrecht Health Project)          | Groot et al. <sup>142</sup>  | Prospective cohort study       | Primary care patients in the Netherlands<br>Aged 38-74 | 2,370 | CVD                                               | SCORE variables                           | ECG abnormalities (. Lausanne criteria) <sup>143</sup>                                                             | 12 lead ECG                         | Risk prediction |
| Community residents living in the Jiading district, Shanghai, China | Niu et al. <sup>71</sup>     | Multi centre Prospective study | Chinese adults age over 40                             | 7,872 | CVD                                               | Traditional CVD risk factors              | Major or minor ECG abnormalities: MI, Q-QS wave abnormalities, left ventricular hypertrophy, Wolff-Parkinson-White | 12 lead ECG (CAM14, GE, US)         | Risk prediction |

|                                                                                                |                                             |                             |                                                                     |       |                             |                     |      |                                                                                                                                                                                                                                                                                       |             |                 |
|------------------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------|---------------------------------------------------------------------|-------|-----------------------------|---------------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------|
|                                                                                                |                                             |                             |                                                                     |       |                             |                     |      | syndrome,<br>bundle branch<br>block or<br>intraventricular<br>block, atrial<br>fibrillation or<br>atrial flutter, and<br>ST-T changes                                                                                                                                                 |             |                 |
| The Cohort Of<br>patients with<br>high Risk for<br>cardiovascular<br>Events (CORE)<br>registry | Krittayaphong<br>et al. <sup>125</sup>      | Multicentre<br>study cohort | Thai adults<br>with prior<br>atherosclerotic<br>disease<br>Age > 45 | 2,009 | MACE                        | Clinical<br>factors | risk | AF, ARB, AVB:<br>IVCD, LVH, PVC,<br>Q-wave or QS-<br>wave; T-wave<br>inversion                                                                                                                                                                                                        | 12 lead ECG | Risk prediction |
| Copenhagen<br>Heart Study                                                                      | Jorgensen <i>et al.</i> 2014 <sup>119</sup> | Prospective<br>cohort study | Community-<br>dwelling<br>elderly<br>individuals                    | 6,991 | Fatal and non-<br>fatal CDV | FRS variables       |      | Major and minor<br>ECG<br>abnormalities:<br>Q waves (1.1.x to<br>1.3.x), ST-<br>segment<br>depressions (4.1<br>to 4.3), T-wave<br>changes (5.1 to<br>5.3), left<br>ventricular<br>conduction<br>defects (7.1.x<br>and 7.2.x), and<br>left ventricular<br>hypertrophy<br>(3.1 and 3.2) | 12-lead ECG | Risk prediction |

| Exercise ECG                                                                      |                                       |                              |                                                         |            |            |     |                                                                                                                                                                                         |                                           |                           |
|-----------------------------------------------------------------------------------|---------------------------------------|------------------------------|---------------------------------------------------------|------------|------------|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------|
| UK Biobank                                                                        | Duijvenboden<br>et al. <sup>132</sup> | Prospective<br>cohort study  | Asymptomatic<br>UK Biobank<br>Subjects aged<br>over 45. | 48,315     | MACE       |     | Premature<br>ventricular<br>contraction<br>(PVC)                                                                                                                                        | Single lead<br>exercise cycle<br>test ECG | Association analysis      |
| Preventive<br>cardiology<br>department of<br>CHU Rangueil,<br>Toulouse,<br>France | Cournot et<br>al. <sup>98</sup>       | Prospective<br>cohort study  | French adults<br>aged 18 to 75                          | 2,561      | CHD        | FRS | Positive exercise<br>test: horizontal<br>or down sloping<br>ST-segment,<br>depression $\geq 1.0$<br>mm at 80<br>milliseconds<br>after the J point,<br>in at least 2<br>contiguous leads | 6 lead ECG                                | Risk prediction           |
| Multiple Risk<br>Factor<br>Intervention<br>Trial (MRFIT)                          | Okin et al. <sup>96</sup>             | Randomized<br>clinical trial | Men aged 35-<br>57 years<br>without prior<br>CHD        | 11,<br>880 | CHD deaths | -   | Exercise-<br>induced ST-<br>segment<br>depression                                                                                                                                       | L8 Lead<br>Treadmill ECG                  | Intervention<br>screening |

|               |                                  |                                                                                       |                                                                                     |     |                  |   |                                             |                                                                                  |                           |
|---------------|----------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----|------------------|---|---------------------------------------------|----------------------------------------------------------------------------------|---------------------------|
|               |                                  |                                                                                       |                                                                                     |     |                  |   | adjusted for<br>heart rate<br>(ST/HR index) |                                                                                  |                           |
| DADDY-D trial | Turrini et<br>al. <sup>117</sup> | Randomized<br>control trial                                                           | Adults aged 50<br>to 70<br><br>Diagnosis of<br>type 2 diabetes<br><br>High CVD risk | 520 | CAD              | - | Treadmill<br>exercise test                  | Silent<br>myocardial<br>ischemia<br>(detected via<br>exercise<br>tolerance test) | Intervention<br>screening |
| DYNAMIT trial | Lièvre et al. <sup>97</sup>      | Prospective,<br>randomized,<br>open,<br>blinded end-<br>point<br>multicentre<br>trial | High risk<br>adults Aged 55<br>to 75 years old<br>with diagnosed<br>diabetes        | 631 | Composite<br>CVD | - | Cycle Exercise<br>ECG                       | Silent ischemia<br>detected via<br>bicycle exercise<br>test or                   | Intervention<br>screening |

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Abbreviations: MACE: Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, FRS Framingham risk score, PCE: pooled cohort equation

**Table 2.2 Performance of resting and exercise ECG risk scores for incident cardiovascular disease.**

| Cohort                                                       | Study reference              | N     | Follow-up        | Events | Outcome                                           | HR                                                   | C-index            | Continuous NRI | Categorical NRI                 | AUC              |
|--------------------------------------------------------------|------------------------------|-------|------------------|--------|---------------------------------------------------|------------------------------------------------------|--------------------|----------------|---------------------------------|------------------|
| <b>Resting ECG</b>                                           |                              |       |                  |        |                                                   |                                                      |                    |                |                                 |                  |
| Health, Aging, and Body Composition Study (Health ABC Study) | Auer et al. <sup>128</sup>   | 2,192 | Median = 8.2     | 351    | Coronary Heart disease                            |                                                      |                    | NR             |                                 |                  |
| Base model                                                   |                              |       |                  |        |                                                   | NR                                                   | 0.58 (0.53 – 0.62) | -              | --                              | NR               |
| ECG model                                                    |                              |       |                  |        |                                                   | Minor abnormalities<br>1.35 (1.02-1.81)              |                    | NR             | NR                              | NR               |
|                                                              |                              |       |                  |        |                                                   | Major abnormalities<br>HR = 1.51 (95% CI, 1.20-1.90) |                    |                |                                 |                  |
| Base + ECG model                                             |                              |       |                  |        |                                                   | -NR                                                  | 0.60(0.56-0.65)    | NR             | 5.7 (-0.4 – 1.8) % <sup>e</sup> | NR               |
| University of Pittsburgh Medical Centre patients             | Maanja et al. <sup>141</sup> | 783   | Duration 6 years | 94     | 1-year Mortality<br>Heart failure hospitalisation |                                                      |                    | -              | -                               | -                |
| Base model                                                   |                              |       |                  |        |                                                   | 1.90 (1.58–2.28) per SD                              | NR                 | NR             | NR                              | 0.77 (0.69–0.84) |



|                                                            |                             |       |            |     |      |                         |                    |     |                                      |                                      |
|------------------------------------------------------------|-----------------------------|-------|------------|-----|------|-------------------------|--------------------|-----|--------------------------------------|--------------------------------------|
| ECG model                                                  |                             |       |            |     |      | 1.79 (1.54–2.08) per SD | NR                 | NR  | NR                                   | 0.78 (0.71–0.84),                    |
| Base + ECG model                                           |                             |       |            |     |      | NR                      | NR                 | NR  | NR                                   | NR                                   |
| National Health and Nutrition Examination Survey           | Shah et al. <sup>70</sup>   | 9,969 | 7 years    | 232 | MACE |                         |                    |     |                                      |                                      |
| Base model                                                 |                             |       |            |     |      | NR                      | 0.76 (, 0.73-0.78) | -   | -                                    | NR                                   |
| ECG model                                                  |                             |       |            |     |      | 2.20 (2.06-2.36) per SD | 0.79 (0.76-0.81)   | NR  | NR                                   | NR                                   |
| Base + ECG model                                           |                             |       |            |     |      | 2.56 (1.98-3.31) per SD | 0.80 (0.77-0.82)   | 56% | 25% <sup>c</sup>                     | NR                                   |
| Netherlands primary care patients (Utrecht Health Project) | Groot et al. <sup>142</sup> | 2,370 | Mean = 3.6 | 26  | CVD  |                         |                    |     |                                      |                                      |
| Base model                                                 |                             |       |            |     |      | NR                      | NR                 | NR  | -                                    | 0.75 (0.71 - 0.79)                   |
| ECG model                                                  |                             |       |            |     |      | 1.2 (0.8 to 1.6)        | NR                 | NR  | NR                                   | NR                                   |
| Base + ECG model                                           |                             |       |            |     |      | NR                      | NR                 | NR  | AF:0.5% (–3.5% to 3.3%) <sup>f</sup> | AF: 0.76 (0.72 to 0.79) <sup>f</sup> |

|                                                                                 |                                      |       |                  |       |                         |                                  |                            |                                            |                                              |
|---------------------------------------------------------------------------------|--------------------------------------|-------|------------------|-------|-------------------------|----------------------------------|----------------------------|--------------------------------------------|----------------------------------------------|
|                                                                                 |                                      |       |                  |       |                         |                                  |                            | MI 1.0%<br>(-3.2% to<br>6.9%) <sup>f</sup> | MI: 0.75<br>(= 0.72 to<br>0.79) <sup>f</sup> |
| Community residents living in the Jiading district, Shanghai, China             | Niu et al. <sup>71</sup>             | 7,872 | Mean = 3.5 years | 54    | CVD                     |                                  |                            |                                            |                                              |
| Base model                                                                      |                                      |       |                  |       |                         | NR                               | 0.699<br>(0.674,<br>0.723) | -                                          | NR                                           |
| ECG model                                                                       |                                      |       |                  |       |                         | 1.45(1.11,<br>1.91).             | NR                         | NR                                         | NR                                           |
| Base + ECG model                                                                |                                      |       |                  |       |                         | NR                               | 0.701<br>(0.677,<br>0.725) | NR                                         | -0.031 (-0.044,<br>0.046) <sup>g</sup>       |
| The Cohort Of patients with high Risk for cardiovascular Events (CORE) registry | Krittayaphong et al. <sup>125</sup>  | 2,009 | Median = 12.6    | 2,175 | MACE                    |                                  |                            |                                            |                                              |
| Base model                                                                      |                                      |       |                  |       |                         | NR                               | NR                         | -                                          | 0.735                                        |
| ECG model                                                                       |                                      |       |                  |       |                         | Multiple significant ECG markers | NR                         | NR                                         | NR                                           |
| Base + ECG model                                                                |                                      |       |                  |       |                         | NR                               | NR                         | NR                                         | 0.823                                        |
| Copenhagen Heart Study                                                          | Jorgensen et al. 2014 <sup>119</sup> | 6,991 | Duration 6 years | 94    | Fatal and non-fatal CVD |                                  |                            |                                            |                                              |
| Base model                                                                      |                                      |       |                  |       |                         | NR                               | 0.651<br>(0.649-<br>0.653) | -                                          | NR                                           |

|                  |  |  |  |  |  |                     |                     |                                   |                                |    |
|------------------|--|--|--|--|--|---------------------|---------------------|-----------------------------------|--------------------------------|----|
| ECG model        |  |  |  |  |  | 1.21 (1.19 to 1.24) | NR                  | NR                                | NR                             | NR |
| Base + ECG model |  |  |  |  |  | NR                  | 0.660 (0.658-0.662) | 29.2% (28.4 to 29.2) <sup>h</sup> | 4.2% (3.5 to 5.6) <sup>h</sup> | NR |

### Exercise ECG

|                                                                    |                                   |         |                  |       |            |                         |    |    |    |       |
|--------------------------------------------------------------------|-----------------------------------|---------|------------------|-------|------------|-------------------------|----|----|----|-------|
| UK Biobank                                                         | Duijvenbode et al. <sup>132</sup> | 48,315  | Median = 12.6    | 2,175 | MACE       |                         |    |    |    |       |
| Base model                                                         |                                   |         |                  |       |            | NR                      | NR | NR | NR | NR    |
| . ECG model                                                        |                                   |         |                  |       |            | Exercise PVC: 1.2 (1–5) | NR | NR | NR | NR    |
|                                                                    |                                   |         |                  |       |            | Recovery PVC: 1.3 (1–5) |    |    |    |       |
| Base + ECG model                                                   |                                   |         |                  |       |            | NR                      | NR | NR | NR | NR    |
| Preventive cardiology department of CHU Rangueil, Toulouse, France | Cournot et al. <sup>98</sup>      | 2,561   | Duration 6 years | 94    | CHD        |                         |    |    |    |       |
| Base model                                                         |                                   |         |                  |       |            | NR                      | NR | NR | NR | 0.732 |
| ECG model                                                          |                                   |         |                  |       |            | 3.70 (2.26 – 6.07)      | NR | NR | NR | NR    |
| Base + ECG model                                                   |                                   |         |                  |       |            | NR                      | NR | NR | NR | 0.762 |
| Multiple Risk Factor Intervention Trial (MRFIT)                    | Okin et al. <sup>96</sup>         | 11, 880 | 7 years          | 232   | CHD deaths |                         |    |    |    |       |

|                  |                               |     |                        |               |  |                     |    |    |    |    |
|------------------|-------------------------------|-----|------------------------|---------------|--|---------------------|----|----|----|----|
|                  |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
|                  |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
|                  |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
| DADDY-D trial    | Turrini et al. <sup>117</sup> | 520 | Mean = 26<br>3.6       | CAD)          |  |                     |    |    |    |    |
| Base model       |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
| ECG model        |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
| Base + ECG model |                               |     |                        |               |  | 0.849 (0.393–1.837) | NR | NR | NR | NR |
| DYNAMIT trial    | Lièvre et al. <sup>97</sup>   | 631 | Mean = 54<br>3.5 years | Composite CVD |  |                     |    |    |    |    |
| Base model       |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
| . ECG model      |                               |     |                        |               |  | NR                  | NR | NR | NR | NR |
| Base + ECG model |                               |     |                        |               |  | 1.00 (0.59 - 1.71)  | NR | NR | NR | NR |

a Primary study endpoint;

b Secondary study endpoint

c NRI category: <1%, 1% to <5%, 5% to 10% ≥10%

d NRI category: <5%,5%, to <10%, 10% to 20%, ≥20

e NRI category: <7.5%, <7.5%, to <15% ≥15%

f NRI category: <10%, 10% to <20%, ≥20%

g NRI category: <10%, ≥10%

h: NRI category: Other

Abbreviations: MACE: Major Adverse Cardiovascular Events, NR: Not reported, SD: Standard deviation, HR Hazard Ratio, AUC: Area under receiver operator curve, Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, AF: Atrial fibrillation, MI: Myocardial infarction, FRS Framingham risk score, PCE: pooled cohort equation, NRI: Net reclassification index

### **2.3.3.5 Deep learning and the ECG for cardiovascular disease risk prediction**

Prior studies assessing the prognostic value of ECGs for CVD risk prediction have primarily relied on hand-selected features, which often lack sensitivity to subtle variations in ECG signals. Additionally, inconsistencies in feature selection across studies have contributed to inconsistent predictive performance, highlighting the need for a more holistic approach to ECG analysis.

In recent years, deep learning has emerged as a promising alternative to traditional rule-based approaches for ECG analysis<sup>144</sup>. Initially recognised for its state-of-the-art performance in tasks such as image recognition and segmentation<sup>145</sup>, this success has now been extended to ECG for various tasks, including delineation, arrhythmia diagnosis and risk prediction, delivering results comparable to previous state-of-the-art methods and human experts<sup>146</sup>. Unlike traditional techniques, deep learning algorithms can automatically learn the underlying structure of data without requiring prior assumptions. Table 2.3 provides an overview of recent prognostic studies combining ECG and deep learning to predict incident CVD.

In a systematic review of 191 studies conducted between 2010 and 2020, Hong et al. evaluated the performance of a range of deep learning algorithms across several domains of ECG analysis. They found that deep learning regularly outperformed traditional methods at tasks, including disease diagnosis and ECG annotation; however, persistent challenges remain in model interoperability, efficiency, and clinical integration<sup>147</sup>. As a systematic review, this work synthesised model performance but did not directly assess prognostic modelling for incident CVD, and no calibration or reclassification analyses were reported. This limits conclusions about the clinical utility of deep learning for long-term risk prediction. In a recent prospective cohort study, Hughes et al. (2023) demonstrated that a deep-learned ECG risk score, based on 12 lead resting ECG recordings, may significantly improve the classification of high-risk individuals when added to the pooled cohort equation (PCE)<sup>148</sup>. ECG risk scores were significantly associated with incident CVD, HR: 2.4 (2.2 – 2.7).

The authors report a categorical NRI of 17.8% compared to the PCE across a threshold of <7.5%, <7.5%, to <20%  $\geq$  20%, and an increase on C-index from 0.658 (0.614–0.672). Model calibration was not reported. This prospective design provides important evidence for the value of deep-learned ECG features in risk prediction; however, the focus on a single ECG modality, the absence of calibration assessment, and reliance on a U.S. healthcare cohort limit generalisability and leave open questions about applicability in broader population-based samples. Additionally, the authors report using a weighted average of ECG and PCE to combine risk scores without explaining how this was derived or validated. This raises concerns about potential bias, as arbitrary or data-dependent weighting can overfit to the development cohort, inflate apparent performance and limit generalisability to new cohorts.

Another investigation conducted by Sau et al. (2024) demonstrated that AI-enhanced ECG risk scores could improve short- and long-term prediction of mortality and cardiovascular events beyond traditional clinical risk factors<sup>149</sup>. Building on this, the authors proposed several plausible mechanisms for the higher CVD risk associated with greater ECG risk scores. Results from phenome-wide association studies (PheWAS) and genome-wide association studies (GWAS) found that AI-ECG risk scores were highly associated with cardiac chamber structure and several genetic markers for accelerated biological ageing and myocardial mass. While the study provides valuable insight into biological mechanisms underlying AI-ECG signals, it primarily reported associations rather than comprehensive prognostic evaluation, and did not benchmark performance against established risk equations, limiting assessment of incremental value. Furthermore, while the authors report improvements in discrimination no analysis of clinical utility via calibration or reclassification was provided.

Lin et al. investigated the use of a multitask deep neural network for 10-year MACE risk prediction, where MACE was broken down into four parts: Heart failure (HF), Myocardial infarction (MI), ischemic stroke (IS) and mortality, with the network providing independent predictions for each component<sup>150</sup>.

Compared to the Framingham risk score, the proposed neural network demonstrated improved AUC for HR: 0,61 to 0.75 and MI 0.69 to 0.70 but reduced performance for IS: 0.63 to 0.59 and mortality 0.88 to 0.62. No overview of calibration or reclassification was provided. This multitask design offers insight into outcome-specific predictive utility; however, external validation was limited and the lack of calibration and reclassification metrics constrains conclusions about potential deployment in clinical settings.

An overview of the predictive performance of deep learning ECG risk scores is provided in Table 2.4.

**Table 2.3 Summary of recent deep learning ECG risk scores studies for incident cardiovascular disease**

| Cohort                                                                           | Study reference               | Study design               | Population                                                                                               | N         | Outcome                                                     | Base model                                          | ECG phenotypes    | ECG lead configuration |
|----------------------------------------------------------------------------------|-------------------------------|----------------------------|----------------------------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------|-----------------------------------------------------|-------------------|------------------------|
| Stanford Estimator of Electrocardiogram Risk (SEER), Cedars Sinai Medical Centre | Hughes <sup>148</sup>         | Prospective cohort studies | Adults aged >18 across multiple cohorts                                                                  | 307,557   | 5-year atherosclerotic disease                              | PCE                                                 | Raw ECG waveforms | 12 Lead ECG            |
| Columbia Medical centre                                                          |                               |                            |                                                                                                          |           |                                                             |                                                     |                   |                        |
| Beth Israel Deaconess Medical Centre BIDMC)                                      | Pastika et al. <sup>151</sup> | Prospective cohort studies | Derivation: secondary care patients<br><br>External validation Uk adults aged over 45 without prior CVD: | 189 539   | 10-year atherosclerotic cardiovascular disease <sup>b</sup> | Atherosclerotic cardiovascular disease risk factors | Raw ECG waveforms | 12 lead ECG            |
| Chang Gung Memorial Hospital database                                            | Lin et al. <sup>150</sup>     | Prospective cohort studies | Hospital inpatients aged over 30, without pacemaker                                                      | 1,078,629 | 10-year MACE <sup>a</sup>                                   | FRS                                                 | Raw ECG waveforms | 12 lead ECG            |

<sup>a</sup> Primary study endpoint

<sup>b</sup> Secondary study endpoint

Abbreviations: MACE: Major Adverse Cardiovascular Events, NR: Not reported, HR Hazard Ratio, AUC: Area under receiver operator curve, Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, FRS Framingham risk score, PCE: pooled cohort equation.



**Table 2.4 Performance of deep learning derived ECG risk scores for incident cardiovascular disease**

| Cohort                                                                                                                          | Study reference               | N       | Follow-up   | Events                                                      | Outcome                                                     | ECG phenotypes    | HR            | C-index                | Continuous NRI | Categorical NRI    | AUC                    |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------|-------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------|---------------|------------------------|----------------|--------------------|------------------------|
| Stanford<br>Estimator of<br>Electrocardiogram Risk (SEER),<br>Cedars Sinai<br>Medical Centre,<br><br>Columbia<br>Medical Centre | Hughes et al. <sup>148</sup>  | 307,557 | 5 years     | Within 5 years:<br>37,540<br><br>Within 10 years:<br>47,033 | 5-year atherosclerotic disease                              | Raw ECG waveforms |               |                        |                |                    |                        |
| Base model                                                                                                                      |                               |         |             |                                                             |                                                             |                   | NR            | 0.658<br>(0.614–0.672) | -              | -                  | 0.668<br>(0.647–0.687) |
| ECG model                                                                                                                       |                               |         |             |                                                             |                                                             |                   | 2.4 (2.2–2.7) | 0.782<br>(0.759–0.817) | NR             | NR                 | 0.708<br>(0.689–0.726) |
| Base + ECG Model                                                                                                                |                               |         |             |                                                             |                                                             |                   | NR            | 0.795<br>(0.781–0.817) | NR             | 17.8% <sup>c</sup> | 0.704<br>(0.685–0.722) |
| Beth Israel<br>Deaconess<br>Medical Centre<br>BIDMC),<br>UKB,<br><br>CODE,<br>SaMi-Trop                                         | Pastika et al. <sup>151</sup> | 189 539 | Mean = 5.46 | -                                                           | 10-year atherosclerotic cardiovascular disease <sup>b</sup> | Raw ECG waveforms |               |                        |                |                    |                        |

|                                                |                           |           |                  |   |                              |                      |    |                            |    |    |                                                        |
|------------------------------------------------|---------------------------|-----------|------------------|---|------------------------------|----------------------|----|----------------------------|----|----|--------------------------------------------------------|
| Base model                                     |                           |           |                  |   |                              |                      | NR | 0.633<br>(0.604-<br>0.662) | NR | NR |                                                        |
| ECG model                                      |                           |           |                  |   |                              |                      | NR | 0.696<br>(0.694-<br>0.698) | NR | NR |                                                        |
| Base + ECG<br>Model                            |                           |           |                  |   |                              |                      | NR | 0.679<br>(0.651-<br>0.708) | NR | NR |                                                        |
| Chang Gung<br>Memorial<br>Hospital<br>database | Shah et al. <sup>70</sup> | 1,078,629 | Duration<br>= 10 | - | 10-year<br>MACE <sup>a</sup> | Raw ECG<br>waveforms |    |                            |    |    |                                                        |
| Base model                                     |                           |           |                  |   |                              |                      | NR | NR                         | NR | NR | HF: 0.61<br>MI: 0.69<br>IS: 0.63<br>Mortality:<br>0.88 |
| ECG model                                      |                           |           |                  |   |                              |                      | NR | NR                         | NR | NR | HF: 0.75<br>MI: 0.70<br>IS: 0.59<br>Mortality:<br>0.62 |
| Base + ECG<br>Model                            |                           |           |                  |   |                              |                      | NR | NR                         | NR | NR | NR                                                     |

<sup>a</sup> Primary study endpoint

<sup>b</sup> Secondary study end point

<sup>c</sup> NRI category: <7.5%, <7.5%, to <20% ≥ 20%

Abbreviations: MACE: Major Adverse Cardiovascular Events, NR: Not reported, HR Hazard Ratio, AUC: Area under receiver operator curve, Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, HF: Heart failure, MI: Myocardial infarction, IS: Ischemic stroke, FRS Framingham risk score, PCE: pooled cohort equation, NRI: Net reclassification index

### **2.3.4 Discussion**

#### **Findings**

Studies highlighted in the above narrative review have consistently reported a robust association between ECG measurements and incident MACCE. These associations persisted across studies following adjustment for various established clinical risk factors. However, the added predictive value of ECG recordings to identify high-risk individuals remains unclear.

Results for resting ECGs suggest modest improvements in predictive performance, with improvements in C-index ranging from 0.001 to 0.05. However, the degree to which a resting ECG improved the stratification of high-risk individuals remains uncertain. Results varied considerably between studies due to differing thresholds, selection of ECG risk factors and study populations.

The added value of exercise ECG to risk prediction remains more uncertain. No prospective cohort studies were identified that assessed the added value of exercise ECG to currently adopted clinical risk models. Furthermore, existing studies had limited sample sizes, often included individuals already identified as being at elevated risk and varied widely in their evaluation criteria. The lack of evidence on the prognostic value of exercise ECG in lower-risk individuals, who would typically be eligible for CVD screening, makes it difficult to holistically assess the added value of exercise ECG testing for primary prevention of CVD.

Deep neural networks have demonstrated great potential to enhance ECG analysis in tasks ranging from ECG delineation to arrhythmia detection and risk prediction. However, there has yet to be a study combining deep learning and exercise ECG with current clinical risk models to enhance CVD prediction. Furthermore, of the studies reviewed above, none reported model calibration, and only one reported reclassification results using nonstandard risk thresholds. This makes it difficult to determine the direct clinical utility of deep learning models in a primary prevention setting.

## **Limitations and research gaps**

First in 2012 and again in 2018, the United States Preventive Services Task Force (USPSTF) underwent a systematic review of the role of the ECG in predicting incident CVD and MACCE. Across all selected studies, the USPSTF reported inadequate sample sizes, insufficient follow-up durations, and inappropriate reporting of calibration and reclassification to sufficiently assess the predictive value of ECG measurements<sup>116,123,128</sup>. The strength of the evidence across most of the studies identified in the review was considered to be of low to moderate quality. Moreover, none of the studies examined the impact of integrating ECG-derived risk factors or equations into existing clinical models for CVD risk prediction at currently recommended clinical risk thresholds, leaving the clinical relevance of ECG-based risk scores unclear. To date, most research on the prognostic value of ECGs for CVD has focused on individuals already at low to high risk of developing the disease. In contrast, the potential benefit of using ECGs to predict CVD in asymptomatic individuals remains largely unexplored across the literature.

Few studies reported adhering to any common publication guidelines for risk prediction. This lack of a unified framework resulted in considerable heterogeneity in evaluation criteria and methodology. This made it difficult to compare results between studies and draw holistic conclusions across the evidence base.

Until recently, most investigations have relied on traditional, hand-selected ECG measurements, which often differ between studies, lack sensitivity to subtle changes, and only explore a narrow subset of available information. The rise of artificial intelligence (AI) and deep learning techniques offers new opportunities for analysing raw ECG signals to predict incident disease. In contrast to traditional methods, deep learning algorithms can automatically identify relevant features and patterns, bypassing the need for prior selection of risk factors.

A growing body of evidence has demonstrated that deep learning technology regularly outperforms conventional ECG markers in predicting cardiovascular conditions such as Atrial fibrillation or premature ventricular and even exceeded cardiologist-level performance in a range of diagnostic and predictive tasks 92,108.

However, no adopted clinical risk models consider the use of deep learning or the ECG when determining the absolute risk of future MACCE. This thesis seeks to leverage the potential of deep learning to investigate the added value of resting and exercise ECG to currently adopted CVD risk scores in primary care in large prospective datasets.

### **2.3.5 Summary**

While numerous proposals have been made for predicting short and long-term CVD risk using an ECG, evidence of the added value of ECG measurements in adopted clinical risk models remains scarce. Few studies have reported following any reporting guidelines for risk prediction, resulting in considerable heterogeneity in methodology, exposures, and target outcomes among studies. The vast majority of studies investigating the predictive value of ECG measurements have been limited by a lack of sufficient sample size, particularly for exercise ECG data, and insufficient follow-up durations to match current clinical guidelines. With the advent of larger prospective cohort studies such as the UK Biobank, which offer prolonged follow-up through healthcare record linkage, and the increased use of deep learning for risk analysis, this thesis aims to address these limitations within a large cohort to assess the added value of resting and exercise ECG data to existing clinical risk models.

To my knowledge, this thesis is the largest population-based cohort study to investigate the added value of exercise ECG to existing clinical risk models in individuals with no history of MACCE and the first to use deep survival models. In contrast to prior studies, this thesis investigated both conventional ECG parameters and raw ECG waveforms, using deep neural networks to predict incident MACCE.

## **2.4 Accelerometer measured Physical activity**

### **2.4.1 Physical Activity**

Physical activity (PA) is integral to human life; regular PA reduces the risk of various non-communicable diseases and is linked to improved cognitive function and mental well-being<sup>73,77</sup>. It is important to first distinguish between PA and exercise. Exercise is a subset of PA<sup>154</sup>, which is structured, planned and aimed at improving overall fitness. In contrast, PA is carried out throughout daily life, whether this is at work (walking/cycling commute or having a physically active job), leisure time (can include exercise or lighter activities such as a walk outside) or daily tasks such as cleaning and gardening<sup>155,156</sup>. Rather than a single state of active or inactive, PA is a continuum encompassing various intensities of activity. PA intensity is typically quantified by the rate of energy expenditure measured by the metabolic Equivalent of Task (MET), with 1 MET representing the resting metabolic rate<sup>157</sup>. PA can also occur at different frequencies and patterns across individuals, depending on a range of factors such as employment status and mode of transport (car vs bike), in addition to social and demographic factors.

### **2.4.2 Measuring Physical activity**

PA exists on a continuum, encompassing various types of activities with different durations and intensities. PA is typically categorised by intensity, including sedentary behaviour (sitting, 1 MET) such as sitting, light physical activity (LPA) performed during daily life (1.5-3 METs), moderate-to-vigorous physical activity (MVPA) (>3 METs) such as walking and cycling, and sleep. These behaviours are collectively referred to as 24-hour movement behaviours. The compendium of Physical Activities provides a broad definition and reference MET values for each 24-hour movement behaviour<sup>157</sup>. MVPA is typically defined as activity exceeding 3 MET, consisting of higher-intensity activities such as brisk walking, running and cycling. The definition of LPA tends to differ between sources; however, it is broadly categorised as an activity between 1.5-3 MET and makes up most of the PA performed incidentally throughout daily life, such as standing or shopping.

Sedentary behaviours are any activity less than 1 MET, such as watching TV or lying in bed. In contrast to sedentary behaviour, sleep has important health benefits and is defined as an active state of unconsciousness where the brain is in a relative state of rest<sup>158</sup>. Figure 2.3 outlines the typical allocation of different PAs throughout a 24-hour day.

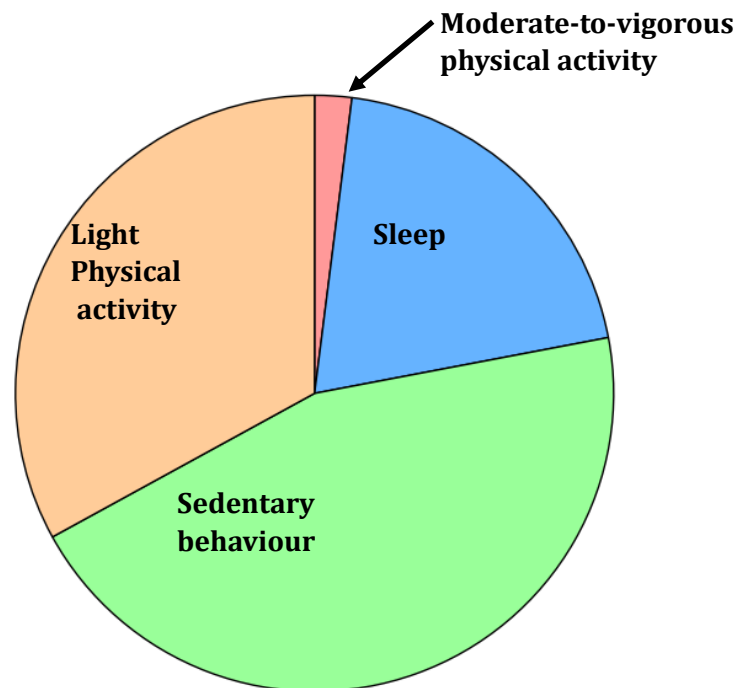


**Figure 2.3: Allocation of Sleep, sedentary, Light physical activity and moderate-vigorous physical activity throughout a 24-hour day**

Capturing movement behaviours and overall, PA has historically relied on self-reported data via activity questionnaires such as the Global Physical Activity Questionnaire (GPAQ), currently in use by the WHO<sup>73,159</sup>. While activity questionnaires are highly scalable, they lack sensitivity to distinguish between certain types of activity and are susceptible to recall and reporting bias, particularly social desirability. For instance, participants tend to overstate time spent in MVPA or have difficulty tracking their sleep consistency over extended periods<sup>160</sup>. In a meta-analysis comparing self-reported PA with direct measurements across 187 studies, Prince et al. reported a mean correlation of 0.37 (standard deviation 0.25) between modalities. Crucially reporting and recall bias is often directional, as demonstrated by in an International Physical Activity Questionnaire short form validation, participants reported ~131 min/day less

sedentary time and more vigorous activity than accelerometry, with discrepancies varying by age and education<sup>161</sup>. Epidemiological evidence suggests that the accuracy of self-reported PA can vary substantially between different populations and activity subtypes, negatively affecting the generalisability of any observed associations. In 2014, Sabia et al. found that the correlation between different measurements of PA was lowest among those with higher levels of deprivation<sup>162</sup>. Furthermore, self-reported PA has been demonstrated to be particularly unreliable at capturing 24-hour movement behaviours such as LPA and sleep. Most LPA is carried out incidentally throughout our daily activities and can often be forgotten in retrospective questionnaires. Additionally, participants may record different activities using proxies such as lying down<sup>160</sup>. Such proxies may coincide with other cardiovascular stresses, such as snacking and may be further confounded by socioeconomic factors, affecting our ability to infer a direct association between the type of activity and CVD risk. A prospective analysis conducted by Paudel et al. showed that the association between CVD risk and proxies for sedentary behaviour, such as high screen time, was much stronger in populations with low Socioeconomic status<sup>163</sup>. These limitations highlight the urgent need for more accurate measurement methods.

In recent years, accelerometer measured PA has emerged as the gold standard for PA monitoring and activity recognition. Accelerometers passively record acceleration over time, capturing the movement behaviours of an individual in more granular detail. Thanks to recent technological advances, such as increased memory for on-device storage, extended battery life and improved analytic techniques, the use of wearable accelerometers has become increasingly scalable and addresses many of the limitations of self-reported questionnaires<sup>164–168</sup>. As an accelerometer can be worn continuously throughout a person's daily activities, it provides a more robust long-term estimate of PA compared to self-report and is not subject to the same degree of recall and reporting bias. Accelerometers have a particular advantage in capturing incidental LPA, which may not be captured in self-reported questionnaires<sup>160</sup>.



Such devices enable researchers to capture both immediate and long-term PA patterns, helping identify complex interactions between PA behaviours and their potential links to disease.<sup>157-161</sup>

Wearable accelerometers have demonstrated good validity for distinguishing between broad activity types. For MVPA, accelerometers have demonstrated strong correlation with energy expenditure when raw data are processed with population-calibrated models<sup>168-170</sup>. Sleep parameters such as total sleep time and sleep efficiency can also be estimated with reasonable accuracy compared with polysomnography. Although wrist-worn devices may misclassify light activity as sedentary and underestimate MVPA when using simple cut-point methods compared to hip-worn devices, recent machine-learning approaches validated against wearable cameras, have demonstrated state-of-the-art performance in estimating 24-hour movement behaviours, including LPA, MVPA and sedentary time. Overall, the wrist remains a highly practical and sufficiently accurate location for large-scale population monitoring of activity, sleep, and sedentary patterns, particularly when analyses focus on aggregated time spent across PA behaviour for large populations.<sup>164-168</sup>. Further details on the measurement of movement behaviours and the prediction of incident MACCE are provided in Chapters 6 and 7.

### **2.4.3 Physical activity and cardiovascular disease**

A lack of PA has been extensively linked to a heightened risk of incident MACCE, with evidence suggesting that not only the overall amount of PA but also the intensity and pattern of activity play critical roles in influencing cardiovascular outcomes<sup>73,77,79,171</sup>. The link between PA and the risk of CVD can be traced back to work conducted by Morris et al. during the 1950s, where Morris observed varying rates of CAD across different occupations<sup>172,173</sup>. It was proposed that the differing rates of CVD could be explained by the PA demands of each profession. Seeking to build on Morris's work, a large body of epidemiological evidence has emerged consisting of various study types aiming to establish the strength, shape and mechanism of the association between PA and incident MACCE. A recent meta-analysis conducted for the 2018 Physical Activity Guidelines for Americans evaluated six systematic reviews on the relationship

between PA and incident coronary artery disease (CAD) and five systematic reviews on stroke. All studies found an inverse association between PA and the risk of incident disease. These findings were further supported by the World Health Organisation 2020 guidelines on physical activity, which found with moderate or high certainty that PA reduced cardiovascular risk in all age groups<sup>73,77</sup>. Increased PA has been shown to help reduce the prevalence of several key risk factors of MACCE, such as SBP and obesity, as well as improve cardiac function, lower resting heart rate and cardiac hypertrophy<sup>174</sup>. In 1968, Saltin et al. presented the first direct evidence beyond statistical associations of the positive effects of exercise on the heart. They found that 20 days of sedentary behaviour decreased cardiac dysfunction and Vo<sub>2</sub>, which is strongly associated with overall CVD risk<sup>175–177</sup>. In a review analysing 93 randomised control trials investigating the effect of various types of exercise on SBP, Cornelissen et al. found that individuals receiving exercise interventions had lower SBP than the control group following four weeks of regular exercise<sup>178</sup>. Exercise has been directly linked to improved electrophysiological profiles, including resting bradycardia and increasing heart rate variability (HRV)<sup>174,179</sup>. HRV has been extensively associated with a decrease in cardiovascular morbidity and mortality. Further benefits include improved insulin sensitivity, lower LDL cholesterol, enlarged LV wall and increased myocyte size (Figure 2.4).

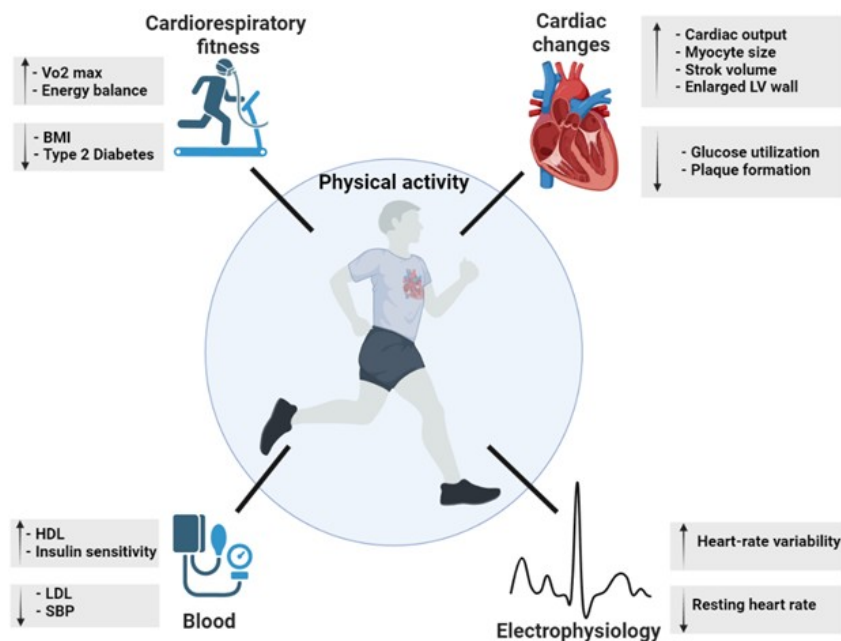


**Figure 2.4: Benefits of Physical activity for reducing cardiovascular disease risk**<sup>174,175,179,180</sup>

#### **2.4.4 Physical activity and primary prevention**

PA plays an important role in the prevention of MACCE at both the population and individual levels. PA interventions are low-risk, relatively cheap to implement and have been shown to benefit a large range of individuals regardless of age or prevalence of existing CVD risk factors<sup>73,181,182</sup>. PA recommendations play a key role in prevention guidelines and wider public health policy. The first public health recommendations for PA came in 1996, following the United States Surgeon General's release of a Report on Physical Activity and Health, which provided recommendations on the amount of MVPA the public should engage in<sup>72</sup>. PA targets are now a mainstay for the primary and secondary prevention of CVD and are promptly featured in national and international strategies such as the NHS and WHO 2020 guidelines<sup>73,183</sup>.

Despite these well-documented benefits, there is significant room for improvement in promoting and achieving optimal PA levels across populations, presenting a critical opportunity to enhance MACCE prevention efforts. Low levels of PA have become increasingly prevalent in high-income countries, contributing to a growing public health burden<sup>184</sup>. As such, even modest improvements in PA can result in significant reductions in overall disease burden. The WHO published its first guidelines for PA in 2010, recommending individuals participate in 150-300 minutes of moderate activity or 75-150 minutes of vigorous activity per week.

Despite the establishment of objective guidelines, low PA is among the top 3 most common risk factors for incident CVD across all age groups in the UK, and 25% of adults globally fail to meet PA recommendations<sup>16,184</sup>. The latest WHO report estimates that up to 8% of all causes of CVD may be prevented by meeting PA guidelines, while Lee et al. estimated that 6% of CAD events globally could be attributed to low PA<sup>185,186</sup>. The trend towards low PA will likely continue into the near future, owing to changes in technology, urbanisation and transportation, highlighting the need for a new approach to promote PA in the population and identifying those who would most benefit from intervention strategies.

#### **2.4.5 Physical activity and risk prediction of incident cardiovascular disease**

Individual risk assessments have been shown to enhance patient motivation and improve adherence to interventions by effectively communicating personal risk and the potential benefits<sup>26,30,401</sup> of lifestyle modifications. Risk scores are widely recommended across clinical guidelines as critical tools for addressing lifestyle changes. In 2021, based on these assessments, the European Society of Cardiology recommended an individualised prescription of physical activity to reduce the risk of the primary occurrence of CVD<sup>40</sup>. Likewise, the UK National Health Service (NHS) recommends routine health checks to support lifestyle modification, such as increased PA<sup>34,35</sup>. However, despite these recommendations and a well-documented protective association between PA and MACCE, no clinical risk models currently incorporate PA measurements to either assess initial risk or track potential changes in risk resulting from PA interventions. Early investigations into the added value of PA to clinical risk factors have returned mixed findings across studies and traditionally relied on self-reported data, limiting the efficacy of such studies<sup>187,188,189</sup>. The advent of new technologies, such as wearable accelerometers, now allows for highly scalable, objective measurements of physical activity, which could refine and personalise predictive tools, making them even more effective in guiding lifestyle changes and improving patient outcomes.

Table 2.5 provides an overview of recent large-scale studies investigating the predictive value of PA for incident CVD.

**Table 2.5 Summary of recent studies on the predictive value of Physical activity measurements for incident cardiovascular disease**

| Cohort                                               | Study reference                   | Study design                                                    | Population                                                       | N                                                               | Outcome                                              | Base model                                                                                      | Movement behaviours                                  | Measurement device                                                                                                 |
|------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Multiple prospective cohorts (35 cohorts; 2014–2025) | Ding et al. (2025) <sup>190</sup> | Systematic review & meta-analysis                               | Adults from included observational studies (general populations) | 57 studies (35 cohorts); meta-analyses: 31 studies (24 cohorts) | CVD                                                  | Random-effects dose-response meta-analysis of study HRs (covariate adjustment varied by cohort) | Daily steps                                          | Device-measured step counts (variable; device placement)                                                           |
| Multiple prospective cohorts (international)         | Liew et al. <sup>191</sup>        | Systematic review + meta-analysis of prospective cohort studies | Adults in community/population-based cohorts (age 40-92)         | 206,970 adults across 29 included studies                       | CVD (5 studies) and all-cause mortality (15 studies) | Random-effects model                                                                            | Total PA, MVPA, LPA, step count, sedentary behaviour | Mixed of accelerometer/pedometers across studies ActiGraph, GENEActiv, Axivity AX3, ActivPAL, Actical, Yamax/Omron |
| Multiple prospective cohorts                         | Qiu et al. (2021) <sup>192</sup>  | Meta-analysis (prospective cohorts)                             | Adults; mixed sex;                                               | <b>13,960</b> participants (6 cohorts; 7 datasets)              | CVD mortality                                        | Random effect model                                                                             | Light intensity activity and Sedentary behaviour     | Wrist and hip worn device                                                                                          |
| UK Biobank                                           | Ramakrishnan et al. <sup>79</sup> | Prospective cohort study                                        | Adults in the UK aged over 45                                    |                                                                 | CVD                                                  | -                                                                                               | MVPA, LIPA                                           | Wrist worn accelerometer, (Axivity AX3)                                                                            |

|              |                                  |                          |                                                              |       |                       |                       |  |                                                                                                                         |                                         |
|--------------|----------------------------------|--------------------------|--------------------------------------------------------------|-------|-----------------------|-----------------------|--|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| UK Biobank   | Walmsley et al. <sup>171</sup>   | Prospective cohort study | Adults in the UK aged over 45                                |       | CVD                   | -                     |  | MVPA, LPA, SB                                                                                                           | Wrist worn accelerometer (Axivity AX3)  |
| Whitehall II | Yerramalla et al. <sup>193</sup> | Prospective cohort study | Civil servants based in London (when recruited in 1985-1988) | 3,319 | CVD                   | -                     |  | waking-day movement behaviour composition (MVPA, LPA, SB)                                                               | wrist-worn accelerometer (GENEActiv)    |
| Whitehall II | Yerramalla et al. <sup>194</sup> | Prospective cohort study | Civil servants based in London (when recruited in 1985-1988) | 3,321 | CVD                   | -                     |  | SB, pattern metrics                                                                                                     | wrist-worn accelerometer (GENEActiv)    |
| NHANES       | Evenson et al. <sup>195</sup>    | Prospective cohort study | Representative adult US population                           | 3,809 | CVD mortality         |                       |  | SB, sedentary bouts, LPA, MPA, VPA, MVPA, moderate-to vigorous bouts, meeting guideline                                 | Hip worn accelerometer (Actigraph 7164) |
| NHANES       | Schmid et al. <sup>196</sup>     | Prospective cohort study | Representative adult US population                           | 3,702 | CVD mortality         | -                     |  | SB, PA                                                                                                                  | Hip worn accelerometer (Actigraph 7164) |
| NHANES       | Ledbetter et al. <sup>197</sup>  | Prospective cohort study | Representative adult US population                           | 2,987 | 10-year CVD mortality | Clinical risk factors |  | Total activity, MVPA, g activity count, LPA, SB/sleep, average log activity during the 10 most active hours of the day, | Hip worn accelerometer (Actigraph 7164) |

|                             |                                       |                          |                                         |        |                                |               |                                                                                                                                                                             |                                                     |  |
|-----------------------------|---------------------------------------|--------------------------|-----------------------------------------|--------|--------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--|
|                             |                                       |                          |                                         |        |                                |               | average log<br>activity during the<br>least five active<br>hours of the day,<br>sedentary<br>transition<br>probability,<br>sedentary to<br>active transition<br>probability |                                                     |  |
| ATTICA                      | Georgousopoulou et al. <sup>187</sup> | Prospective cohort study | Adult Greek population, primarily urban | 2,020  | 10-year incident CVD mortality | HellenicSCORE | Tertile of self-report energy expenditure                                                                                                                                   | Self-report Physical Activity Questionnaire (IPAQ)) |  |
| Copenhagen City Heart study | Graversen et al. <sup>188</sup>       | Prospective cohort study | Adult population from Copenhagen        | 8,476  | 10-year incident CVD mortality | SCORE2        | Walk duration, walking pace, Physical activity – leisure,                                                                                                                   | Self-report                                         |  |
| ARIC, MESA, and CHS         | Pandey et al. <sup>198</sup>          | Prospective cohort study | Older adults from 3 longitudinal cohort | 18,824 | 10-year incident CVD           | PCE           | Leisure-time physical activity                                                                                                                                              | Self-report                                         |  |

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Abbreviations: NR: Not reported, CVD: cardiovascular disease, PCE: pooled cohort equation, ARIC Atherosclerosis Risk in Communities, MESA Multi-Ethnic Study of Atherosclerosis, Cardiovascular Health Study, NHANES National Health and Nutrition Examination survey

#### **2.4.5.1 Association between Physical activity and incident cardiovascular disease**

The use of accelerometer-measured physical activity (PA) in epidemiological research has increased significantly. Much of the evidence linking accelerometer-measured PA with incident CVD now comes from increasingly large prospective cohort studies, such as the UK and China Kadoorie biobanks. Findings from this growing evidence base consistently report stronger associations between accelerometer-measured PA and CVD risk compared to self-reported data<sup>78</sup>. In a prospective cohort analysis, Ramakrishnan et al. (2021) investigated the strength of the association between sedentary, LPA, MVPA and overall activity using wrist-worn accelerometers over a 7-day monitoring period and a median of 5.2 years follow-up. They report a much stronger inverse association between higher levels of PA and CVD risk than what was previously reported in self-reported data<sup>79</sup>. This finding was further substantiated in a harmonised meta-analysis by Ekelund et al. which investigated the association between PA and mortality in a range of cohorts. They found that the relative reduction in CVD risk observed from accelerometer-measured PA was up to twice as strong as that from self-report<sup>78</sup>.

Beyond individual cohort analyses, systematic reviews and meta-analyses on the association of objective PA measurements provide higher-level synthesis across populations, exposure definitions, and device platforms. In a systematic review and dose-response meta-analysis spanning 57 studies from 35 cohorts (meta-analyses: 31 studies from 24 cohorts), Ding et al. (2025) examined the association between device-measured daily steps and cardiovascular outcomes across the general-population<sup>199</sup>. The authors reported inverse associations between daily steps with incident CVD and CVD mortality, with a non-linear relationship for incident CVD and a more linear pattern for CVD mortality. Compared with 2000 steps/day, 7000 steps/day was associated with a 47% lower risks of all-cause mortality and a 25% lower risk of CVD, although evidence by age was limited and studies differed in device placement and covariate adjustment. A complementary systematic review and meta-analysis by Liew et al. synthesised evidence on the association between overall PA, MVPA LIPA and sedentary behaviour with all-cause mortality and CVD mortality, from 29 population-based prospective



cohorts (n=206,970) spanning mid-life to older age<sup>191</sup>. The included studies comprised mixed-sex cohorts, as well as female-only (n=5) and male-only (n=3) cohorts, and excluded samples recruited on the basis of specific diseases.<sup>191</sup>. The authors found that higher total PA, MVPA, and LIPA were each associated with lower CVD mortality, whereas higher sedentary behaviour was associated with higher CVD mortality, consistent with a graded relationship between movement intensity and CVD mortality risk. However, interpretation was limited by variability in intensity cut-points, limited harmonisation of sedentary bout metrics, and comparatively sparse evidence for incident CVD compared with mortality outcomes. A smaller review by Qiu et al. (2021), focusing on lower-intensity movement, also reported protective associations with CVD mortality. In a systematic review of six prospective cohorts (seven datasets; n=13,960) using accelerometer-measured physical activity, higher LIPA was associated with lower cardiovascular mortality. The authors also found that reallocating sedentary time to light activity was associated with reduced risk, with subgroup analyses showing similar patterns in men and women. However, definitions of light-intensity physical activity varied across studies, limiting comparability and alignment with standardised behavioural targets.

In studies which adjusted for time spent across different activities, the literature shows that reallocating time from lower-intensity to higher-intensity activities generally lowers one's risk of CVD. Walmsley et al. investigated the association between reallocating time between SB, LPA and MVPA in the UKB<sup>171</sup>. The study found an inverse association between reallocating time from sedentary to either LPA or MVPA and LPA to MVPA with the risk of incident CVD. Similar findings were reported by Yerramalla et al. in Whitehall II cohort<sup>200</sup>. The authors observed a HR of 1.20 (1.06, 1.37) for cardiovascular disease per standard deviation of SB (100.2 min/day)<sup>194</sup>. Furthermore, in a subsequent study, Yerramalla et al. investigated the association between the composition of 24-hour movement behaviours (MVPA, LPA and SB) and CVD using a compositional analysis. The authors observed that less time spent in MVPA, and additional time spent in either SB or LPA was associated with an increased risk of CVD. However, no association was observed for reallocating time between SB and LPA<sup>193</sup>.

Evenson et al. investigated the association of accelerometer-measured PA and CVD mortality among National Health and Nutrition Examination Survey (NHANES) participants. They found no significant association between increased SB and CVD mortality, following adjustment for other walking behaviours, with a HR comparing the highest quarter (Q4) to the lowest quarter (Q1) of SB of 1.44 (0.71, 2.90). However, their findings support prior evidence of an inverse association between increased MVPA and CVD (Q4 vs Q1: HR = 0.48 (0.23,1.03)). In a separate study, Schmid et al. investigated the association between the reallocation of time between movement behaviours in the NHANES population and CVD mortality. They found that 30 min/day more LPA each day, allocated for SB, was associated with a HR of 0.86 (0.79, 0.93), while 30 min/day more MVPA was associated with a HR of 0.35 (0.14, 0.92)<sup>196</sup>.

An overview of several large association studies between accelerometer-measured PA and CVD is provided in Table 2.6.

**Table 2.6 Overview of the association between Physical activity and incident cardiovascular disease**

| Cohort       | Study reference                   | N      | Follow-up  | Events | Outcome | Hazard ratio                                                                                                               |                                                                                |                                        |                           |                                                |
|--------------|-----------------------------------|--------|------------|--------|---------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------|---------------------------|------------------------------------------------|
|              |                                   |        |            |        |         | SB                                                                                                                         | LPA                                                                            | MVPA                                   | Sleep                     | Other                                          |
| UK Biobank   | Ramakrishnan et al. <sup>79</sup> | 90,211 | Median 5.2 | 3,617  | CVD     | NR                                                                                                                         | NR                                                                             | Q4 vs. Q1 0.46 (0.41, 0.51)            | NR                        | Total volume PA<br>Q4 VS Q1: 0.47 (0.43, 0.52) |
| UK Biobank   | Walmsley et al. <sup>171</sup>    | 87,498 | Mean 6.2   | 4,105  | CVD     | 1.05(1.03 – 1.07) per hour                                                                                                 | 0.99(0.98 – 1.01) per hour                                                     | 0.91 (0.90-0.93) per 20 minutes        | 0.98(0.96 -1.00) per hour |                                                |
| Whitehall II | Yerramalla et al. <sup>193</sup>  | 3,319  | Mean 6.2   | 299    | CVD     | LPA or MVPA to SB:<br>1.34 (1.01–1.79) per SD<br><br>MVPA to SB:<br>1.42 (1.20–1.68)<br><br>LPA to SB:<br>1.17 (0.80–1.72) | SB or MVPA to LPA:<br>1.02 (0.68–1.51)<br><br>MVPA to LPA:<br>1.21 (0.88–1.67) | SB or LPA to MVPA:<br>0.73 (0.60–0.89) | NR                        | -                                              |

|              |                                  |       |          |     |               |                                        |                                                                                        |                                              |    |                                     |
|--------------|----------------------------------|-------|----------|-----|---------------|----------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------|----|-------------------------------------|
| Whitehall II | Yerramalla et al. <sup>194</sup> | 3,321 | Mean 6.2 | 299 | CVD           | Per 100.2 minutes<br>1.20(1.06 – 1.37) | NR                                                                                     | NR                                           | NR | NR                                  |
| NHANES       | Evenson et al. <sup>195</sup>    | 3,809 | Mean 6.4 | 107 | CVD mortality | Q4vsQ1: 1.44 (0.71,2.90)               | Q4vsQ1: 0.9 (0.44,1.84),<br>T3vsT1: low LPA0.63(0.41, 0.99); high LPA: 0.30(0.17,0.51) | T3vsT1: 0.42 (0.24,0.75)                     | NR | NR                                  |
| NHANES       | Schmid et al. <sup>196</sup>     | 3,702 | mean 6.7 | 196 | CVD mortality | T3vsT1: 3.56 (1.73,7.3)                | SB to LPA:0.86 (0.79,0.93)<br>Per30min/day                                             | SB to MVPA: 0.35 (0.14,0.92)<br>Per30min/day | NR | T3vsT1ofLPA + MVPA:0.27 (0.13,0.57) |

Abbreviations: NR: Not reported, HR Hazard Ratio, SD: standard deviation, T: tertile, Q: fourth, AUC: Area under receiver operator curve, Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, FRS Framingham risk score, PCE: pooled cohort equation, NRI: Net reclassification index, NHANES National Health and Nutrition Examination survey

#### **2.4.5.2 Physical activity and CVD risk scores**

While the association between PA and incident CVD has been firmly established, the added value of PA, particularly accelerometer-measured PA, to clinical risk models for CVD remains unclear. The majority of the evidence assessing the added value of PA to clinical CVD risk scores has thus far relied on self-reported data. Table 2.7 provides a summary of the performance of various PA measurements to clinical risk models.

Georgousopoulou et al. (2016) investigated the predictive value of self-reported energy expenditure, assessed using the International Physical Activity Questionnaire (IPAQ), to the HellenicSCORE risk score—a recalibrated version of SCORE2 for the Greek population—in a cohort of 2,020 Greek adults<sup>187</sup>. The authors found an independent association between self-reported energy expenditure and CVD, HR = 2.08, (1.71, 2.54) and a modest increase in predictive performance when added to HellenicSCORE,  $\Delta$ C-index = 0.012; NRI = 0.012 (0.001 - 0.022). In a similar study, Graversen et al. 2016, independently evaluated the added value of self-reported walking pace, walking duration, and leisure-time PA to SCORE2 risk prediction across 8,476 participants from the Copenhagen City Heart study. An independent association was reported between walking pace and incident CVD; however, no such association was found for walking duration or leisure-time PA<sup>188</sup>. No significant improvements in predictive performance were reported, as measured by the AUC and NRI. In a subsequent study, Pandey et al. investigated the added value of leisure-time PA to the PCE in 18,824 participants across three prospective cohort populations<sup>189</sup>. In contrast to Graversen et al. the authors report a significant association between leisure-time PA and CVD (HR = 0.91;(0.86-0.9) per SD). However, only modest improvements were observed in predictive performance vs the PCE across the overall study population,  $\Delta$ C-index = 0.001, while no changes in risk stratification were observed. NRI = -0.003 (-0.010 - 0.010).

Only one study was identified, which investigated the prognostic value of accelerometer-derived PA for incident CVD. In 2022, Ledbetter et al. investigated the added value of Accelerometer-measured PA to established clinical risk factors for predicting incident CVD mortality in 3,772 individuals aged 50-85 over 9.9 years of follow-up. They found significant improvements in predictive performance following the addition of PA measurements to the best-performing clinical risk factor model,  $\Delta C$ -index 0.014. Furthermore, they report that the overall count of PA was the strongest univariate predictor for CVD mortality, surpassing established risk factors such as age and sex<sup>197</sup>. However, no evaluation of model reclassification or calibration was provided, making it difficult to holistically assess the clinical utility of such a risk score.

Despite this strong predictive performance for incident CVD and mortality, a significant gap remains in the literature as to the added value of objectively measured PA to clinically adopted risk scores for primary prevention of fatal and non-fatal CVD.

**Table 2.7 Performance of Physical Activity Risk scores for incident cardiovascular disease**

| Cohort | Study reference                 | N     | Follow-up  | Events | Outcome       | Movement behaviour<br>s                                                                                                                                                                                                                                      | HR | C-index | Continuous<br>NRI | Categorical<br>NRI | AUC |
|--------|---------------------------------|-------|------------|--------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|---------|-------------------|--------------------|-----|
| NHANES | Ledbetter et al. <sup>197</sup> | 2,987 | mean = 9.9 | 161    | CVD mortality | Total activity, MVPA, g activity count, LPA, SB/sleep, average log activity during the 10 most active hours of the day, average log activity during the least five active hours of the day, sedentary transition probability, sedentary to active transition |    |         |                   |                    |     |

|                             |                                       |       |           |     |                       | probability                           |          |        |                                    |    |
|-----------------------------|---------------------------------------|-------|-----------|-----|-----------------------|---------------------------------------|----------|--------|------------------------------------|----|
| Base model                  |                                       |       |           |     |                       |                                       | NR       | 0.8314 | NR                                 | NR |
| . PA model                  |                                       |       |           |     |                       |                                       | NR       | NR     | NR                                 | NR |
| Base + PA model             |                                       |       |           |     |                       |                                       | NR       | 0.8450 | NR                                 | NR |
| ATTICA                      | Georgousopoulou et al. <sup>187</sup> | 2,020 | Mean 8.41 | 317 | 10-year incident CVD  |                                       |          |        |                                    |    |
| Base model                  |                                       |       |           |     |                       | 2.08, (1.71, 2.54) per class increase | NR       | -      | -                                  | -  |
| . PA model                  |                                       |       |           |     |                       | T3 VS T1: 1.91, 95% CI: 0.95, 3.84)   | NR       | NR     | NR                                 | NR |
| PA + base model             |                                       |       |           |     |                       | NR                                    | Δ0.012 , | NR     | 0.012 (0.001 - 0.022) <sup>a</sup> | NR |
| Copenhagen City Heart study | Graversen et al. <sup>188</sup>       | 8,476 | Median 18 | 665 | 10-year CVD mortality | Walk duration, walking pace, Physical |          |        |                                    |    |



|                    | activity –<br>leisure, |                                                                                                                                    |    |    |                                                                                        |                                                          |
|--------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------|----|----|----------------------------------------------------------------------------------------|----------------------------------------------------------|
| Base<br>model      |                        | NR                                                                                                                                 | NR | -  | -                                                                                      | 0.837<br>(0.820–<br>0.855)                               |
| . PA model         |                        | Walk<br>duration:<br>0.56<br>(0.31–<br>1.02) for<br>2-hour<br>walking.<br>Walking<br>pace: 0.65<br>(0.51–<br>0.84) fast<br>vs slow | NR | NR | NR                                                                                     |                                                          |
| PA +<br>base model |                        | Leisure:<br>0.60<br>(0.34–<br>1.06) Q4                                                                                             | NR | NR | Walk<br>duration:<br>0<br>(–0.001–<br>0.001) <sup>c</sup><br>Walking<br>pace:<br>0.003 | Walk<br>duration<br>: 0.008<br>Walking<br>pace:<br>0.001 |

|                           |                              |        |                         |      |                            |                               |       |    |                                                      |                   |
|---------------------------|------------------------------|--------|-------------------------|------|----------------------------|-------------------------------|-------|----|------------------------------------------------------|-------------------|
|                           |                              |        |                         |      |                            |                               |       |    | (-0.001–<br>0.007) <sup>c</sup>                      | Leisure:<br>0.003 |
|                           |                              |        |                         |      |                            |                               |       |    | Leisure:<br>0.001<br>(-0.001–<br>0.002) <sup>c</sup> |                   |
| ARIC,<br>MESA, and<br>CHS | Pandey et al. <sup>198</sup> | 18,824 | Duration<br>10<br>years | 1632 | 10-year<br>incident<br>CVD |                               |       |    |                                                      |                   |
| Base<br>model             |                              |        |                         |      |                            | NR                            | 0.770 | -  | -                                                    | NR                |
| . PA model                |                              |        |                         |      |                            | 0.91;(0.86<br>-0.9) per<br>SD | NR    | NR | NR                                                   | NR                |
| PA +<br>base model        |                              |        |                         |      |                            | NR                            | 0.771 | NR | -0.003 (-<br>0.010 –<br>0.010) <sup>b</sup>          | NR                |

<sup>a</sup> NRI category: < 1%, 1%, 2%, 3 – 4%, 5 – 9%, 10 – 14%, and > 14%

<sup>b</sup> NRI category: 7.5%- 10%%, and > 10%

<sup>c</sup> NRI category: < 5.%, 5- 10%%, and > 10%

Abbreviations: NR: Not reported, HR Hazard Ratio, SD: standard deviation, T: tertile, Q: fourth, AUC: Area under receiver operator curve, Major Adverse Cardiovascular Events, CVD: cardiovascular disease, CHD: Coronary heart disease, CAD: Coronary artery disease, FRS Framingham risk score, PCE: pooled cohort equation, NRI: Net reclassification index, ARIC Atherosclerosis Risk in Communities, MESA Multi-Ethnic Study of Atherosclerosis, Cardiovascular Health Study, NHANES National Health and Nutrition Examination survey

#### **2.4.6 Discussion**

##### **Limitations and future research**

To date, most epidemiological studies assessing the prognostic value of PA for CVD risk prediction have relied on self-reported data, which is prone to reporting bias and lacks granularity. While the association between objectively measured PA from accelerometers and CVD is well established, the added value of objectively measured PA in predicting incident MACCE remains largely unexplored.

Despite the strong association between PA and incident MACCE, no studies have been identified that assess the added value of accelerometer measurements to established clinical risk models for primary prevention. Moreover, no clinically adopted risk scores include PA measurements to identify high-risk individuals. While Ledbetter et al. (2022) reported that accelerometer-measured PA may enhance predictive performance beyond traditional risk factors, significant knowledge gaps remain. Notably, their study did not evaluate PA's integration into existing risk scores, limiting conclusions on its clinical impact. Additionally, no evidence of reclassification or calibration was provided following the inclusion of PA measurements.

None of the identified prognostic studies reported adhering to any reporting or publication guidelines for risk prediction model development. The absence of a standardized framework makes cross-study comparisons challenging and hinders the ability to draw holistic conclusions from the existing literature.

Given the stronger association between accelerometer-measured PA and incident CVD, alongside its improved measurement accuracy over self-report, there is a pressing need to reassess its role in CVD risk prediction. Accelerometers capture a comprehensive range of 24-hour movement behaviours, enabling a more nuanced evaluation of PA's predictive value. Incorporating objectively measured PA into clinical risk models could enhance the identification of high-risk individuals, informing more effective primary prevention strategies.

Additionally, integrating PA into risk prediction tools could empower individuals to lower their risk scores through lifestyle modifications, potentially reducing the need for medical interventions.

#### **2.4.7 Summary**

Despite a well-documented protective association between PA and incident MACCE, the added value of PA in predicting the risk of future MACCE remains unclear. Most epidemiological evidence relies on self-reported data, which is susceptible to both reporting and recall bias, with the robustness of measurements varying significantly between study populations<sup>162,201</sup>. In contrast, device-based accelerometers provide scalable, non-invasive objective measurements of PA, limiting bias and improving generalisability across different subpopulations. Moreover, many studies investigating the additive value of PA for CVD risk prediction have been further hindered by modest sample sizes and a lack of reporting on key performance metrics, such as calibration and performance at clinically meaningful risk thresholds<sup>187–189</sup>.

This thesis addresses these limitations by investigating the added value of objective accelerometer-measured PA to established clinical risk models in a large population with no prior history of MACCE. The analysis takes place using the UKB prospective cohort study, which recruited over 100,000 individuals to take part in 7 days of PA monitoring using a wrist-worn accelerometer. All participants consented to passive follow-up through their medical records. Further details on the study population and subsequent analysis are provided in chapters 3, 6 and 7.

To the best of my knowledge, at the time of writing this thesis represents the largest population-based cohort study to examine the added value of objectively measured PA to existing clinical risk models in individuals without a history of MACCE. This is also the first study to explore the prognostic value of PA using both traditional statistical methods and deep survival models.

## 2.5 Conclusion and objectives

MACCE is the largest contributor to CVD mortality and morbidity globally, presenting a pressing public health challenge<sup>4,5</sup>. The majority of MACCEs are preventable through timely intervention, requiring the identification of high-risk individuals<sup>3,9-11</sup>. Current cardiovascular risk scores are suboptimal, and there is a large scope to improve and simplify current risk prediction methods<sup>26,38,61,62</sup>. Digital sensors offer cheap, non-invasive, and objective measurements of key physiological and behavioural risk factors of MACCE, such as ECG and accelerometer-measured PA. These measurements could improve the detection of individuals at heightened risk of MACCE and enhance intervention strategies<sup>116,148,197,202</sup>. However, due to past constraints on the use of digital sensors in large-scale studies, the added value of ECG and PA in clinical risk prediction remains largely unexplored.

This thesis investigates the added value of integrating ECG and accelerometer measurements into established clinical risk models for CVD, evaluating both traditional and deep learning-derived phenotypes. This work addresses key limitations in ECG and accelerometer-based cardiovascular risk prediction. By leveraging a large prospective dataset, this thesis overcomes prior constraints, including small sample sizes, insufficient follow-up for disease endpoints, and lack of integration with existing clinical models. Chapter 3 introduces the datasets used in this thesis, specifically detailing the UK Biobank (UKB) and the relevant enhancement studies incorporating ECG and accelerometer-based measurements, which are analysed in subsequent chapters.

## Chapter 3 – Datasets

### 3.1 Background

Chapter 2 highlighted how limited sample sizes and insufficient long-term follow-up have hindered prior attempts to assess ECG and accelerometer data for predicting incident CVD. These constraints were predominantly due to the high costs and logistical challenges of large-scale data collection. However, recent technological advancements and the proliferation of affordable health devices, such as low-cost ECG monitors and wrist-worn accelerometers, have enabled the collection of digital biomarkers at an unprecedented scale. This has coincided with the emergence of large prospective cohort studies, such as the UK Biobank, featuring long-term follow-up and extensive device-measured phenotypes. These developments present new opportunities for well-powered analyses of digital sensors in predicting CVD. This chapter details the methods used to collect and process ECG and accelerometer data from the UK Biobank prospective cohort study.

The UK Biobank (UKB) is a large prospective cohort study established between 2006–2010 to research genetic and non-genetic risk factors through longitudinal follow-up of participants. The study recruited 502,636 participants (aged 40-69, 46% male) from the UK general population across 22 assessment centres throughout England, Wales, and Scotland<sup>20</sup>.

At recruitment, all participants provided written informed consent for passive follow-up through linkage to their healthcare records for multiple health-related outcomes. Following this, each participant would attend an initial health assessment at their local assessment centre, where they would undergo a touch screen questionnaire, verbal interview, physical measurements, and laboratory sample collection<sup>203,204</sup>. Additional information was obtained through further invitations to participate in numerous enhancement studies for expanded data collection.

This thesis explores two such enhancement studies, starting with the UKB Cardiorespiratory fitness assessment, which collected exercise ECG recordings from 95,052 participants during a graded submaximal cycle ergometry test (2009-2013)<sup>205</sup>.

The second enhancement study explores accelerometer recordings in a separate sub-cohort of 103,660 individuals following 7 days of physical activity monitoring using a wrist-worn accelerometer (2013-2016)<sup>169,206</sup>. To date, these studies represent the single largest collections of exercise ECG and wearable accelerometer data, respectively, creating an unparalleled opportunity to investigate the role of digital sensors in predicting CVD.

## **3.2 Introduction to UK Biobank**

### **3.2.1 Recruitment**

UK Biobank (UKB) invited all individuals aged 40-69 years from the general UK population who were registered with the National Health Service (NHS) and lived within 25 miles of one of 22 UKB assessment centres to participate in the study. Eligible participants received recruitment letters inviting them to attend their local assessment centre, where they were provided with detailed information on the study objectives and data collection procedures. Those who wished to participate then provided informed consent for the collection of their data and use for research purposes. Between 2006 and 2010, 502,636 individuals consented to participate in UKB, representing 5.5% of the 9.2 million individuals invited. Despite the relatively low response rate, findings from UKB have been shown to be generalisable across the UK<sup>20</sup>. Although respondents are not representative of the UK population in terms of demographic and health characteristics, prior evaluations have demonstrated that exposure–outcome associations remain robust, and follow-up of non-responders was not deemed to be cost-effective<sup>207</sup>. Figure 3.1 provides a timeline of UKB data collection, including the initial baseline assessment, health record linkage, and subsequent enhancement studies. The initial baseline assessment occurred between 2006 and 2010, and a subset of participants were invited to participate in an exercise ECG assessment. A further ECG assessment was conducted from 2012 to 2013, where a new sub-cohort of the UK biobank, along with a subset of participants from the initial ECG assessment were invited to perform a repeat of the exercise ECG test. Following the baseline assessment, an additional subpopulation of the UKB was invited to take accelerometer measurements of physical activity between 2013 and 2015.

Linkage to healthcare records remains ongoing throughout the UK Biobank study and includes data recorded prior to the initial assessment centre visit dating to the start of each individual's healthcare records.

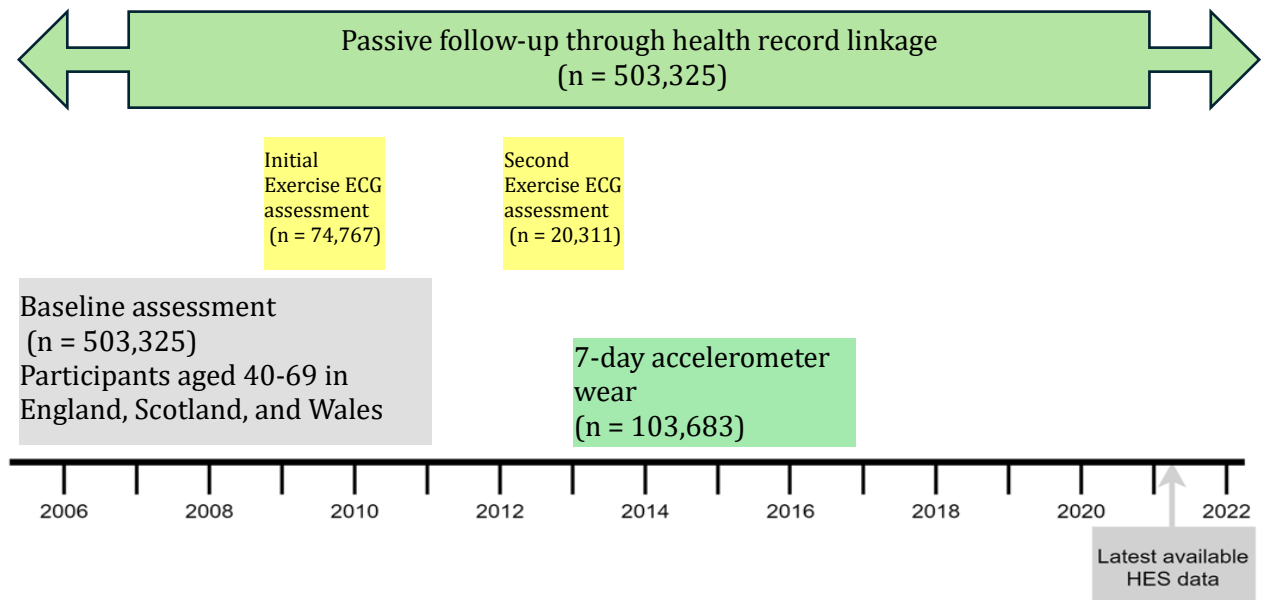


**Figure 3.1: Timeline of the UK Biobank study**, outlining the recruitment of participants who contributed data to this thesis. This included initial recruitment 2006-2010, Cardiorespiratory fitness assessment (2009-2013), and physical activity monitoring (2013-2016).

### 3.2.2 Baseline assessment

Upon recruitment, participants attended an initial baseline assessment of their physical health and health-related factors such as lifestyle behaviours and socioeconomic status. Participants were required to complete a touch screen questionnaire covering their health and lifestyle behaviours, including diet, physical activity, smoking status, and alcohol consumption; socioeconomic information such as employment status, home ownership and education, in addition to their medical history and past medications. Information that could not be obtained through the touch screen questionnaire was obtained during a subsequent interview with a trained member of staff. Interview questions were designed to obtain further information on family history of disease in addition to current medications and were based on information provided during the initial touch screen questionnaire. Participants also consented to provide physical measurements such as weight, height and blood pressure in addition to biological samples, including blood, urine and saliva for subsequent analysis. A complete overview of the data collection protocol is provided in<sup>203,204,208-210</sup>.



### **3.2.3 Disease outcomes and health record linkage**

Participants provided written informed consent for passive follow-up through linkage to their electronic healthcare records for multiple health-related outcomes. Available medical records included hospital episode statistics (HES), reported by the NHS Information Centre and Central Register Scotland, for participants from England, Wales, and Scotland, respectively, and the UK National Death Register for all participants. Primary care data was available for general use for 45% of participants, with plans to extend this to the wider UKB population in the near future. Additional health outcomes were made available through cancer registry data and COVID-19 testing datasets. The primary outcome of interest for this thesis was the occurrence of incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE), defined as the earliest recorded episode of hospitalisation or death due to ischaemic stroke, coronary heart disease, heart failure, or transient ischaemic attack.

The follow-up period was determined by the first appearance of ICD10 or ICD9 codes in either HES or death registration data relating to MACCE (Supplementary Table 1). Participants were censored based on the earliest date of either (i) the first recorded diagnosis of MACCE, (ii) death not caused by MACCE, or (iii) the most recent publication of NHS HES. It should be noted that the dates of the latest available HES and death registry data differ between England, Scotland, and Wales data. As such, participants were assigned the censoring date for England, Scotland, or Wales based on the location of the UKB assessment centre they attended at recruitment. At the time of writing, follow-up of UKB participants remains ongoing; this thesis investigates MACCE outcomes last reported for England: 31st October 2022; Scotland: 31<sup>st</sup> August 2022; and Wales 5<sup>th</sup> May 2022, respectively.

Additional outcomes were obtained from primary care datasets for exclusions of individuals diagnosed with CVD prior to recruitment. I identified prevalent CVD using Read2/3 codes from general practice records based on the definition provided in QRISK3<sup>51</sup>.

A complete list of disease definitions based on ICD 9/10 codes and Read2/3 codes is provided in Supplementary Tables 1 and 2, respectively.

### **3.2.4 Ethical approval**

The UKB obtained ethical approval from the Northwest - Haydock Research Ethics Committee and was most recently renewed on 29<sup>th</sup> June 2021 (reference: 21/NW/0157 Northwest - Haydock Research Ethics Committee) as such researchers do not require separate ethical approval and can operate under the UKB so long as access procedures are met. Ethical approval is reviewed every 5 years, with the next renewal application expected in 2026. Informed consent was obtained from all participants who retain the right to withdraw from the UKB at any time<sup>211</sup>.

The UKB also operates under the advice of the Ethics and Governance Council, later replaced by the Ethics Advisory Committee (EAC) from 2018 onwards. The EAC is responsible for ensuring adherence to the UK Biobank ethics and governance framework and advises more generally on the interest of research participants in addition to the general population. The EAC is tasked with:

- Identify and examine ethical issues.
- Provide recommendations on ethical issues.
- Review and advice on policy decisions with ethical implications.
- Conduct conceptual and empirical research on ethical issues facing the UKB.

Further information on the UKB ethics approval and the role of the UKB is provided in <sup>211</sup>

### **3.2.5 Accessing UK Biobank Data**

UKB access is restricted to bona fide researchers from academic, charitable, and commercial organisations seeking to engage in health research, which aligns with improving the prevention, diagnosis, and treatment of disease<sup>212-214</sup>. Researchers must align with the ethical framework governing UKB and comply with relevant data protection regulations<sup>215</sup>. To access UKB datasets, researchers must first outline the purpose of the research, expected outcomes, and the specific data required.

An independent review is then carried out by the UKB access committee to ensure the research meets the necessary practical and ethical requirements. Following approval, researchers will be required to sign a material transfer agreement prior to the release of the requested data. A full description of UKB data access and management protocol is provided in UKB access procedures<sup>214</sup>.

Data access for this thesis was granted under application 59070, all data was stored and processed on the University of Oxford Bio-Medical Research Computing a high-performance cluster computing system<sup>216</sup> in adherence with UKB governance guidelines. Tabular data and disease outcomes were obtained via UKB assessment centres, HES and death registry datasets were obtained through the UKB research analysis platform. An overview of the data and variable used in this thesis is provided in Supplementary Table 3 along with the relevant UKB field ids, and ICD 9/10 code where applicable.

### **3.2.6 UK Biobank Sub-studies and Resource Enhancement**

UKB was further enhanced in August 2009 following the endorsement of the international peer review panel, extending the range of phenotypes collected during a participant's baseline health assessment. Subsequently, 100,000-150,000 participants yet to undergo their initial assessment were recruited for an expanded baseline assessment, including whole blood measurements, cardiorespiratory assessments, and physical activity monitoring<sup>208</sup>. Such enhancement studies aimed to collect more precise measurements closely correlated with disease outcomes. Notably, from August 2009 to the end of recruitment, over 95,000 participants agreed to participate in submaximal exercise ECG assessments<sup>205</sup>, whilst an additional 100,000 participants consented to wear an accelerometer for seven days<sup>169,206</sup>. 26,295 participants (5.2% of the entire UK Biobank cohort) contributed data to both the ECG and accelerometer sub-cohorts. ECG and accelerometer risk models were developed and evaluated independently; thus no participant was double counted during model development.

### **3.3 UK Biobank Cardio assessment study and cycle ergometry ECG data**

ECG measurements were recorded during a submaximal cycle ergometry exercise test as part of the Cardiorespiratory fitness assessment, announced during the second round of enhancements studies by UKB<sup>205,208</sup>. ECG measurements took place immediately following initial recruitment, with a further 20,077 participants invited to take part in the study during a repeat assessment centre 2-3 years after their baseline health assessment (Figure 3.1). The cardio assessment was designed to assess aerobic capacity and overall cardiovascular health through a ramped exercise test to ensure a safe assessment of physical fitness in a large cohort.

#### **3.3.1 Recruitment**

Of the wider UKB cohort, 74,767 participants consented to participate in a cycle ergometry test between 2009 and 2010, of which 3,112 were invited for a repeat assessment between 2012 and 2013, along with a further 17,199 who had not previously participated. Pre-test screening was used to exclude participants with high-risk conditions such as the test (e.g. angina, aortic stenosis and dysrhythmias<sup>208</sup>). Participants were recruited to undergo exercise ECG testing during their initial assessment centre visit, where they were asked to provide informed consent<sup>203,210</sup>. A total of 97,966 ECGs were recorded following the end of recruitment.

#### **3.3.2 Protocol**

Cardio testing was conducted on a stationary seated cycle ergometer (eBike, Firmware v1.7) in conjunction with a single lead (lead I) ECG device (CAM-USB 6.5, Cardiosoft v6.51, sample rate 500 Hz). Consenting participants were assigned personalised exercise protocols based on 5 pre-assigned cardiovascular risk categories (Supplementary Tables 4-8). The participant's risk category was first calculated to determine whether to perform a resting or exercise ECG. The intensity of activity was then determined for those able to exercise based on the participant's risk category and estimated maximum workload based on respective age, height, weight, sex and resting heart rate.

Once an exercise protocol has been assigned, participants will undergo a 15-second pre-test resting ECG, 6 minutes of graded exercise and 1 minute of recovery (Figure 3.2). Those not allowed to exercise will instead undergo a 2-minute resting ECG. During the exercise stage, participants were categorised into performing either 35% or 50% of their maximum estimated workload. Exercise was terminated early if the participant reaches a pre-defined maximum heart rate, reports any chest pain, dizziness or indicates they wish to stop the test for any reason. Cycle ergometry testing was overseen by a certified member of staff at each UKB assessment centre, who was responsible for overseeing the initial health assessment before assigning participants to a recommended exercise protocol.

The CAM-USB 6.5 was configured to record across a single lead (Lead I) for the duration of the test at a sampling frequency of 500 Hz, resolution 5  $\mu$ V. ECG electrodes are placed on the participant's right and left arms, the right/left antecubital fossa, and the right/left wrists.

A full breakdown of the study protocol can be found at <sup>205</sup>. The initial and final workloads, alongside the formula for workload estimation and risk categorisation, can be found in Figure 3.2 and Supplementary Tables 4-8.

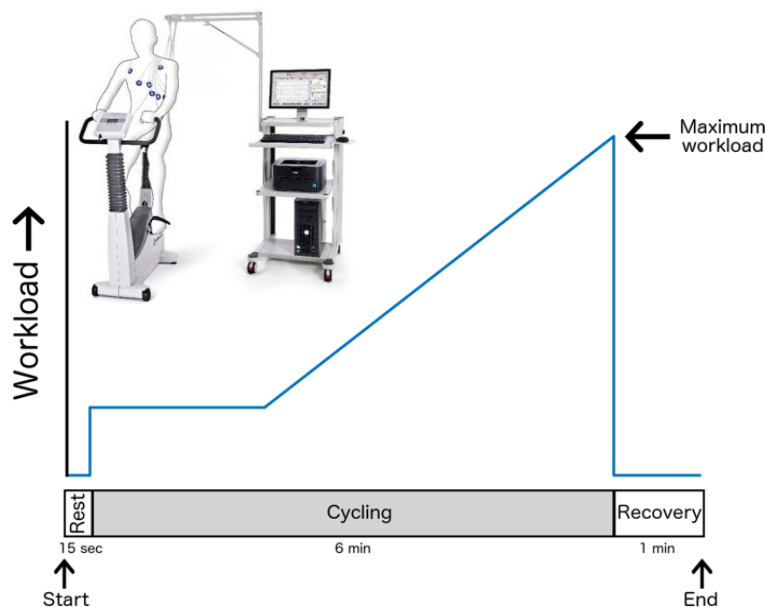


**Figure 3.2:** Cardiorespiratory fitness assessment protocol consisting of:

- Initial 15 seconds rest (pre-test resting ECG)
- 2-minute phase at constant power
- Linear increase over 4 minutes from Start to Peak power level.
- Concluded by a 1-minute recovery period.

### **3.3.3 Data preparation**

#### **3.3.3.1 Participant data**

Participant-level data was obtained from the initial UKB health assessment and health record linkage. In order to assess the added value of the ECG to current risk scores, variables of interest were selected from the QRISK3 risk calculator<sup>51</sup>, currently adopted for clinical use for the primary prevention of CVD in the UK primary care by the National Health Service (NHS). Each variable was mapped to available data in the UKB assessment centre results and hospital episode statistics (HES), reported by the NHS information centre and central register Scotland, for participants from England, Wales, and Scotland, respectively. The definition of each risk factor, along with relevant UKB field IDs and International Classification of Diseases codes, Ninth and Tenth revisions (ICD 9/10), are reported in Supplementary Table 3.

All participant data underwent quality control checks and data cleaning, and preparation prior to analysis, including the removal of high-frequency noise and baseline wandering (further details provided in Chapter 4). In line with previous UK Biobank analyses, missing covariate data were assumed to be missing at random (MAR), given the rich set of observed covariates and outcomes available to model missingness. Variables with <1% missingness were handled using complete-case analysis<sup>217,218</sup>. For variables with >1% missingness, single imputation using Bayesian Ridge regression<sup>219</sup> was applied to estimate missing values from their relationships with other observed covariates.<sup>219</sup> Participants with missing data marked 'Prefer Not to Answer' and 'Do Not Know' were also removed from the study. Multiclass categorical variables were one hot encoded, creating a single binary variable for each sub-category. Participants with continuous variables considered extreme or erroneously entered, i.e. outside of plausible range of values, were removed from the study population.

Due to the heavy class imbalance among ethnicities (Table 3.1), ethnicity was divided into white/non-white. Smoking was factorised into three categories (never, previous, current).

Further details including variable selection and exclusion criteria are provided in chapters 4-5.

### **3.3.3.2 ECG data**

Preparation of ECG signals followed the framework established by Sörnmo et al. in 2005, which serves as a general-purpose guide for ECG signal processing<sup>220</sup>. ECGs were first subject to quality control measures to identify and exclude ECGs with missing data or low signal-to-noise ratio. This was followed by data preprocessing, including noise reduction and removal of baseline wandering using previously established pipelines described in Zheng et al. 2020<sup>221</sup>. For subsequent risk modelling, this work investigated both manually extracted ECG parameters and raw ECG signals as our key exposure variables. As much of the ECG signal was unannotated, this work utilised a deep neural network for QRS detection and wave delineation to assess the morphology and rhythm of each ECG. Further details on the implementation of signal processing and feature extraction are discussed in Chapter 4.

### **3.3.4 Cohort description**

Table 3.1 provides an overview of the demographic, lifestyle, socioeconomic and disease history of participants enrolled in the Cardiorespiratory fitness assessment and the wider UKB cohort. Whilst participants were recruited from across the general population from the entire UK, the final UKB population was not representative of the general UK population. The UKB has a well-documented healthy volunteer bias demonstrated by an overall decrease in all-cause mortality and incidence of various health conditions<sup>20</sup>.

Participants were more likely to be white and female and less likely to smoke or drink. As the Cardiorespiratory fitness assessment was integrated into the initial baseline assessment undertaken by all participants, the demographics, health status and lifestyle factors of this cohort were similar to those of the wider UKB population (Table 3.1).

### 3.3.5 Data quality

Of the 97,966 ECGs recorded during the study, 20,756 (21.2%) were either corrupted or missing ECG data and were excluded from further analysis. The signal quality of the remaining ECGs was evaluated using the signal-to-noise ratio (SNR) and the signal quality index (SQI).

The SNR, measured in decibels (dB), quantifies the ratio of the desired ECG signal to background noise <sup>222</sup>.

ECG signals can be divided into three categories based on the SNR. An SNR above 18 dB indicates high-quality signals suitable for full ECG wave analysis. An SNR between 5 and 17 dB is considered moderate quality, allowing reliable QRS complex detection and rhythm analysis. An SNR below -10 dB is too low for even basic QRS detection, making further analysis unfeasible<sup>223</sup>. A representative figure showing the bottom 5%, median, and top 95% of heartbeats based on the SNR from the UK Biobank Cardiorespiratory fitness assessment is presented in Figure 3.3.

The SQI, derived from the method proposed by Zhao et al<sup>224</sup>, evaluates ECG quality by measuring the agreement between multiple peak detection algorithms based on the position of the R wave identified by each. The SQI is measured on a scale from 0 to 1, where a score of 1 indicates perfect alignment and a score of 0 indicates complete disagreement. The average SQI was calculated across five R-wave detection algorithms provided by the Neurokit software package<sup>225</sup>

The average SQI for all ECG recordings was 0.92, indicating strong agreement among peak detection algorithms. The average SNR was 12.5 dB, falling within the moderate range. This suggests that, despite some background noise, the signal quality was sufficient for reliable analysis, as supported by the high SQI value.

Participant-level data recorded during their initial assessment centre visit was generally of very high quality, with a limited amount of missing data (Table 3.1).



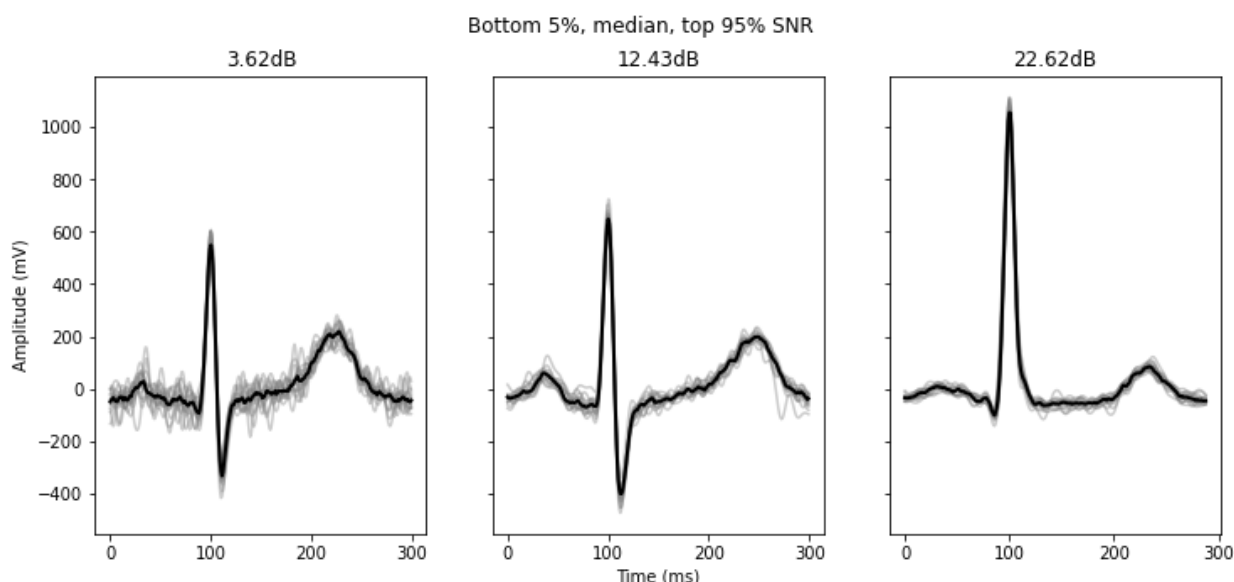


**Figure 3.3 Median resting beat (black) and individual beats (grey) from the bottom 5%, median and top 95% Signal-to-noise-ratio from the UK Biobank cycle ergometry exercise test<sup>205,208</sup>.**

### **3.4 UK Biobank Physical activity monitoring and accelerometry data**

The UKB activity monitoring study was announced during the second wave of enhancement studies by the UKB. Physical activity measurements were recorded 3-10 years following a participant's initial baseline health assessment using wrist-worn accelerometers, involving approximately one fifth of the original cohort (Figure 3.4). Accelerometer recordings were measured continuously throughout the daily lives of each participant over a period of 7 days, after which accelerometer devices were returned to the UKB for further analysis. The study was designed and overseen by a working group of physical activity experts<sup>206,208</sup>.

### 3.4.1 Recruitment

Participants with a registered email address with the UKB were invited via email to wear an accelerometer for 7 days. Initial recruitment took place in February 2013, with a second round of recruitment launched in December 2015. Participants were selected at random, however recruitment from the northwest region was deprioritised, due to a number of ongoing pilot studies resulting in concerns of participant burnout<sup>169</sup>. In total, 236,519 participants were contacted at random to participate in the study, with 106,053 (44.2%) consenting to participate. Of the 106,053 consenting participants, 164 (0.2%) withdrew their consent at a later date, 954 (0.9%) datasets were unreadable, whilst a further 1,273 (1.2%) failed to return their device to the UKB<sup>169</sup>, leaving a final cohort of 103,662 (Figure 3.4).

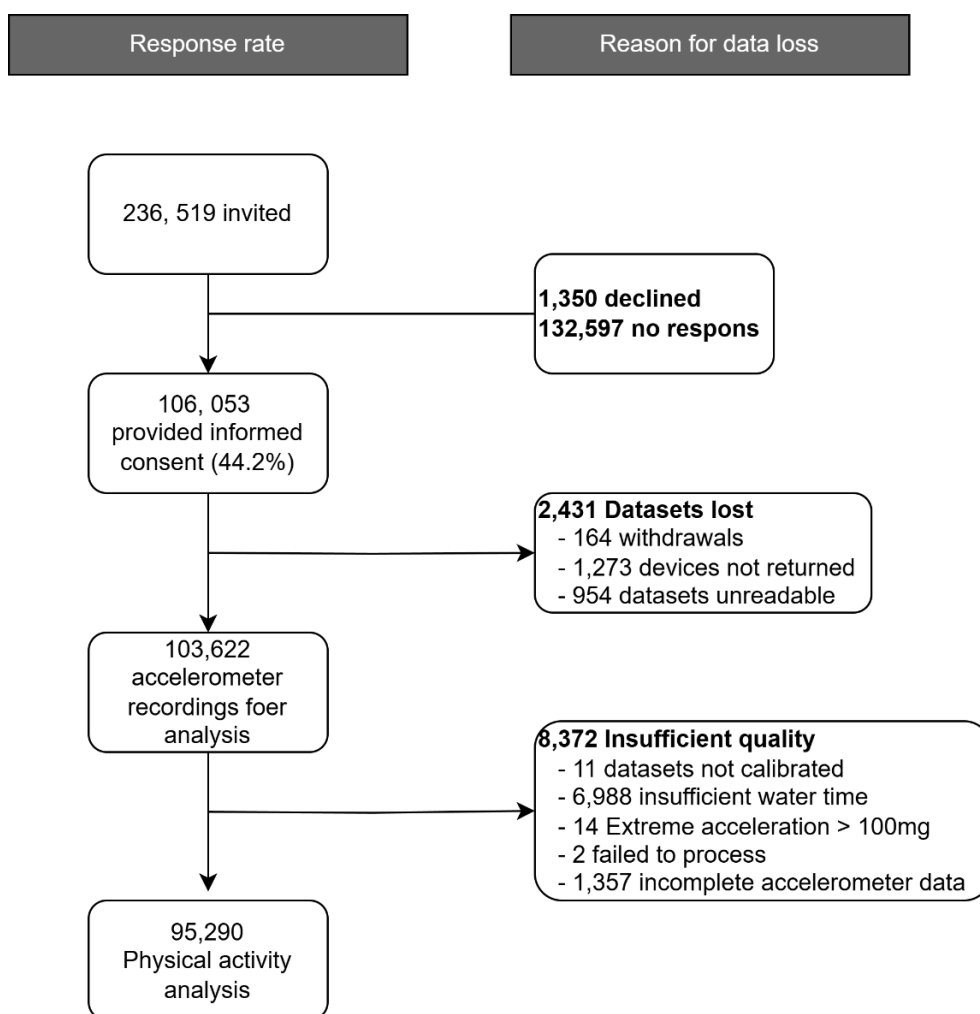


**Figure 3.4 Participant flow chart; the UK Biobank physical activity sub-study 2013–2015 (n = 106,053).**

### 3.4.2 Protocol

Participants were sent a wrist-worn accelerometer (Axivity AX3) to their home address, with each accelerometer preprogrammed to start recording at 10 am, two working days after they were first posted. Participants were instructed to wear the device on their dominant wrist throughout their daily activities (Figure 3.5) for 7 days before returning to the UKB via post in a pre-paid envelope.

Axivity AX3 accelerometers recorded acceleration across three axes of movement at a sampling rate of 100 Hz<sup>169</sup>. Acceleration was recorded in units of gravity 'g', with 1 g equal to 9.8 m/s<sup>2</sup>, natural acceleration under gravity.

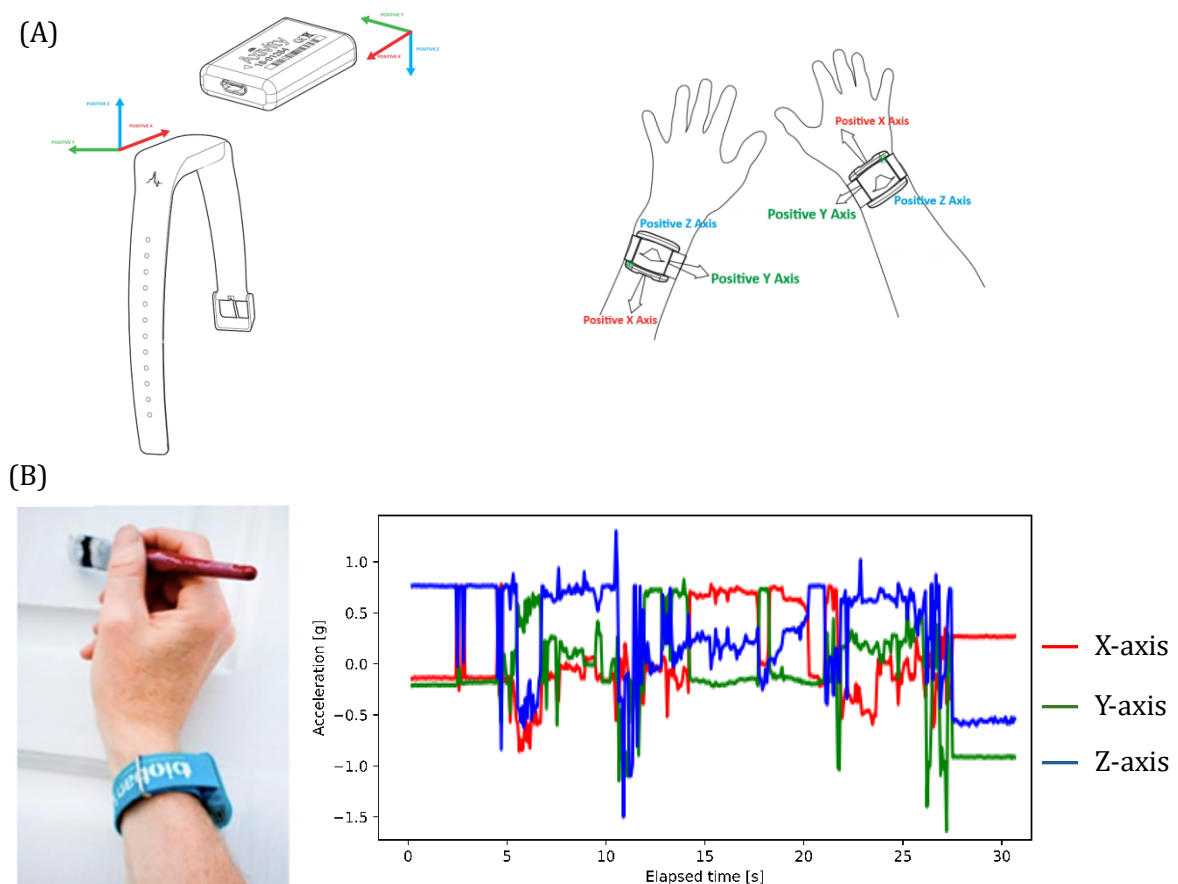


**Figure 3.5 Accelerometer used in the UK Biobank: (a) device orientation (b) sample device wear, with example accelerometer trace elapsed over 30 seconds** The images are taken from Doherty et al.<sup>169</sup> and *Axivity AX3 Technical User Guide*<sup>226</sup>.

### **3.4.3 Data preparation**

#### **3.4.3.1 Participant data**

Tabular participant data was once again obtained from the initial UKB health assessment and health record linkage, as discussed in section 3.3.3. Variables of interest were selected to be compatible with QRISK3<sup>51</sup>, SCORE2<sup>58</sup> and AHA<sup>227</sup> risk calculators, currently adopted for primary prevention of CVD in the UK, Europe and the USA respectively. Each variable was mapped to available data in the UKB assessment centre results, HES reported by the NHS information centre and central register Scotland, for participants from England, Wales, and Scotland, respectively and death registry data. The definition of each risk factor, along with relevant UKB field IDs and International Classification of Diseases codes, Ninth and Tenth revisions (ICD 9/10), are reported in Supplementary Table 3.

Missing data was assumed to be missing at random and was imputed using multiple chained equations (MICE)<sup>228</sup>. Data with entries marked 'Prefer Not to Answer' and 'Do Not Know' were also removed from the study population. Continuous variables were standardised using z-score normalisation, whilst multiclass categorical variables were one hot encoded, creating a single binary variable for each sub-category. Due to the heavy class imbalance among ethnicities (Table 3.1), ethnicity was divided into white/non-white. Smoking was factorised into three categories (never, previous, current).

Further details including variable selection and exclusion criteria are provided in chapters 6-7.

### 3.4.3.2 Accelerometer data

Accelerometer data was processed according to established pipelines outlined in Walmsley et al.<sup>229</sup>, using the biobankAccelerometerAnalysis python package(<https://github.com/OxWearables/biobankAccelerometerAnalysis>), an open-source software package designed to process Activity Ax3 data at scale. Pre-processing of raw accelerometer consisted of a number of steps: (1) Parsing: data was converted from compressed binary format to plain text via a deserializer; (2) Calibration: Raw signals were resampled to a sampling frequency of 100Hz and calibrated to local gravity based on stationary periods;(3)Filtering: Machine noise was removed using a low pass filter with a frequency of 20Hz; (4)Quality control: Checks for poor calibration, insufficient wear time and extreme values. In line with the original UK Biobank accelerometer protocol, non-wear time was defined as  $\geq 60$  minutes of stationary data with a standard deviation  $< 13$  mg across all three axes. Non-wear segments were imputed at one-minute resolution using time-of-day averages from the participant's other valid days<sup>169</sup>. Using intraclass correlation coefficients in 29,765 participants with complete 7-day wear, Doherty et al. showed that  $\geq 72$  hours (3 days) of valid wear are required for average acceleration to be within 10% of the stable seven-day measure. On this basis, participants with  $< 72$  hours of wear or without full 24-hour coverage were therefore excluded to ensure adequate capture of habitual activity<sup>169</sup>.

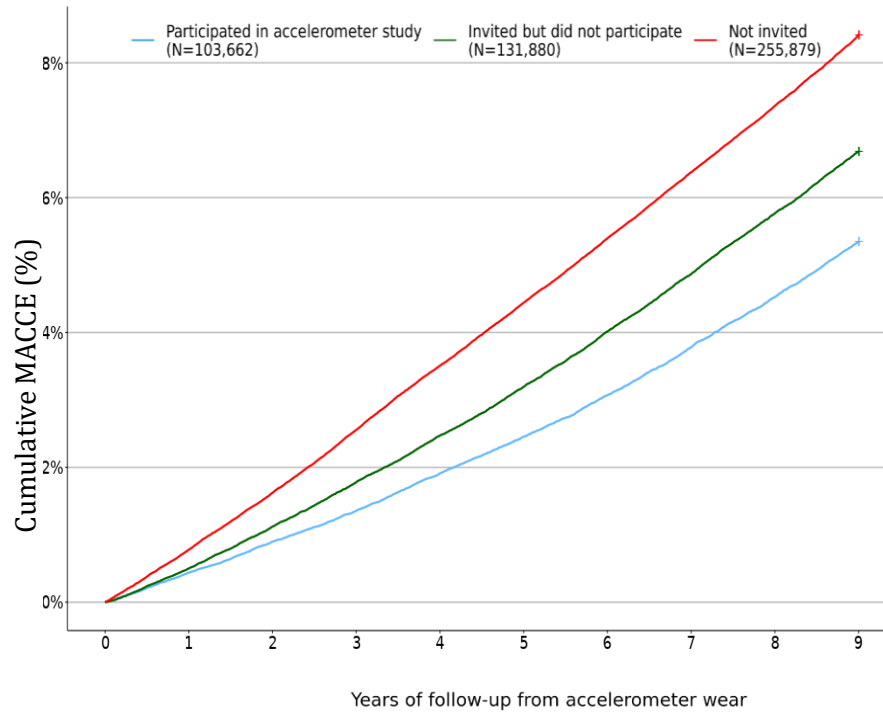
Activity AX3 devices have been demonstrated to provide valid and robust estimates of physical activity in large free-living cohorts. White et al. showed strong agreement between AX3-derived activity energy expenditure and doubly labelled water measurements (RMSE  $\approx 12$  kJ $\cdot$ day<sup>-1</sup> $\cdot$ kg<sup>-1</sup>;  $r \approx 0.71$ )<sup>230</sup>, Complementary validation by Walmsley et al. mapped wrist acceleration from the AX3 to MET-based intensity categories using wearable-camera ground truth, achieving high accuracy ( $\sim 88\%$ ) and substantial agreement ( $\kappa \approx 0.8$ ) for distinguishing sedentary, light, and moderate-to-vigorous physical activity<sup>171,231</sup>.

Validation studies using free-living wearable-camera-labelled datasets paired with AX3 accelerometer recordings have quantified the accuracy of minute-by-minute behaviour classification across a wide range of everyday activities, including household tasks that predominantly involve upper-limb movement. Models developed using the CAPTURE-24 dataset classify 24-hour movement behaviours in free-living adults with accuracies of approximately 80–88% and substantial agreement (Cohen's  $\kappa \approx 0.74$ – $0.81$ ), with most residual misclassification occurring between sedentary and light-intensity categories<sup>231</sup>. Furthermore, modern step-count algorithms and activity-intensity models trained on wearable-camera-annotated datasets markedly reduce the influence of non-ambulatory arm movements on both step estimates and intensity classification in free-living conditions<sup>232</sup>.

#### **3.4.4 Cohort description**

Participants who consented to wear an accelerometer were not representative of the wider UKB population. Participants undergoing physical activity monitoring had a lower incidence of all-cause mortality, cardiovascular disease and numerous other comorbidities (Figure 3.6, Table 3.1). Participants were more likely to be white, female, less socioeconomically deprived and had lower consumption of tobacco and alcohol (Table 3.1). While this may partially be explained by survivorship bias, further selection bias was observed in those who were invited and those who consented to participate in physical activity monitoring. Figure 3.6 shows the cumulative incidence of all-cause mortality and cardiovascular disease for those who consented to physical activity monitoring, those invited but did not consent and the remainder of the UKB. There is a marked decrease in both mortality and incident CVD for those invited to participate vs the wider UKB population; this is further attenuated for those who consented to participate in the study.

(A)



(B)

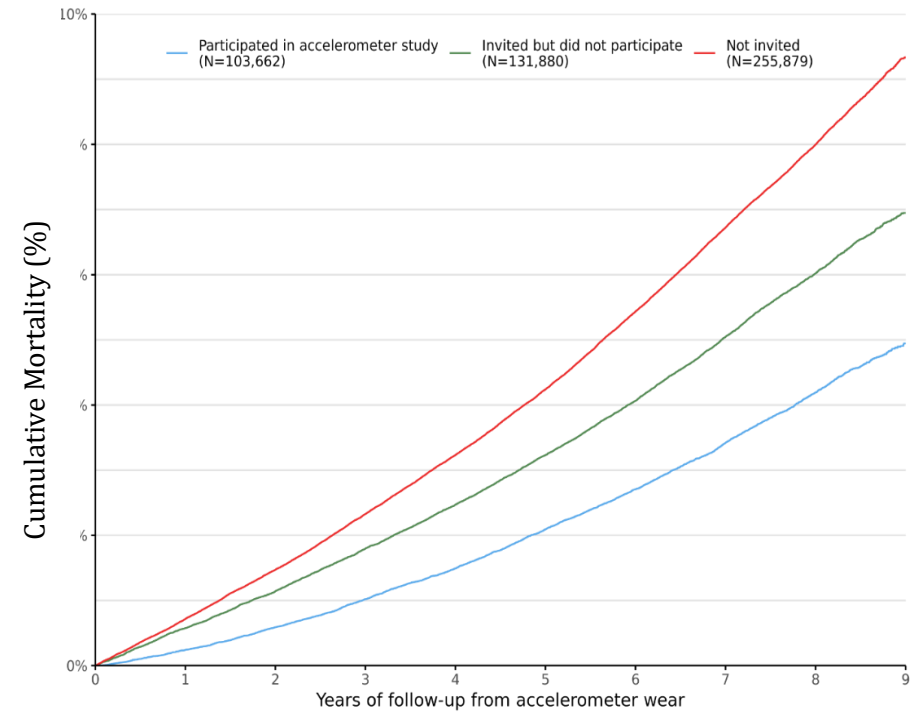


**Figure 3.6: Cumulative incidence of (A) Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) and (B) all-cause mortality, 9 years after initial accelerometer wear time for participants who attended physical activity monitoring, those who were invited but did not attend and the remainder of the UK Biobank population.**

For both MACCE and all-cause mortality, clear signs of healthy volunteer bias were observed for those who were invited to take part in physical activity monitoring, which is further attenuated in those who attended.

It should be noted that the baseline assessment data for this cohort were collected several years before accelerometer wear time (Figure 3.1). To assess the impact of this timing discrepancy, stability of key variables was evaluated in 20,343 participants with repeat measurements recorded 2-7 years after the initial UKB Assessment centre. Categorical variables were assessed using Cohen's kappa (and weighted kappa), while continuous variables were assessed using Pearson's correlation and the Intraclass Correlation Coefficient (ICC). Most measures were highly stable over time (Cohen's kappa > 0.7) (Table 3.2). Alcohol consumption was less stable than most measurements; however, when accounting for the weighted kappa score, most participants only moved a single category. Key biological measures such as LDL-HDL ratio and systolic blood pressure also showed moderate-high correlations over time. Given this stability and the limited number of participants with repeat or primary care data, baseline measurements were used for the main analyses. Sensitivity analysis, substituting UKB assessment data with available primary care data with multiple imputations showed little impact on the results. Detailed information on data preparation, including imputation and sensitivity analysis, is provided in Chapter 6.

### **3.4.5 Data quality**

Of the 103,662 participants who consented to participate in physical activity monitoring, 2,223 were excluded for insufficient wear time, whilst a further 6,166 were excluded due to poor signal quality and extreme average acceleration, defined as acceleration over 100mg. Further details on the processing of accelerometer data are provided in Chapter 6.

Some reactivity to accelerometer wear is possible, whereby participants briefly increase their activity when first wearing the device<sup>233</sup>. However, evidence suggests these changes are modest and typically diminish after one to two days<sup>233,234</sup>. The requirement for seven days of wear and at least 72 hours of valid data, as established in prior work, helps ensure that any short-term reactivity is averaged out and has minimal impact on habitual activity estimates<sup>169</sup>.

Baseline measurements recorded at recruitment were of a high quality in this cohort, with only a limited amount of missing data (Tables 3.1-3.2).



**Table 3.1: Baseline comparison of overall UK Biobank cohort and sub-cohorts who underwent submaximal exercise ECG testing and wearable activity monitoring, respectively.**

| Characteristics            | UK Biobank cohort<br>(N = 502,364) | ECG cohort<br>(N=95,052) | Accelerometer<br>cohort (N<br>=103,660) |
|----------------------------|------------------------------------|--------------------------|-----------------------------------------|
| <b>Demographic</b>         |                                    |                          |                                         |
| Age (years)                | 57.0±8.1                           | 57.5±8.0                 | 56.6±7.8                                |
| Sex(n%)                    |                                    |                          |                                         |
| Female                     | 273,297 (54.4)                     | 51,220 (53.9)            | 45,393 (43.8)                           |
| Male                       | 229,067(45.6)                      | 43,806 (46.1)            | 58,267 (56.2)                           |
| Ethnicity(n%)              |                                    |                          |                                         |
| White                      | 472,000 (94.0)                     | 86,833 (91.4)            | 99,911 (96.4)                           |
| Black                      | 8,058 (1.6)                        | 2,516 (2.6)              | 895 (0.9)                               |
| Asian                      | 11,452 (2.3)                       | 2,978 (3.1)              | 1,276 (1.2)                             |
| Other/Mixed                | 7458 (1.5)                         | 1,971 (2.1)              | 1,137 (1.1)                             |
| Missing                    | 3,396 (0.7)                        | 754 (0.8)                | 441 (0.4)                               |
| <b>Socioeconomic</b>       |                                    |                          |                                         |
| Townsend Deprivation index |                                    |                          |                                         |
| Mean± SD                   | -1.3±3.1                           | -1.2±3.0                 | -1.7±2.8                                |
| Missing                    | 624 (0.1)                          | 104 (0.1)                | 123(0.1)                                |
| Education (n %)            |                                    |                          |                                         |
| School leaver              | 168,530 (33.5)                     | 27,931 (29.4)            | 23,714 (22.9)                           |
| Further education          | 162,602 (32.4)                     | 31,293 (32.9)            | 34,275 (33.1)                           |
| Higher education           | 161,102 (32.1)                     | 34,219 (36.0)            | 44,627 (43.1)                           |
| Missing                    | 10,130 (2.0)                       | 1,609 (1.7)              | 1,404 (1.4)                             |
| <b>Behavioural</b>         |                                    |                          |                                         |
| Smoking status (n %)       |                                    |                          |                                         |
| Non-smoker                 | 273,449 (54.4)                     | 53,065 (55.8)            | 58,951 (56.9)                           |
| Previous Smoker            | 173,006 (34.4)                     | 32,835 (34.6)            | 37,157 (35.8)                           |
| Current smoker             | 52,960 (10.5)                      | 8,548 (9.0)              | 7,275 (7.0)                             |
| Missing                    | 2,949 (0.6)                        | 604 (0.6)                | 277 (0.3)                               |
| Alcohol consumption (n %)  |                                    |                          |                                         |
| Never                      | 40,623(8.1)                        | 7,550 (7.9)              | 5,868 (5.7)                             |
| Special occasions          | 57,989 (11.5)                      | 11,318 (11.9)            | 9,789 (9.4)                             |
| 1-3 times per month        | 55,836 (11.1)                      | 10,581 (11.1)            | 11,236 (10.8)                           |
| 1-2 times per week         | 129,257(25.7)                      | 23,606 (24.8)            | 25,980 (25.1)                           |
| 3-4 times per week         | 115,413 (23.0)                     | 21,984 (23.1)            | 26,943 (26.0)                           |
| Daily                      | 101,745 (20.3)                     | 19,682 (20.7)            | 23,757 (22.9)                           |
| Missing                    | 1,501 (0.3)                        | 331 (0.3)                | 87 (0.1)                                |
| <b>Biological</b>          |                                    |                          |                                         |
| BMI (kg.m <sup>2</sup> )   |                                    |                          |                                         |
| Mean± SD                   | 27.4±4.8                           | 27.3±4.8                 | 26.7±4.5                                |
| Missing                    | 3105 (0.6)                         | 315 (0.3)                | 243 (0.2)                               |
| LDL-C to HDL-C ratio       |                                    |                          |                                         |
| Mean± SD                   | 4.1±1.1                            | 4.0±1.1                  | 4.0±1.1                                 |
| Missing                    | 72,687 (14.5)                      | 12,191 (12.8)            | 14,329 (13.8)                           |

|                                 |                |               |               |
|---------------------------------|----------------|---------------|---------------|
| Systolic blood pressure (mmHg)  |                |               |               |
| Mean± SD                        | 137.8±18.2     | 137.3±18.2    | 136.5±17.7    |
| Missing                         | 0              | 0 (0.0)       | 0 (0.0)       |
| Comorbidities (n%)              |                |               |               |
| Type 1 Diabetes                 | 2,233 (0.4)    | 400 (0.4)     | 251 (0.2)     |
| Type 2 Diabetes                 | 9427 (1.9)     | 1,795 (1.9)   | 1,101 (1.1)   |
| Treated Hypertension            | 39603 (7.9)    | 7,799 (8.2)   | 5,946 (5.7)   |
| Atrial Fibrillation             | 6385 (1.3)     | 1,133 (1.2)   | 1,036 (1.0)   |
| Erectile dysfunction            | 195 (<0.1)     | 26 (<0.01)    | 21 (<0.01)    |
| Family history of CVD           |                |               |               |
| Corticosteroids treatment       | 20298 (4.0)    | 102 (0.1)     | 3,588.0 (3.5) |
| Migraine                        | 1764 (0.4)     | 321 (0.3)     | 330 (0.3)     |
| Rheumatoid arthritis            | 2598 (0.5)     | 483 (0.5)     | 359 (0.3)     |
| Chronic kidney disease          | 1(<0.1)        | 0 (0.0)       | 0 (0.0)       |
| Antipsychotic treatment         | 355 (0.1)      | 73 (0.1)      | 39 (<0.01)    |
| Severe mental illness           | 1,745 (0.3)    | 302 (0.1)     | 180 (0.2)     |
| Self-reported health            |                |               |               |
| Overall health(n%)              |                |               |               |
| Poor                            | 22,768 (4.5)   | 4049 (4.3)    | 2,684 (2.6)   |
| Fair                            | 105,331(21.0)  | 20,337 (21.4) | 16,399 (15.8) |
| Good                            | 288,947 (57.5) | 55,548 (58.5) | 61,885 (59.7) |
| Excellent                       | 81,832 (16.3)  | 14,497 (15.3) | 22,440 (21.6) |
| Missing                         | 3,486 (0.7)    |               |               |
| Treatments and medications(n%)  |                |               |               |
| Blood pressure medication       | 50,540 (10.1)  | 9,232 (9.7)   | 8,969 (8.7)   |
| Cholesterol lowering medication | 86,874 (17.3)  | 17,207 (18.1) | 14,523 (15.3) |

*Participant characteristics were recorded during their initial baseline assessment following the initial recruitment.*

*26,295 (5.2%) participants contributed data to both the ECG and accelerometer sub-cohorts.*

**Table 3.2: Stability measurements of selected UK Biobank variables between the initial baseline assessment after recruitment and the first repeat assessment (2-7 years later)**

| Characteristics                | Participants with repeat | Cohen's kappa       | Weighted kappa                           |
|--------------------------------|--------------------------|---------------------|------------------------------------------|
| Ethnicity                      | 20,221                   | 0.91 (0.89 – 0.93)  | 0.97 (0.97 – 0.98)                       |
| BMI (kg.m <sup>2</sup> )       | 20,257                   | 0.72 (0.71 – 0.73)  | 0.83 (0.82 – 0.84)                       |
| Smoking status                 | 20,243                   | 0.87 (0.86 – 0.88)  | 0.90 (0.90 – 0.91)                       |
| Alcohol consumption            | 20,320                   | 0.52 (0.51 – 0.53)  | 0.83 (0.83 – 0.84)                       |
| Education                      | 19,736                   | 0.83 (0.83 – 0.84)  | 0.90 (0.90 – 0.91)                       |
| Continuous measurements        |                          | Pearson Correlation | Intraclass Correlation Coefficient (ICC) |
| LDL-C to HDL-C ratio           | 4,180                    | 0.74 (0.73 – 0.74)  | 0.74 (0.73 – 0.74)                       |
| Systolic blood pressure (mmHg) | 6,213                    | 0.63 (0.62 – 0.63)  | 0.63 (0.62 -0.63)                        |

## Chapter 4 – Electrocardiogram measurements and the 10-year risk of Major Adverse Cardiovascular/Cerebrovascular Events

### 4.1 Introduction

#### 4.1.1 Background

Early identification of individuals at elevated cardiovascular disease (CVD) risk is crucial for effective primary prevention. To this end, current international guidelines recommend the use of cardiovascular risk scores, such as QRISK3, to identify those who would most benefit from preventative interventions<sup>26,235</sup>. Whilst well validated for clinical use on large populations, traditional risk scores have substantial limitations, including poor generalisability, an over-reliance on non-modifiable factors such as age and sex, and misclassification of individuals, particularly in younger and underrepresented populations<sup>236,237</sup> (see Chapter 1). Many high-risk individuals remain undetected, prompting calls from the National Institute for Health and Care Excellence (NICE) and the American Heart Association (AHA) to identify new risk factors that can simplify and enhance existing clinical risk scores<sup>42,95</sup>.

In this context, the electrocardiogram (ECG) has emerged as a promising candidate to enhance cardiovascular risk prediction. By capturing real-time, patient-specific information on myocardial structure, perfusion and electrical activity, the ECG can provide valuable insights into the impact of clinical and subclinical risk factors on the heart. Current evidence suggests strong associations between various ECG parameters and incident CVD, independent of traditional risk factors (see Chapter 2)<sup>70,95,119,120</sup>. The widespread adoption of the ECG in primary care, combined with its low cost and non-invasive nature, makes it a promising candidate for integration with routine CVD risk assessment. However, while the ECG is widely used to diagnose conditions such as arrhythmia and ischemia, its potential to contribute additional predictive value to established risk scores for Major adverse Cardiovascular & Cerebrovascular events (MACCE) is currently unclear.

Prior research has shown promising results regarding the prognostic value of ECG for predicting incident CVD.

However, significant uncertainties remain as to the strength of this evidence, owing to limited sample sizes, short follow-up durations, and a lack of integration with existing clinical risk scores<sup>95</sup> (see Chapter 2). These challenges are particularly pronounced for exercise ECGs, where safety and ethical concerns further restrict sample sizes. While evidence suggests that ECG measurements can enhance CVD risk scores beyond traditional factors, it is unclear whether this leads to meaningful improvements in identifying high-risk individuals under current clinical guidelines. Additionally, there is a critical need to assess the ECG's utility in clinically relevant populations for primary prevention. Most studies have focused on individuals already at moderate to high risk or those with specific comorbidities, leaving significant gaps in understanding its prognostic value for asymptomatic individuals eligible for routine CVD risk assessment.

Another key research need is the assessment of the ECG's potential to simplify existing clinical risk scores, with the goal of reducing overfitting and improving ease of use. Current risk scores remain overcomplicated and often fail to generalize well beyond the populations in which they were developed. This limitation is emphasized in earlier guidance from NICE, which calls for research to compare the effectiveness of simpler models—using only age and routinely available risk factors—against current multivariable models<sup>26</sup>. Although it is unclear whether this remains an active priority in current NICE guidance, the underlying motivation remains relevant: given its low cost and near-universal availability in clinical practice, the ECG is a plausible candidate to support streamlined, scalable risk assessment. Finally, there remains a significant gap in the literature regarding the validation and clinical applicability of ECG-based risk scores. Many prognostic studies lack proper validation, leading to bias and confounding, further exacerbated by inadequate reporting of model performance. The latest U.S. Preventive Services Task Force (USPSTF) review highlighted that most ECG-based risk scores emphasize model discrimination while neglecting clinically meaningful metrics such as model calibration and risk stratification at clinically relevant thresholds<sup>95</sup>. Addressing these gaps requires comprehensive validation focused on clinical applicability.

#### **4.1.2 Aims**

This chapter outlines the development and validation of three cardiovascular risk scores, derived from resting, exercise and recovery ECG measurements, to predict the 10-year risk of death or hospitalisation due to MACCE in 35,597 UK Biobank participants with no prior history of MACCE. We subsequently assessed the association of ECG risk factors with incident MACCE and their added value to established risk factors from the current adopted UK risk assessment tool, QRISK3<sup>51</sup>. Additionally, this chapter investigated the prognostic value of combining ECG risk factors with one's age and compares this with the performance of the baseline QRISK3-Inspired risk scores, rederived in the study population using Cox proportional hazard models and QRISK3 risk factors.

## **4.2 Methods**

### **4.2.1 UK Biobank Cardio Assessment Study**

This work was conducted using the UK Biobank Prospective cohort dataset, described in Chapter 3. The UK Biobank (UKB) is a large prospective cohort study established between 2006–2010 to research genetic and non-genetic risk factors through longitudinal follow-up of participants. The study recruited 502,636 participants (aged 40-69, 46% male) from the UK general population across 22 assessment centres throughout England, Wales, and Scotland<sup>20</sup>.

Between 2009 and 2013, all newly recruited UKB participants were invited to receive an ECG examination as part of a submaximal Cardiorespiratory fitness assessment. Of the wider UKB cohort, 95,052 participants consented to take part in the Cardio Assessment sub-study conducted. ECG recordings were obtained using a 4-lead electrocardiograph device (CAMUSB 6.5, Cardiosoft v6.51, sampling frequency 500Hz) at rest (15 s) during a graded submaximal cycle ergometry test (6 min; eBike, Firmware) followed by a recovery period (1 min).

Following an initial health assessment, participants were stratified into different cardiovascular risk categories according to multiple factors. The choice of workload was derived from the participant's age, sex, weight, height, and resting heart rate<sup>205</sup>. Participants who were able to exercise were categorised to perform a test at either 35% or 50% of the maximum predicted workload depending on their risk profile. Further details, including maximum workload estimation, are provided in Supplementary Tables 4-8. Participants not selected for exercise or with incomplete, corrupted, or missing ECG data, including those who reached their maximum heart rate and therefore terminated the test early, were excluded from the study (Figure 4.1).

## **4.2.2 Data processing**

### **4.2.2.1 Ascertainment of risk factors and study endpoint**

Clinical risk factors were selected to match those included in the QRISK3 risk calculator<sup>51</sup> (Supplementary Table 3), currently deployed in primary care by the UK's National Health Service (NHS). Each covariate was mapped to available data in the UKB assessment centre results and hospital episode statistics (HES), reported by the NHS information centre and Central Register Scotland, for participants from England, Wales, and Scotland, respectively. The definition of each risk factor, along with relevant UKB field IDs and International Classification of Diseases codes, Ninth and Tenth revisions (ICD 9/10), are reported in Supplementary Table 3.

The primary outcome of interest is the 10-year risk of incident MACCE, defined as the earliest recorded episode of hospitalisation or death due to coronary heart disease, heart failure, ischaemic stroke, or transient ischaemic attack. The follow-up period was determined by the first appearance of ICD10 or ICD9 codes in either HES or death registration data. Participants who did not experience an event were censored at the time of death or the end of the follow-up period. A full definition of MACCE is presented in Supplementary Tables 1-2.

All participants with known MACCE, in addition to those receiving calcium channel blockers or antiarrhythmic medications (Supplementary Table 9) prior to the submaximal exercise ECG test, were excluded from this study.

Follow-up time was calculated for each participant as the number of years from the initial ECG scan until the earliest date of either (i) first recorded MACCE, (ii) death not caused by CVD or (iii) the most recent publication of NHS HES for England: 31st October 2022; Scotland: 31<sup>st</sup> August 2022; and Wales 5<sup>th</sup> May 2022.

Continuous variables were standardised using z-score normalisation, whilst multiclass categorical variables were one hot encoded, creating a single binary variable for each sub-category.

Descriptive statistics were reported as mean  $\pm$  standard deviation for continuous risk factors and percentages for categorical variables. Due to the heavy class imbalance among ethnicities (Table 4.1), ethnicity was divided into white/non-white. Smoking was factorised into three categories (never, previous, current).

Missing risk factors were assumed to be missing at random, and a complete case analysis was performed for covariates with under 1% of missing values. For any covariate with >1% missing values, single imputation was performed using Bayesian Ridge <sup>219</sup>, which models each incomplete covariate as a linear combination of the remaining covariates with Gaussian priors on the regression coefficients, providing shrinkage to reduce overfitting. The imputation model was fitted in the training data set within each cross-validation fold and then applied to the corresponding test set.

#### **4.2.2.2 Electrocardiogram phenotypes from submaximal exercise tests**

ECG analysis follows the framework established by Sörnmo et al. in 2005, which serves as a general-purpose guide for ECG signal processing<sup>220</sup>. ECGs were first processed to identify and exclude corrupted recordings and remove noise following established pipelines previously described by Zheng et al. 2020<sup>221</sup>. Subsequent feature extraction was divided into measurements of ECG morphology via QRS detection and wave delineation, followed by ECG rhythm.

#### **ECG Pre-processing**

Common causes of ECG data contamination include power line interference, electrode contact noise, motion artefacts, muscle contraction, baseline wandering, and high-frequency noise<sup>220</sup>. Several pre-processing steps were applied prior to feature extraction and risk analysis to reduce subsequent confounding resulting from noisy ECGs (see section 3.3.2.2). The steps to pre-process the ECG are as follows (Figure 4.1). ECG time series are decomposed into trend and the baseline ECG signal. The long-term trend was captured using a cumulative moving average and subsequently removed from the ECG signal.



This decomposition isolates the short-term fluctuations that may indicate noise spikes or physiological abnormalities, improving outlier detection. Outliers are removed via *Winsorisation*, with a maximum amplitude threshold set to 1000mV. This threshold ensures that any extreme values beyond this limit are capped, thereby reducing the influence of outliers on subsequent analyses. Once the outlier removal is complete, the trend component is reinserted into the time series to reconstruct the original ECG signal.

A band-pass Butterworth filter, with a frequency range of 0.5 to 50 Hz, was applied to remove baseline wandering and high-frequency noise. While the typical frequency range of an ECG signal is 0.5 to 50 Hz, it is often sampled at a higher frequency to capture all relevant clinical detail<sup>221,238,239</sup>; in this case, a sampling frequency of 500 Hz was used. As such, an upper cutoff frequency of 50Hz was selected to remove this high-frequency noise and powerline interference, while preserving essential clinical information.

The lower cutoff of 0.5Hz was selected based on the recommendations from the American Heart Association (AHA) and later work by Madeiro et al., who proposed that the lowest frequency component should approximately match a heart rate of 40 beats per minute<sup>239,240</sup>. Following this, a local polynomial regression smoother (LOESS)<sup>104</sup> is applied to further reduce low-frequency noise and baseline wandering.

Following signal pre-processing, quality control checks were applied to identify and exclude corrupted ECG signals, including those with incomplete or missing data and ECG measurements with fewer than five recorded heartbeats during rest, 300 during exercise, or 20 during recovery. ECGs with a signal-to-noise ratio (SNR) below 0 dB or baseline interference were also excluded to avoid confounding due to ECG artefacts. Heartbeats were detected via a QRS detection algorithm outlined by used by Duijvenboden et al.<sup>241</sup>.

The SNR was defined as the ratio between the standard deviation of the median amplitude across all heartbeats (signal component) and the median amplitude across all heartbeats (noise component), measured per 5 heartbeats at rest and 20 during exercise.

Baseline interference was assessed using a Fast Fourier Transform (FFT) to isolate low-frequency components. ECGs were excluded if the maximum baseline wander amplitude exceeded 1.5 mV, if the ratio of baseline wander amplitude to median QRS amplitude exceeded 3:1 or the QRS amplitude fell below a minimum threshold of 250<sub>uV</sub>, indicating poor electrode contact.

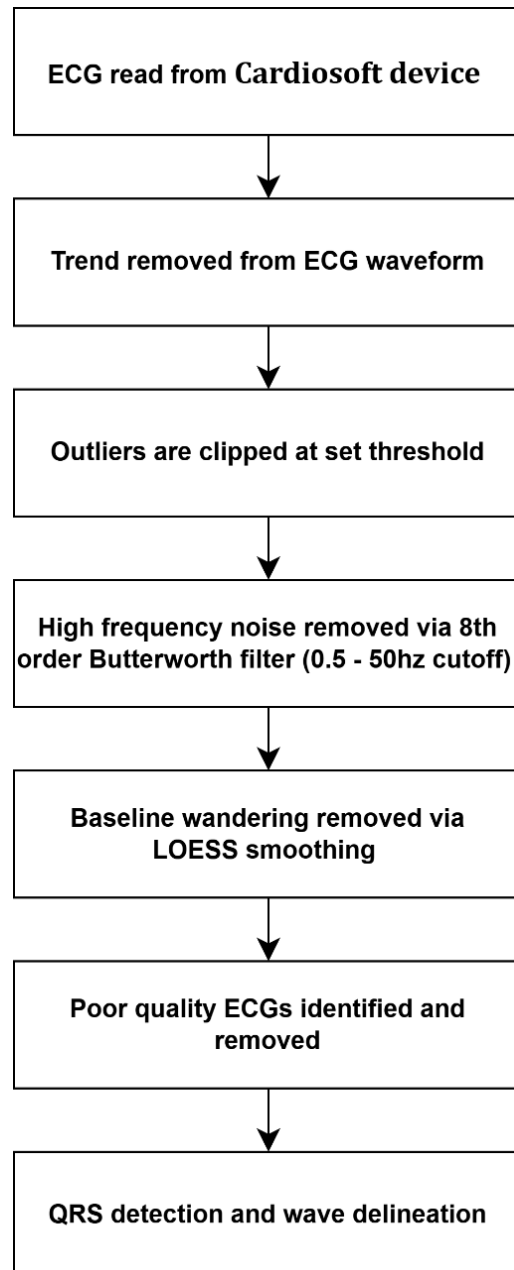


**Figure 4.1: Processing of raw ECG data for feature extraction**

### **QRS detection and wave delineation**

To obtain measurements of ECG morphology and rhythm, I first implement QRS detection and wave delineation using two 1-d convolutional neural networks (CNN), developed by Stefan van Duijvenboden et al., 2023.<sup>132</sup>. The model had previously been trained on lead 1 of the UK Biobank cardio assessment sub-study to detect premature ventricular contractions (PVCs) and returned the probability that a given ECG segment was: (i) normal QRS complex, (ii) PVC or (iii) neither. Once QRS complexes are identified, an extended window is defined to include the P-wave, QRS complex, and T-wave. A second CNN is then used to delineate the onset and offset of each wave, identifying the P, Q, R, S, and T points.

