Adiposity and atrial fibrillation: An observational, genetic, and phenotypic study in UK Biobank

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Abstract

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a number of cardiovascular complications including stroke. While obesity has been shown to be associated with risk of AF, body-size and shape are heterogeneous and differ substantially by sex. Additionally, the independent causal relevance of related anthropometric measures remains uncertain. Pericardial adipose tissue (PAT) has been associated with risk of AF; however, the strength of the association between PAT and risk of AF is unclear. Adiposity has also been associated with inflammation; although, whether inflammation mediates associations between adiposity and risk of AF has not been established.

Methods: Using data from UK Biobank (UKB) the independent associations between anthropometric measures and risk of AF were explored in men and women. A novel PAT area phenotype was developed in a sub-set of UKB participants using cardiac magnetic resonance imaging data and used to examine the association with risk of AF. Genetic scores for a number of anthropometric measures and inflammatory proteins were developed. The associations between genetically predicted anthropometric measures and both inflammation and risk of AF were explored. Mediation analyses used to determine the proportion of the effect of anthropometric measures on risk of AF mediated by a set of systemic inflammatory proteins.

Results: Lean mass, fat mass, and waist circumference were all independently associated with risk of AF in both men and women. A novel PAT phenotype was developed in ~3,500 participants. Greater PAT area was shown to be associated with risk of AF and was comparable to other anthropometric measures. When adjusted for abdominal visceral adipose tissue, the association between PAT area and risk of AF remained similar. Genetically predicted anthropometric measures including body mass index, waist circumference, fat mass, and lean mass were found to be associated with risk of AF. A set of genetically predicted inflammatory proteins were shown to be associated with risk of AF but to only mediate a modest proportion of the effect of anthropometric measures on risk of AF.

Conclusions: Anthropometric measures of both body size and body shape are independently causally associated with risk of AF in both men and women. PAT area was associated with risk of AF to a similar extent to other more easily obtained anthropometric measures. Genetically predicted systemic inflammatory proteins were associated with risk of AF but only mediated a modest proportion of the association between anthropometric measures and risk of AF.

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This thesis and the work presented within would not have been possible without a group of amazing individuals working as collaborators, colleagues, and mentors. In particular the support of Mr Adam Von Ende, Dr Rohan Wijesurendra, and Mr Federico Murgia for their collective wisdom and education on a range of matters detailed in this thesis.

I would like to acknowledge the British Heart Foundation and the Nuffield Department of Population Health for supporting this research. I am truly grateful to all the participants who gave up their time to participate in the UK Biobank and other consortia data used in this thesis without whom this research would not have been possible.

Above all else, my deepest thanks to Katie for your support and love through both the ups and downs, and finally my parents who have nurtured my love of learning and provided life-long support.

This thesis is dedicated to my children, Marcus and Rory.

Declaration and personal contribution to the work

I declare that this thesis is entirely my own work, and except where otherwise stated below, describes my own research.

I was appointed as a Clinical Research Fellow in the Nuffield Department of Population Health at the University of Oxford in February 2019 under the supervision of Professor Jemma Hopewell and Professor Barbara Casadei. Under their guidance, I designed and conducted the work in this thesis.

Along with my supervisors, I developed the hypothesis and designed the studies outlined in Chapters 4-9. Data used from UK Biobank was collected centrally by the UK Biobank team and provided to Professor Hopewell's research group through her application (application number 14568). The received UK Biobank data was originally formatted by two members of Professor Hopewell's team: Dr Elsa Valdes-Marquez and Mr Adam Von Ende. I personally developed datasets and generated novel variables where required.

I developed the search strategy for the systematic review described in Chapter 3 in conjunction with Professor Hopewell. I undertook the search and analysed all the results described. The tables and figures in this chapter and accompanying supplemental appendices are entirely my own work.

The analyses described in Chapter 4 were developed by me with the guidance and assistance of Professor Hopewell and Dr Ben Lacey. I performed all analyses described in this chapter which were subsequently validated by Dr Sofia Massa. I created all figures presented in this chapter. The results of this chapter have subsequently been published:

> **Camm CF**, Lacey B, Massa MS, Von Ende A, Gajendragadkar P, Stiby A, Valdes-Marquez E, Lewington S, Wijesurendra R, Parish S, Casadei B, Hopewell JC. Independent effects of adiposity measures on risk of atrial

fibrillation in men and women: a study of 0.5 million individuals. *Int J Epidemiol*. 2022;51(3):984-95.

Under the guidance of Professor Hopewell, Professor Casadei, and Dr Rohan Wijesurendra, I developed the methodology to obtain pericardial adipose tissue area measures from cardiac magnetic resonance imaging data as described in Chapter 5. I calculated the epicardial fat measurements used in this and subsequent chapters. The pericardial adipose tissue area measurements for the intra-observer validation were undertaken by Ms Tania Domun, who was trained by Dr Rohan Wijesurendra. I planned and undertook all statistical analyses and created all the figures presented.

The genome-wide association study analysis undertaken in Chapter 6 was planned by me in discussion with Professor Hopewell and the team's bioinformatician Mr Federico Murgia. The GWAS was subsequently performed by Federico who also produced the Manhattan and QQ plot figures presented in Chapter 6. I planned and undertook all other analyses described in this chapter and all other presented figures are my own work.

The analyses undertaken in chapters 7 and 8 were planned by me under the guidance of Professor Hopewell and Professor Casadei. Mr Federico Murgia extracted the genetic data required to create the genetic scores from the UK Biobank dataset and performed the clumping analysis under my instruction. I developed and undertook all statistical analyses described in these chapters and all presented figures are my own work.

The analysis undertaken in Chapter 9 were planned by Mr Adam Von Ende and myself under the guidance of Professor Hopewell. Mr Adam Von Ende undertook the initial analyses described in sections 9.5.1 to 9.5.3 of this chapter which were subsequently replicated by me. The analyses described in other sections of this chapter were planned and undertaken by me. All figures presented in this chapter are my own work.

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Contents

ABSTRACT II

ACKNOWLEDGEMENTS IV

DECLARATION AND PERSONAL CONTRIBUTION TO THE WORK V

FUNDING VII

CONTENTS VIII

ABBREVIATIONS XXI

STUDY NAME ABBREVIATIONS XXIII

LIST OF FIGURES XXIV

LIST OF TABLES XXIX

CHAPTER 1 – INTRODUCTION 1

1.1. Importance of atrial fibrillation 1

1.1.1. Epidemiology of atrial fibrillation 1

1.1.2. Risk factors for atrial fibrillation 2

1.1.3. Atrial fibrillation-related outcomes 3

1.2. Scale of the obesity epidemic 4

1.3. Measures of body size 6

1.4. General body size measures and risk of atrial fibrillation 8

1.4.1. Observational associations between body size and risk of atrial fibrillation . 8

1.4.2. Evidence for independent associations between body size measures and atrial fibrillation 8

1.4.3. Sex-based differences in the effects of body size on risk of atrial fibrillation 9

1.4.4. Evidence for weight loss in atrial fibrillation 9

1.5. Ectopic fat deposits and risk of atrial fibrillation 10

1.5.1. Pericardial adipose tissue 10

1.5.2. Abdominal visceral adipose tissue 13

1.6. Assessment of the causal association between anthropometric measures and risk of atrial fibrillation 14

1.6.1. Limitations in traditional epidemiology 14

1.6.2. Mendelian randomization 14

1.6.3. Mendelian randomization analyses suggesting causal roles of anthropometric measures and risk of atrial fibrillation 15

1.6.4. Assumptions in Mendelian randomization analyses 16

1.7. Potential pathways linking body size and risk of atrial fibrillation.. 17

1.7.1. Atrial fibrillation, adiposity, and inflammation 18

1.8. Key limitations in the current research 19

1.8.1. Independent effects of anthropometric measures 19

1.8.2. The role of pericardial adipose tissue in atrial fibrillation 20

1.8.3. Independent causal role for anthropometric measures 20

1.8.4. Links between anthropometric measures, inflammation, and risk of atrial fibrillation 20

1.8.5. Atrial fibrillation detection and diagnosis 21

1.9. Thesis aims and overview 21

CHAPTER 2 – METHODS 23

2.1. UK Biobank 23

2.1.1. Research ethics and permissions 23

2.1.2. UK Biobank recruitment 24

2.1.3. UK Biobank baseline assessment 24

2.2. UK Biobank data collection 24

2.2.1. UK Biobank touch-screen questionnaire 24

2.2.2. UK Biobank nurse-led verbal interview 25

2.2.3. Anthropometric measures in UK Biobank 25

2.2.4. Blood biomarkers in UK Biobank 26

2.2.5. Genetic data in UK Biobank 26

2.2.6. Hospital episode statistics, death registry, and primary care data 27

2.2.6.1. Hospital episode statistics 27

2.2.6.2. Death registry data 28

2.2.6.3. Primary care data 28

2.3. UK Biobank imaging sub-study 29

2.4. Phenotype definitions 30

2.4.1. Atrial fibrillation 30

2.4.2. Comorbid conditions 31

2.5. UK Biobank participants included in this thesis 31

2.5.1. Genetic analysis 32

2.6. Genetic consortia 32
2.6.1. Genetic Investigation of Anthropometric Traits (GIANT) consortium 32
2.6.2. Atrial Fibrillation Genetics (AFGen) consortium 33
2.6.3. FinnGen 34

2.7. Genetic score development 35
2.7.1. Variant selection 35
2.7.2. Proportion of variance explained 35
2.7.3. Estimation of F-statistic 36
2.7.4. Genetic score generation 36
2.7.5. External replication datasets 37
2.7.6. Mendelian randomization sensitivity analyses 37
2.7.6.1. Multivariable Mendelian randomization 38
2.7.6.2. Meta-analysis of summary level results from multiple datasets 38

2.8. Statistical analyses 39

CHAPTER 3 - SYSTEMATIC REVIEW OF ANTHROPOMETRIC MEASURES AND RISK OF ATRIAL FIBRILLATION 40

3.1. Abstract 40
3.1.1. Introduction 40
3.1.2. Methods 40
3.1.3. Results 40
3.1.4. Conclusions 41

3.2. Introduction 42

3.3. Methods 44
3.3.1. Search Strategy 44
3.3.2. Study selection and critical appraisal 44
3.3.2.1. Inclusion criteria 45
3.3.2.2. Exclusion criteria 45
3.3.3. Data collection and analysis 46

3.4. Results 47
3.4.1. Manuscripts identified 47
3.4.2. Body mass index and risk of atrial fibrillation 49
3.4.2.1. Results of the current search 49
3.4.2.2. Effect of body mass index on risk of atrial fibrillation 49
3.4.2.3. Effect of body mass index when adjusted for other anthropometric measures 51
3.4.2.4. Exploration of a non-linear relationship between body mass index and risk of atrial fibrillation 51
3.4.2.5. Effect of body mass index on risk of atrial fibrillation by sex 52

3.4.2.6. Genetically predicted body mass index and risk of atrial fibrillation 53
3.4.2.7. Body mass index evidence summary 54
3.4.3. Height and risk of atrial fibrillation 54
3.4.3.1. Results of the current search 54
3.4.3.2. Effect of height on risk of atrial fibrillation 55
3.4.3.3. Effect of height when adjusted for other anthropometric measures 55
3.4.3.4. Exploration of a non-linear relationship between height and risk of atrial fibrillation 56
3.4.3.5. Effect of height on risk of atrial fibrillation by sex 57
3.4.3.6. Genetically predicted height and risk of atrial fibrillation 57
3.4.3.7. Height evidence summary 57
3.4.4. Waist circumference and risk of atrial fibrillation 58
3.4.4.1. Results of the current search 58
3.4.4.2. Effect of waist circumference on risk of atrial fibrillation 59
3.4.4.3. Effect of waist circumference when adjusted for other anthropometric measures 59
3.4.4.4. Exploration of a non-linear relationship between waist circumference and risk of atrial fibrillation 60
3.4.4.5. Effect of waist circumference on risk of atrial fibrillation by sex 61
3.4.4.6. Genetically predicted waist circumference and risk of atrial fibrillation. 61
3.4.4.7. Waist circumference evidence summary 62
3.4.5. Weight and risk of atrial fibrillation 62
3.4.5.1. Results of the current search 62
3.4.5.2. Effect of weight on risk of atrial fibrillation 62
3.4.5.3. Effect of weight when adjusted for other anthropometric measures 63
3.4.5.4. Exploration of a non-linear relationship between weight and risk of atrial fibrillation 63
3.4.5.5. Effect of weight on risk of atrial fibrillation by sex 64
3.4.5.6. Genetically predicted weight and risk of atrial fibrillation 65
3.4.5.7. Weight evidence summary 65
3.4.6. Waist-hip ratio and risk of atrial fibrillation 66
3.4.6.1. Results of the current search 66
3.4.6.2. Effect of waist-hip ratio on risk of atrial fibrillation 66
3.4.6.3. Effect of waist-hip ratio when adjusted for other anthropometric measures 67
3.4.6.4. Exploration of a non-linear relationship between waist-hip ratio and risk of atrial fibrillation 67
3.4.6.5. Effect of waist-hip ratio on risk of atrial fibrillation by sex 68
3.4.6.6. Genetically predicted waist-hip ratio and risk of atrial fibrillation 68
3.4.6.7. Waist-hip ratio evidence summary 68
3.4.7. Fat mass and risk of atrial fibrillation 69
3.4.7.1. Results of the current search 69
3.4.7.2. Effect of fat mass on risk of atrial fibrillation 69
3.4.7.3. Effect of fat mass when adjusted for other anthropometric measures . 70
3.4.7.4. Exploration of a non-linear relationship between fat mass and risk of atrial fibrillation 70

3.4.7.5. Effect of fat mass on risk of atrial fibrillation by sex 71
3.4.7.6. Genetically predicted fat mass and risk of atrial fibrillation 71
3.4.7.7. Fat mass evidence summary 71
3.4.8. Lean mass and risk of atrial fibrillation 72
3.4.8.1. Results from current search 72
3.4.8.2. Effect of lean mass on risk of atrial fibrillation 72
3.4.8.3. Effect of lean mass when adjusted for other anthropometric measures 73
3.4.8.4. Exploration of a non-linear relationship between lean mass and risk of atrial fibrillation 73
3.4.8.5. Effect of lean mass on risk of atrial fibrillation by sex 74
3.4.8.6. Genetically predicted lean mass and risk of atrial fibrillation 74
3.4.8.7. Lean mass evidence summary 74
3.4.9. Pericardial adipose tissue and risk of atrial fibrillation 75
3.4.9.1. Results from the current search 75
3.4.9.2. Effect of pericardial adipose tissue on risk of atrial fibrillation 75
3.4.9.3. Regional pericardial adipose tissue and risk of atrial fibrillation 76
3.4.9.4. Effect of pericardial adipose tissue when adjusted for other anthropometric measures 77
3.4.9.5. Exploration of a non-linear relationship between pericardial adipose tissue and risk of atrial fibrillation 77
3.4.9.6. Effect of pericardial adipose tissue on risk of atrial fibrillation by sex ... 77
3.4.9.7. Genetically predicted pericardial adipose tissue and risk of atrial fibrillation 77
3.4.9.8. Pericardial adipose tissue evidence summary 77
3.4.10. Non-cardiac visceral adipose tissue 78
3.4.10.1. Results from the current search 78
3.4.10.2. Effect of visceral adipose tissue on risk of atrial fibrillation 78
3.4.10.3. Effect of visceral adipose tissue when adjusted for other anthropometric measures 79
3.4.10.4. Effect of visceral adipose tissue on risk of atrial fibrillation by sex 79
3.4.10.5. Genetically predicted visceral adipose tissue and risk of atrial fibrillation 79
3.4.10.6. Visceral adipose tissue evidence summary 80
3.4.11. Other anthropometric phenotypes 80

3.5. 3.5 Discussion 81

3.5.1. Evidence of associations between anthropometric measures and risk of atrial fibrillation 81
3.5.2. Exploration of sex-based differences in associations between anthropometric measures and risk of atrial fibrillation 82
3.5.3. Evidence of independent associations between anthropometric measures and risk of atrial fibrillation 83
3.5.4. Evidence for causal associations between anthropometric measures and risk of atrial fibrillation 84
3.5.5. Conflicting evidence in the association between pericardial adipose tissue and risk of atrial fibrillation 85

3.5.6. Conclusions 86

CHAPTER 4 - EPIDEMIOLOGY OF ADIPOSITY AND ATRIAL FIBRILLATION 87

4.1. Abstract 87
4.1.1. Background 87
4.1.2. Methods 87
4.1.3. Results 87
4.1.4. Conclusions 88

4.2. Introduction 89

4.3. Methods 90
4.3.1. Study design and participants 90
4.3.2. Atrial fibrillation and other health outcomes 90
4.3.3. Statistical analyses 90
4.3.3.1. Sensitivity analyses 92
4.3.3.2. Regression dilution ratio 92

4.4. Results 94
4.4.1. Baseline characteristics 94
4.4.2. Incident atrial fibrillation 97
4.4.3. Comparing the effects of body mass index, waist circumference, and weight on risk of atrial fibrillation in men and women 98
4.4.4. Comparing the effects of fat mass and lean mass on risk of atrial fibrillation in men and women 102
4.4.5. Determining the relative effects of anthropometric measures on risk of atrial fibrillation separately in men and women 106
4.4.6. Sensitivity analyses 109

4.5. Discussion 110
4.5.1. Strengths and limitations 114
4.5.2. Conclusions 115
4.5.3. Next steps 115

CHAPTER 5 – PERICARDIAL ADIPOSE TISSUE PHENOTYPING IN UK BIOBANK 117

5.1. Abstract 117
5.1.1. Background 117
5.1.2. Methods 117
5.1.3. Results 117
5.1.4. Conclusions 118

5.2. Introduction 119

5.3. Methods 120

5.3.1. Participants 120
5.3.2. Cardiac magnetic resonance imaging data 120
5.3.3. Pericardial adipose tissue phenotype 122
5.3.4. Quality assessment of T1 maps 123
5.3.5. Validation of the pericardial adipose tissue phenotype 124
5.3.6. Baseline characteristics and anthropometric measures 126
5.3.7. Phenotyping prior disease 126
5.3.8. Statistical analyses 126

5.4. Results 128
5.4.1. Comparison between those with and without calculated pericardial adipose tissue areas 128
5.4.2. Pericardial adipose tissue area characteristics 130
5.4.2.1. Total pericardial adipose tissue area characteristics 130
5.4.2.2. Left ventricular pericardial adipose tissue area characteristics 131
5.4.2.3. Correlation between left ventricular and total pericardial adipose tissue 132
5.4.2.4. Pericardial adipose tissue T1 values compared with thoracic fat T1 values 132
5.4.3. Pericardial adipose tissue phenotype validation 134
5.4.3.1. Intra-observer validation 134
5.4.3.2. Inter-observer validation 136
5.4.4. Characteristics of pericardial adipose tissue area cohort at entry into the UK Biobank imaging sub-study 138
5.4.4.1. Baseline characteristics in men and women 140
5.4.5. Association between pericardial adipose tissue and other anthropometric measures 145

5.5. Discussion 147
5.5.1. Quality of T1 maps 147
5.5.2. Adipose tissue T1 values 147
5.5.3. Prior use of cardiac magnetic resonance imaging to assess pericardial adipose tissue 148
5.5.4. Reliability of pericardial adipose tissue measurement 149
5.5.5. Use of cardiac magnetic resonance imaging vs computed tomography 150
5.5.6. Pericardial adipose tissue cohort participant characteristics 151
5.5.7. Pericardial adipose tissue and baseline cardiovascular disease 151
5.5.8. Association between pericardial adipose tissue and other anthropometric measures 152
5.5.9. Limitations 152
5.5.10. Next Steps and Future Work 153
5.5.11. Conclusions 154

CHAPTER 6 - PERICARDIAL ADIPOSE TISSUE AND RISK OF CARDIOVASCULAR DISEASE 155

6.1. Abstract 155
6.1.1. Background 155
6.1.2. Methods 155
6.1.3. Results 155
6.1.4. Conclusions 156

6.2. Introduction 157

6.3. Methods 159
6.3.1. Participants 159
6.3.2. Imaging phenotypes 159
6.3.3. Other anthropometric measures and baseline characteristics 159
6.3.4. Atrial fibrillation and coronary heart disease cases 160
6.3.5. Statistical analysis of observational data 160
6.3.5.1. Power calculation for observational analyses 161
6.3.6. Pericardial adipose tissue genome-wide association study 161
6.3.6.1. Comparison with other anthropometric genome-wide association study results 161
6.3.6.2. Genome-wide association study power calculations 162

6.4. Results 163
6.4.1. Incident cardiovascular disease 163
6.4.2. Association of pericardial adipose tissue with risk of atrial fibrillation and coronary heart disease 163
6.4.3. Association of abdominal visceral adipose tissue with risk of atrial fibrillation and coronary heart disease 164
6.4.4. Relative strength of associations between anthropometric measures and risk of atrial fibrillation and coronary heart disease 165
6.4.5. Independent effect of pericardial adipose tissue and abdominal visceral adipose tissue on risk of incident atrial fibrillation and coronary heart disease .. 167
6.4.5.1. Independent effect of pericardial adipose tissue 167
6.4.5.2. Independent effect of abdominal visceral adipose tissue 167
6.4.6. Genome wide association study of pericardial adipose tissue area 170
6.4.6.1. Residual generation 170
6.4.6.2. Genome-wide association study results 170
6.4.7. Pericardial adipose tissue genetic score 174
6.4.7.1. Genetically predicted pericardial adipose tissue and anthropometric measures 174
6.4.7.2. Association with variants identified in previous genome-wide association study of other anthropometric traits 176

6.5. Discussion 179
6.5.1. Association between pericardial adipose tissue area and incident atrial fibrillation 179
6.5.2. Independent relevance of pericardial adipose tissue and abdominal visceral adipose tissue with atrial fibrillation 180
6.5.3. Independent relevance between abdominal visceral adipose tissue and coronary heart disease 181

6.5.4. GWAS Results 181
6.5.5. Limitations 182
6.5.6. Future Work 183

CHAPTER 7 – CAUSAL RELEVANCE OF ANTHROPOMETRIC MEASURES AND RISK OF ATRIAL FIBRILLATION 185

7.1. Abstract 185
7.1.1. Background 185
7.1.2. Methods 185
7.1.3. Results 186
7.1.4. Conclusions 186

7.2. Introduction 187

7.3. Methods 188
7.3.1. Study design and participants 188
7.3.2. Selection of genetic variants 188
7.3.3. Residual generation 189
7.3.4. Statistical analyses 189
7.3.4.1. Power calculations 189

7.4. Results 191
7.4.1. Baseline characteristics 191
7.4.2. Atrial fibrillation cases in the UK Biobank cohort with genetic data available 191
7.4.3. Genetically predicted body mass index and risk of atrial fibrillation 194
7.4.3.1. Association between body mass index genetic score and body mass index in UK Biobank 194
7.4.3.2. Body mass index genetic score and risk of atrial fibrillation in UK Biobank 194
7.4.3.3. Body mass index genetic score sensitivity analyses 195
7.4.3.4. Genetically predicted body mass index and risk of atrial fibrillation in men and women 196
7.4.4. Genetically predicted waist circumference and risk of atrial fibrillation 197
7.4.4.1. Association between waist circumference genetic score and waist circumference in UK Biobank 197
7.4.4.2. Waist circumference genetic score and risk of atrial fibrillation in UK Biobank 197
7.4.4.3. Waist circumference genetic score sensitivity analyses 198
7.4.4.4. Genetically predicted waist circumference and risk of atrial fibrillation in men and women 199
7.4.5. Independent effect of waist circumference on risk of atrial fibrillation 200
7.4.5.1. Genetically predicted waist circumference adjusted for body mass index and risk of atrial fibrillation 200
7.4.5.2. Multivariable Mendelian randomization analysis of waist circumference and body mass index 203

7.4.6. Genetically predicted fat mass and risk of atrial fibrillation 205
7.4.6.1. Association between fat mass genetic score and fat mass in UK Biobank 205
7.4.6.2. Fat mass genetic score and risk of atrial fibrillation in UK Biobank 205
7.4.6.3. Fat mass genetic score sensitivity analyses 206
7.4.6.4. Genetically predicted fat mass and risk of atrial fibrillation in men and women 207
7.4.7. Genetically predicted lean mass on risk of atrial fibrillation 208
7.4.7.1. Association between lean mass genetic score and lean mass in UK Biobank 208
7.4.7.2. Lean mass genetic score and risk of atrial fibrillation in UK Biobank . 208
7.4.7.3. Lean mass genetic score sensitivity analyses 209
7.4.7.4. Genetically predicted lean mass and risk of atrial fibrillation in men and women 210
7.4.8. Genetically predicted abdominal visceral adipose tissue and risk of atrial fibrillation 211
7.4.8.1. Association between abdominal visceral adipose tissue genetic score and abdominal visceral adipose tissue in UK Biobank 211
7.4.8.2. Genetically predicted abdominal visceral adipose tissue and risk of atrial fibrillation 211
7.4.9. The direct effects of fat mass and lean mass on risk of atrial fibrillation .. 212

7.5. Discussion 215
7.5.1. Limitations 217
7.5.2. Conclusions 218
7.5.3. Next steps 218

CHAPTER 8 - INFLAMMATION, ADIPOSITY, AND RISK OF ATRIAL FIBRILLATION 219

8.1. Abstract 219
8.1.1. Background 219
8.1.2. Methods 219
8.1.3. Results 220
8.1.4. Conclusions 220

8.2. Introduction 221

8.3. Methods 223
8.3.1. Study design and participants 223
8.3.2. C-reactive protein measurement in UK Biobank 223
8.3.3. Development of genetic scores 224
8.3.4. Mediation analysis 227
8.3.5. Statistical analysis 228
8.3.5.1. Power calculations 229

8.4. Results 231

8.4.1. C-reactive protein within UK Biobank 231
8.4.2. Association between baseline anthropometric measures and C-reactive protein 235
8.4.3. Log-C-reactive protein association with atrial fibrillation 235
8.4.4. Observed associations between anthropometric measures and risk of atrial fibrillation adjusted for C-reactive protein 237
8.4.5. Genetically predicted anthropometric measures and observed log-C-reactive protein levels 239
8.4.6. Genetically predicted inflammatory proteins in UK Biobank 240
8.4.7. Genetically predicted inflammatory proteins and risk of atrial fibrillation .. 242
8.4.7.1. Genetically predicted C-reactive protein and risk of atrial fibrillation .. 242
8.4.7.2. Genetically predicted C-reactive protein using a cis-C-reactive protein genetic score and risk of atrial fibrillation 244
8.4.7.3. Other inflammatory proteins 246
8.4.8. Mediation of the effect of anthropometric measures on risk of atrial fibrillation through inflammation 250

8.5. Discussion 252
8.5.1. Observed C-reactive protein levels and risk of atrial fibrillation 252
8.5.2. Evidence for the causal relevance of C-reactive protein on risk of atrial fibrillation 253
8.5.3. Interleukin-6 receptor and risk of atrial fibrillation 253
8.5.4. YKL-40 and risk of atrial fibrillation 254
8.5.5. CD40 and risk of atrial fibrillation 255
8.5.6. Mediation of effects of anthropometric measures on risk of atrial fibrillation through inflammatory proteins 255
8.5.7. Limitations 256
8.5.8. Conclusions 257
8.5.9. Future work 258

CHAPTER 9 – ELECTRONIC HEALTH CARE RECORD PHENOTYPING OF ATRIAL FIBRILLATION WITHIN UK BIOBANK 259

9.1. Abstract 259
9.1.1. Introduction 259
9.1.2. Methods 259
9.1.3. Results 260
9.1.4. Conclusions 260

9.2. Introduction 261

9.3. Methods 264
9.3.1. UK Biobank primary care data 264
9.3.2. Ascertainment of atrial fibrillation 264
9.3.2.1. Primary care phenotyping 264
9.3.3. Censoring 266
9.3.4. Participant selection 268

9.3.5. Participant characteristics 268
9.3.6. Statistical analysis 268
9.3.6.1. Assessment of risk of atrial fibrillation by first source of ascertainment 269

9.4. Results 271
9.4.1. Phenotype development 271
9.4.2. Identification of prevalent atrial fibrillation cases 272
9.4.3. Identification of incident atrial fibrillation cases 272
9.4.4. Baseline characteristics of atrial fibrillation cases 274
9.4.5. Atrial fibrillation ascertainment groups by age and sex 276
9.4.6. Time course of identification of atrial fibrillation cases by ascertainment source 276
9.4.7. Anthropometric measures and ascertainment source of first atrial fibrillation record 278
9.4.7.1. Anthropometric measures and healthcare utilisation in UK Biobank .. 279
9.4.7.2. Association between anthropometric measures and risk of atrial fibrillation by first ascertainment source 279
9.4.7.3. Atrial fibrillation as the primary and non-primary reasons for admission and the association with anthropometric measures 281

9.5. Discussion 283
9.5.1. Additional cases identified through the use of primary care data 283
9.5.2. Baseline characteristics in primary and secondary care based atrial fibrillation 284
9.5.3. Timing of ascertainment of atrial fibrillation cases in primary and secondary care 285
9.5.4. Anthropometrics and risk of atrial fibrillation identified in primary and secondary care 285
9.5.5. Limitations 286
9.5.6. Future work 287
9.5.7. Conclusions 288

CHAPTER 10 - GENERAL CONCLUSIONS 289

10.1. The independent effects of anthropometric measures on risk of atrial fibrillation 289

10.2. Differences in the effect of anthropometric measures on risk of atrial fibrillation in men and women 290

10.3. Creation of a pericardial adipose tissue phenotype 291

10.4. The association between pericardial adipose tissue and risk of atrial fibrillation 291

10.5. The relationship between anthropometric measures, inflammation, and risk of atrial fibrillation 292

10.6. Phenotyping atrial fibrillation in electronic healthcare records .. 292

10.7. Potential future directions of research 293

10.8. Summary 295

BIBLIOGRAPHY 296

APPENDIX A - SYSTEMATIC REVIEW SEARCH STRATEGY 324

APPENDIX B - SYSTEMATIC REVIEW RESULTS TABLES 327

APPENDIX C - ADDITIONAL PHENOTYPES FROM THE SYSTEMATIC REVIEW 430

APPENDIX D - UK BIOBANK DISEASE PHENOTYPE DEFINITIONS 439

APPENDIX E - CHAPTER 4 SUPPLEMENTARY FIGURES AND TABLES 447

APPENDIX F - PERICARDIAL ADIPOSE TISSUE PHENOTYPING: STANDARD OPERATING PROCEDURE.....456

APPENDIX G - CHAPTER 5 SUPPLEMENTARY TABLES AND FIGURES.....463

APPENDIX H - CHAPTER 6 SUPPLEMENTARY TABLES AND FIGURES.....469

APPENDIX I - DEVELOPMENT OF GENETIC SCORES.....472

APPENDIX J - EFFECT OF INDIVIDUAL VARIANTS INCLUDED IN GENETIC SCORES IN UK BIOBANK.....565

APPENDIX K - CHAPTER 8 SUPPLEMENTARY FIGURES 600

APPENDIX L - CHAPTER 9 SUPPLEMENTARY TABLES AND FIGURE 608

Abbreviations

The following list provides details of abbreviations used in this thesis. Each is defined at the time of their first use within the thesis and when used within chapter abstracts. Abbreviations have not been used in thesis headings.

Abbreviation	Term
AF	atrial fibrillation
BF%	body fat percentage
BMI	body mass index
bSSFP	balanced steady state free procession
CI	confidence intervals
CHD	coronary heart disease
CMR	cardiac magnetic resonance imaging
CRP	C-reactive protein
CT	computed tomography imaging
DEXA	dual-energy x-ray absorptiometry
FM	fat mass
GWAS	genome-wide association study
HC	hip circumference
HES	hospital episode statistics
HR	hazard ratio
IL	interleukin
IQR	interquartile range
IQS	image quality score
IV	instrumental variable(s)
LA	left atrium
LV	left ventricle
LD	linkage disequilibrium
LM	lean mass
MAF	minor allele frequency
MeSH	Medical Subject Headings
MR	Mendelian randomization

Abbreviation	Term
MRI	magnetic resonance imaging
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outlier test
MVMR	multivariable Mendelian randomization
NHIS	National Health Insurance Service
NHS	National Health Service
OR	odds ratio
PAT	pericardial adipose tissue
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QC	quality control
RR	risk ratio
RV	right ventricle
RSID	reference single nucleotide polymorphism cluster identification
SD	standard deviation
SE	standard error
ShMOLLI	shortened modified look-locker inversion recovery
SNP	single nucleotide polymorphism
UK	United Kingdom
UKB	UK Biobank
VAT	visceral adipose tissue
WC	waist circumference
WCadjBMI	waist circumference adjusted for body mass index
WHO	World Health Organisation
WHR	waist-hip ratio

Study name abbreviations

The following list provides details of study abbreviations used in this thesis. Each is defined at the time of their first use within the thesis.

Abbreviation	Study Name
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AGES	Age, Gene/Environment Susceptibility cohort
ARIC	Atherosclerosis Risk in Communities cohort
CHS	Cardiovascular Health Study
CRYSTAL-AF	Cryptogenic Stroke and Underlying Atrial Fibrillation
DDCH	Danish Diet, Cancer and Health cohort
FHS	Framingham Heart Study
GPRD	General Practice Research Database
Health ABC	Health, Aging, and Body Composition
JHS	Jackson Heart Study
LOOP	Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals
MESA	Multi-Ethnic Study of Atherosclerosis
PREVEND	Prevention of Renal and Vascular End-stage Disease
PRO.V.A.	Progetto Veneto Anziani
REGARDS	REasons for Geographic And Racial Differences in Stroke Study
RHS	Rotterdam Heart Study
UKB	UK Biobank
VIP	Vasterbotten Intervention Programme
WHI	Women's' Health Initiative
WHS	Women's Health Study

List of figures

Figure 1.1: Temporal trends in atrial fibrillation prevalent cases by socio-demographic index, 1990-2017. 2

Figure 1.2: Temporal trends in adult body mass index over time. 5

Figure 1.3: The anatomy of adipose tissue surrounding the heart. 12

Figure 1.4: Conditions required for instrumental variables in a Mendelian randomization study. 15

Figure 1.5: Confounding, mediation and collider bias. 18

Figure 2.1: Overview of UK Biobank participants used in this thesis. 31

Figure 3.1: Systematic review PRISMA flowchart 48

Figure 3.2: Forest plot of the effects of body mass index (per 5 kg/m²) on risk of atrial fibrillation. 50

Figure 3.3: Forest plot of the effects of body mass index (per 5 kg/m²) on risk of atrial fibrillation separately in men and women. 53

Figure 3.4: Forest plot of the effects of height (per 10 cm) on risk of atrial fibrillation. 56

Figure 3.5: Forest plot of the effects of height (per 10 cm) on risk of atrial fibrillation separately in men and women. 58

Figure 3.6: Forest plot of the effects of waist circumference (per 10 cm) on risk of atrial fibrillation. 60

Figure 3.7: Forest plot of the effects of waist circumference (per 10 cm) on risk of atrial fibrillation separately in men and women. 61

Figure 3.8: Forest plot of the effects of weight (per 10 kg) on risk of atrial fibrillation. 64

Figure 3.9: Forest plot of the effects of weight (per 10 kg) on risk of atrial fibrillation. 65

Figure 3.10: Forest plot of the effects of waist-hip ratio (per 0.1) on risk of atrial fibrillation. 67

Figure 3.11: Forest plot of the effects of fat mass (per 5 kg) on risk of atrial fibrillation. 70

Figure 3.12: Forest plot of the effects of lean mass (per 5 kg) on risk of atrial fibrillation. 73

Figure 3.13: Forest plot of the effects of pericardial adipose tissue volume (per standard deviation) on risk of atrial fibrillation. 76

Figure 3.14: Evidence for associations between anthropometric measures and risk of atrial fibrillation. 82

Figure 3.15: Evidence assessing sex-based differences in associations between anthropometric measures and risk of atrial fibrillation. 83

Figure 3.16: Evidence for associations between anthropometric measures and risk of atrial fibrillation after adjustment for other anthropometric measures 85

Figure 4.1: UK Biobank participant flow chart. 91

FIGURE 4.2: HISTOGRAMS OF ANTHROPOMETRIC AND BIO-IMPEDANCE VARIABLES 96
FIGURE 4.3: INCIDENCE OF ATRIAL FIBRILLATION BY AGE IN UK BIOBANK. 97
FIGURE 4.4: ASSOCIATION OF BODY MASS INDEX, WAIST CIRCUMFERENCE, AND WEIGHT WITH INCIDENT ATRIAL FIBRILLATION. 99
FIGURE 4.5: ASSOCIATION OF BODY MASS INDEX AND WEIGHT WITH INCIDENT ATRIAL FIBRILLATION AFTER ADJUSTMENT FOR WAIST CIRCUMFERENCE. 100
FIGURE 4.6: ASSOCIATION OF WAIST CIRCUMFERENCE WITH INCIDENT ATRIAL FIBRILLATION AFTER ADJUSTMENT FOR BODY MASS INDEX AND WEIGHT. 101
FIGURE 4.7: ASSOCIATION OF LEAN MASS AND FAT MASS WITH INCIDENT ATRIAL FIBRILLATION. 103
FIGURE 4.8: ASSOCIATION OF LEAN MASS AND FAT MASS WITH INCIDENT ATRIAL FIBRILLATION, BEFORE AND AFTER MUTUAL ADJUSTMENT. 104
FIGURE 4.9: INDEPENDENT ASSOCIATION OF LEAN MASS AND FAT MASS WITH INCIDENT ATRIAL FIBRILLATION BY SEX. 105
FIGURE 4.10: COMPARISON OF ASSOCIATIONS BETWEEN LEAN MASS, FAT MASS, AND WAIT CIRCUMFERENCE WITH INCIDENT ATRIAL FIBRILLATION, BY SEX 108
FIGURE 5.1: FLOWCHART OF PARTICIPANTS INCLUDED IN THE PERICARDIAL ADIPOSE TISSUE ANALYSIS. 121
FIGURE 5.2: EXAMPLE OF NATIVE T1 MAP AND MID-VENTRICULAR CINE STILL IMAGE FOR A UK BIOBANK PARTICIPANT. 123
FIGURE 5.3: EXAMPLE OF DETERMINATION OF TOTAL AND LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE FROM MID-VENTRICULAR NATIVE T1 MAP FOR A UK BIOBANK PARTICIPANT. 123
FIGURE 5.4: INDICATIVE EXAMPLE OF A MID-VENTRICULAR SHMOLLI IMAGE AND PARAMETRIC MAP OF GOODNESS-OF-FIT FOR A UK BIOBANK PARTICIPANT 125
FIGURE 5.5: HISTOGRAM OF TOTAL PERICARDIAL ADIPOSE TISSUE VARIABLES. 130
FIGURE 5.6: HISTOGRAM OF LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE VARIABLES. 131
FIGURE 5.7: SCATTER PLOT OF TOTAL AND LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA (N=1,481) 133
FIGURE 5.8: MEAN T1 VALUES FROM ISOLATED AREAS OF PERICARDIAL ADIPOSE TISSUE AND ANTERIOR THORACIC FAT IN 100 RANDOM PARTICIPANTS. 133
FIGURE 5.9: INTRA-OBSERVER VALIDATION OF TOTAL PERICARDIAL ADIPOSE TISSUE AREA. 134
FIGURE 5.10: INTRA-OBSERVER VALIDATION OF LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA. 135
FIGURE 5.11: INTER-OBSERVER VALIDATION OF TOTAL PERICARDIAL ADIPOSE TISSUE AREA. 136
FIGURE 5.12: INTER-OBSERVER VALIDATION OF LEFT-VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA. 137
FIGURE 5.13: SCATTER PLOTS OF TOTAL PERICARDIAL ADIPOSE TISSUE AREA AND ANTHROPOMETRIC MEASURES. 146
FIGURE 5.14: INDICATIVE EXAMPLE OF A BSSFP CINE STILE IMAGE, SHMOLLI MAP AND PARAMETRIC MAP OF GOODNESS OF FIT FROM A UK BIOBANK PARTICIPANT

DEMONSTRATING AN AREA OF NON-FAT TISSUE BETWEEN EPICARDIUM AND PERICARDIUM. 150

FIGURE 6.1: ASSOCIATION OF PERICARDIAL ADIPOSE TISSUE AREA WITH INCIDENT CARDIOVASCULAR OUTCOMES 164

FIGURE 6.2: ASSOCIATION OF ABDOMINAL VISCERAL ADIPOSE TISSUE VOLUME WITH INCIDENT CARDIOVASCULAR OUTCOMES. 165

FIGURE 6.3: COMPARISON OF ASSOCIATIONS BETWEEN ANTHROPOMETRIC MEASURES AND RISK OF INCIDENT ATRIAL FIBRILLATION, BY SEX, IN THE PERICARDIAL ADIPOSE TISSUE COHORT (N=3,402). 166

FIGURE 6.4: COMPARISON OF ASSOCIATIONS BETWEEN ANTHROPOMETRIC MEASURES AND RISK OF INCIDENT CORONARY HEART DISEASE, BY SEX, IN THE PERICARDIAL ADIPOSE TISSUE COHORT (N=3,290). 166

FIGURE 6.5: ASSOCIATION OF PERICARDIAL ADIPOSE TISSUE AREA AND ABDOMINAL VISCERAL ADIPOSE TISSUE WITH INCIDENT ATRIAL FIBRILLATION BEFORE AND AFTER MUTUAL ADJUSTMENT, BY SEX (N=3,402). 168

FIGURE 6.6: ASSOCIATION OF PERICARDIAL ADIPOSE TISSUE AREA AND ABDOMINAL VISCERAL ADIPOSE TISSUE WITH INCIDENT CORONARY HEART DISEASE BEFORE AND AFTER MUTUAL ADJUSTMENT, BY SEX (N=3,290). 169

FIGURE 6.7: MANHATTAN PLOT OF GENOME-WIDE ASSOCIATION STUDY RESULTS FOR PERICARDIAL ADIPOSE TISSUE AREA. 171

FIGURE 6.8: QUANTILE-QUANTILE PLOT OF OBSERVED AND EXPECTED P-VALUES FROM PERICARDIAL ADIPOSE TISSUE AREA GENOME-WIDE ASSOCIATION STUDY 171

FIGURE 6.9: COMPARISON OF BETA VALUES FOR VARIANTS IDENTIFIED IN PERICARDIAL ADIPOSE TISSUE GENOME-WIDE ASSOCIATION STUDY COMPARED WITH BETA VALUES FOR THE SAME VARIANTS IN A GENOME-WIDE ASSOCIATION STUDY OF OTHER ANTHROPOMETRIC TRAITS. 176

FIGURE 6.10: COMPARISON OF BETA VALUES FOR VARIANTS IDENTIFIED IN EXTERNAL ANTHROPOMETRIC GENOME-WIDE ASSOCIATION STUDIES COMPARED WITH BETA VALUES FOR THE SAME VARIANTS IN THE PERICARDIAL ADIPOSE TISSUE GENOME-WIDE ASSOCIATION STUDY. 178

FIGURE 7.1: ASSOCIATION OF GENETICALLY PREDICTED BODY MASS INDEX WITH ATRIAL FIBRILLATION. 195

FIGURE 7.2: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED BODY MASS INDEX ON RISK OF ATRIAL FIBRILLATION. 196

FIGURE 7.3: ASSOCIATION OF GENETICALLY PREDICTED WAIST CIRCUMFERENCE WITH ATRIAL FIBRILLATION. 198

FIGURE 7.4: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED WAIST CIRCUMFERENCE ON RISK OF ATRIAL FIBRILLATION. 199

FIGURE 7.5: ASSOCIATION OF GENETICALLY PREDICTED WAIST CIRCUMFERENCE ADJUSTED FOR BODY MASS INDEX WITH ATRIAL FIBRILLATION. 201

FIGURE 7.6: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED WAIST CIRCUMFERENCE ADJUSTED FOR BODY MASS INDEX ON RISK OF ATRIAL FIBRILLATION. ... 202

FIGURE 7.7: META-ANALYSIS OF THE DIRECT EFFECT OF GENETICALLY PREDICTED WAIST CIRCUMFERENCE ON RISK OF ATRIAL FIBRILLATION IN A MULTIVARIABLE MENDELIAN RANDOMIZATION MODEL WITH BODY MASS INDEX. 204

FIGURE 7.8: META-ANALYSIS OF THE DIRECT EFFECT OF GENETICALLY PREDICTED BODY MASS INDEX ON RISK OF ATRIAL FIBRILLATION IN A MULTIVARIABLE MENDELIAN RANDOMIZATION MODEL WITH WAIST CIRCUMFERENCE. 204

FIGURE 7.9: ASSOCIATION OF GENETICALLY PREDICTED FAT MASS WITH ATRIAL FIBRILLATION IN UK BIOBANK. 206

FIGURE 7.10: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED FAT MASS ON RISK OF ATRIAL FIBRILLATION. 207

FIGURE 7.11: ASSOCIATION OF GENETICALLY PREDICTED LEAN MASS WITH ATRIAL FIBRILLATION IN UK BIOBANK. 209

FIGURE 7.12: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED LEAN MASS ON RISK OF ATRIAL FIBRILLATION. 210

FIGURE 7.13: META-ANALYSIS OF EFFECT OF GENETICALLY PREDICTED VISCERAL ADIPOSE TISSUE ON RISK OF ATRIAL FIBRILLATION. 212

FIGURE 7.14: META-ANALYSIS OF THE DIRECT EFFECT OF GENETICALLY PREDICTED LEAN MASS ON RISK OF ATRIAL FIBRILLATION IN A MULTIVARIABLE MENDELIAN RANDOMIZATION MODEL WITH FAT MASS. 213

FIGURE 7.15: META-ANALYSIS OF THE DIRECT EFFECT OF GENETICALLY PREDICTED FAT MASS ON RISK OF ATRIAL FIBRILLATION IN A MULTIVARIABLE MENDELIAN RANDOMIZATION MODEL WITH LEAN MASS. 214

FIGURE 8.1: SELECTION OF PARTICIPANTS FOR OBSERVATIONAL ANALYSIS OF ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND RISK OF ATRIAL FIBRILLATION. 224

FIGURE 8.2: FLOWCHART OF INFLAMMATORY PROTEIN SELECTION. 226

FIGURE 8.3: MEDIATION DIAGRAM. 227

FIGURE 8.4: DISTRIBUTION OF C-REACTIVE PROTEIN AND LOG-C-REACTIVE-PROTEIN IN THE UK BIOBANK POPULATION. 231

FIGURE 8.5: ASSOCIATION OF ANTHROPOMETRIC MEASURES AND BASELINE LOG-C-REACTIVE PROTEIN. 236

FIGURE 8.6: ASSOCIATION BETWEEN BASELINE LOG-C-REACTIVE PROTEIN AND ATRIAL FIBRILLATION IN UK BIOBANK. 237

FIGURE 8.7: ASSOCIATION BETWEEN ANTHROPOMETRIC MEASURES AND RISK OF INCIDENT ATRIAL FIBRILLATION IN MEN AND WOMEN FOLLOWING ADJUSTMENT FOR C-REACTIVE PROTEIN. 238

FIGURE 8.8: ASSOCIATION BETWEEN GENETICALLY PREDICTED ADIPOSITY TRAITS AND BASELINE LOG-C-REACTIVE PROTEIN IN UK BIOBANK (N=308,490). 239

FIGURE 8.9: ASSOCIATION BETWEEN RISK SCORES FOR INFLAMMATORY PROTEINS AND C-REACTIVE PROTEIN (N=308,490). 241

FIGURE 8.10: ASSOCIATION OF GENETICALLY PREDICTED C-REACTIVE PROTEIN WITH ATRIAL FIBRILLATION IN UK BIOBANK (N=339,214). 243

FIGURE 8.11: META-ANALYSIS OF CAUSAL EFFECT OF GENETICALLY PREDICTED C-REACTIVE PROTEIN ON RISK OF ATRIAL FIBRILLATION. 244

FIGURE 8.12: ASSOCIATION OF GENETICALLY PREDICTED C-REACTIVE PROTEIN WITH ATRIAL FIBRILLATION USING THE CIS-C-REACTIVE PROTEIN GENETIC SCORE. 245

FIGURE 8.13: META-ANALYSIS OF CAUSAL EFFECT OF GENETICALLY PREDICTED C-REACTIVE PROTEIN ON RISK OF ATRIAL FIBRILLATION USING THE CIS-C-REACTIVE PROTEIN GENETIC SCORE. 245

FIGURE 8.14: META-ANALYSIS OF CAUSAL EFFECT OF GENETICALLY PREDICTED INTERLEUKIN-6 RECEPTOR ON RISK OF ATRIAL FIBRILLATION. 247

FIGURE 8.15: META-ANALYSIS OF CAUSAL EFFECT OF GENETICALLY PREDICTED CD40 ON RISK OF ATRIAL FIBRILLATION. 248

FIGURE 8.16: META-ANALYSIS OF CAUSAL EFFECT OF GENETICALLY PREDICTED YKL40 ON RISK OF ATRIAL FIBRILLATION. 250

FIGURE 9.1: FLOWCHART OUTLINING DEVELOPMENT OF A PRIMARY CARE PHENOTYPE. .. 267

FIGURE 9.2: FLOWCHART OF PARTICIPANTS INCLUDED IN THE ANALYSIS OF ATRIAL FIBRILLATION ASCERTAINMENT SOURCE. 269

FIGURE 9.3: SELECTION OF PARTICIPANTS FOR OBSERVATIONAL ANALYSIS OF ASSOCIATION BETWEEN ANTHROPOMETRIC MEASURES AND RISK OF ATRIAL FIBRILLATION BY ASCERTAINMENT SOURCE. 270

FIGURE 9.4: VENN DIAGRAM DEMONSTRATING ASCERTAINMENT SOURCES FOR PREVALENT ATRIAL FIBRILLATION CASES WITHIN UK BIOBANK (N=230,060). 272

FIGURE 9.5: INCIDENT ATRIAL FIBRILLATION ASCERTAINMENT GROUP, BY AGE AT ASCERTAINMENT AND SEX 276

FIGURE 9.6: TIME FROM ATRIAL FIBRILLATION ASCERTAINMENT TO IDENTIFICATION IN AN ALTERNATE SOURCE 278

FIGURE 9.7: ANTHROPOMETRIC MEASURES AND RISK OF ATRIAL FIBRILLATION BY SOURCE OF FIRST ATRIAL FIBRILLATION RECORD (N=218,272). 280

FIGURE 9.8: ANTHROPOMETRIC MEASURES AND RISK OF ATRIAL FIBRILLATION BY SOURCE OF FIRST ATRIAL FIBRILLATION RECORD SPLITTING ATRIAL FIBRILLATION HOSPITAL EPISODE STATISTICS RECORDS INTO PRIMARY AND NON-PRIMARY CAUSES OF ADMISSION. 282

List of tables

TABLE 4.1: UK BIOBANK COUNTRY SPECIFIC CENSOR DATES 90

TABLE 4.2: BASELINE CHARACTERISTICS OF THE 477,904 PARTICIPANTS IN THE PRIMARY ANALYSIS..... 95

TABLE 4.3: EFFECT OF ANTHROPOMETRIC MEASURES ON RISK OF ATRIAL FIBRILLATION IN MEN AND WOMEN 102

TABLE 4.4: RELATIVE ABILITY OF DIFFERENT ANTHROPOMETRIC MEASURES TO PREDICT INCIDENT ATRIAL FIBRILLATION 107

TABLE 5.1: CHARACTERISTICS OF THE CARDIAC MAGNETIC RESONANCE IMAGING SUBSET OF THE UK BIOBANK COHORT DIVIDED INTO THOSE WITH AND WITHOUT PERICARDIAL ADIPOSE TISSUE DATA AVAILABLE (N=45,751) 129

TABLE 5.2: CHARACTERISTICS FOR TOTAL AND LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA PHENOTYPES 132

TABLE 5.3: INTRA-OBSERVER VALIDATION MEASURES FOR TOTAL AND LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA. 135

TABLE 5.4: INTER-OBSERVER VALIDATION MEASURES FOR TOTAL AND LEFT VENTRICULAR PERICARDIAL ADIPOSE TISSUE AREA. 137

TABLE 5.5: CHARACTERISTICS OF THE PERICARDIAL ADIPOSE TISSUE SUB-SET OF UK BIOBANK AT TIME OF ENTRY INTO THE IMAGING SUB-STUDY BY TOTAL PERICARDIAL ADIPOSE TISSUE AREA DIVIDED INTO FIFTHS (N=3,477). 139

TABLE 5.6: CHARACTERISTICS OF WOMEN IN THE PERICARDIAL ADIPOSE TISSUE SUB-SET (N=1,829) OF UK BIOBANK AT TIME OF ENTRY INTO THE IMAGING SUB-STUDY BY TOTAL PERICARDIAL ADIPOSE TISSUE AREA DIVIDED IN TO FIFTHS. 142

TABLE 5.7: CHARACTERISTICS OF MEN IN THE PERICARDIAL ADIPOSE TISSUE SUB-SET (N=1,648) OF UK BIOBANK AT TIME OF ENTRY INTO THE IMAGING SUB-STUDY BY TOTAL PERICARDIAL ADIPOSE TISSUE AREA DIVIDED IN TO FIFTHS. 144

TABLE 6.1: NEAR INDEPENDENT VARIANTS REACHING GENOME-WIDE SUGGESTIVE THRESOLD ($P<1 \times 10^{-5}$) IN PERICARDIAL ADIPOSE TISSUE GENOME-WIDE ASSOCIATION STUDY 172

TABLE 6.2: ASSOCIATION BETWEEN PERICARDIAL ADIPOSE TISSUE SCORE AND ANTHROPOMETRIC TRAITS IN PARTICIPANTS WITH PERICARDIAL ADIPOSE TISSUE DATA ... 175

TABLE 6.3: ASSOCIATION BETWEEN PERICARDIAL ADIPOSE TISSUE SCORE AND ANTHROPOMETRIC TRAITS IN UK BIOBANK. 175

TABLE 6.4: LOCI PREVIOUSLY IDENTIFIED AS BEING ASSOCIATED WITH PERICARDIAL FAT AND THEIR ASSOCIATED BETA VALUES FOR PERICARDIAL ADIPOSE TISSUE IN UK BIOBANK 178

TABLE 7.1: POWER CALCULATIONS FOR ANTHROPOMETRIC GENETIC SCORES AND RISK OF ATRIAL FIBRILLATION 190

TABLE 7.2: BASELINE CHARACTERISTICS OF UK BIOBANK PARTICIPANTS WITH AND WITHOUT GENETIC DATA AVAILABLE (N=502,536). 192

TABLE 7.3: BASELINE CHARACTERISTICS OF UK BIOBANK PARTICIPANTS WITH GENETIC DATA AVAILABLE BY SEX (N=339,214) 193

TABLE 7.4: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED BODY MASS INDEX ON ATRIAL FIBRILLATION IN UK BIOBANK 196

TABLE 7.5: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED WAIST CIRCUMFERENCE ON ATRIAL FIBRILLATION IN UK BIOBANK 199

TABLE 7.6: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED WAIST CIRCUMFERENCE ADJUSTED FOR BODY MASS INDEX ON ATRIAL FIBRILLATION IN UK BIOBANK 202

TABLE 7.7: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED FAT MASS ON ATRIAL FIBRILLATION IN UK BIOBANK 207

TABLE 7.8: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED LEAN MASS ON ATRIAL FIBRILLATION IN UK BIOBANK 210

TABLE 8.1: POWER CALCULATIONS FOR INFLAMMATORY GENETIC SCORES ASSOCIATION WITH RISK OF ATRIAL FIBRILLATION 230

TABLE 8.2: BASELINE CHARACTERISTICS OF THE 446,838 PARTICIPANTS IN THE OBSERVATIONAL ANALYSIS DIVIDED INTO FIFTHS OF LOG-C-REACTIVE PROTEIN LEVEL AT BASELINE..... 233

TABLE 8.3: BASELINE PRIOR DISEASE IN THE 446,838 PARTICIPANTS IN THE OBSERVATIONAL ANALYSIS DIVIDED INTO FIFTHS OF LOG-C-REACTIVE PROTEIN LEVEL AT BASELINE..... 234

TABLE 8.4: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED C-REACTIVE PROTEIN ON ATRIAL FIBRILLATION IN UK BIOBANK 243

TABLE 8.5: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED INTERLEUKIN-6 RECEPTOR ON ATRIAL FIBRILLATION IN UK BIOBANK 247

TABLE 8.6: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED CD40 ON RISK OF ATRIAL FIBRILLATION IN UK BIOBANK 248

TABLE 8.7: SENSITIVITY ANALYSES FOR GENETICALLY PREDICTED YKL40 ON RISK OF ATRIAL FIBRILLATION IN UK BIOBANK 249

TABLE 8.8: EFFECT OF GENETICALLY PREDICTED ANTHROPOMETRIC MEASURES ON RISK OF ATRIAL FIBRILLATION MEDIATED BY GENETICALLY PREDICTED INFLAMMATORY PROTEINS IN UK BIOBANK (N=339,214) 251

TABLE 9.1: PARTICIPANT NUMBERS AND CODING SYSTEMS FOR UK BIOBANK PARTICIPANTS WITH PRIMARY CARE DATA AVAILABLE..... 264

TABLE 9.2: CENSORING DATES FOR PRIMARY CARE PHENOTYPING 266

TABLE 9.3: READ CODES IDENTIFIED AND VALIDATED THROUGH INITIAL STAGE OF THE PRIMARY CARE MAPPING ALGORITHM..... 271

TABLE 9.4: HOSPITAL ADMISSIONS AND PRIMARY CARE ENCOUNTERS BY ASCERTAINMENT GROUP (N=225,683) 274

TABLE 9.5: BASELINE CHARACTERISTICS OF THE 7,142 PARTICIPANTS WITH INCIDENT ATRIAL FIBRILLATION 275

TABLE 9.6: TIME BETWEEN ASCERTAINMENT AND LAST FOLLOW-UP DATE IN PC-ONLY AND HES-ONLY GROUPS..... 278

TABLE 9.7: ASSOCIATION BETWEEN ANTHROPOMETRIC MEASURES AND HEALTHCARE UTILISATION IN UK BIOBANK..... 279

Chapter 1 – Introduction

Atrial fibrillation (AF) and obesity both represent substantial burdens on healthcare systems. The evidence suggesting a relationship between these two epidemics is substantial. However, obesity is a non-homogenous phenotype and cannot easily be defined by a single anthropometric measure. The mechanisms that relate anthropometric measures and risk of AF are complex and incompletely understood. In addition, the role of specific ectopic adipose tissue deposits remains unclear.

1.1. Importance of atrial fibrillation

1.1.1. Epidemiology of atrial fibrillation

AF is a condition in which regular cardiac depolarisations are superseded by chaotic and irregular depolarisations.[1] AF has an age- and sex-adjusted incidence of 10-30 per 1,000 person-years,[2,3] with an age-adjusted prevalence of 0.5-1.0%.[4,5] AF is the most common sustained arrhythmia with a lifetime risk of one-in-three,[6] and at present affects at least 37 million individuals worldwide.[4] The number of people with AF has approximately doubled between 1990 and 2017 (**Figure 1.1**), with a similar increase in incident cases over the same timeframe.[4] This increase in incidence is likely to be partially explained by improved detection and life-expectancy.[1] However, the prevalence of underlying risk factors for AF has also increased over a comparable period.[7] AF has been predicted to directly cost the United Kingdom (UK) National Health Service (NHS) between £1.4 and £2.6 billion pounds annually.[8]

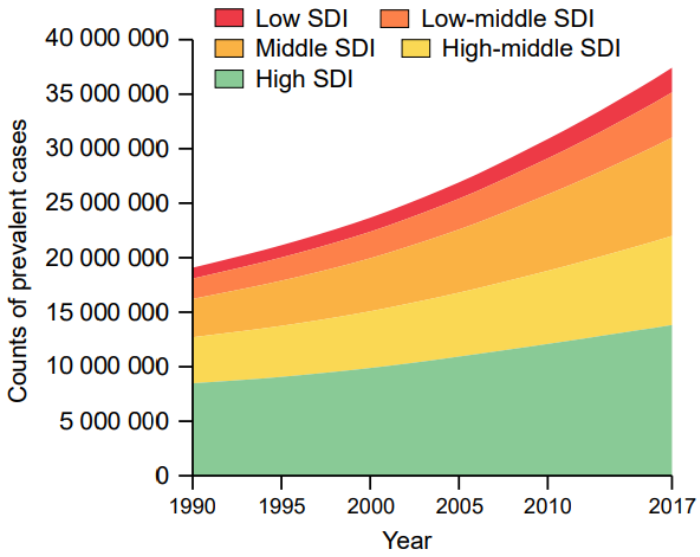


Figure 1.1: Temporal trends in atrial fibrillation prevalent cases by socio-demographic index, 1990-2017.
Taken from: Dai et al.[4], which was published under a creative commons licence, allowing non-commercial, re-use (CC-BY-NC). SDI – socio-demographic index.

AF is not evenly distributed in the population with increasing age strongly associated with a greater risk of the arrhythmia. In those under 45 years AF prevalence is <0.1% increasing to >15% in those aged >85 years.[9] Men are at higher risk of AF than women;[4,9] although it has been suggested that this relationship is not consistent in older age groups.[4] Furthermore, AF is not evenly distributed between ethnicities with higher prevalence reported in white individuals compared to those of Hispanic, Asian, or Black ethnicities.[3]

1.1.2. Risk factors for atrial fibrillation

Established risk factors for AF are extensive and varied. Cardiovascular disease is strongly associated with the risk of developing AF.[10] In addition, cardiovascular disease and AF share a number of common risk factors including hypertension, and diabetes mellitus.[10] This has been suggested to highlight a degree of shared underlying aetiology.[11] However, AF is associated with a number of risk factors

not traditionally identified as risk factors for coronary heart disease, for example thyroid disease, valvular heart disease, and congestive heart failure.[10]

A number of life-style based risk factors for AF have been identified. In particular, greater alcohol intake is associated with a higher risk of AF;[10] although, it is not clear that this relationship is causal.[12,13] In contrast, smoking has not been associated with a greater risk of AF.[14]

1.1.3. Atrial fibrillation-related outcomes

The effects of AF on patients are highly variable. While the majority of those with AF are symptomatic, less than one-in-five have debilitating symptoms.[15] Symptoms include palpitations, fatigue, and breathlessness.[16] Symptom burden is not evenly distributed, with women more likely to be symptomatic than men.[17] As symptoms are generally non-specific, and >50% may initially be asymptomatic,[1] the presence of AF in an individual may remain undetected for a number of years.[18] The presence of symptoms appears to be independent of the risk of cardiovascular outcomes and death in those with AF.[19]

Importantly, in addition to causing symptoms, AF is a significant risk factor for a number of cardiovascular outcomes.[1] In particular, the presence of AF is a significant risk factor for the development of cardioembolic stroke,[10] with AF thought to be responsible for 20-30% of all ischaemic strokes.[20] Not only does AF increase the risk of stroke, strokes that occur in those suffering with AF tend to be larger and more debilitating.[21] Stroke risk in those with AF is not uniform but is modified by the presence of a number of risk factors which can be used clinically to stratify patients.[1]

In addition, to the risk of cardioembolic stroke, AF also predisposes to the development of heart failure, and death.[22,23] This, in part, may be due to increased heart rates which can occur in AF,[24] and may be further exacerbated by irregularity of the ventricular rhythm and the loss of atrial contractile function.[25] However, the causes of heart failure in AF are complex and they both likely represent endpoints from partially overlapping aetiological pathways.[26]

While AF is more common in men, the risks of both cardioembolic stroke and death are greater in women.[4] As such, some risk scores for stroke in AF take account of patient sex.[1] These differences suggest that sex-stratified analyses of AF risk factors and AF prognosis are needed to account for the potential differences in men and women.

1.2. Scale of the obesity epidemic

Obesity is defined by the World Health Organization (WHO) as a body mass index (BMI) of ≥30 kg/m^2,[27] and represents an accumulation of adipose tissue. Obesity is a significant problem in the Western world with an estimated one-in-three adults overweight (defined as a BMI between 25 and 29.9 kg/m^2) or obese.[28] Between 1980 and 2013, the prevalence of obesity has increased by 47% in children and 28% in adults (**Figure 1.2**).[28]

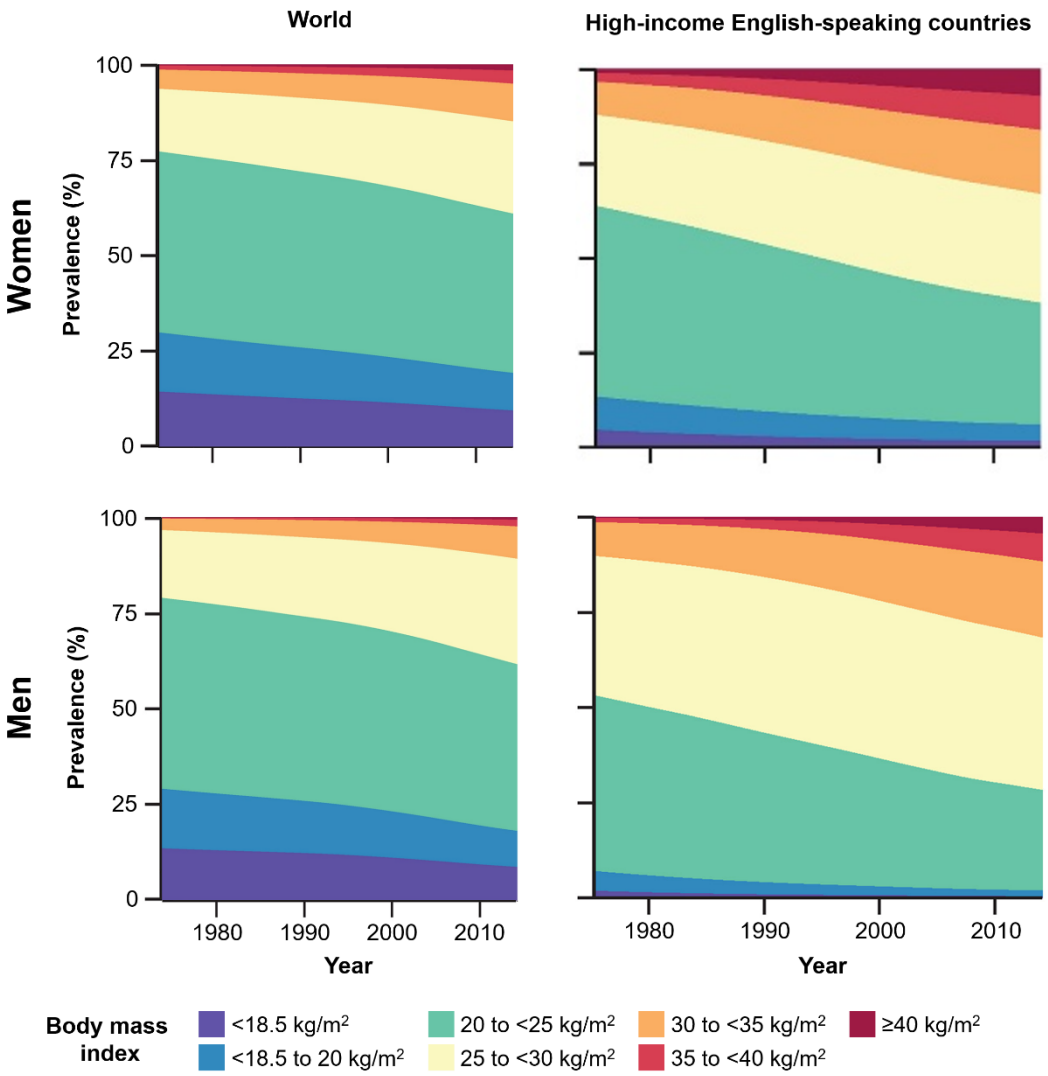


Figure 1.2: Temporal trends in adult body mass index over time.
Adapted from: NCD Risk Factor Collaboration 2017,[29] which was published under a creative commons licence allowing re-use and adaptation (CC-BY).

Physiologically, weight gain is the result of caloric intake outstripping metabolic requirements leading to an increase in energy storage in the form of fat.[30] As a result, the increasing rates of obesity may be the result of increased availability of calorie-dense foods combined with relatively sedentary lifestyles.[28] However, the relative contribution of physical activity and energy expenditure has been debated.[31,32] Potential impacts of changes in the gut microbiome have also been suggested as being important in determining the risk of obesity.[33,34] Importantly, there is also a substantial genetic element to body size,[35] which may predispose

an individual to greater or lower body size or different body shapes. For example, it is estimated that genetic heritability may account for ~20% of the variation in BMI.[35]

1.3. Measures of body size

While BMI has typically been used as a measure of obesity, there are a number of limitations to this approach. Physiologically, obesity is felt to represent a greater amount of adipose tissue. However, BMI does not distinguish between lean and fat mass.[36] As such, greater BMI may not represent greater levels of adipose tissue in all individuals.[37] In particular, BMI does not take into account differences in the relative levels of adipose tissue in different ethnicities,[38] or between men and women.[39-41] This is particularly important as men have a greater degree of lean mass per unit BMI.[42]

In recent years, the ability to determine fat mass (FM) and non-fat (lean) mass (LM) has become more readily available. This can be undertaken using one of two commonly available techniques. The first is dual-energy x-ray absorptiometry (DEXA),[43] while the second is through the use of bio-impedance.[44] These two techniques have been suggested to be interchangeable at a population level.[45] Direct assessment of both FM and LM allows for a more accurate assessment of an individual's adiposity. However, they do not provide information on body shape and body fat distribution.

Body fat distribution is not similar in all individuals. Women have been generally described to have a 'gynoid' pattern of body fat with a greater proportion of fat stored as subcutaneous thigh fat, [46] which has generally been associated with

lower metabolic risk.[47] In comparison, men have been described as being more likely to have an android distribution with more fat stored as abdominal visceral adipose tissue (VAT).[41,48] However, this sex-based dimorphism is not consistent across weight ranges or ages.[40,49]

There are a number of different measures of body shape and body fat distribution. Some, such as waist circumference (WC), and waist-hip ratio, require limited equipment and can be undertaken easily in a clinical environment and have been associated with all-cause mortality.[50] Additionally, non-invasive imaging such as abdominal magnetic resonance imaging (MRI), can provide information on abdominal VAT. Abdominal VAT has been shown to be correlated with WC in men and women (r=0.73-0.78),[51] and is associated with risk of cardiovascular disease, independent of general adiposity.[52] Abdominal VAT, in particular, has been associated with adverse cardio-metabolic risk factors, including elevated blood pressure, dyslipidaemia, higher circulating inflammatory proteins, and insulin resistance.[53-55]

Importantly, different anthropometric measures are not independent of one another. While they may each represent different aspects of body size and shape, many are positively correlated with one another.[56,57] These correlations are particularly salient when considering the mechanisms underpinning apparent associations between anthropometric phenotypes and diseases. Without appropriate adjustments, it is unclear what independent role aspects of body size or shape may have on the risk of AF.

1.4. General body size measures and risk of atrial fibrillation

1.4.1. Observational associations between body size and risk of atrial fibrillation

Higher BMI has repeatedly been associated with a higher risk of AF,[58-64] with a previous meta-analysis demonstrating that a 5 kg/m^2 higher BMI was associated with an ~30% higher risk of AF.[65] Several studies have used measurements of bio-impedance (or other imaging methods) to estimate FM more directly.[66-71] A previous meta-analysis has reported a 10% higher risk of AF per 5 kg higher FM.[65] The effect of central adiposity on risk of AF has been less well described than that of general adiposity. However, a 1-standard deviation (SD) higher WC (approximately 10 cm) was associated with a 30% higher risk of AF (risk ratio [RR] 1.32, 95% confidence intervals [CI] 1.25 to 1.41 per SD, 3,562 AF cases [5 studies]).[72]

1.4.2. Evidence for independent associations between body size measures and atrial fibrillation

Few studies have been sufficiently powered to examine the independent effects of different measures of body size and shape on risk of AF. Fenger-Grøn *et al*. in a Danish cohort (3,868 AF cases) found that, after adjusting for LM, associations between AF and measures of adiposity were almost completely attenuated.[66] This finding contrasts with a recent Mendelian randomization (MR) study, which suggests a possible causal role for both FM and LM on risk of AF.[71]

1.4.3. Sex-based differences in the effects of body size on risk of atrial fibrillation

The effects of BMI on risk of AF in men and women have only been examined in a small number of studies with limited AF cases, resulting in conflicting results; some have suggested a stronger association between BMI and risk of AF in men than women,[73,74] whilst others demonstrated no difference.[75,76] Sex-based differences in the effect of other anthropometric measures on risk of AF have been less thoroughly explored.

1.4.4. Evidence for weight loss in atrial fibrillation

Observational studies of overweight patients have suggested that weight loss was associated with lower AF burden (the percent of time spent in AF). Middeldorp *et al*. demonstrated in a consecutive AF cohort of patients with a BMI ≥27 kg/m^2 (AF cases = 355) that greater weight loss was associated with greater AF freedom (absence of AF episodes in those previously diagnosed with AF), and reduced progression to persistent/permanent AF.[77] In the same cohort, Pathak *et al*. demonstrated that greater weight loss was also associated with reduced AF burden and lower symptom severity.[78] Similarly, risk-factor management, including weight loss, was associated with reduced AF frequency, duration, and symptom severity in individuals after undergoing an AF ablation procedure.[79]

However, the evidence of a causal relationship between weight loss and improvement in AF has been less thoroughly established. Abed *et al*. undertook a randomised trial in 150 overweight patients with AF and suggested reduced

cumulative AF duration and symptom severity with weight reduction.[80] This suggests that anthropometrics may be modifiable risk factors in those with AF. However, trials examining weight loss are unable to assess the life-long impact that increased adiposity exerts on AF risk. The average weight loss in the treatment arm of this trial (14.6kg) is more than can be achieved by many patients.[81] Furthermore, follow-up periods have been short and it is unclear whether the effects of weight loss continue indefinitely. This is particularly important as many individuals who initially lose weight are unable to maintain such losses and eventually return to a pre-intervention level.[81] As a result, randomised trials have limitations as an approach to explore the causal relevance of anthropometric traits and AF.

1.5. Ectopic fat deposits and risk of atrial fibrillation

While general measures of adiposity have been repeatedly associated with risk of AF, a number of specific ectopic fat deposits have also been associated with greater risk of AF.[72]

1.5.1. Pericardial adipose tissue

The human heart is surrounded by the pericardial sac.[82] Adipose tissue can accumulate between the epicardial surface of the heart and the pericardium.[83] This fat tissue is variously termed epicardial fat or pericardial fat. While epicardial fat is often defined as any adipose tissue enclosed within the pericardial sac,[84-86] some have argued for a strict distinction of epicardial fat (adipose tissue sitting between the epicardial surface and the visceral pericardium) and pericardial fat (adipose tissue sitting between the visceral pericardium and parietal

pericardium).[83] Others have suggested that pericardial fat includes fat outside of the pericardium.[87] It is also argued that epicardial fat in particular has paracrine and endocrine effects,[88] which may directly influence arrhythmic risk. However, in the epidemiology literature, both terms (epicardial fat and pericardial fat) have been used largely interchangeably. In imaging studies these two fat deposits (epicardial fat and pericardial fat) have been difficult to distinguish from one another,[89,90] and imaging studies have generally described a combination of both epicardial and pericardial fat.[72,89] In this thesis the term 'pericardial adipose tissue' (PAT) will be used when discussing literature around this ectopic fat deposit, unless previous studies have specifically identified epicardial fat tissue as a specific fat deposit sitting between the epicardium and visceral pericardium. When defining this phenotype in this thesis, PAT will be defined as fat between the epicardial surface and the parietal pericardium (**Figure 1.3**).

The majority of studies exploring PAT have used computed tomography (CT) scans to obtain PAT measurements. [72] CT allows for a high degree of spatial resolution.[91] However, this is coupled with the use of ionizing radiation which limits the use of CT for large-scale imaging studies in healthy populations.[92] Cardiac MRI (CMR) has not been extensively used in the past for assessing PAT but may allow for analysis of PAT measurements without use of radiation.[93]

Previous observational data have suggested a strong association between PAT and AF. In a meta-analysis, higher PAT was associated with a 2.6-fold higher AF risk per SD (odds ratio [OR] 2.61, 95%CI 1.89 to 3.60, AF cases = 1,105 [10 studies].[72] Of the 10 studies included in this meta-analysis, eight were case-control analyses examining the association with prevalent AF. The largest

1 included cohort, containing 50 incident AF cases, showed no significant
2 association between greater PAT volume and risk of AF.[94] Subsequently,
3 Heckbert *et al.* reported data from the Multi-Ethnic Study of Atherosclerosis
4 (MESA) and Jackson Heart Study (JHS, AF cases =756) and demonstrated a
5 weak association between PAT volume and risk of incident AF (hazard ratio [HR]
6 1.12, 95%CI 1.05 to 1.20) which was negated following adjustment for BMI (HR
7 1.06, 95%CI 0.97 to 1.15).[95]

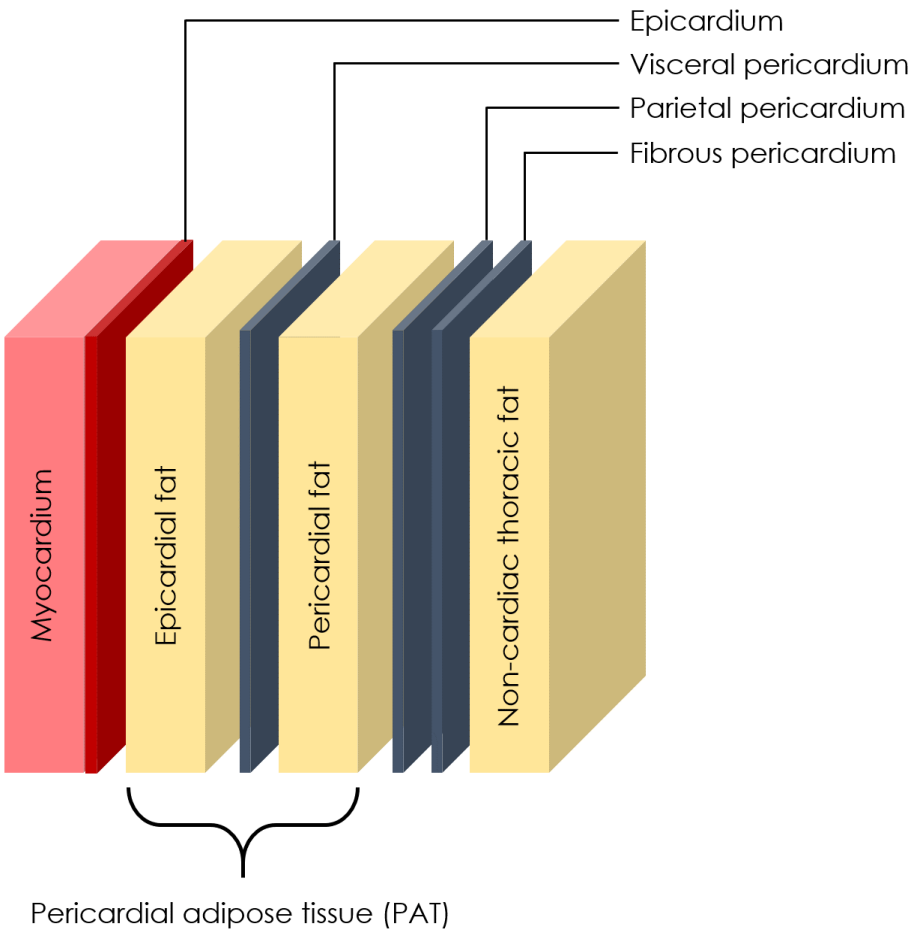


Figure 1.3: The anatomy of adipose tissue surrounding the heart.
Epicardial fat lies between the epicardium and visceral pericardium with pericardial fat sitting between the visceral pericardium and parietal pericardium. In this thesis pericardial adipose tissue (PAT) is defined as a combination of epicardial and pericardial fat.

8

As such, the evidence for a role of PAT on AF risk is not consistent. Positive associations have principally been described in observational analyses with a significant potential for confounding and reverse causation.[72] Additionally, there is heterogeneity relating to differing imaging modalities. Furthermore, there is a strong association between PAT and other regional adiposity measures.[96,97] As such, the independent, and potentially causal, role of PAT in AF risk remains unclear.

Two genome-wide association studies (GWAS) of PAT have previously been undertaken, which identified two independent variants.[98,99] However, effect estimates for these analyses are not available. These GWAS were undertaken using overlapping cohorts with the GWAS by Chu *et al*. involving ~11,000 participants (~7,200 of European ancestry). This GWAS utilised six different cohorts with significant differences in PAT phenotyping and resulting PAT volumes. Further GWAS are required to identify genetic variants for this phenotype, which would allow exploration of the causal association between PAT and AF through MR analysis.

1.5.2. Abdominal visceral adipose tissue

Body imaging has been used in two cohorts to directly assess the association between abdominal VAT and the risk of incident AF. Aronis *et al.* (AF cases = 371) demonstrated that when adjusted for age, sex, and ethnicity abdominal VAT was positively associated with risk of AF (HR 1.11, 95%CI 1.00 to 1.23, per SD) but not when further adjusted for additional covariates including blood pressure, smoking, prevalent coronary heart disease (CHD), and prevalent diabetes (HR 1.07, 95%CI 0.96 to 1.19, per SD).[68] Lee et al. (AF cases = 162) similarly

demonstrated no significant association between abdominal VAT and risk of AF (HR 1.09, 95%CI 0.93 to 1.28 per SD).[100] However, both were small studies limiting their power and thus ability to provide robust conclusions.

1.6. Assessment of the causal association between anthropometric measures and risk of atrial fibrillation

1.6.1. Limitations in traditional epidemiology

Limitations in traditional epidemiology are well recognised.[101] Of particular importance is the risk of reverse causation and residual confounding, which limits the ability to make causal inferences for identified associations.

1.6.2. Mendelian randomization

MR utilises genetic data to make causal inferences from associations between exposure (risk factors) and outcomes.[102] Genetic variants associated with the exposure, termed 'instrumental variables' (IV), are used as proxies for the exposure to assess the causal effect of the exposure on the outcome (**Figure 1.4**). MR is based on Mendel's 2nd law of inheritance (the law of independent assortment).[102] Somatic genetic variants remain constant following conception and are, therefore, not prone to 'reverse causation'.

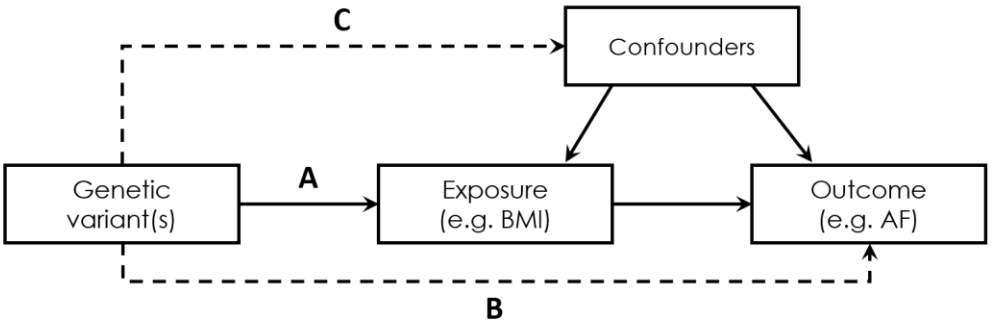


Figure 1.4: Conditions required for instrumental variables in a Mendelian randomization study.
BMI – body mass index, IV – instrumental variables

1.6.3. Mendelian randomization analyses suggesting causal roles of anthropometric measures and risk of atrial fibrillation

Large-scale GWAS have identified a large number of genetic variants associated with a life-long difference in BMI.[35,103] Genetic variants have similarly been associated with a number of other anthropometric measures including height,[35] WC,[104,105] waist-hip ratio,[104] LM,[71] FM,[71] and abdominal VAT.[106] Identified genetic variants can be used to undertake MR analyses.[107] Such analyses utilise identified genetic variants as IVs for the risk factor of interest. This allows for the assessment of a life-long difference in a risk factor, limits potential reverse causation, and may provide evidence of a causal relationship between risk factor and outcome.[107]

Using an MR approach, Chatterjee *et al.* have shown an association between genetically predicted higher BMI and AF risk (OR 1.11 [1.05 to 1.17] per kg/m^2) in 4,178 AF cases.[108] This has been supported by a recent study examining UK Biobank (UKB) data.[109]

The separate roles of genetically predicted LM and FM on risk of AF has been explored by Tikkanen *et al.* in UKB.[71] They suggested a role for both genetically predicted LM (RR 1.55 95%CI [1.38 to 1.75] per SD) and FM (RR 1.30 95%CI [1.17 to 1.45] per SD) in AF risk. However, the use of combined (rather than sex specific) SD units may result in an over-estimate in the predicted effect size of LM. The effect of LM on AF risk has also been clouded by additional research, also in UKB, showing a negative association between genetically predicted LM measures and AF risk (OR 0.75 [0.66 to 0.86] per kg/m^2 lean mass index).[109]

These analyses support a likely causal association between BMI, FM, and potentially LM and risk of AF. However, given correlations between different measures of adiposity, it remains unclear which aspects of body fat distribution or body shape are most relevant in AF development. To date, only one MR analysis has explored the potential causal role for measures of body shape/body fat distribution on risk of AF.[110] Importantly, the effect of sex on the causal role measure of body size/shape remains unexplored.

1.6.4. Assumptions in Mendelian randomization analyses

For an IV to be valid, several assumptions must be satisfied (**Figure 1.4**). Violation of assumptions and/or limitations of MR need to be considered in order to provide robust inference about potential causality. For example:

1. Population stratification can lead to spurious associations (if there is variability in allele frequency, risk factors, and disease frequency within population subgroups).[102]

2. Pleotropic effects of genetic variants occur when the IV affects more than a single biological pathway/trait. [102]
3. Variants may be in linkage disequilibrium and are thus not independently inherited. [102]
4. Weak instrument bias can occur as individual genetic polymorphisms may explain only a small amount of the exposure variance.[111]

If the underlying assumptions for an MR analysis are not valid or if one or more of the scenarios above occurs, this may lead to spurious results. As a result, analyses must be undertaken to ensure the assumptions are valid and limitations are avoided.

1.7. Potential pathways linking body size and risk of atrial fibrillation

At present, the mechanisms mediating the association between body size and risk of AF are not well delineated. As previously outlined, obesity is associated with a number of cardiometabolic effects which may act as confounders, mediators, or colliders in the relationship between adiposity and AF (**Figure 1.5**).[112-114] For example, greater BMI is associated with higher rates of hypertension and cardiovascular disease.[113,114] Both these conditions have been shown to be associated with a greater risk of AF.[10] As such, they may act as mediators between adiposity and risk of AF. However, a number of analyses have included these phenotypes as covariates in their models and continued to demonstrate a strong association between body size and risk of AF,[61-64] suggesting that the mediating pathways cannot fully be explained by these intermediaries. However, a number of traits can develop as a result of both

adiposity and AF. An example may be heart failure for which both body size and AF are risk factors.[26,112] Conditioning on or adjusting for such a trait may result in spurious associations. Such assessments are further complicated by a bidirectional relationship between AF and other traits (e.g. heart failure is associated with risk of AF as well AF being a risk factor for the development of heart failure) such that adjustment for this trait may result in collider bias.[115]

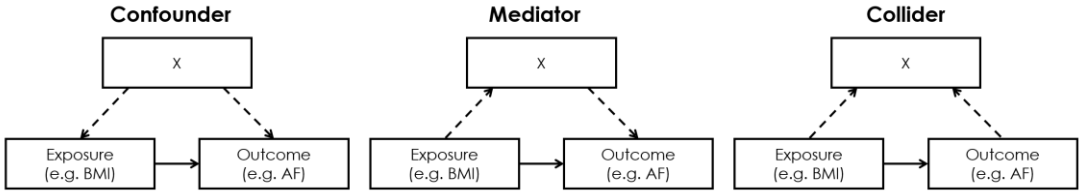


Figure 1.5: Confounding, mediation and collider bias.
AF – atrial fibrillation, BMI – body mass index

1.7.1. Atrial fibrillation, adiposity, and inflammation

The risk of AF has been shown to be greater in those with underlying inflammatory disease.[116,117] Higher levels of C-reactive protein (CRP) and interleukin (IL)-6 have both been shown to be associated with a greater risk of AF.[118-120] While previous studies have not shown CRP to be causally related to AF,[121] higher levels of IL-6 have been causally linked with risk of AF.[120] However, IL-6 is also associated with greater risk of CHD.[122] As such, whether greater inflammation represents an independent causal pathway for the risk of AF or whether greater inflammation works through established pathways remains unclear.

Historically adipose tissue was considered simply a passive energy store. However, in contrast, adipose tissue is now known to be metabolically active.[123] Adiposity is associated with greater inflammation,[124-126] and greater amounts of

adipose tissue are associated with greater levels of circulating inflammatory proteins including CRP.[127] As such, greater inflammation may mediate the effect of adiposity on risk of AF. However, to date, there has been no assessment of the relationship between adiposity, inflammation, and risk of AF.

1.8. Key limitations in the current research

Both obesity and AF represent substantial burdens on modern healthcare systems. The prevalence of both conditions are likely to continue to increase over the near to medium future. However, while extensive research has been undertaken on the role of adiposity and anthropometric measures and their relationship to AF, there are a number of key areas that require substantial further exploration.

1.8.1. Independent effects of anthropometric measures

The effect of overall body size on risk of AF has been well established. However, the relative independent effects of different anthropometric phenotypes require further assessment. This requires assessment in a dataset containing sufficient AF case numbers and accurately determined anthropometric measures. Further, given established differences in risk of AF between men and women and similar sex-based dimorphism in anthropometric measures, any differences in the effect of body size/shape on risk of AF between men and women should be robustly investigated.

1.8.2. The role of pericardial adipose tissue in atrial fibrillation

The role of ectopic fat deposits, in particular PAT, in relation to AF need to be established. Robust assessments of the relationship between PAT and AF are still required to elucidate whether this phenotype is associated with risk of AF. While genetic instruments are available for a range of general anthropometric phenotypes,[35,105] this is not true for PAT despite evidence as a potentially important risk factor for AF.[128,129] Appropriate genetic IVs are needed to allow MR studies and assessment of the causal relevance of ectopic fat deposits and the risk of AF.

1.8.3. Independent causal role for anthropometric measures

A number of MR analyses have been undertaken linking a number of anthropometric measures to the risk of AF.[108,110,130] However, exploration of the independent causal relevance of these phenotypes has been more limited. This is important as identifying the anthropometric traits with independent relevance for AF may allow further consideration of the potential mediating pathways between adiposity and AF.

1.8.4. Links between anthropometric measures, inflammation, and risk of atrial fibrillation

As outlined above, inflammation may represent a biological mechanism linking anthropometric traits and risk of AF. However, this potential mediation has not previously been explored. Given the potentially modifiable nature of inflammation through the use of established pharmacological therapies,[131] any link identified

may allow further exploration of such therapies to reduce the risk of AF in relevant populations.

1.8.5. Atrial fibrillation detection and diagnosis

To ensure robust inference, epidemiological studies require informative, reproducible, and clinically and biologically meaningful phenotypes. This is complex in an era of reliance on electronic healthcare records. Thus, we also consider AF phenotyping complexities.

In the UK there is no formal screening programme for AF,[132] and it is estimated that 45% of UK AF cases are initially recorded in primary care.[132,133] The initial management of AF is principally undertaken in primary care with outpatient cardiology support,[134,135] and individuals may not require hospitalisation for a period of time.[136]

Given that AF is often first recorded in primary care, the use of hospital records to identify participants of AF may result in under-reporting and a set of cases that are unrepresentative of the wider AF population. The use of primary care data to supplement phenotyping of AF from hospital records has not been fully assessed.[133] In particular, whether participants differ based on source of AF identification requires further exploration.

1.9. Thesis aims and overview

General methods used in this thesis are described in **Chapter 2** with additional, chapter specific methods, detailed within each chapter. A systematic review of

the literature surrounding anthropometric measures and risk of AF is outlined in **Chapter 3**.

This thesis was developed to address novel objectives outlined previously and has a number of aims adopting observational, genetic, and phenotypic approaches to elucidate the relevance of adiposity for AF for population health.

1. Determine the independent effects of anthropometric measures on risk of AF in men and women (**Chapter 4**).
2. Establish a PAT phenotype in UKB (**Chapter 5**), and explore the association between PAT and risk of AF using traditional and genetic epidemiological assessments (**Chapter 6**).
3. Examine the causal relationship between anthropometric measures and risk of AF (**Chapter 7**).
4. Elucidate the relationship between adiposity, inflammation, and risk of AF (**Chapter 8**).
5. Consider different sources of electronic health records data including primary and secondary care sources, in phenotyping AF for epidemiological research objectives (**Chapter 9**).

Finally, the overall conclusions to this thesis are briefly described in **Chapter 10**.

Chapter 2 – Methods

This chapter describes methods and data sources used in this thesis. This includes a detailed description of the UKB study, relevant international genetic consortia, the underlying methodology for the development of genetic scores, and statistical methods. Additional, objective specific methods are outlined in individual chapters. Data were utilised from UKB and a number of large genetic consortia.

2.1. UK Biobank

UKB is a large-scale prospective cohort of 0.5 million adults recruited between 2006 and 2010 from 22 recruitment centres across the UK.

2.1.1. Research ethics and permissions

UKB works under a developed ethical framework – the UKB Ethics and Governance Framework.[137] UKB is overseen by an Ethical Advisory Committee (which replaced the UKB Ethics and Governance Council in 2018) alongside regulators including the Human Tissue Authority, the Charity Commission, and the Information Commissioner's Office.[137,138] Ethics approval as a Research Tissue Bank was originally granted in 2011 and is reviewed on a five yearly basis.[139] The most recent ethics approval was provided by the North West – Multi-centre Research Ethics Committee on 29th June 2021 (reference: 21/NW/0157).[139] Research for this thesis was conducted on UKB data under application number 14568.

2.1.2. UK Biobank recruitment

Invitations were sent to 9.2 million individuals in 2006 following the identification of suitable candidates from National Health Service (NHS) records.[140] Participants were selected from the NHS register of men and women aged 40-69 years. Participants were limited to those living within approximately 25 miles of a recruitment centre.[140] UKB had a response rate of 5.5% leading to the recruitment of 503,325 participants. Participants attended an assessment centre between 2006 and 2010.[141]

2.1.3. UK Biobank baseline assessment

As part of recruitment, participants attended a recruitment centre and underwent a baseline assessment.[142] During this assessment participants completed a touch-screen questionnaire detailing sociodemographic, lifestyle, environmental, and other health-related factors.[143] This was followed by a nurse-led interview which obtained further details on the participant's medical history,[144] anthropometric measurements,[145] and collection of blood samples.[146]

2.2. UK Biobank data collection

This section details the data available in UKB with a focus on the data that are material to this thesis.

2.2.1. UK Biobank touch-screen questionnaire

In the assessment centre participants were asked to self-complete a touch-screen-based questionnaire.[143] This questionnaire included questions relating to sociodemographic factors, lifestyle, family history, medical history, and

medication use.[147] Participants provided data on their ethnic background as part of the touch-screen questionnaire. As part of the questionnaire relating to life-style, patients were asked about smoking and alcohol consumption.

2.2.2. UK Biobank nurse-led verbal interview

A nurse-led verbal interview was undertaken on all UKB participants and collected detailed sociodemographic, occupational, and health information.[144] The interview was guided by participant answers to touch-screen questions. Participants were asked '*Has a doctor ever told you that you have any other serious medical conditions?*' as part of the touchscreen questionnaire. If they selected '*Yes*' or '*Unsure*' when asked about '*Other serious medical conditions*' during the touch-screen questionnaire, participants were then asked further questions during the verbal interview to obtain information about the specific condition which was then documented.[144] Conditions identified in this interview were coded using UKB-specific codes.[144]

2.2.3. Anthropometric measures in UK Biobank

During the baseline assessment, following the verbal interview, participants had a range of body size measurements recorded.[145] Weight was measured using a Tanita BC418MA body composition analyser, and height was measured using a Seca 240 cm height measure with participants standing against a vertical scale in bare feet. BMI was calculated as weight (in kg) divided by height (in m) squared. WC and hip circumference (HC) were measured using a Seca 200 cm flexible tape measure. WC was measured at the smallest part of the trunk (the so called 'natural indent') or at the level of the umbilicus if no natural indent could

be identified. Subsequently, hip circumference was measured at the widest part of the hips. Waist-hip ratio (WHR) was calculated by dividing WC by HC. Bio-impedance was used to provide data on whole-body fat mass and lean (fat-free) mass, and was measured using a Tanita BC418MA body composition analyser with participants in bare feet.[148] In 2014-15, 5,170 participants were re-surveyed and underwent DEXA scans.

2.2.4. Blood biomarkers in UK Biobank

Participants had approximately 50 ml of blood collected during the baseline assessment.[146] These samples were tested for 36 biochemical markers selected because of established associations with common diseases.[149] Samples were processed at a central processing laboratory.[150] UKB established a set of quality control procedures to ensure accuracy of biochemical measurements. This included registering all assays with an external quality assurance scheme with external verification of results.[149] For this thesis, measurement of serum C-reactive protein is of particular relevance and is discussed in detail in **Chapter 8**.

2.2.5. Genetic data in UK Biobank

UKB participants had blood samples taken at the baseline assessment which were subsequently genotyped.[151] Samples were genotyped on one of two arrays. A minority (11%) were genotyped at 807,411 variants using the Applied Biosystems UK BiLEVE Axiom array. The remainder were genotyped using the Applied Biosystems UKB Axiom Array (825,927 variants). This second array shares ~95% of variant content with the UK BiLEVE Axiom Array.[152] Genetic imputation was undertaken using variants shared between arrays using 1000

Genomes Phase 3, UK10K, and Haplotype Reference Consortium datasets.[153-155] Genetic imputation resulted in ~93 million autosomal variants available for analysis.[152]

A number of quality control assessments were applied centrally by UKB to confirm both marker and sample-based quality. This process has been outlined in detail previously.[152] The marker quality control process examined for departures from Hardy-Weinberg equilibrium, batch/plate/sex/array effects, and discordance across control replicates. Sample quality control examined for duplicate samples, genetic and self-reported sex discordance, low genetic call rate, and high heterozygosity or missing rates.

2.2.6. Hospital episode statistics, death registry, and primary care data

Follow-up of UKB participants for non-cancer medical conditions is provided from three sources: hospital episode statistics (HES), death registry data, and more recently (for some UKB participants) primary care data.

2.2.6.1. Hospital episode statistics

Data on hospital admissions at NHS hospitals is collected as HES data.[156] The HES dataset is regularly updated (approximately twice a year) and linked to UKB participant records. HES data contains information on each hospital admission including primary and non-primary diagnoses recorded during the admission and procedural data. Diagnoses are recorded using the WHO International Classification of Diseases 10 (ICD-10) format.[157] Procedural data are recorded

using Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) codes.

2.2.6.2. Death registry data

Participants are followed-up for cause-specific mortality through linkage to the NHS death registry.[158] Mortality data are provided by NHS Digital every six months for participants in England and Wales. Mortality data for Scottish participants is provided quarterly by the NHS Central Register. Death records contain data on the date of death, age at death, and primary and contributory causes of death (as ICD-10 codes).[158]

2.2.6.3. Primary care data

Primary care data have been made available for approximately 45% of the UKB cohort (as of September 2019).[159] Data are available for a proportion of UKB participants in England, Scotland, and Wales.[159] This provides data on general practice encounters including diagnostic, procedural, and prescription information. Data relating to general practice encounters is coded using Read Codes versions 2 and 3. Read codes can be mapped to ICD-10 and OPCS-4 codes using mapping files available from NHS digital.[160] Primary care data were not available at the start of this thesis. As a result, primary care data are not used for phenotyping cardiovascular or other phenotypes in this thesis prior to **Chapter 9** where the addition of data from this source to develop an AF phenotype is systematically assessed. Further methods relating to the use of primary care data in phenotype development are detailed in **Chapter 9**.

2.3. UK Biobank imaging sub-study

UKB developed an imaging sub-study aiming to re-invite 100,000 UKB participants to undergo a multi-modality imaging assessment including brain MRI, cardiac and abdominal MRI, DEXA, and carotid ultrasound.[93] The UKB Expert Imaging Working Group developed an imaging protocol with the aim of balancing the value of imaging data collection against scalability.[93] Initially a pilot study of approximately 5,000 participants was undertaken between 2014 and 2015.[93]

This sub-study is ongoing and UKB participants are invited to one of four regional centres (Central [Stockport], Northern [Newcastle upon Tyne], South-East [Reading], and South-West [Bristol]).[161] Participants were notified of the opportunity to take part in this sub-study using email and postal invitations. Participants interested in taking part in this sub-study were invited to undertake a telephone assessment where eligibility for inclusion into the study was assessed.[93,162] Participants were excluded if they had conditions that prevented undergoing an MRI scan (for example, non-MRI safe pacemakers) or were unlikely to be able to tolerate the scan (for example due to claustrophobia or breathing problems).[162] Of those invited to date, ~30% expressed a desire to undertake the imaging sub-study.

Participants undergo four separate scans (brain MRI, cardiac and abdominal MRI, DEXA, and carotid ultrasound).[93] Although multiple centres were used for this sub-study, all staff members underwent a six-week training programme. Participants were scanned using the same scanner models, software, adjustments, and tuning methods in each centre.[93] Images were reviewed by the radiographer for quality control purposes. Further external quality control

assessments were undertaken during the pilot study and confirmed that acquired images were of good quality.[93] Details of the CMR assessment are further outlined in **Chapter 5**.

Following completion of these scans, participants underwent a repeat of the measures collected in the baseline assessment including a touch-screen questionnaire, nurse-led verbal interview, and anthropometric measurements. Protocols for these repeat assessments were similar to those described for the baseline assessment.

2.4. Phenotype definitions

Relevant medical conditions were identified using baseline verbal interview data, HES data, and death registry data. Incident cases were identified using HES data (based on any reason for admission, additional details shown in **Appendix Table D.1**) and death registry data following recruitment. Health outcomes prior to recruitment were identified from HES records and self-reported information during the baseline verbal interview.

2.4.1. Atrial fibrillation

AF was identified through baseline verbal interview data, HES records, and death registry data. ICD-10 classifies both AF and atrial flutter together.[157] Atrial flutter is a cardiac arrhythmia which is related to AF.[163] As a result, and in line with other studies examining AF in UKB and other cohorts,[66,71,164] a combined phenotype of these two related conditions was used in this thesis.

2.4.2. Comorbid conditions

Comorbid conditions were identified using baseline verbal interview data, HES records, and death registry data. In addition, hypertension was determined using self-reported use of antihypertensive agents (either through touch-screen reporting, or in the verbal interview), touchscreen report of a prior diagnosis of hypertension, and blood pressure taken at the recruitment centre (average between two readings ≥160/100 mmHg, **Appendix Table D.1**).

2.5. UK Biobank participants included in this thesis

This thesis makes extensive use of the UKB cohort. However, as UKB recruited participants for sub-study involvement (including an imaging sub-study), and some participants failed genetic quality control measures (see **Genetic data in UK** B), not all participants are included in each analysis (**Figure 2.1**). Specific participant selection criteria and flow-charts are provided in the chapter specific methods of relevant chapters for principal observational analyses (**Chapter 4**), PAT analyses (**Chapter 5**, **Chapter 6**), and primary care analyses (**Chapter 9**).

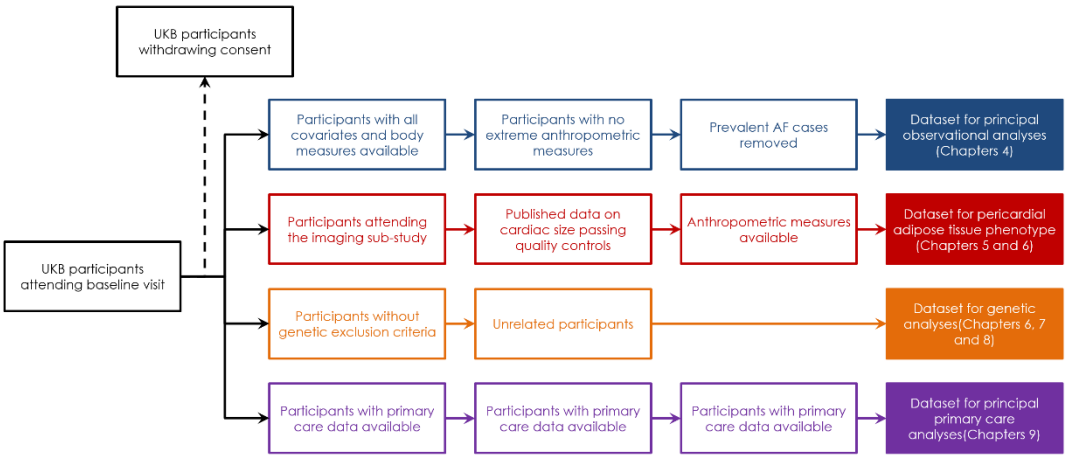


Figure 2.1: Overview of UK Biobank participants used in this thesis.
General flowchart outlining the different divisions of UK Biobank participants used throughout this thesis.

2.5.1. Genetic analysis

For genetic analyses, participants were included with a self-reported white British ancestry and who clustered in this group in a principal component analysis. Participants were excluded if they exhibited sex chromosome aneuploidy, where there was discrepancy between genetic and self-reported sex. Participants who were outliers for heterozygosity, missingness (missing rate on autosomes >0.02), and genotype call rate were excluded. Related participants (up to the 3rd degree) were excluded with those with a diagnosis of AF preferentially retained. The primary analyses included 339,214 participants.

2.6. Genetic consortia

Large-scale genetic consortia were used for two purposes in this thesis: (1) to provide estimates of the association of genetic variants with a range of exposures; notably anthropometric measures, (2) to assess the effect of genetic variants and developed genetic scores on the risk of AF in independent datasets for validation. Three consortia datasets are of particular relevance:

2.6.1. Genetic Investigation of Anthropometric Traits (GIANT) consortium

The GIANT consortium is an international collaboration which has the stated aim of identifying genetic loci that affect human body size and shape.[165] Data from this consortium were used to generate anthropometric genetic scores and examine the effect on risk of AF. The number of studies contributing to each GWAS differ based on available anthropometric data.[35,103-105] Variants were excluded if there was a low imputation quality, a low single nucleotide

polymorphism (SNP) call-rate (<95%) or if out of Hardy-Weinberg equilibrium.[105] In general, analyses of the GIANT consortium have used rank inverse normally transformed sex-specific residuals generated from anthropometric measures after adjustment for age, age^2, and genotype-derived principal components.[35,103-105] Specific adjustments are detailed in Appendix I (**Development of genetic scores**). Associations between variants and anthropometric residuals were modelled using linear regression models. Analyses from separate cohorts were combined using an inverse-variance weighted fixed effect model.[35,105] Summary data from this consortium is available from an online repository.[166]

2.6.2. Atrial Fibrillation Genetics (AFGen) consortium

The AFGen consortium is a collaborative consortium which aims to investigate the genetic causes of AF.[167-169] Data from this consortium was used as an external replication dataset when examining associations between genetic scores and the risk of AF. The number of studies included varies based on the specific genetic analysis undertaken. The consortium data used in this thesis is based on the most recent GWAS that did not include UKB or FinnGen data.[167] This GWAS included data from participants from 31 studies with 17,931 AF cases of which 89% were from a European ancestry.

Participants from studies included in this consortium underwent genotyping and imputation to the 1000 Genomes Project Phase 1 reference panel.[170] Variants with a minor allele frequency <1%, imputation quality <0.3, or variants present only in a single study were excluded.[167] For prevalent cases, logistic regression models were used, while time-to-event analyses using Cox proportion hazards models were used for incident data. Models were adjusted for age, sex, and

principal components of ancestry. Summary level results were then meta-analysed using inverse variance-weighted fixed-effect models. Summary data from this meta-analysis are available from an online repository.[171]

2.6.3. FinnGen

FinnGen is a research project created as a public-private partnership aiming to collect genetic and health data on half a million participants of Finnish biobanks.[172,173] Data from this consortium was used as an external replication dataset when examining associations between genetic scores and the risk of AF. This cohort combines data from a combination of 22 sources including Finnish biobanks, university hospital datasets, and international pharmaceutical industry partners.[174] Data from FinnGen (release 7) contains data from 34,748 AF cases (total sample size 309,154).[175] The AF phenotypes was derived from ICD 8, 9, and 10 codes with diagnoses obtained from national registries.[176,177] Controls were limited to those without pre-existing cardiovascular diseases (hypertension, CHD, peripheral vascular disease, or stroke).

FinnGen participants were genotyped using Illumina (Illumina Inc.) and Affymetrix arrays (Thermo Fisher Scientific).[173,176] A population specific imputation reference panel of 3,775 whole genomes (SISu version 3) was used for genotype imputation.[176,178] Variants with high missingness (>2%), out of Hardy-Weinberg equilibrium, or a minor allele count less than three were removed.[173] Logistic regression models were used to assess associations between variants and phenotypes with models were adjusted for age, sex, batch, and 10 principal components of ancestry.[173,176] Summary data from this meta-analysis is available from an online repository.[175]

2.7. Genetic score development

2.7.1. Variant selection

Variants were selected from published GWAS data. Variants meeting genome-wide significance ($p<5 \times 10^{-8}$) were initially selected. Variants were identified that were present in UKB and had passed UKB quality control procedures using reference SNP cluster ID (RSID) and/or chromosome and base pair position data. Variants with a minor-allele frequency of <1% were removed. Variants were then clumped using Plink with a linkage disequilibrium (LD) score of $r^2<0.01$ and a distance defined by the maximum distance between any two variants of interest on a chromosome. Palindromic variants were defined as having a minor allele frequency of 45-55% and either A/T or C/G alternative alleles. Following clumping, palindromic variants were removed. The development of specific genetic scores are detailed in **Chapter 7**, **Chapter 8**, and Appendix I (**Development of genetic scores**). Risk alleles were defined as the allele for each variant associate with a greater risk of the outcome or trait.

2.7.2. Proportion of variance explained

The proportion of variance in the trait explained by each variant was determined to assess the strength of genetic variants used and assess weak instrument bias for potential MR studies. The proportion of variance explained was determined using the following formula:[179]

$$R^2 = \sum_{i=1}^{n} \frac{2 \times \beta_i^2 \times MAF_{SNPi}(1 - MAF_{SNPi})}{\left(2 \times \beta_i^2 \times MAF_{SNPi}(1 - MAF_{SNPi})\right) + SE_i^2 \times 2 \times N \times MAF_{SNPi}(1 - MAF_{SNPi})}$$

The total variance explained by the score is a sum of the individual variances explained by the SNPs within the score. β_i represents the per-allele effect of the i^{th} SNP on the outcome in the original GWAS, MAF_{SNPi} represents the minor allele frequency for the i^{th} SNP, N is the number of participants in the original GWAS analysis for this variant, and SE_i is the standard error of β_i. The percentage of variance explained is then the variance explained multiplied by 100.

2.7.3. Estimation of F-statistic

Risk of weak-instrument bias for each variant was also assessed by calculating F-statistics.[111] Where variants were selected from summary data the F-statistic was determined as β^2 / SE^2 where β represents the effect per-allele effect of the variant on the outcome in the original GWAS and SE represents the standard error of β.[180] Weak instrument bias is commonly considered to be relevant when F<10.

2.7.4. Genetic score generation

For each measure, genetic scores were developed from selected variants. Variants were harmonised to the UKB dataset and weighted based on the per-allele beta values from the original GWAS analysis and summed for each UKB participant.

Associations between the genetic scores and continuous measures were estimated using linear regression and associations between genetic scores and risk of disease status by using logistic regression. Analyses involving genetic scores were adjusted for sex, age, age^2, genotype array, and a set of seven

principal components of ancestry developed from UKB participants of white British ancestry.

2.7.5. External replication datasets

Replication analyses of associations with AF were undertaken using publicly available summary data from the AFGen and FinnGen consortia GWAS.[167,173] In AFGen, estimates were available for the per-allele log odds of AF for ~11,800,000 genetic variants from 17,931 AF cases and 115,142 controls of primarily European ancestry.[167] FinnGen data came from release 7, estimates were available for the per-allele log odds of AF for ~16,600,000 genetic variants from 34,748 AF cases and 156,457 controls of Finnish decent.[175]

2.7.6. Mendelian randomization sensitivity analyses

MR studies are sensitive to a number of IV assumptions that underpin the observed causal inferences.[102,181] In particular, variables used in MR analyses can affect a number of independent biological pathways associated with the outcome leading to pleiotropy.[182,183] A number of additional analyses were undertaken to explore potential pleiotropy. The weighted median approach allows up to 50% of variants to be invalid IVs.[184] The weighted mode approach allows the majority of variants to be invalid as long as the most common effect estimate is a consistent estimate of the true causal effect.[185] MR–Egger is an approach where all variants may be invalid, provided there is an independent distribution of variant pleiotropic and risk factor effects.[186] The Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) method

evaluates horizontal pleiotropy, determines potential outlier variants, and determines a corrected association following the removal of outliers.[187]

Generation of inverse variance weighted, weighted median, and MR-Egger estimates were undertaken using the R package 'MendelianRandomization' (https://CRAN.R-project.org/package=MendelianRandomization).[188] Weighted mode estimates were obtained using the 'MBE' R package (https://github.com/MRCIEU/mbe).[185] The 'MRPRESSO' R package was used to exclude outlying genetic variants (https://github.com/rondolab/MR-PRESSO).[187]

2.7.6.1. Multivariable Mendelian randomization

Multivariable MR (MVMR) was used to assess the independent relevance of anthropometric measures. Genetic scores for individual anthropometric traits were taken and the variant lists combined. Any variant appearing in more than one anthropometric score was removed. The combined variant lists were re-clumped as outlined above. Associations between variants and each anthropometric trait were identified from the original GWAS summary data. Where exact variant matches were not available in all GWAS, proxy variants were identified using the R package 'LDlinkR' (https://CRAN.R-project.org/package=LDlinkR) and the 1000 Genomes reference dataset.[189] A minimum r^2 threshold of ≥0.6 was established for identified proxies. MVMR analysis was undertaken using the R package 'MendelianRandomization' (https://CRAN.R-project.org/package=MendelianRandomization).[188]

2.7.6.2. Meta-analysis of summary level results from multiple datasets

Where appropriate meta-analysis of summary-level results were undertaken. ORs were estimated using the inverse variance weighted method for each

dataset. Meta-analysis was undertaken using the R package 'metafor' (v2.0.0 - http://www.metafor-project.org/doku.php) using the fixed effects method.[190]

2.8. Statistical analyses

Statistical analyses for this thesis were undertaken using SAS (Version 9.3) and R (Version 4.2.2). In addition to the genetic score analysis outlined above, the statistical methodology differs substantially between chapters. As a result, specific statistical analyses are outlined in the chapter specific methods.

Chapter 3 - Systematic Review of anthropometric measures and risk of atrial fibrillation

3.1. Abstract

3.1.1. Introduction

The association between body mass index (BMI) and risk of atrial fibrillation (AF) has been repeatedly demonstrated. However, the evidence of associations between other anthropometric measures and risk of AF is less clear.

3.1.2. Methods

A comprehensive search was undertaken in OVID Medline, PubMed Medline, and OVID Embase from inception through to 15th July 2022. Papers were included if they detailed observational associations between anthropometric measures and risk of incident AF or the association between genetically predicted anthropometric measures and risk of AF.

3.1.3. Results

A total of 168 papers were included in this systematic review covering 18 different anthropometric phenotypes. Evidence from observational analyses identified positive associations with risk of incident AF for all commonly used adult anthropometric measures. However, considerable heterogeneity between studies means overall effect sizes for most traits remain uncertain. There has

been limited exploration of ectopic adipose tissue deposits including abdominal visceral adipose tissue and pericardial adipose tissue with inconsistent findings between the cohorts examined. The evidence of associations for anthropometric measures independent of related phenotypes was generally scant and, in places, contradictory. With the exception of BMI, there has been little exploration of differences in association between anthropometric measures and risk of AF by sex. Causal associations have been established in multiple studies for BMI. However, the independent causal relevance for other anthropometric phenotypes have not been well explored.

3.1.4. Conclusions

Positive associations have been identified between common anthropometric measures and the risk of AF. However, questions remain regarding the overall strength and independence of associations between such measures and risk of AF, the potential differences between men and women, the role of ectopic fat deposits, and the causal relevance of anthropometric measures on risk of AF.

3.2. Introduction

Obesity is a significant public health concern with approximately 30% of adults in the Western world either overweight or obese.[28] AF has been positively associated with a range of different anthropometric measures,[72] including BMI, as a general measure of body size.[191]

Measures of body size/shape are closely correlated with one another.[56,57] As such, while associations with a range of measures of body size have been reported, without adjustment for correlated anthropometric measures, the independent relevance of these associations is unclear. To date, there has been no systematic approach to consider the independent relevance of these measures and their associations with AF.

Given established physiological and anthropometric differences between men and women,[46] it is intriguing the that risk of AF is higher in men than women.[4,9] However, while individual studies have suggested potential differences in the strength of associations between anthropometric measures and risk of AF in men and women,[73,74] this has not been consistently demonstrated.[75,76] As such, a systematic assessment is required to determine the evidence base for differences in associations between measures of body size and risk of AF by sex.

There is a clear potential for reverse causation when considering observational associations. This may be particularly true when considering chronic conditions such as obesity and AF. However, use of genetic variants as IVs in MR analyses allows this to be avoided.[107] The availability of summary data for both anthropometric measures and AF has allowed a number of analyses to suggest potential causal associations between anthropometric measures and risk of

AF.[35,103,169] However, a systematic review of these studies has not previously been undertaken.

While previous meta-analyses have explored the evidence for associations between some anthropometric measures and risk of AF, they have been limited to only a few measures of body size, have included papers exploring associations with prevalent AF, and do not include data from more contemporary reports.[65,72]

In light of the above, this systematic review had a number of specific aims. (1) To establish the evidence of associations between anthropometric measures and incident AF. (2) To explore the presence of independent associations between anthropometric measures and risk of AF. (3) To review prior work examining differences in associations between anthropometric measures and risk of AF by sex. (4) To explore the evidence of potential causal associations between anthropometric measures and risk of AF using MR analyses.

3.3. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[192]

3.3.1. Search Strategy

A comprehensive search was undertaken in OVID Medline, PubMed Medline, and OVID Embase from inception through to 15th July 2022. Included references from recent meta-analyses examining anthropometric measures and risk of AF were checked and the search strategy refined to ensure that all relevant studies were identified.[65,72] Where appropriate Medical Subject Headings (MeSH), explode function, and wild-card values were used. The final search strategies used are available in Appendix A (**Systematic review search strategy**). Bibliographic records were retrieved as comma-separated values files. Records from different databases were combined and de-duplicated using SAS (Version 9.4).

3.3.2. Study selection and critical appraisal

Duplicate articles were determined through automated comparison of article titles, publication dates, and author details. A single copy of duplicate articles was retained. Studies were screened for eligibility by initially examining the title and abstract. Relevant articles were extracted for assessment of the full text. When results from a single cohort were reported in multiple studies, all studies were included and references was made to cohort overlap in the results tables. Study selection and appraisal was undertaken by a single individual (C.F. Camm).

3.3.2.1. Inclusion criteria

The following inclusion criteria were used to select articles for this systematic review

1. Outcome was the development of incident AF and participants with prevalent AF were excluded

   AND

2. Assessment of associations between one or more anthropometric measures and risk of incident AF

   OR

3. The study was an MR analysis of the association between anthropometric measures and risk of AF.

3.3.2.2. Exclusion criteria

The following criteria were used to exclude search results from the systematic review:

1. Analyses examining post-operative AF as the outcome
2. Articles not presenting new data: Review articles, guidelines, comments, editorials etc.
3. Non-human studies: animal studies, or in vivo/in silico studies
4. Case reports
5. Paediatric population (<18 years old)
6. Non-English language
7. Full text not available
8. Analyses only examining anthropometric variables as part of a composite measure (e.g. in a risk score)

3.3.3. Data collection and analysis

Study details including cohort name, baseline characteristics, inclusion criteria, follow-up time, model adjustments, and results were extracted. For anthropometric measures with multiple methods for assessment (for example LM, FM, and PAT), the method of assessment was extracted.

Where studies reported the results of multiple statistical models, the model defined by the authors as the primary model was extracted. If additional adjustments for other anthropometric variables were undertaken, these were also extracted. Where studies analysed sex-specific associations, results were extracted separately for men and women. Results are displayed as HR (95%CI) unless otherwise specified. Where studies considered anthropometric traits as continuous and categorical variables, data on both were extracted. Studies examining anthropometric traits as categorical variables were examined for evidence of non-linear relationships between anthropometric traits and risk of AF.

Where appropriate, results have been meta-analysed using a fixed-effect model. RRs were re-scaled where appropriate Meta-analysis was undertaken using the R package 'metafor' (v2.0.0 - http://www.metafor-project.org/doku.php).[190]

3.4. Results

3.4.1. Manuscripts identified

A total of 17,659 manuscripts were identified by the search strategy (**Figure 3.1**). Of these, 3,124 were considered duplicates (due to matching titles, publication dates, and author details) and were removed leaving 14,535 for screening. Following screening 13,296 articles did not meet inclusion criteria and were excluded based on assessment of title and abstract; 1,239 full-text articles were further assessed for eligibility. Of these, 168 studies, assessing the association between 18 different anthropometric measures and risk of AF, were considered to have met the inclusion criteria for the systematic review. Of the 168 included studies, 16 included MR analyses examining the association between genetically predicted anthropometric measures and risk of AF (**Appendix Table B.1**).

Subsequent results sections have been organised by anthropometric measure and ordered based on the amount of evidence available for each measure (from most to least). Results tables are displayed in Appendix B (**Systematic review results tables**). Due to space restrictions a number of phenotypes with limited available information are presented in Appendix C (**Additional phenotypes from the systematic review**). A paper published on subsequent research presented in this thesis was included in the search results of this systematic review. This has been presented in the results tables but is not discussed in detail within the prose of this review.

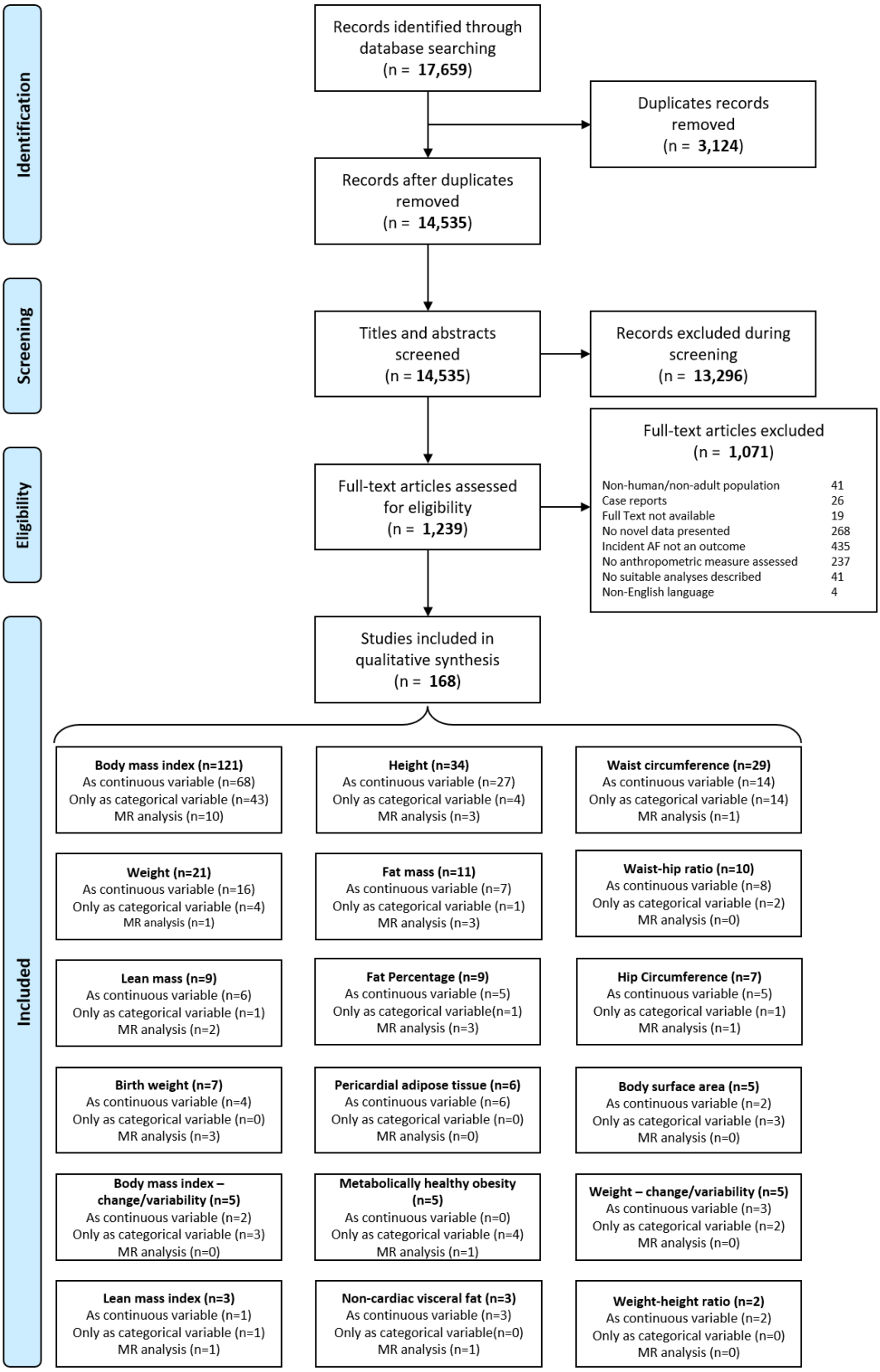


Figure 3.1: Systematic review PRISMA flowchart.
The flowchart outlines the manuscripts identified by the systematic review search strategy. AF – atrial fibrillation, MR – Mendelian randomization

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3.4.2. Body mass index and risk of atrial fibrillation

3.4.2.1. Results of the current search

The effect of BMI against the risk of incident AF was examined in 111 studies. Of these, 10 examined genetically predicted BMI and risk of AF. Studies examining BMI as a continuous variable (n=68) represent 52 separate datasets (**Appendix Table B.2**, 135,128 unique AF cases).

3.4.2.2. Effect of body mass index on risk of atrial fibrillation

Higher BMI has repeatedly been associated with higher risk of AF. Of the 52 datasets identified examining BMI as a continuous variable, 46 have reported a positive association with BMI (**Appendix Table B.3**). Of particular note, in a large study on male Swedish military conscripts (AF cases=23,600), Crump *et al.* demonstrated a ~30% higher risk of AF per 5 kg/m^2 higher BMI (HR 1.31, 1.28 to 1.34).[58] These findings have been confirmed in mixed sex prospective cohorts.[59,62,95,193]

When results are meta-anlaysed, a 5 kg/m^2 greater BMI was associated with a 28% higher risk of AF (RR 1.28, 1.24 to 1.32, **Figure 3.2**). However, there is heterogeneity in the strength of association between BMI and risk of AF (I^2 92%). This is likely explained by differences in populations and model adjustments (**Appendix Table B.3**). The only study demonstrating a negative association between BMI and risk of AF was a small cohort of patients identified after myocardial infarction; such a patient population is distinctly different from a general population at risk of AF.[194]

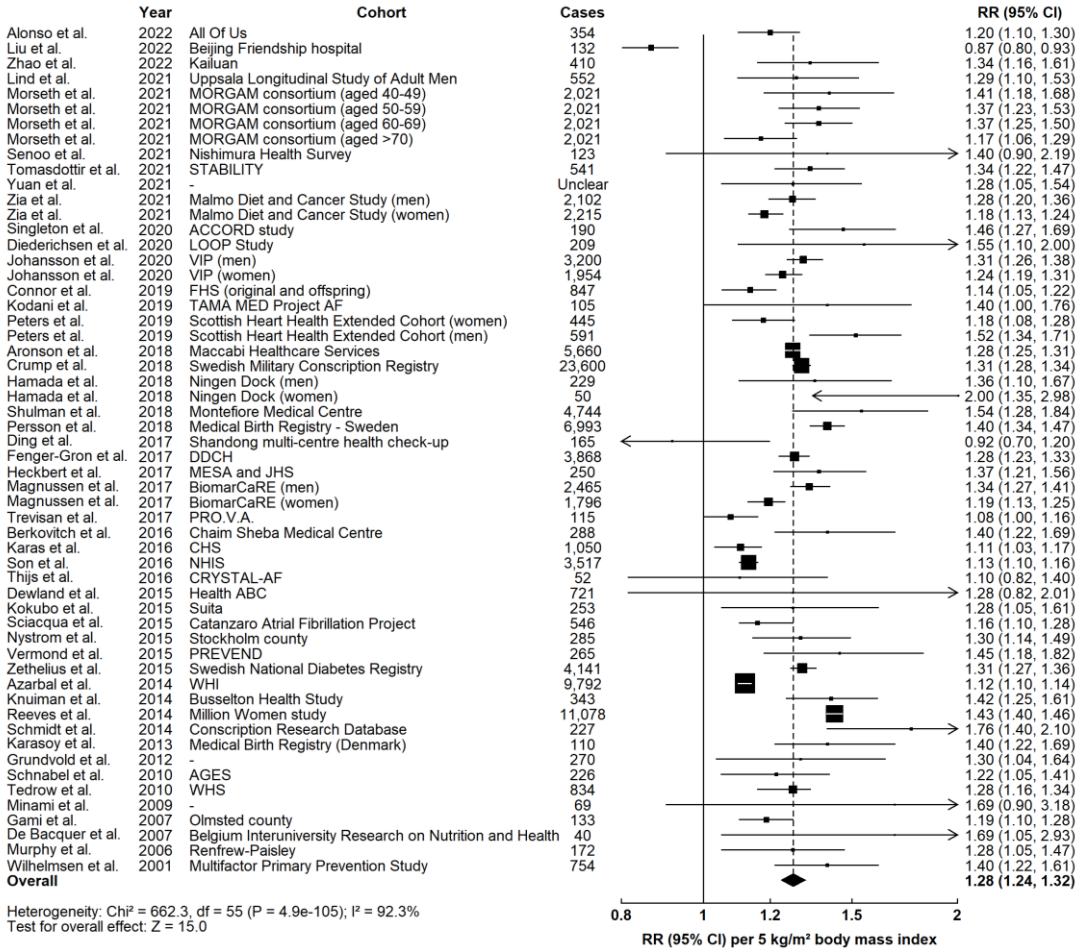


Figure 3.2: Forest plot of the effects of body mass index (per 5 kg/m²) on risk of atrial fibrillation.

Data included from 51 datasets identified in this systematic review. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. The MORGAM consortium contains data from the DAN-MONICA, FINRISK, Moli-sani, MONICA, and Tromso cohorts but did not report associations separately for each cohort. Where associations between BMI and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. Datasets have been excluded from display if the scale units have not been described (n=1). Associations have been re-scaled to 5 kg/m^2 to allow comparison between studies. ***ACCORD*** *- Action to Control Cardiovascular Risk in Diabetes,* ***AF*** *– atrial fibrillation,* ***AGES*** *– age, gene/environment susceptibility cohort,* ***CHS*** *– Cardiovascular Health Study,* ***CI*** *– confidence interval,* ***CRYSTAL-AF*** *- Cryptogenic Stroke and Underlying Atrial Fibrillation,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***FHS*** *– Framingham Heart Study,* ***Health ABC*** *- Health, Aging, and Body Composition,* ***JHS*** *– Jackson Heart Study,* ***LOOP*** *- Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals,* ***MESA*** *– multi-ethnic study of atherosclerosis,* ***NHIS*** *- National Health Insurance Service,* ***PREVEND*** *- Prevention of Renal and Vascular End-stage Disease,* ***PRO.V.A.*** *- Progetto Veneto Anziani,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHI*** *– Women's' Health Initiative,* ***WHS*** *- Women's Health Study.*

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3.4.2.3. Effect of body mass index when adjusted for other anthropometric measures

There has been limited assessment of the independent role of BMI on the risk of AF. In the Danish Diet Cancer and Health (DDCH) study (AF cases=3,868), Fenger-Grøn *et al.* demonstrated that the strong positive association between BMI and risk of AF (HR 1.22, 1.18 to 1.26, per SD) was no longer present following adjustment for LM (HR 1.01, 0.98 to 1.05, per SD).[66] While data from the same study suggests that the effect of BMI remains following adjustment for WC, this is not supported by other cohorts,[195]

Results from the DDCH study suggested that BMI was negatively associated with risk of AF after adjustment for weight (HR 0.77, 0.72 to 0.82, per SD).[66] By contrast, a positive relationship observed in a cohort of Swedish military conscripts (HR 1.28, 1.34 to 1.22, per 5 kg/m^2) remained following adjustment for weight (HR 1.10, 1.05 to 1.16, per 5 kg/m^2).[58]

3.4.2.4. Exploration of a non-linear relationship between body mass index and risk of atrial fibrillation

Seventy-three studies have reported on the effect of BMI as a categorical variable on the risk of incident AF (**Appendix Table B.4**). In the largest analysis, Kim *et al*. (AF cases=196,136) demonstrated a positive relationship between higher BMI and risk of AF in a Korean cohort. However, those with a BMI <18.5 kg/m^2 were at a higher risk of AF than those with a BMI of 18.5-23 kg/m^2 (HR 1.05, 1.03 to 1.08).[70] This is supported by data from a Japanese cohort.[196], Cardiovascular Health Study (CHS),[67] and DDCH.[191] In contrast, Neefs *et al*. (AF cases=2,510) showed a clear linear relationship between BMI and risk of AF.[197] This linear

relationship is similarly seen in analyses of the Clinical Practice Research Datalink cohort,[198] the Health, Aging, and Body Composition (Health ABC) cohort,[68] and others.[199-201] As a result, the underlying shape of the relationship between BMI and risk of AF remains unclear.

3.4.2.5. Effect of body mass index on risk of atrial fibrillation by sex

The assessment of differing effects of BMI in men and women has been explored in nine cohorts;[73-76,202-208] with several other single-sex cohorts having examined the association between BMI and risk of AF (**Figure 3.3**). However, each of these studies has been relatively small. The largest study, performed by Johansson *et al*., containing 5,154 AF cases (men 3,200, women 1,954),[206] demonstrated no clear difference in the effect of higher BMI on risk of AF in men (HR 1.23, 1.19 to 1.28) and women (HR 1.22, 1.17 to 1.28) per SD (men 3.8 kg/m^2, women 4.6 kg/m^2, no interaction p-value provided). A lack of any difference between sexes has been supported by other studies.[75,76,202-204]

By contrast, some studies have suggested larger effects in men. In the Scottish Heart Health Extended cohort (AF cases, men=491, women=445), the effect of BMI on risk of AF, per SD, was greater in men (HR 1.36, 1.24 to 1.49) than in women (HR 1.17, 1.08 to 1.27) with a women-to-men relative HR of 0.86 (0.77 to 0.97).[73] This is supported by the BiomarCaRE cohort (AF cases, men=2,465, women=1,796) which demonstrated a greater association between BMI and risk of AF in men (HR 1.31, 1.25 to 1.38, per SD) than women (HR 1.18, 1.12 to 1.23), p-interaction 0.001.[74] This is supported by data from the Busselton Health Study.[208] The reason why differences in strength of association between men and women were identified in these two cohorts but not others is not clear.

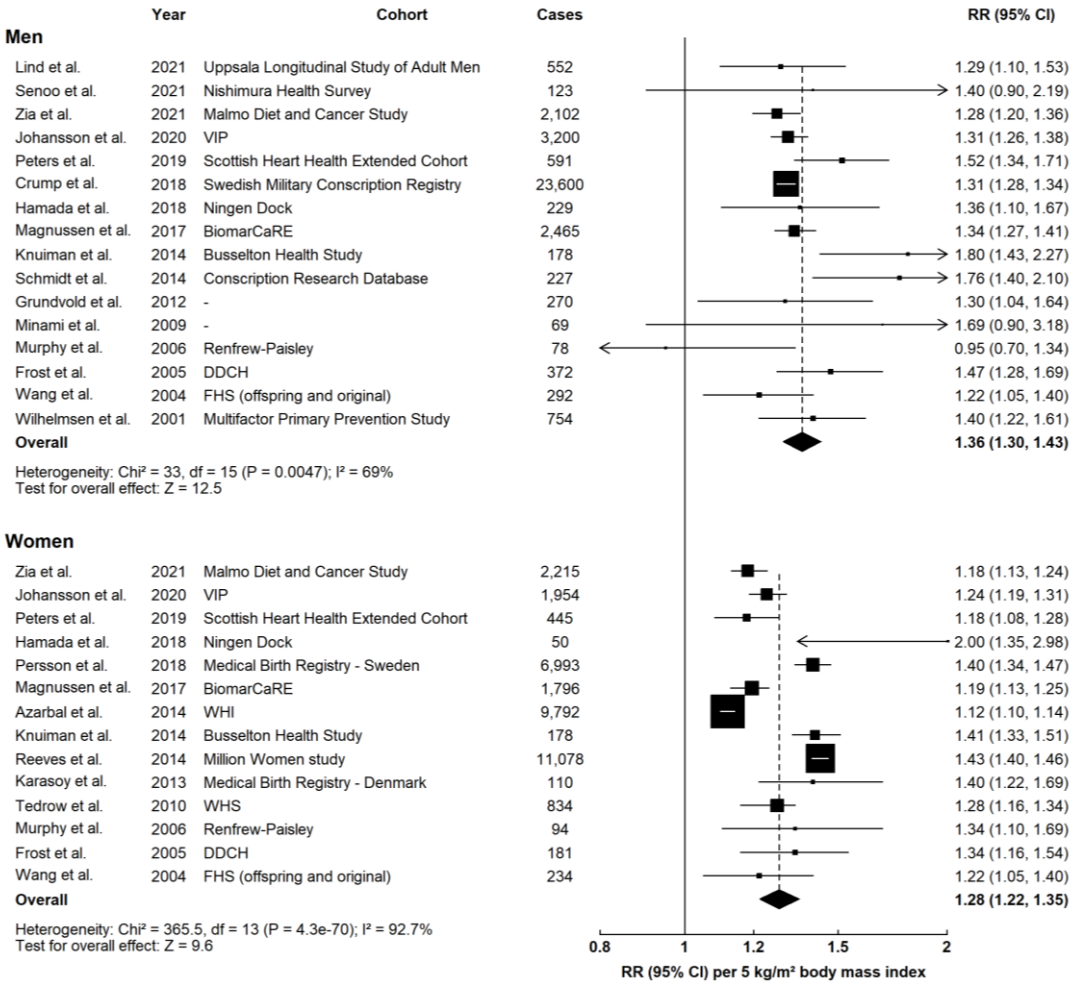


Figure 3.3: Forest plot of the effects of body mass index (per 5 kg/m²) on risk of atrial fibrillation separately in men and women.

Data included from nine datasets examining men and women separately, seven additional male-only datasets, and five female-only datasets were identified in this systematic review. Studies are ordered by year of publication. Where associations between body mass index and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases has been included. Datasets have been excluded from display if continuous effects across the whole range of body mass index values are not described (n=1). Associations have been re-scaled to 5 kg/m^2 to allow comparison between studies. ***AF*** *– atrial fibrillation,* ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***FHS*** *– Framingham Heart Study,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHI*** *– Women's' Health Initiative,* ***WHS*** *- Women's Health Study.*

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2 **3.4.2.6.Genetically predicted body mass index and risk of atrial fibrillation**

3 Ten studies have reported MR analyses examining genetically predicted BMI and

4 risk of AF (**Appendix Table B.1**). These have consistently demonstrated a

5 positive association between higher BMI and risk of AF. This association was

initially demonstrated by Chatterjee *et al*. who showed a 6% higher risk of AF per 1 kg/m^2 higher genetically predicted BMI (OR 1.06, 1.02 to 1.09).[108] This is now supported by data from a range of cohorts.[109,209] Wang *et al*. have recently demonstrated, using MVMR, that genetically predicted BMI seems to be independently associated with risk of AF when included in a model with genetically predicted WC, height, and HC.[110]

3.4.2.7. Body mass index evidence summary

BMI has repeatedly been demonstrated as being positively associated with risk of AF. However, the strength of association remains less clear. While a meta-analysis of available results suggests that a 5 kg/m^2 greater BMI is associated with ~25% higher risk of AF, cohorts including at least 200 AF cases demonstrate a 10-75% higher risk of AF per 5 kg/m^2 greater BMI. MR analyses suggest a potentially causal relationship between BMI and risk of AF. The effect of BMI on risk of AF has been explored in men and women in several cohorts; however, results between different studies do not provide a consistent answer on whether the effect of BMI on risk of AF is the same in men and women. Additionally, the independent effect of BMI on risk of AF remains unclear with limited studies undertaking adjustment for other anthropometric traits and conflicting results.

3.4.3. Height and risk of atrial fibrillation

3.4.3.1. Results of the current search

Thirty-one studies have examined the effect of height on the risk of incident AF. Of these, 27 studies, using data from 24 datasets, considered height as a

continuous variable (**Appendix Table B.5**). A total of 71,737 unique AF cases have been assessed with relation to height in a continuous manner.

3.4.3.2. Effect of height on risk of atrial fibrillation

Of the 24 datasets reporting the effect of height on risk of incident AF, 20 have shown a significant positive association with the remainder being directionally consistent (**Appendix Table B.6**). Of note, Lai *et al*. explored the effect of height on the UKB population (AF cases=15,328) and showed that 10 cm greater height was associated with approximately ~45% higher risk of AF (HR 1.46, 1.42 to 1.50).[210] These findings are supported by results from other datasets.[206,207,211,212]

When results are meta-analysed, a 10 cm greater height was associated with a 40% higher risk of AF (RR 1.40, 1.34 to 1.46, **Figure 3.4).** However, there is heterogeneity in the effect estimates between studies (I^2 88%). As with BMI, there are important differences in population characteristics and model adjustments that likely explain this finding (**Appendix Table B.6**).

3.4.3.3. Effect of height when adjusted for other anthropometric measures

The effect of height, independent of weight or BMI, is supported by data from a number of cohorts,[206,208,211,213] In the DDCH cohort, the addition of weight as a further adjustment to their analysis approximately halved the effect of height on the risk of AF from 29% (24 to 34%) to 16% (11 to 21%) per SD.[191] Also in DDCH, the positive association with risk of AF (HR 1.29, 1.24 to 1.33, per SD) was attenuated when adjusted for LM (HR 1.04, 1.00 to 1.08). In contrast, adjustment for height did not meaningfully impact the association between LM and risk of AF in this cohort suggesting that height may be a proxy for LM rather than acting as an independent risk factor.

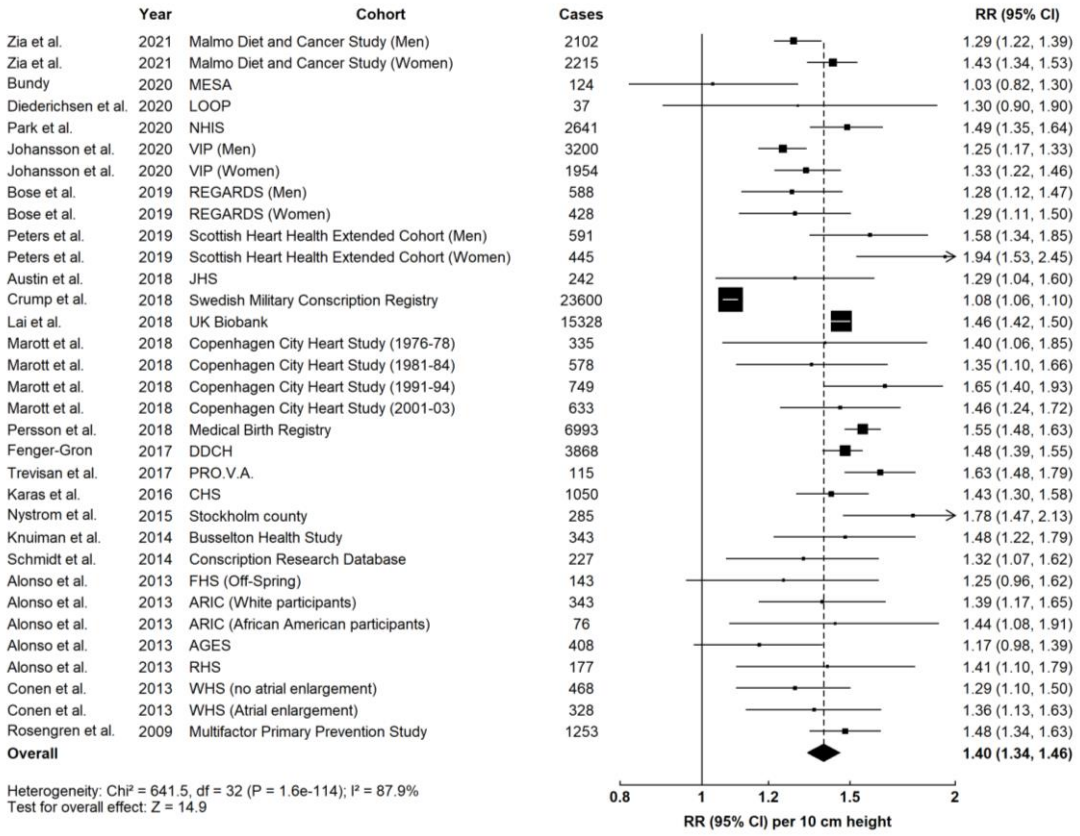


Figure 3.4: Forest plot of the effects of height (per 10 cm) on risk of atrial fibrillation.

