Developing a framework for modelling outcomes in diabetes - A case study with ASCEND



Mi Jun Keng

Exeter College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy

Trinity 2022

Acknowledgements

My deepest gratitude goes to my supervisors. Boby, for being a wonderful mentor, for the time she has dedicated to me, and for always pushing me beyond my boundaries. Jose, for his unwavering support, and for his helpful advice beyond just the DPhil. Louise and Jane, for always making time for me despite their busy schedules, and for their invaluable advice. This work would not have been possible without their guidance and dedication.

I would also like to thank Amanda and Alan for their thorough examination of the thesis and for their extremely helpful feedback.

I would like to acknowledge the financial support from the British Heart Foundation Centre of Research Excellence, Oxford (grant code: RE/13/1/30181).

I am grateful to the many people in the department and HERC who have provided help and useful comments on this work. I am also grateful to many in HERC for their companionship over the past years. I will always remember the lunch breaks, the office conversations, and the (unfortunately) virtual socials.

I have been very fortunate to make so many new friends in and out of the department. Winnie, my office buddy from day one. Gu-Lung, Tzu-Hao, Chee, my cycling and weekend trip buddies. Didi, who walked 100km with me. Juliana, Murong, Junwen, for all the dinners we shared. And many many others. My life in Oxford would not have been so enjoyable if not for them, and I truly hope our paths will cross again.

To my friends, near and far, who have always been present in my time of need. To Su-O and family, who have provided me with a home away from home since I came to the UK. To Kuen-Wei, who has always accepted me at my best and my worst. To my grandparents, who have always respected my decisions and have been understanding of my absence. There are no words to express my gratitude to you all.

Abstract

Decision-analytic modelling is used to synthesise clinical and economic data to evaluate health outcomes and costs of novel healthcare interventions. Diabetes is associated with disabling and costly complications which develop over time, and such models are crucial to capture the impact of treatment over a person's lifetime. Most diabetes simulation models to date are based on risk equations estimated using data from the UK Prospective Diabetes Study (UKPDS), a study conducted more than two decades ago, and may not reflect contemporary event rates given changes in treatment and management of diabetes and its complications.

A Study of Cardiovascular Events iN Diabetes (ASCEND) recruited 15,480 participants with diabetes without previous cardiovascular disease, and is one of the largest diabetes trials conducted to date. Using data from the ASCEND study, I found the UKPDS risk equations to overpredict cardiovascular events and mortality, further adding to the evidence base that the UKPDS risk equations are unsuitable for use in contemporary cohorts. I developed a new framework for modelling long-term health outcomes and costs which can be used to assess cost-effectiveness of treatments for people with diabetes without previous cardiovascular disease. New risk equations were estimated using the ASCEND data, and these were integrated into a simulation model which predicts the likelihood of occurrence of cardiovascular, bleeding, cancer, lower-limb amputation, end-stage renal disease and death events over the lifetime of a patient given their baseline characteristics. The simulation model was externally validated in a cohort of 18,250 participants with diabetes without cardiovascular disease identified from the UK Biobank, a longitudinal prospective observational cohort. The simulation model performed well generally. Where discrepancies between model predictions and observed event rates were found, the reasons behind the discrepancies were identified. A novel issue-driven approach was developed to update the risk equations. New estimates of hospital costs and health-related quality of life (QoL) associated with the adverse events in the simulation model were also derived from the ASCEND study and incorporated into the simulation model to quantify the impact of treatments on lifetime cost and QoL.

To demonstrate an application of the framework, I assessed the cost-effectiveness of aspirin for the primary prevention of cardiovascular disease in people with diabetes. In this population, it is still uncertain if the cardiovascular benefits of aspirin use outweigh the bleeding risks. Using the latest evidence available, I demonstrate that aspirin is likely to be cost-effective in the cohort of UK Biobank participants with diabetes without previous cardiovascular disease. However, significant uncertainties in the results warrant further research.

Contents

List of Figures **ix**

List of Tables **xvi**

List of Abbreviations **xxi**

1 Introduction **1**

1.1 Diabetes simulation models 1

1.1.1 Limitations of existing diabetes models 4

1.1.2 Usage and/or adaptation of diabetes models for cost-effectiveness analysis 7

1.2 The ASCEND study - aspirin for primary prevention of cardiovascular disease in people with diabetes 16

1.3 Research objectives 17

1.4 Structure of thesis 17

2 How well does the UKPDS Outcomes Model 2 predict outcomes in ASCEND **28**

2.1 Background 29

2.2 Methods 30

2.2.1 Validation cohort and endpoints 30

2.2.2 Missing data 31

2.2.3 Statistical analysis 33

2.3 Results 35

2.3.1 Subgroup analysis 42

2.3.2 Sensitivity analysis 42

2.4 Discussion 44

2.4.1 Summary of results 44

2.4.2 Factors attributable to discrepancies observed 44

2.4.3 Limitations 47

2.4.4 Strengths and added value 49

2.5 Implications on cost-effectiveness analysis 49

3 Simulation model for predicting first occurrences of adverse events over a lifetime in people with diabetes without previous cardiovascular disease – model development, validation and updating 57

3.1 Background . . . 58
3.2 Description of datasets . . . 59
3.2.1 Study populations . . . 59
3.2.2 Adverse events . . . 64
3.2.3 Missing baseline data . . . 67
3.3 Model development in ASCEND . . . 67
3.3.1 Variable selection . . . 67
3.3.2 Non-linearity of continuous variables . . . 68
3.3.3 Test for violation of proportional hazard assumptions . . . 69
3.3.4 Sensitivity analysis . . . 69
3.3.5 Specification of parametric risk equations . . . 69
3.3.6 Discrete-time stochastic simulation . . . 71
3.4 Model validation . . . 73
3.4.1 Validity of simulation model . . . 73
3.4.2 Possible sources of discrepancies . . . 80
3.5 Model updating . . . 82
3.5.1 Methods for updating parametric proportional hazard models 82
3.5.2 Strategies for model updating . . . 86
3.6 Discussion . . . 92
3.6.1 Risk equations developed using ASCEND and the UK Biobank 92
3.6.2 Risk factors for bleeding . . . 95
3.6.3 Life expectancies in ASCEND and the UK Biobank compared to other cohorts . . . 95
3.6.4 Issue-driven approach for updating risk equations . . . 100
3.6.5 New framework for diabetes simulation - pros and cons . . . 101
3.6.6 Limitations . . . 102
3.6.7 Strengths and added value . . . 103

4 Hospital costs associated with adverse events in ASCEND 109

4.1 Background . . . 110
4.2 Costing hospital episode data . . . 110
4.2.1 Costing maintenance dialysis . . . 111
4.3 Model specification . . . 112

4.3.1 Variable selection . . . 112
4.3.2 Non-linear relationship between age and hospital costs . . . 113
4.3.3 Model selection . . . 114
4.4 Results . . . 115
4.4.1 Participant characteristics and hospital use . . . 115
4.4.2 Model results . . . 121
4.5 Discussion . . . 126
4.5.1 Summary of results . . . 126
4.5.2 Comparison with published estimates . . . 127
4.5.3 Limitations . . . 129
4.5.4 Strengths and added value . . . 130

5 Decrements in health-related quality of life associated with adverse events in ASCEND 135
5.1 Background . . . 136
5.2 Measurement of health-related QoL . . . 137
5.2.1 Imputing missing questionnaire responses . . . 138
5.3 Model specification . . . 139
5.3.1 Variable selection . . . 139
5.3.2 Non-linear relationship between age and EQ-5D utilities . . . 139
5.3.3 Model selection . . . 140
5.4 Results . . . 141
5.4.1 Participant characteristics and questionnaire responses . . . 141
5.4.2 Model results . . . 147
5.5 Discussion . . . 150
5.5.1 Summary of results . . . 150
5.5.2 Choice of model . . . 151
5.5.3 Comparison with published estimates . . . 151
5.5.4 Limitations . . . 160
5.5.5 Strengths and added value . . . 162

6 Lifetime cost-effectiveness of aspirin for primary prevention of cardiovascular disease in people with diabetes 166
6.1 Background . . . 167
6.2 Methods . . . 169
6.2.1 Model inputs . . . 169

6.2.2 Statistical methods . . . 173
6.3 Results . . . 175
6.3.1 Comparison of treatment effects projected in simulation model with those reported in randomised studies . . . 175
6.3.2 Impact of aspirin on (quality-adjusted) life expectancy . . . 176
6.3.3 Cost-effectiveness of aspirin . . . 178
6.3.4 Scenario analysis . . . 180
6.4 Discussion . . . 183
6.4.1 Summary of results and future work . . . 183
6.4.2 Implications of findings . . . 185
6.4.3 Limitations . . . 187
6.4.4 Strengths and added value . . . 188

7 Conclusion **193**
7.1 Summary of work and contributions to the literature . . . 193
7.2 Areas for further research . . . 196
7.3 Final remarks . . . 199

Appendices

A Publications and presentations **204**

B ASCEND and UK Biobank data **206**
B.1 Endpoint definition in ASCEND . . . 206
B.2 Identifying cohort of participants in the UK Biobank satisfying the ASCEND eligibility criteria . . . 209
B.3 Adverse event ascertainment in the UK Biobank . . . 219
B.4 Derivation of missing data in the UK Biobank . . . 224

C Supplemental tables and figures **226**
C.1 Introduction . . . 226
C.2 How well does the UKPDS Outcomes Model 2 predict outcomes in ASCEND . . . 228
C.3 Simulation model for predicting first occurrences of adverse events over lifetime in people with diabetes without previous cardiovascular disease – model development, validation and updating . . . 245
C.4 Hospital costs associated with adverse events in ASCEND . . . 302

C.5 Decrements in health-related quality of life associated with adverse events in ASCEND 324
C.6 Lifetime cost-effectiveness of aspirin for primary prevention of cardiovascular disease in people with diabetes 336

List of Figures

2.1 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 39

2.2 Comparison of cumulative incidence of myocardial infarction (MI) and other ischaemic heart disease (IHD), predicted by the UKPDS-OM2 over 10 years with that observed in ASCEND, including and excluding coronary revascularisations (CRV). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 40

2.3 Comparison of 7-year cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND, stratified by decile of predicted 7-year cumulative incidence for each outcome . . 41

3.1 Flowchart of patient simulation module. *cycle* in this case is defined as year; i is the order in which events can occur in each cycle; *pat_profile* refers to the time-updated patient characteristics and disease history 72

3.2 Comparison of cumulative incidence observed in ASCEND and UK Biobank (shaded region) vs predicted by simulation model (lines) . 76

3.3 Comparison of 7-year cumulative incidence observed in ASCEND vs predicted by simulation model, stratified by decile of predicted 7-year cumulative incidence for each outcome 78

3.4 Comparison of 11-year* cumulative incidence observed in UK Biobank vs predicted by simulation model, stratified by decile of predicted 11-year* cumulative incidence for each outcome. *TIA was assessed at 8 years of follow-up as primary care data (average follow-up of 8 years available) was used to supplement ascertainment of TIA. All other events assessed at 11 years of follow-up 79

3.5 Effect of updating hazard ratio associated with presence of albuminuria on cumulative incidence of heart failure in the UK Biobank . . 85

3.6 Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) over 10 years before and after model updating . . 90

3.7 Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) over 40 years before and after model updating . . . 91

3.8 Impact of adverse event occurrence on subsequent events estimated in risk equations. The impact of adverse event occurrence (on horizontal x-axis) on subsequent events (on vertical y-axis) is split into three time points – from left to right, in year, in previous year and at least 2 years since event occurrence 94

4.1 Non-linear relationship between age and annual hospital cost 113

4.2 Average annual hospital cost and number of hospital episodes prior to, in year of, and in years subsequent to first adverse event occurrence. The black lines represent the average annual hospital cost and the coloured bars represent the average number of hospital episodes each year. The numbers in brackets are the number of participants who experienced each adverse event during the follow-up of the ASCEND study. Maintenance dialysis sessions are not included in counts of hospital episodes 120

4.3 Annual hospital costs associated with adverse event, after adjusting for diabetes type, sex, Townsend index, age, BMI, diabetes duration, HbA1c, eGFR, presence of albuminuria, retinopathy, and censoring. GI, gastrointestinal; VD, vascular death; NVD, non-vascular death. 95% CIs calculated from standard errors 125

5.1 Non-linear relationship between age and EQ-5D utility 140

5.2 EQ-5D utility by adverse event and time since event occurrence. *For intracranial haemorrhage, there were too few participants who experienced an event within 1 year prior to EQ-5D response, so the EQ-5D utility was presented for participants who had experienced an event irrespective of time of event. $\leq$1 yr, an event occurred within 1 year prior to EQ-5D questionnaire response; >1 yr, an event occurred more than 1 year prior to EQ-5D questionnaire response. The number in brackets is the number of participants who had experienced each adverse event by the time of the EQ-5D questionnaire. 95% CIs calculated from standard errors obtained from 1000 bootstrap resampling of ASCEND participants 146

5.3 Decrements in EQ-5D utility associated with adverse event occurrence, after adjusting for sex, smoking status, age and diabetes duration at time of EQ-5D questionnaire, Townsend index, BMI, eGFR and presence of albuminuria. Full model can be found in Table 5.4. 95% CIs calculated from standard errors 150

6.1 Cost-effectiveness acceptability curves showing how the probability that aspirin is cost-effective compared to no aspirin use varies with different value society places on a QALY gained (willingness-to-pay threshold) 179

6.2 Cost-effectiveness plane showing the distribution of lifetime incremental costs and quality-adjusted life years (QALYs) with aspirin compared to no aspirin use. Dotted line represents the willingness-to-pay threshold of £20,000/QALY. The '+' sign represents the mean incremental cost and QALYs with aspirin compared to no aspirin use 179

B.1 Algorithm 1 to identify participants with diabetes in the UK Biobank 213

B.2 Algorithm 2 to identify participants with diabetes in the UK Biobank 214

B.3 Algorithm 3 to identify participants with diabetes in the UK Biobank 215

C.1 PRISMA flow diagram for literature review 227

C.2 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 using different methods of imputation, for participants in aspirin placebo and omega-3 placebo arm only (N = 3651) 233

C.3 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by sex. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 235

C.4 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by age (years) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 236

C.5 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by HbA1c (%) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 237

C.6 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by duration of diabetes (years) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 238

C.7 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by BMI (kg/m^2) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 239

C.8 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, for participants with complete baseline information (N = 7578). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 240

C.9 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, for participants in aspirin placebo and omega-3 placebo arm only (N = 3651). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis) 242

C.10 Average values of risk factors predicted by UKPDS risk factor progression equations (solid black line) compared to those observed (marked 'X') in a random sample of ASCEND participants who returned blood/urine sample at average 2.5 years into follow-up in the validation cohort (N = 1249) 244

C.11 (a) Log hazard ratio for spline and linear forms of age, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by age subgroup 253

C.12 (a) Log hazard ratio for spline and linear forms of eGFR, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by eGFR subgroup 254

C.13 (a) Log hazard ratio for spline and linear forms of BMI, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by BMI subgroup 255
C.14 (a) Log hazard ratio for spline and linear forms of HbA1c, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by HbA1c subgroup 256
C.15 Plots of Schoenfeld residuals 258
C.16 Comparison of cumulative incidence observed (shaded region) vs predicted by each individual risk equations (lines) in ASCEND with different hazard distributions. The risk equations were used to predict the occurrence of event for each participant in each year, based on participant's baseline characteristics, age in year and disease history in year. These results reflect the validity of the risk equations, independent from the stochastic simulation process 274
C.17 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation model (lines) in ASCEND for different ordering of adverse events. In the unordered simulation, all events were randomly ordered. In the ordered simulation, adverse events were randomly ordered, except for urgent coronary revascularisation occurring after myocardial infarction, and vascular and non-vascular deaths occurring after all other events 276
C.18 Predicted 7-year cumulative incidence for ASCEND cohort with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 277
C.19 Predicted 7-year cumulative incidence for participants <50 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 278
C.20 Predicted 7-year cumulative incidence for participants ≥50, <60 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 279
C.21 Predicted 7-year cumulative incidence for participants ≥60, <70 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 280
C.22 Predicted 7-year cumulative incidence for participants ≥70 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 281

C.23 Predicted 7-year cumulative incidence for participants with no albuminuria in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 282
C.24 Predicted 7-year cumulative incidence for participants with albuminuria in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error 283
C.25 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by sex 285
C.26 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by age 286
C.27 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by diabetes duration 287
C.28 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND with different hazard distributions over 10 years. Exponential (Weibull) + Gompertz: Exponential (Weibull) distribution used for all events but vascular and non-vascular death. Gompertz distribution used for deaths . . . 288
C.29 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND with different hazard distributions over 40 years. Exponential (Weibull) + Gompertz: Exponential (Weibull) distribution used for all events but vascular and non-vascular death. Gompertz distribution used for deaths . . . 289
C.30 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by sex 290
C.31 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by age 291
C.32 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by diabetes duration 292
C.33 Comparison of cumulative incidence of TIA observed in UK Biobank (shaded region) vs predicted by simulation (lines) when ascertainment of TIA was supplemented by primary care data, or not 293
C.34 Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by presence of albuminuria 296

C.35 Age-sex standardised mortality ratio (SMR; using UK lifetable) over the follow-up duration in ASCEND and UK Biobank 297
C.36 Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) before and after model update, stratified by presence of albuminuria 298
C.37 Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) before and after model update, stratified by sex and age 299
C.38 Distribution of non-zero annual hospital cost 303
C.39 Mean prediction error of candidate models in each decile of predicted cost 308
C.40 Distribution of EQ-5D utilities 325
C.41 Mean prediction error of candidate models in each decile of predicted EQ-5D utility value 326
C.42 Monte-Carlo mean (coloured line) and error (coloured region) relative to sample mean (dotted line) and error (boxed region) of incremental outcomes. The coloured line and area represents the Monte-Carlo mean and 95% confidence interval around the mean accounting for Monte-Carlo error respectively. The dotted line and boxed area represents the sample mean and 95% confidence interval around the sample mean evaluated across 1000 bootstrap resamples reflecting sampling uncertainty 344

List of Tables

1.1 Published diabetes patient-level simulation models 3

1.2 Review of cost-effectiveness studies of empagliflozin using patient-level simulation models 11

2.1 Baseline characteristics of 14,569 participants with type 2 diabetes in ASCEND 35

2.2 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in ASCEND 38

2.3 Mean absolute prediction error (%) from comparison of cumulative incidence predicted by the UKPDS-OM2 and observed for participants in the ASCEND validation cohort over 7 years, by risk factor subgroups 43

2.4 Comparison of baseline characteristics of participants with type 2 diabetes in ASCEND and the UKPDS 45

2.5 Scaling factor applied to 7-year vascular death risk predicted by UKPDS-OM2 to match the risk observed in ASCEND 50

2.6 Predicted lifetime costs, life expectancies and quality-adjusted life years from 15% risk reduction in vascular death, based on risk predicted by the UKPDS-OM2 and observed in ASCEND 52

3.1 Baseline characteristics of ASCEND and UK Biobank participants included in the analysis 61

3.2 Number (%) of ASCEND and UK Biobank participants missing baseline characteristics 64

3.3 Number of participants experiencing each adverse event in ASCEND and UK Biobank 66

3.4 Functional forms of parametric proportional hazard models 70

3.5 Uno's C-statistics of simulation model for each endpoint in ASCEND and the UK Biobank 77

3.6 Methods for updating parametric proportional hazard models . . . 83

3.7 Strategies for model updating 88

3.8 Life expectancies of ASCEND and UK Biobank participants compared to life expectancies from other sources 98

4.1 Baseline characteristics of 15,436 participants included in the analysis 116
4.2 Numbers and costs of different types of hospital episodes 118
4.3 Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events 121

5.1 Number (%) of participants included in analysis with missing EQ-5D response 138
5.2 Characteristics of 11,683 participants included in the analysis 142
5.3 EQ-5D-5L questionnaire responses from 11,683 participants 145
5.4 EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events 147
5.5 Comparison of health-related QoL decrements associated with diabetes-related complications across diabetes studies 154
5.6 Comparison of health-related QoL decrements associated with bleeding events across studies 158

6.1 Input parameters for simulation model 171
6.2 Treatment effects of aspirin for different scenarios 172
6.3 Addressing uncertainty 174
6.4 Comparison of treatment effects on deaths and composite endpoints achieved by simulation model at 10 years from those reported . . . 175
6.5 Lifetime gains in quality-adjusted life years (QALYs) and life expectancies (LYs) with aspirin compared to no aspirin use in UK Biobank participants with diabetes without previous cardiovascular disease 177
6.6 Impact of aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank for different sets of aspirin effects 178
6.7 Impact of aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank under different scenarios of aspirin effects 181
6.8 Quality-adjusted life years (discounted at 3.5% per annum) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline 183

B.1 Identifying adverse events from ASCEND 207
B.2 Defining baseline characteristics for participants in the UK Biobank 209
B.3 Classification of diabetes type based on algorithm 212
B.4 Ascertainment of disease history at baseline for 26,430 UK Biobank participants identified with diabetes 216
B.5 Ascertainment of adverse events in the UK Biobank 220
B.6 First-stage imputation of baseline characteristics and clinical risk factors for the UK Biobank 224

C.1 Search strategy for identifying cost-effectiveness analysis of empagliflozin, with no restrictions on population or comparator 226
C.2 Inputs required for UKPDS-OM2 and their availability in ASCEND 228
C.3 Definitions of outcomes in UKPDS-OM2 and definitions of corresponding adverse events in ASCEND 230
C.4 Baseline characteristics of 14,569 participants with type 2 diabetes in ASCEND before and after imputation 234
C.5 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in ASCEND with complete baseline information (N = 7578) 241
C.6 Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in the ASCEND placebo aspirin and placebo omega-3 fatty acid arm only (N = 3651) 243
C.7 Baseline characteristics of ASCEND and UK Biobank participants included in the analysis, after imputation 245
C.8 List of variables included for selection 248
C.9 Number (%) of participants with each disease history at time of occurrence of each adverse event in ASCEND 250
C.10 Hazard ratios of non-linear terms (categorised) estimated in Cox proportional hazard models 257
C.11 Risk equations for predicting risks of adverse events 259
C.12 Akaike's information criteria of parametric models with different hazard distributions 275
C.13 Model performance in ASCEND and the UK Biobank before and after model updating 284
C.14 Event ascertainment of disease endpoints using routine healthcare data 294

C.15 Uno's C-statistics of simulation model for each endpoint in the UK Biobank, before and after model update 300
C.16 Comparison of bleeding risk scores 301
C.17 Estimating the average annual cost of maintenance dialysis 302
C.18 Predictive performance of models using different forms of age 302
C.19 Marginal effects of different forms of age on annual hospital cost . . 302
C.20 Results from Hosmer-Lemeshow test and Pregibon link test 304
C.21 Results from modified Park test 305
C.22 Results from Copas test 306
C.23 Predictive performance of candidate models 307
C.24 Annual hospital costs associated with adverse event occurrence estimated by single-equation and two-part models 309
C.25 Baseline characteristics of 15,436 participants included in the analysis, before and after imputation of missing data 311
C.26 Number and costs of outpatient hospital episodes by treatment speciality (for episodes with no procedures performed) or HRG sub-chapter (for episodes with procedure(s) performed) (top 20 occurrences) 314
C.27 Number and costs of inpatient hospital episodes by HRG subchapter (top 20 occurrences) 317
C.28 Average number of hospital episodes and hospital cost each year, stratified by time since event occurrence 319
C.29 Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events, excluding non-attended outpatient episodes (sensitivity analysis) 321
C.30 Self-reported diabetes medication use at baseline and at about 6.5 years into follow-up 323
C.31 Marginal effects of different forms of age on EQ-5D utility 324
C.32 Predictive performance of models using different forms of age 324
C.33 Predictive performance of candidate models 325
C.34 Results from Copas test 326
C.35 Characteristics of 11,683 participants included in the analysis, before and after imputation of missing data 327
C.36 EQ-5D-5L questionnaire responses from 11,683 participants, before and after imputation of missing data 330
C.37 Mean (SD) of EQ-5D utility by number of comorbid events 331
C.38 Mean (SD) of EQ-5D utility by adverse event and time since adverse event occurrence 332

C.39 EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events, with (a) all adverse events included, and (b) using van Hout tariffs (sensitivity analysis) 334
C.40 Effects of antithrombotic medication (aspirin / other antiplatelet / anticoagulants) estimated in ASCEND risk equations 336
C.41 Summary of treatment effects of aspirin from primary prevention trials 337
C.42 Baseline distribution of risk factors identified from QResearch among 18,250 UK Biobank participants with diabetes without previous cardiovascular disease 342
C.43 Lifetime gains in quality-adjusted life years (QALYs) and life expectancies (LYs) with aspirin compared to no aspirin use in UK Biobank participants with diabetes without previous cardiovascular disease 345
C.44 Life years (discounted at 3.5% per annum) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline 346
C.45 Quality-adjusted life years (QALYs; undiscounted) and life years (LYs; undiscounted) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline, excluding treatment effects on death 346

List of Abbreviations

ASCEND . . . A Study of Cardiovascular Events iN Diabetes

A&E . . . . . Accident and emergency

BMI . . . . . Body mass index

CI . . . . . Confidence interval

CVOT . . . . . Cardiovascular outcomes trial

DBP . . . . . Diastolic blood pressure

DPP-4 . . . . . Dipeptidyl peptidase-4

eGFR . . . . . Estimated glomerular filtration rate

ESRD . . . . . End-stage renal disease

GI . . . . . Gastrointestinal

GLM . . . . . Generalised linear model

GLP-1 . . . . . Glucagon-like peptide-1

HbA1c . . . . Glycated haemoglobin

HDL . . . . . High-density lipoprotein

HES . . . . . Hospital Episode Statistics

HR . . . . . Hazard ratio

HRG . . . . . Healthcare Resource Group

ICER . . . . . Incremental cost-effectiveness ratio

IHD . . . . . Ischaemic heart disease

LDL . . . . . Low-density lipoprotein

MAPE . . . . Mean absolute percentage/prediction error

MICE . . . . . Multivariate imputation by chained equations

MPE . . . . . Mean prediction error

MSE . . . . . Mean squared error

NICE . . . . . National Institute for Health and Care Excellence

NMB . . . . . Net monetary benefit

PMM . . . . . Predictive mean matching

PPV . . . . . Positive predictive value

QALY . . . . . Quality-adjusted life year

QoL . . . . . Quality of life

RCT . . . . . Randomised controlled trial

RMSE . . . . . Root-mean-squared error

SBP . . . . . Systolic blood pressure

SGLT-2 . . . . Sodium-glucose co-transporter-2

SMR . . . . . Standardised mortality ratio

TIA . . . . . Transient ischaemic attack

UKPDS . . . . United Kingdom Prospective Diabetes Study

UKPDS-OM . United Kingdom Prospective Diabetes Study Outcomes Model

1 Introduction

1.1 Diabetes simulation models

Decision-analytic modelling is commonly used to synthesise clinical and economic data to evaluate health outcomes and costs of healthcare interventions [1]. These models are used to estimate clinical- and cost-effectiveness of novel interventions and inform their implementation and reimbursement; allocate limited resources between competing interventions; make comparisons of alternative interventions when there are no relevant trials; and answer other health policy questions. Randomised controlled trials (RCTs) are the gold standard for evaluating efficacy and safety of healthcare interventions, and they inform the treatment effects of interventions based on observations within the follow-up duration of the trial. However, to inform policy or treatment decisions, the duration over which healthcare interventions are evaluated needs to be sufficiently long to capture all important impacts on health outcomes and/or costs [2]. This is particularly relevant for diabetes, a chronic disease associated with multiple complications which develop over lifetime and are major drivers of long-term healthcare costs, deterioration in health-related quality of life (QoL), and mortality [3–8]. Thus, a lifetime analysis is often needed when evaluating novel diabetes treatments. Treatment effects on different clinical outcomes observed within a study or across different studies also need to be combined and extrapolated to the longer-term to comprehensively reflect the lifetime net

benefit of the intervention [2]. This motivated the development and use of lifetime diabetes simulation models.

Decision analytic models can vary in complexity. Decision trees and cohort Markov models are aggregate models which track the proportion of patients undergoing different events. In contrast, discrete-time/discrete-event patient-level simulation models follow the progress of each individual patient in the population across time. The two key factors in deciding the type of model to use are (1) whether interactions (e.g. between individuals, between events, or between risk factors and events) are important, and (2) whether the outcomes of interest are at a cohort level or an individual level [9, 10]. For diabetes, discrete-time and discrete-event patient-level simulation models have been popular choices because of their ability to capture the associations between biomarker values and complications thus better capturing patient heterogeneity, and also to account for interactions between complications. However, developing such models is time-consuming, requiring good quality patient-level data with long follow-up and considerable technical expertise.

The UK Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS-OM) is a landmark model and was the model chosen by the National Institute for Health and Care Excellence (NICE) to inform guidelines for type 2 diabetes management in the UK [11]. The UKPDS-OM is a patient-level simulation model that uses time-variant risk profiles of people with type 2 diabetes to predict the occurrences of diabetes-related macro- and micro-vascular complications over lifetime, and simultaneously quantifies their quality-adjusted life years (QALYs) and healthcare costs [12]. The model was originally developed using UKPDS patient-level data from 1977 to 1997 (median follow-up time 10.3 years). Risk equations in the model (UKPDS 68) were subsequently updated using additional post-trial follow-up data from 1997 to 2007 (overall median follow-up 17.6 years) and version 2 of the model (UKPDS-OM2; UKPDS 82) was released [13]. The key advantage of the UKPDS-OM2 is that it was developed using data from a large diabetes trial following people newly diagnosed with type 2 diabetes over many years, with longitudinal data on adjudicated disease endpoints and risk factors. The risk

equations in both versions of the model (UKPDS 68, UKPDS 82) were published in full, which has allowed researchers to adapt them for their models and needs. Other simulation models have also been developed more recently using de-novo risk equations estimated from trials such as ACCORD [14, 15], EMPA-REG OUTCOME [16, 17], and CREDENCE [18, 19]. Fewer studies have used observational data, with examples being from the Swedish National Diabetes Register [20, 21]. Although observational data benefit from being more representative of the general patient population than participants recruited in trials, significant challenges related to the use of observational data include greater uncertainty in event identification (in contrast to adjudicated endpoints in trials) and higher degree of missingness in patient characteristics and clinical markers.

Table 1.1 summarises published diabetes patient-level simulation models (excluding type 1 only models) and the main data sources informing cardiovascular and mortality risks. These were identified from previous systematic reviews of diabetes models [22–26], a diabetes model registry [27], and a literature search[1].

Table 1.1: Published diabetes patient-level simulation models

Name of model or first author, year of publication	Main source of data for predicting cardiovascular disease and mortality
Archimedes (2003) [28]	Framingham [29], UKPDS etc.
UKPDS-OM1 (UKPDS 68)* (2004) [12]	UKPDS 68
CORE (2004) [30]	UKPDS 68/Framingham, national statistics
IQVIA CORE V9† [31]	UKPDS 68/UKPDS 82/ADVANCE [32]/Swedish National Diabetes Register [21], etc.
Zhou (2005) [33]	UKPDS, UKPDS risk engines 56 [34] and 60 [35], national statistics, etc.
EAGLE (2006) [36]	UKPDS
Cardiff (2006) [37]	UKPDS 68/UKPDS 82, national statistics
Tilden (2007) [38]	UKPDS 68
Ontario Diabetes Economic Model (2007) [39]	UKPDS 68

[1]The latest review searched for articles up till 2020. A PubMed search was conducted for articles released between 2019-2022 using the MESH terms “models, economic”, “computer simulation”, “patient simulation”, with “diabetes” in the title.

Table 1.1: Published diabetes patient-level simulation models *(continued)*

Name of model or first author, year of publication	Main source of data for predicting cardiovascular disease and mortality
Sheffield type 2 diabetes (2007) [40]	UKPDS risk engines 56, 60, and 66 [41]
JADE (2008) [42]	UKPDS 68
ECHO-T2DM (2013) [43]	UKPDS 68/UKPDS 82/ADVANCE/Swedish National Diabetes Register
UKPDS-OM2 (UKPDS 82)* (2013) [13]	UKPDS 82
MDM (2014) [44]	Framingham, UKPDS 56, National Health and Nutrition Examination Survey
BRAVO* (2014) [15]	ACCORD [14]
SPHR Diabetes Prevention Model (2015) [45]	QRISK2 [46], Office for National Statistics
Syreon Diabetes Control Model (2016) [47]	Framingham, UKPDS 56 and 60, etc.
Kansal* (2016) [17]	EMPA-REG OUTCOMES [16], Office for National Statistics
COMT (2018) [48]	RECODe [49] risk equations estimated using ACCORD study data re-calibrated to Chinese cohort
US T2D Policy Model (2018) [50]	UKPDS 82
Cornerstone (2019) [51]	UKPDS 82
CREDEM-DKD* (2020) [19]	CREDENCE [18]
CHIME* (2021) [52]	Hong Kong Hospital Authority Clinical Management System data
JJCEM* (2021) [53]	Japan Diabetes Complications Study/Japanese Elderly Diabetes Intervention Trial [54]

* De-novo risk equations estimated from individual patient-level data.
† Extension of CORE, 2004

1.1.1 Limitations of existing diabetes models

RCTs of diabetes treatments have traditionally focused on short-term glycaemic efficacy [55]. The UKPDS-OM and most subsequent diabetes simulation models were designed to allow propagation of treatment effects through changes in risk factors (e.g. glycated haemoglobin [HbA1c] reduction) observed in short-term trials to long-

term health outcomes (also referred to as "hard" outcomes). Such models require information on risk factor progression over the simulated duration. Treatment effects are then propagated through modification of risk factor progression, which assumes that treatment-associated risk factor modifications have similar impacts on hard outcomes as natural differences in risk factors. Risk factor progression equations were developed using the UKPDS data [12, 56] and are used in most simulation models which use the UKPDS risk equations. The risk factor trajectories estimated in the UKPDS may no longer be representative of those seen in contemporary cohorts due to improvements in treatments and management strategies since the UKPDS-era. More importantly, whether or not treatment-induced changes in risk factors impact hard outcomes similarly to natural differences in risk factors is uncertain. Asche et al. (2014) reviewed the economic analyses of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes published up till 2013 [57]. All 15 studies included in the review propagated treatment effects through risk factor changes (particularly HbA1c and weight), with small absolute changes in risk factors translating into major differences in long-term diabetes complications. The review highlighted that many studies were based on clinical efficacy observed in short-term RCTs (26- to 52-week data) and it was questionable if the effects observed could translate into long-term benefits of the magnitudes predicted. Daly et al. (2022) identified methodological inconsistencies and uncertainty in how surrogate markers influenced hard outcomes as key limitations in economic models of diabetes treatments flagged by the reviewers and clinical experts in NICE's technology appraisal program [58].

In 2008, in response to concerns about potential increase in cardiovascular disease risk associated with the use of certain anti-diabetes drugs [59, 60], the United States Food and Drug Administration issued cardiovascular safety guidelines for the development of anti-diabetes drugs for type 2 diabetes [61]. This has led to the emergence of diabetes cardiovascular outcomes trials (CVOTs), which are placebo-controlled trials designed to evaluate long-term cardiovascular safety of anti-diabetes drugs. Many of these trials were designed to promote glycaemic equipoise

between the treatment groups to assess the effect of new glucose-lowering drugs excluding the influence of different glucose levels between the treatment arms [55]. While they were primarily non-inferiority trials, some have demonstrated superiority of treatment versus placebo [16, 62]. Results from these trials suggested that some of these drugs have effects beyond glucose lowering and changes to other traditional risk factors. Indeed, many studies using existing diabetes models have failed to replicate the full extent of cardiovascular benefits observed in these trials [63–65]. The UKPDS-OM2 is limited structurally to perform evaluations on CVOTs because the model is unable to directly incorporate treatment effects on disease endpoints independently from changes to risk factor(s). Other models provide this flexibility in their software and one can additionally include the "unexplained" treatment effects, although care needs to be taken in adjusting the observed treatment effects to ensure no double counting [66].

More fundamentally, external validations of the UKPDS-OM2 and other models using the UKPDS risk equations in observational cohorts and recent CVOTs have found the risk of cardiovascular outcomes to be overpredicted, with generally poor discrimination[2] [49, 63, 67–69]. These discrepancies may be attributable to the changing pharmacological landscape and improvements in the management of risk factors and complications in people with diabetes, among other factors.

Given the emerging evidence from CVOTs, new simulation models have been developed using more recent trial data and observational cohort data. With the exception of the BRAVO model [15], the external validity of these models have yet to be confirmed. The modelling exercise in the Ninth Mount Hood Diabetes Challenge [63], a forum for diabetes modellers to discuss and compare models, showed that calibration of models to the EMPA-REG OUTCOME trial did not improve model fit in the CANVAS trial. This suggests that even if calibration-in-the-large[3] was achieved, the differential features of CVOTs (e.g. differences in

[2]Discrimination refers to how well the predicted probabilities of a model distinguish between patients with the disease and patients without the disease.

[3]Calibration-in-the-large refers to how well the risk predicted by the model agrees with the risk observed across the population of interest on average.

participant characteristics or trial setting) may not be captured in existing models. More generally, CVOTs to date specifically recruited participants at high risk of cardiovascular disease (people who had a history of cardiovascular disease, or people with known risk factors), and these models are likely not generalisable to people with diabetes without previous cardiovascular disease.

1.1.2 Usage and/or adaptation of diabetes models for cost-effectiveness analysis

As described, issues of existing diabetes simulation models include (1) the inability to accurately predict event rates in contemporary cohorts, and (2) challenges to capture treatment effects of novel glucose-lowering drugs appropriately. Willis et al. (2019) reviewed the mechanisms used in recent cost-effectiveness studies to model the treatment effects found in CVOTs [66]. The most common approach was to directly use hazard ratios (HRs) / relative risk reductions observed in RCTs, without incorporating effects on known risk factors reported in the RCTs. Some studies used a combination of both, risking double-counting (although this can be mitigated by adjusting the relative risk reductions applied). I expand on their previous review by further looking at how cost-effectiveness studies have adapted existing patient-level simulation models to match event rates in the cohort of interest. As this is not intended to be a comprehensive review but rather provide examples of how models have been used or adapted for cost-effectiveness analysis, I restricted the review to include only cost-effectiveness studies on empagliflozin, one of the earliest successful anti-diabetes drugs to have demonstrated cardioprotective effects independent from glucose control (EMPA-REG OUTCOME trial) [16]. No restrictions were placed on the population or comparator used in the study. EMBASE and MEDline were systematically searched for articles published in English up till 01/05/2022 (search terms used in Supplemental Table C.1). The initial search yielded 117 records, of which 20 were duplicates. 55 studies were excluded based on title and abstract screening, and a further 16 were excluded after full-text review (10 did not include cost-effectiveness modelling, six did not use patient-level simulation

models). 26 studies were included in the final review (Table 1.2; PRISMA flow diagram in Supplemental Figure C.1).

10 of the 26 studies used clinical efficacy data from short-term trials of up to 52 weeks which reported treatment efficacy on surrogate endpoints including HbA1c and weight [70–79]. The decision models used in these studies included IQVIA CORE (n = 8), UKPDS-OM1 (n = 1), UKPDS-OM2 (n = 1), ECHO-T2DM (n = 1), and the Cardiff model (n = 1). These studies propagated treatment effects through known biomarkers. Notably, the UKPDS risk equations were used in all frameworks. No model adaptation was adopted in any of the studies beyond using country-specific death rates in three of them. One study evaluating cost-effectiveness from the Chinese perspective [71] used the UKPDS-OM2 as is, despite possible differences in population and health systems not captured in the UKPDS risk equations [80, 81].

15 of the 26 studies used clinical efficacy from longer-term CVOTs which reported HRs on hard endpoints as well as changes to biomarkers such as weight and HbA1c [82–96]. Kansal et al. (2016) developed a new framework with de-novo risk equations estimated from the EMPA-REG OUTCOME trial [17]. The framework deviated from previous diabetes models by predicting complications based on baseline characteristics and event occurrence during follow-up instead of risk factor changes. This modelling approach placed greater emphasis on correlations between event outcomes. The Kansal model was used in nine studies [83–87, 93–96]. Among these, three studies used country-specific life tables to adapt death rates to the country of interest [84, 93, 96], while five studies re-estimated the risk equations using the EMPA-REG OUTCOME data to adapt the model for different endpoints and/or for different subgroups of patients [83, 85–87, 94]. All studies using the Kansal model directly used the HRs observed in the trial(s) to model the treatment effects of empagliflozin. The IQVIA CORE framework was used in five studies [82, 89–92]. In all five studies, an iterative process was used to identify relative risk adjustments to the risks predicted by the UKPDS 82 risk equations to match the 3- or 4-year clinical outcomes observed in the trial. It was assumed that treatment escalation occurred when HbA1c reaches 8.5%, and subsequent to this

the relative risk adjustments would no longer apply. To model the treatment effect of empagliflozin, all studies used a combination of treatment effects mediated by known risk factors and HRs observed in the trial(s). One study used the UKPDS 82 risk equations to predict event risks in people without a first cardiovascular disease and risk equations in the Kansal framework to predict event risks in people who have had a previous cardiovascular disease [88]. Treatment effects on biomarkers were used for people without a first cardiovascular disease, while HRs were used for people with a previous cardiovascular disease to model treatment effects.

One further study used clinical efficacy from both short-term trials and long-term CVOTs [97]. The study used the US T2D Policy Model, applying treatment effects on biomarkers in the first year, and HRs in subsequent years. No model adjustments were made.

Even when long-term trial data were available, most studies included treatment effects on known risk factors in addition to HRs on endpoints observed in trial(s), and none reported how the issue of double-counting was addressed. With the exception of the Kansal model, all other models relied on the UKPDS risk equations for predicting cardiovascular events or mortality, and/or for modelling the progression of risk factors over time (independent of treatment effects). The majority of the studies made no adjustments to the model beyond using country-specific mortality rates. The UKPDS risk equations have been demonstrated to overpredict cardiovascular events and mortality, which could lead to biased cost-effectiveness results. Some studies adapted the IQVIA CORE model to replicate event rates observed in the EMPA-REG OUTCOME trial [82, 89–92]. The mispredictions in the UKPDS risk equations are likely due both to temporal changes in background event rates, as well as to changes in the associations between risk factors and outcomes. For example, statin use has risen sharply since the UKPDS era [98] (only 0.3% of UKPDS participants were taking lipid-lowering drugs at baseline [99]). Cholesterol levels measured in contemporary patient cohorts are thus modified by lipid-lowering treatments, and consequently the association between cholesterol levels and health outcomes may differ from those estimated in the UKPDS. Nine of the 17 studies

which require specification of risk factor progression over time used the equations estimated in UKPDS 68 [70, 72, 73, 75–78, 88, 92]. Hence, even if "calibration-in-the-large" was achieved, the discrimination of the model and calibration of the model in risk factor subgroups may still be poor. A further implication is that treatment effects propagated through these risk factors may lead to biased results. The findings from this review align with findings from a recent systematic review of economic models submitted to NICE's technology appraisal program for diabetes treatments [58]. The main issues repeatedly flagged in multiple submissions by the evidence review group and clinical experts involved were lack of model transparency, methodological inconsistencies and uncertainty in how surrogate markers (e.g. weight and HbA1c) influenced hard outcomes, and lack of external validation of model outputs. Given the rapidly growing evidence base from diabetes CVOTs, new frameworks for diabetes modelling such as that by Kansal et al. and new risk equations reflecting contemporary event rates and associations between risk factors and events are required.

Table 1.2: Review of cost-effectiveness studies of empagliflozin using patient-level simulation models

Framework used	Publication	Clinical evidence	Context	Adaptations	Treatment effects	Progression of risk factors
Clinical evidence from short-term trials						
ECHO-T2DM; Cardiff (UKPDS 82); UKPDS-OM1	Johnston et al., 2017 [70]	Trials of 24-26 weeks	HTA of SGLT-2 inhibitors; UK	-	Treatment effect on known biomarkers only (Tx-biomarkers)	Linear drifts (informed by UKPDS); UKPDS 68
IQVIA CORE	Ramos et al., 2020 [72]	PIONEER 2	UK	-	Tx-biomarkers	UKPDS 68
IQVIA CORE (UKPDS 68)	Bain et al., 2020 [73]	PIONEER 2-4	UK	-	Tx-biomarkers	UKPDS 68; Willis et al. (2017) [100]
IQVIA CORE (UKPDS 68)	Gorgojo-Martinez et al., 2020 [74]	EMPA-REG MET & SUSTAIN 2/7	Spain	Mortality based on Spain-specific life tables	Tx-biomarkers	NR
IQVIA CORE (UKPDS 68)	Capehorn et al., 2021 [75]	PIONEER 2 & SUSTAIN 2/3/8	UK	-	Tx-biomarkers	UKPDS 68; Willis et al.
IQVIA CORE (UKPDS 68)	Malkin et al., 2021 [76]	PIONEER 2-4	Netherlands	Mortality based on Netherlands-specific life tables	Tx-biomarkers	UKPDS 68; Willis et al.
IQVIA CORE (UKPDS 68)	Malkin et al., 2022 [77]	PIONEER 2	Portugal	Mortality based on Portugal-specific life tables	Tx-biomarkers	UKPDS 68; Willis et al.

Table 1.2: Review of cost-effectiveness studies of empagliflozin using patient-level simulation models *(continued)*

Framework used	Publication	Clinical evidence	Context	Adaptations	Treatment effects	Progression of risk factors
IQVIA CORE (UKPDS 82)	Ehlers et al., 2022 [78]	PIONEER 2	Denmark	-	Tx-biomarkers	UKPDS 68
IQVIA CORE (UKPDS 82)	Ehlers et al., 2022 [79]	PIONEER 2 & SUSTAIN 2/3/8	Denmark	-	Tx-biomarkers	Willis et al.
UKPDS-OM2	Hu et al., 2021 [71]	PIONEER 2 & SUSTAIN 2/3/8	China	-	Tx-biomarkers	NR
Clinical evidence from cardiovascular outcomes trials						
IQVIA CORE (UKPDS 82)	Ramos et al., 2019 [82]	EMPA-REG OUTCOME	UK	Iterative process to identify RR adjustment to match 3-year clinical outcomes observed in trials; UKPDS 82 used after treatment escalation occurs at 9 years (HbA1c 8.5%)	Tx-biomarkers + HRs	Linearly extrapolated
IQVIA CORE (UKPDS 82)	Ramos et al., 2020 [89]	EMPA-REG OUTCOME & LEADER	UK	As above in Ramos et al. (2019)	Tx-biomarkers + HRs	Linearly extrapolated
IQVIA CORE (UKPDS 82)	Ehlers et al., 2021 [90]	EMPA-REG OUTCOME	Denmark	As above in Ramos et al. (2019)	Tx-biomarkers + HRs	NR

Table 1.2: Review of cost-effectiveness studies of empagliflozin using patient-level simulation models *(continued)*

Framework used	Publication	Clinical evidence	Context	Adaptations	Treatment effects	Progression of risk factors
IQVIA CORE (UKPDS 82)	Ramos et al., 2021 [91]	EMPA-REG OUTCOME	China	As above in Ramos et al. (2019)	Tx-biomarkers + HRs	Linearly extrapolated
IQVIA CORE (UKPDS 82)	Salem et al., 2021 [92]	EMPA-REG H2H-SU	China	Iterative process to identify RR adjustment to match 4-year clinical outcomes observed in trials; UKPDS 82 used after treatment escalation occurs at HbA1c 8.5%	Tx-biomarkers + HRs	UKPDS 68
Kansal	Gourzoulidis et al., 2018 [93]	EMPA-REG OUTCOME	Greece	Mortality based on Greece-specific life tables	HRs only	-
Kansal	Kaku et al., 2019 [94]	EMPA-REG OUTCOME	Japan	Risk equations re-estimated in Asian subgroup in EMPA-REG OUTCOME trial	HRs only	-
Kansal	Kansal et al., 2019 [95]	EMPA-REG OUTCOME	UK	-	HRs only	-
Kansal	Men et al., 2020 [96]	EMPA-REG OUTCOME	China	Mortality based on China-specific life tables	HRs only	-

Table 1.2: Review of cost-effectiveness studies of empagliflozin using patient-level simulation models *(continued)*

Framework used	Publication	Clinical evidence	Context	Adaptations	Treatment effects	Progression of risk factors
Kansal	Reifsnider et al., 2020 [83]	EMPA-REG OUTCOME	Heart failure subgroup; UK	Risk equations re-estimated in heart failure subgroup in EMPA-REG OUTCOME trial	HRs only	-
Kansal	Gourzoulidis et al., 2021 [84]	EMPA-REG OUTCOME	Greece	Mortality based on Greece-specific life tables	HRs only	-
Kansal	Reifsnider et al., 2021 [85]	EMPA-REG OUTCOME	US	Different renal endpoints used; risk equations re-estimated	HRs only	-
Kansal	Reifsnider et al., 2021 [86]	EMPA-REG OUTCOME	Diabetic kidney disease subgroup; US	Different renal endpoints used; risk equations re-estimated in DKD subgroup in EMPA-REG OUTCOME trial	HRs only	-
Kansal	Reifsnider et al., 2022 [87]	EMPA-REG OUTCOME	Diabetic kidney disease subgroup; US	Different renal endpoints used; risk equations re-estimated in DKD subgroup in EMPA-REG OUTCOME trial	HRs only	-

Table 1.2: Review of cost-effectiveness studies of empagliflozin using patient-level simulation models *(continued)*

Framework used	Publication	Clinical evidence	Context	Adaptations	Treatment effects	Progression of risk factors
UKPDS 82 for people without first CVD; Kansal for people with history of CVD	Reifsnider et al., 2021 [88]	EMPA-REG OUTCOME	US NHANES	-	Tx-biomarkers for people without previous CVD; HRs for people with history of CVD	UKPDS 68
Clinical evidence from both short-term and cardiovascular outcomes trials						
US T2D Policy Model	Guzauskas et al., 2021 [97]	PIONEER 6; SUSTAIN 6; PIONEER 2-4	US NHANES	-	Tx-biomarkers (first year) + HRs	Willis et al.

Note:
HR, hazard ratio; NR, not reported.

1.2 The ASCEND study - aspirin for primary prevention of cardiovascular disease in people with diabetes

A Study of Cardiovascular Events iN Diabetes (ASCEND) is a two-by-two factorial design trial which randomised 15,480 participants in the UK aged 40 and above with established diabetes but without diagnosed cardiovascular disease to 100mg aspirin daily or matching placebo, and, separately, to 1g capsule containing omega-3 fatty acids daily or placebo [101–103]. It is one of the largest RCTs among people with diabetes. Participants were recruited between 2005 and 2011 and were followed for a median of 7 years until 2017, with clinically adjudicated adverse events for key endpoints of interest. Different from many recent CVOTs, the ASCEND study recruited participants without previous diagnosed cardiovascular disease. This makes it an excellent resource to develop a new framework for modelling disease progression in people with diabetes to be used when evaluating treatments for the primary prevention of cardiovascular disease.

The assessment of efficacy and safety of aspirin in ASCEND also provides an interesting case study to apply the envisaged framework. Aspirin is a widely used antithrombotic drug. In people who already have a previous cardiovascular disease, the absolute benefits of aspirin in reducing the risks of serious vascular events substantially exceed the risk of bleeding [104]. However, for people who have yet to experience a cardiovascular event, the balance between benefits and harms is less clear as the absolute risk of cardiovascular disease and thus the absolute benefits are generally lower. This is true even for people with diabetes who are at higher risk of cardiovascular disease. In ASCEND, aspirin was found to reduce the risks of serious vascular events from 9.6% to 8.6% but increased the risks of major bleeding events from 3.2% to 4.1% [102]. This led the authors to conclude that "the absolute benefits were largely counterbalanced by the bleeding hazard". However, a formal quantitative evaluation of the net benefits of aspirin over a lifetime is needed to inform clinical guidelines and recommendations from health

technology assessment agencies. Cost-effectiveness is a familiar, commonly used, and recommended approach [2] to guide decisions about the net benefit of aspirin, where the impacts of aspirin on cardiovascular and bleeding risks can be jointly quantified in terms of healthcare costs and (quality-adjusted) life expectancy over the long term.

1.3 Research objectives

The overarching aim of this thesis is to develop a framework for modelling long-term health outcomes and costs in people with diabetes without cardiovascular disease. The model can combine and extrapolate treatment effects on a number of health outcomes and estimate the net benefit of an intervention for health economic assessments. To achieve this aim, my thesis will also address the following research questions:

- How well does the UKPDS-OM predict outcomes in ASCEND, a contemporary trial in people with diabetes?
- What are the impacts of adverse events on healthcare costs and quality of life in a contemporary setting?

Finally, the developed model will be used to evaluate if long-term aspirin use is cost-effective for the primary prevention of cardiovascular disease in people with diabetes.

1.4 Structure of thesis

In Chapter 2, I assess the performance of the UKPDS-OM2 in ASCEND participants, adding to the evidence base an individual patient data external validation of the model in the UK context. I discuss the implications of model mispredictions on cost-effectiveness analysis, justifying the need for new risk equations for modelling outcomes in people with diabetes.

The new framework for modelling long-term health outcomes and costs in people with diabetes is developed in Chapters 3 to 5, mainly using data from the ASCEND

study. In Chapter 3, I develop a patient-level stochastic discrete-time simulation model to predict first occurrences of cardiovascular, bleeding, cancer, end-stage renal disease, amputation and death events over lifetime based on risk equations estimated using participants' data in ASCEND. The model is validated internally using the ASCEND data and further validated externally in a cohort of participants from the UK Biobank satisfying the ASCEND inclusion criteria. Details of identification of cohort and ascertainment of adverse events from the UK Biobank are described. Discrepancies between model predictions and observations in the UK Biobank are explored, and an issue-driven approach is adopted to update the model.

In Chapters 4 and 5, I analyse the hospital costs and decrements in health-related quality of life (QoL) associated with adverse events included in the framework. I derive hospital costs incurred by each participant over the follow-up duration of the trial using linked hospital records for ASCEND participants, and derive QoL utilities from participants' responses to the EQ-5D questionnaire. The results are compared with previous published estimates, setting the context for the relevance of the results found.

In Chapter 6, I assess the cost-effectiveness of aspirin use in people with diabetes without previous cardiovascular disease using the framework developed. Scenario analyses are performed to assess the impact of different treatment effects on cost-effectiveness. I discuss the implications of this given current guideline recommendations on aspirin use for primary prevention of cardiovascular disease.

Each chapter includes a discussion of strengths and limitations, and highlights the added value of the work. Finally, I conclude in Chapter 7 by summarising the novel contributions of the work in this thesis and propose areas for future research.

References

1. Briggs A, Sculpher M, and Claxton K. Decision Modelling for Health Economic Evaluation. Oxford University Press, 2006.
2. National Institute for Health and Care Excellence. NICE Health Technology Evaluations: The Manual. 2022. URL: https://www.nice.org.uk/process/pmg36 (visited on 10/02/2022).
3. Hex N, Bartlett C, Wright D, Taylor M, and Varley D. Estimating the Current and Future Costs of Type 1 and Type 2 Diabetes in the UK, Including Direct Health Costs and Indirect Societal and Productivity Costs. Diabet Med 2012;29:855–62. DOI: 10.1111/j.1464-5491.2012.03698.x.
4. Alva M, Gray A, Mihaylova B, and Clarke P. The Effect of Diabetes Complications on Health-Related Quality of Life: The Importance of Longitudinal Data to Address Patient Heterogeneity. Health Economics 2014;23:487–500. DOI: 10.1002/hec.2930.
5. Alva ML, Gray A, Mihaylova B, Leal J, and Holman RR. The Impact of Diabetes-Related Complications on Healthcare Costs: New Results from the UKPDS (UKPDS 84). Diabet Med 2015;32:459–66. DOI: 10.1111/dme.12647.
6. Rawshani A, Rawshani A, Franzén S, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. New England Journal of Medicine 2017;376:1407–18. DOI: 10.1056/NEJMoa1608664.
7. Tancredi M, Rosengren A, Svensson AM, et al. Excess Mortality among Persons with Type 2 Diabetes. New England Journal of Medicine 2015;373:1720–32. DOI: 10.1056/NEJMoa1504347.
8. Baena-Díez JM, Peñafiel J, Subirana I, et al. Risk of Cause-Specific Death in Individuals With Diabetes: A Competing Risks Analysis. Diabetes Care 2016;39:1987–95. DOI: 10.2337/dc16-0614.
9. Brennan A, Chick SE, and Davies R. A Taxonomy of Model Structures for Economic Evaluation of Health Technologies. Health Econ 2006;15:1295–310. DOI: 10.1002/hec.1148.
10. Briggs ADM, Wolstenholme J, Blakely T, and Scarborough P. Choosing an Epidemiological Model Structure for the Economic Evaluation of Non-Communicable Disease Public Health Interventions. Population Health Metrics 2016;14:17. DOI: 10.1186/s12963-016-0085-1.
11. National Institute for Health and Care Excellence. Type 2 Diabetes in Adults: Management (NG28). 2022. URL: https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-pdf-78671532569 (visited on 08/19/2022).
12. Clarke PM, Gray AM, Briggs A, et al. A Model to Estimate the Lifetime Health Outcomes of Patients with Type 2 Diabetes: The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS No. 68). Diabetologia 2004;47:1747–59. DOI: 10.1007/s00125-004-1527-z.

13. Hayes AJ, Leal J, Gray AM, Holman RR, and Clarke PM. UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33. DOI: 10.1007/s00125-013-2940-y.

14. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med 2008;358:2545–59. DOI: 10.1056/NEJMoa0802743.

15. Shao H, Fonseca V, Stoecker C, Liu S, and Shi L. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). Pharmacoeconomics 2018;36:1125–34. DOI: 10.1007/s40273-018-0662-1.

16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine 2015;373:2117–28. DOI: 10.1056/NEJMoa1504720.

17. Kansal A, Zheng Y, Proskorovsky I, Krotneva S, Kandaswamy P, and Ruffolo A. Modeling Cardiovascular Outcomes of Treatment with Empagliflozin in Type 2 Diabetes Based on Hard Outcomes Data. Value in Health 2016;19:A203. DOI: 10.1016/j.jval.2016.03.1299.

18. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine 2019;380:2295–306. DOI: 10.1056/NEJMoa1811744.

19. Willis M, Asseburg C, Slee A, Nilsson A, and Neslusan C. Development and Internal Validation of a Discrete Event Simulation Model of Diabetic Kidney Disease Using CREDENCE Trial Data. Diabetes Ther 2020;11:2657–76. DOI: 10.1007/s13300-020-00923-w.

20. Ahmad Kiadaliri A, Clarke PM, Gerdtham UG, et al. Predicting Changes in Cardiovascular Risk Factors in Type 2 Diabetes in the Post-UKPDS Era: Longitudinal Analysis of the Swedish National Diabetes Register. J Diabetes Res 2013;2013:241347. DOI: 10.1155/2013/241347.

21. Cederholm J, Eeg-Olofsson K, Eliasson B, et al. Risk Prediction of Cardiovascular Disease in Type 2 Diabetes: A Risk Equation from the Swedish National Diabetes Register. Diabetes Care 2008;31:2038–43. DOI: 10.2337/dc08-0662.

22. Yi Y, Philips Z, Bergman G, and Burslem K. Economic Models in Type 2 Diabetes. Curr Med Res Opin 2010;26:2105–18. DOI: 10.1185/03007995.2010.494451.

23. Tarride JE, Hopkins R, Blackhouse G, et al. A Review of Methods Used in Long-Term Cost-Effectiveness Models of Diabetes Mellitus Treatment. Pharmacoeconomics 2010;28:255–77. DOI: 10.2165/11531590-000000000-00000.

24. Govan L, Wu O, Lindsay R, and Briggs A. How Do Diabetes Models Measure Up? A Review of Diabetes Economic Models and ADA Guidelines. Journal of Health Economics and Outcomes Research 2015;3:21. DOI: 10.36469/9831.

25. Dadwani RS and Laiteerapong N. Economic Simulation Modeling in Type 2 Diabetes. Curr Diab Rep 2020;20:24. DOI: 10.1007/s11892-020-01306-y.

26. Li J, Bao Y, Chen X, and Tian L. Decision Models in Type 2 Diabetes Mellitus: A Systematic Review. Acta Diabetol 2021;58:1451–69. DOI: 10.1007/s00592-021-01742-6.
27. Diabetes Simulation Modeling Database. Mt Hood Diabetes Challenge Network. URL: https://www.mthooddiabeteschallenge.com/registry (visited on 04/29/2022).
28. Eddy DM and Schlessinger L. Archimedes: A Trial-Validated Model of Diabetes. Diabetes Care 2003;26:3093–101. DOI: 10.2337/diacare.26.11.3093.
29. Anderson KM, Odell PM, Wilson PWF, and Kannel WB. Cardiovascular Disease Risk Profiles. American Heart Journal. Management of Coronary Heart Disease Risk Factors in Hypertensive Patients: Clinical Experience with Doxazosin 1, Part 2 1991;121:293–8. DOI: 10.1016/0002-8703(91)90861-B.
30. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Costeffectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making. Current Medical Research and Opinion sup1 2004;20:S5–S26. DOI: 10.1185/030079904X1980.
31. IQVIA Core Diabetes Model. URL: https://www.core-diabetes.com/Index.aspx?Page=About (visited on 05/04/2022).
32. Kengne AP, Patel A, Marre M, et al. Contemporary Model for Cardiovascular Risk Prediction in People with Type 2 Diabetes. European journal of cardiovascular prevention and rehabilitation 2011;18:393–8. DOI: 10.1177/1741826710394270.
33. Zhou H, Isaman DJ, Messinger S, et al. A Computer Simulation Model of Diabetes Progression, Quality of Life, and Cost. Diabetes Care 2005;28:2856–63. DOI: 10.2337/diacare.28.12.2856.
34. Stevens RJ, Kothari V, Adler AI, Stratton IM, and United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS Risk Engine: A Model for the Risk of Coronary Heart Disease in Type II Diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–9. DOI: 10.1042/cs1010671.
35. Kothari V, Stevens RJ, Adler AI, et al. Risk of Stroke in Type 2 Diabetes Estimated by the UK Prospective Diabetes Study Risk Engine (UKPDS 60). Stroke 2002;33:1776–81. DOI: 10.1161/01.STR.0000020091.07144.C7.
36. Mueller E, Maxion-Bergemann S, Gultyaev D, et al. Development and Validation of the Economic Assessment of Glycemic Control and Long-Term Effects of Diabetes (EAGLE) Model. Diabetes Technology & Therapeutics 2006;8:219–36. DOI: 10.1089/dia.2006.8.219.
37. McEwan P, Peters JR, Bergenheim K, and Currie CJ. Evaluation of the Costs and Outcomes from Changes in Risk Factors in Type 2 Diabetes Using the Cardiff Stochastic Simulation Cost-Utility Model (DiabForecaster). Current Medical Research and Opinion 2006;22:121–9. DOI: 10.1185/030079906X80350.
38. Tilden DP, Mariz S, O'Bryan-Tear G, Bottomley J, and Diamantopoulos A. A Lifetime Modelled Economic Evaluation Comparing Pioglitazone and Rosiglitazone for the Treatment of Type 2 Diabetes Mellitus in the UK. Pharmacoeconomics 2007;25:39–54. DOI: 10.2165/00019053-200725010-00005.

39. O'Reilly D, Hopkins R, Blackhouse G, et al. Long-Term Cost-utility Analysis of a Multidisciplinary Primary Care Diabetes Management Program in Ontario. Canadian Journal of Diabetes. Canadian Journal of Diabetes 2007;31:205–14. DOI: 10.1016/S1499-2671(07)13007-0.

40. Waugh N, Scotland G, McNamee P, et al. Screening for Type 2 Diabetes: Literature Review and Economic Modelling. Health Technol Assess 2007;11:iii–iv, ix–xi, 1–125. DOI: 10.3310/hta11170.

41. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, and Holman RR. Risk Factors for Myocardial Infarction Case Fatality and Stroke Case Fatality in Type 2 Diabetes: UKPDS 66. Diabetes Care 2004;27:201–7. DOI: 10.2337/diacare.27.1.201.

42. Chen J, Alemao E, Yin D, and Cook J. Development of a Diabetes Treatment Simulation Model: With Application to Assessing Alternative Treatment Intensification Strategies on Survival and Diabetes-Related Complications. Diabetes Obes Metab 2008;10 Suppl 1:33–42. DOI: 10.1111/j.1463-1326.2008.00885.x.

43. Willis M, Asseburg C, and He J. Validation of Economic and Health Outcomes Simulation Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Journal of Medical Economics 2013;16:1007–21. DOI: 10.3111/13696998.2013.809352.

44. Smolen HJ, Murphy DR, Gahn JC, Yu X, and Curtis BH. The Evaluation of Clinical and Cost Outcomes Associated with Earlier Initiation of Insulin in Patients with Type 2 Diabetes Mellitus. JMCP 2014;20:968–84. DOI: 10.18553/jmcp.2014.20.9.968.

45. Breeze PR, Thomas C, Squires H, et al. The Impact of Type 2 Diabetes Prevention Programmes Based on Risk-Identification and Lifestyle Intervention Intensity Strategies: A Cost-Effectiveness Analysis. Diabetic Medicine 2017;34:632–40. DOI: 10.1111/dme.13314.

46. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting Cardiovascular Risk in England and Wales: Prospective Derivation and Validation of QRISK2. BMJ 2008;336:1475–82. DOI: 10.1136/bmj.39609.449676.25.

47. Nagy B, Zsólyom A, Nagyjánosi L, et al. Cost-Effectiveness of a Risk-Based Secondary Screening Programme of Type 2 Diabetes. Diabetes Metab Res Rev 2016;32:710–29. DOI: 10.1002/dmrr.2791.

48. Wu B, Ma J, Zhang S, Zhou L, and Wu H. Development and Validation of a Health Policy Model of Type 2 Diabetes in Chinese Setting. J Comp Eff Res 2018;7:749–63. DOI: 10.2217/cer-2018-0001.

49. Basu S, Sussman JB, Berkowitz SA, Hayward RA, and Yudkin JS. Development and Validation of Risk Equations for Complications Of Type 2 Diabetes (RECODe) Using Individual Participant Data from Randomised Trials. The Lancet Diabetes & Endocrinology 2017;5:788–98. DOI: 10.1016/S2213-8587(17)30221-8.

50. Laiteerapong N, Cooper JM, Skandari MR, et al. Individualized Glycemic Control for U.S. Adults With Type 2 Diabetes. Ann Intern Med 2018;168:170–8. DOI: 10.7326/M17-0537.

51. Su ZT, Bartelt-Hofer J, Brown S, et al. The Use of Computer Simulation Modeling to Estimate Complications in Patients with Type 2 Diabetes Mellitus: Comparative Validation of the Cornerstone Diabetes Simulation Model. PharmacoEconomics Open 2020;4:37–44. DOI: 10.1007/s41669-019-0156-x.

52. Quan J, Ng CS, Kwok HHY, et al. Development and Validation of the CHIME Simulation Model to Assess Lifetime Health Outcomes of Prediabetes and Type 2 Diabetes in Chinese Populations: A Modeling Study. PLOS Medicine 2021;18:e1003692. DOI: 10.1371/journal.pmed.1003692.

53. Tanaka S, Langer J, Morton T, et al. Developing a Health Economic Model for Asians with Type 2 Diabetes Based on the Japan Diabetes Complications Study and the Japanese Elderly Diabetes Intervention Trial. BMJ Open Diabetes Res Care 2021;9:e002177. DOI: 10.1136/bmjdrc-2021-002177.

54. Tanaka S, Tanaka S, Iimuro S, et al. Predicting Macro- and Microvascular Complications in Type 2 Diabetes: The Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial Risk Engine. Diabetes Care 2013;36:1193–9. DOI: 10.2337/dc12-0958.

55. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. Diabetes Care 2018;41:14–31. DOI: 10.2337/dci17-0057.

56. Leal J, Alva M, Gregory V, et al. Estimating Risk Factor Progression Equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med 2021;38:e14656. DOI: 10.1111/dme.14656.

57. Asche CV, Hippler SE, and Eurich DT. Review of Models Used in Economic Analyses of New Oral Treatments for Type 2 Diabetes Mellitus. Pharmacoeconomics 2014;32:15–27. DOI: 10.1007/s40273-013-0117-7.

58. Daly MJ, Elvidge J, Chantler T, and Dawoud D. A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for Treatments of T1DM & T2DM. Frontiers in Pharmacology 2022;13. DOI: 10.3389/fphar.2022.887298.

59. Nissen SE, Wolski K, and Topol EJ. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. JAMA 2005;294:2581–6. DOI: 10.1001/jama.294.20.joc50147.

60. Nissen SE and Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. New England Journal of Medicine 2007;356:2457–71. DOI: 10.1056/NEJMoa072761.

61. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. URL: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/diabetes-mellitus-evaluating-cardiovascular-risk-new-antidiabetic-therapies-treat-type-2-diabetes (visited on 09/18/2019).

62. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644–57. DOI: 10.1056/NEJMoa1611925.

63. Si L, Willis MS, Asseburg C, et al. Evaluating the Ability of Economic Models of Diabetes to Simulate New Cardiovascular Outcomes Trials: A Report on the Ninth Mount Hood Diabetes Challenge. Value Health 2020;23:1163–70. DOI: 10.1016/j.jval.2020.04.1832.

64. Kuo S, Ye W, Duong J, and Herman WH. Are the Favorable Cardiovascular Outcomes of Empagliflozin Treatment Explained by Its Effects on Multiple Cardiometabolic Risk Factors? A Simulation of the Results of the EMPA-REG OUTCOME Trial. Diabetes Research and Clinical Practice 2018;141:181–9. DOI: 10.1016/j.diabres.2018.04.040.

65. Coleman RL, Gray AM, Broedl UC, et al. Can the Cardiovascular Risk Reductions Observed with Empagliflozin in the EMPA-REG OUTCOME Trial Be Explained by Concomitant Changes Seen in Conventional Cardiovascular Risk Factor Levels? Diabetes, Obesity and Metabolism 2020;22:1151–6. DOI: 10.1111/dom.14017.

66. Willis M, Asseburg C, Nilsson A, and Neslusan C. Challenges and Opportunities Associated with Incorporating New Evidence of Drug-Mediated Cardioprotection in the Economic Modeling of Type 2 Diabetes: A Literature Review. Diabetes Ther 2019;10:1753–69. DOI: 10.1007/s13300-019-00681-4.

67. Basu S, Sussman JB, Berkowitz SA, et al. Validation of Risk Equations for Complications of Type 2 Diabetes (RECODe) Using Individual Participant Data From Diverse Longitudinal Cohorts in the U.S. Diabetes Care 2018;41:586–95. DOI: 10.2337/dc17-2002.

68. Laxy M, Schöning VM, Kurz C, et al. Performance of the UKPDS Outcomes Model 2 for Predicting Death and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus from a German Population-Based Cohort. Pharmacoeconomics 2019;37:1485–94. DOI: 10.1007/s40273-019-00822-4.

69. Pagano E, Konings SRA, Di Cuonzo D, et al. Prediction of Mortality and Major Cardiovascular Complications in Type 2 Diabetes: External Validation of UK Prospective Diabetes Study Outcomes Model Version 2 in Two European Observational Cohorts. Diabetes Obes Metab 2021;23:1084–91. DOI: 10.1111/dom.14311.

70. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, Dapagliflozin and Empagliflozin Monotherapy for Treating Type 2 Diabetes: Systematic Review and Economic Evaluation. Health Technol Assess 2017;21:1–218. DOI: 10.3310/hta21020.

71. Hu S, Su X, Deng X, and Wang Y. Exploring the Appropriate Price of Semaglutide for Type 2 Diabetes Patients Based on Cost-Utility Analysis in China. Front Pharmacol 2021;12:701446. DOI: 10.3389/fphar.2021.701446.

72. Ramos M, Cummings MH, Ustyugova A, Raza SI, de Silva SU, and Lamotte M. Long-Term Cost-Effectiveness Analyses of Empagliflozin Versus Oral Semaglutide, in Addition to Metformin, for the Treatment of Type 2 Diabetes in the UK. Diabetes Ther 2020;11:2041–55. DOI: 10.1007/s13300-020-00883-1.

73. Bain SC, Hansen BB, Malkin SJP, et al. Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the PIONEER Clinical Trial Programme. Diabetes Ther 2020;11:259–77. DOI: 10.1007/s13300-019-00736-6.

74. Gorgojo-Martínez JJ, Malkin SJP, Martín V, Hallén N, and Hunt B. Assessing the Cost-Effectiveness of a Once-Weekly GLP-1 Analogue versus an SGLT-2 Inhibitor in the Spanish Setting: Once-weekly Semaglutide versus Empagliflozin. J Med Econ 2020;23:193–203. DOI: 10.1080/13696998.2019.1681436.

75. Capehorn M, Hallén N, Baker-Knight J, Glah D, and Hunt B. Evaluating the Cost-Effectiveness of Once-Weekly Semaglutide 1 Mg Versus Empagliflozin 25 Mg for Treatment of Patients with Type 2 Diabetes in the UK Setting. Diabetes Ther 2021;12:537–55. DOI: 10.1007/s13300-020-00989-6.

76. Malkin SJP, Hunt B, Huisman EL, Grand TS, and Chubb B. The Long-Term Cost-Effectiveness of Oral Semaglutide in the Netherlands Based on the PIONEER 2, 3 and 4 Randomized Controlled Trials. Diabetes Res Clin Pract 2021;175:108759. DOI: 10.1016/j.diabres.2021.108759.

77. Malkin SJP, Carvalho D, Costa C, Conde V, and Hunt B. The Long-Term Cost-Effectiveness of Oral Semaglutide versus Empagliflozin and Dulaglutide in Portugal. Diabetol Metab Syndr 2022;14:32. DOI: 10.1186/s13098-022-00801-4.

78. Ehlers LH, Lamotte M, Ramos MC, et al. The Cost-Effectiveness of Oral Semaglutide versus Empagliflozin in Type 2 Diabetes in Denmark. J Comp Eff Res 2022;11:29–37. DOI: 10.2217/cer-2021-0169.

79. Ehlers LH, Lamotte M, Ramos MC, et al. The Cost-Effectiveness of Subcutaneous Semaglutide Versus Empagliflozin in Type 2 Diabetes Uncontrolled on Metformin Alone in Denmark. Diabetes Ther 2022;13:489–503. DOI: 10.1007/s13300-022-01221-3.

80. Glümer C, Vistisen D, Borch-Johnsen K, Colagiuri S, and on behalf of the DETECT-2 Collaboration. Risk Scores for Type 2 Diabetes Can Be Applied in Some Populations but Not All. Diabetes Care 2006;29:410–4. DOI: 10.2337/diacare.29.02.06.dc05-0945.

81. Quan J, Pang D, Li TK, et al. Risk Prediction Scores for Mortality, Cerebrovascular, and Heart Disease Among Chinese People With Type 2 Diabetes. The Journal of Clinical Endocrinology & Metabolism 2019;104:5823–30. DOI: 10.1210/jc.2019-00731.

82. Ramos M, Foos V, Ustyugova A, Hau N, Gandhi P, and Lamotte M. Cost-Effectiveness Analysis of Empagliflozin in Comparison to Sitagliptin and Saxagliptin Based on Cardiovascular Outcome Trials in Patients with Type 2 Diabetes and Established Cardiovascular Disease. Diabetes Ther 2019;10:2153–67. DOI: 10.1007/s13300-019-00701-3.

83. Reifsnider OS, Kansal AR, Franke J, et al. Cost-Effectiveness of Empagliflozin in the UK in an EMPA-REG OUTCOME Subgroup with Type 2 Diabetes and Heart Failure. ESC Heart Failure 2020;7:3910–8. DOI: 10.1002/ehf2.12985.

84. Gourzoulidis G, Tzanetakos C, Ioannidis I, et al. Cost-Effectiveness of Empagliflozin Compared with Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus and Established Cardiovascular Disease in Greece. Clin Drug Investig 2021;41:371–80. DOI: 10.1007/s40261-021-01013-w.

85. Reifsnider OS, Kansal AR, Gandhi PK, et al. Cost-Effectiveness of Empagliflozin versus Canagliflozin, Dapagliflozin, or Standard of Care in Patients with Type 2 Diabetes and Established Cardiovascular Disease. BMJ Open Diabetes Research and Care 2021;9:e001313. DOI: 10.1136/bmjdrc-2020-001313.

86. Reifsnider OS, Kansal AR, Wanner C, et al. Cost-Effectiveness of Empagliflozin in Patients With Diabetic Kidney Disease in the United States: Findings Based on the EMPA-REG Outcome Trial. Am J Kidney Dis 2021:S0272-6386(21)00952–5. DOI: 10.1053/j.ajkd.2021.09.014.

87. Reifsnider OS, Pimple P, Brand S, Bergrath Washington E, Shetty S, and Desai NR. Cost-Effectiveness of Second-Line Empagliflozin versus Liraglutide for Type 2 Diabetes in the United States. Diabetes Obes Metab 2022;24:652–61. DOI: 10.1111/dom.14625.

88. Reifsnider O, Kansal A, Pimple P, Aponte-Ribero V, Brand S, and Shetty S. Cost-effectiveness Analysis of Empagliflozin versus Sitagliptin as Second-line Therapy for Treatment in Patients with Type 2 Diabetes in the United States. Diabetes Obes Metab 2021;23:791–9. DOI: 10.1111/dom.14268.

89. Ramos M, Ustyugova A, Hau N, and Lamotte M. Cost–Effectiveness of Empagliflozin Compared with Liraglutide Based on Cardiovascular Outcome Trials in Type II Diabetes. Journal of Comparative Effectiveness Research 2020;9:781–94. DOI: 10.2217/cer-2020-0071.

90. Ehlers LH, Lamotte M, Monteiro S, et al. The Cost-Effectiveness of Empagliflozin Versus Liraglutide Treatment in People with Type 2 Diabetes and Established Cardiovascular Disease. Diabetes Ther 2021;12:1523–34. DOI: 10.1007/s13300-021-01040-y.

91. Ramos M, Men P, Wang X, Ustyugova A, and Lamotte M. Cost-Effectiveness of Empagliflozin in Patients with Type 2 Diabetes and Established Cardiovascular Disease in China. Cost Effectiveness and Resource Allocation 2021;19:46. DOI: 10.1186/s12962-021-00299-z.

92. Salem A, Men P, Ramos M, Zhang YJ, Ustyugova A, and Lamotte M. Cost-Effectiveness Analysis of Empagliflozin Compared with Glimepiride in Patients with Type 2 Diabetes in China. J Comp Eff Res 2021;10:469–80. DOI: 10.2217/cer-2020-0284.

93. Gourzoulidis G, Tzanetakos C, Ioannidis I, et al. Cost-Effectiveness of Empagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus at Increased Cardiovascular Risk in Greece. Clin Drug Investig 2018;38:417–26. DOI: 10.1007/s40261-018-0620-x.

94. Kaku K, Haneda M, Sakamaki H, et al. Cost-Effectiveness Analysis of Empagliflozin in Japan Based on Results From the Asian Subpopulation in the EMPA-REG OUTCOME Trial. Clinical Therapeutics 2019;41:2021–2040.e11. DOI: 10.1016/j.clinthera.2019.07.016.

95. Kansal A, Reifsnider OS, Proskorovsky I, et al. Cost-Effectiveness Analysis of Empagliflozin Treatment in People with Type 2 Diabetes and Established Cardiovascular Disease in the EMPA-REG OUTCOME Trial. Diabetic Medicine 2019;36:1494–502. DOI: 10.1111/dme.14076.

96. Men P, Liu T, and Zhai S. Empagliflozin in Type 2 Diabetes Mellitus Patients with High Cardiovascular Risk: A Model-Based Cost-Utility Analysis in China. Diabetes Metab Syndr Obes 2020;13:2823–31. DOI: 10.2147/DMSO.S266901.

97. Guzauskas GF, Rind DM, Fazioli K, Chapman RH, Pearson SD, and Hansen RN. Cost-Effectiveness of Oral Semaglutide Added to Current Antihyperglycemic Treatment for Type 2 Diabetes. J Manag Care Spec Pharm 2021;27:455–68. DOI: 10.18553/jmcp.2021.27.4.455.

98. O'Keeffe AG, Nazareth I, and Petersen I. Time Trends in the Prescription of Statins for the Primary Prevention of Cardiovascular Disease in the United Kingdom: A Cohort Study Using The Health Improvement Network Primary Care Data. Clin Epidemiol 2016;8:123–32. DOI: 10.2147/CLEP.S104258.

99. UK Prospective Diabetes Study (UKPDS) Group. Intensive Blood-Glucose Control with Sulphonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes (UKPDS 33). Lancet 1998;352:837–53. DOI: 10.1016/S0140-6736(98)07019-6.

100. Willis M, Asseburg C, Nilsson A, Johnsson K, and Kartman B. Multivariate Prediction Equations for HbA1c Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling. Value in Health 2017;20:357–71. DOI: 10.1016/j.jval.2016.10.004.

101. Bowman L, Mafham M, Stevens W, et al. ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a Randomized Trial of Aspirin and of Omega-3 Fatty Acid Supplementation in 15,480 People with Diabetes. Am Heart J 2018;198:135–44. DOI: 10.1016/j.ahj.2017.12.006.

102. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018;379:1529–39. DOI: 10.1056/NEJMoa1804988.

103. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of N-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med 2018;379:1540–50. DOI: 10.1056/NEJMoa1804989.

104. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative Meta-Analysis of Individual Participant Data from Randomised Trials. The Lancet 2009;373:1849–60. DOI: 10.1016/S0140-6736(09)60503-1.

2

How well does the UKPDS Outcomes Model 2 predict outcomes in ASCEND

This chapter has been published in *Keng MJ, Leal J, Mafham M, Bowman L, Armitage J, and Mihaylova B. Performance of the UK Prospective Diabetes Study Outcomes Model 2 in a Contemporary UK Type 2 Diabetes Trial Cohort. Value in Health 2022;25:435–42. DOI: 10.1016/j.jval.2021.09.005.* The analysis in this chapter has since been updated to include events for heart failure, amputation and end-stage renal disease identified from hospital records, which were unavailable at the time of publication.

Summary

The UKPDS Outcomes Model developed using 30 years (1977-2007) of data from the UKPDS is widely used for projections of health outcomes and economic evaluations of therapies for people with type 2 diabetes. However, its reliability for contemporary type 2 diabetes populations in the UK is unclear. In this chapter, I assessed the performance of version 2 of the model (UKPDS-OM2) using data from 14,569 participants with type 2 diabetes without previous cardiovascular disease in ASCEND, which followed participants between 2005 and 2017. Over the 10-year follow-up period, the UKPDS-OM2 substantially overpredicted myocardial infarction, stroke, vascular death, and non-vascular death. The percentage errors in event rates at year 7 (average follow-up duration in ASCEND) were 149%, 42%,

269% and 52% respectively. Discrimination of the model for myocardial infarction and other ischaemic heart disease (c-statistics 0.58 and 0.60 respectively) were poorer than that for the other outcomes (c-statistics ranging from 0.66 to 0.72). These results suggest that appropriate adjustments or new risk equations are needed for projecting health outcomes in people with diabetes similar to those in ASCEND.

2.1 Background

The UKPDS Outcomes Model is a stochastic patient-level simulation model that uses the risk factor profiles of people with type 2 diabetes to predict the occurrence of diabetes-related macro- and micro-vascular complications over patients' lifetimes, and at the same time quantifies their (quality-adjusted) life expectancies and healthcare costs [1, 2]. It is NICE's model of choice for health technology assessments of diabetes treatments [3], and its risk equations are also used in several other commonly used diabetes simulation models as identified in Chapter 1.

Version 1 of the model was developed using data collected in the UKPDS, which randomised participants between 1977 and 1991, and followed them until 1997 (median follow-up 10.3 years) [1]. Temporal validation of the model using data collected during the 10-year post-trial monitoring period found that the model overpredicted the 10-year risks of heart failure and mortality and underpredicted the 10-year risks of stroke and amputation [4]. Risk equations in the original model were subsequently updated including also the post-trial follow-up data (overall median follow-up 17.6 years) and version 2 of the model (UKPDS-OM2) was released [2]. Internal validation of the UKPDS-OM2 demonstrated good agreement between simulated and observed outcomes amongst UKPDS participants over a period of 25 years.

External validations of the UKPDS-OM2 have been performed in several more recent North American cohorts [5, 6], a German cohort [7], an Italian cohort and a Dutch cohort [8]. All studies report overprediction of mortality. This is consistent with observations in the report from the latest Mount Hood Diabetes Challenge [9],

a forum for diabetes modellers to compare model performance, which found the UKPDS-OM2 and other diabetes models based on risk equations of the UKPDS-OM2 to overestimate vascular death, although the results were generated using simulated patient cohorts instead of individual patient-level data. Overprediction of myocardial infarction was also observed in the North American, Italian, and Dutch cohorts, but not in the German cohort. The performance of a model can vary among countries because of differences in healthcare systems and health of the population in general (reflected by differences in life expectancy, mortality rates, and rates of type 2 diabetes-related complications) [10].

In a guideline for good research practice, the issue of transferability of models across different settings was highlighted and it was suggested that careful consideration needs to be taken to ensure the relevance of models in the population of interest [11]. Findings from a previous study using The Health Improvement Network (THIN) database in the UK suggest that the UKPDS-OM2 overpredicts myocardial infarction, but no direct comparison between predicted and observed risks was presented and no results for mortality were reported [12]. It remains unclear if the UKPDS-OM2 can predict well diabetes-related complications in a contemporary UK cohort. Hence, I took the opportunity presented by the large long-term randomised trial ASCEND to assess the performance of the UKPDS-OM2.

2.2 Methods

2.2.1 Validation cohort and endpoints

The UKPDS-OM2 takes patient demographics (e.g. age, sex, ethnicity), diabetes duration, history of diabetes-related complications and risk factor progression over time (all inputs required listed in Supplemental Table C.2) to predict the occurrence of myocardial infarction, other ischaemic heart disease (IHD), heart failure, stroke, lower-limb amputation, blindness, end-stage renal disease (ESRD), lower extremity ulcer, and deaths (all-cause death and vascular death [defined as death from myocardial infarction, other IHD, heart failure or stroke]) (definition of each endpoint

in Supplemental Table C.3). The UKPDS-OM2 is an improved update from the UKPDS-OM1 [1], with risk equations re-estimated using an additional 38,000 person-years of observational data and including several additional outcomes [2].

Amongst ASCEND participants, only those with type 2 diabetes formed the validation cohort since the UKPDS-OM2 was developed for predicting outcomes in people with type 2 diabetes. The endpoints included deaths (vascular death as defined in UKPDS-OM2 and non-vascular death), myocardial infarction, other IHD (including angina, death from coronary heart disease not due to myocardial infarction, and coronary revascularisation), stroke, heart failure, lower-limb amputation, and ESRD. Deaths, myocardial infarction, other IHD, and stroke were rigorously sought, recorded, and adjudicated in ASCEND. Heart failure, amputation and ESRD were self-reported, so data from hospital records were used to supplement the identification of these events (full details in Appendix Section B.1). Blindness and lower extremity ulcer were excluded from the validation because these outcomes were not routinely sought or recorded in ASCEND and would be difficult to identify from hospital records. 99% of participants had complete follow-up information, with only 1% of participants lost to follow-up and censored. For outcomes included in the analysis, the endpoints were matched as closely as possible to the respective endpoint definitions in the UKPDS-OM2 (Supplemental Table C.3).

2.2.2 Missing data

Imputing values for biomarkers not available in ASCEND

Low-density lipoprotein (LDL) cholesterol, haemoglobin and white blood cell count measurements were not available in ASCEND. Patient-level data from the UKPDS [13] was used to develop linear regression models to predict haemoglobin and white blood cell counts using other patient characteristics and biomarkers. Variables were selected using stepwise selection with p-values from Chi-squared test as the criteria for adding (p-value < 0.05) or dropping (p-value < 0.01) variables. Both white blood cell count and haemoglobin were log-transformed as the quantile-quantile plots for both linear models demonstrated skewed residuals, and this

was confirmed with a Box-Cox test with the optimal λ close to 0. For predicting haemoglobin levels, variables in the final model included sex, ethnicity, smoking status, duration of diabetes, LDL cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c and estimated glomerular filtration rate (eGFR). For predicting white blood cell count, variables in the final model included ethnicity, smoking status, body mass index (BMI), high-density lipoprotein (HDL) cholesterol, LDL cholesterol, SBP, DBP, HbA1c and presence of microalbuminuria.

Statins lower LDL cholesterol and about 75% of ASCEND participants were using statins at baseline. Hence, the UKPDS data was deemed unsuitable for estimating LDL cholesterol from other biomarkers as statin use was much less common at UKPDS recruitment. Instead, patient-level data from the REVEAL study [14] was used to develop a linear regression model to predict LDL cholesterol using other biomarkers, particularly apolipoprotein B which is highly correlated with LDL cholesterol (variables in the final model included HDL cholesterol, non-HDL cholesterol, apolipoprotein B, sex, age, smoking status, SBP, DBP, eGFR, presence of diabetes). In REVEAL, all participants were on statin treatment. The model was fitted using all participants[1], with an indicator for diabetes patients to reflect the effect of diabetes on LDL cholesterol.

Multiple imputation for missing data in ASCEND

Excluding data items not available in ASCEND, 51% of participants had at least one missing variable. Multiple imputation was performed to produce 60 imputed datasets, using the multivariate imputation by the chained equations (MICE) method with predictive mean matching (PMM) [15]. PMM imputes missing data using observations from complete cases that have predicted values closest to the predicted value for the missing data based on the specified model. For the MICE process, briefly, one variable with missing data was first imputed conditional on the other variables without missing data, and the next variable with missing data was imputed conditional on other variables without missing data and also the

[1]Similar coefficients were obtained in a model fitted in the subset of participants with diabetes in REVEAL (37%).

previously imputed variable. This was repeated until all variables were imputed, and the entire cycle was repeated until a stable model was achieved. This process was then repeated 60 times to generate 60 imputed datasets. The missing values were then replaced with the average value (for continuous variables) or the value with the most frequent occurrence (for binary variables) across 60 datasets created[2].

Additionally, the UKPDS-OM2 requires the specification of risk factor progression over time. However, biomarkers were collected only at baseline for most participants in ASCEND. Hence, the risk factor progression equations in the UKPDS-OM2 [16] were used to project risk factor values in subsequent years.

2.2.3 Statistical analysis

The UKPDS-OM2 was used to predict event occurrences over each participant's lifetime. This process was repeated 10,000 times for each participant (Monte Carlo replication) to reduce stochastic (first-order) uncertainty. The proportion of simulated participant who experiences an outcome represents the probability of event occurrence for the participant.

The observed cumulative incidence of each endpoint was estimated in ASCEND accounting for competing risk [17] (from deaths for non-fatal events and from deaths from other causes for cause-specific deaths) and controlling for and excluding the effects of allocation to aspirin and/or omega-3 fatty acids treatments[3] [18, 19]. This was repeated 1000 times using bootstrap resampling (with replacement) of the ASCEND cohort to estimate the 95% confidence intervals (CIs) [20].