### **ECG feature extraction**

Using labelled PQRST complexes, a range of ECG morphology and rhythm features are extracted from three distinct periods of the submaximal exercise test: the first 15 seconds of rest, the final 15 seconds of exercise at peak intensity, and the last 15 seconds of recovery (Figure 4.2). The 15-second time window was selected to match the duration of the initial resting ECG phase. In each 15-second window, 12 features were extracted. The extracted ECG parameters were selected based on previously reported associations with CVD incidence/mortality<sup>70,119</sup> and common risk factors such as atrial fibrillation<sup>242,243</sup>. Candidate morphological features included PR, QRS, QTc and RR interval durations measured from the positions of the P, Q, R, S and T waves returned from the 1-d CNN. QT intervals were adjusted using Bazett's formula for resting ECG<sup>244</sup> and Fridericia's<sup>245</sup> for exercise and recovery ECG measurements.

Rhythm features were selected based on Lake and Moorman et al. 2011<sup>242</sup> and Sarkar et al. 2008<sup>243</sup>. We extracted eight established features with prior links to CVD, starting with the number of premature ventricular contractions (PVC)<sup>132</sup> and coefficient sample entropy (CosEn), which measures the degree of beat-to-beat variability<sup>242</sup> across the ECG.

The remaining features are derived from the Poincare representation of the RR interval over time (Supplementary Figure 2) and consist of (i) irregularity evidence, (ii) regulatory evidence, (iii) density evidence, (iv) anisotropy evidence, and (v) AF evidence. A full description of the candidate features is provided in Appendix Section A p.337 and Supplementary Figure 2

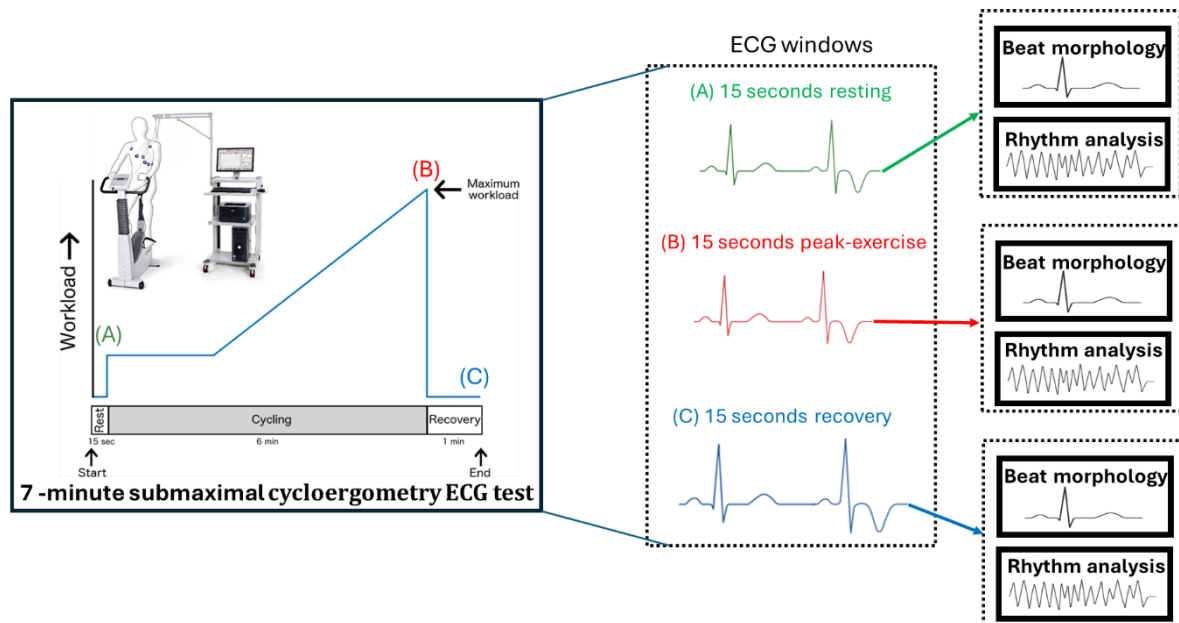


**Figure 4.2: Extraction of 15-second ECG windows during (A) Rest, (B) Peak Exercise, and (C) Recovery following a submaximal Cycle Ergometry ECG test and subsequent Morphology and rhythm Feature Analysis.**

#### 4.2.3 Risk prediction of incident cardiovascular disease

Cox proportional hazard models were used to estimate the 10-year risk of incident MACCE in males and females separately. Following the protocol established in QRISK3<sup>51</sup> regression coefficients for each risk factor were used as weights and combined with the baseline survival function evaluated up to 12.5 years (end of the follow-up period), to derive risk equations over the entire follow-up duration. As a result, a separate risk estimate could be provided for each year of follow-up, with a specific focus on 10-year risk estimates following current guidelines from the National Institute of Health Care Excellence (NICE). The baseline survivor function was calculated using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0.

Clinical risk factors were selected from QRISK3<sup>51</sup> (Supplementary Table 3) as the baseline risk score for model comparison due to its robust validation in the UK population and recommended use in clinical guidelines<sup>26</sup>. Due to documented miscalibration of QRISK3 in the UK Biobank<sup>246</sup>, the original model coefficients provided in QRISK3 were re-estimated in the study population using Cox proportional hazard models<sup>247</sup> to produce a QRISK3-Inspired risk score. Due to a lack of sufficient data on the type of CVD and the age of diagnosis for participants' family members, family history of CVD was removed from the model.

Likewise, due to lack of statistical power and collinearity issues during model fitting, diagnosis of atrial fibrillation, renal failure, lupus and antipsychotic medication was also removed from the model. ECG risk models were developed using statistically significant ECG risk factors identified from each stage of the ECG test (resting, exercise, and recovery). The final model coefficients and baseline survival are presented in Supplementary Section C Tables 1C-2C (Appendix p.475).

#### **4.2.4 Model validation**

Performance was evaluated using a stratified five-fold cross-validation approach. In this method, data are partitioned into separate folds such that each fold maintains a similar distribution of key characteristics (e.g. follow-up times or event labels) to ensure balanced representation for more reliable performance evaluation. In this study, participants were grouped into discrete bins based on two-year follow-up intervals (e.g. 0-2 years, 2-4 years, up to 10 years and beyond), ensuring that each fold contained a comparable distribution of survival times and incident MACCE. This is particularly important in Cox proportional hazards models, where differences in risk set compositions can lead to substantial variation in the estimated effects of covariates across folds. Ensuring an even distribution of incident MACCE and time-to-event was crucial for maintaining consistency in hazard ratio estimates across folds by minimizing variations in risk set compositions. During each cross-validation iteration, one-fold was set aside for model evaluation, while the remaining four folds were combined for model training.

Following the methodology outlined by Steinfeldt et al.<sup>83</sup>, model performance was evaluated on a combined test set containing all individuals from each cross-validation iteration. The final performance metrics were then bootstrapped over 1,000 iterations to obtain empirical 95% confidence intervals, providing robust estimates of model stability and generalisability.

The strength of the associations between candidate ECG risk factors and the 10-year incidence of MACCE was evaluated using multivariable-adjusted Cox proportional hazard analysis, minimally adjusted for key variables known to be strongly associated with ECG physiology and cardiovascular disease including age<sup>248–250</sup>, sex<sup>251–253</sup>, smoking status<sup>254</sup>, ethnicity<sup>255,256</sup>, and deprivation, measured by Townsend's deprivation index<sup>257–259</sup>. These variables were selected based on prior literature, epidemiological theory, and their hypothesised roles as upstream determinants of cardiovascular risk. Formal test of causal pathways (for example, using directed acyclic graphs or mediation analyses) was not carried out in this analysis.<sup>257</sup>

Statistical testing was conducted using a chi-squared test with a significance threshold of 0.05, following adjustment for multiple testing ( $n = 15$ ) using the Benjamini/Hochberg procedure<sup>260</sup>. A complete case analysis was conducted, removing any individual with missing PR, RR, QRS or QTc interval.

Model performance was assessed following the criteria outlined in Section 2.2. Evaluation metrics for discrimination and calibration included Harrell's C-index<sup>99</sup> and the integrated calibration index (ICI)<sup>101</sup>.

To compare ECG risk scores with the baseline QRISK3-Inspired models, participants were stratified into two risk categories based on the NICE recommended 10% risk threshold for MACCE over 10 years<sup>26</sup>. The reclassification of participants into the appropriate risk groups was assessed using the categorical and continuous net reclassification index (NRI)<sup>105</sup> in addition to the standardised net benefit (NB)<sup>106</sup>.

To assess the performance of both QRISK3-Inspired and QRISK3-Inspired + ECG risk scores across age groups, metrics were recalculated for participant subgroups in 5-year age intervals.

Separate models were developed for males and females, in line with the original QRISK3 calculator. p-values and z-statistics were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

This study was reported per the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD)<sup>88</sup> guidelines. The complete TRIPOD checklist for this chapter is provided in Supplementary Material Section D p.543.

## **4.3 Results**

### **4.3.1 Study population**

Of the 95,052 participants who completed a submaximal exercise ECG test, 44,421 (46.7%) had ECG recordings of sufficient quality for further analysis markers and at least ten years of follow-up. A further 5,479 ECGs were excluded because, despite meeting initial quality criteria, the previously published delineation could not reliably identify QRS complexes or derive measurable ECG intervals. Following exclusions outlined in Figure 4.3, 35,597 individuals without a history of CVD and complete covariate data, and measurable ECG morphology were included in the study. The study population consisted of a balanced set of middle-aged males and females (median age: 58.0 male; 50.3 Female). After a median follow-up period of 12.49 years (IQR: 0.26), 3,463(9.7%) individuals were diagnosed with MACCE (2,892 non-fatal and 571 fatal). The baseline characteristics of the study participants are described in Table 4.1, including demographic, lifestyle, resting ECG, and QRISK3 risk factors. Summary statistics for exercise and recovery ECG parameters are available in Supplementary Tables 10-11.



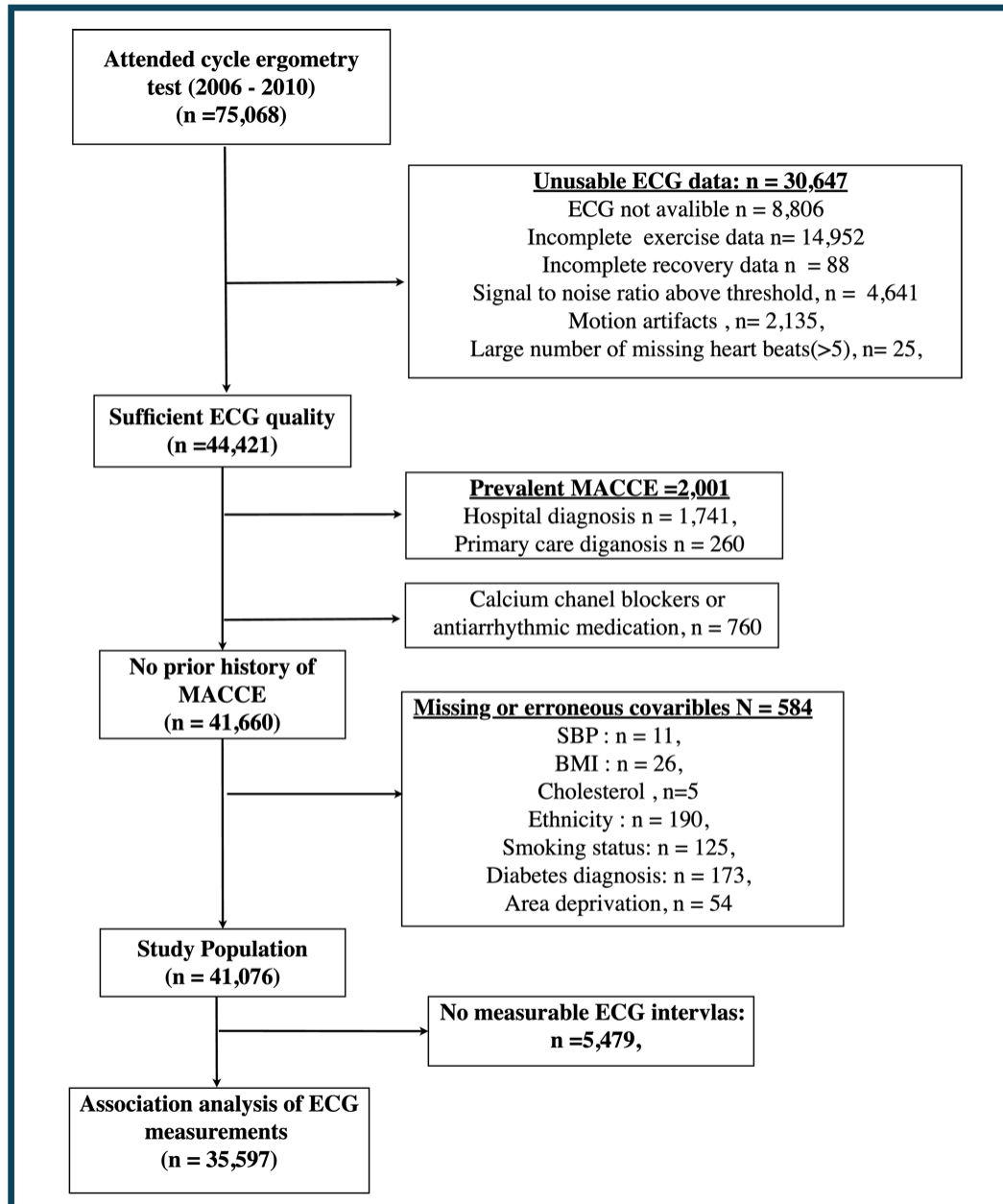


**Figure 4.3: Characteristics of study population: (A) Flowchart illustrating the number of participants included, along with any exclusion criteria and derivation of development/validation sets for MACCE.**

Following the initial exclusion of ECGs with missing data and insufficient signal-to-noise-ratio, A further 5,479 ECGs were excluded because, despite meeting initial quality criteria, our delineation tool could not reliably identify QRS complexes or derive measurable ECG intervals.

**Table 4.1: Baseline characteristics and ECG parameters of 35,597 UK Biobank participants without a history of MACCE who underwent a submaximal cycle ergometry test.**

| Characteristics                | Male (N=17,376) | Female (N = 18,221) |
|--------------------------------|-----------------|---------------------|
| Age (years)                    | 57.1±8.2        | 57.0±7.9            |
| BMI (kg.m <sup>2</sup> )       | 27.8±3.8        | 27.2±4.7            |
| LDL-C to HDL-C ratio           | 4.5±1.1         | 4.0±1.1             |
| Systolic blood pressure (mmHg) | 139.8±15.8      | 134.7±17.8          |
| Townsend Deprivation index     | -1.3±2.9        | -1.3±2.8            |
| Ethnicity                      |                 |                     |
| White ethnicity (n, %)         | 16,851 (92.5)   | 16,224 (93.4)       |
| Non-White ethnicity (n, %)     | 1,370 (7.5)     | 1,152 (6.6)         |
| Smoking status                 |                 |                     |
| Non-smoker (n, %)              | 9,391 (51.4)    | 10,356 (59.6)       |
| Previous Smoker (n, %)         | 6,936 (38.1)    | 5,785 (33.2)        |
| Current smoker (n, %)          | 1,894 (10.4)    | 1,235 (7.1)         |
| Type 1 Diabetes (n, %)         | 51 (0.3)        | 28 (0.2)            |
| Type 2 Diabetes (n, %)         | 235 (1.3)       | 107 (0.6)           |
| Treated Hypertension (n, %)    | 1,031(5.6)      | 786(4.5)            |
| Atrial Fibrillation (n, %)     | 118(0.6)        | 49(0.3)             |
| <b>Resting ECG parameters:</b> |                 |                     |
| PR interval(ms)                | 159.3±21.4      | 153.6±19.2          |
| QRS interval(ms)               | 93.8±11.2       | 92.1±10.4           |
| Qtc interval(ms)               | 415.0±20.9      | 425.6±19.8          |
| RR interval: (ms)              | 883.4±146.0     | 865.8±125.6         |
| Total PVC count                | 0.1±0.5         | >0.1±0.3            |
| CosEn                          | -2.5±0.5        | -2.5±0.5            |
| Irregularity evidence          | 0.8±2.0         | 0.9±1.9             |
| Regularity evidence            | 2.0±1.5         | 2.1±1.5             |
| Density evidence               | 0.1±0.4         | 0.1±0.4             |
| Anisotropy evidence            | 0.3±1.1         | 0.3±1.0             |
| Atrial fibrillation evidence   | -6.0±6.5        | -5.3±6.2            |
| Atrial tachycardia evidence    | 3.1±3.1         | 3.2±2.9             |

Abbreviations: BMI: Body mass index, LDL: Low-density lipoprotein; HDL: High-density lipoprotein, PVC: Premature ventricular contraction, CosEn: Cosine entropy

Data are shown as means±SD for continuous data and me total (%) for categorical data.

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of ΔRR-intervals across pre-defined bins from a Poincare representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns. Premature ventricular contraction (PVC) count: The number of PVCs detected within the 15-second resting ECG recording.

COSEn (Coefficient of sample entropy): Measure of the beat-to-beat RR interval variability obtained by modelling the probability that the RR interval of a short ECG segment will match other segments in the signal<sup>242</sup>.

Irregularity evidence: Number of irregular heartbeats defined as beats outside normal sinus rhythm<sup>243</sup>.

Regularity evidence: Count of the total number of 3-beat windows, with a median RR interval differing no more than 10ms from the average RR interval.<sup>243</sup>

Density evidence: Measures how closely packed the clusters of changes in RR intervals are in a Poincare representation across each segment by subtracting the number of points in a segment by the number of clusters. Lower-density evidence corresponds with greater sparsity in a given segment.

Anisotropy evidence: Measures of the overall direction of change between RR intervals. Higher anisotropy points to a consistent direction of change and helps to distinguish between different types of arrhythmias<sup>243</sup>.

Atrial fibrillation (AF) evidence: Quantifies the presence of atrial fibrillation by offsetting the number of heartbeats in normal sinus rhythm against irregularities evidence and compensatory pauses (PACE)<sup>243</sup>.

Atrial Tachycardia (AT) evidence: Assesses the presence of irregular heart rhythm, changes in RR intervals, clustering of changes in RR interval (Poincare representation), and the occurrence of compensatory pauses<sup>243</sup>.

Further details on the definition and derivation of ECG parameters are defined in Supplementary Material Section A (appendix p.337-p. 33839).

#### **4.3.2 Association between ECG parameters and MACCE**

This study first investigated the independent association between ECG markers and the 10-year risk of incident MACCE. At 10 years, 1,798 (9.9%) and 793 (4.6%) incident MACCE were reported for males and females, respectively. Figure 4.4 presents the adjusted hazard ratio (HR) per standard deviation for selected ECG morphological and rhythm risk factors (Appendix Section A p.33738-p.33839), measured during the initial 15-seconds of rest, the final 15-seconds of exercise and final of 15 seconds of recovery for males and females, respectively.

During the initial resting stage of the submaximal exercise ECG test, the associations between ECG markers and MACCE risk varied greatly by sex (Figure 4.4). In males, significant predictors included the QRS-interval, QTc interval, irregular changes in the RR interval, regularity of the RR interval, Anisotropy and evidence of atrial tachycardia, which were independently associated with an increased risk of MACCE. However, for females, only the regularity of the RR interval was observed to be significantly associated with MACCE.

During the final 15-seconds of exercise, the associations became more pronounced and diverse, particularly in males. Significant ECG parameters included QRS duration, QTc interval, RR interval, premature ventricular contraction (PVC) count, regularity of the RR interval, and atrial tachycardia. In females, the RR interval, QRS and QTc interval were significantly associated with MACCE. In the recovery period, some associations persisted for both males and females. In males, QRS duration, QTc-interval, and atrial tachycardia remained significantly associated with MACCE, indicating the lasting impact of these markers beyond active exertion. Similarly, in females, QRS duration, QTc interval, regularity of the RR interval, CosEn and atrial fibrillation were robust predictors during recovery, aligning closely with the results observed in males.

Following adjustment for multiple testing Anisotropy Evidence and Irregular RR-intervals during recovery were no longer associated with MACCE for males. For females resting QRS-interval, exercise PR-interval and recovery PR-interval were no longer significant following adjustments for multiple testing.

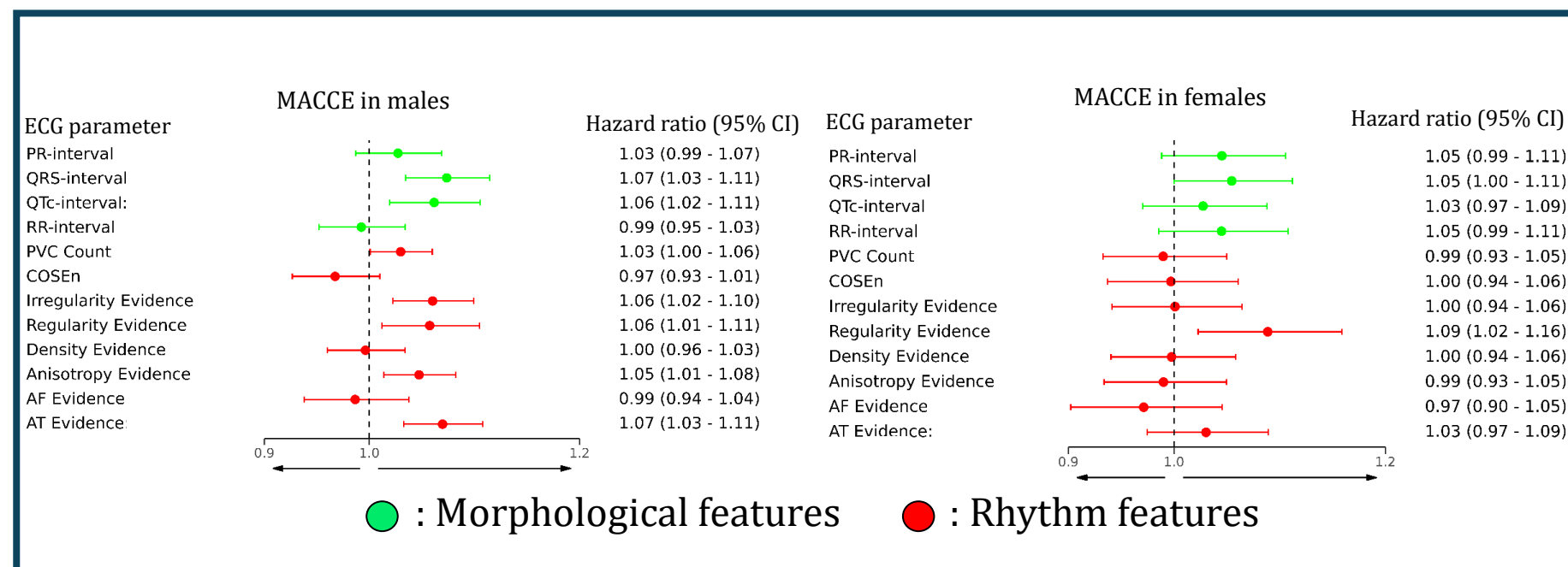
During the first 2 and 5 years of follow-up, 347(1·0%) (males: 260 (1.4%); females: 87(0.5%)) and 1,087(3·1%) (males:770 (4.2%); females: 317(1.8%)) participants were diagnosed with MACCE, respectively. After excluding participants diagnosed with MACCE in the first 2 and 5 years of follow-up, in separate sensitivity analyses, minimal changes in the HR's was observed (Supplementary Tables 12-13).

**Figure 4.4: Association of ECG-derived parameters obtained during (A) 15 seconds of rest; (B) the final 15 seconds of a 6-min period of submaximal exercise, (C) the final 15 seconds of a 1-min recovery period post exercise with the 10-year risk of MACCE.** Each ECG parameter was analysed in a separate Cox model, adjusted for age, smoking status, Townsend deprivation index<sup>257</sup>, and ethnicity<sup>257</sup>, and ethnicity. Irregularity, Pace, Regulatory, Anisotropy and AF evidence were adjusted for the number of beats in the signal to account for higher absolute values in participants with faster heart rates.

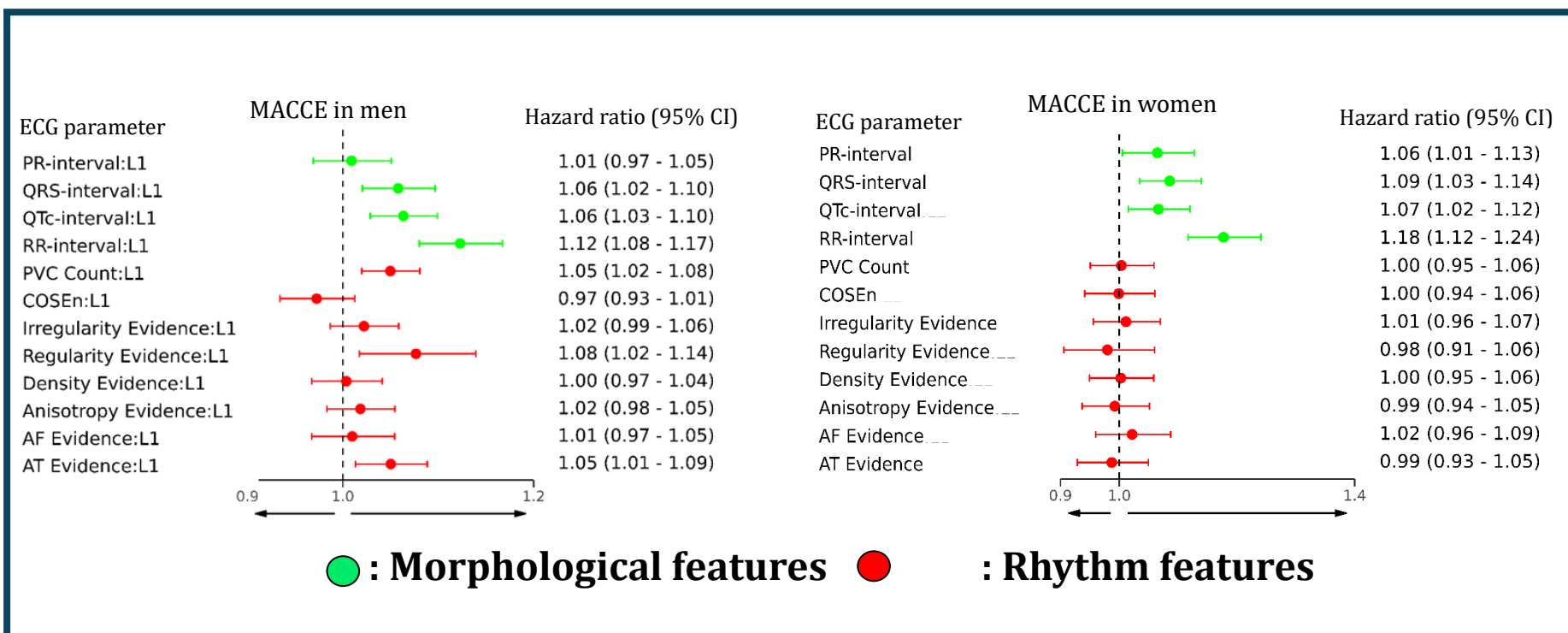
Hazard ratios are reported per standard deviation increase. Cox proportional hazard models were trained using 35,597 UK Biobank participants with measurable ECG parameters, and 2,591 (7.27%) MACCE were observed within 10 years.

The ECG parameters were selected based on previously reported associations with CVD mortality<sup>70,119</sup>, incidence, common risk factors, and other conditions, including chronic kidney disease<sup>120</sup> and atrial fibrillation<sup>242,243</sup>. We also considered rhythm features that have previously demonstrated strong predictive performance for CVD<sup>20,21</sup>.

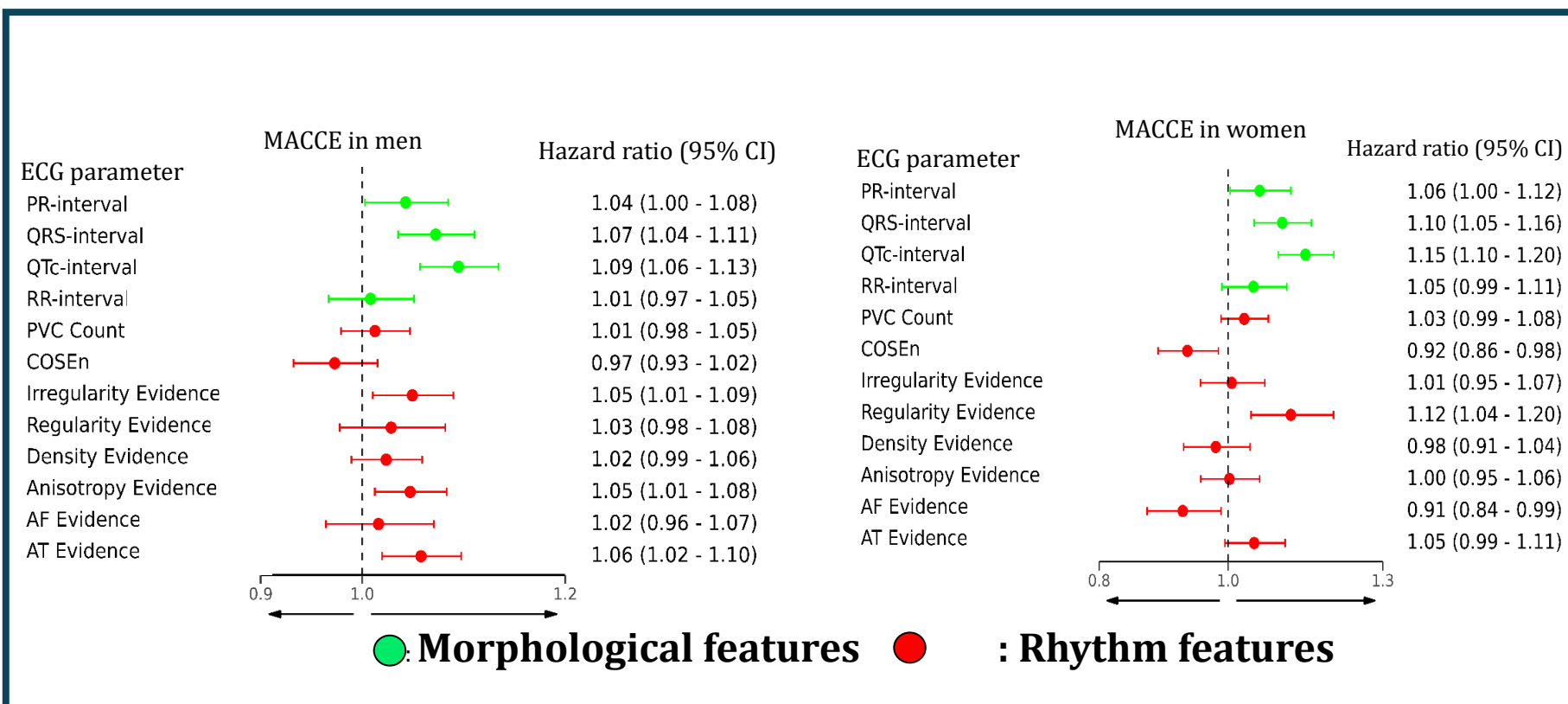
**(A) Resting ECG parameters:** Associations between resting ECG measurements and MACCE were stronger in males than in females, likely owing to the increased number of events observed. At rest, the regularity of the change in RR interval was significantly associated with an increased risk of MACCE for both males and females. For males, a significant positive association was observed between QRS, QTC intervals and evidence of Atrial tachycardia with MACCE. These associations remain much more uncertain for female participants.



**(B) Exercise ECG parameters:** Associations were more pronounced during exercise, with QRS, QTc and RR Intervals significantly associated with incident MACCE for both male and female participants. Similar to rest, no significant markers were found for ECG rhythm in females.



**(C)Recovery ECG parameters:** Associations were similar to those encountered during exercise, with QRS and QTc intervals significantly associated with incident MACCE for both male and female participants. ECG rhythm showed much stronger associations during recovery than rest and exercise, with numerous positive associations for males and females. The regularity of the change in RR interval, in particular, was significant for both male and female participants. Evidence of atrial fibrillation shows a narrow protective association with MACCE for female participants. This is likely due to increased heart rate variability, indicating a healthy recovery from exercise.



### **4.3.3 Predictive value of ECG**

#### **4.3.3.1 Univariate Predictive Performance**

The univariate performance of ECG parameters and QRISK3 risk factors is presented in Supplementary Table 14, while multivariable ECG and QRISK3-Inspired risk scores are shown in Table 4.2. Of the risk factors investigated, age remains the strongest predictor of incident MACCE, for male and female participants, with a C-index of 0.66 (0.65 – 0.68), 0.67 (0.65 – 0.69), and a hazard ratio (HR) of 1.115 (1.10 – 1.12); 1.22 (1.19 -1.24) per year, for males and females respectively. Univariate ECG parameters were shown to be predictive of incident MACCE during all stages of the ECG assessment. The most predictive individual ECG parameters were the QTC interval at rest, the RR interval during exercise, and the QTC interval during recovery. These parameters exhibited a similar level of discrimination as established CVD risk factors such as BMI and systolic blood pressure (Table 4.2). Overall, the exercise RR interval and recovery QRS interval were jointly the third strongest predictor of incident MACCE after age and systolic blood pressure.

At rest, univariate ECG measurements showed modest predictive for incident MACCE. The most predictive parameters were the QTc interval, signal entropy (CosEn), and evidence of Atrial Tachycardia derived from a Poincare distribution<sup>242</sup>. Predictive performance was broadly similar during the exercise stage compared to rest, with the notable exception of the RR interval, which showed a much stronger positive association with MACCE risk during exercise (HR = 1.12 for males, 1.17 for females). This positive association was significantly attenuated during the recovery stage, where the QTc interval once again emerged as the strongest predictor. A full breakdown of the predictive performance of univariate ECG measurements during exercise and recovery is provided in Supplementary Table 14.

Multivariable ECG risk models were developed using statistically significant ECG risk factors identified from each stage (rest, exercise and recovery) of the ECG test during the previous association analysis (Section 4.3.2). These models demonstrated moderate levels of discrimination, similar to risk factors such as systolic blood pressure.



The most predictive ECG risk score was a combined model of significant ECG risk factors measured at rest, exercise and recovery. However, model discrimination remained lower than that of the age and QRISK3-Inspired risk scores (Table 4.2).

Supplementary Figures 3–4 show sex-stratified Spearman correlation matrices for all ECG parameters analysed univariately in this chapter, including resting, exercise, recovery, and multivariate ECG risk scores. Only correlations remaining statistically significant after Benjamini–Hochberg adjustment ( $p < 0.05$ ) are displayed. Morphology-based measures (RR, PR, QRS, QTc) showed mostly weak correlations, with moderate correlations observed during exercise between RR and PR (men:  $\rho = 0.44$ ; women:  $\rho = 0.53$ ). Stronger correlations were observed among rhythm- and regularity parameters, including irregularity–anisotropy (men:  $\rho = 0.80$ ; women:  $\rho = 0.77$ ), regularity–RR (men:  $\rho = -0.51$ ; women:  $\rho = -0.49$ ), AF evidence–COSEn (rest: men  $\rho = 0.58$ ; women  $\rho = 0.59$ ; recovery: men  $\rho = 0.62$ ; women  $\rho = 0.62$ ), and irregularity evidence–PVC count (men:  $\rho = 0.46$ ; women:  $\rho = 0.42$ ). ECG risk scores were strongly correlated with each other. In both men and women, the combined ECG risk score showed strong correlations with the resting ( $\rho = 0.72$ ), exercise ( $\rho = 0.70$ ), and recovery ( $\rho = 0.75$ ) ECG risk scores with  $p < 0.001$  for each pairing.

Model calibration varied significantly across the different stages of the ECG test. Each ECG risk score generally underestimated risk in participants observed to have the lowest risk of MACCE. This was especially acute for risk scores constructed using resting ECG parameters, which considerably underestimated risk in those with an observed risk of under 5% over 10 years. In contrast, exercise-based ECG models tended to underestimate risk in participants with a higher observed risk of MACCE, with greater underestimation observed in female participants compared to males. Recovery and combined ECG risk scores were more accurately calibrated for both males and females, showing stronger alignment with observed risk than resting and exercise scores (see Supplementary Figure 5-6).

Despite high levels of discrimination and strong calibration, ECG risk scores significantly underperform QRISK3-Inspired risk scores for risk stratification. All ECG risk scores showed a marked decrease in reclassification performance at the clinically recommended threshold of 10% risk for both male and female participants, as evaluated by net benefit and the net reclassification index (NRI) (Supplementary Table 15-16). Further details on the predictive performance of multivariable ECG risk scores are provided in Supplementary Table 17.

**Table 4.2: Performance of sex-stratified age, ECG and QRISK3-Inspired risk scores for 10-year risk of incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE)**

| Model                                   | Hazard ratio (95% CI) | C-index (95% CI)      |
|-----------------------------------------|-----------------------|-----------------------|
| <b>Male (N = 17,376, MACCE = 1,798)</b> |                       |                       |
| Age                                     | 1.11 (1.10 - 1.12)    | 0.662 (0.652 - 0.673) |
| QRISK3-Inspired score                   | 1.07 (1.06 - 1.08)    | 0.685 (0.672 - 0.702) |
| ECG Risk score                          |                       |                       |
| Resting                                 | 1.07 (1.05 - 1.09)    | 0.566(0.556 - 0.577)  |
| Peak exercise                           | 1.05 (1.04 - 1.06)    | 0.589(0.579 - 0.600)  |
| Late-stage recovery                     | 1.04 (1.03 - 1.08)    | 0.573(0.561 - 0.584)  |
| Combined features                       | 1.05 (1.04 - 1.06)    | 0.626(0.616 - 0.637)  |
| <b>Female (N = 18,221, MACCE = 793)</b> |                       |                       |
| Age                                     | 1.22 (1.19 - 1.24)    | 0.671 (0.655 - 0.687) |
| QRISK3-Inspired score                   | 1.05 (1.04 - 1.15)    | 0.685 (0.672 - 0.702) |
| ECG Risk score                          |                       |                       |
| Resting                                 | 1.11(1.06 - 1.23)     | 0.553(0.534 - 0.568)  |
| Peak exercise                           | 1.07 (1.05 - 1.16)    | 0.576(0.561 - 0.591)  |
| Late-stage recovery                     | 1.04 (1.03 - 1.09)    | 0.579(0.561 - 0.592)  |
| Combined features                       | 1.05 (1.04 - 1.10)    | 0.622(0.607 - 0.637)  |

Data are reported on 35,597 participants, 2,591 MACCE events (7.27%) occurred over 10 years, including 1,798 events in 17,376 males (10.3%) and 793 events in 18,221 females (4.6%).95% confidence intervals were obtained via 1000 bootstrap iterations.

Male- and female-specific risk scores were derived from separate sex-stratified Cox models.

Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases

Hazard ratios are reported per unit increase in predicted risk.

#### **ECG parameters:**

Resting ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*

Exercise ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*

Recovery ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*

#### 4.3.4 Added value of ECG to MACCE risk prediction

##### 4.3.4.1 Discrimination

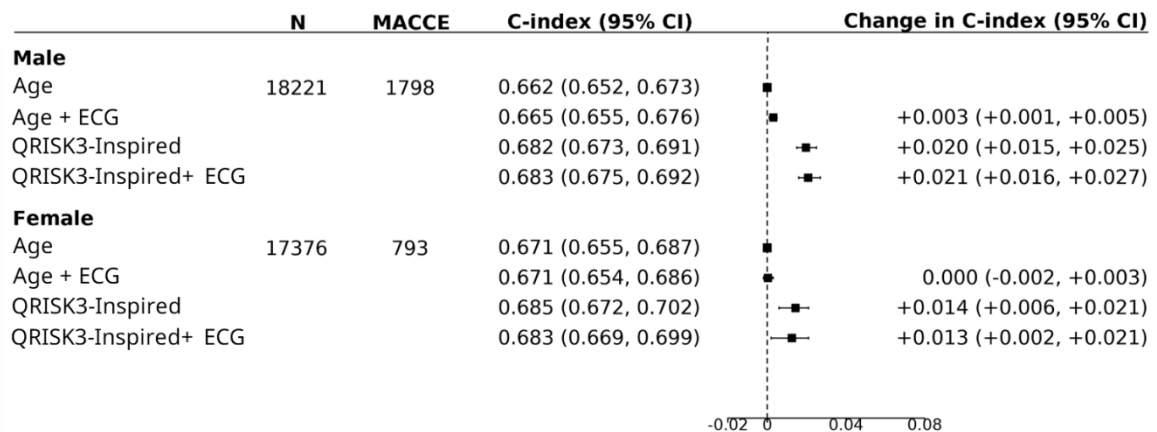
Model discrimination, assessed using Harrell's C-index for age, age + ECG, QRISK3-Inspired and QRISK3-Inspired + ECG risk scores, are shown for males and females in Figure 4.5. Among participants without prior CVD, age alone yielded a C-index of 0.662(0.652 – 0.668) and 0.671 (0.655 – 0.687) for males and females, respectively. The addition of ECG parameters to the age-only model resulted in modest but statistically significant improvements in C-index for males across all stages of the ECG test with C-index: rest; 0.665(95 % CI 0.655 - 0.676);  $\Delta$  0.003(0.001 - 0.005,  $p < 0.001$ ); exercise: 0.667(0.657 - 0.676)  $\Delta$  0.004(0.002 - 0.008  $p < 0.001$ ) and recovery 0.667(0.657 - 0.678)  $\Delta$  0.005(0.002 - 0.007  $p < 0.001$ ). For female participants, only ECG parameters measured at recovery significantly improved model discrimination compared to age alone. Improvement from resting and exercise ECGs were attenuated for female participants and resulted in no significant changes to model C-index. The corresponding C-index values for females were as follows: rest: 0.671(0.654 - 0.686),  $\Delta$  0.00(-0.002 - 0.003,  $p = 0.9$ ); exercise 0.674(0.659 - 0.689)  $\Delta$  0.003(-0.001 – 0.009,  $p = 0.14$ ),  $\Delta$ ; recovery 0.677(0.659 - 0.692),  $\Delta$  0.006(0.001 - 0.010,  $p \leq 0.001$ ).

ECG parameters were subsequently integrated with QRISK3 risk factors to assess the potential value of adding ECG measurements to adopted clinical risk models. At baseline, QRISK3-Inspired risk scores yielded a C-index of 0.682 (0.673 – 0.691) and 0.685 (0.672 – 0.702) for males and females, respectively. For males, there was a significant improvement in model discrimination following the addition of exercise and recovery ECG measurements to QRISK3-Inspired risk scores; however, no significant changes were found in resting ECGs. Rest  $\Delta$  0.001(-0.001 - 0.003)  $p = 0.38$ ; exercise  $\Delta$  0.006(0.003 - 0.009)  $p < 0.001$ , recovery  $\Delta$  0.004(0.002 - 0.006)  $p < 0.001$ . For female participants, changes to discrimination were once again much more modest, with no significant changes in model discrimination for any stage of the ECG test. Rest  $\Delta$  -0.002(-0.006 - 0.004)  $p = 0.52$ , exercise  $\Delta$  -0.002(-0.006 - 0.004)  $p = 0.52$ , recovery  $\Delta$  0.001(-0.004 - 0.006)  $p = 0.74$ .

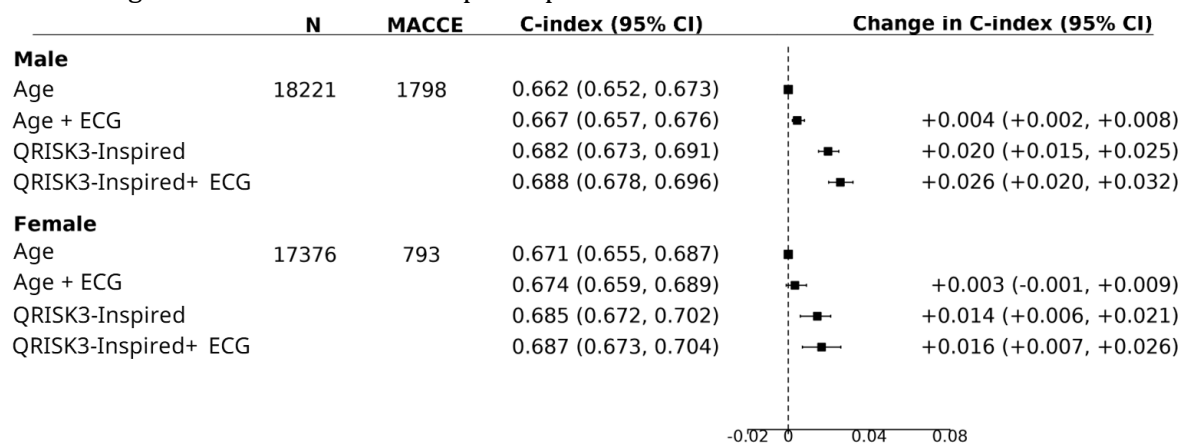
No significant changes were observed when combining ECG parameters from all three stages—rest, exercise, and recovery—with QRISK3 risk factors.

**Figure 4.5: Forest Plot showing Harrell's C-index for ECG risk scores derived from Age, Age + ECG parameters and QRISK3-Inspired risk scores ; in 35,597 UKB participants with ECG collected from 2009-2013. 2,591 MACCE events (7.27%) occurred over 10 years, including 1,798 events in 17,376 males (10.3%) and 793 events in 18,221 females (4.6%).**

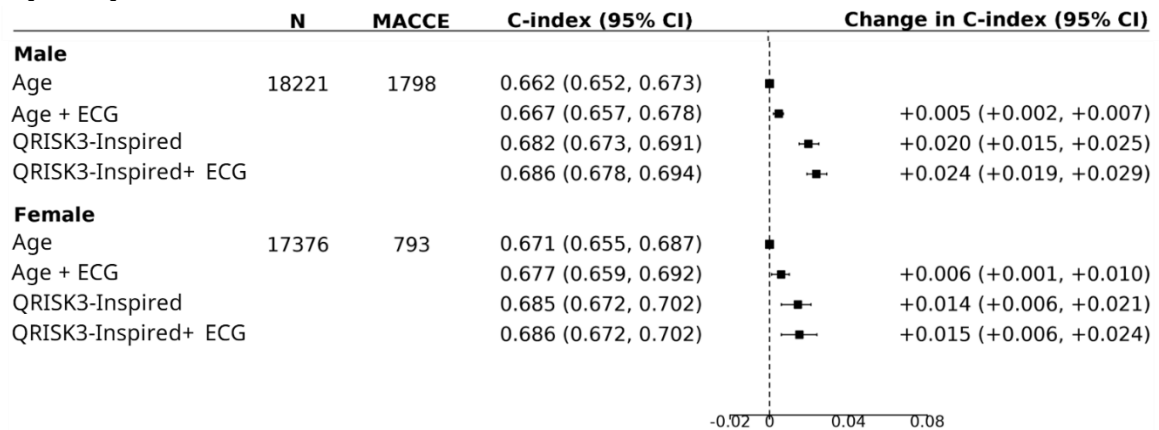
**(A) Resting ECG:** Change in Harrell's C-index following the addition of resting ECG parameters to age and QRISK3-Inspired risk scores. Resting ECG parameters add little to model discrimination beyond either age or QRISK3-Inspired risk scores. The added value of ECG parameters is slightly attenuated for female participants.



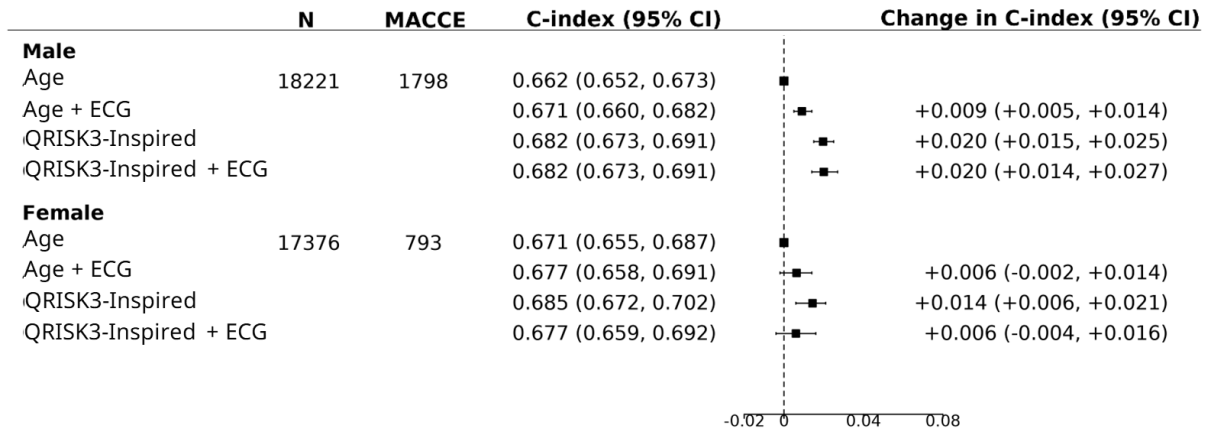
**(B) Exercise ECG:** Exercise ECG parameters marginally improve the predictive performance of age and the baseline QRISK3-Inspired risk score. The added value of ECG parameters is once again attenuated for female participants.



**(C) Recovery ECG:** Recovery ECG parameters marginally improve the predictive performance of age and the baseline QRISK3-Inspired risk score with attenuated performance for female participants.



**(D) Combined ECG:** Combined ECG risk factors from rest, exercise and recovery ECG parameters marginally improve the predictive performance of age and the baseline QRISK3-Inspired risk score with attenuated performance for female participants.



Abbreviations: =Major Adverse Cardiovascular & cerebrovascular Event, CI = Confidence interval

Squares represent change in C-index compared to age; horizontal lines are 95% confidence intervals generated using 1,000 bootstrap resamples.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

ECG parameters: Resting QRS interval, Resting QTc interval, Resting Anisotropy evidence, Resting Atrial Tachycardia evidence, Resting PVC count, Resting regularity Evidence, Exercise PR interval, Exercise QRS interval, Exercise QTc interval, Exercise RR Interval, Exercise Atrial Tachycardia evidence, Exercise PVC count, Exercise regularity evidence, Recovery Irregularity evidence, Recovery QRS interval, Recovery QTc interval, Recovery Atrial Tachycardia evidence, Recovery regularity evidence

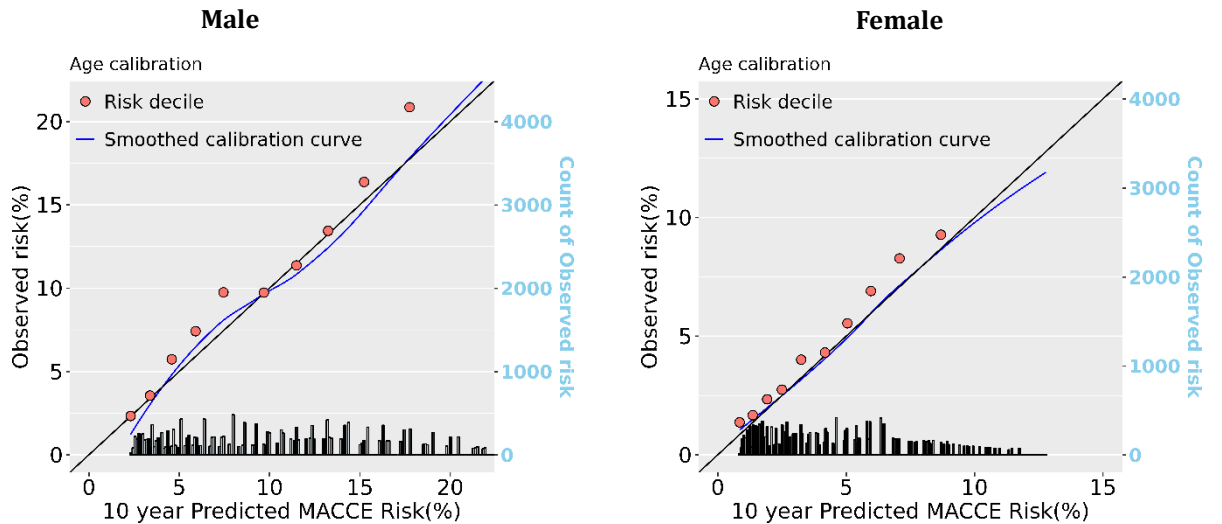
#### **4.3.4.2 Calibration**

Age as a univariate risk score and QRISK3-Inspired risk scores were both well-calibrated, showing close alignment between the observed and predicted risks in males and females, respectively. When combined ECG parameters from rest, exercise, and recovery were added to age, modest improvements in calibration were observed. However, for QRISK3-Inspired risk scores, the changes in calibration were minimal (Figures 4.6–4.7). The calibration curves of extended age and QRISK3-Inspired risk scores with resting, exercise and recovery ECG parameters, respectively, are shown in Supplementary Figures 7-8.

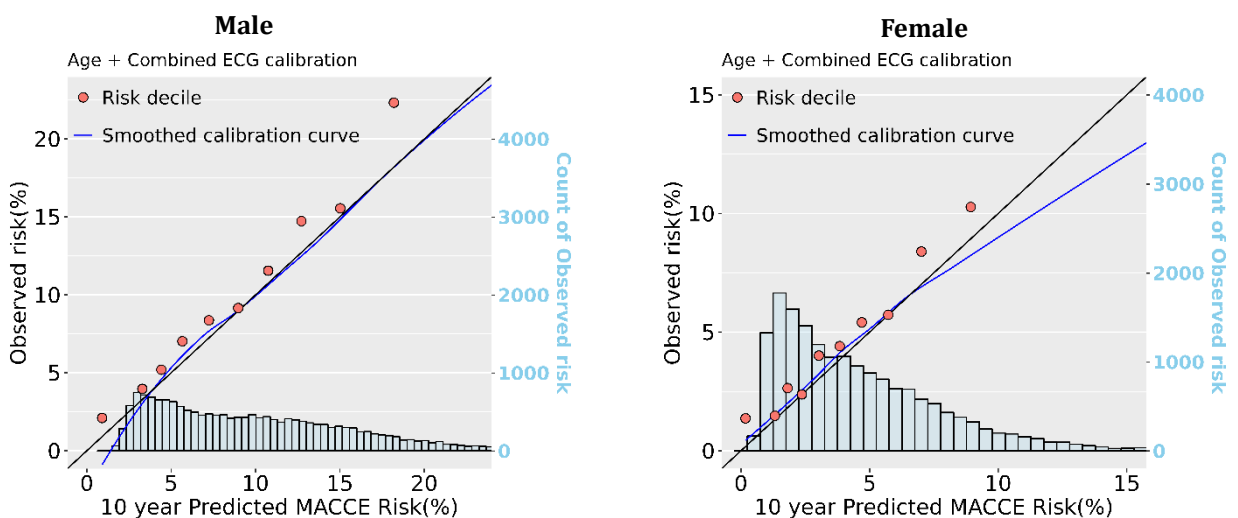
In female participants, there was a degree of misalignment in the higher-risk tenths, where age and QRISK3-Inspired risk scores tended to overestimate the risk of MACCE compared to the actual observed risk. This over-prediction was somewhat reduced after the addition of exercise or recovery ECG parameters. For male participants, evidence of overfitting was observed in models based on Age and Age + ECG parameters, where the risk scores tended to underpredict risk in lower-risk groups and overpredict in higher-risk groups relative to observed outcomes. Supplementary Tables 18-19) presents the calibration for each risk score using the Integrated Calibration Index (ICI), which quantifies the weighted distance between predicted and observed risks, with lower values indicating better calibration.

**Figure 4.6 Smoothed calibration curve: for (A) Age, (B) Age + resting ECG, (C) Age + exercise ECG, and (D) Age + recovery ECG risk scores. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.**

**(A) Univariate Age risk scores**



**(B) Age + combined ECG risk scores**

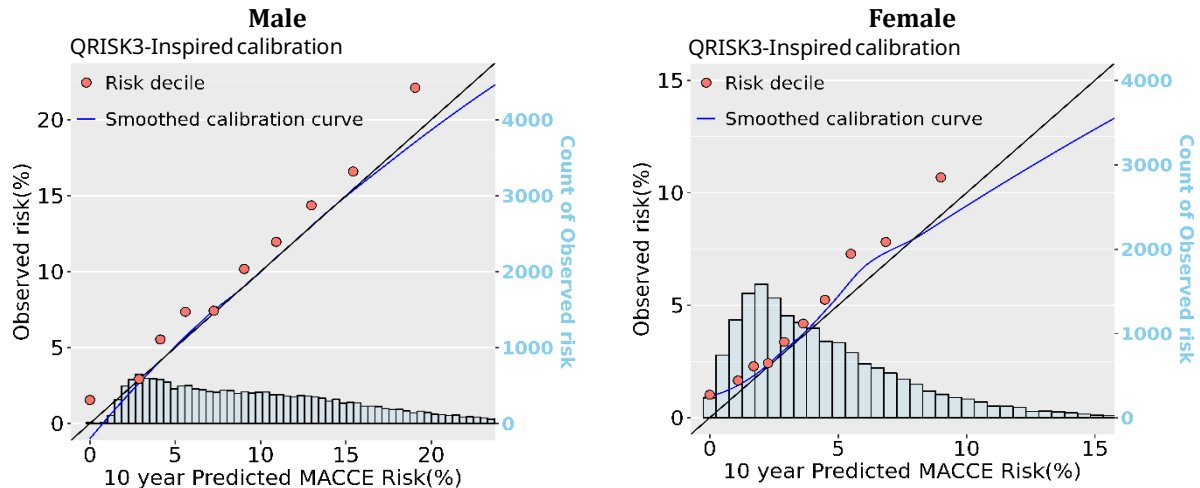


Red circles represent the observed 10-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

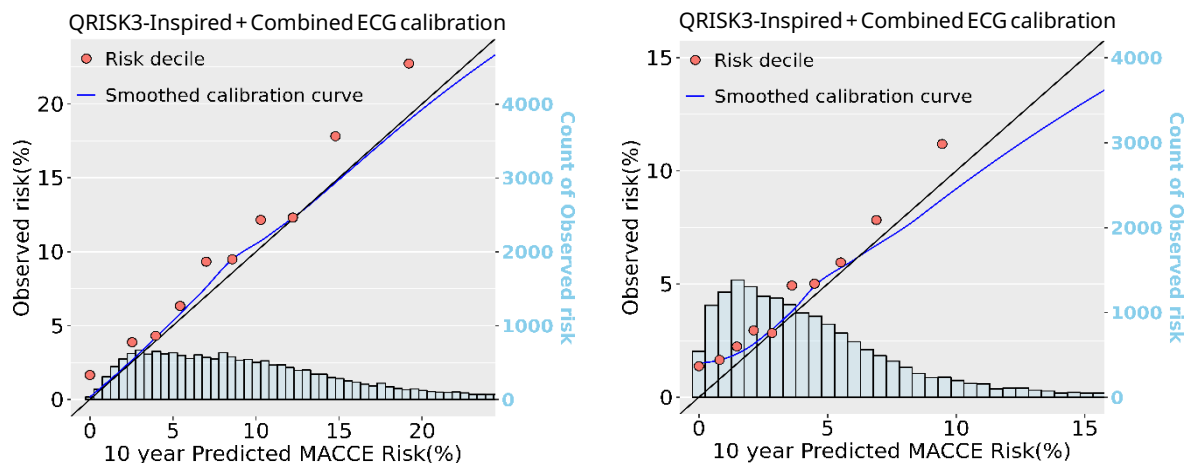
ECG parameters: Resting QRS interval, Resting QTc interval, Resting Anisotropy evidence, Resting Atrial Tachycardia evidence, Resting PVC count, Resting regularity Evidence, Exercise PR interval, Exercise QRS interval, Exercise QTc interval, Exercise RR Interval, Exercise Atrial Tachycardia evidence, Exercise PVC count, Exercise regularity evidence, Recovery Irregularity evidence, Recovery QRS interval, Recovery QTc interval, Recovery Atrial Tachycardia evidence, Recovery regularity evidence.

**Figure 4.7 Smoothed calibration curve for QRISK3-Inspired and QRISK3-Inspired + ECG risk scores derived for male and female participants. Calibration curves are shown in the order of: (A) QRISK3-Inspired; (B) QRISK3-Inspired+ resting ECG; (C) QRISK3-Inspired+ exercise ECG; (D) QRISK3-Inspired+ recovery ECG risk scores.**

**(A) QRISK3-Inspired**



**(B) QRISK3 + Combined ECG**



Red circles represent the observed 10-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

ECG parameters: Resting QRS interval, Resting QTc interval, Resting Anisotropy evidence, Resting Atrial Tachycardia evidence, Resting PVC count, Resting regularity Evidence, Exercise PR interval, Exercise QRS interval, Exercise QTc interval, Exercise RR Interval, Exercise Atrial Tachycardia evidence, Exercise PVC count, Exercise regularity evidence, Recovery Irregularity evidence, Recovery QRS interval, Recovery QTc interval, Recovery Atrial Tachycardia evidence, Recovery regularity evidence.



#### 4.3.4.3 Reclassification

Reclassification statistics consisting of, Net benefit, categorical net reclassification index (NRI) and continuous NRI, for age vs. age + ECG and QRISK3-Inspired vs QRISK3-Inspired + ECG risk scores are provided in Table 4.3.

The addition of ECG parameters to age-based risk scores showed consistent improvements in risk discrimination measured by the continuous NRI, indicating enhanced performance in absolute predictive performance. However, improvements in risk stratification, based on current clinically recommended risk thresholds, remained modest. For males the addition of resting and combined (rest, exercise, and recovery) ECG parameters resulted in small but significant improvements in the classification of high-risk individuals (10-year risk  $\geq 10\%$ ). For females, the impact of ECG parameters on risk stratification was more varied across each stage of the submaximal ECG test. Significant improvements in risk stratification were observed following the addition of exercise, recovery, and combined ECG parameters. However, changes in net benefit were minimal and non-significant. In contrast to what was observed in male participants, resting ECG alone did not lead to significant classification changes in continuous NRI or reclassification at a risk threshold of 10%.

For QRISK3-Inspired risk scores, the addition of recovery and combined ECG parameters resulted in significant improvements in the continuous NRI for both males (recovery: NRI = 0.085 (95% CI 0.034 – 0.136); combined: NRI = 0.106 (95% CI 0.055 – 0.158)) and females (recovery: NRI = 0.081 (95% CI 0.011 – 0.151); combined: NRI = 0.094 (95% CI 0.024 – 0.160)) alike. However, these changes did not translate into meaningful improvements in risk stratification, with no significant changes observed in categorical NRI or net benefit at a 10% risk threshold.

In males, the inclusion of exercise ECG parameters resulted in a significant increase in continuous NRI, but no significant changes were observed in net benefit or categorical NRI.

The relative performance of age + ECG risk scores vs QRISK3-Inspired risk scores is shown in Supplementary Table 20. Overall, while the difference in performance between age and multivariable QRISK3-Inspired scores is attenuated following the addition of ECG parameters, age + ECG risk scores fail to match the performance of the original QRISK3-Inspired risk score.

**Table 4.3: Net reclassification and net-benefit improvement following the addition of ECG parameters to QRISK3-Inspired risk scores at a 10% risk threshold.**

| Model                                    | Comparator                     | $\Delta$ Net-benefit<br>(95% CI) | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|------------------------------------------|--------------------------------|----------------------------------|-----------------------------|----------------------------|
| <b>Male (N = 17,376, MACCE = 1,798)</b>  |                                |                                  |                             |                            |
| Age                                      | Age + Resting ECG              | *0.012(0.003 - 0.021)            | *0.012(0.003 - 0.021)       | ** 0.128(0.087 - 0.169)    |
| Age                                      | Age + Exercise ECG             | 0.011(-0.002 - 0.02)             | 0.011(-0.002 - 0.02)        | **0.094(0.051 - 0.14)      |
| Age                                      | Age + Recovery ECG             | 0.002(-0.005 - 0.01)             | 0.002(-0.005 - 0.010)       | **0.134(0.095 - 0.174)     |
| Age                                      | Age + Combined ECG             | *0.018(0.002 - 0.03)             | *0.018(0.002 - 0.03)        | **0.18(0.136 - 0.227)      |
| QRISK3-Inspired                          | QRISK3-Inspired + Resting ECG  | -0.005(-0.014 - 0.003)           | -0.006 (-0.014 - 0.003)     | 0.03 (-0.021 - 0.08)       |
| QRISK3-Inspired                          | QRISK3-Inspired + Exercise ECG | 0.003(-0.008 - 0.016)            | 0.003 (-0.009 - 0.015)      | **0.104(0.057 - 0.156)     |
| QRISK3-Inspired                          | QRISK3-Inspired + Recovery ECG | 0.001(-0.009 - 0.012)            | 0.001 (-0.009 - 0.011)      | **0.085 (0.034 - 0.136)    |
| QRISK3-Inspired                          | QRISK3-Inspired + Combined ECG | -0.005(-0.02 - 0.01)             | -0.006 (-0.02 - 0.009)      | **0.106 (0.055 - 0.158)    |
| <b>Female (N = 18,221 , MACCE = 793)</b> |                                |                                  |                             |                            |
| Age                                      | Age + Resting ECG              | -0.015(-0.031 - 0.003)           | -0.007(-0.022 - 0.012)      | 0.048(-0.038 - 0.115)      |
| Age                                      | Age + Exercise ECG             | 0.019(-0.004 - 0.043)            | **0.035(0.013 - 0.06)       | 0.036(-0.030 - 0.104)      |
| Age                                      | Age + Recovery ECG             | 0.010(-0.01 - 0.032)             | *0.025(0.006 - 0.047)       | **0.124(0.087 - 0.164)     |
| Age                                      | Age + Combined ECG             | 0.016(-0.01 - 0.051)             | **0.05(0.027 - 0.083)       | **0.171(0.102 - 0.245)     |
| QRISK3-Inspired                          | QRISK3-Inspired + Resting ECG  | -0.012(-0.024 - 0)               | -0.01 (-0.022 - 0.001)      | 0.015 (-0.053 - 0.088)     |
| QRISK3-Inspired                          | QRISK3-Inspired + Exercise ECG | 0.008(-0.015 - 0.031)            | 0.009 (-0.013 - 0.031)      | 0.033 (-0.041 - 0.105)     |
| QRISK3-Inspired                          | QRISK3-Inspired + Recovery ECG | 0(-0.017 - 0.018)                | 0.003 (-0.014 - 0.02)       | **0.081 (0.011 - 0.151)    |
| QRISK3-Inspired                          | QRISK3-Inspired + Combined ECG | 0(-0.025 - 0.024)                | 0.008 (-0.016 - 0.032)      | **0.094(0.024 - 0.16)      |

Data are reported on 35,597 participants, 2,591 MACCE events (7.27%) occurred over 10 years, including 1,798 events in 17,376 males (10.3%) and 793 events in 18,221 females (4.6%).95% confidence intervals were obtained via 1000 bootstrap iterations.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment ;Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

#### ECG parameters

Resting ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*

Exercise ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*

Recovery ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*

## 4.4 Discussion

### 4.4.1 Overall findings

To date, this is the largest population-based prospective cohort study to examine the added value of exercise ECG to establish clinical risk models for predicting risk of MACCE in individuals without a history of MACCE. This work reports the development and internal validation of several new ECG risk scores, using ECG parameters measured during rest, exercise and recovery. The main findings of this investigation are: (i) ECG measurements recorded during rest, exercise and recovery are independently associated with the 10-year risk of incident MACCE; (ii) ECG measurements show meaningful prognostic value for 10-year MACCE demonstrating discriminative ability in the absence of established clinical risk factor; (iii) while ECG measurements provide independent prognostic information, they offer limited improvement in risk stratification beyond age and traditional clinical risk models, at currently recommended risk thresholds.

First, this study confirms the established associations between ECG morphology, including QTc, heart rate, and QRS duration, with the risk of incident CVD<sup>70,120</sup>, while validating these associations during exercise and recovery. This work also identifies new associations between ECG rhythm measurements and MACCE, including evidence of atrial tachycardia (AT), measured from a Poincare distribution<sup>243</sup>, and the regularity of the time between heartbeats.

Second, this work shows that ECG measurements alone are predictive of incident MACCE in the absence of established clinical risk factors, with a combination of parameters from rest, exercise and recovery showing the strongest predictive performance for the 10-year risk of incident MACCE. ECG risk scores were constructed using a linear combination of parameters identified as significantly associated with MACCE in a adjusted Cox proportional hazard analysis. Multivariable ECG risk scores, derived from combining ECG risk factors from all stages of the ECG test, were the second strongest single predictor of MACCE surpassed by only age, as measured by Harrell's C-index.

Finally, although ECG measurements were positively associated with MACCE and led to modest improvements in model discrimination, this work found no added value in performing resting or exercise ECG for improving MACCE classification in individuals with no prior history MACCE. Both the net reclassification index (NRI) and net benefit analyses showed no significant changes in risk stratification compared to QRISK3-Inspired risk scores at clinically recommended thresholds. This finding further supports the conclusion made by the US Preventive Services Task Force (USPSTF), which found that while ECG measurements improve absolute model discrimination, they are of little added value for risk stratification. This strengthens the USPSTF recommendation advising against the use of exercise ECG screening for asymptomatic individuals<sup>95</sup>. The combination of resting, exercise, and recovery ECG provided minimal additional improvement to QRISK3-Inspired risk scores beyond what was achieved by incorporating each stage independently.

Several factors may explain why ECG did not improve performance beyond QRISK3 risk factors. First, the submaximal exercise protocol used in this study may have been insufficient to reveal additional ECG abnormalities. Limiting participants to exercise to 50% of their maximum predicted heart rate, may not induce enough physiological stress to uncover latent ischemia, or repolarization abnormalities which might provide stronger prognostic value. In contrast, maximal or near-maximal exertion, such as that used in stress echocardiography testing, may be more effective in detecting exercise-induced arrhythmias and ischemic changes that indicate higher cardiovascular risk. Additionally, participants who completed the exercise ECG were likely healthier than those who did not, as individuals with cardiovascular conditions or poor exercise tolerance were less likely to participate. This healthy volunteer bias may have led to a lower prevalence of ECG abnormalities than in the general population, reducing the predictive value of exercise testing in this cohort.

Second, the effect size of the ECG risk factors examined in this study were relatively modest compared with established risk factors such as age, BMI and smoking status (Supplementary Table 14). As a result, improvements tended to be incremental rather than transformative.

Finally, many ECG-derived risk factors, such as prolonged QT interval and increased RR interval, are influenced by hypertension, diabetes, and smoking—factors already accounted for in QRISK3. This suggests that while the ECG may contain prognostic information, the overlap with existing risk factors, may diminish its independent contribution to risk stratification. There are several methodological differences between the QRISK3-Inspired model used in this study and the published QRISK3 algorithm, which may help explain the limited added value of ECG markers. First, the MACCE endpoint used here is broader than the original QRISK3 CVD outcome and may involve different pathophysiological pathways less directly captured by ECG. Second, the lower-risk profile of the study population reduces variability in baseline risk, limiting the potential for additional predictors to improve classification. Third, refitting the coefficients of key QRISK3 predictors to this cohort captures much of the available prognostic signal, leaving less residual risk for ECG markers to explain. As a result, the conventional 10% threshold, derived for QRISK3's narrower outcome and higher-risk population, may attenuate the apparent incremental value of ECG for predicting MACCE.

Interestingly, there are notable sex-specific differences in the performance of ECG risk scores. The strength of the association and added value of resting ECG parameters are significantly lower in females compared to their male counterparts. While the lower incidence of MACCE in females may partly account for this disparity, the improvement seen in exercise and recovery ECGs suggests that factors beyond statistical power contribute to these differences. While sex specific variations in cardiovascular physiology, including lower prevalence of resting ECG abnormalities among females<sup>262</sup>, and physiological factors impacting recovery dynamics such as faster heart rate and longer QTc in females may partially explain these observations. Further research is needed to investigate the underlying causes of these sex-specific discrepancies.

#### **4.4.2 Comparison with previous work in the UK Biobank**

Consistent with prior works by Ramírez et al. and Duijvenbodenetal, the association analysis in this study found significant positive associations between the QTc interval and the number of PCVs during exercise with incident MACCE. While numerous studies have assessed the association between resting and ECG measurements with incident MACCE, no such study has yet investigated the prognostic value of these markers for individualised risk prediction. This work extends upon the work by Oster et al., who investigated the predictive performance of ECG data for Atrial fibrillation using a Poincare transformation.

By applying this transformation in the context of MACCE risk prediction, this research explores a novel approach to understanding the association between ECG parameters and cardiovascular risk, which does not rely on prior expert annotation of the ECG. This research, therefore, fills an important gap by assessing the prognostic utility of dynamic ECG data with incident MACCE in a large population with no prior history of CVD.

#### **4.4.3 Comparison with the wider literature**

This study contributes to the existing literature by building upon the recommendations by Jonas et al.<sup>95</sup> in a recent review for the USPSTF, addressing key limitations found across the current evidence. Namely, inadequate sample sizes, insufficient follow-up durations, inappropriate reporting of calibration and reclassification, and a lack of evidence for low-risk individuals<sup>95</sup>. First, the current study includes a large cohort of low-risk individuals without prior CVD (n = 35,597). Second, passive linkage to primary care and hospital episode data provides long-term follow-up (median 12.5 years) for all participants, enabling a more direct comparison with current clinical risk models. This work reports both model calibration and reclassification at the recommended clinical endpoints, following National Institute for Health and Care Excellence (NICE) guidelines and the recommendation provided by Jonas et al.<sup>95</sup>, including a 10% risk threshold over ten years<sup>26</sup>, providing greater evidence of the clinical utility of exercise ECG testing.

This is of great importance, as whilst prior evidence suggests exercise ECG tests resulted in absolute improvements in predictive performance, improvements in reclassification for clinical decision-making were rarely assessed.

Additionally, this work addresses a central research question put forward by the NICE in assessing the added value of novel risk factors in the ECG to age alone as a means of simplifying current risk prediction tools. While this work reports a modest improvement in model discrimination and risk stratification, the predictive performance of age + ECG risk score fails to match that of the baseline QRISK3-Inspired risk score (Supplementary Table18).

Furthermore, improvements in predictive performance were more significant for male than female participants. This likely reflects a range of factors including the lower number of MACCE reported for females, reducing statistical power when estimating model coefficients. Women in midlife typically have lower absolute CVD event rates and more heterogeneous symptom profiles, are at higher risk of under-diagnosis and delayed diagnosis compared to men<sup>263-265</sup>. Additional existing risk scores generally show poorer calibration and discrimination in women than in men and are less sensitive at conventional risk thresholds <sup>266</sup>. Under-recording of events in women may attenuate estimated associations and potentially mask any additional prognostic information contained in ECG measures for women.

The Predictive performance reported in this work challenges the degree to which ECG measurements add to CVD risk prediction, as previously suggested in the literature. Joanas et al. reported improvements in C-index ranging from 0.0001 – 0.05 for resting ECGs (9 cohort studies n = 68,475) and 0.02- 0.03 for exercise ECGs (5 studies n = 9,582) when added to traditional risk factors.

However, for exercise ECGs, only one study reported p values, which were non-significant (p = 0.3); confidence intervals were not provided in any studies identified. In contrast, the current study found that although the absolute change in C-index for resting ECGs fell within the reported range, these improvements were non-significant for both males and females.

Whilst for exercise ECGs, the observed improvement was smaller for males compared to previous findings and non-significant for females (males: 0.006 [95% CI 0.003 – 0.009],  $p < 0.001$ ; females: 0.002 [95% CI -0.004 – 0.008],  $p = 0.52$ ).

Assessing changes in reclassification across studies was challenging owing to heterogeneous study endpoints and risk thresholds. Absolute changes in reclassification varied greatly between studies, ranging from 3.6% to 30% for resting ECG risk scores. No studies were identified that evaluated the impact of exercise ECGs on reclassification when combined with existing clinical risk models. Work by Auer et al demonstrated that the choice of baseline model can partially explain the discrepancy in performance between past studies. Of the previous studies that investigated the prognostic value of ECG, this work is the first to investigate the addition of ECG parameters to QRISK3 risk factors, following the same derivation protocol. Jorgensen et al. investigated the addition of ECG parameters to the Framingham risk score. They found a significant improvement in risk stratification following the addition of ECG changes, such as ST depression, in addition to Q-wave and T-wave changes. However, the use of nonstandard risk thresholds makes it difficult to cross-comparison with traditional models and assess the clinical utility of such an improvement. Groot et al. subsequently added the value of ECG abnormalities to SCORE2; however, following adjustment for optimism, no statistically significant improvements were found at clinical risk thresholds<sup>142</sup>. Shah et al. investigated the addition of ECG parameters to Framingham risk score and PCE to predict CVD mortality<sup>70</sup>. They found a significant improvement in the combined categorical NRI across three risk thresholds (1%, 5% and 10%). However, the authors did not report the individual NRI for each threshold; thus, the impact on treatment recommendation based on a 10% risk threshold could not be assessed. Of these studies, only Groot et al. reported re-calibrating the baseline model to the study population, allowing for a fairer comparison between models. In contrast, it remains unclear whether re-calibration was performed in the other studies.



This potential lack of adjustment may favour the new ECG risk scores, where coefficients were optimized specifically for the study cohort, potentially inflating performance estimates and undermining the generalisability of the findings across broader populations.

This work specifically addresses calibration bias by re-fitting QRISK3 coefficients to the same derivation data as those used for each ECG risk score. This ensures consistency in how each model was derived, ensuring a fair comparison. In the current study, significant improvements in continuous NRI were found for males, ranging from 8.5% for recovery ECGs to 11.1% for combined resting, exercise and recovery ECG parameters ECGs. However, no significant changes were observed for categorical NRI or net benefit at currently recommended risk thresholds. For female participants, improvements in continuous NRI were reported following the addition of recovery ECG parameters (8.1 [95% CI 1.1% – 15.1%]). However, no significant changes were found for resting ECGs and no improvements were observed in categorical NRI and net benefit.

### **Study Limitations**

As with any epidemiological study, there are several limitations inherent to this investigation. First is the well-documented healthy volunteer selection within the UK Biobank (UKB), demonstrated by an overall decrease in all-cause mortality and incidence of various health conditions<sup>20</sup>. Furthermore, the strict eligibility criterion for the submaximal exercise test further exacerbates the healthy volunteer bias in the study population. The 7.3% 10-year incidence of MACCE is substantially lower than the estimated risk of the wider UK population of 18%<sup>267</sup>, meaning current clinical risk thresholds may be sub-optimal in the study population, potentially biasing the reclassification and net benefit analysis.

Second, the study protocol itself risks potentially confounding the association between the RR-interval and incident MACCE, as the maximum heart rate a participant can reach and the intensity at which they exercise is partially determined by one's prevalence of existing CVD risk factors, including age, sex, BMI and blood pressure. To minimise this confounding, all participants who reached their maximum heart rate, thus ending their test early, were removed

from the study population. Furthermore, the majority of participants were assigned to the highest intensity of exercise (83%), whilst 13% were assigned to category 2 and 4% exercised at a constant intensity. As a result, the exercise program was mostly consistent across the study population.

Third, several methodological aspects of this study differ from the published QRISK3 algorithm and should be considered when interpreting the findings. The outcome used here (10-year MACCE) is broader than QRISK3's CVD endpoint. The study cohort also differs from the original QRISK3 populations in terms of baseline risk profile and exclusion criteria and importantly included participants receiving statin therapy at baseline. In addition, QRISK3 predictors were re-estimated within this cohort rather than applying the published coefficients. These differences mean that the QRISK3-Inspired model used here is not directly comparable to the QRISK3 score used in primary care which may influence the apparent contribution of ECG markers when assessed clinical recommended risk threshold of 10%, derived for QRISK3 narrower endpoint and higher risk population.

Fourth, this study employed a single imputation, assuming data were missing at random (MAR), instead of multiple imputations for covariates with a large degree of missingness. This was to ensure consistency and enable direct comparison with Chapter 5, where due to the added computational complexity of deep learning models, multiple imputation proved to be resource intensive. The MAR assumption was not formally evaluated, and no sensitivity analyses were conducted; therefore, bias due to informative missingness cannot be ruled out. Because the level of missingness is relatively limited (10.1%), it is suspected this will have little impact on the stability of the results; however, given more resources, ideally multiple imputations would be implemented for model development and evaluation.

Finally, due to a lack of access to a comparable dataset, these results have yet to be validated in an external dataset, limiting the ability to assess how well findings generalise outside the UKB.

#### 4.4.4 Summary

In conclusion, while conventional ECG measurements show an independent association with incident MACCE, their incremental value remains minimal when added to existing clinical risk models. Although these ECG-derived risk factors modestly improved model discrimination, there was no significant added value for risk stratification at current clinical thresholds using resting or exercise ECGs.

One notable limitation in this work is a reliance on hand-selected ECG phenotypes from unannotated ECG. Traditional approaches to feature extraction may fail to capture the full spectrum of clinically relevant information embedded in the ECG signal, such as subtle waveform variations, arrhythmias, or repolarization abnormalities that are not reflected in basic ECG intervals. Recent advances in deep learning, such as convolutional and recurrent neural networks (CNNs and RNNs), offer a solution by automatically learning complex patterns within raw ECG signals without requiring manual annotations. Deep neural networks can detect subtle patterns invisible to the naked eye, often outperforming traditional methods in identifying cardiovascular conditions like atrial fibrillation and premature ventricular contractions<sup>132,153</sup>. However, evidence on the added value of deep learning for predicting long-term incident CVD is limited. Chapter 5 explores whether deep-learning models can enhance risk stratification by better accounting for complex, non-linear relationships between ECG parameters and MACCE.

## Chapter 5 – Deep learning of the Electrocardiogram measurements and the 10-year risk of Major Adverse Events

### Cardiovascular/Cerebrovascular

## 5.1 Introduction

### 5.1.1 Background

The previous chapter established that conventional ECG measurements obtained during rest, exercise, and recovery are associated with 10-year MACCE risk, yet provide minimal improvement when added to established clinical risk factors. This chapter investigates the potential added value of deep learning algorithms to further enhance ECG-based risk scores and improve prediction accuracy.

Previous investigations on the prognostic value of ECGs for CVD risk prediction have relied on hand-selected features, which lack sensitivity to subtle changes within the ECG and have often varied across studies, leading to inconsistent performance<sup>132,153</sup>. Recently, deep neural networks have gained significant attention for disease risk prediction and prognostic modelling, with recent reviews highlighting their state-of-the-art performance. These models have been shown to outperform classical methods such as Cox regression in predicting a range of diseases, including incident CVD. A systematic review by Teshie et al. identified 33 studies on machine learning and deep learning for CVD risk prediction, finding that deep neural networks consistently outperformed classical approaches, regardless of the type of risk factor used<sup>268</sup>. Unlike conventional regression models, deep learning can capture complex patterns within large datasets without predefined assumptions, making it ideal for analysing high-dimensional medical data like ECGs and integrating them with traditional risk factors<sup>268,269</sup>. However, concerns about bias and inadequate validation remain, emphasizing the need for more rigorous clinical evaluations.

Prior attempts to evaluate the performance of ECG-based deep learning risk models for the prediction of incident CVD were hindered by various forms of bias, such as a choice of arbitrary risk thresholds and calibration bias. Of the studies discussed in sections 2.3.3 none assessed

the added value of directly integrating deep-learned ECG risk scores to clinically adopted methods such as QRISK3<sup>148,149</sup>. Additionally, none of the studies reported recalibration of the baseline model, potentially leading to biased comparisons with the newly derived ECG risk scores. A review by Javaid et al. 2022 identified three studies which used machine learning models and ECG measurements to predict long-term CVD risk. None of the studies identified reported recalibration of the baseline risk model or directly integrated ECG measurements with existing clinical risk models<sup>80</sup>.

No studies were identified that combine exercise ECGs with deep learning for CVD risk prediction, revealing a significant gap in the current literature. Exercise-induced changes in heart rate, arrhythmias, ST-segment depression, and recovery of the ST-segment can reveal latent abnormalities that are not detectable in resting ECGs<sup>270</sup>. These markers provide critical prognostic information by capturing the heart's response to cardiovascular stress, which may otherwise go unnoticed. This highlights a promising opportunity to enhance CVD risk prediction by leveraging the dynamic data from exercise ECGs in conjunction with advanced pattern recognition of deep learning models.

This chapter details the development and validation of a novel deep-learning risk model designed to predict the 10-year risk of death or hospitalization due to MACCE, using ECG data from 41,076 UK Biobank participants with no prior history of MACCE. In addition to assessing the added value of deep learning models, this work then aims to further investigate the research questions posed in Chapter 4, including the added value of ECG measurements to age and established clinical risk factors from QRISK3 risk scores used in UK primary care.

### **5.1.2 Aims**

This chapter has two primary objectives. First, to investigate the added value of deep learning to CVD risk prediction using QRISK3 risk factors and ECG data introduced in Chapter 4. Second, this chapter assesses the added value of deep learning feature extraction from raw ECG data against conventional ECG parameters derived in Chapter 4 and whether deep-learned ECG features can further improve the ECG's contribution to established clinical risk models.

## **5.2 Methods**

### **5.2.1 Study population**

This work used the UK Biobank cardiorespiratory fitness dataset<sup>205,271</sup>, described in Chapter 3. The initial study population was identical to that described in Chapter 4. Protocols for UKB data collection and ECG signal processing are described in Chapter 4, section 4.2.2.2. Any relevant changes in data processing and exclusion criteria are described in detail in the relevant sections below.

### **5.2.2 Data processing**

#### **5.2.2.1 Ascertainment of study endpoint and risk factors**

Clinical risk factors were selected to match those included in the QRISK3 risk calculator<sup>51</sup> as described in Chapter 4 and provided in Supplementary Table 3.

As described in Chapter 4, the primary outcome of interest is the 10-year risk of incident Major Adverse Cardiovascular or Cerebrovascular Events (MACCE), defined as the earliest recorded episode of hospitalisation or death due to ischaemic stroke, coronary heart disease, heart failure, or transient ischaemic attack. A full definition of MACCE is presented in Supplementary Tables 1-2.

All participants with known MACCE, in addition to those receiving calcium channel blockers or antiarrhythmic medications (Supplementary Table 9) prior to the submaximal exercise ECG test, were excluded from this study.

Follow-up time for each participant was calculated as the number of years from the initial ECG scan until the earliest date of either (i) first recorded MACCE, (ii) death not caused by CVD or (iii) the most recent publication of NHS HES for England: 31st October 2022; Scotland: 31<sup>st</sup> August 2022; and Wales 5<sup>th</sup> May 2022.

Continuous variables were standardised using z-score normalisation, whilst multiclass categorical variables were one hot encoded, creating a single binary variable for each sub-category.

Descriptive statistics were reported as mean  $\pm$  standard deviation for continuous risk factors and percentages for categorical variables. Due to the heavy class imbalance among ethnicities (Table 5.1), ethnicity was divided into white/non-white. Smoking was factorised into three categories (never, previous, current).

Missing risk factors were assumed to be missing at random, and a complete case analysis was performed for covariates with under 1% of missing values. For any covariate with >1% missing values, a single imputation was performed using Bayesian Ridge <sup>219</sup>, fitted using the training data set and deployed in the testing set for each cross-fold validation (see section 4.2.2.1).

#### **5.2.2.2 Electrocardiogram phenotypes from submaximal exercise tests**

Data pre-processing and data quality exclusions for ECG data were described in detail in Chapter 4. In short, ECG signals were processed to remove high-frequency noise and baseline wandering. ECGs with a low signal-to-noise ratio (<0 dB) incomplete or missing data, in addition to ECG measurements with less than five recorded heart beats during rest, 300 during exercise or 20 during recovery, were also excluded (see Figure 4.1).

#### **5.2.3 ECG-net implementation**

ECG-net comprises three core components: (i) a convolutional neural network (CNN) for extracting key ECG features, (ii) an LSTM model to capture temporal changes in the ECG over time, and (iii) a fully connected deep-survival network to evaluate overall cardiovascular risk. The CNN produces a learned representation of the ECG, highlighting critical features, which the LSTM analyses for temporal relationships. The deep-survival network then uses this learned representation to provide a single risk metric (Q-ECG), analogous to the log partial hazard in traditional Cox regression for estimating the hazard of a cardiovascular event based on the ECG alone.

This work employs an adapted Resnet-V2 with 50 layers<sup>272</sup> and 1D convolutions, totalling 17M parameters, for ECG feature extraction, chosen for its state-of-the-art performance and robust validation for ECG analysis<sup>273</sup>. ECGs were processed in 15-second windows as 3-dimensional vectors of size (3,7500) (3 leads by 15\* 500Hz). The learned feature vector was of size 2048.

An LSTM was added to model temporal dependencies between each ECG window. The resulting latent representation of the ECG is passed through a fully connected layer to identify the most relevant features associated with MACCE. Separately, QRISK3 risk factors are processed by a multilayer perceptron to capture non-linear interactions before being combined with the ECG-based score to generate a 10-year MACCE risk prediction.

Details of the model architecture for the LSTM and deep-survival networks are provided in Appendix Section A, p.3400.

### **Model training implementation.**

To optimize the model, the Adam optimizer<sup>274</sup> with an initial learning rate of 1e-3 was used. Training focused on minimizing the negative log partial likelihood over a 12-year follow-up period, as outlined in the original deep-survival framework<sup>81</sup>. A learning rate scheduler dynamically adjusted the rate, reducing it after 5 consecutive epochs without improvement to help the optimizer reach a better local minimum. Training was distributed across four Tesla V100-SXM2 GPUs, each with 32GB of memory.

Due to the need for large volumes of data and strong statistical power to effectively train a deep neural network, model parameters were derived using the entire study population. This is in contrast to Chapter 4, where models were sex-stratified, following the approach outlined in the derivation of QRISK3<sup>51</sup>.

Model development and validation were implemented in Python 3.7 and Pytorch 1.5; training was performed using the Pycox<sup>275</sup> package for deep-survival networks, and lifelines<sup>276</sup> for Cox proportional hazard models.

### **Generation of AI ECG risk score (Q-ECG)**

A total of four ECG risk models were developed using resting, exercise, recovery and complete 7 minute 15 second submaximal exercise ECG recordings, respectively. Single-stage ECG risk scores (resting, exercise or recovery) were derived using separate CNNs followed by a fully connected deep survival network excluding the LSTM network, as previously described.



ECG risk scores developed from complete ECG recordings, were derived using a combination of CNN + LSTM networks.

The output of each ECG deep survival risk model (Q-ECG) was combined with the baseline survival function evaluated up to 12.5 years (end of the follow-up period), to generate time-specific risk estimates with a primary focus on 10-year risk scores, (equation 5.2) as per the recommendation from the National Institute of Health Care Excellence (NICE)<sup>26</sup>.

Following the approach outlined in Chapter 4, the baseline survivor function (S) was calculated using Breslow's method<sup>261</sup> based on the output of the neural network.

$$Risk\ score = 100 * (1 - S_{t(10)}^{e^{Q-ECG}}) \quad (5.2)$$

Where  $S_{t(10)}$  is the baseline survival after 10-years of follow-up, and Q-ECG is the output of the deep-survival network.

Figure 5.1 provides a schematic overview of ECG risk score derivation using the full 7 minute 15 second ECG data and deep survival networks. First, a deep convolutional neural network is trained on 206 person-days of ECG data, recorded across 41,076 individuals, to identify features associated with the target outcome; second, a feedforward neural network is employed to uncover non-linear interactions between participant demographics and comorbidities (see Supplementary Table 3); third, latent features from each network are combined to estimate the survival function for each participant using Breslow's method. The analysis was repeated in the study population described in Chapter 4, where deep survival ECG risk scores were instead derived using conventional ECG parameters outlined in Section 4.2.2, Supplementary Section A (Appendix p.337-p.33839), and Supplementary Figure 2 Further details on model implementation and architecture are provided in Supplementary material, Section A (Appendix p.340).

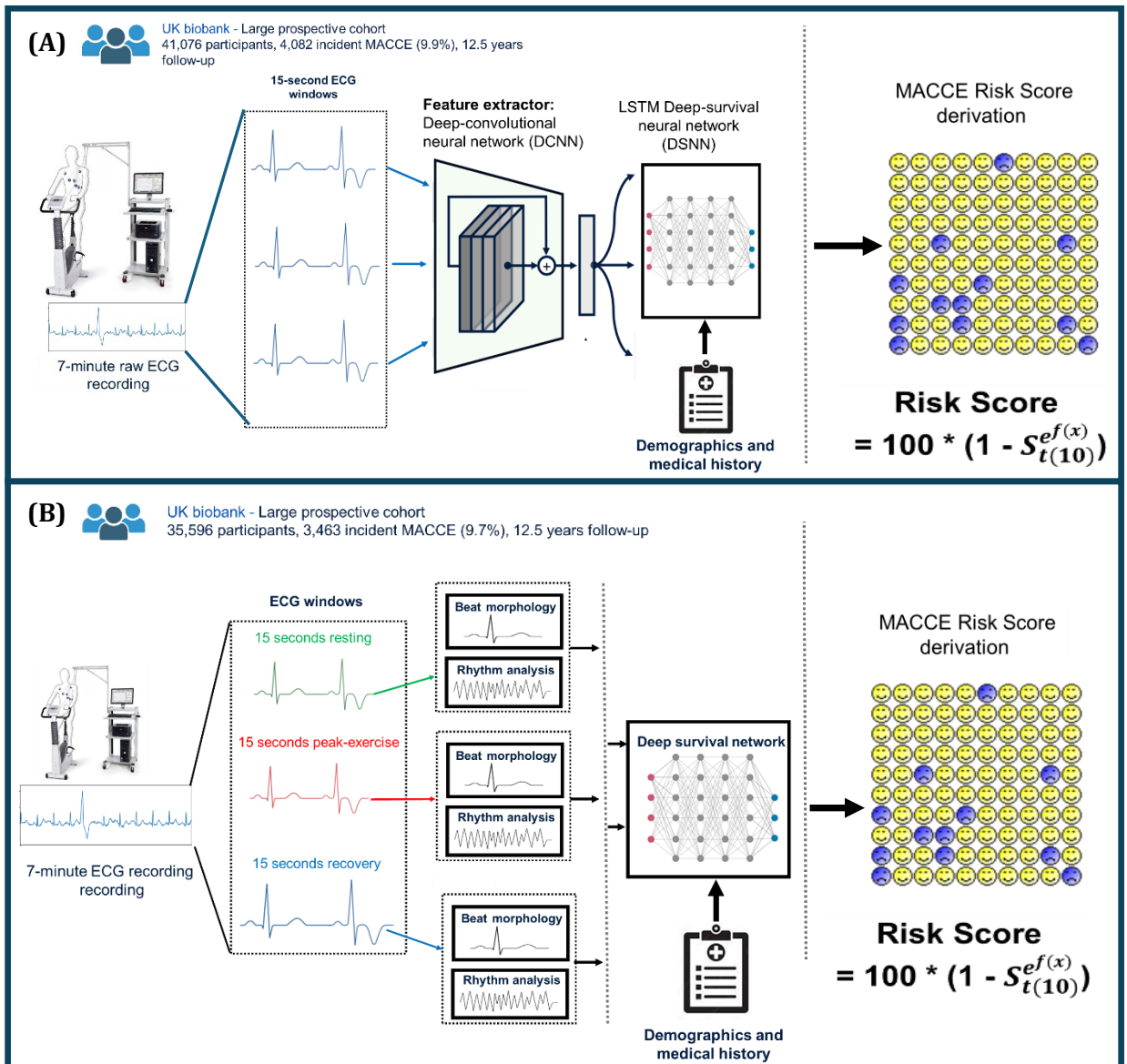


**Figure 5.1:** Overview of the derivation of deep survival ECG risk scores using (A) Raw ECG waveforms taken from the final 15 seconds of rest, exercise and recovery in addition to complete 7 minute 15 second submaximal exercise ECG recording from 41,076 participants (4,082, MACCE; 9.9%) spanning a combined 206 person-days of ECG data; (B) Hand-crafted ECG morphology and rhythm features, including PR-interval, RR-interval, QRS duration and QTC interval from 35,597 participants (3,463 MACCE;9.6%).

QT intervals were adjusted using Bazett's<sup>244</sup> and Fridericia's<sup>245</sup> formulas for resting and exercise ECG measurements, respectively.

Rhythm features were extracted from a Poincare distribution of the change in RR interval over time<sup>242,243,277</sup> (Appendix Section A p.337-p.33839).

#### **5.2.4 Model development and evaluation**

Model validation followed the same procedure outlined in section 4.2.4 to ensure a fair comparison of model performance. Briefly, model performance was assessed using a stratified nested five-fold cross-validation, excluding a single fold for model testing each iteration. The remaining data was aggregated for model training, with 10% of the training data randomly portioned for model validation and parameter selection. The model was trained to predict the risk of incident MACCE over time based on incident MACCE status and the time of event or censoring time from participant healthcare records. The model was trained by minimizing the negative log partial likelihood, ensuring proper handling of censored observations. Early stopping with a patience of 15 epochs was applied to avoid overfitting. Following the example established by Steinfeldt et al. 2022<sup>83</sup>, model performance was evaluated on an aggregated test set of all individuals from each cross-validation, followed by 1000 bootstrap iterations to obtain 95% confidence intervals for further details on model development and validation. Refer to section 4.2.4 and appendix Section A (appendix p.338-p.341).

ECG risk scores were evaluated against three baseline models, including a QRISK3-Inspired risk score, derived using QRISK3 risk factors and functional forms, in separate Cox proportional hazard models for males and females, as described in section 4.2.3, a linear Cox proportional hazard model using QRISK3 risk factors (Cox clinical), and a deep survival network of QRISK3 risk factors, referred to as clinical deep survival (Supplementary Table 3). A shared implementation was adopted across all model training, evaluation and preprocessing procedures for each respective model. This includes cross-validation splits, training rates, early stopping criteria and learning rate schedulers.

A unified approach ensures a fair comparison across various baseline models, as outlined by Oliver et al<sup>278</sup>. Whilst the authors focus on the development of semi-supervised models, they note this framework is applicable across all model types and is essential for ensuring fair model comparison and reproducibility.

Deep survival ECG risk scores based on raw ECG data were also compared to conventional ECG parameters described in chapter 4 using both traditional Cox regression and deep survival neural networks. The list of conventional ECG parameters used in Cox proportional hazards regression and Fully-connected deep survival networks is provided in Appendix Section A. (Tables 1A-2A). This study independently assessed each stage of the sub-maximal exercise test for its contribution to MACCE risk prediction, deriving separate risk scores from: the first 15 seconds at rest, the final 15 seconds of exercise, and the last 15 seconds of recovery.

The strength of the associations between deep survival ECG risk factors and the 10-year incidence of MACCE was evaluated using minimally adjusted Cox proportional hazard models as outlined in section 4.2.4. To address reverse causation, Cox regression association analyses was repeated after removing MACCE that occurred within the 2 years and 5 years of follow-up. Model performance was assessed following the criteria in Section 2.2. Evaluation metrics included Harrell's C-index<sup>99</sup>, and the integrated calibration index (ICI). Reclassification of individuals into low and high-risk groups was assessed using standardised net benefit (NB)<sup>106</sup> and net reclassification index (NRI)<sup>105</sup> at the currently recommended clinical threshold of 10%. p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

To assess the performance of this model by age and sex subgroup, the performance metrics were recalculated in participant subgroups.

As in chapter 4, this study was reported per the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD)<sup>88</sup>. The complete TRIPOD checklist for this chapter is provided in Supplementary Material Section D p.545.

## 5.3 Results

### 5.3.1 Study population

Of the 95,052 participants who completed a submaximal exercise ECG test, 44,421 (46.7%) had complete ECG recordings of sufficient quality and at least ten years of follow-up. Following exclusions outlined in Figure 5.2, 41,076 individuals without a history of CVD and complete covariate data were included in the study. The study population consisted of a balanced set of middle-aged males and females (median age: 58.0 (IQR: 14) male; 50.3 (IQR: 13) female). After a median follow-up period of 12.49 years (IQR: 0.26), 4,082 (9.9%) individuals were diagnosed with MACCE (3,392 non-fatal and 690 fatal). The baseline characteristics of the study participants are described in Table 5.1, including demographic, lifestyle, QRISK3 risk factors. Summary statistics for conventional ECG parameters measured at rest, exercise and recovery can be found in Table 4.1 and Supplementary Tables 10-11 respectively.

When investigating conventional ECG parameters and the risk of incident CVD, a further 5,479 participants were excluded because at least one of the PR, RR, QT or QRS intervals could not be reliably delineated from the ECG (see section 4.4). As their raw ECGs were still of sufficient quality, these participants were retained in the deep learning analyses, which do not rely on interval extraction. No significant differences in the incidence of MACCE were found between those with measurable ECG parameters and the whole cohort of 41,076 participants (Chi-squared statistic = 0.92; p-value = 0.34); incident MACCE = 3,463 (9.7%) median follow-up = 12.49 (IQR 0.27).

**Table 5.1: Baseline characteristics of 41,076 UK Biobank participants without a history of MACCE who underwent a submaximal cycle ergometry test.**

| <b>Characteristics</b>         | <b>ECG cohort (N=41,076)</b> |
|--------------------------------|------------------------------|
| Age (years)                    | 56.9±8.1                     |
| BMI (kg.m <sup>2</sup> )       | 27.4±4.3                     |
| LDL-C to HDL-C ratio           | 4.3±1.0.                     |
| Systolic blood pressure (mmHg) | 136.9±17.0                   |
| Townsend Deprivation index     | -1.2±2.9                     |
| Ethnicity                      |                              |
| White ethnicity (n, %)         | 37,933 (92.3)                |
| Non-White ethnicity (n, %)     | 3,143 (7.7)                  |
| Sex                            |                              |
| Female (n, %)                  | 20,657 (50.3)                |
| Male (n, %)                    | 20,419 (49.7)                |
| Smoking status                 |                              |
| Non-smoker (n, %)              | 22,908 (55.8)                |
| Previous Smoker (n, %)         | 14,516 (35.3)                |
| Current smoker (n, %)          | 3,652 (8.9)                  |
| Type 1 Diabetes (n, %)         | 95 (0.2)                     |
| Type 2 Diabetes (n, %)         | 429 (1.0)                    |
| Treated Hypertension (n, %)    | 2,086(5.1)                   |
| Atrial Fibrillation (n, %)     | 206 (0.5)                    |

Abbreviations: BMI: Body mass index, LDL: Low-density lipoprotein; HDL: High-density Lipoprotein

Data are shown as means±SD for continuous data and me total (%) for categorical data.

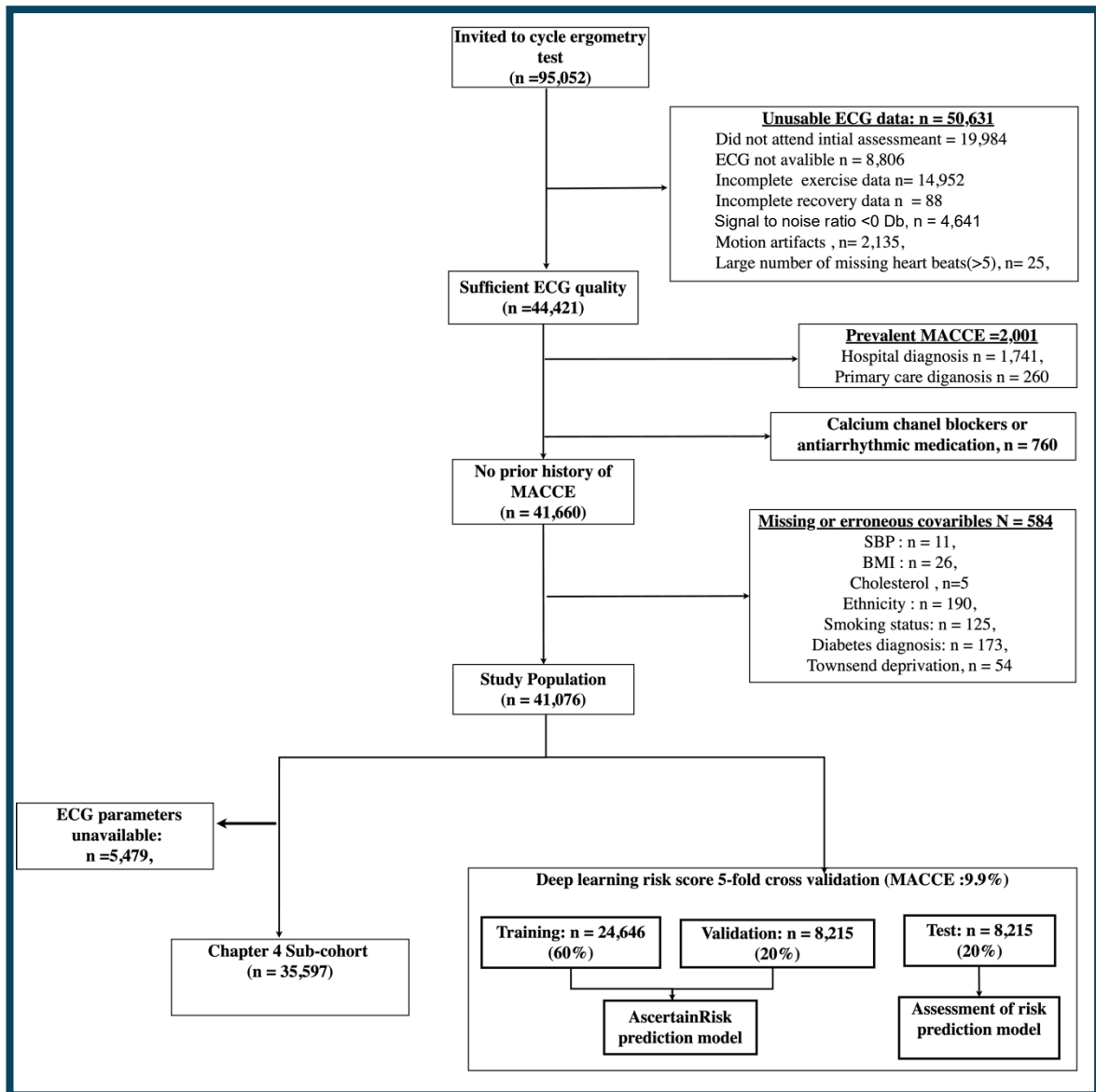


**Figure 5.2: Characteristics of study population:** Flowchart illustrating the number of participants included in the study, along with exclusion criteria and derivation of development/validation sets, including a sub-cohort of 35,597 from chapter 4 (Figure 4.2)

### 5.3.2 Association between ECG and MACCE

This work first compares the strength of the independent association between deep-learned ECG risk scores (Q-ECG) and conventional ECG markers from Chapter 4, with the 10-year risk of incident MACCE. At 10 years 2,591 (7.3%) incident MACCE were reported among participants with measurable conventional ECG parameters. Cox regression analysis revealed an incremental association between the newly derived Q-ECG score —obtained from the complete 7-minute 15-second ECG recording—and incident MACCE, following adjustment for age, sex, smoking status, ethnicity, and deprivation, measured by Townsend's deprivation index<sup>257</sup>. Figure 5.3, illustrates the association between deep-learned Q-ECG risk scores and the 10-year incidence of MACCE, analysed both per fifth and on a continuous scale using penalised splines with 3 degrees of freedom. The spline analysis suggested the association was broadly monotonic and approximately linear across the central range of Q-ECG, with only mild curvature at the extremes and wider uncertainty in the tails, consistent with fewer observations at very low or high Q-ECG values. On the linear scale a significant positive association was observed between Q-ECG and incident MACCE, with a hazard ratio (HR) of 1.18 (95% CI: 1.15-1.21,  $p < 0.001$ ), per standard deviation increase in Q-ECG, following adjustment for age, sex, social deprivation, ethnicity, and smoking status. A significant increase in the risk of MACCE was observed between the top 60-80 and 80-100% of Q-ECG fifths relative to the bottom 20% of Q-ECG HR = 1.20 (95% CI: 1.07-1.34  $p < 0.001$ ), HR = 1.31 (95% CI: 1.18-1.47,  $p < 0.001$ ) respectively. Figure 5.4 presents the adjusted HR per standard deviation for the newly derived Q-ECG risk scores, obtained separately from resting, peak exercise, and end-of-recovery ECG measurements. These are shown alongside selected ECG morphological and rhythm risk factors, as outlined in Chapter 4 (Figure 4.2). ECG measurements, including Q-ECG risk scores and selected conventional ECG parameters, were consistently positively associated with incident MACCE across all stages of the submaximal cycle ergometry test.



Supplementary Figures 9-11 show the HR, per standard deviation, of Q-ECG scores, recalculated for males and females, respectively, for resting, exercise and recovery ECG measurements.

In contrast to conventional ECG parameters presented in Chapter 4, Q-ECG scores showed similar associations with incident MACCE in both males and females across resting, exercise, and recovery measurements.

To assess for reverse causality, sensitivity analyses were conducted by excluding participants diagnosed with MACCE within the first 2 and 5 years of follow-up. During these periods, 347 (1.0%) participants (males: 260 [1.4%]; females: 87 [0.5%]) and 1,087 (3.1%) participants (males: 770 [4.2%]; females: 317 [1.8%]) were diagnosed with MACCE, respectively. Excluding these early cases resulted in minimal changes in the hazard ratios (HRs), and the association of the newly derived Q-ECG risk score persisted across all stages of the submaximal exercise test (see Supplementary Tables 12-13).

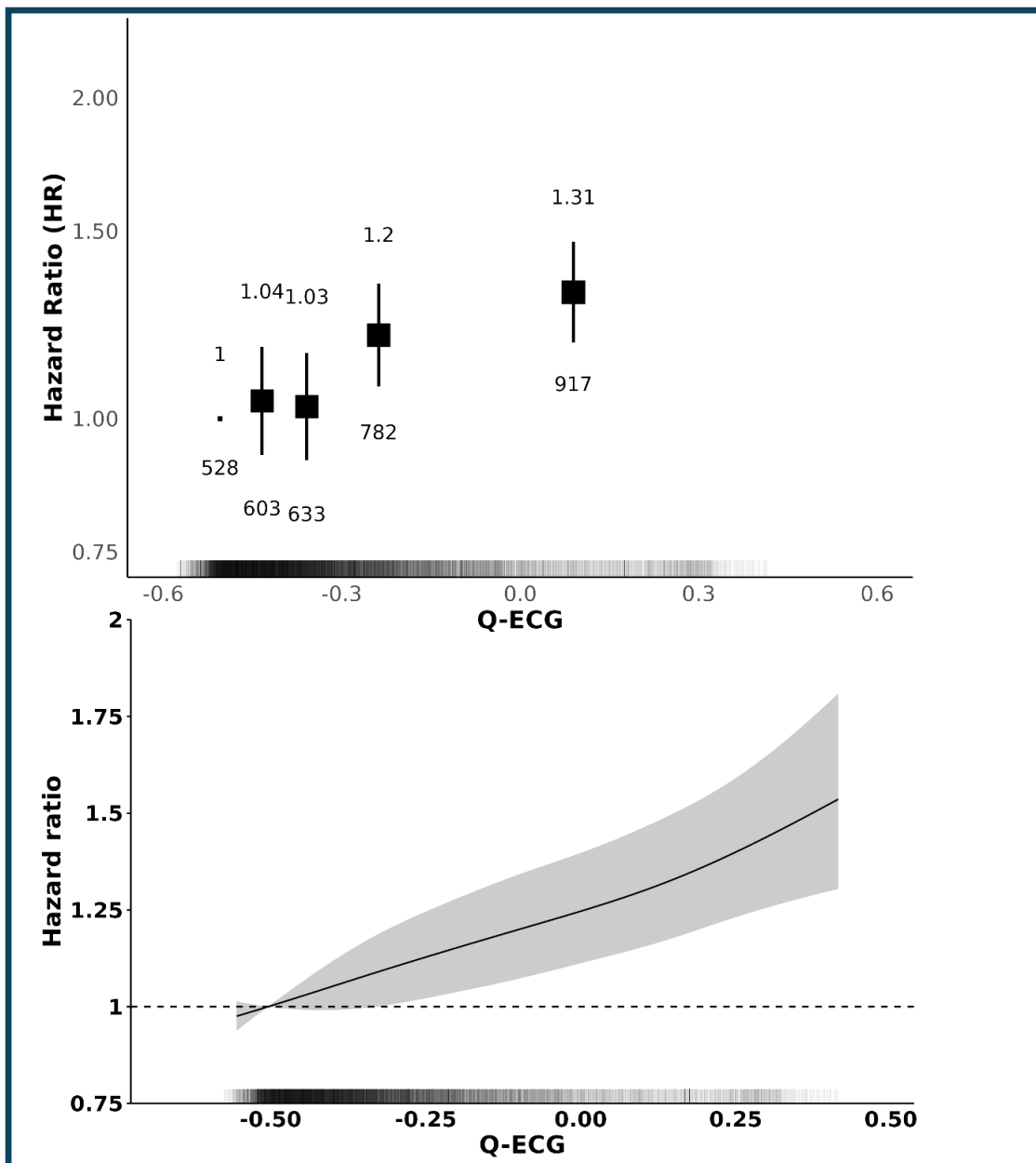


**Figure 5.3: Association between the output of a deep survival network trained on 7-minute 15-second submaximal exercise ECG recordings (Q-ECG) and the 10-year risk of incident Major Adverse Cardiovascular and Cerebrovascular Events (MACCE), adjusted for age, sex, smoking status, ethnicity, and Townsend's deprivation index (Top) Forest plots for the associations between MACCE with fifths of deep learning derived ECG risk scores (Q-ECG), (Bottom) continuous Q-ECG score among 35,597 UK Biobank participants with valid ECG parameters, 2,591 (7.27%) MACCE.**

In the top figure, the HR and number of events is plotted above and below each data point, respectively. The bottom figure shows a spline plot of the hazard ratio and 95% confidence interval of the association of continuously modelled Q-ECG risk scores. Vertical bars along the Q-ECG axis indicate the distribution of participant Q-ECG risk scores. The grayscale bar at the bottom represents the distribution of Q-ECG values across the study population. Darker regions indicate a higher density of participants with corresponding Q-ECG values, while lighter regions indicate lower density.

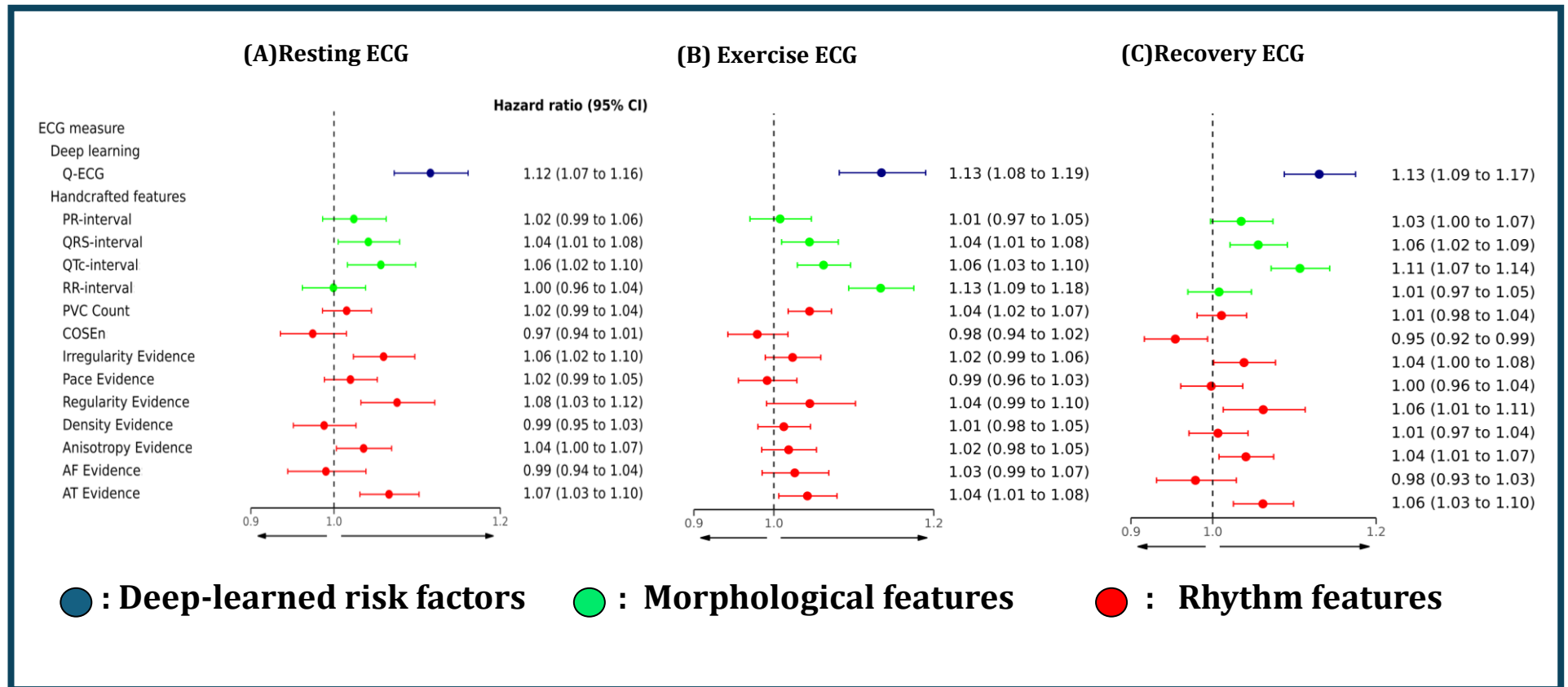


**Figure 5.4: Association of deep-learned ECG risk scores (Q-ECG) and conventional ECG parameters obtained during (A) 15 seconds of rest, (B) the final 15 seconds of a 6-min period of submaximal exercise, (C) the final 15 seconds of a 1-min recovery period post exercise with the 10-year risk of MACCE.**

Each risk factor was adjusted for age, sex, smoking status, social deprivation measured by Townsend deprivation index<sup>257</sup>, and ethnicity. Irregularity, Pace, Regulatory, Anisotropy and AF evidence were adjusted for the number of beats in the signal to account for higher absolute values in participants with faster heart rates.

Hazard ratios are reported per standard deviation increase. Cox proportional hazard models were developed on the aggregated test sets across five cross-validation folds, consisting of 35,597 participants and 2,591 (7.27%) MACCE within 10 years.

The ECG parameters were selected based on previously reported associations with CVD mortality<sup>70,119</sup>, incidence, common risk factors, and other conditions, including chronic kidney disease<sup>120</sup> and atrial fibrillation<sup>242,243</sup>. We also considered rhythm features<sup>242,243</sup>, which have previously demonstrated strong predictive performance for CVD<sup>20,21</sup>.

Premature ventricular contraction (PVC) count: The number of PVCs detected within the ECG signal.

COSEn (ECG signal entropy): Measure of the beat-to-beat RR interval variability obtained by modelling the probability that the RR interval of a short ECG segment will match with other segments in the signal<sup>242</sup>.

Irregularity evidence: Number of irregular heartbeats defined as beats outside normal sinus rhythm<sup>243</sup>.

Regularity evidence: Count of the total number of 3-beat windows, with a median RR interval differing no more than 10ms from the average RR interval.<sup>243</sup>

Density evidence: Measures how closely packed the clusters of changes in RR intervals are in Poincare representation. Lower density evidence corresponds with greater sparsity and greater irregularity in the change in RR interval.

Anisotropy evidence: Measures of the overall direction of change between RR intervals. Higher anisotropy points to a consistent direction of change and helps to distinguish between different types of arrhythmias<sup>243</sup>.

Atrial fibrillation (AF) evidence: Quantifies the presence of atrial fibrillation by offsetting the number of heartbeats in normal sinus rhythm against irregularities evidence and compensatory pauses (PACE)<sup>243</sup>.

Atrial Tachycardia (AT) evidence: Assesses the presence of irregular heart rhythm, changes in RR intervals, clustering of changes in RR interval (Poincare representation), and the occurrence of compensatory pauses<sup>243</sup>.

### **5.3.3 Predictive value of ECG**

#### **5.3.3.1 Univariate Predictive Performance of ECG risk scores**

Next, this work assessed the univariate performance of ECG measurements for the prediction of 10-year risk for incident MACCE. The newly derived Q-ECG risk scores individually predicted the risk of incident MACCE in the absence of clinical risk factors (Table 5.2), with the most predictive component coming from the exercise stage of the ECG test; C-index of 0.591 (95% CI 0.583 - 0.599) and a net benefit of 0.044 (0.029 – 0.058), at a risk threshold of 10%.

Table 5.2 presents the unadjusted hazard ratio, per standard deviation, Harrell's C-index and net benefit at a 10% risk thresholds for Age, QRISK3-Inspired, clinical deep survival and ECG risk scores derived from raw ECG data (Q-ECG) using deep survival networks. This analysis was performed using the study population from Chapter 4, ensuring comparisons were made only for those with available conventional ECG parameters.

Supplementary Table 21 presents the performance of conventional ECG risk scores across the entire study population. Deep survival risk models based on conventional ECG parameters showed improved model discrimination compared to traditional Cox proportional hazard models presented in Chapter 4. However, this improvement did not translate into a higher predictive net benefit at a 10% risk threshold. In contrast, while deep-learned Q-ECG scores derived from raw ECG data were individually predictive of incident MACCE, they did not significantly enhance predictive performance beyond conventional ECG parameters.

Q-ECG risk scores significantly underperform conventional risk models including age + sex, QRISK3-Inspired and Cox clinical risk scores. The relative net benefit and NRI of Q-ECG and each baseline risk score is presented in Supplementary Table 22.

Continuous calibration curves of univariate Q-ECG risk scores showed signs of systematic underprediction in individuals with low observed risk of MACCE, however are generally well-calibrated for those with an observed risk greater than 5%; Supplementary Figure 12).

A full breakdown of the predictive performance of deep survival ECG risk scores is provided in Table 5.2, while Supplementary Table 14 provides the univariate performance of conventional ECG parameters and QRISK3 risk factors.

**Table 5.2: Association and predictive performance of ECG risk scores derived from 15-second recordings during rest, peak exercise and late-stage recovery for 10-year incident Major Adverse Cardiovascular & Cerebrovascular Events**

| Model                  |              | Hazard Ratio<br>(95% CI) | C-index<br>(95% CI) | Net-benefit<br>(95% CI) |
|------------------------|--------------|--------------------------|---------------------|-------------------------|
| Age                    |              | 1.12 (1.11 - 1.13)       | 0.66(0.66 - 0.67)   | 0.18(0.16 - 0.20)       |
| QRISK3-Inspired score  |              | 1.06 (1.06 - 1.08)       | 0.67 (0.67 - 0.68)  | 0.22 (0.20 - 0.24)      |
| Clinical deep survival |              | 1.09 (1.07 - 1.12)       | 0.70(0.70 - 0.71)   | 0.21 (0.18 - 0.24)      |
| Q-ECG                  | Rest         | 1.08(1.07- 1.12)         | 0.57 (0.56 - 0.58)  | 0.03 (0.017 - 0.04)     |
|                        | Exercise     | 1.06(1.05 - 1.11)        | 0.59 (0.58 - 0.60)  | 0.04 (0.029 - 0.06)     |
|                        | Recovery     | 1.07(1.06 - 1.13)        | 0.57 (0.56 - 0.58)  | 0.05 (0.027- 0.06)      |
|                        | Complete ECG | 1.11 (1.09 - 1.12)       | 0.57 (0.56 - 0.58)  | 0.03 (0.016 - 0.04)     |

Data are reported on 35,597 participants with valid ECG parameters, and 2,591 (7.27%) MACCE were reported within 10 years. 95% confidence intervals were obtained via 1000 bootstrap iterations.

Complete ECG = Full 7 minutes 15 seconds of raw ECG data from the complete submaximal exercise ECG test.

Hazard ratios are derived from separate Cox proportional hazard models unadjusted for other risk factors.

Unadjusted Hazard ratios are reported per unit increase, while net benefit is reported at a 10% risk threshold. Age and QRISK3-Inspired risk scores were derived from separate Cox proportional hazard models.

Q-ECG risk scores were derived in separate deep-survival models trained on the final 15-seconds of raw resting ECG measurements, the final 15-seconds of exercise, final 15-seconds of recovery and Full 7 minutes 15 seconds of raw ECG data from the complete submaximal exercise

Each risk score was derived using independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0

### **5.3.4 Added value of ECG to MACCE risk prediction**

#### **5.3.4.1 Discrimination**

To assess the added value of deep-learned ECG risk scores (Q-ECG), this study investigated two approaches to integrating Q-ECG with established clinical risk factors: first, by adding Q-ECG scores to traditional risk factors using Cox proportional hazards models, and second, by combining raw ECG recordings with QRISK3 risk factors through deep survival networks.

Baseline models included age + sex, QRISK3-Inspired risk models, and a linear Cox regression model using QRISK3 risk factors (referred to as "Cox clinical"). Among the baseline models, the best-performing was a linear Cox regression model (Cox clinical), derived from QRISK3 risk factors (Supplementary Table 3), with an overall C-index of 0.714 (95% CI: 0.706–0.721) (supplementary Table 23).

Figures 5.5 and 5.6 show the relative discriminative performance of each model, as measured by Harrell's C-index, before and after the addition of Q-ECG risk scores, derived from complete 7 minute 15 second ECG recordings. To assess the performance across sex performance metrics were recalculated for male and female subgroups respectively.

Across all models, the inclusion of Q-ECG risk scores led to modest improvements in discrimination in the overall study population. However, this improvement was more pronounced in male participants, with no significant changes in C-index reported for female participants over QRISK3-Inspired or Cox clinical risk models. Supplementary Tables 23–24 provide a detailed breakdown of model performance for baseline age + sex, QRISK3-Inspired, and Cox clinical risk models , before and after the addition of Q-ECG risk scores.

#### **Added value of Q-ECG to clinical risk models**

This work first assessed the added value of directly incorporating Q-ECG risk scores into existing models as a new risk factor. The baseline model comprising age and sex alone yielded a C-index of 0.693 (95% CI: 0.686, 0.700) in the overall population, indicating high levels of discrimination.

When Q-ECG risk scores, derived from complete raw ECG data, was added to this model, the C-index increased to 0.699 (95% CI: 0.692, 0.706), demonstrating a modest but significant improvement in discrimination ( $\Delta$ C-index = +0.005 95% CI: 0.004, 0.007,  $p < 0.001$ ).

The sex-stratified results show a similarly modest but significant improvement across both male and female sub cohorts. In the male subgroup the addition of Q-ECG scores yielded an improvement in C-index of +0.008 (95% CI: 0.006, 0.011,  $p < 0.001$ ). While for female participants a change in C-index of +0.005, 95% CI: 0.001, 0.008,  $p = 0.01$  was observed.

The addition of Q-ECG to establish clinical risk factors, yielded minor but statistically significant improvements in discrimination. In the overall population, QRISK3-Inspired risk models yielded a C-index of 0.672 (95% CI: 0.665, 0.680), which increased slightly to 0.673 (95% CI: 0.665, 0.681) after incorporating Q-ECG ( $\Delta$ C-index = 0.002, 95% CI: 0.00, -0.003,  $p = 0.002$ ). A similar improvement was observed in the linear Cox model with an observed increase in C-index of +0.002 (95% CI: 0.001, 0.003,  $p < 0.001$ ).

The sex-stratified results showed a similar trend. In the male subgroup, the addition of Q-ECG led to a significant improvement over QRISK3-Inspired and Cox clinical models, with an increase of  $\Delta$ C-index = +0.003 (95% CI: 0.002, 0.005,  $p = 0.002$ );  $\Delta$ C-index = +0.003 (95% CI: 0.002, 0.005,  $p \leq 0.001$ ), respectively. No significant changes were observed for female participants.

Supplementary Table 23-24 presents the added value of resting, exercise, and recovery Q-ECG scores to each baseline model. For age + sex risk scores, the addition of Q-ECG scores from rest, exercise and recovery led to significant improvements in the C-index. When added to QRISK3-Inspired risk models, only exercise and recovery ECG risk scores provided a significant enhancement in C-index.



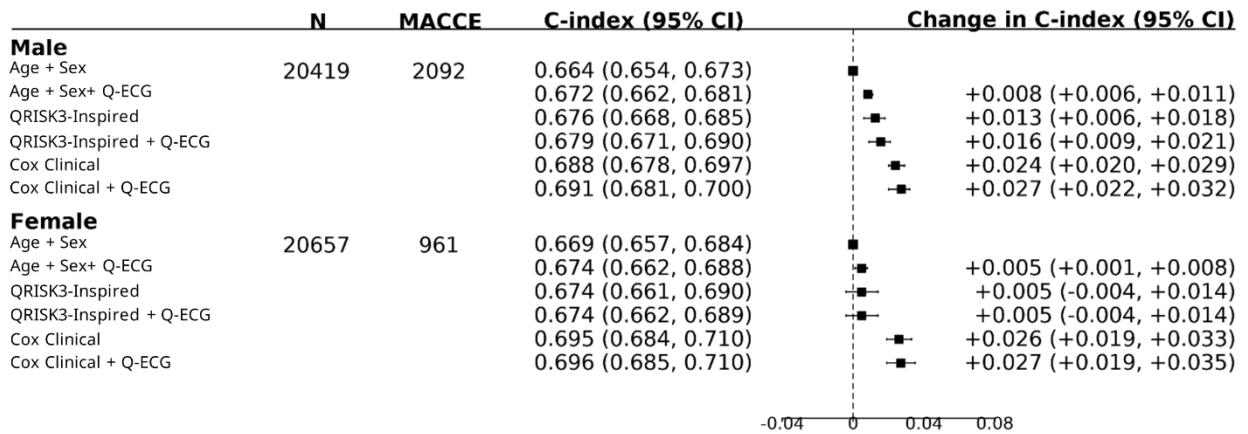


**Figure 5.5: Forest Plot showing Harrell's C-index of clinical risk models derived from Age + Sex, QRISK3-Inspired risk models, and linear Cox model of QRISK3 risk factors combined with ECG risk scores derived from 7-minute15 second submaximal ECG recordings using a Deep neural network (Q-ECG); in 41,076 UKB participants with ECG collected from 2009-2013.**

Abbreviations: CI = Confidence interval, MACCE = Major Adverse Cardiovascular/Cerebrovascular Events;95% confidence intervals were derived via 1000 bootstrap iterations.

Squares represent change in C-index compared to age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness

### Added value of Deep Survival Networks and ECG Data

To determine if neural networks improve risk prediction over conventional models, I first compared a deep-survival network, trained using the original QRISK3 risk factors (Clinical DSN) against two baseline models: QRISK3-Inspired and Cox Clinical risk models. Clinical DSN showed a significant improvement in model discrimination over the baseline QRISK3-Inspired risk models ( $\Delta$ C-index = +0.032, 95% CI: 0.026, 0.038, p<0.001), however failed to match the performance of a linear Cox regression trained using the same risk factors. ( $\Delta$ C-index = -0.01 95% CI: -0.014 - -0.008, p<0.001)

When evaluating the sex specific performance of clinical DSN risk scores, there were no significant improvements across either male or female participants over QRISK3-Inspired or Cox clinical models. A full breakdown of model performance for DSN and DSN + ECG risk scores is shown in Supplementary Table 25.

Figure 5.6 shows the change in C-index after integrating 7-minute, 15-second raw ECG recordings into deep survival networks alongside age, sex, and QRISK3 risk factors (DSN clinical), respectively.

In the overall population, adding ECG recordings did not significantly improve discrimination when combined with either an age+sex neural network ( $p = 0.3$ ), relative to linear age+ sex risk scores, or a clinical deep survival network ( $p = 0.6$ ) derived from QRISK3 risk factors.

Sex-stratified results showed a significant improvement in C-index for female participants with the addition of ECG data to the clinical deep survival network ( $\Delta$ C-index = +0.007, 95% CI: 0.002–0.011,  $p < 0.001$ ). However, in contrast to the improvements observed in traditional risk models (Figure 5.5 and Supplementary Table 26), the addition of ECG data to the clinical DSN yielded no significant improvement in discrimination for male participants.

Supplementary Tables 25-26 and Supplementary Figures 13-15 present the added value of individual ECG components (rest, exercise, and recovery) to age + sex and clinical deep survival networks. In the age + sex models, the inclusion of resting, exercise, or recovery ECG data significantly improved C-index values compared to the baseline age + sex risk scores.

Additionally, within the clinical DSN model, adding either resting or recovery ECG data led to significant improvements in C-index, with  $\Delta$ C-index = +0.011 (95% CI: 0.0203 - 0.019,  $p < 0.001$ ) for resting ECG and  $\Delta$ C-index = +0.001 (95% CI: 0.003 - 0.018,  $p < 0.001$ ) for recovery ECG. Similar findings were reported in the female sub cohort. However, no significant improvements were observed in the male subgroup.

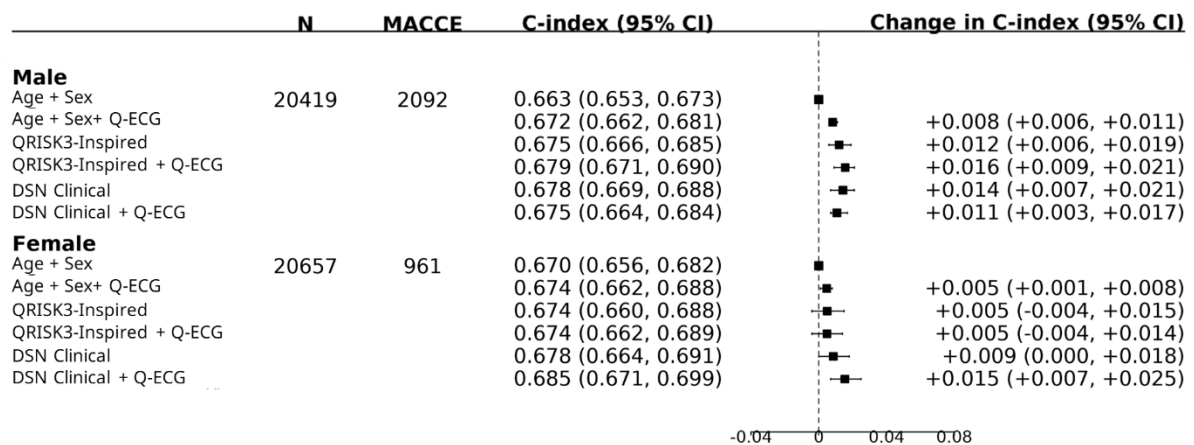


**Figure 5.6: Forest plot of Harrell's C-index for clinical risk scores derived from Age + Sex, QRISK3-Inspired, risk scores and deep survival networks with clinical risk factors and ECG data (Q-ECG).** Q-ECG scores were derived from a deep survival network using 7-minute 15-second submaximal exercise ECG recording.