Data included from 24 datasets identified in this systematic review. Studies are ordered by year of publication. Where associations between height and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. Associations have been re-scaled to 10 cm to allow comparison between studies. ***AF*** *– atrial fibrillation,* ***AGES*** *– age, gene/environment susceptibility cohort,* ***ARIC*** *– atherosclerosis risk in communities cohort,* ***CHS*** *– Cardiovascular Health Study,* ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***FHS*** *– Framingham Heart Study,* ***JHS*** *– Jackson Heart Study,* ***LOOP*** *- Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals,* ***MESA*** *– multi-ethnic study of atherosclerosis,* ***NHIS*** *- National Health Insurance Service,* ***PREVEND*** *- Prevention of Renal and Vascular End-stage Disease,* ***PRO.V.A.*** *- Progetto Veneto Anziani,* ***REGARDS*** *- REasons for Geographic And Racial Differences in Stroke Study,* ***RHS*** *– Rotterdam Heart Study,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHS*** *- Women's Health Study.*

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2 **3.4.3.4. Exploration of a non-linear relationship between height and risk of**

3 **atrial fibrillation**

4 Height has been considered as a categorical variable in 13 studies (**Appendix**

5 **Table B.7**) with 12 exploring height in at least three groups. A strong positive

relationship has been demonstrated in all studies with no evidence of a non-linear relationship between height and risk of AF. A linear relationship is supported by spline regression analysis using data from DDCH.[191]

3.4.3.5. Effect of height on risk of atrial fibrillation by sex

Height, as a continuous variable, has been examined separately in men and women in five small cohorts;[73,206,207,213,214] and five single-sex cohorts (**Figure 3.5**). Data from the Malmo diet and Cancer Study shows that there are similar effects in men (HR 1.19, 1.14 to 1.24, AF cases=2,102) and women (HR 1.24, 1.19 to 1.29, AF cases=2,215) per SD.[207] This is supported by data from other cohorts.[73,206,213,214]

3.4.3.6.Genetically predicted height and risk of atrial fibrillation

Three studies have reported MR analyses examining genetically predicted height and risk of AF (**Appendix Table B.1**). All three demonstrated a positive association with risk of AF.[110,215,216] Additionally, Wang *et al*. demonstrated that genetically predicted height appears to be independently associated with risk of AF when included in a model with genetically predicted WC, BMI, and HC.[110]

3.4.3.7. Height evidence summary

A positive association has been consistently demonstrated between height and risk of AF. However, the strength of association is less clear. Meta-analysis of the identified studies demonstrate that 10 cm greater height is associated with a 40% greater risk of AF; however, cohorts including at least 200 AF cases demonstrate a 10-95% greater risk of AF per 10 cm greater height. A potentially causal relationship between height and risk of AF is suggested by MR analyses. Despite exploration in a number of studies, there is no evidence of sex-based

differences in the effect of height on risk of AF. The effect of height on risk of AF appears independent of weight and BMI. However, attenuation following adjustment for LM may suggest that the effect of height on risk of AF is principally due to height acting as a proxy for LM.

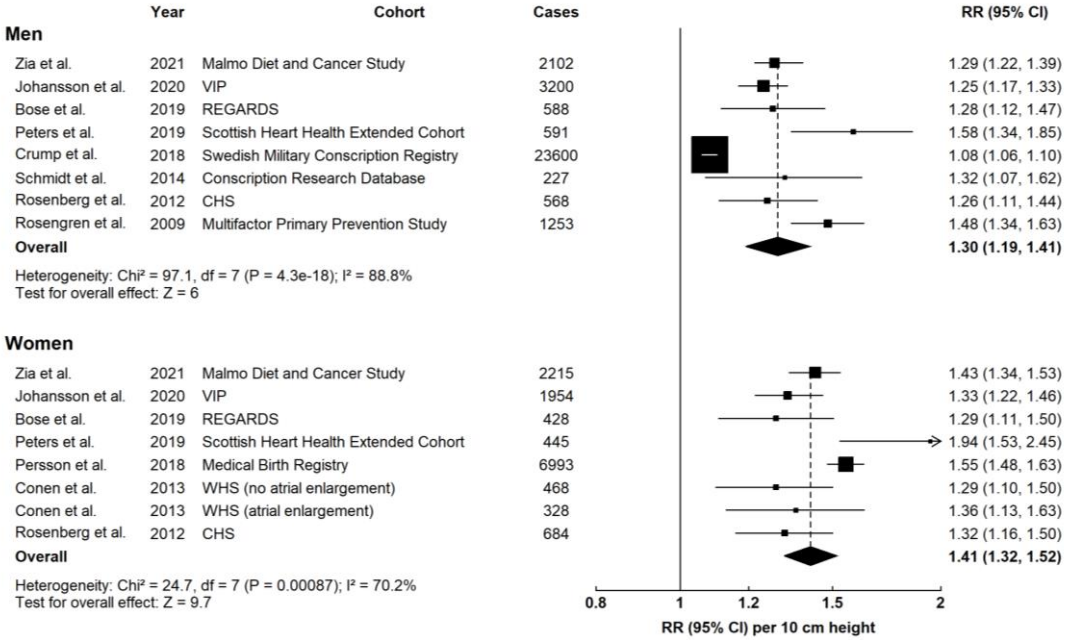


Figure 3.5: Forest plot of the effects of height (per 10 cm) on risk of atrial fibrillation separately in men and women.
Data included from five datasets examining men and women separately, three additional male-only datasets, and two female-only datasets identified in this systematic review. Studies are ordered by year of publication. Where associations between height and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases has been included. Associations have been re-scaled to 10 cm to allow comparison between studies. ***AF*** *– atrial fibrillation,* ***CHS*** *– Cardiovascular Health Study,* ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer, and Health cohort,* ***REGARDS*** *- REasons for Geographic And Racial Differences in Stroke Study,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHS*** *- Women's Health Study.*

3.4.4. Waist circumference and risk of atrial fibrillation

3.4.4.1. Results of the current search

Twenty-eight studies report the effect of WC on the risk of incident AF, of which 14 examined WC as a continuous variable (**Appendix Table B.8**, unique AF cases=38,786). These studies represent 13 separate datasets.

3.4.4.2. Effect of waist circumference on risk of atrial fibrillation

Of the 14 studies identified, 13 demonstrated a positive association between WC and AF (**Appendix Table B.9**). Of these, Baek *et al*. demonstrated ~20% greater risk of AF per 10 cm greater WC (HR 1.19, 1.12 to 1.28).[195] This finding of a strong positive association is generally supported by those of other prospective cohorts.[67,68,195,204,217] A meta-analysis of the identified studies demonstrates that 10 cm greater waist circumference is associated with ~25% greater risk of AF (RR 1.25, 1.13 to 1.31). Differences in sample demographics, model adjustments, and the inclusion of a number of small studies may underlie the identified heterogeneity between effect estimates which caution interpretation (I^2 93%, **Figure 3.6**).

3.4.4.3. Effect of waist circumference when adjusted for other anthropometric measures

Three studies have examined the effect of WC on risk of AF following adjustment for a measure of general adiposity or LM. Knuiman *et al.* (AF cases=343) demonstrated that a strongly positive association between WC and risk of AF (HR 1.37, 1.21 to 1.55, per SD) was removed when further adjusted for BMI (HR 0.97, 0.72 to 1.31 per SD).[208] This is not supported by the data from Fenger-Grøn *et al.* (AF cases=3,868) which showed that the association between WC and risk of AF (HR 1.24, 1.20 to 1.28, per SD) remained following adjustment for BMI (HR 1.18, 1.11 to 1.24, per SD).[66] However, this group did demonstrate that the effect of WC was fully attenuated following adjustment for LM (HR 1.02, 0.98 to 1.04, per SD). In a Korean cohort (AF cases=3,443) WC was strongly associated with risk of AF when adjusted for BMI (HR 1.18, 1.11 to 1.26, per SD).[195] In summary,

it remains unclear whether central adiposity, as proxied by WC, is an independent risk factor for AF.

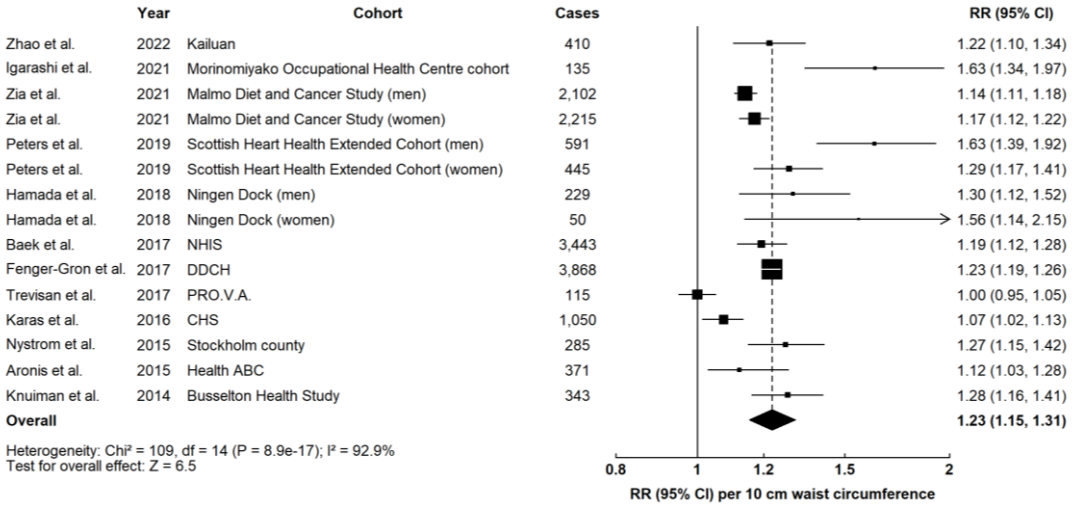


Figure 3.6: Forest plot of the effects of waist circumference (per 10 cm) on risk of atrial fibrillation.
Data included from 12 datasets identified in this systematic review. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. Where associations between waist circumference and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. One study has been excluded from display as it is the result of later work in this thesis. Associations have been re-scaled to 10 cm to allow comparison between studies. ***CHS*** *– Cardiovascular Health Study,* ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***FHS*** *– Framingham Heart Study,* ***Health ABC*** *- Health, Aging, and Body Composition,* ***MESA*** *– multi-ethnic study of atherosclerosis,* ***NHIS*** *- National Health Insurance Service,* ***PRO.V.A.*** *- Progetto Veneto Anziani,* ***RR*** *- risk ratio.*

3.4.4.4. Exploration of a non-linear relationship between waist circumference and risk of atrial fibrillation

Twenty studies have examined the effect of WC as a categorical variable on the risk of incident AF (**Appendix Table B.10**). In the largest analysis, Kim *et al*. used the National Health Insurance Service (NHIS) cohort (AF cases=196,136) and divided participants into five groups by WC.[70] Higher WC was associated with greater risk of AF and there was no evidence of a non-linear relationship. A linear relationship is supported by data from several other cohorts.[68,191,207]

3.4.4.5. Effect of waist circumference on risk of atrial fibrillation by sex

The effect of WC on the risk of AF has only been presented separately for men and women in three cohorts (AF cases=5,632, **Figure 3.7**).[73,204,207] None has shown a difference in effect size between sexes. In the largest study, Zia *et al*. (AF cases=4,317) showed that higher WC was associated with an 18% greater risk of AF per SD in both men (HR 1.18, 1.14 to 1.23) and women (HR 1.18, 1.13 to 1.23, no interaction p-value was provided).[207] This is supported by the findings in the other studies identified.[73,204]

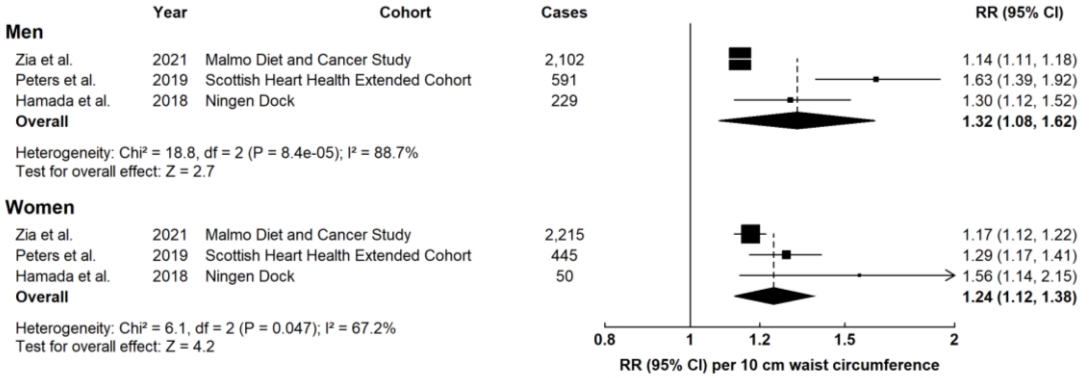


Figure 3.7: Forest plot of the effects of waist circumference (per 10 cm) on risk of* atrial fibrillation *separately in men and women.
Data included from three datasets examining men and women separately identified in this systematic review. Studies are ordered by year of publication. Associations have been re-scaled to 10 cm to allow comparison between studies. ***CI*** *– confidence interval,* ***RR*** *- risk ratio.*

3.4.4.6. Genetically predicted waist circumference and risk of atrial fibrillation

One study has examined the association between genetically predicted WC and risk of AF (**Appendix Table B.1**). Wang *et al*. showed a strong positive association between genetically predicted WC and risk of AF (OR 1.54, 1.43 to 1.65 per SD).[110] However, once adjusted for BMI, height, and HC, this association was completely attenuated (OR 0.93, 0.73 to 1.18 per SD). However,

the confidence intervals in this analysis remain wide and cannot exclude a residual effect of genetically predicted WC on risk of AF.

3.4.4.7. Waist circumference evidence summary

WC has been demonstrated to be positively associated with risk of AF. MR analyses have suggested a potential causal role for WC on risk of AF. In cohorts including at least 200 AF cases, 10 cm greater WC was associated with a ~10-65% greater risk of AF. There is no evidence that the effect of WC on risk of AF is different in men and women, albeit having only been explored in a small number of cohorts (n=3). However, the independent effect of WC on risk of AF remains unclear with conflicting results when adjusted for BMI in observational analyses. A single MR analysis adjusting for other genetically predicted anthropometric measures resulted in a null result, albeit with a large margin of error.

3.4.5. Weight and risk of atrial fibrillation

3.4.5.1. Results of the current search

Twenty-one publications reported associations between weight and risk of incident AF (**Appendix Table B.11**). Of these, 16 publications, reporting data from 17 prospective cohorts, treated weight as a continuous variable (unique AF cases=77,143).

3.4.5.2. Effect of weight on risk of atrial fibrillation

Positive associations with weight were found in all of the 16 publications identified (**Appendix Table B.12**). Of particular note is the analysis by Crump *et al*. of the Swedish military conscripts cohort (AF cases=23,600) which showed a 27%

higher risk of incident AF for each 10 kg higher weight (25 to 28%).[58] Similar effect sizes have been seen in other cohorts.[66,73,214,217,218] However, the association in CHS was weaker (HR 1.11, 1.05 to 1.17, per 10 kg, AF cases=1,050),[67] and similar to the strength of association seen in a number of other cohorts.[67,219,220] When meta-analysed, the identified studies demonstrate that 10 kg greater weight is associated with ~20% greater risk of AF (RR 1.21, 1.18 to 1.24). The heterogeneity of effect estimates (I^2 90%, **Figure 3.8**) is similar to other anthropometric measures and are underpinned by similar reasons.

3.4.5.3. Effect of weight when adjusted for other anthropometric measures

Analyses from a number of cohorts adjusted for height as part of their main analysis and continued to show a strong positive association between weight and risk of AF.[58,73,191,218,221] Analysis of the DDCH cohort showed the effect of higher weight on risk of AF (HR 1.33, 1.29 to 1.36, per SD) was removed when adjusted for LM (HR 1.05, 0.99 to 1.11).[66] Meaningful attenuation was not seen when adjusted for FM in the same cohort.

3.4.5.4. Exploration of a non-linear relationship between weight and risk of atrial fibrillation

The effect of weight as a categorical variable has been reported in seven cohorts (**Appendix Table B.13**).[58,197,206,207,222-224] All demonstrate strong positive associations between weight and AF. In those studies where participants were divided into ≥three groups, there was a step-wise progression in AF risk across groups with no evidence to suggest a non-linear relationship.[206,207,222] A linear relationship between weight and risk of AF is supported by data from DDCH.[191]

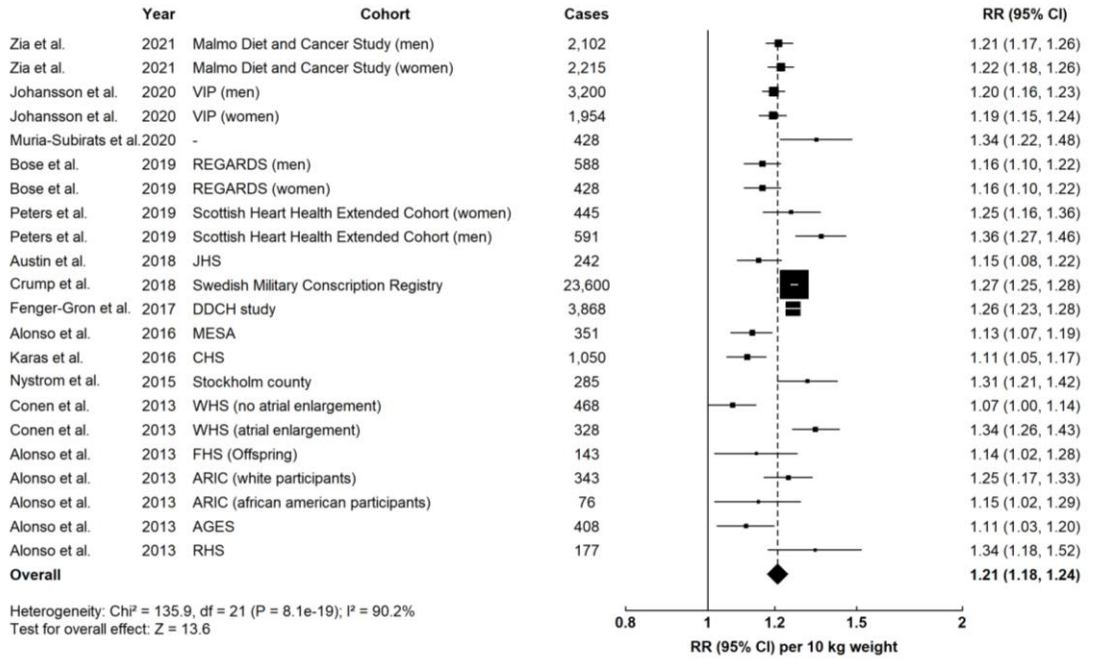


Figure 3.8: Forest plot of the effects of weight (per 10 kg) on risk of atrial fibrillation.

Data included from 16 datasets identified in this systematic review. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. Where associations between weight and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. One study has been excluded from display, as it is the result of later work in this thesis. Associations have been re-scaled to 10 kg to allow comparison between studies. **AGES** – age, gene/environment susceptibility, **ARIC** – atherosclerosis risk in communities cohort, ***CHS*** *– Cardiovascular Health Study,* ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***FHS*** *– Framingham Heart Study,* ***JHS*** *– Jackson Heart Study,* ***LOOP*** *- Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals,* ***MESA*** *– multi-ethnic study of atherosclerosis,* ***REGARDS*** *- REasons for Geographic And Racial Differences in Stroke Study,* ***RHS*** *– Rotterdam Heart Study,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHS*** *- Women's Health Study.*

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2 **3.4.5.5. Effect of weight on risk of atrial fibrillation by sex**

3 Single sex cohorts have both shown a strong association between weight and
4 AF.[58,221] In addition, four studies have looked at the effect of weight in men and
5 women separately (**Figure 3.9**). In all four, there was no difference in the strength
6 of effect.[73,206,207,214] For example, in the Vasterbotten Intervention Programme
7 cohort (AF cases, men 3,200, women 1,954) greater weight, per SD, was

associated with a 27% higher risk of AF (22 to 32%) in men and 26% in women (20 to 32%).[206]

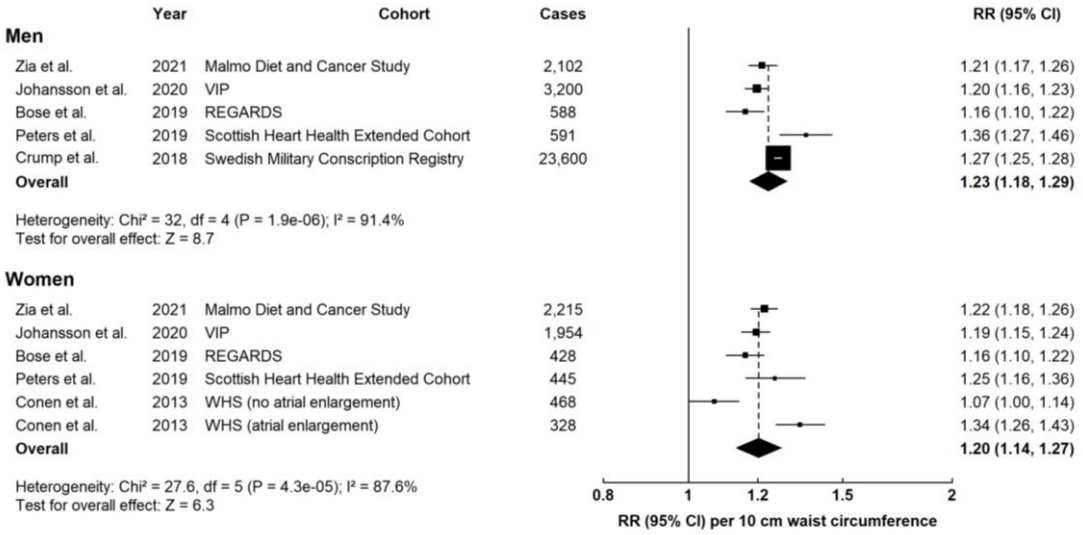


Figure 3.9: Forest plot of the effects of weight (per 10 kg) on risk of atrial fibrillation.
Data included from four datasets examining men and women separately, one additional male-only dataset, and one female-only datasets identified in this systematic review. Studies are ordered by year of publication. Associations have been re-scaled to 10 kg to allow comparison between studies. ***CI*** *– confidence interval,* ***REGARDS*** *- REasons for Geographic And Racial Differences in Stroke Study,* ***RR*** *- risk ratio,* ***VIP*** *– Vasterbotten Intervention Programme,* ***WHS*** *- Women's Health Study.*

3.4.5.6.Genetically predicted weight and risk of atrial fibrillation

Wang *et al*. showed a strong positive association between weight and risk of AF (OR 1.67, 1.57 to 1.77, per SD, **Appendix Table B.1**).[110] The association remained significant following adjustment for BMI, WC, and HC (OR 1.26, 1.18 to 1.34, per SD).

3.4.5.7.Weight evidence summary

As with other anthropometric traits, multiple studies have associated weight and risk of AF with 10 kg greater weight associated with a ~10-35% greater risk of AF. No differences has been demonstrated in the association between weight and risk of AF by sex. A causal association between weight and AF has been

suggested by MR analyses. Both observational and MR analyses have supported a relationship between weight and risk of AF which is potentially independent of other anthropometric measures.

3.4.6. Waist-hip ratio and risk of atrial fibrillation

3.4.6.1. Results of the current search

Eight studies (AF cases=11,014, seven separate datasets) have examined the effect of WHR as a continuous variable on the risk of incident AF (**Appendix Table B.14**).

3.4.6.2. Effect of waist-hip ratio on risk of atrial fibrillation

Three cohorts have identified a significant positive association between WHR and the risk of AF (**Appendix Table B.15**, **Figure 3.10**). Data from the DDCH study (AF cases=3,868) demonstrated an approximately 14% higher risk of AF per 0.1 higher WHR (HR 1.14, 1.09 to 1.21),[66] and is supported by data from two other cohorts.[207,208] In contrast, analyses of data from CHS (AF cases=1,050),[67] and the Stockholm county cohort (AF cases=285)[217] did not reveal any significant association with risk of AF. The reason for the negative association identified by Trevisan *et al.*, in contrast to other studies, is not immediately clear as the study demographics and model adjustments are not meaningfully different from a number of other cohorts included in this analysis.

A meta-analysis of the identified studies did not demonstrate a significant association between WHR and risk of AF (RR 1.08, 0.98 to 1.19). However, as with other anthropometric measures, heterogeneity between studies limits interpretation of this effect estimate.

3.4.6.3. Effect of waist-hip ratio when adjusted for other anthropometric measures

Evidence for an independent role of WHR on the risk of AF is further weakened by data showing complete attenuation of the effect when adjusted for other anthropometric measures. In the DDCH study, there was no significant effect of WHR on risk of AF after adjusting for LM (HR 1.01, 0.98 to 1.04, per SD).[66] Similarly, when adjusted for BMI, the positive association seen in the Australian cohort was removed (HR 0.98, 0.81 to 1.18, per SD).[208]

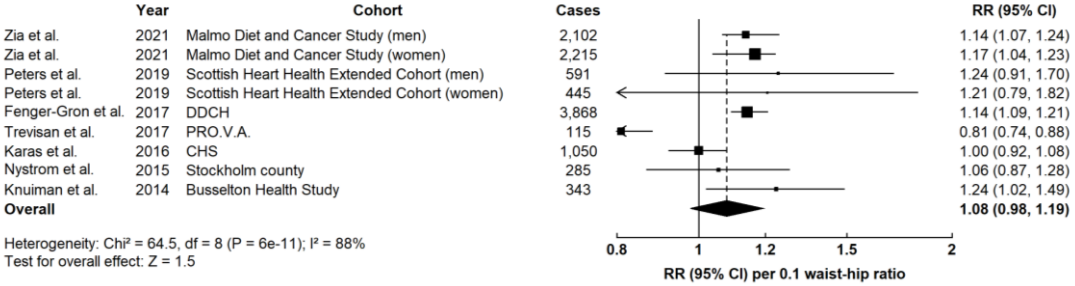


Figure 3.10: Forest plot of the effects of waist-hip ratio (per 0.1) on risk of atrial fibrillation.
Data included from seven datasets identified in this systematic review. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. Where associations between waist-hip ratio and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. Associations have been re-scaled to 0.1 to allow comparison between studies. **CHS** – Cardiovascular Health Study, ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* **PRO.V.A.** – Progetto Veneto Anziani, ***RR*** *- risk ratio.*

3.4.6.4.Exploration of a non-linear relationship between waist-hip ratio and risk of atrial fibrillation

WHR has been explored as a categorical variable in four studies (**Appendix Table B.16**). Zia *et al*. demonstrated an association between WHR and risk of AF in both men and women; however, this was only apparent between the bottom and top quartile, whereas there was no difference between the bottom quartile and the middle two quartiles.[207] Neefs *et al*. demonstrated an association

between WHR and risk of AF in men (HR 1.30, 1.08 to 1.55, Q5 vs Q1) but not women (HR 1.14, 0.91 to 1.42, Q5 vs Q1); there was no evidence of a non-linear relationship.[197] Verdecchia *et al*. (AF cases=2,092) did not demonstrate an association between WHR and risk of AF.[225]

3.4.6.5. Effect of waist-hip ratio on risk of atrial fibrillation by sex

Using data from the Malmo Diet and Cancer Study, Zia *et al*. examined the effect of WHR on risk of AF separately in men and women.[207] This analysis showed similar effects in both sexes (HR 1.08, 1.04 to 1.14 per SD in men and HR 1.07, 1.02 to 1.11 per SD in women). Peters *et al*. similarly showed no difference in the effect of WHR on risk of AF between sexes.[73]

3.4.6.6. Genetically predicted waist-hip ratio and risk of atrial fibrillation

To date, no MR analysis has been undertaken of the effect of genetically predicted WHR and risk of AF.

3.4.6.7. Waist-hip ratio evidence summary

The association between WHR and risk of AF remains unclear with studies not consistently demonstrating a positive association. Evidence for an independent role for WHR on risk of AF is sparse; in those studies demonstrating a positive association, adjustment for other anthropometric measures including BMI and LM remove the association between WHR and risk of AF. To date, no assessment of the potential causal relationship between WHR and risk of AF has been undertaken using MR analyses.

3.4.7. Fat mass and risk of atrial fibrillation

3.4.7.1. Results of the current search

Eight published studies examined the effect of FM on the risk of incident AF (**Appendix Table B.17**).[63,66-68,71,191,222,226] FM was examined as a continuous variable in five cohorts; the DDCH study and UKB have both been included in two reports.[66,71,191,226] These results include a total of 17,539 AF cases. An additional cohort examined FM as a categorical variable.[222]

3.4.7.2. Effect of fat mass on risk of atrial fibrillation

All studies identified a positive association between FM and risk of AF (**Appendix Table B.18**, **Figure 3.11**). Tikkanen *et al.*, using UKB data (AF cases=10,365 – bio-impedance measurement), demonstrated a 16% higher risk of AF per 5 kg higher FM (15 to 18).[71] A similar magnitude was found in the DDCH study.[66] However, other cohorts have suggested smaller effects of FM. In the Women's Health Initiative (WHI, AF cases=1,035 – DEXA measurement), 5 kg higher FM was only associated with a 4% higher risk of AF (1 to 7%).[63]

Meta-analysis of identified studies demonstrate that a 5 kg greater FM was associated with a 10% greater risk of AF (RR 1.10, 1.05 to 1.15). The heterogeneity in effect estimate (I^2 95%) does not appear to be due to differences in measurement technique (bio-impedance vs DEXA) with the CHS cohort (AF cases=1,050 – bio-impedance values) also showing a similarly small association (HR 1.05, 1.02 to 1.09, per 5 kg).[67] Instead it may represent considerable differences in the characteristics of those included in each study; for example, CHS excluded those with CHD at baseline while WHI included only women.[63,67]

3.4.7.3.Effect of fat mass when adjusted for other anthropometric measures

The effect of FM adjusted for other measures of body size has been assessed in DDCH and UKB. In DDCH the effect of FM was completely attenuated (HR 1.03, 1.00 to 1.07, per SD) following adjustment for LM.[66] However, in UKB, while LM did partially attenuate the effect of FM, it remained significantly associated with risk of AF (HR 1.28, 1.03 to 1.58, per SD).[71]

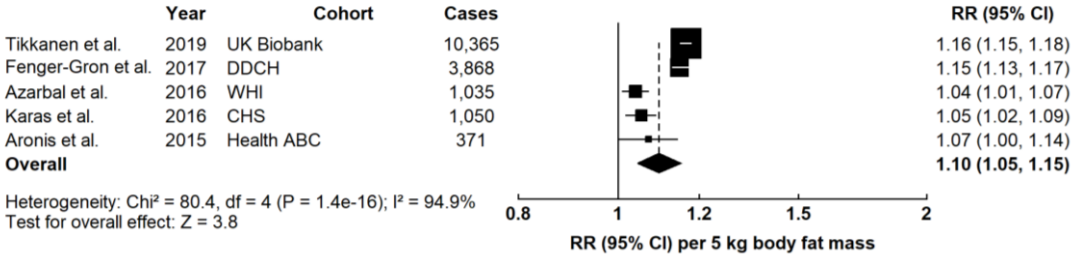


Figure 3.11: Forest plot of the effects of fat mass (per 5 kg) on risk of atrial fibrillation.
Data included from five datasets identified in this systematic review where fat mass was examined as a continuous variable. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. Where associations between body fat mass and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. One study has been excluded from display, as it is the result of later work in this thesis. Associations have been re-scaled to 5 kg to allow comparison between studies. **CHS** – Cardiovascular Health Study, ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***Health ABC*** *- Health, Aging, and Body Composition,* **WHI** – Women's Health Initiative, ***RR*** *- risk ratio.*

3.4.7.4. Exploration of a non-linear relationship between fat mass and risk of atrial fibrillation

One study examined FM as a categorical variable (**Appendix Table B.19**). Worm *et al*. demonstrated a positive relationship between FM and risk of AF and did not identify evidence of a non-linear relationship.[222] In contrast, Tikkanen *et al*. using a spline regression suggested a potential non-linear relationship between FM and

risk of AF with lower levels of FM having no association with risk of AF.[71] A non-linear relationship is also supported by data from Azarbal *et al*.[63] and DDCH.[191]

3.4.7.5. Effect of fat mass on risk of atrial fibrillation by sex

To date, the effect of FM on risk of AF has only been reported in a single study. Tikkanen *et al*. suggested that the association between FM and risk of AF was greater in women (HR 1.49, 1.44 to 1.54 per SD) than in men (HR 1.35, 1.31 to 1.30 per SD).[71]

3.4.7.6.Genetically predicted fat mass and risk of atrial fibrillation

The effect of genetically predicted FM on risk of AF has been explored in three studies (**Appendix Table B.1**). These have all shown a positive association between FM and risk of AF. Zeng *et al*., using the FinnGenn dataset, demonstrated that the effect of genetically predicted FM remains significantly positively associated with risk of AF following adjustment for LM (HR 1.44, 1.39 to 1.58, per SD).[227] This is supported by results from Tikkanen *et al*. using genetic variants identified in UKB.[71]

3.4.7.7. Fat mass evidence summary

FM has consistently been associated with risk of AF, with a 5 kg greater FM associated with 5-15% greater risk of AF. However, the effect of FM on risk of AF independent of other anthropometric measures (in particular LM) is unclear with conflicting findings between studies. Differences in the effect of FM on risk of AF by sex has only been explored in a single study, which suggested a stronger association between FM and risk of AF in women than men. MR analyses have suggested a potentially causal association between FM and risk of AF; however,

the effect of genetically predicted FM independent of body fat distribution has not been undertaken.

3.4.8. Lean mass and risk of atrial fibrillation

3.4.8.1. Results from current search

Seven publications detailing the association between LM and the risk of incident AF (**Appendix Table B.20**).[63,66,67,71,191,222,226] Of these, six publications examined LM as a continuous variable and represent data from four cohorts (unique AF cases=29,937); data from the DDCH and UKB cohorts are each present in two publications.[66,71,191,226]

3.4.8.2. Effect of lean mass on risk of atrial fibrillation

All published reports show a significant association between LM and the risk of AF (**Appendix Table B.21**). Of note, Tikkanen *et al.* have suggested that a 5 kg higher LM is associated with a ~25% higher risk of AF (HR 1.26, 1.24 to 1.28).[71] A similar magnitude has been seen in the DDCH cohort.[66,191] However, data from the CHS cohort demonstrates a smaller association with each 5 kg greater LM associated with a 12% greater risk of AF (HR 1.12, 1.06 to 1.19).[67]

Meta-analysis of identified studies demonstrate that 5 kg greater LM was associated with ~25% greater risk of AF (RR 1.23, 1.15 to 1.33, **Figure 3.12**). Caution is required in interpreting this effect estimate due to substantial heterogeneity between studies. The reason for this heterogeneity in effect estimates (I^2 94%) may be due participants with CHD at baseline being excluded form enrolment in the CHS cohort,[67] in contrast to UKB or DDCH.[66,71]

3.4.8.3.Effect of lean mass when adjusted for other anthropometric measures

The effect of LM when adjusted for other measures of body size has only been assessed in the DDCH cohort to date. Fenger-Grøn *et al*. demonstrated no meaningful difference in the association of LM with risk of AF before (HR 1.37, 1.33 to 1.42, per SD) and after adjustment for FM (HR 1.36, 1.30 to 1.41, per SD).[66] Similar results were reported by this group when the association between LM and risk of AF was adjusted for other anthropometric measures.

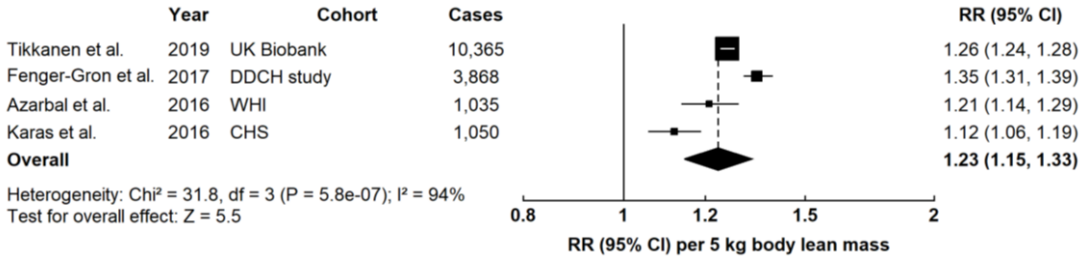


Figure 3.12: Forest plot of the effects of lean mass (per 5 kg) on risk of atrial fibrillation.
Data included from four datasets identified in this systematic review where body fat mass was examined as a continuous variable. Studies are ordered by year of publication. Where effects are only reported in sub-groups these have been listed separately. Where associations between body lean mass and risk of atrial fibrillation have been reported more than once in the same cohorts, the report with the largest number of atrial fibrillation cases described in a single analysis has been included. One study has been excluded from display, as it is the result of later work in this thesis. Associations have been re-scaled to 5 kg to allow comparison between studies. **CHS** – Cardiovascular Health Study, ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***Health ABC*** *- Health, Aging, and Body Composition,* **WHI** – Women's Health Initiative, ***RR*** *- risk ratio.*

3.4.8.4.Exploration of a non-linear relationship between lean mass and risk of atrial fibrillation

A single study has examined LM as a categorical variable (**Appendix Table B.22**). As with FM, Worm *et al*. demonstrated a positive relationship between LM and risk of AF and did not identify evidence of a non-linear relationship.[222] A linear relationship is supported by data from Azarbal *et al*.[63] and DDCH.[191] By contrast,

Tikkanen *et al*. using a spline regression suggested a potential non-linear relationship between LM and risk of AF with lower levels of LM having no association with risk of AF.[71]

3.4.8.5. Effect of lean mass on risk of atrial fibrillation by sex

To date, the effect of LM on risk of AF only been examined in a single study. Tikkanen *et al*. suggested there was no difference in strength of association with risk of AF in men and women per SD greater LM.[71]

3.4.8.6. Genetically predicted lean mass and risk of atrial fibrillation

Genetically predicted LM has been examined in three studies with another study examining genetically predicted LM indexed for height (**Appendix Table B.1**). Zeng *et al*. demonstrated that genetically predicted LM, per SD, was strongly associated with risk of AF (OR 2.13, 1.84 to 2.45) and remained associated when adjusted for genetically predicted FM (OR 1.65, 1.31 to 2.09).[227] In contrast, Larsson *et al*. examined genetically predicted LM index and demonstrated a negative association with risk of AF (OR 0.75, 0.66 to 0.86, per 1 kg/m^2).[109] However, Larsson *et al*. used 82 genetic variants identified by Rask-Andersen *et al*. in a GWAS of body composition (rather than a GWAS of LM itself).[228] Larsson *et al*. calculated associations with LM index in UKB from this limited sub-set of variants.

3.4.8.7. Lean mass evidence summary

An association between LM and risk of AF has been shown in all identified studies, with 5 kg greater LM associated with ~10-25% greater risk of AF. The effect of LM on risk of AF independent of most other anthropometric measures has not been thoroughly explored. However, there is evidence to suggest that

the association between LM and risk of AF is independent of FM. Differences in the effect of LM on risk of AF by sex have only been explored in a single study which suggested no difference in strength of association in women than men. MR analyses have suggested a potentially causal association between LM and risk of AF.

3.4.9. Pericardial adipose tissue and risk of atrial fibrillation

PAT is an ectopic fat deposit found between the outer lining of the heart (epicardium) and the pericardial sac. There is inconsistent use of terminology in the literature,[229] with both 'pericardial' and 'epicardial' fat being used without clear delineation. In this systematic review both have been considered together and termed 'pericardial adipose tissue'.

3.4.9.1. Results from the current search

Six studies (from seven cohorts) have explored the effect of PAT on the risk of incident AF (**Appendix Table B.23, Appendix Table B.24, Appendix Table B.25**, unique AF cases=1,198). Four of the identified studies utilised Cardiac CT to determine PAT volume,[94,95,100,230] one using cardiac CT to examine PAT volume indexed to body surface area,[231] with the remaining study examining PAT thickness by transthoracic echocardiography.[232]

3.4.9.2.Effect of pericardial adipose tissue on risk of atrial fibrillation

The association between PAT and risk of AF has been inconsistently demonstrated (**Figure 3.13**). Heckbert *et al*., examining MESA and JHS (AF cases=756), demonstrated a positive association between PAT volume and risk of AF (HR 1.12, 1.05 to 1.20).[95] This is supported by results from the Rotterdam

Heart Study (RHS, AF cases=142) which identified ~30% greater risk of AF per SD higher PAT volume (HR 1.31, 1.05 to 1.65). However, the other studies identified in this search have not supported a positive association for total PAT volume.[94,100] Meta-analysis of these four studies demonstrates that a 1-SD greater PAT volume was associated with a 14% greater risk of AF (RR 1.14, 1.07 to 1.20).

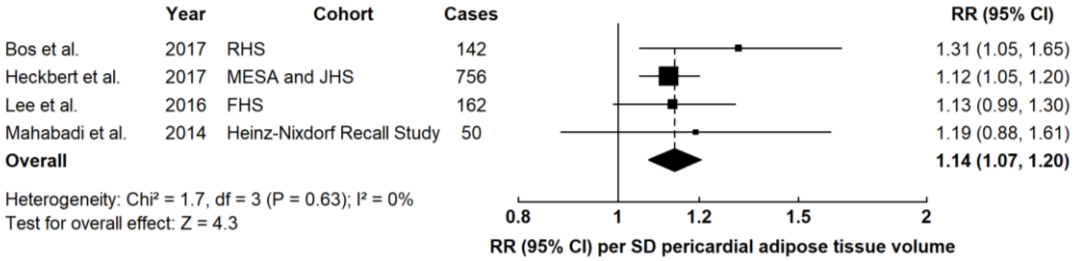


Figure 3.13: Forest plot of the effects of pericardial adipose tissue volume (per standard deviation) on risk of atrial fibrillation.
Data included from four datasets identified in this systematic review where pericardial adipose tissue was examined as a continuous variable. Studies are ordered by year of publication. Data from Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study were only reported jointly. A study detailing pericardial fat thickness is not displayed due to the significantly different analysis method. Associations have been scaled to one standard deviation to allow comparison between studies. **CHS** – Cardiovascular Health Study, ***CI*** *– confidence interval,* ***DDCH*** *– Danish Diet, Cancer and Health cohort,* ***Health ABC*** *- Health, Aging, and Body Composition,* **WHI** – Women's Health Initiative, ***RR*** *- risk ratio,* ***SD*** *– standard deviation*

3.4.9.3. Regional pericardial adipose tissue and risk of atrial fibrillation

In a small study, Nakanishi *et al*. (AF cases=17) showed an association between peri-atrial PAT volume index and risk of AF (HR 1.28, 1.13 to 1.45) but not total PAT volume index (HR 0.98, 0.93 to 1.03).[231] However, this study is small and has not been confirmed in other datasets.

3.4.9.4. Effect of pericardial adipose tissue when adjusted for other anthropometric measures

Heckbert *et al.* showed that the association between PAT volume and risk of AF (HR 1.12, 1.05 to 1.20, per SD) was removed after further adjustment for BMI (HR 1.06, 0.97 to 1.15).[95] In contrast, data from the RHS included BMI as an adjustment within their model and showed a positive association between PAT volume and risk of AF (HR 1.31, 1.05 to 1.65).

3.4.9.5. Exploration of a non-linear relationship between pericardial adipose tissue and risk of atrial fibrillation

The shape of the relationship between PAT and risk of AF has not previously been well explored. However, Lee *et al*. demonstrated that there was no difference in AF incidence rate in the lower two tertiles of PAT with an increase only seen in the upper tertile; however, these were un-adjusted estimates.[100]

3.4.9.6. Effect of pericardial adipose tissue on risk of atrial fibrillation by sex

To date, the effect of PAT has not been examined separately in men or women.

3.4.9.7. Genetically predicted pericardial adipose tissue and risk of atrial fibrillation

The association between genetically predicted PAT has not been examined in any published study to date. Two small GWAS of pericardial fat are available which have identified two variants associated with pericardial fat.[98,99]

3.4.9.8. Pericardial adipose tissue evidence summary

The association between PAT and risk of AF has only been explored in a limited number of cohorts with small numbers of AF cases. A positive association has

been demonstrated in some but not all cohorts. In studies demonstrating a positive association between PAT and risk of AF, there are conflicting results regarding whether this association is independent of the effect of BMI on risk of AF. No assessment has been made of whether difference in the effect of PAT on risk of AF exist in men and women. Further, there has been no examination of the causal relevance of this phenotype for AF through the use of MR analyses.

3.4.10. Non-cardiac visceral adipose tissue

Non-cardiac VAT is a collection of related phenotypes representing visceral fat deposits excluding PAT.

3.4.10.1. Results from the current search

The association between non-cardiac VAT and risk of incident AF has been presented in three studies from two different cohorts (unique AF cases=533, **Appendix Table B.26**).[68,100,233] The phenotypes identified were all measures of intra-thoracic or intra-abdominal adipose tissue.

3.4.10.2. Effect of visceral adipose tissue on risk of atrial fibrillation

Lee *et al.* (AF cases=162) examined the effect of intrathoracic fat (excluding PAT) and abdominal VAT on risk of AF in the FHS cohort (**Appendix Table B.27**).[100] This demonstrated an association between intrathoracic fat (HR 1.19, 1.01 to 1.40, per SD) but not abdominal VAT (HR 1.09, 0.93 to 1.28, per SD) and risk of AF. In the same cohort, Long *et al.* (AF cases=153) demonstrated no association between liver fat and risk of AF (HR 1.01, 0.76 to 1.33, per SD).[100] Aronis *et al.*, examining the Health ABC cohort (AF cases=371), found no association between abdominal VAT and risk of AF (HR 1.07, 0.96 to 1.19, per SD).[68] However, all

three of these studies included small numbers of AF cases. As such, there was limited power to detect a signal and further investigation is warranted.

3.4.10.3. Effect of visceral adipose tissue when adjusted for other anthropometric measures

Lee *et al*. adjusted the associations between intra-thoracic fat and risk of AF for BMI and pericardial fat. In the FHS cohort, the association identified between intra-thoracic fat and risk of AF (HR 1.19, 1.01 to 1.40, per SD) was not seen following additional adjustment for either BMI (HR 1.15, 0.96 to 1.38, per SD) or PAT (HR 1.14, 0.87 to 1.48, per SD).[100]

3.4.10.4. Effect of visceral adipose tissue on risk of atrial fibrillation by sex

To date, the effect of VAT has not been examined separately in men or women.

3.4.10.5. Genetically predicted visceral adipose tissue and risk of atrial fibrillation

Huang *et al*. examined the association between genetically predicted abdominal VAT and risk of AF and demonstrated a positive association (OR 1.41, 1.33 to 1.50, per SD).[234] However, the genetic variants for abdominal VAT were identified from a phenotype of predicted VAT in UKB.[235] This phenotype was developed through an imputation model which included other anthropometric measures including WC, HC, and whole body bio-impedance values (from which FM and LM can be derived) with the variants identified having overlap with those found in GWAS of other anthropometric measures.[235] As a result, the association identified here may be due to pleiotropic associations and confounding between predicted VAT, other anthropometric measures, and risk of AF.

3.4.10.6. Visceral adipose tissue evidence summary

An analysis of the effect of VAT on risk of AF is limited by phenotypic heterogeneity and limited study data. There is some evidence to support a positive association between non-cardiac intra-thoracic adipose tissue and risk of AF. However, the relevance of this phenotype independent of PAT is not clear. The causal relevance of VAT for risk of AF is unclear with a single MR study of VAT suggesting a positive association between VAT and risk of AF. However, this result must be interpreted with caution given the use of predicted VAT in the discovery GWAS.

3.4.11. Other anthropometric phenotypes

The other anthropometric phenotypes identified by this systematic review are detailed in Appendix C (**Additional phenotypes from the systematic review**).

3.5.3.5 Discussion

This systematic review has identified 168 studies exploring the associations between 18 anthropometric phenotypes and risk of AF. Of these different phenotypes, the majority have been positively associated with the risk of AF. In particular, there is strong evidence for associations between BMI, height, WC, and weight with risk of AF. However, a number of areas remain incompletely investigated. In particular, for the majority of anthropometric measures there has been insufficient assessment of differences in strength of association with risk of AF in men and women. Furthermore, the independent relevance of phenotypes has only been examined in a small number of cohorts with inconsistent results.

3.5.1. Evidence of associations between anthropometric measures and risk of atrial fibrillation

BMI is the most well explored anthropometric phenotype identified in this systematic review with 52 cohorts reporting associations between BMI and risk of AF (**Figure 3.14**). In almost all studies, a positive association has been identified between BMI and AF. Other phenotypes have been less well explored. LM, FM, and WC have all been shown to have consistently positive associations with risk of AF. However, despite considerable evidence of positive associations, there are meaningful differences in effect sizes reported by studies examining each trait. As a result, the true strength of association between these anthropometric traits and risk of AF remains uncertain. Substantial heterogeneity between identified studies means that effect estimates derived from meta-analyses of the included studies must be interpreted with caution. This heterogeneity likely has a range of sources including differences in inclusion

criteria and model adjustments. Such variation in effect estimates support the need for further high quality studies to confirm strength of association between anthropometric measures and risk of AF.

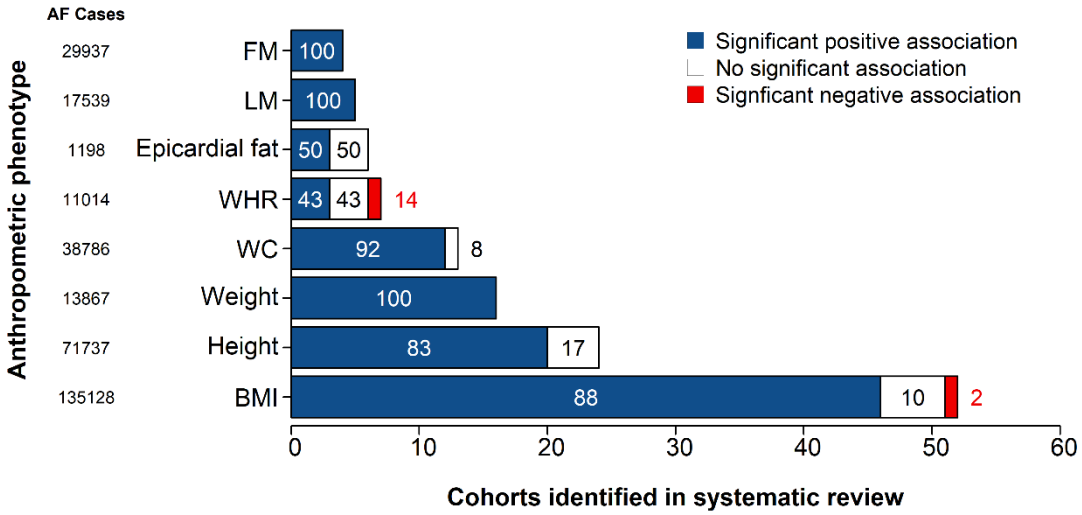


Figure 3.14: Evidence for associations between anthropometric measures and risk of atrial fibrillation.
Ordered by number of cohorts examining each phenotype as a continuous variable. Numbers within or adjacent to bars represent the percentage of cohorts in each group. ***BMI*** *– body mass index,* ***WC*** *– waist circumference,* ***WHR*** *– waist-hip ratio,* ***FM*** *– fat mass,* ***LM*** *– lean mass.*

3.5.2. Exploration of sex-based differences in associations between anthropometric measures and risk of atrial fibrillation

Limited assessment of the effect of sex on the associations between anthropometric measures has been undertaken (**Figure 3.15**). Sex-based differences in the strength of association with risk of incident AF have been demonstrated in some studies examining BMI. By contrast, no sex-specific effects have been shown in the majority of studies examining height, WC, weight, and WHR. However, most of these studies have been too small to provide reliable estimates and assessment of any difference by sex. At present, limited assessment of sex-based differences has been published for FM or LM, with no assessment of these differences for PAT, or VAT. Given the differences in body

fat distribution,[46] risk of AF,[9] and AF outcomes between men and women,[17] determination of any differences in such associations has important clinical implications.

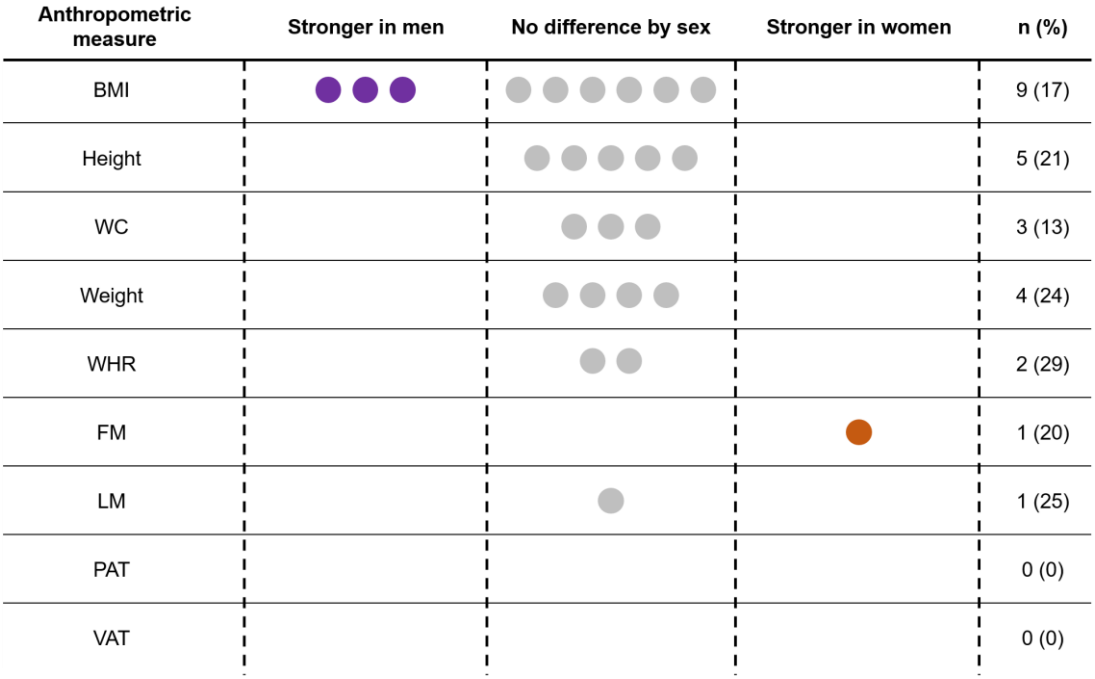


Figure 3.15: Evidence assessing sex-based differences in associations between anthropometric measures and risk of atrial fibrillation.
Number of cohorts in which sex-based assessment are provided is displayed in the right-hand column and as a percentage of all cohorts examining the association between each anthropometric measure (as a continuous measures) and risk of atrial fibrillation. Each dot represents a separate cohort examining associations between anthropometric measures and risk of atrial fibrillation in men and women. ***BMI*** *– body mass index,* ***WC*** *– waist circumference,* ***WHR*** *– waist-hip ratio,* ***FM*** *– fat mass,* ***LM*** *– lean mass,* ***PAT*** *–pericardial adipose tissue,* ***VAT*** *– visceral (non-cardiac) adipose tissue.*

3.5.3. Evidence of independent associations between anthropometric measures and risk of atrial fibrillation

While many anthropometric measures have been shown to be associated with risk of incident AF, the independent relevance of each anthropometric measure remains unclear at present. Determining the independent relevance of these correlated phenotypes is important to allow the correct individuals to be potentially targeted for appropriate interventions,[236] as well as for further

consideration of the mechanisms linking anthropometric traits and AF. Individual studies have attempted to mutually adjust for anthropometric measures. However, these analyses have generally been small and the independent relevance of identified associations remains unclear for many anthropometric measures (**Figure 3.16**). In particular, there is conflicting evidence regarding the effect of BMI on risk of AF independent of other anthropometric measures. For example, one study has suggested that adjustment for LM removes the association between other anthropometric measures and risk of AF.[66] Additionally, BMI may not be associated with risk of AF independent of WC or FM.[66,195] However, these findings have not been confirmed in additional cohorts. Importantly the association between FM and risk of AF after adjustment for measures of body fat distribution (for example waist circumference) has not been clearly established.

3.5.4.Evidence for causal associations between anthropometric measures and risk of atrial fibrillation

Data supporting a causal role for anthropometric measures is growing with a number of different phenotypes being explored. Furthermore, some evidence for the independent causal relevance of LM and FM exists within the literature.[71] However, a large number of potential anthropometric phenotypes have been incompletely explored including ectopic fat deposits and measures of body fat distribution.

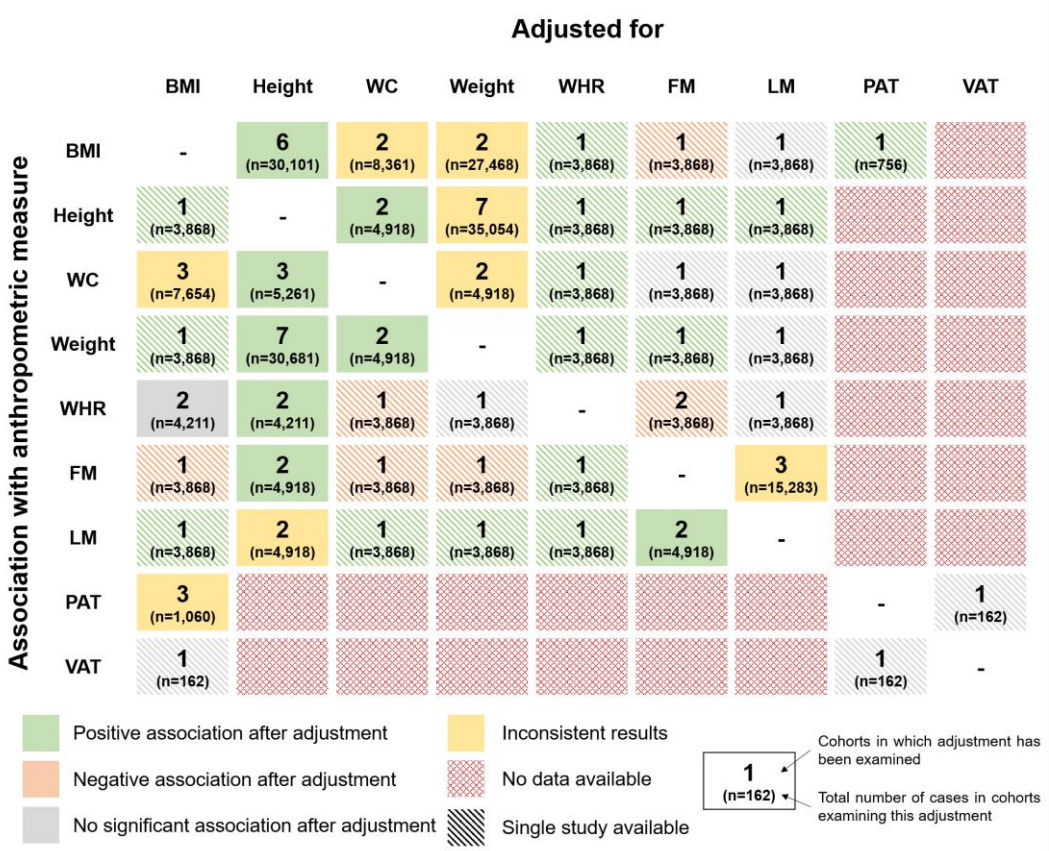


Figure 3.16: Evidence for associations between anthropometric measures and risk of atrial fibrillation after adjustment for other anthropometric measures.
For each study represented, models adjusting for other anthropometric measures were identified. ***BMI*** *– body mass index,* ***WC*** *– waist circumference,* ***WHR*** *– waist-hip ratio,* ***FM*** *– fat mass,* ***LM*** *– lean mass,* ***PAT*** *–pericardial adipose tissue,* ***VAT*** *– visceral (non-cardiac) adipose tissue.*

3.5.5. Conflicting evidence in the association between pericardial adipose tissue and risk of atrial fibrillation

There are a number of anthropometric phenotypes where the association with risk of AF has been incompletely investigated or where conflicting evidence is available. The most clear of these is PAT. There is considerable evidence suggesting potential mechanisms linking PAT and risk of AF.[128,129] However, to date, there are a limited number of prospective cohorts assessing the association between PAT and risk of AF. Importantly a meta-analysis by Wong *et al*. demonstrated a very large positive association between PAT and risk of AF (OR 2.61, 1.89 to 3.60, per SD).[72] However, that analysis included a large number of

case-control studies which are prone to reverse causation as well as studies utilising a number of different methods for measuring PAT. When limited to prospective studies, the association between PAT and risk of AF appears generally more modest (~10-30% higher risk of AF per SD greater PAT). The effect of reverse causation in increasing the apparent effect of PAT on risk of AF is supported by data from Mahabadi *et al.* which showed a strong association between PAT volume and prevalent AF cases (OR 1.55, 1.16 to 2.09, per SD) but not with incident AF cases (OR 1.19, 0.88 to 1.61, per SD).[94] As a result, the association of this phenotype with risk of AF remains unclear. To date, no assessment of the causal relevance of PAT has been undertaken.

3.5.6. Conclusions

There are a large number of studies examining the associations between a range of anthropometric traits and risk of AF. While the presence of a positive association is clear between some anthropometric measures and risk of AF (e.g. BMI, WC, LM, FM), the evidence is less clear for other measures (e.g. PAT, VAT). Additionally, the strength of association between many anthropometric measures and risk of AF is not clear due to significant heterogeneity between identified studies. Furthermore, the associations between these traits by sex and independent of one another has not been comprehensively explored despite important implications for future research and patient management. Finally, there is limited evidence from prospective cohorts to support an association between PAT and risk of AF at present. However, given the potential strong associations identified in case-control studies and mechanisms identified which may link PAT to risk of AF, further analysis of this phenotype is required.

Chapter 4 - Epidemiology of adiposity and atrial fibrillation

4.1. Abstract

4.1.1. Background

Atrial fibrillation (AF) has a higher prevalence in men than women and is associated with measures of adiposity and lean mass (LM). However, it remains uncertain if the risks of AF associated with these measures vary by sex.

4.1.2. Methods

Among 477,904 UK Biobank participants aged 40-69 without prior AF, 23,134 incident AF cases were identified (14,400 men, 8,734 women; median follow-up 11.1 years). Cox proportional hazards models were used to estimate covariate adjusted hazard ratios (HR) describing the association of AF with weight, measures of adiposity (fat mass [FM], waist circumference [WC]), and LM and their independent relevance, by sex.

4.1.3. Results

Weight and WC were independently associated with risk of AF (HR:1.25 [1.23-1.27] per-10 kg, HR:1.11 [1.09-1.14] per-10 cm respectively), with comparable effects in both sexes. The association with weight was principally driven by LM which, per-5 kg, conferred double the risk of AF compared to FM when mutually adjusted (HR:1.20 [1.19-1.21], HR:1.10 [1.09-1.11] respectively); however, the

effect of LM was weaker in men than women (p-interaction=$4.3x10^{-9}$). Comparing the relative effects of LM, FM, and WC identified different patterns within each sex; LM was the strongest predictor for both, whereas WC was stronger than FM in men but not women.

4.1.4. Conclusions

LM and FM (as constituents of body weight), and WC are risk factors for AF. However, the independent relevance of general adiposity for AF was more limited in men than women. The relevance of both WC and LM suggest a potentially important role for both visceral adiposity and muscle mass in AF development.

4.2. Introduction

Observational studies have shown positive associations between risk of AF and measures of general adiposity (such as BMI), central adiposity (such as WC), and LM.[65,66,72] Conversely, weight loss has been associated with lower AF burden and maintenance of sinus rhythm.[78] Genetic studies also support a causal role for both LM and FM in the development of AF.[71]

Body fat distribution differs between sexes,[39-41] with men having lower FM and higher LM (per unit BMI) compared with women.[42] Men also have higher levels of visceral fat compared with women.[41,48] Visceral adiposity has been shown to be correlated with WC in small studies,[237] and is associated with risk of cardiovascular disease, independently of general adiposity.[52] Visceral adipose tissue is also positively correlated with levels of pro-inflammatory cytokines, such as IL-6, which have been associated with risk of AF.[55,120] LM has previously been correlated with left ventricular mass and left atrial size, which may underlie some of the association between LM and risk of AF.[238,239] Consequently, differences in LM and fat distribution, through their potential impact on biological pathways, may contribute to the sex-related differences in the prevalence of AF and provide important insights into the pathogenesis of AF and its complications.

Reliable assessments of sex-specific effects of general adiposity, body-fat distribution, and LM on the risk of AF have been limited by data availability.[73,74,240,241] Large-scale prospective cohorts now offer the possibility to obtain more robust assessments. Here, this study aimed to compare the independent effects of general adiposity, central adiposity, and LM on the risk of AF in 215,196 men and 262,708 women in UKB.

4.3. Methods

4.3.1. Study design and participants

Details of the UKB study design and participant selection have been detailed in **Chapter 2** (**UK Biobank data collection**). Censor dates for HES and death data were dependent on the country in which the participant was resident. The censor dates used for this analysis are outlined in **Table 4.1**.

Table 4.1: UK Biobank country specific censor dates

	Censor Date
England	30th June 2020
Scotland	31st October 2016
Wales	29th February 2016

4.3.2. Atrial fibrillation and other health outcomes

Incident cases of AF (and comorbid diseases) were identified using hospital inpatient admissions data from HES (based on any reason for admission), and death registry data following recruitment. Health outcomes prior to recruitment were identified from HES records and self-reported information. Specific phenotype codes are displayed in Appendix D (**UK Biobank disease phenotype definitions**).

4.3.3.Statistical analyses

A total of 477,904 participants were included in the primary analyses, after excluding 17,635 participants with missing or extreme anthropometric values or pre-defined covariates,[242,243] and 6,954 with prevalent AF (**Figure 4.1**). Cox

proportional hazards regression models were used to estimate hazard ratios (HR) describing the associations between incident AF and each anthropometric measure: BMI, WC, weight, FM, and LM. Results were adjusted for the following potentially confounding covariates: age at risk (in 5-year age groups), sex, ethnicity, Townsend deprivation index,[244] alcohol intake, and smoking (never, former, current).

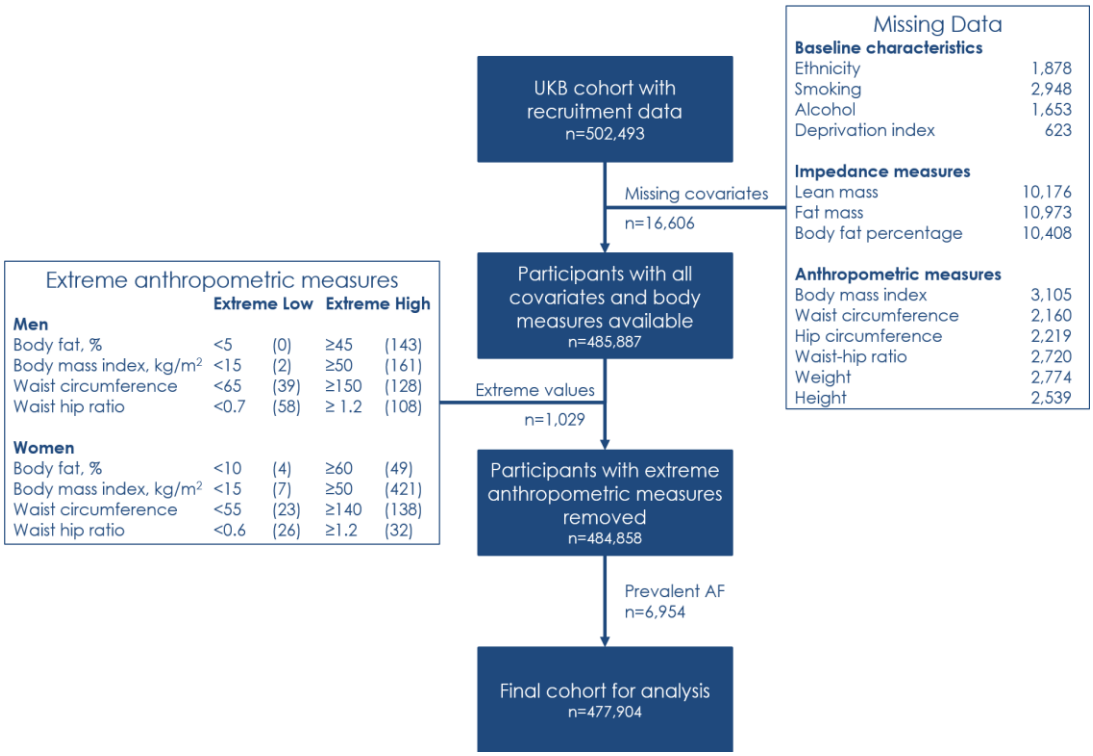


Figure 4.1: UK Biobank participant flow chart.
Flow chart illustrating participants included in the analyses in Chapter 4.

In order to explore the shape of the associations, anthropometric measures were classified, separately in men and women, into fifths, with the top group being further subdivided in two (corresponding to the top two tenths of the distribution) thereby keeping case numbers similar in each group. Relative independence of different anthropometric traits was assessed by additional adjustment for these grouped variables.

In figures, estimates for each group are shown relative to a defined reference group (the second fifth was the selected reference group). Group-specific variances were used to calculate 95% CIs to enable comparisons between any two groups (rather than with the arbitrary reference group).[245]

Estimated HRs are based on using the anthropometric measure as a continuous variable throughout the text except where indicated and are displayed with 95%CIs. χ^2 values are derived from likelihood ratio statistics.

4.3.3.1.Sensitivity analyses

Sensitivity analyses were conducted to (a) evaluate the impact of regression dilution bias by calculating the regression dilution ratio for each anthropometric measure using the group method,[246] (b) address residual confounding by further covariate adjustment (i.e. physical activity, bread consumption, processed meat consumption, fruit consumption, vegetable consumption), and (c) consider potential reverse causality by excluding participants with vascular disease prior to baseline and censoring on vascular disease during follow-up, and excluding AF in the first two years of follow-up.

4.3.3.2. Regression dilution ratio

As part of a sensitivity analysis, the effect of regression dilution on associations between anthropometric measures and risk of AF was assessed. Approximately 4-5 years after enrolment, a subset of the cohort (approximately 20,000 participants) attended for a repeat assessment of baseline measurements. The regression dilution ratio for each anthropometric measure was calculated using the group method using 20,346 participants re-surveyed (2009-2013) using the same measurement methods used at baseline (**Appendix Table E.1**).[246] To

achieve this, the value of anthropometric measures were corrected by dividing each anthropometric measure into fifths and determining the mean value within the top and bottom fifths at baseline and re-survey and calculating the range between the top and bottom fifths. The mean range from the re-survey measure is divided by the mean range from the baseline measurement to give a regression dilution ratio.[246]

4.4. Results

4.4.1. Baseline characteristics

Of the 477,904 participants included in the analyses, 55% were women. At baseline, participants had a mean age of 56.4 years (standard deviation [SD] 8.1), which was similar between sexes (**Table 4.2**). Participants were primarily of white ethnicity (95%) and about half (46%) were from the least disadvantaged fifth of the UK population (as defined by Townsend deprivation index scores). About 10% of both sexes were current smokers and most were current alcohol drinkers (92%). There was a higher prevalence of CHD (6.5% vs. 2.2%) and diabetes (6.5% vs 3.3%) in men versus women.

On average, BMI, WC, and weight were higher in men than women but had similar variance (**Table 4.2**). As expected, LM was higher in men (mean 63.6kg, SD 7.7) than women (44.5 kg, SD 5.0), whereas FM was higher in women (mean 26.8 kg, SD 9.8) than men (mean 22.2 kg, SD 8.0, **Table 4.2**, **Figure 4.2**). In each sex, FM was strongly correlated with BMI and WC (r=0.88-0.94 after adjustment for age; **Appendix Table E.2**), and these measures were also correlated with LM (r=0.60-0.71).

Table 4.2: Baseline characteristics of the 477,904 participants in the primary analysis

	Men (n=215,196)	**Women** (n=262,708)	**Total** (n=477,904)
Demographic and lifestyle factors			
Age, mean (SD)	56.6 (8.2)	56.3 (8.0)	56.4 (8.1)
White, n(%)	203,737 (94.7)	248,797 (94.7)	452,534 (94.7)
Current smoker, n(%)	26,906 (12.5)	23,469 (8.9)	50,375 (10.5)
Current alcohol drinker, n(%)	202,093 (93.9)	238,354 (90.7)	440,447 (92.2)
Townsend deprivation index*, mean (SD)	-1.3 (3.1)	-1.4 (3.0)	-1.3 (3.1)
Anthropometric measures, mean (SD)			
Height, cm	175.6 (6.8)	162.5 (6.3)	168.4 (9.3)
Weight, kg	85.8 (13.9)	71.3 (13.7)	77.8 (15.6)
Body mass index, kg/m^2	27.8 (4.1)	27.0 (5.0)	27.4 (4.7)
Waist circumference, cm	96.8 (11.0)	84.5 (12.3)	90.1 (13.2)
Hip circumference, cm	103.3 (7.3)	103.2 (10.1)	103.3 (9.0)
Waist-hip ratio	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)			
Lean mass, kg	63.6 (7.7)	44.5 (5.0)	53.1 (11.4)
Fat mass, kg	22.2 (8.0)	26.8 (9.8)	24.7 (9.3)
Prior disease, n(%)			
Congestive cardiac failure	1,099 (0.5)	469 (0.2)	1,568 (0.3)
Coronary heart disease	13,924 (6.5)	5,891 (2.2)	19,815 (4.1)
Diabetes	13,955 (6.5)	8,707 (3.3)	22,662 (4.7)
Hypertension	88,719 (41.2)	82,898 (31.6)	171,617 (35.9)
Sleep apnoea	2,272 (1.1)	735 (0.3)	3,007 (0.6)
Stroke	3,375 (1.6)	2,444 (0.9)	5,819 (1.2)
Valvular heart disease	1,834 (0.9)	2,375 (0.9)	4,209 (0.9)

People with missing or out-of-range anthropometric measures, missing covariates, or prior atrial fibrillation at baseline were excluded. *Area level measure of material deprivation (UK range:-5.5 [least deprived] to 14.0 [most deprived]).[244] SD – standard deviation.

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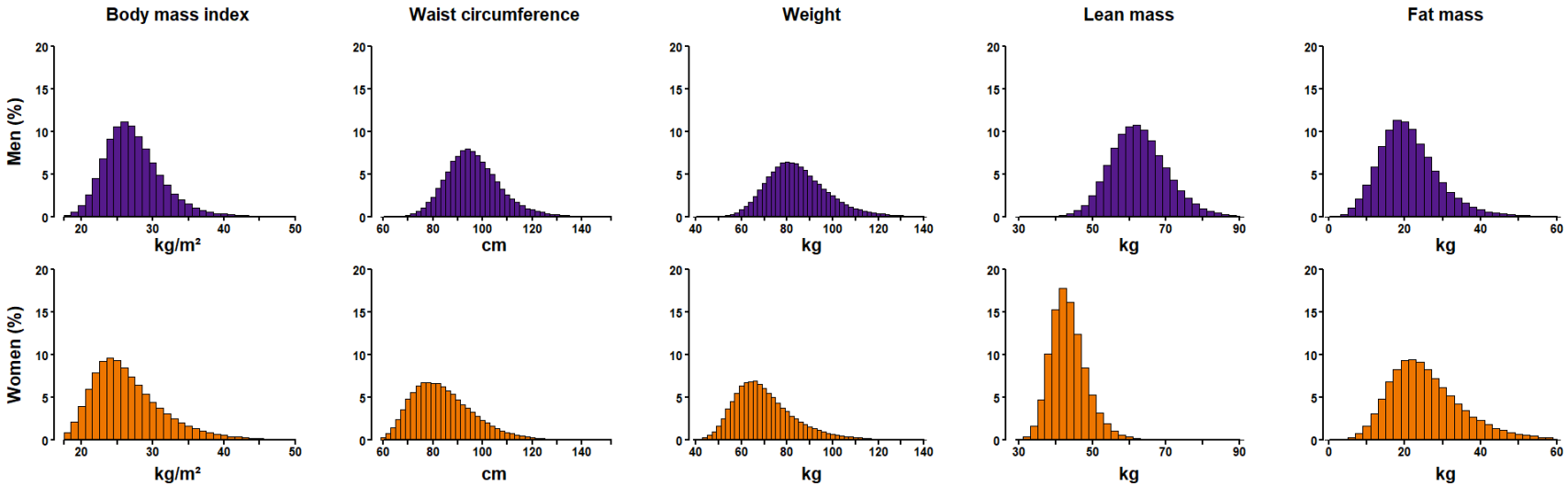
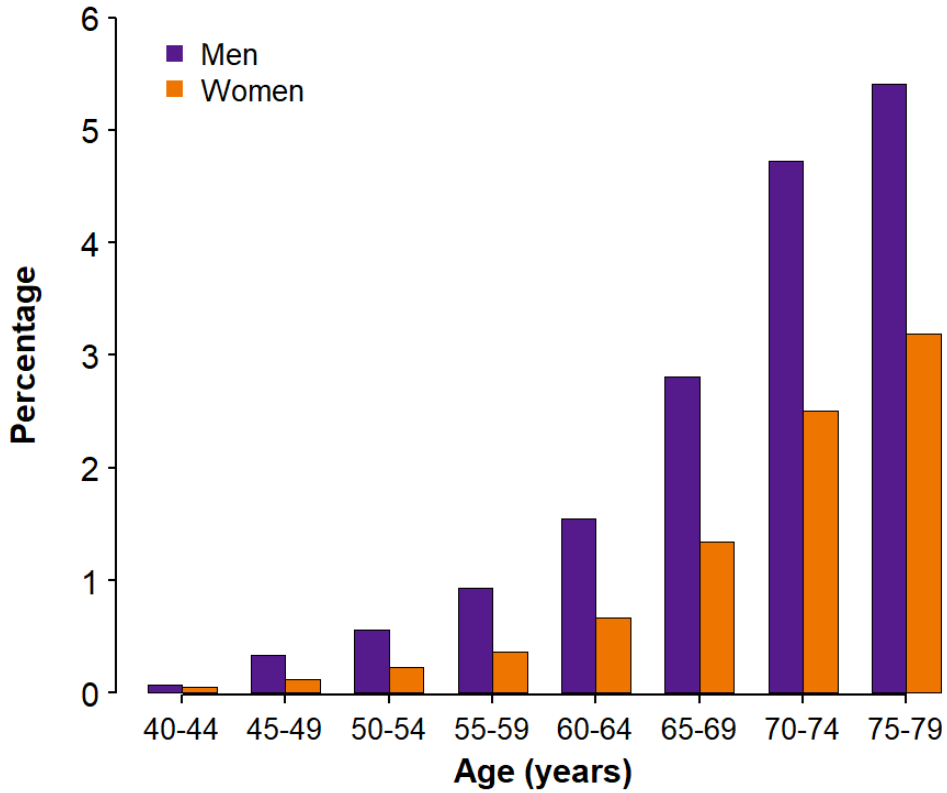


Figure 4.2: Histograms of anthropometric and bio-impedance variables
Histograms demonstrating the distribution of values for anthropoemtric and bio-impedance variables in men and women seperately. Exclusions as per ***Table 4.2****.*

4.4.2. Incident atrial fibrillation

During a median follow-up of 11.1 years (interquartile range 10.4-11.8), 23,134 incident AF cases were identified (14,400 in men and 8,734 in women). A higher incidence of AF in men than women was observed in all age groups (**Figure 4.3**). The mean age at which AF was reported was 69.1 years (SD 6.7), and was similar in both sexes.



Cases (Men)	17	172	456	955	1929	3777	4508	2419
Cases (Women)	13	77	236	481	1075	2196	2884	1676
Participants (Men)	22966	50937	81566	101870	124904	134469	95509	44754
Participants (Women)	26739	62373	103341	132164	160377	163246	114899	52513

Figure 4.3: Incidence of atrial fibrillation by age in UK Biobank.
Barplot showing the incidence of atrial fibrillation by age and sex. Exclusions as per ***Table 4.2****. Participants are grouped by age during follow-up. Cases relate to incident AF cases occurring in each age band. Participants are those at risk of atrial fibrillation in each age band. Bars represent the percentage developing atrial fibrillation from those at risk of atrial fibrillation within each age group.*

4.4.3. Comparing the effects of body mass index, waist circumference, and weight on risk of atrial fibrillation in men and women

Initially, the associations between measures of adiposity most commonly used in clinical practice, namely BMI, WC and weight, and the risk of AF were investigated. The range of values for these anthropometric measures were comparable between sexes (**Figure 4.2**, **Figure 4.4**). Risk of AF was strongly and positively associated with BMI, WC, and weight, and the associations were approximately log-linear in both men and women (**Figure 4.4**, **Appendix Figure E.1**).

For a given BMI, men were at about double the risk of AF compared to women. BMI was associated with an approximately 40% higher risk of AF, per 5 kg/m^2, amongst all participants (HR 1.37 [95%CI 1.35-1.38]), with a slightly greater effect in men than in women (p-interaction=0.01; **Figure 4.4**). However, the risk associated with BMI was more than halved after adjusting for WC (HR 1.15 [1.12-1.18] per 5 kg/m^2), after which the effects in both sexes were equivalent (**Figure 4.5**).

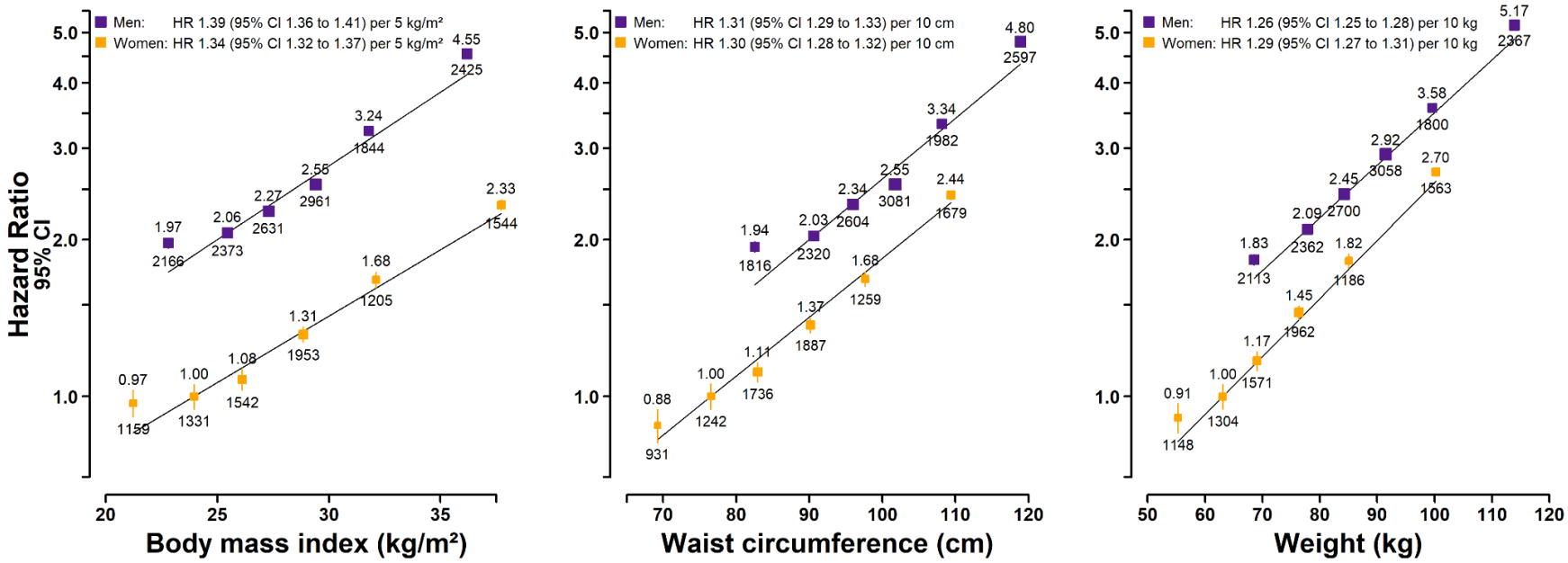


Figure 4.4: Association of body mass index, waist circumference, and weight with incident atrial fibrillation.
Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Plotted on a floating absolute scale in men (purple squares) and women (orange squares). Sex-specific regression lines are plotted. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Hazard ratios shown above each square and the number of AF cases below.*

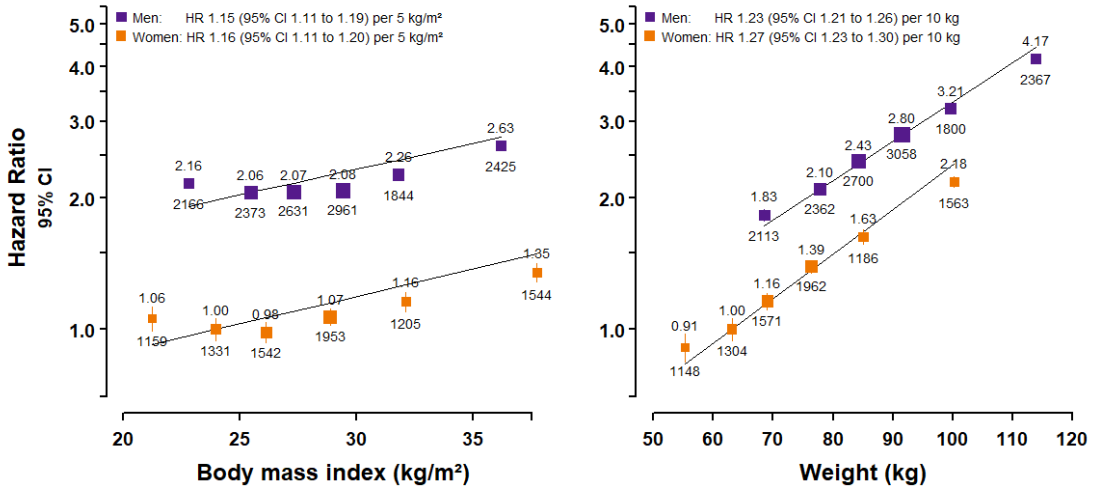


Figure 4.5: Association of body mass index and weight with incident atrial fibrillation after adjustment for waist circumference.

Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Hazard ratios shown above each square and the number of AF cases below.*

1

2 Similarly, for a given WC, men were at higher risk of AF than women. Overall,
3 WC was associated with a 30% higher risk of AF (HR 1.30 [1.29-1.32]), per 10cm
4 (equivalent to a 3.5-4kg/m^2 change in BMI); with comparable effects in men and
5 women (p-interaction=0.67). This association was independent of BMI, but
6 attenuated after adjustment for weight (HR 1.11 [1.09-1.14] per 10cm, **Figure**
7 **4.6**).

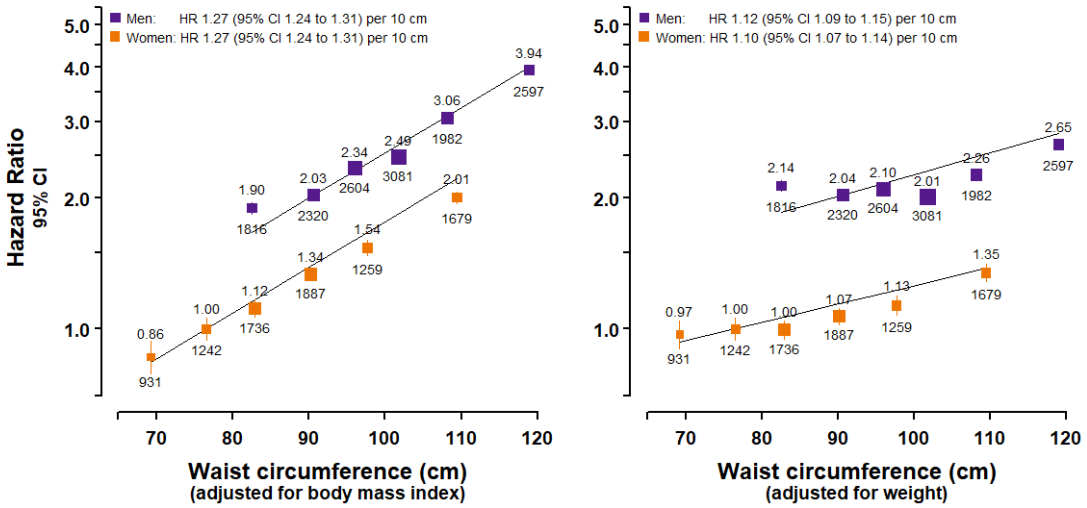


Figure 4.6: Association of waist circumference with incident atrial fibrillation after adjustment for body mass index and weight.
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Hazard ratios shown above each square and the number of AF cases below.*

Finally, weight was associated with a 30% higher risk of AF (HR 1.28 [1.26-1.29]) per 10kg (equivalent to a 3-3.5kg/m^2 change in BMI), with comparable associations in both sexes (p-interaction=0.09). In men and women, weight most strongly predicted AF (**Table 4.3**). The association between weight and risk of AF was independent of WC (HR 1.25 [1.23-1.27], per 10kg) with similar effects in both sexes (**Figure 4.5**).

In summary, considered in turn, BMI, WC, and weight each predict risk of AF, with weight showing the strongest association in both men and women. The strong and independent association between weight and AF warrants further investigation.

Table 4.3: Effect of anthropometric measures on risk of atrial fibrillation in men and women

	Units	HR (95%CI)	X_1^2
Men			
Body mass index	5 kg/m^2	1.39 (1.36 to 1.41)	1102
Waist circumference	10 cm	1.31 (1.29 to 1.33)	1302
Weight	10 kg	1.26 (1.25 to 1.28)	1610
Lean mass	5 kg	1.24 (1.23 to 1.25)	1512
Fat mass	5 kg	1.18 (1.17 to 1.19)	1114
Women			
Body mass index	5 kg/m^2	1.34 (1.32 to 1.37)	832
Waist circumference	10 cm	1.30 (1.28 to 1.32)	947
Weight	10 kg	1.29 (1.27 to 1.31)	1187
Lean mass	5 kg	1.40 (1.37 to 1.43)	1046
Fat mass	5 kg	1.18 (1.17 to 1.20)	1033

Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Effects are reported per the units specified as measured at baseline. χ^2 values derived from type 1 likelihood ratio values. CI – confidence intervals

4.4.4. Comparing the effects of fat mass and lean mass on risk of atrial fibrillation in men and women

Weight is the sum of FM and LM, therefore the separate effects of FM and LM (derived from bio-impedance measures) on the risk of AF were assessed. The distributions for FM were comparable between sexes (**Figure 4.7**, **Table 4.2**). However, for LM, men had substantially higher mean levels and variability than women (SD 7.7 vs 4.9kg), and the mean LM:FM ratio was higher in men than in women (3.21 vs 1.85).

FM and LM were both positively associated with AF and associations were approximately log-linear (**Figure 4.7**, **Figure 4.8**). For a given FM, men had approximately a two-fold higher risk of AF than women. In contrast, despite limited overlap in the range of LM values between men and women, women appeared to be at slightly higher risk of AF than men for a given LM. Overall, 5kg

higher FM was associated with a 20% higher risk of AF (HR 1.18 [1.17-1.19]), with similar effect sizes in both sexes (p-interaction=0.95). LM was associated with a 30% higher AF risk per 5kg (HR 1.28 [1.27-1.29]), with a somewhat weaker effect in men (HR 1.24 [1.23-1.25]) than in women (HR 1.40 [1.37-1.43]), p-interaction=$3x10^{-20}$.

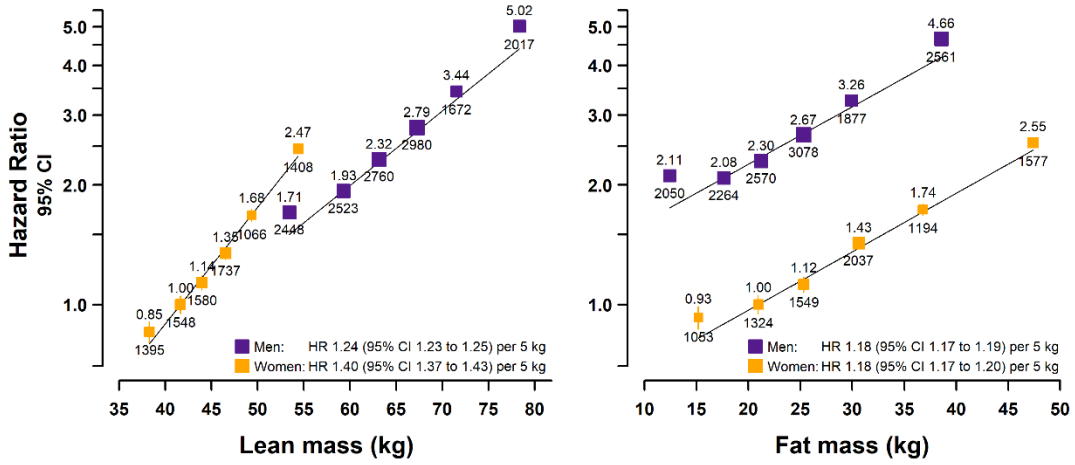


Figure 4.7: Association of lean mass and fat mass with incident atrial fibrillation. *Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Plotted on a floating absolute scale in men (purple open squares) and women (orange closed squares). Sex-specific regression lines are plotted. Exclusions as per* ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprise 10% of the sample. Hazard ratios shown above each square and the number of AF cases below.*

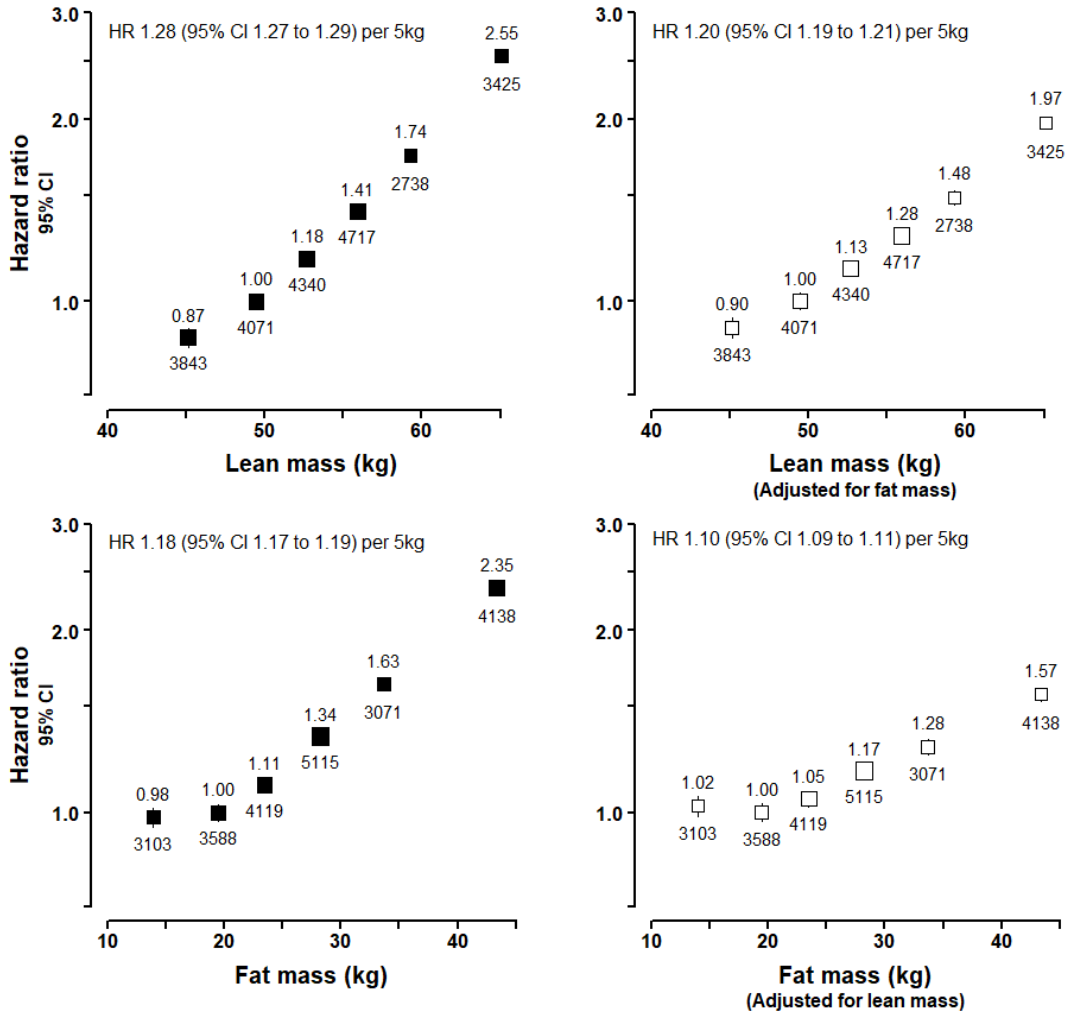


Figure 4.8: Association of lean mass and fat mass with incident atrial fibrillation, before and after mutual adjustment.
Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Plotted on a floating absolute scale in men (purple open squares) and women (orange closed squares). Sex-specific regression lines are plotted. Exclusions as per **Table 4.2***. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprise 10% of the sample. Hazard ratios shown above each square and the number of AF cases below.*

To assess the independent effects of FM and LM on the risk of AF effect sizes were examined following mutual adjustment. The effect of FM on AF was halved after adjustment for LM (overall, and by sex), with a 10% higher risk of AF (HR 1.10 [1.09-1.11] per 5kg, **Figure 4.8**, **Figure 4.9**). The effect of LM on AF was attenuated by about one-third after adjustment for FM, showing a 20% higher risk

of AF (HR 1.20 [1.19-1.21] per 5kg). However, whilst FM was equally relevant to both sexes, the effect per 5kg between LM and AF remained slightly weaker in men (HR 1.19 [1.17-1.20]) than in women (HR 1.25 [1.22-1.29]), p-interaction=4.3×10^{-9}. These associations were not materially altered by further adjustment for height (**Appendix Figure E.2**).

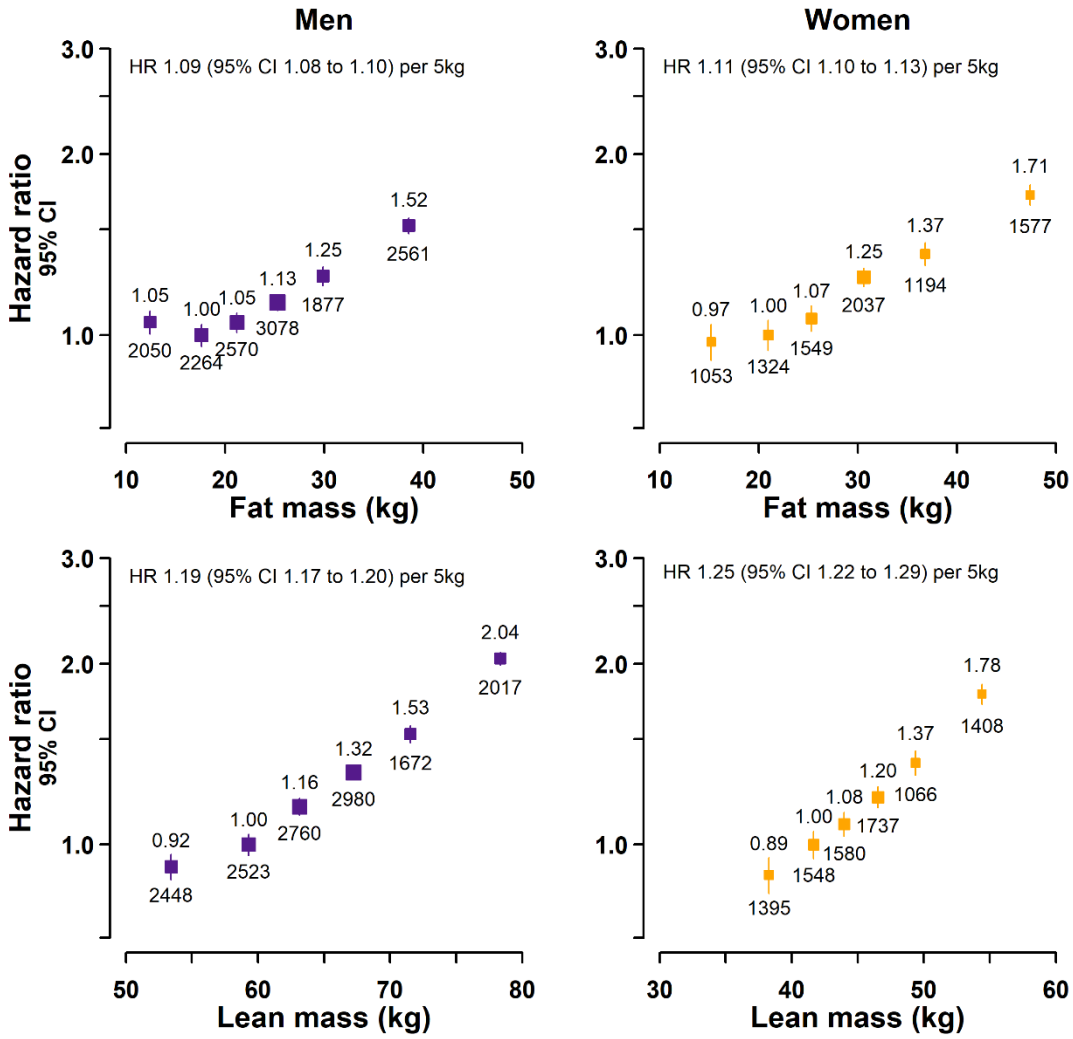


Figure 4.9: Independent association of lean mass and fat mass with incident atrial fibrillation by sex.
Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Associations of fat mass were also adjusted for lean mass, and those of lean mass were also adjusted for fat mass. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Hazard ratios shown above each square and numbers of AF cases below. The range of the X−axes has been kept consistent between men and women to allow for visual comparison.*

In summary, both FM and LM have independent relevance for risk of AF, and overall LM appears to confer about double the risk of AF per kg compared to FM. While the AF risk associated with FM was similar in men and women, the association with LM was weaker in men than in women.

4.4.5. Determining the relative effects of anthropometric measures on risk of atrial fibrillation separately in men and women

The relative strengths of different body size measures within sex were compared using sex-specific SD units (**Table 4.4**). The separate effects of LM and FM (as the constituents of weight) and WC (as a measure of central adiposity) on AF with and without mutual adjustment are shown in **Figure 4.10** (**Appendix Figure E.3**). In women, the three measures were each independently associated with about a 20% higher risk per SD (ranging from 15% for WC to 23% for LM). By contrast, in men, LM and WC were associated with a 30% and 20% higher risk per SD respectively, whilst FM was associated with only around a 7% higher risk per SD.

As illustrated in **Figure 4.10**, LM remained the strongest predictor of AF risk in both sexes after accounting for FM and WC (which together explained 69% of the association in men and 80% in women, based on changes in the χ^2 statistic). Most of the effect of FM on risk of AF was explained by LM in both men and women (82% and 79% respectively). LM also explained much of the effect of WC on the risk of AF (80% in both sexes). As a result, in men, the independent effect of WC was a stronger predictor of AF than FM, whilst in women, they were more comparable.

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Table 4.4: Relative ability of different anthropometric measures to predict incident atrial fibrillation

	HR per 1-SD baseline higher measure		HR per 1-SD usual higher measure	
	Baseline SD	**HR (95%CI)**	**Usual SD**	**HR (95%CI)**
Men				
Body mass index, kg/m^2	4.1	1.31 (1.29 to 1.33)	4.0	1.33 (1.31 to 1.35)
Waist circumference, cm	11.0	1.34 (1.32 to 1.36)	10.0	1.43 (1.41 to 1.46)
Weight, kg	13.9	1.38 (1.36 to 1.40)	13.5	1.41 (1.39 to 1.44)
Lean mass, kg	7.7	1.40 (1.37 to 1.42)	7.5	1.43 (1.40 to 1.45)
Fat mass, kg	8.0	1.31 (1.29 to 1.33)	7.6	1.34 (1.32 to 1.36)
Women				
Body mass index, kg/m^2	5.0	1.34 (1.32 to 1.37)	4.9	1.37 (1.34 to 1.40)
Waist circumference, cm	12.3	1.38 (1.35 to 1.41)	11.4	1.45 (1.42 to 1.49)
Weight, kg	13.7	1.42 (1.39 to 1.45)	13.2	1.46 (1.43 to 1.49)
Lean mass, kg	4.9	1.40 (1.37 to 1.42)	4.7	1.44 (1.41 to 1.48)
Fat mass, kg	9.8	1.39 (1.37 to 1.42)	9.4	1.44 (1.41 to 1.47)

Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Effects are reported per sex-specific standard deviation from a measurement at baseline (Baseline SD) and after correction for regression dilution bias (Usual SD). CI – confidence intervals, SD – standard deviation

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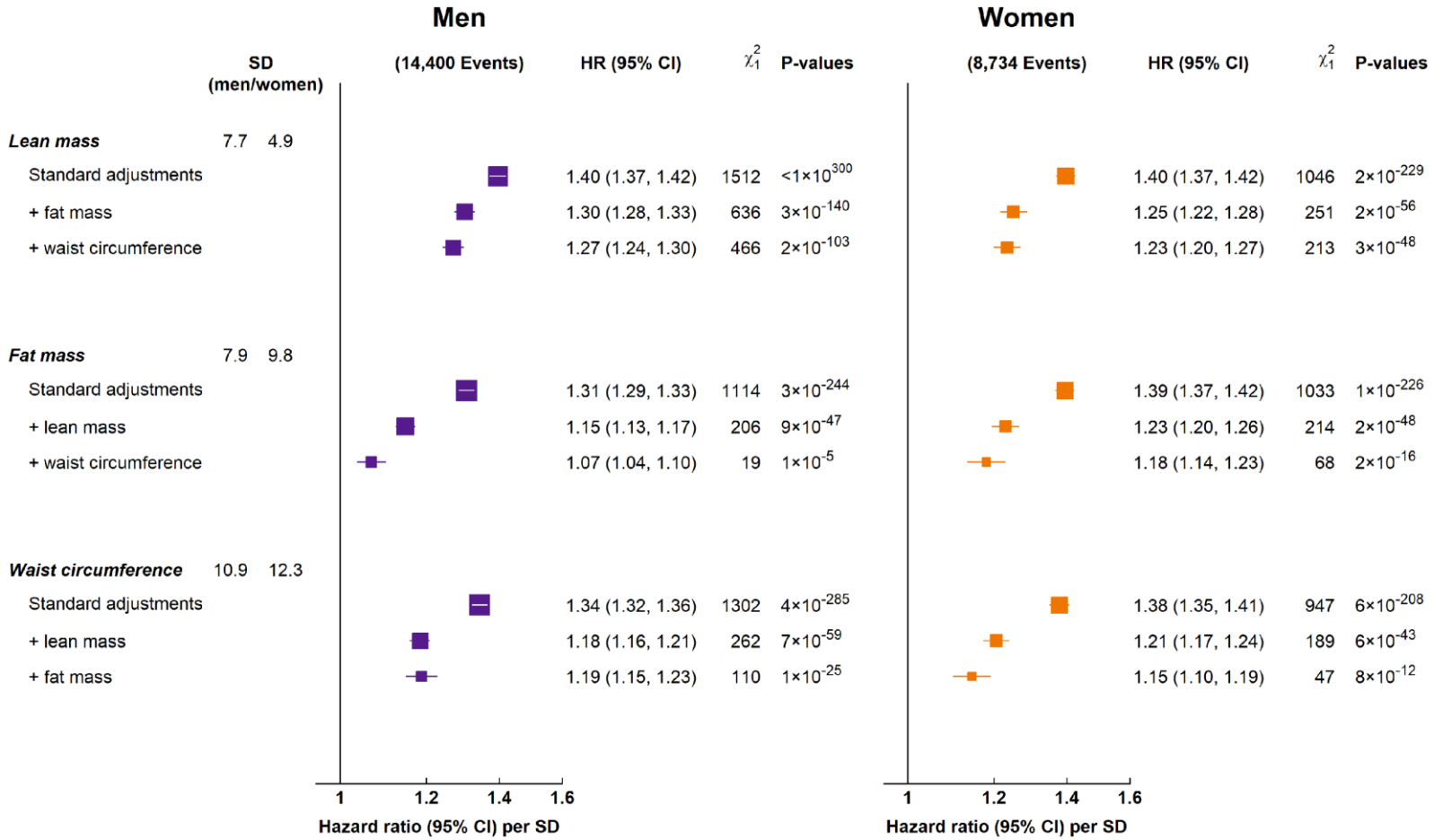


Figure 4.10: Comparison of associations between lean mass, fat mass, and wait circumference with incident atrial fibrillation, by sex.

Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking and alcohol, with progressive adjustments were indicated. Exclusions as per table 1. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars).

4.4.6. Sensitivity analyses

The impact of regression dilution bias was assessed based on the subset of participants with data at re-survey (approximately 4 years after baseline). Mean values of each anthropometric measure were relatively stable over time, and regression dilution ratios were very high (range 0.82-0.94; **Appendix Table E.1**). Consequently, correcting for regression dilution bias did not substantially change the associations, with the exception of those for WC, which became further strengthened (**Table 4.4**).

Residual confounding and reverse causation were also considered. The AF associations were comparable following further adjustment for additional potential confounders (physical activity, bread consumption, processed meat consumption, fruit consumption, vegetable consumption); for factors potentially on the causal pathway (baseline hypertension and sleep apnoea, **Appendix Table E.3**); after censoring those with vascular disease and the first two years of follow-up (**Appendix Table E.4**); and within different age groups (**Appendix Figure E.4**).

4.5. Discussion

In this large prospective study, incident AF was positively associated with measures of general adiposity, central adiposity, and LM. Weight was most strongly associated with risk of AF with similar effects in both sexes, chiefly driven by the association with LM, albeit LM and FM were both associated with risk of AF. FM had similar effects, per-kg, on risk of AF in both sexes while the effect of LM was weaker in men versus women. Assessment of the relative strength of the associations with different body size measures (LM, FM, and WC) suggested different patterns within men and women. In both sexes, LM was the strongest predictor of AF (after mutual adjustment, **Figure 4.10**). However, WC was materially stronger than FM in men, whilst this was not the case in women. This sex-related disparity suggests that the relative importance of general and central adiposity in AF prediction may differ between sexes.

Previous prospective studies have reported strong positive associations between BMI and risk of AF.[58,60,211] The overall results of the present study are broadly in keeping with those of a previous meta-analysis, which found 5kg/m^2 higher BMI was associated with an approximately 30% higher risk of AF.[65] However, the effects of BMI on risk of AF in men and women have only been examined in a small number of studies with limited AF cases, resulting in conflicting results; some have suggested a stronger association between BMI and risk of AF in men than women,[73,74] whilst others demonstrated no difference.[75,76] In the present large-scale study, there was no difference in the effect of BMI on AF risk between men and women. In both sexes, following adjustment for WC, the association between BMI and risk of AF was attenuated. Conversely, WC remained strongly predictive of AF after adjustment for BMI. The findings of this study support an

independent role for weight and WC, as easy-to-assess clinical measures, in predicting risk of AF in both sexes and suggest that both should be considered when assessing the risk of an individual developing AF.

Most prospective studies exploring the relationship between adiposity and AF have used BMI as a measure of general adiposity. However, neither BMI nor weight distinguish between FM and LM, or other aspects of body composition, such as body-fat distribution, which are important when considering potential differences in association with AF in men and women. Several studies have used measurements of bio-impedance (or other imaging methods) to estimate FM more directly.[66-70] A meta-analysis reported a 10% higher risk of AF per 5kg higher FM.[65] However, the prospective studies included did not provide comparative strengths of association for men and women, nor did they adjust for the effects of LM.

There is increasing evidence to support an effect of LM on the risk of AF.[58,60,73] Based on an analysis of non-sex specific SD units among around 14,000 AF cases in UKB, Tikkanen *et al.* reported that the effect of LM on risk of AF was approximately double that of FM (SD=9.6kg).[71] Importantly, LM, FM, and measures of central adiposity are highly correlated and adjustment for one another is required to establish the independent information these traits contribute to the risk of AF. Fenger-Grøn *et al*. in a Danish cohort (3,868 AF cases) found that, after adjusting for LM, associations between AF and measures of adiposity were almost completely attenuated.[66] This finding contrasts with a recent MR study, which suggests a possible causal role for both FM and LM on risk of AF.[71] However, whether there are differences in the effects between men

or women has not been established. Our results, based on 23,134 AF cases, suggest some differences between men and women. In women, following adjustment for one another and WC, the per-SD effects of LM and FM on risk of AF were similar. However, in men, the effect of LM on risk of AF was greater than that of FM. Differences in risks associated with LM and FM accompanied by higher contribution of LM to weight in men compared with women may account for some of the observed differences in AF prevalence. LM may vary with age, with lower LM in older adults.[247] However, the current results suggest LM associations are independent of age, with higher LM associated with greater risk of AF across all age groups studied.

Differences between sexes in the independent effect of FM on risk of AF have potentially important implications. While weight loss has been associated with a reduced AF burden,[78] it has not been clearly established whether this effect is due to a reduction in adipose or lean tissue. In those who are overweight/obese, LM accounts for 20-30% of weight loss due to calorie restriction,[248] suggesting that LM reduction, which has typically been associated with risk of frailty, may also contribute to the beneficial effects of weight loss on the recurrence rate and burden of AF. Importantly, to date, studies assessing the effect of weight loss on AF have normally combined calorie restriction with physical exercise.[78,80] The findings from the current study support public health messaging and individual weight loss programmes, and suggest that the impact of body composition on the incidence or recurrence of AF, particularly in the context of such programmes, should be further investigated.

The effect of central adiposity on risk of AF has been less well described than that of general adiposity. Our findings are comparable with a meta-analysis reporting a 1-SD (approximately 10cm) higher WC was associated with a 30% higher risk of AF.[72] However, the current study is the first to show a role for central adiposity on the risk of AF independent of LM and general adiposity that is present in both sexes. Consequently, a reduction of 6-15cm in WC as observed in weight loss studies, if causal, could translate to an 8-19% and 7-16% lower risk of AF in men and women respectively even after adjustment for LM and FM.[249-251]

WC has been shown to be correlated with visceral abdominal fat in men and women (r=0.73-0.78).[51] Measures of abdominal VAT and PAT have been associated with adverse cardio-metabolic risk factors, including elevated blood pressure, dyslipidaemia, inflammatory markers, and insulin resistance.[53-55] These are, in turn, associated with risk of AF.[120,252] Two prospective studies have used body imaging to directly assess the association between abdominal VAT and the risk of AF, but were insufficiently powered to provide robust conclusions.[68,100] Our results suggest that as further abdominal MRI data (including measures of visceral abdominal fat volume) become available, exploration of the relationship between visceral adiposity and AF may improve understanding of the biological mechanisms by which central adiposity affects risk of AF. The association between PAT has previously been explored in a number of small studies which suggest a strong positive association with risk of AF.[72] However, many of these are case-control studies and subject to the risk of reverse causation. When explored in prospective cohorts, the strength of association has been more modest,[100,230] with some demonstrating no significant

association with risk of AF.[94,95] The future development of a large-scale PAT cohort would allow further exploration of the relationship between PAT and risk of AF.

The effects of adiposity and lean mass on cardiac structure are not well established. Higher LM has been positively correlated with left ventricular mass and left atrial size,[238,239] both of which are associated with risk of AF. Future large-scale data will enable further assessment of these potential mechanisms and help to establish the biological pathways by which LM and measures of adiposity are associated with risk of AF, which may inform the selection of therapeutic targets.

4.5.1. Strengths and limitations

This study has a number of strengths such as its large size and high-quality measurements of adiposity. With over 23,000 incident AF events, the study was able to reliably quantify the strengths of the associations and their relative independence, overall and by sex. Furthermore, it was possible to adjust for a wide range of potential confounders. Despite this, observational associations can be subject to uncontrolled residual confounding, as well as bias from measurement and correlated errors. Although representativeness is not required for relative risks to be fully generalisable, caution should be used when extending these findings to some population subgroups on which there are limited data (e.g. the young, the very old, and some ethnic minority groups). In addition, information on incident AF was taken from hospital records and death registries only; given AF may initially be diagnosed in the community there may be a lead-time bias and some participants with asymptomatic paroxysmal AF may not have been

identified. It was not possible to assess associations outside of the anthropometric variable ranges observed in UKB.

4.5.2. Conclusions

This study quantifies the strengths of the associations between common measures of body composition and incident AF in men and women and demonstrates a key role of central adiposity and LM in both sexes. However, in contrast to women, the relevance of general adiposity for AF, independent of central adiposity and LM, was more limited in men. Given these findings, the mechanisms by which weight loss leads to improvement in AF in men and women should be further explored.

The results of this chapter have also been published:[226]

> **Camm CF**, Lacey B, Massa MS, Von Ende A, Gajendragadkar P, Stiby A, Valdes-Marquez E, Lewington S, Wijesurendra R, Parish S, Casadei B, Hopewell JC. Independent effects of adiposity measures on risk of atrial fibrillation in men and women: a study of 0.5 million individuals. *Int J Epidemiol*. 2022;51(3):984-95.

4.5.3. Next steps

PAT is correlated with a number of anthropometric measures,[96] and may represent a common pathway through which adiposity phenotypes are associated with AF.[72,253] The presence of CMR data in a sub-set of the UKB population allows exploration of PAT and the development of a PAT phenotype (**Chapter 5**).

The associations identified in this chapter suggests differences in role of measures of body size and shape on the risks of AF in men and women. However, independent causal relevance of these measures and any differences in the causal relationship in men and women has not been well established. To this end, MR analyses of anthropometric phenotypes will be undertaken to explore this question (**Chapter 7**).

Chapter 5 – Pericardial adipose tissue phenotyping in UK Biobank

5.1. Abstract

5.1.1. Background

There is evidence to suggest that pericardial adipose tissue (PAT) may be associated with the risk of atrial fibrillation. However, there has been limited assessment of PAT in large-scale cohorts due to difficulty phenotyping this trait. This study aimed to develop a PAT phenotype from cardiac magnetic resonance imaging (CMR) data available in UK Biobank (UKB).

5.1.2. Methods

PAT area was calculated in 3,477 UKB participants using mid-ventricular shortened modified look-locker inversion recovery (ShMOLLI) and cine images. PAT areas were manually contoured on mid-ventricular ShMOLLI images. Intra- and inter-observer reproducibility was assessed using random re-sampling. Correlations between PAT area and other anthropometric traits were quantified using Pearson's correlation coefficients.

5.1.3. Results

Mid-ventricular PAT area was 13.4 cm^2 (standard deviation [SD] 6.1 cm^2); and was larger in men (15.4 cm^2, SD 6.4 cm^2) than women (mean 11.6 cm^2, SD 5.2 cm^2). This difference was removed when normalised for left-ventricular size. The

quality of PAT images was generally high; median R^2 value was 0.92 (inter-quartile range 0.91 to 0.96), with 90% having a high subjective image quality score rating (n=3,125). There was high intra- and inter-observer correlation (r^2 0.87 and 0.89 respectively). Those with greater PAT area had a higher burden of prevalent cardiovascular disease including hypertension, diabetes, and coronary heart disease. PAT area was positively correlated with anthropometric measures such as body mass index, waist circumference, and visceral adipose tissue.

5.1.4. Conclusions

A mid-ventricular ShMOLLI CMR image can be used to obtain a PAT area phenotype. PAT area varied significantly between participants and was positively associated with other anthropometric traits and prevalent cardiovascular disease.

5.2. Introduction

PAT has been suggested as a link between general adiposity and risk of AF.[72] PAT is the fat surrounding the heart (sitting between the epicardial surface of the heart and the pericardium, **Figure 1.3**).[229] There is evidence that epicardial fat tissue, which forms part of PAT, shares a micro-circulation with the myocardium;[254] therefore, it has been suggested that substances secreted from the adipocytes may locally impact the myocardium. PAT has been associated with a higher risk of CHD as well as AF.[72,255,256]

Unlike most well-established anthropometric measures which have a single method of measurement (for example BMI), a range of imaging modalities have been used for quantifying PAT which may result in substantial heterogeneity between studies.[72] Furthermore, PAT thickness, area, and volume have all been reported in the literature.[257] Echocardiography and cardiac CT have frequently been used,[95,100,232] Echocardiography is limited to the assessment of PAT thickness. Cardiac CT is considered the gold-standard for assessment of PAT.[258] However, cardiac CT utilises ionising radiation limiting use in large-scale datasets. In contrast, CMR has not been widely used in this area,[259] although recent studies have highlighted the potential of this imaging modality for the evaluation of PAT.[260,261]

This research aimed to develop and validate a novel PAT phenotype using CMR data available in a subset of UKB participants to elucidate our understanding of PAT for AF through further epidemiological and genetic epidemiology research.

5.3. Methods

5.3.1. Participants

The UKB cohort has been detailed in **Chapter 2** (**UK Biobank**). A selection of UKB participants have undergone full-body MRI imaging as part of a re-survey 4-5 years after enrolment. This re-survey is ongoing with the aim of scanning 20% of the original cohort.[262]

5.3.2. Cardiac magnetic resonance imaging data

MRI scans were undertaken at four UK sites (Reading, Stockport, Newcastle, and Bristol) and undertaken using a custom 20-minute protocol on a 1.5T scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) without a pharmacological stressor or the use of contrast agents.[262,263] Anatomical information was provided using a balanced steady state free procession (bSSFP) sequence. Additional tissue characterisation information was obtained from a native T1 ShMOLLI map in the mid-ventricular short axis.[262] At the time of initiating this research, data from 45,751 participants was available for analysis.

UKB participants were included in the PAT analysis if they met the following inclusion criteria: (1) had bulk imaging data available from the CMR scout images, short axis cine images, and a mid-ventricular native T1 map; (2) had published values for their left atrial and left ventricular (LV) volumes available;[264] (3) passed quality control criteria for left atrial and LV volumes in prior

analyses;[264] (4) had anthropometric data available at baseline; and (5) had genetic data available (**Figure 5.1**).

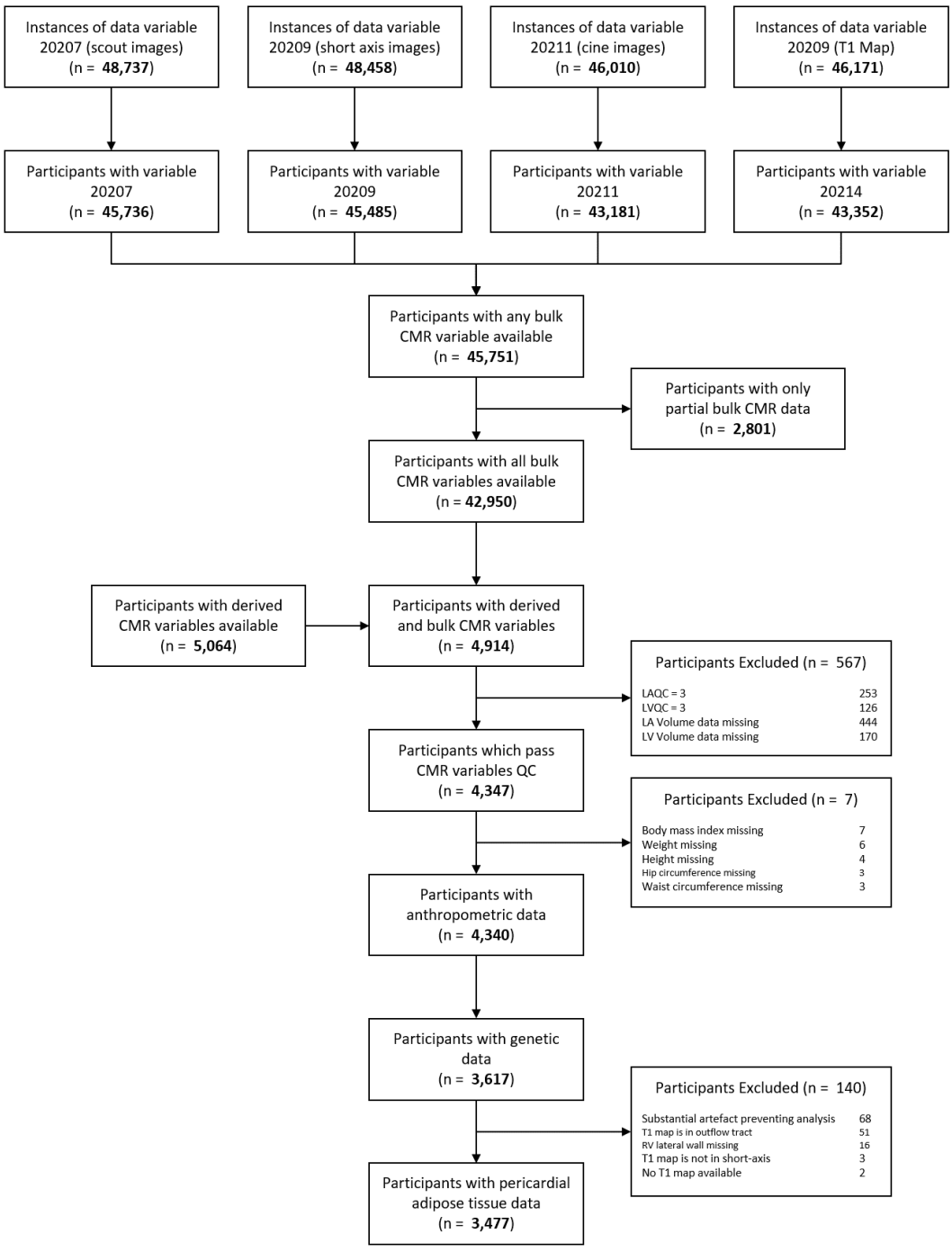


Figure 5.1: Flowchart of participants included in the pericardial adipose tissue analysis.
CMR – cardiac magnetic resonance imaging; LA – left atrial, LV – left ventricular, RV – right ventricular, QC – quality control

5.3.3. Pericardial adipose tissue phenotype

PAT was defined as fat tissue between the epicardial surface and the internal surface of the visceral pericardium across the whole heart in the mid-ventricular ShMOLLI native T1 image. A standard operating procedure was developed to calculate the PAT area (Appendix F - **Pericardial adipose tissue phenotyping: standard operating procedure**). In brief, the native T1 map was used to allow clear identification of fat tissue and to allow differentiation of fat tissue from other tissues surrounding the heart (e.g. pericardial effusions, lung tissue, etc.). Where the pericardium was not clear on the T1 map, the equivalent cine slice from the mid ventricle was identified and used to locate the pericardium (**Figure 5.2**).[265] Areas of PAT were contoured using a free-form shape and exported. If multiple areas of PAT were identified, a total area was determined by summation of each individual region of PAT identified. Manual contouring of PAT area was undertaken by one individual (CF Camm) who was blinded to other patient characteristics. CMR scans were analysed using OsiriX MD (version 12.0.3, Pixmeo, Switzerland).[266]

In addition to the above measurements of total mid-ventricular PAT area, in a sub-set of participants (n=1,481) mid-ventricular LV PAT area values were obtained. LV PAT areas were obtained after beginning the acquisition of total PAT area as an informal review of the images suggested that LV PAT area might be more consistently measured between observers. LV PAT was defined as fat tissue between the epicardial surface and pericardium over the LV as far as the border between the intraventricular septum and the right ventricle (**Figure 5.3**). Analysis of LV PAT was principally undertaken from week 16 of the analysis with

retrospective assessment of some scans that were initially contoured in weeks 1-15 when validation checks were undertaken.

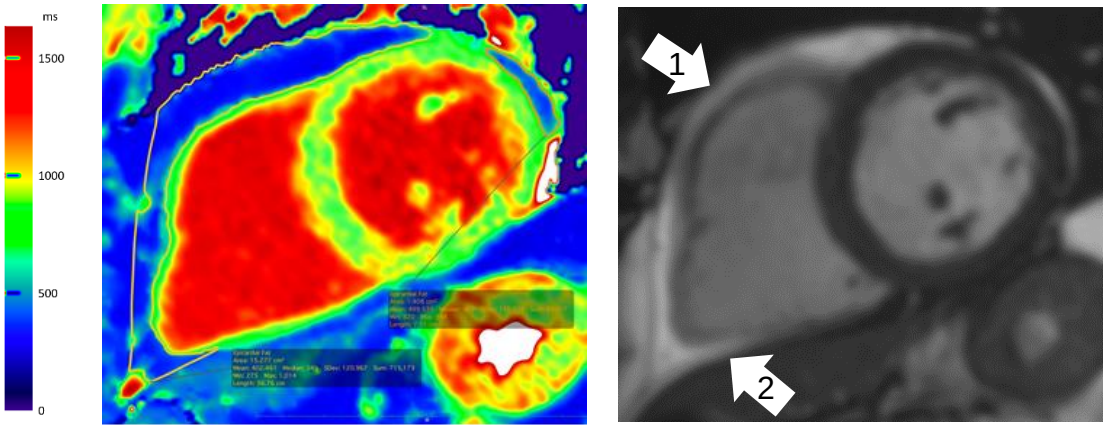


Figure 5.2: Example of native T1 map and mid-ventricular cine still image for a UK Biobank participant.
The native T1 map (left panel) is used to distinguish fat (blue) from fluid (red/white). Pericardial adipose tissue is defined as fat tissue between the epicardial surface and pericardium. The cine image (right panel) is used to help distinguish additional anatomy including the pericardium (arrow one) and diaphragm (arrow two) where required. Free-form regions of interest are drawn around the pericardial adipose tissue to define the area (seen in left panel).

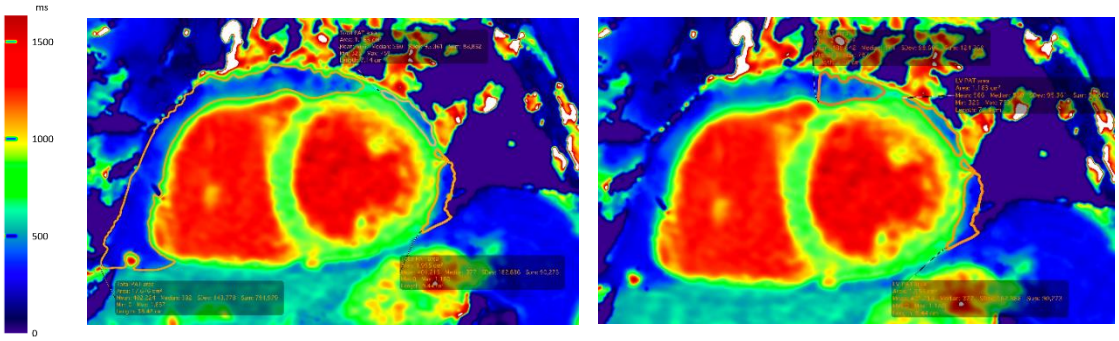


Figure 5.3: Example of determination of total and left ventricular pericardial adipose tissue from mid-ventricular native T1 map for a UK Biobank participant.
In native T1 maps (both panels), fat tissue (blue colour) can be differentiated from other tissues (green/red/white). The native T1 maps include free-form regions of interest are drawn around the total area of pericardial adipose tissue (left panel) and left ventricular pericardial adipose tissue (right panel).

5.3.4. Quality assessment of T1 maps

Initial central quality control measures were undertaken by UKB during image acquisition. In particular, images were assessed in real time by the operator and again after acquisition for image quality and artefacts.[267] In this study, to assess

image quality, participant ShMOLLI images were each given an image quality score from 1 to 3 (1 – good quality image, 2 – some artefacts that may affect assessment of PAT area, 3 – substantial artefacts or other issues which prevent assessment of PAT area).

T1 maps are derived from non-linear estimation from a sequential series of bSSFP images.[268] As a result, a number of factors including breathing motion, off-resonance artefacts, and poor T1 model fit may lead to inappropriately high or low T1 values.[269] To assess T1 model fitting, parametric maps of goodness-of-fit are provided (R^2 maps). These provide an R^2 value for each voxel of the T1 map image and provide an opportunity to identify artefacts or areas with potential for limited T1 accuracy (**Figure 5.4**). The median R^2 value for the PAT area was calculated for each participant.[270]

5.3.5. Validation of the pericardial adipose tissue phenotype

A random sample of 100 participants were selected for intra-observer validation assessment. Each participant was given a new unique number to ensure the assessment was blinded. Total and LV PAT area was contoured in the same manner as described for the original assessment. Pearson's correlation coefficients were calculated as an assessment of intra-observer correlation with Bland-Altman plots developed to examine systemic bias.

A similar technique was utilised for independent inter-observer validation. A separate sample of 100 randomly selected participants were analysed by a blinded second individual. This second individual was trained independently of the first to prevent individual biases being transferred. It was subsequently

discovered that all 100 participants had an image quality score of one and a further 10 images (seven with an image quality score of two) were added to the inter-observer dataset.

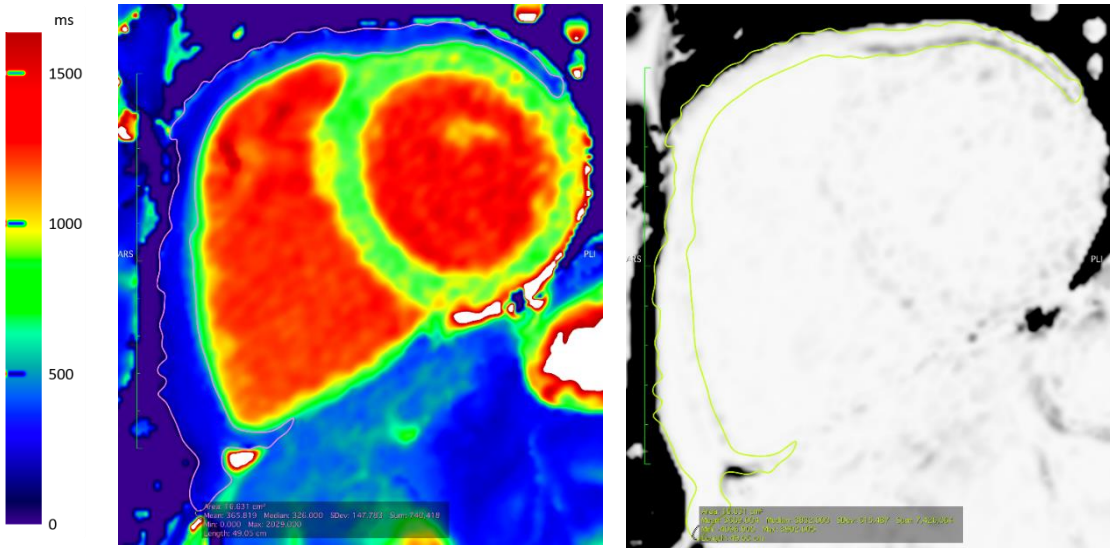


Figure 5.4: Indicative example of a mid-ventricular ShMOLLI image and parametric map of goodness-of-fit for a UK Biobank participant.
Left panel: mid-ventricular native T1 map ShMOLLI image. Fat tissue is represented in blue, with muscle in green and fluid in red/white. A region of interest has been created around the tissue representing pericardial adipose tissue to generate a measure of paroxysmal adipose tissue area. Right panel: parametric map of goodness-of-fit for the same ShMOLLI image. Each voxel has an R^2 value ascribed to it with higher R^2 values appearing white. The region of interest created for the participant's pericardial adipose tissue area is copied across to the R^2 map to determine the median R^2 value for the region of interest.

Once all scans had been examined and measured, a pre-defined selection of scans were chosen for re-assessment. In particular, all cases with a total PAT area of >30 cm^2, all participants with an image quality score of two or three, and a random selection of 2% of cases were re-examined.

T1 values for adipose tissue are not well established in the literature and PAT T1 values may be affected by inclusion of voxels representing surrounding structures (e.g. the myocardium). To assess adipose tissue T1 values, isolated areas of PAT and adipose tissue form the anterior thoracic region were identified

in 100 randomly selected participants. These regions were selected as they had no areas of visible artefact and contained no other structures. Regions of interest were drawn around these areas and the mean T1 values for these areas recorded.

5.3.6. Baseline characteristics and anthropometric measures

Participants taking part in the UKB imaging sub-study had a complete re-assessment of baseline characteristics and anthropometric measures (**Chapter 2**). These data were collected in the same way as the baseline assessment. Values for baseline characteristics and anthropometric measures were taken from the data provided as part of the imaging sub-study assessment. In individuals where baseline characteristic or anthropometric measure data were not available from the imaging sub-study (≤5% of participants for any variable, **Appendix Table G.1**), data from the baseline assessment was utilised.

5.3.7. Phenotyping prior disease

Medical conditions were phenotyped as outlined in **Chapter 2** (**Phenotype definitions**). Prior disease was defined as conditions identified in the HES record prior to entering the imaging sub-study, or if outlined in the verbal interview undertaken at the baseline assessment centre.

5.3.8. Statistical analyses

Continuous variables were described as mean (SD) or median (inter-quartile range [IQR]) as appropriate. Categorical variables were described using frequency (percentage). For continuous variables, differences between groups

used students T or Wilcoxon tests as appropriate. For categorical variables, differences in groups were assessed using a Chi squared analysis. To examine the association with baseline characteristics, PAT area was classified into fifths. To compare PAT area with other anthropometric measures, these traits were converted into SD units separately in men and women. Associations were examined using Pearson's correlation coefficients (r). All statistical analyses were undertaken using SAS (Version 9.3).

5.4. Results

Following participant selection, total PAT area was calculated in 3,477 participants with 140 excluded due to poor image quality or other problems with the CMR data (**Figure 5.1**). Of the included images, the majority were of a high quality (image quality score=1 in 3,125 participants [90%]).

5.4.1. Comparison between those with and without calculated pericardial adipose tissue areas

Included participants had a mean age of 55.5 years (SD 7.6 years) and 47.4% were men. Three-in-ten of those with a calculated PAT area suffered from hypertension at the time of the scan (n=1,079, 31%) with smaller proportions having CHD (n=187, 5.4%) and diabetes (n131, 3.8%). Those with PAT data were similar to those in the imaging sub-study without PAT data in terms of demographics, anthropometric measures, and prior disease (**Table 5.1**). Anthropometric measures had similar distributions in the PAT sub-set compared with the entire UKB cohort (**Appendix Figure G.1**).

Table 5.1: Characteristics of the cardiac magnetic resonance imaging subset of the UK Biobank cohort divided into those with and without pericardial adipose tissue data available (n=45,751)

	PAT imaging subset	
	No	Yes
Participants	42,274 (92.4)	3,477 (7.6)
Demographics		
Age, mean (SD)	63.5 (7.5)	61.8 (7.5)
Male, n(%)	20,405 (48.3)	1,648 (47.4)
White, n(%)	40,768 (96.4)	3,477 (100.0)
Current smoker, n(%)	1825 (4.3)	159 (4.6)
Current alcohol drinker, n(%)	39,704 (93.9)	3,281 (94.4)
Townsend deprivation index, mean (SD)	-1.9 (2.7)	-2.0 (2.7)
Anthropometric measures, mean (SD)		
Height, cm	169.3 (9.2)	169.2 (9.2)
Weight, kg	76.3 (15.1)	76.7 (15.1)
Body mass index, kg/m^2	26.5 (4.3)	26.7 (4.4)
Waist circumference, cm	88.3 (12.6)	87.4 (12.2)
Hip circumference, cm	101.5 (8.5)	101.5 (8.6)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)		
Body lean mass, kg	53.6 (11.4)	53.6 (11.4)
Body fat mass, kg	23.2 (8.6)	23.6 (8.6)
Prior disease, n(%)		
Coronary heart disease	2,355 (5.6)	187 (5.4)
Diabetes	1,633 (3.9)	131 (3.8)
Congestive cardiac failure	286 (0.7)	24 (0.7)
Hypertension	12,721 (30.1)	1,079 (31.0)
Sleep apnoea	457 (1.1)	27 (0.8)
Stroke	427 (1.0)	27 (0.8)
Valvular heart disease	435 (1.0)	28 (0.8)

Demographics and prior disease at the time of undertaking the imaging sub-study. PAT – pericardial adipose tissue; SD – standard deviation.

1

5.4.2. Pericardial adipose tissue area characteristics

5.4.2.1. Total pericardial adipose tissue area characteristics

Mean PAT area was 13.4 cm^2 (SD 6.1 cm^2) and was larger in men (mean 15.4 cm^2, SD 6.4 cm^2) than in women (mean 11.6 cm^2, SD 5.2 cm^2, p<0.0001, **Figure 5.5**). When indexed to body surface area, PAT area remained greater in men (mean 7.5 cm^2/m^2, SD 2.9 cm^2/m^2) and women (mean 6.5 cm^2/m^2, SD 2.8 cm^2/m^2, p<0.0001). However, when normalized to LV end-systolic volume there was no difference in PAT area between men (mean 0.24 cm^{-1}, SD 0.13 cm^{-1}) and women (mean 0.25 cm^{-1}, SD 0.13 cm^{-1}, p=0.13).

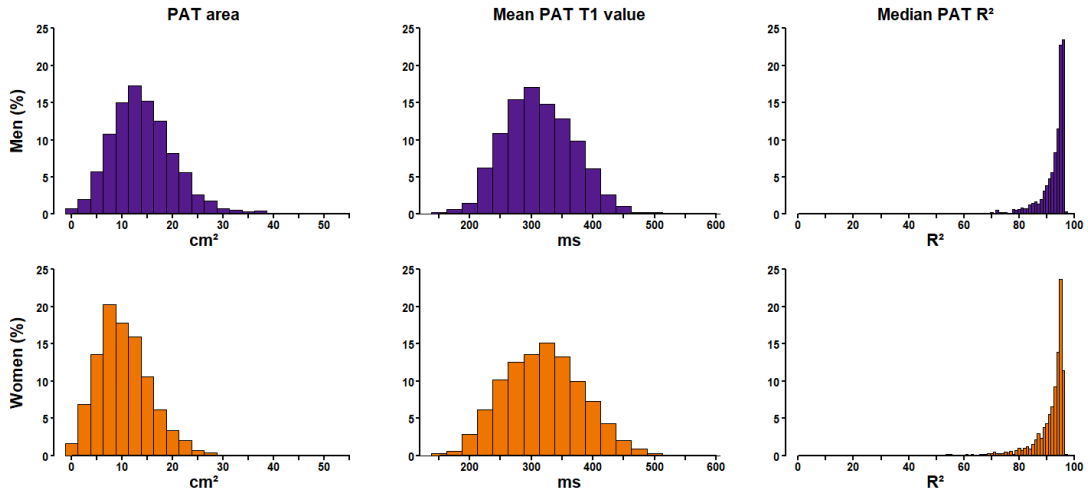


Figure 5.5: Histogram of total pericardial adipose tissue variables.
Histograms demonstrate the distribution of values for pericardial adipose tissue variables in men and women separately. PAT – pericardial adipose tissue.

The mean T1 value was 354 ms (SD 61 ms) and was not meaningfully different in men (mean 351 ms, SD 57 ms) and women (mean 357 ms, SD 64 ms). The majority of participants had a mean T1 value <500 ms (n=3,440, 98.9%). The median R^2 value was 0.92 (IQR 0.91 to 0.96) and was similar in men (median R^2 0.92 [0.91 to 0.96]) and in women (median R^2 0.91 [0.90 to 0.95]). There was no evidence to suggest calculated PAT area, T1 values, or R^2 values systemically

varied over the period of data collection (**Appendix Figure G.2** to **Appendix Figure G.4**).

5.4.2.2. Left ventricular pericardial adipose tissue area characteristics

LV PAT area was obtained in 1,481 participants (43%). The mean LV PAT area was 4.1 cm^2 (SD 3.1 cm^2). LV PAT area was larger in men (mean 4.9 cm^2, SD 3.4 cm^2) than in women (mean 3.4 cm^2, SD 2.6 cm^2, p<0.0001, **Figure 5.6**). As with total PAT area, when adjusted for LV end-systolic volume there was no difference in LV PAT area between men (mean 0.08 cm^{-1}, SD 0.13 cm^{-1}) and women (mean 0.07 cm^{-1}, SD 0.06 cm^{-1}, p=0.19).

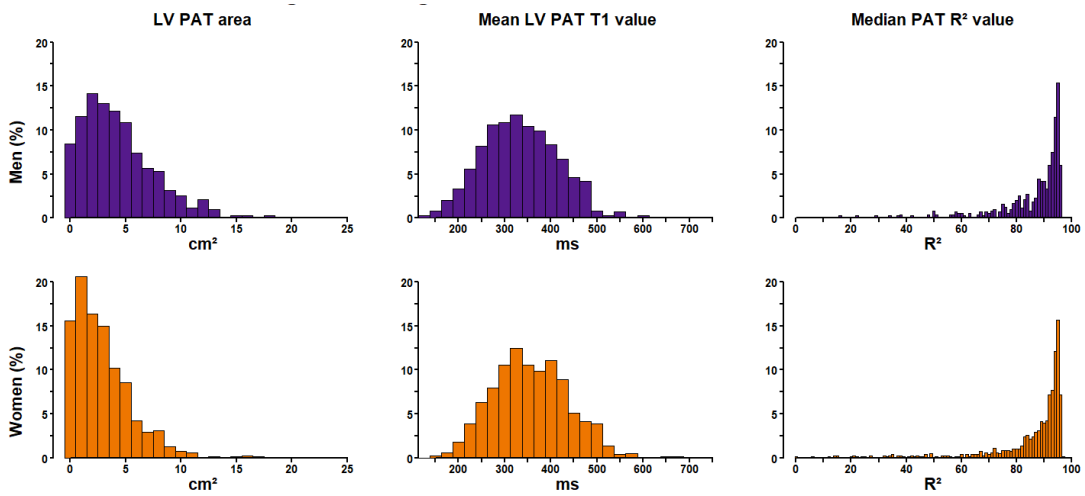


Figure 5.6: Histogram of left ventricular pericardial adipose tissue variables. *Histograms demonstrate the distribution of values for left ventricular PAT variables in men and women separately. LV – left ventricular, PAT – pericardial adipose tissue*

The mean T1 value was 382 ms (SD 82 ms) and was lower in men (mean 371, SD 82 ms) than in women (mean 393 ms, SD 81 ms, p<0.0001). The median R^2 value was 0.92 (IQR 0.83 to 0.95) and was similar in men (median R^2 0.91 [0.81 to 0.95) and women (median R^2 0.92 [0.84 to 0.95, p=0.10). With the exception of PAT area, there were no other meaningful differences between the characteristics of total PAT and LV PAT (**Table 5.2**). There was no evidence to

suggest calculated LV PAT area, T1 values, or R^2 values systemically varied over time (**Appendix Figure G.5** to **Appendix Figure G.7**).