Performance of the UKPDS-OM2 was assessed based on its calibration (i.e. agreement between predicted and observed cumulative incidence) and discrimination

[2]Results pooled across simulations of all 60 imputed datasets were compared to results from simulation of a single dataset with missing values imputed with mean (for continuous variables) / most frequent (for binary variables) value across the 60 imputed datasets. Similar results were found using the two approaches (Supplemental Figure C.2). Hence, the results from the latter approach are presented in this Chapter.

[3]Treatment allocation (aspirin-omega-3 fatty acids, aspirin-placebo, placebo-omega-3 fatty acids, placebo-placebo) was included as a covariate in a Cox proportional hazard model, and the predicted survivor function for the placebo-placebo arm from this model was used to estimate the cumulative incidence.

(i.e. the ability of the model to differentiate individuals who experience events from those who do not) [21]. Calibration was assessed graphically for each endpoint by comparing the year-on-year (up to 10 years) cumulative incidence observed in ASCEND to that predicted by the UKPDS-OM2. The percentage error and the absolute difference between the predicted and observed 7-year cumulative incidence were used to quantify and compare the magnitude of discrepancy for each endpoint. The mean absolute percentage error (MAPE) over 7 years was used to compare the overall accuracy across endpoints. Calibration was also assessed for each endpoint by dividing the cohort into risk deciles based on 7-year cumulative incidence predicted by the UKPDS-OM2 and plotting the observed 7-year cumulative incidence against that predicted for each decile. Uno's C-statistic estimated at 7 years of follow-up was used to assess the model's discrimination of risk for different endpoints [22].

Subgroup analysis

For mortality outcomes, model calibration was further assessed in subgroups by sex (male, female), age (< 60, $\geq 60 < 70$, ≥ 70 years), HbA1c ($< 7.5\%$, $\geq 7.5\%$), duration of diabetes (< 5, $\geq 5 < 10$, ≥ 10 years), and BMI (< 25, $\geq 25 < 30$, $\geq 30 < 35$, ≥ 35 kg/m^2) at baseline.

Sensitivity analysis

To assess the impact of using the risk factor progression equations in the UKPDS-OM2 to impute missing risk factor trajectories over time, the alternative scenario whereby all risk factors were held constant at their baseline value over years was considered. That is, if a person had baseline HbA1c of 6.0%, their HbA1c was assumed to be 6.0% for the entire duration of the simulation. Additionally, participants with missing baseline information (for variables collected in ASCEND) in the ASCEND validation cohort were excluded to assess if the results are robust to the imputation of missing baseline information. Finally, to assess the impact of aspirin and omega-3 fatty acid treatment adjustment on the endpoints, participants who were assigned to receive either one or both treatments in ASCEND were

excluded and a comparison of the predicted and observed cumulative incidence of each endpoint among participants allocated to placebo aspirin and placebo omega-3 fatty acid was presented.

2.3 Results

Of 15,480 participants in ASCEND, 14,569 (94%) participants with type 2 diabetes formed the validation cohort. Baseline characteristics of participants with type 2 diabetes in ASCEND can be found in Table 2.1. Participants in this cohort were mostly White Caucasians (97%). At baseline, they were on average 64-year-old, with a median duration of diabetes of 6 years, and no previous cardiovascular disease. They were generally well-managed with average HbA1c 7.1% (54 mmol/mol), total cholesterol 4.1 mmol/L, and SBP 136 mmHg. A summary of the baseline characteristics, after imputing missing data required by the UKPDS-OM2, can be found in Supplemental Table C.4.

Table 2.1: Baseline characteristics of 14,569 participants with type 2 diabetes in ASCEND

Variable	N (%), mean (SD) or median (IQR)
Baseline characteristics	
Male	9166 (62.9%)
Current smoker	1195 (8.2%)
Ethnicity	
White	14037 (96.3%)
South Asian	138 (0.9%)
Afro-Caribbean	181 (1.2%)
Others/Missing	213 (1.5%)
Age (years)	63.8 (8.9)
Diabetes duration (years)	6 (3-11)
Urinary albumin ≥50 mg/L	681 (7%)
Biomarkers	
HbA1c (%)	7.1 (1.2)
Systolic blood pressure (mmHg)	136.4 (15.2)
Body-mass index (kg/m^2)	31.4 (6.5)
eGFR (mL/min/1.73m^2)	84.5 (20.9)
Total cholesterol (mmol/L)	4.1 (0.9)
HDL cholesterol (mmol/L)	1.2 (0.3)
Heart rate (bpm)	75.0 (11.5)

Table 2.1: Baseline characteristics of 14,569 participants with type 2 diabetes in ASCEND *(continued)*

Variable	N (%), mean (SD) or median (IQR)

Note:
Missing values excluded from tabulation.

At 7 years of follow-up, the cumulative incidence of all-cause death predicted by UKPDS-OM2 was overestimated by 98% (absolute difference, 9.3%), which is due to the model overpredicting both vascular death by 269% (absolute difference, 5.5%) and deaths from other causes by 52% (absolute difference, 3.9%) (Table 2.2; Figure 2.1). The cumulative incidence of myocardial infarction and stroke were also overpredicted by 149% (absolute difference, 4.1%) and 42% (absolute difference, 1.2%) respectively. By contrast, the observed cumulative incidence of other IHD was similar to that predicted by the UKPDS-OM2. This was driven by the much higher rate of coronary revascularisations in ASCEND (accounting for 40% of events contributing to the other IHD endpoint) compared to the UKPDS study period. Excluding coronary revascularisation from the other IHD endpoint, similar overprediction as for myocardial infarction was observed (Figure 2.2). Heart failure was overpredicted by 83% (absolute difference, 1.6%). Amputation and ESRD were generally well-predicted. However, in contrast to the gradual decrease in the rate of amputation observed in ASCEND, the amputation rate was predicted to steadily increase, resulting in the divergence between observed and predicted cumulative incidence in later years. After stratifying by decile of predicted 7-year cumulative incidence, greater deviations were noted between the observed and predicted risks for participants at higher predicted risks for all endpoints except for other IHD, amputation and ESRD (Figure 2.3). Overall, over 7 years of follow-up, the MAPE of the UKPDS-OM2 was worst for vascular death (302%), heart failure (175%), and myocardial infarction (151%).

Discrimination of the model for myocardial infarction and other IHD (c-statistics of 0.58 and 0.60 respectively) were poorer than that for other endpoints (c-statistics ranging from 0.66 to 0.77) (Table 2.2). This is also reflected in the plot comparing

predicted against observed 7-year cumulative incidence stratified by predicted risk (Figure 2.3) where, while clear gradients of increasing risks were observed across deciles of predicted risk for other endpoints, these gradients were much less distinct for myocardial infarction and other IHD across the risk deciles.

Table 2.2: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in ASCEND

Endpoints	Observed cumulative incidence (%) (95% CI)	Predicted[1]				Predicted[2]			
		Cumulative incidence (%)	% error	MAPE (%)	C-statistic	Cumulative incidence (%)	% error	MAPE (%)	C-statistic
All-cause death	9.4 (8.5, 10.3)	18.7	98	158	0.72	17.0	79	146	0.73
Vascular death	2.0 (1.6, 2.5)	7.5	269	302	0.70	5.6	178	246	0.71
Non-vascular death	7.4 (6.7, 8.3)	11.3	52	115	0.72	11.3	53	116	0.73
Myocardial infarction	2.8 (2.2, 3.3)	6.9	149	151	0.58	5.5	100	122	0.58
Other IHD	5.8 (5.1, 6.5)	5.1	-12	13	0.60	4.2	-28	23	0.60
Stroke	2.8 (2.3, 3.3)	4.0	42	47	0.66	3.1	11	29	0.66
Heart failure	2.0 (1.6, 2.4)	3.6	83	175	0.72	2.9	44	152	0.72
Amputation	1.0 (0.7, 1.3)	1.0	-1	13	0.76	0.6	-38	33	0.76
End-stage renal disease	0.5 (0.3, 0.7)	0.4	-25	16	0.77	0.3	-46	24	0.78

Note:
% error, percentage error; MAPE, mean absolute percentage error. Vascular death is defined as death from myocardial infarction, other IHD, heart failure or stroke (as in UKPDS-OM2). Percentage error is the degree of overprediction as percentage of observed (negative values represent underprediction) calculated using the cumulative incidences at year 7. MAPE is the absolute percentage error averaged across the 7 years of follow-up.

[1] UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case).

[2] Values of risk factors during follow-up fixed to baseline values (sensitivity analysis).

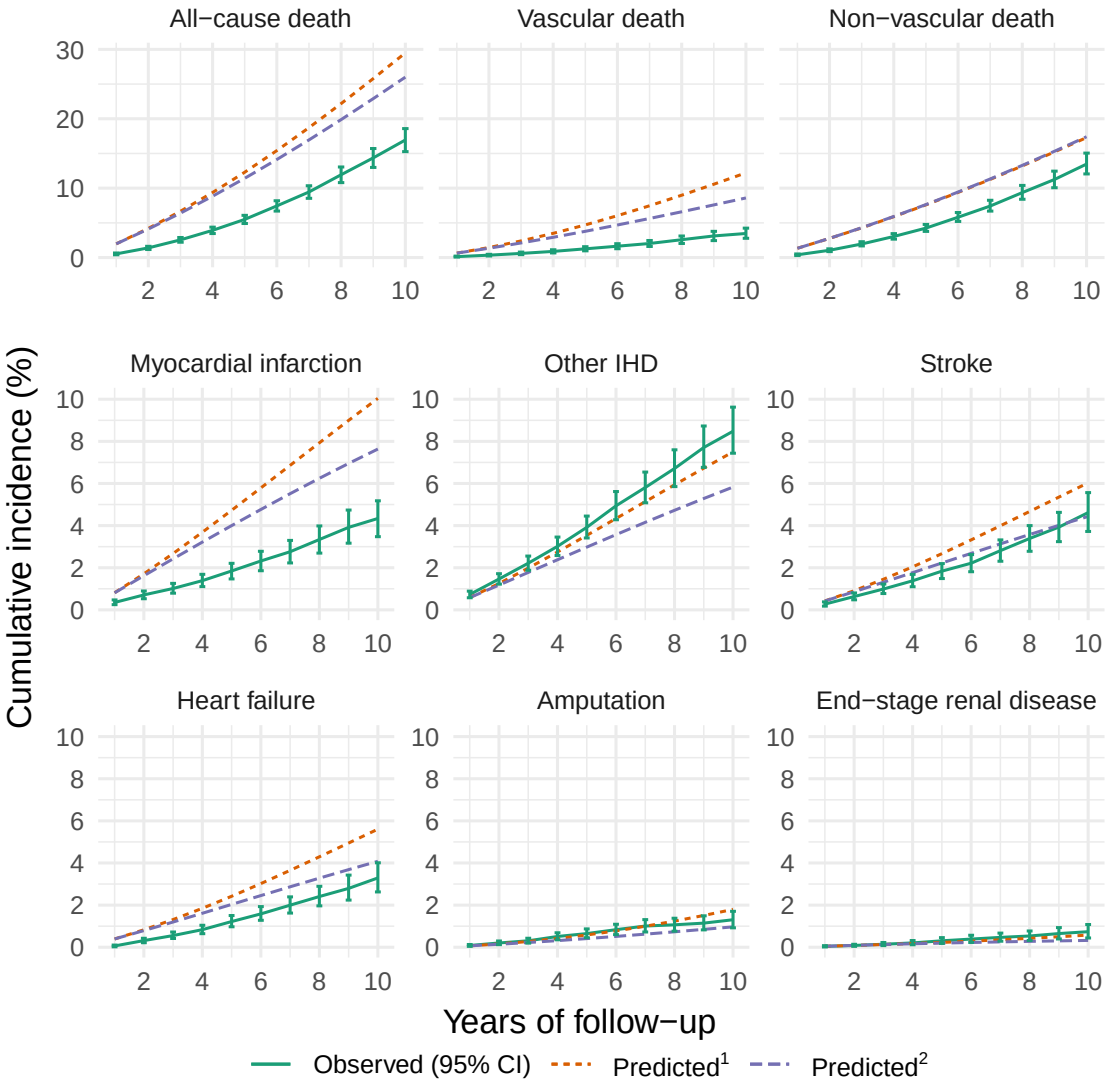


Figure 2.1: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

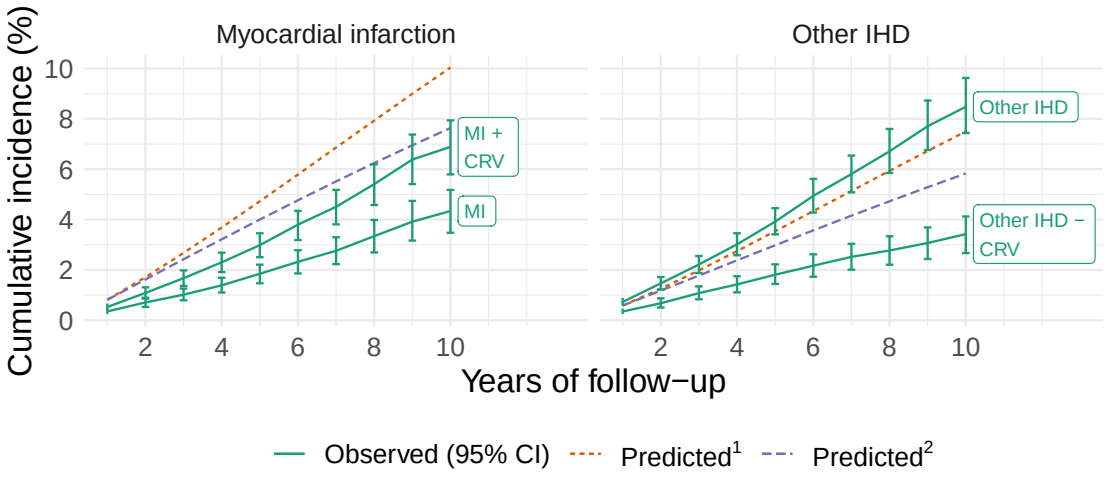


Figure 2.2: Comparison of cumulative incidence of myocardial infarction (MI) and other ischaemic heart disease (IHD), predicted by the UKPDS-OM2 over 10 years with that observed in ASCEND, including and excluding coronary revascularisations (CRV). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

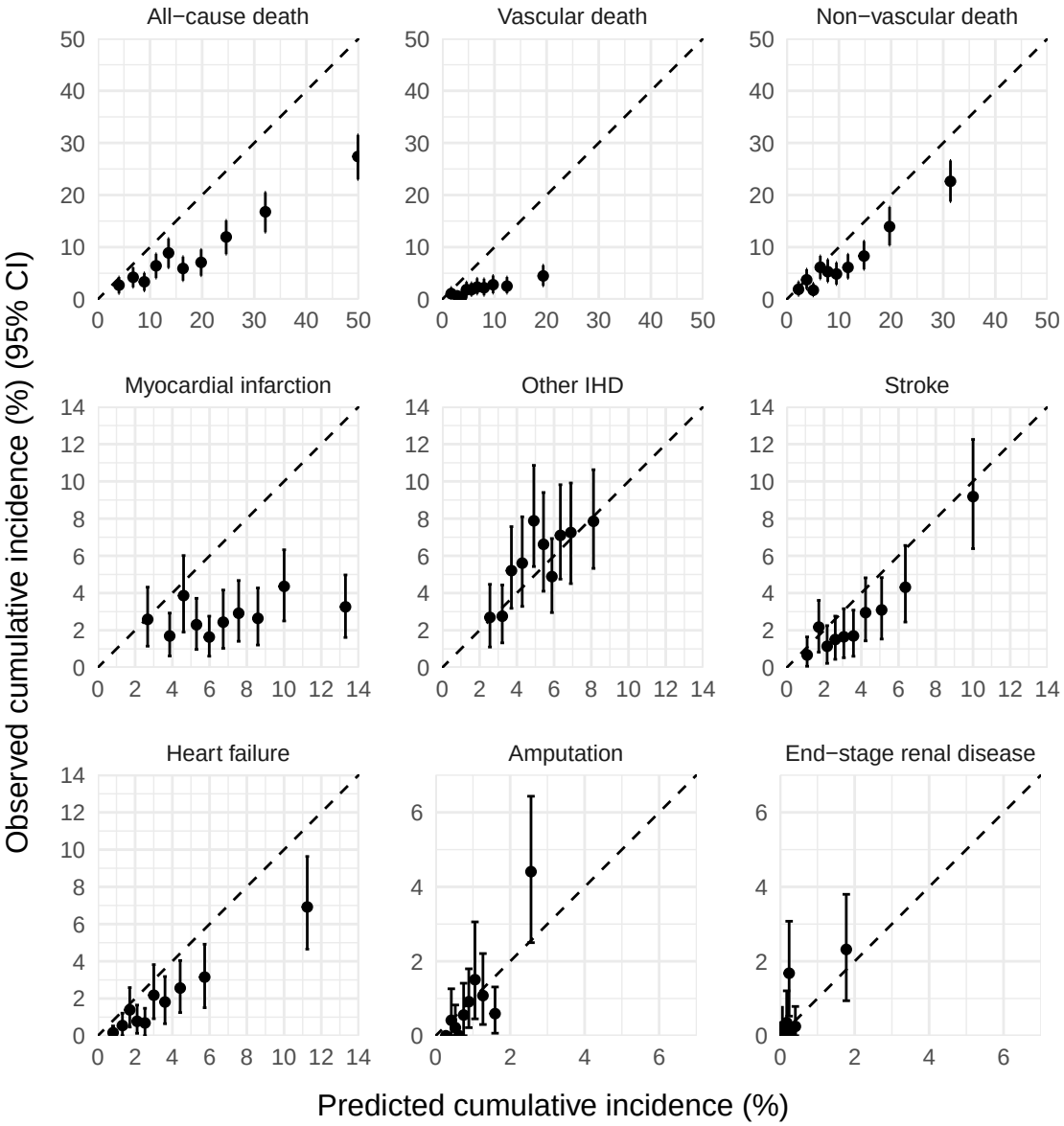


Figure 2.3: Comparison of 7-year cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND, stratified by decile of predicted 7-year cumulative incidence for each outcome

2.3.1 Subgroup analysis

Overall, the model overpredicted mortality across all risk factor subgroups examined (sex, age, HbA1c, duration of diabetes, BMI; see Supplemental Figures C.3 - C.7). Lower levels of bias were observed in the following subgroups (Table 2.3): for vascular deaths, participants below 60-year-old (MAPE 99% compared to 350% for participants between 60 and 70-year-old and 403% for participants at least 70-year-old) and participants with duration of diabetes at least 5 years (MAPE 256% for participants with more than 10 years of diabetes, 197% for participants with 5 to 10 years of diabetes, and 658% for participants with less than 5 years of diabetes); for death from other causes, participants with HbA1c at least 7.5% (MAPE 74% compared to 224% for participants with HbA1c less than 7.5%) and participants with BMI of at least 35 kg/m^2 (MAPE 24%, compared to at least 100% for participants with BMI less than 35 kg/m^2).

2.3.2 Sensitivity analysis

In the sensitivity analyses in which all risk factors were held constant at their baseline values, the predicted cumulative incidences were smaller than in the main analyses, with somewhat smaller discrepancies compared to the observed cumulative incidences. However, the model still substantially overpredicted death and myocardial infarction (percentage error at year 7, 79% and 100% respectively). In the subgroup of participants with complete baseline information (N = 7578), with the exception of heart failure, the percentage error at year 7 and the MAPE across 7 years are both higher in this subgroup of participants across all endpoints, particularly for vascular death and myocardial infarction (Supplemental Figure C.8; Supplemental Table C.5). Discrimination and absolute differences between the predicted and observed cumulative incidences across all endpoints were similar to results in the main analyses with missing data imputed. In the subgroup of participants allocated placebo aspirin and placebo omega-3 fatty acid (N = 3651), the performance of the UKPDS-OM2 is similar to the main analyses with adjustments for

effects of allocation to aspirin and/or omega-3 fatty acids treatments (Supplemental Figure C.9; Supplemental Table C.6).

Table 2.3: Mean absolute prediction error (%) from comparison of cumulative incidence predicted by the UKPDS-OM2 and observed for participants in the ASCEND validation cohort over 7 years, by risk factor subgroups

Subgroup	All-cause death	Vascular death	Non-vascular death
By sex			
male	157	260	120
female	165	450	108
By age (years)			
<60	92	99	85
≥60 <70	159	350	103
≥70	181	403	130
By HbA1c (%)			
<7.5	270	447	224
≥7.5	132	470	74
By duration of diabetes (years)			
<5	192	658	121
≥5 <10	139	197	115
≥10	153	256	120
By BMI (kg/m^2)			
<25	134	237	100
≥25 <30	233	409	182
≥30 <35	178	270	141
≥35	70	303	24

Note:
Vascular death is defined as death from myocardial infarction, other IHD, heart failure or stroke (as in UKPDS-OM2). Values are absolute percentage errors averaged across the 7 years of follow-up.

2.4 Discussion

2.4.1 Summary of results

The UKPDS-OM2 substantially overpredicted the risks of myocardial infarction, heart failure and death (particularly vascular death) over 10 years of follow-up in the ASCEND study. Stroke was also overpredicted, although to a lesser extent. In terms of discrimination, the model was positively predictive for all endpoints but discriminated risks of myocardial infarction and other IHD less well than other endpoints.

Despite myocardial infarction being overpredicted, other IHD (which includes coronary revascularisations) appears well predicted. However, the number of coronary revascularisations performed each year in the UK has increased over the last decades with percutaneous coronary interventions increasing 3-fold between 2000 and 2010 [23]. People are now more likely to receive preventive coronary revascularisation possibly contributing to the decline in the risk of myocardial infarction and the apparent increase in the risk of other IHD (which includes coronary revascularisation). Excluding coronary revascularisation from the other IHD endpoint leads to a similar pattern of overprediction. Furthermore, the observed cumulative incidence of a combined endpoint of myocardial infarction or coronary revascularisation (assuming that coronary revascularisations prevented some myocardial infarctions) was also lower than the cumulative incidence of myocardial infarction predicted by the UKPDS-OM2. These exploratory analyses suggest that the UKPDS-OM2 is overpredicting the risk of IHD in general, and that other IHD appears well predicted partly because of the higher rate of coronary revascularisations in ASCEND.

2.4.2 Factors attributable to discrepancies observed

The UKPDS is a significantly older trial with participants followed between 1977 and 2007. Compared with UKPDS participants, ASCEND participants had better

managed lipids (76% of ASCEND participants took a statin vs 0.3% on lipid-lowering drugs in the UKPDS), blood pressure (67% of ASCEND participants on antihypertensive drugs vs 12% in the UKPDS) and blood glucose (similar HbA1c levels despite ASCEND participants having a median 6 years of diabetes vs newly diagnosed in UKPDS); higher use of coronary revascularisation; and reduced likelihood of smoking (8% in ASCEND vs 31% in UKPDS) (Table 2.4) [24]. This may reflect earlier diagnosis of diabetes in ASCEND participants compared to participants in UKPDS as well as improved risk factor control in recent years.

Table 2.4: Comparison of baseline characteristics of participants with type 2 diabetes in ASCEND and the UKPDS

Characteristic	ASCEND (N = 14,569)*	UKPDS (N = 3867)†
Baseline characteristics		
Male	63%	61%
Current smoker	8%	31%
Ethnicity		
White	96%	81%
South Asian	1%	10%
Afro-Caribbean	1%	8%
Others/Missing	1%	1%
Age (years)	63.8 (8.9)	53.3 (8.6)
Diabetes duration (years)	6 (3-11)	0
Diabetic retinopathy	17% (self-reported)	36%
Biomarkers		
HbA1c (%)	7.1 (1.2)	7.1 (1.5)
Systolic blood pressure (mmHg)	136.4 (15.2)	135 (20)
Body-mass index (kg/m^2)	31.4 (6.5)	27.5 (5.2)
eGFR (mL/min/1.73m^2)	84.5 (20.9)	-
Total cholesterol (mmol/L)	4.1 (0.9)	5.4 (1.1)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.1 (0.2)
Medication use		
Use of cardiovascular treatments		
Antihypertensive	67% (ACE inhibitor or ARB; Beta-blocker; Calcium channel blocker)	12%
Lipid-lowering	76% (statin)	0.3%
Diuretic	20%	13%

Table 2.4: Comparison of baseline characteristics of participants with type 2 diabetes in ASCEND and the UKPDS *(continued)*

Characteristic	ASCEND (N = 14,569)*	UKPDS (N = 3867)†
Aspirin	50% (treatment allocation in study)	1.6% (more than one aspirin daily)
Use of diabetes treatments		
Insulin	21%	45%
Sulphonylurea	28%	43%
Metformin	69%	8.8%
Other hypoglycaemic treatments	4.8%	-

Note:
Values are mean (SD), median (interquartile range) or percentage.
* Missing values excluded from tabulation.
† Baseline characteristics of participants in the UKPDS study comparing intensive blood-glucose control vs conventional treatment [24]. Tabulation of diabetes treatment in the UKPDS based on treatment allocation.

Given that the overpredictions for death and myocardial infarction were consistently observed in other validation studies [5–8], this suggests that perhaps improvements in diabetes and cardiovascular disease diagnosis and treatment, as well as dietary and lifestyle changes, have an impact on vascular risks beyond the impact from risk factors accounted for by the UKPDS-OM2. Previous studies have also observed a decline in age-adjusted cardiovascular disease incidence and case-fatality rates in the last two decades [23, 25–28], over and above the effects explained by improvement in risk factors [29–32]. Therefore, the UKPDS-OM2 needs to be updated or de-novo estimation of at least mortality and vascular event risks using contemporary data is needed.

Additionally, the performance of the UKPDS-OM2 was found to be poorer in participants who were older or had a shorter duration of diabetes at baseline. In particular, poorer performance in older people was also observed in a Dutch and an Italian cohort from an earlier patient-level validation study [8]. In the UKPDS, participants were diagnosed with diabetes at a mean age of 53 [24]. In contrast, participants in ASCEND (mean age 64; mean duration of diabetes 6), the Dutch cohort (mean age 65, mean duration of diabetes 7) and the Italian cohort

(mean age 68; mean duration of diabetes 11) were diagnosed on average about 5 years later. Diagnosis of diabetes at an older age compared with a younger age has been found to be associated with a slower rate of glycaemic deterioration [33] and lower cardiovascular disease and mortality risks [34]. The UKPDS data may not generalise well to older people diagnosed with diabetes at an older age, which may explain the poorer performance of the model in this patient category. Hence, new equations based on more contemporary cohorts would be helpful in better capturing disease risks in these patient categories.

2.4.3 Limitations

Firstly, data on some baseline risk factors such as LDL cholesterol, haemoglobin and white blood cell count were not available in ASCEND and were imputed based on their relationships with other markers (e.g. total cholesterol) derived in external datasets. This assumes the generalisability of such relationships to participants in the ASCEND cohort. For other risk factors with missing data, the missing at random assumption was made in imputing these values. In the subset of participants with no missing baseline data (for variables collected in ASCEND), similar magnitudes of overprediction and discrimination were found. MAPE of the UKPDS-OM2 was generally higher suggesting that the bias reported may be an underestimation, but the conclusion is still robust.

Secondly, follow-up blood and urine samples were only collected in a random sample of about 1200 ASCEND participants, so risk factors were projected over time using the risk factor progression equations in the UKPDS-OM2. Exploratory tabulations (Supplemental Figure C.10) suggest that the rates of deterioration of these cardio-metabolic markers were slightly overpredicted at 2.5 years into the follow-up. There are insufficient data to reliably assess the validity of these equations for the ASCEND participants. However, the use of these equations to project missing risk factor progression over time reflects how other users are likely to use the model in absence of risk factor progression data. Moreover, results with

risk factors held constant at their baseline values were provided as a benchmark for the range within which the actual predictions could lie.

Thirdly, although adverse events in ASCEND were chosen to match the definitions of endpoints in the UKPDS-OM2, differences may exist. Changes in diagnostic criteria for some complications contributed to these differences. For example, studies have found that the newer definition of myocardial infarction based on cardiac troponin testing recommended by guidelines since 2000 identified substantially more patients with myocardial infarction in contrast to older definition based on creatinine phosphokinase [35]. This would imply that the number of myocardial infarctions predicted by the UKPDS-OM2 is an under-estimation of the actual number of myocardial infarction for the same population. However, the model substantially over-predicted the rate of myocardial infarction in the ASCEND cohort, suggesting that the issue of misclassification is outweighed by the inaccuracies of the model in itself. Additionally, blindness and lower extremity ulcer which are endpoints in the UKPDS-OM2 were excluded from the analysis as they were not routinely sought or recorded in ASCEND and the incidence of occurrence of these endpoints could not be reliably estimated.

Lastly, the inclusion/exclusion criteria in ASCEND may restrict the generalisability of the results to other type 2 diabetes cohorts. Participants in ASCEND had no previous cardiovascular disease (exclusion criteria in ASCEND) despite a median duration of diabetes of 6 years, in contrast to the 6% and 4% of participants with myocardial infarction and other IHD respectively 6 years after diabetes diagnosis in the UKPDS [1]. There are also further exclusion criteria in ASCEND (e.g. people with liver disease excluded) that make the ASCEND cohort more selective. Additionally, participants in ASCEND were predominantly White. Nevertheless, many of these factors are covariates in the UKPDS-OM2 risk equations and it is expected that the model can account for these differences. There may be other systematic differences between the ASCEND and the UKPDS cohorts that were not observed and unaccounted for, but these differences are unlikely to account for the degree of discrepancy in event rates reported here.

2.4.4 Strengths and added value

The major strengths of the present analysis are the large sample size of ASCEND, availability of long follow-up data, and high quality individual patient data with complete follow-up for 99% of participants and clinically adjudicated endpoints (for myocardial infarction, other IHD, stroke, and deaths). The model validation was also performed on a UK cohort which eliminates the uncertainty due to geographic and ethnic differences present in previous external validations of the UKPDS-OM2 that were performed in North American or other European cohorts [5–8].

2.5 Implications on cost-effectiveness analysis

Previous validation studies have demonstrated that despite overestimating absolute risks, models can predict the relative risks of treatment well [36]. Although estimation of relative effects is important, accurate estimates of absolute effects are necessary if the aim is to evaluate the magnitude of impact of the treatment on the number of adverse events, costs and (quality-adjusted) life years (QALYs). Overestimating disease risks will directly result in overestimating health benefits, which is likely to affect estimates of cost-effectiveness [37, 38].

I illustrate the implications of mispredictions on cost-effectiveness analysis for the ASCEND type 2 diabetes cohort included in this study. Lifetime healthcare costs, life expectancies and QALYs were estimated for each ASCEND participant using the default costs and quality of life utility values provided in the UKPDS-OM2 [39]. All outcomes were discounted at 3.5% per annum. The relationship between the 7-year risk of vascular death and lifetime healthcare costs, life expectancies, and QALYs predicted by the UKPDS-OM2 were estimated using linear regression models. Models included covariates sex, age, 7-year vascular death risk and the interaction between age and 7-year vascular death risk. Natural cubic splines were used to model the non-linear relationship between costs, life expectancies, QALYs and age. The fitted models were used to predict these outcomes in the ASCEND cohort, whereby the 7-year vascular death risks for all participants in the

ASCEND cohort were adjusted to simulate the impact of overpredicting vascular death risk on cost-effectiveness:

(1) UKPDS-OM2 predicted risks scenario

   a. Vascular death risk for each participant as predicted by the UKPDS-OM2 (i.e. overestimated risk)
   b. 15% relative risk reduction in vascular death risk in (a)

(2) ASCEND risks scenario

   a. Vascular death risk for each participant predicted by the UKPDS-OM2 scaled by a scaling factor (see Table 2.5)
   b. 15% relative risk reduction in vascular death risk in (a)

Table 2.5: Scaling factor applied to 7-year vascular death risk predicted by UKPDS-OM2 to match the risk observed in ASCEND

	Risk observed in ASCEND	Risk predicted by UKPDS-OM2	Scaling factor
All participants in ASCEND cohort	2.0%	7.5%	0.267
Lowest vascular death risk decile	1.1%	1.7%	0.647
Highest vascular death risk decile	4.5%	19.3%	0.233

Results from (1) were used to estimate the incremental cost-effectiveness ratio (ICER) for the scenario where vascular death risk is overestimated by the UKPDS-OM2. Results from (2) were used to estimate the ICER for the scenario where vascular death risk corresponds to the risk observed in ASCEND. The estimated lifetime costs in scenarios with added treatment further included an illustrative treatment cost of £1.30 per day. These calculations were also performed separately among ASCEND participants in the lowest vascular death risk decile and the highest vascular death risk decile respectively.

A 15% risk reduction in vascular death resulted in a 0.058 increase in quality-adjusted life years (QALYs) based on the 7-year vascular death risk observed in ASCEND, in contrast to 0.218 QALYs based on the overestimated 7-year vascular death risk predicted by the UKPDS-OM2 (Table 2.6). The difference in incremental lifetime cost is less pronounced (£6137 vs £5579), which overall translates into a substantial difference in the ICER (£105,540/QALY vs £25,585/QALY). Furthermore, the magnitude of bias in these incremental impacts can vary across different risk groups, as illustrated by the separate comparisons among participants in the lowest and highest vascular death risk deciles. Based on NICE's cost-effectiveness threshold which is in the range of £20,000 to £30,000 per QALY, the treatment would have been deemed a cost-effective use of NHS resources based on predictions from the UKPDS-OM2, but would actually be vastly beyond this threshold even for people in the highest risk decile based on the disease risks observed in ASCEND.

The results from this analysis, together with findings from previous external validations of the UKPDS-OM2 [5–8], indicate that the UKPDS-OM2 may not provide reliable estimates of absolute event rates for contemporary type 2 diabetes cohorts such as those in ASCEND. Appropriate adjustments would be needed when using the model for clinical or economic analyses in contemporary cohorts particularly when absolute risk and/or total cost and (quality-adjusted) life expectancy are of interest. There have been efforts to improve prediction accuracy of the UKPDS-OM, resulting in either updated equations for the UKPDS-OM or new diabetes models sharing a similar framework to the UKPDS-OM [12, 16, 40]. Due to the lack of data, many diabetes models still rely on the original UKPDS-OM equations in some way. Hence, external validation of these models are still required, but the inter-dependencies between the risk factor progression equations and risk equations of each event make it extremely challenging to untangle and identify the underlying reason of mis-predictions. A new framework for predicting long-term outcomes in diabetes may thus be required.

Table 2.6: Predicted lifetime costs, life expectancies and quality-adjusted life years from 15% risk reduction in vascular death, based on risk predicted by the UKPDS-OM2 and observed in ASCEND

	Lifetime cost (£)			QALYs			Life expectancy (years)			
Baseline 7-year risk of vascular death	W/o tx	With tx	Incremental cost	W/o tx	With tx	Incremental QALYs	W/o tx	With tx	Incremental life years	ICER (£/QALY)
In entire cohort										
2.0% (observed in ASCEND)	28790	34927	6137	10.318	10.377	0.058	12.909	12.976	0.066	105540
7.5% (predicted by UKPDS-OM2)	29233	34812	5579	9.252	9.470	0.218	11.692	11.941	0.249	25585
In lowest risk decile										
1.1% (observed in ASCEND)	32399	40075	7676	12.856	12.919	0.063	16.152	16.223	0.071	121573
1.7% (predicted by UKPDS-OM2)	32497	40054	7558	12.626	12.724	0.098	15.894	16.004	0.109	77450
In highest risk decile										
4.5% (observed in ASCEND)	19530	23531	4001	6.727	6.792	0.065	8.405	8.482	0.077	61340
19.3% (predicted by UKPDS-OM2)	20100	23332	3232	5.297	5.577	0.280	6.711	7.042	0.331	11552

Note:
W/o tx, with no treatment effect; With tx, with treatment effect i.e. 15% relative risk reduction applied; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio. Vascular death is defined as death from myocardial infarction, other IHD, heart failure or stroke (as in UKPDS-OM2). A hypothetical treatment that reduces vascular death risk by 15% and costs UK £1.30/day was used. Costs, QALYs and life years (individually and as inputs to calculate ICER), were discounted at 3.5% per annum.

References

1. Clarke PM, Gray AM, Briggs A, et al. A Model to Estimate the Lifetime Health Outcomes of Patients with Type 2 Diabetes: The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS No. 68). Diabetologia 2004;47:1747–59. DOI: 10.1007/s00125-004-1527-z.
2. Hayes AJ, Leal J, Gray AM, Holman RR, and Clarke PM. UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33. DOI: 10.1007/s00125-013-2940-y.
3. National Institute for Health and Care Excellence. Type 2 Diabetes in Adults: Management (NG28). 2022. URL: https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-pdf-78671532569 (visited on 08/19/2022).
4. Leal J, Hayes AJ, Gray AM, Holman RR, and Clarke PM. Temporal Validation of the UKPDS Outcomes Model Using 10-Year Posttrial Monitoring Data. Diabetes Care 2013;36:1541–6. DOI: 10.2337/dc12-1120.
5. Basu S, Sussman JB, Berkowitz SA, Hayward RA, and Yudkin JS. Development and Validation of Risk Equations for Complications Of Type 2 Diabetes (RECODe) Using Individual Participant Data from Randomised Trials. The Lancet Diabetes & Endocrinology 2017;5:788–98. DOI: 10.1016/S2213-8587(17)30221-8.
6. Basu S, Sussman JB, Berkowitz SA, et al. Validation of Risk Equations for Complications of Type 2 Diabetes (RECODe) Using Individual Participant Data From Diverse Longitudinal Cohorts in the U.S. Diabetes Care 2018;41:586–95. DOI: 10.2337/dc17-2002.
7. Laxy M, Schöning VM, Kurz C, et al. Performance of the UKPDS Outcomes Model 2 for Predicting Death and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus from a German Population-Based Cohort. Pharmacoeconomics 2019;37:1485–94. DOI: 10.1007/s40273-019-00822-4.
8. Pagano E, Konings SRA, Di Cuonzo D, et al. Prediction of Mortality and Major Cardiovascular Complications in Type 2 Diabetes: External Validation of UK Prospective Diabetes Study Outcomes Model Version 2 in Two European Observational Cohorts. Diabetes Obes Metab 2021;23:1084–91. DOI: 10.1111/dom.14311.
9. Si L, Willis MS, Asseburg C, et al. Evaluating the Ability of Economic Models of Diabetes to Simulate New Cardiovascular Outcomes Trials: A Report on the Ninth Mount Hood Diabetes Challenge. Value Health 2020;23:1163–70. DOI: 10.1016/j.jval.2020.04.1832.
10. Pagano E, Gray A, Rosato R, et al. Prediction of Mortality and Macrovascular Complications in Type 2 Diabetes: Validation of the UKPDS Outcomes Model in the Casale Monferrato Survey, Italy. Diabetologia 2013;56:1726–34. DOI: 10.1007/s00125-013-2933-x.

11. Drummond M, Barbieri M, Cook J, et al. Transferability of Economic Evaluations across Jurisdictions: ISPOR Good Research Practices Task Force Report. Value Health 2009;12:409–18. DOI: 10.1111/j.1524-4733.2008.00489.x.

12. McEwan P, Bennett H, Ward T, and Bergenheim K. Refitting of the UKPDS 68 Risk Equations to Contemporary Routine Clinical Practice Data in the UK. Pharmacoeconomics 2015;33:149–61. DOI: 10.1007/s40273-014-0225-z.

13. Holman RR, Paul SK, Bethel MA, Matthews DR, and Neil HAW. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med 2008;359:1577–89. DOI: 10.1056/NEJMoa0806470.

14. HPS3/TIMI55–REVEAL Collaborative Group, Bowman L, Hopewell JC, et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. N Engl J Med 2017;377:1217–27. DOI: 10.1056/NEJMoa1706444.

15. White IR, Royston P, and Wood AM. Multiple Imputation Using Chained Equations: Issues and Guidance for Practice. Stat Med 2011;30:377–99. DOI: 10.1002/sim.4067.

16. Leal J, Alva M, Gregory V, et al. Estimating Risk Factor Progression Equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med 2021;38:e14656. DOI: 10.1111/dme.14656.

17. Therneau T, Crowson C, and Atkinson E. Multi-State Models and Competing Risks. CRAN 2022.

18. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018;379:1529–39. DOI: 10.1056/NEJMoa1804988.

19. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of N-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med 2018;379:1540–50. DOI: 10.1056/NEJMoa1804989.

20. Efron B and Tibshirani R. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science 1986;1:54–75. DOI: 10.2333/bhmk.12.17_1.

21. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the Performance of Prediction Models: A Framework for Traditional and Novel Measures. Epidemiology 2010;21:128–38. DOI: 10.1097/EDE.0b013e3181c30fb2.

22. Uno H, Cai T, Pencina MJ, D'Agostino RB, and Wei LJ. On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data. Stat Med 2011;30:1105–17. DOI: 10.1002/sim.4154.

23. Bhatnagar P, Wickramasinghe K, Wilkins E, and Townsend N. Trends in the Epidemiology of Cardiovascular Disease in the UK. Heart 2016;102:1945–52. DOI: 10.1136/heartjnl-2016-309573.

24. UK Prospective Diabetes Study (UKPDS) Group. Intensive Blood-Glucose Control with Sulphonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes (UKPDS 33). Lancet 1998;352:837–53. DOI: 10.1016/S0140-6736(98)07019-6.

25. Conrad N, Judge A, Tran J, et al. Temporal Trends and Patterns in Heart Failure Incidence: A Population-Based Study of 4 Million Individuals. Lancet 2018;391:572–80. DOI: 10.1016/S0140-6736(17)32520-5.

26. Gregg EW, Sattar N, and Ali MK. The Changing Face of Diabetes Complications. Lancet Diabetes Endocrinol 2016;4:537–47. DOI: 10.1016/S2213-8587(16)30010-9.

27. Read SH, Fischbacher CM, Colhoun HM, et al. Trends in Incidence and Case Fatality of Acute Myocardial Infarction, Angina and Coronary Revascularisation in People with and without Type 2 Diabetes in Scotland between 2006 and 2015. Diabetologia 2019;62:418–25. DOI: 10.1007/s00125-018-4796-7.

28. Smolina K, Wright FL, Rayner M, and Goldacre MJ. Determinants of the Decline in Mortality from Acute Myocardial Infarction in England between 2002 and 2010: Linked National Database Study. BMJ 2012;344:d8059. DOI: 10.1136/bmj.d8059.

29. Ford ES and Capewell S. Proportion of the Decline in Cardiovascular Mortality Disease Due to Prevention versus Treatment: Public Health versus Clinical Care. Annu Rev Public Health 2011;32:5–22. DOI: 10.1146/annurev-publhealth-031210-101211.

30. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, and Morris RW. How Much of the Recent Decline in the Incidence of Myocardial Infarction in British Men Can Be Explained by Changes in Cardiovascular Risk Factors? Evidence from a Prospective Population-Based Study. Circulation 2008;117:598–604. DOI: 10.1161/CIRCULATIONAHA.107.705947.

31. Hotchkiss JW, Davies CA, Dundas R, et al. Explaining Trends in Scottish Coronary Heart Disease Mortality between 2000 and 2010 Using IMPACTSEC Model: Retrospective Analysis Using Routine Data. BMJ 2014;348:g1088. DOI: 10.1136/bmj.g1088.

32. Unal B, Critchley JA, and Capewell S. Explaining the Decline in Coronary Heart Disease Mortality in England and Wales between 1981 and 2000. Circulation 2004;109:1101–7. DOI: 10.1161/01.CIR.0000118498.35499.B2.

33. Donnelly LA, Zhou K, Doney ASF, Jennison C, Franks PW, and Pearson ER. Rates of Glycaemic Deterioration in a Real-World Population with Type 2 Diabetes. Diabetologia 2018;61:607–15. DOI: 10.1007/s00125-017-4519-5.

34. Sattar N, Rawshani A, Franzén S, et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. Circulation 2019;139:2228–37. DOI: 10.1161/CIRCULATIONAHA.118.037885.

35. Amit G, Gilutz H, Cafri C, Wolak A, Ilia R, and Zahger D. What Have the New Definition of Acute Myocardial Infarction and the Introduction of Troponin Measurement Done to the Coronary Care Unit? CRD 2004;102:171–6. DOI: 10.1159/000080487.

36. Palmer AJ, Mount Hood 5 Modeling Group, Clarke P, et al. Computer Modeling of Diabetes and Its Complications: A Report on the Fifth Mount Hood Challenge Meeting. Value Health 2013;16:670–85. DOI: 10.1016/j.jval.2013.01.002.

37. Raikou M, McGuire A, Colhoun HM, et al. Cost-Effectiveness of Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes: Results from the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia 2007;50:733–40. DOI: 10.1007/s00125-006-0561-4.

38. Reifsnider O, Kansal A, Pimple P, Aponte-Ribero V, Brand S, and Shetty S. Cost-Effectiveness Analysis of Empagliflozin versus Sitagliptin as Second-Line Therapy for Treatment in Patients with Type 2 Diabetes in the United States. Diabetes Obes Metab 2021;23:791–9. DOI: 10.1111/dom.14268.

39. UKPDS Outcomes Model User Manual. 2015. URL: https://www.dtu.ox.ac.uk/outcomesmodel/OM2Manual.pdf (visited on 03/01/2022).

40. Willis M, Asseburg C, and He J. Validation of Economic and Health Outcomes Simulation Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Journal of Medical Economics 2013;16:1007–21. DOI: 10.3111/13696998.2013.809352.

3

Simulation model for predicting first occurrences of adverse events over a lifetime in people with diabetes without previous cardiovascular disease – model development, validation and updating

Summary

In this Chapter, I used data from ASCEND to estimate new risk equations for predicting first-occurrences of cardiovascular, bleeding, cancer, lower-limb amputation, end-stage renal disease, and death events over lifetime in people with diabetes without previous cardiovascular disease. These risk equations were integrated into a patient-level discrete-time stochastic simulation model, which predicts the likelihood of occurrence of each adverse event over the lifetime of a patient given their baseline characteristics and events as they occur within the simulation. The simulation model was demonstrated to perform well internally, replicating the event rates observed in ASCEND well. The model was validated externally in a cohort of UK Biobank participants identified to match the ASCEND recruitment criteria. Myocardial infarction, coronary revascularisation and cancers were generally well-predicted, displaying good calibration and discrimination. Discrepancies were found for other events, which were likely due to risk factor measurement error, errors in event ascertainment from routine healthcare records in the UK Biobank, and differences

in background event rates due to differences in participants recruited in the two cohorts. Depending on the reason for the discrepancies, different strategies were adopted to update the risk equations using the UK Biobank data.

The set of new risk equations provides an alternative to the UKPDS risk equations, reflecting contemporary event rates in people with diabetes without previous cardiovascular disease. The framework developed based on these risk equations will be useful for evaluating diabetes treatments for the primary prevention of cardiovascular disease. Additionally, a novel issue-driven approach for updating risk equations was introduced, which can be adopted to address issues of discrepancies beyond those identified in this work.

3.1 Background

Decision-analytic disease models are used to synthesise clinical and economic data and inform assessments of overall health effects and/or cost-effectiveness of healthcare interventions. In diabetes, which is associated with disabling and costly complications over time, such models are crucial to simulate the impact of treatments over a person's lifetime. The diabetes model of choice in the UK used by NICE is the UKPDS-OM [1, 2] developed using patient data from 1977-2007 and thus reflects historic patterns of care and event rates. I have shown in Chapter 2 that the model overpredicts cardiovascular events and deaths in ASCEND, further adding to the evidence base that the model is unsuitable for use in contemporary cohorts [3–7]. There have been efforts to re-calibrate the UKPDS risk equations [8] or develop new risk equations [3, 9, 10]. The data used in these studies are mostly from recent cardiovascular outcomes trials, which recruited people with diabetes selected to be at high risk of cardiovascular disease, with a significant proportion of participants already having some history of cardiovascular disease. A further issue of existing diabetes simulation models is the reliance on changes to risk factor progression when simulating treatment effects on outcomes, as discussed in Chapter 1. The equations from the UKPDS-OM for predicting risk factor progression are

likely outdated. More fundamentally however, the framework does not align well with long-term trials which report treatment effects on hard outcomes independent from treatment effects on surrogate markers (e.g. trials of novel glycaemic drugs which report cardioprotective effects independent from glucose control).

Different from many recent cardiovascular outcomes trials, the ASCEND study recruited participants without previous cardiovascular disease. I used data from the ASCEND study to develop new risk equations for predicting adverse events in people with diabetes without previous cardiovascular disease. These risk equations were integrated into a patient-level discrete-time stochastic simulation model, which predicts the likelihood of occurrence of adverse events over the lifetime of a patient given their baseline characteristics and events as they occur within the simulation. A cohort of participants from the UK Biobank was identified matching the ASCEND recruitment criteria to assess the performance of the model. I discuss some data considerations in the model updating process in external cohorts and demonstrate methods to update the risk equations in the event of discrepancies between observed and predicted event rates.

3.2 Description of datasets

3.2.1 Study populations

For model development and internal validation, data from 15,480 participants in ASCEND were used [11]. Baseline characteristics and biomarker measurements were retrieved from the study data. For external validation, data from participants in the UK Biobank matching the ASCEND inclusion criteria at the time of recruitment were used. The UK Biobank is a longitudinal prospective observational cohort that enrolled over half a million participants aged 37 to 73 between 2006 and 2010 [12]. Participants were followed for an average of 11 years as of 29/02/2020 (cut-off date). Baseline characteristics and biomarker measurements were obtained from a combination of participants' responses to a questionnaire and nurse-led interviews, physical assessment measures, and hospital inpatient records. Using the

algorithm developed by Eastwood et al. (2016) [13] which accounts for self-reports of diabetes, reports of diabetes in hospital or primary care records, and reports of diabetes-related drug use, 26,430 (5.3%) participants in the UK Biobank were identified to have either type 1 or type 2 diabetes. Aligning with the ASCEND inclusion criteria and further excluding participants with a history of cardiovascular disease, hepatic disease, or end-stage renal disease (ESRD) prior to recruitment, with a history of gastrointestinal (GI) haemorrhage or peptic ulcer within 6 months prior to recruitment, or with a history of cancer diagnosis or treatment within 5 years prior to recruitment, 18,250 (3.6%) participants in the UK Biobank were identified for inclusion in the analysis. Full details of cohort identification from the UK Biobank can be found in Appendix B.2.

Baseline characteristics of participants in ASCEND (N = 15,480) and in the UK Biobank (N = 18,250) are summarised in Table 3.1 (missing data summarised in Table 3.2). Participants in both ASCEND and the UK Biobank were mostly White Caucasians (97% in ASCEND, 86% in the UK Biobank) living in regions with the lowest deprivation (43%, 37% living in quintile of least deprivation). In contrast to the ASCEND cohort, the UK Biobank cohort had a greater proportion of participants with type 1 diabetes (13% in the UK Biobank vs 6% in ASCEND), was on average younger (mean age 59 vs 63), had a shorter duration of diabetes (median duration 5 years vs 7 years), and had a greater proportion of current smokers (11% vs 8%). In terms of clinical risk factors, the UK Biobank cohort had worse lipid profile (37% vs 21% with non-HDL cholesterol $\geq$ 3.5 mmol/L), worse blood pressure profile (51% vs 41% with SBP $\geq$ 140mmHg), and worse renal function profile (11% vs 13% with eGFR <60ml/min/1.73m^2; 17% vs 13% with urinary albumin-to-creatinine ratio $\geq$ 3mg/mmol).

Table 3.1: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
Diabetes type		
Type 1	911 (5.9%)	2432 (13.3%)
Type 2	14569 (94.1%)	15818 (86.7%)
Sex		
Male	9684 (62.6%)	10827 (59.3%)
Female	5796 (37.4%)	7423 (40.7%)
Smoking status		
Current smoker	1279 (8.4%)	1921 (10.6%)
Former/Never smoker	14028 (91.6%)	16121 (89.4%)
Race		
White	14935 (96.5%)	15642 (85.7%)
South Asian	184 (1.2%)	1000 (5.5%)
Black	140 (0.9%)	691 (3.8%)
Other/unknown	221 (1.4%)	917 (5%)
Townsend Index*		
Q1: <-2.42 (least deprived)	6690 (43.3%)	6664 (36.6%)
Q2: ≥-2.42, <-0.44	3793 (24.6%)	3866 (21.2%)
Q3: ≥-0.44, < 1.79	2499 (16.2%)	2982 (16.4%)
Q4: ≥ 1.79, < 4.75	1820 (11.8%)	3038 (16.7%)
Q5: ≥ 4.75 (most deprived)	640 (4.1%)	1674 (9.2%)
Hypertension		
Y	9533 (62%)	12771 (70%)
N	5835 (38%)	5479 (30%)
Diabetic retinopathy		
Y	3023 (19.7%)	1532 (8.4%)
N	12313 (80.3%)	16718 (91.6%)
Statin use		
Y	11653 (75.3%)	12532 (68.7%)
N	3827 (24.7%)	5718 (31.3%)
Use of ACE Inhibitor or ARB		
Y	9055 (58.5%)	9276 (50.8%)
N	6425 (41.5%)	8974 (49.2%)
Aspirin use†		
Y	5508 (35.6%)	7974 (43.7%)
N	9972 (64.4%)	10276 (56.3%)
Age (years)		
Mean (SD)	63.3 (9.2)	59.0 (7.3)

Table 3.1: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis *(continued)*

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
<50	1089 (7%)	2415 (13.2%)
≥50, <60	4501 (29.1%)	5744 (31.5%)
≥60, <70	6247 (40.4%)	9956 (54.6%)
≥70, <80	3086 (19.9%)	135 (0.7%)
≥80	557 (3.6%)	-
Diabetes duration (years)		
Mean (SD)	9.8 (9.4)	8.5 (9.9)
Median (IQR)	7.0 (3.0, 13.0)	5.0 (2.0, 10.0)
<5	4891 (33.4%)	7743 (42.9%)
≥5, <10	4334 (29.6%)	5116 (28.3%)
≥10, <20	3537 (24.2%)	3408 (18.9%)
≥20	1862 (12.7%)	1796 (9.9%)
Body-mass index (kg/m^2)		
Mean (SD)	31.1 (6.5)	31.2 (5.9)
<25	2068 (13.5%)	2274 (12.6%)
≥25, <30	5472 (35.6%)	6278 (34.8%)
≥30, <35	4525 (29.5%)	5419 (30%)
≥35	3296 (21.5%)	4092 (22.7%)
HbA1c (IFCC mmol/mol)		
Mean (SD)	54.8 (12.9)	52.8 (13.9)
< 48	3272 (33.3%)	7090 (42.2%)
≥ 48, < 64	4664 (47.5%)	6830 (40.7%)
≥ 64	1877 (19.1%)	2876 (17.1%)
HDL cholesterol (mmol/L)[‡]		
Mean (SD)	1.27 (0.35)	1.23 (0.34)
< 1.0	2170 (22.1%)	3962 (25.5%)
≥ 1.0, < 1.5	5523 (56.4%)	8882 (57.2%)
≥ 1.5	2107 (21.5%)	2697 (17.4%)
Non-HDL cholesterol (mmol/L)		
Mean (SD)	2.90 (0.84)	3.33 (0.98)
< 2.5	3390 (34.6%)	2997 (19.3%)
≥ 2.5, < 3.5	4393 (44.8%)	6835 (44%)
≥ 3.5	2017 (20.6%)	5708 (36.7%)
Systolic blood pressure (mmHg)		
Mean (SD)	136.2 (15.3)	141.5 (17.0)
<130	3394 (30.7%)	4585 (25.2%)
≥130, <140	3091 (28%)	4247 (23.4%)
≥140	4555 (41.3%)	9343 (51.4%)

Table 3.1: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis *(continued)*

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
Diastolic blood pressure (mmHg)		
Mean (SD)	77.1 (9.5)	82.1 (9.5)
<75	4223 (38.3%)	3968 (21.8%)
≥75, <85	4619 (41.9%)	7287 (40.1%)
≥85	2191 (19.9%)	6920 (38.1%)
Urinary albumin/creatinine ratio (mg/mmol)§		
<3	8526 (87.2%)	14420 (82.7%)
≥3, <30	1088 (11.1%)	2700 (15.5%)
≥30	160 (1.6%)	311 (1.8%)
eGFR (ml/min/1.73m^2)¶		
< 45	407 (4.1%)	461 (2.7%)
≥ 45, < 60	869 (8.9%)	1356 (8%)
≥ 60, < 90	4016 (40.9%)	8545 (50.4%)
≥ 90	4523 (46.1%)	6599 (38.9%)

Note:
Summary statistics are N (%) unless otherwise specified. Missing data are excluded from the tabulation. Number of participants with missing data are tabulated in Table 3.2.
In ASCEND, only 9,908 (64%) participants returned usable blood/urine sample in the study.

* Townsend index stratified according to the range of scores of 2011 UK population quintiles.

† Aspirin use prior to treatment randomisation in ASCEND.

‡ For UK Biobank, the Friedwald equation was used to derive HDL-cholesterol, if not recorded, from total cholesterol, LDL-cholesterol and triglycerides (not exceeding 4.5 mmol/L).

§ 2403 participants in ASCEND and 8451 participants in UK Biobank who had undetectable albumin levels were reclassified as having no albuminuria (urinary albumin/creatinine ratio <3mg/mmol).

¶ Calculated from blood cystatin C concentration using the CKD-EPI formula. Serum creatinine formula was used for 12 UK Biobank participants with no blood cystatin C concentration but with serum creatinine values.

Table 3.2: Number (%) of ASCEND and UK Biobank participants missing baseline characteristics

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
Smoking status	173 (1.1%)	208 (1.1%)
Townsend Index	38 (0.2%)	26 (0.1%)
Hypertension	112 (0.7%)	-
Diabetic retinopathy	144 (0.9%)	-
Diabetes duration (years)	856 (5.5%)	187 (1%)
Body-mass index (kg/m^2)	119 (0.8%)	187 (1%)
HbA1c (IFCC mmol/mol)	5667 (36.6%)	1454 (8%)
HDL cholesterol (mmol/L)	5680 (36.7%)	2709 (14.8%)
Non-HDL cholesterol (mmol/L)	5680 (36.7%)	2710 (14.8%)
Systolic blood pressure (mmHg)	4440 (28.7%)	75 (0.4%)
Diastolic blood pressure (mmHg)	4447 (28.7%)	75 (0.4%)
Urinary albumin/creatinine ratio (mg/mmol)	5706 (36.9%)	819 (4.5%)
eGFR (ml/min/1.73m^2)	5665 (36.6%)	1289 (7.1%)

3.2.2 Adverse events

The adverse events of interest included first occurrences of the following: for cardiovascular disease, myocardial infarction, urgent and non-urgent coronary revascularisation, transient ischaemic attack (TIA), ischaemic stroke, heart failure; for bleeding, intracranial haemorrhage, GI bleed, other major bleed (excludes eye bleed); for cancer, GI tract cancer and non-GI tract cancer (excludes non-melanoma skin cancer); for other diabetes complications, lower-limb amputation and ESRD; for deaths, vascular (excludes intracranial haemorrhage) and non-vascular deaths.

Time to event was established relative to the date of randomisation in ASCEND and the date of recruitment in the UK Biobank. In ASCEND, adverse events were collected through 6-monthly follow-up questionnaires over the follow-up period, with additional follow-up for hospitalisations, cancer and death obtained from routine hospital records, the cancer registry and the death registry respectively. Key outcomes were clinically adjudicated. Events were identified from adverse events reported in the ASCEND study and from linkage to Hospital Episode Statistics (HES). For the UK Biobank, events were identified from data linkage to

the death registry, the cancer registry and hospital inpatient records from HES. For heart failure, GI bleed and other major bleed, only hospital inpatient records with corresponding codes in the primary diagnosis position were included. A further condition was imposed for heart failure to exclude non-emergency admissions that have a length of stay shorter than one day [14]. Death records with a cardiovascular event (excluding intracranial haemorrhage) recorded as the primary cause of death were considered vascular death, while all other deaths were considered non-vascular death. Primary care records were available for roughly 45% of participants in the UK Biobank, and these were further used to supplement the identification of TIA as TIA may not be captured in hospital records [15]. For the main analysis, all evaluations of TIA were performed only in the subset of participants with primary care records, and TIA events identified from other sources in all participants were used for sensitivity analysis. The censoring date for each event was set to 29/02/2020 or the latest date of data availability for the source of data [16]. Details on identifying adverse events in ASCEND and the UK Biobank are in Appendix B.1 and B.3 respectively.

In ASCEND, the average follow-up time is 7.4 years. In the UK Biobank, the average follow-up times are 7.7 years for outcomes identified from primary care records, 10.9 years for outcomes identified from the cancer registry, 11.0 years for outcomes identified from hospital inpatient data, and 11.1 years for outcomes identified from the death registry. The numbers of participants who experienced each adverse event in the two cohorts over the follow-up period are summarised in Table 3.3. Rates of myocardial infarction (3.89 in ASCEND vs 3.85 in the UK Biobank per 1000 person-year), coronary revascularisations (urgent 2.28 vs 2.42; non-urgent, 2.45 vs 2.50), cancers (GI tract cancer, 2.63 vs 2.56; non-GI tract cancer, 13.52 vs 12.47) and ESRD (0.87 vs 0.86) were similar in the two cohorts. Higher rates of ischaemic stroke (3.82 vs 2.07) and amputation (1.20 vs 0.88), and lower rate of intracranial haemorrhage (0.83 vs 1.09) were observed in ASCEND. Death rates were higher in ASCEND (vascular death 3.43 vs 2.52; non-vascular death 9.33

vs 8.55). Rates of TIA, heart failure, GI bleed and other major bleed may not be comparable due to issues with identifying these events in the UK Biobank[1].

Table 3.3: Number of participants experiencing each adverse event in ASCEND and UK Biobank

Adverse event	ASCEND (N = 15480)		UK Biobank (N = 18250)	
	N (%)	N / 1000 person-year	N (%)	N / 1000 person-year
Myocardial infarction	465 (3.0%)	3.89	764 (4.2%)	3.85
Coronary revascularisation (urgent)	273 (1.8%)	2.28	482 (2.6%)	2.42
Coronary revascularisation (non-urgent)	293 (1.9%)	2.45	496 (2.7%)	2.50
Transient ischaemic attack	365 (2.4%)	3.06	183 (1.0%)	0.91
	-	-	78 (1.0%)*	1.22
Ischaemic stroke	456 (2.9%)	3.82	292 (1.6%)	2.07
Heart failure	357 (2.3%)	2.97	430 (2.4%)	2.15
Intracranial haemorrhage	100 (0.6%)	0.83	219 (1.2%)	1.09
GI bleed	238 (1.5%)	1.98	199 (1.1%)	0.99
Other major bleed	117 (0.8%)	0.97	225 (1.2%)	1.12
GI tract cancer	315 (2.0%)	2.63	510 (2.8%)	2.56
Non-GI tract cancer	1577 (10.2%)	13.52	2401 (13.2%)	12.47
Amputation	144 (0.9%)	1.20	177 (1.0%)	0.88
End-stage renal disease	105 (0.7%)	0.87	174 (1.0%)	0.86
Vascular death	414 (2.7%)	3.43	510 (2.8%)	2.52
Non-vascular death	1126 (7.3%)	9.33	1732 (9.5%)	8.55

Note:
GI, gastrointestinal
* In subset of 8180 (45%) participants with primary care data which was used to supplement identification of transient ischaemic attack

[1]Issues with adverse event ascertainment in the UK Biobank are discussed in detail in Section 3.4.2.

3.2.3 Missing baseline data

For the UK Biobank, a first-stage imputation was performed by deriving missing data from other information in the dataset where possible (e.g. eGFR from cystatin C; further details in Appendix B.4). Following this, less than 2% of participants in both ASCEND and the UK Biobank had missing sociodemographic characteristics (reflected in Table 3.2). Missing patient characteristics (ethnicity, smoking status, Townsend index, hypertension, retinopathy) were imputed with the modal group (White, non-smoker, least deprived quintile [Q1], with hypertension, no retinopathy, respectively).

About 36% of participants in ASCEND had missing biomarker values as they did not return a usable blood/urine sample. About 15% of participants in the UK Biobank were missing cholesterol values, while less than 10% of participants were missing other biomarker values. Missing biomarker values were imputed by predictive mean matching using the method of multivariate imputation by chained equations [17–19], with all patient characteristics, clinical risk factors and adverse event occurrences included in the imputation model. 40 and 15 imputations were performed for ASCEND and the UK Biobank cohort respectively, and the average values across all imputed datasets were used. Summary statistics of participants' baseline characteristics after imputation can be found in Supplemental Table C.7.

3.3 Model development in ASCEND

3.3.1 Variable selection

Cox proportional hazard models predicting time to first occurrences of each adverse event in ASCEND were used for covariate selection. Candidate variables included patient characteristics and clinical risk factors measured at baseline. Time-updated covariates include age and event occurrence in the study, as well as the proportion of participants taking antithrombotic medication (study/non-study aspirin, anticoagulants, antiplatelet) in each follow-up year stratified by treatment

arm[2]. All candidate variables are listed and described in Supplemental Table C.8. To align with the simulation model where annual cycles are employed, time to event was split into follow-up years. Time-updated disease histories were split into 4 levels – no occurrence, event occurrence in the year, in the previous year, or at least 2 years ago – to capture the decay in impact on hazard with time since event. However, these levels were combined when there were too few participants having each disease history (Supplemental Table C.9), or when there was no evidence of a difference between the immediate and longer-term impact on hazard. Stepwise selection of covariates was performed based on the likelihood ratio test with p-value < 0.05 and < 0.01 for inclusion and exclusion, respectively. The proportion of participants on antithrombotic medication, age and sex were included in all models regardless of statistical significance.

3.3.2 Non-linearity of continuous variables

Continuous splines with 4 degrees of freedom were used to assess if there were suggestions of non-linearity (p-value < 0.05 for higher degree terms) between a variable and event hazard. Where there were suggestions of a non-linear relationship, the log hazard ratio (HR) estimated as a continuous spline was plotted to explore the shape of the relationship, and the calibration plot (observed cumulative incidence in ASCEND plotted alongside the predicted cumulative incidence) for each model with the linear forms of each variable by the subgroup of interest was used to explore the extent of non-linearity (Supplemental Figures C.11-C.14). Categories or polynomial forms of such variables were considered.

There was evidence of non-linear relationships between BMI and hazards of vascular and non-vascular deaths, and eGFR and hazard of non-vascular death. BMI and eGFR were replaced with their respective categorised forms. There was also evidence of non-linear relationships between age and hazards of non-urgent coronary

[2]The proportion of participants that were taking antithrombotic medication in each treatment arm was included in the model to estimate the full impact of actually taking aspirin or other antithrombotic medication [20]. In contrast to adjusting for treatment adherence on an individual patient level basis, adjustment at a treatment arm level aligns with the intention-to-treat approach.

revascularisation and non-vascular death. For non-urgent coronary revascularisation, although no obvious trend was observed across age, it was clear that participants above 80 years old had a significantly lower risk than participants below 80 years old (Supplemental Table C.10). An indicator for age $>$ 80 years old was used as a covariate for predicting the hazard of non-urgent coronary revascularisation. Polynomial form of age with degree 2 matches the continuous spline well and was used for predicting the hazard of non-vascular death.

3.3.3 Test for violation of proportional hazard assumptions

The Pearson correlations between the Schoenfeld residuals and follow-up years were calculated for all models and p-value < 0.05 from the χ^2 test was used as an indicator for suggestion of violation of the proportional hazard assumption. There were suggestions of violation of the proportional hazard assumption between eGFR and hazard of myocardial infarction, and between HbA1c and hazard of ischaemic stroke. However, plots of Schoenfeld residuals suggest that these violations were not severe (Supplemental Figure C.15).

3.3.4 Sensitivity analysis

The Cox proportional hazard models estimated Lin ASCEND with both the imputed dataset and complete cases (N = 9908) are presented in Supplemental Table C.11. Generally, no evidence of a difference was found between estimates of HRs derived from the imputed dataset to those from the complete case analysis, suggesting that the estimates are robust to the imputation of missing data. This was with the exception of HRs associated with presence of albuminuria (consequence of this is discussed in further detail in Section 3.4), where statistically significant differences were found between the estimates.

3.3.5 Specification of parametric risk equations

Parametric risk equations were fitted using the final set of covariates selected using the Cox proportional hazard models. As there was no evidence of a violation

of the proportional hazard assumption, the Exponential, Weibull, and Gompertz distributions were considered for modelling the hazard function (functional forms in Table 3.4). The Gompertz distribution was used for predicting deaths, as it captures the increasing rate of death most appropriately. The Exponential and Weibull distributions were contrasted for modelling the hazards of other adverse events[3].

Table 3.4: Functional forms of parametric proportional hazard models

		Exponential	**Weibull**	**Gompertz**
Parameters		b: scale	α: shape b: scale	α: shape b: rate
Baseline hazard	$h_0(\alpha, b, t)$	b	$\alpha b t^{\alpha-1}$	$be^{\alpha t}$
Hazard for patient with profile $X = x_{j=1,\ldots,n}$	$h(\alpha, b, t\|X)$	be^{λ}	$\alpha b t^{\alpha-1} e^{\lambda}$	$be^{\alpha t}e^{\lambda}$
Integrated hazard	$H(\alpha, b, t\|X)$	bte^{λ}	$bt^{\alpha}e^{\lambda}$	$\frac{b}{\alpha}(e^{\alpha t}-1)e^{\lambda}$

Note:
$\lambda = \sum_j \beta_j x_j$, where β_j is the coefficient corresponding to variable x_j in the risk equations. The probability of an event occurring between time t and $t+1$ is $1 - e^{H(t|X)-H(t+1|X)}$.

The validity of the risk equations was assessed based on their calibration[4] using a calibration plot. The risk equations for each endpoint were used to predict the occurrence of adverse events in each annual cycle using each participant's baseline characteristics, age in cycle and disease history as of cycle over each participant's duration of follow-up in the study. The year-on-year cumulative incidence for each event observed in the cohort was plotted against that predicted by the risk equations, accounting for competing risk (from deaths for non-fatal events and deaths from other causes for cause-specific deaths). Additionally, Akaike's information criteria of the risk equations were used to assess model fit and inform the choice of parametric specifications. For ESRD, the Weibull distribution achieved better calibration (Supplemental Figure C.16). For other events, neither distribution demonstrated a

[3]The Gompertz distribution is generally ill-suited for modelling events where the baseline hazard is weakly increasing, as numerical problems in the estimation process are likely to occur [21]. When the baseline hazard is only weakly increasing, $\alpha \to 0$ and the distribution approaches an Exponential distribution.

[4]Calibration is the agreement between predicted and observed cumulative incidence.

clear advantage over the other within the observed duration of follow-up in terms of overall calibration or Akaike's information criteria (Supplemental Table C.12).

3.3.6 Discrete-time stochastic simulation

The parametric risk equations were integrated into a patient-level discrete-time stochastic simulation model which predicts the occurrence of adverse events in each annual cycle over the lifetime of a patient given the baseline profile of the patient. A flowchart of the patient simulation module is illustrated in Figure 3.1.

To allow for competing risks, in each cycle, events are randomly ordered, except for urgent coronary revascularisation being ordered after myocardial infarction, and vascular and non-vascular deaths being ordered after all other events (impact of ordering on predictions illustrated in Supplemental Figure C.17). The risks of occurrence of each adverse event are calculated sequentially using the parametric risk equations developed. Based on this risk, a random number is drawn to determine event occurrence. Event occurrences are recorded, affecting the risks of subsequent events in the same cycle and subsequent cycles. Event occurrences are predicted sequentially until all events are exhausted before the next cycle begins. The model predicts only first occurrences of each event, so events that have occurred cannot occur again in the remaining lifetime of the patient. The patient simulation module terminates when either (1) vascular or non-vascular death has occurred, or (2) the specified maximum number of cycles has been reached. This entire process is repeated k number of times (Monte-Carlo loops) for each patient. k must be sufficiently large to ensure convergence of results, which in this case are the cumulative incidences of adverse events. Setting k to 1000 achieves this, even in different subgroups (Supplemental Figures C.18 - C.24).

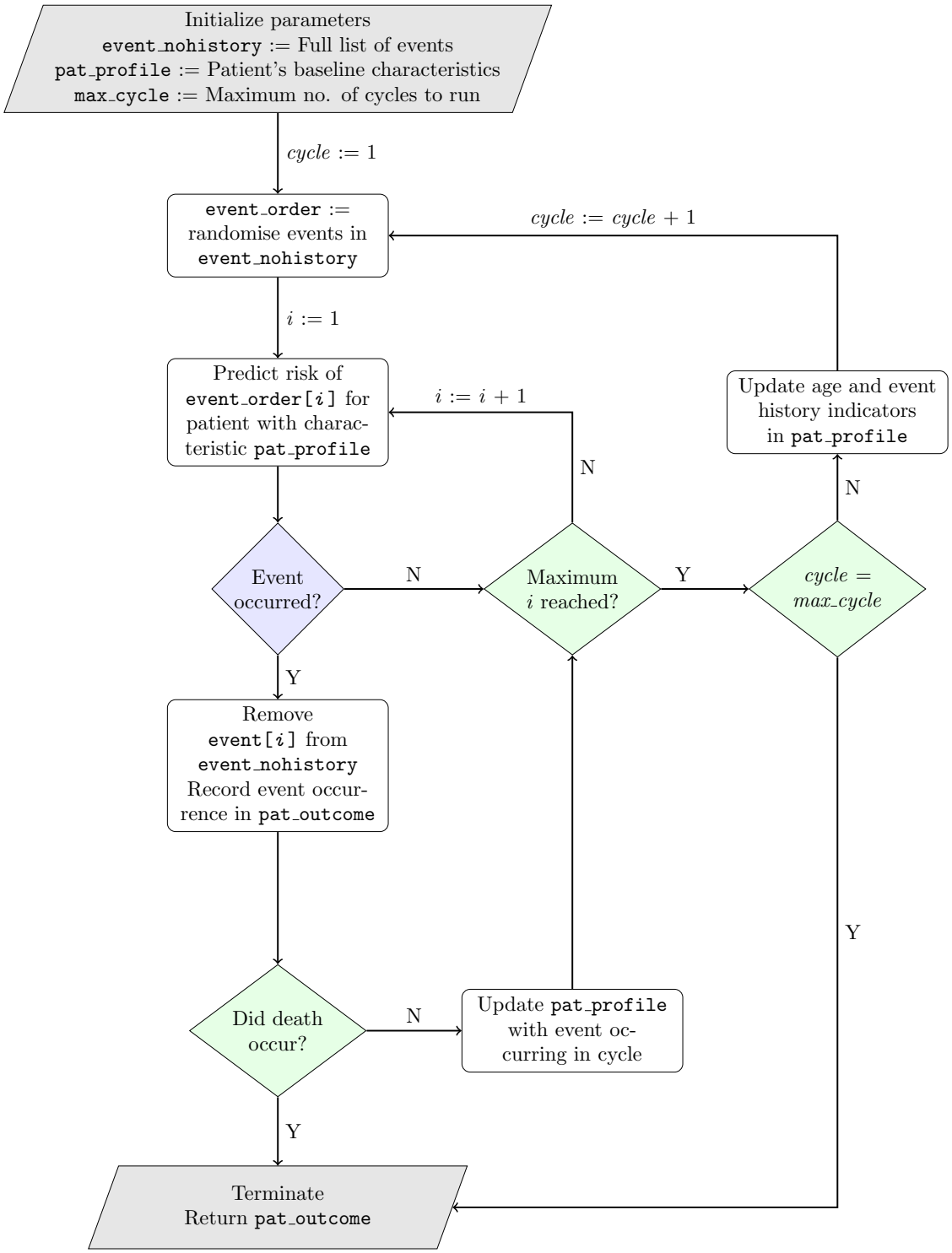


Figure 3.1: Flowchart of patient simulation module. *cycle* in this case is defined as year; i is the order in which events can occur in each cycle; *pat_profile* refers to the time-updated patient characteristics and disease history

3.4 Model validation

3.4.1 Validity of simulation model

The validity of the simulation model incorporating the risk equations developed was assessed among participants in ASCEND (internal validation) and further among participants in the UK Biobank (external validation). The simulation model was used to predict the occurrence of adverse events in each annual cycle using only participants' baseline characteristics and risk factors. Performance of the simulation model was assessed based on its calibration and discrimination[5] [22]. To assess calibration of the model, the year-on-year cumulative incidence observed in the cohort was plotted against that predicted by the simulation model accounting for competing risk (from deaths for non-fatal events and deaths from other causes for cause-specific deaths). Calibration was further assessed for each endpoint by subgroups (age, sex, duration of diabetes) and deciles of risk. The cohort was divided into risk deciles based on cumulative incidence predicted by the simulation model at average follow-up time for each endpoint, and the observed cumulative incidence was plotted against that predicted in each decile. The absolute difference between the predicted cumulative incidence and the observed cumulative incidence (bias), the percentage error and the mean absolute percentage error (MAPE) were used to quantify the magnitude of discordance for each endpoint. Discrimination was assessed for each endpoint using Uno's c-statistic [23]. These assessments were made at the average follow-up time of 7 years for ASCEND and 11 years for the UK Biobank unless otherwise specified.

Internal validity in ASCEND

The simulation model developed using the ASCEND data had good internal validity, demonstrating good calibration over 10 years of follow-up in ASCEND (Figure 3.2), with MAPE between 2% to 12% (Supplemental Table C.13). The

[5]Discrimination is the ability of the model to differentiate individuals who experience events from those who do not.

model demonstrated satisfactory discrimination for most outcomes (Table 3.5), with discrimination for other major bleed being the poorest (c-statistics 0.60). This was reflected in the calibration plot by risk deciles, in which clear gradients of increasing risks were observed across deciles of predicted risks for most events (Figure 3.3). The model performed well in subgroups of participants by sex, age and diabetes duration (Supplemental Figures C.25-C.27). Both the Weibull and the Exponential distributions performed similarly for the first 10 years of follow-up (Supplemental Figure C.28), with results diverging in the longer term (Supplemental Figure C.29), although there is no data to inform the choice of distribution. Generally, greater lifetime cumulative incidences were observed for most events when the Weibull distribution was used in contrast to the Exponential distribution. However, there was no substantial difference in death rates regardless of the choice of distribution. The average predicted life expectancies were 22.0 years and 21.9 years when the Exponential and Weibull distributions, respectively, were used for all non-death events. For all subsequent results and analyses, the Weibull distribution was used. Compared to the Exponential distribution, the Weibull distribution has an additional degree of freedom (the shape parameter α) and this added flexibility would be helpful to account for varying shapes of hazard if and when the risk equations need to be updated in future[6].

External validity in the UK Biobank

In the UK Biobank, the predicted event rates were similar to those in ASCEND for most events, although lower rates of ischaemic stroke and deaths and higher rate of ESRD were predicted than in ASCEND (Figure 3.2). Compared with observed rates in the UK Biobank, myocardial infarction, coronary revascularisation and cancers were generally well-predicted, displaying good calibration and discrimination. For these events, the model also performed well in subgroups of participants by age, sex and diabetes duration (Supplemental Figures C.30 - C.32). This brought about confidence that the hazard rates and the associations between the risk factors

[6]The Weibull distribution reduces to the Exponential distribution when the shape parameter α is 1.

and hazards found in ASCEND can be generalisable to the UK Biobank cohort. However, discrepancies in calibration were found for TIA, heart failure, GI bleed, other major bleed, amputation, ESRD and deaths. Greater discrepancy was found for TIA if primary care records were not used to supplement the identification of TIA (Supplemental Figure C.33). Discrimination was also poorer in the UK Biobank than in ASCEND for these events (Table 3.5). In particular, for other major bleed, similar risks were observed across deciles of predicted risks (Figure 3.4) suggesting that the model was unable to distinguish people who experienced an event from those who do not. Generally, the relative bias seems consistent across subgroups by sex, age and diabetes duration. This is with the exception of vascular death, where the relative bias is much greater for females and participants at least 60 years old.

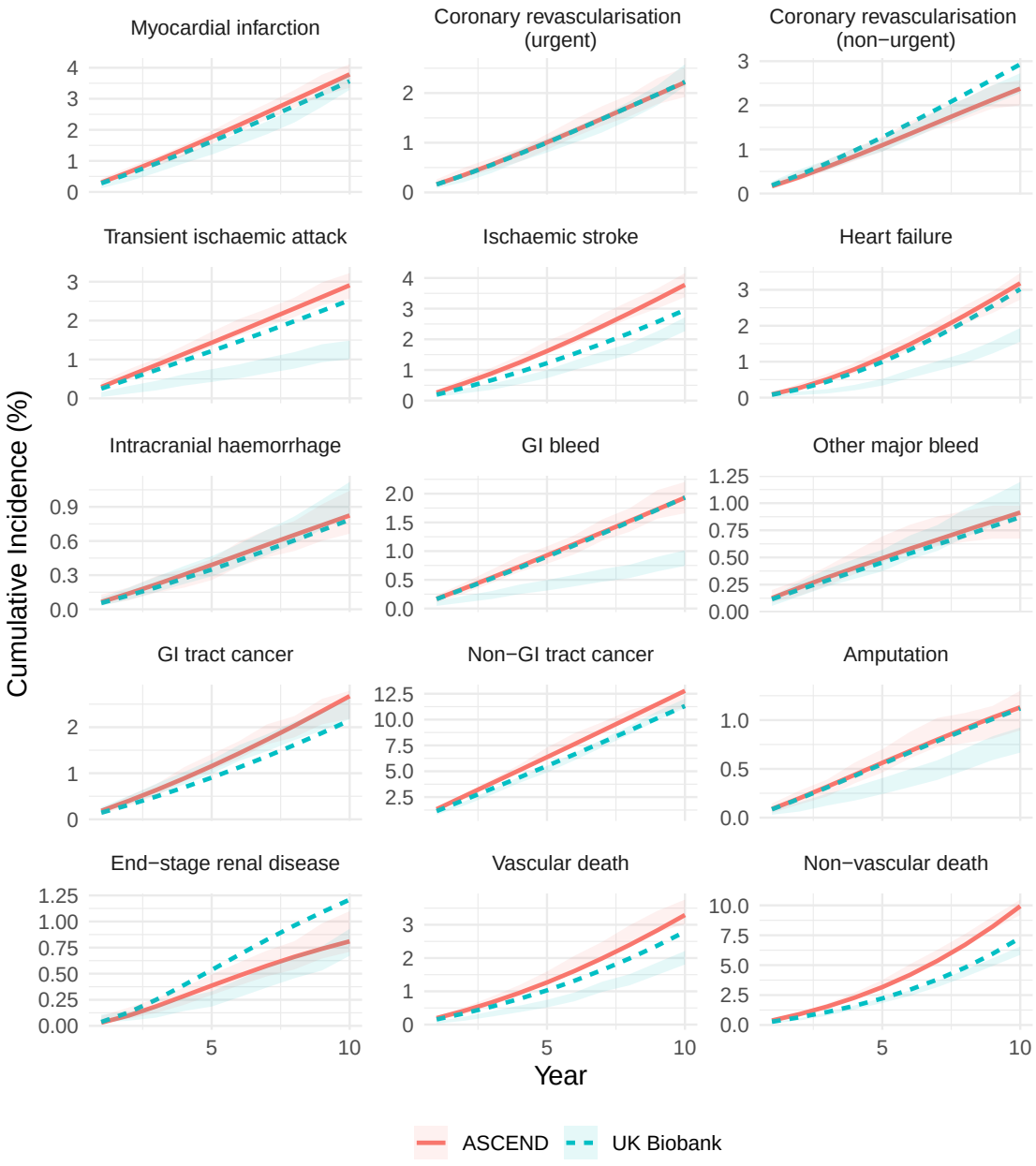


Figure 3.2: Comparison of cumulative incidence observed in ASCEND and UK Biobank (shaded region) vs predicted by simulation model (lines)

Table 3.5: Uno's C-statistics of simulation model for each endpoint in ASCEND and the UK Biobank

Adverse event	ASCEND	UK Biobank
Myocardial infarction	0.687	0.674
Coronary revascularisation (urgent)	0.647	0.640
Coronary revascularisation (non-urgent)	0.651	0.658
Transient ischaemic attack	0.671	0.655*
Ischaemic stroke	0.711	0.675
Heart failure	0.829	0.739
Intracranial haemorrhage	0.827	0.600
GI bleed	0.663	0.631
Other major bleed	0.600	0.517
GI tract cancer	0.673	0.636
Non-GI tract cancer	0.652	0.620
Amputation	0.844	0.810
End-stage renal disease	0.942	0.903
Vascular death	0.802	0.696
Non-vascular death	0.757	0.674

* Assessed at 8 years of follow-up as primary care data (average follow-up of 8 years available) was used to supplement ascertainment of transient ischaemic attack. All other events assessed at 11 years of follow-up in the UK Biobank.

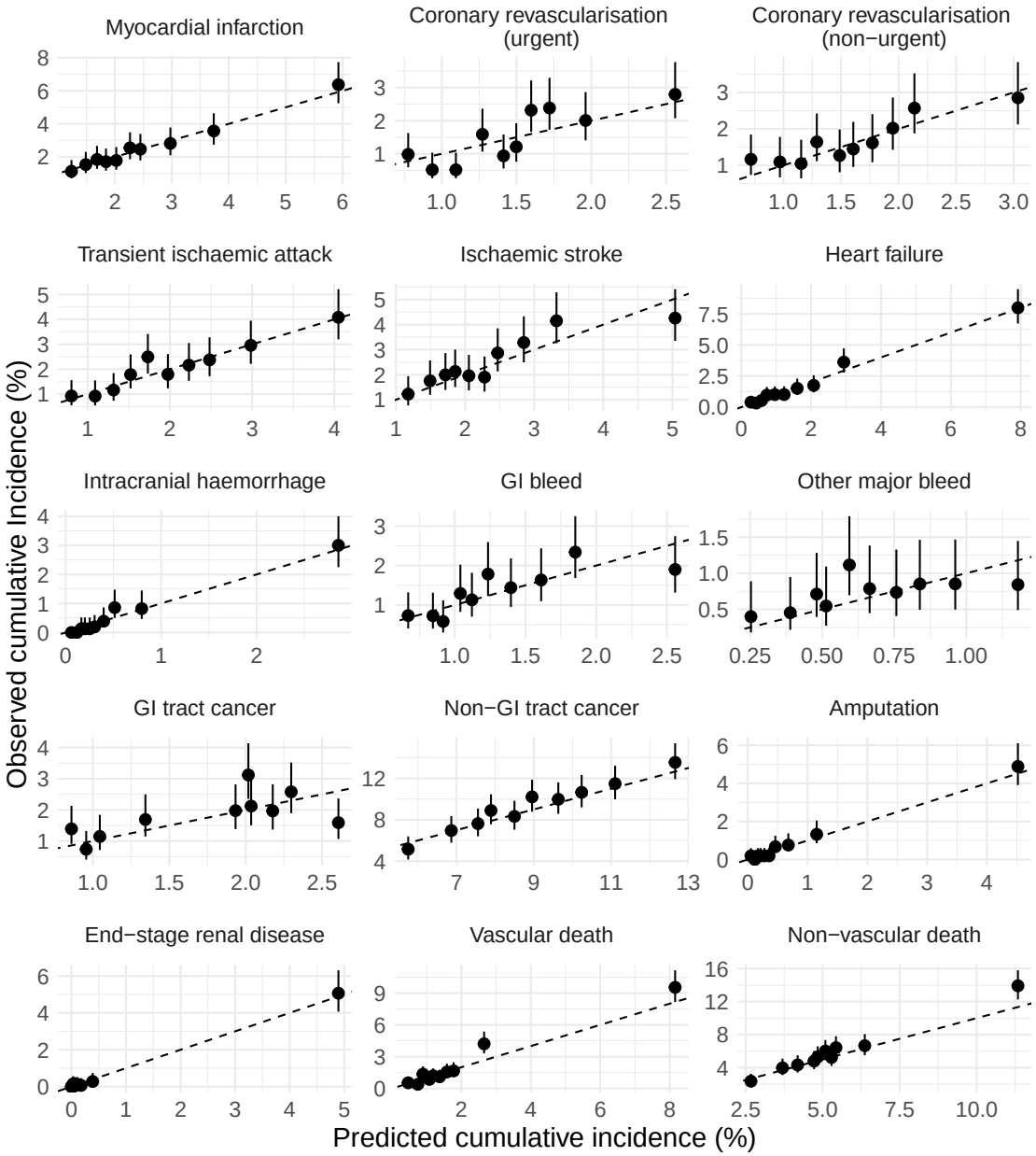


Figure 3.3: Comparison of 7-year cumulative incidence observed in ASCEND vs predicted by simulation model, stratified by decile of predicted 7-year cumulative incidence for each outcome

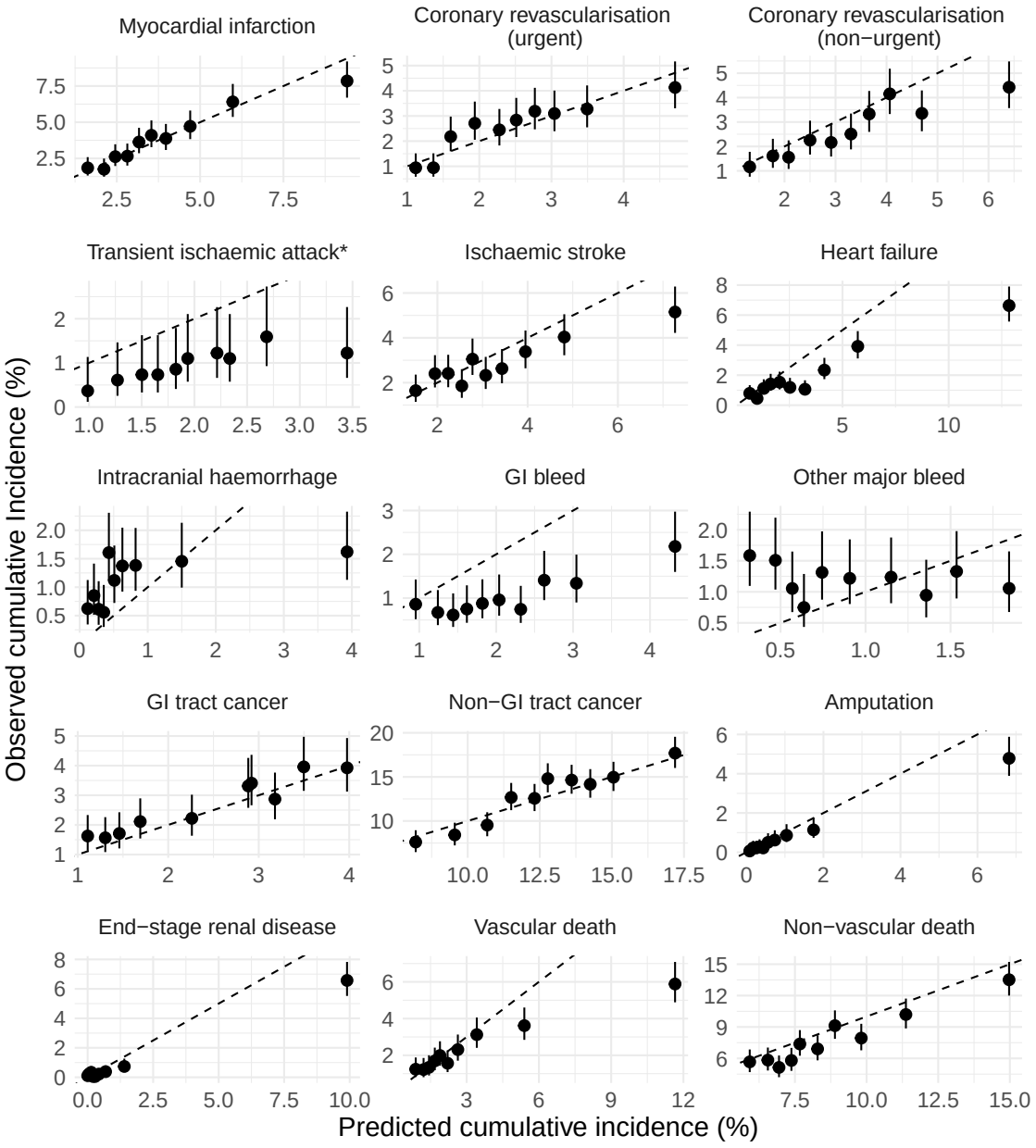


Figure 3.4: Comparison of 11-year* cumulative incidence observed in UK Biobank vs predicted by simulation model, stratified by decile of predicted 11-year* cumulative incidence for each outcome. *TIA was assessed at 8 years of follow-up as primary care data (average follow-up of 8 years available) was used to supplement ascertainment of TIA. All other events assessed at 11 years of follow-up

3.4.2 Possible sources of discrepancies

Possible sources of discrepancies between the predicted and observed event rates in the UK Biobank were identified to inform the strategy for updating the risk equations developed in ASCEND for application in the UK Biobank. Firstly, adverse events from the UK Biobank were ascertained from routine healthcare records, which could be susceptible to issues such as coding error and under-detection. In the UK, hospital diagnostic coding is often done by non-clinical clerical staff and relies on their interpretation of medical notes and application of appropriate codes [24]. Previous audit reports have noted problems relating to data completeness, accuracy of clinical coding, and engagement of clinicians [25]. Coding accuracy has improved over the years [26], particularly for diseases such as strokes [15]. Harper et al. (2021) compared adverse events reported in ASCEND to adverse events in hospital inpatient data for ASCEND participants and found sensitivity[7] of 79% and 67% for non-fatal myocardial infarction and non-fatal ischaemic stroke respectively, but only 30% for TIA (Supplemental Table C.14) [27]. About one-third of stroke patients are not admitted to the hospital in the UK, and most TIAs are managed in outpatient clinics [15], which could explain the under-detection of these events from hospital inpatient records. However, the positive predictive value[8] (PPV) for these events was about 80%, suggesting that the events identified from inpatient records were likely to be true events. Similar findings were reported in other UK studies [15, 28, 29]. In ASCEND, about 70% of heart failure events were identified from hospital records. Comparing primary care records with hospital records, Koudstaal et al. (2017) reported that 26% of heart failure diagnoses in primary care have no heart failure-related hospitalisations [30], and Bottle et al. (2018) reported that only 79% of patients have their first heart failure diagnosis in the hospital [31]. Hence, heart failure may be under-detected in hospital records. Given the above,

[7]Sensitivity is the number of people with the disease that were identified (true positives) vs the actual number of people with the disease including those unidentified (true positives and false negatives).