Abbreviations: DSN = Deep survival network CI = Confidence interval

Squares represent change in C-index compared to age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap resamples

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

DSN clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1+ Diabetes type 2, HDL ratio, Townsend deprivation index+ Smoker former, Smoker current, Smoker never+ Ethnic Background, Corticosteroid+ Migraine, Hypertension, Severe mental illness ,Rheumatoid Arthritis

#### 5.3.4.2 Calibration

Age + Sex and QRISK3-Inspired risk scores were well-calibrated to the study population, showing close alignment between the observed and predicted risks. Figure 5.7 shows the continuous calibration curves for age+ sex and QRISK3-Inspired risk scores, before and after the addition of resting ECG measurements using deep survival networks.

The addition of age, sex and complete ECG recordings to deep survival networks, showed modest signs of overfitting, with slight overprediction for individuals with observed risks around 10% and underprediction for those above 12.5%. No significant changes in the absolute calibration measured by the integrated calibration index (ICI) were observed (Supplementary Table 26).

Supplementary Figure 16 shows the calibration curves for resting, exercise and recovery ECG recordings, combined with age and sex in a deep survival network. No significant changes in ICI were reported across any stage of the ECG recording (Supplementary Table 25-26).

Clinical DSN + ECG models demonstrated strong calibration within the study population (Figure 5.7 and Supplementary Table 25). Adding complete ECG data to the deep survival network resulted in a slight improvement in Integrated Calibration Index (ICI), with a reduction of -0.002 (95% CI: -0.004 to 0,  $p = 0.04$ ). A lower ICI indicates closer alignment between observed and predicted risks, suggesting enhanced calibration accuracy.

Clinical DSN + ECG data measured during the final 15-seconds of rest, exercise, recovery in addition to complete ECG recordings demonstrated improved calibration compared to the baseline QRISK3-Inspired models across all ECG risk scores (Supplementary Table 26).

Supplementary Figure 17 presents the calibration curves for Clinical DSN + ECG risk scores from resting, exercise, and recovery ECG recordings.

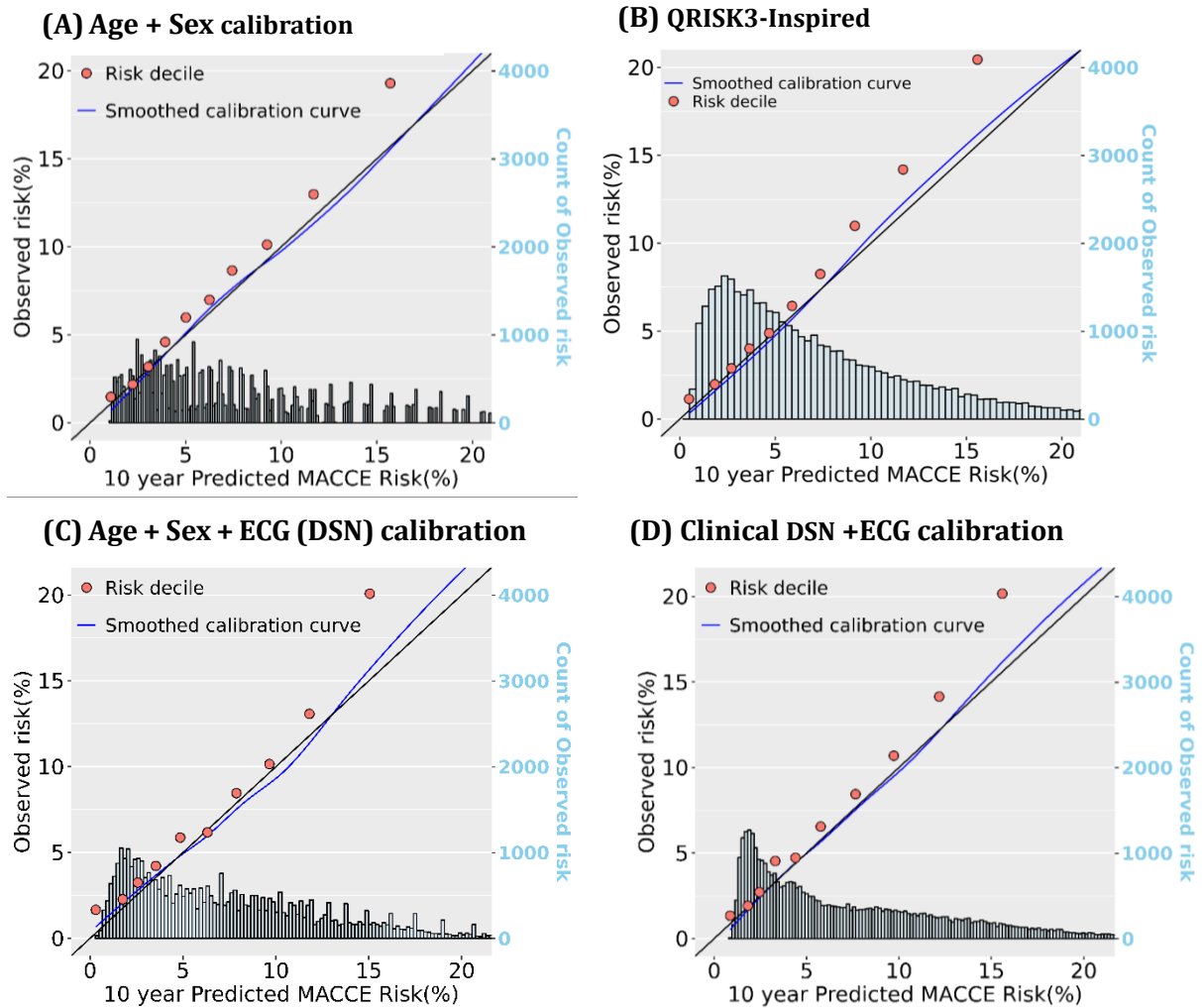


**Figure 5.7 Smoothed calibration curve: for (A) Age + Sex, (B) QRISK3-Inspired, (C) Age + Sex + 7 minute 15 second ECG, and (D) QRISK3-Inspired + 7 minute 15 second ECG risk scores.**

DSN: Deep survival network, ECG = Full 7 minutes 15 seconds of raw ECG data from the complete submaximal exercise ECG test.

The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.

Age + Sex risk scores were derived using Cox proportional hazard regression, while QRISK3 was recalibrated to the study population using in separate Cox regression models for males and females, respectively.

QRISK3-Inspired: *Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension*

*Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension + Age FP 2 \* Corticosteroid treatment*

Fractional polynomials: *Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )*

DSN clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1+ Diabetes type 2, HDL ratio, Townsend deprivation index+ Smoker former, Smoker current, Smoker never+ Ethnic Background, Corticosteroid+ Migraine, Hypertension, Severe mental illness, Rheumatoid Arthritis

### 5.3.4.3 Reclassification

Table 5.3 presents the reclassification performance of Q-ECG risk scores, derived from a complete 7-minute 15-second submaximal exercise ECG, when added to four baseline models: age+sex, QRISK3-Inspired, Cox Clinical, and Clinical DSN risk scores.

Among the baseline models, Cox Clinical demonstrated the best predictive performance, showing improved continuous Net Reclassification index (NRI) over QRISK3-Inspired risk scores (NRI = 0.185; 95% CI: 0.149–0.221,  $p < 0.001$ ) and Clinical DSN (NRI = 0.089; 95% CI: 0.052–0.126,  $p < 0.001$ ) respectively. However, no significant differences in reclassification were observed at the 10% risk threshold for any of the baseline models (Supplementary Table 27).

### Added value of Q-ECG to clinical risk models

Across all baseline risk scores, the addition of Q-ECG resulted in significant improvement in continuous NRI, indicating enhanced discrimination. However, improvements in risk stratification at the 10% clinical threshold were limited.

The addition of Q-ECG risk scores yielded modest but significant improvements in net benefit for age+sex models. Additionally, when integrated with Clinical DSN models a slight improvement in categorical NRI was observed at a 10% risk threshold. However, no significant classification improvements were observed when adding Q-ECG to QRISK3-Inspired or Cox Clinical risk scores (Table 5.3).

Supplementary Table 28 presents the added value of Q-ECG scores derived from resting, exercise, recovery and complete ECG measurements across all baseline models. Significant improvements in the continuous NRI were reported for all age+sex + Q-ECG models compared to age+sex alone. When assessing the added value of Q-ECG to established clinical risk models, a significant improvement in continuous NRI was reported across all sub-stages of the ECG recording, with the exception of recovery. Risk scores derived from complete ECG measurements outperformed those from individual ECG components (rest, exercise, and recovery), yielding the greatest improvement in predictive performance.

However, no significant classification changes were observed at the 10% risk threshold incorporated into QRISK3-Inspired risk scores (Table 5.3; Supplementary Table 28).

**Table 5.3: Changes in Net Reclassification and Net Benefit following the addition of Q-ECG to Age + Sex, QRISK3-Inspired, Cox Clinical, and Clinical DSN risk scores, derived from QRISK3 risk factors.**

| Model           | Comparator             | Net-benefit (95% CI)  | Categorical NRI (95% CI) | Continuous NRI (95% CI)  |
|-----------------|------------------------|-----------------------|--------------------------|--------------------------|
| Age + Sex       | Age + Sex + Q-ECG      | **0.01(0.002 - 0.018) | 0.007 (-0.002 - 0.016)   | ** 0.144 (0.107 - 0.181) |
| QRISK3-Inspired | QRISK3-Inspired+ Q-ECG | 0.001(-0.006 - 0.007) | 0.000(-0.007 - 0.007)    | **0.097 (0.061 - 0.133)  |
| Cox clinical    | Cox clinical+ Q-ECG    | 0.004(-0.005 - 0.012) | 0.003 (-0.006 - 0.011)   | **0.103 (0.066 - 0.139)  |
| Clinical DSN    | Clinical DSN+ Q-ECG    | 0.005(-0.007 - 0.016) | * 0.014 (0.003 - 0.025)  | **0.272 (0.235 - 0.308)  |

Data are reported on 41,076 participants with 3,053 (7.4%) MACCE over 10 years.

Abbreviations: NRI = Net reclassification index, CI = Confidence interval

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

The Cox-clinical and clinical DSN models include an identical set of clinical risk factors (age, BMI, systolic blood pressure and SBP5, diabetes type 1 and 2, HDL cholesterol ratio, Townsend deprivation index, smoking status, ethnicity, corticosteroid use, migraine, hypertension, and severe mental illness), differing only in modelling framework and were fitted using sperate linear Cox regression and deep survival network, respectively.

95% CI's and p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

\*p value <0.05

\*\* p value < 0.001

### Added value of Deep Survival Networks and ECG Data

Table 5.4 evaluates the newly developed Clinical DSN + Q-ECG model against each baseline risk score. Compared to age+sex, significant improvements were seen in both categorical and continuous NRI. When evaluated against QRISK3-Inspired risk scores, Clinical DSN + ECG resulted in a significant increase in continuous NRI but showed a decrease when compared to Cox Clinical risk scores. No significant changes in net benefit or categorical NRI, models at a 10% risk threshold, were observed compared to QRISK3-Inspired or Cox clinical models.

Supplementary Table 29 separately examines the predictive performance of clinical DSN + Q-ECG risk scores derived from resting, exercise, and recovery subcomponents against each baseline model. A similar trend was observed for each subcomponent with significant improvements in continuous NRI over Age + Sex and QRISK3-Inspired models, and a significant decrease in continuous NRI vs. Cox clinical. No significant improvements in net benefit or categorical NRI were reported.

**Table 5.4: Performance of Q-ECG Deep survival networks (DSN) versus Age + Sex, risk models and Cox clinical risk scores for stratifying high-risk individuals.**

| Model           | Comparator                | Net-benefit<br>(95% CI) | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|-----------------|---------------------------|-------------------------|-----------------------------|----------------------------|
| Age + Sex       | Age + Sex+ Full ECG (DSN) | 0.006(-0.005 - 0.017)   | *0.013 (0.002 - 0.024)      | **0.127 (0.090 - 0.164)    |
| QRISK3-Inspired | Clinical DSN +Full ECG    | -0.004(-0.016 - 0.008)  | 0.0051 (-0.007 - 0.017)     | - **0.230 (0.193 - 0.266)  |
| Cox clinical    | Clinical DSN +Full ECG    | -0.004(-0.013 - 0.007)  | 0.005 (-0.005 - 0.015)      | ** -0.025 (-0.062 - 0.012) |

Abbreviations: NRI = Net reclassification index, CI = Confidence interval

Data are reported on 41,076 participants with 3,053 (7.4%) MACCE over 10 years. 95% CI's and p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

The Cox-clinical and clinical DSN models include an identical set of clinical risk factors (age, BMI, systolic blood pressure and SBP5, diabetes type 1 and 2, HDL cholesterol ratio, Townsend deprivation index, smoking status, ethnicity, corticosteroid use, migraine, hypertension, Rheumatoid Arthritis and severe mental illness), differing only in modelling framework and were fitted using sperate linear Cox regression and deep survival network, respectively.

\*p value <0.05; \*\* p value < 0.001



Supplementary Table 30 presents the added value of conventional ECG parameters measured during the final 15 seconds of rest, exercise and recovery stages of the submaximal exercise ECG test, to QRISK3-Inspired, Cox clinical and clinical DSN risk scores. Despite superior discrimination and net benefit of conventional ECG parameters compared with Q-ECG outlined in Table 5.2, no significant improvements were reported to any of the baseline models when combined with clinical risk models.

Further building on the work of chapter 4, Supplementary Table 31 presents the added value of conventional ECG parameters to each baseline model for males and females separately, while Supplementary Table 32 compares clinical DSN+ conventional ECG parameters against QRISK3-Inspired, Cox clinical and clinical DNS risk scores in males and females respectively.

All deep survival models combining conventional ECG parameters and QRISK3 risk factors exhibited a significant decrease in continuous NRI. By contrast, deep survival networks trained on raw ECG data achieved a significant increase in continuous NRI across all ECG-derived risk scores compared to QRISK3-Inspired risk scores. However, neither conventional ECG or Q-ECG models improved risk stratification at the 10% risk threshold relative to either QRISK3-Inspired or Cox clinical risk scores.

#### **5.3.4.4 Subgroup analysis**

Supplementary Tables 33-34 present the reclassification results across male and female sub cohorts following the addition of Q-ECG to QRISK3-Inspired and Cox clinical risk scores. A significant improvement in the continuous NRI was observed for QRISK3-Inspired + Q-ECG risk scores, however, no improvements in net benefit or categorical NRI were reported for either sub cohort (Supplementary Table 33).

When comparing clinical DSN + complete submaximal ECG recordings with clinical risk models, a significant improvement in categorical NRI was observed for female participants at the 10% risk threshold compared to QRISK3-Inspired (categorical NRI = 0.085, 95% CI: 0.061–0.108,  $p < 0.001$ ) and Cox clinical risk scores (NRI = 0.020, 95% CI: 0.002–0.037,  $p = 0.03$ ) respectively.

Participants were further divided into four age groups; under 45's (n = 3,830); 45-55 (n = 11,863); 55-65 (n= 16,943) and over 65's (n = 6,781). Reclassification performance across age and sex subgroups are summarized in Supplementary Tables 35–38.

Compared to QRISK3-Inspired the Clinical DSN + ECG risk scores demonstrated the greatest improvements in younger male participants (under 45) and older female participants (over 55).

Among males, significant improvements were reported for those under the age of 45, significant with an observed increase in net benefit of 4.8% (95% CI: 2.3–7.7%,  $p = 0.048$ ) and a categorical NRI of 1.1% (95% CI: 0.5–1.7%,  $p < 0.001$ ). For females aged 55–65, an increase in categorical NRI of 3.6% (95% CI: 0.9–6.4%,  $p = 0.01$ ) was observed. While females over 65 experienced the largest gains in risk stratification, with an increase in net benefit of 6.8% (95% CI: 1.0–12.5%,  $p = 0.026$ ) and a categorical NRI of 9.5% (95% CI: 4.2–14.8%,  $p < 0.001$ ).

When compared to Cox Clinical models, the reclassification benefits of Clinical DSN + ECG models were greatly attenuated. Significant improvements were observed for males aged 45–55.

## **5.4 Discussion**

### **5.4.1 Overall findings**

The work presented in Chapter 5 builds upon the findings of Chapter 4 by exploring the potential added value of deep learning for integrating ECG data into clinical risk models. In contrast to the previous chapter, this work adopts a more holistic approach by leveraging raw ECG recordings rather than relying on a limited set of hand-selected features, to capture a wider range of potentially informative patterns within ECG recordings.

This chapter makes three primary contributions: first, it examines the use of deep learning to predict incident MACCE directly from raw ECG data; second, it assesses the additional predictive value of deep-learned ECG risk scores to established clinical risk factors; and third, it compares the performance of models based on raw ECG data with those using conventional ECG parameters, as described in Chapter 4.

Through the development and internal validation of a novel deep-learned ECG risk score this work shows that risk scores derived from raw ECG data alone are predictive of incident MACCE, however failed to significantly improve predictive performance beyond conventional ECG parameters, when analysed using deep-survival networks (Supplementary Table 21). Additionally, despite the positive association between ECG measurements and the risk of MACCE, the addition of deep-learned ECG risk scores to QRISK3-Inspired scores yielded only modest gains for identifying new high-risk individuals at the 10-year, 10 % risk threshold for preventive treatment.

Finally, this study found notable differences in the performance of deep-learned ECG risk scores across age and sex subgroups when combined with QRISK3-Inspired risk scores. ECG risk scores demonstrated higher levels of discrimination and significantly improved reclassification for female participants at the clinically relevant risk threshold of 10%, as per current UK clinical guidelines<sup>26</sup>.

Differences in performance between sexes became more pronounced when further stratified by age. In particular ECG risk scores showed high levels of discrimination and significantly improved risk classification for older female participants, aged 55 and above, and younger male participants under the age of 55. These groups are typically at intermediate risk of MACCE (between 5%-10% within the study population), with increased age and male sex recognised as significant risk factors for incident MACCE. These findings suggest that deep learning ECG risk scores may enhance risk stratification for individuals at moderate to high risk of MACCE. However, further research is necessary to validate these findings and elucidate the mechanisms underlying this improved performance.

#### **5.4.2 Comparison with the wider literature**

To my knowledge, this is the largest population-based prospective cohort study investigating the added value of submaximal exercise ECG recordings to clinical risk models in individuals with no history of CVD. It is also the first study to directly compare the predictive performance of deep-survival networks using raw ECG data against conventional ECG parameters for ECG measurements recorded during rest, exercise and post-exercise recovery.

This chapter addresses several key limitations in the existing evidence on the predictive value of ECG-based risk scores for primary prevention of CVD, outlined in Chapters 2, 4 and the USPSTF review. Namely previous studies on the use of ECG for CVD risk prediction were often limited by small sample sizes, short follow-up durations, and insufficient data on low-risk populations<sup>95</sup>. By leveraging a large cohort of asymptomatic individuals (n = 41,076) with over 12.5 years of follow-up via medical record linkage, this work provides a robust foundation to assess the added value of ECG recordings for long-term cardiovascular risk prediction.

Moreover, whereas prior investigations focused on a handful of hand selected conventional ECG parameters, which often differ between studies and lack sensitivity to subtle changes in ECG traces. The deep-learning models developed in this study draws on complete raw ECG data, without any a priori assumptions as to the key features and risk factors.

The predictive performance of Q-ECG risk scores was broadly consistent with the literature on deep learning–derived ECG risk models, with prior studies showing similarly modest levels of discrimination within the UK Biobank (C-indices 0.55–0.64)<sup>148,149</sup>. However, the literature provides little direct evidence on the incremental benefit of deep-learning ECG risk scores to traditional clinical models for primary-prevention.

Sau et al. (2024) showed that combining deep-survival ECG risk scores (AI-ECG) from hospital outpatient recordings with risk factors from the Pooled Cohort Equation (PCE) improved C-index by 0.037 vs. 0.033 in the present study. However, AI-ECG predictions were made over a 5-year period vs. the 10-year currently recommend in UK clinical practice and used in this work and. Differences in sample size and ECG characteristics were also notable: with the Ai model from Sau et al. including far more ECG recordings (41,076 vs. 1,163,401) and used primarily 12- and 8-lead data, while this study focused on single-lead recordings across rest, exercise, and recovery phases.

In a separate prospective cohort study, Hughes et al. found that 12-lead AI-ECG risk scores matched the discrimination PCE and improved classification across low, moderate, and high-risk groups<sup>148</sup>. However, this study did not directly assess the added value of ECG to PCE, instead composite scores were derived using a weighted mean of PCE and ECG risk scores. It is unclear how the relative weighting was derived, and which population was used, raising concerns about potential selection biases in the approach. As this weighting was derived from a specific population, it may lack generalisability, particularly if the relative importance of risk factor differs across different cohorts.

Results relating to the reclassification of participants into low and high-risk groups along current clinical guidelines are not comparable across previous studies. Many studies in the literature either lacked reclassification metrics, such as the investigation by Sau et al<sup>149</sup>, or used arbitrary thresholds specific to their individual datasets and models<sup>148</sup>. Likewise, no studies were identified which reported model calibration of deep-learned ECG risk scores, limiting the reliability of these predictions in clinical settings.

As a result, the claim of improved predictive performance cannot be reliably established<sup>279</sup>. Furthermore, prior studies often did not report whether baseline models were recalibrated to their specific populations. For instance, Hughes et al. used the pooled cohort equation as a baseline without recalibration, potentially favouring the ECG risk score which was trained directly on the study population<sup>148</sup>.

This work builds upon prior evidence by evaluating model calibration and reclassification for all models, using clinically recommended risk thresholds adhering to NICE guidelines and the recommendations of the USPSTF<sup>26,95</sup>. This places the reported performance of each model into a wider clinical context and provides a broader picture of the overall added value of ECG measurements to current clinical risk prediction practices.

The predictive value of ECG recordings was assessed by directly integrating ECG risk factors with QRISK3-Inspired risk scores, the risk model currently recommended in UK primary care. QRISK3 coefficients were recalibrated to the study population using Cox proportional hazards models, following the same training procedures applied to all other models. This ensured consistency across models and enabled a fair comparison between ECG-based risk scores and current clinical practice.

### **Study Limitations**

This study has a few key limitations to be taken into consideration when interpreting the findings. Many of the study limitations are shared with those outlined in Chapter 4, reflecting broader challenges associated with UKB and prospective cohort data more generally. Importantly, many of these limitations are method-agnostic and apply broadly to the study population. First, as outlined in chapter 4, this study suffers from a well-documented healthy volunteer selection within the UK Biobank (UKB), demonstrated by an overall decrease in all-cause mortality and incidence of various health conditions<sup>20</sup>. Furthermore, due to a strict eligibility criterion for the submaximal exercise test, this healthy volunteer bias is further compounded in the study population.

The 7.3% 10-year incidence of MACCE is substantially lower than the estimated risk of the wider UK population of 18%<sup>267</sup>, meaning current clinical risk thresholds may be sub-optimal in the study population, potentially harming the reclassification and net benefit analysis.

Second, due to motion artefacts and noise resulting from various movements during exercise, ECG morphology could not be reliably measured across the entire study population. As a result, several participants had to be removed from the association analysis comparing Q-ECG risk scores to conventional ECG parameters.

Due to the resource constraints of training large deep learning models, this work adopted single imputation instead of multiple imputations for covariates with a large degree of missingness. Missing at random assumptions were not formally evaluated, and no sensitivity analyses were conducted; therefore, bias due to informative missingness cannot be ruled out. Because the level of missingness is relatively limited (10.1%), it is unlikely to impact the stability of the results.

Finally, owing to a lack of access to a comparable dataset, these results have yet to be validated in an external dataset, limiting the ability to assess how well our findings generalise outside the UKB.

### **5.4.3 Summary**

This work found that deep neural networks can successfully identify risk factors for incident MACCE from raw ECG recordings, measured during rest, exercise and recovery. When added to risk factors used from the current risk prediction tool in the UK, QRISK3, this study shows that ECG measurements resulted in marginal improvements in predictive performance. However, little change in treatment groups was observed, based on current clinical guidelines. This supports current findings from the USPSTF advising against the use of exercise ECG for low-risk individuals. While deep learning was found to improve model discrimination and potentially improve the classification of female participants, more research is required to validate this finding across a wider population.

## Chapter 6 – Accelerometer measured physical activity and the 6-year risk of Major Adverse Cardiovascular/Cerebrovascular Events

### 6.1 Introduction

#### 6.1.1 Background

Physical activity (PA) is integral to human life; regular PA reduces the risk of various non-communicable diseases and is linked to improved cognitive function and mental well-being<sup>73,77</sup>. As a result, PA targets—spanning sedentary behaviour, light physical activity (LPA), and moderate-to-vigorous physical activity (MVPA)—are central to national and international strategies for preventing CVD<sup>22</sup>. Despite the establishment of objective guidelines, PA levels remain alarmingly low. Low levels of PA are among the top 3 most common risk factors for incident CVD across all age groups in the UK, and 25% of adults globally fail to meet PA recommendations<sup>16,184</sup>. The latest WHO report estimates that up to 8% of all causes of CVD may be prevented by meeting PA guidelines, while Lee et al. estimated that 6% of CAD events globally could be attributed to low PA<sup>185,186</sup>. As such, there is a critical need for a new approach to promote PA in the population and identify those who would most benefit from targeted interventions.

International guidelines, including those from the WHO<sup>280</sup>, the United Kingdom<sup>26</sup>, and Europe<sup>32</sup>, recommend the use of CVD risk prediction tools to identify high-risk individuals who are most likely to benefit from targeted interventions. Such individualised risk assessments have been shown to enhance patient motivation and improve adherence to interventions by effectively communicating personal risk and the potential benefits of lifestyle modifications<sup>26,30,40</sup>. In response, the European Society of Cardiology (ESC) and the UK National Health Service now recommend individual risk assessments and tailored PA prescriptions to mitigate CVD risk<sup>4034,35</sup>. However, no established clinical risk models currently incorporate PA measurements, limiting opportunities for clinicians to prescribe personalised interventions and for individuals to actively modify their behaviour to reduce risk.



Despite the well-documented protective association between PA and CVD<sup>79,281–283</sup>, the added predictive value of PA in MACCE risk prediction remains uncertain. Early attempts to integrate PA into clinical risk models have yielded inconsistent results, constrained by modest sample sizes and a reliance on self-reported PA data<sup>187,188,284</sup>. Such data is often affected by substantial recall bias, social-desirability bias, and limited generalisability across diverse socioeconomic groups, further complicating its utility in accurate risk prediction<sup>187,188,189</sup>. In contrast, more robust improvements in predictive performance have been observed for objectively measured fitness levels. However, such tests are not easily self-administered, require specialist equipment and may be ill-suited for those with difficulty performing structured exercise<sup>285–287</sup>. Recent technological advances have led public health organisations to consider the role of digital devices, such as wrist-worn accelerometers, which can objectively capture PA over prolonged periods. These devices are highly scalable, easily self-administered and enable health organisations to continuously monitor an individual's physical activity, providing greater insights into their risk<sup>288</sup>. Wrist-worn accelerometers, such as the Axivity AX3, provide robust objective PA estimates, showing strong agreement with ground-truth energy expenditure (doubly labelled water)<sup>230</sup> and high-accuracy for classifying sedentary, light, and moderate-to-vigorous activity when validated against a wearable-camera<sup>171,231</sup>. By contrast, self-reported PA typically shows only modest agreement with objective measures due to recall and social desirability bias when validated against objective PA measurements<sup>161</sup>. Recent evidence has shown that the associations between objective accelerometer-measured PA and incident CVD far exceed those previously observed from self-reported data<sup>78,162,189,289</sup>.

However, substantial gaps in knowledge remain as to how accelerometer-measured PA may impact risk prediction for primary prevention<sup>78,162,189,289</sup> (see Chapter 2). Prior works have largely focused on a range of activity metrics that are not commonly available across commercial devices and are often difficult to interpret, limiting opportunities for clear intervention. Furthermore, while there is strong evidence supporting the general prognostic value of accelerometer-measured PA<sup>197</sup>, little attention has been given to its added value when

integrated into established clinical risk models, such as QRISK3 or SCORE2, for the primary prevention of MACCE and related mortality. This gap highlights the need for a more targeted investigation into the clinical utility of interpretable and actionable PA metrics within the context of widely adopted risk models.

### **6.1.2 Aims**

This work aims to assess the added value of accelerometer-derived 24-hour movement behaviours, commonly featured in public health guidelines, in enhancing CVD risk prediction for primary prevention. Leveraging a large, prospective cohort of 100,000 individuals with seven days of wrist-worn accelerometer data from the UK Biobank, this study develops and validates novel accelerometry-based risk scores to quantify the incremental predictive value of objectively measured PA when added to risk factors from established CVD risk scores including QRISK3 and SCORE2, the currently adopted risk models in the UK and Europe in primary care.

Additionally, in line with NICE recommendations, this work examines the added value of PA data to age alone and contrasts this with complete multivariable clinical risk models, aiming to explore how wearable data could simplify existing prediction models.

A key strength is its large sample size, far exceeding previous investigations on the use of accelerometer-derived PA for CVD risk prediction and its integration into routine clinical risk scoring, offering a more comprehensive assessment of its clinical utility.

## 6.2 Methods

### 6.2.1 UK Biobank activity monitoring study

This work was conducted using the UK Biobank Prospective cohort dataset, described in Chapter 3. Between June 2013 and December 2015, 230,000 participants with a valid email address were invited to wear an Axivity AX3 wrist-worn accelerometer for seven days<sup>290</sup>. In total, 103,662 participants consented to the study. The median time between baseline assessment and accelerometer wear was 5.7 years (interquartile range [IQR] 4.9-6.5).

Participants were instructed to wear the device on their dominant wrist throughout their daily activities for 7 days before returning to the UKB via post in a pre-paid envelope. Acceleration was recorded across three axes of movement at a sampling rate of 100 Hz<sup>169</sup>. Acceleration was recorded in units of gravity 'g', with 1 g equal to 9.8 m/s<sup>2</sup>, natural acceleration under gravity.

### 6.2.2 Data processing

#### 6.2.2.1 Ascertainment of study endpoint: cardiovascular disease diagnosis

Clinical risk factors were selected to match those of the QRISK3 risk calculator<sup>51</sup>. The protocol to obtain clinical risk factors is described in section 4.2.2.1 and [Supplementary Table 3](#).

The primary outcome of interest was the 6-year risk of incident MACCE, described in section 3.2.3. Follow-up began one day after the end of accelerometer wear time and continued until the first appearance of ICD10 or ICD9 codes for MACCE in either HES or death registration data. Participants who did not experience an event were censored at the time of death or the end of the follow-up period (see section 4.2.2.1). A full breakdown of the definition of MACCE is presented in Supplementary Tables 1-2.

All participants with known MACCE prior to the start of accelerometer monitoring were excluded from the study. To ensure all participants had adequate accelerometer data quality, those with unreadable accelerometer readings, poor calibration, poor wear time (<3 days), unrealistic acceleration (>100mg), or step values equal to zero were further excluded from the study<sup>171</sup>.

All missing data were multiply imputed by Chained Equations (MICE)<sup>228</sup>. Five imputed datasets were generated as outlined in the development of QRISK3<sup>51</sup>. Continuous variables were imputed via predictive mean matching, while categorical data was imputed via logistic regression. The imputation model included all available data, including MACCE outcomes and time to event or censoring date<sup>291</sup>. Rubin's rules were used to combine results across imputed datasets<sup>292</sup>.

#### **6.2.2.2 Processing of raw Accelerometer data**

Accelerometer preprocessing followed an established pipeline outlined by Doherty et al.<sup>290</sup>. In short, accelerometer signals were resampled to 100Hz using linear interpolation. Accelerometer data was calibrated using stationary periods as described by Hees et al<sup>293</sup>. Non-wear time was identified as periods of at least 60 minutes in which all three axes had a standard deviation of less than 13.0 mg. Recording interruptions and non-wear (and any resulting missing minutes within the 7-day protocol) were imputed using the participant's mean value for the corresponding minute-of-day on remaining valid days to minimise diurnal bias. Participants were required to have  $\geq 3$  days ( $\geq 72$  hours) of data and data present in each 1-hour period of the 24-hour cycle; this threshold was chosen based on missing-data simulations indicating 72 hours was sufficient to be within  $\sim 10\%$  of a full 7-day estimate<sup>290</sup>. A schematic overview of accelerometer data preprocessing and human activity recognition pipeline for extracting 24-hour movement behaviours is provided in Figure 6.1.

Movement behaviours, including vector magnitude, a proxy for overall physical activity, hours of sedentary behaviours, LPA, MVPA, sleep and median total daily step count, were extracted using a previously validated algorithm (OxWearables "stepcount" package version 3.7.2)<sup>232,294</sup>. The movement-behaviour classifier was trained/validated against CAPTURE-24 ground-truth labels derived from Axivity AX3 plus wearable camera and time-use/sleep diary and mapped to activity labels from the Compendium of Physical Activities<sup>157,231</sup>.

Based on prior work of Walmsley et al describing intensity in metabolic equivalent of task (METs)<sup>171</sup>, behaviours were defined as (i)sleep (non-waking behaviour), post-processed to require  $\geq 1$ -hour continuous blocks, with shorter sleep segments reclassified as sedentary behaviour; (ii)sedentary behaviour (waking behaviour at  $\leq 1.5$  METs in a sitting/lying/reclining posture); (iii)LIPA (waking behaviour at  $< 3$  METs not meeting the sedentary definition); and (iv)MVPA (behaviour at  $\geq 3$  METs). Daily steps were predicted across each participant's entire wear time, with missing periods due to non-wear imputed by averaging the step counts in the corresponding times on all other valid days<sup>290,293</sup>.

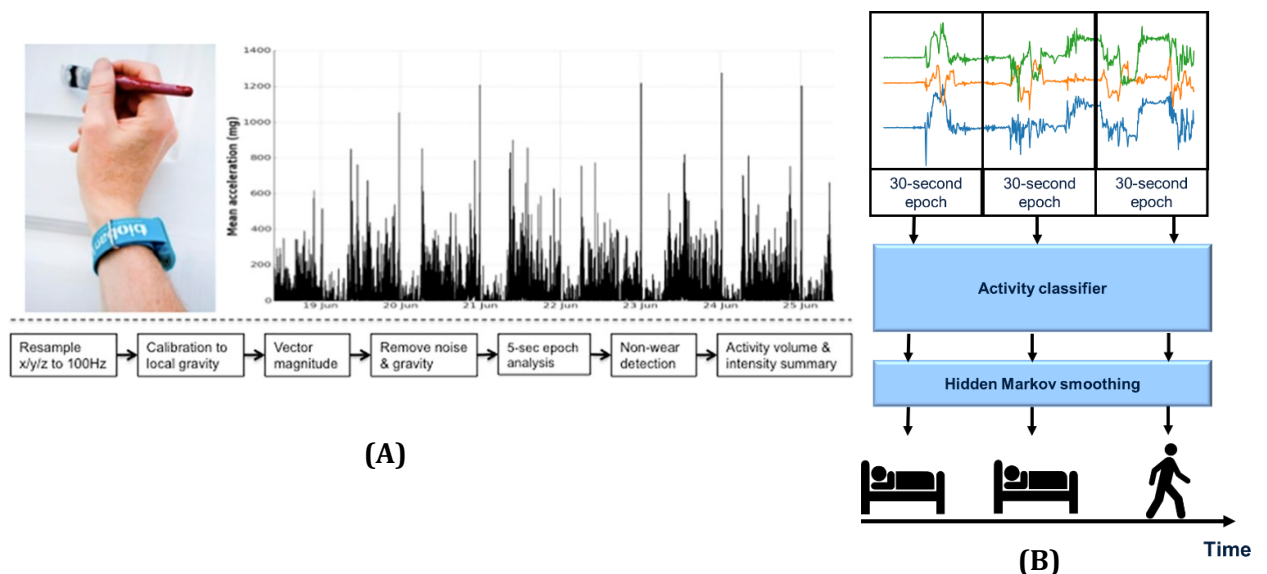


**Figure 6.1. Triaxial Accelerometer and Data Processing Workflow for Physical Activity Extraction Consisting of (A) raw accelerometry preprocessing and feature extraction (Doherty et al.<sup>169</sup>) and (B) activity classification.**

### 6.2.3 Risk prediction of incident cardiovascular disease

Cox proportional hazard models were used to develop prediction models for the 6-year risk of incident MACCE in males and females separately. Regression coefficients for each risk factor were used as weights and combined with the baseline survival function evaluated up to 6 years after accelerometer wear time (Equation 6.1). The baseline survivor function was calculated using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0.

Fractional polynomials<sup>295</sup> were used to model non-linear risk relationships between accelerometer measurements and incident MACCE across five multiply imputed datasets combined in a stacked (long) format. In this approach, all imputed datasets are combined into a single larger dataset, and polynomial exponents are selected across the combined data<sup>296,297</sup>. Optimal fractional polynomials were chosen by iteratively fitting polynomials of increasing complexity until no further significant improvements were observed. Significance tests were conducted using an approximate likelihood-ratio test (LRT)<sup>298</sup>. Using the selected fractional polynomials, separate Cox models were fitted in each imputed dataset. The models from each imputed dataset were combined using Rubin's rules, yielding a final set of coefficients.<sup>292</sup>

Model coefficients were adjusted for optimism using uniform shrinkage following 1000 bootstrap iterations (Figure 6.2). Shrinkage was determined by the average miscalibration across all bootstrap resamples, quantified using the calibration slope ( $\beta_{LP}$ ). For each bootstrap iteration, data were randomly resampled with replacement to create training sets, and the entire modelling process was repeated, including the fitting of separate imputation models, fractional polynomials, and Cox proportional hazards models. Linear predictors (\*LP) were then calculated on the original data (validation dataset) using the model derived from each bootstrap resample (training dataset). The calibration slope in the original data ( $*\beta_{LP}$ ) was estimated by regressing the observed outcome on \*LP.

The uniform shrinkage was calculated as the mean of 1000  $*\beta_{LP}$  estimates. Following this, the baseline survival function ( $*S_{0(t)}$ ) and model coefficients were adjusted to account for optimism. Where the final optimism-adjusted model is given by:

$$Risk\ score = *S_{(t)} e^{*\overline{\beta_{LP}} (\beta^T X)} \quad (6.1)$$

Where:  $*S_{(t)}$  is the baseline survival at time t;  $*\overline{\beta_{LP}}$  average calibration slope across 1000 bootstrap resamples;  $\beta$  represents the original pooled model coefficients (using Rubin's rules); X are the original covariates

The (\*): Is used to denote bootstrap-derived objects.

Three baseline models were evaluated, starting with age as a univariate predictor, SCORE2-Inspired<sup>58</sup> and QRISK3-Inspired<sup>51</sup> risk scores. Model coefficients for QRISK3-Inspired and SCORE2-Inspired risk scores were re-estimated in the study population using Cox proportional hazard models<sup>247</sup>. Due to a lack of sufficient data on the type of CVD and the age of diagnosis for participants' family members, family history of CVD was removed from QRISK3-Inspired risk scores. Likewise, due to lack of statistical power and collinearity issues during model fitting, diagnosis of renal failure, severe mental illness, lupus antipsychotic medication, migraine, and rheumatoid arthritis were also removed from the model.

An additional analysis was conducted to evaluate the added value of accelerometer-measured PA to SCORE2-Inspired and QRISK3-Inspired risk scores, after excluding blood measurements such as HDL cholesterol and systolic blood pressure (SBP). This approach was taken due to the variability of these measurements across medical practices and individuals, as well as the cost and limited availability in many settings. In the original derivation of QRISK3, over 70% of HDL values were imputed, highlighting the challenges associated with obtaining consistent laboratory data<sup>51</sup>.

The final model coefficients and baseline survival estimates for the baseline and extended QRISK3-Inspired and SCORE2-Inspired risk scores are presented in Supplementary Section C, Tables 5C–10C (Appendix p.490).

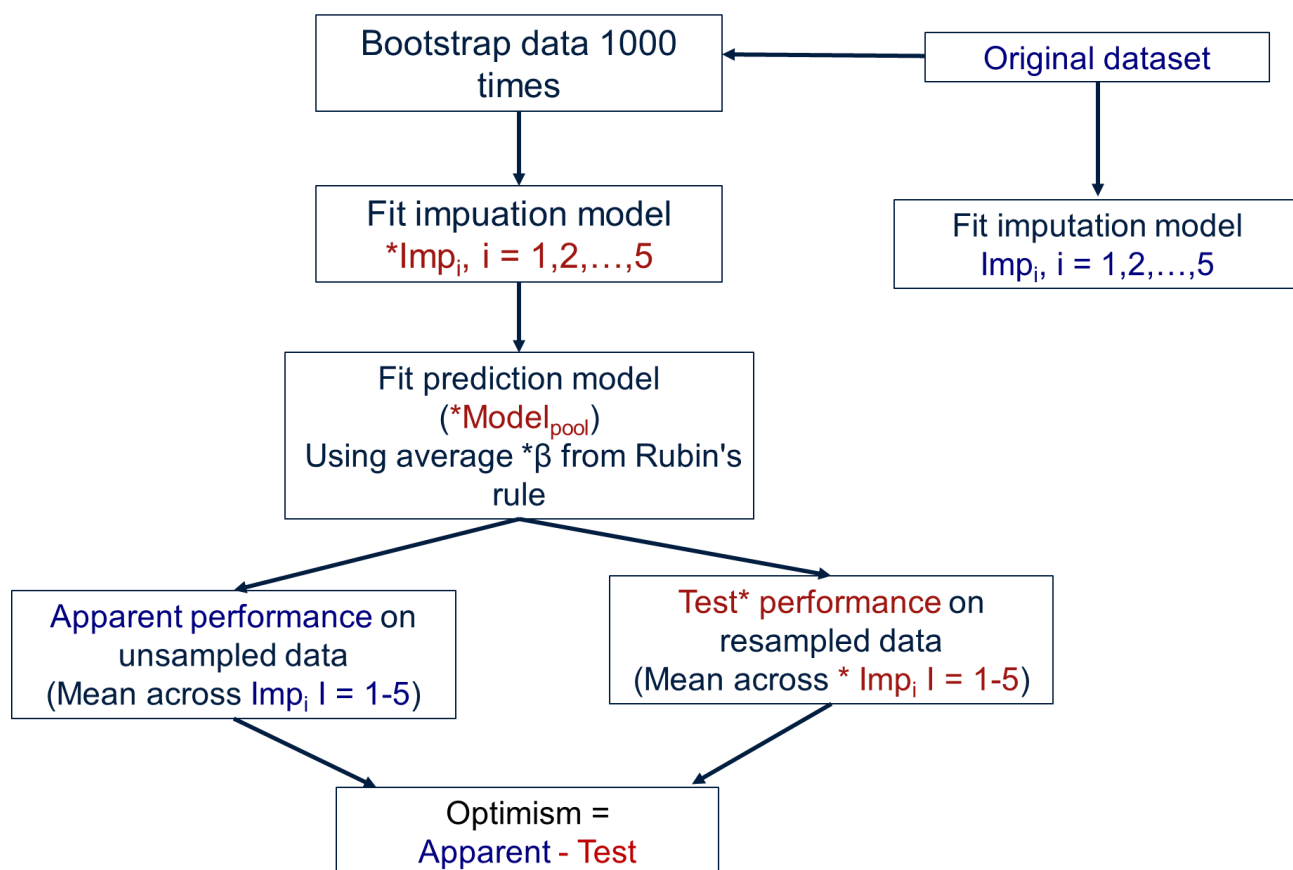


**Figure 6.2 Internal validation pipeline to calculate optimism in the presence of multiply imputed data** based on Harrell et al.<sup>299</sup> and Musoro et al<sup>300</sup>.

The true performance = Apparent – Optimism

\* Is used to denote bootstrap objects

#### 6.2.4 Model development and evaluation

Bootstrap resampling was applied for internal validation and optimism adjustment based on Harrell et al. (1996)<sup>299</sup> and Musoro et al. 2014<sup>300</sup>. Optimism was calculated separately for each performance metric as the average difference between the apparent performance (performance on the bootstrap sample) and the test performance (performance on the original dataset) (Figure 6.2). Optimism-corrected performance, or "true" performance, was estimated by taking the apparent performance of the original model on the unsampled data and subtracting the average optimism across all bootstrap resamples.

Model performance was evaluated based on the criteria outlined in Section 2.2, using Harrell's C-index<sup>99</sup> for discrimination and the integrated calibration index (ICI)<sup>101</sup> for calibration.



Reclassification across risk groups was assessed using the net reclassification index (NRI)<sup>105</sup> and standardized net benefit (NB)<sup>106</sup> at risk thresholds of 5%, 7.5% and 10%. p-values were calculated for each metric using a Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations, with a significance threshold of 0.05<sup>301–303</sup>.

The strength of the associations between accelerometer-measured PA risk factors and the 6-year incidence of MACCE was evaluated using multivariable-adjusted Cox proportional hazard analysis, minimally adjusted for age, sex, smoking status, ethnicity, and deprivation, measured by Townsend's deprivation index<sup>257</sup>. Statistical testing was conducted using a chi-squared test with a significance threshold of 0.05, following adjustment for multiple testing using the Benjamini/Hochberg procedure<sup>260</sup>. To address reverse causation, I repeated the association analysis after removing MACCE that occurred within the first 2 years of follow-up.

Minimum sample sizes were computed following the recommendation of Riley et al. (2018) using the "pmsampsize" package<sup>304</sup>. These calculations incorporated the event rate, mean follow-up time, and expected explained variance (Cox-Snell  $R^2$ ), which was estimated from previously reported C-statistics<sup>246,305,306</sup> for QRISK3 and SCORE2 in the UK Biobank.

The calculations assumed the maximum number of potential model coefficients, including fractional polynomials with two degrees of freedom for each PA risk factor and interaction terms between each PA polynomial and age polynomials in QRISK3. Additional details, including parameter estimates, event rate and minimum sample size calculations, are provided in Supplementary Table 39.

Performance metrics were recalculated within age subgroups to assess model performance across age strata.

A sensitivity analysis was conducted by substituting UK Biobank (UKB) HDL and systolic blood pressure (SBP) measurements with values from primary care records, measured within five years of accelerometer monitoring, following the QRISK3 methodology. Primary care data was available for 230,045 UKB participants (45.8%).

This study was reported per the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines<sup>88</sup>. The complete TRIPOD checklist for this chapter is provided in Supplementary Material Section D, p.547.

## 6.3 Results

### 6.3.1 Study population

Of the 103,622 participants who agreed to take part in physical activity monitoring, 95,266 (91.9%) had accelerometer data of sufficient quality for further analysis. Following the exclusions outlined in Figure 6.3, 88,422 individuals without a history of MACCE were included in the study. The study population consisted of 37,068 males (41.9%; median age: 63.9 (IQR: 12.5)) and 51,354 females (58.1%; median age 62.5 (IQR: 12.2)). The baseline characteristics of the study participants are described in Table 6.1. Compared with participants in the lowest category (quartile 1) of total PA, participants in the highest category of total PA engaged more moderate to vigorous activity, had a lower BMI, smoked less and were less likely to be diagnosed with hypertension, type 2 diabetes and atrial fibrillation.

After 6 years of follow-up, 2,571 (6.9%; 2187 non-fatal, 384 fatal) males and 1,656 (3.2%; 1,473 non-fatal, 183 fatal) females were diagnosed with incident MACCE.

Sample size calculations confirmed that there were sufficient participants and recorded MACCE events in the study population to develop and validate the prediction models for males (minimum sample size  $\geq 15,968$ ; events needed  $\geq 1,108$ ) and females (minimum sample size  $\geq 25,896$ ; events needed  $\geq 835$ ), respectively (Supplementary Table 39).

Of the 88,422 participants in this study, 20,913 (23.7 %) had available primary care records with cholesterol and Systolic blood pressure measurements taken within 5 years of accelerometer wear time. No significant differences in the incidence of MACCE between those available primary care data and the whole cohort (Chi-squared statistic = 0.16; p-value = 0.69). Measurements of Systolic blood pressure and HDL cholesterol ratio differed by -8.1 (standard deviation 17.8)  $p < 0.001$  and 1.3 (standard deviation 1.5)  $p < 0.001$  respectively between primary care records and UK Biobank.

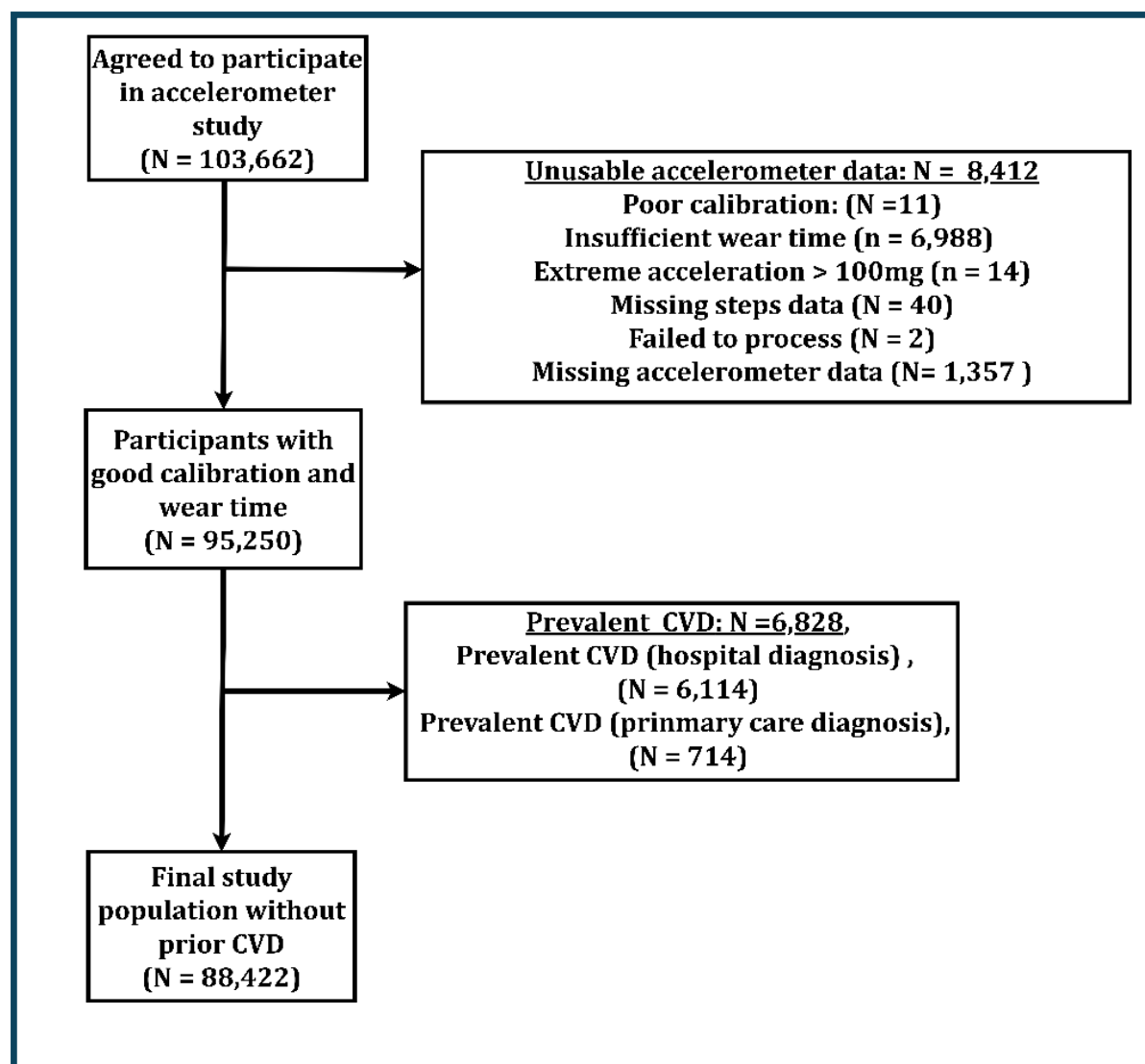


**Figure 6.3: Exclusion of study participants:** Flowchart including the number of participants included in the study, along with any exclusion criteria and derivation of development/validation sets for Major Adverse Cardiovascular/Cerebrovascular Events (MACCE).

**Table 6.1: Baseline characteristics of 88,422 UK Biobank participants without a history of Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) who consented to wear a wrist worn accelerometer for 7 days, stratified by overall activity quartile.**

|                                | Overall activity<br>Quartile 1 | Overall activity<br>Quartile 2 | Overall activity<br>Quartile 3 | Overall activity<br>Quartile 4 |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Summary characteristics        |                                |                                |                                |                                |
| Age (years)                    | 64.7 ±7.4                      | 62.8 ±7.7                      | 61.4 ±7.7                      | 59.5 ±7.6                      |
| BMI (kg.m2)                    | 28.3 ±5.1                      | 26.8 ±4.4                      | 26.1 ±4.0                      | 25.1 ±3.7                      |
| LDL-C to HDL-C ratio           | 4.3 ±1.1                       | 4.1 ±1.1                       | 4.0 ±1.1                       | 3.8 ±1.0                       |
| Systolic Blood pressure (mmHg) | 139.5 ±18.3                    | 136.9 ±18.0                    | 135.2 ±18.0                    | 133.3 ±17.6                    |
| Townsend Deprivation index     | -1.6 ±2.9                      | -1.8 ±2.8                      | -1.8 ±2.8                      | -1.7 ±2.8                      |
| MACCE events (%)               | 1,627(7.4)                     | 1,058(4.8)                     | 890(4.0)                       | 655(3.0)                       |
| Ethnicity                      |                                |                                |                                |                                |
| White ethnicity (%)            |                                |                                |                                |                                |
| Non-White ethnicity (%)        | 643 (2.9)                      | 715 (3.2)                      | 781 (3.5)                      | 917 (4.1)                      |
| Sex                            |                                |                                |                                |                                |
| Female (%)                     |                                |                                |                                |                                |
| Male (%)                       | 10,427 (47.2)                  | 9,116 (41.2)                   | 8,749 (39.6)                   | 8,783 (39.7)                   |
| Smoking status                 |                                |                                |                                |                                |
| Non-smoker (%)                 | 12,078 (54.6)                  | 12,792 (57.9)                  | 13,073 (59.1)                  | 13,273 (60.0)                  |
| Previous Smoker (%)            | 8,048 (36.4)                   | 7,818 (35.4)                   | 7,620 (34.5)                   | 7,485 (33.9)                   |
| Current smoker (%)             | 1,920 (8.7)                    | 1,443 (6.5)                    | 1,357 (6.1)                    | 1,299 (5.9)                    |
| Daily activity (hours)         |                                |                                |                                |                                |
| Sleep duration                 | 9.1 ±1.4                       | 8.7 ±1.1                       | 8.5 ±1.0                       | 8.3 ±0.9                       |
| Sedentary behaviour            | 10.4 ±1.7                      | 9.5 ±1.5                       | 8.9 ±1.4                       | 8.0 ±1.6                       |
| Light activity                 | 4.2 ±1.1                       | 5.4 ±1.1                       | 6.1 ±1.3                       | 7.0 ±1.6                       |
| Moderate vigorous activity     | 0.3 ±0.3                       | 0.4 ±0.3                       | 0.6 ±0.4                       | 0.8 ±0.6                       |
| Average daily steps            | 6544.2±2524.5                  | 8757.8±2663.8                  | 10226.9±3030.4                 | 12574.5±4006.2                 |
| Overall activity(mg)           | 19.2±2.8                       | 25.1±1.3                       | 29.9±1.5                       | 39.2±6.8                       |
| QRISK3 comorbidities           |                                |                                |                                |                                |
| Type 1 Diabetes (%)            | 126 (0.6)                      | 49 (0.2)                       | 55 (0.2)                       | 41 (0.2)                       |
| Type 2 Diabetes (%)            | 928 (4.2)                      | 390 (1.8)                      | 278 (1.3)                      | 146 (0.7)                      |
| Treated Hypertension (%)       | 3,844 (17.4)                   | 2,451 (11.1)                   | 1,894 (8.6)                    | 1,289 (5.8)                    |
| Atrial Fibrillation (%)        | 551 (2.5)                      | 342 (1.5)                      | 258 (1.2)                      | 185 (0.8)                      |
| Corticosteroid                 | 770 (3.5)                      | 737 (3.3)                      | 760 (3.4)                      | 729 (3.3)                      |
| Migraine                       | 127 (0.6)                      | 144 (0.7)                      | 86 (0.4)                       | 107 (0.5)                      |
| Rheumatoid arthritis.          | 232 (1.0)                      | 135 (0.6)                      | 99 (0.4)                       | 84 (0.4)                       |
| Severe mental illness          | 108 (0.5)                      | 43 (0.2)                       | 44 (0.2)                       | 32 (0.1)                       |

Data are shown as means±SD for continuous data and total (%) for categorical data.

All data (participant characteristics, accelerometer-derived activity measures, and MACCE outcomes) were obtained from UK Biobank.

### 6.3.2 Association between physical activity and MACCE

This study first investigated the independent association between accelerometer-derived Physical activity (PA) measurements and the 6-year risk of incident MACCE. Figure 6.4 presents the adjusted hazard ratio (HR) for daily step count, overall PA, measured by the vector magnitude, and time spent in MVPA, LIPA, SB or sleep, as described in 6.2.2 recorded over seven days of continuous wear time for males and females, respectively.

The findings of this study provide further evidence of the protective association of increased PA, greater step count, and time spent in moderate-to-vigorous activity with regard to MACCE. Additionally, this work finds an increase in time spent in sedentary behaviour is associated with a 7% (95% CI 3%-11%) and 12% (95% CI 7% - 18%) increase in risk of incident MACCE per hour of SB each day for males and females, respectively. The association between Light intensity PA (LIPA) were more modest and non-significant, with a reported decrease in risk of -3% (95% CI -7% - 1%) and 4% (-9% - 1%) per hour of LIPA each day, respectively. Time spent sleeping was observed to be non-significant for male participants with a -2% (-6% - 2%) in the risk of MACCE per hour of sleep each day. Conversely, a modest but significant effect was observed among females; with a -6% (-10% - -1%) reduction in the risk of MACCE per hour of sleep each day.

To assess potential non-linear associations, sex-stratified penalised spline models (3 degrees of freedom) were fitted for each PA measure, adjusted for (Supplementary Figure 18-19). For daily step count, overall physical activity, and MVPA, hazard ratios declined with increasing activity, with steeper gradients at lower activity levels and evidence of attenuation at higher values. This pattern was observed in both men and women.

Sedentary behaviour showed a positive, non-linear association with MACCE risk, with progressively higher hazard ratios at longer sedentary durations, particularly at the upper end of the distribution. In contrast, associations for LIPA were weak and broadly compatible with the null across the exposure range.

The spline analyses were consistent with the linear models while indicating non-linear exposure–response relationships for several activity measures.

During the first 2 years of follow-up, 1,244 (1.4%) (males: 777 (2.1 %); females: 467(0.9%)) were diagnosed with MACCE, respectively. Following a sensitivity analyses excluding participants diagnosed with MACCE in the first 2 years of follow-up, minimal changes in the HRs were observed (Supplementary Table 40).

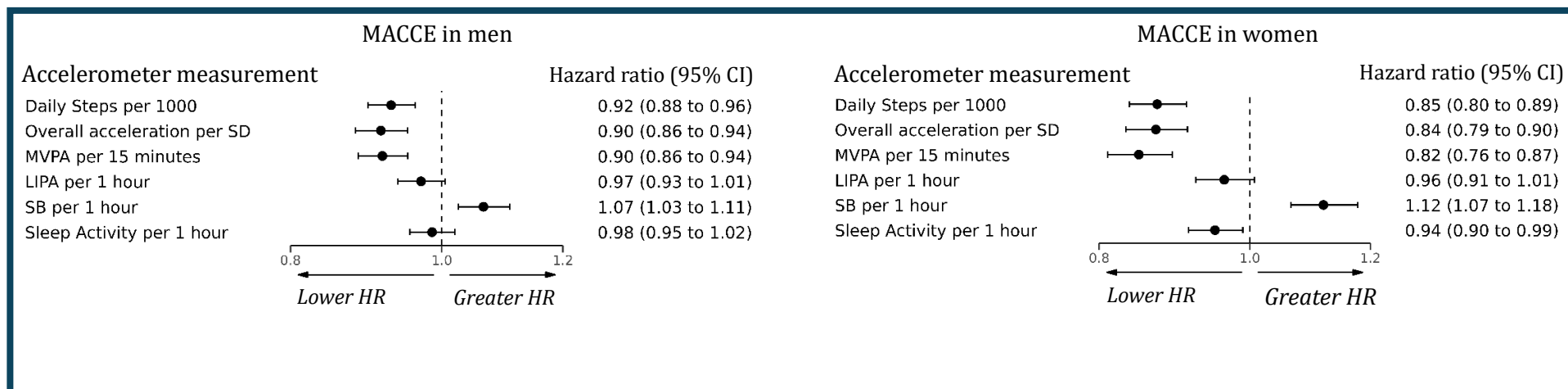


**Figure 6.4: Association between accelerometer-derived physical activity and sleep, obtained over 7 days of continuous monitoring in a free-living environment with the 6-year risk of MACCE for males and females, respectively.**

Each risk factor was adjusted for age, smoking status, social deprivation measured by Townsend deprivation index<sup>257</sup>, and ethnicity.

Hazard ratios are reported per 1000 average daily steps, per standard deviation increase in overall acceleration measured by vector magnitude, 15 minutes of moderate-to-vigorous Physical activity (MVPA), 1 hour of light activity (LIPA), 1 hour of sedentary behaviour (SB) and 1 hour of sleep. .

Separate Cox models were trained for each PA risk factor on 37,068 males (41.9%) with 2,571 (6.9%) incident MACCE and 51,354 females (58.1%) with 1,656 (3.2%) MACCE observed over 6 years.

The accelerometer measurements were selected based on previously reported associations with CVD incidence and mortality<sup>79,171,181,281</sup>.

Abbreviations: HR: Hazard ratio; CI = Confidence intervals; SD = Standard deviation; MVPA = Moderate/vigorous activity; LIPA = light intensity physical activity, SB = Sedentary Behaviour

95% confidence intervals were calculated from the standard error of the coefficient estimate from Cox regression analysis, assuming normally distributed estimates.



### **6.3.3 Predictive value of physical activity**

#### **6.3.3.1 Univariate Predictive Performance**

The univariate performance of accelerometer-derived PA and QRISK3-Inspired risk scores is presented in Table 6.2. Each PA variable was evaluated in a separate, sex-stratified Cox proportional hazards model as the only covariate, with each PA metric entered as a continuous linear predictor. Of the risk factors investigated, age remains the strongest predictor of incident MACCE, for male and female participants, with a C-index of 0.66 (0.65 – 0.68), 0.67 (0.65 – 0.69), and an unadjusted hazard ratio (HR) of 1.95 (1.84 – 2.06); 1.97 (1.80 -2.15) per standard deviation, for males and females respectively.

Univariate PA measures were shown to be predictive of incident MACCE in the absence of clinical risk factors. The most predictive individual measure of PA was average overall daily activity, with a C-index of 0.588 (95% CI: 0.577–0.597) for males and 0.614 (95% CI: 0.602–0.625) for females. For males, the predictive performance of overall activity exceeded all conventional risk factors included in QRISK3-Inspired risk scores except age. For females, overall activity outperformed all QRISK3-Inspired risk factors except systolic blood pressure and age.

Multivariable PA risk models combining daily step count, overall activity, sedentary behaviour (SB), LIPA and MVPA were developed separately for males and females using sex-stratified Cox models, with PA variables modelled using fractional polynomial transformations. These models demonstrated moderate levels of discrimination, exceeding all traditional risk factors other than age. For males, multivariable PA risk scores yielded a C-index of 0.607 (95% CI: 0.596 - 0.617), representing a modest improvement over the most predictive univariate PA statistic, overall activity, with a  $\Delta$  C-index of 0.019 (95% CI: 0.003–0.034,  $p = 0.02$ ). For females, the multivariable PA risk score had a C-index of 0.645 (95% CI: 0.632–0.657), showing a similar level of improvement compared to overall activity, with a  $\Delta$  C-index of 0.029 (95% CI: 0.015–0.043,  $p < 0.001$ ).

Supplementary Table 41 presents sex-specific descriptive statistics for all accelerometer-derived PA measures, including the standard deviations for overall activity (vector magnitude) and multivariable PA risk scores. Hazard ratios and discrimination metrics for each QRISK3 risk factor are detailed in Supplementary Table 42.

Supplementary Figure 20 shows the sex-stratified Spearman correlation matrices for accelerometer-derived PA measures. Only correlations remaining statistically significant after Benjamini–Hochberg adjustment ( $p < 0.05$ ) are displayed. Overall activity and daily step count were strongly positively correlated with LIPA and moderately correlated MVPA in both males and females ( $\rho \approx 0.47$ – $0.65$ ). Multivariable PA risk scores showed strong inverse correlations with overall activity and daily step count (men:  $\rho \approx -0.86$  and  $-0.52$ ; women:  $\rho \approx -0.80$  and  $-0.62$ ).

The continuous calibration curves for multivariable PA risk scores are presented in Supplementary Figure 21. Overall Multivariate PA risk scores demonstrated strong calibration across the range of predicted risks. In men, the smoothed calibration curve was closely aligned to line of perfect agreement, with only modest underprediction at the lower end ( $<3\%$ ) and upper end of predicted risks ( $10\%$ ), where observed risks tended to be higher than predicted. In women, the smoothed curve was generally closer aligned to perfect fit than for men across low-to-moderate risk, however underprediction became more apparent as observed MACCE risk increased, particularly above  $10\%$ .

The histograms indicate that predicted risks were heavily right-skewed, with the majority of individuals clustered at low predicted risk and only a small fraction in the  $>10\%$  range. Consequently, calibration in the extreme upper tail is estimated with greater uncertainty thus underprediction at higher risk are had limited influence on the overall calibration performance in this cohort.

**Table 6.2: Performance of sex-stratified age, Physical activity (PA) and QRISK3-Inspired risk scores for 6-year risk of incident Major Adverse Cardiovascular & Cerebrovascular Events (MACCE)**

| Model                                   | Hazard ratio (95% CI) | C-index (95% CI)      |
|-----------------------------------------|-----------------------|-----------------------|
| <b>Male (N = 37,068 MACCE = 2,571)</b>  |                       |                       |
| Age                                     | 1.800 (1.72 - 1.884)  | 0.651 (0.642 - 0.66)  |
| QRISK3-Inspired score                   | 1.509 (1.464 - 1.556) | 0.68 (0.67 - 0.689)   |
| Accelerometer measurements              |                       |                       |
| Step count                              | 0.956 (0.946 - 0.966) | 0.55 (0.54 - 0.559)   |
| Overall activity                        | 0.963 (0.958 - 0.968) | 0.588 (0.577 - 0.597) |
| Sedentary behaviour                     | 1.047 (1.024 - 1.069) | 0.518 (0.508 - 0.528) |
| Light activity                          | 0.963 (0.94 - 0.986)  | 0.515 (0.505 - 0.525) |
| Moderate to vigorous activity           | 0.887 (0.867 - 0.908) | 0.567 (0.557 - 0.577) |
| Multivariable PA risk score             | 1.458 (1.402 - 1.517) | 0.607(0.596 - 0.617)  |
| <b>Female (N = 51,354 MACCE =1,656)</b> |                       |                       |
| Age                                     | 2.084 (1.967 - 2.208) | 0.688 (0.678 - 0.698) |
| QRISK3-Inspired score                   | 1.372 (1.325 - 1.421) | 0.736 (0.725 - 0.748) |
| Accelerometer measurements              |                       |                       |
| Step count                              | 0.912 (0.899 - 0.926) | 0.588 (0.576 - 0.601) |
| Overall activity                        | 0.945 (0.939 - 0.952) | 0.614 (0.602 - 0.625) |
| Sedentary behaviour                     | 1.119 (1.088 - 1.152) | 0.548 (0.535 - 0.56)  |
| Light activity                          | 0.942 (0.914 - 0.971) | 0.525 (0.513 - 0.537) |
| Moderate to vigorous activity           | 0.766 (0.736 - 0.799) | 0.606 (0.594 - 0.618) |
| Multivariable PA risk score             | 1.598 (1.535 - 1.663) | 0.645(0.632 - 0.657)  |

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported C-index and 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Unadjusted hazard ratios for Age, QRISK3-Inspired and Multivariable PA risk score are reported per standard deviation.

Hazard ratios for step count are reported per 1,000 steps.

Hazard ratios for Sedentary behaviour, Light activity and sleep were reported per 1-hour increase each day, while moderate to vigorous activity was reported per 15 minutes.

$$\begin{aligned}
 \text{Multivariate PA risk score (males)} &= \left( \frac{\text{Daily step count}}{10000} \right) + \text{Hours of MVPA}^{0.5} + \\
 & \left( \text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}) \right) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \\
 & \frac{\text{Overall activity}}{10} \\
 \text{Multivariate PA risk score (Females)} &= \left( \frac{\text{Daily step count}}{10000} \right)^{-1} + \left( \frac{\text{Daily step count}}{10000} \right)^{-0.5} + \text{Hours of MVPA} + \\
 & + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}
 \end{aligned}$$

Where: MVPA =daily hours of moderate-to-vigorous PA , LPA = Light intensity PA, and SB = sedentary behaviour.

### **6.3.4 Added value of device measured Physical activity to MACCE risk prediction**

#### **6.3.4.1 Discrimination**

The discriminative performance of each baseline model and the baseline model plus device-measured PA variables, described in Section 6.2.2.2 and consisting of daily step count, overall activity (vector magnitude), and time spent in sedentary behaviour (SB), light-intensity physical activity (LIPA), and moderate-to-vigorous physical activity (MVPA), is presented in Figure 6.5. Among participants without prior cardiovascular disease (CVD), age alone yielded a C-index of 0.651 (95% CI: 0.641–0.661) for males and 0.688 (95% CI: 0.666–0.700) for females. The inclusion of accelerometer-measured PA—comprising daily step count, overall activity, and time spent in sedentary, light, and moderate-to-vigorous physical activity—resulted in significant improvements in the C-index for both males and females. Specifically, the C-index increased by  $\Delta$  0.007 (95% CI: 0.003–0.010,  $p < 0.001$ ) for males and by  $\Delta$  0.016 (95% CI: 0.010–0.022,  $p < 0.001$ ) for females, following the addition of PA measurements.

At baseline, QRISK3-Inspired scores yielded a C-index of 0.680 (0.670 – 0.689) and 0.736 (0.725 – 0.748) for males and females, respectively. When integrating PA measurements into QRISK3-Inspired scores, no significant improvements over the baseline model were observed, with QRISK3-Inspired + PA yielding a C-index of 0.679 (0.670 – 0.689) ( $\Delta$  -0.001; 95% CI -0.004 - 0.001) and 0.738 (95% CI 0.728 – 0.749) ( $\Delta$  0.002(95% CI -0.002 - 0.005) for males and females respectively.

The exclusion of high-density lipoprotein (HDL) and systolic blood pressure (SBP) from QRISK3-Inspired risk scores did not significantly alter the C-index compared to the baseline QRISK3-Inspired model for either males,  $\Delta$ 0.003 (95% CI -0.01 - 0.017,  $p = 0.65$ ) or females  $\Delta$  0.006(95% CI -0.01 - 0.021,  $p = 0.50$ ). Similarly, when substituting HDL and SBP for PA data, no significant changes in the C-index were observed compared to either the reduced or original QRISK3-Inspired risk score. A detailed breakdown of model performance for each baseline and baseline + PA risk scores is provided in Supplementary Tables 43–44.

For SCORE2-Inspired risk scores, the addition of PA resulted in a modest but significant increase in the C-index for female participants ( $\Delta$ C-index = 0.005; 95% CI: 0.001 to 0.009). However, no significant changes were observed for male participants.

Substituting HDL and SBP for PA led to a modest but significant improvement in the C-index for both males ( $\Delta$ 0.004; 95% CI: 0 to 0.007) and females ( $\Delta$ 0.01; 95% CI: 0.005 to 0.015). However, substituting HDL and SBP with PA failed to match the predictive performance complete SCORE2-Inspired risk scores. Detailed results are presented in Supplementary Figures 23-24 and Tables 45-46

Discrimination results for QRISK3-Inspired and SCORE2-Inspired risk scores, where UKB-measured HDL and SBP were replaced with measurements recorded in primary care, are presented in Supplementary Figures 21–24 When substituting HDL cholesterol ratios and SBP measurements from the UKB with primary care data a slight decrease in model discrimination was observed, however the relative added value of PA measurements to QRISK3-Inspired and SCORE2-Inspired risk scores remained stable.

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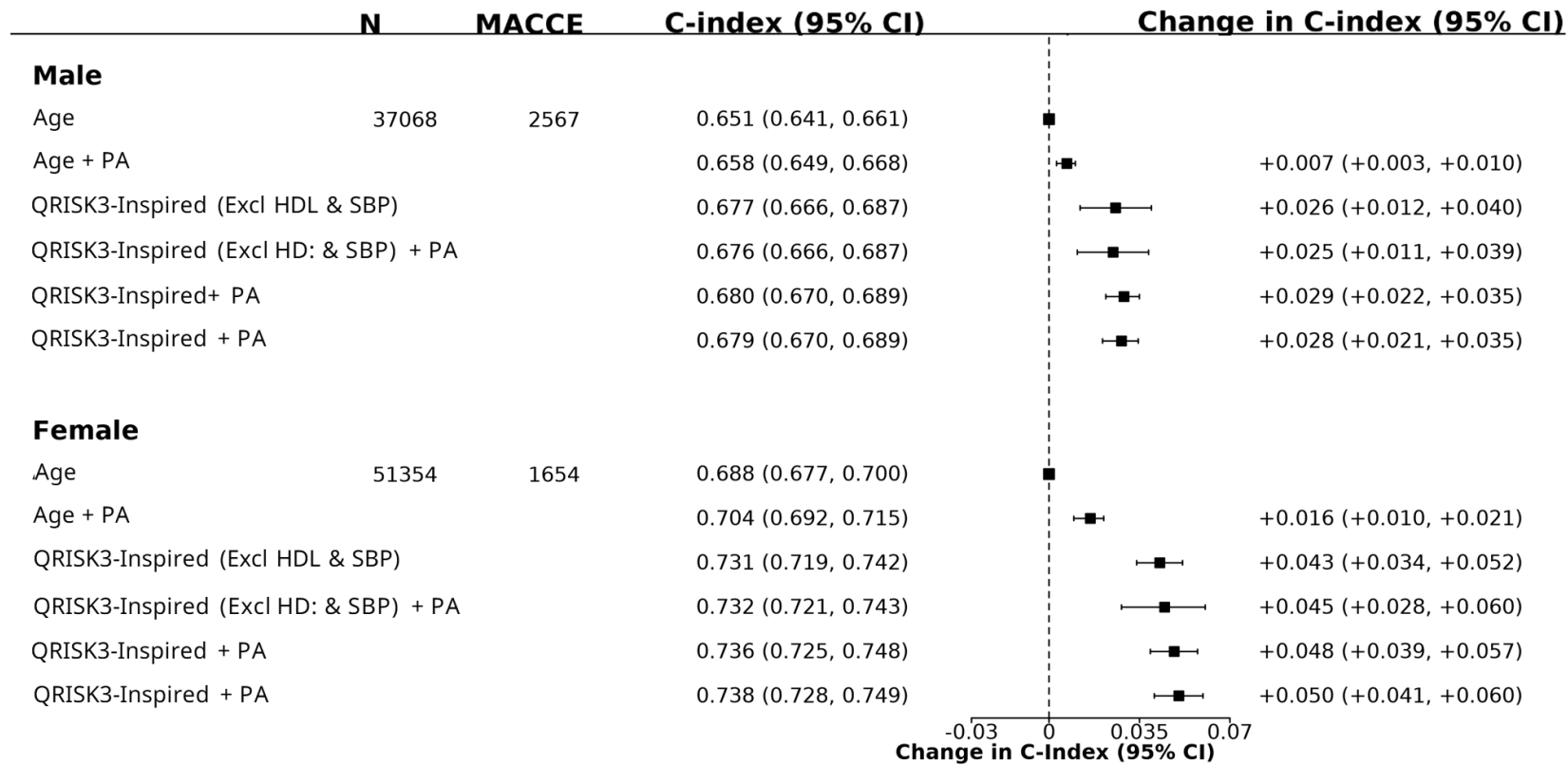


**Figure 6.5 Optimism adjusted Harrell's C-index for risk scores derived from Age, Age + Physical activity (PA) and a QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) extended with PA; and QRISK3-Inspired risk scores extend by PA. in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015. After 6 years of follow-up, 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**

Abbreviations: CI = confidence intervals; PA = Physical activity; HDL = High-density lipoprotein; SBP = Systolic blood pressure.

Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Townsend deprivation index + AgeFP2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter .

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA) and sedentary behaviour (SB)

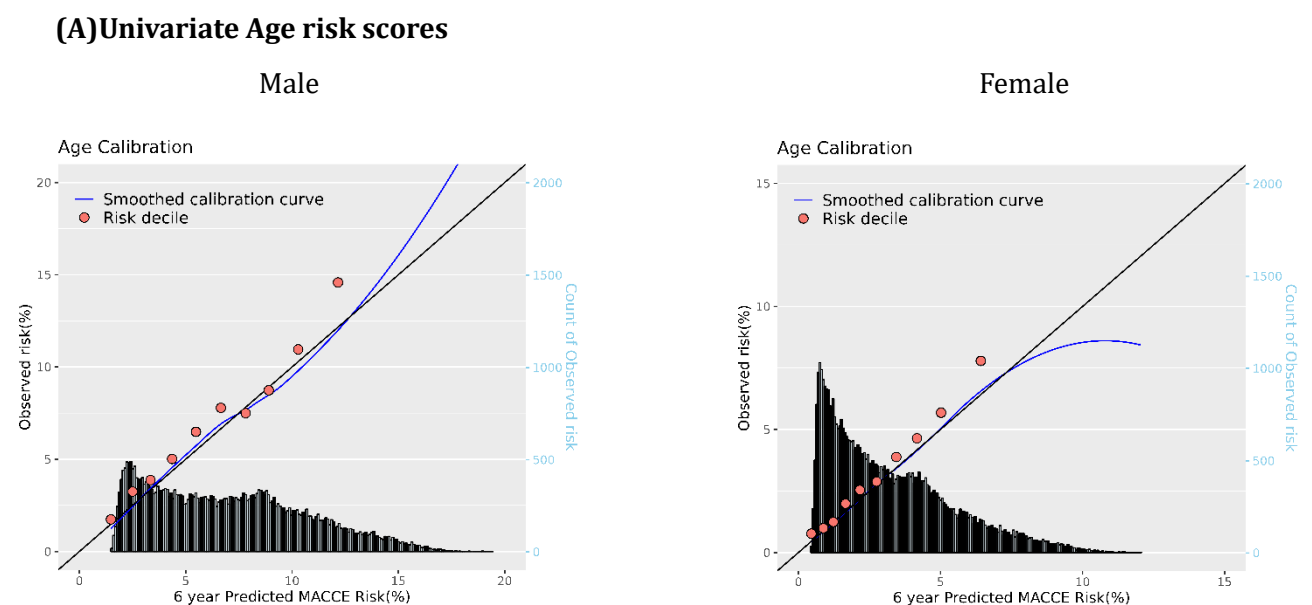
Multivariate PA risk score (males) =  $\left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$

Multivariate PA risk score (Females) =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$

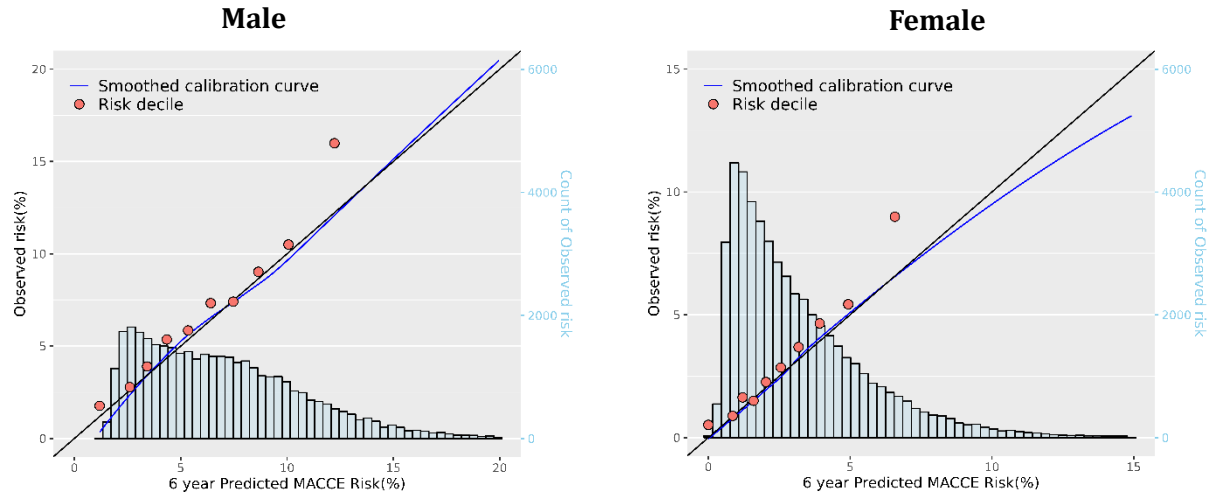
### 6.3.4.2 Calibration

Figure 6.6 shows the continuous calibration curves for univariate age and age + PA risk scores. Age as a univariate risk score shows close alignment with the observed risk for those at a lower risk of MACCE (<10%). However, substantial deviations appear for those at higher observed risk, with systematic underprediction for males and overprediction for females, respectively. For males, combined age and PA risk scores greatly attenuated the degree of underprediction for those with higher observed risk of incident MACCE., however no significant changes were reported in the overall calibration measured by the ICI (Supplementary Table 43-44). For female participants, a substantial improvement in the alignment between predicted and observed risk scores can be seen, particularly for those with greater observed risk. In contrast to the overprediction seen at higher observed risk groups for age alone, age +PA shows much more moderate signs of overprediction within these higher observed risk individuals. However, no significant changes in overall ICI were reported (Supplementary Tables 43-44).

**Figure 6.6 Smoothed calibration curve for (A) Age and (B) Age + physical activity (PA) risk scores derived for male and female participants.** Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.



## (B) Age + combined physical activity (PA) risk scores



Red circles represent the observed 6-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA, Light intensity, PA and sedentary behaviour.

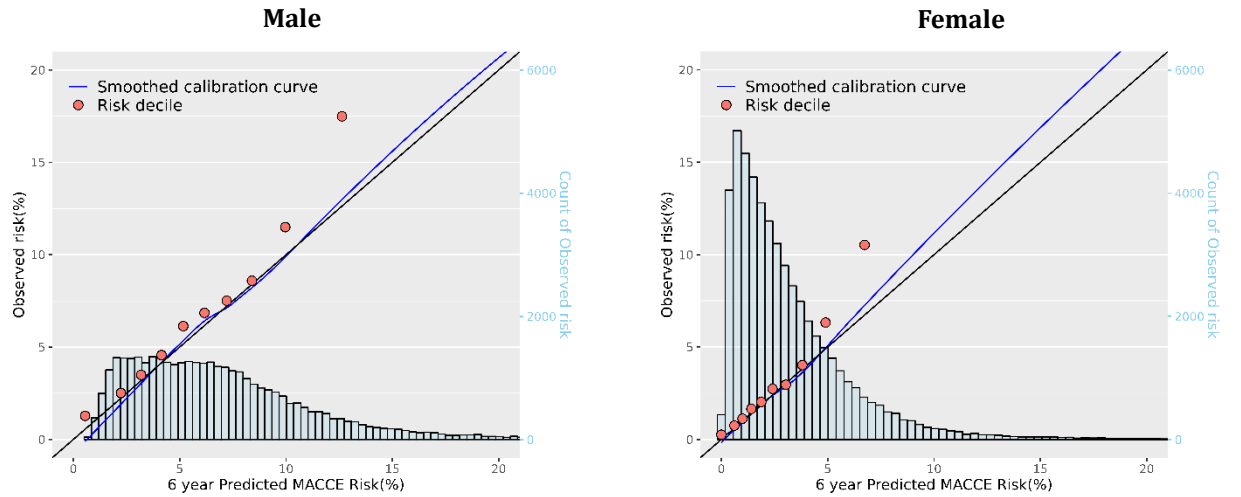
$$\text{PA risk fractional polynomial (males)} = \left( \frac{\text{Daily step count}}{10000} \right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

$$\text{PA fractional polynomial (Females)} = \left( \frac{\text{Daily step count}}{10000} \right)^{-1} + \left( \frac{\text{Daily step count}}{10000} \right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$$

QRISK3-Inspired risk scores were well-calibrated within the study population, demonstrating a substantial improvement over age-only risk scores and aligning closely with the observed risk. Figure 6.7 presents the continuous calibration curve for QRISK3-Inspired and QRISK3-Inspired + PA risk scores among males and females. In the male cohort, modest underprediction was observed among individuals with higher observed risk ( $\approx >10\%$ ). After incorporating PA this overprediction was further extenuated, with the smoothed curve became steeper for those at the upper end of the risk distribution. Among female participants, QRISK3-Inspired risk scores showed greater underprediction compared with males, particularly for those above 5% observed risk. The addition of PA attenuated this miscalibration, resulting in closer agreement between predicted and observed risks, although modest overprediction remained at the upper end of observed risk, particularly above 10% observed risk. Despite modest shifts in calibration after the addition of PA, no significant changes in ICI were reported for either male or female cohorts (Figure 6.7 Supplementary Tables 43-44). The continuous calibration curves for QRISK3-Inspired and QRISK3-Inspired + PA risk scores, excluding Systolic blood pressure and HDL cholesterol, are presented in Supplementary Figure 25.



### (A) QRISK3-Inspired



### (B) QRISK3-Inspired + PA

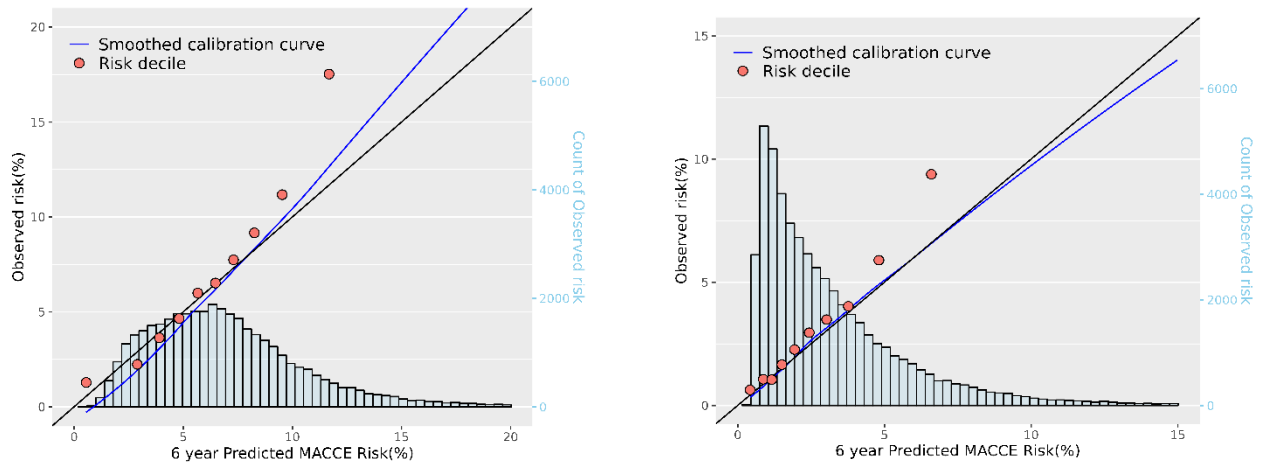


**Figure 6.7 Smoothed calibration curve for (A) QRISK3-Inspired and (B) QRISK3-Inspired + physical activity (PA) risk scores derived for male and female participants. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.**

Red circles represent the observed 6-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP1 + Age FP 1 X BMI FP2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP1 + Age FP 2 X BMI FP2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**QRISK3-Inspired Fractional polynomials:** Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Physical activity (PA): Average daily step count, Overall PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA), and sedentary behaviour (SB)

**PA risk fractional polynomial (males)** =  $\left(\frac{\text{Daily step count}}{10000}\right) +$

$\frac{\text{Hours of MVPA}^{0.5}}{10} \left( \text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}) \right) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$ ;

**PA fractional polynomial (Females)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \frac{\text{Hours of MVPA}}{10} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$

#### 6.3.4.3 Reclassification

Reclassification statistics, including net benefit and categorical NRI, were evaluated at three risk thresholds (5%, 7.5%, and 10%), along with the continuous NRI, following the addition of physical activity (PA) measurements to each baseline risk model. A complete breakdown of the added value of PA to age and QRISK3-Inspired risk scores are provided in Supplementary Tables 47-48 for males and females, respectively.

The addition of PA to both age-based and QRISK3-Inspired risk scores resulted in significant improvements in the continuous net reclassification index (NRI). However, changes in risk classification based on common risk thresholds were much more limited.

The decision curves presented in Figure 6.8 indicate a slightly larger net benefit for age + PA compared to age alone, particularly for female participants and higher intervention thresholds. Changes in net benefit for QRISK3-Inspired +PA risk scores were more modest, with only limited gains in net benefit observed at higher risk thresholds, among female participants. Similar to age and age +PA, changes in net benefit were more pronounced for female participants at risk thresholds exceeding 7.5%.

When evaluating categorical NRI and net benefit at common risk thresholds of 5%, 7.5% and 10%, adding PA to age resulted in only modest benefit for male participants, with a modest but significant improvement in net benefit and NRI at a threshold of 7.5%. No significant changes were observed for other risk thresholds (Supplementary Table 47). In contrast, for female participants, the addition of PA led to significant improvements in both net benefit and NRI across all three thresholds (Supplementary Table 48).

For QRISK3-Inspired risk scores, the addition of PA yielded significant improvements in net benefit ( $\Delta 0.014$  95% CI 0.001-0.025) and NRI (0.018 95% CI 0.007 – 0.036) for female participants at a treatment threshold of 10%. However, no further improvements were observed for male participants at any risk threshold.

Reclassification metrics for QRISK3-Inspired risk scores, derived from primary care data, and SCORE2-Inspired risk scores are presented in Supplementary Tables 49-52. Results were broadly consistent with those presented for QRISK3-Inspired and QRISK3-Inspired +PA models derived from UKB data, with significant improvements in continuous NRI for all risk scores and more limited improvement in reclassification at risk thresholds of 10% for female participants.

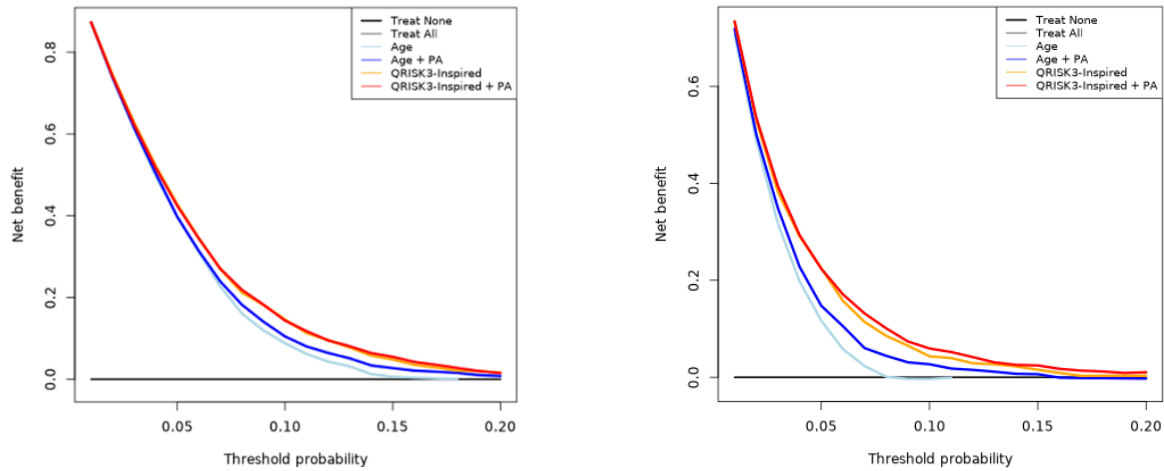


**Figure 6.8 Decision curves for Age, Age +Physical activity (PA), QRISK3-Inspired and QRISK3-Inspired +PA risk scores**

Abbreviations: CI = confidence intervals; PA = Physical activity

Decision curves showing the standardised net benefit for males and females. Decision curves for Age, Age +PA, QRISK3 and QRISK3 +PA are compared to those for ‘Treat All’ (intervention in all individuals irrespective of risk threshold) and ‘Treat None’ (intervention in no individuals).

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP1 + Age FP 2 X BMI FP2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**QRISK3-Inspired Fractional polynomials:** Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA), and sedentary behaviour. (SB)

**PA risk fractional polynomial (males)** =  $\left(\frac{\text{Daily step count}}{10000}\right) +$

$\frac{\text{Hours of MVPA}^{0.5}}{10} \left( \text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}) \right) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$

**PA fractional polynomial (Females)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$

#### 6.3.4.4 Subgroup analysis

Figure 6.9 presents the relative change in model discrimination after incorporating PA measurements into QRISK3-Inspired risk scores across different age groups. Consistent with the findings for the full study population in Figure 6.5, QRISK3-Inspired and QRISK3-Inspired+PA risk scores show higher levels of discrimination for female than male participants. However, no significant changes in the C-index were observed in any age subgroup for either males or females following the addition of PA to QRISK3 risk factors.

When assessing model reclassification among male participants, the PA risk scores showed greater improvements in older individuals, with significant increases in the optimism-adjusted continuous NRI observed for those aged 65–75 (NRI = 0.106, 95% CI: 0.084–0.126) and those over 75 (NRI = 0.228, 95% CI: 0.206–0.249). Among female participants, significant improvements in continuous NRI were reported among all age groups including under 55's (NRI = 0.125, 95% CI 0.107 - 0.142), 55–65's (NRI = 0.106, 95% CI: 0.087–0.123), 65–75's (NRI = 0.145, 95% CI: 0.126–0.162) and over 75's (NRI = 0.23, 95% CI 0.215 - 0.251). Modest but significant improvements in categorical NRI and net benefit were observed for female participants ages 65-75 at risk thresholds of 10% ( $\Delta$ NB = 0.018 95% CI 0.005 – 0.028; NRI = 0.021 95% CI, 0.003 – 0.039) and 7.5% ( $\Delta$ NB = 0.013 95% CI 0.00 – 0.024; NRI = 0.013 95% CI, 0.005 – 0.03). However, no further improvements were observed for male or female sub-cohorts at any of the evaluated risk thresholds (Supplementary Tables 53–54)

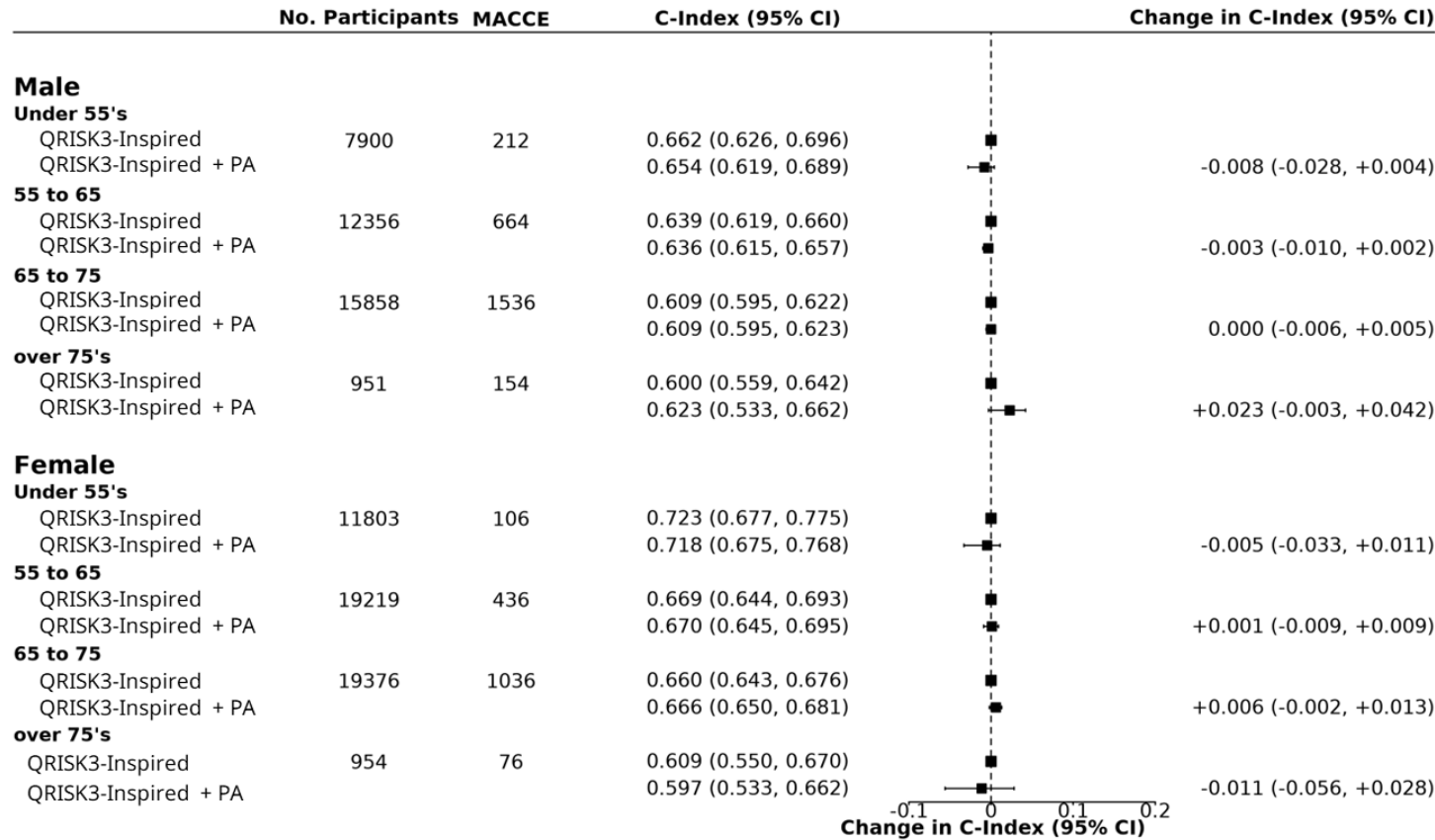


**Figure 6.9 Optimism adjusted Harrell's C-index stratified by age and sex for QRISK3-Inspired and QRISK3-Inspired + PA risk scores.** Participants are divided across 4 age groups: Under 55, 55-65, 65-75 and over 75s across 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE

Abbreviations: CI = confidence intervals; PA = Physical activity.

Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP 1 + Age FP 2 X BMI FP 2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**QRISK3-Inspired Fractional polynomials:** Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**PA risk fractional polynomial (males)** =  $\left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} \left(\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})\right) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$ ;

**PA fractional polynomial (Females)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$

## 6.4 Discussion

### 6.4.1 Overall findings

At the time of writing, this work represents the largest population-based prospective cohort study to investigate the predictive value of accelerometer-derived PA measurements for incident CVD. This work reports the development and internal validation of a novel accelerometer-based risk scores for incident MACCE. This work fills a vital gap in the literature by addressing two central research questions posed by NICE and the AHA: evaluating the added value of PA for both simplifying and improving existing clinical risk models<sup>26,67</sup>.

In this prospective cohort analysis, several findings are reported. First, higher levels of activity, including increased step count and time in moderate-to-vigorous activity, are inversely associated with the risk of incident MACCE. Conversely, increased time spent in sedentary behaviour was positively associated with the risk of MACCE. These associations were consistent across male and female cohorts. Second, univariate 24-hour movement behaviours, derived from seven days of continuous monitoring, were predictive of incident MACCE. Among these, overall activity, measured by the vector magnitude<sup>169</sup>, emerged as the strongest predictor, surpassing all established clinical risk factors used in QRISK3-Inspired and SCORE2-Inspired risk scores, with the exception of age (Table 6.2, Supplementary Table 47). Multivariable PA risk scores, consisting of overall activity, daily step count, and time spent in sedentary behaviour, LPA, or MVPA, showed enhanced predictive performance over univariate PA measurements as measured by Harrell's C-index.

Third, the addition of PA measurements to age alone resulted in significant improvements in risk discrimination and reclassification across a range of commonly used risk thresholds (Supplementary Tables 44, 47-48). Finally, despite the independent association between accelerometer-measured PA and incident MACCE, as well as its strong univariate predictive performance, the addition of PA to established clinical risk models had minimal impact on overall predictive performance. No improvements were observed in discrimination, as measured by the C-index, while only marginal improvements in reclassification measured by

categorical NRI and net benefit were observed for female participants at a 10% risk threshold. Additionally, no significant improvements were observed when substituting HDL and SBP with PA compared to reduced risk scores (excluding HDL and SBP) or complete QRISK3-Inspired and SCORE2-Inspired risk scores.

These findings suggest that broad 24-hour PA measures provide limited clinical utility beyond established risk factors in low-risk primary prevention cohorts. One plausible explanation is overlap in explained variance between PA and predictors within QRISK3 and SCORE2 (e.g., BMI, blood pressure, and smoking), leaving relatively little residual risk for PA to capture. Additionally, UK Biobank participants who completed PA monitoring are generally healthier and more active than the wider UK population, resulting in a narrower spread of activity behaviours. Together with the low incidence of MACCE, this reduces contrast between lower- and higher-risk individuals, attenuating effect sizes and added predictive value. Future work should assess whether incremental value is greater in more representative or younger populations, and whether richer accelerometer features capturing activity patterns and temporal regularity add information beyond duration-based summaries

Notable sex-specific differences were observed in the predictive performance of QRISK3-Inspired and PA risk scores, with each model demonstrating stronger calibration for female participants. Both clinical risk factors and PA measurements also exhibit stronger levels of risk discrimination in females compared to males. The strength of the association and the added predictive value of PA are notably greater for females than for males. Significant improvements in net benefit and categorical NRI were observed across all evaluated risk thresholds for the age + PA risk scores in female participants. Additionally, for high-risk female participants (>10%), significant improvements were reported when PA was added to QRISK3-Inspired risk scores (Supplementary Table 48).

In contrast, the changes in NRI and net benefit were far more modest for male participants, with no significant improvements in classification performance observed for either QRISK3-Inspired or SCORE2-Inspired risk scores following the addition of PA.

While this may be partly explained by the sample size imbalance (37,068 men vs 51,354 women), both sex-stratified models exceeded minimum sample size requirements for development (Supplementary Table 39). Observed sex differences in performance may also reflect underlying differences in baseline risk and rate of clinical diagnosis: women in midlife typically have lower absolute CVD event rates, more heterogeneous symptom profiles, and a higher likelihood of under- or delayed diagnosis compared with men<sup>263–265</sup>. In addition, established clinical risk scores often demonstrate poorer calibration and discrimination in women<sup>266</sup>, partly because female-specific risk factors (e.g., pregnancy-related complications and premature menopause) are absent or under-represented, leaving a greater proportion of unexplained variance. Together, these limitations may allow activity-derived health scores to capture additional risk beyond conventional models, particularly in women.

#### **6.4.2 Comparison with the wider literature**

While direct comparisons of effect sizes are limited by differences in outcome definitions, population characteristics, and accelerometer placement, the associations reported in this analysis are consistent with a growing body of evidence from UK Biobank and other large-scale device-based cohort studies. For example, Walmsley et al. (2022) analysed wrist-worn accelerometer data from over 87,000 UK Biobank participants aged 40–79, without prior CVD, and found that reallocating an additional hour per day to sedentary behaviour was associated with a 5% increase in incident CVD risk (95% CI: 3%–7%), while reallocating 20 minutes to MVPA was associated with a 9% decrease (95% CI: 7%–10%)<sup>171</sup>. Similarly, Ramakrishnan et al. (2019) reported a hazard ratio of 0.46 for the highest versus lowest quartile of MVPA in relation to incident CVD (including non-fatal MI, stroke, and CHD death) among ~90,000 participants aged 40–69, without prior CVD<sup>79</sup>. Small et al. (2023) similarly analysed wrist-worn accelerometer data from middle-aged UK Biobank participants and found an inverse curvilinear association between daily step count and incident cardiovascular events<sup>307</sup>.

Comparable findings have been reported in studies using hip-worn accelerometers. In a meta-analysis of eight prospective studies using hip-worn accelerometers (n > 30,000; mixed-age



adults) del Pozo Cruz et al. reports that each additional 1,000 steps/day was associated with an 11% lower risk of all-cause mortality and a 14% lower risk of cardiovascular events (vs 8% for men and 15% for women in the present study), with consistent associations across fatal and non-fatal endpoints<sup>308</sup>. In the Women's Health Initiative OPACH study (n = 5,861; mean age 78.5; CVD-free at baseline), LaCroix et al. (2019) reported significant inverse associations between PA and incident cardiovascular outcomes. Women in the highest quartile of LIPA had a 22% lower risk of incident CVD (HR = 0.78; 95% CI: 0.60–1.00) and a 42% lower risk of coronary heart disease (CHD) (HR = 0.58; 95% CI: 0.34–0.99), compared to the lowest quartile, after full adjustment. Each additional hour of LIPA per day was associated with a 14% lower risk of CHD (HR = 0.86; 95% CI: 0.73–1.00) and an 8% lower risk of CVD (HR = 0.92; 95% CI: 0.85–0.99), independent of MVPA<sup>309</sup>. These findings contrast with this thesis in which LIPA was not associated with CVD risk, possibly due to differences in sex, age, baseline activity across study populations. Furthermore, the use of hip-worn accelerometers may enhance the accuracy of LIPA measurement by better capturing ambulatory movements<sup>171,231,232</sup>.

In contrast to these previous studies, which focused on population-level associations, this work further evaluates the predictive value of PA to established clinical risk scores for individualised risk prediction by integrating PA with clinical risk factors from QRISK3 and SCORE2. Direct comparison with previous studies investigating the added predictive value of PA measurements remains challenging due to differences in study endpoints, measurement modalities, and choice of baseline risk scores. Comparing this work to the only other study investigating device-measured PA for CVD risk prediction, several important similarities and differences emerge. Ledbetter et al. (2022) investigated the prognostic value of device-measured PA using hip-worn accelerometers for CVD mortality in 2,987 adults aged 50–85 years, with and without baseline CVD. Consistent with this study, the authors univariate PA metrics, including MVPA, LPA, and sedentary behaviour, were highly predictive of CVD mortality<sup>197</sup>, with MVPA demonstrating greater discriminative performance than all established clinical risk factors except age. In contrast to the present findings, C-index of total

physical activity counts exceeded that of age, while but significant improvements in cross-validated concordance were observed when adding PA measurements to established clinical risk factors.

These differences may reflect variation in both endpoints and study design. While Ledbetter et al. (2022) focused solely on CVD mortality, whereas the present study modelled incident MACCE, a broader endpoint that includes non-fatal events. In addition, Ledbetter et al. included participants with prevalent CVD, who are at substantially higher baseline risk of subsequent cardiovascular events and CVD mortality, whereas the present analyses were restricted to individuals without prior CVD, focusing solely on primary prevention.

Furthermore, this earlier study had a substantially smaller sample size (2,987 versus 88,422) and fewer events (161 versus 4,221), suggesting it may have been underpowered. Additionally, the lack of reporting on key clinical utility metrics, such as calibration and reclassification of high-risk individuals, and the absence of direct comparisons to clinical risk factors from established scores such as QRISK3 and SCORE2 limits its ability to inform the clinical utility of device-measured PA. Importantly, Ledbetter et al. emphasised the need for further research into the integration of device-measured PA into established clinical risk models, a gap this study aims to address.

The modest impact of PA on established clinical risk factors observed in this study is consistent with prior literature investigating the addition of self-reported PA to clinical risk models<sup>187,188,198</sup>. For instance, Graversen et al. 2020, assessed the added value of leisure time PA to SCORE2 in individuals with no prior CVD. They found no significant improvement in 10-year predictive performance after adding PA<sup>188</sup>. In a subsequent study, Pandey et al. assessed the added value of self-reported leisure-time PA to the pooled cohort equation for the 10-year risk of CVD. They found no significant improvements in predictive performance after adding PA<sup>198</sup>. While one study by Georgousopoulou et al. (2020) reported significant improvements in AUC following the addition of self-reported daily MET minutes to clinical risk models, several limitations may bias these findings. These include a relatively small sample size and a lack of

internal validation or resampling techniques, potentially leading to overly optimistic results due to overfitting.

Beyond a reliance on self-reported data, these initial studies faced several limitations. They often focused on a narrow subset of PA metrics, such as light physical activity (LPA), walking pace, and estimated intensity, while neglecting more strongly associated predictors of incident CVD, including moderate-to-vigorous physical activity (MVPA) and sedentary behaviour. Sample sizes were modest, ranging from 2,020 to 18,824 participants, limiting the statistical power and generalisability of findings. Moreover, only Georgousopoulou et al. reported any form of internal validation, which was limited to a single train-test split, leaving results susceptible to overfitting and optimism bias.

This work makes numerous contributions to addressing these limitations and strengthening the current evidence base. First, this is the largest study to date investigating the added value of accelerometer-derived physical activity data to established clinical risk models for predicting incident CVD. Second, this work explores a broad range of PA measurements, many of which are targets of international guidelines for increasing PA, including MVPA, LPA and sedentary time<sup>310</sup>. Third, all PA measurements considered in this study were derived using open-source software, ensuring transparency and facilitating reproducibility. Fourth, this study adheres to Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines<sup>88</sup>, enhancing the transparency and reliability of its findings. The complete TRIPOD checklist for this chapter is provided in Supplementary Material Section D, p.547. Finally, this work implements robust internal validation using bootstrapping to adjust for optimism and provides a comprehensive evaluation of model performance, extending beyond discrimination metrics to include assessments of calibration and reclassification.

## **Study Limitations**

Several limitations should be considered when interpreting the findings of this work. First, accelerometer data was collected over a limited period of seven days, preventing the analysis from accounting for potential changes in PA behaviours over time, which may be predictive of incident MACCE.

Second, in the UKB, HDL cholesterol and systolic blood pressure were obtained up to six years prior to accelerometer wear, and no repeat measurements were recorded to coincide with PA monitoring. This exceeds the maximum window of 5 years between HDL and SBP specified in the derivation of QRISK3 and may not reflect values at the start of follow-up. These outdated baseline characteristics could introduce regression dilution bias, attenuating the coefficients for these predictors and pulling predicted risks towards the population average. As a result the performance of clinical risk factor-based model may be attenuate, inflating the incremental value of PA risk factors. However, the analysis presented in Chapter 3 suggests that the baseline measurements remained stable among participants who consented to participate in repeat studies conducted several years apart. Additionally, sensitivity analysis using HDL and SBP from primary care records, recorded 5 years prior to accelerometer wear time, revealed minimal impact on overall model performance or the relative value of PA measurements to clinical risk models.

Third, associations between PA and MACCE were not explicitly adjusted for accelerometer wear time or season of wear. This may be important because wear-time differences can influence derived PA summaries, and seasonality may confound associations as both activity patterns may vary by season. In UK Biobank, posting dates were distributed across the calendar year, meaning wear occurred throughout multiple seasons; however, residual seasonal confounding cannot be excluded. Furthermore, PA behaviours were not modelled using mutually adjusted pairs given the finite daily time budget and strong interdependence between PA components, this may limit interpretation of individual PA terms and may attenuate model coefficients.

Fourth, while QRISK3 and SCORE2 provide 10-year risk estimates for incident CVD in current clinical practice, this study was limited to six years of follow-up, limiting the ability to evaluate how the models perform within the framework of current clinical guidelines. Finally, as outlined in Chapter 3, the UK Biobank is subject to a well-documented healthy volunteer selection bias, further exacerbated by the requirement to survive to recruitment and participate in the accelerometer sub study. Together, these selection processes are likely to attenuate associations towards the null by preferentially excluding individuals with higher baseline risk of MACCE, and, plausibly, lower activity. This likely reduces the contrast between exposure and outcome, underestimating the strength of associations. In addition, this selection may limit generalisability of absolute risk to other populations.

#### **6.4.3 Summary**

In conclusion, while device-measured PA is independently predictive of MACCE, the addition of PA to clinical risk factors does not appear to significantly improve predictive performance. Although adding PA to age improved prediction compared with age alone, age + PA scores failed to match the performance of multivariable risk scores derived from QRISK3 and SCORE2 risk factors. Furthermore, substituting HDL and SBP with PA in clinical risk models does not achieve the predictive performance of the complete risk scores. However, PA does improve risk discrimination and classification over reduced risk scores that exclude HDL and SBP, highlighting its potential value in scenarios where these clinical measurements are unavailable. As discussed in Chapter 2, while 24-hour movement behaviours, such as step count, LPA, and MVPA, are easy to interpret, simplifying PA interventions, these broad categories often fail to capture the full spectrum of PA. They frequently overlook finer details, such as short bouts of activity, precise intensities, and the complex interactions between these behaviours over time. Recent advances in deep learning have shown state-of-the-art performance in PA monitoring, with the ability to identify novel patterns from raw accelerometer data. Chapter 7 will explore whether deep learning models can enhance risk stratification by better accounting for complex patterns in raw movement data and their relationship with incident MACCE.

## Chapter 7 – Development and validation of deep neural network risk models using wearable accelerometer data for the prediction of Major Adverse Cardiovascular/Cerebrovascular Events in the UK Biobank

### 7.1 Introduction

#### 7.1.1 Background

In Chapter 6, risk scores for 6-year incidence of Major Adverse Cardiovascular & Cerebrovascular events were developed using device-measured 24-hour movement behaviours from over 88,000 individuals in the UK Biobank activity monitoring sub-study. These models demonstrated that 24-hour movement behaviours were not only independently associated with incident Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) but also showed strong univariate predictive performance. However, despite this performance, PA measurements showed minimal incremental value to established clinical risk factors from established risks scores, such as QRISK3 and SCORE2. Chapter 7 builds on this foundation by developing a novel deep-learning-based risk model capable of considering a wider range of movement behaviours captured by wearable accelerometers.

While traditional 24-hour summaries of PA help to provide a broad overview of overall activity levels, they fail to capture more granular patterns of activity that are important for cardiovascular health. Emerging evidence suggests that beyond total activity volume, how activity is accumulated, its temporal distribution, and regularity, may play a critical role in predicting cardiovascular outcomes<sup>311-314</sup>.

Rapid advancements in wearable sensors are enabling ever richer data streams at greater temporal resolution. Traditional approaches to handling the high-dimensional data produced from wearable accelerometers have been to reduce this information to a few key summary statistics, including overall step count and 24-hour movement behaviours explored in Chapter 6. Prior works have successfully demonstrated that high-resolution time series features may offer new insights beyond broad summaries of activity for the management and prevention of CVD<sup>315</sup>.

The integration of wearable sensors into practical prevention pipelines for CVD remains a significant challenge in clinical research. Current risk prediction methods used in clinical practice, such as Cox proportional hazards and logistic regression, are often limited to a small number of established risk factors and frequently assume a linear relationship between risk factors and the target outcome. In contrast, wearable accelerometers can capture hundreds of readings per second, creating data with complex structural and temporal dependencies. This presents a pressing need for new analytical methods which can better handle complex patterns present in such high-frequency data.

In recent years, there has been growing interest in the use of deep learning to analyse high-resolution sensor data for predicting disease outcomes. Unlike traditional regression-based methods, deep learning excels at capturing complex interactions within high-dimensional data without prior assumptions as to the relationship between risk factors<sup>80</sup>. Deep neural networks have shown considerable success in relating accelerometer time-series data from wearable devices to various disease outcomes, including atrial fibrillation, sleep apnoea, and various CVD risk factors, surpassing traditional approaches<sup>316–318</sup>. However, no previous studies have explored the potential of deep neural networks, coupled with wearable accelerometers, for incident CVD risk prediction.

This chapter sets out to address this gap through the development and internal validation of a novel deep-learning risk model designed to predict the 6-year risk of death or hospitalization due to MACCE. First, this chapter describes the development of a deep neural network risk model, based on deep survival machines<sup>319,320</sup> described in section 5.2.3, to capture the risk of incident chronic disease based on individual PA dynamics. Predictions from the model will then be included in downstream MACCE risk scores to evaluate both the univariate performance and added value to established clinical risk factors from established risk scores including QRISK3 and SCORE2.

### **7.1.2 Aims**

Building on the work presented in Chapter 6, this study investigates the added value of deep learning applied to accelerometer recordings for the prediction of incident Major Adverse Cardiac and Cerebrovascular Events (MACCE). The purpose of this study was threefold: 1) To develop a deep learning-based risk score, using physical activity data, to predict the risk of first incident hospitalisation due to a composite chronic disease outcome including cardiovascular disease, chronic kidney disease, stroke and cancers associated with physical inactivity., 2) Evaluate the added value of deep learning activity derived risk scores to clinical risk factors from QRISK3 and SCORE2, the primary risk calculators used in UK and European primary care, 3) Investigate the added predictive value of AHS to age alone and its potential to substitute cholesterol and blood pressure values in established clinical risk models.



## **7.2 Methods**

### **7.2.1 Study population**

This work was conducted using a subset of ~100,000 UK participants who consented to 7 days of physical activity monitoring using wrist-worn accelerometers<sup>205,271</sup>, as described in Chapter 3. The initial study population, exclusion criteria and accelerometer signal processing are described in Chapter 6.

### **7.2.2 Data processing**

#### **7.2.2.1 Ascertainment of study endpoint: cardiovascular disease diagnosis**

Clinical risk factors were selected to match those included in the QRISK3 risk calculator<sup>51</sup> as described in section 6.2. The relevant definitions, ICD 9/10 and UKB identifiers are provided in Supplementary Table 3.

The primary outcome of interest was the 6-year risk of incident MACCE, described in section 4.2.2.1. Follow-up duration and censoring are described in section 6.2.2.1. The Definition of MACCE is presented in Supplementary Tables 1-2.

All missing exposure data were multiply imputed by Chained Equations (MICE)<sup>228</sup> using five imputed datasets, as outlined in section 6.2.2.1 and the initial derivation study for QRISK3<sup>51</sup>.

### **7.2.3 Deep Learning for CVD Risk Prediction**

#### **7.2.3.1 Deep survival of accelerometer data**

The motivations behind the use of deep survival neural networks over conventional regression models are outlined in detail in Chapters 1. In short, as datasets become larger and more complex, the number of parameters and the potential for non-linear interactions grows exponentially. Regression models are poorly equipped to handle this high-dimensional data, and many assumptions underpinning common regression frameworks can no longer be relied on. In contrast, deep neural networks can identify complex relationships without relying on prior hypothesis and are better equipped to handle complex high dimensional data from high-frequency time series such as free-living accelerometer recordings.<sup>46,94</sup>

Using disease outcomes derived from hospital episode statistics, a deep survival network was trained to estimate the risk of incident hospitalisation due to chronic disease, referred to as Activity Health Scores (AHS), from 1-minute time windows using 26 rotation-invariant features of the accelerometer signal (Supplementary Section A p.342). The outcome used for model training was a composite of first incident hospitalisation due to CVD and other chronic conditions, including chronic kidney disease, diabetes, stroke, and selected cancers with established links to physical inactivity, including colorectal (ICD-10 C18–C20), breast (C50), and endometrial cancer (C54)<sup>321–324</sup>, the outcome definition is provided in Supplementary Table 55. The composite AHS hospitalisation endpoint includes cardiovascular and cerebrovascular ICD-10 code blocks that overlap with the MACCE definition (e.g., I20–I23 for ischaemic heart disease and myocardial infarction, I46–I49 for cardiac arrest and arrhythmias, I50 for heart failure, and I63/G45 for cerebral infarction and transient ischaemic attack; Supplementary Tables 1 and 55).

The AHS was developed as a generalisable, indicator of activity-related health conditions, intended for use beyond this thesis and MACCE. The model was pre-trained to predict a higher-prevalence composite outcome of incident hospitalisation for conditions linked to physical inactivity (Supplementary Table 55), enabling it to learn salient health-related features from accelerometer data. The resulting score can be interpreted as a broad measure of morbidity and frailty and used as an input to downstream disease-specific risk models, including MACCE.

### **7.2.3.2 Feature engineering**

In each 1-minute window of acceleration, 26 features were extracted. These features were selected based on prior work from Walmsley et al.<sup>171</sup> and Willetts et al.<sup>164</sup> and included time domain features, such as median, minimum and maximum acceleration, in addition to frequency domain features derived from Fast Fourier Transforms. To mitigate potential inaccuracies caused by device orientation relative to the wrist, this analysis was restricted to a subset of 26 features that were rotation-invariant. A full list of the selected features is provided in Supplementary Section A (Appendix p.342).

Following feature extraction, three transformations were applied to support model training:

- **Random resampling:** For every 5-minute segment of the accelerometer data, a single 1-minute window was randomly selected for model training. This helps to increase variability and decrease overfitting based on temporal patterns, as the order in which activity was completed would not be expected to impact one's risk.
- **Data shifting:** Randomly shifts the data forward or backward in time by a fixed amount, changing the alignment but mandating its temporal structure. By simulating time shifts in the data, the model becomes more invariant to temporal translations.
- **Noise:** Adds random noise to the data to simulate variations and make the model more robust to small changes in input

#### 7.2.3.3 Network Training

This work employs a custom convolutional neural network (CNN) architecture with residual connections<sup>272</sup> totalling 31 layers and over 43 million parameters. A residual CNN architecture was selected based on the previously observed state-of-the-art performance of residual CNN in accelerometer analysis. The learned feature vector was of size 1024. The resulting latent representation of the activity data is passed through a fully connected layer to identify the most relevant features associated with incident hospitalisation with a chronic condition (Supplementary table 55). Further details on the model architecture are provided in Appendix Section A, p.344.

Accelerometer data was processed in 5-second windows consisting of 26 summary features described in 6.2.3.1. For each Subject, a single 5-second window was randomly sampled from each minute of the day, giving an input vector of (7,26, 1440) (7 days, 26 features, by 1440 1-minute windows). Data augmentations were then applied to the connected windows for each training batch. A batch size of 512 was used for model training.

For optimisation, Adam<sup>274</sup>, with an initial learning rate of  $3e-4$ , was used. A learning rate scheduler dynamically adjusted the rate, reducing it following five consecutive epochs without improvement to help the optimiser reach a better local minimum. The network was trained to minimise the negative log partial likelihood over a 6-year follow-up period, as outlined in the original deep-survival framework<sup>81</sup> (see section 5.2.3). In contrast to the original loss function proposed by Katzman et al. 2018, this work normalises the negative log partial likelihood by the size of the risk set for each mini batch to handle an inconsistent number of events between batches. Early stopping was applied with a patience of 15 epochs to prevent overfitting. Training was distributed across four Tesla V100-SXM2 GPUs, each with 32GB of memory.

As highlighted in Chapter 5, large volumes of data are required to effectively train a deep neural network. Consequently, the study population was not stratified by sex during model training and evaluation. This approach contrasts with Chapter 6 and the downstream MACCE risk scores discussed in this chapter, where models were sex-stratified following the methodology used to derive the original QRISK3 risk score<sup>51</sup>.

Model development and validation were implemented using Python 3.9 and PyTorch Lightning 1.5.

#### **7.2.3.4 Model development and evaluation for MACCE risk prediction**

The predictive performance deep learning risk model was evaluated using a nested  $10 \times 5$  cross-fold validation. Each internal cross-validation had a 7:2:1 split ratio for train/validation and test sets. While each outer fold had a split of 9:1 between derivation and test sets. Predictions for the outer fold test set are based on an ensemble of five models trained in the inner fold, where the final prediction is the average across the models.

To minimise optimism, when applying AHS for MACCE risk prediction Out-of-fold predictions were generated for each of the ten outer folds in the nested cross-validation, ensuring each participant's AHS was produced by models trained without that participant.

Using a technique known as meta-modelling, these predictions were aggregated into a single dataset and incorporated into clinical risk models through Cox proportional hazards models for downstream MACCE risk prediction<sup>325,326</sup>.

A schematic overview of the derivation of the Activity Health Score (AHS) and its integration into downstream MACCE risk prediction scores is provided in Figure 7.1.

For downstream MACCE risk prediction, model development and validation follow the same protocol as outlined in section 6.2.3. In short, AHS predictions were combined with clinical risk models using Cox proportional hazard models to estimate the 6-year risk of incident MACCE in males and females using separate regression models. Fractional polynomials<sup>295</sup> were estimated for AHS across five multiply imputed datasets combined in a stacked (long) format. Using the selected fractional polynomials, separate Cox models were fitted in each imputed dataset. The models from each imputed dataset were combined using Rubin's rules, yielding a final set of coefficients.<sup>292</sup> Model coefficients were adjusted for optimism using uniform shrinkage following 1000 bootstrap iterations as described in Figure 6.2. As a sensitivity analysis, MACCE risk scores were additionally developed within the derivation data of each outer fold and evaluated on the corresponding held-out outer-fold test set, with performance summarised across folds.

As described in Chapter 6, Three baseline models were evaluated, starting with age as a univariate predictor, in addition to re-calibrated SCORE2-Inspired<sup>58</sup> and QRISK3-Inspired<sup>51</sup> risk scores, derived from QRISK3 and SCORE2 risk factors (Supplementary Table 3). and functional form, respectively To assess the potential of wearable-derived Activity Health Scores (AHS) to substitute for traditional clinical measurements, where HDL cholesterol and systolic blood pressure (SBP) were excluded from the SCORE2-Inspired and QRISK3-Inspired risk scores. A full list of clinical risk factors used to derive QRISK3-Inspired and SCORE2-Inspired risk scores is provided in Supplementary Table 3.

Following the methodology outlined in Section 2.2, Harrell's C-index<sup>99</sup> and the integrated calibration index (ICI)<sup>101</sup> were applied to assess discrimination and calibration, respectively. Reclassification performance was evaluated using the net reclassification index (NRI)<sup>105</sup> standardised net benefit (NB)<sup>106</sup> at risk thresholds of 5%, 7.5% and 10%.

A sensitivity analysis was conducted by substituting UK Biobank (UKB) HDL and systolic blood pressure (SBP) measurements with values from primary care records, measured within five years of accelerometer monitoring, following the methodology outlined in the derivation of QRISK3<sup>51</sup>. For further details on the derivation and internal validation of Cox regression risk scores, see sections 6.2.3 and 6.2.4.

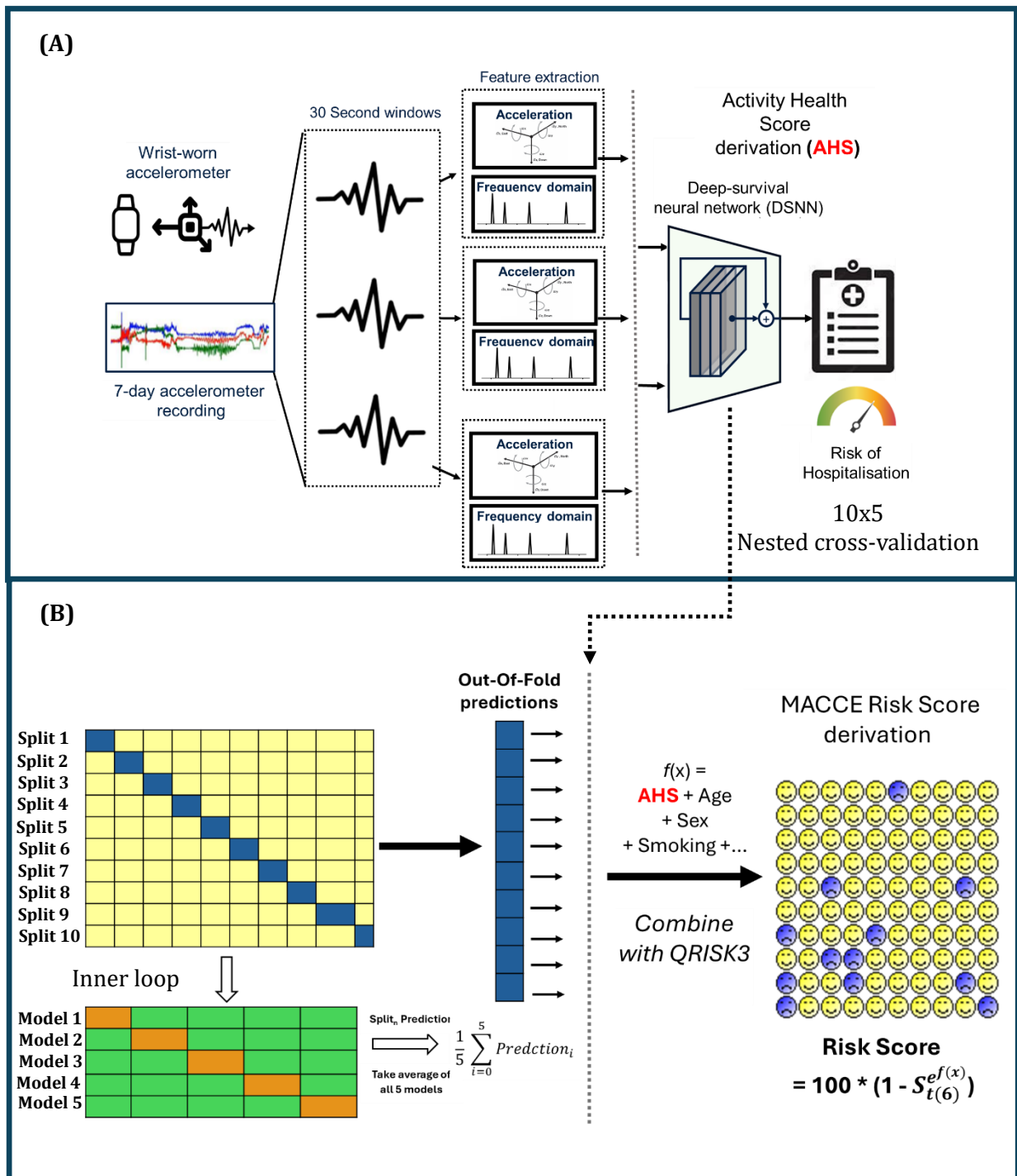


**Figure 7.1: Overview of derivation (A) and validation (B) of deep survival Activity Health Scores (AHS) derived from 88,422 participants (4,221, MACCE; 4.8%) and over 600,000 person-days of accelerometer data. (A) Raw accelerometer data is decomposed into 30-second summaries of acceleration and frequency domain features and analysed by a convolutional neural network to predict the 6-year risk of hospitalisation due to a broad range of health conditions associated with sedentary behaviour (B) Risk scores are generated for all participants via 10x5-fold nested cross-validation with predictions pooled together and integrated with QRISK3 risk factors.**

## 7.3 Results

### 7.3.1 Activity Health Score Pre-training- Predicting incident hospitalisation

Following the exclusion criteria outlined in Chapter 6, 88,422 individuals were used to develop an Activity Health Score (AHS), to predict the risk of incident hospitalisation due to a range of disease endpoints related to Physical activity (PA), including CVD, cancer, chronic kidney disease, diabetes, and stroke, relevant ICD- 9/10 codes are provided in Supplementary Table 55. In total 25,544 (28.9%) incident hospitalisations were reported with 12,603 (34.0%) occurring for males and 12,941 for females (25.2%) following 6 years of follow-up. Of the 4,227 participants who experienced MACCE, 4,136 (97.8%) participants also had a reported hospitalisation captured within the AHS endpoint. This overlap was expected given shared ascertainment via hospital episode statistics and overlapping ICD definition; the analysis avoids individual-level leakage through out-of-fold AHS predictions, but the overlap means AHS should be interpreted as a broad morbidity risk score with MACCE as a major component. Table 7.1 summarises the discrimination and calibration of AHS for incident hospitalisation, based on the average hazard ratio, Harrell C-index and Integrated calibration Index (ICI), across a nested 10-fold cross validation. The proposed deep survival network showed robust discrimination and modest calibration within the study population.

**Table 7.1: Upstream performance of deep survival derived Activity Health Scores (AHS) for predicting incident hospitalisations due to cardiovascular disease, cancers, chronic kidney disease and stroke.**

| Model                                             | Hazard ratio | C-index (95 CI) | ICI (95% CI)  |
|---------------------------------------------------|--------------|-----------------|---------------|
| <b>Male (N = 37,068; hospitalised =12,603)</b>    |              |                 |               |
| AHS                                               | 1.61±0.08    | 0.66 ±0.001     | 0.0605±0.009  |
| <b>Female (N = 51,354; hospitalised = 12,941)</b> |              |                 |               |
| AHS                                               | 1.76±0.16    | 0.68±0.01       | 0.0559±0.006  |
| <b>Overall</b>                                    |              |                 |               |
| AHS                                               | 1.77± 0.05   | 0.65± 0.01      | 0.0563± 0.002 |

Abbreviations: AHS: Activity Health Score, ICI: Integrated Calibration Index, CI: Confidence Interval

Data are reported on 37,068 males (41.9%) with 12,603 (34.0%) incident hospitalisations and 51,354 females (58.1%) with 12,941 (25.2%) hospitalisations over 6 years. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Average performance of deep-learning derived AHS for predicting incident hospitalisation due to chronic disease, following nested 10-fold cross-validation (± standard deviation).

Hazard ratios are reported per standard deviation increase in Activity Health Score.



### 7.3.2 Association of Activity Health Scores with MACCE

The Cox regression analysis cohorts had a median follow-up of 6.0 years for males and females. During this time, 2,571 males (6.9%; 2,187 non-fatal and 384 fatal) and 1,656 females (3.2%; 1,473 non-fatal and 183 fatal) experienced incident MACCE. Figure 7.2 illustrates the association between deep-learning-derived Activity Health Scores (AHS) and the 6-year incidence of MACCE, analysed both per fifth and on a continuous scale using penalized splines with 3 degrees of freedom. A significant non-linear association was observed for both males and females, with a hazard ratio (HR) per standard deviation increase in AHS of 1.22 (95% CI 1.16 – 1.29,  $p < 0.001$ ) and 1.44 (1.35 – 1.54,  $p < 0.001$ ), respectively.