Table 5.2: Characteristics for total and left ventricular pericardial adipose tissue area phenotypes

	Total PAT (n=3,477)	**LV PAT (n=1,481)**
PAT characteristics		
PAT area (cm^2), mean (SD)	13.4 (6.1)	4.1 (3.1)
T1 value (ms), mean (SD)	354 (61)	382 (82)
R^2, median (Q1-Q3)	0.92 (0.91 to 0.96)	0.91 (0.83 to 0.95)
Image quality score, n (%)		
1	3,125 (90)	1,297 (88)
2	352 (10)	184 (12)

LV – left ventricular, PAT – pericardial adipose tissue

5.4.2.3. Correlation between left ventricular and total pericardial adipose tissue

There was significant positive correlation between LV and total PAT (r = 0.81, **Figure 5.7**).

5.4.2.4. Pericardial adipose tissue T1 values compared with thoracic fat T1 values

Given the close relationship between PAT, the myocardium, and left lung, it is possible that the mean T1 values obtained have been affected by inclusion of voxels with T1 values related to these other structure. To assess this, in a random subset of 100 participants a sample of PAT was identified in each participant that did not contain voxels bordering any other structures and were free of visible artefacts. This demonstrated a mean T1 value of 294ms (SD 59 ms, **Figure 5.8**), with a range similar to that seen in the total PAT cohort. A similar process

undertaken for non-PAT intrathoracic fat demonstrated a similar mean T1 value (267 ms, SD 34 ms).

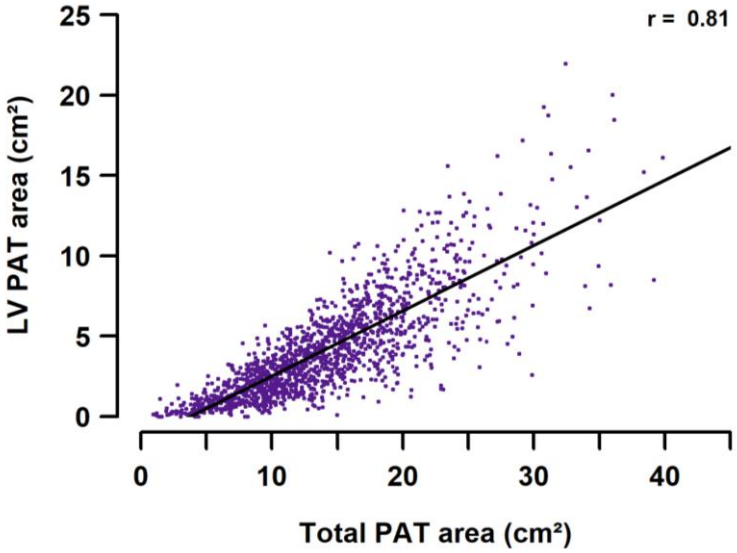


Figure 5.7: Scatter plot of total and left ventricular pericardial adipose tissue area (n=1,481).
The black line represents linear regression between total and LV pericardial adipose tissue areas. Displayed r-value is a Pearson's correlation coefficient. LV – left ventricular; PAT - pericardial adipose tissue.

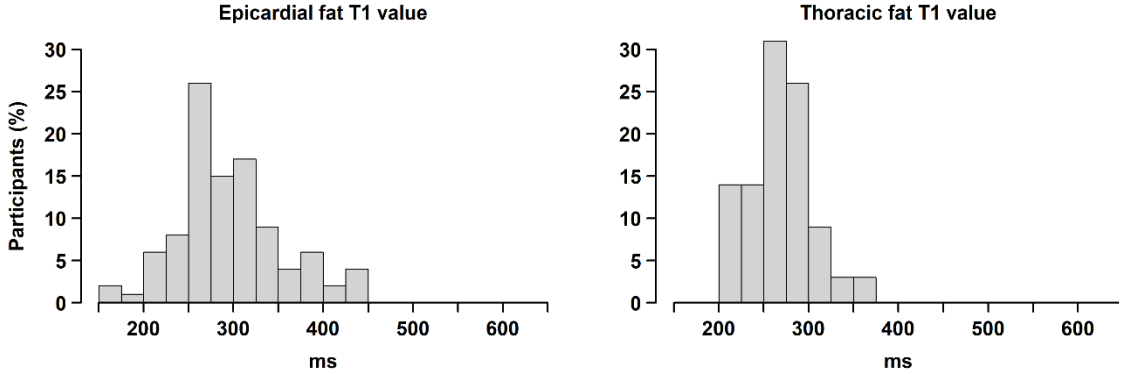


Figure 5.8: Mean T1 values from isolated areas of pericardial adipose tissue and anterior thoracic fat in 100 random participants.
Histograms demonstrating the distribution of T1 values in adipose tissue. Isolated values are from ≤1cm² areas of pericardial adipose tissue or thoracic fat without areas of visible artefact or alternative tissue.

5.4.3. Pericardial adipose tissue phenotype validation

5.4.3.1. Intra-observer validation

In 100 randomly selected samples there was high intra-observer correlation for total PAT area (r^2 = 0.87) and no substantial systemic bias (mean difference 0.39 cm^2, SD of the difference 1.91 cm^2, **Figure 5.9**). There was higher intra-observer correlation for LV PAT area (r^2 = 0.97) than seen for total PAT area, and no substantial systemic bias (mean difference 0.18 cm^2, SD of the difference 0.43 cm^2, **Figure 5.10**). Intra-observer correlation was higher in images with an image quality score of one than those with an image quality score of two (**Table 5.3**).

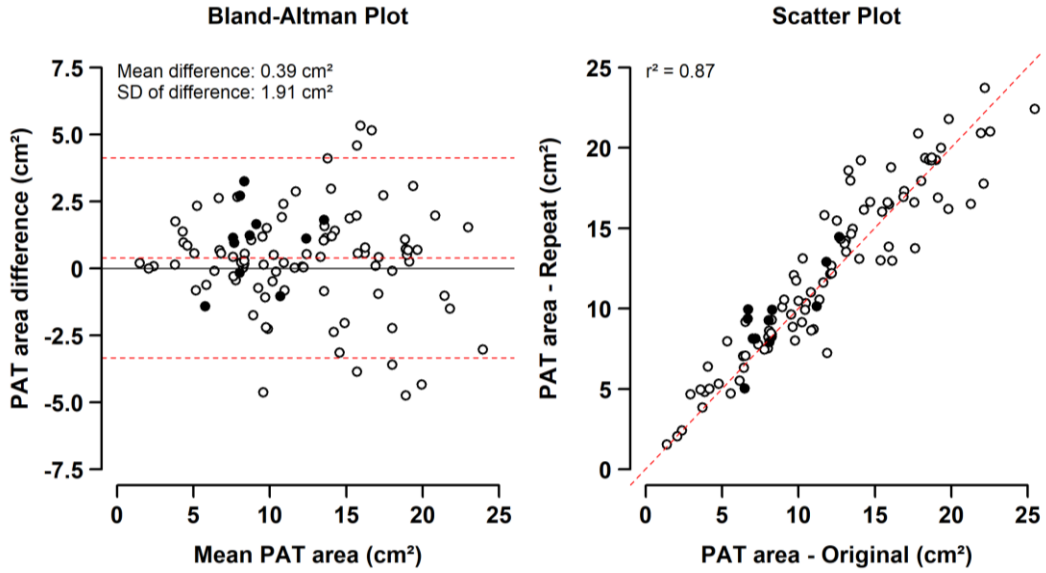


Figure 5.9: Intra-observer validation of total pericardial adipose tissue area. *Bland-Altman plot (left panel) and scatter plot (right panel) demonstrating intra-observer validation of pericardial adipose tissue area phenotype. Red dashed lines in the Bland-Altman plot represent the mean difference ± 1.96 standard deviations. The red dashed line in the scatter plot represents the parity line between original and repeat measures. Observations are divided into those with an image quality score of 1 (open circles) and an image quality score of 2 (closed circles). PAT – pericardial adipose tissue.*

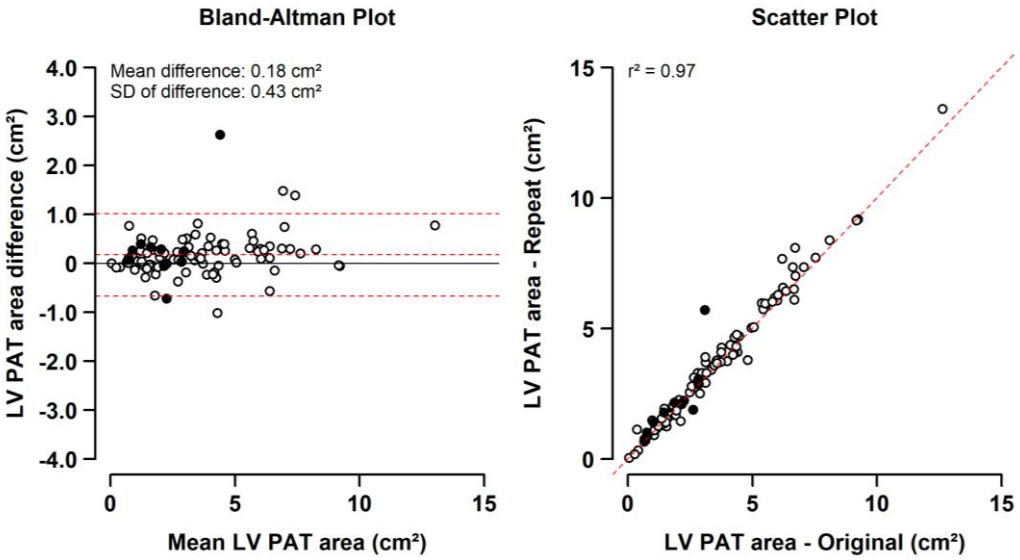


Figure 5.10: Intra-observer validation of left ventricular pericardial adipose tissue area.

Bland-Altman plot (left panel) and scatter plot (right panel) demonstrating intra-observer validation of left ventricular pericardial adipose tissue area phenotype. Red dashed lines in the Bland-Altman plot represent the mean difference ± 1.96 standard deviations. The red dashed line in the scatter plot represents the parity line between original and repeat measures. Observations are divided into those with an image quality score of 1 (open circles) and an image quality score of 2 (closed circles). LV – left ventricular; PAT - pericardial adipose tissue.

1

Table 5.3: Intra-observer validation measures for total and left ventricular pericardial adipose tissue area.

	r^2	Mean difference (cm^2)	SD of the difference (cm^2)
Total PAT			
All cases (n=100)	0.87	0.39	1.91
IQS 1 (n=89)	0.88	0.31	1.95
IQS 2 (n=11)	0.62	1.03	1.43
LV PAT			
All cases (n=100)	0.97	0.18	0.43
IQS 1 (n=89)	0.98	0.16	0.36
IQS 2 (n=11)	0.64	0.31	0.82

IQS – image quality score; LV – left ventricular; PAT - pericardial adipose tissue; SD – standard deviation; r^2 – Pearson's correlation coefficient squared.

2

5.4.3.2. Inter-observer validation

In an additional 110 samples there was high inter-observer correlation for total PAT area (r^2 = 0.89) and no evidence of substantial systemic bias (mean difference -0.53 cm^2, SD of the difference 2.22 cm^2, **Figure 5.11**). There was similarly high intra-observer correlation for LV PAT area (r^2 = 0.96) and no evidence of substantial systemic bias (mean difference -0.02 cm^2, SD of the difference 0.71 cm^2, **Figure 5.12**). As with the intra-observer validation, inter-observer correlation was higher in images with an image quality score of one than those with an image quality score of two (**Table 5.4**).

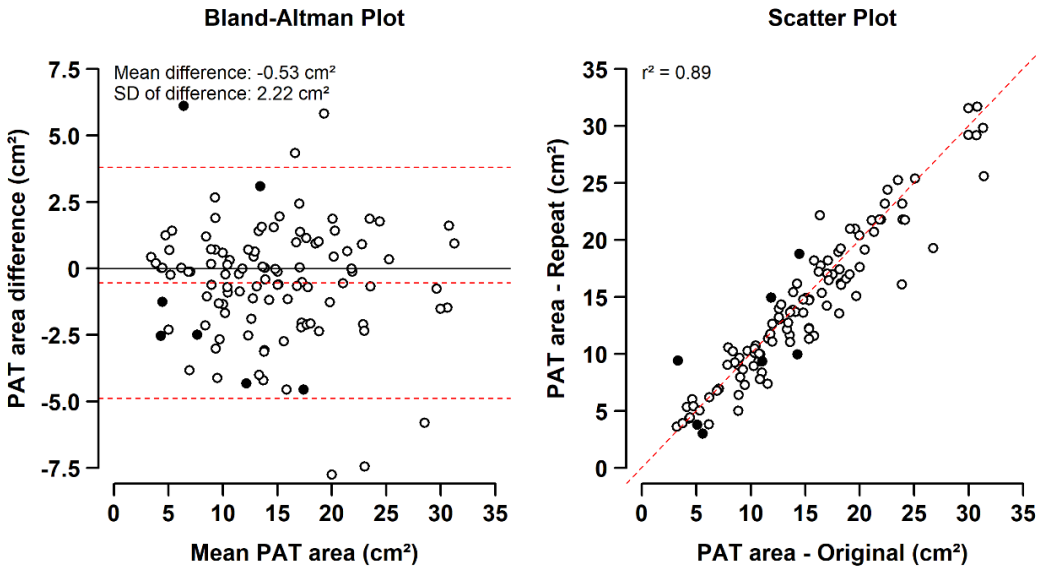


Figure 5.11: Inter-observer validation of total pericardial adipose tissue area. *Bland-Altman plot (left panel) and scatter plot (right panel) inter-observer validation of pericardial adipose tissue area phenotype. Red dashed lines in the Bland-Altman plot represent the mean difference ± 1.96 standard deviations. The red dashed line in the scatter plot represents the parity line between original and repeat measures. Observations are divided into those with an image quality score of 1 (closed circles) and an image quality score of 2 (black circles). PAT – pericardial adipose tissue.*

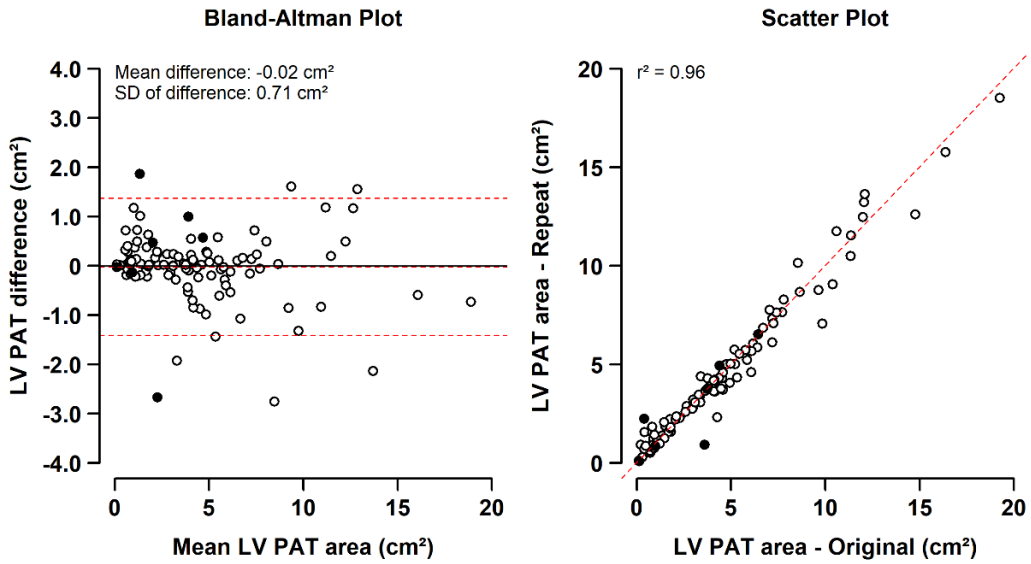


Figure 5.12: Inter-observer validation of left-ventricular pericardial adipose tissue area.
Bland-Altman plot (left panel) and scatter plot (right panel) demonstrating inter-observer validation of left ventricular pericardial adipose tissue area phenotype. Red dashed lines in the Bland-Altman plot represent the mean difference ± 1.96 standard deviations. The red dashed line in the scatter plot represents the parity line between original and repeat measures. Observations are divided into those with an image quality score of 1 (open circles) and an image quality score of 2 (black circles). LV – left ventricular; PAT - pericardial adipose tissue

1

Table 5.4: Inter-observer validation measures for total and left ventricular pericardial adipose tissue area.

	r^2	Mean difference (cm^2)	SD of the difference (cm^2)
Total PAT			
All cases (n=110)	0.89	-0.53	2.22
IQS 1 (n=103)	0.90	-0.51	2.08
IQS 2 (n=7)	0.54	-0.85	3.99
LV PAT			
All cases (n=110)	0.96	-0.02	0.71
IQS 1 (n=103)	0.97	-0.03	0.65
IQS 2 (n=7)	0.47	0.16	1.41

IQS – image quality score; LV – left ventricular; PAT - pericardial adipose tissue; SD – standard deviation; r^2 – Pearson's correlation coefficient squared.

2

5.4.4. Characteristics of pericardial adipose tissue area cohort at entry into the UK Biobank imaging sub-study

When divided into fifths, those with greater total PAT area were older (lowest fifth 53.3 years vs highest fifth 57.6 years) and contained a greater proportion of male participants (lowest fifth 184 [26.5%] vs highest fifth 488 [70.2%], **Table 5.5**). Those with greater total PAT area were taller (lowest fifth 166.7 cm vs highest fifth 172.4 cm), had greater body lean mass (lowest fifth 47.6 kg vs highest fifth 60.3 kg), and greater abdominal VAT (lowest fifth 1.8 L vs highest fifth 6.0 L). Measures of atrial and ventricular size were greater in those with greater total PAT area. For example, mean LV end diastolic volume was 14.2 cm^3 greater in the top fifth (mean 152.9 cm^3, SD 34.9 cm^3) than the bottom fifth (mean 138.7 cm^3, SD 30.4 cm^3). Similarly, mean left atrial (LA) minimum volume was 4.9 cm^3 greater in the top fifth (mean 31.5 cm^3, SD 18.1 cm^3) than the bottom fifth (mean 26.6 cm^3, SD 11.2 cm^3).

Table 5.5: Characteristics of the pericardial adipose tissue sub-set of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided into fifths (n=3,477).

	Total pericardial adipose tissue area (fifths)				
	1 (n=695)	**2 (n=696)**	**3 (n=695)**	**4 (n=696)**	**5 (n=695)**
PAT measures, mean (SD)					
Total PAT Area, cm^2	5.9 (1.8)	9.8 (0.9)	12.7 (0.8)	16.0 (1.1)	22.6 (4.3)
R^2 value	0.87 (0.11)	0.92 (0.06)	0.92 (0.06)	0.93 (0.06)	0.94 (0.05)
T1 value, ms	369.2 (74.6)	367.7 (63.1)	353.6 (56.8)	350.0 (51.5)	330.3 (46.1)
Demographics					
Age (years), mean (SD)	59.5 (7.7)	60.8 (7.6)	62.3 (7.2)	62.3 (7.4)	63.8 (7.1)
Male, n(%)	184 (26.5)	254 (36.5)	324 (46.6)	398 (57.2)	488 (70.2)
Current smoker, n(%)	27 (3.9)	27 (3.9)	34 (4.9)	32 (4.6)	39 (5.6)
Current alcohol drinker, n(%)	661 (95.1)	657 (94.4)	658 (94.7)	646 (92.8)	659 (94.8)
Townsend deprivation index, mean (SD)	-2.2 (2.6)	-2.0 (2.7)	-2.0 (2.7)	-2.0 (2.6)	-1.9 (2.7)
Anthropometric measures, mean (SD)					
Height, cm	166.7 (8.4)	167.7 (9.1)	169.1 (9.1)	170.4 (9.1)	172.4 (9.3)
Weight, kg	65.5 (10.6)	71.7 (11.6)	76.9 (12.7)	80.6 (13.5)	88.7 (15.8)
Body mass index, kg/m^2	23.6 (3.2)	25.5 (3.5)	26.9 (3.9)	27.8 (4.0)	29.8 (4.5)
Waist circumference, cm	77.1 (9.1)	83.3 (9.3)	87.9 (10.1)	91.0 (10.3)	97.7 (11.4)
Hip circumference, cm	96.4 (7.0)	99.7 (7.4)	101.9 (7.9)	103.2 (8.2)	106.2 (9.1)
Waist-hip ratio,	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)					
Body lean mass, kg	46.5 (8.4)	49.4 (9.7)	52.4 (10.6)	55.0 (10.8)	59.5 (11.6)
Body fat mass, kg	19.3 (7.1)	22.0 (7.6)	24.0 (8.2)	24.8 (8.2)	28.2 (9.1)
Abdominal MRI measures, mean (SD)					
Liver fat, %	1.9 (2.4)	2.8 (3.3)	4.1 (4.9)	4.3 (4.6)	6.3 (5.8)
Abdominal visceral adipose tissue, L	1.8 (1.2)	2.8 (1.4)	3.7 (1.6)	4.4 (1.9)	6.0 (2.3)
Abdominal sub-cutaneous adipose tissue, L	5.4 (2.6)	6.6 (2.8)	7.3 (3.0)	7.5 (3.3)	8.3 (3.2)
Total abdominal fat, L	7.2 (3.3)	9.3 (3.5)	11.0 (3.8)	11.8 (4.2)	14.3 (4.3)
Prior disease, n(%)					
Coronary heart disease	13 (1.9)	29 (4.2)	29 (4.2)	42 (6.0)	74 (10.6)
Congestive cardiac failure	1 (0.1)	5 (0.7)	3 (0.4)	7 (1.0)	8 (1.2)
Diabetes	15 (2.2)	14 (2.0)	21 (3.0)	21 (3.0)	60 (8.6)
Hypertension	124 (17.8)	191 (27.4)	208 (29.9)	255 (36.6)	301 (43.3)
Sleep apnoea	1 (0.1)	1 (0.1)	5 (0.7)	4 (0.6)	16 (2.3)
Stroke	3 (0.4)	5 (0.7)	5 (0.7)	9 (1.3)	5 (0.7)
Valvular heart disease	1 (0.1)	8 (1.1)	2 (0.3)	10 (1.4)	7 (1.0)

Table 5.5: Characteristics of the pericardial adipose tissue sub-set of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided into fifths (n=3,477).

	Total pericardial adipose tissue area (fifths)				
	1 (n=695)	**2 (n=696)**	**3 (n=695)**	**4 (n=696)**	**5 (n=695)**
Cardiac volumes, mean (SD)					
LA max volume (biplane), cm^3	65.2 (19.2)	66.7 (21.3)	67.0 (19.6)	69.7 (20.3)	71.3 (24.6)
LA min volume (biplane), cm^3	26.6 (11.2)	27.7 (15.1)	27.7 (11.6)	29.5 (13.4)	31.5 (18.1)
LV end diastolic volume, cm^3	138.7 (30.4)	141.9 (32.1)	145.4 (34.3)	149.0 (32.8)	152.9 (34.9)
LV end systolic volume, cm^3	56.3 (17.5)	58.6 (18.2)	60.0 (19.7)	61.5 (19.7)	63.3 (20.4)
LV ejection fraction, %	59.7 (5.8)	59.1 (6.2)	59.2 (6.3)	59.2 (6.6)	59.0 (6.6)
RV end diastolic volume, cm^3	146.1 (34.1)	150.0 (37.2)	154.1 (37.9)	157.7 (35.6)	161.9 (37.9)
RV ejection fraction, %	56.7 (6.1)	56.4 (6.7)	56.4 (6.4)	56.2 (6.5)	55.9 (6.5)

Total pericardial adipose tissue area divided into fifths (1 – lowest, 5 – highest). Total abdominal fat is a combination of visceral and sub-cutaneous abdominal fat. LA – left atrial; LV – left ventricular; PAT – pericardial adipose tissue; RV – right ventricular; SD – standard deviation.

5.4.4.1. Baseline characteristics in men and women

To assess whether the associations between PAT and other anthropometric measures were principally driven by the association between male sex and PAT area, men and women were examined separately (**Table 5.6** and **Table 5.7**). In both men and women, those with greater PAT were older (in women: lowest fifth 52.1 years vs highest fifth 57.1 years; in men: lowest fifth 55.6 years vs highest fifth 57.9 years). However, height was similar across fifths in both men and women. The difference in lean mass across fifths was less pronounced when examined separately by sex (in women: difference between lowest and highest fifth 3.7 kg; in men: difference between lowest and highest fifth 6.5 kg) than when using non-sex-specific fifths (difference between lowest and highest non-sex-specific fifth 13 kg). Differences in other anthropometric measures across fifths were generally unchanged.

In both men and women, those with greater PAT also had higher rates of cardiovascular disease at the time of their MRI. In particular, between the lowest and highest fifth, the proportion of participants with diabetes (in women: 5 [1.4%] vs. 22 [6.0%]; in men: 10 [3.0%] vs. 32 [9.7%]), CHD (in women: 6 [1.6%] vs. 27 [7.4%]; in men: 17 [5.2%] vs. 41 [12.5%]), and hypertension (in women: 66 [18.1%] vs 137 [37.4%]; in men: 78 [23.7%] vs. 158 [48.0%]) were more than double.

Across PAT fifths, measures of cardiac size were greater in men than in women. Greater PAT was not associated with measures of ventricular size when considered in men and women separately. While, LA minimum volume was significantly greater in men with more PAT (difference between lowest and highest fifth: 4 cm^3) this was not seen in women (difference between lowest and highest fifth: 1.8 cm^3). Additionally, LA maximum volume was not difference across fifths in either men or women.

Table 5.6: Characteristics of women in the pericardial adipose tissue sub-set (n=1,829) of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided in to fifths.

	Total pericardial adipose tissue area (fifths)				
	1 (n=365)	**2 (n=366)**	**3 (n=366)**	**4 (n=366)**	**5 (n=366)**
PAT measures, mean (SD)					
Total PAT Area, cm^2	5.0 (1.6)	8.5 (0.7)	11.0 (0.8)	13.9 (0.9)	19.4 (3.3)
Median R^2 value	0.86 (0.12)	0.91 (0.07)	0.92 (0.05)	0.93 (0.06)	0.93 (0.05)
T1 value, ms	371.6 (76.5)	366.3 (71.2)	360.8 (59.8)	349.7 (52.4)	337.2 (48.9)
Demographics					
Age, mean (SD)	58.3 (7.6)	60.0 (7.3)	61.0 (7.5)	62.3 (7.2)	63.4 (7.1)
Current smoker, n(%)	17 (4.7)	13 (3.6)	13 (3.6)	9 (2.5)	18 (4.9)
Current alcohol drinker, n(%)	345 (94.5)	350 (95.6)	345 (94.3)	340 (92.9)	336 (91.8)
Townsend deprivation index, mean (SD)	-2.3 (2.5)	-1.8 (2.7)	-1.9 (2.7)	-2.0 (2.7)	-2.0 (2.7)
Anthropometric measures, mean (SD)					
Height, cm	163.4 (6.5)	163.3 (6.5)	162.6 (6.2)	163.2 (6.3)	162.4 (6.2)
Weight, kg	61.7 (9.1)	66.3 (10.2)	69.9 (11.9)	72.3 (12.3)	77.8 (13.9)
Body mass index, kg/m^2	23.1 (3.2)	24.9 (3.6)	26.4 (4.2)	27.1 (4.5)	29.5 (5.1)
Waist circumference, cm	73.6 (7.6)	78.3 (8.9)	82.3 (9.8)	84.4 (10.2)	90.6 (11.5)
Hip circumference, cm	95.3 (7.4)	99.0 (7.5)	101.4 (9.3)	102.9 (9.0)	107.1 (10.8)
Waist-hip ratio,	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
Bio-impedance measures, mean (SD)					
Body lean mass, kg	42.0 (4.0)	43.0 (4.2)	43.6 (4.5)	44.2 (4.8)	45.7 (5.5)
Body fat mass, kg	20.1 (6.5)	23.5 (7.1)	26.0 (8.4)	27.5 (8.3)	31.6 (9.6)
Abdominal MRI measures, mean (SD)					
Liver fat, %	1.8 (2.3)	2.2 (3.0)	3.3 (4.4)	4.1 (5.2)	5.6 (5.7)
Abdominal visceral adipose tissue, L	1.4 (0.8)	2.0 (1.0)	2.6 (1.2)	3.0 (1.3)	3.9 (1.5)
Abdominal sub-cutaneous adipose tissue, L	5.6 (2.5)	7.1 (2.7)	8.2 (3.2)	8.8 (3.1)	10.2 (3.4)
Total abdominal fat, L	7.0 (3.2)	9.1 (3.6)	10.9 (4.1)	11.8 (4.1)	14.2 (4.5)
Prior disease, n(%)					
Coronary heart disease	6 (1.6)	4 (1.1)	13 (3.6)	9 (2.5)	27 (7.4)
Congestive cardiac failure	0 (0.0)	2 (0.5)	3 (0.8)	1 (0.3)	0 (0.0)
Diabetes	5 (1.4)	6 (1.6)	8 (2.2)	10 (2.7)	22 (6.0)
Hypertension	66 (18.1)	69 (18.9)	110 (30.1)	104 (28.4)	137 (37.4)
Sleep apnoea	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Stroke	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Valvular heart disease	0 (0.0)	3 (0.8)	3 (0.8)	3 (0.8)	4 (1.1)
Cardiac volumes, mean (SD)					
LA max volume (biplane), cm^3	63.4 (17.0)	63.8 (17.8)	64.3 (18.2)	63.4 (17.2)	65.0 (20.2)
LA min volume (biplane), cm^3	25.7 (9.7)	25.9 (10.9)	26.1 (11.4)	25.8 (9.8)	27.5 (15.0)

Table 5.6: Characteristics of women in the pericardial adipose tissue sub-set (n=1,829) of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided in to fifths.

	Total pericardial adipose tissue area (fifths)				
	1 (n=365)	**2 (n=366)**	**3 (n=366)**	**4 (n=366)**	**5 (n=366)**
LV end diastolic volume, cm^3	129.2 (24.2)	127.7 (22.7)	127.4 (22.6)	127.5 (23.2)	128.0 (25.2)
LV end systolic volume, cm^3	52.0 (16.1)	50.7 (13.2)	51.1 (13.9)	50.6 (12.7)	49.9 (13.8)
LV ejection fraction, %	60.0 (5.6)	60.5 (6.2)	60.1 (6.1)	60.5 (5.8)	61.2 (5.8)
RV end diastolic volume, cm^3	133.6 (25.0)	132.9 (26.3)	131.4 (24.0)	132.6 (25.1)	132.5 (25.5)
RV ejection fraction, %	57.4 (6.0)	58.2 (6.4)	58.2 (5.6)	58.2 (6.2)	58.9 (6.0)

Total pericardial adipose tissue area divided into fifths in women (1 – lowest, 5 – highest). Total abdominal fat is a combination of visceral and sub-cutaneous abdominal fat. LA – left atrial; LV – left ventricular; PAT – pericardial adipose tissue; RV – right ventricular; SD – standard deviation.

1

Table 5.7: Characteristics of men in the pericardial adipose tissue sub-set (n=1,648) of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided in to fifths.

	Total pericardial adipose tissue area (fifths)				
	1 (n=329)	2 (n=330)	3 (n=330)	4 (n=330)	5 (n=329)
PAT measures, mean (SD)					
Total PAT area, cm^2	7.5 (2.1)	11.8 (0.9)	14.8 (0.9)	18.1 (1.1)	24.9 (4.7)
Median R^2 value	0.89 (0.10)	0.92 (0.07)	0.93 (0.06)	0.93 (0.05)	0.94 (0.05)
T1 value, ms	370.4 (65.0)	359.8 (61.5)	354.4 (52.6)	344.5 (51.7)	325.4 (42.8)
Demographics					
Age, mean (SD)	61.9 (7.7)	62.6 (7.2)	61.9 (7.3)	62.6 (7.9)	64.1 (7.0)
Current smoker, n(%)	10 (3.0)	24 (7.3)	17 (5.2)	19 (5.8)	19 (5.8)
Current alcohol drinker, n(%)	311 (94.5)	315 (95.5)	311 (94.2)	318 (96.4)	310 (94.2)
Townsend deprivation index, mean (SD)	-2.3 (2.6)	-2.2 (2.6)	-1.9 (2.8)	-2.1 (2.5)	-1.7 (2.8)
Anthropometric measures, mean (SD)					
Height, cm	176.0 (6.3)	175.7 (6.6)	176.3 (6.4)	176.5 (6.7)	176.3 (6.8)
Weight, kg	75.6 (9.6)	80.2 (10.4)	84.7 (11.7)	87.9 (12.8)	94.1 (14.8)
Body mass index, kg/m^2	24.4 (2.9)	25.9 (2.9)	27.2 (3.3)	28.2 (3.5)	30.2 (4.2)
Waist circumference, cm	86.4 (7.8)	90.7 (7.9)	93.2 (8.3)	96.4 (9.1)	101.3 (10.6)
Hip circumference, cm	97.9 (5.4)	99.9 (5.8)	102.0 (6.6)	103.3 (6.8)	106.2 (8.3)
Waist-hip ratio,	0.9 (0.1)	0.9 (0.1)	0.9 (0.0)	0.9 (0.0)	1.0 (0.1)
Bio-impedance measures, mean (SD)					
Body lean mass, kg	59.2 (6.1)	60.8 (6.6)	62.8 (7.1)	63.5 (7.6)	65.7 (8.5)
Body fat mass, kg	15.9 (5.4)	19.2 (5.7)	21.0 (6.1)	23.5 (7.2)	27.1 (7.7)
Abdominal MRI measures, mean (SD)					
Liver fat, %	2.6 (2.9)	3.5 (3.8)	4.3 (4.4)	5.0 (4.8)	6.7 (5.9)
Abdominal visceral adipose tissue, L	3.0 (1.6)	4.1 (1.7)	4.9 (1.8)	5.7 (2.0)	7.1 (2.2)
Abdominal sub-cutaneous adipose tissue, L	4.3 (1.8)	5.3 (1.8)	5.9 (2.2)	6.6 (2.4)	7.6 (2.7)
Total abdominal fat, L	7.3 (3.2)	9.3 (3.1)	10.8 (3.5)	12.3 (3.9)	14.7 (4.2)
Prior disease, n(%)					
Coronary heart disease	17 (5.2)	22 (6.7)	21 (6.4)	27 (8.2)	41 (12.5)
Congestive cardiac failure	2 (0.6)	1 (0.3)	4 (1.2)	6 (1.8)	5 (1.5)
Diabetes	10 (3.0)	13 (3.9)	8 (2.4)	17 (5.2)	32 (9.7)
Hypertension	78 (23.7)	101 (30.6)	117 (35.5)	139 (42.1)	158 (48.0)
Sleep apnoea	1 (0.3)	2 (0.6)	5 (1.5)	3 (0.9)	13 (4.0)
Stroke	2 (0.6)	3 (0.9)	6 (1.8)	0 (0.0)	5 (1.5)
Valvular heart disease	2 (0.6)	1 (0.3)	4 (1.2)	4 (1.2)	4 (1.2)
Cardiac volumes, mean (SD)					
LA max volume (biplane), cm^3	70.9 (25.2)	70.3 (21.3)	71.8 (21.6)	73.7 (22.3)	75.6 (25.8)
LA min volume (biplane), cm^3	30.0 (18.4)	29.6 (13.0)	30.3 (12.7)	32.7 (17.0)	34.0 (18.8)

Table 5.7: Characteristics of men in the pericardial adipose tissue sub-set (n=1,648) of UK Biobank at time of entry into the imaging sub-study by total pericardial adipose tissue area divided in to fifths.

	Total pericardial adipose tissue area (fifths)				
	1 (n=329)	**2 (n=330)**	**3 (n=330)**	**4 (n=330)**	**5 (n=329)**
LV end diastolic volume, cm^3	165.8 (29.9)	165.7 (32.9)	165.0 (30.9)	164.8 (32.2)	164.3 (32.1)
LV end systolic volume, cm^3	70.5 (17.8)	70.3 (18.9)	70.1 (19.2)	69.8 (21.8)	69.1 (19.1)
LV ejection fraction, %	57.7 (5.8)	57.7 (6.1)	57.9 (6.3)	58.1 (7.4)	58.2 (6.6)
RV end diastolic volume, cm^3	180.6 (31.0)	178.6 (35.3)	177.8 (33.0)	176.2 (33.5)	175.0 (33.7)
RV ejection fraction, %	53.6 (5.7)	54.0 (6.2)	54.6 (6.4)	54.2 (6.5)	54.9 (6.2)

Total pericardial adipose tissue area divided into fifths in men (1 – lowest, 5 – highest). Total abdominal fat is a combination of visceral and sub-cutaneous abdominal fat. LA – left atrial; LV – left ventricular; PAT – pericardial adipose tissue; RV – right ventricular; SD – standard deviation.

5.4.5. Association between pericardial adipose tissue and other anthropometric measures

PAT area was correlated with all assessed anthropometric measures except for height (**Figure 5.13**). It was most strongly associated with abdominal VAT (r = 0.63). Similar correlations were seen between LV PAT and other anthropometric measures (**Appendix Figure G.8**), albeit slightly weaker.

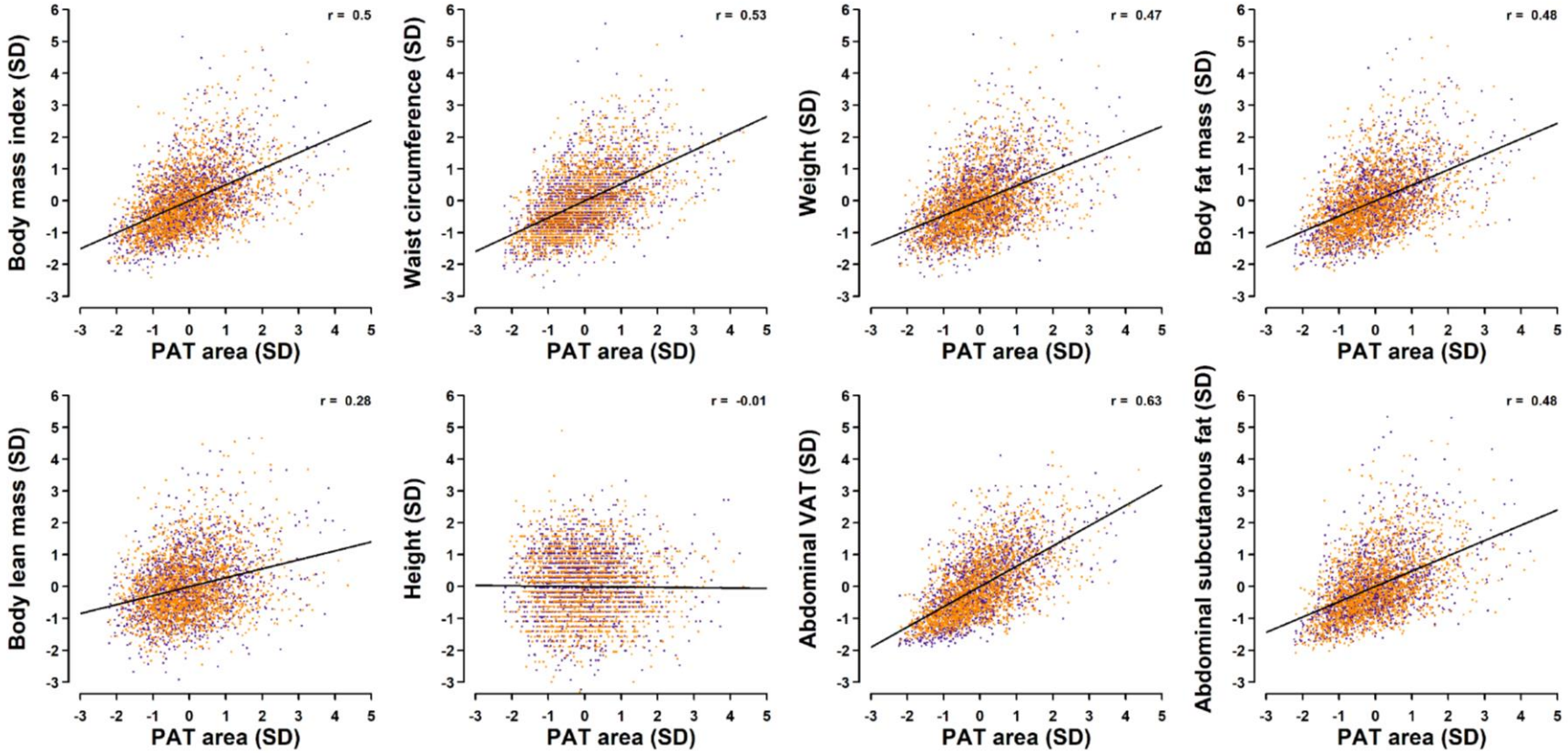


Figure 5.13: Scatter plots of total pericardial adipose tissue area and anthropometric measures.
Women are displayed in orange and men are displayed in purple. Lines represent linear regression between pericardial adipose tissue area and anthropometric measures. Displayed r-values are Pearson's correlation coefficients. Standard deviations are calculated separately in men and women. PAT – pericardial adipose tissue, VAT – visceral adipose tissue. SD – standard deviation

5.5. Discussion

In this chapter, a novel PAT phenotype using CMR data available in UKB has been developed. Mid ventricular native T1 maps were generally of a high quality and were appropriately able to identify PAT. The intra-observer and inter-observer reproducibility of this phenotype was high. Furthermore, and as expected, PAT area was correlated with a number of other adiposity measures and baseline cardiovascular disease states.

5.5.1. Quality of T1 maps

The median R^2 value of PAT across the cohort (0.92 [IQR 0.91 to 0.96]) was lower than has previously been reported by groups assessing native T1 maps. Ferreira *et al*. reported a median R^2 value of 0.99 in a set of healthy volunteers (n=15).[270] While some studies have suggested an R^2 threshold,[271] this has not been widely adopted. However, prior reports of R^2 values have been in myocardial tissue rather than in PAT and, as such, the comparability of these values may be limited.[269,272] The generally good quality of the images was supported by a subjective image quality score assigned to each image. The majority of images (90%) were given an image quality score of one (good quality image).

5.5.2. Adipose tissue T1 values

The ShMOLLI sequence offers robust and fast quantification of T1 values without the need for manual post-processing.[268] Healthy myocardial tissues have been shown to have a value between 900 and 1,100 ms.[273] Published measurements of T1 values of adipose tissue are sparse and reported to be generally <500

ms.[273-275] In this cohort, more than 98% of participants had a PAT mean T1 value <500 ms suggesting that fat tissue was correctly identified. When isolated samples of PAT were considered (to avoid potential overlap relating adjacent structures), the mean PAT T1 value was 294 ms (SD 59 ms) with a similar range to that obtained for the total PAT area.

5.5.3. Prior use of cardiac magnetic resonance imaging to assess pericardial adipose tissue

Recently a number of studies have shown the utility of CMR to assess PAT. [90,259-261] The largest of these has used a machine learning algorithm to calculate PAT area in the UKB imaging cohort (Bard *et al*. n=45,519) using a single apical four-chamber image.[90] This was based on a training set of 345 CMR images that were manually contoured. While the phenotype obtained in this project has only provided information on 3,477 UKB participants these have all been manually contoured providing a large potential training set for future machine learning approaches in the wider UKB cohort.

The PAT area phenotype developed by Bard *et al*. has potential to examine the association between PAT area and risk of incident cardiovascular diseases.[90,261] However, a limitation of the utilisation of CMR for the assessment of PAT tissue has been the ability to differentiate fat tissue. In particular, bSSFP sequences were utilised in UKB as part of the CMR sequence to obtain cine stacks and the apical images.[262] bSSFP produce bright fat and water signals.[276] As a result, it is not possible to separate out PAT from pericardial effusions (fluid surrounding the heart).[276] In contrast, fluid has a substantially higher T1 value than seen with fat.[273,277] While the number of participants in UKB with substantial pericardial

effusions is likely to be low, this has important implications were CMR to be used for the assessment of PAT in clinical practice (**Figure 5.14**).

A further advantage of this phenotype over other PAT phenotypes is that it provides details of tissue characteristics.[270] While at present it is unclear whether the differing T1 values of PAT may represent clinically meaningful differences in histological phenotype of the adipose tissue, this may warrant further exploration.

5.5.4. Reliability of pericardial adipose tissue measurement

As this project developed a new phenotype, a number of assessments to determine the reliability of this measurement were undertaken. A random selection of 100 participants were re-assessed by the first assessor to determine intra-observer validity. This demonstrated high intra-observer correlation (r^2 0.87) with little systemic bias (mean difference 0.39 cm^2). The SD of the difference (1.91 cm^2) was 31% of PAT area SD (6.1 cm^2). Similar findings were seen when assessing inter-observer correlation. These correlations were lower than has previously been shown for PAT area using cardiac CT (r^2 0.99),[95,278,279] but similar to values from other groups using CMR,[90,280] and greater than previously reported for intra-observer correlation for echocardiographically assessed PAT thickness (r^2 0.63).[281] While the correlations were lower when considering only those participants with poorer quality native T1 maps (image quality score 2), these participants make up only a small minority the total PAT cohort (~10%).

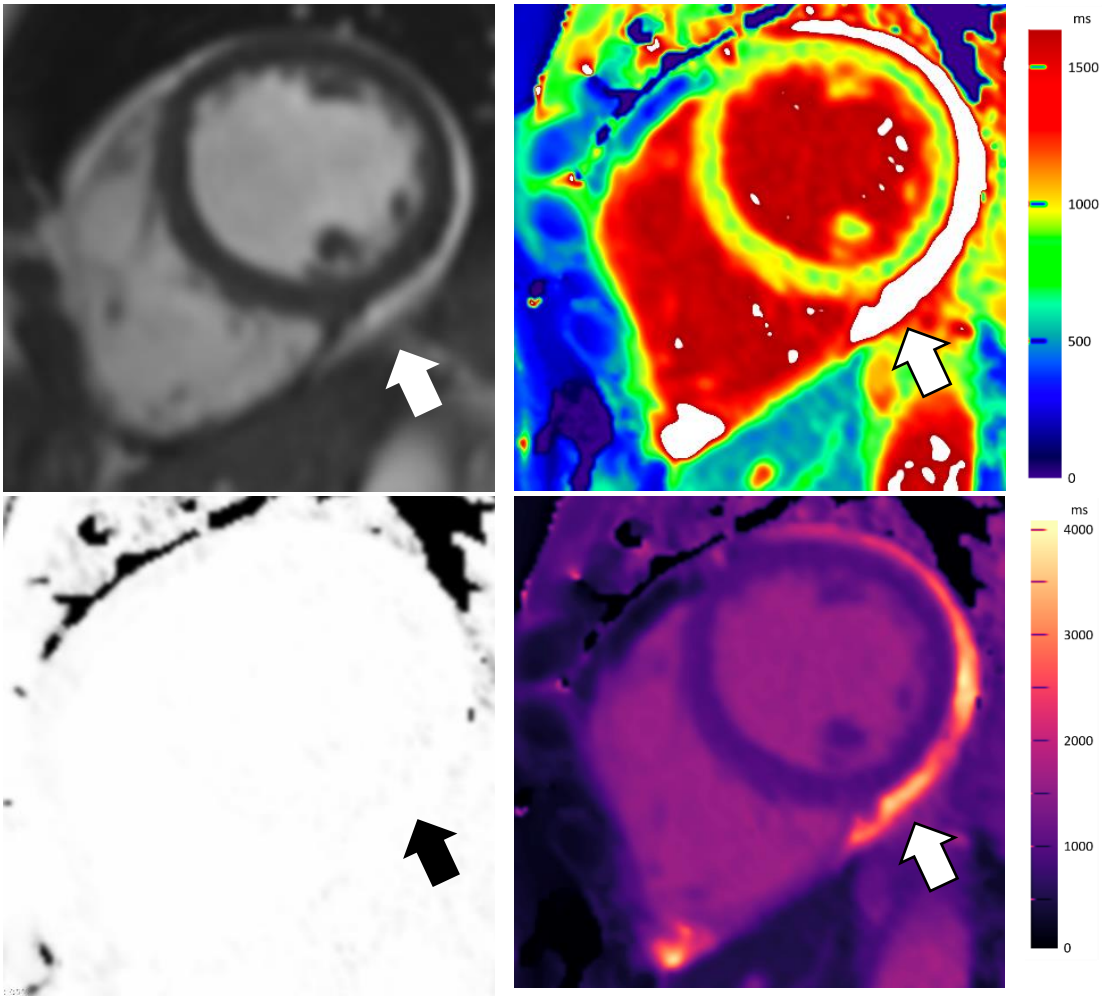


Figure 5.14: Indicative example of a bSSFP cine stile image, ShMOLLI map and parametric map of goodness of fit from a UK Biobank participant demonstrating an area of non-fat tissue between epicardium and pericardium.
The bSSFP cine still image (top left panel) shows both fat and fluid and white; there is an area of white in the inferior and infero-lateral aspect of the left ventricle (arrow) which appears similar to fat tissue. The native T1 ShMOLLI map (top right panel) demonstrates fat in blue. In this panel, the same area is clearly demonstrated not to be fat tissue (arrow). The goodness-of-fit map (bottom left panel) demonstrates that this is not due to artefact. When scaled across a wider spectrum, this area is shown to have a T1 value between 2,500 and 3,500 ms in keeping with known T1 values for pericardial effusions.[282]

5.5.5. Use of cardiac magnetic resonance imaging vs computed tomography

Cardiac CT is considered the gold standard for measurement of PAT area/volume due to excellent special resolution provided by this imaging modality.[85] However, cardiac CT requires exposure to ionising radiation,

administration of contrast, and beta-blockade, thus limiting use in large-scale datasets.[263] A number of groups have started to use CMR to assess PAT area.[90,259-261] However, to date, native T1 mapping has not been used for this phenotype. When PAT values obtained from CMR and cardiac CT (n=109) have been compared there has been a good correlation between PAT area obtained in the two imaging modalities (r=0.72).[90]

5.5.6. Pericardial adipose tissue cohort participant characteristics

Those UKB participants in whom PAT area was calculated did not differ substantially from the wider UKB imaging sub-study cohort. However, the cohort is comparatively young with a mean age (61.8 years) lower than most individuals developing AF.[283] They also had a low proportion of prior cardiovascular disease at the time of their CMR scan similar to the broader UKB cohort.[141] However, they represented a broad spread of anthropometric measures similar to the broader UKB cohort.

5.5.7. Pericardial adipose tissue and baseline cardiovascular disease

The results of this study have demonstrated that those with greater mid-ventricular PAT area had greater levels of baseline cardiovascular disease. In particular, both men and women in the top fifth of PAT area had triple the rate of diabetes, and twice the rate of CHD and hypertension than those in the lowest fifth of PAT area. This is in keeping with other cohorts that have explored associations between PAT and prevalent cardiovascular disease.[86,284]

5.5.8. Association between pericardial adipose tissue and other anthropometric measures

It has been suggested that PAT may be a central pathway through which adiposity increases the risk of AF.[257] In this analysis, PAT was associated with a range of anthropometric measures. In particular, it was most strongly associated with abdominal VAT (r=0.63) and PAT area was not associated with height when considered in sex-specific SDs (r=-0.01). Previous studies have suggested that PAT area is more strongly associated with BMI than body fat percentage (r=0.53 and r=0.19 respectively).[278] While others, using PAT volume obtained from cardiac CT, have shown strong associations between PAT area and BMI,[85,279,284] and WC in line with our findings.[85,284]

5.5.9. Limitations

Assessments of intra- and inter-observer reliability have suggested that this PAT area phenotype is reliable. However, it has not been possible to undertake a direct assessment of the PAT area calculated in this analysis against the gold-standard assessment of PAT volume calculated by cardiac CT. Furthermore, the measured PAT area obtained in this study has not been compared against the against PAT areas obtained from bSSFP apical four chamber images in UKB,[90] as the data were not at the time of writing this thesis.

While PAT is found across the surface of the heart,[128] and PAT area has previously been associated with cardiovascular disease, there is also evidence to suggest that localised deposits may be important in certain phenotypes.[285-287] However, the use of single mid-ventricular slice to calculate PAT area in this

study prevents consideration of the regional distribution of PAT. Additionally, PAT volume provides a global value of the total amount of PAT surrounding the heart. However, as only a single mid-ventricular native T1 map image was available in UKB participants, it has only been possible to calculate area. While the use of PAT area is in keeping with a number of other studies,[90,288] this only provides a two dimensional representation of the amount of PAT in each participant.

This work has developed a mid-ventricular PAT area phenotype. It has been argued that epicardial fat (defined as adipose tissue sitting between the epicardium and visceral pericardium) may share a blood supply with the heart and have paracrine effects on the heart.[83,289] As such, some have argued that epicardial fat, rather than broader pericardial adipose tissue, could have specific effects on the heart and may be specifically associated with risk of cardiovascular disease.[83] As with previous studies, the visceral pericardium was not routinely identified, preventing accurate phenotyping of epicardial fat area.[90,98] As such, it was not possible to develop a specific epicardial fat area phenotype. However, the associations identified between PAT area, baseline cardiovascular disease, and other anthropometric phenotypes suggests that PAT area may have meaningful associations with incident cardiovascular phenotypes including AF and requires further investigation.

5.5.10. Next Steps and Future Work

Following development of this phenotype in UKB, the next steps are to determine the association between PAT area and risk of AF. Furthermore, to explore the causal relevance of PAT on atrial fibrillation, a GWAS of this phenotype is

required followed by a MR analysis utilising identified variants predictive of PAT to assess association with risk of AF.

The current research has developed a novel PAT phenotype using native T1 maps from CMR data in UKB. At present, this is a labour-intensive approach requiring individual contouring for each participant. However, machine learning may allow for the development of a method for the scaling up of this phenotype to the entire UKB population with suitable imaging data.[90] As such, the current dataset could be used as a training set for the development of this algorithm.

5.5.11. Conclusions

In this chapter, a novel PAT area phenotype using native T1 maps has been developed in 3,477 UKB participants. Mid ventricular PAT area is associated with a number of other anthropometric measures, and most strongly associated with visceral adipose tissue. The role of this mid-ventricular PAT area phenotype on risk of incident cardiovascular events including AF requires further investigation.

Chapter 6 - Pericardial adipose tissue and risk of cardiovascular disease

6.1. Abstract

6.1.1. Background

Pericardial adipose tissue (PAT) has previously been associated with risk of atrial fibrillation (AF). However, the strength and causal relevance of the relationship between PAT and AF remain unclear.

6.1.2. Methods

Participants from UK Biobank (UKB) with cardiac magnetic resonance imaging (MRI) derived mid-ventricular PAT area were included (n=3,477). Abdominal visceral adipose tissue (VAT) volumes were determined from abdominal MRI data. AF was determined using hospital episode statistics and death registry data. Cox proportional hazards models were used to estimate covariate adjusted hazard ratios (HR) describing the association of AF with PAT and abdominal VAT. In addition, a genome-wide association study (GWAS) of PAT was undertaken.

6.1.3. Results

In 3,402 participants without prevalent AF, 104 developed incident AF over a mean follow-up of 6.6 years. PAT was associated with risk of AF (HR 1.29, 95%

confidence interval [95%CI] 1.08 to 1.54 per standard deviation) and was similar in men and women. Following adjustment for abdominal VAT, the association between PAT and risk of AF was similar (HR 1.24, 95%CI 0.99 to 1.55 per standard deviation). A GWAS of PAT (n=3,477) revealed no variants at a GWAS-significant threshold of $p<5 \times 10^{-8}$.

6.1.4. Conclusions

PAT is associated with the risk of incident AF in men and women. However, the effect size is in keeping with other anthropometric measures. A GWAS of PAT was not able to generate variants for an appropriate genetic score for subsequent MR studies.

6.2. Introduction

The association between a range of anthropometric measures and risk of AF has been demonstrated on a number of occasions.[66,72] However, whether measures of general body size act directly to increase the risk of AF or are surrogate markers for visceral fat deposits has not been clarified. WC has been shown to be associated with both abdominal VAT and risk of AF,[51,226] suggesting that such deposits may be key to the link between adiposity and the development of AF.

Two important ectopic fat deposits are PAT and abdominal VAT. PAT sits between the epicardium and pericardium and surrounds the heart.[290] This apposition may allow the portions of PAT to interact intimately with myocardial cells through paracrine mechanisms.[291] In particular, the epicardial component of PAT is thought to secrete inflammatory mediators and perivascular PAT may regulate myocardial blood flow through vasocrine mechanisms.[292,293] Importantly, these two ectopic fat deposits are correlated with one another (**Chapter 5**), as such, any exploration of these fat deposits must adjust for the effect of the other.

A meta-analysis of observational studies has suggested a significant association between greater PAT volume and higher risk of AF (OR 2.61, 95%CI [1.89 to 3.50] per SD).[72] However, prospective observational studies have indicated that any association may be more moderate, and may not be independent of other anthropometric measures.[95,100] Indeed, adjustment for BMI in the MESA and JHS cohorts reduced the association between PAT volume and risk of AF by ~50%.[95]

Abdominal VAT has similarly been shown to be hormonally active and to secrete inflammatory proteins including C-reactive protein.[53-55] Abdominal VAT is also associated with elevated blood pressure, dyslipidaemia, and insulin

resistance.[51,294] To date, abdominal VAT has not been significantly associated with risk of incident AF. However, the association between abdominal VAT and risk of AF has only been directly considered in a two small cohorts with limited power.[68,100]

There is evidence that both PAT and abdominal VAT are associated with risk of CHD.[255,256] While CHD and AF share some common aetiologies,[11] it is unclear whether both PAT area and abdominal VAT have similar associations for risk of AF and risk of CHD. It is suggested that peri-coronary fat volume and characteristics may be particularly related to the risk of CHD,[295-297] as such, the association with a more general measure of PAT may be more limited in CHD than AF. In contrast, as abdominal VAT is associated with a range of CHD risk factors including hyperlipidaemia, this anthropometric trait may be more strongly associated with risk of CHD than risk of AF.[284]

This investigation had two main aims: (1) to examine the associations between PAT area and risk of incident AF (and in comparison to CHD), and the independent relevance from abdominal VAT and (2) to identify genetic determinants of PAT area in order to create a genetic score for use in MR analyses to assess the causality of association between PAT and risk of AF.

6.3. Methods

6.3.1. Participants

The UKB cohort has been detailed in **Chapter 2** (**UK Biobank**) and the participant selection process for the development of the PAT cohort outlined in **Chapter 5** (**Pericardial adipose tissue phenotype**). For observational analyses, those with PAT area measurements were further limited to exclude those with prevalent AF. Participant selection for genetic analyses within UKB are outlined in **Chapter 2** (**Genetic analysis**).

6.3.2. Imaging phenotypes

A selection of UKB participants have undergone cardiac and abdominal MRI imagining as part of a re-survey. This re-survey is ongoing with the aim of scanning 20% of the original cohort.[262] Participants were scanned using a Siemens MAGNETOM Aera 1.5-tesla MRI Scanner.[298] This re-survey is further described in **Chapter 2** (**UK Biobank imaging** sub-study). PAT area was calculated in 3,477 participants as outlined in **Chapter 5**. Abdominal composition data, including abdominal VAT, were derived by AMRA (Advanced MR Analytics AB, AMRA, Sweden) using a validated technique.[299 300,301]

6.3.3. Other anthropometric measures and baseline characteristics

As outlined in **Chapter 5**, values for baseline characteristics and anthropometric measures were taken from the data provided as part of the imaging sub-study assessment. In individuals where baseline characteristic or anthropometric measure data were not available from the imaging sub-study (≤ 5% of

participants for any variable, **Appendix Table G.1**), data from the baseline assessment was utilised.

6.3.4. Atrial fibrillation and coronary heart disease cases

As outlined in **Chapter 4**, incident cases of AF and CHD (and other comorbid diseases) were identified using admissions data from HES and death registry data. Incident events were considered to have occurred after the participants CMR scan date with any event occurring before this date being considered prevalent.

6.3.5. Statistical analysis of observational data

Cox proportional hazards regression models were used to estimate HRs describing the associations between PAT and incident cardiovascular disease phenotypes. Results were adjusted for the following potentially confounding covariates: age at baseline, sex, ethnicity, Townsend deprivation index, alcohol intake, and smoking (never, former, current) and displayed as HR (95%CI). Additional adjustments are detailed within the text. All statistical analyses were undertaken using SAS (Version 9.3).

In order to explore the shape of the associations, anthropometric measures were classified, separately in men and women, into fifths. In figures, estimates for each group are shown relative to a reference group, and group-specific variances used to calculate 95% confidence intervals to enable comparisons between any two groups (rather than with the arbitrary reference group).[245] Relative independence of different anthropometric traits were assessed by additional adjustment for these grouped variables.

6.3.5.1. Power calculation for observational analyses

A power calculation for the observational analysis was undertaken in R using the powerSurvEpi package (https://CRAN.R-project.org/package=powerSurvEpi).[302] Based on 3,400 participants with PAT data, and 3.1% with incident AF, there was ≥80% power to identify a 34% greater risk of AF per SD greater PAT area.

6.3.6. Pericardial adipose tissue genome-wide association study

A GWAS was undertaken of PAT with the aim of developing a genetic tool for use in MR analyses. In line with previous GWAS of anthropometric phenotypes from the GIANT consortium,[103,104] PAT area residuals were calculated following adjustment for age, age^2, sex, and principal components of ancestry 1 to 7, and inverse normal transformed. The analysis was undertaken using a linear regression model in PLINK (Version 2.00a2LM). An additive genetic model was used (i.e. estimating per allele effects) to estimate associations with ~93 million measured and imputed genetic variants. Variants with a minor allele frequency <0.01 and an imputation quality <0.3 were excluded from further analyses.

6.3.6.1.Comparison with other anthropometric genome-wide association study results

Loci identified from prior GWAS of anthropometric phenotypes were used to explore the results of the PAT GWAS.[103-106] Effect estimates of variants identified in anthropometric GWAS were compared against the effect estimates of the same variants in the PAT GWAS for directional consistency by using a binomial distribution. Visual comparisons were made by plotting the effect size in variant in the PAT GWAS against the effect size of the same variant in the other anthropometric GWAS.

6.3.6.2. Genome-wide association study power calculations

Power for discovery in the PAT GWAS was calculated using the 'genpwr' package in R (https://CRAN.R-project.org/package=genpwr),[303] Setting alpha to 5×10^{-8} with the sample size in this study (n=3,477) there was more than 80% power to detect loci explaining at least 1.1% of the trait variance. Using a GWAS-suggestive threshold of $p<1 \times 10^{-5}$, there was more than 80% power to detect loci explaining at least 0.8% of the trait variance (50% power to detect loci explaining at least 0.5% trait variance).

6.4. Results

6.4.1. Incident cardiovascular disease

Three thousand, four hundred and two participants were free from AF at the time of their CMR. Over a mean follow-up of 6.6 years (SD 0.4 years), 104 participants (3.1%) developed AF. Of 3,290 participants free of CHD at the time of their CMR, 131 (4.0%) developed CHD during follow-up

6.4.2. Association of pericardial adipose tissue with risk of atrial fibrillation and coronary heart disease

A 1-SD greater PAT area was associated with a ~30% higher risk for incident AF (HR 1.29, 1.08 to 1.54, **Figure 6.1**). There was no difference in the strength of association between men (HR 1.27, 1.01 to 1.59, per SD) and women (HR 1.35, 1.01 to 1.81, per SD, p-interaction=0.93).

PAT area was also associated with risk of CHD, with a 1-SD greater PAT area associated with ~20% higher risk for incident CHD (HR 1.21, 1.03 to 1.43, per SD, **Figure 6.1**). The association between PAT area and risk of CHD was similar in men (HR 1.25, 1.02 to 1.54, per SD) and women (HR 1.15, 0.87 to 1.52, per SD, p-interaction=0.51).

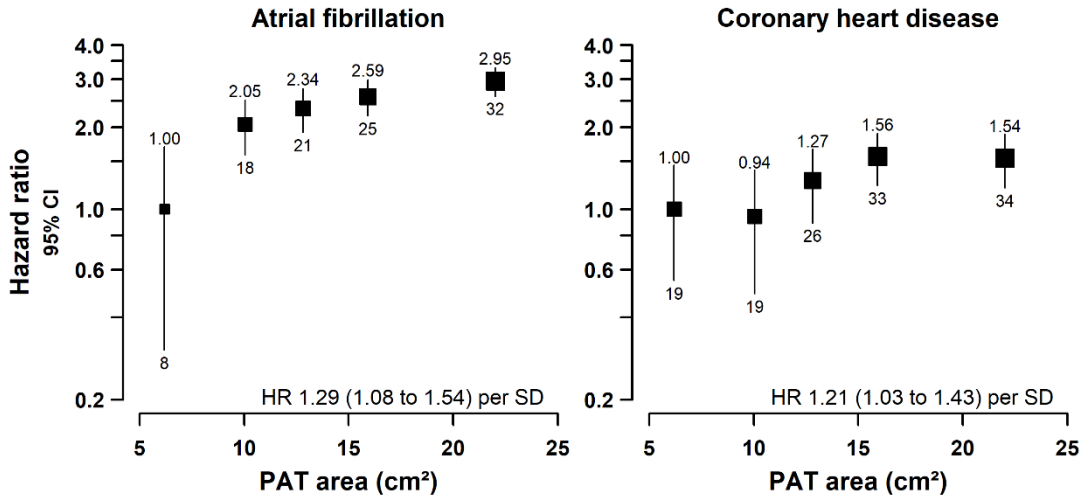


Figure 6.1: Association of pericardial adipose tissue area with incident cardiovascular outcomes

Left panel (n=3,402), right panel (n=3,290). Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation. Plotted on a floating absolute scale. For each category, the area of the score is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). Each group comprises 20% of the sample. HRs shown above each square and the number of cases below. PAT – pericardial adipose tissue, SD – standard deviation.

6.4.3. Association of abdominal visceral adipose tissue with risk of atrial fibrillation and coronary heart disease

The strength of association seen between abdominal VAT and risk for AF (HR 1.27, 1.06 to 1.53 per SD, **Figure 6.2**) was comparable with that seen for PAT area, with no significant difference between men (HR 1.19, 0.94 to 1.52 per SD) and women (HR 1.41, 1.06 to 1.87 per SD, p-interaction=0.19). Abdominal VAT was similarly associated with risk of CHD (HR 1.29, 1.10 to 1.43, per SD) with no significant difference between men (HR 1.22, 0.99 to 1.51, per SD) and women (HR 1.41, 1.09 to 1.83, per SD, p-interaction=0.08).

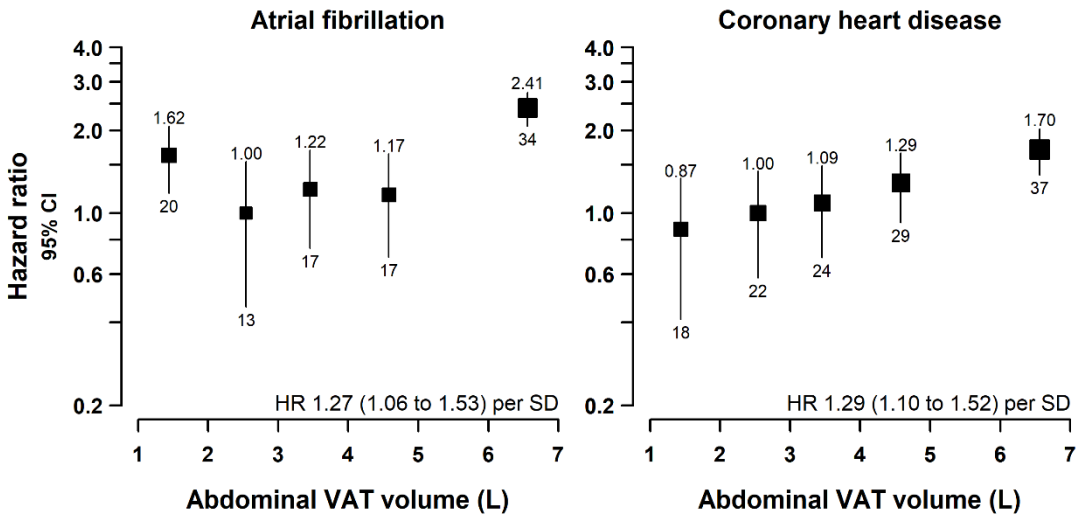


Figure 6.2: Association of abdominal visceral adipose tissue volume with incident cardiovascular outcomes.
Left panel (n=3,402), right panel (n=3,290). Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation. Plotted on a floating absolute scale. For each category, the area of the score is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). Each group comprises 20% of the sample. HRs shown above each square and the number of cases below. SD – standard deviation, VAT – visceral adipose tissue.

6.4.4. Relative strength of associations between anthropometric measures and risk of atrial fibrillation and coronary heart disease

Within the cohort with PAT data, the per 1-SD effect of PAT and abdominal VAT on risk of incident AF were comparable with other anthropometric measures in both men and women (**Figure 6.3**). Similarly, both PAT area and abdominal VAT had similar strengths of association with risk of CHD as seen with other anthropometric measures (**Figure 6.4**).

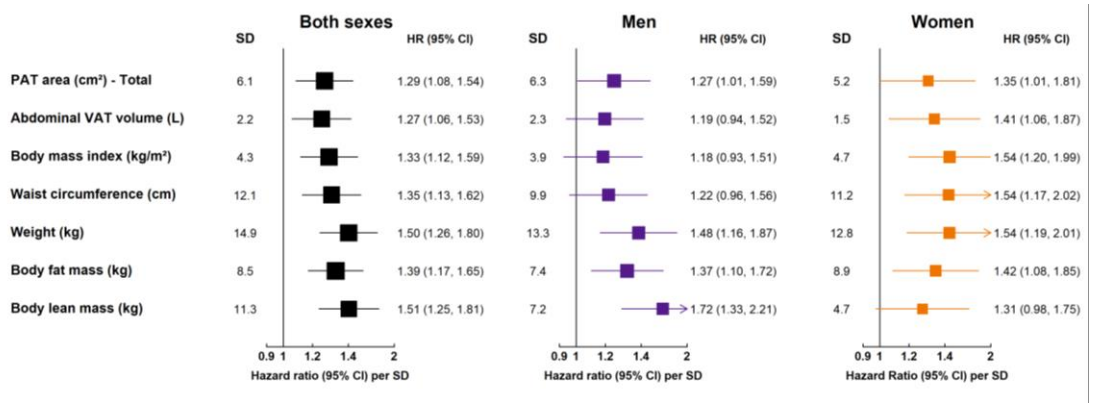


Figure 6.3: Comparison of associations between anthropometric measures and risk of incident atrial fibrillation, by sex, in the pericardial adipose tissue cohort (n=3,402).

Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). PAT – pericardial adipose tissue, SD – standard deviation, VAT – visceral adipose tissue.

1

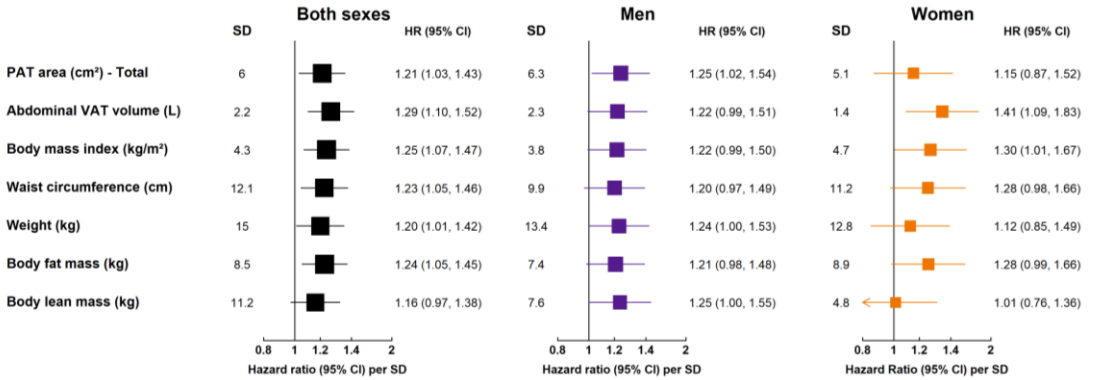


Figure 6.4: Comparison of associations between anthropometric measures and risk of incident coronary heart disease, by sex, in the pericardial adipose tissue cohort (n=3,290).

Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). PAT – pericardial adipose tissue, SD – standard deviation, VAT – visceral adipose tissue.

2

6.4.5. Independent effect of pericardial adipose tissue and abdominal visceral adipose tissue on risk of incident atrial fibrillation and coronary heart disease

PAT area is strongly correlated with abdominal VAT volume; therefore, the effects of PAT and abdominal VAT on the risk of AF and CHD were assessed following mutual adjustment.

6.4.5.1. Independent effect of pericardial adipose tissue

The effect of PAT on AF was reduced by ~15% following adjustment for abdominal VAT, with a ~25% higher risk of AF (HR 1.24, 0.99 to 1.55) per SD greater PAT (**Figure 6.5**, **Appendix Figure H.1**). After adjustment for abdominal VAT, the association between PAT and risk of AF remained similar in men (HR 1.26, 0.94 to 1.68) and women (HR 1.21, 0.84 to 1.74, p-interaction=0.91). The effect of PAT on risk of CHD was reduced by ~50% following adjustment for abdominal VAT (HR 1.11, 0.90 to 1.36, **Figure 6.6**, **Appendix Figure H.2**), and no longer statistically significant. In men, adjustment for abdominal VAT did not meaningfully reduce the effect of PAT on risk of CHD; while in contrast, there was complete attenuation in women. However, this difference was not statistically significant (p-interaction=0.52).

6.4.5.2.Independent effect of abdominal visceral adipose tissue

The effect of abdominal VAT on risk of AF was halved following adjustment for PAT (HR 1.16, 0.92 to 1.46, per SD, **Figure 6.5**, **Appendix Figure H.1**) and no longer statistically significant. Adjustment for PAT completely attenuated the association between abdominal VAT and risk of AF in men; however, there was no statistically significant different in association by sex (p-interaction=0.42). In

contrast to AF, adjustment for PAT had no meaningful impact on the association between abdominal VAT and risk of CHD (HR 1.26, 1.04 to 1.54, **Figure 6.6**, **Appendix Figure H.2**).

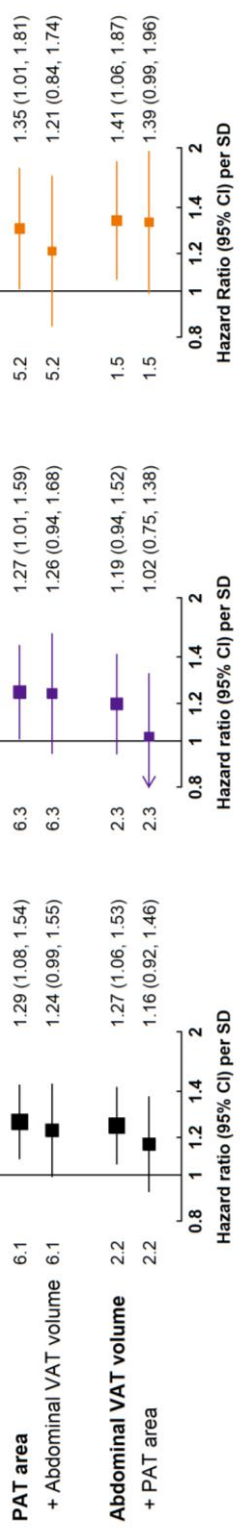


Figure 6.5: Association of pericardial adipose tissue area and abdominal visceral adipose tissue with incident atrial fibrillation before and after mutual adjustment, by sex (n=3,402).

Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation and mutually adjusted as indicated. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). PAT – pericardial adipose tissue, SD – standard deviation, VAT – visceral adipose tissue

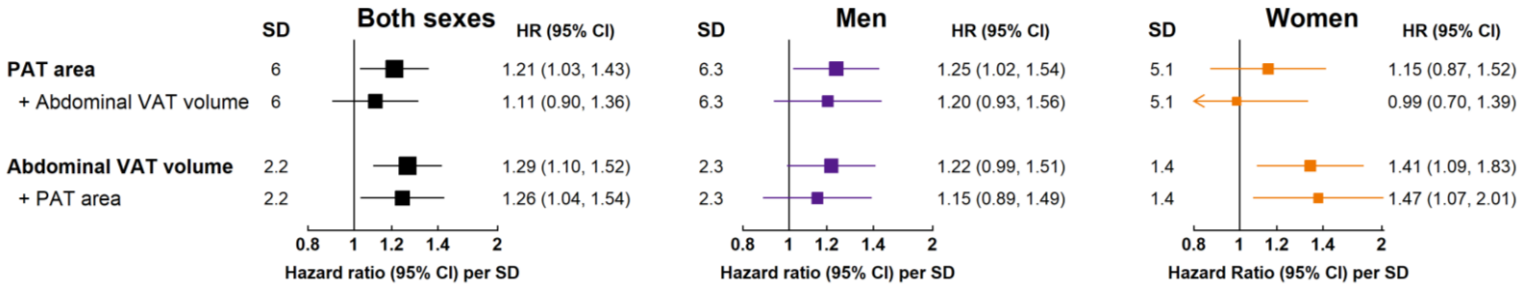


Figure 6.6: Association of pericardial adipose tissue area and abdominal visceral adipose tissue with incident coronary heart disease before and after mutual adjustment, by sex (n=3,290).
Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation and mutually adjusted as indicated. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars). PAT – pericardial adipose tissue, VAT – visceral adipose tissue.

6.4.6. Genome wide association study of pericardial adipose tissue area

To explore the causal relevance of identified observational associations between PAT area and risk of AF and CHD using an MR approach, an appropriate genetic score is required. To achieve this, a GWAS of PAT area was undertaken.

6.4.6.1. Residual generation

PAT inverse-normally transformed residuals were created in all 3,477 participants with PAT data available (**Appendix Figure H.3**).

6.4.6.2. Genome-wide association study results

A GWAS was conducted on 3,477 participants in whom PAT area had been derived. **Figure 6.7** shows a Manhattan plot for this analysis. There was no significant evidence of genomic inflation (λ = 1.01, **Figure 6.8**). No variants reached genome-wide significant level ($p < 5 \times 10^{-8}$). However, 159 variants reached a genome-wide suggestive threshold ($p<1 \times 10^{-5}$) with a minor allele frequency ≥1%. Following clumping, 36 near-independent variants remained (**Table 6.1, Appendix Figure H.4**), of which 17 (47%) were low frequency (minor allele frequency <5%). Genetic heritability was estimated at 17.2%. No replication data were available at the time of writing this thesis.

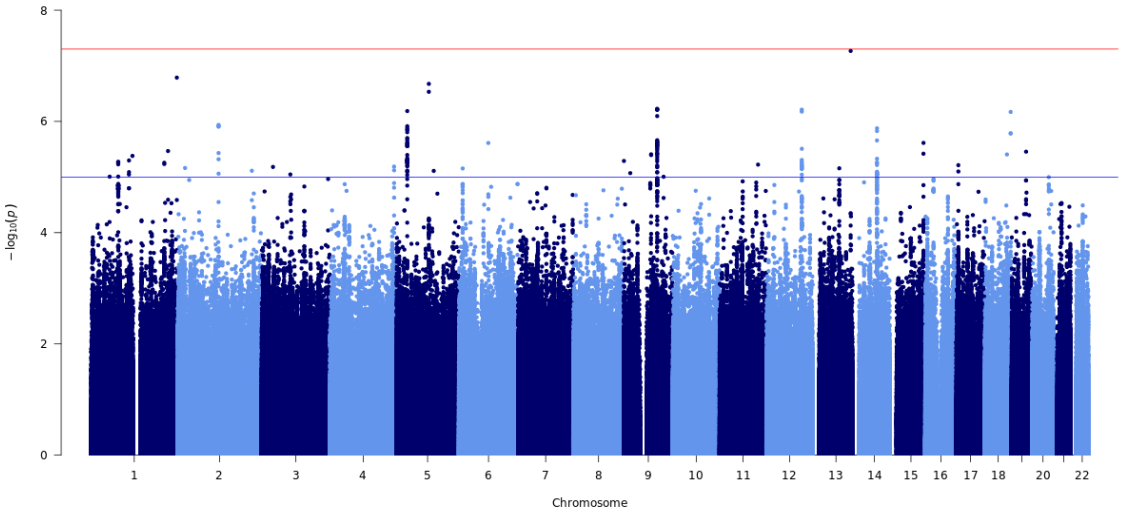


Figure 6.7: Manhattan plot of genome-wide association study results for pericardial adipose tissue area.
Genome wide association study of pericardial adipose tissue area residuals undertaken in 3,477 participants. Residuals adjusted for age, age^2, sex, principal components 1-7. The genome-wide significance level is set at 5 x 10^{-8} and plotted as a red line with a genome-wide suggestive level of 1 x 10^{-5} plotted as a blue line.

1

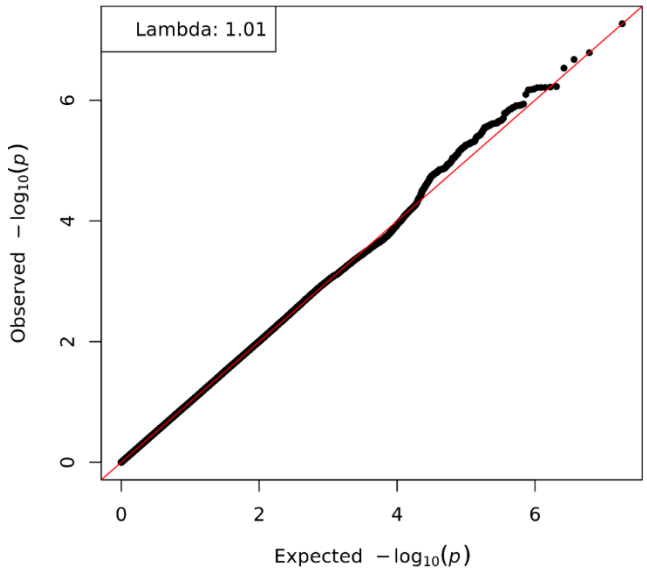


Figure 6.8: Quantile-quantile plot of observed and expected p-values from pericardial adipose tissue area genome-wide association study.

2

Table 6.1: Near independent variants reaching genome-wide suggestive thresold ($p<1 \times 10^{-5}$) in pericardial adipose tissue genome-wide association study

RSID	Chr	Position	Effect allele	Other Allele	Beta	SE	P	EAF	F-stat	Closest gene
rs10651054	1	53664757	C	CAG	-0.394	0.09	9.9×10^{-6}	0.98	19.6	CPT2
rs148644337	1	78307707	G	A	0.274	0.06	5.3×10^{-6}	0.04	20.8	MIGA1
rs12402255	1	109364696	C	T	0.136	0.03	5.0×10^{-6}	0.20	20.9	AKNAD1
rs1416143	1	119370614	A	T	-0.136	0.03	4.2×10^{-6}	0.73	21.2	TBX15
rs1591747	1	211341767	T	A	0.294	0.07	5.5×10^{-6}	0.97	20.7	KCHH1
rs75220604	1	222188743	T	C	0.486	0.10	3.4×10^{-6}	0.01	21.6	LINC01705
rs149447263	1	247615681	G	A	0.526	0.10	1.6×10^{-7}	0.01	27.5	OR2B11
2:22184102	2	22184102	T	TA	-0.503	0.11	6.9×10^{-6}	0.01	20.3	TDRD15
rs72839639	2	118889620	T	G	0.198	0.04	1.2×10^{-6}	0.10	23.6	INSIG2
rs144330706	2	215027100	T	C	0.527	0.12	7.7×10^{-6}	0.01	20.1	SPAG16
rs140644590	3	32943593	G	T	0.452	0.10	6.6×10^{-6}	0.02	20.4	CCR4
3:83061151	3	83061151	A	AT	-0.382	0.09	9.0×10^{-6}	0.02	19.8	GBE1
rs114562117	4	22989315	G	A	-0.375	0.08	7.0×10^{-6}	0.02	20.3	GPR125
rs62342217	4	184703567	G	C	-0.138	0.03	6.5×10^{-6}	0.18	20.4	TRAPPC11
rs147147745	5	31692340	A	G	-0.164	0.03	6.5×10^{-7}	0.16	16.4	PDZD2
rs76896582	5	94034844	G	T	0.417	0.08	2.1×10^{-7}	0.02	27.0	SLF1
rs371018217	5	108163523	C	CT	0.127	0.03	7.8×10^{-6}	0.55	20.0	FER
rs10484891	6	10930371	C	G	-0.125	0.03	7.0×10^{-6}	0.24	20.2	SYCP2L
6:84997336	6	84997336	A	AAT	0.316	0.07	2.4×10^{-6}	0.03	22.3	CEP162
rs73179956	7	104119163	A	G	-0.227	0.05	8.7×10^{-6}	0.06	19.8	LHFPL3
rs529837080	9	178919	T	C	0.535	0.12	5.1×10^{-6}	0.02	20.8	CBWD1
rs139979398	9	18410802	C	T	-0.431	0.10	8.5×10^{-6}	0.02	19.9	ADAMTSL1

Table 6.1: Near independent variants reaching genome-wide suggestive thresold ($p<1 \times 10^{-5}$) in pericardial adipose tissue genome-wide association study

RSID	Chr	Position	Effect allele	Other Allele	Beta	SE	P	EAF	F-stat	Closest gene
rs55986604	9	78725538	A	G	0.172	0.04	3.9×10^{-6}	0.12	21.4	PCSK5
rs2184255	9	96176203	A	G	0.124	0.03	5.9×10^{-6}	0.61	25.0	FAM120AOS
rs112900534	9	114802531	T	C	0.402	0.09	9.9×10^{-6}	0.02	19.6	SUSD1
rs11603018	11	110761461	C	T	-0.178	0.04	6.0×10^{-6}	0.12	20.5	ARHGAP20
rs11111026	12	102192803	T	G	0.157	0.03	6.2×10^{-7}	0.18	24.9	GNPTAB
rs17065811	13	76731802	G	T	0.130	0.03	7.0×10^{-6}	0.24	20.3	C13orf45
rs117468092	13	109552611	A	G	0.520	0.10	5.4×10^{-8}	0.02	29.7	MYO16
rs12883649	14	70438450	C	A	0.122	0.03	1.3×10^{-6}	0.33	23.4	SMOC1
rs62022887	15	97418055	G	T	0.135	0.03	2.4×10^{-6}	0.25	22.3	SPATA8
rs62029574	16	23985900	G	A	0.178	0.04	8.4×10^{-6}	0.10	19.9	PRKCB
rs769569169	17	5344475	A	AGGCA	-0.119	0.03	6.1×10^{-6}	0.33	20.5	DHX33
rs145314662	18	64563802	G	T	0.522	0.11	3.9×10^{-6}	0.01	21.4	CDH19
rs8093917	18	75205685	T	C	-0.265	0.05	6.8×10^{-7}	0.06	24.8	GALR1
rs34271878	19	41697491	G	A	-0.164	0.04	3.5×10^{-6}	0.13	21.6	CYP2S1

Chr – chromosome, BP – base pair position, EAF – effect allele frequency, F-stat – F-statistic, SE – standard error, PVE – proportion of variance explained. Beta values represent the effect estimate (per allele) between the variant and pericardial adipose tissue area residuals in the genome-wide association study.

6.4.7. Pericardial adipose tissue genetic score

Despite only sub-GWAS significant loci being identified, we attempted to explore the information based on the 36 variants. A PAT area genetic score was created including data from these variants in white British UKB participants with available genetic data (n=339,214). The number of alleles associated with higher PAT area (risk alleles) and the genetic score were approximately normally distributed within the white British UKB population (**Appendix Figure H.5**).

6.4.7.1. Genetically predicted pericardial adipose tissue and anthropometric measures

As PAT has been shown to be correlated with other anthropometric measures (**Chapter 5**), associations between the developed PAT score and anthropometric measures correlated with PAT were assessed. Within the derivation cohort, genetically predicted PAT was associated with higher anthropometric measures including abdominal VAT and BMI (**Table 6.2**). However, when examined in the total UKB cohort, there was no association with other anthropometric measures (**Table 6.3**).

Table 6.2: Association between pericardial adipose tissue score and anthropometric traits in participants with pericardial adipose tissue data

Anthropometric Trait	Beta (95%CI) per SD greater PAT	N
VAT	0.27 (0.24 to 0.30)	2,677
BMI	0.20 (0.17 to 0.23)	2,973
WC	0.21 (0.18 to 0.25)	2,973
WCadjBMI	0.09 (0.06 to 0.12)	2,973
FM	0.22 (0.19 to 0.25)	2,936
LM	0.12 (0.09 to 0.16)	2,937

BMI – body mass index, CI – confidence intervals, FM – body fat mass, LM – body lean mass, PAT – pericardial adipose tissue, SD – standard deviation, VAT – visceral adipose tissue, WC – waist circumference, WCadjBMI – waist circumference adjusted for body mass index.

1

Table 6.3: Association between pericardial adipose tissue score and anthropometric traits in UK Biobank.

Anthropometric Trait	Beta (95%CI) per SD greater PAT	N
BMI	0.00 (0.00 to 0.01)	338,107
WC	0.00 (0.00 to 0.01)	338,634
WCadjBMI	0.00 (0.00 to 0.00)	338,042
FM	0.00 (0.00 to 0.01)	332,600
LM	0.00 (0.00 to 0.00)	333,114

BMI – body mass index, CI – confidence intervals, FM – body fat mass, LM – body lean mass, SD – standard deviation, WC – waist circumference, WCadjBMI – waist circumference adjusted for body mass index.

2

3 To assess this further the 36 variants identified by the PAT GWAS were
4 examined individually and compared to the beta values obtained from GWAS of
5 other anthropometric measures previously undertaken in UKB.[304] The beta
6 values from the PAT GWAS were compared against beta values for BMI, WC,
7 FM, and LM within UKB. There was no evidence of an association between the
8 beta values for PAT and other anthropometric traits (**Figure 6.9**).

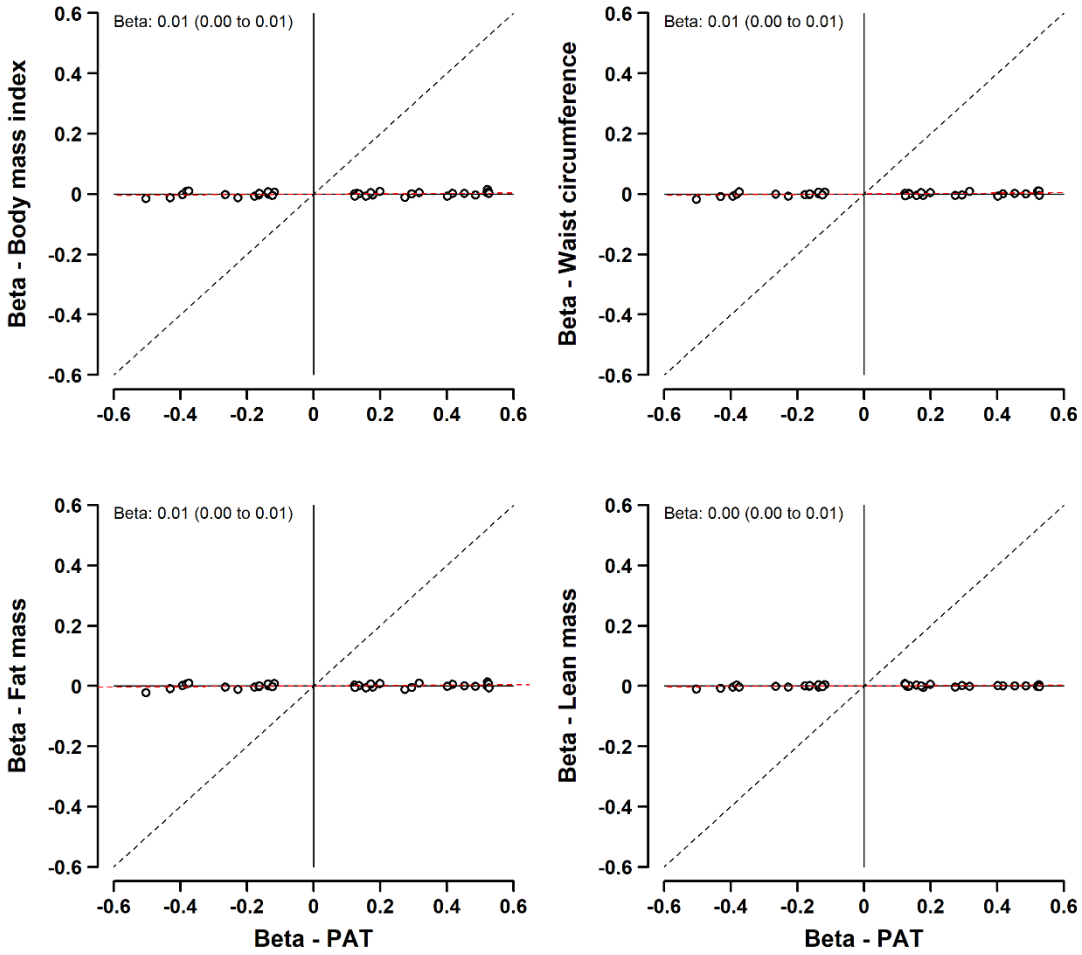


Figure 6.9: Comparison of beta values for variants identified in pericardial adipose tissue genome-wide association study compared with beta values for the same variants in a genome-wide association study of other anthropometric traits.

Scatter plot of beta values from 36 near-independent variants meeting genome-wide suggestive threshold form genome-wide association study for pericardial adipose tissue compared with beta values in genome-wide association study of body mass index, waist circumference, fat mass, and lean mass in UK biobank.[304] *Black solid line represents parity between beta values. Red dashed line demonstrates linear regression of beta values. PAT – pericardial adipose tissue*

6.4.7.2. Association with variants identified in previous genome-wide association study of other anthropometric traits

Given the lack of association between the variants in the PAT genetic score and anthropometric measures in the full UKB sample, the relationship between known loci for BMI (n=96),[103] WC (n=37),[104] WCadjBMI (n=46),[105] and abdominal VAT (n=6),[106] and PAT were evaluated. We examined the beta values for the known

loci for other anthropometric traits and compared them with beta values obtained in this PAT GWAS (**Figure 6.10**). This demonstrated no significant association between BMI or WC variant beta values and PAT. There was a significant association between WCadjBMI and VAT variant beta values and PAT; however, it should be noted that the VAT GWAS was undertaken in an overlapping sub-set of the UKB population.[106]

Two previous GWAS have examined PAT volume and identified two independent loci for this phenotype but have not provided summary statistics.[98,99] In this analysis both loci were directionally consistent with PAT area p (unadjusted for multiple testing) <0.05 (**Table 6.4**).

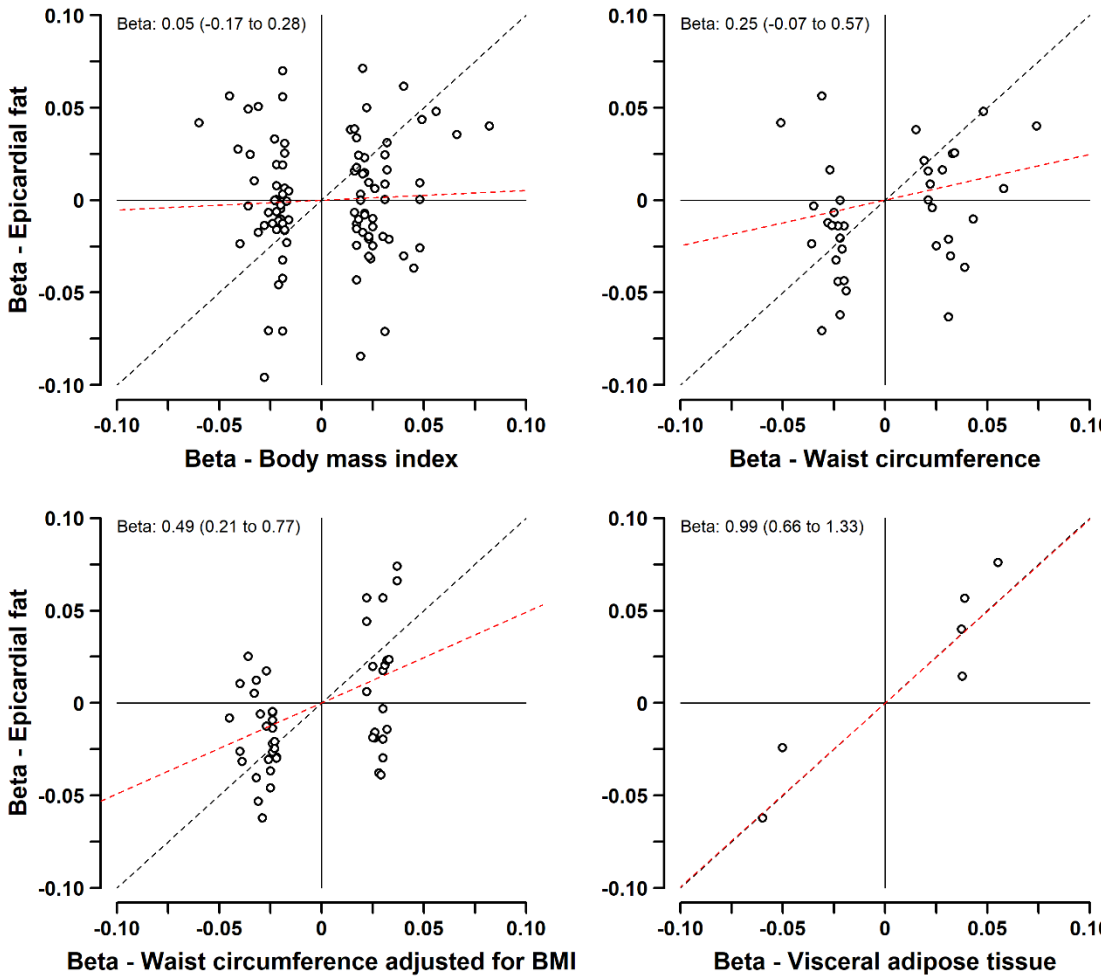


Figure 6.10: Comparison of beta values for variants identified in external anthropometric genome-wide association studies compared with beta values for the same variants in the pericardial adipose tissue genome-wide association study.

Scatter plot of effect estimates (beta) from near-independent variants meeting genome-wide significant threshold from genome-wide association studies of anthropometric measures (body mass index,[103] waist circumference,[104] waist circumference adjusted for body mass index,[105] and visceral adipose tissue)[106] compared with effect estimates (beta) in a genome-wide association study of pericardial adipose tissue area in UK Biobank. Black dotted line represents parity between beta values. Red dotted line represent results from linear regression model.

1

Table 6.4: Loci previously identified as being associated with pericardial fat and their associated beta values for pericardial adipose tissue in UK Biobank

RSID	Effect allele	Other allele	Effect allele frequency	Beta	SE	P	Chu *et al.* Z-score[99]
rs10198628	A	G	0.47	-0.081	0.025	0.001	-7.87
rs2434264	G	T	0.34	-0.056	0.026	0.021	-5.93

Beta, standard error (SE), and p-values displayed are from UK Biobank pericardial adipose tissue area genome-wide association study.

2

6.5.Discussion

This study examined a novel phenotype; CMR derived mid-ventricular PAT, within UKB. Results demonstrated an association between PAT and both incident AF and CHD with a similar strength of association seen in men and women. In contrast to prior reports, the association between 1-SD greater PAT area and risk of AF was of a similar magnitude to that seen with other anthropometric measures.

6.5.1. Association between pericardial adipose tissue area and incident atrial fibrillation

This study demonstrated that mid-ventricular PAT is associated with the risk of incident AF with a ~30% higher risk per SD greater PAT. Findings from the Rotterdam Heart Study, demonstrated a 31% higher risk of AF per SD greater CT determined PAT volume.[230] In contrast, Heckbert *et al*. examining the MESA and JHS cohorts demonstrated a weaker association (12% higher risk of AF per SD greater PAT volume).[95] Other cohorts have not shown a significant association between PAT and risk of AF.[94,100,231] The non-significant associations seen in the Heinz-Nixdorf recall study and the Osaka MDCT study may be due to the small number of incident AF cases (n=50 and n=17 respectively).[94,231] Associations in other cohorts may also be lower due to the inclusion of potentially mediating phenotypes (for example blood pressure) as model covariates. Additionally, the PAT phenotype in these cohorts are volumes across the whole heart compared with a mid-ventricular PAT area used in this chapter limiting comparison of effect estimates. These findings are generally smaller than those reported in a prior meta-analysis which suggested more than a 2.5-fold greater

risk of AF per SD greater PAT (OR 2.61, 95%CI [1.89 to 3.50] per SD).[72] However, there is substantial heterogeneity in this meta-analysis and inclusion of a number of small case-control studies which demonstrated greater effect sizes and are at risk of selection bias and reverse causation.

6.5.2. Independent relevance of pericardial adipose tissue and abdominal visceral adipose tissue with atrial fibrillation

It has been suggested that PAT may be a central pathway through which adiposity increases the risk of AF.[87] We have shown that PAT is most strongly associated with abdominal VAT when compared to a range of anthropometric measures including BMI, WC, and FM (**Chapter 5**). While abdominal VAT has similarly been considered a key potential mediator for the association between broader anthropometric phenotypes and risk of cardiovascular disease,[305] the evidence for the association between abdominal VAT and risk of AF is mixed.[100,233] Prior studies adjusting for BMI have suggested that PAT may not be independent of the effect of BMI on risk of AF.[100] In this current analysis, following adjustment for abdominal VAT, there was only slight attenuation in the association between PAT and risk of incident AF (HR 1.24, 0.99 to 1.55, per SD); while nominally non-significant, the general trend of the relationship remained similar to that seen without adjustment for abdominal VAT.

In this analysis, abdominal VAT was associated with risk of incident AF. This association is in contrast to previous studies which have not demonstrated significant associations with incident AF.[68,100] However, when adjusted for PAT, the association between VAT and risk of AF was substantially attenuated (HR 1.16, 0.92 to 1.46, per SD). Whilst recognising potentially limited power, these

results suggest that the relationship between PAT and risk of AF may, at least partially, be independent of abdominal VAT; this warrants further investigation as more data becomes available.

6.5.3. Independent relevance between abdominal visceral adipose tissue and coronary heart disease

Abdominal VAT has previously been associated with a number of metabolic risk factors for cardiovascular disease.[284] This study has demonstrated that abdominal VAT is associated with risk of CHD (HR 1.29, 1.10 to 1.43, per SD). However, in contrast to AF, the association between abdominal VAT and risk of CHD was not significantly reduced after adjustment for PAT area. The difference in the association of abdominal VAT with AF and CHD after adjustment for PAT may be due to the strong association between abdominal VAT and CHD risk factors such as hyperlipidaemia and metabolic syndrome,[284,306] and warrants further investigation.

6.5.4. GWAS Results

The GWAS of PAT undertaken in this chapter revealed no variants meeting genome wide significance. Thirty-six near-independent variants met the genome-wide suggestive threshold ($p<1 \times 10^{-5}$) and were used to create a genetic score for PAT. Given that PAT is highly correlated with a range of other anthropometric measures (**Chapter 5**), it would be expected that this genetic score would also be correlated with other anthropometric measures. While predictive of a range of anthropometric measures in the derivation sub-set of UKB, when expanded to the entire UKB cohort, this genetic score was not predictive of other

anthropometric measures. Examining these 36 variants individually in GWAS data of other anthropometric measures showed no evidence of association.[304] This suggests that these variants, identified using a GWAS-suggestive threshold, may be the result of chance rather than being truly associated with mid-ventricular PAT area. As a result, the MR analyses that had initially been planned as part of this research were not undertaken.

Previous GWAS of pericardial fat have been performed,[98,99] which have identified two variants meeting the genome-wide significant threshold. Importantly, the terminology surrounding PAT is heterogenous,[289] and the phenotypes included in these analyses were variable.[98,99] While there was directional consistency in these variants, they were not replicated at a genome-wide level within this current study (albeit both $p<0.05$). Summary data from these prior GWAS are not available which precludes meta-analyses of results to increase power.

6.5.5. Limitations

This study has a number of potential limitations. While the population undertaking the UKB imaging sub-study is generally similar to the entire UKB population, the UKB cohort is known to have a 'healthy volunteer' bias.[141] Information on incident AF diagnosis was taken from hospital records and death registries only; given AF may initially be diagnosed in the community there may be a lead-time bias and some participants with asymptomatic AF may not have been identified.

The most significant limitation to this analysis is that the GWAS was underpowered to detect variants associated with PAT. This GWAS was powered to identify variants explaining ≥ 1.1% of PAT area variance. In comparison, prior

GWAS of PAT have identified variants explaining ~0.5% of the variance,[98] and the *FTO* locus associated with BMI explains 0.34% of the variance in BMI.[307] This limitation in power was principally a function of limitations in the available data at the time of the analysis.

The phenotype developed and used in this analysis is a measure of mid-ventricular PAT. However, some prior studies have suggested that atrial adipose tissue may be a more informative risk factor for AF.[231,308] This analysis was unable to investigate the effect of atrial PAT on risk of AF.

6.5.6. Future Work

The current research has developed a novel PAT phenotype using native T1 maps from CMR data in UKB. However, at present this is a labour-intensive approach requiring individual contouring for each participants. Machine learning may allow for the development of a method for the scaling up of this phenotype to the entire UKB population with suitable imaging data.[309] As such, the current dataset could be used as a training set for the development of this algorithm.

In addition, since undertaking this work another group have used a machine learning approach to determine PAT area in the imaging sub-population of UKB using apical four chamber cine images.[90] There are limitations to this approach, which have been discussed in **Chapter 5**. These data were not yet available for analysis at the time of writing this thesis. However, an important future research direction would be to compare the PAT developed in **Chapter 5** with the developed PAT area phenotype. It is important to consider that these data represent a different phenotypic trait (PAT area from an apical four-chamber

image) from that explored in this chapter (mid-ventricular PAT). However, these data may also provide sufficient power to examine the association with AF using both observational and genetic epidemiology techniques.

Potential differences in the independent relevance of abdominal VAT identified here require further investigation. Further data from the UKB imaging sub-study becomes available, combined with extended follow-up time, will allow inclusion of a larger number of CHD and AF cases. This resulting greater power would allow further inferences to be drawn from the data. Additionally, consideration of the role of inter-related abdominal adiposity phenotypes including liver fat percentage could be explored.

Chapter 7 – Causal relevance of anthropometric measures and risk of atrial fibrillation

7.1. Abstract

7.1.1. Background

Observational associations have linked anthropometric measures with risk of atrial fibrillation (AF). However, the independent causal role for these phenotypes remains unclear. Additionally, despite substantial differences in anthropometric measures between men and women, and differences identified in observational analyses, the sex-specific nature of these causal associations remains unexplored.

7.1.2. Methods

Using published genome-wide association studies (GWAS) of anthropometric measures, genetic scores were developed for body mass index (BMI), waist circumference (WC), WC adjusted for BMI, lean mass (LM), fat mass (FM), and visceral adipose tissue. The causal relevance of associations of anthropometric measures for AF were explored using Mendelian randomization (MR) methodology in UK Biobank (UKB) scaled to one unit greater genetic score (equivalent to one standard deviation greater anthropometric measure in the original GWAS). Multivariable MR (MVMR) was undertaken to explore the direct effects of anthropometric measures on risk of AF. Additional analyses were

undertaken in AFGen and FinnGen datasets to provide further validation of the results. The effects were examined separately in men and women in UKB to determine the extent of any sex-based differences.

7.1.3. Results

Genetically predicted BMI, WC, LM, and FM were all positively associated with risk of AF. In an MVMR model with BMI, there was a significant direct effect of WC on risk of AF (odds ratio [OR] 1.32, 95% confidence interval [95%CI] 1.05 to 1.67 per unit WC genetic score). Similarly, in an MVMR model, there were significant direct effects of both FM (OR 1.26, 95%CI 1.14 to 1.39) and LM (OR 1.62, 95%CI 1.44 to 1.82). There were no differences in the strength of associations between men and women for any anthropometric measure.

7.1.4. Conclusions

MR analyses provide support for independent causal associations between LM, FM, and WC and risk of AF. There is no evidence of a sex-based difference in the causal associations of anthropometric measures and risk of AF.

7.2. Introduction

AF has been repeatedly associated with a number of anthropometric measures.[66,226] Furthermore, a number of MR analyses have been undertaken in an attempt to demonstrate a causal association between individual anthropometric measures and risk of AF. These have shown positive associations between genetically predicted BMI, LM, FM, and height with risk of AF.[71,108,110,215]

However, given the correlations between anthropometric phenotypes,[226] the independent relevance of these identified relationships remains unclear. The use of MVMR allows for the assessment of the independent effect of correlated phenotypes on an outcome.[310] Previous phenome-wide MVMR analyses have examined a number of anthropometric measures and suggest that BMI and height may be independently and causally related to AF.[110]

Additionally, potential differences in the effect of anthropometric measures on the risk of AF in men and women have previously been identified in observational studies.[226] Limited availability of sex-specific GWAS has largely prevented analysis of sex-based differences in associations between genetically predicted measures and outcomes. As a result, to date, any differences in the causal relationship between common anthropometric phenotypes and risk of AF between sexes remain unclear.

There were several aims in this MR study: (1) to examine the causal relevance of anthropometric measures and risk of AF in men and women; (2) to determine the independent causal effects of anthropometric measures and risk of AF.

7.3. Methods

7.3.1. Study design and participants

Details of the UKB study design including participant selection for genetic analyses has been detailed in **Chapter 2**. In brief, participants were included with a self-reported white British ancestry and who clustered in this group in a principal component analysis. Participants were excluded if they exhibited sex chromosome aneuploidy, where there was discrepancy between genetic and self-reported sex. Participants who were outliers for heterozygosity, missingness (missing rate on autosomes >0.02), and genotype call rate were also excluded. Related participants were excluded. The primary analyses included 339,214 participants.

7.3.2. Selection of genetic variants

For each anthropometric measure, variants were identified from published GWAS data.[35,71,104,105] GWAS significiant variants were selected and underwent clumping and removal of palindromic variants. Details of the selection process are presented in **Chapter 2** and Appendix I (**Development of genetic scores**). The reference panel for clumping was 1000 Genomes (n=503 individuals of European descent). Following clumping and removal of palindromic variants, the BMI score comprised 348 variants (**Appendix Table I.1**), the WC score comprised 37 variants (**Appendix Table I.2**), WCadjBMI score comprised of 46 variants (**Appendix Table I.3**), the FM score comprised 157 variants (**Appendix Table I.5**), the LM score comprised 222 variants (**Appendix Table I.6**), and the abdominal VAT score comprised six variants (**Appendix Table I.7**).

7.3.3. Residual generation

To illustrate associations of scores in the UKB data, residuals of relevant anthropometric measures were developed in line with published methods.[103] Residuals were calculated following adjustment for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. To calculate WC adjusted for BMI, WC was additionally adjusted for BMI. These residuals were then transformed using inverse normal scores.

7.3.4. Statistical analyses

Associations between the genetic scores and anthropometric parameters (as the exposure in the MR analysis, **Figure 1.4**) were estimated using linear regression and associations between genetic scores and risk of AF using logistic regression. UKB analyses using genetic scores as the independent variable were adjusted for age, age^2, sex, genotyping array, and seven principal components of ancestry. For sex-specific analyses, scores were weighted by their published overall per-allele effect size. If male and female effect estimates were provided separately in the original GWAS, a further sex-specific analysis was undertaken using scores weighted using these sex-specific effect estimates. Analyses were weighted to one unit greater genetic score which was equivalent to a 1 SD greater anthropometric measure in the original GWAS.

7.3.4.1. Power calculations

Power calculations were undertaken using an online calculator (https://shiny.cnsgenomics.com/mRnd/),[311] and the results are outlined in **Table 7.1**. The variance explained for each genetic score was estimated as outlined in **Chapter 2** (**Proportion of variance explained**). The proportion of AF cases was

taken to be 8.3%. A causal detection effect of 1.25 per SD unit was obtained from prior analyses.[226] A significance level of 0.05 was used.

Table 7.1: Power calculations for anthropometric genetic scores and risk of atrial fibrillation

Anthropometric trait	Number of variants	Variance explained (%)	Calculated power (%)
Body mass index	348	3.6	100
Waist circumference	37	0.9	96
WCadjBMI	46	1.3	99
Lean mass	222	5.0	100
Fat mass	157	2.6	100
VAT	6	0.6	85

Power calculations undertaken for each genetic score using the variance explained outlined in the table, an 8.3% proportion of AF cases and a causal detection effect of 1.25 per SD. VAT – visceral adipose tissue; WCadjBMI – waist circumference adjusted for body mass index.

7.4. Results

7.4.1. Baseline characteristics

Of the 339,214 participants with available genetic data, 54% were women. Participants had a mean age at baseline of 56.9 years (SD 8.0). With the exception of ethnicity, there was no meaningful difference between the baseline characteristics of those with and without genetic data available (**Table 7.2**). As seen in the total cohort (**Chapter 4**), in those with genetic data, average BMI, WC, weight, and LM were higher in men than women (**Table 7.3**). FM was higher in women (27.0 kg, SD 10.0) than in men (22.4 kg, SD 8.3).

7.4.2. Atrial fibrillation cases in the UK Biobank cohort with genetic data available

A total of 30,630 AF cases (8.9%) were identified in this cohort (19,527 in men and 11,103 in women). Of these, 6,497 were prevalent AF cases and 24,133 were incident AF cases.

Table 7.2: Baseline characteristics of UK Biobank participants with and without genetic data available (n=502,536).

	Genetic data	
	Not available (n=163,322)	**Available** (n=339,214)
Demographic and lifestyle factors		
Age, mean (SD)	55.7 (8.2)	56.9 (8.0)
Male, n(%)	71,439 (43.7)	157,695 (46.5)
White, n(%)	133,126 (81.5)	339,183 (100.0)
Current smoker, n(%)	19,162 (11.7)	33,817 (10.0)
Current alcohol drinker, n(%)	143,618 (87.9)	316,768 (93.4)
Townsend Deprivation Index, mean (SD)	-0.7 (3.3)	-1.6 (2.9)
Anthropometric measures, mean (SD)		
Height, cm	167.6 (9.3)	168.9 (9.3)
Weight, kg	77.4 (16.0)	78.4 (15.9)
Body mass index, kg/m^2	77.4 (16.0)	78.4 (15.9)
Waist circumference, cm	90.1 (13.4)	90.4 (13.5)
Hip circumference, cm	103.3 (9.4)	103.5 (9.2)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)		
Body lean mass, kg	52.5 (11.3)	53.5 (11.6)
Body fat mass, kg	24.8 (9.7)	24.9 (9.5)
Prior disease, n(%)		
Diabetes	9,362 (5.8)	15,859 (4.7)
Stroke	2,113 (1.3)	4,835 (1.4)
Coronary heart disease	7,226 (4.4)	16,372 (4.8)
Congestive cardiac failure	771 (0.5)	2,126 (0.6)
Valvular heart disease	1,555 (1.0)	4,015 (1.2)
Hypertension	58,243 (35.9)	125,871 (37.1)
Sleep apnoea	1,186 (0.7)	2,250 (0.7)

SD – standard deviation

1

Table 7.3: Baseline characteristics of UK Biobank participants with genetic data available by sex (n=339,214)

	Women (n=181,519)	**Men** (n=157,695)
Demographic and lifestyle factors		
Age, mean (SD)	56.7 (7.9)	57.2 (8.1)
White, n(%)	181,507 (100.0)	157,676 (100.0)
Current smoker, n(%)	15,399 (8.5)	18,418 (11.7)
Current alcohol drinker, n(%)	166,950 (92.0)	149,818 (95.0)
Townsend Deprivation Index, mean (SD)	-1.6 (2.9)	-1.5 (3.0)
Anthropometric measures, mean (SD)		
Height, cm	162.7 (6.2)	176.0 (6.8)
Weight, kg	71.5 (14.0)	86.3 (14.3)
Body mass index, kg/m^2	71.5 (14.0)	86.3 (14.3)
Waist circumference, cm	84.6 (12.5)	97.1 (11.4)
Hip circumference, cm	103.4 (10.3)	103.6 (7.6)
Waist-hip ratio	0.8 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)		
Body lean mass, kg	44.6 (5.0)	63.9 (7.7)
Body fat mass, kg	27.0 (10.0)	22.4 (8.3)
Prior disease, n(%)		
Diabetes	5,751 (3.2)	10,108 (6.4)
Stroke	1,875 (1.0)	2,960 (1.9)
Coronary heart disease	4,504 (2.5)	11,868 (7.5)
Congestive cardiac failure	523 (0.3)	1,603 (1.0)
Valvular heart disease	2,041 (1.1)	1,974 (1.3)
Hypertension	58,344 (32.1)	67,527 (42.8)
Sleep apnoea	509 (0.3)	1,741 (1.1)

SD – standard deviation

1

7.4.3. Genetically predicted body mass index and risk of atrial fibrillation

When applied to the UKB population, the risk alleles for the selected variants and the developed BMI genetic score were normally distributed (**Appendix Figure I.2**).

7.4.3.1. Association between body mass index genetic score and body mass index in UK Biobank

When combined as a weighted genetic score, as expected, a one unit greater score was associated with a 0.98 SD (95%CI 0.96 to 1.00) higher BMI. In UKB, the individual per-allele effects for each of the included variants were comparable with those shown in prior GWAS not including UKB (**Appendix Figure I.3**).[103] Associations between individual variants and baseline BMI in UKB are displayed in **Appendix Table J.1**.

7.4.3.2. Body mass index genetic score and risk of atrial fibrillation in UK Biobank

There was an approximately log-linear association between greater genetically predicted BMI and a greater risk of AF in UKB (OR 1.41, 95%CI 1.32 to 1.50, per unit higher BMI genetic score, **Figure 7.1**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.1** (**Appendix Figure J.1**).

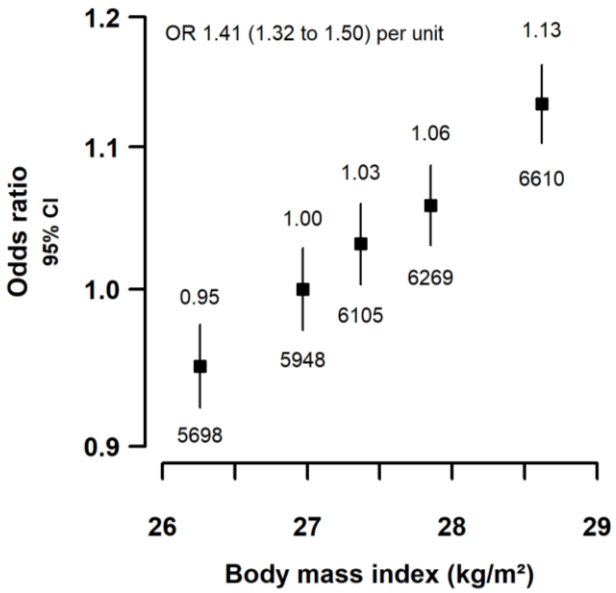


Figure 7.1: Association of genetically predicted body mass index with atrial fibrillation.

Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. ORs shown above each square and number of atrial fibrillation cases below.

1

2 **7.4.3.3. Body mass index genetic score sensitivity analyses**

3 Comparable estimates were obtained from weighted median and weighted mode
4 methods. The MR-Egger analysis did not provide evidence of directional
5 pleiotropy (**Table 7.4**). When meta-analysed with results from AFGen and
6 FinnGen datasets, a one unit higher BMI genetic score was associated with
7 ~45% higher risk of AF (OR 1.46, 95% 1.27 to 1.68, **Figure 7.2**). Comparable
8 effects were seen in UKB and AFGen with somewhat greater effects in FinnGen.

Table 7.4: Sensitivity analyses for genetically predicted body mass index on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.41 (1.32 to 1.50)	5.0×10^{-24}
IVW estimate	1.41 (1.29 to 1.55)	1.5×10^{-13}
Weighted median estimate	1.41 (1.25 to 1.58)	5.4×10^{-9}
Weighted mode estimate	1.41 (1.17 to 1.70)	3.5×10^{-4}
MR- Egger	1.39 (1.14 to 1.69)	0.001
*Egger-intercept test**		0.83
MR-PRESSO corrected estimate	1.41 (1.29 to 1.54)	2.8×10^{-13}

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher body mass index genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

1

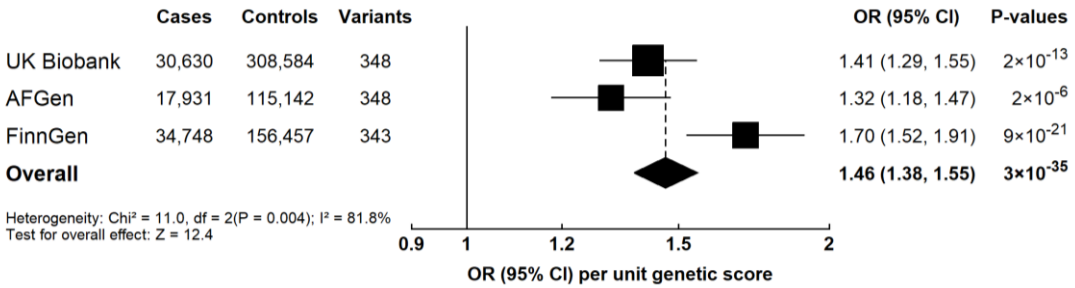


Figure 7.2: Meta-analysis of effect of genetically predicted body mass index on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher body mass index score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

2

3 **7.4.3.4. Genetically predicted body mass index and risk of atrial fibrillation**

4 **in men and women**

5 In UKB, the strength of association between genetically predicted BMI and risk

6 of AF was similar in men (OR 1.44, 95%CI 1.32 to 1.56) and women (OR 1.36,

7 95%CI 1.22 to 1.51, p-interaction = 0.39). Furthermore, there remained no

8 difference in strength of the association between men (OR 1.43, 95%CI 1.31 to

1.55) and women (OR 1.34, 95%CI 1.21 to 1.48) when sex-specific weights were used to derive the genetic score (p-interaction = 0.30).

7.4.4. Genetically predicted waist circumference and risk of atrial fibrillation

When applied to the UKB population, the risk alleles for the selected variants and the developed WC genetic score were normally distributed (**Appendix Figure I.5**).

7.4.4.1. Association between waist circumference genetic score and waist circumference in UK Biobank

When combined as a weighted genetic score, the association with baseline WC was somewhat lower than the original GWAS with a one unit greater score was associated with a 0.82 SD (95%CI 0.79 to 0.85) higher WC. In UKB, the individual per-allele effects for each of the included variants were strongly correlated with, albeit somewhat weaker than, those shown in the discovery GWAS (**Appendix Figure I.6**).[104] Associations between individual variants and baseline WC in UKB are displayed in **Appendix Table J.2**.

7.4.4.2. Waist circumference genetic score and risk of atrial fibrillation in UK Biobank

Greater genetically predicted WC was log-linearly associated with a greater risk of AF in UKB (OR 1.38, 95%CI 1.24 to 1.53, per unit higher WC genetic score **Figure 7.3**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.2** (**Appendix Figure J.2**).

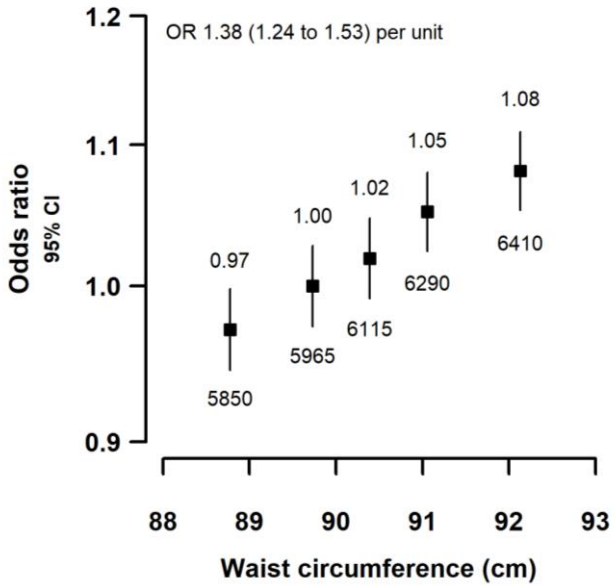


Figure 7.3: Association of genetically predicted waist circumference with atrial fibrillation.

Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. ORs shown above each square and number of atrial fibrillation cases below.

1

2 **7.4.4.3. Waist circumference genetic score sensitivity analyses**

3 Comparable estimates were obtained from weighted median and weighted mode
4 methods. The MR-Egger analysis did not provide evidence of directional
5 pleiotropy (**Table 7.5**). When meta-analysed with results from AFGen and
6 FinnGen datasets, a one unit higher WC genetic score was associated with ~45%
7 higher risk of AF (OR 1.45, 95% 1.34 to 1.57, **Figure 7.4**). Effect estimates were
8 comparable between AFGen and UKB and somewhat higher in FinnGen.

Table 7.5: Sensitivity analyses for genetically predicted waist circumference on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.38 (1.24 to 1.53)	1.4×10^{-9}
IVW estimate	1.38 (1.13 to 1.55)	2.4×10^{-8}
Weighted median estimate	1.32 (1.23 to 1.54)	4.9×10^{-4}
Weighted mode estimate	1.26 (1.04 to 1.52)	0.02
MR- Egger	1.06 (0.79 to 1.41)	0.71
*Egger-intercept test**		0.05
MR-PRESSO corrected estimate	1.38 (1.23 to 1.54)	2.5×10^{-6}

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher WC genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian Randomization Pleiotropy Residual Sum and Outlier.

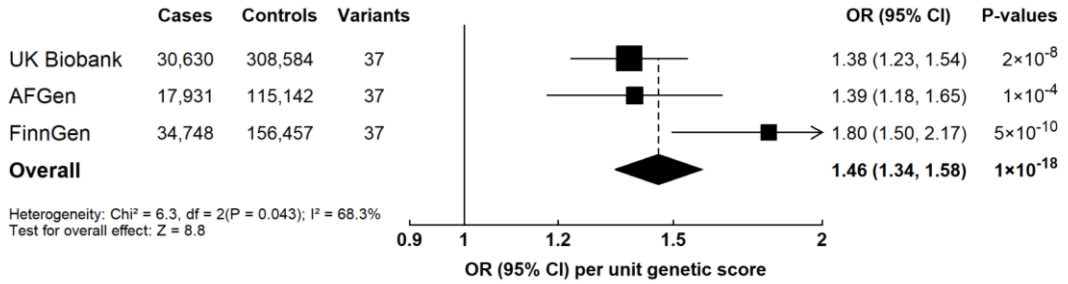


Figure 7.4: Meta-analysis of effect of genetically predicted waist circumference on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher waist circumference score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

7.4.4.4. Genetically predicted waist circumference and risk of atrial fibrillation in men and women

In UKB, when using overall weights, the strength of association between genetically predicted WC and risk of AF was similar in men (OR 1.42, 95%CI 1.24 to 1.62) and women (OR 1.31, 95%CI 1.10 to 1.54, p-interaction = 0.43). There remained no difference in strength of the association between men (OR

1.39, 95%CI 1.22 to 1.59) and women (OR 1.30, 95%CI 1.10 to 1.53) when sex-specific weights were used to derive the genetic score (p-interaction = 0.49).

7.4.5. Independent effect of waist circumference on risk of atrial fibrillation

The effect of genetically predicted WC on risk of AF independent of BMI has been assessed using two different approaches. First, using a genetic score developed from a GWAS of WCadjBMI. Second, using MVMR utilising a joint WC and BMI model.

7.4.5.1. Genetically predicted waist circumference adjusted for body mass index and risk of atrial fibrillation

When applied to the UKB population, the risk alleles for the selected variants and the developed WCadjBMI genetic score were normally distributed (**Appendix Figure I.8**).

7.4.5.1.1. Association between waist circumference adjusted for body mass index genetic score and waist circumference adjusted for body mass index in UK Biobank

When combined as a weighted genetic score, the association with baseline WCadjBMI was somewhat lower than the original GWAS with a one unit greater score associated with a 0.88 SD (95%CI 0.86 to 0.91) higher WCadjBMI. The individual per-allele effects for each of the included variants in UKB were comparable with those shown in the discovery GWAS (**Appendix Figure I.9**).[105] Associations between individual variants and baseline WC in UKB are displayed in **Appendix Table J.3**.

7.4.5.1.2. Waist circumference adjusted for body mass index genetic score and risk of atrial fibrillation in UK Biobank

Greater genetically predicted WCadjBMI was associated with a greater risk of AF in UKB in a log-linear fashion (OR 1.33, 95%CI 1.21 to 1.47, per unit higher WCadjBMI genetic score **Figure 7.5**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.3** (**Appendix Figure J.3**).

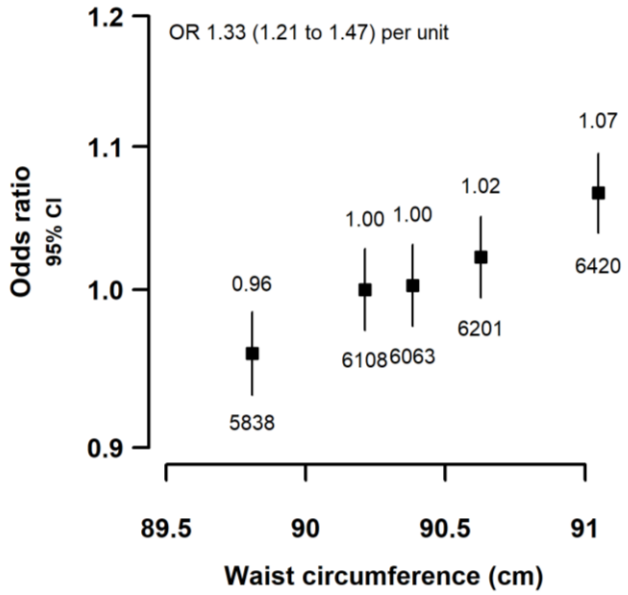


Figure 7.5: Association of genetically predicted waist circumference adjusted for body mass index with atrial fibrillation.
Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. ORs shown above each square and number of atrial fibrillation cases below.

7.4.5.1.3. Waist circumference adjusted for body mass index genetic score sensitivity analyses

Comparable estimates were obtained from weighted median and weighted mode methods. The MR-Egger analysis did not provide evidence of directional pleiotropy (**Table 7.6**). When meta-analysed with results from AFGen and

FinnGen datasets, a one unit higher WCadjBMI genetic score was associated with ~30% higher risk of AF (OR 1.30, 95% 1.20 to 1.40, **Figure 7.6**). The effect estimates were similar between all three datasets.

Table 7.6: Sensitivity analyses for genetically predicted waist circumference adjusted for body mass index on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.33 (1.21 to 1.47)	4.1×10^{-9}
IVW estimate	1.34 (1.14 to 1.58)	3.9×10^{-4}
Weighted median estimate	1.37 (1.16 to 1.60)	1.3×10^{-4}
Weighted mode estimate	1.36 (0.95 to 1.93)	0.10
MR- Egger	1.64 (0.67 to 4.05)	0.28
*Egger-intercept test**		0.66
MR-PRESSO corrected estimate	1.28 (1.10 to 1.48)	0.002

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher WCadjBMI genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

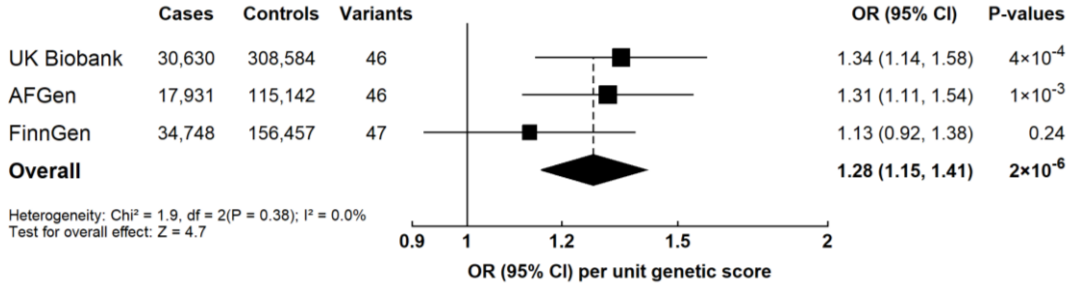


Figure 7.6: Meta-analysis of effect of genetically predicted waist circumference adjusted for body mass index on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher waist circumference adjusted for body mass index score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

7.4.5.1.4. Genetically predicted waist circumference adjusted for body mass index and risk of atrial fibrillation in men and women

In UKB, the strength of association between genetically predicted WCadjBMI and risk of AF was similar in men (OR 1.27, 95%CI 1.12 to 1.43) and women (OR

1.44, 95%CI 1.23 to 1.68, p-interaction = 0.21). There remained no difference in strength of the association between men (OR 1.20, 95%CI 1.07 to 1.35) and women (OR 1.37, 95%CI 1.18 to 1.60) when sex-specific weights were used to derive the genetic score (p-interaction = 0.16).

7.4.5.2. Multivariable Mendelian randomization analysis of waist circumference and body mass index

Variants from the BMI and WC genetic scores were used to generate a joint list of variants after harmonisation, and re-clumping. The resulting joint variant list contained 323 variants (**Appendix Table I.4**) and was used to determine the direct effects of WC and BMI on risk of AF.

Using an MVMR model in UKB, the direct effect of WC on risk of AF was partially attenuated (OR 1.28, 0.90 to 1.81, per unit genetic score, p=0.18) compared with the univariate inverse-variance weighted MR analysis (OR 1.34, 1.14 to 1.58, per unit genetic score). When meta-analysed with results from MVMR analyses in the AFGen and FinnGen datasets the point estimate for the effect estimate of genetically predicted WC on risk of AF remained similar and suggested a direct effect for WC on risk of AF independent of the effect of BMI (OR 1.32, 95%CI 1.05 to 1.67 per unit WC genetic score, **Figure 7.7**).

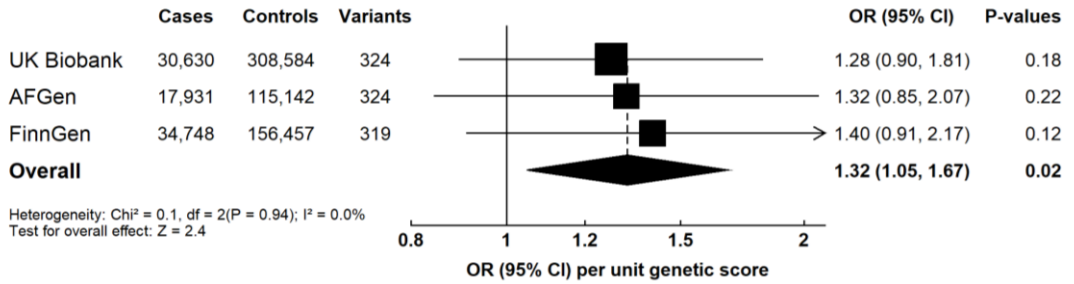


Figure 7.7: Meta-analysis of the direct effect of genetically predicted waist circumference on risk of atrial fibrillation in a multivariable Mendelian randomization model with body mass index.
Boxes represent point estimates of the direct effect per unit higher waist circumference score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

In UKB, the direct effect of genetically predicted BMI on risk of AF was also attenuated (OR 1.14, 0.84 to 1.56, p=0.40) when compared with the univariate inverse-variance weighted MR analysis (OR 1.41, 1.29 to 1.55). When meta-analysed with results from MVMR analyses in AFGen and FinnGen datasets the point estimate remained similar and the direct effect for BMI on risk of AF remained non-significant (OR 1.18, 95%CI 0.96 to 1.45 per unit BMI genetic score, **Figure 7.8**).

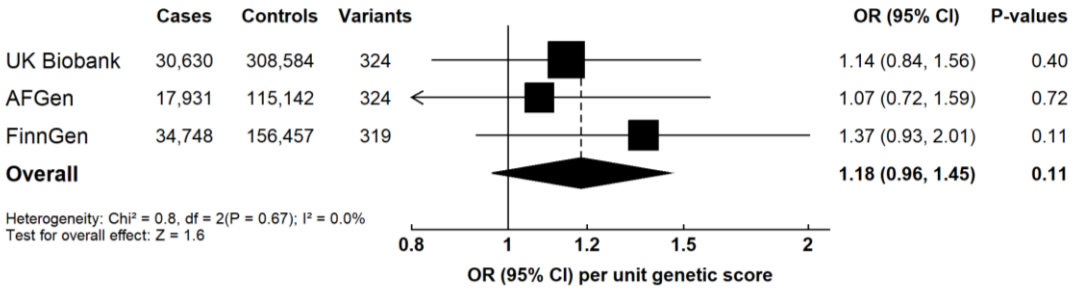


Figure 7.8: Meta-analysis of the direct effect of genetically predicted body mass index on risk of atrial fibrillation in a multivariable Mendelian randomization model with waist circumference.
Boxes represent point estimates of the direct effect per unit higher waist circumference score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

7.4.6. Genetically predicted fat mass and risk of atrial fibrillation

Risk alleles for the selected variants and the developed FM genetic score were normally distributed in UKB (**Appendix Figure I.13**).

7.4.6.1. Association between fat mass genetic score and fat mass in UK Biobank

When combined as a genetic score, a one unit greater score was associated with 1.02 SD (95%CI 1.00 to 1.04) higher FM. Associations between individual variants and baseline FM in UKB are displayed in **Appendix Table J.4**.

7.4.6.2. Fat mass genetic score and risk of atrial fibrillation in UK Biobank

There was a log-linear association between greater genetically predicted FM and risk of AF in UKB (OR 1.58, 95%CI 1.46 to 1.71, per unit higher FM genetic score **Figure 7.9**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.4** (**Appendix Figure J.4**).

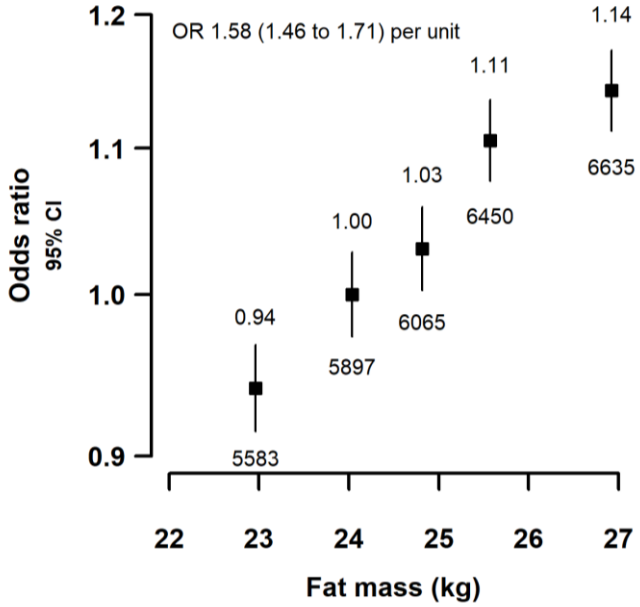


Figure 7.9: Association of genetically predicted fat mass with atrial fibrillation in UK Biobank.
Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. ORs shown above each square and number of atrial fibrillation cases below.

1

2 **7.4.6.3. Fat mass genetic score sensitivity analyses**

3 Comparable estimates were obtained from weighted median and weighted mode
4 methods. The MR-Egger analysis did not provide evidence of directional
5 pleiotropy (**Table 7.7**). When meta-analysed with results from AFGen and
6 FinnGen datasets, a one unit higher FM genetic score was associated with ~55%
7 higher risk of AF (OR 1.55, 95% 1.23 to 1.95, **Figure 7.10**). However, there were
8 substantial differences in point estimates in the three different datasets.

Table 7.7: Sensitivity analyses for genetically predicted fat mass on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.58 (1.46 to 1.71)	$<1 \times 10^{-300}$
IVW estimate	1.59 (1.43 to 1.77)	2.2×10^{-17}
Weighted median estimate	1.49 (1.32 to 1.70)	5.1×10^{-10}
Weighted mode estimate	1.38 (1.12 to 1.70)	0.003
MR- Egger	1.42 (1.03 to 1.95)	0.03
*Egger-intercept test**		0.47
MR-PRESSO corrected estimate	1.58 (1.43 to 1.75)	2.6×10^{-15}

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher FM genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

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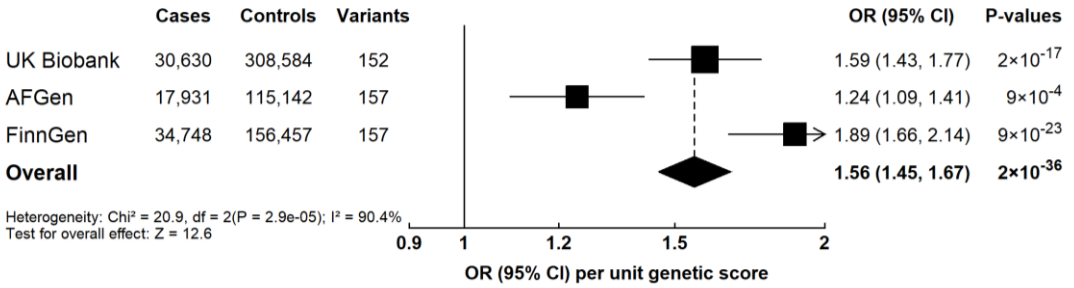


Figure 7.10: Meta-analysis of effect of genetically predicted fat mass on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher fat mass score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

2

3 **7.4.6.4. Genetically predicted fat mass and risk of atrial fibrillation in men**

4 **and women**

5 In UKB, the strength of association between genetically predicted FM and risk of

6 AF was similar in men (OR 1.55, 95%CI 1.41 to 1.71) and women (OR 1.62,

7 95%CI 1.43 to 1.84, p-interaction = 0.63). There remained no difference in

8 strength of the association between men (OR 1.49, 95%CI 1.36 to 1.63) and

women (OR 1.61, 95%CI 1.42 to 1.82) when sex-specific weights were used (p-interaction = 0.37).

7.4.7. Genetically predicted lean mass on risk of atrial fibrillation

Risk alleles for the selected variants and the developed LM genetic score were normally distributed in UKB (**Appendix Figure I.16**).

7.4.7.1. Association between lean mass genetic score and lean mass in UK Biobank

When combined as a genetic score, a one unit greater score was associated with a 1.58 SD (95%CI 1.56 to 1.61) higher LM. Associations between individual variants and baseline LM in UKB are displayed in **Appendix Table J.5**.

7.4.7.2. Lean mass genetic score and risk of atrial fibrillation in UK Biobank

Greater genetically predicted LM was log-linearly associated with a greater risk of AF in UKB (OR 1.98, 95%CI 1.81 to 2.16, per unit higher LM genetic score **Figure 7.11**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.5** (**Appendix Figure J.5**).

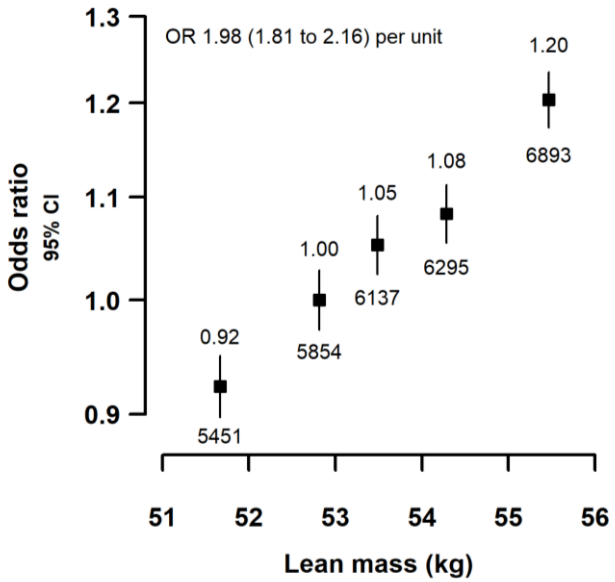


Figure 7.11: Association of genetically predicted lean mass with atrial fibrillation in UK Biobank.
Boxes represent point estimates of effect per unit higher lean mass score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

7.4.7.3.Lean mass genetic score sensitivity analyses

Comparable estimates were obtained from weighted median and weighted mode methods. The MR-Egger analysis did not provide evidence of directional pleiotropy (**Table 7.8**). When meta-analysed with results from AFGen and FinnGen datasets, a one unit higher FM genetic score was associated with ~90% higher risk of AF (OR 1.90, 95% 1.64 to 2.21, **Figure 7.12**). There were comparable effects in UKB and FinnGen with a somewhat lower effect demonstrated in AFGen.