[8]PPV is the number of people who have the disease (true positives) amongst those identified to have the disease (true positives and false positives).

it is likely that at least some of the overpredictions observed for TIA, ischaemic stroke, and heart failure were due to issues with under-detection of events from hospital records in the UK Biobank.

For major bleeding events, Faridi et al. (2021) reported good sensitivity of 77% comparing adjudicated events in the Dual Antiplatelet Therapy (DAPT) Study with administrative claims data in the US Medicare [32], while Guimaraes et al. (2017) reported 71% comparing adjudicated events with administrative claims data in the Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study [33]. Both studies reported poor PPV of 40%. Harper et al. (private communication) found PPV for identifying major bleeding events to improve using bleeding codes in the primary diagnosis position only compared to using bleeding codes in any diagnosis position. Despite the improvement, the sensitivity and PPV were still poor for major GI bleed (sensitivity 55%, PPV 58%) and other major bleed (44%, 31%). This could perhaps be because of the difficulty in separating hospitalisation for acute major bleeding events with bleeds following other events or procedures. These suggest that the events identified to be major bleeding events were not the same as those reported in ASCEND, which explains the poor discrimination of the risk equations developed in ASCEND to identify bleeding events in the UK Biobank (as evident in Table 3.5 and Figure 3.4), particularly for other major bleed. Hence, the external validation for GI bleed and other major bleed could be unreliable.

Secondly, comparing the discordance between observed and predicted cumulative incidence in people with and without albuminuria in the UK Biobank, it is evident that the HRs for presence of albuminuria were overestimated for heart failure, intracranial haemorrhage, non-GI tract cancer, amputation, ESRD and vascular death (Supplemental Figure C.34). 35% of participants in ASCEND did not return a usable blood/urine sample and had missing biomarker data including urinary albumin and creatinine values which were used to determine presence of albuminuria. In the complete case analyses, the estimated HRs for presence of albuminuria were

significantly different for heart failure, non-GI tract cancer, intracranial haemorrhage, amputation, ESRD and vascular death (Supplemental Table C.11).

Lastly, after adjusting for observable risk factors, the death rates in the UK Biobank seem to increasingly diverge with time from the death rates observed in ASCEND. Although the age- and sex- standardised mortality ratios (SMRs)[9] relative to UK national lifetables [34] were similar for the first 10 years of follow-up on average between the ASCEND and the UK Biobank cohorts, the SMRs diverge beyond 10 years (Supplemental Figure C.35). This divergence was observed in subgroups of participants by age and by sex. Furthermore, the SMR for females and participants older than 70 years old seem to be generally lower in the UK Biobank than in ASCEND. Using SMR as a proxy for selection bias suggests that the extent of bias is different between the two cohorts, particularly in these subgroups.

3.5 Model updating

3.5.1 Methods for updating parametric proportional hazard models

The parametric proportional hazard equations can be expressed as

$$h(\alpha, b|X) = h_0(\alpha, b) * e^{\sum_j \beta_j x_j} \tag{3.1}$$

where $h_0(\alpha, b)$ is the baseline hazard for the reference individual ($X = 0$) with parameters shape α and scale/rate b, and β_j is the estimated coefficient (log HR) for variable x_j. The mathematical formulations for Equation (3.1) for the different distributions can be found in Table 3.4. For proportional hazard models, the effects of covariates act multiplicatively on the hazard. By extension of this property, (1) the parameters of the baseline hazard can be quantified independently of the

[9]Standardised mortality ratio is the ratio between the number of deaths observed in a cohort and the number of deaths expected based on the age- and sex-specific death rates in a reference population, in this case the UK general population. SMR < 1 indicates that there were fewer than expected deaths, while SMR > 1 indicates that there were excess deaths in the cohort of interest.

coefficients, and (2) $h_0(\alpha, b) * e^{\lambda} = h_0(\alpha, b * e^{\lambda})$. The methods for updating parametric proportional hazard models are summarised in Table 3.6.

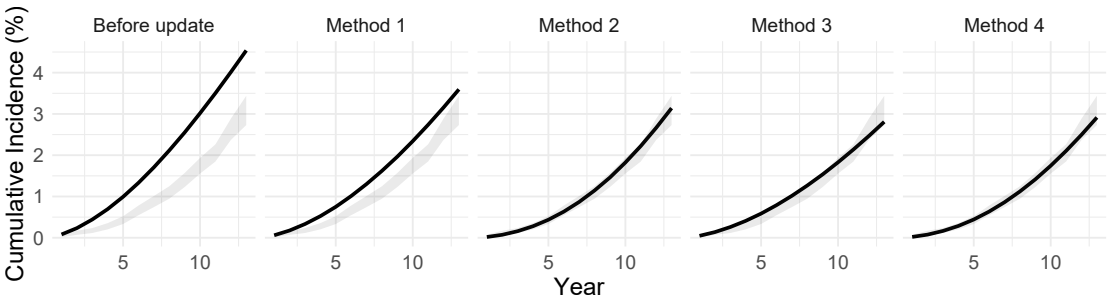
Table 3.6: Methods for updating parametric proportional hazard models

Method	**Re-estimated hazard** $\bar{h}(\alpha, b\|X)$	**Assumptions**
(1) Re-estimate coefficients for variable (β_1)	$h_0(\alpha, b)e^{\overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$	The baseline hazard for the reference level in the development cohort is the same as for the new cohort.
(2) Re-estimate parameters for baseline hazard (α, b)	$h_0(\bar{\alpha}, \bar{b})e^{\sum_j \beta_j x_j}$	The hazard ratios from the development cohort applies to the new cohort.
(3) Introduce dummy variable for reference level (β_0) and re-estimate coefficients for variable (β_1). Equivalently, re-estimate coefficients for variable (β_1) and rate/scale parameter (b)	$h_0(\alpha, b)e^{\overline{\beta_0}x_0 + \overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$ $= (h_0(\alpha, b)e^{\overline{\beta_0}x_0})e^{\overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$ $= h_0(\alpha, b * e^{\overline{\beta_0}x_0})e^{\overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$ $= h_0(\alpha, \bar{b})e^{\overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$	If association between x_1 and hazard differs in the two cohorts, and event rate for $x = 0$ (reference group) in original cohort affected.
(4) Re-estimate coefficients for variable (β_1) and parameters for baseline hazard (α, b)	$h_0(\bar{\alpha}, \bar{b})e^{\overline{\beta_1}x_1 + \sum_{j>1}\beta_j x_j}$	(3) + If believe that the "shape" of the baseline hazard is different for the reference group in the development and new cohort.

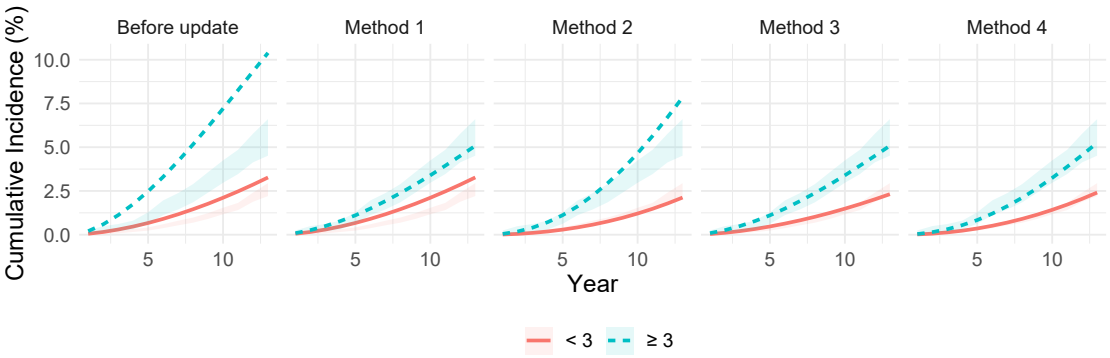
The impact of the different methods for model updating on the predicted cumulative incidence is illustrated using the variable for presence of albuminuria in the risk equation for heart failure as an example (Figure 3.5) and scenarios in which each method would be appropriate are proposed[10]. Method (1) which

[10]All methods described for model updating are conditional on the distribution of the baseline hazard used. In this case, the Weibull distribution was used for modelling the baseline hazard of heart failure.

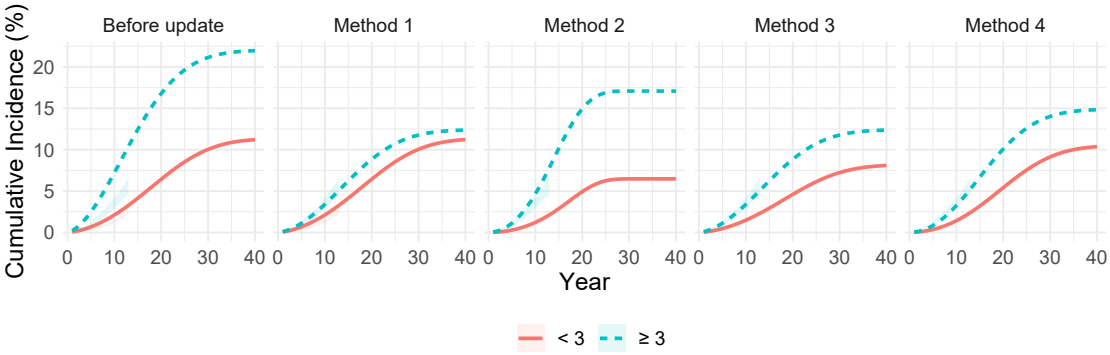
re-estimates only the HR associated with albuminuria improves model fit only in the subgroup of participants with albuminuria. This method would be appropriate if the baseline hazard in the subgroup of participants without albuminuria is a good fit, and only the HR associated with albuminuria needs re-estimating. Method (2) re-estimates only the parameters for the baseline hazard distribution improving the overall fit, but not specifically in the albuminuria subgroups. This method would be appropriate if HRs in the original equations are generalisable to the new cohort and only the background hazard rate needs to be updated. This is indicated by similar relative bias across subgroups of interest. Methods (3) and (4) which re-estimate the HR associated with albuminuria as well as the baseline hazard improve model fit similarly for both subgroups. However, while method (3) re-estimates only the rate/scale b of the distribution of hazard from the UK Biobank data and retains the shape of the distribution α estimated in ASCEND, method (4) re-estimates both α and b. Both methods can be appropriate when the assumptions for methods (1) and (2) are invalid. The shape of the distribution has significant influence on the lifetime cumulative incidence (Figure 3.5(c)), and there is usually limited data to validate predictions into the lifetime. The difference between the two methods would be that method (3) relies more heavily on the data used to develop the model, while method (4) relies more heavily on the external data.



(a) In all participants; over 13 years



(b) By albuminuria subgroup; over 13 years



(c) By albuminuria subgroup; over 40 years

Figure 3.5: Effect of updating hazard ratio associated with presence of albuminuria on cumulative incidence of heart failure in the UK Biobank

3.5.2 Strategies for model updating

For heart failure, non-GI tract cancer, intracranial haemorrhage, amputation, ESRD and vascular death, the HRs of albuminuria were likely overestimated in the original risk equations and need to be updated. For vascular and non-vascular deaths, the parameters of the hazard rate as well as the HRs of age and sex need to be updated as the sex- and age-adjusted SMR suggested that the background death rates in the UK Biobank may be different from those in ASCEND. Depending on the reliability of event ascertainment in the UK Biobank, different strategies were adopted for model updating (Table 3.7).

For amputation and ESRD, method (3) was adopted to re-estimate the HR associated with albuminuria. For non-GI tract cancer, the risk equation includes the history of occurrence of other major bleed, and ascertainment of other major bleed is likely unreliable in the UK Biobank (see discussion in Section 3.4.2). Hence, the probability of occurrence of other major bleed predicted by the simulation model for each participant in the UK Biobank, obtained by averaging the number of event occurrences across all Monte-Carlo loops, was used in place of the observed event occurrence for re-estimating the risk equation. Method (4) was adopted to re-estimate the HR of albuminuria and the parameter of the baseline hazard to account for the different scale of the disease history indicator, but the baseline hazard of non-GI tract cancer in ASCEND was retained in the final equation. Although heart failure and intracranial haemorrhage were likely under-detected in the UK Biobank, events detected were likely true events (see discussion in Section 3.4.2). Method (4) was adopted to re-estimate the HR of albuminuria and the parameter of the baseline hazard to account for differing event rates in the UK Biobank from ASCEND, but the baseline hazard in ASCEND was retained in the final equations as the event rates in the UK Biobank underestimate the actual event rates. For vascular and non-vascular deaths, given the suggestion of different extent of selection bias particularly for females and for older participants, method (4) was adopted to

re-estimate the HRs of age and sex as well as the parameters of the baseline hazard. For vascular death, the HR associated with albuminuria was also re-estimated.

For vascular and non-vascular deaths, the updated equations improved calibration overall (Figure 3.6; Supplemental Table C.13) and in subgroups of participants by sex, age, and albuminuria (Supplemental Figures C.36 & C.37). For amputation, ESRD and non-GI tract cancer, the updated equations improved the fit of these events in the subgroup of participants with albuminuria. For heart failure and intracranial haemorrhage, the relative bias in the subgroup of participants with albuminuria is now similar to that in the subgroup with no albuminuria. Discrimination of the model for vascular death improved from 0.696 to 0.719, and remained similar for other events (Supplemental Table C.15).

Table 3.7: Strategies for model updating

Is event of interest reliable in new data?	Underlying event rates differ?	HRs for risk factors differ?	Are event histories in the risk equation reliable in new data?	Method for model updating
N				Keep ASCEND equations as is
Y	Y	Y	Y / no event histories in equation	Method (4)
Y	Y	Y	N	Use predicted event histories + method (4)
Y	Y	N	Y / no event histories in equation	Method (2)
Y	Y	N	N	Use predicted event histories + Method (2); or if using predicted event histories on different scale, method (4) but keep only re-estimated parameters for hazard
Y	N	Y	Y / no event histories in equation	Method (3); or Method (1) if baseline hazard for reference individual believe to be well-predicted
Y	N	Y	N	Use predicted event histories + method (4); or if using predicted event histories on different scale, method (4) but keep only re-estimated coefficients

Table 3.7: Strategies for model updating *(continued)*

Is event of interest reliable in new data?	Underlying event rates differ?	HRs for risk factors differ?	Are event histories in the risk equation reliable in new data?	Method for model updating
Y but under-detected	N	Y	Y / no event histories in equation	Method (4) but keep only re-estimated coefficients and use original parameters for hazard
Y but under-detected	N	Y	N	Use predicted event histories from simulation and re-estimate coefficients for variable and parameters for baseline hazard using method (4) but keep only re-estimated coefficients and use original parameters for hazard

Note:
Event histories refer to histories of other events included in the risk equations.

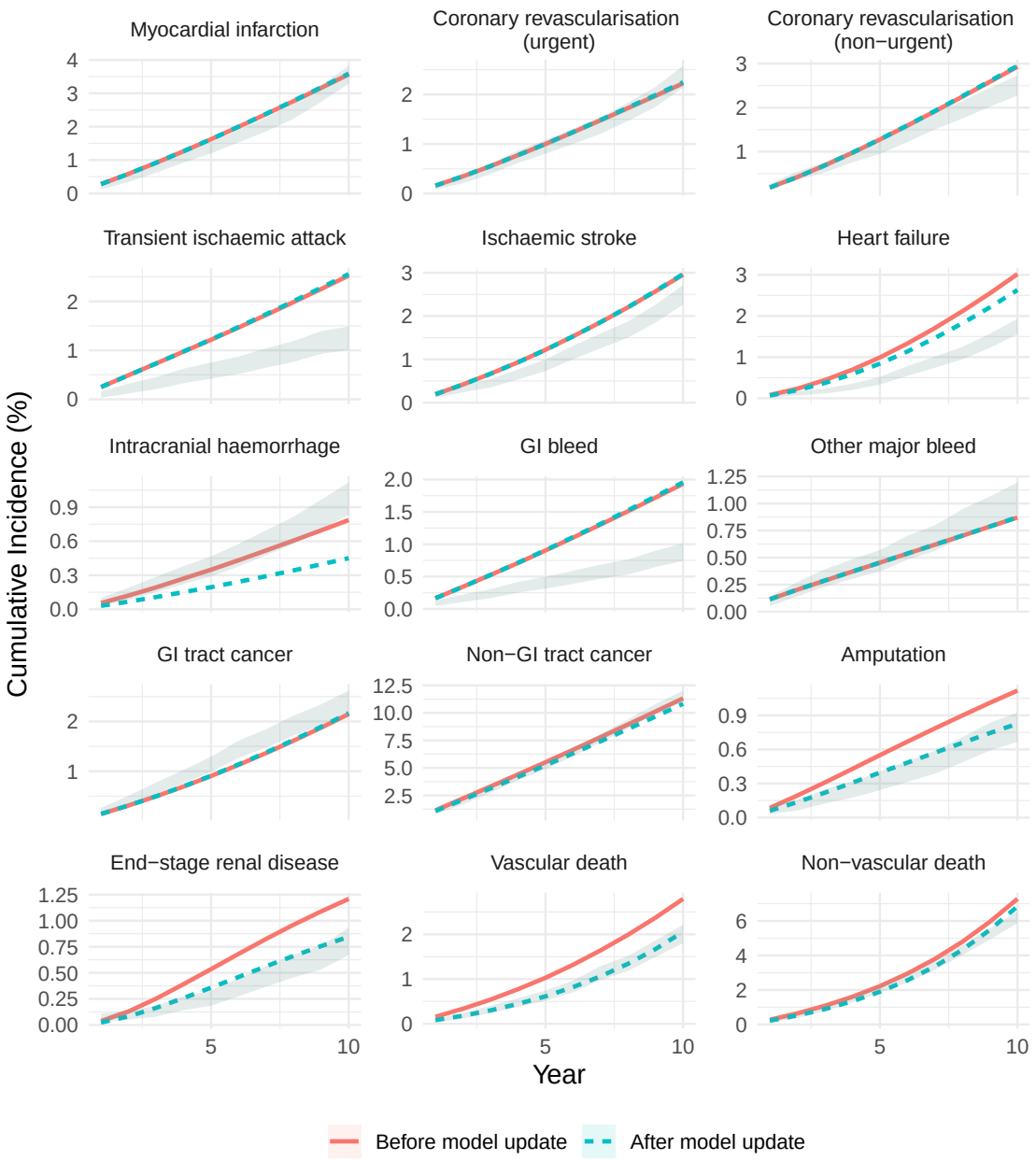


Figure 3.6: Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) over 10 years before and after model updating

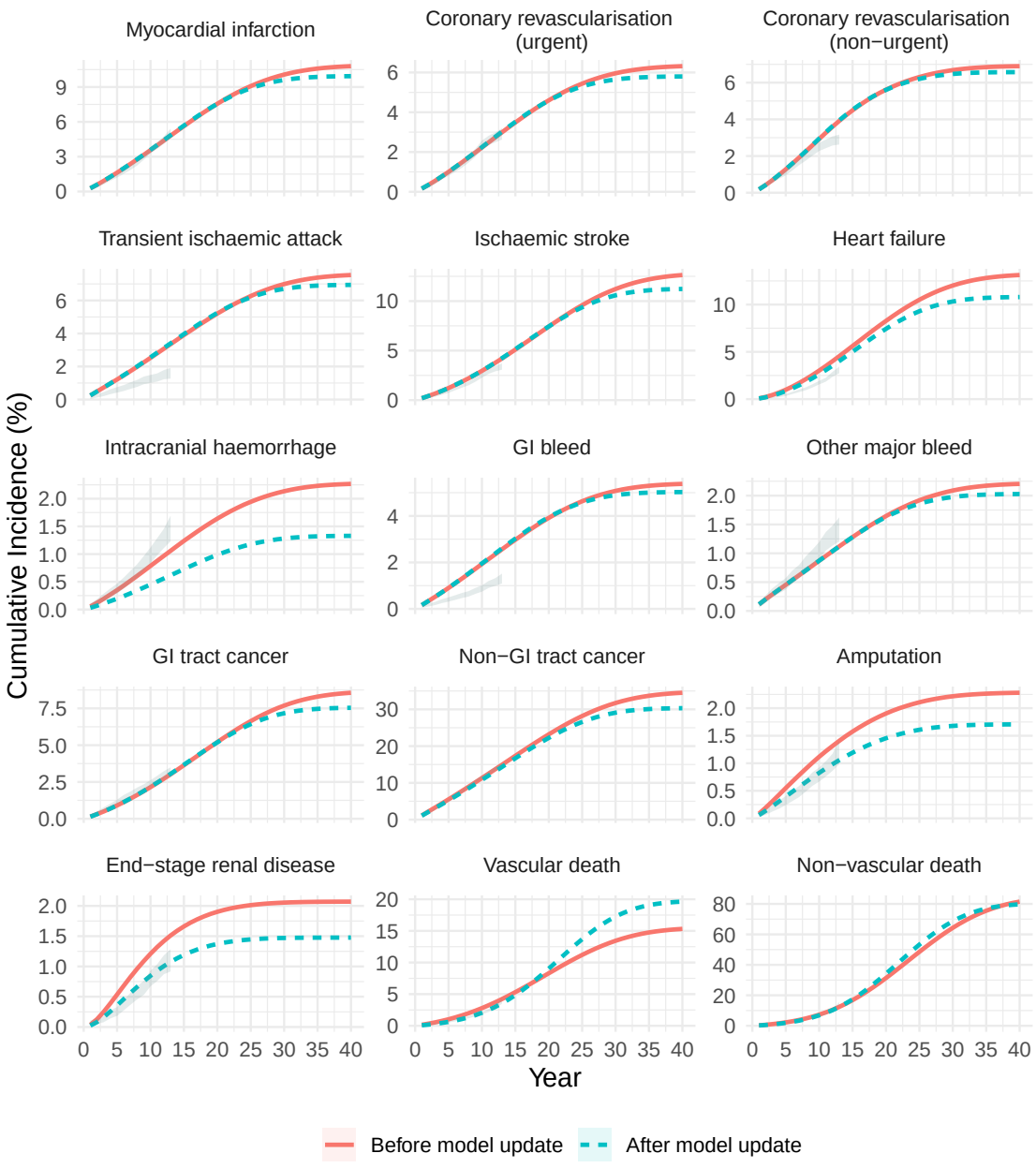


Figure 3.7: Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) over 40 years before and after model updating

3.6 Discussion

3.6.1 Risk equations developed using ASCEND and the UK Biobank

A simulation model incorporating parametric proportional hazard risk equations was developed for predicting first occurrences of cardiovascular, bleeding, cancer, amputation, ESRD and death events over lifetime in people with diabetes without previous cardiovascular disease, based on baseline sociodemographic information, biomarkers, current age, and history of events as they occur in the simulation. The risk equations were developed and internally validated using participant data from ASCEND, and externally validated in a cohort of participants in the UK Biobank satisfying the ASCEND inclusion criteria. Where appropriate, the equations were adapted for the UK Biobank cohort. Both cohorts consist of participants who were recruited between 2005 to 2011 and followed up to recent years, so the risk equations developed would reflect more contemporary event rates in contrast to the older UKPDS risk equations.

As with previous diabetes models, the simulation model developed included associations between different adverse events (Figure 3.8). For example, participants who had experienced a myocardial infarction were at a higher risk of heart failure than if they had not experienced a myocardial infarction, while participants who had undergone coronary revascularisations (mostly triggered by an occurrence of myocardial infarction) were at a lower risk of vascular death than if they had not had the coronary revascularisation. There was evidence of a time trend where the impact of an adverse event occurrence on another event decreases with time. Having a vascular-related event increased the risk of vascular death by more than 10-fold in the year of event, but the effect wanes in subsequent years (HRs decrease from 55 to 7 for myocardial infarction, 18 to 3 for ischaemic stroke, and 13 to 8 for heart failure).

One notable difference in comparing the risk equations developed in ASCEND with the UKPDS risk equations [2] was the significance of lipid markers for predicting vascular events. Time-varying LDL cholesterol was a driver of risks of vascular

events including myocardial infarction, heart failure and stroke in the UKPDS 82 risk equations, with 1-4% increase in event hazard per 0.1 mmol/L increase in LDL cholesterol. No lipid markers (measured at baseline) were featured in the risk equations estimated in ASCEND. The mean non-HDL cholesterol levels were 2.9 mmol/L in ASCEND and 4.3 mmol/L in the UKPDS cohort [35]. This reflects the changing landscape of lipid-lowering treatments in contemporary cohorts, with 75% of participants in ASCEND using a statin at baseline in contrast to $< 1\%$ in the UKPDS for example. The Prospective Studies Collaboration (2007) found a log-linear association between LDL cholesterol lowering and vascular risk [36] which has been demonstrated in randomised controlled trials [37, 38], implying that the proportional benefit for LDL cholesterol reduction for people with already low baseline LDL cholesterol levels may be small. Participants in ASCEND have on average well managed lipid profiles, which could explain why no associations were detected between lipid markers and vascular risks in ASCEND.

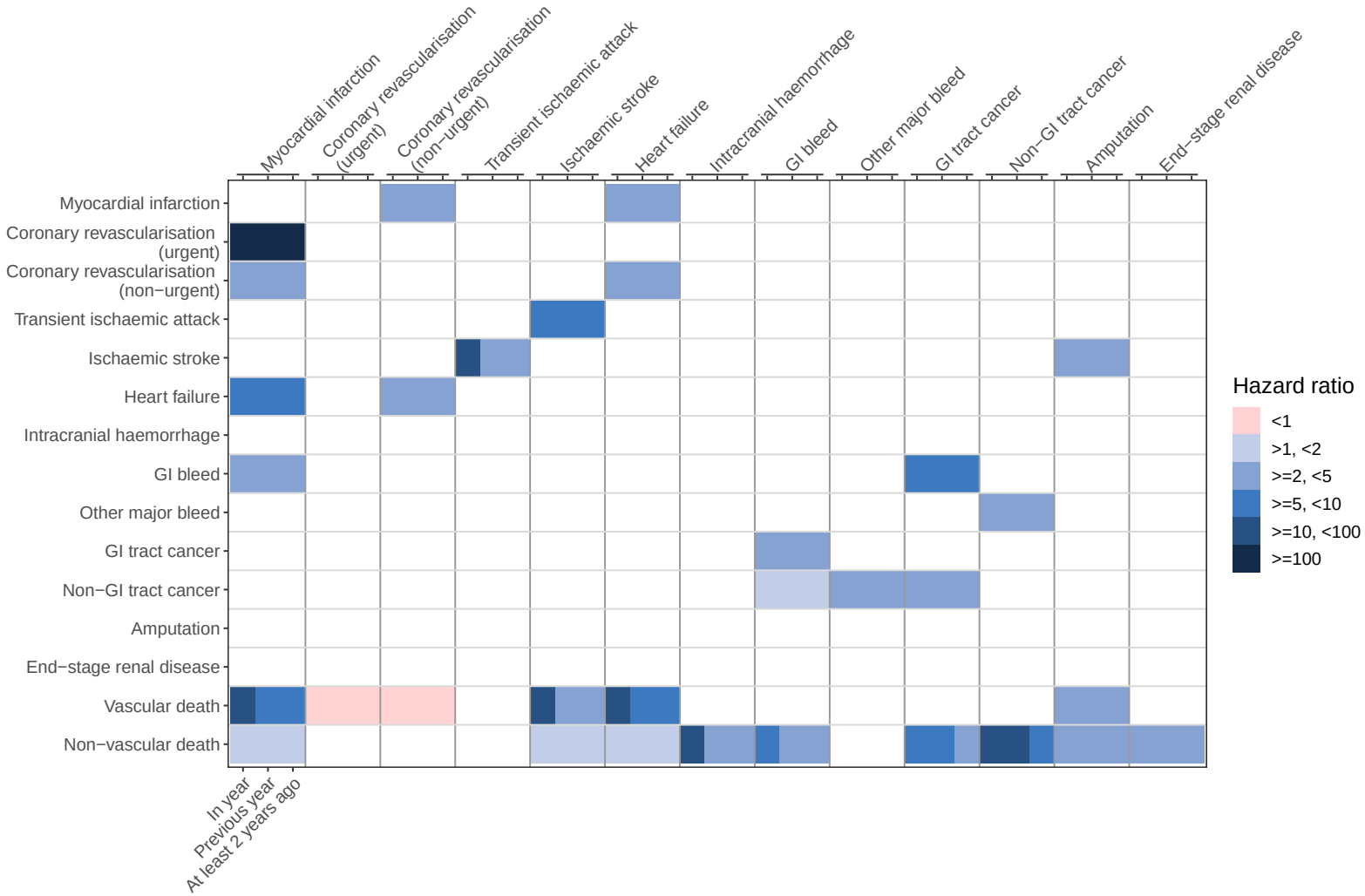


Figure 3.8: Impact of adverse event occurrence on subsequent events estimated in risk equations. The impact of adverse event occurrence (on horizontal x-axis) on subsequent events (on vertical y-axis) is split into three time points – from left to right, in year, in previous year and at least 2 years since event occurrence

3.6.2 Risk factors for bleeding

Most risk scores for bleeding were developed in people with previous history of atrial fibrillation or other acute coronary syndrome to inform the prescription of (dual-) antiplatelet or anticoagulation therapy [39–41]. This was with the exception of Selak et al. (2019) where a risk score was developed to assess bleeding risk for people without cardiovascular disease using primary care data in New Zealand [42], and the QBleed scores which were developed to assess the risks of upper GI bleed and intracranial bleed using primary care data in the UK [43] (comparison of risk scores in Supplemental Table C.16). Common risk factors identified in these risk scores for bleeding included older age, renal dysfunction, history of bleeding, and cancer. These were similarly identified in the risk equations for major bleeding events developed using ASCEND.

Selak et al. (2019) found a 48% increase in bleeding risk for every 10 years increase in age, while this ranged from 16% for intracranial haemorrhage to 34% for other major bleed in ASCEND. Any cancer was found to be associated with 40% to 80% increase in the risk of major bleeding in Selak et al. (2019) and 20% to 40% increase in the risk of upper GI bleed in QBleed. In ASCEND, more specifically, GI tract cancer was found to be associated with 480% increase in the risk of GI bleed, and non-GI tract cancer was found to be associated with 260% increase in the risk of other major bleed. It should be noted however that both Selak et al. (2019) and QBleed were developed using routine healthcare data, and bleeding events were identified using ICD codes from linked routine hospital records. As discussed in Section 3.4.2, poor sensitivity and poor PPV were observed for identifying major bleeds from hospital records. Hence, this may limit the comparability of the estimates between the different risk scores.

3.6.3 Life expectancies in ASCEND and the UK Biobank compared to other cohorts

The life expectancies predicted by the simulation model in both ASCEND and the UK Biobank cohorts are longer than those predicted by the UKPDS Outcomes

Model particularly in older age groups (Table 3.8) [44], reflecting the lower mortality rates in contemporary diabetes cohorts in contrast to the UKPDS-era. In line with this, Magliano et al. (2022) found the SMR for people with diabetes compared to people without to have fallen in most high-income countries, with SMR ranging from between 1.2 to 2.2 in 2015 for the European countries included (about 1.3 to 1.5 for Scotland in 2015) [45]. The UK National Diabetes Audit 2017-18 reported an SMR of 1.9 in males and 1.6 in females for people with type 2 diabetes between ages 65 and 74, falling to 1.6 and 1.5 respectively for those between ages 75 and 84 [46]. The SMRs for the ASCEND and UK Biobank cohorts are expected to be lower than these estimates given that people with previous cardiovascular disease or other severe comorbidities which are associated with increased risk of mortality have been excluded.

Overall, the age-sex-standardised life expectancy (to the UK lifetable [34]) in the ASCEND and UK Biobank cohorts are about 22 years, while the average life expectancies predicted by the model are 21 years and 24 years respectively. In contrast to the general population, people with diabetes without cardiovascular disease in the UK Biobank cohort were predicted to have about 9 years shorter life expectancy if aged between 40 and 50, about 4 years shorter life expectancy if between 50 and 60, similar life expectancy if between 60 and 70, and about 2 years longer life expectancy if between 70 and 80 (Table 3.8). A similar trend was observed for the ASCEND cohort, and this trend is reflected in the SMRs of both ASCEND and the UK Biobank cohorts which fall with increasing age (Supplemental Figure C.35). This is in part an artefact of the exclusion of people with previous cardiovascular disease or other severe comorbidities. As the prevalence of these diseases increases with age group, the cohort selected would be increasingly healthier relative to the same age-sex cohort in the general population. Additionally, there is likely selection bias in both the ASCEND and UK Biobank cohorts.

Using data from 1998 to 2015, Wright et al. (2016) estimated the life-year loss associated with diabetes (with or without cardiovascular disease) to be about 3 to 5 years, even in older age groups [47]. Heald et al. (2020) estimated the life-years

loss associated with type 2 diabetes to be about 1.4 years for males and 2 years for females [48]. In contrast, the expected life expectancies for people older than 60 years old recruited in the ASCEND and UK Biobank cohorts without cardiovascular disease at baseline are similar or even greater than the general population. This could suggest that the life-years gained from not having cardiovascular disease outweighs the life-years loss (if any) from having diabetes itself.

Table 3.8: Life expectancies of ASCEND and UK Biobank participants compared to life expectancies from other sources

Population	ASCEND		UK Biobank		UKPDS-OM2 [44]	CPRD 1998-2015 [47]	
	Diabetes without previous CVD (predicted)	Age-sex standardised to UK general population	Diabetes without previous CVD (predicted)	Age-sex standardised to UK general population	Non-smoker, HbA1c 6%, Total/HDL cholesterol 4, SBP 140 mmHg, BMI 30-33kg/m^2 (predicted)	Type 2 diabetes	Without type 2 diabetes
Male, by age group (years)							
<50	30.3	34.2	26.1	34.5	-	37.0 (40-44); 32.8 (45-49)	42.4 (40-44); 37.6 (45-49)
≥50, <60	25.9	26.1	22.6	25.8	18-24 (at 55)	28.6 (50-54); 24.5 (55-59)	33.0 (50-54); 28.5 (55-59)
≥60, <70	20.9	18.5	18.8	18.2	13-16 (at 65)	20.6 (60-64); 16.9 (65-69)	24.2 (60-64); 20.3 (65-69)
≥70, <80	15.5	11.8	16.2	14	9-13 (at 75)	13.6 (70-74); 10.7 (75-79)	16.7 (70-74); 13.7 (75-79)
≥80	10.3	6.8	-	-	-	8.3 (≥80)	11.1 (≥80)
Female, by age group (years)							
<50	31.4	37.8	28.5	37.8	-	39.1 (40-44); 34.5 (45-49)	45.4 (40-44); 40.5 (45-49)
≥50, <60	26.6	28.6	24.6	29	19-24 (at 55)	30.4 (50-54); 26.3 (55-59)	35.8 (50-54); 31.2 (55-59)
≥60, <70	21.8	21.2	20.6	20.9	14-18 (at 65)	22.3 (60-64); 18.6 (65-69)	26.7 (60-64); 22.5 (65-69)

Table 3.8: Life expectancies of ASCEND and UK Biobank participants compared to life expectancies from other sources *(continued)*

Population	Diabetes without previous CVD (predicted)	Age-sex standardised to UK general population	Diabetes without previous CVD (predicted)	Age-sex standardised to UK general population	Non-smoker, HbA1c 6%, Total/HDL cholesterol 4, SBP 140 mmHg, BMI 30-33kg/m^2 (predicted)	Type 2 diabetes	Without type 2 diabetes
≥70, <80	16.7	13.9	17.9	16.3	7-10 (at 75)	15.1 (70-74); 11.9 (75-79)	18.5 (70-74); 14.9 (75-79)
≥80	11.4	8	-	-	-	9.0 (≥80)	11.9 (≥80)

Note:
CVD, cardiovascular disease.

3.6.4 Issue-driven approach for updating risk equations

Moons et al. (2012) described an incremental approach for model updating [49], leveraging on existing models as much as possible. In order, the methods described achieve calibration-in-the-large by re-scaling the "intercept" (equivalent to the baseline hazard function), followed by re-estimation of regression coefficients, before considering adding additional predictors. The methods were described primarily to achieve model accuracy when a model needs to be applied to a new setting, or when a new predictor is considered. However, as demonstrated in this thesis, a more nuanced interpretation of model accuracy may sometimes be required due to limitations of the data. The methods have also not been formalised in the context of time-to-event models. In this thesis, I described in detail the mathematical formulations specifically for updating proportional hazard models, and propose an issue-driven approach in which the choice of method to use is driven by the possible source(s) of discrepancies.

The sources of discrepancies identified in ASCEND and the UK Biobank can be classed into three categories: risk factor measurement error, differences in background event rates, and error in endpoint ascertainment. The first two issues are relatively straightforward and were resolved by re-estimating the HRs associated with the risk factors in question and/or parameters of the baseline hazard function. However, issues with ascertainment of adverse events required a more nuanced approach. Most adverse events in ASCEND were clinically adjudicated, and the process of model updating relied more heavily on the associations and event rates estimated in ASCEND. Parameters of baseline hazard and/or HRs of risk factors were only updated when there was cause to believe they would be different in the UK Biobank, as with the case of HRs associated with albuminuria.

Previous studies have found poor PPV for bleeding events identified from routine administrative data, particularly for other major bleed. Thus, the UK Biobank data was deemed unsuitable for use to validate or update the risk equations for these events and the original equations were kept. For TIA, ischaemic stroke, heart

failure, and intracranial haemorrhage, despite the under-detection of these events in the UK Biobank, they were likely true events. Although the model did not perform well in terms of calibration for these events, the model demonstrated satisfactory discrimination. Furthermore, the relative bias between the predicted and observed event rates was similar across subgroups of age, sex and diabetes duration. These generated confidence that the associations found in ASCEND, other than that for albuminuria, were largely generalisable to the UK Biobank. However, given issues with event ascertainment, the observed absolute event rates were likely unreliable, and thus the baseline event rates in ASCEND were retained in the updated equations.

3.6.5 New framework for diabetes simulation - pros and cons

The key difference between the simulation model developed in this chapter and most existing diabetes models is the way risk factors informed the estimation of risk equations used in the model. In most previous diabetes models including the UKPDS-OM, events are predicted based on risk factor values in the previous year. By extension, such models propagate treatment effects on surrogate markers (e.g. HbA1c) onto effects on hard endpoints. These models require further equations or assumptions to simulate risk factor progression over time and require information on the effects of treatments on risk factor progression, adding further aspects of uncertainty to the model. Such models come with increased complexity which makes model updating more challenging. Additionally, the approach of propagating treatment effects through changes in risk factor trajectories assumes that treatment-induced changes in risk factors have similar impact on hard endpoints as natural differences in risk factors not related to treatment, which is uncertain [50]. For example, novel diabetes drugs such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors have demonstrated cardiovascular benefits independent of glucose control [51, 52]. Some cost-effectiveness studies attempted to mitigate this issue by accounting for both treatment-associated changes in risk factor trajectories and risk reductions observed in trials (see Section 1.1.2), but this is not straightforward

to do in complex models and could lead to double-counting of treatment effects if not appropriately adjusted for.

In the new framework adopted, similar to Kansal et al. (2016) [53], events are predicted based on baseline risk factors, with age as the only time-varying factor included in the model. Treatment effects on hard endpoints reported in longer-term trials such as the many recent cardiovascular outcomes trials can be directly incorporated without the need to specify progression of risk factors, risking double counting of treatment effects if not appropriately adjusted for. However, the impacts of risk factor progression on health outcomes are not explicitly modelled and are instead captured in the background hazard rate. The generalisability of the background hazard rate to other cohorts could be limited by, for example, different treatment strategies (e.g. timing of treatment escalation, medication use), as this impacts how risk factor progresses on average over time. Models simulating risk factor progression directly capture these differences, although the assumption there would be that the associations between risk factors and events are translatable across different settings. However, the new framework being less complex is also easier to update, and the methods for updating such risk equations have been described in detail in Section 3.5.

3.6.6 Limitations

Only 63% of ASCEND participants returned usable blood/urine samples. For these participants, the imputation model is based solely on participants' baseline characteristics such as age, sex, ethnicity and smoking status in addition to their history of adverse event occurrences. Participants who returned a usable blood/urine sample were on average older and less likely to be smokers, but were generally representative of the full study population [11]. It is not known if there were reasons that would account for this missingness that is related to the values of the missing biomarkers themselves, so the possibility that the data is missing not at random cannot be excluded. To assess the impact of imputation on the results, the Cox proportional hazard models were re-estimated using only the subset of participants

who returned usable blood/urine samples in a complete-case analysis. The estimated HRs were generally robust to missing data imputation except for those associated with albuminuria, and these were subsequently re-estimated using the UK Biobank for events that were reliably detected. Where significant issues with adverse event ascertainment were suspected in the UK Biobank, such as for GI bleed and other major bleed, the risk equations developed in ASCEND were preferred and assumed generalisable to the UK Biobank. Further external validation of these equations would be necessary. In the case of heart failure and ischaemic stroke where events may be under-detected, the HRs estimated in the UK Biobank may be biased downwards (towards no effect) if the error in detection is somehow associated with the risk factor. Although this cannot be formally tested, the re-estimated HRs of albuminuria roughly corresponded to the estimates from the complete-case analysis using the ASCEND data, which suggests that the bias is not severe.

Other common complications in diabetes such as hypoglycemia and diabetic retinopathy were not included in the model as these events were not sought for in ASCEND and would be difficult to reliably identify from hospital records.

Both ASCEND and the UK Biobank have a disproportionately high percentage of participants who are of White ethnicity and from areas of low deprivation (proportion of participants living in region belonging to 2011 UK population quintile of lowest deprivation based on Townsend Index, 43% in ASCEND, 37% in UK Biobank). This may restrict the generalisability of the risk equations to cohorts with more variation in ethnicity and socioeconomic status. The accuracy of the model in these populations would need to be assessed, and the risk equations may need to be further updated to include ethnicity and socioeconomic status.

3.6.7 Strengths and added value

Different from many recent cardiovascular outcomes trials in diabetes, ASCEND recruited participants who did not have previous cardiovascular disease, creating the opportunity to develop a model specific for this subgroup of patients. Increasingly, novel diabetes treatments that have previously demonstrated efficacy in patients

with high cardiovascular risk are being trialed in patients at lower cardiovascular risk. This model will be useful for evaluating diabetes treatments for primary prevention of cardiovascular disease, and the risk equations estimated provide an alternative to the UKPDS risk equations.

The risk equations were developed using high quality clinically adjudicated adverse events data. This allowed classification of stroke subtypes and identification of major bleeds, which are difficult to accurately identify from routine electronic healthcare records.

In applications, the validity of models needs to be checked and in the event discrepancies are found, the models may need to be updated. Although methods of model updating have been described previously, I detail the mathematical formulations of methods specifically for updating parametric proportional hazard equations and proposed an issue-driven approach in selecting the method to use for model updating. The issues discussed, though limited to those identified in ASCEND and the UK Biobank, are sufficient to demonstrate how the different methods can be adopted to address issues beyond those discussed.

References

1. Clarke PM, Gray AM, Briggs A, et al. A Model to Estimate the Lifetime Health Outcomes of Patients with Type 2 Diabetes: The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS No. 68). Diabetologia 2004;47:1747–59. DOI: 10.1007/s00125-004-1527-z.
2. Hayes AJ, Leal J, Gray AM, Holman RR, and Clarke PM. UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33. DOI: 10.1007/s00125-013-2940-y.
3. Basu S, Sussman JB, Berkowitz SA, Hayward RA, and Yudkin JS. Development and Validation of Risk Equations for Complications Of Type 2 Diabetes (RECODe) Using Individual Participant Data from Randomised Trials. The Lancet Diabetes & Endocrinology 2017;5:788–98. DOI: 10.1016/S2213-8587(17)30221-8.
4. Basu S, Sussman JB, Berkowitz SA, et al. Validation of Risk Equations for Complications of Type 2 Diabetes (RECODe) Using Individual Participant Data From Diverse Longitudinal Cohorts in the U.S. Diabetes Care 2018;41:586–95. DOI: 10.2337/dc17-2002.

5. Laxy M, Schöning VM, Kurz C, et al. Performance of the UKPDS Outcomes Model 2 for Predicting Death and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus from a German Population-Based Cohort. Pharmacoeconomics 2019;37:1485–94. DOI: 10.1007/s40273-019-00822-4.
6. Pagano E, Konings SRA, Di Cuonzo D, et al. Prediction of Mortality and Major Cardiovascular Complications in Type 2 Diabetes: External Validation of UK Prospective Diabetes Study Outcomes Model Version 2 in Two European Observational Cohorts. Diabetes Obes Metab 2021;23:1084–91. DOI: 10.1111/dom.14311.
7. Si L, Willis MS, Asseburg C, et al. Evaluating the Ability of Economic Models of Diabetes to Simulate New Cardiovascular Outcomes Trials: A Report on the Ninth Mount Hood Diabetes Challenge. Value Health 2020;23:1163–70. DOI: 10.1016/j.jval.2020.04.1832.
8. Willis M, Asseburg C, Slee A, Nilsson A, and Neslusan C. Macrovascular Risk Equations Based on the CANVAS Program. PharmacoEconomics 2021;39:447–61. DOI: 10.1007/s40273-021-01001-0.
9. Willis M, Asseburg C, Slee A, Nilsson A, and Neslusan C. Development and Internal Validation of a Discrete Event Simulation Model of Diabetic Kidney Disease Using CREDENCE Trial Data. Diabetes Ther 2020;11:2657–76. DOI: 10.1007/s13300-020-00923-w.
10. Shao H, Fonseca V, Stoecker C, Liu S, and Shi L. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). Pharmacoeconomics 2018;36:1125–34. DOI: 10.1007/s40273-018-0662-1.
11. Bowman L, Mafham M, Stevens W, et al. ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a Randomized Trial of Aspirin and of Omega-3 Fatty Acid Supplementation in 15,480 People with Diabetes. Am Heart J 2018;198:135–44. DOI: 10.1016/j.ahj.2017.12.006.
12. UK Biobank Coordinating Centre. UK Biobank: Protocol for a Large-Scale Prospective Epidemiological Resource. 2007. URL: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf.
13. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLOS ONE 2016;11:e0162388. DOI: 10.1371/journal.pone.0162388.
14. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation 2018;137:961–72. DOI: 10.1161/CIRCULATIONAHA.117.033502.
15. Li L, Binney LE, Luengo-Fernandez R, Silver LE, and Rothwell PM. Temporal Trends in the Accuracy of Hospital Diagnostic Coding for Identifying Acute Stroke: A Population-Based Study. European Stroke Journal 2020;5:26–35. DOI: 10.1177/2396987319881017.
16. Data Providers and Dates of Data Availability. UK Biobank showcase. URL: https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates (visited on 09/21/2021).

17. White IR, Royston P, and Wood AM. Multiple Imputation Using Chained Equations: Issues and Guidance for Practice. Stat Med 2011;30:377–99. DOI: 10.1002/sim.4067.

18. Marshall A, Altman DG, Royston P, and Holder RL. Comparison of Techniques for Handling Missing Covariate Data within Prognostic Modelling Studies: A Simulation Study. BMC Med Res Methodol 2010;10:7. DOI: 10.1186/1471-2288-10-7.

19. Marshall A, Altman DG, and Holder RL. Comparison of Imputation Methods for Handling Missing Covariate Data When Fitting a Cox Proportional Hazards Model: A Resampling Study. BMC Med Res Methodol 2010;10:112. DOI: 10.1186/1471-2288-10-112.

20. Collaborative HPS. Lifetime Cost Effectiveness of Simvastatin in a Range of Risk Groups and Age Groups Derived from a Randomised Trial of 20 536 People. BMJ 2006;333:1145. DOI: 10.1136/bmj.38993.731725.BE.

21. Brostrom G. Event History Analysis with R. 1st ed. Vol. 3. Chapman & Hall/CRC the R Series. Boca Raton: Boca Raton: CRC Press, 2012. DOI: 10.1201/9781315373942.

22. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the Performance of Prediction Models: A Framework for Traditional and Novel Measures. Epidemiology 2010;21:128–38. DOI: 10.1097/EDE.0b013e3181c30fb2.

23. Uno H, Cai T, Pencina MJ, D'Agostino RB, and Wei LJ. On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data. Stat Med 2011;30:1105–17. DOI: 10.1002/sim.4154.

24. Li L and Rothwell PM. Biases in Detection of Apparent "Weekend Effect" on Outcome with Administrative Coding Data: Population Based Study of Stroke. BMJ 2016;353:i2648. DOI: 10.1136/bmj.i2648.

25. Spencer SA and Davies MP. Hospital Episode Statistics: Improving the Quality and Value of Hospital Data: A National Internet e-Survey of Hospital Consultants. BMJ Open 2012;2:e001651. DOI: 10.1136/bmjopen-2012-001651.

26. Burns EM, Rigby E, Mamidanna R, et al. Systematic Review of Discharge Coding Accuracy. J Public Health (Oxf) 2012;34:138–48. DOI: 10.1093/pubmed/fdr054.

27. Harper C, Mafham M, Herrington W, et al. Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial-Adjudicated Direct Follow-up Data in the UK: Secondary Analysis of the ASCEND Randomized Clinical Trial. JAMA Netw Open 2021;4:e2139748. DOI: 10.1001/jamanetworkopen.2021.39748.

28. Kivimäki M, Batty GD, Singh-Manoux A, Britton A, Brunner EJ, and Shipley MJ. Validity of Cardiovascular Disease Event Ascertainment Using Linkage to UK Hospital Records. Epidemiology 2017;28:735–9. DOI: 10.1097/EDE.0000000000000688.

29. Rannikmäe K, Ngoh K, Bush K, et al. Accuracy of Identifying Incident Stroke Cases from Linked Health Care Data in UK Biobank. Neurology 2020;95:e697–e707. DOI: 10.1212/WNL.0000000000009924.

30. Koudstaal S, Pujades-Rodriguez M, Denaxas S, et al. Prognostic Burden of Heart Failure Recorded in Primary Care, Acute Hospital Admissions, or Both: A Population-based Linked Electronic Health Record Cohort Study in 2.1 Million People. Eur J Heart Fail 2017;19:1119–27. DOI: 10.1002/ejhf.709.

31. Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, and Hayhoe B. Routes to Diagnosis of Heart Failure: Observational Study Using Linked Data in England. Heart 2018;104:600–5. DOI: 10.1136/heartjnl-2017-312183.

32. Faridi KF, Tamez H, Butala NM, et al. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the DAPT Study: Findings From the EXTEND-DAPT Study. Circ Cardiovasc Qual Outcomes 2021;14:e006589. DOI: 10.1161/CIRCOUTCOMES.120.006589.

33. Guimarães PO, Krishnamoorthy A, Kaltenbach LA, et al. Accuracy of Medical Claims for Identifying Cardiovascular and Bleeding Events After Myocardial Infarction : A Secondary Analysis of the TRANSLATE-ACS Study. JAMA Cardiology 2017;2:750–7. DOI: 10.1001/jamacardio.2017.1460.

34. Office for National Statistics. National Life Tables: UK. 2021.

35. UK Prospective Diabetes Study (UKPDS) Group. Intensive Blood-Glucose Control with Sulphonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes (UKPDS 33). Lancet 1998;352:837–53. DOI: 10.1016/S0140-6736(98)07019-6.

36. Prospective Studies Collaboration, Lewington S, Whitlock G, et al. Blood Cholesterol and Vascular Mortality by Age, Sex, and Blood Pressure: A Meta-Analysis of Individual Data from 61 Prospective Studies with 55,000 Vascular Deaths. Lancet 2007;370:1829–39. DOI: 10.1016/S0140-6736(07)61778-4.

37. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and Safety of More Intensive Lowering of LDL Cholesterol: A Meta-Analysis of Data from 170,000 Participants in 26 Randomised Trials. Lancet 2010;376:1670–81. DOI: 10.1016/S0140-6736(10)61350-5.

38. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of Statins and Non-Statin LDL-lowering Medications on Cardiovascular Outcomes in Secondary Prevention: A Meta-Analysis of Randomized Trials. European Heart Journal 2018;39:1172–80. DOI: 10.1093/eurheartj/ehx566.

39. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT Bleeding Score: A Simple Bedside Score to Assess Bleeding Risk in Atrial Fibrillation. European Heart Journal 2015;36:3258–64. DOI: 10.1093/eurheartj/ehv476.

40. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, and Lip GYH. A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation: The Euro Heart Survey. Chest 2010;138:1093–100. DOI: 10.1378/chest.10-0134.

41. Costa F, van Klaveren D, James S, et al. Derivation and Validation of the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) Score: A Pooled Analysis of Individual-Patient Datasets from Clinical Trials. The Lancet 2017;389:1025–34. DOI: 10.1016/S0140-6736(17)30397-5.

42. Selak V, Jackson R, Poppe K, et al. Predicting Bleeding Risk to Guide Aspirin Use for the Primary Prevention of Cardiovascular Disease. Ann Intern Med 2019;170:357–68. DOI: 10.7326/M18-2808.

43. Hippisley-Cox J and Coupland C. Predicting Risk of Upper Gastrointestinal Bleed and Intracranial Bleed with Anticoagulants: Cohort Study to Derive and Validate the QBleed Scores. BMJ 2014;349:g4606. DOI: 10.1136/bmj.g4606.

44. Leal J, Gray AM, and Clarke PM. Development of Life-Expectancy Tables for People with Type 2 Diabetes. European Heart Journal 2009;30:834–9. DOI: 10.1093/eurheartj/ehn567.

45. Magliano DJ, Chen L, Carstensen B, et al. Trends in All-Cause Mortality among People with Diagnosed Diabetes in High-Income Settings: A Multicountry Analysis of Aggregate Data. The Lancet Diabetes & Endocrinology 2022;10:112–9. DOI: 10.1016/S2213-8587(21)00327-2.

46. NHS Digital. National Diabetes Audit - Report 2 Complications and Mortality, 2017-18. 2019. URL: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-2--complications-and-mortality-2017-18 (visited on 05/11/2022).

47. Wright AK, Kontopantelis E, Emsley R, et al. Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes: A Population-Based Cohort Study Quantifying Relationships in Ethnic Subgroups. Diabetes Care 2016;40:338–45. DOI: 10.2337/dc16-1616.

48. Heald AH, Stedman M, Davies M, et al. Estimating Life Years Lost to Diabetes: Outcomes from Analysis of National Diabetes Audit and Office of National Statistics Data. Cardiovascular Endocrinology & Metabolism 2020;9:183–5. DOI: 10.1097/XCE.0000000000000210.

49. Moons KGM, Kengne AP, Grobbee DE, et al. Risk Prediction Models: II. External Validation, Model Updating, and Impact Assessment. Heart 2012;98:691–8. DOI: 10.1136/heartjnl-2011-301247.

50. Daly MJ, Elvidge J, Chantler T, and Dawoud D. A Review of Economic Models Submitted to NICE's Technology Appraisal Programme, for Treatments of T1DM & T2DM. Frontiers in Pharmacology 2022;13. DOI: 10.3389/fphar.2022.887298.

51. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine 2015;373:2117–28. DOI: 10.1056/NEJMoa1504720.

52. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017;377:644–57. DOI: 10.1056/NEJMoa1611925.

53. Kansal A, Zheng Y, Proskorovsky I, Krotneva S, Kandaswamy P, and Ruffolo A. Modeling Cardiovascular Outcomes of Treatment with Empagliflozin in Type 2 Diabetes Based on Hard Outcomes Data. Value in Health 2016;19:A203. DOI: 10.1016/j.jval.2016.03.1299.

4

Hospital costs associated with adverse events in ASCEND

This chapter has been published in *Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, and ASCEND Study Collaborative Group. Hospital costs associated with adverse events in people with diabetes in the UK. Diabetes Obes Metab 2022; 1- 10. DOI: 10.1111/dom.14796.*

Summary

Robust contemporary cost estimates are required to inform economic analysis of diabetes interventions. In this chapter, I estimated the annual hospital costs associated with adverse events to inform the simulation model developed in the previous chapter using data linkage to longitudinal hospital records for ASCEND participants.

Annual hospital costs (2019/20 GBP£) were derived from routine hospital records of 15,436 participants between 2005 and 2017 (120,420 person-years). The annual costs associated with adverse events were estimated using a generalised linear model following adjustment for participants' sociodemographic and clinical risk factors. In the year of the event, ESRD was associated with the largest increase in annual hospital cost (£20,954), followed by lower-limb amputation (£17,887), intracranial haemorrhage (£12,080), GI tract cancer (£10,160), coronary revascularisation (£8531 if urgent; £8302 if non-urgent), heart failure (£8319), non-GI tract cancer (£7409), ischaemic stroke (£7170), GI bleed (£5557), myocardial

infarction (£4913), other major bleed (£3825), and TIA (£1523). In subsequent years, most adverse events were associated with lasting but smaller increases in hospital costs, except for ESRD where the additional cost remained high (£20,090). These cost estimates highlight the potential cost savings that could be derived from the prevention of these costly complications and can inform future cost-effectiveness analyses of diabetes interventions.

4.1 Background

Robust estimation of the costs associated with adverse events requires accurate and contemporary patient-level information on diabetes diagnosis, healthcare use and adverse event occurrences. There are only a limited number of studies in the UK that have reported the impact of diabetes complications on patient-level costs [1–4]. The estimates by Alva et al. (2015) are still frequently used in cost-effectiveness analyses of diabetes treatments [5–9]. However, these costs were derived using data from 1998 to 2007 and may not reflect the contemporary costs of diabetes complications because of changing patterns of care and the availability of new treatments. Contemporary estimates of costs reflecting modern treatment and management practices are needed to inform future economic analyses of diabetes treatments. McMeekin et al. (2020) compared the costs incurred by people with type 2 diabetes who experienced an incident cardiovascular event with those who did not using more recent data from the Scottish Care Information-Diabetes Collaboration [4]. The confidence intervals for estimates of secondary care costs associated with different cardiovascular events reported in the study were very wide, reflecting large uncertainty in their results. In this chapter, I used hospital data from participants in ASCEND to estimate the impact of adverse events on annual hospital costs in the UK.

4.2 Costing hospital episode data

Data on hospital attendances and admissions obtained from Hospital Episodes Statistics (HES), Scottish Morbidity Records and Scottish accident and emergency

data were available for all participants (excluding those who moved abroad or withdrew from the trial) in the ASCEND study in England, Wales and Scotland. Linked hospital data were not available for participants in Northern Ireland so they were excluded from the analysis.

Hospital activity data on admitted patient care (elective and non-elective), outpatient attendances and procedures, and accident and emergency attendances (A&E) were included in the analysis. Each hospital attendance and admission (referred to as a hospital episode or finished consultant episode) was assigned a Healthcare Resource Group (HRG) using the 2017/18 reference cost grouper [10]. HRGs are UK groups of diagnoses (ICD-10) and procedures (OPCS-4) codes that use comparable levels of healthcare resources. The cost (GBP£) for each hospital episode was calculated using the 2017/18 NHS reference costs [11] inflated to 2019/20 values using the NHS cost inflation index [12] in line with NICE's guidelines [13]. Each HRG has a corresponding upper length of stay trim point, and any excess bed days in hospital beyond this trim point were assigned further cost related to this excess bed days [10, 11]. Cancelled or postponed outpatient episodes were excluded from the analysis. Unattended outpatient episodes were included to account for the opportunity costs of a missed scheduled appointment. For sensitivity analysis, unattended outpatient episodes were excluded to reflect the actual cost incurred.

Annual costs were established by aggregating the costs incurred by each participant each year relative to their recruitment date in ASCEND. The analysis was restricted to costs incurred within the follow-up period in the study.

4.2.1 Costing maintenance dialysis

Maintenance dialysis sessions for chronic kidney diseases are recorded in the National Renal Dataset and healthcare service providers are not expected to record associated admission or attendance in the inpatient or outpatient commissioning dataset when people attend solely for dialysis. Where providers do report dialysis activity within the commissioning dataset, the renal HRG "LA97A same day dialysis admission or attendance" will be generated which is associated with no cost [14]. I did not

have access to the National Renal Dataset, so the patient-level data on dialysis is incomplete. However, dialysis is highly costly and excluding this would severely underestimate the cost associated with ESRD. Hence, for participants identified to have ESRD, the cost of dialysis was estimated by multiplying the time-on-dialysis with the annual cost of dialysis.

The time-on-dialysis was calculated from the date of first report of ESRD to the date of transplant, death or censoring. 13 (12%) of the 105 participants identified with ESRD had a transplant recorded within the trial duration, and it was assumed that dialysis was no longer required for these participants post-transplant. The unit cost of each type of dialysis was obtained from the 2017/18 reference cost [11] inflated to 2019/20 values [12]. The average annual dialysis cost is estimated to be £25,283, calculated as a weighted average across the different dialysis types, based on the percentage of patients on each dialysis type in 2019 reported by the UK Renal Registry [15] (Supplemental Table C.17).

4.3 Model specification

4.3.1 Variable selection

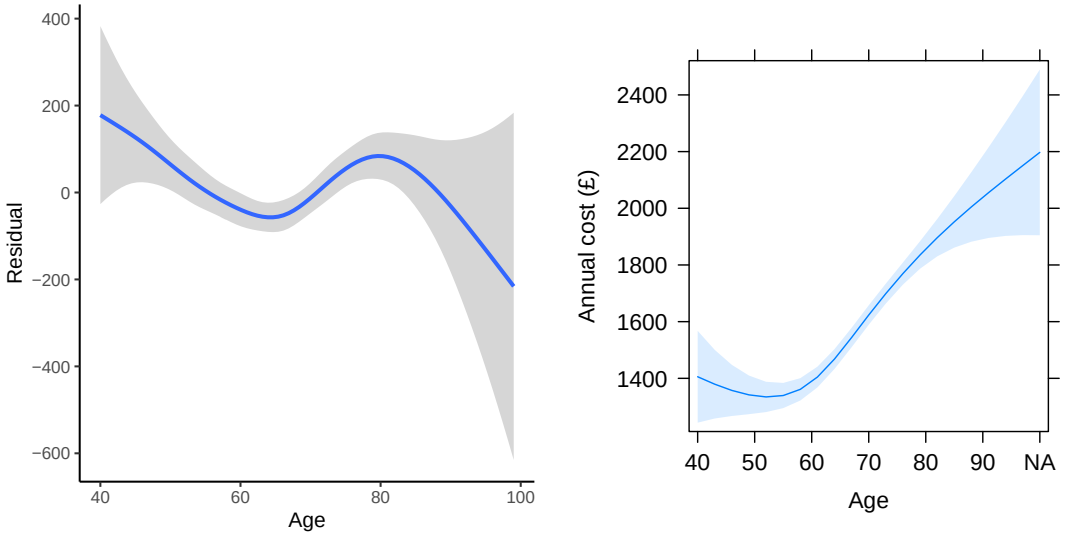
Candidate covariates of the statistical model were: time since occurrence of adverse events as a categorical variable (no history, event occurring in year, event occurring the previous year, and event occurring 2 or more years ago), current age, diabetes type (1 or 2), sociodemographic characteristics and clinical risk factors measured at recruitment into the trial[1]. The history of adverse event occurrence in each annual period was stratified into four levels to reflect the immediate and longer-term impacts of the adverse event on annual hospital costs. The levels were combined if there was no evidence of temporal difference based on the Wald test (p-value ≥ 0.05). Natural cubic splines were fitted to test for and explore the shape of non-linearity of current age. Interactions between event occurrence in the same year were considered. Stepwise selection of covariates was performed based on the

[1]The full list of variables is listed in Supplemental Table C.8. Missing sociodemographic and clinical risk factors were imputed as described in Section 3.2.3.

likelihood ratio test, with p-values < 0.1 and p-value < 0.05 used for inclusion and exclusion, respectively. An indicator for the proportion of year observed was included in the model to account for censoring. Clustered standard errors were used to account for correlation between observations of annual costs for each participant.

4.3.2 Non-linear relationship between age and hospital costs

In the single-equation model (model specification described in Section 4.3.3) including all covariates, the martingale residual plot of age suggested that there may be a non-linear relationship between age and annual hospital cost (Figure 4.1(a)). There was no evidence of non-linearity of age for the two-part model.



(a) Martingale residual of age **(b)** Marginal effect of age (natural cubic spline)

Figure 4.1: Non-linear relationship between age and annual hospital cost

A natural cubic spline was fitted to explore the shape of the relationship in the single-equation model. The fitted spline is u-shaped suggesting that the polynomial form with degree 2 (quadratic polynomial) might be an appropriate functional form for age (Figure 4.1(b)). The model with polynomial form of age had a smaller mean squared error (MSE) but greater mean absolute prediction error (MAPE) than the model with the spline form of age (Supplemental Table C.18). Despite so, the excess hospital costs for every 10 years of age relative to a 60-year-old estimated by

the model with polynomial form of age matches moderately well the excess costs predicted by the model with a natural cubic spline (Supplemental Table C.19). Hence, the polynomial form was selected since it is easy to compute.

4.3.3 Model selection

Typical of healthcare costs data, a high proportion of zero-cost observations (no hospital use in year) and a highly skewed distribution for non-zero costs were observed (Supplemental Figure C.38). Thus, for modelling the annual cost associated with adverse events, in addition to single-equation generalised linear models (GLMs), two-part models (logistic regression for the first part predicting the likelihood of hospital use, GLMs for the second part predicting cost conditional on hospital use) were considered. GLMs with the identity, log and square-root link functions were considered for both the single-equation model and for the second part of the two-part model, and the Gaussian, Poisson and Gamma distributions were considered for modelling the mean-variance relationship in the data.

The appropriateness of each link function was assessed using the Pregibon link test [16] and the modified Hosmer-Lemeshow test [17]. The tests generally rejected the log link (Supplemental Table C.20). The modified Park test [18] indicated that the Poisson and Gamma distribution may be appropriate for the identity and square-root links (Supplemental Table C.21). The Copas test implemented using 3-fold cross-validation repeated 1000 times was used to assess the out-of-sample performance of the models [19]. The identity link had the lowest rejection rate, and overfitting was evident for models with the log link (Supplemental Table C.22).

Finally, the performance of the models was evaluated based on mean prediction error (MPE), MAPE, root-mean-squared error (RMSE), and Efron's R^2 (Supplemental Table C.23). Generally, models with the identity link demonstrated the best performance with low bias. Plots of the MPE by decile (Supplemental Figure C.39) indicated that models with log link have significant bias in the highest decile of predicted costs. This bias was worst for the Gamma variance.

Overall, from the assessments above, the GLM with Poisson-identity specification had the best overall performance for both the single-equation and two-part models. Generally, the single-equation models performed similarly to two-part models. The marginal impact on annual hospital costs associated with adverse events estimated by the single-equation and the two-part models were similar (Supplemental Table C.24). Hence, the single-equation GLM with Poisson-identity specification was chosen for parsimony.

4.4 Results

4.4.1 Participant characteristics and hospital use

Of the 15,480 participants in ASCEND, 44 (0.3%) participants from Northern Ireland, for whom no hospital episode data were available, were excluded from the analysis. The baseline characteristics of the remaining 15,436 participants in England, Wales and Scotland are summarised in Table 4.1 (see Supplemental Table C.25 for characteristics after imputation). 14,528 (94.1%) participants included in the analysis had type 2 diabetes. At recruitment, participants' mean age was 63 years and their median duration of diabetes was 7 years. Participants were followed up for an average of 7.4 years, with only 97 (0.6%) participants lost to follow-up having withdrawn or moved abroad.

Table 4.1: Baseline characteristics of 15,436 participants included in the analysis

Variable	N (%), mean (SD) or median (IQR)
Diabetes type	
Type 1	908 (5.9%)
Type 2	14528 (94.1%)
Sex	
Male	9650 (62.5%)
Female	5786 (37.5%)
Smoking status	
Current smoker	1274 (8.3%)
Former/Never smoker	13989 (90.6%)
Missing	173 (1.1%)
Race	
White	14892 (96.5%)
South Asian	183 (1.2%)
Black	140 (0.9%)
Other/unknown	221 (1.4%)
Townsend Index	
Q1: <-2.42 (least deprived)	6674 (43.2%)
Q2: ≥-2.42, <-0.44	3783 (24.5%)
Q3: ≥-0.44, < 1.79	2492 (16.1%)
Q4: ≥ 1.79, < 4.75	1814 (11.8%)
Q5: ≥ 4.75 (most deprived)	635 (4.1%)
Missing	38 (0.2%)
Hypertension	
Y	9502 (61.6%)
N	5822 (37.7%)
Missing	112 (0.7%)
Diabetic retinopathy	
Y	3017 (19.5%)
N	12277 (79.5%)
Missing	142 (0.9%)
Statin use	
Y	11619 (75.3%)
N	3817 (24.7%)
Use of ACE Inhibitor or ARB	
Y	9024 (58.5%)
N	6412 (41.5%)
Age (years)	
Mean (SD)	63.3 (9.2)

Table 4.1: Baseline characteristics of 15,436 participants included in the analysis *(continued)*

Variable	N (%), mean (SD) or median (IQR)
Diabetes duration (years)	
Median (IQR)	7.0 (3.0, 13.0)
Missing	853 (5.5%)
Body-mass index (kg/m^2)	
Mean (SD)	31.1 (6.5)
Missing	118 (0.8%)
HbA1c (IFCC mmol/mol)	
Mean (SD)	54.8 (12.9)
Missing	5652 (36.6%)
HDL cholesterol (mmol/L)	
Mean (SD)	1.27 (0.35)
Missing	5665 (36.7%)
Non-HDL cholesterol (mmol/L)	
Mean (SD)	2.90 (0.84)
Missing	5665 (36.7%)
Systolic blood pressure (mmHg)	
Mean (SD)	136.1 (15.3)
Missing	4430 (28.7%)
Diastolic blood pressure (mmHg)	
Mean (SD)	77.1 (9.5)
Missing	4436 (28.7%)
Urinary albumin/creatinine ratio (mg/mmol)	
< 3	8503 (55.1%)
≥ 3	1242 (8%)
Missing	5691 (36.9%)
eGFR (ml/min/1.73m^2)	
< 45	405 (2.6%)
$\geq 45, < 60$	863 (5.6%)
$\geq 60, < 90$	4007 (26%)
≥ 90	4511 (29.2%)
Missing	5650 (36.6%)

Note:
Only 9879 (64%) participants returned usable blood/urine sample in the study. Mean (SD) and median (IQR) in table excludes missing data. Summary statistics after imputation can be found in Supplemental Table C.25.

4. Hospital costs associated with adverse events

A total of 120,420 person-years of observations were available for analysis, and hospital use was recorded in 66% of these annual periods. 67,706 inpatient episodes (0.56 per person-year), 375,952 outpatient episodes (3.12 per person-year), and 28,423 A&E episodes (0.24 per person-year) were recorded (Table 4.2). On average, participants with type 1 diabetes experienced a greater number of hospital episodes each year than participants with type 2 diabetes, particularly for outpatient episodes. Participants with type 1 diabetes had twice as many ophthalmology consultations (0.72 vs 0.35 per person-year), four times as many diabetic medicine speciality consultations (1.31 vs 0.30), three times as many nephrology consultations (0.14 vs 0.05), and twice as many eye procedures performed (0.30 vs 0.14) in the outpatient setting (Supplemental Table C.26). Although there is smaller contrast in inpatient episodes between type 1 and type 2 diabetes (0.63 vs 0.56), greater numbers of episodes in the renal (0.05 vs 0.02) and diabetic medicine specialities (0.04 vs 0.01) were observed (Supplemental Table C.27).

Table 4.2: Numbers and costs of different types of hospital episodes

Type of hospital episode	No. of hospital episodes (%)	No. of episodes per person-year	Cost (£) per episode, median (IQR)
All participants (N = 15436; No. of person-years = 120420)			
Inpatient	67706 (14.3%)	0.56	828 (476, 2,074)
Outpatient	375952 (79.6%)	3.12	126 (96, 147)
A&E	28423 (6%)	0.24	180 (110, 219)
Participants with type 2 diabetes (N = 14528; No. of person-years = 112492)			
Inpatient	62720 (14.8%)	0.56	848 (476, 2,080)
Outpatient	335932 (79.1%)	2.99	125 (96, 149)
A&E	26019 (6.1%)	0.23	180 (110, 219)
Participants with type 1 diabetes (N = 908; No. of person-years = 7928)			
Inpatient	4986 (10.5%)	0.63	712 (422, 1,856)
Outpatient	40020 (84.4%)	5.05	134 (104, 142)
A&E	2404 (5.1%)	0.30	170 (110, 219)

Note:
IQR, interquartile range. Maintenance dialysis sessions are not included in hospital episodes (see Supplemental Table C.17 for more information on how dialysis cost was derived).

4. Hospital costs associated with adverse events

Over the follow-up period, 1573 (10.2%) participants had experienced a non-GI tract cancer, 465 (3%) a myocardial infarction, 455 (2.9%) an ischaemic stroke, 365 (2.4%) a transient ischaemic attack, 356 (2.3%) a heart failure, 315 (2%) a GI tract cancer, 292 (1.9%) a non-urgent coronary revascularisation, 272 (1.8%) an urgent coronary revascularisation, 238 (1.5%) a GI bleed, 143 (0.9%) an amputation, 117 (0.8%) other major bleed, 105 (0.7%) an ESRD and 100 (0.6%) an intracranial haemorrhage. 414 (2.7%) participants died of vascular causes, with 191 (1.2%) having had a vascular event in the same year. 1126 (7.3%) participants died of non-vascular causes, with 363 (2.4%) having had a non-vascular event in the same year. A peak in hospital use and hospital cost in the year of event occurrence was evident for all events (Figure 4.2, Supplemental Table C.28), and these tailed off immediately in the year following event occurrence for all adverse events except for ESRD, where cost remained high in the years after the ESRD event.

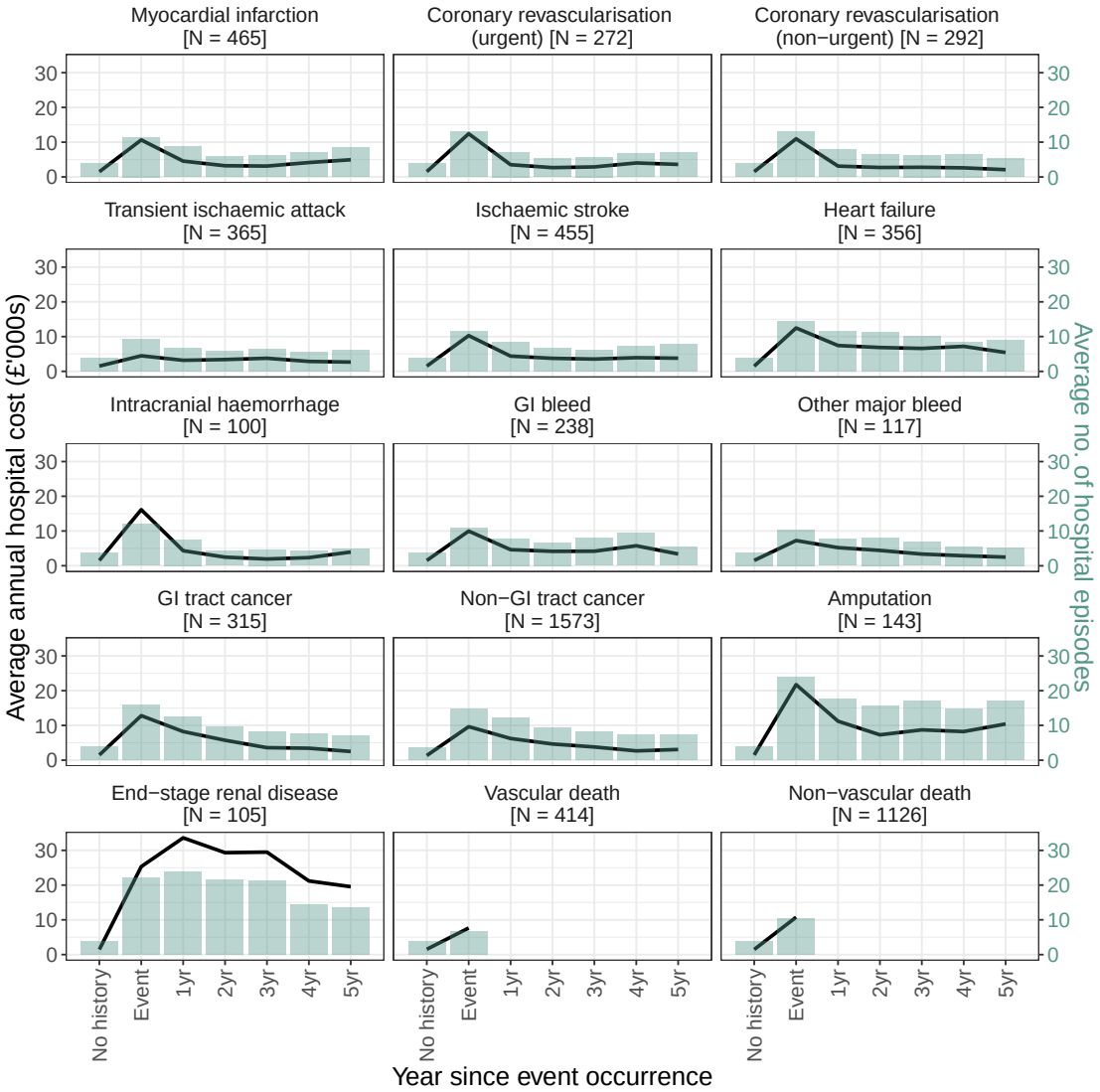


Figure 4.2: Average annual hospital cost and number of hospital episodes prior to, in year of, and in years subsequent to first adverse event occurrence. The black lines represent the average annual hospital cost and the coloured bars represent the average number of hospital episodes each year. The numbers in brackets are the number of participants who experienced each adverse event during the follow-up of the ASCEND study. Maintenance dialysis sessions are not included in counts of hospital episodes

4.4.2 Model results

The mean annual hospital cost incurred for a 60-year-old male with type 2 diabetes, living in a region in the lowest quintile of socioeconomic deprivation, with BMI <25kg/m^2, diabetes duration <5 years, HbA1c <48mmol/mol, eGFR ≥ 90ml/min/1.73m^2, no albuminuria, no retinopathy and no history of adverse events was £598 (95% CI: £538, £636). Relative to this reference case, the cost associated with adverse event occurrences, sociodemographic and clinical risk factors are presented in Table 4.3. Results were similar in the sensitivity analysis excluding 53,269 (12.4%) unattended outpatient episodes (Supplemental Table C.29).

Table 4.3: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events

Variable	Annual hospital cost (£)
Diabetes type (ref: Type 2)	
Type 1	149 (30, 267)*
Sex (ref: Male)	
Female	104 (63, 146)**
Townsend index (ref: Q1 (least deprived))	
Q2	8 (-17, 33)
Q3	4 (-47, 55)
Q4	170 (98, 242)**
Q5 (most deprived)	532 (357, 706)**
Age (per 10 years; centered at 60)	
Age	96 (71, 121)**
Age^2	63 (46, 80)**
BMI (ref: <25 kg/m^2)	
≥25, <30	13 (8, 18)**
≥30, <35	66 (23, 109)**
≥35	218 (158, 279)**
Diabetes duration (ref: <5 years)	
≥5, <10	36 (5, 67)*
≥10, <20	154 (100, 208)**
≥20	275 (184, 365)**
HbA1c (ref: <48 mmol/mol)	
≥ 48, < 64	0 (-31, 31)
≥ 64	174 (107, 241)**

Table 4.3: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events *(continued)*

Variable	Annual hospital cost (£)
eGFR (ref: ≥90 ml/min/1.73m^2)	
≥60, <90	32 (-16, 80)
≥45, <60	156 (49, 263)**
<45	651 (417, 886)**
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)	
Y	190 (110, 269)**
Retinopathy (ref: N)	
Y	117 (62, 172)**
Disease history (ref: no event)	
Myocardial infarction	
In year	4913 (3640, 6186)**
At least 1 year ago	600 (123, 1077)*
Coronary revascularisation (urgent)	
In year; MI in same year	4521 (2736, 6307)**
In year; no MI in same year	8531 (5921, 11141)**
At least 1 year ago	112 (-398, 622)
Coronary revascularisation (non-urgent)	
In year	8302 (7462, 9142)**
At least 1 year ago	547 (297, 797)**
Transient ischaemic attack	
In year	1523 (1089, 1958)**
At least 1 year ago	591 (281, 901)**
Ischaemic stroke	
In year	7170 (6123, 8216)**
At least 1 year ago	1074 (699, 1449)**
Heart failure	
In year	8319 (7192, 9446)**
At least 1 year ago	2399 (1743, 3056)**
Intracranial haemorrhage	
In year	12080 (8850, 15310)**
At least 1 year ago	376 (-109, 861)
GI bleed	
In year	5557 (4431, 6682)**
At least 1 year ago	1209 (602, 1816)**
Other major bleed	
In year	3825 (2084, 5566)**
At least 1 year ago	692 (230, 1154)**

Table 4.3: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events *(continued)*

Variable	Annual hospital cost (£)
GI tract cancer	
In year	10160 (8947, 11373)**
In previous year	5149 (3444, 6855)**
At least 2 years ago	1260 (683, 1837)**
Non-GI tract cancer	
In year	7409 (6900, 7919)**
In previous year	3688 (3209, 4166)**
At least 2 years ago	1623 (1318, 1928)**
Amputation	
In year	17887 (15326, 20448)**
In previous year	7283 (5274, 9291)**
At least 2 years ago	3957 (2890, 5025)**
End-stage renal disease	
In year	20954 (18171, 23737)**
In previous year	28894 (25612, 32176)**
At least 2 years ago	20090 (16729, 23451)**
Death in year (ref: No death in year)	
VD; vascular event[a] in year	-377 (-2094, 1341)
VD; no vascular event[a] in year	2922 (1726, 4118)**
NVD; non-vascular event[b] in year	2437 (1108, 3765)**
NVD; no non-vascular event[b] in year	5935 (5178, 6693)**

Note:
**: p-value < 0.01; *: p-value < 0.05; GI, gastrointestinal; VD, vascular death; NVD, non-vascular death. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. The mean annual hospital cost for the reference individual (60-year-old male with type 2 diabetes, living in least deprived region, with BMI <25kg/m^2, diabetes duration <5 years, HbA1c <48mmol/mol, eGFR ≥90ml/min/1.73m^2, no albuminuria, no retinopathy, with no disease history) is £598 (95% CI: £538, £636).
Vascular death refers to any vascular-related deaths that may or may not be a result of vascular events included in the model. Similarly, non-vascular death refers to any non-vascular-related deaths that may or may not be a result of non-vascular events included in the model.

[a] Vascular event refers to myocardial infarction, coronary revascularisation, transient ischaemic attack, ischaemic stroke, or heart failure.

[b] Non-vascular event refers to cancer, intracranial haemorrhage, GI bleed, other major bleed, amputation, or end-stage renal disease.

Annual hospital costs associated with adverse events

Holding all else constant, in the year of an event, ESRD was associated with the largest increase in annual hospital cost of £20,954 (£18,171, £23,737), followed by amputation (£17,887 [£15,326, £20,448]), intracranial haemorrhage (£12,080 [£8850, £15,310]) and GI tract cancer (£10,160 [£8947, £11,373]) (Figure 4.3). Myocardial infarction was associated with a cost of £4913 (£3640, £6186) and an additional £4521 (£2736, £6307) if urgent coronary revascularisation was performed in the same year. There was no evidence of an additional cost for vascular death if vascular events (myocardial infarction, coronary revascularisation, transient ischaemic attack, ischaemic stroke, heart failure) occurred in the same year. When no vascular event occurred in the same year, vascular death was associated with an additional cost of £2922 (£1726, £4118). Non-vascular death was associated with an additional cost of £2437 (£1108, £3765) if a non-vascular event (cancer, intracranial haemorrhage, GI bleed, other major bleed, amputation, ESRD) occurred in the same year, and £5935 (£5178, £6693) otherwise.

There was evidence of a lasting impact on cost for all adverse events except urgent coronary revascularisation and intracranial haemorrhage. Generally, the cost associated with an event declines significantly in subsequent years, holding all else constant. For example, the cost associated with GI tract cancer declines from £10,160 in the year of event, to £5149 (£3444, £6855) in the year after the event, and to £1260 (£683, £1837) in subsequent years. This was with the exception of ESRD, where the additional costs remained above £20,000 in years subsequent to the event (£28,894 [£25,612, £32,176] in year after the event and £20,090 [£16,729, £23,451] in subsequent years).

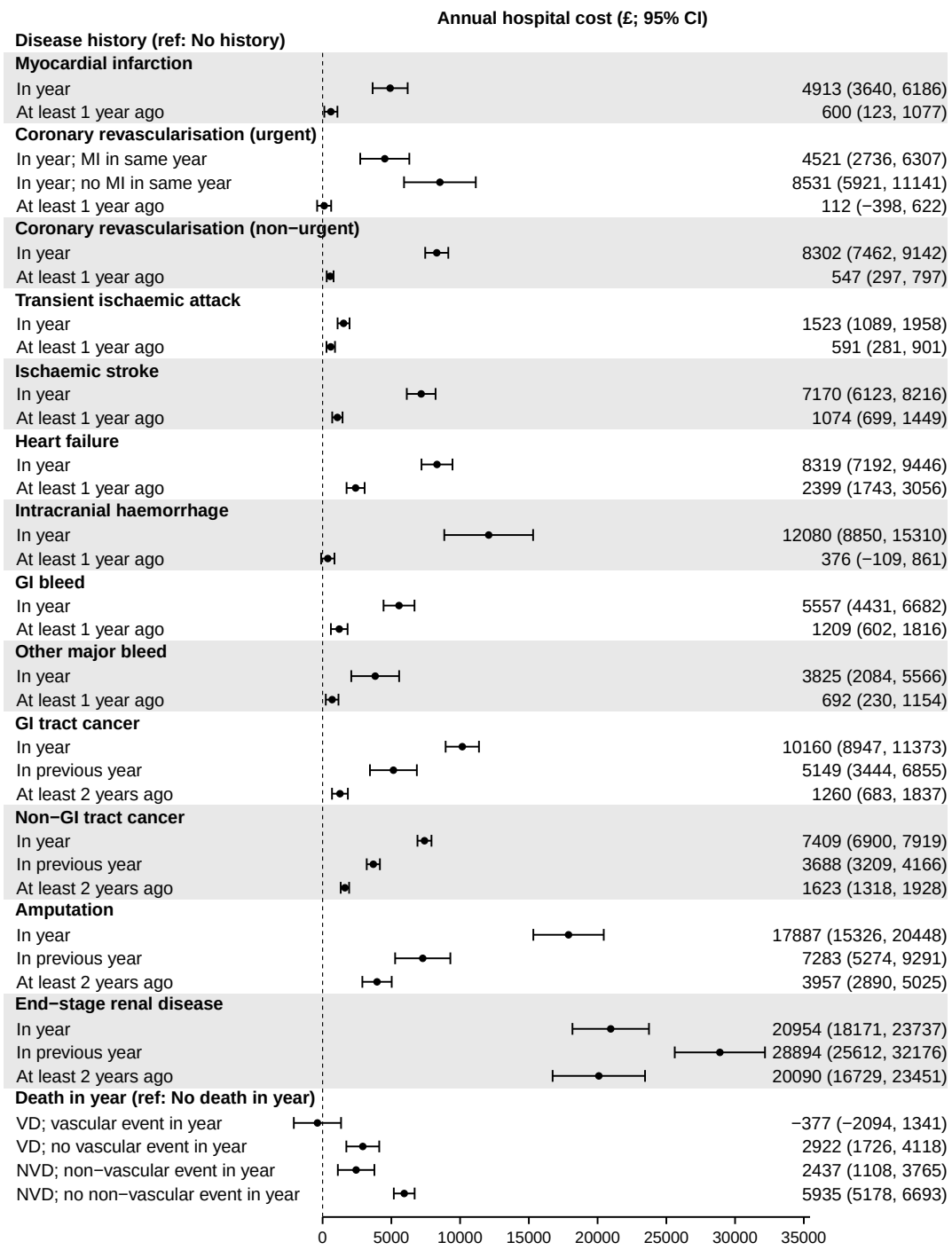


Figure 4.3: Annual hospital costs associated with adverse event, after adjusting for diabetes type, sex, Townsend index, age, BMI, diabetes duration, HbA1c, eGFR, presence of albuminuria, retinopathy, and censoring. GI, gastrointestinal; VD, vascular death; NVD, non-vascular death. 95% CIs calculated from standard errors

Annual hospital costs associated with other factors

Holding all else constant and adjusting for the occurrence of adverse events, higher annual hospital costs were associated with having type 1 instead of type 2 diabetes, being female, living in a region of greater socioeconomic deprivation, having higher BMI, longer duration of diabetes, higher HbA1c, decreased renal function, and having retinopathy. Annual hospital costs also increased with age. Relative to a 60-year-old and holding all else constant, the annual hospital costs of a 70- and 80-year-old were higher by £159 and £444, respectively, following adjustments for other covariates.