For males, in the bottom 60% of AHS, the hazard ratio remains relatively stable, with no significant increase between the bottom 20% and those in the 40–60% fifth of the distribution. However, a sharp rise in the hazard ratio (HR) is observed for those in the top 60–80% and 80–100% of AHS fifths relative to the bottom 20%, with HR = 1.17 (95% CI: 1.03–1.34,  $p = 0.02$ ) and HR = 1.56 (95% CI: 1.36–1.79,  $p < 0.001$ ), respectively.

For females, a much greater increase in the associated risk of MACCE is evident, with a significant rise in the hazard ratio observed for each successive fifth increase in AHS, indicating a more consistent and stronger relationship compared to males.

During the first 2 years of follow-up, 1,244(1.4%) (males: 777 (2.1 %); females: 467(0.9%)) were diagnosed with MACCE, respectively. After excluding participants diagnosed with MACCE in the first 2 years of follow-up, in a sensitivity analyses, minimal changes in the HRs were observed, HR = 1.24 (1.17 – 1.32,  $p < 0.001$ ) for males and HR = 1.40 (1.30 – 1.52,  $p < 0.001$ ) for females.

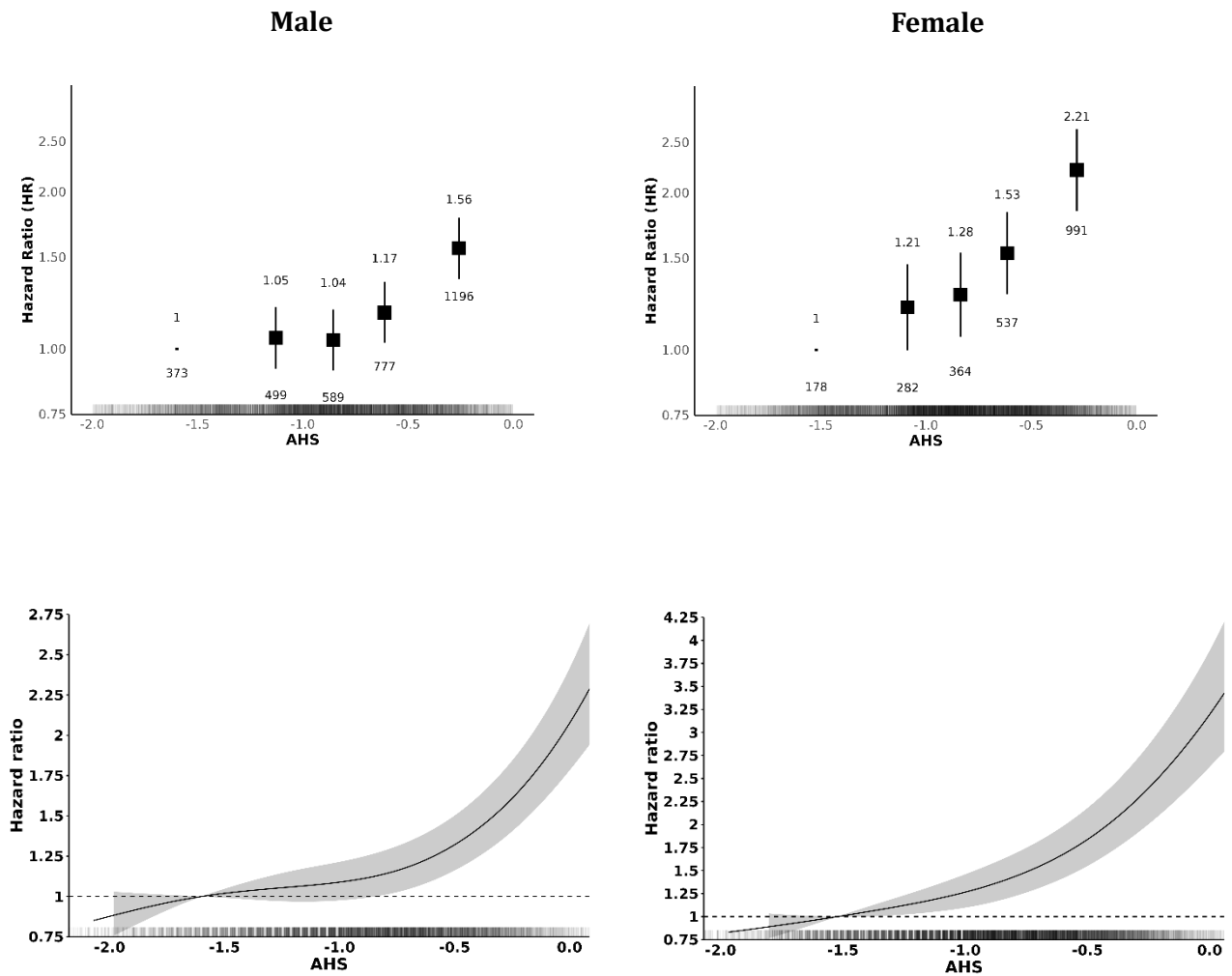


**Figure 7.2 Association between deep learning-derived Activity Health Scores (AHS) and 6-year incidence of MACCE.**

**(Top) Forest plots for the associations between Major Adverse Cardiovascular & Cerebrovascular Events (MACCE) with fifths of deep learning derived Activity Health Scores (AHS), (Bottom) continuous AHS for 37,068 male and 51,354 female UK Biobank participants.**

Hazard ratios (HR) and 95% confidence intervals were adjusted for age, sex, body mass index, ethnicity, smoking status and Townsend deprivation index. In the top figure, the HR is plotted, with the number of events plotted above and below each data point, respectively. The bottom figures show a spline plot of the hazard ratio and 95% confidence interval of the association of continuously modelled AHS. Vertical bars along the AHS axis indicate the distribution of deep learning-derived AHS.

### **7.3.3 Predictive value of Activity Health Score**

#### **7.3.3.1 Univariate Predictive Performance of Activity Health Scores**

For downstream MACCE risk predictions, univariate AHS yielded a C-index of 0.632 (95% CI: 0.622–0.643) in males and 0.684 (95% CI: 0.671–0.697) in females. This exceeded the C-index of any univariate measures of PA. Deep survival AHS outperformed conventional multivariable PA risk scores outlined in Chapter 6, which combined traditional measurements of PA into a single risk model. The C-index of AHS exceeded that of multivariate PA risk scores for incident MACCE by +0.028(95% CI 0.018 - 0.038,  $p < 0.001$ ) and +0.042(95% CI 0.03 - 0.054,  $p < 0.001$ ) was reported over conventional PA risk scores for males and females respectively. For both males and females, the model discrimination of AHS exceeded that of all univariate clinical risk factors, with the exception of age (Supplementary Table 42).

Compared to the multivariable PA risk scores presented in Chapter 6, AHS showed a similarly strong unadjusted association with MACCE and significantly stronger calibration measured by the ICI, for males, with a decrease in ICI (the smaller the ICI the closer the prediction is to the observed risk) of -0.003(95% CI -0.006 - -0.001,  $p = 0.009$ ) and a non-significant improvement for females of -0.001(95% CI -0.003 - 0,  $p = 0.12$ ). The unadjusted hazard ratios along with the discrimination and calibration of AHS for MACCE risk predictions are shown in Table 7.2.

The continuous calibration curves for AHS are presented in Supplementary Figure 26. In contrast to PA risk scores derived from traditional measurements (Supplementary Figure 22), AHS were well calibrated within the study population, showing close alignment to the observed risk. For male participants, the extent to which activity derived risk scores underpredict MACCE was greatly attenuated with only slight underprediction reported for observed risks greater than 15%.

For female participants, the AHS calibration curve closely aligns with observed MACCE risks below 5%, indicating good calibration in lower-risk groups. However, at higher observed risks (above 10%), the curve deviates above the diagonal, showing consistent overprediction. However, given the small number of observations with greater than 10% observed risk, the impact of this overprediction on the overall calibration of the AHS model is limited, and the model remains robust for the majority of the study population.

**Table 7.2: Performance of Univariate Activity Health Scores for 6-year MACCE risk prediction**

| Model                                   | Hazard Ratio (95% CI) | C-index (95% CI)    | ICI (95% CI)             |
|-----------------------------------------|-----------------------|---------------------|--------------------------|
| <b>Male (N = 37,068 MACCE = 2,571)</b>  |                       |                     |                          |
| AHS                                     | 1.445 (1.42 - 1.471)  | 0.632 (0.622–0.643) | 0.0026 (0.0009 - 0.0045) |
| <b>Female (N = 51,354 MACCE =1,656)</b> |                       |                     |                          |
| AHS                                     | 1.347 (1.311 - 1.383) | 0.684 (0.671–0.697) | 0.0014 (0.0004 0.0024)   |

Abbreviations CI: confidence interval; AHS Activity Health Score; MACCE= Major Adverse Cardiovascular & Cerebrovascular Event

Data are reported on 37,068 males (41.9%) with 2,571 (6.9%) incident MACCE and 51,354 females (58.1%) with 1,656 (3.2%) MACCE observed over 6 years.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow’s method, based on mean-centred continuous variables, with all binary risk factors set to 0

Unadjusted hazard ratios for Activity Health Score are reported per standard deviation. increase

Performance metrics were adjusted for optimism, and 95% confidence intervals were obtained via 1000 bootstrap iterations.

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).

AHS fractional polynomial (male) =  $(AHS/0.1)^{-2} + (AHS/0.1)^2$

AHS fractional polynomial (female)=  $(AHS/0.1)$

### 7.3.4 Added value of Activity Health Scores to MACCE risk prediction

#### 7.3.4.1 Discrimination

Figure 7.3 presents the added value of deep learning derived Activity Health Scores (AHS) to model discrimination for each baseline risk model, age, QRISK3-Inspired excluding HDL and SBP, and complete QRISK3-Inspired risk scores for males and females respectively. Age + AHS yielded an improvement in C-index  $\Delta$  0.012 (0.007 – 0.016;  $p < 0.001$ ) for males and  $\Delta$  0.025 (95% CI 0.018 - 0.03;  $p < 0.001$ ) for females. The C-index for age + AHS risk scores was significantly greater than that reported for Age + traditional physical activity measurements presented in section 6.3.4.

A similar result was observed when extending QRISK3-Inspired risk scores with AHS. A significant improvement in model discrimination was reported for both male and female cohorts following the addition of AHS with an increase in C-index of  $\Delta$ 0.003 (95% CI 0.001 - 0.005,  $p = 0.003$ ) and  $\Delta$ 0.007 (95% CI 0.004 - 0.01,  $p < 0.001$ ), respectively.

When combined with QRISK3-Inspired risk scores, AHS showed superior discrimination compared to conventional PA measurements, with a significantly higher C-index. For males a further improvement of 0.003 (95% CI 0.001–0.005) and 0.007 (95% CI 0.004–0.01) for females were observed compared to QRISK3-Inspired + PA risk scores.

Discrimination results for QRISK3-Inspired and SCORE2-Inspired risk scores, where UKB-measured HDL and SBP were replaced with primary care measurements, are presented in Supplementary Figures 27–29 and Tables 58–59. While substituting UKB measurements with primary care data led to a slight decrease in model discrimination, the added value of AHS measurements to QRISK3-Inspired and SCORE2-Inspired risk scores remained consistent with the original UKB derived models

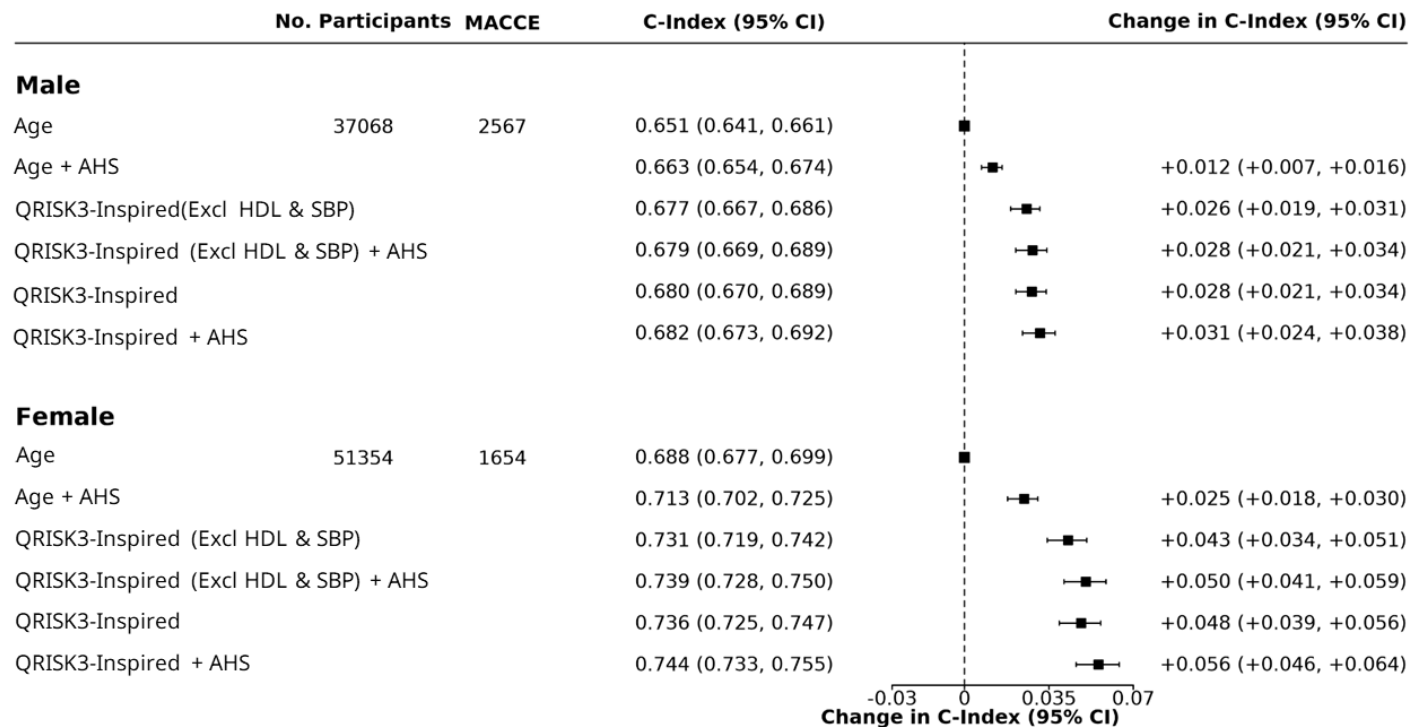


**Figure 7.3 Optimism adjusted Harrell's C-index for risk scores derived from Age, Age deep learning derived Activity Health Scores (AHS) and a recalibrated QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) extended with AHS; and full QRISK3-Inspired risk scores extended by AHS. in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**

Abbreviations: CI = confidence intervals; AHS = Activity Health Scores = High-density lipoprotein; SBP = Systolic blood pressure; MACCE= Major Adverse Cardiovascular & Cerebrovascular Event

Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

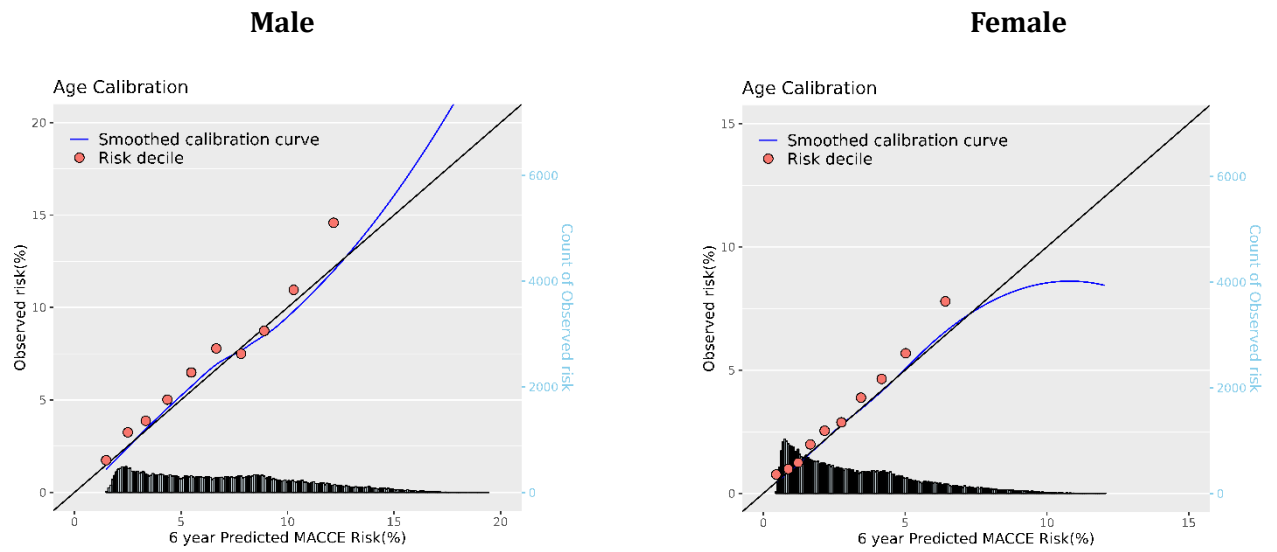
Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Age AHS fractional polynomial (male) = (AHS/0.1)<sup>3</sup>; Age AHS fractional polynomial (female) = (AHS/0.1)<sup>2</sup>; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) = (AHS/0.1)<sup>3</sup>; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) = (AHS/0.1)<sup>0.5</sup> + AHS/0.1; QRISK3-Inspired AHS fractional polynomial (male) = (AHS/0.1)<sup>2</sup> + (AHS/0.1)<sup>3</sup>; QRISK3-Inspired AHS fractional polynomial (female) = AHS/0.1 + ((AHS/0.1) X log(AHS/0.1))

#### **7.3.4.2 Calibration**

The continuous calibration curves for age and QRISK3-Inspired risk scores, as described in section 6.3.4, in addition to age + AHS and QRISK3-Inspired + AHS risk scores are presented in Figure 7.4. The addition of AHS substantially improved the calibration for male and female cohorts, removing the underprediction reported in male participants at higher observed risk and greatly attenuated the overprediction for female participants. The inclusion of AHS to age-based risk scores also expanded the distribution of predicted risks compared to age alone indicating that the age + AHS model captures more of the variance in risk within the study population. While age + AHS modestly overpredict risk in higher observed risk group, the predicted risk remains more closely aligned with observed risks than age risk scores alone. The overall model calibration, measured by the integrated calibration index is presented in Supplementary Tables 56 -59. The smoothed calibration curves for QRISK3-Inspired (excluding HDL cholesterol and SBP) and QRISK3-Inspired (excluding HDL cholesterol and SBP) + AHS risk scores are shown in Supplementary Figure 30.

## (A) Univariate Age risk scores



## (B) Age + Activity Health Scores (AHS)

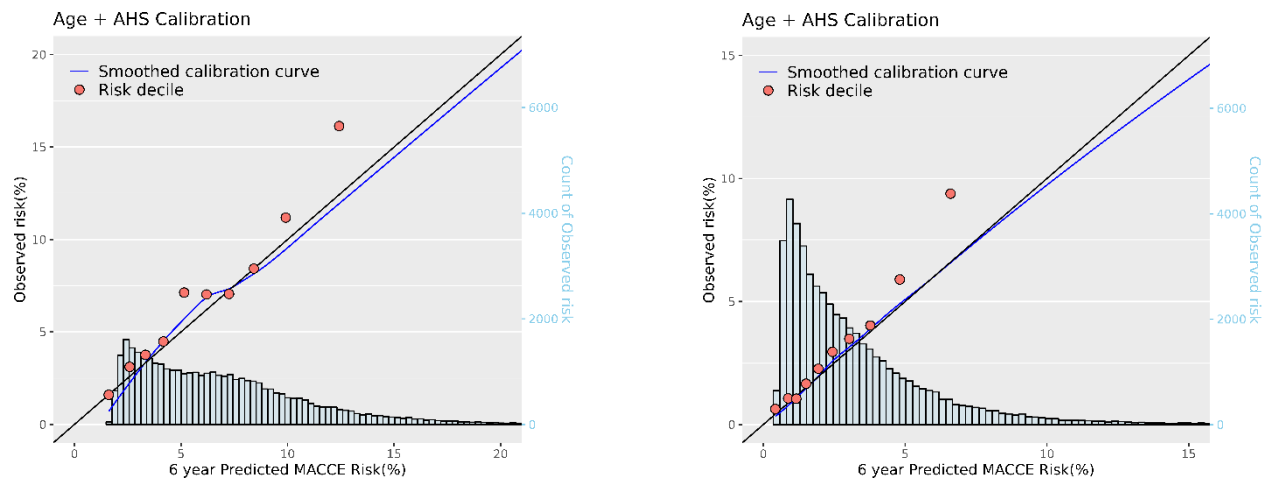


**Figure 7.4 Smoothed calibration curve for (A) Age and (B) Age + Activity Health Scores (AHS) derived for male and female participants. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.**

Red circles represent the observed 6-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).

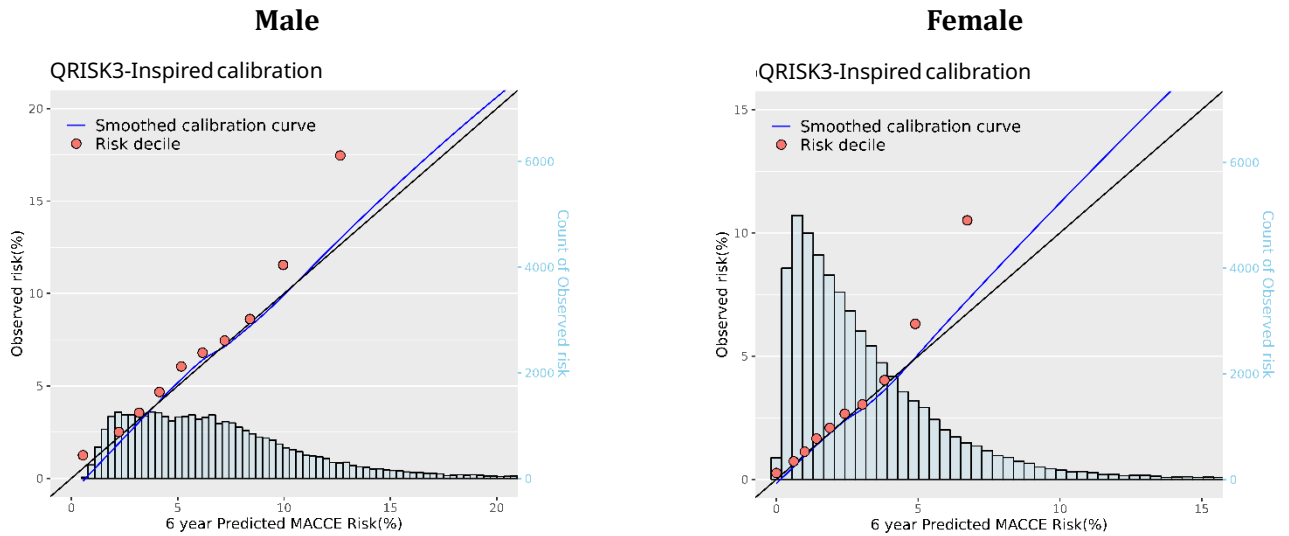
AHS fractional polynomial (male)  $= (AHS/0.1)^3$ ;

AHS fractional polynomial (female)  $= (AHS/0.1)^2$



The changes in model calibration to QRISK3-Inspired risk scores following the addition of AHS, closely mirrors the changes observed following the addition of conventional PA measurements shown in Figure 7.5. For the male cohort a modest reduction in the underprediction for higher risk groups was observed following the addition of AHS. For female participants, there was little change in alignment between observed and predicted risk or in the distribution of predicted risk scores between the baseline and AHS-extended QRISK3-Inspired models.. Additionally, no significant changes in the ICI were observed following the addition of AHS (Supplementary Tables 56-59).

### (A) QRISK3-Inspired



### (B) QRISK3-Inspired +AHS

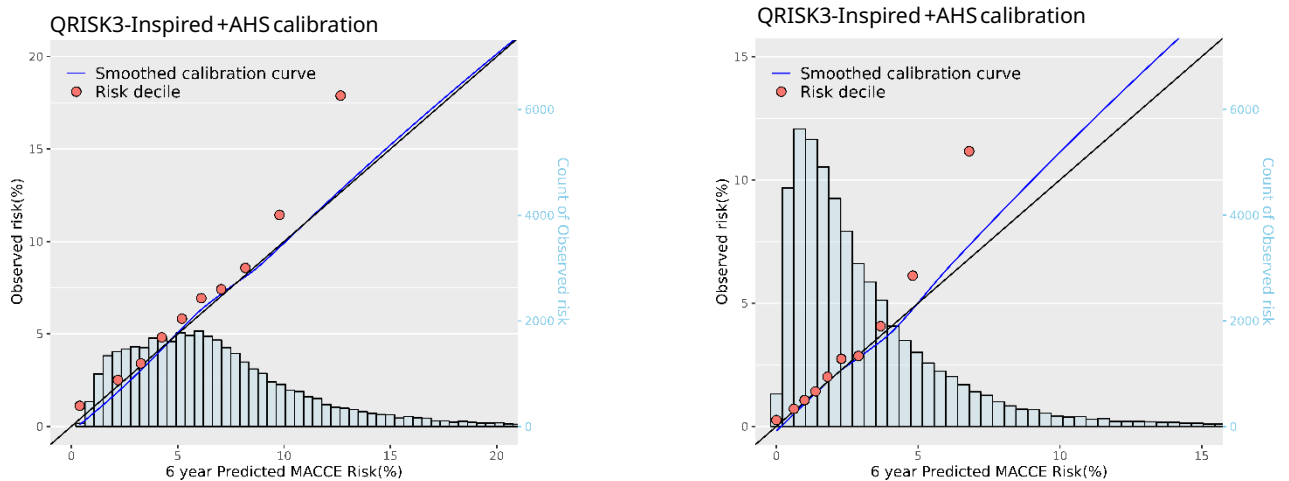


**Figure 7.5 Smoothed calibration curve for (A) QRISK3-Inspired and (B) QRISK3-Inspired + Activity Health Scores (AHS) risk scores derived for male and female participants. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.**

Red circles represent the observed 6-year risk of Major adverse Cardiovascular & Cerebrovascular Events at each decile of predicted 10-year risk. Black line represents perfect calibration. Blue line represents the smoothed calibration curve of all risk deciles generated using jack-knife methods.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; AHS fractional polynomial (female) =  $AHS/0.1 + ((AHS/0.1) \times \log(AHS/0.1))$ .

### 7.3.4.3 Reclassification

Reclassification was again evaluated by the net reclassification index (NRI) and standardised net benefit, on both a continuous scale and at three common clinical thresholds of 5%, 7.5% and 10%.

Figure 7.6 presents the decision curves for age, age + AHS, QRISK3-Inspired and QRISK3-Inspired + AHS risk scores up to a risk threshold of 20%, for male and female participants respectively. For male participants, the decision curves show a modest increase in net benefit following the addition of AHS to age risk scores, particularly at higher risk thresholds. A significant improvement in net benefit was reported at a risk threshold of 10% for age vs age + AHS risk scores  $\Delta$ net benefit = 0.031(95% CI 0.016 - 0.046, <0.001). The increase in  $\Delta$ net benefit was more pronounced for female participants, with Figure 7.6 demonstrating greater separation between age and age + AHS risk scores at lower risk thresholds. A similar pattern was observed for the NRI with modest but significant improvement in the male cohort at thresholds of 5% and 10% and a significant improvement at all evaluated threshold in the female cohort. A significant improvement in the continuous NRI was reported for both male and female subgroups.

For QRISK3-Inspired risk scores, improvements in classification following the addition of AHS were much more modest in male and female sub cohorts alike. For males, no significant improvements were observed following the addition of AHS to QRISK3-Inspired risk scores. For female participants, modest but significant improvements in continuous NRI, net benefit, and categorical NRI were observed at thresholds of 10% and 7.5%. The overall and relative change in net benefit and NRI are reported in Supplementary Table 60-61 for males and females, respectively.

When assessing the added value of AHS compared to conventional PA measurements to QRISK3-Inspired risk scores, no improvements were observed in risk stratification at any evaluated risk threshold, as measured by net benefit or categorical NRI.

When comparing risk discrimination on a continuous scale, a modest but significant improvement in continuous NRI was reported for female participants, increasing from 0.095(0.048 - 0.137) for QRISK3-Inspired + PA to 0.153(0.108 - 0.200) for QRISK3-Inspired + AHS risk scores, corresponding to a change of  $\Delta+0.06$  (95% CI 0.007 - 0.119,  $p = 0.04$ ). No significant changes were reported in the male cohort.

Reclassification metrics for SCORE2-Inspired, QRISK3-Inspired excluding HDL and SBP and QRISK3-Inspired risk scores derived from primary care data are shown in Supplementary Tables 62-65. Results were broadly consistent with those presented for QRISK3-Inspired and QRISK3-Inspired +AHS risk scores derived from UKB data, with significant improvements in continuous NRI for all models and more limited improvement in reclassification along common risk thresholds.

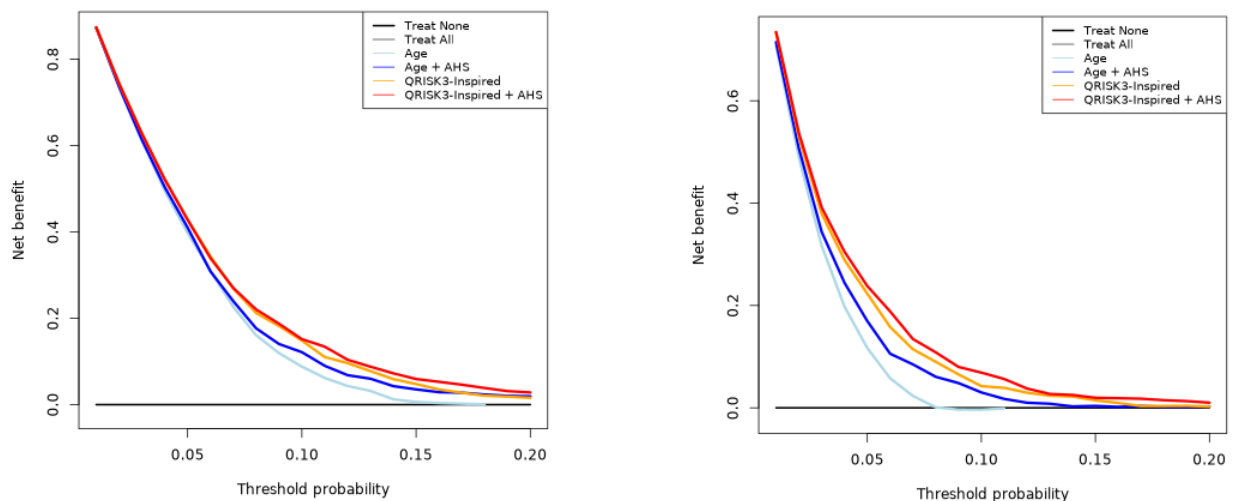


**Figure 7.6 Decision curves for Age, Age +Activity Health Scores (AHS), QRISK3-Inspired and QRISK3-Inspired +Activity Health Score (AHS) risk scores**

Decision curves showing the standardised net benefit for males and females. Decision curves for Age, Age + AHS, QRISK3 and QRISK3 +AHS are compared to those for ‘Treat All’ (intervention in all individuals irrespective of risk threshold) and ‘Treat None’ (intervention in no individuals)

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity+ previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP 2 X BMI FP1 +Age FP 2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; AHS fractional polynomial (female)=  $AHS/0.1 + (AHS/0.1) \times \log(AHS/0.1)$ .

#### 7.3.4.4 Subgroup analysis

Activity risk scores tended to perform better in older individuals within both male and female cohorts, with significant increases in discrimination for participants aged 65-75, with an increase in C-index of 0.005 (0.00 – 0.009), for males and 0.019 (0.010-0.026) for females (Figure 7.7).

Significant improvements in the continuous net reclassification index were also reported across all participants over the age of 65, optimism adjusted continuous NRI was 0.132(0.082 - 0.181,  $p < 0.001$ ) for males aged 65-75 and 0.193(0.015 - 0.349,  $p = 0.03$ ) for males aged over 75. No significant changes in classification were observed at any of the evaluated risk thresholds of 5%, 7.5% and 10%.

An even greater increase was observed with improvements in continuous NRI of 0.244(0.184 - 0.307,  $p < 0.001$ ) for females aged 65-75 and 0.271(0.054 - 0.495,  $p = 0.3$ ) for those ages over 75. Furthermore, significant improvements in both net benefit and categorical NRI were reported at all risk thresholds for females aged 65-75. The relative change in risk classification, measured by net benefit, categorical NRI and continuous NRI are presented in Supplementary Table 66-67 for males and females respectively.

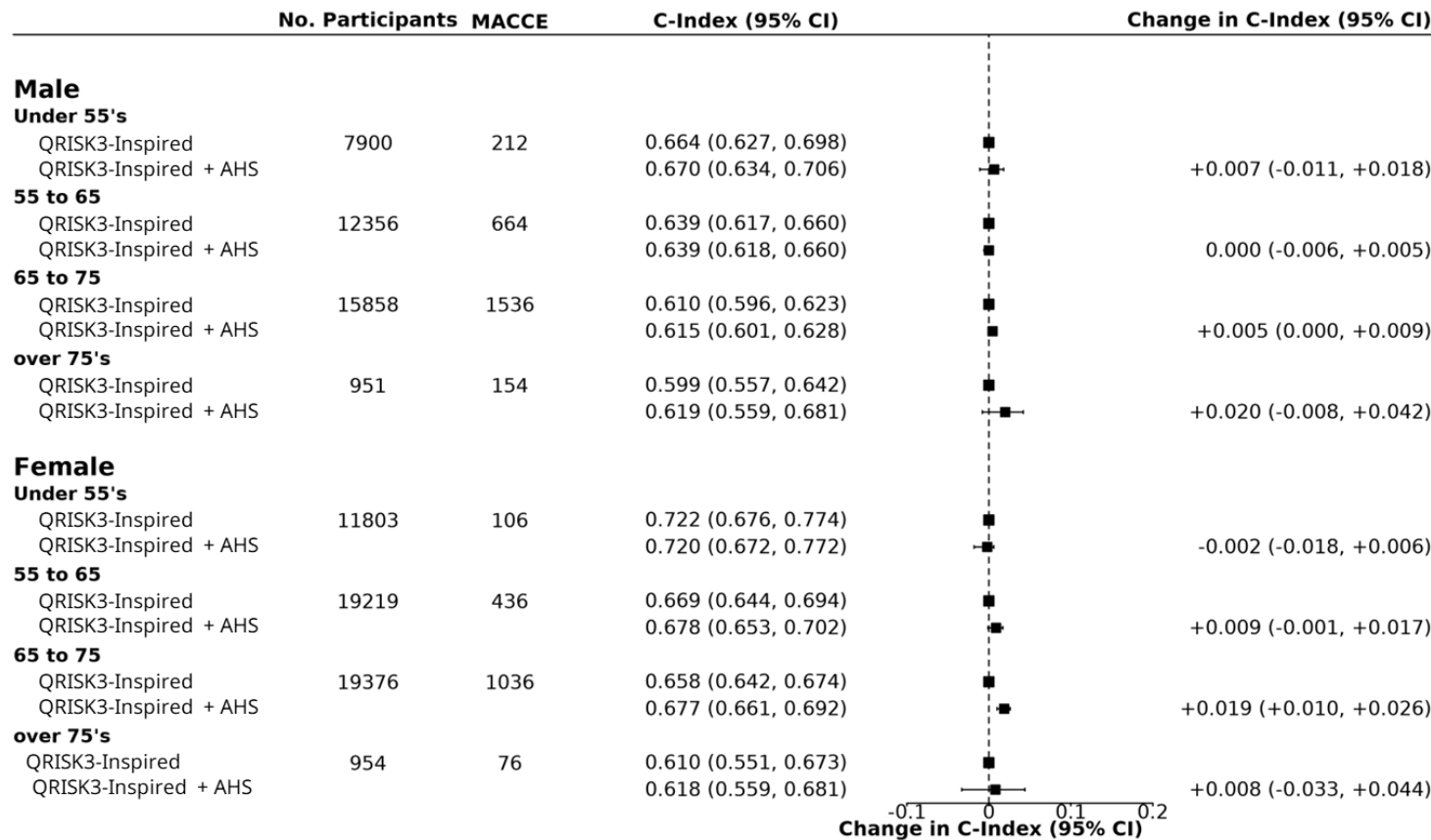


**Figure 7.7 Optimism adjusted Harrell's C-index stratified by age and sex for QRISK3-Inspired and QRISK3-Inspired + AHS risk scores.** Participants are divided across 4 age groups: Under 55, 55-65, 65-75 and over 75s across 37,068 males and 51,354 females from the UK Biobank with Accelerometer data from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE

Abbreviations: CI = confidence intervals; AHS = Activity Health Score; MACCE= Major Adverse Cardiovascular & Cerebrovascular Event

Squares represent change in C-index compared to QRISK3-Inspired risk scores and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). AHS fractional polynomial (male) = (AHS/0.1)<sup>2</sup> + (AHS/0.1)<sup>3</sup>; AHS fractional polynomial (female) = AHS/0.1 + ((AHS/0.1) X log(AHS/0.1)).

#### **7.3.4.5 Cross validation performance**

QRISK3-Inspired and QRISK3-Inspired + AHS risk scores were further evaluated within the same 10×5 nested cross-validation framework used to derive the AHS score. Within each fold, model coefficients and the baseline survival function were estimated using Cox regression and Breslow's methods, respectively using the derivation and then evaluated in the corresponding held-out outer-fold test set; performance was summarised per fold and as the mean across the 10 outer folds.

Discrimination in nested CV closely matched the optimism-adjusted bootstrap estimates (men: 0·679 vs 0·680 for QRISK3-Inspired; 0·681 vs 0·682 for QRISK3-Inspired + AHS; women: 0·736 vs 0·736 and 0·743 vs 0·744, respectively), while calibration error remained low in both approaches, albeit with slightly higher ICI in nested CV (men: 0·009 vs 0·0024–0·0026; women: 0·005 vs 0·0016). Net benefit patterns were also broadly consistent, but showed modest attenuation for QRISK3-Inspired + AHS risk scores, most noticeably at the 10% threshold for QRISK3-Inspired + AHS (men: 0·124 nested CV vs 0·132 bootstrap; women: 0·041 vs 0·053), supporting that the bootstrap findings generalised across folds with only small reductions in decision-curve benefit.

## **7.4 Discussion**

### **7.4.1 Overall findings**

This work outlines the development of a novel risk factor for MACCE, using deep survival networks, termed activity health score (AHS), which aims to capture a broad overview of an individual's health based on movement patterns extracted from wrist-worn accelerometer data. First, this work found that deep-learned activity health scores possess robust model discrimination when identifying individuals at high risk of incident hospitalisations due to cardiovascular/cerebrovascular disease, type 2 diabetes, and physical inactivity-related cancers. Second, AHS showed a strong positive non-linear relationship with MACCE, which persisted following the removal of MACCE during the first two years of follow-up. Third, the downstream predictive value of AHS for incident MACCE exceeds all conventional PA measurements explored in Chapter 6, demonstrating superior discrimination to multivariable risk scores composed of daily step count, overall daily acceleration, hours of light activity, moderate-to-vigorous activity and sedentary behaviour in a single model.

Fourth, the addition of AHS to univariate age risk scores yielded a significant improvement in discrimination and reclassification across a range of commonly used risk thresholds (Supplementary Tables 57,60-61). Finally, AHS yielded incremental improvements over established clinical risk factors included in QRISK3, with significant improvements observed in model discrimination and modest improvements in classifying high-risk individuals. When substituting SBP and HDL cholesterol with AHS, the new risk score matched the discrimination of the baseline QRISK3-Inspired risk score and showed superior clinical utility for identifying high-risk individuals as measured by the standardised net benefit (Supplementary Tables 56-57; 60-61;63-64).



Similar to conventional PA measurements explored in Chapter 6, there were notable differences in the predictive performance of AHS across age and sex sub-cohorts. AHS were more strongly associated with MACCE in females than for males, showing a higher degree of univariate discrimination and a greater increase in the added value to existing clinical risk, measured by the discrimination and reclassification.

As briefly noted in Chapter 6, observed sex differences in performance may be partly attributable to sample size imbalance (37,068 men vs 51,354 women). In addition, women in midlife typically have lower absolute CVD event rates, more heterogeneous symptom profiles, and a higher likelihood of under, or delayed diagnosis compared with men. Existing clinical risk scores also show poorer calibration and discrimination in women, in part due to the absence or limited representation of female-specific risk factors, such as pregnancy-related complications and premature menopause, resulting in a greater proportion of unexplained variance which may be captured by AHS. Together, these limitations may allow activity-derived health scores to capture additional risk not explained by conventional models.

Across both males and females, AHS tended to perform better in older individuals, with no significant improvements reported in discrimination when added to QRISK3-Inspired risk scores, for individuals under the age of 65. The stronger incremental performance of AHS in older age groups is likely partly attributable to higher event incidence, increasing statistical power and more precise estimates of discrimination and reclassification. However, this discrepancy may also reflect the greater clinical relevance of activity-derived health status in later life, when heterogeneity in functional capacity and frailty is less well captured by conventional risk factors in QRISK3. Further research should evaluate generalisability in external populations, and to identify the underlying mechanism behind AHS predictions. These findings should be interpreted cautiously, particularly in the oldest strata, where smaller samples and fewer events resulted in wider confidence intervals.

### **7.4.2 Comparison with the wider literature**

This study offers new insights into how device-measured physical activity (PA) can enhance the prediction of future health outcomes, with important implications for the assessment of incident CVD.

At the time of writing, this is the first study to use deep learning to evaluate the predictive value of free-living accelerometer recordings for primary prevention of MACCE. This study substantially extends previous work in the use of deep learning and wearable devices for CVD monitoring and prevention. Tison et.al. (2018) demonstrated that deep learning can accurately predict a range of risk factors for CVD including hypertension, adverse lipid levels and diabetes, using wearable measurements including PA measurements such as step count<sup>318</sup>. Zhou et al (2022), further extended this work beyond aggregate summary of activity, instead focusing on of high-resolution digital phenotypes from time series data. The authors demonstrate that such high-resolution digital phenotypes can enhance the prediction of CVD risk factors beyond conventional summary summaries of PA<sup>315</sup>. The present study builds upon these previous publications, by going beyond simply assessing the relationship between PA and CVD risk factors, instead focusing on the independent added value of high-resolution activity measurement to these existing risk factors in clinical risk models.

Comparing, the findings to those outlined in the previous chapter this work finds that deep learned AHS exceed the predictive value of traditional PA measurements. Similar to Chapter 6 AHS exceeded the predictive value of all traditional clinical risk factors used in QRISK3, with the exceptions of Age (Table 7.2). Similar findings were noted by Alaa et al. (2019), and Ledbetter et al. (2022), which reported the predictive value of PA measurements such as walking pace and moderate-to-vigorous activity exceed that of traditional CVD risk factors including HDL cholesterol and systolic blood pressure<sup>315,317</sup>.

Only age and smoking in the former and age alone in the latter demonstrated stronger predictive value. Furthermore, this work shows that deep-learned activity Health Scores (AHS) outperform conventional measurements of PA and possess added value beyond broad summaries of PA to existing clinical risk scores, with significant improvements reported in discrimination and reclassification of high-risk individuals compared to baseline QRISK3-Inspired and SCORE2-Inspired risk scores.

When compared to previous studies investigating the prognostic value of PA measurements for incident CVD outcomes, several important caveats remain, owing to differences in study endpoints, selection of risk factors, and a lack of comparable studies investigating the use of deep learning for incident CVD outcomes with device-based activity measurement. Perhaps the most comparable previous work in terms of risk prediction studies investigating PA for CVD risk prediction is the 2022 study by Ledbetter et al<sup>197</sup>. The authors found an improvement in C-index of up to 0.014 ( $p < 0.001$ ) when combining objective PA measurements with traditional CVD risk factors. While somewhat higher than the change in C-index reported in this study, results are likely to be impacted by differences in the selection of baseline model, definitions of study endpoint (incident MACCE vs CVD mortality) and inclusion of participants with prevalent CVD.

Studies investigating the addition of self-reported summaries of PA to CVD risk scores reported changes in C-index ranging from 0.003-0.012<sup>187,188</sup>. Georgousopoulos et al. reported an increase in C-index of 0.012 to HellenicSCORE ( $p = 0.03$ ), however no improvements in reclassification were reported. While Graversen et al. found no improvements to SCORE following the addition of self-reported PA.

In contrast deep-learned AHS demonstrated significant improvements over QRISK3-Inspired and SCORE2-Inspired risk scores, as measured by the C-index, and continuous NRI.

Furthermore, for female participants AHS may help to reclassify high risk individuals into appropriate risk groups (Supplementary Table 60-67). No previous studies investigated differences in performance across sex, despite the fact that common risk scores often stratify risk models by sex at the time of development.

This work has many strengths and seeks to address limitations within the current literature. As discussed in section 6.4.3, this is the largest study to investigate the added value of objective PA measurements to establish clinical risk models for primary prevention of MACCE. Second, this work implements robust internal validation using bootstrapping to adjust for optimism. This study provides a comprehensive evaluation of the added value of objective PA measurements to clinical risk models, extending beyond discrimination metrics to include assessments of calibration and reclassification. Finally, this study adheres to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines<sup>88</sup> (Supplementary section D p.549).

### **Study Limitations**

As discussed in Section 6.4.3, this study has several limitations to be considered when interpreting the findings. The seven-day accelerometer data collection period limits the ability to capture long-term variations in PA behaviours. Additionally, HDL cholesterol and systolic blood pressure in the UKB were measured up to six years before accelerometer wear, exceeding the five-year window specified in QRISK3. However, sensitivity analyses using primary care records from within five years of accelerometer wear showed minimal impact on model performance. Finally, the six-year follow-up period restricts direct comparisons with clinical guidelines based on 10-year CVD risk estimation.

Additional constraints introduced in this chapter include difficulties in interpreting the causal relationship between deep learning-derived AHS subsequent risk of incident disease.

Due to the black-box nature of deep neural networks, it is unclear which behaviours drive elevated AHS risk scores, limiting opportunities for targeted intervention. Given the potential added value of deep learning methods over conventional PA markers, further research into the explainability of AHS is warranted to guide public health messaging and tailor PA interventions for MACCE prevention. Prior research has shown that explainable AI methods applied to accelerometer-based deep neural networks, such as linear probing and saliency maps, can identify which aspects of accelerometer data (e.g., intensity, timing, or prolonged inactivity) contribute to human activity recognition. Applied to this work, such methods could help determine which dimensions of physical activity drive elevated AHS risk scores, enabling more targeted, behaviour-focused PA interventions for MACCE prevention. Second, the sample size calculations provided in Chapter 6 are not directly applicable to deep neural networks, which typically require sample sizes on the order of tens to hundreds of thousands of observations to train reliably. The sample sizes used here ( $\approx 88,000$  individuals) are consistent with, prior deep learning studies using accelerometer data for human activity recognition and health-related outcomes. Nevertheless, further work could formally assess sample size sensitivity through ablation analysis by varying training set size to evaluate performance stability. Finally, owing to a lack of access to a comparable dataset, these results have yet to be validated in an external dataset, limiting the ability to assess how well our findings generalise outside the UKB.

### **7.4.3 Summary**

This work found that deep neural networks can successfully identify risk factors in movement behaviours from wrist-worn accelerometer data, that are predictive of incident MACCE. Deep-learned AHS outperform conventional PA measurements for MACCE risk prediction. When integrating AHS with existing CVD risk scores, this study found incremental improvements in predictive performance, including improved risk stratification of high-risk female participants. Furthermore, substituting HDL and SBP with AHS in clinical risk models demonstrated equivalent discrimination and superior clinical utility, measured by the standardised net benefit, to QRISK3-Inspired and SCORE2-Inspired risk scores. This suggests an opportunity exists to explore wearable sensors as cost-effective alternatives in resource-limited settings where access to laboratory-based biomarkers may be restricted. Future research should investigate the feasibility, scalability, and clinical integration of accelerometer-derived risk factors to clinical risk assessment, evaluating their long-term utility in diverse populations and healthcare systems.

## Chapter 8– Discussion

This thesis aimed to evaluate the added value of ECG and accelerometer recordings to existing clinical risk models for MACCE and investigate the added value of deep learning beyond traditional risk prediction methods. To this end, this thesis sought to satisfy four objectives:

1. Assess the prospective associations of conventional ECG parameters, which can be extracted from unannotated exercise ECG, with incident CVD and to evaluate their added value to existing clinical risk models.
2. Develop deep-learning risk models to predict incident CVD from raw ECG data and assess their added value to current clinical risk models compared to conventional ECG parameters.
3. Investigate the added value of objective measurements of 24-hour movement behaviours to existing clinical risk models.
4. Develop and integrate a deep-learning risk prediction tool with existing clinical risk models based on large time series accelerometer data.

### 8.1 Summary of findings

This thesis started with an overview of current clinical practices and the existing literature on predicting the risk of incident Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) (Chapter 1-2). The studies identified provide strong evidence supporting the association between ECG data and objective physical activity (PA) measurements with incident MACCE. However, there remains a lack of robust evidence regarding their additive predictive value to established clinical risk models. This gap is primarily due to limitations such as small sample sizes, insufficient longitudinal follow-up of key health outcomes, and incomplete reporting on the clinical utility of digital measurements.

Starting with the ECG, a review of the current risk prediction literature from the USPSTF revealed a significant lack of integration of ECG parameters into clinically adopted risk models, considerable heterogeneity in ECG phenotypes and a failure to report clinically meaningful metrics such as model calibration and reclassification. This limits the generalisability and applicability of ECG data in real-world clinical settings.

Evidence of the added value of PA for MACCE risk prediction is mostly limited to self-reported data and is thus subject to a range of reporting biases<sup>160, 197</sup>. These prior studies were further constrained by modest sample sizes and a lack of reporting on key performance metrics, such as calibration and performance at clinically meaningful risk thresholds<sup>187–189</sup>. Only one study was identified that used objective accelerometer measurements to evaluate the risk of CVD<sup>197</sup>.

Finally, there is a great deal of uncertainty regarding the added value of deep learning over conventional clinical risk models. This is largely due to inadequate model validation practices. A high risk of bias was found across many studies, and numerous studies fail to include key clinically relevant measures such as model calibration or net reclassification, which are critical for assessing the true predictive power and clinical utility of the models<sup>279</sup>.

This has promoted a need for a holistic assessment of the predictive value of digital phenotypes such as the ECG and accelerometer recordings for incident CVD risk prediction, which closely adhere to the established reporting guidelines<sup>88,279</sup>.

**Extracting features from unannotated exercise ECG for CVD risk prediction:** The first aim of the thesis was to assess the prospective associations between conventional ECG parameters, which can be extracted without prior annotations, and incident MACCE and their added value to clinical risk models. Chapter 4 presents the development and validation of three multivariable ECG risk scores derived from ECG measurements recorded during rest, exercise and recovery and their incremental value in to QRISK3 risk factors. ECG features based on rhythm and morphology were independently associated with the 10-year risk of incident MACCE during rest, exercise and recovery stages of the ECG submaximal exercise test.



The predictive value of ECG parameters was subsequently evaluated using univariate and multivariable analyses, as well as in combination with age and QRISK3 risk factors. In the absence of clinical risk factors univariate, ECG parameters showed moderate levels of discrimination; C-index = 0.49 – 0.57, a similar level of discrimination as established CVD risk factors such as BMI and systolic blood pressure. Multivariable ECG risk scores, derived from a combination of parameters measured during rest, exercise and recovery, ranked as the second strongest predictor of MACCE after age, with a C-index of 0.63 (95% CI: 0.62–0.64) vs. 0.66 (95% CI: 0.65–0.68) for males and 0.622 (95% CI: 0.61–0.64) vs. 0.67 (95% CI: 0.65–0.69) for females. When integrated with age and QRISK3-Inspired risk scores, ECG recordings provided a modest increase in model discrimination to the baseline model. However, no changes were observed for reclassifying high-risk individuals at recommended treatment thresholds. These findings further support the conclusion made by the US Preventive Services Task Force (USPSTF) that while ECG measurements improve absolute model discrimination, they are of little added value for risk stratification. This further supports the USPSTF recommendation advising against the use of resting and exercise ECG screening for asymptomatic individuals<sup>95</sup>. Compared with previous works, this was the first study to assess the impact of ECG recordings on risk stratification at recommended treatment thresholds within UK primary care. This was also the first study to consider the addition of exercise ECG parameters to QRISK3-Inspired risk scores. All model coefficients, formulas and baseline survival values have been made freely available within the Supplementary material ([Section C](#) p.475) to allow others to recreate and fine-tune this work in other study populations.

**Deep learning ECG risk scores for MACCE:** The second aim was to develop a deep learning risk prediction tool capable of processing raw-ECG signals for MACCE risk prediction. Chapter 5 explores the added benefit of deep neural networks for developing ECG risk scores (Q-ECG) for predicting incident MACCE and to subsequently assess the added value to QRISK3-Inspired risk scores.

Q-ECG risk scores showed moderate discriminative performance for incident MACCE, equivalent to the strongest individual ECG risk factors identified in Chapter 4, such as the RR and QT intervals. However, Q-ECG based on raw ECG data failed to match the predictive performance of multivariable prediction models based on conventional ECG parameters. The strongest predictor of incident MACCE was a deep survival neural network based on a combination of conventional ECG parameters across all substages of the submaximal exercise test (rest, exercise and recovery), C-index = 0.639 (95% CI: 0.631 - 0.648). However, when combined with QRISK3 risk factors, no improvements in predictive performance were observed compared to baseline QRISK3-Inspired risk scores. This work next assessed the added value of the Q-ECG risk score derived from raw ECG recordings when combined with QRISK3-Inspired risk scores and linear Cox regression models. While a modest improvement in overall model discrimination was observed, the incorporation of Q-ECG did not result in changes to risk stratification at the recommended treatment thresholds.

Finally, when comparing deep survival models integrating both QRISK3 risk factor and raw ECG measurements, this work reported only modest improvements in discrimination and no improvements in risk stratification at current clinical risk thresholds.

Compared with previous works, this study was the first to investigate the added value of deep neural network ECG risk scores for exercise ECG and contrast this with conventional ECG measurements. In contrast to prior studies, this work goes beyond raw predictive performance to assess the clinical utility of deep-learned ECG risk scores against established clinical models and practices. All model weights, formulas and baseline survival values have been made freely available within the Supplementary material ([Section C](#) p.485).

**Accelerometer-measured Physical Activity and Risk Prediction of Major Adverse Cardiovascular & Cerebrovascular Events:** The third aim of this thesis was to investigate the added value of objective measurements of physical activity to existing clinical risk models.

Chapter 6 details the development and validation of a novel risk prediction score for incident MACCE based on objective 24-hour movement behaviours obtained from accelerometer recordings. This work confirms previous findings reported in the literature of an inverse association between increased physical activity levels and incident MACCE<sup>79,171</sup>.

Univariate 24-hour movement behaviours demonstrated moderate levels of discrimination for the risk of incident MACCE in the absence of established clinical risk factors, with overall activity, measured by the vector magnitude<sup>169</sup>, emerging as the strongest predictor, exceeding all traditional clinical risk factors used in QRISK3 other than age, male cohort C-index = 0.588 (0.577 - 0.597); female cohort C-index = 0.614 (0.602 - 0.625). Multivariable PA risk scores, consisting of overall activity, daily step count, and time spent in sedentary behaviour, LPA, or MVPA, showed enhanced predictive performance over univariate PA measurements in the male cohort; C-index = 0.607 (0.596 - 0.617); and female cohort C-index = 0.645 (0.632 - 0.657). When combining PA measurements with age, a significant increase in risk discrimination and stratification was observed for male and female cohorts. However, no significant improvements were observed when incorporating PA with QRISK3-Inspired risk scores. While PA measurements are independently predictive of incident MACCE, broad 24-hour movement behaviours alone may be insufficient to further enhance prediction and prevention efforts in primary care.

At the time of writing, this study was the largest to investigate the predictive value of accelerometer-derived PA measurements for incident CVD and the first study to focus on primary prevention of MACCE. All model coefficients, formulas and baseline survival values have been made freely available within the Supplementary material ([Section C](#) p.490).

**Deep learning of activity data for MACCE risk prediction:** The final aim of this thesis was to assess the added value of a deep learning risk tool for integrating a broader range of movement behaviours and accelerometer time series measurements into MACCE risk scores. The goal was to provide a more holistic assessment of PA beyond broad 24-hour movement behaviours in order to further enhance predictive performance.

Chapter 7 outlines the development of deep neural network-derived Activity Health Scores (AHS), trained to predict the risk of incident hospitalisation due to a range of chronic health conditions based on a range of movement behaviours and time series measurements extracted from raw accelerometer data. AHS scores showed a strong independent non-linear association with incident MACCE among male and female cohorts.

Univariate AHS demonstrated strong discriminative performance for risk of MACCE, exceeding the performance of all 24-hour movement behaviours, including multivariable models combining all behaviours as outlined in Chapter 6, male cohort C-index = 0.632 (0.622–0.643); female cohort = 0.684 (0.671–0.697). In contrast to conventional PA measurements, significant improvements in model discrimination were observed when combining AHS with QRISK3-Inspired risk scores. Furthermore, a significant improvement in risk stratification was observed for female participants following the addition of AHS to QRISK3-Inspired risk scores, demonstrating the ability of AHS to potentially identify high-risk female participants who may benefit from further preventive interventions.

At the time of writing, this is the first study to use deep learning to evaluate the predictive value of free-living accelerometer recordings for primary prevention of MACCE. In contrast to prior studies, this work goes beyond the use of broad summary measures of activity when assessing new risk factors. Instead, through the use of large neural networks, this work was able to assess a broader range of high-resolution features present in high-frequency accelerometer time series, highlighting their potential added value of deep learning to conventional risk scores. All model weights, formulas and baseline survival values have been made freely available within the Supplementary material ([Section C](#) p.519).

## **8.2 Limitations**

Several limitations should be considered when interpreting the findings of this work. As outlined in Chapters 3-7, the study population of this work suffers from an inherent healthy volunteer bias demonstrated by an overall decrease in all-cause mortality and incidence of various health conditions within the UK Biobank (UKB)<sup>20</sup>.

This is particularly acute within the activity monitoring sub-cohort explored in Chapters 6-7. On top of the existing healthy volunteer bias, participants in the physical activity sub-study had a lower incidence of all-cause mortality and MACCE compared with the wider UKB cohort (Chapter 3). A lack of population diversity could further limit the generalisability of the models developed in this thesis. The majority of the study population in this work tended to be Caucasian, received more years of education than the general population and were far less likely to suffer from social deprivation<sup>20</sup>. Consequently, risk models developed in this thesis may not generalise well to other settings, particularly in terms of absolute risk calibration, owing to fewer events and higher baseline survival, while some coefficients, especially for behavioural exposures such as PA, may be attenuated due to restricted risk and exposure ranges. This may in turn attenuate the added predictive value of PA beyond established clinical risk factors, such as age and sex.

The second limitation is a lack of access to an appropriate external validation dataset, which limits the ability to assess how well findings generalise outside the UKB. This further compounds the previous set of limitations regarding a lack of diversity amongst the existing study population.

The third limitation pertains to the measurement protocol for obtaining submaximal exercise ECG recording. The study protocol risks potentially confounding the association between the RR-interval and incident MACCE, as the maximum heart rate a participant can reach and the intensity at which they exercise is partially determined by one's prevalence of existing CVD risk factors, including age, sex, BMI and blood pressure. The strict eligibility criteria for exercise ECG testing also risk reinforcing the healthy volunteer bias present within the population. To minimise this confounding, all participants who reached their maximum heart rate, thus ending their test early, were removed from the study population. Furthermore, the majority of participants were assigned to the highest intensity of exercise (83%), whilst 13% were assigned to category 2 and 4% exercised at a constant intensity.

Additionally, the use of a submaximal exercise test as opposed to a maximal one, may not elicit sufficient cardiovascular stress to unmask latent electrophysiological or ischemic abnormalities. Under maximal workloads, demand-supply mismatch is more likely to occur, which can make exercise-induced ST-segment depression more pronounced and improve ischaemia detection relative to lower-intensity protocols<sup>327</sup>. A maximal test would also be expected to produce a wider dynamic range of heart rate and repolarisation responses. However, this may come with a trade-off of increased noise and movement artefacts during periods of peak intensity which may mask important morphological ECG features.

A further limitation relates to the use of clinical risk factors from QRISK3, which were originally selected and optimised for prediction of a narrower CVD outcome of myocardial infarction, stroke and related vascular events, whereas the primary endpoint was a broader composite outcome of MACCE. This mismatch may result in lower variance explained by clinical risk factors for MACCE, affecting assessment of the incremental value of novel predictors by either increasing scope for added value if new factors capture MACCE-relevant mechanisms, or attenuating coefficients of clinical risk factors. Further differences include eligibility criteria between the current study and derivation cohort for QRISK3, notably the current study focuses on any primary incidence of MACCE and includes those receiving statin treatment.

When assessing the added predictive value of physical activity measures beyond clinical risk factors, an important limitation is the restriction of the prediction horizon to six years. In Chapters 6–7, evaluation of physical activity–derived measures for MACCE risk were therefore limited to a shorter timeframe than the 10-year horizon used in clinical risk prediction frameworks such as QRISK3. This mismatch may influence estimates of incremental predictive value, particularly surrounding the reclassification of individuals at fixed treatment thresholds. Future research should evaluate the contribution of physical activity measures over longer follow-up periods, particularly 10 years post-assessment, to better align with established clinical risk models such as QRISK3<sup>51</sup> or SCORE2<sup>58</sup>.

Finally, accelerometer measurements, were recorded up to six years after the baseline assessment. As a result of this disconnect, there exists a risk of reverse causality when interpreting the association between PA measurements and AHS with incident MACCE. Socio-demographic variables such as BMI, in addition to physical measurements including HDL cholesterol, may not be the same as those at accelerometer wear time. These outdated baseline characteristics could introduce regression dilution bias, leading to an underestimation of the effect size of such measurements, subsequently altering risk predictions<sup>328</sup>. This attenuation may partly account for the poorer performance of clinical risk factor-based models and may also inflate the apparent added value of physical activity measurements, which were recorded at the start of the observation period. However, the analysis presented in Chapter 3 suggests that the baseline measurements remained stable among participants who consented to participate in repeat studies conducted several years apart. Additionally, sensitivity analysis replacing baseline physical measurements such as systolic blood pressure and HDL cholesterol with more recent measurements from primary care showed little difference in the performance of clinical risk models or the added value of PA measurements.

The regression equations in Supplementary Section C are provided to enable transparent implementation and reproduction of the risk scores rather than interpretation of individual covariate effects. Many coefficients, particularly those of low-prevalence comorbidities such as migraines and interaction terms including those between age polynomials and Townsend deprivation index, are close to null and have large standard errors, consistent with sparse data. As a result, these risk factors provide little independent predictive information in this cohort. Accordingly, the thesis emphasises overall model performance (discrimination, calibration, and reclassification) rather than interpretation of individual coefficients.

## 8.3 Ethical implications

The increasing adoption of digital sensors throughout healthcare and daily life raises vital ethical considerations for future research and the practical use of such technologies. Key concerns include user privacy, consent, and biases that affect access and equity in healthcare. This section outlines the ethical considerations relevant to this thesis in addition to how future works can help navigate such issues for both research and practical applications.

### Privacy

As digital sensors become increasingly widespread, more affordable, and ever more accurate, their integration into our daily lives is likely to become even more pervasive. Of particular interest is the growing use of personal wearable devices, such as wrist-worn accelerometers, explored in detail in Chapters 2 and 6-7. Wearable devices enable passive continuous monitoring in free-living environments, including a person's home and place of work. While this high-resolution data has immense potential to improve personal health and well-being, it also raises pressing privacy concerns.

While no direct personally identifiable information was used in the production of this thesis, privacy and the potential for re-identification remain important concerns in large prospective cohort studies. Although all data used in this study were de-identified and anonymised, such measures may offer limited long-term protection as analytical methods and re-identification technologies continue to advance. A systematic review conducted across 64 studies using wearable devices, including accelerometers and ECG sensors, found that 86-100% of the participants could be reidentified despite prior anonymisation<sup>329</sup>. The risk of re-identification, risks eroding public trust and subsequent participation in public health research programs, particularly when sensitive medical information may be concerned. As such, it is vital that future work considers appropriate storage and sharing of wearable data in a transparent manner, potentially incorporating privacy-preserving methods such as federated learning and differential privacy to ensure data security and user confidentiality.



## **Consent**

The adequacy of current consent procedures for long-term cohort studies, such as the UK Biobank (UKB), remains a subject of debate. While informed consent is obtained, concerns persist regarding issues of expiry, secondary data use and the risk of re-identification, prompting calls to move beyond traditional consent models.

The UKB uses a broad consent framework, where participants agree in general terms to share their data for future, unspecified research. This consent is obtained through a recruitment questionnaire, ensuring that participants understand the study and have an opportunity to ask questions<sup>215,330</sup>. However, ethical concerns regarding the long-term validity of this consent remain. For example, the UKB periodically revises access procedures, which could undermine the original consent terms. Participants may not have anticipated these changes, and evolving research or societal views could shift beyond the initial mutual understanding of what was agreed.

Ploug et al. argue that changes to the original UKB framework cannot be assumed to align with participants' original understanding of 'health-related research,' implying that the broad consent may no longer be valid<sup>331</sup>. While a review of UKB access procedures is beyond the scope of this thesis, careful consideration was given to ensuring alignment with participants' expectations. The research objectives remained consistent with UKB's aims, and all data were used solely for medical research to improve cardiovascular disease prevention strategies.

## **Bias**

Bias remains a persistent challenge in prospective cohort studies and medical research, potentially undermining the reliability, fairness, and inclusivity of findings. The work presented in this thesis sits at a critical intersection of personalised healthcare, ubiquitous computing, and artificial intelligence (AI), each of which is uniquely susceptible to different forms of bias.

First, clinical risk models, tend to generalise poorly to new populations and often underperform in underrepresented groups<sup>62,246,332</sup>.

The outputs of clinical risk scores can heavily influence decisions regarding whether an individual receives potentially lifesaving interventions. Therefore, any underlying bias may cause a detrimental impact, leading to further disparities in healthcare access and outcomes. As the vast majority of participants were of Caucasian origin, the results presented in this work cannot be assumed to generalise across other populations.

Second, despite growing adoption, wearable devices are disproportionately used by healthier individuals with higher education and income, while uptake remains slow in deprived populations, risking the exacerbation of healthcare inequalities. Future research should focus on improving access to these devices through public health campaigns while safeguarding privacy and protecting users from discrimination<sup>333</sup>.

Finally, concerns regarding bias are amplified by the use of AI, particularly supervised learning, where models may inherit systemic biases from labelled data. This includes an increase in missing data among underrepresented populations<sup>63,64</sup> and well-documented gender disparities, such as fewer females receiving appropriate diagnoses or interventions for CVD<sup>263-265</sup>. This bias may be further propagated in the model predictions. For example, Obermeyer et al. found that a widely used algorithm in U.S. hospitals discriminated against African American patients by prioritising past healthcare expenses over current medical needs<sup>334</sup>. It is vital that future research minimises bias where possible and clearly outlines any remaining risks were not. Additionally, more targeted recruitment of underrepresented populations should be considered to ensure that advancements benefit all of society.

## **8.4 Future work**

This work highlights both the potential value and limitations of incorporating digital sensors into clinical risk models. As technology advances and new data sources emerge, numerous exciting opportunities exist to build on the findings of this thesis and address existing limitations. The following section outlines potential directions for further exploration.

#### **8.4.1 Multimodal modelling**

Cardiovascular disease (CVD) arises from a complex interplay of behavioural and physiological factors that synergistically contribute to disease onset. This thesis explored the independent added value of ECG and physical activity measurements to clinical risk models using deep neural networks. However, analysing these factors in isolation may overlook critical interactions, such as how the heart responds to exercise or how exercise intensity impacts cardiac activity.

Many consumer and research-grade wearable devices now enable simultaneous multimodal measurements, including ECG, accelerometry, PPG, and temperature sensors. Combining measurements across these modalities within a single model may offer new insights into how different behaviours and physiological signals interact, potentially improving the predictive value of each measurement beyond the sum of its parts<sup>335,336</sup>. A recent review of multimodal deep neural networks in precision medicine found that combining different data modalities improved predictive performance across various health outcomes from cancer to CVD<sup>336</sup>. Ballinger et al. reported that combining ECG and accelerometer measurements together improved the prediction of key CVD risk factors, including diabetes and high blood pressure<sup>318</sup>. Li et al. demonstrated that combining ECG and PPG using multimodal neural networks outperforms both ECG and PPG in isolation. These results were further supported in a follow-up study by Zhu et al., which evaluated the performance of a dual-scale deep neural network for joint ECG and PPG feature extraction<sup>337</sup>.

Despite growing interest, multimodal deep-learning frameworks for CVD management and prevention remains in its early stages. A recent review found that, of 128 identified studies, only 15 targeted CVD, and fewer than 40% were published in clinical journals, highlighting limited clinical focus. Additionally, only a small subset compared multimodal approaches with single-modal models, leaving gaps in understanding their added value<sup>336</sup>. The increasing availability of advanced sensors capable of monitoring multiple behavioural and physiological parameters presents an exciting opportunity to address these gaps.

Of particular relevance is the UK Biobank (UKB) heart monitoring study, which integrates ECG and accelerometer data<sup>338</sup>. This approach has the potential to capture the interplay between cardiac and physical activity patterns, offering new insights for improving arrhythmia detection, management and prevention of adverse cardiovascular events.

#### **8.4.2 Explainability and targeted interventions**

Risk prediction in primary care extends beyond stratifying patients into risk categories. A key purpose is to effectively communicate to patients why they are at risk and emphasize the necessity of lifestyle and medical interventions. The ability to clearly explain the rationale behind predictions enables patient engagement by helping them understand their risk factors and the importance of modifying behaviour or adhering to prescribed interventions. Additionally, clinical risk models help to inform the type and intensity of interventions based on the prevalence and severity of identified risk factors<sup>26</sup>.

While this thesis has explored the potential added value of deep learning-based measurements to augment existing clinical risk models, these models are largely considered black boxes. The rationale behind their predictions, including the key information derived from ECG or accelerometer data, often remains unclear. This lack of interpretability limits their utility in clinical practice and provides little scope for targeted intervention in relation to either ECG or activity risk factors.

Explainable AI (XAI) is a rapidly growing field that aims to address these challenges by making more interpretable and transparent model predictions. Significant advancements have been made in recent years. For ECG analysis, saliency-based methods have become a popular option for identifying important ECG morphologies to model predictions by highlighting the portions of the ECG that contribute to the model's output<sup>339,340</sup>. Another popular method is Gradient-weighted Class Activation Mapping (Grad-CAM), which is typically applied to images to highlight specific regions that help to distinguish between different classes of images. Melzi et al. applied Grad-CAM to a deep neural network tasked with detecting prevalent atrial fibrillation from raw ECG data to identify lead-specific contributions to model predictions<sup>341</sup>.

XAI has become increasingly adopted in the field of human activity recognition when applying machine learning algorithms. Yuan et al. presented a self-supervised deep neural network for sleep detection. By pairing accelerometer data with time-synced video observations, researchers were able to interpret attribution heatmaps in the context of real-world activities, such as handshaking and playing tennis<sup>294</sup>.

While explainable AI has shown great promise, it remains an area of ongoing research. It is inherently difficult to visually interpret attribute-based methods for explaining features in time-series data. Temporal relationships and non-linear patterns present within the data further complicate efforts. Moreover, clinical validation of features identified by explainable AI is critical to ensure models are not influenced by noise specific to a particular dataset or population. Without such validation, there is a risk that predictions may lack generalisability or clinical relevance.

Future research should focus on validating explainable models with clinicians and domain experts to ensure model interpretations align with clinical knowledge. In terms of the work presented in this thesis, explainable AI methods could help elicit which features are identified as important for predicting incident MACCE. This can guide clinical decision-making and inform the best course of intervention for each individual. The emergence of new datasets, such as the UKB heart monitoring study, which collected concurrent ECG and accelerometer data, provides new opportunities to further validate explainable features across measurement devices<sup>338</sup>.

#### **8.4.3 Policy relevant deep learning**

To effectively support primary prevention of MACCE, models must move beyond risk stratification and towards identifying modifiable risk factors that are plausibly linked to prevention. Building on the earlier discussion on explainable AI (which primarily addresses why a model predicts higher risk), a transition to policy-relevant models additionally asks what changes could be recommended to reduce risk based on the features the model identifies as important, and whether those recommendations can be expressed in forms that align with

existing prevention pathways. For example, when assessing the added value of activity data to MACCE risk prediction, rather than explaining risk in terms of opaque time-series patterns, policy-facing outputs would ideally map model signal onto guideline-aligned targets such as MVPA accumulation, sedentary behaviour, or shifting activity timing. Liao et al. recently demonstrated how reinforcement learning can be used to help optimise PA behaviours to improve cardiovascular health. The authors showed that an adaptive algorithm, trained to decide whether to deliver a context-tailored activity prompt based on smartphone data to update the policy in real time based on step count over the past 30 minutes. In simulation and early pilot data, the learned policy increased short-term step counts compared with non-personalised approaches, suggesting a feasible way to use real-time data to support physical activity change in populations at elevated cardiovascular risk.<sup>342</sup> Counterfactual methods for time series data also present a promising avenue to translate neural network outputs into concrete intervention recommendations. For example, Ates et al. demonstrated that Counterfactual Explanations for Multivariate Time Series could be derived, which capture the smallest set of which need to be changed to alter a model's prediction, while constraining these changes to remain plausible by substituting across channels. Such approaches could be applied to PA monitoring to identify behaviours which can be altered to lower one's risk of disease.

For ECG-derived deep learning models, policy relevance looks slightly different as ECG morphology itself does not represent a behaviour to change in the same way as physical activity. Instead, ECG explanations can be made policy relevant by translating model-identified features into clinically actionable pathways: identifying physiological abnormalities that warrant testing, treatment or further monitoring (e.g., patterns suggestive of subclinical conduction disease, atrial fibrillation propensity, ischaemia-related signatures during exercise, or impaired autonomic recovery). For example, Sau et al. developed, an actionable and explainable AI-ECG risk estimation platform intended for short- and long-term risk estimation, positioning AI-ECG outputs as triggers for downstream actions such as targeted follow-up, preventive therapy, or monitoring<sup>149,343</sup>.

Using explainable AI methods, the authors linked high-risk predictions to abnormal ECG feature patterns including QRS duration/voltage, QRS-T angle, and QT interval.

#### **8.4.4 Consumer grade devices**

Thus far the majority of the literature assessing the use of digital sensors in CVD prevention has focused on research and medical grade devices.

Considerations such as cost, user burden, data access and ownership have thus far limited the uptake of consumer-grade devices in medical research. Research grade devices are often cheap to provide at scale, can store raw data without the need for continuous charging, due to a focus on a limited set of tasks, and allow researchers to access to raw data maximising available information. As time has progressed consumer-grade devices have become increasingly affordable and ubiquitous across the population. Currently, approximately 520 million wearable devices are entering the market globally each year, according to the International Data Corporation, with this pace set to accelerate significantly in the coming decade.

With a large percentage of the population now owning some form of wearable device there is growing interest in assessing their utility in health research and population health at large. In 2017 the Apple heart study was launched, which demonstrated the ability of smartwatch technology to detect a range of cardiac arrhythmia, including ventricular arrhythmias, premature ventricular contractions and atrial fibrillation<sup>344</sup>. In 2024 the Apple Watch was granted regulatory approval for atrial fibrillation and sleep apnoea detection by the Food and Drug Administration (FDA). In 2022 the British heart foundation underwent an initial review of how consumer owned smartphone and wearable devices can improve cardiovascular research and healthcare. The authors identified 13 high-priority measures, such as continuous heart rate, heart rhythm, moderate and vigorous activity, time spent sedentary, and sleep duration, which share a strong association with incident CVD and widespread public acceptance to share these measurements for further research. Passive measurements such as heart rate and physical activity were generally favoured among clinicians and the general public due to low participant burden and increased accuracy vs. self-report<sup>345</sup>.

While consumer devices hold many advantages over traditional research counterparts—including greater availability across the population, considerably longer follow-up durations, and the potential to provide fast access to large volumes of data through retrospective consent—several issues remain. A large proportion of the underlying technology for deriving key measurements, such as sleep duration, human activity recognition, and arrhythmia detection, remains proprietary. Additionally, access to raw data is often unavailable, with many consumer-grade devices instead opting to provide only summary-level statistics of key metrics. This lack of transparency makes comparisons across devices challenging and complicates the integration of measurements taken from multiple devices into a single cohesive and transparent model.

Future work should focus on how easily accessible metrics from consumer-grade devices can be integrated into clinical practice, ensuring these devices are made viable for individuals without access and building trust through validation of device measurements, including agreement with current research-grade devices. Enhanced standardization and improved accessibility to raw data will also be essential for creating interoperable datasets that support robust and inclusive cardiovascular research.

## **8.5 Conclusion**

This thesis investigates the added value of ECG and accelerometer time series signals to predict MACCE for primary prevention. This work compares the performance of conventional risk prediction methods based on a narrow set of conventional measurements from ECG and accelerometer recordings and contrasts this to the performance of state-of-the-art deep survival networks.

This investigation showed that ECG and accelerometer measurements are independently associated with incident MACCE and have modest levels of predictive performance in the absence of established clinical risk factors.



The proposed deep survival framework successfully identified risk factors within ECG and accelerometer time series, which were independently associated with incident MACCE and showed comparable or greater predictive value than conventional measurements.

The addition of ECG measurements recorded during a submaximal exercise test provided modest improvements in predictive performance to established clinical risk factors. However, little change in treatment groups was observed based on current clinical guidelines. This supports current findings from the United States Preventive Services Task Force (USPSTF).

Conventional measurements of PA based on 24-hour movement behaviours provided limited added value to established clinical risk factors and provided no improvement in risk stratification. The use of deep survival risk models for accelerometer analysis led to significant improvements in model discrimination to clinical risk models and significant improvements in risk stratification for female participants. Future research is warranted to explain observed differences in performance across sex in diverse populations.

Future work should seek to incorporate multimodal signals, such as simultaneous recordings of ECG and accelerometer measurements, to further enhance model performance. To this end, the emergence of new datasets, including the UKB heart monitoring study, presents a promising avenue to extend this research to new populations and measurement modalities.

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## Thesis Supplementary material

### **Section A: Model development ..... 337**

#### 1.1 Development of Electrocardiogram risk scores for the 10-year risk prediction of Major Adverse Cardiovascular and Cerebrovascular Events..... 337

##### 1.1.1 Feature engineering ..... 337

##### 1.1.2 ECG-net implementation..... 340

##### 1.1.3 QRISK3 implementation..... 341

#### 1.2 Added value of deep learned activity risk scores to QRISK3 ..... 342

##### 1.2.1 Feature engineering ..... 342

##### 1.2.2 Activity health score-network implementation..... 344

##### 1.2.3 QRISK3 implementation..... 345

### **Section B: Supplementary Figures and Tables..... 347**

#### Supplementary Figures ..... 347

##### Supplementary Figure 1 ..... 347

##### Supplementary Figure 2 ..... 348

##### Supplementary figure 3..... 349

##### Supplementary figure 4..... 350

##### Supplementary figure 5..... 351

##### Supplementary figure 6..... 352

##### Supplementary figure 7:..... 353

##### Supplementary figure 8:..... 354

##### Supplementary figure 9 ..... 355

##### Supplementary figure 10 ..... 356

|                                |     |
|--------------------------------|-----|
| Supplementary figure 11 .....  | 357 |
| Supplementary figure 12 .....  | 358 |
| Supplementary Figure 13 .....  | 359 |
| Supplementary Figure 14 .....  | 360 |
| Supplementary Figure 15 .....  | 361 |
| Supplementary figure 16 .....  | 362 |
| Supplementary figure 17 .....  | 363 |
| Supplementary Figure 18 .....  | 364 |
| Supplementary Figure 19 .....  | 365 |
| Supplementary figure 20 .....  | 366 |
| Supplementary figure 21 .....  | 367 |
| Supplementary Figure 22 .....  | 368 |
| Supplementary Figure 23 .....  | 370 |
| Supplementary Figure 24 .....  | 372 |
| Supplementary figure 25: ..... | 373 |
| Supplementary figure 26 .....  | 374 |
| Supplementary Figure 27 .....  | 375 |
| Supplementary Figure 28 .....  | 376 |
| Supplementary Figure 29 .....  | 377 |
| Supplementary figure 30: ..... | 378 |
| Supplementary Tables.....      | 380 |
| Supplementary Table 1 .....    | 380 |
| Supplementary Table 2 .....    | 383 |

|                              |     |
|------------------------------|-----|
| Supplementary Table 3 .....  | 392 |
| Supplementary Table 4 .....  | 393 |
| Supplementary Table 5 .....  | 394 |
| Supplementary Table 6 .....  | 395 |
| Supplementary Table 7 .....  | 396 |
| Supplementary Table 8 .....  | 397 |
| Supplementary Table 9 .....  | 398 |
| Supplementary Table 10 ..... | 399 |
| Supplementary Table 11 ..... | 400 |
| Supplementary Table 12 ..... | 401 |
| Supplementary Table 13 ..... | 402 |
| Supplementary Table 14 ..... | 403 |
| Supplementary Table 15 ..... | 405 |
| Supplementary Table 16 ..... | 406 |
| Supplementary Table 17 ..... | 407 |
| Supplementary Table 18 ..... | 408 |
| Supplementary Table 19 ..... | 409 |
| Supplementary Table 20 ..... | 410 |
| Supplementary Table 21 ..... | 411 |
| Supplementary Table 22 ..... | 412 |
| Supplementary Table 23 ..... | 413 |
| Supplementary Table 24 ..... | 414 |
| Supplementary Table 25 ..... | 416 |



|                               |     |
|-------------------------------|-----|
| Supplementary Table 26 .....  | 417 |
| Supplementary Table 27 .....  | 419 |
| Supplementary Table 28 .....  | 420 |
| Supplementary Table 29 .....  | 421 |
| Supplementary Table 30 .....  | 422 |
| Supplementary Table 31 .....  | 423 |
| Supplementary Table 32 .....  | 425 |
| Supplementary Table 33 .....  | 426 |
| Supplementary Table 34 .....  | 428 |
| Supplementary Table 35 .....  | 430 |
| Supplementary Table 36: ..... | 432 |
| Supplementary Table 37 .....  | 434 |
| Supplementary Table 38 .....  | 436 |
| Supplementary Table 39: ..... | 438 |
| Supplementary Table 40: ..... | 440 |
| Supplementary Table 41 .....  | 439 |
| Supplementary Table 42 .....  | 441 |
| Supplementary Table 43 .....  | 442 |
| Supplementary Table 44 .....  | 443 |
| Supplementary Table 45 .....  | 444 |
| Supplementary Table 46 .....  | 445 |
| Supplementary Table 47 .....  | 446 |
| Supplementary Table 48 .....  | 446 |

|                                                                |            |
|----------------------------------------------------------------|------------|
| Supplementary Table 49 .....                                   | 448        |
| Supplementary Table 50 .....                                   | 449        |
| Supplementary Table 51 .....                                   | 450        |
| Supplementary Table 52 .....                                   | 451        |
| Supplementary Table 53 .....                                   | 452        |
| Supplementary Table 54 .....                                   | 452        |
| Supplementary Table 55 .....                                   | 454        |
| Supplementary Table 56 .....                                   | 459        |
| Supplementary Table 57 .....                                   | 460        |
| Supplementary Table 58: .....                                  | 461        |
| Supplementary Table 59 .....                                   | 462        |
| Supplementary Table 60 .....                                   | 463        |
| Supplementary Table 61 .....                                   | 464        |
| Supplementary Table 62 .....                                   | 465        |
| Supplementary Table 63 .....                                   | 466        |
| Supplementary Table 64 .....                                   | 467        |
| Supplementary Table 65 .....                                   | 468        |
| Supplementary Table 66 .....                                   | 469        |
| Supplementary Table 67 .....                                   | 471        |
| Supplementary Table 68 .....                                   | 473        |
| Supplementary Table 69 .....                                   | 474        |
| <b>Section C: Model coefficients, formulas and usage .....</b> | <b>475</b> |
| Chapter 4 Conventional ECG risk scores .....                   | 475        |

|                                                                                                                                     |     |
|-------------------------------------------------------------------------------------------------------------------------------------|-----|
| Table 1C QRISK3 .....                                                                                                               | 475 |
| Table 2C QRISK3 + Conventional ECG parameters.....                                                                                  | 479 |
| Chapter 5 Deep learning derived Q-ECG risk scores .....                                                                             | 485 |
| Table 3C QRISK3 .....                                                                                                               | 485 |
| Table 4C QRISK3 + Q-ECG .....                                                                                                       | 487 |
| Chapter 6 Physical activity risk scores.....                                                                                        | 490 |
| Table 5C QRISK3 AND QRISK3 +PA models .....                                                                                         | 490 |
| Table 6C QRISK3 (Excluding Systolic blood pressure and HDL cholesterol ratio) and<br>QRISK3 +PA models.....                         | 496 |
| Table 7C SCORE2 AND SCORE2 +PA models.....                                                                                          | 502 |
| Table 8C SCORE2 (Excluding Systolic blood pressure and HDL cholesterol ratio) and<br>SCORE2 +PA models.....                         | 505 |
| Table 9C QRISK3 AND QRISK3 +PA risk scores with Cholesterol and systolic blood<br>pressure derived from primary care records .....  | 508 |
| Table 10C SCORE2 AND SCORE2 +PA risk scores with Cholesterol and systolic blood<br>pressure derived from primary care records ..... | 515 |
| Chapter 7AHS risk scores .....                                                                                                      | 519 |
| Table 11c QRISK3 AND QRISK3 +AHS models.....                                                                                        | 519 |
| Table 12C QRISK3 and QRISK3 + AHS Models (Excluding Systolic Blood Pressure and HDL<br>Cholesterol Ratio) .....                     | 525 |
| Table 13C SCORE2 AND SCORE2 +AHS models.....                                                                                        | 530 |
| Table 14C SCORE2 and SCORE2 + AHS Models (Excluding Systolic Blood Pressure and HDL<br>Cholesterol Ratio) .....                     | 533 |

|                                                                                                                                 |            |
|---------------------------------------------------------------------------------------------------------------------------------|------------|
| Table 15c QRISK3 and QRISK3 + AHS Risk Scores Using Systolic Blood Pressure and HDL Cholesterol from Primary Care Records ..... | 535        |
| Table 16c SCORE2 and SCORE2 + AHS Risk Scores Using Systolic Blood Pressure and HDL Cholesterol from Primary Care Records ..... | 541        |
| <b>Section D: Tripod guidelines for predictive model development .....</b>                                                      | <b>543</b> |
| Chapter 4 TRIPOD Checklist: Prediction Model Development.....                                                                   | 543        |
| Chapter 5 TRIPOD Checklist: Prediction Model Development.....                                                                   | 545        |
| Chapter 6 TRIPOD Checklist: Prediction Model Development.....                                                                   | 547        |
| Chapter 7 TRIPOD Checklist: Prediction Model Development.....                                                                   | 549        |

## **Section A: Model development**

### **1.1 Development of Electrocardiogram risk scores for the 10-year risk prediction of Major Adverse Cardiovascular and Cerebrovascular Events**

#### **1.1.1 Feature engineering**

##### **Morphological feature extraction**

Candidate Morphological consisted of the average PR, RR, QRS, and QTc interval durations. We compute the average PR and RR interval by calculating the elapsed time between the onset set of the preceding P and R wave and the subsequent R wave, respectively, this is then averaged across all beats in the signal. For QRS and QTc extraction, I first computed the median heartbeat via a Hilbert transform. The QRS duration is then measures as the time elapsed between the onset of the Q wave and subsequent S wave., whilst the QT interval is the time elapsed between the Q and T wave. The QTc is then calculated using Bazett's<sup>1</sup> and Fridericia's<sup>3</sup> formulas for resting and exercise ECG segments, respectively.

##### **Rhythm feature extraction**

Using the RR interval time series obtained from wave delineation, a Poincare representation of first-order derivatives was constructed for consecutive RR intervals (Section B figure 2). ECG rhythm can then be characterised by specific patterns present in the Poincare representation, allowing for further feature extraction. Following the example in Sarkar et al., 2008<sup>6</sup>, the Poincare plot is split into 13 unique segment and divided into bins of 30ms by 30ms. Normal sinus rhythm is defined as any beat within the origin segment (segments 0), which had a radius of 80ms. The number of beats in each segment and bin is then counted to capture specific traits of the ECGs rhythm. The definition and formula used to derive each feature is presented Tables 1A-2A.

**Table 1A: ECG Morphological features.**

| ECG morphological features | Description                                                                       |
|----------------------------|-----------------------------------------------------------------------------------|
| Mean PR interval           | Time interval between the peak of the P wave and the peak of the R wave           |
| Mean QRS duration          | Total duration from the start of the Q wave to the end of the S wave              |
| Mean QTc interval          | Time interval between the peak of the Q wave and the peak of the T wave           |
| Mean RR interval           | Time interval between the peak of the R wave to the peak of the subsequent R wave |

**Table 2A: ECG Rhythm features**

| Feature                                      | Description                                                                                                                                                                                                                    | Formula                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| COSEn entropy                                | Quantifies the variability in the RR interval, by modelling the probability that the RR of a given set of beats will closely match with another set in the ECG.<br><br>Higher CoseEn indicates a more irregular cardiac cycle. | <b>SampEn – ln(2r) – ln (mean RR interval)</b><br><br>Where:<br>SampEn = -ln(p) = -ln(A/B) – ln(B) – ln(A)<br><br>r: Maximum distance of two RR intervals to be considered a match.<br>A = Number of RR interval matches within given range<br>B = Number of RR intervals within a given range<br>P = Conditional probability of a match A/B                                                                                              |
| Number of Premature ventricular contractions | Number of ectopic beats observed per 15-second ECG window.                                                                                                                                                                     | $Total\ PVC = \sum Observed\ PVC$                                                                                                                                                                                                                                                                                                                                                                                                         |
| Irregularity evidence                        | Number of irregular heartbeats defined as beats outside of Normal sinus rhythm (NSR).                                                                                                                                          | $\sum_{n=1}^{12} BinCount_n$                                                                                                                                                                                                                                                                                                                                                                                                              |
| Regularity evidence                          | Number of short-term median RR-windows, defined as 3 consecutive beats, that differed no more than 10ms from the median RR of the full 15 second segment.                                                                      | $\sum_{i=1}^{n=w/m} \begin{cases}  RR_{i\_short} - RR_{long}  \leq 10ms : 1 \\  RR_{i\_short} - RR_{long}  > 10ms : 0 \end{cases}$<br><br>Where:<br>w = The number of RR intervals in the current window<br>m = The number of RR intervals in a single segment<br>$RR_{long} : \text{Median}(RR_1, RR_1, \dots, RR_w)$<br>$RR_{i\_short} : \text{Median}(RR_j \dots RR_k)$<br>for $j = (i-1) * m + 1, k = i * m$ for $i = 1, 2, \dots, n$ |
| Density evidence                             | Measures how closely clustered the changes in RR intervals are across the Poincare representation, within segments, by subtracting the number of                                                                               | $\sum_{n=5}^{12} (PointCount_n - BinCount_n)$                                                                                                                                                                                                                                                                                                                                                                                             |

|                                 |                                                                                                                                                                                                                                                                                          |                                                                                                                                                            |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 | points in a segment by the number of clusters. Lower density estimates point to a sparser distribution of beats in each cluster.                                                                                                                                                         |                                                                                                                                                            |
| Anisotropy evidence             | Measured the direction of change of the RR interval across the current time window. Provides a measure for the orientation of the Poincare representation. Higher Anisotropy points to a consistent direction of change and helps to distinguish between different types of arrhythmias. | $\left  \sum_{n=9,11} (PointCount_n) - \sum_{n=10,12} (PointCount_n) \right $ $+ \left  \sum_{n=6,7} (PointCount_n) - \sum_{n=5,8} (PointCount_n) \right $ |
| PAC evidence                    | Measures the number of premature atrial contractions.                                                                                                                                                                                                                                    | $\sum_{n=1}^4 (PointCount_n - BinCount_n)$ $+ \sum_{n=5,6,10} (PointCount_n - BinCount_n)$ $- \sum_{n=7,8,12} (PointCount_n - BinCount_n)$                 |
| Evidence of Atrial fibrillation | A composite measure which measures the presence and severity of Atrial fibrillation by offsetting evidence of irregularity against the number of normal heartbeats and premature atrial contractions                                                                                     | $\sum_{i=1}^n \{  RR_{i-1} - RR_i  = 0 : 1$ $ RR_{i-1} - RR_i  \neq 0 : 0$ $- 2 * PAC \text{ evidence}$                                                    |
| Evidence of atrial tachycardia  | A composite measure assessing the presence of irregular heart rhythm, changes in RR intervals, clustering of changes in RR interval (Poincare representation), and the occurrence of compensatory pauses.                                                                                | $\text{Irregularity Evidence}$ $+ \text{Anisotropy Evidence} + \text{Density Evidence}$ $+ \text{Regularity Evidence} - 4 * \text{PAC Evidence}$           |

Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta RR$ -intervals across pre-defined bins from a Poincare representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.

### 1.1.2 ECG-net implementation

**Table 3A: LSTM and Deep-survival model architecture**

| Hyper-parameter                  | Value     |
|----------------------------------|-----------|
| Network: LSTM network            |           |
| Hidden layers                    | 3         |
| Hidden size                      | 256       |
| Dropout rate                     | 0.2       |
| Network: ECG hazard network      |           |
| Hidden layers                    | 2         |
| Hidden nodes [layer1, layer2]    | [256,128] |
| Dropout rate                     | 0.4       |
| Network: non-linear risk network |           |
| Hidden layers                    | 2         |
| Hidden nodes [layer1, layer2]    | [12,12]   |
| Dropout rate                     | 0.1       |

**Table 4A: Model Training protocol for deep-survival network including hyper-parameters and testing procedure.**

|                              |                                         |
|------------------------------|-----------------------------------------|
| Batch Size                   | 1024                                    |
| Epochs                       | 200                                     |
| Loss function                | Average negative log partial likelihood |
| Optimiser                    | Adam                                    |
| Learning rate                | $1e^{-5}$                               |
| Learning rate decay          | 0.05                                    |
| Learning rate decay patience | 10                                      |
| <b>Train-test procedure</b>  |                                         |
| Train split                  | 60%                                     |
| Validation split             | 20%                                     |
| Test split                   | 20%                                     |
| Evaluation                   | Boot strapping (1000 iterations)        |



### **1.1.3 QRISK3 implementation**

Fifteen covariates were selected from the original QRISK3 risk scores (Supplementary Table 3), Fractional polynomials for age, BMI, and interaction terms for age with BMI, smoking status, type1/2 diabetes, systolic blood pressure, deprivation, and hypertension were selected to match the original QRISK3 algorithm. Model coefficients were re-calculated using Cox Proportional hazard models to re-calibrate the model to the study population The 10-year baseline survival rates and coefficients for each model are provided in Supplementary section C Table 1C.

## 1.2 Added value of deep learned activity risk scores to QRISK3

### 1.2.1 Feature engineering

**Table 5A: Orientation invariant time-series features derived from 7-days of wrist worn accelerometer recordings.**

| Accelerometer Feature                                              | Description                                                                                                                                                                  |
|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Time domain</b>                                                 |                                                                                                                                                                              |
| Median absolute acceleration across x, y, z axis                   | Absolute median of the acceleration along the x, y, and z axes, respectively. Provides the central tendency of the absolute acceleration values.                             |
| Acceleration range across x, y, z axis                             | Range of acceleration along the x, y, and z axes, respectively. Calculated as the difference between the maximum and minimum values, indicating variability in acceleration. |
| Interquartile range of the acceleration along the x, y, and z axes | Interquartile range of the acceleration along the x, y, and z axes, respectively. Measures the statistical dispersion or spread of the middle 50% of the data points.        |
| Median                                                             | Median value of the acceleration data representing the middle value when the data is sorted.                                                                                 |
| Minimum acceleration                                               | Minimum value of the acceleration data, indicating the lowest observed acceleration.                                                                                         |
| Maximum acceleration                                               | Maximum value of the acceleration data, indicating the highest observed acceleration.                                                                                        |
| Acceleration quartiles                                             | The 25th percentile (first quartile) and the 75th percentile (third quartile) of the acceleration data, providing a sense of the distribution.                               |
| <b>Frequency-Domain</b>                                            |                                                                                                                                                                              |
| Pentropy                                                           | Permutation entropy, a measure of the complexity of the time series data, providing information about the predictability of the signal.                                      |
| f1, f2                                                             | Specific frequency components of the accelerometer data, representing dominant frequencies in the signal.                                                                    |
| SB_MotifThree_quantile_hh                                          | Feature related to motifs or patterns in the time series data. Indicates repeated patterns of high acceleration.                                                             |
| FC_LocalSimple_mean1_tauresrat                                     | Captures local simple statistics, potentially related to the mean value over a specific tau (time) resolution ratio.                                                         |
| MD_hrv_classic_pnn40                                               | Heart rate variability (HRV) measure (pNN40), indicating the proportion of consecutive inter-beat intervals differing by more than 40 milliseconds.                          |
| SB_BinaryStats_mean_longstretch1                                   | Binary statistic indicating the mean length of long stretches of continuous activity or inactivity.                                                                          |
| IN_AutoMutualInfoStats_40_gaussian_fmmi                            | Captures dependency between time series values at a lag of 40, assuming a Gaussian                                                                                           |

|                                      |                                                                                                     |
|--------------------------------------|-----------------------------------------------------------------------------------------------------|
|                                      | distribution.                                                                                       |
| CO_f1ecac                            | Complexity measure related to the first lag of the auto-correlation function of the time series.    |
| Number of peaks in Fourier transform | Number of peaks in the acceleration signal, representing significant movements or activities.       |
| Peak Prominence                      | Prominence of the peaks, indicating how much a peak stands out relative to its neighbouring values. |
| Peak Promin inter quartile range     | Interquartile range of the peak prominences, providing a measure of variability in peak prominence. |

### 1.2.2 Activity health score-network implementation

**Table 6A: Hyper parameters and evaluation protocols for activity health score network**

| Hyper parameter                | Value                                   |
|--------------------------------|-----------------------------------------|
| Batch Size                     | 512                                     |
| Max epochs                     | 100                                     |
| Loss function                  | Average negative log partial likelihood |
| Optimiser                      | Adam                                    |
| Learning rate                  | $3_e^{-4}$                              |
| Learning rate decay            | 0.001                                   |
| Learning rate decay patience   | 5 epochs                                |
| <b>Cross validation splits</b> |                                         |
| <b>Outer folds</b>             |                                         |
| Train split                    | 90%                                     |
| Test split                     | 10%                                     |
| <b>Inner folds</b>             |                                         |
| Train split                    | 70%                                     |
| Validation split               | 10%                                     |
| Test split                     | 20%                                     |

### **1.2.3 QRISK3 implementation**

Fourteen covariates were selected from the original QRISK3 risk scores (Supplementary Table 3), Fractional polynomials for age, BMI, and interaction terms for age with smoking status, Atrial fibrillation, type1/2 diabetes, systolic blood pressure, deprivation, and hypertension were original were selected to match the original QRISK3 algorithm. Model coefficients were re-calculated using Cox Proportional hazard models to re-calibrate the model to the study population The 10-year baseline survival rates and coefficients for each model are provided in Supplementary section C Table 5C.

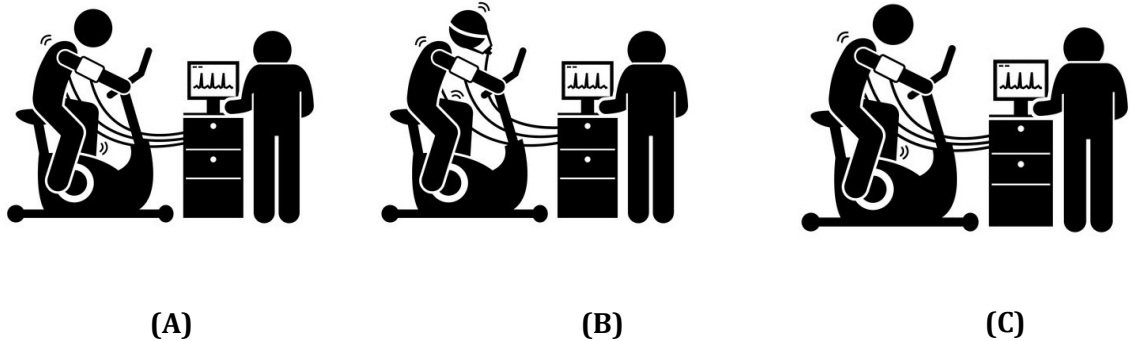
## References

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2. Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)* 57, 289–300 (1995).
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5. Katzman, J. L. et al. DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network. *BMC Med Res Methodol* 18, 24 (2018).
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## Section B: Supplementary Figures and Tables

### Supplementary Figures

**Supplementary Figure 1: Cycle stress test ECG protocol.**



(A) 15 Second resting ECG      (B) 6 Minute 15 Seconds stress test ECG      (C) 1 Minute recovery ECG

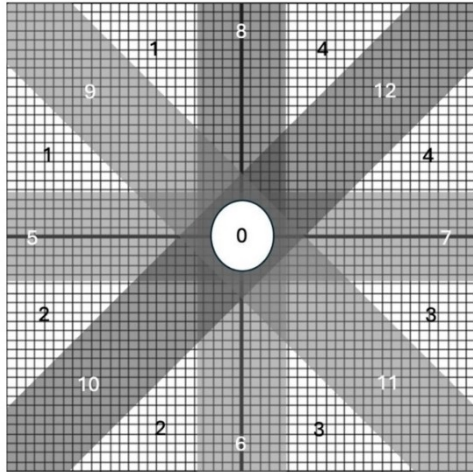
*Software: eBike Comfort Ergometer, General Electric, firmware version 1.7*

All bicycle protocols consist, in order, of

- Initial 15 seconds rest (pre-test resting ECG)
- 2-minute phase at constant power
- Linear increase over 4 minutes from Start to Peak power level.
- Concluded by a 1-minute recovery period.

The ECG measurement is taken throughout the 7 minutes 15 second's period.

## Supplementary Figure 2 Poincare representation of ECG rhythm profiles



(a)

| Segment | Sequence | $\Delta RR$ Values                      |
|---------|----------|-----------------------------------------|
| 0       | SSS/LLL  | $ \Delta RR  < 80\text{ms}$             |
| 1       | S-L-S    | $ \Delta RR(i-1)  \neq  \Delta RR(i) $  |
| 2       | L-M-S    | $ \Delta RR(i-1)  \neq  \Delta RR(i) $  |
| 3       | L-S-L    | $ \Delta RR(i-1)  \neq  \Delta RR(i) $  |
| 4       | S-M-L    | $ \Delta RR(i-1)  \neq  \Delta RR(i) $  |
| 5       | L-L-S    | At least one $ \Delta RR $ in segment 0 |
| 6       | L-S-S    | At least one $ \Delta RR $ in segment 0 |
| 7       | S-S-L    | At least one $ \Delta RR $ in segment 0 |
| 8       | S-L-L    | At least one $ \Delta RR $ in segment 0 |
| 9       | S-L-S    | $\Delta RR(i-1) \cong -\Delta RR(i)$    |
| 10      | S-L-S    | $\Delta RR(i-1) \cong \Delta RR(i)$     |
| 11      | L-S-L    | $\Delta RR(i-1) \cong -\Delta RR(i)$    |
| 12      | L-M-L    | $\Delta RR(i-1) \cong \Delta RR(i)$     |

(b)

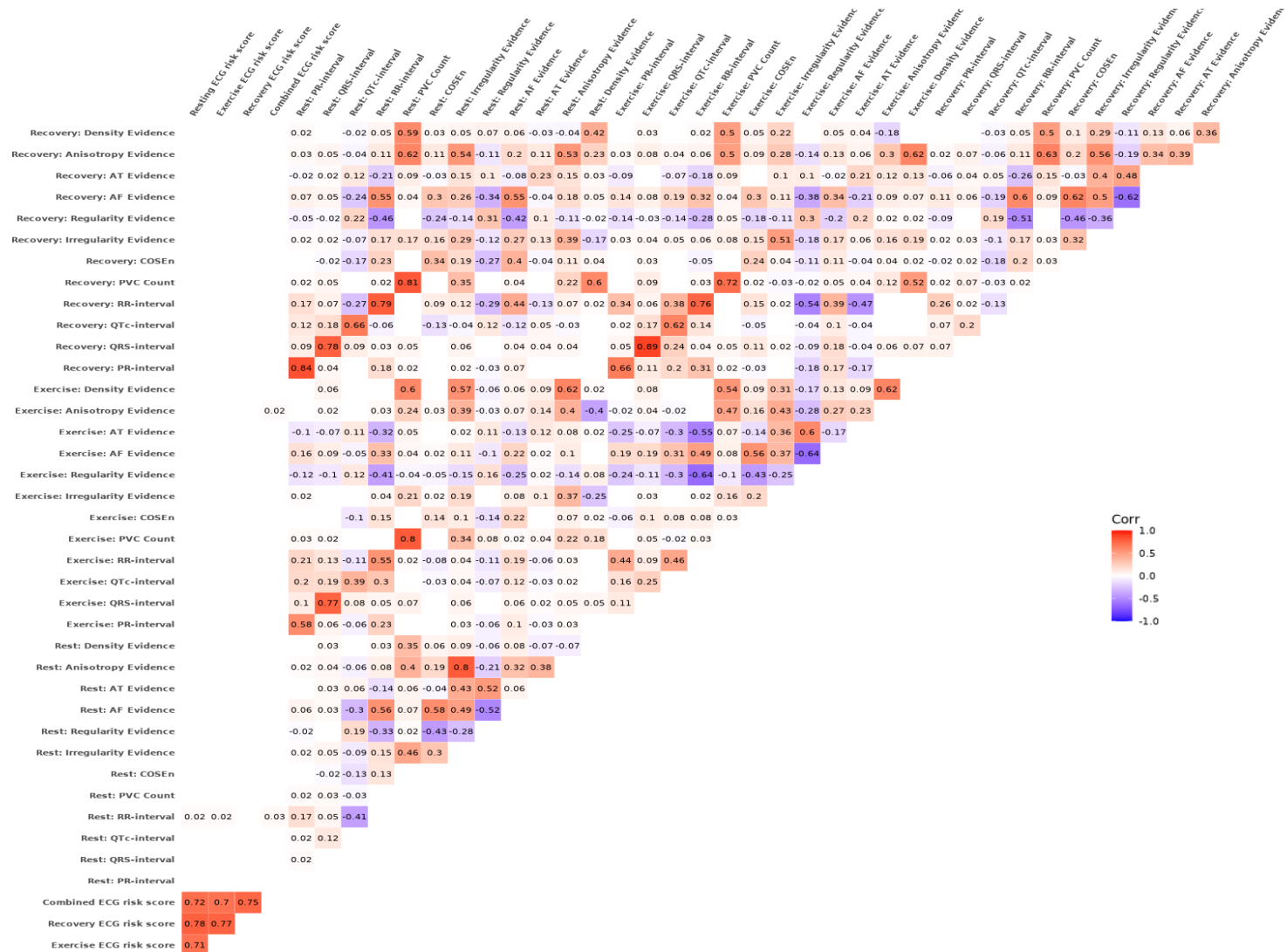
(a) 2-D histogram (Poincare plot) showing the rate of Change in  $\Delta RR$  at one time step  $i$  on the x axis against the  $\Delta RR$  at the previous time step  $i-1$  on the y axis. The Poincaré plot is divided into 13 segments donated in (b) and populated by the rate of change in RR interval ( $\Delta RR(i)$ ,  $\Delta RR(i-1)$ ). Segment 0 represents heart beats in normal sinus rhythm and has a radius of 80mns. (b) divides the Poincaré plot into segments based on the rate of change in RR interval, small (D) medium (M) or large(L), with a sequence of S-M-L indicating a short RR interval followed by a medium RR interval followed by a large RR interval.

Abbreviations: S = short RR interval; M = medium RR interval; L = large RR interval.

Adapted from: Shantanu Sarkar\* et al, A Detector for a Chronic Implantable Atrial Tachyarrhythmia Monitor.



**Supplementary figure 3 : Spearman correlation matrix for ECG parameters derived from final 15-seconds of rest, exercise and recovery among male participants (n = 18,221; MACCE = 2,336)**



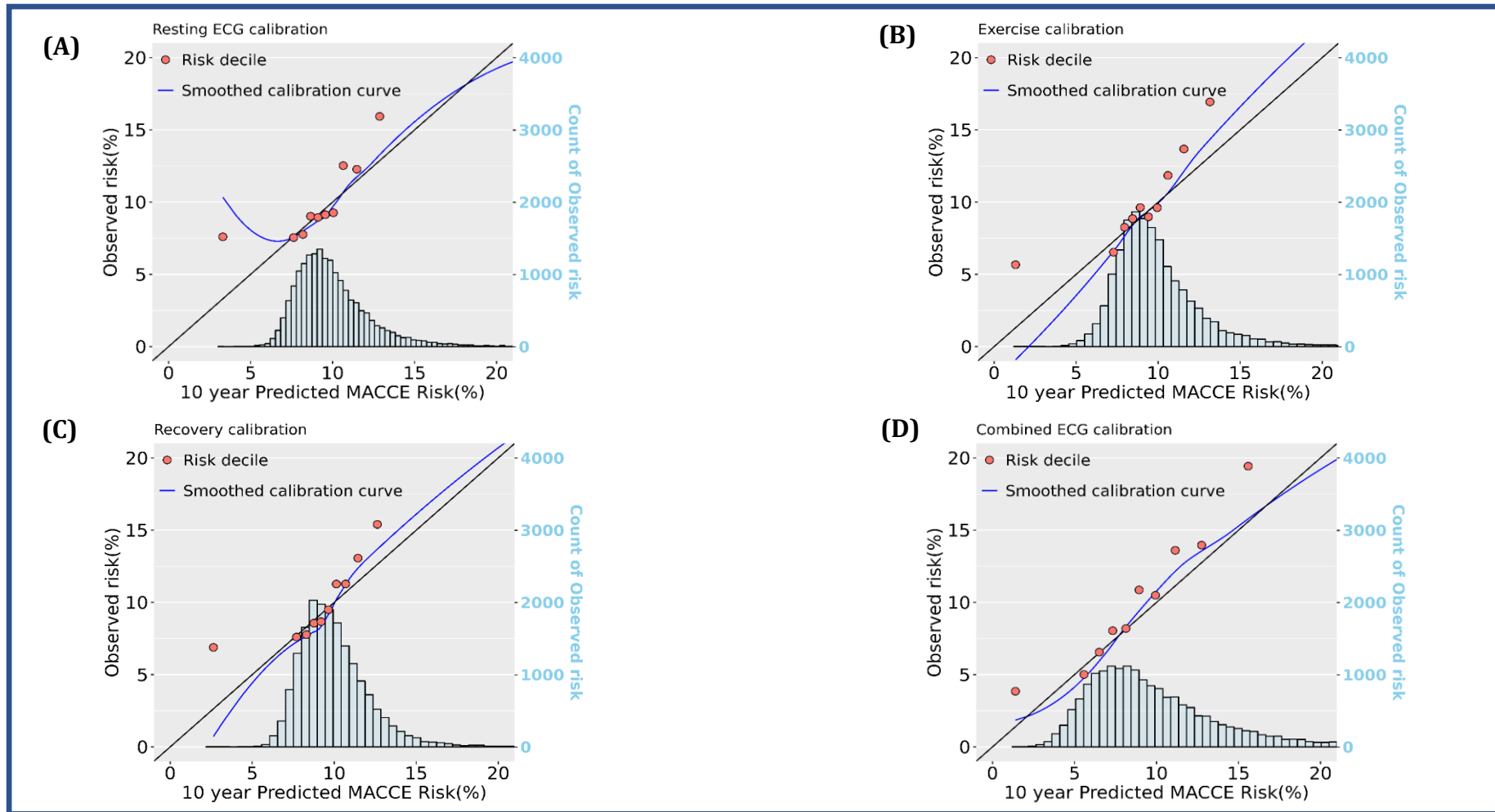
Pairwise Spearman correlations ( $\rho$ ) were computed among the ECG-parameters recorded across rest, exercise, and recovery phases. Statistical significance was assessed using asymptotic p-values for Spearman correlation with Benjamini–Hochberg false discovery rate correction applied to unique pairwise tests; only correlations with BH-adjusted  $q < 0.05$  are shown.

**Supplementary figure 4: Spearman correlation matrix for ECG parameters derived from final 15-seconds of rest, exercise and recovery among female participants (n = 17,376; MACCE = 1127)**



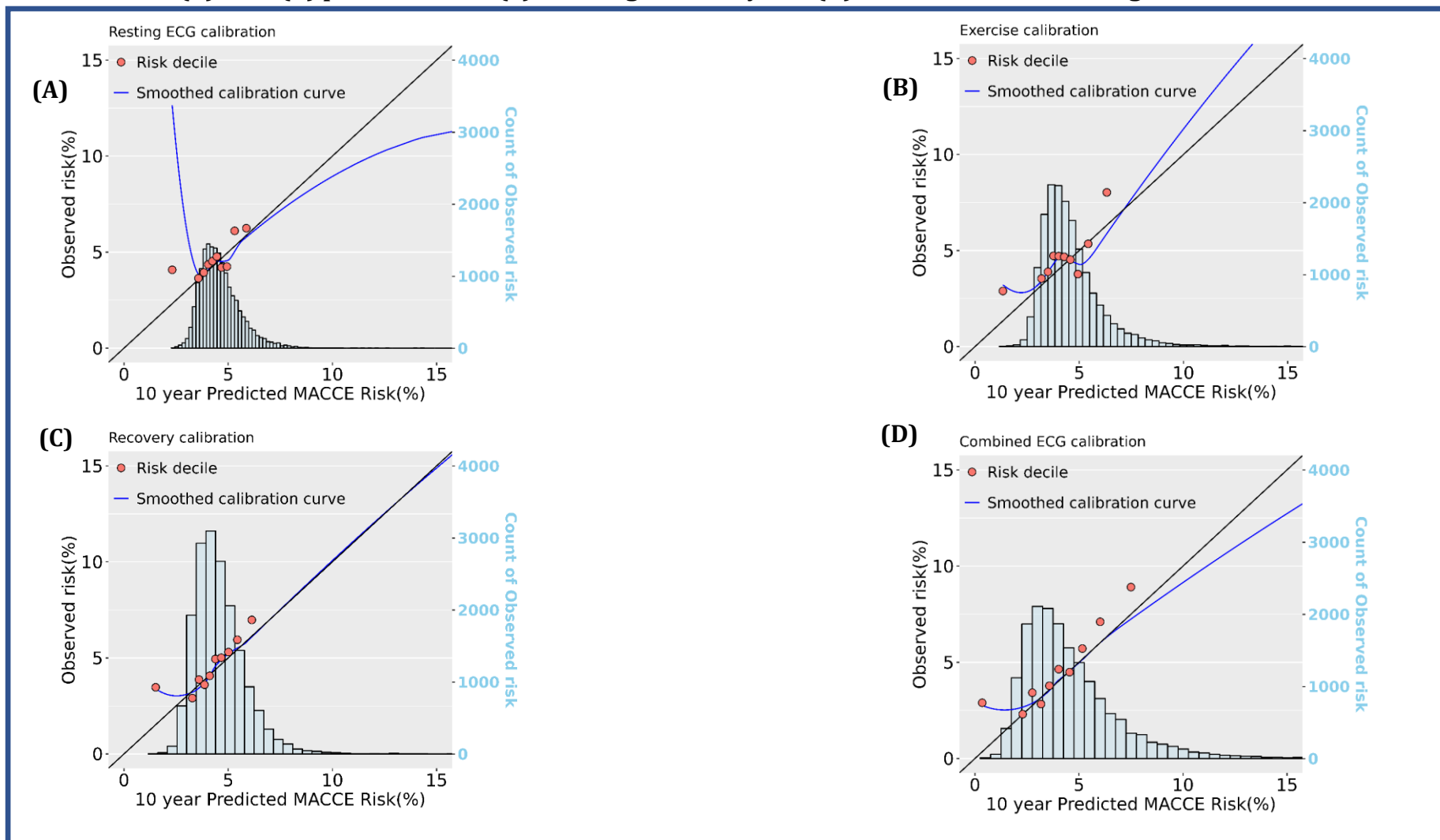
Pairwise Spearman correlations ( $\rho$ ) were computed among the ECG-parameters recorded across rest, exercise, and recovery phases. Statistical significance was assessed using asymptotic p-values for Spearman correlation with Benjamini–Hochberg false discovery rate correction applied to unique pairwise tests; only correlations with BH-adjusted  $q < 0.05$  are shown.

**Supplementary figure 5: Smoothed calibration curve for ECG risk scores derived for male participants from ECG parameters measured at: (A) rest; (B) peak-exercise; (C) late-stage recovery and (D) a combination of all stages.**



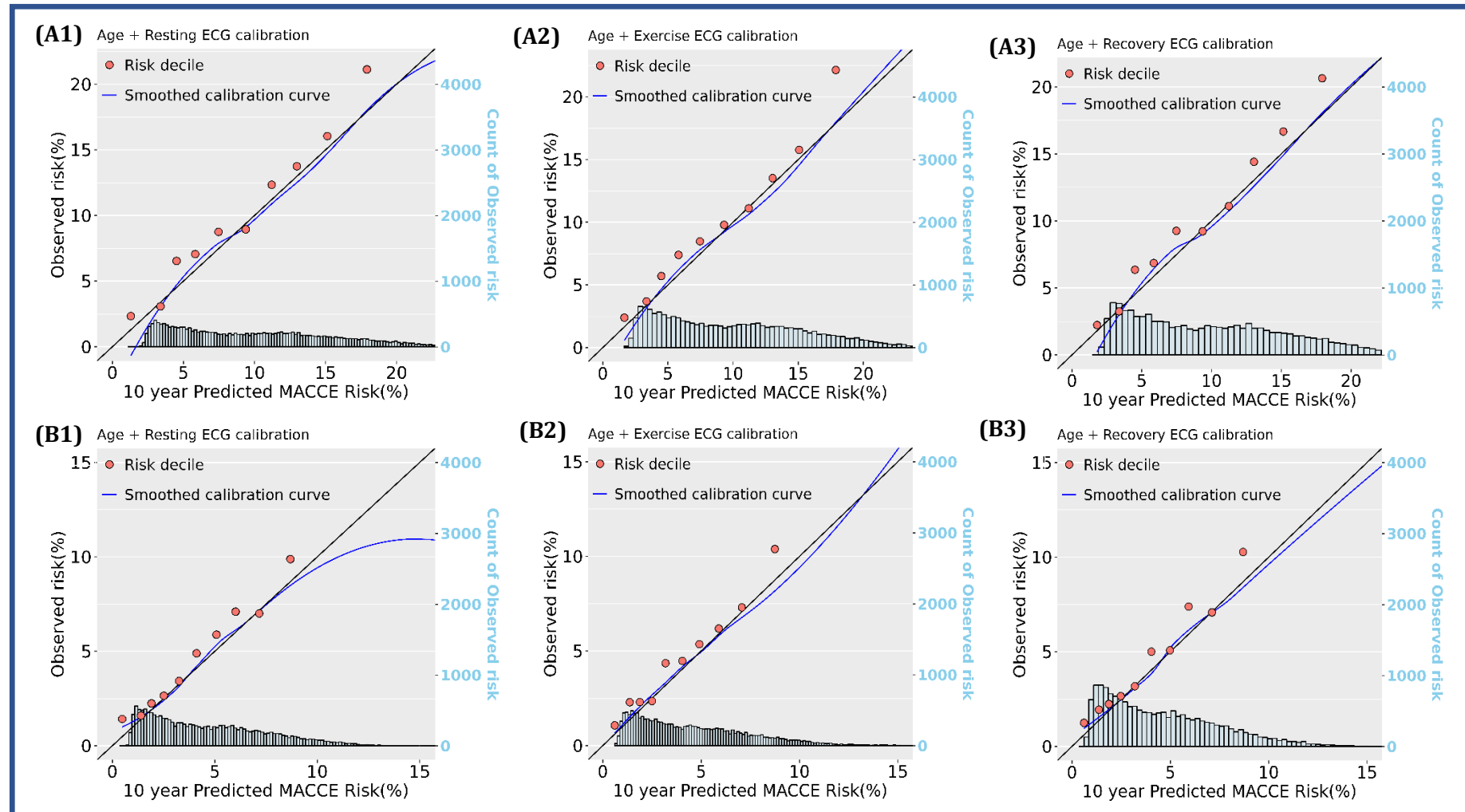
The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. **ECG parameters:** **Resting** ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*, **Exercise** ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*, **Recovery** ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*. Combined ECG parameters include a combination of parameters from rest, exercise and recovery

**Supplementary figure 6: Smoothed calibration curve for ECG risk scores derived for female participants from ECG parameters measured at: (A) rest; (B) peak-exercise; (C) late-stage recovery and (D) a combination of all stages.**



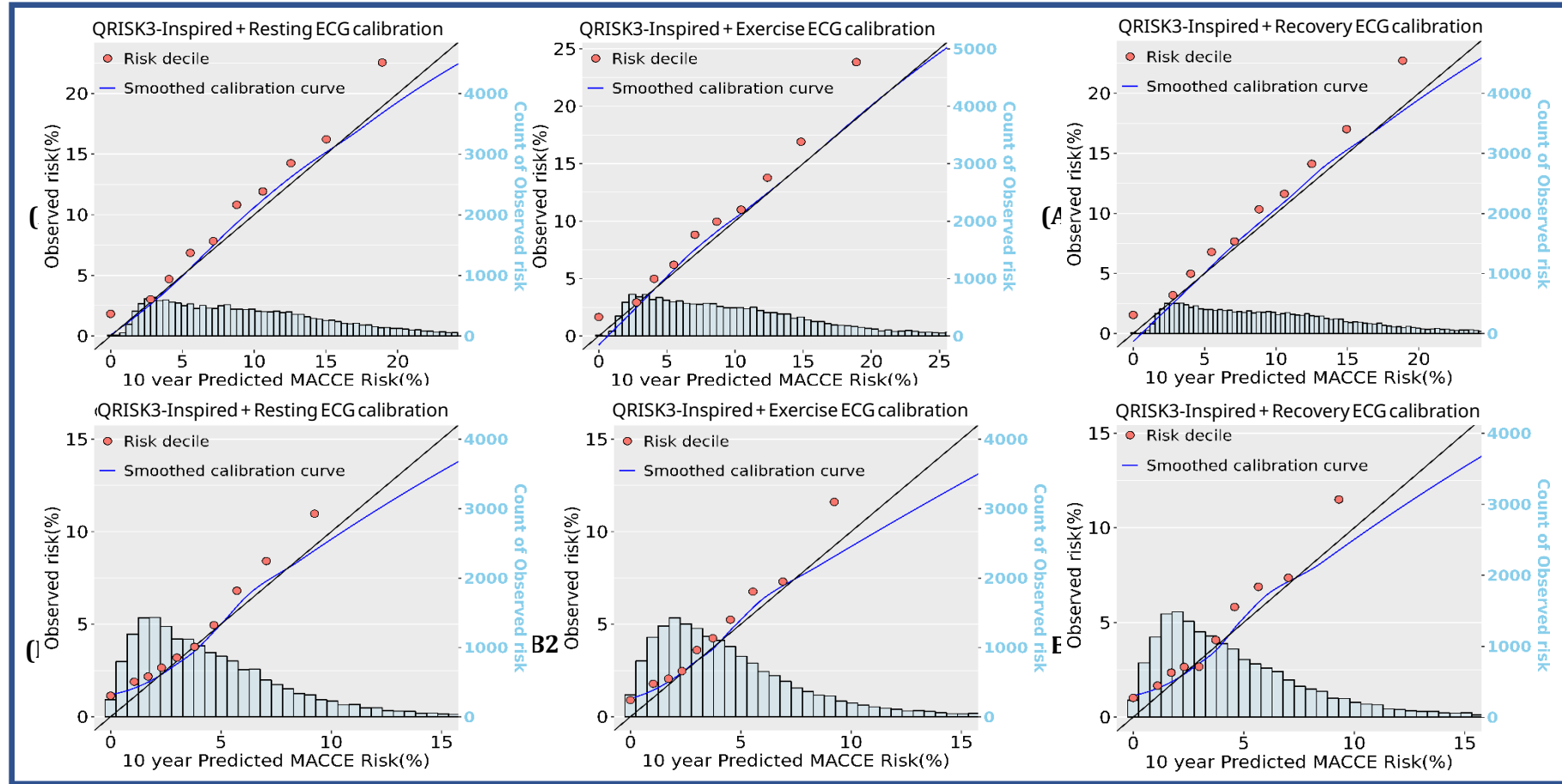
The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. **ECG parameters:** Resting ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*, Exercise ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*, Recovery ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*. Combined ECG parameters include a combination of parameters from rest, exercise and recovery

**Supplementary figure 7: Smoothed calibration curve for Age + ECG risk scores derived for male (A) & female (B) participants using ECG parameters measured at: (1) rest; (2) peak-exercise; (3) late-stage recovery**



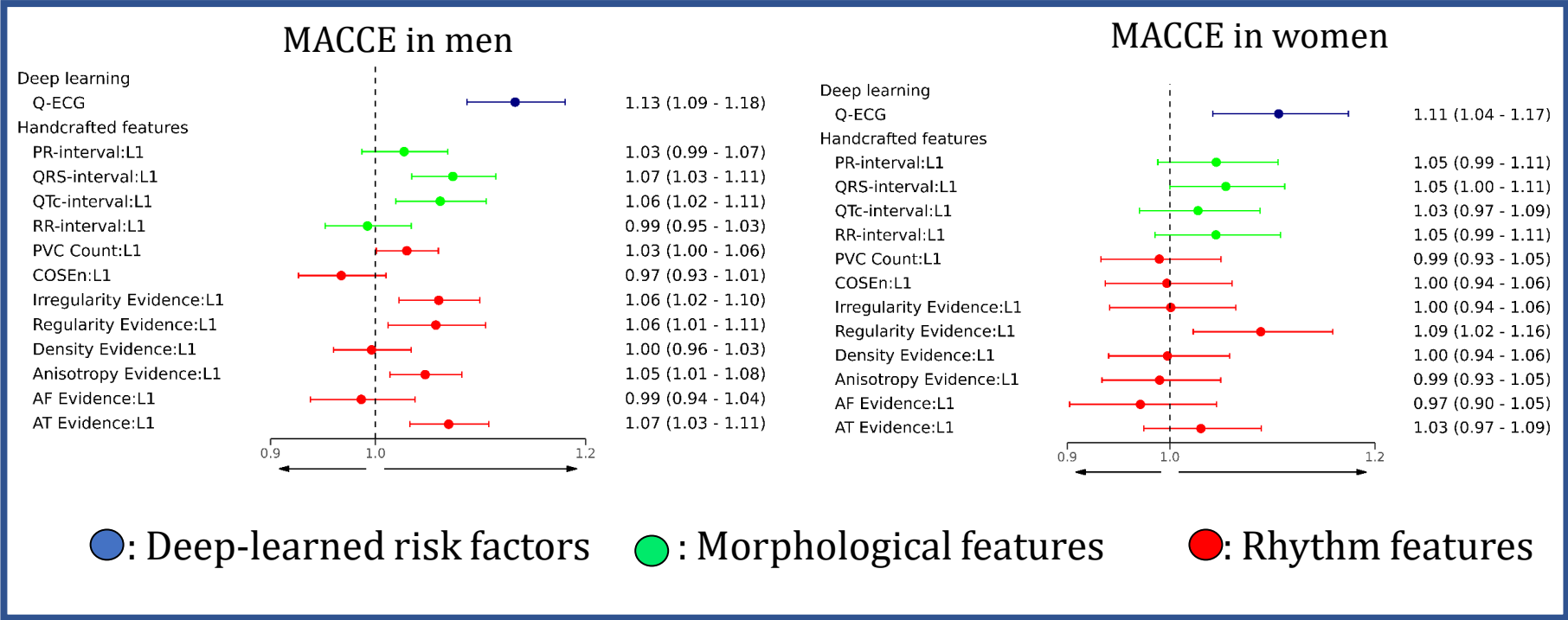
The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. **ECG parameters:** **Resting** ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*, **Exercise** ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*, **Recovery** ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*. Combined ECG parameters include a combination of parameters from rest, exercise and recovery

**Supplementary figure 8: Smoothed calibration curve for QRISK3-Inspired + ECG risk scores derived for male (A) & female (B) participants using ECG parameters measured at: (1) rest; (2) peak-exercise; (3) late-stage recovery**



The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. **ECG parameters:** Resting ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*, Exercise ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence*, Recovery ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*. Combined ECG parameters include a combination of parameters from rest, exercise and recovery; QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment; Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

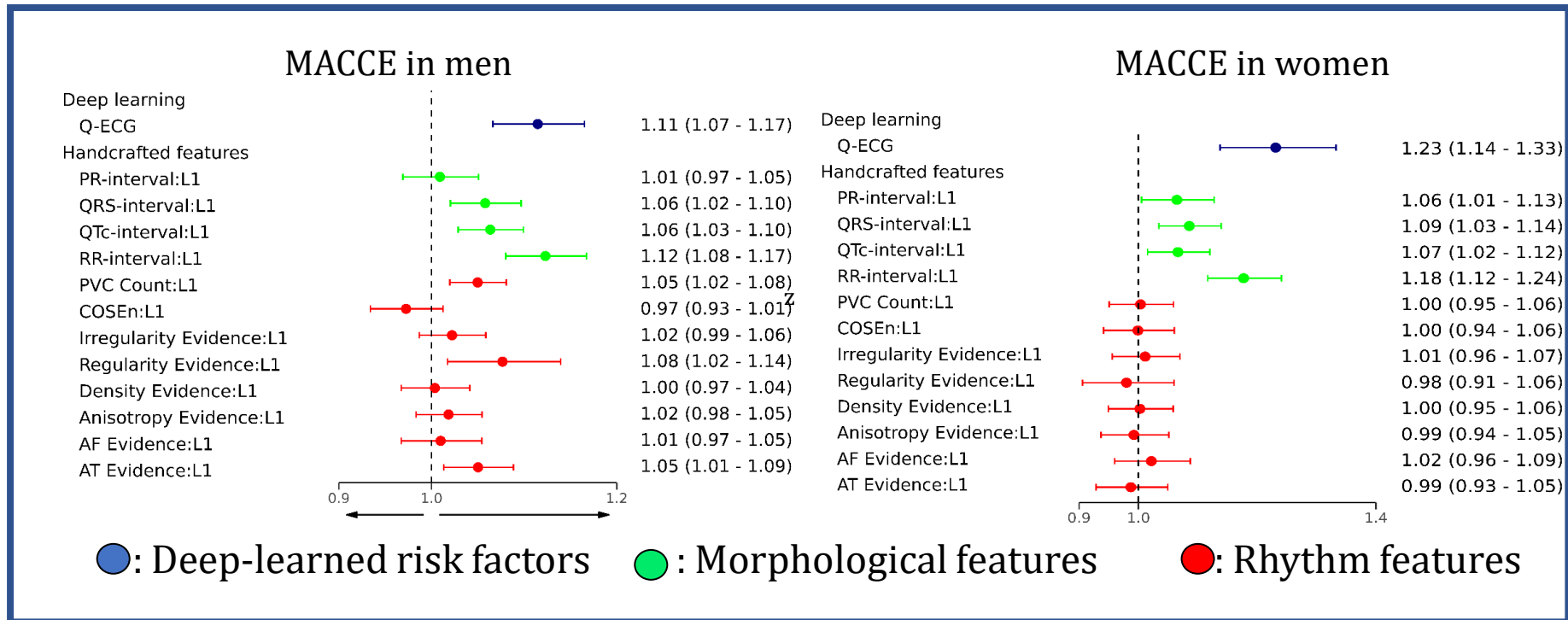
**Supplementary figure 9: Hazard ratio per standard deviation of deep-learned ECG risk scores (Q-ECG) and conventional ECG parameters obtained during 15 seconds of rest with the 10-year risk of MACCE.**



Hazard ratios are derived from sperate Cox proportional hazard models adjusted for age, sex, smoking status, social deprivation measured by Townsend deprivation index, and ethnicity. Irregularity, Pace, Regulatory, Anisotropy and AF evidence were adjusted for the number of beats in the signal to account for higher absolute values in participants with faster heart rates. Hazard ratios are reported per standard deviation increase. Cox proportional hazard models were developed on the aggregated test sets across five cross-validation folds, consisting of 35,597 participants and 2,591 (7·27%) MACCE within 10 years.



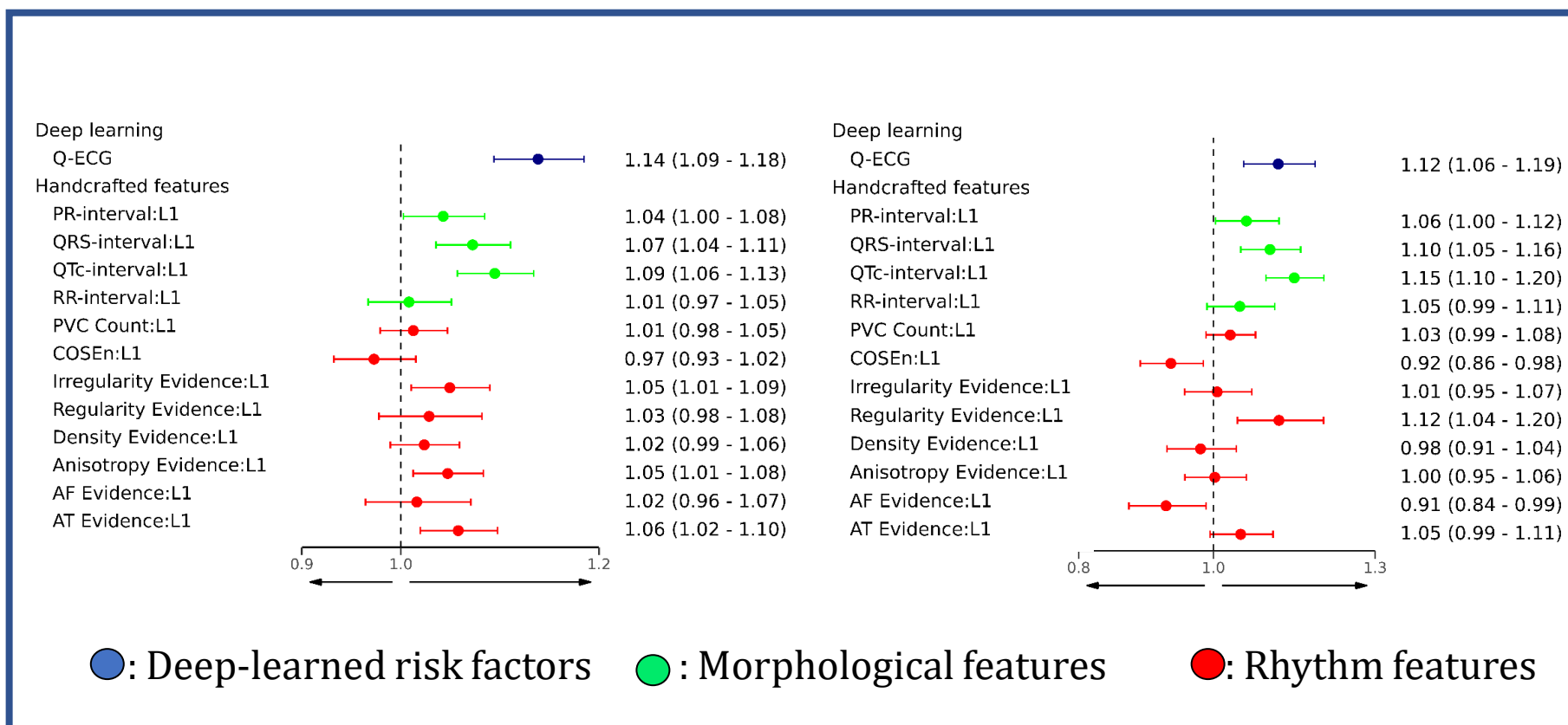
**Supplementary figure 10: Hazard ratio per standard deviation of Deep survival ECG risk scores (Q-ECG) derived from the final 15 seconds (maximum intensity of exercise) of a 6-min period of submaximal exercise compared with conventional ECG parameters**



Hazard ratios are derived from separate Cox proportional hazard models adjusted for age, sex, smoking status, social deprivation measured by Townsend deprivation index, and ethnicity. Irregularity, Pace, Regulatory, Anisotropy and AF evidence were adjusted for the number of beats in the signal to account for higher absolute values in participants with faster heart rates. Hazard ratios are reported per standard deviation increase. Cox proportional hazard models were developed on the aggregated test sets across five cross-validation folds, consisting of 35,597 participants and 2,591 (7.27%) MACCE within 10 years.