Table 7.8: Sensitivity analyses for genetically predicted lean mass on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.98 (1.81 to 2.16)	4.7×10^{-53}
IVW estimate	2.02 (1.78 to 2.29)	1.3×10^{-28}
Weighted median estimate	2.04 (1.76 to 2.37)	9.9×10^{-21}
Weighted mode estimate	1.82 (1.34 to 2.46)	1.4×10^{-4}
MR- Egger	2.19 (1.63 to 2.93)	1.6×10^{-7}
*Egger-intercept test**		0.55
MR-PRESSO corrected estimate	2.09 (1.87 to 2.34)	7.6×10^{-29}

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher LM genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

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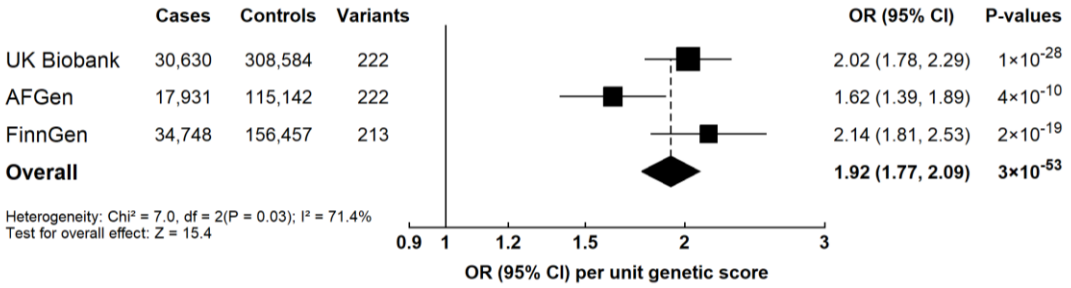


Figure 7.12: Meta-analysis of effect of genetically predicted lean mass on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher lean mass score, and the diamond represents meta-analysis estimates with sizes inversely proportional to their variance. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods.

2

3 **7.4.7.4. Genetically predicted lean mass and risk of atrial fibrillation in men**
4 **and women**

5 In UKB, the strength of association between genetically predicted LM and risk of
6 AF was similar in men (OR 1.96, 95%CI 1.75 to 2.19) and women (OR 2.01,
7 95%CI 1.74 to 2.31, p-interaction = 0.81). When sex-specific weights were used,
8 there remained no difference in strength of the association between men and
9 women. However, the association between one unit greater LM score and risk of

AF was substantially reduced in both men (OR 1.50, 95%CI 1.41 to 1.60) and women (OR 1.55, 95%CI 1.42 to 1.69) when sex-specific weights were used (p-interaction = 0.63). This reduction in effect sizes is due to the differing distributions of LM in men and women (see **Figure 4.2**) resulting in smaller SDs if calculated separately in men and women (men 7.7 kg, women 5.0 kg, see **Table 4.2**) compared with when calculated in both sexes together (11.4 kg).

7.4.8.Genetically predicted abdominal visceral adipose tissue and risk of atrial fibrillation

Risk alleles for the selected variants and the developed abdominal VAT genetic score were approximately normally distributed in UKB (**Appendix Figure I.19**).

7.4.8.1. Association between abdominal visceral adipose tissue genetic score and abdominal visceral adipose tissue in UK Biobank

When combined as a genetic score, a one unit greater score was associated with 1.07 SD (95%CI 0.63 to 1.52, n=3,954) higher abdominal VAT.

7.4.8.2. Genetically predicted abdominal visceral adipose tissue and risk of atrial fibrillation

Greater genetically predicted abdominal VAT was not associated with a greater risk of AF in UKB (OR 0.88, 95%CI 0.91 to 1.08, p=0.21, per unit higher abdominal VAT genetic score). When meta-analysed with results from the FinnGen and AFGen datasets, abdominal VAT was not associated with risk of AF (**Figure 7.13**).

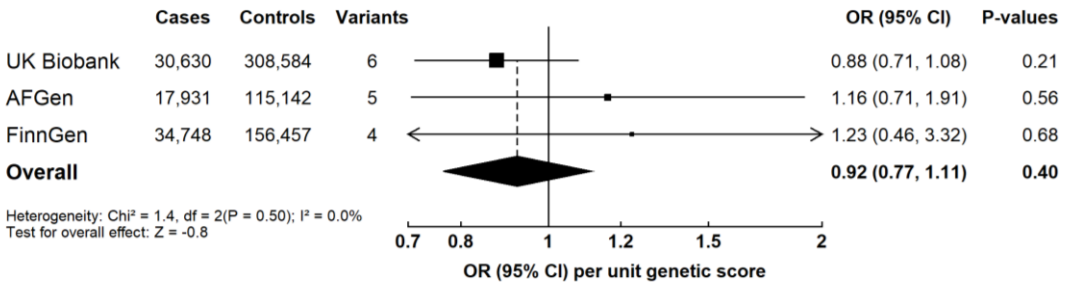


Figure 7.13: Meta-analysis of effect of genetically predicted visceral adipose tissue on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher lean mass score, and the diamond represents meta-analysis estimates with sizes inversely proportional to their variance. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods.

7.4.9. The direct effects of fat mass and lean mass on risk of atrial fibrillation

Variants from the FM and LM genetic scores were used to generate a joint list of variants after harmonisation and re-clumping. The resulting joint variant list contained 325 variants (**Appendix Table I.8**) and was used to examine the direct effects of FM and LM on risk of AF.

Using the MVMR model in UKB, the direct effect of LM was partially attenuated (OR 1.70, 95%CI 1.43 to 2.04, per unit genetic score) compared with the inverse-variance weighted MR analysis (OR 2.02, 1.78 to 2.29, per unit genetic score). When meta-analysed with results from MVMR analyses in AFGen and FinnGen, comparable effects were seen in all three datasets, and suggest a direct effect for LM on risk of AF independent of the effect of FM (OR 1.62, 1.44 to 1.82, per unit genetic score, **Figure 7.14**).

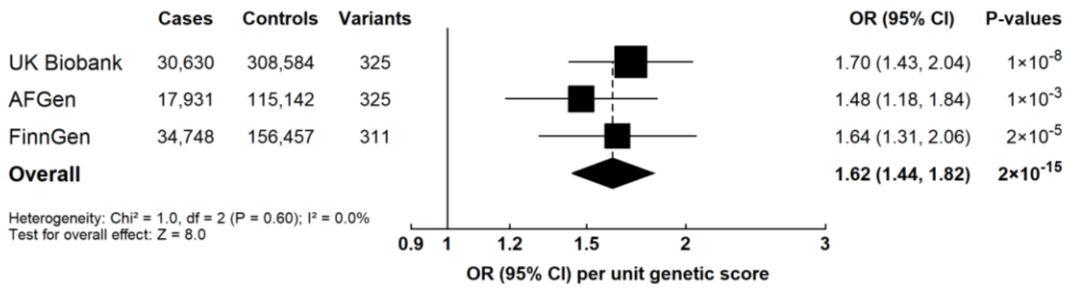


Figure 7.14: Meta-analysis of the direct effect of genetically predicted lean mass on risk of atrial fibrillation in a multivariable Mendelian randomization model with fat mass.

Boxes represent point estimates of the direct effect per unit higher lean mass score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

In UKB, the direct effect of genetically predicted FM on risk of AF was also attenuated (OR 1.24, 1.07 to 1.44) when compared with the univariate inverse-variance weighted MR analysis (OR 1.59, 1.43 to 1.77, per unit genetic score). On meta-analysis with results from MVMR analyses in AFGen and FinnGen, there remained a significant direct effect of genetically predicted FM on risk of AF independent of the effect of LM (OR 1.26, 95%CI 1.09 to 1.46, **Figure 7.15**). Effects were directionally consistent in all datasets; however, there was heterogeneity in the effect estimates with FinnGen being somewhat stronger and AFGen being somewhat weaker than UKB.

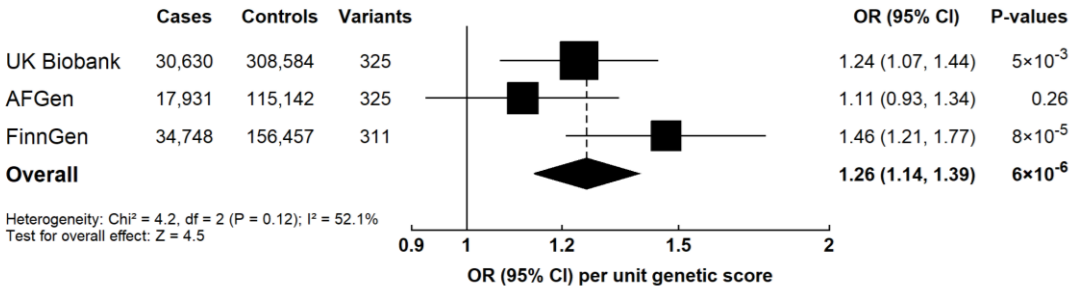


Figure 7.15: Meta-analysis of the direct effect of genetically predicted fat mass on risk of atrial fibrillation in a multivariable Mendelian randomization model with lean mass.

Boxes represent point estimates of the direct effect per unit higher fat mass score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

1

7.5. Discussion

This study demonstrates support for causal associations between a number of common anthropometric measures of body size and risk of AF. The association between WC and risk of AF appears independent of the effect of BMI. Both LM and FM have independent effects on risk of AF with the effect of LM being greater than that of FM. In contrast, there was no evidence for a causal role in genetically predicted VAT in determining risk of AF. There was no substantial differences in the effects of anthropometric measures on risk of AF in men and women even when using sex-specific weighting.

BMI has been repeatedly associated with risk of AF in observational analyses. A number of MR analyses have previously demonstrated a causal association between higher BMI and risk of AF.[108,109,312-314] Our analysis demonstrates a log-linear association between genetically predicted BMI and risk of AF that was similar in men and women. A previous MVMR analysis by Wang *et al*. has suggested that BMI may have a causal effect independent of waist circumference.[110] However, the current findings which show no direct effect of BMI in a joint model with WC, are in keeping with previous observational analyses demonstrating a substantial attenuation to the association between BMI and risk of AF following adjustment for WC.[226]

Previous observational analysis has suggested an independent role for WC.[226] WC has not been well analysed through genetic epidemiology approaches. We demonstrated evidence that WC was causally associated with risk of AF with each unit higher genetic score (roughly equivalent to a 1-SD greater WC) associated with a ~45% greater risk of AF. MVMR analysis demonstrated a

significant direct effect of WC on risk of AF independent of the effect of BMI. In contrast, Wang *et al*. suggested that WC was not independently causally relevant for risk of AF.[110] However, this was after adjustment for BMI, HC, and height. Given the significant correlations between BMI, HC, and WC, such adjustments may potentially result in less reliable effect estimates due to multicollinearity.

Our analysis demonstrates direct causal associations for genetically predicted LM and FM and risk of AF. This is in keeping with prior observational analyses,[226] and supported by findings from Tikkanen *et al*.[71]

These findings do not support a causal association between abdominal VAT and risk of AF. Observational analysis has suggested that abdominal VAT is associated with risk of AF (**Chapter 6**), although this may not be independent of the effect of other anthropometric measures. In contrast to our findings, a previous MR analysis has demonstrated a potential causal association between abdominal VAT and risk of AF (OR 1.41, 95%CI 1.33 to 1.50, per 1-SD higher genetically predicted abdominal VAT).[234] However, the genetic score utilised by Huang *et al*. was based on a GWAS of predicted visceral fat undertaken by Karlsson *et al*.,[235] rather than a GWAS of observed abdominal VAT. As such, the variants utilised by Huang *et al*. may not be predictive of abdominal VAT volume itself. Another explanation for our findings may be weak instrument bias; however, the F-statistics calculated for the variants included in the abdominal VAT genetic score suggest there is a low risk of weak instrument bias.

Men are approximately twice as likely to suffer from AF at any age.[5] There are significant differences in anthropometric measures between men and women.[39,42] Potential differences in the strength of causal associations between

anthropometric measures and risk of AF in men and women could help explain sex-based differences in AF incidence. To date there has been no assessment of the differences in strength of association between genetically predicted anthropometric measures and risk of AF. In contrast to prior observational analyses,[226] these results suggest that there are no meaningful differences between men and women. This remained the case when sex-specific weights were utilised to derive the genetic scores.

7.5.1. Limitations

The FM, LM, and abdominal VAT variants used in this analysis were identified in a GWAS using UKB,[71,106] and no alternative sources of variants on FM or LM were available at the time of the analysis. Undertaking MR analysis in the same dataset as the original GWAS may result in overfitting of the result and bias towards the direction of the observational association.[315] However, where undertaken in large biobanks, undertaking MR analyses in the same dataset as the original GWAS has not been show to result in substantial bias.[316] To overcome this risk of bias, results were assessed in two genetic consortia not using UKB data (AFGen and FinnGen). Results from the three datasets were generally directionally consistent. However, analyses of the FinnGen dataset generally demonstrated stronger associations than seen in UKB and AFGen. This difference may result from the FinnGen controls which excluded those with baseline cardiovascular disease thus leading to a healthier control group than seen in the other two datasets.

7.5.2.Conclusions

Genetically predicted BMI, WC, FM, and LM are all positively associated with risk of AF. There were no differences in the strength of association between men and women. There was evidence of a direct effect of WC on risk of AF independent of the effect of BMI. Similarly, there was evidence of direct effects of both FM and LM of risk of AF.

7.5.3. Next steps

Having identified likely independent and causal associations between a number of anthropometric measures and risk of AF it remains unclear how adiposity impacts risk of AF. This research has developed a number of valid instrumental variables for anthropometric measures. Such measures can be used to undertake mediation analysis examining potential mechanisms which may link adiposity and AF (**Chapter 8**).

Chapter 8 - Inflammation, adiposity, and risk of atrial fibrillation

8.1. Abstract

8.1.1. Background

Both inflammation and adiposity have been associated with higher risk of atrial fibrillation (AF). In addition, greater adiposity is positively correlated with C-reactive protein (CRP) levels. However, the degree to which inflammation mediates the association between adiposity and risk of AF has not been explored.

8.1.2. Methods

Using UK Biobank (UKB), observational associations of CRP with anthropometric measures and risk of AF were assessed using linear and Cox regression models respectively. The causal association of inflammation for AF was assessed through Mendelian randomization analyses using genetic scores for 27 inflammatory proteins including CRP and interleukin-6 receptor (IL6R). Associations were scaled to one unit greater genetic score (equivalent to one standard deviation difference in the original GWAS). Mediation analysis was used to determine the extent by which associations between genetically predicted anthropometric measures and risk of AF were mediated by inflammatory proteins.

8.1.3. Results

In observational analyses, log-CRP was positively correlated with measures of adiposity and associated with risk of AF (hazard ratio 1.18, 95% confidence interval [95%CI] 1.17 to 1.20, per standard deviation).

Genetically predicted anthropometric measures were positively associated with CRP in UKB. Genetically predicted CRP was associated with higher risk of AF (odds ratio [OR] 1.10, 95%CI 1.04 to 1.15, per unit genetic score). In contrast, genetically predicted IL6R, CD40, and Chitinase-3-like protein 1 (YKL40) were negatively associated with risk of AF (OR 0.97, 95%CI 0.96 to 0.99; OR 0.94, 95%CI 0.91 to 0.98; OR 0.95, 95%CI 0.93 to 0.98 per unit higher genetic score respectively). However, inflammatory proteins mediated <5% of the effect of genetically predicted anthropometric measures on risk of AF.

8.1.4. Conclusions

Mendelian randomization provides support for causal relationships between four genetically predicted inflammatory biomarkers (CRP, IL6R, CD40, and YKL40) and risk of AF. However, inflammation does not substantially mediate the association between adiposity and risk of AF.

8.2. Introduction

The aetiological pathway leading to AF is complex and incompletely understood.[317] However, evidence supports a role for inflammation in the development of this arrhythmia. Systemic inflammatory disease phenotypes have been associated with AF.[116,318] Although GWAS of AF have not revealed genetic variants directly associated with inflammatory cytokines,[167,319] inflammatory mediators including Interleukin (IL)-6 and C-reactive protein (CRP) have been associated with AF in observational analyses.[120,320-322]

Adipose tissue is known to be metabolically active,[323] and secrete inflammatory cytokines.[324] The latter have been suggested to be a key factor in the development of adiposity related phenotypes, such as AF and type-2 diabetes mellitus.[325] Higher BMI is associated with higher levels of circulating inflammatory proteins including CRP, IL-6, IL-1 receptor antagonist, and Chitinase-3-like protein 1 (YKL40);[127,326-328] in turn, CRP, Tumour Necrosis Factor (TNF) α, and CD40 have been shown to increase adipokine and adipokine receptor expression.[329-332] There is evidence that BMI is causally associated with CRP.[125]

Previous analyses have not demonstrated causal associations between CRP and cardiovascular phenotypes, including AF and CHD.[121,322,333] In contrast, genetically predicted IL-6 has been shown to be associated with risk of AF.[120] A number of other inflammatory proteins have been associated with risk of AF in small datasets including TNFα,[334] IL-1,[335], IL-18,[336] and YKL40.[337] However, the causal relevance of these inflammatory proteins has not been explored to date. More recently, data have highlighted CRP as an inflammatory marker downstream of IL-6 and IL-1,[338,339] and a large-scale GWAS of CRP has

uncovered multiple additional variants and pathways impacting CRP levels,[340] suggesting that re-visiting the impact of genetically predicted CRP on AF may be warranted.

Given correlations between adiposity and inflammatory phenotypes, it is plausible that inflammation may mediate some of the associations between adiposity and AF, or vice versa. This project had the following objectives: (1) explore the observational associations between CRP and both anthropometric phenotypes and risk of AF; (2) undertake MR analyses to consider the causal relevance of inflammation for risk of AF; and (3) examine the extent by which associations between genetically predicted anthropometric measures and risk of AF are mediated by inflammation.

8.3. Methods

8.3.1. Study design and participants

Details of the UKB study design and participant selection has been detailed in **Chapter 2**. For the observational analysis, exclusion criteria are as outlined in **Chapter 4** (**Figure 4.1**). In addition, participants without an available baseline CRP level were excluded leaving 446,838 participants for the observational analysis (**Figure 8.1**). Genetic analyses in this chapter utilised the same participants as utilised in **Chapter 7** (n=339,214). When examining association between genetically predicted anthropometric measures or inflammatory proteins and baseline CRP, UKB participants with genetic data but missing baseline CRP levels or anthropometric measures were excluded (n=30,724) providing a dataset for those analyses of 308,490.

8.3.2. C-reactive protein measurement in UK Biobank

In UKB, serum CRP levels (reported as mg/L) were measured through immune-turbidimetric high-sensitivity analysis using a Beckman Coulter AU5800.[341] CRP levels are reported down to a minimum level of 0.08 mg/l and a maximum level of 80 mg/l. As CRP levels within UKB are non-normally distributed they were log transformed for observational analyses.[342] CRP residuals were calculated for use in genetic analyses. Residuals were calculated following adjustment for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7 and inverse normal transformation.

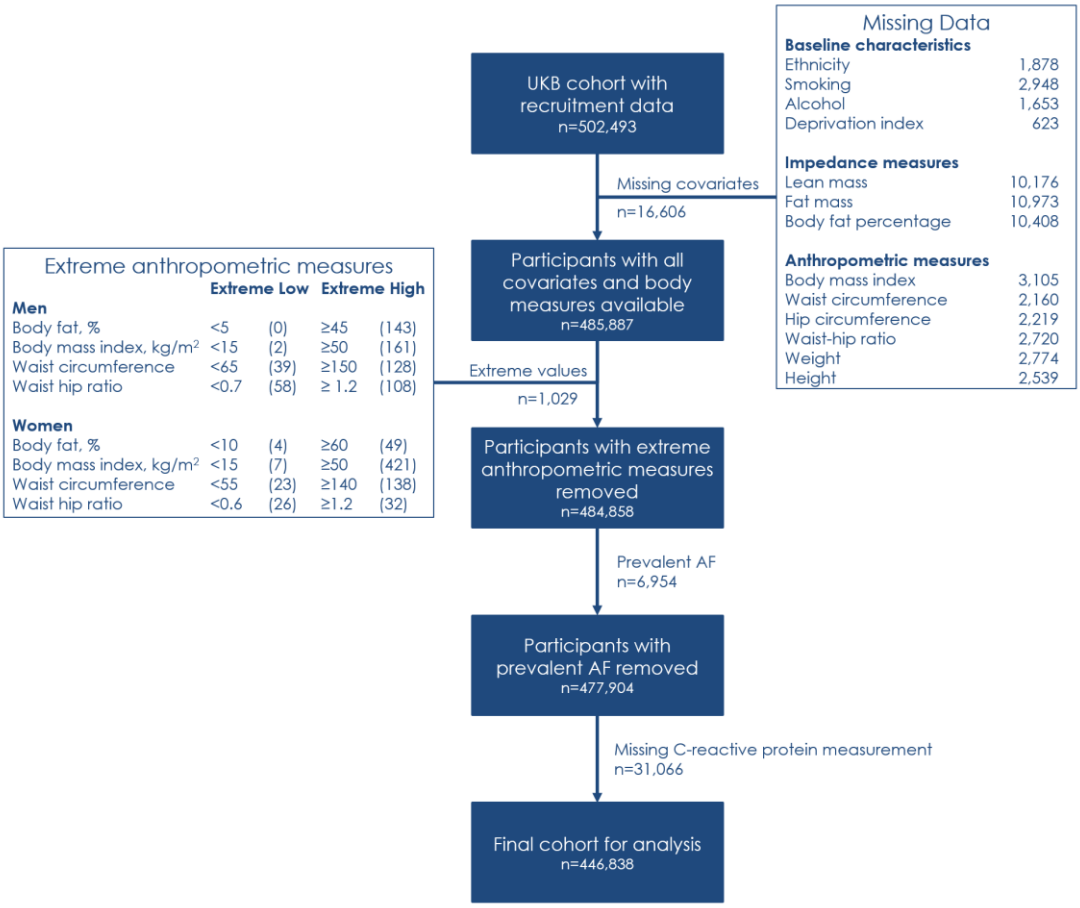


Figure 8.1: Selection of participants for observational analysis of association between C-reactive protein and risk of atrial fibrillation.
Flow chart illustrating participants included in the observational analyses. AF – atrial fibrillation, UKB – UK Biobank.

8.3.3. Development of genetic scores

Genetic scores for anthropometric measures developed in **Chapter 7** were used in this analysis. In addition, inflammatory genetic scores for CRP, IL-6 receptor (IL-6R), and other inflammatory proteins were developed using similar methods (Appendix I, **Development of genetic scores**). The CRP score was based on a GWAS for CRP,[340] while the IL6R score was based on a prior genetic score for IL6R.[120] Genetic scores for additional inflammatory proteins were identified from a proteomic analysis of 92 proteins.[343] Proteins were selected from this analysis if they had variants explaining at least 3.3% of the variance (as this would allow 80% power for the analysis of association with risk of AF). Proteins were

considered inflammatory proteins if they were part of commercially available inflammatory panels or there was additional evidence of an inflammatory role (**Figure 8.2, Appendix Table I.12**). Variants were selected if they met genome-wide significance (and were not limited to cis variants unless otherwise stated). Clumping was undertaken using a white-British sub-section of UKB participants (n=337,448) as the reference panel. For display purposes, inflammatory proteins were grouped based on related functions or structural similarity into the following categories: chemokines, interleukins, matrix metalloproteinases, TNF-related, growth factors, and others.

To further consider whether associations between genetically predicted CRP, anthropometric measures, and risk of AF were directly the result of effects on CRP, SNPs in the vicinity of the *CRP* gene were selected to develop a 'cis-acting' genetic score (cis-CRP). This was undertaken using similar methods to those outlined by Said *et al*.[340] Namely, proximity to the *CRP* gene was defined as being between 50 kb downstream of the nearest gene upstream of *CRP* (*APCS*) and 50 kb downstream of *CRP*. Variants with a p-value $< 5 \times 10^{-8}$ in the CRP GWAS were extracted and clumped using a 10,000 kb window and an r^2 threshold of 0.1.

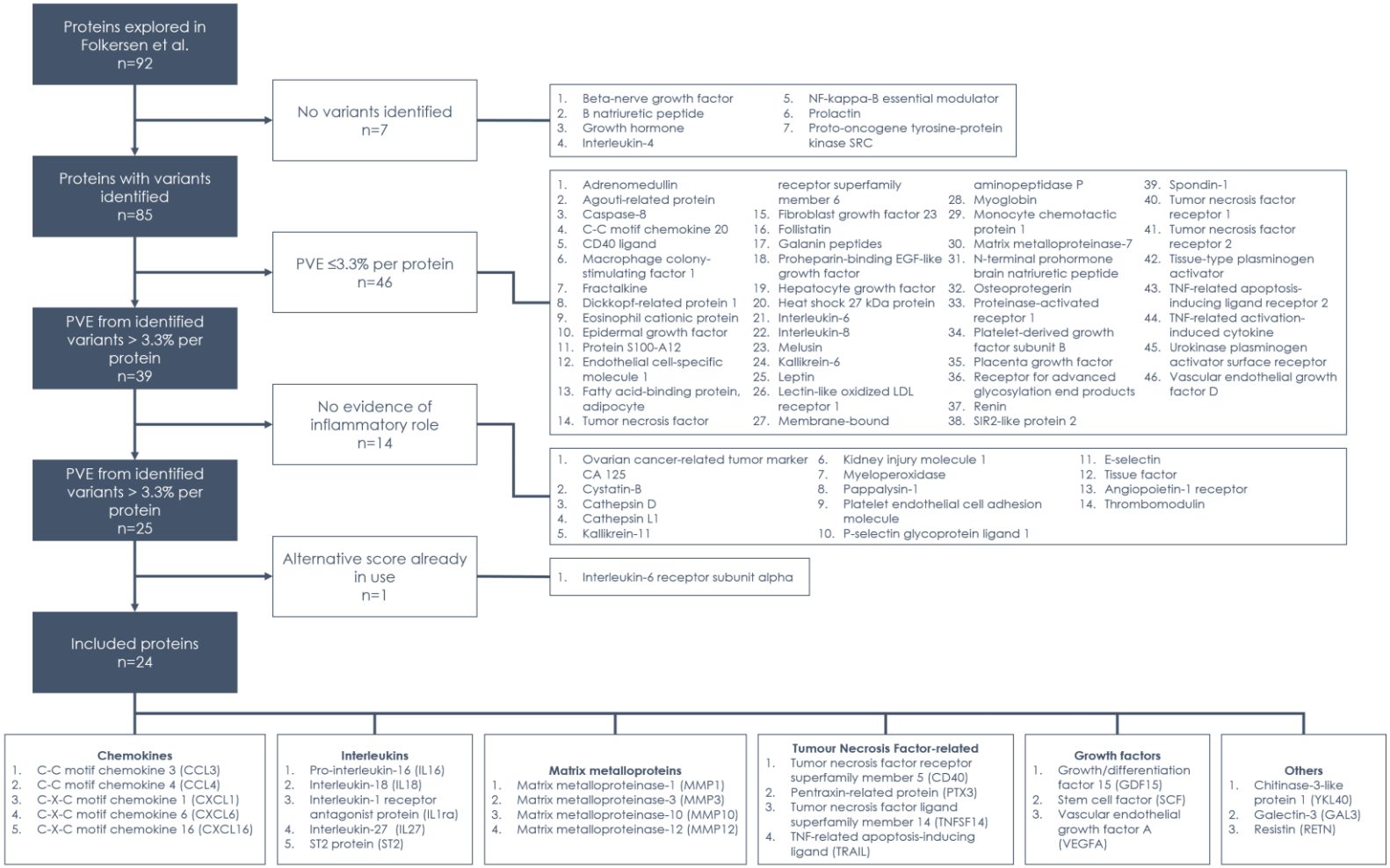


Figure 8.2: Flowchart of inflammatory protein selection.
PVE – proportion of variance explained

8.3.4. Mediation analysis

Mediation analysis was used to determine the proportion of an association between an independent (X) and dependent variable (Y) that is mediated through a third variable (M, see **Figure 8.3**).[344] To establish mediation, the following three criteria must be met:

1. X should be associated with Y (**Figure 8.3**, line c).
2. X should be associated with M (**Figure 8.3**, line a).
3. M should be associated with Y (**Figure 8.3**, line b).

If the mediating criteria are met, the effect mediated by M was determined by subtracting the direct effect (c') from the total effect (c).

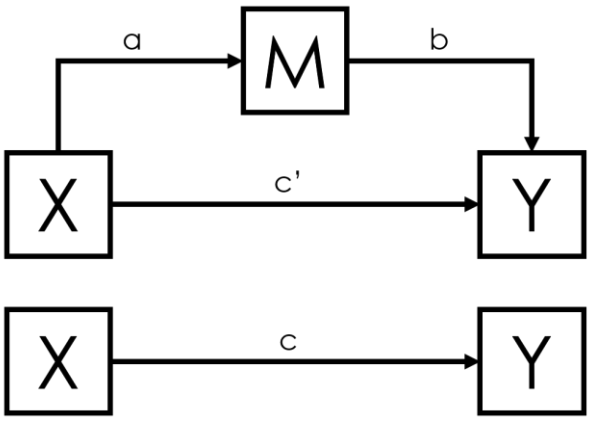


Figure 8.3: Mediation diagram.
Flowchart indicating mediation of the effect of independent variable (X) on the dependent variable (Y) through a mediator (M).

Mediation analysis was undertaken by adjusting the association between genetically predicted anthropometric measures and risk of AF for genetically predicted inflammatory proteins. Mediation analysis was undertaken for anthropometric measures where a potential causal association with risk of AF had been demonstrated (**Chapter 7**). Genetically predicted inflammatory proteins

were considered as potential mediators if they demonstrated a causal association with risk of AF.

8.3.5. Statistical analysis

Associations between baseline anthropometric measures and log-CRP were estimated using linear regression models adjusting for the following potentially confounding covariates: age, sex, ethnicity, Townsend deprivation index,[244] alcohol intake, and smoking (never, former, current) in line with previous examination of the association between anthropometric measures and risk of AF (**Chapter 4**). To explore the shape of the relationship, anthropometric measures were classified, separately in men and women, into fifths, with the top group being further subdivided in two (corresponding to the top two tenths of the distribution) and plotted against the least-squares mean log-CRP adjusted for the same covariates.

Cox proportional hazards regression models were used to estimate HRs describing the associations between log-CRP and incident AF. Results were adjusted for the same covariates as linear models. In order to explore the shape of the associations, CRP was classified, separately in men and women, into fifths.

Associations between genetic scores and anthropometric parameters were estimated using linear regression and associations between genetic scores and risk of AF using logistic regression. Analyses using genetic scores as the independent variable in UKB were adjusted for age, age^2, sex, genotyping array, and principal components of ancestry 1-7. For analyses using summary data from other datasets, the inverse-variance weighted method was used.

To mitigate for the number of genetic scores being assessed, the significance threshold was adjusted using the Bonferroni method.[345] A p-value of $<1.8 \times 10^{-3}$ (0.05/27) was considered significant with a p-value <0.05 being considered suggestive when exploring genetically predicted inflammatory proteins.

8.3.5.1. Power calculations

Power calculations were undertaken using an online calculator (https://shiny.cnsgenomics.com/mRnd/),[311] and the results are outlined in **Table 8.1**. The variance explained for each genetic score was estimated as outlined in **Chapter 2** (**Proportion of variance explained**). The proportion of AF cases was taken to be 8.3%. A causal detection effect of 1.14 per SD unit was obtained from prior observational analyses.[322] A significance level of 1.8×10^{-3} was selected.

Table 8.1: Power calculations for inflammatory genetic scores association with risk of atrial fibrillation

Inflammatory protein	Variants	PVE (%)	Calculated power (%)
CRP	225	4.8	96
Cis-CRP	28	4.0	91
Chemokines (5)			
CCL3 (C-C motif chemokine 3)	5	6.6	100
CCL4 (C-C motif chemokine 4)	7	13.3	100
CXCL1 (C-X-C motif chemokine 1)	3	4.1	92
CXCL6 (C-X-C motif chemokine 6)	3	14.1	100
CXCL16 (C-X-C motif chemokine 16)	14	4.8	96
Growth factors (3)			
GDF15 (Growth/differentiation factor 15)	3	4.0	91
SCF (Stem cell factor)	16	7.5	100
VEGF-A (Vascular endothelial growth factor A)	4	11.5	100
Interleukins (6)			
IL1RA (Interleukin-1 receptor antagonist)	3	4.5	95
IL6R (Interleukin-6 receptor)	8	74.1	100
IL16 (Interleukin-16)	6	14.7	100
IL18 (Interleukin-18)	8	6.1	99
IL27 (Interleukin-27)	12	24.8	100
ST2 (ST Protein)	6	22.8	100
Matrix metalloproteinases (4)			
MMP1 (Matrix metalloproteinase 1)	7	11.2	100
MMP3 (Matrix metalloproteinase 3)	7	13.8	100
MMP10 (Matrix metalloproteinase 10)	6	8.5	100
MMP12 (Matrix metalloproteinase 12)	6	16.3	100
TNF-related (4)			
CD40 (TNF receptor superfamily member 5)	3	10.7	100
PTX3 (Pentraxin-related protein)	5	9.5	100
TNFSF14 (TNF ligand superfamily member 14)	4	11.5	100
TRAIL (TNF-related apoptosis-inducing ligand)	8	8.8	100
Other (3)			
GAL3 (Galectin-3)	9	12.2	100
RETN (Resistin)	12	4.0	91
YKL40 (Chitinase-3-like protein 1)	5	18.8	100

Power calculations undertaken for each genetic score using the variance explained outlined in the table, an 8.3% proportion of AF cases and a causal detection effect of 1.14 per SD. CRP – C-reactive protein, TNF – Tumour Necrosis Factor, PVE – proportion of variance explained

1

8.4. Results

8.4.1. C-reactive protein within UK Biobank

Amongst 466,838 participants included in the observational analysis, median CRP levels were similar in men (1.27 mg/l, IQR 0.66 to 2.50 mg/l) and women (1.36 mg/l, IQR 0.65 to 2.93 mg/l). There was positively skewed distribution for baseline CRP in both men and women that was normalised following a log transformation (**Figure 8.4**).

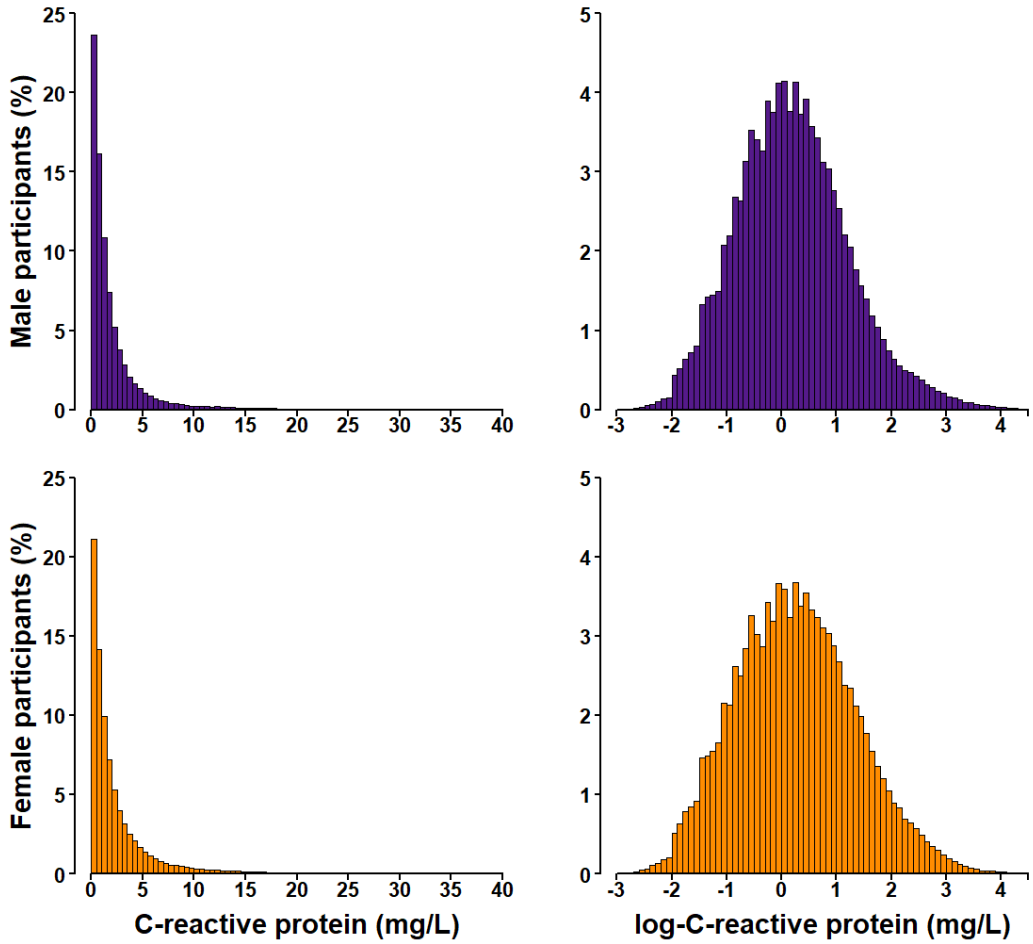


Figure 8.4: Distribution of C-reactive protein and log-C-reactive-protein in the UK Biobank population.
Histograms demonstrating the distribution of C-reactive protein and log-C-reactive protein in the UK Biobank population separately in men (purple) and women (orange).

When considered in fifths, those with higher baseline CRP were likely to be older, more deprived, be current smokers, and less likely to be current alcohol drinkers (**Table 8.2**). Compared with participants in the lowest fifth for baseline CRP, those in the highest fifth were more likely to have cardio-metabolic disease at baseline including diabetes mellitus (6.8 vs 3.2%), coronary heart disease (5.2 vs 3.5%), and hypertension (46.7 vs 24.4%, **Table 8.3**). Similarly, higher CRP levels were associated with a higher prevalence of inflammatory disease at baseline including rheumatoid arthritis (2.6 vs 0.5% in highest vs lowest fifth) and gout (2.4 vs 0.6% in highest vs lowest fifth).

Table 8.2: Baseline characteristics of the 446,838 participants in the observational analysis divided into fifths of log-C-reactive protein level at baseline.

	CRP fifth				
	1	**2**	**3**	**4**	**5**
Participants	90,121 (20.2)	88,222 (19.7)	89,718 (20.1)	89,439 (20.0)	89,338 (20.0)
C-reactive protein, mg/L					
log-CRP, mean (SD)	-1.1 (0.4)	-0.3 (0.2)	0.3 (0.2)	0.9 (0.2)	1.9 (0.6)
CRP, median (Q1 to Q3)	0.36 (0.22 to 0.46)	0.76 (0.65 to 0.88)	1.32 (1.15 to 1.51)	2.31 (1.99 to 2.72)	5.45 (4.10 to 8.66)
Demographics					
Age, mean (SD)	54.6 (8.1)	56.1 (8.1)	56.9 (8.0)	57.3 (7.9)	57.3 (7.9)
Male, n(%)	40,649 (45.1)	39,872 (45.2)	40,835 (45.5)	40,256 (45.0)	40,438 (45.3)
White, n(%)	85,315 (94.7)	83,883 (95.1)	85,220 (95.0)	84,824 (94.8)	84,265 (94.3)
TDI, mean (SD)*	-1.6 (3.0)	-1.5 (3.0)	-1.5 (3.0)	-1.3 (3.1)	-0.9 (3.3)
Current smoker, n(%)	6,985 (7.8)	7,427 (8.4)	8,659 (9.7)	10,318 (11.5)	13,568 (15.2)
Current alcohol drinker, n(%)	84,337 (93.6)	82,342 (93.3)	83,223 (92.8)	81,823 (91.5)	80,314 (89.9)
Anthropometric measures, mean (SD)					
Height, cm	169.4 (9.1)	168.8 (9.2)	168.4 (9.2)	168.0 (9.3)	167.6 (9.3)
Weight, kg	70.7 (13.0)	74.7 (13.8)	77.8 (14.5)	81.0 (15.2)	85.0 (16.9)
Body mass index, kg/m^2	24.5 (3.3)	26.1 (3.6)	27.3 (3.9)	28.6 (4.4)	30.2 (5.4)
Waist circumference, cm	82.7 (11.2)	86.9 (11.8)	90.1 (12.1)	93.4 (12.5)	97.2 (13.4)
Hip circumference, cm	98.7 (6.7)	101.2 (7.1)	103.1 (7.8)	105.2 (8.7)	107.9 (10.8)
Waist-hip ratio,	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)					
Body lean mass, kg	51.7 (11.0)	52.4 (11.4)	53.1 (11.5)	53.8 (11.6)	54.6 (11.5)
Body fat mass, kg	19.0 (6.4)	22.3 (7.0)	24.7 (7.8)	27.3 (8.9)	30.3 (11.2)

Participants divided into fifths based on log-C-reactive protein level and arranged from lowest fifth (1) to highest fifth (5). Participants with missing or out-of-range anthropometric measures, missing covariates, or prior atrial fibrillation at baseline were excluded. TDI – Townsend deprivation index. *Area level measure of material deprivation (UK range:-5.5 [least deprived] to 14.0 [most deprived]). CRP – C-reactive protein, SD – standard deviation.

Table 8.3: Baseline prior disease in the 446,838 participants in the observational analysis divided into fifths of log-C-reactive protein level at baseline.

	CRP fifth				
	1	**2**	**3**	**4**	**5**
Cardiometabolic disease, n(%)					
Diabetes	2,886 (3.2)	3,316 (3.8)	3,954 (4.4)	4,702 (5.3)	6,189 (6.9)
Stroke	798 (0.9)	908 (1.0)	1,013 (1.1)	1,171 (1.3)	1,515 (1.7)
Coronary heart disease	3,133 (3.5)	3,248 (3.7)	3,563 (4.0)	3,893 (4.4)	4,603 (5.2)
Congestive cardiac failure	189 (0.2)	208 (0.2)	264 (0.3)	316 (0.4)	477 (0.5)
Valvular heart disease	672 (0.7)	751 (0.9)	775 (0.9)	822 (0.9)	914 (1.0)
Hypertension	21,993 (24.4)	27,385 (31.0)	32,389 (36.1)	36,747 (41.1)	41,688 (46.7)
Sleep apnoea	291 (0.3)	415 (0.5)	544 (0.6)	650 (0.7)	922 (1.0)
Inflammatory disease, n(%)					
Gout	569 (0.6)	833 (0.9)	1,196 (1.3)	1,572 (1.8)	2,116 (2.4)
Inflammatory bowel disease	634 (0.7)	702 (0.8)	859 (1.0)	1,062 (1.2)	1,470 (1.6)
Systemic lupus erythematosus	103 (0.1)	114 (0.1)	112 (0.1)	123 (0.1)	165 (0.2)
Psoriatic arthritis	837 (0.9)	959 (1.1)	1,053 (1.2)	1,204 (1.3)	1,812 (2.0)
Rheumatoid arthritis	447 (0.5)	639 (0.7)	849 (0.9)	1,292 (1.4)	2,321 (2.6)

Participants divided into fifths based on log-C-reactive protein level and arranged from lowest fifth (1) to highest fifth (5). Participants with missing or out-of-range anthropometric measures, missing covariates, or prior atrial fibrillation at baseline were excluded. CRP – C-reactive protein.

8.4.2. Association between baseline anthropometric measures and C-reactive protein

With the exception of height, anthropometric measures were positively associated with log-CRP (**Figure 8.5**). FM was the most strongly associated with log-CRP (beta 0.45, 0.45 to 0.45, per SD). The association between anthropometric measures and log-CRP were 30 to 50% weaker in men than women (**Appendix Figure K.1**).

8.4.3. Log-C-reactive protein association with atrial fibrillation

There was an approximately log-linear positive association between log-CRP and risk of AF (HR 1.17, 95%CI 1.16 to 1.19 per SD, **Figure 8.6**). When considered separately by sex, the association was weaker in men (HR 1.14, 1.12 to 1.16, per SD) than in women (HR 1.23, 1.21 to 1.26, per SD, p-interaction = 1.0×10^{-12}, **Appendix Figure K.2**).

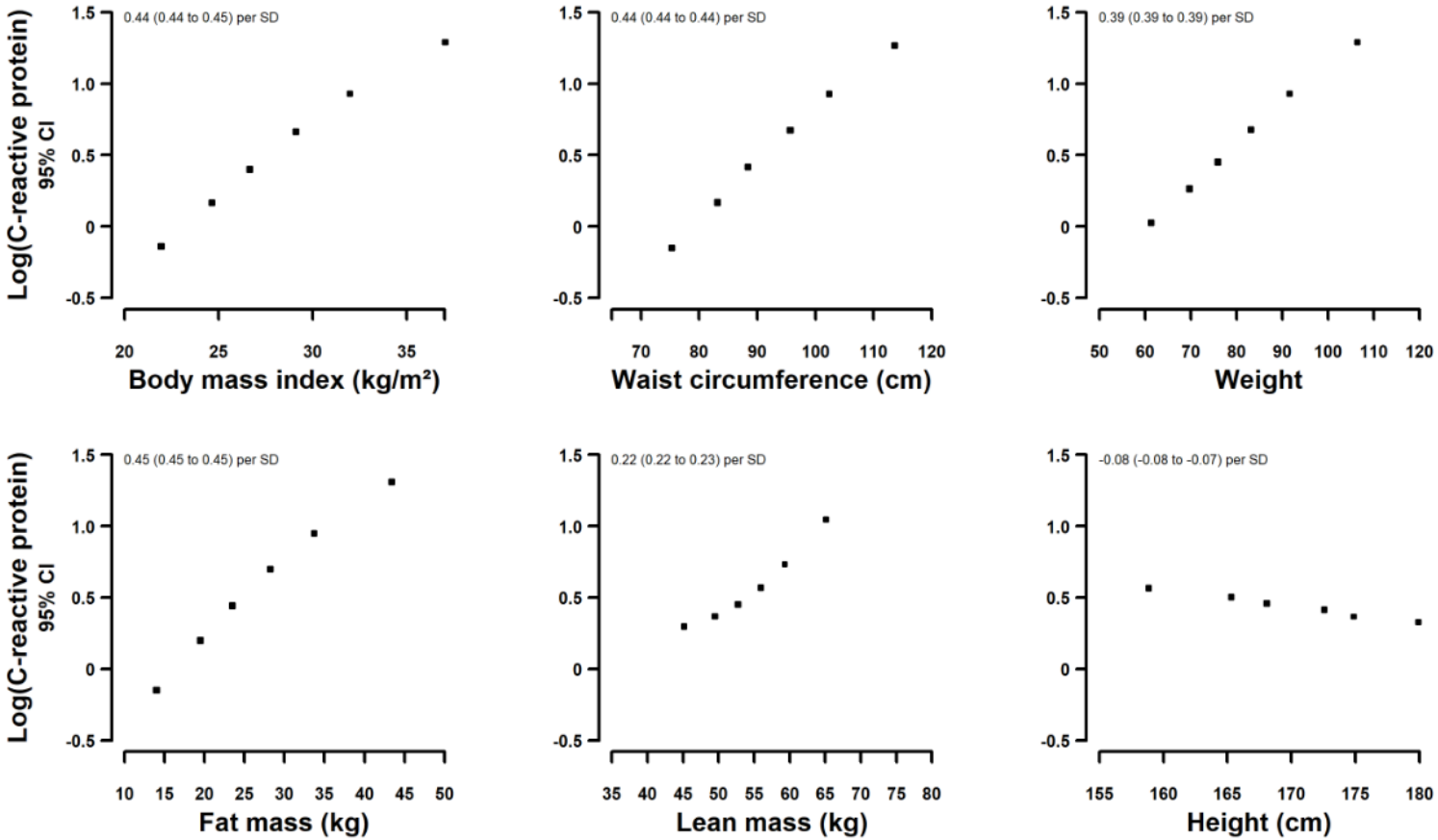


Figure 8.5: Association of anthropometric measures and baseline log-C-reactive protein.
Mean log-C-reactive protein levels (measured in mg/L) for each group determined using least-squares method adjusting for age, sex, alcohol, smoking, deprivation, and ethnicity. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. SD – standard deviation.

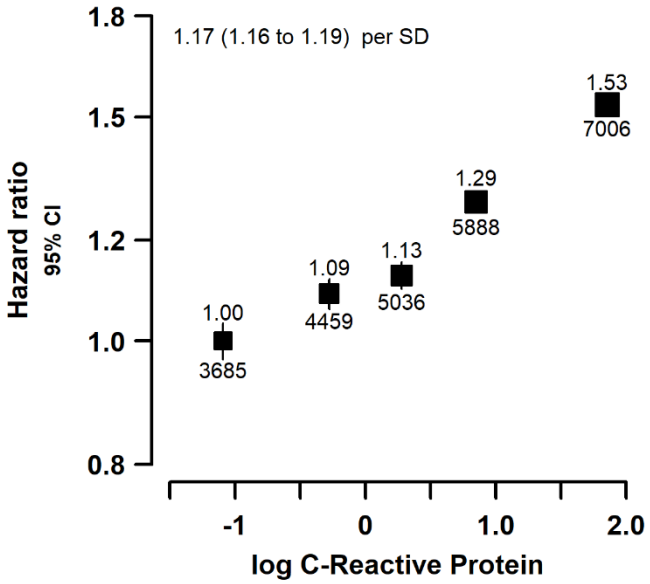


Figure 8.6: Association between baseline log-C-reactive protein and atrial fibrillation in UK Biobank.
Hazard ratios (HRs) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation in UK Biobank participants (n=446,838). For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars). The groups each comprised 20% of the sample. HRs ratios are plotted against the mean baseline log-C-reactive protein level (measured in mg/L) within that group. HRs shown above each square and numbers of AF cases below. SD – standard deviation.

8.4.4. Observed associations between anthropometric measures and risk of atrial fibrillation adjusted for C-reactive protein

Given associations between anthropometric measures and CRP, the association between anthropometric measures and risk of AF was considered following adjustment for log-CRP. Following adjustment for log-CRP, there was minimal attenuation (<10%) of observed associations for LM, BMI, FM, and WC and risk of AF (**Figure 8.7**). The attenuation was similar in both sexes.

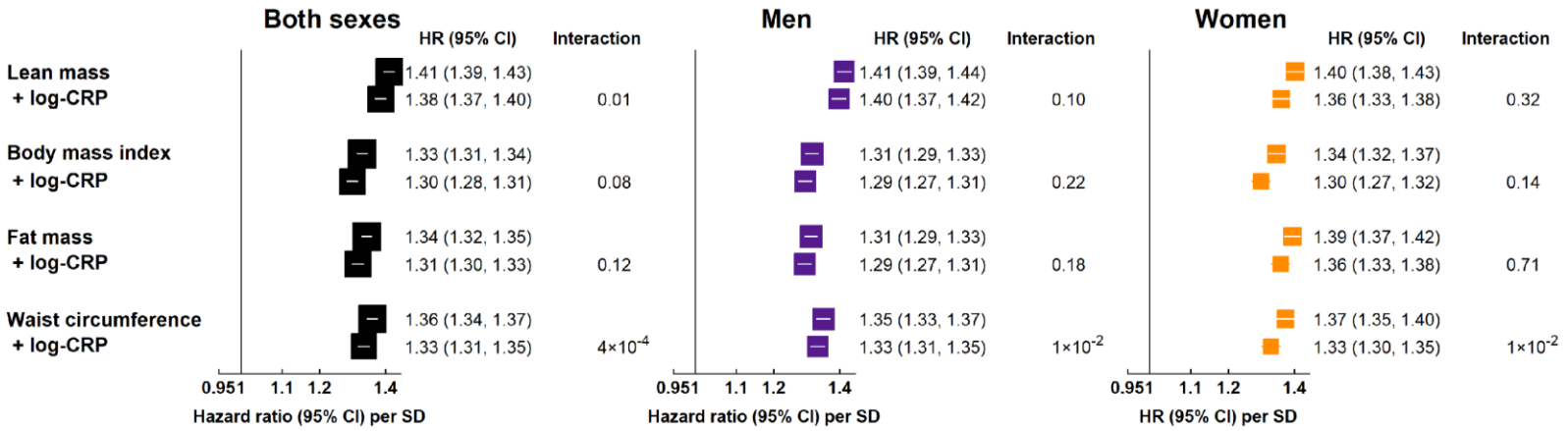


Figure 8.7: Association between anthropometric measures and risk of incident atrial fibrillation in men and women following adjustment for C-reactive protein.

Hazard ratios (HR) were adjusted for age, sex, smoking, alcohol, ethnicity, and deprivation in UK Biobank participants (n=446,838). For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI represented by error bars). CRP – C-reactive protein, SD – standard deviation.

8.4.5. Genetically predicted anthropometric measures and observed log-C-reactive protein levels

To examine whether there might be a causal relationship between anthropometric measures and CRP, genetic scores for a range of anthropometric measures developed in **Chapter 7** were used in UKB participants with genetic and baseline CRP data available (n=308,490). These demonstrated strong positive associations between genetically predicted BMI, WC, and FM with observed log-CRP levels (**Figure 8.8**). When considered separately in men and women, associations of BMI, FM, and WC with log-CRP levels were all substantially lower in men than women (**Appendix Figure K.3**). These associations were broadly in line with values from the observational analysis.

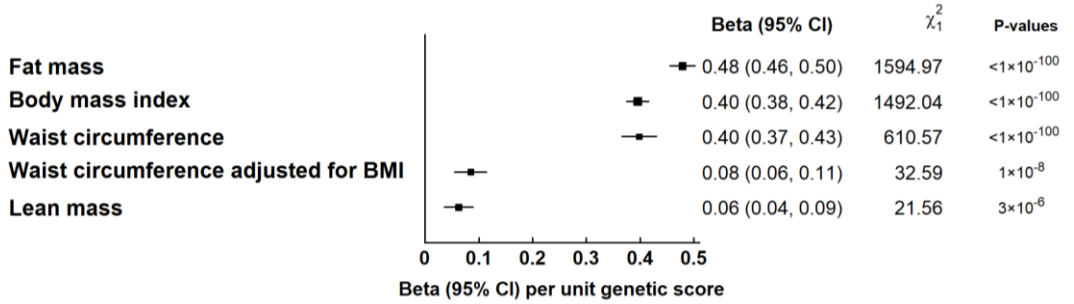


Figure 8.8: Association between genetically predicted adiposity traits and baseline log-C-reactive protein in UK Biobank (n=308,490).
Effect of anthropometric genetic scores on baseline log-C-reactive protein in UK Biobank participants. Effect estimates (betas) were adjusted for sex, age, age^2, genotyping array, and principal components of ancestry 1-7 and scaled per unit increase in genetic score for each adiposity measure. For each category, the area of the square is inversely proportional to the variance of the category-specific risk, which also determines the 95%confidence intervals (95%CI, represented by error bars). Baseline log-C-reactive protein level measured in mg/L. BMI – body mass index.

8.4.6. Genetically predicted inflammatory proteins in UK Biobank

Given established associations between some cytokines (e.g. IL-1, IL-6) and circulating CRP levels, the association between genetically predicted inflammatory proteins and baseline CRP was explored. When variants were combined and weighted as a genetic score, a one unit greater CRP score was associated with 0.95 SD (95%CI 0.93 to 0.96, **Figure 8.9**) higher CRP, while a one unit greater cis-CRP score was associated with 0.44 SD (95%CI 0.42 to 0.45) higher CRP. As expected, associations between other inflammatory proteins and baseline CRP were smaller with IL1RA, IL6R, SCF, TRAIL, and GAL3 all being significantly associated with log-CRP (**Figure 8.9**). In contrast, the lack of substantial associations with other genetically predicted inflammatory proteins suggests they may operate through CRP-independent mechanisms.

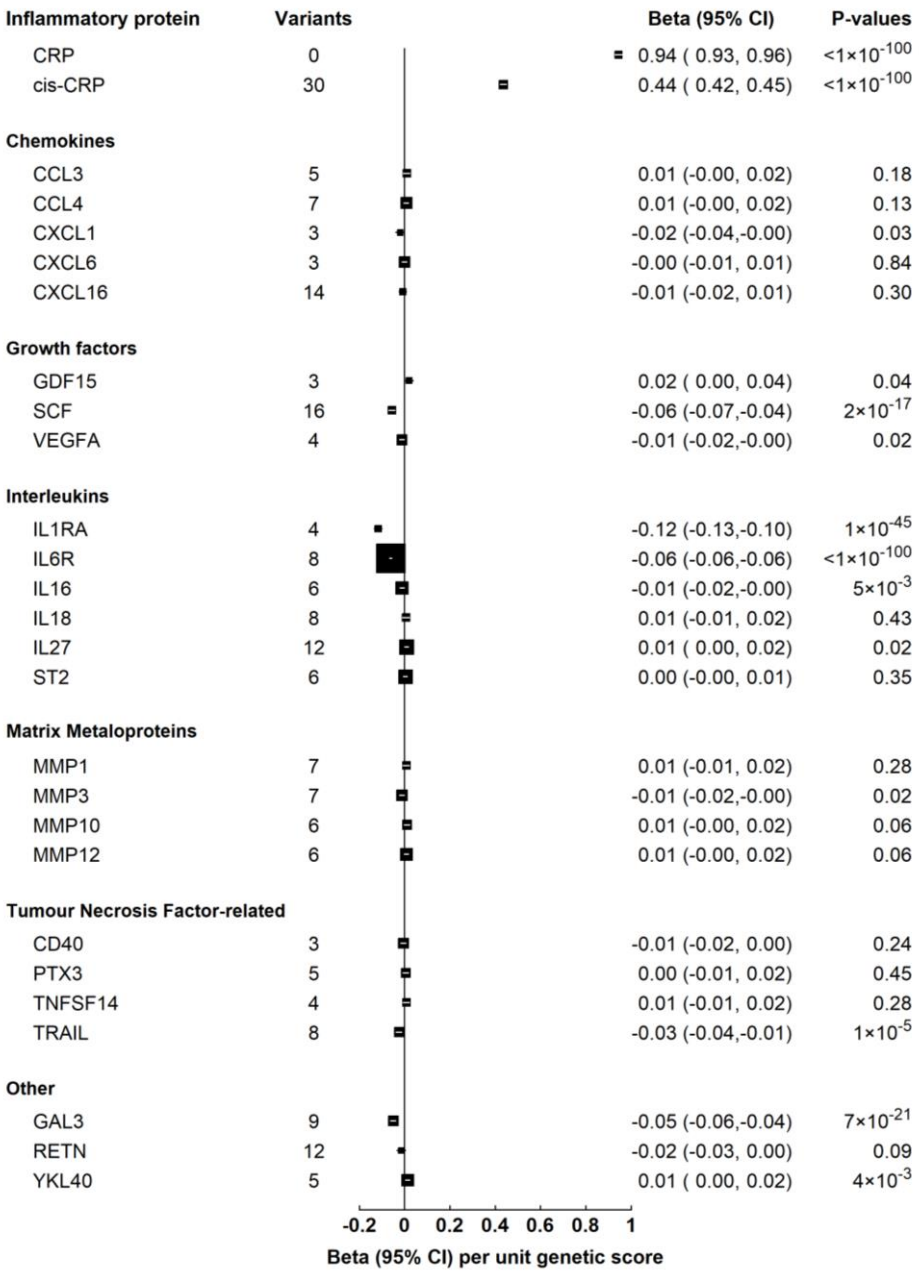


Figure 8.9: Association between risk scores for inflammatory proteins and C-reactive protein (n=308,490).

Effect of inflammatory protein genetic scores on baseline C-reactive protein (per SD) in UK Biobank participants. Effect estimates (beta) are per unit genetic score – approximately equivalent to a one standard deviation greater inflammatory protein in the original GWAS. Effect estimates were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each protein, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). CD40 – TNF Receptor Superfamily Member 5, CRP – C-reactive protein, CCL – C-C Motif Chemokine, CXCL – C-X-C Motif Chemokine, GAL – Galectin-3, GDF – Growth/Differenation Factor, IL – Interleukin, MMP – matrix metalloproteinase, PTX – pentraxin-related protein, RETN – Resistin, SCF – Stem Cell Factor, ST2 – ST Protein, TNF – Tumour Necrosis Factor, TNFSF14 – TNF Ligand Superfamily Member 14, TRAIL – TNF-Related Apoptosis-Inducing Ligand, VEGF – Vascular Endothelial Growth Factor, YKL40 – Chitinase-3-like Protein 1

8.4.7. Genetically predicted inflammatory proteins and risk of atrial fibrillation

8.4.7.1. Genetically predicted C-reactive protein and risk of atrial fibrillation

Given the observed positive association between baseline CRP and risk of incident AF, associations between genetically predicted CRP and risk of AF was explored in UKB participants with genetic data available (n=339,214). Greater genetically predicted CRP was associated with a greater risk of AF in UKB (OR 1.10, 95%CI 1.04 to 1.15, per unit higher CRP genetic score (**Figure 8.10**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.6** (**Appendix Figure J.6**). Comparable estimates were obtained from the weighted median method and the MR-Egger analysis (**Table 8.4**). However, after exclusion of variants resulting in heterogeneity, MR-PRESSO demonstrated no significant association suggesting a degree of pleiotropy.

When meta-analysed with results from AFGen and FinnGen datasets, a one unit higher CRP genetic score was associated with ~10% higher risk of AF (OR 1.08, 95%CI 1.03 to 1.14) with no evidence of heterogeneity (**Figure 8.11**). In UKB, the strength of association between genetically predicted CRP and risk of AF in men (OR 1.07, 95%CI 1.00 to 1.14) and women (OR 1.14, 95%CI 1.05 to 1.24, p-interaction = 0.25) showed no statistical difference.

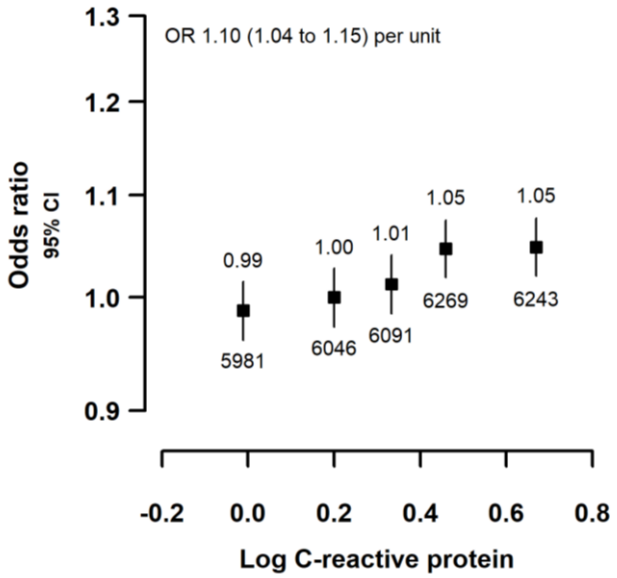


Figure 8.10: Association of genetically predicted C-reactive protein with atrial fibrillation in UK Biobank (n=339,214).
Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. Odds ratios shown above each square and number of atrial fibrillation cases below. Odds ratios are plotted against the mean baseline log-C-reactive protein level (measured in mg/L) within that group.

1

Table 8.4: Sensitivity analyses for genetically predicted C-reactive protein on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	1.10 (1.04 to 1.15)	4.3×10^{-4}
IVW estimate	1.10 (1.02 to 1.18)	0.01
Weighted median estimate	1.07 (0.96 to 1.19)	0.20
Weighted mode estimate	0.95 (0.84 to 1.09)	0.49
MR- Egger	1.12 (0.99 to 1.26)	0.08
*Egger-intercept test**		0.73
MR-PRESSO corrected estimate	1.04 (0.97 to 1.11)	0.27

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher C-reactive protein genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

2

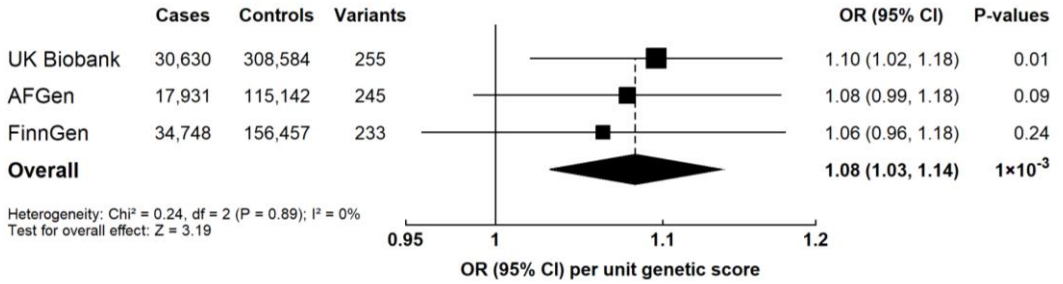


Figure 8.11: Meta-analysis of causal effect of genetically predicted C-reactive protein on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher C-reactive protein score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

8.4.7.2. Genetically predicted C-reactive protein using a cis-C-reactive protein genetic score and risk of atrial fibrillation

Having identified the association between genetically predicted CRP and risk of AF, a cis-CRP score was used to explore if this was the result of a direct effect of CRP on risk of AF. There was no association between the cis-CRP score with greater risk of AF (OR 0.99, 95%CI 0.95 to 1.03, per unit, **Figure 8.12**). The associations between individual variants and risk of AF are displayed in **Appendix Table J.7** (**Appendix Figure J.7**). When meta-analysed with results from AFGen and FinnGen datasets, there remained no significant association with risk of AF (OR 0.98, 95%CI 0.94 to 1.02, per unit genetic score, **Figure 8.13**).

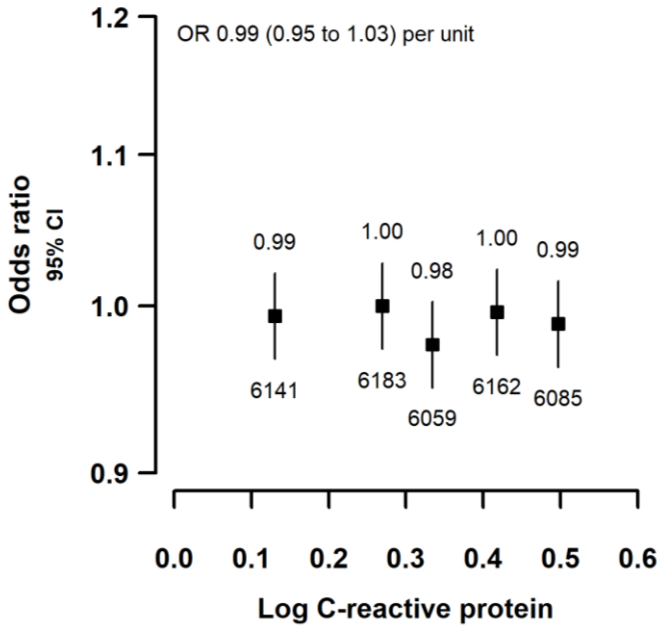


Figure 8.12: Association of genetically predicted C-reactive protein with atrial fibrillation using the cis-C-reactive protein genetic score.
Odds ratios (ORs) were adjusted for age, age^2, sex, genotype array, and principal components of ancestry 1 to 7. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (95%CI, represented by error bars). Each group comprises 20% of the sample. Odds ratios shown above each square and number of atrial fibrillation cases below. Odds ratios are plotted against the mean baseline log-C-reactive protein level (measured in mg/L) within that group.

1

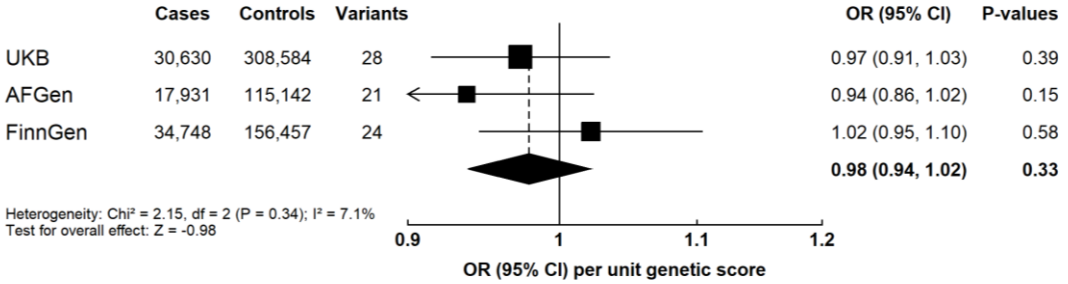


Figure 8.13: Meta-analysis of causal effect of genetically predicted C-reactive protein on risk of atrial fibrillation using the cis-C-reactive protein genetic score.
Boxes represent point estimates of effect per unit higher cis-C-reactive protein score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

2

8.4.7.3. Other inflammatory proteins

The null result from the cis-CRP score suggests that effects of CRP itself may not explain the association between inflammation and risk of AF. To explore this further, additional inflammatory proteins were examined through meta-analysis of UKB, AFGen, and FinnGen datasets (**Appendix Figure K.4** to **Appendix Figure K.9**). Of the inflammatory proteins assessed, three (IL6R, CD40, and YKL40) were associated with AF after accounting for multiple comparisons. All three proteins were negatively associated with risk of AF and were taken forward for further analysis.

In UKB, genetically predicted IL6R was associated with lower risk of AF (OR 0.97, 95%CI 0.96 to 0.99, per unit higher IL6R genetic score). The associations between individual variants and risk of AF are displayed in **Appendix Table J.8** (**Appendix Figure J.8**). Comparable estimates were obtained from weighted median and weighted mode estimates. The MR-Egger analysis did not provide evidence of directional pleiotropy (**Table 8.5**). When meta-analysed with results from AFGen and FinnGen datasets, a one unit higher IL6R genetic score was associated with ~4% lower risk of AF (OR 0.96, 95% 0.95 to 0.98) with no evidence of significant heterogeneity (**Figure 8.14**). In UKB, the strength of association between genetically predicted IL6R and risk of AF was similar in men (OR 0.97, 95%CI 0.96 to 0.99) and women (OR 0.97 95%CI 0.96 to 0.99, p-interaction = 0.95).

Table 8.5: Sensitivity analyses for genetically predicted interleukin-6 receptor on atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	0.97 (0.96 to 0.99)	2.5×10^{-5}
IVW estimate	0.97 (0.95 to 0.98)	1.0×10^{-6}
Weighted median estimate	0.96 (0.95 to 0.98)	2.4×10^{-6}
Weighted mode estimate	0.96 (0.95 to 0.98)	0.002
MR- Egger	0.96 (0.92 to 0.99)	0.014
*Egger-intercept test**		0.57
MR-PRESSO corrected estimate	0.97 (0.96 to 0.98)	2.7×10^{-4}

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher interleukin-6 receptor genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier.

1

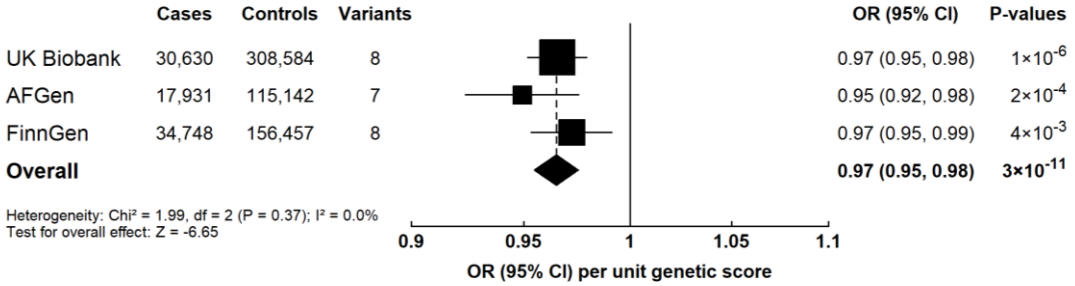


Figure 8.14: Meta-analysis of causal effect of genetically predicted interleukin-6 receptor on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher interleukin-6 receptor score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.

2

3 Genetically predicted CD40 was associated with a lower risk of AF in UKB (OR
4 0.94, 95%CI 0.91 to 0.98, per unit higher CD40 genetic score). The associations
5 between individual variants and risk of AF are displayed in (**Appendix Table J.9**
6 (**Appendix Figure J.9**). Comparable estimates were obtained from weighted
7 median and weighted mode methods. The MR-Egger analysis did not provide
8 evidence of directional pleiotropy (**Table 8.6**). When meta-analysed with results
9 from AFGen and FinnGen datasets, a one unit higher CD40 genetic score was

associated with ~5% lower risk of AF (OR 0.95, 95% 0.92 to 0.98, **Figure 8.15**).

In UKB, the strength of association between genetically predicted CD40 and risk of AF was similar in men (OR 0.94, 95%CI 0.90 to 0.98) and women (OR 0.95, 95%CI 0.90 to 1.01, p-interaction = 0.75).

Table 8.6: Sensitivity analyses for genetically predicted CD40 on risk of atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	0.94 (0.91 to 0.98)	1.1×10^{-3}
IVW estimate	0.94 (0.91 to 0.97)	7.6×10^{-4}
Weighted median estimate	0.94 (0.90 to 0.97)	6.0×10^{-4}
Weighted mode estimate	0.93 (0.90 to 0.97)	0.08
MR- Egger	0.91 (0.86 to 0.97)	0.003
*Egger-intercept test**		0.24
MR-PRESSO corrected estimate	NA	NA

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher CD40 genetic score. * OR not applicable to Egger-intercept test. CD40 - TNF receptor superfamily member 5, IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier. The MR-PRESSO estimate could not be calculated, as there were too few variants in the developed genetic score.

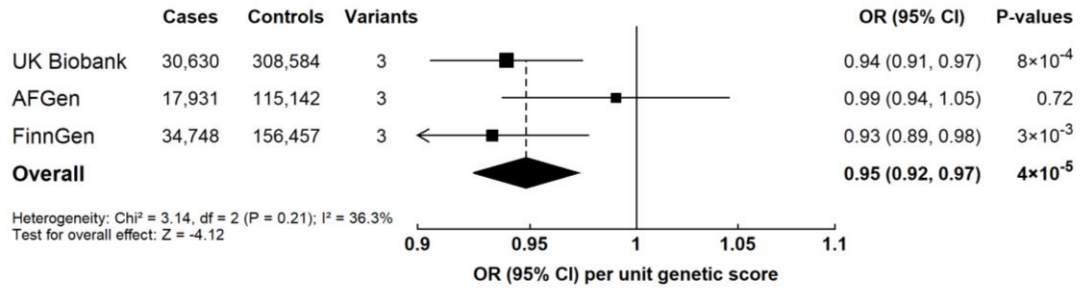


Figure 8.15: Meta-analysis of causal effect of genetically predicted CD40 on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher CD40 score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.CD40 - TNF receptor superfamily member 5.

YKL40 was inversely associated with risk of AF in UKB (OR 0.95, 95%CI 0.93 to 0.98, per unit higher YKL40 genetic score). The associations between individual variants and risk of AF are displayed in **Appendix Table J.10** (**Appendix Figure J.10**). Comparable estimates were obtained from weighted median and weighted mode methods. The MR-Egger analysis did not provide evidence of directional pleiotropy (**Table 8.7**). When meta-analysed with results from AFGen and FinnGen datasets, a one unit higher YKL40 genetic score was associated with ~4% lower risk of AF (OR 0.96, 95% 0.94 to 0.98, **Figure 8.16**) with no evidence of significant heterogeneity. In UKB, the strength of association between genetically predicted YKL40 and risk of AF was similar in men (OR 0.95, 95%CI 0.92 to 0.99) and women (OR 0.96, 95%CI 0.91 to 1.00, p-interaction = 0.93).

Table 8.7: Sensitivity analyses for genetically predicted YKL40 on risk of atrial fibrillation in UK Biobank

	Atrial fibrillation	
	OR (95%CI)	**P**
Primary genetic score	0.95 (0.93 to 0.98)	0.002
IVW estimate	0.95 (0.93 to 0.98)	0.002
Weighted median estimate	0.95 (0.93 to 0.98)	0.003
Weighted mode estimate	0.95 (0.92 to 0.98)	0.04
MR- Egger	0.96 (0.92 to 1.00)	0.06
*Egger-intercept test**		0.52
MR-PRESSO corrected estimate	0.95 (0.93 to 0.98)	0.03

Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit higher YKL40 genetic score. * OR not applicable to Egger-intercept test. IVW – inverse variance weighted; MR – Mendelian randomization; MR-PRESSO – Mendelian randomization Pleiotropy Residual Sum and Outlier, YKL40 - Chitinase-3-like protein 1.

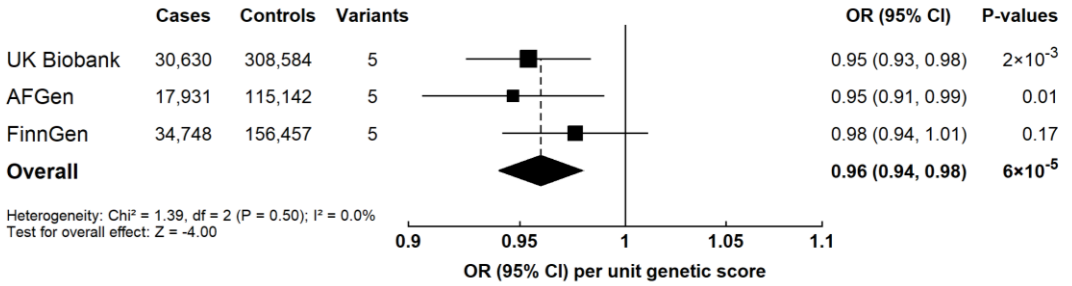


Figure 8.16: Meta-analysis of causal effect of genetically predicted YKL40 on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher YKL40 score with sizes inversely proportional to their variance, which also determines the 95% confidence interval (95%CI, represented by error bars). The diamond represents the meta-analysis estimate. UK Biobank, AFGen, and FinnGen odds ratios were calculated using inverse variance weighted methods. OR – odds ratio.YKL40 - Chitinase-3-like protein 1.

8.4.8. Mediation of the effect of anthropometric measures on risk of atrial fibrillation through inflammation

To explore the observed findings suggesting that inflammation minimally attenuated the association between anthropometric measures and risk of AF, inflammatory proteins associated with risk of AF were taken forward for consideration as potential mediators of the association between genetically predicted anthropometric measures and risk of AF. In assessing the proportion of the effect of anthropometric measures on risk of AF mediated through CRP, IL6R, CD40, or YKL40, there was little evidence to support a substantial impact of inflammation when using individual patient data from UKB (<5%, **Table 8.8**). Given differences in the strength of association between anthropometric measures and CRP between sexes, this was examined separately in men and women. When broken down by sex, CRP mediated approximately half the proportion of the effect of anthropometric measures on risk of AF in men compared with women.

Table 8.8: Effect of genetically predicted anthropometric measures on risk of atrial fibrillation mediated by genetically predicted inflammatory proteins in UK Biobank (n=339,214)

	Total effect	Proportion mediated (%)			
		CRP	IL6R	CD40	YKL40
Body mass index					
Both	1.41 (1.32 to 1.50)	2.2	0.1	0.0	-0.1
Men	1.44 (1.32 to 1.56)	1.3	0.1	-0.1	-0.2
Women	1.36 (1.22 to 1.51)	4.1	0.1	0.0	-0.1
Waist circumference					
Both	1.38 (1.24 to 1.53)	4.9	0.1	0.1	0.1
Men	1.42 (1.25 to 1.62)	2.9	0.0	0.0	0.1
Women	1.31 (1.10 to 1.55)	9.1	0.3	0.1	0.1
Fat mass					
Both	1.56 (1.45 to 1.69)	2.0	0.0	0.1	0.1
Men	1.54 (1.40 to 1.70)	1.3	0.1	0.0	0.0
Women	1.60 (1.41 to 1.81)	3.0	0.0	0.1	0.1
Lean mass					
Both	1.97 (1.80 to 2.15)	0.7	0.1	0.0	-0.1
Men	1.95 (1.74 to 2.18)	0.5	0.2	-0.1	0.0
Women	2.00 (1.74 to 2.30)	1.0	0.0	0.0	-0.1

The total effect the association between the genetic score for the anthropometric variable and risk of atrial fibrillation adjusted for age, sex, age^2, array, and principal components 1-7. The proportion mediated is determined by subtracting the effect of the genetically predicted anthropometric measure on risk of atrial fibrillation additionally adjusted the outlined genetically predicted inflammatory protein from the effect of the genetically predicted anthropometric measure on risk of atrial fibrillation without adjustment for the outlined genetically predicted inflammatory protein and converted to a percentage. Result of total effect are presented are hazard ratios (95% confidence intervals). CRP – C-reactive protein, CD40 - TNF receptor superfamily member 5, IL6R - Interleukin-6 receptor, YKL40 - Chitinase-3-like protein 1.

1

2

8.5. Discussion

Both inflammation and anthropometric measures have been associated with risk of AF in observational analyses. This analysis is the largest to date examining the observational association between CRP and risk of incident AF and demonstrates a positive association. Furthermore, the genetically predicted levels of inflammatory proteins (CRP, CD40, IL6R, and YKL40) are associated with risk of AF, with similar effects in men and women, suggesting a causal role for inflammation in determining the risk of AF. While CRP and a range of anthropometric measures were associated with one another in observational analyses, inflammation mediated <5% of the effect of genetically predicted anthropometric measures on risk of AF. As such, there is no evidence to suggest that the causal associations between anthropometric measures and risk of AF are substantially mediated through inflammation.

8.5.1.Observed C-reactive protein levels and risk of atrial fibrillation

CRP is a commonly used marker of inflammation. In observational studies, raised levels have been associated with CHD,[346] AF,[322,347] and other cardio-metabolic conditions including type-2 diabetes mellitus.[348] The current study has demonstrated a strong positive association between baseline CRP and risk of incident AF. The results of this study are in keeping with a recent meta-analysis examining the association between CRP and AF (AF cases=5,440) which demonstrated ~30% higher risk per 1-SD greater baseline log-CRP level (RR 1.27, 95%CI 1.14 to 1.42).[322]

8.5.2. Evidence for the causal relevance of C-reactive protein on risk of atrial fibrillation

Whether raised inflammatory proteins are causally linked to AF has not been fully explored. Previous analyses of genetically predicted CRP have not shown an association with risk of AF.[121,322,333] This contrasts with the findings from this current study which demonstrate a positive association between genetically predicted CRP and risk of AF. The reason for this discrepancy may be explained by a number of factors. First, this study includes a substantially greater number of AF cases (n=30,630) compared with previous studies providing greater power to identify a signal. The use of variants from the most recent GWAS explains twice the variance of CRP than previously available.[340] However, the association between genetically predicted CRP and risk of AF may reflect a causal association between up-stream inflammatory mediators, such as IL6, rather than CRP itself. This hypothesis is supported by the finding that, when using a cis-CRP genetic score, there was no association with AF despite a strong link between the score and CRP levels. This suggests that the association between the genetic score for CRP may represent a more general effect of inflammation that is not specifically driven by CRP.

8.5.3. Interleukin-6 receptor and risk of atrial fibrillation

In addition to CRP, three other inflammatory proteins were significantly associated with risk of AF. In keeping with these findings, genetically predicted circulating IL6R has previously been shown to be associated with a lower risk of AF.[120,349] IL6R, encoded by the *IL6R* gene, exists both as a transmembrane protein and as a soluble receptor. Transmembrane IL-6R plays an important role

in the IL-6 signalling cascade. *IL6R* variants have previously been shown to alter the proportion of soluble IL6R and thus signalling through the IL-6R pathway.[350] As such, greater circulating IL6R results in lower transmembrane IL6R and thus reduced IL-6 inflammatory signalling. Greater circulating IL6R has also been shown to lower the rate of stroke in MEGASTROKE consortium data.[120] As such, the IL-6R-related mediated inflammatory pathway presents a promising drug target. Tocilizumab reduces systemic inflammation by blocking IL-6R,[351] and has been shown to be highly effective for the treatment of rheumatoid arthritis.[352,353] Tocilizumab has been suggested as a potential therapeutic option for CHD.[122] The findings of this current analysis, suggest that further work should be undertaken to explore whether tocilizumab may also reduce the risk of AF in those at very high risk of the developing the arrhythmia.

8.5.4. YKL-40 and risk of atrial fibrillation

YKL-40 has been previously shown to be associated with risk of AF. Marott *et al*. reported that higher YKL-40 levels were associated with a greater risk of AF in the Copenhagen General Population Study (AF cases=337).[337] This has been supported by smaller case-control studies demonstrating an association with AF.[354] In contrast, these current findings demonstrate that greater genetically predicted YKL-40 was associated with lower risk of AF. The biological function of YKL40 is unknown. However, YKL-40 is produced at the site of inflammation by macrophages and neutrophils,[355] and has been associated with a range of inflammatory conditions in observational analyses.[356] Previous groups have suggested that genetically predicted YKL40 levels, in contrast to observed YKL40, are not associated with pro-inflammatory conditions.[357,358] Given the lack

of an established function for YKL40, it may be that YKL40 is produced in response to inflammation but does not have a directly pro-inflammatory function.

8.5.5. CD40 and risk of atrial fibrillation

CD40 is expressed on a range of inflammatory and immune cells including B-lymphocytes, and macrophages,[359] and operates through binding to CD40 ligand. Mutations in CD40 have been associated with immunodeficiency syndromes.[360] As with IL6R, CD40 can exist in transmembrane or soluble forms. The soluble form of CD40 is generated through either alternative mRNA splicing, or proteolytic cleavage of transmembrane CD40.[359] Furthermore, greater soluble CD40 is associated with downregulation of transmembrane CD40.[361] As such, variants that increase the amount of soluble CD40 are associated with lower levels of transmembrane CD40 thus lowering inflammatory signalling. This is in keeping with the findings from this current analysis which demonstrate that soluble CD40 is negatively associated with risk of AF and with previous reports indicating that higher genetically predicted soluble CD40 levels are associated with lower risk of large artery stroke.[362] Iscalimab, a monoclonal antibody which targets CD40, has been shown in early reports to lower risk of the inflammatory condition Sjogren's syndrome.[363] As such, transmembrane CD40 may represent a potential target for lowering risk of AF and resultant stroke.

8.5.6. Mediation of effects of anthropometric measures on risk of atrial fibrillation through inflammatory proteins

A correlation between adiposity and inflammatory phenotypes has previously been established.[364] Our findings are in keeping with this, demonstrating strong

correlations between adiposity phenotypes (FM in particular) and CRP. Previous studies suggested that the strength of association of BMI,[125,365,366] and FM,[366] with CRP may be higher in women than men. However, the relationship between other anthropometric measures and CRP levels in men and women has not been previously explored. Our data indicate that both observational and genetically predicted anthropometric measures, which demonstrate associations between FM, BMI, and WC and baseline CRP, are stronger in women than men. The association between genetically predicted LM and baseline CRP was negligible.

Our analysis has demonstrated that CRP met the three criteria to be considered a potential mediator for genetically predicted anthropometric phentoypes.[344] However, inflammation (in the form of genetically predicted CRP, IL6R, CD40, and YKL40) was only responsible for mediating a very small proportion of the association between genetically predicted anthropometric measures and risk of AF (<5%). As such, while correlated, the effect of adiposity on risk of AF appears to be independent of inflammation.

8.5.7. Limitations

The CRP variants used in this analysis were identified in a GWAS using UKB.[340] However, weighting of these variants was shown to be similar in a CRP GWAS not involving UKB participants (**Appendix Figure I.26**).[367] Undertaking MR analyses in the same dataset as the original GWAS has not been show to result in substantial bias.[316] in addition, results were assessed in two genetic consortia not using UKB data (AFGen and FinnGen) both of which also demonstrated directionally consistent results between genetically predicted CRP and risk of AF.

The genetic scores developed for inflammatory proteins in this analysis, with the exception of the cis-CRP score, included trans variants. As such, while there was no evidence of horizontal pleiotropy in the non-CRP genetic scores, the effect of vertical pleiotropy cannot be excluded.

The analyses outlined in this chapter suggests there is no substantial mediation of the effect of anthropometric measures on risk of AF through systemic inflammatory proteins. However, no measure of precession of these estimates have been calculated. As such, there is uncertainty regarding the precession of the estimates provided and the exact proportion of the effect mediated.

This analysis examined the association between genetically predicted systemic inflammatory protein levels and risk of AF. As such, while these analyses suggest that there is limited mediation of the effect of anthropometric measures on risk of AF through selected systemic inflammatory proteins, this does not preclude localised inflammation mediating some aspect of this relationship.

This analysis has been undertaken in a population with a low level of systemic inflammation. While this is likely a reasonable representation of the degree of inflammation in the general population, these results cannot be extrapolated to populations with chronic inflammation.

8.5.8.Conclusions

In the UKB cohort, CRP was strongly associated with adiposity anthropometric measures with greater strength of association seen in women compared with men. Four genetically predicted inflammatory proteins (CRP, CD40, IL6R, and YKL40) were associated with risk of AF. Despite meeting the criteria to be

considered potential mediators, inflammatory proteins appear to mediate little of the causal association between anthropometric measures and risk of AF.

8.5.9. Future work

Proteomics data from UKB was not available at the time of analysis. However, this is likely to provide significant additional information about inflammatory proteins in this cohort. When available, further analysis of these data will be undertaken. This would allow the development of cis-scores for a range of inflammatory proteins and better consider the direct effects of these proteins on risk of AF.

Chapter 9 – Electronic health care record phenotyping of atrial fibrillation within UK Biobank

9.1. Abstract

9.1.1. Introduction

Hospital admissions data are often used to develop cardiovascular phenotypes in large-scale studies. However, this may result in incomplete ascertainment of conditions, such as atrial fibrillation (AF), that are principally managed in outpatient or primary care (PC) settings. Data from UK Biobank (UKB) was used to investigate whether AF cases identified from PC records differed systematically from hospital episode statistics (HES) identified cases.

9.1.2. Methods

Data from UKB participants with linked PC records available were used. A PC AF phenotype was developed from a clinically-validated HES phenotype. Kaplan-Meier curves were used to compare incidence of time-to-event outcomes by ascertainment source, and Cox proportional hazards regression was used to examine the associations of anthropometric measures with risk of AF based on first source of identification.

9.1.3. Results

During a median follow-up of 7 years in 225,683 participants, 7,142 incident AF cases were identified. About half (48%) were identified in both PC and HES data, 30% only in HES data, and 22% only in PC data. HES identified AF cases had more baseline comorbidities than those found in PC records. There was an average 1.3-year lag between a PC ascertainment of AF and subsequent appearance in the HES record. Adiposity measures were similarly associated with risk of AF when considered in HES-first vs PC-first groups. However, lean mass was less strongly associated with risk of AF in the HES-first group compared with the PC-first group. This weaker effect was specific to when AF was diagnosed as the non-primary reason for hospital admission.

9.1.4. Conclusions

PC phenotyping resulted in additional cases of AF. Adiposity-based anthropometric measures were similarly associated with risk of AF regardless of source of first ascertainment. There was a weaker effect between lean mass and risk of AF diagnosed as a non-primary reason for hospital admission.

9.2. Introduction

Atrial Fibrillation (AF) is a heterogeneous chronic cardiac condition.[1] While patients developing AF may present acutely to hospital, this is not always the case. Management of patients with AF is often undertaken in the community with outpatient cardiology support.[134,135] In the UK, management of AF is principally undertaken by primary care (PC) teams,[132] and 45% of AF cases have previously been shown to be first recorded in PC.[133] Evidence from Germany and the United States similarly demonstrate that only 24-40% of AF diagnoses occur during an inpatient admission.[134,368]

A principal facilitator of large-scale datasets has been the ability to link participant data to electronic health records (EHR).[369-371] In UKB, incident disease events are determined through hospital admissions (via Hospital Episode Statistics [HES]) or through death registry data.[370] However, given the proportion of AF cases initially diagnosed in the community,[133] the use of inpatient data to determine incident cases of AF may result in incomplete ascertainment thus limiting power, particularly when considering sub-groups.

Not only may using only inpatient data to determine AF cases lead to incomplete ascertainment, participants with AF that are admitted to hospital may substantially differ from those with AF who do not require hospital admission. Hospital admissions in those with AF are commonly due to AF-related symptoms,[136] cardiovascular and non-cardiovascular comorbidities, AF-related outcomes,[372] or entirely unrelated to AF. In those with AF admitted to hospital in the UK, the arrhythmia is not the primary diagnosis in ~50% of cases,[373] and internationally this may be the case in up to 80%.[374]

AF is associated with age, male sex, and a number of comorbid conditions including CHD and heart failure.[252] These associated demographic features and comorbid conditions have also been shown to lead to higher rates of hospitalisation. [375-377] In particular, CHD and heart failure increase hospitalisation in those with AF by ~20% (HR 1.18, 102 to 1.37, and HR 1.21, 1.04 to 1.41 respectively).[378] Furthermore, there is evidence that chronic conditions, such as AF, may be "under-coded" in UK and international hospital admissions data.[379,380] As a result, use of admissions data to determine AF incidence may bias representation toward a non-representative phenotype with subsequent impacts on the understanding of associated risks and downstream consequences of the disease.

Anthropometric phenotypes have repeatedly been associated with risk of AF in large-scale datasets. The principal largescale datasets where these associations have been examined include UKB,[71,226] DDCH,[66,202],MESA,[95] FHS,[75] JHS.[95] Each of these have used hospital admissions data either automatically or through active follow-up to determine incident AF events. As such, the identified associations between anthropometric measures and risk of AF may represent a risk of AF hospitalisation rather than risk of the development of AF itself.

Given the potential limitations in phenotyping incident AF through hospital admissions and death registry data alone, this study had a number of objectives: (1) to determine the extent to which primary care data identifies additional AF cases to those identified in hospital admissions; (2) to determine whether AF cases derived from PC records differ systematically from those identified in hospital admissions; (3) to estimate the time between community ascertainment

and hospital admission ascertainment: and (4) to examine whether previously identified associations between anthropometric measures and risk of AF differ when considered by AF ascertainment group.

9.3. Methods

9.3.1. UK Biobank primary care data

An outline of the UKB resource has been provided in **Chapter 2** (**UK Biobank**). During recruitment, participants provided written consent for linkage to their health-related records including PC data. At present data from PC has been made available in ~45% of participants (n=230,060) for general research (**Table 9.1**).[159] This data comes from a range of different general practice groups using several different computer systems and is coded using two different Read Code Versions (Versions 2 and 3).[381]

Table 9.1: Participant numbers and coding systems for UK Biobank participants with primary care data available.

Nation	Approximate UKB participants	Computer system supplier	Read Code for clinical coding
England	165,000	TPP	Version 3
	18,000	Vision	Version 2
Wales	27,000	EMIS / Vision	Version 2
Scotland	21,000	EMIS / Vision	Version 2

Table adapted from information provided by UK Biobank.[159] BNF – British national formulary; EMIS – Egton Medical Information Systems; UKB – UK Biobank

9.3.2. Ascertainment of atrial fibrillation

AF hospitalisations were determined using inpatient HES as previously outlined (**Chapter 2, Hospital episode statistics**).

9.3.2.1. Primary care phenotyping

To allow comparability between hospital admission and PC records, PC phenotypes were derived from ICD-10 and OPCS-4 codes used in the HES-based AF phenotype, using mapping files provided by UKB (**Figure 9.1**). These

mapping files link ICD-10 and OPCS-4 codes to Read Codes (version 2 and 3). As some Read Codes and ICD-10/OPCS-4 codes are linked together through many-to-many mapping, an algorithm was developed to identify the single best map. Read Code to ICD-10/OPCS-4 maps were preferentially retained based on 'mapping status' provided in the UKB mapping file. Maps with mapping status 'E' (Exact), 'G' (General), or 'D' (default) were retained. Maps with the mapping status 'R' (requires checking), or 'A' (alternative) were only retained if no default map had been identified.

Each Read Code has one or more descriptions associated with it. Where multiple Read Code descriptions were available, descriptions that exactly matched ICD-10/OPCS-4 descriptions were preferentially retained. If no exact match was identified then descriptions with the 'description_type' of 'P' (primary) were preferentially selected.

In addition to the use of the UKB supplied mapping files, a keyword search was utilised to ensure any unmapped Read Codes relevant to the phenotype were identified. The keywords used for the AF phenotype were 'atrial fibrillation' and 'atrial flutter'. The keyword search algorithm identified any descriptions involving these words and extracted the relevant Read Code. Read Codes already identified by the mapping algorithm were excluded. Additionally, descriptions suggestive of not having the diagnosis were also removed based on a set of pre-defined terms (**Appendix Table D.2**). Likely non-index events were also flagged based on pre-defined terms. All Read Codes obtained through the keyword search and ICD-10/OPCS-4 mapping were verified before confirming the final phenotype.

After initial mapping, a preliminary phenotype was generated and underwent clinical validation. Identified Read Codes were defined either as appropriate or inappropriate. To prevent appropriate Read Codes being misidentified as 'inappropriate' due to the preferential retention of a potentially inappropriate description or map, rejected Read Codes were reassessed. All available maps and descriptions for rejected Read Codes were extracted and underwent a second stage of clinical validation. Any Read Codes found to be appropriate at this stage were added to the PC phenotype and a final phenotype generated. A list of Read Version 2 and Read Version 3 (CTV3) codes used to identify AF and how they were derived is provided in **Appendix Table D.3**.

Prevalent cases of AF were identified through self-reported AF at the baseline assessment centre visit or AF ascertained from HES or PC records occurring prior to recruitment. Incident AF was identified through HES and PC records occurring after enrolment.

9.3.3.Censoring

Participants were censored to ensure there was overlap between HES derived and PC derived phenotypes. Censoring occurred at date of death, withdrawal from the study, or country-specific censoring data for PC data (**Table 9.2**).

Table 9.2: Censoring dates for primary care phenotyping

Country	PC	HES	Combined
England	31 May 2016	30 June 2020	31 May 2016
Scotland	31 March 2017	31 October 2016	31 October 2016
Wales	31 August 2017	29 February 2016	29 February 2016

HES – hospital episode statistics; PC – primary care

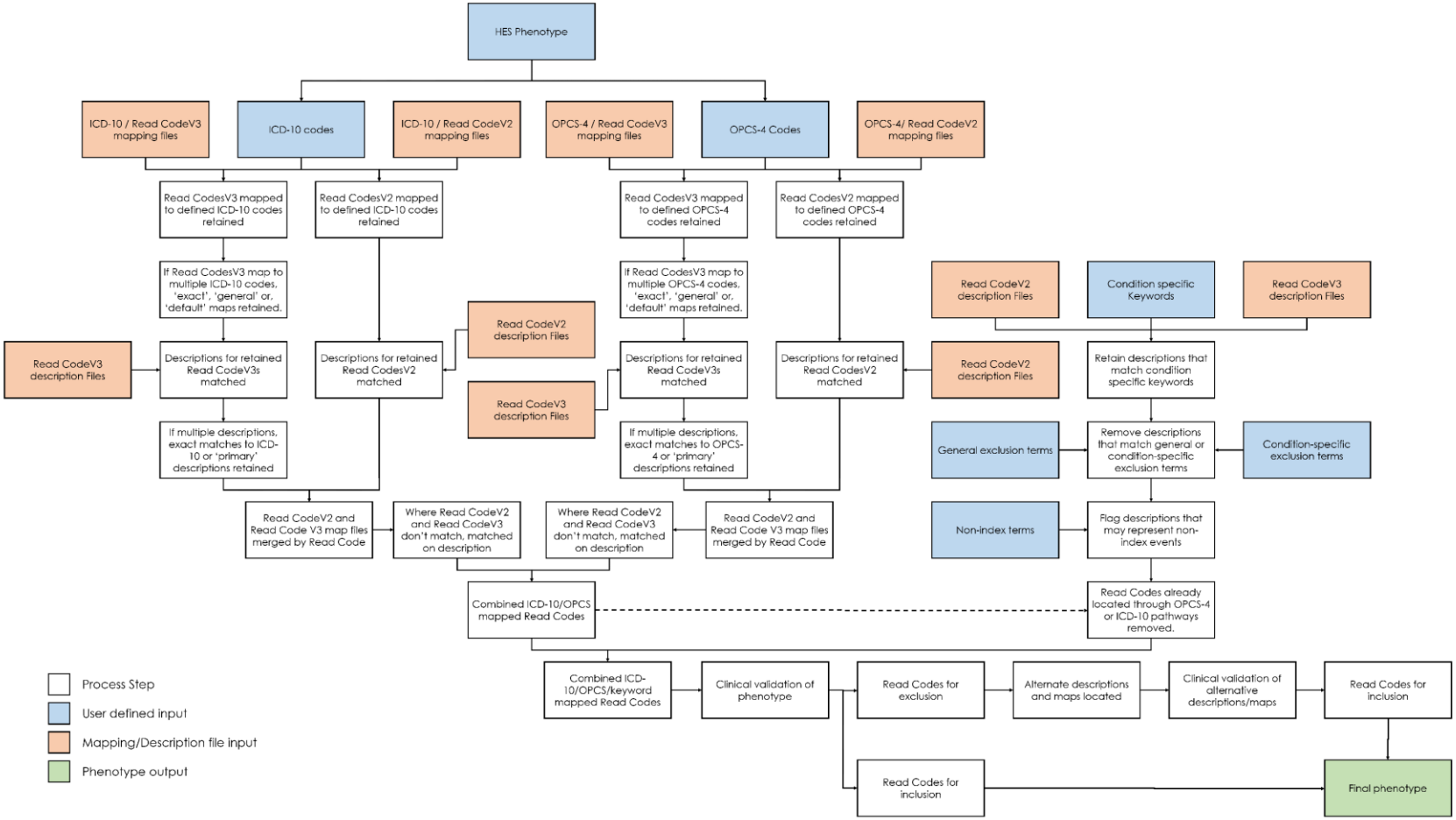


Figure 9.1: Flowchart outlining development of a primary care phenotype.
Primary care phenotypes are developed from an established International classification of disease-10/OPCS Classification of Interventions and Procedures--4 phenotype. Blue boxes represent user inputs, orange boxes represent UK Biobank-provided mapping files, and green box represents final output. HES – hospital episode statistics.

9.3.4. Participant selection

UKB participants were included if linkage to PC records was available. Participants identified as an AF case were divided into three ascertainment groups: those identified in both the HES and PC record (PC + HES), those found only in the HES record (HES-only), and those only found in the PC record (PC-only, **Figure 9.2**).

9.3.5. Participant characteristics

Demographic features including age, sex, ethnicity, smoking status, alcohol status, and Townsend deprivation index were obtained from the baseline assessment (**Chapter 2**). To avoid mismatches in HES data availability between AF ascertainment groups, prior disease phenotypes were constructed based only on self-reported disease states.

9.3.6.Statistical analysis

Continuous variables were described using means (SD) and median (IQR), where appropriate, and categorical variables were described using frequency (%), respectively. Chi squared analyses were used to determine differences between categorical variables and ANOVA or Wilcoxon analyses used to test the differences in continuous variables. Kaplan-Meier curves were utilised to explore the cumulative incidence of a HES record of AF subsequent to a PC ascertainment of AF and vice versa, and the log rank test was used to assess differences between groups. All statistical analyses were undertaken using SAS (Version 9.3).

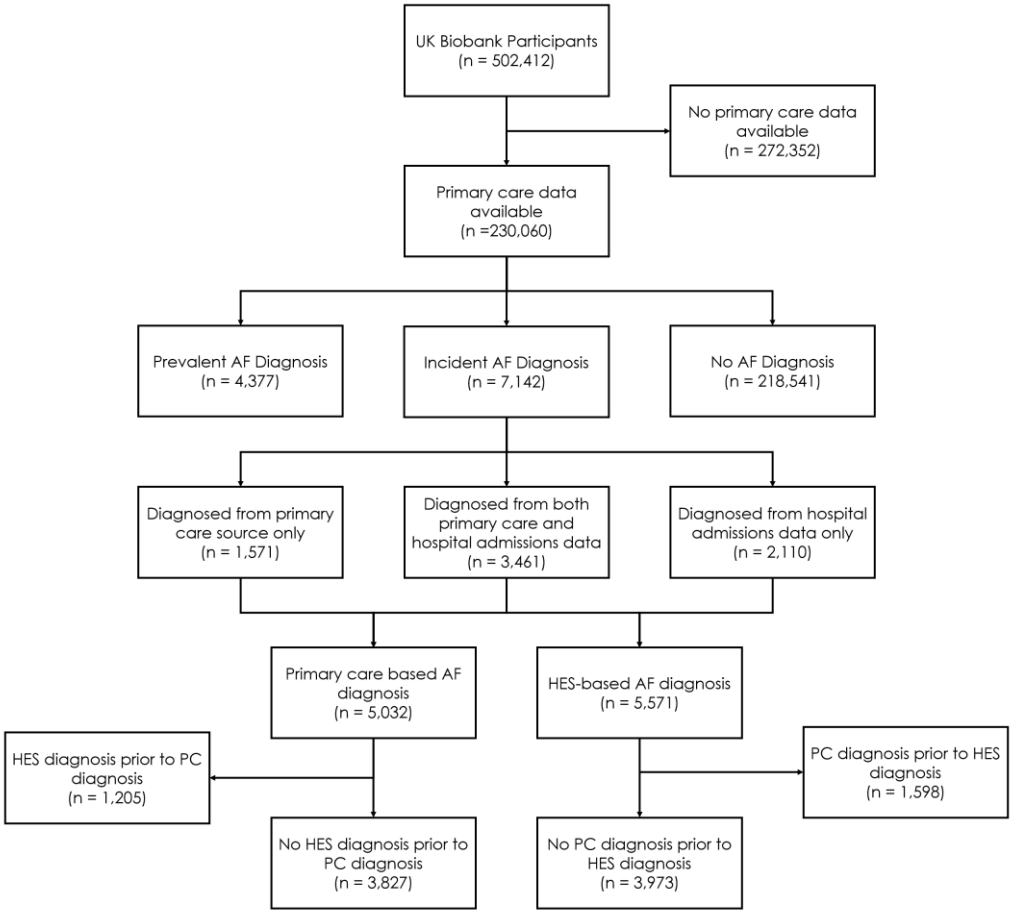


Figure 9.2: Flowchart of participants included in the analysis of atrial fibrillation ascertainment source.
AF – atrial fibrillation, HES – hospital episode statistics, PC – primary care.

9.3.6.1. Assessment of risk of atrial fibrillation by first source of ascertainment

To assess the association between anthropometric measures and risk of AF, a total of 218,272 participants were included after excluding 4,377 participants with prevalent AF (to minimise risk of reverse causation) and 7,411 with missing or extreme anthropometric values or pre-defined covariates (**Figure 9.3**). Cox proportional hazards regression models were used to estimate HRs describing the association between anthropometric measures and first source of AF ascertainment (HES first, PC first). Where participants were identified in both sources on the same day they were assigned to the 'HES first' group. Results

were adjusted for age, sex, ethnicity, Townsend deprivation index,[244,382] and alcohol and smoking status (never, former, current). Additional adjustments for baseline comorbidities and healthcare utilisation (hospital admissions and PC encounters) were undertaken as sensitivity analyses. Differences in the strength of association between ascertainment groups were assessed using a heterogeneity assessment.[383]

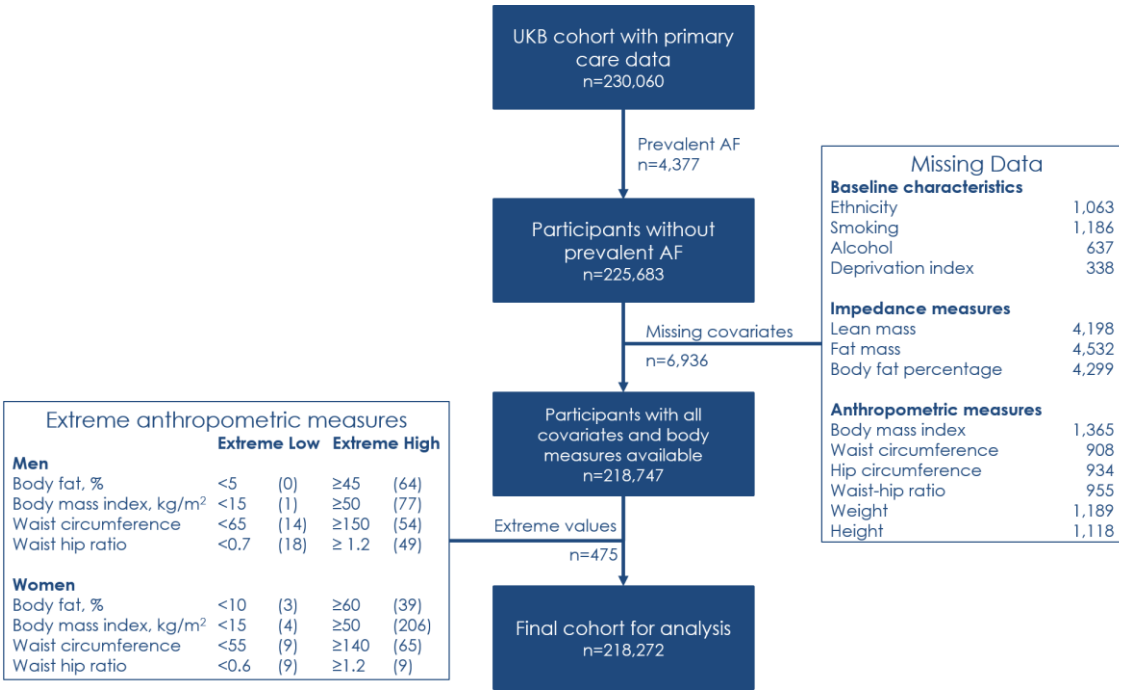


Figure 9.3: Selection of participants for observational analysis of association between anthropometric measures and risk of atrial fibrillation by ascertainment source.

AF – atrial fibrillation, UKB – UK Biobank.

9.4. Results

9.4.1. Phenotype development

Seven ICD-10 codes and ten OCPS-4 Codes were used to create the hospital admission AF phenotype. From these codes, 153 Read Codes were identified (**Table 9.3**). Of these, 110 (72%) were retained following clinical validation. The 36 ICD-10/OPCS-4-Read Code maps rejected by initial clinical validation were reconsidered with all maps and descriptions provided and none were suitable for inclusion.

Table 9.3: Read codes identified and validated through initial stage of the primary care mapping algorithm.

	Identified		**Validated**	
Initial phenotype location	RCV2	RCV3	RCV2	RCV3
ICD-10, n	12	17	12	17
OPCS-4, n	15	61	15	25
Keyword, n	23	25	20	21
Total	*50*	*103*	*47*	*63*

ICD-10 – International Classification of Disease 10, OPCS-4 - OPCS Classification of Interventions and Procedures, RCV2 – Read Code version 2, RCV3 – Read Code version 3.

The final PC phenotype was composed of 110 Read Codes relating to AF diagnoses (**Appendix Table D.3**). Of these, 22 codes (20%) included terms referring to monitoring or other non-index events. A majority of Read Codes (n=69, 63%) were mapped from ICD-10 or OPCS-4 codes and the remainder identified by the key-word search.

9.4.2. Identification of prevalent atrial fibrillation cases

Of 230,060 UKB participants with available PC data, 4,377 prevalent AF cases were identified (1.9%), of which 3,189 were identified in the PC record. There was substantial overlap between sources of identification for prevalent cases with 60% of cases identified from ≥1 source (**Figure 9.4**). An additional 706 (19%) prevalent cases were identified only through the use of PC data when compared to the use of HES and self-reported ascertainment alone.

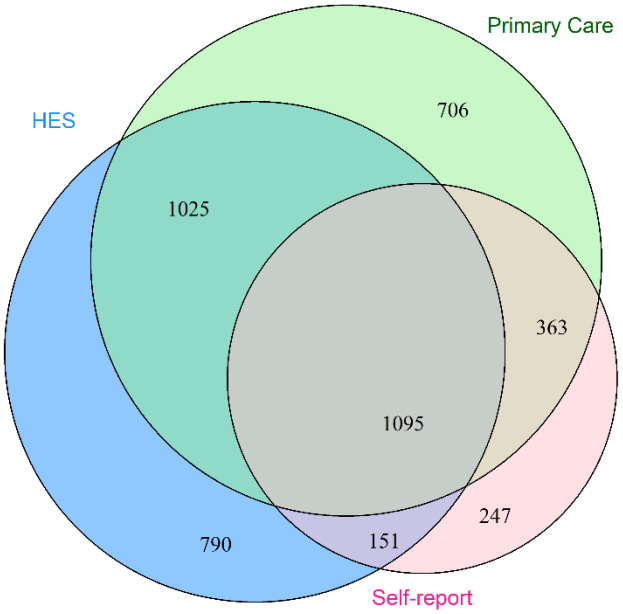


Figure 9.4: Venn diagram demonstrating ascertainment sources for prevalent atrial fibrillation cases within UK Biobank (n=230,060).
Circles area and areas of overlap are proportion to the number of prevalent atrial fibrillation cases identified from each source. HES – hospital episode statistics data.

9.4.3. Identification of incident atrial fibrillation cases

After exclusion of prevalent cases, 225,683 UKB participants were included in the incident analysis. Over a median follow-up period of 7 years (IQR 6.6 to 8.0 years), 7,142 incident AF cases were identified (3.2%). Of the incident AF cases, 1,571 (22%) were identified only in the PC group (PC-only group), 2,110 (30%)

were only identified in the hospital admissions and death registry data (HES-only group), and 3,461 (48%) were found in both sources (PC+HES group).

Of 5,032 incident AF cases identified in PC records, the majority (n=2,904, 57.7%) were identified from a single Read Code (G5730 ‘Atrial Fibrillation’ in both version 2 and version 3). Of the cases identified, only 290 cases (5.8%) were ascertained using Read Codes identified through the key-word search (**Appendix Table L.1**).

AF is commonly identified opportunistically when individuals attend medical settings for different reasons. To explore this, relative differences in hospital or GP attendances were explored to determine if they may explain some proportion of participants identified in the ‘PC-only’ or ‘HES-only’ groups. Of ‘PC-Only’ participants, 1,371 (87%) had at least one hospital admission during the study window; however, only 523 (33%) had at least one hospital admission after their AF ascertainment (**Table 9.4**). The median number of non-AF hospital admissions was substantially lower in the PC-only group compared with the PC+HES and HES-only groups ($p<0.001$). The PC-only group also had lower median levels of hospital admissions after AF ascertainment compared with other groups ($p<0.001$).

Almost all participants with an incident ascertainment of AF had at least one GP record within the study window (**Table 9.4**). The majority of those in the HES-only group also had at least one GP encounter after their AF ascertainment (n=1,764, 84%). The median number of GP encounters was higher in those in the PC+HES group compared with the HES-Only and PC-only groups ($p<0.001$).

This pattern was also seen when limited to GP encounters occurring after their initial AF ascertainment ($p<0.001$).

Table 9.4: Hospital admissions and primary care encounters by ascertainment group (n=225,683)

	PC-Only (n=1,571)	**PC+HES** (n=3,461)	**HES-Only** (n=2,110)	**No AF** (n=218,541)
Hospital admissions				
Any admission				
≥1 admission	1,371 (87)	3,461 (100)	2,110 (100)	177,395 (81)
Admissions	3 (1 to 6)	7 (4 to 11)	9 (5 to 15)	2 (1 to 5)
Non-AF admission				
≥1 admission	1,371 (87)	3,412 (99)	2,100 (99)	177,395 (81)
Admissions	3 (1 to 6)	6 (3 to 11)	8 (5 to 15)	2 (1 to 5)
Admission after AF ascertainment				
≥1 admission	523 (33)	3,027 (87)	1,398 (66)	177,395 (81)
Admissions	0 (0 to 1)	2 (1 to 4)	1 (0 to 4)	2 (1 to 5)
Primary care encounters				
Any encounter				
≥1 GP record	1,571 (100)	3,461 (100)	2,102 (100)	218,242 (100)
GP records	148 (99 to 211)	188 (127 to 264)	142 (48 to 234)	100 (57 to 158)
Encounters after AF ascertainment				
≥1 GP record	1,552 (99)	3,458 (100)	1,764 (84)	218,242 (100)
GP records	32 (14 to 61)	69 (36 to 116)	18 (2 to 55)	100 (57 to 158)

Hospital admissions and primary care encounters are displayed as median (IQR). ≥1 encounters are displayed as n(%). AF – atrial fibrillation, HES – hospital episode statistics, PC – primary care.

9.4.4. Baseline characteristics of atrial fibrillation cases

To assess whether substantial differences existed between the three incident AF ascertainment groups, baseline characteristics were considered (**Table 9.5**). There were no substantial differences in age at baseline, ethnicity, or alcohol use between groups. Age at AF ascertainment was similar across groups (PC-only: 66.4 years [SD 6.4], PC+HES: 66.0 years [SD 6.1], HES-Only: 66.0 years [SD

6.6]).There were no material differences in anthropometric or bio-impedance measures between groups.

In contrast, the proportion of participants with prior disease differed meaningfully between groups. In particular, there was a step-wise increase in the prevalence of myocardial infarction, diabetes, and ischaemic stroke, and smoking burden between the PC only, PC and HES, and HES only groups. Hypertension was common across all groups.

Table 9.5: Baseline characteristics of the 7,142 participants with incident atrial fibrillation

	PC Only (n=1,571)	**PC and HES** (n=3,461)	**HES Only** (n=2,110)
Demographic and lifestyle factors			
Age, mean (SD)	61.8 (6.1)	62.2 (5.8)	61.6 (6.2)
Male sex, n(%)	947 (60.3)	2,251 (65.0)	1,272 (60.3)
White, n(%)	1,533 (97.6)	3,374 (97.5)	2,035 (96.4)
Current smoker, n(%)	130 (8.3)	345 (10.0)	312 (14.8)
Current alcohol drinker, n(%)	1,457 (92.7)	3,168 (91.5)	1,886 (89.4)
Townsend deprivation index*, mean (SD)	-1.5 (3.0)	-1.4 (3.0)	-1.0 (3.3)
Anthropometric measures, mean (SD)			
Height, cm	171.0 (9.4)	171.5 (9.5)	169.7 (9.2)
Weight, kg	83.6 (17.0)	86.3 (17.9)	83.2 (17.1)
Body mass index, kg/m^2	28.5 (5.2)	29.3 (5.5)	28.9 (5.3)
Waist circumference, cm	95.0 (14.1)	97.6 (14.1)	96.4 (14.2)
Hip circumference, cm	105.5 (9.8)	106.6 (10.4)	105.4 (10.3)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Bio-impedance measures, mean (SD)			
Lean mass, kg	57.2 (12.0)	58.7 (12.0)	56.2 (11.5)
Fat mass, kg	26.4 (10.2)	27.6 (11.1)	26.8 (10.4)
Prior disease, n(%)			
Diabetes	106 (6.8%)	276 (8.1%)	192 (9.4%)
Heart failure	8 (0.5%)	17 (0.5%)	11 (0.5%)
Hypertension	659 (41.9%)	1,638 (47.3%)	958 (45.4%)
Myocardial infarction	75 (4.8%)	260 (7.5%)	188 (8.9%)
Stroke	36 (2.3%)	109 (3.1%)	101 (4.8%)

People with atrial fibrillation at baseline were excluded. HES – hospital episode statistics, PC – primary care, SD – standard deviation.

9.4.5. Atrial fibrillation ascertainment groups by age and sex

As both age and sex are important predictors of health-care utilisation and risk of AF, differences in AF ascertainment groups based on these factors were considered. When stratified there was evidence of differences in the proportions of AF cases by ascertainment group in men and women ($p=2 \times 10^{-4}$) while there was no difference based on age at ascertainment ($p=0.06$, **Figure 9.5**).

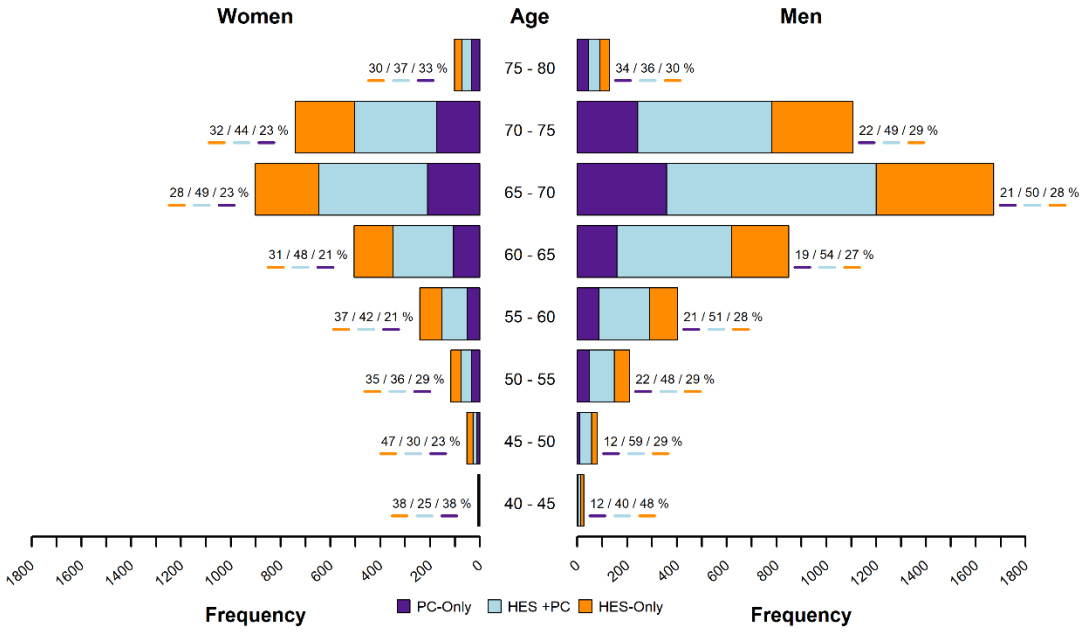


Figure 9.5: Incident atrial fibrillation ascertainment group, by age at ascertainment and sex.
Miami plot demonstrating the frequency of incident atrial fibrillation by ascertainment group. Participants are split into women (left) and men (right) and age at ascertainment. HES – hospital episode statistics, PC – primary care

9.4.6. Time course of identification of atrial fibrillation cases by ascertainment source

To consider the potential lag time between identification of AF cases between ascertainment sources, participants with an initial AF ascertainment from either PC or HES were examined. Of 5,032 incident AF cases identified from PC records, 3,827 cases without an earlier HES ascertainment had a subsequent

HES record of AF or were censored at time of death or last follow-up. Of these, a HES ascertainment was recorded on the same day as the PC ascertainment in 17% of participants (n=658) and 29% had a HES record within three months of their PC ascertainment. The median time between a PC ascertainment of AF and a subsequent identification in the HES record was 1.3 years (**Figure 9.6**). The time to HES ascertainment was substantially greater in women (median 1.6 years) than men (median 1.1 years, **Appendix Figure L.1**, p=0.006). There was no difference across age groups (**Appendix Figure L.2**, p=0.18).

Of 5,571 incident AF cases identified from HES records, 3,973 cases without an earlier PC ascertainment had a subsequent PC record of AF or were censored. Of these, 17% (n=658) had a PC ascertainment on the same day as the HES record, and 40% had a subsequent PC ascertainment within 3 months of the HES record. Overall, the median delay before AF was subsequently recorded in PC was 5.0 years (**Figure 9.6**). There was no difference in time to PC record in men and women (**Appendix Figure L.1**, p=0.26). There was no difference across age groups (**Appendix Figure L.2**, p=0.72).

We considered that short follow-up periods following initial identification in one ascertainment source may explain some proportion of patients identified in either PC or HES and not subsequently identified in the other source. To explore this, the dates of ascertainment relative to the last date of follow-up in the ‘PC-only’ and ‘HES-only’ groups were examined. Of 1,571 PC-only cases, 397 (25%) had a last follow-up date within one year of initial identification. Of 2,110 HES-only cases, 441 (21%) were identified within one year of last follow-up date (**Table 9.6**).

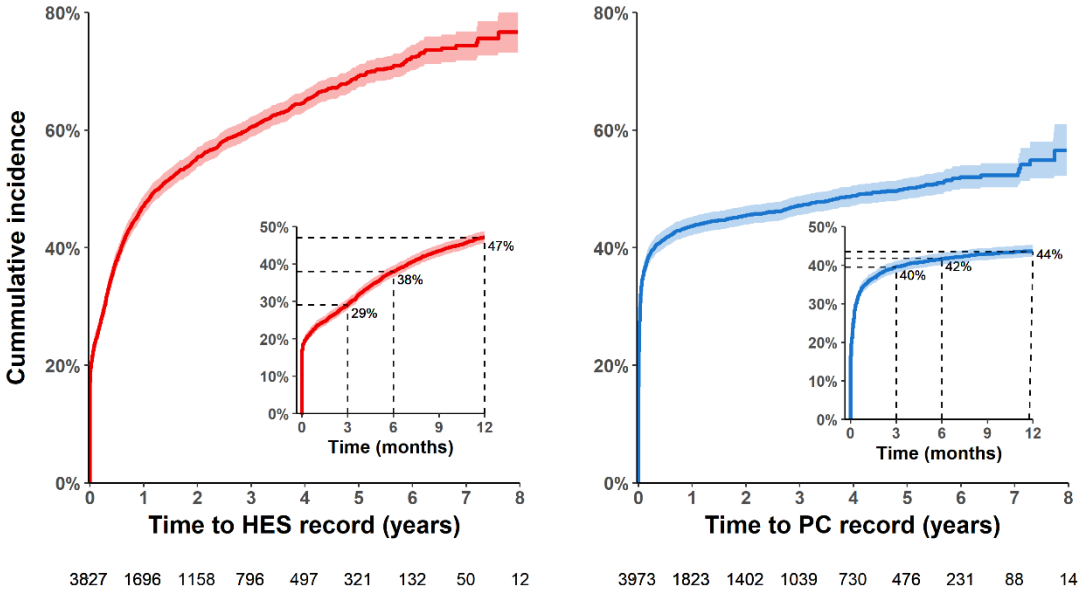


Figure 9.6: Time from atrial fibrillation ascertainment to identification in an alternate source.

Cumulative incidence plots showing years to subsequent hospital episode statistic atrial fibrillation ascertainment for those first identified in primary care (left, n=3,827) and years to subsequent primary care atrial fibrillation ascertainment for those first identified in hospital episode statistics (right, n=3,973). Individuals without a subsequent ascertainment in the alternative source are censored. Inset plots show individuals identified within 1 year. Values below the x-axis are numbers at risk. Analyses exclude participants who had a prior ascertainment in the alternate source. HES – hospital episode statistics, PC – primary care.

Table 9.6: Time between ascertainment and last follow-up date in PC-Only and HES-Only groups

	PC-Only	HES-Only	P-value
Years to censor, median(IQR)	2.45 (0.99 to 4.08)	2.75 (1.21 to 4.71)	<0.001
<1 year of follow-up after identification, n(%)	397 (25)	441 (21)	0.002

HES – hospital episode statistics, IQR – inter-quartile range, PC – primary care

9.4.7. Anthropometric measures and ascertainment source of first atrial fibrillation record

Given similarities in the AF phenotype between ascertainment groups, the strength of association between anthropometric measures and AF first recorded from PC compared with those first identified in HES was explored. Of those with

PC data, 218,272 participants were included in the observational analysis. Distribution of anthropometric measures was the same in the cohort with PC data and the entire UKB cohort utilised in **Chapter 4** (**Appendix Figure L.3**).

9.4.7.1. Anthropometric measures and healthcare utilisation in UK Biobank

Greater anthropometric measures were positively associated with number of total hospital admissions and PC encounters, with LM being substantially less strongly associated than other measures of body size. Once adjusted for other anthropometric measures of adiposity, LM was negative associated with healthcare utilisation (**Table 9.7**).

Table 9.7: Association between anthropometric measures and healthcare utilisation in UK Biobank.

Anthropometric Measure (per SD)	Hospital admissions, Beta (95%CI)	Primary care encounters, Beta (95%CI)
Body mass index	0.60 (0.56 to 0.65)	15.4 (15.1 to 15.8)
Waist circumference	0.69 (0.64 to 0.73)	15.8 (15.4 to 16.1)
Lean mass	0.35 (0.31 to 0.40)	9.0 (8.6 to 9.3)
Fat mass	0.58 (0.54 to 0.63)	14.3 (14.0 to 14.7)
Lean mass adjusted for		
Body mass index	-0.12 (-0.18 to -0.05)	-3.2 (-3.7 to -2.7)
Waist circumference	-0.19 (-0.25 to -0.13)	-2.9 (-3.4 to -2.4)
Fat mass	-0.08 (-0.14 to -0.01)	-1.3 (-1.8 to -0.8)
Adjusted for lean mass		
Body mass index	0.68 (0.62 to 0.74)	17.6 (17.1 to 18.1)
Waist circumference	0.82 (0.76 to 0.88)	17.7 (17.2 to 18.2)
Fat mass	0.63 (0.57 to 0.69)	15.2 (14.7 to 15.6)

Beta values obtained from a linear regression model adjusted for age, sex, alcohol, smoking, deprivation, and ethnicity. CI – confidence interval, SD – standard deviation.

9.4.7.2. Association between anthropometric measures and risk of atrial fibrillation by first ascertainment source

Participants were divided by source of first AF record into two groups: HES-first (n=3,708) and PC-first (n=3,026). BMI, WC, and FM were all positively

associated with similar effect estimates in the HES first and PC first groups. In contrast, the strength of association between LM and risk of AF was substantially lower in the HES first group (HR 1.23, 95%CI 1.20 to 1.26, per 5 kg) compared with the PC first group (HR 1.35, 95%CI 1.32 to 1.39, per 5 kg, p-heterogeneity<0.001, **Figure 9.7**). When split by sex, this LM pattern was seen in men (p-heterogeneity <0.001) but not women (p=0.27, **Appendix Figure L.4**).

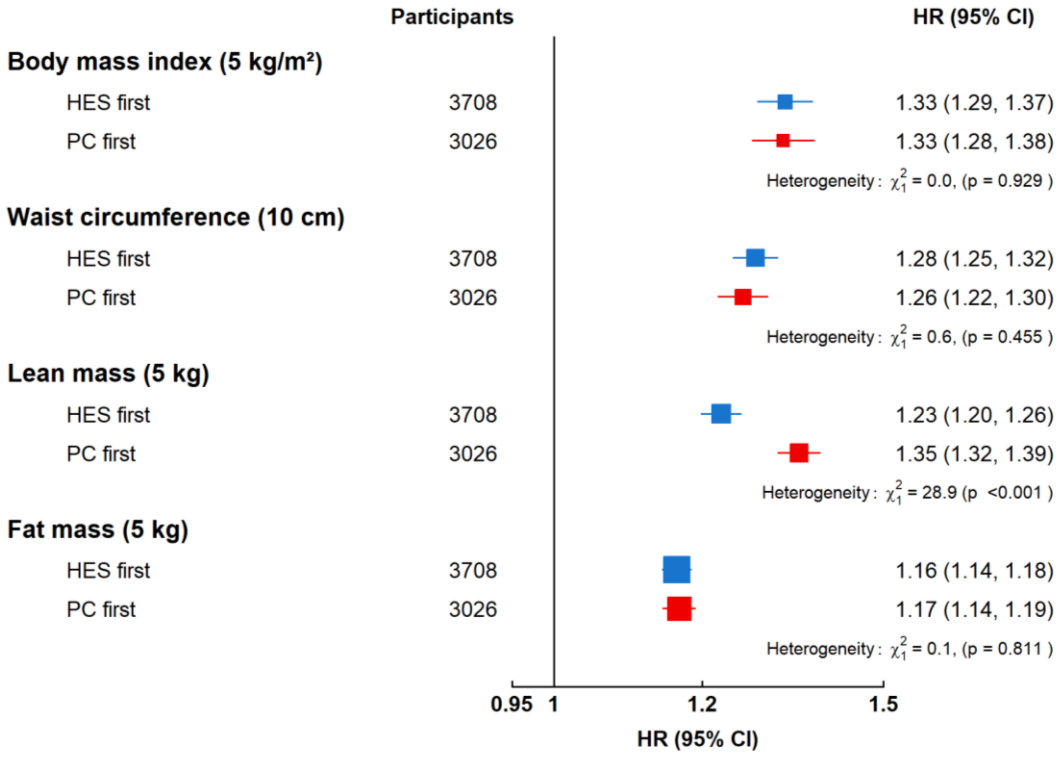


Figure 9.7: Anthropometric measures and risk of atrial fibrillation by source of first atrial fibrillation record (n=218,272).
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). HES – hospital episode statistics, PC – primary care.

Given differences in baseline comorbidities and health care utilisation (hospital admissions and GP encounters) identified between AF ascertainment groups, these were added as additional covariates to the model. While there was some

attenuation in the strength of association between anthropometric measures and risk of AF when additionally adjusted for baseline comorbidities and health care utilisation there was no difference in the observed pattern of association between groups (**Appendix Figure L.5**).

Greater LM may be associated with a greater degree of physical activity or differences in diet. However, further adjustment for physical activity and dietary variables did not alter the differences identified (**Appendix Figure L.6**). To consider whether this relationship may be the result of reverse causation, those censored in the first two years of follow-up were removed and demonstrated a similar difference in the strength of association with LM (**Appendix Figure L.7**).

9.4.7.3. Atrial fibrillation as the primary and non-primary reasons for admission and the association with anthropometric measures

AF may be the primary reason for hospital admission but may also be identified coincidentally when a patient is admitted for another reason. Anthropometric measures may be positively associated with risk of AF due to a greater risk of presenting primarily for their AF or due to a greater risk of coincidental identification of AF. To explore this further the HES-first group was further divided by whether the first recorded AF episode was the primary cause of admission (primary group) or a non-primary cause for admission ('not primary' group). When the associations with anthropometric measures were examined, there was no difference in the strength of associations between groups for BMI, WC, or FM. However, for LM, the strength of association was much lower in the non-primary group (HR 1.19, 95%CI 1.16 to 1.23) compared with the primary group (HR 1.32, 95%CI 1.26 to 1.38, p-heterogeneity<0.001, **Figure 9.8**). The effect estimate of

the primary group was similar to that seen in the PC first group (p-heterogeneity = 0.35).

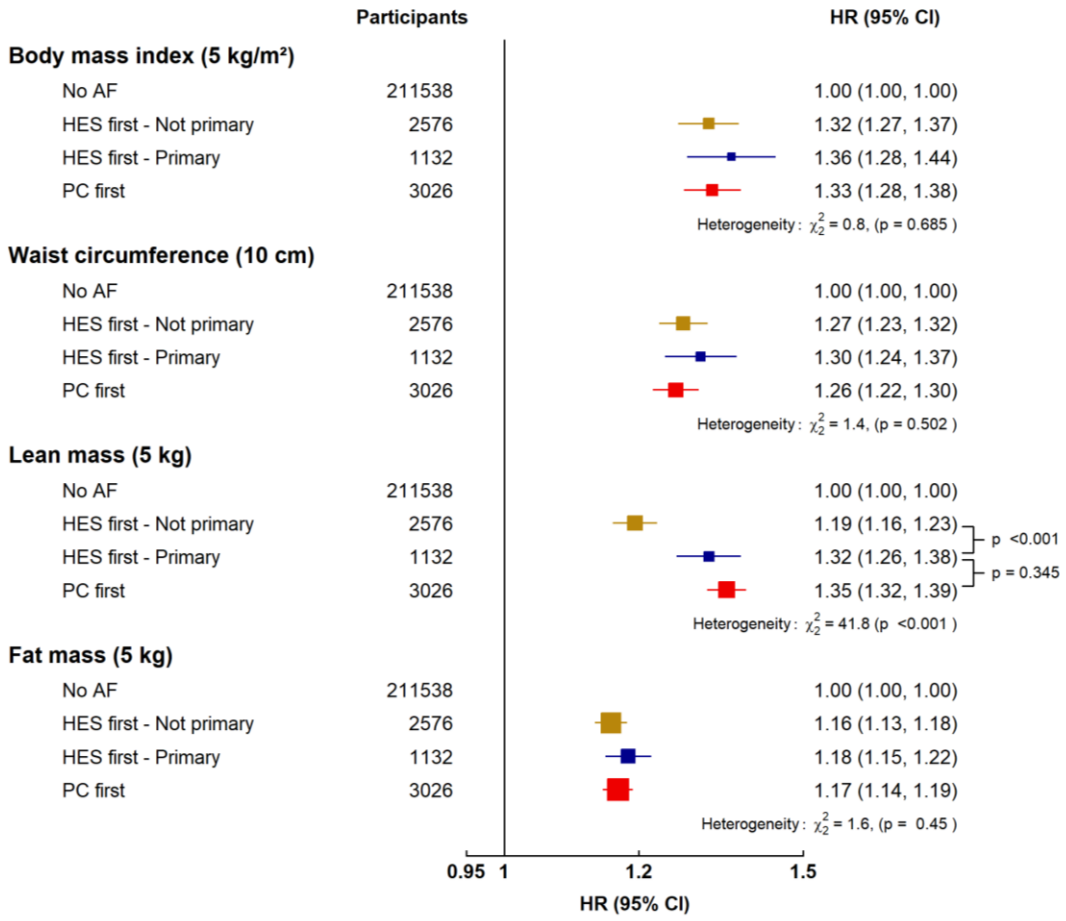


Figure 9.8: Anthropometric measures and risk of atrial fibrillation by source of first atrial fibrillation record splitting atrial fibrillation hospital episode statistics records into primary and non-primary causes of admission.
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). Where overall assessments of heterogeneity were significant, pairwise assessments are displayed.

9.5. Discussion

This analysis has demonstrated that a PC AF phenotype can be developed in UKB by mapping from an established and clinically validated phenotype based on HES data. The use of PC data identified 19% additional prevalent AF cases. Furthermore, an additional 28% of incident cases were identified when PC information was added to hospital admissions and death registry data. Participants with AF identified through HES records had a slightly higher prevalence of baseline cardiovascular disease and medication use compared with those identified only through PC. When initially identified in PC, 50% of cases appeared in the HES record within 1.3 years. Adiposity traits including BMI, WC, and FM were similarly associated with risk of AF regardless of whether identified first in the HES or PC record.

9.5.1. Additional cases identified through the use of primary care data

Integration of PC data identified ~30% additional incident AF cases compared with use of HES data alone. This is higher than the 18% additional AF cases reported by Morely *et al*. when examining the addition of PC data to secondary care data in the UK-based CALIBER cohort[133]. The greater rate of additional AF cases identified here may represent a greater focus on AF identification in primary care between 2010 (censoring date for Morely *et al*.)[133] and 2016. Interestingly, when examining stroke diagnoses from England-wide healthcare records, Wood *et al*. demonstrated that an additional 43% of stroke diagnoses were identified using PC data.[384] Similarly, data from CALIBER showed that an additional 22% of myocardial infarctions were identified using PC data.[385] This

highlights the importance of PC data to ensure both chronic and acute cardiovascular cases are identified.

9.5.2. Baseline characteristics in primary and secondary care based atrial fibrillation

While PC data leads to additional numbers, cases identified in PC may also be different from those identified through HES data. In particular, those with AF may be admitted to hospital for a number of different AF- and non-AF-related reasons.[136,372] For example, as general hospital admissions are higher in those with CHD and heart failure,[378] these comorbidities may be disproportionately present in cases identified in HES data. As such, using only HES data to define a phenotype may result in an incident case group that are not representative of the cases in the original population, potentially resulting in ascertainment bias.[386]

In this analysis, the additional cases identified through PC data had a lower burden of cardiovascular comorbidities to those identified in the HES record. However, in keeping with previous data from the CALIBER cohort,[133] the differences were generally small between those identified through HES data and those only identified in the PC record. Importantly there appeared to be no meaningful difference in the distribution of anthropometric or bio-impedance measures by AF ascertainment group. This suggests that the risk of a substantial ascertainment bias through use or non-use of PC data to identify AF cases is likely to be low.

9.5.3. Timing of ascertainment of atrial fibrillation cases in primary and secondary care

Traditional epidemiological analyses are prone to reverse causation.[387] As such, the presence of a substantial delay between initial event occurrence and appearance in the medical record may result in a proportion of cases being mis-identified as controls at baseline.[388] There was a particular concern for AF as it is a chronic condition that is commonly identified in the community,[132,133,368] does not necessarily require hospital admission, and may be asymptomatic.[389] These analyses demonstrated that there was a median delay of 1.3 years between PC and hospital ascertainment of AF which is comparable with results from the CALIBER cohort.[133] The presence of underlying cardiac disease may result in shorter time between initial identification and hospitalisation.[390] The identified lag time, coupled with the identification of additional prevalent cases using PC data, means a substantial number of prevalent AF cases may be misidentified as incident cases in a prospective analysis if only HES data are utilised to develop the AF phenotype. This has the potential to substantially reduce statistical power. Additionally, while not using PC data in phenotyping AF may increase the risk of reverse causation, this is likely to be mitigated by excluding the first two years of follow-up in sensitivity analyses.[226,391]

9.5.4. Anthropometrics and risk of atrial fibrillation identified in primary and secondary care

Obesity is associated with risk of hospitalisation for cardiovascular disease.[392] In contrast LM is generally protective against risk of hospital admission,[393] and lower LM has been associated with longer duration of hospitalisation.[394] Our

findings demonstrate that, independent of other anthropometric measures, LM is associated with a lower number of hospital admissions and GP encounters. Because of these differences, associations between anthropometric measures and risk of AF by first ascertainment source were explored. Our analyses demonstrate that anthropometric measures were positively associated with risk of AF regardless of first AF ascertainment source. The strength of association was similar for BMI, WC, and FM for risk of AF in both the HES first and PC first groups. However, for LM, the strength of association for was substantially greater for risk of AF identified in the PC record first compared with those identified in the HES record first.

When first AF HES records were split into whether AF was recorded as the primary cause of admission or not there were meaningful differences in the strength of association of LM and risk of AF between groups. This demonstrated that the association between LM and risk of AF as a primary cause of HES admission was similar to the association with risk of AF being first recorded in PC. In contrast, the association between LM and risk of AF being identified as a non-primary finding during a hospital admission was much smaller. This may support the hypothesis that while LM is a risk factor for AF, as LM is associated with less frequent hospital admission, LM is likely to be less strongly associated with coincidental diagnosis of AF when admitted for other causes.

9.5.5. Limitations

A number of limitations in these analyses need to be recognised. In particular, a lack of information in hospital admissions data prevents determination of differences in ascertainment related to AF sub-type (i.e. paroxysmal, persistent,

and permanent). Furthermore, while it would be expected that most individuals developing AF would present to a medical setting, those that are truly asymptomatic may only be identified incidentally.[18] As such, while it appears that the inclusion of PC data allows for earlier identification of a proportion of AF cases, some participants may still have AF but have not presented to any medical setting.

The PC phenotype was mapped from an established ICD-10/OPCS-4 phenotype for AF and the resulting Read Codes were clinically validated. However, the accuracy of the phenotype for identifying AF identified electronic healthcare record data has not been assessed.

9.5.6. Future work

This work highlights the potential strengths of utilising PC data in the development of phenotypes in large-scale datasets. Within AF specifically, additional cases may lead to greater power in both traditional epidemiological and genetic epidemiological analyses. The methodology for developing a PC phenotype from an established HES phenotype is likely to be useful to explore a number of other cardiovascular phenotypes were a substantial proportion of care may be undertaken in the community (for example hypertension).

While this work expands AF phenotyping into PC, the proportion of participants with asymptomatic AF remains unknown. However, studies screening for AF using wearable monitors will likely provide information in this area.[395]

MR analysis has been used to consider the causal association between anthropometric measures and risk of AF.[71,108,110] Given the use of this technique

in earlier chapters, it would be reasonable to consider whether the associations between genetically predicted anthropometric measures and risk of AF demonstrated a similar pattern to that seen in the observational analyses when considering AF cases identified only in PC. However, as PC data are only available in 45% of the UKB population and follow-up limited to 2016, this dataset was underpowered to consider this question appropriately. When the remainder of the PC data are available in UKB with further follow-up, the potential causal relevance of the observational findings identified here should be considered using genetically predicted anthropometric measures.

9.5.7. Conclusions

The use of PC data to supplement the ascertainment of AF through electronic healthcare records adds a meaningful number of prevalent and incident cases, with a median of 1.3 years between ascertainment in PC and subsequent appearance in the HES record. There were no differences in the associations between adiposity measures and risk of AF by ascertainment source of first AF diagnosis. The weaker association observed between LM and risk of AF in those first identified in the HES record (compared with those first identified in the PC record) are the result of a lower association between LM and records of AF in non-primary positions within the HES record.

Chapter 10 - General conclusions

This thesis has provided important and novel insights into the association between anthropometric measures and risk of AF. This chapter lays out the main findings from this thesis before exploring potential directions for future research.

10.1. The independent effects of anthropometric measures on risk of atrial fibrillation

This thesis has confirmed that common anthropometric measures including BMI, WC, LM, and FM are associated with risk of AF (**Chapter 4**). When mutually adjusted to explore independent relevance, LM, FM, and WC, all remained associated with risk of AF. This suggests that body fat distribution and LM have a role in the development of AF independent of measures of general body size. These findings are supported by MR analyses (**Chapter 7**) which demonstrate that genetically predicted WC is associated with risk of AF and that this association remains when using an MVMR model including BMI. In addition, LM and FM (which if combined together would be 'body weight') were both associated with risk of AF when examined in an MVMR model.

These findings have important practical implications when considering risk of AF. In particular, an independent role for weight and WC, as easy-to-assess clinical measures, in predicting risk of AF suggest that both should be considered. Furthermore, given that weight loss may reduce AF burden, the findings of an independent relevance of body-fat distribution in this thesis suggest that the

anthropometric changes by which weight loss leads to improvement in AF should be further explored.

10.2. Differences in the effect of anthropometric measures on risk of atrial fibrillation in men and women

Subtle differences in the association between anthropometric measures and risk of AF were demonstrated between men and women in observational analyses (**Chapter 4**). Notably, FM (as a measure of general adiposity), once adjusted for LM and WC (as a measure of central adiposity), was of limited relevance in determining risk of AF compared with LM or central adiposity in men. In contrast, in women, FM, LM, and WC were all similarly associated with risk of AF. Our analyses did not reveal meaningful differences in the associations between genetically predicted anthropometric measures and risk of AF in women compared with men (**Chapter 7**). However, the ability to identify such differences between men and women using MR is contingent on differences in genetic variants associated with anthropometric measures being identified in the original GWAS.

While their causal relevance requires further investigation, these findings are important as they highlight potential differences in anthropometric determinants of AF between men and women. This adds to the evidence of differences between men and women when considering cardiovascular phenotypes,[396] and supports the need to ensure sex-based differences are explored as a routine part of AF-based research.