4.5 Discussion

4.5.1 Summary of results

The impacts of cardiovascular, bleeding, cancer, amputation, ESRD, and death events on annual hospital costs were estimated using an average of 7 years of data on more than 15,000 participants with diabetes from the ASCEND study. Holding all else constant, ESRD was associated with the largest acute impact on costs (£20,954), followed by amputation (£17,887), intracranial haemorrhage (£12,080) and GI tract cancer (£10,160). Vascular death with no vascular event in the same year was associated with additional costs of £2922. Non-vascular death was associated with additional costs of £2437 if a non-vascular event occurred in the same year and £5935 if not. Generally, most adverse events were also associated with increased hospital costs in subsequent years for surviving participants.

ESRD was the largest cost driver both in year and in subsequent years of event occurrence. The costs associated with ESRD remained above £20,000 in years subsequent to event occurrence, largely driven by the costs of maintenance dialysis. 13 (12%) of 105 participants with ESRD had a transplant within the trial duration, with 9 participants having a transplant within the first 2 years from the date of first record of ESRD. The proportion of participants on dialysis among those with ESRD decreased from 90% in the year after first record of ESRD to

74% after 4 years, among participants still being followed up. This is because more participants received a transplant with time and also possibly because of better survival among transplant recipients.

The excess hospital costs associated with each adverse events were estimated in additon to the excess costs associated with socio-demographic characteristics such as age, BMI, and duration of diabetes. For example, in contrast to someone with shorter duration of diabetes, someone with longer duration of diabetes would incur an additional excess hospital cost each year due to having more advanced diabetes to account for increased complexity of treatment in hospital and/or higher frequency of hospital visits.

4.5.2 Comparison with published estimates

Annual hospital costs associated with diabetes-related complications

Two other studies, Alva et al. (2015) and McMeekin et al. (2020), have previously analysed the impact of cardiovascular disease on costs in people with type 2 diabetes using patient-level data in the UK context [1, 4]. McMeekin et al. found cerebrovascular disease to be associated with the largest cost, while Alva et al. found stroke to be associated with the second largest cost (after ischaemic heart disease [excluding myocardial infarction]). Assuming approximately 80% of strokes are ischaemic [20], the combined impact of stroke on costs would be the largest among the cardiovascular events included in this study. Additionally, an impact of adverse events beyond the year of the event was observed, as was reported in both these studies as well as in several non-UK-based studies [21–24]. Although some parallels in trends could be drawn, comparison of the cost estimates themselves is less straightforward due to differences in populations, analytical approach and adverse event definitions. Similar cost estimates to those reported in Alva et al. for stroke, lower estimates for myocardial infarction and greater estimates for heart failure were found. The impact of coronary revascularisation on cost was estimated separately from myocardial infarction, which could explain the discrepancy in the estimates for myocardial infarction. The components of cost included in this

study (hospital inpatient, outpatient, and A&E records) were also different from those in Alva et al., which used patient-reported resource use for non-inpatient care. Additionally, the estimates of inpatient costs in Alva et al. were derived from hospital records between 1998 and 2007, but treatment patterns and costs have changed in the intervening years. Also, the costs of hospital episodes would have been captured more comprehensively in this study given the improvement in HES data quality over time [25].

Annual hospital costs associated with bleeding events

Limited studies on costs associated with bleeding in the UK context are available [26, 27], and none specific to people with diabetes. Ramagopalan et al. (2019) found GI bleed to be associated with excess cost of £3989 in the year of the bleed for patients with atrial fibrillation, which is smaller than what was found in ASCEND (£5557 [95% CI: £4431, £6682]). They found the excess cost to fall to £1816 in the following year, while £1209 (£602, £1816) in all subsequent years following the event was found in ASCEND. Campbell et al. (2015) estimated the initial inpatient costs for acute GI bleeding to be £2458. However, this does not account for subsequent hospital episodes that may be attributable to the bleed, which were included in the estimates in this study.

Annual hospital costs associated with other factors

People with type 1 diabetes were found to incur £149 greater annual hospital costs than those with type 2 diabetes, holding all else constant. A previous study looking at costs of hospital use for diabetes patients in the UK found that people with type 1 diabetes had about 1.5 times more outpatient attendances than people with type 2 diabetes, which the authors suggested could be attributable to larger numbers of eye and foot checks and management of renal complications for those with type 1 diabetes [28]. This agrees with observations in ASCEND, where participants with type 1 diabetes had a greater number of outpatient attendances

(5 vs 3 per person-year), with two to four times as many ophthalmology, diabetic medicine and nephrology consultations.

People living in areas in the greatest sociodemographic deprivation quintile were found to incur an additional £532 in hospital costs each year compared to those living in areas in the lowest sociodemographic deprivation quintile, even after adjusting for adverse event occurrences. Previous studies have found that socioeconomic gradients in healthcare costs were associated with increased morbidity [29, 30]. This finding suggests that there is excess morbidity among people living in the more deprived areas in addition to the clinical risk factors and adverse events included in the model.

4.5.3 Limitations

First, I did not have ASCEND individual participant data from the National Renal Dataset and instead applied an estimated average annual dialysis cost based on proportions of people on different dialysis modalities from the UK Renal Registry data [15], which has coverage of all renal centres in the UK. The variance in costs associated with ESRD may thus be under-estimated.

Second, I was unable to assess the excess costs associated with some common diabetes complications such as visual loss and hypoglycaemia as these events were not specifically sought in ASCEND. I was also unable to investigate further the effects of having multiple events. Other than myocardial infarction and urgent coronary revascularisation (n = 240), there were fewer than 35 participants who had other combinations of events co-occurring in the same year, too few to reliably assess interactions between these events. Additionally, given that the aim of the cost model is to enable predictions of costs associated with adverse events for use in cost-effectiveness analyses, interactions between patient characteristics (e.g. age and BMI) and disease history were not considered. Indeed, older patients may have more complications when hospitalised for a myocardial infarction for example, when compared to younger patients. This excess cost for the myocardial infarction event associated with age is not directly captured. Given the number of events of interest (15 in total), it is not feasible to include interactions between each

patient characteristic and each event. The chosen approach of accounting for excess costs associated with patient characteristics in addition to event occurrence should capture this excess cost indirectly, although it cannot be explicitly quantified.

Third, although no statistical difference was found between the estimates of the costs associated with adverse events for type 1 diabetes and type 2 diabetes when stratifying the analysis by diabetes type, this is likely due to the small number of participants with type 1 diabetes (6%) in the ASCEND cohort. Additionally, the ASCEND study population is largely of White ethnicity (97%), in contrast to 82% reported in a study of people with type 2 diabetes without cardiovascular disease identified from the general population in England [31]. Most other sociodemographic and clinical risk factors are similar between the two cohorts, and these factors are adjusted for in our model. However, there may be unobservable factors associated with differences in hospital costs across ethnic groups.

Fourth, an increase in uptake of modern diabetes medication including GLP-1 receptor agonists (1.5% at baseline to 3.3% at approximately 6.5 years into follow-up) and DPP-4 inhibitors (2.2% to 8.2%) was observed in ASCEND (Supplemental Table C.30), and these drugs have been shown to reduce HbA1c and possibly reduce re-hospitalisation rates after a cardiovascular event [32]. However, the diabetes care received by participants in ASCEND is not expected to be different from the general diabetes population, so these estimates should be generalisable.

Lastly, the analysis was limited to costs of hospital care and did not include costs of primary care use or prescriptions. However, previous studies that included these costs reported that the bulk of healthcare costs associated with complications for people with diabetes come from hospital use (more than 80% reported in McMeekin et al.) [4, 33].

4.5.4 Strengths and added value

The estimates in this study were derived from a large longitudinal patient-level dataset with more than 120,000 person-years of observations. This allowed reliable estimation of the acute and long-term impact on healthcare costs associated with

adverse events. This study also benefits from the high quality adverse events data reported in ASCEND. With the exception of heart failure, amputation and ESRD, all the other adverse events were clinically adjudicated. This made it possible, for example, to categorise strokes, which are usually sub-optimally recorded in routinely collected health data [34]. Our study is also the first to report costs associated with bleeding in people with diabetes in the UK. These estimates will be useful, for example, in evaluating the net benefits of antiplatelet treatments in people with diabetes where cardiovascular benefits need to be weighed against bleeding risks.

References

1. Alva ML, Gray A, Mihaylova B, Leal J, and Holman RR. The Impact of Diabetes-Related Complications on Healthcare Costs: New Results from the UKPDS (UKPDS 84). Diabet Med 2015;32:459–66. DOI: 10.1111/dme.12647.
2. Clarke P, Gray A, Legood R, Briggs A, and Holman R. The Impact of Diabetes-Related Complications on Healthcare Costs: Results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabetic Medicine 2003;20:442–50. DOI: 10.1046/j.1464-5491.2003.00972.x.
3. Govan L, Wu O, Briggs A, et al. Inpatient Costs for People with Type 1 and Type 2 Diabetes in Scotland: A Study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2011;54:2000–8. DOI: 10.1007/s00125-011-2176-7.
4. McMeekin P, Geue C, Mocevic E, et al. The Cost of Prevalent and Incident Cardiovascular Disease in People with Type 2 Diabetes in Scotland: Data from the Scottish Care Information–Diabetes Collaboration. Diabetic Medicine 2020;37:1927–34. DOI: 10.1111/dme.14253.
5. Capehorn M, Hallén N, Baker-Knight J, Glah D, and Hunt B. Evaluating the Cost-Effectiveness of Once-Weekly Semaglutide 1 Mg Versus Empagliflozin 25 Mg for Treatment of Patients with Type 2 Diabetes in the UK Setting. Diabetes Ther 2021;12:537–55. DOI: 10.1007/s13300-020-00989-6.
6. Johansen P, Chubb B, Hunt B, Malkin SJP, Sandberg A, and Capehorn M. Evaluating the Long-Term Cost-Effectiveness of Once-Weekly Semaglutide Versus Once-Daily Liraglutide for the Treatment of Type 2 Diabetes in the UK. Adv Ther 2020;37:2427–41. DOI: 10.1007/s12325-020-01337-7.
7. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, Dapagliflozin and Empagliflozin Monotherapy for Treating Type 2 Diabetes: Systematic Review and Economic Evaluation. Health Technol Assess 2017;21:1–218. DOI: 10.3310/hta21020.

8. Viljoen A, Hoxer CS, Johansen P, Malkin S, Hunt B, and Bain SC. Evaluation of the Long-term Cost-effectiveness of Once-weekly Semaglutide versus Dulaglutide for Treatment of Type 2 Diabetes Mellitus in the UK. Diabetes Obes Metab 2019;21:611–21. DOI: 10.1111/dom.13564.
9. Willis M, Nilsson A, Kellerborg K, et al. Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model. Diabetes Ther 2021;12:313–28. DOI: 10.1007/s13300-020-00968-x.
10. Health and Social Care Information Centre. HRG4+ 2017/18 Reference Costs Grouper. 2018. URL: https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/costing-hrg4-2017-18-reference-costs-grouper (visited on 08/25/2021).
11. NHS England and NHS Improvement. National Schedule of Reference Costs 2017/18. 2018. URL: https://webarchive.nationalarchives.gov.uk/ukgwa/20200501111106/https://improvement.nhs.uk/resources/reference-costs/ (visited on 08/25/2021).
12. Curtis LA and Burns A. Unit Costs of Health & Social Care 2020. Personal Social Services Research Unit, University of Kent, Canterbury. 2020. URL: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/ (visited on 05/05/2021).
13. National Institute for Health and Care Excellence. NICE Health Technology Evaluations: The Manual. 2022. URL: https://www.nice.org.uk/process/pmg36 (visited on 10/02/2022).
14. NHS England and NHS Improvement. 2021/22 National Tariff Payment System Annex C: Guidance on Best Practice Tariffs. 2021. URL: https://www.england.nhs.uk/wp-content/uploads/2020/11/21-22NT_Annex-C-Best-practice-tariffs.pdf (visited on 02/09/2022).
15. UK Renal Registry. UK Renal Registry 23rd Annual Report - Data to 31/12/2019. 2021. URL: https://ukkidney.org/sites/renal.org/files/23rd_UKRR_ANNUAL_REPORT.pdf (visited on 02/08/2022).
16. Pregibon D. Goodness of Link Tests for Generalized Linear Models. Journal of the Royal Statistical Society. Series C (Applied Statistics) 1980;29:15–4. DOI: 10.2307/2346405.
17. Hosmer DW, Lemeshow S, and Klar J. Goodness-of-Fit Testing for the Logistic Regression Model When the Estimated Probabilities Are Small. Biometrical Journal 1988;30:911–24. DOI: 10.1002/bimj.4710300805.
18. Park RE. Estimation with Heteroscedastic Error Terms. Econometrica 1966;34:888–8. DOI: 10.2307/1910108.
19. Bilger M and Manning WG. Measuring Overfitting in Nonlinear Models: A New Method and an Application to Health Expenditures. Health Econ 2015;24:75–85. DOI: 10.1002/hec.3003.

20. Bhatnagar P, Scarborough P, Smeeton NC, and Allender S. The Incidence of All Stroke and Stroke Subtype in the United Kingdom, 1985 to 2008: A Systematic Review. BMC Public Health 2010;10:539. DOI: 10.1186/1471-2458-10-539.

21. Chen HY, Kuo S, Su PF, Wu JS, and Ou HT. Health Care Costs Associated With Macrovascular, Microvascular, and Metabolic Complications of Type 2 Diabetes Across Time: Estimates From a Population-Based Cohort of More Than 0.8 Million Individuals With Up to 15 Years of Follow-up. Diabetes Care 2020;43:1732–40. DOI: 10.2337/dc20-0072.

22. Clarke PM, Glasziou P, Patel A, et al. Event Rates, Hospital Utilization, and Costs Associated with Major Complications of Diabetes: A Multicountry Comparative Analysis. PLOS Medicine 2010;7:e1000236. DOI: 10.1371/journal.pmed.1000236.

23. O'Brien JA, Shomphe LA, Kavanagh PL, Raggio G, and Caro JJ. Direct Medical Costs of Complications Resulting From Type 2 Diabetes in Hie U.S. Diabetes Care 1998;21:1122–8. DOI: 10.2337/diacare.21.7.1122.

24. Yang W, Cintina I, Hoerger T, et al. Estimating Costs of Diabetes Complications in People <65 years in the U.S. Using Panel Data. Journal of Diabetes and its Complications 2020;34:107735. DOI: 10.1016/j.jdiacomp.2020.107735.

25. Burns EM, Rigby E, Mamidanna R, et al. Systematic Review of Discharge Coding Accuracy. J Public Health (Oxf) 2012;34:138–48. DOI: 10.1093/pubmed/fdr054.

26. Campbell HE, Stokes EA, Bargo D, et al. Costs and Quality of Life Associated with Acute Upper Gastrointestinal Bleeding in the UK: Cohort Analysis of Patients in a Cluster Randomised Trial. BMJ Open 2015;5:e007230. DOI: 10.1136/bmjopen-2014-007230.

27. Ramagopalan SV, Samnaliev M, Weir S, Sammon CJ, Carroll R, and Alikhan R. Costs of Gastrointestinal Bleeding Events in Atrial Fibrillation: A UK Clinical Practice Research Datalink Study. Future Cardiology 2019;15:367–75. DOI: 10.2217/fca-2019-0033.

28. Stedman M, Lunt M, Davies M, et al. Cost of Hospital Treatment of Type 1 Diabetes (T1DM) and Type 2 Diabetes (T2DM) Compared to the Non-Diabetes Population: A Detailed Economic Evaluation. BMJ Open 2020;10:e033231. DOI: 10.1136/bmjopen-2019-033231.

29. Asaria M, Doran T, and Cookson R. The Costs of Inequality: Whole-Population Modelling Study of Lifetime Inpatient Hospital Costs in the English National Health Service by Level of Neighbourhood Deprivation. J Epidemiol Community Health 2016;70:990–6. DOI: 10.1136/jech-2016-207447.

30. Charlton J, Rudisill C, Bhattarai N, and Gulliford M. Impact of Deprivation on Occurrence, Outcomes and Health Care Costs of People with Multiple Morbidity. J Health Serv Res Policy 2013;18:215–23. DOI: 10.1177/1355819613493772.

31. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 Diabetes and Incidence of Cardiovascular Diseases: A Cohort Study in 1 · 9 Million People. The Lancet Diabetes & Endocrinology 2015;3:105–13. DOI: 10.1016/S2213-8587(14)70219-0.

32. Evans M, Chandramouli AS, Faurby M, Matthiessen KS, Mogensen PB, and Verma S. Healthcare Costs and Hospitalizations in US Patients with Type 2 Diabetes and Cardiovascular Disease: A Retrospective Database Study (OFFSET). Diabetes, Obesity and Metabolism 2022. DOI: 10.1111/dom.14703.

33. Einarson TR, Acs A, Ludwig C, and Panton UH. Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review. Value in Health 2018;21:881–90. DOI: 10.1016/j.jval.2017.12.019.

34. Morgan A, Sinnott SJ, Smeeth L, Minassian C, and Quint J. Concordance in the Recording of Stroke across UK Primary and Secondary Care Datasets: A Population-Based Cohort Study. BJGP Open 2021;5. DOI: 10.3399/BJGPO.2020.0117.

5

Decrements in health-related quality of life associated with adverse events in ASCEND

This chapter has been published in *Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, and ASCEND Study Collaborative Group. Decrements in Health-Related Quality of Life Associated with Adverse Events in People with Diabetes. Diabetes Obes Metab 2022;24:530–8. DOI: 10.1111/dom.14610.* At the time of publication, NICE's position statement [1] recommended the mapping function developed by van Hout et al. [2] (van Hout tariffs) for deriving EQ-5D utilities from EQ-5D-5L responses. The alternative set of tariffs developed by the NICE Decision Support Unit (DSU) [3] available then (DSU tariffs) were used for sensitivity analysis. NICE's guidelines for health technology assessments have since been updated [4] and the DSU tariffs generated using a new dataset [5] are now recommended. The updated analysis using the new DSU tariffs is now presented in this chapter as the main analysis, and the original analysis using the van Hout tariffs is presented in a sensitivity analysis.

Summary

Estimates of health-related quality of life (QoL) are used to quantify the health effects of interventions for health economics analysis. The last study which reported QoL estimates for a UK-based diabetes cohort is the UKPDS (QoL survey from 1996-2007), which may be outdated given improvements in management and treatment

of diabetes and related complications. In this chapter, I provide updated estimates of decrements in QoL associated with adverse events to inform the simulation model developed in the previous chapter using data from the ASCEND study. Participants' QoL utility measures were derived from the five-level EuroQoL five-dimensional (EQ-5D-5L) questionnaires completed by 11,683 ASCEND participants (76% of 15,480 recruited). EQ-5D utility decrements associated with adverse events were estimated using a linear regression model following adjustment for participants' sociodemographic and clinical risk factors. Lower-limb amputation was associated with the largest EQ-5D utility decrement (-0.205), followed by heart failure (-0.186), intracranial haemorrhage (-0.143), GI bleed (-0.091), other major bleed (-0.102), ischaemic stroke (-0.061), TIA (-0.069), and non-GI tract cancer (-0.028). There was no evidence of decrements in EQ-5D utility associated with myocardial infarction, coronary revascularisation, GI tract cancer, or ESRD, likely due to the low number of events.

5.1 Background

Quality-adjusted life-years (QALYs), a combined measure of life expectancy and health-related quality of life (QoL), is a widely adopted metric used to quantify the effectiveness of interventions [6]. In the UK, NICE requires health effects to be expressed in terms of QALYs for health technology assessments [4, 7]. Thus, decrements in QoL associated with adverse events are needed to inform cost-effectiveness models.

Estimates of decrements in QoL associated with common cardiovascular and microvascular complications in diabetes have been reported previously [8–18]. The last study that reported estimates for a UK-based cohort was the UKPDS, based on longitudinal QoL data collected from 1996 to 2007. These results may be outdated given improvements in management and treatments of diseases since then. Estimates from more recent multinational studies that include participants from the UK may not truly reflect the preferences of patients in the UK because of

regional variations in how people report their health status [19]. Using data from the ASCEND study, I provide updated results for the UK context, as well as first estimates for bleeding and cancer events in people with diabetes.

5.2 Measurement of health-related QoL

QoL for ASCEND participants was measured by utility scores derived from the five-level version of the EuroQoL five-dimensional (EQ-5D-5L) questionnaire [20]. The EQ-5D-5L questionnaire was mailed to participants towards the end of follow-up with responses collected during 2016 and 2017, an average of 6.7 years into study follow-up. The EQ-5D-5L questionnaire was only administered once[1], so only cross-sectional data were available for analysis. At the time the EQ-5D questionnaire was mailed, of the 15,480 participants in ASCEND, 2305 (14.9%) were lost to follow-up or followed up through administrative data only, and 1492 (9.6%) had died. 11,683 (75.5%) of the remaining participants were included in the analysis.

Participants were asked to rate their health across five domains—namely, mobility, self-care, usual activities, anxiety/depression, and pain—by selecting one of five possible levels: 'no problem', 'slight problems', 'moderate problems', 'severe problems', or 'extreme problems/unable to'. These responses were mapped onto EQ-5D utility values, with 1 representing perfect health, 0 representing a health state equivalent to death, and values less than 0 representing a health state worse than death. In line with NICE's latest guidelines on health technology evaluations [4], the EQ-5D utility values were calculated by mapping onto the UK EQ-5D-3L value set using the mapping function developed by Hernandez Alava et al. [5] (DSU tariff). Alternative tariff values developed by van Hout et al. [2] (van Hout tariff) recommended in NICE's previous position statement [1] were used in sensitivity analysis.

[1]The EQ-5D-5L was administered only once to reduce patient burden, and also in consideration of program budget prioritisation.

5.2.1 Imputing missing questionnaire responses

Of the 11,683 participants, 11,247 (96.3%) participants responded to the questionnaire, with 11,028 (98.1%) responding to all five domains (Table 5.1). Given the small percentage of missing questionnaire responses, missing data were imputed at the domain level by predictive mean matching using the method of multivariate imputation by chained equations, with 5 imputations and 10 iterations [21]. The most frequently occurring response across the 5 imputation datasets was used. Patient characteristics and clinical risk factors at baseline[2], age at questionnaire response, and history of adverse event occurrence at time of questionnaire were included in the imputation model. The questionnaire further included a visual analogue scale (VAS), where participants were asked to rate their health between 0 (labelled "the worst health you can imagine") and 100 (labelled "the best health you can imagine"). The VAS scores were included in the imputation model as well.

Table 5.1: Number (%) of participants included in analysis with missing EQ-5D response

EQ-5D response	N (%)
Did not respond	436 (3.7%)
Returned response	11247 (96.3%)
No. of domains missing among returned responses	
0	11028 (98.1%)
1	144 (1.3%)
2	30 (0.3%)
3	15 (0.1%)
4	9 (0.1%)
5	20 (0.2%)*

* Of the 20 participants who responded to the questionnaire with all 5 domains missing, 9 had a VAS score.

[2]Missing sociodemographic and clinical risk factors were imputed as described in Section 3.2.3.

5.3 Model specification

5.3.1 Variable selection

Candidate variables of the statistical model were: time since occurrence of adverse events as a categorical variable (no history, event occurred within 1 year prior to questionnaire response, and event occurred more than 1 year prior to questionnaire response), age and duration of diabetes at time of questionnaire response, and sociodemographic characteristics and clinical risk factors measured at recruitment into the trial[3]. Time since occurrence of adverse event was split into three levels to reflect the acute and long-term impacts on EQ-5D utility associated with the occurrence of adverse event [8, 13, 17, 18]. These levels were combined if there were fewer than 10 events in each level or if there was no evidence of a difference between acute and long-term decrements in EQ-5D utility based on the Wald test (p-value $\geq$ 0.05). Stepwise selection of covariates was performed based on the likelihood ratio test, with p-value < 0.1 and < 0.05 used for inclusion and exclusion, respectively.

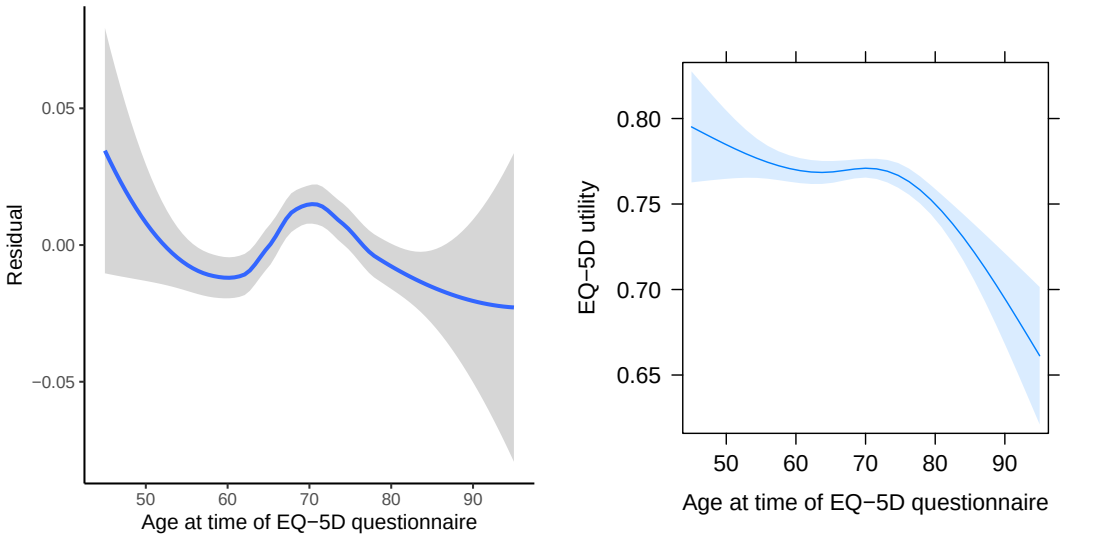
5.3.2 Non-linear relationship between age and EQ-5D utilities

The martingale residual of the model (model specification described in Section 5.3.3) including all covariates was plotted against age, and there were suggestions of a non-linear relationship between age and EQ-5D utility (Figure 5.1(a)). A natural cubic spline was fitted to explore the shape of the relationship. The shape of the spline fitted suggested that the polynomial form with degree 2 (quadratic polynomial)[4] or a linear spline with a knot at 70 might be appropriate functional forms for age (Figure 5.1(b)), both of which are easy to compute. The marginal effect of the polynomial form of age seems to match that of the natural cubic spline most closely

[3]The full list of variables is listed in Supplemental Table C.8.

[4]Polynomial form with degree 3 (cubic polynomial) was tested but did not offer significant benefit over the polynomial with degree 2 due to large uncertainty around the tails of the age distribution.

(Supplemental Table C.31). In terms of performance metrics (Supplemental Table C.32), all three models performed similarly. Hence, the polynomial form was selected.



(a) Martingale residual of age **(b)** Marginal effect of age (natural cubic spline)

Figure 5.1: Non-linear relationship between age and EQ-5D utility

5.3.3 Model selection

The EQ-5D utility data are positively skewed, with a high proportion of participants reporting full health (utility values close to 1; Supplemental Figure C.40). Hence, for modelling the EQ-5D utility decrements associated with adverse events, in addition to the frequently used ordinary least squares (OLS) regression, generalized linear models (GLMs) and beta regression model were also considered.

In terms of predictive performance, with the exception of the beta regression model, all other models performed similarly (Supplemental Table C.33). The beta regression model had significantly greater bias reflected in the mean prediction error (MPE), and this is consistent across deciles of predicted utility values (Supplemental Figure C.41). The Copas test, performed with 3-fold cross-validation repeated 1000 times, was used to assess the out-of-sample performance of the model [22]. Results from the Copas test (Supplemental Table C.34) suggest that the GLM with log link and Gamma distribution had poor out-of-sample performance. Other

models performed similarly. Accounting for all the above, the OLS was chosen for its predictive performance and for parsimony.

5.4 Results

5.4.1 Participant characteristics and questionnaire responses

The characteristics of the 11,683 participants included in the analysis are presented in Table 5.2 (see Supplemental Table C.35 for characteristics after imputation). 94% of participants included in the analysis had type 2 diabetes. At the time of EQ-5D questionnaire response, participants' mean age was 68 years and their median duration of diabetes was 14 years.

About 60% of participants reported some pain/discomfort, 40% reported some problems with mobility and performing usual activities, 30% reported some problems with depression/anxiety, and 15% reported some problems with self-care (Table 5.3). The mean EQ-5D utility across the cohort was 0.77, with 3110 (27%) participants reporting full health (Supplemental Table C.36). The mean EQ-5D utility for participants who did not experience an event was 0.78, decreasing to 0.71 and 0.68 for participants who had experienced one or two adverse events, respectively (Supplemental Table C.37). The adverse event that participants had experienced the most by the time of EQ-5D questionnaire response was non-GI tract cancer (677 [5.8%]), followed by TIA (214 [1.8%]), ischaemic stroke (198 [1.7%]), myocardial infarction (189 [1.6%]), non-urgent coronary revascularisation (187 [1.6%]), urgent coronary revascularisation (150 [1.3%]), GI tract cancer (119 [1.0%]), heart failure (105 [0.9%]), GI bleed (103 [0.8%]), other major bleed (70 [0.6%]), lower-limb amputation (60 [0.5%]), ESRD (42 [0.4%]), and intracranial haemorrhage (22 [0.2%]). The unadjusted mean EQ-5D utility stratified by time since occurrence of each adverse event is summarised in Figure 5.2 (also see Supplemental Table C.38).

Table 5.2: Characteristics of 11,683 participants included in the analysis

Variable	N (%), mean (SD) or median (IQR)
Participant characteristics at EQ-5D questionnaire response	
Age (years)	
Mean (SD)	68.5 (8.3)
Diabetes duration (years)	
Median (IQR)	13.6 (10.0, 19.2)
Missing	588 (5%)
Participant characteristics at entry into ASCEND study	
Diabetes type	
Type 1	707 (6.1%)
Type 2	10976 (93.9%)
Sex	
Male	7347 (62.9%)
Female	4336 (37.1%)
Smoking status	
Current smoker	813 (7%)
Former/Never smoker	10734 (91.9%)
Missing	136 (1.2%)
Race	
White	11282 (96.6%)
South Asian	147 (1.3%)
Black	86 (0.7%)
Other/unknown	168 (1.4%)
Townsend Index	
Q1: <-2.42 (least deprived)	5232 (44.8%)
Q2: ≥-2.42, <-0.44	2934 (25.1%)
Q3: ≥-0.44, < 1.79	1851 (15.8%)
Q4: ≥ 1.79, < 4.75	1237 (10.6%)
Q5: ≥ 4.75 (most deprived)	403 (3.4%)
Missing	26 (0.2%)
Hypertension	
Y	7173 (61.4%)
N	4435 (38%)
Missing	75 (0.6%)
Diabetic retinopathy	
Y	2232 (19.1%)
N	9359 (80.1%)
Missing	92 (0.8%)

Table 5.2: Characteristics of 11,683 participants included in the analysis *(continued)*

Variable	N (%), mean (SD) or median (IQR)
Statin use	
Y	8919 (76.3%)
N	2764 (23.7%)
Use of ACE Inhibitor or ARB	
Y	6818 (58.4%)
N	4865 (41.6%)
Age (years)	
Mean (SD)	62.8 (8.5)
Diabetes duration (years)	
Median (IQR)	7.0 (3.0, 12.0)
Missing	588 (5%)
Body-mass index (kg/m^2)	
Mean (SD)	31.0 (6.4)
Missing	82 (0.7%)
HbA1c (IFCC mmol/mol)	
Mean (SD)	54.4 (12.4)
Missing	4165 (35.7%)
HDL cholesterol (mmol/L)	
Mean (SD)	1.27 (0.35)
Missing	4175 (35.7%)
Non-HDL cholesterol (mmol/L)	
Mean (SD)	2.88 (0.83)
Missing	4175 (35.7%)
Systolic blood pressure (mmHg)	
Mean (SD)	135.9 (15.0)
Missing	3192 (27.3%)
Diastolic blood pressure (mmHg)	
Mean (SD)	77.3 (9.3)
Missing	3197 (27.4%)
Urinary albumin/creatinine ratio (mg/mmol)	
< 3	6644 (56.9%)
≥ 3	854 (7.3%)
Missing	4185 (35.8%)

Table 5.2: Characteristics of 11,683 participants included in the analysis *(continued)*

Variable	N (%), mean (SD) or median (IQR)
eGFR (ml/min/1.73m^2)	
< 45	209 (1.8%)
$\geq 45, < 60$	584 (5%)
$\geq 60, < 90$	3081 (26.4%)
≥ 90	3645 (31.2%)
Missing	4164 (35.6%)

Note:
Only 7589 (65%) participants returned usable blood/urine sample in the study. Mean (SD) and median (IQR) in table excludes missing data. Summary statistics after imputation can be found in Supplemental Table C.35.

Table 5.3: EQ-5D-5L questionnaire responses from 11,683 participants

	Mobility	Self-care	Usual activities	Pain/Discomfort	Anxiety/Depression
1 No problem	6212 (53.2%)	9494 (81.3%)	6868 (58.8%)	4204 (36%)	7905 (67.7%)
2 Slight problems	2453 (21%)	970 (8.3%)	2264 (19.4%)	4041 (34.6%)	2133 (18.3%)
3 Moderate problems	1641 (14%)	545 (4.7%)	1430 (12.2%)	2053 (17.6%)	923 (7.9%)
4 Severe problems	836 (7.2%)	137 (1.2%)	492 (4.2%)	768 (6.6%)	144 (1.2%)
5 Extreme problems/unable to	39 (0.3%)	16 (0.1%)	119 (1%)	111 (1%)	47 (0.4%)
Missing	502 (4.3%)	521 (4.5%)	510 (4.4%)	506 (4.3%)	531 (4.5%)

Note:
Summary values are N (%). Summary statistics after imputation can be found in Supplemental Table C.36.

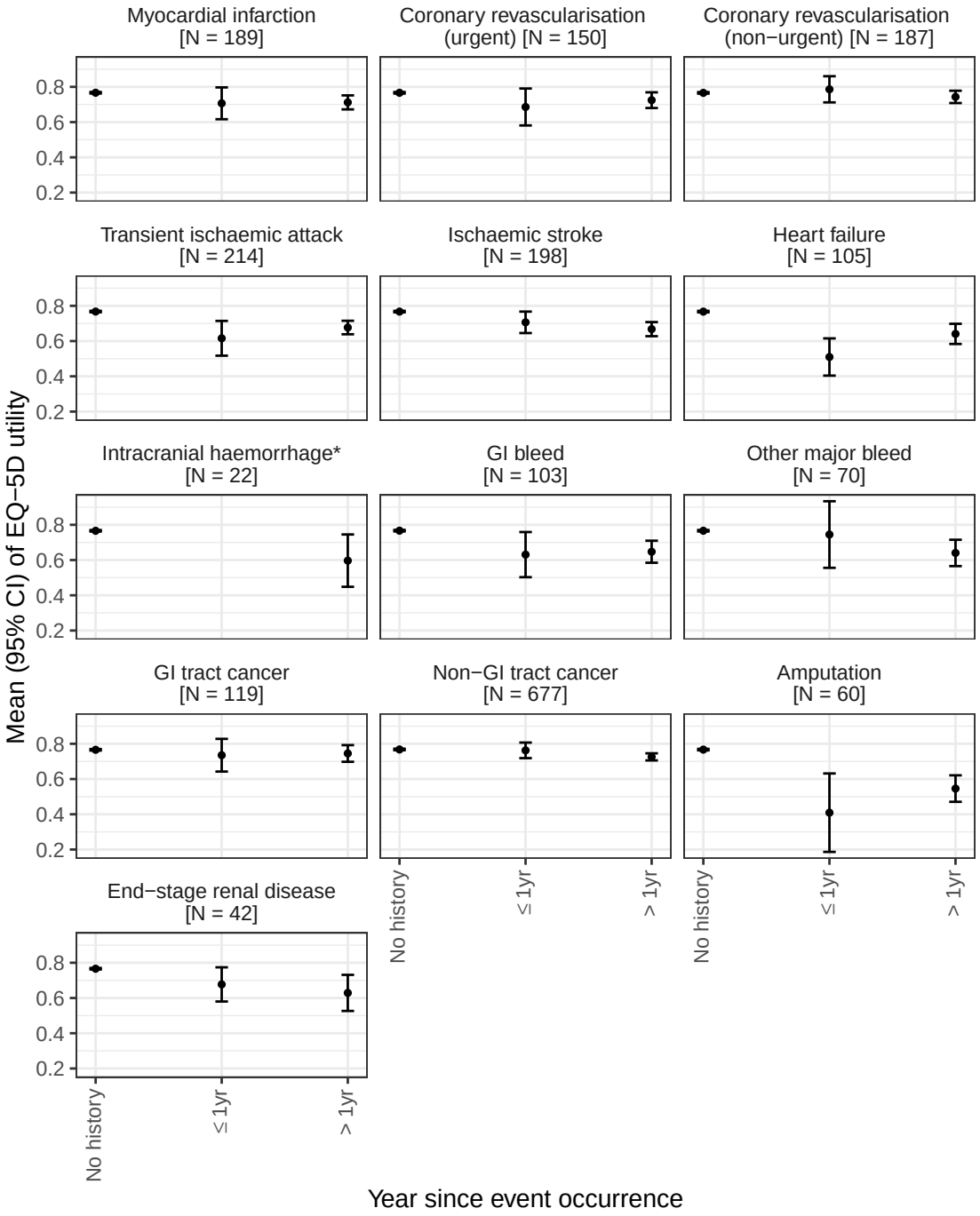


Figure 5.2: EQ-5D utility by adverse event and time since event occurrence. *For intracranial haemorrhage, there were too few participants who experienced an event within 1 year prior to EQ-5D response, so the EQ-5D utility was presented for participants who had experienced an event irrespective of time of event. $\leq$1 yr, an event occurred within 1 year prior to EQ-5D questionnaire response; >1 yr, an event occurred more than 1 year prior to EQ-5D questionnaire response. The number in brackets is the number of participants who had experienced each adverse event by the time of the EQ-5D questionnaire. 95% CIs calculated from standard errors obtained from 1000 bootstrap resampling of ASCEND participants

5.4.2 Model results

The mean EQ-5D utility value for a 70-year-old male[5] who is not a current smoker, living in the least deprived region, with BMI less than 25 kg/m^2, diabetes duration of less than 10 years, eGFR of 90 mL/min/1.73m^2 or higher, no albuminuria, and no disease history, was 0.910 (95% CI: 0.895, 0.925). Relative to this reference case, the decrements in EQ-5D utility associated with sociodemographic, clinical risk factors, and the occurrence of adverse events are presented in Table 5.4. Results were similar in the sensitivity analysis in which the van Hout tariffs were used to calculate the EQ-5D utility values instead of the DSU tariffs (Supplemental Table C.39).

Table 5.4: EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events

Variable	EQ-5D utility (95% CI)
(Intercept)	0.910 (0.895, 0.925)**
Sex (ref: Male)	
Female	-0.029 (-0.037, -0.020)**
Current smoker (ref: N)	
Y	-0.057 (-0.073, -0.041)**
Townsend index (ref: Q1 (least deprived))	
Q2	-0.010 (-0.020, -0.000)*
Q3	-0.044 (-0.056, -0.032)**
Q4	-0.075 (-0.089, -0.062)**
Q5 (most deprived)	-0.078 (-0.101, -0.056)**
Age at time of EQ-5D questionnaire (per 10 years, centered at 70)	
Age	-0.013 (-0.019, -0.007)**
Age^2	-0.007 (-0.011, -0.002)**
BMI (ref: <25 kg/m^2)	
≥25, <30	-0.033 (-0.046, -0.020)**
≥30, <35	-0.068 (-0.082, -0.055)**
≥35	-0.141 (-0.156, -0.126)**
Diabetes duration at time of EQ-5D questionnaire (ref: <10 years)	
≥10, <15	-0.012 (-0.023, -0.002)*
≥15, <25	-0.028 (-0.039, -0.017)**
≥25	-0.033 (-0.047, -0.019)**
eGFR (ref: ≥90 ml/min/1.73m^2)	

[5]Note that in the cost model in Chapter 4, age is centered at 60 years. Centering is based on the rounded mean age across the dataset.

Table 5.4: EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events *(continued)*

Variable	EQ-5D utility (95% CI)
≥60, <90	-0.031 (-0.041, -0.021)**
≥45, <60	-0.072 (-0.090, -0.054)**
<45	-0.084 (-0.114, -0.054)**
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)	
Y	-0.018 (-0.032, -0.004)**
Disease history (ref: no event)	
Transient ischaemic attack	
Any history	-0.069 (-0.100, -0.039)**
Ischaemic stroke	
Any history	-0.061 (-0.092, -0.029)**
Heart failure	
≤1yr	-0.186 (-0.266, -0.107)**
>1yr	-0.053 (-0.104, -0.003)*
Intracranial haemorrhage	
Any history	-0.143 (-0.236, -0.050)**
GI bleed	
Any history	-0.091 (-0.134, -0.048)**
Other major bleed	
Any history	-0.102 (-0.155, -0.050)**
Non-GI tract cancer	
Any history	-0.028 (-0.046, -0.011)**
Amputation	
Any history	-0.205 (-0.262, -0.149)**

Note:
**: p-value < 0.01; *: p-value < 0.05. ≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response. Intercept value gives the EQ-5D utility for the reference individual (male, not current smoker, living in least deprived region, aged 70, BMI <25kg/m^2, diabetes duration <10 years, eGFR ≥90ml/min/1.73m^2, no albuminuria, with no disease history). Model with all adverse events (including myocardial infarction, coronary revascularisation, GI tract cancer and end-stage renal disease) is presented in Supplemental Table C.39.

Decrements in EQ-5D utility associated with adverse events

Other than heart failure, there was no evidence of differential impacts of adverse events on EQ-5D utility between the acute phase (in year of event) and longer-term (in later years) (Figure 5.3). Overall, amputation was associated with the largest EQ-5D utility decrement (-0.205 [-0.262, -0.149]). For cardiovascular events, heart failure was associated with the largest EQ-5D utility decrement in the year of event (-0.186 [-0.266, -0.107]), but in subsequent years, its effect was smaller (-0.053 [-0.104, -0.003]). TIA (-0.069 [-0.100, -0.039]) and ischaemic stroke (-0.061 [-0.092, -0.029]) were associated with similar decrements in EQ-5D utility. Among bleeding-related events, intracranial haemorrhage was associated with the largest EQ-5D utility decrement (-0.143 [-0.236, -0.050]), followed by GI bleed (-0.091 [-0.134, -0.048]) and other major bleed (-0.102 [-0.155, -0.050]). Non-GI tract cancer was also associated with an EQ-5D utility decrement (-0.028 [-0.046, -0.011]). No decrements in EQ-5D utility were detected for myocardial infarction, coronary revascularisations, GI tract cancer, or ESRD, so these events were not included in the final model.

Decrements in EQ-5D utility associated with other factors

Independent of the occurrence of adverse events, being female, a smoker, living in a more deprived region, having higher BMI, a longer duration of diabetes, and decreased renal function, were all associated with lower EQ-5D utility. In particular, morbid obesity (BMI $\geq$ 35 kg/m^2) was associated with lower EQ-5D utility (-0.141 [-0.156, -0.126]) relative to normal weight (BMI $<$ 25 kg/m^2). A generally lower EQ-5D utility was also observed with increasing age. EQ-5D utility remained comparatively stable below 70 years of age (difference $<$0.010 from 50 to 70 years old), but then decreased beyond 70 years of age (Figure 5.1(b)). Following adjustments for other covariates, relative to a 70-year-old, the EQ-5D utility of an 80- and a 90-year-old was lower by -0.020 and -0.054, respectively.

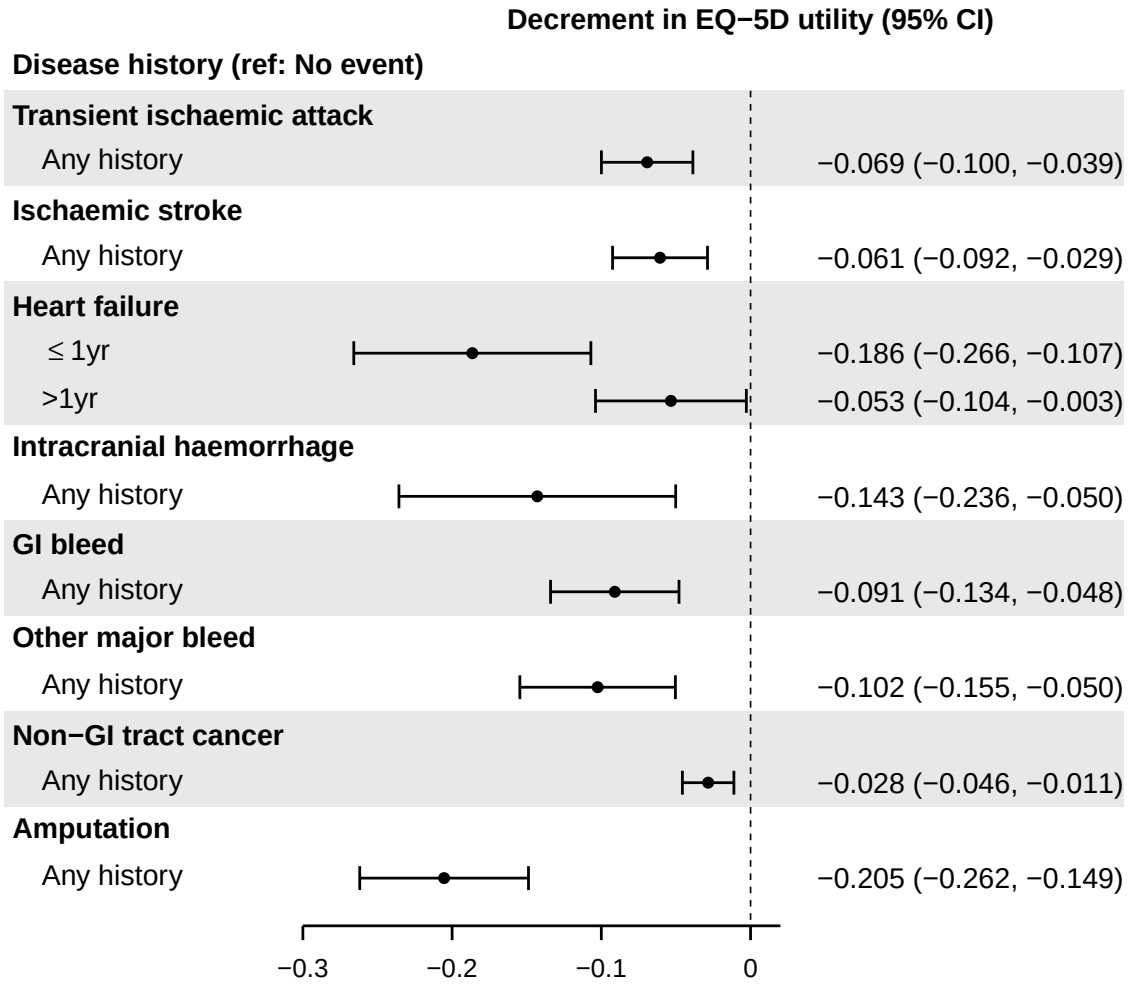


Figure 5.3: Decrements in EQ-5D utility associated with adverse event occurrence, after adjusting for sex, smoking status, age and diabetes duration at time of EQ-5D questionnaire, Townsend index, BMI, eGFR and presence of albuminuria. Full model can be found in Table 5.4. 95% CIs calculated from standard errors

5.5 Discussion

5.5.1 Summary of results

In this chapter, data from 11,683 participants in the ASCEND study were used to estimate the decrements in EQ-5D utility associated with cardiovascular, bleeding, cancer, amputation, and ESRD events. Amputation was found to be associated with the largest EQ-5D utility decrement (-0.205). This was followed by heart failure (-0.186), intracranial haemorrhage (-0.143), other major bleed (-0.102), GI bleed (-0.091), TIA (-0.069), ischaemic stroke (-0.061) and non-GI tract cancer

(-0.028). Following adjustments for participants' sociodemographic and clinical risk factors and the occurrence of other adverse events, there was no evidence of decrements in EQ-5D utility associated with myocardial infarction, coronary revascularisations, GI tract cancer, and ESRD.

5.5.2 Choice of model

OLS regression was selected for modelling EQ-5D utility for parsimony and because its performance was at least as good as other model specifications. One downside of using OLS regression for modelling EQ-5D utility is the possibility of predictions exceeding 1. However, the intercept value of the OLS regression is 0.910 and coefficients of the OLS regression for all variables of interest are negative relative to the reference individual, except for age < 70 years. The minimum age in ASCEND is 50 years, so the predicted EQ-5D utility for participants in the ASCEND cohort is at most 0.916 (at age 60). Even when accounting for uncertainty[6], the maximum utility value does not exceed 1.

Although NICE has expressed preference for a multiplicative approach to account for utility decrements [4], there was no case to justify the use of multiplicative models (i.e. log-link model) for the ASCEND data (see Section 5.3.3). Additionally, in the ASCEND primary prevention population, less than 3% of participants experienced 2 or more comorbid events. Hence, a multiplicative approach should not differ significantly from an additive approach [23].

5.5.3 Comparison with published estimates

EQ-5D-5L responses in 2018 Health Survey for England

The EQ-5D-5L responses from ASCEND participants (mean age 68 years at time of EQ-5D-5L response) were largely in line with EQ-5D-5L responses from adults aged 65-74 years in the 2018 Health Survey for England (HSE) [24]. Pain/discomfort was the most commonly reported problem, with about 60% of participants reporting at least some problems in both surveys. This was followed

[6]Re-estimated risk equations from 1000 bootstrap resampling (with replacement) of data.

by problems with mobility and usual activities, although these problems were more prevalent among ASCEND participants (for mobility, 42% in ASCEND vs 33% in HSE; for usual activities, 37% in ASCEND vs 25% in HSE). At least some problems with depression/anxiety and, separately, self-care, were reported by about 30% and 15% of participants in both surveys.

Decrements in health-related QoL associated with diabetes-related complications

Table 5.5 summarises the decrements in health-related QoL associated with diabetes-related complications reported in several previous studies [8–18]. The estimated decrements in QoL associated with myocardial infarction, stroke, and heart failure were somewhat smaller in more recent studies. For example, stroke was associated with -0.046 and -0.099 lower QoL in the LEADER [16] and ADVANCE [14] studies, respectively, in contrast to the larger -0.165 decrement in the older UKPDS study [8]. This may be a reflection of improvements in the treatment and management of cardiovascular disease over the years. In this study, which uses the latest QoL data, the estimated QoL decrement associated with heart failure was similar to other studies. This study is the first to differentiate the QoL decrement associated with ischaemic and haemorrhagic stroke. The QoL decrement associated with intracranial haemorrhage was found to be two times that of ischaemic stroke. Given that more than 80% of strokes are ischaemic strokes [25], the combined QoL decrement of stroke in this study would be roughly similar to estimates from other more recent studies.

Different from other studies, no evidence of an acute impact of myocardial infarction on QoL was found in this study, which could be because of the decreasing impact over time (a QoL decrement of -0.028 was reported in the ACCORD and Look AHEAD studies [17] in contrast to -0.065 in the UKPDS). In addition, there were only 34 myocardial infarction events in the year prior to the EQ-5D questionnaire response, which may be too small a number to detect a small effect. Also different from the ACCORD and Look AHEAD studies, there was no evidence

of differential impacts on QoL between the acute and longer-term periods following stroke and amputation in this study, possibly also because of the small number of events (42 ischaemic stroke events, 10 amputation events in the year prior to EQ-5D questionnaire response). A separate acute impact of heart failure (-0.183) was observed, although this was much larger in magnitude than estimated in the ACCORD and Look AHEAD studies (-0.051). It should be noted that the ACCORD and Look AHEAD studies used the Health Utilities Index Mark 3 (HUI-3) instrument to measure QoL, which may limit comparability.

The finding that amputation is associated with the largest QoL reduction is consistent with observations in other studies, although the QoL decrement observed in this study is considerably greater than those reported in other studies. In the model that included all disease histories (Supplemental Table C.39), the estimated QoL decrement associated with ESRD (-0.041 [-0.110, 0.028]) is similar to previous studies [14, 17]. However, this was not statistically significant, again possibly because there were only 42 people with ESRD and a QoL measurement in ASCEND. The QoL decrement associated with ESRD, therefore, may have not been reliably captured.

Table 5.5: Comparison of health-related QoL decrements associated with diabetes-related complications across diabetes studies

	ASCEND	ACCORD and Look AHEAD	ACCORD	LEADER	SAVOR-TIMI 53	ADVANCE	MEPS	UKPDS	TRIAD	Review (Beaudet et al., 2014)
Reference	-	[17]	[18]	[16]	[12]	[14]	[9]	[8]	[10]	[11]
No. of participants	11,683	15,252	8,713	3,014	16,488	11,130	20,705	3,380	7,327	-
Repeated measures of QoL	N	Y	Y	Y	Y	Y	N	Y	N	-
Years QoL survey conducted	2016/2017	2001-2012	2001-2012	2010-2015	2010-2013	2001-2008	2000-2011	1996-2007	2000/2001	-
Previous CVD	0%	35% (ACCORD); 14% (Look AHEAD)	35%	81%	79%	32%	-	-	31%	-
Instrument	EQ-5D	HUI-3	HUI-3	EQ-5D	EQ-5D	EQ-5D	EQ-5D; SF-12	EQ-5D	EQ-5D	-
Model	OLS	FE	FE	Mixed effects	Descriptive	FE	Median regression	FE	OLS	-

Table 5.5: Comparison of health-related QoL decrements associated with diabetes-related complications across diabetes studies *(continued)*

	ASCEND	ACCORD and Look AHEAD	ACCORD	LEADER	SAVOR-TIMI 53	ADVANCE	MEPS	UKPDS	TRIAD	Review (Beaudet et al., 2014)
Disease history (ref: no event)										
Myocardial infarction										
Any history	(NS)	-	-	0.004 (NS)	-0.051	-0.026	-0.047	-	-0.019*	-0.055
≤1yr	-	-0.028	-0.018	-	-	-	-	-0.065	-	-
>1yr	-	-0.006 (NS)	-	-	-	-	-	0.008 (NS)	-	-
Revascularisation										
Any history	(NS)	-	-	-	-	-	-	-	-	-
≤1yr	-	-0.005 (NS)	-0.013	-	-	-	-	-	-	-
>1yr	-	-0.001 (NS)	-	-	-	-	-	-	-	-
TIA										
Any history	-0.057 (-0.100, -0.039)	-	-	-	-	-	-0.07	-	-0.029	-
≤1yr	-	-	-	-	-	-	-	-	-	-
>1yr	-	-	-	-	-	-	-	-	-	-
Stroke										
Any history	-0.077†	-	-	-0.046	-0.111	-0.099	-0.06	-0.165	-0.035	-0.164
≤1yr	-	-0.109	-0.202	-	-	-	-	-	-	-
>1yr	-	-0.051	-	-	-	-	-	-	-	-
Heart failure‡										

Table 5.5: Comparison of health-related QoL decrements associated with diabetes-related complications across diabetes studies *(continued)*

	ASCEND	ACCORD and Look AHEAD	ACCORD	LEADER	SAVOR-TIMI 53	ADVANCE	MEPS	UKPDS	TRIAD	Review (Beaudet et al., 2014)
Any history	-	-	-	-0.055	-0.065	-0.045	-0.05	-0.101	-0.042	-0.108
≤1yr	-0.186 (-0.266, -0.107)	-0.051	-0.067	-	-	-	-	-	-	-
>1yr	-0.053 (-0.104, -0.003)	-0.041	-	-	-	-	-	-	-	-
Amputation										
Any history	-0.205 (-0.262, -0.149)	-	-	-	-	-0.122	-0.095	-0.172	-0.108	-0.28
≤1yr	-	-0.092	-	-	-	-	-	-	-	-
>1yr	-	-0.15	-	-	-	-	-	-	-	-
ESRD										
Any history	(NS)	-	-0.029	-	-	-0.049	-0.038[§]	-	-0.06	-0.164
≤1yr	-	-0.039	-	-	-	-	-	-	-	-
>1yr	-	-0.015	-	-	-	-	-	-	-	-

Note:
NS, Effect is not statistically significant at p-value < 0.05. ≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response.

[*] Coronary heart disease other than heart failure

[†] The combined estimate of QoL decrement associated with ischaemic stroke (-0.061 [-0.092, -0.029]) and intracranial haemorrhage (-0.143 [-0.236, -0.050]), assuming 80% of strokes are ischaemic strokes.

[‡] Refers to hospitalisation for heart failure in ACCORD, Look AHEAD, LEADER, ADVANCE, SAVOR-TIMI 53 studies

[§] Nephropathy including ESRD

Decrements in health-related QoL associated with bleeding events

There are a limited number of studies reporting decrements in health-related QoL associated with bleeding events [26–28], and none specific to people with diabetes. These are summarised in Table 5.6. The decrements in QoL associated with bleeding events in ASCEND (GI bleed -0.091, other major bleed -0.102) were larger than those reported in other studies (e.g. in ENGAGE AF-TIMI 48 [28], -0.029 at 3 months after GI bleed, -0.029 at 3 months after other major extracranial bleed; in TRANSLATE-ACS [26], -0.0381 after Bleeding Academic Research Consortium [BARC] type 2-4 bleed). Participants in both these studies had previous cardiovascular disease, so the additional change in QoL from a bleeding event on top of their existing cardiovascular disease could be lower than in people who did not previously have cardiovascular disease, as in ASCEND. Interactions between bleeding and cardiovascular disease events were not explored in this study as there were fewer than 10 participants who had both bleeding and cardiovascular events prior to the EQ-5D questionnaire.

Table 5.6: Comparison of health-related QoL decrements associated with bleeding events across studies

	ASCEND	TRANSLATE-ACS	ENGAGE AF-TIMI 48
Reference	-	[26]	[28]
No. of participants	11,683	9,290	10,706
Study population	Patients with diabetes without previous vascular disease, treatment arm assigned to aspirin use	Patients on dual antiplatelet therapies after percutaneous coronary intervention for acute myocardial infarction	Patients with atrial fibrillation on antiplatelet therapies
Repeated measures of QoL	N	Y	Y
Years QoL survey conducted	2016/2017	2010-2012	2008-2013
Instrument	EQ-5D	EQ-5D	EQ-5D
Model	OLS	Mixed effect	Mixed effect
Disease history (ref: no event)			
Any major bleed			
Any history	-	-	-
≤1yr	-	BARC 2-4, at 6 months: -0.0381; BARC 3-4, at 6 months: -0.0445	-
>1yr	-	-	-
Intracranial haemorrhage			
Any history	-0.143 (-0.236, -0.050)	-	-
≤1yr	-	-	-
>1yr	-	-	-

Table 5.6: Comparison of health-related QoL decrements associated with bleeding events across studies *(continued)*

	ASCEND	TRANSLATE-ACS	ENGAGE AF-TIMI 48
Gastrointestinal bleed			
Any history	-0.091 (-0.134, -0.048)	-	-
≤1yr	-	-	At 3 months: -0.029
>1yr	-	-	At 12 months: -0.010
Other major bleed			
Any history	-0.102 (-0.155, -0.050)	-	-
≤1yr	-	-	At 3 months: -0.029
>1yr	-	-	At 12 months: (NS)

Note:
BARC, Bleeding Academic Research Consortium's definition for bleeding types (type 2 and above are "actionable" bleeds requiring healthcare intervention). ≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. In ASCEND, other major bleed also excludes eye bleeds.

Decrements in health-related QoL associated with other factors

An association between obesity and lower health-related QoL independent of co-morbid conditions was observed. In particular, the QoL decrement from being morbidly obese relative to being of normal weight is even more pronounced than experiencing an ischaemic stroke. This is concordant with previous reports [9, 10, 29], with findings suggesting that obesity in itself may impair physical functioning and cause health distress, leading to lower QoL, irrespective of obesity-related co-morbidities.

The QoL decline with older age observed in this study, in addition to the occurrence of disease events, was previously reported in the ADVANCE study [14]. However, the impact observed in this study is much smaller. For example, compared to a 70-year-old patient, an 80-year-old patient (all other factors being the same) has 0.03 lower QoL (inclusive of the effect of increasing duration of diabetes) in contrast to 0.08 lower QoL reported in ADVANCE. This could be a reflection of the generally healthier patient population in ASCEND, which recruited people without previous cardiovascular disease, in contrast to ADVANCE, where 32% of participants had cardiovascular disease at entry.

5.5.4 Limitations

In addition to temporal changes in impacts on health-related QoL from improvements in healthcare, differences in population characteristics, and differences in the instruments used to measure QoL that have been described above, another key factor that could contribute to differences in estimates observed in ASCEND and other studies is the methodology used. Studies with repeated measures of QoL could control for unobserved variation of QoL across participants (e.g. people with lower QoL independent of modelled characteristics and disease history experiencing an adverse event) by using fixed effects models, for example. This typically results in smaller estimates of QoL decrements associated with adverse events [8, 14]. Only one measure of QoL per participant was available in ASCEND, which could be a

reason for the larger estimated QoL decrements associated with amputation and bleeding events than those reported in other studies [14, 17, 26, 28].

Another limitation of the study is that participants who died prior to QoL measurement could not contribute to the study, so there may be survival bias. In applications, QoL is evaluated concurrently with survival in assessing the net effects of treatments, and this analysis is in line with how these estimates are intended for use. This does assume that the QoL decrements estimated also apply to those participants who have since died while they were still alive. This may not be true if, for example, participants who survived have experienced a better recovery from adverse events, and thus may rate their health more positively than participants who experienced an event and later died. Secondly, there may be volunteer bias where healthier or more health-conscious people were enrolled into the study, and these people may adhere to medical treatments better than the average person with diabetes. This is a common problem across QoL studies using clinical trial data, and it is difficult to quantify the impact this has on the results.

Thirdly, I have chosen to model the decrements in QoL using the generalised linear model framework. Other methods are also available, and in particular a mixture model approach has been developed specifically for analysing utility data [30]. This method accounts for typical features of utility data including limits (utility bounded between -0.594 and 1 for UK tariffs), gaps (gap between mass at 1 and next feasible value at 0.883 for UK tariffs), and multi-modal distributions (mass at 1, high degree of skewness). The model assumes that participants in the dataset belong in different classes, estimated using a multinomial logit model, with utility values in each class following a tobit-like distribution. I have previously fitted a two-part model (similar to a mixture model with two classes (people in full health vs people not in full health), but with class membership estimated using a logit distribution and utility values in each class estimated using a generalised linear model framework) and demonstrated no significant benefit over a simpler one-part

model for the ASCEND data[7] [31]. I acknowledge that formal testing would have been useful to assess the extent of added value of different approaches (as with the two-part model). However, the single-equation model approach was ultimately used for simplicity of interpretation, and adoption in a cost-effectiveness framework[8].

Lastly, interactions between different complications were not investigated because of the small number of co-occurring events. The most frequent co-occurring events in ASCEND were myocardial infarction and urgent coronary revascularisations (N = 140), and stroke and TIA (N = 44). No significant interactions were detected between these events. There were fewer than 20 co-occurrences of all other event combinations. Previous studies have not found significant interactions between events, suggesting that the additive specification of the effects of experiencing multiple conditions may be justified [8, 14].

5.5.5 Strengths and added value

Despite the limitations described, this study benefits from the high quality of data in ASCEND. Other than heart failure, amputation, and ESRD, all other endpoints were clinically adjudicated. There was also good completeness of the EQ-5D-5L questionnaire, with 94% of participants included in the analysis responding to all five domains of the EQ-5D questionnaire. Additionally, ASCEND consisted exclusively of participants from the UK. This mitigates the issue of regional variations in how people report their health status that has been reported previously [19],

[7]A two-part model was fitted previously when the van Hout tariffs was used. The first part of the model predicted the likelihood of perfect health for an individual (QoL of 1), while the second part of the model, conditional on imperfect health (QoL not 1), predicted the utility value associated with an individual given their characteristics and disease history. However, with the DSU tariffs, QoL might vary even when patients report perfect health and the tariffs are calculated conditional on age and sex. Hence, I did not use two-part models for the DSU tariffs.

[8]In a cost-effectiveness framework, the interest is in the utility decrement associated with an event. In a mixed model approach, an event affects the likelihood of class membership, and also affects the underlying distribution of utilities within each class. In patient-level simulation models, the prediction of utilities can be performed at an individual level-event basis using the mixed model equations directly. However, in an aggregate model, the average utility (or utility decrement) associated with each health state is needed, and this is not straightforward to interpret from the mixed model

which may affect estimates from multinational studies like LEADER, SAVOR-TIMI 53, and ADVANCE.

This study provides the latest estimates of QoL decrements associated with a wide range of adverse events in people with diabetes, particularly for the UK context, where the last study was the UKPDS with QoL surveys conducted from 1996 to 2007. This study is also the first to report separate estimates for ischaemic stroke and intracranial haemorrhage, as well as estimates for bleeding events for people with diabetes. These estimates will be useful, for example, in evaluating the net benefits of antiplatelet and anticoagulant treatments in people with diabetes where cardiovascular benefits need to be weighed against bleeding risks.

References

1. National Institute for Health and Care Excellence. Position Statement on Use of the EQ-5D-5L Value Set for England (Updated October 2019). 2019. URL: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (visited on 11/05/2020).
2. Van Hout B, Janssen MF, Feng YS, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value Health 2012 Jul-Aug;15:708–15. DOI: 10.1016/j.jval.2012.02.008.
3. Hernandez-Alava M, Wailoo A, and Pudney S. Methods for Mapping between the EQ-5D-5L and the 3L for Technology Appraisal. Decision Support Unit, 2017.
4. National Institute for Health and Care Excellence. NICE Health Technology Evaluations: The Manual. 2022. URL: https://www.nice.org.uk/process/pmg36 (visited on 10/02/2022).
5. Hernandez-Alava M, Pudney S, and Wailoo A. Estimating the Relationship between EQ-5D-5L and EQ-5D-3L: Results from an English Population Study. Report 063. Policy Research Unit in Economic Evaluation of Health and Care Interventions: Universities of Sheffield and York, 2020.
6. Kind P, Lafata JE, Matuszewski K, and Raisch D. The Use of QALYs in Clinical and Patient Decision-Making: Issues and Prospects. Value Health 2009;12 Suppl 1:S27–30. DOI: 10.1111/j.1524-4733.2009.00519.x.
7. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. 2013. URL: https://www.nice.org.uk/process/pmg9/ (visited on 09/19/2019).
8. Alva M, Gray A, Mihaylova B, and Clarke P. The Effect of Diabetes Complications on Health-Related Quality of Life: The Importance of Longitudinal Data to Address Patient Heterogeneity. Health Economics 2014;23:487–500. DOI: 10.1002/hec.2930.

9. Sullivan PW and Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. Value in Health 2016;19:1002–8. DOI: 10.1016/j.jval.2016.05.018.

10. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, and Herman WH. Health Utility Scores for People With Type 2 Diabetes in U.S. Managed Care Health Plans: Results from Translating Research Into Action for Diabetes (TRIAD). Diabetes Care 2012;35:2250–6. DOI: 10.2337/dc11-2478.

11. Beaudet A, Clegg J, Thuresson PO, Lloyd A, and McEwan P. Review of Utility Values for Economic Modeling in Type 2 Diabetes. Value in Health 2014;17:462–70. DOI: 10.1016/j.jval.2014.03.003.

12. Briggs AH, Bhatt DL, Scirica BM, et al. Health-Related Quality-of-Life Implications of Cardiovascular Events in Individuals with Type 2 Diabetes Mellitus: A Subanalysis from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-TIMI 53 Trial. Diabetes Research and Clinical Practice 2017;130:24–33. DOI: 10.1016/j.diabres.2016.12.019.

13. Clarke P, Gray A, and Holman R. Estimating Utility Values for Health States of Type 2 Diabetic Patients Using the EQ-5D (UKPDS 62). Med Decis Making 2002 Jul-Aug;22:340–9. DOI: 10.1177/0272989X0202200412.

14. Hayes A, Arima H, Woodward M, et al. Changes in Quality of Life Associated with Complications of Diabetes: Results from the ADVANCE Study. Value in Health 2016;19:36–41. DOI: 10.1016/j.jval.2015.10.010.

15. Lung TWC, Hayes AJ, Hayen A, Farmer A, and Clarke PM. A Meta-Analysis of Health State Valuations for People with Diabetes: Explaining the Variation across Methods and Implications for Economic Evaluation. Qual Life Res 2011;20:1669–78. DOI: 10.1007/s11136-011-9902-y.

16. Nauck MA, Buse JB, Mann JFE, et al. Health-Related Quality of Life in People with Type 2 Diabetes Participating in the LEADER Trial. Diabetes, Obesity and Metabolism 2019;21:525–32. DOI: 10.1111/dom.13547.

17. Neuwahl SJ, Zhang P, Chen H, et al. Patient Health Utility Equations for a Type 2 Diabetes Model. Diabetes Care 2021;44:381–9. DOI: 10.2337/dc20-1207.

18. Shao H, Yang S, Fonseca V, Stoecker C, and Shi L. Estimating Quality of Life Decrements Due to Diabetes Complications in the United States: The Health Utility Index (HUI) Diabetes Complication Equation. Pharmacoeconomics 2019;37:921–9. DOI: 10.1007/s40273-019-00775-8.

19. Salomon JA, Patel A, Neal B, et al. Comparability of Patient-reported Health Status: Multicountry Analysis of EQ-5D Responses in Patients With Type 2 Diabetes. Medical Care 2011;49:962–70. DOI: 10.1097/MLR.0b013e3182239489.

20. Herdman M, Gudex C, Lloyd A, et al. Development and Preliminary Testing of the New Five-Level Version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36. DOI: 10.1007/s11136-011-9903-x.

21. White IR, Royston P, and Wood AM. Multiple Imputation Using Chained Equations: Issues and Guidance for Practice. Stat Med 2011;30:377–99. DOI: 10.1002/sim.4067.

22. Bilger M and Manning WG. Measuring Overfitting in Nonlinear Models: A New Method and an Application to Health Expenditures. Health Econ 2015;24:75–85. DOI: 10.1002/hec.3003.

23. Cure S, Despiégel N, and Guerra I. Impact of Using Either Multiplicative or Additive Utility Decrements in Decision Models. Value in Health 2013;16:A579. DOI: 10.1016/j.jval.2013.08.1579.

24. Scholes S and Gebert S. Health Survey for England 2018: Adult Health. NHS Digital. 2019. URL: https://files.digital.nhs.uk/E4/DAA235/HSE18-Adult-Health-rep.pdf (visited on 09/29/2021).

25. Bhatnagar P, Scarborough P, Smeeton NC, and Allender S. The Incidence of All Stroke and Stroke Subtype in the United Kingdom, 1985 to 2008: A Systematic Review. BMC Public Health 2010;10:539. DOI: 10.1186/1471-2458-10-539.

26. Amin AP, Wang TY, McCoy L, et al. Impact of Bleeding on Quality of Life in Patients on DAPT: Insights From TRANSLATE-ACS. J Am Coll Cardiol 2016;67:59–65. DOI: 10.1016/j.jacc.2015.10.034.

27. Doble B, Pufulete M, Harris JM, et al. Health-Related Quality of Life Impact of Minor and Major Bleeding Events during Dual Antiplatelet Therapy: A Systematic Literature Review and Patient Preference Elicitation Study. Health Qual Life Outcomes 2018;16:191. DOI: 10.1186/s12955-018-1019-3.

28. Wang K, Li H, Kwong WJ, et al. Impact of Spontaneous Extracranial Bleeding Events on Health State Utility in Patients with Atrial Fibrillation: Results from the ENGAGE AF-TIMI 48 Trial. Journal of the American Heart Association 2017;6:e006703. DOI: 10.1161/JAHA.117.006703.

29. Hlatky MA, Chung SC, Escobedo J, et al. The Effect of Obesity on Quality of Life in Patients with Diabetes and Coronary Artery Disease. American Heart Journal 2010;159:292–300. DOI: 10.1016/j.ahj.2009.11.004.

30. Alava MH and Wailoo A. Fitting Adjusted Limited Dependent Variable Mixture Models to EQ-5D. The Stata Journal 2015;15:737–50. DOI: 10.1177/1536867X1501500307.

31. Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, and ASCEND Study Collaborative Group. Decrements in Health-Related Quality of Life Associated with Adverse Events in People with Diabetes. Diabetes, Obesity and Metabolism 2022;24:530–8. DOI: 10.1111/dom.14610.

6

Lifetime cost-effectiveness of aspirin for primary prevention of cardiovascular disease in people with diabetes

Summary

To demonstrate an application of the decision model developed in this thesis, I assessed the cost-effectiveness of aspirin for the primary prevention of cardiovascular disease in people with diabetes. Aspirin use has been shown to reduce cardiovascular risk but also increase the risk of bleeding. The net benefit of aspirin use for people with diabetes without previous cardiovascular disease is uncertain. Using the framework developed in the previous chapters and using the latest evidence for the effects of aspirin available, I assessed the net benefit of aspirin on costs and quality of life in the cohort of UK Biobank participants identified to have diabetes without previous cardiovascular disease.

Using evidence from the ASCEND study and from meta-analyses of trials of aspirin in primary prevention, aspirin was found to have a 92% and 78% chance, respectively, of being cost-effective at a willingness-to-pay threshold of £20,000/quality-adjusted life year (QALY). At this threshold, the expected value of perfect information for the UK over 10 years was estimated to be £240 million and £500 million, respectively. Small net gains in QALY (discounted at 3.5% per annum) of 0.100 and 0.026 over lifetime, respectively, were projected with aspirin compared to no aspirin use, although these estimates were not statistically

significant after accounting for uncertainties around the treatment effects of aspirin. Results were similar in subgroups of participants by sex and age, cardiovascular risk, and bleeding risk. Results from scenario analyses demonstrated that a large proportion of benefits was lost with stopping aspirin after a period of use compared to lifetime use, and this finding does not support previous recommendations of stopping aspirin at age 75 based on the 2022 US Preventive Service Task Force modelling study. The magnitude of benefit with aspirin importantly depended on its effects on mortality, but significant uncertainty remains around aspirin's net effect on mortality. Further studies in progress will help strengthen the evidence.

6.1 Background

Aspirin is a widely used antithrombotic drug. In people who already have a history of cardiovascular disease, the benefits of aspirin use in reducing the risks of serious vascular events substantially exceed the risk of bleeding [1]. However, for people who have not experienced a cardiovascular event, the balance between benefits and risks is less clear as the absolute risk of cardiovascular disease and thus the absolute benefits with aspirin are generally lower. This is true even for people with diabetes who are at higher risk of cardiovascular disease. In the randomised controlled trial ASCEND, allocation to 100mg daily aspirin was found to reduce the risks of serious vascular events from 9.6% to 8.6%, but increased the risks of major bleeding events from 3.2% to 4.1% [2]. To add to the uncertainty, although aspirin had no impact on cancer in ASCEND (average 7.4 years of follow-up), previous observational post-trial follow-up of a small number of trials have reported aspirin to be associated with a reduction in the risk of GI tract cancer which was evident only approximately 7 to 10 years after initiation [3–6].

In current guidelines for aspirin use in the primary prevention of cardiovascular disease [7–10], the general consensus is to not routinely prescribe aspirin, but to consider it for patients who are at high cardiovascular risk but not at increased risk of bleeding. There is no clear definition of who to prescribe aspirin to, with

6. Cost-effectiveness of aspirin

NICE recommending aspirin to be considered for "people with high risk of stroke or myocardial infarction", while the American College of Cardiology/American Heart Association recommends aspirin for "select adults aged 40 to 70 years at higher risk of cardiovascular disease but not at increased risk of bleeding". The US Preventive Service Task Force (USPSTF) advises that aspirin could be initiated in adults aged 40 to 59 years with 10% or greater 10-year risk of cardiovascular disease [11]. Primary care providers are thus tasked with making individual clinical judgements, and communicating benefit-risk balance to patients [12]. Despite the abundance of tools available for predicting cardiovascular risk, these scores have inconsistent results and demonstrate poor predictive ability in people with type 2 diabetes [13]. NICE recommends the QRISK assessment tool [14, 15], which has shown moderate to good discrimination in external validations [16, 17]. The tool had moderate discriminative ability and overpredicts the risk of cardiovascular disease in people with type 2 diabetes [13]. Most risk scores for bleeding, including ORBIT [18] which is recommended by NICE, were developed in patients with atrial fibrillation as they aimed to inform the prescription of anticoagulation therapy. For other patient groups, the QBleed risk score is an alternative given that it was developed using data from the general population [19]. Even with the availability of these tools, it may be difficult to weigh the absolute cardiovascular benefits against bleeding risks, as severity and long-term consequences of different events can vary considerably [20, 21]. Selak et al. (2019) explored assigning different sets of weights to cardiovascular and bleeding events, and found the proportion who would derive net benefit ranged from 2.5% of women and 12.1% of men if 1 cardiovascular event was assumed equivalent to 1 major bleed, to 21.4% of women and 40.7% of men if 1 cardiovascular event was assumed equivalent to 2 major bleeds [21]. However, the weights assigned are arbitrary, and such assessments also do not account for the long-term consequences of preventing a cardiovascular disease event or causing a bleeding event in terms of subsequent event risks and mortality for example. Cost-effectiveness analysis is a recommended method for combining all available evidence and estimates the net value of an intervention [22]. The impact of aspirin on cardiovascular and bleeding

risks can be quantified in terms of healthcare costs and individuals' (health-related quality of life-adjusted) life expectancy, and long-term health impacts (if included in the analytical/modelling framework) can be accounted for.

Previous studies that have shown aspirin to be cost-effective for primary prevention in diabetes [23] pre-dated the ASCEND study, the largest trial assessing the efficacy and safety of aspirin specifically in people with diabetes. A recent modelling study by the USPSTF published in 2022 [11] used a US cardiovascular disease microsimulation model [24] and included evidence from the three recent trials of aspirin for primary prevention of cardiovascular disease (ASCEND [2], ASPREE [25], ARRIVE [26]). The study reported lifetime net gains in quality-adjusted life years (QALYs) ranging from 0.001 to 0.052 in people aged 40-59 with 10-year risk of cardiovascular disease $\geq$ 5% and in people aged 60-69 with 10-year risk of cardiovascular disease $\geq$ 10% [11]. However, the study did not estimate outcomes specifically for people with diabetes. Jiang et al. (2019) used a de-novo Markov model and evidence from ASCEND, and demonstrated that aspirin is cost-effective for primary prevention, with an estimated 0.08 QALY gain (discounted at 3% per annum) in diabetes patients in China [27].

In this chapter, I assessed the cost-effectiveness of aspirin for the primary prevention of cardiovascular disease in people with diabetes in the UK Biobank cohort, using the simulation model developed in Chapter 3 with updated estimates of hospital costs (Chapter 4) and health utility (Chapter 5) associated with adverse events.

6.2 Methods

6.2.1 Model inputs

The cost-effectiveness of aspirin was assessed in the cohort of people with diabetes without previous cardiovascular disease identified from the UK Biobank (N = 18250)[1]. Participants' sociodemographic characteristics and risk factor values

[1]Baseline characteristics of the UK Biobank participants included in this analysis can be found in Table 3.1 in Chapter 3.

measured at recruitment were used as inputs to the model. Values of parameters used in the simulation model including treatment effects, costs and quality of life utilities are summarised in Table 6.1. Cost of aspirin was obtained from the Prescription Cost Analysis England 2020/21 [28], using the cost of the most frequently prescribed generic aspirin. For each individual in the simulation, hospital care costs (2020/21 GBP£) and quality of life utilities were estimated based on each individual's characteristics and adverse events as they occur in the simulation (see Chapters 4 and 5).

Two different sets of aspirin treatment effects were considered (Table 6.2). Firstly, the effects of aspirin reported in ASCEND, the only primary prevention randomised clinical trial that exclusively recruited people with diabetes, were used [2]. The endpoints included in the model correspond directly to the endpoints reported in the trial as ASCEND data were used to develop the model with modelled adverse events being defined as in the trial. Secondly, the effects of aspirin reported in USPSTF [29] and Abdelaziz et al. (2019) [30] meta-analyses of randomised trials were used. In both the 2009 Antithrombotic Treatment Trialists' (ATT) Collaboration individual patient data meta-analysis of primary prevention trials and the recent meta-analysis by Abdelaziz et al. (2019) which included the most recent aspirin trials, there was no evidence that relative risk reductions with aspirin differed between people with and without diabetes [1, 30]. Hence, the treatment effects of aspirin from the broader meta-analyses of primary prevention trials, not specific to the diabetes subgroups, were used. The USPSTF meta-analysis was chosen as it has clearly defined endpoints and stratified treatment effects based on aspirin dosage (estimates for low-dose [$\leq$ 100mg/d] aspirin used). TIA was not included in the USPSTF meta-analysis, so the effect of aspirin on TIA from the meta-analysis by Abdelaziz et al. (2019) was used. All treatment effects are based on intention-to-treat analyses of the respective trials. The treatment effects reported in ASCEND are rate ratios, while the effects reported in the meta-analyses are odds ratios/risk ratios. Given the low event rates, risk ratios and odds ratios are roughly equivalent. They are used in the simulation model as hazard ratios without conversion. As a check of

validity, I present a comparison of rate ratios estimated with the simulated data and the values reported in ASCEND.

For both analyses, I further considered separate scenarios listed as follows:

- no risk reduction in deaths with aspirin;
- risk reduction in GI tract cancer with aspirin after 10 years [29];
- no impact on risks of heart failure and amputation with aspirin (effects reported in ASCEND but not in the meta-analyses);
- aspirin stoppage after 10 years, 20 years, and at 75 years of age (no further treatment effects were applied after stopping aspirin treatment [31]);
- full compliance, using effects of antithrombotic medication use estimated in the ASCEND risk equations as an approximation (Supplemental Table C.40).

Table 6.1: Input parameters for simulation model

Input parameters	
Population	UK Biobank participants with diabetes without previous cardiovascular disease at recruitment (details of cohort identification in Appendix B.2)
Risk equations	Risk equations developed in ASCEND, updated with UK Biobank data (Chapter 3)
Treatment effect of aspirin	Treatment effects reported in ASCEND [2] and, separately, in meta-analyses [29, 30] (see Table 6.2)
Cost	
Treatment cost	£12.79 each year*
Hospital cost	Estimates from ASCEND (Chapter 4); inflated to 2020/21 values using NHS cost inflation index [32]
Health utility	
Quality of life utility	Estimates from ASCEND (Chapter 5). The final model was used and this does not include disutilities for myocardial infarction, coronary revascularisations, GI tract cancer, or ESRD.

* Cost of most frequently prescribed generic aspirin from Prescription Cost Analysis England 2020/21 [28]

Table 6.2: Treatment effects of aspirin for different scenarios

	From ASCEND [2]	From meta-analyses [29, 30]
Myocardial infarction	0.95 (0.80 – 1.19)	0.89 (0.82 – 0.96)
Coronary revascularisation (non-urgent)	0.89 (0.75 – 1.05)	Myocardial infarction: 0.89 (0.82 – 0.96)
Coronary revascularisation (urgent)	-	-
TIA	0.85 (0.69 – 1.04)	0.80 (0.71 – 0.89)
Ischaemic stroke	0.92 (0.77 – 1.11)	0.82 (0.72 – 0.92)
Heart failure	0.84 (0.64 – 1.10)*	-
Intracranial haemorrhage	1.22 (0.82 – 1.81)	1.31 (1.11 – 1.54)
GI bleed	1.36 (1.05 – 1.75)	1.58 (1.38 – 1.80)
Other major bleed	1.70 (1.18 – 2.44)	1.41 (1.19 – 1.67)
GI tract cancer†	-	-
Non-GI tract cancer	-	-
Amputation	0.76 (0.52 – 1.10)*	-
ESRD	-	-
Vascular death‡	0.91 (0.75 – 1.10)	0.95 (0.86 – 1.05)
Non-vascular death‡	0.95 (0.84 – 1.07)	0.99 (0.93 – 1.05)

Note:
Treatment effects reported in different sources summarised in Supplemental Table C.41. Values are rate ratios for ASCEND and odds ratios/risk ratios for meta-analyses (95% CI). Given the low event rates, risk ratios and odds ratios are roughly equivalent. They are used in the simulation model as hazard ratios.

* No treatment effect on heart failure and amputation in a scenario analysis

† Hazard ratio of 0.64 (0.52 – 0.79) assumed after 10 years in a scenario with latent effect of aspirin on GI tract cancer [29]

‡ No treatment effect on deaths in a scenario analysis

6.2.2 Statistical methods

Changes in QALYs and life expectancies (LYs) with aspirin relative to the scenario of no aspirin use were calculated. The incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB, evaluated at a willingness-to-pay threshold[2] of £20,000/QALY) with aspirin relative to the scenario of no aspirin use were calculated using incremental cost and QALYs discounted at 3.5% per annum, in line with NICE's guidance for health technology evaluations [22]. A treatment is considered cost-effective if the ICER is below £20,000/QALY and if the NMB is above £0. A lifetime horizon was adopted for all calculations unless otherwise stated.

The results were assessed in participant subgroups by age and sex, cardiovascular risk, and bleeding risk at baseline. The QRISK risk calculator [15] was used to assess the 10-year risk of cardiovascular disease based on NICE's recommendations [14], and the QBleed risk calculator [19] was used to assess the 5-year risk of GI bleeding. A summary of risk factors in the QRISK and QBleed risk calculators among the UK Biobank participants can be found in Supplemental Table C.42.

The expected value of perfect information[3] (EVPI) per person was calculated using the willingness-to-pay threshold of £20,000/QALY for the UK Biobank cohort. This was extrapolated to the UK diabetes population over a 10-year period, with discounting at 3.5% per annum, assuming two-thirds of the four million people currently estimated to have diabetes do not yet have cardiovascular disease [33, 34], and an incidence of 60,000 diabetes cases a year [35] of whom 75% do not have prevalent cardiovascular disease (as estimated in the UK Biobank; see Appendix B.2).

Quantifying uncertainty

For each participant, 600 Monte-Carlo simulations were performed and this was sufficient to achieve convergence and reduce stochastic (first-order) uncertainty (Supplemental Figure C.42). To account for parameter (second-order) uncertainty,

[2]The willingness-to-pay threshold is the maximum amount a decision maker is willing to pay for a unit of health outcome (in this case a QALY).

[3]EVPI is the maximum price that decision makers should be willing to invest in further research to have perfect information on all parameters

500 sets of risk equations estimated from bootstrap resampling (with replacement) of ASCEND participants updated using the UK Biobank data (as described in Chapter 3) were used. For each of the 500 bootstrap samples, the risk equations for all events, and simultaneously for hospital costs and health-related QoL, were re-estimated to account for correlations between the equations. Treatment effects of aspirin for each adverse event were assumed independent from other events and 500 sets of log hazard ratios were resampled independently assuming a normal distribution, based on standard errors calculated from the reported confidence intervals.

Table 6.3: Addressing uncertainty

Type of uncertainty / error	Method to address
Sampling error	Bootstrapped resampling (with replacement) of participants; bootstrapped standard errors calculated assuming a normal distribution
Stochastic (first-order) uncertainty / Monte-Carlo error	Sufficient Monte-Carlo loops to ensure convergence and to reduce Monte-Carlo error
Parameter uncertainty from model estimation (risk, cost and utility equations)	All equations re-estimated with bootstrapped re-sampling of development cohort. Probabilistic sensitivity analysis used to account for parameter uncertainty
Parameter uncertainty around treatment effect	Probabilistic sensitivity analysis used to account for parameter uncertainty in treatment effect. Assume log hazard ratio follows a normal distribution. Assume independence between treatment effects of different events

To briefly explain the flow of an individual in the simulation, for each of the 500 set of bootstrapped equations, each of the 18,250 participants were simulated 600 times each. The incidence of event for an individual is averaged across the 600 X 500 simulations. To calculate participant sampling error, 1000 bootstrap resampling (with replacement) of participants were performed and the bootstrapped standard errors for the outcomes of interest were calculated assuming a normal distribution. Stochastic uncertainty, sampling uncertainty and parameter uncertainty were assumed independent and combined by summing the variances [36]. All estimates presented are the central estimate, with these uncertainties reflected in the 95%

confidence intervals of the results (summarised in Table 6.3). Cost-effectiveness acceptability curves and scatterplots of incremental costs against incremental QALYs were used to visualise the parameter uncertainty related to the ICER.

6.3 Results

6.3.1 Comparison of treatment effects projected in simulation model with those reported in randomised studies

Treatment effects in trials are typically reported on composite outcomes. Although the reported treatment effects on individual adverse events were used in the simulation model, the model is able to replicate the effects on composite outcomes as reported in the respective studies (Table 6.4).

Table 6.4: Comparison of treatment effects on deaths and composite endpoints achieved by simulation model at 10 years from those reported

	ASCEND		Meta-analyses	
Endpoint	Reported	Projected in model	Reported	Projected in model
Vascular death	0.91 (0.75 – 1.10)	0.89	0.95 (0.86 – 1.05)	0.92
Non-vascular death	0.95 (0.84 – 1.07)	0.97	0.99 (0.93 - 1.05)	1.01
All-cause death	0.94 (0.85 – 1.04)	0.95	0.98 (0.93 – 1.03)	0.98
Major cardiovascular events	0.92 (0.82 – 1.03)	0.93	0.90 (0.85 – 0.95)	0.88
Major bleeding events	1.29 (1.09 – 1.52)*	1.41	1.44 (1.32 – 1.57)	1.48

Note:
Model projections are from the base case simulation and do not account for the simulation runs for probabilistic sensitivity analysis.

* The rate ratio for major bleeding events reported in ASCEND is lower than that projected in the model because major bleeding events in ASCEND included eye bleeds which are not included in the simulation model. The rate ratio for eye bleeds in ASCEND was reported to be 0.89, and the adjusted rate ratio excluding this endpoint would roughly align with the model projections.