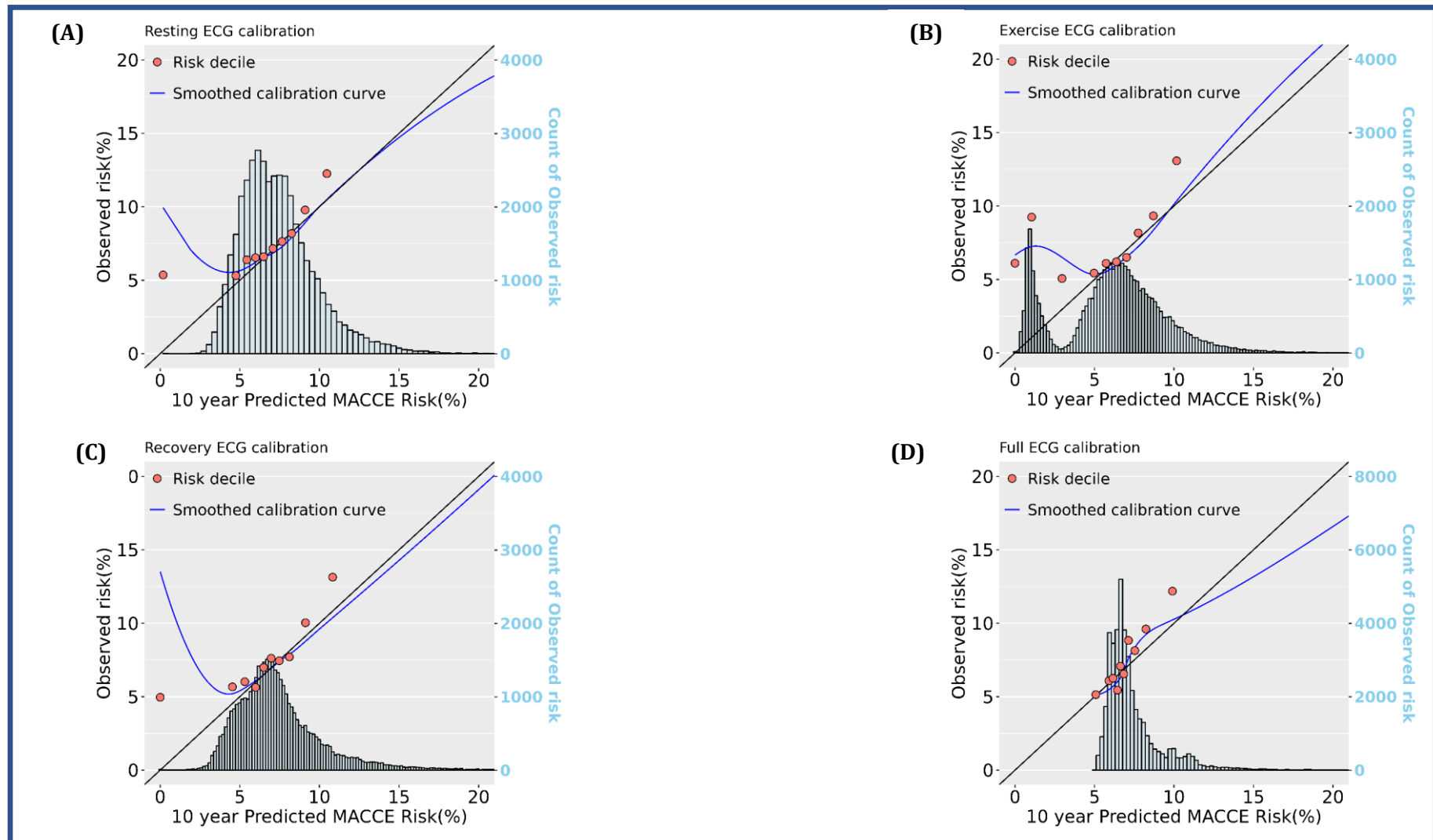


**Supplementary figure 11: Hazard ratio per standard deviation of Deep survival ECG risk scores (Q-ECG) derived from the final 15 seconds of a 1-min recovery, compared with conventional ECG parameters**



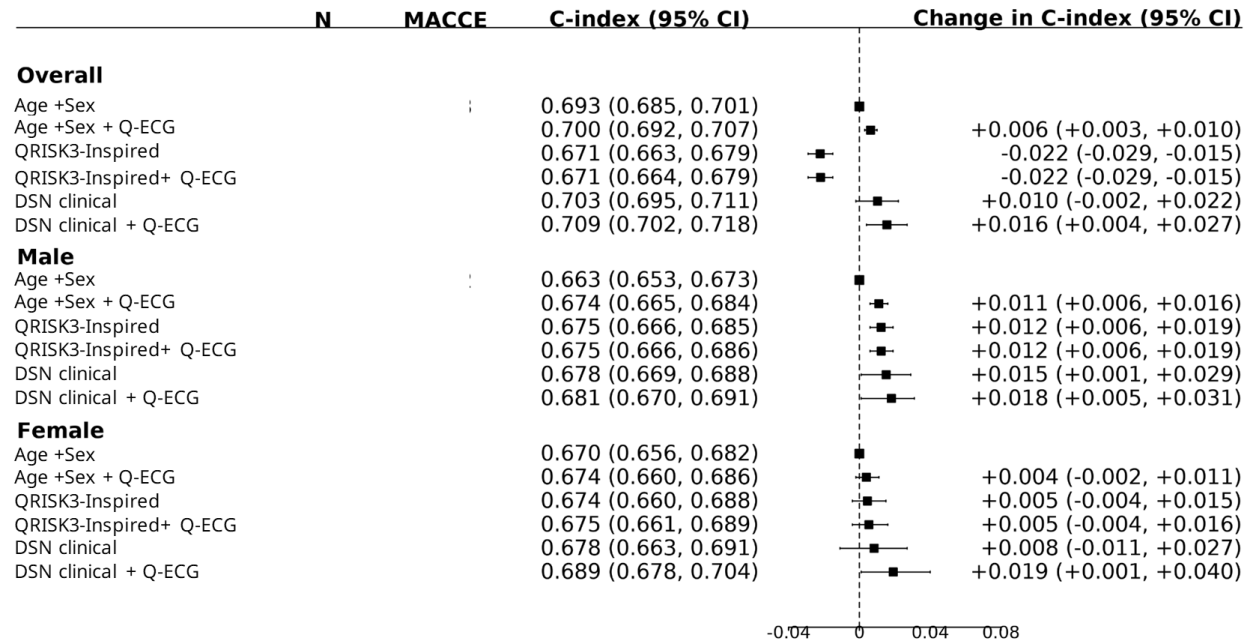
Hazard ratios are derived from separate Cox proportional hazard models adjusted for age, sex, smoking status, social deprivation measured by Townsend deprivation index, and ethnicity. Irregularity, Pace, Regulatory, Anisotropy and AF evidence were adjusted for the number of beats in the signal to account for higher absolute values in participants with faster heart rates. Hazard ratios are reported per standard deviation increase. Cox proportional hazard models were developed on the aggregated test sets across five cross-validation folds, consisting of 35,597 participants and 2,591 (7.27%) MACCE within 10 years.

**Supplementary figure 12: Smoothed calibration curve for ECG risk scores derived using deep survival neural networks from Raw ECG data measured at: (A) rest; (B) peak-exercise; (C) late-stage recovery and (D) a full 7-minute 15 second ECG**



The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. ECG scores were derived from a deep survival network trained on ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), final 15-seconds of recovery and full 7-minute 15-second submaximal exercise ECG recording. Abbreviations DSN: Deep survival network

**Supplementary Figure 13: Forest plot of Harrell's C-index for Age + Sex, QRISK3-Inspired risk scores, and deep survival models derived from QRISK3 risk factors combined with 15-second resting ECG data (Q-ECG) in 41,076 UK Biobank participants with 4,086 MACCE (2009–2013)**



Abbreviations: CI = Confidence interval, MACCE = Major Adverse Cardiovascular & Cerebrovascular Events; DSN: Deep survival network 95% confidence intervals were derived via 1000 bootstrap iterations.

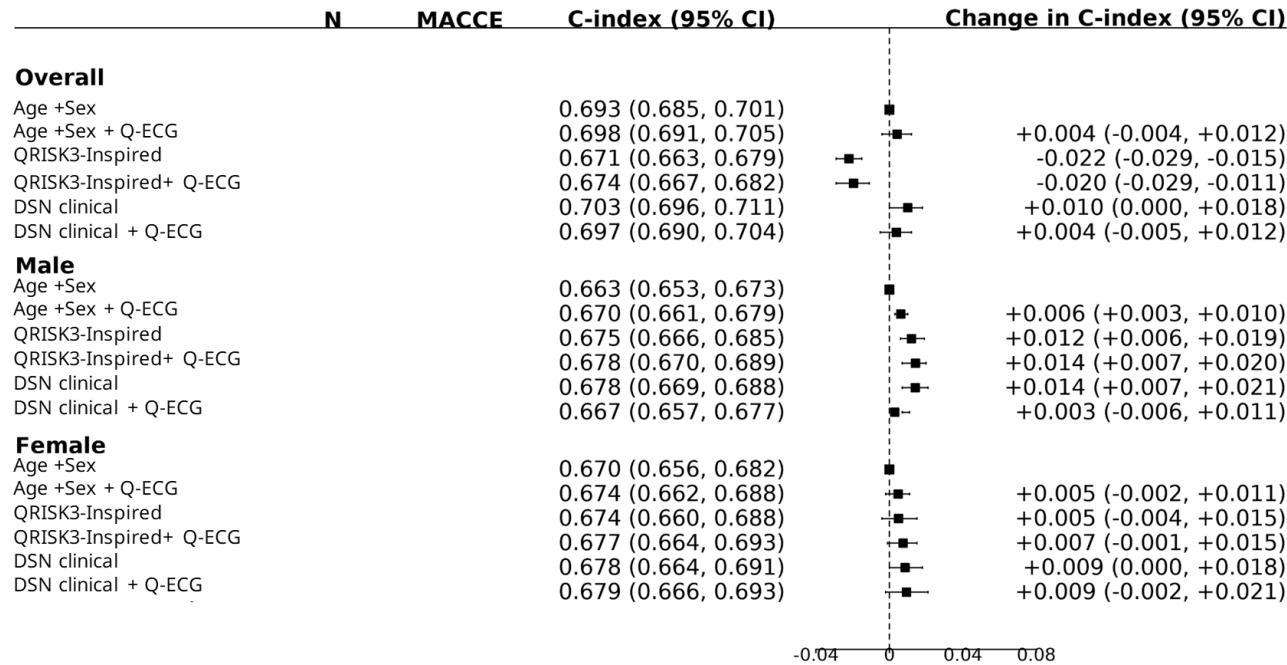
Squares represent change in C-index compared to age + sex models and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05

DSN clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1+ Diabetes type 2, HDL ratio, Townsend deprivation index+ Smoker former, Smoker current, Smoker never+ Ethnic Background, Corticosteroid+ Migraine, Hypertension, Severe mental illness, Rheumatoid Arthritis

Q-ECG scores were derived from a deep survival network trained on 15-second ECG recordings obtained at rest.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index + Age FP1 X BMI FP1 + Age FP1 X BMI FP2 + Age FP1 X Systolic blood pressure + Age FP1 X Diabetes type 1 + Age FP1 X Diabetes type 2 + Age FP1 X hypertension + Age FP1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Systolic blood pressure + Age FP2 X Diabetes type 1 + Age FP2 X Diabetes type 2 + Age FP2 X Hypertension . + Age FP2 \* Corticosteroid treatment; Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ );

**Supplementary Figure 14: Forest plot of Harrell's C-index for Age + Sex, QRISK3-Inspired risk scores, and deep survival models derived from QRISK3 risk factors combined with the final 15 seconds of exercise ECG data (Q-ECG) in 41,076 UK Biobank participants (2009–2013).**



Abbreviations: CI = Confidence interval, MACCE = Major Adverse Cardiovascular & Cerebrovascular Events; DSN: Deep survival network 95% confidence intervals were derived via 1000 bootstrap iterations.

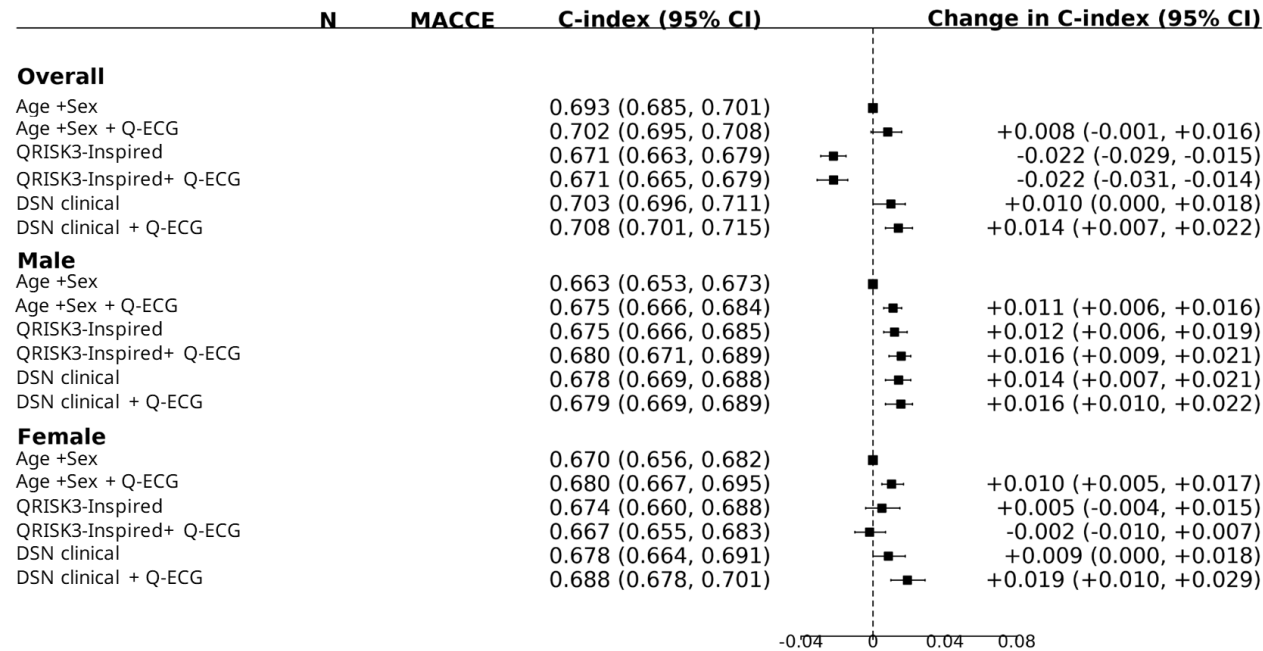
Squares represent change in C-index compared to age+ Sex models and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05

DSN clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1+ Diabetes type 2, HDL ratio, Townsend deprivation index+ Smoker former, Smoker current, Smoker never+ Ethnic Background, Corticosteroid+ Migraine, Hypertension, Severe mental illness, Rheumatoid Arthritis

Q-ECG scores were derived from a deep survival network trained on ECG recordings obtained during the final 15-seconds of exercise, corresponding to the maximum intensity exercise obtained

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment; Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

**Supplementary Figure 15: Forest plot of Harrell's C-index for Age + Sex, QRISK3-Inspired risk scores, and deep survival models derived from QRISK3 risk factors combined with the final 15 seconds of recovery ECG data (Q-ECG) in 41,076 UK Biobank participants (2009–2013)**



Abbreviations: CI = Confidence interval, MACCE = Major Adverse Cardiovascular & Cerebrovascular Events; DSN: Deep survival network 95% confidence intervals were derived via 1000 bootstrap iterations.

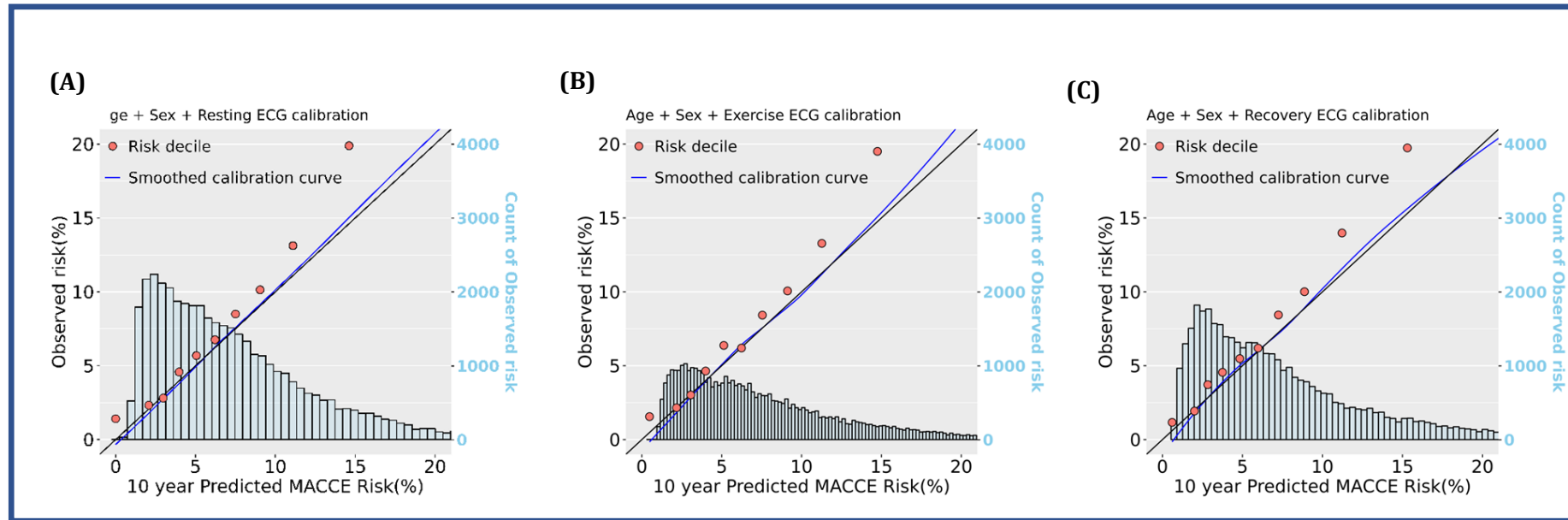
Squares represent change in C-index compared to age + sex models and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95% CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05

DSN clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1+ Diabetes type 2, HDL ratio, Townsend deprivation index+ Smoker former, Smoker current, Smoker never+ Ethnic Background, Corticosteroid+ Migraine, Hypertension, Severe mental illness, Rheumatoid Arthritis

Q-ECG scores were derived from a deep survival network trained on ECG recordings obtained during the final 15-seconds of exercise, corresponding to the maximum intensity exercise obtained

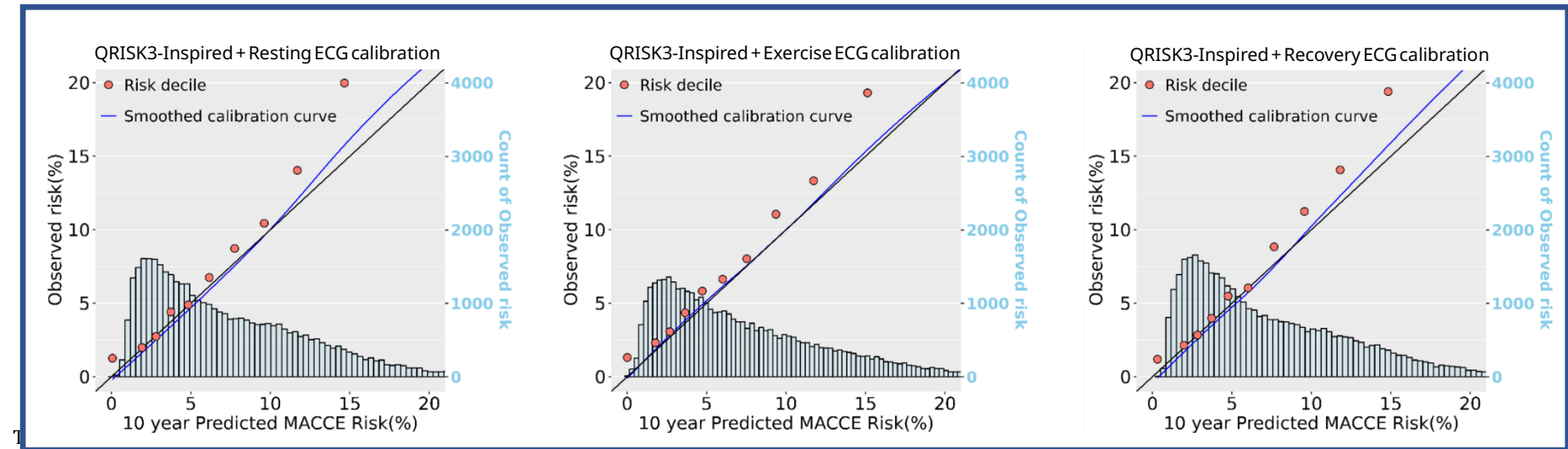
QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness + SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index + Age FP1 X BMI FP1 + Age FP1 X BMI FP2 + Age FP1 X Systolic blood pressure + Age FP1 X Diabetes type 1 + Age FP1 X Diabetes type 2 + Age FP1 X hypertension + Age FP1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Systolic blood pressure + Age FP2 X Diabetes type 1 + Age FP2 X Diabetes type 2 + Age FP2 X Hypertension. + Age FP2 \* Corticosteroid treatment; Fractional polynomials: Age FP1 (males) =  $(age/10)^{-1}$ , Age FP2 (males) =  $(age/10)^3$ , BMI FP1 (males) =  $(BMI/10)^{-2}$ , BMI FP2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP1 (Females) =  $age/10^{-2}$ , Age FP2 (Females) =  $age/10$ , BMI FP1 (Females) =  $(BMI/10)^{-2}$ , BMI FP2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

**Supplementary figure 16: Smoothed calibration curve for Age + ECG risk scores derived using deep survival neural networks for ECG parameters measured at: (A) rest; (B) peak-exercise; and (C) late-stage recovery**



The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. ECG scores were derived from a deep survival network trained on ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), and the final 15-seconds of recovery. Abbreviations DSN: Deep survival network

**Supplementary figure 17: Smoothed calibration curve for QRISK3-Inspired + ECG risk scores derived using deep survival neural networks for ECG parameters measured at: (A) rest; (B) peak-exercise; and (C) late-stage recovery**

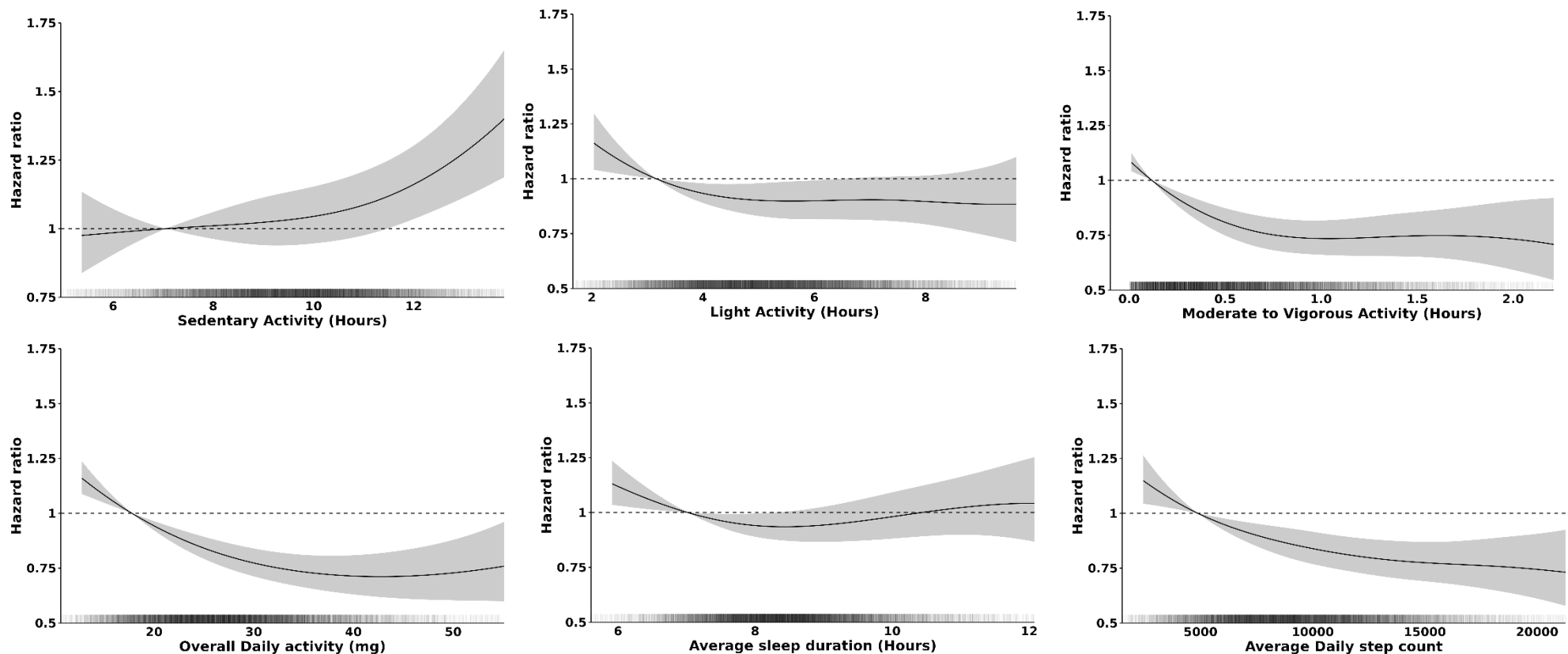


risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. ECG scores were derived from a deep survival network trained on ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), and the final 15-seconds of recovery. Abbreviations DSN: Deep survival network

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness + SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index + Age FP1 X BMI FP1 + Age FP1 X BMI FP2 + Age FP1 X Systolic blood pressure + Age FP1 X Diabetes type 1 + Age FP1 X Diabetes type 2 + Age FP1 X hypertension + Age FP1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Systolic blood pressure + Age FP2 X Diabetes type 1 + Age FP2 X Diabetes type 2 + Age FP2 X Hypertension . + Age FP2 \* Corticosteroid treatment.

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

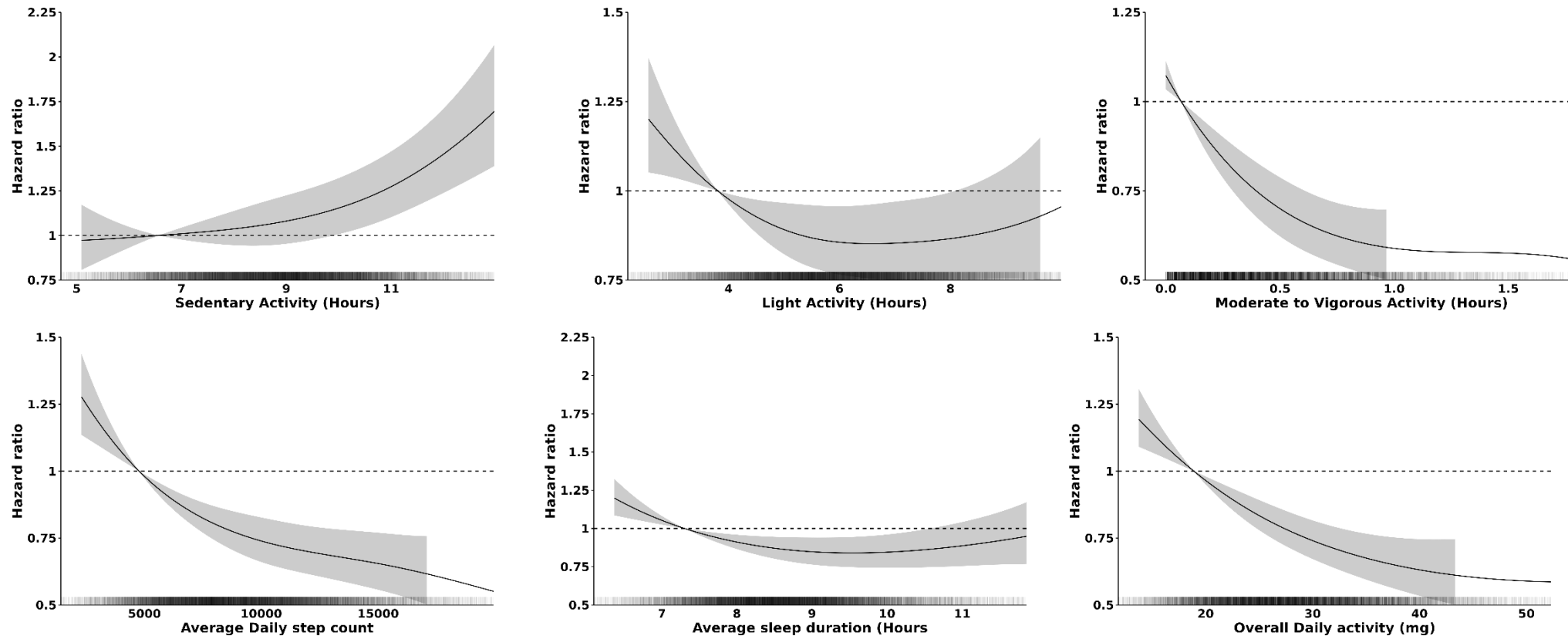
**Supplementary Figure 18. Continuous cubic spline of the hazard ratio between (A) sedentary behaviour, (B) light physical activity, (C) moderate-to-vigorous physical activity, (D) step count, and (E) overall physical activity and 6-year risk of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) among 37,068 male UK Biobank participants (incident MACCE = 2,571(6.9%)).**



Hazard ratios (HRs) and 95% confidence intervals were estimated using penalised spline models (3 degrees of freedom) for sedentary behaviour, light activity, moderate-to-vigorous physical activity, step count, and overall activity among 37,068 men and 51,354 women. Models were adjusted for age, sex, body mass index, ethnicity, smoking status, and Townsend deprivation index.

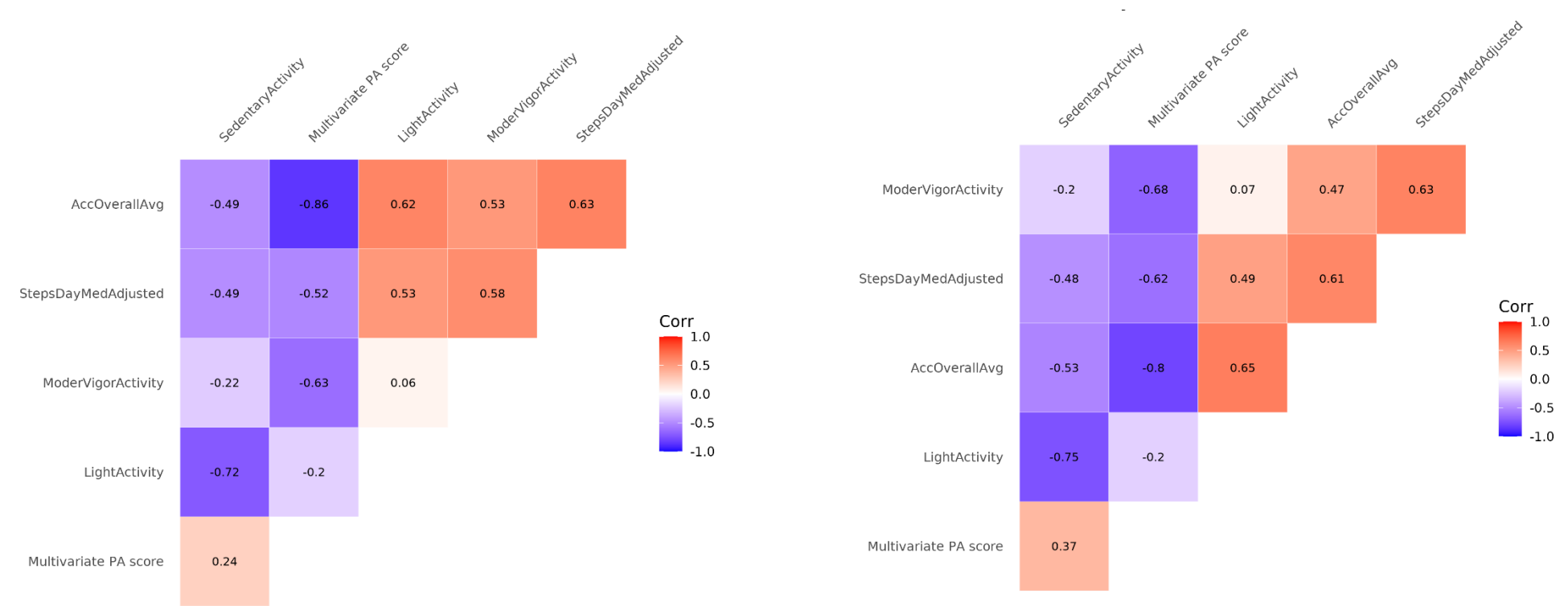


**Supplementary Figure 19 Continuous cubic spline of the hazard ratio between (A) sedentary behaviour, (B) light physical activity, (C) moderate-to-vigorous physical activity, (D) step count, and (E) overall physical activity and 6-year risk of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) among 51,354 female UK Biobank participants (Incident MACCE = 1,656(3.2%)).**



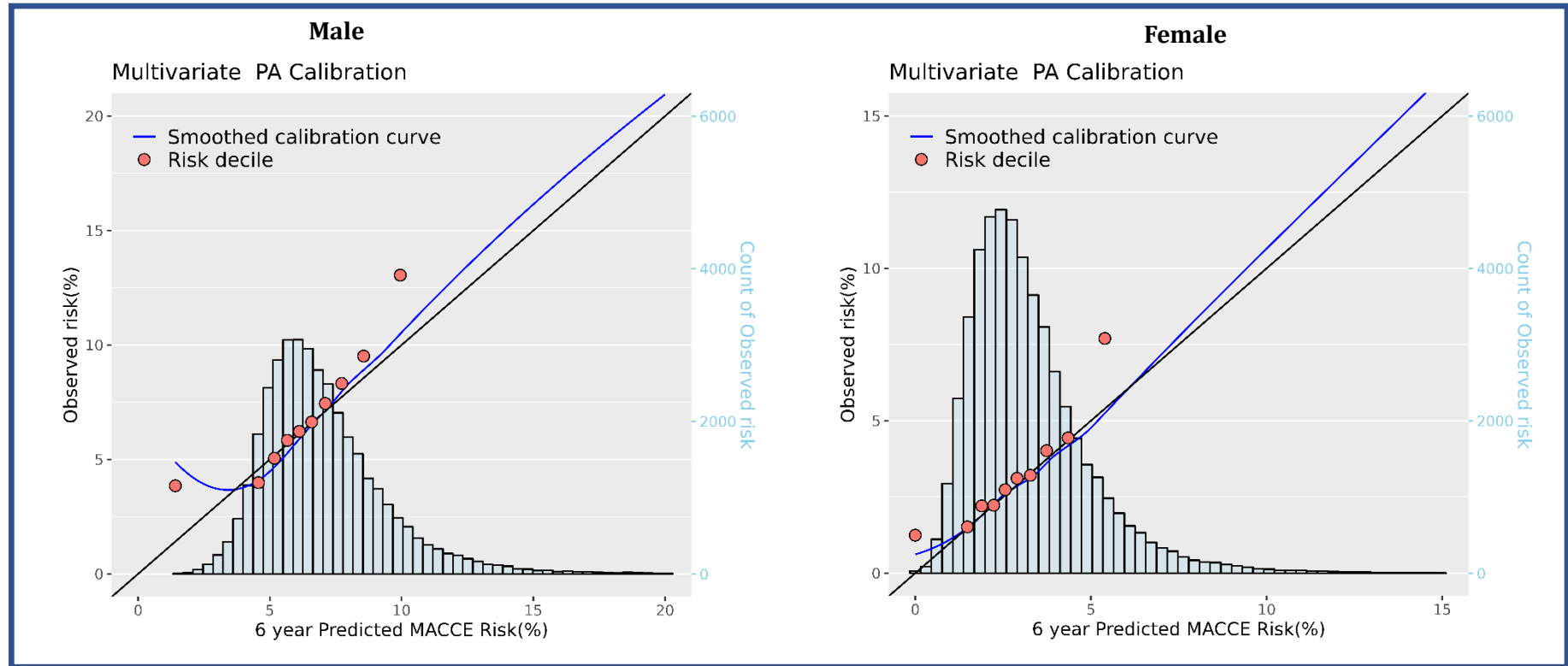
Hazard ratios (HRs) and 95% confidence intervals were estimated using penalised spline models (3 degrees of freedom) for sedentary behaviour, light activity, moderate-to-vigorous physical activity, step count, and overall activity among 37,068 men and 51,354 women. Models were adjusted for age, sex, body mass index, ethnicity, smoking status, and Townsend deprivation index.

**Supplementary figure 20: Spearman correlation matrix for accelerometer-derived physical activity obtained over 7 days of continuous monitoring in a free-living environment for male (n = 37,068 ; MACCE = 2,571(6.9%)) and female (n = 51,354 MACCE = 1,656(3.2%)), participants, respectively**



Pairwise Spearman correlations ( $\rho$ ) were computed among the Physical activity measurements recorded 7-dyas of continuous monitoring using a wrist worn-device . Statistical significance was assessed using asymptotic p-values for Spearman correlation with Benjamini–Hochberg false discovery rate correction applied to unique pairwise tests; only correlations with BH-adjusted  $q < 0.05$  are shown.

**Supplementary figure 21: Smoothed calibration curve for multivariable physical activity (PA) risk scores consisting of overall step count, overall activity, and hours spent in sedentary behaviour, light PA and moderate/vigorous PA.**

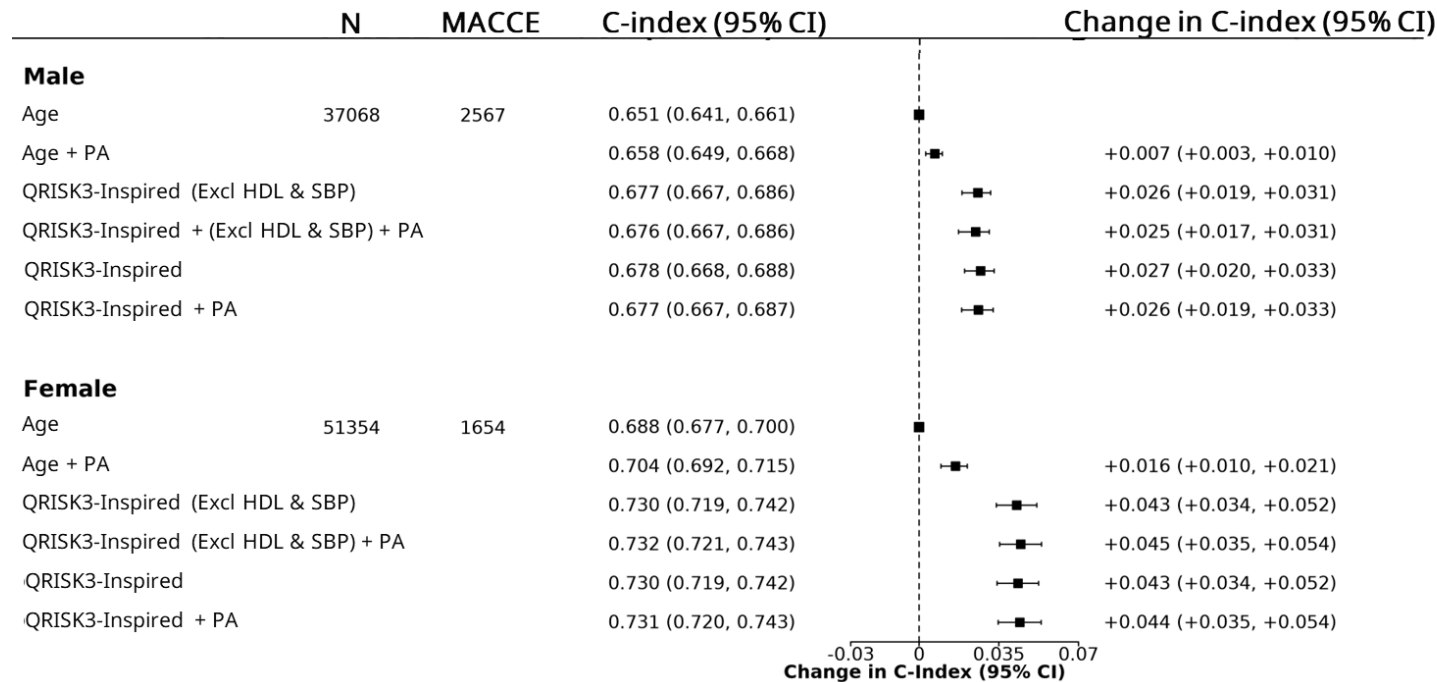


The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. Multivariate Physical activity (PA) was derived from Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

$$\text{Multivariate PA risk score (males)} = \left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}^{0.5}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

$$\text{Multivariate PA risk score (Females)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{-2}}{10} + \frac{\text{Overall activity}^{-0.5}}{10}$$

**Supplementary Figure 22: Optimism adjusted Harrell's C-index for Age , QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) and QRISK3-Inspired risk scores, derived using blood measurements obtained from primary care data, following the addition of accelerometer measured physical activity (PA) in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**



Abbreviations: CI = confidence intervals; PA = Physical activity; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score. QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP1 X hypertension + Age FP1 X Diabetes + Age FP1 X BMI FP1 + Age FP1 X BMI FP2 + Age FP1 X Townsend deprivation index + Age FP1 X Systolic blood pressure + Age FP1 \* Atrial fibrillation and flutter + Age FP1 \* Corticosteroid treatment + Age FP2 X Hypertension + Age FP2 X Diabetes + Age FP2 X Diabetes + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Townsend deprivation index + Age FP2 X Systolic blood pressure + Age FP2 \* Corticosteroid treatment + Age FP2 \* Atrial fibrillation and flutter. Fractional polynomials: Age FP1 (males) =  $(age/10)^{-1}$ , Age FP2 (males) =  $(age/10)^3$ , BMI FP1 (males) =  $(BMI/10)^{-2}$ , BMI FP2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP1 (Females) =  $age/10^{-2}$ , Age FP2 (Females) =  $age/10$ , BMI FP1 (Females) =  $(BMI/10)^{-2}$ , BMI FP2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA), and sedentary behaviour. (SB)

$$\text{Age PA fractional polynomials (male)} = \left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10};$$

QRISK3-Inspired (Excl HDL & SBP) +A fractional polynomials (male) =

$$\left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

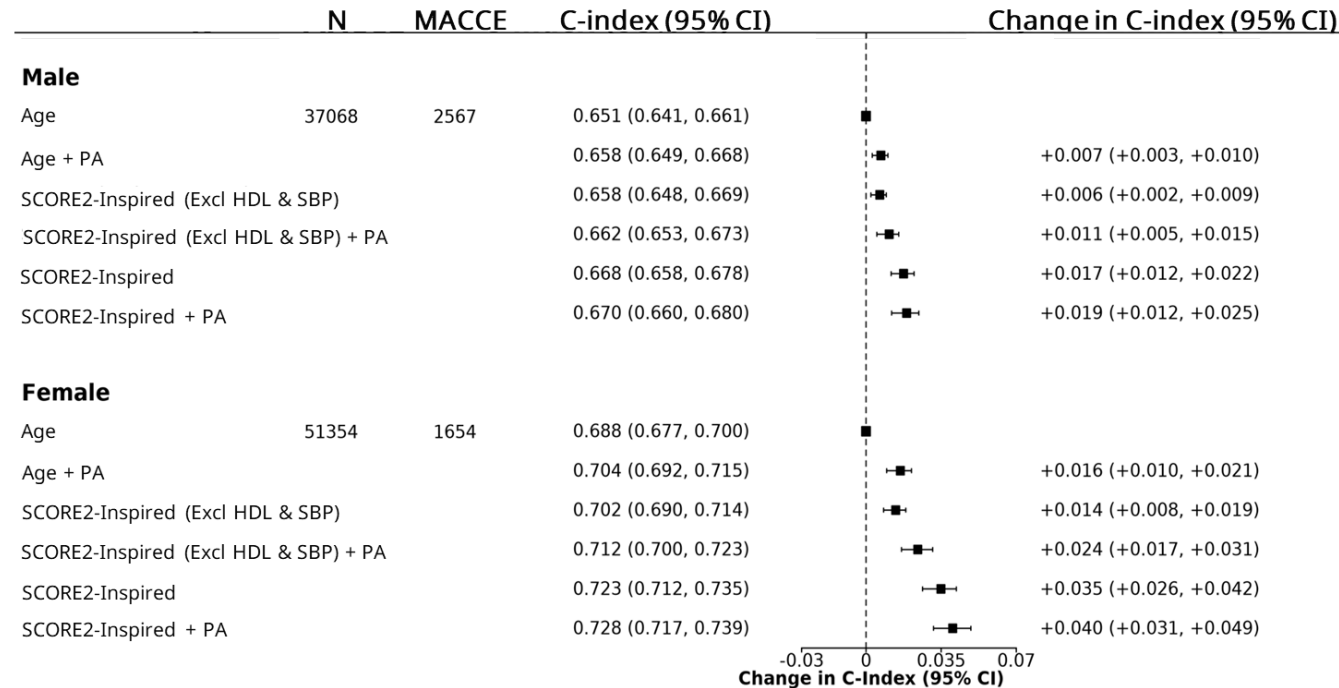
$$\text{QRISK3-Inspired PA fractional polynomials (male)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

$$\text{Age PA fractional polynomials (female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right);$$

$$\text{QRISK3-Inspired (Excl HDL & SBP) PA fractional polynomials (female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$$

$$\text{QRISK3-Inspired PA fractional polynomials (Female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$$

**Supplementary Figure 23 Optimism adjusted Harrell's C-index for risk scores derived from Age, SCORE2-Inspired (excluding High-density lipoprotein and Systolic blood pressure) and SCORE2-Inspired risk scores before and after the addition of Physical Activity (PA) measurements ; in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**



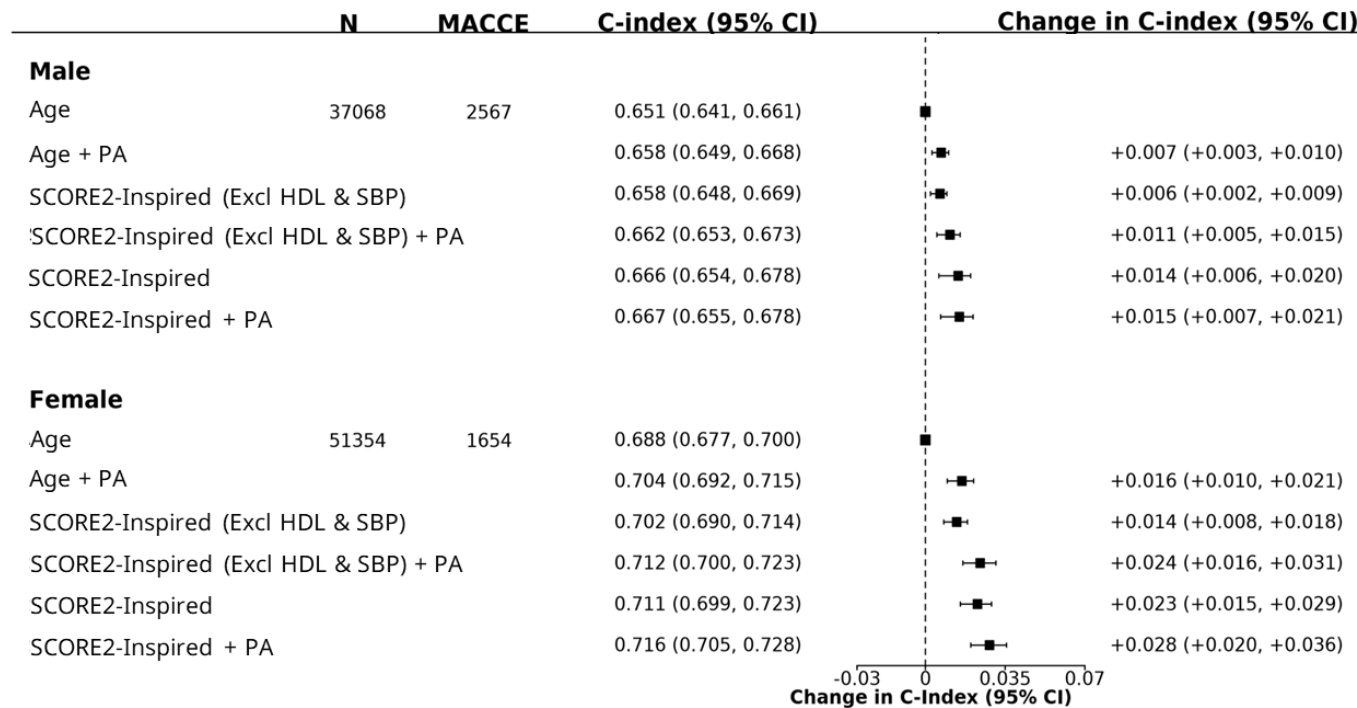
*Abbreviations: CI = confidence intervals; PA = Physical activity; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score.*

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

$$\begin{aligned}
\text{Age PA fractional polynomials (male)} &= \left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10}; \\
\text{SCORE2-Inspired (Excl HDL \& SBP) PA fractional polynomials (male)} &= \left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^1\right) \\
\text{SCORE2-Inspired PA fractional polynomials (male)} &= \left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right) \\
\text{Age PA fractional polynomials (female)} &= \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right); \\
\text{SCORE2-Inspired (Excl HDL \& SBP) PA fractional polynomials (female)} &= \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA}^{0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}}{10} \\
\text{SCORE2-Inspired PA fractional polynomials (female)} &= \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)
\end{aligned}$$

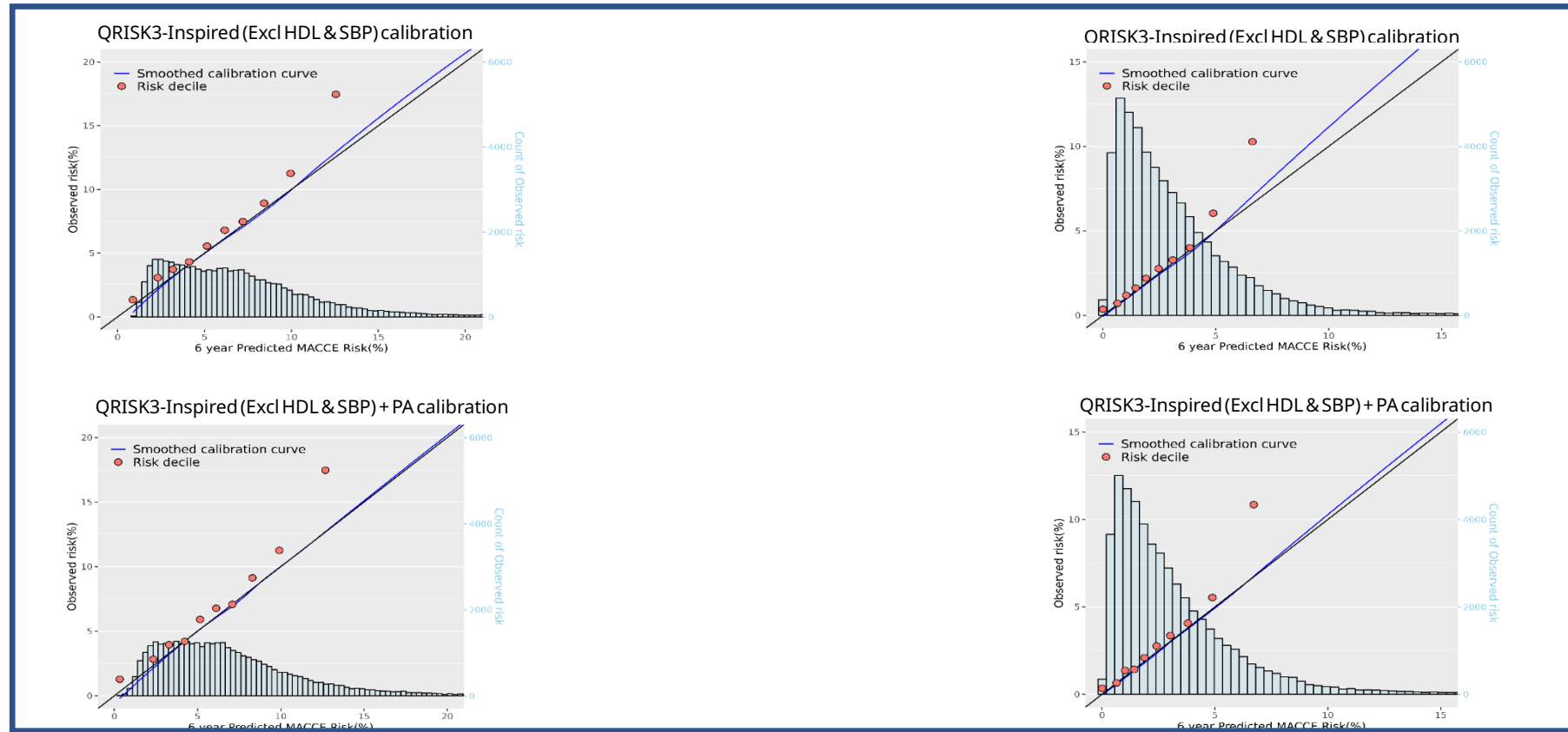
**Supplementary Figure 24: Optimism-adjusted Harrell's C-index for Age, SCORE2-Inspired (excluding HDL and SBP), and SCORE2-Inspired risk scores (including HDL and SBP from primary care records) before and after the addition of Physical Activity (PA) measurements. Analysis includes 37,068 males and 51,354 females from the UK Biobank with accelerometer data (2013–2015). After 6 years, 2,571 males (6.9%) and 1,656 females (3.2%) developed incident MACCE.**



Abbreviations: CI = confidence intervals; PA = Physical activity; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score. ; **SCORE2-Inspired** = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio **Physical activity (PA)**: Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB) ; **Age PA fractional polynomials (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10}$  ; **SCORE2-Inspired PA fractional polynomials (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right)$  ; **Age PA fractional polynomials (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} +$

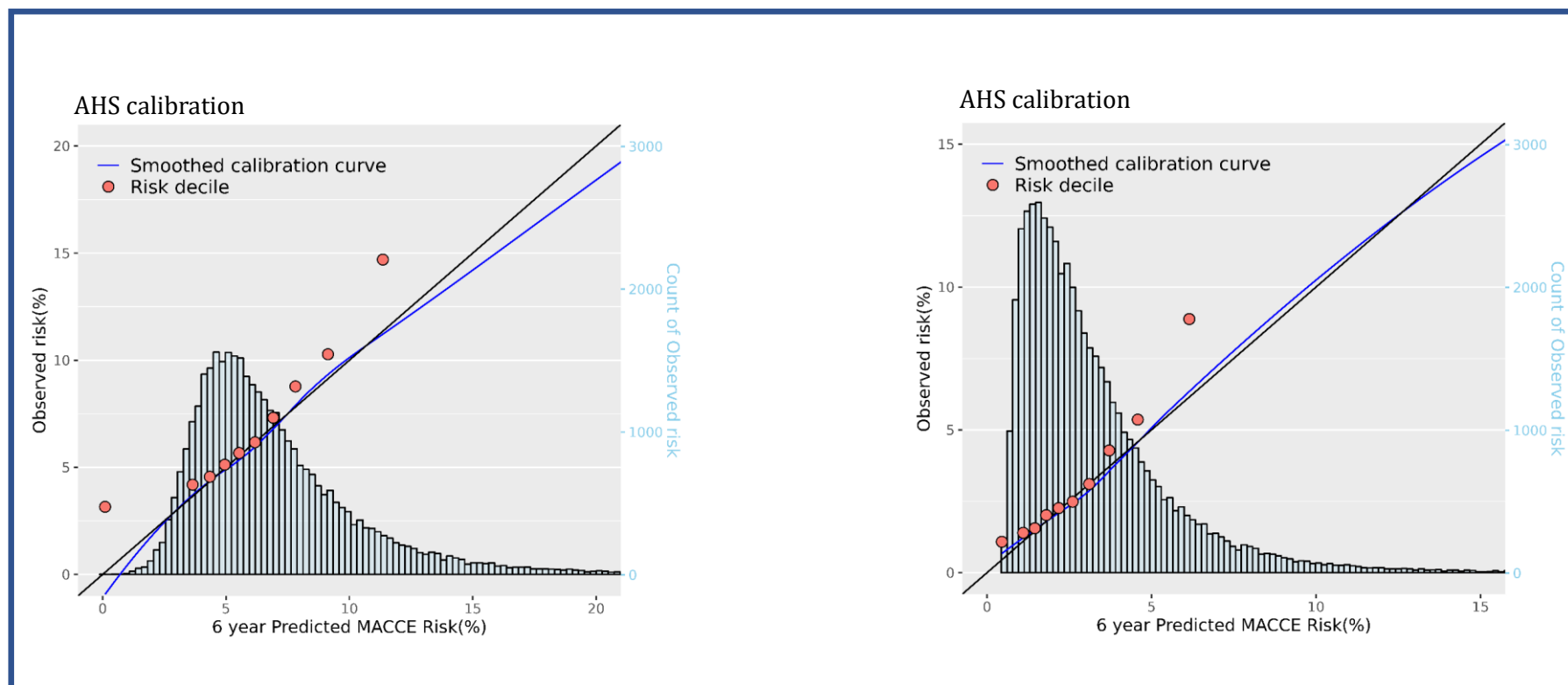


**Supplementary figure 25: Smoothed calibration curve for QRISK3-Inspired risk scores (excluding High-density lipoprotein and Systolic blood pressure) before and after the addition of physical activity (PA) risk scores consisting of overall step count, overall activity, and hours spent in sedentary behaviour, light PA and moderate/vigorous PA.**



Analysis includes 37,068 males and 51,354 females from the UK Biobank with accelerometer data (2013–2015). After 6 years, 2,571 males (6.9%) and 1,656 females (3.2%) developed incident MACCE. The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. ; **QRISK3-Inspired**: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1+Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment; **Fractional polynomials**: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; **Physical activity (PA)**: Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB); **PA fractional polynomial (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$ ; **PA fractional polynomial (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$

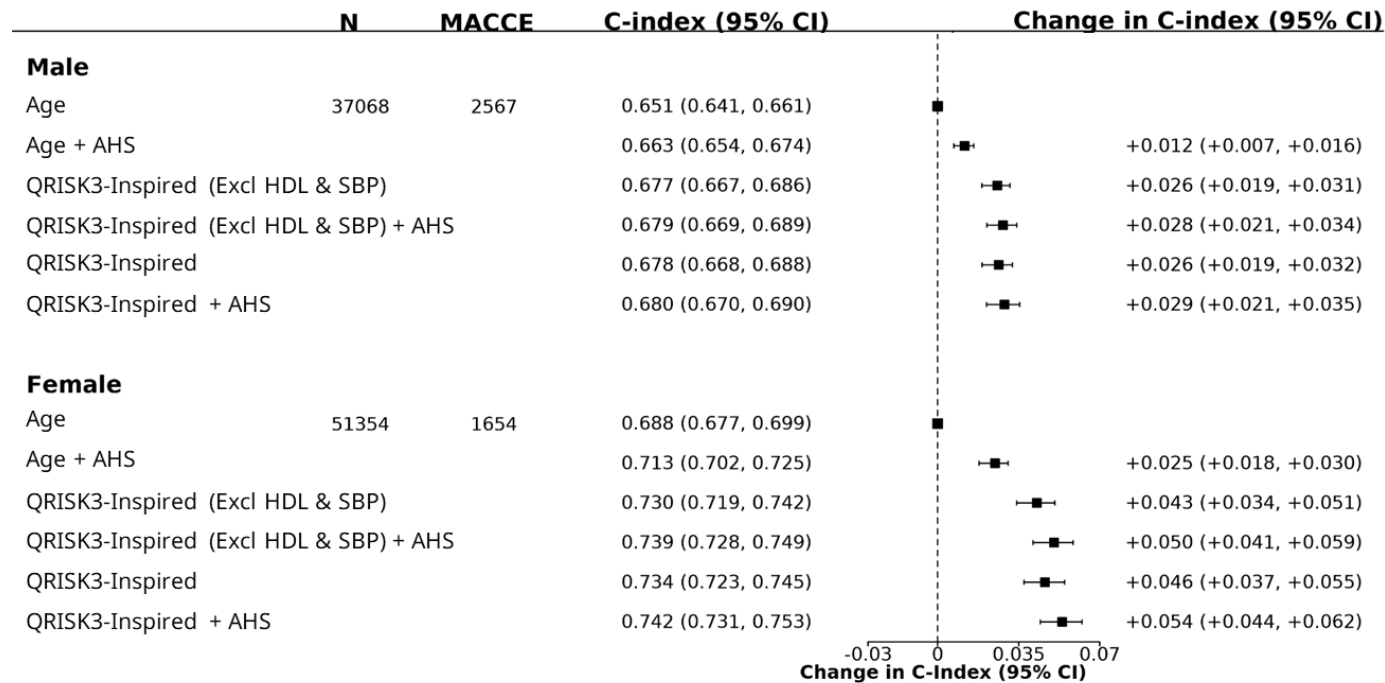
**Supplementary figure 26: Smoothed calibration curve for Activity health scores (AHS) and 6 Year MACCE risk predictions.**



Analysis includes 37,068 males and 51,354 females from the UK Biobank with accelerometer data (2013–2015). After 6 years, 2,571 males (6.9%) and 1,656 females (3.2%) developed incident MACCE.

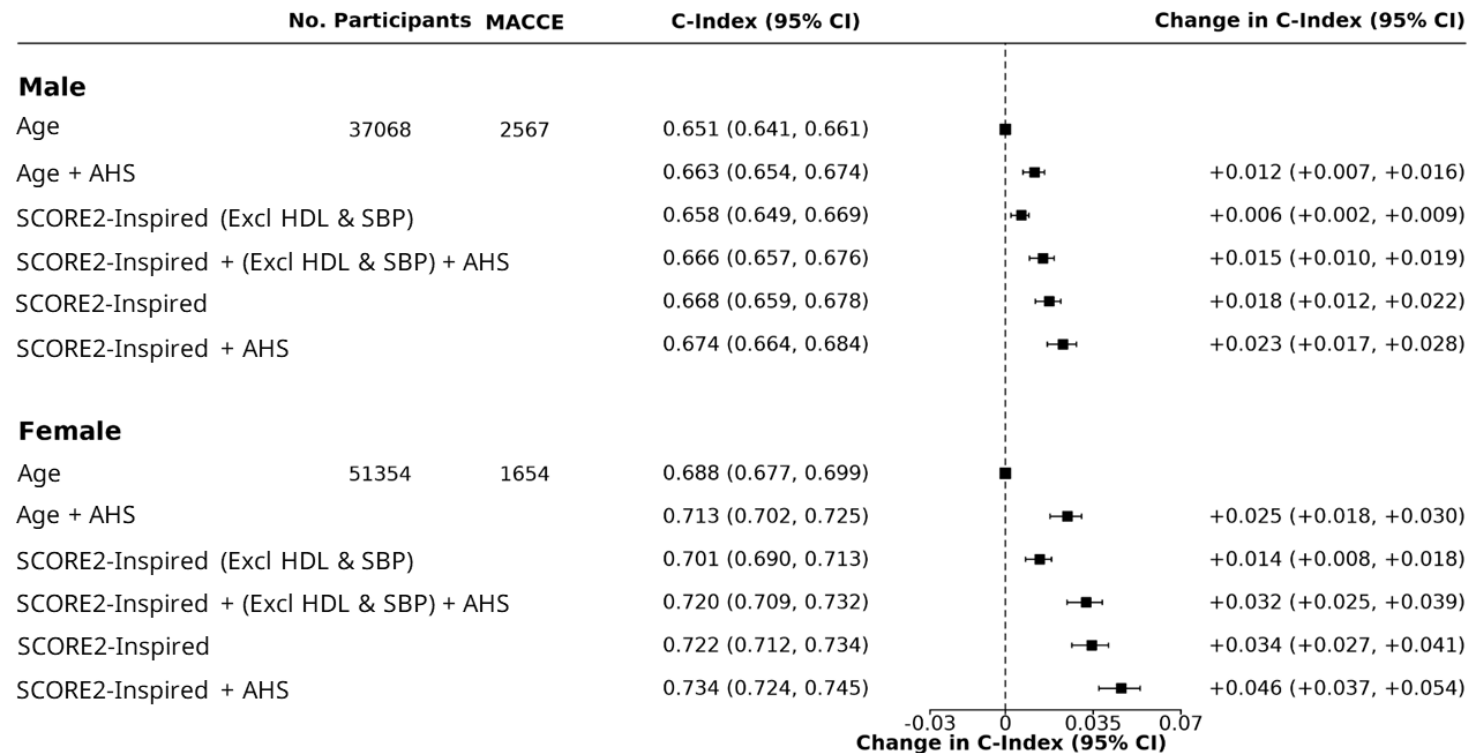
The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist worn accelerometry, validated via 5x10 nested cross fold validation (Supplementary methods section 1.2). 6-year MACCE risk scores were subsequently derived by fitting Cox proportional hazard models on an aggregated dataset of out of fold AHS predictions. AHS fractional polynomial (male) =  $(AHS/0.1)^{-2} + (AHS/0.1)^2$ ; AHS fractional polynomial (female) =  $(AHS/0.1)$  ; Baseline survival estimates were obtained via Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0

**Supplementary Figure 27: Optimism adjusted Harrell's C-index for Age, Age + AHS, QRISK3-Inspired (excluding High-density lipoprotein and Systolic blood pressure) and QRISK3-Inspired risk scores, derived using blood measurements obtained from primary care data, following the addition of accelerometer derived Activity Health Scores (AHS) in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**



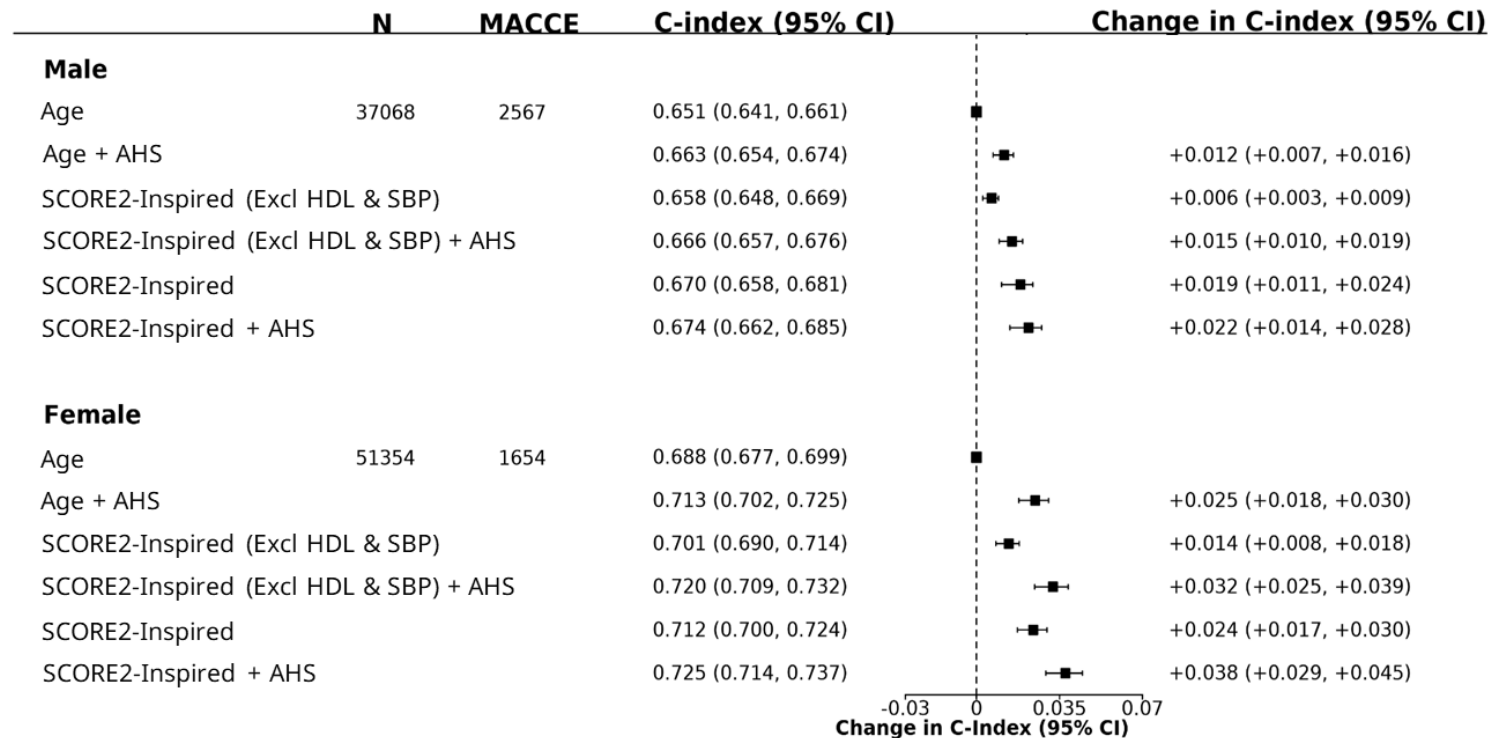
Abbreviations: CI = confidence intervals; AHS = Activity Health Score; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score. QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP 1 + Age FP 2 X BMI FP 2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter. Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} \times (AHS/0.1)$ ; QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + (AHS/0.1)$

**Supplementary Figure 28 Optimism adjusted Harrell's C-index for risk scores derived from Age, Age + Activity Health Scores (AHS) and SCORE2-Inspired (excluding High-density lipoprotein and Systolic blood pressure) extended with AHS; and complete SCORE2-Inspired risk scores extend by AHS; in 37,068 males and 51,354 females from the UK Biobank with Accelerometer recordings from 2013-2015 After 6 years of follow-up 2,571 (6.9%) males and 1,656 (3.2%) females were diagnosed with incident MACCE.**



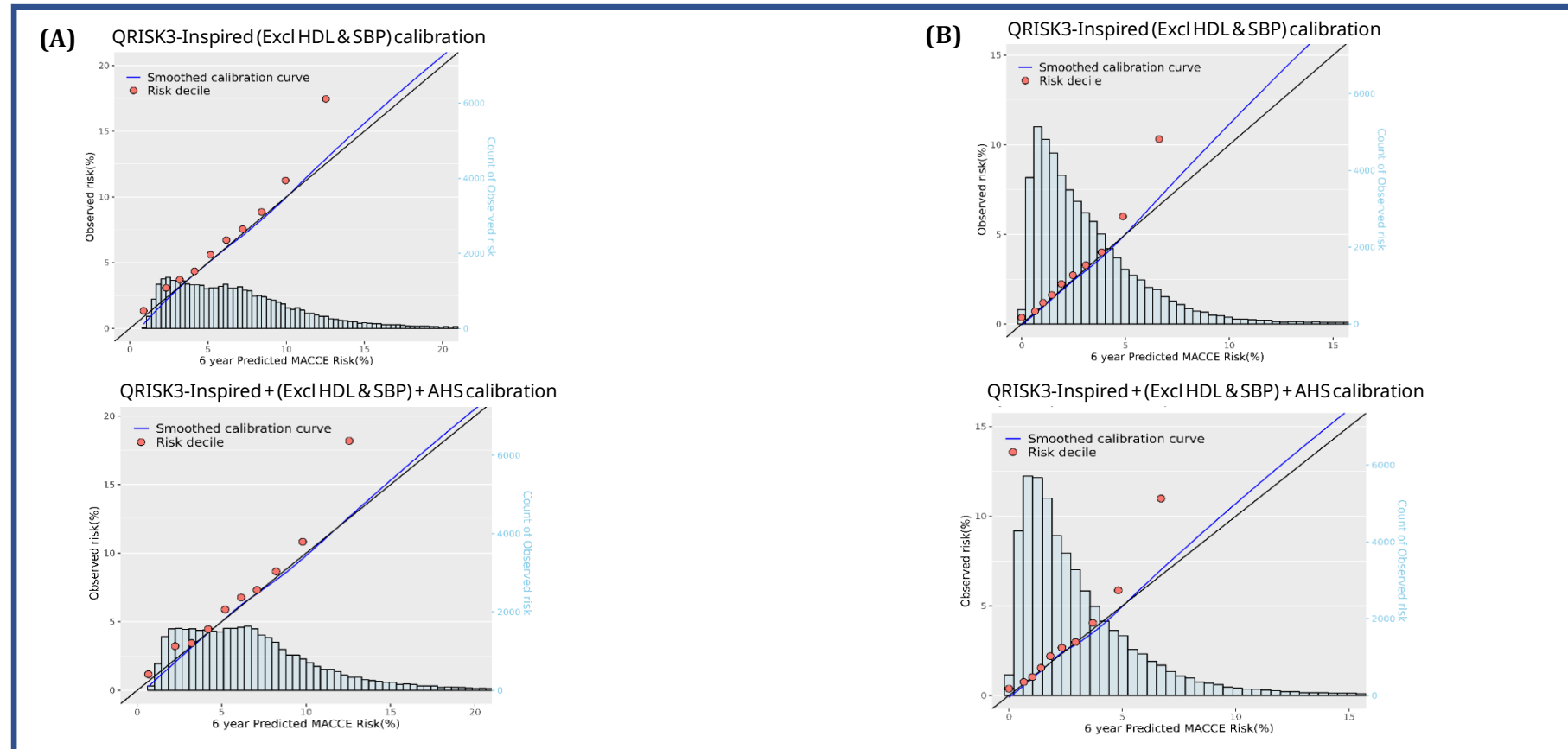
Abbreviations: CI = confidence intervals; AHS = Activity Health Score; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score. SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + ((AHS/0.1)^3 \times \log(AHS/0.1))$ ; SCORE2-Inspired AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + (AHS/0.1)$ .

**Supplementary Figure 29: Optimism-adjusted Harrell's C-index for risk scores based on Age, Age + Activity Health Scores (AHS), SCORE2-Inspired (excluding HDL and SBP from primary care records) extended with AHS, and complete SCORE2-Inspired risk scores (including HDL and SBP from primary care records) extended with AHS. Analysis includes 37,068 males and 51,354 females from the UK Biobank with accelerometer data (2013–2015). After 6 years, 2,571 males (6.9%) and 1,656 females (3.2%) developed incident MACCE.**



Abbreviations: CI = confidence intervals; AHS = Activity Health Score; HDL = High-density lipoprotein; SBP = Systolic blood pressure. Squares represent change in C-index compared to Age and horizontal lines are 95% confidence intervals generated using 1,000 bootstrap samples. 95 % CIs were derived via bootstrapping for 1000 iterations: significance threshold = 0.05. Change in C-index was calculated as the 2.5% and 97.5% percentiles of the delta between 1000 optimism-adjusted bootstraps between Age and each risk score. SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + (AHS/0.1)$ ; Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + (AHS/0.1)^3 \times \log(AHS/0.1)$ ; SCORE2-Inspired AHS fractional polynomial (female) =  $(AHS/0.1)^2$ .

**Supplementary figure 30: Smoothed calibration curve for QRISK3 (excluding High-density lipoprotein and Systolic blood pressure) before and after the addition of Deep learning Derived Activity Health Scores (AHS) in (A) Males and (B) Females.**



Analysis includes 37,068 males and 51,354 females from the UK Biobank with accelerometer data (2013–2015). After 6 years, 2,571 males (6.9%) and 1,656 females (3.2%) developed incident MACCE. The red dots show the mean predicted risk vs observed risk at each risk tenth. The black line shows perfect calibration, where the predicted risk perfectly matches the observed risk. Observed risk was estimated using pseudo probabilities obtained via a jackknife approach.; QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment; Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1$

$(\text{males}) = (\text{BMI}/10)^{-2}$ ,  $\text{BMI FP 2 (males)} = (\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$ ,  $\text{Age FP 1 (Females)} = \text{age}/10^{-2}$ ,  $\text{Age FP 2 (Females)} = \text{age}/10$ ,  $\text{BMI FP 1 (Females)} = (\text{BMI}/10)^{-2}$ ,  $\text{BMI FP 2 (Females)} =$   
 $(\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$ . Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous  
 wrist-worn accelerometry (Supplementary methods section 1.2). QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(\text{AHS}/0.1)^3$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional  
 polynomial (female) =  $(\text{AHS}/0.1)^{0.5} \times (\text{AHS}/0.1)$

## Supplementary Tables

### Supplementary Table 1 ICD-10 codes defining Major Adverse Cardiovascular and Cerebrovascular Events

| ICD-10 Code | Condition                                                                               |
|-------------|-----------------------------------------------------------------------------------------|
| I20         | Angina pectoris                                                                         |
| I21         | Acute myocardial infarction                                                             |
| I210        | Acute transmural myocardial infarction of anterior wall                                 |
| I211        | Acute transmural myocardial infarction of inferior wall                                 |
| I212        | Acute transmural myocardial infarction of other sites                                   |
| I213        | Acute transmural myocardial infarction of unspecified site                              |
| I214        | Acute subendocardial myocardial infarction                                              |
| I219        | Acute myocardial infarction, unspecified                                                |
| I22         | Subsequent myocardial infarction                                                        |
| I220        | Subsequent myocardial infarction of anterior wall                                       |
| I221        | Subsequent myocardial infarction of inferior wall                                       |
| I228        | Subsequent myocardial infarction of other sites                                         |
| I229        | Subsequent myocardial infarction of unspecified site                                    |
| I23         | Certain current complications following acute myocardial infarction                     |
| I230        | Haemopericardium as current complication following acute myocardial infarction          |
| I231        | Atrial septal defect as current complication following acute myocardial infarction      |
| I232        | Ventricular septal defect as current complication following acute myocardial infarction |



|       |                                                                                                                        |
|-------|------------------------------------------------------------------------------------------------------------------------|
| I233  | Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction         |
| I234  | Rupture of chordae tendineae as current complication following acute myocardial infarction                             |
| I235  | Rupture of papillary muscle as current complication following acute myocardial infarction                              |
| I236  | Thrombosis of atrium, auricular appendage and ventricle as current complications following acute myocardial infarction |
| I238  | Thrombosis of atrium, auricular appendage and ventricle as current complications following acute myocardial infarction |
| I50   | Heart failure                                                                                                          |
| I50-0 | Congestive heart failure                                                                                               |
| I50-1 | Left ventricular failure                                                                                               |
| I50-9 | Heart failure, unspecified                                                                                             |
| I472  | Ventricular tachycardia                                                                                                |

|                                                      |                                              |
|------------------------------------------------------|----------------------------------------------|
| I490                                                 | Ventricular fibrillation and flutter         |
| I46-0                                                | Cardiac arrest with successful resuscitation |
| I461                                                 | Sudden cardiac death, so described           |
| I469                                                 | Cardiac arrest, unspecified                  |
| I470                                                 | Re-entry ventricular arrhythmia              |
| Cerebral infarction                                  | I63                                          |
| Stroke not specified as<br>haemorrhage or infarction | I64                                          |
| Transient ischaemic attack and<br>related syndromes  | G45                                          |
| ICD-9 codes                                          | Condition                                    |
| 4109                                                 | Acute myocardial infarction                  |
| 4280                                                 | Congestive heart failure                     |
| 4281                                                 | Left heart failure                           |
| 4289                                                 | Heart failure, unspecified                   |

**Supplementary Table 2 Primary care codes for Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)**

|    | <b>Read 2 code</b> | <b>Read 3 code</b> | <b>Term 3 code</b> | <b>Read 2 description</b>                                  | <b>read 3 description</b>                                     |
|----|--------------------|--------------------|--------------------|------------------------------------------------------------|---------------------------------------------------------------|
| 0  | G3...              | XE2uV              | Y201T              | Ischaemic heart disease                                    | Ischaemic heart disease                                       |
| 1  | G30..              | XE0UUh             | Y202N              | Acute myocardial infarction                                | Acute myocardial infarction                                   |
| 2  | G300.              | G300.              | Y202d              | Acute anterolateral infarction                             | Acute anterolateral myocardial infarction                     |
| 3  | G301.              | G301.              | Y202Q              | Other specified anterior myocardial infarction             | Other specified anterior myocardial infarction                |
| 4  | G3010              | G3010              | Y202V              | Acute anteroapical infarction                              | Acute anteroapical infarction                                 |
| 5  | G3011              | G3011              | Y202a              | Acute anteroseptal infarction                              | Acute anteroseptal myocardial infarction                      |
| 6  | G301z              | G301z              | Y202R              | Anterior myocardial infarction NOS                         | Anterior myocardial infarction NOS                            |
| 7  | G302.              | G302.              | Y202I              | Acute inferolateral infarction                             | Acute inferolateral myocardial infarction                     |
| 8  | G303.              | G303.              | Y202h              | Acute inferoposterior infarction                           | Acute inferoposterior infarction                              |
| 9  | G304.              | G304.              | Y202x              | Posterior myocardial infarction NOS                        | Posterior myocardial infarction NOS                           |
| 10 | G305.              | G305.              | Y202p              | Lateral myocardial infarction NOS                          | Lateral myocardial infarction NOS                             |
| 11 | G306.              | G306.              | Y202w              | True posterior myocardial infarction                       | True posterior myocardial infarction                          |
| 12 | G307.              | G307.              | Y202W              | Acute subendocardial infarction                            | Acute subendocardial infarction                               |
| 13 | G3070              | XaAzi              | YaaA4              | Acute non-Q wave infarction                                | Acute non-Q wave infarction                                   |
| 14 | G3071              | XalwY              | Yali5              | Acute non-ST segment elevation myocardial infarction       | Acute non-ST segment elevation myocardial infarction          |
| 15 | G308.              | G308.              | Y202i              | Inferior myocardial infarction NOS                         | Inferior myocardial infarction NOS                            |
| 16 | G309.              | XaAC3              | Yah3m              | Acute Q-wave infarct                                       | Acute Q-wave infarct                                          |
| 17 | G30A.              | X202q              | YabUP              | Mural thrombosis                                           | Mural thrombosis                                              |
| 18 | G30B.              | XaJX0              | YambR              | Acute posterolateral myocardial infarction                 | Acute posterolateral myocardial infarction                    |
| 19 | G30X.              | Gyu34              | YMAH8              | Acute transmural myocardial infarction of unspecified site | [X]Acute transmural myocardial infarction of unspecified site |
| 20 | G30X0              | XalwM              | Yalhn              | Acute ST segment elevation myocardial infarction           | Acute ST segment elevation myocardial infarction              |

|    |         |       |       |                                                  |                                                   |
|----|---------|-------|-------|--------------------------------------------------|---------------------------------------------------|
| 21 | G30y.   | G30y. | Y202S | Other acute myocardial infarction                | Other acute myocardial infarction                 |
| 22 | G30y0   | G30y0 | Y202X | Acute atrial infarction                          | Acute atrial infarction                           |
| 23 | G30y1   | G30y1 | Y202Y | Acute papillary muscle infarction                | Acute papillary muscle infarction                 |
| 24 | G30y2   | G30y2 | Y202Z | Acute septal infarction                          | Acute septal infarction                           |
| 25 | G30yz   | G30yz | Y202T | Other acute myocardial infarction NOS            | Other acute myocardial infarction NOS             |
| 26 | G30z.   | G30z. | Y202U | Acute myocardial infarction NOS                  | Acute myocardial infarction NOS                   |
| 27 | G30..-1 | X200E | Y202H | Acute myocardial infarction                      | Myocardial infarction                             |
| 28 | G30..-2 | X200E | Ya0vv | Acute myocardial infarction                      | Coronary thrombosis                               |
| 29 | G30..-3 | X200e | Y203J | Acute myocardial infarction                      | Cardiac rupture after acute myocardial infarction |
| 30 | G30..-4 | X200E | Ya0rZ | Acute myocardial infarction                      | Heart attack                                      |
| 31 | G30..-5 | XE0Uh | Y202N | Acute myocardial infarction                      | Acute myocardial infarction                       |
| 32 | G30..-6 | X203v | YM1kK | Acute myocardial infarction                      | Thrombosis - coronary                             |
| 33 | G30..-7 | X200a | Y2034 | Acute myocardial infarction                      | Silent myocardial infarction                      |
| 34 | G31..   | G31.. | Y201b | Other acute and subacute ischaemic heart disease | Other acute and subacute ischaemic heart disease  |
| 35 | G310.   | G310. | Y20CX | Postmyocardial infarction syndrome               | Post-myocardial infarction syndrome               |
| 36 | G311.   | XE0Ui | Y2021 | Preinfarction syndrome                           | Worsening angina                                  |
| 37 | G311.   | XE0Ui | Y2021 | Preinfarction syndrome                           | Worsening angina                                  |
| 38 | G311.-1 | XE0Ui | Y2023 | Preinfarction syndrome                           | Crescendo angina                                  |
| 39 | G311.-2 | XE0Ui | Y2024 | Preinfarction syndrome                           | Impending infarction                              |
| 40 | G311.-3 | X2009 | Y201z | Preinfarction syndrome                           | Unstable angina                                   |
| 41 | G311.-4 | X2007 | Y201u | Preinfarction syndrome                           | Angina at rest                                    |
| 42 | G3110   | G3110 | Y2035 | Myocardial infarction aborted                    | Aborted myocardial infarction                     |

|    |          |       |       |                                                            |                                                            |
|----|----------|-------|-------|------------------------------------------------------------|------------------------------------------------------------|
| 43 | G3110-1  | G3110 | Y2035 | Myocardial infarction aborted                              | Aborted myocardial infarction                              |
| 44 | G3111    | X2009 | Y201z | Unstable angina                                            | Unstable angina                                            |
| 45 | G3112    | X2007 | Y201u | Angina at rest                                             | Angina at rest                                             |
| 46 | G3113    | XaFsG | Yah38 | Refractory angina                                          | Refractory angina                                          |
| 47 | G3114    | XE0Ui | Y2021 | Worsening angina                                           | Worsening angina                                           |
| 48 | G3115    | XaINF | YakmH | Acute coronary syndrome                                    | Acute coronary syndrome                                    |
| 49 | G311z    | G311z | Y2026 | Preinfarction syndrome NOS                                 | Preinfarction syndrome NOS                                 |
| 50 | G312.    | G312. | YMAkD | Coronary thrombosis not resulting in myocardial infarction | Coronary thrombosis not resulting in myocardial infarction |
| 51 | G31y.    | G31.. | Y201b | Other acute and subacute ischaemic heart disease           | Other acute and subacute ischaemic heart disease           |
| 52 | G31y0    | G31y0 | Y2022 | Acute coronary insufficiency                               | Acute coronary insufficiency                               |
| 53 | G31y1    | G31y1 | Y201d | Microinfarction of heart                                   | Microinfarction of heart                                   |
| 54 | G31y2    | G31y2 | Y202F | Subendocardial ischaemia                                   | Subendocardial ischaemia                                   |
| 55 | G31y3    | XaFsH | Yah39 | Transient myocardial ischaemia                             | Transient myocardial ischaemia                             |
| 56 | G31yz    | G31yz | Y201e | Other acute and subacute ischaemic heart disease NOS       | Other acute and subacute ischaemic heart disease NOS       |
| 57 | G32..    | XE2aA | Y202y | Old myocardial infarction                                  | Old myocardial infarction                                  |
| 58 | G32...-1 | XE2aA | Y202z | Old myocardial infarction                                  | Healed myocardial infarction                               |
| 59 | G32...-2 | XaQk7 | YatIS | Old myocardial infarction                                  | History of myocardial infarction                           |
| 60 | G33..    | G33.. | Y201n | Angina pectoris                                            | Angina pectoris                                            |
| 61 | G330.    | G330. | Y201w | Angina decubitus                                           | Angina decubitus                                           |
| 62 | G3300    | G3300 | Y201v | Nocturnal angina                                           | Nocturnal angina                                           |
| 63 | G330z    | G330z | Y201x | Angina decubitus NOS                                       | Angina decubitus NOS                                       |

|    |         |       |       |                                        |                                        |
|----|---------|-------|-------|----------------------------------------|----------------------------------------|
| 64 | G331.   | G331. | Y202A | Prinzmetal's angina                    | Prinzmetal's angina                    |
| 65 | G331.-1 | G331. | Y202A | Prinzmetal's angina                    | Prinzmetal's angina                    |
| 66 | G332.   | X200B | Y2028 | Coronary artery spasm                  | Coronary artery spasm                  |
| 67 | G33z.   | G33z. | Y201p | Angina pectoris NOS                    | Angina pectoris NOS                    |
| 68 | G33z0   | G33z0 | Y201q | Status anginosus                       | Status anginosus                       |
| 69 | G33z1   | G33z1 | Y201r | Stenocardia                            | Stenocardia                            |
| 70 | G33z2   | G33z2 | Y201s | Syncope anginosa                       | Syncope anginosa                       |
| 71 | G33z3   | Xa7nH | YaYAM | Angina on effort                       | Angina on effort                       |
| 72 | G33z4   | Ua1eH | YMFz7 | Ischaemic chest pain                   | Ischaemic chest pain                   |
| 73 | G33z5   | XaEXt | Yaf3g | Post infarct angina                    | Post infarct angina                    |
| 74 | G33z6   | X200A | Y2020 | New onset angina                       | New onset angina                       |
| 75 | G33z7   | X2008 | Y201y | Stable angina                          | Stable angina                          |
| 76 | G33zz   | G33z. | Y201p | Angina pectoris NOS                    | Angina pectoris NOS                    |
| 77 | G34..   | G34.. | Y201f | Other chronic ischaemic heart disease  | Other chronic ischaemic heart disease  |
| 78 | G340.   | XM0rN | Y201U | Coronary atherosclerosis               | Coronary atherosclerosis               |
| 79 | G3400   | G3400 | YaYAN | Single coronary vessel disease         | Single coronary vessel disease         |
| 80 | G3401   | G3401 | YaYAO | Double coronary vessel disease         | Double coronary vessel disease         |
| 81 | G340.-1 | X2006 | Y201g | Coronary atherosclerosis               | Triple vessel disease of the heart     |
| 82 | G340.-2 | XE2uV | Y201Z | Coronary atherosclerosis               | Coronary artery disease                |
| 82 | G340.-2 | XE2uV | Y201Z | Coronary atherosclerosis               | Coronary artery disease                |
| 83 | G342.   | G70.. | YMAjY | Atherosclerotic cardiovascular disease | Atherosclerotic cardiovascular disease |
| 84 | G343.   | G343. | YMAkP | Ischaemic cardiomyopathy               | Ischaemic cardiomyopathy               |

|     |       |       |       |                                                                                                                |                                                                                                                |
|-----|-------|-------|-------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| 85  | G344. | X200D | Y202G | Silent myocardial ischaemia                                                                                    | Silent myocardial ischaemia                                                                                    |
| 86  | G34y. | G34y. | Y201h | Other specified chronic ischaemic heart disease                                                                | Other specified chronic ischaemic heart disease                                                                |
| 87  | G34y0 | G34y1 | Y202E | Chronic coronary insufficiency                                                                                 | Chronic coronary insufficiency                                                                                 |
| 88  | G34y1 | G34y1 | Y202D | Chronic myocardial ischaemia                                                                                   | Chronic myocardial ischaemia                                                                                   |
| 89  | G34yz | G34yz | Y201i | Other specified chronic ischaemic heart disease NOS                                                            | Other specified chronic ischaemic heart disease NOS                                                            |
| 90  | G34z. | G34z. | Y201j | Other chronic ischaemic heart disease NOS                                                                      | Other chronic ischaemic heart disease NOS                                                                      |
| 91  | G34z0 | XaG1Q | YahGt | Asymptomatic coronary heart disease                                                                            | Asymptomatic coronary heart disease                                                                            |
| 92  | G35.. | G35.. | YMAk7 | Subsequent myocardial infarction                                                                               | Subsequent myocardial infarction                                                                               |
| 93  | G350. | G350. | YMAk8 | Subsequent myocardial infarction of anterior wall                                                              | Subsequent myocardial infarction of anterior wall                                                              |
| 94  | G351. | G351. | YMAk9 | Subsequent myocardial infarction of inferior wall                                                              | Subsequent myocardial infarction of inferior wall                                                              |
| 95  | G353. | G353. | Ya3p0 | Subsequent myocardial infarction of other sites                                                                | Subsequent myocardial infarction of other sites                                                                |
| 96  | G35X. | Gyu36 | YMAHA | Subsequent myocardial infarction of unspecified site                                                           | [X]Subsequent myocardial infarction of unspecified site                                                        |
| 97  | G36.. | G36.. | YMAkA | Certain current complications following acute myocardial infarction                                            | Certain current complications following acute myocardial infarction                                            |
| 98  | G360. | G360. | YMAkB | Haemopericardium as current complication following acute myocardial infarction                                 | Haemopericardium as current complication following acute myocardial infarction                                 |
| 99  | G361. | G361. | YMAkC | Atrial septal defect as current complication following acute myocardial infarction                             | Atrial septal defect as current complication following acute myocardial infarction                             |
| 100 | G362. | X200d | YMAkE | Ventricular septal defect as current complication following acute myocardial infarction                        | Ventricular septal defect as current complication following acute myocardial infarction                        |
| 101 | G363. | G363. | YMAkF | Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction | Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction |
| 102 | G364. | G364. | YMAzL | Rupture of chordae tendinae as current complication following acute myocardial infarction                      | Rupture of chordae tendinae as current complication following acute myocardial infarction                      |

|     |         |       |       |                                                                                                                           |                                                                                                                           |
|-----|---------|-------|-------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| 103 | G365.   | G365. | YMAzM | Rupture of papillary muscle as current complication following acute myocardial infarction                                 | Rupture of papillary muscle as current complication following acute myocardial infarction                                 |
| 104 | G366.   | G366. | YMAkT | "Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction" | "Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction" |
| 105 | G38..   | XaD2b | Yad42 | Postoperative myocardial infarction                                                                                       | Postoperative myocardial infarction                                                                                       |
| 106 | G380.   | XaD2d | Yad46 | Postoperative transmural myocardial infarction of anterior wall                                                           | Postoperative transmural myocardial infarction of anterior wall                                                           |
| 107 | G381.   | XaD2e | Yad47 | Postoperative transmural myocardial infarction of inferior wall                                                           | Postoperative transmural myocardial infarction of inferior wall                                                           |
| 108 | G382.   | XaD2f | Yad48 | Postoperative transmural myocardial infarction of other sites                                                             | Postoperative transmural myocardial infarction of other sites                                                             |
| 109 | G383.   | XaD2g | Yad49 | Postoperative transmural myocardial infarction of unspecified site                                                        | Postoperative transmural myocardial infarction of unspecified site                                                        |
| 110 | G384.   | XaD2h | Yad4A | Postoperative subendocardial myocardial infarction                                                                        | Postoperative subendocardial myocardial infarction                                                                        |
| 111 | G38z.   | XaD2i | Yad4B | "Postoperative myocardial infarction, unspecified"                                                                        | "Postoperative myocardial infarction, unspecified"                                                                        |
| 112 | G3y..   | G3y.. | Y201k | Other specified ischaemic heart disease                                                                                   | Other specified ischaemic heart disease                                                                                   |
| 113 | G3z..   | G3z.. | Y201l | Ischaemic heart disease NOS                                                                                               | Ischaemic heart disease NOS                                                                                               |
| 114 | G3...-1 | XE2uV | Y201T | Ischaemic heart disease                                                                                                   | Ischaemic heart disease                                                                                                   |
| 115 | G3...-2 | XE2uV | Y201Y | Ischaemic heart disease                                                                                                   | Atherosclerotic heart disease                                                                                             |
| 116 | G3...-3 | XE2uV | Y201W | Ischaemic heart disease                                                                                                   | IHD - Ischaemic heart disease                                                                                             |
| 117 | G501.   | X201u | YadYu | Post infarction pericarditis                                                                                              | Post-infarction pericarditis                                                                                              |
| 118 | G64..   | XE0VI | Y20FP | Cerebral arterial occlusion                                                                                               | Cerebral arterial occlusion                                                                                               |
| 119 | G640.   | G640. | Y00cj | Cerebral thrombosis                                                                                                       | Cerebral thrombosis                                                                                                       |
| 120 | G6400   | G6400 | YMAiF | Cerebral infarction due to thrombosis of cerebral arteries                                                                | Cerebral infarction due to thrombosis of cerebral arteries                                                                |



|     |         |       |       |                                                          |                                                                 |
|-----|---------|-------|-------|----------------------------------------------------------|-----------------------------------------------------------------|
| 121 | G641.   | G641. | Y20G2 | Cerebral embolism                                        | Cerebral embolism                                               |
| 122 | G6410   | G6410 | YMAiG | Cerebral infarction due to embolism of cerebral arteries | Cerebral infarction due to embolism of cerebral arteries        |
| 123 | G641.-1 | G641. | Y20G1 | Cerebral embolism                                        | Cerebral embolus                                                |
| 124 | G64z.   | XE0VJ | Y00cn | Cerebral infarction NOS                                  | Cerebral infarction NOS                                         |
| 125 | G64z0   | Xa00K | Ya0re | Brainstem infarction                                     | Brainstem infarction                                            |
| 126 | G64z1   | Xa00M | Ya0rg | Wallenberg syndrome                                      | Wallenberg syndrome                                             |
| 127 | G64z1-1 | Xa00M | Ya3VD | Wallenberg syndrome                                      | Lateral medullary syndrome                                      |
| 128 | G64z2   | XaBEC | YaaWG | Left sided cerebral infarction                           | Left sided cerebral infarction                                  |
| 129 | G64z3   | XaBED | YaaWH | Right sided cerebral infarction                          | Right sided cerebral infarction                                 |
| 130 | G64z4   | XaJgQ | YamIC | Infarction of basal ganglia                              | Infarction of basal ganglia                                     |
| 131 | G64z.-1 | X00D9 | Y00d0 | Cerebral infarction NOS                                  | Brainstem infarction NOS                                        |
| 132 | G64z.-2 | Xa00J | Ya0rd | Cerebral infarction NOS                                  | Cerebellar infarction                                           |
| 133 | G64.-1  | X00D3 | Y00co | Cerebral arterial occlusion                              | CVA - cerebrovascular accident due to cerebral artery occlusion |
| 134 | G64.-2  | Xa0kZ | Y00ci | Cerebral arterial occlusion                              | Cerebral infarction                                             |
| 135 | G64.-3  | G640. | Y00cj | Cerebral arterial occlusion                              | Cerebral thrombosis                                             |
| 136 | G65..   | XE0VK | Y00ds | Transient cerebral ischaemia                             | Transient cerebral ischaemia                                    |
| 137 | G650.   | G650. | Y00e3 | Basilar artery syndrome                                  | Basilar artery syndrome                                         |
| 138 | G650.-1 | G650. | Y00e4 | Basilar artery syndrome                                  | Insufficiency - basilar artery                                  |
| 139 | G652.   | G652. | Y00e6 | Subclavian steal syndrome                                | Subclavian steal syndrome                                       |
| 140 | G653.   | G653. | YMAiN | Carotid artery syndrome hemispheric                      | Carotid artery syndrome hemispheric                             |
| 141 | G654.   | G654. | YMAiQ | Multiple and bilateral precerebral artery syndromes      | Multiple and bilateral precerebral artery syndromes             |
| 142 | G656.   | X00DW | Y00e5 | Vertebrobasilar insufficiency                            | Vertebrobasilar insufficiency                                   |

|     |         |       |       |                                                                      |                                                                      |
|-----|---------|-------|-------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| 143 | G65y.   | G65y. | Y00dv | Other transient cerebral ischaemia                                   | Other transient cerebral ischaemia                                   |
| 144 | G65z.   | G65z. | Y00du | Transient cerebral ischaemia NOS                                     | Transient cerebral ischaemia NOS                                     |
| 145 | G65z1   | G65z1 | Y00cZ | Intermittent cerebral ischaemia                                      | Intermittent cerebral ischaemia                                      |
| 146 | G65zz   | G65z. | Y00du | Transient cerebral ischaemia NOS                                     | Transient cerebral ischaemia NOS                                     |
| 147 | G65..-1 | Xa00T | Ya0ry | Transient cerebral ischaemia                                         | Drop attack                                                          |
| 148 | G65..-2 | XE0VK | Y00dq | Transient cerebral ischaemia                                         | Transient ischaemic attack                                           |
| 149 | G65..-3 | X00DW | Y00e5 | Transient cerebral ischaemia                                         | Vertebrobasilar insufficiency                                        |
| 150 | G66..   | XE2aB | Y00ch | Stroke and cerebrovascular accident unspecified                      | Stroke and cerebrovascular accident unspecified                      |
| 151 | G667.   | G667. | YaYAW | Left sided CVA                                                       | Left sided CVA                                                       |
| 152 | G668.   | G668. | YaYAX | Right sided CVA                                                      | Right sided CVA                                                      |
| 153 | G66..-1 | XE2aB | Y00ch | Stroke and cerebrovascular accident unspecified                      | Stroke and cerebrovascular accident unspecified                      |
| 154 | G66..-2 | G66.. | YaeBs | Stroke and cerebrovascular accident unspecified                      | Stroke unspecified                                                   |
| 155 | G66..-3 | G66.. | YabW4 | Stroke and cerebrovascular accident unspecified                      | CVA - Cerebrovascular accident unspecified                           |
| 156 | Gyu34   | Gyu34 | YMAH8 | [X]Acute transmural myocardial infarction of unspecified site        | [X]Acute transmural myocardial infarction of unspecified site        |
| 157 | F4236   | F4236 | Y00dy | Amaurosis fugax                                                      | Amaurosis fugax                                                      |
| 158 | Fyu55   | Fyu55 | YMADV | [X]Other transient cerebral ischaemic attacks and related syndromes  | [X]Other transient cerebral ischaemic attacks and related syndromes  |
| 159 | G63y0   | G63y0 | YMAiD | Cerebral infarct due to thrombosis of precerebral arteries           | Cerebral infarct due to thrombosis of precerebral arteries           |
| 160 | G63y1   | G63y1 | YMAiE | Cerebral infarction due to embolism of precerebral arteries          | Cerebral infarction due to embolism of precerebral arteries          |
| 161 | G6760   | G6760 | YadUZ | "Cerebral infarction due to cerebral venous thrombosis, nonpyogenic" | "Cerebral infarction due to cerebral venous thrombosis, nonpyogenic" |

|     |        |       |       |                                                                                      |                                                                                         |
|-----|--------|-------|-------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 162 | G6W..  | Gyu6G | YMAIB | Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries | [X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries |
| 163 | G6X..  | Gyu63 | YMAHy | Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries    | [X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries    |
| 164 | Gyu63  | Gyu63 | YMAHy | [X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries | [X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries    |
| 165 | Gyu64  | Gyu64 | YMAHz | [X]Other cerebral infarction                                                         | [X]Other cerebral infarction                                                            |
| 166 | Gyu65  | Gyu65 | YMAI0 | [X]Occlusion and stenosis of other precerebral arteries                              | [X]Occlusion and stenosis of other precerebral arteries                                 |
| 167 | Gyu66  | Gyu66 | YMAI1 | [X]Occlusion and stenosis of other cerebral arteries                                 | [X]Occlusion and stenosis of other cerebral arteries                                    |
| 168 | ZV12D  | XaX16 | YatuJ | [V]Personal history of transient ischaemic attack                                    | [V]Personal history of transient ischaemic attack                                       |
| 169 | 14A6.  | 14A6. | Ya04n | H/0: Heart failure                                                                   | H/0: Heart failure                                                                      |
| 170 | G580.. | XEV8  | Y20Bq | Heart failure                                                                        | Heart failure                                                                           |

**Supplementary Table 3 Definition of Traditional risk factors included in QRISK3, within UK Biobank**

| Category                        | Risk factor                                | UKB data field      | Hospital episode statistics reported ICD-10 codes with date of event/visit | Hospital episode statistics reported ICD-9 codes with date of event/visit                                                                                                                                                                                                                    |
|---------------------------------|--------------------------------------------|---------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Demographics & socio economic   | Age                                        | 34,52               | -                                                                          | -                                                                                                                                                                                                                                                                                            |
|                                 | Sex                                        | 31                  | -                                                                          | -                                                                                                                                                                                                                                                                                            |
|                                 | Townsend deprivation index                 | 189                 |                                                                            |                                                                                                                                                                                                                                                                                              |
|                                 | Ethnicity                                  | 21000               | -                                                                          | -                                                                                                                                                                                                                                                                                            |
| Lifestyle                       | Smoker status                              | 20116               | -                                                                          | -                                                                                                                                                                                                                                                                                            |
| Anthropometrics                 | BMI                                        | 21001               | -                                                                          | -                                                                                                                                                                                                                                                                                            |
| Blood pressure                  | Systolic blood pressure                    | 93,4080             | -                                                                          | -                                                                                                                                                                                                                                                                                            |
|                                 | Systolic blood pressure standard deviation | 93,4080             | -                                                                          | -                                                                                                                                                                                                                                                                                            |
| Lipids                          | HDL ratio                                  | 30760, 30690, 30780 |                                                                            |                                                                                                                                                                                                                                                                                              |
| Cardiometabolic / comorbidities | Atrial Fibrillation                        | 131350              | I48                                                                        | -                                                                                                                                                                                                                                                                                            |
|                                 | Diabetes type 1 and 2                      | 2443                | E10, O230, E11, O231                                                       | 25001, 25011, 25021, 25031, 25041, 25051, 25061, 25071, 25081, 25091, 25003, 25013, 25023, 25033, 25043, 25053, 25063, 25073, 25083, 25093<br><br>25000, 25010, 25020, 25030, 25040, 25050, 25060, 25070, 25080, 25090, 25002, 25012, 25022, 25032, 25042, 25052, 25062, 25072, 25082, 25092 |
|                                 | Primary hypertension                       | 131287              | I10                                                                        | -                                                                                                                                                                                                                                                                                            |
|                                 | Previous Corticosteroid use                | -                   | Z7951, Z7952                                                               | -                                                                                                                                                                                                                                                                                            |
|                                 | Migraine                                   | -                   | G43, G440, N943                                                            | 346                                                                                                                                                                                                                                                                                          |
|                                 | Prevalent Rheumatoid arthritis             | -                   | M05, M06                                                                   | 714                                                                                                                                                                                                                                                                                          |
|                                 | Severe mental illness                      |                     |                                                                            |                                                                                                                                                                                                                                                                                              |

**Supplementary Table 4 Uk Biobank cardio respiratory fitness study participant risk category**

| Risk Factor                         | Risk Category |
|-------------------------------------|---------------|
| heart condition                     | 2             |
| chest pain during physical activity | 3             |
| chest pain at rest                  | 4             |
| unable to walk/cycle                | 4             |
| pregnant                            | 4             |
| height unknown                      | 3             |
| weight unknown                      | 4             |
| heart rate unknown                  | 3             |
| bp unknown                          | 4             |
| bp very high                        | 4             |
| bp high                             | 2             |
| Weight high                         | 4             |
| pacemaker unknown                   | 4             |
| pacemaker                           | 5             |

Peak power is calculated as follows:

Absolute maximum workload =  $105.2749 + (-0.0935 \times \text{age}) + (-0.0280973 \times \text{age} \times \text{age}) + (2.809493 \times \text{sex}) + (119.0087 \times \text{height}) + (0.309456 \times \text{weight}) + (-2.698067 \times \text{RHR}) + (0.0090985 \times \text{RHR} \times \text{RHR}) + (-0.3783405 \times \text{age} \times \text{sex}) + (60.72548 \times \text{height} \times \text{sex}) + (-0.15016 \times \text{weight} \times \text{sex}) + (-0.3730664 \times \text{RHR} \times \text{sex}) + (0.0180811 \times \text{RHR} \times \text{age})$

*RHR = Resting heart Rate*

1. Minimal risk, cycle at 50% level
2. Small risk, cycle at 35% level
3. Medium risk, cycle at constant level
4. High risk, take measurement at rest-only
5. ECG to be avoided, either unsafe or pointless

**Supplementary Table 5 Uk Biobank cardio respiratory fitness study Female exercise protocol**

| Number | Name | Start power (W) | Peak power(W) |
|--------|------|-----------------|---------------|
| 60     | F30  | 30              | 30            |
| 61     | F40  | 30              | 40            |
| 62     | F50  | 30              | 50            |
| 63     | F60  | 30              | 60            |
| 64     | F70  | 30              | 70            |
| 65     | F80  | 30              | 80            |
| 66     | F90  | 30              | 90            |
| 67     | F100 | 30              | 100           |
| 68     | F110 | 30              | 110           |
| 69     | F120 | 30              | 120           |
| 70     | F130 | 30              | 130           |

**Supplementary Table 6 Uk Biobank cardiorespiratory fitness study Male exercise protocol**

| Number | Name | Start power (W) | Peak power(W) |
|--------|------|-----------------|---------------|
| 60     | M40  | 40              | 40            |
| 61     | M50  | 40              | 50            |
| 62     | M60  | 40              | 60            |
| 63     | M70  | 40              | 70            |
| 64     | M80  | 40              | 80            |
| 65     | M90  | 40              | 90            |
| 66     | M100 | 40              | 100           |
| 67     | M110 | 40              | 110           |
| 68     | M120 | 40              | 120           |
| 69     | M130 | 40              | 130           |
| 70     | M140 | 40              | 140           |

**Supplementary Table 7    Uk Biobank cardiorespiratory fitness study ECG collection protocol**

|                    |                                                           |
|--------------------|-----------------------------------------------------------|
| Metric             | Value                                                     |
| Sampling Frequency | 500Hz                                                     |
| Voltage            | 5µV                                                       |
| Leads              | 3 limb leads (I, II, III)                                 |
| Software package   | CAMUSB 6.5 and operated using Cardio soft v6.51 software. |

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**Supplementary Table 8 Uk Biobank cardiorespiratory fitness study Risk category criteria as**

| <b>Risk Factor</b>                  | <b>Definition</b>                                                                                                                                              |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Heart condition                     | answer to: "Has a doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor" is "yes" or „unsure" |
| Chest pain during physical activity | answer to "Do you feel pain in your chest when you do physical activity" is „yes" or „unsure"                                                                  |
| Chest pain at rest                  | answer to "In the past month, have you had chest pain when you were NOT doing physical activity" is „yes" or „unsure"                                          |
| Unable to walk/cycle                | answer to "Are you able to walk or cycle unaided for 10 minutes" is „no" or „unsure"                                                                           |
| Pregnant                            | participant is female and has not been declared as definitely not pregnant                                                                                     |
| Height unknown                      | participant's height is unknown                                                                                                                                |
| Weight unknown                      | participant's weight is unknown                                                                                                                                |
| Heart rate unknown                  | participant's resting heart rate is unknown                                                                                                                    |
| Blood pressure unknown              | systolic or diastolic bp is unknown                                                                                                                            |
| Blood pressure very high            | lowest systolic bp $\geq 180$ or lowest diastolic bp $\geq 110$                                                                                                |
| Blood pressure high                 | lowest systolic bp $\geq 160$ or lowest diastolic bp $\geq 95$                                                                                                 |
| Weight high                         | Weight $\geq 150$ kg                                                                                                                                           |
| Pacemaker unknown                   | participant has not declared as not having pacemaker                                                                                                           |
| Pacemaker                           | participant has pacemaker                                                                                                                                      |

**Supplementary Table 9 Cardiovascular medication, with accompanying Anatomical Therapeutic Chemical (ATC) codes**

| ATC code | Description                                          |
|----------|------------------------------------------------------|
| C08D     | Calcium channel Blocker                              |
| C01BD01  | Anti-arrhythmic class: I/III                         |
| C01AA05  | Cardiac Glycosides                                   |
| C07AA02  | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA03  | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA05Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA06Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA07Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA12Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA15Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AA23Â | <a href="#">Beta blocking agents</a> (non-selective) |
| C07AB02Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB03Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB04Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB05Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB07Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB08Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AB12Â | <a href="#">Beta blocking agents</a> (Selective)     |
| C07AG01Â | Alpha/ <a href="#">Beta blocking agents</a>          |
| C07AG02Â | Alpha/ <a href="#">Beta blocking agents</a>          |

**Supplementary Table 10 Summary of ECG parameters measured during the final 15-seconds of exercise during a sub-maximal cycle ergometry test, corresponding to peak exercise intensity.**

| Characteristics              | ECG cohort (N=35,597) |
|------------------------------|-----------------------|
| PR interval(ms)              | 148.5±21.3            |
| QRS interval(ms)             | 94.8±8.7              |
| QTc interval(ms)             | 397.7±24.6            |
| RR interval: (ms)            | 550.2±66.4            |
| PVC count                    | 0.1±0.6               |
| CosEn                        | -2.9±0.4              |
| Irregularity evidence        | 0.8±2.2               |
| Regularity evidence          | 7.2±2.1               |
| Density evidence             | 0.1±0.8               |
| Anisotropy evidence          | 0.5±1.6               |
| PACE evidence                | >0.1±0.5              |
| Atrial fibrillation evidence | -18.9±9.2             |
| Atrial tachycardia evidence  | 8.4±3.9               |

Data are shown as means±SD

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were obtained via 1000 bootstrap iterations.

*ECG measurements were recorded from the final 15 seconds of rest, exercise, recovery*

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta$ RR-intervals across pre-defined bins from a Poincaré representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.

**Supplementary Table 11 Summary of ECG parameters measured during 15-seconds of recovery following a sub-maximal cycle ergometry test.**

| Characteristics              | ECG cohort (N=35,597) |
|------------------------------|-----------------------|
| PR interval(ms)              | 149.4±18.9            |
| QRS interval(ms)             | 94.2±9.1              |
| QTc interval(ms)             | 391.2±17.5            |
| RR interval: (ms)            | 743.5±128.1           |
| PVC count                    | 0.1±0.7               |
| CosEn                        | -2.4±0.5              |
| Irregularity evidence        | 1.0±2.3               |
| Regularity evidence          | 2.8±1.9               |
| Density evidence             | 0.4±0.5               |
| Anisotropy evidence          | 0.4±1.3               |
| PACE evidence                | >0.1±0.4              |
| Atrial fibrillation evidence | -7.9±8.3              |
| Atrial tachycardia evidence  | 4.2±3.6               |

Data are shown as means±SD

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were obtained via 1000 bootstrap iterations.

*ECG measurements were recorded from the final 15 seconds of rest, exercise, recovery*

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta$ RR-intervals across pre-defined bins from a Poincaré representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.

**Supplementary Table 12 Hazard ratio of Q-ECG scores and conventional ECG parameters measured during rest, exercise, and recovery after removing the first 2-years of follow-up.**

| ECG Parameter                | Rest                    |                         | Exercise                |                         | Recovery                |                         |
|------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                              | Male                    | Female                  | Male                    | Female                  | Male                    | Female                  |
| Q-ECG                        | **1.13<br>(1.08 - 1.18) | **1.12<br>(1.05 - 1.19) | **1.10<br>(1.05 - 1.15) | **1.25<br>(1.15 - 1.36) | **1.13<br>(1.09 - 1.18) | **1.14<br>(1.08 - 1.22) |
| PR interval(ms)              | 1.03<br>(0.99 - 1.07)   | 1.01<br>(0.97 - 1.05)   | 1.01<br>(0.97 - 1.05)   | 0.99<br>(0.95 - 1.04)   | 1.04<br>(1.00 - 1.09)   | 1.03<br>(0.98 - 1.07)   |
| QRS interval(ms)             | *1.07<br>(1.03 - 1.114) | 1.07<br>(1.03 - 1.11)   | *1.06<br>(1.02 - 1.10)  | *1.05<br>(1.01 - 1.09)  | *1.07<br>(1.04 - 1.11)  | **1.07<br>(1.03 - 1.11) |
| QTc interval(ms)             | *1.06<br>(1.02 - 1.106) | 1.06<br>(1.01 - 1.10)   | *1.06<br>(1.03 - 1.10)  | *1.05<br>(1.01 - 1.09)  | **1.10<br>(1.06 - 1.13) | **1.09<br>(1.05 - 1.13) |
| RR interval: (ms)            | 0.99<br>(0.95 - 1.034)  | 0.99<br>(0.95 - 1.03)   | **1.12<br>(1.08 - 1.17) | **1.12<br>(1.07 - 1.16) | 1.01<br>(0.97 - 1.05)   | 1.00<br>(0.96 - 1.05)   |
| PVC count                    | *1.03<br>(1.00 - 1.060) | 1.04<br>(1.01 - 1.07)   | *1.05<br>(1.02 - 1.08)  | 1.05<br>(1.02 - 1.08)   | 1.01<br>(0.98 - 1.05)   | 1.01<br>(0.98 - 1.05)   |
| CosEn                        | 0.97<br>(0.93 - 1.010)  | 0.97<br>(0.93 - 1.02)   | 0.97<br>(0.93 - 1.01)   | 0.98<br>(0.94 - 1.02)   | 0.97<br>(0.93 - 1.02)   | 0.99<br>(0.94 - 1.02)   |
| Irregularity evidence        | *1.06<br>(1.02 - 1.100) | 1.07<br>(1.03 - 1.11)   | 1.02<br>(0.99 - 1.06)   | 1.03<br>(0.99 - 1.07)   | *1.05<br>(1.01 - 1.09)  | 1.05<br>(1.01 - 1.09)   |
| Regularity evidence          | 1.06<br>(1.01 - 1.105)  | *1.05<br>(1.02 - 1.16)  | *1.08<br>(1.02 - 1.14)  | 1.07<br>(1.01 - 1.14)   | 1.03<br>(0.98 - 1.08)   | *1.02<br>(0.97 - 1.08)  |
| Density evidence             | 1.00<br>(0.96 - 1.034)  | 0.99<br>(0.95 - 1.03)   | 1.00<br>(0.97 - 1.04)   | 1.00<br>(0.97 - 1.04)   | 1.02<br>(0.99 - 1.06)   | 1.03<br>(0.99 - 1.07)   |
| Anisotropy evidence          | *1.05<br>(1.01 - 1.082) | 1.05<br>(1.01 - 1.09)   | 1.02<br>(0.98 - 1.06)   | 1.03<br>(0.99 - 1.06)   | *1.05<br>(1.01 - 1.08)  | 1.05<br>(1.01 - 1.09)   |
| PACE evidence                | 1.01<br>(0.98 - 1.047)  | 1.02<br>(0.98 - 1.05)   | 0.98<br>(0.94 - 1.02)   | 0.99<br>(0.95 - 1.03)   | 1.01<br>(0.98 - 1.05)   | 1.02<br>(0.98 - 1.06)   |
| Atrial fibrillation evidence | 0.99<br>(0.94 - 1.038)  | 0.98<br>(0.93 - 1.04)   | 1.01<br>(0.97 - 1.05)   | 1.01<br>(0.96 - 1.05)   | 1.02<br>(0.96 - 1.07)   | 1.01<br>(0.96 - 1.07)   |
| Atrial tachycardia evidence  | *1.07<br>(1.03 - 1.108) | 1.07<br>(1.03 - 1.11)   | *1.05<br>(1.01 - 1.09)  | 1.05<br>(1.02 - 1.09)   | *1.06<br>(1.02 - 1.10)  | 1.06<br>(1.02 - 1.10)   |

Abbreviations: PVC =Premature ventricular contraction Index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years

*ECG measurements were recorded from the final 15 seconds of rest, exercise, recovery*

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta$ RR-intervals across pre-defined bins from a Poincare representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.

Each row corresponds to a separate univariate Cox model in which each listed ECG risk factors was fitted individually.

Hazard ratios are presented per Standard deviation increase in selected risk factors.

95% confidence intervals and p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05, following adjustment for multiple testing using the Benjamini/Hochberg procedure<sup>260</sup>; \*p value <0.05; \*\*p value < 0.001

**Supplementary Table 13 Hazard ratio of Q-ECG scores and conventional ECG parameters measured during rest, exercise, and recovery after removing the first 5-years of follow-up.**

| ECG Parameter                | Rest                    |                         | Exercise                |                         | Recovery                |                         |
|------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                              | Male                    | Female                  | Male                    | Female                  | Male                    | Female                  |
| Q-ECG                        | **1.12<br>(1.06 - 1.18) | **1.16<br>(1.08 - 1.25) | **1.12<br>(1.06 - 1.18) | **1.30<br>(1.19 - 1.43) | **1.11<br>(1.05 - 1.16) | **1.15<br>(1.07 - 1.23) |
| PR interval(ms)              | 1.04<br>(0.99 - 1.09)   | 1.06<br>(0.99 - 1.13)   | 1.01<br>(0.96 - 1.06)   | 1.08<br>(1.01 - 1.15)   | 1.04<br>(1.00 - 1.10)   | 1.08<br>(1.01 - 1.15)   |
| QRS interval(ms)             | *1.07<br>(1.03 - 1.12)  | *1.07<br>(1.01 - 1.14)  | *1.06<br>(1.02 - 1.11)  | *1.10<br>(1.04 - 1.16)  | *1.08<br>(1.04 - 1.13)  | **1.13<br>(1.06 - 1.19) |
| QTc interval(ms)             | 1.04<br>(0.99 - 1.09)   | 1.05<br>(0.98 - 1.12)   | *1.06<br>(1.02 - 1.11)  | *1.09<br>(1.04 - 1.15)  | *1.09<br>(1.04 - 1.14)  | **1.17<br>(1.11 - 1.24) |
| RR interval: (ms)            | 1.02<br>(0.97 - 1.07)   | 1.07<br>(1.01 - 1.14)   | **1.13<br>(1.08 - 1.19) | **1.19<br>(1.12 - 1.27) | 1.03<br>(0.98 - 1.08)   | 1.07<br>(1.00 - 1.15)   |
| PVC count                    | *1.04<br>(1.01 - 1.08)  | *1.04<br>(1.01 - 1.08)  | *1.05<br>(1.02 - 1.09)  | 1.02<br>(0.96 - 1.08)   | 1.02<br>(0.98 - 1.06)   | 1.04<br>(0.98 - 1.09)   |
| CosEn                        | 0.99<br>(0.94 - 1.04)   | 1.01<br>(0.94 - 1.09)   | 1.00<br>(0.95 - 1.05)   | 1.00<br>(0.93 - 1.07)   | 1.02<br>(0.96 - 1.07)   | *0.91<br>(0.85 - 0.98)  |
| Irregularity evidence        | 1.05<br>(1.00 - 1.10)   | 1.01<br>(0.95 - 1.09)   | 1.03<br>(0.99 - 1.07)   | 1.02<br>(0.95 - 1.09)   | *1.06<br>(1.01 - 1.11)  | 0.99<br>(0.91 - 1.07)   |
| Regularity evidence          | 1.04<br>(0.98 - 1.09)   | 1.09<br>(1.02 - 1.18)   | 1.05<br>(0.98 - 1.13)   | 1.00<br>(0.91 - 1.09)   | 0.96<br>(0.91 - 1.03)   | *1.13<br>(1.04 - 1.23)  |
| Density evidence             | 0.99<br>(0.95 - 1.04)   | 1.01<br>(0.95 - 1.08)   | 1.00<br>(0.95 - 1.04)   | 0.99<br>(0.93 - 1.06)   | 1.03<br>(0.99 - 1.07)   | 0.98<br>(0.91 - 1.06)   |
| Anisotropy evidence          | 1.04<br>(1.00 - 1.09)   | 1.02<br>(0.96 - 1.09)   | 1.03<br>(0.99 - 1.07)   | 0.97<br>(0.90 - 1.04)   | *1.06<br>(1.01 - 1.10)  | 1.01<br>(0.94 - 1.08)   |
| PACE evidence                | 1.03<br>(0.99 - 1.07)   | 0.99<br>(0.92 - 1.07)   | 0.97<br>(0.92 - 1.02)   | 1.01<br>(0.94 - 1.07)   | 1.02<br>(0.97 - 1.07)   | 1.00<br>(0.93 - 1.07)   |
| Atrial fibrillation evidence | 0.98<br>(0.93 - 1.05)   | 0.96<br>(0.88 - 1.05)   | *1.02<br>(0.97 - 1.08)  | 1.02<br>(0.95 - 1.10)   | 1.05<br>(0.99 - 1.12)   | *0.90<br>(0.82 - 0.98)  |
| Atrial tachycardia evidence  | 1.05<br>(1.00 - 1.09)   | 1.06<br>(0.99 - 1.13)   | 1.06<br>(1.01 - 1.10)   | 0.99<br>(0.92 - 1.06)   | 1.05<br>(1.00 - 1.09)   | 1.04<br>(0.98 - 1.11)   |

Abbreviations: PVC =Premature ventricular contraction, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years

*ECG measurements were recorded from the final 15 seconds of rest, exercise, recovery*

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta$ RR-intervals across pre-defined bins from a Poincare representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.

Each row corresponds to a separate univariate Cox model in which each listed ECG risk factors was fitted individually.

Hazard ratios are presented per Standard deviation increase in selected risk factors.

95% confidence intervals and p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05, following adjustment for multiple testing using the Benjamini/Hochberg procedure<sup>260</sup>; \*p value <0.05; \*\*p value < 0.001

**Supplementary Table 14 Univariate predictive performance of ECG risk factors (derived from the final 15 seconds of rest, exercise, and recovery) and QRISK3 risk factors for 10-year MACCE risk prediction.**

| ECG parameters               | C-index (95% CI)   |                    | Hazard ratio (95% CI) |                    |
|------------------------------|--------------------|--------------------|-----------------------|--------------------|
|                              | Male               | Female             | Male                  | Female             |
| <b>Resting ECG</b>           |                    |                    |                       |                    |
| PR interval(ms)              | 0.52 (0.51 – 0.53) | 0.52 (0.5-0.54)    | 1.02 (0.97 - 1.06)    | 1.06 (0.98 - 1.13) |
| QRS interval(ms)             | 0.53(0.51 – 0.54)  | 0.53 (0.5-0.55)    | 1.06 (1.01 - 1.1)     | 1.03 (0.96 - 1.1)  |
| QTc interval(ms)             | 0.55(0.53 – 0.56)  | 0.52 (0.5-0.54)    | 1.09 (1.03 - 1.14)    | 1.03 (0.95 - 1.11) |
| RR interval: (ms)            | 0.50(0.49 – 0.52)  | 0.5 (0.48-0.52)    | 0.97 (0.93 - 1.03)    | 1.03 (0.96 - 1.12) |
| PVC count                    | 0.52 (0.51 – 0.53) | 0.5 (0.48-0.52)    | 1.02 (0.99 - 1.05)    | 0.98 (0.89 - 1.04) |
| CosEn                        | 0.55 (0.54-0.57)   | 0.55 (0.53-0.57)   | 0.96 (0.91 - 1.01)    | 0.99 (0.92 - 1.06) |
| Irregularity evidence        | 0.5 (0.49-0.52)    | 0.52 (0.5-0.54)    | 1.07 (1.03 - 1.12)    | 1.00 (0.93 - 1.08) |
| Regularity evidence          | 0.55 (0.53-0.56)   | 0.54 (0.52-0.56)   | 1.09 (1.04 - 1.14)    | 1.07 (1 - 1.14)    |
| Atrial fibrillation evidence | 0.53 (0.52-0.54)   | 0.53 (0.51-0.55)   | 0.97 (0.93 - 1.02)    | 0.99 (0.91 - 1.06) |
| Atrial tachycardia evidence  | 0.55 (0.53-0.56)   | 0.52 (0.5-0.54)    | 1.09 (1.05 - 1.13)    | 1.02 (0.95 - 1.08) |
| Anisotropyevidence           | 0.55 (0.53-0.56)   | 0.52 (0.5-0.54)    | 1.05 (1.01 - 1.09)    | 0.97 (0.88 - 1.03) |
| Density evidence             | 0.5 (0.49-0.51)    | 0.49 (0.47-0.51)   | 0.99 (0.95 - 1.03)    | 0.97 (0.89 - 1.03) |
| <b>Exercise ECG</b>          |                    |                    |                       |                    |
| PR interval(ms)              | 0.52 (0.5 - 0.53)  | 0.53 (0.51 - 0.55) | 0.99 (0.95 - 1.04)    | 1.06 (0.99 - 1.14) |
| QRS interval(ms)             | 0.51 (0.5 - 0.53)  | 0.53 (0.51 - 0.55) | 1.05 (1 - 1.09)       | 1.06 (0.99 - 1.12) |
| QTc interval(ms)             | 0.54 (0.52 - 0.55) | 0.53 (0.51 - 0.55) | 1.07 (1.04 - 1.11)    | 1.05 (0.99 - 1.1)  |
| RR interval: (ms)            | 0.57 (0.55 - 0.58) | 0.57 (0.55 - 0.59) | 1.12 (1.07 - 1.17)    | 1.17 (1.09 - 1.24) |
| PVC count                    | 0.51 (0.5 - 0.53)  | 0.51 (0.49 - 0.53) | 1.06 (1.02 - 1.09)    | 1.00 (0.92 - 1.05) |
| CosEn                        | 0.52 (0.5 - 0.53)  | 0.53 (0.52 - 0.55) | 0.97 (0.93 - 1.01)    | 0.98 (0.91 - 1.05) |
| Irregularity evidence        | 0.53 (0.52 - 0.54) | 0.47 (0.46 - 0.49) | 1.04 (1 - 1.08)       | 1.01 (0.94 - 1.07) |
| Regularity evidence          | 0.52 (0.51 - 0.53) | 0.53 (0.51 - 0.55) | 0.98 (0.93 - 1.03)    | 0.91 (0.85 - 0.97) |
| Atrial fibrillation evidence | 0.55 (0.54 - 0.56) | 0.53 (0.51 - 0.55) | 1.06 (1.01 - 1.11)    | 1.05 (0.98 - 1.12) |
| Atrial tachycardia evidence  | 0.51 (0.5 - 0.53)  | 0.52 (0.5 - 0.54)  | 1.05 (1 - 1.09)       | 0.94 (0.87 - 1.02) |
| Anisotropy evidence          | 0.52 (0.51 - 0.53) | 0.48 (0.46 - 0.5)  | 1.03 (0.99 - 1.07)    | 1.01 (0.93 - 1.07) |
| Density evidence             | 0.51 (0.5 - 0.53)  | 0.51 (0.49 - 0.53) | 1.01 (0.97 - 1.05)    | 1.02 (0.95 - 1.07) |
| <b>Recovery ECG</b>          |                    |                    |                       |                    |
| PR interval(ms)              |                    |                    |                       |                    |
| QRS interval(ms)             | 0.52 (0.5 - 0.53)  | 0.53 (0.51 - 0.55) | 1.06 (1.02 - 1.1)     | 1.08 (1.01 - 1.14) |
| QTc interval(ms)             | 0.57 (0.55 - 0.58) | 0.56 (0.54 - 0.59) | 1.11 (1.07 - 1.15)    | 1.15 (1.08 - 1.21) |
| RR interval: (ms)            | 0.49 (0.48 - 0.5)  | 0.49 (0.47 - 0.51) | 0.99 (0.94 - 1.04)    | 1.02 (0.94 - 1.09) |
| PVC count                    | 0.51 (0.5 - 0.53)  | 0.52 (0.5 - 0.54)  | 1.01 (0.97 - 1.04)    | 1.02 (0.97 - 1.07) |
| CosEn                        | 0.55 (0.54 - 0.57) | 0.57 (0.56 - 0.6)  | 0.96 (0.91 - 1.01)    | 0.92 (0.85 - 0.99) |
| Irregularity evidence        | 0.51 (0.49 - 0.52) | 0.52 (0.5 - 0.54)  | 1.04 (1 - 1.09)       | 1.00(0.91 - 1.07)  |
| Regularity evidence          | 0.54 (0.52 - 0.55) | 0.55 (0.54 - 0.57) | 1.05 (1 - 1.1)        | 1.08 (1.01 - 1.16) |
| Atrial fibrillation evidence | 0.52 (0.51 - 0.53) | 0.55 (0.53 - 0.57) | 0.98 (0.94 - 1.03)    | 0.94 (0.88 - 1.01) |
| Atrial tachycardia evidence  | 0.54 (0.53 - 0.55) | 0.54 (0.51 - 0.56) | 1.07 (1.03 - 1.12)    | 1.04 (0.98 - 1.1)  |
| Anisotropy evidence          | 0.51 (0.5 - 0.53)  | 0.5 (0.48 - 0.52)  | 1.05 (1.01 - 1.09)    | 0.99 (0.92 - 1.05) |

|                                      |                    |                    |                    |                     |
|--------------------------------------|--------------------|--------------------|--------------------|---------------------|
| Density evidence                     | 0.51 (0.49 - 0.52) | 0.51 (0.5 - 0.53)  | 1.02 (0.98 - 1.06) | 0.93 (0.84 - 1.01)  |
| <b>QRISK3 risk factor</b>            |                    |                    |                    |                     |
| Age                                  | 0.66 (0.65 - 0.68) | 0.67 (0.65 - 0.69) | 1.95 (1.84 - 2.06) | 1.97 (1.80 - 2.15)  |
| Body mass index (kg/M <sup>2</sup> ) | 0.56 (0.55 - 0.57) | 0.57 (0.55 - 0.59) | 1.24 (1.19 - 1.29) | 1.29 (1.21 - 1.36)  |
| Ethnicity                            | 0.5 (0.5 - 0.51)   | 0.51 (0.51 - 0.52) | 1.19 (0.98 - 1.43) | 1.19 (0.98 - 1.43)  |
| Townsend deprivation index           | 0.5 (0.49 - 0.52)  | 0.5 (0.48 - 0.51)  | 1.05 (1.00 - 1.10) | 1.01 (0.93 - 1.09)  |
| Current smoker                       | 0.51 (0.5 - 0.52)  | 0.5 (0.5 - 0.51)   | 1.51 (1.29 - 1.73) | 1.54 (1.17 - 1.95)  |
| Former smoker                        | 0.52 (0.51 - 0.53) | 0.52 (0.5 - 0.53)  | 1.07 (0.97 - 1.18) | 1.17 (1.02 - 1.37)  |
| Systolic blood pressure mmHg         | 0.58 (0.57 - 0.6)  | 0.59 (0.57 - 0.61) | 1.14 (1.08 - 1.19) | 1.14 (1.06 - 1.23)  |
| Type 1 diabetes                      | 0.5 (0.5 - 0.5)    | 0.5 (0.5 - 0.5)    | 1.49 (0.50 - 2.70) | 3.91 (0.001 - 8.74) |
| Type 2 diabetes                      | 0.51 (0.51 - 0.51) | 0.5 (0.5 - 0.51)   | 2.21 (1.64 - 2.78) | 1.99 (0.90 - 3.23)  |
| HDL: ratio                           | 0.52 (0.51 - 0.54) | 0.58 (0.56 - 0.6)  | 1.18 (1.12 - 1.23) | 1.25 (1.18 - 1.32)  |
| Hypertension                         | 0.53 (0.52 - 0.54) | 0.53 (0.52 - 0.54) | 1.78 (1.51 - 2.07) | 2.12 (1.65 - 2.62)  |
| Rheumatoid arthritis                 | 0.5 (0.5 - 0.5)    | 0.5 (0.49 - 0.5)   | 2.06 (0.62 - 3.86) | 1.03 (0.001 - 2.34) |
| Severe mental illness                | 0.5 (0.5 - 0.5)    | 0.5 (0.5 - 0.5)    | 0.51 (0.01 - 1.42) | 3.86 (0.001 - 9.04) |

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations

Each row corresponds to a separate univariate Cox model in which each listed ECG risk factors was fitted individually.