10.3. Creation of a pericardial adipose tissue phenotype

This thesis has demonstrated that native T1 maps can be used to generate a mid-ventricular PAT area phenotype (**Chapter 5**). This phenotype was associated with a number of other anthropometric measures including abdominal VAT. This finding is important as it highlights that a PAT area can be generated using CMR data. ShMOLLI sequences used to create native T1 maps do not require contrast agents and could be incorporated into routine clinical scans. This dataset of PAT areas also provides a potential training set for future machine-learning algorithms which could allow scaling this phenotype to the wider UKB imaging sub-set.

10.4. The association between pericardial adipose tissue and risk of atrial fibrillation

This thesis has demonstrated an observational association between PAT area and risk of AF (**Chapter 6**). This was seen in both men and women and was only partially attenuated following further adjustment for abdominal VAT. This suggests a potential independent association between PAT and risk of AF. However, the findings in this thesis confirm that the association between PAT and risk of AF was more modest than had been previously suggested. Indeed the association between PAT and risk of AF was in line with other anthropometric measures. Notwithstanding the limitation that we did no evaluate the impact of atrial PAT, these findings suggest that it is unlikely that PAT is a central unifying pathway by which adiposity is associated with risk of AF.

10.5. The relationship between anthropometric measures, inflammation, and risk of atrial fibrillation

This thesis has demonstrated that genetically predicted inflammatory proteins including CRP, IL-6R, YKL40, and CD40 were associated with risk of AF (**Chapter 8**) supporting a causal role for systemic inflammation in risk of AF. The finding that a cis-CRP score was not associated with risk of AF demonstrates that this is not through CRP itself. There are a number of therapeutic interventions that can target inflammation and specific inflammatory mediators. These findings suggest that therapeutic interventions targeting IL-6, YKL40, and CD40 may be able to reduce the risk of AF.

Genetically predicted adiposity measures were shown to be significantly associated with CRP level. This, combined with the associations identified between inflammation and risk of AF, suggested that inflammation might mediate some part of the relationship between adiposity and risk of AF. However, this thesis has demonstrated that none of the genetically predicted inflammatory proteins identified as being associated with risk of AF mediated a meaningful portion of the relationship between adiposity and AF. This suggests that other pathways, including localised inflammation, linking adiposity to risk of AF should be explored.

10.6. Phenotyping atrial fibrillation in electronic healthcare records

The addition of PC data to HES and death registry information adds a meaningful number of AF cases (**Chapter 9**). There appears to be no substantial differences

in baseline characteristics based on ascertainment source suggesting the risk of bias is low. Adiposity measures were similarly associated with risk of AF regardless of ascertainment source, highlighting that associations between adiposity traits and risk of AF are not simply associations with risk of AF hospitalisation. The additional cases identified using PC data suggests this data source, whenever possible, should be incorporated into follow-up when exploring AF.

10.7. Potential future directions of research

There are a number of potential future directions for research based on the findings in this thesis:

1. The effect of anthropometric measures on risk of AF requires exploration in different populations. This thesis has principally used UKB as a datasource. This is a cohort composed predominantly of white British middle- to older-age individuals. The effect of anthropometric measures on risk of AF in younger cohorts should also be explored. Additionally, given known differences in body fat distribution and risk of AF in other ethnicities,[3,38] the association between anthropometric measures and risk of AF should be further explored in multi-ethnic populations.
2. The causal relevance of PAT remains unclear. The development of a machine-learning algorithm to phenotype future UKB participants with available CMR data would allow a GWAS of 50,000-100,000 participants providing a significant opportunity to identify suitable genetic variants. This would allow consideration of the causal relevance of this phenotype in relation to AF and a wider group of cardiovascular phenotypes.

3. The association between systemic inflammation and risk of AF, while not part of the adiposity pathway, has important implications for future research. Given the presence of established therapies for IL-6 and CD40, these may be promising areas of future research to explore their effect on lowering risk of AF in high-risk populations.
4. The effect of inflammation as a mediator for the association between PAT and risk of AF warrants further investigation. Given evidence that PAT is a pro-inflammatory adipose tissue deposit,[397] the relevance of inflammation as a mediator of the relationship between PAT and risk of AF may differ to that seen in other anthropometric measures.
5. The fact that systemic inflammation, as assessed in this thesis, was not found to be a meaningful mediator between adiposity and risk of AF, suggests that the effect of locally mediated inflammatory processes and other potential mediators should be explored. It is important to identify such mediators as they may be more readily targeted with therapeutic interventions than anthropometric traits themselves.
6. The relevance of PC data in phenotyping AF has been clearly highlighted. However, the benefit of this additional data source for the identification of other cardiovascular phenotypes that do not routinely require hospital admission (for example hypertension) requires further exploration. Furthermore, PC data provides additional information related to PC-based prescribing allowing exploration of treatment decisions (for example anticoagulation) in those with AF.

10.8.Summary

This thesis has added meaningfully to knowledge surrounding adiposity and risk of AF. In particular, causal relationships between anthropometric measures inflammatory proteins, and risk of AF suggests further investigation of interventions targeting adiposity and inflammation should be explored for the potential to lower the risk of developing AF.

Bibliography

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373-498.
2. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes.* 2012;5(1):85-93.
3. Rodriguez CJ, Soliman EZ, Alonso A, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol.* 2015;25(2):71-76.
4. Dai H, Zhang Q, Much AA, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes.* 2021;7(6):574-582.
5. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129(8):837-847.
6. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
7. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2224-2260.
8. Burdett P, Lip GYH. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. *Eur Heart J Qual Care Clin Outcomes.* 2022;8(2):187-194.
9. Wilke T, Groth A, Mueller S, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace.* 2013;15(4):486-493.
10. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med.* 1995;98(5):476-484.
11. Liang F, Wang Y. Coronary heart disease and atrial fibrillation: a vicious cycle. *Am J Physiol Heart Circ Physiol.* 2021;320(1):H1-H12.
12. Jiang Q, Wang K, Shi J, Li M, Chen M. No association between alcohol consumption and risk of atrial fibrillation: A two-sample Mendelian randomization study. *Nutr Metab Cardiovasc Dis.* 2020;30(8):1389-1396.
13. Lu Y, Guo Y, Lin H, Wang Z, Zheng L. Genetically determined tobacco and alcohol use and risk of atrial fibrillation. *BMC Med Genomics.* 2021;14(1):73.
14. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of atrial fibrillation: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol.* 2018;25(13):1437-1451.
15. Freeman JV, Simon DN, Go AS, et al. Association between atrial fibrillation symptoms, quality of life, and patient outcomes: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes.* 2015;8(4):393-402.

16. Wynn GJ, Todd DM, Webber M, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace.* 2014;16(7):965-972.
17. Piccini JP, Simon DN, Steinberg BA, et al. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol.* 2016;1(3):282-291.
18. Turakhia MP, Shafrin J, Bognar K, et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One.* 2018;13(4):e0195088.
19. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol.* 2015;191:172-177.
20. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014;6:213-220.
21. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke.* 1996;27(10):1760-1764.
22. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation.* 2003;107(23):2920-2925.
23. Lee E, Choi EK, Han KD, et al. Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study. *PLoS One.* 2018;13(12):e0209687.
24. Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clin Proc.* 2000;75(8):790-795.
25. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardiol.* 1998;32(1):197-204.
26. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation.* 2009;119(18):2516-2525.
27. World Health Organization. Obesity. https://www.who.int/topics/obesity/en/. Published 2021. Accessed 29th December 2021.
28. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014;384(9945):766-781.
29. N. C. D. Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet.* 2016;387(10026):1377-1396.
30. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation.* 2012;126(1):126-132.
31. Blair SN, Archer E, Hand GA. Commentary: Luke and Cooper are wrong: physical activity has a crucial role in weight management and determinants of obesity. *Int J Epidemiol.* 2013;42(6):1836-1838.
32. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol.* 2013;42(6):1831-1836.
33. Greenblum S, Turnbaugh PJ, Borenstein E. Metagenomic systems biology of the human gut microbiome reveals topological shifts associated with obesity and inflammatory bowel disease. *Proc Natl Acad Sci U S A.* 2012;109(2):594-599.
34. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature.* 2013;500(7464):541-546.

35. Yengo L, Sidorenko J, Kemper KE, et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. *Hum Mol Genet.* 2018;27(20):3641-3649.
36. Buss J. Limitations of body mass index to assess body fat. *Workplace Health Saf.* 2014;62(6):264.
37. Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond).* 2010;34(5):791-799.
38. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN, Jr. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr.* 1994;60(1):23-28.
39. Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol.* 1996;143(3):228-239.
40. Wells JC. Sexual dimorphism of body composition. *Best Pract Res Clin Endocrinol Metab.* 2007;21(3):415-430.
41. Schreiner PJ, Terry JG, Evans GW, Hinson WH, Crouse JR, 3rd, Heiss G. Sex-specific associations of magnetic resonance imaging-derived intra-abdominal and subcutaneous fat areas with conventional anthropometric indices. The Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 1996;144(4):335-345.
42. Schorr M, Dichtel LE, Gerweck AV, et al. Sex differences in body composition and association with cardiometabolic risk. *Biol Sex Differ.* 2018;9(1):28.
43. Andreoli A, Scalzo G, Masala S, Tarantino U, Guglielmi G. Body composition assessment by dual-energy X-ray absorptiometry (DXA). *Radiol Med.* 2009;114(2):286-300.
44. Kyle UG, Bosaeus I, De Lorenzo AD, et al. Bioelectrical impedance analysis--part I: review of principles and methods. *Clin Nutr.* 2004;23(5):1226-1243.
45. Achamrah N, Colange G, Delay J, et al. Comparison of body composition assessment by DXA and BIA according to the body mass index: A retrospective study on 3655 measures. *PLoS One.* 2018;13(7):e0200465.
46. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond).* 2010;34(6):949-959.
47. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest.* 1983;72(3):1150-1162.
48. Demerath EW, Sun SS, Rogers N, et al. Anatomical patterning of visceral adipose tissue: race, sex, and age variation. *Obesity (Silver Spring).* 2007;15(12):2984-2993.
49. Wells JC, Treleaven P, Cole TJ. BMI compared with 3-dimensional body shape: the UK National Sizing Survey. *Am J Clin Nutr.* 2007;85(2):419-425.
50. Bajaj HS, Brennan BM, BHoogwerf BJ, Doshi KB, Kashyap SR. Clinical utility of waist circumference in predicting all-cause mortality in a preventive cardiology clinic population: a PreCIS Database Study. *Obesity (Silver Spring).* 2009;17(8):1615-1620.
51. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation.* 2007;116(1):39-48.
52. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol.* 2013;62(10):921-925.
53. Lemieux I, Pascot A, Prud'homme D, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol.* 2001;21(6):961-967.

54. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation.* 2007;116(11):1234-1241.
55. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes.* 2007;56(4):1010-1013.
56. Wei W, Xin X, Shao B, Zeng FF, Love EJ, Wang BY. The relationship between anthropometric indices and type 2 diabetes mellitus among adults in north-east China. *Public Health Nutr.* 2015;18(9):1675-1683.
57. Staub K, Floris J, Koepke N, et al. Associations between anthropometric indices, blood pressure and physical fitness performance in young Swiss men: a cross-sectional study. *BMJ Open.* 2018;8(6):e018664.
58. Crump C, Sundquist J, Winkleby MA, Sundquist K. Height, weight, and aerobic fitness in relation to risk of atrial fibrillation. *Am J Epidemiol.* 2017;187(3):417-426.
59. Shulman E, Chudow JJ, Shah T, et al. Relation of body mass index to development of atrial fibrillation in hispanics, blacks, and non-hispanic whites. *Am J Cardiol.* 2018;121(10):1177-1181.
60. Persson CE, Adiels M, Bjorck L, Rosengren A. Young women, body size and risk of atrial fibrillation. *Eur J Prev Cardiol.* 2017;25(2):173-180.
61. Schrage B, Geelhoed B, Niiranen TJ, et al. Comparison of cardiovascular risk factors in European population cohorts for predicting atrial fibrillation and heart failure, their subsequent onset, and death. *J Am Heart Assoc.* 2020;9(9):e015218.
62. Aronson D, Shalev V, Katz R, Chodick G, Mutlak D. Risk score for prediction of 10-year atrial fibrillation: a community-based study. *Thromb Haemost.* 2018;118(9):1556-1563.
63. Azarbal F, Stefanick ML, Assimes TL, et al. Lean body mass and risk of incident atrial fibrillation in post-menopausal women. *Eur Heart J.* 2016;37(20):1606-1613.
64. Rodriguez F, Stefanick ML, Greenland P, et al. Racial and ethnic differences in atrial fibrillation risk factors and predictors in women: Findings from the Women's Health Initiative. *Am Heart J.* 2016;176:70-77.
65. Aune D, Sen A, Schlesinger S, et al. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* 2017;32(3):181-192.
66. Fenger-Gron M, Overvad K, Tjonneland A, Frost L. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. *J Am Coll Cardiol.* 2017;69(20):2488-2497.
67. Karas MG, Yee LM, Biggs ML, et al. Measures of body size and composition and risk of incident atrial fibrillation in older people: the Cardiovascular Health Study. *Am J Epidemiol.* 2016;183(11):998-1007.
68. Aronis KN, Wang N, Phillips CL, et al. Associations of obesity and body fat distribution with incident atrial fibrillation in the biracial health aging and body composition cohort of older adults. *Am Heart J.* 2015;170(3):498-505.
69. Azarbal F, Stefanick ML, Salmoirago-Blotcher E, et al. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. *J Am Heart Assoc.* 2014;3(4):e001127.
70. Kim YG, Han KD, Choi JI, et al. The impact of body weight and diabetes on new-onset atrial fibrillation: a nationwide population based study. *Cardiovasc Diabetol.* 2019;18(1):128.
71. Tikkanen E, Gustafsson S, Knowles JW, Perez M, Burgess S, Ingelsson E. Body composition and atrial fibrillation: a Mendelian randomization study. *Eur Heart J.* 2019;40(16):1277-1282.

72. Wong CX, Sun MT, Odutayo A, et al. Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2016;9(12):e004378.
73. Peters SAE, Woodward M. Established and novel risk factors for atrial fibrillation in women compared with men. *Heart.* 2019;105(3):226-234.
74. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation.* 2017;136(17):1588-1597.
75. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA.* 2004;292(20):2471-2477.
76. Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol.* 2010;25(2):95-102.
77. Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace.* 2018;20(12):1929-1935.
78. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol.* 2015;65(20):2159-2169.
79. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol.* 2014;64(21):2222-2231.
80. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA.* 2013;310(19):2050-2060.
81. Heymsfield SB, Harp JB, Reitman ML, et al. Why do obese patients not lose more weight when treated with low-calorie diets? A mechanistic perspective. *Am J Clin Nutr.* 2007;85(2):346-354.
82. Hoit BD. Anatomy and physiology of the pericardium. *Cardiol Clin.* 2017;35(4):481-490.
83. Iacobellis G. Epicardial and pericardial fat: close, but very different. *Obesity (Silver Spring).* 2009;17(4):625.
84. Kim JS, Kim SW, Lee JS, et al. Association of pericardial adipose tissue with left ventricular structure and function: a region-specific effect? *Cardiovasc Diabetol.* 2021;20(1):26.
85. Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr.* 2009;90(3):499-504.
86. Shah RV, Anderson A, Ding J, et al. Pericardial, but not hepatic, fat by CT is associated with CV outcomes and structure: the Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging.* 2017;10(9):1016-1027.
87. Patel KHK, Hwang T, Se Liebers C, Ng FS. Epicardial adipose tissue as a mediator of cardiac arrhythmias. *Am J Physiol Heart Circ Physiol.* 2022;322(2):H129-H144.
88. Antonopoulos AS, Antoniades C. The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles. *J Physiol.* 2017;595(12):3907-3917.
89. Liu J, Fox CS, Hickson D, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson Heart Study. *Diabetes Care.* 2010;33(7):1635-1639.
90. Bard A, Raisi-Estabragh Z, Ardissino M, et al. Automated quality-controlled cardiovascular magnetic resonance pericardial fat quantification using a

convolutional neural network in the UK Biobank. *Front Cardiovasc Med.* 2021;8:677574.
91. Lin E, Alessio A. What are the basic concepts of temporal, contrast, and spatial resolution in cardiac CT? *J Cardiovasc Comput Tomogr.* 2009;3(6):403-408.
92. Power SP, Moloney F, Twomey M, James K, O'Connor OJ, Maher MM. Computed tomography and patient risk: Facts, perceptions and uncertainties. *World J Radiol.* 2016;8(12):902-915.
93. Littlejohns TJ, Holliday J, Gibson LM, et al. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun.* 2020;11(1):2624.
94. Mahabadi AA, Lehmann N, Kalsch H, et al. Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: the Heinz Nixdorf Recall Study. *Eur Heart J Cardiovasc Imaging.* 2014;15(8):863-869.
95. Heckbert SR, Wiggins KL, Blackshear C, et al. Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis and Jackson Heart Study. *Obesity (Silver Spring).* 2017;25(6):1115-1121.
96. Rabkin SW. The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis. *Metab Syndr Relat Disord.* 2014;12(1):31-42.
97. Fernandez Munoz MJ, Basurto Acevedo L, Cordova Perez N, et al. Epicardial adipose tissue is associated with visceral fat, metabolic syndrome, and insulin resistance in menopausal women. *Rev Esp Cardiol (Engl Ed).* 2014;67(6):436-441.
98. Fox CS, White CC, Lohman K, et al. Genome-wide association of pericardial fat identifies a unique locus for ectopic fat. *PLoS Genet.* 2012;8(5):e1002705.
99. Chu AY, Deng X, Fisher VA, et al. Multiethnic genome-wide meta-analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. *Nat Genet.* 2017;49(1):125-130.
100. Lee JJ, Yin X, Hoffmann U, Fox CS, Benjamin EJ. Relation of pericardial fat, intrathoracic fat, and abdominal visceral fat with incident atrial fibrillation (from the Framingham Heart Study). *Am J Cardiol.* 2016;118(10):1486-1492.
101. Smith GD. Reflections on the limitations to epidemiology. *J Clin Epidemiol.* 2001;54(4):325-331.
102. Burgess S, Thompson SG. *Mendelian randomization: methods for using genetic variants in causal estimation.* 1st Edition. ed: CRC Press; 2015.
103. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature.* 2015;518(7538):197-206.
104. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature.* 2015;518(7538):187-196.
105. Graff M, Scott RA, Justice AE, et al. Genome-wide physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet.* 2017;13(4):e1006528.
106. Liu Y, Basty N, Whitcher B, et al. Genetic architecture of 11 organ traits derived from abdominal MRI using deep learning. *Elife.* 2021;10.
107. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ.* 2018;362:k601.
108. Chatterjee NA, Giulianini F, Geelhoed B, et al. Genetic obesity and the risk of atrial fibrillation: causal estimates from Mendelian randomization. *Circulation.* 2017;135(8):741-754.
109. Larsson SC, Back M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur Heart J.* 2020;41(2):221-226.
110. Wang Q, Richardson TG, Sanderson E, et al. A phenome-wide bidirectional Mendelian randomization analysis of atrial fibrillation. *Int J Epidemiol.* 2022:dyac041.

111. Burgess S, Thompson SG, Collaboration. GCG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol.* 2011;40(3):755-764.
112. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail.* 2013;1(2):93-102.
113. De Schutter A, Lavie CJ, Milani RV. The impact of obesity on risk factors and prevalence and prognosis of coronary heart disease-the obesity paradox. *Prog Cardiovasc Dis.* 2014;56(4):401-408.
114. Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, Zakopoulos N. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. *Hypertension.* 2005;45(4):602-607.
115. Holmberg MJ, Andersen LW. Collider bias. *JAMA.* 2022;327(13):1282-1283.
116. Kim SC, Liu J, Solomon DH. Risk of incident atrial fibrillation in gout: a cohort study. *Ann Rheum Dis.* 2016;75(8):1473-1478.
117. Kim SC, Liu J, Solomon DH. The risk of atrial fibrillation in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2014;73(6):1091-1095.
118. Schnabel RB, Kerr KF, Lubitz SA, et al. Large-scale candidate gene analysis in whites and African Americans identifies IL6R polymorphism in relation to atrial fibrillation: the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe) project. *Circ Cardiovasc Genet.* 2011;4(5):557-564.
119. Ferreira RC, Freitag DF, Cutler AJ, et al. Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. *PLoS Genet.* 2013;9(4):e1003444.
120. Rosa M, Chignon A, Li Z, et al. A Mendelian randomization study of IL6 signaling in cardiovascular diseases, immune-related disorders and longevity. *NPJ Genom Med.* 2019;4:23.
121. Marott SC, Nordestgaard BG, Zacho J, et al. Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population. *J Am Coll Cardiol.* 2010;56(10):789-795.
122. The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *The Lancet.* 2012;379(9822):1214-1224.
123. Luo L, Liu M. Adipose tissue in control of metabolism. *J Endocrinol.* 2016;231(3):R77-R99.
124. Teng MS, Hsu LA, Wu S, Chang HH, Chou HH, Ko YL. Association between C-reactive protein gene haplotypes and C-reactive protein levels in Taiwanese: interaction with obesity. *Atherosclerosis.* 2009;204(2):e64-69.
125. Timpson NJ, Nordestgaard BG, Harbord RM, et al. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. *Int J Obes (Lond).* 2011;35(2):300-308.
126. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science.* 1993;259(5091):87-91.
127. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA.* 1999;282(22):2131-2135.
128. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol.* 2022.
129. Zhou M, Wang H, Chen J, Zhao L. Epicardial adipose tissue and atrial fibrillation: Possible mechanisms, potential therapies, and future directions. *Pacing Clin Electrophysiol.* 2020;43(1):133-145.

130. Martin S, Tyrrell J, Thomas EL, et al. Disease consequences of higher adiposity uncoupled from its adverse metabolic effects using Mendelian randomisation. *Elife.* 2022;11:e72452.
131. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377(12):1119-1131.
132. National Institute for Health and Care Excellence. *Atrial fibrillation: diagnosis and management.* 2021.
133. Morley KI, Wallace J, Denaxas SC, et al. Defining disease phenotypes using national linked electronic health records: a case study of atrial fibrillation. *PLoS One.* 2014;9(11):e110900.
134. Kirchhof P, Schmalowsky J, Pittrow D, et al. Management of patients with atrial fibrillation by primary-care physicians in Germany: 1-year results of the ATRIUM registry. *Clin Cardiol.* 2014;37(5):277-284.
135. Cox JL, Parkash R, Foster GA, et al. Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF): A cluster randomized trial of a computerized clinical decision support tool. *Am Heart J.* 2020;224:35-46.
136. Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2014;167(5):735-742 e732.
137. UK Biobank. *UK Biobank ethics and governance framework.* 2007.
138. UK Biobank. Ethics advisory committee. https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/governance/ethics-advisory-committee. Published 2022. Accessed 30th December 2022.
139. UK Biobank. UK Biobank research ethics approval. https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics. Published 2021. Accessed 27th December 2022.
140. Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. *Health Policy and Technology.* 2012;1(3):123-126.
141. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol.* 2017;186(9):1026-1034.
142. UK Biobank. Reception. biobank.ndph.ox.ac.uk/ukb/ukb/docs/Reception.pdf. Published 2011. Accessed 30th December 2022.
143. UK Biobank. Touch screen questionnaire. https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=100247. Published 2011. Accessed 27th December 2022.
144. UK Biobank. Verbal interview stage. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Interview.pdf. Published 2012. Accessed 27th December 2022.
145. UK Biobank. Anthropometry. 2014. *Access date: 22nd July 2021.*http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Anthropometry.pdf.
146. UK Biobank. Blood sample collection, processing and transport. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Bloodsample.pdf. Published 2011. Accessed 30th December 2022.
147. UK Biobank. UK Biobank touch-screen questionnaire questions: final version. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/TouchscreenQuestionsMainFinal.pdf. Accessed 27th December 2022.
148. UK Biobank. Body Composition Measurement. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/body_composition.pdf. Published 2011. Accessed 27th December 2022.
149. UK Biobank. Biomarker assay quality procedures: approaches used to minimise systematic and random errors (and the wider epidemiological implications).

Version 1.2. https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/biomarker_issues.pdf. Published 2019. Accessed 30th December 2022.
150. Elliott P, Peakman TC, Biobank UK. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol.* 2008;37(2):234-244.
151. Welsh S. Genotyping of 500,000 UK Biobank participants. Description of sample processing workflow and preparation of DNA for genotyping. https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/ukb_dna_processing.pdf. Published 2017. Accessed 27th December 2022.
152. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature.* 2018;562(7726):203-209.
153. Genomes Project C, Auton A, Brooks LD, et al. A global reference for human genetic variation. *Nature.* 2015;526(7571):68-74.
154. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet.* 2016;48(10):1279-1283.
155. Huang J, Howie B, McCarthy S, et al. Improved imputation of low-frequency and rare variants using the UK10K haplotype reference panel. *Nat Commun.* 2015;6:8111.
156. UK Biobank. Hospital inpatient data, version 3.0. https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/HospitalEpisodeStatistics.pdf. Published 2020. Accessed 27th December 2022.
157. World Health Organisation. ICD-10 Version: 2019. https://icd.who.int/browse10/2019/en#/. Published 2019. Accessed 27th December 2022.
158. UK Biobank. Mortality data: linkage to death registries. Version 2.0. https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/DeathLinkage.pdf. Published 2020. Accessed 30th December 2022.
159. UK Biobank. Primary care linked data. https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf . Published 2019. Accessed.
160. NHS Digital. NHS UK Read codes. https://isd.digital.nhs.uk/trud/user/guest/group/0/pack/9. Published 2022. Accessed 30th December 2022.
161. UK Biobank. How to find us. https://www.ukbiobank.ac.uk/explore-your-participation/contribute-further/imaging-study/how-to-find-us. Published 2022. Accessed 30th December 2022.
162. UK Biobank. UK biobank imaging assessment visit information leaflet. https://www.ukbiobank.ac.uk/media/aj2iqv43/information-booklet_20pp-booklet_20-10-2022-002.pdf. Published 2022. Accessed 30th December 2022.
163. Cosio FG. Atrial flutter, typical and atypical: a review. *Arrhythm Electrophysiol Rev.* 2017;6(2):55-62.
164. Schnabel RB, Aspelund T, Li G, et al. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med.* 2010;170(21):1909-1917.
165. Broad Institute. GIANT consortium. https://portals.broadinstitute.org/collaboration/giant/index.php/Main_Page. Published 2019. Accessed 30th December 2022.
166. Broad Institute. GIANT consortium data files. https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Published 2022. Accessed 30th December 2022.
167. Christophersen IE, Rienstra M, Roselli C, et al. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet.* 2017;49(6):946-952.

168. Lubitz SA, Lunetta KL, Lin H, et al. Novel genetic markers associate with atrial fibrillation risk in Europeans and Japanese. *J Am Coll Cardiol.* 2014;63(12):1200-1210.
169. Roselli C, Chaffin MD, Weng LC, et al. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet.* 2018;50(9):1225-1233.
170. Genomes Project C, Abecasis GR, Altshuler D, et al. A map of human genome variation from population-scale sequencing. *Nature.* 2010;467(7319):1061-1073.
171. AMP Accelerating Medicines Partnership. CMDKP downloads. https://hugeamp.org/downloads.html. Published 2022. Accessed 29th December 2022.
172. FinnGen Consortium. About us. https://www.finngen.fi/en/node/17. Published 2022. Accessed 29th December 2022.
173. Kurki MI, Karjalainen J, Palta P, et al. FinnGen: unique genetic insights from combining isolated population and national health register data. *medRxiv.* 2022.
174. FinnGen. Release 7 participanting biobanks/cohorts. https://finngen.gitbook.io/documentation/v/r7/methods/cohort-description. Published 2021. Accessed 30th December 2022.
175. FinnGen Consortium. FinnGen Release 7 data. https://r7.finngen.fi/pheno/I9_AF. Published 2021. Accessed.
176. Sinnott-Armstrong N, Tanigawa Y, Amar D, et al. Genetics of 35 blood and urine biomarkers in the UK Biobank. *Nat Genet.* 2021;53(2):185-194.
177. FinnGen. Release 7 endpoints. https://finngen.gitbook.io/documentation/v/r7/methods/endpoints. Published 2021. Accessed 30th December 2022.
178. FinnGen. Release 7 genotype data. https://finngen.gitbook.io/documentation/v/r7/methods/genotype-imputation/genotype-data. Published 2021. Accessed 30th December 2022.
179. Shim H, Chasman DI, Smith JD, et al. A multivariate genome-wide association analysis of 10 LDL subfractions, and their response to statin treatment, in 1868 Caucasians. *PLoS One.* 2015;10(4):e0120758.
180. Li B, Martin EB. An approximation to the F distribution using the chi-square distribution. *Computational Statistics & Data Analysis.* 2002;40(1):21-26.
181. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol.* 2000;29(4):722-729.
182. Burgess S, Foley CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. *Nat Commun.* 2020;11(1):376.
183. Nitsch D, Molokhia M, Smeeth L, DeStavola BL, Whittaker JC, Leon DA. Limits to causal inference based on Mendelian randomization: a comparison with randomized controlled trials. *Am J Epidemiol.* 2006;163(5):397-403.
184. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol.* 2016;40(4):304-314.
185. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol.* 2017;46(6):1985-1998.
186. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015;44(2):512-525.
187. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* 2018;50(5):693-698.
188. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol.* 2017;46(6):1734-1739.

189. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics.* 2015;31(21):3555-3557.
190. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software.* 2010;36(3):1-48.
191. Frost L, Benjamin EJ, Fenger-Gron M, Pedersen A, Tjonneland A, Overvad K. Body fat, body fat distribution, lean body mass and atrial fibrillation and flutter. A Danish cohort study. *Obesity (Silver Spring).* 2014;22(6):1546-1552.
192. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
193. Conner SC, Lodi S, Lunetta KL, et al. Refining the association between body mass index and atrial fibrillation: G-formula and restricted mean survival times. *J Am Heart Assoc.* 2019;8(16):e013011.
194. Liu L, Liu X, Ding X, Chen H, Li H. Body mass index and new-onset atrial fibrillation in patients with acute myocardial infarction. *Int J Gen Med.* 2022;15:5717-5728.
195. Baek YS, Yang PS, Kim TH, et al. Associations of abdominal obesity and new-onset atrial fibrillation in the general population. *J Am Heart Assoc.* 2017;6(6):e004705.
196. Senoo K, Nakata M, Teramukai S, et al. Relationship between body mass index and incidence of atrial fibrillation in young japanese men - the Nishimura Health Survey. *Circ J.* 2021;85(3):243-251.
197. Neefs J, Boekholdt SM, Khaw KT, et al. Body mass index and body fat distribution and new-onset atrial fibrillation: Substudy of the European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) study. *Nutr Metab Cardiovasc Dis.* 2019;29(7):692-700.
198. Haase CL, Eriksen KT, Lopes S, Satylganova A, Schnecke V, McEwan P. Body mass index and risk of obesity-related conditions in a cohort of 2.9 million people: Evidence from a UK primary care database. *Obes Sci Pract.* 2021;7(2):137-147.
199. Zethelius B, Gudbjornsdottir S, Eliasson B, Eeg-Olofsson K, Svensson AM, Cederholm J. Risk factors for atrial fibrillation in type 2 diabetes: report from the Swedish National Diabetes Register (NDR). *Diabetologia.* 2015;58(10):2259-2268.
200. Zhao M, Song L, Zhao Q, et al. Elevated levels of body mass index and waist circumference, but not high variability, are associated with an increased risk of atrial fibrillation. *BMC Med.* 2022;20(1):215.
201. Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V, Million Women Study Collaborators. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. *BMC Med.* 2014;12:45.
202. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Med.* 2005;118(5):489-495.
203. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). *Eur Heart J.* 2006;27(1):96-106.
204. Hamada R, Lee JS, Mori K, Watanabe E, Muto S. Influence of abdominal obesity and habitual behaviors on incident atrial fibrillation in Japanese. *J Cardiol.* 2018;71(2):118-124.
205. Kang SH, Choi EK, Han KD, et al. Underweight is a risk factor for atrial fibrillation: A nationwide population-based study. *Int J Cardiol.* 2016;215:449-456.
206. Johansson C, Lind MM, Eriksson M, Johansson L. Weight, height, weight change, and risk of incident atrial fibrillation in middle-aged men and women. *J Arrhythm.* 2020;36(6):974-981.

207. Zia I, Johnson L, Memarian E, Borne Y, Engstrom G. Anthropometric measures and the risk of developing atrial fibrillation: a Swedish Cohort Study. *BMC Cardiovasc Disord.* 2021;21(1):602.
208. Knuiman M, Briffa T, Divitini M, et al. A cohort study examination of established and emerging risk factors for atrial fibrillation: the Busselton Health Study. *Eur J Epidemiol.* 2014;29(3):181-190.
209. Ardissino M, Reddy RK, Slob EAW, et al. Sleep disordered breathing, obesity and atrial fibrillation: a Mendelian randomisation study. *Genes (Basel).* 2022;13(1):104.
210. Lai FY, Nath M, Hamby SE, Thompson JR, Nelson CP, Samani NJ. Adult height and risk of 50 diseases: a combined epidemiological and genetic analysis. *BMC Med.* 2018;16(1):187.
211. Rosengren A, Hauptman PJ, Lappas G, Olsson L, Wilhelmsen L, Swedberg K. Big men and atrial fibrillation: effects of body size and weight gain on risk of atrial fibrillation in men. *Eur Heart J.* 2009;30(9):1113-1120.
212. Park YM, Moon J, Hwang IC, Lim H, Cho B. Height is associated with incident atrial fibrillation in a large Asian cohort. *Int J Cardiol.* 2020;304:82-84.
213. Rosenberg MA, Patton KK, Sotoodehnia N, et al. The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study. *Eur Heart J.* 2012;33(21):2709-2717.
214. Bose A, O'Neal WT, Wu C, et al. Sex differences in risk factors for incident atrial fibrillation (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol.* 2019;123(9):1453-1457.
215. Levin MG, Judy R, Gill D, et al. Genetics of height and risk of atrial fibrillation: A Mendelian randomization study. *PLoS Med.* 2020;17(10):e1003288.
216. Raghavan S, Huang J, Tcheandjieu C, et al. A multi-population phenome-wide association study of genetically-predicted height in the Million Veteran Program. *PLoS Genet.* 2022;18(6):e1010193.
217. Nystrom PK, Carlsson AC, Leander K, de Faire U, Hellenius ML, Gigante B. Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. *PLoS One.* 2015;10(5):e0127111.
218. Bundy JD, Heckbert SR, Chen LY, Lloyd-Jones DM, Greenland P. Evaluation of risk prediction models of atrial fibrillation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol.* 2020;125(1):55-62.
219. Austin TR, Wiggins KL, Blackshear C, et al. Atrial fibrillation in an African-American cohort: the Jackson Heart Study. *Clin Cardiol.* 2018;41(8):1049-1054.
220. Alonso A, Roetker NS, Soliman EZ, Chen LY, Greenland P, Heckbert SR. Prediction of atrial fibrillation in a racially diverse cohort: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc.* 2016;5(2):e003077.
221. Conen D, Glynn RJ, Sandhu RK, Tedrow UB, Albert CM. Risk factors for incident atrial fibrillation with and without left atrial enlargement in women. *Int J Cardiol.* 2013;168(3):1894-1899.
222. Worm MS, Bager CL, Blair JPM, et al. Atrial fibrillation is associated with lean body mass in postmenopausal women. *Sci Rep.* 2020;10(1):573.
223. Andersen K, Rasmussen F, Neovius M, Tynelius P, Sundstrom J. Body size and risk of atrial fibrillation: a cohort study of 1.1 million young men. *J Intern Med.* 2018;283(4):346-355.
224. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. *J Intern Med.* 2001;250(5):382-389.
225. Verdecchia P, Dagenais G, Healey J, et al. Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant

subjects with cardiovascular Disease studies. *J Hypertens.* 2012;30(5):1004-1014.
226. Camm CF, Lacey B, Massa MS, et al. Independent effects of adiposity measures on risk of atrial fibrillation in men and women: a study of 0.5 million individuals. *Int J Epidemiol.* 2022;51(3):984-995.
227. Zeng H, Lin C, Wang S, Zheng Y, Gao X. Genetically predicted body composition in relation to cardiometabolic traits: a Mendelian randomization study. *Eur J Epidemiol.* 2021;36(11):1157-1168.
228. Rask-Andersen M, Karlsson T, Ek WE, Johansson A. Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. *Nat Commun.* 2019;10(1):339.
229. Wong CX, Mahajan R, Pathak R, D JT, Sanders P. The Role of pericardial and epicardial fat in atrial fibrillation pathophysiology and ablation outcomes. *J Atr Fibrillation.* 2013;5(5):790.
230. Bos D, Vernooij MW, Shahzad R, et al. Epicardial fat volume and the risk of atrial fibrillation in the general population free of cardiovascular disease. *JACC Cardiovasc Imaging.* 2017;10(11):1405-1407.
231. Nakanishi K, Fukuda S, Tanaka A, et al. Peri-atrial epicardial adipose tissue is associated with new-onset nonvalvular atrial fibrillation. *Circ J.* 2012;76(12):2748-2754.
232. Lai YH, Liu LY, Sung KT, et al. Diverse adiposity and atrio-ventricular dysfunction across obesity phenotypes: implication of epicardial fat analysis. *Diagnostics (Basel).* 2021;11(3):408.
233. Long MT, Yin X, Larson MG, et al. Relations of liver fat with prevalent and incident atrial fibrillation in the Framingham Heart Study. *J Am Heart Assoc.* 2017;6(5):e005227.
234. Huang Y, Liu Y, Ma Y, et al. Associations of visceral adipose tissue, circulating protein biomarkers, and risk of cardiovascular diseases: a Mendelian randomization analysis. *Front Cell Dev Biol.* 2022;10:840866.
235. Karlsson T, Rask-Andersen M, Pan G, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med.* 2019;25(9):1390-1395.
236. Bays H, Pi-Sunyer X, Hemmingsson JU, Claudius B, Jensen CB, Van Gaal L. Liraglutide 3.0 mg for weight management: weight-loss dependent and independent effects. *Curr Med Res Opin.* 2017;33(2):225-229.
237. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol.* 1994;73(7):460-468.
238. Whalley G, Gamble G, Walksh H, et al. Echocardiographic left atrial volumes are optimally indexed to lean body mass to adjust for differences in body size. *Heart, Lung, and Circulation.* 2008;17S:S45.
239. Bella JN, Devereux RB, Roman MJ, et al. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. *Circulation.* 1998;98(23):2538-2544.
240. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: A meta-analysis. *J Cardiovasc Electrophysiol.* 2018;29(5):725-732.
241. Liu X, Guo L, Xiao K, et al. The obesity paradox for outcomes in atrial fibrillation: evidence from an exposure-effect analysis of prospective studies. *Obes Rev.* 2020;21(3):e12970.
242. Malden D, Lacey B, Emberson J, et al. Body fat distribution and systolic blood pressure in 10,000 adults with whole-body imaging: UK Biobank and Oxford BioBank. *Obesity (Silver Spring).* 2019;27(7):1200-1206.

243. Friedl KE, Moore RJ, Martinez-Lopez LE, et al. Lower limit of body fat in healthy active men. *J Appl Physiol (1985).* 1994;77(2):933-940.
244. Yousaf S, Bonsall A. UK Townsend deprivation scores from 2011 census data. *Access Date: 22nd July 2021.* 2017;http://s3-eu-west-1.amazonaws.com/statistics.digitalresources.jisc.ac.uk/dkan/files/Townsend_Deprivation_Scores/UK%20Townsend%20Deprivation%20Scores%20from%202011%20census%20data.pdf.
245. Plummer M. Improved estimates of floating absolute risk. *Stat Med.* 2004;23(1):93-104.
246. Clarke R, Emberson JR, Breeze E, et al. Biomarkers of inflammation predict both vascular and non-vascular mortality in older men. *Eur Heart J.* 2008;29(6):800-809.
247. Suetta C, Haddock B, Alcazar J, et al. The Copenhagen Sarcopenia Study: lean mass, strength, power, and physical function in a Danish cohort aged 20-93 years. *J Cachexia Sarcopenia Muscle.* 2019;10(6):1316-1329.
248. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr.* 2017;8(3):511-519.
249. Rothberg AE, McEwen LN, Kraftson AT, et al. Impact of weight loss on waist circumference and the components of the metabolic syndrome. *BMJ Open Diabetes Res Care.* 2017;5(1):e000341.
250. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med.* 2009;360(9):859-873.
251. Han TS, Richmond P, Avenell A, Lean ME. Waist circumference reduction and cardiovascular benefits during weight loss in women. *Int J Obes Relat Metab Disord.* 1997;21(2):127-134.
252. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994;271(11):840-844.
253. Hasebe H, Yoshida K, Nogami A, Ieda M. Difference in epicardial adipose tissue distribution between paroxysmal atrial fibrillation and coronary artery disease. *Heart Vessels.* 2020;35(8):1070-1078.
254. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol.* 2018;71(20):2360-2372.
255. Sarin S, Wenger C, Marwaha A, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am J Cardiol.* 2008;102(6):767-771.
256. Cheng VY, Dey D, Tamarappoo B, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging.* 2010;3(4):352-360.
257. Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur Heart J.* 2017;38(17):1294-1302.
258. Dey D, Suzuki Y, Suzuki S, et al. Automated quantitation of pericardiac fat from noncontrast CT. *Invest Radiol.* 2008;43(2):145-153.
259. Ng ACT, Strudwick M, van der Geest RJ, et al. Impact of epicardial adipose tissue, left ventricular myocardial fat content, and interstitial fibrosis on myocardial contractile function. *Circ Cardiovasc Imaging.* 2018;11(8):e007372.
260. Daude P, Ancel P, Confort Gouny S, et al. Deep-learning segmentation of epicardial adipose tissue using four-chamber cardiac magnetic resonance imaging. *Diagnostics (Basel).* 2022;12(1):126.
261. Ardissino M, McCracken C, Bard A, et al. Pericardial adiposity is independently linked to adverse cardiovascular phenotypes: a CMR study of 42 598 UK Biobank participants. *Eur Heart J Cardiovasc Imaging.* 2022.

262. Raisi-Estabragh Z, Harvey NC, Neubauer S, Petersen SE. Cardiovascular magnetic resonance imaging in the UK Biobank: a major international health research resource. *Eur Heart J Cardiovasc Imaging.* 2021;22(3):251-258.
263. Petersen SE, Matthews PM, Bamberg F, et al. Imaging in population science: cardiovascular magnetic resonance in 100,000 participants of UK Biobank - rationale, challenges and approaches. *J Cardiovasc Magn Reson.* 2013;15:46.
264. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson.* 2017;19(1):18.
265. Teme T, Sayegh B, Syed M, Wilber D, Bakhos L, Rabbat M. Quantification of epicardial fat volume using cardiovascular magnetic resonance imaging. *J Cardiovasc Magn Reson.* 2014;16(Suppl 1):O112.
266. Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging.* 2004;17(3):205-216.
267. UK Biobank. *Imaging modality cardiovascular magnetic resonance (CMR).* 2015.
268. Piechnik SK, Ferreira VM, Dall'Armellina E, et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. *J Cardiovasc Magn Reson.* 2010;12:69.
269. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2012;14:42.
270. Ferreira VM, Wijesurendra RS, Liu A, et al. Systolic ShMOLLI myocardial T1-mapping for improved robustness to partial-volume effects and applications in tachyarrhythmias. *J Cardiovasc Magn Reson.* 2015;17:77.
271. Teixeira T, Hafyane T, Stikov N, Akdeniz C, Greiser A, Friedrich MG. Comparison of different cardiovascular magnetic resonance sequences for native myocardial T1 mapping at 3T. *J Cardiovasc Magn Reson.* 2016;18(1):65.
272. Wijesurendra R, Liu A, Casadei B, et al. Systolic ShMOLLI T1-mapping is feasible in tachyarrhythmia, with improved image quality compared to diastolic readout. *J Cardiovasc Magn Reson.* 2015;17(Suppl 1):Q5.
273. Germain P, El Ghannudi S, Jeung MY, et al. Native T1 mapping of the heart - a pictorial review. *Clin Med Insights Cardiol.* 2014;8(Suppl 4):1-11.
274. Garnov N, Linder N, Schaudinn A, et al. Comparison of T1 relaxation times in adipose tissue of severely obese patients and healthy lean subjects measured by 1.5 T MRI. *NMR Biomed.* 2014;27(9):1123-1128.
275. Ferreira VM, Holloway CJ, Piechnik SK, Karamitsos TD, Neubauer S. Is it really fat? Ask a T1-map. *Eur Heart J Cardiovasc Imaging.* 2013;14(11):1060.
276. Yuan J, Madore B, Panych LP. Fat-water selective excitation in balanced steady-state free precession using short spatial-spectral RF pulses. *J Magn Reson.* 2011;208(2):219-224.
277. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 mapping: basic techniques and clinical applications. *JACC Cardiovasc Imaging.* 2016;9(1):67-81.
278. Sadouni M, Boldeanu I, Durand M, et al. Quantification of epicardial fat using non contrast cardiac CT in an HIV population: Reproducibility and association with other body fat indices. *Eur J Radiol Open.* 2021;8:100317.
279. Milanese G, Silva M, Bruno L, et al. Quantification of epicardial fat with cardiac CT angiography and association with cardiovascular risk factors in symptomatic patients: from the ALTER-BIO (Alternative Cardiovascular Bio-Imaging markers) registry. *Diagn Interv Radiol.* 2019;25(1):35-41.
280. van Woerden G, van Veldhuisen DJ, Gorter TM, et al. Importance of epicardial adipose tissue localization using cardiac magnetic resonance imaging in patients

with heart failure with mid-range and preserved ejection fraction. *Clin Cardiol.* 2021;44(7):987-993.
281. Saura D, Oliva MJ, Rodriguez D, et al. Reproducibility of echocardiographic measurements of epicardial fat thickness. *Int J Cardiol.* 2010;141(3):311-313.
282. Rosmini S, Seraphim A, Knott K, et al. Non-invasive characterization of pleural and pericardial effusions using T1 mapping by magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging.* 2022;23(8):1117-1126.
283. Morseth B, Geelhoed B, Linneberg A, et al. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart.* 2021;8(2):e001624.
284. Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation.* 2008;117(5):605-613.
285. Nakanishi K, Fukuda S, Tanaka A, Otsuka K, Taguchi H, Shimada K. Relationships between periventricular epicardial adipose tissue accumulation, coronary microcirculation, and left ventricular diastolic dysfunction. *Can J Cardiol.* 2017;33(11):1489-1497.
286. Mahabadi AA, Reinsch N, Lehmann N, et al. Association of pericoronary fat volume with atherosclerotic plaque burden in the underlying coronary artery: a segment analysis. *Atherosclerosis.* 2010;211(1):195-199.
287. Gaborit B, Venteclef N, Ancel P, et al. Human epicardial adipose tissue has a specific transcriptomic signature depending on its anatomical peri-atrial, peri-ventricular, or peri-coronary location. *Cardiovasc Res.* 2015;108(1):62-73.
288. Yong HS, Kim EJ, Seo HS, et al. Pericardial fat is more abundant in patients with coronary atherosclerosis and even in the non-obese patients: evaluation with cardiac CT angiography. *Int J Cardiovasc Imaging.* 2010;26 Suppl 1:53-62.
289. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med.* 2005;2(10):536-543.
290. Bertaso AG, Bertol D, Duncan BB, Foppa M. Epicardial fat: definition, measurements and systematic review of main outcomes. *Arq Bras Cardiol.* 2013;101(1):e18-28.
291. Hirata Y, Kurobe H, Akaike M, et al. Enhanced inflammation in epicardial fat in patients with coronary artery disease. *Int Heart J.* 2011;52(3):139-142.
292. Baker AR, Silva NF, Quinn DW, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol.* 2006;5:1.
293. Yudkin JS, Eringa E, Stehouwer CD. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet.* 2005;365(9473):1817-1820.
294. Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis.* 2007;17(4):319-326.
295. Mahabadi AA, Berg MH, Lehmann N, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol.* 2013;61(13):1388-1395.
296. Ma R, van Assen M, Ties D, et al. Focal pericoronary adipose tissue attenuation is related to plaque presence, plaque type, and stenosis severity in coronary CTA. *Eur Radiol.* 2021;31(10):7251-7261.
297. Kluner LV, Oikonomou EK, Antoniades C. Assessing Cardiovascular Risk by Using the Fat Attenuation Index in Coronary CT Angiography. *Radiol Cardiothorac Imaging.* 2021;3(1):e200563.

298. UK Biobank. Body (abdominal) MRI scan. https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/body_mri_explan.pdf. Published 2015. Accessed 23rd September 2022.
299. Linge J, Borga M, West J, et al. Body composition profiling in the UK Biobank imaging study. *Obesity (Silver Spring).* 2018;26(11):1785-1795.
300. Borga M, Thomas EL, Romu T, et al. Validation of a fast method for quantification of intra-abdominal and subcutaneous adipose tissue for large-scale human studies. *NMR Biomed.* 2015;28(12):1747-1753.
301. Borga M, West J, Bell JD, et al. Advanced body composition assessment: from body mass index to body composition profiling. *J Investig Med.* 2018;66(5):1-9.
302. *powerSurvEpi: Power and sample size calculation for survival analysis of epidemiological studies* [computer program]. Version 0.1.32022.
303. Moore CM, Jacobson SA, Fingerlin TE. Power and sample size calculations for genetic association studies in the presence of genetic model misspecification. *Hum Hered.* 2019;84(6):256-271.
304. Neale Lab. Neale Lab GWAS Results (Round 2). http://www.nealelab.is/uk-biobank. Published 2018. Accessed 4th July 2022.
305. Abraham TM, Pedley A, Massaro JM, Hoffmann U, Fox CS. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. *Circulation.* 2015;132(17):1639-1647.
306. Lee JJ, Pedley A, Hoffmann U, Massaro JM, Fox CS. Association of changes in abdominal fat quantity and quality with incident cardiovascular disease risk factors. *J Am Coll Cardiol.* 2016;68(14):1509-1521.
307. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010;42(11):937-948.
308. Nakamori S, Nezafat M, Ngo LH, Manning WJ, Nezafat R. Left atrial epicardial fat volume is associated with atrial fibrillation: a prospective cardiovascular magnetic resonance 3D dixon study. *J Am Heart Assoc.* 2018;7(6).
309. Willemink MJ, Koszek WA, Hardell C, et al. Preparing medical imaging data for machine learning. *Radiology.* 2020;295(1):4-15.
310. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol.* 2015;181(4):251-260.
311. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol.* 2013;42(5):1497-1501.
312. Kember RL, Levin MG, Cousminer DL, et al. Genetically determined birthweight associates with atrial fibrillation: a Mendelian randomization study. *Circ Genom Precis Med.* 2020;13(3):e002553.
313. Power GM, Tyrrell J, Frayling TM, Davey Smith G, Richardson TG. Mendelian randomization analyses suggest childhood body size indirectly influences end points from across the cardiovascular disease spectrum through adult body size. *J Am Heart Assoc.* 2021;10(17):e021503.
314. Lind L, Ingelsson M, Sundstrom J, Arnlov J. Impact of risk factors for major cardiovascular diseases: a comparison of life-time observational and Mendelian randomisation findings. *Open Heart.* 2021;8(2):e001735.
315. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol.* 2016;40(7):597-608.
316. Minelli C, Del Greco MF, van der Plaat DA, Bowden J, Sheehan NA, Thompson J. The use of two-sample methods for Mendelian randomization analyses on single large datasets. *Int J Epidemiol.* 2021;50(5):1651-1659.
317. Iwasaki YK, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: implications for management. *Circulation.* 2011;124(20):2264-2274.

318. Chen SK, Barbhaiya M, Solomon DH, et al. Atrial fibrillation/flutter hospitalizations among US Medicaid recipients with and without systemic lupus erythematosus. *J Rheumatol.* 2020;47(9):1359-1365.
319. Nielsen JB, Thorolfsdottir RB, Fritsche LG, et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet.* 2018;50(9):1234-1239.
320. Schnabel RB, Larson MG, Yamamoto JF, et al. Relation of multiple inflammatory biomarkers to incident atrial fibrillation. *Am J Cardiol.* 2009;104(1):92-96.
321. Amdur RL, Mukherjee M, Go A, et al. Interleukin-6 is a risk factor for atrial fibrillation in chronic kidney disease: findings from the CRIC study. *PLoS One.* 2016;11(2):e0148189.
322. Li X, Peng S, Wu X, et al. C-reactive protein and atrial fibrillation: Insights from epidemiological and Mendelian randomization studies. *Nutr Metab Cardiovasc Dis.* 2022;32(6):1519-1527.
323. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci.* 2013;9(2):191-200.
324. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol.* 2021;320(3):C375-C391.
325. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest.* 2003;112(12):1821-1830.
326. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab.* 1997;82(12):4196-4200.
327. Hempen M, Kopp HP, Elhenicky M, et al. YKL-40 is elevated in morbidly obese patients and declines after weight loss. *Obes Surg.* 2009;19(11):1557-1563.
328. Fruhbeck G, Catalan V, Ramirez B, et al. Serum levels of IL-1 RA increase with obesity and type 2 diabetes in relation to adipose tissue dysfunction and are reduced after bariatric surgery in parallel to adiposity. *J Inflamm Res.* 2022;15:1331-1345.
329. Gan L, Guo K, Cremona ML, McGraw TE, Leibel RL, Zhang Y. TNF-alpha up-regulates protein level and cell surface expression of the leptin receptor by stimulating its export via a PKC-dependent mechanism. *Endocrinology.* 2012;153(12):5821-5833.
330. Grunfeld C, Zhao C, Fuller J, et al. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *J Clin Invest.* 1996;97(9):2152-2157.
331. Yuan M, Wu B, Zhang L, Wang H, Yang Y. CD40L/CD40 regulates adipokines and cytokines by H3K4me3 modification in epicardial adipocytes. *J Cardiovasc Pharmacol.* 2021;78(2):228-234.
332. Yuan G, Chen X, Ma Q, et al. C-reactive protein inhibits adiponectin gene expression and secretion in 3T3-L1 adipocytes. *J Endocrinol.* 2007;194(2):275-281.
333. C Reactive Protein Coronary Heart Disease Genetics Collaboration, Wensley F, Gao P, et al. Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. *BMJ.* 2011;342:d548.
334. Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. *Int J Cardiol.* 2013;169(1):62-72.
335. Szekely Y, Arbel Y. A review of interleukin-1 in heart disease: where do we stand today? *Cardiol Ther.* 2018;7(1):25-44.
336. Zhou X, Dudley SC, Jr. Evidence for inflammation as a driver of atrial fibrillation. *Front Cardiovasc Med.* 2020;7:62.

337. Marott SC, Benn M, Johansen JS, Jensen GB, Tybjaerg-Hansen A, Nordestgaard BG. YKL-40 levels and atrial fibrillation in the general population. *Int J Cardiol.* 2013;167(4):1354-1359.
338. Szalai AJ, van Ginkel FW, Dalrymple SA, Murray R, McGhee JR, Volanakis JE. Testosterone and IL-6 requirements for human C-reactive protein gene expression in transgenic mice. *J Immunol.* 1998;160(11):5294-5299.
339. Weinhold B, Bader A, Poli V, Ruther U. Interleukin-6 is necessary, but not sufficient, for induction of the humanC-reactive protein gene in vivo. *Biochem J.* 1997;325 (Pt 3):617-621.
340. Said S, Pazoki R, Karhunen V, et al. Genetic analysis of over half a million people characterises C-reactive protein loci. *Nat Commun.* 2022;13(1):2198.
341. Fry D, Almond R, Moffat S, Gordon M, Singh P. UK Biobank Biomarker Project: companion document to accompany serum biomarker data. https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/serum_biochemistry.pdf. Published 2019. Accessed 31st December 2022.
342. Kennedy E, Niedzwiedz CL. The association of anxiety and stress-related disorders with C-reactive protein (CRP) within UK Biobank. *Brain Behav Immun Health.* 2022;19:100410.
343. Folkersen L, Gustafsson S, Wang Q, et al. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. *Nat Metab.* 2020;2(10):1135-1148.
344. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986;51(6):1173-1182.
345. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ.* 1995;310(6973):170.
346. Hingorani AD, Shah T, Casas JP, Humphries SE, Talmud PJ. C-reactive protein and coronary heart disease: predictive test or therapeutic target? *Clin Chem.* 2009;55(2):239-255.
347. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation.* 2003;108(24):3006-3010.
348. Thorand B, Lowel H, Schneider A, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. *Arch Intern Med.* 2003;163(1):93-99.
349. Georgakis MK, Malik R, Gill D, et al. Interleukin-6 signaling effects on ischemic stroke and other cardiovascular outcomes: a Mendelian randomization study. *Circ Genom Precis Med.* 2020;13(3):e002872.
350. Garbers C, Monhasery N, Aparicio-Siegmund S, et al. The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases. *Biochim Biophys Acta.* 2014;1842(9):1485-1494.
351. Venkiteshwaran A. Tocilizumab. *MAbs.* 2009;1(5):432-438.
352. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis.* 2010;69(1):88-96.
353. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 2006;54(9):2817-2829.
354. Henningsen KM, Therkelsen SK, Johansen JS, Bruunsgaard H, Svendsen JH. Plasma YKL-40, a new biomarker for atrial fibrillation? *Europace.* 2009;11(8):1032-1036.
355. Kastrup J, Johansen JS, Winkel P, et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. *Eur Heart J.* 2009;30(9):1066-1072.

356. Tizaoui K, Yang JW, Lee KH, et al. The role of YKL-40 in the pathogenesis of autoimmune diseases: a comprehensive review. *Int J Biol Sci.* 2022;18(9):3731-3746.
357. Kjaergaard AD, Johansen JS, Bojesen SE, Nordestgaard BG. Observationally and genetically high YKL-40 and risk of venous thromboembolism in the general population: cohort and Mendelian randomization studies. *Arterioscler Thromb Vasc Biol.* 2016;36(5):1030-1036.
358. Ismail H, Helby J, Holmich LR, et al. Measured and genetically predicted plasma YKL-40 levels and melanoma mortality. *Eur J Cancer.* 2019;121:74-84.
359. Chatzigeorgiou A, Lyberi M, Chatzilymperis G, Nezos A, Kamper E. CD40/CD40L signaling and its implication in health and disease. *Biofactors.* 2009;35(6):474-483.
360. Ferrari S, Giliani S, Insalaco A, et al. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. *Proc Natl Acad Sci U S A.* 2001;98(22):12614-12619.
361. Tone M, Tone Y, Fairchild PJ, Wykes M, Waldmann H. Regulation of CD40 function by its isoforms generated through alternative splicing. *Proc Natl Acad Sci U S A.* 2001;98(4):1751-1756.
362. Chen L, Peters JE, Prins B, et al. Systematic Mendelian randomization using the human plasma proteome to discover potential therapeutic targets for stroke. *Nat Commun.* 2022;13(1):6143.
363. Fisher BA, Szanto A, Ng W-F, et al. Assessment of the anti-CD40 antibody iscalimab in patients with primary Sjögren's syndrome: a multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study. *The Lancet Rheumatology.* 2020;2(3):e142-e152.
364. Lear SA, Chen MM, Birmingham CL, Frohlich JJ. The relationship between simple anthropometric indices and C-reactive protein: ethnic and gender differences. *Metabolism.* 2003;52(12):1542-1546.
365. Kim T, Ganocy SJ, Antonelli M, Einstadter D, Ballou S. Association of CRP with BMI in males and females [abstract]. *Athritis Rheumatol.* 2017;69.
366. Khera A, Vega GL, Das SR, et al. Sex differences in the relationship between C-reactive protein and body fat. *J Clin Endocrinol Metab.* 2009;94(9):3251-3258.
367. Ligthart S, Vaez A, Vosa U, et al. Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *Am J Hum Genet.* 2018;103(5):691-706.
368. Williams BA, Chamberlain AM, Blankenship JC, Hylek EM, Voyce S. Trends in atrial fibrillation incidence rates within an integrated health care delivery system, 2006 to 2018. *JAMA Netw Open.* 2020;3(8):e2014874.
369. All of Us Research Program I, Denny JC, Rutter JL, et al. The "All of Us" research program. *N Engl J Med.* 2019;381(7):668-676.
370. Littlejohns TJ, Sudlow C, Allen NE, Collins R. UK Biobank: opportunities for cardiovascular research. *Eur Heart J.* 2019;40(14):1158-1166.
371. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol.* 2016;70:214-223.
372. Naccarelli GV, Johnston SS, Dalal M, Lin J, Patel PP. Rates and implications for hospitalization of patients >/=65 years of age with atrial fibrillation/flutter. *Am J Cardiol.* 2012;109(4):543-549.
373. Stewart S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986--1996. *Eur Heart J.* 2001;22(8):693-701.
374. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation.* 2003;108(6):711-716.

375. O'Halloran R, Mihaylova B, Cairns BJ, Kent S. BMI and cause-specific hospital admissions and costs: the UK Biobank cohort study. *Obesity (Silver Spring).* 2020;28(7):1332-1341.
376. Cameron KA, Song J, Manheim LM, Dunlop DD. Gender disparities in health and healthcare use among older adults. *J Womens Health (Larchmt).* 2010;19(9):1643-1650.
377. Marcusson J, Nord M, Dong HJ, Lyth J. Clinically useful prediction of hospital admissions in an older population. *BMC Geriatr.* 2020;20(1):95.
378. Meyre P, Aeschbacher S, Blum S, et al. The Admit-AF risk score: A clinical risk score for predicting hospital admissions in patients with atrial fibrillation. *Eur J Prev Cardiol.* 2020:2047487320915350.
379. Peng M, Southern DA, Williamson T, Quan H. Under-coding of secondary conditions in coded hospital health data: Impact of co-existing conditions, death status and number of codes in a record. *Health Informatics J.* 2017;23(4):260-267.
380. Nouraei SA, Virk JS, Hudovsky A, Wathen C, Darzi A, Parsons D. Accuracy of clinician-clinical coder information handover following acute medical admissions: implication for using administrative datasets in clinical outcomes management. *J Public Health (Oxf).* 2016;38(2):352-362.
381. Robinson D, Schulz E, Brown P, Price C. Updating the Read Codes: user-interactive maintenance of a dynamic clinical vocabulary. *J Am Med Inform Assoc.* 1997;4(6):465-472.
382. Townsend P. Deprivation. *Journal of Social Policy.* 2009;16(2):125-146.
383. Dinnes J, Deeks J, Kirby J, Roderick P. A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy. *Health Technol Assess.* 2005;9(12):1-113, iii.
384. Wood A, Denholm R, Hollings S, et al. Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: data resource. *BMJ.* 2021;373:n826.
385. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ.* 2013;346:f2350.
386. Delgado-Rodriguez M, Llorca J. Bias. *J Epidemiol Community Health.* 2004;58(8):635-641.
387. Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. *J Natl Cancer Inst.* 2013;105(19):1456-1462.
388. Sun J, Ludvigsson JF, Ingre C, et al. Hospital-treated infections in early- and mid-life and risk of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis: A nationwide nested case-control study in Sweden. *PLoS Med.* 2022;19(9):e1004092.
389. Sgreccia D, Manicardi M, Malavasi VL, et al. Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients. *J Clin Med.* 2021;10(17).
390. Vinter N, Cordsen P, Lip GYH, et al. Newly diagnosed atrial fibrillation and hospital utilization in heart failure: a nationwide cohort study. *ESC Heart Fail.* 2021;8(6):4808-4819.
391. Wu C, Smit E, Peralta CA, Sarathy H, Odden MC. Functional status modifies the association of blood pressure with death in elders: health and retirement study. *J Am Geriatr Soc.* 2017;65(7):1482-1489.
392. Maksimovic M, Vlajinac H, Radak D, Marinkovic J, Maksimovic J, Jorga J. Association of overweight and obesity with cardiovascular risk factors in patients with atherosclerotic diseases. *J Med Biochem.* 2020;39(2):215-223.

393. Zhang X, Zhang W, Wang C, Tao W, Dou Q, Yang Y. Sarcopenia as a predictor of hospitalization among older people: a systematic review and meta-analysis. *BMC Geriatr.* 2018;18(1):188.
394. Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr.* 2004;79(4):613-618.
395. AMALFI - Active Monitoring for Atrial Fibrillation. https://www.amalfitrial.org/. Published 2022. Accessed 11th April 2022.
396. Peters SAE, Muntner P, Woodward M. Sex Differences in the Prevalence of, and Trends in, Cardiovascular Risk Factors, Treatment, and Control in the United States, 2001 to 2016. *Circulation.* 2019;139(8):1025-1035.
397. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation.* 2003;108(20):2460-2466.
398. Ma M, Zhi H, Yang S, Yu EY, Wang L. Body mass index and the risk of atrial fibrillation: a Mendelian randomization study. *Nutrients.* 2022;14(9).
399. Chen S, Xu T, Yang F, et al. Genetic determinants of increased body mass index partially mediate the effect of elevated birth weight on the increased risk of atrial fibrillation. *Front Cardiovasc Med.* 2021;8:701549.
400. Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet.* 2019;51(5):804-814.
401. Chen W, Yao D, Yan H, Wang M, Pan Y. Genetically predicted childhood obesity and adult atrial fibrillation: A mendelian randomization study. *Nutr Metab Cardiovasc Dis.* 2022;32(4):1019-1026.
402. Felix JF, Bradfield JP, Monnereau C, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum Mol Genet.* 2016;25(2):389-403.
403. Horikoshi M, Beaumont RN, Day FR, et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature.* 2016;538(7624):248-252.
404. Sinner MF, Tucker NR, Lunetta KL, et al. Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation. *Circulation.* 2014;130(15):1225-1235.
405. Yang P, Zhao Y, Wong ND. Development of a risk score for atrial fibrillation in adults with diabetes mellitus (from the ACCORD study). *Am J Cardiol.* 2020;125(11):1638-1643.
406. Singleton MJ, German CA, Soliman EZ, et al. Body mass index, sex, and incident atrial fibrillation in diabetes: the ACCORD trial. *JACC Clin Electrophysiol.* 2020;6(13):1713-1720.
407. Alonso A, Alam AB, Kamel H, et al. Epidemiology of atrial fibrillation in the All of Us Research Program. *PLoS One.* 2022;17(3):e0265498.
408. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123(14):1501-1508.
409. Huxley RR, Misialek JR, Agarwal SK, et al. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. *Circ Arrhythm Electrophysiol.* 2014;7(4):620-625.
410. Almuwaqqat Z, O'Neal WT, Norby FL, et al. Joint associations of obesity and NT-proBNP with the incidence of atrial fibrillation in the ARIC study. *J Am Heart Assoc.* 2019;8(19):e013294.
411. Diouf I, Magliano DJ, Carrington MJ, Stewart S, Shaw JE. Prevalence, incidence, risk factors and treatment of atrial fibrillation in Australia: The Australian Diabetes, Obesity and Lifestyle (AusDiab) longitudinal, population cohort study. *Int J Cardiol.* 2016;205:127-132.

412. Sciacqua A, Perticone M, Tripepi G, et al. CHADS2 and CHA2DS2-VASc scores are independently associated with incident atrial fibrillation: the Catanzaro Atrial Fibrillation Project. *Intern Emerg Med.* 2015;10(7):815-821.
413. Berkovitch A, Kivity S, Klempfner R, et al. Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. *Am Heart J.* 2016;173:41-48.
414. Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Combined impact of healthy lifestyle factors on risk of atrial fibrillation: Prospective study in men and women. *Int J Cardiol.* 2016;203:46-49.
415. Schmidt M, Botker HE, Pedersen L, Sorensen HT. Comparison of the frequency of atrial fibrillation in young obese versus young nonobese men undergoing examination for fitness for military service. *Am J Cardiol.* 2014;113(5):822-826.
416. Thijs VN, Brachmann J, Morillo CA, et al. Predictors for atrial fibrillation detection after cryptogenic stroke: Results from CRYSTAL AF. *Neurology.* 2016;86(3):261-269.
417. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study. *Ther Adv Neurol Disord.* 2019;12:1756286419842698.
418. Parahuleva MS, Kreutz J, Euler G, et al. Incidence of atrial fibrillation in postmenopausal women with endometrial cancer. *J Clin Med.* 2021;10(2):266.
419. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet.* 2009;373(9665):739-745.
420. Staerk L, Wang B, Preis SR, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ.* 2018;361:k1453.
421. Hodgkinson JA, Taylor CJ, Hobbs FD. Predictors of incident atrial fibrillation and influence of medications: a retrospective case-control study. *Br J Gen Pract.* 2011;61(587):e353-361.
422. Dewland TA, Vittinghoff E, Harris TB, et al. Inflammation as a mediator of the association between race and atrial fibrillation: results from the Health, Aging, and Body Composition study. *JACC Clin Electrophysiol.* 2015;1(4):248-255.
423. Hata J, Nagata T, Sakata S, et al. Risk prediction model for incident atrial fibrillation in a general Japanese population - the Hisayama Study. *Circ J.* 2021;85(8):1373-1382.
424. Garnvik LE, Malmo V, Janszky I, Wisloff U, Loennechen JP, Nes BM. Physical activity modifies the risk of atrial fibrillation in obese individuals: The HUNT3 study. *Eur J Prev Cardiol.* 2018;25(15):1646-1652.
425. Feng T, Vegard M, Strand LB, et al. Weight and weight change and risk of atrial fibrillation: the HUNT study. *Eur Heart J.* 2019;40(34):2859-2866.
426. Koshiyama M, Tamaki K, Ohsawa M. Age-specific incidence rates of atrial fibrillation and risk factors for the future development of atrial fibrillation in the Japanese general population. *J Cardiol.* 2021;77(1):88-92.
427. Itoh H, Kaneko H, Fujiu K, et al. Risk factors and lifestyles in the development of atrial fibrillation among individuals aged 20-39 years. *Am J Cardiol.* 2021;155:40-44.
428. Matsuoka S, Kaneko H, Okada A, et al. Age modified relationship between modifiable risk factors and the risk of atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2022;15(1):e010409.
429. Diederichsen SZ, Haugan KJ, Brandes A, et al. Incidence and predictors of atrial fibrillation episodes as detected by implantable loop recorder in patients at risk: From the LOOP study. *Am Heart J.* 2020;219:117-127.
430. Foy AJ, Mandrola J, Liu G, Naccarelli GV. Relation of obesity to new-onset atrial fibrillation and atrial flutter in adults. *Am J Cardiol.* 2018;121(9):1072-1075.

431. Mazzone A, Scalese M, Paradossi U, et al. Development and validation of a risk stratification score for new-onset atrial fibrillation in STEMI patients undergoing primary percutaneous coronary intervention. *Int J Clin Pract.* 2018;72(4):e13087.
432. Karasoy D, Bo Jensen T, Hansen ML, et al. Obesity is a risk factor for atrial fibrillation among fertile young women: a nationwide cohort study. *Europace.* 2013;15(6):781-786.
433. Ogunmoroti O, Michos ED, Aronis KN, et al. Life's Simple 7 and the risk of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis.* 2018;275:174-181.
434. Singleton MJ, German CA, Carnethon M, Soliman EZ, Bertoni AG, Yeboah J. Race, body mass index, and the risk of atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc.* 2021;10(1):e018592.
435. Shulman E, Chudow JJ, Essien UR, et al. Relative contribution of modifiable risk factors for incident atrial fibrillation in Hispanics, African Americans and non-Hispanic Whites. *Int J Cardiol.* 2019;275:89-94.
436. Hallstrom S, Pivodic A, Rosengren A, Olafsdottir AF, Svensson AM, Lind M. Risk factors for atrial fibrillation in people with type 1 diabetes: an observational cohort study of 36,258 patients from the Swedish National Diabetes Registry. *Diabetes Care.* 2019;42(8):1530-1538.
437. Son MK, Lim NK, Cho MC, Park HY. Incidence and risk factors for atrial fibrillation in Korea: the National Health Insurance Service database (2002-2010). *Korean Circ J.* 2016;46(4):515-521.
438. Kim YG, Han KD, Choi JI, et al. Non-genetic risk factors for atrial fibrillation are equally important in both young and old age: A nationwide population-based study. *Eur J Prev Cardiol.* 2021;28(6):666-676.
439. Kim IS, Choi YJ, Choi EY, et al. Comparison of risk profiles for new-onset atrial fibrillation between patients aged <60 and >/=60 years. *PLoS One.* 2021;16(11):e0258770.
440. Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation.* 2008;117(10):1255-1260.
441. Senoo K, Nakata M, Teramukai S, Yamamoto T, Nishimura H, Matoba S. Age-specific association between body mass index and the incidence of atrial fibrillation in Japanese men. *Circ Rep.* 2020;2(9):466-470.
442. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol.* 2007;49(5):565-571.
443. Vermond RA, Geelhoed B, Verweij N, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol.* 2015;66(9):1000-1007.
444. Hobbelt AH, Siland JE, Geelhoed B, et al. Clinical, biomarker, and genetic predictors of specific types of atrial fibrillation in a community-based cohort: data of the PREVEND study. *Europace.* 2017;19(2):226-232.
445. Trevisan C, Maggi S, Curreri C, et al. Anthropometric parameters and the incidence of atrial fibrillation in older people: the PRO.V.A study. *Clin Cardiol.* 2017;40(7):461-468.
446. O'Neal WT, Judd SE, Limdi NA, et al. Differential impact of risk factors in blacks and whites in the development of atrial fibrillation: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Racial Ethn Health Disparities.* 2017;4(4):718-724.
447. Grundvold I, Bodegard J, Nilsson PM, et al. Body weight and risk of atrial fibrillation in 7,169 patients with newly diagnosed type 2 diabetes; an observational study. *Cardiovasc Diabetol.* 2015;14:5.
448. Fumagalli C, Maurizi N, Day SM, et al. Association of obesity with adverse long-term outcomes in hypertrophic cardiomyopathy. *JAMA Cardiol.* 2020;5(1):65-72.

449. Ding L, Li J, Wang C, et al. Incidence of atrial fibrillation and its risk prediction model based on a prospective urban Han Chinese cohort. *J Hum Hypertens.* 2017;31(9):574-579.
450. Lipworth L, Okafor H, Mumma MT, et al. Race-specific impact of atrial fibrillation risk factors in blacks and whites in the southern community cohort study. *Am J Cardiol.* 2012;110(11):1637-1642.
451. Tomasdottir M, Held C, Hadziosmanovic N, et al. Risk markers of incident atrial fibrillation in patients with coronary heart disease. *Am Heart J.* 2021;233:92-101.
452. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology.* 2017;138(3):133-140.
453. Kokubo Y, Watanabe M, Higashiyama A, et al. Interaction of blood pressure and body mass index with risk of incident atrial fibrillation in a Japanese urban cohort: the Suita study. *Am J Hypertens.* 2015;28(11):1355-1361.
454. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a basic risk score for incident atrial fibrillation in a Japanese general population - the Suita study. *Circ J.* 2017;81(11):1580-1588.
455. Kodani E, Kaneko T, Fujii H, et al. Prevalence and incidence of atrial fibrillation in the general population based on national health insurance special health checkups - TAMA MED Project-AF. *Circ J.* 2019;83(3):524-531.
456. Ball J, Lochen ML, Wilsgaard T, et al. Sex differences in the impact of body mass index on the risk of future atrial fibrillation: insights from the longitudinal population-based Tromso study. *J Am Heart Assoc.* 2018;7(9):e008414.
457. Tsai SY, Chen HH, Hsu HY, et al. Obesity phenotypes and their relationships with atrial fibrillation. *PeerJ.* 2021;9:e12342.
458. Abbott KC, Reynolds JC, Taylor AJ, Agodoa LY. Hospitalized atrial fibrillation after renal transplantation in the United States. *Am J Transplant.* 2003;3(4):471-476.
459. Kamil-Rosenberg S, Kokkinos P, Grune de Souza ESC, et al. Association between cardiorespiratory fitness, obesity, and incidence of atrial fibrillation. *Int J Cardiol Heart Vasc.* 2020;31:100663.
460. Perez MV, Wang PJ, Larson JC, et al. Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study. *Heart.* 2013;99(16):1173-1178.
461. Tedrow UB, Conen D, Ridker PM, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol.* 2010;55(21):2319-2327.
462. Sandhu RK, Conen D, Tedrow UB, et al. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. *J Am Heart Assoc.* 2014;3(3):e000916.
463. Grundvold I, Skretteberg PT, Liestol K, et al. Importance of physical fitness on predictive effect of body mass index and weight gain on incident atrial fibrillation in healthy middle-age men. *Am J Cardiol.* 2012;110(3):425-432.
464. Carrazco C, Golyan D, Kahen M, Black K, Libman RB, Katz JM. Prevalence and risk factors for paroxysmal atrial fibrillation and flutter detection after cryptogenic ischemic stroke. *J Stroke Cerebrovasc Dis.* 2018;27(1):203-209.
465. Yuan H, Medina-Inojosa JR, Lopez-Jimenez F, et al. The long-term impact of bariatric surgery on development of atrial fibrillation and cardiovascular events in obese patients: an historical cohort study. *Front Cardiovasc Med.* 2021;8:647118.
466. Vukmirovic M, Boskovic A, Tomasevic Vukmirovic I, et al. Predictions and outcomes of atrial fibrillation in the patients with acute myocardial infarction. *Open Med (Wars).* 2017;12:115-124.

467. Minami M, Kobayashi Y, Toyokawa S, Inoue K, Takeshita Y. Risk factors for new-onset atrial fibrillation during routine medical checkups of Japanese male workers. *Int Heart J.* 2009;50(4):457-464.
468. De Bacquer D, Willekens J, De Backer G. Long-term prognostic value of p-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. *Am J Cardiol.* 2007;100(5):850-854.
469. Guenancia C, Stamboul K, Garnier F, et al. Obesity and new-onset atrial fibrillation in acute myocardial infarction: a gender specific risk factor. *Int J Cardiol.* 2014;176(3):1039-1041.
470. Wang W, Norby FL, Rooney MR, et al. Association of Life's Simple 7 with atrial fibrillation burden (from the Atherosclerosis Risk in Communities study). *Am J Cardiol.* 2020;137:31-38.
471. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc.* 2013;2(2):e000102.
472. Wannamethee SG, Papacosta O, Lennon L, Hingorani A, Whincup P. Adult height and incidence of atrial fibrillation and heart failure in older men: The British Regional Heart Study. *Int J Cardiol Heart Vasc.* 2021;35:100835.
473. Rosenberg MA, Kaplan RC, Siscovick DS, et al. Genetic variants related to height and risk of atrial fibrillation: the cardiovascular health study. *Am J Epidemiol.* 2014;180(2):215-222.
474. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation.* 1997;96(7):2455-2461.
475. Marott JL, Skielboe AK, Dixen U, Friberg JB, Schnohr P, Jensen GB. Increasing population height and risk of incident atrial fibrillation: the Copenhagen City Heart Study. *Eur Heart J.* 2018;39(45):4012-4019.
476. Yeboah J, Blaha MJ, Michos ED, et al. Adult height, prevalent coronary artery calcium score, and incident cardiovascular disease outcomes in a multiethnic cohort. *Am J Epidemiol.* 2017;186(8):935-943.
477. Schmidt M, Botker HE, Pedersen L, Sorensen HT. Adult height and risk of ischemic heart disease, atrial fibrillation, stroke, venous thromboembolism, and premature death: a population based 36-year follow-up study. *Eur J Epidemiol.* 2014;29(2):111-118.
478. Ninomiya Y, Kawasoe S, Kubozono T, et al. Sex-specific relationship between abdominal obesity and new-onset atrial fibrillation in the general Japanese population. *Heart Vessels.* 2021;36(12):1879-1884.
479. Kwon CH, Kim H, Kim SH, et al. The impact of metabolic syndrome on the incidence of atrial fibrillation: a nationwide longitudinal cohort study in South Korea. *J Clin Med.* 2019;8(8):1095.
480. Choe WS, Choi EK, Han KD, et al. Association of metabolic syndrome and chronic kidney disease with atrial fibrillation: A nationwide population-based study in Korea. *Diabetes Res Clin Pract.* 2019;148:14-22.
481. Igarashi Y, Nochioka K, Sakata Y, et al. Risk prediction for new-onset atrial fibrillation using the Minnesota code electrocardiography classification system. *Int J Cardiol Heart Vasc.* 2021;34:100762.
482. Hamada R, Muto S. Simple risk model and score for predicting of incident atrial fibrillation in Japanese. *J Cardiol.* 2019;73(1):65-72.
483. Kim J, Arora P, Kwon SY, et al. Relation of abdominal obesity to risk of atrial fibrillation (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] study). *Am J Cardiol.* 2022;162:116-121.
484. Kim YG, Choi KJ, Han S, et al. Metabolic syndrome and the risk of new-onset atrial fibrillation in middle-aged East Asian men. *Circ J.* 2018;82(7):1763-1769.
485. Muria-Subirats E, Clua-Espuny JL, Ballesta-Ors J, et al. Incidence and risk assessment for atrial fibrillation at 5 Years: hypertensive diabetic retrospective cohort. *Int J Environ Res Public Health.* 2020;17(10):3491.

486. Lawani SO, Demerath EW, Lopez FL, et al. Birth weight and the risk of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk In Communities (ARIC) study. *BMC Cardiovasc Disord.* 2014;14:69.
487. Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Incidence of atrial fibrillation in relation to birth weight and preterm birth. *Int J Cardiol.* 2015;178:149-152.
488. Johnson LSB, Salonen M, Kajantie E, et al. Early life risk factors for incident atrial fibrillation in the Helsinki Birth Cohort study. *J Am Heart Assoc.* 2017;6(6):e006036.
489. Conen D, Tedrow UB, Cook NR, Buring JE, Albert CM. Birth weight is a significant risk factor for incident atrial fibrillation. *Circulation.* 2010;122(8):764-770.
490. Fauchier G, Bisson A, Bodin A, et al. Metabolically healthy obesity and cardiovascular events: A nationwide cohort study. *Diabetes Obes Metab.* 2021;23(11):2492-2501.
491. Feng T, Vegard M, Strand LB, et al. Metabolically healthy obesity and risk for atrial fibrillation: the HUNT study. *Obesity (Silver Spring).* 2019;27(2):332-338.
492. Itoh H, Kaneko H, Kiriyama H, et al. Metabolically healthy obesity and the risk of cardiovascular disease in the general population - analysis of a nationwide epidemiological database. *Circ J.* 2021;85(6):914-920.
493. Lee H, Choi EK, Lee SH, et al. Atrial fibrillation risk in metabolically healthy obesity: A nationwide population-based study. *Int J Cardiol.* 2017;240:221-227.
494. Lim YM, Yang PS, Jang E, et al. Body mass index variability and long-term risk of new-onset atrial fibrillation in the general population: a Korean nationwide cohort study. *Mayo Clin Proc.* 2019;94(2):225-235.
495. Lee SR, Choi EK, Han KD, Lee SH, Oh S. Effect of the variability of blood pressure, glucose level, total cholesterol level, and body mass index on the risk of atrial fibrillation in a healthy population. *Heart Rhythm.* 2020;17(1):12-19.
496. Johnson LS, Juhlin T, Engstrom G, Nilsson PM. Risk factor changes and incident atrial fibrillation among middle-aged men in the Malmo Preventive Project cohort. *Eur Heart J Cardiovasc Pharmacother.* 2016;2(2):81-87.
497. Lee HJ, Choi EK, Han KD, et al. Bodyweight fluctuation is associated with increased risk of incident atrial fibrillation. *Heart Rhythm.* 2020;17(3):365-371.
498. Lee HJ, Choi EK, Han KD, et al. High variability in bodyweight is associated with an increased risk of atrial fibrillation in patients with type 2 diabetes mellitus: a nationwide cohort study. *Cardiovasc Diabetol.* 2020;19(1):78.
499. Park CS, Choi YJ, Rhee TM, et al. U-Shaped associations between body weight changes and major cardiovascular events in type 2 diabetes mellitus: a longitudinal follow-up study of a nationwide cohort of over 1.5 million. *Diabetes Care.* 2022;45(5):1239-1246.
500. Khatun M, Monir MM, Xu T, Xu H, Zhu J. Genome-wide conditional association study reveals the influences of lifestyle cofactors on genetic regulation of body surface area in MESA population. *PLoS One.* 2021;16(6):e0253167.
501. Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature.* 2018;558(7708):73-79.
502. Abel S, Hundhausen C, Mentlein R, et al. The transmembrane CXC-chemokine ligand 16 is induced by IFN-gamma and TNF-alpha and shed by the activity of the disintegrin-like metalloproteinase ADAM10. *J Immunol.* 2004;172(10):6362-6372.
503. Wischhusen J, Melero I, Fridman WH. Growth/Differentiation Factor-15 (GDF-15): From biomarker to novel targetable immune checkpoint. *Front Immunol.* 2020;11:951.
504. Nissinen L, Kahari VM. Matrix metalloproteinases in inflammation. *Biochim Biophys Acta.* 2014;1840(8):2571-2580.
505. Kastrup J. Can YKL-40 be a new inflammatory biomarker in cardiovascular disease? *Immunobiology.* 2012;217(5):483-491.

506. Lee CG, Da Silva CA, Dela Cruz CS, et al. Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. *Annu Rev Physiol.* 2011;73:479-501.
507. Olink. Olink® Target 96 Inflammation Panels. https://olink.com/products-services/target/inflammation/. Published 2022. Accessed 12th January 2023.
508. ThermoFisher Scientific. Immune Response 80-Plex Human ProcartaPlex™ Panel. https://www.thermofisher.com/order/catalog/product/EPX800-10080-901?gclid=Cj0KCQiAyracBhDoARIsACGFcS7GzdPlaScQU7c75N5RJX_nn31miOpJGmk2LvsYixTp-WeuchCOWOMaAr8ZEALw_wcB&ef_id=Cj0KCQiAyracBhDoARIsACGFcS7GzdPlaScQU7c75N5RJX_nn31miOpJGmk2LvsYixTp-WeuchCOWOMaAr8ZEALw_wcB:G:s&s_kwcid=AL!3652!3!595010117423!p!!g!!inflammation%20panel!352132722!49450409201&cid=bid_pca_ilu_r01_co_cp1359_pjt0000_bid00000_0se_gaw_nt_pur_con. Published 2022. Accessed 12th January 2022.
509. BioLegend. LEGENDplex™ Multiplex Assays. https://www.biolegend.com/en-us/legendplex?gclid=Cj0KCQiAvqGcBhCJARIsAFQ5ke5FLxTf-TbA19STUqlqqH66NqQlL58NVq7ws_XXGIRi-bhHy6uSpXwaAtQ4EALw_wcB. Published 2022. Accessed 12th January 2023.

Appendix A - Systematic review search strategy

The details of the methods of the systematic review undertaken as part of this thesis are available in **Chapter 3**. The search strategies for OVID Embase, OVID Medline, and PubMed Medline are detailed in **Appendix Table A.1**, **Appendix Table A.2**, and **Appendix Table A.3.,** including details for search results when the search was run on 15th July 2022.

Appendix Table A.1: Search strategy used to search Embase using OVID

#	Search Term	Results
1	exp Obesity/ or exp Obesity, Abdominal/ or exp Obesity, Morbid/	600,886
2	exp Adipose Tissue/	185,665
3	exp Adiposity/	600,886
4	exp Body Weight/	585,749
5	exp Body Mass Index	551461
6	exp Weight-Hip Ratio/	17,219
7	exp Waist-Height Ratio/	3,761
8	exp Waist Circumference/	64,486
9	exp Body Height/	78,123
10	exp Weight Gain/	33,669
11	exp Weight Loss/	67,682
12	exp Body Composition/	116,799
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1,541,665
14	exp Atrial Fibrillation/	103,757
18	13 and 14	11,761
19	Limit 18 to Embase	7,293
19	Limit 19 to English language	7,196

exp – explode function

Appendix Table A.2: Search strategy used to search Medline using OVID

#	Search Term	Results
1	exp Obesity/ or exp Obesity, Abdominal/ or exp Obesity, Morbid/	246,729
2	exp Adipose Tissue/	107,989
3	exp Adiposity/	14,826
4	exp Body Weight/	511,900
5	exp Body Mass Index	144,290
6	exp Weight-Hip Ratio/	4,492
7	exp Waist-Height Ratio/	709
8	exp Waist Circumference/	12,431
9	exp Body Height/	38,678
10	exp Weight Gain/	35,187
11	exp Weight Loss/	47,629
12	exp Body Composition/	61,839
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	689,249
14	exp Atrial Fibrillation/	66,482
15	Atri* fibrillation	97,763
16	exp Arrhythmias, Cardiac/	229,883
17	14 or 15 or 16	257,023
18	13 and 17	3,120
19	Limit 18 to English language	2,824

exp – explode function, * is a wildcard term

1

Appendix Table A.3: Search strategy used to search Medline using PubMed

#	Search Term	Results
1	Adiposity	35,105
2	Adipose	150,189
3	Adipose*	150,362
4	BMI	178,902
5	Body mass index	279,666
6	Excess weight	6,158
7	Fat	308,231
8	Height	198,921
9	Lean mass	6,706
10	Obes*	441,270
11	Overweight	87,072
12	Over weight	528
13	Weight height ratio	159
14	Waist hip ratio	8,093
15	Waist height	1,329
16	Waist hip	8,783
17	Weigh	6,994
18	Weight	1,175,189
19	Weight gain	85,205
20	Weight loss	113,649
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	1,981,348
22	Atrial fibrillation	97,934
23	Auricular fibrillation	1,549
24	Atrium fibrillation	12
25	Atria fibrillation	7
26	Atri* fibrillation	100,321
27	Arrhythmia	84,108
28	22 or 23 or 24 or 25 or 26 or 27	164,770
29	21 and 28	8,248
30	Limit 29 to English language	7,638

* is a wildcard term

Appendix B - Systematic review results tables

B.1. Mendelian randomization analyses

Appendix Table B.1: Details of studies examining anthropometric variables on risk of atrial fibrillation using Mendelian randomization

	Study	Date	Genetic variant source	Outcome source	Anthropometric phenotype	AF Cases	Total Size	Variants	Average F-stat	PVE (%)	Univariate OR (95%CI)	Multivariate OR (95%CI)	Phenotypes in multivariate analysis
1	Ardissino *et al.*[209]	2022	GIANT (2018)[35]	Roselli *et al.*[169]	BMI	55,114	482,295	453	-	-	1.33 (1.24 to 1.42) per SD	1.40 (1.30 to 1.51) per SD	Sleep disordered breathing
2	Huang *et al.*[234]	2022	UKB	Nielsen *et al.*[319]	Predicted VAT mass	60,620	1,030,836	221	-	-	1.41 (1.33 to 1.50) per SD	-	-
3	Ma *et al.*[398]	2022	GIANT (2018)[35]	Nielsen *et al.*[319]	BMI	60,620	1,030,836	303	61	2.5	1.43 (1.35 to 1.51)	-	-
4	Martin *et al.*[130]	2022	UKB	FinnGen	Body fat %	17,325	114,539	696	-	-	1.53 (1.21 to 1.92) per SD	-	-
			GIANT (2015)[103]		BMI			73	-	-	1.65 (1.33 to 2.05) per SD	-	
			UKB		Metabolically health obesity			38	-	-	0.79 (0.39 to 1.61)	-	
5	Raghavan *et al.*[216]	2022	Million Veterans Program	Million Veterans Program	Height	30,266	147,854	3,290	-	18	1.34 (1.32 to 1.36) per SD	-	-
6	Wang *et al.*[110]	2022	UKB	Nielsen *et al.*[319]	Body fat %	60,620	1,030,836	395	-	-	1.45 (1.34 to 1.58) per SD	-	BMI, waist circumference, height, hip circumference
					BMI			459	62	-	1.45 (1.33 to 1.57) per SD	1.25 (1.07 to 1.47) per SD	
					Waist circumference			376	57	-	1.54 (1.43 to 1.65) per SD	0.93 (0.73 to 1.18) per SD	
					Fat mass			437	-	-	1.51 (1.42 to 1.60) per SD	-	
					Lean mass			556	-	-	1.89 (1.72 to 2.01) per SD	-	
					Height			779	78	-	1.30 (1.25 to 1.36) per SD	1.26 (1.18 to 1.34) per SD	
					Trunk fat			571	-	-	1.48 (1.39 to 1.49) per SD	-	
					Weight			496	-	-	1.67 (1.57 to 1.77) per SD	-	
					Hip circumference			417	64	-	1.60 (1.50 to 1.70) per SD	1.26 (1.02 to 1.56) per SD	
					Birthweight			142	-	-	1.29 (1.18 to 1.40) per SD	-	
7	Chen *et al.*[399]	2021	Warrington *et al.*[400]	Nielsen *et al.*[319]	BMI	60,620	1,030,836	-	-	-	-	1.70 (1.02 to 2.84) per SD	BMI and birth weight
					Birth weight			144	44	-	1.27 (1.14 to 1.40) per SD	1.16 (1.01 to 1.33) per SD	
8	Chen *et al.*[401]	2021	Felix *et al.*[402]	Nielsen *et al.*[319]	Childhood BMI	60,620	1,030,836	15	70	2	1.22 (1.11 to 1.34) per SD	-	-

9	Lind *et al.*[314]	2021	GIANT (2015)[103]	Roselli *et al.*[169]	BMI	55,114	482,295	-	-	-	1.44 (1.35 to 1.54) per SD	1.26 (1.18 to 1.34) per SD	TG, HDL, LDL, SBP, DM, Smoking
10	Power *et al.*[313]	2021	UKB	FinnGen	BMI	17,325	114,539	562	16	-	2.16 (1.86 to 2.51)	-	BMI and childhood body size
					Childhood body size			302	13.6	-	1.69 (1.39 to 2.06)	0.91 (0.71 to 1.17)	
11	Zeng *et al.*[227]	2021	UKB	FinnGen	Fat mass	22,068	116926	409	69	-	1.78 (1.59 to 1.99) per SD	1.44 (1.39 to 1.58) per SD	Fat mass and lean mass
					Lean mass			523	99	-	2.13 (1.84 to 2.45) per SD	1.65 (1.31 to 2.09) per SD	
					Body fat %			370	65	-	1.80 (1.55 to 2.09) per SD	1.49 (1.20 to 1.85)	Body fat % and lean mass
12	Kember *et al.*[312]	2020	Horikoshi *et al.*[403]	Nielsen *et al.*[319]	Birth weight	60,620	1,030,836	42	-	-	1.27 (1.14 to 1.41) per SD	1.32 (1.17 to 1.48) per SD	LDL, type-2 DM, CHD, BMI, birth weight
					BMI			-	-	-	-	1.34 (1.22 to 1.47) per SD	
13	Levin *et al.*[215]	2020	GIANT (2018)[35]	Roselli *et al.*[169]	Height	65,446	522,744	707	110	11	1.34 (1.29 to 1.40) per SD	-	-
14	Larsson *et al.*[109]	2019	GIANT (2015)	UKB	BMI	13,538	367,703	96	61	1.6	1.07 (1.04 to 1.09) per 1 kg/m^2	-	-
			Rask-Andersen *et al.*[228]	UKB	Fat mass index			82	52	0.8	1.27 (1.14 to 1.40) per 1 kg/m^2	-	
			Rask-Andersen *et al.*[228]	UKB	Lean mass index			82	45	0.7	0.75 (0.66 to 0.86) per 1 kg/m^2	-	
15	Tikkanen *et al.*[71]	2019	UKB	Christophersen *et al.*[167]	Fat mass	17,931	115,142	268	-	-	1.30 (1.17 to 1.45) per SD	1.28 (1.03 to 1.58) per SD	Fat mass and lean mass
					Lean mass			446	-	-	1.55 (1.38 to 1.75) per SD	1.37 (1.06 to 1.75) per SD	Fat mass and lean mass
16	Chatterjee *et al.*[108]	2017	AGES, ARIC, FHS, PREVEND, RHS, WGHS	Sinner *et al.*[404]	BMI	4,178	51,646	39	-	-	1.06 (1.02 to 1.09) per 1 kg/m^2	-	-

AF – atrial fibrillation, AGES - Age, Gene/Environment Susceptibility Reykjavik Study, ARIC - Atherosclerosis Risk in Communities, BMI – body mass index, CHD – coronary heart disease, CI – confidence interval, DM – diabetes mellitus, FHS – Framingham Heart Study, GIANT – Genetic Investigation of Anthropometric Traits, HDL – high-density lipoprotein, HR – hazard ratio, HTN – hypertension, LDL – low-density lipoprotein, NHIS - National Health Insurance Service, OR – odds ratio, PREVEND - Prevention of Renal and Vascular End-stage Disease study, PVE – proportion of variance explained, Q – quintile, RHS – Rotterdam Heart Study, SBP – systolic blood pressure, SD - standard deviation, TG – triglycerides, UKB – UK Biobank, WGHS - Women's Genome Healthy Study

B.2. Body mass index

Appendix Table B.2: Studies reporting estimates of the association between body mass index and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	BMI as a continuous variable	*BMI and a categorical variable*		
ACCORD	2	1	USA	[405,406]
AGES	1	0	USA	[164]
All Of Us	1	0	USA	[407]
ARIC	0	4	USA	[222,408-410]
AusDiab	0	1	Australia	[411]
Beijing Friendship Hospital	1	1	China	194
BiomarCaRE	2	0	Denmark, Finland, Sweden	[61,74]
Busselton Health Study	1	0	Australia	[208]
Catanzaro Atrial Fibrillation Project	1	0	Italy	[412]
CHS	2	0	USA	[67,164] ([164]also reports FHS and AGES)
Chaim Sheba Medical Centre cohort	1	1	Israel	[413]
Cohort of Swedish men	0	1	Sweden	[414] (also reports Swedish mammography cohort)
Conscription Research Database	1	1	Denmark	[415]
CPRD	0	1	UK	[198]
CRYSTAL-AF	1	1	USA	[416,417]
DAN-MONICA	1	0	Denmark	[283] (as part of the MORGAM consortium)
DDCH	3	1	Denmark	[66,191,202]
Endometrial cancer cohort	0	1	Bulgaria	[418]
EPIC-Norfolk	0	1	UK	[197]
FHS	4	3	USA	[75,164,193,419,420] ([164] also reports CHS and AGES)
FINRISK	1	0	Finland	[283] (as part of the MORGAM consortium)
GPRD	0	1	UK	[421]
Health ABC	2	0	USA	[68,422]
Hisayama study	0	1	Japan	[423]
HUNT3	0	2	Norway	[424,425]
Iwate Prefecture cohort	0	1	Japan	[426]
JHS	1	0	USA	[95] (also reports MESA)
JMDC claims database	0	2	Japan	[427,428]
Kailuan	1	1	China	[200]
LOOP	1	0	Denmark	[429]
Maccabi Healthcare Services cohort	1	0	Israel	[62]

Appendix Table B.2: Studies reporting estimates of the association between body mass index and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	BMI as a continuous variable	*BMI and a categorical variable*		
Malmo Diet and Cancer Study	2	2	Sweden	[76,207]
MarketScan Commercial Claims and Encounters	0	1	USA	[430]
Massa Hospital STEMI	0	1	Italy	[431]
Medical Birth Registry - Denmark	1	1	Denmark	[432]
Medical Birth Registry – Sweden	1	1	Sweden	[60]
MESA	1	2	USA	[95,433,434] ([95] also reports JHS)
Million Women Study	1	1	UK	[201]
Moli-sani	1	0	Italy	[283] (as part of the MORGAM consortium)
MONICA	1	0	Sweden	[283] (as part of the MORGAM consortium)
Montefiore Medical Centre Cohort	1	1	USA	[59,435]
Multifactor Primary Prevention Study	2	2	Sweden	[211,224]
National Diabetes Registry	2	1	Sweden	[199,436]
NHIS cohort**	3	6	Korea	[70,195,205,212,437-439]
Niigata Preventive Medicine study	0	1	Japan	[440]
Ningen Dock	1	1	Japan	[204]
Nishimura Health Study	2	1	Japan	[196,441]
Olmstead County	1	0	USA	[442]
ONTARGET/TRANSCEND	0	1	International	[225]
PREVEND	2	0	The Netherlands	[443,444]
PRO.V.A.	1	1	Italy	[445]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
REGARDS	0	1	USA	[446]
Renfrew-Paisley Study	1	1	UK	[203]
ROSE	0	1	Sweden	[447]
SHARE	0	1	International	[448]
Scottish Heart Health Extended cohort	1	0	UK	[73]
Shandong multi-centre health check-up longitudinal study	1	0	China	[449]
SCCS	0	1	USA	[450]
STABILITY	1	0	Sweden	[451]
STRIDE	0	1	USA	[452]
Stockholm county cohort	1	1	Sweden	[217]
Suita	1	2	Japan	[453,454]
Swedish mammography cohort	0	1	Sweden	[414](also reports Cohort of Swedish men)
Swedish Military Conscription cohort	1	2	Sweden	[58,223]
TAMA MED Project AF	1	0	Japan	[455]

Appendix Table B.2: Studies reporting estimates of the association between body mass index and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	BMI as a continuous variable	*BMI and a categorical variable*		
Tromso	1	1	Norway	[283,456] ([283] as part of the MORGAM consortium)
TwSHHH	0	1	Taiwan	[457]
UKB	1	0	UK	[226]
United States Renal Data System	0	1	USA	[458]
Uppsala Longitudinal Study of Adult Men	1	0	Sweden	[314]
VA Cohort	0	1	USA	[459]
VIP	1	1	Sweden	[206]
WHI	4	1	USA	[63,64,69,460]
WHS	2	2	USA	[461,462]
Individual un-named cohorts	2	2	Varied	[463-465]
Non-cohort studies	3	1	Varied	[466-469]
Total studies	**68***	**73***		
Of which presented continuous and categorical data		**30**		

* Studies that include more than a single cohort are only counted once in the total. ** Includes studies using the National Sample cohort selection from the National Health Insurance Service cohort. **ACCORD** - Action to Control Cardiovascular Risk in Diabetes, **AF** – atrial fibrillation, **AGES** – age, gene/environment susceptibility, **ARIC** – atherosclerosis risk in communities cohort, **AusDiab** – Australian Diabetes, Obesity and Lifestyle Study, **BiomarCaRE** – Biomarker for Cardiovascular Risk Assessment across Europe, **BMI** – body mass index, **CHS** – Cardiovascular Health Study, **CPRD** – Clinical Practice Research Datalink, **CRYSTAL**-AF - Cryptogenic Stroke and Underlying Atrial Fibrillation, **DDCH** - Danish Diet, Cancer and Health, **EPIC** - European Prospective Investigation into Cancer, **FHS** – Framingham Heart Study, **GPRD** – General Practice Research Database, **Health ABC** - Health, Aging, and Body Composition, **HUNT3** – Trøndelag Healthy study, **JHS** - Jackson Heart Study, **LOOP** - Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals, **MESA** - Multi-ethnic study of atherosclerosis, **MONICA** – MONitoring of Trends and Determinants in Cardiovascular Disease, **MORGAM** – Monica Risk, Genetics, Archiving, and Monograph, **NHIS** - National Health Insurance Service, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PREVEND** - Prevention of Renal and Vascular Endstage Disease, **PRO.V.A.** - Progetto Veneto Anziani, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **ROSE** - Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering Drug Treatment in Primary Care, **SCCS** - Southern Community Cohort Study, **SHARE** - Sarcomeric Human Cardiomyopathy Registry, **STABILITY** – Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy, **STRIDE** - Stanford Translational Research Integrated Database Environment, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease, **TwSHHH** - Taiwan's Hypertensive, Hyperglycaemia, Hyperlipidaemia Survey, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **VA** – Veterans' Administration, **VIP** – Vasterbotten Intervention Programme, **WHI** – Women's Health Initiative, **WHS** - Women's Health Study

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Alonso *et al.*[407]	2022	All Of Us	Prospective cohort	USA	Aged 18-90 years at enrolment. Prevalent AF excluded.	354	92,318	52.1	61	16 months	1.2 (1.1 to 1.3) per 5 kg/m^2	Age, sex, ethnicity, SBP, DBP, smoking, DM, CCF, CHD, CVA	-
2	Liu *et al*.[194]	2022	Beijing Friendship hospital	Prospective cohort	China	Acute MI attending Beijing Friendship hospital. Prevalent AF excluded.	132	4,282	63.9	74	42 months	0.90 (0.85 to 0.95) per SD [3.7 kg/m^2]	Age, sex, LA size, Killip class, CTO, eGFR, TG, NT-proBNP, peak troponin	-
3	Zhao *et al*.[200]	2022	Kailuan	Prospective cohort	China	Employees of Kailuan Group (coal mining company). Enrolled 2006-7. Excluded history of AF, MI, CVA, CCF, or cancer.	410	44,135	48.8	78	9.7	1.06 (1.03 to 1.10) per 1 kg/m^2	Age, sex, physical activity, smoking, alcohol, LDL, heart rate, HTN, DM	-
4	Camm *et al*.[226]	2021	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded, Missing or extreme anthropometric measures excluded	14,400	215,196	56.6	100	11.1	1.39 (1.36 to 1.41) per 5 kg/m^2	Age, ethnicity, deprivation, smoking, alcohol	-
												1.15 (1.11 to 1.19) per 5 kg/m^2	+ WC	
							8,734	262,708	56.3	0	11.1	1.34 (1.32 to 1.37) per 5 kg/m^2	Age, ethnicity, deprivation, smoking, alcohol	
												1.16 (1.11 to 1.20) per 5 kg/m^2	+ WC	
5	Lind *et al.*[314]	2021	Uppsala Longitudinal Study of Adult Men	Prospective cohort	Sweden	Men aged 50 at enrolment living in Uppsala Sweden	552	2,322	50	100	40	1.17 (1.06 to 1.30) per SD (3.1 kg/m^2)	TG, HDL, LDL, SBP, DM, smoking	-
6	Morseth *et al.*[283]	2021	MORGAM consortium (DAN-MONICA, FINRISK, Moli-sani, MONICA, Tromso)	Prospective cohorts	Denmark, Finland, Italy, Norway, Sweden	Prevalent AF excluded. Those aged ≥40 years at enrolment included.	2,021	24,914	40-49	49	10	1.41 (1.18 to 1.68) per 5 kg/m^2	Age, sex, total cholesterol, smoking, DM, HTN, alcohol, study site	-
								21,824	50-59			1.37 (1.23 to 1.53) per 5 kg/m^2		
								13,441	60-69			1.37 (1.25 to 1.50) per 5 kg/m^2		

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
								6772	≥79			1.17 (1.06 to 1.29) per 5kg/m^2		
7	Senoo *et al.*[196]	2021	Nishimura Health Survey	Prospective cohort	Japan	Aged ≥30 years at enrolment with ≥2 health screening visits. Prevalent AF excluded.	123	17,865	43.8	100	4.0	1.07 (0.98 to 1.17) per 1 kg/m^2	Age, HTN, DM, dyslipidaemia, hyperuricemia	Senoo *et al.* (2020)[441]
8	Tomasdottir *et al.*[451]	2021	STABILITY	Post-trial follow-up	Sweden	Patients with CHD with at least one of: age ≥60 years, DM, HDL <40 mg/dL, smoking > 4 cigarettes per day, moderate renal dysfunction, or PVD. Randomized to either darapladib or placebo. Prevalent AF excluded	541	13,153	64	81	3.5	1.06 (1.04 to 1.08) per 1kg/m^2	Treatment group, age, sex, region, SBP, HTN, MI, DM, PAD, CCF, COPD, coronary intervention, smoking, alcohol, physical activity	-
9	Yuan *et al.*[465]	2021	-	Retrospective cohort	USA	Patients undergoing roux-en-Y gastric bypass surgery or medical management for obesity	Unclear	1,009	43.8	22	1.0	1.05 (1.01 to 1.09) per 1kg/m^2	age, sex	Gami *et al*. (2007)[442]
10	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.18 (1.13 to 1.23) per SD [3.4 kg/m^2]	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	Smith *et al*. (2010)[76]
							2,215	16,078	57	0	19.7	1.15 (1.11 to 1.20) per SD [4.2 kg/m^2]		
11	Diederichsen *et al*.[429]	2020	LOOP Study	Prospective cohort	Denmark	Age >70 years at baseline. At least one of HTN, DM, CVA, CCF. Prevalent AF excluded	209	570	76	57	3.3	1.5 (1.1 to 2.0) per 5 kg/m^2 (from Figure 3)	OUTCOME: AF > 24 hours duration. Sex, age, CHA_2DS_2-VAsc score, resting sinus rate, NT-proBNP, troponin	-
12	Johansson *et al*.[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded	3,200	53,376	46.4	100	14.3	1.23 (1.19 to 1.28) per SD (3.8 kg/m^2)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity	-
							1,954	55,041	46.3	0	15.6	1.22 (1.17 to 1.28) per SD (4.6 kg/m^2)		

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
13	Schrage *et al.*[61]	2020	BiomarCaRE	Prospective Cohorts	Finland, Denmark, Italy, & Sweden	Prevalent AF excluded	3141	59,913	50.5	49	13.8	1.31 (1.25 to 1.31) per 5 kg/m^2	Age, sex, cholesterol, HTN medication, smoking, DM, MI, NT-proBNP, CRP, eGFR	Magnussen *et al.* (2017)[74]
14	Senoo *et al.*[441]	2020	Nishimura Health Survey	Prospective cohort	Japan	Aged ≥40 years at enrolment with ≥2 health screening visits. Prevalent AF excluded.	118	10,921	49.6	100	5.0	1.07 (1.00 to 1.13) per 1 kg/m^2	age, SBP, HDL, TG, glucose	Senoo *et al.* (2021)[196]
15	Singleton *et al.*[406]	2020	ACCORD study	Post-trial follow-up	USA	Aged 40-79 years, all have type 2 diabetes mellitus, prevalent AF excluded.	190	10,074	62.7	61	5.0	1.51 (1.29 to 1.76) per SD [5.4 kg/m^2]	age, sex, ethnicity, CHD, smoking, treatment group, SBP, total cholesterol, HDL cholesterol, HbA1c	Yang *et al.* (2020)[405]
16	Yang *et al.*[405]	2020	ACCORD Study	Post-trail cohort	USA	Aged 40-79 years, all have type 2 diabetes mellitus, prevalent AF excluded	165	9,075	62.6	62	4.9	1.53 (1.31 to 1.78) per 5 kg/m^2	Age, sex, ethnicity, CCF, DBP, lipids, HbA1c, DM duration, HTN medications, creatinine concentration	Singleton *et al.* (2020)[406]
17	Connor *et al.*[193]	2019	FHS – original and offspring	Prospective Cohort	USA	Attended examination 50±5 years Prevalent AF excluded.	847	4,392	50.7	47	23.8	0.88 (0.82 to 0.95) per 5 kg/m^2 lower BMI	SBP, DBP, smoking, HTN medications, DM, CCF, MI	Wang *et al.* (2004)[75] Schnabel *et al.* (2010)[164] Schnabel *et al.* (2009)[419]
18	Hallstrom *et al.*[436]	2019	Swedish National Diabetes Registry	Prospective Cohort	Sweden	Age >18 years old with Type-1 DM. Prevalent AF excluded. BMI time updated	749	36,258	35.6	55	9.7	1.16 (1.06 to 1.27) per 5 kg/m^2	Age, sex, education, Swedish-born, time-updated: DM duration, baseline comorbidities, smoking, HbA1c, and SBP	Zethelius *et al.*[199] (2015)
19	Kodani *et al.*[455]	2019	TAMA MED Project AF	Prospective cohort	Japan	Age: 40-70 years at entry No cardiac disease or HTN at entry Those with AF excluded	105	9,992	64.9	40.4	7	1.07 (1.00 to 1.12) per 1 kg/m^2	Age, sex, HTN, DM, LDL-C, TG, γ-GTP	-
20	Peters *et al.*[73]	2019	Scottish Heart Health Extended Cohort (Scottish Heart Health Study and Scottish MONICA)	Prospective cohort	Scotland	Age: 30-74 years at recruitment No history of CHD at baseline No exclusion of those with AF (unable to ascertain)	445	8,185	49.0	0	22.6	1.17 (1.08 to 1.27) per SD (4.8 kg/m^2)	Age, CHD FHx, deprivation, smoking, SBP, total cholesterol, HDL	-
							591	7,552	49.0	100	22.6	1.36 (1.24 to 1.49) per SD (3.7 kg/m^2)		

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
21	Aronson *et al*.[62]	2018	Maccabi Healthcare Services	Prospective cohort	Israel	Random selection from ambulatory clinics, patients with AF excluded	5,660	96,778	62	46	10	1.05 (1.05 to 1.06) per 1 kg/m^2	Age, sex, SBP, MI, PAD, HTN, CCF, COPD, inflammatory disease, age at CCF.	-
22	Crump *et al*.[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	1.05 (1.05 to 1.06) per 1 kg/m^2	Age, conscription year, height, weight, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	-
23	Hamada *et al*.[204]	2018	Ningen Dock	Retrospective Cohort	Japan	Age at entry 40-79 years undergoing health check-up 2008-2014. Prevalent AF excluded.	229 50	42,942 22,693	52.4 52.6	100 0	5.5	1.20 (1.06 to 1.36) per SD (3.0 kg/m^2) 1.56 (1.21 to 2.01) per SD (3.2 kg/m^2)	Age, BP, lipids, glucose, smoking, alcohol, physical activity, renal function, CVA, CHD	-
24	Shulman *et al*.[59]	2018	Montefiore Medical Centre	Retrospective cohort	USA	>1 ECG between 2000 and 2013. Excluded if AF on first ECG	4,744	48,323	60.1	39	2.3	1.09 (1.05 to 1.13) per 1 kg/m^2	Ethnicity, CCF, sex, age, HTN, DM, PR interval, SBP, LVH, SES, use of digoxin, calcium channel blocker or beta-blocker	
25	Persson *et al*.[60]	2018	Medical Birth Registry - Sweden	Prospective Cohort	Sweden	Women born after 1973 who were pregnant 1982-2014. > 18 years old Height 140-200 cm Exclusions: prevalent AF (at time of pregnancy), BMI <15 or >60 kg/m^2	6,993	1,522,329	28.3	0	16.6	1.07 (1.06 to 1.08) per 1 kg/m^2	Age, DM, HTN, CCF, smoking, pregnancy year, previous parity, education level, CCF during follow-up.	
26	Vukmirovic *et al*.[466]	2018	-	Consecutive series	Montenegro	Patients admitted with MI to CCU	48	600	64	71	While in hospital	1.17 (1.04 to 1.33) – units unclear	Age, admission heart rate, Killip class, left ventricular ejection fraction, LA diameter, mitral regurgitation, BNP, CRP, and CIN.	-
27	Baek *et al*.[195]	2017	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population. AF excluded based on healthcare data.	3,443	501,690	47.6 ± 14.3	50	3.9	1.04 (0.99 to 1.10) per SD (3.7 kg/m^2)	Age, sex, WC	Son *et al.* (2016)[437] Kang *et al.* (2016)[205]
28	Ding *et al*.[449]	2017	Shandong multi-centre health check-up	Prospective cohort	China	AF excluded at baseline, at least two	165	9,075	56.7	67	2.6	0.94 (0.77 to 1.14) per SD	Age, sex	-

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
			longitudinal study			health check-up with ECGs						(3.64 kg/m^2)		
29	Fenger-Grøn *et al.*[66]	2017	DDCH	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56 (IQR 51 to 63)	47	8.3	1.22 (1.18 to 1.26) per SD (3.6 kg/m^2 [M]/4.4 kg/m^2[F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Frost *et al*. (2005)[202] Frost *et al*. (2014)[191]
												1.01 (0.98 to 1.05) per SD	+ lean mass	
30	Heckbert *et al*.[95]	2017	MESA and JHS	Prospective Cohort	USA	MESA: 45-84 years at baseline, no CHD JHS: black residents aged 20-95 at baseline. Only BMI ≥30 kg/m^2	250	2,862	61.5	45	10	1.46 (1.26 to 1.70) per SD (6 kg/m^2)	Age, study, sex, ethnicity, height, SBP, HTN, glucose, pericardial adipose tissue	-
						BMI <30 kg/m^2	506	5,125				1.01 (0.86 to 1.19) per SD (6 kg/m^2)		
31	Hobbelt *et al.*[444]	2017	PREVEND	Prospective cohort	The Netherlands	Aged 28-75, resident in Groningen (the Netherlands) in 1997. Prevalent AF excluded. Outcome: paroxysmal AF	158	8,042	48.5	49	Unclear	1.77 (1.15 to 2.71) per 5 kg/m^2	Age, sex, heart rate, statin, NT-proBNP, eGFR, urinary albumin-creatinine ratio	Vermond *et al*. (2015)[443]
						Outcome: persistent AF	58					1.41 (1.12 to 1.78) per 5 kg/m^2		
32	Magnussen *et al.*[74]	2017	BiomarCaRE	Prospective cohort(s)	Finland, Denmark, Italy, and Sweden	Prevalent AF excluded	2,465	38,567	50	100	12.4	1.31 (1.25 to 1.38) per SD (4.67 kg/m^2)	SBP, DM, smoking, HTN medications, total cholesterol. Age used as the timescale	Schrage *et al*. (2020)[61]
							1,796	41,226	49.2	0	12.4	1.18 (1.12 to 1.23) per SD (4.67 kg/m^2)		
33	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	OR 1.02 (1.00 to 1.03) per 1 kg/m^2	Age, sex	-

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
34	Azarbal *et al*.[63]	2016	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded. Subset with DEXA imaging	1,035	8,832	63.3 ± 7.8	0	11.6	1.07 (1.01 to 1.13) per 5 kg/m^2	Age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, dietary modification, hormone therapy	Rodriguez et al. (2016)[64] Azarbal *et al*. (2014)[69] Perez *et al*. (2013)[460]
35	Berkovitch *et al*.[413]	2016	Chaim Sheba Medical Centre	Prospective cohort	Israel	Outpatients attending health-screening examinations. At least two visits required. Excluded if BMI <18 kg/m^2, if height/weight missing or if prevalent AF.	288	18,290	49	73	6.4	HR 1.07 (1.04 to 1.11) per 1 kg/m^2	age, sex, CHD (time-dependent), HTN (time-dependent), DM (time-dependent), LDL, low HDL, physical activity	-
36	Rodriguez *et al*.[64]	2016	WHI	Prospective cohort	USA	Age: 50-79 years. Prevalent AF excluded. White participants only	18,090	114083	63.5	0	13.7	1.12 (only in figure) per 5 kg/m^2	Age, education, statin, WHI intervention assignment, HTN, DM, hyperlipidaemia, smoking, PAD, CCF, CHD, alcohol	Azarbal *et al*. (2016)[63] Azarbal *et al*. (2014)[69] Perez *et al*. (2013)[460]
						African American participants only	1,097	11,876	61.4	0	13.7	1.16 (only in figure) per 5 kg/m^2		
						Asian participants only	295	5,174	60.2	0	13.7	1.18 (only in figure) per 5 kg/m^2		
37	Kang *et al.*[205]	2016	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population.	3237	132,063	52.6	53	9	BMI <20 kg/m^2: 1.13 (1.06 to 1.21) per 1 kg/m^2 decrease >20 kg/m^2: 1.06 (1.05 to 1.07) per 1 kg/m^2	Age, alcohol, exercise, HTN, DM, CHD, CCF, CKD, COPD, malignancy, thyroid disease, glucose, urine protein	Baek *et al*. (2017)[195] Son *et al*. (2016)[437]
38	Karas *et al*.[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.10 (1.03 to 1.16) per SD (4.7 kg/m^2) 1.03 (0.96 to 1.10) per SD	Age, sex, ethnicity + smoking, physical activity, alcohol, oestrogen therapy,	Schnabel *et al*. (2010)[164]

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
												(4.7 kg/m^2)	creatinine, SBP, HTN medications, glucose, DM, LDL, HDL, TG, CRP	
												0.92 (0.82 to 1.03) per SD (4.7 kg/m^2)	+ WC	
												0.80 (0.70 to 0.91) per SD (4.7 kg/m^2)	+ HC	
39	Son *et al*.[437]	2016	NHIS	Prospective cohort	Korea	Random sample of Korean population. Age >30 years. AF excluded based on healthcare data.	3,517	206,013	Unclear, only age bands given	59	6	1.02 (1.02 to 1.03) per 1 kg/m2	Age, sex, HTN, CHD, CCF, cholesterol	Baek *et al*. (2017)[195] Kang *et al*. (2016)[205]
40	Thijs *et al*.[416]	2016	CRYSTAL-AF	Post-trial cohort	USA	Implantable monitors put into cryptogenic stroke/TIA patients.	52	441	61.6	64	3	1.02 (0.96 to 1.07) per 1 kg/m^2	Univariate	-
41	Aronis *et al*.[68]	2015	Health ABC	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 years at baseline. Absence of functional disability/life-threatening illness. Prevalent AF and BMI <18.5 kg/m^2 excluded.	371	2,717	74	48	10	1.14 (1.02 to 1.28) per SD (4.7 kg/m^2)	age, sex, ethnicity, site, smoking, SBP, DBP, HTN treatment, total:HDL ratio, heart rate, LVH on ECG, PR interval, CCF, CHD, DM	Dewland *et al*. (2015)[422]
42	Dewland *et al*.[422]	2015	Health ABC	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 years at baseline. Absence of functional disability/life-threatening illness. Prevalent AF and BMI <18.5 kg/m^2 excluded	721	2,768	73	48	10.9	1.05 (0.96 to 1.15) per 1 kg/m^2	Age, sex, smoking, alcohol, statin, HTN, DM, CHD, CCF	Aronis *et al*. (2015)[68]
43	Kokubo *et al*.[453]	2015	Suita	Prospective cohort	Japan	Aged 30-79 years at baseline. Random selection from Suita city. Original and secondary cohort included. Prevalent AF excluded.	253	6,906	55.7	46	12.8	1.05 (1.01 to 1.10) per 1 kg/m^2	Age, sex, hypercholesterolemia, DM, smoking, alcohol, cohort group, CKD, CVA, CHD, CCF, premature ventricular contractions on ECG, SBP, DBP	-

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
44	Sciacqua *et al*.[412]	2015	Catanzaro Atrial Fibrillation Project	Prospective cohort	Italy	Outpatients with cardiovascular risk factors. Excluded: thyroid disease/drugs, VHD, CCF, cardiomyopathy, CKD. Prevalent AF excluded.	546	3,549	60.7	52	3.4	1.03 (1.02 to 1.05) per 1 kg/m^2	Age, sex, glucose, LDL, smoking, SBP, CHA_2DS_2-VASc score	-
45	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2. Prevalent AF excluded	285	4,021	60	48	13.6	1.25 (1.12 to 1.40) per SD (4.2 kg/m^2)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
46	Vermond *et al*.[443]	2015	PREVEND	Prospective cohort	The Netherlands	Aged 28-75 years at baseline in city of Groningen. Those with urinary albumin >10mg/l and random controls selected for cohort. Excluded: IDDM, pregnant women, those without ECG. Prevalent AF excluded	265	8,265	49.4	50	9.7	1.45 (1.18 to 1.82) per 5 kg/m^2	Age, sex, HTN drug use, previous MI, previous stroke	Hobbelt *et al*. (2017)[444]
47	Zethelius *et al*.[199]	2015	Swedish National Diabetes Registry	Prospective Cohort	Sweden	Aged 30-79 years. BMI ≥18 kg/m^2 with Type 2 DM and HbA1c ≥5%. No history of bariatric surgery. Prevalent AF excluded.	4,141	83,162	64.1	0.58	6.8	1.31 (1.27 to 1.36) per 5 kg/m2	Age, sex, duration, HbA1c, cholesterol, HDL, triacylglycerol, smoking, albuminuria, DM treatment, statins, education, CHD, CCF	Hallstrom *et al*. (2019)[436]
48	Azarbal *et al*.[69]	2014	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded.	9,792	81,317	63.4	0	11.5	1.12 (1.10 to 1.14) per 5 kg/m^2	Age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, physical activity	Azarbal *et al*. (2016)[63] Rodriguez *et al*. (2016)[64] Perez *et al*. (2013)[460]
49	Frost *et al*.[191]	2014	DDCH	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.26 (1.21 to 1.30) per SD (3.6 kg/m^2 [M]/4.4 kg/m^2[F])	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, VHD	Frost *et al*. (2005)[202] Fenger-Grøn *et al*. (2017)[66]
50	Knuiman *et al*.[208]	2014	Busselton Health Study	Prospective cohort	Australia	Busselton residents. Age 25-84 at baseline. Prevalent AF and	343	4,267	52	44	15	1.34 (1.21 to 1.49) per SD	Age, sex, height	-

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
						missing covariates excluded						(4.2 kg/m^2)		
							178	2,406	52	0		1.16 (1.02 to 1.32) per SD (4.2 kg/m^2)	Age, sex, height	
							164	1,861	52	100		1.64 (1.35 to 1.99) per SD (4.2 kg/m^2)	Age, sex, height	
51	Reeves *et al.*[201]	2014	Million Women study	Prospective Cohort	UK	Aged 50 to 64 years at baseline. Recruited through breast screening clinics. Excluded: missing BMI, any cancer, prevalent AF hospitalization	11,078	1,251,619	56.2	0	9.2	1.43 (1.40 to 1.46) per 5 kg/m^2	age, region, SES, age at first birth, parity, smoking, alcohol, physical activity	-
52	Sandhu *et al.*[462]	2014	WHS	Prospective cohort (post-trial)	USA	Women health professionals without CHD. Prevalent AF excluded	394	34,720	53	16.4	16.4	1.03 (1.02 to 1.05) per 1 kg/m^2	OUTCOME: Paroxysmal AF Age, aspirin, vitamin E, beta-carotene, HTN, DM, cholesterol, alcohol, smoking, exercise, MI, stroke, revascularization, CCF	Tedrow *et al.* (2010)[461]
							690					1.07 (1.05 to 1.09) per 1 kg/m^2	OUTCOME: Persistent AF Adjustments as above	
53	Schmidt *et al.*[415]	2014	Conscription Research Database	Prospective cohort	Denmark	All men presenting to the draft board in 1955 and 1965 birth cohorts in northern Denmark.	227	12,850	19 (at baseline)	100	26	1.12 (1.07 to 1.16) per 1 kg/m^2	Years of education, height, age as the time scale	-
54	Karasoy *et al.*[432]	2013	Medical Birth Registry – Denmark	Prospective cohort	Denmark	Women giving birth 2004-9 aged 20 to 50 years. Prior AF, VHD, digoxin or amiodarone use were excluded.	110	271,203	30.6	0	4.6	1.07 (1.04 to 1.11) per 1 kg/m^2	Age, year of inclusion, thyroid disease, beta-blockers	-
55	Perez *et al.*[460]	2013	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded	8,252	81,892	63	0	9.8	1.12 (1.10 to 1.14) per 5 kg/m^2	Age, ethnicity, HTN, DM, Lipids, CCF, MI, CHD, PAD, smoking, alcohol, hormone therapy, educational level	Azarbal *et al.* (2016)[63] Rodriguez *et al.* (2016)[64] Azarbal *et al.* (2014)[69]

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
56	Grundvold *et al*.[463]	2012	-	Prospective cohort	Norway	Men aged 40-59 without history of CHD, HTN, DM, thyroid disease, cancer, pulmonary, renal or liver disease.	270	2,014	50	100	35	1.16 (1.02 to 1.32) per SD (2.8 kg/m^2)	Age, SBP, smoking, total cholesterol, blood glucose	-
57	Schnabel *et al*.[164]	2010	AGES	Prospective Cohort	Iceland	Men and women born 1907-35, living in Reykjavik in 1967 and alive in 2002. Prevalent AF excluded by baseline ECG.	226	4,238	76.3	37.3	5	1.22 (1.05 to 1.41) per 5 kg/m^2	Age, sex	-
			CHS	Prospective Cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded. White participants	832	8,254 (person intervals)	75.1	40.6	5	1.14 (1.05 to 1.23) per 5 kg/m^2		Karas *et al*. (2016)[67]
						African American participants	126	1,552 (person intervals)	75.3	35.8	5	1.29 (1.10 to 1.51) per 5 kg/m^2		
			FHS – Original and Offspring	Prospective Cohort	USA	Prevalent AF excluded	175	8,044 (person intervals)	60.9	44.6	5	1.20 (1.01 to 1.42) per 5 kg/m^2		Connor *et al*. (2019)[193] Schnabel *et al*. (2009)[419] Wang *et al*. (2004)[75]
58	Smith *et al*.[76]	2010	Malmo Diet and Cancer Study	Prospective cohort	Sweden	All men born 1923-45 and women 1923-50 in Malmo, Sweden. Baseline exam 1991-6. Prevalent AF excluded	807	12,118	59.1	100	11.2	1.08 (1.06 to 1.10) per 1 kg/m^2	Age, HTN, CCF, MI, smoking	Zia *et al.* (2020)[207]
							623	18,323	57.3	0		1.06 (1.04 to 1.08) per 1 kg/m^2		
59	Tedrow *et al*.[461]	2010	WHS	Prospective cohort (post-trial)	USA	Women health professionals without CHD. Prevalent AF excluded	834	33,990	54.6	0	12.9	1.05 (1.03 to 1.06) per 1 kg/m^2	Age, ethnicity, vitamin E, beta carotene, aspirin, DM, HTN, hypercholesterolemia, alcohol, smoking, physical activity	Sandhu *et al*. (2014)[462]
60	Minami *et al*.[467]	2009	-	Nested case-control	Japan	Cases: male workers newly diagnosed with AF on routine ECG who had not had AF on 3 prior annual check-ups. Controls: male	69	207	57.6	100	3 years (retrospective)	OR 1.11 (0.98 to 1.26) per 1 kg/m^2	Age, SBP, cardiomegaly at onset of AF, alcohol	-

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
						workers without AF on current/prior check-ups								
61	Rosengren *et al*.[211]	2009	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	1,253	6,903	51.5	100	Maximum 34.3 (no average given)	1.04 (1.02 to 1.06) per 1 kg/m^2	Age at baseline, CCF, MI, SBP, HTN, smoking, DM, alcohol, occupational class	Wilhelmsen *et al*. (2001)[224]
62	Schnabel *et al*.[419]	2009	FHS – Original and Offspring	Prospective Cohort	USA	11th or 17th examination of original cohort and 3rd examination of offspring cohort. Age ≥35 years	457	4764	60.9	45	10	1.19 (1.08 to 1.30) per SD (4.3 kg/m^2)	Age, sex	Connor *et al*. (2019)[193] Schnabel *et al*. (2010)[164] Wang *et al*. (2004) [75]
63	Gami *et al*.[442]	2007	Olmsted county	Retrospective cohort	USA	Adults undergoing polysomnography diagnosed with obstructive sleep apnoea. Prevalent AF excluded	133	3,542	49	66	4.7	1.03 (1.02 to 1.05) per 1 kg/m^2	Age, sex, smoking, HTN, DM, CHD, CCF	-
						Those developing AF <65 years old	Unclear		Unclear	Unclear		1.07 (1.05 to 1.10) per 1 kg/m^2		
64	De Bacquer *et al*.[468]	2007	Belgium Interuniversity Research on Nutrition and Health survey	Nested case-control	Belgium	Age 65 to 84 at baseline (1994). AF at initial screening excluded. Cases: Those developing AF during follow-up. Controls: age and sex matched.	40	160	64.6	55	10 years (retrospective)	OR 1.11 (1.01 to 1.24) per 1 kg/m^2	SBP, ischaemic ECG changes, P-wave duration, P-wave morphology	-
65	Murphy *et al*.[203]	2006	Renfrew-Paisley	Prospective cohort	Scotland	Age: 45-64 at recruitment. From Renfrew or Paisley in Scotland. Excluded those with BMI <18.5 kg/m^2.	78	6,992	54	100	20	0.99 (0.93 to 1.06) per 1 kg/m^2	Age, adjusted FEV_1, smoking, social class	
							94	8,152	54	0		1.06 (1.02 to 1.11) per 1 kg/m^2		
							172	15,144	54	46		1.05 (1.01 to 1.08) per 1 kg/m^2		
66	Frost *et al*.[202]	2005	DDCH	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	372	22,482	56	100	5.7	1.08 (1.05 to 1.11) per 1 kg/m^2	Age, sex, height, education, smoking, alcohol, total cholesterol, HTN treatment, SBP	Frost *et al*. (2014)[191] Fenger-Grøn *et al*. (2017) [66]
							181	25,107		0		1.06 (1.03 to 1.09)		

Appendix Table B.3: Details of studies examining the association of body mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
												per 1kg/m^2		
67	Wang *et al*.[75]	2004	FHS – Original and Offspring	Prospective Cohort	USA	16th examination of original cohort and 2nd examination of offspring cohort. Age ≥35 years. Prevalent AF excluded BMI ≥18.5 kg/m^2	292	2,384	55.5	100	13.7	1.04 (1.01 to 1.07) per 1 kg/m^2	Age, SBP, HTN medication, DM, LVH on echocardiography, prior MI or CCF, smoking, murmur	Connor *et al*. (2019)[193] Schnabel *et al*. (2010)[164] Schnabel *et al*. (2009)[419]
							234	2,898	57.7	0	13.7	1.04 (1.01 to 1.07) per 1 kg/m^2		
68	Wilhelmsen *et al*.[224]	2001	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	754	7,495	Unclear	100	25.2	1.07 (1.04 to 1.10) per 1 kg/m^2	Age, sex, MI, CCF, height, HTN	Rosengren *et al*. (2009)[211]

ACCORD - Action to Control Cardiovascular Risk in Diabetes, **AF** – atrial fibrillation, **AGES** – age, gene/environment susceptibility, **Apo** – apolipoprotein, **BMI** – body mass index, **BNP** – brain natriuretic peptide, **BP** – blood pressure, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** – Cardiovascular Health Study, **CI** – confidence interval, **CIN** – contrast induced nephropathy, **CKD** – chronic kidney disease, **COPD** – chronic obstructive pulmonary disease, **CRP** – C-reactive protein, **CRYSTAL-AF** – Cryptogenic Stroke and Underlying Atrial Fibrillation, **CTO** – chronic total occlusion, **CVA** – cerebrovascular accident/stroke **DBP** – diastolic blood pressure, **DDCH** – Danish Diet, Cancer and Health, **DEXA** – dual energy X-ray absorptiometry, **DM** – diabetes mellitus, **ECG** – electrocardiogram, **eGFR** – estimated glomerular filtration rate, **FEV_1** – forced expiratory volume in 1 second, **FHS** – Framingham Heart Study, **FHx** – family history, **γ-GTP** – gamma-glutamyl transpeptidase, **HbA1c** – glycated haemoglobin, **HDL** – high density lipoprotein, **Health ABC** - Health, Aging, and Body Composition, **HR** – hazard ratio, **hsCRP** – high-sensitivity C-reactive protein, **HTN** - hypertension, **IQR** – inter-quartile range, **JHS** – Jackson Heart Study, **LA** – left atrial, **LDL** – low-density lipoprotein, **LOOP** - Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals, **LVH** – left-ventricular hypertrophy, **MESA** – multi-ethnic study of atherosclerosis, **MI** – myocardial infarction, **NHIS** - National Health Insurance Service, **NT-proBNP** – N-terminal-pro-brain natriuretic peptide, **PAD** – peripheral arterial disease, **PREVEND** - Prevention of Renal and Vascular End-stage Disease, **PRO.V.A.** - Progetto Veneto Anziani, **RR** – risk ratio, **SBP** – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, TIA – transient ischaemic attack, TG – triglycerides, **UKB** – UK Biobank, USA - United States of America, **VHD** – valvular heart disease, **VIP** – Vasterbotten Intervention Programme, **WC** – waist circumference, **WHI** – Women's Health Initiative, **WHS** – Womens' Health Study

1

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
1	Liu *et al*.[194]	2022	Beijing Friendship hospital	Prospective cohort	China	Acute MI attending Beijing Friendship hospital. Prevalent AF excluded.	132	4,282	63.9	74	42 months	<23.0 kg/m^2	≥30 kg/m^2	1.64 (0.76 to 3.52)	Age, sex, LA size, Killip class, CTO, eGFR, TG, NT-proBNP, peak troponin	-	Yes[194]
												23.0-24.9 kg/m^2		1.61 (0.75 to 3.48)			
												25.0-29.9 kg/m^2		1.08 (0.51 to 2.29)			
2	Zhao *et al*.[200]	2022	Kailuan	Prospective cohort	China	Employees of Kailuan Group (coal mining company). Enrolled 2006-7. Excluded history of AF, MI, CVA, CCF, or cancer.	410	44,135	48.8	78	9.7	<18.5 kg/m^2	18.5 to 23.9 kg/m^2	0.77 (0.25 to 2.44)	Age, sex, physical activity, smoking, alcohol, LDL, heart rate, HTN, DM	-	Yes[200]
												24.0 to 27.9 kg/m^2		1.15 (0.90 to 1.46)			
												≥28.0 kg/m^2		1.73 (1.03 to 1.10)			
3	Hata *et al.*[423]	2021	Hisayama Study	Prospective cohort	Japan	Aged ≥40 years at enrolment. Prevalent AF excluded	230	2,442	59	43	24	<18.5 kg/m^2	18.5-24.9 kg/m^2	1.09 (0.66 to 1.81)	Age, sex	-	No
												≥25 kg/m^2		1.31 (0.97 to 1.77)			
4	Itoh *et al.*[427]	2021	JMDC Claims Database	Retrospective cohort	Japan	Insurance claims database. Aged 20-39 at analysis. Prevalent AF excluded.	267	286,876	34	54	2.8	≥25 kg/m^2	<25 kg/m^2	1.67 (1.28 to 2.17)	Age, sex	Matsuoka *et al.* (2021)[428]	No
														0.91 (0.60 to 1.37)	+ high WC, HTN, DM, dyslipidaemia, smoking, alcohol, poor sleep quality		
5	Kim *et al.*[439]	2021	NHIS - National Sample Cohort	Prospective cohort	Korea	Aged >18 years old. Excluded participants with baseline AF, mitral stenosis, or heart valve surgery. Aged <60 years	2,227	109,336	41.9	51.3	46 months	>25 kg/m^2	≤25 kg/m^2	1.37 (1.22 to 1.55)	age, sex, CVA or TIA, MI, CCF, HTN, DM, COPD, CKD, smoking, alcohol, physical activity	Kang *et al.* (2016)[205] Baek *et al*.(2017)[195] Kim *et al*. (2019)[70] Park *et al*. (2020)[212] Kim *et al*. (2020)[438]	Yes†, partial[195,205,437]

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
						Aged ≥60 years	1,189	392,332	68.0	45.0				1.05 (0.96 to 1.15)			
6	Koshiyama *et al.*[426]	2021	Iwate Prefecture Cohort	Prospective cohort	Japan	Residents of Iwate prefecture attending annual health check-ups. Prevalent AF excluded.	147	33,586	59.3	0	3	≥25 kg/m^2	<25 kg/m^2	1.64 (1.17 to 2.30)	Age, HTN, DM, dyslipidaemia, CVA, smoking, alcohol, exercise, CHD	-	No
							563	38,840	57.2	100				1.55 (1.30 to 1.85)			
7	Matsuoka *et al.*[428]	2021	JMDC Claims Database	Retrospective cohort	Japan	Insurance claims database. Aged ≥20 years at analysis. Prevalent AF or CHD excluded. Missing covariates excluded.	4,270	1,676,217	20-49 years	Unclear	3.3	≥25 kg/m^2	<25 kg/m^2	1.14 (1.04 to 1.24)	Age, sex, high WC, HTN, DM, dyslipidaemia, smoking, alcohol, physical inactivity	Itoh *et al.* (2021)[427]	No
							5,027	639,648	50-59 years		3.5			1.10 (1.02 to 1.18)			
							3,476	281,576	60-75 years		2.7			1.07 (0.98 to 1.17)			
8	Parahuleva *et al.*[418]	2021	Endometrial cancer cohort	Prospective cohort	Bulgaria	Post-menopausal Bulgarian women with endometrial cancer (n=310) or normal endometrium (n=205). Those with previous AF, DVT, PE, cancer, MR, CCF, and PVD excluded.	46	515	<60 years	0	2.5	25 to 29.9 kg/m^2	18.5 to 24.9 kg/m^2	0.94 (0.69 to 1.79)	Age, alcohol, smoking, HTN, DM, hyperlipidaemia, MI, CRP	-	No
												≥30 kg/m^2		1.80 (1.01 to 3.02)			
									≥60 years			25 to 29.9 kg/m^2		0.95 (0.51 to 1.78)			
												≥30 kg/m^2	18.5 to 24.9 kg/m^2	1.86 (1.09 to 3.23)			
9	Singleton *et al.*[434]	2021	MESA	Prospective cohort	USA	Baseline 45-84 years, no CHD. Prevalent AF excluded.	970	6,739	62	47	13.8	25.0 to 29.9 kg/m^2	<25 kg/m^2	0.96 (0.82 to 1.13)	Age, sex, ethnicity, smoking, alcohol, DM, SBP, HTN medication,	Ogunmoroti *et al.* (2018)[433]	Yes†[95]
												30.0 to 34.9 kg/m^2		1.07 (0.88 to 1.30)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
												35.0 to 39.9 kg/m^2		1.53 (1.16 to 2.00)	income, education, LVH on ECG, physical activity		
												≥40.0 kg/m^2		2.16 (1.51 to 3.10)			
10	Tsai *et al.*[457]	2021	TwSHHH	Prospective cohort	Taiwan	Sampled from the Taiwan national health interview survey. ≥20 years old. Those with missing anthropometrics and prevalent AF were excluded.	148	5,742	44.1	50	13.7	≥24 kg/m^2 and metabolically healthy	18.5 to 23.9 kg/m^2	1.97 (0.80 to 4.86)	Age, sex, smoking, alcohol, regular exercise, marital status, education, income	-	No
												≥24 kg/m^2 and metabolically unhealthy		2.64 (1.34 to 5.17)			
11	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.05 (0.92 to 1.19)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	Smith *et al*. (2010)[76]	Yes[200]
												Q3		1.12 (0.98 to 1.28)			
												Q4		1.62 (1.42 to 1.84)			
							2,215	16,078	57	0	19.7	Q2		1.09 (0.96 to 1.25)			
												Q3		1.22 (1.07 to 1.40)			
												Q4		1.52 (1.33 to 1.73)			
12	Feng *et al.*[425]	2020	HUNT3	Prospective cohort	Norway	Resident of Nord-Trøndelag County (Norway), aged >20 years in 2006-2008. Prevalent	1,149	15,214	66.6	43	8.0	25-29.9 kg/m^2	20-24.9 kg/m^2 Average BMI	1.2 (1.0 to 1.4)	Age, sex, height, smoking, education, marital status, physical activity, alcohol	Garnvik *et al*. (2018)[424]	No
												≥30 kg/m^2		1.6 (1.2 to 2.0)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
						AF excluded. Missing BMI excluded.											
13	Haase *et al.*[198]	2020	CPRD	Prospective cohort	UK	Aged ≥18 years with ≥1 height and weight measurement, registered on database for ≥3 years.	Unclear	2,924,952	51	43	11.4	25-29.9 kg/m^2	18.5 – 24.9 kg/m^2	1.15 (1.14 to 1.17)	age, sex, smoking	-	No
												30-34.9 kg/m^2		1.51 (1.48 to 1.53)			
												35-39.9 kg/m^2		2.02 (1.97 to 2.06)			
												40-45 kg/m^2		2.78 (2.68 to 2.87)			
14	Johansson *et al.*[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded	3,200	53,376	46.4	100	14.3	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	0.45 (0.14 to 1.40)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity		Yes[206]
												25.0 to 29.9 kg/m^2		1.21 (1.11 to 1.31)			
												30-34.9 kg/m^2		1.80 (1.61 to 2.02)			
												≥35.0 kg/m^2		2.37 (1.93 to 2.90)			
							1,954	55,041	46.3	0	15.6	<18.5 kg/m^2		0.64 (0.33 to 1.24)			
												25.0 to 29.9 kg/m^2		1.14 (1.02 to 1.26)			
												30-34.9 kg/m^2		1.43 (1.25 to 1.65)			
												≥35.0 kg/m^2		2.19 (1.83 to 2.62)			
15	Kamil-Rosenberg *et al.*[459]	2020	VA Cohort (Washington and Palo Alto)	Prospective cohort	USA	US armed forces veterans who attended a treadmill test for clinical reasons.	2,155	16,397	58.7	0.96	10.7	30 to 34.9 kg/m^2	18.5 to 24.9 kg/m^2	1.13 (0.99 to 1.28)	age, BP, ethnicity, sex, HTN DM, dyslipidaemia, smoking, alcohol	-	No
												≥35 kg/m^2		1.32 (1.13 to 1.55)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
						Those with prevalent AF excluded.											
16	Kim *et al*.[438]	2020	NHIS	Prospective cohort	Korea	Korean people undergoing a health check in 2009. Prior AF excluded	196,136	9,797,418	47	55	8.2	Age-stratified analysis of the same data presented in Kim *et al*. (2019)[70]			Age, sex, alcohol, physical activity, social income, DM, HTN, dyslipidaemia, ESRD, CCF, CHD, thyroid, malignancy, COPD	Kang *et al.* (2016)[205] Baek *et al*.(2017)[195] Kim *et al*. (2019)[70] Park *et al*. (2020)[212] Kim *et al.* (2021)[439]	Yes†, partial[195,205,437]
17	Park *et al*.[212]	2020	NHIS - National Sample Cohort	Prospective cohort	Korea	Random selection from NHIS cohort. Prevalent AF excluded	2,641	368,206	44.1	53	8.5	23 – 24.9 kg/m^2	18.5 – 22.9 kg/m^2	1.26 (1.15 to 1.39)	Age, sex, income, smoking, alcohol, height, HTN, DM	Kang *et al.* (2016)[205] Baek *et al*.(2017)[195] Kim *et al*. (2020)[438] Kim *et al*. (2019)[70] Kim *et al.* (2021)[439]	Yes†, partial[195,205,437]
												≥25 kg/m^2		1.13 (1.01 to 1.25)			
18	Senoo *et al.*[441]	2020	Nishimura Health Survey	Prospective cohort	Japan	Aged ≥40 years at enrolment with ≥2 health screening visits. Prevalent AF excluded.	118	10,921	49.6	100	5.0	≥25 kg/m^2 and <65-years-old	<25 kg/m^2 and < 65-years-old	0.74 (0.47 to 1.17)	age, SBP, HDL, TG, glucose	-	Yes[441]
												≥25 kg/m^2 and ≥65-years-old		6.50 (2.58 to 16.38)			
19	Singleton *et al.*[406]	2020	ACCORD study	Post-trial follow-up	USA	Aged 40-79 years, all have type 2 diabetes mellitus, prevalent AF excluded.	190	10,074	62.7	61	5.0	25.0 to 29.9 kg/m^2	18.5 to 249 kg/m^2	1.24 (0.65 to 2.62)	age, sex, ethnicity, CHD, smoking, treatment group, SBP, total cholesterol, HDL cholesterol, HbA1c	-	Yes[406]
												30.0 to 39.9 kg/m^2		1.91 (1.03 to 3.93)			
												≥ 40.0 kg/m^2		3.69 (1.79 to 8.22)			
20	Wang *et al.*[470]	2020	ARIC	Prospective cohort	USA	45-64 years at baseline. Excluded if	83	2,363	56.7	41	Unclear	25-29.9 kg/m^2	<25 kg/m^2	0.59 (0.32 to 1.07)	Outcome: Paroxysmal AF	Almuwaqqat *et al*. (2019)[410]	No