6.3.2 Impact of aspirin on (quality-adjusted) life expectancy

For participants with diabetes without previous cardiovascular disease in the UK Biobank, the model projected small net gains in QALYs and LYs (discounted at 3.5% per annum) over lifetime with aspirin compared to no aspirin (Table 6.5; undiscounted estimates in Supplemental Table C.43). However, these estimates were not statistically significant and varied substantially depending on the treatment effects applied (QALYs gained 0.100 [95% CI: -0.056, 0.256] with ASCEND treatment effect, 0.026 [-0.057, 0.108] with meta-analyses treatment effect). There was no substantial difference in results across subgroups of participants by sex and age, 10-year cardiovascular risk, or 5-year GI bleeding risk.

Table 6.5: Lifetime gains in quality-adjusted life years (QALYs) and life expectancies (LYs) with aspirin compared to no aspirin use in UK Biobank participants with diabetes without previous cardiovascular disease

		ASCEND treatment effects		Meta-analyses treatment effects	
Subgroups	N	QALYs	LYs	QALYs	LYs
All participants	18250	0.100 (-0.056, 0.256)	0.142 (-0.081, 0.364)	0.026 (-0.057, 0.108)	0.041 (-0.076, 0.158)
By sex and age (years)					
Male					
<50	1405	0.110 (-0.059, 0.279)	0.146 (-0.084, 0.376)	0.021 (-0.069, 0.111)	0.038 (-0.084, 0.160)
≥50, <60	3374	0.108 (-0.056, 0.272)	0.146 (-0.079, 0.372)	0.030 (-0.057, 0.117)	0.047 (-0.073, 0.167)
≥60	6048	0.104 (-0.057, 0.265)	0.145 (-0.079, 0.369)	0.032 (-0.053, 0.117)	0.048 (-0.070, 0.167)
Female					
<50	1010	0.090 (-0.062, 0.241)	0.128 (-0.090, 0.347)	0.012 (-0.069, 0.093)	0.025 (-0.091, 0.141)
≥50, <60	2370	0.095 (-0.053, 0.243)	0.140 (-0.079, 0.358)	0.022 (-0.057, 0.101)	0.039 (-0.077, 0.155)
≥60	4043	0.090 (-0.058, 0.238)	0.135 (-0.086, 0.357)	0.019 (-0.059, 0.097)	0.032 (-0.084, 0.148)
By 10-year risk of cardiovascular disease estimated by QRISK-3 (%)					
<5	6713	0.097 (-0.061, 0.254)	0.134 (-0.084, 0.352)	0.020 (-0.064, 0.104)	0.034 (-0.081, 0.150)
≥5, <10	8036	0.099 (-0.057, 0.256)	0.141 (-0.082, 0.364)	0.028 (-0.054, 0.111)	0.044 (-0.074, 0.162)
≥10	3501	0.109 (-0.045, 0.263)	0.158 (-0.072, 0.388)	0.030 (-0.051, 0.110)	0.048 (-0.073, 0.168)
By 5-year risk of GI bleeding estimated by QBleed (%)					
<0.45	5885	0.097 (-0.060, 0.255)	0.133 (-0.084, 0.350)	0.021 (-0.063, 0.105)	0.036 (-0.079, 0.151)
≥0.45, <0.7	5772	0.101 (-0.057, 0.258)	0.141 (-0.081, 0.364)	0.029 (-0.054, 0.112)	0.045 (-0.073, 0.162)
≥0.7	6593	0.103 (-0.052, 0.257)	0.149 (-0.078, 0.376)	0.026 (-0.054, 0.107)	0.043 (-0.076, 0.162)

Note:
Values are mean (95% CI). QALYs and LYs were discounted at 3.5% per annum.

6.3.3 Cost-effectiveness of aspirin

Despite the small net gains in QALYs, the incremental costs of aspirin relative to no aspirin were small (Table 6.6). The ICER for aspirin relative to no aspirin was £2374 and £6701 per QALY using treatment effects of aspirin from ASCEND and meta-analyses respectively. This is considerably below the threshold of £20,000/QALY and suggests aspirin is cost-effective. Accounting for uncertainty, aspirin is likely to be more cost-effective than no aspirin with a 92% and 78% probability using treatment effects of aspirin from ASCEND and meta-analyses (Figures 6.1 & 6.2), respectively, and the recommended threshold of £20,000/QALY. At this threshold, the EVPI was estimated to be £84/person and £173/person using the treatment effects of aspirin from ASCEND and meta-analyses, respectively. This extrapolates to £240 million and £500 million, respectively, for the UK over 10 years.

Table 6.6: Impact of aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank for different sets of aspirin effects

Scenarios	Hospital cost (£)	Treatment cost (£)	QALYs	NMB (£)	ICER (£/QALY)
No aspirin use	31579 (30177, 32981)	-	11.034 (10.817, 11.252)	-	-
Impact of aspirin					
ASCEND treatment effects	46 (-703, 795)	192 (187, 197)	0.100 (-0.056, 0.256)	1768 (-837, 4374)	2374
Meta-analyses treatment effects	-19 (-402, 364)	191 (187, 195)	0.026 (-0.057, 0.108)	341 (-993, 1676)	6701

Note:
Values are mean (95% CI). QALY, quality-adjusted life year; NMB, net monetary benefit with £20,000/QALY threshold; ICER, incremental cost-effectiveness ratio. Costs and QALYs were discounted at 3.5% per annum.

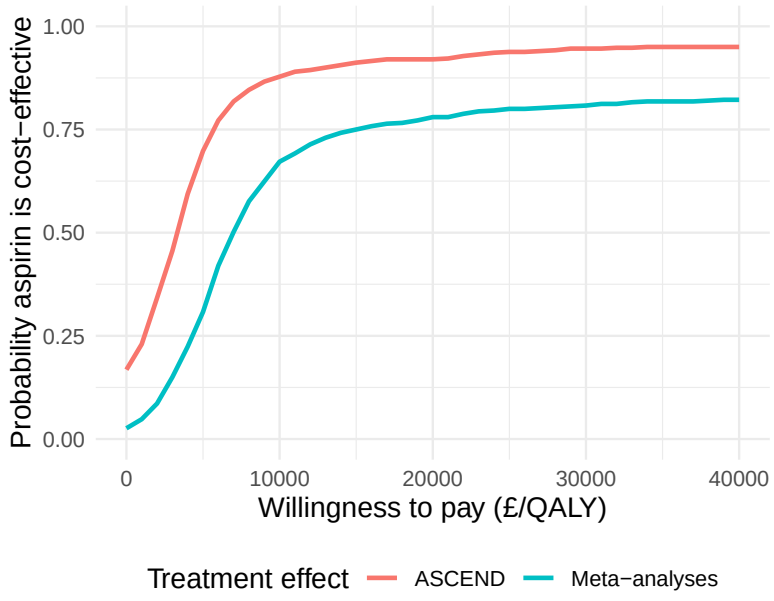


Figure 6.1: Cost-effectiveness acceptability curves showing how the probability that aspirin is cost-effective compared to no aspirin use varies with different value society places on a QALY gained (willingness-to-pay threshold)

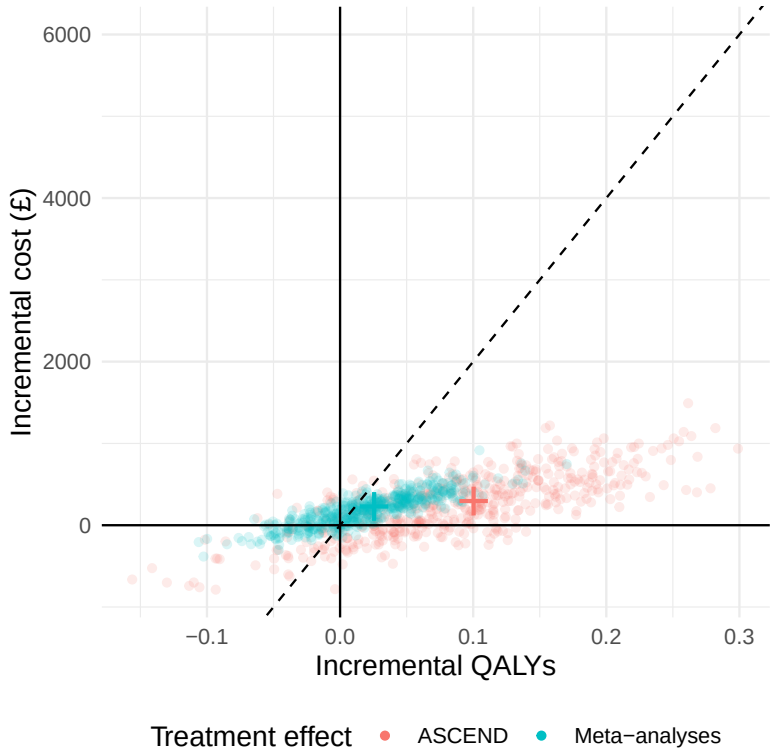


Figure 6.2: Cost-effectiveness plane showing the distribution of lifetime incremental costs and quality-adjusted life years (QALYs) with aspirin compared to no aspirin use. Dotted line represents the willingness-to-pay threshold of £20,000/QALY. The '+' sign represents the mean incremental cost and QALYs with aspirin compared to no aspirin use

6.3.4 Scenario analysis

Scenarios excluding treatment effects of aspirin on death, on heart failure and amputation, and/or including latent risk reduction of aspirin on GI tract cancer were considered (Table 6.7).

The different scenarios illustrate the workings of the model. Compared to the base case of using the ASCEND treatment effect, in the scenario where risk reductions in deaths were excluded, a substantial proportion of QALYs gained was lost due to a reduction in life expectancy (QALYs gained decreased from 0.100 to 0.013). At the same time, because individuals live shorter, they incur less hospital costs (excess hospital cost decreased from £46 to -£386). In the scenario where the risk reduction in heart failure and amputation were removed, about 25% of QALYs gained was lost due to both reduction in quality of life and reduction in life expectancy from experiencing these events (QALYs gained decreased from 0.100 to 0.073). The increase in hospital cost due to experiencing heart failure and amputation exceeds the decrease in cost due to shorter life expectancy, resulting in an overall increase in excess hospital costs from taking aspirin compared to the base case (excess hospital cost increased from £46 to £280). In the scenario where a latent risk reduction in GI tract cancer (effect of aspirin only applied after 10 years) was included, there was an increase in QALYs gained due to longer life expectancy and better quality of life from avoiding GI tract cancer (QALYs gained decreased from 0.100 to 0.127). The savings in hospital cost from preventing GI tract cancer exceeded the increase in hospital cost from living longer, resulting in a smaller excess hospital cost than the base case (excess hospital cost decreased from £46 to -£49).

In all scenarios, the incremental costs of aspirin relative to no aspirin were small. Hence, the likelihood of aspirin being cost-effective was driven mainly by QALYs gained with aspirin relative to no aspirin. This in turn was driven primarily by risk reduction in death from aspirin, evident from the scenario where exclusion of risk reduction in deaths reduced the net QALYs (discounted) gained from 0.100 to 0.013 (change in QALYs gained of -0.087) and from 0.026 to -0.003 (change

of -0.029) for the ASCEND and meta-analyses cases respectively. In the scenario where there is a latent risk reduction in GI tract cancer with aspirin, an increase in QALYs (discounted) gained by 0.027 and 0.025 were observed respectively. Using the compliance-adjusted treatment effect of aspirin estimated from the ASCEND data more than doubled the net benefit of aspirin, with QALYs gained increasing from 0.100 to 0.239 (Table 6.7). This was driven primarily by the much greater benefit on vascular death (HR 0.69 [estimated from ASCEND, adjusted for compliance] vs 0.91 [as reported in the ASCEND study]).

In the scenarios with aspirin stoppage, 75-90% of QALYs and LYs gained with aspirin were lost if aspirin was stopped after year 10, and 35-45% if after year 20. Generally, the net benefit of aspirin in each year increases with age, with people in the oldest age group gaining the greatest QALYs and LYs at least up to 20 years (Tables 6.8; Supplemental Table C.44). However, the cumulative net benefit was greatest in those aged < 50 years old with lifetime aspirin use. This is because people in the younger age groups have on average longer life expectancy (26.9, 23.1 and 19.2 years for those aged < 50, ≥ 50 and < 60, and ≥ 60 respectively) and accumulate more benefits over lifetime, so the cumulative benefit of aspirin is greater for people who are younger if aspirin were used over a lifetime, with a large proportion of QALYs gain coming at a later age. A large proportion of benefits were lost if aspirin was stopped at 75 years old as recommended based on the USPSTF modelling study.

Table 6.7: Impact of aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank under different scenarios of aspirin effects

	Discounted at 3.5% per annum					Undiscounted	
Scenario	Hospital cost (£)	Treatment cost (£)	QALYs	NMB (£)	ICER (£/QALY)	QALYs	LYs
ASCEND treatment effect	**46**	**192**	**0.100**	**1768**	**2374**	**0.205**	**0.291**
No risk reductions in deaths	-386	190	0.013	447	Aspirin dominates	0.026	0.029

Table 6.7: Impact of aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank under different scenarios of aspirin effects *(continued)*

Scenario	Hospital cost (£)	Treatment cost (£)	QALYs	NMB (£)	ICER (£/QALY)	QALYs	LYs
Latent risk reduction in GI tract cancer	-49	193	0.127	2402	1130	0.266	0.377
No risk reduction in heart failure and amputation	280	192	0.073	981	6487	0.151	0.232
No risk reduction in heart failure, amputation and deaths	-144	190	-0.017	-383	Aspirin dominated	-0.031	-0.034
Adjusted for compliance	970	195	0.239	3621	4871	0.494	0.734
Meta-analyses treatment effect	**-19**	**191**	**0.026**	**341**	**6701**	**0.055**	**0.084**
No risk reduction in death	-165	190	-0.003	-92	Aspirin dominated	-0.004	-0.001
Latent risk reduction in GI tract cancer	-100	191	0.051	920	1798	0.111	0.165

Note:
QALY, quality-adjusted life year; LY, life year; NMB, net monetary benefit with £20,000/QALY threshold; ICER, incremental cost-effectiveness ratio.
Estimates are from the base case simulation (with respective changes to reflect scenario). PSA was not performed for scenario analyses due to the time-consuming nature of the simulation.

Table 6.8: Quality-adjusted life years (discounted at 3.5% per annum) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline

	ASCEND treatment effects			Meta-analyses treatment effects		
Scenario	<50	≥50, <60	≥60	<50	≥50, <60	≥60
Lifetime use	0.102	0.103	0.099	0.017	0.027	0.027
Stopping after 20 years	0.052	0.071	0.082	0.002	0.016	0.020
Stopping after 10 years	0.017	0.029	0.034	-0.006	0.004	0.006
Stopping at 75 years old	0.085	0.071	0.037	0.016	0.011	0.006

Note:
Estimates are from the base case simulation (with respective changes to reflect scenario). PSA was not performed for scenario analyses due to the time-consuming nature of the simulation.

6.4 Discussion

6.4.1 Summary of results and future work

I demonstrate an application of the decision model developed in this thesis by assessing the cost-effectiveness of aspirin for the primary prevention of cardiovascular disease in people with diabetes. In the cohort of participants with diabetes without cardiovascular disease identified in the UK Biobank, the probability that aspirin is more cost-effective than no aspirin is 92% and 78% when aspirin effects reported in ASCEND and the meta-analyses were used, respectively. Small net gains in QALYs and LYs were observed (0.205 QALYs and 0.291 LYs for ASCEND treatment effects; 0.055 QALYs and 0.084 LYs for meta-analyses treatment effects), and the results were similar in participant categories by sex and age, cardiovascular risk, and bleeding risk. However, the estimates of net benefit did not reach statistical significance because significant uncertainty remains around the treatment effects of aspirin.

Risks of cardiovascular events and mortality increase with age, but so do risks of bleeding. Using the simulation model developed, I was able to assess the balance

of benefits and risks in different subgroups of patients. With increasing age, the projected increasing benefits from risk reduction in cardiovascular and mortality events outweigh the projected increasing harms from increased risk of bleeding. The projected net benefit of aspirin was thus greatest in those from the oldest age group, at least up to 20 years. The harms may outweigh the costs for those who are younger (< 50 years old; for meta-analyses treatment effects) if aspirin is stopped before 20 years of use. However, with lifetime aspirin use, cumulative benefits of aspirin are greater for people who are younger with longer life expectancy.

In the scenario whereby a potential risk reduction in GI tract cancer was included after 10 years, the average lifetime QALYs gain with aspirin increased by about 0.025. Although the lifetime QALYs gain seems small on average, this benefit is derived from the delay or prevention of GI cancer in the 7.3% of participants predicted to develop GI tract cancer over lifetime without aspirin use, which roughly translates to QALYs gain of 0.34 per person. This scenario is based on reports from observational post-trial follow-up of a small number of trials which have suggested possible benefits for colorectal cancer prevention that is evident only over the long term [3–6]. However, there is insufficient evidence from randomised clinical trials to support this finding. Longer-term follow-up of ASCEND participants is in progress to assess this.

The net benefits estimated using the treatment effects of aspirin reported in ASCEND are significantly greater than those estimated using the effects reported in the meta-analyses. This is due to aspirin's beneficial effects on heart failure and amputation reported in ASCEND, which, although not statistically significant, were used for the former case. Also, the reported risk reductions in vascular and non-vascular deaths were greater in ASCEND than in the meta-analyses. Heart failure and amputation events were not specifically sought and were not clinically adjudicated in ASCEND. Excluding these effects reduced the average QALYs gained by about 0.027. A recent observational study reported aspirin to be associated with increased risk of heart failure (hazard ratio of 1.27 [1.10 – 1.46]) in people who do not have previous cardiovascular disease [37]. Although this result could be biased by reverse causality, it remains that there is significant uncertainty as to

whether or not aspirin has a causal impact on heart failure. Clinical adjudication of heart failure events and an intention-to-treat analysis of heart failure in ASCEND is currently in progress that will inform this.

The most influential parameter driving the net benefit is the treatment effect of aspirin on death, with QALYs gained falling from 0.205 to 0.026 when treatment effects on deaths were excluded from the ASCEND treatment effects (0.055 to -0.004 for meta-analyses treatment effects). Both the USPSTF modelling study [9] and Jiang et al. (2019) [27] also reported that their results were sensitive to treatment effects on death. There is still significant uncertainty as to whether or not aspirin reduces the risk of vascular death. The ATT meta-analysis of primary prevention trials found that fatal haemorrhagic strokes outnumber fatal ischaemic strokes, resulting in an adverse effect on overall stroke mortality. The USPSTF meta-analysis did not find this, but the number of fatal haemorrhagic strokes is inconsistent with those reported in the ATT meta-analysis, possibly because of inconsistencies in reporting across trials and different sets of trials included in the meta-analyses. In ASCEND, fatal confirmed intracranial haemorrhage was specifically excluded from vascular death to separate bleeding harms. The impact of aspirin on vascular death is 0.93 (0.77 – 1.12) if intracranial haemorrhage was included, and 0.91 (0.75 – 1.10) if intracranial haemorrhage was excluded. The change is small and not statistically significant, but does suggest the importance of separating fatal intracranial haemorrhage from other vascular death to separate the benefits and harms of aspirin. An updated ATT individual patient data meta-analysis is planned [38] which will have more consistent endpoint definitions to inform this.

6.4.2 Implications of findings

Despite these uncertainties, based on the current evidence, aspirin is likely cost-effective on average in the cohort of participants with diabetes without previous cardiovascular disease in the UK Biobank. The EVPI was estimated to be about £500 million if the meta-analyses treatment effects of aspirin were applied, which suggests that further research to reduce uncertainties may be good value for money.

Longer term follow-up of ASCEND is in progress to assess the longer-term impact of aspirin on cancer, and adjudication of heart failure events to inform an intention-to-treat analysis of aspirin's effect on heart failure in ASCEND is also in progress. An updated ATT individual patient data meta-analysis will also provide further insight into the effect of aspirin on vascular death. If the benefits of aspirin on cancer risks, heart failure, and/or vascular death are confirmed, this would strengthen the argument that aspirin for primary prevention is cost-effective for people with diabetes. Additionally, it remains to be confirmed if long-term routine use of proton-pump inhibitors is safe and effective in lowering the risk of GI bleeding [39]. If confirmed, given that these agents are priced similarly to aspirin, they may be considered for use alongside aspirin to prevent bleeding with a small impact on cost.

Ultimately the decision whether or not to take aspirin is down to individual patients in consultation with their physician. Prognostic models such as the one developed in this thesis could be used to aid the assessment of benefits and risks associated with aspirin use for individual patients. Generally, more caution may be needed for younger people, where the harms may outweigh the benefits. If prescribed, it will be important to ensure adherence to treatment to maximise the benefits gained, given the suggestion that substantial benefits are incurred at a later age.

The magnitude of overall net benefit found in this study differs from the USPSTF study mainly due to the effect of aspirin on vascular death which was excluded from the USPSTF modelling study. The sensitivity analysis in the USPSTF study which included the effect of vascular death found estimates that were more similar to the estimates in this analysis. The other key difference is that although the simulation in this study found increasing net benefits each year with age, with the gains in cardiovascular benefits increasing at a faster rate than the harms in bleeding[4], the USPSTF modelling study found the opposite. This observation led the USPSTF to recommend stopping aspirin at age 75, which is not supported by the findings in this analysis. This difference is due to the underlying differences

[4]Similar pattern was found even when treatment effects on death were excluded (see Supplemental Table C.45).

in the modelling framework. Relative to a person aged 40-49, the risk ratio of major GI bleeding events in the USPSTF model is about 1.2, 1.8 and 2.9 for people aged 50-59, 60-69 and 70-79 respectively [40], in contrast to about 1.2, 1.3 and 1.5 respectively estimated in ASCEND (see Chapter 3). The absolute increase in risk of GI bleeding with age, and thus the absolute increase in harms with aspirin is much greater in the USPSTF model.

6.4.3 Limitations

First, the treatment effects used in this study were based on intention-to-treat estimates reported in trials. In ASCEND, the mean adherence to study treatment in both the aspirin and placebo arms were 70%. Adherence to study aspirin fell in the aspirin arm, while the use of non-trial aspirins and antiplatelets increased. Hence, the treatment effects of aspirin use were likely under-estimated. However, the adherence rates reflect those in this population of people with well-treated diabetes. Results from the sensitivity analysis using the treatment effects of antithrombotic drug use (roughly 80% aspirin) estimated in the ASCEND risk equations give an approximation of the benefits of aspirin with full compliance.

Second, the analysis only included hospital costs associated with adverse events and costs of aspirin use. It does not include costs related to primary care (e.g. assessment of suitability to use aspirin) or medication use. However, as noted in the previous chapter, hospital care costs are the greatest driver of costs and account for more than 80% of healthcare costs for people with diabetes [41]. Also, extra consultations may not be required if monitoring and management of aspirin treatment are incorporated into regular diabetes check-ups for example. Additionally, the full cost of aspirin prescription was applied without adjustment for adherence. However, this should have little impact on the results as the cost-effectiveness of aspirin was mainly driven by incremental QALYs.

Third, uncertainties around estimates for the different scenario analyses were not presented. The simulation process is computationally expensive and quantification of parameter uncertainty is extremely time-consuming. The simulation model may

require further optimisation for computation speed, or perhaps dimension-reduction techniques could be explored.

Fourth, the treatment effect for each outcome were sampled independently for each of the 500 sets of equations used for probabilistic sensitivity analysis. In reality, reatment effects between outcomes are likely correlated. For example, if aspirin causes intracranial haemorrhage, it may also be more likely to cause other bleeding events. Not accounting for these correlations could have over-estimated the true variance in the results. However, it is clear that the key driver of uncertainty is the treatment effect of death, and the contribution of the inter-relationship between treatment effects to the overall variance is likely small compared to that from the treatment effect of death.

Finally, the results presented are conditional on the accuracy of the simulation model. Although the model has been externally validated in the UK Biobank data, as previously noted, the UK Biobank cohort comprised of 86% White ethnicity, with 37% living in regions in the lowest quintile of deprivation. This restricts the generalisability of the risk equations and by extension, the findings in this analysis to non-White cohorts and cohorts of people living in regions of greater socioeconomic deprivation, and further external validation of the model is required in these cohorts.

6.4.4 Strengths and added value

Previous attempts have been made to compare the benefits and risks of aspirin, for example, by assigning different weights to cardiovascular and bleeding events. However, the weights used for such evaluations can be arbitrary, and such evaluations do not account for the long-term consequences of aspirin use (e.g. effect on mortality over lifetime). The benefits of using a cost-effectiveness model such as the one developed in this thesis include (1) the ability to synthesise both benefits and harms into quantifiable measures, in this case, cost and (QA)LYs, and (2) the ability to propagate treatment effects into the lifetime and account for long-term consequences. The ability of cost-effectiveness models to take into account the full impact on mortality is especially important given that mortality is the key driver of net benefit.

This analysis was performed using a decision model developed based on the ASCEND and UK Biobank data, reflecting contemporary event rates for the population of people with diabetes without cardiovascular disease. The analysis also uses updated costs and quality of life estimates developed for this specific population. In particular, the quality of life estimates were derived from a single source and directly reflect patient's self-rating of decrement in quality of life for the different adverse events included in the model. Parameter uncertainty was quantified accounting for correlations between all equations and parameters (except for treatment effects).

References

1. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative Meta-Analysis of Individual Participant Data from Randomised Trials. The Lancet 2009;373:1849–60. DOI: 10.1016/S0140-6736(09)60503-1.
2. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018;379:1529–39. DOI: 10.1056/NEJMoa1804988.
3. Rothwell PM, Price JF, Fowkes FGR, et al. Short-Term Effects of Daily Aspirin on Cancer Incidence, Mortality, and Non-Vascular Death: Analysis of the Time Course of Risks and Benefits in 51 Randomised Controlled Trials. The Lancet 2012;379:1602–12. DOI: 10.1016/S0140-6736(11)61720-0.
4. Rothwell PM, Wilson M, Elwin CE, et al. Long-Term Effect of Aspirin on Colorectal Cancer Incidence and Mortality: 20-Year Follow-up of Five Randomised Trials. The Lancet 2010;376:1741–50. DOI: 10.1016/S0140-6736(10)61543-7.
5. Algra AM and Rothwell PM. Effects of Regular Aspirin on Long-Term Cancer Incidence and Metastasis: A Systematic Comparison of Evidence from Observational Studies versus Randomised Trials. The Lancet Oncology 2012;13:518–27. DOI: 10.1016/S1470-2045(12)70112-2.
6. Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:814. DOI: 10.7326/M15-2117.
7. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J. Am. Coll. Cardiol. 2019;74. DOI: 10.1016/j.jacc.2019.03.010.

8. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of 10 Societies and by Invited Experts)Developed with the Special Contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal 2016;37:2315–81. DOI: 10.1093/eurheartj/ehw106.

9. US Preventive Services Task Force. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. JAMA 2022;327:1577–84. DOI: 10.1001/jama.2022.4983.

10. National Institute for Health and Care Excellence. Antiplatelet Treatment: Scenario: Antiplatelet Treatment for Primary Prevention of Cardiovascular Disease (CVD). 2022. URL: https://cks.nice.org.uk/topics/antiplatelet-treatment/management/primary-prevention-of-cvd/ (visited on 08/18/2022).

11. Dehmer SP, O'Keefe LR, Evans CV, Guirguis-Blake JM, Perdue LA, and Maciosek MV. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Updated Modeling Study for the US Preventive Services Task Force. JAMA 2022;327:1598–607. DOI: 10.1001/jama.2022.3385.

12. Gitin A, Pfeffer MA, DeMets DL, and Hennekens CH. Aspirin in Primary Prevention: Needs Individual Clinical Judgments. The American Journal of Medicine 2020;133:774–6. DOI: 10.1016/j.amjmed.2020.01.006.

13. Dziopa K, Asselbergs FW, Gratton J, Chaturvedi N, and Schmidt AF. Cardiovascular Risk Prediction in Type 2 Diabetes: A Comparison of 22 Risk Scores in Primary Care Settings. Diabetologia 2022;65:644–56. DOI: 10.1007/s00125-021-05640-y.

14. National Institute for Health and Care Excellence. Cardiovascular Disease: Risk Assessment and Reduction, Including Lipid Modification (CG181). 2019. URL: https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-pdf-78671532569 (visited on 02/14/2019).

15. Hippisley-Cox J, Coupland C, and Brindle P. Development and Validation of QRISK3 Risk Prediction Algorithms to Estimate Future Risk of Cardiovascular Disease: Prospective Cohort Study. BMJ 2017;357:j2099. DOI: 10.1136/bmj.j2099.

16. Livingstone S, Morales DR, Donnan PT, et al. Effect of Competing Mortality Risks on Predictive Performance of the QRISK3 Cardiovascular Risk Prediction Tool in Older People and Those with Comorbidity: External Validation Population Cohort Study. The Lancet Healthy Longevity 2021;2:e352–e361. DOI: 10.1016/S2666-7568(21)00088-X.

17. Collins GS and Altman DG. An Independent and External Validation of QRISK2 Cardiovascular Disease Risk Score: A Prospective Open Cohort Study. BMJ 2010;340:c2442. DOI: 10.1136/bmj.c2442.

18. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT Bleeding Score: A Simple Bedside Score to Assess Bleeding Risk in Atrial Fibrillation. European Heart Journal 2015;36:3258–64. DOI: 10.1093/eurheartj/ehv476.

19. Hippisley-Cox J and Coupland C. Predicting Risk of Upper Gastrointestinal Bleed and Intracranial Bleed with Anticoagulants: Cohort Study to Derive and Validate the QBleed Scores. BMJ 2014;349:g4606. DOI: 10.1136/bmj.g4606.

20. Puhan MA, Yu T, Stegeman I, Varadhan R, Singh S, and Boyd CM. Benefit-Harm Analysis and Charts for Individualized and Preference-Sensitive Prevention: Example of Low Dose Aspirin for Primary Prevention of Cardiovascular Disease and Cancer. BMC Med 2015;13:250. DOI: 10.1186/s12916-015-0493-2.

21. Selak V, Jackson R, Poppe K, et al. Personalized Prediction of Cardiovascular Benefits and Bleeding Harms From Aspirin for Primary Prevention: A Benefit–Harm Analysis. Ann Intern Med 2019;171:529. DOI: 10.7326/M19-1132.

22. National Institute for Health and Care Excellence. NICE Health Technology Evaluations: The Manual. 2022. URL: https://www.nice.org.uk/process/pmg36 (visited on 10/02/2022).

23. Siegel KR, Ali MK, Zhou X, et al. Cost-Effectiveness of Interventions to Manage Diabetes: Has the Evidence Changed Since 2008? Diabetes Care 2020;43:1557–92. DOI: 10.2337/dci20-0017.

24. Dehmer SP, Maciosek MV, LaFrance AB, and Flottemesch TJ. Health Benefits and Cost-Effectiveness of Asymptomatic Screening for Hypertension and High Cholesterol and Aspirin Counseling for Primary Prevention. The Annals of Family Medicine 2017;15:23–36. DOI: 10.1370/afm.2015.

25. McNeil JJ, Wolfe R, Woods RL, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. New England Journal of Medicine 2018;379:1509–18. DOI: 10.1056/NEJMoa1805819.

26. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE): A Randomised, Double-Blind, Placebo-Controlled Trial. The Lancet 2018;392:1036–46. DOI: 10.1016/S0140-6736(18)31924-X.

27. Jiang M, Li P, You JHs, et al. Cost-Effectiveness Analysis of Aspirin for Primary Prevention of Cardiovascular Events among Patients with Type 2 Diabetes in China. PLOS ONE 2019;14:e0224580. DOI: 10.1371/journal.pone.0224580.

28. NHS Business Services Authority. Prescription Cost Analysis – England 2020/21. 2021. URL: https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-202021 (visited on 03/18/2022).

29. Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, and Senger CA. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2022;327:1585–97. DOI: 10.1001/jama.2022.3337.

30. Abdelaziz HK, Saad M, Pothineni NVK, et al. Aspirin for Primary Prevention of Cardiovascular Events. Journal of the American College of Cardiology 2019;73:2915–29. DOI: 10.1016/j.jacc.2019.03.501.

31. Awtry EH and Loscalzo J. Aspirin. Circulation 2000;101:1206–18. DOI: 10.1161/01.CIR.101.10.1206.

32. Jones KC and Burns A. Unit Costs of Health and Social Care 2021. Kent, UK: Personal Social Services Research Unit, 2021. 185 pp.

33. Einarson TR, Acs A, Ludwig C, and Panton UH. Prevalence of Cardiovascular Disease in Type 2 Diabetes: A Systematic Literature Review of Scientific Evidence from across the World in 2007–2017. Cardiovascular Diabetology 2018;17:83. DOI: 10.1186/s12933-018-0728-6.

34. McGurnaghan S, Blackbourn LaK, Mocevic E, et al. Cardiovascular Disease Prevalence and Risk Factor Prevalence in Type 2 Diabetes: A Contemporary Analysis. Diabetic Medicine 2019;36:718–25. DOI: 10.1111/dme.13825.

35. Public Health England. Diabetes Prevalence Estimates for Local Populations. 2016.

36. Dakin HA, Leal J, Briggs A, Clarke P, Holman RR, and Gray A. Accurately Reflecting Uncertainty When Using Patient-Level Simulation Models to Extrapolate Clinical Trial Data. Med Decis Making 2020;40:460–73. DOI: 10.1177/0272989X20916442.

37. Mujaj B, Zhang ZY, Yang WY, et al. Aspirin Use Is Associated with Increased Risk for Incident Heart Failure: A Patient-Level Pooled Analysis. ESC Heart Failure 2022;9:685–94. DOI: 10.1002/ehf2.13688.

38. Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford. ATT: Antithrombotic Trialists' Collaboration. URL: https://www.ctsu.ox.ac.uk/research/att (visited on 06/22/2022).

39. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. Gastroenterology 2019;157:682–691.e2. DOI: 10.1053/j.gastro.2019.05.056.

40. Selak V, Kerr A, Poppe K, et al. Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy. JAMA 2018;319:2507–20. DOI: 10.1001/jama.2018.8194.

41. McMeekin P, Geue C, Mocevic E, et al. The Cost of Prevalent and Incident Cardiovascular Disease in People with Type 2 Diabetes in Scotland: Data from the Scottish Care Information–Diabetes Collaboration. Diabetic Medicine 2020;37:1927–34. DOI: 10.1111/dme.14253.

7 Conclusion

7.1 Summary of work and contributions to the literature

A new framework for diabetes model

This thesis details the development of a novel cost-effectiveness model based on patient-level data, from estimating risk equations, to model validation, updating, parameterisation and finally, implementation. The simulation model integrates a set of validated risk equations and robust estimates of costs and quality of life derived from one of the largest trials in diabetes to date. The risk equations and estimates of costs and quality of life reflect those in contemporary UK cohorts, providing an alternative set of parameters to those estimated from the UKDPS (data from more than a decade ago). The model predicts lifetime health outcomes using baseline socio-demographic and clinical risk factors, and at the same time quantifies hospital costs and (quality-adjusted) life expectancies to inform health economic analyses.

The model was developed using a cohort consisting exclusively of people without previous cardiovascular disease, which will be useful for evaluating primary prevention strategies. On top of common diabetes complications, the model further includes bleeding and cancer endpoints, and is the first to separate ischaemic strokes from haemorrhagic strokes, which will be useful for evaluating antiplatelet or anticoagulant treatments in particular. As a case study, I evaluated the cost-effectiveness of aspirin for the primary prevention of cardiovascular disease in

people with diabetes using the latest available evidence, and demonstrated that aspirin is likely to be cost-effective.

As discussed in Section 3.6.5, the key difference between the framework developed here and previous diabetes models is the way risk factors are used and how treatment effects are incorporated. In previous frameworks, patient heterogeneity in disease progression and/or risk factor management was directly captured through risk factor progression, making them more transferable across settings. At the same time, such models require further equations or assumptions to simulate risk factor progression over time and across different settings, adding further uncertainty and complexity to the model. An additional implication is that these models propagate treatment effects on surrogate endpoints, which may be necessary for evaluating treatment strategies where long-term trials are unavailable. This, however, requires the assumption that the treatment-associated changes in risk factors have similar impact on event outcomes as the impact of differences in risk factors not related to the treatment, which is uncertain. Although this could theoretically be circumvented by separating the natural trajectory of risk factor progression from treatment-associated impact on risk factor progression, this technique does not align well with how treatment effects are reported in clinical trials, and there is the risk of double-counting or under-counting treatment effects if not appropriately adjusted for. The framework I developed in this thesis only uses risk factors at baseline, reducing model complexity. Heterogeneity is captured in the baseline event rates, and using the model in a different setting will require the assumption that the average impact of this heterogeneity in disease progression and/or risk factor management on event rates is similar. However, the framework is less complex and easier to validate and update if required. Furthermore, the model directly uses treatment effects on endpoints as reported in long-term trials without the need to specify treatment effects on risk factor progression, eliminating the risk of double-counting.

One further advantage of the framework developed is the ability to account for correlations between event risks, costs and quality of life. Typically, estimates of event risks, costs and utilities used in health economics analyses are derived

from separate analyses. In many cases, these values are retrieved from different sources and are thus derived from different datasets. However, this is also the case when the same dataset is used to derive these information [1]. For example, the UKDPS was used to derive risk equations [2], costs [3] and health utilities [4] of diabetes complications in separate analyses, but these estimates are used independently from each other in cost-effectiveness analyses. In doing so, the inherent dependencies between these values are not accounted for, and in turn they are assumed independent when quantifying uncertainties around cost-effectiveness estimates leading to the tendency to over-estimate the size of the uncertainty. One major advantage of the framework developed is that the estimates of risks, costs, and utility values were derived concurrently from each bootstrap resampling of the same dataset. This captures the inherent covariation between these values, allowing better characterization of uncertainty in the cost-effectiveness estimates.

Strategies for updating parametric proportional hazard models

Methods of model updating have been described in the literature [5], and different strategies have been adopted for updating risk equations for diabetes simulation models [6, 7]. In Section 3.5, I detailed the mathematical formulations specifically for updating parametric proportional hazard models. Making use of the proportional hazard properties, I proposed a framework to select appropriate methods for model updating from an issue-driven perspective, which is novel to the literature. The specific issues discussed in the thesis are limited to those identified in ASCEND and the UK Biobank, but are sufficient to demonstrate how different model updating methods can be adopted to address issues beyond those discussed.

Development of simulation "engine" in R

The UKPDS-OM was distributed in the form of a software, which limited direct adaptation of the simulation "engine". In the adaptations of the UKPDS risk equations for use in other models, such as the CORE model, the ECHO-T2DM model or the Cardiff model [8–10], each adaptation used a de-novo "engine",

adapting the UKPDS risk equations for their use. Despite using the same risk equations, the adaptations have led to differing results when simulating the same scenarios [11]. It is inevitable that risk equations would require updating, whether to account for temporal changes or to adapt to different countries for example. In hope that future adaptations can be made in a transparent and reproducible way, the code for the simulation "engine", written in R, was developed to be independent of the risk equations estimated in this thesis and was written as a set of compartmentalised tasks. This means that it can be used in whole or in part, and is easily adaptable to accommodate different risk equations or further scenarios. The code for running the simulation model is available on GitHub https://github.com/mjkeng/phd_outputs.

7.2 Areas for further research

Uncertainty in patient-level simulation models and further code optimisation

Patient-level stochastic simulation models are needed to capture patient heterogeneity, especially for diabetes which is associated with complications that are inter-dependent. However, many layers of uncertainty exist for such models, beyond those discussed in this thesis [12]. One key barrier to the exploration and quantification of uncertainties is that the simulation process is computationally expensive. Currently, it takes approximately 5 hours (including overhead time to set up parallel simulations) to run 1000 Monte-Carlo loops for 18,250 participants for each parameter set using 10 parallel processes. Although extensive efforts have been made to optimise the code, further optimisation could be possible to reduce running time. Alternative programming languages (e.g. C++) could be explored for faster computation speed. A more efficient estimation of variance from probabilistic sensitivity analysis has been proposed [13] and can be considered. Further research into how patient-level simulation models can be optimised for computation speed is required to reduce computational time and encourage the adoption of these types of models for use in economic analysis. Development of

a generic simulation "engine" optimised for computation speed which can then be adapted by other users would be useful.

Adoption of complex models for personalised medicine

Prognostic models are helpful to assess disease risks to inform treatment strategies to use for each patient. In the context of aspirin for example, Selak et al. (2019) developed a risk score for predicting cardiovascular event and separately a risk score for predicting bleeding events to inform the overall net benefit of aspirin use. These independent prognostic models fail to capture the inter-relationship between cardiovascular benefits and bleeding risks. They also do not capture downstream impact of aspirin use such as the impact on death, which is a key driver of net benefit of aspirin use. Individual patient simulation models such as the one developed in this thesis are better suited to capture these inter-dependencies and long-term impact. However, these models are typically too complex to be adopted in clinical practice, as they are not designed to be user-friendly for physicians and are slow to run. Dimension-reduction techniques such as Gaussian process modelling [14] may be explored to reduce these models into simpler risk scores that are sufficiently informative for use by physicians.

Generalisability of framework

Although the simulation model has been validated using the UK Biobank data, issues with adverse event ascertainment for endpoints such as TIA and bleeding restricted the ability to assess the external validity of the risk equations for these endpoints. Further external validation of model predictions for these endpoints in other independent cohorts is desirable. Additionally, as previously noted, both the ASCEND and UK Biobank cohorts consist of disproportionately high percentages of participants who are of White ethnicity, and from regions of low deprivation. The generalisability of the simulation model to cohorts with more variation in ethnicity and socioeconomic status remains to be confirmed. Databases such as the Clinical Practice Research Datalink [15] and QResearch [16] could be used to

identify such a cohort. However, adverse events for these databases will similarly need to be identified from linkages to electronic health records, and similar issues with adverse event ascertainment would arise.

Separate from the issue of transferability across cohorts, the validity of the model beyond 10 years also needs to be confirmed. The UK Biobank has follow-up data up to about 13 years (average of 11 years), but longer-term data would be necessary to validate the lifetime predictions of the simulation model. Ongoing follow-up in ASCEND for the long-term [17] will be helpful for this. Data is being collected from central NHS registries for the long-term follow-up phase in ASCEND, which will be useful to validate long-term predictions of cancers and deaths.

The validity of the simulation model developed is also subject to temporal changes which may not be accounted for by changes in risk factors included in the model. This was one of the underlying reasons for the poor performance of the UKPDS-OM in contemporary cohorts as discussed in Chapter 2. It is thus important to constantly validate the model and update the risk equations if necessary. Similarly, costs and quality of life estimates would also need to reflect the most up-to-date evidence.

Leveraging real-world healthcare data

Real-world data is the data typically from sources outside the clinical trial setting, such as electronic health records, administrative data, disease registries, audit evaluations etc. The use of real-world data to generate "real-world evidence" (RWE) has been gaining traction in recent years, with many regulatory authorities and health technology assessment bodies expressing interest in using RWE to supplement evidence from randomised controlled trials [18, 19]. Many initiatives are now in place to develop data standards and facilitate the harmonisation of real-world data across healthcare delivery systems to a consistent format and content to allow systematic analysis of disparate real-world databases [20–22]. The use of real-world data is not new in health economics. The Institute for Clinical and Economic Review in the US found that the proportion of real-world data used in their studies to inform model inputs averaged at 32.7% [23], with real-world

data more commonly used to inform disease progression and costs, less so for treatment-related parameters (e.g. treatment effect, discontinuation rate). For health economic modelling, one common criticism of models developed from clinical trial data is that the models may not be generalisable to real-world cohorts due to selection bias or different standards of care for people enrolled in the trial, and it is thus desirable for such models to be validated using real-world data. However, there are challenges involved in using real-world data, including cohort definition and ascertainment of adverse events of interest, as highlighted in Section 3.5. The push from regulatory bodies to develop frameworks and set standards for the use of real-world data will hopefully encourage better reporting and further research into these areas, which will in turn improve the quality of real-world data and the transparency of evidence generated from real-world databases.

7.3 Final remarks

Model development is a dynamic process. Cost-effectiveness models need to be able to account for treatment-related benefits and risks, the inter-relationship between these events, costs, and quality of life. For a policy maker, the assessment of cost-effectiveness of an intervention must be relevant to the population of interest, in the context of their health system, at the time the decision is being made. Quoting a recent publication [24], "there is no such thing as a validated prediction model", as performance of any model is expected to be heterogenous between settings, locations, patient populations, and across time. Hence, it is important that model performance should be assessed in the cohort of interest, and there may be a need to update the model. This applies also to the ASCEND-UK Biobank model developed in this thesis. In future, when current models are insufficient to capture the benefit-risk profile of new treatments, new models are needed. This thesis illustrates the process of developing each component of a cost-effectiveness model (risk equations, cost and utility equations), the process of model validation and model updating (if required), as well as an application of the model. The methods described can be used to further validate and update the ASCEND-UK Biobank model developed in this

thesis, but are also generalisable to any future model development efforts.

References

1. Guyot P, Welton NJ, Ouwens MJNM, and Ades AE. Survival Time Outcomes in Randomized, Controlled Trials and Meta-Analyses: The Parallel Universes of Efficacy and Cost-Effectiveness. Value in Health 2011;14:640–6. DOI: 10.1016/j.jval.2011.01.008.
2. Hayes AJ, Leal J, Gray AM, Holman RR, and Clarke PM. UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33. DOI: 10.1007/s00125-013-2940-y.
3. Alva ML, Gray A, Mihaylova B, Leal J, and Holman RR. The Impact of Diabetes-Related Complications on Healthcare Costs: New Results from the UKPDS (UKPDS 84). Diabetic Medicine 2015;32:459–66. DOI: 10.1111/dme.12647.
4. Alva M, Gray A, Mihaylova B, and Clarke P. The Effect of Diabetes Complications on Health-Related Quality of Life: The Importance of Longitudinal Data to Address Patient Heterogeneity. Health Economics 2014;23:487–500. DOI: 10.1002/hec.2930.
5. Moons KGM, Kengne AP, Grobbee DE, et al. Risk Prediction Models: II. External Validation, Model Updating, and Impact Assessment. Heart 2012;98:691–8. DOI: 10.1136/heartjnl-2011-301247.
6. Willis M, Asseburg C, Slee A, Nilsson A, and Neslusan C. Macrovascular Risk Equations Based on the CANVAS Program. PharmacoEconomics 2021;39:447–61. DOI: 10.1007/s40273-021-01001-0.
7. Shao H, Yang S, Stoecker C, Fonseca V, Hong D, and Shi L. Addressing Regional Differences in Diabetes Progression: Global Calibration for Diabetes Simulation Model. Value in Health 2019;22:1402–9. DOI: 10.1016/j.jval.2019.08.007.
8. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: Projecting Long-term Clinical Outcomes, Costs and Costeffectiveness of Interventions in Diabetes Mellitus (Types 1 and 2) to Support Clinical and Reimbursement Decision-making. Current Medical Research and Opinion sup1 2004;20:S5–S26. DOI: 10.1185/030079904X1980.
9. Willis M, Asseburg C, and He J. Validation of Economic and Health Outcomes Simulation Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Journal of Medical Economics 2013;16:1007–21. DOI: 10.3111/13696998.2013.809352.
10. McEwan P, Peters JR, Bergenheim K, and Currie CJ. Evaluation of the Costs and Outcomes from Changes in Risk Factors in Type 2 Diabetes Using the Cardiff Stochastic Simulation Cost-Utility Model (DiabForecaster). Current Medical Research and Opinion 2006;22:121–9. DOI: 10.1185/030079906X80350.

11. Tew M, Willis M, Asseburg C, et al. Exploring Structural Uncertainty and Impact of Health State Utility Values on Lifetime Outcomes in Diabetes Economic Simulation Models: Findings from the Ninth Mount Hood Diabetes Quality-of-Life Challenge. Med Decis Making 2021:0272989X211065479. DOI: 10.1177/0272989X211065479.
12. Dakin HA, Leal J, Briggs A, Clarke P, Holman RR, and Gray A. Accurately Reflecting Uncertainty When Using Patient-Level Simulation Models to Extrapolate Clinical Trial Data. Med Decis Making 2020;40:460–73. DOI: 10.1177/0272989X20916442.
13. O'Hagan A, Stevenson M, and Madan J. Monte Carlo Probabilistic Sensitivity Analysis for Patient Level Simulation Models: Efficient Estimation of Mean and Variance Using ANOVA. Health Econ 2007;16:1009–23. DOI: 10.1002/hec.1199.
14. Stevenson MD, Oakley J, and Chilcott JB. Gaussian Process Modeling in Conjunction with Individual Patient Simulation Modeling: A Case Study Describing the Calculation of Cost-Effectiveness Ratios for the Treatment of Established Osteoporosis. Med Decis Making 2004;24:89–100. DOI: 10.1177/0272989X03261561.
15. Clinical Practice Research Datalink (CPRD). URL: https://www.cprd.com/node/120 (visited on 06/11/2022).
16. QResearch. URL: https://www.qresearch.org/ (visited on 06/11/2022).
17. Long-Term Study — A Study of Cardiovascular Events in Diabetes. URL: https://ascend.medsci.ox.ac.uk/about/long-term-study (visited on 06/11/2022).
18. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. URL: https://www.fda.gov/media/120060/download (visited on 05/13/2022).
19. National Institute for Health and Care Excellence. NICE Real-World Evidence Framework. 2022. URL: https://www.nice.org.uk/corporate/ecd9 (visited on 07/10/2022).
20. Belenkaya R, Gurley MJ, Golozar A, et al. Extending the OMOP Common Data Model and Standardized Vocabularies to Support Observational Cancer Research. JCO Clin Cancer Inform 2021;5:12–20. DOI: 10.1200/CCI.20.00079.
21. Klann JG, Joss MAH, Embree K, and Murphy SN. Data Model Harmonization for the All Of Us Research Program: Transforming I2b2 Data into the OMOP Common Data Model. PLOS ONE 2019;14:e0212463. DOI: 10.1371/journal.pone.0212463.
22. OHDSI CDM Working Group. OMOP Common Data Model. URL: https://ohdsi.github.io/CommonDataModel/ (visited on 05/13/2022).
23. Lee W, Dayer V, Jiao B, Carlson JJ, Devine B, and Veenstra DL. Use of Real-World Evidence in Economic Assessments of Pharmaceuticals in the United States. J Manag Care Spec Pharm 2021;27:5–14. DOI: 10.18553/jmcp.2021.27.1.005.

24. Van Calster B, Steyerberg EW, Wynants L, and van Smeden M. There Is No Such Thing as a Validated Prediction Model. BMC Medicine 2023;21:70. DOI: 10.1186/s12916-023-02779-w.

Appendices

A

Publications and presentations

Published manuscripts

1. Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, and ASCEND Study Collaborative Group. Hospital Costs Associated with Adverse Events in People with Diabetes in the UK. Diabetes, Obesity and Metabolism 2022. DOI: 10.1111/dom.14796

2. Keng MJ, Leal J, Bowman L, Armitage J, Mihaylova B, and ASCEND Study Collaborative Group. Decrements in Health-Related Quality of Life Associated with Adverse Events in People with Diabetes. Diabetes, Obesity and Metabolism 2022;24:530–8. DOI: 10.1111/dom.14610

3. Keng MJ, Leal J, Mafham M, Bowman L, Armitage J, and Mihaylova B. Performance of the UK Prospective Diabetes Study Outcomes Model 2 in a Contemporary UK Type 2 Diabetes Trial Cohort. Value in Health 2022;25:435–42. DOI: 10.1016/j.jval.2021.09.005

Working papers

1. Keng MJ, Leal J, Bowman L, Armitage J, and Mihaylova B, on behalf of ASCEND Study Collaborative Group. Simulation model for predicting lifetime outcomes in people with diabetes without previous cardiovascular disease. *In preparation.*

2. Keng MJ, Leal J, Bowman L, Armitage J, and Mihaylova B. Tutorial paper: data-driven strategies for updating parametric proportional hazard risk equations. *In preparation.*

3. Keng MJ, Leal J, Bowman L, Armitage J, and Mihaylova B. Cost-effectiveness of aspirin use for primary prevention of cardiovascular events in people with diabetes, a UK perspective. *In preparation.*

Oral presentations

1. Keng MJ. Developing a Framework for Modelling Outcomes in Patients with T2D: Case Study with ASCEND. HERC Internal Seminar. 2020

2. Keng MJ. Optimizing Your Code in R. R for trial and model-based cost-effectiveness analysis. 2020. URL: https://mjkeng.github.io/rhta_markovspeedup/markovspeedup

3. Keng MJ. Can the UKPDS Outcomes Model Be Used to Predict Outcomes in Contemporary Well-Manged Diabetes Patients? NDPH Symposium. 2019

Poster presentations

1. Keng MJ. Hospital Costs and Health Related Quality of Life Associated with Adverse Events in People with Diabetes (Selected as Best Posters for Cardiovascular and Hypertension). IDF Virtual Congress 2021. 2021. URL: https://doi.org/10.26226/morressier.617c37317c09fc044a975210

2. Keng MJ. Simulation Model for Lifetime Prediction of Complications in People with Diabetes without Previous Cardiovascular Disease Using ASCEND Risk Equations (Finalist for Best Poster). Oxford BHF CRE Research Symposium 2021. 2021. URL: https://github.com/mjkeng/phd_presentations/blob/main/2021-11%20BHF%20symposium_poster.pdf

B

ASCEND and UK Biobank data

B.1 Endpoint definition in ASCEND

Participants in ASCEND received 6-monthly follow-up questionnaires and were asked to report the occurrence of any cardiovascular events, bleeding events, cancer diagnoses and other serious illnesses or hospital admissions. Additional follow-up for hospitalisations, cancer and death were obtained from routine hospital records, the cancer registry and the death registry respectively, and information from these sources were used to supplement adverse event identification. All primary (myocardial infarction, stroke, major bleeds and vascular death) and secondary outcomes (GI tract cancer and coronary revascularisation) in the trial were clinically adjudicated in ASCEND. For heart failure, amputation, and end-stage renal disease, events were not specifically sought nor adjudicated in ASCEND. Hospital episode data were used to supplement the identification of these events. The earliest recorded date between the two sources was used. Appendix Table B.1 summarises the definition of each adverse event.

Table B.1: Identifying adverse events from ASCEND

Adverse events	Definitions in ASCEND	ICD-10 or OPCS-4 codes
Cardiovascular disease		
Myocardial infarction†	Evidence of cardiac necrosis and other evidence of acute myocardial infarction and no other diagnosis was likely. Silent myocardial infarction not included	
Coronary revascularisation†	Coronary angioplasty, stenting or coronary artery bypass grafting. Distinguished by urgency. Revascularisation that occurs on the same day as a myocardial infarction is assumed to occur after the myocardial infarction	
Transient ischaemic attack†	Transient episode of neurological dysfunction, lasting less than 24 hours, without clear evidence of acute infarction, haemorrhage, trauma or other cause	
Ischaemic stroke†	Acute symptomatic episode of focal or global neurological dysfunction as a result of infraction which lasted more than 24 hours, lead to death, or was associated with imaging evidence of acute infarct corresponding with clinical syndrome	
Heart failure‡		ICD-10 codes in primary diagnosis position: I50 Heart failure; I110, I130, I132 Hypertensive heart disease with (congestive) heart failure; I255, I420, I425, I426, I427, I428, I429, I430, I431, I432, I438 Congestive cardiomyopathy
Bleeding		

Table B.1: Identifying adverse events from ASCEND *(continued)*

Adverse events	Definitions in ASCEND	ICD-10 or OPCS-4 codes
Intracranial haemorrhage†	Includes spontaneous intracranial bleeds or those associated with injury in the absence of major trauma	
GI bleed†		
Other major bleed†		
Cancer		
GI tract cancer†		
Non-GI tract cancer†	Excludes non-melanoma skin cancer	
Other complications		
Amputation‡	Lower limb amputation	OPCS-4 codes: X09 Amputation of leg; X10 Amputation of foot; X11 Amputation of toe
End-stage renal disease‡	Includes participants who had dialysis or renal transplant	Algorithm & ICD-10 codes from Bush et al. (2017) [1]
Death		
Vascular death†	Excludes intracranial haemorrhage	
Non-vascular death†		

Note:
†: Events corresponding to these endpoints were specifically sought and adjudicated in the ASCEND study. The dates of event occurrence recorded in the study were used.
‡: These endpoints were not specifically sought and were not adjudicated in ASCEND. Hospital episode data were used to supplement the identification of these events. Earliest recorded date between the two sources was used.

B.2 Identifying cohort of participants in the UK Biobank satisfying the ASCEND eligibility criteria

Participants' baseline sociodemographic characteristics were extracted from the UK Biobank database at the point of recruitment. Medication use at baseline was extracted from information obtained from participants' responses to the touchscreen questionnaire (TS) and/or the nurse-led interview (NI). Codes for each class of medication were identified by matching product names corresponding to the relevant British National Formulary (BNF) paragraphs, subparagraphs and/or chemical substance in the 2021 BNF. The code list to identify medication use can be found on GitHub https://github.com/mjkeng/phd_outputs. Disease histories were identified from hospital inpatient records and/or medical history from nurse-led interviews. For certain health outcomes, the first-occurrence algorithm (FO) in the UK Biobank which identifies the earliest record of a health condition defined using 3-character ICD-10 codes from primary care records, hospital inpatient records, and/or participants' self-report was used.

Table B.2: Defining baseline characteristics for participants in the UK Biobank

Baseline profile	Codes used
Medication use	
Insulin	TS: 2986 Started insulin within one year diagnosis of diabetes 6177/6153 Medication for cholesterol, blood pressure or diabetes == insulin NI: insulin product
Anti-diabetic drugs	NI (BNF): Antidiabetic drugs
Aspirin	NI (BNF): Antiplatelet drugs > Aspirin
Antiplatelet	NI (BNF): Antiplatelet drugs
Anticoagulants	NI (BNF): Oral anticoagulants Parenteral anticoagulants
Statins	NI (BNF): Lipid-regulating drugs > Atorvastatin; fluvastatin; pravastatin; rosuvastatin; simvastatin

Table B.2: Defining baseline characteristics for participants in the UK Biobank *(continued)*

Baseline profile	Codes used
Non-steroidal anti-inflammatory pain killers (NSAIDs)	NI (BNF): Non-steroidal anti-inflammatory drugs
Antihypertensive drugs	TS: 6177/6153 Medication for cholesterol, blood pressure or diabetes == blood pressure medication NI (BNF): Renin-angiotensin system drugs > Angiotensin-converting enzyme inhibitors; Angiotensin-II receptor antagonists Calcium-channel blockers Beta-adrenoceptor blocking drugs Diuretics Alpha-adrenoceptor blocking drugs Centrally-acting antihypertensive drugs Vasodilator antihypertensive drugs
Anticonvulsants	NI (BNF): Control of epilepsy
Antidepressants	NI (BNF): Antidepressant drugs
Corticosteroids	NI (BNF): Prednisolone, Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Deflazacort
Atypical antipsychotic medication	Prednisolone, Betamethasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Deflazacort
Disease history	
Diabetes (any type)	NI: 1220 diabetes 1221 gestational diabetes 1222 type 1 diabetes 1223 type 2 diabetes 1276 diabetic eye disease 1468 diabetic neuropathy/ulcers 1521 diabetes insipidus 1607 diabetic nephropathy FO: E10 insulin-dependent diabetes E11 non-insulin-dependent diabetes E13 other specified diabetes E14 unspecified diabetes TS: 4041/10844 Gestational diabetes only

Table B.2: Defining baseline characteristics for participants in the UK Biobank *(continued)*

Baseline profile	Codes used
Diabetic retinopathy	NI: 1276 diabetic eye disease
Treated hypertension	NI: 1065 hypertension 1072 essential hypertension
Atrial fibrillation	NI: 1471 atrial fibrillation
Oesophageal varices	NI: 1141 oesophageal varicies
Venous thromboembolism	NI: 1068 venous thromboembolic disease 1093 pulmonary embolism with or without dvt 1094 deep venous thrombosis (dvt)
Systemic lupus erythematosus	NI: 1381 systemic lupus erythematosis/sle
Rheumatoid arthritis	NI: 1464 rheumatoid arthritis
Migraine	NI: 1265 Migraine*
Erectile dysfunction	NI: 1518 Erectile dysfunction
Severe mental illness	FO: F20 schizophrenia F31 bipolar disorder F33 recurrent depressive disorder* NI: 1289 schizophrenia 1290 deliberate self-harm/suicide attempt 1291 mania/bipolar disorder/manic depression
Anaemia	NI: 1330 iron deficiency anaemia* 1331 pernicious anaemia* 1446 anaemia* FO: D50-53 nutritional anaemia* D55-59 haemolytic anaemia D60-64 aplastic and other anaemias

Note:
Sources of information used to derive patient profile from the UK Biobank include: FO, UK Biobank's algorithm for first occurrence of health outcomes; NI, face-to-face nurse-led interview; TS, touchscreen questionnaires. NI (BNF) indicates that product names corresponding to BNF paragraphs/subparagraphs/chemical substance were used to identify drugs from nurse-led interview responses.

* Within one year of recruitment date.

Of the 502,461 participants in the UK Biobank, 26,430 participants (5.3%) with diabetes (Appendix Table B.3) were identified using the algorithms developed by Eastwood et al. (2016) [2] (Appendix Figures B.1 - B.3). The algorithms account for self-report of diabetes, reports of diabetes in hospital or primary care records, and reports of diabetes-related drug use.

In line with the ASCEND eligibility criteria, participants with a history of cardiovascular disease diagnosis or revascularisation surgeries, hepatic disease, or ESRD prior to recruitment, with a history of GI haemorrhage or peptic ulcer within 6 months prior to recruitment, or with a history of cancer diagnosis / treatment within 5 years prior to recruitment were further excluded. These events were identified from hospital records and/or medical histories reported in the nurse-led interview (codes used to identify these events are in Appendix Table B.4). The final UK Biobank cohort used for analysis in this thesis consists of 18,250 (3.6%) participants.

Table B.3: Classification of diabetes type based on algorithm

Diabetes type	N (%)
Diabetes unlikely	475245 (94.6%)
Possible gestational diabetes	786 (0.2%)
Type 1 diabetes	3687 (0.7%)
Probable	3412 (0.7%)
Possible	275 (0.1%)
Type 2 diabetes	22743 (4.5%)
Probable	21315 (4.2%)
Possible	1428 (0.3%)

B. ASCEND and UK Biobank data

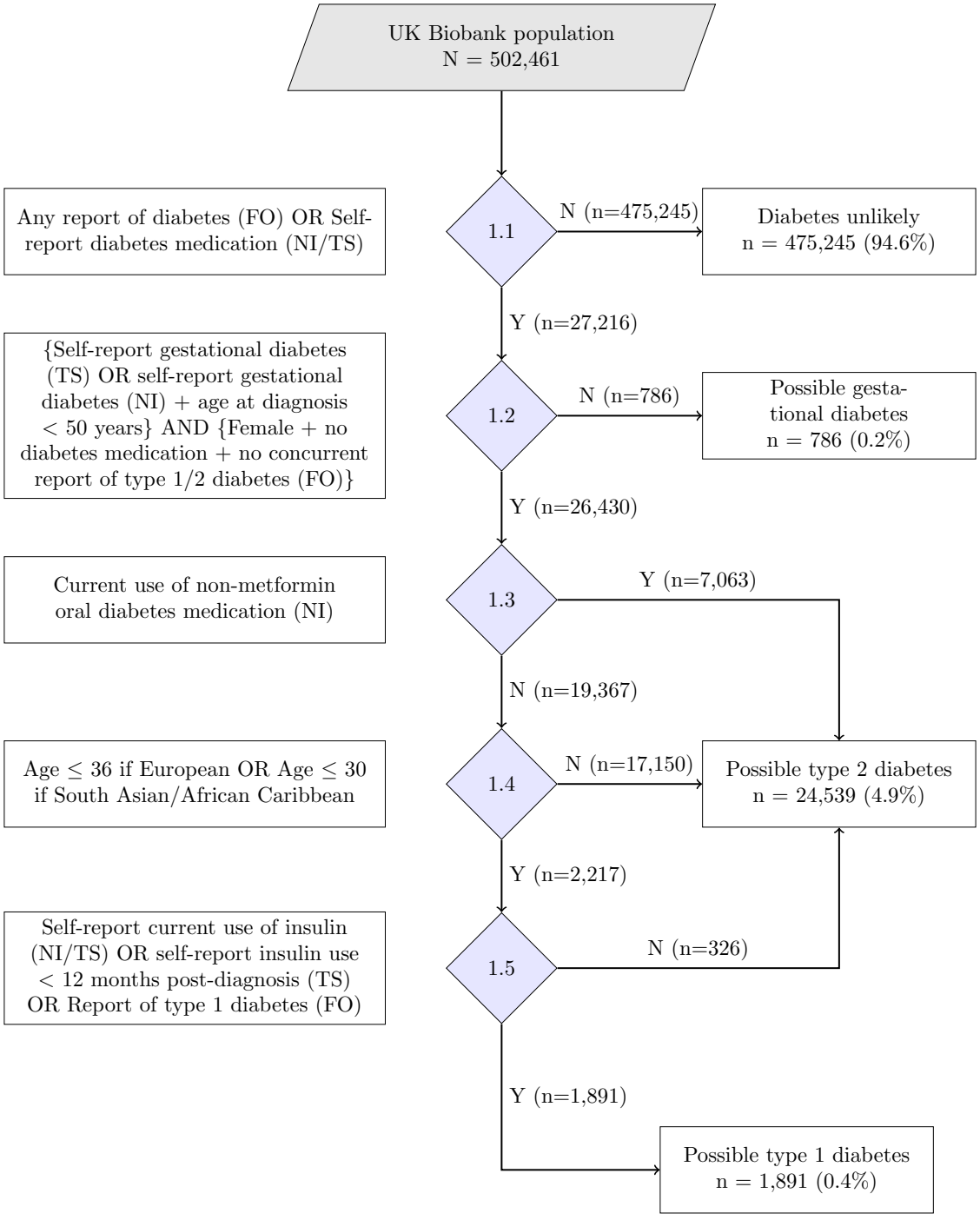


Figure B.1: Algorithm 1 to identify participants with diabetes in the UK Biobank

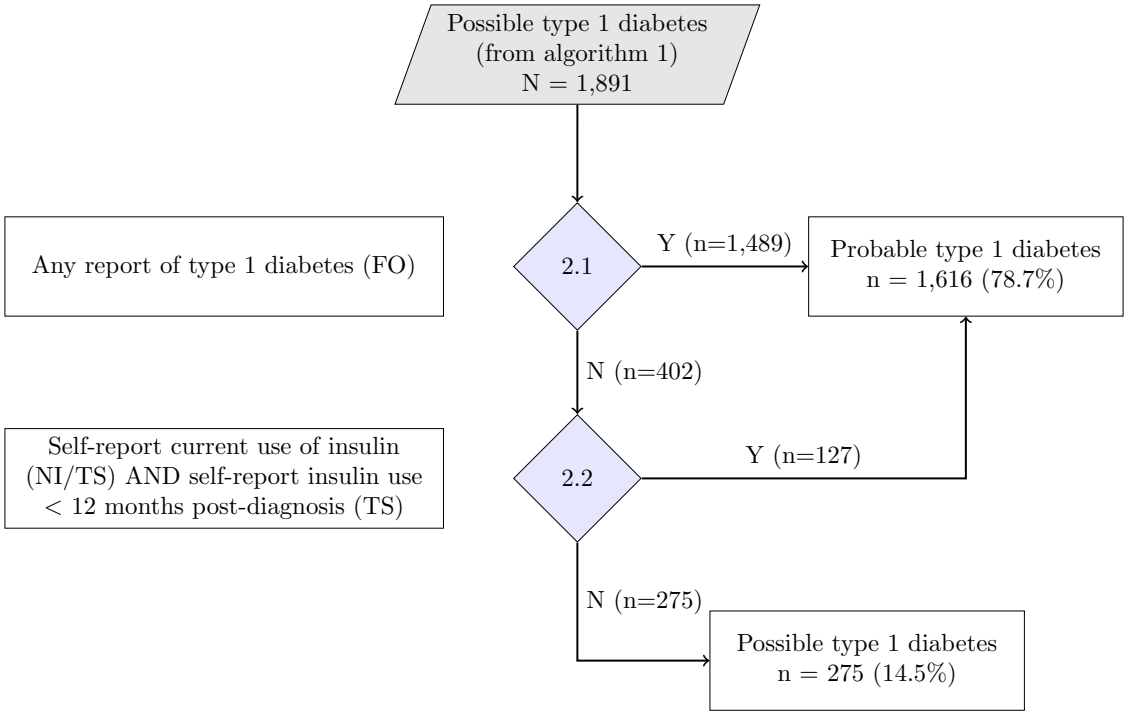


Figure B.2: Algorithm 2 to identify participants with diabetes in the UK Biobank

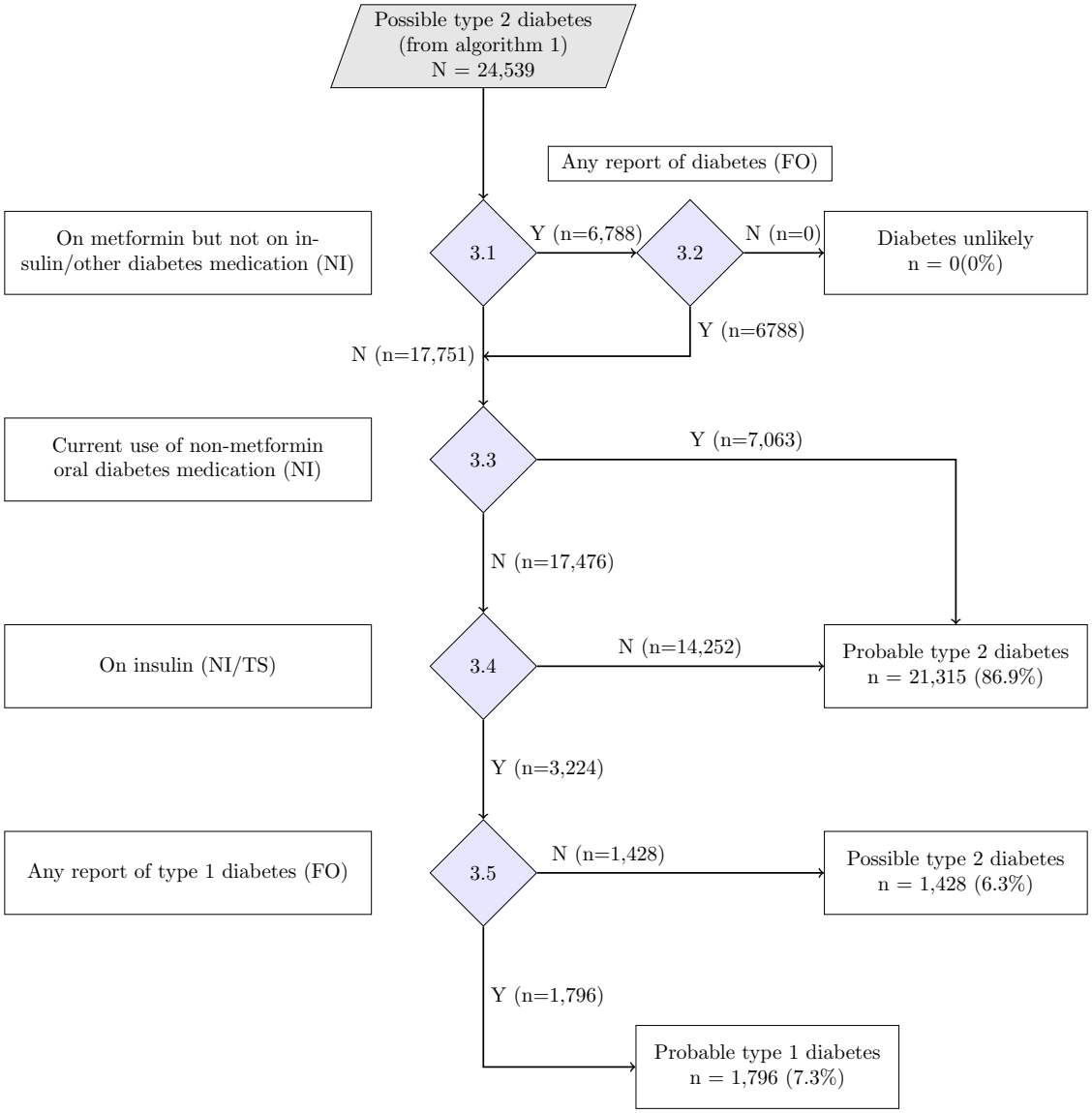


Figure B.3: Algorithm 3 to identify participants with diabetes in the UK Biobank

Table B.4: Ascertainment of disease history at baseline for 26,430 UK Biobank participants identified with diabetes

Disease history	N (%)	ICD-10, ICD-9 or OPCS codes	UK Biobank codes
CVD diagnosis or revascularisation procedure	6493 (24.6%)	ICD-10: I11, I13 Hypertensive heart disease I20-25 Ischaemic heart disease I42-43 Cardiomyopathy I46 Cardiac arrest I50 Heart failure I60-69 Cerebrovascular disease G45 Transient cerebral ischaemic attacks (exclude G454 transient global amnesia) OPCS-4: K234, K40-50, K75 Coronary artery bypass grafting or coronary angioplasty L16, L18-21, L23, L25-31, L37, L48-54, L56-60, L62-63, L66, L68 Non-coronary revascularisation (includes peripheral angioplasty, atherectomy, thrombectomy, embolectomy, catheter directed thrombolysis, arterial bypass surgery and aneurysm repair (surgical or endovascular). Arterial embolization (e.g. cranial aneurysm coiling or embolization procedures to treat haemorrhage), amputation procedures and procedures on the venous or pulmonary systems are not included)	1070 coronary angioplasty (ptca) +/- stent 1095 coronary artery bypass grafts (cabg) 1071 other arterial surgery/revascularisation procedures 1102 fem-pop bypass/leg artery bypass 1103 leg artery aneurysm repair 1105 carotid artery surgery/endarterectomy 1107 non-coronary artery angioplasty +/- stent 1108 leg artery angioplasty +/- stent 1555 femoral/popliteal/iliac aneurysm repair

Table B.4: Ascertainment of disease history at baseline for 26,430 UK Biobank participants identified with diabetes *(continued)*

Disease history	N (%)	ICD-10, ICD-9 or OPCS codes	UK Biobank codes
GI bleed*	109 (0.4%)	ICD-10: I850, I983 Oesophageal varices with bleeding K223 Perforation of oesophagus K226 Gastro-oesophageal laceration-haemorrhage syndrome K250-252, K254-256, K259 Gastric ulcer with haemorrhage and/or perforation K260-262, K264-266 Duodenal ulcer with haemorrhage and/or perforation K270-272, K274-276 Peptic ulcer with haemorrhage and/or perforation K280-282, K284-286 Gastrojejunal ulcer with haemorrhage and/or perforation K290 Acute haemorrhagic gastritis K625 Haemorrhage of anus and rectum K631 Perforation of intestine (nontraumatic) K661 Haemoperitoneum K920 Haematemesis K921 Melaena K922 Gastrointestinal haemorrhage, unspecified	
Peptic ulcer*	50 (0.2%)	ICD10: K25 Gastric ulcer K26 Duodenal ulcer K27 Peptic ulcer, site unspecified K28 Gastrojejunal ulcer K633 Ulcer of intestine	
Cancer†	1594 (6%)	ICD-10: C Malignant neoplasms ICD-9: 140-208 Malignant neoplasms 2090 – 2093 Malignant neuroendocrine tumors	All cancer codes except 1072 cin/pre-cancer cells cervix
Hepatic disease	734 (2.8%)	ICD10: K70 Alcoholic liver disease K71 Toxic liver disease K72 Hepatic failure, not elsewhere classified K73 Chronic hepatitis, not elsewhere classified K74 Fibrosis and cirrhosis of liver K75 Other inflammatory liver diseases K76 Other diseases of liver K77 Liver disorders in diseases classified elsewhere	

Table B.4: Ascertainment of disease history at baseline for 26,430 UK Biobank participants identified with diabetes *(continued)*

Disease history	N (%)	ICD-10, ICD-9 or OPCS codes	UK Biobank codes
End-stage renal disease	135 (0.5%)		42026 Date of ESRD based on UK Biobank algorithm by Bush et al. (2017) [1]

* Within 6 months prior to recruitment date (identified from HES)
† Diagnosis or treatment within 5 years prior to recruitment date (from HES/cancer registry)

B.3 Adverse event ascertainment in the UK Biobank

Data linkages to the death registry, the cancer registry and hospital inpatient records are available for all participants in the UK Biobank. For heart failure, only hospital inpatient records with corresponding codes recorded in the primary diagnosis position, with length of stay of at least 1 day if elective were included to avoid including heart failure recorded as a comorbidity and mis-codings. For gastrointestinal bleed and other major bleeds, only hospital inpatient records with corresponding codes in the primary diagnosis position were included to avoid including bleeds that are sequelae to other events or procedures. Death records with a cardiovascular event recorded as the primary cause of death were considered vascular deaths, while all other deaths were considered non-vascular deaths. Primary care records were available for roughly 45% of participants in the UK Biobank, and these were further used to supplement the identification of TIA as TIAs may not be captured in hospital inpatient records. The codes used to identify these events are in Appendix Table B.5. Censoring date for each event was set to 29/02/2020 or the latest date of data availability for the source of data [3].

Table B.5: Ascertainment of adverse events in the UK Biobank

Adverse event	ICD-10, ICD-9, OPCS or READ codes	Notes
Cardiovascular disease		
Myocardial infarction†‡	ICD-10: I21 Acute MI I22 Subsequent MI I23 Certain current complications following acute MI I241 Dressler syndrome	
Coronary revascularisation†	OPCS-4: K234, K40-50, K75 Coronary artery bypass grafting or coronary angioplasty	Coronary revascularisation is considered urgent if classed as emergency admission or if occurrence is within 7 days of myocardial infarction or unstable angina (I200)
Transient ischaemic attack†‡*	ICD-10: G45 except G454 Transient global amnesia READ: F4236 Amaurosis fugax Fyu55 [X]Other transient cerebral ischaemic attacks and related syndromes G65.. (Drop attack) or (trans cereb isch) or (verteb-basil insuff) G65y. Other transient cerebral ischaemia G65z. G65zz Transient cerebral ischaemia NOS XaEGK XE0VK Transient ischaemic attacks X00DU Carotid territory transient ischaemic attack X00DV Vertebrobasilar territory transient ischaemic attack	
Ischaemic stroke†‡	ICD-10: I63 Cerebral infarction I64 Stroke, not specified as haemorrhage or infarction	
Heart failure†‡	ICD-10: I50 Heart failure I110, I130, I132 Hypertensive heart disease with (congestive) heart failure I255, I420, I425, I426, I427, I428, I429, I430, I431, I432, I438 Congestive cardiomyopathy	ICD codes in primary diagnosis position only
Bleeding		

Table B.5: Ascertainment of adverse events in the UK Biobank *(continued)*

Adverse event	ICD-10, ICD-9, OPCS or READ codes	Notes
Intracranial haemorrhage†‡	ICD-10: I60 Subarachnoid haemorrhage I61 Intracerebral haemorrhage I62 Other nontraumatic intracranial haemorrhage S065 Traumatic subdural haemorrhage S066 Traumatic subarachnoid haemorrhage	
GI bleed†‡	ICD-10: I850, I983 Oesophageal varices with bleeding K223 Perforation of oesophagus K226 Gastro-oesophageal laceration-haemorrhage syndrome K250-252, K254-256, K259 Gastric ulcer with haemorrhage and/or perforation K260-262, K264-266 Duodenal ulcer with haemorrhage and/or perforation K270-272, K274-276 Peptic ulcer with haemorrhage and/or perforation K280-282, K284-286 Gastrojejunal ulcer with haemorrhage and/or perforation K290 Acute haemorrhagic gastritis K625 Haemorrhage of anus and rectum K631 Perforation of intestine (nontraumatic) K661 Haemoperitoneum K920 Haematemesis K921 Melaena K922 Gastrointestinal haemorrhage, unspecified	ICD codes in primary diagnosis position only

Table B.5: Ascertainment of adverse events in the UK Biobank *(continued)*

Adverse event	ICD-10, ICD-9, OPCS or READ codes	Notes
Other major bleed[†‡]	ICD-10: N020- N029 Recurrent and persistent haematuria N421 Congestion and haemorrhage of prostate N921 Excessive and frequent menstruation with irregular cycle N925 Other specified irregular menstruation N926 Irregular menstruation, unspecified N930 Postcoital and contact bleeding N938 Other specified abnormal uterine and vaginal bleeding N939 Abnormal uterine and vaginal bleeding, unspecified N950 Postmenopausal bleeding N951-959 Menopausal and perimenopausal disorder R040 Epistaxis R042 Haemoptysis R31X Unspecified haematuria R58X Haemorrhage, not elsewhere classified T792 Traumatic secondary and recurrent haemorrhage T810 Haemorrhage and haematoma complicating a procedure, not elsewhere classified	ICD codes in primary diagnosis position only
Cancer		
GI tract cancer[§]	ICD-10: C15 Malignant neoplasms of oesophagus C16 Malignant neoplasms of stomach C17 Malignant neoplasms 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 C26 Malignant neoplasm of other and ill-defined digestive organs ICD-9: 150 Malignant neoplasms of oesophagus 151 Malignant neoplasms of stomach 152 Malignant neoplasms of small intestine 153 Malignant neoplasm of colon 154 Malignant neoplasm of rectum, rectosigmoid junction, and anus 159 Malignant neoplasm of other and ill-defined digestive organs	

Table B.5: Ascertainment of adverse events in the UK Biobank *(continued)*

Adverse event	ICD-10, ICD-9, OPCS or READ codes	Notes
Non-GI tract cancer[§]	All cancer codes C except codes for GI tract cancer	
Other complications		
Amputation[†]	OPCS-4 codes: X09 Amputation of leg X10 Amputation of foot X11 Amputation of toe	
End-stage renal disease[†‡]		Algorithm & ICD-10 codes from Bush et al. (2017) [1]
Death		
Vascular death[‡]	ICD-10: I00-52, I63-99 (i.e. excludes I60 subarachnoid haemorrhage, I61 intracerebral haemorrhage, I62 non-traumatic intracranial haemorrhage)	ICD codes recorded as primary cause of death
Non-vascular death[‡]	All codes except codes for non-vascular death	

Note:
Earliest recorded date between the sources used.
[*] Primary care data used to supplement identification of TIA for 8180 (45%) participants with GP data based on READ codes.
[†] Hospital inpatient records were used to identify events based on ICD-10 or OPCS codes.
[‡] Data from the death registry were used to identify deaths based on ICD-10 codes.
[§] Data from the cancer registry were used to identify cancers based on ICD-10 and ICD-9 codes.

B.4 Derivation of missing data in the UK Biobank

For the UK Biobank, imputation of missing data was performed in two stages. In the first stage, missing data that can be derived from other variables were derived as described in Appendix Table B.6.

Table B.6: First-stage imputation of baseline characteristics and clinical risk factors for the UK Biobank

Variable	Derivation
Region	Participants determined to be in England, Wales or Scotland based on source of latest record of hospital episode (Hospital Episode Statistics [HES] – England; Scottish Morbidity Record [SMR] – Scotland; Patient Episode Database for Wales [PEDW] – Wales). Otherwise, based on Index of Multiple Deprivation [IMD] region information at baseline.
eGFR	CKD-EPI cystatin C formula used to calculate eGFR from cystatin C values [4]; CKD-EPI serum creatinine formula used to calculate eGFR from serum creatinine value if cystatin C values not available.
Urinary albumin-creatinine ratio	8451 patients (46%) with missing urinary albumin has a flag for urinary albumin < 6.7 mg/L (undetectable by measurement device). Imputed with minimum detectable value of 6.7.
LDL-/HDL-/Total cholesterol/Triglycerides	Friedewald's equation [5] used to calculate missing value if only one of these variables missing. Equation only valid for triglyceride < 4.5 mmol/L; also exclude if imputed value seems infeasible (HDL < 0.219 mmol/L; triglyceride < 0.231 mmol/L)

Note:
Summary values in Table 3.1 already account for this first-stage imputation.

References

1. Bush K, John Nolan, Qiuli Zhang, Will Herrington, and Cathie Sudlow. Definitions of End Stage Renal Disease for UK Biobank Phase 1 Outcomes Adjudication. 2017. URL: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/alg_outcome_esrd.pdf (visited on 05/07/2021).
2. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLOS ONE 2016;11:e0162388. DOI: 10.1371/journal.pone.0162388.

3. Data Providers and Dates of Data Availability. UK Biobank showcase. URL: https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates (visited on 09/21/2021).
4. Lees JS, Welsh CE, Celis-Morales CA, et al. Glomerular Filtration Rate by Differing Measures, Albuminuria and Prediction of Cardiovascular Disease, Mortality and End-Stage Kidney Disease. Nat Med 11 2019;25:1753–60. DOI: 10.1038/s41591-019-0627-8.
5. Friedewald WT, Levy RI, and Fredrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clinical chemistry 1972. DOI: 10.1093/clinchem/18.6.499.

C

Supplemental tables and figures

C.1 Introduction

Table C.1: Search strategy for identifying cost-effectiveness analysis of empagliflozin, with no restrictions on population or comparator

Set	Search statement
1.	empagliflozin.mp.[mp=ti, ab, tx, ct, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]
2.	exp "cost effectiveness analysis"/ or exp economic evaluation/ or exp "cost utility analysis"/
3.	1 and 2
4.	limit 3 to english
5.	diabete*.mp.[mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
6.	4 and 5
7.	limit 6 to (original articles or reports or "review articles" or article or article in press or "review" or comparative study or journal article or meta analysis or observational study, veterinary or observational study or "systematic review" or validation study)

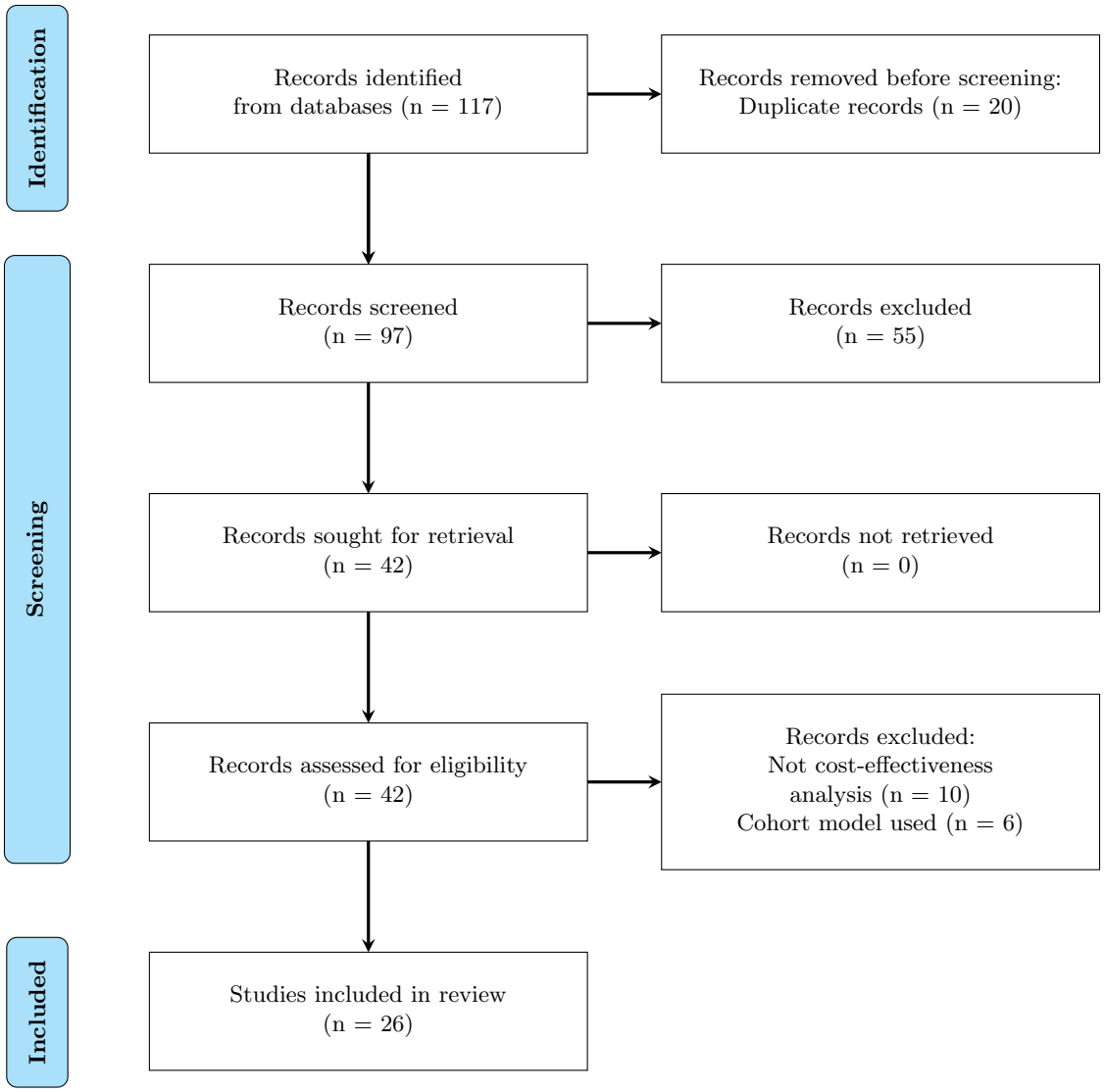


Figure C.1: PRISMA flow diagram for literature review

C.2 How well does the UKPDS Outcomes Model 2 predict outcomes in ASCEND

Table C.2: Inputs required for UKPDS-OM2 and their availability in ASCEND

Inputs required for the UKPDS-OM2	N (%) missing in ASCEND	Notes
Baseline characteristics		
Ethnicity	43 (0.3%)	Categories in ASCEND: White, Indian/Pakistani/Bangladeshi (South Asian), African/Caribbean (Afro-Caribbean), Other, Unknown. Participants with other/unknown ethnicity were grouped together with White
Sex		
Age		
Duration of diabetes	856 (5.9%)	
Weight (kg)	84 (0.6%)	
Height (m)	53 (0.4%)	
Atrial fibrillation (Y/N; defined from Minnesota codes 831 [atrial fibrillation (persistent)] and 833 [intermittent atrial fibrillation])	†	Assume no atrial fibrillation – patients on anti-coagulants excluded at baseline
Peripheral vascular disease (Y/N; defined from presence of intermittent claudication or ankle brachial pressure index < 0.9)	†	Assume no peripheral vascular disease
Current smoker (Y/N)	162 (1.1%)	
Albuminuria (Y/N; defined as presence of micro-/macro-albuminuria)	5328 (36.6%)	Albuminuria defined as urinary albumin $\geq$ 50mg/L
Biomarkers		
HDL cholesterol (mmol/L; CDC aligned assay)	5316 (36.5%)	

Table C.2: Inputs required for UKPDS-OM2 and their availability in ASCEND *(continued)*

Inputs required for the UKPDS-OM2	N (%) missing in ASCEND	Notes
LDL cholesterol (mmol/L; CDC aligned assay)	†	Triglycerides not measured in ASCEND. Predicted LDL from Apo(B), HDL cholesterol, non-HDL cholesterol and other biomarkers. Further details in Section 2.2.2
Systolic blood pressure (mm Hg)	4141 (28.4%)	
HbA1c (%; DCCT/NGSP aligned assay)	5303 (36.4%)	
Heart rate (bpm)	5020 (34.5%)	
White blood count (x10^9 per litre)	†	
Haemoglobin (g/dL)	†	
eGFR (mL/min/1.73m^2; estimated from serum creatinine using MDRD equation)	5304 (36.4%)	In ASCEND, eGFR estimated from blood cystatin C levels using CKD-EPI equation
History of complication (Y/N)		
Myocardial infarction	‡	No history of myocardial infarction
Stroke	‡	No history of stroke
Other ischaemic heart disease	‡	No history of other ischaemic heart disease
Heart failure	‡	No history of heart failure
Blindness	§	Assume no history of blindness
Renal failure	§	Assume no history of renal failure
Ulcer	§	Assume no history of ulcer

Note:
†: Not available in ASCEND. ‡: In ASCEND, participants with previous cardiovascular disease were excluded from the trial. §: Participants were assumed not to have (and likely did not have, as individuals with compliance limiting conditions were ineligible) a history of blindness, renal failure and ulcer at baseline.