Hazard ratios are presented per Standard deviation increase for continuous risk factors.

*ECG measurements were recorded from the final 15 seconds of rest, exercise, recovery*

All ECG intervals (PR, QRS, QTc, RR) are reported in milliseconds. Premature ventricular contraction (PVC) represents counts of ectopic beats observed within the 15-second resting ECG segment. CosEn is a dimensionless score presenting ECG signal entropy. Evidence-based indices (irregularity, regularity, density, anisotropy) count the number of  $\Delta$ RR-intervals across pre-defined bins from a Poincare representation over the 15-second ECG recording. Atrial fibrillation, and atrial tachycardia evidence are dimensionless scores derived from the RR-interval series and Poincaré-plot representation, with higher values indicating greater rhythm irregularity or stronger evidence for the respective arrhythmia patterns.



**Supplementary Table 15 Reclassification performance of Age vs ECG risk scores**

| Model         | Comparator   | ΔNet-benefit (95% CI)    | Categorical NRI (95% CI) | Continuous NRI (95% CI)    |
|---------------|--------------|--------------------------|--------------------------|----------------------------|
| <b>Male</b>   |              |                          |                          |                            |
| Age           | Resting ECG  | *-0.127(-0.159 - -0.096) | -0.132(-0.161 - -0.108)  | ** -0.415(-0.459 - -0.366) |
| Age           | Exercise ECG | *-0.104(-0.135 - -0.074) | -0.108(-0.139 - -0.078)  | ** -0.369(-0.422 - -0.32)  |
| Age           | Recovery ECG | *-0.112(-0.142 - -0.079) | -0.113(-0.141 - -0.088)  | ** -0.406(-0.449 - -0.352) |
| Age           | Combined ECG | -0.046(-0.074 - -0.017)  | -0.047(-0.074 - -0.018)  | ** -0.231(-0.281 - -0.184) |
| <b>Female</b> |              |                          |                          |                            |
| Age           | Resting ECG  | -0.012(-0.037 - 0.013)   | -0.06(-0.083 - -0.038)   | ** -0.478(-0.544 - -0.413) |
| Age           | Exercise ECG | -0.007(-0.033 - 0.021)   | -0.044(-0.067 - -0.019)  | ** -0.415(-0.469 - -0.344) |
| Age           | Recovery ECG | -0.011(-0.037 - 0.013)   | -0.056(-0.075 - -0.035)  | ** -0.415(-0.489 - -0.35)  |
| Age           | Combined ECG | 0.006(-0.022 - 0.035)    | -0.001(-0.03 - 0.034)    | ** -0.218(-0.293 - -0.152) |

**at a 10% risk**

*Abbreviations: NRI =Net reclassification Index, CI = Confidence interval*

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations

*Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

*For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases*

**ECG parameters:**

Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence

Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence

Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

\**p value <0.05*

\*\* *p value < 0.001*

**Supplementary Table16 Reclassification performance of QRISK3-Inspired vs ECG risk scores at a 10% risk threshold**

| Model           | Comparator   | ΔNet-benefit (95% CI)      | Categorical NRI (95% CI)   | Continuous NRI (95% CI)    |
|-----------------|--------------|----------------------------|----------------------------|----------------------------|
| <b>Male</b>     |              |                            |                            |                            |
| QRISK3-Inspired | Resting ECG  | ** -0.168(-0.198 - -0.14)  | ** -0.169(-0.199 - -0.141) | ** -0.512(-0.557 - -0.465) |
| QRISK3-Inspired | Exercise ECG | ** -0.145(-0.176 - -0.116) | ** -0.146(-0.177 - -0.116) | ** -0.444(-0.491 - -0.398) |
| QRISK3-Inspired | Recovery ECG | ** -0.153(-0.181 - -0.123) | ** -0.153(-0.182 - -0.123) | ** -0.525(-0.571 - -0.478) |
| QRISK3-Inspired | Combined ECG | ** -0.087(-0.113 - -0.06)  | ** -0.088(-0.114 - -0.06)  | ** -0.326(-0.373 - -0.28)  |
| <b>Female</b>   |              |                            |                            |                            |
| QRISK3-Inspired | Resting ECG  | ** -0.033(-0.062 - -0.003) | ** -0.12(-0.147 - -0.093)  | ** -0.552(-0.619 - -0.485) |
| QRISK3-Inspired | Exercise ECG | -0.028(-0.058 - 0.002)     | ** -0.104(-0.133 - -0.075) | ** -0.485(-0.553 - -0.412) |
| QRISK3-Inspired | Recovery ECG | * -0.032(-0.063 - -0.003)  | ** -0.116(-0.144 - -0.088) | ** -0.493(-0.56 - -0.428)  |
| QRISK3-Inspired | Combined ECG | -0.015(-0.045 - 0.017)     | ** -0.062(-0.092 - -0.031) | ** -0.327(-0.393 - -0.26)  |

*Abbreviations: NRI =Net reclassification Index, CI = Confidence interval*

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals and p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05(\**p value* <0.05; \*\**p value* < 0.001)

*Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

*For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases*

#### **ECG parameters:**

Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence

Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence

Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials: *Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ );*

**Supplementary Table 17 Predictive performance of multivariable ECG risk scores**

| Model               | C-Index              | ICI                     | Net benefit           |
|---------------------|----------------------|-------------------------|-----------------------|
| <b>Male</b>         |                      |                         |                       |
| ECG Risk score      |                      |                         |                       |
| Resting             | 0.665(0.655 - 0.676) | 0.0051(0.0029 - 0.0077) | 0.103(0.075 - 0.127)  |
| Peak exercise       | 0.667(0.657 - 0.676) | 0.0057(0.0032 - 0.0083) | 0.127(0.098 - 0.152)  |
| Late-stage recovery | 0.667(0.657 - 0.678) | 0.0072(0.0042 - 0.0106) | 0.121(0.093 - 0.15)   |
| Combined features   | 0.671(0.66 - 0.682)  | 0.0072(0.004 - 0.0108)  | 0.186(0.157 - 0.215)  |
| <b>Female</b>       |                      |                         |                       |
| ECG Risk score      |                      |                         |                       |
| Resting             | 0.671(0.654 - 0.686) | 0.0043(0.0023 - 0.0066) | 0(-0.003 - 0.005)     |
| Peak exercise       | 0.674(0.659 - 0.689) | 0.0052(0.0028 - 0.0078) | 0.005(-0.006 - 0.018) |
| Late-stage recovery | 0.677(0.659 - 0.692) | 0.0032(0.0015 - 0.0051) | 0.001(-0.007 - 0.008) |
| Combined features   | 0.677(0.658 - 0.691) | 0.004(0.0021 - 0.0068)  | 0.019(-0.002 - 0.042) |

Abbreviations: ICI = Integrated Calibration Index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations

*Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

*For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases.*

**ECG parameters:**

Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence

Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence

Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

**Supplementary Table 18 predictive performance of age and age + ECG risk factors measured at rest, exercise and recovery**

| Model               | C-Index               | ICI                     | Net benefit            |
|---------------------|-----------------------|-------------------------|------------------------|
| <b>Male</b>         |                       |                         |                        |
| Age                 | 0.662 (0.652 – 0.673) | 0.0041(0.0033 - 0.0049) | 0.234(0.203 - 0.260)   |
| Age + ECG           |                       |                         |                        |
| Resting             | 0.665 (0.655 – 0.676) | 0.0032(0.003 - 0.0034)  | 0.246(0.214 - 0.273)   |
| Peak exercise       | 0.667 (0.657 – 0.676) | 0.0033(0.0022 - 0.0043) | 0.244(0.217 - 0.272)   |
| Late-stage recovery | 0.667 (0.657 – 0.678) | 0.0041(0.0037 - 0.0044) | 0.236(0.205 - 0.263)   |
| Combined features   | 0.671(0.66 - 0.682)   | 0.0052(0.0026 - 0.0085) | 0.251(0.222 - 0.28)    |
| <b>Female</b>       |                       |                         |                        |
| Age                 | 0.671 (0.655 – 0.687) | 0.0028(0.0011 - 0.0055) | 0.012(-0.009 - 0.036)  |
| Age + ECG           | 0                     |                         |                        |
| Resting             | 0.671 (0.654 – 0.686) | 0.0032(0.0017 - 0.0053) | -0.003(-0.023 - 0.019) |
| Peak exercise       | 0.674 (0.659 – 0.689) | 0.0035(0.0017 - 0.0061) | 0.031(0.001 - 0.056)   |
| Late-stage recovery | 0.686 (0.672 – 0.702) | 0.0031(0.0013 - 0.0052) | 0.022(-0.003 - 0.047)  |
| Combined features   | 0.677(0.659 - 0.692)  | 0.0044(0.0021 - 0.007)  | 0.028(-0.001 - 0.057)  |

Abbreviations: ICI = Integrated Calibration Index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations

*Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

*For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases*

**ECG parameters:**

Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence

Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence

Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

**Supplementary Table 19 predictive performance of QRISK3-Inspired risk scores and age + ECG risk factors measured at rest, exercise and recovery**

| Model                 | C-Index               | ICI                     | Net benefit           |
|-----------------------|-----------------------|-------------------------|-----------------------|
| <b>Male</b>           |                       |                         |                       |
| QRISK3-Inspired       | 0.682 (0.673 – 0.691) | 0.0038(0.0032 - 0.0043) | 0.273(0.242 - 0.296)  |
| QRISK3-Inspired + ECG |                       |                         |                       |
| Resting               | 0.683 (0.675 – 0.692) | 0.0046(0.0035 - 0.0058) | 0.266(0.236 - 0.292)  |
| Peak exercise         | 0.688 (0.678 – 0.696) | 0.0027(0.0022 - 0.0032) | 0.275(0.247 - 0.298)  |
| Late-stage recovery   | 0.686 (0.678 – 0.694) | 0.0042(0.0034 - 0.0051) | 0.273(0.245 - 0.300)  |
| Combined features     | 0.682(0.673 - 0.691)  | 0.007(0.0039 - 0.0111)  | 0.268(0.237 - 0.298)  |
| <b>Female</b>         |                       |                         |                       |
| QRISK3-Inspired       | 0.685 (0.672 – 0.702) | 0.0046(0.003 - 0.0072)  | 0.031(0.002 - 0.06)   |
| QRISK3-Inspired + ECG |                       |                         |                       |
| Resting               | 0.683 (0.699 – 0.699) | 0.0048(0.0028 - 0.0066) | 0.022(-0.006 - 0.056) |
| Peak exercise         | 0.687 (0.673 – 0.704) | 0.0052(0.0026 - 0.0077) | 0.042(0.01 - 0.083)   |
| Late-stage recovery   | 0.686 (0.672 – 0.702) | 0.0048(0.0028 - 0.0069) | 0.034(-0.003 - 0.069) |
| Combined features     | 0.677(0.659 - 0.692)  | 0.0067(0.0041 - 0.0098) | 0.035(0.003 - 0.069)  |

Abbreviations: ICI = Integrated Calibration Index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations

*Each row corresponds to a separate Cox model in which the model was fitted independently with the selected risk factors. Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

*For each sex, four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases*

ECG parameters: Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence; Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 1 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ );

**Supplementary Table 20 Reclassification performance of QRISK3-Inspired vs Age + ECG risk factors at a 10% risk threshold**

| Model           | Comparator         | Net-benefit<br>(95% CI) | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|-----------------|--------------------|-------------------------|-----------------------------|----------------------------|
| <b>Male</b>     |                    |                         |                             |                            |
| QRISK3-Inspired | Age                | -0.039(-0.055 - -0.023) | ** -0.039(-0.055 - -0.023)  | ** -0.311(-0.351 - -0.267) |
| QRISK3-Inspired | Age + Resting ECG  | -0.027(-0.027 - -0.01)  | ** -0.027(-0.041 - -0.01)   | -0.265(-0.311 - -0.221)    |
| QRISK3-Inspired | Age + Exercise ECG | -0.028(-0.028 - -0.012) | ** -0.028(-0.043 - -0.012)  | -0.213(-0.261 - -0.167)    |
| QRISK3-Inspired | Age + Recovery ECG | -0.037(-0.037 - -0.021) | ** -0.037(-0.051 - -0.021)  | -0.259(-0.303 - -0.215)    |
| <b>Female</b>   |                    |                         |                             |                            |
| QRISK3-Inspired | Age                | -0.019(-0.042 - 0.008)  | ** -0.058(-0.081 - -0.031)  | ** -0.281(-0.281 - -0.21)  |
| QRISK3-Inspired | Age + Resting ECG  | -0.034(-0.065 - -0.008) | ** -0.065(-0.093 - -0.038)  | ** -0.272(-0.272 - -0.202) |
| QRISK3-Inspired | Age + Exercise ECG | 0(0.028 - 0.032)        | -0.023(-0.050 - 0.006)      | ** -0.208(-0.208 - -0.143) |
| QRISK3-Inspired | Age + Recovery ECG | -0.009(-0.034 - 0.013)  | ** -0.032(-0.058 - -0.009)  | ** -0.201(-0.201 - -0.123) |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals were derived via bootstrapping for 1000 iterations *For each sex, three ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters,*

ECG parameters: Resting ECG parameters: *QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence*; Exercise ECG parameters: *PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence* Recovery ECG parameters: *Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence*

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials: *Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ );*

p-values were derived via bootstrapping for 1000 iterations, with a significance threshold of 0.05.

\**p value <0.05; \*\* p value < 0.001*

**Supplementary Table 21 Association and predictive performance of ECG risk scores derived from 15-second recordings during rest, peak exercise and late stage recovery using Cox proportional hazard models for 10-year incident Major Adverse Cardiovascular & Cerebrovascular Events as measured by Harrell's C-index and Net benefit at a 10% risk threshold across 35,597 participants with valid ECG parameters**

| Model                                                         |          | Hazard Ratio<br>(95% CI) | C-index<br>(95% CI) | Net-benefit<br>(95% CI) |
|---------------------------------------------------------------|----------|--------------------------|---------------------|-------------------------|
| Conventional<br>ECG parameters:<br>Cox proportional<br>hazard | Rest     | 1.09 (1.08 – 1.12)       | 0.560 (0.550 0.569) | 0.072 (0.051 0.090)     |
|                                                               | Exercise | 1.06 (1.05 -1.08)        | 0.584 (0.576 0.591) | 0.090 (0.069 0.108)     |
|                                                               | Recovery | 1.05 (1.04 – 1.09)       | 0.573 (0.564 0.583) | 0.084 (0.064 0.106)     |
|                                                               | Combined | 1.05 (1.05 -1.07)        | 0.622(0.615 0.632)  | 0.139 (0.123-<br>0.151) |

*Abbreviation: CI = Confidence intervals*

Data are reported on 35,597 participants with valid ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years.95% confidence intervals were obtained via 1000 bootstrap iterations.

*Each row corresponds to a separate Cox model in which the model was fitted independently with the selected risk factors. Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method, based on mean-centred continuous variables, with all binary risk factors set to 0*

Hazard ratios are derived from sperate Cox proportional hazard models unadjusted for other risk factors.

Unadjusted Hazard ratios are reported per unit increase, while net benefit is reported at a 10% risk threshold.*ECG measurements were recoded from the final 15 seconds of rest, exercise, recovery*

*Four ECG risk scores were constructed using a linear combination of risk factors from: (1) resting ECG parameters, (2) peak-exercise ECG parameters, (3) a late-stage recovery parameters, and (4) a combined ECG score including ECG parameters from all three phases.*

**ECG parameters:**

Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence

Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence

Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence



**Supplementary Table 22 Reclassification performance of Age + Sex, QRISK3-Inspired and linear Cox proportional hazard (Cox clinical) risk scores, vs Deep survival ECG risk scores at a 10% risk threshold**

| Model           | Comparator   | Δ Net-benefit (95% CI)     | Categorical NRI<br>(95% CI)  | Continuous NRI<br>(95% CI)    |
|-----------------|--------------|----------------------------|------------------------------|-------------------------------|
| Age + Sex       | Resting ECG  | ** -0.146(-0.165 - -0.127) | ** -0.194 ( -0.216 - -0.172) | ** -0.490( -0.525 - -0.454)   |
| Age + Sex       | Exercise ECG | ** -0.134(-0.155 - -0.111) | ** -0.189 ( -0.210 - -0.167) | ** -0.397 ( -0.423 - -0.363)  |
| Age + Sex       | Recovery ECG | ** -0.133(-0.153 - -0.114) | ** -0.175 ( -0.198 - -0.152) | ** -0.463 ( -0.498 - -0.427)  |
| Age + Sex       | Complete ECG | ** -0.15(-0.166 - -0.131)  | ** -0.210 ( -0.232 - -0.189) | ** -0.505 ( -0.541 - -0.470)  |
| QRISK3-Inspired | Resting ECG  | ** -0.186(-0.205 - -0.167) | ** -0.231 ( -0.253 - -0.210) | ** -0.501 ( -0.535 - -0.466)  |
| QRISK3-Inspired | Exercise ECG | ** -0.174(-0.194 - -0.153) | ** -0.226 ( -0.248 - -0.205) | ** -0.361 ( -0.393 - -0.328)  |
| QRISK3-Inspired | Recovery ECG | ** -0.173(-0.197 - -0.151) | ** -0.213 ( -0.235 - -0.190) | ** -0.420 ( -0.4552 - -0.385) |
| QRISK3-Inspired | Complete ECG | ** -0.19(-0.21 - -0.17)    | ** -0.248 ( -0.269 - -0.227) | ** -0.495 ( -0.5294 - -0.460) |
| Cox clinical    | Resting ECG  | ** -0.186(-0.209 - -0.166) | ** -0.231 ( -0.253 - -0.20)  | ** -0.611 ( -0.646 - -0.577)  |
| Cox clinical    | Exercise ECG | ** -0.174(-0.198 - -0.155) | ** -0.226 ( -0.248 - -0.205) | ** -0.482 ( -0.515 - -0.445)  |
| Cox clinical    | Recovery ECG | ** -0.173(-0.196 - -0.149) | ** -0.213 ( -0.235 - -0.19)  | ** -0.548 ( -0.583 - -0.513)  |
| Cox clinical    | Complete ECG | ** -0.189(-0.214 - -0.168) | ** -0.248 ( -0.269 - -0.227) | ** -0.618 ( -0.652 - -0.584)  |

Abbreviation: NRI = Net re classification index CI = Confidence intervals

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \*p value <0.05; \*\* p value < 0.001

ECG scores were derived from separate deep survival networks trained on raw ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), final 15-seconds of recovery and full 7-minute 15-second submaximal exercise ECG recording, respectively.

Age + Sex risk scores were derived using Cox proportional hazard regression, while QRISK3-Inspired risk scores were derived in separate Cox regression models for males and females, respectively.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 + Age FP 1 X Diabetes type 2 + Age FP 1 X hypertension + Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Systolic blood pressure + Age FP 2 X Diabetes type 1 + Age FP 2 X Diabetes type 2 + Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 + Diabetes type 1 + Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness Complete ECG = Full 7 minutes 15 seconds of raw ECG data from the complete submaximal exercise ECG test..



**Supplementary Table 23 Overall Performance of regression models for Age+ Sex, QRISK3-Inspired and Cox proportional hazard (Cox clinical) risk scores combined with Q-ECG risk scores measured by Harrell's C-index, Integrated calibration index (ICI) and Net benefit at a 10% risk threshold.**

| Model                   | C-Index               | ICI                      | Net benefit           |
|-------------------------|-----------------------|--------------------------|-----------------------|
| Age+ Sex                | 0.693(0.686 - 0.7)    | 0.0029(0.0016 - 0.0046)  | 0.178(0.16 - 0.198)   |
| Age + Sex + Q-ECG       |                       |                          |                       |
| Resting                 | 0.697(0.689 - 0.706)  | 0.0032(0.0016 - 0.0051)  | 0.185(0.165 - 0.206)) |
| Peak exercise           | 0.697(0.69 - 0.704)   | 0.0031(0.0016 - 0.0046)  | 0.185(0.167 - 0.205)  |
| Late-stage recovery     | 0.698(0.691 - 0.705)  | 0.0033(0.0019 - 0.0048)  | 0.185(0.165 - 0.205)  |
| Complete ECG            | 0.699(0.692 - 0.706)  | 0.0031(0.0017 - 0.0049)  | 0.189(0.17 - 0.208)   |
| QRISK3-Inspired         | 0.672(0.665 - 0.678)  | 0.0095 (0.0077 - 0.0116) | 0.218(0.196 - 0.238)  |
| QRISK3-Inspired + Q-ECG |                       |                          |                       |
| Resting                 | 0.672(0.665 - 0.68)   | 0.0094(0.0076 - 0.0115)  | 0.21(0.187 - 0.229)   |
| Peak exercise           | 0.674(0.667 - 0.682)) | 0.0095(0.0076 - 0.0118)  | 0.213(0.191 - 0.236)  |
| Late-stage recovery     | 0.671(0.665 - 0.679)  | 0.0104(0.0085 - 0.0123)  | 0.217(0.193 - 0.236)  |
| Complete ECG            | 0.673(0.667 - 0.681)  | 0.0096(0.0077 - 0.0118)  | 0.219(0.195 - 0.239)  |
| Cox clinical            | 0.714(0.707 - 0.722)  | 0.0035(0.002 - 0.0055)   | 0.218(0.197 - 0.242)  |
| Cox clinical+ Q-ECG     |                       |                          |                       |
| Resting                 | 0.711(0.704 - 0.718)  | 0.0032(0.002 - 0.0049)   | 0.212(0.191 - 0.235)  |
| Peak exercise           | 0.712(0.704 - 0.718)  | 0.0035(0.0019 - 0.0053)  | 0.215(0.193 - 0.235)  |
| Late-stage recovery     | 0.713(0.705 - 0.72)   | 0.0031(0.0016 - 0.005)   | 0.226(0.203 - 0.247)  |
| Complete ECG            | 0.716(0.705 - 0.72)   | 0.0029(0.0015 - 0.0047)  | 0.222(0.2 - 0.243)    |

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals were obtained via 1000 bootstrap iterations

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), final 15-seconds of recovery and full 7-minute 15-second submaximal exercise ECG recording, respectively.

Age + Sex risk scores were derived using Cox proportional hazard regression, while QRISK3-Inspired risk scores were derived in separate Cox regression models for males and females, respectively.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness

**Supplementary Table 24: Change in Discrimination (C-index) and Calibration (ICI) following the Addition of ECG risk scores derived from 15-Second Resting, Exercise, Recovery, and complete sub-maximal ECG recordings respectively from the UK biobank cardiorespiratory fitness study to Clinical Risk Models**

| Model                   | Comparator                      | $\Delta$ C-index        | $\Delta$ ICI           |
|-------------------------|---------------------------------|-------------------------|------------------------|
| <b>Study population</b> |                                 |                         |                        |
| Age + Sex               | Age + Sex+ Resting ECGQ-ECG     | ** 0.004(0.002 - 0.005) | 0(-0.001 - 0.001)      |
| Age + Sex               | Age + Sex+ Exercise Q-ECG       | * 0.003(0.001 - 0.005)  | 0(-0.001 - 0.001)      |
| Age + Sex               | Age + Sex+ Recovery Q-ECG       | ** 0.004(0.003 - 0.006) | 0.000(-0.001 - 0.002)  |
| Age + Sex               | Age + Sex+ Full Q-ECG           | ** 0.005(0.004 - 0.007) | 0(-0.001 - 0.001)      |
| QRISK3-Inspired         | QRISK3-Inspired+ Resting Q-ECG  | 0(-0.001 - 0.001)       |                        |
| QRISK3-Inspired         | QRISK3-Inspired+ Exercise Q-ECG | ** 0.002(0.001 - 0.004) | 0(-0.001 - 0.001)      |
| QRISK3-Inspired         | QRISK3-Inspired+ Recovery Q-ECG | 0(-0.002 - 0.001)       | *0.001(0 - 0.002)      |
| QRISK3-Inspired         | QRISK3-Inspired+ Full Q-ECG     | ** 0.002(0 - 0.003)     | 0(-0.001 - 0.001)      |
| Cox clinical            | Cox clinical + Resting Q-ECG    | 0.001(0 - 0.002)        | 0(-0.001 - 0)          |
| Cox clinical            | Cox clinical + Exercise Q-ECG   | 0.001(0 - 0.003)        | 0(-0.001 - 0.001)      |
| Cox clinical            | Cox clinical + Recovery Q-ECG   | ** 0.002(0.001 - 0.003) | 0(-0.001 - 0)          |
| Cox clinical            | Cox clinical + Full Q-ECG       | ** 0.002(0.001 - 0.003) | -0.001(-0.001 - 0)     |
| <b>Male</b>             |                                 |                         |                        |
| Age + Sex               | Age + Sex+ Resting Q-ECG        | ** 0.005(0.002 - 0.008) | -0.000(-0.002 - 0.002) |
| Age + Sex               | Age + Sex+ Exercise Q-ECG       | ** 0.003(0.001 - 0.006) | 0(-0.002 - 0.002)      |
| Age + Sex               | Age + Sex+ Recovery Q-ECG       | ** 0.007(0.005 - 0.01)  | 0(-0.002 - 0.002)      |
| Age + Sex               | Age + Sex+ Full Q-ECG           | ** 0.009(0.006 - 0.012) | -0.000(-0.002 - 0.002) |
| QRISK3-Inspired         | QRISK3-Inspired+ Resting Q-ECG  | 0(-0.002 - 0.002)       | *-0.002(-0.003 - 0)    |
| QRISK3-Inspired         | QRISK3-Inspired+ Exercise Q-ECG | ** 0.002(0 - 0.004)     | 0(-0.002 - 0.001)      |
| QRISK3-Inspired         | QRISK3-Inspired+ Recovery Q-ECG | ** 0.003(0.002 - 0.005) | 0(-0.001 - 0.002)      |
| QRISK3-Inspired         | QRISK3-Inspired+ Full Q-ECG     | ** 0.003(0.001 - 0.005) | 0(-0.002 - 0.001)      |
| Cox clinical            | Cox clinical + Resting Q-ECG    | 0.001(0 - 0.003)        | 0(-0.002 - 0.001)      |
| Cox clinical            | Cox clinical + Exercise Q-ECG   | 0.001(0 - 0.003)        | 0(-0.002 - 0.001)      |
| Cox clinical            | Cox clinical + Recovery Q-ECG   | ** 0.003(0.001 - 0.004) | -0.001(-0.002 - 0.001) |
| Cox clinical            | Cox clinical + Full Q-ECG       | ** 0.003(0.002 - 0.005) | 0(-0.002 - 0.001)      |
| <b>Female</b>           |                                 |                         |                        |
| Age + Sex               | Age + Sex+ Resting Q-ECG        | 0.004(-0.001 - 0.008)   | 0.000(-0.001 - 0.002)  |
| Age + Sex               | Age + Sex+ Exercise Q-ECG       | ** 0.006(0.002 - 0.01)  | 0.000(-0.001 - 0.001)  |
| Age + Sex               | Age + Sex+ Recovery Q-ECG       | ** 0.005(0.001 - 0.009) | 0(-0.001 - 0.001)      |
| Age + Sex               | Age + Sex+ Full Q-ECG           | ** 0.005(0.001 - 0.008) | 0.000(-0.001 - 0.001)  |
| QRISK3-Inspired         | QRISK3-Inspired+ Resting Q-ECG  | 0.001(-0.001 - 0.003)   | 4e-04(0 - 0.001)       |
| QRISK3-Inspired         | QRISK3-Inspired+ Exercise Q-ECG | ** 0.003(0 - 0.005)     | 3e-04(-0.001 - 0.001)  |
| QRISK3-Inspired         | QRISK3-Inspired+ Recovery Q-ECG | -0.007(-0.01 - -0.004)  | -0.001(-0.001 - 0.001) |
| QRISK3-Inspired         | QRISK3-Inspired+ Full Q-ECG     | 0(-0.002 - 0.002)       | 0.000(-0.001 - 0.001)  |

|              |                               |                       |                   |
|--------------|-------------------------------|-----------------------|-------------------|
| Cox clinical | Cox clinical + Resting Q-ECG  | 0.001(-0.001 - 0.003) | 0(-0.001 - 0.001) |
| Cox clinical | Cox clinical + Exercise Q-ECG | 0.002(0 - 0.005)      | 0(-0.001 - 0.001) |
| Cox clinical | Cox clinical + Recovery Q-ECG | 0.002(0 - 0.004)      | 0(-0.001 - 0.001) |
| Cox clinical | Cox clinical + Full Q-ECG     | 0.001(-0.001 - 0.003) | 0(-0.001 - 0.001) |

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals were obtained via 1000 bootstrap iterations.

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), final 15-seconds of recovery and full 7-minute 15-second submaximal exercise ECG recording, respectively.

Age + Sex risk scores were derived using Cox proportional hazard regression, while QRISK3-Inspired risk scores were derived in separate Cox regression models for males and females, respectively.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness

**Supplementary Table 25: Overall Performance Metrics of Deep Survival Models derived from Age + Sex and QRISK3 Risk Factors, respectively, combined with ECG Scores from Resting, Peak Exercise, Late-Stage Recovery, and Complete ECG Recordings, Evaluated by Harrell's C-index, Integrated Calibration Index (ICI), and Net Benefit at a 10% Risk Threshold**

| Model                        | C-Index (95% CI)     | ICI (95% CI)             | Net benefit (95% CI) |
|------------------------------|----------------------|--------------------------|----------------------|
| Age+ Sex                     | 0.693(0.686 - 0.7)   | 0.0030(0.0015 - 0.0049)  | 0.178(0.16 - 0.198)  |
| Age + Sex + ECG (DSN)        |                      |                          |                      |
| Resting                      | 0.700(0.693 - 0.707) | 0.0026(0.0013 - 0.0044)  | 0.191(0.175 - 0.208) |
| Peak exercise                | 0.692(0.685 - 0.699) | 0.0032(0.0017 - 0.0048)  | 0.186(0.167 - 0.206) |
| Late-stage recovery          | 0.702(0.695 - 0.708) | 0.0031(0.0019 - 0.0047)  | 0.204(0.182 - 0.221) |
| Complete ECG                 | 0.692(0.685 - 0.699) | 0.0044(0.0026 - 0.0063)  | 0.185(0.165 - 0.205) |
| Clinical deep survival       | 0.7(0.692 - 0.708)   | 0.004(0.003 - 0.006)     | 0.209(0.193 - 0.232) |
| Clinical deep survival + ECG |                      |                          |                      |
| Resting                      | 0.709(0.702 - 0.717) | 0.0040 (0.0020 - 0.0061) | 0.207(0.188 - 0.229) |
| Peak exercise                | 0.697(0.69 - 0.704)  | 0.0035 (0.0016 - 0.0055) | 0.189(0.168 - 0.208) |
| Late-stage recovery          | 0.708(0.701 - 0.715) | 0.0026 (0.0013 - 0.0041) | 0.211(0.189 - 0.23   |
| Complete ECG                 | 0.704(0.697 - 0.712) | 0.0026 (0.0011 - 0.0042) | 0.214 (0.194 0.238)  |

Abbreviations: ICI = Integrated calibration index; CI = confidence intervals;

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals were obtained via 1000 bootstrap iterations

Each row corresponds to a separate risk score, fitted independently with the selected risk factors, and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

Age + Sex and clinical risk factors were integrated with ECG recordings in separate deep survival networks trained on raw ECG recordings during 15-seconds of rest, the final 15-seconds of exercise (peak exercise intensity), final 15-seconds of recovery and full 7-minute 15-second submaximal exercise ECG recording, respectively.

Clinical deep survival: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 26: Relative Change in Model Discrimination and Calibration for Age + Sex vs. Age + Sex + ECG Deep Survival Networks, QRISK3-Inspired risk scores vs. Clinical DSN, and Clinical DSN vs. Clinical DSN + ECG. Discrimination and calibration were assessed using Harrell's C-index and Integrated Calibration Index (ICI), respectively, after adding ECG data from resting, exercise, recovery, and complete ECG recordings.**

| Model                   | Comparator                  | ΔC-index                 | ΔICI                      |
|-------------------------|-----------------------------|--------------------------|---------------------------|
| <b>Study population</b> |                             |                          |                           |
| Age + Sex               | Age + Sex+ Resting ECG      | **0.006(0.003 - 0.01)    | 0.000(-0.002 - 0.002)     |
| Age + Sex               | Age + Sex+ Exercise ECG     | *0.004(0.002 - 0.007)    | 0.000(-0.001 - 0.002)     |
| Age + Sex               | Age + Sex+ Recovery ECG     | **0.008(0.005 - 0.012)   | 0.000(-0.002 - 0.002)     |
| Age + Sex               | Age + Sex+ Full ECG         | -0.002(-0.005 - 0.002)   | 0.001(-0.001 - 0.004)     |
| QRISK3-Inspired         | DSN clinical + Resting ECG  | **0.037(0.032 - 0.042)   | **0.006(-0.007 - -0.004)  |
| QRISK3-Inspired         | DSN clinical + Exercise ECG | **0.025(0.02 - 0.031)    | **0.007(-0.009 - -0.004)  |
| QRISK3-Inspired         | DSN clinical + Recovery ECG | **0.036(0.03 - 0.04)     | **0.006(-0.008 - -0.004)  |
| QRISK3-Inspired         | DSN clinical + Full ECG     | **0.033(0.027 - 0.038)   | **0.007(-0.009 - -0.005)  |
| DSN clinical            | DSN clinical + Resting ECG  | **0.006(0.003 - 0.01)    |                           |
| DSN clinical            | DSN clinical + Exercise ECG | *0.004(0.002 - 0.007)    | -0.001(-0.002 - 0.001)    |
| DSN clinical            | DSN clinical + Recovery ECG | **0.008(0.005 - 0.012)   | -0.002(-0.005 - 0.001)    |
| DSN clinical            | DSN clinical + Full ECG     | **0.002(-0.005 - 0.002)  | -0.001(-0.002 - 0)        |
| DSN clinical            | DSN clinical + Full ECG     | 0.001(-0.002 - 0.003)    | *-0.002(-0.004 - 0)       |
| <b>Male</b>             |                             |                          |                           |
| Age + Sex               | Age + Sex+ Resting ECG      | **0.011(0.006 - 0.016)   | 0.001(-0.005 - 0.003)     |
| Age + Sex               | Age + Sex+ Exercise ECG     | *0.007(0.003 - 0.011)    | 0.000(-0.004 - 0.004)     |
| Age + Sex               | Age + Sex+ Recovery ECG     | **0.012(0.007 - 0.017)   | -0.001(-0.004 - 0.003)    |
| Age + Sex               | Age + Sex+ Full ECG         | -0.001(-0.006 - 0.003)   | 0(-0.004 - 0.004)         |
| QRISK3-Inspired         | DSN clinical + Resting ECG  | 0.005(-0.001 - 0.01)     | **0.017(-0.02 - -0.014)   |
| QRISK3-Inspired         | DSN clinical + Exercise ECG | **0.009(-0.016 - -0.003) | **0.0192(-0.024 - -0.014) |
| QRISK3-Inspired         | DSN clinical + Recovery ECG | 0.003(-0.002 - 0.008)    | **0.0173(-0.02 - -0.015)  |
| QRISK3-Inspired         | DSN clinical + Full ECG     | -0.002(-0.007 - 0.003)   | **0.0198(-0.023 - -0.016) |
| DSN clinical            | DSN clinical + Resting ECG  | 0.003(-0.002 - 0.007)    | -0.001(-0.003 - 0.001)    |
| DSN clinical            | DSN clinical + Exercise ECG | -0.011(-0.017 - -0.006)  | -0.003(-0.007 - 0)        |
| DSN clinical            | DSN clinical + Recovery ECG | 0.001(-0.004 - 0.006)    | 0.001(-0.003 - 0.001)     |
| DSN clinical            | DSN clinical + Full ECG     | -0.004(-0.007 - 0.001)   | **0.004(-0.006 - -0.002)  |
| <b>Female</b>           |                             |                          |                           |
| Age + Sex               | Age + Sex+ Resting ECG      | 0.004(-0.002 - 0.011)    | 0.0001(-0.001 - 0.002)    |
| Age + Sex               | Age + Sex+ Exercise ECG     | 0.005(0 - 0.01)          | *0.0019(0 - 0.003)        |
| Age + Sex               | Age + Sex+ Recovery ECG     | *0.01(0.003 - 0.017)     | -0.000(-0.001 - 0.002)    |
| Age + Sex               | Age + Sex+ Full ECG         | -0.004(-0.012 - 0.003)   | 0.0021(0 - 0.004)         |
| QRISK3-Inspired         | DSN clinical + Resting ECG  | **0.015(0.008 - 0.021)   | -0.0026(-0.006 - 0.001)   |
| QRISK3-Inspired         | DSN clinical + Exercise ECG | 0.005(-0.005 - 0.013)    | *-0.004(-0.009 - -0.001)  |

|                 |                             |                        |                         |
|-----------------|-----------------------------|------------------------|-------------------------|
| QRISK3-Inspired | DSN clinical + Recovery ECG | **0.014(0.009 - 0.021) | -0.0034(-0.007 - 0)     |
| QRISK3-Inspired | DSN clinical + Full ECG     | **0.011(0.005 - 0.018) | -0.0032(-0.008 - 0.001) |
| DSN clinical    | DSN clinical + Resting ECG  | **0.011(0.003 - 0.019) | 0.001(-0.001 - 0.002)   |
| DSN clinical    | DSN clinical + Exercise ECG | 0.001(-0.007 - 0.008)  | -0.001(-0.003 - 0.001)  |
| DSN clinical    | DSN clinical + Recovery ECG | **0.011(0.003 - 0.018) | 0(-0.002 - 0.001)       |
| DSN clinical    | DSN clinical + Full ECG     | **0.007(0.002 - 0.011) | 0(-0.001 - 0.001)       |

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p-values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p* value < 0.05; \*\* *p* value < 0.001

Each row corresponds to a separate risk score, fitted independently with the selected risk factors.05; \*d independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

Age+Sex and QRISK3-Inspired risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate (Age+Sex+Q-ECG; QRISK3-Inspired+Q-ECG).

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

DSN-clinical: Age, BMI, systolic blood-pressure, SBP5, Diabetes typ1,, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 27: Comparative Reclassification Performance of QRISK3-Inspired, Cox Proportional Hazards (Cox Clinical), and Clinical Deep Survival Models Using QRISK3-Inspired Risk Factors at a 10% Risk Threshold. Metrics include Net Benefit, Categorical Net Reclassification Index (NRI), and Continuous NRI, evaluated across the overall population, plus male, and female subgroups.**

| Model                                  | Comparator   | ΔNet-benefit<br>(95% CI) | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|----------------------------------------|--------------|--------------------------|-----------------------------|----------------------------|
| <b>Overall</b>                         |              |                          |                             |                            |
| QRISK3-Inspired Cox clinical           |              | 0.00(-0.01 - 0.01)       | 0.00 ( -0.01 - 0.010)       | **0.185 (0.149 - 0.221)    |
| QRISK3-Inspired Clinical deep survival |              | -0.009(-0.022 - 0.003)   | -0.009 ( -0.022 - 0.004)    | **0.089 (0.052 - 0.126)    |
| Clinical deep survival                 | Cox clinical | 0.009(-0.003 - 0.02)     | -0.009 ( -0.020 - 0.002)    | **0.240 ( -0.276 - 0.204)  |
| <b>Male</b>                            |              |                          |                             |                            |
| QRISK3-Inspired Cox clinical           |              | -0.01(-0.019 - 0.001)    | -0.009 ( -0.019 - 0.001)    | **0.289 (0.244 - 0.334)    |
| QRISK3-Inspired Clinical deep survival |              | *-0.017(-0.032 - -0.001) | -0.017 ( -0.031- -0.002)    | **0.163 (0.118 - 0.208)    |
| Clinical deep survival                 | Cox clinical | 0.006(-0.006 - 0.021)    | 0.01 ( -0.007 - 0.021)      | **0.240 (0.195 - 0.284)    |
| <b>Female</b>                          |              |                          |                             |                            |
| QRISK3-Inspired Cox clinical           |              | *0.022(0.001 - 0.049)    | **0.065(0.042 - 0.088)      | **0.217 (0.159 - 0.276)    |
| QRISK3-Inspired Clinical deep survival |              | 0.006(-0.02 - 0.032)     | ** 0.056 (0.033 - 0.080)    | **0.144 (0.081 - 0.207)    |
| Clinical deep survival                 | Cox clinical | 0.016(-0.005 - 0.039)    | : 0.009 ( -0.010 - 0.0282)  | **0.191 (0.127 - 0.256)    |

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value <0.05*; \*\**p value <0.001*

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness

Clinical deep survival: Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 28 Reclassification performance following the addition of ECG risk scores derived from rest, exercise, recovery and complete submaximal exercise ECG recording, to, Age + Sex, QRISK3-Inspired and linear cox regression (Cox clinical) risk scores, at a 10% risk threshold**

| Model           | Comparator                    | Net-benefit<br>(95% CI)  | Categorical NRI (95% CI)     | Continuous NRI<br>(95% CI) |
|-----------------|-------------------------------|--------------------------|------------------------------|----------------------------|
| Age + Sex       | Age + Sex+ Resting ECG        | 0.007(-0.002 - 0.016)    | 0.007 ( -0.0024 - 0.016)     | **0.144 (0.107 - 0.181)    |
| Age + Sex       | Age + Sex+ Exercise ECG       | 0.006(-0.002 - 0.015)    | 0.006 (-0.0028 - 0.015)      | **0.119 (0.082 - 0.156)    |
| Age + Sex       | Age + Sex+ Recovery ECG       | 0.006(-0.001 - 0.015)    | 0.006 (-0.0028 - 0.015)      | **0.139 (0.102 - 0.176)    |
| Age + Sex       | Age + Sex+ Full ECG           | **0.01(0.002 - 0.018)    | 0.009 ( -0.003 - 0.018)      | **0.175 (0.139 - 0.211)    |
| QRISK3-Inspired | QRISK3-Inspired+ Resting ECG  | *-0.009(-0.015 - -0.003) | * -0.0095 ( -0.016 - -0.003) | *0.056 (0.019 - 0.093)     |
| QRISK3-Inspired | QRISK3-Inspired+ Exercise ECG | -0.005(-0.011 - 0.001)   | *-0.0071 ( -0.0137 - -5e-04) | **0.072 (0.035 - 0.109)    |
| QRISK3-Inspired | QRISK3-Inspired+ Recovery ECG | -0.001(-0.007 - 0.004)   | -0.0022 ( -0.0078 - 0.003)   | 0.031 (-0.006 - 0.068)     |
| QRISK3-Inspired | QRISK3-Inspired+ Full ECG     | 0.001(-0.006 - 0.007)    | 0.000( -0.007 - 0.007)       | **0.097 (0.061 - 0.133)    |
| Cox clinical    | Cox clinical + Resting ECG    | 0.004(-0.005 - 0.012)    | -0.006 ( -0.0134 - 0.001)    | **0.088 (0.051 - 0.125)    |
| Cox clinical    | Cox clinical + Exercise ECG   | -0.003(-0.011 - 0.005)   | -0.004 ( -0.0126 - 0.004)    | ** 0.084 (0.047 - 0.120)   |
| Cox clinical    | Cox clinical + Recovery ECG   | *0.008(0.001 - 0.017)    | *0.008 (0.001 - 0.015)       | ** 0.085 (0.048 - 0.121)   |
| Cox clinical    | Cox clinical + Full ECG       | 0.004(-0.005 - 0.012)    | 0.003 ( -0.0055 - 0.0105)    | **0.103 (0.066 - 0.139)    |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* <0.05; \*\* *p value* < 0.001; Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

Age+Sex, QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression.

Extended Cox models additionally included the Q-ECG score as a covariate (Age+Sex+Q-ECG; QRISK3-Inspired+Q-ECG); Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ; **Fractional polynomials:**  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

**Cox-clinical:** Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness

**DSN-clinical:** Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness



**Supplementary Table 29 Reclassification Performance following the Addition of ECG Risk Scores (Resting, Exercise, Recovery, and Complete ECG) to Age + Sex, QRISK3-Inspired, Cox Clinical risk scores and Deep Survival Networks (DSN) developed using QRSIK3 factors at a 10% Risk Threshold**

| Model           | Comparator                    | Net-benefit (95% CI)       | Categorical NRI (95% CI)     | Continuous NRI (95% CI)      |
|-----------------|-------------------------------|----------------------------|------------------------------|------------------------------|
| Age + Sex       | Age + Sex+ Resting ECG (DSN)  | *0.013(0.00 - 0.026)       | 0.007 ( -0.006 - 0.019)      | *0.055 (0.018 - 0.092)       |
| Age + Sex       | Age + Sex+ Exercise ECG (DSN) | 0.008(-0.004 - 0.02)       | 0.004 ( -0.008 - 0.017)      | 0.035 ( -0.002 - 0.071)      |
| Age + Sex       | Age + Sex+ Recovery ECG (DSN) | **0.026(0.013 - 0.038)     | *0.018 (0.005 - 0.030)       | **0.179 (0.142 - 0.216)      |
| Age + Sex       | Age + Sex+ Full ECG (DSN)     | 0.006(-0.005 - 0.017)      | *0.013 (0.002 - 0.024)       | **0.127 (0.090 - 0.164)      |
| QRISK3-Inspired | Clinical DSN + Resting ECG    | -0.011(-0.023 - 0.001)     | -0.004 ( -0.016 - 0.008)     | **0.146 (0.110 - 0.182)      |
| QRISK3-Inspired | Clinical DSN +Exercise ECG    | ** -0.029(-0.041 - -0.016) | ** -0.025 ( -0.039 - -0.011) | ** 0.144 (0.108 - 0.180)     |
| QRISK3-Inspired | Clinical DSN +Recovery ECG    | -0.007(-0.018 - 0.004)     | -0.0014 ( -0.014 - 0.011)    | **0.136 (0.099 - 0.172)      |
| QRISK3-Inspired | Clinical DSN +Complete ECG    | -0.004(-0.016 - 0.008)     | 0.0051 ( -0.007 - 0.017)     | **0.230 (0.193 - 0.266)      |
| Cox clinical    | Clinical DSN +Resting ECG     | -0.01(-0.021 - 0.001)      | -0.004 ( -0.015 - 0.006)     | ** -0.198 ( -0.235 - -0.162) |
| Cox clinical    | Clinical DSN +Exercise ECG    | ** -0.029(-0.04 - -0.014)  | -0.025 (-0.039 - -0.011)     | ** -0.109 (-0.146 - -0.072)  |
| Cox clinical    | Clinical DSN +Recovery ECG    | -0.007(-0.018 - 0.002)     | -0.001 ( -0.012 - 0.009)     | ** -0.210 ( -0.247 - -0.174) |
| Cox clinical    | Clinical DSN +Complete ECG    | -0.004(-0.013 - 0.007)     | 0.005 ( -0.005 - 0.015)      | ** -0.025 ( -0.062 - 0.012)  |
| Clinical DSN    | Clinical DSN +Resting ECG     | -0.001(-0.013 - 0.01)      | 0.005 ( -0.008 - 0.017)      | **0.074 (0.038 - 0.111)      |
| Clinical DSN    | Clinical DSN +Exercise ECG    | ** -0.02(-0.03 - -0.005)   | * -0.016 ( -0.030 - -0.003)  | **0.074 (0.037 - 0.110)      |
| Clinical DSN    | Clinical DSN +Recovery ECG    | 0.002(-0.01 - 0.012)       | 0.008 ( -0.005 - 0.020)      | **0.050 (0.013 - 0.086)      |
| Clinical DSN    | Clinical DSN +Complete ECG    | 0.005(-0.007 - 0.016)      | * 0.014 (0.003 - 0.025)      | **0.272 (0.235 - 0.308)      |

Abbreviations: NRI = Net re classification index, CI = Confidence interval, DSN = Deep survival network

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* <0.05; \*\**p value* < 0.001; Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0; QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate (QRISK3-Inspired+Q-ECG, **Cox clinical**); Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively; **QRISK3-Inspired**: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ; Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; **Cox-clinical**: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness; DSN-clinical: Age, BMI, systolic blood-pressure, SBP5,Diabetes type 1, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 30 : Changes in Net reclassification and net-benefit to QRISK3-Inspired risk scores, linear cox regression (Cox clinical) and deep survival networks (clinical DSN) derived from QRISK3 risk factors, following the addition of conventional ECG parameters combined from rest, exercise, and recovery ECG recordings, and at a recommend risk threshold of 10%**

| Model           | Comparator       | Net-benefit<br>(95% CI) | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|-----------------|------------------|-------------------------|-----------------------------|----------------------------|
| QRISK3-Inspired | QRISK3-Inspired+ | -0.004(-0.016 - 0.009)  | -0.007 (-0.019 - 0.006)     | **0.114 (0.074 - 0.154)    |
| Cox clinical    | Combined-ECG     |                         |                             |                            |
| Cox clinical    | Cox clinical+    | 0.01(-0.002 - 0.022)    | 0.007(-0.005 - 0.019)       | **0.088 (0.049 - 0.128)    |
| Clinical DSN    | Combined-ECG     |                         |                             |                            |
| Clinical DSN    | Clinical DSN+    | 0.01(-0.004 - 0.024)    | 0.006(-0.008 - 0.019)       | 0.036(-0.004 - 0.074)      |
| DSN             | Combined-ECG     |                         |                             |                            |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \*p value <0.05; \*\*p value < 0.001

ECG parameters: Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence; Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate (QRISK3-Inspired+Q-ECG; Cox clinical + Q-ECG).

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type + Diabetes type 2 + HDL ratio + Townsend deprivation index + Smoker former + Smoker current + Smoker never + Ethnic Background + Corticosteroid + Migraine + Hypertension + Severe mental illness

DSN-clinical: Age, BMI, systolic blood-pressure, SBP5,Diabetes type 1 , Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 31: Reclassification Performance, at a 10% Risk Threshold, Following the addition of Conventional ECG Parameters – recorded During Rest, Exercise, Recovery, and Combined intervals of all 3 stages to QRISK3-Inspired and Cox clinical risk scores .**

| Model           | Comparator                    | Net-benefit<br>(95% CI)  | Categorical NRI<br>(95% CI) | Continuous NRI<br>(95% CI) |
|-----------------|-------------------------------|--------------------------|-----------------------------|----------------------------|
| <b>Male</b>     |                               |                          |                             |                            |
| QRISK3-Inspired | QRISK3-Inspired+ Resting ECG  | -0.006(-0.013 - 0.002)   | -0.006 ( -0.014 - 0.003)    | 0.03 ( -0.018 - 0.078)     |
| QRISK3-Inspired | QRISK3-Inspired+ Exercise ECG | 0.003(-0.009 - 0.016)    | 0.003 ( -0.009 - 0.014)     | **0.104 (0.055 - 0.152)    |
| QRISK3-Inspired | QRISK3-Inspired+ Recovery ECG | 0.001(-0.008 - 0.01)     | 0.001 ( -0.009 - 0.010)     | ** 0.085 (0.037 - 0.134)   |
| QRISK3-Inspired | QRISK3-Inspired+ Combined ECG | -0.006(-0.019 - 0.008)   | -0.006 ( -0.021 - 0.009)    | **0.106 (0.058 - 0.155)    |
| Cox clinical    | Cox clinical + Resting ECG    | -0.002(-0.009 - 0.004)   | -0.002 ( -0.010 - 0.005)    | * 0.053 (0.005 - 0.101)    |
| Cox clinical    | Cox clinical + Exercise ECG   | 0(-0.013 - 0.011)        | 0.000 ( -0.013 - 0.012)     | ** 0.107 (0.058 - 0.155)   |
| Cox clinical    | Cox clinical + Recovery ECG   | -0.004(-0.014 - 0.007)   | -0.004 ( -0.014 - 0.006)    | ** 0.077 (0.028 - 0.125)   |
| Cox clinical    | Cox clinical + Combined ECG   | 0.009(-0.003 - 0.026)    | 0.009 ( -0.006 - 0.023)     | ** 0.126 (0.077 - 0.174)   |
| <b>Female</b>   |                               |                          |                             |                            |
| QRISK3-Inspired | QRISK3-Inspired+ Resting ECG  | *-0.012(-0.024 - -0.001) | -0.010 ( -0.022 - 0.001)    | 0.016 ( -0.055 - 0.087)    |
| QRISK3-Inspired | QRISK3-Inspired+ Exercise ECG | 0.009(-0.017 - 0.035)    | 0.009 ( -0.012 - 0.031)     | 0.035 ( -0.035 - 0.105)    |
| QRISK3-Inspired | QRISK3-Inspired+ Recovery ECG | 0(-0.016 - 0.018)        | 0.003 ( -0.0136 - 0.020)    | * 0.081 (0.011 - 0.151)    |
| QRISK3-Inspired | QRISK3-Inspired+ Combined ECG | 0(-0.026 - 0.032)        | 0.009 ( -0.015 - 0.033)     | *0.096 (0.026 - 0.167)     |
| Cox clinical    | Cox clinical + Resting ECG    | -0.006(-0.021 - 0.004)   | -0.008 ( -0.0201 - 0.005)   | -0.051 ( -0.1217 - 0.019)  |
| Cox clinical    | Cox clinical + Exercise ECG   | 0.017(-0.001 - 0.036)    | *0.019 (0.002 - 0.035)      | 0.045 ( -0.0261 - 0.115)   |
| Cox clinical    | Cox clinical + Recovery ECG   | 0.004(-0.013 - 0.02)     | 0.004 ( -0.01 - 0.019)      | 0.059 ( -0.013 - 0.130)    |
| Cox clinical    | Cox clinical + Combined ECG   | 0.013(-0.011 - 0.036) p  | 0.016 ( -0.006 - 0.038)     | 0.057 ( -0.0143 - 0.128)   |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \*p value <0.05; \*\* p value < 0.001

ECG parameters: Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence; Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate (QRISK3-Inspired+Q-ECG; Cox clinical + Q-ECG).

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Migraine + Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1 + Diabetes type 2 + HDL ratio + Townsend deprivation index + Smoker former + Smoker current + Smoker never + Ethnic Background + Corticosteroid + Migraine + Hypertension + Severe mental illness

**Supplementary Table 32: Reclassification Performance of QRISK3-Inspired and Cox Proportional Hazards Models Compared to Clinical DSN + Conventional ECG Parameters at a 10% Risk Threshold – ECG Measurements Derived from Rest, Exercise, Recovery, and Combined intervals of all 3 stages**

| Model           | Comparator                  | Net-benefit (95% CI)      | Categorical NRI (95% CI) | Continuous NRI (95% CI)       |
|-----------------|-----------------------------|---------------------------|--------------------------|-------------------------------|
| <b>Male</b>     |                             |                           |                          |                               |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.012(-0.027 - 0.003)    | -0.012 ( -0.027 - 0.002) | ** -0.131 ( -0.177 - -0.084)  |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.011(-0.028 - 0.006)    | -0.012 ( -0.029 - 0.005) | -0.0716 ( -0.119 - -0.024)    |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | 0.009(-0.006 - 0.025)     | 0.009 ( -0.006 - 0.024)  | ** -0.110 ( -0.158 - -0.062)  |
| QRISK3-Inspired | Clinical DSN + Combined ECG | -0.011(-0.025 - 0.004)    | -0.011 ( -0.026 - 0.004) | ** -0.097 ( -0.144 - -0.049)  |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.011(-0.026 - 0.003)    | -0.012 ( -0.027 - 0.002) | ** -0.137 ( -0.185 - -0.0900) |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.01(-0.027 - 0.007)     | -0.013 ( -0.029 - 0.004) | * -0.059 ( -0.107 - -0.011)   |
| Cox clinical    | Clinical DSN + Recovery ECG | 0.01(-0.005 - 0.025)      | 0.009 ( -0.006 - 0.024)  | ** -0.114 ( -0.162 - -0.065)  |
| Cox clinical    | Clinical DSN + Combined ECG | -0.009(-0.024 - 0.005)    | -0.012 ( -0.026 - 0.003) | ** -0.094 ( -0.143 - -0.046)  |
| <b>Female</b>   |                             |                           |                          |                               |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.007(-0.03 - 0.016)     | 0.008 ( -0.013 - 0.029)  | * -0.076 ( -0.146 - -0.006)   |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.011(-0.038 - 0.014)    | 0.020 ( -0.006 - 0.046)  | -0.031 ( -0.101 - 0.039)      |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | -0.018(-0.041 - 0.003)    | 0.006 ( -0.016 - 0.027)  | -0.021 ( -0.091 - 0.048)      |
| QRISK3-Inspired | Clinical DSN + Combined ECG | 0.003(-0.019 - 0.025)     | 0.011 ( -0.011 - 0.032)  | * -0.115 ( -0.185 - -0.045)   |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.013(-0.035 - 0.009)    | 0.013 ( -0.007 - 0.033)  | -0.024 ( -0.096 - 0.047)      |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.017(-0.045 - 0.009)    | * 0.025 (0.000 - 0.050)  | 0.047 ( -0.024 - 0.118)       |
| Cox clinical    | Clinical DSN + Recovery ECG | * -0.024(-0.047 - -0.001) | 0.010 ( -0.011 - 0.032)  | 0.043 ( -0.028 - 0.114)       |
| Cox clinical    | Clinical DSN + Combined ECG | -0.003(-0.027 - 0.021)    | 0.015 ( -0.0062 - 0.037) | * 0.104 ( -0.175 - -0.033)    |

Data are reported on 35,597 participants with measurable ECG parameters, 2,591 (7.27%) MACCE were reported within 10-years. 95% confidence intervals and p-values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* < 0.05; \*\**p value* < 0.001; Each row corresponds to a separate risk score, fitted independently with the selected risk factors, and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0; QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

**ECG parameters:** Resting ECG parameters: QRS interval, QTc interval, Anisotropy evidence, Atrial Tachycardia evidence, PVC count, regularity Evidence; Exercise ECG parameters: PR interval, QRS interval, QTc interval, RR Interval, Atrial Tachycardia evidence, PVC count, regularity evidence Recovery ECG parameters: Irregularity evidence, QRS interval, QTc interval, Atrial Tachycardia evidence, regularity evidence.

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment;

**Fractional polynomials:** Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

**DSN-clinical/ Cox clinical:** Age, BMI, systolic blood-pressure, SBP5, Diabetes type 1, Diabetes type 2, HDL ratio, Townsend deprivation index, Smoker former, Smoker current, Smoker never, Ethnic Background, Corticosteroid, Migraine, Hypertension, Severe mental illness

**Supplementary Table 33 Reclassification performance of QRISK3-Inspired and linear Cox proportional hazard (Cox clinical) risk scores following the addition of ECG risk scores, at a 10% risk threshold. ECG measurements were recorded during the first 15 seconds of rest, final 15 seconds of exercise, and final 15 seconds of recovery and complete ECG recordings**

| Model           | Comparator                    | Net-benefit (95% CI)    | Categorical NRI (95% CI)    | Continuous NRI (95% CI)   |
|-----------------|-------------------------------|-------------------------|-----------------------------|---------------------------|
| <b>Male</b>     |                               |                         |                             |                           |
| QRISK3-Inspired | QRISK3-Inspired+ Resting ECG  | -0.005(-0.012 - 0.002)  | * -0.012 ( -0.020 - -0.003) | * 0.065 (0.019 - 0.110)   |
| QRISK3-Inspired | QRISK3-Inspired+ Exercise ECG | *-0.01(-0.018 - -0.002) | *-0.010 ( -0.018 - -0.001)  | *0.053 (0.008 - 0.098)    |
| QRISK3-Inspired | QRISK3-Inspired+ Recovery ECG | 0(-0.008 - 0.008)       | -0.001 ( -0.008 - 0.007)    | **0.090 (0.045 - 0.135)   |
| QRISK3-Inspired | QRISK3-Inspired+ Full ECG     | -0.001(-0.01 - 0.008)   | -0.001 ( -0.010 - 0.009)    | **0.108 (0.063 - 0.152)   |
| Cox clinical    | Cox clinical + Resting ECG    | 0.002(-0.007 - 0.012)   | -0.008 ( -0.017 - 0.001)    | 0.065 (0.020 - 0.111)     |
| Cox clinical    | Cox clinical + Exercise ECG   | -0.008(-0.017 - 0.002)  | -0.007 ( -0.018 - 0.003)    | **0.085 (0.040 - 0.131)   |
| Cox clinical    | Cox clinical + Recovery ECG   | 0.008(-0.001 - 0.016)   | 0.008 ( -0.001 - 0.016)     | **0.091 (0.045 - 0.136)   |
| Cox clinical    | Cox clinical + Full ECG       | 0.002(-0.007 - 0.012)   | 0.003 ( -0.007 - 0.012)     | ** 0.107 (0.063 - 0.151)  |
| <b>Female</b>   |                               |                         |                             |                           |
| QRISK3-Inspired | QRISK3-Inspired+ Resting ECG  | -0.001(-0.006 - 0.004)  | -0.001 ( -0.006 - 0.005)    | 0.034 ( -0.031 - 0.098)   |
| QRISK3-Inspired | QRISK3-Inspired+ Exercise ECG | 0.005(-0.007 - 0.017)   | 0.004 ( -0.007 - 0.016)     | 0.069 (0.005 - 0.1342)    |
| QRISK3-Inspired | QRISK3-Inspired+ Recovery ECG | -0.002(-0.007 - 0.005)  | -0.002 ( -0.009 - 0.004)    | -0.052 ( -0.117 - 0.0124) |
| QRISK3-Inspired | QRISK3-Inspired+ Full ECG     | 0.005(-0.002 - 0.014)   | 0.007 ( -0.001 - 0.015)     | * 0.093 (0.029 - 0.157)   |
| Cox clinical    | Cox clinical + Resting ECG    | 0.007(-0.008 - 0.022)   | 0 ( -0.012 - 0.013)         | **0.096 (0.031 - 0.1604)  |
| Cox clinical    | Cox clinical + Exercise ECG   | 0.006(-0.011 - 0.023)   | 0.005 ( -0.009 - 0.02)      | *0.072 (0.007 - 0.137)    |
| Cox clinical    | Cox clinical + Recovery ECG   | 0.01(-0.006 - 0.026)    | 0.011 ( -0.004 - 0.026)     | * 0.076 (0.012 - 0.141)   |
| Cox clinical    | Cox clinical + Full ECG       | 0.007(-0.008 - 0.022)   | 0.007 ( -0.008 - 0.022)     | ** 0.105 (0.042 - 0.169)  |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p-values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p* value < 0.05; \*\* *p* value < 0.001; Each row corresponds to a separate risk score, fitted independently with the selected risk factors, and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate;

Q-ECG scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ; **Fractional polynomials:**  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

**Cox-clinical:** Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

**Supplementary Table 34 Reclassification performance of QRISK3-Inspired and linear Cox proportional hazard (Cox clinical) risk scores vs clinical DSN + ECG measurements recorded at rest, exercise, recovery and complete ECG recordings at 10% risk thresholds**

| Model           | Comparator                  | Net-benefit (95% CI)       | Categorical NRI (95% CI)     | Continuous NRI (95% CI)      |
|-----------------|-----------------------------|----------------------------|------------------------------|------------------------------|
| <b>Male</b>     |                             |                            |                              |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.020(-0.033 - -0.007)    | *-0.020 ( -0.033 - -0.007)   | ** 0.213 (0.168 - 0.258)     |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *-0.049(-0.064 - -0.032)   | ** -0.048 ( -0.064 - -0.031) | ** 0.181 (0.136 - 0.226)     |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | *-0.018(-0.03 - -0.006)    | *-0.018 ( -0.031 - -0.004)   | **0.196 (0.151 - 0.241)      |
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.013(-0.025 - 0)         | -0.013 ( -0.025 - 0)         | **0.268 (0.224 - 0.313)      |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.01(-0.021 - 0.003)      | -0.010 ( -0.023 - 0.002)     | -0.235 ( -0.279 - -0.190)    |
| Cox clinical    | Clinical DSN + Exercise ECG | ** -0.038(-0.055 - -0.018) | ** -0.038 ( -0.055 - -0.022) | ** -0.214 ( -0.259 - -0.168) |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.007(-0.018 - 0.002)     | -0.008 ( -0.021 - 0.004)     | ** -0.251 ( -0.295 - -0.206) |
| Cox clinical    | Clinical DSN + Full ECG     | -0.002(-0.013 - 0.01)      | -0.003 ( -0.015 - 0.009)     | -0.038 ( -0.082 - 0.007)     |
| <b>Female</b>   |                             |                            |                              |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | 0.011(-0.014 - 0.04)       | ** 0.079 (0.055 - 0.103)     | ** 0.228 (0.169 - 0.287)     |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | 0.014(-0.012 - 0.038)      | **0.067 (0.041 - 0.092)      | ** 0.172 (0.110 - 0.235)     |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | 0.015(-0.01 - 0.04)        | **0.080 (0.055 - 0.104)      | **0.218 (0.158 - 0.277)      |
| QRISK3-Inspired | Clinical DSN + Full ECG     | 0.015(-0.01 - 0.0437)      | **0.085 (0.061 - 0.108)      | ** 0.252 (0.189 - 0.314)     |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.012(-0.034 - 0.01)      | 0.014 ( -0.007 - 0.035)      | -0.005 ( -0.069 - 0.059)     |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.009(-0.03 - 0.017)      | 0.002 ( -0.022 - 0.025)      | 0.026 ( -0.039 - 0.090)      |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.007(-0.023 - 0.015)     | 0.014 ( -0.007 - 0.035)      | -0.081 ( -0.146 - -0.017)    |
| Cox clinical    | Clinical DSN + Full ECG     | -0.007(-0.026 - 0.01)      | *0.020 (0.002 - 0.037)       | 0.036 ( -0.029 - 0.101)      |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p* value <0.05; \*\* *p* value < 0.001.

Each row corresponds to a separate risk score, fitted independently with the selected risk factor05; \*and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0 ;

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ;



Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

**Clinical DSN:** Age + BMI + systolic blood-pressure + SBP5 + Diabetes type 1 + Diabetes type 2 + HDL ratio + Townsend deprivation index + Smoker former + Smoker current + Smoker never + Ethnic Background + Corticosteroid + Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

**Cox-clinical:** Age + BMI + systolic blood-pressure + SBP5 + Diabetes type 1 + Diabetes type 2 + HDL ratio + Townsend deprivation index + Smoker former + Smoker current + Smoker never + Ethnic Background + Corticosteroid + Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

**Supplementary Table 35: Reclassification Performance for Participants Aged 45 or Below at a 10% Risk Threshold. Comparing QRISK3-Inspired, Linear Cox Proportional Hazard (Cox Clinical), and Clinical DSN + ECG risk scores Using ECG Measurements from Rest, Exercise, Recovery, and Complete ECG Recordings**

| Model           | Comparator                  | Net-benefit (95% CI)   | Categorical NRI (95% CI)  | Continuous NRI (95% CI)  |
|-----------------|-----------------------------|------------------------|---------------------------|--------------------------|
| <b>Overall</b>  |                             |                        |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | **0.035(0.019 - 0.053) | **0.006 (0.003 - 0.009)   | 0.102 ( -0.113 - 0.317)  |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *0.021(0.004 - 0.04)   | *0.004 (0.001- 0.007)     | 0.006 ( -0.205 - 0.217)  |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | **0.033(0.016 - 0.053) | **0.006 (0.003 - 0.009)   | -0.020 ( -0.233 - 0.193) |
| QRISK3-Inspired | Clinical DSN + Full ECG     | **0.034(0.017 - 0.053) | **0.006 (0.003 - 0.009)   | -0.008 ( -0.219 - 0.203) |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.004(-0.028 - 0.028) | 0.010 ( -0.016 - 0.036)   | -0.027 ( -0.238 - 0.183) |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.018(-0.044 - 0.015) | 0.008 ( -0.018 - 0.034)   | 0.119 ( -0.084 - 0.32)   |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.006(-0.029 - 0.028) | 0.010 ( -0.016 - 0.036)   | 0.007 ( -0.167 - 0.180)  |
| Cox clinical    | Clinical DSN + Full ECG     | -0.006(-0.029 - 0.027) | 0.010 ( -0.016 - 0.036)   | -0.153 ( -0.379 - 0.073) |
| <b>Male</b>     |                             |                        |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | **0.05(0.026 - 0.079)  | **0.011 (0.006 - 0.017)   | 0.039 ( -0.214 - 0.293)  |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *0.029(0.005 - 0.058)  | * 0.007 (0.001 - 0.013)   | 0.006 ( -0.247 - 0.260)  |
|                 | Clinical DSN + Recovery ECG | **0.048(0.021 - 0.079) | ** 0.011 (0.005 - 0.017)  | -0.049 ( -0.303 - 0.205) |
| QRISK3-Inspired | Clinical DSN + Full ECG     | **0.048(0.023 - 0.077) | ** 0.011 (0.005 - 0.017)  | -0.017 ( -0.253 - 0.219) |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.007(-0.042 - 0.042) | 0.013 ( -0.025 - 0.052)   | -0.033 ( -0.300 - 0.232) |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.027(-0.068 - 0.022) | 0.0087 ( -0.0296 - 0.047) | 0.038 ( -0.21 - 0.287)   |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.009(-0.045 - 0.043) | 0.0129 ( -0.025 - 0.051)  | 0.045 ( -0.167 - 0.258)  |
| Cox clinical    | Clinical DSN + Full ECG     | -0.009(-0.045 - 0.041) | 0.0129 ( -0.025 - 0.051)  | -0.024 ( -0.297 - 0.250) |
| <b>Female</b>   |                             |                        |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | 0.005(0 - 0.018)       | 0.001 ( -0.001 - 0.002)   | 0.252 ( -0.144 - 0.649)  |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | 0.005(0 - 0.018)       | 0.001 ( -0.001 - 0.002)   | 0.033 ( -0.347 - 0.413)  |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | 0.005(0 - 0.018)       | 0.001 ( -0.001 - 0.002)   | 0.066 ( -0.324 - 0.456)  |
| QRISK3-Inspired | Clinical DSN + Full ECG     | 0.005(0 - 0.018)       | 0.001 ( -0.001 - 0.002)   | 0.155 ( -0.246 - 0.557)  |

## Full ECG

|              |                             |          |          |                          |
|--------------|-----------------------------|----------|----------|--------------------------|
| Cox clinical | Clinical DSN + Resting ECG  | 0(0 - 0) | 0 (0 -0) | 0.078 ( -0.249 - 0.406)  |
| Cox clinical | Clinical DSN + Exercise ECG | 0(0 - 0) | 0 (0 -0) | 0.220 ( -0.129 - 0.569)  |
| Cox clinical | Clinical DSN + Recovery ECG | 0(0 - 0) | 0 (0 -0) | -0.028 ( -0.329 - 0.273) |
| Cox clinical | Clinical DSN + Full ECG     | 0(0 - 0) | 0 (0 -0) | 0.058 ( -0.165 - 0.281)  |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* <0.05; \*\**p value* < 0.001;

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0;

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ;

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

Clinical DSN: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness , Migraine, Hypertension, Severe mental illness

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness , Migraine, Hypertension, Severe mental illness

**Supplementary Table 36: Reclassification Performance for Participants Aged 45-55 at a 10% Risk Threshold. Comparing QRISK3-Inspired, Linear Cox Proportional Hazard (Cox Clinical), and Clinical DSN + ECG risk scores Using ECG Measurements from Rest, Exercise, Recovery, and Complete ECG Recordings**

| Model           | Comparator                  | Net-benefit<br>(95% CI) | Categorical NRI (95% CI)  | Continuous NRI (95% CI)  |
|-----------------|-----------------------------|-------------------------|---------------------------|--------------------------|
| <b>Overall</b>  |                             |                         |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.006(-0.031 - 0.019)  | -0.008 ( -0.034 - 0.018)  | 0.051 ( -0.0411 - 0.143) |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.026(-0.058 - 0.008)  | -0.012 ( -0.042 - 0.018)  | 0.061 ( -0.033 - 0.155)  |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | -0.001(-0.029 - 0.028)  | -0.003 ( -0.031 - 0.025)  | 0.037 ( -0.056 - 0.131)  |
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.008(-0.036 - 0.021)  | -0.009 ( -0.035 - 0.018)  | 0.049 ( -0.040 - 0.139)  |
| Cox clinical    | Clinical DSN + Resting ECG  | 0.017(-0.008 - 0.042)   | *0.047 (0.023 - 0.070)    | 0.047 ( -0.042 - 0.137)  |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.003(-0.033 - 0.027)  | *0.043 (0.016 - 0.069)    | *0.123 (0.036 - 0.211)   |
| Cox clinical    | Clinical DSN + Recovery ECG | 0.022(-0.004 - 0.049)   | **0.051 (0.027 - 0.075)   | 0.070 ( -0.017 - 0.156)  |
| Cox clinical    | Clinical DSN + Full ECG     | 0.015(-0.01 - 0.039)    | **0.046 (0.023 - 0.069)   | ** 0.117 (0.023 - 0.212) |
| <b>Male</b>     |                             |                         |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.005(-0.041 - 0.029)  | -0.010 ( -0.046 - 0.025)  | *0.172 (0.065 - 0.279)   |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.031(-0.076 - 0.016)  | -0.019 ( -0.0618 - 0.023) | *0.131 (0.020 - 0.242)   |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | 0.007(-0.033 - 0.048)   | 0.0018 ( -0.037 - 0.041)  | *0.179 (0.069 - 0.288)   |
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.005(-0.042 - 0.033)  | -0.009 ( -0.046 - 0.028)  | ** 0.201 (0.096 - 0.306) |
| Cox clinical    | Clinical DSN + Resting ECG  | 0.024(-0.009 - 0.057)   | **0.051 (0.019 - 0.083)   | 0.064 ( -0.044 - 0.172)  |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.003(-0.043 - 0.039)  | *0.042 (0.005 - 0.079)    | 0.036 ( -0.064 - 0.136)  |
| Cox clinical    | Clinical DSN + Recovery ECG | *0.036(0.002 - 0.072)   | **0.063 (0.031 - 0.096)   | 0.073 ( -0.032 - 0.177)  |
| Cox clinical    | Clinical DSN + Full ECG     | 0.023(-0.011 - 0.057)   | *0.052 (0.021 - 0.084)    | ** 0.253 (0.139 - 0.367) |
| <b>Female</b>   |                             |                         |                           |                          |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | 0.009(-0.034 - 0.02)    | 0.004 ( -0.022 - 0.029)   | 0.105 ( -0.065 - 0.275)  |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.015(-0.036 - 0.006)  | -0.003 ( -0.023 - 0.018)  | 0.137 ( -0.03 - 0.307)   |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | -0.021(-0.048 - 0.005)  | -0.010 ( -0.035 - 0.015)  | 0.074 ( -0.096 - 0.243)  |

|                 |                             |                        |                          |                          |
|-----------------|-----------------------------|------------------------|--------------------------|--------------------------|
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.014(-0.036 - 0.008) | -0.003 ( -0.023 - 0.018) | 0.007 ( -0.161 - 0.174)  |
| Cox clinical    | Clinical DSN + Resting ECG  | 0.001(-0.024 - 0.031)  | 0.018 ( -0.007 - 0.043)  | 0.009 ( -0.153 - 0.172)  |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.006(-0.026 - 0.019) | 0.011 ( -0.010 - 0.031)  | 0.046 ( -0.122 - 0.215)  |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.011(-0.038 - 0.017) | 0.004 ( -0.0212 - 0.029) | 0.038 ( -0.121 - 0.197)  |
| Cox clinical    | Clinical DSN + Full ECG     | -0.005(-0.025 - 0.021) | 0.011 ( -0.010- 0.031)   | -0.031 ( -0.200 - 0.139) |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* <0.05; \*\* *p value* < 0.001;

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0 ;

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ;

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

Clinical DSN: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness.

**Supplementary Table 37: Reclassification Performance for Participants Aged 55-65 at a 10% Risk Threshold. Comparing QRISK3-Inspired, Linear Cox Proportional Hazard (Cox Clinical), and Clinical DSN + ECG risk scores Using ECG Measurements from Rest, Exercise, Recovery, and Complete ECG Recordings**

| Model           | Comparator                  | Net-benefit (95% CI)        | Categorical NRI (95% CI)     | Continuous NRI (95% CI)      |
|-----------------|-----------------------------|-----------------------------|------------------------------|------------------------------|
| <b>Overall</b>  |                             |                             |                              |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | *-0.029(-0.049 - -0.009)    | -0.024 ( -0.043 - -0.005)    | 0.033 ( -0.0205 - 0.087 )    |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *-0.034(-0.057 - -0.012)    | *-0.030 ( -0.052 - -0.009 )  | *0.085 (0.031 - 0.138)       |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | *-0.024(-0.043 - -0.004)    | -0.019 ( -0.038 - 0.001)     | * 0.061 (0.007 - 0.115)      |
| QRISK3-Inspired | Clinical DSN + Full ECG     | *-0.023(-0.043 - -0.004)    | -0.016 ( -0.035 - 0.002)     | ** 0.176 (0.122 - 0.230 )    |
| Cox clinical    | Clinical DSN + Resting ECG  | *-0.019(-0.038 - 0)         | -0.011 ( -0.029 - 0.008)     | -0.042 ( -0.098 - 0.013 )    |
| Cox clinical    | Clinical DSN + Exercise ECG | *-0.025(-0.046 - -0.002)    | -0.017 ( -0.039 - 0.005)     | : -0.002 ( -0.058 - 0.053 )  |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.015(-0.032 - 0.003)      | -0.006 ( -0.023 - 0.011)     | -0.014 ( -0.070 - 0.041)     |
| Cox clinical    | Clinical DSN + Full ECG     | -0.014(-0.031 - 0.005)      | -0.003 ( -0.020 - 0.016)     | ** 0.134 (0.078 - 0.189 )    |
| <b>Male</b>     |                             |                             |                              |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | ** -0.038(-0.064 - -0.013 ) | * -0.036 ( -0.061 - -0.012 ) | *0.096 (0.027 - 0.165)       |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | ** -0.047(-0.075 - -0.016)  | *-0.046 ( -0.075 - -0.018)   | **0.114 (0.046 - 0.182)      |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | *-0.031(-0.055 - -0.008)    | * -0.030 ( -0.054 - -0.006 ) | * 0.115(0.046 - 0.184)       |
| QRISK3-Inspired | Clinical DSN + Full ECG     | *-0.027(-0.051 - -0.003)    | *-0.027 ( -0.051 - -0.002 )  | **0.170(0.102 - 0.237)       |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.023(-0.048 - 0.002)      | * -0.025 ( -0.049 - -0.001)  | ** -0.116 ( -0.186 - -0.047) |
| Cox clinical    | Clinical DSN + Exercise ECG | -0.031(-0.06 - 0.001)       | *-0.035 ( -0.065 - -0.005 )  | *-0.111 ( -0.179 - -0.040)   |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.016(-0.039 - 0.007)      | -0.019 ( -0.042 - 0.004)     | *-0.090 ( -0.159 - -0.02 )   |
| Cox clinical    | Clinical DSN + Full ECG     | -0.012(-0.036 - 0.013)      | -0.015 ( -0.039 - 0.008)     | -0.006 ( -0.074 - 0.063)     |
| <b>Female</b>   |                             |                             |                              |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.01(-0.045 - 0.023)       | 0.047 (0.018 - 0.076)        | ** 0.134 (0.054 - 0.214 )    |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | -0.01(-0.045 - 0.026)       | * 0.036 (0.005 - 0.067)      | *0.114 (0.026 - 0.202)       |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | -0.011(-0.042 - 0.02)       | * 0.042(0.014 - 0.071)       | ** 0.161 (0.079 - 0.244 )    |
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.016(-0.046 - 0.015)      | * 0.036 (0.009 - 0.064)      | **0.203 (0.112 - 0.293)      |

|              |                             |                        |                         |                          |
|--------------|-----------------------------|------------------------|-------------------------|--------------------------|
| Inspired     | ECG                         |                        |                         |                          |
| Cox clinical | Clinical DSN + Resting ECG  | -0.013(-0.043 - 0.016) | 0.023 ( -0.004 - 0.050) | ** 0.133 (0.042 - 0.224) |
| Cox clinical | Clinical DSN + Exercise ECG | -0.013(-0.044 - 0.018) | 0.013 ( -0.017 - 0.042) | * 0.106 (0.012 - 0.200)  |
| Cox clinical | Clinical DSN + Recovery ECG | -0.013(-0.039 - 0.015) | 0.019 ( -0.007 - 0.045) | * 0.107 (0.013 - 0.201)  |
| Cox clinical | Clinical DSN + Full ECG     | -0.018(-0.045 - 0.01)  | 0.013 ( -0.012 - 0.037) | **0.190 (0.096 - 0.284)  |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p- values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p value* <0.05; \*\* *p value* < 0.001;

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0 ;

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ;

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

Clinical DSN: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness.

**Supplementary Table 38: Reclassification Performance for Participants Aged over 65 at a 10% Risk Threshold. Comparing QRISK3-Inspired, Linear Cox Proportional Hazard (Cox Clinical), and Clinical DSN + ECG risk scores Using ECG Measurements from Rest, Exercise, Recovery, and Complete ECG Recordings**

| Model           | Comparator                  | Net-benefit (95% CI)        | Categorical NRI (95% CI)      | Continuous NRI (95% CI)      |
|-----------------|-----------------------------|-----------------------------|-------------------------------|------------------------------|
| <b>Overall</b>  |                             |                             |                               |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | 0.006(-0.014 - 0.026)       | -0.005 ( -0.025 - 0.015)      | -0.014 ( -0.072 - 0.045)     |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *-0.025(-0.049 - 0)         | -0.011 ( -0.032 - 0.011)      | -0.028 ( -0.088 - 0.032)     |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | 0.006(-0.014 - 0.026)       | -0.025 ( -0.051 - 0.001)      | -0.012 ( -0.072 - 0.049)     |
| QRISK3-Inspired | Clinical DSN + Full ECG     | 0.017(-0.002 - 0.036)       | -0.011 ( -0.032 - 0.010)      | -0.046 ( -0.105 - 0.014)     |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.012(-0.029 - 0.005)      | -0.010 ( -0.0273 - 0.007 ** ) | -0.143 ( -0.199 - -0.088)    |
| Cox clinical    | Clinical DSN + Exercise ECG | ** -0.043(-0.064 - -0.021 ) | *-0.025 ( -0.047 - -0.002 )   | * -0.071 ( -0.130 - -0.011)  |
| Cox clinical    | Clinical DSN + Recovery ECG | -0.012(-0.027 - 0.005)      | -0.010 ( -0.027 - 0.008)      | ** -0.133 ( -0.188 - -0.078) |
| Cox clinical    | Clinical DSN + Full ECG     | 0(-0.013 - 0.012)           | -0.004 ( -0.017 - 0.009)      | ** -0.125 ( -0.183 - -0.066) |
| <b>Male</b>     |                             |                             |                               |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | -0.01(-0.025 - 0.002)       | 0.0137 ( -0.001 - 0.028)      | 0.023 ( -0.051 - 0.098)      |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | ** -0.06(-0.083 - -0.036)   | -0.004 ( -0.028 - 0.020)      | -0.026 ( -0.100 - 0.049)     |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | * -0.017(-0.031 - -0.003)   | 0.006 ( -0.009 - 0.021)       | -0.019 ( -0.094 - 0.056)     |
| QRISK3-Inspired | Clinical DSN + Full ECG     | -0.004(-0.015 - 0.006)      | 0.010 ( -0.001 - 0.022)       | -0.041 ( -0.113 - 0.032)     |
| Cox clinical    | Clinical DSN + Resting ECG  | -0.009(-0.022 - 0.003)      | 0.008 ( -0.007 - 0.022)       | -0.004 ( -0.061 - 0.05)      |
| Cox clinical    | Clinical DSN + Exercise ECG | ** -0.058(-0.079 - -0.036 ) | -0.0100 ( -0.034 - 0.014 )    | -0.032 ( -0.102 - 0.038)     |
| Cox clinical    | Clinical DSN + Recovery ECG | * -0.015(-0.028 - -0.003)   | -0.001( -0.0139 - 0.014)      | -0.054 ( -0.115 - 0.008)     |
| Cox clinical    | Clinical DSN + Full ECG     | -0.002(-0.011 - 0.007)      | 0.004 ( -0.006 - 0.014)       | ** -0.118 ( -0.185 - -0.05)  |
| <b>Female</b>   |                             |                             |                               |                              |
| QRISK3-Inspired | Clinical DSN + Resting ECG  | 0.044(-0.016 - 0.104)       | * 0.069 (0.015 - 0.123)       | 0.000 ( -0.098 - 0.099)      |
| QRISK3-Inspired | Clinical DSN + Exercise ECG | *0.058(-0.003 - 0.115)      | * 0.076 (0.019 - 0.132)       | 0.039 ( -0.0684 - 0.146)     |
| QRISK3-Inspired | Clinical DSN + Recovery ECG | **0.46(0.396 - 0.527)       | *0.085 (0.030 - 0.139)        | 0.075 ( -0.025 - 0.174)      |
| QRISK3-Inspired | Clinical DSN + Full ECG     | *0.068(0.01 - 0.125)        | ** 0.095(0.042 - 0.148)       | *0.099 (0.001 - 0.198)       |



| Inspired     | Full ECG                    |                        |                          |                           |
|--------------|-----------------------------|------------------------|--------------------------|---------------------------|
| Cox clinical | Clinical DSN + Resting ECG  | -0.02(-0.067 - 0.027)  | -0.015 ( -0.061 - 0.031) | -0.0118 ( -0.122 - 0.098) |
| Cox clinical | Clinical DSN + Exercise ECG | 0.006(-0.059 - 0.048)  | -0.008 ( -0.059 - 0.043) | 0.0212 ( -0.089 - 0.131)  |
| Cox clinical | Clinical DSN + Recovery ECG | -0.004(-0.054 - 0.047) | 0.001 ( -0.047 - 0.049)  | -0.040 ( -0.149 - 0.070)  |
| Cox clinical | Clinical DSN + Full ECG     | 0.004(-0.033 - 0.042)  | 0.011 ( -0.026 - 0.047)  | 0.070 ( -0.041 - 0.180)   |

Abbreviations: NRI = Net re classification index, CI = Confidence interval

Data are reported on 41,076 participants with valid ECG parameters, 3,053 (7.4%) MACCE were reported within 10-years. 95% confidence intervals and p-values were obtained via 1000 bootstrap iterations with a significance threshold of 0.05. \**p* value <0.05; \*\**p* value < 0.001;

Each row corresponds to a separate risk score, fitted independently with the selected risk factors., and independent estimates of the baseline survival using Breslow's method, with mean-centred continuous variables, with all binary risk factors set to 0 ;

QRISK3-Inspired and Cox clinical risk scores were derived using Cox proportional hazards regression. Extended Cox models additionally included the Q-ECG score as a covariate.

ECG risk scores were derived from separate deep survival networks trained on raw ECG recordings from: 15 s rest, final 15 s of exercise (peak intensity), final 15 s recovery, and the full 7 min 15 s submaximal ECG, respectively.

Clinical DSN + ECG integrated QRISK3 risk factors and raw ECG data directly within a single deep survival model,

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes type 1 + Diabetes type 2 + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Migraine +Rheumatoid Arthritis + Severe mental illness+ SBP5 + Ethnic Background + Smoker previous + Smoker current + Age FP1 X Townsend deprivation index +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP 1 X Systolic blood pressure + Age FP 1 X Diabetes type 1 +Age FP 1 X Diabetes type 2+Age FP 1 X hypertension +Age FP 1 \* Corticosteroid treatment + Age FP2 X Townsend deprivation index +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 + AgeFP2 X Systolic blood pressure +Age FP 2 X Diabetes type 1 +Age FP 2 X Diabetes type 2+Age FP 2 X Hypertension . + Age FP 2 \* Corticosteroid treatment. ;

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

Clinical DSN: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness

Cox-clinical: Age + BMI + systolic blood-pressure + SBP5 +Diabetes type 1+ Diabetes type 2 + HDL ratio + Townsend deprivation index+ Smoker former + Smoker current + Smoker never+ Ethnic Background+ Corticosteroid+ Migraine + Hypertension + Severe mental illness, Migraine, Hypertension, Severe mental illness.

**Supplementary Table 39: Minimum sample size calculation for QRISK3-Inspired + Physical activity and SCORE2-Inspired +physical activity risk scores**

| Model                       | # Model parameters | Event rate | Estimate Cox-snell R-squared | Minimum EPP | # Minimum MACCE | Minimum Sample size |
|-----------------------------|--------------------|------------|------------------------------|-------------|-----------------|---------------------|
| <b>QRISK3-Inspired</b>      |                    |            |                              |             |                 |                     |
| Male                        | 30                 | 0.007      | 0.033                        | 11.08       | 332.4           | 7,984               |
| Female                      | 30                 | 0.003      | 0.021                        | 8.35        | 249.6           | 12,948              |
| <b>QRISK3-Inspired + PA</b> |                    |            |                              |             |                 |                     |
| Male                        | 60                 | 0.007      | 0.033                        | 18.46       | 1,108           | 15,968              |
| Female                      | 60                 | 0.003      | 0.021                        | 13.92       | 835             | 25,896              |
| <b>SCORE2-Inspired</b>      |                    |            |                              |             |                 |                     |
| Male                        | 10                 | 0.007      | 0.054                        | 11.19       | 111.9           | 1,613               |
| Female                      | 10                 | 0.003      | 0.027                        | 10.59       | 105.9           | 3,285               |
| <b>SCORE2-Inspired + PA</b> |                    |            |                              |             |                 |                     |
| Male                        | 30                 | 0.007      | 0.054                        | 11.19       | 335.7           | 4,838               |
| Female                      | 30                 | 0.003      | 0.027                        | 10.59       | 317.7           | 9,855               |

Abbreviations: EPP = Event per parameter, MACCE = Major Adverse Cardiovascular & Cerebrovascular Event

**Supplementary Table 40 Hazard ratio of accelerometer measured Physical activity with 6-year incident of Major Adverse Cardiovascular & Cerebrovascular Events. after removing the first 2-years of follow-up**

| Accelerometer measurement     | Hazard ratio (95% CI)   |
|-------------------------------|-------------------------|
| <b>Male</b>                   |                         |
| Step count                    | *0.932(0.886 - 0.980)   |
| Overall activity              | **0.901 (0.851- 0.954)  |
| Sedentary behaviour           | **0.891 (0.844 - 0.942) |
| Light activity                | 0.972 (0.925 - 1.020)   |
| Moderate to vigorous activity | *1.065 (1.015 - 1.117)  |
| Sleep                         | 0.985 (0.942 - 1.031)   |
| <b>Female</b>                 |                         |
| Step count                    | **0.859 (0.804 - 0.917) |
| Overall activity              | **0.853 (0.794 - 0.915) |
| Sedentary behaviour           | **0.817 (0.756 - 0.882) |
| Light activity                | 0.958 (0.902 - 1.017)   |
| Moderate to vigorous activity | **1.117 (1.054 - 1.185) |
| Sleep                         | 0.948 (0.896 - 1.002)   |

Abbreviations: , CI = Confidence interval

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Each row corresponds to a separate univariate Cox model in which PA risk factors was fitted individually.

Hazard ratios are report pre standard deviation for Overall activity; per 1,000 steps for step-count, per 15 minutes of MVPA and 1-hour increase in Sedentary behaviour, Light activity and sleep each day, while .

p-values were derived via a chi-squared test, and were adjusted for multiple testing using the Benjamini/Hochberg procedure<sup>260</sup>

\**p value <0.05*

\*\* *p value < 0.001*

**Supplementary Table 41: Distribution of device-measured physical activity and sedentary behaviour metrics in UK Biobank participants (N = 35,597; males n = 17,376; females n = 18,221)**

| Measure                                | Unit      | Mean (SD)        | Median (IQR)  | Min-Max     | Quartile cut points   |
|----------------------------------------|-----------|------------------|---------------|-------------|-----------------------|
| <b>Male</b>                            |           |                  |               |             |                       |
| Average Daily step count               | steps/day | 9707.27(3944.3)  | 9228.5 (4991) | 8–37505     | 6960 / 9228.5 / 11951 |
| Moderate-to-vigorous Physical activity | hours/day | 0.63 (0.49)      | 0.52 (0.60)   | 0–5.62      | 0.27 / 0.52 / 0.86    |
| Light intensity physical activity      | hours/day | 5.25 (1.62)      | 5.12 (2.16)   | 0.05–14.38  | 4.10 / 5.12 / 6.26    |
| Sedentary behaviour                    | hours/day | 9.582 (1.796)    | 9.603 (2.382) | 2.737–19.72 | 8.39 / 9.60 / 10.78   |
| Overall activity (VM)                  | mg        | 27.94 (8.66)     | 26.82 (10.24) | 4.33–179.13 | 22.14 / 26.82 / 32.38 |
| Multivariate PA risk score             | % risk    | 7.01 (2.75)      | 6.48 (3.02)   | 1.12–35.56  | 5.19 / 6.48 / 8.21    |
| <b>Female</b>                          |           |                  |               |             |                       |
| Average Daily step count               | steps/day | 9394.87 (3698.8) | 9001 (4742)   | 6–40660     | 6814 / 9001 / 11556   |
| Moderate-to-vigorous Physical activity | hours/day | 0.46 (0.40)      | 0.36 (0.47)   | 0–4.30      | 0.17 / 0.36 / 0.64    |
| Light intensity physical activity      | hours/day | 5.93 (1.60)      | 5.84 (2.14)   | 0.01–14.14  | 4.82 / 5.84 / 6.96    |
| Sedentary behaviour                    | hours/day | 8.90 (1.68)      | 8.89 (2.25)   | 2.44–19.00  | 7.76 / 8.89 / 10.01   |
| Overall activity (VM)                  | mg        | 28.59 (7.96)     | 27.69 (9.83)  | 3.99–176.55 | 23.18 / 27.69 / 33.01 |
| Multivariate PA risk score             | % risk    | 3.25 (1.85)      | 2.86 (2.02)   | 0–29.68     | 2.01 / 2.86 / 4.03    |

Physical activity behaviours were derived using a validated movement-behaviour classifier trained against CAPTURE-24 ground-truth labels and mapped to activity intensities using metabolic equivalent of task (MET) thresholds. Sedentary behaviour ( $\leq 1.5$  METs), light activity ( $< 3$  METs), and moderate-to-vigorous physical activity ( $\geq 3$  METs) were defined from wrist-worn accelerometry; sleep was identified as non-waking behaviour and post-processed to require  $\geq 1$ -hour continuous blocks, with shorter segments reclassified as sedentary. Daily step count was predicted across wear time, with non-wear periods imputed using the mean step counts from corresponding times on other valid days; overall activity represents vector magnitude acceleration.

**Supplementary Table 42 Optimism adjusted univariate predictive performance of QRISK3 and SCORE2 risk factors for the 6-year incidence of Major Adverse Cardiovascular & Cerebrovascular Events.**

| Model                           | Hazard ratio (95% CI) | C-index (95% CI)      |
|---------------------------------|-----------------------|-----------------------|
| <b>Male</b>                     |                       |                       |
| Age                             | 1.8 (1.72 - 1.884)    | 0.651 (0.642 - 0.66)" |
| Body mass index                 | 1.208 (1.167 - 1.251) | 0.558 (0.548 - 0.568) |
| Ethnicity                       | 0.957 (0.756 - 1.21)  | 0.5 (0.499 - 0.502)   |
| Townsend deprivation index      | 1.031 (0.993 - 1.071) | 0.508 (0.498 - 0.517) |
| Current smoker                  | 1.145 (1.001 - 1.309) | 0.506 (0.501 - 0.511) |
| Former smoker                   | 1.351 (1.249 - 1.46)  | 0.536 (0.528 - 0.545) |
| Systolic blood pressure         | 1.284 (1.239 - 1.331) | 0.576 (0.567 - 0.586) |
| Diabetes                        | 2.406 (2.055 - 2.816) | 0.519 (0.515 - 0.523) |
| HDL: ratio                      | 1.071 (1.029 - 1.114) | 0.519 (0.509 - 0.529) |
| Hypertension                    | 2.242 (2.047 - 2.455) | 0.559 (0.551 - 0.566) |
| Corticosteroid treatment        | 0.945 (0.747 - 1.197) | 0.501 (0.498 - 0.503) |
| Atrial fibrillation and flutter | 3.106 (2.65 - 3.642)  | 0.521 (0.517 - 0.525) |
| <b>Female</b>                   |                       |                       |
| Age                             | 2.084 (1.967 - 2.208) | 0.688 (0.678 - 0.698) |
| Body mass index                 | 1.318 (1.267 - 1.371) | 0.59 (0.578 - 0.601)  |
| Ethnicity                       | 0.858 (0.64 - 1.151)  | 0.502 (0.499 - 0.506) |
| Townsend deprivation index      | 1.023 (0.975 - 1.073) | 0.505 (0.497 - 0.515) |
| Current smoker                  | 1.396 (1.167 - 1.668) | 0.511 (0.505 - 0.516) |
| Former smoker                   | 1.246 (1.128 - 1.377) | 0.525 (0.515 - 0.534) |
| Systolic blood pressure         | 1.503 (1.441 - 1.568) | 0.632 (0.621 - 0.642) |
| Diabetes                        | 4.091 (3.321 - 5.04)  | 0.522 (0.518 - 0.526) |
| HDL: ratio                      | 1.261 (1.206 - 1.318) | 0.575 (0.562 - 0.586) |
| Hypertension                    | 3.363 (3.009 - 3.758) | 0.58 (0.572 - 0.589)  |
| Corticosteroid treatment        | 0.818 (0.619 - 1.081) | 0.503 (0.5 - 0.507)   |
| Atrial fibrillation and flutter | 5.812 (4.661 - 7.247) | 0.521 (0.517 - 0.525) |

Abbreviations: , CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Hazard ratios are report pre standard deviation for continuous risk factors

Reported C-index and 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

**Supplementary Table 43: Optimism adjusted predictive performance of Age, QRISK3-Inspired (Excl HDL & SBP) and QRISK3-Inspired risk scores before and after the addition of Physical activity (PA) risk factors.**

| Model                                 | C-Index (95% CI)      | ICI (95% CI)              |
|---------------------------------------|-----------------------|---------------------------|
| <b>Male</b>                           |                       |                           |
| Age                                   | 0.651 (0.641 - 0.661) | 0.0028 (0.0008 - 0.0047)  |
| Age + PA                              | 0.658 (0.649 - 0.668) | 0.0033(0.001 - 0.0055)    |
| QRISK3-Inspired (Excl HDL & SBP)      | 0.677 (0.666 - 0.687) | 0.0015(-0.0004 - 0.0036)  |
| QRISK3-Inspired (Excl HDL & SBP) + PA | 0.676 (0.666 - 0.687) | 0.0027 (0.0001 - 0.0049)  |
| QRISK3-Inspired                       | 0.680 (0.670 - 0.689) | 0.0024(0.0005 - 0.0045)   |
| QRISK3-Inspired +PA                   | 0.679 (0.670 - 0.689) | 0.0029(0.0007 - 0.0052)   |
| <b>Female</b>                         |                       |                           |
| Age                                   | 0.688 (0.677 - 0.700) | 0.0006 (-0.0004 - 0.0016) |
| Age + PA                              | 0.704 (0.692 - 0.715) | 0.0012 (0.0001 - 0.0023)  |
| QRISK3-Inspired (Excl HDL & SBP)      | 0.731 (0.719 - 0.742) | 0.0013(0.0002 - 0.0026)   |
| QRISK3-Inspired (Excl HDL & SBP) + PA | 0.732 (0.721 - 0.743) | 0.0008(-0.0004 - 0.002)   |
| QRISK3                                | 0.736 (0.725 - 0.748) | 0.0016(0.0004 - 0.0028)   |
| QRISK3 +PA                            | 0.738 (0.728 - 0.749) | 0.0009(-0.0003 - 0.002)   |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually. Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0. Reported C-index, ICI and corresponding 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP 1 + Age FP 2 X BMI FP 2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter.

Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Age + PA fractional polynomial (male) = ( $\frac{\text{Daily step count}}{10000}$ ) + Hours of MVPA<sup>0.5</sup> +

(Hours of MVPA<sup>0.5</sup> X log(Hours of MVPA)) +  $\frac{\text{Hours of LPA}}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  +  $\frac{\text{Overall activity}^{0.5}}{10}$

QRISK3-Inspired(Excl HDL & SBP) +A fractional polynomial (male) = ( $\frac{\text{Daily step count}}{10000}$ )<sup>-2</sup> + Hours of MVPA<sup>0.5</sup> +

(Hours of MVPA<sup>0.5</sup> X log(Hours of MVPA)) +  $\frac{\text{Hours of LPA}}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  +  $\frac{\text{Overall activity}^{0.5}}{10}$  +  $\frac{\text{Overall activity}}{10}$

QRISK3-Inspired PA fractional polynomial (male) = ( $\frac{\text{Daily step count}}{10000}$ )<sup>-2</sup> + Hours of MVPA<sup>0.5</sup> +

(Hours of MVPA<sup>0.5</sup> X log(Hours of MVPA)) +  $\frac{\text{Hours of LPA}}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  +  $\frac{\text{Overall activity}^{0.5}}{10}$  +  $\frac{\text{Overall activity}}{10}$

Age + PA fractional polynomial (female) = ( $\frac{\text{Daily step count}}{10000}$ )<sup>-1</sup> + ( $\frac{\text{Daily step count}}{10000}$ )<sup>-0.5</sup> + Hours of MVPA +  $\frac{\text{Hours of LPA}}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  + log( $\frac{\text{Overall activity}}{10}$ )

QRISK3-Inspired(Excl HDL & SBP) +PA fractional polynomial (female) = ( $\frac{\text{Daily step count}}{10000}$ )<sup>-1</sup> + ( $\frac{\text{Daily step count}}{10000}$ )<sup>-0.5</sup> +

Hours of MVPA +  $\frac{\text{Hours of LPA}^{-2}}{10}$  +  $\frac{\text{Hours of LPA}^2}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  + log( $\frac{\text{Overall activity}}{10}$ )

QRISK3-Inspired PA fractional polynomial (female) = ( $\frac{\text{Daily step count}}{10000}$ )<sup>-1</sup> + ( $\frac{\text{Daily step count}}{10000}$ )<sup>-0.5</sup> + Hours of MVPA +

$\frac{\text{Hours of LPA}^{-2}}{10}$  +  $\frac{\text{Hours of LPA}^2}{10}$  +  $\frac{\text{Hours of SBA}}{10}$  + log( $\frac{\text{Overall activity}}{10}$ )

**Supplementary Table 44: Relative change in optimism adjusted predictive performance of Age, QRISK3-Inspired (Excl HDL & SBP) and QRISK3-Inspired risk scores following the addition of Physical activity (PA) risk factors**

| Model                            | Comparator                            | $\Delta C$ -index      | $\Delta ICI$              |
|----------------------------------|---------------------------------------|------------------------|---------------------------|
| <b>Male</b>                      |                                       |                        |                           |
| Age                              | Age + PA                              | **0.007(0.003 - 0.01)  | 0.0005(-0.0015 - 0.0025)  |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired (Excl HDL & SBP) + PA | -0.001(-0.004 - 0.001) | 0.0012(-0.0007 - 0.0031)  |
| QRISK3-Inspired                  | QRISK3-Inspired (Excl HDL & SBP) + PA | -0.004(-0.019 - 0.009) | 0.0003(-0.0024 - 0.0029)  |
| QRISK3-Inspired                  | QRISK3-Inspired + PA                  | -0.001(-0.004 - 0.001) | 0.0005(-0.0012 - 0.0024)  |
| <b>Female</b>                    |                                       |                        |                           |
| Age                              | Age + PA                              | **0.016(0.01 - 0.021)  | 0.0006(-0.0005 - 0.0019)  |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired (Excl HDL & SBP) + PA | 0.002(-0.002 - 0.005)  | -0.0008(-0.0024 - 0.0009) |
| QRISK3-Inspired                  | QRISK3-Inspired (Excl HDL & SBP) + PA | -0.004(-0.019 - 0.012) | -0.0006(-0.0021 - 0.0013) |
| QRISK3-Inspired                  | QRISK3-Inspired + PA                  | 0.002(-0.002 - 0.005)  | -0.0034(-0.0162 - 0.0072) |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported  $\Delta C$ -index,  $\Delta ICI$  and corresponding 95% confidence intervals were derived from optimism adjusted values following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value < 0.05; \*\*p value < 0.001;

Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP1 + Age FP 2 X BMI FP2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA), and sedentary behaviour (SB)

$$\text{Age + PA fractional polynomial (male)} = \left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10}$$

$$\text{QRISK3-Inspired(Excl HDL \& SBP) + A fractional polynomial (male)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

$$\text{QRISK3-Inspired PA fractional polynomial (male)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \frac{\text{Overall activity}}{10}$$

$$\text{Age + PA fractional polynomial (female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$$

$$\text{QRISK3-Inspired(Excl HDL \& SBP) + PA fractional polynomial (female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$$

$$\text{QRISK3-Inspired PA fractional polynomial (female)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}}{10}\right)$$

**Supplementary Table 45: Optimism adjusted predictive performance of SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores before and after the addition of Physical activity (PA) risk factors**

| Model                                 | C-Index               | ICI                      |
|---------------------------------------|-----------------------|--------------------------|
| <b>Male</b>                           |                       |                          |
| SCORE2-Inspired (Excl HDL & SBP)      | 0.658(0.648 - 0.669)  | 0.002(0 - 0.0041)        |
| SCORE2-Inspired (Excl HDL & SBP) + PA | 0.662(0.653 - 0.673)  | 0.0029(0.0005 - 0.0052)  |
| SCORE2-Inspired                       | 0.668(0.658 - 0.678)  | 0.002(0.0002 - 0.0041)   |
| SCORE2-Inspired +PA                   | 0.67(0.66 - 0.68)     | 0.0029(0.0006 - 0.0052)  |
| <b>Female</b>                         |                       |                          |
| SCORE2-Inspired (Excl HDL & SBP)      | 0.702(0.69 - 0.714)   | 0.0006(-0.0004 - 0.0017) |
| SCORE2-Inspired (Excl HDL & SBP) + PA | 0.712(0.7 - 0.723)    | 0.0009(-0.0001 - 0.0022) |
| SCORE2-Inspired                       | 0.723(0.712 - 0.735)" | 0.0013(0.0003 - 0.0023)  |
| SCORE2-Inspired +PA                   | 0.728(0.717 - 0.739)  | 0.0009(-0.0002 - 0.002)  |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Reported C-index, ICI and corresponding 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**Score2-Inspired Fractional Polynomials excluding HDL & SBP (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} +$

$\left(\text{Hours of MVPA}^{0.5} \times \log\left(\frac{\text{Hours of MVPA}}{10}\right) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^1\right)\right)$

**Score2-Inspired PA fractional polynomial (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} +$

$\left(\text{Hours of MVPA}^{0.5} \times \log\left(\frac{\text{Hours of MVPA}}{10}\right) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right)\right)$

**Score2-Inspired Fractional Polynomials excluding HDL & SBP (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} +$   
 $\text{Hours of MVPA}^{0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}}{10}$

**Score2-Inspired PA fractional polynomial (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} +$   
 $+ \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}^{0.5}}{10}\right)$



**Supplementary Table 46: Relative change in optimism adjusted predictive performance of SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Physical activity (PA) risk factors**

| Model                            | Comparator                            | ΔC-index                 | ΔICI                     |
|----------------------------------|---------------------------------------|--------------------------|--------------------------|
| <b>Male</b>                      |                                       |                          |                          |
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + PA | *0.004(0 - 0.007)        | 0.0012(-0.0007 - 0.003)  |
| SCORE2-Inspired                  | SCORE2-Inspired (Excl HDL & SBP) + PA | *-0.007(-0.011 - -0.002) | 0.001(-0.0016 - 0.0037)  |
| SCORE2-Inspired                  | SCORE2-Inspired +PA                   | 0.001(-0.002 - 0.004)    | 0.001(-0.0008 - 0.0028)  |
| <b>Female</b>                    |                                       |                          |                          |
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + PA | **0.01(0.005 - 0.015)    | 0.0003(-0.0012 - 0.0022) |
| SCORE2-Inspired                  | SCORE2-Inspired (Excl HDL & SBP) + PA | *-0.011(-0.017 - -0.004) | -0.0003(-0.002 - 0.0013) |
| SCORE2-Inspired                  | SCORE2-Inspired +PA                   | *0.005(0.001 - 0.009)    | -0.0032(-0.016 - 0.0074) |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations

\*p value <0.05; \*\* p value < 0.001

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Reported ΔC-index, ΔICI and corresponding 95% confidence intervals were derived from optimism adjusted values following 1000 bootstrap iterations.

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**Score2-Inspired Fractional Polynomials excluding HDL & SBP (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^1\right)$

**Score2-Inspired PA fractional polynomial (male)** =  $\left(\frac{\text{Daily step count}}{10000}\right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right)$

**Score2-Inspired Fractional Polynomials excluding HDL & SBP (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA}^{0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}}{10}$

**Score2-Inspired PA fractional polynomial (female)** =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}^{0.5}}{10}\right)$

**Supplementary Table 47: Reclassification Performance for male participants comparing age, QRISK3-Inspired (Excl HDL & SBP) and QRISK3-Inspiredrisk scores following the addition of Physical activity risk factors. Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                          | Threshold         | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                           |
|----------------------------------|-------------------------------------|-------------------|------------------------|------------------------|------------------------|-------------------------------|
| Age                              | Age +PA                             | 10%               | 0.08(0.058 - 0.102)    | 0.091(0.069 - 0.113)   | 0.011(-0.004 - 0.027)  | 0.007(-0.008 - 0.021)         |
|                                  |                                     | 7.5%              | 0.177(0.152 - 0.204)   | 0.192(0.167 - 0.217)   | *0.015(0.001 - 0.028)" | *0.012(-0.002 - 0.025)        |
|                                  |                                     | 5%                | 0.387(0.364 - 0.411)   | 0.387(0.363 - 0.41)    | 0(-0.009 - 0.009)      | 0.005(-0.004 - 0.015)         |
|                                  |                                     | <b>Continuous</b> |                        |                        |                        | <b>**0.144(0.135 - 0.153)</b> |
|                                  |                                     |                   |                        |                        |                        |                               |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired(Excl HDL & SBP) +PA | 10%               | 0.128(0.106 - 0.149)   | 0.122(0.101 - 0.144)   | -0.006(-0.019 - 0.006) | -0.008(-0.03 - 0.012)         |
|                                  |                                     | 7.5%              | 0.22(0.196 - 0.245)    | 0.223(0.2 - 0.247)     | 0.003(-0.008 - 0.014)  | 0.001(-0.021 - 0.022)         |
|                                  |                                     | 5%                | 0.403(0.381 - 0.427)   | 0.407(0.386 - 0.43)    | 0.004(-0.004 - 0.012)  | 0.002(-0.019 - 0.023)         |
|                                  |                                     | <b>Continuous</b> |                        |                        |                        | <b>**0.085(0.064 - 0.106)</b> |
|                                  |                                     |                   |                        |                        |                        |                               |
| QRISK3-Inspired                  | QRISK3-Inspired +PA                 | 10%               | 0.13(0.108 - 0.152)    | 0.121(0.1 - 0.141)     | -0.009(-0.021 - 0.001) | -0.015(-0.037 - 0.006)        |
|                                  |                                     | 7.5%              | 0.219(0.196 - 0.243)   | 0.225(0.202 - 0.25)    | 0.005(-0.006 - 0.015)  | 0.002(-0.02 - 0.023)          |
|                                  |                                     | 5%                | 0.412(0.39 - 0.436)    | 0.41(0.388 - 0.432)    | -0.002(-0.011 - 0.005) | -0.006(-0.028 - 0.015)        |
|                                  |                                     | <b>Continuous</b> |                        |                        |                        | <b>**0.066(0.045 - 0.087)</b> |
|                                  |                                     |                   |                        |                        |                        |                               |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\*p value < 0.001; Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure. + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP 1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension . + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Townsend deprivation index + AgeFP2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**Fractional polynomials:** Age FP 1 =  $(age/10)^{-1}$ , Age FP 2 =  $(age/10)^3$ , BMI FP 1 =  $(BMI/10)^{-2}$ , BMI FP 2 =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**Age + PA fractional polynomial (male)** =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-2} + Hours\ of\ MVPA^{0.5} + (Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA)) + \frac{Hours\ of\ LPA}{10} + \frac{Hours\ of\ SBA}{10} + \frac{Overall\ activity^{0.5}}{10}$

**QRISK3-Inspired(Excl HDL & SBP) +A fractional polynomial (male)** =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-2} + Hours\ of\ MVPA^{0.5} + (Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA)) + \frac{Hours\ of\ LPA}{10} + \frac{Hours\ of\ SBA}{10} + \frac{Overall\ activity^{0.5}}{10} + \frac{Overall\ activity}{10}$

**QRISK3-Inspired PA fractional polynomial (male)** =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-2} + Hours\ of\ MVPA^{0.5} + (Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA)) + \frac{Hours\ of\ LPA}{10} + \frac{Hours\ of\ SBA}{10} + \frac{Overall\ activity^{0.5}}{10} + \frac{Overall\ activity}{10}$

**Supplementary Table 48: Reclassification Performance for female participants comparing age, QRISK3-Inspired (Excl HDL & SBP) and QRISK3-Inspired risk scores following the addition of Physical activity risk factors. Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                           | Threshold         | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                           |
|----------------------------------|--------------------------------------|-------------------|------------------------|------------------------|------------------------|-------------------------------|
| Age                              | Age +PA                              | 10%               | -0.004(-0.011 - 0)     | 0.019(0.003 - 0.033)   | *0.023(0.006 - 0.036)  | **0.065(0.05 - 0.077)"        |
|                                  |                                      | 7.5%              | 0.008(-0.01 - 0.025)   | 0.048(0.028 - 0.069)   | **0.04(0.02 - 0.058)   | **0.06(0.04 - 0.077)          |
|                                  |                                      | 5%                | 0.111(0.082 - 0.14)    | 0.136(0.108 - 0.162)   | *0.025(0.003 - 0.044)  | *0.021(0 - 0.039)             |
|                                  |                                      | <b>Continuous</b> |                        |                        |                        | <b>**0.216(0.195 - 0.234)</b> |
|                                  |                                      |                   |                        |                        |                        |                               |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired (Excl HDL & SBP) +PA | 10%               | 0.038(0.02 - 0.055)    | 0.048(0.029 - 0.065)   | 0.01(-0.005 - 0.022)   | *0.019(0.001 - 0.036)         |
|                                  |                                      | 7.5%              | 0.085(0.061 - 0.109)   | 0.096(0.072 - 0.119)   | 0.011(-0.005 - 0.027)" | *0.018(0.001 - 0.036)         |
|                                  |                                      | 5%                | 0.2(0.171 - 0.227)     | 0.192(0.166 - 0.219)   | -0.007(-0.023 - 0.007) | -0.007(-0.025 - 0.01)         |
|                                  |                                      | <b>Continuous</b> |                        |                        |                        | <b>**0.13(0.112 - 0.147)</b>  |
|                                  |                                      |                   |                        |                        |                        |                               |
| QRISK3-Inspired                  | QRISK3-Inspired +PA                  | 10%               | 0.035(0.016 - 0.052)   | 0.049(0.03 - 0.069)    | *0.014(0.001 - 0.025)  | *0.018(0 - 0.036)             |
|                                  |                                      | 7.5%              | 0.093(0.07 - 0.116)    | 0.098(0.073 - 0.122)   | 0.009(-0.004 - 0.02)   | 0.01(-0.008 - 0.027)          |
|                                  |                                      | 5%                | 0.213(0.184 - 0.24)    | 0.207(0.179 - 0.234)   | -0.003(-0.016 - 0.007) | -0.008(-0.026 - 0.009)        |
|                                  |                                      | <b>Continuous</b> |                        |                        |                        | <b>**0.122(0.103 - 0.139)</b> |
|                                  |                                      |                   |                        |                        |                        |                               |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\* p value < 0.001

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**Fractional polynomials**, Age FP 1 =  $age/10^{-2}$ , Age FP 2 =  $age/10$ , BMI FP 1 =  $(BMI/10)^{-2}$ , BMI FP 2 =  $(BMI/10)^{-2} \times \log(\frac{BMI}{10})$

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**Age + PA fractional polynomial** =  $(\frac{\text{Daily step count}}{10000})^{-1} + (\frac{\text{Daily step count}}{10000})^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}}{10} + \log(\frac{\text{Overall activity}}{10})$

**QRISK3-Inspired(Excl HDL & SBP) +PA fractional polynomial** =  $(\frac{\text{Daily step count}}{10000})^{-1} + (\frac{\text{Daily step count}}{10000})^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log(\frac{\text{Overall activity}}{10})$

**QRISK3-Inspired PA fractional polynomial** =  $(\frac{\text{Daily step count}}{10000})^{-1} + (\frac{\text{Daily step count}}{10000})^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log(\frac{\text{Overall activity}}{10})$

**Supplementary Table 49: Reclassification Performance for QRISK3-Inspired versus QRISK3-Inspired+ physical activity (PA) risk scores using primary care high-density lipoprotein cholesterol (HDL) and Systolic blood pressure (SBP) measurements in Male and Female Participants at 5%, 7.5%, and 10% Thresholds**

| Model                               | Threshold         | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                           |
|-------------------------------------|-------------------|------------------------|------------------------|------------------------|-------------------------------|
| <b>Male</b>                         |                   |                        |                        |                        |                               |
| QRISK3-Inspired QRISK3-Inspired +PA | 10%               | 0.129(0.107 - 0.15)    | 0.122(0.101 - 0.142)   | -0.007(-0.019 - 0.003) | -0.012(-0.034 - 0.009)        |
|                                     | 7.5%              | 0.23(0.206 - 0.254)    | 0.229(0.206 - 0.253)   | -0.002(-0.013 - 0.008) | -0.005(-0.027 - 0.016)        |
|                                     | 5%                | 0.405(0.383 - 0.429)   | 0.402(0.381 - 0.425)   | -0.003(-0.011 - 0.004) | -0.007(-0.029 - 0.014)        |
|                                     | <b>Continuous</b> |                        |                        |                        | <b>**0.071(0.049 - 0.092)</b> |
| <b>Female</b>                       |                   |                        |                        |                        |                               |
| QRISK3-Inspired QRISK3-Inspired +PA | 10%               | 0.033(0.015 - 0.05)    | 0.05(0.03 - 0.069)     | *0.017(0.004 - 0.027)  | *0.021(0.003 - 0.038)         |
|                                     | 7.5%              | 0.086(0.068 - 0.104)   | 0.097(0.078 - 0.117)   | 0.011(-0.002 - 0.021)  | *0.013(-0.005 - 0.031)        |
|                                     | 5%                | 0.203(0.185 - 0.22)    | 0.198(0.179 - 0.218)   | -0.005(-0.018 - 0.006) | -0.009(-0.027 - 0.008)        |
|                                     | <b>Continuous</b> |                        |                        |                        | <b>**0.119(0.101 - 0.137)</b> |

Abbreviations CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* < 0.05; \*\**p value* < 0.001

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials: *Age FP 1 (males)* = (*age*/10)<sup>-1</sup>, *Age FP 2 (males)* = (*age*/10)<sup>3</sup>, *BMI FP 1 (males)* = (*BMI*/10)<sup>-2</sup>, *BMI FP 2 (males)* = (*BMI*/10)<sup>-2</sup> X log(<sup>*BMI*</sup><sub>10</sub>), *Age FP 1 (Females)* = *age*/10<sup>-2</sup>, *Age FP 2 (Females)* = *age*/10, *BMI FP 1 (Females)* = (*BMI*/10)<sup>-2</sup>, *BMI FP 2 (Females)* = (*BMI*/10)<sup>-2</sup> X log(<sup>*BMI*</sup><sub>10</sub>)

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**PA fractional polynomial (males)** = (<sup>Daily step count</sup><sub>10000</sub>)<sup>-2</sup> + *Hours of MVPA*<sup>0.5</sup> + (*Hours of MVPA*<sup>0.5</sup> X log(*Hours of MVPA* ) + <sup>Hours of LPA</sup><sub>10</sub> + <sup>Hours of SBA</sup><sub>10</sub> + <sup>Overall activity</sup><sub>10</sub><sup>0.5</sup> + <sup>Overall activity</sup><sub>10</sub>;

**PA fractional polynomial (Females)** = (<sup>Daily step count</sup><sub>10000</sub>)<sup>-1</sup> + (<sup>Daily step count</sup><sub>10000</sub>)<sup>-0.5</sup> + *Hours of MVPA* + <sup>Hours of LPA</sup><sub>10</sub><sup>-2</sup> + <sup>Hours of LPA</sup><sub>10</sub><sup>2</sup> + <sup>Hours of SBA</sup><sub>10</sub> + log(<sup>Overall activity</sup><sub>10</sub> ).

**Supplementary Table 50 Reclassification Performance for male participants comparing SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Physical activity risk factors. Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                            | Threshold         | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                           |
|----------------------------------|---------------------------------------|-------------------|------------------------|------------------------|------------------------|-------------------------------|
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + PA | 10%               | 0.085(0.064 - 0.106)   | 0.088(0.067 - 0.11)    | 0.003(-0.01 - 0.015)   | -0.003(-0.025 - 0.017)        |
|                                  |                                       | 7.5%              | 0.189(0.165 - 0.214)   | 0.2(0.177 - 0.224)     | 0.011(0 - 0.021)       | 0.006(-0.015 - 0.027)         |
|                                  |                                       | 5%                | 0.39(0.368 - 0.413)    | 0.391(0.37 - 0.414)    | 0.001(-0.007 - 0.009)  | 0.004(-0.017 - 0.025)         |
|                                  |                                       | <b>Continuous</b> |                        |                        |                        | <b>**0.123(0.101 - 0.144)</b> |
| SCORE2-Inspired                  | SCORE2-Inspired +PA                   | 10%               | 0.093(0.071 - 0.114)   | 0.099(0.079 - 0.12)    | 0.003(-0.01 - 0.014)   | -0.003(-0.025 - 0.018)        |
|                                  |                                       | 7.5%              | 0.2(0.176 - 0.224)     | 0.203(0.18 - 0.228)    | 0.003(-0.008 - 0.012)  | -0.002(-0.024 - 0.019)        |
|                                  |                                       | 5%                | 0.403(0.382 - 0.427)   | 0.398(0.376 - 0.42)    | -0.006(-0.014 - 0.001) | -0.006(-0.028 - 0.015)        |
|                                  |                                       | <b>Continuous</b> |                        |                        |                        | <b>**0.066(0.045 - 0.087)</b> |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. .p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value < 0.05*; \*\* *p value < 0.001*

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

$$\text{PA fractional polynomial} = \left( \frac{\text{Daily step count}}{10000} \right) + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log \left( \left( \frac{\text{Overall activity}}{10} \right)^{0.5} \times \log \left( \frac{\text{Overall activity}}{10} \right) \right)$$

$$\text{Fractional Polynomials for scores excluding HDL \& SBP} = \left( \frac{\text{Daily step count}}{10000} \right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log \left( \left( \frac{\text{Overall activity}}{10} \right)^1 \right)$$

**Supplementary Table 51 Reclassification Performance for female participants comparing SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Physical activity risk factors. Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                            | Threshold         | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                          |
|----------------------------------|---------------------------------------|-------------------|------------------------|------------------------|------------------------|------------------------------|
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + PA | 10%               | 0.008( -0.009 - 0.026) | 0.022(0.003 - 0.04)    | *0.014(-0.001 - 0.026) | *0.016(0 - 0.03)             |
|                                  |                                       | 7.5%              | 0.026(0.002 - 0.05)    | 0.05(0.027 - 0.073)    | *0.025(0.008 - 0.04)   | **0.04(0.023 - 0.057)        |
|                                  |                                       | 5%                | 0.139(0.11 - 0.166)    | 0.154(0.128 - 0.181)   | *0.016(0 - 0.03)       | *0.015(-0.003 - 0.032)       |
|                                  |                                       | <b>Continuous</b> |                        |                        |                        | <b>**0.197(0.18 - 0.215)</b> |
| SCORE2-Inspired                  | SCORE2-Inspired +PA                   | 10%               | 0.007( -0.011 - 0.025) | 0.026(0.007 - 0.046)   | **0.019(0.006 - 0.029) | **0.03(0.012 - 0.048)        |
|                                  |                                       | 7.5%              | 0.057(0.039 - 0.074)   | 0.07(0.051 - 0.09)     | *0.013(0 - 0.024)      | *0.019(0 - 0.036)            |
|                                  |                                       | 5%                | 0.171(0.153 - 0.188)   | 0.181(0.161 - 0.2)     | 0.009(-0.003 - 0.02)   | 0.001(-0.017 - 0.018)        |
|                                  |                                       | <b>Continuous</b> |                        |                        |                        | <b>**0.138(0.12 - 0.155)</b> |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* <0.05;\*\**p value* < 0.001

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA, Light intensity, PA and sedentary behaviour.