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
						prior AF or cardiac device implanted.						≥30 kg/m^2		1.61 (0.92 to 2.81)	Age, sex, ethnicity, education, alcohol, CHD, CVA, CCF, beta-blocker, calcium channel blocker	Huxley *et al*. (2011)[408] Huxley *et al*. (2014)[409]	
							117					25-29.9 kg/m^2		0.93 (0.55 to 1.57)	Outcome: Persistent AF		
												≥30 kg/m^2		1.83 (1.08 to 3.13)			
21	Worm *et al.*[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Post-menopausal women. Prevalent AF excluded	850	4,854	70.7	0	14.4	25 - 29.9 kg/m2	<25 kg/m^2	0.99 (0.84 to 1.16)	Age, alcohol, smoking education, exercise, HRT, HTN, hyperlipidaemia, DM, CHD, PVD, CCF, thyroid disease, scanner model	-	No
												≥30 kg/m^2		1.27 (1.03 to 1.55)			
22	Almuwaqqat *et al.*[410]	2019	ARIC	Prospective cohort	USA	45-64 years at baseline. At least two BNP readings. Prior AF excluded	1,806	9,556	62.6	57	18.3	BMI ≥30 kg/m^2 and low NT-proBNP	BMI <30 kg/m^2 and low NT-proBNP	1.51 (1.33 to 1.71)	Age, sex, centre, ethnicity, height, smoking, education, alcohol, DM, MI aspirin, statin, hypnotic drugs, LVH, p-wave terminal force, SBP	Huxley *et al*. (2011)[408] Huxley *et al*. (2014)[409] Wang *et al.* (2020)[470]	No
												BMI ≥30 kg/m^2 and high NT-proBNP		2.87 (2.47 to 3.35)			
23	Connor *et al*.[193]	2019	FHS – original and offspring	Prospective Cohort	USA	Attended examination 50±5 years Prevalent AF excluded.	847	4,392	50.7	47	23.8	<30 kg/m^2	≥30 kg/m^2	0.77 (0.49 to 1.21)	SBP, DBP, smoking, HTN medications, DM, CCF, MI	Wang *et al*. (2004)[75]	Yes[193]

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
24	Fumagalli *et al.*[448]	2019	SHARE	Registry	International	Participants with hypertrophic cardiomyopathy with BMI data and at least one follow-up	717	3,282	55	62	>1	25-30 kg/m^2	<25 kg/m^2	1.07 (0.85 to 1.35)	Age at diagnosis, sex, LVOT obstruction, LA size	-	No
												>30 kg/m^2		1.42 (1.12 to 1.80)			
25	Hallstrom *et al.*[436]	2019	Swedish National Diabetes Registry	Prospective Cohort	Sweden	Age >18 years old with Type-1 DM. Prevalent AF excluded. BMI time updated	749	36,258	35.6	55	9.7	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	1.30 (0.64 to 2.63)	Age, sex, education, Swedish-born, time-updated: DM duration, baseline comorbidities, smoking, HbA1c, and SBP	-	Yes[436]
												25 to 29.9 kg/m^2		1.01 (0.85 to 1.19)			
												30 to 34.9 kg/m^2		1.19 (0.92 to 1.53)			
												≥35.0 kg/m^2		1.96 (1.35 to 2.84)			
26	Kim *et al.*[70]	2019	NHIS	Prospective cohort	Korea	Korean people undergoing a health check in 2009. Prior AF excluded	196,136	9,797,418	47	55	8.2	<18.5 kg/m^2	18.5 to 23 kg/m^2	1.05 (1.03 to 1.08)	Age, sex, alcohol, physical activity, social income, DM, HTN, dyslipidaemia, ESRD, CCF, CHD, thyroid, malignancy, COPD	Kang *et al.* (2016)[205] Baek *et al.*(2017)[195] Kim *et al.* (2020)[438] Park *et al.* (2020)[212] Kim *et al.* (2021)[439]	Yes†, partial[195,205,437]
												23-25 kg/m^2		1.04 (1.03 to 1.06)			
												25-30 kg/m^2		1.13 (1.12 to 1.14)			
												>30 kg/m^2		1.33 (1.30 to 1.35)			
27	Neefs *et al.*[197]	2019	EPIC-Norfolk	Prospective cohort	UK	Men and women aged 45-79 years at baseline. Prior AF excluded	1,408	10,885	58.9	100	19	Quintile 5	Quintile 1	1.58 (1.32 to 1.89)	Age, DM, SBP, thyroid disease, cholesterol	-	No
							1,102	12,857		0				1.54 (1.25 to 1.89)			
28	Shulman *et al.*[435]	2019	Montefiore Medical Centre	Retrospective cohort	USA	>1 ECG between 2000 and 2013. Excluded if AF on first ECG.	4724	48,323	60.1	39	2.3	≥40 kg/m^2	<40kg/m^2	OR 1.19 (1.07 to 1.32)	Age >65, sex, CHD, deprivation, DM, SBP >140 mmHg, ethnicity	-	Yes†[59]

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
29	Zhao *et al.*[417]	2019	CRYSTAL-AF	Prospective cohort	USA	CRYSTAL-AF participants with an implantable cardiac monitor. Prevalent AF excluded	40	214	61.4	66	>1	>30 kg/m^2	≤30 kg/m^2	0.87 (0.43 to 1.76)	Age, HTN, VHD, PVD, CCF, CHD	-	Yes†[416]
30	Andersen *et al.*[223]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription 1972-1995	9,753	1,153,151	44.6	100	26.3	19.6-20.7 kg/m^2	<19.6 kg/m^2	0.98 (0.91 to 1.05)	Region, conscription date, CHD, HTN, CCF, DM, thyroid disease	-	Yes†[58]
												20.8 to 21.9 kg/m^2		1.01 (0.94 to 1.08			
												22.0 to 23.6 kg/m^2		1.07 (1.00 to 1.15)			
												>23.6 kg/m^2		1.42 (1.33 to 1.52)			
31	Ball *et al.*[456]	2018	Tromso	Prospective cohort	Norway	Birth cohort from Tromso, those attending screening in 86-87 and 94-95 included. Prevalent AF excluded	918	11,673	45	100	15.7	18 kg/m^2	23 kg/m^2	0.75 (0.70 to 0.81	Age, SBP, cholesterol, HDL, TG, smoking, physical activity, CHD, DM, HTN medication	-	No
												20 kg/m^2		0.84 (0.80 to 0.88)			
												25 kg/m^2		1.14 (1.10 to 1.18)			
												28 kg/m^2		1.42 (1.30 to 1.56)			
												35 kg/m^2		2.63 (2.04 to 3.38)			
							811	13,126		0		18 kg/m^2		0.82 (0.76 to 0.89)			
												20 kg/m^2		0.89 (0.85 to 0.93)			
												25 kg/m^2		1.08 (1.05 to 1.12)			
												28 kg/m^2		1.22 (1.12 to 1.32)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
												35 kg/m^2		1.60 (1.32 to 1.94)			
32	Carrazco *et al*.[464]	2018	-	Retrospective cohort	USA	Cryptogenic ischaemic stroke patients fitted with ILR	31	100	65.8	48	Unclear	≥30 kg/m^2	<30 kg/m^2	1.24 (1.12 to 1.36)	Age	-	No
33	Crump *et al*.[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	25.6 to 28.9 kg/m^2	≤25.5 kg/m^2	1.47 (1.40 to 1.55)	Age, conscription year, height, weight, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	-	Yes[58]
												≥29.0 kg/m^2		2.22 (2.07 to 2.38)			
34	Foy *et al*.[430]	2018	MarketScan Commercial Claims and Encounters	Retrospective cohort	USA	National claims database from 2005 to 2013. Participant with continuous enrolment between 2005 and 2013.	1,511	67,278	43.8	23	8	ICD-9 code for obesity	No ICD-9 code for obesity	OR 1.40 (1.26 to 1.56)	Age, sex, HTN, DM	-	No
35	Garnvik *et al*.[424]	2018	HUNT3	Prospective cohort	Norway	Resident of Nord-Trøndelag County (Norway), aged >20 years in 2006-2008. Prevalent AF excluded. Missing BMI excluded.	1,459	43,602	52.1	46		25-30 kg/m^2	20-25 kg/m^2	1.18 (1.03 to 1.35)	Age, sex, smoking, alcohol. CHD, occupational status	Feng *et al*. (2019)[425]	No
												≥30 kg/m^2		1.58 (1.36 to 1.83)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
36	Hamada *et al.*[204]	2018	Ningen Dock	Retrospective Cohort	Japan	Age at entry 40-79 years undergoing health check-up 2008-2014. Prevalent AF excluded.	229	42,942	52.4	100	5.5	≥25 kg/m^2 and WC ≥85 cm	<25 kg/m^2 and WC <85 cm	1.53 (1.15 to 2.03)	Age, BP, lipids, glucose, smoking, alcohol, physical activity, renal function, CVA, CHD	-	Yes[204]
							50	22,693	52.6	0		≥25 kg/m^2 and WC ≥90 cm	<25 kg/m^2 and WC <90 cm	3.19 (1.52 to 6.66)			
37	Mazzone *et al.*[431]	2018	Massa Hospital STEMI	Prospective cohort	Italy	STEMI patients undergoing PCI. Excluded: death in hospital, cardiogenic shock, cancer, renal impairment, previous AF.	88	1,135	65.7	74	2	Underweight	Normal	0.88 (0.12 to 6.60)	Univariate	-	No
												Overweight		1.47 (0.85 to 2.54)			
												Obese		2.07 (1.09 to 3.92)			
38	Ogunmoroti *et al.*[433]	2018	MESA	Prospective cohort	USA	Baseline 45-84 years, no CHD. Prevalent AF excluded.	709	6,506	62	47	11.2	20-25 kg/m^2	≥30 kg/m^2	0.77 (0.63 to 0.94)	Age, sex, ethnicity, education, income, health insurance	Singleton *et al.* (2021)[434]	Yes†[95]
39	Persson *et al.*[60]	2018	Medical Birth Registry - Sweden	Prospective Cohort	Sweden	Women born after 1973 who were pregnant 1982-2014. > 18 years old Height 140-200 cm Exclusions: prevalent AF (at time of pregnancy), BMI <15 or >60 kg/m^2	6,993	1,522,329	28.3	0	16.6	<18.5 kg/m^2	20.0 to 22.4 kg/m^2	0.97 (0.81 to 1.15)	Age, DM, HTN, CCF, smoking, pregnancy year, previous parity, education level, CCF during follow-up.	-	Yes[60]
												18.5 to 19.9 kg/m^2		0.96 (0.86 to 1.06)			
												22.5 to 24.9 kg/m^2		1.10 (1.03 to 1.18)			
												25.0 to 27.4 kg/m^2		1.43 (1.33 to 1.55)			
												27.5 to 29.9 kg/m^2		1.74 (1.58 to 1.91)			
												30.0 to 34.9 kg/m^2		2.26 (2.07 to 2.46)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
												≥35.0 kg/m^2		2.77 (2.43 to 3.16)			
40	Staerk *et al.*[420]	2018	FHS (Original, offspring, 3rd generation)	Prospective cohort	USA	Age 55 at enrolment. Prior AF excluded.	816	5,338	Index age 55	47	14	25-29 kg/m^2	<25 kg/m^2	OR 1.26 (1.05 to 1.50)	Univariate	-	Yes†[75,164,193,419]
												≥30 kg/m^2		OR 1.32 (1.08 to 1.60)			
41	Baek *et al.*[195]	2017	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population. AF excluded based on healthcare data.	3,443	501,690	47.6	50	3.9	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	1.10 (0.92 to 1.32)	Age, sex, WC	Kang *et al.* (2016)[205] Kim et al. (2019)[70] Kim *et al*. (2020)[438] Park *et al*. (2020)[212] Kim *et al.* (2021)[439]	Yes[195]
												25.0 to 29.9 kg/m^2		1.29 (1.20 to 1.38)			
												≥30.0 kg/m^2		1.93 (1.64 to 2.24)			
42	Kokubo *et al*.[454]	2017	Suita	Prospective cohort	Japan	Aged 30-79 at baseline. Random selection from Suita city. original and secondary cohort included. Prevalent AF excluded.	311	6,898	55.7	47	Unclear	<18.5 kg/m^2	18.5-25 kg/m^2	1.01 (0.62 to 1.63)	Age, sex, SBP, HTN treatment, smoking, alcohol, cholesterol, CHD, arrhythmia, murmur	-	Yes†[453]
												≥25 kg/m^2		1.53 (1.19 to 1.98			
43	Kwong *et al.*[452]	2017	STRIDE	Retrospective cohort	USA	Age >40 years and cryptogenic stroke/TIA	390	7,671	67.5	51		>30 kg/m^2	≤30 kg/m^2	OR 1.53 (1.05 to 2.18)	Age, HTN, VHD, PVD, CCF, CHD	-	No
44	O'Neal *et al.*[446]	2017	REGARDS	Prospective cohort	USA	Age >45 years who completed a 10-year follow-up examination. Baseline AF excluded. White participants.	781	8,611	63	48	9.4	≥30 kg/m^2	<30 kg/m^2	RR 1.38 (1.20 to 1.60)	Age, sex, income, smoking, DM, HTN, exercise, dyslipidaemia, LVH, CHD	-	No

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
						Black participants	216	5,077	63	36				RR 1.40 (1.06 to 1.85)			
45	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	<20 kg/m^2	20.0 to 24.9 kg/m^2	0.90 (0.56 to 1.44)	Age, sex		Yes[445]
												25.0 to 29.9 kg/m^2		1.18 (1.01 to 1.38)			
												≥30.0 kg/m^2		1.47 (1.25 to 1.74)			
46	Berkovitch *et al*.[413]	2016	Chaim Sheba Medical Centre	Prospective cohort	Israel	Outpatients attending health-screening examinations. At least two visits required. Excluded if BMI <18 kg/m^2, if height/weight missing or if prevalent AF.	288	18,290	49	73	6.4	25.0 to 29.9 kg/m^2	18.0 to 24.9 kg/m^2	1.49 (1.11 to 2.00)	age, sex, CHD (time-dependent), HTN (time-dependent), DM (time-dependent), LDL, low HDL, physical activity	-	Yes[413]
												≥30 kg/m^2		2.34 (1.64 to 3.34)			
47	Diouf *et al*.[411]	2016	AusDiab	Prospective cohort	Australia	Adults ≥25 years	53	5,389	56.6	48	Unclear	≥30 kg/m^2	<25 kg/m^2	2.8 (1.3 to 6.2)	Age, sex, smoking status, alcohol, physical activity, level of education	-	No
48	Kang *et al.*[205]	2016	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population.	3,237	132,063	52.6	53	9	<18.5 kg/m^2	18.5 to 22.9 kg/m^2	1.66 (1.35 to 2.03)	Age, alcohol, exercise, HTN, DM, CHD, CCF, CKD, COPD, malignancy, thyroid disease, glucose, urine protein	Baek *et al*.(2017)[195] Kim *et al*. (2019)[70] Kim *et al*. (2020)[438] Park *et al*. (2020)[212] Kim *et al.* (2021)[439]	Yes[205]
												23.0 to 24.9 kg/m^2		1.18 (1.08 to 1.30)			
												25.0 to 29.9 kg/m^2		1.35 (1.24 to 1.47)			
												≥30 kg/m^2		2.49 (2.12 to 2.92)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
49	Larsson *et al*.[414]	2016	Cohort of Swedish Men, Swedish Mammography Cohort	Prospective cohort	Sweden	Men born 1918 to 1952 and women born 1914 to 1948 alive in 1997. Prevalent AF excluded	6,567	72,390	60.5	54	10.9	<25 kg/m^2	≥25 kg/m^2	RR (0.72 (0.68 to 0.76)	Univariate	-	No
50	Grundvold *et al*.[447]	2015	ROSE	Retrospective cohort	Sweden	Aged 35-79 years with a diagnosis of Type 2 DM in primary care. Exclusions for baseline AF, CHD, or cancer	287	7,169	59.5	53	4.6	25-30 kg/m^2	<25 kg/m^2	1.85 (1.10 to 3.09)	Age, sex, SBP, previous angina pectoris	-	No
												≥30 kg/m^2		2.85 (1.73 to 4.71)			
51	Kokubo *et al*.[453]	2015	Suita	Prospective cohort	Japan	Aged 30-79 years at baseline. Random selection from Suita city. Original and secondary cohort included. Prevalent AF excluded.	253	6,906	55.7	46	12.8	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	1.05 (0.62 to 1.78)	Age, sex, hypercholesterolemia, DM, smoking, alcohol, cohort group, CKD, CVA, CHD, CCF, premature ventricular contractions on ECG, SBP, DBP	-	Yes[453]
												≥25 kg/m^2		1.34 (1.01 to 1.79)			
52	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2. Prevalent AF excluded	285	4,021	60	48	13.6	25.0 to 29.9 kg/m^2 and no metabolic syndrome	18.5 to 24.9 kg/m^2 and no metabolic syndrome	1.01 (0.73 to 1.40)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-	Yes[217]
												≥30 kg/m^2 and no metabolic syndrome		1.75 (1.11 to 2.74)			
												25.0 to 29.9 kg/m^2 and metabolic syndrome		1.67 (1.16 to 2.41)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
												≥30 kg/m^2 and metabolic syndrome		1.92 (1.34 to 2.74)			
53	Azarbal *et al*.[69]	2014	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded.	9,792	81,317	63.4	0	11.5	25.0 to 29.9 kg/m^2 and >9 MET-hours/week	18.5 to 24.9 kg/m^2 and >9 MET-hours/week	1.03	Age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, physical activity	-	Yes[69]
												≥30 kg/m^2 and >9 MET-hours/week		1.17			
												18.5 to 24.9 kg/m^2 and ≤3 MET-hours/week		1.07			
												≥30 kg/m^2 and ≤3 MET-hours/week		1.44			
54	Guenancia *et al*.[469]	2014	Unnamed	Case-control	France	Age >18 years, LA dimensions on echo available, Prevalent AF excluded	91	1123	65.8	69	Unclear	≥30 kg/m^2	<30 kg/m^2	OR 2.28 (1.33 to 3.91)	Age, HTN, CHD history, left ventricular ejection fraction <40%, LA indexed volume, CRP>10	-	No
55	Huxley *et al*.[409]	2014	ARIC	Prospective cohort	USA	Aged 45-64 at baseline. Baseline AF and BMI <18.5 kg/m^2 excluded	1,775	14,219	54.2	45	Unclear	25-29.9 kg/m^2	<25 kg/m^2	1.20 (1.06 to 1.36)	Age, sex, ethnicity, study site, education, income, CHD, smoking, height, physical activity, alcohol	Almuwaqqat *et al*. (2019)[410] Huxley *et al*.[408] (2011) Wang *et al.* (2020)[470]	No
												≥30 kg/m^2		1.95 (1.72 to 2.21)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
56	Reeves *et al*.[201]	2014	Million Women study	Prospective Cohort	UK	Aged 50 to 64 years at baseline. Recruited through breast screening clinics. Excluded: missing BMI, any cancer, prevalent AF hospitalization	11,078	1,251,619	56.2	0	9.2	<22.5 kg/m^2	22.5 to 24.9 kg/m^2 (floating absolute risk used)	0.95 (0.91 to 1.00)	age, region, SES, age at first birth, parity, smoking, alcohol, physical activity	-	Yes[201]
												25.0 to 29.9 kg/m^2		1.24 (1.20 to 1.28)			
												30.0 to 34.9 kg/m^2		1.75 (1.67 to 1.82)			
												≥35.0 kg/m^2		2.90 (2.74 to 3.07)			
57	Sandhu *et al*.[462]	2014	WHS	Prospective cohort (post-trial)	USA	Women health professionals without CHD. Prevalent AF excluded	394	34,720	53	16.4	16.4	25.0 to 29.9 kg/m^2	<25 kg/m^2	1.30 (1.08 to 1.55)	OUTCOME: Paroxysmal AF Age, aspirin, vitamin E, beta-carotene, HTN, DM, cholesterol, alcohol, smoking, exercise, MI, stroke, revascularization, CCF	Tedrow *et al*. (2010)[461]	Yes[462]
												>30 kg/m^2		1.50 (1.22 to 1.84)			
							690					25.0 to 29.9 kg/m^2	<25 kg/m^2	1.51 (1.15 to 1.97)	OUTCOME: Persistent AF Adjustments as above		
												>30 kg/m^2		2.57 (1.93 to 3.40)			
58	Schmidt *et al*.[415]	2014	Conscription Research Database	Prospective cohort	Denmark	All men presenting to the draft board in 1955 and 1965 birth cohorts in northern Denmark.	227	12,850	19 (at baseline)	100	26	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	0.99 (0.52 to 1.87)	Years of education, height, age as the time scale	-	Yes[415]
												25.0 to 29.9 kg/m^2		2.08 (1.48 to 2.92)			
												>30 kg/m^2		2.87 (1.46 to 5.62)			
59	Karasoy *et al*.[432]	2013	Medical Birth Registry	Prospective cohort	Denmark	Women giving birth 2004-9 aged	110	271,203	30.6	0	4.6	<18.5 kg/m^2	18.5 to 24.9 kg/m^2	1.65 (0.88 to 3.35)	Age, year of inclusion, thyroid		

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
			– Denmark			20 to 50 years. Prior AF, VHD, digoxin or amiodarone use were excluded.						25.0 to 29.9 kg/m^2		1.13 (0.68 to 1.88)	disease, beta-blockers		
												30.1 to 35.0 kg/m^2		2.04 (1.13 to 3.69)			
												>35 kg/m^2		3.50 (1.86 to 6.58)			
60	Grundvold *et al*.[463]	2012	-	Prospective cohort	Norway	Men aged 40-59 without history of CHD, HTN, DM, thyroid disease, cancer, pulmonary, renal or liver disease.	270	2,014	50	100	35	25.0 to 27.9 kg/m^2		1.08 (0.81 to 1.45)	Age, SBP, smoking, total cholesterol, blood glucose	-	Yes[463]
												≥28.0 kg/m^2	<25 kg/m^2	1.74 (1.16 to 2.56)			
61	Lipworth *et al*.[450]	2012	SCCS	Prospective cohort	USA	Aged 40-79 at baseline. Included those aged ≥65 in 2008. Black participants only	617	5,810	71.8	0.33	5.8	≥40 kg/m^2	18.5-24.9 kg/m^2	OR 1.48 (1.04 to 2.12)	Age, sex, length of Medicare follow-up	-	No
						White participants only	445	3,026	71.6	0.32	5.6			OR 1.73 (1.06 to 2.81)			
62	Verdecchia *et al*.[225]	2012	ONTARGET / TRANSCEND	Post-hoc trial analysis	International	Age >55 without CCF and with CHD, PAD, CVA, or DM. Those with AF excluded at baseline	2,092	30,424	66.4	70	4.7	Q5	Q1	1.4 (1.2 to 1.6)	Age, sex, smoking, HTN, DM, CVA, CHD, PAD, ethnicity, SBP, Creatinine, LVH, WHR	-	No
63	Hodgkinson *et al*.[421]	2011	GPRD	Prospective cohort	UK	≥18 years. Excluded: VHD and AF at baseline	55,412	271,812	73.8	50	NA	≥30 kg/m^2	20-24 kg/m^2	RR (1.29 (1.15 to 1.45)	COPD, CVA, DM, CCF, hyperthyroidism, CHD, HTN, bisphosphonate, steroids, statins,		
												25-29 kg/m^2		RR (1.02 (0.91 to 1.14)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
															Xanthine derivative, drugs affecting RAA axis, alcohol, smoking,		
64	Huxley *et al*.[408]	2011	ARIC	Prospective cohort	USA	45-64 at baseline. At least two BNP readings. Prior AF excluded	1,511	14,598	54.2	45	17.1	<25 kg/m^2	≥30 kg/m^2	RR 0.65 (0.56 to 0.74)	Age, gender, ethnicity, study site, education, income, height, cardiac disease, BP, DM, smoking history	Almuwaqqat *et al*. (2019)[410] Huxley *et al*. (2014)[409] Wang *et al.* (2020)[470]	No
65	Smith *et al*.[76]	2010	Malmo Diet and Cancer Study	Prospective cohort	Sweden	All men born 1923-45 and women 1923-50 in Malmo, Sweden. Baseline exam 1991-6. Prevalent AF excluded	807	12,118	59.1	100	11.2	>30 kg/m^2	≤30 kg/m^2	1.88 (1.59 to 2.23)	Age, HTN, CCF, MI, smoking	Zia *et al.* (2021)[207]	Yes[76]
							623	18,323	57.3	0		>30 kg/m^2	≤30 kg/m^2	1.66 (1.38 to 2.00)			
66	Tedrow *et al*.[461]	2010	WHS	Prospective cohort (post-trial)	USA	Women health professionals without CHD. Prevalent AF excluded	834	33,990	54.6	0	12.9	25-29.9 kg/m^2	<25 kg/m^2	1.13 (0.96 to 1.34)	Age, ethnicity, vitamin E, beta carotene, aspirin, DM, HTN, hypercholesterolemia, alcohol, smoking, physical activity	Sandhu *et al*. (2014)[462]	Yes[461]
												≥30 kg/m^2		1.77 (1.47 to 2.11)			
67	Rosengren *et al*.[211]	2009	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	1,253	6,903	51.5	100	Maximum 34.3 (no average given)	<20.0 kg/m^2	20.0 to 22.4 kg/m^2	1.11 (0.67 to 1.78)	Age at baseline, CCF, MI, SBP, HTN, smoking, DM, alcohol,	Wilhelmsen *et al*. (2001)[224]	Yes
												22.5 to 24.9 kg/m^2		1.15 (0.94 to 1.41)			

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
												25.0 to 27.4 kg/m^2		1.32 (1.10 to 1.66)	occupational class		
												27.5 to 29.9 kg/m^2		1.50 (1.21 to 1.88)			
												≥30 kg/m^2		1.56 (1.20 to 2.02)			
68	Watanabe *et al*.[440]	2008	Niigata Preventive Medicine study	Prospective cohort	Japan	≥20 years old at baseline with ≥1 blood test and ≥1 follow-up exam. Excluded AF and PPM at baseline.	265	28,449	59.2	34	4.5	≥25 kg/m^2	<25 kg/m^2	(1.64 (1.26 to 2.15)	Age, sex	-	No
69	Murphy *et al*.[203]	2006	Renfrew-Paisley	Prospective cohort	Scotland	Age: 45-64 at recruitment. From Renfrew or Paisley in Scotland. Excluded those with BMI <18.5 kg/m^2.	94	8,152	54	0	20	25.0 to 29.9 kg/m^2	18.5 to 24.9 kg/m^2	1.02 (0.63 to 1.64)	Age, adjusted FEV_1, smoking, social class	-	Yes[203]
												≥30 kg/m^2		2.02 (1.20 to 3.39)			
							172	15,144	54	46		25.0 to 29.9 kg/m^2		1.19 (0.74 to 1.92)			
												≥30 kg/m^2		0.96 (0.42 to 2.20)			
70	Frost *et al*.[202]	2005	DDCH	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	372	22,482	56	100	5.7	25.0 to 29.9 kg/m^2	18.5 to 24.9 kg/m^2	1.75 (1.35 to 2.27)	Age, sex, height, education, smoking, alcohol, total cholesterol, HTN treatment, SBP		Yes[202]
												≥30 kg/m^2		2.35 (1.70 to 3.25)			
							181	25,107		0		25.0 to 29.9 kg/m^2		1.39 (0.99 to 1.94)			
												≥30 kg/m^2		1.99 (1.31 to 3.02)			
71	Wang *et al*.[75]	2004	FHS – Original	Prospective Cohort	USA	16th examination of original	292	2,384	55.5	100	13.7	25.0 to 29.9 kg/m^2	<25 kg/m^2	1.09 (0.82 to 1.43)	Age, SBP, HTN medication,	Connor *et al*. (2019)[193]	Yes[75]

Appendix Table B.4: Details of studies examining the association of body mass index, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
			and Offspring			cohort and 2nd examination of offspring cohort. Age ≥35 years. Prevalent AF excluded BMI ≥18.5 kg/m²	234	2,898	57.7	0	13.7	≥30 kg/m²		1.49 (1.06 to 2.09)	DM, LVH on echocardiography, prior MI or CCF, smoking, murmur		
												25.0 to 29.9 kg/m²		1.11 (0.83 to 1.50)			
												≥30 kg/m²		1.45 (1.03 to 2.05)			
72	Abbott *et al.*[458]	2003	United States Renal Data System	Retrospective cohort	USA	Renal transplant recipient.	709	39,628	43.4	47	3 years (truncated)	>28.3 kg/m²	<21.6 kg/m²	1.79 (1.30 to 2.47)	Graft loss, age, dialysis in first week, rejection, cause of ESRD, medications	-	No
73	Wilhelmsen *et al.*[224]	2001	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	754	7,495	Unclear	100	25.2	24.0 to 26.9 kg/m²	<24.0 kg/m²	1.41 (1.19 to 1.68)	Age, sex, MI, CCF, height, HTN	Rosengren *et al.* (2009)[211]	Yes[224]
												≥27.0 kg/m²		1.80 (1.33 to 2.44)			

ACCORD – Action to Control Cardiovascular Risk in Diabetes, **AF** – atrial fibrillation, **Apo** – apolipoprotein, **ARIC** – Anteherosclerosis risk in Communities, **AusDiab** – Australian Diabetes, Obesity, and Lifestyle Study, **BMI** – body mass index, **BNP** – brain natriuretic peptide, **BP** – blood pressure, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **CKD** – chronic kidney disease, **COPD** – chronic obstructive pulmonary disease, **CPRD** – Clincial Practice Research Datalink, **CRP** – C-reactive protein, CRYSTAL-AF – Cryptogenic Stroke and Underlying Atrial Fibrillation, **CTO** – chronic total occlusion, **CVA** – cerebrovascular accident, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **DVT** – deep vein thrombosis, **ECG** – electrocardiogram, **eGFR** – estimated glomerular filtration rate, **ESRD** – end-stage renal disease, **FEV_1** – forced expiratory volume in one second, FHS – Framingham Heart Study, **FHx** – family history, **HbA1c** – glycated haemoglobin, **GPRD** – General Practice Research Database, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HUNT3** –Nord-Trøndelag Health Study, **LA** – left atrial, **LDL** – low-density lipoprotein, **LVH** – left ventricular hypertrophy, **MESA** – Multi-Ethnic Study of Antherosclerosis, **MI** – myocardial infarction, MR – mitral regurgitation, **NHIS** – national health insurance service, **NT-proBNP** – N-terminal pro brain natriuretic peptide, **ONTARGET** – Ongoing Telmisartan Alone and in Combination with Ramiril Global Endpoint Trial, **PCI** – percutaneous coronary intervention, **PE** – pulmonary embolism, **PPM** – perminant pacemaker, **PRO.V.A.** – Progetto Veneto Anziani, **PVD** – peripheral vascular disease, **ROSE** – Retrospecitve Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering Drug Treatment in Primary Care, **RR** – risk ratio, **SBP** – systolic blood pressure, **SCCS** – Southern Community Cohort Study, **SES** – socioeconomic status, **STEMI** – ST-elevation myocardial infarction, **STRIDE** – Stanford Translational Research Integrated Database Envornment, **TIA** – transient ischaemic attack, **TG** – triglycerides, **TRANSCEND** – Telmisartan Randomised Assessment Study in ACE Intelerant Subjects with Cardiovascualr Disease, **TwSHHH** – Taiwan Survey on Hypertension, Hyperglycemia, and Hyperlipidemia, **UK** – United Kingdom, **USA** – United States of America, **VHD** – valvular heart disease, **VIP** – Vasterbotten Intervention Programme, **WC** – waist circumference, **WHI** – Womens' Health Initiative, **WHR** – waist-hip ratio, **WHS** – Women's Health Study

B.3. Height

Appendix Table B.5: Studies reporting estimates of the association between height and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Height as a continuous variable	*Height and a categorical variable*		
AGES	1	0	Iceland	[471] (also reports from ARIC, CHS, FHS, and RHS)
ARIC	1	0	USA	[471] (also reports from AGES, CHS, FHS, and RHS)
British Regional Heart Study	0	1	UK	[472]
Busselton Health Study	1	0	Australia	[208]
CHS	5	1	USA	[67,213,471,473,474] ([471] also reports from AGES, ARIC, FHS, and RHS)
Conscription Research Database	1	1	Denmark	[415]
Copenhagen city heart study	1	0	Denmark	[475]
DDCH	2	0	Denmark	[66,191]
FHS	1	0	USA	[471] (also reports from AGES, ARIC, CHS, and RHS)
JHS	1	0	USA	[219]
LOOP	1	0	Denmark	[429]
Malmo Diet and Cancer Study	1	1	Sweden	[207]
Medical Birth Registry – Sweden	1	1	Sweden	[60]
MESA	2	1	USA	[218,220,476]
Multifactor Primary Prevention Study	2	2	Sweden	[211,224]
NHIS cohort**	1	0	Korea	[212]
PRO.V.A.	1	1	Italy	[445]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
REGARDS	1	0	USA	[214]
RHS	1	0	The Netherlands	[471] (also reports from AGES, ARIC, CHS, and FHS)
Scottish Heart Health Extended cohort	1	0	UK	[73]
Stockholm county cohort	1	0	Sweden	[217]
Swedish Military Conscription cohort	1	2	Sweden	[58,223]
UKB	1	0	UK	[210]
VIP	1	1	Sweden	[206]
WHS	1	0	USA	[221]
Total studies	**27***	**13**		
Of which presented continuous and categorical data	**9**			

* Studies that include more than a single cohort are only counted once in the total. ** Includes studies using the National Sample cohort selection from the National Health Insurance Service cohort. **AGES** - Age, Gene and Environment-Reykjavik study **ARIC** – atherosclerosis risk in communities cohort, **CHS** - Cardiovascular Health

Study, **DDCH** - Danish Diet, Cancer and Health, **FHS** - Framingham Heart Study, **JHS** – Jackson Heart Study, **LOOP** - Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals, **MESA** - Multi-ethnic study of atherosclerosis, **NHIS** - National Health Insurance Service, **PRO.V.A.** - Progetto Veneto Anziani, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **RHS** – Rotterdam Heart Study, **UK** – United Kingdom, **USA** - United States of America, **VIP** – Vasterbotten Intervention Programme, **WHS** - Women's Health Study, **UKB** – UK Biobank

1

Appendix Table B.6: Details of studies examining height, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.19 (1.14 to 1.24) per SD (6.6 cm)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
							2,215	16,078	57	0	19.7	1.24 (1.19 to 1.29) per SD (6.0 cm)		
2	Bundy *et al*.[218]	2020	MESA	Prospective Cohort	USA	45-84 at baseline, prevalent CHD and AF excluded.	124	3,534	61.3	48	5	1.03 (0.82 to 1.30) per 10 cm	Age, ethnicity, weight, SBP, DBP, smoking, HTN medication, DM, BNP	Alonso *et al*. (2016)[220]
3	Diederichsen *et al*.[429]	2020	LOOP	Prospective Cohort	Denmark	Age >70 at baseline ≥1 of HTN, DM, CVA, CCF. Prevalent AF excluded	37	597	76	57	3.3	1.30 (0.90 to 1.90) per 10 cm	OUTCOME: AF > 24 hours duration. Sex, age, CHA_2DS_2-VASc score, resting heart rate, NT-proBNP, troponin	-
4	Park *et al*.[212]	2020	NHIS – National Sample Cohort	Prospective cohort	Korea	Age >20 years who had received a health check-up randomly selected from NHIS database. Prevalent AF excluded.	2,641	368,206	44.1	53	8.5	1.22 (1.16 to 1.28) per 5 cm	Age, sex, income, smoking, alcohol, BMI, HTN, Type-2 DM	-
5	Johansson *et al*.[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination 1988-2014 with data on height and weight. Prevalent AF excluded	3,200	53,376	46.4	100	14.3	1.16 (1.11 to 1.21) per SD (6.7 cm)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity, weight	-
							1,954	55,041	46.3	0	15.6	1.19 (1.13 to 1.26) per SD (6.1 cm)		
6	Bose *et al*.[214]	2019	REGARDS	Prospective Cohort	USA	Recruitment from multiple USA centres, ethnically diverse group. Baseline AF excluded.	588	5,290	62.4	100	9	OR 1.87 (1.32 to 2.65) per 10 inches	Age, ethnicity, weight, HTN medications, CHD, DM	-
							428	6,516	62.7	0		OR 1.91 (1.30 to 2.81) per 10 inches		
7	Peters *et al*.[73]	2019	Scottish Heart Health Extended Cohort (Scottish Heart Health Study and Scottish MONICA)	Prospective cohort	Scotland	Age: 30-74 at recruitment. No history of CHD at baseline. No exclusion of those with AF (unable to ascertain)	445	8,185	49.0	0	22.6	1.49 (1.29 to 1.71) per SD (6 cm)	Age, FHx of CHD, SES, smoking, SBP, cholesterol, HDL	-
							591	7,552	49.0	100	22.6	1.38 (1.23 to 1.54) per SD (7 cm)		

Appendix Table B.6: Details of studies examining height, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
8	Austin *et al*.[219]	2018	JHS	Prospective cohort	USA	Residents of Jackson, Mississippi. Crossover with ARIC (31%). Prevalent AF excluded.	242	5,240	55.2	36	8.5	1.29 (1.04 to 1.60) per 10 cm	Age, sex, weight, glycaemic status, HTN medication, SBP, DBP, CHD history, FEV_1, eGFR, PR interval, smoking, education, insurance status	-
9	Crump *et al*.[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	1.04 (1.03 to 1.05) per 5 cm	Age, conscription year, weight, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	-
10	Lai *et al*.[210]	2018	UKB	Prospective cohort	UK	Participants with genotype data, white ethnic background. Excluded extreme height. Combined prevalent and incident	15,328	417,434	56.8	46		1.42 (1.38 to 1.45) per SD (9.2 cm)	Age, sex, obesity, SES, smoking, physical activity, SBP, use of insulin, FHx of CHD	-
11	Marott *et al*.[475]	2018	Copenhagen City Heart Study	Prospective cohort	Denmark	Random sample from Copenhagen, men and women >20 years old in 1976-8 Incident AF from 1976-1978 survey	335	12,782	53	46		1.40 (1.06 to 1.85) per 10 cm	Age, age^2, sex, survey number	-
						Incident AF from 1981-84 survey	578	12,172	56	45		1.35 (1.10 to 1.66) per 10 cm		
						Incident AF from 1991-4 survey	749	9,135	58	43		1.65 (1.40 to 1.93) per 10 cm		
						Incident AF from 2001-3 survey	633	5,496	58	42		1.46 (1.24 to 1.72) per 10 cm		
12	Persson *et al*.[60]	2018	Medical Birth Registry	Prospective Cohort	Sweden	Women born after 1973 who became pregnant 1982 to 2014. > 18 years old Height 140 to 200 cm Excluded prevalent AF (at time of pregnancy), and BMI <15 or >60 kg/m^2	6,993	1,522,329	28.3	0	16.6	1.05 (1.05 to 1.05) per 1 cm	Age, DM, HTN, CCF, smoking, pregnancy year, previous parity, education level, CCF during follow-up.	-
13	Fenger-Grøn *et al*.[66]	2017	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56	47	8.3	1.29 (1.24 to 1.33) per SD (6.5 cm [M], 6.0 cm[F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Frost *et al*. (2014)[191]

Appendix Table B.6: Details of studies examining height, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
												1.04 (1.00 to 1.08) per SD (6.5 cm [M], 6.0 cm[F])	+ lean body mass	
14	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	36	4.4	OR 1.05 (1.04 to 1.06) per 1 cm	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-
15	Alonso *et al*.[220]	2018	MESA	Prospective cohort	USA	45-84 at baseline, no CHD at baseline. Prevalent AF excluded.	351	6663	62	47	10.2	1.3 (1.1 to 1.4) per 10 cm	Age, ethnicity, height, SBP, DBP, smoking, HTN medication, DM	Bundy *et al*. (2020)[218]
16	Karas *et al*.[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.40 (1.28 to 1.54) per SD (9.4 cm)	age, sex, ethnicity, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medications, glucose, DM, LDL, HDL, triglycerides, CRP	Rosenberg *et al*. (2014)[473] Alonso *et al*. (2013)[471] Rosenberg *et al*. (2012)[213] Psaty *et al*. (1997)[474]
												1.30 (1.18 to 1.44) per SD (9.4 cm)	+ weight	
												1.35 (1.23 to 1.48) per SD (9.4 cm)	+ WC	
17	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, or BMI <18.5 kg/m^2. Prevalent AF excluded	285	4,021	60	48	13.6	1.72 (1.44 to 2.04) per SD (9.1 cm)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
18	Frost *et al*.[191]	2014	DDCH study	Prospective cohort	Denmark	Age: 50-64 and born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.29 (1.24 to 1.34) per SD (6.5 cm [M], 6.0 cm[F])	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, VHD	Fenger-Grøn *et al*. (2017) [66]
												1.16 (1.11 to 1.21) per SD (6.5 cm [M], 6.0 cm[F])	+ weight	

Appendix Table B.6: Details of studies examining height, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
19	Knuiman *et al.*[208]	2014	Busselton Health Study	Prospective cohort	Australia	Busselton residents. Age 25-84 at baseline. Prevalent AF and missing covariates excluded.	343	4,267	52	44	15	1.04 (1.02 to 1.06) per 1 cm	Age, sex, HTN treatment	-
20	Rosenberg *et al.*[473]	2014	CHS	Prospective Cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded	879	3,906	72.5	38	13.2	1.38 (1.24 to 1.54) per 10 cm	Age, sex	Karas *et al.* (2016)[67] Alonso *et al*. (2013)[471] Rosenberg *et al*. (2012)[213] Psaty *et al*. (1997)[474]
21	Schmidt *et al*. [477]	2014	Conscription Research Database	Prospective cohort	Denmark	All men presenting to the draft board in 1955 and 1965 birth cohorts in northern Denmark. No AF at baseline.	227	12,850	19 (at baseline)	100	26	1.32 (1.07 to 1.62) per 10 cm	Years of education, age as the time scale	-
22	Alonso *et al.*[471]	2013	FHS (Offspring)	Prospective cohort	USA	Recruited 1971 to 1975. Free of AF at 6th examination cycle.	143	2,838	60	45	5	1.25 (0.96 to 1.62) per 10 cm	Age, sex	
			CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded. White only.	560	4,324	73	41	5	1.26 (1.11 to 1.44) per 10 cm		Karas *et al.* (2016)[67] Rosenberg *et al.* (2014)[473] Rosenberg *et al.* (2012)[213] Psaty *et al*. (1997)[474]
						African American	64	719	73	34	5	1.11 (0.76 to 1.64) per 10 cm		
			ARIC	Prospective cohort	USA	Aged 45-64 at baseline between 1987-9. Prevalent AF excluded. White only	343	8,305	63	45	5	1.39 (1.17 to 1.65) per 10 cm		
						African American	76	2,370	62	36	5	1.44 (1.08 to 1.91) per 10 cm		
			AGES	Prospective cohort	Iceland	Men and women in Reykjavik born between 1907 and 1935 surviving to 2002-6. Prevalent AF excluded.	408	4,469	76	40	5	1.17 (0.98 to 1.39) per 10 cm		
			RHS	Prospective cohort	The Netherlands	Men and women >55 years old, living in Rotterdam. Prevalent AF excluded.	177	3,203	72	41	5	1.41 (1.10 to 1.79) per 10 cm		

Appendix Table B.6: Details of studies examining height, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
23	Conen *et al*.[221]	2013	WHS	Prospective Cohort	USA	Women health professionals without CHD. Prevalent AF excluded. No atrial enlargement	468	34,713	58	0	16.4	1.29 (1.10 to 1.50) per 10 cm	Age, weight, HTN, DM, ethnicity, education, alcohol, smoking, exercise, using time-varying covariates	-
						Atrial enlargement	328		60			1.36 (1.13 to 1.63) per 10 cm		
24	Rosenberg *et al*.[213]	2012	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded.	684	3,022	72	0	13.6	1.32 (1.16 to 1.50) per 10 cm	Age, BMI, clinical site, ethnicity, education	Karas *et al*. (2016)[67] Rosenberg *et al*. (2014)[473] Alonso *et al*. (2013)[471] Psaty *et al*. (1997)[474]
							568	2,095	73	100	13.6	1.26 (1.11 to 1.44) per 10 cm		
25	Rosengren *et al*.[211]	2009	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded.	1,253	6,903	51.5	100	Maximum 34.3 (no average given)	1.04 (1.03 to 1.05) per 1 cm	Age, CCF, MI, SBP, HTN, smoking, DM, alcohol, occupational class	Wilhelmsen *et al*. (2001)[224]
26	Wilhelmsen *et al*.[224]	2001	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded.	754	7,495	Unclear	100	25.2	1.04 (1.03 to 1.06) per 1 cm	Age, sex, MI, CCF, stroke, height, BMI, HTN	Rosengren *et al*.(2009)[211]
27	Psaty *et al*.[474]	1997	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded.	304	4,844	72.6	42	3	1.03 (1.02 to 1.05) per 1 cm	Age, sex, alcohol, SBP, cholesterol, glucose, VHD, beta-blocker, diuretics, CHD, cardiac injury score, FEV_1, LA size, ethnicity	Karas *et al*. (2016)[67] Rosenberg *et al*. (2014)[473] Alonso *et al*. (2013)[471] Rosenberg *et al*. (2012)[213]

AF – atrial fibrillation, **ARIC** – atherosclerosis risk in communities cohort, **BMI** – body mass index, **BNP** - brain natriuretic peptide, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** - Cardiovascular Health Study, **CI** – confidence interval, **CRP** – C-reactive protein, **CVA** – cerebrovascular accident, **DBP** – diastolic blood pressure, **DDCH** - Danish Diet, Cancer and Health, **DM** – diabetes mellitus, **eGFR** – estimated glomerular filtration rate, **FEV_1** – forced expiratory volume in one second, **FHx** – family history, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **JHS** – Jackson Heart Study, **LA** – left atrium, **LDL** – low-density lipoprotein, **LOOP** - Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals, **MESA** - Multi-ethnic study of atherosclerosis, **MI** – myocardial infarction, **NHIS** - National Health Insurance Service, **NT-proBNP** – N-terminal-pro-brain natriuretic peptide, **PRO.V.A**. - Progetto Veneto Anziani, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **RHS** - Rotterdam Heart Study, **RR** – risk ratio, **SBP** – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, **UKB** – UK Biobank, **VIP** – Vasterbotten Intervention Programme, **VHD** – valvular heart disease, **WHS** - Women's Health Study

Appendix Table B.7: Details of studies examining height, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported
1	Wannameth ee *et al*.[472]	2021	British Regional Heart Study	Prospective cohort	UK	Men aged 40-59 at enrolment who attended a 30-year re-examination. Prevalent AF excluded.	456	3,346	68.4	100	16	<168.2 cm	168.2 to 172.5 cm	0.65 (0.47 to 0.85)	Age, smoking, physical activity, alcohol, social class, BP, waist circumference, cholesterol, FEV_1, renal function, DM, HTN medication, LVH, CRP	-	No
												172.6 to 176.9 cm		1.05 (0.80 to 1.36)			
												177.0 to 183 cm		1.37 (1.05 to 1.78)			
												>183.0 cm		1.71 (1.13 to 2.51)			
2	Zia *et al*.[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.16 (1.01 to 1.332)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status		Yes[207]
												Q3		1.36 (1.20 to 1.54)			
												Q4		1.66 (1.46 to 1.89)			
							2,215	16,078	57	0	19.7	Q2	Q1	1.20 (1.06 to 1.36)			
												Q3		1.42 (1.26 to 1.61)			
												Q4		1.93 (1.71 to 2.18)			
3	Johansson *et al*.[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination 1988-2014 with data on height and weight.	3,200	53,376	46.4	100	14.3	174 to 177 cm	< 174 cm	1.13 (1.01 to 1.25)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity, weight	-	Yes[206]
												178 to 182 cm		1.16 (1.05 to 1.28)			

Appendix Table B.7: Details of studies examining height, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported
						Prevalent AF excluded						≥183 cm		1.47 (1.31 to 1.64)			
							1,954	55,041	46.3	0	15.6	161 to 164 cm	<161 cm	1.15 (1.02 to 1.30)			
												165 to 168 cm		1.23 (1.08 to 1.40)			
												≥169 cm		1.50 (1.31 to 1.72)			
4	Worm *et al.*[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Post-menopausal women. Baseline AF excluded	850	5,704	70.7	0	11.5	Highest third	Lowest third	1.53 (1.28 to 1.83)	Age, alcohol, smoking education, exercise, HTN, hormone replacement therapy, DM, CHD, PAD, CCF, thyroid disease, scanner model	-	No
5	Crump *et al.*[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	175 to 181.4 cm	<175 cm	1.05 (1.01 to 1.09)	Age, conscription year, weight, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	-	Yes[58]
												≥181.5 cm		1.53 (1.48 to 1.59)			
6	Persson *et al.*[60]	2018	Medical Birth Registry	Prospective Cohort	Sweden	Women born after 1973 who became pregnant 1982 to 2014. > 18 years old Height 140 to 200 cm Excluded prevalent AF (at time of	6,993	1,522,329	28.3	0	16.6	162 to 166 cm	< 162cm	1.22 (1.12 to 1.32)	Age, DM, HTN, CCF, smoking, pregnancy year, previous parity, education level, CCF during follow-up.	-	Yes[60]
												167 to 170 cm		1.46 (1.35 to 1.58)			
												≥170 cm		2.01 (1.87			

Appendix Table B.7: Details of studies examining height, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported
						pregnancy), and BMI <15 or >60 kg/m^2								to 2.15)			
7	Andersen *et al*.[223]	2017	Swedish military conscripts	Prospective cohort	Sweden	Military conscripts excluding those with pre-existing CHD or AF	9,753	1,153,151	44.6	100	26.3	Highest quintile	Lowest quintile	1.95 (1.82 to 2.10)	Region, conscription date, education, weight, muscle strength, exercise capacity	-	Yes†[58]
8	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	36	4.4	162 to 166 cm [M] / 149 to 152 cm [W]	<162 cm [men] / < 149 cm [women]	1.04 (0.85 to 1.28)	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-	Yes[445]
												167 to 170 cm [M] / 153 to 156 cm [W]		2.31 (1.89 to 2.82)			
												≥171 cm [M] / ≥157 cm [W]		2.42 (1.88 to 3.12)			
9	Yeboah *et al*.[476]	2017	MESA	Prospective cohort	USA	Aged 45-84 years at baseline. Baseline AF excluded.	539	6,814	62.2	48	10.2	Above median	Below median	1.38 (1.07 to 1.79)	Age, sex, ethnicity, weight, SBP, DBP, cholesterol, HDL, DM, smoking, HTN medication, statin	-	Yes†[218,220]
10	Schmidt *et al*.[477]	2014	Conscription Research Database	Prospective cohort	Denmark	All men presenting to the draft board in 1955 and 1965 birth cohorts in northern Denmark. No AF at baseline.	227	12,850	19 (at baseline)	100	26	175 to 178 cm	<175 cm	1.24 (0.84 to 1.83	Years of education, age as the time scale	-	Yes[477]
												179 to 182 cm		1.61 (1.10 to 2.34)			
												>182 cm		1.60 (1.11 to 2.33)			

Appendix Table B.7: Details of studies examining height, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported
11	Rosenberg *et al.* [213]	2012	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded.	684	3,022	72	0	13.6	≤150 cm	155 to 160 cm	0.74 (0.53 to 1.04)	Age, BMI, clinical site, ethnicity, education	-	Yes[213]
												150 to 155 cm		0.76 (0.60 to 0.96)			
												160 to 165 cm		1.11 (0.91 to 1.35)			
												>165 cm		1.31 (1.05 to 1.64)			
							568	2,095	73	100	13.6	≤165 cm	170 to 175 cm	0.73 (0.52 to 1.00)			
												165 to 170 cm		0.86 (0.67 to 1.10)			
												175 to 180 cm		1.10 (0.87 to 1.37)			
												>180 cm		1.18 (0.91 to 1.54)			
12	Rosengren *et al.*[211]	2009	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded.	1,253	6,903	51.5	100	Maximum 34.3 (no average given)	172 to 175 cm	<172 cm	1.32 (1.11 to 1.57)	Age, CCF, MI, SBP, HTN, smoking, DM, alcohol, occupational class	Wilhelmsen *et al.* (2001)[224]	Yes[211]
												176 to 179 cm		1.51 (1.27 to 1.79)			
												>179 cm		1.81 (1.53 to 2.13)			
13	Wilhelmsen *et al.*[224]	2001	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded.	754	7,495	Unclear	100	25.2	173 to 179 cm	≤172 cm	1.48 (1.22 to 1.80)	Age, sex, MI, CCF, stroke, height, BMI, HTN	Rosengren *et al.* (2009)[211]	Yes[224]

Appendix Table B.7: Details of studies examining height, as a categorical variable, on risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported

† continuous effects are reported from the same dataset but not in the same paper. **AF** – atrial fibrillation, **BP** – blood pressure, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **CRP** – C-reactive protein, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **FEV_1** – forced expiratory volume in one second, **FHx** – family history, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **LVH** – left ventricular hypertrophy, **MESA** – multi-ethnic study of atherosclerosis, **MI** – myocardial infarction, **PAD** – peripheral artery disease, **SBP** – systolic blood pressure, **SES** – socioeconomic status, **UK** – United Kingdom, **USA** – United states of America.

B.4. Waist circumference

Appendix Table B.8: Studies reporting estimates of the association between waist circumference and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	WC as a continuous variable	*WC as a categorical variable*		
ARIC	0	1	USA	409
Busselton Health Study	1	0	Australia	208
CHS	1	0	USA	67
DDCH study	2	0	Denmark	66,191
EPIC-Norfolk	0	1	UK	197
Hisayama Study	0	1	Japan	423
Health ABC	1	0	USA	68
JA Kagoshima Kouseiren	0	1	Japan	478
JMDC claims database	0	2	Japan	427,428
Kailuan cohort	1	1	China	200
NHIS cohort*	1	5	Korea	70,195,438,479,480
Malmo Diet and Cancer Study	1	1	Sweden	207
Morinomiyako Occupational Health Centre cohort	1	0	Japan	*481*
Ningen Dock	1	2	Japan	204,482
ONTARGET/TRANSCEND	0	1	International	225
PRO.V.A.	1	1	Italy	445
REGARDS	0	1	USA	483
Scottish Heart Health Extended cohort	1	0	UK	73
Stockholm county cohort	1	1	Sweden	217
UKB	1	0	UK	226
Individual un-named cohorts	0	1	Varied	484
Total studies	**14**	**20**		
Of which presented continuous and categorical data	**6**			

* Includes studies using the National Sample cohort selection from the National Health Insurance Service cohort. **ARIC** – atherosclerosis risk in communities cohort, **CHS** – Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **EPIC** - European Prospective Investigation into Cancer, **Health ABC** - Health, Aging, and Body Composition, **NHIS** - National Health Insurance Service, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PRO.V.A.** - Progetto Veneto Anziani, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **WC** – waist circumference

Appendix Table B.9: Details of studies examining waist circumference, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Zhao *et al*.[200]	2022	Kailuan	Prospective cohort	China	Employees of Kailuan Group (coal mining company). Enrolled 2006-7. Excluded history of AF, MI, CVA, CCF, or cancer.	410	44,135	48.8	78	9.7	1.02 (1.01 to 1.03) per 1 cm	Age, sex, physical activity, smoking, alcohol, LDL, heart rate, HTN, DM	-
2	Camm *et al.*[226]	2021	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded, Missing or extreme anthropometric measures excluded	14,400	215,196	56.6	100	11.1	1.31 (1.29 to 1.33) per 10 cm	Age, ethnicity, deprivation, smoking, alcohol	-
												1.27 (1.24 to 1.31) per 10 cm	+ BMI	
							8,734	262,708	56.3	0	11.1	1.30 (1.28 to 1.32) per 10 cm	Age, ethnicity, deprivation, smoking, alcohol	
												1.27 (1.24 to 1.31) per 10 cm	+ BMI	
3	Igarashi *et al.*[481]	2021	Morinomiyako Occupational Health Centre cohort	Prospective cohort	Japan	Age ≥40 years old with at least 2 annual follow-up health check-ups. Prevalent AF excluded.	135	56,288	51.5	33	3	1.05 (1.03 to 1.07) per 1 cm	age, LDL cholesterol, ECG code	-
4	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.18 (1.14 to 1.23) per SD [12.7 cm]	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
							2,215	16,078	57	0	19.7	1.18 (1.13 to 1.23) per SD [10.5 cm]		
5	Peters *et al.*[73]	2019	Scottish Heart Health Extended Cohort (Scottish Heart Health Study and Scottish MONICA)	Prospective cohort	Scotland	Age: 30-74 at recruitment No history of CHD at baseline. No exclusion of those with AF (unable to ascertain)	445	8,185	49.0	0	22.6	1.36 (1.21 to 1.52) per SD (12.2 cm)	Age, FHx of CHD, deprivation, smoking, SBP, cholesterol, HDL	-
							591	7,552	49.0	100	22.6	1.49 (1.31 to 1.71) per SD (11.6 cm)		
6	Hamada *et al.*[204]	2018	Ningen Dock	Retrospective Cohort	Japan	Age at entry 40-79 undergoing health check-up 2008 to 2014. Prevalent AF excluded	229	42,942	52.4	100	5.5	1.24 (1.10 to 1.41) per SD (8.2 cm)	Age, BP, lipids, glucose, smoking, alcohol, physical activity, renal function, stroke, CHD	-
							50	22,693	52.6	0		1.47 (1.12 to 1.95) per SD (8.7 cm)		
7	Baek *et al.*[195]	2017	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population. AF excluded based on healthcare data.	3,443	501,690	47.6	50	3.9	1.18 (1.11 to 1.26) per SD (9.4 cm)	Age, sex, BMI	-
8	Fenger-Grøn *et al.*[66]	2017	DDCH study	Prospective cohort	Denmark	Age 50-64 and born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56	47	8.3	1.24 (1.20 to 1.27) per SD (9.9 cm [M]/11.2 cm [F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Frost *et al.* (2014)[191]

Appendix Table B.9: Details of studies examining waist circumference, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
												1.02 (0.99 to 1.06) per SD (9.9 cm [M]/11.2 cm [F])	+ lean mass	
9	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	36	4.4	OR 1.00 (0.99 to 1.00) per 1cm	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-
10	Karas *et al*.[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.10 (1.02 to 1.18) per SD (13.2 cm)	Age, sex, ethnicity, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medication, glucose, DM, LDL, HDL, triglyceride level, CRP	-
												1.11 (1.04 to 1.19)	+ height	
												0.96 (0.86 to 1.08)	+ weight	
11	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2, or prevalent AF.	285	4,021	60	48	13.6	1.35 (1.19 to 1.54) per SD (12.4 cm)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
12	Aronis *et al*.[68]	2015	Health ABC	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 at baseline. Absence of functional disability/life-threatening illness. Prevalent AF excluded. BMI<18.5 kg/m^2 excluded	371	2,717	74	48	10	1.16 (1.04 to 1.28) per SD (12.9 cm)	Age, sex, ethnicity, site, smoking, SBP, DBP, HTN treatment, total:HDL ratio, heart rate, LVH on ECG, PR interval, CCF, CHD, DM	-
13	Frost *et al*.[191]	2014	DDCH	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.3 (1.23 to 1.38) per SD (9.9 cm [men]/11.2 cm [women])	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolaemia, CHD, CCF, valve disease	Fenger-Grøn *et al*. (2017)[66]
14	Knuiman *et al*.[208]	2014	Busselton Health Study	Prospective cohort	Australia	Busselton residents age 25-84 at baseline. Prevalent AF and missing covariates excluded.	343	4,267	52	44	15	1.37 (1.21 to 1.55) per SD (12.7 cm)	Age, sex, height	-
												0.97 (0.72 to 1.31) per SD (12.7 cm)	+ HTN treatment, BMI	

AF – atrial fibrillation, **BP** – blood pressure, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** – Cardiovascular Health Study, **CRP** – C-reactive protein, **CVA** – cerebrovascular accident, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **ECG** – electrocardiogram, **FHx** – family history, **DDCH** - Danish Diet, Cancer and Health, **ECG** – electrocardiogram, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **IQR** – interquartile

Appendix Table B.9: Details of studies examining waist circumference, as a continuous variable, and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data

range, **LDL** – low-density lipoprotein, **LVH** – left ventricular hypertrophy, **MI** – myocardial infarction, NHIS - National Health Insurance Service, **PRO.V.A.** - Progetto Veneto Anziani, **SBP** – systolic blood pressure, **SD** – standard deviation, **RR** – risk ratio, **UKB** – UK Biobank

1

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
1	Kim *et al.*[483]	2022	REGARDS	Prospective cohort	USA	Recruitment from multiple US centres, ethnically diverse group. Baseline AF excluded	999	11,617	63.0	45	9.4	>88 [Men]/ 102 [Women]	≤88 [Men]/ 102 [Women]	1.43 (1.24 to 1.65)	Age, sex, ethnicity, education, income, region, smoking, physical activity, alcohol, HTN, dyslipidaemia, DM, CHD, CVA	-	No
														1.13 (0.95 to 1.35)	+ BMI		
2	Zhao *et al.*[200]	2022	Kailuan	Prospective cohort	China	Employees of Kailuan Group (coal mining company). Enrolled 2006-7. Excluded history of AF, MI, CVA, CCF, or cancer.	410	44,135	48.8	78	9.7	≥90 cm [Men] / ≥80 cm [Women]	<90 cm [Men] / <80 cm [Women]	1.38 (1.11 to 1.60	Age, sex, physical activity, smoking, alcohol, LDL, heart rate, HTN, DM	-	Yes[200]
3	Hata *et al.*[423]	2021	Hisayama Study	Prospective cohort	Japan	Aged ≥40 years at enrolment. Prevalent AF excluded	230	2,442	59	43	24	≥85 [Men] / ≥90 [Women]	<85 [Men] / <90 [Women]	1.44 (1.08 to 1.91)	age, sex, SBP, glucose, HDL, non-HDL, TG, eGFR, CHD, murmur, R-wave amplitude, other arrhythmia, smoking, alcohol, exercise	-	No
4	Itoh *et al.*[427]	2021	JMDC Claims Database	Retrospective cohort	Japan	Insurance claims database. Aged 20-39 at analysis. Prevalent AF excluded.	267	286,876	34	54	2.8	≥85 [Men] / ≥90 [Women]	<85 [Men] / <90 [Women]	1.47 (0.99 to 2.18)	age, sex, obesity, HTN, DM, dyslipidaemia, smoking, alcohol, sleep quality	Matsuoka *et al.* (2021)[428]	No
5		2021		Retrospective cohort	Japan	Insurance claims	4,270	1,676,217	20-49 years	Unclear	3.3	≥85 [Men]/	<85 [Men]/	1.39 (1.27	Age, sex, high BMI,	Itoh *et al.* (2021)[427]	No

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
	Matsuoka *et al*.[428]		JMDC Claims Database			database. Aged ≥20 years at analysis. Prevalent AF or CHD excluded. Missing covariates excluded.	5,027	639,648	50-59 years		3.5	≥90 [Women]	<90 [Women]	to 1.52) 1.28 (1.19 to 1.38)	HTN, DM, dyslipidaemia, smoking, alcohol, physical inactivity		
							3,476	281,576	60-75 years		2.7			1.26 (1.16 to 1.38)			
6	Ninomiya *et al*.[478]	2021	JA Kagoshima Kouseiren Cohort	Prospective cohort	Japan	Adults undertaking ≥2 check-ups at JA Kagoshima Kouseiren Medical Health Care Centre. Prevalent AF excluded.	280	33,562	53.4	100	5	≥85 cm	<85 cm	1.76 (1.31 to 2.36)	age, HTN, dyslipidaemia, eGFR, alcohol, DM	-	No
								33,817	55.2	0		≥90 cm	<90 cm	1.22 (0.68 to 2.18)			
7	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.14 (1.10 to 1.30)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-	Yes[207]
												Q3		1.23 (1.08 to 1.41)			
												Q4		1.67 (1.46 to 1.90)			
							2,215	16,078	57	0	19.7	Q2	Q1	1.13 (0.98 to 1.30)			
												Q3		1.31 (1.14 to 1.50)			
												Q4		1.63 (1.42 to 1.88)			
8	Kim *et al*.[438]	2020	NHIS	Prospective cohort	Korea	Korean people undergoing a health check	196,136	9,797,418	47	55	8.2	Age-stratified analysis of the same data presented in Kim *et al*. (2019)[70]			Age, sex, alcohol, physical	Kim *et al*. (2019)[70], Kwon *et*	Yes†[195]

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
						in 2009. Prior AF excluded.									activity, social income, DM, HTN, dyslipidaemia, ESRF, CCF, CHD, thyroid, malignancy, COPD	*al*. (2019)[479], Choe *et al*. (2018)[480] Baek *et al*. (2017)[195]	
9	Hamada *et al*.[482]	2019	Ningen Dock	Retrospective Cohort	Japan	Age 40-79 years at entry undergoing check-up 2008-2014. Prevalent AF excluded	349	65,984	52.4	66	5.5	>90/85 cm [Men/ Women]	≤90/85 cm [Men/ Women]	1.66 (1.33 to 2.07)	Age, sex, DBP, Alcohol, murmur	-	Yes†[204]
10	Kim *et al*.[70]	2019	NHIS	Prospective cohort	Korea	Korean people undergoing a health check in 2009. Prior AF excluded.	196,136	9,797,418	47	55	8.2	<80/74 cm [Men/ Women]	85-90/80-85 cm [Men/ Women]	0.84 (0.83 to 0.85)	Age, sex, alcohol, physical activity, social income, DM, HTN, dyslipidaemia, ESRF, CCF, CHD, thyroid, malignancy, COPD	Kim *et al*. (2020)[438], Kwon *et al*. (2019)[479], Choe *et al*. (2018)[480] Baek *et al*. (2017)[195]	Yes†[195]
												80-85/75-80 cm [Men/ Women]		0.93 (0.92 to 0.94)			
												90-95/85-90 cm [Men/ Women]		1.09 (1.08 to 1.11)			
												95-100/90-95 cm [Men/ Women]		1.16 (1.14 to 1.18)			
												>100/95 cm [Men/ Women]		1.37 (1.34 to 1.40)			
11	Kwon *et al*.[479]	2019	NHIS	Prospective cohort	Korea	Korean people undergoing a health check in 2009. Prior AF excluded.	20,708	7,830,602	50.6	56	7.3	>90/85 cm [Men/ Women]	≤90/85 cm [Men/ Women]	1.32 (1.26 to 1.38)	Sex, age, smoking, exercise, FHx HTN, stroke, DM, CHD, BMI, Hb, creatinine, total cholesterol, LDL, ALT, HTN, raised glucose, TG, HDL	Kim *et al*. (2020)[438], Kim *et al*. (2019)[70], Choe *et al*. (2018)[480] Baek *et al*. (2017)[195]	Yes†[195]

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
12	Neefs *et al*.[197]	2019	EPIC-Norfolk	Prospective cohort	UK	Men and women aged 45-79 years at baseline. Prior AF excluded.	1,408 1,102	10,885 12,857	58.9	100 0	19	Q5	Q1	1.56 (1.30 to 1.87) 1.76 (1.39 to 2.22)	Age, DM, SBP, thyroid disease, cholesterol	-	No
13	Hamada *et al*.[204]	2018	Ningen Dock	Retrospective Cohort	Japan	Age at entry 40-79 undergoing health check-up 2008 to 2014. Prevalent AF excluded	229 50	42,942 22,693	52.4 52.6	100 0	5.5	≥85 cm and < 25 kg/m^2 BMI ≥85 cm and ≥ 25 kg/m^2 BMI ≥90 cm and < 25 kg/m^2 BMI ≥90 cm and ≥ 25 kg/m^2 BMI	<85 cm and < 25 kg/m^2 BMI <90 cm and < 25 kg/m^2 BMI	1.46 (1.10 to 1.94) 1.53 (1.15 to 2.03) 1.95 (0.59 to 6.42) 3.19 (1.52 to 6.66)	Age, BP, lipids, glucose, smoking, alcohol, physical activity, renal function, stroke, CHD	-	Yes[204]
14	Kim *et al*.[484]	2018	Ulsan Hospital cohort	Retrospective cohort	Korea	Participated in annual/biennial health screening programme. Prior AF excluded	168	21,981	45.9	100	8.7	≥90 cm	<90 cm	HR 1.62 (1.13 to 2.33)	Age, smoking, exercise, alcohol, CKD, HTN, glucose, TG, HDL	-	No
15	Choe *et al*.[480]	2018	NHIS	Prospective cohort	Korea	Korean people undergoing a health check in 2009. Prior AF excluded	225,529	11,886,661	47.5	51	5.4	>90/80 cm [Men/ Women]	≤90/80 cm [Men/ Women]	1.37 (1.36 to 1.38)	Age, sex, alcohol, smoking, physical activity	Kim *et al*. (2020)[438], Kim *et al*. (2019)[70], Kwon *et al*. (2019)[479] Baek *et al*. (2017)[195]	Yes†[195]
16	Baek *et al*.[195]	2017	National Sample Cohort – NHIS	Prospective cohort	Korea	Random sample of Korean population. AF excluded based on	3,443	501,690	47.6	50	3.9	≥90/80 cm [Men/ Women]	<90/80 cm [Men/ Women]	1.20 (1.10 to 1.31)	Age, sex, BMI	Kim *et al*. (2020)[438], Kim *et al*. (2019)[70], Kwon *et*	Yes[195]

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
						healthcare data.										*al*. (2019)[479] Choe *et al*. (2018)[480]	
17	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	36	4.4	94 to 100/91 to 100 [Men/ Women]	<94/91 cm [Men/ Women]	1.60 (1.37 to 1.86)	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-	Yes[445]
												≥101 cm		1.12 (0.96 to 1.31)			
18	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2, or prevalent AF.	285	4,021	60	48	13.6	94 to 102 / 80 to 88 cm [Men/ Women] and no metabolic syndrome	<94 / 80 cm [Men/ Women] and no metabolic syndrome	1.19 (0.80 to 1.78)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-	Yes[217]
												94 to 102 / 80 to 88 cm [Men/ Women] and metabolic syndrome		1.33 (0.86 to 2.04)			
												≥102 / 88 cm [Men/ Women] and no metabolic syndrome		1.37 (0.91 to 2.07)			
												≥102 / 88 cm [Men/ Women] and metabolic syndrome		2.03 (1.44 to 2.87)			
19	Huxley *et al*.[409]	2014	ARIC	Prospective cohort	USA	Aged 45-64 at baseline between 1987-9. Prevalent AF excluded.	1,775	14,219	54.2	45	Unclear	Q4	Q1	2.13 (1.85 to 2.46)	Age, sex, ethnicity, study site, education, income, prior CHD,	-	No

Appendix Table B.10: Details of studies examining waist circumference, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95% CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
															smoking, height, physical activity, alcohol		
20	Verdacchia *et al.*[225]	2012	ONTARGET / TRANSCEND	Post-trial cohort	USA	men/women ≥55 years with CHD, PAD, stroke, or DM, but no CCF	2,092	30,424	66.4	70	4.7	Q5	Q1	1.36 (1.13 to 1.63)	Age, sex, smoking, HTN, DM, stroke, CHD, PAD, ethnicity, SBP, creatinine, LVH, BMI	-	No

† Continuous effects are reported from the same dataset but not in the same paper. **AF** – atrial fibrillation, **ALT** - alanine aminotransferase, **BMI** – body mass index, **BP** – blood pressure, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CKD** – chronic kidney disease, **COPD** – chronic obstructive pulmonary disease, **CVA** – cerebrovascular accident/stroke, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **eGFR** – estimated glomerular filtration rate, **EPIC** - European Prospective Investigation into Cancer, **ESRF** – end-stage renal failure, **FHx** – family history, **Hb** – haemoglobin, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **LDL** – low-density lipoprotein, **LVH** – left ventricular hypertrophy, **MI** – myocardial infarction, **NHIS** – National Health Insurance Service, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PAD** – peripheral arterial disease, **Q** – quintile, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **RR** – risk ratio, **SBP** – systolic blood pressure, **TG** - triglycerides, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease

B.5. Weight

Appendix Table B.11: Studies reporting estimates of the association between weight and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Weight as a continuous variable	*Weight as a categorical variable*		
AGES	1	0	Iceland	[471] (reports from ARIC, CHS, FHS, and RHS as well)
ARIC	1	0	USA	[471] (reports from AGES, CHS, FHS, and RHS as well)
CHS	2	0	USA	[471] (reports from AGES, ARIC, FHS, and RHS as well) [67]
DDCH	2	0	Denmark	[66,191]
EPIC-Norfolk	0	1	UK	[197]
FHS	1	0	USA	[471] (reports from AGES, ARIC, CHS, and RHS as well)
JHS	1	0	USA	[219]
Malmo Diet and Cancer Study	1	1	Sweden	[207]
MESA	2	0	USA	[218,220]
Multifactor Primary Prevention Study	0	1	Sweden	[224]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
REGARDS	1	0	USA	[214]
RHS	1	0	The Netherlands	[471] (reports from AGES, ARIC, CHS, and FHS as well)
Scottish Heart Health Extended cohort	1	0	UK	[73]
Stockholm county cohort	1	0	Sweden	[217]
Swedish Military Conscription cohort	1	2	Sweden	[58,223]
UKB	1	0	UK	[226]
VIP	1	1	Sweden	[206]
WHS	1	0	USA	[221]
Individual un-named cohorts	1	0	Varied	[485]
Total studies	**16***	**7**		
Of which presented continuous and categorical data	**3**			

* Studies that include more than a single cohort are only counted once in the total. **AGES** – age, gene/environment susceptibility, **ARIC** – atherosclerosis risk in communities cohort, **CHS** – Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **EPIC** - European Prospective Investigation into Cancer, **FHS** – Framingham Heart Study, **JHS** - Jackson Heart Study, **MESA** – Multi-Ethnic Study of Atherosclerosis, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **RHS** - Rot-terdam Study, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **VIP** – Vasterbotten Intervention Programme, **WHS** – Women's Health Study

Appendix Table B.12: Details of studies examining weight as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Camm et al.[226]	2021	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded, Missing or extreme anthropometric measures excluded.	14,400	215,196	56.6	100	11.1	1.26 (1.25 to 1.28) per 10 kg	Age, ethnicity, deprivation, smoking, alcohol	-
												1.23 (1.21 to 1.26) per 10 kg	+ WC	
							8,734	262,708	56.3	0	11.1	1.29 (1.27 to 1.31) per 10 kg	Age, ethnicity, deprivation, smoking, alcohol	
												1.27 (1.23 to 1.30) per 10 kg	+ WC	
2	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.26 (1.21 to 1.32) per SD (12.0 kg)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
							2,215	16,078	57	0	19.7	1.26 (1.21 to 1.31) per SD (11.6 kg)		
3	Bundy *et al.*[218]	2020	MESA	Prospective Cohort	USA	45-84 at baseline, prevalent CHD and AF excluded.	124	3,534	61.3	48	5	1.37 (1.11 to 1.69) per 15 kg	Age, ethnicity, height, SBP, DBP, smoking, HTN medication, DM, BNP	Alonso *et al.* (2016)[220]
4	Johansson *et al.*[206]	2020	VIP	Prospective cohort	Sweden	Invited participants aged 30, 40, 50, or 60 years old. Prevalent AF excluded	3,200	53,376	46.4	100	15.6	1.27 (1.22 to 1.32) per SD (13.3 kg)	Age, cholesterol. education, smoking, MI, HTN, DM, alcohol, physical activity, height	-
							1,954	55,041	46.3	0		1.26 (1.20 to 1.32) per SD (13.0 kg)		
5	Muria-Subirats *et al.*[485]	2020	-	Retrospective cohort	Spain	≥18 years old with both HTN and DM. Baseline AF excluded.	428	8,237	79.6	55	4.9	1.03 (1.02 to 1.04) per 1 kg	Age, sex, heart rate, CHA_2DS_2-VASc	-
6	Bose *et al.*[214]	2019	REGARDS	Prospective Cohort	USA	Recruitment from multiple USA centres, ethnically diverse group. Baseline AF excluded	588	5290	62.4	100	9	OR 1.02 (1.01 to 1.02) per 1 kg	Age, ethnicity, height, HTN medications, CHD history, DM	-
							428	6516	62.7	0		OR 1.01 (1.01 to 1.02) per 1 kg		
7	Peters *et al.*[73]	2019	Scottish Heart Health Extended Cohort (Scottish Heart Health Study and Scottish MONICA)	Prospective cohort	United Kingdom	Age: 30-74 at recruitment No history of CHD at baseline	445	8,185	49.0	0	22.6	1.33 (1.21 to 1.47) per SD (12.6 kg)	Age, FHx of CHD, deprivation, smoking, SBP, cholesterol, HDL	-
							591	7,552	49.0	100	22.6	1.47 (1.35 to 1.60) per		

Appendix Table B.12: Details of studies examining weight as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
						No exclusion of those with AF (unable to ascertain)						SD (12.5 kg)		
8	Austin *et al*.[219]	2018	JHS	Prospective cohort	USA	Residents of Jackson, Mississippi. Crossover with ARIC (31%).	242	5240	55.2	36	8.5	1.23 (1.13 to 1.35) per 15 kg	Age, sex	-
9	Crump *et al*.[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	1.13 (1.12 to 1.13) per 5 kg	Age, conscription year, height, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	-
10	Fenger-Grøn *et al*.[66]	2017	DDCH study	Prospective cohort	Denmark	Age: 50-64 Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56	47	8.3	1.33 (1.29 to 1.36) per SD (12.4 kg [M] / 12.2 kg [F]) 1.05 (0.99 to 1.11) per SD (12.4 kg [M] / 12.2 kg [F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake + lean mass	Frost *et al*. (2014)[191]
11	Alonso *et al*.[220]	2016	MESA	Prospective Cohort	USA	45-84 at baseline, prior CHD or AF excluded	351	6,663	62	47	10.2	1.20 (1.10 to 1.30) per 15 kg	Age, ethnicity, height, SBP, DBP, smoking, HTN medication, DM	Bundy *et al*. (2020)[218]
12	Karas *et al*.[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.17 (1.08 to 1.26) per SD (14.6 kg) 1.12 (1.03 to 1.21) per SD (14.6 kg) 1.24 (1.10 to 1.40) per SD (14.6 kg)	Age, sex, ethnicity, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medication, glucose, DM, LDL, HDL, triglyceride level, CRP + Height + WC	Alonso *et al*. (2013)[471]
13	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5kg/m^2, prevalent AF	285	4,021	60	48	13.6	1.47 (1.31 to 1.65) per SD (14.2 kg)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
14	Frost *et al*.[191]	2014	DDCH study	Prospective cohort	Denmark	Age: 50-64 Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.2	1.36 (1.31 to 1.40) per SD (14.1 kg)	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valvular heart disease	Fenger-Grøn *et al*. (2017)[66]

Appendix Table B.12: Details of studies examining weight as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
												1.29 (1.24 to 1.34) per SD (14.1 kg)	+ height	
15	Conen *et al.*[221]	2013	WHS	Prospective cohort	USA	Women health professionals without CHD. Prevalent AF excluded. No atrial enlargement	468	34,713	58	0	16.4	1.07 (1.00 to 1.14) per 10 kg	Age, height, HTN, DM, ethnicity, alcohol, smoking, exercise	-
						Atrial enlargement	328					1.34 (1.26 to 1.43) per 10 kg		
16	Alonso *et al.*[471]	2013	FHS (Offspring)	Prospective cohort	USA	Recruited 1971 to 1975. Free of AF at 6th examination cycle.	143	2,838	60	45	5	1.22 (1.03 to 1.44) per 15 kg	Age, sex	-
			CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF excluded. White only.	560	4,324	73	41	5	1.18 (1.07 to 1.31) per 15 kg		Karas *et al.* (2016)[67]
						African American	64	7,19	73	34	5	1.31 (1.04 to 1.65) per 15 kg		
			ARIC	Prospective cohort	USA	Aged 45-64 at baseline between 1987-9. Prevalent AF excluded. White only	343	8,305	63	45	5	1.39 (1.26 to 1.53) per 15 kg		-
						African American	76	2,370	62	36	5	1.23 (1.03 to 1.46) per 15 kg		
			AGES	Prospective cohort	Iceland	Men and women in Reykjavik born between 1907 and 1935 surviving to 2002-6. Prevalent AF excluded.	408	4,469	76	40	5	1.17 (1.04 to 1.31) per 15 kg		-
			RHS	Prospective cohort	The Netherlands	Men and women >55 years old, living in Rotterdam. Prevalent AF excluded.	177	3,203	72	41	5	1.55 (1.28 to 1.87) per 15 kg		-

AF – atrial fibrillation, **AGES** – age, gene/environment susceptibility, **ARIC** – atherosclerosis risk in communities cohort, **BMI** – body mass index, **BNP** – brain natriuretic peptide, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** – Cardiovascular Health Study, **CI** – confidence interval, **CRP** – C-reactive protein, **DBP** – diastolic blood pressure, **DDCH** - Danish Diet, Cancer and Health, **DM** – diabetes mellitus, **FHS** – Framingham Heart Study, **FHx** – family history, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **JHS** - Jackson Heart Study, **LDL** – low-density lipoprotein, **MESA** - Multi-ethnic study of atherosclerosis, **MI** – myocardial infarction, **OR** – odds ratio, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **RHS** – Rotterdam Heart Study, **RR** – risk ratio,

Appendix Table B.12: Details of studies examining weight as a continuous variable and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data

SBP – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **VIP** – Vasterbotten Intervention Programme, **WC** – waist circumference, **WHS** - Women's Health Study

1

Appendix Table B.13: Details of studies examining weight, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.25 (1.08 to 1.43)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-	Yes[207]
												Q3		1.46 (1.27 to 1.68)			
												Q4		2.02 (1.76 to 2.32)			
							2,215	16,078	57	0	19.7	Q2	Q1	1.13 (0.98 to 1.30)			
												Q3		1.44 (1.27 to 1.65)			
												Q4		1.93 (1.70 to 2.20)			
2	Johansson *et al*.[206]	2020	VIP	Prospective cohort	Sweden	Invited participants aged 30, 40, 50, or 60 years old. Prevalent AF excluded	3,200	53,376	46.4	100	15.6	75 to 81 kg	<75 kg	1.18 (1.06 to 1.32)	Age, cholesterol. education, smoking, MI, HTN, DM, alcohol, physical activity, height	-	Yes[206]
												82 to 90 kg		1.24 (1.11 to 1.38)			
												≥91 kg		1.79 (1.60 to 2.01)			
							1,954	55,041	46.3	0		60 to 66 kg	<60 kg	1.13 (0.97 to 1.31)			
												67 to 74 kg		1.20 (1.03 to 1.40)			
												≥75 kg		1.67 (1.44 to 1.93)			
3	Worm *et al*.[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Post-menopausal women. Baseline AF excluded	850	5,704	70.7	0	11.5	Highest third	Lowest third	1.44 (1.21 to 1.73)	Age, alcohol, smoking education, exercise, hormone replacement therapy, HTN, hyperlipidaemia, DM, CHD, PAD, CCF, thyroid	No	No

Appendix Table B.13: Details of studies examining weight, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
															disease, scanner model		
														1.23 (1.00 to 1.52)	+ lean mass		
4	Neefs *et al*.[197]	2019	EPIC-Norfolk	Prospective cohort	UK	Men and women aged 45-79 years at baseline. Prior AF excluded	1,408	10,885	58.9	100	19	Quintile 5	Quintile 1	1.90 (1.59 to 2.25)	Age, DM, SBP, thyroid disease, cholesterol	No	No
							1,102	12,857		0				1.90 (1.55 to 2.33)			
5	Andersen *et al*.[223]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription 1972 to 1995	9,753	1,153,151	44.6	100	26.3	Quintile 5	Quintile 1	1.66 (1.54 to 1.79)	Region, date of conscription, education, height and hyperthyroidism	Crump *et al*. (2018)[58]	Yes†[58]
6	Crump *et al*.[58]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription (starting 1969)	23,600	1,547,478	47.4	100	28.2	64.0 to 71.3 kg	<64.0 kg	0.98 (0.94 to 1.02)	Age, conscription year, height, aerobic fitness, muscular strength, educational level, neighbourhood SES, FHx of AF	Andersen *et al*. (2018)[223]	Yes[58]
												≥71.4 kg		1.18 (1.13 to 1.23)			
7	Wilhelmsen *et al*.[224]	2002	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	754	7,495		100	25.2	≥84.0kg	≤72.9kg	2.19 (1.78 to 2.69)	Age	No	No

† Continuous effects are reported from the same dataset but not in the same paper. **AF** – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **EPIC** - European Prospective Investigation into Cancer, **FHx** – family history, **HTN** – hypertension, **HR** – hazard ratio, **MI** – myocardial infarction, **PAD** – peripheral artery disease, **SBP** – systolic blood pressure, **SES** – socioeconomic status, **UK** – United Kingdom, **VIP** – Vasterbotten Intervention Programme

B.6. Waist-hip ratio

Appendix Table B.14: Studies reporting estimates of the association between waist-hip ratio and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	WHR as a continuous variable	*WHR as a categorical variable*		
Busselton Health Study	1	0	Australia	[208]
CHS	1	0	United States of America	[67]
DDCH	2	0	Denmark	[66,191]
EPIC-Norfolk	0	1	United Kingdom	[197]
Malmo Diet and Cancer Study	1	1	Sweden	[207]
ONTARGET/TRANSCEND	0	1	International	[225]
PRO.V.A.	1	1	Italy	[445]
Scottish Heart Health Extended cohort	1	0	United Kingdom	[73]
Stockholm county cohort	1	0	Sweden	[217]
Total studies	**8**	**4**		
Of which presented continuous and categorical data	**2**			

CHS – Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **EPIC** - European Prospective Investigation into Cancer, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PRO.V.A.** – Progetto Veneto Anziani, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease, **WHR** – waist-hip ratio

Appendix Table B.15: Details of studies examining waist-hip ratio, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.08 (1.04 to 1.14) per SD [0.06]	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
							2,215	16,078	57	0	19.7	1.07 (1.02 to 1.11) per SD [0.05]		
2	Peters *et al.*[73]	2019	Scottish Heart Health Extended Cohort (Scottish Heart Health Study and Scottish MONICA)	Prospective cohort	Scotland	Age: 30-74 at recruitment No history of CHD at baseline. No exclusion of those with AF (unable to ascertain)	445	8,185	49.0	0	22.6	1.14 (0.85 to 1.52) per SD (0.07 units)	Age, FHx of CHD, deprivation, smoking, SBP, cholesterol, HDL	-
							591	7,552	49.0	100	22.6	1.19 (0.93 to 1.53) per SD (0.08 units)		
3	Fenger-Grøn *et al.*[66]	2017	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56 (IQR 51 to 63)	47	8.3	1.09 (1.06 to 1.13) per SD (0.06 [M] / 0.07 units [F])	age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Frost *et al.* (2014)[191]
												1.01 (0.98 to 1.04) per SD (0.06 [M] / 0.07 units [F])	+ lean mass	
4	Trevisan *et al.*[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach.	115	1,764	74.3	0.36	4.4	OR 0.12 (0.05 to 0.28) per 1 unit	age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	
5	Karas *et al.*[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.00 (0.93 to 1.07) per SD (0.09 units)	age, sex, ethnicity, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medications, glucose, DM, LDL, HDL, triglycerides, CRP	-
6	Nystrom *et al.*[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2. Prevalent AF excluded	285	4,021	60	48	13.6	1.05 (0.88 to 1.25) per SD (0.09 units)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
7	Frost *et al.*[191]	2014	DDCH	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.11 (1.07 to 1.16) per SD (0.06 [M] / 0.07 units [F])	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valve disease	Fenger-Grøn *et al.* (2017)[66]
8	Knuiman *et al.*[208]	2014	Busselton Health Study	Prospective cohort	Australia	Busselton residents. Age 25-84 at baseline. Prevalent AF excluded. Missing covariates excluded	343	4,267	52	44	15	1.21 (1.02 to 1.43) per SD (0.09 units)	age, sex, height	-
												0.98 (0.81 to 1.18) per SD (0.09 units)	+ HTN treatment, BMI	

Appendix Table B.15: Details of studies examining waist-hip ratio, as a continuous variable, and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHS** – Cardiovascular Health Study, **CHD** – coronary heart disease, **CI** – confidence interval, **CRP** – C-reactive protein, **DDCH** - Danish Diet, Cancer and Health, **DM** – diabetes mellitus, **FHx** – family history, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **LDL** – low-density lipoprotein, **MI** – myocardial infarction, **PRO.V.A.** – Progetto Veneto Anziani, **RR** - risk ratio, **SBP** – systolic blood pressure, **SD** – standard deviation, **USA** – United States of America

Appendix Table B.16: Details of studies examining waist-hip ratio, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.05 (0.93 to 1.19)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-	Yes[207]
												Q3		1.04 (0.92 to 1.18)			
												Q4		1.30 (1.14 to 1.47)			
							2,215	16,078	57	0	19.7	Q2	Q1	1.05 (0.93 to 1.19)			
												Q3		1.03 (0.91 to 1.12)			
												Q4		1.24 (1.09 to 1.40)			
2	Neefs *et al*.[197]	2019	EPIC-Norfolk	Prospective cohort	UK	Men and women aged 45-79 years at baseline. Prior AF excluded	1,408	10,885	58.9	100	19	Q5	Q1	1.30 (1.08 to 1.55)	Age, DM, SBP, thyroid disease, cholesterol	-	No
							1,102	12,857		0				1.14 (0.91 to 1.42)			
3	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach.	115	1,764	74.3	0.36	4.4	≥90/85 [men/ women]	<90/85 [men/ women]	0.68 (0.56 to 0.83)	age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-	Yes[445]
4	Verdecchia *et al*.[225]	2012	ONTARGET/ TRANSCEND	Post-trial cohort	USA	Men/women ≥55 years with CHD, PAD, stroke, DM, but no CCF	2,092	30,424	66.4	70	4.7	Q5	Q1	0.95 (0.81 to 1.11)	Age, sex, smoking, HTN, DM, stroke, CHD, PAD, ethnicity, SBP, creatinine, LVH, BMI	-	No

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **EPIC** – European Prospective Investigation into Cancer, **HR** – hazard ratio, **HTN** - hypertension, **LVH** – left ventricular hypertrophy, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PAD** – peripheral artery disease, **PRO.V.A.** – Progetto Veneto Anziani, **Q** – quintile, **SBP** – systolic blood pressure, **SD** – standard deviation, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease, **UK** – United Kingdom, **USA** – United States of America

B.7. Fat mass

Appendix Table B.17: Studies reporting estimates of the association between fat mass and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	FM as a continuous variable	*FM as a categorical variable*		
CHS	1	0	USA	[67]
DDCH	2	0	Denmark	[66,191]
Health ABC	1	0	USA	[68]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
UKB	2	0	United Kingdom	[71,226]
WHI	1	0	USA	[63]
Total studies	**7**	**1**		
Of which presented continuous and categorical data	**0**			

CHS - Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **FM** – fat mass, **Health ABC** – Health, Aging, and Body Composition, **UKB** – UK Biobank, **USA** – United States of America, **WHI** – Women's Health Initiative

Appendix Table B.18: Details of studies examining fat mass as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Phenotype assessment method	Studies from same data
1	Camm *et al.*[226]	2021	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded, Missing or extreme anthropometric measures excluded	14,400	215,196	56.6	100	11.1	1.18 (1.17 to 1.19) per 5 kg	Age, ethnicity, deprivation, smoking, alcohol	Bioimpedance	Tikkanen *et al.* (2019)[71]
												1.09 (1.08 to 1.10) per 5 kg	+ lean mass		
							8,734	262,708	56.3	0	11.1	1.18 (1.17 to 1.20) per 5 kg	Age, ethnicity, deprivation, smoking, alcohol		
												1.11 (1.10 to 1.13) per 5 kg	+ lean mass		
2	Tikkanen *et al.*[71]	2019	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded.	10,365	487,404	56.5	46	6.1	1.34 (1.31 to 1.37) per SD (9.6 kg)	Age, sex, region, physical activity, smoking, alcohol consumption, BP, DM, lipid medication	Bioimpedance	Camm *et al.* (2021)[226]
										100		1.35 (1.31 to 1.39) per SD (9.6 kg)			
										0		1.49 (1.44 to 1.54) per SD (9.6 kg)			
3	Fenger-Grøn *et al.*[66]	2017	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56	47	8.3	1.25 (1.22 to 1.29) per SD (7.5 kg [M] / 8.8 kg [F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Bioimpedance	Frost *et al.* (2014)[191]
												1.03 (1.00 to 1.07) per SD (7.5 kg [M] / 8.8 kg [F])	+ lean mass		
4	Azarbal *et al.*[63]	2016	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded. Subset with DEXA imaging	1,035	8,832	63.3	0	11.6	1.04 (1.01 to 1.07) per 5 kg	Age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, dietary modification, hormone therapy	DEXA	-
												1.04 (0.97 to 1.10) per 5 kg	+ body mass index		
5	Karas *et al.*[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.12 (1.04 to 1.20) per SD (10.8 kg)	age, sex, ethnicity, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medication, glucose, DM, LDL, HDL, TG level, CRP	Bioimpedance	-
												1.12 (1.05 to 1.20) per SD (10.8 kg)	+ lean mass		
												1.11 (1.03 to 1.18) per SD (10.8 kg)	+ height		

6	Aronis *et al*.[68]	2015	Health ABC	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 at baseline. Absence of functional disability/life-threatening illness. Prevalent AF excluded. BMI<18.5kg/m^2 excluded	371	2,717	74	48	10	1.13 (1.00 to 1.27) per SD (9 kg)	Age, sex, ethnicity, site, smoking, SBP, DBP, HTN treatment, total:HDL ratio, heart rate, left ventricular hypertrophy on ECG, PR interval, CCF, CHD, DM	DEXA	-
7	Frost *et al*.[191]	2014	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.29 (1.24 to 1.33) per SD (8.3 kg)	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valve disease	Bioimpedance	Fenger-Grøn *et al*. (2017)[66]
												1.03 (0.99 to 1.09) per SD (8.3 kg)	+ lean mass		

AF – atrial fibrillation, **BP** – blood pressure, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** - Cardiovascular Health Study, **CI** – confidence interval, **CRP** – C-reactive protein, **DBP** – diastolic blood pressure, **DDCH** – Danish Diet, Cancer and Health, **DEXA** – dual-energy X-ray absorptiometry, **DM** – diabetes mellitus, **ECG** – electrocardiogram, **HDL** – high density lipoprotein, **Health ABC** - Health, Aging, and Body Composition, **HR** – hazard ratio, **HTN** – hypertension, **PAD** – peripheral arterial disease, **SBP** – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, **TG** – triglycerides, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **WHI** – Women's Health Initiative

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Appendix Table B.19: Details of studies examining fat mass, as a categorical variable, on risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
Worm *et al*.[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Women without AF at baseline who had participated in clinical prevention trials at the Centre for Clinical and Basic Research	850	5,704	70.7	0	11.5	Tertile 3	Tertile 1	1.23 (1.03 to 1.47)	age, alcohol, smoking education, exercise, HRT, HTN, hyperlipidaemia, DM, CHD, PAD, CCF, thyroid disease, scanner model	-	No
													1.15 (0.96 to 1.38)	+ height		

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HTN** – hypertension, **PAD** – peripheral artery disease.

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B.8. Lean mass

Appendix Table B.20: Studies reporting estimates of the association between lean mass and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	LM as a continuous variable	*LM as a categorical variable*		
CHS	1	0	USA	[67]
DDCH	2	0	Denmark	[66,191]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
UKB	2	0	United Kingdom	[71,226]
WHI	1	0	USA	[63]
Total studies	**6**	**1**		
Of which presented continuous and categorical data	**0**			

CHS - Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **LM** – lean mass, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **WHI** – Women's Health Initiative

Appendix Table B.21: Details of studies examining lean mass as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Method	Studies from same data
1	Camm *et al.*[226]	2021	UKB	Prospective cohort	UK	Aged 40-69 years at enrolment. Prevalent AF excluded, Missing or extreme anthropometric measures excluded	14,400	215,196	56.6	100	11.1	1.24 (1.23 to 1.25) per 5 kg	Age, ethnicity, deprivation, smoking, alcohol	Bioimpedance	Tikkanen *et al*. (2019)[71]
												1.19 (1.17 to 1.20) per 5kg	+ fat mass		
							8,734	262,708	56.3	0	11.1	1.40 (1.37 to 1.43) per 5 kg	Age, ethnicity, deprivation, smoking, alcohol		
												1.25 (1.22 to 1.29) per 5 kg	+ fat mass		
2	Tikkanen *et al.*[71]	2019	UKB	Prospective cohort	UK	UKB standard entry requirements	10,365	487,404	56.5	46	6.1	1.70 (1.65 to 1.76) per SD (11.5 kg)	age, sex, region, physical activity, smoking, alcohol consumption, blood pressure, diabetes, lipid medication	Bioimpedance	Camm *et al.* (2021)[226]
										100		1.77 (1.71 to 1.84) per SD (11.5 kg)			
										0		1.75 (1.65 to 1.85) per SD (11.5 kg)			
3	Fenger-Grøn *et al.*[66]	2017	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56 (IQR 51 to 63)	47	8.3	1.37 (1.33 to 1.42) per SD (6.1 kg[M] / 4.5 kg[F])	age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Bioimpedance	Frost *et al*. (2014)[191]
												1.36 (1.30 to 1.41) per SD (7.5 kg[M] / 8.8 kg[F])	+ fat mass		
4	Azarbal *et al.*[63]	2016	WHI	Prospective cohort	USA	Age: 50-79 years. Prevalent AF excluded. Subset with DEXA imaging	1,035	8,832	63.3	0	11.6	1.21 (1.14 to 1.29) per 5 kg	age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, dietary modification, hormone therapy	DEXA	-
												1.24 (1.14 to 1.34) per 5 kg	+ body mass index		
5	Karas *et al.*[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare	1,050	4,276	72.4	38	13	1.23 (1.11 to 1.37) per SD (9.2 kg)	age, sex, race, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medications,	Bioimpedance	-

						eligibility list. Prevalent AF and CHD excluded.								glucose, DM, LDL, HDL, TG level, CRP			
													1.19 (1.06 to 1.33) per SD (9.2 kg)	+ fat mass			
													1.08 (0.96 to 1.22) per SD (9.2 kg)	+ height			
6	Frost *et al*.[191]	2014	DDCH study	Prospective cohort	Denmark	Age: 50-64. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5		1.40 (1.35 to 1.45) per SD (9.7 kg)	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valve disease,	Bioimpedance	Fenger-Grøn *et al*. (2017)[66]
													1.37 (1.30 to 1.44) per SD (8.3 kg)	+ fat mass			

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** – Cardiovascular Health Study, **CI** – confidence interval, **DBP** – diastolic blood pressure, **DDCH** – Danish Diet, Cancer and Health, **DEXA** – dual-energy X-ray absorptiometry, **DM** – diabetes mellitus, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **PAD** – peripheral artery disease, **SBP** – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, **UK** – United Kingdom, **UKB** – UK Biobank, **USA** – United States of America, **WHI** – Women's Health Initiative

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Appendix Table B.22: Details of studies examining lean mass as a categorical variable and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
Worm *et al*.[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Women without AF at baseline who had participated in clinical prevention trials at the Centre for Clinical and Basic Research.	850	5,704	70.7	0	11.5	Tertile 3	Tertile 1	1.51 (1.26 to 1.81)	age, alcohol, smoking education, exercise, HRT, HTN, hyperlipidaemia, DM, CHD, PAD, CCF, thyroid disease, scanner model	-	No
													1.27 (1.03 to 1.56)	+ height		

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HTN** – hypertension, **PAD** – peripheral artery disease

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B.9. Pericardial adipose tissue

Appendix Table B.23: Studies reporting estimates of the association between pericardial adipose tissue and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Pericardial adipose tissue as a continuous variable	*Pericardial adipose tissue as a categorical variable*		
FHS	1	0	USA	[100]
Heinz Nixdorf Recall	1	0	Germany	[94]
JHS	1	0	USA	[95](also reports MESA)
MESA	1	0	USA	[95](also reports JHS)
Osaka MDCT	1	0	Japan	[231]
Rotterdam Heart Study	1	1	The Netherlands	[230]
Taipei cardiovascular screening	1	0	Taiwan	[232]
Total studies	**6***	**1**		
Of which presented continuous and categorical data	**1**			

* Studies that include more than a single cohort are only counted once in the total. **FHS** – Framingham Heart Study, **JHS** – Jacksonville heart Study, **MDCT** – Multi-detector computer tomography, **MESA** – Multi-ethnic study of atherosclerosis, **USA** – United States of America

Appendix Table B.24: Details of studies examining pericardial adipose tissue as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Phenotype	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Method	Studies from same data
1	Lai *et al.*[232]	2021	Taipei cardiovascular screening	Retrospective cohort	Taiwan	Epicardial fat thickness	Patients undertaking CHD screening. Prevalent HTN, DM, CHD, AF, CCF, VHD excluded.	71	2,944	47.5	67	5.3	1.8 (1.3 to 2.5) per 1 mm	Age, sex, SBP, heart rate, glucose, TG, HDL, eGFR, LA volume	Echo	-
2	Bos *et al.*[230]	2017	RHS	Prospective cohort	The Netherlands	Epicardial fat volume	Participants undergoing CT imaging 2003 to 2006 and free of CHD, CCF, stroke, and AF at baseline.	142	1,990	68.8	45	7.9	1.31 (1.05 to 1.65) per SD	Age, sex, BMI, SBP, DBP, HTN medication, DM, smoking, HDL, cholesterol, statin	Cardiac CT	-
													1.26 (1.01 to 1.58) per SD	+ LA size, coronary calcification score		
3	Heckbert *et al.*[95]	2017	MESA and JHS	Prospective cohort	USA	Pericardial fat volume	MESA: 45-84 years old free of CHD. JHS: African-American residents aged 20-95 years at baseline.	756	7,991	62	45	10	1.12 (1.05 to 1.20) per SD (41 cm^3)	Age, study, sex, ethnicity, height, SBP, HTN, DM	Cardiac CT	-
													1.06 (0.97 to 1.15) per SD (41 cm^3)	+ BMI		
4	Lee *et al.*[100]	2016	FHS	Prospective cohort	USA	Pericardial fat volume	7th examination cohort (1998 to 2001) and 3rd generation cohort (2002 to 2005). Women >40 and men >35 years. Excluded prevalent AF or with missing covariates.	162	2,135	58.8	47	9.7	1.13 (0.99 to 1.30) per SD (46 cm^3)	Age, sex, SBP, DBP, smoking, HTN medication, DM, CCF, MI	Cardiac CT	-
													1.09 (0.94 to 1.27) per SD (46 cm^3)	+ BMI		
													1.13 (0.95 to 1.34) per SD (46 cm^3)	+ Visceral fat		
5	Mahabadi *et al.*[94]	2014	Heinz-Nixdorf Recall Study	Prospective cohort	Germany	Epicardial fat volume	Randomly selected from residence lists of three towns in Germany. Aged 45-75 between 2000 and 2003. Excluded those with known CHD, stroke, pacemaker, or VHD.	50	3859	58.9	47	5	1.19 (0.88 to 1.61) per SD (47 cm^3)	Age, gender, BMI, SBP, HTN medication	Cardiac CT	-
													1.10 (0.81 to 1.50) per SD (47 cm^3)	+ LA Size		

6	Nakanishi *et al*.[231]	2012	Osaka MDCT	Prospective cohort	Japan	Peri-atrial pericardial fat volume index / Total pericardial fat volume index	Sequential patients undergoing MDCT analysis. Excluded prevalent AF, VHD, open heart surgery, thyroid disease, kidney disease.	17	279	65	63	3.3	1.28 (1.13 to 1.45) per 1 ml/m^2 / 0.98 (0.93 to 1.03) per 1 ml/m^2	Age, sex, CRP, LV mass index, LA volume index	Cardiac CT	-

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **CRP** – c-reactive protein, **CT** – computed tomography, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **eGFR** – estimated glomerular filtration rate, **FHS** – Framingham Heart Study, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **JHS** – Jackson Heart Study, **LA** – left atrium, **LV** – left ventricle, **MDCT** – Multi-detector computer tomography, **MESA** – Multi-Ethnic Study of Atherosclerosis, **MI** – myocardial infarction, **RHS** – Rotterdam Heart Study, **SBP** – systolic blood pressure, **SD** – standard deviation, **TG** – triglycerides, **USA** – United States of America, **VHD** – valvular heart disease

1

Appendix Table B.25: Details of studies examining pericardial adipose tissue, as a categorical variable, and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Pericardial fat volume	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
Bos *et al*.[230]	2017	RHS	Prospective cohort	The Netherlands	Epicardial fat volume	Participants undergoing CT imaging 2003 to 2006 and free of CHD, CCF, stroke, and AF at baseline.	142	1,990	68.8	45	7.9	Q2	Q1	1.80 (0.97 to 3.31)	Age, sex, BMI, SBP, DBP, HTN medication, DM, smoking, HDL, cholesterol, statin	-	Yes[230]
												Q2		1.60 (0.85 to 3.02)			
												Q3		1.93 (0.98 to 3.78)			

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** – hypertension, **RHS** – Rotterdam Heart Study, **SBP** – systolic blood pressure, **SD** – standard deviation

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B.10. Non-cardiac visceral fat

Appendix Table B.26: Studies reporting estimates of the association between visceral fat and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Visceral fat as a continuous variable	*Visceral fat as a categorical variable*		
FHS	2	0	USA	[100,233]
Health ABC	1	0	USA	[68]
Total studies	**3**	**0**		

AF – atrial fibrillation, **FHS** – Framingham Heart Study, **Health ABC** – Health Aging, and Body Composition, **USA** – United States of America

Appendix Table B.27: Details of studies examining visceral fat as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Phenotype	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Long *et al*.[233]	2017	FHS	Liver fat	Prospective cohort	USA	FHS offspring and third generation cohort who underwent abdominal CT between 2002 and 2005 who were >45 years old.	153	2,060	59.0	47	9.3	1.01 (0.76 to 1.33) per SD	Sex, age, SBP, DBP, smoking, HTN medications, DM, CCF, MI	Lee *et al*. (2016)[100]
													0.95 (0.71 to 1.27) per SD	+ BMI	
2	Lee *et al*.[100]	2016	FHS	Intrathoracic Fat*	Prospective cohort	USA	7th examination cohort (1998 to 2001) and 3rd generation cohort (2002 to 2005). Women >40 and men >35 years. Excluded prevalent AF or with missing covariates.	162	2,135	58.8	47	9.7	1.19 (1.01 to 1.40) per SD [63 cm^3]	Age, sex, SBP, DBP, smoking, HTN medications, DM, CCF, MI	Long *et al*. (2017)[233]
													1.15 (0.96 to 1.38) per SD [63 cm^3]	+ BMI	
													1.14 (0.87 to 1.48) per SD [63 cm^3]	+ Pericardial fat	
				Abdominal visceral fat									1.09 (0.93 to 1.28) per SD (1,061 cm^3)	Age, sex, SBP, DBP, smoking, HTN medications, DM, CCF, MI	
													1.02 (0.82 to 1.26) per SD (1,061 cm^3)	+ BMI	
													0.88 (0.66 to 1.19) per SD (1,061 cm^3)	+ Pericardial fat	
3	Aronis *et al*.[68]	2015	Health ABC	Abdominal visceral fat	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 at baseline. Absence of functional disability/life-threatening illness. BMI <18.5 kg/m^2 and prevalent AF excluded.	371	2,717	74	48	10	1.07 (0.96 to 1.19) per SD (67 cm^3)	Age, sex, ethnicity, site, smoking, SBP, DBP, HTN treatment, total:HDL ratio, heart rate, LVH on ECG, PR interval, CCF, CHD, DM	-

* Intra-thoracic fat was defined as total thoracic fat minus pericardial fat. **AF** – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **ECG** – electrocardiogram, **FHS** – Framingham Heart Study, **HDL** – high-density lipoprotein, **Health ABC** – Health Aging, and Body Composition, **HR** – hazard ratio, **HTN** - hypertension, **LDL** – low-density lipoprotein, **LVH** – left ventricular hypertrophy, **MI** – myocardial infarction, **SBP** – systolic blood pressure, **SD** – standard deviation

B.11. Hip circumference

Appendix Table B.28: Studies reporting estimates of the association between hip circumference and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	HC as a continuous variable	*HC as a categorical variable*		
CHS	1	0	United States of America	[67]
DDCH	2	0	Denmark	[66,191]
ONTARGET/TRANSCEND	0	1	International	[225]
PRO.V.A.	1	1	Italy	[445]
Stockholm county cohort	1	0	Sweden	[217]
Total studies	5	2		
Of which presented continuous and categorical data	1			

CHS – Cardiovascular Health Study, **DDCH** - Danish Diet, Cancer and Health, **HC** – hip circumference, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PRO.V.A.** - Progetto Veneto Anziani, **REGARDS** - REasons for Geographic And Racial Differences in Stroke Study, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease.

Appendix Table B.29: Details of studies examining hip circumference as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Fenger-Grøn *et al*.[66]	2017	DDCH	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56	47	8.3	1.26 (1.22 to 1.30) per SD (6.7 cm [M] / 8.8 cm [F])	age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Frost *et al*. (2014)[191]
												1.03 (0.99 to 1.06) per SD (6.7 cm [M] / 8.8 cm [F])	+ lean mass	
2	Trevisan *et al*.[445]	2017	PRO.V.A	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	OR 1.01 (1.00 to 1.01) per 1 cm	age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-
3	Karas *et al*.[67]	2016	CHS	Prospective cohort	USA	≥65 years old in 1989-1990. On Medicare eligibility list. Prevalent AF and CHD excluded.	1,050	4,276	72.4	38	13	1.13 (1.06 to 1.21) per SD (10 cm)	age, sex, race, smoking, physical activity, alcohol, oestrogen therapy, creatinine, SBP, HTN medication, glucose, DM, LDL, HDL, triglyceride level, CRP	-
												1.15 (1.04 to 1.19) per SD (10 cm)	+ WC	
												1.13 (1.06 to 1.20) per SD (10 cm)	+ height	
												1.03 (0.90 to 1.17)	+ weight	
4	Nystrom *et al*.[217]	2015	Stockholm county	Prospective cohort	Sweden	Random selection from Stockholm county born 1937-8. Excluded: missing body size data, BMI <18.5 kg/m^2. Prevalent AF excluded	285	4,021	60	48	13.6	1.38 (1.24 to 1.53) per SD (8.4 cm)	HTN, glucose, sex, smoking, alcohol, MI, physical activity, Swedish born	-
5	Frost *et al*.[191]	2014	DDCH study	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.29 (1.24 to 1.33) per SD (7.9 cm)	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valvular heart disease	Fenger-Grøn *et al*. (2017)[66]

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CHS** - Cardiovascular Health Study, **CI** – confidence interval, **CRP** – C-reactive protein, **DDCH** - Danish Diet, Cancer and Health, **DM** – diabetes mellitus, **HDL** – high density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **LDL** – low-density lipoprotein, **MI** – myocardial infarction, **PRO.V.A.** - Progetto Veneto Anziani, **RR** – risk ratio, **SBP** – systolic blood pressure, **SD** – standard deviation, **WC** – waist circumference

Appendix Table B.30: Details of studies examining hip circumference, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
1	Trevisan *et al*.[445]	2017	PRO.V.A	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	>99/100.8 cm [Men/ Women]	<99/100.8 cm [Men/ Women]	OR 1.39 (1.23 to 1.58)	age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-	Yes[445]
2	Verdecchia *et al*.[225]	2012	ONTARGET / TRANSCEND	Post-hoc trial analysis	International	Age >55 years without CCF and with CHD, PAD, stroke, or DM. Those with AF excluded at baseline.	2,092	30,424	66.4	70	4.7	Quintile 5	Quintile 1	1.53 (1.28 to 1.82)	Age, sex, ethnicity, smoking, HTN, DM, alcohol consumption stroke/TIA, CHD, PAD, creatinine, SBP.	-	No

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** – hypertension, **PAD**- peripheral artery disease, **ONTARGET** - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, **PRO.V.A.** - Progetto Veneto Anziani, **SBP** – systolic blood pressure, **TIA** – transient ischaemic attack, **TRANSCEND** - Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease

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B.12. Body surface area

Appendix Table B.31: Studies reporting estimates of the association between body surface area and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	BSA as a continuous variable	*BSA as a categorical variable*		
Medical Birth Registry	0	1	Sweden	[60]
Multifactor Primary Prevention Study	0	1	Sweden	[211]
PRO.V.A.	1	1	Italy	[445]
Swedish Military Conscripts	0	1	Sweden	[223]
VIP	1	1	Sweden	[206]
Total studies	**2**	**5**		
Of which presented continuous and categorical data	2			

BSA – body surface area, **PRO.V.A.** - Progetto Veneto Anziani, **VIP** – Vasterbotten Intervention Programme

Appendix Table B.32: Details of studies examining body surface area, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Johansson *et al.*[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded	3,200	53,376	46.4	100	14.3	1.29 (1.35 to 1.45) per SD (0.2 m^2)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity	-
							1,954	55,041	46.3	0	15.6	1.38 (1.32 to 1.44) per SD (0.2 m^2)		
2	Trevisan *et al.*[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-1997 using age- and sex-stratified approach.	115	1,764	74.3	0.36	4.4	OR 1.04 (1.03 to 1.05) per 0.1 m^2	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications	-

AF – atrial fibrillation, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** – hypertension, **MI** – myocardial infarction, **PRO.V.A.** – Progetto Veneto Anziani, **SD** – standard deviation, **VIP** – Vasterbotten Intervention Programme

Appendix Table B.33: Details of studies examining body surface area, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
1	Johansson *et al*.[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded	3,200	53,376	46.4	100	14.3	1.91 to 2.01	<1.91 m^2	1.35 (1.22 to 1.50)	Age, cholesterol. Education, smoking, MI, HTN, DM, alcohol, physical activity	-	Yes[206]
												2.01 to 2.12		1.63 (1.47 to 1.81)			
												≥2.12 m^2		2.28 (2.06 to 2.53)			
							1,954	55,041	46.3	0	15.6	1.65 to 1.74 m^2	<1.65 m^2	1.36 (1.18 to 1.56)			
												1.74 to 1.84 m^2		1.53 (1.33 to 1.75)			
												≥1.84 m^2		2.23 (1.95 to 2.55)			
2	Persson *et al*.[60]	2018	Medical Birth Registry	Prospective Cohort	Sweden	Women born after 1973 who became pregnant 1982 to 2014. > 18 years old Height 140-200 cm. Exclusions: prevalent AF (at time of pregnancy), or BMI <15 or >60 kg/m^2	6,993	1,522,329	28.3	0	16.6	1.63-1.71 m^2	<1.63 m^2	1.21 (1.12 to 1.30)	Age, DM, HTN, CCF at baseline, smoking, pregnancy year, parity, education level, CCF during follow-up (time-dependent).	-	No
												1.72-1.82 m^2		1.45 (1.35 to 1.56)			
												>1.82 m^2		2.11 (1.97 to 2.26)			
3	Andersen *et al*.[223]	2018	Swedish Military Conscription Registry	Prospective cohort	Sweden	All males undergoing military conscription 1972 to 1995. No AF at baseline.	9,753	1,153,151	44.6	100	26.3	1.76-1.82 m^2	<1.76 m^2	1.31 (1.22 to 1.42)	Region, date of conscription, education, muscle strength, maximal exercise capacity, CHD, HTN, CCF, DM, thyroid disease	-	No
												1.83-1.89 m^2		1.59 (1.47 to 1.72)			
												1.90-1.99 m^2		1.94 (1.80 to 2.09)			
												>1.99 m^2		2.86 (2.66 to 3.09)			
	Trevisan *et al*.[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded. Randomly selected 1995-	115	1,764	74.3	36	4.4	2.59 to 2.99 m^2	<2.59 m^2	1.58 (1.30 to 1.91)	Age, sex, DM, HTN, CHD, educational level, physical		Yes[445]

						1997 using age- and sex-stratified approach.					3.00 to 3.49 m^2 ≥3.5 m^2		1.77 (1.46 to 2.14) 2.12 (1.73 to 2.59)	activity, smoking habits, number of prescription medications		
4	Rosengren *et al*.[211]	2009	Multifactor Primary Prevention Study	Prospective cohort	Sweden	Men born in Goteborg 1915-25. Prevalent AF excluded	1,253	6,903	51.5	100	Maximum 34.3 (no average given)	1.75-1.83 m^2 1.83-1.91 m^2 >1.91 m^2	<1.75 m^2	1.39 (1.16 to 1.66) 1.52 (1.28 to 1.81) 1.95 (1.65 to 2.31)	age at baseline, CCF, MI, SBP, HTN, smoking, DM, alcohol, occupational class	-	No

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** – hypertension, **MI** – myocardial infarction, **PRO.V.A.** – Progetto Veneto Anziani, **SBP** – systolic blood pressure, **VIP** – Vasterbotten Intervention Programme

1

B.13. Body fat percentage

Appendix Table B.34: Studies reporting estimates of the association between body fat percentage and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Body fat percent as a continuous variable	*Body fat percent as a categorical variable*		
DDCH	2	0	Denmark	[66,191]
Health ABC	1	0	USA	[68]
Malmo Diet and Cancer Study	1	1	Sweden	[207]
WHI	1	0	USA	[63]
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
Total studies	5	1		
Of which presented continuous and categorical data	1			

DDCH - Danish Diet, Cancer and Health, **Health ABC** – Health Aging, and Body Composition, **USA** – United States of America, **WHI** – Women's Health Initiative

Appendix Table B.35: Details of studies examining body fat percentage, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Method	Studies from same data
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.08 (1.04 to 1.13) per SD (5%)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	Bioimpedance	-
							2,215	16,078	57	0	19.7	1.13 (1.08 to 1.18) per SD (5%)			
2	Fenger-Grøn *et al.*[66]	2017	DDCH	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	3,868	55,273	56 (IQR 51 to 63)	47	8.3	1.16 (1.12 to 1.20) per SD (5.4% [M] / 6.7% [F])	Age, sex, smoking, education, physical activity, fruit and vegetable intake, alcohol, and total energy intake	Bioimpedance	Frost *et al.* (2014)[191]
												1.01 (0.98 to 1.05) per SD (5.4% [M] / 6.7% [F])	+ lean mass		
3	Azarbal *et al.*[63]	2016	WHI	Prospective cohort	USA	Age: 50-79 years. Prevalent AF excluded. Subset with DEXA imaging.	1,035	8,832	63.3	0	11.6	1.00 (0.95 to 1.04) per 5%	Age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, dietary modification, hormone therapy	DEXA	-
												0.92 (0.86 to 0.98) per 5%	+ body mass index		
4	Aronis *et al.*[68]	2015	Health ABC	Prospective cohort	USA	Random sample of Medicare in Pittsburgh and Memphis. Aged 70-79 years at baseline. Absence of functional disability/ life-threatening illness. Prevalent AF and BMI <18.5 kg/m^2 excluded	371	2,717	74	48	10	1.03 (0.87 to 1.22) per SD (8%)	Age, sex, race, site, smoking, SBP, DBP, HTN treatment, total:HDL ratio, heart rate, left ventricular hypertrophy on ECG, PR interval, CCF, CHD, DM	DEXA	-
5	Frost *et al.*[191]	2014	DDCH	Prospective cohort	Denmark	Age: 50-64 years. Born in Denmark, no previous cancer diagnosis. AF excluded based on healthcare data.	2,581	55,273	56.1	47	13.5	1.19 (1.14 to 1.24) per SD (7.4%)	Age, sex, smoking, fruit and vegetable intake, alcohol. physical activity, total energy, education, HTN, DM, hypercholesterolemia, CHD, CCF, valve disease	Bioimpedance	Fenger-Grøn *et al.* (2017)[66]

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DBP** – diastolic blood pressure, **DDCH** - Danish Diet, Cancer and Health, **DEXA** – dual-energy X-ray absorptiometry, **DM** – diabetes mellitus, **ECG** – electrocardiogram, **HDL** – high density lipoprotein, **Health ABC** – Health Aging, and Body Composition, **HR** – hazard ratio, **HTN** - hypertension, **PAD** – peripheral arterial disease, **SBP** – systolic blood pressure, **SD** – standard deviation, **SES** – socioeconomic status, **USA** – United States of America, **WHI** – Women's Health Initiative

1

Appendix Table B.36: Details of studies examining body fat percentage, as a categorical variable, and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	0.90 (0.79 to 1.04)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-	Yes
											Q3		1.03 (0.92 to 1.18)			
											Q4		1.21 (1.06 to 1.39)			
						2,215	16,078	57	0	19.7	Q2	Q1	1.14 (0.98 to 1.32)			
											Q3		1.13 (0.97 to 1.31)			
											Q4		1.45 (1.26 to 1.67)			
Worm *et al.*[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Women without AF at baseline who had participated in clinical prevention trials at the Centre for Clinical and Basic Research.	850	5,704	70.7	0	11.5	Tertile 3	Tertile 1	1.16 (0.97 to 1.39)	Age, alcohol, smoking education, exercise, HRT, HTN, hyperlipidaemia, DM, CHD, PAD, CCF, thyroid disease, scanner model	-	No
													1.18 (0.99 to 1.42)	+ height		

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HTN** – hypertension, **PAD** – peripheral artery disease

B.14. Birth weight

Appendix Table B.37: Studies reporting estimates of the association between birth weight and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Birth weight as a continuous variable	*Birth weight as a categorical variable*		
ARIC	0	1	USA	[486]
Cohort of Swedish Men	0	1	Sweden	[487](also reports Swedish Mammography Cohort)
Helsinki Birth Cohort	0	1	Finland	[488]
Swedish Mammography Cohort	0	1	Sweden	[487](also reports Cohort of Swedish Men)
WHS	0	1	USA	[489]
Total studies	**0**	**4***		

* Studies that include more than a single cohort are only counted once in the total. **ARIC** – atherosclerosis risk in communities cohort, **USA** – United States of America, **WHS** - Women's Health Study

Appendix Table B.38: Details of studies examining birth weight as a categorical variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	Finding HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
1	Johnson *et al*.[488]	2017	Helsinki Birth Cohort	Prospective cohort	Finland	Singleton births between 1934 and 1944 still alive in 1971.	907	13,345	65.3	52	70.5	<2,500 g	3,000-3,999 g	1.42 (0.93 to 2.19)	Socioeconomic status at birth, gestational age, sex, maternal BMI	-	No
												2,500-2,999 g		1.22 (1.00 to 1.50)			
												≥4,000 g		1.12 (0.90 to 1.39)			
							547	6,044		100		<2,500 g		1.38 (0.82 to 2.30)			
												2,500-2,999 g		1.06 (0.81 to 1.38)			
												≥4,000 g		1.11 (0.86 to 1.42)			
							241	5,576		0		<2,500 g		1.64 (0.75 to 3.62)			
												2,500-2,999 g		1.54 (1.12 to 2.12)			
												≥4,000 g		1.19 (0.75 to 1.58)			
2	Larsson *et al*.[487]	2015	Cohort of Swedish Men	Prospective cohort	Sweden	Men born 1918 to 1952 alive in	2,711	29,551	58.1	100	12	<1,500 g		1.59 (0.99 to 2.55)	Age, preterm birth, education, smoking,	-	No

						1997 who resided in two Swedish counties.					1,500-2,499 g	2,500-3,999 g	1.14 (0.96 to 1.35)	family history of MI, CHD, CCF, HTN, DM, BMI			
											4,000-4,999 g		1.00 (0.90 to 1.10)				
											≥5,000 g		1.25 (1.02 to 1.53)				
			Swedish mammography cohort	Prospective cohort	Sweden	Women who lived in two Swedish counties.	1,491	23,454	59.3	0	<1,500 g		0.67 (0.29 to 1.56)		-	No	
											1,500-2,499 g		0.99 (0.83 to 1.20)				
											4,000-4,999 g		1.07 (0.90 to 1.27)				
											≥5,000 g		1.41 (0.94 to 2.10)				
3	Lawani *et al*.[486]	2014	ARIC	Prospective cohort	USA	Aged 45-64 at baseline. BMI <18.5kg/m^2 and prevalent AF excluded.	882	10,132	62.7	44	10.3	<2,500 g	2,500-4,000 g	1.42 (1.06 to 1.90)	Age, sex, ethnicity, study centre, income, education, DM, SBP, HTN medications, smoking, height, BMI, MI, CCF	-	No
												>4,000 g		0.86 (0.69 to 1.07)			
4	Conen *et al*.[489]	2010	WHS	Prospective cohort	USA	Women >45 years old at recruitment. Prevalent CHD and AF excluded.	735	27,982	52	0	14.5	2,500-3,200 g	<2,500 g	1.28 (0.94 to 1.74)	Age, hypercholesterolemia, smoking, exercise, alcohol, education, ethnicity, HRT, BMI, SBP, DBP, DM, height	-	No
												3,200-3,900 g		1.13 (0.85 to 1.50)			
												3,900-4,500 g		1.43 (1.02 to 1.99)			
												≥4,500 g		1.34 (0.87 to 2.05)			

AF – atrial fibrillation, **ARIC** – atherosclerosis risk in communities cohort, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DBP** – diastolic blood pressure, **DM** – diabetes mellitus, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HTN** – hypertension, **MI** – myocardial infarction, **PAD** – peripheral artery disease, **SBP** – systolic blood pressure, **USA** – United States of America, **WHS** - Women's Health Study

B.15. Metabolically healthy obesity

Appendix Table B.39: Studiesreporting estimates of the association between metabolically healthy obesity and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Metabolically healthy obesity as a continuous variable	*Metabolically healthy obesity as a categorical variable*		
French hospital admissions cohort	0	1	France	[490]
HUNT	0	1	Norway	[491]
JMDC Claims Database	0	1	Japan	[492]
NHIS	0	1	Korea	[493]
Total studies	**0**	**4**		

AF- atrial fibrillation, **HUNT** – Trøndelag Healthy study, **NHIS** - National Health Insurance Service

Appendix Table B.40: Details of studies examining metabolically healthy obesity, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported
1	Itoh *et al.*[492]	2021	JMDC Claims Database	Retrospective cohort	Japan	Insurance claims database. Aged 20-39 at analysis. Prevalent AF excluded.	2,084	802,288	42.8	45	3.1	BMI ≥25 kg/m^2 and metabolically healthy	BMI <25 kg/m^2 and metabolically healthy	1.15 (1.00 to 1.32)	Unclear	-	No
												BMI ≥25 kg/m^2 and metabolically unhealthy		1.34 (1.23 to 1.47)			
2	Fauchier et al.[490]	2021	French hospital admissions cohort	Retrospective cohort	France	Hospitalized adults (≥18 years old) with 5 years follow-up. Prevalent AF excluded.	257,289	2,873,039	56.6	45	4.9	BMI ≥25 kg/m^2 and metabolically healthy	BMI <25 kg/m^2 and metabolically healthy	1.33 (1.30 to 1.37)	age, sex, smoking	-	No
												BMI ≥25 kg/m^2 and metabolically unhealthy		1.68 (1.64 to 1.73)			

3	Feng *et al*.[491]	2019	HUNT	Prospective cohort	Norway	Participants ≥20 years old living in Nord- Trøndelag county who underwent a clinical examination. Prevalent AF and missing BMI/metabolic status excluded	1,758	47,870	52.6	55	8.1	BMI ≥30 kg/m^2 and metabolically healthy	BMI <25 kg/m^2 and metabolically healthy	1.6 (1.2 to 2.1)	Age at baseline, height, smoking, time since last meal, type of work, marital status, physical activity, alcohol, C-reactive protein, sex	-	No
												BMI ≥30 kg/m^2 and metabolically unhealthy		1.6 (1.3 to 1.9)			
4	Lee *et al*.[493]	2017	NHIS	Prospective cohort	Korea	Korean citizen randomly selected, > 20 years old. Prevalent AF, or valvular heart disease excluded	5,106	389,321	45.6	52.1	7.5	BMI ≥25 kg/m^2 and metabolically healthy	BMI <25 kg/m^2 and metabolically healthy	1.30 (1.14 to 1.48)	Age, sex, income, area, smoking, alcohol, exercise, CHD, PAD, CCF, cancer, COPD	-	No
												BMI ≥25 kg/m^2 and metabolically unhealthy		1.71 (1.56 to 1.86)			
												BMI <25 kg/m^2 and metabolically unhealthy		1.43 (1.31 to 1.55)			

AF – atrial fibrillation, BMI – body mass index, CCF – congestive cardiac failure, CHD – coronary heart disease, CI – confidence interval, COPD – chronic obstructive pulmonary disease, DM – diabetes mellitus, HR – hazard ratio, HRT – hormone replacement therapy, HTN – hypertension, HUNT – Trøndelag Healthy study, NHIS - National Health Insurance Service, PAD – peripheral artery disease

B.16. Waist-height ratio

Appendix Table B.41: Studies that have reported estimates of the effect of waist-height ratio on risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Waist-height ratio as a continuous variable	*Waist-height ratio and a categorical variable*		
Malmo Diet and Cancer Study	1	1	Sweden	[207]
PRO.V.A.	1	1	Italy	[445]
Total studies	**2**	**2**		
Of which presented continuous and categorical data	2			

PRO.V.A. – Progetto Veneto Anziani

Appendix Table B.42: Details of studies examining waist-height ratio, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	1.11 (1.06 to 1.16) per SD (0.07)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
							2,215	16,078	57	0	19.7	1.12 (1.07 to 1.17) per SD (0.07)		
2	Trevisan *et al.*[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	OR 0.12 (0.05 to 0.28) per 1 unit	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications.	-

AF – atrial fibrillation, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** - hypertension, **PRO.V.A.** – Progetto Veneto Anziani, **SBP** – systolic blood pressure, **SD** – standard deviation

Appendix Table B.43: Details of studies examining waist-height ratio, as a categorical variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data
1	Zia *et al.*[207]	2021	Malmo Diet and Cancer Study	Prospective cohort	Sweden	Men born 1923-45 and women born 1923-50 living in Malmo in 1991-6. Prevalent AF excluded.	2,102	9,883	59	100	18	Q2	Q1	1.00 (0.88 to 1.14)	age, HTN medication, lipid-lowering medication, SBP, smoking, low physical activity, Apo-A levels, Apo-B levels, DM, alcohol, education, marital status, immigration status	-
												Q3		1.04 (0.92 to 1.19)		
												Q4		1.37 (1.20 to 1.56)		
							2,215	16,078	57	0	19.7	Q2	Q1	1.10 (0.96 to 1.26)		
												Q3		1.22 (1.06 to 1.39)		
												Q4		1.39 (1.21 to 1.59)		
2	Trevisan *et al.*[445]	2017	PRO.V.A.	Prospective cohort	Italy	Prevalent AF excluded Randomly selected 1995-1997 using age- and sex-stratified approach	115	1,764	74.3	0.36	4.4	>0.61	≤0.61	0.72 (0.56 to 0.92)	Age, sex, DM, HTN, CHD, educational level, physical activity, smoking habits, number of prescription medications.	-

AF – atrial fibrillation, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** - hypertension, **PRO.V.A.** – Progetto Veneto Anziani, **SBP** – systolic blood pressure, **SD** – standard deviation

B.17. Body mass index – change or variability

Appendix Table B.44: Studies reporting estimates of the association between body mass index change/variability and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	BMI variability/change as a continuous variable	*BMI variability/change as a categorical variable*		
Claim Sheba Medical Centre	1	0	Israel	[413]
HUNT3	0	1	Norway	[425]
NHIS	1	2	Korea	[494,495]
ROSE	0	1	Sweden	[447]
Total studies	**2**	**4**		
Of which presented continuous and categorical data	**1**			

BMI – body mass index, **HUNT3** - Trøndelag Healthy study, **NHIS** - National Health Insurance Service, **ROSE** - Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering Drug Treatment in Primary Care

Appendix Table B.45: Details of studies examining body mass index change/variability as a continuous variable and risk of incident atrial fibrillation

	Study	Date	Data-source	Phenotype	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Lim *et al.*[494]	2019	NHIS-Health Screening Cohort	BMI variability	Prospective cohort	Korea	Adults 40-79 with at least four national health check-ups between 2022 and 2009. Prevalent AF excluded.	1,959	171,324	Unclear	61	4	1.07 (0.99 to 1.16) per 1 kg/m^2 variability	Age, sex, initial BMI, HTN, DM, dyslipidaemia, MI, excessive alcohol intake, excessive exercise, smoking	-
2	Berkovitch *et al.*[413]	2016	Chaim Sheba Medical Centre	BMI change over follow-up	Prospective cohort	Israel	Outpatients attending health-screening examinations. ≥2 visits required. Excluded if BMI <18 kg/m^2, height/weight missing, or prevalent AF.	288	18,290	49	73	6.4	0.93 (0.88 to 0.99) per -1 kg/m^2 change	Age, sex, CHD (time-dependent), HTN (time-dependent), DM (time-dependent), LDL, low HDL, physical activity, baseline BMI	-

AF – atrial fibrillation, **BMI** – body mass index, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **LDL** – low-density lipoprotein, **MI** – myocardial infarction, **NHIS** - National Health Insurance Service, **SD** – standard deviation.

Appendix Table B.46: Details of studies examining body mass index change/variability, as a categorical variable, on the risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Phenotype	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
1	Feng *et al*.[425]	2019	HUNT3	Prospective cohort	Norway	BMI change	Residents ≥20 years old in Nord-Trøndelag County in Norway between 2006 and 2008.	1,149	15,214	66.6	0.43	8.0	-5 to -2.5 kg/m^2 2.5 to 5 kg/m^2 ≥5 kg/m^2	-2.5 to 2.5 kg/m^2	1.3 (0.3 to 5.4) 1.1 (0.9 to 1.5) 2.6 (1.3 to 5.2)	Sex, age, smoking, education, marital status, physical activity, alcohol, regression slope of BMI	-	No
2	Lee *et al*.[495]	2019	NHIS	Prospective cohort	Korea	BMI variability	Participants with ≥3 health check-ups during a 5-year period. Those with prevalent AF or missing covariates excluded.	31,302	6,819,829	42.9	0.57	5.3	Q2 Q3 Q4	Q1	1.00 (0.97 to 1.03) 1.00 (0.97 to 1.04) 1.08 (1.05 to 1.12)	Age, sex, smoking, alcohol, exercise, income, baseline BMI, fasting glucose, total cholesterol, SBP	Lim *et al*. (2019)[494]	Yes†[494]
3	Lim *et al*.[494]	2019	NHIS-Health Screening Cohort	BMI variability	Prospective cohort	Korea	Adults 40-79 with at least four national health check-ups between 2022 and 2009. Prevalent AF excluded.	1,959	171,324	Unclear	61	4	Increased BMI Decreased BMI	Stable BMI	1.32 (1.01 to 1.71) 1.13 (0.82 to 1.56)	Age, sex, initial BMI, HTN, DM, dyslipidaemia, MI, excessive alcohol intake, excessive exercise, smoking	Lee *et al*. (2019)[495]	Yes[494]
4	Grundvold *et al*.[447]	2015	ROSE	Retrospective cohort	Sweden	BMI change	Aged 35-79 years with a diagnosis of Type 2 DM in primary care. Exclusions for baseline DM, CHD, AF, or cancer.	287	7,169	59.5	53	4.6	>1 kg/m^2 gain <-1 kg/m^2	-1 to +1 kg/m^2 change	1.53 (1.10 to 2.12) 1.06 (0.81 to 1.38)	Age, sex, BMI at baseline, previous CHD, SBP	-	No

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** – hypertension, **HUNT3** - Trøndelag Healthy study, **NHIS** - National Health Insurance Service, **Q** – quartile, **ROSE** - Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering Drug Treatment in Primary Care, **SBP** – systolic blood pressure.

B.18. Weight – change or variability

Appendix Table B.47: Studies reporting estimates of the association between weight change/variability and risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Weight change/variability as a continuous variable	*Weight change/variability as a categorical variable*		
Malmo Preventive Project Cohort	1	0	Sweden	[496]
NHIS	1	3	Korea	[497-499]
VIP	1	1	Sweden	[206]
Total studies	**3**	**4**		
Of which presented continuous and categorical data	**2**			

NHIS - National Health Insurance Service, **VIP** – Vasterbotten Intervention Programme

Appendix Table B.48: Details of studies examining weight change/variability, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Phenotype	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Johansson *et al*.[206]	2020	VIP	Weight change	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded.	3,200	53,376	46.3	100	14.3	1.00 (0.99 to 1.01) per 1%	Age, cholesterol. education, smoking, MI, HTN, DM, alcohol, physical activity	-
								1,954	55,041	46.3	0	15.6	1.00 (0.98 to 1.01) per 1%		
2	Lee *et al*.[497]	2019	NHIS	Weight variability	Prospective cohort	Korea	Participants ≥20 years who underwent a health examination between 2009 and 2010 with ≥ annual examination. Those with prevalent AF and missing parameters were excluded.	158,347	8,091,401	48	59	8.1	1.05 (1.04 to 1.05) per SD	Age, sex, smoking, alcohol, exercise, low income, DM, HTN	-
3	Johnson *et al*.[496]	2016	Malmo Preventive Project Cohort	Weight change	Prospective cohort	Sweden	Men from Malmo Sweden recruited in 1974-84 and rescreened on average 6 years later. AF prevalent to rescreening excluded.	618	4,056	100	100	22.3	1.14 (1.03 to 1.26) per 1 kg increase	Age, weight, height, SBP, glucose, smoking status, sedentary life style, screening year, HTN medication at baseline, low socioeconomic status, FEV_1, alcohol risk use	-

AF – atrial fibrillation, **BMI** – body mass index, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **FEV_1** – forced expiratory volume in one second, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **LDL** – low-density lipoprotein, **MI** – myocardial infarction, **NHIS -** National Health Insurance Service, **SBP** – systolic blood pressure, **SD** – standard deviation, **VIP** – Vasterbotten Intervention Programme

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Appendix Table B.49: Details of studies examining change/weight variability, as a categorical variable, on risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
1	Park *et al.*[499]	2022	NHIS	Prospective cohort	Korea	Participants ≥20 years with prevalent type-2 DM who underwent a health examination between 2009 and 2010 with ≥1 annual examination. Those with prevalent AF, MI, or CCF and missing parameters were excluded.	34,953	1,522,241	56.3	64	7.0	≤-10% -10 to -5% 5 to 10% >10%	-5 to +5%	1.31 (1.24 to 1.38) 1.12 (1.08 to 1.15) 1.04 (1.00 to 1.09) 1.23 (1.15 to 1.32)	Age, sex, HTN, dyslipidaemia, cancer, hyperthyroidism, CKD, PAD, COPD, income, smoking, alcohol, physical activity	Lee *et al*. (2019)[497] Lee *et al*. (2020)[498]	Yes†[497]
2	Johansson *et al.*[206]	2020	VIP	Prospective cohort	Sweden	Participated in health examination between 1988 and 2014 with data on height and weight. Prevalent AF excluded.	3,200 1,954	53,376 55,041	46.3 46.3	100 0	14.3 15.6	<-7% -7 to -3% +3 to 7% >7%	Stable weight	0.88 (0.60 to 1.30) 1.02 (0.78 to 1.33) 0.92 (0.76 to 1.12) 0.92 (0.76 to 1.10) 1.06 (0.71 to 1.60) 1.01 (0.68 to 1.48) 1.02 (0.77 to 1.35) 0.88 (0.68 to 1.13)	Age, cholesterol. education, smoking, MI, HTN, DM, alcohol, physical activity		Yes[206]
3	Lee *et al.*[498]	2020	NHIS	Prospective cohort	Korea	Participants ≥20 years with prevalent type-2 DM who underwent a health examination between 2009 and 2010 with ≥1 annual examination. Those with prevalent AF and missing parameters were excluded.	22,019	670,797	57.8	65	7.0	Q5	Q1-Q4	1.16 (1.12 to 1.20)	Baseline BMI, age, sex, smoking, alcohol, exercise, low income, HTN, dyslipidaemia, DM medication, insulin use, DM duration, fasting glucose	Lee *et al*. (2019)[497] Park *et al*. (2022)[499]	Yes†[497]

4	Lee *et al*.[497]	2019	NHIS	Prospective cohort	Korea	Participants ≥20 years who underwent a health examination between 2009 and 2010 with ≥ annual examination. Those with prevalent AF and missing parameters were excluded.	158,347	8,091,401	48	59	8.1	Q2 Q3 Q4	Q1 weight variability	1.00 (0.99 to 1.02) 1.04 (1.03 to 1.06) 1.14 (1.12 to 1.15)	Age, sex, smoking, alcohol, exercise, low income, DM, HTN	Lee *et al*. (2020)[498] Park *et al*. (2022)[499]	Yes[497]

AF – atrial fibrillation, **BMI** – body mass index, **CCF** – congestive cardiac failure, **CI** – confidence interval, **CKD** – chronic kidney disease, **COPD** – chronic obstructive pulmonary disease, **DM** – diabetes mellitus, **HR** – hazard ratio, **HTN** – hypertension, **MI** – myocardial infarction, **NHIS -** National Health Insurance Service, **PAD** – peripheral arterial disease, **Q** – quintile, **VIP** – Vasterbotten Intervention Programme

B.19.Lean mass index

Appendix Table B.50: Studies reporting estimates of the association between lean mass index and the risk of incident atrial fibrillation

Dataset	Number of studies		Location	References
	Lean mass index as a continuous variable	*Lean mass index as a categorical variable*		
Prospective Epidemiological Risk Factor	0	1	Denmark	[222]
WHI	1	0	USA	[63]
Total studies	**1**	**1**		

USA – United States of America, **WHI** – Women's Health Initiative

Appendix Table B.51: Details of studies examining lean mass index, as a continuous variable, and risk of incident atrial fibrillation

	Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	HR (95%CI)	Adjustments	Studies from same data
1	Azarbal *et al*.[63]	2016	WHI	Prospective cohort	USA	Age: 50-79. Prevalent AF excluded. Subset with DEXA imaging	1,035	8,832	63.3	0	11.6	1.39 (1.15 to 1.67) per 5 kg/m^2	age, ethnicity, education, HTN, DM, hyperlipidaemia, CHD, CCF, PAD, smoking, dietary modification, hormone therapy	-

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HDL** – high-density lipoprotein, **HR** – hazard ratio, **HTN** - hypertension, **PAD** – peripheral artery disease, **USA** – United States of America, **WHI** – Women's Health Initiative

Appendix Table B.52: Details of studies examining lean mass index, as a categorical variable, and risk of incident atrial fibrillation

Study	Date	Data-source	Study type	Location	Entry requirements	AF Cases	Total Size	Average age	Male (%)	Follow-up (years)	Effect group	Reference group	HR (95%CI)	Adjustments	Studies from same data	Continuous effects reported elsewhere
Worm *et al.*[222]	2020	Prospective Epidemiological Risk Factor	Prospective cohort	Denmark	Women without AF at baseline who had participated in clinical prevention trials at the Centre for Clinical and Basic Research.	850	5,704	70.7	0	11.5	Tertile 3	Tertile 1	1.15 (0.96 to 1.38)	age, alcohol, smoking education, exercise, HRT, HTN, hyperlipidaemia, DM, CHD, PAD, CCF, thyroid disease, scanner model	-	No
													1.21 (1.01 to 1.46)	+ height		

AF – atrial fibrillation, **CCF** – congestive cardiac failure, **CHD** – coronary heart disease, **CI** – confidence interval, **DM** – diabetes mellitus, **HR** – hazard ratio, **HRT** – hormone replacement therapy, **HTN** – hypertension, **PAD** – peripheral artery disease.

Appendix C - Additional phenotypes from the systematic review

The following appendix describes studies exploring additional anthropometric phenotypes identified through the systematic review outlined in **Chapter 3**.

C.1. Effect of hip circumference on risk of incident atrial fibrillation

Five studies reporting data from four prospective cohorts assessed the association between hip circumference (HC) as a continuous measure and risk of atrial fibrillation (AF) (**Appendix Table B.28**). These studies included a total of 5,318 unique AF cases. A single additional cohort (AF cases=2,092) examined HC as a categorical variable. Data from the Danish Diet, Cancer, and Health (DDCH) study has been presented in two separate publications.[66,191]

All the cohorts found in this search have shown a positive association between HC, as a continuous variable, and the risk of incident AF (**Appendix Table B.29**). Of note, Fenger-Grøn *et al*. (AF cases=3,868) demonstrated a 26% higher risk of AF per SD (95%CI 22 to 30%).[66] Data from the Cardiovascular Health Study (AF cases=1,050) showed a similar positive association, albeit with a smaller magnitude (HR 1.13, 95%CI 1.06 to 1.21, per SD).[67] A similar result was seen when HC was examined in fifths (**Appendix Table B.30**).