Table C.3: Definitions of outcomes in UKPDS-OM2 and definitions of corresponding adverse events in ASCEND

Outcomes	Definition in UKPDS-OM2 (ICD-9 codes) [1, 2]	Outcomes in ASCEND [3]
All-cause death	All-cause death	All-cause death
Vascular death	Deaths from myocardial infarction, other ischaemic heart disease, stroke, and heart failure as defined below	Deaths from myocardial infarction, other ischaemic heart disease, stroke, and heart failure as defined below
Non-vascular death	All-cause death excluding cardiovascular death (as defined in the UKPDS)	All-cause death excluding vascular death (as defined in ASCEND)
Myocardial infarction	WHO clinical criteria with electrocardiogram/enzyme changes or new pathological Q wave 410 (Acute myocardial infarction); ≥798 & ≤798.9 (Sudden death)	Myocardial infarction (fatal/non-fatal) "Evidence of cardiac necrosis (consistent elevation in cardiac biomarkers or relevant autopsy findings) and there was other evidence of an acute MI (including symptoms of ischemia, recent coronary intervention, death, new ECG changes, evidence of a new myocardial defect on cardiac imaging or an acute coronary occlusion at angiography) and no other diagnosis was likely."
Other ischaemic heart disease	Angina/ischaemic heart disease - WHO clinical criteria confirmed by a new ECG abnormality or an ECG which becomes abnormal on exercise ≥411 & ≤414.9 (Ischaemic heart disease excluding acute myocardial infarction)	Angina; Coronary revascularizations (coronary artery bypass graft, percutaneous transluminal coronary angioplasty); Death from other coronary heart disease (not myocardial infarction)

Table C.3: Definitions of outcomes in UKPDS-OM2 and definitions of corresponding adverse events in ASCEND *(continued)*

Outcomes	Definition in UKPDS-OM2 (ICD-9 codes) [1, 2]	Outcomes in ASCEND [3]
Stroke	Stroke with symptoms that persisted for more than one month ≥430 & ≤434.9 (haemorrhagic, ischemic strokes [for fatal and non-fatal strokes]); 436 (acute but ill-defined strokes [for other non-fatal strokes])	Any stroke (fatal/non-fatal) "Acute symptomatic episode of focal or global neurological dysfunction caused by brain, spinal or retinal vascular injury as a result of hemorrhage or infarction which lasted >24 hours, lead to death or was associated with evidence of an acute infarct or hemorrhage on brain imaging corresponding with the clinical syndrome."
Heart failure	≥ 428 & ≤428.9 (Heart failure)	Heart failure (fatal/non-fatal; includes pulmonary oedema)
Amputation	Amputation of digit or limb for any reason Procedure codes ≥5.845 & ≤5.848 (Amputation of digit or limb); 250.6 (diabetes with peripheral circulatory disorder) Fatal peripheral vascular event 997.2 (peripheral vascular complications); 997.6 (late amputation stump complication); 250.6 (diabetes with peripheral circulatory disorder); 440.2 (atherosclerosis of arteries of extremities)	Amputation (above knee, toe, below knee, foot, leg, finger/thumb)

Table C.3: Definitions of outcomes in UKPDS-OM2 and definitions of corresponding adverse events in ASCEND *(continued)*

Outcomes	Definition in UKPDS-OM2 (ICD-9 codes) [1, 2]	Outcomes in ASCEND [3]
End-stage renal disease	Dialysis and/or plasma creatinine >250 μmol/l not ascribable to any acute intercurrent illness 250.3; $\geq$ 585 & $\leq$ 586 Death due to renal failure $\geq$ 580 & $\leq$593.9	Renal failure; includes both renal dialysis and renal transplant

Note:
Further details of endpoint definition in the ASCEND study can be found in Appendix B.1

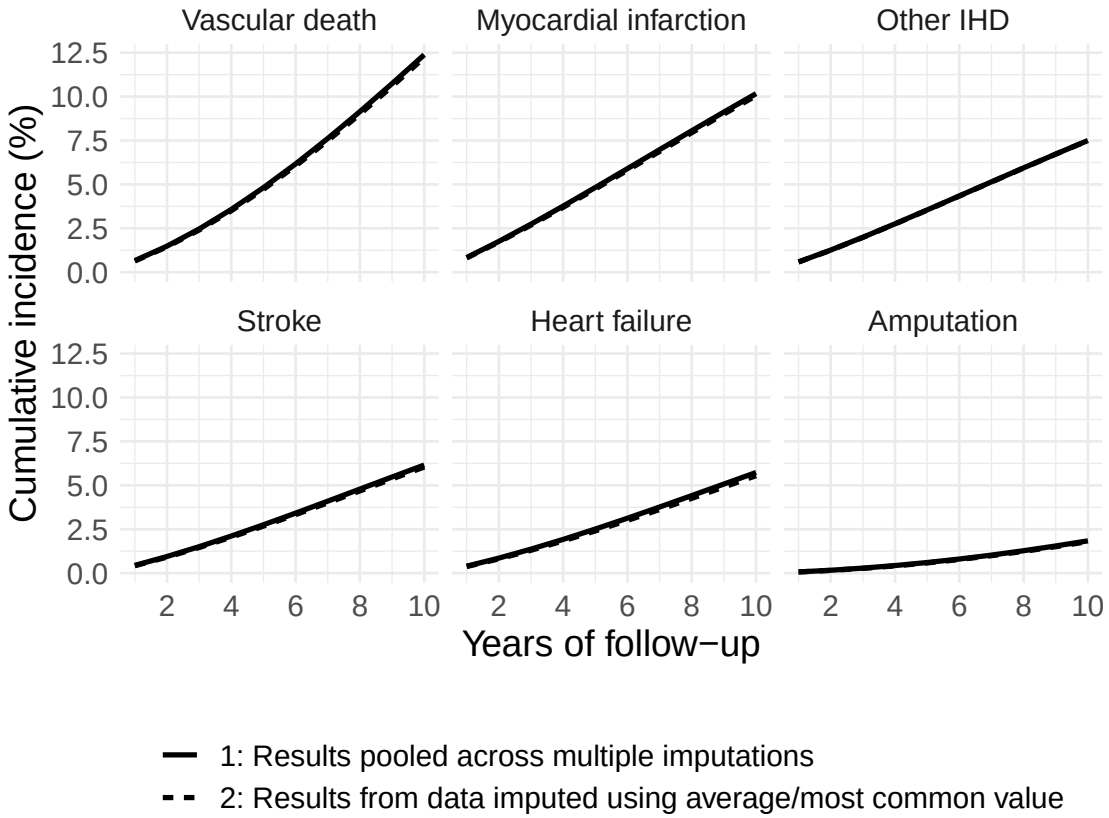


Figure C.2: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 using different methods of imputation, for participants in aspirin placebo and omega-3 placebo arm only (N = 3651)

Table C.4: Baseline characteristics of 14,569 participants with type 2 diabetes in ASCEND before and after imputation

Variable	Before imputation	After imputation
Baseline characteristics		
Male	9166 (62.9%)	9166 (62.9%)
Current smoker	1195 (8.2%)	1195 (8.2%)
Ethnicity		
White	14037 (96.3%)	14250 (97.8%)
South Asian	138 (0.9%)	138 (0.9%)
Afro-Caribbean	181 (1.2%)	181 (1.2%)
Others/Missing	213 (1.5%)	0 (0%)
Age (years)	63.8 (8.9)	63.8 (8.9)
Diabetes duration (years)	6 (3-11)	6 (3-11)
Urinary albumin ≥50 mg/L	681 (7%)	683 (5%)
Atrial fibrillation	-	0 (0%)
Peripheral vascular disease	-	0 (0%)
Biomarkers		
HbA1c (%)	7.1 (1.2)	7.1 (1.0)
Systolic blood pressure (mmHg)	136.4 (15.2)	136.2 (13.1)
Body-mass index (kg/m^2)	31.4 (6.5)	31.4 (6.5)
eGFR (mL/min/1.73m^2)	84.5 (20.9)	85.4 (18.3)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.3)
LDL cholesterol (mmol/L)	-	2.2 (0.5)
White blood cell count (x10^9 per litre)	-	6.4 (0.6)
Haemoglobin (g/dl)	-	14.3 (0.8)
Heart rate (bpm)	75.0 (11.5)	75.1 (9.5)
History of complication		
Myocardial infarction	0 (0%)	0 (0%)
Stroke	0 (0%)	0 (0%)
Other ischaemic heart disease	0 (0%)	0 (0%)
Heart failure	0 (0%)	0 (0%)
Blindness	-	0 (0%)
Renal failure	-	0 (0%)
Ulcer	-	0 (0%)

Note:
Summary values are N (%), mean (SD), or median (interquartile range)

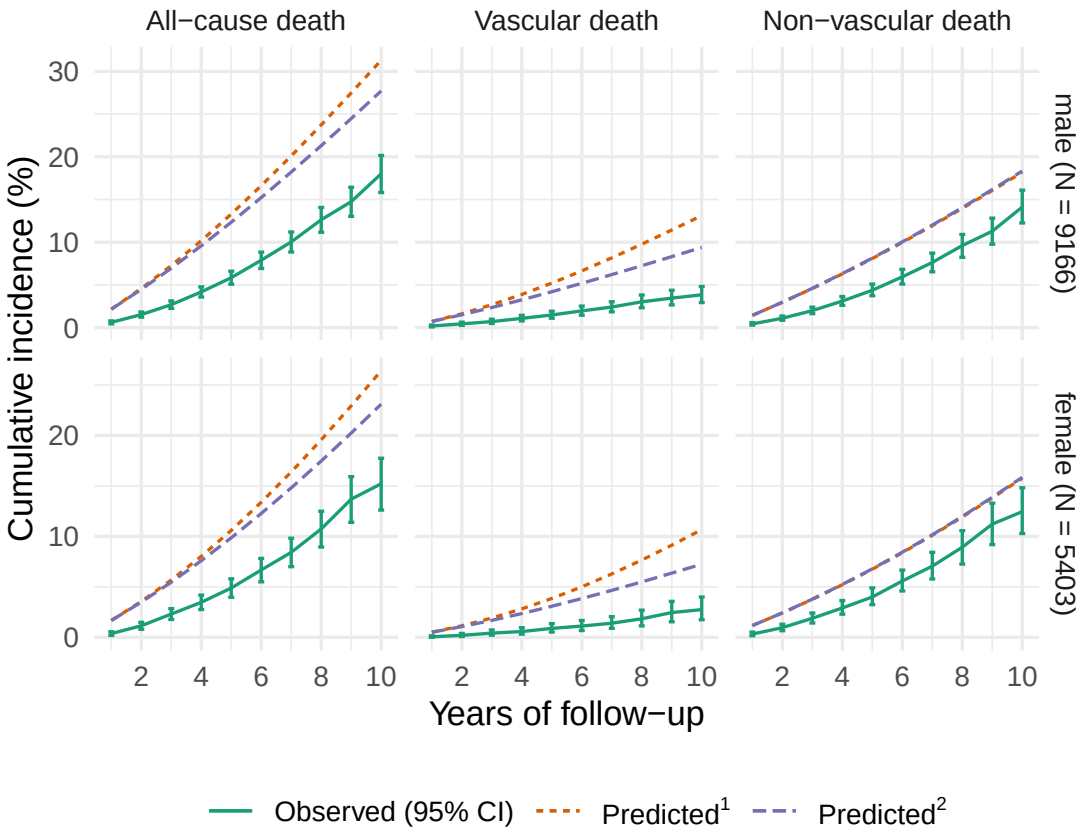


Figure C.3: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by sex. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

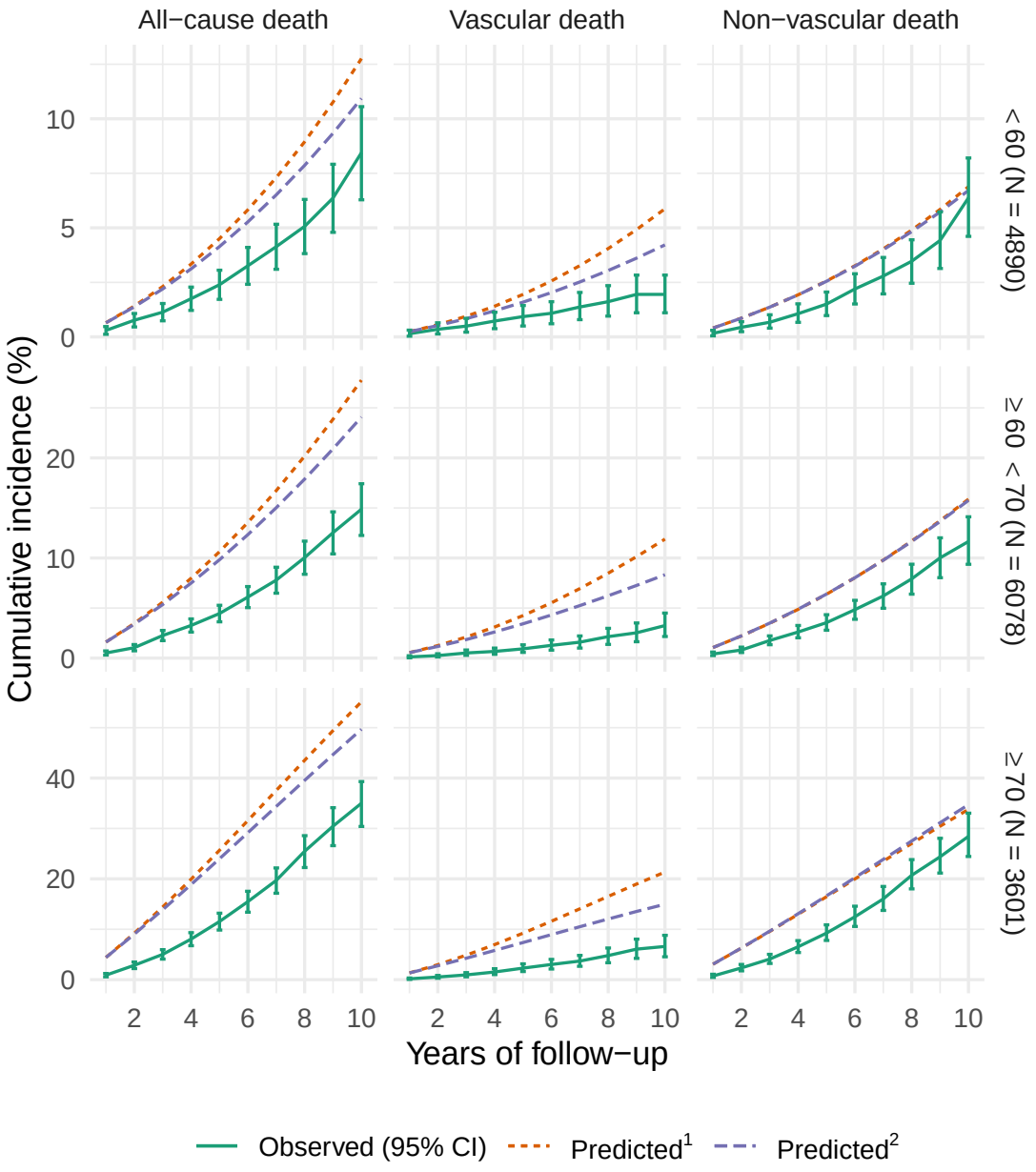


Figure C.4: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by age (years) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

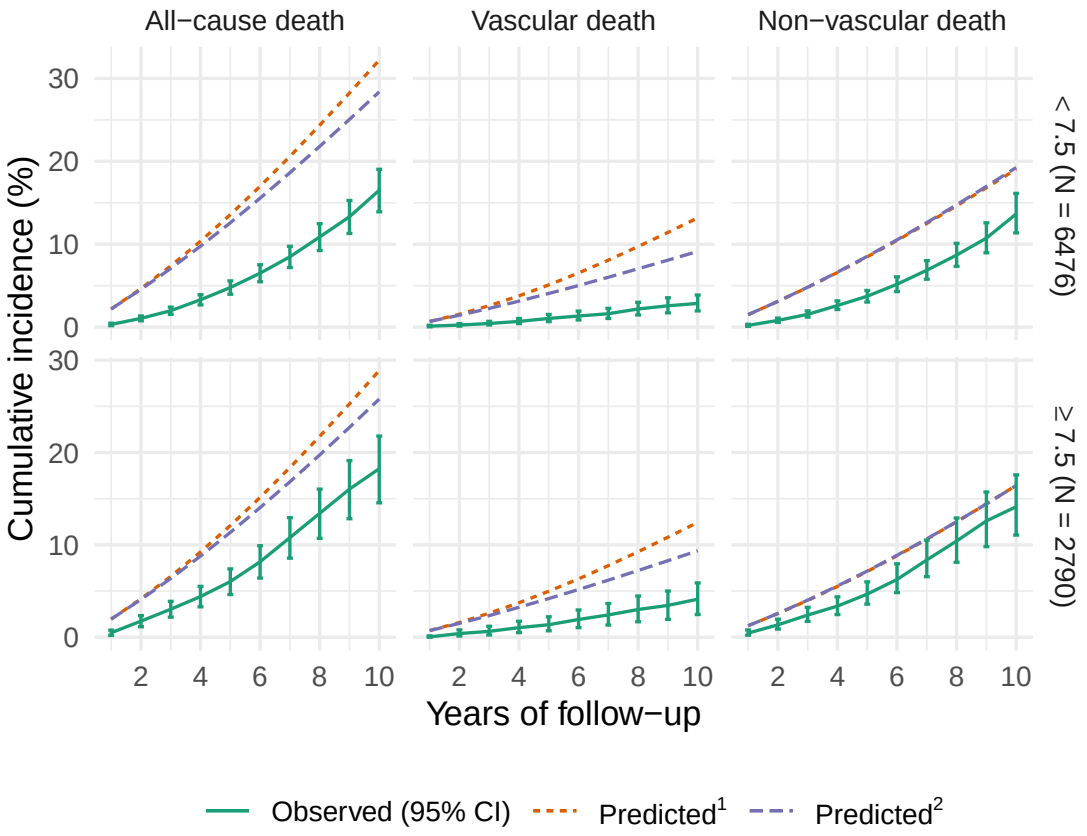


Figure C.5: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by HbA1c (%) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

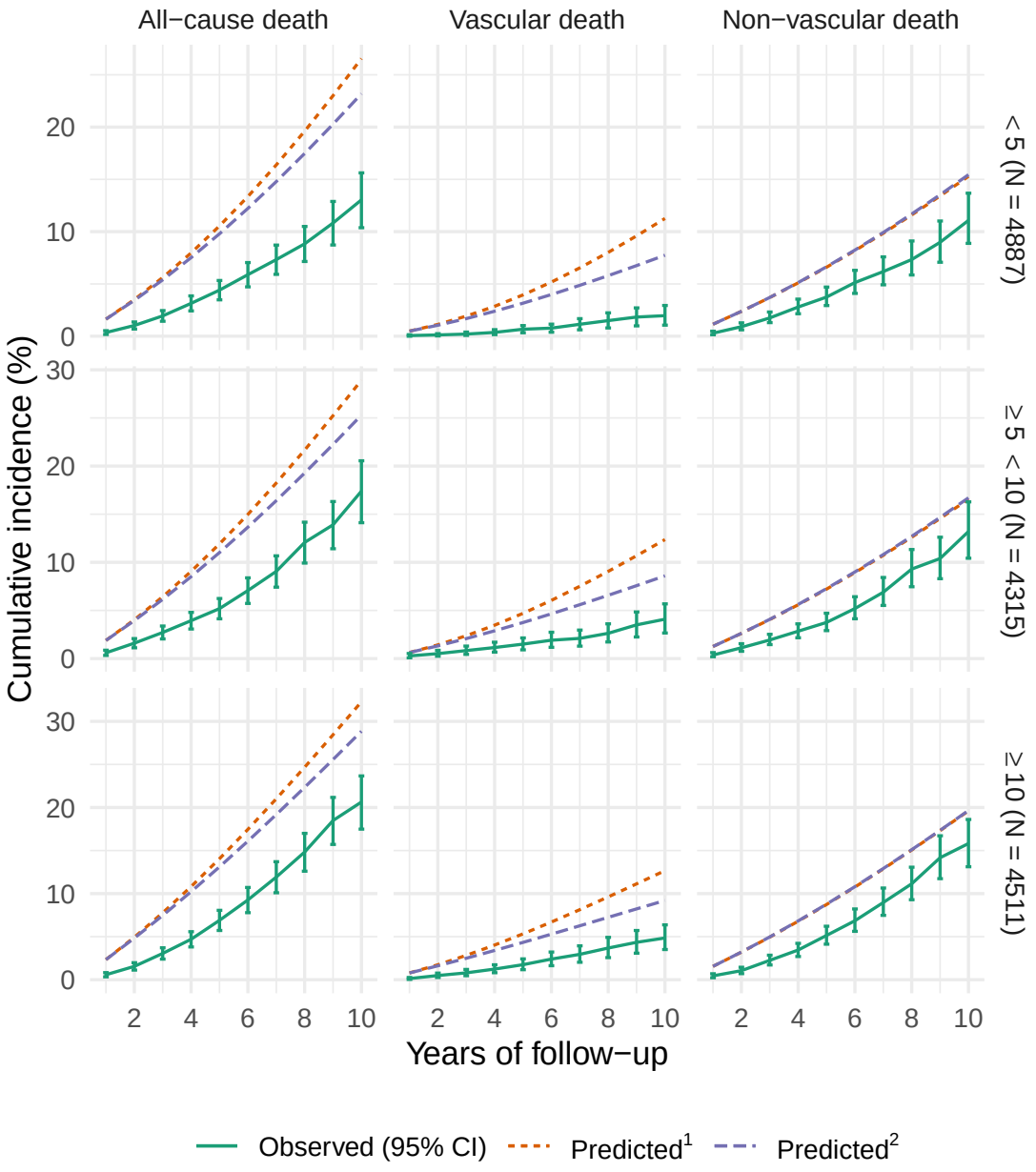


Figure C.6: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by duration of diabetes (years) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

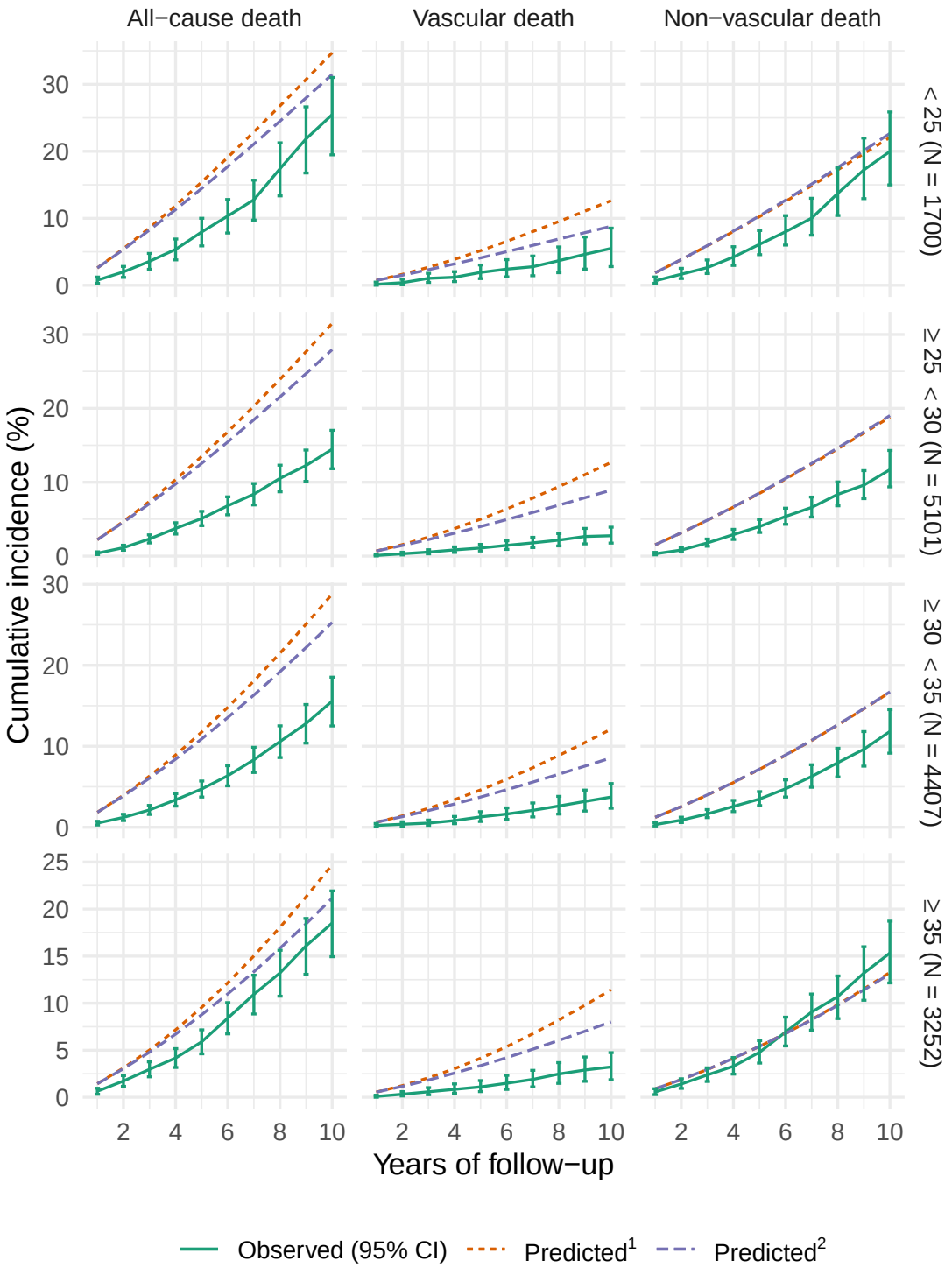


Figure C.7: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, by BMI (kg/m^2) at baseline. [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

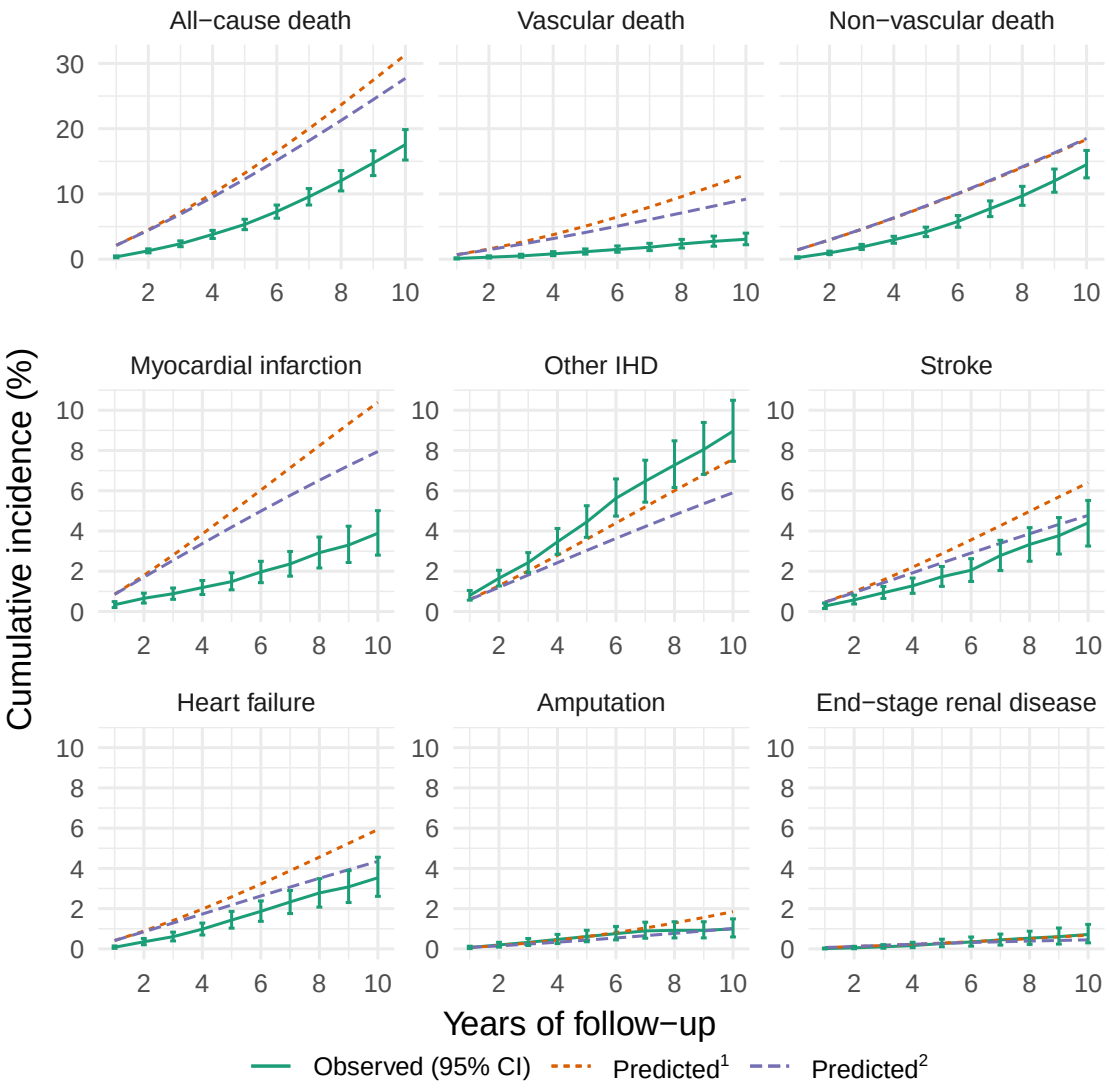


Figure C.8: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, for participants with complete baseline information (N = 7578). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

Table C.5: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in ASCEND with complete baseline information (N = 7578)

Endpoints	Observed cumulative incidence (%) (95% CI)	Predicted[1]				Predicted[2]			
		Cumulative incidence (%)	% error	MAPE (%)	C-statistic	Cumulative incidence (%)	% error	MAPE (%)	C-statistic
All-cause death	9.6 (8.3, 10.8)	20.0	109	213	0.73	18.2	90	200	0.73
Vascular death	1.8 (1.3, 2.4)	8.0	335	382	0.73	6.1	231	318	0.74
Non-vascular death	7.7 (6.5, 8.9)	12.0	55	167	0.72	12.1	56	168	0.73
Myocardial infarction	2.4 (1.8, 3.0)	7.1	202	202	0.61	5.8	144	167	0.62
Other IHD	6.5 (5.4, 7.5)	5.2	-20	21	0.59	4.2	-35	30	0.60
Stroke	2.8 (2.0, 3.5)	4.3	53	68	0.67	3.4	22	49	0.66
Heart failure	2.3 (1.8, 2.9)	3.9	67	147	0.73	3.1	32	126	0.74
Amputation	0.9 (0.5, 1.3)	1.0	16	9	0.78	0.7	-27	24	0.77
End-stage renal disease	0.4 (0.2, 0.7)	0.4	-3	90	0.81	0.4	-21	96	0.82

Note:
% error, percentage error; MAPE, mean absolute percentage error. Vascular death is defined as death from myocardial infarction, other IHD, heart failure or stroke (as in UKPDS-OM2). Percentage error is the degree of overprediction as percentage of observed (negative values represent under-prediction) calculated using the cumulative incidences at year 7. MAPE is the absolute percentage error averaged across the 7 years of follow-up.

[1] UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case).

[2] Values of risk factors during follow-up fixed to baseline values (sensitivity analysis).

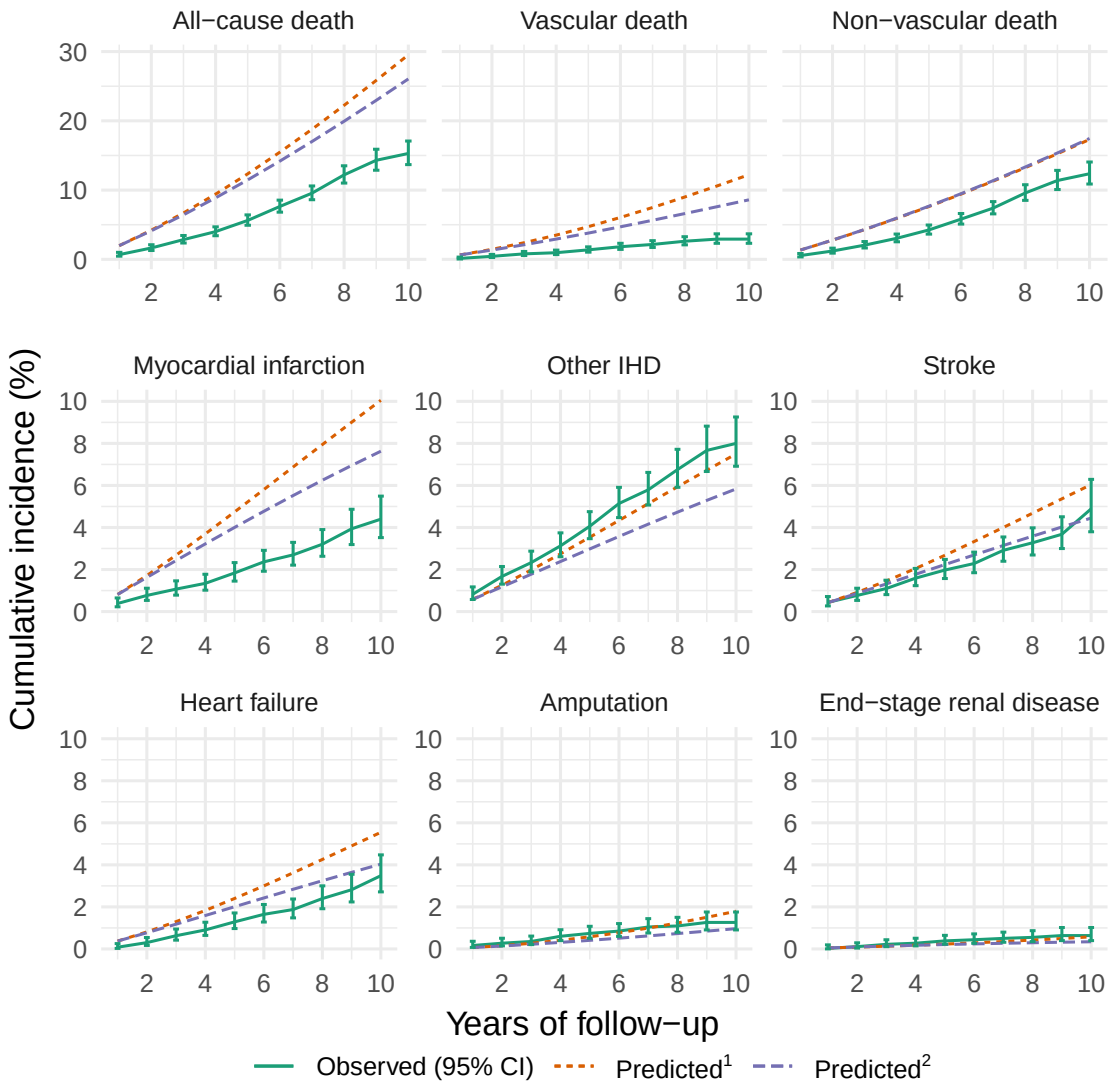


Figure C.9: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with that observed in ASCEND over 10 years, for participants in aspirin placebo and omega-3 placebo arm only (N = 3651). [1]UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case). [2]Values of risk factors during follow-up fixed to baseline values (sensitivity analysis)

Table C.6: Comparison of cumulative incidence of complications predicted by the UKPDS-OM2 with observed rates at 7 years of follow-up for participants in the ASCEND placebo aspirin and placebo omega-3 fatty acid arm only (N = 3651)

Endpoints	Observed cumulative incidence (%) (95% CI)	Predicted[1]				Predicted[2]			
		Cumulative incidence (%)	% error	MAPE (%)	C-statistic	Cumulative incidence (%)	% error	MAPE (%)	C-statistic
All-cause death	9.6 (8.6, 10.6)	18.8	97	133	0.69	17.0	78	122	0.69
Vascular death	2.2 (1.7, 2.7)	7.5	248	255	0.64	5.6	162	205	0.65
Non-vascular death	7.4 (6.6, 8.3)	11.3	53	96	0.71	11.4	54	97	0.71
Myocardial infarction	2.7 (2.2, 3.3)	6.9	155	146	0.53	5.5	105	116	0.53
Other IHD	5.8 (5.1, 6.6)	5.1	-11	17	0.58	4.2	-28	27	0.58
Stroke	2.9 (2.4, 3.5)	4.0	37	29	0.70	3.1	8	12	0.70
Heart failure	1.9 (1.5, 2.4)	3.6	93	142	0.75	2.8	51	119	0.74
Amputation	1.0 (0.8, 1.4)	1.0	-5	28	0.74	0.6	-41	46	0.72
End-stage renal disease	0.5 (0.3, 0.8)	0.4	-30	40	0.74	0.3	-47	44	0.76

Note:
% error, percentage error; MAPE, mean absolute percentage error. Vascular death is defined as death from myocardial infarction, other IHD, heart failure or stroke (as in UKPDS-OM2). Percentage error is the degree of overprediction as percentage of observed (negative values represent under-prediction) calculated using the cumulative incidences at year 7. MAPE is the absolute percentage error averaged across the 7 years of follow-up.

[1] UKPDS-OM2 risk factor progression equations used to project risk factor values during follow-up (base case).

[2] Values of risk factors during follow-up fixed to baseline values (sensitivity analysis).

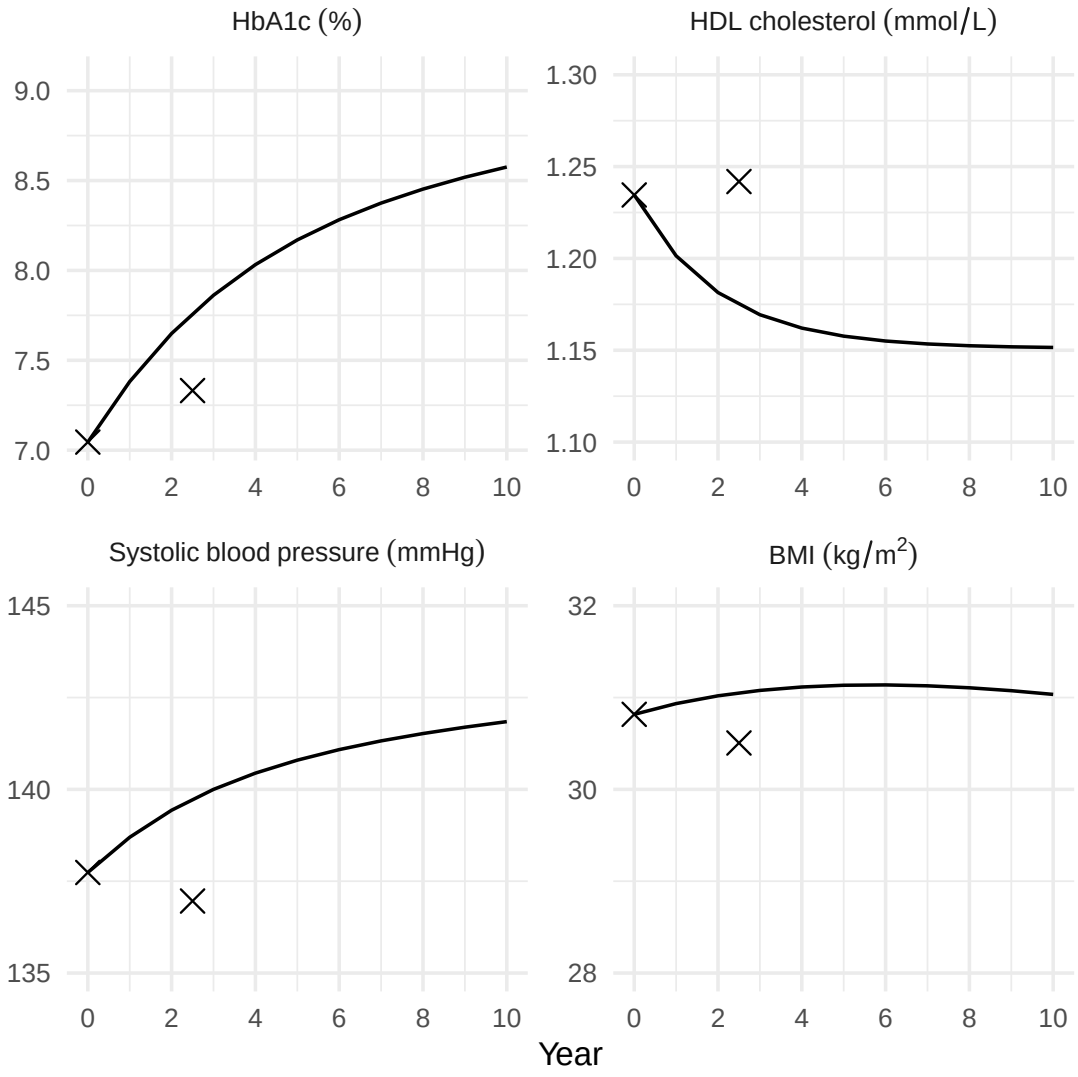


Figure C.10: Average values of risk factors predicted by UKPDS risk factor progression equations (solid black line) compared to those observed (marked 'X') in a random sample of ASCEND participants who returned blood/urine sample at average 2.5 years into follow-up in the validation cohort (N = 1249)

C.3 Simulation model for predicting first occurrences of adverse events over lifetime in people with diabetes without previous cardiovascular disease – model development, validation and updating

Table C.7: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis, after imputation

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
Diabetes type		
Type 1	911 (5.9%)	2432 (13.3%)
Type 2	14569 (94.1%)	15818 (86.7%)
Sex		
Male	9684 (62.6%)	10827 (59.3%)
Female	5796 (37.4%)	7423 (40.7%)
Smoking status		
Current smoker	1279 (8.3%)	1921 (10.5%)
Former/Never smoker	14201 (91.7%)	16329 (89.5%)
Race		
White	15156 (97.9%)	16559 (90.7%)
South Asian	184 (1.2%)	1000 (5.5%)
Black	140 (0.9%)	691 (3.8%)
Other/unknown	-	-
Townsend Index		
Q1: <-2.42 (least deprived)	6728 (43.5%)	6690 (36.7%)
Q2: ≥-2.42, <-0.44	3793 (24.5%)	3866 (21.2%)
Q3: ≥-0.44, < 1.79	2499 (16.1%)	2982 (16.3%)
Q4: ≥ 1.79, < 4.75	1820 (11.8%)	3038 (16.6%)
Q5: ≥ 4.75 (most deprived)	640 (4.1%)	1674 (9.2%)
Hypertension		
Y	9645 (62.3%)	12771 (70%)
N	5835 (37.7%)	5479 (30%)
Diabetic retinopathy		
Y	3023 (19.5%)	1532 (8.4%)
N	12457 (80.5%)	16718 (91.6%)
Statin use		
Y	11653 (75.3%)	12532 (68.7%)
N	3827 (24.7%)	5718 (31.3%)

Table C.7: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis, after imputation *(continued)*

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
Use of ACE Inhibitor or ARB		
Y	9055 (58.5%)	9276 (50.8%)
N	6425 (41.5%)	8974 (49.2%)
Aspirin use (prior to treatment randomisation)		
Y	5508 (35.6%)	7974 (43.7%)
N	9972 (64.4%)	10276 (56.3%)
Age (years)		
Mean (SD)	62.8 (9.2)	59.0 (7.3)
<50	1089 (7%)	2415 (13.2%)
≥50, <60	4501 (29.1%)	5744 (31.5%)
≥60, <70	6247 (40.4%)	9956 (54.6%)
≥70, <80	3086 (19.9%)	135 (0.7%)
≥80	557 (3.6%)	-
Diabetes duration (years)		
Mean (SD)	9.8 (9.3)	8.5 (9.9)
Median (IQR)	7.0 (4.0, 12.2)	5.0 (2.0, 10.0)
<5	5034 (32.5%)	7801 (42.7%)
≥5, <10	4820 (31.1%)	5213 (28.6%)
≥10, <20	3711 (24%)	3440 (18.8%)
≥20	1915 (12.4%)	1796 (9.8%)
Body-mass index (kg/m^2)		
Mean (SD)	31.1 (6.5)	31.2 (5.9)
<25	2070 (13.4%)	2284 (12.5%)
≥25, <30	5541 (35.8%)	6345 (34.8%)
≥30, <35	4565 (29.5%)	5495 (30.1%)
≥35	3304 (21.3%)	4126 (22.6%)
HbA1c (IFCC mmol/mol)		
Mean (SD)	55.0 (11.2)	52.8 (13.5)
< 48	4098 (26.5%)	7393 (40.5%)
≥ 48, < 64	8749 (56.5%)	7886 (43.2%)
≥ 64	2633 (17%)	2971 (16.3%)
HDL cholesterol (mmol/L)		
Mean (SD)	1.27 (0.29)	1.23 (0.32)
< 1.0	2205 (14.2%)	4311 (23.6%)
≥ 1.0, < 1.5	11003 (71.1%)	10906 (59.8%)
≥ 1.5	2272 (14.7%)	3033 (16.6%)
Non-HDL cholesterol (mmol/L)		
Mean (SD)	2.90 (0.69)	3.33 (0.95)

Table C.7: Baseline characteristics of ASCEND and UK Biobank participants included in the analysis, after imputation *(continued)*

Variable	ASCEND (N = 15480)	UK Biobank (N = 18250)
< 2.5	3739 (24.2%)	3295 (18.1%)
≥ 2.5, < 3.5	9623 (62.2%)	8318 (45.6%)
≥ 3.5	2118 (13.7%)	6637 (36.4%)
Systolic blood pressure (mmHg)		
Mean (SD)	135.9 (13.3)	141.5 (17.0)
<130	4252 (27.5%)	4593 (25.2%)
≥130, <140	5667 (36.6%)	4267 (23.4%)
≥140	5561 (35.9%)	9390 (51.5%)
Diastolic blood pressure (mmHg)		
Mean (SD)	77.3 (8.3)	82.1 (9.5)
<75	5274 (34.1%)	3969 (21.7%)
≥75, <85	7798 (50.4%)	7335 (40.2%)
≥85	2408 (15.6%)	6946 (38.1%)
Urinary albumin/creatinine ratio (mg/mmol)		
<3	13541 (87.5%)	15003 (82.2%)
≥3, <30	1674 (10.8%)	2917 (16%)
≥30	265 (1.7%)	330 (1.8%)
eGFR (ml/min/1.73m^2)		
< 45	542 (3.5%)	462 (2.5%)
≥ 45, < 60	1351 (8.7%)	1417 (7.8%)
≥ 60, < 90	6020 (38.9%)	9392 (51.5%)
≥ 90	7567 (48.9%)	6979 (38.2%)

Note:
Summary statistics are N (%) unless otherwise specified. Summary statistics exclude missing data.

Table C.8: List of variables included for selection

Variables	Categories (if categorical)
Time-invariant variables; measured at recruitment into ASCEND	
Diabetes type	Type 1
	Type 2
Sex	Male
	Female
Smoking status	Current smoker
	Former/never smoker
Race	White
	South Asian (Indian/Pakistani/Bangladeshi)
	Black (African/Caribbean)
Townsend Index*	Q1: <-2.42
	Q2: ≥-2.42, <-0.44
	Q3: ≥-0.44, <1.79
	Q4: ≥ 1.79, <4.75
	Q5: ≥ 4.75
Hypertension	Y / N
Diabetic retinopathy	Y / N
Use of statin	Y / N
Use of ACE inhibitor or ARB	Y / N
Diabetes duration (years)	<10
	≥10, <15
	≥15, <25
	≥25
BMI (kg/m^2)†	<25
	≥25, <30
	≥30, <35
	≥35
HbA1c (IFCC mmol/mol)	< 48
	≥ 48, < 64
	≥ 64
HDL cholesterol (mmol/L)	< 1.0
	≥ 1.0, < 1.5
	≥ 1.5
Non-HDL cholesterol (mmol/L)	< 2.5
	≥ 2.5, < 3.5
	≥ 3.5
Systolic blood pressure (mmHg)	<130
	≥130, <140
	≥140
Diastolic blood pressure (mmHg)	<75
	≥75, <85
	≥85

Table C.8: List of variables included for selection *(continued)*

Variables	Categories (if categorical)
Urinary albumin/creatinine ratio (mg/mmol)	< 3
	≥ 3
eGFR (ml/min/1.73m^2)‡	< 45
	$\geq 45, < 60$
	$\geq 60, < 90$
	≥ 90
Time-varying variables	
Age (years)	-
Disease history (adverse events listed below)	No history
	In year
	Previous year
	At least 2 years ago
Adverse event	Myocardial infarction
	Coronary revascularisation (non-urgent)
	Coronary revascularisation (urgent)
	Transient ischaemic attack
	Ischaemic stroke
	Heart failure
	Intracranial haemorrhage
	GI bleed
	Other major bleed
	GI tract cancer
	Non-GI tract cancer
	Amputation
	End-stage renal disease

* Measure of socioeconomic status calculated using postcode at randomisation. Higher value indicates greater deprivation. Stratified according to range of scores of 2011 UK population quintiles.

† Based on self-reported height and weight.

‡ Calculated from blood cystatin C concentration using the CKD-EPI formula.

Table C.9: Number (%) of participants with each disease history at time of occurrence of each adverse event in ASCEND

		MI	CRV (u)	CRV (nu)	TIA	Istroke	HF	Intrac haem	GI bleed	Other bleed	GI tract cancer	Other cancer	Amp	ESRD	VD	NVD
N	**-**	**465**	**273**	**293**	**365**	**456**	**357**	**100**	**238**	**117**	**315**	**1577**	**144**	**105**	**414**	**1126**
MI	In year	-	237 (86.8%)	14 (4.8%)	1 (0.3%)	4 (0.9%)	17 (4.8%)	4 (4%)	7 (2.9%)	1 (0.9%)	0 (0%)	6 (0.4%)	3 (2.1%)	4 (3.8%)	89 (21.5%)	11 (1%)
	Previous years	-	13 (4.8%)	3 (1%)	6 (1.6%)	13 (2.9%)	25 (7%)	1 (1%)	6 (2.5%)	4 (3.4%)	2 (0.6%)	16 (1%)	7 (4.9%)	3 (2.9%)	25 (6%)	29 (2.6%)
CRV (u)	In year	3 (0.6%)	-	10 (3.4%)	1 (0.3%)	1 (0.2%)	3 (0.8%)	0 (0%)	2 (0.8%)	1 (0.9%)	0 (0%)	1 (0.1%)	3 (2.1%)	3 (2.9%)	7 (1.7%)	3 (0.3%)
	Previous years	1 (0.2%)	-	2 (0.7%)	4 (1.1%)	6 (1.3%)	17 (4.8%)	0 (0%)	3 (1.3%)	0 (0%)	1 (0.3%)	8 (0.5%)	4 (2.8%)	1 (1%)	5 (1.2%)	14 (1.2%)
CRV (nu)	In year	6 (1.3%)	3 (1.1%)	-	1 (0.3%)	4 (0.9%)	2 (0.6%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	4 (0.3%)	1 (0.7%)	1 (1%)	3 (0.7%)	0 (0%)
	Previous years	12 (2.6%)	7 (2.6%)	-	1 (0.3%)	8 (1.8%)	12 (3.4%)	1 (1%)	2 (0.8%)	2 (1.7%)	2 (0.6%)	11 (0.7%)	0 (0%)	2 (1.9%)	6 (1.4%)	14 (1.2%)
TIA	In year	2 (0.4%)	0 (0%)	0 (0%)	-	23 (5%)	3 (0.8%)	1 (1%)	0 (0%)	0 (0%)	1 (0.3%)	4 (0.3%)	0 (0%)	0 (0%)	2 (0.5%)	2 (0.2%)
	Previous years	13 (2.8%)	8 (2.9%)	7 (2.4%)	-	17 (3.7%)	9 (2.5%)	1 (1%)	3 (1.3%)	2 (1.7%)	2 (0.6%)	19 (1.2%)	4 (2.8%)	1 (1%)	16 (3.9%)	32 (2.8%)
Istroke	In year	2 (0.4%)	1 (0.4%)	1 (0.3%)	17 (4.7%)	-	5 (1.4%)	1 (1%)	4 (1.7%)	1 (0.9%)	3 (1%)	8 (0.5%)	0 (0%)	2 (1.9%)	45 (10.9%)	10 (0.9%)
	Previous years	9 (1.9%)	4 (1.5%)	3 (1%)	21 (5.8%)	-	11 (3.1%)	5 (5%)	7 (2.9%)	2 (1.7%)	4 (1.3%)	15 (1%)	3 (2.1%)	3 (2.9%)	28 (6.8%)	50 (4.4%)

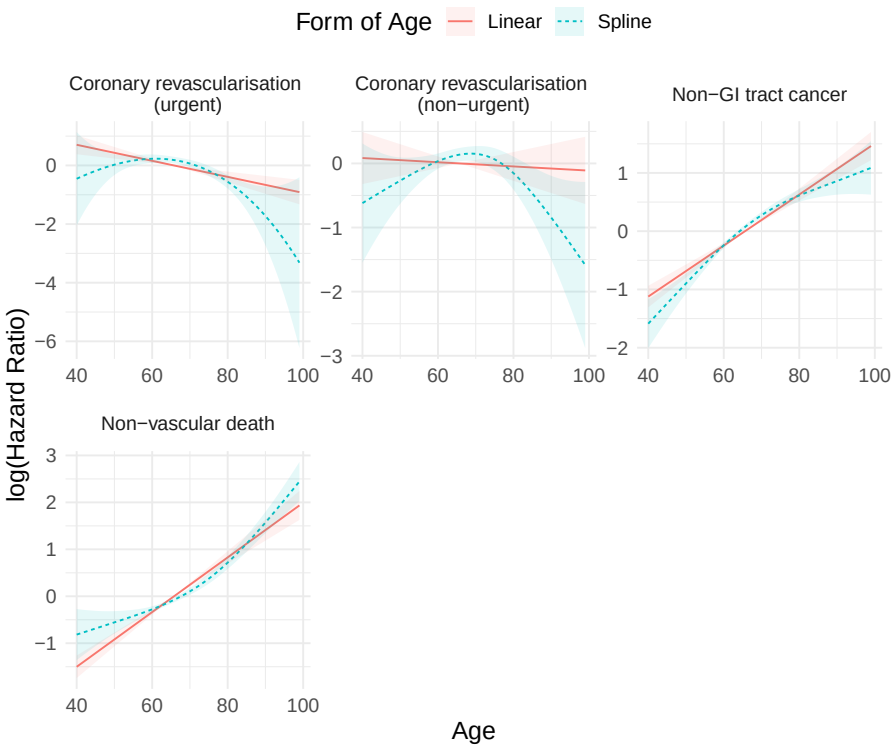
Table C.9: Number (%) of participants with each disease history at time of occurrence of each adverse event in ASCEND *(continued)*

		MI	CRV (u)	CRV (nu)	TIA	Istroke	HF	Intrac haem	GI bleed	Other bleed	GI tract cancer	Other cancer	Amp	ESRD	VD	NVD
HF	In year	10 (2.2%)	6 (2.2%)	6 (2%)	0 (0%)	3 (0.7%)	-	0 (0%)	2 (0.8%)	1 (0.9%)	0 (0%)	5 (0.3%)	0 (0%)	3 (2.9%)	59 (14.3%)	22 (2%)
	Previous years	11 (2.4%)	8 (2.9%)	7 (2.4%)	4 (1.1%)	4 (0.9%)	-	1 (1%)	4 (1.7%)	2 (1.7%)	1 (0.3%)	9 (0.6%)	4 (2.8%)	10 (9.5%)	39 (9.4%)	31 (2.8%)
Intrac haem	In year	2 (0.4%)	2 (0.7%)	0 (0%)	0 (0%)	1 (0.2%)	2 (0.6%)	-	1 (0.4%)	0 (0%)	0 (0%)	2 (0.1%)	0 (0%)	0 (0%)	1 (0.2%)	30 (2.7%)
	Previous years	0 (0%)	0 (0%)	0 (0%)	3 (0.8%)	4 (0.9%)	0 (0%)	-	1 (0.4%)	0 (0%)	1 (0.3%)	5 (0.3%)	1 (0.7%)	0 (0%)	2 (0.5%)	16 (1.4%)
GI bleed	In year	5 (1.1%)	2 (0.7%)	3 (1%)	1 (0.3%)	4 (0.9%)	3 (0.8%)	0 (0%)	-	0 (0%)	7 (2.2%)	15 (1%)	0 (0%)	1 (1%)	5 (1.2%)	31 (2.8%)
	Previous years	4 (0.9%)	0 (0%)	2 (0.7%)	1 (0.3%)	5 (1.1%)	8 (2.2%)	2 (2%)	-	3 (2.6%)	4 (1.3%)	13 (0.8%)	1 (0.7%)	3 (2.9%)	8 (1.9%)	34 (3%)
Other bleed	In year	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.4%)	-	1 (0.3%)	11 (0.7%)	0 (0%)	0 (0%)	1 (0.2%)	5 (0.4%)
	Previous years	3 (0.6%)	1 (0.4%)	4 (1.4%)	0 (0%)	2 (0.4%)	5 (1.4%)	1 (1%)	4 (1.7%)	-	2 (0.6%)	9 (0.6%)	0 (0%)	0 (0%)	5 (1.2%)	16 (1.4%)
GI tract cancer	In year	0 (0%)	0 (0%)	1 (0.3%)	1 (0.3%)	2 (0.4%)	1 (0.3%)	1 (1%)	6 (2.5%)	0 (0%)	-	17 (1.1%)	0 (0%)	0 (0%)	0 (0%)	55 (4.9%)
	Previous years	4 (0.9%)	2 (0.7%)	0 (0%)	3 (0.8%)	3 (0.7%)	6 (1.7%)	1 (1%)	7 (2.9%)	1 (0.9%)	-	26 (1.6%)	0 (0%)	1 (1%)	1 (0.2%)	77 (6.8%)

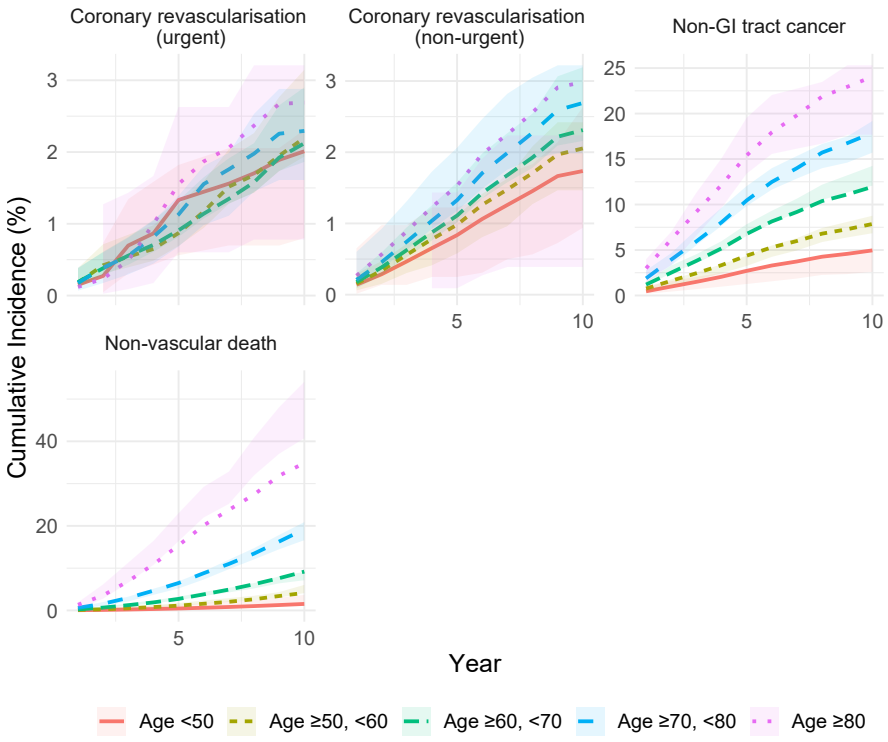
Table C.9: Number (%) of participants with each disease history at time of occurrence of each adverse event in ASCEND *(continued)*

		MI	CRV (u)	CRV (nu)	TIA	Istroke	HF	Intrac haem	GI bleed	Other bleed	GI tract cancer	Other cancer	Amp	ESRD	VD	NVD
Other cancer	In year	10 (2.2%)	1 (0.4%)	5 (1.7%)	5 (1.4%)	5 (1.1%)	3 (0.8%)	2 (2%)	10 (4.2%)	8 (6.8%)	11 (3.5%)	-	1 (0.7%)	3 (2.9%)	13 (3.1%)	259 (23%)
	Previous years	24 (5.2%)	10 (3.7%)	7 (2.4%)	11 (3%)	17 (3.7%)	28 (7.8%)	4 (4%)	16 (6.7%)	10 (8.5%)	17 (5.4%)	-	6 (4.2%)	6 (5.7%)	23 (5.6%)	328 (29.1%)
Amp	In year	2 (0.4%)	2 (0.7%)	0 (0%)	0 (0%)	2 (0.4%)	1 (0.3%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)	2 (0.5%)	1 (0.1%)
	Previous years	6 (1.3%)	2 (0.7%)	2 (0.7%)	3 (0.8%)	12 (2.6%)	6 (1.7%)	4 (4%)	1 (0.4%)	0 (0%)	1 (0.3%)	7 (0.4%)	-	6 (5.7%)	15 (3.6%)	22 (2%)
ESRD	In year	2 (0.4%)	1 (0.4%)	1 (0.3%)	3 (0.8%)	2 (0.4%)	2 (0.6%)	1 (1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-	1 (0.2%)	4 (0.4%)
	Previous years	3 (0.6%)	1 (0.4%)	2 (0.7%)	5 (1.4%)	5 (1.1%)	4 (1.1%)	2 (2%)	0 (0%)	3 (2.6%)	1 (0.3%)	5 (0.3%)	6 (4.2%)	-	6 (1.4%)	20 (1.8%)

Note:
MI, myocardial infarction; CRV(u), urgent coronary revascularisation; CRV(nu), non-urgent coronary revascularisation; TIA, transient ischaemic attack; Istroke, ischaemic stroke; HF, heart failure; Intrac haem, intracranial haemorrhage; GI, gastrointestinal; Amp, amputation; ESRD, end-stage renal disease; VD, vascular death; NVD, non-vascular death.

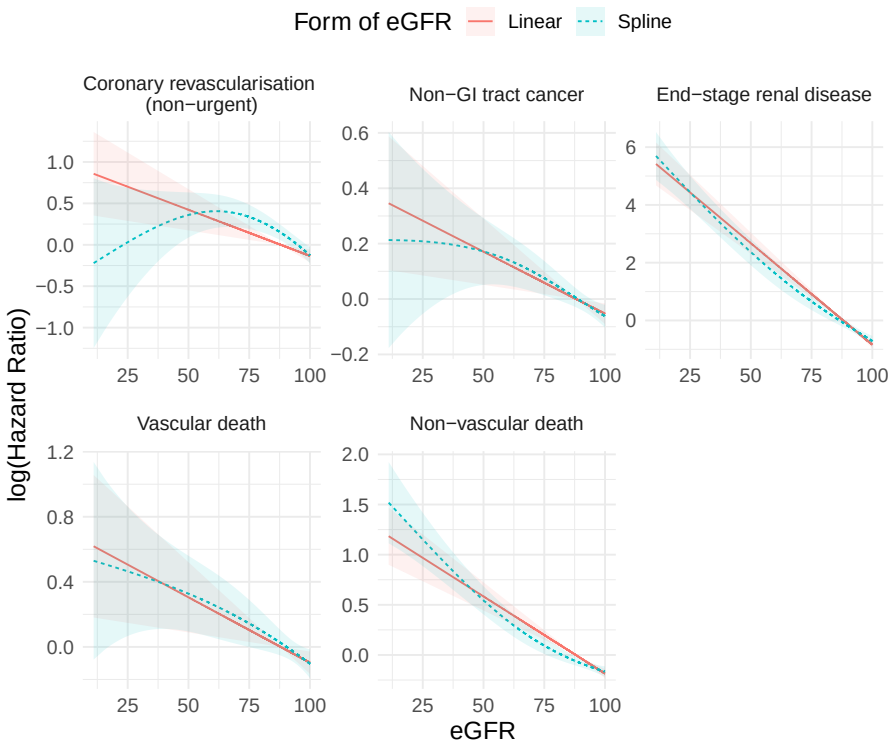


(a)

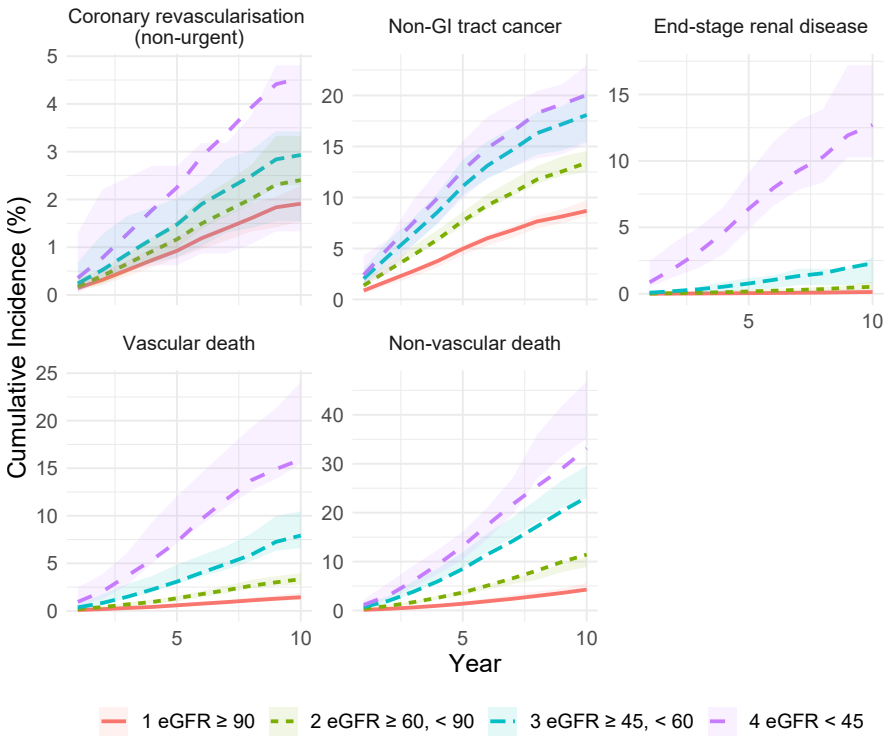


(b)

Figure C.11: (a) Log hazard ratio for spline and linear forms of age, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by age subgroup

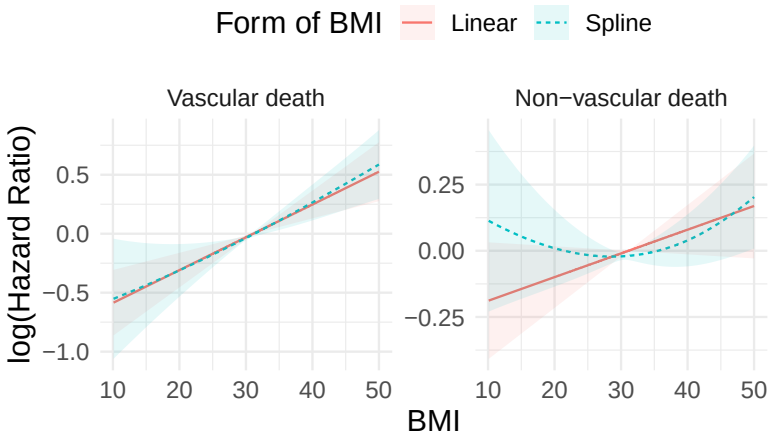


(a)

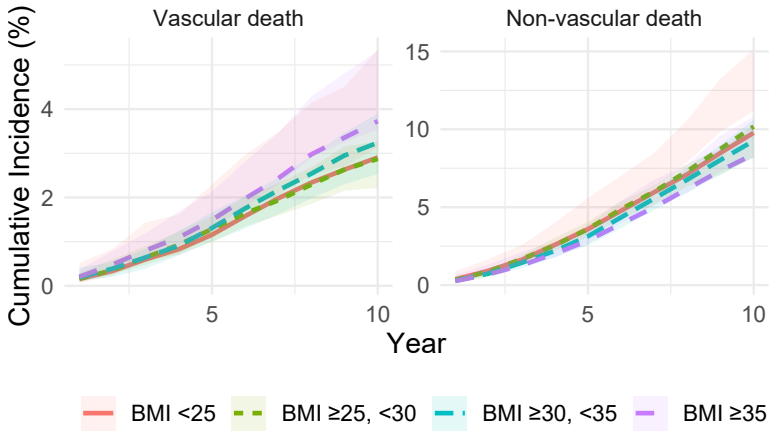


(b)

Figure C.12: (a) Log hazard ratio for spline and linear forms of eGFR, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by eGFR subgroup

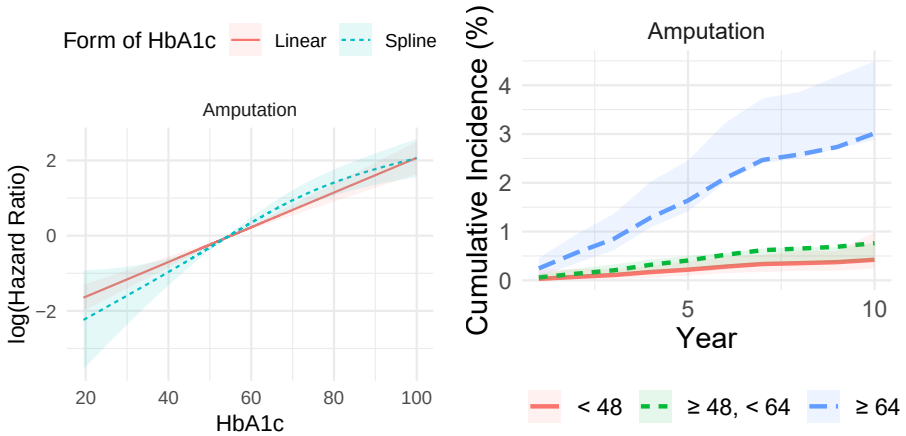


(a)



(b)

Figure C.13: (a) Log hazard ratio for spline and linear forms of BMI, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by BMI subgroup



(a) **(b)**

Figure C.14: (a) Log hazard ratio for spline and linear forms of HbA1c, and (b) comparison of cumulative incidence observed in ASCEND (shaded region) vs predicted by models (lines) for the linear Cox proportional hazard models by HbA1c subgroup

Table C.10: Hazard ratios of non-linear terms (categorised) estimated in Cox proportional hazard models

	Coronary revascularisation (non-urgent)	Vascular death	Non-vascular death
Age (ref: <50)			
≥50, <60	0.88 (0.41, 1.88)	-	2.09 (0.84, 5.17)
≥60, <70	0.97 (0.46, 2.02)	-	2.51 (1.03, 6.12)
≥70, <80	1.09 (0.51, 2.34)	-	3.26 (1.33, 7.98)
≥80	0.35 (0.14, 0.89)	-	6.92 (2.79, 17.12)
BMI (ref: <25 kg/m^2)			
≥25, <30	-	0.72 (0.53, 0.98)	0.66 (0.56, 0.79)
≥30, <35	-	0.79 (0.57, 1.09)	0.76 (0.63, 0.91)
≥35	-	1.22 (0.87, 1.72)	0.88 (0.72, 1.09)
eGFR (ref: <60 ml/min/1.73m^2)			
≥60, <90	-	-	0.52 (0.45, 0.60)
≥90	-	-	0.46 (0.38, 0.56)

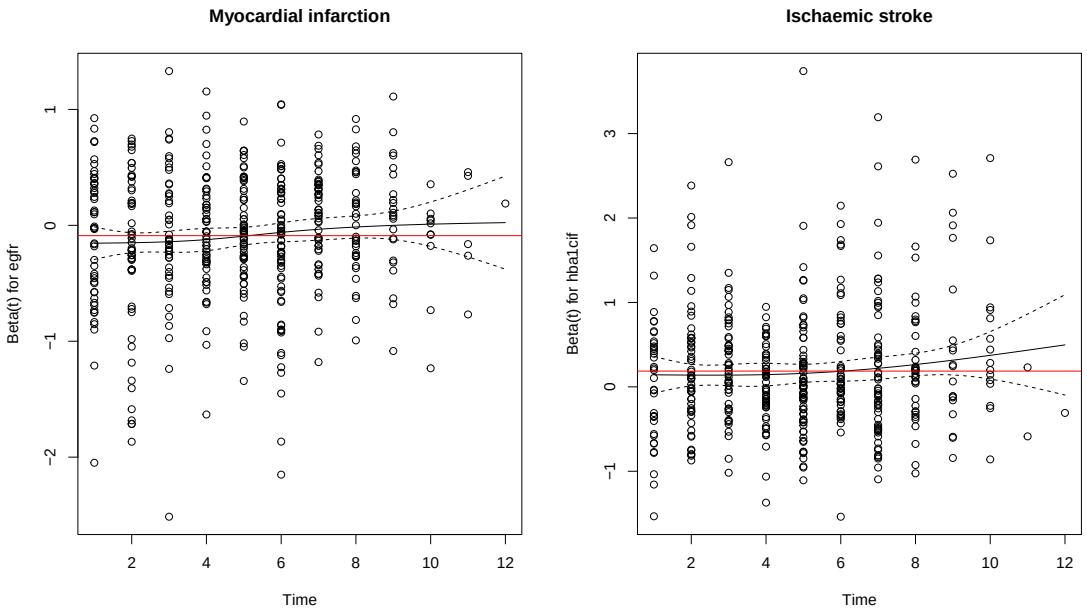


Figure C.15: Plots of Schoenfeld residuals

Table C.11: Risk equations for predicting risks of adverse events

	Cox proportional hazard models		Parametric proportional hazard models	
	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Myocardial infarction				
No. of events	*465*	*283*	*465*	
Person-years	*119523*	*77036*	*119523*	
Distribution (shape, scale)			*Weibull (1.068170, 0.000302)*	
Antithrombotic drug use	0.90 (0.69, 1.17)	0.90 (0.64, 1.26)	0.91 (0.70, 1.18)	
Sex (ref: Female)				
Male	1.61 (1.31, 1.99)	1.40 (1.09, 1.81)	1.61 (1.31, 1.99)	
Current smoker (ref: N)				
Y	1.63 (1.22, 2.17)	1.79 (1.22, 2.62)	1.63 (1.22, 2.17)	
Age (per 10 years)	1.28 (1.13, 1.46)	1.49 (1.28, 1.73)	1.29 (1.14, 1.46)	
Diabetes duration (per year)	1.01 (1.01, 1.02)	1.26 (1.13, 1.39)	1.16 (1.06, 1.27)	
HbA1c (per 10 mmol/mol)	1.15 (1.07, 1.24)	1.14 (1.05, 1.25)	1.15 (1.07, 1.24)	
eGFR (per 10 ml/min/1.73m^2)	0.91 (0.87, 0.96)	0.92 (0.87, 0.98)	0.92 (0.87, 0.96)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	1.93 (1.54, 2.42)	1.38 (1.02, 1.87)	1.94 (1.55, 2.43)	
Coronary revascularisation (non-urgent)				
Any history	2.75 (1.70, 4.44)	2.07 (1.05, 4.07)	2.74 (1.70, 4.43)	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Heart failure				
Any history	2.65 (1.68, 4.20)	2.20 (1.17, 4.11)	2.69 (1.70, 4.25)	
Coronary revascularisation (urgent)				
No. of events	*273*	*161*	*273*	
Person-years	*119828*	*77237*	*119828*	
Distribution (shape, scale)			*Weibull (1.068849, 0.000802)*	
Antithrombotic drug use	0.98 (0.69, 1.38)	1.15 (0.73, 1.81)	1.03 (0.73, 1.46)	
Sex (ref: Female)				
Male	1.47 (1.11, 1.97)	1.51 (1.05, 2.18)	1.48 (1.11, 1.97)	
Age (per 10 years)	0.76 (0.67, 0.86)	0.74 (0.62, 0.87)	0.76 (0.67, 0.86)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	0.54 (0.40, 0.75)	0.82 (0.53, 1.25)	0.56 (0.41, 0.77)	
Myocardial infarction				
In year	4313.27 (2793.64, 6659.52)	5088.35 (2798.57, 9251.61)	4185.42 (2715.95, 6449.94)	
At least 1 year ago	229.56 (115.27, 457.16)	321.32 (133.25, 774.81)	224.76 (113.01, 447.03)	
Coronary revascularisation (non-urgent)				
No. of events	*293*	*201*	*293*	
Person-years	*119689*	*77053*	*119689*	
Distribution (shape, scale)			*Weibull (1.206315, 0.000533)*	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Antithrombotic drug use	0.87 (0.62, 1.20)	0.73 (0.49, 1.09)	0.87 (0.63, 1.21)	
Sex (ref: Female)				
Male	2.08 (1.58, 2.73)	2.16 (1.55, 3.01)	2.10 (1.60, 2.76)	
Age < 80 (ref: N)				
Y	0.34 (0.19, 0.59)	0.27 (0.13, 0.57)	0.33 (0.19, 0.58)	
Systolic blood pressure (per 10 mmHg)	1.13 (1.04, 1.23)	1.12 (1.02, 1.22)	1.13 (1.05, 1.23)	
Diabetes duration (per year)	1.18 (1.06, 1.31)	1.15 (1.01, 1.30)	1.17 (1.05, 1.30)	
eGFR (per 10 ml/min/1.73m^2)	0.87 (0.82, 0.92)	0.91 (0.85, 0.97)	0.87 (0.82, 0.91)	
Myocardial infarction				
Any history	3.06 (1.83, 5.12)	4.40 (2.51, 7.71)	2.99 (1.79, 4.99)	
Heart failure				
Any history	3.09 (1.70, 5.61)	4.74 (2.50, 8.99)	2.97 (1.64, 5.38)	
Transient ischaemic attack				
No. of events	*365*	*251*	*365*	
Person-years	*119455*	*76893*	*119455*	
Distribution (shape, scale)			*Weibull (0.950114, 0.000983)*	
Antithrombotic drug use	0.80 (0.60, 1.06)	1.00 (0.71, 1.42)	0.80 (0.60, 1.07)	
Sex (ref: Female)				

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Male	0.99 (0.79, 1.23)	0.92 (0.71, 1.19)	0.99 (0.80, 1.24)	
Age (per 10 years)	1.39 (1.21, 1.59)	1.53 (1.31, 1.80)	1.37 (1.19, 1.57)	
eGFR (per 10 ml/min/1.73m^2)	0.89 (0.84, 0.94)	0.90 (0.84, 0.96)	0.89 (0.83, 0.94)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	1.51 (1.15, 1.97)	1.08 (0.77, 1.53)	1.50 (1.15, 1.96)	
Retinopathy (ref: N)				
Y	1.39 (1.10, 1.77)	1.32 (0.99, 1.77)	1.39 (1.10, 1.76)	
Ischaemic stroke				
In year	10.03 (6.12, 16.43)	8.72 (4.60, 16.52)	9.97 (6.09, 16.33)	
At least 1 year ago	5.19 (3.30, 8.17)	5.26 (3.07, 9.02)	5.10 (3.25, 8.02)	
Ischaemic stroke				
No. of events	*456*	*308*	*456*	
Person-years	*119432*	*76909*	*119432*	
Distribution (shape, scale)			*Weibull (1.057890, 0.000010)*	
Antithrombotic drug use	0.88 (0.67, 1.14)	0.85 (0.61, 1.18)	0.88 (0.67, 1.14)	
Sex (ref: Female)				
Male	1.24 (1.01, 1.51)	1.24 (0.98, 1.58)	1.24 (1.02, 1.52)	
Current smoker (ref: N)				
Y	1.67 (1.23, 2.25)	1.62 (1.11, 2.38)	1.66 (1.23, 2.24)	
Age (per 10 years)	1.93 (1.73, 2.14)	1.94 (1.71, 2.22)	1.92 (1.73, 2.13)	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
HbA1c (per 10 mmol/mol)	1.21 (1.12, 1.30)	1.17 (1.08, 1.27)	1.20 (1.12, 1.29)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	2.01 (1.61, 2.50)	1.67 (1.28, 2.19)	2.02 (1.62, 2.50)	
Transient ischaemic attack				
In year	13.65 (8.93, 20.85)	14.99 (9.14, 24.58)	13.43 (8.79, 20.52)	
At least 1 year ago	2.77 (1.70, 4.53)	2.77 (1.54, 4.97)	2.79 (1.71, 4.55)	
Amputation				
Any history	3.24 (1.87, 5.64)	4.29 (2.30, 7.98)	3.28 (1.89, 5.68)	
Heart failure				
No. of events	*357*	*247*	*357*	*430*
Person-years	*120041*	*77294*	*120041*	*200287*
Distribution (shape, scale)			*Weibull (1.507411, 0.000133)*	
Antithrombotic drug use	0.92 (0.67, 1.26)	0.90 (0.62, 1.32)	0.92 (0.67, 1.26)	
Sex (ref: Female)				
Male	1.12 (0.90, 1.41)	1.05 (0.81, 1.37)	1.13 (0.90, 1.42)	
Current smoker (ref: N)				
Y	1.61 (1.15, 2.26)	1.49 (0.96, 2.31)	1.61 (1.15, 2.24)	
Age (per 10 years)	1.38 (1.20, 1.59)	1.73 (1.46, 2.04)	1.37 (1.19, 1.57)	
BMI (per 1 kg/m^2)	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)	
HbA1c (per 10 mmol/mol)	1.16 (1.06, 1.26)	1.18 (1.07, 1.29)	1.15 (1.06, 1.26)	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
eGFR (per 10 ml/min/1.73m^2)	0.72 (0.68, 0.76)	0.75 (0.70, 0.80)	0.72 (0.68, 0.76)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	2.51 (1.96, 3.20)	1.83 (1.36, 2.46)	2.51 (1.97, 3.20)	1.58 (1.29, 1.93)
Myocardial infarction				
Any history	5.04 (3.62, 7.02)	4.21 (2.71, 6.53)	5.07 (3.64, 7.06)	
Coronary revascularisation (non-urgent)				
Any history	2.28 (1.33, 3.92)	3.06 (1.65, 5.65)	2.23 (1.30, 3.83)	
Intracranial haemorrhage				
No. of events	*100*	*58*	*100*	*219*
Person-years	*120489*	*77652*	*120489*	*200500*
Distribution (shape, scale)			*Weibull (1.116991, 0.000927)*	
Antithrombotic drug use	1.53 (0.86, 2.71)	1.40 (0.65, 3.04)	1.52 (0.87, 2.68)	
Sex (ref: Female)				
Male	1.06 (0.69, 1.65)	1.12 (0.65, 1.95)	1.06 (0.69, 1.64)	
Age (per 10 years)	1.36 (1.05, 1.77)	1.61 (1.14, 2.27)	1.40 (1.08, 1.82)	
BMI (per 1 kg/m^2)	0.94 (0.90, 0.98)	0.93 (0.88, 0.98)	0.94 (0.90, 0.98)	
eGFR (per 10 ml/min/1.73m^2)	0.81 (0.73, 0.90)	0.82 (0.71, 0.94)	0.82 (0.74, 0.91)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	6.15 (3.99, 9.49)	1.60 (0.85, 3.03)	6.14 (3.98, 9.46)	1.57 (1.17, 2.12)

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
GI bleed				
No. of events	*238*	*161*	*238*	
Person-years	*120021*	*77293*	*120021*	
Distribution (shape, scale)			*Weibull (1.029123, 0.001399)*	
Antithrombotic drug use	1.59 (1.10, 2.29)	1.77 (1.13, 2.76)	1.58 (1.10, 2.28)	
Sex (ref: Female)				
Male	1.11 (0.84, 1.46)	1.18 (0.85, 1.65)	1.11 (0.84, 1.46)	
Age (per 10 years)	1.15 (0.97, 1.37)	1.24 (1.02, 1.51)	1.16 (0.98, 1.37)	
eGFR (per 10 ml/min/1.73m^2)	0.86 (0.80, 0.93)	0.88 (0.81, 0.96)	0.87 (0.81, 0.93)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	1.71 (1.24, 2.36)	1.44 (0.97, 2.15)	1.71 (1.24, 2.37)	
Myocardial infarction				
Any history	3.27 (1.85, 5.77)	2.92 (1.36, 6.27)	3.32 (1.88, 5.84)	
GI tract cancer				
Any history	5.73 (3.24, 10.10)	4.93 (2.39, 10.16)	5.76 (3.27, 10.16)	
Other major bleed				
No. of events	*117*	*78*	*117*	
Person-years	*120294*	*77501*	*120294*	
Distribution (shape, scale)			*Weibull (0.800109, 0.000114)*	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Antithrombotic drug use	2.10 (1.26, 3.49)	1.89 (1.02, 3.48)	2.19 (1.30, 3.68)	
Sex (ref: Female)				
Male	1.28 (0.86, 1.88)	1.13 (0.71, 1.81)	1.29 (0.87, 1.91)	
Age (per 10 years)	1.36 (1.11, 1.66)	1.34 (1.04, 1.73)	1.34 (1.09, 1.63)	
Retinopathy (ref: N)				
Y	0.49 (0.27, 0.89)	0.42 (0.19, 0.92)	0.49 (0.27, 0.89)	
Non-GI tract cancer				
Any history	3.74 (2.23, 6.26)	3.73 (1.99, 7.01)	3.63 (2.17, 6.07)	
GI tract cancer				
No. of events	*315*	*211*	*315*	
Person-years	*119967*	*77241*	*119967*	
Distribution (shape, scale)			*Weibull (1.084022, 0.000041)*	
Antithrombotic drug use	0.98 (0.72, 1.35)	0.90 (0.61, 1.33)	0.99 (0.72, 1.36)	
Sex (ref: Female)				
Male	2.41 (1.83, 3.17)	2.53 (1.80, 3.55)	2.42 (1.84, 3.18)	
Age (per 10 years)	1.65 (1.46, 1.86)	1.65 (1.42, 1.93)	1.63 (1.45, 1.84)	
GI bleed				
Any history	3.88 (2.12, 7.11)	5.09 (2.68, 9.64)	3.82 (2.09, 6.99)	
Non-GI tract cancer				
No. of events	*1577*	*1061*	*1577*	*2401*
Person-years	*116670*	*75019*	*116670*	*192467*

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Distribution (shape, scale)			*Weibull (0.945640, 0.001699)*	
Antithrombotic drug use	1.03 (0.90, 1.18)	1.02 (0.86, 1.21)	1.04 (0.90, 1.19)	
Sex (ref: Female)				
Male	1.07 (0.96, 1.20)	1.07 (0.94, 1.23)	1.09 (0.97, 1.22)	
Current smoker (ref: N)				
Y	1.50 (1.27, 1.78)	1.55 (1.26, 1.90)	1.49 (1.26, 1.75)	
Age (per 10 years)	1.55 (1.44, 1.66)	1.56 (1.44, 1.69)	1.51 (1.41, 1.62)	
HDL cholesterol (per 0.1 mmol/L)	0.98 (0.96, 0.99)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	
eGFR (per 10 ml/min/1.73m^2)	0.96 (0.93, 0.99)	0.98 (0.94, 1.01)	0.95 (0.92, 0.98)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
N				1.00 (0.93, 1.07)
Y	1.28 (1.11, 1.47)	1.17 (0.99, 1.38)	1.28 (1.11, 1.47)	0.98 (0.87, 1.10)
GI bleed				
Any history	1.76 (1.20, 2.58)	1.50 (0.92, 2.45)	1.68 (1.15, 2.46)	
Other major bleed				
Any history	2.85 (1.82, 4.46)	3.01 (1.79, 5.06)	2.87 (1.84, 4.49)	
GI tract cancer				
Any history	2.66 (1.95, 3.62)	2.37 (1.61, 3.47)	2.57 (1.89, 3.50)	
Amputation				

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
No. of events	*144*	*96*	*144*	*177*
Person-years	*120235*	*77435*	*120235*	*200458*
Distribution (shape, scale)			*Weibull (1.228211, 0.000308)*	
Antithrombotic drug use	0.77 (0.48, 1.22)	0.81 (0.46, 1.43)	0.77 (0.48, 1.23)	
Sex (ref: Female)				
Male	2.23 (1.48, 3.36)	2.43 (1.48, 3.97)	2.24 (1.49, 3.38)	
Age (per 10 years)	0.79 (0.65, 0.97)	0.88 (0.70, 1.12)	0.80 (0.66, 0.97)	
HbA1c (per 10 mmol/mol)	1.59 (1.44, 1.74)	1.59 (1.42, 1.77)	1.59 (1.44, 1.74)	
eGFR (per 10 ml/min/1.73m^2)	0.80 (0.74, 0.86)	0.77 (0.71, 0.85)	0.80 (0.74, 0.86)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
N				0.99 (0.81, 1.19)
Y	3.07 (2.11, 4.47)	1.33 (0.83, 2.14)	3.08 (2.12, 4.48)	1.51 (1.20, 1.90)
Retinopathy (ref: N)				
Y	2.81 (2.01, 3.94)	3.36 (2.23, 5.07)	2.82 (2.01, 3.95)	
Use of ACE-ARB (ref: N)				
Y	1.70 (1.13, 2.57)	2.07 (1.22, 3.48)	1.71 (1.13, 2.58)	
End-stage renal disease				
No. of events	*105*	*59*	*105*	*174*
Person-years	*120416*	*77613*	*120416*	*202061*

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Distribution (shape, scale)			*Weibull (1.915356, 4.445840)*	
Antithrombotic drug use	0.82 (0.46, 1.44)	1.17 (0.54, 2.52)	0.82 (0.47, 1.45)	
Sex (ref: Female)				
Male	1.77 (1.14, 2.75)	1.74 (0.97, 3.13)	1.81 (1.16, 2.80)	
Age (per 10 years)	0.36 (0.29, 0.44)	0.42 (0.31, 0.55)	0.36 (0.29, 0.44)	
eGFR (per 10 ml/min/1.73m^2)	0.50 (0.45, 0.54)	0.55 (0.49, 0.62)	0.50 (0.45, 0.54)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
N				0.70 (0.52, 0.95)
Y	9.01 (5.16, 15.72)	5.70 (3.08, 10.53)	8.99 (5.15, 15.70)	5.33 (4.49, 6.33)
Retinopathy (ref: N)				
Y	1.80 (1.19, 2.73)	2.33 (1.35, 4.03)	1.80 (1.19, 2.73)	
Vascular death				
No. of events	*414*	*266*	*414*	*510*
Person-years	*120715*	*77777*	*120715*	*202566*
Distribution (shape, scale)			*Gompertz (0.029706, 0.000146)*	*Gompertz (0.097879, 0.000086)*
Antithrombotic drug use	0.70 (0.52, 0.94)	0.89 (0.61, 1.30)	0.69 (0.52, 0.93)	
Sex (ref: Female)				
Male	1.01 (0.82, 1.25)	1.02 (0.79, 1.33)	1.05 (0.84, 1.30)	2.00 (1.64, 2.44)
Current smoker (ref: N)				

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Y	1.80 (1.32, 2.45)	1.84 (1.23, 2.75)	1.80 (1.33, 2.45)	
Age (per 10 years)	1.55 (1.35, 1.77)	1.62 (1.37, 1.91)	1.56 (1.35, 1.81)	1.50 (1.31, 1.71)
BMI (ref: <25 kg/m^2)				
≥25, <30	0.72 (0.53, 0.98)	0.76 (0.52, 1.11)	0.71 (0.52, 0.96)	
≥30, <35	0.79 (0.57, 1.09)	0.83 (0.56, 1.23)	0.79 (0.57, 1.09)	
≥35	1.22 (0.87, 1.72)	1.24 (0.81, 1.90)	1.23 (0.86, 1.74)	
Diabetes duration (per year)	1.16 (1.06, 1.26)	1.25 (1.12, 1.38)	1.15 (1.05, 1.25)	
eGFR (per 10 ml/min/1.73m^2)	0.91 (0.86, 0.97)	0.91 (0.85, 0.97)	0.91 (0.86, 0.97)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	2.77 (2.21, 3.47)	1.60 (1.19, 2.15)	2.76 (2.20, 3.46)	1.67 (1.36, 2.04)
Myocardial infarction				
In year	54.54 (41.63, 71.44)	60.88 (43.45, 85.31)	54.51 (41.76, 71.14)	
At least 1 year ago	6.81 (4.36, 10.65)	7.31 (4.14, 12.93)	7.26 (4.63, 11.40)	
Coronary revascularisation (urgent)				
Any history	0.10 (0.06, 0.19)	0.12 (0.05, 0.26)	0.10 (0.06, 0.19)	
Coronary revascularisation (non-urgent)				
Any history	0.31 (0.15, 0.64)	0.24 (0.10, 0.54)	0.34 (0.17, 0.69)	
Ischaemic stroke				
In year	18.86 (13.66, 26.05)	16.59 (10.90, 25.26)	18.03 (13.09, 24.84)	
At least 1 year ago	3.33 (2.22, 4.98)	4.76 (2.97, 7.64)	3.20 (2.12, 4.82)	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
Heart failure				
In year	12.84 (9.45, 17.45)	13.80 (9.39, 20.28)	13.18 (9.73, 17.86)	
At least 1 year ago	7.17 (4.98, 10.32)	9.28 (6.12, 14.09)	7.62 (5.17, 11.24)	
Amputation				
Any history	2.08 (1.23, 3.51)	2.67 (1.47, 4.83)	2.04 (1.19, 3.49)	
Non-vascular death				
No. of events	*1126*	*746*	*1126*	*1732*
Person-years	*120715*	*77777*	*120715*	*202566*
Distribution (shape, scale)			*Gompertz (0.073367, 0.016524)*	*Gompertz (0.106176, 0.026051)*
Antithrombotic drug use	0.89 (0.74, 1.06)	0.98 (0.78, 1.22)	0.89 (0.75, 1.07)	
Sex (ref: Female)				
Male	1.17 (1.02, 1.33)	1.22 (1.03, 1.43)	1.18 (1.03, 1.35)	1.32 (1.19, 1.46)
Current smoker (ref: N)				
Y	1.75 (1.45, 2.11)	1.94 (1.53, 2.45)	1.75 (1.44, 2.12)	
Townsend index (ref: Q1 (least deprived))				
Q2	1.17 (1.01, 1.36)	1.24 (1.03, 1.48)	1.18 (1.01, 1.37)	
Q3	1.20 (1.00, 1.43)	1.06 (0.85, 1.33)	1.18 (0.99, 1.41)	
Q4	1.31 (1.09, 1.59)	1.33 (1.05, 1.67)	1.30 (1.07, 1.56)	
Q5 (most deprived)	1.59 (1.22, 2.09)	1.71 (1.23, 2.36)	1.65 (1.26, 2.16)	
Age (per 10 years)	0.38 (0.19, 0.79)	0.37 (0.14, 0.98)	0.40 (0.19, 0.83)	0.32 (0.13, 0.80)
Age^2	1.11 (1.06, 1.17)	1.13 (1.06, 1.20)	1.11 (1.06, 1.17)	1.13 (1.05, 1.21)

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
BMI (ref: <25 kg/m^2)				
≥25, <30	0.67 (0.56, 0.80)	0.70 (0.56, 0.87)	0.66 (0.55, 0.79)	
≥30, <35	0.81 (0.67, 0.97)	0.87 (0.69, 1.09)	0.81 (0.67, 0.97)	
≥35	0.94 (0.77, 1.16)	1.05 (0.81, 1.36)	0.95 (0.77, 1.17)	
eGFR (ref: <60 ml/min/1.73m^2)				
≥60, <90	0.53 (0.45, 0.61)	0.67 (0.56, 0.80)	0.52 (0.45, 0.61)	
≥90	0.43 (0.35, 0.53)	0.59 (0.47, 0.75)	0.43 (0.35, 0.54)	
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)				
Y	1.26 (1.08, 1.46)	0.92 (0.76, 1.11)	1.25 (1.07, 1.46)	
Myocardial infarction				
At least 1 year ago	1.26 (0.86, 1.85)	1.44 (0.92, 2.25)	1.27 (0.86, 1.86)	
Ischaemic stroke				
Any history	1.66 (1.27, 2.17)	1.52 (1.10, 2.11)	1.65 (1.26, 2.16)	
Heart failure				
Any history	1.73 (1.30, 2.32)	1.76 (1.25, 2.49)	1.78 (1.32, 2.40)	
Intracranial haemorrhage				
In year	15.58 (10.68, 22.71)	23.54 (14.65, 37.82)	15.67 (10.76, 22.80)	
At least 1 year ago	2.54 (1.53, 4.22)	2.84 (1.37, 5.88)	2.86 (1.72, 4.77)	
GI bleed				
In year	5.61 (3.91, 8.06)	5.52 (3.57, 8.54)	5.65 (3.93, 8.10)	
At least 1 year ago	2.36 (1.67, 3.34)	2.44 (1.60, 3.72)	2.38 (1.67, 3.38)	

Table C.11: Risk equations for predicting risks of adverse events *(continued)*

	All ASCEND participants (N = 15480)	Complete cases in ASCEND only (N = 9908)	All ASCEND participants (N = 15480)	Updated using UK Biobank cohort (N = 18250)
GI tract cancer				
In year or previous year	10.07 (8.11, 12.50)	8.75 (6.67, 11.49)	9.97 (8.04, 12.37)	
At least 2 years ago	3.85 (2.76, 5.38)	3.75 (2.54, 5.53)	3.91 (2.79, 5.48)	
Non-GI tract cancer				
In year or previous year	22.85 (20.03, 26.07)	24.28 (20.64, 28.55)	23.29 (20.32, 26.71)	
At least 2 years ago	7.86 (6.55, 9.43)	8.11 (6.50, 10.13)	7.99 (6.55, 9.74)	
Amputation				
Any history	2.05 (1.34, 3.15)	2.45 (1.53, 3.92)	2.02 (1.31, 3.14)	
End-stage renal disease				
Any history	2.03 (1.31, 3.15)	4.44 (2.56, 7.69)	2.12 (1.36, 3.30)	

Note:

Values are hazard ratios (95% CI) unless otherwise stated.