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

$$\text{PA fractional polynomial} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \log\left(\frac{\text{Overall activity}^{0.5}}{10}\right)$$

$$\text{Fractional Polynomials for scores excluding HDL \& SBP} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA}^{0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}}{10}$$

**Supplementary Table 52 Reclassification Performance for SCORE2-Inspired versus SCORE2-Inspired + physical activity (PA) risk factors using primary care high-density lipoprotein cholesterol (HDL) and Systolic blood pressure (SBP) measurements in Male and Female Participants at 5%, 7.5%, and 10% Thresholds**

| Model           | Comparator          | Threshold  | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                          |
|-----------------|---------------------|------------|------------------------|------------------------|------------------------|------------------------------|
| Male            |                     |            |                        |                        |                        |                              |
| SCORE2-Inspired | SCORE2-Inspired +PA | 10%        | 0.102(0.08 - 0.124)    | 0.1(0.079 - 0.12)      | -0.003(-0.015 - 0.008) | -0.012(-0.034 - 0.009)       |
|                 |                     | 7.5%       | 0.201(0.177 - 0.225)   | 0.2(0.178 - 0.225)     | 0(-0.011 - 0.009)      | -0.005(-0.027 - 0.016)       |
|                 |                     | 5%         | 0.395(0.374 - 0.419)   | 0.396(0.375 - 0.419)   | 0.001(-0.007 - 0.008)  | .001(-0.021 - 0.022)         |
|                 |                     | Continuous |                        |                        |                        | <b>**0.09(0.068 - 0.111)</b> |
| Female          |                     |            |                        |                        |                        |                              |
| SCORE2-Inspired | SCORE2-Inspired +PA | 10%        | 0.005( -0.013 - 0.022) | 0.029(0.01 - 0.049)    | **0.024(0.011 - 0.035) | **0.042(0.024 - 0.059)       |
|                 |                     | 7.5%       | 0.035(0.017 - 0.053    | 0.062(0.043 - 0.082)   | **0.027(0.014 - 0.037) | **0.038(0.02 - 0.055)        |
|                 |                     | 5%         | 0.163(0.145 - 0.18)    | 0.164(0.145 - 0.184)   | 0.001(-0.012 - 0.012)  | -0.005(-0.023 - 0.013)       |
|                 |                     | Continuous |                        |                        |                        | <b>**0.18(0.162 - 0.197)</b> |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value < 0.05*; \*\**p value < 0.001*

Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

$$\text{PA fractional polynomial (males)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-2} + \text{Hours of MVPA}^{0.5} + (\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA})) + \frac{\text{Hours of LPA}}{10} + \frac{\text{Hours of SBA}^3}{10} + \frac{\text{Overall activity}^{0.5}}{10} + \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right)$$

$$\text{PA fractional polynomial (Females)} = \left(\frac{\text{Daily step count}}{10000}\right)^{-1} + \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} + \text{Hours of MVPA}^{0.5} + \text{Hours of MVPA} + \frac{\text{Hours of LPA}^{-2}}{10} + \frac{\text{Hours of LPA}^2}{10} + \frac{\text{Hours of SBA}}{10} + \frac{\text{Overall activity}^{0.5}}{10}$$



**Supplementary Table 53 Reclassification Performance of QRISK3-Inspired risk scores versus QRISK3-Inspired + Physical activity (PA) measurements, stratified by age, in Male Participants at 5%, 7.5%, and 10% risk thresholds**

| Model                               | Comparator          | Threshold  | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit             | NRI                           |
|-------------------------------------|---------------------|------------|------------------------|-------------------------|--------------------------|-------------------------------|
| Under 55: N =7,900, #MACCE = 212    |                     |            |                        |                         |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ PA | 10%        | 0.006( -0.025 - 0.03)  | 0.004( -0.029 - 0.031)  | -0.002(-0.021 - 0.014)   | -0.007(-0.029 - 0.014)        |
|                                     |                     | 7.5%       | 0.003( -0.038 - 0.035) | 0.009( -0.031 - 0.045)  | 0.006(-0.023 - 0.028)    | 0.006(-0.015 - 0.027)         |
|                                     |                     | 5%         | 0.043( -0.011 - 0.094) | 0.038( -0.02 - 0.095)   | -0.005(-0.046 - 0.027)   | 0(-0.021 - 0.021)             |
|                                     |                     | Continuous |                        |                         |                          | <b>**0.112(0.09 - 0.133)</b>  |
| 55 to 65: N =12,356, #MACCE = 664   |                     |            |                        |                         |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ PA | 10%        | 0.419(0.328 - 0.526)   | 0.431(0.346 - 0.535)    | 0.012(-0.033 - 0.052)    | 0(-0.022 - 0.021)             |
|                                     |                     | 7.5%       | 0.059(0.022 - 0.095)   | 0.076(0.036 - 0.11)     | 0.017(-0.002 - 0.035)    | *0.017(-0.005 - 0.038)        |
|                                     |                     | 5%         | 0.237(0.19 - 0.285)    | 0.232(0.187 - 0.279)    | -0.005(-0.029 - 0.016)   | -0.006(-0.028 - 0.014)        |
|                                     |                     | Continuous |                        |                         |                          | <b>-0.004(-0.026 - 0.017)</b> |
| 65 to 75: N =15,858, #MACCE = 1,536 |                     |            |                        |                         |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ PA | 10%        | 0.16(0.128 - 0.192)    | 0.143(0.113 - 0.173)    | *-0.017(-0.034 - -0.002) | -0.02(-0.042 - 0.001)         |
|                                     |                     | 7.5%       | 0.282(0.249 - 0.315)   | 0.283(0.251 - 0.318)    | 0.001(-0.014 - 0.015)    | 0.008(-0.014 - 0.029)         |
|                                     |                     | 5%         | 0.506(0.483 - 0.533)   | 0.505(0.482 - 0.532)    | -0.001(-0.008 - 0.005)   | 0(-0.022 - 0.021)             |
|                                     |                     | Continuous |                        |                         |                          | <b>**0.106(0.084 - 0.126)</b> |
| Over 75: N =951, #MACCE = 154       |                     |            |                        |                         |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ PA | 10%        | 0.419(0.328 - 0.526)   | 0.431(0.346 - 0.535)    | 0.012(-0.033 - 0.052)    | *0.029(0.007 - 0.049)         |
|                                     |                     | 7.5%       | 0.586(0.522 - 0.667)   | 0.583(0.517 - 0.661)    | -0.003(-0.026 - 0.017)   | 0.002(-0.02 - 0.023)          |
|                                     |                     | 5%         | 0.732(0.69 - 0.786)    | 0.732(0.689 - 0.785)    | 0(-0.007 - 0.002)        | -0.008(-0.029 - 0.013)        |
|                                     |                     | Continuous |                        |                         |                          | <b>**0.228(0.206 - 0.249)</b> |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\*p value <0.001; Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Townsend deprivation index + Age FP2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**Fractional polynomials:** Age FP 1 =  $(age/10)^{-1}$ , Age FP 2 =  $(age/10)^3$ , BMI FP 1 =  $(BMI/10)^{-2}$ , BMI FP 2 =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA (LPA), and sedentary behaviour (SB)

**PA fractional polynomial (male)** =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-2} + Hours\ of\ MVPA^{0.5} + (Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA)) + \frac{Hours\ of\ LPA}{10} + \frac{Hours\ of\ SBA}{10} + \frac{Overall\ activity^{0.5}}{10} + \frac{Overall\ activity}{10}$



**Supplementary Table 54 Reclassification Performance of QRISK3 versus QRISK3 + Physical activity (PA) measurements, stratified by age, in Female Participants at 5%, 7.5%, and 10% risk thresholds**

| Model                               | Comparator | Threshold  | Net benefit (baseline)   | Net Benefit (After AHS)  | ΔNet Benefit               | NRI                           |
|-------------------------------------|------------|------------|--------------------------|--------------------------|----------------------------|-------------------------------|
| Under 55: N =11,803, #MACCE = 106   |            |            |                          |                          |                            |                               |
| QRISK3                              | QRISK3+ PA | 10%        | -0.027( -0.045 - -0.01)  | -0.023( -0.042 - -0.003) | 0.005(-0.008 - 0.015)      | 0.003(-0.015 - 0.02)          |
|                                     |            | 7.5%       | -0.019( -0.037 - -0.002) | -0.027( -0.046 - -0.007) | -0.008(-0.021 - 0.002)     | -0.015(-0.034 - 0.002)        |
|                                     |            | 5%         | 0.047(0.029 - 0.064)     | 0.043(0.023 - 0.062)     | -0.004(-0.017 - 0.006)     | -0.007(-0.025 - 0.011)        |
|                                     |            | Continuous |                          |                          |                            | <b>**0.125(0.107 - 0.142)</b> |
| 55 to 65: N =19,219, #MACCE = 436   |            |            |                          |                          |                            |                               |
| QRISK3                              | QRISK3+ PA | 10%        | 0.087(0.069 - 0.104)     | 0.079(0.059 - 0.098)     | -0.008(-0.021 - 0.002)     | 0.009(-0.009 - 0.027)         |
|                                     |            | 7.5%       | 0.025(0.007 - 0.042)     | 0.037(0.018 - 0.057)     | *0.012(-0.001 - 0.023)     | *0.012(-0.006 - 0.03)         |
|                                     |            | 5%         | 0.076(0.058 - 0.093)     | 0.075(0.056 - 0.095)     | -0.001(-0.014 - 0.01)      | -0.001(-0.019 - 0.017)        |
|                                     |            | Continuous |                          |                          |                            | <b>**0.106(0.087 - 0.123)</b> |
| 65 to 75: N =19,375, #MACCE = 1,036 |            |            |                          |                          |                            |                               |
| QRISK3                              | QRISK3+ PA | 10%        | 0.053(0.035 - 0.07)      | 0.07(0.051 - 0.09)       | *0.018(0.005 - 0.028)      | *0.021(0.003 - 0.039)"        |
|                                     |            | 7.5%       | 0.127(0.109 - 0.144)     | 0.14(0.121 - 0.16)       | *0.013(0 - 0.024)          | *0.013(-0.005 - 0.03)         |
|                                     |            | 5%         | 0.273(0.255 - 0.29)      | 0.268(0.249 - 0.288)     | -0.005(-0.018 - 0.006)     | -0.008(-0.026 - 0.009)        |
|                                     |            | Continuous |                          |                          |                            | <b>**0.145(0.126 - 0.162)</b> |
| Over 75: N =954, #MACCE = 76        |            |            |                          |                          |                            |                               |
| QRISK3                              | QRISK3+ PA | 10%        | 0.087(0.069 - 0.104)     | 0.079(0.059 - 0.098)     | -0.008(-0.021 - 0.002)     | -0.005(-0.023 - 0.012)        |
|                                     |            | 7.5%       | 0.198(0.18 - 0.215)      | 0.156(0.137 - 0.176)     | ** -0.041(-0.054 - -0.031) | ** -0.044(-0.062 - -0.027)    |
|                                     |            | 5%         | 0.414(0.396 - 0.431)     | 0.414(0.395 - 0.434)     | 0(-0.013 - 0.011)          | *0.015(-0.003 - 0.032)        |
|                                     |            | Continuous |                          |                          |                            | <b>**0.234(0.215 - 0.251)</b> |

Abbreviations: CI = Confidence interval PA = Physical activity, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations. p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\*p value < 0.001; Each risk score was derived from separate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

**QRISK3-Inspired:** Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP 1 + Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP2 X BMI FP1 + Age FP2 X BMI FP2 + Age FP2 X Townsend deprivation index + Age FP2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter

**Fractional polynomials, Age FP 1 =  $age/10^{-2}$ , Age FP 2 =  $age/10$ , BMI FP 1 =  $(BMI/10)^{-2}$ , BMI FP 2 =  $(BMI/10)^{-2} \times \log(\frac{BMI}{10})$**

Physical activity (PA): Average daily step count, Overall, PA (vector magnitude), daily hours of moderate-to-vigorous PA (MVPA), Light intensity PA(LPA), and sedentary behaviour. (SB)

**PA fractional polynomial (female) =  $(\frac{Daily\ step\ count}{10000})^{-1} + (\frac{Daily\ step\ count}{10000})^{-0.5} + Hours\ of\ MVPA + \frac{Hours\ of\ LPA^{-2}}{10} + \frac{Hours\ of\ LPA^2}{10} + \frac{Hours\ of\ SBA}{10} + \log(\frac{Overall\ activity}{10})$**

**Supplementary Table 55: Composite outcome of hospitalisation due to chronic disease for training Activity health scores (ICD-10 codes)**

| ICD-10 Code | Description                                                                                                                                  |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| I00         | Rheumatic fever without heart involvement.                                                                                                   |
| I01         | Rheumatic fever with heart involvement.                                                                                                      |
| I02         | Rheumatic chorea.                                                                                                                            |
| I05         | Rheumatic mitral valve diseases.                                                                                                             |
| I06         | Rheumatic aortic valve diseases.                                                                                                             |
| I07         | Rheumatic tricuspid valve diseases.                                                                                                          |
| I08         | Multiple valve diseases.                                                                                                                     |
| I09         | Other rheumatic heart diseases.                                                                                                              |
| I10         | Essential (primary) hypertension.                                                                                                            |
| I11         | Hypertensive heart disease.                                                                                                                  |
| I12         | Hypertensive chronic kidney disease.                                                                                                         |
| I13         | Hypertensive heart and chronic kidney disease.                                                                                               |
| I15         | Secondary hypertension.                                                                                                                      |
| I16         | Hypertensive crisis.                                                                                                                         |
| I20         | Angina pectoris.                                                                                                                             |
| I21         | Acute myocardial infarction.                                                                                                                 |
| I22         | Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction.                                                         |
| I23         | Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28-day period). |
| I24         | Other acute ischemic heart diseases.                                                                                                         |
| I25         | Chronic ischemic heart disease.                                                                                                              |
| I26         | Pulmonary embolism.                                                                                                                          |
| I27         | Other pulmonary heart diseases.                                                                                                              |
| I28         | Other diseases of pulmonary vessels.                                                                                                         |
| I30         | Acute pericarditis.                                                                                                                          |
| I31         | Other diseases of pericardium.                                                                                                               |
| I32         | Pericarditis in diseases classified elsewhere.                                                                                               |
| I33         | Acute and subacute endocarditis.                                                                                                             |
| I34         | Nonrheumatic mitral valve disorders.                                                                                                         |
| I35         | Nonrheumatic aortic valve disorders.                                                                                                         |
| I36         | Nonrheumatic tricuspid valve disorders.                                                                                                      |
| I37         | Nonrheumatic pulmonary valve disorders.                                                                                                      |
| I38         | Endocarditis, valve unspecified.                                                                                                             |
| I39         | Endocarditis and heart valve disorders in diseases classified elsewhere.                                                                     |
| I40         | Acute myocarditis.                                                                                                                           |
| I41         | Myocarditis in diseases classified elsewhere.                                                                                                |
| I42         | Cardiomyopathy.                                                                                                                              |

|     |                                                                                       |
|-----|---------------------------------------------------------------------------------------|
| I43 | Cardiomyopathy in diseases classified elsewhere.                                      |
| I44 | Atrioventricular and left bundle-branch block.                                        |
| I45 | Other conduction disorders.                                                           |
| I46 | Cardiac arrest.                                                                       |
| I47 | Paroxysmal tachycardia.                                                               |
| I48 | Atrial fibrillation and flutter.                                                      |
| I49 | Other cardiac arrhythmias.                                                            |
| I50 | Heart failure.                                                                        |
| I51 | Complications and ill-defined descriptions of heart disease.                          |
| I52 | Other heart disorders in diseases classified elsewhere.                               |
| I60 | Nontraumatic subarachnoid hemorrhage.                                                 |
| I61 | Nontraumatic intracerebral hemorrhage.                                                |
| I62 | Other and unspecified nontraumatic intracranial hemorrhage.                           |
| I63 | Cerebral infarction.                                                                  |
| I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction. |
| I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction.    |
| I67 | Other cerebrovascular diseases.                                                       |
| I68 | Cerebrovascular disorders in diseases classified elsewhere.                           |
| I69 | Sequelae of cerebrovascular disease.                                                  |
| I70 | Atherosclerosis.                                                                      |
| I71 | Aortic aneurysm and dissection.                                                       |
| I72 | Other aneurysm.                                                                       |
| I73 | Other peripheral vascular diseases.                                                   |
| I74 | Arterial embolism and thrombosis.                                                     |
| I75 | Atheroembolism.                                                                       |
| I76 | Septic arterial embolism.                                                             |
| I77 | Other disorders of arteries and arterioles.                                           |
| I78 | Diseases of capillaries.                                                              |
| I79 | Disorders of arteries, arterioles, and capillaries in diseases classified elsewhere.  |
| I80 | Phlebitis and thrombophlebitis.                                                       |
| I81 | Portal vein thrombosis.                                                               |
| I82 | Other venous embolism and thrombosis.                                                 |
| I83 | Varicose veins of lower extremities.                                                  |
| I85 | Esophageal varices.                                                                   |
| I86 | Varicose veins of other sites.                                                        |
| I87 | Other disorders of veins.                                                             |
| I88 | Nonspecific lymphadenitis.                                                            |

|     |                                                                                                                |
|-----|----------------------------------------------------------------------------------------------------------------|
| I89 | Other noninfective disorders of lymphatic vessels and lymph nodes.                                             |
| I95 | Hypotension.                                                                                                   |
| I96 | Gangrene, not elsewhere classified.                                                                            |
| I97 | Intraoperative and postprocedural complications and disorders of circulatory system, not elsewhere classified. |
| I99 | Other and unspecified disorders of circulatory system.                                                         |
| G45 | Transient cerebral ischemic attacks and related syndromes.                                                     |
| C00 | Malignant neoplasm of lip.                                                                                     |
| C01 | Malignant neoplasm of base of tongue.                                                                          |
| C02 | Malignant neoplasm of other and unspecified parts of tongue.                                                   |
| C03 | Malignant neoplasm of gum.                                                                                     |
| C04 | Malignant neoplasm of floor of mouth.                                                                          |
| C05 | Malignant neoplasm of palate.                                                                                  |
| C06 | Malignant neoplasm of other and unspecified parts of mouth.                                                    |
| C07 | Malignant neoplasm of parotid gland.                                                                           |
| C08 | Malignant neoplasm of other and unspecified major salivary glands.                                             |
| C09 | Malignant neoplasm of tonsil.                                                                                  |
| C10 | Malignant neoplasm of oropharynx.                                                                              |
| C11 | Malignant neoplasm of nasopharynx.                                                                             |
| C12 | Malignant neoplasm of pyriform sinus.                                                                          |
| C13 | Malignant neoplasm of hypopharynx.                                                                             |
| C14 | Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx.                        |
| C15 | Malignant neoplasm of esophagus.                                                                               |
| C16 | Malignant neoplasm of stomach.                                                                                 |
| C17 | Malignant neoplasm of small intestine.                                                                         |
| C18 | Malignant neoplasm of colon.                                                                                   |
| C19 | Malignant neoplasm of rectosigmoid junction.                                                                   |
| C20 | Malignant neoplasm of rectum.                                                                                  |
| C21 | Malignant neoplasm of anus and anal canal.                                                                     |
| C22 | Malignant neoplasm of liver and intrahepatic bile ducts.                                                       |
| C23 | Malignant neoplasm of gallbladder.                                                                             |
| C24 | Malignant neoplasm of other and unspecified parts of biliary tract.                                            |
| C25 | Malignant neoplasm of pancreas.                                                                                |
| C26 | Malignant neoplasm of other and ill-defined digestive organs.                                                  |

|     |                                                                                                       |
|-----|-------------------------------------------------------------------------------------------------------|
| C30 | Malignant neoplasm of nasal cavity and middle ear.                                                    |
| C31 | Malignant neoplasm of accessory sinuses.                                                              |
| C32 | Malignant neoplasm of larynx.                                                                         |
| C33 | Malignant neoplasm of trachea.                                                                        |
| C34 | Malignant neoplasm of bronchus and lung.                                                              |
| C37 | Malignant neoplasm of thymus.                                                                         |
| C38 | Malignant neoplasm of heart, mediastinum, and pleura.                                                 |
| C39 | Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs. |
| C40 | Malignant neoplasm of bone and articular cartilage of limbs.                                          |
| C41 | Malignant neoplasm of bone and articular cartilage of other and unspecified sites.                    |
| C43 | Malignant melanoma of skin.                                                                           |
| C44 | Other malignant neoplasms of skin.                                                                    |
| C45 | Mesothelioma.                                                                                         |
| C46 | Kaposi's sarcoma.                                                                                     |
| C47 | Malignant neoplasm of peripheral nerves and autonomic nervous system.                                 |
| C48 | Malignant neoplasm of retroperitoneum and peritoneum.                                                 |
| C49 | Malignant neoplasm of other connective and soft tissue.                                               |
| C50 | Malignant neoplasm of breast.                                                                         |
| C51 | Malignant neoplasm of vulva.                                                                          |
| C52 | Malignant neoplasm of vagina.                                                                         |
| C53 | Malignant neoplasm of cervix uteri.                                                                   |
| C54 | Malignant neoplasm of corpus uteri.                                                                   |
| C55 | Malignant neoplasm of uterus, part unspecified.                                                       |
| C56 | Malignant neoplasm of ovary.                                                                          |
| C57 | Malignant neoplasm of other and unspecified female genital organs.                                    |
| C58 | Malignant neoplasm of placenta.                                                                       |
| C60 | Malignant neoplasm of penis.                                                                          |
| C61 | Malignant neoplasm of prostate.                                                                       |
| C62 | Malignant neoplasm of testis.                                                                         |
| C63 | Malignant neoplasm of other and unspecified male genital organs.                                      |
| C64 | Malignant neoplasm of kidney, except renal pelvis.                                                    |
| C65 | Malignant neoplasm of renal pelvis.                                                                   |
| C66 | Malignant neoplasm of ureter.                                                                         |
| C67 | Malignant neoplasm of bladder.                                                                        |
| C68 | Malignant neoplasm of other and unspecified urinary organs.                                           |

|     |                                                                                               |
|-----|-----------------------------------------------------------------------------------------------|
| C69 | Malignant neoplasm of eye and adnexa.                                                         |
| C70 | Malignant neoplasm of meninges.                                                               |
| C71 | Malignant neoplasm of brain.                                                                  |
| C72 | Malignant neoplasm of spinal cord, cranial nerves, and other parts of central nervous system. |
| C73 | Malignant neoplasm of thyroid gland.                                                          |
| C74 | Malignant neoplasm of adrenal gland.                                                          |
| C75 | Malignant neoplasm of other endocrine glands and related structures.                          |
| C76 | Malignant neoplasm of other and ill-defined sites.                                            |
| C77 | Secondary and unspecified malignant neoplasm of lymph nodes.                                  |
| C78 | Secondary malignant neoplasm of respiratory and digestive organs.                             |
| C79 | Secondary malignant neoplasm of other sites.                                                  |
| C80 | Malignant neoplasm without specification of site.                                             |
| C81 | Hodgkin's disease.                                                                            |
| C82 | Follicular [nodular] non-Hodgkin's lymphoma.                                                  |
| C83 | Diffuse non-Hodgkin's lymphoma.                                                               |
| C84 | Peripheral and cutaneous T-cell lymphomas.                                                    |
| C85 | Other and unspecified types of non-Hodgkin's lymphoma.                                        |
| C88 | Malignant immunoproliferative diseases.                                                       |
| C90 | Multiple myeloma and malignant plasma cell neoplasms.                                         |
| C91 | Lymphoid leukemia.                                                                            |
| C92 | Myeloid leukemia.                                                                             |
| C93 | Monocytic leukemia.                                                                           |
| C94 | Other leukemias of specified cell type.                                                       |
| C95 | Leukemia of unspecified cell type.                                                            |
| C96 | Other and unspecified malignant neoplasms of lymphoid, hematopoietic, and related tissue.     |
| C97 | Malignant neoplasms of independent (primary) multiple sites.                                  |
| E11 | Type 2 diabetes mellitus.                                                                     |

**Supplementary Table 56: Optimism adjusted predictive performance of Age, QRISK3-Inspired (Excl HDL & SBP) and QRISK3-Inspired risk scores before and after the addition of Activity health Scores (AHS)**

| Model                                  | C-Index (95% CI)      | ICI (95% CI)            |
|----------------------------------------|-----------------------|-------------------------|
| <b>Male</b>                            |                       |                         |
| Age                                    | 0.651 (0.641 – 0.661) | 0.0028(0.009- 0.0047)   |
| Age + AHS                              | 0.663 (0.654 – 0.674) | 0.0045(0.0021 - 0.0068) |
| QRISK3-Inspired (Excl HDL & SBP)       | 0.677(0.667 - 0.686)  | 0.0015(-4e-04 - 0.0036) |
| QRISK3-Inspired (Excl HDL & SBP) + AHS | 0.679(0.669 - 0.689)  | 0.0021(3e-04 - 0.0043)  |
| QRISK3-Inspired                        | 0.680(0.670 - 0.689)  | 0.0024(5e-04 - 0.0044)  |
| QRISK3-Inspired + AHS                  | 0.682(0.673 - 0.692)  | 0.0026(6e-04 - 0.0047)  |
| <b>Female</b>                          |                       |                         |
| Age                                    | 0.688(0.677 - 0.699)  | 6e-04(-0.0004 - 0.0016) |
| Age + AHS                              | 0.713(0.702 - 0.725)  | 0.001(-0.0002 - 0.0023) |
| QRISK3-Inspired (Excl HDL & SBP)       | 0.731(0.719 - 0.742)  | 0.0013(0.0002 - 0.0026) |
| QRISK3-Inspired (Excl HDL & SBP) + AHS | 0.739(0.728 - 0.75)   | 0.0011(0.0000 - 0.0023) |
| QRISK3-Inspired                        | 0.736(0.725 - 0.747)  | 0.0016(5e-04 - 0.0029)  |
| QRISK3-Inspired + AHS                  | 0.744(0.733 - 0.755)  | 0.0016(4e-04 - 0.0028)  |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval AHS =Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported C-index, ICI and corresponding 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter.

Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2)

Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + AHS/0.1$ ; QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (female) =  $AHS/0.1 + (AHS/0.1) \times \log(AHS/0.1)$

**Supplementary Table 57: Relative change in optimism adjusted predictive performance of Age, QRISK3-Inspired (Excl HDL & SBP) AND QRISK3-Inspired risk scores following the addition Activity health Scores (AHS)**

| Model                            | Comparator                             | $\Delta C$ -index      | $\Delta ICI$              |
|----------------------------------|----------------------------------------|------------------------|---------------------------|
| <b>Male</b>                      |                                        |                        |                           |
| Age                              | Age + AHS                              | **0.012(0.007 - 0.016) | 0.002(-0.001 - 0.004)     |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired (Excl HDL & SBP) + AHS | *0.002(0.000 - 0.004)  | 0.0007(-0.003 - 0.009)    |
| QRISK3-Inspired                  | QRISK3-Inspired (Excl HDL & SBP) + AHS | 0.000(-0.003 - 0.004)  | -0.0002(-0.0018 - 0.0014) |
| QRISK3-Inspired                  | QRISK3-Inspired +AHS                   | *0.003(0.001 - 0.005)  | 0.0003(-0.0011 - 0.0016)  |
| <b>Female</b>                    |                                        |                        |                           |
| Age                              | Age + AHS                              | **0.025(0.018 - 0.03)  | 0.0004(-9e-04 - 0.0018)   |
| QRISK3-Inspired (Excl HDL & SBP) | QRISK3-Inspired (Excl HDL & SBP) + AHS | **0.007(0.004 - 0.01)  | -0.0002(-0.0015 - 0.001)  |
| QRISK3-Inspired                  | QRISK3-Inspired (Excl HDL & SBP) + AHS | 0.002(-0.002 - 0.006)  | -0.0005(-0.0017 - 0.0008) |
| QRISK3-Inspired                  | QRISK3-Inspired +AHS                   | **0.007(0.004 - 0.01)  | -0.001(-0.0011 - 0.001)   |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Reported  $\Delta C$ -index,  $\Delta ICI$  and corresponding 95% confidence intervals were derived from optimism adjusted values following 1000 bootstrap iterations.

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter.

QRISK3-InspiredFractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).

Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + AHS/0.1$ ; QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (female) =  $AHS/0.1 + (AHS/0.1) \times \log(AHS/0.1)$



**Supplementary Table 58: Optimism adjusted predictive performance of SCORE2-Inspired(Excl HDL & SBP) and SCORE2-Inspired risk scores before and after the addition of Activity health Scores (AHS)**

| Model                                  | C-Index               | ICI                      |
|----------------------------------------|-----------------------|--------------------------|
| <b>Male</b>                            |                       |                          |
| SCORE2-Inspired (Excl HDL & SBP)       | 0.658(0.649 - 0.669)  | 0.0019(0 - 0.0041)       |
| SCORE2-Inspired (Excl HDL & SBP) + AHS | 0.666(0.657 - 0.676)  | 0.0043(0.0021 - 0.0066)  |
|                                        |                       | 0.0035(0.0013 - 0.0059)  |
| SCORE2-Inspired                        | 0.668(0.659 - 0.678)  | 0.0022(0.0003 - 0.0043)  |
| SCORE2-Inspired +AHS                   | 0.674(0.664 - 0.684)  |                          |
| <b>Female</b>                          |                       |                          |
| SCORE2-Inspired (Excl HDL & SBP)       | 0.701(0.69 - 0.713)   | 0.0006(-0.0004 - 0.0017) |
| SCORE2-Inspired (Excl HDL & SBP) + AHS | 0.72(0.709 - 0.732)   | 0.005(-0.005 - 0.0017)   |
|                                        |                       |                          |
| SCORE2-Inspired                        | 0.722(0.712 - 0.734)" | 0.0013(0.0002 - 0.0023)  |
| SCORE2-Inspired +AHS                   | 0.734(0.724 - 0.745)  | 0.0015(0.0003 - 0.0027)  |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Reported C-index, ICI and corresponding 95% confidence intervals were adjusted for optimism following 1000 bootstrap iterations.

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).

Age AHS fractional polynomial (male)  $= (AHS/0.1)^3$ ; Age AHS fractional polynomial (female)

$= (AHS/0.1)^2$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =

$(AHS/0.1)^3$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (female)=

$(AHS/0.1)^2$ ; SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + ((AHS/$

$0.1)^3 \times \log(AHS/0.1)$  ); SCORE2-Inspired AHS fractional polynomial (female)=  $(AHS/0.1)^{0.5} +$

$(AHS/0.1)$

**Supplementary Table 59 Relative change in optimism adjusted predictive performance of SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Activity health Scores (AHS)**

| Model                            | Comparator                             | $\Delta C$ -index       | $\Delta ICI$                |
|----------------------------------|----------------------------------------|-------------------------|-----------------------------|
| <b>Male</b>                      |                                        |                         |                             |
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + AHS | **0.008 (0.003 - 0.011) | *0.0024(0.0007 - 0.0043)    |
| SCORE2-Inspired                  | SCORE2-Inspired (Excl HDL & SBP) + AHS | -0.002(-0.008 - 0.003)  | *0.0021(0.0003 - 0.004)     |
| SCORE2-Inspired                  | SCORE2-Inspired + AHS                  | **0.005(0.002 - 0.008)  | 0.0013(-0.0001 - 0.0029)    |
| <b>Female</b>                    |                                        |                         |                             |
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + AHS | **0.019(0.012 - 0.024)  | -0.0001 ( -0.0012 - 0.0011) |
| SCORE2-Inspired                  | SCORE2-Inspired (Excl HDL & SBP) + AHS | -0.002(-0.009 - 0.004)  | -0.0008(-0.0019 - 0.0005)   |
| SCORE2-Inspired                  | SCORE2-Inspired + AHS                  | **0.012(0.004 - 0.01)   | 0.0002(-0.0009 - 0.0011)    |

Abbreviations: ICI = Integrated calibration Index, CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Each row corresponds to a separate univariate Cox model in which each risk factors was fitted individually.

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

Reported  $\Delta C$ -index,  $\Delta ICI$  and corresponding 95% confidence intervals were derived from optimism adjusted values following 1000 bootstrap iterations.

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).

Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; Age AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (female) =  $(AHS/0.1)^2$ ; SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + ((AHS/0.1)^3 \times \log(AHS/0.1))$ ; SCORE2-Inspired AHS fractional polynomial (female) =  $(AHS/0.1)^{0.5} + (AHS/0.1)$

**Supplementary Table 60: Reclassification Performance for male participants comparing age, QRISK3 (Excl HDL & SBP) and QRISK3 following the addition of Activity health Scores (AHS). Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                   | Comparator                   | Threshold         | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit            | NRI                            |
|-------------------------|------------------------------|-------------------|------------------------|-------------------------|-------------------------|--------------------------------|
| Age                     | Age + AHS                    | 10%               | 0.08(0.058 - 0.102)    | 0.111(0.088 - 0.133)    | **0.031(0.016 - 0.046)" | *0.019(0.004 - 0.034)          |
|                         |                              | 7.5%              | 0.177(0.152 - 0.204)   | 0.189(0.165 - 0.216)    | 0.012(0.004 - 0.026)    | 0.008(-0.007 - 0.021)          |
|                         |                              | 5%                | 0.387(0.364 - 0.411)   | 0.399(0.377 - 0.422)    | *0.012(0.002 - 0.021)   | **0.021(0.011 - 0.03)          |
|                         |                              | <b>Continuous</b> |                        |                         |                         | <b>**0.124 (0.084- 0.164)</b>  |
| QRISK3 (Excl HDL & SBP) | QRISK3(Excl HDL & SBP) + AHS | 10%               | 0.128(0.106 - 0.148)   | 0.134(0.112 - 0.155)    | 0.006(-0.006 - 0.017)   | 0.002(-0.01 - 0.013)           |
|                         |                              | 7.5%              | 0.219(0.194 - 0.243)   | 0.221(0.198 - 0.246)    | 0.003(-0.006 - 0.017)   | 0.002(-0.008 - 0.011)          |
|                         |                              | 5%                | 0.403(0.381 - 0.426)   | 0.407(0.386 - 0.43)     | 0.004(-0.002 - 0.01)    | 0.003(-0.003 - 0.009)          |
|                         |                              | <b>Continuous</b> |                        |                         |                         | <b>**0.117 (0.079 - 0.155)</b> |
| QRISK3                  | QRISK3 + AHS                 | 10%               | 0.131(0.109 - 0.151)   | 0.132(0.111 - 0.153)    | 0.002(-0.01 - 0.012)    | -0.002(-0.014 - 0.008)         |
|                         |                              | 7.5%              | 0.219(0.195 - 0.244)   | 0.22(0.198 - 0.244)     | 0.001(-0.009 - 0.011)   | -0.001(-0.01 - 0.009)          |
|                         |                              | 5%                | 0.412(0.39 - 0.435)    | 0.409(0.388 - 0.432)    | -0.002(-0.009 - 0.003)  | -0.004(-0.011 - 0.002)         |
|                         |                              | <b>Continuous</b> |                        |                         |                         | <b>0.026(-0.011- 0.063)</b>    |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure; ; Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).Age AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations;

\*p value <0.05; \*\*p value < 0.001

**Supplementary Table 61: Reclassification Performance for female participants comparing age, QRISK3 (Excl HDL & SBP) and QRISK3 following the addition of Activity health Scores (AHS). Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                   | Comparator                   | Threshold         | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit           | NRI                            |
|-------------------------|------------------------------|-------------------|------------------------|-------------------------|------------------------|--------------------------------|
| Age                     | Age + AHS                    | 10%               | -0.004(-0.011 - 0)     | 0.026(0.009 - 0.04)     | **0.03(0.013 - 0.044)  | **0.085(0.069 - 0.098)         |
|                         |                              | 7.5%              | 0.008(-0.01 - 0.025)   | 0.07(0.046 - 0.091)     | **0.061(0.039 - 0.081) | **0.085(0.065 - 0.105)         |
|                         |                              | 5%                | 0.111(0.082 - 0.14)    | 0.162(0.135 - 0.189)    | **0.051(0.029 - 0.072) | **0.041(0.019 - 0.062)         |
|                         |                              | <b>Continuous</b> |                        |                         |                        | <b>**0.279 (0.231 - 0.324)</b> |
| QRISK3 (Excl HDL & SBP) | QRISK3(Excl HDL & SBP) + AHS | 10%               | 0.038(0.021 - 0.055)   | 0.057(0.038 - 0.077)    | *0.019(0.004 - 0.032)  | **0.031(0.019 - 0.041)         |
|                         |                              | 7.5%              | 0.083(0.059 - 0.107)   | 0.104(0.082 - 0.127)    | *0.021(0.005 - 0.037)  | **0.028(0.012 - 0.044)         |
|                         |                              | 5%                | 0.198(0.17 - 0.226)    | 0.213(0.187 - 0.238)    | 0.014(-0.004 - 0.03)   | 0.011(-0.007 - 0.026)          |
|                         |                              | <b>Continuous</b> |                        |                         |                        | <b>**0.156 (0.110 - 0.202)</b> |
| QRISK3                  | QRISK3 + AHS                 | 10%               | 0.032(0.014 - 0.049)   | 0.053(0.034 - 0.073)    | *0.022(0.007 - 0.035)  | **0.033(0.019 - 0.046)         |
|                         |                              | 7.5%              | 0.087(0.066 - 0.11)    | 0.109(0.086 - 0.133)    | *0.021(0.006 - 0.037)  | **0.026(0.011 - 0.041)         |
|                         |                              | 5%                | 0.209(0.181 - 0.237)   | 0.224(0.198 - 0.252)    | 0.014(-0.002 - 0.03)   | 0.011(-0.005 - 0.026)          |
|                         |                              | <b>Continuous</b> |                        |                         |                        | <b>**0.153(0.108 - 0.200)</b>  |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure; ; Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials: , Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2).. Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). Age AHS fractional polynomial (female) = (AHS/0.1)<sup>2</sup>; QRISK3-Inspired (Excl HDL & SBP) AHS fractional polynomial (female)= (AHS/0.1)<sup>0.5</sup> + AHS/0.1 ;QRISK3-Inspired AHS fractional polynomial (female)= AHS/0.1 + [(AHS/0.1 X log(AHS/0.1))]; p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\* p value < 0.001

**Supplementary Table 62: Reclassification Performance for QRISK3 versus QRISK3+ Activity health Scores (AHS) using primary care high-density lipoprotein cholesterol (HDL) and Systolic blood pressure (SBP) measurements in Male and Female Participants at 5%, 7.5%, and 10% Thresholds**

| Model  | Comparator   | Threshold  | Net benefit (baseline) | Net Benefit (After PA) | ΔNet Benefit           | NRI                    |
|--------|--------------|------------|------------------------|------------------------|------------------------|------------------------|
| Male   |              |            |                        |                        |                        |                        |
| QRISK3 | QRISK3 + AHS | 10%        | 0.126(0.105 - 0.147)"  | 0.128(0.108 - 0.148)   | 0.002(-0.008 - 0.011)  | -0.001(-0.011 - 0.008) |
|        |              | 7.5%       | 0.224(0.201 - 0.249)   | 0.222(0.199 - 0.246)   | -0.002(-0.008 - 0.011) | -0.003(-0.011 - 0.004) |
|        |              | 5%         | 0.404(0.383 - 0.426)   | 0.403(0.382 - 0.424)"  | -0.001(-0.007 - 0.004) | -0.002(-0.008 - 0.003) |
|        |              | Continuous |                        |                        |                        | **0.105(0.069 - 0.143) |
| Female |              |            |                        |                        |                        |                        |
| QRISK3 | QRISK3 + AHS | 10%        | 0.039(0.022 - 0.056)   | 0.056(0.038 - 0.076)   | *0.018(0.004 - 0.03)   | **0.032(0.019 - 0.043) |
|        |              | 7.5%       | 0.083(0.06 - 0.105)    | 0.11(0.088 - 0.133)    | **0.027(0.004 - 0.03)  | **0.032(0.017 - 0.046) |
|        |              | 5%         | 0.209(0.182 - 0.234)   | 0.223(0.198 - 0.249)   | 0.014(-0.001 - 0.028)  | 0.011(-0.004 - 0.024)  |
|        |              | Continuous |                        |                        |                        | **0.154(0.107 - 0.201) |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure;

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP 2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials: Age FP 1 (males) = (age/10)<sup>-1</sup>, Age FP 2 (males) = (age/10)<sup>3</sup>, BMI FP 1 (males) = (BMI/10)<sup>-2</sup>, BMI FP 2 (males) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ ), Age FP 1 (Females) = age/10<sup>-2</sup>, Age FP 2 (Females) = age/10, BMI FP 1 (Females) = (BMI/10)<sup>-2</sup>, BMI FP 2 (Females) = (BMI/10)<sup>-2</sup> X log( $\frac{BMI}{10}$ )

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). QRISK3-Inspired AHS fractional polynomial (male) = (AHS/0.1)<sup>3</sup>; QRISK3-Inspired AHS fractional polynomial (female)= (AHS/0.1)<sup>0.5</sup> + (AHS/0.1)

p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\* p value < 0.001

**Supplementary Table 63 Reclassification Performance for male participants comparing SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Activity health Scores (AHS). Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                             | Threshold         | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit           | NRI                            |
|----------------------------------|----------------------------------------|-------------------|------------------------|-------------------------|------------------------|--------------------------------|
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + AHS | 10%               | 0.09(0.068 - 0.113)    | 0.108(0.087 - 0.13)"    | *0.017 (0.002 - 0.032) | 0.011(-0.004 - 0.026)          |
|                                  |                                        | 7.5%              | 0.193(0.169 - 0.22)    | 0.193(0.168 - 0.219)    | 0.000(0.002 - 0.032)   | -0.003(-0.017 - 0.008)         |
|                                  |                                        | 5%                | 0.391(0.369 - 0.415)"  | 0.402(0.38 - 0.425)     | *0.011(0.002 - 0.019)  | **0.018(0.009 - 0.026)         |
|                                  |                                        | <b>Continuous</b> |                        |                         |                        | <b>**0.141 (0.104 - 0.181)</b> |
| SCORE2-Inspired                  | SCORE2-Inspired + AHS                  | 10%               | 0.099(0.077 - 0.121)   | 0.106(0.084 - 0.128)    | 0.007(-0.006 - 0.02)   | 0.001(-0.012 - 0.013)          |
|                                  |                                        | 7.5%              | 0.205(0.181 - 0.231)   | 0.206(0.183 - 0.233)    | 0.002 (-0.006 - 0.02)  | 0.000(-0.011 - 0.011)          |
|                                  |                                        | 5%                | 0.406(0.385 - 0.428)   | 0.412(0.391 - 0.434)    | 0.006(-0.001 - 0.012)  | *0.009(0.002 - 0.015)          |
|                                  |                                        | <b>Continuous</b> |                        |                         |                        | <b>**0.103 (0.066 - 0.141)</b> |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure.

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations;

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (male) =  $(AHS/0.1)^3$ ; SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + ((AHS/0.1)^3 \times \log(AHS/0.1))$ ;

p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* <0.05; \*\**p value* < 0.001

**Supplementary Table 64 Reclassification Performance for female participants comparing SCORE2-Inspired (Excl HDL & SBP) and SCORE2-Inspired risk scores following the addition of Activity health Scores (AHS) . Reclassification is presented for 5%, 7.5% and 10% risk thresholds.**

| Model                            | Comparator                             | Threshold         | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit           | NRI                            |
|----------------------------------|----------------------------------------|-------------------|------------------------|-------------------------|------------------------|--------------------------------|
| SCORE2-Inspired (Excl HDL & SBP) | SCORE2-Inspired (Excl HDL & SBP) + AHS | 10%               | 0.012(-0.001 - 0.024)  | 0.034(0.017 - 0.05)     | *0.022(0.006 - 0.036)  | **0.053(0.039 - 0.067)         |
|                                  |                                        | 7.5%              | 0.03(0.01 - 0.049)     | 0.082(0.061 - 0.104)    | **0.052(0.034 - 0.07)  | **0.07(0.052 - 0.087)          |
|                                  |                                        | 5%                | 0.142(0.114 - 0.172)"  | 0.173(0.146 - 0.201)    | *0.031(0.009 - 0.051)  | *0.028(0.007 - 0.048)          |
|                                  |                                        | <b>Continuous</b> |                        |                         |                        | <b>**0.304 (0.256 – 0.348)</b> |
| SCORE2-Inspired                  | SCORE2-Inspired + AHS                  | 10%               | 0.01(-0.005 - 0.024)   | 0.029(0.011 - 0.046)    | *0.018 (0.004 - 0.033) | **0.042(0.027 - 0.056)         |
|                                  |                                        | 7.5%              | 0.061(0.037 - 0.082)"  | 0.099(0.075 - 0.121)"   | **0.038(0.02 - 0.056)  | **0.047(0.029 - 0.064)         |
|                                  |                                        | 5%                | 0.177(0.148 - 0.206)   | 0.188(0.159 - 0.216)    | 0.011(-0.008 - 0.028)  | 0.002(-0.015 - 0.019)"         |
|                                  |                                        | <b>Continuous</b> |                        |                         |                        | <b>**0.231 (0.181 – 0.278)</b> |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure.

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%).

Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.;

Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). SCORE2-Inspired (Excl HDL & SBP) AHS fractional polynomial (female)=  $(AHS/0.1)^2$ ; SCORE2-Inspired AHS fractional polynomial (female)=  $(AHS/0.1)^{0.5} + (AHS/0.1)$

p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* <0.05; \*\**p value* < 0.001



**Supplementary Table 65 Reclassification Performance for SCORE2-Inspired versus SCORE2-Inspired + Activity health Scores (AHS) risk scores using primary care high-density lipoprotein cholesterol (HDL) and Systolic blood pressure (SBP) measurements in Male and Female Participants at 5%, 7.5%, and 10% Thresholds**

| Model           | Comparator            | Threshold  | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit           | NRI                       |
|-----------------|-----------------------|------------|------------------------|-------------------------|------------------------|---------------------------|
| Male            |                       |            |                        |                         |                        |                           |
| SCORE2-Inspired | SCORE2-Inspired + AHS | 10%        | 0.107(0.082 - 0.131)   | 0.13(0.108 - 0.154)     | **0.023(0.011 - 0.034) | *0.015(0.004 - 0.026)     |
|                 |                       | 7.5%       | 0.212(0.188 - 0.239)   | 0.204(0.18 - 0.23)      | -0.008(-0.018 - 0.001) | -0.009(-0.02 - -0.001)    |
|                 |                       | 5%         | 0.399(0.377 - 0.422)   | 0.403(0.381 - 0.426)    | 0.004(-0.003 - 0.01)   | *0.006(-0.001 - 0.012)    |
|                 |                       | Continuous |                        |                         |                        | **0.099(CI 0.065 - 0.137) |
| Female          |                       |            |                        |                         |                        |                           |
| SCORE2-Inspired | SCORE2-Inspired + AHS | 10%        | 0.012(-0.001 - 0.025)  | 0.035(0.018 - 0.051)    | **0.023(0.009 - 0.035) | **0.051(0.038 - 0.063)    |
|                 |                       | 7.5%       | 0.042(0.022 - 0.061)   | 0.088(0.067 - 0.11)     | **0.046(0.029 - 0.062) | **0.064(0.047 - 0.079)    |
|                 |                       | 5%         | 0.175(0.147 - 0.202)   | 0.19(0.163 - 0.218)     | 0.016(-0.003 - 0.031)  | 0.013(-0.005 - 0.028)     |
|                 |                       | Continuous |                        |                         |                        | **0.265(0.217 - 0.31)     |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure.

Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0; p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* <0.05; \*\**p value* < 0.001

SCORE2-Inspired = Age + Systolic blood pressure + Total Cholesterol + HDL Cholesterol ratio + Diabetes + Smoking status + Age x Smoking status + Age x Diabetes + Age x Systolic blood pressure + Age x Cholesterol + Age x HDL Cholesterol ratio

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). SCORE2-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^3 + (AHS/0.1)^3 \times \log(AHS/0.1)$  ;SCORE2-Inspired AHS fractional polynomial (female)=  $(AHS/0.1)^2$



**Supplementary Table 66 Reclassification Performance of QRISK3-Inspired versus QRISK3-Inspired + Activity Health Scores (AHS) risk scores, stratified by age, in Male Participants at 5%, 7.5%, and 10% risk thresholds**

| Model                               | Comparator           | Threshold  | Net benefit (baseline) | Net Benefit (After AHS) | ΔNet Benefit           | NRI                               |
|-------------------------------------|----------------------|------------|------------------------|-------------------------|------------------------|-----------------------------------|
| Under 55: N =7,900, #MACCE = 212    |                      |            |                        |                         |                        |                                   |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0(-0.03 - 0.025)       | -0.01(-0.043 - 0.017)   | -0.011(-0.034 - 0.009) | -0.005(-0.027 - 0.014)            |
|                                     |                      | 7.5%       | 0.008(-0.031 - 0.04)   | 0.006(-0.034 - 0.041)   | -0.002(-0.033 - 0.023) | 0.004(-0.025 - 0.028)             |
|                                     |                      | 5%         | 0.043(-0.011 - 0.093)  | 0.029(-0.027 - 0.084)   | -0.013(-0.052 - 0.02)  | -0.008(-0.045 - 0.025)            |
|                                     |                      | Continuous |                        |                         |                        | <b>**0.173(0.039 - 0.299)</b>     |
| 55 to 65: N =12,356, #MACCE = 664   |                      |            |                        |                         |                        |                                   |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0.033(0.005 - 0.058)   | 0.033(0.004 - 0.058)    | 0(-0.018 - 0.013)      | 0.006(-0.01 - 0.019)              |
|                                     |                      | 7.5%       | 0.06(0.022 - 0.096)    | 0.075(0.037 - 0.112)    | 0.016(-0.004 - 0.033)  | *0.019(0 - 0.036)                 |
|                                     |                      | 5%         | 0.238(0.192 - 0.287)   | 0.23(0.183 - 0.279)     | -0.008 (-0.027 - 0.01) | -0.009(-0.029 - 0.009)            |
|                                     |                      | Continuous |                        |                         |                        | <b>** -0.144(-0.214 - -0.067)</b> |
| 65 to 75: N =15,858, #MACCE = 1,536 |                      |            |                        |                         |                        |                                   |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0.162(0.131 - 0.193)   | 0.166(0.135 - 0.195)    | 0.005(-0.013 - 0.021)  | 0.004(-0.014 - 0.02)              |
|                                     |                      | 7.5%       | 0.28(0.248 - 0.314)    | 0.276(0.245 - 0.309)    | -0.005(-0.019 - 0.007) | 0.007(-0.007 - 0.019)             |
|                                     |                      | 5%         | 0.506(0.482 - 0.532)   | 0.507(0.482 - 0.533)    | 0.001(-0.003 - 0.005)  | 0.004(-0.001 - 0.008)             |
|                                     |                      | Continuous |                        |                         |                        | <b>**0.132(0.082 - 0.181)</b>     |
| Over 75: N =951, #MACCE = 154       |                      |            |                        |                         |                        |                                   |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0.421(0.332 - 0.526)   | 0.421(0.33 - 0.524)     | 0(-0.038 - 0.04)       | 0.008(-0.032 - 0.053)             |
|                                     |                      | 7.5%       | 0.586(0.523 - 0.668)   | 0.581(0.515 - 0.661)    | -0.005(-0.022 - 0.014) | -0.002(-0.022 - 0.019)            |
|                                     |                      | 5%         | 0.732(0.69 - 0.786)    | 0.732(0.691 - 0.786)    | 0(0 - 0)               | 0(0 - 0.001)                      |
|                                     |                      | Continuous |                        |                         |                        | *0.193(0.015 - 0.349)             |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure; ; Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \**p value* <0.05; \*\**p value* < 0.001; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP 2 X

BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ;

**Supplementary Table 67 Reclassification Performance of QRISK3-Inspired versus QRISK3-Inspired + Activity Health Scores (AHS) risk scores, stratified by age, in Female Participants at 5%, 7.5%, and 10% risk thresholds**

| Model                               | Comparator           | Threshold  | Net benefit (baseline)  | Net Benefit (After AHS)  | ΔNet Benefit             | NRI                           |
|-------------------------------------|----------------------|------------|-------------------------|--------------------------|--------------------------|-------------------------------|
| Under 55: N =11,803, #MACCE = 106   |                      |            |                         |                          |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | -0.029( -0.073 - 0.001) | -0.033( -0.078 - -0.001) | -0.004(-0.024 - 0.013)   | -0.001( -0.02 - 0.013)        |
|                                     |                      | 7.5%       | -0.023( -0.076 - 0.015) | -0.013( -0.069 - 0.026)  | 0.01( -0.013 - 0.031)    | 0.009( -0.011 - 0.03)         |
|                                     |                      | 5%         | 0.037( -0.031 - 0.093)  | 0.006( -0.059 - 0.06)    | *-0.031(-0.059 - -0.004) | *-0.03( -0.058 - -0.001)      |
|                                     |                      | Continuous |                         |                          |                          | <b>0.003(-0.191 - 0.187)</b>  |
| 55 to 65: N =19,219, #MACCE = 436   |                      |            |                         |                          |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | -0.004( -0.028 - 0.017) | 0.006( -0.02 - 0.028)    | 0.01(-0.007 - 0.026)     | 0.013( -0.003 - 0.029)        |
|                                     |                      | 7.5%       | 0.029( -0.001 - 0.054)  | 0.04(0.009 - 0.071)      | 0.012( -0.01 - 0.033)    | 0.018( -0.004 - 0.039)        |
|                                     |                      | 5%         | 0.079(0.039 - 0.117)    | 0.079(0.039 - 0.119)     | 0.001(-0.024 - 0.022)    | 0.002( -0.022 - 0.024)        |
|                                     |                      | Continuous |                         |                          |                          | <b>**0.163(0.068 - 0.257)</b> |
| 65 to 75: N =19,375, #MACCE = 1,036 |                      |            |                         |                          |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0.05(0.025 - 0.075)     | 0.084(0.057 - 0.112)     | **0.034(0.013 - 0.053)   | **0.046(0.026 - 0.065)        |
|                                     |                      | 7.5%       | 0.117(0.086 - 0.149)    | 0.145(0.115 - 0.177)     | *0.028(0.004 - 0.05)     | *0.032(0.009 - 0.053)         |
|                                     |                      | 5%         | 0.268(0.232 - 0.305)    | 0.293(0.258 - 0.33)      | *0.025(0.002 - 0.048)    | *0.026(0.003 - 0.049)         |
|                                     |                      | Continuous |                         |                          |                          | <b>**0.244(0.184 - 0.307)</b> |
| Over 75: N =954, #MACCE = 76        |                      |            |                         |                          |                          |                               |
| QRISK3-Inspired                     | QRISK3-Inspired+ AHS | 10%        | 0.075( -0.059 - 0.222)  | 0.03( -0.116 - 0.184)    | -0.045(-0.147 - 0.053)   | -0.044( -0.145 - 0.052)       |
|                                     |                      | 7.5%       | 0.191(0.035 - 0.374)    | 0.191(0.055 - 0.366)     | 0(-0.093 - 0.086)        | 0.005( -0.082 - 0.091)        |
|                                     |                      | 5%         | 0.418(0.292 - 0.584)    | 0.422(0.298 - 0.58)      | 0.004(-0.046 - 0.06)     | 0.026( -0.022 - 0.083)        |
|                                     |                      | Continuous |                         |                          |                          | <b>*0.271(0.054 - 0.495)</b>  |

Abbreviations: NRI = Net reclassification index CI = Confidence interval AHS = Activity Health Score, HDL = high-density lipoprotein cholesterol, SBP = Systolic blood pressure; Data are reported on 88,422 participants, 4,227 MACCE events (4.8%) occurred over 6 years, including 2,571 events in 37,068 males (6.9%) and 1,656 events in 51,354 females (3.2%). Reported Net benefit NRI and corresponding 95% confidence intervals were derived adjusted for optimism following 1000 bootstrap iterations.; p-values are calculated via Z-statistic based on the mean difference and standard error derived from 1000 bootstrap iterations; \*p value <0.05; \*\* p value < 0.00; Each risk score was derived from sperate Cox proportional hazard models, with independent estimates of the baseline survival using Breslow's method<sup>261</sup>, based on mean-centred continuous variables, with all binary risk factors set to 0

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter Fractional polynomials:  $Age\ FP\ 1\ (males) = (age/10)^{-1}$ ,  $Age\ FP\ 2\ (males) = (age/10)^3$ ,  $BMI\ FP\ 1\ (males) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (males) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,  $Age\ FP\ 1\ (Females) = age/10^{-2}$ ,  $Age\ FP\ 2\ (Females) = age/10$ ,  $BMI\ FP\ 1\ (Females) = (BMI/10)^{-2}$ ,  $BMI\ FP\ 2\ (Females) = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2). QRISK3-Inspired AHS fractional polynomial (female)=  $AHS/0.1 + \{(AHS/0.1) \times \log(AHS/0.1)\}$

**Supplementary Table 68: 10×5 nested cross-validation: per-fold and mean performance of QRISK3-Inspired risk scores, derived within each outer-fold derivation set and validated in the corresponding held-out outer-fold test set, across 88,422 UK Biobank participants ; including 37,068 men and 51,354 women; after 6 years, 2,571 men (6.9%) and 1,656 women (3.2%) developed incident MACCE**

| Fold          | C-Index | ICI   | Net benefit 10% | Net benefit 7.5% | Net benefit 5% |
|---------------|---------|-------|-----------------|------------------|----------------|
| <b>Male</b>   |         |       |                 |                  |                |
| 1             | 0.686   | 0.006 | 0.156           | 0.255            | 0.438          |
| 2             | 0.668   | 0.008 | 0.095           | 0.207            | 0.408          |
| 3             | 0.704   | 0.011 | 0.158           | 0.286            | 0.464          |
| 4             | 0.703   | 0.008 | 0.166           | 0.298            | 0.466          |
| 5             | 0.690   | 0.004 | 0.164           | 0.224            | 0.406          |
| 6             | 0.673   | 0.010 | 0.162           | 0.215            | 0.423          |
| 7             | 0.659   | 0.010 | 0.068           | 0.161            | 0.402          |
| 8             | 0.692   | 0.009 | 0.183           | 0.268            | 0.413          |
| 9             | 0.663   | 0.008 | 0.099           | 0.147            | 0.348          |
| 10            | 0.654   | 0.011 | 0.051           | 0.148            | 0.352          |
| Mean          | 0.679   | 0.009 | 0.13            | 0.221            | 0.412          |
| <b>Female</b> |         |       |                 |                  |                |
| 1             | 0.731   | 0.006 | -0.012          | 0.059            | 0.248          |
| 2             | 0.758   | 0.004 | 0.054           | 0.116            | 0.245          |
| 3             | 0.731   | 0.005 | 0.056           | 0.077            | 0.143          |
| 4             | 0.742   | 0.005 | 0.007           | 0.048            | 0.200          |
| 5             | 0.763   | 0.005 | 0.034           | 0.067            | 0.185          |
| 6             | 0.741   | 0.004 | -0.025          | 0.084            | 0.173          |
| 7             | 0.726   | 0.003 | 0.012           | 0.083            | 0.159          |
| 8             | 0.732   | 0.004 | 0.029           | 0.060            | 0.210          |
| 9             | 0.742   | 0.005 | 0.101           | 0.127            | 0.267          |
| 10            | 0.698   | 0.007 | 0.064           | 0.116            | 0.226          |
| Mean          | 0.736   | 0.005 | 0.032           | 0.084            | 0.206          |

Abbreviations: ICI = Integrated Calibration index; MACCE = Major adverse Cardiovascular and cerebrovascular event

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure.+ Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment +Atrial fibrillation and flutter +SBP5 + Ethnicity previous smoker + current +Age FP 1 X hypertension +Age FP 1 X Diabetes +Age FP 1 X BMI FP 1 +Age FP 1 X BMI FP 2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter +Age FP 1 \* Corticosteroid treatment +Age FP 2 X Hypertension . +Age FP 2 X Diabetes +Age FP 2 X Diabetes +Age FP 2 X BMI FP1 +Age FP2 X BMI FP2 +Age FP2 X Townsend deprivation index +AgeFP2 X Systolic blood pressure +Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter.

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

**Supplementary Table 69: 10×5 nested cross-validation: per-fold and mean performance of QRISK3-Inspired risk scores + Activity Health Scores, derived within each outer-fold derivation set and validated in the corresponding held-out outer-fold test set, across 88,422 UK Biobank participants ; including 37,068 men and 51,354 women; 6 after 6 years, 2,571 men (6.9%) and 1,656 women (3.2%) developed incident MACCE**

| Fold          | C-Index | ICI   | Net benefit 10% | Net benefit 7.5% | Net benefit 5% |
|---------------|---------|-------|-----------------|------------------|----------------|
| <b>Male</b>   |         |       |                 |                  |                |
| 1             | 0.687   | 0.006 | 0.177           | 0.236            | 0.444          |
| 2             | 0.672   | 0.007 | 0.084           | 0.206            | 0.406          |
| 3             | 0.706   | 0.015 | 0.146           | 0.271            | 0.466          |
| 4             | 0.709   | 0.010 | 0.142           | 0.308            | 0.456          |
| 5             | 0.692   | 0.005 | 0.164           | 0.223            | 0.397          |
| 6             | 0.688   | 0.007 | 0.147           | 0.195            | 0.413          |
| 7             | 0.659   | 0.010 | 0.062           | 0.158            | 0.413          |
| 8             | 0.694   | 0.011 | 0.144           | 0.283            | 0.412          |
| 9             | 0.677   | 0.006 | 0.110           | 0.177            | 0.350          |
| 10            | 0.657   | 0.010 | 0.065           | 0.134            | 0.345          |
| Mean          | 0.681   | 0.009 | 0.124           | 0.219            | 0.410          |
| <b>Female</b> |         |       |                 |                  |                |
| 1             | 0.735   | 0.007 | 0.001           | 0.076            | 0.273          |
| 2             | 0.765   | 0.005 | 0.064           | 0.155            | 0.247          |
| 3             | 0.742   | 0.003 | 0.044           | 0.126            | 0.157          |
| 4             | 0.753   | 0.006 | 0.020           | 0.070            | 0.212          |
| 5             | 0.769   | 0.006 | 0.008 -         | 0.082            | 0.196          |
| 6             | 0.749   | 0.005 | 0.008           | 0.081            | 0.188          |
| 7             | 0.729   | 0.004 | 0.045           | 0.095            | 0.169          |
| 8             | 0.737   | 0.005 | 0.030           | 0.054            | 0.235          |
| 9             | 0.748   | 0.007 | 0.127           | 0.138            | 0.281          |
| 10            | 0.702   | 0.007 | 0.083           | 0.124            | 0.212          |
| Mean          | 0.743   | 0.005 | 0.041           | 0.10             | 0.217          |

Abbreviations: ICI = Integrated Calibration index; MACCE = Major adverse Cardiovascular and cerebrovascular event

QRISK3-Inspired: Age FP1 + Age FP2 + BMI FP1 + BMI FP2 + Diabetes + Hypertension + Systolic blood pressure + Townsend deprivation index + HDL cholesterol ratio + Corticosteroid treatment + Atrial fibrillation and flutter + SBP5 + Ethnicity previous smoker + current + Age FP 1 X hypertension + Age FP 1 X Diabetes + Age FP 1 X BMI FP1 + Age FP 1 X BMI FP2 + Age FP1 X Townsend deprivation index + Age FP 1 X Systolic blood pressure + Age FP 1 \* Atrial fibrillation and flutter + Age FP 1 \* Corticosteroid treatment + Age FP 2 X Hypertension + Age FP 2 X Diabetes + Age FP 2 X Diabetes + Age FP 2 X BMI FP1 + Age FP 2 X BMI FP2 + Age FP 2 X Townsend deprivation index + Age FP 2 X Systolic blood pressure + Age FP 2 \* Corticosteroid treatment + Age FP 2 \* Atrial fibrillation and flutter.

Fractional polynomials: Age FP 1 (males) =  $(age/10)^{-1}$ , Age FP 2 (males) =  $(age/10)^3$ , BMI FP 1 (males) =  $(BMI/10)^{-2}$ , BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ , Age FP 1 (Females) =  $age/10^{-2}$ , Age FP 2 (Females) =  $age/10$ , BMI FP 1 (Females) =  $(BMI/10)^{-2}$ , BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ;

Activity Health Scores (AHS) were derived using deep survival models trained on 26 rotation-invariant time- and frequency-domain features extracted from 7 days of continuous wrist-worn accelerometry (Supplementary methods section 1.2) QRISK3-Inspired AHS fractional polynomial (male) =  $(AHS/0.1)^2 + (AHS/0.1)^3$ ; QRISK3-Inspired AHS fractional polynomial (female) =  $AHS/0.1 + (AHS/0.1) \times \log(AHS/0.1)$

## Section C: Model coefficients, formulas and usage

### Chapter 4 Conventional ECG risk scores

**Table 1C QRISK3**

| Risk Factor                                                        | Beta Estimate (SD)       | Standard Error (SD)       | Fisher's p-value |
|--------------------------------------------------------------------|--------------------------|---------------------------|------------------|
| <b>QRISK3 Male Baseline survival = 0.9194677672636795 (0.0008)</b> |                          |                           |                  |
| Corticosteroid                                                     | -3.058324<br>(4.821383)  | 93.970671<br>(185.938480) | 0.868            |
| Ethnic Background                                                  | 0.231215 (0.026039)      | 0.094921<br>(0.000765)    | 0.000            |
| Migraine                                                           | -2.969078<br>(4.840460)  | 88.402198<br>(174.802476) | 0.927            |
| Smoker current                                                     | 0.409467 (0.030721)      | 0.074885<br>(0.000529)    | 0.000            |
| Smoker former                                                      | 0.032706 (0.033036)      | 0.050601<br>(0.000222)    | 0.552            |
| Townsend deprivation index                                         | 0.003743 (0.003855)      | 0.009491<br>(0.000066)    | 0.933            |
| Age FP 1                                                           | -8.239010<br>(1.216513)  | 4.335058<br>(0.026215)    | 0.001            |
| Age FP 2                                                           | 0.005252 (0.000353)      | 0.001333<br>(0.000004)    | 0.000            |
| BMI FP1                                                            | 5.737902 (1.501906)      | 4.179753<br>(0.194800)    | 0.048            |
| BMI FP2                                                            | -20.451175<br>(2.824710) | 7.976247<br>(0.271968)    | 0.000            |
| bp                                                                 | 0.008276 (0.001047)      | 0.001891<br>(0.000021)    | 0.000            |
| Diabetes type 1                                                    | -0.155624<br>(0.290918)  | 0.489431<br>(0.086359)    | 0.934            |
| Diabetes type 2                                                    | 0.829499 (0.111686)      | 0.180215<br>(0.006348)    | 0.000            |
| HDL ratio                                                          | 0.126299 (0.004742)      | 0.021151<br>(0.000133)    | 0.000            |
| Hypertension                                                       | 0.470482 (0.060258)      | 0.117152<br>(0.005449)    | 0.000            |
| Rheumatoid Arthritis                                               | 0.487297 (0.194260)      | 0.427857<br>(0.028182)    | 0.120            |
| SBP5                                                               | -0.000004<br>(0.000131)  | 0.000271<br>(0.000006)    | 0.957            |
| Severe mental illness                                              | -0.335986<br>(0.501976)  | 0.616577<br>(0.194329)    | 0.913            |
| Age FP1 X Townsend deprivation index                               | 0.739400 (0.788227)      | 1.333724                  | 0.672            |

|                                                                     |                             |                            |       |
|---------------------------------------------------------------------|-----------------------------|----------------------------|-------|
|                                                                     |                             | (0.023397)                 |       |
| Age FP2 X Townsend deprivation index                                | 0.000366 (0.000247)         | 0.000415<br>(0.000007)     | 0.334 |
| Age FP 1 X BMI FP 1                                                 | 378.082310<br>(163.583901)  | 588.273681<br>(33.062337)  | 0.739 |
| Age FP 1 X BMI FP 2                                                 | -445.675590<br>(341.704069) | 1146.118123<br>(47.757791) | 0.950 |
| Age FP 1 X SBP                                                      | 0.346595 (0.009164)         | 0.264453<br>(0.002704)     | 0.084 |
| Age FP 1 X Diabetes type 1                                          | 30.476196<br>(26.056294)    | 59.072283<br>(14.485844)   | 0.705 |
| Age FP 1 X Diabetes type 2                                          | 25.773126<br>(8.472790)     | 23.913016<br>(1.128218)    | 0.203 |
| Age FP 1 X hypertension                                             | 14.765519<br>(9.519468)     | 15.957665<br>(0.960540)    | 0.248 |
| Age FP 2 X BMI FP 1                                                 | 0.096373 (0.071765)         | 0.188144<br>(0.009526)     | 0.859 |
| Age FP 2 X BMI FP 2                                                 | -0.088298<br>(0.129062)     | 0.366196<br>(0.013420)     | 0.978 |
| Age FP 2 X SBP                                                      | 0.000063 (0.000013)         | 0.000078<br>(0.000001)     | 0.548 |
| Age FP 2 X Diabetes type 1                                          | 0.011983 (0.008168)         | 0.019220<br>(0.002877)     | 0.676 |
| Age FP 2 X Diabetes type 2                                          | 0.003589 (0.002686)         | 0.007168<br>(0.000226)     | 0.867 |
| Age FP 2 X hypertension                                             | 0.003347 (0.002564)         | 0.004511<br>(0.000196)     | 0.486 |
| <b>QRISK3 Female baseline survival = 0.9674000393032509 (0.003)</b> |                             |                            |       |
| Corticosteroid                                                      | -1.859872<br>(5.116782)     | 121.300363<br>(240.596065) | 0.824 |
| Ethnic Background                                                   | -0.089060<br>(0.115363)     | 0.167134<br>(0.005411)     | 0.625 |
| Migraine                                                            | -3.411411<br>(4.984203)     | 107.695642<br>(213.386305) | 0.605 |
| Smoker current                                                      | 0.550494 (0.052170)         | 0.122283<br>(0.001990)     | 0.000 |
| Smoker former                                                       | 0.093190 (0.025772)         | 0.072182<br>(0.001013)     | 0.077 |
| Townsend deprivation index                                          | 0.001645 (0.011488)         | 0.014240<br>(0.000256)     | 0.636 |
| Age FP 1                                                            | 16.735322<br>(12.314826)    | 25.469804<br>(0.914644)    | 0.584 |
| Age FP 2                                                            | 1.051904 (0.107542)         | 0.276632<br>(0.006315)     | 0.000 |



|                                      |                                 |                                   |       |
|--------------------------------------|---------------------------------|-----------------------------------|-------|
| BMI FP1                              | -6.897666<br>(0.837690)         | 4.921792<br>(0.277077)            | 0.050 |
| BMI FP2                              | 1.489601 (1.523853)             | 9.248453<br>(0.371809)            | 0.998 |
| Bp                                   | 0.004204 (0.001637)             | 0.002628<br>(0.000061)            | 0.007 |
| Diabetes type 1                      | -24.687989<br>(50.004439)       | 1189.912221<br>(2377.291972)      | 0.553 |
| Diabetes type 2                      | -0.960672<br>(0.749314)         | 1.223582<br>(0.535338)            | 0.701 |
| HDL ratio                            | 0.126130 (0.006158)             | 0.029783<br>(0.000297)            | 0.000 |
| Hypertension                         | 0.580602 (0.112253)             | 0.202014<br>(0.022301)            | 0.000 |
| Rheumatoid Arthritis                 | -0.086852<br>(0.269346)         | 0.574247<br>(0.075469)            | 0.939 |
| SBP5                                 | -0.000379<br>(0.000139)         | 0.000363<br>(0.000009)            | 0.246 |
| Severe mental illness                | 0.851659 (0.185567)             | 0.578152<br>(0.075784)            | 0.017 |
| Age FP1 X Townsend deprivation index | -1.638954<br>(3.466888)         | 7.031087<br>(0.181435)            | 0.928 |
| Age FP2 X Townsend deprivation index | -0.033317<br>(0.038805)         | 0.080747<br>(0.001885)            | 0.862 |
| Age FP 1 X BMI FP 1                  | -3783.364927<br>(756.469300)    | 2586.829714<br>(147.201885)       | 0.033 |
| Age FP 1 X BMI FP 2                  | 6329.416234<br>(1418.786650)    | 4886.174778<br>(221.731868)       | 0.085 |
| Age FP 1 X SBP                       | 0.775537 (0.551594)             | 1.250151<br>(0.025152)            | 0.720 |
| Age FP 1 X Diabetes type 1           | -11416.091500<br>(22425.393370) | 531331.050924<br>(1061545.206705) | 0.981 |
| Age FP 1 X Diabetes type 2           | -786.445935<br>(291.852989)     | 588.448527<br>(203.441580)        | 0.075 |
| Age FP 1 X hypertension              | -46.702277<br>(55.296550)       | 100.715091<br>(10.086351)         | 0.819 |
| Age FP 2 X BMI FP 1                  | -35.685588<br>(9.610732)        | 28.285309<br>(1.360998)           | 0.096 |
| Age FP 2 X BMI FP 2                  | 64.022863<br>(19.900540)        | 54.558957<br>(2.090358)           | 0.145 |
| Age FP 2 X SBP                       | 0.009105 (0.006177)             | 0.013623<br>(0.000206)            | 0.658 |
| Age FP 2 X Diabetes type 1           | -150.563739<br>(296.919332)     | 6968.439068<br>(13926.117170)     | 0.969 |

|                            |                         |                        |       |
|----------------------------|-------------------------|------------------------|-------|
| Age FP 2 X Diabetes type 2 | -7.883906<br>(2.401493) | 5.406887<br>(1.598062) | 0.036 |
| Age FP 2 X hypertension    | -0.570664<br>(0.519654) | 1.018803<br>(0.075489) | 0.732 |

Abbreviations: FP= Fractional polynomial, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = Systolic blood pressure

Results are presented as mean value (Standard deviation)

Beta estimates and standard errors are derived from the mean value across 5-cross validation folds.

p values are derived across 5-cross validation folds using fisher's approach.

Age FP 1 (males) =  $(age/10)^{-1}$

Age FP 2 (males) =  $(age/10)^3$

BMI FP 1 (males) =  $(BMI/10)^{-2}$

BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Age FP 1 (Females) =  $age/10^{-2}$

Age FP 2 (Females) =  $age/10$

BMI FP 1 (Females) =  $(BMI/10)^{-2}$

BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

**Table 2C QRISK3 + Conventional ECG parameters**

| <b>Risk Factor</b>                                                      | <b>Beta Estimate (SD)</b>   | <b>Standard Error (SD)</b> | <b>Fisher's p-value</b> |
|-------------------------------------------------------------------------|-----------------------------|----------------------------|-------------------------|
| <b>QRISK3 + ECG Male Baseline survival = 0.921173895014286 (0.0006)</b> |                             |                            |                         |
| Corticosteroid                                                          | -3.053305<br>(4.928603)     | 103.763729<br>(205.523500) | 0.907                   |
| Ethnic Background                                                       | 0.250329 (0.032275)         | 0.096403 (0.000771)        | 0.000                   |
| Migraine                                                                | -2.977797<br>(4.910584)     | 94.050879 (186.098164)     | 0.939                   |
| Smoker current                                                          | 0.393048 (0.030481)         | 0.075608 (0.000497)        | 0.000                   |
| Smoker former                                                           | 0.031042 (0.033947)         | 0.050802 (0.000236)        | 0.559                   |
| Townsend deprivation index                                              | 0.004286 (0.003832)         | 0.009566 (0.000061)        | 0.901                   |
| Age FP 1                                                                | -8.417533<br>(0.762423)     | 4.793997 (0.034306)        | 0.005                   |
| Age FP 2                                                                | 0.004361 (0.000229)         | 0.001452 (0.000008)        | 0.000                   |
| BMI FP1                                                                 | 5.271504 (1.474828)         | 4.231986 (0.193271)        | 0.096                   |
| BMI FP2                                                                 | -18.155179<br>(2.846709)    | 8.084144 (0.276214)        | 0.000                   |
| SBP                                                                     | 0.007690 (0.000911)         | 0.001911 (0.000022)        | 0.000                   |
| Diabetes type 1                                                         | -0.178577<br>(0.275120)     | 0.489687 (0.085230)        | 0.935                   |
| Diabetes type 2                                                         | 0.842291 (0.101461)         | 0.183713 (0.005994)        | 0.000                   |
| HDL ratio                                                               | 0.134318 (0.004345)         | 0.021270 (0.000140)        | 0.000                   |
| Hypertension                                                            | 0.445556 (0.057521)         | 0.118724 (0.005726)        | 0.000                   |
| Rheumatoid Arthritis                                                    | 0.438986 (0.181216)         | 0.429511 (0.027734)        | 0.215                   |
| SBP5                                                                    | -0.000083<br>(0.000158)     | 0.000271 (0.000005)        | 0.798                   |
| Severe mental illness                                                   | -0.387358<br>(0.510011)     | 0.618803 (0.193933)        | 0.859                   |
| Age FP1 X Townsend deprivation index                                    | 0.845549 (0.748499)         | 1.353870 (0.022023)        | 0.668                   |
| Age FP2 X Townsend deprivation index                                    | 0.000416 (0.000239)         | 0.000421 (0.000006)        | 0.233                   |
| Age FP 1 X BMI FP 1                                                     | 369.867793<br>(180.171687)  | 597.982099 (32.585041)     | 0.768                   |
| Age FP 1 X BMI FP 2                                                     | -419.371622<br>(327.293821) | 1166.765160<br>(49.373498) | 0.966                   |
| Age FP 1 X SBP                                                          | 0.348686 (0.033844)         | 0.269527 (0.003464)        | 0.090                   |
| Age FP 1 X Diabetes type 1                                              | 24.486686<br>(26.253692)    | 59.814473 (14.027401)      | 0.811                   |
| Age FP 1 X Diabetes type 2                                              | 27.424743<br>(7.995900)     | 24.413108 (1.004441)       | 0.175                   |
| Age FP 1 X hypertension                                                 | 11.603035<br>(9.715555)     | 16.296883 (1.000434)       | 0.483                   |
| Age FP2 X BMI FP1                                                       | 0.095773 (0.081485)         | 0.190143 (0.009574)        | 0.859                   |
| Age FP2 X BMI FP2                                                       | -0.085509<br>(0.136296)     | 0.371030 (0.014183)        | 0.983                   |
| Age FP2 X SBP                                                           | 0.000069 (0.000019)         | 0.000079 (0.000001)        | 0.454                   |
| Age FP 2 X Diabetes type1                                               | 0.009794 (0.007708)         | 0.019483 (0.002827)        | 0.797                   |
| Age FP 2 X Diabetes type2                                               | 0.004038 (0.002644)         | 0.007263 (0.000207)        | 0.821                   |

|                                                 |                         |                      |       |
|-------------------------------------------------|-------------------------|----------------------|-------|
| Age FP 2 X Hypertension                         | 0.002422 (0.002649)     | 0.004583 (0.000195)  | 0.735 |
| Resting QRS interval                            | -0.001491<br>(0.002469) | 0.004261 (0.000231)  | 0.771 |
| Resting QTc interval                            | 0.000274 (0.000965)     | 0.001771 (0.000044)  | 0.892 |
| Resting Anisotropy evidence                     | -0.014432<br>(0.019842) | 0.052518 (0.002170)  | 0.937 |
| Resting Atrial Tachycardia evidence             | 0.008658 (0.005951)     | 0.017767 (0.000811)  | 0.894 |
| Resting PVC count                               | 0.017749 (0.013509)     | 0.065853 (0.012905)  | 0.973 |
| Resting regularity Evidence                     | 0.021694 (0.007705)     | 0.025395 (0.000503)  | 0.465 |
| Exercise PR interval                            | -0.001065<br>(0.000418) | 0.001418 (0.000012)  | 0.604 |
| Exercise QRS interval                           | -0.004797<br>(0.002576) | 0.007670 (0.000163)  | 0.752 |
| Exercise QTc interval                           | 0.000648 (0.000422)     | 0.001196 (0.000097)  | 0.796 |
| Exercise RR Interval                            | 0.002148 (0.000268)     | 0.000633 (0.000012)  | 0.000 |
| Exercise Atrial Tachycardia evidence            | 0.009421 (0.001185)     | 0.008089 (0.000417)  | 0.158 |
| Exercise PVC count                              | 0.007653 (0.023160)     | 0.060136 (0.004161)  | 0.979 |
| Exercise regularity evidence                    | 0.013677 (0.007157)     | 0.017741 (0.000129)  | 0.550 |
| Recovery Irregularity evidence                  | 0.013567 (0.005374)     | 0.024248 (0.000731)  | 0.833 |
| Recovery QRS interval                           | 0.005704 (0.003537)     | 0.007506 (0.000155)  | 0.538 |
| Recovery QTc interval                           | 0.002429 (0.000491)     | 0.002024 (0.000173)  | 0.132 |
| Recovery Atrial Tachycardia evidence            | 0.001788 (0.003885)     | 0.015750 (0.000312)  | 0.994 |
| Recovery regularity evidence                    | 0.018562 (0.004559)     | 0.022748 (0.000214)  | 0.536 |
| Age FP 1 X Resting QRS interval                 | -0.099509<br>(0.283266) | 0.645164 (0.021378)  | 0.937 |
| Age FP 1 X Resting QTc interval                 | 0.186839 (0.140490)     | 0.249661 (0.009373)  | 0.492 |
| Age FP 1 X Resting Anisotropy evidence          | -7.323903<br>(2.947289) | 6.967514 (0.350952)  | 0.237 |
| Age FP 1 X Resting Atrial tachycardia evidence  | 1.478490 (0.626584)     | 2.413532 (0.137146)  | 0.769 |
| Age FP 1 X Resting PVC count                    | 1.877899 (5.945336)     | 10.002778 (2.321090) | 0.789 |
| Age FP 1 X Resting regularity evidence          | 0.081740 (1.813632)     | 3.541294 (0.099657)  | 0.960 |
| Age FP 1 X Exercise PR interval                 | 0.175616 (0.042983)     | 0.199580 (0.000926)  | 0.450 |
| Age FP 1 X Exercise QRS interval                | 0.563302 (0.349615)     | 1.115918 (0.016077)  | 0.870 |
| Age FP 1 X Exercise QTc interval                | -0.164137<br>(0.067765) | 0.176132 (0.013207)  | 0.392 |
| Age FP 1 X Exercise RR interval                 | 0.004875 (0.049124)     | 0.084489 (0.001378)  | 0.870 |
| Age FP 1 X Exercise Atrial tachycardia evidence | 1.186696 (0.473332)     | 1.060608 (0.048358)  | 0.166 |
| Age FP 1 X Exercise PVC count                   | 0.619285 (3.045315)     | 7.871910 (0.260239)  | 0.980 |
| Age FP 1 X Exercise regularity evidence         | -2.131547<br>(0.641735) | 2.470027 (0.022713)  | 0.464 |
| Age FP 1 X Recovery Irregularity evidence       | -2.946675<br>(1.156957) | 3.452341 (0.054666)  | 0.461 |
| Age FP 1 X Recovery QRS interval                | -0.006782<br>(0.493191) | 1.089161 (0.013787)  | 0.948 |
| Age FP 1 X Recovery QTc interval                | -0.015081               | 0.269611 (0.034398)  | 1.000 |

|                                                                           |                      |                         |       |
|---------------------------------------------------------------------------|----------------------|-------------------------|-------|
|                                                                           | (0.035581)           |                         |       |
| Age FP 1 X Recovery Atrial tachycardia evidence                           | 1.276569 (0.764689)  | 2.185623 (0.021819)     | 0.787 |
| Age FP 1 X Recovery regularity evidence                                   | -2.922880 (0.683230) | 3.215600 (0.042486)     | 0.414 |
| Age FP 2 X Resting QRS interval                                           | -0.000021 (0.000084) | 0.000185 (0.000008)     | 0.944 |
| Age FP 2 X Resting QTc interval                                           | 0.000061 (0.000040)  | 0.000079 (0.000002)     | 0.498 |
| Age FP 2 X Resting Anisotropy evidence                                    | -0.002281 (0.000956) | 0.001948 (0.000093)     | 0.125 |
| Age FP 2 X Resting Atrial tachycardia evidence                            | 0.000569 (0.000310)  | 0.000711 (0.000044)     | 0.485 |
| Age FP 2 X Resting PVC count                                              | 0.000969 (0.001750)  | 0.002840 (0.000462)     | 0.731 |
| Age FP 2 X Resting regularity evidence                                    | -0.000113 (0.000538) | 0.001056 (0.000027)     | 0.931 |
| Age FP 2 X Exercise PR interval                                           | 0.000051 (0.000011)  | 0.000059 (0.000000)     | 0.478 |
| Age FP 2 X Exercise QRS interval                                          | 0.000110 (0.000102)  | 0.000323 (0.000003)     | 0.967 |
| Age FP 2 X Exercise QTc interval                                          | -0.000060 (0.000020) | 0.000056 (0.000003)     | 0.239 |
| Age FP 2 X Exercise RR interval                                           | 0.000012 (0.000014)  | 0.000024 (0.000000)     | 0.721 |
| Age FP 2 X Exercise Atrial tachycardia evidence                           | 0.000382 (0.000179)  | 0.000300 (0.000015)     | 0.078 |
| Age FP 2 X Exercise PVC count                                             | 0.000388 (0.000901)  | 0.001987 (0.000107)     | 0.941 |
| Age FP 2 X Exercise regularity evidence                                   | -0.000237 (0.000157) | 0.000762 (0.000010)     | 0.980 |
| Age FP 2 X Recovery Irregularity evidence                                 | -0.000857 (0.000370) | 0.000985 (0.000019)     | 0.431 |
| Age FP 2 X Recovery QRS interval                                          | 0.000109 (0.000172)  | 0.000315 (0.000003)     | 0.788 |
| Age FP 2 X Recovery QTc interval                                          | -0.000025 (0.000011) | 0.000090 (0.000006)     | 0.990 |
| Age FP 2 X Recovery Atrial tachycardia evidence                           | 0.000389 (0.000200)  | 0.000616 (0.000005)     | 0.744 |
| Age FP 12X Recovery regularity evidence                                   | -0.001205 (0.000263) | 0.000948 (0.000010)     | 0.093 |
| <b>QRISK3 + ECG Female baseline survival = 0.9693602558896434 (0.003)</b> |                      |                         |       |
| Corticosteroid                                                            | -1.976697 (5.132148) | 124.923166 (247.831108) | 0.907 |
| Ethnic Background                                                         | -0.081440 (0.124964) | 0.168970 (0.005530)     | 0.613 |
| Migraine                                                                  | -3.609918 (5.165232) | 132.426195 (262.841494) | 0.482 |
| Smoker current                                                            | 0.507017 (0.060319)  | 0.123494 (0.001923)     | 0.000 |
| Smoker former                                                             | 0.077114 (0.024866)  | 0.072560 (0.000997)     | 0.224 |
| Townsend deprivation index                                                | -0.000473 (0.011481) | 0.014366 (0.000259)     | 0.676 |
| Age FP 1                                                                  | 3.721850 (16.802543) | 27.610876 (1.292915)    | 0.858 |
| Age FP 2                                                                  | 0.857354 (0.158731)  | 0.299144 (0.009086)     | 0.000 |

|                                      |                                 |                                  |       |
|--------------------------------------|---------------------------------|----------------------------------|-------|
| BMI FP1                              | -7.514021<br>(1.135243)         | 4.942824 (0.250173)              | 0.023 |
| BMI FP2                              | 3.057241 (2.200450)             | 9.325692 (0.332151)              | 0.978 |
| SBP                                  | 0.003717 (0.001581)             | 0.002632 (0.000054)              | 0.028 |
| Diabetes type 1                      | -22.379224<br>(45.542274)       | 869.822657<br>(1737.289983)      | 0.515 |
| Diabetes type 2                      | -0.986806<br>(0.728800)         | 1.228215 (0.579733)              | 0.662 |
| HDL ratio                            | 0.126508 (0.005539)             | 0.029975 (0.000306)              | 0.000 |
| Hypertension                         | 0.126508 (0.005539)             | 0.029975 (0.000306)              | 0.000 |
| Rheumatoid Arthritis                 | 0.126508 (0.005539)             | 0.029975 (0.000306)              | 0.000 |
| SBP5                                 | -0.000341<br>(0.000142)         | 0.000363 (0.000011)              | 0.355 |
| Severe mental illness                | 0.740934 (0.222092)             | 0.583057 (0.076613)              | 0.054 |
| Age FP1 X Townsend deprivation index | -2.087138<br>(3.108249)         | 7.119993 (0.194404)              | 0.932 |
| Age FP2 X Townsend deprivation index | -0.034975<br>(0.035063)         | 0.081635 (0.001986)              | 0.892 |
| Age FP 1 X BMI FP 1                  | -3371.361814<br>(555.995914)    | 2553.405342<br>(118.897499)      | 0.077 |
| Age FP 1 X BMI FP 2                  | 5473.807363<br>(1037.883455)    | 4838.456657<br>(176.877494)      | 0.189 |
| Age FP 1 X SBP                       | 0.538023 (0.503669)             | 1.266520 (0.020029)              | 0.916 |
| Age FP 1 X Diabetes type 1           | -10352.721262<br>(20406.986824) | 388406.333520<br>(775759.628090) | 0.991 |
| Age FP 1 X Diabetes type 2           | -720.655938<br>(264.868341)     | 581.468761 (218.054415)          | 0.115 |
| Age FP 1 X hypertension              | -57.926764<br>(47.699574)       | 100.693454 (9.196135)            | 0.793 |
| Age FP2 X BMI FP1                    | -30.370274<br>(7.966515)        | 28.066404 (1.143397)             | 0.222 |
| Age FP2 X BMI FP2                    | 53.301410<br>(16.675324)        | 54.326897 (1.744596)             | 0.323 |
| Age FP2 X SBP                        | 0.006292 (0.005611)             | 0.013833 (0.000169)              | 0.879 |
| Age FP 2 X Diabetes type1            | -136.878917<br>(270.553390)     | 5093.740868<br>(10177.089348)    | 0.983 |
| Age FP 2 X Diabetes type2            | -7.099495<br>(2.127908)         | 5.317743 (1.683223)              | 0.068 |
| Age FP 2 X Hypertension              | -0.688814<br>(0.442698)         | 1.021964 (0.069304)              | 0.693 |
| Resting QRS interval                 | -0.001761<br>(0.003582)         | 0.006059 (0.000251)              | 0.801 |
| Resting QTc interval                 | -0.002664<br>(0.000842)         | 0.002806 (0.000044)              | 0.351 |
| Resting Anisotropy evidence          | -0.008412<br>(0.044730)         | 0.074704 (0.004472)              | 0.812 |
| Resting Atrial Tachycardia evidence  | -0.002372                       | 0.026471 (0.000984)              | 0.973 |

|                                                 |                            |                       |       |
|-------------------------------------------------|----------------------------|-----------------------|-------|
|                                                 | (0.009682)                 |                       |       |
| Resting PVC count                               | -0.114437<br>(0.290023)    | 0.185674 (0.139764)   | 0.815 |
| Resting regularity Evidence                     | 0.040423 (0.022615)        | 0.037707 (0.000746)   | 0.169 |
| Exercise PR interval                            | -0.000776<br>(0.001236)    | 0.002382 (0.000053)   | 0.884 |
| Exercise QRS interval                           | -0.012047<br>(0.004132)    | 0.010324 (0.000601)   | 0.147 |
| Exercise QTc interval                           | -0.003578<br>(0.001225)    | 0.002502 (0.000174)   | 0.039 |
| Exercise RR Interval                            | 0.002660 (0.000473)        | 0.001001 (0.000040)   | 0.000 |
| Exercise Atrial Tachycardia evidence            | -0.005038<br>(0.002353)    | 0.013421 (0.000504)   | 0.964 |
| Exercise PVC count                              | -0.069540<br>(0.055870)    | 0.087795 (0.018104)   | 0.554 |
| Exercise regularity evidence                    | -0.033686<br>(0.004360)    | 0.025142 (0.000513)   | 0.069 |
| Recovery Irregularity evidence                  | 0.005679 (0.021770)        | 0.036617 (0.001334)   | 0.850 |
| Recovery QRS interval                           | 0.019844 (0.004846)        | 0.010762 (0.000358)   | 0.002 |
| Recovery QTc interval                           | 0.006335 (0.001739)        | 0.003505 (0.000052)   | 0.002 |
| Recovery Atrial Tachycardia evidence            | 0.008599 (0.008700)        | 0.022401 (0.000637)   | 0.946 |
| Recovery regularity evidence                    | 0.030303 (0.023593)        | 0.033592 (0.000497)   | 0.231 |
| Age FP 1 X Resting QRS interval                 | 4.685456 (0.594696)        | 3.009125 (0.067449)   | 0.018 |
| Age FP 1 X Resting QTc interval                 | -0.176955<br>(0.349030)    | 1.407983 (0.035738)   | 0.993 |
| Age FP 1 X Resting Anisotropy evidence          | 8.352663<br>(18.032953)    | 30.291483 (2.122153)  | 0.813 |
| Age FP 1 X Resting Atrial tachycardia evidence  | 8.835450 (2.459381)        | 11.138656 (0.469317)  | 0.558 |
| Age FP 1 X Resting PVC count                    | -94.513262<br>(124.159024) | 84.552187 (62.640771) | 0.358 |
| Age FP 1 X Resting regularity evidence          | -20.554959<br>(4.125426)   | 17.691073 (0.536867)  | 0.163 |
| Age FP 1 X Exercise PR interval                 | 2.199981 (0.298083)        | 1.150989 (0.032806)   | 0.001 |
| Age FP 1 X Exercise QRS interval                | -6.852584<br>(1.632544)    | 5.038986 (0.231211)   | 0.052 |
| Age FP 1 X Exercise QTc interval                | 0.574648 (0.351687)        | 1.179718 (0.116625)   | 0.874 |
| Age FP 1 X Exercise RR interval                 | 0.416345 (0.162504)        | 0.482972 (0.016394)   | 0.453 |
| Age FP 1 X Exercise Atrial tachycardia evidence | 5.560724 (3.275170)        | 5.985036 (0.417762)   | 0.261 |
| Age FP 1 X Exercise PVC count                   | 3.089575<br>(31.518151)    | 39.706749 (13.408190) | 0.750 |
| Age FP 1 X Exercise regularity evidence         | 2.454565 (7.280798)        | 12.243339 (0.449209)  | 0.869 |
| Age FP 1 X Recovery Irregularity evidence       | 22.590040<br>(7.618744)    | 16.768233 (0.871248)  | 0.055 |
| Age FP 1 X Recovery QRS interval                | 2.098954 (1.396131)        | 5.444468 (0.145017)   | 0.954 |

|                                                 |                          |                      |       |
|-------------------------------------------------|--------------------------|----------------------|-------|
| Age FP 1 X Recovery QTc interval                | -0.539083<br>(0.308646)  | 1.735982 (0.047608)  | 0.983 |
| Age FP 1 X Recovery Atrial tachycardia evidence | -19.636307<br>(4.706738) | 10.856460 (0.370094) | 0.002 |
| Age FP 1 X Recovery regularity evidence         | 25.542789<br>(4.782398)  | 16.519767 (0.376644) | 0.018 |
| Age FP 2 X Resting QRS interval                 | 0.043897 (0.002105)      | 0.031205 (0.000893)  | 0.048 |
| Age FP 2 X Resting QTc interval                 | -0.003399<br>(0.003709)  | 0.015837 (0.000385)  | 0.990 |
| Age FP 2 X Resting Anisotropy evidence          | 0.092205 (0.211727)      | 0.356851 (0.016620)  | 0.838 |
| Age FP 2 X Resting Atrial tachycardia evidence  | 0.103347 (0.029834)      | 0.131377 (0.003768)  | 0.563 |
| Age FP 2 X Resting PVC count                    | -1.079614<br>(1.026884)  | 0.875222 (0.493449)  | 0.172 |
| Age FP 2 X Resting regularity evidence          | -0.262693<br>(0.048790)  | 0.199977 (0.005325)  | 0.078 |
| Age FP 2 X Exercise PR interval                 | 0.023647 (0.003339)      | 0.012813 (0.000302)  | 0.002 |
| Age FP 2 X Exercise QRS interval                | -0.062718<br>(0.016338)  | 0.056917 (0.002275)  | 0.192 |
| Age FP 2 X Exercise QTc interval                | 0.008246 (0.004597)      | 0.014017 (0.000899)  | 0.787 |
| Age FP 2 X Exercise RR interval                 | 0.004504 (0.001331)      | 0.005247 (0.000145)  | 0.472 |
| Age FP 2 X Exercise Atrial tachycardia evidence | 0.076592 (0.033659)      | 0.065696 (0.002800)  | 0.110 |
| Age FP 2 X Exercise PVC count                   | 0.023321 (0.312937)      | 0.445748 (0.106361)  | 0.782 |
| Age FP 2 X Exercise regularity evidence         | 0.036292 (0.080110)      | 0.140957 (0.002857)  | 0.880 |
| Age FP 2 X Recovery Irregularity evidence       | 0.295465 (0.087365)      | 0.191575 (0.009956)  | 0.017 |
| Age FP 2 X Recovery QRS interval                | 0.019746 (0.015226)      | 0.060462 (0.001508)  | 0.974 |
| Age FP 2 X Recovery QTc interval                | -0.005112<br>(0.005899)  | 0.018979 (0.000831)  | 0.975 |
| Age FP 2 X Recovery Atrial tachycardia evidence | -0.255495<br>(0.055515)  | 0.122944 (0.004240)  | 0.000 |
| Age FP 2X Recovery regularity evidence          | 0.309347 (0.058496)      | 0.185464 (0.004070)  | 0.008 |

Abbreviations: FP= Fractional polynomial, BMI = Body mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = Systolic blood pressure, PVC = Premature ventricular contraction

Results are presented as mean value (Standard deviation)

Beta estimates and standard errors are derived from the mean value across 5-cross validation folds.

p values are derived across 5-cross validation folds using fisher's approach.

$$\text{Age FP 1 (males)} = (\text{age}/10)^{-1}$$

$$\text{Age FP 2 (males)} = (\text{age}/10)^3$$

$$\text{BMI FP 1 (males)} = (\text{BMI}/10)^{-2}$$

$$\text{BMI FP 2 (males)} = (\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$$

$$\text{Age FP 1 (Females)} = \text{age}/10^{-2}$$

$$\text{Age FP 2 (Females)} = \text{age}/10$$

$$\text{BMI FP 1 (Females)} = (\text{BMI}/10)^{-2}$$

$$\text{BMI FP 2 (Females)} = (\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$$



## Chapter 5 Deep learning derived Q-ECG risk scores

**Table 3C QRISK3**

| Risk Factor                                                          | Beta (SD)               | SE (SD)                 | Fisher's p-value |
|----------------------------------------------------------------------|-------------------------|-------------------------|------------------|
| <b>QRISK3 Male Baseline survival = 0.9161849602568788 (0.0005)</b>   |                         |                         |                  |
| Corticosteroid                                                       | -0.350024 (0.265888)    | 0.825519 (0.143430)     | 0.958            |
| Ethnic Background                                                    | 0.322027 (0.032464)     | 0.082256 (0.000262)     | 0.000            |
| Migraine                                                             | 0.184532 (0.221974)     | 0.656670 (0.063183)     | 0.957            |
| Smoker current                                                       | 0.430147 (0.020874)     | 0.068663 (0.000522)     | 0.000            |
| Smoker former                                                        | 0.044320 (0.027935)     | 0.046955 (0.000217)     | 0.280            |
| Townsend deprivation index                                           | 0.002594 (0.004377)     | 0.008761 (0.000064)     | 0.936            |
| Age FP 1                                                             | -8.281537 (1.401022)    | 3.997923 (0.035174)     | 0.000            |
| Age FP 2                                                             | 0.005247 (0.000401)     | 0.001232 (0.000006)     | 0.000            |
| BMI FP1                                                              | 6.623690 (0.889086)     | 3.541770 (0.065505)     | 0.002            |
| BMI FP2                                                              | -21.853227 (1.710794)   | 6.882238 (0.111236)     | 0.000            |
| bp                                                                   | 0.007739 (0.001017)     | 0.001745 (0.000027)     | 0.000            |
| Diabetes type 1                                                      | 0.163047 (0.298926)     | 0.383420 (0.091198)     | 0.448            |
| Diabetes type 2                                                      | 0.734839 (0.086062)     | 0.162680 (0.006020)     | 0.000            |
| HDL ratio                                                            | 0.114304 (0.003476)     | 0.019567 (0.000135)     | 0.000            |
| Hypertension                                                         | 0.449234 (0.058902)     | 0.110537 (0.004092)     | 0.000            |
| Rheumatoid Arthritis                                                 | 0.410248 (0.198477)     | 0.400636 (0.031606)     | 0.186            |
| SBP5                                                                 | 0.000081 (0.000149)     | 0.000249 (0.000006)     | 0.791            |
| Severe mental illness                                                | -0.375736 (0.320073)    | 0.521429 (0.096206)     | 0.705            |
| Age FP1 X Townsend deprivation index                                 | 0.389646 (0.859947)     | 1.237686 (0.019319)     | 0.655            |
| Age FP2 X Townsend deprivation index                                 | 0.000208 (0.000262)     | 0.000385 (0.000005)     | 0.579            |
| Age FP 1 X BMI FP 1                                                  | 180.825332 (140.377654) | 507.026874 (13.27348)   | 0.964            |
| Age FP 1 X BMI FP 2                                                  | 6.137352 (276.787202)   | 1005.158734 (20.5467)   | 0.996            |
| Age FP 1 X SBP                                                       | 0.559086 (0.038647)     | 0.244762 (0.003328)     | 0.000            |
| Age FP 1 X Diabetes type 1                                           | 1.025598 (34.260935)    | 52.580719 (16.247853)   | 0.917            |
| Age FP 1 X Diabetes type 2                                           | 31.543949 (10.307556)   | 22.061615 (1.103530)    | 0.026            |
| Age FP 1 X hypertension                                              | 3.441496 (9.051975)     | 15.118433 (0.697914)    | 0.898            |
| Age FP 2 X BMI FP 1                                                  | 0.021124 (0.050468)     | 0.161500 (0.003384)     | 0.985            |
| Age FP 2 X BMI FP 2                                                  | 0.076797 (0.084614)     | 0.319911 (0.005387)     | 0.986            |
| Age FP 2 X SBP                                                       | 0.000127 (0.000018)     | 0.000072 (0.000001)     | 0.004            |
| Age FP 2 X Diabetes type 1                                           | -0.001408 (0.010203)    | 0.017267 (0.003672)     | 0.947            |
| Age FP 2 X Diabetes type 2                                           | 0.005581 (0.003391)     | 0.006605 (0.000189)     | 0.402            |
| Age FP 2 X hypertension                                              | 0.000346 (0.002649)     | 0.004225 (0.000148)     | 0.887            |
| <b>QRISK3 Female baseline survival = 0.9642753682636174 ( 0.001)</b> |                         |                         |                  |
| Corticosteroid                                                       | -2.131646 (5.104756)    | 114.333002 (226.662800) | 0.975            |
| Ethnic Background                                                    | 0.042184 (0.102007)     | 0.137585 (0.004452)     | 0.604            |
| Migraine                                                             | -0.650955 (0.273151)    | 0.827189 (0.142690)     | 0.617            |
| Smoker current                                                       | 0.582761 (0.048526)     | 0.108828 (0.000903)     | 0.000            |
| Smoker former                                                        | 0.062849 (0.027752)     | 0.066280 (0.000827)     | 0.321            |

|                                      |                            |                         |       |
|--------------------------------------|----------------------------|-------------------------|-------|
| Townsend deprivation index           | -0.002225 (0.009944)       | 0.012890 (0.000183)     | 0.698 |
| Age FP 1                             | 23.438344 (9.796006)       | 21.238341 (0.514248)    | 0.163 |
| Age FP 2                             | 1.064908 (0.096568)        | 0.238237 (0.003999)     | 0.000 |
| BMI FP1                              | -3.412544 (1.597298)       | 3.771709 (0.098042)     | 0.387 |
| BMI FP2                              | -2.647527 (3.095258)       | 7.461164 (0.191163)     | 0.900 |
| bp                                   | 0.005591 (0.001549)        | 0.002388 (0.000074)     | 0.000 |
| Diabetes type 1                      | -0.529207 (3.636028)       | 1.235246 (1.539416)     | 0.000 |
| Diabetes type 2                      | -0.923512 (0.744213)       | 0.841830 (0.469805)     | 0.312 |
| HDL ratio                            | 0.120117 (0.001921)        | 0.027162 (0.000197)     | 0.000 |
| Hypertension                         | 0.553000 (0.078572)        | 0.194864 (0.013675)     | 0.000 |
| Rheumatoid Arthritis                 | 0.414370 (0.251212)        | 0.382957 (0.043465)     | 0.084 |
| SBP5                                 | -0.000233 (0.000073)       | 0.000324 (0.000005)     | 0.657 |
| Severe mental illness                | 0.849891 (0.181746)        | 0.513339 (0.058582)     | 0.004 |
| Age FP1 X Townsend deprivation index | 0.231371 (3.668057)        | 6.230333 (0.149250)     | 0.898 |
| Age FP2 X Townsend deprivation index | -0.010007 (0.042433)       | 0.072340 (0.001443)     | 0.919 |
| Age FP 1 X BMI FP 1                  | -644.273512 (1396.518951)  | 1870.052338 (107.76346) | 0.775 |
| Age FP 1 X BMI FP 2                  | 907.220093 (2798.051262)   | 3717.504987 (203.6192)  | 0.759 |
| Age FP 1 X SBP                       | 0.583749 (0.487352)        | 1.108127 (0.029894)     | 0.803 |
| Age FP 1 X Diabetes type 1           | -1012.073225 (1708.487561) | 556.827521 (625.965467) | 0.180 |
| Age FP 1 X Diabetes type 2           | -682.034530 (304.368144)   | 404.067616 (175.569874) | 0.007 |
| Age FP 1 X hypertension              | -93.313401 (40.250325)     | 93.878203 (5.374447)    | 0.307 |
| Age FP 2 X BMI FP 1                  | -7.057003 (16.845839)      | 21.728503 (1.039829)    | 0.730 |
| Age FP 2 X BMI FP 2                  | 12.53618 (33.51847)        | 43.638486 (1.967705)    | 0.731 |
| Age FP 2 X SBP                       | 0.006074 (0.005385)        | 0.012155 (0.000239)     | 0.829 |
| Age FP 2 X Diabetes type 1           | -14.682401 (23.657940)     | 7.404937 (8.656602)     | 0.068 |
| Age FP 2 X Diabetes type 2           | -6.854104 (2.579645)       | 3.826777 (1.377621)     | 0.003 |
| Age FP 2 X hypertension              | -1.025834 (0.357974)       | 0.946764 (0.038957)     | 0.219 |

Abbreviations: FP= Fractional polynomial, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = Systolic blood pressure  
Results are presented as mean value (Standard deviation)

Beta estimates and standard errors are derived from the mean value across 5-cross validation folds.

p values are derived across 5-cross validation folds using fisher's approach.

Age FP 1 (males) =  $(age/10)^{-1}$

Age FP 2 (males) =  $(age/10)^3$

BMI FP 1 (males) =  $(BMI/10)^{-2}$

BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Age FP 1 (Females) =  $age/10^{-2}$

Age FP 2 (Females) =  $age/10$

BMI FP 1 (Females) =  $(BMI/10)^{-2}$

BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

**Table 4C QRISK3 + Q-ECG**

| Risk Factor                                                                | Beta (SD)                  | SE (SD)                    | Fisher's p-value |
|----------------------------------------------------------------------------|----------------------------|----------------------------|------------------|
| <b>QRISK3 + Q-ECG Male Baseline survival = 0.9166735485427895 (0.0005)</b> |                            |                            |                  |
| Corticosteroid                                                             | -0.370238<br>(0.266196)    | 0.825496 (0.143416)        | 0.946            |
| Ethnic Background                                                          | 0.290444 (0.032006)        | 0.082346 (0.000279)        | 0.000            |
| Migraine                                                                   | 0.210158 (0.221488)        | 0.656778 (0.063105)        | 0.945            |
| Smoker current                                                             | 0.436015 (0.020976)        | 0.068675 (0.000530)        | 0.000            |
| Smoker former                                                              | 0.046825 (0.027336)        | 0.046968 (0.000219)        | 0.233            |
| Townsend deprivation index                                                 | 0.002671 (0.004375)        | 0.008753 (0.000066)        | 0.934            |
| Age FP 1                                                                   | -8.518373<br>(1.295476)    | 4.011238 (0.033318)        | 0.000            |
| Age FP 2                                                                   | 0.005080 (0.000381)        | 0.001237 (0.000006)        | 0.000            |
| BMI FP1                                                                    | 6.757441 (0.875046)        | 3.533547 (0.066149)        | 0.001            |
| BMI FP2                                                                    | -20.898572<br>(1.745010)   | 6.874848 (0.113803)        | 0.000            |
| SBP                                                                        | 0.007043 (0.001052)        | 0.001755 (0.000028)        | 0.000            |
| Diabetes type 1                                                            | 0.194762 (0.293970)        | 0.382739 (0.089915)        | 0.375            |
| Diabetes type 2                                                            | 0.735350 (0.087638)        | 0.162933 (0.006129)        | 0.000            |
| HDL ratio                                                                  | 0.113551 (0.003666)        | 0.019612 (0.000138)        | 0.000            |
| Hypertension                                                               | 0.432364 (0.058689)        | 0.110793 (0.004159)        | 0.000            |
| Rheumatoid Arthritis                                                       | 0.415374 (0.203391)        | 0.400724 (0.031577)        | 0.174            |
| SBP5                                                                       | 0.000057 (0.000147)        | 0.000249 (0.000006)        | 0.851            |
| Severe mental illness                                                      | -0.440769<br>(0.327000)    | 0.521602 (0.096207)        | 0.546            |
| Q-ECG                                                                      | 0.462110 (0.043070)        | 0.096530 (0.003854)        | 0.000            |
| Age FP1 X Townsend deprivation index                                       | 0.485253 (0.833823)        | 1.238102 (0.019558)        | 0.653            |
| Age FP2 X Townsend deprivation index                                       | 0.000239 (0.000253)        | 0.000386 (0.000005)        | 0.568            |
| Age FP 1 X BMI FP 1                                                        | 171.723203<br>(138.168174) | 507.958201<br>(13.061271)  | 0.972            |
| Age FP 1 X BMI FP 2                                                        | -6.817696<br>(258.165962)  | 1007.034792<br>(20.238167) | 0.997            |
| Age FP 1 X SBP                                                             | 0.554449 (0.034274)        | 0.246882 (0.003440)        | 0.000            |
| Age FP 1 X Diabetes type 1                                                 | 1.746634<br>(33.619637)    | 52.596934<br>(16.070136)   | 0.918            |
| Age FP 1 X Diabetes type 2                                                 | 30.617253<br>(10.630635)   | 22.185117<br>(1.149150)    | 0.035            |
| Age FP 1 X hypertension                                                    | 3.280180 (9.148926)        | 15.158096<br>(0.699693)    | 0.891            |
| Age FP2 X BMI FP1                                                          | 0.018698 (0.049549)        | 0.161648 (0.003429)        | 0.987            |
| Age FP2 X BMI FP2                                                          | 0.075541 (0.080288)        | 0.320294 (0.005579)        | 0.989            |
| Age FP2 X SBP                                                              | 0.000124 (0.000019)        | 0.000073 (0.000001)        | 0.006            |
| Age FP 2 X Diabetes type1                                                  | -0.001344<br>(0.010102)    | 0.017343 (0.003665)        | 0.951            |

|                                                                             |                              |                             |       |
|-----------------------------------------------------------------------------|------------------------------|-----------------------------|-------|
| Age FP 2 X Diabetes type2                                                   | 0.005360 (0.003489)          | 0.006643 (0.000198)         | 0.442 |
| Age FP 2 X Hypertension                                                     | 0.000250 (0.002659)          | 0.004238 (0.000147)         | 0.878 |
| Age FP 1 X Q-ECG                                                            | -6.395473<br>(5.826748)      | 13.747958<br>(0.504315)     | 0.803 |
| Age FP 2 X Q-ECG                                                            | -0.000762<br>(0.001674)      | 0.004066 (0.000144)         | 0.946 |
| <b>QRISK3 + Q-ECG Female Baseline survival = 0.9644312655209759 (0.001)</b> |                              |                             |       |
| Corticosteroid                                                              | -2.139429<br>(5.103004)      | 114.458049<br>(226.912626)  | 0.977 |
| Ethnic Background                                                           | 0.022929 (0.104888)          | 0.137888 (0.004484)         | 0.632 |
| Migraine                                                                    | -0.677080<br>(0.270921)      | 0.827188 (0.142713)         | 0.575 |
| Smoker current                                                              | 0.590358 (0.049218)          | 0.108917 (0.000905)         | 0.000 |
| Smoker former                                                               | 0.064222 (0.027305)          | 0.066286 (0.000832)         | 0.300 |
| Townsend deprivation index                                                  | -0.002337<br>(0.009850)      | 0.012894 (0.000183)         | 0.707 |
| Age FP 1                                                                    | 23.825739<br>(9.609024)      | 21.283544<br>(0.515667)     | 0.154 |
| Age FP 2                                                                    | 1.064066 (0.094973)          | 0.238916 (0.004066)         | 0.000 |
| BMI FP1                                                                     | -3.530345<br>(1.637779)      | 3.773620 (0.097908)         | 0.348 |
| BMI FP2                                                                     | -1.658469<br>(3.252635)      | 7.478075 (0.191622)         | 0.933 |
| SBP                                                                         | 0.005278 (0.001563)          | 0.002389 (0.000073)         | 0.000 |
| Diabetes type 1                                                             | -0.454064<br>(3.522284)      | 1.230700 (1.530636)         | 0.000 |
| Diabetes type 2                                                             | -0.973155<br>(0.721668)      | 0.828864 (0.455175)         | 0.218 |
| HDL ratio                                                                   | 0.117952 (0.002153)          | 0.027192 (0.000207)         | 0.000 |
| Hypertension                                                                | 0.547235 (0.078572)          | 0.194440 (0.013951)         | 0.000 |
| Rheumatoid Arthritis                                                        | 0.417022 (0.256338)          | 0.383005 (0.043505)         | 0.078 |
| SBP5                                                                        | -0.000227<br>(0.000072)      | 0.000323 (0.000006)         | 0.681 |
| Severe mental illness                                                       | 0.790257 (0.169078)          | 0.514784 (0.058477)         | 0.011 |
| Q-ECG                                                                       | 0.384236 (0.072835)          | 0.148093 (0.005023)         | 0.000 |
| Age FP1 X Townsend deprivation index                                        | 0.123873 (3.783475)          | 6.217625 (0.147836)         | 0.889 |
| Age FP2 X Townsend deprivation index                                        | -0.010818<br>(0.043583)      | 0.072232 (0.001433)         | 0.910 |
| Age FP 1 X BMI FP 1                                                         | -732.526109<br>(1397.753777) | 1875.995740<br>(105.434279) | 0.758 |
| Age FP 1 X BMI FP 2                                                         | 1058.890455<br>(2764.128820) | 3732.372230<br>(200.383356) | 0.773 |
| Age FP 1 X SBP                                                              | 0.566389 (0.469419)          | 1.109153 (0.028284)         | 0.821 |
| Age FP 1 X Diabetes type 1                                                  | -985.923818<br>(1647.445015) | 552.423937<br>(620.415592)  | 0.185 |
| Age FP 1 X Diabetes type 2                                                  | -694.088226                  | 398.602823                  | 0.004 |

|                           |                           |                         |       |
|---------------------------|---------------------------|-------------------------|-------|
|                           | (287.494510)              | (169.015913)            |       |
| Age FP 1 X hypertension   | -90.168697<br>(41.267719) | 93.623455<br>(5.479881) | 0.340 |
| Age FP2 X BMI FP1         | -7.792538<br>(16.906717)  | 21.780690<br>(1.022958) | 0.731 |
| Age FP2 X BMI FP2         | 13.437998<br>(33.337130)  | 43.767508<br>(1.946698) | 0.740 |
| Age FP2 X SBP             | 0.006018 (0.005299)       | 0.012177 (0.000225)     | 0.837 |
| Age FP 2 X Diabetes type1 | -14.340859<br>(22.826342) | 7.348574 (8.584039)     | 0.068 |
| Age FP 2 X Diabetes type2 | -6.953663<br>(2.430628)   | 3.784072 (1.320469)     | 0.002 |
| Age FP 2 X Hypertension   | -0.990301<br>(0.366134)   | 0.944880 (0.039521)     | 0.251 |
| Age FP 1 X Q-ECG          | -4.638380<br>(36.636766)  | 72.965922<br>(2.715443) | 0.929 |
| Age FP 2 X Q-ECG          | -0.227338<br>(0.419115)   | 0.824399 (0.025195)     | 0.904 |

Abbreviations: FP= Fractional polynomial, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = Systolic blood pressure

Results are presented as mean value (Standard deviation)

Beta estimates and standard errors are derived from the mean value across 5-cross validation folds.

p values are derived across 5-cross validation folds using fisher's approach.

Age FP 1 (males) =  $(age/10)^{-1}$

Age FP 2 (males) =  $(age/10)^3$

BMI FP 1 (males) =  $(BMI/10)^{-2}$

BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

Age FP 1 (Females) =  $age/10^{-2}$

Age FP 2 (Females) =  $age/10$

BMI FP 1 (Females) =  $(BMI/10)^{-2}$

BMI FP 2 (Females) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$

## Chapter 6 Physical activity risk scores

**Table 5C QRISK3 AND QRISK3 +PA models**

| Risk factor                                                    | Beta Estimate | Standard Error | p-value       |
|----------------------------------------------------------------|---------------|----------------|---------------|
| <b>Recalibrated QRISK3 Male: Baseline survival = 0.9423994</b> |               |                |               |
| Age FP 1                                                       | 2.62769       | 78.62382       | 0.4257882     |
| Age FP 2                                                       | -0.003851393  | 0.01671447     | 0.8177821     |
| BMI FP 1                                                       | -12.30258     | 99.56482       | 0.9016708     |
| BMI FP 2                                                       | 28.16927      | 206.4584       | 0.8914841     |
| Diabetes                                                       | -3.810557     | 4.586265       | 0.4061301     |
| Hypertension                                                   | -0.6840875    | 2.884233       | 0.8125349     |
| Systolic Blood Pressure                                        | -0.09525114   | 0.05970155     | 0.1107355     |
| Townsend Deprivation Index                                     | -0.006365634  | 0.3225725      | 0.9842571     |
| HDL Cholesterol Ratio                                          | 0.08317759    | 0.01991600     | 0.00004946307 |
| Corticosteroid Treatment                                       | -8.028494     | 5.439010       | 0.1400425     |
| Atrial Fibrillation and Flutter                                | -4.221300     | 4.600499       | 0.3589290     |
| SBP5                                                           | -0.0005380189 | 0.004560719    | 0.9061158     |
| Ethnicity (non-white)                                          | 0.2673579     | 0.1214732      | 0.02782856    |
| Previous Smoker                                                | 0.1019975     | 0.04242883     | 0.01628976    |
| Current Smoker                                                 | 0.2960192     | 0.07212049     | 4.179988e-05  |
| Age FP 1 * Hypertension                                        | 5.440667      | 13.86387       | 0.6947698     |
| Age FP 1 * Diabetes                                            | 20.98811      | 21.88218       | 0.3375800     |
| Age FP 1 * BMI FP 1                                            | 108.6213      | 459.6992       | 0.8132287     |
| Age FP 1 * BMI FP 2                                            | -268.1715     | 953.0316       | 0.7784362     |
| Age FP 1 * Townsend Deprivation Index                          | -0.1498332    | 1.501949       | 0.9205434     |
| Age FP 1 * Systolic Blood Pressure                             | 0.5180102     | 0.2826998      | 0.06701404    |
| Age FP 1 * Atrial Fibrillation and Flutter                     | 27.82625      | 22.13210       | 0.2087679     |
| Age FP 1 * Corticosteroid Treatment                            | 36.77399      | 25.58024       | 0.1506726     |
| Age FP 2 * Hypertension                                        | 0.0006703487  | 0.002640777    | 0.7996356     |
| Age FP 2 * Diabetes                                            | 0.003328341   | 0.004257471    | 0.4344262     |
| Age FP 2 * BMI FP 1                                            | 0.01359674    | 0.1000543      | 0.8919162     |
| Age FP 2 * BMI FP 2                                            | -0.03341266   | 0.2080274      | 0.8724082     |
| Age FP 2 * Townsend Deprivation Index                          | 0.0001863275  | 0.0003176764   | 0.5575700     |

|                                                        |                   |                 |             |
|--------------------------------------------------------|-------------------|-----------------|-------------|
| Age FP 2 * Systolic Blood Pressure                     | 0.00007333802     | 0.00005665023   | 0.1955848   |
| Age FP 2 * Atrial Fibrillation and Flutter             | 0.002775114       | 0.004178753     | 0.5066861   |
| Age FP 2 * Corticosteroid Treatment                    | 0.007688209       | 0.005128263     | 0.1339503   |
| <b>QRISK3 + PA male: Baseline survival = 0.9383829</b> |                   |                 |             |
| Daily step count FP 1                                  | -0.0000057862903  | 0.0006235433717 | 0.926072    |
| Hours of Moderate-to-Vigorous-Activity FP 1            | -0.0438595812495  | 6.73271053951   | 0.994803    |
| Hours of Moderate-to-Vigorous-Activity FP 2            | -4.06728880298    | 4.58795681572   | 0.375425    |
| Hours of Light intensity Activity FP1                  | -21.5171718097    | 11.5729058445   | 0.0631054   |
| Hours of Sedentary behaviour FP 1                      | -0.705977939243   | 7.97170143073   | 0.929438    |
| Overall Physical activity FP1                          | 45.6310707358     | 30.602841996    | 0.136068    |
| Overall Physical activity FP2                          | -9.34106185036    | 8.35038722923   | 0.263401    |
| Age FP 1                                               | 102.811244184     | 140.957001375   | 0.465837    |
| Age FP 2                                               | 0.0378227702019   | 0.0292548634896 | 0.196174    |
| BMI FP 1                                               | -12.8861847733    | 100.026018806   | 0.897504    |
| BMI FP 2                                               | 18.7164444984     | 208.900134639   | 0.928616    |
| Diabetes                                               | -3.27341169527    | 4.65870821295   | 0.482344    |
| Hypertension                                           | 0.322117380991    | 2.9440950995    | 0.912885    |
| Systolic Blood Pressure                                | -0.0944142809815  | 0.0602346866886 | 0.117138    |
| Townsend Deprivation Index                             | -0.00412197718729 | 0.325539798091  | 0.989898    |
| Cholesterol Ratio                                      | 0.0750285076758   | 0.0202104433047 | 0.000304895 |
| Corticosteroid Treatment                               | -7.15229257676    | 5.49274313711   | 0.192989    |
| Atrial Fibrillation and Flutter                        | -3.54914610075    | 4.67226188879   | 0.447553    |
| SBP5                                                   | -0.00042261961641 | 0.0045499703837 | 0.926012    |
| Ethnicity (non-white)                                  | 0.250098186798    | 0.121791526771  | 0.0401279   |
| Previous Smoker                                        | 0.104467217232    | 0.0425339106566 | 0.0141131   |
| Current Smoker                                         | 0.251949844845    | 0.0726918071836 | 0.000537137 |
| Age FP 1 * Hypertension                                | 0.656223789922    | 14.1723540865   | 0.963072    |
| Age FP 1 * Diabetes                                    | 18.3363936891     | 22.260239917    | 0.410173    |
| Age FP 1 * BMI FP 1                                    | 105.910421173     | 463.58138556    | 0.819306    |
| Age FP 1 * BMI FP 2                                    | -212.234872004    | 967.812625427   | 0.82644     |
| Age FP 1 * Townsend Deprivation Index                  | -0.155122840739   | 1.51827374145   | 0.918629    |

|                                                        |                   |                 |           |
|--------------------------------------------------------|-------------------|-----------------|-----------|
| Age FP 1 * Systolic Blood Pressure                     | 0.51209453046     | 0.285623991788  | 0.0731098 |
| Age FP 1 * Atrial Fibrillation and Flutter             | 24.7367736569     | 22.5063358279   | 0.271828  |
| Age FP 1 * Corticosteroid Treatment                    | 33.017064612      | 25.8591857802   | 0.20179   |
| Age FP 2 * Hypertension                                | -0.00032067441538 | 0.0026847057887 | 0.904932  |
| Age FP 2 * Diabetes                                    | 0.00273253707038  | 0.0043067517327 | 0.525827  |
| Age FP 2 * BMI FP 1                                    | 0.0119714736657   | 0.0994087191152 | 0.904155  |
| Age FP 2 * BMI FP 2                                    | -0.0136241004106  | 0.208286811678  | 0.947853  |
| Age FP 2 * Townsend Deprivation Index                  | 0.00017810510863  | 0.0003193113069 | 0.577045  |
| Age FP 2 * Systolic Blood Pressure                     | 7.438024876e-05   | 5.69335433e-05  | 0.191523  |
| Age FP 2 * Atrial Fibrillation and Flutter             | 0.00203376060726  | 0.0042304935067 | 0.630744  |
| Age FP 2 * Corticosteroid Treatment                    | 0.00661923647246  | 0.0051698945775 | 0.200543  |
| Daily step count FP 1* Age FP 1                        | 0.00021013701267  | 0.0032893906147 | 0.949068  |
| Hours of Moderate-to-Vigorous-Activity FP 1 * Age FP 1 | -2.84471220553    | 31.8252777798   | 0.928783  |
| Hours of Moderate-to-Vigorous-Activity FP 2* Age FP 1  | 20.5781992765     | 21.5918856151   | 0.340655  |
| Hours of Light intensity Activity FP 1* Age FP 1       | 100.258161278     | 54.1362338891   | 0.0641486 |
| Hours of Sedentary behaviour FP 1 * Age FP 1           | 5.62042584709     | 37.4590498112   | 0.880744  |
| Overall Physical activity FP 1 * Age FP 1              | -205.77163779     | 143.145968673   | 0.150702  |
| Overall Physical activity FP 2 * Age FP 1              | 41.6976066237     | 38.7985491829   | 0.282603  |
| Daily step count FP 1* Age FP 2                        | 7.493871e-08      | 4.418449e-07    | 0.865335  |
| Hours of Moderate-to-Vigorous-Activity FP 1 * Age FP 2 | 0.0005766866075   | 0.0063670870382 | 0.927839  |
| Hours of Moderate-to-Vigorous-Activity FP 2* Age FP 2  | 0.00367416192351  | 0.0043926364138 | 0.402989  |
| Hours of Light intensity Activity FP 1* Age FP 2       | 0.02294003724     | 0.0112769362619 | 0.0420317 |
| Hours of Sedentary behaviour FP 1 * Age FP 2           | 0.00060248341013  | 0.0076754699109 | 0.937441  |
| Overall Physical activity FP 1 * Age FP 2              | -0.0539033194208  | 0.030188319941  | 0.0742895 |
| Overall Physical activity FP 2 * Age FP 2              | 0.0113926570382   | 0.0083908394468 | 0.174665  |
| <b>QRISK3 female: Baseline survival = 0.9779604</b>    |                   |                 |           |
| Age FP 1                                               | -73.59084         | 314.3532        | 0.8149352 |
| Age FP 2                                               | 0.4340244         | 2.663602        | 0.8705812 |
| BMI FP 1                                               | 46.68488          | 145.8587        | 0.7489595 |



|                                                         |             |              |              |
|---------------------------------------------------------|-------------|--------------|--------------|
| BMI FP 2                                                | -27.90143   | 299.5528     | 0.9258015    |
| Diabetes                                                | 5.652492    | 8.467563     | 0.5045187    |
| Hypertension                                            | 0.05804769  | 4.717130     | 0.9901832    |
| Systolic Blood Pressure                                 | -0.05978868 | 0.09768807   | 0.5405996    |
| Townsend Deprivation Index                              | 0.4535288   | 0.6027011    | 0.4518634    |
| Cholesterol Ratio                                       | 0.1245675   | 0.02788021   | 2.476169e-05 |
| Corticosteroid Treatment                                | 11.17888    | 11.68239     | 0.3387602    |
| Atrial Fibrillation and Flutter                         | 84.72013    | 29.17629     | 0.003737326  |
| SBP5                                                    | 0.002834783 | 0.005165206  | 0.5832297    |
| Ethnicity (non-white)                                   | 0.1098694   | 0.1539011    | 0.4753953    |
| Previous Smoker                                         | 0.1459096   | 0.05253807   | 0.005545844  |
| Current Smoker                                          | 0.6127372   | 0.09514881   | 1.572138e-10 |
| Age FP 1 * Hypertension                                 | 39.71871    | 61.21383     | 0.5165259    |
| Age FP 1 * Diabetes                                     | -45.88777   | 108.7061     | 0.6729888    |
| Age FP 1 * BMI FP 1                                     | -846.7782   | 1867.001     | 0.6502161    |
| Age FP 1 * BMI FP 2                                     | 468.5859    | 3777.733     | 0.9013003    |
| Age FP 1 * Townsend Deprivation Index                   | -5.582213   | 7.583259     | 0.4617621    |
| Age FP 1 * Systolic Blood Pressure                      | 1.052182    | 1.269434     | 0.4073063    |
| Age FP 1 * Atrial Fibrillation and Flutter              | -1277.938   | 456.1459     | 0.00514541   |
| Age FP 1 * Corticosteroid Treatment                     | -137.8085   | 155.9581     | 0.3770297    |
| Age FP 2 * Hypertension                                 | -0.05602168 | 0.4971365    | 0.9102913    |
| Age FP 2 * Diabetes                                     | -0.5843811  | 0.8966425    | 0.5146594    |
| Age FP 2 * BMI FP 1                                     | -3.994544   | 15.48764     | 0.7965050    |
| Age FP 2 * BMI FP 2                                     | 1.542911    | 32.00779     | 0.9615597    |
| Age FP 2 * Townsend Deprivation Index                   | -0.04629518 | 0.06438903   | 0.4722496    |
| Age FP 2 * Systolic Blood Pressure                      | 0.006585079 | 0.01029752   | 0.5225999    |
| Age FP 2 * Atrial Fibrillation and Flutter              | -8.171554   | 2.833642     | 0.003981393  |
| Age FP 2 * Corticosteroid Treatment                     | -1.228811   | 1.217747     | 0.3130841    |
| <b>QRISK3 +PA female: Baseline survival = 0.9785204</b> |             |              |              |
| Daily step count FP 1                                   | 2.774391745 | 3.55857164   | 0.43572      |
| Daily step count FP 2                                   | -1.7822789  | 14.805811127 | 0.9042       |
| Hours of Moderate-to-Vigorous-Activity FP 1             | 4.589411089 | 7.372047467  | 0.533674     |

|                                            |                |               |             |
|--------------------------------------------|----------------|---------------|-------------|
| Hours of Light intensity Activity FP1      | 0.370613054    | 0.378395951   | 0.327515    |
| Hours of Light intensity Activity FP2      | -6.441467405   | 16.706284226  | 0.699865    |
| Hours of Sedentary behaviour FP 1          | -20.66230156   | 15.942445693  | 0.195143    |
| Overall Physical activity FP1              | -6.68781849    | 11.062501028  | 0.545565    |
| Age FP 1                                   | 2.774391745    | 3.55857164    | 0.43572     |
| Age FP 2                                   | -1.7822789     | 14.805811127  | 0.9042      |
| BMI FP 1                                   | 4.589411089    | 7.372047467   | 0.533674    |
| BMI FP 2                                   | 0.370613054    | 0.378395951   | 0.327515    |
| Diabetes                                   | -6.441467405   | 16.706284226  | 0.699865    |
| Hypertension                               | -20.66230156   | 15.942445693  | 0.195143    |
| Systolic Blood Pressure                    | -6.68781849    | 11.062501028  | 0.545565    |
| Townsend Deprivation Index                 | -288.59512109  | 482.964764495 | 0.550226    |
| Cholesterol Ratio                          | -1.59489854    | 3.960586791   | 0.687229    |
| Corticosteroid Treatment                   | 26.392125895   | 148.062492213 | 0.858551    |
| Atrial Fibrillation and Flutter            | 27.864142437   | 304.777520094 | 0.927167    |
| SBP5                                       | 5.354087843    | 8.554914758   | 0.531503    |
| Ethnicity (non-white)                      | -0.180760644   | 4.717230632   | 0.969438    |
| Previous Smoker                            | -0.037333604   | 0.098730371   | 0.705379    |
| Current Smoker                             | 0.387764394    | 0.609563499   | 0.52478     |
| Age FP 1 * Hypertension                    | 0.116239041    | 0.02754537    | 5.35301e-05 |
| Age FP 1 * Diabetes                        | 10.553166465   | 11.777806725  | 0.370376    |
| Age FP 1 * BMI FP 1                        | 75.998011607   | 28.616258306  | 0.00799146  |
| Age FP 1 * BMI FP 2                        | 0.002264641    | 0.005161146   | 0.660891    |
| Age FP 1 * Townsend Deprivation Index      | 0.071090486    | 0.154527718   | 0.645543    |
| Age FP 1 * Systolic Blood Pressure         | 0.139881765    | 0.052676729   | 0.0079984   |
| Age FP 1 * Atrial Fibrillation and Flutter | 0.528262566    | 0.096065336   | 4.43872e-08 |
| Age FP 1 * Corticosteroid Treatment        | 43.583375414   | 61.171936782  | 0.476275    |
| Age FP 2 * Hypertension                    | -39.34326375   | 109.848643978 | 0.720272    |
| Age FP 2 * Diabetes                        | -591.568279252 | 1890.6694708  | 0.754408    |
| Age FP 2 * BMI FP 1                        | -228.836689193 | 3833.97467601 | 0.952413    |
| Age FP 2 * BMI FP 2                        | -4.695046603   | 7.669750341   | 0.540525    |
| Age FP 2 * Townsend Deprivation Index      | 0.782531421    | 1.284286426   | 0.542404    |

|                                                        |                |               |           |
|--------------------------------------------------------|----------------|---------------|-----------|
| Age FP 2 * Systolic Blood Pressure                     | -1147.91872334 | 445.681046166 | 0.0100942 |
| Age FP 2 * Atrial Fibrillation and Flutter             | -128.840107236 | 157.13243217  | 0.412369  |
| Age FP 2 * Corticosteroid Treatment                    | -0.039366553   | 0.497298728   | 0.936915  |
| Daily step count FP 1 * Age FP 1                       | -52.449493255  | 56.794204968  | 0.355885  |
| Daily step count FP 2 * Age FP 1                       | 69.684176512   | 215.527329145 | 0.746496  |
| Hours of Moderate-to-Vigorous-Activity FP 2 * Age FP 1 | -51.100291956  | 93.541237981  | 0.584945  |
| Hours of Light intensity Activity FP 1 * Age FP 1      | -4.205449889   | 5.054485764   | 0.40552   |
| Hours of Light intensity Activity FP 2 * Age FP 1      | 77.503018005   | 212.973768904 | 0.715974  |
| Hours of Sedentary behaviour FP 1 * Age FP 1           | 246.061308528  | 203.457451595 | 0.226688  |
| Overall Physical activity FP 1 * Age FP 1              | 72.82769821    | 142.21229131  | 0.608648  |
| Daily step count FP 1 * Age FP 2                       | -0.249990777   | 0.34299492    | 0.466202  |
| Daily step count FP 2 * Age FP 2                       | 0.125383416    | 1.494425677   | 0.933146  |
| Hours of Moderate-to-Vigorous-Activity FP 2 * Age FP 2 | -0.514310768   | 0.786662518   | 0.513342  |
| Hours of Light intensity Activity FP 1 * Age FP 2      | -0.042215144   | 0.039970656   | 0.291058  |
| Hours of Light intensity Activity FP 2 * Age FP 2      | 0.866189507    | 1.775137253   | 0.625648  |
| Hours of Sedentary behaviour FP 1 * Age FP 2           | 2.381844741    | 1.693489629   | 0.159778  |
| Overall Physical activity FP 1 * Age FP 2              | 0.658320739    | 1.172662241   | 0.57461   |

Abbreviations: FP= Fractional polynomial, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

Fractional polynomials (males) = Age FP 1 (males) =  $(age/10)^{-1}$ ; Age FP 2 =  $(age/10)^3$

; BMI FP 1 =  $\left(\frac{BMI}{10}\right)^{-2}$ ; BMI FP 2 =  $\left(\frac{BMI}{10}\right)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA))$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 1 =  $\frac{Overall\ activity^{0.5}}{10}$ ; Overall Physical activity FP 2 =  $\frac{Overall\ activity}{10}$

Fractional polynomials (females) = Age FP 1 =  $age/10^{-2}$ ; Age FP 2 =  $age/10$ ; BMI FP 1 =  $(BMI/10)^{-2}$ ; BMI FP 2 =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1}$ ; Daily step count FP 2 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^1$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA^{-2}}{10}$ ; Hours of Light intensity Activity FP 2 =  $\frac{Hours\ of\ LPA^2}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 2 =  $\log\left(\frac{Overall\ activity}{10}\right)$