Of those cohorts examining the effect of HC as a continuous measure, only Fenger-Grøn *et al.* has further adjusted for other anthropometric measures. When adjusted for lean mass, HC was no longer significantly associated with risk of AF (HR 1.03, 0.99 to 1.07, per SD).[66]

To date, the effect of HC on risk of AF has not been examined separately in men and women.

The association between genetically predicted HC and risk of AF has been examined by Wang *et al.* (**Appendix Table B.1**).[110] They demonstrated a strong positive association between genetically predicted HC and risk of AF (OR 1.60, 1.50 to 1.70, per SD). This association remained significant when adjusted for genetically predicted body mass index, waist circumference, and height (OR 1.26, 1.02 to 1.56, per SD).

C.2. Body surface area and risk of incident atrial fibrillation

Five papers have explored the association between higher body surface area (BSA) and risk of incident AF (**Appendix Table B.31**).[60,211,223,445]

Trevisan *et al.* explored the effect of BSA on risk of AF in the PRO.V.A cohort (AF cases=115), and demonstrated a strong positive correlation between higher BSA, per 0.1m^2, and risk of incident AF (HR 1.04, 1.03 to 1.05, **Appendix Table B.32**).[445] A significant positive association between BSA and risk of incident AF is supported by the cohorts examining BSA as a categorical variable and no

evidence of a non-linear association was identified (**Appendix Table B.33**).[60,211,223]

To date, there are no published reports of the association of BSA when adjusted for other anthropometric measures. As BSA is calculated using weight and height, it is possible that the positive association represents the effects of these two measures on the risk of AF.

To date, the effect of BSA on risk of AF has not been examined separately in men and women. The association between genetically predicted BSA has not been examined in any published study to date. However, appropriate variants have been identified in recent GWAS.[500]

C.3. Effect of fat percentage on risk of atrial fibrillation

Six studies have examined the effect of body fat percentage (BF%, five as a continuous variable) on risk of incident AF (**Appendix Table B.34**, unique AF cases=15,295). These studies report data from five different data sets; the DDCH study has been included in two reports (**Appendix Table B.35**, **Appendix Table B.36**).[66,191]

Of the five datasets identified, a positive association between BF% and risk of AF was only demonstrated in the DDCH study (AF cases=3,868), and Malmo Diet and Cancer Study (AF cases=4,317). Results from the DDCH study demonstrated a positive association between BF% and the risk of AF (HR 1.16, 95%CI 1.12 to 1.20, per SD).[66] Comparatively, results from both the Women's Health Initiative cohort (AF cases=1,035 – dual-energy X-ray absorptiometry

[DEXA] values) and the Health ABC cohort (AF cases=371 – DEXA values) were both null.[63,68] The positive effect between BF% and risk of AF seen in the DDCH cohort was completely attenuated when adjusted for either LM (HR 1.02, 0.98 to 1.05).[66]

The association between BF% and risk of AF has been examined separately by sex in a single cohort. Zia *et al*. demonstrated similar associations between BF%, per 5%, in both men (HR 1.08, 1.04 to 1.13) and women (HR 1.13, 1.08 to 1.18).[207] However, the study only contained 4,317 AF cases (men 2,102, women 2,215) and small differences in effects cannot be excluded.

The effect of genetically predicted BF% on risk of AF has been explored in three studies with each demonstrating a positive association (**Appendix Table B.1**).[110,130,227] Of note, Zeng *et al*. demonstrated that the association between genetically predicted BF% and risk of AF (OR 1.80, 1.55 to 2.09, per SD) remained significant following further adjustment for genetically predicted LM (OR 1.49, 1.20 to 1.85, per SD).[227] This goes against the epidemiological evidence from the DDCH study and is more in line with results from genetically predicted FM suggesting a potential independent causal role for BF% in determining the risk of AF.[71]

C.4. Birthweight and risk of incident atrial fibrillation

Four reports have explored the association between birth weight and risk of incident AF (AF cases=7,514).[60,211,223,445] Of these, all treated birthweight as a categorical variable (**Appendix Table B.37**).

All cohorts examining the association between birth weight and risk of AF have included BMI in their primary models (**Appendix Table B.38**). Overall, there is limited evidence to suggest an association between birth weight and risk of incident AF. In the largest study, Larsson *et al.* examined birth weight in the Cohort of Swedish Men and Swedish Mammography Cohort.[487] This suggested that higher birthweight (≥4,000 g) may be a risk for AF (HR 1.25, 1.02 to 1.53 in men, HR 1.41, 0.94 to 2.10 in women) compared with a lower reference birth weight (3,000 to 3,999 g). Comparatively, results from the remaining cohorts have not shown significant associations between high or low birth weight and risk of AF.[486,488,489]

Both Larsson *et al*. and Johnson *et al*. examined the effect of birth weight separately in men and women.[487,488] While high birth weight was only significantly associated with incident AF in men in the Larsson *et al*. analysis, the difference between sexes was small and no significant difference was identified.

Associations between genetically predicted birth weight and risk of AF has been explored in three studies (**Appendix Table B.1**). In contrast to the epidemiological evidence, all three have demonstrated significant associations between genetically predicted birth weight and risk of AF. For example, Wang *et al*. demonstrated a ~30% greater risk of AF per 1-SD higher genetically predicted birth weight (OR 1.29, 1.18 to 1.40).[110]

C.5. Metabolically healthy obesity

The association between metabolically healthy obesity and risk of AF has been presented in four studies from four different cohorts (AF cases=266,237, **Appendix Table B.39**, **Appendix Table B.40**).[491,493]

Fauchier *et al*. used French hospital admissions data to examine the impact of metabolic health on the association between obesity and risk of AF (AF cases=257,289).[490] They defined metabolic health as a lack of hypertension, dyslipidaemia or diabetes mellitus. Compared with a metabolically healthy and normal weight group, those with a BMI ≥25 kg/m^2 and no metabolic abnormalities had a 33% greater risk of AF (HR 1.33, 1.30 to 1.37). However, this risk was significantly greater in those with a BMI ≥25 kg/m^2 and metabolic abnormalities (HR 1.68, 1.64 to 1.74). This is supported by data from the NHIS cohort (AF cases=5,106).[493] In contrast, Feng *et al.*, examining the HUNT cohort (AF cases=1,758), showed that those with a BMI ≥30 kg/m^2 had an greater risk of AF whether they were classed as 'metabolically healthy' (HR 1.6, 1.2 to 2.1) or 'metabolically unhealthy' (HR 1.6, 1.3 to 1.9) when compared to those <25kg/m^2 and metabolically healthy.[491]

Martin *et al*. assessed the association between genetically predicted metabolically healthy obesity and risk of AF.[130] They demonstrated no significant association between metabolically healthy obesity and risk of AF (OR 0.79, 0.39 to 1.61). However, the study does not provide evidence of the strength of the genetic variants and this study may be at risk of weak instrument bias. Furthermore, a number phenotypes of that may mediate the association between adiposity and risk of AF are metabolic abnormalities were adjusted for in

developing the metabolically healthy obesity phenotype (for example hypertension).

C.6. Waist-height ratio

Two studies have examined the effect of waist-height ratio on the risk of AF (AF cases=4,432, **Appendix Table B.41, Appendix Table B.42**, and **Appendix Table B.43**).

Zia *et al*. demonstrated that greater weight-height ratio was positively associated with risk of incident AF in both men (HR 1.11, 1.06 to 1.16, per SD) and women (HR 1.12, 1.07 to 1.17, per SD).[207] In contrast, in a small study (AF cases=115) Trevisan *et al*. suggested that a 1-unit increase in waist-height ratio was associated with a substantially lower risk of AF (HR 0.12, 95%CI 0.05 to 0.28).[445] Neither of the identified studies have examined the association of waist-height ratio and risk of AF following adjustment for other anthropometric measures or separately in men and women. The association between genetically predicted waist-height ratio has not been examined in any published study to date.

C.7. Body mass index change/variability and the risk of atrial fibrillation

Change or variability in BMI has been assessed in five studies across three cohorts (**Appendix Table B.44**, **Appendix Table B.45**, and **Appendix Table B.46**).[413,425,447,494,495] The results have not been entirely concordant. Berkovitch

et al. examined an Israeli cohort (AF cases=288). They demonstrated that for each 1 kg/m^2 reduction in BMI during follow-up (mean 6 years), there was a corresponding 7% lower risk of incident AF (95%CI 1 to 12%).[413] However, while data from the ROSE cohort (AF cases=287) demonstrated that BMI gain during follow-up (mean 4.6 years) had a higher risk of incident AF (HR 1.53, 1.10 to 2.12), there was no significant effect seen with weight loss.[447] Feng *et al.* (AF cases=1,149) suggested that there was a higher risk of AF in participants who either gained or lost BMI during follow-up.[425] However, only a gain of ≥5 kg/m^2 was associated with a significantly higher risk of AF (HR 2.6, 1.3 to 5.2). When considering variability, data from the NHIS cohort (AF Cases=31,302) which has demonstrated that those in the highest quartile of BMI variability (defined using variability independent of the mean) had an 8% higher risk of AF (95%CI 5 to 12%).[495]

C.8. Effect of weight change on risk of incident atrial fibrillation

Five studies have examined the effect of weight change on the risk of AF (three examining weight change/variability as a continuous variable, **Appendix Table B.47**, **Appendix Table B.48**, and **Appendix Table B.49**). Examining the Malmo Preventive Project cohort (AF cases=616), Johnson *et al*. demonstrated a 14% greater risk of incident AF per 1kg greater weight change over a six year period. (HR 1.14, 1.03 to 1.26).[496] However this has not a consistent finding; data from the Vasterbotten Intervention Programme showed no effect in men (HR 1.00,

0.99 to 1.01, per 1%, AF cases=3,200) or women (HR 1.00, 0.98 to 1.01, per 1%, AF cases=1,954).[206]

C.9. Effect of lean mass index on risk of atrial fibrillation

LM index has been explored in two cohorts with conflicting results (**Appendix Table B.50**). Azarbal *et al*. examined LM index as a continuous variable in the WHI cohort (**Appendix Table B.51**) and showed a strong positive association with incident AF (HR 1.39, 1.15 to 1.67, per 5 kg/m^2).[63] While results from the Prospective Epidemiological Risk Factor cohort (**Appendix Table B.52**), examining LM index in thirds, did not show a significant association between LM index and risk of AF, it was directionally consistent (HR 1.15, 0.96 to 1.38 between top and bottom third).[222]

Appendix D - UK Biobank disease phenotype definitions

This appendix provides further details of development of UK Biobank (UKB) phenotypes used in this thesis. The International Classification of Diseases 10th edition [ICD-10]/Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 [OPCS-4]/UKB codes used to develop UKB phenotypes are detailed in **Appendix Table D.1**. Additional information regarding the primary care phenotype are detailed in **Appendix Table D.2** and **Appendix Table D.3**.

Appendix Table D.1: Disease endpoints and codes used for hospital episode statistics, death data, and baseline verbal interview phenotype definitions

Disease	Code Book	Codes
Atrial Fibrillation	ICD10	I48, I480, I481, I482, I483, I484, I489
	OPCS-4	K223, K571, K575, K621, K622, K623, K624, K625, X501, X502
	UKB Code 6	1471, 1483
	UKB Code 5	1524, 1553
Coronary Heart Disease		
Myocardial Infarction	ICD10	I21, I210, I211, I212, I213, I214, I215, I216, I217, I218, I219, I22, I220, I221, I222, I223, I224, I225, I226, I227, I228, I229, I23, I230, I231, I232, I233, I234, I235, I236, I237, I238, I239
	UKB Code 6	1075
Angina	ICD10	I20, I200, I201, I202, I203, I204, I205, I206, I207, I208, I209
Other IHD	ICD10	I24, I240, I241, I242, I243, I244, I245, I246, I247, I248, I249, I25, I250, I251, I252, I253, I254, I256, I257, I258, I259
	OPCS-4	K40, K401, K402, K403, K404, K408, K409, K41, K411, K412, K413, K414, K418, K419, K42, K421, K422, K423, K424, K428, K429, K43, K431, K432, K433, K434, K438, K439, K44, K441, K442, K448, K449, K45, K451, K452, K453, K454, K455, K456, K458, K459, K46, K461, K462, K463, K464, K465, K468, K469, K49, K491, K492, K493, K494, K498, K499, K50, K501, K502, K503, K504, K508, K509, K75, K751, K752, K753, K754, K758, K759
	UKB Code 5	1070, 1095, 1523
Heart Failure		
Congestive Cardiac Failure	ICD10	I110, I130, I132, I50, I500, I501, I509
	UKB Code 6	1076
Cardiomyopathy [Not HCM]	ICD10	I255, I420, I423, I424, I425, I426, I427, I428, I429, I43, I430, I431, I432, I438

Appendix Table D.1: Disease endpoints and codes used for hospital episode statistics, death data, and baseline verbal interview phenotype definitions

Disease	Code Book	Codes
	UKB Code 6	1079
Other Conditions		
Valvular Disease	ICD10	I05, I050, I051, I052, I058, I059, I06, I060, I061, I062, I068, I069, I34, I35
	OPCS-4	K25, K251, K252, K253, K254, K255, K258, K259, K26, K261, K262, K263, K264, K265, K268, K269, K27, K271, K272, K273, K274, K275, K276, K278, K279, K28, K281, K282, K283, K284, K285, K288, K289, K29, K291, K292, K293, K294, K295, K296, K297, K298, K299, K30, K301, K302, K303, K304, K305, K308, K309, K318, K319, K328, K329, K341, K342, K343, K344, K345, K346, K348, K349, K356, K357, K358, K359, K361, K362, K368, K369
	UKB Code 6	1078, 1489, 1490, 1584, 1585, 1586, 1587
	UKB Code 5	1097, 1099, 1100, 1101
Stroke	ICD10	I63, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64
	UKB Code 6	1081, 1583
Sleep apnoea	ICD10	G473
	UKB Code 6	1123
Hypertension	ICD10	I10, I11, I110, I119, I12, I120, I129, I13, I130, I131, I132, I139, I15, I150, I151, I152, I158, I159

Appendix Table D.1: Disease endpoints and codes used for hospital episode statistics, death data, and baseline verbal interview phenotype definitions

Disease	Code Book	Codes
	UKB Code 4	1140851332, 1140851336, 1140851338, 1140851360, 1140851362, 1140851364, 1140851368, 1140851480, 1140851484, 1140851492, 1140851522, 1140851556, 1140851576, 1140851658, 1140851790, 1140851794, 1140851798, 1140851800, 1140860172, 1140860180, 1140860192, 1140860194, 1140860212, 1140860220, 1140860222, 1140860230, 1140860232, 1140860244, 1140860250, 1140860266, 1140860274, 1140860278, 1140860292, 1140860294, 1140860304, 1140860362, 1140860380, 1140860382, 1140860402, 1140860434, 1140860492, 1140860498, 1140860696, 1140860714, 1140860728, 1140860750, 1140860752, 1140860758, 1140860776, 1140860802, 1140860806, 1140860878, 1140860882, 1140860892, 1140860904, 1140860912, 1140860918, 1140861090, 1140861106, 1140861110, 1140861114, 1140861120, 1140861176, 1140861190, 1140861194, 1140861202, 1140861276, 1140861282, 1140863724, 1140864410, 1140866072, 1140866074, 1140866078, 1140866084, 1140866086, 1140866090, 1140866092, 1140866094, 1140866096, 1140866102, 1140866104, 1140866108, 1140866110, 1140866122, 1140866128, 1140866132, 1140866136, 1140866138, 1140866140, 1140866144, 1140866146, 1140866156, 1140866158, 1140866162, 1140866164, 1140866168, 1140866446, 1140866692, 1140866704, 1140866712, 1140866724, 1140866726, 1140866738, 1140866756, 1140866758, 1140866764, 1140866766, 1140866778, 1140866782, 1140866784, 1140866798, 1140866800, 1140866802, 1140866804, 1140872472, 1140872568, 1140875808, 1140875840, 1140878098, 1140879758, 1140879760, 1140879762, 1140879802, 1140879810, 1140879818, 1140879822, 1140879824, 1140879826, 1140879830, 1140879834, 1140879842, 1140879854, 1140879866, 1140881702, 1140881706, 1140881712, 1140881722, 1140881882, 1140881890, 1140888552, 1140888556, 1140888560, 1140888646, 1140888918, 1140888922, 1140909368, 1140909706, 1140910442, 1140910614, 1140911088, 1140916342, 1140916356, 1140916362, 1140916730, 1140916868, 1140916870, 1140916930, 1140917068, 1140917076, 1140922930, 1140923572, 1140923712, 1140923718, 1140926188, 1140926966, 1140927934, 1140927940, 1140928212, 1140928226, 1140928234, 1141145658, 1141145660, 1141145668, 1141145870, 1141146378, 1141150328, 1141150500, 1141150538, 1141150560, 1141151382, 1141152076, 1141152600, 1141152998, 1141153006, 1141153026, 1141153032, 1141156754, 1141156808, 1141156836, 1141156846, 1141157140, 1141162546, 1141164148, 1141164154, 1141164276, 1141164280, 1141166006, 1141166752, 1141167758, 1141167822, 1141168498, 1141169730, 1141170870, 1141171152, 1141171336, 1141171344, 1141172492, 1141172742, 1141173766, 1141179974, 1141182904, 1141182968, 1141184324, 1141187048, 1141187094, 1141187780, 1141187962, 1141188152, 1141188408, 1141188576, 1141188636, 1141188836, 1141188920, 1141188936, 1141190160, 1141190548, 1141193282, 1141193346, 1141194794, 1141199858, 1141199940, 1141200400, 1141200698, 1141200782, 1141201814
	UKB Code 6	1065, 1072
	Touchscreen	High blood pressure reported on touch screen (field 6150) or blood pressure medication reported on touchscreen (field 6177)
	Physical measures	Systolic blood pressure ≥160 mmHg or diastolic blood pressure >100 mmHg

HCM – Hypertrophic cardiomyopathy; HES – Hospital episode statistics; ICD – International Disease Classification; IHD – ischaemic heart disease; OPCS-4 – Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4; UKB – UK Biobank. ICD10 and OPCS codes used to determine disease status from HES and death registry data. UKB 4 used to determine medication use at baseline. UKB Code 5 and UKB Code 6 used to determine disease status from verbal interview records.

Appendix Table D.2: Predefined terms for non-index events or diagnoses not being present from key-word search.

Non-index terms	Diagnosis not present
Annual review	Excluded
H/O	Not detected
History of	High risk of
Monitoring	At risk of
Resolved	FH
	Family history
	Suspected
	Screening for

H/O is common medical terminology for 'history of', FH is common medical short-hand for 'family history.

Appendix Table D.3: Read Codes used to derive primary care phenotype for atrial fibrillation.

Read Code	Read Code Type	Read Code Description	Map Type	Mapped ICD-10/OPCS-4 Code	
G573.	V2	Atrial fibrillation and flutter	ICD10	I489	
G5730	V2	Atrial fibrillation	ICD10	I489	
G5731	V2	Atrial flutter	ICD10	I489	
G5732	V2	Paroxysmal atrial fibrillation	ICD10	I480	
G5733	V2	Non-rheumatic atrial fibrillation	ICD10	I489	
G5734	V2	Permanent atrial fibrillation	ICD10	I489	
G5735	V2	Persistent atrial fibrillation	ICD10	I481	
G5736	V2	Paroxysmal atrial flutter	ICD10	I489	
G5737	V2	Chronic atrial fibrillation	ICD10	I482	
G5738	V2	Typical atrial flutter	ICD10	I483	
G5739	V2	Atypical atrial flutter	ICD10	I484	
G573z	V2	Atrial fibrillation and flutter NOS	ICD10	I489	
790G2	V2	Percutaneous occlusion of left atrial appendage	OPCS 4	K625	
790G3	V2	Exclusion of left atrial appendage	OPCS 4	K223	
79340	V2	Percutaneous transluminal ablation of atrioventricular node	OPCS 4	K571	
79345	V2	Percutaneous transluminal ablation of atrial wall	OPCS 4	K575	
79348	V2	Percutaneous transluminal ablation of atrial wall NEC	OPCS 4	K575	
793M0	V2	Percutaneous transluminal ablation of pulmonary vein to left atrium conducting system	OPCS 4	K621	
793M1	V2	Percutaneous transluminal ablation of atrial wall for atrial flutter	OPCS 4	K622	
793M2	V2	Percutaneous transluminal internal cardioversion NEC	OPCS 4	K624	
793M3	V2	Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC	OPCS 4	K623	
7L1H0	V2	Direct current cardioversion	OPCS 4	X501	
7L1H1	V2	External cardioversion NEC	OPCS 4	X502	
7L1H2	V2	Internal electrode cardioversion	OPCS 4	K624	
7L1H3	V2	Electrical sinus rhythm conversion	OPCS 4	X501	
7L1H4	V2	Electrical operative cardiac stimulation	OPCS 4	X501	
7L1H8	V2	Chemical cardioversion	OPCS 4	X502	
14AN.	V2	H/O: atrial fibrillation	KW	NA	*
14AR.	V2	History of atrial flutter	KW	NA	*

Appendix Table D.3: Read Codes used to derive primary care phenotype for atrial fibrillation.

Read Code	Read Code Type	Read Code Description	Map Type	Mapped ICD-10/OPCS-4 Code	
212R.	V2	Atrial fibrillation resolved	KW	NA	*
3272	V2	ECG: atrial fibrillation	KW	NA	
3273	V2	ECG: atrial flutter	KW	NA	
662S.	V2	Atrial fibrillation monitoring	KW	NA	*
6A9..	V2	Atrial fibrillation annual review	KW	NA	*
7936A	V2	Implantation of intravenous pacemaker for atrial fibrillation	KW	NA	
8CMW2	V2	Atrial fibrillation care pathway	KW	NA	
8HTy.	V2	Referral to atrial fibrillation clinic	KW	NA	
8OAD.	V2	Provision of written information about atrial fibrillation	KW	NA	
9Os..	V2	Atrial fibrillation monitoring administration	KW	NA	*
9Os0.	V2	Atrial fibrillation monitoring first letter	KW	NA	*
9Os1.	V2	Atrial fibrillation monitoring second letter	KW	NA	*
9Os2.	V2	Atrial fibrillation monitoring third letter	KW	NA	*
9Os3.	V2	Atrial fibrillation monitoring verbal invite	KW	NA	*
9Os4.	V2	Atrial fibrillation monitoring telephone invite	KW	NA	*
9hF..	V2	Exception reporting: atrial fibrillation quality indicators	KW	NA	
9hF0.	V2	Excepted from atrial fibrillation quality indicators: Patient unsuitable	KW	NA	
9hF1.	V2	Excepted from atrial fibrillation quality indicators: Informed dissent	KW	NA	
G573.	V3	Atrial fibrillation and flutter	ICD10	I489	
G5730	V3	Atrial fibrillation	ICD10	I489	
G5731	V3	Atrial flutter	ICD10	I489	
G573z	V3	Atrial fibrillation and flutter NOS	ICD10	I489	
X202R	V3	Lone atrial fibrillation	ICD10	I489	
X202S	V3	Non-rheumatic atrial fibrillation	ICD10	I489	
Xa2E8	V3	Paroxysmal atrial fibrillation	ICD10	I480	
Xa3rp	V3	Pacer controlled atrial fibril	ICD10	I489	
Xa7nI	V3	Controlled atrial fibrillation	ICD10	I489	
XaEga	V3	Rapid atrial fibrillation	ICD10	I489	
XaOfa	V3	Persistent atrial fibrillation	ICD10	I481	
XaOft	V3	Permanent atrial fibrillation	ICD10	I489	
XaaUH	V3	Paroxysmal atrial flutter	ICD10	I489	
XaeUP	V3	Chronic atrial fibrillation	ICD10	I482	
XaeUQ	V3	Typical atrial flutter	ICD10	I483	

Appendix Table D.3: Read Codes used to derive primary care phenotype for atrial fibrillation.

Read Code	Read Code Type	Read Code Description	Map Type	Mapped ICD-10/OPCS-4 Code
XaeUR	V3	Atypical atrial flutter	ICD10	I484
Xafis	V3	Atrial fibrillation detected	ICD10	I489
79340	V3	Percutaneous transluminal ablation of atrioventricular node	OPCS 4	K571
7A6A1	V3	Operation on the pulmonary venous system	OPCS 4	K621
7L1H0	V3	Direct current cardioversion	OPCS 4	X501
7L1H1	V3	External cardioversion NEC	OPCS 4	X502
7L1H2	V3	Internal electrode cardioversion	OPCS 4	K624
7L1H3	V3	Electrical sinus rhythm conversion	OPCS 4	X501
7L1H4	V3	Electrical operative cardiac stimulation	OPCS 4	X501
X011n	V3	Synchronised direct current defibrillation	OPCS 4	X501
XE0Jj	V3	External cardioversion NEC	OPCS 4	X502
XM1KN	V3	External electrode cardioversion	OPCS 4	X501
Xa1nl	V3	Direct current cardiac shock	OPCS 4	X501
Xa3ru	V3	Electrical cardioversion NOS	OPCS 4	X501
XaBdb	V3	Direct current defibrillation	OPCS 4	X501
XaLgF	V3	Percutaneous transluminal ablation of atrial wall	OPCS 4	K575
XaLjD	V3	Operations on individual pulmonary veins	OPCS 4	K621
XaLjI	V3	Other specified operations on individual pulmonary veins	OPCS 4	K621
XaLjJ	V3	Operations on individual pulmonary veins NOS	OPCS 4	K621
XaMmb	V3	Percutaneous transluminal internal cardioversion NEC	OPCS 4	K624
XaMmc	V3	Percutaneous transluminal ablation of atrial wall for atrial flutter	OPCS 4	K622
XaMmd	V3	Percutaneous transluminal ablation of pulmonary vein to left atrium conducting system	OPCS 4	K621
XaMrA	V3	Percutaneous transluminal ablation of atrial wall NEC	OPCS 4	K575
XaMrB	V3	Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC	OPCS 4	K623
XaOfF	V3	Chemical cardioversion	OPCS 4	X502

Appendix Table D.3: Read Codes used to derive primary care phenotype for atrial fibrillation.

Read Code	Read Code Type	Read Code Description	Map Type	Mapped ICD-10/OPCS-4 Code	
XaabV	V3	Percutaneous occlusion of left atrial appendage	OPCS 4	K625	
Xaasw	V3	Exclusion of left atrial appendage	OPCS 4	K223	
3272	V3	ECG: atrial fibrillation	KW	NA	
3273	V3	ECG: atrial flutter	KW	NA	
7936A	V3	Implantation of intravenous pacemaker for atrial fibrillation	KW	NA	
XE0Wk	V3	(Atrial fibrillation) or (atrial flutter)	KW	NA	
XaDv6	V3	H/O: atrial fibrillation	KW	NA	*
XaIIT	V3	Atrial fibrillation monitoring	KW	NA	*
XaLFh	V3	Exception reporting: atrial fibrillation quality indicators	KW	NA	
XaLFi	V3	Excepted from atrial fibrillation quality indicators: Patient unsuitable	KW	NA	
XaLFj	V3	Excepted from atrial fibrillation quality indicators: Informed dissent	KW	NA	
XaLFz	V3	Atrial fibrillation resolved	KW	NA	*
XaMDF	V3	Atrial fibrillation monitoring administration	KW	NA	*
XaMDG	V3	Atrial fibrillation monitoring first letter	KW	NA	*
XaMDH	V3	Atrial fibrillation monitoring second letter	KW	NA	*
XaMDI	V3	Atrial fibrillation monitoring third letter	KW	NA	*
XaMDK	V3	Atrial fibrillation monitoring verbal invite	KW	NA	*
XaMFn	V3	Atrial fibrillation monitoring telephone invite	KW	NA	*
XaMGD	V3	Atrial fibrillation annual review	KW	NA	*
XaNRA	V3	History of atrial flutter	KW	NA	*
XaXrZ	V3	Referral to atrial fibrillation clinic	KW	NA	
XaZdc	V3	Atrial fibrillation care pathway	KW	NA	
XaaaD	V3	Provision of written information about atrial fibrillation	KW	NA	

Mapped code refers to the ICD-10 or OPCS-4 code used to identify the relevant Read Code. Non-index events identify Read Codes which suggest a prior or historical diagnosis of AF. ICD-10 – international classification of disease 10 code, KW – keyword, NA – not applicable, OPCS-4 – OPCS classification of interventions and procedures version 4, V2 – Read Code version 2, V3 – Read Code version 3. * - likely non-index event.

1

Appendix E - Chapter 4 supplementary figures and tables

This appendix contains supplementary tables and figures from **Chapter 4**. Tables and figures are listed chronologically as referenced within the chapter.

Appendix Table E.1: Regression dilution ratio estimation

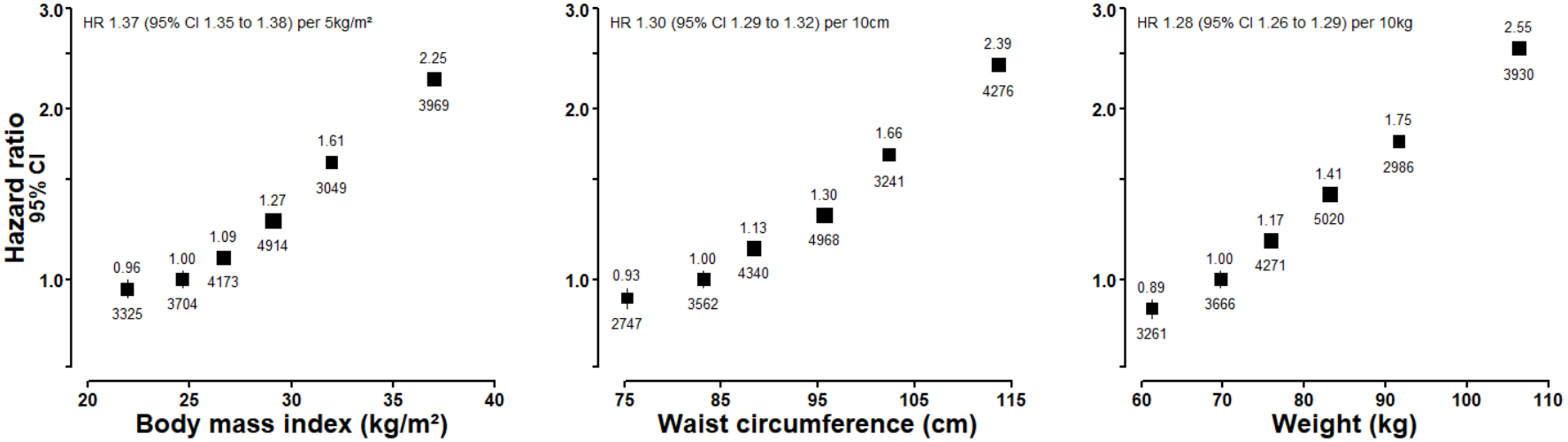
Adiposity Measure	Men							Women						
	Means		Standard deviation		Mean range		**Regression dilution ratio**	Means		Standard deviation		Mean range		**Regression dilution ratio**
	Baseline	Resurvey	Baseline	Resurvey	Baseline	Resurvey		Baseline	Resurvey	Baseline	Resurvey	Baseline	Resurvey	
Impedance Measures														
Lean mass (kg)	63.08	62.03	7.35	7.30	21.11	19.78	**0.94**	44.16	43.55	4.75	4.71	13.23	12.04	**0.91**
Fat mass (kg)	21.34	22.12	7.68	7.84	21.53	19.69	**0.91**	25.93	26.15	9.35	9.39	26.47	24.09	**0.91**
Anthropomorphic Measures														
Body mass index (kg/m^2)	27.25	27.33	3.88	3.93	10.95	10.27	**0.94**	26.40	26.45	4.76	4.82	13.56	12.72	**0.94**
Waist Circumference (cm)	95.04	96.56	10.74	10.81	30.52	25.07	**0.82**	82.46	84.51	11.67	12.10	33.69	28.95	**0.86**
Weight (kg)	84.41	84.14	13.32	13.40	37.53	35.42	**0.94**	70.08	69.69	13.04	13.05	36.81	34.33	**0.93**

Baseline and re-survey values provided for participants attending for re-survey between 2009 and 2013 (n=19,283) following the same exclusions as the main analysis. Mean range value is the difference between the mean value within the top 20% (defined by the value at baseline) and mean value within the bottom 20% (defined by the value at baseline). Regression dilution ratio value is derived as the mean range at re-survey divided by the mean range at baseline.

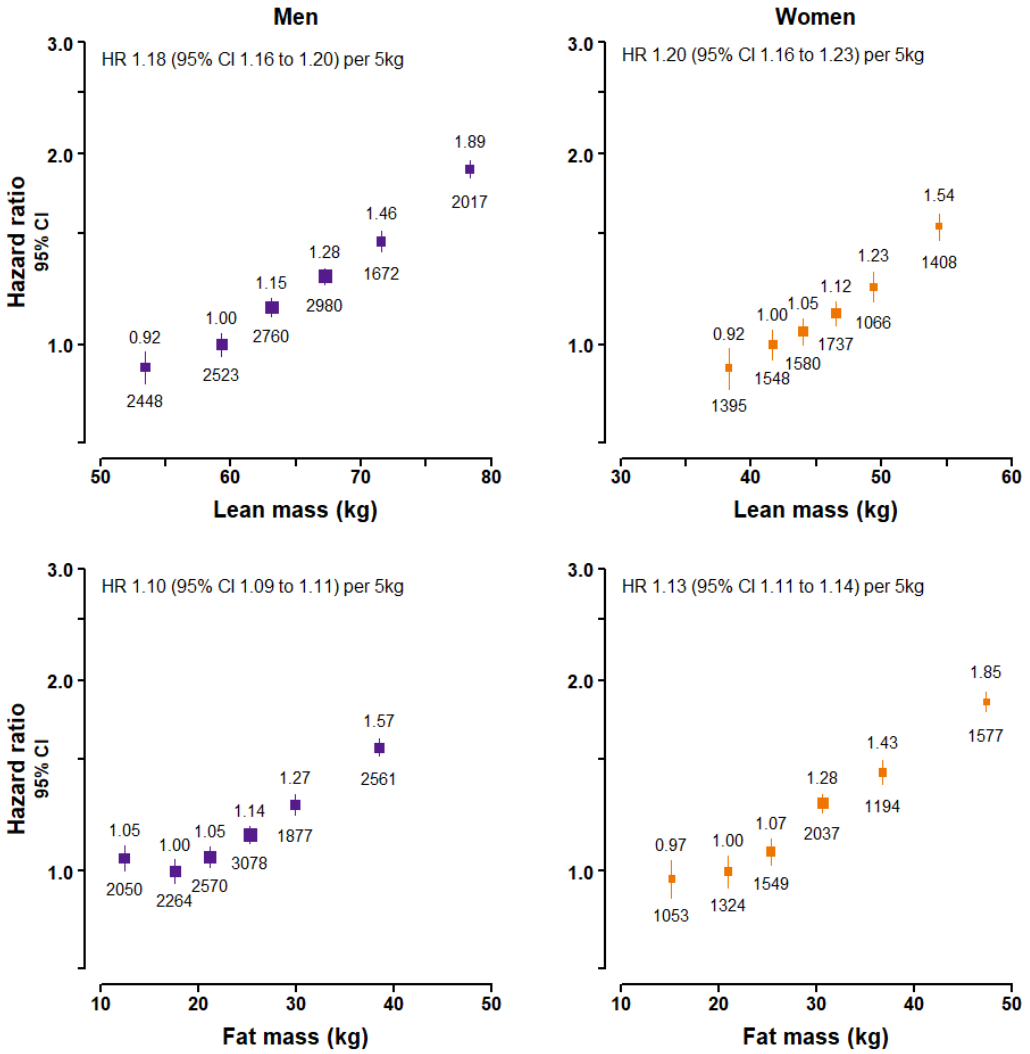
Appendix Table E.2: Partial Pearson's correlation coefficients between bio-impedance and anthropometric measures

		Lean mass	Fat mass	BMI	WC	WHR	HC	Height	Weight	Lean mass (DXA)*
Fat mass	Male	0.60	1.00							
	Female	0.71	1.00							
	All	0.62	1.00							
BMI	Male	0.65	0.92	1.00						
	Female	0.69	0.94	1.00						
	All	0.64	0.93	1.00						
WC	Male	0.65	0.89	0.88	1.00					
	Female	0.66	0.88	0.87	1.00					
	All	0.63	0.88	0.87	1.00					
WHR	Male	0.32	0.61	0.60	0.80	1.00				
	Female	0.28	0.44	0.46	0.75	1.00				
	All	0.29	0.50	0.51	0.77	1.00				
HC	Male	0.72	0.83	0.81	0.83	0.32	1.00			
	Female	0.72	0.91	0.89	0.82	0.24	1.00			
	All	0.67	0.88	0.86	0.82	0.27	1.00			
Height	Male	0.62	0.14	-0.06	0.15	-0.05	0.28	1.00		
	Female	0.48	0.15	-0.12	0.04	-0.08	0.13	1.00		
	All	0.55	0.14	-0.09	0.09	-0.07	0.19	1.00		
Weight	Male	0.89	0.90	0.88	0.87	0.53	0.87	0.42	1.00	
	Female	0.86	0.97	0.92	0.86	0.42	0.91	0.28	1.00	
	All	0.86	0.93	0.90	0.86	0.46	0.88	0.34	1.00	
Lean mass (DXA)*	Male	0.90	0.52	0.55	0.53	0.23	0.64	0.62	0.79	1.00
	Female	0.87	0.60	0.53	0.53	0.22	0.59	0.55	0.75	1.00
	All	0.89	0.54	0.52	0.52	0.22	0.58	0.58	0.76	1.00
Fat mass (DXA)*	Male	0.59	0.84	0.79	0.79	0.53	0.73	0.19	0.80	0.47
	Female	0.59	0.87	0.83	0.83	0.40	0.79	0.07	0.84	0.53
	All	0.57	0.86	0.82	0.82	0.47	0.76	0.13	0.82	0.49

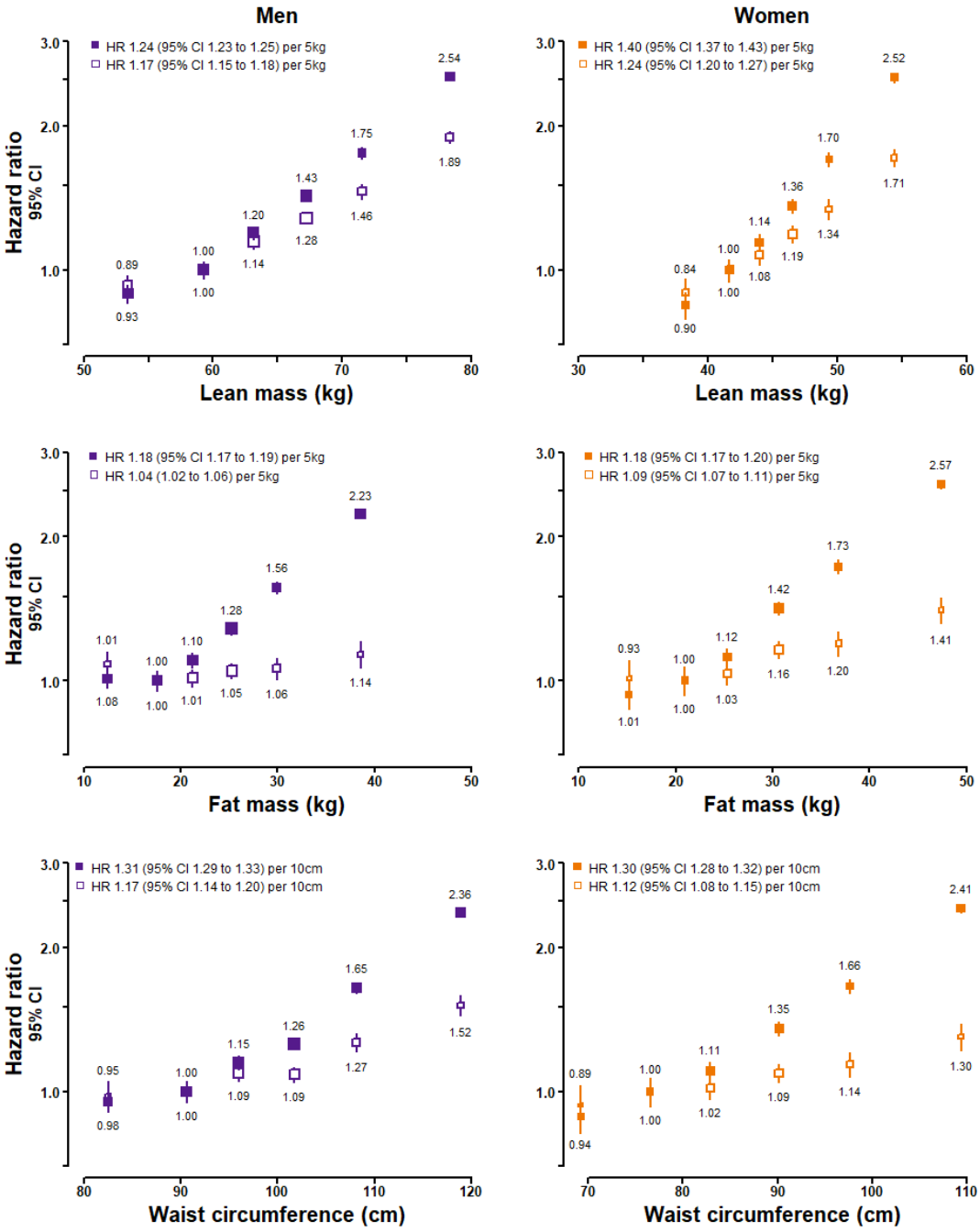
Correlation coefficients are calculated after adjustment for age at baseline in 5 year bands. Combined sex correlation coefficients are additionally adjusted for sex. DXA = dual-energy X-ray absorptiometry. *Correlations with DXA measures were undertaken in a subset of 4,955 individuals (2,346 men and 2,609 women) with DXA measures of lean mass and fat mass. BMI – body mass index; HC – hip circumference; WC – waist circumference; WHR – waist-hip ratio.



Appendix Figure E.1: Association of body mass index, waist circumference, and weight with incident atrial fibrillation.
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence interval (represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Hazard ratios shown above each square and the number of atrial fibrillation cases below.*



Appendix Figure E.2: Association of lean mass and fat mass with incident atrial fibrillation by sex following mutual adjustment and adjustment for height.
Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Plotted on a floating absolute scale in men (purple open squares) and women (orange closed squares). Sex-specific regression lines are plotted. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprise 10% of the sample. Hazard ratios shown above each square and the number of atrial fibrillation cases below. The range of the X-axes have been kept consistent between men and women to allow for visual comparison.*



Appendix Figure E.3: Association of lean mass, fat mass, and wait circumference with incident atrial fibrillation, before and after mutual adjustment

Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Plotted on a floating absolute scale in men (purple open squares) and women (orange closed squares). Sex-specific regression lines are plotted. Exclusions as per ***Table 4.2****. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprise 10% of the sample. Hazard ratios shown above (filled) and below (open) each square. The range of the X-axes have been kept consistent between men and women to allow for visual comparison.*

Appendix Table E.3: Associations of anthropometric traits with incident atrial fibrillation after sequential covariate adjustment

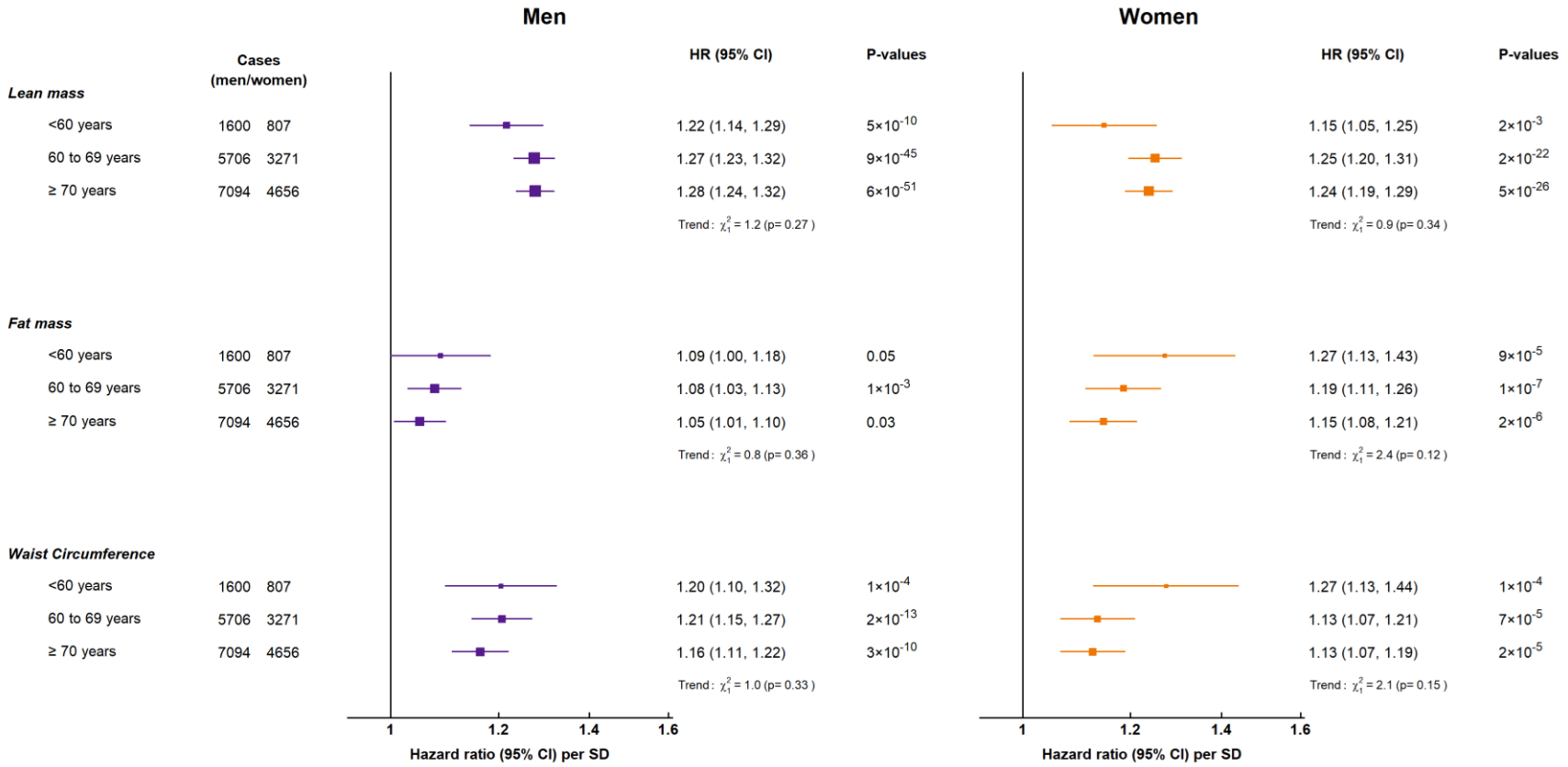
Predictor	Both Sexes			Men Only			Women Only		
	Model A	Model B	Model C	Model A	Model B	Model C	Model A	Model B	Model C
Body mass index, kg/m^2	1.32 (1.31 to 1.34)	1.32 (1.30 to 1.34)	1.25 (1.24 to 1.27)	1.31 (1.29 to 1.33)	1.31 (1.28 to 1.33)	1.24 (1.22 to 1.26)	1.34 (1.32 to 1.37)	1.35 (1.32 to 1.39)	1.26 (1.23 to 1.29)
Waist circumference, cm	1.36 (1.34 to 1.37)	1.36 (1.34 to 1.37)	1.29 (1.27 to 1.25)	1.34 (1.32 to 1.36)	1.34 (1.32 to 1.36)	1.28 (1.26 to 1.30)	1.38 (1.35 to 1.41)	1.39 (1.35 to 1.43)	1.30 (1.27 to 1.32)
Weight, kg	1.40 (1.38 to 1.42)	1.40 (1.38 to 1.42)	1.34 (1.32 to 1.36)	1.38 (1.36 to 1.40)	1.39 (1.36 to 1.41)	1.33 (1.31 to 1.36)	1.42 (1.39 to 1.45)	1.43 (1.40 to 1.47)	1.35 (1.32 to 1.37)
Lean mass, kg	1.40 (1.38 to 1.42)	1.40 (1.38 to 1.42)	1.35 (1.34 to 1.37)	1.40 (1.37 to 1.42)	1.40 (1.38 to 1.42)	1.36 (1.34 to 1.39)	1.40 (1.37 to 1.42)	1.39 (1.36 to 1.42)	1.34 (1.31 to 1.36)
Fat mass, kg	1.34 (1.32 to 1.35)	1.34 (1.32 to 1.35)	1.27 (1.26 to 1.29)	1.31 (1.29 to 1.33)	1.31 (1.29 to 1.33)	1.25 (1.23 to 1.27)	1.39 (1.37 to 1.42)	1.39 (1.36 to 1.42)	1.32 (1.29 to 1.35)

Effects are reported as hazard ratio (95% confidence intervals) per sex-specific standard deviation. Model A: adjusted for age at risk, alcohol status, smoking status, deprivation index. Model B: adjusted for the covariates in Model A + bread consumption, processed meat consumption, fruit and vegetable consumption, and physical activity. Model C: adjusted for the covariates in Model B + baseline hypertension and baseline sleep apnoea.

Appendix Table E.4: Associations of anthropometric traits with incident atrial fibrillation after exclusion of early follow-up and comorbid vascular disease.

Anthropometric Measure		No follow-up excluded		First two years of follow-up excluded	
		No censoring for vascular disease	Vascular disease censored	No censoring for vascular disease	Vascular disease censored
Incident AF Cases	Men	14,400	7,417	12,931	6,627
	Women	8,734	5,372	7,913	4,841
Body mass index	Men	1.31 (1.29 to 1.33)	1.27 (1.24 to 1.30)	1.31 (1.29 to 1.33)	1.28 (1.25 to 1.31)
	Women	1.34 (1.32 to 1.37)	1.33 (1.30 to 1.36)	1.35 (1.32 to 1.37)	1.34 (1.30 to 1.37)
Waist circumference	Men	1.34 (1.32 to 1.36)	1.31 (1.28 to 1.34)	1.35 (1.32 to 1.37)	1.32 (1.29 to 1.35)
	Women	1.38 (1.35 to 1.41)	1.36 (1.33 to 1.40)	1.38 (1.36 to 1.41)	1.37 (1.34 to 1.41)
Weight	Men	1.38 (1.36 to 1.40)	1.40 (1.37 to 1.43)	1.38 (1.36 to 1.41)	1.41 (1.38 to 1.44)
	Women	1.42 (1.39 to 1.45)	1.44 (1.41 to 1.48)	1.42 (1.40 to 1.45)	1.45 (1.42 to 1.49)
Lean mass	Men	1.40 (1.37 to 1.42)	1.46 (1.43 to 1.50)	1.39 (1.37 to 1.42)	1.46 (1.43 to 1.50)
	Women	1.40 (1.37 to 1.42)	1.44 (1.41 to 1.48)	1.40 (1.37 to 1.43)	1.46 (1.38 to 1.45)
Fat mass	Men	1.31 (1.29 to 1.33)	1.29 (1.26 to 1.31)	1.31 (1.29 to 1.33)	1.30 (1.27 to 1.33)
	Women	1.39 (1.37 to 1.42)	1.40 (1.37 to 1.44)	1.40 (1.37 to 1.43)	1.41 (1.38 to 1.45)

Effects are reported as hazard ratio (95% confidence intervals) per sex-specific standard deviation. Cox regression model adjusted for age, alcohol, smoking, ethnicity, and deprivation index. Comorbidities censored – participants with prevalent coronary heart disease, heart failure, stroke, and valvular heart disease were excluded, participants developing incident comorbid events were censored at that point. . AF – atrial fibrillation.



Appendix Figure E.4: Anthropometric measures and risk of atrial fibrillation by age group.
Anthropometric measures and risk of atrial fibrillation broken down by age group and sex. Exclusions as per ***Table 4.2****. Hazard ratios (HR) were adjusted for age, ethnicity, deprivation, smoking, and alcohol. Lean mass additionally adjusted for waist circumference and fat mass. Fat mass additionally adjusted for lean mass and waist circumference. Waist circumference additionally adjusted for fat mass and lean mass. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars). CI – confidence intervals, SD – standard deviation.*

Appendix F - Pericardial adipose tissue phenotyping: standard operating procedure

F.1. Setting up the native T1 map images

Window level and window width is set to the following values: Window Level 750, Window Width 1,800. A colour panel ‘NIH’ available in Osirix is selected which presents fat as a blue/turquoise colour while the myocardium will appear green and blood/fluid will appear red/white.

F.2. Creating and editing regions of interest

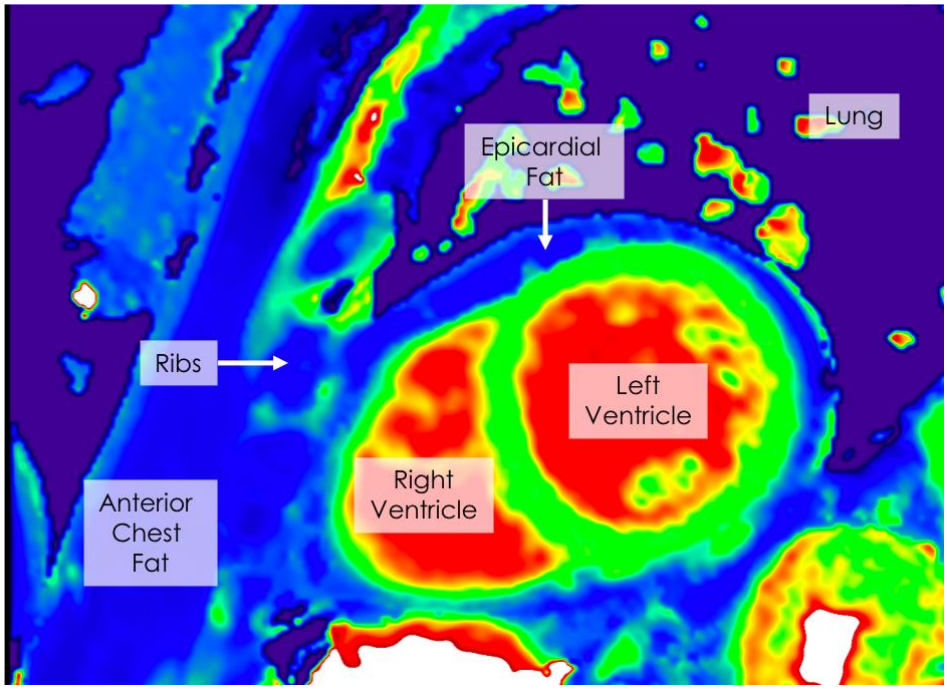
To create appropriate regions of interest (ROIs), the ‘closed polygon’ option is used. Where appropriate the image should be zoomed to ensure the appropriate level of detail is available. Once an ROI has been generated, it may be edited to ensure it appropriately matches pericardial adipose tissue (PAT) area.

F.3. Defining pericardial adipose tissue

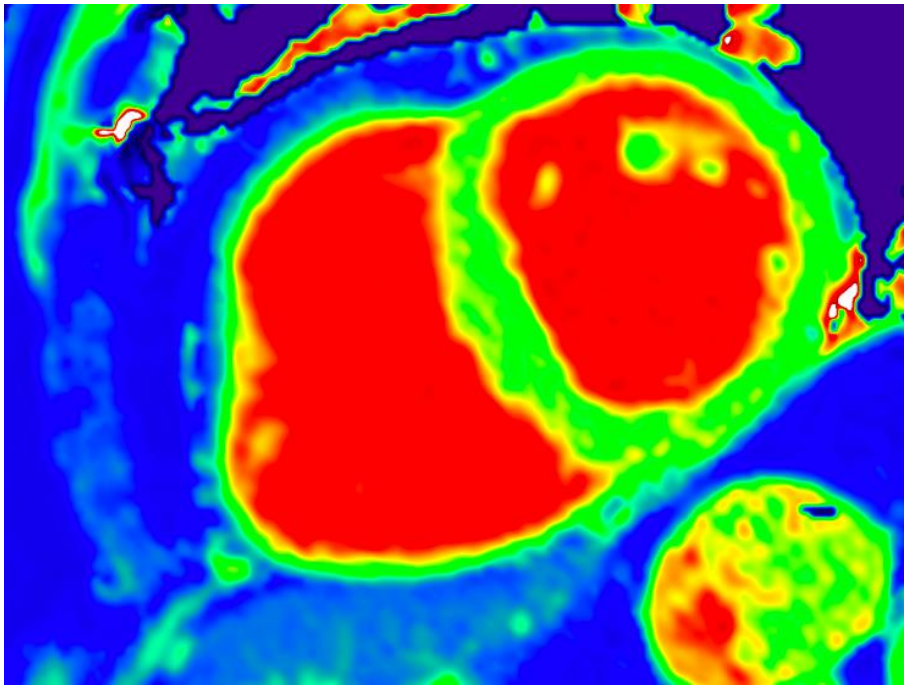
PAT is defined as the fat surrounding the heart within the pericardium. When the T1 map is appropriately set up, fat should appear blue/turquoise. In some cases PAT is clear but in others it requires use of several sources to determine what is PAT vs intra-thoracic fat (i.e. fat outside of the pericardium).

F.3.1. Overall anatomy

The images are aligned to the cardiac axis. **Appendix Figure F.1** provides an outline of the general anatomy in a standard T1 image. The diaphragm and pericardium should be identified on the T1 map (**Appendix Figure F.2** and **Appendix Figure F.3**). If the pericardium is not clear on the T1 map then it should be identified on the cine image. If identified on the cine image then the distance from the epicardium on the cine image should be measured from the external edge of the PAT to be calculated on the T1 map.

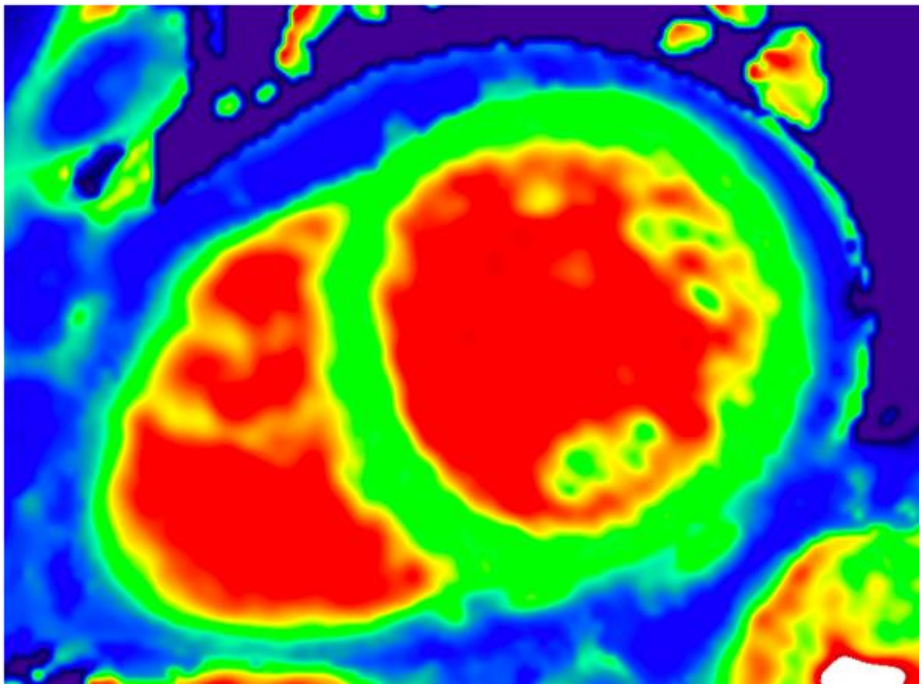


Appendix Figure F.1: Representative T1 map with relevant anatomy highlighted on a representative native T1 map image.



Appendix Figure F.2: Diaphragm visible on a representative T1 map on a representative native T1 map image.

1



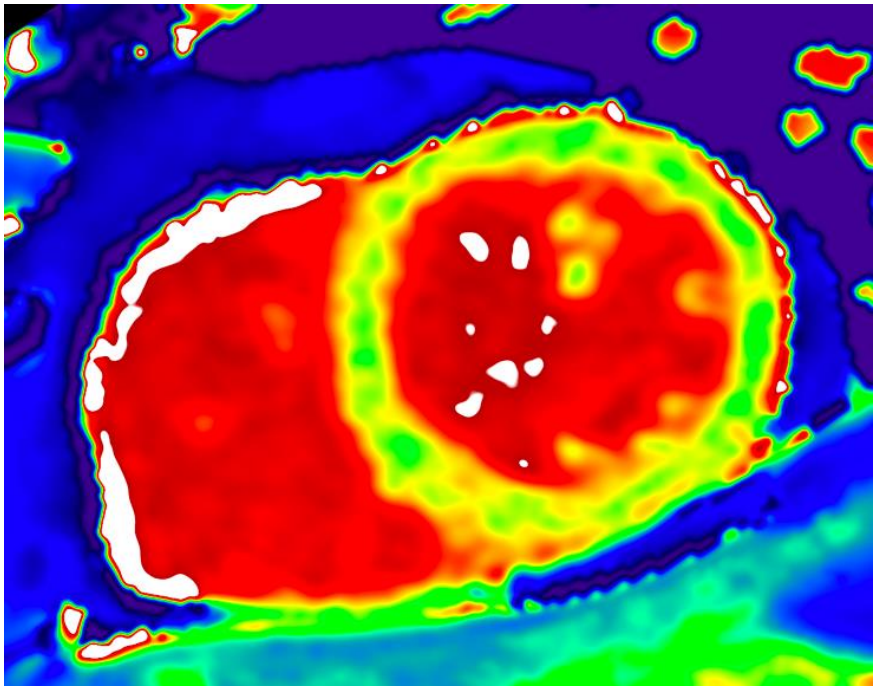
Appendix Figure F.3: Pericardium clearly visible on representative T1 map on a representative native T1 map image.

2

3

F.3.2. T1 map artefacts

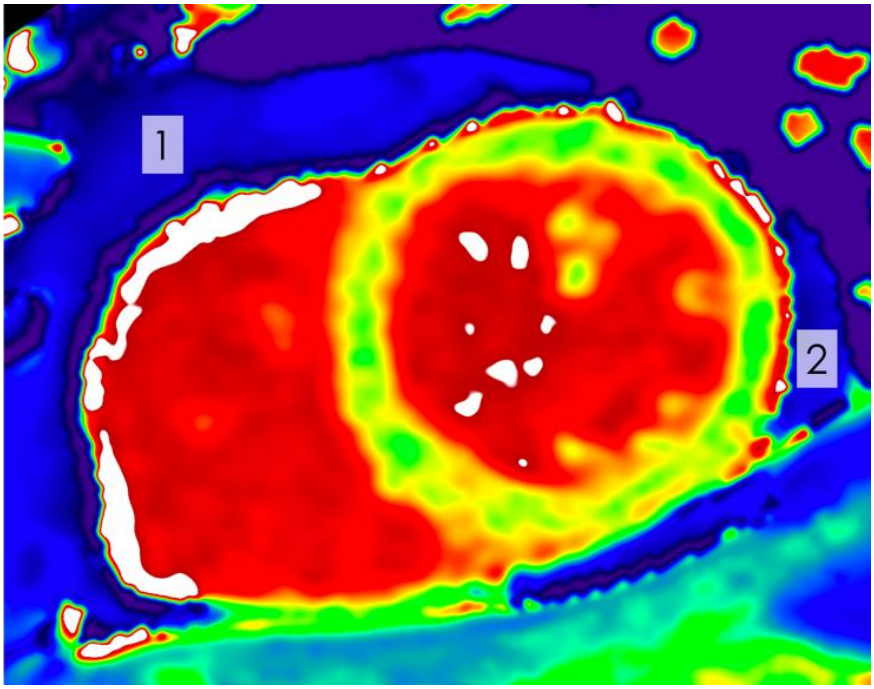
ROIs of PAT must have a component touching the epicardium and should not be 'free floating' away from the epicardial wall. In some images, there is a rim of artefact separating the epicardial border and the PAT (**Appendix Figure F.4**). This artefact between the epicardial border and PAT has been included as part of the PAT area. If there are low signal artefacts in the centre of an area of PAT, this should be included in the fat ROI.



Appendix Figure F.4: Rim of artefact separating the epicardium from adipose tissue on a representative native T1 map image.

F.3.3. Loculated PAT

PAT may be 'loculated' forming several distinct areas of PAT on a two dimensional image (**Appendix Figure F.5**). There can be areas of the epicardium that are not surrounded by fat. It is not required that PAT regions are connected together (i.e. multiple ROIs can be created).



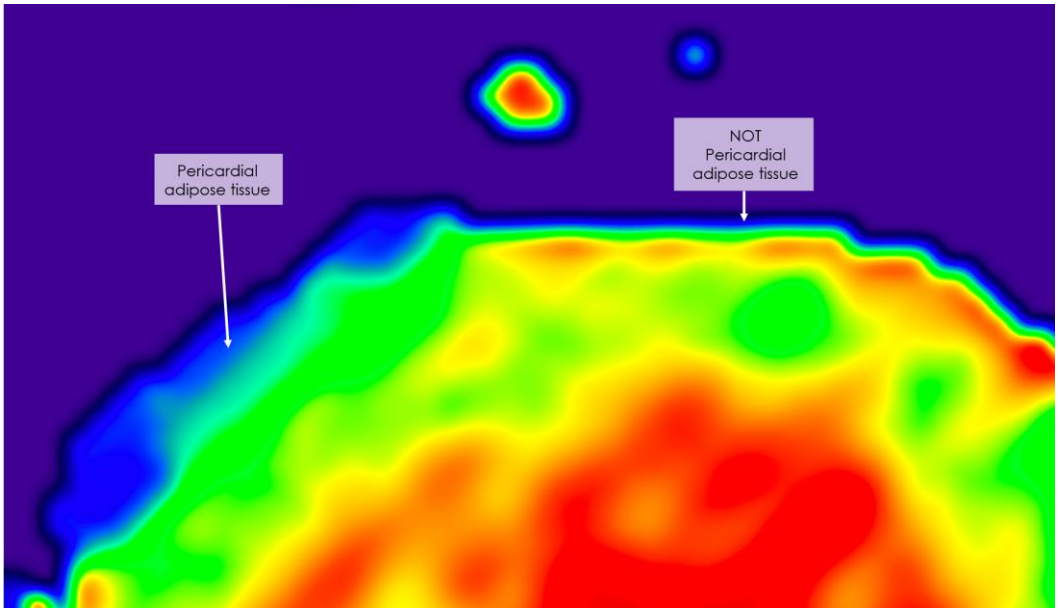
Appendix Figure F.5: Separate areas of pericardial adipose tissue (1 and 2) on a representative native T1 map image.

F.3.4. Areas of high T1 signal within the PAT

Areas of high T1 signal in the centre of an area of PAT should be excluded from the ROI.

F.3.5. Epicardial/lung border

At the transition/border between the epicardium and lungs where there is no evidence of PAT, there will normally be a very thin strip of blue (**Appendix Figure F.6**). This is artefact due to the transition of T1 values in the bordering voxels and should not be included as PAT.



Appendix Figure F.6: Thin blue sections on T1 map at border between epicardium and lung which are not pericardial adipose tissue.

F.4. Subjective image quality score

While the R^2 value gives an objective measure of the tissue characterisation, it is not effective at highlighting participants where the cardiac magnetic resonance images are of a reduced quality such that it limits interpretation of the PAT area. To combat this, a subjective image quality score measure has been generated. This has three levels:

1- Good quality images or some artefacts that do not impact assessment of PAT area
2- Moderate quality image where there are artefacts that impact the ability to interpret PAT area
3- Low quality image where it is not possible or appropriate to assess PAT area. In addition, T1 images which are not appropriately aligned (e.g. aligned to the long axis or a the left-ventrciular outflow tract level rather than mid-ventricular level)

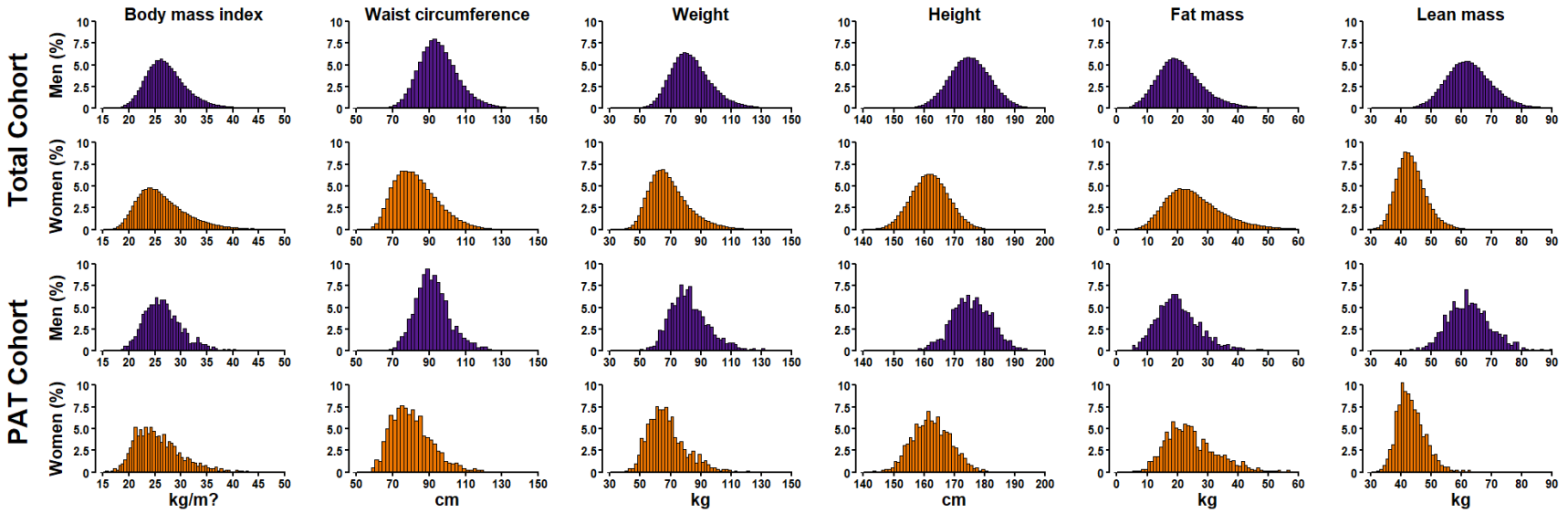
It is important to note that the presence of artefacts does not preclude having a QC score of 1. Artefacts which cause a small uncertainty in PAT area are common and can still have a score of 1. The important aspect is that the artefacts must substantially impact the ability to interpret PAT areas to have a score of 2.

Appendix G - Chapter 5 supplementary tables and figures

This appendix contains supplementary tables and figures from **Chapter 5**. Tables and figures are listed chronologically as referenced within the chapter.

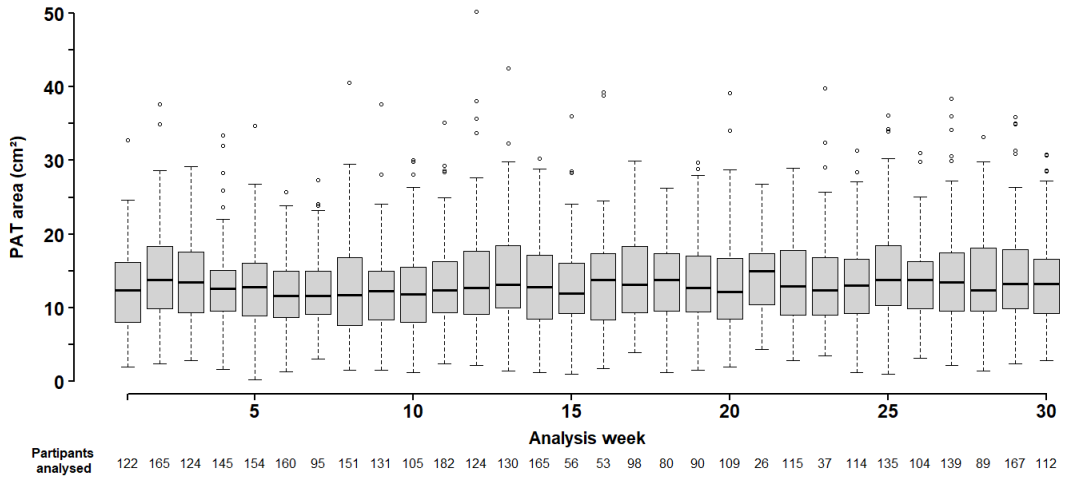
Appendix Table G.1: Proportions of characteristics and measures taken from re-assessment value

Baseline characteristics	Total imaging cohort, n(%)	PAT cohort, n(%)
Participants	45,751	3,477
Demographics		
Current smoker	45,274 (99)	3,436 (99)
Current alcohol drinker	45,405 (99)	3,447 (99)
Anthropometric measures		
Height	44,274 (97)	3,461 (100)
Weight	44,230 (97)	3,460 (100)
Body mass index	44,190 (97)	3,460 (100)
Waist circumference	44,312 (97)	3,462 (100)
Hip circumference	44,314 (97)	3,462 (100)
Bio-impedance values		
Body lean mass	43,295 (95)	3,396 (98)
Body fat mass	43,254 (95)	3,393 (98)

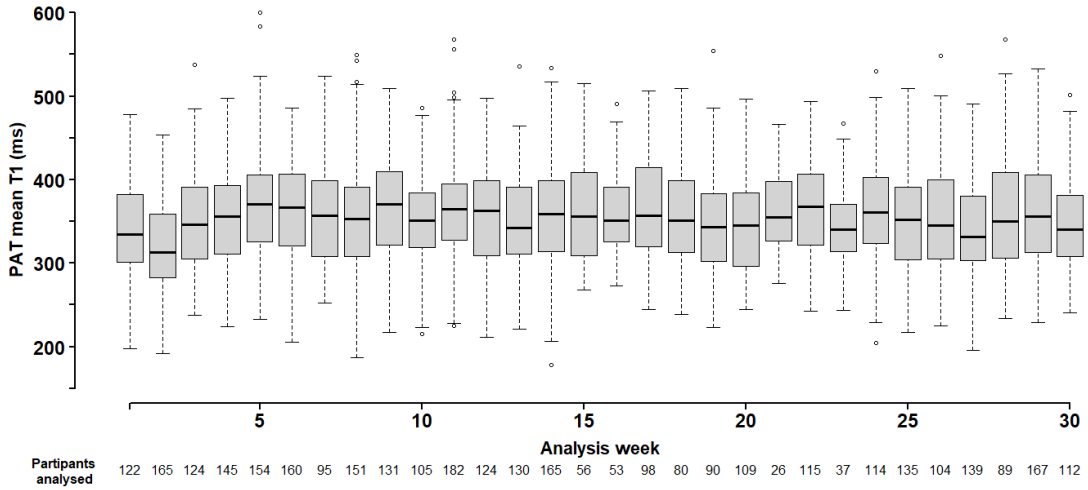


Appendix Figure G.1: Distribution of anthropometric measures in the total UK Biobank cohort and pericardial adipose tissue sub-set.

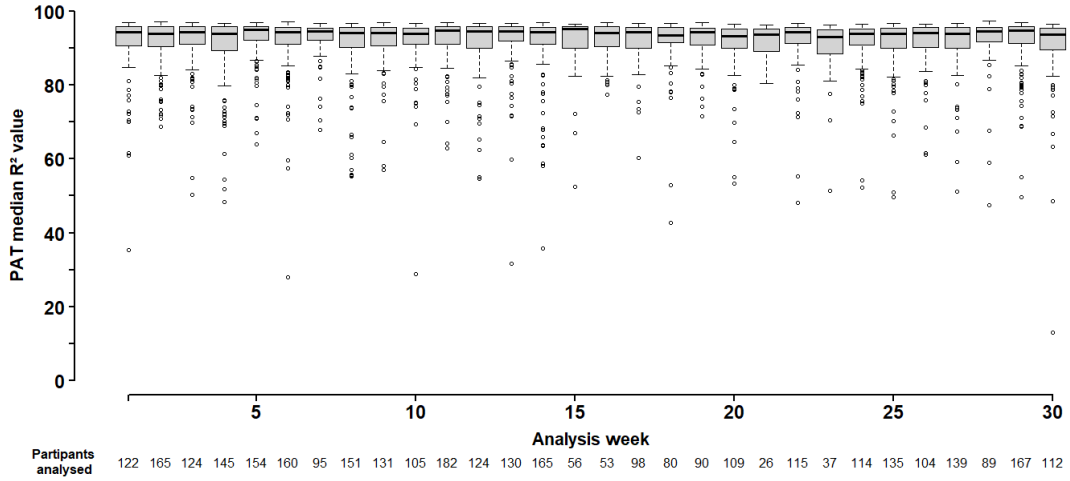
Histograms of anthropometric measures split between men and women. Women are displayed in orange and men are displayed in purple. The total cohort includes participants in UK Biobank with appropriate anthropmetric measures analysed in ***Chapter 4*** *(n=477,904). The perciardial adipose tissue sub-set includes 3,477 participants in whom pericardial adipose tissue area has been calculated. PAT – pericardial adipose tissue.*



Appendix Figure G.2: Total pericardial adipose tissue area by analysis week.
Box and Whisker plot demonstrating total pericardial adipose tissue areas for participants analysed by analysis week. The number of participants analysed per week is displayed below. PAT – pericardial adipose tissue.



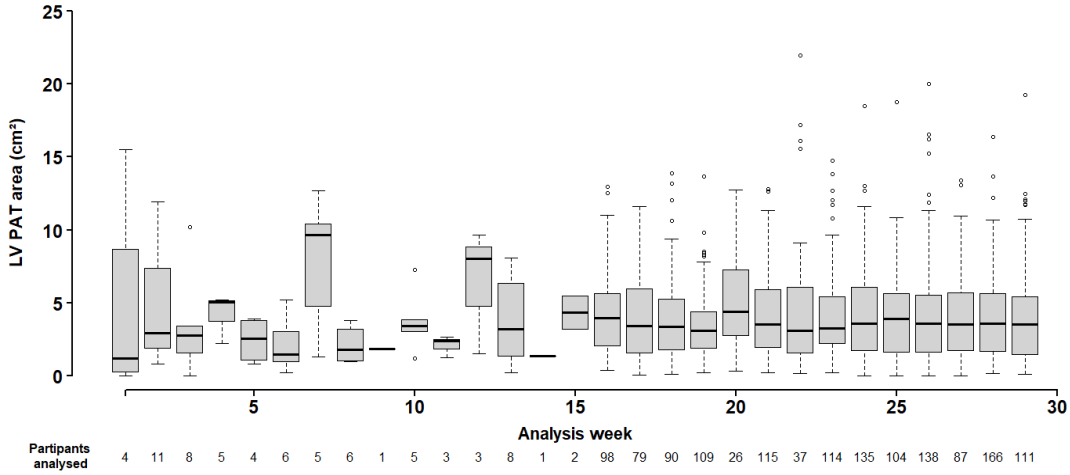
Appendix Figure G.3: Total pericardial adipose tissue mean T1 values by analysis week.
Box and Whisker plot demonstrating total pericardial adipose tissue mean T1 values for participants analysed by analysis week. The number of participants analysed per week is displayed below. PAT – pericardial adipose tissue.



Appendix Figure G.4: Total pericardial adipose tissue R2 values by analysis week.

Box and Whisker plot demonstrating pericardial adipose tissue median R^2 values for participants analysed by analysis week. The number of participants analysed per week is displayed below. PAT – pericardial adipose tissue.

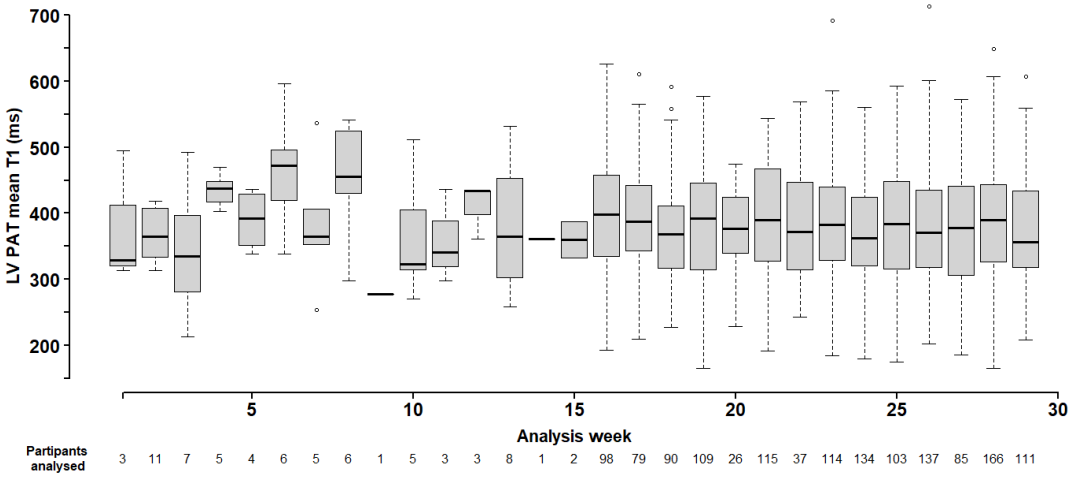
1



Appendix Figure G.5: Left ventricular pericardial adipose tissue area by analysis week.

Box and Whisker plot demonstrating left ventricular pericardial adipose tissue areas for participants analysed by analysis week. Left ventricular pericardial adipose tissue area was principally collected from week 16 with retrospective collection of data in a small number of participants initially analysed in earlier weeks. LV – left ventricular; PAT – pericardial adipose tissue

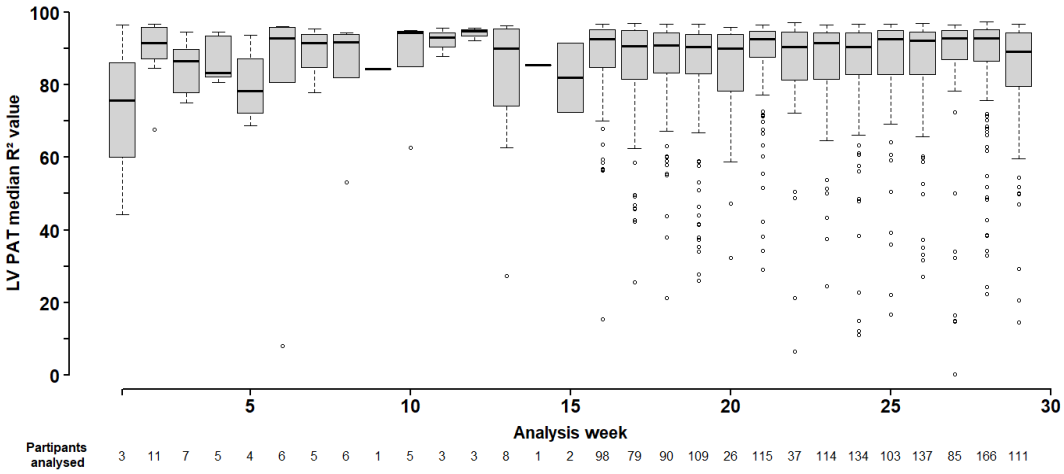
2



Appendix Figure G.6: Left ventricular pericardial adipose tissue mean T1 values by analysis week.

Box and Whisker plot demonstrating left ventricular pericardial adipose tissue mean T1 values for participants analysed by analysis week. The number of participants analysed per week is displayed below. Left ventricular pericardial adipose tissue area was principally collected from week 16 with retrospective collection of data in a small number of participants initially analysed in earlier weeks. LV – left ventricular; PAT - pericardial adipose tissue.

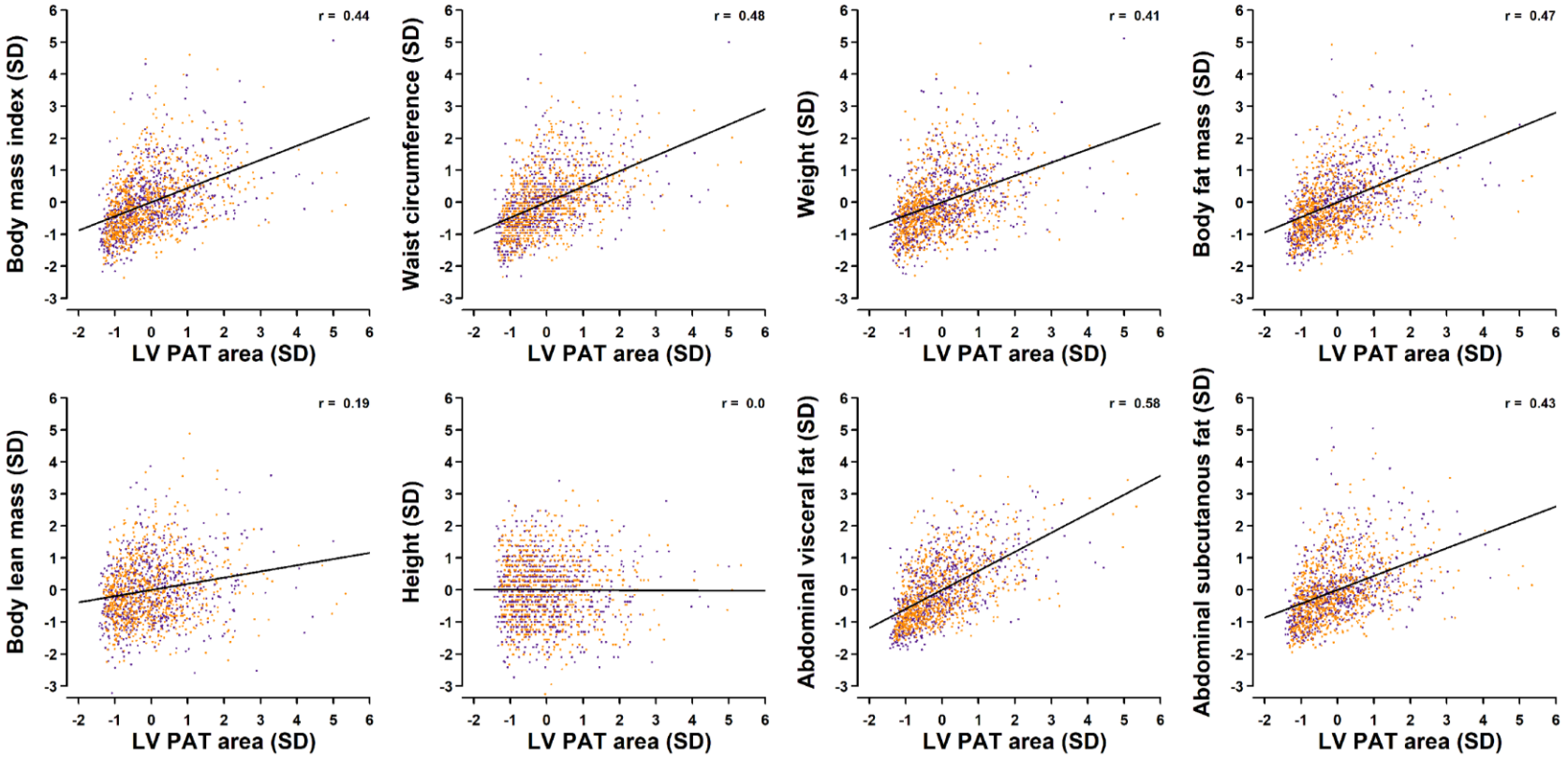
1



Appendix Figure G.7: Left ventricular pericardial adipose tissue median R2 values by analysis week.

Box and Whisker plot demonstrating left ventricular pericardial adipose tissue median R^2 values for participants analysed by analysis week. The number of participants analysed per week is displayed below. Left ventricular pericardial adipose tissue area was principally collected from week 16 with retrospective collection of data in a small number of participants initially analysed in earlier weeks. LV – left ventricular; PAT - pericardial adipose tissue.

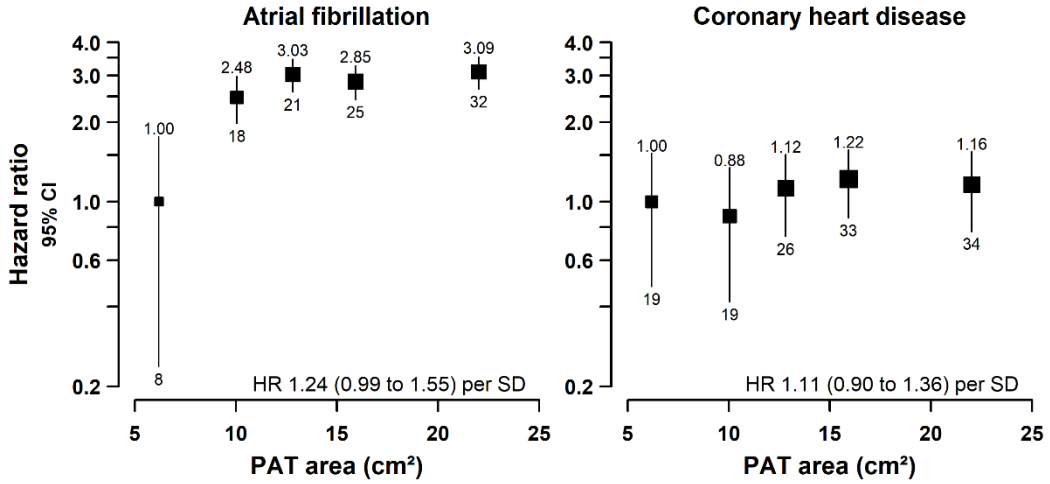
2



Appendix Figure G.8: Scatter plots of left ventricular pericardial adipose tissue area and anthropometric measures.
Women are displayed in orange and men are displayed in purple. Lines represent linear regression between left ventricular pericardial adipose tissue area and anthropometric measures. Displayed r values are Pearson's correlation coefficients. Standard deviations are calculated separately in men and women. LV – left ventricular, PAT – pericardial adipose tissue, SD – standard deviation.

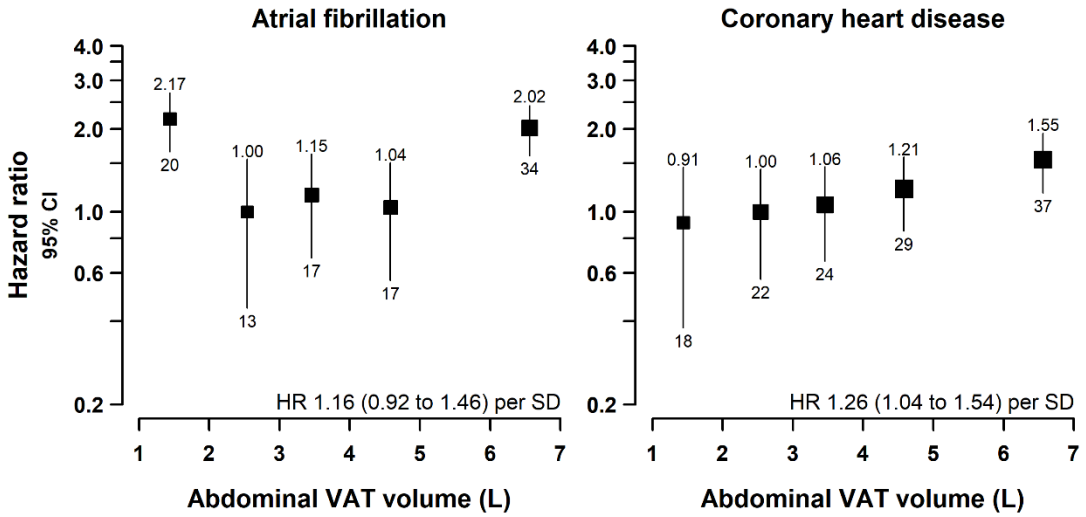
Appendix H - Chapter 6 supplementary tables and figures

This appendix contains supplementary tables and figures from **Chapter 6**. Tables and figures are listed chronologically as referenced within the chapter.



Appendix Figure H.1: Association of pericardial adipose tissue area with incident cardiovascular outcomes following adjustment for abdominal visceral adipose tissue.

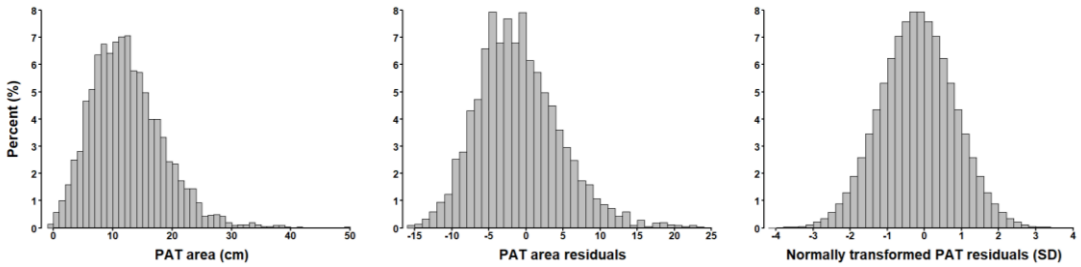
Left panel (n=3,402), right panel (n=3,290). Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, deprivation, and abdominal visceral adipose tissue. Plotted on a floating absolute scale. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). Each group comprises 20% of the sample. Hazard ratios shown above each square and the number of cases below. PAT – pericardial adipose tissue.



Appendix Figure H.2: Association of abdominal visceral adipose tissue with incident cardiovascular outcomes following adjustment for pericardial adipose tissue area.

Left panel (n=3,402), right panel (n=3,290). Hazard ratios (HR) were adjusted for age and sex. Plotted on a floating absolute scale. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). Each group comprises 20% of the sample. HRs shown above each square and the number of cases below. VAT – visceral adipose tissue

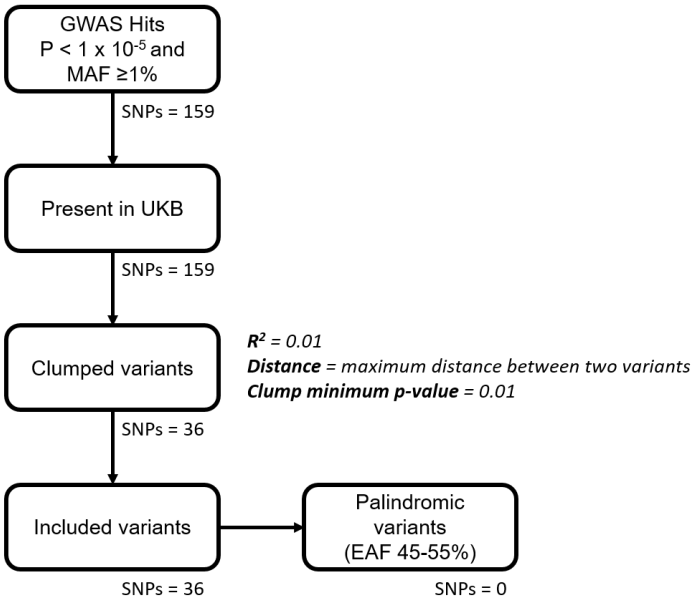
1
2



Appendix Figure H.3: Histograms of pericardial adipose tissue area and residuals in pericardial adipose tissue sub-set of UK Biobank.

Histogram of pericardial adipose tissue area and residuals in 3,477 UK Biobank participants. Residuals are adjusted for sex, age, age^2, and principle components 1-7. PAT – pericardial adipose tissue

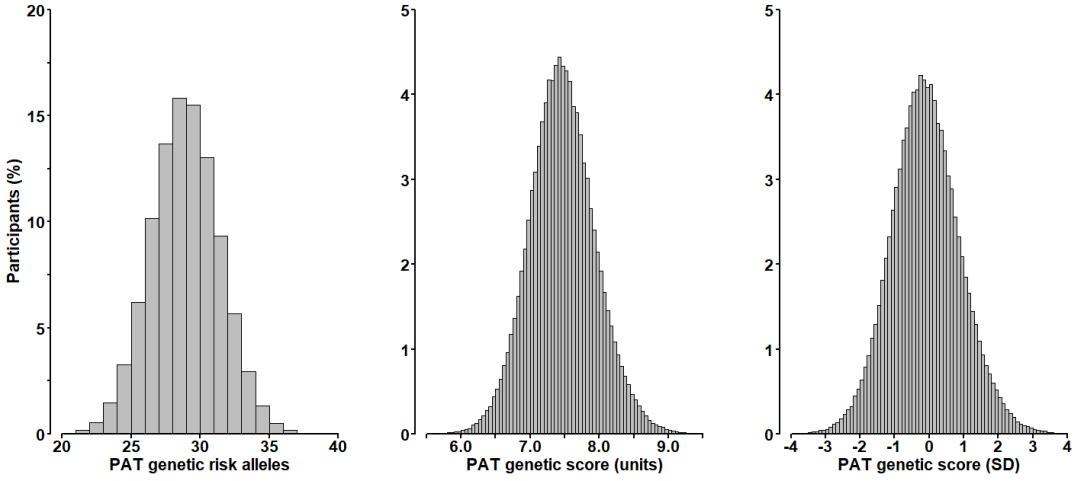
3



Appendix Figure H.4: Flowchart of variants identified by pericardial adipose tissue genome wide association study.
EAF – effect allele frequency, GWAS – genome-wide association study, MAF – minor allele frequency, SNP – single nucleotide polymorphism, UKB – UK Biobank.

1

2



Appendix Figure H.5: Distribution of pericardial adipose tissue variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of pericardial adipose tissue genetic score values and alleles in the UK Biobank population. Risk alleles are defined as the allele associated with higher pericardial adipose tissue area. PAT – pericardial adipose tissue, SD – standard deviation.

3

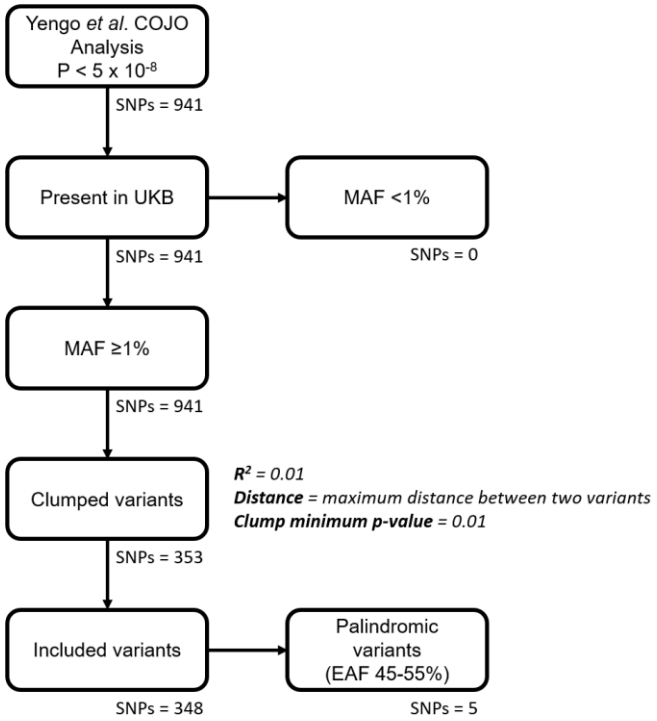
Appendix I - Development of genetic scores

I.1. Selection of genetic variants for body mass index score

A large-scale genome-wide association study (GWAS) meta-analysis for body mass index (BMI) identified 941 near-independent single nucleotide polymorphisms (SNPs) meeting genome-wide significance in approximately 700,000 individuals of European ancestry including data from UKB.[35] In each cohort, BMI was adjusted in a linear model for sex, age, age^2, and principal components of ancestry and residuals were rank inverse normally transformed. The summary data were taken from the meta-analysis and all 941 variants were available in UKB. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 242,014,091 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR).

Three hundred and forty-eight variants were included in the BMI score (**Appendix Figure I.1**, **Appendix Table I.1**). Weightings for the variants included in this score were obtained for a separate GWAS that did not include UKB data.[103] The median F-stat for included variants was 23 (range 0 to 312). The proportion of variance explained was 3.6%. Risk alleles for selected variants and the developed BMI genetic score were normally distributed in UKB (**Appendix**

Figure I.2). When variants from the BMI genetic score were examined in UKB there was significant correlation between the beta values obtained when compared with the original GWAS beta values (r=0.79, **Appendix Figure I.3**).



Appendix Figure I.1: Flowchart of variant selection for body mass index score.
Variants identified from Yengo et al.[35] COJO – conditional joint model, EAF – effect allele frequency, MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs10920678	1	A	G	0.015	0.57
rs10923724	1	C	T	0.012	0.44
rs11583122	1	T	C	0.022	0.08
rs11803119	1	A	T	0.014	0.02
rs12035149	1	G	C	0.018	0.78
rs12035349	1	G	A	0.021	0.88
rs12039524	1	G	A	0.002	0.83
rs12042959	1	A	G	0.014	0.86

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs12731372	1	T	C	0.012	0.24
rs17014375	1	G	T	0.012	0.13
rs17302346	1	C	T	0.038	0.02
rs2030342	1	T	C	0.017	0.44
rs2154297	1	C	T	0.007	0.3
rs2275426	1	A	G	0.015	0.56
rs2282231	1	T	C	0.010	0.21
rs2820311	1	G	A	0.022	0.67
rs284227	1	C	T	0.014	0.76
rs346722	1	C	T	0.005	0.88
rs3753549	1	C	T	0.021	0.86
rs3768486	1	G	A	0.012	0.81
rs543874	1	G	A	0.048	0.8
rs6577584	1	G	T	0.012	0.66
rs7531118	1	C	T	0.033	0.48
rs7531656	1	A	G	0.021	0.33
rs7550711	1	T	C	0.066	0.03
rs905938	1	C	T	0.014	0.74
rs967605	1	C	T	0.020	0.83
rs10168197	2	G	C	0.012	0.2
rs10182181	2	G	A	0.031	0.51
rs10203277	2	A	G	0.004	0.87
rs10929925	2	C	A	0.015	0.43
rs12694021	2	A	C	0.009	0.44
rs12713433	2	T	C	0.007	0.8
rs13021737	2	G	A	0.060	0.83
rs13417156	2	C	T	0.018	0.56
rs1437929	2	A	G	0.017	0.71
rs17551974	2	C	A	0.016	0.19
rs4372836	2	T	C	0.015	0.69
rs4671328	2	T	G	0.022	0.45
rs6545714	2	G	A	0.018	0.39
rs6548221	2	A	G	0.014	0.78
rs6710871	2	A	G	0.022	0.86
rs7425440	2	T	C	0.005	0.19
rs7557796	2	T	C	0.013	0.35
rs7560871	2	A	G	0.015	0.93
rs7601895	2	C	G	0.012	0.31
rs7607351	2	T	C	0.010	0.41
rs919433	2	A	G	0.008	0.36
rs934515	2	A	G	0.025	0.12
rs9630985	2	C	A	0.019	0.67
rs968972	2	A	G	0.006	0.36
rs972540	2	G	A	0.018	0.27
rs980329	2	C	T	0.015	0.25
rs10460960	3	A	G	0.020	0.12
rs13321566	3	G	A	0.007	0.16
rs1436343	3	G	A	0.012	0.42
rs1452075	3	T	C	0.013	0.73
rs1454148	3	T	C	0.012	0.27
rs17080319	3	T	C	0.005	0.12
rs17681451	3	G	A	0.019	0.92
rs2230590	3	C	T	0.015	0.51
rs28350	3	A	G	0.015	0.18
rs355777	3	C	G	0.014	0.59
rs3772934	3	T	C	0.013	0.73

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs3849570	3	A	C	0.019	0.35
rs39654	3	G	A	0.016	0.55
rs4342060	3	C	T	0.003	0.8
rs580438	3	T	C	0.011	0.67
rs6442021	3	C	T	0.011	0.61
rs6443750	3	C	T	0.014	0.19
rs6767619	3	C	G	0.014	0.66
rs6786125	3	G	C	0.015	0.18
rs6786582	3	C	T	0.016	0.27
rs6803870	3	T	C	0.008	0.83
rs6804181	3	A	T	0.018	0.17
rs6804842	3	G	A	0.019	0.57
rs775731	3	C	T	0.012	0.4
rs827092	3	T	C	0.010	0.41
rs9827072	3	G	A	0.001	0.9
rs1000096	4	C	T	0.015	0.4
rs10938397	4	G	A	0.040	0.43
rs11736228	4	A	T	0.014	0.25
rs13107325	4	T	C	0.048	0.93
rs1323068	4	G	A	0.006	0.32
rs1403846	4	T	C	0.010	0.83
rs1477887	4	G	A	0.008	0.46
rs1866510	4	C	T	0.009	0.65
rs2192158	4	A	G	0.007	0.55
rs331949	4	C	T	0.012	0.63
rs4524456	4	G	A	0.003	0.48
rs6448587	4	A	C	0.006	0.18
rs6818414	4	C	T	0.007	0.49
rs6843738	4	G	A	0.013	0.33
rs7683836	4	G	A	0.004	0.45
rs7692088	4	C	G	0.008	0.47
rs9291467	4	T	C	0.015	0.46
rs10066835	5	T	C	0.018	0.02
rs12189178	5	T	C	0.035	0.03
rs12514473	5	T	C	0.013	0.76
rs159032	5	T	C	0.012	0.24
rs160401	5	T	C	0.013	0.3
rs17591778	5	A	G	0.007	0.23
rs2190788	5	T	G	0.015	0.69
rs2304607	5	G	A	0.017	0.86
rs254428	5	T	G	0.009	0.42
rs2611742	5	C	T	0.018	0.61
rs329124	5	A	G	0.010	0.42
rs3822683	5	A	G	0.011	0.77
rs3844598	5	G	A	0.006	0.48
rs40067	5	G	A	0.024	0.18
rs4518345	5	G	A	0.010	0.72
rs6877851	5	G	C	0.014	0.77
rs6879326	5	C	T	0.009	0.48
rs6888159	5	C	G	0.005	0.33
rs7444298	5	A	G	0.017	0.76
rs7702514	5	T	C	0.002	0.18
rs7710595	5	A	C	0.011	0.53
rs7730898	5	A	G	0.013	0.27
rs10499276	6	T	C	0.016	0.12
rs11753081	6	T	G	0.011	0.82

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs1178060	6	A	G	0.007	0.86
rs12207241	6	G	A	0.009	0.63
rs13191362	6	A	G	0.028	0.12
rs13201877	6	G	A	0.023	0.87
rs13203153	6	G	A	0.009	0.19
rs1475774	6	A	G	0.010	0.98
rs17757975	6	T	C	0.015	0.14
rs1853639	6	G	A	0.016	0.63
rs2033529	6	G	A	0.019	0.28
rs2228213	6	G	A	0.016	0.34
rs2252300	6	T	A	0.002	0.8
rs2357760	6	A	G	0.017	0.68
rs2653365	6	C	T	0.005	0.83
rs2781668	6	T	C	0.021	0.17
rs2875762	6	C	G	0.010	0.25
rs3734572	6	C	T	0.005	0.04
rs3819299	6	T	G	0.013	0.06
rs487060	6	T	C	0.014	0.47
rs498240	6	G	A	0.021	0.93
rs6919443	6	G	A	0.012	0.42
rs6922214	6	G	A	0.010	0.85
rs6938239	6	G	A	0.021	0.14
rs765332	6	G	T	0.009	0.1
rs853679	6	A	C	0.010	0.17
rs901630	6	C	T	0.013	0.61
rs9349239	6	A	G	0.011	0.48
rs9362662	6	A	G	0.010	0.51
rs9475173	6	A	G	0.011	0.35
rs9688431	6	T	C	0.019	0.06
rs1048365	7	T	C	0.011	0.16
rs11496125	7	T	C	0.011	0.43
rs13227658	7	C	T	0.013	0.46
rs17207196	7	C	T	0.020	0.58
rs1852006	7	G	A	0.017	0.64
rs2283093	7	T	C	0.012	0.2
rs329277	7	G	T	0.010	0.48
rs3800649	7	A	G	0.014	0.72
rs3807566	7	G	T	0.014	0.57
rs6463489	7	T	C	0.015	0.11
rs7777102	7	G	A	0.009	0.87
rs12458	8	T	A	0.002	0.68
rs13263601	8	C	A	0.017	0.66
rs1431659	8	A	G	0.011	0.73
rs16906845	8	G	A	0.022	0.94
rs16907751	8	C	T	0.035	0.9
rs16932761	8	G	A	0.008	0.75
rs17446091	8	C	T	0.010	0.8
rs2170382	8	T	C	0.018	0.89
rs4841659	8	T	C	0.007	0.48
rs497417	8	T	A	0.004	0.78
rs881301	8	C	T	0.007	0.41
rs903959	8	A	T	0.007	0.39
rs10867256	9	C	T	0.008	0.55
rs10962549	9	T	C	0.011	0.17
rs10971712	9	C	T	0.024	0.1
rs10989568	9	A	G	0.012	0.47

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs13290794	9	G	A	0.015	0.64
rs1412235	9	C	G	0.025	0.68
rs1865341	9	T	C	0.007	0.77
rs1928295	9	T	C	0.019	0.57
rs3829849	9	T	C	0.015	0.36
rs450231	9	G	A	0.013	0.75
rs4515655	9	C	T	0.004	0.6
rs483752	9	T	C	0.006	0.74
rs6474945	9	G	T	0.017	0.45
rs6477694	9	C	T	0.017	0.36
rs7871866	9	C	G	0.022	0.15
rs12098284	10	T	C	0.016	0.13
rs12411886	10	A	C	0.031	0.08
rs12776880	10	A	T	0.014	0.28
rs17636031	10	C	T	0.015	0.72
rs1937684	10	A	T	0.013	0.65
rs7083450	10	T	C	0.018	0.85
rs7899106	10	G	A	0.040	0.95
rs7903146	10	C	T	0.023	0.29
rs845084	10	A	G	0.007	0.26
rs1003081	11	T	C	0.013	0.45
rs10459012	11	A	C	0.011	0.23
rs1048932	11	C	A	0.019	0.59
rs10769165	11	C	T	0.006	0.47
rs12364470	11	G	T	0.014	0.16
rs12420725	11	G	A	0.010	0.94
rs12575252	11	G	C	0.021	0.36
rs12577642	11	T	A	0.018	0.68
rs1452134	11	C	T	0.011	0.46
rs1552717	11	A	T	0.017	0.14
rs1625427	11	T	C	0.016	0.36
rs17197116	11	C	T	0.004	0.92
rs223051	11	T	C	0.011	0.67
rs2440885	11	A	G	0.009	0.46
rs329651	11	T	G	0.016	0.19
rs4936671	11	C	G	0.005	0.64
rs573455	11	G	A	0.009	0.47
rs587230	11	A	G	0.013	0.16
rs6265	11	C	T	0.042	0.19
rs7102454	11	C	T	0.010	0.35
rs7117238	11	G	A	0.015	0.83
rs7123876	11	C	T	0.015	0.25
rs7124681	11	A	C	0.026	0.4
rs7941030	11	C	T	0.010	0.62
rs9332817	11	G	C	0.033	0.03
rs10745785	12	C	T	0.006	0.33
rs10773049	12	C	T	0.014	0.4
rs10876418	12	C	T	0.019	0.23
rs11115176	12	T	C	0.015	0.23
rs11611246	12	T	G	0.021	0.79
rs12422552	12	G	C	0.013	0.73
rs17608150	12	T	C	0.011	0.08
rs1819844	12	A	G	0.015	0.17
rs2731222	12	A	C	0.020	0.27
rs2733287	12	C	A	0.017	0.51
rs3887080	12	A	G	0.016	0.88

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4077093	12	T	G	0.007	0.79
rs6490055	12	G	A	0.010	0.26
rs7138803	12	A	G	0.032	0.64
rs7313924	12	C	G	0.009	0.28
rs884282	12	C	T	0.011	0.43
rs10467530	13	C	G	0.006	0.12
rs12429545	13	A	G	0.033	0.87
rs1333423	13	A	T	0.015	0.76
rs1927790	13	C	T	0.015	0.59
rs2479958	13	A	G	0.014	0.51
rs629443	13	T	G	0.011	0.23
rs7334078	13	T	C	0.011	0.28
rs892261	13	C	T	0.008	0.44
rs9507983	13	C	T	0.020	0.63
rs9538141	13	A	G	0.010	0.51
rs9540493	13	A	G	0.017	0.46
rs9571687	13	C	A	0.014	0.67
rs9595908	13	T	C	0.014	0.64
rs9603697	13	T	C	0.013	0.33
rs10146527	14	T	C	0.017	0.37
rs11844682	14	G	C	0.008	0.32
rs1205106	14	G	A	0.013	0.54
rs12147845	14	T	C	0.016	0.88
rs12888545	14	G	A	0.011	0.24
rs17096552	14	G	A	0.013	0.87
rs17105272	14	T	C	0.011	0.67
rs17522122	14	T	G	0.015	0.47
rs1951455	14	C	T	0.013	0.72
rs2160077	14	A	G	0.012	0.57
rs217671	14	G	A	0.006	0.72
rs3803286	14	A	G	0.014	0.34
rs4981693	14	A	G	0.020	0.23
rs7144011	14	T	G	0.029	0.22
rs8016771	14	G	T	0.015	0.08
rs8016859	14	C	G	0.046	0.96
rs13329567	15	C	T	0.031	0.77
rs17238110	15	A	G	0.024	0.97
rs2459359	15	C	G	0.004	0.95
rs3736485	15	A	G	0.018	0.47
rs403656	15	A	G	0.010	0.15
rs4886869	15	G	A	0.013	0.6
rs6495252	15	T	C	0.013	0.39
rs7181498	15	T	C	0.017	0.35
rs7181610	15	A	T	0.013	0.15
rs8033510	15	T	C	0.010	0.63
rs10083803	16	C	T	0.009	0.73
rs11866815	16	C	T	0.019	0.26
rs12443621	16	G	A	0.008	0.47
rs12446632	16	G	A	0.040	0.14
rs12448257	16	A	G	0.024	0.22
rs12448738	16	C	A	0.019	0.86
rs12922346	16	C	G	0.014	0.27
rs1862451	16	A	G	0.010	0.27
rs2307022	16	A	G	0.016	0.33
rs2534760	16	T	A	0.011	0.71
rs3814883	16	T	C	0.017	0.48

Appendix Table I.1: Variants included in body mass index score

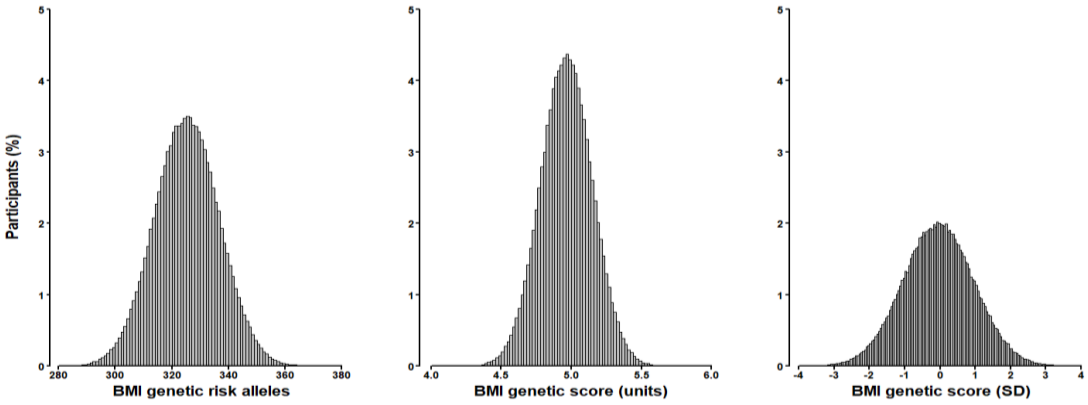
RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4985155	16	A	G	0.015	0.34
rs6564360	16	G	A	0.017	0.81
rs7187776	16	G	A	0.030	0.6
rs7206608	16	G	C	0.013	0.32
rs756717	16	G	A	0.013	0.61
rs7919	16	C	A	0.011	0.46
rs825680	16	A	T	0.008	0.6
rs977540	16	A	G	0.014	0.76
rs9931164	16	A	G	0.034	0.02
rs1038088	17	G	T	0.010	0.51
rs1106908	17	G	A	0.015	0.44
rs11079849	17	C	T	0.010	0.68
rs1285245	17	G	C	0.011	0.62
rs12939549	17	A	G	0.018	0.56
rs208015	17	T	C	0.034	0.93
rs4516268	17	C	A	0.016	0.81
rs4796243	17	G	A	0.016	0.71
rs4969387	17	G	C	0.015	0.26
rs4986044	17	C	T	0.016	0.54
rs7209235	17	G	A	0.013	0.7
rs7211567	17	C	T	0.009	0.78
rs7217226	17	G	T	0.015	0.65
rs8069296	17	C	T	0.012	0.2
rs8070454	17	C	T	0.011	0.38
rs8081039	17	T	C	0.027	0.94
rs9299	17	T	C	0.014	0.65
rs11150911	18	A	C	0.015	0.29
rs11659764	18	T	A	0.006	0.95
rs1241986	18	G	A	0.010	0.16
rs12964689	18	A	G	0.020	0.51
rs1941697	18	A	G	0.013	0.45
rs2000746	18	A	G	0.015	0.26
rs2229616	18	C	T	0.088	0.98
rs273697	18	G	A	0.009	0.53
rs663129	18	A	G	0.056	0.24
rs7243357	18	T	G	0.022	0.18
rs954018	18	G	A	0.013	0.69
rs11672660	19	C	T	0.035	0.19
rs2075650	19	A	G	0.026	0.86
rs29938	19	C	T	0.018	0.34
rs3810291	19	A	G	0.028	0.34
rs3826705	19	C	T	0.015	0.12
rs12625413	20	C	T	0.007	0.34
rs13041173	20	G	A	0.008	0.33
rs17806379	20	C	T	0.023	0.18
rs1884897	20	G	A	0.016	0.37
rs2425241	20	C	T	0.020	0.07
rs2425857	20	A	G	0.010	0.56
rs559267	20	G	A	0.010	0.33
rs6019482	20	C	T	0.014	0.84
rs6060151	20	G	T	0.005	0.39
rs6061162	20	T	C	0.010	0.09
rs8567	20	G	A	0.011	0.52
rs13047416	21	C	G	0.019	0.62
rs2836961	21	C	A	0.003	0.37
rs427943	21	C	A	0.018	0.44

Appendix Table I.1: Variants included in body mass index score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs762147	21	G	A	0.014	0.73
rs9979651	21	G	C	0.010	0.07
rs4820408	22	T	G	0.015	0.61
rs9615905	22	T	C	0.009	0.45

Variants oriented so that effect allele is associated with greater BMI in the original GWAS. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank

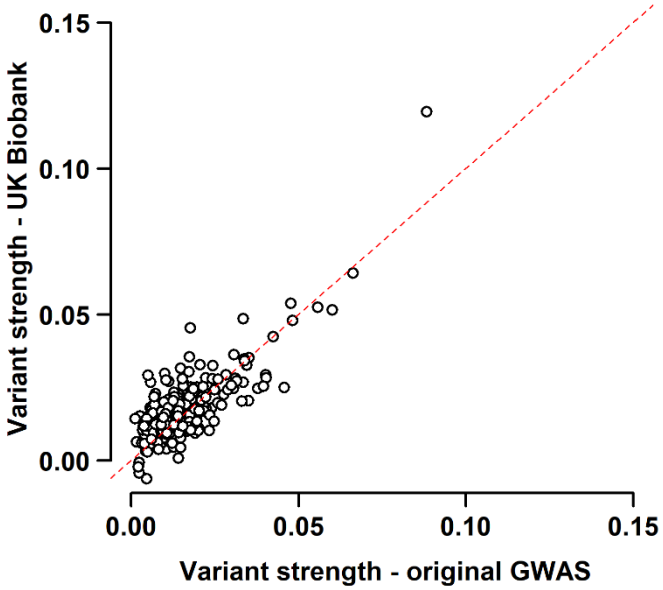
1



Appendix Figure I.2: Distribution of body mass index variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of body mass index genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher body mass index. BMI – body mass index, SD – standard deviation.

2



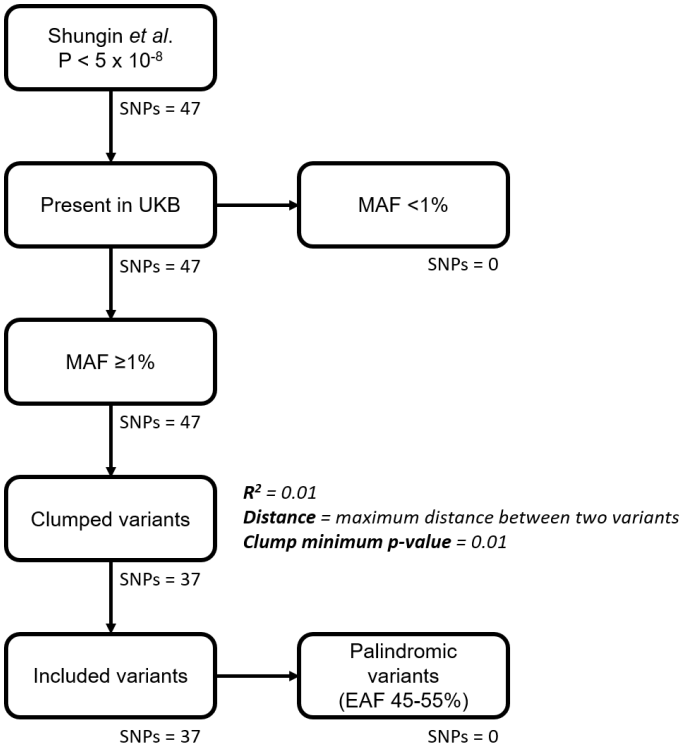
Appendix Figure I.3: Scatter plot of beta values from body mass index genome-wide association study and UK Biobank.
Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates were identified from summary data.[103] UK Biobank effect estimate values calculated as per-allele effects on body mass index residuals. The red dotted line represents the line of parity.

1

I.2. Selection of genetic variants for waist circumference score

A GWAS meta-analysis for waist circumference (WC) identified 47 SNPs meeting genome-wide significance in approximately 142,000 individuals of European ancestry and did not include data from UKB.[104] In each cohort, WC was adjusted in a linear model for age, age^2, and principal components of ancestry and residuals were rank inverse normally transformed. Summary data were taken from the meta-analysis and all 47 variants were available in UKB. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 226,175,325 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR).

Thirty-seven variants were included in the waist circumference score (**Appendix Figure I.4**, **Appendix Table I.2**). The median F-stat for included variants was 38 (range 14 to 342). The proportion of variance explained was 0.95%. Risk alleles for selected variants and the developed WC genetic score were normally distributed in UKB (**Appendix Figure I.5**). When variants from the WC genetic score were examined in UKB there was significant correlation between the beta values obtained when compared with the original GWAS beta values (r=0.93, **Appendix Figure I.6**).



Appendix Figure I.4: Flowchart of variant selection for waist circumference score.
Variants identified from Shungin et al.[104] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

1

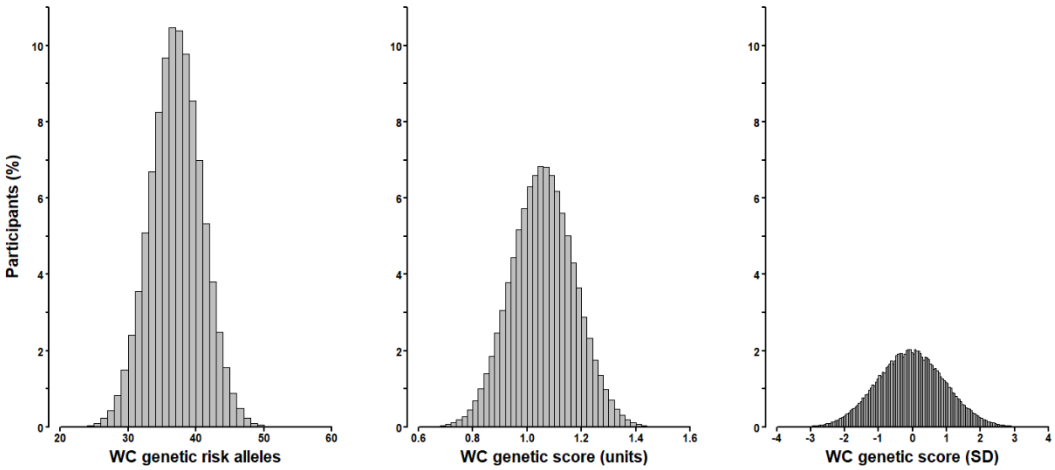
Appendix Table I.2: Variants included in waist circumference score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs3127553	1	*AGBL4*	G	A	0.023	0.37
rs633715	1	*SEC16B*	C	T	0.043	0.21
rs7531118	1	*NEGR1*	C	T	0.027	0.52
rs7550711	1	*GPR61*	T	C	0.058	0.03
rs2176040	2	*IRS1*	A	G	0.015	0.35
rs6545714	2	*FLJ30838*	G	A	0.022	0.39
rs6755502	2	*TMEM18*	C	T	0.051	0.83
rs929641	2	*FANCL*	A	G	0.021	0.58
rs1516725	3	*ETV5*	C	T	0.031	0.86
rs2325036	3	*CADM2*	A	C	0.023	0.62
rs3849570	3	*GBE1*	A	C	0.021	0.35
rs10938397	4	*GNPDA2*	G	A	0.032	0.43
rs2112347	5	*C5orf37*	T	G	0.025	0.63
rs2489623	6	*RSPO3*	C	A	0.019	0.54
rs806794	6	*HIST1H2BF*	A	G	0.022	0.72
rs9400239	6	*FOXO3*	C	T	0.024	0.69
rs943005	6	*TFAP2B*	T	C	0.039	0.17
rs10968576	9	*LINGO2*	G	A	0.025	0.31
rs6163	10	*CYP17A1*	A	C	0.019	0.38
rs7903146	10	*TCF7L2*	C	T	0.022	0.71
rs10767658	11	*BDNF*	C	G	0.031	0.31

rs10840100	11	*TRIM66*	G	A	0.02	0.65
rs2293576	11	*SLC39A13*	G	A	0.022	0.67
rs7138803	12	*BCDIN3D*	A	G	0.028	0.36
rs12429545	13	*OLFM4*	A	G	0.031	0.13
rs7144011	14	*NRXN3*	T	G	0.033	0.22
rs4776970	15	*MAP2K5*	A	T	0.02	0.63
rs12446632	16	*GPRC5B*	G	A	0.036	0.86
rs1558902	16	*FTO*	A	T	0.074	0.39
rs2531992	16	*ADCY9*	G	A	0.028	0.84
rs7498665	16	*SH2B1*	G	A	0.034	0.39
rs6567160	18	*MC4R*	C	T	0.048	0.23
rs7239883	18	*RIT2*	G	A	0.021	0.38
rs2075650	19	*TOMM40*	A	G	0.031	0.86
rs2287019	19	*QPCTL*	C	T	0.035	0.82
rs3810291	19	*ZC3H4*	A	G	0.026	0.66
rs16996700	20	*ZFP64*	T	C	0.023	0.72

Variants oriented so that effect allele is associated with greater waist circumference adjusted for BMI in the original GWAS. Ordered by chromosome. Nearest gene defined by the original GWAS.[104] Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

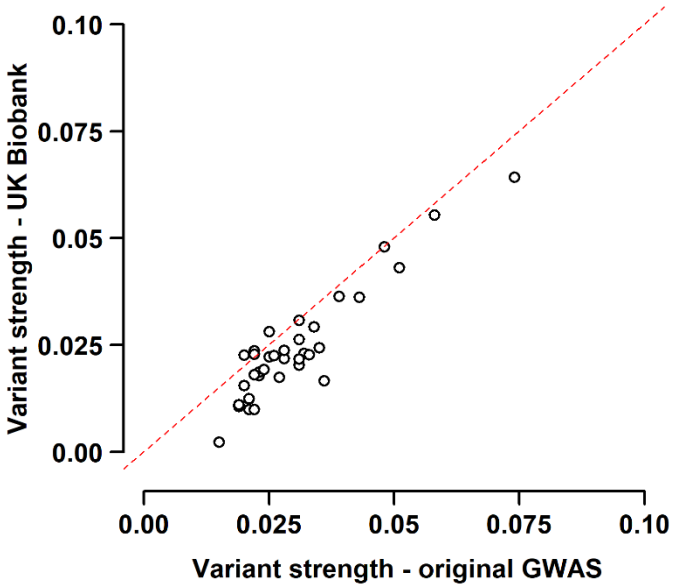
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Appendix Figure I.5: Distribution of waist circumference variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of waist circumference genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher waist circumference. WC – waist circumference, SD –standard deviation

2



Appendix Figure I.6: Scatter plot of beta values from waist circumference GWAS and UK Biobank.

Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data and oriented to result in positive values.[104] UKB beta values calculated as per-allele effects on waist circumference residuals and oriented in line with the GWAS results. The red dotted line represents the line of parity.

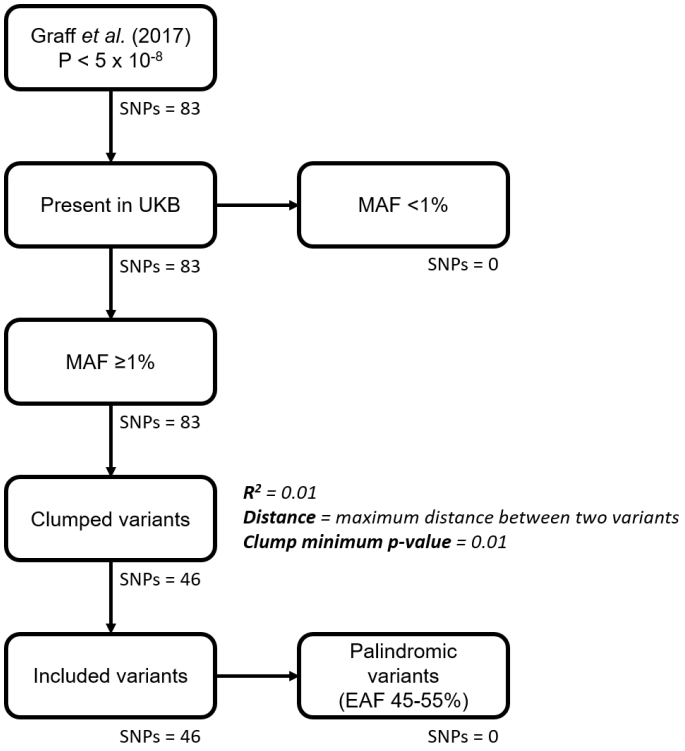
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I.3. Selection of genetic variants for waist circumference adjusted for body mass index

A GWAS meta-analysis for waist circumference adjusted for body mass index (WCadjBMI) identified 83 SNPs meeting genome-wide significance in approximately 180,000 individuals of European ancestry and did not include data from UKB.[105] WC was adjusted for age, age^2, sex, BMI, and principle components of ancestry. Residuals were rank inverse normally transformed. Summary data were taken from the meta-analysis. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 207,698,282 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR).

Forty-six variants were included in the WCadjBMI score (**Appendix Figure I.7**, **Appendix Table I.3**). The median F-stat for included variants was 39 (range 25 to 100). The proportion of variance explained was 1.3%. Risk alleles for selected variants and the developed WCadjBMI genetic score were normally distributed in UKB (**Appendix Figure I.8**). When variants from the WCadjBMI genetic score were examined in UKB there was significant correlation between the beta values obtained when compared with the original GWAS beta values (r=0.61, **Appendix Figure I.9**).



Appendix Figure I.7: Flowchart of variant selection for waist circumference adjusted for body mass index score.

Variants identified from Graff et al.[105] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

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Appendix Table I.3: Variants included in waist circumference adjusted for body mass index score

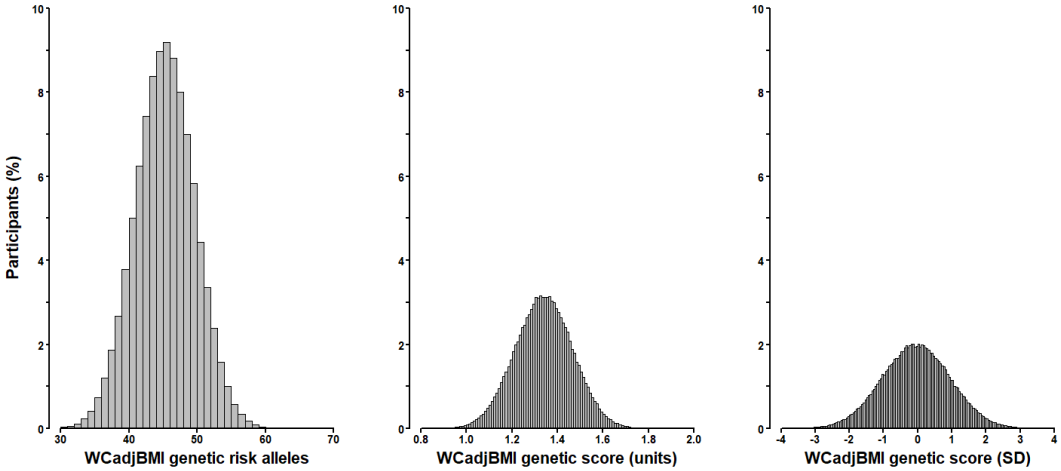
RSID	Chr	Nearest Gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs10429950	1	*ITGB8*	C	T	0.03	0.28
rs11205303	1	*TGFB2, LYPLAL1*	C	T	0.031	0.40
rs7536458	1	*UBA52P1*	T	G	0.033	0.74
rs984222	1	*CCDC91*	G	C	0.039	0.60
rs12991495	2	*PTCH1*	T	C	0.027	0.70
rs3116162	2	*DNAH10*	A	G	0.045	0.92
rs3791675	2	*MTMR11*	C	T	0.036	0.77
rs12330322	3	*ADAMTS9*	C	T	0.027	0.78
rs12493901	3	*FNDC3B*	G	A	0.024	0.53
rs13083798	3	*DNMT3A*	A	G	0.024	0.52
rs17451107	3	*DIS3L2*	T	C	0.03	0.61
rs6772896	3	*FILIP1*	T	C	0.023	0.68
rs1812175	4	*NUCB2*	G	A	0.032	0.83
rs710841	4	*VEGFA*	T	C	0.026	0.26
rs2062708	5	*JAZF1*	C	T	0.028	0.16
rs2637030	5	*ZBTB38*	G	A	0.022	0.36
rs3843467	5	*HHIP*	T	G	0.029	0.21
rs4868126	5	*FLJ40113*	G	T	0.023	0.60
rs6556301	5	*NPR3*	T	G	0.033	0.37

Appendix Table I.3: Variants included in waist circumference adjusted for body mass index score

RSID	Chr	Nearest Gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs13192994	6	*RSPO3*	C	A	0.037	0.11
rs1358980	6	*NDUFS4, ARL15*	T	C	0.032	0.48
rs2503111	6	*NPPC*	A	G	0.025	0.55
rs395962	6	*PEPD*	T	G	0.03	0.32
rs615672	6	*EFEMP1*	G	C	0.025	0.66
rs806794	6	*MAP3K1*	A	G	0.029	0.72
rs10231365	7	*RP3-439I14.1*	T	C	0.024	0.51
rs1055144	7	*CABLES1*	T	C	0.037	0.20
rs1708299	7	*MYO1F*	A	G	0.03	0.29
rs7801581	7	*C5orf50*	T	C	0.025	0.25
rs10990303	9	*SERPINH1*	T	C	0.03	0.23
rs780159	10	*HLA-DRB1*	G	A	0.022	0.59
rs1330	11	*FGFR4*	T	C	0.022	0.35
rs606452	11	*AMOTL2*	A	C	0.032	0.15
rs10843151	12	*PRKG2*	G	A	0.031	0.71
rs11057397	12	*ADAMTSL3*	C	T	0.022	0.67
rs754133	12	*ADAMTSL3*	A	G	0.03	0.36
rs8007661	14	*ACAN*	C	T	0.024	0.53
rs1879529	15	*SPAG17*	G	T	0.026	0.74
rs7162542	15	*HOXC6*	G	C	0.04	0.57
rs7176527	15	*ATAD5, ITPR2-SSPN*	C	T	0.032	0.82
rs741677	17	*HOXA11*	A	G	0.024	0.57
rs757608	17	*LOC283050*	A	G	0.026	0.33
rs4239436	18	*TRIP11*	G	A	0.04	0.79
rs3786897	19	*HIST1H2BF*	G	A	0.022	0.42
rs4542783	19	*LOC149844*	T	C	0.024	0.55
rs979012	20	*TBX15*	T	C	0.025	0.37

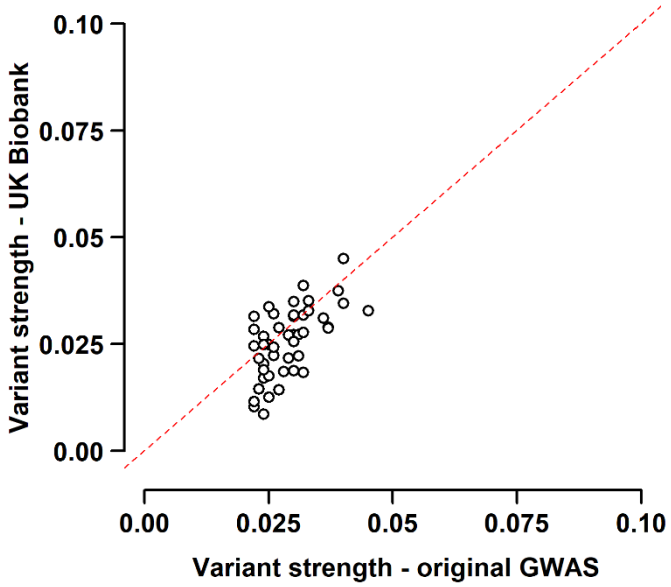
Variants oriented so that effect allele is associated with greater waist circumference adjusted for BMI in the original GWAS. Ordered by chromosome. Nearest gene defined by the original GWAS.[105] Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

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Appendix Figure I.8: Distribution of waist circumference adjusted for body mass index variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of waist circumference adjusted for body mass index genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher waist circumference adjusted for body mass index. WCadjBMI – waist circumference adjusted for body mass index, SD – standard deviation.

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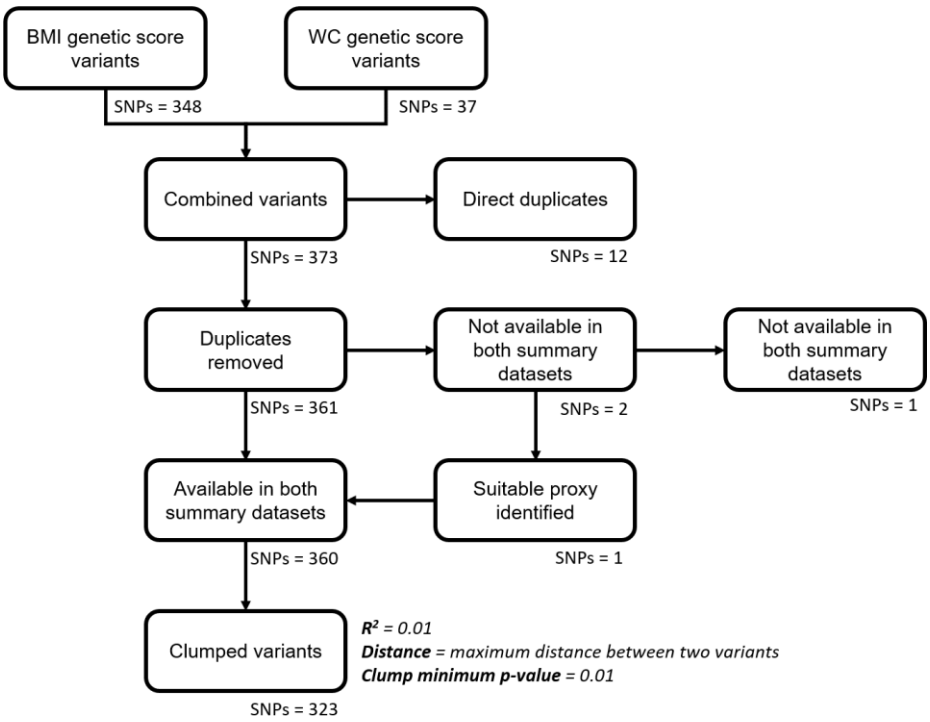
Appendix Figure I.9: Scatter plot of beta values from waist circumference adjusted for body mass index genome-wide association study and UK Biobank.
Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data and oriented to result in positive values.[105] UKB beta values calculated as per-allele effects on waist circumference residuals adjusted for body mass index and oriented in line with the GWAS results. The red dotted line represents the line of parity.

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I.4. Selection of genetic variants for multivariable MR analysis of BMI and waist circumference

When the 37 WC variants and 348 BMI variants were combined into one list, 12 were duplications and were removed. Two variants from the BMI score were not available from the summary data from the original WC GWAS (rs346722, rs9332817).[104] A suitable proxy was identified using the 1000G reference set for rs346722 (rs4484960, r^2 0.67). Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 237,007,502 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from UKB. A total of 323 variants were included in the multivariable Mendelian randomization (MR) analysis for BMI and WC (**Appendix Figure I.10, Appendix Table I.4**). Of these, 313 (97%) were originally identified from the BMI GWAS with 10 (3%) coming from the WC GWAS. The correlation between BMI and WC beta values is shown in **Appendix Figure I.11**.



Appendix Figure I.10: Flowchart of variant selection for combined body mass index and waist circumference score for multivariable Mendelian randomization analysis.
Variants identified from Yengo et al. [35] and Shungin et al.[104] BMI – body mass index, EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, WC – waist circumference.