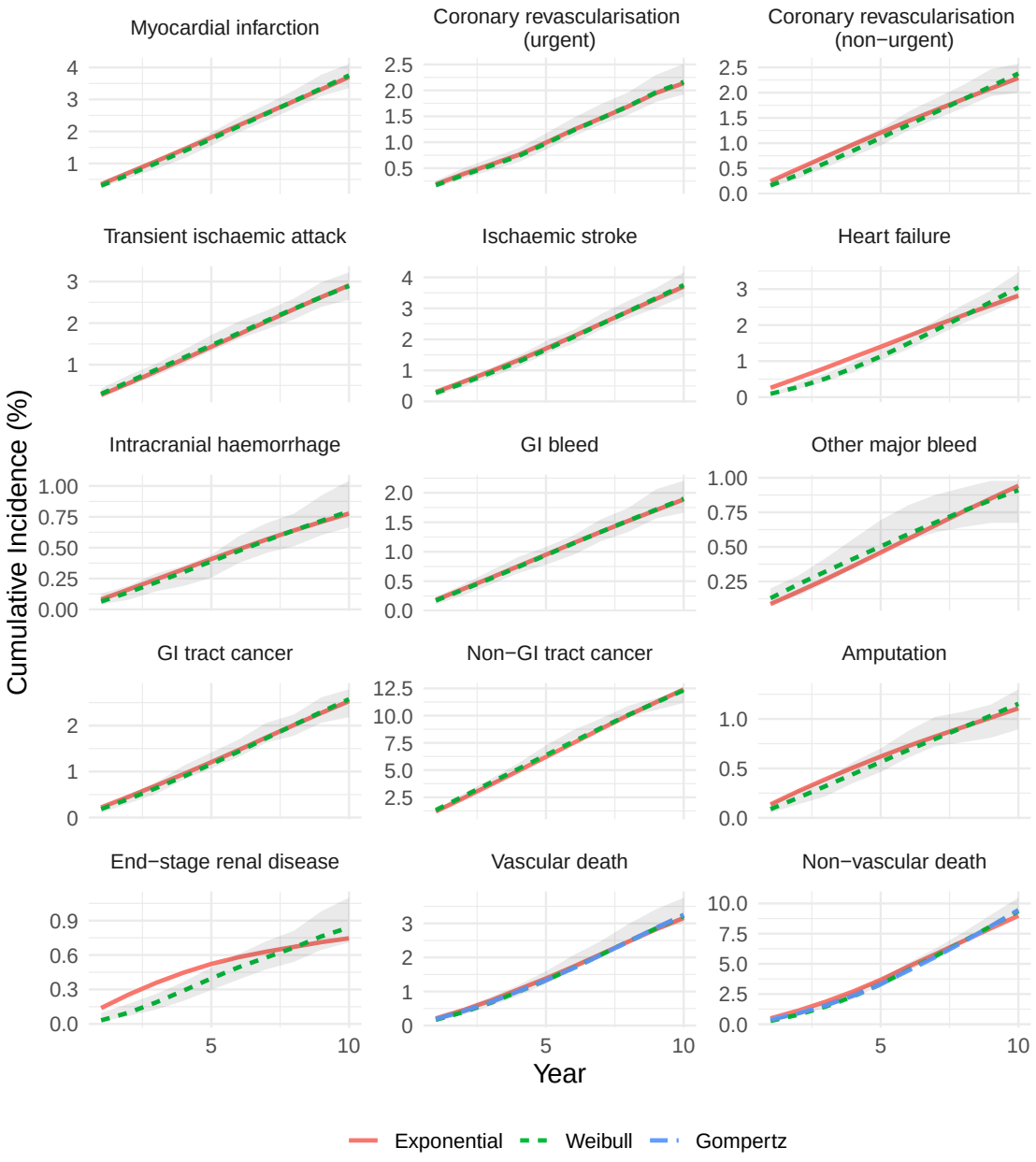


Figure C.16: Comparison of cumulative incidence observed (shaded region) vs predicted by each individual risk equations (lines) in ASCEND with different hazard distributions. The risk equations were used to predict the occurrence of event for each participant in each year, based on participant's baseline characteristics, age in year and disease history in year. These results reflect the validity of the risk equations, independent from the stochastic simulation process

Table C.12: Akaike's information criteria of parametric models with different hazard distributions

Adverse event	Exponential	Weibull	Gompertz
Myocardial infarction	11353	11353	-
Coronary revascularisation (urgent)	4391	4392	-
Coronary revascularisation (non-urgent)	7463	7455	-
Transient ischaemic attack	9058	9059	-
Ischaemic stroke	11005	11006	-
Heart failure	8480	8432	-
Intracranial haemorrhage	2645	2646	-
GI bleed	6150	6152	-
Other major bleed	3205	3201	-
GI tract cancer	7967	7967	-
Non-GI tract cancer	34887	34885	-
Amputation	3629	3625	-
End-stage renal disease	2393	2346	-
Vascular death	8848	8847	8848
Non-vascular death	22366	22322	22338

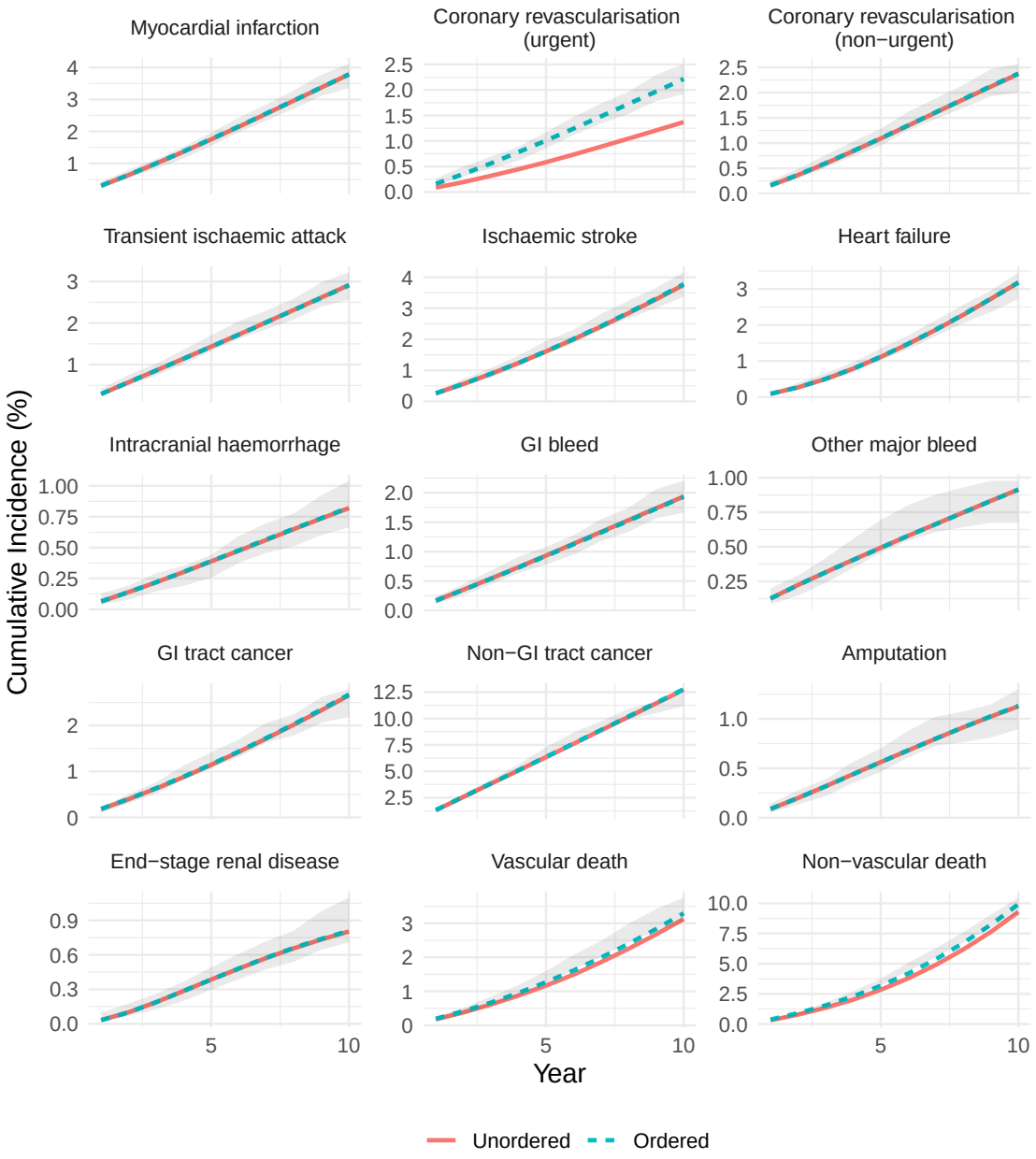


Figure C.17: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation model (lines) in ASCEND for different ordering of adverse events. In the unordered simulation, all events were randomly ordered. In the ordered simulation, adverse events were randomly ordered, except for urgent coronary revascularisation occurring after myocardial infarction, and vascular and non-vascular deaths occurring after all other events

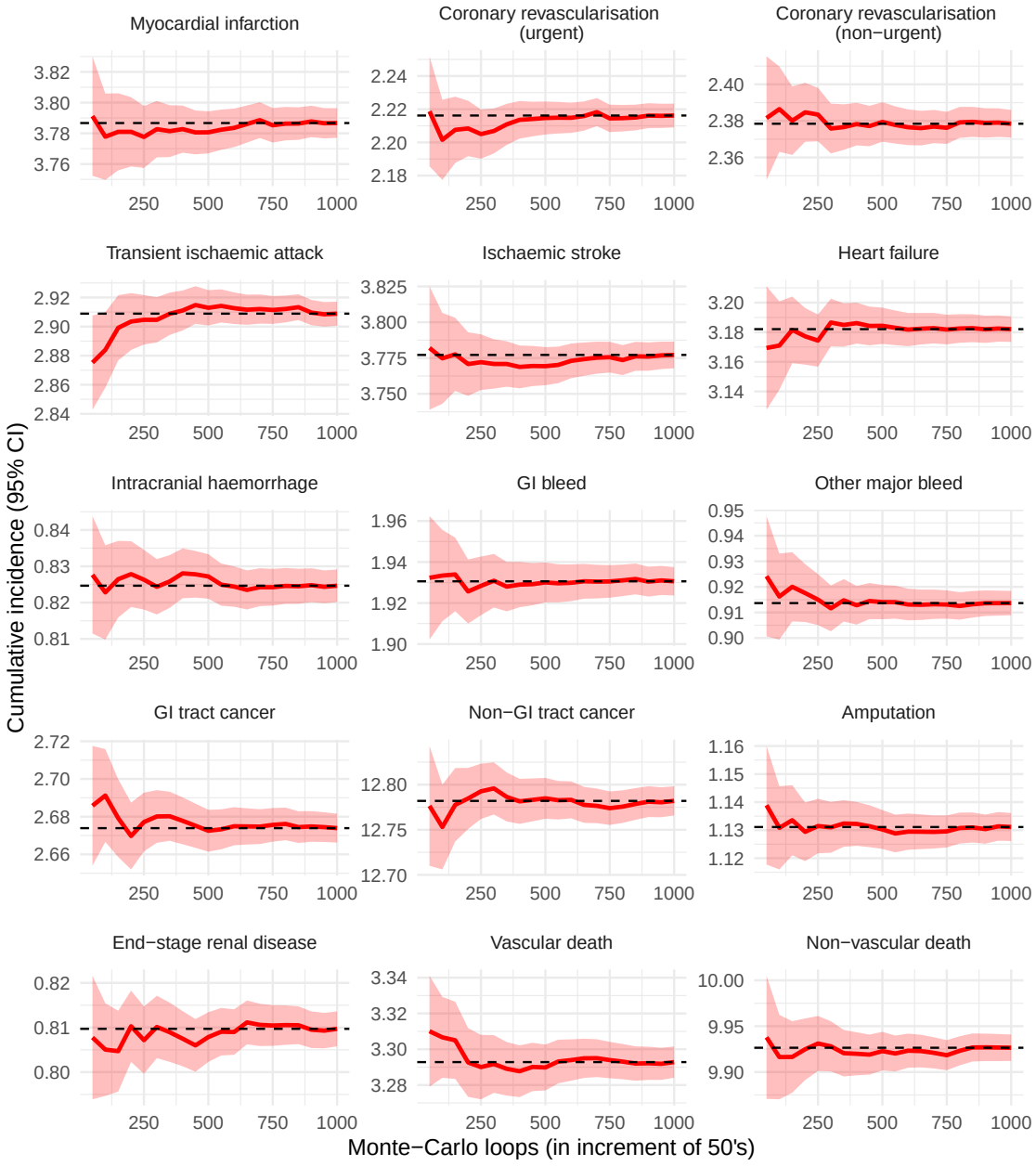


Figure C.18: Predicted 7-year cumulative incidence for ASCEND cohort with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

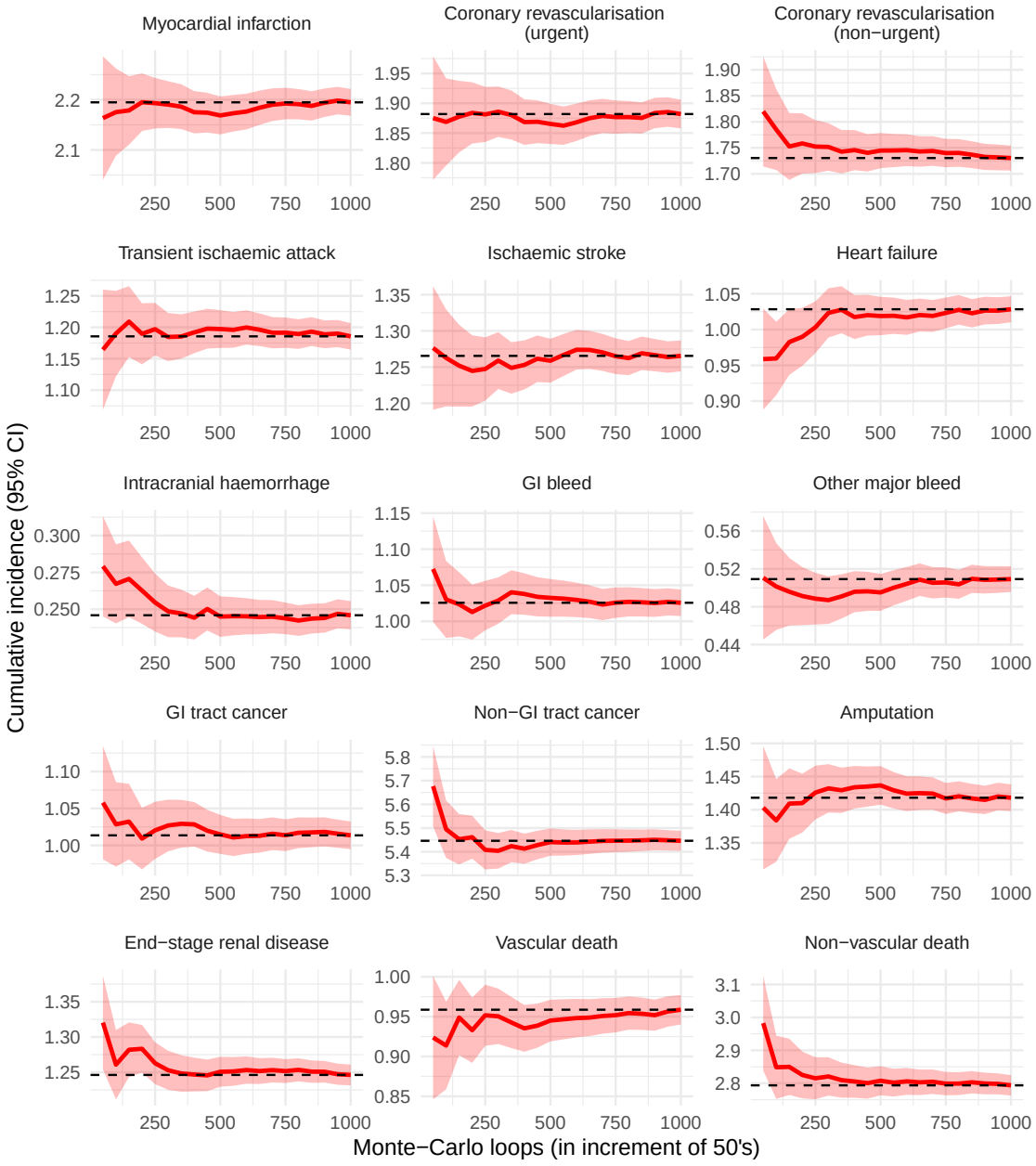


Figure C.19: Predicted 7-year cumulative incidence for participants <50 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

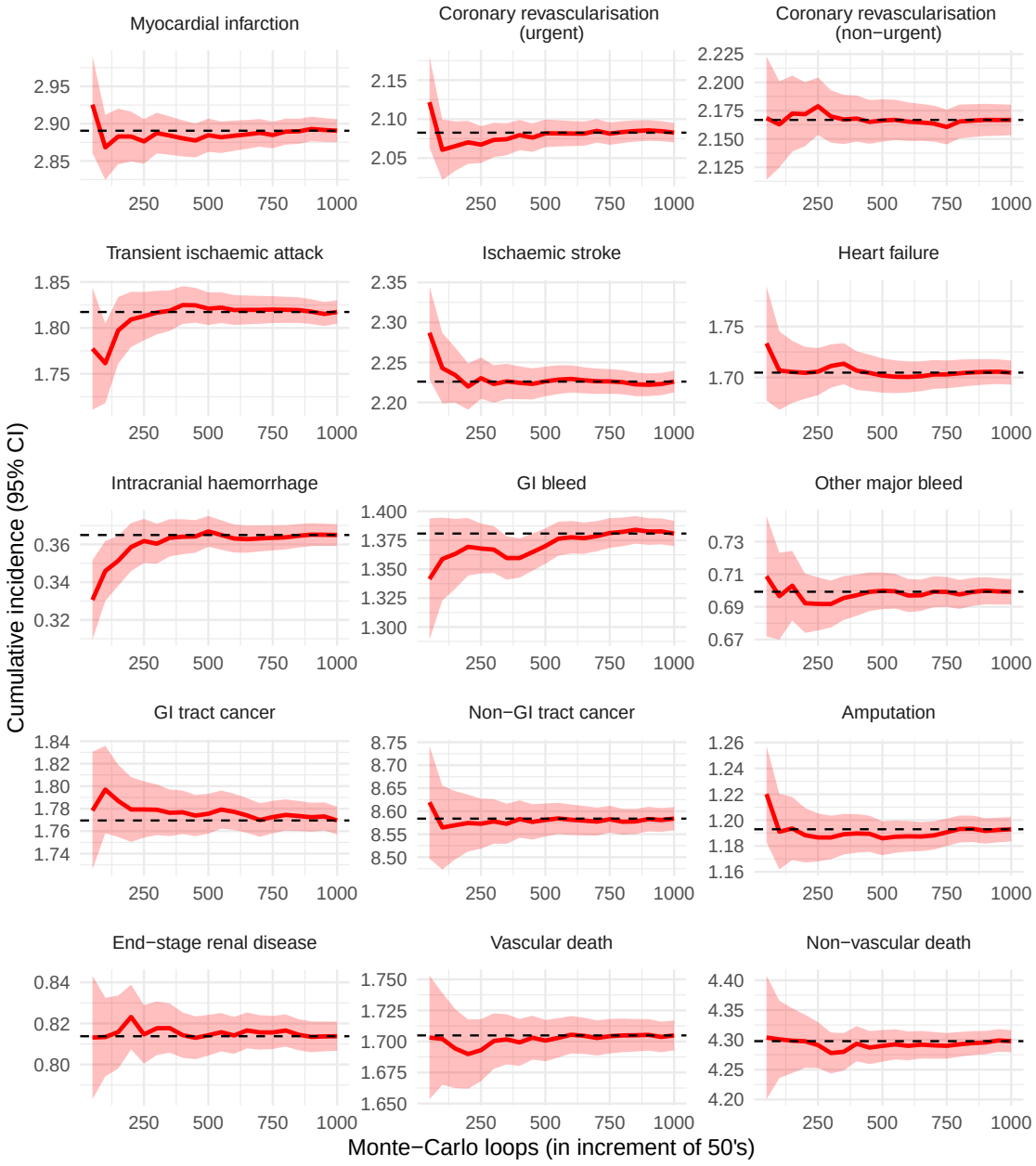


Figure C.20: Predicted 7-year cumulative incidence for participants ≥50, <60 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

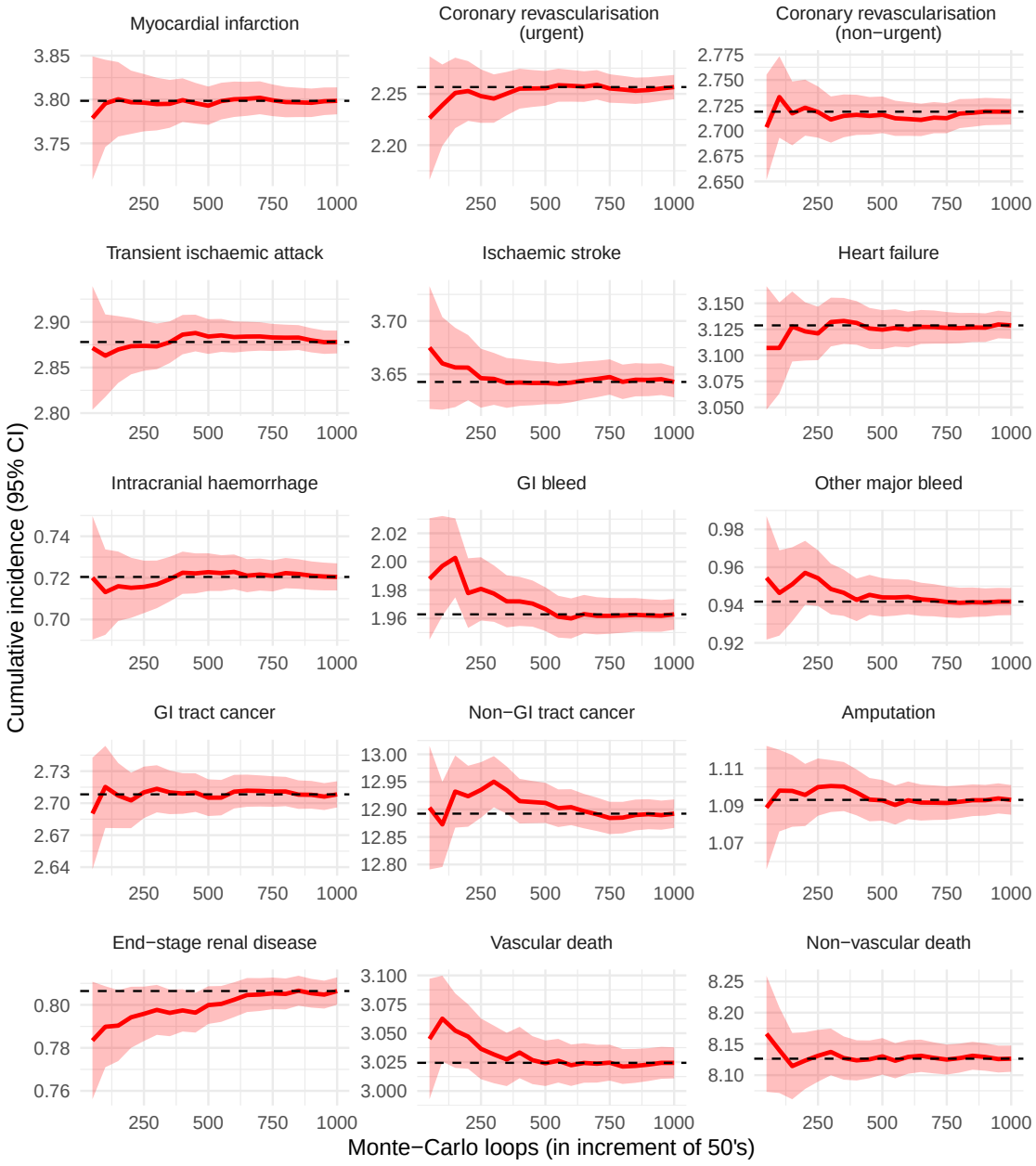


Figure C.21: Predicted 7-year cumulative incidence for participants ≥60, <70 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

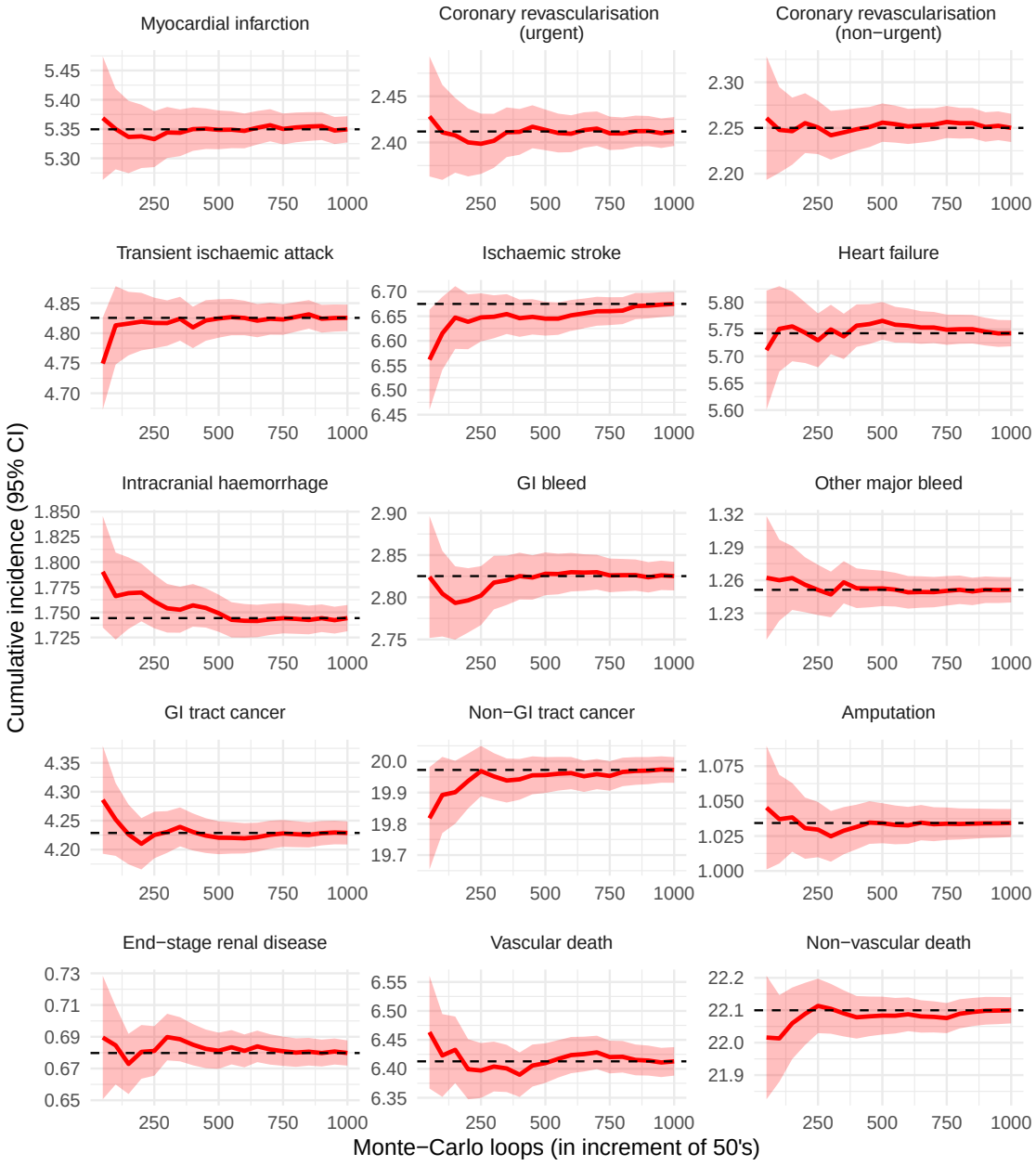


Figure C.22: Predicted 7-year cumulative incidence for participants ≥70 years old in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

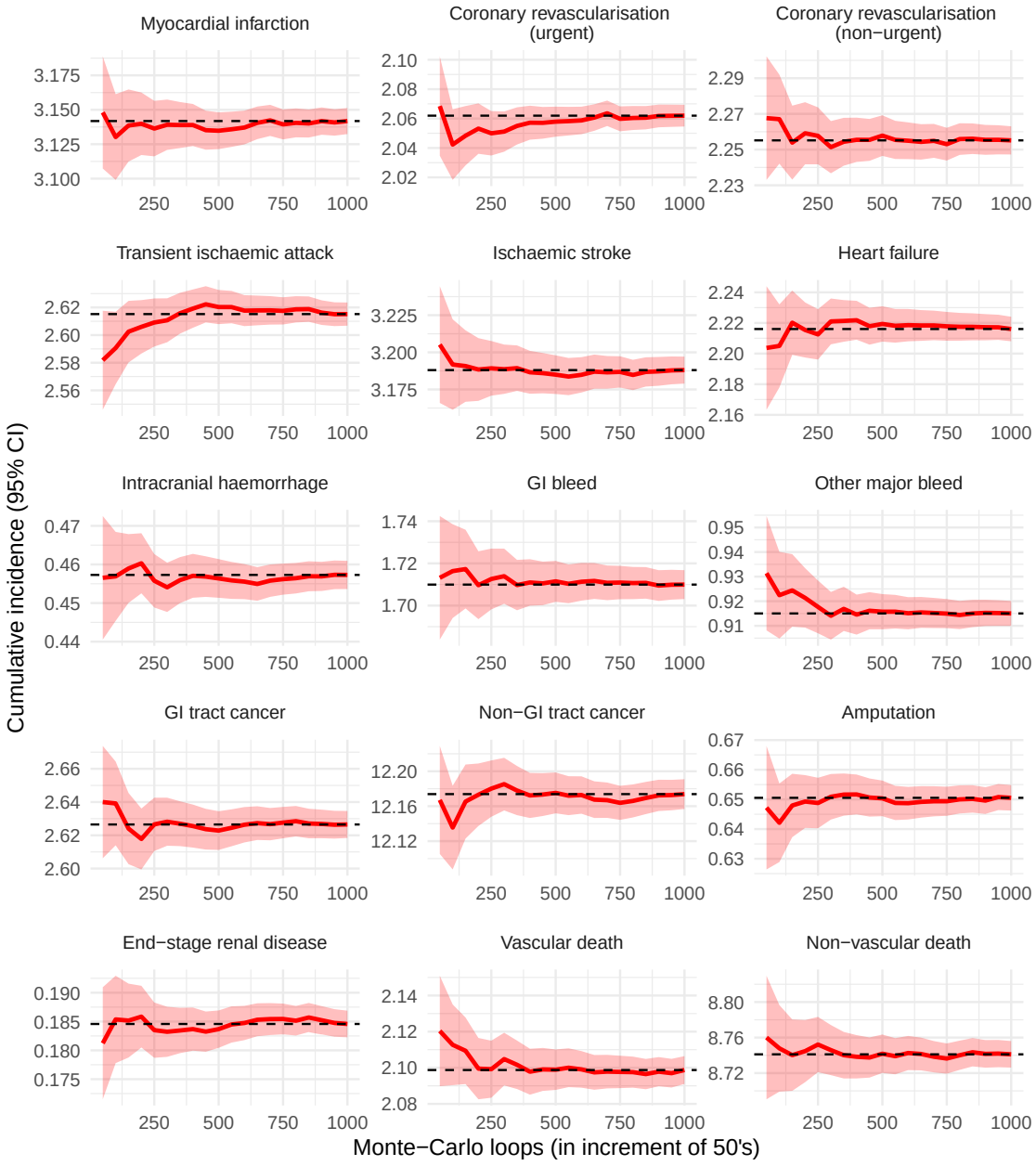


Figure C.23: Predicted 7-year cumulative incidence for participants with no albuminuria in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

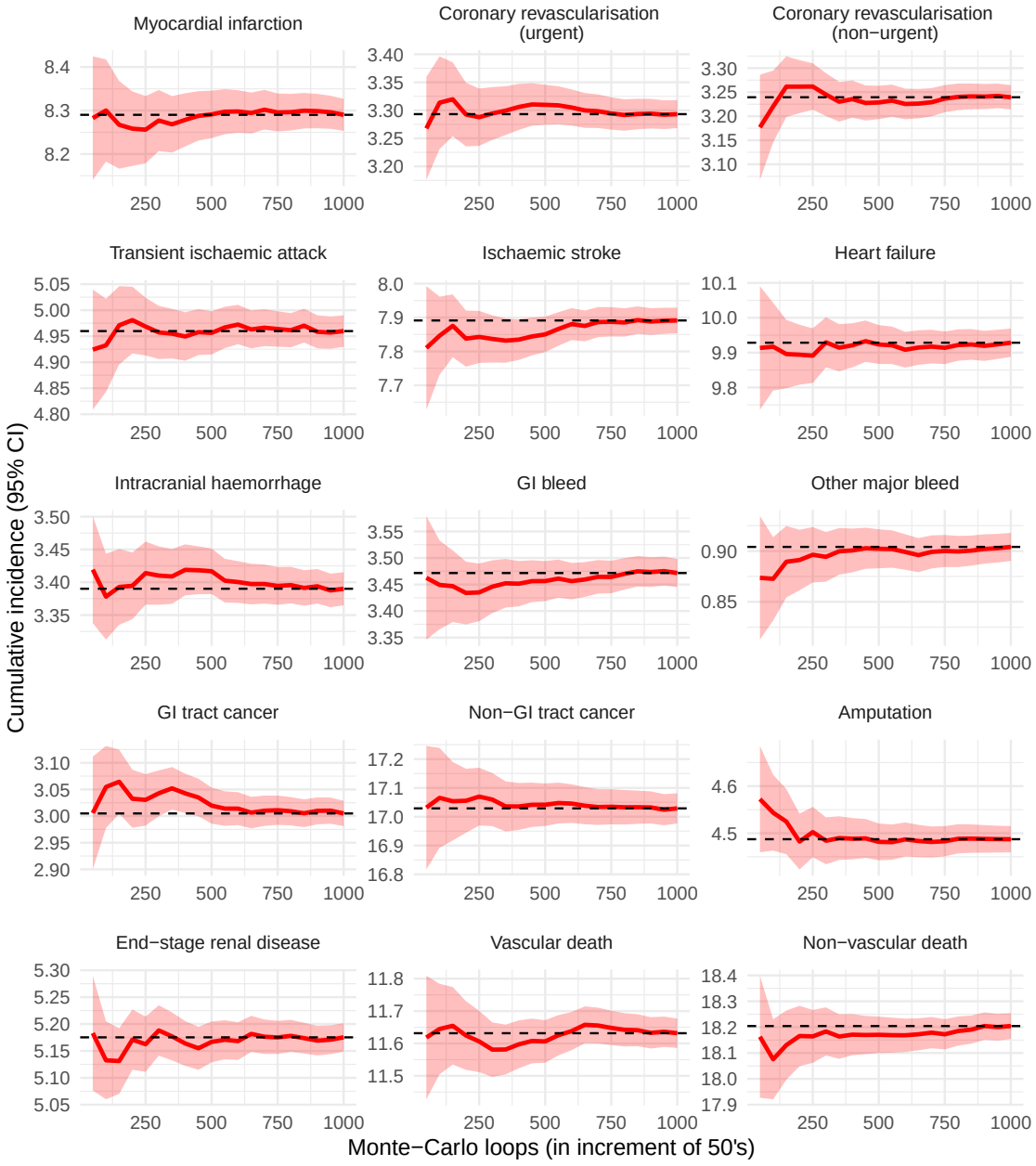


Figure C.24: Predicted 7-year cumulative incidence for participants with albuminuria in ASCEND with increasing Monte-Carlo loops (in increment of 50 loops). Shaded region reflects the Monte-Carlo error

Table C.13: Model performance in ASCEND and the UK Biobank before and after model updating

Adverse events	ASCEND			UK Biobank (before update)			UK Biobank (after update)		
	Bias (%)	% error	MAPE (%)	Bias (%)	% error	MAPE (%)	Bias (%)	% error	MAPE (%)
Myocardial infarction	-0.01	-0.6	2.7	0.03	0.8	19.9	0.06	1.5	20.0
Coronary revascularisation (urgent)	-0.04	-2.8	4.7	-0.09	-3.6	10.4	-0.07	-2.6	10.4
Coronary revascularisation (non-urgent)	-0.06	-3.4	3.5	0.62	23.3	13.5	0.64	24.3	13.9
Transient ischaemic attack	-0.05	-2.2	4.5	1.03	108.1	137.4	1.05	110.2	138.1
Ischaemic stroke	-0.13	-5.0	4.7	0.47	16.2	32.1	0.49	16.9	32.0
Heart failure	-0.03	-1.3	11.9	1.46	71.4	113.5	1.03	50.3	82.0
Intracranial haemorrhage	0.00	0.3	9.2	-0.24	-21.7	9.8	-0.62	-54.9	49.2
GI bleed	-0.03	-2.1	3.2	1.10	105.8	124.8	1.13	108.5	126.3
Other major bleed	-0.07	-9.0	7.5	-0.24	-20.4	11.1	-0.24	-20.3	11.0
GI tract cancer	-0.10	-5.7	7.3	-0.24	-9.1	17.9	-0.22	-8.2	17.4
Non-GI tract cancer	-0.36	-3.9	4.7	-0.20	-1.6	7.2	-0.73	-5.7	6.0
Amputation	-0.06	-7.1	4.8	0.33	37.3	63.3	0.02	2.0	17.9
End-stage renal disease	-0.01	-1.6	7.7	0.43	48.8	76.5	0.04	4.8	25.2
Vascular death	-0.25	-11.0	8.4	0.84	35.2	69.9	0.10	4.0	7.5
Non-vascular death	-0.53	-9.1	10.1	1.04	13.4	20.3	0.68	8.8	8.2

Note:
% error, percentage error; MAPE, mean absolute percentage error. Bias is the absolute difference between the observed and the predicted cumulative incidence. Percentage error is the degree of overprediction as percentage of observed (negative values represent under-prediction). MAPE is the absolute percentage error averaged across follow-up years. These were assessed at 7 years for ASCEND and 11 years for the UK Biobank, except for TIA which was assessed at 8 years for the UK Biobank.

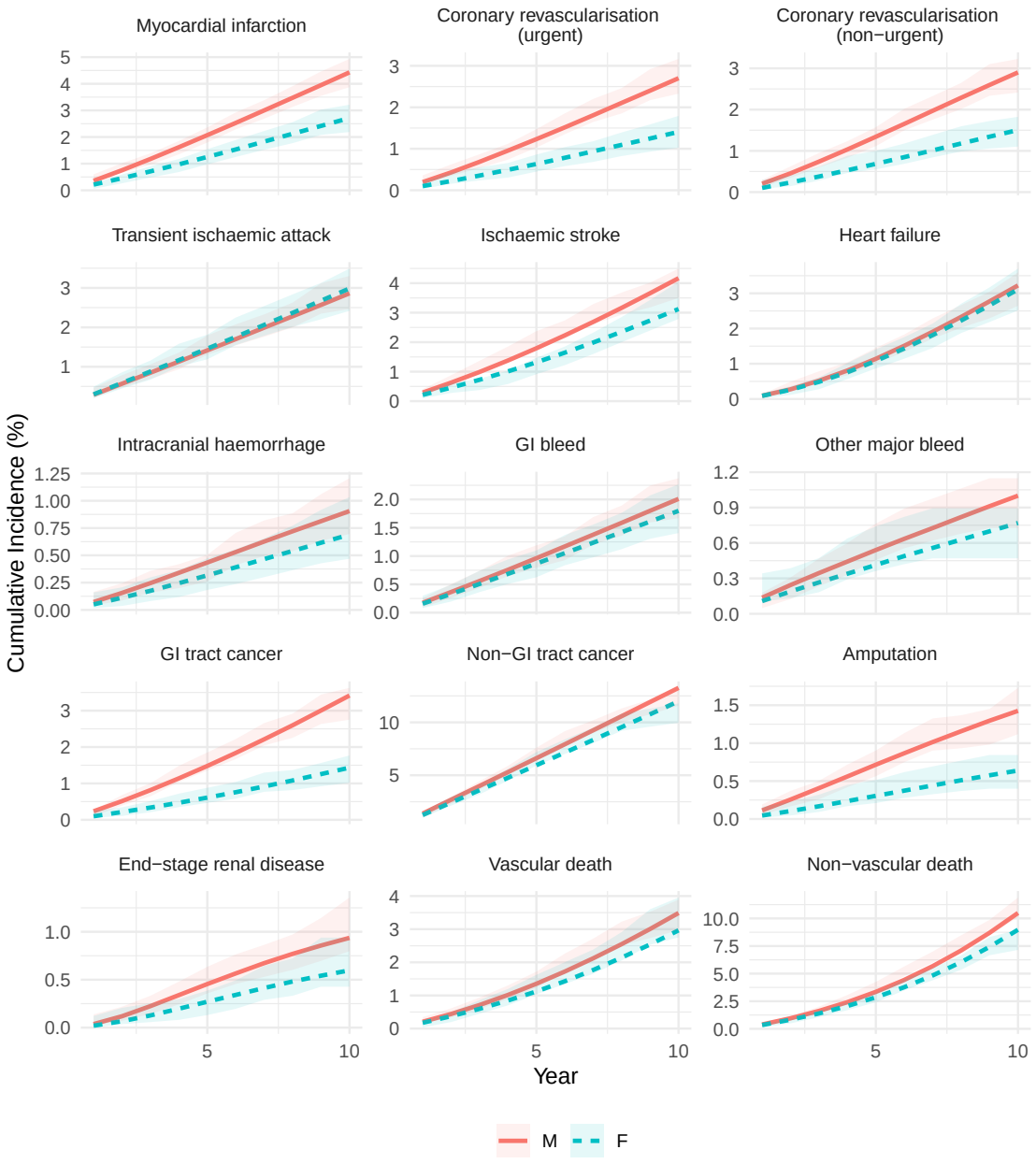


Figure C.25: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by sex

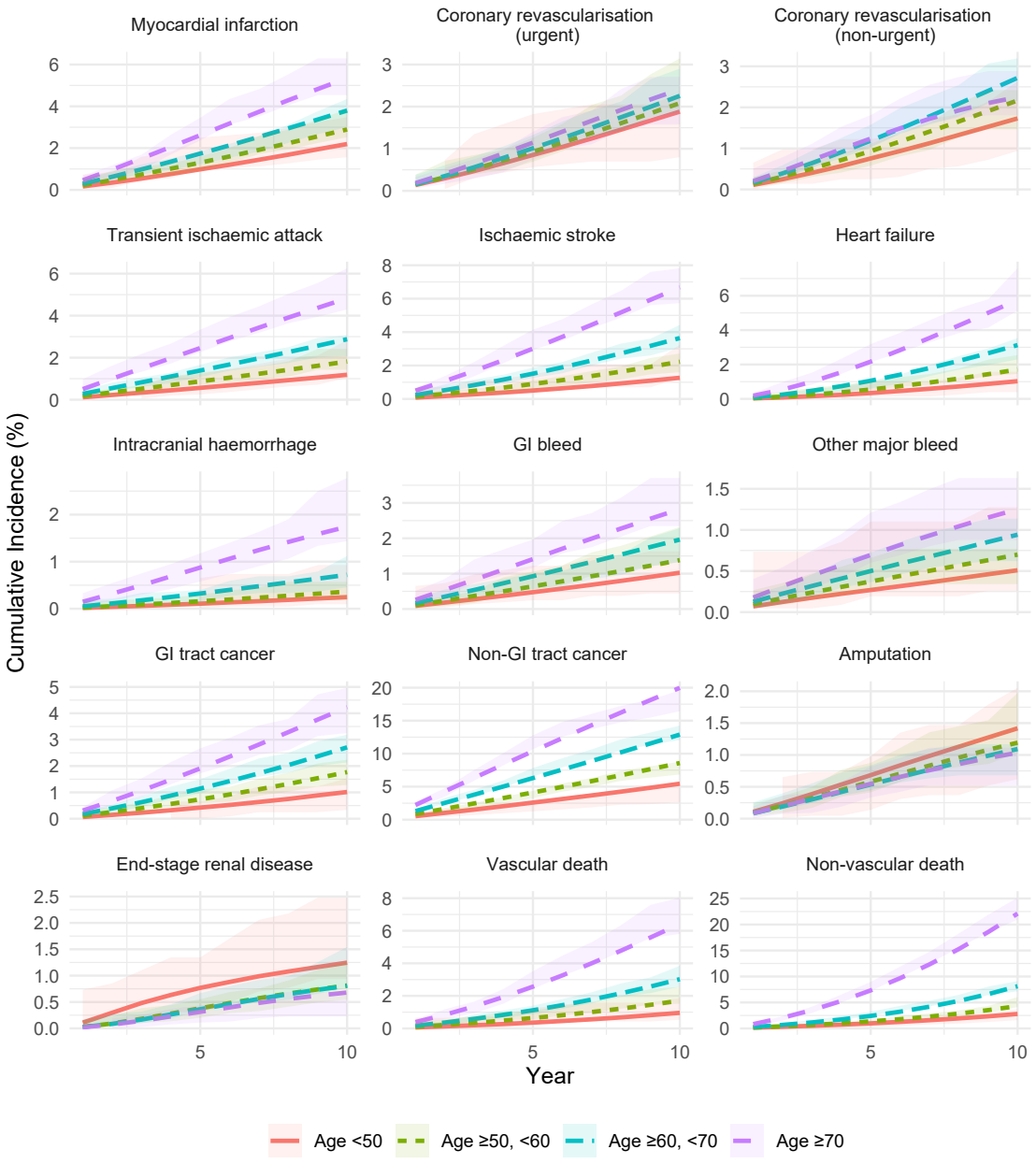


Figure C.26: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by age

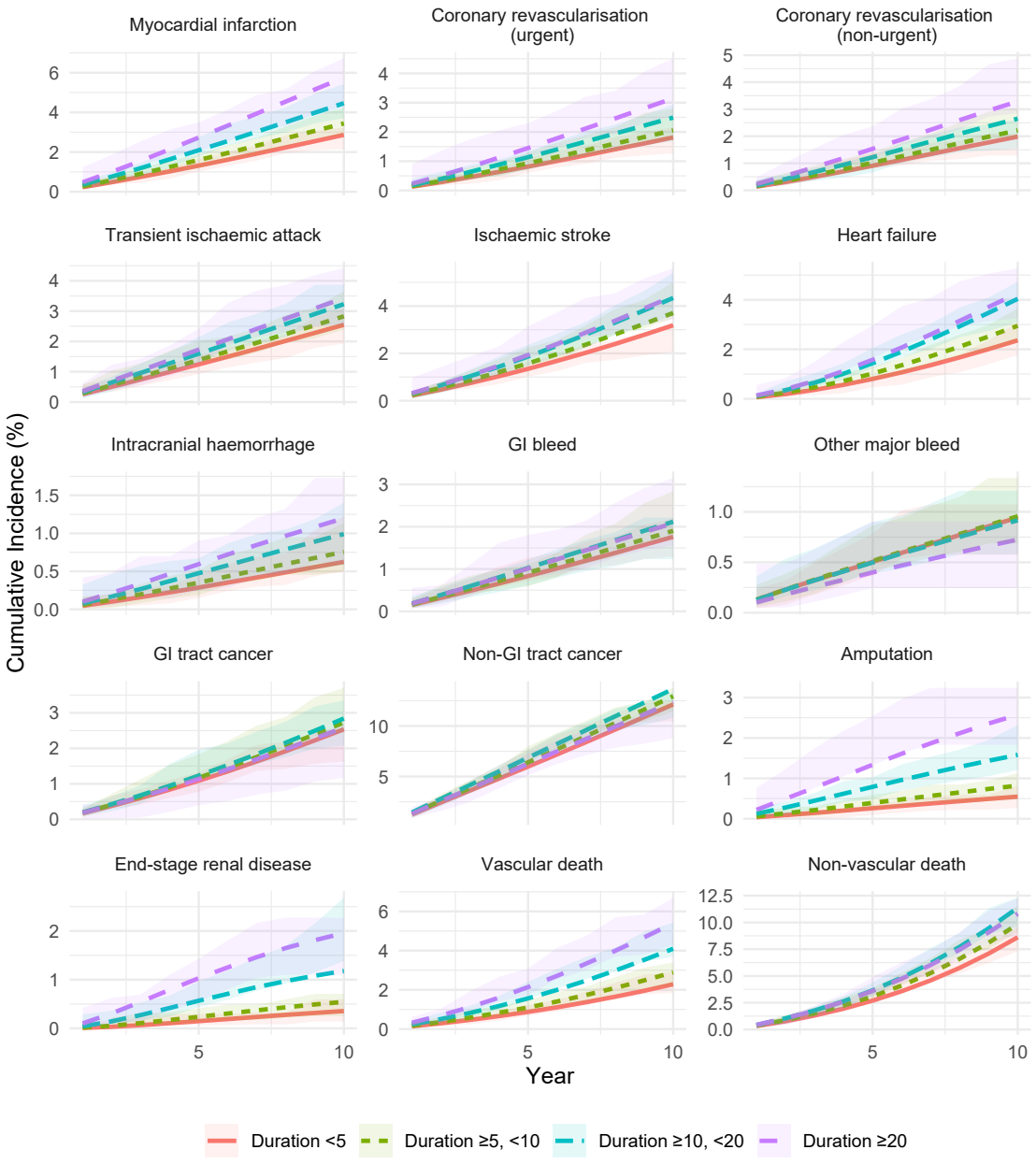


Figure C.27: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND participants stratified by diabetes duration

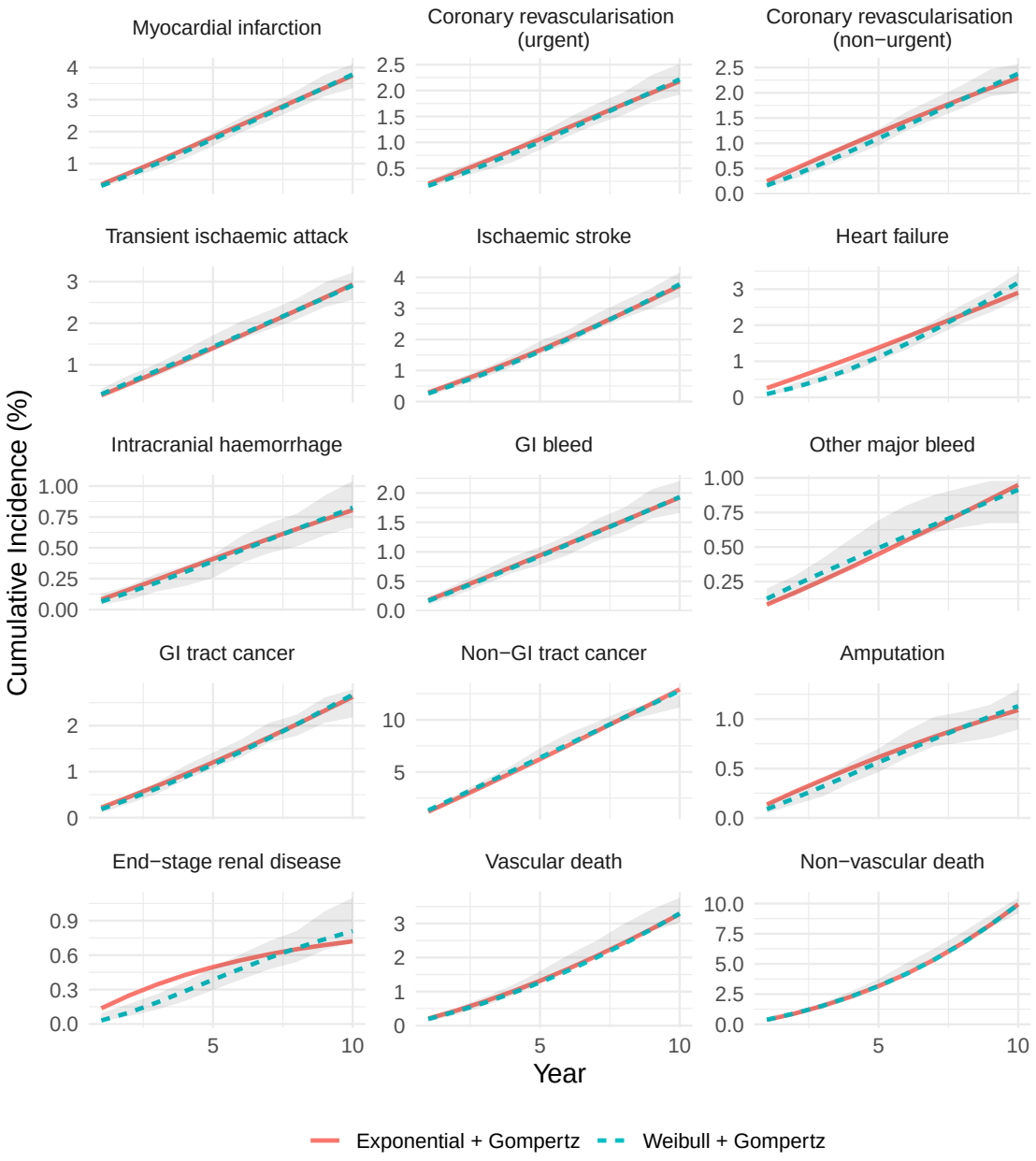


Figure C.28: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND with different hazard distributions over 10 years. Exponential (Weibull) + Gompertz: Exponential (Weibull) distribution used for all events but vascular and non-vascular death. Gompertz distribution used for deaths

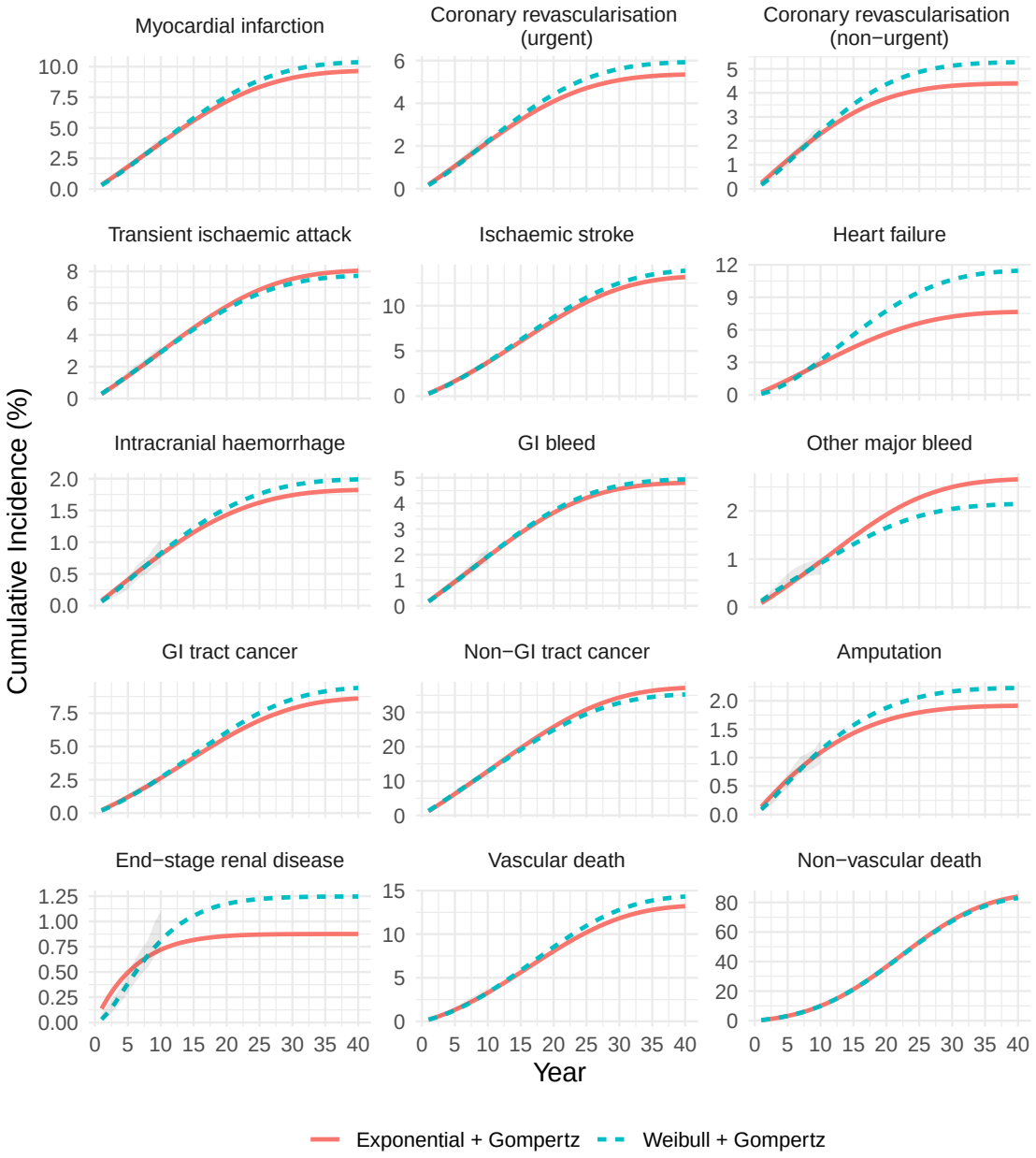


Figure C.29: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in ASCEND with different hazard distributions over 40 years. Exponential (Weibull) + Gompertz: Exponential (Weibull) distribution used for all events but vascular and non-vascular death. Gompertz distribution used for deaths

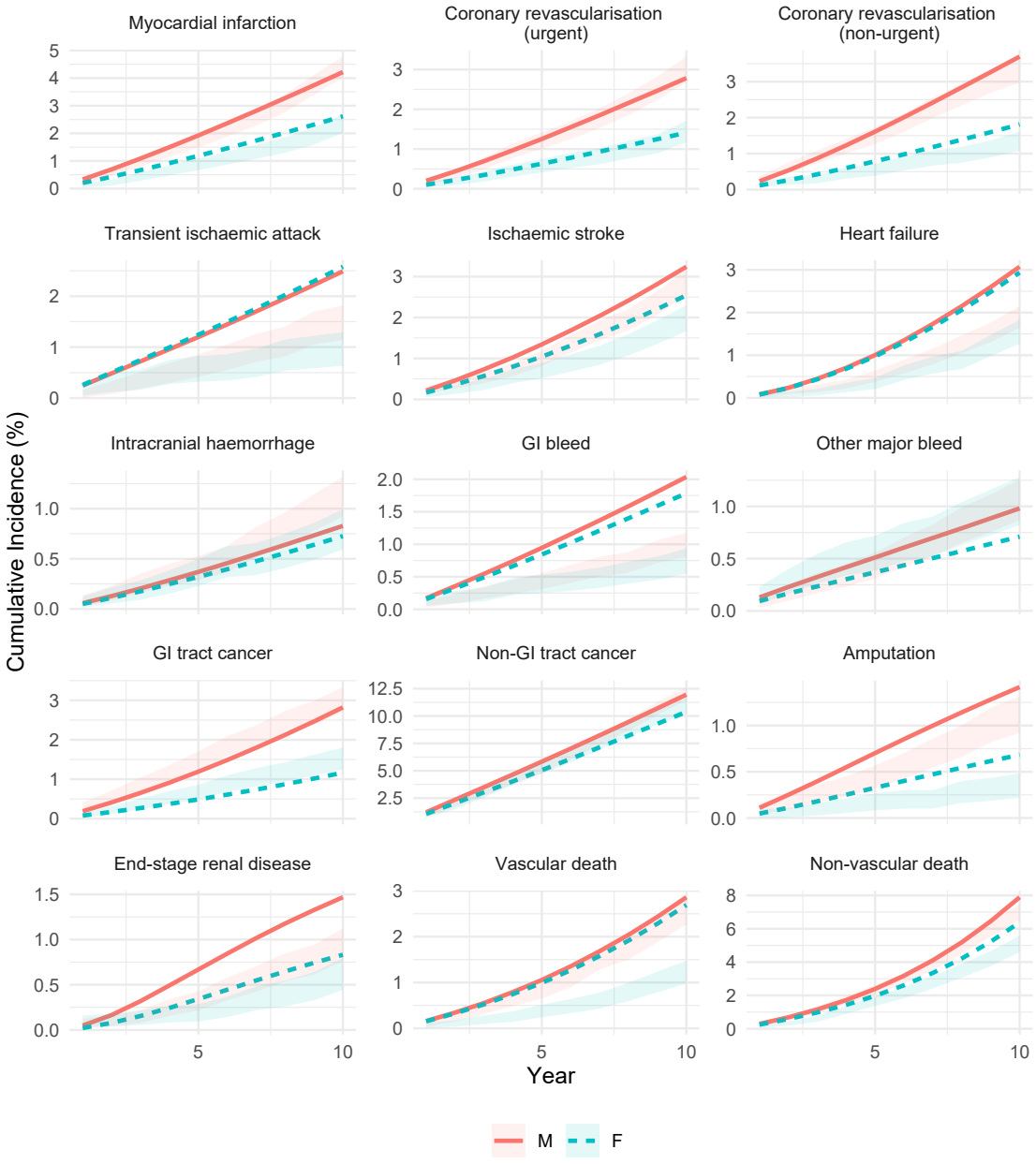


Figure C.30: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by sex

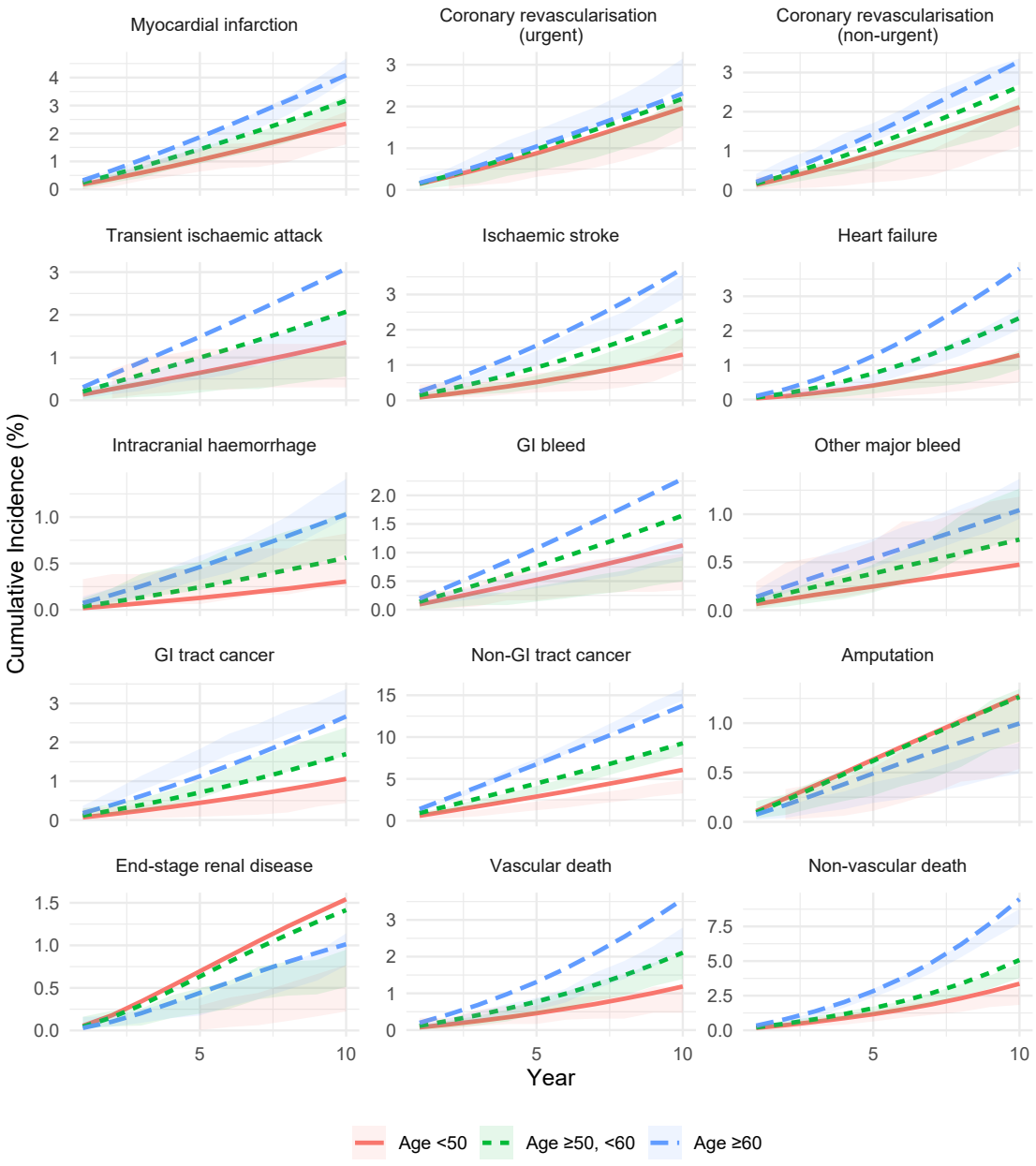


Figure C.31: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by age

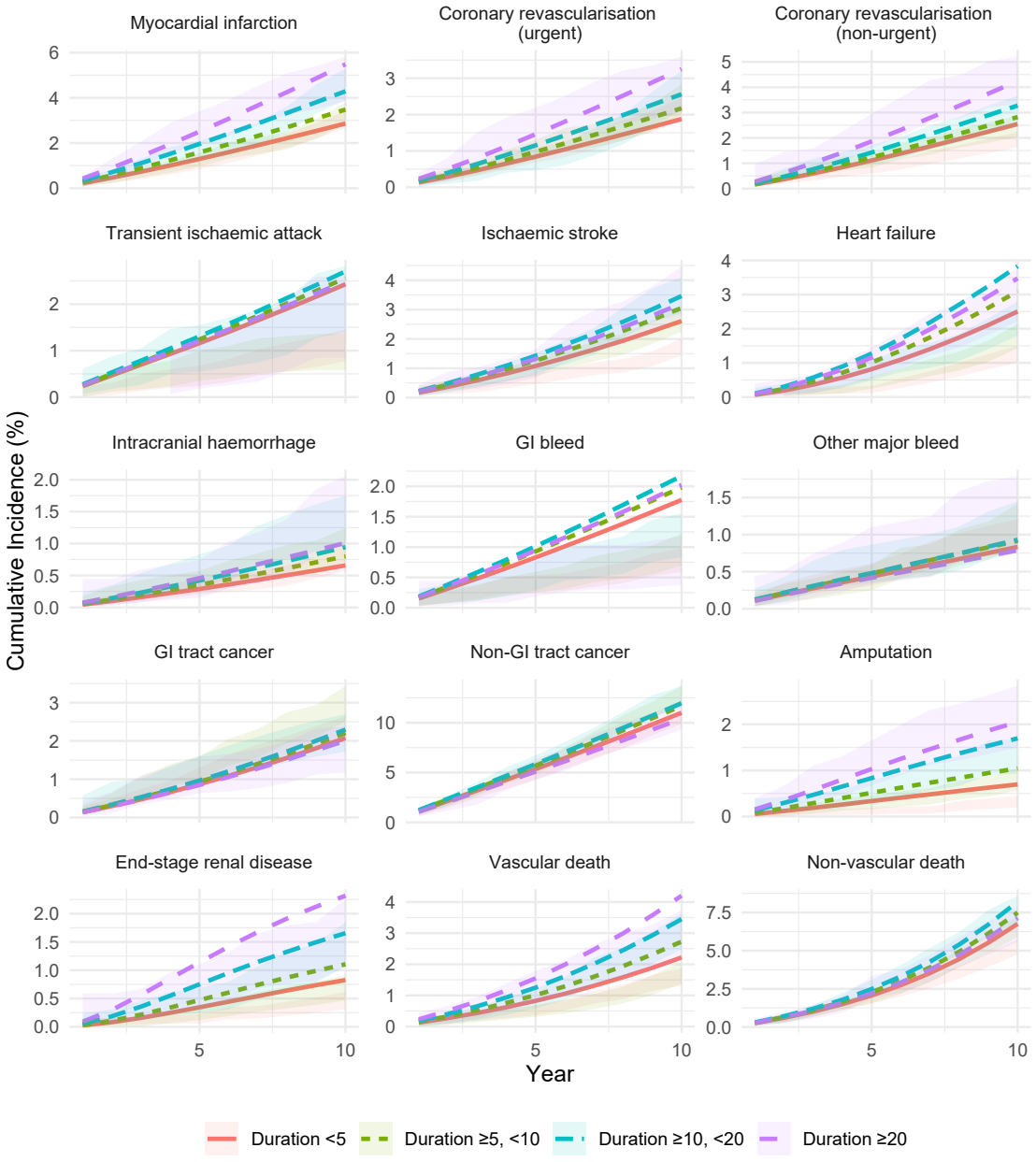


Figure C.32: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by diabetes duration

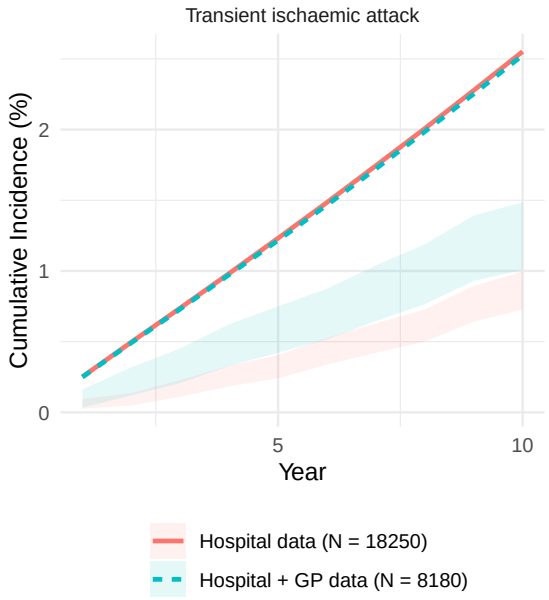


Figure C.33: Comparison of cumulative incidence of TIA observed in UK Biobank (shaded region) vs predicted by simulation (lines) when ascertainment of TIA was supplemented by primary care data, or not

Table C.14: Event ascertainment of disease endpoints using routine healthcare data

Disease endpoint	Sensitivity	Positive predictive value	Ratio of expected rate to observed rate
ASCEND [4]			
Non-fatal myocardial infarction	79%	79%	1.00
Non-fatal ischaemic stroke	67%	82%	1.22
Transient ischaemic attack	30%	78%	2.60
UK Whitehall [5]			
Non-fatal myocardial infarction and coronary revascularisations	70%	72%	1.03
Non-fatal stroke	71%	79%	1.11
Oxford Vascular Study [6]			
Ischaemic stroke	-	82%	-
Intracerebral haemorrhage	-	76%	-
Subarachnoid haemorrhage	-	37%	-
UK Biobank [7]			
Ischaemic stroke	-	83%	-
Intracerebral haemorrhage	-	42%	-
Intracerebral haemorrhage, primary diagnosis only	-	52%	-
Subarachnoid haemorrhage	-	71%	-
Subarachnoid haemorrhage, primary diagnosis only	-	74%	-
ASCEND (Harper, private communication)			
Intracranial haemorrhage	87%	64%	0.74
Serious GI bleeding, primary diagnosis only	55%	58%	1.05
Other major bleeding, primary diagnosis only	44%	31%	0.70
EXTEND-DAPT [8]			
Myocardial infarction	66%	86%	1.30
Stroke	62%	47%	0.76
Major bleeding	77%	39%	0.51
TRANSLATE-ACS [9]			
Myocardial infarction	86%	84%	0.98
Stroke	93%	84%	0.90
GUSTO scale moderate or severe bleeding	71%	40%	0.56
GUSTO scale moderate or severe bleeding, primary diagnosis only	38%	39%	1.03

Table C.14: Event ascertainment of disease endpoints using routine healthcare data *(continued)*

Disease endpoint	Sensitivity	Positive predictive value	Ratio of expected rate to observed rate

Note:
Sensitivity is the proportion of people with an event identified to have the event. Positive predictive value is the proportion of people identified to have an event that actually have an event.
EXTEND-DAPT and TRANSLATE-ACS are US-based studies and events were ascertained from US administrative data. All other studies are UK based and events were ascertained from Hospital Episode Statistics.

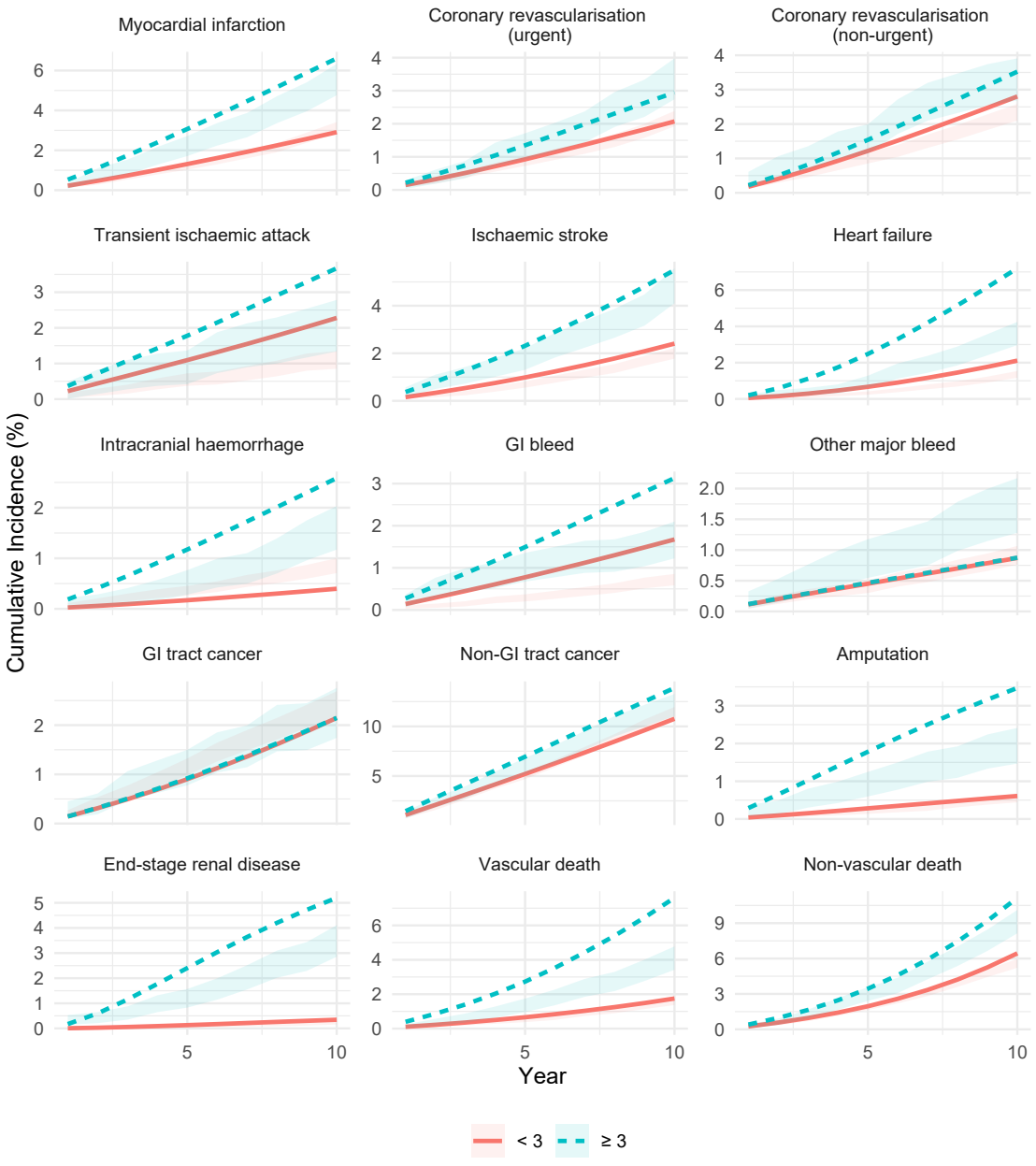
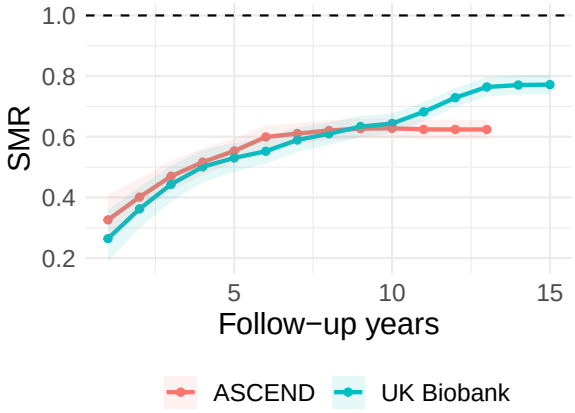
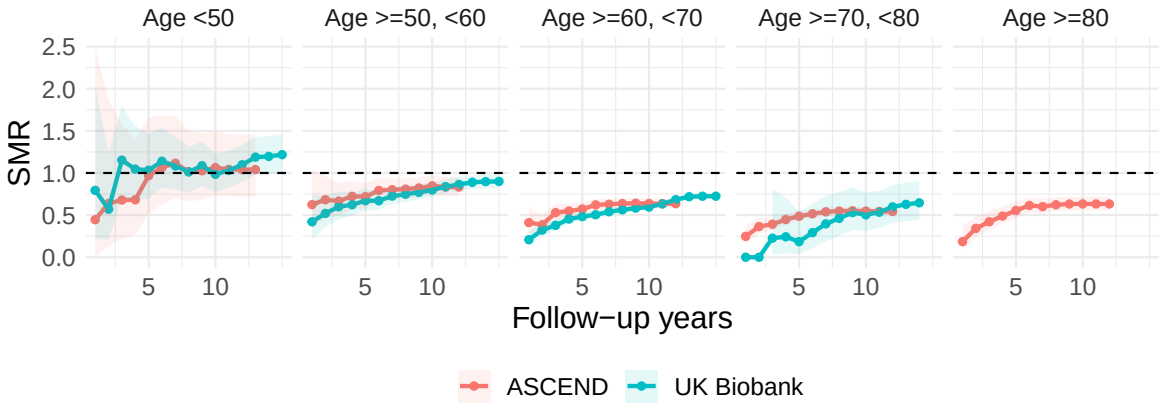


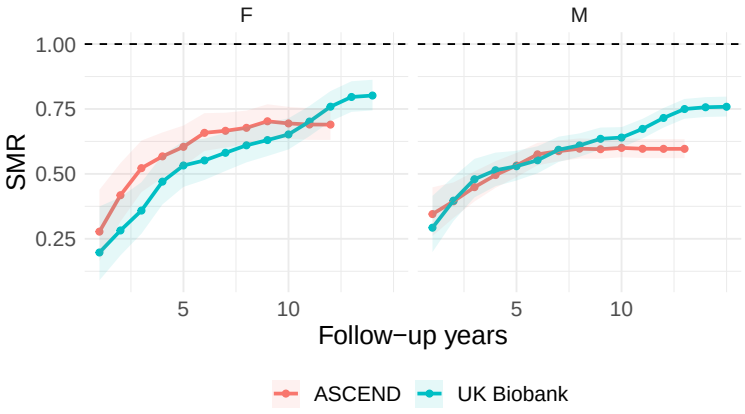
Figure C.34: Comparison of cumulative incidence observed (shaded region) vs predicted by simulation (lines) in the UK Biobank stratified by presence of albuminuria



(a) In all participants



(b) By age group at baseline



(c) By sex

Figure C.35: Age-sex standardised mortality ratio (SMR; using UK lifetable) over the follow-up duration in ASCEND and UK Biobank

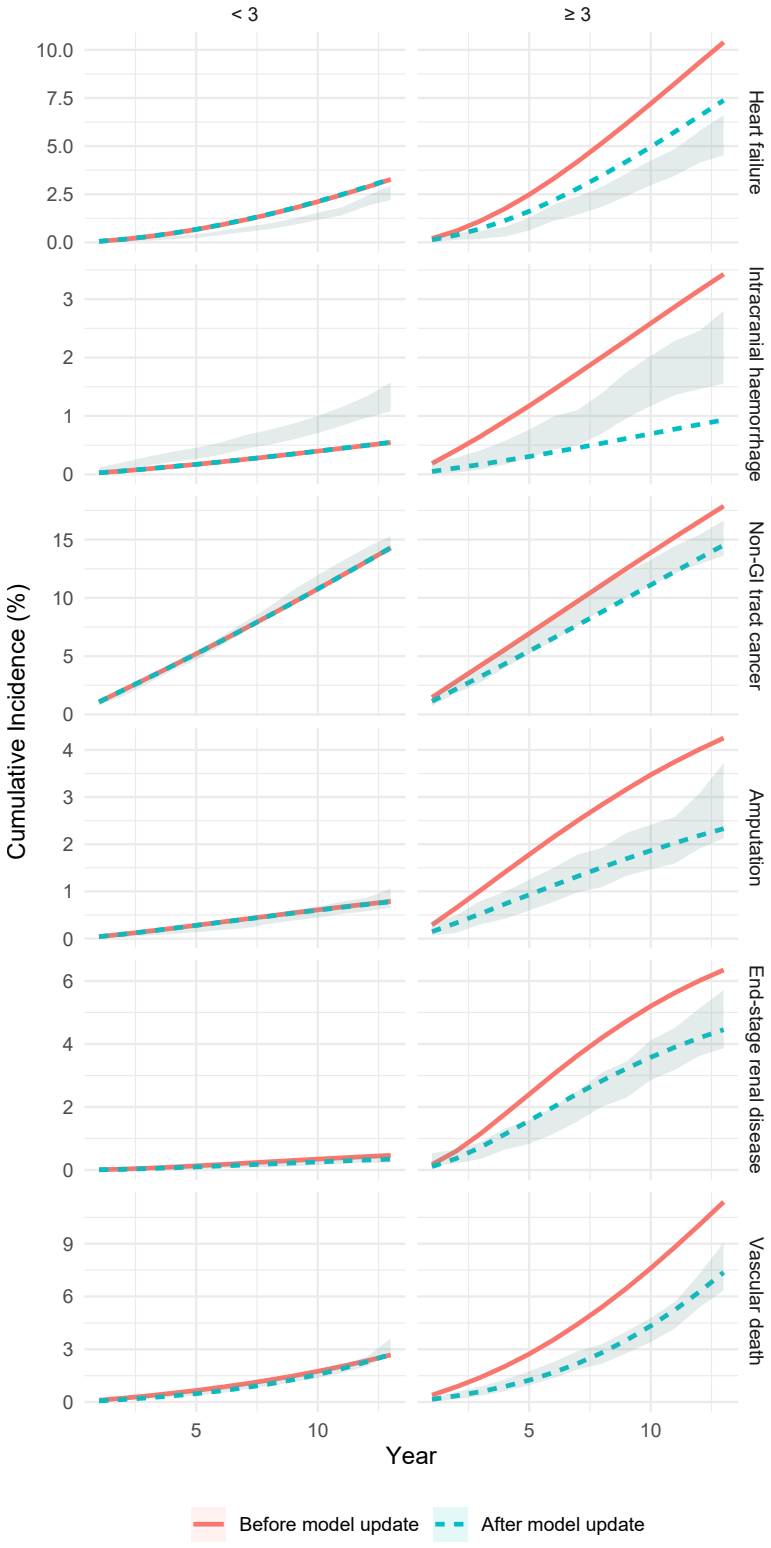
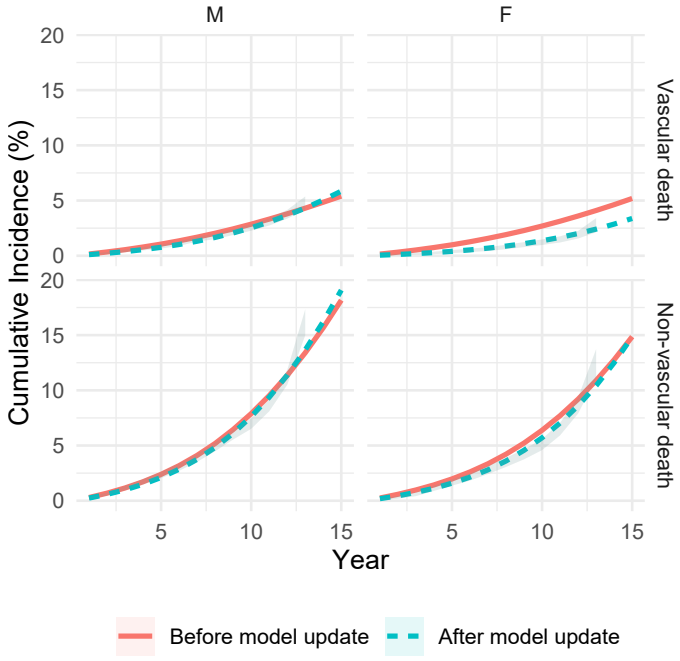
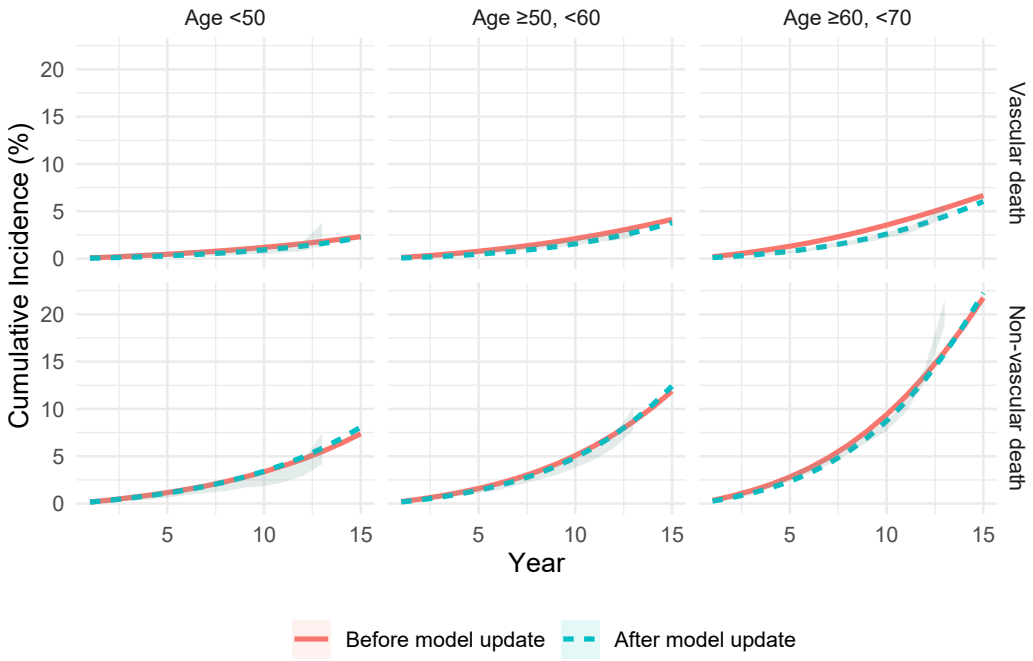


Figure C.36: Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) before and after model update, stratified by presence of albuminuria



(a) By sex



(b) By age

Figure C.37: Cumulative incidence in UK Biobank (observed: shaded regions; predicted: lines) before and after model update, stratified by sex and age

Table C.15: Uno's C-statistics of simulation model for each endpoint in the UK Biobank, before and after model update

Adverse event	Before update	After update
Myocardial infarction	0.674	0.667
Coronary revascularisation (urgent)	0.640	0.642
Coronary revascularisation (non-urgent)	0.658	0.664
Transient ischaemic attack*	0.655	0.664
Ischaemic stroke	0.675	0.679
Heart failure	0.739	0.745
Intracranial haemorrhage	0.600	0.597
GI bleed	0.631	0.648
Other major bleed	0.517	0.524
GI tract cancer	0.636	0.632
Non-GI tract cancer	0.620	0.622
Amputation	0.810	0.811
End-stage renal disease	0.903	0.891
Vascular death	0.696	0.719
Non-vascular death	0.674	0.675

* Assessed at 8 years of follow-up as primary care data (average follow-up of 8 years available) was used to supplement ascertainment of transient ischaemic attack. All other events assessed at 11 years of follow-up in the UK Biobank.