**Table 6C QRISK3 (Excluding Systolic blood pressure and HDL cholesterol ratio) and QRISK3 +PA models**

| Risk factor                                                                                                  | Beta Estimate    | Standard Error | p-value  |
|--------------------------------------------------------------------------------------------------------------|------------------|----------------|----------|
| <b>Recalibrated QRISK3 (Excluding SBP and HDL cholesterol ratio) Male: Baseline survival = 0.9419250</b>     |                  |                |          |
| Age FP 1                                                                                                     | 19.40966         | 67.86407       | 0.7749   |
| Age FP 2                                                                                                     | 0.00769          | 0.01489        | 0.6058   |
| BMI FP 1                                                                                                     | -14.29372        | 100.2164       | 0.8866   |
| BMI FP 2                                                                                                     | 47.50877         | 207.3885       | 0.8188   |
| Diabetes                                                                                                     | -3.27956         | 4.56415        | 0.4725   |
| Hypertension                                                                                                 | -1.80902         | 2.82707        | 0.5223   |
| Townsend Deprivation Index                                                                                   | -0.00397         | 0.32105        | 0.9901   |
| Corticosteroid Treatment                                                                                     | -8.16087         | 5.39011        | 0.1301   |
| Atrial Fibrillation and Flutter                                                                              | -4.13007         | 4.48867        | 0.3576   |
| Ethnicity (non-white)                                                                                        | 0.24997          | 0.12143        | 0.0396   |
| Previous Smoker                                                                                              | 0.10162          | 0.04237        | 0.0165   |
| Current Smoker                                                                                               | 0.30807          | 0.07205        | 0.00002  |
| Age FP 1 * Hypertension                                                                                      | 11.36892         | 13.59534       | 0.4031   |
| Age FP 1 * Diabetes                                                                                          | 17.81052         | 21.78253       | 0.4136   |
| Age FP 1 * BMI FP 1                                                                                          | 105.4435         | 462.5411       | 0.8197   |
| Age FP 1 * BMI FP 2                                                                                          | -356.6052        | 956.9140       | 0.7094   |
| Age FP 1 * Townsend Deprivation Index                                                                        | -0.16634         | 1.49365        | 0.9113   |
| Age FP 1 * Atrial Fibrillation and Flutter                                                                   | 27.23944         | 21.56658       | 0.2067   |
| Age FP 1 * Corticosteroid Treatment                                                                          | 37.36240         | 25.32813       | 0.1403   |
| Age FP 2 * Hypertension                                                                                      | 0.00152          | 0.00259        | 0.5579   |
| Age FP 2 * Diabetes                                                                                          | 0.00300          | 0.00424        | 0.4785   |
| Age FP 2 * BMI FP 1                                                                                          | 0.01617          | 0.10084        | 0.8726   |
| Age FP 2 * BMI FP 2                                                                                          | -0.04825         | 0.20926        | 0.8177   |
| Age FP 2 * Townsend Deprivation Index                                                                        | 0.00018          | 0.00032        | 0.5641   |
| Age FP 2 * Atrial Fibrillation and Flutter                                                                   | 0.00266          | 0.00409        | 0.5154   |
| Age FP 2 * Corticosteroid Treatment                                                                          | 0.00786          | 0.00509        | 0.1229   |
| <b>Recalibrated QRISK3 (Excluding SBP and HDL cholesterol ratio) +PA Male: Baseline survival = 0.9380904</b> |                  |                |          |
| Daily step count FP 1                                                                                        | -4.623797317e-05 | 0.000618953713 | 0.940457 |

|                                             |                   |                 |             |
|---------------------------------------------|-------------------|-----------------|-------------|
| Hours of Moderate-to-Vigorous-Activity FP 1 | 0.329842150069    | 6.77612809053   | 0.96118     |
| Hours of Moderate-to-Vigorous-Activity FP 2 | -4.23140815019    | 4.61255337324   | 0.359038    |
| Hours of Light intensity Activity FP1       | -21.2397967407    | 11.498338022    | 0.0648344   |
| Hours of Sedentary behaviour FP 1           | -0.518098344986   | 7.97781339541   | 0.948225    |
| Overall Physical activity FP1               | 44.7746146721     | 30.6398667535   | 0.144053    |
| Overall Physical activity FP2               | -9.05141256701    | 8.36693733989   | 0.279442    |
| Age FP 1                                    | 184.718891779     | 134.483406023   | 0.169705    |
| Age FP 2                                    | 0.0493633444895   | 0.0281105298561 | 0.0792023   |
| BMI FP 1                                    | -15.2937856169    | 100.679855788   | 0.879274    |
| BMI FP 2                                    | 38.3135015683     | 209.946107297   | 0.855211    |
| Diabetes                                    | -2.77099572172    | 4.64056502683   | 0.550478    |
| Hypertension                                | -0.81008864728    | 2.88954087746   | 0.77923     |
| Townsend Deprivation Index                  | -0.00566982221162 | 0.324272132684  | 0.986051    |
| Corticosteroid Treatment                    | -7.19901086155    | 5.44086899425   | 0.18591     |
| Atrial Fibrillation and Flutter             | -3.30620204723    | 4.55936019207   | 0.46843     |
| Ethnicity (non-white)                       | 0.230013196735    | 0.121756815064  | 0.0589906   |
| Previous Smoker                             | 0.105526554667    | 0.0424704134608 | 0.0130305   |
| Current Smoker                              | 0.261617031232    | 0.0726410620236 | 0.000322539 |
| Age FP 1 * Hypertension                     | 6.61566773662     | 13.9166122408   | 0.634558    |
| Age FP 1 * Diabetes                         | 15.3155033578     | 22.1831181624   | 0.489999    |
| Age FP 1 * BMI FP 1                         | 104.646716658     | 466.468484424   | 0.822512    |
| Age FP 1 * BMI FP 2                         | -300.164922533    | 972.317105174   | 0.757567    |
| Age FP 1 * Townsend Deprivation Index       | -0.15216646611    | 1.51135699342   | 0.919811    |
| Age FP 1 * Atrial Fibrillation and Flutter  | 23.4436874287     | 21.9403164719   | 0.285388    |
| Age FP 1 * Corticosteroid Treatment         | 33.2172576457     | 25.5954197592   | 0.194481    |
| Age FP 2 * Hypertension                     | 0.00054001660675  | 0.0026329767187 | 0.837513    |
| Age FP 2 * Diabetes                         | 0.00242792734358  | 0.0042870129048 | 0.57121     |
| Age FP 2 * BMI FP 1                         | 0.0150687273309   | 0.100188603109  | 0.880458    |
| Age FP 2 * BMI FP 2                         | -0.0291417521654  | 0.2095943402    | 0.889431    |
| Age FP 2 * Townsend Deprivation Index       | 0.00017785706436  | 0.0003186408968 | 0.576775    |

|                                                                                                            |                  |                 |           |
|------------------------------------------------------------------------------------------------------------|------------------|-----------------|-----------|
| Age FP 2 * Atrial Fibrillation and Flutter                                                                 | 0.00176782010121 | 0.0041426653929 | 0.669609  |
| Age FP 2 * Corticosteroid Treatment                                                                        | 0.00670500644038 | 0.0051323825126 | 0.191532  |
| Daily step count FP 1* Age FP 1                                                                            | 0.00015071904951 | 0.003266394268  | 0.9632    |
| Daily step count FP 2* Age FP 1                                                                            | -4.78683965184   | 32.0494500548   | 0.881283  |
| Hours of Moderate-to-Vigorous-Activity<br>FP 2* Age FP 1                                                   | 21.4123491501    | 21.7215017207   | 0.324342  |
| Hours of Light intensity Activity FP 1* Age<br>FP 1                                                        | 99.0466294338    | 53.7718623927   | 0.0655956 |
| Hours of Light intensity Activity FP 2* Age<br>FP 1                                                        | 4.79094925406    | 37.4953869025   | 0.898338  |
| Hours of Sedentary behaviour FP 1 * Age<br>FP 1                                                            | -202.402300399   | 143.341316483   | 0.158064  |
| Overall Physical activity FP 1 * Age FP 1                                                                  | 40.5184626841    | 38.8900654543   | 0.297571  |
| Daily step count FP 1* Age FP 2                                                                            | 6.617844e-08     | 4.381589e-07    | 0.879958  |
| Daily step count FP 2* Age FP 2                                                                            | 0.00029214687874 | 0.0063962372063 | 0.963573  |
| Hours of Moderate-to-Vigorous-Activity<br>FP 2* Age FP 2                                                   | 0.00377075350115 | 0.0044078029947 | 0.392371  |
| Hours of Light intensity Activity FP 1* Age<br>FP 2                                                        | 0.0225444866203  | 0.0112162083376 | 0.0445384 |
| Hours of Light intensity Activity FP 2* Age<br>FP 2                                                        | 0.00037799402183 | 0.0076810362503 | 0.960755  |
| Hours of Sedentary behaviour FP 1 * Age<br>FP 2                                                            | -0.0527539989255 | 0.0301850967885 | 0.0806405 |
| Overall Physical activity FP 1 * Age FP 2                                                                  | 0.011024582802   | 0.0083898244715 | 0.188952  |
| <b>Recalibrated QRISK3 (Excluding SBP and HDL cholesterol ratio) Female: Baseline survival = 0.9775558</b> |                  |                 |           |
| Age FP 1                                                                                                   | 52.99112         | 261.0622        | 0.8392    |
| Age FP 2                                                                                                   | 1.088376         | 2.264139        | 0.6308    |
| BMI FP 1                                                                                                   | 57.86552         | 146.0918        | 0.6921    |
| BMI FP 2                                                                                                   | -53.50923        | 299.4068        | 0.8582    |
| Diabetes                                                                                                   | 5.93808          | 8.413452        | 0.4804    |
| Hypertension                                                                                               | -0.6537455       | 4.572346        | 0.8863    |
| Townsend deprivation index                                                                                 | 0.4206728        | 0.5982225       | 0.482     |
| Corticosteroid treatment                                                                                   | 11.8799          | 11.56023        | 0.3043    |
| Atrial fibrillation and flutter                                                                            | 85.26908         | 29.52695        | 0.0039    |
| Ethnicity (non-white)                                                                                      | 0.1057255        | 0.1536123       | 0.4914    |

|                                                                                                                    |                |              |          |
|--------------------------------------------------------------------------------------------------------------------|----------------|--------------|----------|
| Previous smoker                                                                                                    | 0.1313886      | 0.05249988   | 0.0124   |
| Current smoker                                                                                                     | 0.6197063      | 0.09482831   | 8.49e-11 |
| Age FP 1 * Hypertension                                                                                            | 54.41898       | 59.22857     | 0.3583   |
| Age FP 1 * Diabetes                                                                                                | -49.88415      | 107.9946     | 0.6442   |
| Age FP 1 * BMI FP 1                                                                                                | -969.7023      | 1870.29      | 0.6042   |
| Age FP 1 * BMI FP 2                                                                                                | 631.9878       | 3776.272     | 0.8671   |
| Age FP 1 * Townsend deprivation index                                                                              | -5.240655      | 7.518645     | 0.4859   |
| Age FP 1 * Corticosteroid treatment                                                                                | -1293.351      | 462.1263     | 0.0052   |
| Age FP 1 * Atrial fibrillation and flutter                                                                         | -146.8491      | 154.0302     | 0.3405   |
| Age FP 2 * Hypertension                                                                                            | 0.01023442     | 0.4822235    | 0.9831   |
| Age FP 2 * Diabetes                                                                                                | -0.6228715     | 0.8910081    | 0.4846   |
| Age FP 2 * BMI FP 1                                                                                                | -5.428584      | 15.51117     | 0.7264   |
| Age FP 2 * BMI FP 2                                                                                                | 4.784044       | 31.99294     | 0.8812   |
| Age FP 2 * Townsend deprivation index                                                                              | -0.04291663    | 0.06394327   | 0.5022   |
| Age FP 2 * Corticosteroid treatment                                                                                | -8.209869      | 2.866079     | 0.0042   |
| Age FP 2 * Atrial fibrillation and flutter                                                                         | -1.300506      | 1.206214     | 0.2811   |
| <b>Recalibrated QRISK3(Excluding SBP and HDL cholesterol ratio) + PA Female:<br/>Baseline survival = 0.9782157</b> |                |              |          |
| Daily step count FP 1                                                                                              | 2.7534046      | 3.53213447   | 0.435782 |
| Daily step count FP 2                                                                                              | -1.992062698   | 14.76273084  | 0.892677 |
| Hours of Moderate-to-Vigorous-Activity<br>FP 1                                                                     | 4.864206118    | 7.37634359   | 0.509712 |
| Hours of Light intensity Activity FP1                                                                              | 0.370170307    | 0.36803046   | 0.314656 |
| Hours of Light intensity Activity FP2                                                                              | -7.532317905   | 16.60784637  | 0.650221 |
| Hours of Sedentary behaviour FP 1                                                                                  | -20.64579448   | 15.99300122  | 0.196915 |
| Overall Physical activity FP1                                                                                      | -6.88515883    | 10.97017341  | 0.530339 |
| Age FP1                                                                                                            | -199.266572175 | 445.67883308 | 0.654858 |
| Age FP 2                                                                                                           | -1.325147169   | 3.67699268   | 0.718604 |
| BMI FP 1                                                                                                           | 33.854705112   | 148.29410965 | 0.819448 |
| BMI FP 2                                                                                                           | 9.156264773    | 304.68094326 | 0.97603  |
| Diabetes                                                                                                           | 5.232466035    | 8.47851036   | 0.537227 |
| Hypertension                                                                                                       | -0.623092852   | 4.58736823   | 0.891974 |
| Townsend Deprivation Index                                                                                         | 0.367480385    | 0.60615672   | 0.544437 |

|                                                          |                |               |             |
|----------------------------------------------------------|----------------|---------------|-------------|
| Corticosteroid Treatment                                 | 11.144142919   | 11.69923625   | 0.34096     |
| Atrial Fibrillation and Flutter                          | 76.612466611   | 28.97553881   | 0.00827204  |
| Ethnicity (non-white)                                    | 0.071740103    | 0.15425011    | 0.641931    |
| Previous Smoker                                          | 0.125735799    | 0.05263348    | 0.0170144   |
| Current Smoker                                           | 0.531753244    | 0.09576826    | 3.29202e-08 |
| Age FP 1 * Hypertension                                  | 54.887315238   | 59.36845712   | 0.355355    |
| Age FP 1 * Diabetes                                      | -38.175935704  | 108.78622509  | 0.72569     |
| Age FP 1 * BMI FP 1                                      | -662.010715232 | 1894.53440668 | 0.726813    |
| Age FP 1 * BMI FP 2                                      | -166.697651689 | 3834.50747111 | 0.96533     |
| Age FP 1 * Townsend Deprivation Index                    | -4.509768741   | 7.62256305    | 0.554179    |
| Age FP 1 * Atrial Fibrillation and Flutter               | -1164.56733909 | 451.76769896  | 0.0100315   |
| Age FP 1 * Corticosteroid Treatment                      | -136.267936489 | 155.90533949  | 0.382226    |
| Age FP 2 * Hypertension                                  | -0.001740869   | 0.48397951    | 0.99713     |
| Age FP 2 * Diabetes                                      | -0.568935353   | 0.89801257    | 0.526465    |
| Age FP 2 * BMI FP 1                                      | -3.057940204   | 15.76052083   | 0.846182    |
| Age FP 2 * BMI FP 2                                      | -0.988778101   | 32.58936507   | 0.975799    |
| Age FP 2 * Townsend Deprivation Index                    | -0.0376034     | 0.06478564    | 0.561707    |
| Age FP 2 * Atrial Fibrillation and Flutter               | -7.355904764   | 2.81780127    | 0.00912473  |
| Age FP 2 * Corticosteroid Treatment                      | -1.226997044   | 1.22050758    | 0.314896    |
| Daily step count FP 1* Age FP 1                          | -51.306997291  | 56.35413904   | 0.362728    |
| Daily step count FP 2* Age FP 1                          | 68.350328152   | 214.55440597  | 0.750095    |
| Hours of Moderate-to-Vigorous-Activity<br>FP 2* Age FP 1 | -54.95897851   | 93.51309968   | 0.556807    |
| Hours of Light intensity Activity FP 1* Age<br>FP 1      | -4.211567928   | 4.90658057    | 0.390827    |
| Hours of Light intensity Activity FP 2* Age<br>FP 1      | 90.431662532   | 211.5498894   | 0.669093    |
| Hours of Sedentary behaviour FP 1 * Age<br>FP 1          | 246.229743946  | 204.16741265  | 0.227988    |
| Overall Physical activity FP 1 * Age FP 1                | 75.505509707   | 140.96033562  | 0.592274    |
| Daily step count FP 1* Age FP 2                          | -0.250430729   | 0.34052463    | 0.462187    |
| Daily step count FP 2* Age FP 2                          | 0.16073626     | 1.49131676    | 0.914183    |
| Hours of Moderate-to-Vigorous-Activity<br>FP 2* Age FP 2 | -0.545500011   | 0.78741845    | 0.488554    |



|                                                      |              |            |          |
|------------------------------------------------------|--------------|------------|----------|
| Hours of Light intensity Activity FP 1 * Age<br>FP 2 | -0.042116935 | 0.03893012 | 0.279477 |
| Hours of Light intensity Activity FP 2 * Age<br>FP 2 | 0.98066354   | 1.76512538 | 0.578577 |
| Hours of Sedentary behaviour FP 1 * Age<br>FP 2      | 2.373884906  | 1.69848188 | 0.162411 |
| Overall Physical activity FP 1 * Age FP 2            | 0.67874509   | 1.16315715 | 0.559614 |

Abbreviations: FP= Fractional polynomial, BMI = Boday mass index,

Fractional polynomials (males) = Age FP 1 (males) =  $(age/10)^{-1}$ ; Age FP 2 =  $(age/10)^3$

; BMI FP 1 =  $\left(\frac{BMI}{10}\right)^{-2}$ ; BMI FP 2 =  $\left(\frac{BMI}{10}\right)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-2}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA))$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 1 =  $\frac{Overall\ activity^{0.5}}{10}$ ; Overall Physical activity FP 2 =  $\frac{Overall\ activity}{10}$

Fractional polynomials (females) = Age FP 1 =  $age/10^{-2}$ ; Age FP 2 =  $age/10$ ; BMI FP 1 =  $(BMI/10)^{-2}$ ; BMI FP 2 =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-1}$ ; Daily step count FP 2 =  $\left(\frac{Daily\ step\ count}{10000}\right)^{-0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^1$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA^{-2}}{10}$ ; Hours of Light intensity Activity FP 2 =  $\frac{Hours\ of\ LPA^2}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 2 =  $\log\left(\frac{Overall\ activity}{10}\right)$

**Table 7C SCORE2 AND SCORE2 +PA models**

| <b>Risk factor</b>                                                | <b>Beta Estimate</b> | <b>Standard Error</b> | <b>p-value</b> |
|-------------------------------------------------------------------|----------------------|-----------------------|----------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9418511</b>    |                      |                       |                |
| Age                                                               | 0.96068              | 0.1539141             | 6.089763e-10   |
| Systolic blood pressure                                           | 0.63307558           | 0.24130172            | 0.008752928    |
| Total Cholesterol                                                 | 1.10967081           | 0.19266205            | 1.512299e-08   |
| HDL cholesterol                                                   | -0.86663939          | 0.41362894            | 0.04025781     |
| Diabetes                                                          | 2.45751573           | 0.92957145            | 0.008294131    |
| Smoker (yes/no)                                                   | 0.90062473           | 0.60672218            | 0.1378236      |
| Age * smoker                                                      | -0.0486498           | 0.04660488            | 0.2966408      |
| Age * Diabetes                                                    | -0.1358001           | 0.06849351            | 0.04760914     |
| Age * Systolic blood pressure                                     | -0.03605207          | 0.01786357            | 0.04367616     |
| Age * Cholesterol                                                 | -0.08186682          | 0.01445724            | 2.622944e-08   |
| Age * HDL Cholesterol                                             | 0.0473289            | 0.03043281            | 0.1242993      |
| <b>Recalibrated SCORE2+PA Male: Baseline survival = 0.9391192</b> |                      |                       |                |
| Daily step count FP 1                                             | 1.47454093           | 0.78460443            | 0.060312       |
| Hours of Moderate-to-Vigorous-Activity FP 1                       | -2.28919934          | 1.47879389            | 0.121743       |
| Hours of Moderate-to-Vigorous-Activity FP 2                       | 0.7175777            | 0.96042               | 0.455042       |
| Hours of Light intensity Activity FP1                             | -2.35580904          | 2.30683819            | 0.307243       |
| Hours of Sedentary behaviour FP 1                                 | -0.09347972          | 0.45091643            | 0.835784       |
| Overall Physical activity FP1                                     | 12.56987849          | 10.41803748           | 0.227718       |
| Overall Physical activity FP2                                     | -3.93249481          | 3.33145977            | 0.237947       |
| Age                                                               | 2.11494273           | 0.83537262            | 0.0114105      |
| Systolic blood pressure                                           | 0.65160766           | 0.24049125            | 0.00678425     |
| Total Cholesterol                                                 | 1.05219478           | 0.19078296            | 5.46033e-08    |
| HDL cholesterol                                                   | -0.83955643          | 0.41079802            | 0.0447854      |
| Diabetes                                                          | 2.49189225           | 0.93245038            | 0.00761207     |
| Smoker (yes/no)                                                   | 0.95453222           | 0.60241328            | 0.113201       |
| Age * smoker                                                      | -0.05792503          | 0.04626617            | 0.210687       |
| Age * Diabetes                                                    | -0.14587008          | 0.06869713            | 0.0338893      |
| Age * Systolic blood pressure                                     | -0.03783779          | 0.01780023            | 0.0336256      |

|                                                                       |               |             |              |
|-----------------------------------------------------------------------|---------------|-------------|--------------|
| Age * Cholesterol                                                     | -0.07759575   | 0.01430755  | 8.98892e-08  |
| Age * HDL Cholesterol                                                 | 0.04910618    | 0.03016828  | 0.10739      |
| Age * Daily step count FP 1                                           | -0.11728464   | 0.05964678  | 0.0493704    |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1                     | 0.14362068    | 0.10946844  | 0.189645     |
| Age * Hours of Moderate-to-Vigorous-Activity FP 2                     | -0.03471027   | 0.0715108   | 0.627445     |
| Age * Hours of Light intensity Activity FP 1                          | 0.23723816    | 0.17377022  | 0.172298     |
| Age * Hours of Sedentary behaviour FP 1                               | 0.01821585    | 0.03360791  | 0.587859     |
| Age * Overall Physical activity FP 1                                  | -1.18506554   | 0.77503216  | 0.126376     |
| Age * Overall Physical activity FP 2                                  | 0.36237251    | 0.24877477  | 0.145342     |
| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9772510</b>      |               |             |              |
| Age                                                                   | 0.84640408    | 0.17645412  | 1.853072e-06 |
| Systolic blood pressure                                               | 0.77805727    | 0.27008654  | 0.004018645  |
| Total Cholesterol                                                     | 1.06028366    | 0.26066224  | 5.850772e-05 |
| HDL cholesterol                                                       | -1.73804417   | 0.40375563  | 2.037805e-05 |
| Diabetes                                                              | 4.64765022    | 1.0997425   | 2.508738e-05 |
| Smoker (yes/no)                                                       | 0.05617036    | 0.87559598  | 0.9488578    |
| Age * smoker                                                          | 0.03716772    | 0.06706141  | 0.5794944    |
| Age * Diabetes                                                        | -0.27309295   | 0.0825189   | 0.0009550804 |
| Age * Systolic blood pressure                                         | -0.03971096   | 0.02010187  | 0.0483806    |
| Age * Cholesterol                                                     | -0.07908731   | 0.01945598  | 5.875189e-05 |
| Age * HDL Cholesterol                                                 | 0.10697583    | 0.03012747  | 0.0004283532 |
| <b>Recalibrated SCORE2 +PA Female: Baseline survival = .0.9796755</b> |               |             |              |
| Daily step count FP 1                                                 | -0.2614496525 | 0.310225859 | 0.39948      |
| Daily step count FP 2                                                 | 0.795387869   | 1.796586746 | 0.658026     |
| Hours of Moderate-to-Vigorous-Activity FP 1                           | -0.0211036369 | 0.136982582 | 0.877581     |
| Hours of Light intensity Activity FP1                                 | 0.0076114006  | 0.050610784 | 0.880475     |
| Hours of Light intensity Activity FP2                                 | 0.0769087605  | 2.18802021  | 0.971964     |
| Hours of Sedentary behaviour FP 1                                     | -0.5044682832 | 2.259962759 | 0.823393     |
| Overall Physical activity FP1                                         | -1.3004378601 | 1.47115567  | 0.37685      |
| Age                                                                   | 0.645442211   | 0.310845634 | 0.0380314    |
| Systolic blood pressure                                               | 0.8320943086  | 0.271910935 | 0.00224828   |

|                                                   |               |             |             |
|---------------------------------------------------|---------------|-------------|-------------|
| Total Cholesterol                                 | 0.9483082487  | 0.259662005 | 0.000301536 |
| HDL cholesterol                                   | -1.5088670519 | 0.40494761  | 0.000222477 |
| Diabetes                                          | 4.460841382   | 1.107708751 | 5.90846e-05 |
| Smoker (yes/no)                                   | 0.0092186872  | 0.88197158  | 0.991662    |
| Age * smoker                                      | 0.0328158359  | 0.067555988 | 0.627205    |
| Age * Diabetes                                    | -0.2711458278 | 0.083030845 | 0.00111513  |
| Age * Systolic blood pressure                     | -0.0450067705 | 0.020250646 | 0.0263876   |
| Age * Cholesterol                                 | -0.0705602218 | 0.019376935 | 0.000312746 |
| Age * HDL Cholesterol                             | 0.0945915736  | 0.03022122  | 0.00189824  |
| Age * Daily step count FP 1                       | 0.0141300829  | 0.021627561 | 0.513632    |
| Age * Daily step count FP 2                       | -0.0142936366 | 0.129659646 | 0.912233    |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1 | 0.0004338557  | 0.010073595 | 0.965652    |
| Age * Hours of Light intensity Activity FP1       | -0.0012276272 | 0.003922885 | 0.754366    |
| Age * Hours of Light intensity Activity FP2       | 0.0817308604  | 0.164137793 | 0.618593    |
| Age * Hours of Sedentary behaviour FP 1           | 0.1131507079  | 0.169070029 | 0.503429    |
| Age * Overall Physical activity FP1               | 0.048595521   | 0.110118275 | 0.659052    |

Abbreviations: FP= Fractional polynomial, HDL = High-density lipoprotein, SBP = systolic blood pressure

Fractional polynomial (males) = Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\text{Hours of MVPA}^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}))$ ; Hours of Light intensity Activity FP1 =  $\frac{\text{Hours of LPA}}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{\text{Hours of SBA}^3}{10}$ ; Overall Physical activity FP1 =  $\frac{\text{Overall activity}^{0.5}}{10}$ ; Overall Physical activity FP2 =  $\log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5} \times \log\left(\frac{\text{Overall activity}}{10}\right)\right)$

Fractional polynomial (females) = Daily step count FP 1  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1}$ ; Daily step count FP 2 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\log(\text{Hours of MVPA})$ ; Hours of Light intensity Activity FP1 =  $\left(\frac{\text{Hours of LPA}}{10}\right)^{-2}$ ; Light intensity Activity FP1 =  $\left(\frac{\text{Hours of LPA}}{10}\right)^2$ ; Hours of Sedentary behaviour FP 1 =  $\frac{\text{Hours of SBA}}{10}$ ; Overall Physical activity FP1 =  $\log\left(\frac{\text{Overall activity}}{10}\right)$

**Table 8C SCORE2 (Excluding Systolic blood pressure and HDL cholesterol ratio) and SCORE2 +PA models**

| Risk factor                                                       | Beta Estimate   | Standard Error | p-value       |
|-------------------------------------------------------------------|-----------------|----------------|---------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9401369</b>    |                 |                |               |
| Age                                                               | 0.38233178      | 0.01599676     | 3.962422e-114 |
| Diabetes                                                          | 1.88577405      | 0.91095815     | 0.03856807    |
| Smoker (yes/no)                                                   | 1.08043227      | 0.60526897     | 0.07437223    |
| Age * smoker                                                      | -0.06164965     | 0.04650236     | 0.1850467     |
| Age * Diabetes                                                    | -0.08699321     | 0.06707064     | 0.1947675     |
| <b>Recalibrated SCORE2+PA Male: Baseline survival = 0.9380322</b> |                 |                |               |
| Daily step count FP 1                                             | -5.2002589e-05  | 7.088983e-05   | 0.463279      |
| Hours of Moderate-to-Vigorous-Activity FP 1                       | -1.61853273448  | 1.39611621484  | 0.246438      |
| Hours of Moderate-to-Vigorous-Activity FP 2                       | 0.867655462069  | 0.949576048154 | 0.360945      |
| Hours of Light intensity Activity FP1                             | -0.088245717205 | 2.11401850901  | 0.966707      |
| Hours of Sedentary behaviour FP 1                                 | 0.126006940899  | 0.454042344031 | 0.781401      |
| Overall Physical activity FP1                                     | 7.32522257135   | 6.72894272186  | 0.276427      |
| Overall Physical activity FP2                                     | -2.00066100778  | 1.86496360514  | 0.28348       |
| Age                                                               | 0.905503988934  | 0.408082154915 | 0.0265795     |
| Diabetes                                                          | 1.86463335478   | 0.917249712461 | 0.0421964     |
| Smoker (yes/no)                                                   | 1.10097670193   | 0.60054086708  | 0.0668732     |
| Age * smoker                                                      | -0.069241213136 | 0.046130250402 | 0.133481      |
| Age * Diabetes                                                    | -0.095636735957 | 0.067537121429 | 0.156913      |
| Age * Daily step count FP 1                                       | 3.576629e-06    | 4.738615e-06   | 0.450449      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1                 | 0.084361319567  | 0.103073655189 | 0.413173      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 2                 | -0.045687160275 | 0.070616804595 | 0.517708      |
| Age * Hours of Light intensity Activity FP1                       | 0.062185595754  | 0.159361921706 | 0.696409      |
| Age * Hours of Sedentary behaviour FP 1                           | 0.001541717305  | 0.033902222517 | 0.963732      |
| Age * Overall Physical activity FP1                               | -0.717523807439 | 0.500230699045 | 0.151585      |

|                                                                     |                |                |               |
|---------------------------------------------------------------------|----------------|----------------|---------------|
| Age * Overall Physical activity FP2                                 | 0.185878936389 | 0.139141364743 | 0.181701      |
| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9752419</b>    |                |                |               |
| Age                                                                 | 0.49035704     | 0.02059067     | 5.556207e-108 |
| Diabetes                                                            | 5.06133936     | 1.06685811     | 2.274789e-06  |
| Smoker (yes/no)                                                     | 0.29798883     | 0.86178979     | 0.7295529     |
| Age * smoker                                                        | 0.02084902     | 0.06603001     | 0.7522318     |
| Age * Diabetes                                                      | -0.28742564    | 0.07997615     | 0.0003353605  |
| <b>Recalibrated SCORE2 +PA Female: Baseline survival =0.9782629</b> |                |                |               |
| Daily step count FP 1                                               | -0.3380903035  | 0.32748455     | 0.302044      |
| Daily step count FP 2                                               | 1.4810422185   | 1.893907831    | 0.434326      |
| Hours of Moderate-to-Vigorous-Activity FP 1                         | -0.7154905677  | 3.230945552    | 0.82477       |
| Hours of Moderate-to-Vigorous-Activity FP 1                         | 0.6607673666   | 2.461011383    | 0.788353      |
| Hours of Light intensity Activity FP1                               | 0.0008615614   | 0.048536136    | 0.98584       |
| Hours of Light intensity Activity FP2                               | 1.2567399097   | 2.369804251    | 0.595966      |
| Hours of Sedentary behaviour FP 1                                   | -0.003618881   | 2.284046005    | 0.998736      |
| Overall activity FP 1                                               | -2.8848975458  | 1.950031749    | 0.139224      |
| Age                                                                 | 0.1717167992   | 0.332077928    | 0.605158      |
| Diabetes                                                            | 4.5422058803   | 1.083252614    | 0.0000028994  |
| Smoker (yes/no)                                                     | 0.1172603538   | 0.870195424    | 0.892825      |
| Age * smoker                                                        | 0.0242029611   | 0.066676247    | 0.716658      |
| Age * Diabetes                                                      | -0.2675763446  | 0.081106024    | 0.000990874   |
| Age * Daily step count FP 1                                         | 0.0195961781   | 0.022761234    | 0.389395      |
| Age * Daily step count FP 2                                         | -0.0628516392  | 0.136176545    | 0.644469      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1                   | 0.0034904373   | 0.241441132    | 0.988467      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1                   | -0.0214250618  | 0.185810517    | 0.908217      |
| Age * Hours of Light intensity Activity FP1                         | -0.0006126047  | 0.003772122    | 0.871008      |
| Age * Hours of Light intensity Activity FP2                         | -0.0022085197  | 0.177474743    | 0.990073      |
| Age * Hours of Sedentary behaviour FP 1                             | 0.079737512    | 0.170840695    | 0.640751      |
| Age * Overall activity FP 1                                         | 0.1474530378   | 0.146667101    | 0.314873      |

Abbreviations: FP= Fractional polynomial, MVPA =Moderate to vigorous physical activity, LPA = Light physical activity, SB = Sedentary behaviour, BMI = Boday mass index

Fractional polynomial (males) = Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\text{Hours of MVPA}^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}))$ ; Hours of Light intensity Activity FP1 =  $\frac{\text{Hours of LPA}}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{\text{Hours of SBA}^3}{10}$ ; Overall Physical activity FP1 =  $\frac{\text{Overall activity}^{0.5}}{10}$ ; Overall Physical activity FP2 =  $\log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5}\right)$

Fractional polynomial (females) = Daily step count FP 1  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1}$ ; Daily step count FP 2 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\text{Hours of MVPA}^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\text{Hours of MVPA}$  Hours of Light intensity Activity FP1 =  $\left(\frac{\text{Hours of LPA}}{10}\right)^{-2}$ ; Light intensity Activity FP1 =  $\left(\frac{\text{Hours of LPA}}{10}\right)^2$ ; Hours of Sedentary behaviour FP 1 =  $\frac{\text{Hours of SBA}}{10}$ ; Overall Physical activity FP1 =  $\left(\frac{\text{Overall activity}}{10}\right)$

**Table 9C QRISK3 AND QRISK3 +PA risk scores with Cholesterol and systolic blood pressure derived from primary care records**

| <b>Risk factor</b>                                             | <b>Beta Estimate</b> | <b>Standard Error</b> | <b>p-value</b> |
|----------------------------------------------------------------|----------------------|-----------------------|----------------|
| <b>Recalibrated QRISK3 Male: Baseline survival = 0.9371967</b> |                      |                       |                |
| Age FP 1                                                       | 32.46609             | 83.93902              | 0.69908        |
| Age FP 2                                                       | 0.008312             | 0.018088              | 0.64599        |
| BMI FP 1                                                       | -17.56808            | 100.1175              | 0.86072        |
| BMI FP 2                                                       | 57.55544             | 207.3309              | 0.78134        |
| Diabetes                                                       | -3.164228            | 4.556223              | 0.48744        |
| Hypertension                                                   | -1.752254            | 2.840280              | 0.53734        |
| Systolic Blood Pressure                                        | 0.016156             | 0.077671              | 0.83583        |
| Townsend Deprivation Index                                     | -0.003492            | 0.321274              | 0.99133        |
| Cholesterol Ratio                                              | 0.069888             | 0.051146              | 0.22159        |
| Corticosteroid Treatment                                       | -8.057751            | 5.394998              | 0.13542        |
| Atrial Fibrillation and Flutter                                | -4.169399            | 4.492731              | 0.35348        |
| SBP5                                                           | -0.000122            | 0.003757              | 0.97516        |
| Ethnicity (non-white)                                          | 0.256690             | 0.122231              | 0.03586        |
| Previous Smoker                                                | 0.109946             | 0.042387              | 0.00954        |
| Current Smoker                                                 | 0.301481             | 0.072866              | 0.00004        |
| Age FP 1 * Hypertension                                        | 11.08394             | 13.65301              | 0.41696        |
| Age FP 1 * Diabetes                                            | 17.43537             | 21.73524              | 0.42253        |
| Age FP 1 * BMI FP 1                                            | 121.6997             | 461.7716              | 0.79214        |
| Age FP 1 * BMI FP 2                                            | -401.8560            | 956.1421              | 0.67431        |
| Age FP 1 * Townsend Deprivation Index                          | -0.166356            | 1.494717              | 0.91139        |
| Age FP 1 * Systolic Blood Pressure                             | -0.074219            | 0.364344              | 0.83919        |
| Age FP 1 * Atrial Fibrillation and Flutter                     | 27.48591             | 21.58147              | 0.20292        |
| Age FP 1 * Corticosteroid Treatment                            | 36.89577             | 25.35061              | 0.14568        |
| Age FP 2 * Hypertension                                        | 0.001471             | 0.002602              | 0.57182        |
| Age FP 2 * Diabetes                                            | 0.002921             | 0.004232              | 0.49013        |
| Age FP 2 * BMI FP 1                                            | 0.019532             | 0.100956              | 0.84660        |
| Age FP 2 * BMI FP 2                                            | -0.056296            | 0.209495              | 0.78817        |
| Age FP 2 * Townsend Deprivation Index                          | 0.000182             | 0.000317              | 0.56508        |



|                                                        |                   |                 |            |
|--------------------------------------------------------|-------------------|-----------------|------------|
| Age FP 2 * Systolic Blood Pressure                     | -0.000001         | 0.000077        | 0.98870    |
| Age FP 2 * Atrial Fibrillation and Flutter             | 0.002735          | 0.004102        | 0.50498    |
| Age FP 2 * Corticosteroid Treatment                    | 0.007769          | 0.005100        | 0.12781    |
| <b>QRISK3 + PA male: Baseline survival = 0.9351460</b> |                   |                 |            |
| Daily step count FP 1                                  | -4.243910504e-05  | 0.0006285955689 | 0.946178   |
| Hours of Moderate-to-Vigorous-Activity FP 1            | 0.106028256461    | 6.77301507618   | 0.987511   |
| Hours of Moderate-to-Vigorous-Activity FP 2            | -4.09453438366    | 4.61015885304   | 0.374543   |
| Hours of Light intensity Activity FP1                  | -21.3627635193    | 11.5172080811   | 0.0637342  |
| Hours of Sedentary behaviour FP 1                      | -0.400933965174   | 7.98690490378   | 0.959968   |
| Overall Physical activity FP1                          | 44.5908834818     | 30.6902297416   | 0.146367   |
| Overall Physical activity FP2                          | -8.95019558426    | 8.38040904586   | 0.285627   |
| Age FP 1                                               | 206.816105191     | 145.584686551   | 0.15569    |
| Age FP 2                                               | 0.0519351707495   | 0.0303601846796 | 0.0873744  |
| BMI FP 1                                               | -19.0133056259    | 100.639663335   | 0.850167   |
| BMI FP 2                                               | 50.5512026844     | 210.008776778   | 0.8098     |
| Diabetes                                               | -2.70352034349    | 4.6299477089    | 0.559327   |
| Hypertension                                           | -0.79974051478    | 2.89923521501   | 0.78269    |
| Systolic Blood Pressure                                | 0.0306506952997   | 0.0785932852697 | 0.69777    |
| Townsend Deprivation Index                             | -0.00230034027806 | 0.324398158913  | 0.994343   |
| Cholesterol Ratio                                      | 0.0609006990377   | 0.0516960755317 | 0.284283   |
| Corticosteroid Treatment                               | -7.08944636028    | 5.44844165481   | 0.193313   |
| Atrial Fibrillation and Flutter                        | -3.35700772738    | 4.56259393679   | 0.461941   |
| SBP5                                                   | -0.00018226960638 | 0.0037478492693 | 0.962758   |
| Ethnicity (non-white)                                  | 0.237901238262    | 0.122655245438  | 0.0525872  |
| Previous Smoker                                        | 0.113319088069    | 0.042485475361  | 0.00769676 |

|                                                        |                  |                 |             |
|--------------------------------------------------------|------------------|-----------------|-------------|
| Current Smoker                                         | 0.257730324372   | 0.0732209220181 | 0.000440593 |
| Age FP 1 * Hypertension                                | 6.54690656195    | 13.9577395996   | 0.639073    |
| Age FP 1 * Diabetes                                    | 15.1661641395    | 22.1207141376   | 0.493023    |
| Age FP 1 * BMI FP 1                                    | 122.947134536    | 465.877210881   | 0.791875    |
| Age FP 1 * BMI FP 2                                    | -356.369149584   | 971.915696889   | 0.713899    |
| Age FP 1 * Townsend Deprivation Index                  | -0.166311538105  | 1.51194267362   | 0.912419    |
| Age FP 1 * Systolic Blood Pressure                     | -0.141994860863  | 0.370808252813  | 0.703079    |
| Age FP 1 * Atrial Fibrillation and Flutter             | 23.7452697848    | 21.9513613316   | 0.27948     |
| Age FP 1 * Corticosteroid Treatment                    | 32.7140900367    | 25.6303356124   | 0.201939    |
| Age FP 2 * Hypertension                                | 0.00053917683308 | 0.0026444875569 | 0.838458    |
| Age FP 2 * Diabetes                                    | 0.00238445674131 | 0.0042814493985 | 0.577627    |
| Age FP 2 * BMI FP 1                                    | 0.0188698360058  | 0.10043058294   | 0.850979    |
| Age FP 2 * BMI FP 2                                    | -0.0395725691931 | 0.210093169047  | 0.850612    |
| Age FP 2 * Townsend Deprivation Index                  | 0.00017477285534 | 0.0003187731921 | 0.583557    |
| Age FP 2 * Systolic Blood Pressure                     | -1.555891869e-05 | 7.70763761e-05  | 0.840699    |
| Age FP 2 * Atrial Fibrillation and Flutter             | 0.00184678589156 | 0.0041493210475 | 0.6563      |
| Age FP 2 * Corticosteroid Treatment                    | 0.00661089617719 | 0.0051404113596 | 0.198539    |
| Daily step count FP 1* Age FP 1                        | 0.00012993508319 | 0.0033165975777 | 0.968752    |
| Hours of Moderate-to-Vigorous-Activity FP 1 * Age FP 1 | -3.75852069826   | 32.0333331411   | 0.906607    |
| Hours of Moderate-to-Vigorous-Activity FP 2* Age FP 1  | 20.8132566891    | 21.7098506271   | 0.337802    |
| Hours of Light intensity Activity FP 1* Age FP 1       | 99.5481384009    | 53.8500737518   | 0.0646309   |
| Hours of Sedentary behaviour FP 1 * Age FP 1           | 4.29599164513    | 37.5329099425   | 0.908883    |
| Overall Physical activity FP 1 * Age FP 1              | -201.567370922   | 143.561174879   | 0.160427    |

|                                                        |                  |                 |                    |
|--------------------------------------------------------|------------------|-----------------|--------------------|
| Overall Physical activity FP 2 * Age FP 1              | 40.0941760707    | 38.9498651924   | 0.303401           |
| Daily step count FP 1 * Age FP 2                       | 6.353359e-08     | 4.450922e-07    | 0.886505           |
| Hours of Moderate-to-Vigorous-Activity FP 1 * Age FP 2 | 0.00054978319043 | 0.0063955122884 | 0.931502           |
| Hours of Moderate-to-Vigorous-Activity FP 2 * Age FP 2 | 0.00364215329418 | 0.0044050234446 | 0.408419           |
| Hours of Light intensity Activity FP 1 * Age FP 2      | 0.0227494639253  | 0.0112417542758 | 0.0431119          |
| Hours of Sedentary behaviour FP 1 * Age FP 2           | 0.00026843840128 | 0.0076933151934 | 0.972168           |
| Overall Physical activity FP 1 * Age FP 2              | -0.0525807740544 | 0.0302381762665 | 0.0821771          |
| Overall Physical activity FP 2 * Age FP 2              | 0.0109121590077  | 0.0084041983844 | 0.194263           |
| <b>QRISK3 female: Baseline survival = 0.9738397</b>    |                  |                 |                    |
| Age FP 1                                               | -28.993728277    | 405.365342148   | 0.9432991195055447 |
| Age FP 2                                               | 0.612160312      | 3.507843205     | 0.8623282061088524 |
| BMI FP 1                                               | 66.877933591     | 146.182827752   | 0.6473775617924509 |
| BMI FP 2                                               | -75.406114819    | 300.205006632   | 0.8017059097253858 |
| Diabetes                                               | 5.483346042      | 8.403587198     | 0.5141710515248100 |
| Hypertension                                           | -0.601925986     | 4.598105373     | 0.8958651783548466 |
| Systolic Blood Pressure                                | -0.022762691     | 0.178629655     | 0.9003011477815390 |
| Townsend Deprivation Index                             | 0.432144404      | 0.599083952     | 0.4708033626153085 |
| Cholesterol Ratio                                      | 0.097055455      | 0.057558436     | 0.1357595675527775 |
| Corticosteroid Treatment                               | 11.807394131     | 11.588390426    | 0.3084031360654486 |
| Atrial Fibrillation and Flutter                        | 84.167870280     | 29.531829057    | 0.0044261431752382 |

|                                                         |                 |               |                    |
|---------------------------------------------------------|-----------------|---------------|--------------------|
| SBP5                                                    | -0.001605195    | 0.004367371   | 0.7276453838659557 |
| Ethnicity (non-white)                                   | 0.104923357     | 0.154442278   | 0.4970077545713601 |
| Previous Smoker                                         | 0.135124378     | 0.052953842   | 0.01082287313376   |
| Current Smoker                                          | 0.600792323     | 0.096258407   | 0.00000000058553   |
| Age FP 1 * Hypertension                                 | 53.094266968    | 59.531971380  | 0.37260197516631   |
| Age FP 1 * Diabetes                                     | -43.297107637   | 107.84932692  | 0.68813515822319   |
| Age FP 1 * BMI FP 1                                     | -1,060.78759985 | 1,872.3937146 | 0.57110539331527   |
| Age FP 1 * BMI FP 2                                     | 896.279399521   | 3,788.1961742 | 0.81299910319148   |
| Age FP 1 * Townsend Deprivation Index                   | -5.375647175    | 7.528760178   | 0.47532090551675   |
| Age FP 1 * Systolic Blood Pressure                      | 0.483063759     | 2.223524777   | 0.83072729832152   |
| Age FP 1 * Atrial Fibrillation and Flutter              | -1,277.1663385  | 462.298424215 | 0.00579821853721   |
| Age FP 1 * Corticosteroid Treatment                     | -145.69250215   | 154.477056464 | 0.34575303687750   |
| Age FP 2 * Hypertension                                 | 0.007925004     | 0.484971402   | 0.98696426386341   |
| Age FP 2 * Diabetes                                     | -0.571802442    | 0.890237705   | 0.52076753967114   |
| Age FP 2 * BMI FP 1                                     | -6.464822201    | 15.518512709  | 0.6770363187192    |
| Age FP 2 * BMI FP 2                                     | 7.375574380     | 32.076657235  | 0.8181714200389    |
| Age FP 2 * Townsend Deprivation Index                   | -0.044127896    | 0.064034829   | 0.4908444411384    |
| Age FP 2 * Systolic Blood Pressure                      | 0.002248561     | 0.019134446   | 0.90805896250091   |
| Age FP 2 * Atrial Fibrillation and Flutter              | -8.097384799    | 2.866271091   | 0.00478503524115   |
| Age FP 2 * Corticosteroid Treatment                     | -1.293239917    | 1.208798852   | 0.28484364360604   |
| <b>QRISK3 +PA female: Baseline survival = 0.9746997</b> |                 |               |                    |
| Daily step count FP 1                                   | 2.759924935     | 3.526086827   | 0.43391            |
| Daily step count FP 2                                   | -2.275931999    | 14.776744294  | 0.877612           |
| Hours of Moderate-to-Vigorous-Activity FP 1             | 4.689256566     | 7.392631993   | 0.525966           |
| Hours of Light intensity Activity FP1                   | 0.354136319     | 0.366755293   | 0.334395           |
| Hours of Light intensity Activity FP2                   | -7.536411101    | 16.611207286  | 0.65011            |
| Hours of Sedentary behaviour FP 1                       | -20.252137806   | 15.967993506  | 0.204877           |
| Overall Physical activity FP1                           | -6.871637967    | 10.973020541  | 0.531253           |
| Age FP 1                                                | -277.466344132  | 542.980924606 | 0.610153           |
| Age FP 2                                                | -1.766079855    | 4.542778896   | 0.698166           |
| BMI FP 1                                                | 44.305067367    | 148.487720155 | 0.765456           |

|                                                       |                |               |             |
|-------------------------------------------------------|----------------|---------------|-------------|
| BMI FP 2                                              | -16.119048585  | 305.705445883 | 0.957956    |
| Diabetes                                              | 4.956061927    | 8.451157371   | 0.557665    |
| Hypertension                                          | -0.583543497   | 4.606625198   | 0.899214    |
| Systolic Blood Pressure                               | -0.018184228   | 0.174515055   | 0.918254    |
| Townsend Deprivation Index                            | 0.382290464    | 0.60653826    | 0.5286      |
| Cholesterol Ratio                                     | 0.083440495    | 0.058656787   | 0.198821    |
| Corticosteroid Treatment                              | 11.097540728   | 11.722164712  | 0.343927    |
| Atrial Fibrillation and Flutter                       | 75.498779511   | 28.978769712  | 0.00926405  |
| SBP5                                                  | -0.001608628   | 0.004356788   | 0.726446    |
| Ethnicity (non-white)                                 | 0.071608069    | 0.154972958   | 0.644099    |
| Previous Smoker                                       | 0.129074857    | 0.053047807   | 0.0150891   |
| Current Smoker                                        | 0.51591894     | 0.097075944   | 1.25151e-07 |
| Age FP 1 * Hypertension                               | 53.804206397   | 59.596565851  | 0.366766    |
| Age FP 1 * Diabetes                                   | -33.93985106   | 108.355365413 | 0.754149    |
| Age FP 1 * BMI FP 1                                   | -772.510682922 | 1897.78761409 | 0.68402     |
| Age FP 1 * BMI FP 2                                   | 137.816294375  | 3849.25750657 | 0.971444    |
| Age FP 1 * Townsend Deprivation Index                 | -4.696138756   | 7.625935331   | 0.538107    |
| Age FP 1 * Systolic Blood Pressure                    | 0.424530629    | 2.178290816   | 0.847646    |
| Age FP 1 * Atrial Fibrillation and Flutter            | -1148.29542201 | 451.971831775 | 0.0111589   |
| Age FP 1 * Corticosteroid Treatment                   | -135.421574269 | 156.267176579 | 0.38629     |
| Age FP 2 * Hypertension                               | -0.003118401   | 0.486010229   | 0.994881    |
| Age FP 2 * Diabetes                                   | -0.536912428   | 0.895614442   | 0.548931    |
| Age FP 2 * BMI FP 1                                   | -4.247028136   | 15.77925233   | 0.787848    |
| Age FP 2 * BMI FP 2                                   | 1.941085303    | 32.69714592   | 0.952669    |
| Age FP 2 * Townsend Deprivation Index                 | -0.039171171   | 0.064829246   | 0.545783    |
| Age FP 2 * Systolic Blood Pressure                    | 0.001734356    | 0.018672303   | 0.927129    |
| Age FP 2 * Atrial Fibrillation and Flutter            | -7.242128223   | 2.817679954   | 0.0102524   |
| Age FP 2 * Corticosteroid Treatment                   | -1.222468249   | 1.222621487   | 0.317522    |
| Daily step count FP 1* Age FP 1                       | -51.384079688  | 56.258785342  | 0.361195    |
| Daily step count FP 2* Age FP 1                       | 72.385311744   | 214.698022562 | 0.736049    |
| Hours of Moderate-to-Vigorous-Activity FP 2* Age FP 1 | -52.094908921  | 93.762497077  | 0.578559    |

|                                                       |               |               |          |
|-------------------------------------------------------|---------------|---------------|----------|
| Hours of Light intensity Activity FP 1* Age FP 1      | -4.017670934  | 4.881242344   | 0.410584 |
| Hours of Light intensity Activity FP 2* Age FP 1      | 90.251379165  | 211.598357441 | 0.669785 |
| Hours of Sedentary behaviour FP 1 * Age FP 1          | 240.625991444 | 203.797163753 | 0.237892 |
| Overall Physical activity FP 1 * Age FP 1             | 75.501195859  | 140.957270017 | 0.592288 |
| Daily step count FP 1* Age FP 2                       | -0.251007229  | 0.339967261   | 0.460424 |
| Daily step count FP 2* Age FP 2                       | 0.188724862   | 1.492969535   | 0.899424 |
| Hours of Moderate-to-Vigorous-Activity FP 2* Age FP 2 | -0.526813107  | 0.789052617   | 0.504452 |
| Hours of Light intensity Activity FP 1* Age FP 2      | -0.040342818  | 0.038830768   | 0.298991 |
| Hours of Light intensity Activity FP 2* Age FP 2      | 0.983709298   | 1.765448161   | 0.577468 |
| Hours of Sedentary behaviour FP 1 * Age FP 2          | 2.334795998   | 1.696024921   | 0.16882  |
| Overall Physical activity FP 1 * Age FP 2             | 0.677482966   | 1.163600515   | 0.560494 |

Abbreviations: FP= Fractional polynomial, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

Fractional polynomials (males) = Age FP 1 (males) =  $(age/10)^{-1}$ ; Age FP 2 =  $(age/10)^3$

; BMI FP 1 =  $\left(\frac{BMI}{10}\right)^{-2}$ ; BMI FP 2 =  $\left(\frac{BMI}{10}\right)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(Hours\ of\ MVPA^{0.5} \times \log(Hours\ of\ MVPA))$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 1 =  $\frac{Overall\ activity^{0.5}}{10}$ ; Overall Physical activity FP 2 =  $\frac{Overall\ activity}{10}$

Fractional polynomials (females) = Age FP 1 =  $age/10^{-2}$ ; Age FP 2 =  $age/10$ ; BMI FP 1 =  $(BMI/10)^{-2}$ ; BMI FP 2 =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ; Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-1}$ ; Daily step count FP 2 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $Hours\ of\ MVPA^1$ ; Hours of Light intensity Activity FP 1 =  $\frac{Hours\ of\ LPA^{-2}}{10}$ ; Hours of Light intensity Activity FP 2 =  $\frac{Hours\ of\ LPA^2}{10}$ ; Hours of Sedentary behaviour FP 1 =  $\frac{Hours\ of\ SBA}{10}$ ; Overall Physical activity FP 2 =  $\log\left(\frac{Overall\ activity}{10}\right)$

**Table 10C SCORE2 AND SCORE2 +PA risk scores with Cholesterol and systolic blood pressure derived from primary care records**

| Risk factor                                                       | Beta Estimate   | Standard Error | p-value    |
|-------------------------------------------------------------------|-----------------|----------------|------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9371967</b>    |                 |                |            |
| Age                                                               | 0.395613301     | 0.28576362     | 0.20278612 |
| Systolic blood pressure                                           | -0.050371507    | 0.45346079     | 0.91375478 |
| Total Cholesterol                                                 | 0.260814133     | 0.26397425     | 0.33064619 |
| HDL cholesterol                                                   | -0.218786914    | 0.41064514     | 0.60270007 |
| Diabetes                                                          | 1.962982977     | 0.93068472     | 0.03505396 |
| Smoker (yes/no)                                                   | 1.054687960     | 0.60610385     | 0.08196228 |
| Age * smoker                                                      | -0.060678480    | 0.04657509     | 0.19275981 |
| Age * Diabetes                                                    | -0.098591726    | 0.06843886     | 0.14985699 |
| Age * Systolic blood pressure                                     | 0.012885942     | 0.03586682     | 0.72778850 |
| Age * Cholesterol                                                 | -0.021296429    | 0.01927891     | 0.27630693 |
| Age * HDL Cholesterol                                             | 0.002507962     | 0.03165104     | 0.93810918 |
| <b>Recalibrated SCORE2+PA Male: Baseline survival = 0.9351460</b> |                 |                |            |
| Daily step count FP 1                                             | -5.3009443e-05  | 7.3179914e-05  | 0.468904   |
| Hours of Moderate-to-Vigorous-Activity FP 1                       | -1.67225625285  | 1.40184257719  | 0.233021   |
| Hours of Moderate-to-Vigorous-Activity FP 2                       | 0.993241063096  | 0.956881505938 | 0.299371   |
| Hours of Light intensity Activity FP1                             | 0.037221856927  | 2.13021312307  | 0.986061   |
| Hours of Sedentary behaviour FP 1                                 | 0.153806595348  | 0.455189065146 | 0.735471   |
| Overall Physical activity FP1                                     | 12.2288230979   | 10.4345768829  | 0.241346   |
| Overall Physical activity FP2                                     | -3.89560305585  | 3.3355953961   | 0.242977   |
| Age                                                               | 1.59387184639   | 0.890516973146 | 0.0748053  |
| Systolic blood pressure                                           | -0.014074130649 | 0.438035322721 | 0.974953   |
| Total Cholesterol                                                 | 0.261108455282  | 0.260724546149 | 0.32387    |
| HDL cholesterol                                                   | -0.192648018454 | 0.426507615233 | 0.659138   |
| Diabetes                                                          | 1.97401208482   | 0.936374287044 | 0.035152   |
| Smoker (yes/no)                                                   | 1.07630726168   | 0.602898179305 | 0.0743473  |

|                                                                      |                 |                |               |
|----------------------------------------------------------------------|-----------------|----------------|---------------|
| Age * smoker                                                         | -0.067495150239 | 0.046307798068 | 0.145096      |
| Age * Diabetes                                                       | -0.107288694259 | 0.068844927316 | 0.1193        |
| Age * Systolic blood pressure                                        | 0.009294910312  | 0.034704332172 | 0.794574      |
| Age * Cholesterol                                                    | -0.020967611206 | 0.019062800921 | 0.278052      |
| Age * HDL Cholesterol                                                | 0.003274573536  | 0.032860288649 | 0.922335      |
| Age * Daily step count FP 1                                          | 3.639254e-06    | 4.891296e-06   | 0.456929      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1                    | 0.09165889385   | 0.103501756363 | 0.375929      |
| Age * Hours of Moderate-to-Vigorous-Activity FP 2                    | -0.055388897224 | 0.071200062782 | 0.436682      |
| Age * Hours of Light intensity Activity FP 1                         | 0.048524863682  | 0.160490827643 | 0.762411      |
| Age * Hours of Sedentary behaviour FP 1                              | -0.001536554079 | 0.033964151976 | 0.963919      |
| Age * Overall Physical activity FP 1                                 | -1.16774486286  | 0.776676259783 | 0.132857      |
| Age * Overall Physical activity FP 2                                 | 0.36222992087   | 0.249190192167 | 0.146194      |
| Age * Overall activity                                               | -0.00157682357  | 0.003047017322 | 0.60485552    |
| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9738397</b>     |                 |                |               |
| Age                                                                  | 0.800777485     | 0.25878352     | 0.00413502487 |
| Systolic blood pressure                                              | 0.587924474     | 0.53606164     | 0.29405479281 |
| Total Cholesterol                                                    | 0.296078600     | 0.49116187     | 0.56288436948 |
| HDL cholesterol                                                      | -0.272439805    | 0.38084776     | 0.48192743842 |
| Diabetes                                                             | 5.194251264     | 1.17842863     | 0.00001617429 |
| Smoker (yes/no)                                                      | 0.279218742     | 0.86619084     | 0.74722676742 |
| Age * smoker                                                         | 0.020453792     | 0.06637328     | 0.75799740747 |
| Age * Diabetes                                                       | -0.302415910    | 0.08899951     | 0.00082716701 |
| Age * Systolic blood pressure                                        | -0.034385830    | 0.03830769     | 0.38435188390 |
| Age * Cholesterol                                                    | -0.021747291    | 0.03811491     | 0.58451778565 |
| Age * HDL Cholesterol                                                | 0.007857153     | 0.02671519     | 0.77054571566 |
| <b>Recalibrated SCORE2 +PA Female: Baseline survival = 0.9746997</b> |                 |                |               |
| Daily step count FP 1                                                | -0.3381940183   | 0.327264644    | 0.301572      |
| Daily step count FP 2                                                | 1.4623411857    | 1.895070994    | 0.440431      |



|                                                   |               |             |             |
|---------------------------------------------------|---------------|-------------|-------------|
| Hours of Moderate-to-Vigorous-Activity FP 1       | -0.6869161992 | 3.231961895 | 0.831714    |
| Hours of Moderate-to-Vigorous-Activity FP 2       | 0.7282267068  | 2.464946701 | 0.767701    |
| Hours of Light intensity Activity FP1             | 0.0005070881  | 0.048085791 | 0.991587    |
| Hours of Light intensity Activity FP2             | 1.053154297   | 2.391163782 | 0.659681    |
| Hours of Sedentary behaviour FP 1                 | -0.028525189  | 2.296219572 | 0.99009     |
| Overall Physical activity FP1                     | -2.6058792828 | 1.97172953  | 0.186494    |
| Age                                               | 0.5048737137  | 0.42414266  | 0.235239    |
| Systolic blood pressure                           | 0.5268557173  | 0.540977271 | 0.349316    |
| Total Cholesterol                                 | 0.2844833112  | 0.473015978 | 0.56295     |
| HDL cholesterol                                   | -0.152259194  | 0.393646056 | 0.703028    |
| Diabetes                                          | 4.7941337649  | 1.172036268 | 5.32063e-05 |
| Smoker (yes/no)                                   | 0.1267154817  | 0.874482612 | 0.884805    |
| Age * smoker                                      | 0.0228055384  | 0.067005848 | 0.733636    |
| Age * Diabetes                                    | -0.28853473   | 0.088385541 | 0.00122634  |
| Age * Systolic blood pressure                     | -0.0313908527 | 0.0388048   | 0.432221    |
| Age * Cholesterol                                 | -0.0204424414 | 0.036682745 | 0.592399    |
| Age * HDL Cholesterol                             | 0.001978061   | 0.027639272 | 0.943457    |
| Age * Daily step count FP 1                       | 0.0197390979  | 0.022737068 | 0.385443    |
| Age * Daily step count FP 2                       | -0.0625317528 | 0.136225201 | 0.646272    |
| Age * Hours of Moderate-to-Vigorous-Activity FP 1 | 0.0021534637  | 0.241564764 | 0.992888    |
| Age * Hours of Moderate-to-Vigorous-Activity FP 2 | -0.0243652386 | 0.186125954 | 0.895865    |
| Age * Hours of Light intensity Activity FP1       | -0.0005789229 | 0.003744116 | 0.877139    |
| Age * Hours of Light intensity Activity FP2       | 0.0113926748  | 0.179014895 | 0.949264    |
| Age * Hours of Sedentary behaviour FP 1           | 0.0790870847  | 0.171720393 | 0.645178    |
| Age * Overall Physical activity FP1               | 0.1304551266  | 0.148187433 | 0.378814    |

Abbreviations: FP= Fractional polynomial, , BMI = Body mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

Fractional polynomial (males) = Daily step count FP 1 =  $\left(\frac{\text{Daily step count}}{10000}\right)^{-2}$ ; Hours of Moderate-to-Vigorous-Activity FP 1 =  $\text{Hours of MVPA}^{0.5}$ ; Hours of Moderate-to-Vigorous-Activity FP 2 =  $(\text{Hours of MVPA}^{0.5} \times \log(\text{Hours of MVPA}))$ ; Hours of Light intensity Activity FP1 =

$$\begin{aligned}
& \frac{\text{Hours of LPA}}{10} ; \text{Hours of Sedentary behaviour FP 1} = \frac{\text{Hours of SBA}^3}{10} ; \text{Overall Physical activity FP1} = \\
& \frac{\text{Overall activity}^{0.5}}{10} ; \text{Overall Physical activity FP2} = \log\left(\left(\frac{\text{Overall activity}}{10}\right)^{0.5}\right) \times \log\left(\frac{\text{Overall activity}}{10}\right) \\
& \text{Fractional polynomial (females)} = \text{Daily step count FP 1} \left(\frac{\text{Daily step count}}{10000}\right)^{-1} ; \text{Daily step count FP 2} \\
& = \left(\frac{\text{Daily step count}}{10000}\right)^{-0.5} ; \text{Hours of Moderate-to-Vigorous-Activity FP 1} = (\text{Hours of MVPA})^{0.5} ; \text{Hours of} \\
& \text{Moderate-to-Vigorous-Activity FP 2} = \text{Hours of MVPA} ; \text{Hours of Light intensity Activity FP1} = \\
& \left(\frac{\text{Hours of LPA}}{10}\right)^{-2} ; \text{Light intensity Activity FP1} = \left(\frac{\text{Hours of LPA}}{10}\right)^2 ; \text{Hours of Sedentary behaviour FP 1} = \\
& \frac{\text{Hours of SBA}}{10} ; \text{Overall Physical activity FP1} = \left(\frac{\text{Overall activity}}{10}\right)^{0.5}
\end{aligned}$$

## Chapter 7AHS risk scores

**Table 11c QRISK3 AND QRISK3 +AHS models**

| Risk factor                                                    | Beta Estimate | Standard Error | p-value      |
|----------------------------------------------------------------|---------------|----------------|--------------|
| <b>Recalibrated Qrisk3 Male: Baseline survival = 0.9424133</b> |               |                |              |
| Age FP 1                                                       | -56.77482     | 78.58057       | 0.4700513    |
| Age FP 2                                                       | -0.002644386  | 0.01673324     | 0.8744443    |
| BMI FP 1                                                       | -19.21211     | 99.51742       | 0.8469333    |
| BMI FP 2                                                       | 45.90422      | 206.3809       | 0.8240013    |
| Diabetes                                                       | -3.699177     | 4.597418       | 0.4211154    |
| Hypertension                                                   | -0.6778716    | 2.88269        | 0.8141094    |
| Systolic blood pressure                                        | -0.09618775   | 0.05965683     | 0.1070099    |
| Townsend deprivation index                                     | -0.008903207  | 0.322748       | 0.9779948    |
| HDL cholesterol ratio                                          | 0.08628676    | 0.01925039     | 9.83546e-06  |
| Corticosteroid treatment                                       | -8.095977     | 5.43858        | 0.1367119    |
| Atrial fibrillation and flutter                                | -4.235466     | 4.598495       | 0.3571094    |
| SBP5                                                           | -0.0005026096 | 0.004799382    | 0.916706     |
| Ethnicity (non-white)                                          | 0.2713731     | 0.1213815      | 0.02545921   |
| Previous smoker                                                | 0.1032722     | 0.04247627     | 0.01511493   |
| Current smoker                                                 | 0.2958256     | 0.07218207     | 4.293337e-05 |
| Age FP 1 * Hypertension                                        | 5.439007      | 13.85478       | 0.6946681    |
| Age FP 1 * Diabetes                                            | 20.38215      | 21.93804       | 0.3529385    |
| Age FP 1 * BMI FP 1                                            | 139.9576      | 459.1884       | 0.7605488    |
| Age FP 1 * BMI FP 2                                            | -348.1360     | 951.9979       | 0.7146273    |
| Age FP 1 * Townsend deprivation index                          | -0.1368236    | 1.502665       | 0.9274569    |
| Age FP 1 * Systolic blood pressure                             | 0.5218652     | 0.2824901      | 0.06480914   |
| Age FP 1 * Corticosteroid treatment                            | 37.11115      | 25.57641       | 0.146906     |
| Age FP 1 * Atrial fibrillation and flutter                     | 27.89499      | 22.12244       | 0.2074476    |
| Age FP 2 * Hypertension                                        | 0.0006570869  | 0.002640142    | 0.8034713    |
| Age FP 2 * Diabetes                                            | 0.003270103   | 0.004266611    | 0.443487     |

|                                                                      |               |              |              |
|----------------------------------------------------------------------|---------------|--------------|--------------|
| Age FP 2 * BMI FP 1                                                  | 0.01998960    | 0.1001417    | 0.8417993    |
| Age FP 2 * BMI FP 2                                                  | -0.05014445   | 0.2082664    | 0.8097524    |
| Age FP 2 * Townsend deprivation index                                | 0.0001882637  | 0.0003179184 | 0.5537854    |
| Age FP 2 * Systolic blood pressure                                   | 0.00007443066 | 5.661752e-05 | 0.1887556    |
| Age FP 2 * Corticosteroid treatment                                  | 0.00279488    | 0.004176856  | 0.5034703    |
| Age FP 2 * Atrial fibrillation and flutter                           | 0.007.741842  | 0.005128592  | 0.1312841    |
| <b>Recalibrated QRISK3 + AHS male: Baseline survival = 0.9429463</b> |               |              |              |
| AHS FP 1                                                             | -1.262525     | 0.910564     | 0.1657069    |
| AHS FP 2                                                             | 0.1447946     | 0.1693349    | 0.3925886    |
| Age FP 1                                                             | -103.0684     | 80.85107     | 0.2025       |
| Age FP 2                                                             | -0.01362402   | 0.01704807   | 0.4242766    |
| BMI FP 1                                                             | -12.61182     | 101.0617     | 0.9006972    |
| BMI FP 2                                                             | 3.147284      | 209.5423     | 0.9880176    |
| Diabetes                                                             | -2.8161       | 4.668654     | 0.546435     |
| Hypertension                                                         | 1.322518      | 2.966919     | 0.6558125    |
| Systolic Blood Pressure                                              | -0.07892785   | 0.06059638   | 0.192858     |
| Townsend Deprivation Index                                           | 0.05190438    | 0.3243343    | 0.8728674    |
| HDL Cholesterol Ratio                                                | 0.08194601    | 0.01918407   | 2.428892e-05 |
| Corticosteroid Treatment                                             | -7.205861     | 5.444819     | 0.1858105    |
| Atrial Fibrillation and Flutter                                      | -3.843338     | 4.663123     | 0.4099045    |
| SBP5                                                                 | -0.000647387  | 0.00480612   | 0.8929971    |
| Ethnicity (non-white)                                                | 0.2792652     | 0.1214812    | 0.02159666   |
| Previous Smoker                                                      | 0.09235163    | 0.0425479    | 0.0300605    |
| Current Smoker                                                       | 0.2300826     | 0.07293554   | 0.001626267  |
| Age FP 1 * Hypertension                                              | -4.090002     | 14.28745     | 0.7746983    |
| Age FP 1 * Diabetes                                                  | 15.98132      | 22.32738     | 0.4741989    |
| Age FP 1 * BMI FP 1                                                  | 102.1311      | 468.4899     | 0.8274463    |
| Age FP 1 * BMI FP 2                                                  | -128.9685     | 970.8372     | 0.8943285    |
| Age FP 1 * Townsend Deprivation Index                                | -0.4357557    | 1.514454     | 0.773576     |
| Age FP 1 * Systolic Blood Pressure                                   | 0.4401508     | 0.2873133    | 0.1256588    |

|                                                                  |               |              |              |
|------------------------------------------------------------------|---------------|--------------|--------------|
| Age FP 1 * Atrial Fibrillation and Flutter                       | 26.06667      | 22.47063     | 0.246145     |
| Age FP 1 * Corticosteroid Treatment                              | 33.07595      | 25.66854     | 0.1976622    |
| Age FP 2 * Hypertension                                          | -0.001295034  | 0.002702831  | 0.6318805    |
| Age FP 2 * Diabetes                                              | 0.002378523   | 0.004306758  | 0.5808082    |
| Age FP 2 * BMI FP 1                                              | 0.01016785    | 0.100442     | 0.9193751    |
| Age FP 2 * BMI FP 2                                              | 0.00226276    | 0.2090379    | 0.9913642    |
| Age FP 2 * Townsend Deprivation Index                            | 0.0001277953  | 0.0003171881 | 0.6870554    |
| Age FP 2 * Systolic Blood Pressure                               | 5.84186e-05   | 5.727576e-05 | 0.3078481    |
| Age FP 2 * Atrial Fibrillation and Flutter                       | 0.002286301   | 0.004216214  | 0.5876844    |
| Age FP 2 * Corticosteroid Treatment                              | 0.006792923   | 0.005105236  | 0.1834472    |
| AHS FP 1* Age FP 1                                               | 5.779181      | 4.319382     | 0.1810281    |
| AHS FP 2* Age FP 1                                               | -0.614        | 0.8155492    | 0.4515999    |
| AHS FP 1* Age FP 2                                               | 0.001167484   | 0.0008670773 | 0.1782749    |
| AHS FP 2* Age FP 2                                               | -0.0001354347 | 0.0001551352 | 0.38274      |
| <b>Recalibrated QRISK3 female: Baseline survival = 0.9779264</b> |               |              |              |
| Age FP 1                                                         | -93.1658      | 314.444      | 0.7670485    |
| Age FP 2                                                         | 0.2524785     | 2.66245      | 0.9244621    |
| BMI FP 1                                                         | 56.67664      | 145.593      | 0.6971191    |
| BMI FP 2                                                         | -47.93047     | 299.041      | 0.87268      |
| Diabetes                                                         | 5.458594      | 8.453192     | 0.518537     |
| Hypertension                                                     | 0.1255367     | 4.718109     | 0.9787761    |
| Systolic blood pressure                                          | -0.06271675   | 0.09764105   | 0.5207566    |
| Townsend deprivation index                                       | 0.4525676     | 0.6027354    | 0.4528481    |
| HDL cholesterol ratio                                            | 0.1190057     | 0.0264539    | 1.062116e-05 |
| Corticosteroid treatment                                         | 11.24021      | 11.68416     | 0.3361908    |
| Atrial fibrillation and flutter                                  | 84.39221      | 29.12781     | 0.003814328  |
| SBP5                                                             | 0.002527548   | 0.005214641  | 0.6280038    |
| Ethnicity (non-white)                                            | 0.1171228     | 0.1536404    | 0.445986     |
| Previous smoker                                                  | 0.1466895     | 0.05253854   | 0.005299324  |
| Current smoker                                                   | 0.6147396     | 0.09521379   | 1.413658e-10 |

|                                                                       |             |            |              |
|-----------------------------------------------------------------------|-------------|------------|--------------|
| Age FP 1 * Hypertension                                               | 38.83175    | 61.2321    | 0.5260572    |
| Age FP 1 * Diabetes                                                   | -43.09216   | 108.4976   | 0.6912933    |
| Age FP 1 * BMI FP 1                                                   | -960.4898   | 1864.91    | 0.6066003    |
| Age FP 1 * BMI FP 2                                                   | 693.6023    | 3773.575   | 0.8541893    |
| Age FP 1 * Townsend deprivation index                                 | -5.577697   | 7.584023   | 0.4621697    |
| Age FP 1 * Systolic blood pressure                                    | 1.093757    | 1.269019   | 0.3888744    |
| Age FP 1 * Corticosteroid treatment                                   | -1272.353   | 455.3552   | 0.005264069  |
| Age FP 1 * Atrial fibrillation and flutter                            | -138.4962   | 155.982    | 0.3747268    |
| Age FP 2 * Hypertension                                               | -0.06330769 | 0.4972201  | 0.8987003    |
| Age FP 2 * Diabetes                                                   | -0.5651539  | 0.895237   | 0.5279402    |
| Age FP 2 * BMI FP 1                                                   | -5.114071   | 15.45496   | 0.7407616    |
| Age FP 2 * BMI FP 2                                                   | 3.788746    | 31.94706   | 0.9056113    |
| Age FP 2 * Townsend deprivation index                                 | -0.04616536 | 0.06439067 | 0.4735037    |
| Age FP 2 * Systolic blood pressure                                    | 0.006883127 | 0.01029191 | 0.5037246    |
| Age FP 2 * Corticosteroid treatment                                   | -8.141268   | 2.829043   | 0.004057723  |
| Age FP 2 * Atrial fibrillation and flutter                            | -1.235439   | 1.217932   | 0.3105557    |
| <b>Recalibrated QRISK3 +AHS female: Baseline survival = 0.9783053</b> |             |            |              |
| AHS FP 1                                                              | -25.02217   | 22.5224    | 0.2667376    |
| AHS FP 2                                                              | 13.33428    | 10.23576   | 0.1928577    |
| Age FP 1                                                              | -486.7979   | 499.6358   | 0.3300507    |
| Age FP 2                                                              | -2.477161   | 4.345774   | 0.568746     |
| BMI FP 1                                                              | 33.72412    | 146.9872   | 0.8185592    |
| BMI FP 2                                                              | 22.79171    | 301.5171   | 0.9397546    |
| Diabetes                                                              | 4.10823     | 8.44734    | 0.6267964    |
| Hypertension                                                          | 0.2684105   | 4.699978   | 0.9544655    |
| Systolic Blood Pressure                                               | -0.07786943 | 0.09900118 | 0.4316605    |
| Townsend Deprivation Index                                            | 0.4535904   | 0.6032603  | 0.4522218    |
| HDL Cholesterol Ratio                                                 | 0.11677     | 0.02669825 | 2.005007e-05 |
| Corticosteroid Treatment                                              | 11.19157    | 11.68882   | 0.338479     |
| Atrial Fibrillation and Flutter                                       | 78.59708    | 28.98438   | 0.006764774  |

|                                            |             |             |              |
|--------------------------------------------|-------------|-------------|--------------|
| SBP5                                       | 0.002177959 | 0.005269584 | 0.6795154    |
| Ethnicity (non-white)                      | 0.125353    | 0.1537612   | 0.4150578    |
| Previous Smoker                            | 0.1363152   | 0.05257652  | 0.009608731  |
| Current Smoker                             | 0.5011005   | 0.09610171  | 2.085279e-07 |
| Age FP 1 * Hypertension                    | 37.44565    | 60.83662    | 0.5383035    |
| Age FP 1 * Diabetes                        | -24.83263   | 108.0726    | 0.8182939    |
| Age FP 1 * BMI FP 1                        | -638.1811   | 1878.596    | 0.7341178    |
| Age FP 1 * BMI FP 2                        | -296.3068   | 3794.097    | 0.9377607    |
| Age FP 1 * Townsend Deprivation Index      | -5.574978   | 7.5714      | 0.4616425    |
| Age FP 1 * Systolic Blood Pressure         | 1.291039    | 1.28236     | 0.314197     |
| Age FP 1 * Atrial Fibrillation and Flutter | -1191.22    | 452.2763    | 0.008523333  |
| Age FP 1 * Corticosteroid Treatment        | -136.7055   | 155.7217    | 0.3801376    |
| Age FP 2 * Hypertension                    | -0.08869932 | 0.4959129   | 0.8580695    |
| Age FP 2 * Diabetes                        | -0.4423753  | 0.8958998   | 0.6215305    |
| Age FP 2 * BMI FP 1                        | -3.046638   | 15.61875    | 0.8453682    |
| Age FP 2 * BMI FP 2                        | -2.281389   | 32.25246    | 0.9436171    |
| Age FP 2 * Townsend Deprivation Index      | -0.04643554 | 0.06451747  | 0.4717917    |
| Age FP 2 * Systolic Blood Pressure         | 0.008431048 | 0.01044884  | 0.4198498    |
| Age FP 2 * Atrial Fibrillation and Flutter | -7.557339   | 2.817591    | 0.007388563  |
| Age FP 2 * Corticosteroid Treatment        | -1.235063   | 1.219557    | 0.311348     |
| AHS FP 1* Age FP 1                         | 360.2526    | 281.6321    | 0.2010241    |
| AHS FP 2* Age FP 1                         | -189.1073   | 130.1486    | 0.1464147    |
| AHS FP 1* Age FP 2                         | 2.32593     | 2.425211    | 0.3376704    |
| AHS FP 2* Age FP 2                         | -1.243433   | 1.094044    | 0.2558959    |

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

Age FP 1 (males) =  $(age/10)^{-1}$

Age FP 2 (males) =  $(age/10)^3$

BMI FP 1 (males) =  $(BMI/10)^{-2}$ ,

BMI FP 2 (males) =  $(BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$ ,

AHS FP 1 (males) =  $(AHS/0.1)^2$

AHS FP 2 (males) =  $(AHS/0.1)^3$

Age FP 1 (Females) =  $age/10^{-2}$

Age FP 2 (Females) =  $age/10$

$$\text{BMI FP 1 (Females)} = (BMI/10)^{-2}$$

$$\text{BMI FP 2 (Females)} = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right)$$

$$\text{AHS FP 1 (Females)} = (AHS/0.1)^1$$

$$\text{AHS FP2 (Females)} = (AHS/0.1)^1 \times \text{Log} (AHS/0.1)$$



**Table 12C QRISK3 and QRISK3 + AHS Models (Excluding Systolic Blood Pressure and HDL Cholesterol Ratio)**

| Risk factor                                                                                              | Beta Estimate | Standard Error | p-value      |
|----------------------------------------------------------------------------------------------------------|---------------|----------------|--------------|
| <b>Recalibrated QRISK3 (Excluding SBP and HDL cholesterol ratio) Male: Baseline survival = 0.8992529</b> |               |                |              |
| Age FP 1                                                                                                 | 25.34249      | 67.81412       | 0.7086549    |
| Age FP 2                                                                                                 | 0.008862884   | 0.01491291     | 0.552358     |
| BMI FP 1                                                                                                 | -21.23174     | 100.1766       | 0.8321685    |
| BMI FP 2                                                                                                 | 64.44369      | 207.3385       | 0.7559676    |
| Diabetes                                                                                                 | -3.1915       | 4.572229       | 0.4852301    |
| Hypertension                                                                                             | -1.800513     | 2.825711       | 0.5240589    |
| Townsend deprivation index                                                                               | -0.002984485  | 0.3211756      | 0.9925866    |
| Corticosteroid treatment                                                                                 | -8.195104     | 5.392726       | 0.1287211    |
| Atrial fibrillation and flutter                                                                          | -4.143749     | 4.485806       | 0.3557057    |
| Ethnicity (non-white)                                                                                    | 0.2529174     | 0.1213558      | 0.03725274   |
| Previous smoker                                                                                          | 0.1024216     | 0.04240022     | 0.0157805    |
| Current smoker                                                                                           | 0.3081793     | 0.07201979     | 1.946269e-05 |
| Age FP 1 * Hypertension                                                                                  | 11.36246      | 13.58685       | 0.4030737    |
| Age FP 1 * Diabetes                                                                                      | 17.32254      | 21.82108       | 0.4273608    |
| Age FP 1 * BMI FP 1                                                                                      | 137.229       | 462.096        | 0.7665132    |
| Age FP 1 * BMI FP 2                                                                                      | -433.8208     | 956.1079       | 0.6500576    |
| Age FP 1 * Townsend deprivation index                                                                    | -0.1687687    | 1.49423        | 0.9100815    |
| Age FP 1 * Corticosteroid treatment                                                                      | 27.29179      | 21.55147       | 0.2055024    |
| Age FP 1 * Atrial fibrillation and flutter                                                               | 37.53706      | 25.34122       | 0.1386599    |
| Age FP 2 * Hypertension                                                                                  | 0.001494218   | 0.002586745    | 0.5635556    |
| Age FP 2 * Diabetes                                                                                      | 0.002956799   | 0.004243237    | 0.4859758    |
| Age FP 2 * BMI FP 1                                                                                      | 0.02219593    | 0.1009155      | 0.8259311    |
| Age FP 2 * BMI FP 2                                                                                      | -0.06329915   | 0.2094737      | 0.7625382    |
| Age FP 2 * Townsend deprivation index                                                                    | 0.0001805627  | 0.0003169837   | 0.5689805    |
| Age FP 2 * Corticosteroid treatment                                                                      | 0.002683165   | 0.00409197     | 0.5120671    |
| Age FP 2 * Atrial fibrillation and flutter                                                               | 0.00788887    | 0.00509638     | 0.1217622    |

| <b>Recalibrated QRISK3 (Excluding SBP and HDL cholesterol ratio) +AHS Male: Baseline survival = 0.9271013</b> |               |              |              |
|---------------------------------------------------------------------------------------------------------------|---------------|--------------|--------------|
| AHS FP 1                                                                                                      | -0.08795293   | 0.03086587   | 0.004413795  |
| Age FP 1                                                                                                      | -16.22416     | 69.69706     | 0.8159501435 |
| Age FP 2                                                                                                      | -0.0009568349 | 0.01507394   | 0.949392382  |
| BMI FP 1                                                                                                      | -5.750122     | 101.0132     | 0.9546098868 |
| BMI FP 2                                                                                                      | 7.396736      | 209.3088     | 0.971812327  |
| Diabetes                                                                                                      | -2.21214      | 4.632149     | 0.6330031434 |
| Hypertension                                                                                                  | 0.2892044     | 2.920592     | 0.921128203  |
| Townsend Deprivation Index                                                                                    | 0.06050956    | 0.3212408    | 0.8506079255 |
| Corticosteroid Treatment                                                                                      | -6.949099     | 5.378665     | 0.1964834959 |
| Atrial Fibrillation and Flutter                                                                               | -3.817227     | 4.565867     | 0.4032136175 |
| Ethnicity (non-white)                                                                                         | 0.2599041     | 0.1213892    | 0.0323640078 |
| Previous Smoker                                                                                               | 0.09165071    | 0.04245621   | 0.0309668626 |
| Current Smoker                                                                                                | 0.2398177     | 0.07266899   | 0.0009797848 |
| Age FP 1 * Hypertension                                                                                       | 1.408412      | 14.07215     | 0.9202847219 |
| Age FP 1 * Diabetes                                                                                           | 12.421        | 22.16115     | 0.5751984089 |
| Age FP 1 * BMI FP 1                                                                                           | 58.13319      | 468.2264     | 0.9012015176 |
| Age FP 1 * BMI FP 2                                                                                           | -146.0392     | 969.8538     | 0.8803201983 |
| Age FP 1 * Townsend Deprivation Index                                                                         | -0.4800643    | 1.499153     | 0.7488250887 |
| Age FP 1 * Atrial Fibrillation and Flutter                                                                    | 25.79449      | 21.98974     | 0.2408962811 |
| Age FP 1 * Corticosteroid Treatment                                                                           | 31.86416      | 25.33981     | 0.2086975954 |
| Age FP 2 * Hypertension                                                                                       | -0.0005454925 | 0.002658174  | 0.8374219855 |
| Age FP 2 * Diabetes                                                                                           | 0.002012317   | 0.004270516  | 0.6375304163 |
| Age FP 2 * BMI FP 1                                                                                           | 0.004840008   | 0.1004919    | 0.9615900178 |
| Age FP 2 * BMI FP 2                                                                                           | 0.000603766   | 0.2088954    | 0.9976941214 |
| Age FP 2 * Townsend Deprivation Index                                                                         | 0.0001190059  | 0.0003146203 | 0.7052746667 |
| Age FP 2 * Atrial Fibrillation and Flutter                                                                    | 0.002229597   | 0.004137594  | 0.5900285519 |
| Age FP 2 * Corticosteroid Treatment                                                                           | 0.006591505   | 0.005054327  | 0.192307073  |
| AHS FP 1* Age FP 1                                                                                            | 0.454483      | 0.1509018    | 0.0026228251 |
| AHS FP 1* Age FP 2                                                                                            | 7.983195e-05  | 2.708237e-05 | 0.003230174  |

| <b>Recalibrated QRISK3QRISK3 (Excluding SBP and HDL cholesterol ratio) Female:<br/>Baseline survival = 0.9944228</b> |             |            |              |
|----------------------------------------------------------------------------------------------------------------------|-------------|------------|--------------|
| Age FP 1                                                                                                             | 39.23474    | 261.2051   | 0.8806202    |
| Age FP 2                                                                                                             | 0.951963    | 2.263636   | 0.6741422    |
| BMI FP 1                                                                                                             | 68.14422    | 145.9194   | 0.6405632    |
| BMI FP 2                                                                                                             | -73.40675   | 299.1163   | 0.8061683    |
| Diabetes                                                                                                             | 5.885214    | 8.408659   | 0.4840903    |
| Hypertension                                                                                                         | -0.624906   | 4.573022   | 0.8913239    |
| Townsend deprivation index                                                                                           | 0.4177818   | 0.5981657  | 0.485003     |
| Corticosteroid treatment                                                                                             | 11.85971    | 11.56158   | 0.3051449    |
| Atrial fibrillation and flutter                                                                                      | 85.28102    | 29.52409   | 0.003921738  |
| Ethnicity (non-white)                                                                                                | 0.1151518   | 0.1533353  | 0.452776     |
| Previous smoker                                                                                                      | 0.1325706   | 0.05249777 | 0.01165582   |
| Current smoker                                                                                                       | 0.620271    | 0.09484542 | 8.235417e-11 |
| Age FP 1 * Hypertension                                                                                              | 54.01479    | 59.24033   | 0.3620139    |
| Age FP 1 * Diabetes                                                                                                  | -49.21931   | 107.9331   | 0.6484389    |
| Age FP 1 * BMI FP 1                                                                                                  | -1088.119   | 1869.657   | 0.5606551    |
| Age FP 1 * BMI FP 2                                                                                                  | 859.1152    | 3775.435   | 0.8200216    |
| Age FP 1 * Townsend deprivation index                                                                                | -5.220192   | 7.518128   | 0.4875636    |
| Age FP 1 * Corticosteroid treatment                                                                                  | -1293.453   | 462.0676   | 0.005182223  |
| Age FP 1 * Atrial fibrillation and flutter                                                                           | -146.5817   | 154.053    | 0.3414911    |
| Age FP 2 * Hypertension                                                                                              | 0.007372737 | 0.4822839  | 0.987805     |
| Age FP 2 * Diabetes                                                                                                  | -0.6173629  | 0.890545   | 0.4882568    |
| Age FP 2 * BMI FP 1                                                                                                  | -6.568543   | 15.48801   | 0.6715454    |
| Age FP 2 * BMI FP 2                                                                                                  | 7.002245    | 31.9527    | 0.8265653    |
| Age FP 2 * Townsend deprivation index                                                                                | -0.04255786 | 0.06393527 | 0.5057358    |
| Age FP 2 * Corticosteroid treatment                                                                                  | -8.211296   | 2.865844   | 0.00422059   |
| Age FP 2 * Atrial fibrillation and flutter                                                                           | -1.29833    | 1.206335   | 0.2819705    |
| <b>Recalibrated QRISK3(Excluding SBP and HDL cholesterol ratio) + AHS Female:<br/>Baseline survival = 0.9940752</b>  |             |            |              |
| AHS FP 1                                                                                                             | -93.57982   | 71.54815   | 0.1910832    |

|                                            |             |            |              |
|--------------------------------------------|-------------|------------|--------------|
| AHS FP 2                                   | 30.13168    | 20.02133   | 0.1325243    |
| Age FP 1                                   | -896.0604   | 818.1576   | 0.273584     |
| Age FP 2                                   | -5.342855   | 7.187926   | 0.4574019    |
| BMI FP 1                                   | 44.81586    | 147.1349   | 0.7607173    |
| BMI FP 2                                   | 0.542376    | 301.3153   | 0.998564     |
| Diabetes                                   | 4.528645    | 8.390098   | 0.5894362    |
| Hypertension                               | -0.6883054  | 4.58342    | 0.8806469    |
| Townsend Deprivation Index                 | 0.4258163   | 0.5988271  | 0.4771346    |
| Corticosteroid Treatment                   | 12.05122    | 11.57558   | 0.297989     |
| Atrial Fibrillation and Flutter            | 79.86957    | 29.46868   | 0.006792663  |
| Ethnicity (non-white)                      | 0.1297446   | 0.1534811  | 0.3980459    |
| Previous Smoker                            | 0.1220499   | 0.05252073 | 0.02025734   |
| Current Smoker                             | 0.5061806   | 0.09567283 | 1.385835e-07 |
| Age FP 1 * Hypertension                    | 55.06952    | 59.19698   | 0.3523668    |
| Age FP 1 * Diabetes                        | -30.9216    | 107.2912   | 0.7732285    |
| Age FP 1 * BMI FP 1                        | -765.6506   | 1881.291   | 0.6840754    |
| Age FP 1 * BMI FP 2                        | -160.247    | 3793.724   | 0.9663126    |
| Age FP 1 * Townsend Deprivation Index      | -5.315082   | 7.50567    | 0.4789588    |
| Age FP 1 * Atrial Fibrillation and Flutter | -1218.188   | 460.4151   | 0.008227435  |
| Age FP 1 * Corticosteroid Treatment        | -147.8166   | 153.8916   | 0.3369346    |
| Age FP 2 * Hypertension                    | 0.003604652 | 0.4840115  | 0.9940588    |
| Age FP 2 * Diabetes                        | -0.4937876  | 0.8900364  | 0.5791116    |
| Age FP 2 * BMI FP 1                        | -4.438352   | 15.6322    | 0.7765052    |
| Age FP 2 * BMI FP 2                        | 0.5661491   | 32.2253    | 0.9859853    |
| Age FP 2 * Townsend Deprivation Index      | -0.04354342 | 0.06408148 | 0.4969176    |
| Age FP 2 * Atrial Fibrillation and Flutter | -7.664599   | 2.862762   | 0.007495683  |
| Age FP 2 * Corticosteroid Treatment        | -1.323678   | 1.209017   | 0.2737501    |
| AHS FP 1* Age FP 1                         | 1323.154    | 898.3037   | 0.1409593    |
| AHS FP 2* Age FP 1                         | -420.8221   | 256.1456   | 0.1005971    |
| AHS FP 1* Age FP 2                         | 8.741423    | 7.695327   | 0.2561498    |

|                    |           |          |           |
|--------------------|-----------|----------|-----------|
| AHS FP 2* Age FP 2 | -2.819368 | 2.134867 | 0.1868112 |
|--------------------|-----------|----------|-----------|

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Boday mass index

$$\text{Age FP 1 (males)} = (age/10)^{-1},$$

$$\text{Age FP 2 (males)} = (age/10)^3,$$

$$\text{BMI FP 1 (males)} = (BMI/10)^{-2},$$

$$\text{BMI FP 2 (males)} = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right),$$

$$\text{AHS FP 1 (males)} = (AHS/0.1)^3$$

$$\text{Age FP 1 (Females)} = age/10^{-2},$$

$$\text{Age FP 2 (Females)} = age/10,$$

$$\text{BMI FP 1 (Females)} = (BMI/10)^{-2},$$

$$\text{BMI FP 2 (Females)} = (BMI/10)^{-2} \times \log\left(\frac{BMI}{10}\right),$$

$$\text{AHS FP 1 (Females)} = (AHS/0.1)^{0.5}$$

$$\text{AHS FP2 (Females)} = (AHS/0.1)^1$$

**Table 13C SCORE2 AND SCORE2 +AHS models**

| Risk factor                                                        | Beta Estimate | Standard Error | p-value      |
|--------------------------------------------------------------------|---------------|----------------|--------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9418479</b>     |               |                |              |
| Age                                                                | 0.96068       | 0.1539141      | 6.089763e-10 |
| Systolic blood pressure                                            | 0.63307558    | 0.24130172     | 0.008752928  |
| Total Cholesterol                                                  | 1.10967081    | 0.19266205     | 1.512299e-08 |
| HDL cholesterol                                                    | -0.86663939   | 0.41362894     | 0.04025781   |
| Diabetes                                                           | 2.45751573    | 0.92957145     | 0.008294131  |
| Smoker (yes/no)                                                    | 0.90062473    | 0.60672218     | 0.1378236    |
| Age * smoker                                                       | -0.0486498    | 0.04660488     | 0.2966408    |
| Age * Diabetes                                                     | -0.1358001    | 0.06849351     | 0.04760914   |
| Age * Systolic blood pressure                                      | -0.03605207   | 0.01786357     | 0.04367616   |
| Age * Cholesterol                                                  | -0.08186682   | 0.01445724     | 2.622944e-08 |
| Age * HDL Cholesterol                                              | 0.0473289     | 0.03043281     | 0.1242993    |
| <b>Recalibrated SCORE2+AHS Male: Baseline survival = 0.9771475</b> |               |                |              |
| AHS FP 1                                                           | 0.080771043   | 0.059379111    | 0.1738695    |
| AHS FP 2                                                           | -0.040016046  | 0.035816072    | 0.2639875    |
| Age                                                                | 0.917331794   | 0.156612472    | 6.653352e-09 |
| Systolic blood pressure                                            | 0.61795446    | 0.245963082    | 0.0120535    |
| Total Cholesterol                                                  | 1.049786108   | 0.18905014     | 3.42929e-08  |
| HDL cholesterol                                                    | -0.941604137  | 0.401564819    | 0.02132373   |
| Diabetes                                                           | 2.346977748   | 0.927062145    | 0.01142756   |
| Smoker (yes/no)                                                    | 0.783712965   | 0.608228703    | 0.1976829    |
| Age * smoker                                                       | -0.046038513  | 0.046689894    | 0.3242027    |
| Age * Diabetes                                                     | -0.137216442  | 0.068267062    | 0.04456252   |
| Age * Systolic blood pressure                                      | -0.036103653  | 0.018215927    | 0.04758922   |
| Age * Cholesterol                                                  | -0.077009145  | 0.014221709    | 7.584339e-08 |
| Age * HDL Cholesterol                                              | 0.055533682   | 0.029436723    | 0.06189643   |
| Age * AHS FP 1                                                     | -0.006400496  | 0.004355482    | 0.1418147    |
| Age * AHS FP 2                                                     | 0.003468473   | 0.002604769    | 0.1831164    |

| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9772502</b>      |              |            |              |
|-----------------------------------------------------------------------|--------------|------------|--------------|
| Age                                                                   | 0.84640408   | 0.17645412 | 1.853072e-06 |
| Systolic blood pressure                                               | 0.77805727   | 0.27008654 | 0.004018645  |
| Total Cholesterol                                                     | 1.06028366   | 0.26066224 | 5.850772e-05 |
| HDL cholesterol                                                       | -1.73804417  | 0.40375563 | 2.037805e-05 |
| Diabetes                                                              | 4.64765022   | 1.0997425  | 2.508738e-05 |
| Smoker (yes/no)                                                       | 0.05617036   | 0.87559598 | 0.9488578    |
| Age * smoker                                                          | 0.03716772   | 0.06706141 | 0.5794944    |
| Age * Diabetes                                                        | -0.27309295  | 0.0825189  | 0.0009550804 |
| Age * Systolic blood pressure                                         | -0.03971096  | 0.02010187 | 0.0483806    |
| Age * Cholesterol                                                     | -0.07908731  | 0.01945598 | 5.875189e-05 |
| Age * HDL Cholesterol                                                 | 0.10697583   | 0.03012747 | 0.0004283532 |
| <b>Recalibrated SCORE2 +AHS Female: Baseline survival = 0.9777007</b> |              |            |              |
| AHS FP 1                                                              | 3.141943007  | 9.15633232 | 0.7315339936 |
| AHS FP 2                                                              | -0.232905019 | 2.55956354 | 0.9275084632 |
| Age                                                                   | 1.373884211  | 0.64888762 | 0.0343854837 |
| Systolic blood pressure                                               | 0.753193644  | 0.27735719 | 0.0066850332 |
| Total Cholesterol                                                     | 0.948482156  | 0.25401065 | 0.000204933  |
| HDL cholesterol                                                       | -1.305190347 | 0.38918037 | 0.0008271261 |
| Diabetes                                                              | 4.209169381  | 1.11549523 | 0.0001667982 |
| Smoker (yes/no)                                                       | -0.005396743 | 0.87544162 | 0.9950821473 |
| Age * smoker                                                          | 0.032129378  | 0.06701588 | 0.6316972586 |
| Age * Diabetes                                                        | -0.256489174 | 0.08350398 | 0.0021643384 |
| Age * Systolic blood pressure                                         | -0.039788696 | 0.02066231 | 0.0543195907 |
| Age * Cholesterol                                                     | -0.069431257 | 0.0190231  | 0.0002855372 |
| Age * HDL Cholesterol                                                 | 0.079000787  | 0.02879774 | 0.0061738329 |
| Age * AHS FP 1                                                        | -0.60225632  | 0.70991660 | 0.3963682628 |
| Age * AHS FP 2                                                        | 0.144566398  | 0.19578981 | 0.4603921603 |

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Body mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

AHS FP 1 (males) =  $(AHS/0.1)^3$ ;

$$\text{AHS FP 2 (males)} = (\text{AHS}/0.1)^3 \times \log(\text{AHS}/0.1)$$

$$\text{AHS FP 1 (Females)} = (\text{AHS}/0.1)^{0.5}$$

$$\text{AHS FP 2 (Females)} = (\text{AHS}/0.1)^1$$



**Table 14C SCORE2 and SCORE2 + AHS Models (Excluding Systolic Blood Pressure and HDL Cholesterol Ratio)**

| Risk factor                                                           | Beta Estimate | Standard Error | p-value       |
|-----------------------------------------------------------------------|---------------|----------------|---------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9401367</b>        |               |                |               |
| Age                                                                   | 0.38233178    | 0.01599676     | 3.962422e-114 |
| Diabetes                                                              | 1.88577405    | 0.91095815     | 0.03856807    |
| Smoker (yes/no)                                                       | 1.08043227    | 0.60526897     | 0.07437223    |
| Age * smoker                                                          | -0.06164965   | 0.04650236     | 0.1850467     |
| Age * Diabetes                                                        | -0.08699321   | 0.06707064     | 0.1947675     |
| <b>Recalibrated SCORE2+AHS Male: Baseline survival = 0.9409108</b>    |               |                |               |
| AHS FP 1                                                              | 0.0136364845  | 0.0061055018   | 0.02560371    |
| Age                                                                   | 0.3181167727  | 0.0222037724   | 7.637633e-45  |
| Diabetes                                                              | 1.801944676   | 0.9167659765   | 0.04946228    |
| Smoker (yes/no)                                                       | 0.9632186965  | 0.604254268    | 0.1110455     |
| Age * smoker                                                          | -0.0601168458 | 0.0464021733   | 0.1952435     |
| Age * Diabetes                                                        | -0.09293276   | 0.0674580636   | 0.1684393     |
| Age * AHS FP 1                                                        | -0.0004796911 | 0.0004397243   | 0.2754237     |
| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9752214</b>      |               |                |               |
| Age                                                                   | 0.49035704    | 0.02059067     | 5.556207e-108 |
| Diabetes                                                              | 5.06133936    | 1.06685811     | 2.274789e-06  |
| Smoker (yes/no)                                                       | 0.29798883    | 0.86178979     | 0.7295529     |
| Age * smoker                                                          | 0.02084902    | 0.06603001     | 0.7522318     |
| Age * Diabetes                                                        | -0.28742564   | 0.07997615     | 0.0003353605  |
| <b>Recalibrated SCORE2 +AHS Female: Baseline survival = 0.9763296</b> |               |                |               |
| Daily step count                                                      | 0.121252585   | 0.039317915    | 0.002076995   |
| Age                                                                   | 0.399131298   | 0.039595851    | 3.140762e-23  |
| Diabetes                                                              | 4.109226467   | 1.096176375    | 0.0001839008  |
| Smoker (yes/no)                                                       | 0.017929302   | 0.865856484    | 0.9834819     |
| Age * smoker                                                          | 0.030448192   | 0.066313401    | 0.6461828     |
| Age * Diabetes                                                        | -0.240218555  | 0.081987715    | 0.00343702    |

|                |              |             |          |
|----------------|--------------|-------------|----------|
| Age * AHS FP 1 | -0.004296489 | 0.002895515 | 0.138042 |
|----------------|--------------|-------------|----------|

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Boday mass index,

AHS FP 1 (males) =  $(AHS/0.1)^3$

AHS FP 1 (Females) =  $(AHS/0.1)^2$

**Table 15c QRISK3 and QRISK3 + AHS Risk Scores Using Systolic Blood Pressure and HDL Cholesterol from Primary Care Records**

| Risk factor                                                   | Beta Estimate    | Standard Error  | p-value       |
|---------------------------------------------------------------|------------------|-----------------|---------------|
| <b>Recalibrated Qrisk3 Male: Baseline survival = 0.936819</b> |                  |                 |               |
| Age FP 1                                                      | 21.80628142284   | 82.42790722292  | 0.79140444969 |
| Age FP 2                                                      | 0.00556529544    | 0.01885753866   | 0.76822521462 |
| BMI FP 1                                                      | -19.54235733937  | 100.24332131886 | 0.84544911008 |
| BMI FP 2                                                      | 63.02560896347   | 207.26300939031 | 0.76108843305 |
| Diabetes                                                      | -3.16932495590   | 4.57634195731   | 0.48865858812 |
| Hypertension                                                  | -1.74568508649   | 2.84304147655   | 0.53925785691 |
| Systolic blood pressure                                       | -0.00687360807   | 0.07769744533   | 0.92975584753 |
| Townsend deprivation index                                    | -0.01005203630   | 0.32157121966   | 0.97506535298 |
| HDL cholesterol ratio                                         | 0.07626874008    | 0.02361923024   | 0.00149170905 |
| Corticosteroid treatment                                      | -8.10588201995   | 5.39199525801   | 0.13288169720 |
| Atrial fibrillation and flutter                               | -3.99785061088   | 4.50320802849   | 0.37474450838 |
| SBP5                                                          | -0.00034785867   | 0.00162693615   | 0.83124614501 |
| Ethnicity (non-white)                                         | 0.25477939242    | 0.12133086656   | 0.03583993441 |
| Previous smoker                                               | 0.10771870712    | 0.04259475203   | 0.01150680435 |
| Current smoker                                                | 0.29966590510    | 0.07235019985   | 0.00003562302 |
| Age FP 1 * Hypertension                                       | 11.15311539962   | 13.67431977400  | 0.41479290721 |
| Age FP 1 * Diabetes                                           | 17.35823785712   | 21.84093257574  | 0.42682967294 |
| Age FP 1 * BMI FP 1                                           | 129.89657606293  | 462.14080623142 | 0.77867612123 |
| Age FP 1 * BMI FP 2                                           | -425.10544367419 | 955.22132543250 | 0.65633402138 |
| Age FP 1 * Townsend deprivation index                         | -0.13610061588   | 1.49583671578   | 0.92751069714 |
| Age FP 1 * Systolic blood pressure                            | 0.02171938126    | 0.34731573505   | 0.95022447350 |
| Age FP 1 * Corticosteroid treatment                           | 26.59217033316   | 21.63875872406  | 0.21921849011 |
| Age FP 1 * Atrial fibrillation and flutter                    | 37.24817022496   | 25.34222807957  | 0.14173829054 |

|                                                                      |                 |                 |               |
|----------------------------------------------------------------------|-----------------|-----------------|---------------|
| Age FP 2 * Hypertension                                              | 0.00143046709   | 0.00260174119   | 0.58249764729 |
| Age FP 2 * Diabetes                                                  | 0.00296636036   | 0.00424810630   | 0.48506760935 |
| Age FP 2 * BMI FP 1                                                  | 0.02153417977   | 0.10113155325   | 0.83139829812 |
| Age FP 2 * BMI FP 2                                                  | -0.06230309859  | 0.20980279862   | 0.76652249884 |
| Age FP 2 * Townsend deprivation index                                | 0.00018909295   | 0.00031752560   | 0.55154927668 |
| Age FP 2 * Systolic blood pressure                                   | 0.00002398835   | 0.00008289305   | 0.77421666026 |
| Age FP 2 * Corticosteroid treatment                                  | 0.00259866806   | 0.00410717569   | 0.52697784823 |
| Age FP 2 * Atrial fibrillation and flutter                           | 0.00779744448   | 0.00509459319   | 0.12600957906 |
| <b>Recalibrated QRISK3 + AHS male: Baseline survival = 0.9371708</b> |                 |                 |               |
| AHS FP 1                                                             | -0.087528615340 | 0.03109124063   | 0.004912465   |
| Age FP 1                                                             | -5.471245004395 | 83.87942788908  | 0.948007370   |
| Age FP 2                                                             | -0.001341805458 | 0.01889005014   | 0.943448589   |
| BMI FP 1                                                             | -3.899666748781 | 101.09179160147 | 0.969232004   |
| BMI FP 2                                                             | 7.963073209708  | 209.17683989044 | 0.969636016   |
| Diabetes                                                             | -2.115360883669 | 4.63159635353   | 0.647908747   |
| Hypertension                                                         | 0.260865033771  | 2.93129241117   | 0.929094429   |
| Systolic Blood Pressure                                              | 0.013612162294  | 0.07916812203   | 0.864031344   |
| Townsend Deprivation Index                                           | 0.055649523479  | 0.32148535417   | 0.862585707   |
| HDL Cholesterol Ratio                                                | 0.067833220498  | 0.02352512342   | 0.004394547   |
| Corticosteroid Treatment                                             | -6.823525863426 | 5.38210670529   | 0.204980071   |
| Atrial Fibrillation and Flutter                                      | -3.592447541369 | 4.57823520544   | 0.432715305   |
| SBP5                                                                 | -0.000377005886 | 0.00167235668   | 0.822352831   |
| Ethnicity (non-white)                                                | 0.262332567196  | 0.12136673996   | 0.030752360   |
| Previous Smoker                                                      | 0.096606800587  | 0.04262148367   | 0.023503012   |
| Current Smoker                                                       | 0.233346817973  | 0.07297594635   | 0.001403564   |
| Age FP 1 * Hypertension                                              | 1.583751243479  | 14.12637160618  | 0.910742732   |
| Age FP 1 * Diabetes                                                  | 12.102751290186 | 22.15682850540  | 0.584955288   |

|                                                                  |                   |                 |                    |
|------------------------------------------------------------------|-------------------|-----------------|--------------------|
| Age FP 1 * BMI FP 1                                              | 49.801781754898   | 468.35549589717 | 0.915326635        |
| Age FP 1 * BMI FP 2                                              | -146.800025650670 | 968.66461537201 | 0.879554945        |
| Age FP 1 * Townsend Deprivation Index                            | -0.457876124251   | 1.49986867591   | 0.760179977        |
| Age FP 1 * Systolic Blood Pressure                               | -0.076481728403   | 0.35578589116   | 0.830175732        |
| Age FP 1 * Atrial Fibrillation and Flutter                       | 24.705334769123   | 22.04692641568  | 0.262573638        |
| Age FP 1 * Corticosteroid Treatment                              | 31.390500270114   | 25.36032046089  | 0.215912579        |
| Age FP 2 * Hypertension                                          | -0.000528260751   | 0.00266795910   | 0.843059628        |
| Age FP 2 * Diabetes                                              | 0.001947083759    | 0.00427156393   | 0.648555322        |
| Age FP 2 * BMI FP 1                                              | 0.004153851850    | 0.10070176096   | 0.967100805        |
| Age FP 2 * BMI FP 2                                              | -0.000751638475   | 0.20912903817   | 0.997132593        |
| Age FP 2 * Townsend Deprivation Index                            | 0.000125424677    | 0.00031511595   | 0.690644054        |
| Age FP 2 * Systolic Blood Pressure                               | 0.000004620872    | 0.00008324508   | 0.956090919        |
| Age FP 2 * Atrial Fibrillation and Flutter                       | 0.002076433396    | 0.00415112963   | 0.616971709        |
| Age FP 2 * Corticosteroid Treatment                              | 0.006469043138    | 0.00505622842   | 0.200866244        |
| AHS FP 1* Age FP 1                                               | 0.452516659941    | 0.15198241958   | 0.002934660        |
| AHS FP 1* Age FP 2                                               | 0.000079032234    | 0.00002729157   | 0.003813992        |
| <b>Recalibrated QRISK3 female: Baseline survival = 0.9739522</b> |                   |                 |                    |
| Age FP 1                                                         | 10.23662216665    | 397.9477722354  | 0.9795703199631081 |
| Age FP 2                                                         | 0.88875520441     | 3.4045703199    | 0.7950565575322686 |
| BMI FP 1                                                         | 78.24807152207    | 146.2981822730  | 0.5928263424586426 |
| BMI FP 2                                                         | -88.56969082987   | 299.8966230743  | 0.7677768354826903 |
| Diabetes                                                         | 5.91909957973     | 8.3945924531    | 0.4808438566116465 |
| Hypertension                                                     | -0.52901084702    | 4.6056292919    | 0.9085692461593827 |
| Systolic blood pressure                                          | -0.00110819787    | 0.1743722218    | 0.9950029666281617 |
| Townsend deprivation index                                       | 0.41999422566     | 0.5984542170    | 0.4829056573894372 |

|                                                                       |                    |                  |                    |
|-----------------------------------------------------------------------|--------------------|------------------|--------------------|
| HDL cholesterol ratio                                                 | 0.14256058367      | 0.0352835669     | 0.0003172641950559 |
| Corticosteroid treatment                                              | 12.00438577771     | 11.5707333939    | 0.2996678027717218 |
| Atrial fibrillation and flutter                                       | 83.86991347693     | 29.6694790057    | 0.0047609517235933 |
| SBP5                                                                  | 0.00001968282      | 0.0006481755     | 0.9759109588832737 |
| Ethnicity (non-white)                                                 | 0.11605222093      | 0.1539863001     | 0.4511783882010686 |
| Previous smoker                                                       | 0.13827664931      | 0.0526670607     | 0.0087361955619294 |
| Current smoker                                                        | 0.59390494938      | 0.0953511209     | 0.0000000006009991 |
| Age FP 1 * Hypertension                                               | 52.31092253147     | 59.6437400466    | 0.3805888979859786 |
| Age FP 1 * Diabetes                                                   | -47.99277627194    | 107.6670561966   | 0.6558360912733342 |
| Age FP 1 * BMI FP 1                                                   | -1,202.31979146091 | 1,875.2961557485 | 0.5215267786716795 |
| Age FP 1 * BMI FP 2                                                   | 1,069.24261355633  | 3,788.3680121203 | 0.7777930719732018 |
| Age FP 1 * Townsend deprivation index                                 | -5.26354808095     | 7.5215295957     | 0.4841541956169995 |
| Age FP 1 * Systolic blood pressure                                    | 0.15661761553      | 2.2014661859     | 0.9440833246431082 |
| Age FP 1 * Corticosteroid treatment                                   | -1,272.38242708725 | 464.4340881285   | 0.0062199016494787 |
| Age FP 1 * Atrial fibrillation and flutter                            | -147.69963977461   | 154.1561345218   | 0.3381465500938438 |
| Age FP 2 * Hypertension                                               | 0.00025420323      | 0.4857789296     | 0.9995825410918046 |
| Age FP 2 * Diabetes                                                   | -0.61850669639     | 0.8893630988     | 0.4868735427775486 |
| Age FP 2 * BMI FP 1                                                   | -7.66570816573     | 15.5276330004    | 0.6215995373500898 |
| Age FP 2 * BMI FP 2                                                   | 8.77844036870      | 32.0299146623    | 0.7840660016585190 |
| Age FP 2 * Townsend deprivation index                                 | -0.04264724810     | 0.0639673328     | 0.5050563990134957 |
| Age FP 2 * Systolic blood pressure                                    | 0.00004829865      | 0.0187140861     | 0.9979719030946632 |
| Age FP 2 * Corticosteroid treatment                                   | -8.06973425836     | 2.8795794406     | 0.0051346690226130 |
| Age FP 2 * Atrial fibrillation and flutter                            | -1.31423211199     | 1.2073029581     | 0.2765061039380521 |
| <b>Recalibrated QRISK3 +AHS female: Baseline survival = 0.9741924</b> |                    |                  |                    |
| AHS FP 1                                                              | -94.12819819911    | 71.559367643     | 0.1885675281672    |

|                                            |                    |                 |                 |
|--------------------------------------------|--------------------|-----------------|-----------------|
| AHS FP 2                                   | 30.36015923073     | 20.009887550    | 0.1293974443573 |
| Age FP 1                                   | -942.35374504956   | 853.742826682   | 0.2699486373893 |
| Age FP 2                                   | -5.54313986694     | 7.467422255     | 0.4580710164904 |
| BMI FP 1                                   | 54.57493636156     | 147.629294532   | 0.7116740088894 |
| BMI FP 2                                   | -15.31460664464    | 302.305209204   | 0.9596032419244 |
| Diabetes                                   | 4.64684519777      | 8.378833869     | 0.5792495818488 |
| Hypertension                               | -0.58241961205     | 4.604186884     | 0.8993537998237 |
| Systolic Blood Pressure                    | -0.00991477367     | 0.180265703     | 0.9568410464826 |
| Townsend Deprivation Index                 | 0.42200434509      | 0.599192770     | 0.4813548992824 |
| HDL Cholesterol Ratio                      | 0.13437775862      | 0.036386279     | 0.0010353432852 |
| Corticosteroid Treatment                   | 12.18287421307     | 11.590481448    | 0.2933652732090 |
| Atrial Fibrillation and Flutter            | 79.01490448746     | 29.651545815    | 0.0077825435189 |
| SBP5                                       | 0.00003180758      | 0.000657894     | 0.9616395493839 |
| Ethnicity (non-white)                      | 0.12828016961      | 0.154094646     | 0.4052754301439 |
| Previous Smoker                            | 0.12740472844      | 0.052714879     | 0.0157687025799 |
| Current Smoker                             | 0.48525604104      | 0.096173342     | 0.0000005047606 |
| Age FP 1 * Hypertension                    | 53.47220932983     | 59.443611317    | 0.3684977053640 |
| Age FP 1 * Diabetes                        | -30.90212298445    | 107.091313334   | 0.7729561593577 |
| Age FP 1 * BMI FP 1                        | -874.43027841243   | 1,888.257715144 | 0.6433648045646 |
| Age FP 1 * BMI FP 2                        | 48.86465285022     | 3,809.027272053 | 0.9897661054203 |
| Age FP 1 * Townsend Deprivation Index      | -5.27581451947     | 7.510506117     | 0.4824948640097 |
| Age FP 1 * Systolic Blood Pressure         | 0.25900685499      | 2.264183391     | 0.9103333537556 |
| Age FP 1 * Atrial Fibrillation and Flutter | -1,205.53000231602 | 463.376154661   | 0.0093651756720 |
| Age FP 1 * Corticosteroid Treatment        | -148.79599351486   | 154.075724652   | 0.3343224270154 |
| Age FP 2 * Hypertension                    | -0.00523688798     | 0.486269977     | 0.9914086891667 |
| Age FP 2 * Diabetes                        | -0.50334280072     | 0.889056215     | 0.5713676172895 |
| Age FP 2 * BMI FP 1                        | -5.50826465907     | 15.684388613    | 0.7254898008966 |

|                                            |                   |               |                 |
|--------------------------------------------|-------------------|---------------|-----------------|
| Age FP 2 * BMI FP 2                        | 2.43159449148     | 32.325679461  | 0.9400476809112 |
| Age FP 2 * Townsend Deprivation Index      | -0.04304230513    | 0.064120802   | 0.5021451762302 |
| Age FP 2 * Systolic Blood Pressure         | 0.00096316305     | 0.019406459   | 0.9610790101299 |
| Age FP 2 * Atrial Fibrillation and Flutter | -7.57743567759    | 2.880090094   | 0.0085972791762 |
| Age FP 2 * Corticosteroid Treatment        | -1.33840291397    | 1.210565736   | 0.2690639505209 |
| AHS FP 1* Age FP 1                         | 1,330.85503960451 | 898.368785636 | 0.1386923108445 |
| AHS FP 2* Age FP 1                         | -424.16708366772  | 256.025272368 | 0.0977666297675 |
| AHS FP 1* Age FP 2                         | 8.77704781412     | 7.697226826   | 0.2543364411938 |
| AHS FP 2* Age FP 2                         | -2.83759989834    | 2.133673723   | 0.1837349540548 |

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Boday mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

$$\text{Age FP 1 (males)} = (\text{age}/10)^{-1}$$

$$\text{Age FP 2 (males)} = (\text{age}/10)^3$$

$$\text{BMI FP 1 (males)} = (\text{BMI}/10)^{-2}$$

$$\text{BMI FP 2 (males)} = (\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$$

$$\text{AHS FP 1 (males)} = (\text{AHS}/0.1)^3$$

$$\text{Age FP 1 (Females)} = \text{age}/10^{-2}$$

$$\text{Age FP 2 (Females)} = \text{age}/10$$

$$\text{BMI FP 1 (Females)} = (\text{BMI}/10)^{-2}$$

$$\text{BMI FP 2 (Females)} = (\text{BMI}/10)^{-2} \times \log\left(\frac{\text{BMI}}{10}\right)$$

$$\text{AHS FP 1 (Females)} = \text{AHS}/0.1^{0.5}$$

$$\text{AHS FP2 (Females)} = \text{AHS}/0.1^1$$



**Table 16c SCORE2 and SCORE2 + AHS Risk Scores Using Systolic Blood Pressure and HDL Cholesterol from Primary Care Records**

| <b>Risk factor</b>                                                | <b>Beta Estimate</b> | <b>Standard Error</b> | <b>p-value</b> |
|-------------------------------------------------------------------|----------------------|-----------------------|----------------|
| <b>Recalibrated SCORE2 Male: Baseline survival = 0.9403624</b>    |                      |                       |                |
| Age                                                               | 0.3450794678         | 0.22234230            | 0.14042421     |
| Systolic blood pressure                                           | -0.1042656811        | 0.42711120            | 0.81139391     |
| Total Cholesterol                                                 | 0.0917796458         | 0.39065973            | 0.82009811     |
| HDL cholesterol                                                   | -0.2303888556        | 0.29028223            | 0.42766187     |
| Diabetes                                                          | 1.9084190373         | 0.96041491            | 0.04751534     |
| Smoker (yes/no)                                                   | 1.0001087078         | 0.60653405            | 0.09929294     |
| Age * smoker                                                      | -0.0565363501        | 0.04661066            | 0.22526176     |
| Age * Diabetes                                                    | -0.0968893273        | 0.07019308            | 0.16800340     |
| Age * Systolic blood pressure                                     | 0.0134029586         | 0.02949307            | 0.65589221     |
| Age * Cholesterol                                                 | -0.0093193054        | 0.02745693            | 0.74200692     |
| Age * HDL Cholesterol                                             | -0.0002471985        | 0.02173113            | 0.99092754     |
| <b>Recalibrated SCORE2+AHS Male: Baseline survival =0.9411759</b> |                      |                       |                |
| AHS FP 1                                                          | 0.109334115          | 0.060084606           | 0.06899900     |
| AHS FP 2                                                          | -0.056708657         | 0.036103431           | 0.11640909     |
| Age                                                               | 0.354505028          | 0.224179763           | 0.13314187     |
| Systolic blood pressure                                           | -0.136048392         | 0.427871355           | 0.75597428     |
| Total Cholesterol                                                 | 0.097858013          | 0.400975574           | 0.81353228     |
| HDL cholesterol                                                   | -0.203032061         | 0.293304230           | 0.48908158     |
| Diabetes                                                          | 1.798022943          | 0.966678010           | 0.06344377     |
| Smoker (yes/no)                                                   | 0.900808993          | 0.609270901           | 0.13939730     |
| Age * smoker                                                      | -0.055345100         | 0.046789865           | 0.23698216     |
| Age * Diabetes                                                    | -0.097932173         | 0.070722576           | 0.16660006     |
| Age * Systolic blood pressure                                     | 0.014398144          | 0.029462804           | 0.63165167     |
| Age * Cholesterol                                                 | -0.009030498         | 0.028335081           | 0.75760688     |
| Age * HDL Cholesterol                                             | 0.000418720          | 0.021914152           | 0.98476231     |
| Age * AHS FP 1                                                    | -0.008381437         | 0.004401570           | 0.05705712     |

|                                                                       |              |             |               |
|-----------------------------------------------------------------------|--------------|-------------|---------------|
| Age * AHS FP 2                                                        | 0.004618438  | 0.002623775 | 0.07852372    |
| <b>Recalibrated SCORE2 Female: Baseline survival = 0.9754067</b>      |              |             |               |
| Age                                                                   | 0.645386855  | 0.28103576  | 0.03278704242 |
| Systolic blood pressure                                               | 0.264263006  | 0.51234379  | 0.61367959176 |
| Total Cholesterol                                                     | 0.138287689  | 0.51982073  | 0.79733817450 |
| HDL cholesterol                                                       | -0.166966873 | 0.33563837  | 0.62068754007 |
| Diabetes                                                              | 5.061087243  | 1.19684714  | 0.00003931287 |
| Smoker (yes/no)                                                       | 0.276271251  | 0.86789252  | 0.75028100896 |
| Age * smoker                                                          | 0.020614303  | 0.06648637  | 0.75656135898 |
| Age * Diabetes                                                        | -0.294244621 | 0.08908597  | 0.00114639623 |
| Age * Systolic blood pressure                                         | -0.013572772 | 0.03670057  | 0.71594811836 |
| Age * Cholesterol                                                     | -0.010275852 | 0.03799541  | 0.79382105094 |
| Age * HDL Cholesterol                                                 | -0.002834552 | 0.02528323  | 0.91114910638 |
| <b>Recalibrated SCORE2 +AHS Female: Baseline survival = 0.9764168</b> |              |             |               |
| AHS FP                                                                | 0.111502051  | 0.042277150 | 0.0086670820  |
| Age                                                                   | 0.506361898  | 0.283928083 | 0.0912697819  |
| Systolic blood pressure                                               | 0.122784063  | 0.531741610 | 0.8208952664  |
| Total Cholesterol                                                     | 0.112001273  | 0.515941522 | 0.8339007323  |
| HDL cholesterol                                                       | -0.061836464 | 0.344109192 | 0.8581107501  |
| Diabetes                                                              | 4.253992148  | 1.206565036 | 0.0005287701  |
| Smoker (yes/no)                                                       | 0.020935063  | 0.869960114 | 0.9808042405  |
| Age * smoker                                                          | 0.029331363  | 0.066634669 | 0.6598649818  |
| Age * Diabetes                                                        | -0.254221339 | 0.089604635 | 0.0049635962  |
| Age * Systolic blood pressure                                         | -0.005239854 | 0.037982948 | 0.8920261546  |
| Age * Cholesterol                                                     | -0.007524344 | 0.037572935 | 0.8463662229  |
| Age * HDL Cholesterol                                                 | -0.007723454 | 0.025851499 | 0.7664373971  |
| Age * AHS FP 1                                                        | -0.003829494 | 0.003101023 | 0.2174924947  |

Abbreviations: FP= Fractional polynomial, AHS = Activity Health Score, BMI = Body mass index, SBP5 = Standard deviation of two blood pressure readings, HDL = High-density lipoprotein, SBP = systolic blood pressure

AHS FP 1 (males) =  $(AHS/0.1)^3$ ; AHS FP 1 (Females) =  $(AHS/0.1)^3 \times \log(AHS/0.1)$

# Section D: Tripod guidelines for predictive model development.



## Chapter 4 TRIPOD Checklist: Prediction Model Development

| Section/Topic                | Item | Checklist Item                                                                                                                                                                                   | Page                                       |
|------------------------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| <b>Title and abstract</b>    |      |                                                                                                                                                                                                  |                                            |
| Title                        | 1    | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.                                                     | <b>P.127</b>                               |
| Abstract                     | 2    | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.                                          | <b>P.3-P.5</b>                             |
| <b>Introduction</b>          |      |                                                                                                                                                                                                  |                                            |
| Background and objectives    | 3a   | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | <b>P.127</b>                               |
|                              | 3b   | Specify the objectives, including whether the study describes the development or validation of the model or both.                                                                                | <b>P.129</b>                               |
| <b>Methods</b>               |      |                                                                                                                                                                                                  |                                            |
| Source of data               | 4a   | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.                          | <b>P.129-P.132</b>                         |
|                              | 4b   | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.                                                                                   | <b>P.131</b>                               |
| Participants                 | 5a   | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.                                                     | <b>P.130</b>                               |
|                              | 5b   | Describe eligibility criteria for participants.                                                                                                                                                  | <b>P.130-P.134</b>                         |
|                              | 5c   | Give details of treatments received, if relevant.                                                                                                                                                | <b>N/A</b>                                 |
| Outcome                      | 6a   | Clearly define the outcome that is predicted by the prediction model, including how and when assessed.                                                                                           | <b>P.131</b>                               |
|                              | 6b   | Report any actions to blind assessment of the outcome to be predicted.                                                                                                                           | <b>N/A</b>                                 |
| Predictors                   | 7a   | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.                                                    | <b>P.130-131<br/>Supplementary Table 3</b> |
|                              | 7b   | Report any actions to blind assessment of predictors for the outcome and other predictors.                                                                                                       | <b>N/A</b>                                 |
| Sample size                  | 8    | Explain how the study size was arrived at.                                                                                                                                                       | <b>P.130-p.136<br/>P.141</b>               |
| Missing data                 | 9    | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.                                             | <b>P.132</b>                               |
| Statistical analysis methods | 10a  | Describe how predictors were handled in the analyses.                                                                                                                                            | <b>P.133-P.132<br/>P.136</b>               |
|                              | 10b  | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.                                                                    | <b>P.137-P.139</b>                         |

|                           |     |                                                                                                                                                                                                       |                                                     |
|---------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
|                           | 10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models.                                                                                                   | <b>P.137-P.139</b>                                  |
| Risk groups               | 11  | Provide details on how risk groups were created, if done.                                                                                                                                             | <b>P.138</b>                                        |
| <b>Results</b>            |     |                                                                                                                                                                                                       |                                                     |
| Participants              | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | <b>P.140-P.141</b>                                  |
|                           | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.    | <b>P.125-P.126<br/>P.140, P.142</b>                 |
| Model development         | 14a | Specify the number of participants and outcome events in each analysis.                                                                                                                               | <b>P.140</b>                                        |
|                           | 14b | If done, report the unadjusted association between each candidate predictor and outcome.                                                                                                              | <b>Supplementary Table 14</b>                       |
| Model specification       | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).                           | <b>Supplementary material section C: Tables 1-2</b> |
|                           | 15b | Explain how to use the prediction model.                                                                                                                                                              | <b>X</b>                                            |
| Model performance         | 16  | Report performance measures (with CIs) for the prediction model.                                                                                                                                      | <b>P.143-P.158</b>                                  |
| <b>Discussion</b>         |     |                                                                                                                                                                                                       |                                                     |
| Limitations               | 18  | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).                                                                                      | <b>P.165</b>                                        |
| Interpretation            | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.                                                    | <b>P.159</b>                                        |
| Implications              | 20  | Discuss the potential clinical use of the model and implications for future research.                                                                                                                 | <b>P.167</b>                                        |
| <b>Other information</b>  |     |                                                                                                                                                                                                       |                                                     |
| Supplementary information | 21  | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.                                                                         | <b>P.106-P.115</b>                                  |
| Funding                   | 22  | Give the source of funding and the role of the funders for the present study.                                                                                                                         | <b>P.25</b>                                         |

## Chapter 5 TRIPOD Checklist: Prediction Model Development



| Section/Topic                | Item | Checklist Item                                                                                                                                                                                   | Page                                            |
|------------------------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>Title and abstract</b>    |      |                                                                                                                                                                                                  |                                                 |
| Title                        | 1    | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.                                                     | P.168                                           |
| Abstract                     | 2    | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.                                          | P.3-P.5                                         |
| <b>Introduction</b>          |      |                                                                                                                                                                                                  |                                                 |
| Background and objectives    | 3a   | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | P.169                                           |
|                              | 3b   | Specify the objectives, including whether the study describes the development or validation of the model or both.                                                                                | P.169                                           |
| <b>Methods</b>               |      |                                                                                                                                                                                                  |                                                 |
| Source of data               | 4a   | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.                          | P.129-P.132<br>P.170                            |
|                              | 4b   | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.                                                                                   | P.170                                           |
| Participants                 | 5a   | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.                                                     | P.131, P.170                                    |
|                              | 5b   | Describe eligibility criteria for participants.                                                                                                                                                  | P.170-P.171                                     |
|                              | 5c   | Give details of treatments received, if relevant.                                                                                                                                                | N/A                                             |
| Outcome                      | 6a   | Clearly define the outcome that is predicted by the prediction model, including how and when assessed.                                                                                           | P.170                                           |
|                              | 6b   | Report any actions to blind assessment of the outcome to be predicted.                                                                                                                           | N/A                                             |
| Predictors                   | 7a   | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.                                                    | P.170<br>Supplementary Table 3                  |
|                              | 7b   | Report any actions to blind assessment of predictors for the outcome and other predictors.                                                                                                       | N/A                                             |
| Sample size                  | 8    | Explain how the study size was arrived at.                                                                                                                                                       | P.170-P.171<br>P.179                            |
| Missing data                 | 9    | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.                                             | P.171                                           |
| Statistical analysis methods | 10a  | Describe how predictors were handled in the analyses.                                                                                                                                            | P.170-P.171                                     |
|                              | 10b  | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.                                                                    | P.171-P.174<br>Supplementary material Section A |
|                              | 10d  | Specify all measures used to assess model performance and, if relevant, to compare multiple models.                                                                                              | P.175-176                                       |
| Risk groups                  | 11   | Provide details on how risk groups were created, if done.                                                                                                                                        | P.176                                           |

| <b>Results</b>            |     |                                                                                                                                                                                                       |                                                     |
|---------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Participants              | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | <b>P.179</b>                                        |
|                           | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.    | <b>P.125-P.126<br/>P.171</b>                        |
| Model development         | 14a | Specify the number of participants and outcome events in each analysis.                                                                                                                               | <b>P.178</b>                                        |
|                           | 14b | If done, report the unadjusted association between each candidate predictor and outcome.                                                                                                              | <b>P.185<br/>Supplementary Table 14</b>             |
| Model specification       | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).                           | <b>Supplementary material section C: Tables 3-4</b> |
|                           | 15b | Explain how to use the prediction model.                                                                                                                                                              | <b>X</b>                                            |
| Model performance         | 16  | Report performance measures (with CIs) for the prediction model.                                                                                                                                      | <b>P.180-P.198</b>                                  |
| <b>Discussion</b>         |     |                                                                                                                                                                                                       |                                                     |
| Limitations               | 18  | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).                                                                                      | <b>P.202</b>                                        |
| Interpretation            | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.                                                    | <b>P.199</b>                                        |
| Implications              | 20  | Discuss the potential clinical use of the model and implications for future research.                                                                                                                 | <b>P.203</b>                                        |
| <b>Other information</b>  |     |                                                                                                                                                                                                       |                                                     |
| Supplementary information | 21  | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.                                                                         | <b>P.106-P.115</b>                                  |
| Funding                   | 22  | Give the source of funding and the role of the funders for the present study.                                                                                                                         | <b>P.25</b>                                         |

## Chapter 6 TRIPOD Checklist: Prediction Model Development



| Section/Topic                | Item | Checklist Item                                                                                                                                                                                   | Page                           |
|------------------------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Title and abstract</b>    |      |                                                                                                                                                                                                  |                                |
| Title                        | 1    | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.                                                     | P.204                          |
| Abstract                     | 2    | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.                                          | P.3-P.5                        |
| <b>Introduction</b>          |      |                                                                                                                                                                                                  |                                |
| Background and objectives    | 3a   | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | P.204-P.205                    |
|                              | 3b   | Specify the objectives, including whether the study describes the development or validation of the model or both.                                                                                | P.206                          |
| <b>Methods</b>               |      |                                                                                                                                                                                                  |                                |
| Source of data               | 4a   | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.                          | P.206-207                      |
|                              | 4b   | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.                                                                                   | P.207                          |
| Participants                 | 5a   | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.                                                     | P.207                          |
|                              | 5b   | Describe eligibility criteria for participants.                                                                                                                                                  | P.207                          |
|                              | 5c   | Give details of treatments received, if relevant.                                                                                                                                                | N/A                            |
| Outcome                      | 6a   | Clearly define the outcome that is predicted by the prediction model, including how and when assessed.                                                                                           | P.207-209                      |
|                              | 6b   | Report any actions to blind assessment of the outcome to be predicted.                                                                                                                           | N/A                            |
| Predictors                   | 7a   | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.                                                    | P.207<br>Supplementary Table 3 |
|                              | 7b   | Report any actions to blind assessment of predictors for the outcome and other predictors.                                                                                                       | N/A                            |
| Sample size                  | 8    | Explain how the study size was arrived at.                                                                                                                                                       | P.206, P.216                   |
| Missing data                 | 9    | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.                                             | P.208- 210                     |
| Statistical analysis methods | 10a  | Describe how predictors were handled in the analyses.                                                                                                                                            | P.209-212                      |
|                              | 10b  | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.                                                                    | P.200-P.202                    |
|                              | 10d  | Specify all measures used to assess model performance and, if relevant, to compare multiple models.                                                                                              | P.212-214                      |
| Risk groups                  | 11   | Provide details on how risk groups were created, if done.                                                                                                                                        | P.213                          |
| <b>Results</b>               |      |                                                                                                                                                                                                  |                                |

|                           |     |                                                                                                                                                                                                       |                                                      |
|---------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Participants              | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | <b>P.215-P.216</b>                                   |
|                           | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.    | <b>P.122-P.124<br/>P.215, P.217</b>                  |
| Model development         | 14a | Specify the number of participants and outcome events in each analysis.                                                                                                                               | <b>P.215</b>                                         |
|                           | 14b | If done, report the unadjusted association between each candidate predictor and outcome.                                                                                                              | <b>P.223</b>                                         |
| Model specification       | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).                           | <b>Supplementary material section C: Tables 5-10</b> |
|                           | 15b | Explain how to use the prediction model.                                                                                                                                                              | <b>X</b>                                             |
| Model performance         | 16  | Report performance measures (with CIs) for the prediction model.                                                                                                                                      | <b>P.221-P.233</b>                                   |
| <b>Discussion</b>         |     |                                                                                                                                                                                                       |                                                      |
| Limitations               | 18  | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).                                                                                      | <b>P.240</b>                                         |
| Interpretation            | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.                                                    | <b>P.234</b>                                         |
| Implications              | 20  | Discuss the potential clinical use of the model and implications for future research.                                                                                                                 | <b>P.241</b>                                         |
| <b>Other information</b>  |     |                                                                                                                                                                                                       |                                                      |
| Supplementary information | 21  | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.                                                                         | <b>P.117-P.126</b>                                   |
| Funding                   | 22  | Give the source of funding and the role of the funders for the present study.                                                                                                                         | <b>P.25</b>                                          |



## Chapter 7 TRIPOD Checklist: Prediction Model Development



| Section/Topic                | Item | Checklist Item                                                                                                                                                                                   | Page                                                  |
|------------------------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Title and abstract</b>    |      |                                                                                                                                                                                                  |                                                       |
| Title                        | 1    | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.                                                     | P.242                                                 |
| Abstract                     | 2    | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.                                          | P.3-P.5                                               |
| <b>Introduction</b>          |      |                                                                                                                                                                                                  |                                                       |
| Background and objectives    | 3a   | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | P.242-243                                             |
|                              | 3b   | Specify the objectives, including whether the study describes the development or validation of the model or both.                                                                                | P.244                                                 |
| <b>Methods</b>               |      |                                                                                                                                                                                                  |                                                       |
| Source of data               | 4a   | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.                          | p.245                                                 |
|                              | 4b   | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.                                                                                   | P.207, P.245                                          |
| Participants                 | 5a   | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.                                                     | P.207, P.245                                          |
|                              | 5b   | Describe eligibility criteria for participants.                                                                                                                                                  | P.207, P.245                                          |
|                              | 5c   | Give details of treatments received, if relevant.                                                                                                                                                | N/A                                                   |
| Outcome                      | 6a   | Clearly define the outcome that is predicted by the prediction model, including how and when assessed.                                                                                           | P.245-P.246                                           |
|                              | 6b   | Report any actions to blind assessment of the outcome to be predicted.                                                                                                                           | N/A                                                   |
| Predictors                   | 7a   | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.                                                    | P.245-P.247<br>Supplementary Table 3, Section A (1.2) |
|                              | 7b   | Report any actions to blind assessment of predictors for the outcome and other predictors.                                                                                                       | N/A                                                   |
| Sample size                  | 8    | Explain how the study size was arrived at.                                                                                                                                                       | P.207, P.216, P.246-247                               |
| Missing data                 | 9    | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.                                             | P.208-210<br>P.245                                    |
| Statistical analysis methods | 10a  | Describe how predictors were handled in the analyses.                                                                                                                                            | P.208-212<br>P.245-P.249                              |
|                              | 10b  | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.                                                                    | P.245-P.250                                           |
|                              | 10d  | Specify all measures used to assess model performance and, if relevant, to compare multiple models.                                                                                              | P.248-250                                             |
| Risk groups                  | 11   | Provide details on how risk groups were created, if done.                                                                                                                                        | P.250                                                 |

| Results                   |     |                                                                                                                                                                                                       |                                                |
|---------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Participants              | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | P.215-P.216, p.236                             |
|                           | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.    | P.122-P.126<br>P.215,217<br>P.252              |
| Model development         | 14a | Specify the number of participants and outcome events in each analysis.                                                                                                                               | P.215                                          |
|                           | 14b | If done, report the unadjusted association between each candidate predictor and outcome.                                                                                                              | P.252                                          |
| Model specification       | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).                           | Supplementary material section C: Tables 11-16 |
|                           | 15b | Explain how to use the prediction model.                                                                                                                                                              | X                                              |
| Model performance         | 16  | Report performance measures (with CIs) for the prediction model.                                                                                                                                      | P.253-P.267                                    |
| Discussion                |     |                                                                                                                                                                                                       |                                                |
| Limitations               | 18  | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).                                                                                      | P.272                                          |
| Interpretation            | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.                                                    | P.268                                          |
| Implications              | 20  | Discuss the potential clinical use of the model and implications for future research.                                                                                                                 | P.274                                          |
| Other information         |     |                                                                                                                                                                                                       |                                                |
| Supplementary information | 21  | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.                                                                         | P.117-P.126                                    |
| Funding                   | 22  | Give the source of funding and the role of the funders for the present study.                                                                                                                         | P.25                                           |

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