Table C.16: Comparison of bleeding risk scores

	ASCEND, 2018 [3]	Selak et al., 2019 [10]	QBleed, 2014 [11]
Population	People with diabetes without cardiovascular disease in UK recruited into ASCEND trial	New Zealand primary care population without cardiovascular disease	UK primary care population
Data source	Trial data; adjudicated bleeding events	National and regional database; ICD codes used to identify bleeding events	Linked hospital and mortality records; ICD codes used to identify bleeding events
Outcomes	Intracranial haemorrhage; GI bleed; other major bleed	Major bleed	Upper GI bleed; intracranial bleed
Adjusted hazard ratio			
Age	(Per 10 years) Intracranial haemorrhage: 1.36 GI bleed 1.15 Other major bleed 1.36	1.04 (women), 1.04 (men)	Note: Fractional polynomial used for age - not calculated here
Cancer	GI bleed: GI tract cancer 5.73 Other major bleed: non-GI tract cancer 3.74	1.35 (women), 1.76 (men)	Upper GI bleed: 1.22 (women), 1.39 (men)

Note:
GI, gastrointestinal.
The table aims to highlight some key differences between the risk scores and does not serve as a comprehensive review

C.4 Hospital costs associated with adverse events in ASCEND

Table C.17: Estimating the average annual cost of maintenance dialysis

Dialysis type	% of prevalent dialysis	Cost (£) per unit*	Basis of payment	Annual cost (£)
In-center haemodialysis	77.5%	157	Per session	24477†
Home haemodialysis	0.5%	241	Per week	12512
Peritoneal dialysis	21.9%	78	Per day	28453
Average annual dialysis cost (£)				25283

Note:
* The unit cost for each dialysis type is the weighted average (based on total no. of sessions recorded in the national schedule of reference cost) across the different dialysis access as reported in the National Renal Dataset.
† Average of 3 haemodialysis sessions per week is assumed.

Table C.18: Predictive performance of models using different forms of age

Form of age	MSE	RMSE	MAPE	MPE	R^2
Linear	14223525	3771	1619	0.0	0.299
Natural cubic spline	14683684	3832	1550	-227.1	0.300
Polynomial degree 2	14229452	3772	1679	110.0	0.299

Note:
MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R^2: Efron's R^2 which is the square of the correlation between the predicted and observed values.

Table C.19: Marginal effects of different forms of age on annual hospital cost

	Marginal effect of age relative to 60-year-old				
Form of age	50	60	70	80	90
Linear	-122	0	130	256	382
Natural cubic spline	-17	0	128	353	643
Polynomial degree 2	-22	0	159	445	860

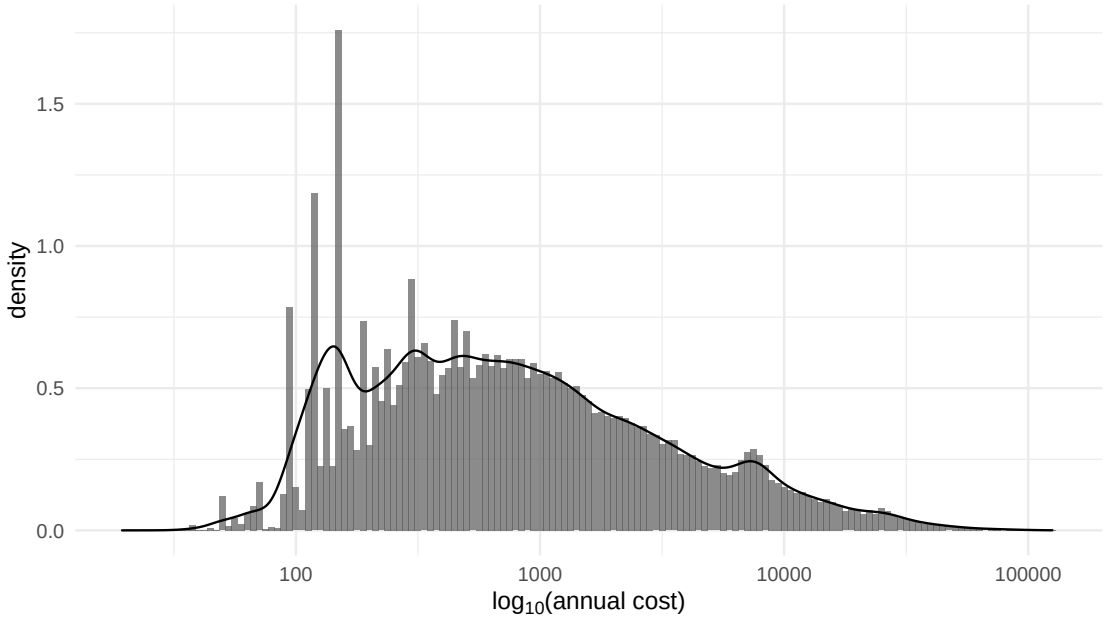


Figure C.38: Distribution of non-zero annual hospital cost

Table C.20: Results from Hosmer-Lemeshow test and Pregibon link test

		Hosmer-Lemeshow test	Pregibon link test	
Link	Distribution	p-value	p-value	Coefficient*
Single-equation				
Identity	Gaussian	0.000	0.108	0.000
	Poisson	0.000	0.000	0.000
	Gamma	0.000	0.013	0.000
Log	Gaussian	0.000	0.000	-0.188
	Poisson	0.000	0.000	-0.172
	Gamma	0.000	0.000	-0.078
Sqrt	Gaussian	0.000	1.000	0.000
	Poisson	0.101	0.101	0.000
	Gamma	0.000	0.269	0.000
Two-part†				
Identity	Gaussian	0.002	0.134	0.000
	Poisson	0.254	0.828	0.000
	Gamma	0.422	0.900	0.000
Log	Gaussian	0.000	0.000	-0.193
	Poisson	0.000	0.000	-0.184
	Gamma	0.000	0.000	-0.104
Sqrt	Gaussian	0.000	1.000	0.000
	Poisson	0.024	0.000	-0.001
	Gamma	0.000	0.010	-0.001

* Coefficient of $\hat{y}^2$.
† The tests are performed on second part of two-part model.

Table C.21: Results from modified Park test

Link	Slope*
Single-equation	
Identity	1.504
Log	1.831
Sqrt	1.419
Two-part†	
Identity	1.488
Log	1.858
Sqrt	1.486

* Slope refers to the exponent of power function reflecting the mean-variance relationship in the modified Park test. Indications: 0 - Gaussian; 1 - Poisson; 2 - Gamma; 3 - Inverse Gaussian.

† The tests are performed on the second part of the two-part model.

Table C.22: Results from Copas test

Link	Distribution	Mean (SD) of percentage (%) $1-\alpha$	$1-\delta$	$1-\gamma$	% rejected
Single-equation					
Identity	Gaussian	0 (0)	1 (4)	1 (4)	13
	Poisson	-0.8 (0.3)	0 (4)	0.9 (4)	11
	Gamma	0.8 (1.8)	1.5 (4.2)	0.7 (4.1)	16
Log	Gaussian	-9.5 (0.7)	33.6 (24.8)	39.4 (22.6)	64
	Poisson	46.2 (2.7)	63.5 (18.8)	31 (37.1)	100
	Gamma	96.6 (1.7)	95 (3.9)	-89.5 (171.5)	100
Sqrt	Gaussian	10.3 (2.8)	11.4 (4.8)	1.3 (4.6)	83
	Poisson	9.1 (1.5)	10.1 (4.1)	1 (4.7)	79
	Gamma	16.9 (1.1)	17.5 (3.4)	0.6 (4.7)	100
Two-part					
Identity	Gaussian	-5 (0.5)	-3.3 (4)	1.6 (4)	19
	Poisson	-5.4 (0.7)	-3.9 (3.9)	1.4 (4)	22
	Gamma	-4.9 (0.9)	-3.3 (3.8)	1.4 (4)	18
Log	Gaussian	-9 (0.6)	21.1 (19.8)	27.6 (18.2)	44
	Poisson	38.5 (2.8)	51.7 (18.2)	20.5 (31.8)	99
	Gamma	88.9 (3.5)	86.1 (7.2)	-44.6 (94.8)	100
Sqrt	Gaussian	-1.3 (2.4)	0.7 (5)	2 (4.6)	16
	Poisson	5.6 (0.8)	6.6 (4)	1.1 (4.7)	47
	Gamma	12.8 (1.2)	13.6 (3.5)	0.8 (4.7)	97

Note:
α: in-sample calibration, captures effect of misspecification; $1-\alpha$: in-sample shrinkage; δ: out-of-sample calibration, captures both effect of misspecification and overfitting; $1-\delta$: out-of-sample shrinkage; $1-\gamma$: combines in-sample and out-of-sample shrinkage, captures effect of overfitting; % rejected: Percentage of iterations in which test failed with 5% significance threshold

Table C.23: Predictive performance of candidate models

Link	Distribution	MSE	RMSE	MAPE	MPE	R^2
Single-equation						
Identity	Gaussian	14184050	3766.172	1621.656	0.00000	0.30107
Identity	Poisson	14310384	3782.907	1605.641	-58.90354	0.29944
Identity	Gamma	14245401	3774.308	1605.252	-22.85855	0.29808
Log	Gaussian	15500057	3937.011	1893.552	243.85878	0.24151
Log	Poisson	20226215	4497.356	1710.842	0.00001	0.15963
Log	Gamma	868440661	29469.317	2177.627	599.42835	0.03673
Sqrt	Gaussian	14405148	3795.411	1799.346	280.75859	0.29408
Sqrt	Poisson	14452626	3801.661	1617.013	0.00000	0.29066
Sqrt	Gamma	14740115	3839.286	1628.593	33.66606	0.28530
Two-part						
Identity	Gaussian	14189530	3766.899	1613.974	1.51905	0.30083
Identity	Poisson	14216319	3770.453	1613.923	1.56321	0.29949
Identity	Gamma	14238227	3773.358	1612.428	-1.26144	0.29842
Log	Gaussian	15088376	3884.376	1800.717	158.84396	0.25930
Log	Poisson	18096108	4253.952	1685.125	5.25473	0.19129
Log	Gamma	128919260	11354.262	1852.722	256.24470	0.07712
Sqrt	Gaussian	14271304	3777.738	1660.217	57.70814	0.29694
Sqrt	Poisson	14429045	3798.558	1618.956	3.17796	0.29144
Sqrt	Gamma	14662875	3829.213	1627.280	29.19941	0.28641

Note:
MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R^2: Efron's R^2 which is the square of the correlation between the predicted and observed values.

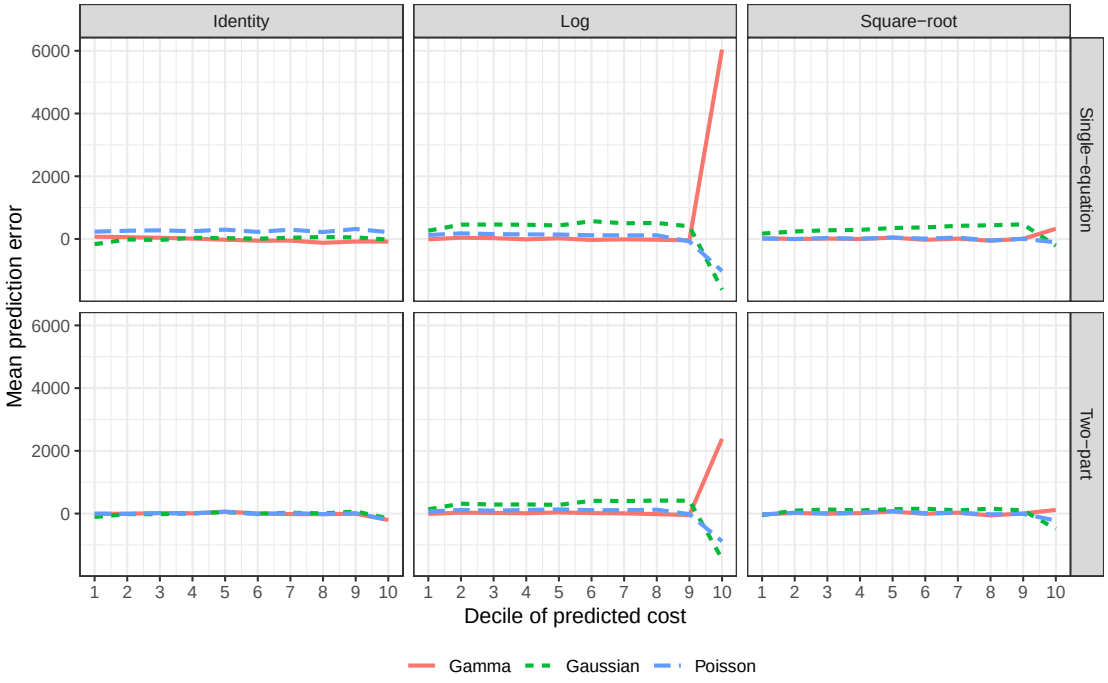


Figure C.39: Mean prediction error of candidate models in each decile of predicted cost

Table C.24: Annual hospital costs associated with adverse event occurrence estimated by single-equation and two-part models

Disease history (ref: no event)	Single-equation model	Two-part model
Myocardial infarction		
In year	4114 (3016, 5212)	3832 (2947, 4830)
In previous year	1162 (277, 2047)	1204 (505, 1884)
At least 2 years ago	268 (-180, 715)	299 (-80, 721)
Coronary revascularisation (urgent)		
In year	5734 (4311, 7158)	5201 (4014, 6438)
In previous year	118 (-859, 1095)	77 (-426, 769)
At least 2 years ago	146 (-332, 624)	188 (-232, 668)
Coronary revascularisation (non-urgent)		
In year	8388 (7549, 9226)	8319 (7440, 9154)
In previous year	741 (258, 1225)	786 (351, 1406)
At least 2 years ago	432 (164, 699)	503 (242, 812)
Transient ischaemic attack		
In year	1582 (1151, 2013)	1526 (1148, 1966)
In previous year	466 (43, 889)	475 (116, 942)
At least 2 years ago	631 (275, 986)	685 (339, 1113)
Ischaemic stroke		
In year	6857 (5815, 7899)	6661 (5699, 7728)
In previous year	1348 (666, 2029)	1302 (781, 2019)
At least 2 years ago	1002 (594, 1411)	1023 (617, 1467)
Heart failure		
In year	7935 (6842, 9028)	7638 (6602, 8745)
In previous year	3180 (2168, 4192)	3035 (2071, 4145)
At least 2 years ago	1826 (1107, 2546)	1786 (1065, 2637)
Intracranial haemorrhage		
In year	11816 (8519, 15113)	11542 (8638, 14596)
In previous year	995 (84, 1906)	1005 (90, 2003)
At least 2 years ago	287 (-268, 843)	293 (-190, 995)
GI bleed		
In year	5293 (4153, 6432)	5156 (4078, 6362)
In previous year	1605 (728, 2481)	1556 (774, 2531)
At least 2 years ago	1060 (431, 1688)	1134 (511, 1900)
Other major bleed		
In year	3906 (2159, 5653)	3817 (2379, 5634)
In previous year	1139 (158, 2121)	1199 (293, 2347)
At least 2 years ago	522 (59, 985)	557 (63, 1102)
GI tract cancer		

Table C.24: Annual hospital costs associated with adverse event occurrence estimated by single-equation and two-part models *(continued)*

Disease history (ref: no event)	Single-equation model	Two-part model
In year	9879 (8673, 11084)	9697 (8584, 10935)
In previous year	5165 (3460, 6871)	5121 (3656, 6955)
At least 2 years ago	1186 (618, 1754)	1223 (694, 1943)
Non-GI tract cancer		
In year	7098 (6608, 7588)	6978 (6546, 7440)
In previous year	3719 (3240, 4198)	3673 (3189, 4199)
At least 2 years ago	1596 (1292, 1900)	1639 (1336, 1969)
Amputation		
In year	17656 (15096, 20216)	17246 (14740, 19875)
In previous year	7061 (5025, 9097)	6898 (4903, 9190)
At least 2 years ago	3858 (2786, 4930)	3713 (2638, 4829)
End-stage renal disease		
In year	20758 (17942, 23574)	20785 (17961, 23951)
In previous year	28821 (25511, 32131)	28871 (25492, 32280)
At least 2 years ago	20042 (16693, 23391)	20463 (16971, 23854)
Death in year (ref: No death in year)		
Vascular death	2155 (1162, 3148)	1612 (901, 2385)
Non-vascular death	5394 (4732, 6055)	4272 (3740, 4853)

Note:
GI, gastrointestinal. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. Model does not include interaction terms. Estimation adjusted for other sociodemographic and clinical risk factors.

* Average marginal effect for two-part model estimated using 1000 bootstrap [12].

Table C.25: Baseline characteristics of 15,436 participants included in the analysis, before and after imputation of missing data

Variable	Before imputation	After imputation
Diabetes type		
Type 1	908 (5.9%)	908 (5.9%)
Type 2	14528 (94.1%)	14528 (94.1%)
Sex		
Male	9650 (62.5%)	9650 (62.5%)
Female	5786 (37.5%)	5786 (37.5%)
Smoking status		
Current smoker	1274 (8.3%)	1274 (8.3%)
Former/Never smoker	13989 (90.6%)	14162 (91.7%)
Missing	173 (1.1%)	-
Race		
White	14892 (96.5%)	15113 (97.9%)
South Asian	183 (1.2%)	183 (1.2%)
Black	140 (0.9%)	140 (0.9%)
Other/unknown	221 (1.4%)	-
Townsend Index		
Q1: <-2.42 (least deprived)	6674 (43.2%)	6712 (43.5%)
Q2: ≥-2.42, <-0.44	3783 (24.5%)	3783 (24.5%)
Q3: ≥-0.44, < 1.79	2492 (16.1%)	2492 (16.1%)
Q4: ≥ 1.79, < 4.75	1814 (11.8%)	1814 (11.8%)
Q5: ≥ 4.75 (most deprived)	635 (4.1%)	635 (4.1%)
Missing	38 (0.2%)	-
Hypertension		
Y	9502 (61.6%)	9614 (62.3%)
N	5822 (37.7%)	5822 (37.7%)
Missing	112 (0.7%)	-
Diabetic retinopathy		
Y	3017 (19.5%)	3017 (19.5%)
N	12277 (79.5%)	12419 (80.5%)
Missing	142 (0.9%)	-
Statin use		
Y	11619 (75.3%)	11619 (75.3%)
N	3817 (24.7%)	3817 (24.7%)
Use of ACE Inhibitor or ARB		
Y	9024 (58.5%)	9024 (58.5%)
N	6412 (41.5%)	6412 (41.5%)
Age (years)		
Mean (SD)	63.3 (9.2)	62.8 (9.2)

Table C.25: Baseline characteristics of 15,436 participants included in the analysis, before and after imputation of missing data *(continued)*

Variable	Before imputation	After imputation
<50	1087 (7%)	1087 (7%)
≥50, <60	4486 (29.1%)	4486 (29.1%)
≥60, <70	6229 (40.4%)	6229 (40.4%)
≥70	3634 (23.5%)	3634 (23.5%)
Diabetes duration (years)		
Median (IQR)	7.0 (3.0, 13.0)	7.0 (4.0, 12.1)
<5	4875 (31.6%)	5017 (32.5%)
≥5, <10	4325 (28%)	4810 (31.2%)
≥10, <20	3526 (22.8%)	3700 (24%)
≥20	1857 (12%)	1909 (12.4%)
Missing	853 (5.5%)	-
Body-mass index (kg/m^2)		
Mean (SD)	31.1 (6.5)	31.1 (6.5)
<25	2064 (13.4%)	2066 (13.4%)
≥25, <30	5455 (35.3%)	5523 (35.8%)
≥30, <35	4510 (29.2%)	4550 (29.5%)
≥35	3289 (21.3%)	3297 (21.4%)
Missing	118 (0.8%)	-
HbA1c (IFCC mmol/mol)		
Mean (SD)	54.8 (12.9)	55.0 (11.2)
< 48	3261 (21.1%)	4081 (26.4%)
≥ 48, < 64	4651 (30.1%)	8730 (56.6%)
≥ 64	1872 (12.1%)	2625 (17%)
Missing	5652 (36.6%)	-
HDL cholesterol (mmol/L)		
Mean (SD)	1.27 (0.35)	1.27 (0.29)
< 1.0	2162 (14%)	2197 (14.2%)
≥ 1.0, < 1.5	5506 (35.7%)	10971 (71.1%)
≥ 1.5	2103 (13.6%)	2268 (14.7%)
Missing	5665 (36.7%)	-
Non-HDL cholesterol (mmol/L)		
Mean (SD)	2.90 (0.84)	2.90 (0.69)
< 2.5	3383 (21.9%)	3731 (24.2%)
≥ 2.5, < 3.5	4379 (28.4%)	9595 (62.2%)
≥ 3.5	2009 (13%)	2110 (13.7%)
Missing	5665 (36.7%)	-
Systolic blood pressure (mmHg)		
Mean (SD)	136.1 (15.3)	135.9 (13.3)
<130	3389 (22%)	4245 (27.5%)
≥130, <140	3080 (20%)	5649 (36.6%)

Table C.25: Baseline characteristics of 15,436 participants included in the analysis, before and after imputation of missing data *(continued)*

Variable	Before imputation	After imputation
≥140	4537 (29.4%)	5542 (35.9%)
Missing	4430 (28.7%)	-
Diastolic blood pressure (mmHg)		
Mean (SD)	77.1 (9.5)	77.3 (8.3)
<75	4217 (27.3%)	5266 (34.1%)
≥75, <85	4600 (29.8%)	7772 (50.3%)
≥85	2183 (14.1%)	2398 (15.5%)
Missing	4436 (28.7%)	-
Urinary albumin/creatinine ratio (mg/mmol)		
< 3	8503 (55.1%)	13505 (87.5%)
≥ 3	1242 (8%)	1931 (12.5%)
Missing	5691 (36.9%)	-
eGFR (ml/min/1.73m^2)		
< 45	405 (2.6%)	540 (3.5%)
≥ 45, < 60	863 (5.6%)	1345 (8.7%)
≥ 60, < 90	4007 (26%)	6007 (38.9%)
≥ 90	4511 (29.2%)	7544 (48.9%)
Missing	5650 (36.6%)	-

Note:
Summary values are N (%) unless otherwise specified.

Table C.26: Number and costs of outpatient hospital episodes by treatment speciality (for episodes with no procedures performed) or HRG subchapter (for episodes with procedure(s) performed) (top 20 occurrences)

HRG subchapter / treatment speciality	Cost (£) per episode, median (IQR)	No. of episodes per 100 person-year		
		All	Type 2 diabetes	Type 1 diabetes
Episodes with no procedure performed, by treatment specialty				
130 Ophthalmology	92 (92, 92)	37.1	34.6	72.1
307 Diabetic Medicine	142 (142, 142)	36.9	30.2	130.9
110 Trauma & Orthopaedics	116 (116, 141)	26.8	26.3	34.3
650 Physiotherapy	52 (52, 52)	14.7	14.2	22.0
653 Podiatry	47 (47, 47)	10.1	10.1	10.0
101 Urology	104 (104, 126)	10.0	10.2	7.1
320 Cardiology	123 (123, 150)	9.9	10.0	8.3
300 General Medicine	158 (158, 158)	9.3	8.2	24.2
100 General Surgery	130 (130, 158)	7.9	8.0	7.9
330 Dermatology	105 (105, 123)	6.4	6.4	7.4
340 Respiratory Medicine	141 (141, 196)	5.8	6.0	3.3
800 Clinical Oncology (Previously Radiotherapy)	129 (129, 129)	5.5	5.6	4.2
361 Nephrology	174 (174, 174)	5.3	4.7	14.0
301 Gastroenterology	142 (142, 179)	5.3	5.3	5.6
410 Rheumatology	131 (131, 131)	5.0	4.8	8.9
120 ENT	96 (96, 115)	4.9	4.8	6.4
303 Clinical Haematology	154 (154, 154)	4.9	5.1	2.4
302 Endocrinology	151 (151, 151)	4.3	3.9	9.3
840 Audiology	87 (87, 87)	3.9	4.1	2.1
370 Medical Oncology	161 (161, 161)	3.7	3.7	3.4

Table C.26: Number and costs of outpatient hospital episodes by treatment speciality (for episodes with no procedures performed) or HRG subchapter (for episodes with procedure(s) performed) (top 20 occurrences) *(continued)*

HRG subchapter / treatment speciality	Cost (£) per episode, median (IQR)	All	Type 2 diabetes	Type 1 diabetes
Episodes with procedures performed, by HRG subchapter				
BZ Eyes and Periorbita Procedures and Disorders	114 (114, 121)	15.1	14.0	30.1
JC Skin Procedures	151 (117, 155)	6.7	6.6	7.8
CA Ear, Nose, Mouth, Throat and Neck Procedures	105 (105, 125)	4.0	4.0	4.5
LB Urological and Male Reproductive System Procedures and Disorders	151 (151, 194)	2.2	2.2	1.2
SC Radiotherapy	154 (154, 211)	2.1	2.2	1.3
DZ Respiratory System Procedures and Disorders	181 (150, 195)	1.3	1.4	1.0
EY Interventional Cardiology for Acquired Conditions	141 (139, 141)	1.2	1.2	0.7
HN Orthopaedic Non-Trauma Procedures	154 (151, 172)	0.8	0.8	1.5
FE Digestive System Endoscopic Procedures	181 (177, 308)	0.8	0.8	0.5
MA Female Reproductive System Procedures	186 (184, 213)	0.7	0.7	0.7
SB Chemotherapy	692 (483, 1,147)	0.7	0.7	0.4
CD Dental and Orthodontic Procedures	172 (170, 201)	0.6	0.6	0.3
AB Pain Management	139 (125, 139)	0.5	0.5	0.4
RD Diagnostic Imaging Procedures	152 (124, 184)	0.4	0.4	0.3
AA Nervous System Procedures and Disorders	189 (189, 189)	0.3	0.3	0.4
YR Vascular Imaging Interventions	141 (141, 153)	0.2	0.2	0.6

Table C.26: Number and costs of outpatient hospital episodes by treatment speciality (for episodes with no procedures performed) or HRG subchapter (for episodes with procedure(s) performed) (top 20 occurrences) *(continued)*

HRG subchapter / treatment speciality	Cost (£) per episode, median (IQR)	All	Type 2 diabetes	Type 1 diabetes
FF Digestive System Open and Laparoscopic Procedures	171 (159, 208)	0.2	0.2	0.1
YJ Breast Imaging Interventions	289 (218, 340)	0.2	0.2	0.3
RN Nuclear Medicine Procedures	325 (278, 545)	0.2	0.2	0.2
LA Renal Procedures and Disorders*	230 (203, 249)	0.1	0.1	0.1

Note:
IQR, interquartile range.
* Maintenance dialysis sessions are not included in hospital episodes (see Section 4.2.1 for more information).

Table C.27: Number and costs of inpatient hospital episodes by HRG subchapter (top 20 occurrences)

HRG subchapter	Cost (£) per episode, median (IQR)	No. of episodes per 100 person-year		
		All	Type 2 diabetes	Type 1 diabetes
FE Digestive System Endoscopic Procedures	525 (476, 632)	6.5	6.6	5.5
BZ Eyes and Periorbita Procedures and Disorders	900 (326, 900)	5.1	4.9	7.2
LB Urological and Male Reproductive System Procedures and Disorders	749 (493, 1,853)	3.6	3.7	2.0
HN Orthopaedic Non-Trauma Procedures	2,659 (1,288, 6,267)	3.5	3.5	4.2
DZ Respiratory System Procedures and Disorders	1,472 (476, 2,228)	3.5	3.6	2.2
EB Cardiac Disorders	559 (386, 1,949)	3.2	3.3	2.7
SB Chemotherapy	1,000 (695, 1,660)	2.8	2.8	2.6
FD Digestive System Disorders	1,330 (447, 2,100)	2.6	2.6	2.9
WH Poisoning, Toxic Effects, Special Examinations, Screening and Other Healthcare Contacts	437 (338, 617)	2.6	2.5	3.9
LA Renal Procedures and Disorders*	760 (453, 2,226)	2.0	1.9	4.6
AA Nervous System Procedures and Disorders	1,397 (523, 3,473)	2.0	1.9	3.4
SA Haematological Procedures and Disorders	499 (294, 527)	1.8	1.8	1.7
EY Interventional Cardiology for Acquired Conditions	1,784 (1,053, 2,927)	1.5	1.6	1.5
HD Musculoskeletal and Rheumatological Disorders	398 (355, 2,378)	1.1	1.1	1.8
JC Skin Procedures	670 (670, 1,035)	1.1	1.1	1.1
KB Diabetic Medicine	636 (428, 2,282)	1.1	0.9	3.6

Table C.27: Number and costs of inpatient hospital episodes by HRG subchapter (top 20 occurrences) *(continued)*

HRG subchapter	Cost (£) per episode, median (IQR)	All	Type 2 diabetes	Type 1 diabetes
FF Digestive System Open and Laparoscopic Procedures	2,571 (1,369, 5,521)	1.1	1.1	0.8
AB Pain Management	711 (616, 714)	1.0	1.0	0.7
GC Hepatobiliary and Pancreatic System Disorders	1,852 (545, 2,539)	1.0	1.0	0.4
JD Skin Disorders	1,488 (413, 2,237)	0.9	0.9	0.8

Note:
IQR, interquartile range.
* Maintenance dialysis sessions are not included in hospital episodes (see Section 4.2.1 for more information).

Table C.28: Average number of hospital episodes and hospital cost each year, stratified by time since event occurrence

Adverse event	N (%)	No. of episodes* per 100 person-year				Hospital cost (£) per person-year			
		No history	In year	Previous year	At least 2 years ago	No history	In year	Previous year	At least 2 years ago
Myocardial infarction	465 (3.0%)	3.86	11.45	8.63	6.18	1489	10649	4549	3400
Coronary revascularisation (non-urgent)	292 (1.9%)	3.88	13.09	7.83	6.09	1513	10972	3113	2500
Coronary revascularisation (urgent)	272 (1.8%)	3.88	13.09	7.16	5.61	1510	12427	3512	2966
Transient ischaemic attack	365 (2.4%)	3.88	9.38	6.66	6.11	1519	4474	3180	3222
Ischaemic stroke	455 (2.9%)	3.85	11.58	8.32	6.82	1487	10281	4376	3722
Heart failure	356 (2.3%)	3.85	14.52	11.72	10.09	1483	12474	7428	6677
Intracranial haemorrhage	100 (0.6%)	3.91	11.99	7.56	4.87	1531	16138	4327	2685
GI bleed	238 (1.5%)	3.89	10.94	7.73	7.05	1513	9975	4626	4279
Other major bleed	117 (0.8%)	3.90	10.38	7.72	6.39	1533	7254	5212	3243
GI tract cancer	315 (2.0%)	3.85	16.01	12.32	7.90	1493	12813	8231	3837
Non-GI tract cancer	1573 (10.2%)	3.59	14.77	12.20	7.95	1336	9644	6233	3597
Amputation	143 (0.9%)	3.85	23.93	17.55	15.40	1492	21745	11217	8297
End-stage renal disease	105 (0.7%)	3.86	22.27	23.81	17.90	1462	25325	33603	24290
Vascular death	414 (2.7%)	3.91	6.63	-	-	1525	7648	-	-
Vascular event† in year	191 (1.2%)	3.91	7.66	-	-	1534	9414	-	-
No vascular event† in year	223 (1.4%)	3.92	5.74	-	-	1538	6136	-	-
Non-vascular death	1126 (7.3%)	3.86	10.54	-	-	1459	10755	-	-
Non-vascular event‡ in year	363 (2.4%)	3.90	11.90	-	-	1512	12734	-	-
No non-vascular event‡ in year	763 (4.9%)	3.88	9.89	-	-	1493	9813	-	-

Table C.28: Average number of hospital episodes and hospital cost each year, stratified by time since event occurrence *(continued)*

Adverse event	N (%)	No history	In year	Previous year	At least 2 years ago	No history	In year	Previous year	At least 2 years ago

Note:
N (%), no. (percentage) of participants who experienced each adverse event; GI, gastrointestinal.
* Hospital episodes refer to hospital inpatient, outpatient and accident and emergency attendances and admissions. Dialysis sessions not included in counts of hospital episodes. See Section 4.2.1 for further information.
† Vascular event refers to myocardial infarction, coronary revascularisation, transient ischaemic attack, ischaemic stroke, or heart failure.
‡ Non-vascular event refers to cancer, intracranial haemorrhage, GI bleed, other major bleed, amputation, or end-stage renal disease.

Table C.29: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events, excluding non-attended outpatient episodes (sensitivity analysis)

Variable	Annual hospital cost (£)
(Intercept)	-35 (-70, -1)*
Proportion of year observed	639 (601, 677)**
Diabetes type (ref: Type 2)	
Type 1	144 (27, 262)*
Sex (ref: Male)	
Female	98 (57, 139)**
Townsend index (ref: Q1 (least deprived))	
Q2	10 (-15, 35)
Q3	-2 (-52, 48)
Q4	162 (91, 233)**
Q5 (most deprived)	509 (337, 681)**
Age (per 10 years; centered at 60)	
Age	93 (69, 118)**
Age^2	63 (47, 80)**
BMI (ref: <25 kg/m^2)	
≥25, <30	13 (7, 18)**
≥30, <35	65 (23, 108)**
≥35	215 (155, 275)**
Diabetes duration (ref: <5 years)	
≥5, <10	32 (1, 62)*
≥10, <20	147 (93, 200)**
≥20	267 (177, 356)**
HbA1c (ref: <48 mmol/mol)	
≥ 48, < 64	-5 (-36, 25)
≥ 64	164 (98, 230)**
eGFR (ref: ≥90 ml/min/1.73m^2)	
≥60, <90	28 (-19, 76)
≥45, <60	159 (53, 265)**
<45	643 (410, 875)**
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)	
Y	184 (105, 262)**
Retinopathy (ref: N)	
Y	111 (57, 165)**
Disease history (ref: no event)	
Myocardial infarction	
In year	4932 (3662, 6203)**
At least 1 year ago	567 (97, 1037)*

Table C.29: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events, excluding non-attended outpatient episodes (sensitivity analysis) *(continued)*

Variable	Annual hospital cost (£)
Coronary revascularisation (urgent)	
In year; MI in same year	4498 (2717, 6279)**
In year; no MI in same year	8366 (5765, 10966)**
At least 1 year ago	111 (-389, 610)
Coronary revascularisation (non-urgent)	
In year	8305 (7466, 9143)**
At least 1 year ago	535 (289, 782)**
Transient ischaemic attack	
In year	1537 (1105, 1969)**
At least 1 year ago	578 (268, 887)**
Ischaemic stroke	
In year	7126 (6084, 8168)**
At least 1 year ago	1064 (691, 1436)**
Heart failure	
In year	8269 (7146, 9391)**
At least 1 year ago	2342 (1694, 2989)**
Intracranial haemorrhage	
In year	12087 (8858, 15316)**
At least 1 year ago	394 (-91, 880)
GI bleed	
In year	5493 (4370, 6616)**
At least 1 year ago	1195 (591, 1799)**
Other major bleed	
In year	3871 (2136, 5606)**
At least 1 year ago	675 (214, 1136)**
GI tract cancer	
In year	10165 (8956, 11375)**
In previous year	5134 (3435, 6832)**
At least 2 years ago	1223 (652, 1794)**
Non-GI tract cancer	
In year	7392 (6884, 7900)**
In previous year	3680 (3205, 4156)**
At least 2 years ago	1597 (1294, 1900)**
Amputation	
In year	17719 (15170, 20267)**
In previous year	7146 (5156, 9135)**
At least 2 years ago	3874 (2819, 4928)**

Table C.29: Annual hospital costs associated with sociodemographic characteristics, clinical risk factors and adverse events, excluding non-attended outpatient episodes (sensitivity analysis) *(continued)*

Variable	Annual hospital cost (£)
End-stage renal disease	
In year	20897 (18127, 23668)**
In previous year	28829 (25561, 32098)**
At least 2 years ago	20036 (16663, 23408)**
Death in year (ref: No death in year)	
VD; vascular event in year	-196 (-1912, 1520)
VD; no vascular event in year	2923 (1728, 4117)**
NVD; non-vascular event in year	2495 (1172, 3819)**
NVD; no non-vascular event in year	5956 (5200, 6711)**

Note:
**: p-value < 0.01; *: p-value < 0.05; GI, gastrointestinal; VD, vascular death; NVD, non-vascular death. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed.
Vascular death refers to any vascular-related deaths that may or may not be a result of vascular events included in the model. Similarly, non-vascular death refers to any non-vascular-related deaths that may or may not be a result of non-vascular events included in the model.
* Vascular event refers to myocardial infarction, coronary revascularisation, transient ischaemic attack, ischaemic stroke, or heart failure.
† Non-vascular event refers to cancer, intracranial haemorrhage, GI bleed, other major bleed, amputation, or end-stage renal disease.

Table C.30: Self-reported diabetes medication use at baseline and at about 6.5 years into follow-up

	At baseline (N = 15436)	At ∼6.5 years into follow-up (N = 11207)
GLP-1 receptor agonists	234 (1.5%)	513 (3.3%)
DPP-4 inhibitors	347 (2.2%)	1269 (8.2%)
Metformin	10068 (65.2%)	7735 (69.0%)
Insulin	3920 (25.4%)	3062 (27.3%)
Sulphonylurea	4139 (26.8%)	3387 (30.2%)

Note:
ASCEND participants were asked to report their medication use at baseline and when the EQ-5D-5L was administered, which is approximately 6.5 years into follow-up. For the latter time point, medication use was reported by 11207 participants who responded to the EQ-5D-5L questionnaire.

C.5 Decrements in health-related quality of life associated with adverse events in ASCEND

Table C.31: Marginal effects of different forms of age on EQ-5D utility

	Marginal effect of age relative to 70-year-old						
Form of age	55	60	65	70	75	80	85
Linear	0.017	0.012	0.006	0.000	-0.006	-0.012	-0.017
Natural cubic spline	0.005	-0.001	-0.002	0.000	-0.005	-0.021	-0.046
Polynomial degree 2	0.006	0.007	0.005	0.000	-0.008	-0.020	-0.035
Linear spline, knot at 70	0.004	0.003	0.001	0.000	-0.016	-0.032	-0.047

Table C.32: Predictive performance of models using different forms of age

Form of age	MSE	RMSE	MAPE	MPE	R^2
Linear	0.04877	0.22084	0.16100	-6.20e-15	0.11002
Natural cubic spline	0.04871	0.22070	0.16086	-3.42e-15	0.11121
Polynomial degree 2	0.04874	0.22077	0.16088	-5.97e-15	0.11058
Linear spline, knot at 70	0.04870	0.22069	0.16078	-6.20e-15	0.11126

Note:
MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R^2: Efron's R^2 which is the square of the correlation between the predicted and observed values.

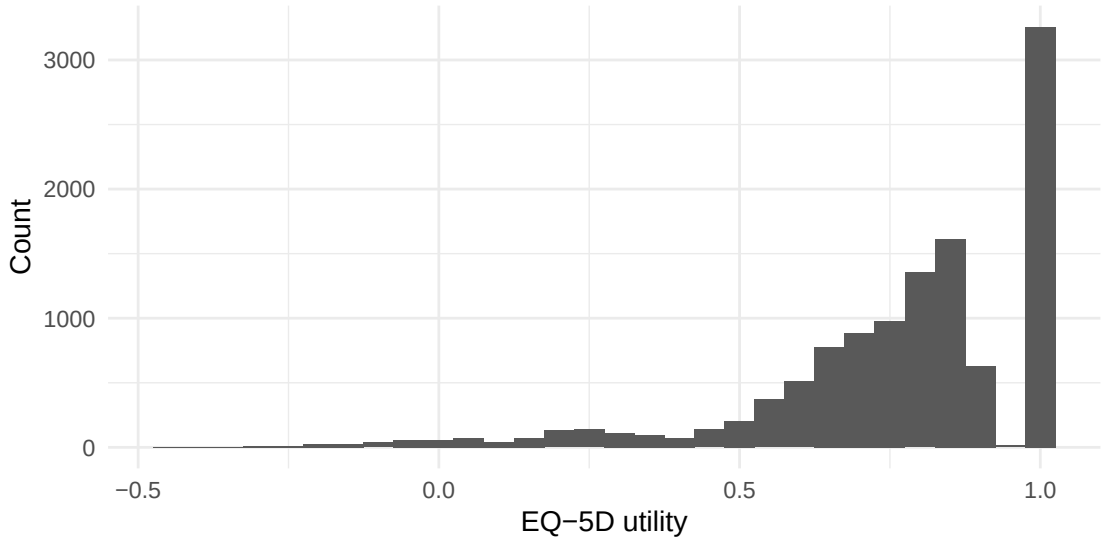


Figure C.40: Distribution of EQ-5D utilities

Table C.33: Predictive performance of candidate models

Model	MSE	RMSE	MAPE	MPE	R^2
OLS	0.04878	0.22087	0.16102	0.00000	0.10984
Beta	0.04943	0.22233	0.16018	0.01269	0.10090
GLM: Log-Gamma	0.04891	0.22115	0.16115	0.00037	0.10799
GLM: Identity-Gamma	0.04885	0.22101	0.16076	-0.00065	0.10899
GLM: Log-Gaussian	0.04878	0.22086	0.16134	0.00037	0.10989

Note:
MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R^2: Efron's R^2 which is the square of the correlation between the predicted and observed values.

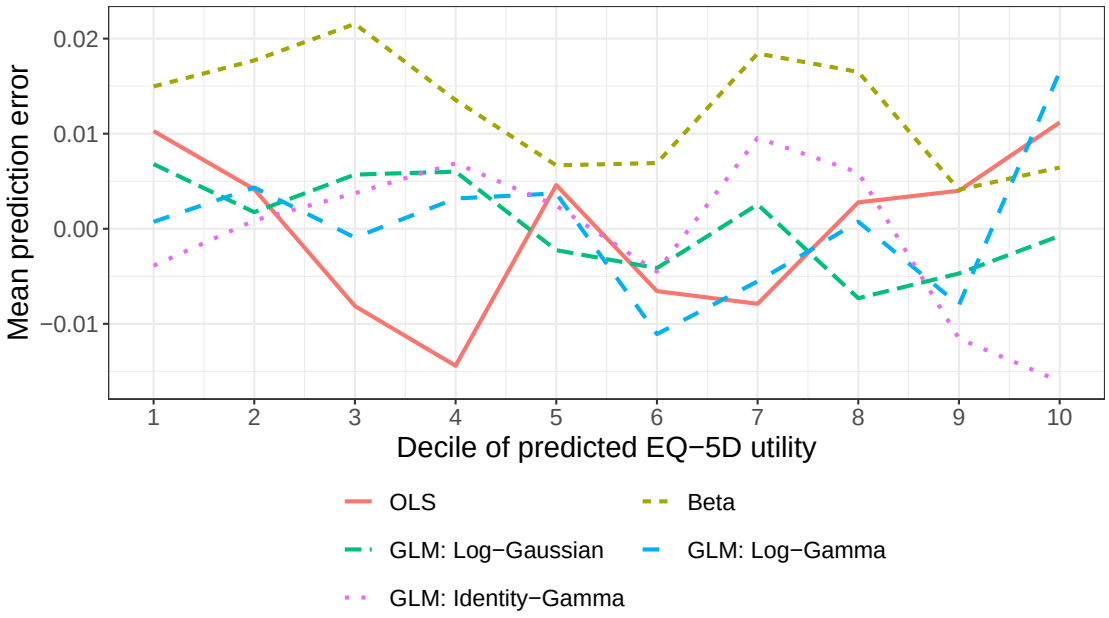


Figure C.41: Mean prediction error of candidate models in each decile of predicted EQ-5D utility value

Table C.34: Results from Copas test

	Mean (SD) of percentage (%)			
Model	$1-\alpha$	$1-\delta$	$1-\gamma$	% rejected
OLS	0 (0)	3.4 (6)	3.4 (6)	16
Beta	-0.9 (1.8)	1.9 (6.3)	2.8 (6.6)	10
GLM: Log-Gamma	6.7 (1.3)	9.9 (6.1)	3.5 (6.5)	52
GLM: Identity-Gamma	-4.8 (1.3)	-1.3 (6.2)	3.3 (6)	10
GLM: Log-Gaussian	-1.4 (0.4)	2.9 (6.5)	4.2 (6.3)	15

Note:
α: in-sample calibration, captures effect of misspecification; $1-\alpha$: in-sample shrinkage; δ: out-of-sample calibration, captures both effect of misspecification and overfitting; $1-\delta$: out-of-sample shrinkage; $1-\gamma$: combines in-sample and out-of-sample shrinkage, captures effect of overfitting; % rejected: Percentage of iterations in which test failed with 5% significance threshold

Table C.35: Characteristics of 11,683 participants included in the analysis, before and after imputation of missing data

Variable	Before imputation	After imputation
Participant characteristics at EQ-5D questionnaire response		
Age (years)		
Mean (SD)	68.5 (8.3)	68.5 (8.3)
<60	1693 (14.5%)	1693 (14.5%)
≥60, <70	4856 (41.6%)	4856 (41.6%)
≥70, <80	3978 (34%)	3978 (34%)
≥80	1156 (9.9%)	1156 (9.9%)
Diabetes duration (years)		
Median (IQR)	13.6 (10.0, 19.2)	13.6 (10.2, 19.0)
<10	2732 (23.4%)	2769 (23.7%)
≥10, <15	3663 (31.4%)	3999 (34.2%)
≥15, <25	3131 (26.8%)	3303 (28.3%)
≥25	1569 (13.4%)	1612 (13.8%)
Missing	588 (5%)	-
Participant characteristics at entry into ASCEND study		
Diabetes type		
Type 1	707 (6.1%)	707 (6.1%)
Type 2	10976 (93.9%)	10976 (93.9%)
Sex		
Male	7347 (62.9%)	7347 (62.9%)
Female	4336 (37.1%)	4336 (37.1%)
Smoking status		
Current smoker	813 (7%)	813 (7%)
Former/Never smoker	10734 (91.9%)	10870 (93%)
Missing	136 (1.2%)	-
Race		
White	11282 (96.6%)	11450 (98%)
South Asian	147 (1.3%)	147 (1.3%)
Black	86 (0.7%)	86 (0.7%)
Other/unknown	168 (1.4%)	-
Townsend Index		
Q1: <-2.42 (least deprived)	5232 (44.8%)	5258 (45%)
Q2: ≥-2.42, <-0.44	2934 (25.1%)	2934 (25.1%)
Q3: ≥-0.44, < 1.79	1851 (15.8%)	1851 (15.8%)
Q4: ≥ 1.79, < 4.75	1237 (10.6%)	1237 (10.6%)
Q5: ≥ 4.75 (most deprived)	403 (3.4%)	403 (3.4%)
Missing	26 (0.2%)	-
Hypertension		

Table C.35: Characteristics of 11,683 participants included in the analysis, before and after imputation of missing data *(continued)*

Variable	Before imputation	After imputation
Y	7173 (61.4%)	7248 (62%)
N	4435 (38%)	4435 (38%)
Missing	75 (0.6%)	-
Diabetic retinopathy		
Y	2232 (19.1%)	2232 (19.1%)
N	9359 (80.1%)	9451 (80.9%)
Missing	92 (0.8%)	-
Statin use		
Y	8919 (76.3%)	8919 (76.3%)
N	2764 (23.7%)	2764 (23.7%)
Use of ACE Inhibitor or ARB		
Y	6818 (58.4%)	6818 (58.4%)
N	4865 (41.6%)	4865 (41.6%)
Age (years)		
Mean (SD)	62.8 (8.5)	62.3 (8.5)
<50	757 (6.5%)	757 (6.5%)
≥50, <60	3542 (30.3%)	3542 (30.3%)
≥60, <70	5024 (43%)	5024 (43%)
≥70	2360 (20.2%)	2360 (20.2%)
Diabetes duration (years)		
Median (IQR)	7.0 (3.0, 12.0)	7.0 (3.6, 12.0)
<5	3765 (32.2%)	3867 (33.1%)
≥5, <10	3348 (28.7%)	3680 (31.5%)
≥10, <20	2608 (22.3%)	2730 (23.4%)
≥20	1374 (11.8%)	1406 (12%)
Missing	588 (5%)	-
Body-mass index (kg/m^2)		
Mean (SD)	31.0 (6.4)	31.0 (6.4)
<25	1539 (13.2%)	1540 (13.2%)
≥25, <30	4224 (36.2%)	4269 (36.5%)
≥30, <35	3426 (29.3%)	3456 (29.6%)
≥35	2412 (20.6%)	2418 (20.7%)
Missing	82 (0.7%)	-
HbA1c (IFCC mmol/mol)		
Mean (SD)	54.4 (12.4)	54.6 (10.9)
< 48	2532 (21.7%)	3134 (26.8%)
≥ 48, < 64	3625 (31%)	6653 (56.9%)
≥ 64	1361 (11.6%)	1896 (16.2%)
Missing	4165 (35.7%)	-

Table C.35: Characteristics of 11,683 participants included in the analysis, before and after imputation of missing data *(continued)*

Variable	Before imputation	After imputation
HDL cholesterol (mmol/L)		
Mean (SD)	1.27 (0.35)	1.27 (0.29)
< 1.0	1630 (14%)	1655 (14.2%)
≥ 1.0, < 1.5	4206 (36%)	8243 (70.6%)
≥ 1.5	1672 (14.3%)	1785 (15.3%)
Missing	4175 (35.7%)	-
Non-HDL cholesterol (mmol/L)		
Mean (SD)	2.88 (0.83)	2.88 (0.68)
< 2.5	2650 (22.7%)	2902 (24.8%)
≥ 2.5, < 3.5	3398 (29.1%)	7247 (62%)
≥ 3.5	1460 (12.5%)	1534 (13.1%)
Missing	4175 (35.7%)	-
Systolic blood pressure (mmHg)		
Mean (SD)	135.9 (15.0)	135.8 (13.2)
<130	2622 (22.4%)	3233 (27.7%)
≥130, <140	2390 (20.5%)	4283 (36.7%)
≥140	3479 (29.8%)	4167 (35.7%)
Missing	3192 (27.3%)	-
Diastolic blood pressure (mmHg)		
Mean (SD)	77.3 (9.3)	77.5 (8.2)
<75	3149 (27%)	3834 (32.8%)
≥75, <85	3650 (31.2%)	6004 (51.4%)
≥85	1687 (14.4%)	1845 (15.8%)
Missing	3197 (27.4%)	-
Urinary albumin/creatinine ratio (mg/mmol)		
< 3	6644 (56.9%)	10481 (89.7%)
≥ 3	854 (7.3%)	1202 (10.3%)
Missing	4185 (35.8%)	-
eGFR (ml/min/1.73m^2)		
< 45	209 (1.8%)	243 (2.1%)
≥ 45, < 60	584 (5%)	817 (7%)
≥ 60, < 90	3081 (26.4%)	4636 (39.7%)
≥ 90	3645 (31.2%)	5987 (51.2%)
Missing	4164 (35.6%)	-

Note:
Summary values are N (%) unless otherwise specified.

Table C.36: EQ-5D-5L questionnaire responses from 11,683 participants, before and after imputation of missing data

	Before imputation	After imputation
EQ-5D utility		
Mean (SD)	0.77 (0.23)	0.77 (0.23)
Median (IQR)	0.80 (0.68, 0.99)	0.80 (0.67, 0.99)
Missing	655 (5.6%)	-
VAS score		
Mean (SD)	77.3 (17.9)	77.3 (17.9)
Median (IQR)	80.0 (70.0, 90.0)	80.0 (70.0, 90.0)
Missing	498 (4.3%)	-
Reported full health*		
Y	3110 (26.6%)	3258 (27.9%)
N	7918 (67.8%)	8425 (72.1%)
Missing	655 (5.6%)	-
EQ-5D dimensions		
Mobility		
1	6212 (53.2%)	6466 (55.3%)
2	2453 (21%)	2584 (22.1%)
3	1641 (14%)	1720 (14.7%)
4	836 (7.2%)	871 (7.5%)
5	39 (0.3%)	42 (0.4%)
Missing	502 (4.3%)	-
Self-care		
1	9494 (81.3%)	9925 (85%)
2	970 (8.3%)	1023 (8.8%)
3	545 (4.7%)	571 (4.9%)
4	137 (1.2%)	147 (1.3%)
5	16 (0.1%)	17 (0.1%)
Missing	521 (4.5%)	-
Usual activities		
1	6868 (58.8%)	7156 (61.3%)
2	2264 (19.4%)	2380 (20.4%)
3	1430 (12.2%)	1503 (12.9%)
4	492 (4.2%)	516 (4.4%)
5	119 (1%)	128 (1.1%)
Missing	510 (4.4%)	-
Pain/Discomfort		
1	4204 (36%)	4392 (37.6%)
2	4041 (34.6%)	4214 (36.1%)
3	2053 (17.6%)	2155 (18.4%)
4	768 (6.6%)	805 (6.9%)

Table C.36: EQ-5D-5L questionnaire responses from 11,683 participants, before and after imputation of missing data *(continued)*

	Before imputation	After imputation
5	111 (1%)	117 (1%)
Missing	506 (4.3%)	-
Anxiety/Depression		
1	7905 (67.7%)	8255 (70.7%)
2	2133 (18.3%)	2249 (19.3%)
3	923 (7.9%)	981 (8.4%)
4	144 (1.2%)	148 (1.3%)
5	47 (0.4%)	50 (0.4%)
Missing	531 (4.5%)	-

Note:
Summary values are N (%) unless otherwise specified.
The five levels of EQ-5D-5L are defined as follows: 1 no problem, 2 slight problems, 3 moderate problems, 4 severe problems, 5 extreme problems/unable to.
* Full health refers to rating 1 for all EQ-5D dimensions.

Table C.37: Mean (SD) of EQ-5D utility by number of comorbid events

		Mean (SD) of EQ-5D utility	
No. of comorbid events	N (%)	DSU tariff	van Hout tariff
0	9970 (85.3%)	0.78 (0.23)	0.78 (0.22)
1	1375 (11.8%)	0.71 (0.25)	0.72 (0.24)
2	267 (2.3%)	0.68 (0.27)	0.68 (0.26)
≥3	71 (0.6%)	0.64 (0.25)	0.65 (0.24)

Note:
The most frequent co-occurring events among ASCEND participants were myocardial infarction and urgent coronary revascularisation (N = 140), followed by stroke and TIA (N = 44). There were fewer than 20 occasions for other co-occurring events.

Table C.38: Mean (SD) of EQ-5D utility by adverse event and time since adverse event occurrence

		Mean (SD) of EQ-5D utility	
Time since event occurrence	No. of participants (%)	DSU tariff	van Hout tariff
Myocardial infarction			
No history	11494 (98.4%)	0.77 (0.23)	0.77 (0.22)
≤1yr	34 (0.3%)	0.71 (0.27)	0.71 (0.26)
>1yr	155 (1.3%)	0.71 (0.25)	0.72 (0.24)
Coronary revascularisation (urgent)			
No history	11533 (98.7%)	0.77 (0.23)	0.77 (0.22)
≤1yr	25 (0.2%)	0.69 (0.27)	0.69 (0.26)
>1yr	125 (1.1%)	0.72 (0.25)	0.73 (0.24)
Coronary revascularisation (non-urgent)			
No history	11496 (98.4%)	0.77 (0.23)	0.77 (0.22)
≤1yr	28 (0.2%)	0.79 (0.20)	0.78 (0.21)
>1yr	159 (1.4%)	0.74 (0.22)	0.75 (0.21)
Transient ischaemic attack			
No history	11469 (98.2%)	0.77 (0.23)	0.77 (0.22)
≤1yr	38 (0.3%)	0.62 (0.31)	0.64 (0.28)
>1yr	176 (1.5%)	0.68 (0.26)	0.69 (0.24)
Ischaemic stroke			
No history	11485 (98.3%)	0.77 (0.23)	0.77 (0.22)
≤1yr	42 (0.4%)	0.71 (0.20)	0.70 (0.19)
>1yr	156 (1.3%)	0.67 (0.26)	0.67 (0.25)
Heart failure			
No history	11578 (99.1%)	0.77 (0.23)	0.77 (0.22)
≤1yr	30 (0.3%)	0.51 (0.30)	0.52 (0.27)
>1yr	75 (0.6%)	0.64 (0.25)	0.65 (0.23)
Intracranial haemorrhage			
No history	11661 (99.8%)	0.77 (0.23)	0.77 (0.22)
≤1yr	2 (0.0%)	0.49 (0.37)	0.49 (0.35)
>1yr	20 (0.2%)	0.61 (0.36)	0.59 (0.38)
GI bleed			
No history	11580 (99.1%)	0.77 (0.23)	0.77 (0.22)
≤1yr	16 (0.1%)	0.63 (0.26)	0.64 (0.27)
>1yr	87 (0.7%)	0.65 (0.30)	0.65 (0.29)
Other major bleed			
No history	11613 (99.4%)	0.77 (0.23)	0.77 (0.22)
≤1yr	7 (0.1%)	0.74 (0.26)	0.75 (0.23)
>1yr	63 (0.5%)	0.64 (0.30)	0.65 (0.28)
GI tract cancer			

Table C.38: Mean (SD) of EQ-5D utility by adverse event and time since adverse event occurrence *(continued)*

Time since event occurrence	No. of participants (%)	DSU tariff	van Hout tariff
No history	11564 (99.0%)	0.77 (0.23)	0.77 (0.22)
≤1yr	26 (0.2%)	0.74 (0.24)	0.74 (0.24)
>1yr	93 (0.8%)	0.75 (0.23)	0.74 (0.24)
Non-GI tract cancer			
No history	11006 (94.2%)	0.77 (0.23)	0.77 (0.22)
≤1yr	113 (1.0%)	0.76 (0.24)	0.77 (0.22)
>1yr	564 (4.8%)	0.73 (0.24)	0.73 (0.23)
Amputation			
No history	11623 (99.5%)	0.77 (0.23)	0.77 (0.22)
≤1yr	10 (0.1%)	0.41 (0.36)	0.42 (0.36)
>1yr	50 (0.4%)	0.55 (0.27)	0.55 (0.24)
End-stage renal disease			
No history	11641 (99.6%)	0.77 (0.23)	0.77 (0.22)
≤1yr	8 (0.1%)	0.68 (0.14)	0.68 (0.14)
>1yr	34 (0.3%)	0.63 (0.30)	0.64 (0.28)

Note:
≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than one year prior to EQ-5D questionnaire response. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed.

Table C.39: EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events, with (a) all adverse events included, and (b) using van Hout tariffs (sensitivity analysis)

	EQ-5D utility (95% CI)	
Variable	(a) All adverse events included	(b) Van Hout tariffs
(Intercept)	0.910 (0.895, 0.926)**	0.906 (0.891, 0.920)**
Sex (ref: Male)		
Female	-0.029 (-0.038, -0.020)**	-0.023 (-0.031, -0.015)**
Current smoker (ref: N)		
Y	-0.057 (-0.073, -0.041)**	-0.052 (-0.067, -0.037)**
Townsend index (ref: Q1 (least deprived))		
Q2	-0.011 (-0.021, -0.001)*	-0.009 (-0.019, 0.000)
Q3	-0.044 (-0.056, -0.032)**	-0.042 (-0.053, -0.030)**
Q4	-0.075 (-0.089, -0.062)**	-0.069 (-0.082, -0.056)**
Q5 (most deprived)	-0.079 (-0.101, -0.056)**	-0.074 (-0.095, -0.053)**
Age at time of EQ-5D questionnaire (per 10 years, centered at 70)		
Age	-0.013 (-0.019, -0.007)**	-0.014 (-0.020, -0.009)**
Age^2	-0.007 (-0.011, -0.002)**	-0.006 (-0.010, -0.002)**
BMI (ref: <25 kg/m^2)		
≥25, <30	-0.033 (-0.046, -0.020)**	-0.033 (-0.045, -0.020)**
≥30, <35	-0.068 (-0.082, -0.054)**	-0.066 (-0.079, -0.053)**
≥35	-0.141 (-0.156, -0.126)**	-0.134 (-0.148, -0.120)**
Diabetes duration at time of EQ-5D questionnaire (ref: <10 years)		
≥10, <15	-0.012 (-0.023, -0.001)*	-0.011 (-0.021, -0.000)*
≥15, <25	-0.028 (-0.039, -0.017)**	-0.026 (-0.037, -0.015)**
≥25	-0.032 (-0.046, -0.018)**	-0.029 (-0.043, -0.016)**
eGFR (ref: ≥90 ml/min/1.73m^2)		
≥60, <90	-0.031 (-0.041, -0.021)**	-0.030 (-0.039, -0.020)**
≥45, <60	-0.071 (-0.090, -0.053)**	-0.072 (-0.089, -0.054)**
<45	-0.081 (-0.112, -0.050)**	-0.080 (-0.108, -0.051)**
Albuminuria (urinary albumin/creatinine ratio ≥3 mg/mmol) (ref: N)		
Y	-0.017 (-0.031, -0.003)*	-0.018 (-0.031, -0.005)**
Myocardial infarction		
Any history	-0.027 (-0.084, 0.031)	-
Coronary revascularisation (urgent)		
Any history	0.003 (-0.061, 0.067)	-
Coronary revascularisation (non-urgent)		
Any history	-0.004 (-0.037, 0.028)	-
Transient ischaemic attack		
Any history	-0.069 (-0.100, -0.038)**	-0.057 (-0.086, -0.028)**

Table C.39: EQ-5D utility associated with sociodemographic characteristics, clinical risk factors and adverse events, with (a) all adverse events included, and (b) using van Hout tariffs (sensitivity analysis) *(continued)*

Variable	(a) All adverse events included	(b) Van Hout tariffs
Ischaemic stroke		
Any history	-0.060 (-0.092, -0.028)**	-0.062 (-0.092, -0.032)**
Heart failure		
≤1yr	-0.182 (-0.261, -0.102)**	-0.183 (-0.258, -0.108)**
>1yr	-0.050 (-0.100, 0.001)	-0.046 (-0.094, 0.001)
Intracranial haemorrhage		
Any history	-0.140 (-0.233, -0.048)**	-0.164 (-0.251, -0.076)**
GI bleed		
Any history	-0.089 (-0.132, -0.045)**	-0.091 (-0.132, -0.051)**
Other major bleed		
Any history	-0.101 (-0.153, -0.049)**	-0.096 (-0.146, -0.047)**
GI tract cancer		
Any history	-0.010 (-0.050, 0.031)	-
Non-GI tract cancer		
Any history	-0.028 (-0.045, -0.011)**	-0.026 (-0.043, -0.010)**
Amputation		
Any history	-0.203 (-0.260, -0.147)**	-0.206 (-0.259, -0.152)**
End-stage renal disease		
Any history	-0.041 (-0.110, 0.028)	-

Note:
**: p-value < 0.01; *: p-value < 0.05. ≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than one year prior to EQ-5D questionnaire response. Intercept value gives the EQ-5D utility for the reference individual (70-year-old male, not current smoker, living in least deprived region, BMI <25kg/m^2, diabetes duration <10 years, eGFR≥90ml/min/1.73m^2, no albuminuria, with no disease history).

C.6 Lifetime cost-effectiveness of aspirin for primary prevention of cardiovascular disease in people with diabetes

Table C.40: Effects of antithrombotic medication (aspirin / other antiplatelet / anticoagulants) estimated in ASCEND risk equations

	Hazard ratio (95% CI)
Myocardial infarction	0.91 (0.70 - 1.18)
Coronary revascularisation (non-urgent)	0.87 (0.63 - 1.21)
Coronary revascularisation (urgent)	-
Transient ischaemic attack	0.80 (0.60 - 1.07)
Ischaemic stroke	0.88 (0.67 - 1.14)
Heart failure	0.92 (0.67 - 1.26)
Intracranial haemorrhage	1.52 (0.87 - 2.68)
GI bleed	1.58 (1.10 - 2.28)
Other major bleed	2.19 (1.30 - 3.68)
GI tract cancer	-
Non-GI tract cancer	-
Amputation	0.77 (0.48 - 1.23)
End-stage renal disease	-
Vascular death	0.69 (0.52 - 0.93)
Non-vascular death	0.89 (0.75 - 1.07)

Note:
These treatment effects were estimated in the risk equations in Chapter 3, see Supplemental Table C.11. Percentage of ASCEND participant in each trial arm on antithrombotic medication updated each follow-up year.
About 80% of antithrombotic medication use at 7 years into the trial was aspirin (both study and non-study aspirin).

Table C.41: Summary of treatment effects of aspirin from primary prevention trials

	ASCEND, 2018 [3]	USPSTF review, 2022 [13]	ATT, 2009 [14]	Zheng, 2019 [15]	Abdelaziz, 2019 [16]	Khan, 2020 [17]
Sample	ASCEND (diabetes only)	11 trials (100mg or less aspirin)	6 trials	13 trials	15 trials	10 trials, diabetes (subgroup) only
Method if meta-analysis	-	Peto fixed-effects	Individual patient data meta-analysis	Bayesian (MCMC) fixed and random effects	DerSimonian and Laird random effects	DerSimonian and Laird random effects
Effect reported	Rate ratio	Odds ratio[§]	Rate ratio	Rate ratio	Risk ratio	Risk ratio
Myocardial infarction	Non-fatal MI: 0.98 (0.80 - 1.19) All MI: 0.95 (0.79 - 1.13)[‡]	0.89 (0.82 - 0.96)	All MI: 0.86 (0.74 - 1.00) Non-fatal MI: 0.77 (0.69 - 0.86)	0.85 (0.73 - 0.99)	0.85 (0.76 - 0.95)	0.91 (0.75 - 1.11)*
CRV (non-urgent)	Any coronary revascularisation: 0.89 (0.75 - 1.05)	NR	NR	NR	NR	Any revascularisation: 0.88 (0.77 - 1.00)
CRV (urgent)	-	NR	NR	NR	NR	-
TIA	0.85 (0.69 - 1.04)	NR	NR	NR	0.80 (0.71 - 0.89)	0.84 (0.69 - 1.01)

Table C.41: Summary of treatment effects of aspirin from primary prevention trials *(continued)*

	ASCEND, 2018 [3]	USPSTF review, 2022 [13]	ATT, 2009 [14]	Zheng, 2019 [15]	Abdelaziz, 2019 [16]	Khan, 2020 [17]
Ischaemic stroke	Non-fatal ischaemic stroke: 0.88 (0.73 - 1.06) All ischaemic stroke: 0.92 (0.77 - 1.11)‡	0.82 (0.72 - 0.92)	0.86 (0.74 - 1.00)	0.81 (0.76 - 0.87)	Any stroke: 0.97 (0.89 - 1.04)	Any stroke: 0.91 (0.76 - 1.10)
Heart failure	0.84 (0.64 - 1.10)	NR	NR	NR	NR	NR
Intracranial haemorrhage	1.22 (0.82 - 1.81)	1.31 (1.11 - 1.54)	Haemorrhagic stroke: 1.32 (1.00 - 1.75)	1.34 (1.14 - 1.57)	1.32 (1.12 - 1.55)	1.13 (0.80 - 1.60)
GI bleed	1.36 (1.05 - 1.75)	1.58 (1.38 - 1.80)	-	1.56 (1.38 - 1.78)	1.52 (1.34 - 1.73)	1.50 (0.92 - 2.45)
Other major bleed	1.70 (1.18 - 2.44)	Major extracranial bleeding*: 1.53 (1.39 - 1.70) Other major bleed‡: 1.41 (1.19 - 1.67)	Major extracranial bleed: 1.54 (1.30 - 1.82)	NR	NR	NR

Table C.41: Summary of treatment effects of aspirin from primary prevention trials *(continued)*

	ASCEND, 2018 [3]	USPSTF review, 2022 [13]	ATT, 2009 [14]	Zheng, 2019 [15]	Abdelaziz, 2019 [16]	Khan, 2020 [17]
GI tract cancer	0.99 (0.80 - 1.24)	From primary prevention RCT only: 1.07 (0.92 - 1.24) From primary and secondary prevention RCT + observational phase (at 10 years): 0.99 (0.86 - 1.14) From primary & secondary prevention RCT + observational phase (up to 20 years): 0.79 (0.68 - 0.92) From primary & secondary prevention RCT + observational phase (from 10 to 20 years): 0.64 (0.52 - 0.79)	NR	Any cancer: 1.01 (0.93 - 1.08)	NR	0.99 (0.88 - 1.11)
Non-GI tract cancer	1.01 (0.92 - 1.11)	NR	NR	-	NR	NR
Amputation	0.76 (0.52 - 1.10)	NR	NR	NR	NR	NR

Table C.41: Summary of treatment effects of aspirin from primary prevention trials *(continued)*

	ASCEND, 2018 [3]	USPSTF review, 2022 [13]	ATT, 2009 [14]	Zheng, 2019 [15]	Abdelaziz, 2019 [16]	Khan, 2020 [17]
ESRD	NR	NR	NR	NR	NR	NR
Vascular death	Excluding intracranial haemorrhage: 0.91 (0.75 - 1.10) Including intracranial haemorrhage: 0.93 (0.77 - 1.12)	0.95 (0.86 - 1.05)†	0.97 (0.87 - 1.09)†	0.94 (0.83 - 1.05)†	0.93 (0.86 - 1.00)†	0.95 (0.83 - 1.09)†
Non-vascular death	Including intracranial haemorrhage: 0.95 (0.84 - 1.07)	All-cause mortality: 0.98 (0.93 - 1.03) Non-vascular death‡: 0.99 (0.93 - 1.05)	0.93 (0.85-1.02)	All-cause mortality: 0.94 (0.88 -1.01)	All-cause mortality: 0.97 (0.93 -1.01)	All-cause mortality: 0.99 (0.90 - 1.09)
Major CV events	MI, ischaemic stroke, CV death: 0.92 (0.82 - 1.03) Include TIA: 0.88 (0.79 - 0.97) Include arterial revascularisation: 0.88 (0.80 - 0.97)	MI, stroke, CV death: 0.90 (0.85 - 0.95)	MI, stroke, CV death: 0.88 (0.82 - 0.94)	MI, stroke, CV death: 0.89 (0.84 - 0.94)	MI, stroke, TIA CV death: 0.90 (0.85 - 0.96)	MI, stroke, CV death: 0.93 (0.87 - 1.00)

Table C.41: Summary of treatment effects of aspirin from primary prevention trials *(continued)*

	ASCEND, 2018 [3]	USPSTF review, 2022 [13]	ATT, 2009 [14]	Zheng, 2019 [15]	Abdelaziz, 2019 [16]	Khan, 2020 [17]
Any major bleeding	1.29 (1.09 - 1.52)* includes eye bleeds	1.44 (1.32 - 1.57)	Major extracranial bleed: 1.54 (1.30 - 1.82)	1.43 (1.30 - 1.56)	1.50 (1.33 - 1.69)	1.29 (1.07 - 1.55)
All-cause death	0.94 (0.85 - 1.04)	0.98 (0.93 - 1.03)	-	0.94 (0.88 - 1.01)	0.97 (0.93 -1.01)	0.99 (0.90 - 1.09)

Note:
NR, not reported. If not otherwise stated, treatment effects are for a compositie of fatal and non-fatal events
* Inconsistently defined across trials (fatal vs non-fatal)
† Inconsistently defined across trials (composition of vascular death)
‡ Estimated directly from data in publication
§ Given low event rates, odds ratio approximately equals risk ratio

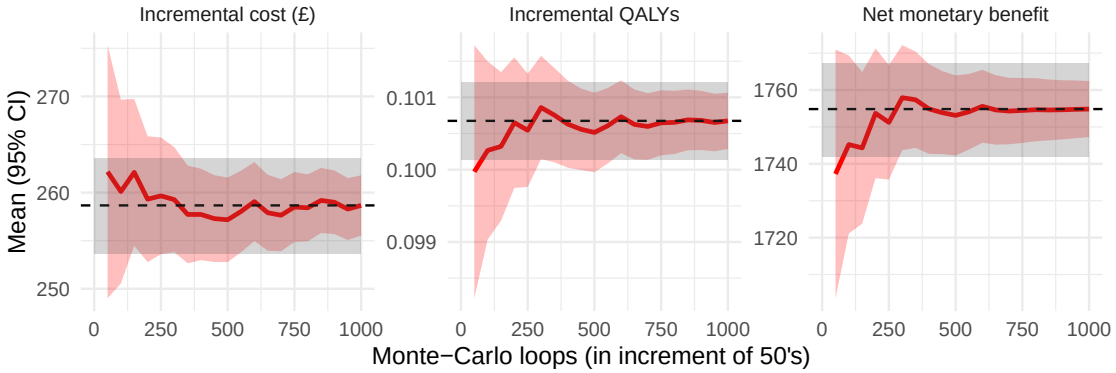
Table C.42: Baseline distribution of risk factors identified from QResearch among 18,250 UK Biobank participants with diabetes without previous cardiovascular disease

Variable	N (%)
Smoking status	
Current	1921 (10.5%)
Former	7234 (39.6%)
Never	9095 (49.8%)
Alcohol status (per day)	
None	2770 (15.2%)
< 1 unit	9805 (53.7%)
1-2 units	5119 (28%)
3-6 units	399 (2.2%)
7-9 units	155 (0.8%)
> 9 units	2 (0%)
Medication use	
Non-steroidal anti-inflammatory pain killers	2712 (14.9%)
Antidepressants	1090 (6%)
Anticonvulsants	49 (0.3%)
Atypical antipsychotics	131 (0.7%)
Corticosteroids	321 (1.8%)
Disease history	
Atrial fibrillation	152 (0.8%)
Treated hypertension	12771 (70%)
Previous cancer	908 (5%)
Chronic kidney disease (stage 3 or higher)	2059 (11.3%)
Migraine	7 (0%)
Erectile dysfunction	45 (0.2%)
Oesophageal varices	9 (0%)
Venous thromboembolism	433 (2.4%)
Previous bleed	733 (4%)
Systemic lupus erythematosus	23 (0.1%)
Severe mental illness	213 (1.2%)
Heart failure†	0 (0%)
Chronic liver disease†	0 (0%)
QRISK score	
<5	6713 (36.8%)
≥5, <10	8036 (44%)
≥10	3501 (19.2%)
QBleed score	
<0.45	5885 (32.2%)
≥0.45, <0.7	5772 (31.6%)
≥0.7	6593 (36.1%)

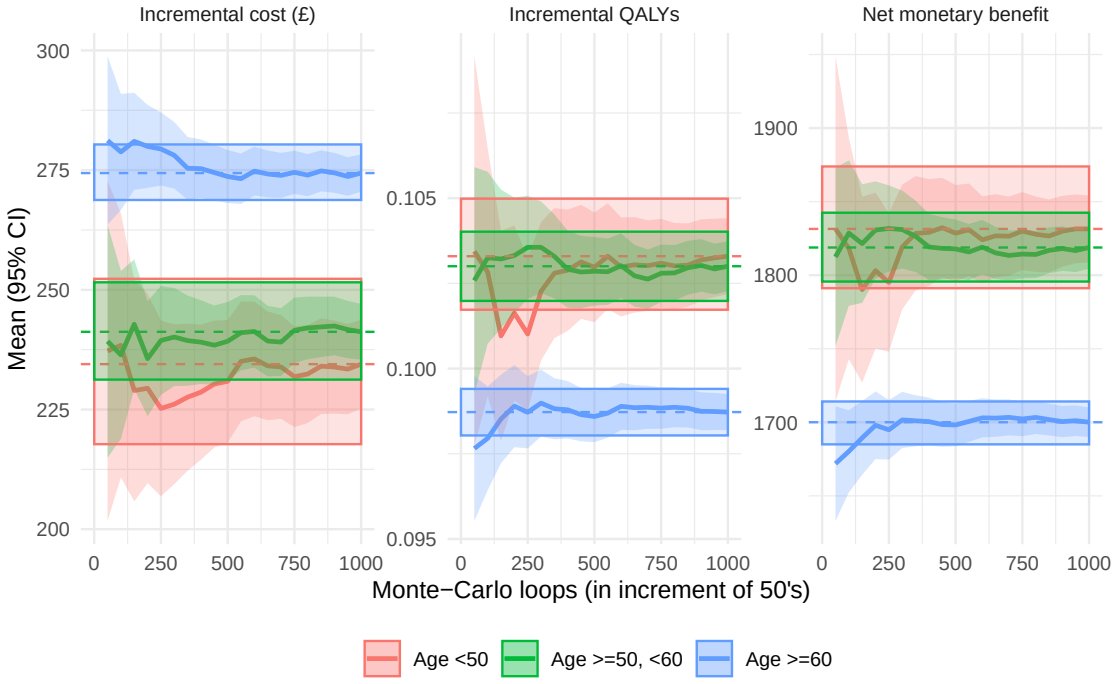
Table C.42: Baseline distribution of risk factors identified from QResearch among 18,250 UK Biobank participants with diabetes without previous cardiovascular disease *(continued)*

Variable	N (%)

* Participants with previous bleeding event within 6 months prior to recruitment were excluded from selection.
† Participants with previous heart failure or hepatic disease were excluded from selection.



(a) In all participants



(b) By age group

Figure C.42: Monte-Carlo mean (coloured line) and error (coloured region) relative to sample mean (dotted line) and error (boxed region) of incremental outcomes. The coloured line and area represents the Monte-Carlo mean and 95% confidence interval around the mean accounting for Monte-Carlo error respectively. The dotted line and boxed area represents the sample mean and 95% confidence interval around the sample mean evaluated across 1000 bootstrap resamples reflecting sampling uncertainty

Table C.43: Lifetime gains in quality-adjusted life years (QALYs) and life expectancies (LYs) with aspirin compared to no aspirin use in UK Biobank participants with diabetes without previous cardiovascular disease

		ASCEND treatment effects		Meta-analyses treatment effects	
Subgroups	N	QALYs	LYs	QALYs	LYs
All participants	18250	0.205 (-0.114, 0.524)	0.291 (-0.166, 0.748)	0.055 (-0.112, 0.222)	0.084 (-0.154, 0.323)
By sex and age (years)					
Male					
<50	1405	0.258 (-0.139, 0.654)	0.344 (-0.196, 0.885)	0.055 (-0.154, 0.264)	0.090 (-0.195, 0.374)
≥50, <60	3374	0.225 (-0.117, 0.568)	0.308 (-0.166, 0.782)	0.067 (-0.113, 0.247)	0.100 (-0.149, 0.350)
≥60	6048	0.194 (-0.104, 0.492)	0.271 (-0.148, 0.689)	0.061 (-0.095, 0.217)	0.090 (-0.129, 0.309)
Female					
<50	1010	0.227 (-0.156, 0.610)	0.327 (-0.227, 0.881)	0.035 (-0.167, 0.237)	0.063 (-0.227, 0.353)
≥50, <60	2370	0.211 (-0.118, 0.541)	0.312 (-0.178, 0.802)	0.053 (-0.121, 0.227)	0.088 (-0.169, 0.345)
≥60	4043	0.178 (-0.112, 0.468)	0.268 (-0.169, 0.705)	0.041 (-0.111, 0.192)	0.065 (-0.163, 0.292)
By 10-year risk of cardiovascular disease estimated by QRISK-3 (%)					
<5	6713	0.222 (-0.138, 0.583)	0.309 (-0.193, 0.811)	0.051 (-0.139, 0.240)	0.080 (-0.183, 0.344)
≥5, <10	8036	0.197 (-0.110, 0.504)	0.281 (-0.161, 0.723)	0.058 (-0.103, 0.219)	0.088 (-0.144, 0.319)
≥10	3501	0.191 (-0.080, 0.462)	0.280 (-0.128, 0.688)	0.054 (-0.086, 0.194)	0.085 (-0.127, 0.296)
By 5-year risk of GI bleeding estimated by QBleed (%)					
<0.45	5885	0.223 (-0.137, 0.584)	0.308 (-0.192, 0.807)	0.053 (-0.137, 0.242)	0.082 (-0.180, 0.345)
≥0.45, <0.7	5772	0.203 (-0.112, 0.518)	0.287 (-0.164, 0.738)	0.062 (-0.103, 0.227)	0.092 (-0.144, 0.328)
≥0.7	6593	0.191 (-0.096, 0.478)	0.280 (-0.146, 0.706)	0.050 (-0.099, 0.200)	0.080 (-0.142, 0.301)

Note:
Values are mean (95% CI). QALYs and LYs were undiscounted.

Table C.44: Life years (discounted at 3.5% per annum) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline

	ASCEND treatment effects			Meta-analyses treatment effects		
Scenario	<50	≥50, <60	≥60	<50	≥50, <60	≥60
Lifetime use	0.139	0.144	0.141	0.032	0.044	0.042
Stopping after 20 years	0.069	0.098	0.116	0.010	0.028	0.032
Stopping after 10 years	0.022	0.039	0.048	-0.003	0.010	0.011
Stopping at 75 years old	0.116	0.097	0.051	0.028	0.022	0.012

Table C.45: Quality-adjusted life years (QALYs; undiscounted) and life years (LYs; undiscounted) gained with aspirin compared to no aspirin use in people with diabetes without previous cardiovascular disease in the UK Biobank with lifetime use, stoppage at 10 years, at 20 years, and at 75 years old, stratified by age at baseline, excluding treatment effects on death

	ASCEND treatment effects			Meta-analyses treatment effects		
Scenario	<50	≥50, <60	≥60	<50	≥50, <60	≥60
QALYs gained						
Lifetime use	0.012	0.031	0.026	0.046	0.061	0.053
Stopping after 20 years	0.007	0.015	0.019	0.001	0.032	0.037
Stopping after 10 years	0.001	0.002	0.006	-0.015	0.008	0.009
Stopping at 75 years old	0.008	0.022	0.007	0.039	0.022	0.010
LYs gained						
Lifetime use	0.010	0.036	0.030	0.079	0.095	0.080
Stopping after 20 years	0.003	0.016	0.023	0.014	0.053	0.056
Stopping after 10 years	-0.003	0.001	0.007	-0.013	0.016	0.016
Stopping at 75 years old	0.005	0.025	0.007	0.064	0.040	0.017

References

1. Hayes AJ, Leal J, Gray AM, Holman RR, and Clarke PM. UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013;56:1925–33. DOI: 10.1007/s00125-013-2940-y.
2. UK Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study (UKPDS). VIII. Study Design, Progress and Performance. Diabetologia 1991;34:877–90. DOI: 10.1046/j.1365-2125.1999.00092.x.
3. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018;379:1529–39. DOI: 10.1056/NEJMoa1804988.
4. Harper C, Mafham M, Herrington W, et al. Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial-Adjudicated Direct Follow-up Data in the UK: Secondary Analysis of the ASCEND Randomized Clinical Trial. JAMA Netw Open 2021;4:e2139748. DOI: 10.1001/jamanetworkopen.2021.39748.
5. Kivimäki M, Batty GD, Singh-Manoux A, Britton A, Brunner EJ, and Shipley MJ. Validity of Cardiovascular Disease Event Ascertainment Using Linkage to UK Hospital Records. Epidemiology 2017;28:735–9. DOI: 10.1097/EDE.0000000000000688.
6. Li L, Binney LE, Luengo-Fernandez R, Silver LE, and Rothwell PM. Temporal Trends in the Accuracy of Hospital Diagnostic Coding for Identifying Acute Stroke: A Population-Based Study. European Stroke Journal 2020;5:26–35. DOI: 10.1177/2396987319881017.
7. Rannikmäe K, Ngoh K, Bush K, et al. Accuracy of Identifying Incident Stroke Cases from Linked Health Care Data in UK Biobank. Neurology 2020;95:e697–e707. DOI: 10.1212/WNL.0000000000009924.
8. Faridi KF, Tamez H, Butala NM, et al. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the DAPT Study: Findings From the EXTEND-DAPT Study. Circ Cardiovasc Qual Outcomes 2021;14:e006589. DOI: 10.1161/CIRCOUTCOMES.120.006589.
9. Guimarães PO, Krishnamoorthy A, Kaltenbach LA, et al. Accuracy of Medical Claims for Identifying Cardiovascular and Bleeding Events After Myocardial Infarction : A Secondary Analysis of the TRANSLATE-ACS Study. JAMA Cardiology 2017;2:750–7. DOI: 10.1001/jamacardio.2017.1460.
10. Selak V, Jackson R, Poppe K, et al. Predicting Bleeding Risk to Guide Aspirin Use for the Primary Prevention of Cardiovascular Disease. Ann Intern Med 2019;170:357–68. DOI: 10.7326/M18-2808.
11. Hippisley-Cox J and Coupland C. Predicting Risk of Upper Gastrointestinal Bleed and Intracranial Bleed with Anticoagulants: Cohort Study to Derive and Validate the QBleed Scores. BMJ 2014;349:g4606. DOI: 10.1136/bmj.g4606.
12. Li Z and Mahendra G. Using "Recycled Predictions" for Computing Marginal Effects. In: *SAS Global Forum 2010*. 2010.

13. Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, and Senger CA. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2022;327:1585–97. DOI: 10.1001/jama.2022.3337.

14. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative Meta-Analysis of Individual Participant Data from Randomised Trials. The Lancet 2009;373:1849–60. DOI: 10.1016/S0140-6736(09)60503-1.

15. Zheng SL and Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. JAMA 2019;321:277. DOI: 10.1001/jama.2018.20578.

16. Abdelaziz HK, Saad M, Pothineni NVK, et al. Aspirin for Primary Prevention of Cardiovascular Events. Journal of the American College of Cardiology 2019;73:2915–29. DOI: 10.1016/j.jacc.2019.03.501.

17. Khan SU, Ul Abideen Asad Z, Khan MU, et al. Aspirin for Primary Prevention of Cardiovascular Outcomes in Diabetes Mellitus: An Updated Systematic Review and Meta-Analysis. European Journal of Preventive Cardiology 2020;27:2034–41. DOI: 10.1177/2047487319825510.