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Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs1000096	C	T	0.010	0.015
rs1003081	T	C	0.010	0.013
rs10066835	T	C	0.017	0.018
rs10083803	C	T	0.003	0.009
rs10146527	T	C	0.014	0.017
rs10168197	G	C	0.010	0.012
rs10182181	G	A	0.018	0.031
rs10203277	A	G	0.005	0.004
rs1038088	G	T	0.003	0.010
rs10460960	A	G	0.017	0.020
rs10467530	C	G	0.004	0.006
rs1048365	T	C	0.014	0.011
rs1048932	C	A	0.015	0.019
rs10499276	T	C	0.021	0.016
rs10745785	C	T	0.005	0.006
rs10769165	C	T	0.003	0.006
rs10773049	C	T	0.002	0.014
rs10867256	C	T	0.007	0.008
rs10876418	C	T	0.014	0.019
rs10920678	A	G	0.010	0.015

Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs10923724	C	T	-0.006	0.012
rs10929925	C	A	0.017	0.015
rs10962549	T	C	0.011	0.011
rs10971712	C	T	0.019	0.024
rs10989568	A	G	0.015	0.012
rs1106908	G	A	0.014	0.015
rs11079849	C	T	0.009	0.010
rs11115176	T	C	0.012	0.015
rs11150911	A	C	0.014	0.015
rs11496125	T	C	0.010	0.011
rs11583122	T	C	0.010	0.022
rs11611246	T	G	0.013	0.021
rs11659764	T	A	0.003	0.006
rs11672660	C	T	0.033	0.035
rs11736228	A	T	0.011	0.014
rs11753081	T	G	0.011	0.011
rs1178060	A	G	0.007	0.007
rs11803119	A	T	0.000	0.014
rs11844682	G	C	0.001	0.008
rs11866815	C	T	0.017	0.019
rs12035149	G	C	0.016	0.018
rs12035349	G	A	0.013	0.021
rs12039524	G	A	0.007	0.002
rs12042959	A	G	0.012	0.014
rs1205106	G	A	0.011	0.013
rs12098284	T	C	0.019	0.016
rs12147845	T	C	0.011	0.016
rs12189178	T	C	0.021	0.035
rs12207241	G	A	0.008	0.009
rs12364470	G	T	0.010	0.014
rs12411886	A	C	0.019	0.031
rs1241986	G	A	0.009	0.010
rs12420725	G	A	-0.004	0.010
rs12422552	G	C	0.014	0.013
rs12443621	G	A	0.006	0.008
rs12448257	A	G	0.019	0.024
rs12448738	C	A	0.013	0.019
rs12514473	T	C	0.015	0.013
rs12575252	G	C	0.020	0.021
rs12577642	T	A	0.020	0.018
rs12694021	A	C	0.005	0.009
rs12713433	T	C	0.006	0.007
rs12731372	T	C	-0.006	0.012
rs12776880	A	T	0.009	0.014
rs1285245	G	C	0.010	0.011
rs12888545	G	A	0.012	0.011
rs12922346	C	G	0.012	0.014
rs12939549	A	G	0.015	0.018
rs12964689	A	G	0.020	0.020
rs13021737	G	A	0.051	0.060
rs13041173	G	A	0.011	0.008
rs13047416	C	G	0.016	0.019
rs13107325	T	C	0.023	0.048
rs13191362	A	G	0.025	0.028
rs13201877	G	A	0.024	0.023
rs13203153	G	A	0.010	0.009

Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs13227658	C	T	0.004	0.013
rs1323068	G	A	0.006	0.006
rs13263601	C	A	0.013	0.017
rs13290794	G	A	0.014	0.015
rs13321566	G	A	0.000	0.007
rs13329567	C	T	0.022	0.031
rs13417156	C	T	0.018	0.018
rs1403846	T	C	0.008	0.010
rs1412235	C	G	0.025	0.025
rs1431659	A	G	0.013	0.011
rs1436343	G	A	0.014	0.012
rs1437929	A	G	0.019	0.017
rs1452075	T	C	0.016	0.013
rs1452134	C	T	0.008	0.011
rs1454148	T	C	0.011	0.012
rs1475774	A	G	0.020	0.010
rs1477887	G	A	0.007	0.008
rs1516725	C	T	0.031	0.045
rs1552717	A	T	0.016	0.017
rs1558902	A	T	0.074	0.082
rs159032	T	C	0.009	0.012
rs160401	T	C	0.009	0.013
rs1625427	T	C	0.014	0.016
rs16906845	G	A	0.011	0.022
rs16907751	C	T	0.025	0.035
rs16932761	G	A	0.011	0.008
rs17014375	G	T	0.014	0.012
rs17096552	G	A	0.009	0.013
rs17105272	T	C	0.005	0.011
rs17197116	C	T	0.005	0.004
rs17207196	C	T	0.013	0.020
rs17238110	A	G	0.033	0.024
rs17302346	C	T	-0.015	0.038
rs17446091	C	T	0.014	0.010
rs17522122	T	G	0.016	0.015
rs17551974	C	A	0.013	0.016
rs17608150	T	C	0.008	0.011
rs17636031	C	T	0.012	0.015
rs17681451	G	A	0.017	0.019
rs17757975	T	C	0.011	0.015
rs17806379	C	T	0.027	0.023
rs1819844	A	G	0.011	0.015
rs1852006	G	A	0.014	0.017
rs1853639	G	A	0.018	0.016
rs1862451	A	G	0.008	0.010
rs1865341	T	C	0.003	0.007
rs1866510	C	T	0.005	0.009
rs1884897	G	A	-0.004	0.016
rs1927790	C	T	0.013	0.015
rs1928295	T	C	0.018	0.019
rs1937684	A	T	0.011	0.013
rs1941697	A	G	0.007	0.013
rs1951455	C	T	0.007	0.013
rs2030342	T	C	0.015	0.017
rs2033529	G	A	0.021	0.019
rs208015	T	C	0.027	0.034

Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs2112347	G	T	-0.025	-0.026
rs2154297	C	T	0.009	0.007
rs2160077	A	G	0.001	0.012
rs2170382	T	C	0.005	0.018
rs2176040	G	A	-0.015	-0.014
rs217671	G	A	0.007	0.006
rs2190788	T	G	0.010	0.015
rs2192158	A	G	0.005	0.007
rs2228213	G	A	0.017	0.016
rs2229616	C	T	0.083	0.088
rs223051	T	C	0.006	0.011
rs2230590	C	T	0.011	0.015
rs2252300	T	A	0.003	0.002
rs2275426	A	G	0.009	0.015
rs2282231	T	C	0.017	0.010
rs2283093	T	C	0.014	0.012
rs2304607	G	A	0.014	0.017
rs2307022	A	G	0.009	0.016
rs2325036	C	A	-0.023	-0.020
rs2357760	A	G	0.019	0.017
rs2425857	A	G	0.005	0.010
rs2440885	A	G	0.009	0.009
rs2479958	A	G	0.013	0.014
rs2489623	C	A	0.019	0.005
rs2531992	G	A	0.028	0.022
rs2534760	T	A	0.014	0.011
rs254428	T	G	0.007	0.009
rs2611742	C	T	0.011	0.018
rs2653365	C	T	0.001	0.005
rs2731222	A	C	0.020	0.020
rs2733287	C	A	0.019	0.017
rs273697	G	A	0.008	0.009
rs2781668	T	C	0.019	0.021
rs2820311	G	A	0.019	0.022
rs28350	A	G	0.008	0.015
rs2836961	C	A	0.001	0.003
rs284227	C	T	0.012	0.014
rs2875762	C	G	0.003	0.010
rs29938	C	T	0.011	0.018
rs329124	A	G	0.010	0.010
rs329277	G	T	0.004	0.010
rs329651	T	G	0.013	0.016
rs331949	C	T	0.009	0.012
rs355777	C	G	0.013	0.014
rs3734572	C	T	-0.005	0.005
rs3736485	A	G	0.015	0.018
rs3753549	C	T	0.012	0.021
rs3768486	G	A	0.015	0.012
rs3772934	T	C	0.005	0.013
rs3800649	A	G	0.008	0.014
rs3803286	A	G	0.011	0.014
rs3807566	G	T	0.011	0.014
rs3814883	T	C	0.019	0.017
rs3819299	T	G	0.002	0.013
rs3822683	A	G	0.007	0.011
rs3826705	C	T	0.009	0.015

Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs3829849	T	C	0.015	0.015
rs3844598	G	A	0.006	0.006
rs3887080	A	G	0.020	0.016
rs39654	G	A	0.018	0.016
rs40067	G	A	0.018	0.024
rs403656	A	G	0.002	0.010
rs4077093	T	G	-0.004	0.007
rs427943	C	A	0.016	0.018
rs4372836	T	C	0.012	0.015
rs450231	G	A	0.016	0.013
rs4515655	C	T	0.004	0.004
rs4516268	C	A	0.014	0.016
rs4518345	G	A	0.006	0.010
rs4524456	G	A	0.006	0.003
rs4671328	T	G	0.020	0.022
rs4796243	G	A	0.014	0.016
rs4820408	T	G	0.011	0.015
rs483752	T	C	0.001	0.006
rs4841659	T	C	0.003	0.007
rs487060	T	C	0.009	0.014
rs4936671	C	G	0.005	0.005
rs4969387	G	C	0.015	0.015
rs4981693	A	G	0.018	0.020
rs498240	G	A	0.020	0.021
rs4985155	A	G	0.019	0.015
rs4986044	C	T	0.016	0.016
rs543874	G	A	0.042	0.048
rs559267	G	A	0.013	0.010
rs573455	G	A	0.010	0.009
rs580438	T	C	0.003	0.011
rs587230	A	G	0.008	0.013
rs6019482	C	T	0.002	0.014
rs6060151	G	T	0.013	0.005
rs6061162	T	C	0.014	0.010
rs6265	C	T	0.033	0.042
rs629443	T	G	0.008	0.011
rs6443750	C	T	0.013	0.014
rs6448587	A	C	0.009	0.006
rs6463489	T	C	0.024	0.015
rs6474945	G	T	0.017	0.017
rs6477694	C	T	0.018	0.017
rs6490055	G	A	0.009	0.010
rs6548221	A	G	0.011	0.014
rs6564360	G	A	0.022	0.017
rs6567160	C	T	0.048	0.056
rs6577584	G	T	0.013	0.012
rs6710871	A	G	0.018	0.022
rs6767619	C	G	0.009	0.014
rs6786125	G	C	0.011	0.015
rs6786582	C	T	0.006	0.016
rs6803870	T	C	0.009	0.008
rs6804181	A	T	0.008	0.018
rs6804842	G	A	0.014	0.019
rs6818414	C	T	0.005	0.007
rs6843738	G	A	0.006	0.013
rs6877851	G	C	0.014	0.014

Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs6879326	C	T	0.010	0.009
rs6888159	C	G	0.007	0.005
rs6919443	G	A	0.011	0.012
rs6922214	G	A	0.007	0.010
rs7083450	T	C	0.017	0.018
rs7102454	C	T	0.006	0.010
rs7117238	G	A	0.005	0.015
rs7123876	C	T	0.016	0.015
rs7124681	A	C	0.020	0.026
rs7181498	T	C	0.015	0.017
rs7181610	A	T	0.014	0.013
rs7187776	G	A	0.033	0.030
rs7206608	G	C	0.011	0.013
rs7209235	G	A	0.016	0.013
rs7211567	C	T	0.002	0.009
rs7217226	G	T	0.010	0.015
rs7239883	A	G	-0.021	-0.016
rs7243357	T	G	0.021	0.022
rs7313924	C	G	0.006	0.009
rs7334078	T	C	0.013	0.011
rs7425440	T	C	0.005	0.005
rs7444298	A	G	0.017	0.017
rs7531656	A	G	0.022	0.021
rs7557796	T	C	0.010	0.013
rs7560871	A	G	0.010	0.015
rs756717	G	A	0.014	0.013
rs7601895	C	G	0.005	0.012
rs7607351	T	C	0.009	0.010
rs762147	G	A	0.012	0.014
rs765332	G	T	0.001	0.009
rs7683836	G	A	0.002	0.004
rs7692088	C	G	0.006	0.008
rs7710595	A	C	0.009	0.011
rs7730898	A	G	0.013	0.013
rs775731	C	T	0.012	0.012
rs7777102	G	A	0.001	0.009
rs7871866	C	G	0.020	0.022
rs7899106	G	A	0.031	0.040
rs7919	C	A	0.009	0.011
rs7941030	C	T	0.009	0.010
rs8016771	G	T	0.001	0.015
rs8016859	C	G	0.035	0.046
rs8033510	T	C	0.007	0.010
rs8069296	C	T	0.011	0.012
rs8070454	C	T	0.008	0.011
rs8081039	T	C	0.026	0.027
rs825680	A	T	0.004	0.008
rs827092	T	C	0.003	0.010
rs845084	A	G	0.002	0.007
rs853679	A	C	0.004	0.010
rs8567	G	A	0.011	0.011
rs881301	C	T	0.011	0.007
rs884282	C	T	0.011	0.011
rs901630	C	T	0.011	0.013
rs903959	A	T	0.009	0.007
rs905938	C	T	0.004	0.014

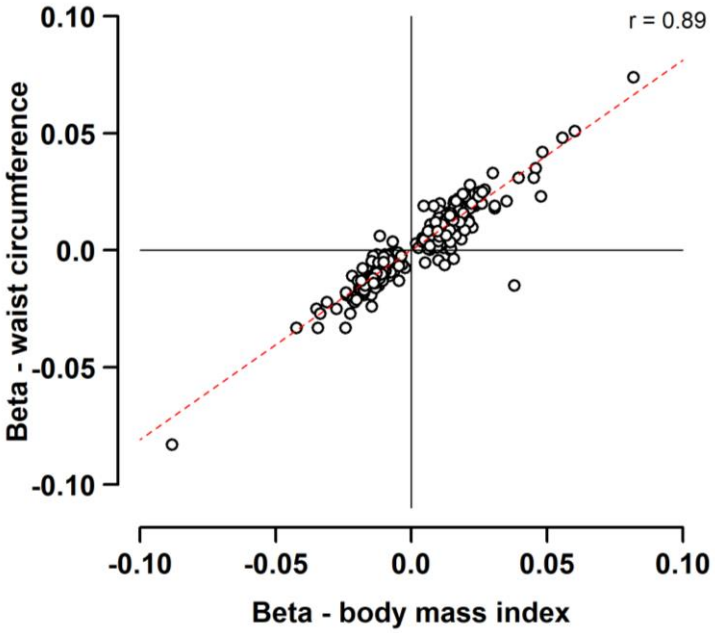
Appendix Table I.4: Variants included in the combined body mass index and waist circumference score

RSID	Effect Allele	Other Allele	WC weighting	BMI weighting
rs919433	A	G	0.019	0.008
rs9291467	T	C	0.011	0.015
rs9299	T	C	0.009	0.014
rs934515	A	G	0.023	0.025
rs9349239	A	G	0.010	0.011
rs9362662	A	G	0.005	0.010
rs9400239	C	T	0.024	0.019
rs9507983	C	T	0.009	0.020
rs9538141	A	G	0.006	0.010
rs954018	G	A	0.010	0.013
rs9540493	A	G	0.015	0.017
rs9571687	C	A	0.013	0.014
rs9595908	T	C	0.012	0.014
rs9603697	T	C	0.006	0.013
rs9615905	T	C	0.012	0.009
rs9630985	C	A	0.016	0.019
rs967605	C	T	0.021	0.020
rs9688431	T	C	0.013	0.019
rs968972	A	G	0.008	0.006
rs972540	G	A	0.012	0.018
rs977540	A	G	0.014	0.014
rs980329	C	T	0.013	0.015
rs9979651	G	C	0.008	0.010

BMI – body mass index, WC – waist circumference

1

2



Appendix Figure I.11: Scatter plot of beta values body mass index and waist circumference.

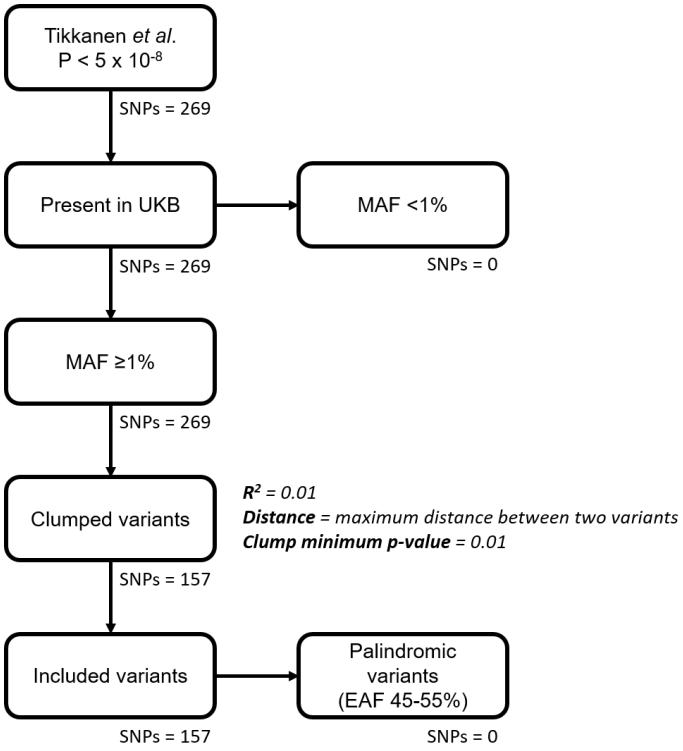
Beta values for body mass index and waist circumference variants included in the combined body mass index-waist circumference genetic score used for multivariable Mendelian randomization analysis (n=324). Red dashed line represents the results from a regression model, r value from Pearson's correlation coefficient.

1

I.5. Selection of genetic variants for fat mass score

A GWAS for fat mass (FM, based on bio-impedance data) has previously been undertaken in UKB using approximately 332,000 participants and identified 269 variants.[71] FM was inverse normally transformed and the analysis was adjusted for age, sex, genotype array, and 10 principal components of ancestry. Summary data were taken from the meta-analysis. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 241,993,824 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR). As p-values were not provided in the summary data, these were recalculated from UKB data.

On hundred and fifty-seven variants were included in the FM score (**Appendix Figure I.12**, **Appendix Table I.5**). The median F-stat for included variants was 39 (range 29 to 648). The proportion of variance explained was 2.6%. Sex-specific beta values were calculated for each variant within UKB using FM residuals calculated separately in men and women. Risk alleles for selected variants and the developed FM genetic score were normally distributed in UKB (**Appendix Figure I.13**). To confirm the accuracy of calculated p-values and sex-specific beta values, the calculated UKB beta-values were compared with those provided in the original GWAS (r=0.99, **Appendix Figure I.14**).



Appendix Figure I.12: Flowchart of variant selection for fat mass score.
Variants identified from Tikkanen et al.[71] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

1

Appendix Table I.5: Variants included in fat mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs10128597	11	G	A	0.019	0.72
rs10153031	15	G	T	0.023	0.60
rs10172196	2	A	G	0.019	0.30
rs1017529	17	A	C	0.018	0.17
rs10195808	2	A	G	0.016	0.34
rs10216829	8	A	G	0.016	0.26
rs10259620	7	A	G	0.016	0.22
rs10490530	2	G	A	0.019	0.14
rs10492229	12	T	C	0.017	0.23
rs10787738	10	T	C	0.019	0.26
rs10820852	9	C	A	0.016	0.72
rs10829932	10	C	T	0.016	0.77
rs10873302	14	T	C	0.015	0.29
rs10938398	4	A	G	0.027	0.43
rs10947793	6	A	G	0.016	0.64
rs11001963	10	T	C	0.014	0.58
rs11030119	11	A	G	0.031	0.31
rs11642015	16	T	C	0.061	0.39
rs11655587	17	C	T	0.016	0.64
rs11714279	3	G	A	0.017	0.72
rs11780222	8	A	C	0.015	0.74
rs11781222	8	T	C	0.023	0.86

Appendix Table I.5: Variants included in fat mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs11782074	8	T	G	0.015	0.37
rs11856579	15	G	A	0.016	0.74
rs11951885	5	C	T	0.049	0.02
rs11968025	6	G	T	0.014	0.46
rs12037698	1	G	A	0.019	0.86
rs12140153	1	G	T	0.033	0.91
rs1218822	13	A	G	0.017	0.65
rs12218858	10	T	C	0.014	0.57
rs12222235	11	C	T	0.015	0.67
rs12330631	3	C	T	0.014	0.64
rs12339822	9	G	A	0.016	0.54
rs12477088	2	T	C	0.017	0.59
rs12578952	12	A	G	0.018	0.74
rs12583517	13	G	T	0.017	0.77
rs12619178	2	C	T	0.017	0.61
rs13135092	4	G	A	0.041	0.08
rs13156484	5	G	A	0.015	0.52
rs13174863	5	G	A	0.024	0.14
rs1342395	1	A	C	0.014	0.67
rs1373349	18	C	T	0.016	0.32
rs1426371	12	G	A	0.017	0.74
rs1427325	14	A	C	0.016	0.70
rs1441264	13	A	G	0.017	0.60
rs1458156	12	T	C	0.014	0.49
rs1470749	7	G	T	0.014	0.50
rs1477290	5	C	T	0.031	0.14
rs1516725	3	C	T	0.024	0.86
rs16895130	6	G	A	0.018	0.26
rs17014332	1	C	T	0.017	0.21
rs17256211	14	G	A	0.016	0.64
rs1731260	2	T	G	0.017	0.48
rs17770336	9	T	C	0.022	0.32
rs1783541	11	T	C	0.018	0.21
rs1834144	18	C	A	0.018	0.62
rs1857883	3	A	G	0.014	0.54
rs1881505	11	T	C	0.028	0.06
rs1886558	13	A	G	0.018	0.40
rs1891215	1	C	T	0.015	0.45
rs2016469	3	A	G	0.014	0.37
rs208477	6	T	C	0.017	0.19
rs217672	14	C	A	0.017	0.28
rs2181375	1	G	A	0.019	0.59
rs2192527	4	G	A	0.019	0.47
rs2289379	7	C	T	0.017	0.61
rs236660	7	C	T	0.019	0.57
rs2370982	14	T	C	0.028	0.21
rs2418507	3	T	C	0.017	0.57
rs2439823	10	G	A	0.019	0.54
rs2474896	6	T	C	0.017	0.55
rs2494196	1	A	C	0.022	0.28
rs249612	5	T	C	0.015	0.71
rs2678204	1	G	T	0.024	0.34
rs28642975	12	A	G	0.018	0.47
rs2869950	4	C	T	0.015	0.61
rs2979655	8	G	T	0.018	0.17
rs301806	1	T	C	0.013	0.58

Appendix Table I.5: Variants included in fat mass score

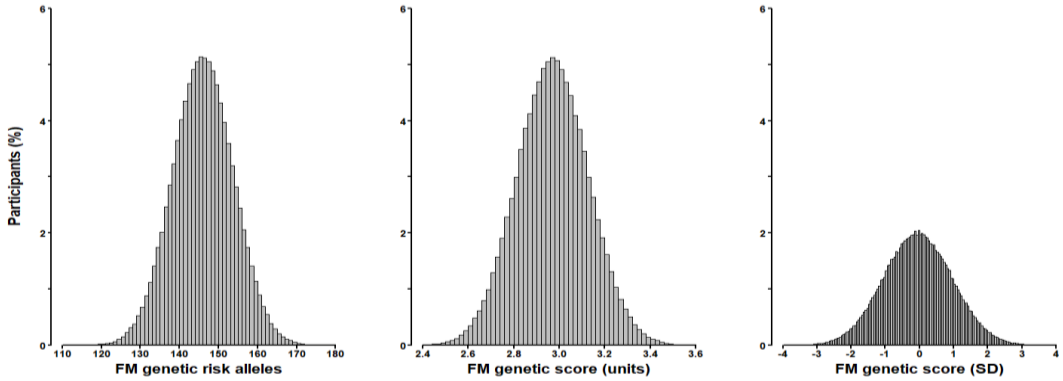
RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs314279	6	C	A	0.023	0.11
rs329118	5	C	T	0.014	0.58
rs34517439	1	A	C	0.041	0.12
rs35014268	16	C	A	0.015	0.27
rs35343344	19	C	A	0.019	0.73
rs3759094	12	C	T	0.015	0.67
rs3803286	14	A	G	0.020	0.34
rs4072917	8	A	G	0.014	0.47
rs41310284	10	C	A	0.029	0.90
rs41313250	1	A	G	0.026	0.88
rs4398538	4	T	C	0.015	0.36
rs4477562	13	T	C	0.026	0.13
rs4671328	2	T	G	0.019	0.45
rs4673617	2	T	C	0.017	0.28
rs4709745	6	C	T	0.016	0.31
rs4785955	16	T	G	0.018	0.21
rs4794222	17	A	G	0.015	0.25
rs4876611	8	G	A	0.022	0.72
rs4981693	14	A	G	0.022	0.77
rs529200	3	G	A	0.014	0.53
rs55637757	16	C	T	0.024	0.87
rs55714539	19	C	A	0.022	0.34
rs55726687	12	A	G	0.022	0.21
rs55931203	17	T	C	0.031	0.19
rs56288810	17	G	A	0.019	0.21
rs59104534	8	T	C	0.015	0.30
rs6029180	20	G	A	0.014	0.33
rs6031847	20	T	C	0.018	0.27
rs60572790	11	C	T	0.024	0.32
rs6060455	20	G	A	0.037	0.97
rs60898782	6	A	G	0.017	0.20
rs6127658	20	C	T	0.015	0.71
rs61765651	1	C	T	0.029	0.81
rs61903695	11	G	A	0.016	0.25
rs62025854	15	G	T	0.023	0.73
rs62082913	18	G	A	0.023	0.10
rs62104483	19	A	G	0.023	0.32
rs62178054	2	T	C	0.017	0.63
rs62246314	3	A	G	0.025	0.10
rs62259475	3	A	G	0.015	0.36
rs62621197	19	C	T	0.044	0.96
rs6452788	5	G	A	0.022	0.75
rs6545714	2	G	A	0.020	0.39
rs6567160	18	C	T	0.046	0.23
rs6686901	1	C	T	0.017	0.46
rs67536595	2	C	T	0.018	0.81
rs67844506	20	A	G	0.025	0.82
rs6857	19	C	T	0.022	0.83
rs6893495	5	T	C	0.016	0.21
rs704061	12	C	T	0.018	0.46
rs7171864	15	A	G	0.018	0.66
rs7238896	18	G	A	0.022	0.14
rs72892910	6	T	G	0.035	0.17
rs73041988	11	T	G	0.024	0.84
rs73225274	8	G	A	0.019	0.14
rs73622719	16	A	G	0.033	0.05

Appendix Table I.5: Variants included in fat mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs7503604	17	C	A	0.014	0.49
rs75983170	13	G	T	0.015	0.34
rs76040172	21	G	A	0.040	0.95
rs76095247	15	A	C	0.016	0.76
rs7649970	3	T	C	0.030	0.12
rs76895963	12	G	T	0.078	0.02
rs76929617	12	A	G	0.054	0.96
rs7701886	5	G	A	0.015	0.46
rs7845090	8	G	A	0.025	0.30
rs7925100	11	A	G	0.014	0.39
rs7934638	11	A	G	0.017	0.25
rs79704991	6	T	G	0.022	0.12
rs8132491	21	G	A	0.015	0.68
rs815163	1	T	C	0.015	0.44
rs845084	10	A	G	0.016	0.26
rs854917	6	C	T	0.016	0.26
rs894347	8	A	G	0.014	0.60
rs9320823	6	C	T	0.021	0.61
rs9321191	6	T	C	0.018	0.80
rs9471333	6	C	T	0.022	0.45
rs9610311	22	C	T	0.015	0.30
rs9843653	3	C	T	0.028	0.50
rs9847186	3	G	A	0.014	0.57

Variants oriented so that effect allele is associated with greater fat mass in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

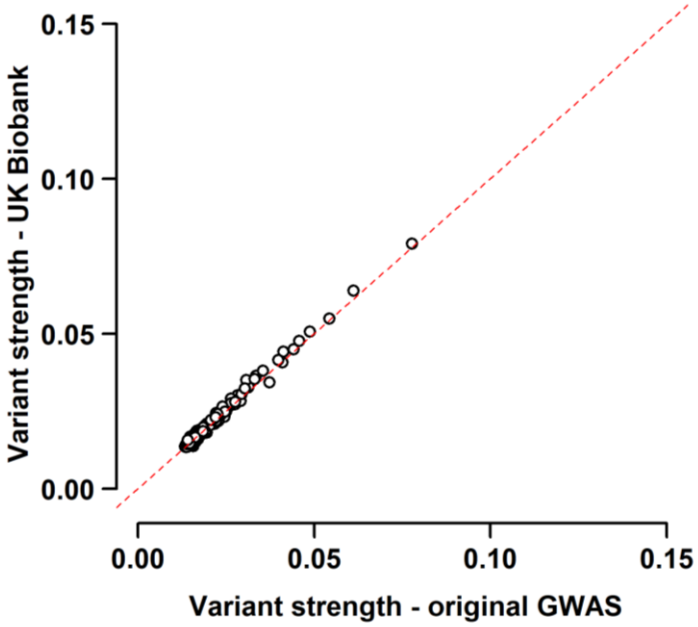
1



Appendix Figure I.13: Distribution of fat mass variants in the UK Biobank population.

Histograms demonstrating the distribution of body mass index genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher fat mass. FM – fat mass, SD – standard deviation.

2



Appendix Figure I.14: Scatter plot of beta values from fat mass genome-wide association study and UK Biobank.
Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data.[71] *UKB beta values calculated as per-allele effects on fat mass residuals. The red dotted line represents the line of parity.*

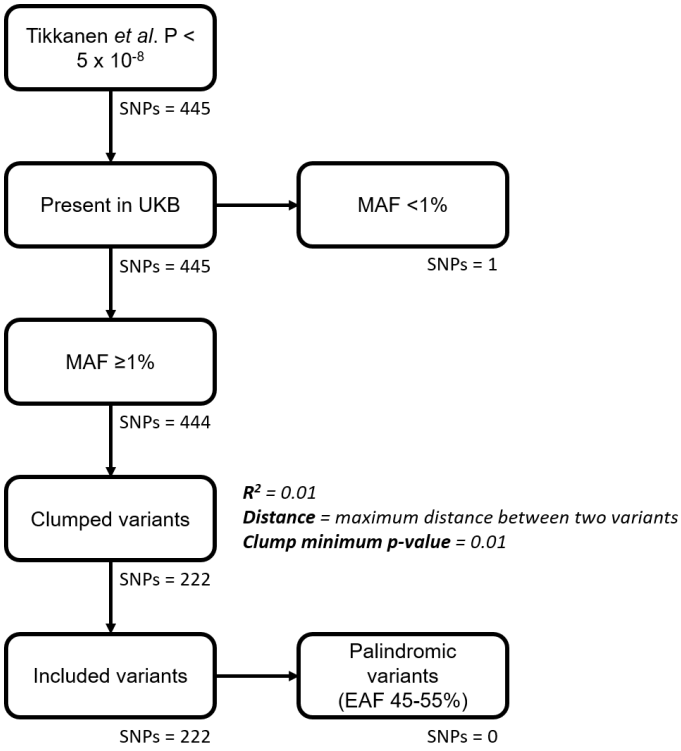
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2

I.6. Selection of genetic variants for lean mass score

A GWAS for LM (based on bio-impedance data) has previously been undertaken in UKB using approximately 332,000 participants and identified 446 variants (of which one was multi-allelic and not included in the final score).[71] LM was rank inverse normally transformed and the analysis was adjusted for age, sex, genotype array, and 10 principal components of ancestry. Summary data were taken from the meta-analysis. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 241,885,035 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR). As p-values were not provided in the summary data, these were recalculated from UKB data.

Two hundred and twenty-two variants were included in the LM score (**Appendix Figure I.15**, **Appendix Table I.6**). The median F-stat for included variants was 49 (range 23 to 610). The proportion of variance explained was 5.0%. Sex-specific beta values were calculated for each variant within UKB using LM residuals calculated separately in men and women. Risk alleles for selected variants and the developed LM genetic score were normally distributed in UKB (**Appendix Figure I.16**). To confirm the accuracy of calculated p-values and sex-specific beta values, the calculated UKB beta-values were compared with those provided in the original GWAS (r=0.99, **Appendix Figure I.17**).



Appendix Figure I.15: Flowchart of variant selection for lean mass score.
Variants identified from Tikkanen et al.[71] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank

1

Appendix Table I.6: Variants included in lean mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs1004030	14	T	C	0.009	0.58
rs10076828	5	A	G	0.009	0.62
rs10091194	8	G	A	0.010	0.51
rs10139746	14	A	G	0.009	0.46
rs10202701	2	T	C	0.011	0.54
rs10202845	2	A	G	0.016	0.89
rs10231036	7	G	A	0.009	0.45
rs10434434	4	A	C	0.014	0.86
rs10514136	5	A	G	0.018	0.77
rs10746837	9	G	A	0.010	0.43
rs10811901	9	A	G	0.010	0.57
rs11014285	10	A	G	0.018	0.16
rs11030119	11	A	G	0.017	0.31
rs11042717	11	T	C	0.012	0.52
rs11160601	14	T	C	0.018	0.09
rs11187838	10	A	G	0.016	0.44
rs11196169	10	A	G	0.009	0.47
rs11564039	7	T	C	0.029	0.02
rs11568828	17	T	C	0.026	0.89
rs11578046	1	G	A	0.013	0.68
rs11589536	1	A	C	0.010	0.39
rs11707955	3	C	T	0.010	0.46

Appendix Table I.6: Variants included in lean mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs11709402	3	G	A	0.011	0.27
rs11717749	3	T	C	0.017	0.11
rs11747434	5	C	T	0.014	0.28
rs11783086	8	C	T	0.009	0.36
rs11880992	19	A	G	0.014	0.40
rs11907497	20	C	T	0.013	0.23
rs12072845	1	G	A	0.015	0.61
rs12209223	6	A	C	0.017	0.10
rs12344584	9	A	G	0.014	0.91
rs12378054	9	T	C	0.019	0.91
rs12422933	12	A	C	0.011	0.25
rs12540011	7	A	G	0.014	0.28
rs12713004	2	G	A	0.019	0.72
rs12879423	14	G	A	0.014	0.67
rs12900116	15	T	C	0.013	0.38
rs12986369	19	A	G	0.009	0.54
rs13186522	5	T	C	0.012	0.39
rs1347247	5	G	A	0.016	0.08
rs1355603	4	C	T	0.029	0.83
rs1390498	6	A	G	0.015	0.72
rs1474055	2	T	C	0.014	0.12
rs14976	2	T	C	0.011	0.30
rs1528450	2	C	T	0.009	0.60
rs1541597	12	T	G	0.012	0.20
rs1692584	1	C	T	0.010	0.38
rs17024393	1	C	T	0.027	0.03
rs174047	5	G	T	0.008	0.53
rs17806016	14	A	G	0.009	0.67
rs181895	5	A	G	0.009	0.59
rs1837367	2	A	G	0.009	0.47
rs1864193	19	C	A	0.016	0.86
rs1926034	10	A	G	0.013	0.38
rs1927635	9	C	T	0.010	0.36
rs1967315	8	A	G	0.013	0.27
rs1984119	9	T	C	0.014	0.75
rs2075060	17	A	G	0.011	0.55
rs2102278	4	G	A	0.011	0.34
rs2115459	5	T	C	0.011	0.47
rs2158045	7	T	C	0.013	0.47
rs2252720	20	C	T	0.014	0.33
rs2319817	14	A	G	0.016	0.11
rs2396348	2	T	C	0.013	0.30
rs2413592	22	G	A	0.011	0.75
rs244711	5	T	C	0.017	0.69
rs2455561	15	T	G	0.013	0.47
rs246177	16	T	C	0.010	0.37
rs247008	5	G	A	0.015	0.66
rs2508710	11	T	G	0.012	0.19
rs2539999	16	C	T	0.017	0.30
rs254963	5	A	G	0.010	0.55
rs2592831	4	C	T	0.013	0.34
rs2633266	2	C	T	0.017	0.89
rs2678204	1	G	T	0.013	0.34
rs2744965	6	T	C	0.040	0.14
rs2842385	6	G	A	0.015	0.20
rs28457693	9	G	A	0.027	0.11

Appendix Table I.6: Variants included in lean mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs2866719	7	T	C	0.009	0.37
rs2870132	20	C	A	0.010	0.75
rs2885697	1	G	T	0.020	0.33
rs2900208	12	A	C	0.014	0.35
rs2979655	8	G	T	0.011	0.17
rs29938	19	C	T	0.010	0.66
rs310802	12	T	C	0.009	0.77
rs3118903	13	G	A	0.032	0.79
rs33966734	6	C	A	0.074	0.99
rs33967909	5	A	G	0.015	0.22
rs34045288	6	T	C	0.012	0.33
rs343935	2	C	T	0.014	0.16
rs34517439	1	A	C	0.035	0.12
rs34776209	7	C	T	0.019	0.76
rs34776495	18	G	A	0.013	0.43
rs35288270	10	T	C	0.017	0.87
rs35506085	11	G	A	0.020	0.81
rs35651070	2	G	A	0.011	0.84
rs357501	3	A	G	0.011	0.38
rs3731321	7	T	C	0.022	0.84
rs3778157	6	C	T	0.012	0.16
rs3795503	1	T	C	0.011	0.31
rs3798519	6	C	A	0.021	0.18
rs3809570	15	A	C	0.014	0.24
rs3818416	13	C	A	0.016	0.76
rs3853252	6	A	G	0.016	0.45
rs3923783	17	C	A	0.011	0.82
rs4073717	5	G	T	0.018	0.80
rs4128460	6	A	G	0.014	0.79
rs4143843	15	C	T	0.011	0.56
rs42044	7	G	T	0.029	0.27
rs4270917	8	C	T	0.009	0.66
rs4477562	13	T	C	0.016	0.13
rs4752689	10	A	G	0.012	0.59
rs475591	1	C	T	0.011	0.59
rs4778918	15	T	C	0.009	0.58
rs4804090	19	C	T	0.013	0.62
rs4819021	21	T	C	0.010	0.52
rs4858697	3	G	A	0.013	0.57
rs4888153	16	A	G	0.011	0.76
rs4895917	6	C	T	0.010	0.68
rs4985148	16	A	C	0.011	0.69
rs501332	1	A	G	0.010	0.27
rs514328	19	A	G	0.014	0.88
rs55681913	5	C	T	0.028	0.10
rs55726687	12	A	G	0.015	0.21
rs55760822	9	G	T	0.016	0.08
rs55872725	16	T	C	0.037	0.39
rs56238630	15	T	C	0.047	0.97
rs5752989	22	G	A	0.011	0.43
rs57635800	11	A	G	0.012	0.29
rs57790054	16	G	A	0.013	0.27
rs58403320	9	G	A	0.011	0.78
rs58670122	1	A	G	0.015	0.85
rs60804050	1	G	A	0.012	0.74
rs6088638	20	C	T	0.018	0.17

Appendix Table I.6: Variants included in lean mass score

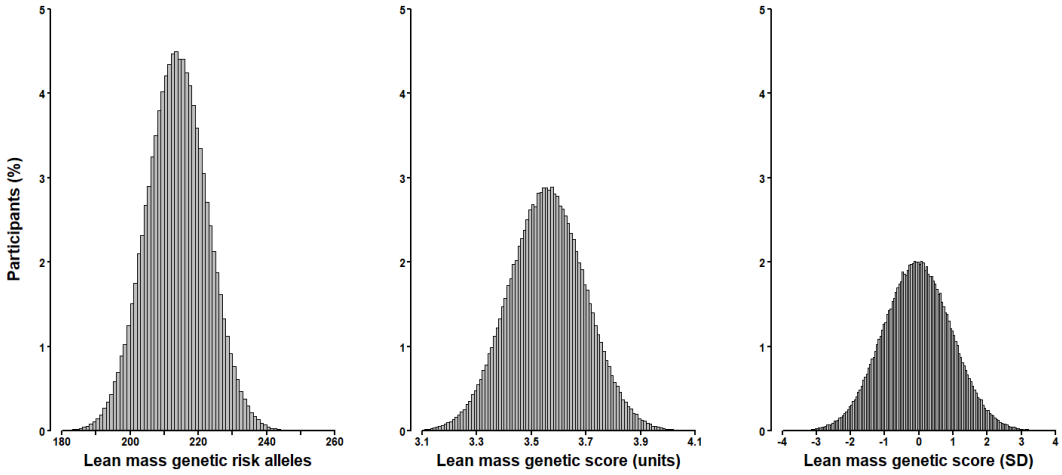
RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs6096886	20	A	G	0.019	0.81
rs61628776	9	A	G	0.016	0.86
rs61732778	3	A	G	0.017	0.07
rs61765651	1	C	T	0.013	0.81
rs62064921	17	C	T	0.028	0.96
rs62129346	19	T	C	0.011	0.26
rs62370476	5	G	A	0.012	0.80
rs62515437	8	T	G	0.021	0.22
rs62621197	19	C	T	0.036	0.96
rs62621812	7	A	G	0.048	0.02
rs632224	17	A	G	0.011	0.57
rs6505216	17	G	T	0.029	0.77
rs6563808	13	T	C	0.010	0.27
rs662115	10	T	C	0.010	0.45
rs663112	1	T	C	0.013	0.16
rs668871	6	T	C	0.013	0.47
rs66922415	18	G	A	0.044	0.24
rs6719296	2	A	G	0.009	0.49
rs6755489	2	A	G	0.010	0.73
rs676105	11	C	T	0.013	0.30
rs6762578	3	A	G	0.017	0.78
rs67674827	8	T	C	0.021	0.28
rs6800021	3	A	G	0.014	0.42
rs68156080	10	A	G	0.011	0.73
rs6874142	5	G	T	0.020	0.11
rs6902789	6	A	G	0.010	0.36
rs6995599	8	C	T	0.019	0.69
rs703593	12	A	G	0.012	0.52
rs705159	10	A	G	0.009	0.46
rs7072873	10	C	T	0.013	0.47
rs7129320	11	G	A	0.024	0.84
rs7137828	12	T	C	0.014	0.54
rs7141420	14	T	C	0.012	0.52
rs71414738	2	T	C	0.012	0.17
rs7156335	14	C	T	0.016	0.09
rs7184768	16	A	G	0.010	0.41
rs7208285	17	G	A	0.011	0.47
rs7218001	17	A	C	0.014	0.19
rs7220854	17	C	T	0.011	0.66
rs7229520	18	G	A	0.011	0.34
rs7230581	18	A	G	0.015	0.83
rs7235010	18	A	G	0.027	0.78
rs7255927	19	G	A	0.012	0.29
rs72656010	8	T	C	0.036	0.87
rs72704611	1	C	T	0.035	0.01
rs7278123	21	A	G	0.010	0.77
rs73013411	6	A	C	0.013	0.13
rs73052033	3	T	C	0.016	0.82
rs73163931	7	G	A	0.015	0.10
rs73175572	3	G	A	0.028	0.11
rs73228208	8	A	G	0.012	0.22
rs73601548	10	T	C	0.014	0.11
rs73619441	20	T	G	0.017	0.85
rs7396827	11	T	C	0.011	0.45
rs74411434	2	T	C	0.019	0.08
rs74494415	18	C	T	0.029	0.96

Appendix Table I.6: Variants included in lean mass score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs755481	10	G	T	0.010	0.47
rs7559547	2	T	C	0.032	0.82
rs757558	17	G	T	0.019	0.85
rs7590946	2	T	C	0.009	0.56
rs76098726	1	C	T	0.021	0.08
rs76227980	18	C	T	0.057	0.98
rs7624087	3	C	T	0.009	0.54
rs76364830	8	G	A	0.023	0.94
rs7649884	3	A	G	0.009	0.45
rs76513770	16	T	C	0.017	0.87
rs76520574	16	C	T	0.028	0.96
rs7663887	4	C	A	0.033	0.84
rs76798800	1	T	G	0.023	0.26
rs76895963	12	G	T	0.105	0.02
rs7812293	7	T	C	0.009	0.53
rs78378222	17	G	T	0.087	0.01
rs7845090	8	G	A	0.011	0.30
rs7849060	9	C	T	0.014	0.29
rs78870364	2	C	T	0.020	0.95
rs78964719	2	T	G	0.016	0.07
rs7910211	10	C	T	0.013	0.16
rs8019890	14	A	C	0.011	0.52
rs8066863	17	A	G	0.017	0.88
rs8107967	19	A	G	0.010	0.45
rs8133137	21	G	A	0.010	0.66
rs877041	1	A	G	0.009	0.39
rs9128	1	T	C	0.046	0.01
rs9295	2	A	G	0.011	0.29
rs9350850	6	C	T	0.024	0.08
rs9379084	6	G	A	0.015	0.89
rs983399	7	C	T	0.012	0.49
rs9894577	17	G	A	0.016	0.68

Variants oriented so that effect allele is associated with greater lean mass in the original GWAS. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency.

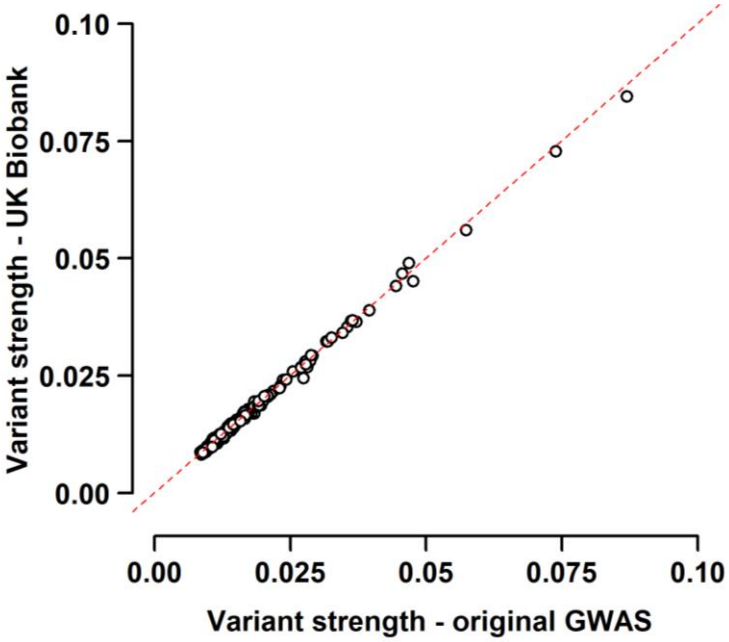
1



Appendix Figure I.16: Distribution of lean mass variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of body mass index genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher lean mass. SD – standard deviation.

1



Appendix Figure I.17: Scatter plot of beta values from lean mass genome-wide association study and UK Biobank.

Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data.[71] *UK Biobank beta values calculated as per-allele effects on lean mass residuals. The red dotted line represents the line of parity.*

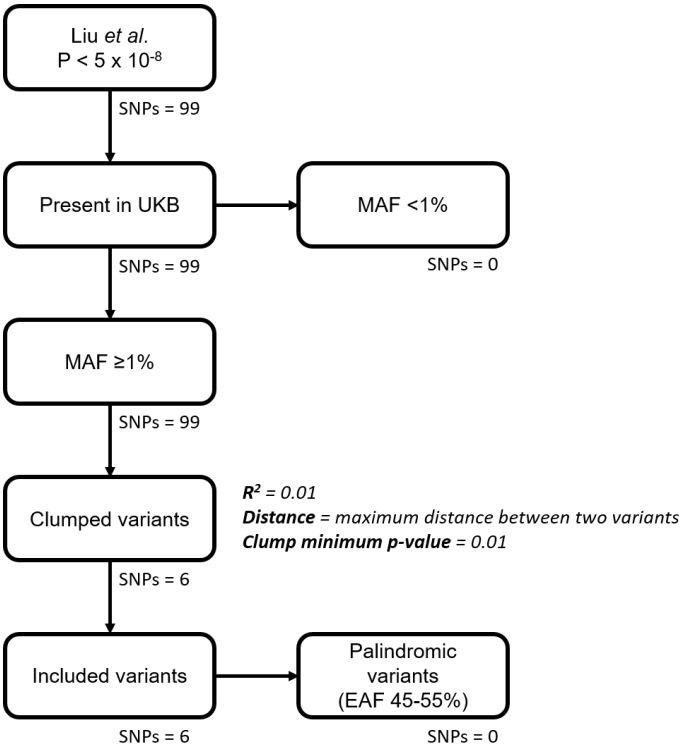
2

3

I.7. Selection of genetic variants for visceral adipose tissue score

A GWAS for abdominal visceral adipose tissue (VAT) using a sub-set of UKB of approximately 38,000 participants and identified 99 SNPs meeting genome-wide significance.[106] abdominal VAT was adjusted for age, age^2, sex, imaging centre, scan date, scan time, and genotype batch, and genotype relatedness matrix as a random effect in a linear model. Residuals were rank inverse normally transformed. Summary data were taken from the meta-analysis. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 15,640,744 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from 1000 Genomes Phase 1 (EUR).

Six variants were included in the abdominal VAT score (**Appendix Figure I.18**, **Appendix Table I.7**). The median F-stat for included variants was 34 (range 24 to 53). The proportion of variance explained was 0.6%. Risk alleles for selected variants and the developed abdominal VAT genetic score were normally distributed in UKB (**Appendix Figure I.19**).



Appendix Figure I.18: Flowchart of variant selection for visceral adipose tissue score.
Variants identified from Liu et al.[106] *EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.*

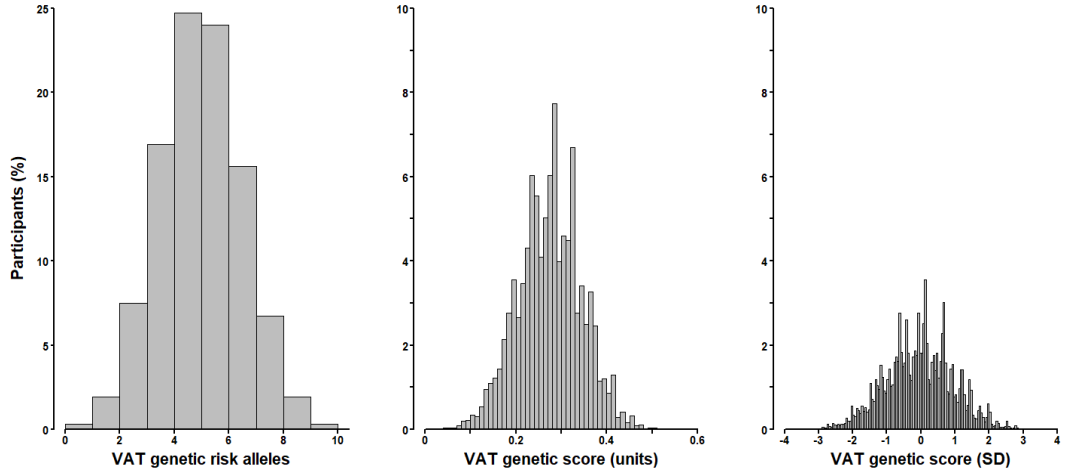
1

Appendix Table I.7: Variants included in visceral adipose tissue score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
3:49799046	3	IP6K1	C	CA	0.039	0.46
5:55802127	5	C5orf67	TCAAGGATTCC TTGACTTAAG	T	0.055	0.21
rs73221948	8	CDCA2	G	T	0.050	0.71
rs62048402	16	FTO	A	G	0.037	0.39
19:33785832	19	CEBPA	CA	C	0.060	0.82
rs11666808	19	IQCN	T	C	0.038	0.37

Variants oriented so that effect allele is associated with greater visceral adipose tissue in the original genome-wide association study. Ordered by chromosome. Nearest gene defined by the original GWAS.[106] Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

2



Appendix Figure I.19: Distribution of visceral adipose tissue variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of visceral adipose tissue genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher visceral adipose tissue. VAT – visceral adipose tissue, SD – standard deviation.

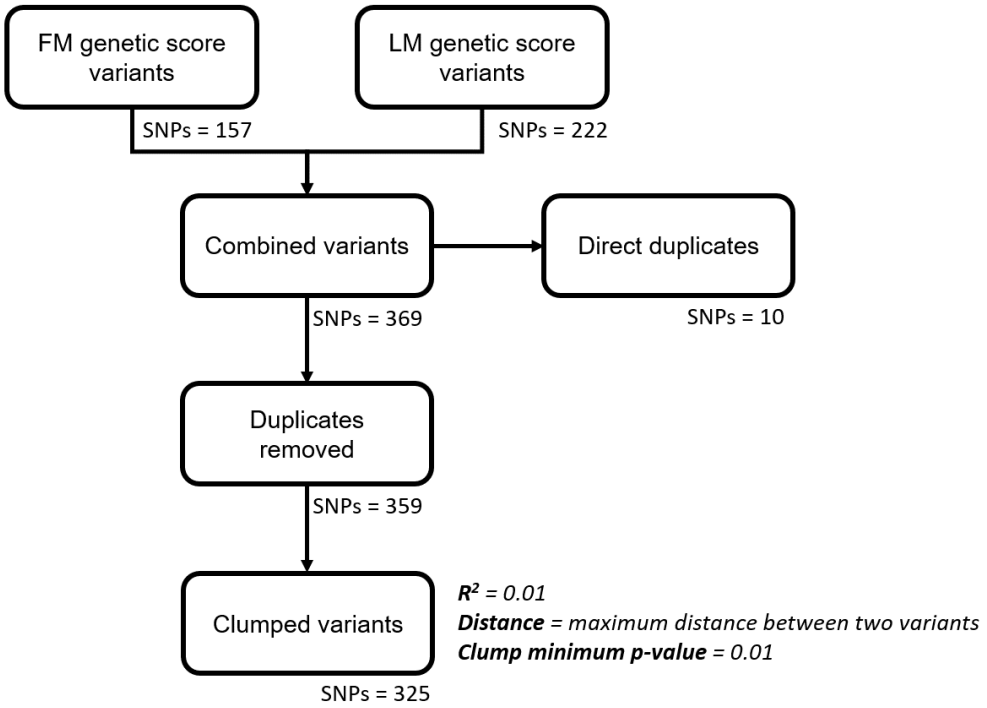
1

2

I.8.Selection of genetic variants for multivariable Mendelian randomization analysis of lean and fat mass

When the 157 FM variants and 222 LM variants were combined into one list, 10 were direct duplicates and were removed. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 15,640,744 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from UKB. A total of 325 variants were included in the multivariable Mendelain randomization analysis for FM and LM (**Appendix Figure I.20**, **Appendix Table I.8**). Of these 134 (41%) were originally identified from the FM GWAS with 191 (59%) coming from the LM GWAS. The correlation between FM and LM beta values is shown in **Appendix Figure I.21**.

As beta values for both FM and LM were not provided for all variants in summary data from the original GWAS, beta values were re-calculated in UKB. For variants where beta values were provided in summary data, comparison was made with re-calculated beta values to demonstrate accuracy of the re-calculation (**Appendix Figure I.22** and **Appendix Figure I.23**).



Appendix Figure I.20: Flowchart of variant selection for combined fat mass and waist circumference score for multivariable Mendelian randomization analysis.

Variants identified from Tikkanen et al.[71] EAF – effect allele frequency; FM – body fat mass; LM – body lean mass; MAF – minor allele frequency, SNPs – single nucleotide polymoprhisms

1

Appendix Table I.8: Variants included in the combined fat mass and lean mass score

RSID	Effect Allele	Other Allele	LM weighting	FM weighting
rs1004030	T	C	0.009	0.005
rs10076828	A	G	0.009	0.012
rs10091194	G	A	0.010	0.009
rs10128597	G	A	0.009	0.020
rs10139746	A	G	0.009	0.000
rs10153031	G	T	0.009	0.023
rs10172196	A	G	0.010	0.018
rs10195808	A	G	0.003	0.016
rs10202701	T	C	0.012	-0.002
rs10202845	A	G	0.016	0.003
rs10216829	A	G	0.007	0.016
rs10231036	G	A	0.009	0.001
rs10259620	A	G	-0.001	0.016
rs10434434	A	C	0.014	0.008
rs10490530	G	A	0.008	0.019
rs10492229	T	C	0.009	0.017
rs10514136	A	G	0.018	0.019
rs10746837	G	A	0.011	0.008
rs10787738	T	C	0.009	0.020
rs10811901	A	G	0.010	0.009

rs10820852	C	A	0.011	0.016
rs10829932	C	T	0.006	0.015
rs10873302	T	C	0.006	0.015
rs10938398	A	G	0.011	0.026
rs10947793	A	G	0.008	0.016
rs11001963	T	C	0.005	0.013
rs11014285	A	G	0.020	0.007
rs11042717	T	C	0.012	-0.007
rs11160601	T	C	0.017	0.022
rs11187838	A	G	0.016	-0.011
rs11196169	A	G	0.009	0.008
rs11564039	T	C	0.030	0.016
rs11568828	T	C	0.026	0.003
rs11578046	G	A	0.012	0.008
rs11589536	A	C	0.011	0.011
rs11642015	T	C	0.036	0.060
rs11707955	C	T	0.010	0.015
rs11709402	G	A	0.010	0.019
rs11714279	G	A	0.007	0.017
rs11717749	T	C	0.018	0.007
rs11747434	C	T	0.014	0.010
rs11780222	A	C	0.008	0.015
rs11781222	T	C	0.011	0.023
rs11782074	T	G	0.006	0.014
rs11783086	C	T	0.009	0.006
rs11856579	G	A	0.007	0.016
rs11880992	A	G	0.014	0.004
rs11907497	C	T	0.013	-0.005
rs11951885	C	T	0.024	0.044
rs12037698	G	A	0.003	0.020
rs12072845	G	A	0.015	0.007
rs12140153	G	T	0.016	0.033
rs1218822	A	G	0.009	0.017
rs12209223	A	C	0.018	0.012
rs12218858	T	C	0.005	0.014
rs12222235	C	T	0.004	0.015
rs12330631	C	T	0.002	0.015
rs12339822	G	A	0.002	0.017
rs12344584	A	G	0.013	0.013
rs12378054	T	C	0.020	-0.005
rs12422933	A	C	0.011	0.007
rs12477088	T	C	0.007	0.017
rs12540011	A	G	0.015	0.005
rs12578952	A	G	0.010	0.017
rs12583517	G	T	0.010	0.016
rs12619178	C	T	0.006	0.018
rs12713004	G	A	0.019	0.002
rs12879423	G	A	0.014	0.018
rs12900116	T	C	0.013	0.007
rs12986369	A	G	0.009	0.000
rs13135092	G	A	0.006	0.040
rs13156484	G	A	0.020	0.015
rs13174863	G	A	0.013	0.024
rs13186522	T	C	0.013	0.012
rs1342395	A	C	0.010	0.015
rs1355603	C	T	0.029	0.019
rs1373349	C	T	0.007	0.016
rs1390498	A	G	0.014	0.011
rs1426371	G	A	-0.005	0.018
rs1427325	A	C	0.004	0.016

rs1441264	A	G	0.007	0.017
rs1458156	T	C	0.008	0.013
rs1470749	G	T	0.010	0.013
rs1474055	T	C	0.013	0.002
rs1477290	C	T	0.011	0.031
rs14976	T	C	0.011	0.006
rs1541597	T	G	0.012	0.011
rs16895130	G	A	0.018	0.017
rs1692584	C	T	0.010	-0.001
rs17014332	C	T	0.010	0.017
rs17024393	C	T	0.025	0.057
rs17256211	G	A	0.012	0.016
rs1731260	T	G	0.009	0.017
rs174047	G	T	0.008	0.009
rs17770336	T	C	0.011	0.021
rs17806016	A	G	0.009	0.004
rs181895	A	G	0.009	0.010
rs1834144	C	A	0.006	0.019
rs1837367	A	G	0.009	0.009
rs1857883	A	G	0.008	0.014
rs1881505	T	C	0.005	0.029
rs1886558	A	G	0.006	0.018
rs1891215	C	T	0.006	0.014
rs1926034	A	G	0.012	0.008
rs1927635	C	T	0.010	0.010
rs1967315	A	G	0.013	0.004
rs1984119	T	C	0.014	0.007
rs2016469	A	G	0.008	0.013
rs2075060	A	G	0.011	0.002
rs208477	T	C	0.007	0.018
rs2102278	G	A	0.012	0.017
rs2115459	T	C	0.010	0.006
rs2158045	T	C	0.013	0.009
rs217672	C	A	0.005	0.017
rs2181375	G	A	0.008	0.020
rs2192527	G	A	0.008	0.019
rs2252720	C	T	0.014	0.002
rs2289379	C	T	0.006	0.017
rs2319817	A	G	0.017	0.014
rs236660	C	T	0.006	0.019
rs2370982	T	C	0.013	0.029
rs2396348	T	C	0.012	-0.004
rs2413592	G	A	0.011	0.006
rs2439823	G	A	0.008	0.020
rs244711	T	C	0.017	0.009
rs2455561	T	G	0.012	-0.001
rs246177	T	C	0.010	0.000
rs247008	G	A	0.015	0.012
rs2474896	T	C	0.008	0.017
rs2494196	A	C	-0.003	0.022
rs249612	T	C	0.007	0.014
rs2508710	T	G	0.012	0.015
rs2539999	C	T	0.016	0.012
rs254963	A	G	0.010	0.005
rs2592831	C	T	0.013	0.009
rs2633266	C	T	0.018	0.012
rs2744965	T	C	0.039	0.046
rs2842385	G	A	0.016	0.009
rs28457693	G	A	0.027	0.008
rs28642975	A	G	0.013	0.018

rs2866719	T	C	0.009	0.012
rs2869950	C	T	-0.001	0.014
rs2870132	C	A	0.010	0.001
rs2885697	G	T	0.020	0.007
rs2900208	A	C	0.014	0.003
rs29938	C	T	0.010	0.009
rs301806	T	C	-0.002	0.013
rs310802	T	C	0.008	0.003
rs3118903	G	A	0.033	0.010
rs329118	C	T	0.007	0.014
rs33966734	C	A	0.073	0.060
rs33967909	A	G	0.016	0.011
rs343935	C	T	0.015	0.011
rs34776209	C	T	0.019	0.006
rs34776495	G	A	0.013	0.005
rs35014268	C	A	0.006	0.015
rs35288270	T	C	0.018	0.007
rs35343344	C	A	0.005	0.020
rs35506085	G	A	0.019	0.009
rs35651070	G	A	0.011	0.005
rs357501	A	G	0.011	0.014
rs3759094	C	T	0.012	0.015
rs3795503	T	C	0.011	0.003
rs3803286	A	G	0.009	0.019
rs3809570	A	C	0.013	0.001
rs3818416	C	A	0.016	0.009
rs3853252	A	G	0.016	0.013
rs3923783	C	A	0.011	0.026
rs4072917	A	G	0.006	0.014
rs4073717	G	T	0.017	0.012
rs4128460	A	G	0.014	0.010
rs41310284	C	A	0.013	0.029
rs4143843	C	T	0.011	0.000
rs42044	G	T	0.029	0.018
rs4398538	T	C	0.008	0.016
rs4671328	T	G	0.009	0.020
rs4673617	T	C	0.005	0.017
rs4709745	C	T	0.009	0.016
rs4752689	A	G	0.012	0.009
rs475591	C	T	0.011	0.008
rs4778918	T	C	0.010	0.012
rs4785955	T	G	0.005	0.017
rs4794222	A	G	0.008	0.014
rs4804090	C	T	0.012	0.007
rs4858697	G	A	0.013	0.013
rs4876611	G	A	0.005	0.021
rs4888153	A	G	0.011	0.004
rs4895917	C	T	0.010	0.011
rs4981693	A	G	0.010	0.022
rs4985148	A	C	0.011	0.010
rs501332	A	G	0.010	0.012
rs514328	A	G	0.014	0.005
rs529200	G	A	0.006	0.014
rs55637757	C	T	0.010	0.024
rs55681913	C	T	0.028	0.011
rs55714539	C	A	0.005	0.022
rs55760822	G	T	0.017	0.007
rs55931203	T	C	0.011	0.030
rs56238630	T	C	0.049	0.030
rs56288810	G	A	0.009	0.019

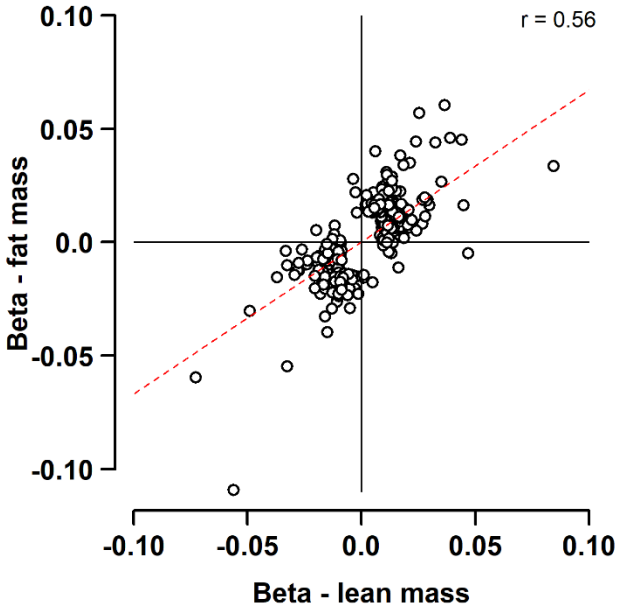
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rs57790054	G	A	0.014	0.014
rs58403320	G	A	0.011	0.002
rs58670122	A	G	0.015	0.008
rs59104534	T	C	0.006	0.016
rs6029180	G	A	0.006	0.015
rs6031847	T	C	0.012	0.018
rs60572790	C	T	0.009	0.024
rs6060455	G	A	0.017	0.038
rs60804050	G	A	0.013	0.004
rs6088638	C	T	0.019	0.016
rs60898782	A	G	0.012	0.017
rs6096886	A	G	0.018	0.023
rs6127658	C	T	0.004	0.014
rs61628776	A	G	0.016	0.007
rs61732778	A	G	0.017	0.009
rs61903695	G	A	0.006	0.016
rs62025854	G	T	0.001	0.023
rs62064921	C	T	0.027	0.012
rs62082913	G	A	0.009	0.023
rs62104483	A	G	0.015	0.023
rs62129346	T	C	0.010	0.004
rs62178054	T	C	0.009	0.017
rs62246314	A	G	0.013	0.024
rs62259475	A	G	0.008	0.015
rs62370476	G	A	0.012	-0.004
rs62515437	T	G	0.021	0.006
rs62621812	A	G	0.045	0.016
rs632224	A	G	0.011	0.007
rs6452788	G	A	0.013	0.022
rs6505216	G	T	0.028	0.012
rs6545714	G	A	0.009	0.020
rs662115	T	C	0.009	0.001
rs663112	T	C	0.013	0.005
rs6686901	C	T	0.005	0.016
rs668871	T	C	0.013	0.014
rs66922415	G	A	0.044	0.045
rs6719296	A	G	0.009	0.002
rs67536595	C	T	0.012	0.017
rs6755489	A	G	0.010	-0.001
rs676105	C	T	0.013	0.015
rs6762578	A	G	0.017	0.011
rs67674827	T	C	0.020	0.008
rs68156080	A	G	0.011	0.007
rs6857	C	T	0.010	0.023
rs6893495	T	C	0.002	0.017
rs6902789	A	G	0.011	0.011
rs6995599	C	T	0.019	0.012
rs703593	A	G	0.012	0.009
rs704061	C	T	0.006	0.018
rs7072873	C	T	0.013	0.003
rs7129320	G	A	0.024	0.010
rs7137828	T	C	0.014	0.006
rs71414738	T	C	0.011	0.004
rs7156335	C	T	0.017	0.014
rs7171864	A	G	0.004	0.017
rs7184768	A	G	0.010	0.008
rs7208285	G	A	0.011	0.012
rs7218001	A	C	0.013	0.006
rs7220854	C	T	0.010	0.008

rs7229520	G	A	0.010	0.004
rs7230581	A	G	0.015	0.015
rs7235010	A	G	0.027	0.019
rs7238896	G	A	0.010	0.021
rs7255927	G	A	0.011	0.007
rs72656010	T	C	0.037	0.015
rs72704611	C	T	0.035	0.027
rs7278123	A	G	0.010	0.011
rs72892910	T	G	0.021	0.035
rs73041988	T	G	0.006	0.023
rs73052033	T	C	0.016	0.020
rs73163931	G	A	0.014	0.012
rs73175572	G	A	0.028	0.020
rs73225274	G	A	0.008	0.019
rs73601548	T	C	0.014	0.014
rs73619441	T	G	0.016	0.015
rs73622719	A	G	0.018	0.034
rs7396827	T	C	0.011	0.007
rs74411434	T	C	0.018	0.016
rs74494415	C	T	0.029	0.014
rs7503604	C	A	0.006	0.015
rs755481	G	T	0.010	0.001
rs7559547	T	C	0.032	0.044
rs757558	G	T	0.020	0.007
rs75983170	G	T	0.008	0.015
rs76040172	G	A	0.015	0.040
rs76095247	A	C	0.004	0.016
rs76098726	C	T	0.021	0.014
rs76227980	C	T	0.056	0.109
rs76364830	G	A	0.024	0.008
rs7649884	A	G	0.008	0.019
rs7649970	T	C	-0.004	0.028
rs76513770	T	C	0.017	0.019
rs76520574	C	T	0.028	0.009
rs7663887	C	A	0.033	0.004
rs76798800	T	G	0.022	0.010
rs76929617	A	G	0.033	0.055
rs7701886	G	A	0.006	0.014
rs7812293	T	C	0.009	0.008
rs78378222	G	T	0.084	0.034
rs7849060	C	T	0.014	0.000
rs78870364	C	T	0.020	0.020
rs78964719	T	G	0.016	0.011
rs7910211	C	T	0.012	0.002
rs7925100	A	G	0.003	0.014
rs7934638	A	G	0.006	0.017
rs79704991	T	G	0.012	0.023
rs8019890	A	C	0.011	0.000
rs8066863	A	G	0.017	0.007
rs8107967	A	G	0.009	-0.001
rs8133137	G	A	0.009	0.011
rs815163	T	C	0.009	0.015
rs845084	A	G	0.008	0.017
rs854917	C	T	0.008	0.016
rs877041	A	G	0.009	0.011
rs9128	T	C	0.047	-0.005
rs9320823	C	T	0.002	0.021
rs9321191	T	C	0.009	0.017
rs9350850	C	T	0.024	0.005
rs9379084	G	A	0.015	0.005

rs9471333	C	T	0.009	0.021
rs9610311	C	T	0.006	0.015
rs983399	C	T	0.013	-0.002
rs9843653	C	T	0.013	0.027
rs9894577	G	A	0.015	0.001

FM – fat amss, LM – lean mass

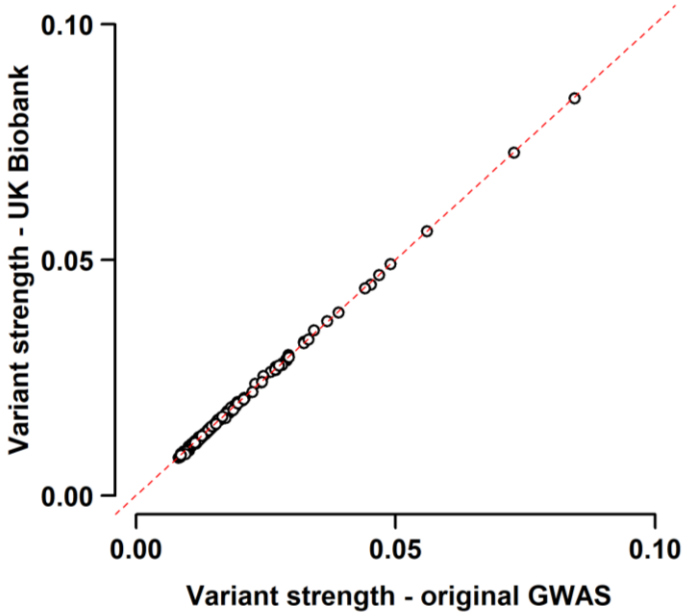
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Appendix Figure I.21: Scatter plot of beta values lean mass and fat mass.

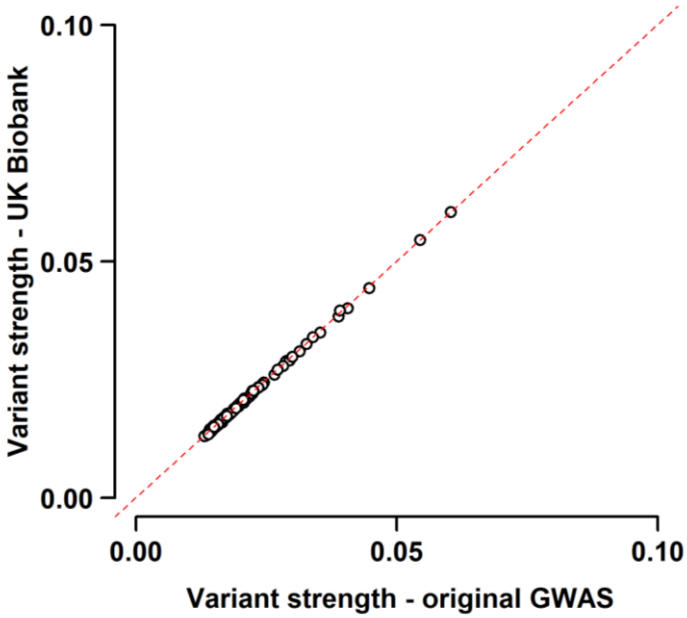
Beta values for lean mass and fat mass in variants included in the combined lean mass-fat mass genetic score used for multivariable Mendelian randomization analysis (n=325). Red dashed line represents the results from a regression model, r-value from Pearson's correlation coefficient.

2



Appendix Figure I.22: Scatter plot of beta values from lean mass genome-wide association study and recalculation in UK Biobank.
Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data.[71] UK Biobank beta values calculated as per-allele effects on lean mass residuals. The red dotted line represents the line of parity.

1



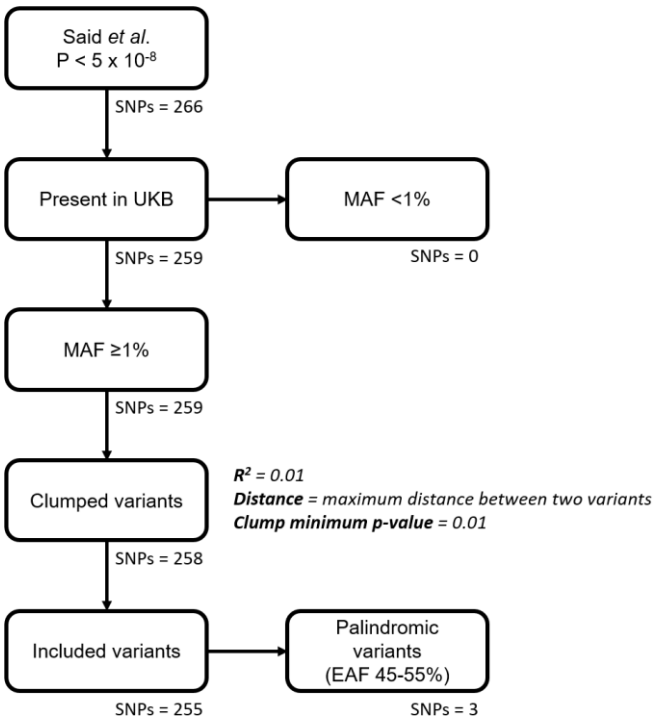
Appendix Figure I.23: Scatter plot of beta values from fat mass genome-wide association study and recalculation in UK Biobank.
Beta-values displayed as per-allele effects. Genome-wide association study (GWAS) per-allele effect estimates identified from summary data.[71] UK Biobank beta values calculated as per-allele effects on fat mass residuals. The red dotted line represents the line of parity.

2

I.9. Selection of genetic variants for C-reactive protein score

A GWAS for C-reactive protein (CRP) identified 266 SNPs meeting genome-wide significance in approximately 575,000 individuals of European ancestry and did include data from UKB.[340] CRP was transformed using the natural log and adjusted for age, sex, genotyping array, and principle components of ancestry. Summary data were taken from the meta-analysis and 259 variants were available in UKB. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 246,037,401 base pairs (maximum distance between any two variants on the same chromosome) using a reference panel from UKB.

Two hundred and fifty-five variants were included in the CRP score (**Appendix Figure I.24**, **Appendix Table I.9**). The median F-stat for included variants was 50 (range 29 to 2,205). The proportion of variance explained was 4.8%. Risk alleles for selected variants and the developed CRP genetic score were normally distributed in UKB (**Appendix Figure I.25**). Of these 255 variants, 200 could be identified either directly or through use of proxies in summary data for a separate GWAS which did not include UKB data.[367] There was significant correlation between the beta values from these two GWAS (**Appendix Figure I.26**, r=0.94).



Appendix Figure I.24: Flowchart of variant selection for C-reactive protein score.
Variants identified from Said et al. [340] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

1

Appendix Table I.9: Variants included in C-reactive protein score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs10864088	1	PROX1; SMYD2	G	A	0.016	0.31
rs10924372	1	GPR137B	C	T	0.015	0.37
rs11118625	1	RP11-453O22.1; HLX	A	G	0.019	0.73
rs11208685	1	LEPR	A	T	0.097	0.81
rs112957492	1	DOCK7	G	A	0.016	0.83
rs12132412	1	NBPF3; ALPL	C	T	0.017	0.80
rs12140498	1	RP11-815M8.1	G	T	0.012	0.32
rs12239046	1	NLRP3	A	G	0.014	0.75
rs17391694	1	GIPC2; RNFT1P2	G	A	0.015	0.26
rs17417252	1	TMCC2	T	C	0.014	0.22
rs197419	1	KCND3	A	C	0.028	0.06
rs28582591	1	RP11-490G2.2; RP11-272L13.3	C	G	0.021	0.59
rs34761529	1	ZBTB40; RP11-415K20.1	A	T	0.021	0.77
rs3768321	1	RP11-69E11.8	A	C	0.014	0.39
rs3935032	1	MIB2	C	C	0.015	0.66
rs4656241	1	CRPP1; OR10J6P	A	C	0.035	0.81
rs4658403	1	AKT3	G	A	0.018	0.35
rs469882	1	RPL5P6; HFM1	C	T	0.020	0.52
rs531479718	1	IL6R	C	T	0.027	0.63
rs552693039	1	CELSR2	G	C	0.016	0.85

rs583040	1	PTPRF	A	T	0.018	0.33
rs630372	1	RP4-798P15.3; RP11-63B19.1	T	C	0.031	0.60
rs6686560	1	NEK7; ATP6V1G3	A	G	0.019	0.30
rs6695390	1	CAMTA1	A	G	0.013	0.31
rs7539725	1	UBE4B	G	C	0.022	0.68
rs75460349	1	ZDHHC18	C	T	0.059	0.99
rs787488	1	RP11-393N21.1; RN7SL392P	C	T	0.013	0.73
rs946551	1	LINC00862	T	C	0.014	0.32
rs10497423	2	RP11-394I13.2; RP11-394I13.3	G	T	0.013	0.41
rs10498240	2	TRIP12	A	C	0.013	0.31
rs11689543	2	ADCY3	G	A	0.013	0.24
rs1260326	2	GCKR	T	C	0.014	0.62
rs12613751	2	SPHKAP	C	T	0.013	0.44
rs12620844	2	NCL	C	G	0.013	0.72
rs12621948	2	MEIS1	G	A	0.012	0.55
rs13021775	2	VIT; AC007382.1	C	T	0.026	0.83
rs13028310	2	TMEM18; AC093326.3	C	A	0.013	0.60
rs13416992	2	LINC01122; AC007131.1	A	G	0.013	0.65
rs1441169	2	RP11-105N14.2; RP11-105N14.3	G	A	0.029	0.96
rs17050272	2	AC073257.2; AC073257.1	G	C	0.023	0.07
rs1869358	2	AC074286.1	A	G	0.025	0.50
rs2161037	2	ABCB11; DHRS9	C	T	0.019	0.53
rs4141632	2	IL1R1	A	C	0.013	0.44
rs4246598	2	FABP1; THNSL2	G	A	0.012	0.32
rs56045434	2	EXOC6B	A	AT	0.016	0.54
rs570916461	2	NOP58	C	T	0.015	0.73
rs59916403	2	FARP2	G	A	0.016	0.67
rs6734238	2	IL1F10; RNU6-1180P	G	A	0.016	0.70
rs75265117	2	COBLL1	T	A	0.017	0.66
rs930035	2	TLK1	T	C	0.011	0.47
rs11708067	3	ADCY5	A	G	0.011	0.44
rs11711864	3	RARB	G	A	0.027	0.84
rs11928797	3	UBP1	G	A	0.018	0.38
rs13066686	3	NSUN3; ARMC10P1	T	G	0.014	0.64
rs1470560	3	ARPP21; RNU6-243P	G	A	0.212	0.97
rs1905505	3	RNU1-70P; KLF7P1	A	G	0.013	0.30
rs1969066	3	RP11-550I24.2	C	A	0.012	0.40
rs2280406	3	CTD-2330K9.3	G	A	0.031	0.94
rs2596937	3	SETD5	C	T	0.023	0.84
rs34169656	3	CPNE4	C	T	0.018	0.79
rs35415272	3	MBNL1	T	G	0.034	0.19
rs3732356	3	NR1I2	C	T	0.022	0.80
rs6443429	3	TBL1XR1	G	C	0.016	0.82
rs6768108	3	TRANK1; RNU6ATAC4P	C	T	0.025	0.23
rs6775319	3	AC144521.1	A	G	0.022	0.21
rs6792725	3	THRB	C	T	0.014	0.28
rs6801781	3	FOXP1	A	G	0.050	0.47
rs687339	3	RP11-463H24.1; PCCB	G	A	0.013	0.49
rs7639927	3	ITPR1	C	T	0.013	0.70
rs10008492	4	RNA5SP158; TLR10	T	C	0.014	0.35
rs10027275	4	ARHGAP10	G	C	0.014	0.26

rs141936164	4	AF213884.2; AF213884.1	C	C	0.014	0.35
rs4690098	4	HGFAC	C	T	0.017	0.39
rs72712556	4	MAML3	G	T	0.018	0.86
rs74904971	4	ABCG2	A	C	0.095	0.98
rs7662792	4	RP11-362I1.1; PRKRIRP9	A	G	0.014	0.72
rs78716428	4	KIT; AC006552.1	G	A	0.013	0.39
rs10078214	5	YTHDC2	A	C	0.013	0.76
rs12516176	5	TNIP1	G	A	0.012	0.67
rs166169	5	MAP3K1; AC008937.3	C	T	0.031	0.07
rs17056278	5	EBF1	G	C	0.013	0.75
rs2161374	5	CTB-79E8.2; RP11-779O18.1	G	A	0.016	0.17
rs2289852	5	CYFIP2	G	A	0.022	0.08
rs245767	5	RANBP17	C	T	0.024	0.56
rs288183	5	FBXL17	C	T	0.100	0.98
rs2926851	5	GRIA1	G	C	0.015	0.33
rs56821385	5	POLD2P1; NR2F1-AS1	C	T	0.013	0.45
rs6453434	5	JMY	C	T	0.017	0.34
rs6595549	5	RP11-436H11.1; ZNF608	C	T	0.011	0.57
rs72799498	5	AFF4	C	A	0.019	0.89
rs77704739	5	CTD-2288O8.1	A	C	0.021	0.61
rs12191817	6	LINC00271	C	T	0.015	0.60
rs12523793	6	LATS1; KATNA1	T	C	0.076	0.39
rs1338071	6	RGS17	A	C	0.012	0.40
rs1490384	6	MIR588; RNU6-200P	C	G	0.059	0.03
rs174373	6	TRAF3IP2-AS1	A	G	0.134	0.93
rs2177382	6	ANKS1A	A	G	0.049	0.03
rs2307377	6	ORC3	A	C	0.022	0.80
rs4354188	6	FRK	T	C	0.012	0.45
rs459625	6	TCF21; TBPL1	C	T	0.018	0.18
rs4714508	6	TFEB	C	T	0.017	0.39
rs5017416	6	MIR548A1; RNF144B	C	CAA	0.090	0.57
rs543492421	6	RP11-436D23.1	T	C	0.020	0.71
rs6920220	6	RP11-95M15.1; RP11-95M15.2	T	C	0.022	0.79
rs6925389	6	RREB1	T	A	0.021	0.19
rs7756870	6	L3MBTL3	G	C	0.013	0.57
rs113585586	7	ZMIZ2	C	T	0.016	0.18
rs114947103	7	CDHR3	A	G	0.014	0.26
rs11772470	7	GS1-259H13.10	T	G	0.012	0.34
rs1635852	7	JAZF1	C	T	0.019	0.85
rs17138528	7	AC073130.3; AC002066.1	T	C	0.017	0.13
rs1880241	7	AC002480.2; AC073072.5	T	C	0.018	0.88
rs2700938	7	AC083864.3	A	G	0.016	0.16
rs35462231	7	RP11-632K21.7; GIMAP4	T	C	0.015	0.80
rs3808348	7	CYP2W1	G	A	0.032	0.93
rs385417	7	CUX1	A	G	0.022	0.24
rs73137144	7	GTF2I	T	C	0.037	0.88
rs75229905	7	BAZ1B	A	G	0.019	0.90
rs7801838	7	RP11-309L24.6; IRF5	C	A	0.013	0.41
rs10095930	8	LINC00536	T	C	0.029	0.59
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rs11782130	8	PDLIM2	G	A	0.020	0.16

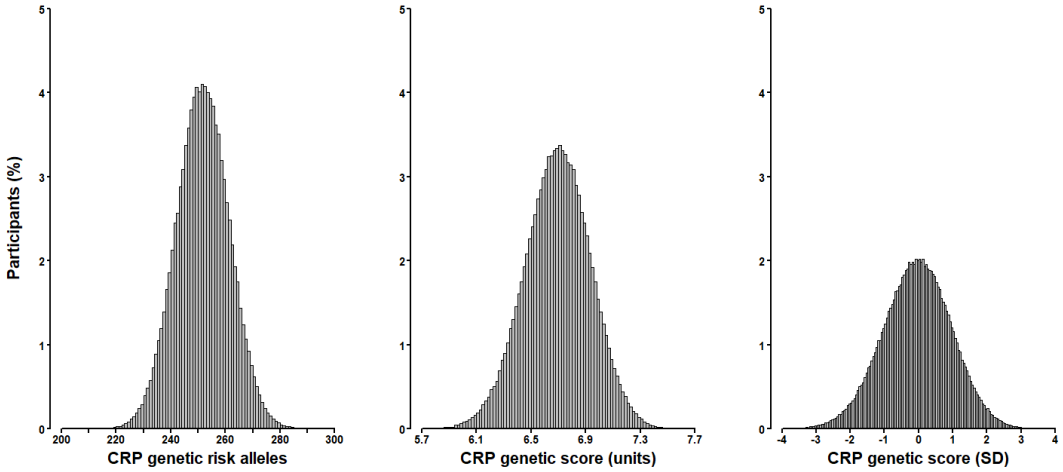
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rs4149349	9	ABCA1	T	C	0.018	0.58
rs424539	9	NFIB; RP11-408A13.2	G	T	0.017	0.55
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rs7908825	10	ZSWIM8	G	T	0.023	0.74
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rs11217192	11	CBL	T	G	0.013	0.73
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rs12270146	11	NA	G	C	0.013	0.39
rs2030291	11	SOX6	A	G	0.014	0.27
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rs4647725	11	DDB2	T	C	0.017	0.23
rs4755720	11	HSD17B12	C	A	0.034	0.72
rs62618693	11	QSER1	A	G	0.011	0.56
rs6486122	11	ARNTL	A	G	0.026	0.11
rs663015	11	STARD10; ARAP1	T	A	0.013	0.73
rs66553261	11	AMPD3	C	T	0.017	0.37
rs7103411	11	BDNF-AS	T	C	0.016	0.50
rs7127808	11	PACS1	A	G	0.019	0.81
rs75423534	11	OR4C11	T	C	0.048	0.96
rs7933202	11	MS4A6A; AP001257.1	C	T	0.020	0.65
rs10770829	12	GYS2	T	C	0.019	0.20
rs10880868	12	SCAF11	T	C	0.014	0.21
rs11047224	12	MIR920; SOX5	G	C	0.052	0.96
rs11054402	12	ETV6;RP11-434C1.1	C	T	0.012	0.60
rs12231235	12	RP11-490G8.1; RNU6-735P	C	T	0.040	0.62
rs17098829	12	AVPR1A; RSL24D1P5	A	C	0.034	0.13
rs1800693	12	TNFRSF1A	C	T	0.107	0.97
rs1800973	12	LYZ	A	T	0.053	0.97
rs2429473	12	SLC38A4	G	A	0.015	0.73
rs2657896	12	RBMS2	C	T	0.024	0.37

rs4764939	12	RP11-328J6.1	A	C	0.028	0.05
rs61946383	12	HNF1A-AS1; RPL12P33	T	G	0.018	0.65
rs7310135	12	RP11-567C2.1; RP11-654D12.2	A	G	0.016	0.71
rs77738620	12	NR1H4	G	T	0.015	0.28
rs7956514	12	APOLD1	A	C	0.021	0.27
rs12428361	13	LINC00676; LINC00399	C	T	0.020	0.69
rs34633805	13	SLITRK6	A	AAA	0.013	0.45
rs76620584	13	LINC00283; TEX30	C	T	0.020	0.42
rs7993752	13	VWA8; RPS28P8	C	T	0.012	0.34
rs9604045	13	LDHBP1; CUL4A	A	T	0.012	0.65
rs11156891	14	HNRNPC	T	A	0.016	0.80
rs11624418	14	RP11-293M10.2	T	C	0.020	0.10
rs146424514	14	KIAA0391; KIAA0391	A	G	0.012	0.37
rs2239222	14	RGS6	C	T	0.012	0.67
rs28929474	14	SERPINA1	T	C	0.012	0.46
rs34864350	14	RP11-349A22.5	G	T	0.024	0.07
rs55981844	14	AK7	C	T	0.038	0.03
rs72694393	14	NYNRIN	G	A	0.018	0.50
rs149624078	15	WDR72; RP11-209E8.1	A	G	0.015	0.39
rs1532085	15	ALDH1A2	C	T	0.024	0.78
rs189400382	15	VPS13C	A	G	0.020	0.29
rs339969	15	RP11-219B17.1	C	A	0.014	0.74
rs55707100	15	MAP1A	G	A	0.027	0.40
rs62011286	15	AC007950.1; USP3	T	C	0.030	0.69
rs72730950	15	RP11-313P18.1	T	C	0.014	0.76
rs12716972	16	KCTD13	G	A	0.021	0.54
rs12927172	16	IL4R	T	C	0.016	0.60
rs17616063	16	HNRNPA1P48; RP11-437L7.1	T	C	0.016	0.55
rs4018180	16	RP11-304L19.2	G	C	0.012	0.39
rs4788095	16	RP11-1348G14.5	T	G	0.012	0.38
rs4988483	16	SSTR5	C	T	0.024	0.32
rs56094641	16	FTO	G	A	0.013	0.63
rs562609617	16	RP11-345M22.1	T	C	0.036	0.07
rs60037105	16	ZFPM1	C	T	0.030	0.96
rs6500446	16	FANCA	T	G	0.011	0.43
rs67890964	16	RP11-505K9.4	G	A	0.015	0.61
rs1037170	17	CD300LF; RAB37	T	C	0.028	0.71
rs11078597	17	MIR22HG	T	C	0.019	0.81
rs11653826	17	NUFIP2; RPL35AP35	G	A	0.042	0.95
rs11868378	17	RP11-806H10.4	C	A	0.019	0.88
rs1292061	17	VMP1	A	G	0.019	0.39
rs142122735	17	ASGR1	A	G	0.021	0.47
rs145604770	17	RP11-387H17.4	A	G	0.016	0.17
rs149394327	17	APOH	C	T	0.140	0.99
rs17138478	17	HNF1B	T	C	0.012	0.73
rs178826	17	NCOR1	T	C	0.022	0.60
rs3785568	17	SCN4A	C	T	0.015	0.64
rs4468667	17	BPTF	C	T	0.088	0.20
rs577034922	17	ZZEF1	T	G	0.017	0.35
rs68085814	17	IGF2BP1; CTD-2244F11.2	A	G	0.016	0.43
rs8072566	17	STAT3	A	C	0.017	0.25
rs10871777	18	RP11-795H16.2; RNU4-17P	G	A	0.020	0.24
rs12605964	18	ZBTB7C	G	A	0.012	0.34

rs2542153	18	PTPN2; RP11-973H7.1	C	T	0.017	0.22
rs34284056	18	ZCCHC2	G	A	0.030	0.05
rs55855238	18	ONECUT2; ST8SIA3	G	G	0.018	0.31
rs59427082	18	NPM1P2; TAF4B	T	C	0.028	0.80
rs11666245	19	ZNF573	A	C	0.030	0.04
rs11667234	19	CARM1	T	A	0.019	0.45
rs123698	19	PTBP1	C	T	0.014	0.26
rs12459419	19	CD33	C	T	0.015	0.27
rs147711004	19	PVRL2; BCAM	C	T	0.028	0.50
rs1688043	19	HPN-AS1	C	A	0.034	0.04
rs1801272	19	CYP2A6	T	C	0.017	0.24
rs2239949	19	ARHGAP33	C	T	0.018	0.45
rs516316	19	FUT2	T	C	0.069	0.03
rs58542926	19	TM6SF2	C	T	0.018	0.30
rs59737437	19	GNG7	A	G	0.082	0.65
rs1056441	20	LIME1	C	T	0.021	0.68
rs12220	20	NPEPL1	C	A	0.015	0.34
rs1800961	20	HNF4A	A	C	0.029	0.06
rs1886008	20	TAF4	G	A	0.012	0.39
rs2207132	20	SNORD112; MAFB	G	A	0.036	0.36
rs2261790	20	PYGB	T	C	0.012	0.37
rs6020459	20	RP11-290F20.2; RN7SL636P	A	G	0.015	0.23
rs6073958	20	PCIF1; PLTP	A	C	0.013	0.35
rs16988471	21	TPT1P1; AP000255.6	A	G	0.011	0.40
rs2156407	21	AP000688.14	A	G	0.021	0.55
rs4817984	21	AF064858.10; RPL23AP12	T	G	0.027	0.05
rs6519133	22	JOSD1	G	A	0.045	0.40
rs9611454	22	RBX1; Y_RNA	T	C	0.012	0.35

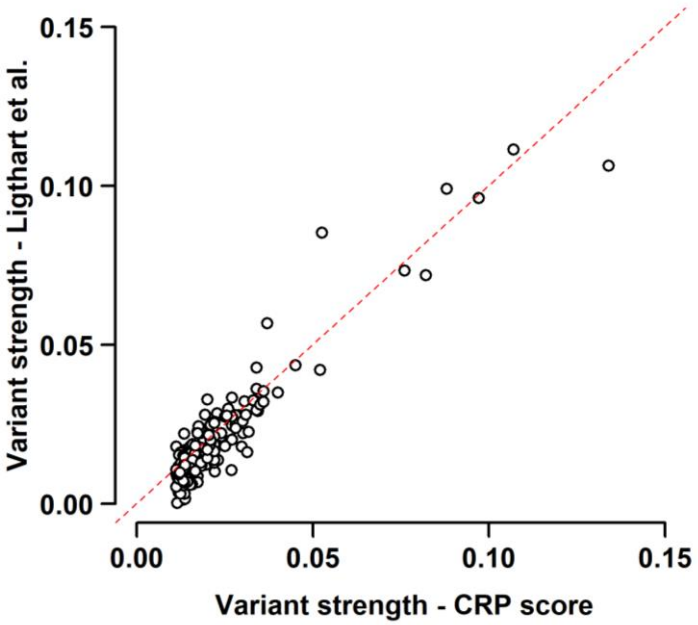
Variants oriented so that effect allele is associated with greater C-reactive protein in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

1



Appendix Figure I.25: Distribution of C-reactive protein variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of C-reactive protein genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher C-reactive protein. CRP – C-reactive protein, SD – standard deviation.



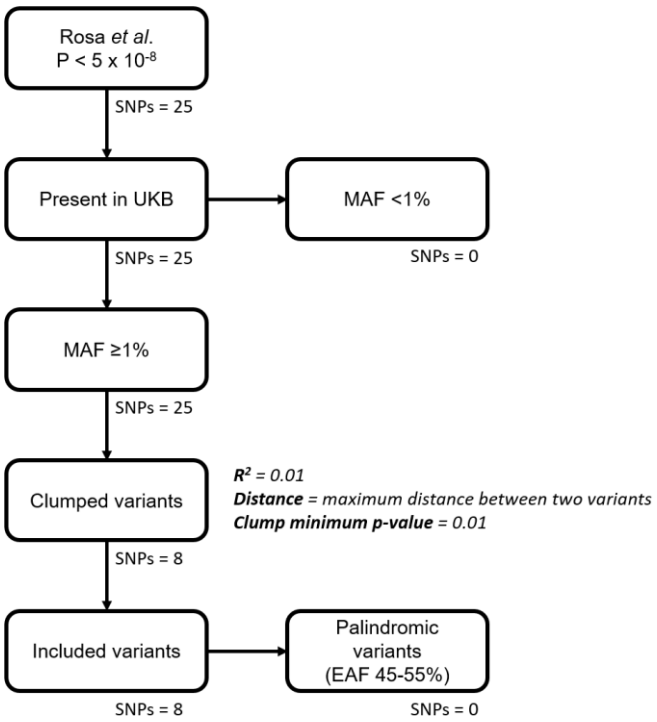
Appendix Figure I.26: Scatter plot of beta values from C-reactive protein genome-wide associations study including and excluding UK Biobank.

Variant strength displayed as per-allele effect estimates. Effect estimate values for the C-reactive protein score identified from summary data,[340] *and compared against per-allele effect estimate values from a prior C-reactive protein genome-wide association study excluding UK Biobank data.*[367] *Variants included if either variant itself or suitable proxy identified within the summary data for the genome-wide association study excluding UK Biobank data (n=200). The red dotted line represents the line of parity. CRP – C-reactive protein.*

I.10. Selection of genetic variants for interleukin-6 score

A genetic score for soluble interleukin-6 receptor (sIL6R) levels has previously been developed.[120] This was generated by taking variants within ± 250kb of the *IL6R* gene that were found to be associated with sIL6R concentrations in a previous proteomic analysis which did not involve UKB data.[501] sIL6R levels were adjusted for age, sex, duration between blood draw and processing and for three principal components of ancestry.

Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ within a distance of 472,626 base pairs (maximum distance between any two variants) using a reference panel from UKB. Eight variants were included in the IL6R score (**Appendix Figure I.27**, **Appendix Table I.10**). The median F-stat for included variants was 54 (range 37 to 5,042). The proportion of variance explained was 74%. Risk alleles for selected variants and the developed IL6R genetic score were normally distributed in UKB (**Appendix Figure I.28**).



Appendix Figure I.27: Flowchart of variant selection for interleukin-6 receptor score.
Variants identified from Rosa et al.[120] *EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.*

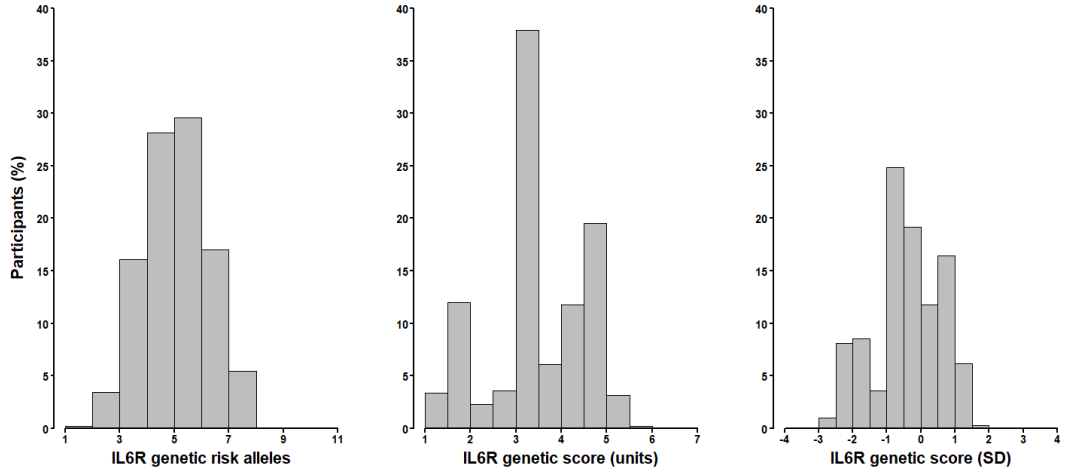
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Appendix Table I.10: Variants included in interleukin-6 receptor score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs116805289	1	TDRD10	A	C	0.627	0.98
rs139952834	1	IL6R	C	T	0.651	0.99
rs149551556	1	UBE2Q1	C	T	0.665	0.98
rs3766924	1	ADAR	C	T	0.386	0.79
rs4129267	1	IL6R	T	C	1.115	0.40
rs61806853	1	TPM3	C	T	0.496	0.05
rs76518735	1	SHE	A	C	0.565	0.98
rs79925547	1	IL6R	T	C	0.752	0.01

Variants oriented so that effect allele is associated with higher interleukin-6 receptor levels in the original GWAS. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

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Appendix Figure I.28: Distribution of interleukin-6 receptor variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of Interleukin-6 receptor genetic score values and risk alleles in the UK Biobank population. Risk alleles defined as those associated with higher IL6R. IL6R – Interleukin-6 receptor, SD – standard deviation.

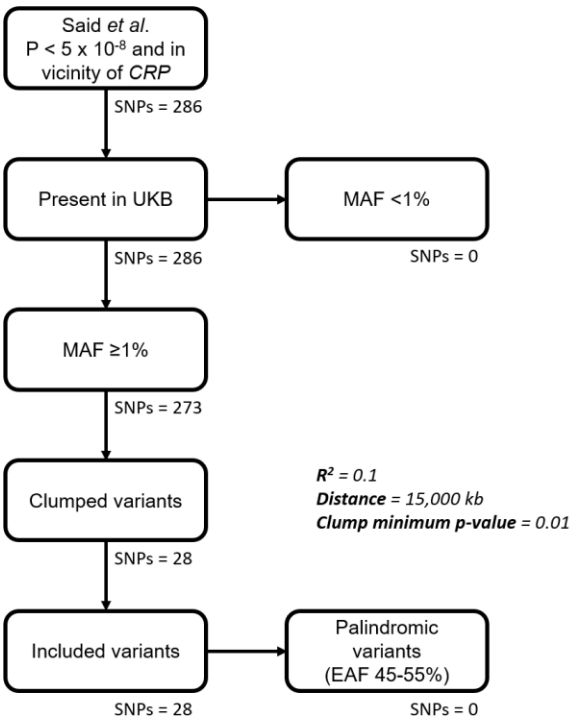
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I.11. Selection of genetic variants for cis C-reactive protein score (cis-CRP)

To further investigate the direct effect of CRP on cardiovascular phenotypes, a genetic score of cis-acting SNPs at the *CRP* gene was developed. Variants were identified from summary statistics from the same GWAS used for the CRP genetic score.[340] Variants meeting a genome-wide significance threshold ($p<5 \times 10^{-8}$) and within the vicinity of the *CRP* gene were identified. As in the original GWAS, the window around the *CRP* gene was between 50kb downstream of the nearest gene upstream of *CRP* [*APCS*] and 50kb downstream of the *CRP* gene were selected (in build 37, this is between 159,608,655 and 159,734,379 base pairs on chromosome 1).[340] Variants were clumped using a LD threshold of $r^2<0.1$ and all variants considered within the same window. Twenty-eight variants were included in the cis-CRP score (**Appendix Figure I.29, Appendix Table I.11**). The median F-statistic for included variants was 256 (range 31 to 7,056). The proportion of variance explained was 4.0%. Risk alleles for selected variants and the developed cis-CRP genetic score were normally distributed in UKB (**Appendix Figure I.30**).



Appendix Figure I.29: Flowchart of variant selection for cis-C-reactive protein.
Variants identified from Said et al. [340] EAF – effect allele frequency; MAF – minor allele frequency, SNPs – single nucleotide polymorphisms, UKB – UK Biobank.

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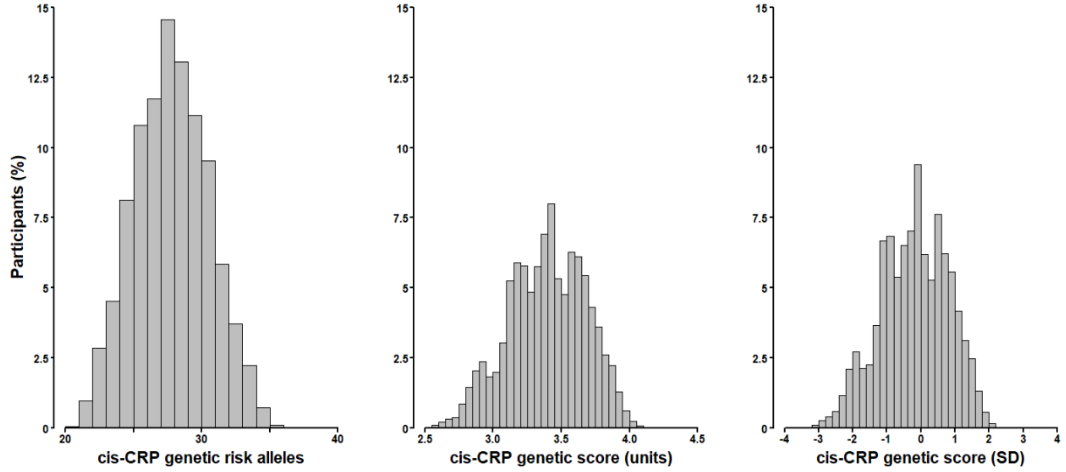
Appendix Table I.11: Variants included in cis-C-reactive protein score

RSID	Chr	Effect allele	Other allele	Weighting for score	EAF (UKB)
_1_159683234	1	G	GCGGGAGGTACCAGAGACA GAGACGTGGGGCCCATGC GGTGTAAAAAAC	0.057	0.02
rs11265263	1	C	A	0.230	0.93
rs113188187	1	T	C	0.121	0.02
rs115585839	1	T	G	0.114	0.02
rs11579148	1	C	T	0.301	0.99
rs11589667	1	C	T	0.035	0.66
rs116073407	1	A	G	0.070	0.02
rs116247097	1	G	A	0.123	0.02
rs116337989	1	A	G	0.067	0.98
rs116702045	1	G	A	0.145	0.96
rs12026296	1	T	C	0.062	0.92
rs12094103	1	A	G	0.091	0.35
rs12116869	1	T	C	0.072	0.08
rs12760385	1	G	A	0.138	0.02
rs151313645	1	C	A	0.101	0.98
rs188497920	1	G	A	0.146	0.01
rs200372148	1	G	GT	0.076	0.98
rs2592904	1	T	C	0.058	0.36
rs3091244	1	A	G	0.138	0.06
rs3093070	1	G	T	0.115	0.02

rs368274510	1	T	C	0.015	0.36
rs547550247	1	C	A	0.074	0.99
rs58785319	1	ACACC	A	0.119	0.01
rs61821592	1	C	T	0.086	0.98
rs72698563	1	T	A	0.101	0.96
rs7551731	1	T	C	0.176	0.67
rs76769546	1	G	A	0.029	0.95
rs77013776	1	A	C	0.257	0.96

Variants oriented so that effect allele is associated with higher C-reactive protein in the original GWAS. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank.

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Appendix Figure I.30: Distribution of cis-C-reactive protein variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of cis-C-reactive protein genetic score values and risk alleles in the UK Biobank population. Risk alleles defined as those associated with higher C-reactive protein. CRP – C-reactive protein, SD – Standard deviation.

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I.12. Selection of inflammatory protein genetic scores

A GWAS meta-analysis of proteomic analyses examined 92 proteins in ~31,000 individuals not including data from UKB.[343] This identified variants associated with 85 proteins of which 24 were identified as having an inflammatory nature and sufficient proportion of variance explained. Inflammatory proteins were identified as being presented on one or more commercially available inflammatory protein panels or significant alternative evidence supporting an inflammatory role (**Appendix Table I.12**). Proteins were further sub-categorised by protein family into chemokines, growth factors, interleukins, matrix metalloproteinases, TNF-related, and other for display purposes.

Protein levels were inverse-normal transformed. Summary data were taken from the meta-analysis and variants identified in UKB. Additional clumping of SNPs was performed utilising a linkage disequilibrium (LD) threshold of $r^2<0.01$ with a window equal to the maximum distance between any two variants on the same chromosome using a reference panel from UKB. Variants included in the final scores are shown in **Appendix Table I.13**.

Appendix Table I.12: Inflammatory proteins identified from proteomic analysis

Protein	Name	Inflammatory protein group	Inflammatory panel or other evidence
CCL3	C-C motif chemokine 3	Chemokine	Olink, BioLegend
CCL4	C-C motif chemokine 4	Chemokine	Olink, BioLegend
CD40	TNF receptor superfamily member 5	TNF-related	Olink
CXCL1	C-X-C motif chemokine 1	Chemokine	Olink
CXCL6	C-X-C motif chemokine 6	Chemokine	Olink, Thermofisher
CXCL16	C-X-C motif chemokine 16	Chemokine	[502]
GAL3	Galectin-3	Other	Thermofisher
GDF15	Growth/differentiation factor 15	Growth factor	[503]
IL1RA	Interleukin-1 receptor antagonist	Interleukin	BioLegend
IL16	Interleukin-16	Interleukin	Thermofisher
IL18	Interleukin-18	Interleukin	Olink, Thermofisher, BioLegend
IL27	Interleukin-27	Interleukin	Olink, Thermofisher, BioLegend
MMP1	Matrix metalloproteinase-1	Matrix metalloprotease	Olink, Thermofisher, BioLegend
MMP3	Matrix metalloproteinase-3	Matrix metalloprotease	[504]
MMP10	Matrix metalloproteinase-10	Matrix metalloprotease	Olink
MMP12	Matrix metalloproteinase-12	Matrix metalloprotease	Olink
PTX3	Pentraxin-related protein PTX3	TNF-related	Thermofisher, BioLegend
RETN	Resistin	Other	BioLegend
SCF	Stem cell factor	Growth factor	Thermofisher
ST2	ST2 protein	Interleukin	BioLegend
TNFSF14	TNF ligand superfamily member 14	TNF-related	Olink
TRAIL	TNF-related apoptosis-inducing ligand	TNF-related	Olink, Thermofisher
VEGFA	Vascular endothelial growth factor A	Growth factor	Olink, Thermofisher
YKL40	Chitinase-3-like protein 1	Other	[505,506]

Olink – present in the Olink Target 96 Inflammation or Target 48 Cytokine panels[507]; **Thermofisher** – present in the ThermoFisher 80-Plex immune response panel[508]; **BioLegend** – present in inflammation, cytokine, or chemokine panels[509]. TNF – Tumour Necrosis Factor

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Appendix Table I.13: Variants for inflammatory proteins identified from proteomic analysis included in genetic scores

Protein	Initial variants	Present in UKB	MAF ≥1%	Clumped variants	Palindromic variants	Included variants
CCL3	8	8	8	5	0	5
CCL4	8	8	8	7	0	7
CD40	3	3	3	3	0	3
CXCL1	4	4	3	3	0	3
CXCL6	4	4	3	3	0	3
CXCL16	14	14	14	3	0	14
GAL3	12	12	12	9	0	9
GDF15	4	4	0	3	0	3
IL1RA	6	6	0	4	0	4
IL16	11	11	8	6	0	6
IL18	11	11	11	8	0	8
IL27	15	15	15	12	0	12
MMP1	10	10	8	7	0	7
MMP3	8	8	8	7	0	7
MMP10	7	7	7	6	0	6
MMP12	6	6	6	6	0	6
PTX3	6	6	6	5	0	5
RETN	15	15	14	12	0	12
SCF	17	17	17	16	0	16
ST2	10	10	9	6	0	6
TNFSF14	5	5	5	4	0	4
TRAIL	8	8	8	8	0	8
VEGFA	5	5	5	5	1	4
YKL40	5	5	5	5	0	5

CD40 – TNF receptor superfamily member 5, CRP – C-reactive protein, CCL – C-C motif chemokine, CXCL – C-X-C motif chemokine, GAL – galectin-3, GDF – growth/differenation factor, IL – interleukin, MAF – minor allele frequency, *MMP – matrix metalloproteinase, PTX – pentraxin-related protein, RETN – resistin, SCF – stem cell factor, ST2 – ST protein, TNF – tumour necrosis factor, TNFSF14 – TNF ligand superfamily member 14, TRAIL – TNF-related apoptosis-inducing ligand, UKB – UK Biobank, VEGF – vascular endothelial growth factor, YKL40 – chitinase-3-like protein 1*

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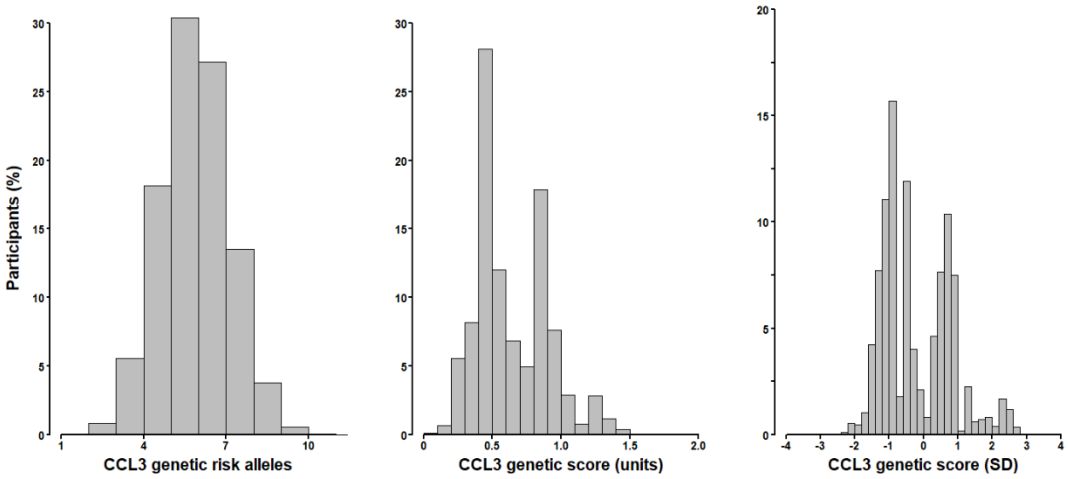
I.12.1. CCL3 (C-C motif chemokine 3) genetic score

Five variants were included in the CCL3 genetic score (**Appendix Table I.14**). The median F-stat for included variants was 39 (range 30 to 1,111). The proportion of variance explained was 6.6%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.31**).

Appendix Table I.14: Variants included in CCL3 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4543123	4	TLR1	G	A	0.074	0.21
rs3184504	12	SH2B3	T	C	0.069	0.46
rs112911514	16	PLCG2	T	G	0.120	0.93
rs1634517	17	CCL4	A	C	0.400	0.24
rs9911791	17	TBC1D3G	A	G	0.130	0.83

Variants oriented so that effect allele is associated with greater CCL3 in the original genome-wide association study. Ordered by chromosome. CCL3 – C-C motif chemokine 3, Chr – Chromosome, EAF – effect allele frequency, UKB – UK Biobank



Appendix Figure I.31: Distribution of CCL3 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of C-C motif chemokine 3 genetic score values and risk alleles in the UK Biobank population. Risk alleles defined as those associated with higher CCL3. CCL3 – C-C motif chemokine 3, SD – standard deviation..

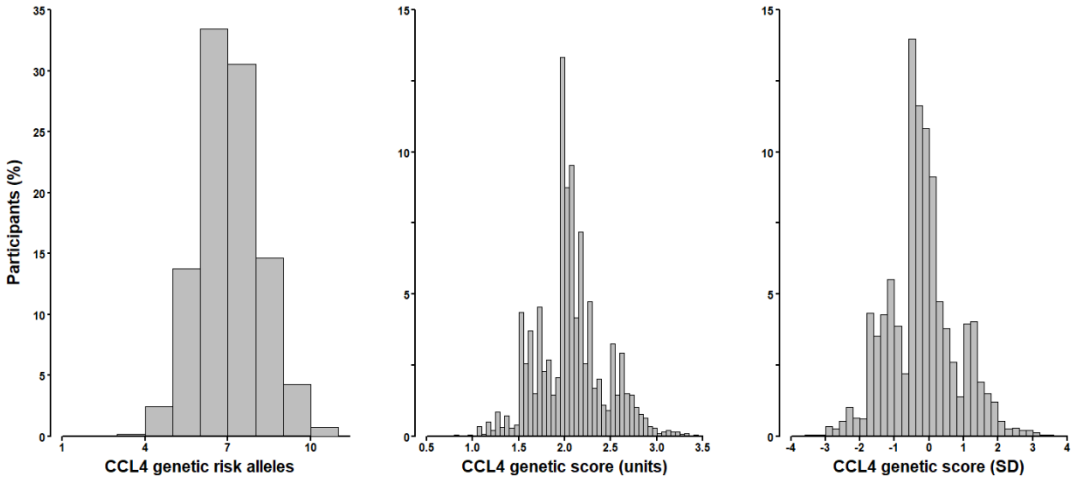
I.12.2. CCL4 (C-C motif chemokine 4) genetic score

Seven variants were included in the CCL4 genetic score (**Appendix Table I.15**). The median F-stat for included variants was 89 (range 34 to 1,164). The proportion of variance explained was 13.3%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.32**).

Appendix Table I.15: Variants included in CCL4 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs113010081	3	CCRL2	C	T	0.580	0.11
rs5743604	4	TLR1	G	A	0.082	0.22
rs211997	17	MRM1	A	G	0.320	0.97
rs2376468	17	CCL4	G	C	0.120	0.24
rs8064426	17	TBC1D3G	G	A	0.440	0.86
rs17692864	17	GGNBP2	T	C	0.240	0.94
rs79943102	17	MRM1	T	C	0.220	0.09

Variants oriented so that effect allele is associated with greater CCL4 in the original genome-wide association study. Ordered by chromosome. CCL4 – C-C motif chemokine 4, Chr – Chromosome, EAF – effect allele frequency, UKB – UK Biobank



Appendix Figure I.32: Distribution of CCL4 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of C-C motif chemokine 4 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher CCL4. CCL4 – C-C motif chemokine 4, SD – standard deviation.

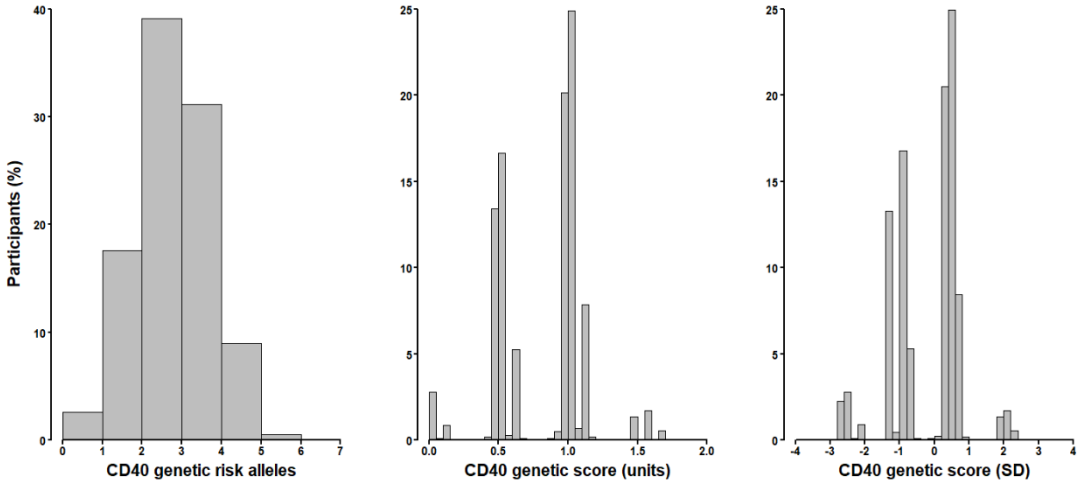
I.12.3. CD40 (Tumour necrosis factor receptor superfamily member 5) genetic score

Three variants were included in the CD40 genetic score (**Appendix Table I.16**). The median F-stat for included variants was 165 (range 48 to 1,736). The proportion of variance explained was 10.7%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.33**).

Appendix Table I.16: Variants included in CD40 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4801216	19	ZNF543	C	T	0.090	0.39
rs4810485	20	CD40	G	T	0.500	0.76
rs41282788	20	CD40	C	G	0.540	0.02

Variants oriented so that effect allele is associated with greater CD40 in the original genome-wide association study. Ordered by chromosome. CD40 – Tumour necrosis factor receptor superfamily member 5, Chr – Chromosome, EAF – effect allele frequency, UKB – UK Biobank.



Appendix Figure I.33: Distribution of CD40 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Tumour necrosis factor receptor superfamily member 5 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher CD40. CD40 – Tumour necrosis factor receptor superfamily member 5, SD – standard deviation.

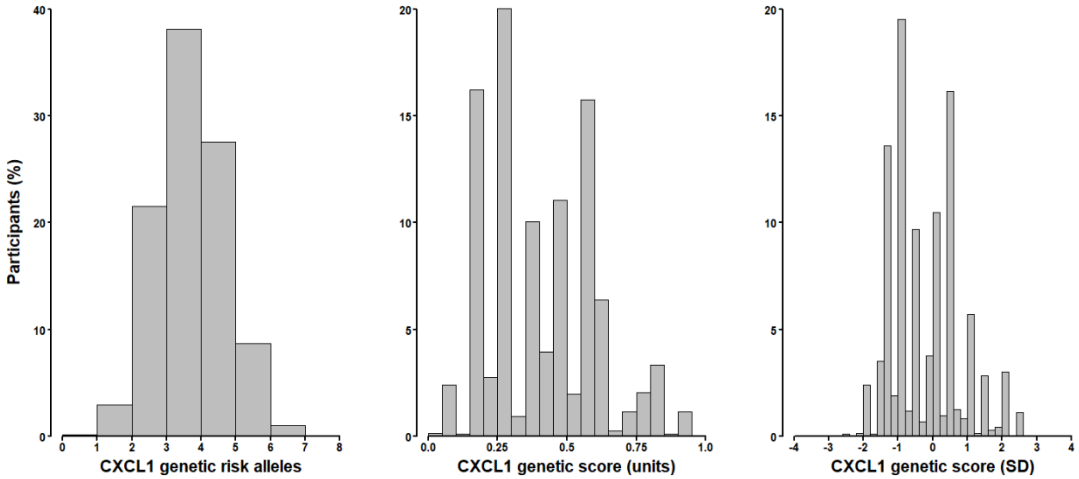
I.12.4. CXCL1 (C-X-C motif chemokine 1) genetic score

Three variants were included in the CXCL1 genetic score (**Appendix Table I.17**). The median F-stat for included variants was 69 (range 36 to 544). The proportion of variance explained was 4.1%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.34**).

Appendix Table I.17: Variants included in CXCL1 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs3117604	4	CXCL1	C	T	0.280	0.31
rs78716942	4	ALB	G	A	0.120	0.91
rs7896518	10	JMJD1C	G	A	0.087	0.43

Variants oriented so that effect allele is associated with greater CXCL1 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome, CXCL1 – C-X-C motif chemokine 1, EAF – effect allele frequency, UKB – UK Biobank



Appendix Figure I.34: Distribution of CXCL1 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of C-X-C motif chemokine 1 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher CXCl1. CXCL1 – C-X-C motif chemokine 1, SD – standard deviation.

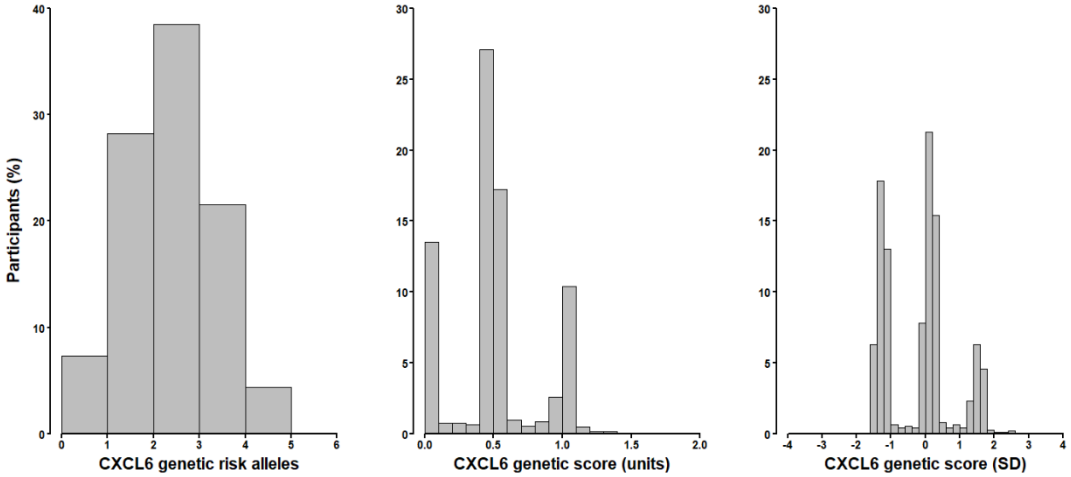
I.12.5. CXCL6 (C-X-C motif chemokine 6) genetic score

Three variants were included in the CXCL6 genetic score (**Appendix Table I.18**). The median F-stat for included variants was 39 (range 32 to 1,951). The proportion of variance explained was 14.1%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.35**).

Appendix Table I.18: Variants included in CXCL6 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs12075	1	ACKR1	A	G	0.062	0.58
rs5836103	2	SCN7A	C	CT	0.320	0.03
rs16850073	4	CXCL6	T	C	0.530	0.37

Variants oriented so that effect allele is associated with greater CXCL6 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome, CXCL6 – C-X-C motif chemokine 6, EAF – effect allele frequency, UKB – UK Biobank.



Appendix Figure I.35: Distribution of CXCL6 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of C-X-C motif chemokine 6 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher CXCL6. CXCL6 – C-X-C motif chemokine 6, SD – standard deviation.

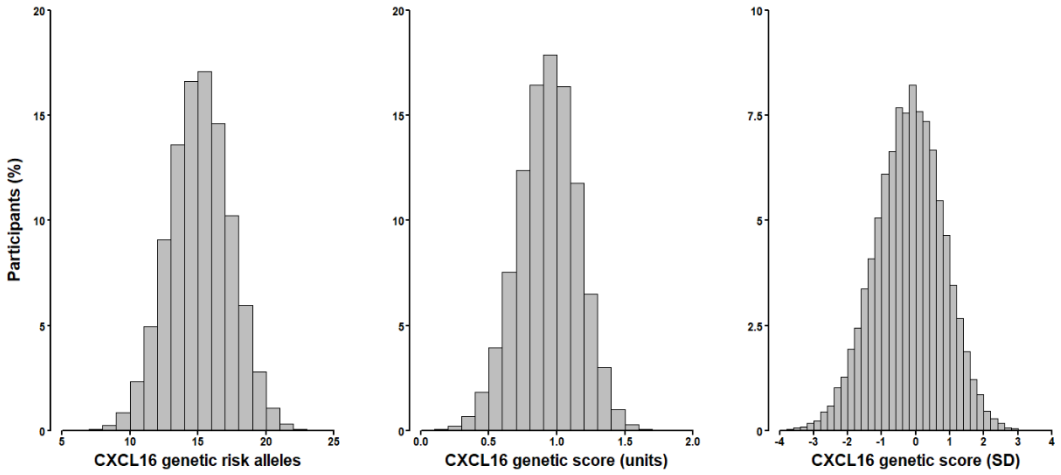
I.12.6. CXCL16 (C-X-C motif chemokine 16) genetic score

Fourteen variants were included in the CXCL16 genetic score (**Appendix Table I.19**). The median F-statistic for included variants was 53 (range 29 to 201). The proportion of variance explained was 4.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.36**).

Appendix Table I.19: Variants included in CXCL16 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs2009581	2	ACOXL	A	G	0.130	0.28
rs2175824	2	ACOXL	G	T	0.070	0.59
rs1029732	3	LZTFL1	A	G	0.062	0.28
rs1602580	3	CCR1	C	T	0.100	0.8
rs35087390	6	HLA-DQA1	G	A	0.270	0.98
rs748113	10	CDH23	T	C	0.081	0.57
rs1250559	10	ZMIZ1	G	A	0.072	0.6
rs34775308	11	RPS3	T	G	0.080	0.88
rs10774624	12	SH2B3	A	G	0.071	0.53
rs4790231	17	TM4SF5	A	G	0.095	0.5
rs35186877	17	ARRB2	G	A	0.170	0.79
rs113120414	17	ABCA8	G	A	0.120	0.06
rs6512104	19	EPS15L1	G	A	0.065	0.33
rs6031303	20	TOX2	A	G	0.081	0.27

Variants oriented so that effect allele is associated with greater CXCL16 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome, CXCL16 – C-X-C motif chemokine 16, EAF – effect allele frequency, UKB – UK Biobank.



Appendix Figure I.36: Distribution of CXCL16 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of C-X-C motif chemokine 16 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher CXCL16. CXCL16 - C-X-C motif chemokine 16, SD – standard deviation.

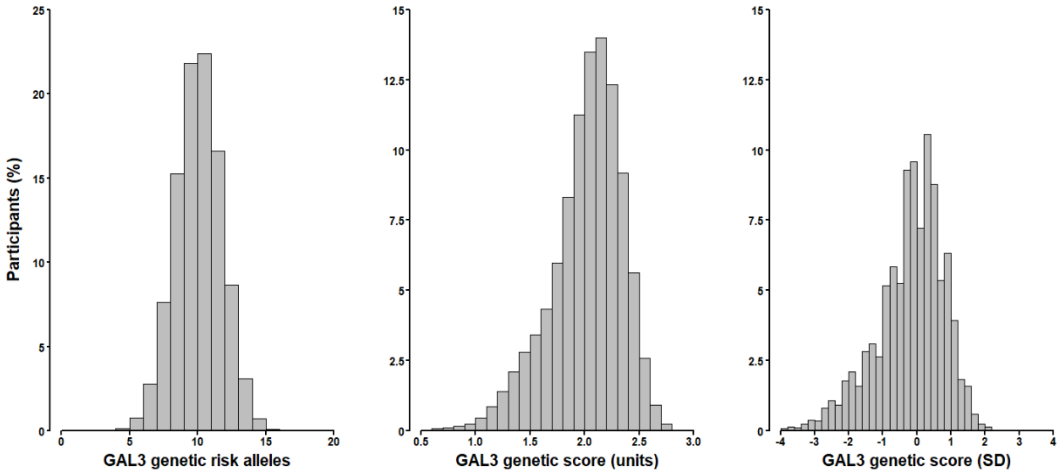
I.12.7. GAL3 (Galectin-3) genetic score

Nine variants were included in the GAL3 genetic score (**Appendix Table I.20**). The median F-stat for included variants was 88 (range 39 to 1,600). The proportion of variance explained was 12.2%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.37**).

Appendix Table I.20: Variants included in GAL3 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs3735080	7	GIMAP7	T	C	0.094	0.23
rs59379014	11	ST3GAL4	T	C	0.130	0.08
rs7979473	12	HNF1A	A	G	0.096	0.39
rs3742564	14	MAPK1IP1L	T	C	0.200	0.61
rs4363781	14	GCH1	A	G	0.100	0.87
rs76480089	14	ATG14	A	G	0.600	0.92
rs660745	19	MAMSTR	C	T	0.088	0.54
rs812936	19	FUT3	A	G	0.097	0.82
rs62143199	19	NLRP12	T	C	0.200	0.53

Variants oriented so that effect allele is associated with greater GAL3 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency; GAL3 - Galectin-3, UKB – UK Biobank.



Appendix Figure I.37: Distribution of GAL3 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Galectin-3 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher GAL3. GAL3 - Galectin-3, SD – standard deviation.

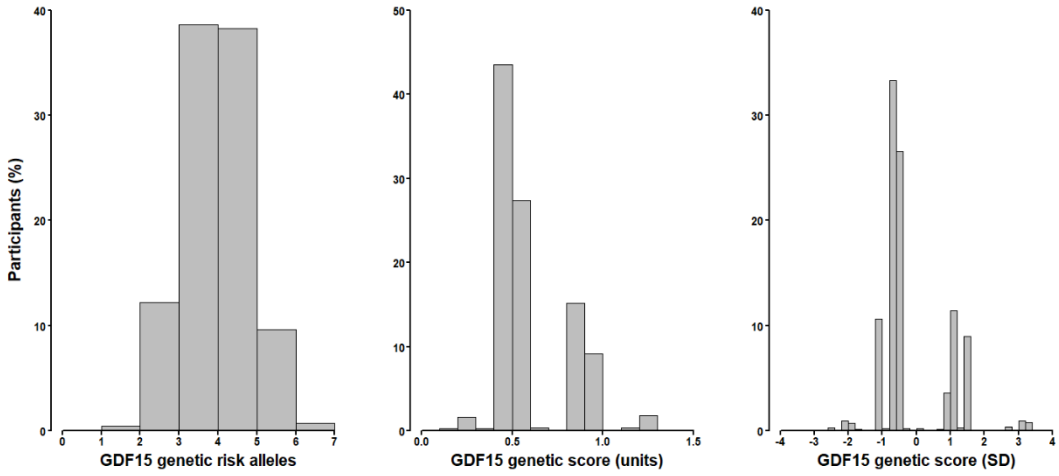
I.12.8. GDF15 (Growth/differentiation factor 15) genetic score

Three variants were included in the GDF15 genetic score (**Appendix Table I.21**). The median F-stat for included variants was 38 (range 33 to 810). The proportion of variance explained was 4.0%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.38**).

Appendix Table I.21: Variants included in GDF15 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs2517481	6	C6orf15	G	C	0.059	0.6
rs1227734	19	LRRC25	T	C	0.37	0.14
rs112253475	19	CRTC1	A	G	0.27	0.99

Variants oriented so that effect allele is associated with greater GDF15 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, GDF15 - Growth/differentiation factor 15, UKB – UK Biobank.



Appendix Figure I.38: Distribution of GDF15 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Growth/differentiation factor 15 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher GDF15. GDF15 - Growth/differentiation factor 15, SD – standard deviation.

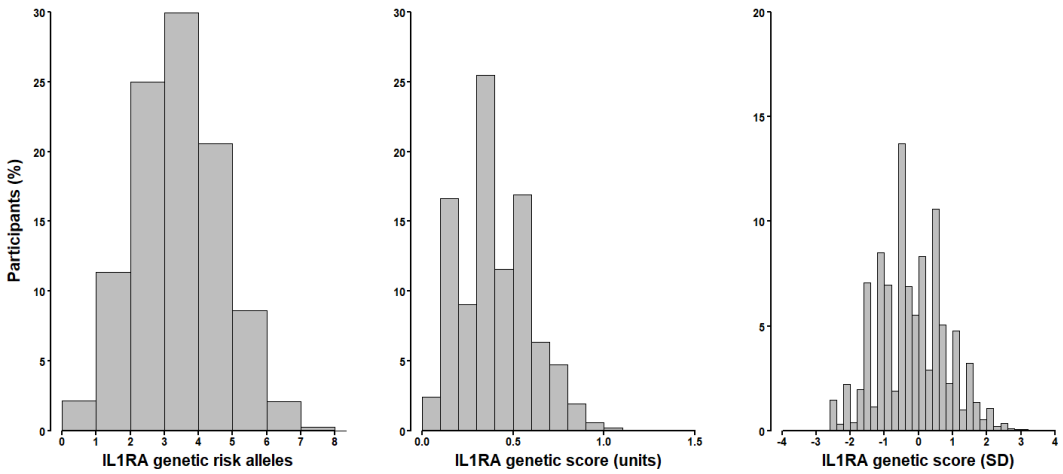
I.12.9. IL1RA (Interleukin-1 receptor antagonist) genetic score

Four variants were included in the IL1RA genetic score (**Appendix Table I.22**). The median F-statistic for included variants was 224 (range 35 to 400). The proportion of variance explained was 4.7%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.39**).

Appendix Table I.22: Variants included in Il1RA genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4848312	2	IL36B	A	G	0.140	0.31
rs6734238	2	IL1F10	A	G	0.200	0.60
rs149418433	17	PSMD3	A	AT	0.065	0.38
rs62143194	19	NLRP12	G	C	0.220	0.21

Variants oriented so that effect allele is associated with greater IL1RA in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, IL1RA - Interleukin-1 receptor antagonist, UKB – UK Biobank



Appendix Figure I.39: Distribution of IL1RA variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Interleukin-1 receptor antagonist genetic score values and risk alleles in the UK Biobank population. Risk alleles defined as those associated with higher IL1RA. IL1RA - Interleukin-1 receptor antagonist, SD – standard deviation.

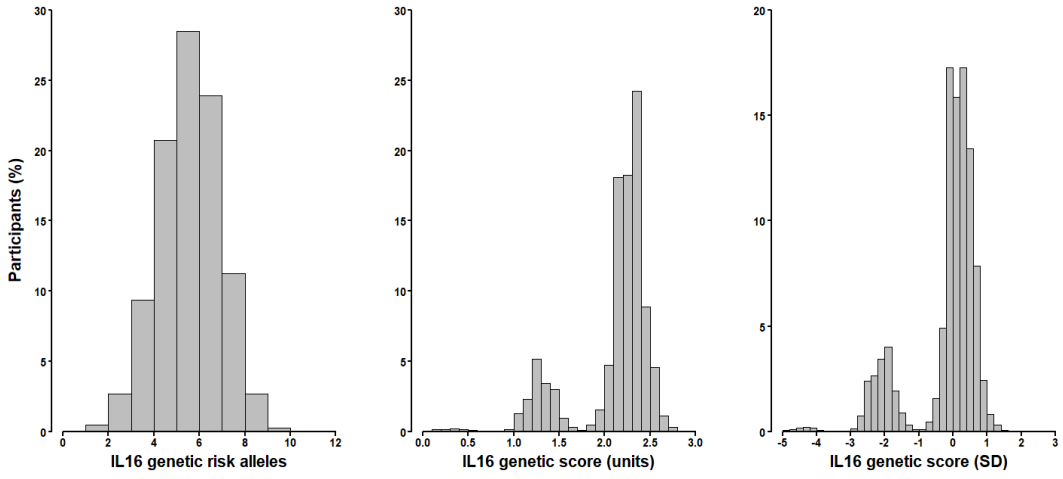
I.12.10. IL16 (Interleukin-16) genetic score

Six variants were included in the IL16 genetic score (**Appendix Table I.23**). The median F-stat for included variants was 64 (range 31 to 2,844). The proportion of variance explained was 14.7%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.40**).

Appendix Table I.23: Variants included in IL16 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs58623354	3	GRK7	G	T	0.078	0.77
rs117089718	9	MLLT3	C	T	0.220	0.04
rs859	15	IL16	A	G	0.140	0.73
rs1564641	15	STARD5	A	G	0.067	0.47
rs4778639	15	IL16	T	G	0.960	0.91
rs10424405	19	NLRP12	G	A	0.120	0.22

Variants oriented so that effect allele is associated with greater IL16 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, IL16 - Interleukin-16, UKB – UK Biobank.



Appendix Figure I.40: Distribution of IL16 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Interleukin-16 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher IL16. IL16 - Interleukin-16, SD – standard deviation.

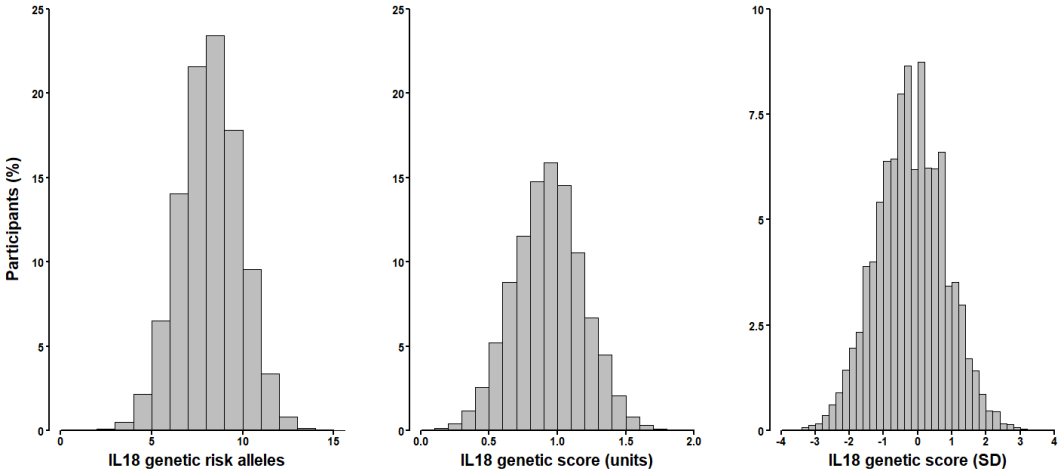
I.12.11. IL18 (Interleukin-18) genetic score

Eight variants were included in the IL18 genetic score (**Appendix Table I.24**). The median F-stat for included variants was 48 (range 32 to 341). The proportion of variance explained was 6.1%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.41**).

Appendix Table I.24: Variants included in IL18 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs385076	2	NLRC4	C	T	0.180	0.64
rs9867857	3	LEKR1	T	C	0.060	0.48
rs17229943	5	RAD17	C	A	0.180	0.05
rs916964	7	NFE2L3	C	G	0.074	0.79
rs4606077	8	NAPRT	C	T	0.088	0.76
rs5002812	11	CARD18	G	A	0.078	0.26
rs5744249	11	IL18	A	C	0.220	0.75
rs10424405	19	NLRP12	G	A	0.240	0.22

Variants oriented so that effect allele is associated with greater IL18 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, IL18 - Interleukin-18, UKB – UK Biobank.



Appendix Figure I.41: Distribution of IL18 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Interleukin-18 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher IL18. IL18 - Interleukin-18, SD – standard deviation.

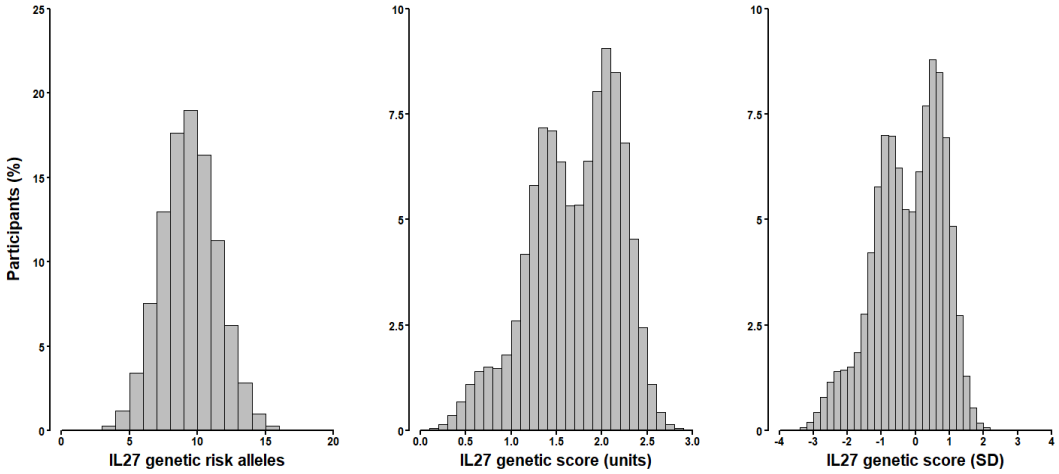
I.12.12. IL27 (Interleukin-27) genetic score

Twelve variants were included in the IL27 genetic score (**Appendix Table I.25**). The median F-stat for included variants was 43 (range 30 to 4,489). The proportion of variance explained was 24.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.42**).

Appendix Table I.25: Variants included in IL27 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs1257169	2	MGAT5	C	A	0.097	0.48
rs11711157	3	CPN2	C	T	0.090	0.72
rs9715769	4	TLR10	C	A	0.096	0.15
rs11599750	10	CPN1	C	T	0.180	0.60
rs10774624	12	SH2B3	G	A	0.076	0.47
rs10843390	12	ERGIC2	T	C	0.062	0.29
rs704	17	VTN	G	A	0.130	0.52
rs111072793	17	ASGR1	A	C	0.098	0.19
rs4905	19	EBI3	A	G	0.670	0.70
rs59975010	19	ZNF799	C	T	0.084	0.25
rs150106684	19	EBI3	C	G	0.250	0.04
rs12625762	20	ERGIC3	A	G	0.082	0.14

Variants oriented so that effect allele is associated with greater IL27 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, IL27 - Interleukin-27, UKB – UK Biobank.



Appendix Figure I.42: Distribution of IL27 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Interleukin-27 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher IL27. IL27 - Interleukin-27, SD – standard deviation.

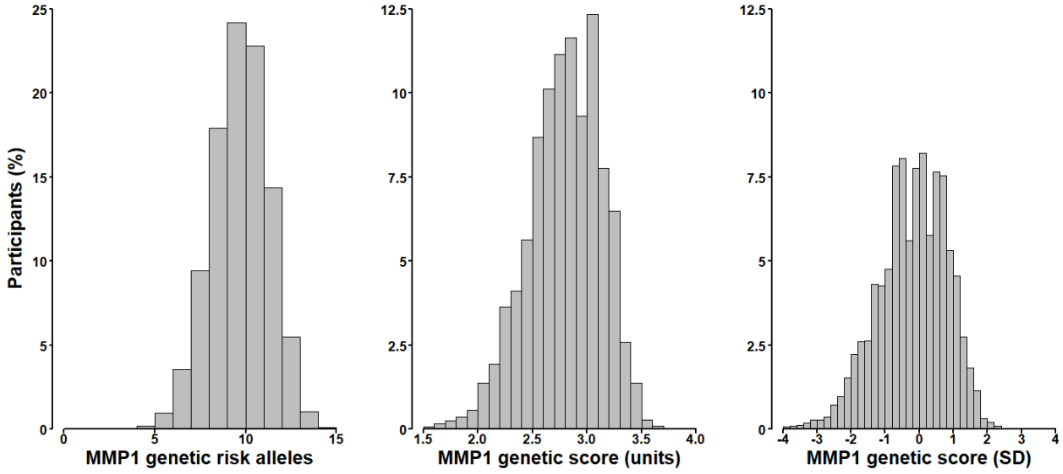
I.12.13. MMP1 (Matrix metalloproteinase-1) genetic score

Seven variants were included in the MMP1 genetic score (**Appendix Table I.26**). The median F-statistic for included variants was 133 (range 40 to 1,071). The proportion of variance explained was 11.2%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.43**).

Appendix Table I.26: Variants included in MMP1 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs12141791	1	MEF2D	A	G	0.083	0.70
rs6993770	8	ZFPM2	A	T	0.120	0.71
rs471994	11	MMP3	G	A	0.360	0.63
rs12290253	11	MMP10	C	T	0.200	0.20
rs17297226	11	MMP13	A	G	0.150	0.78
rs17879749	11	MMP1	CA	C	0.880	0.99
rs2958130	12	PRIM1	A	G	0.076	0.63

Variants oriented so that effect allele is associated with greater MMP1 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, MMP1 - Matrix metalloproteinase-1, UKB – UK Biobank.



Appendix Figure I.43: Distribution of MMP1 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Matrix metalloproteinase-1 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher MMP1. MMP1 - Matrix metalloproteinase-1, SD – standard deviation.

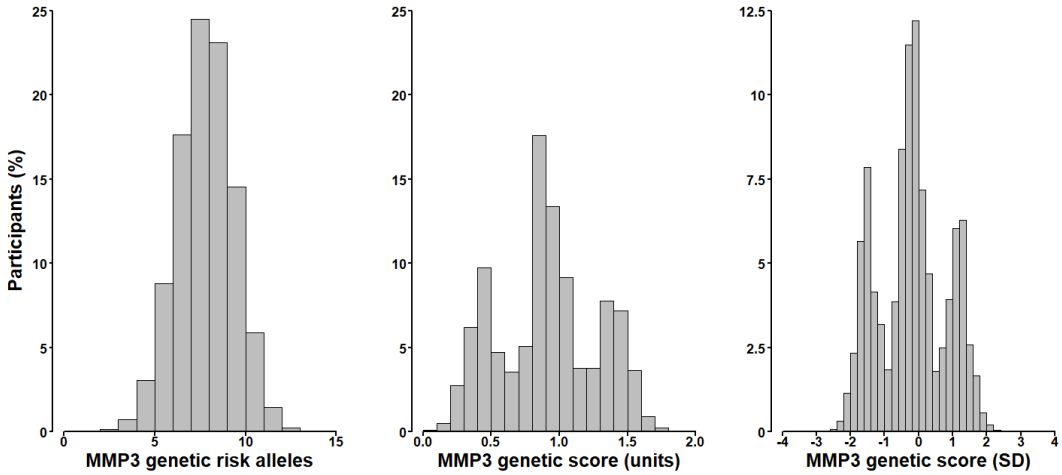
I.12.14. MMP3 (Matrix metalloproteinase-3) genetic score

Seven variants were included in the MMP3 genetic score (**Appendix Table I.27**). The median F-stat for included variants was 41 (range 31 to 2,909). The proportion of variance explained was 13.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.44**).

Appendix Table I.27: Variants included in MMP3 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs632478	11	MMP3	G	T	0.480	0.49
rs1291326	11	MMP27	C	T	0.170	0.09
rs4614414	11	DYNC2H1	C	T	0.086	0.19
rs11225452	11	MMP12	T	A	0.077	0.78
rs74973608	11	DYNC2H1	G	A	0.120	0.93
rs11668189	19	LILRB5	C	A	0.056	0.64
rs2267373	22	MAFF	T	C	0.057	0.58

Variants oriented so that effect allele is associated with greater MMP3 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, MMP3 - Matrix metalloproteinase-3, UKB – UK Biobank.



Appendix Figure I.44: Distribution of MMP3 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Matrix metalloproteinase-3 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher MMP3. MMP3 - Matrix metalloproteinase-3, SD – standard deviation.

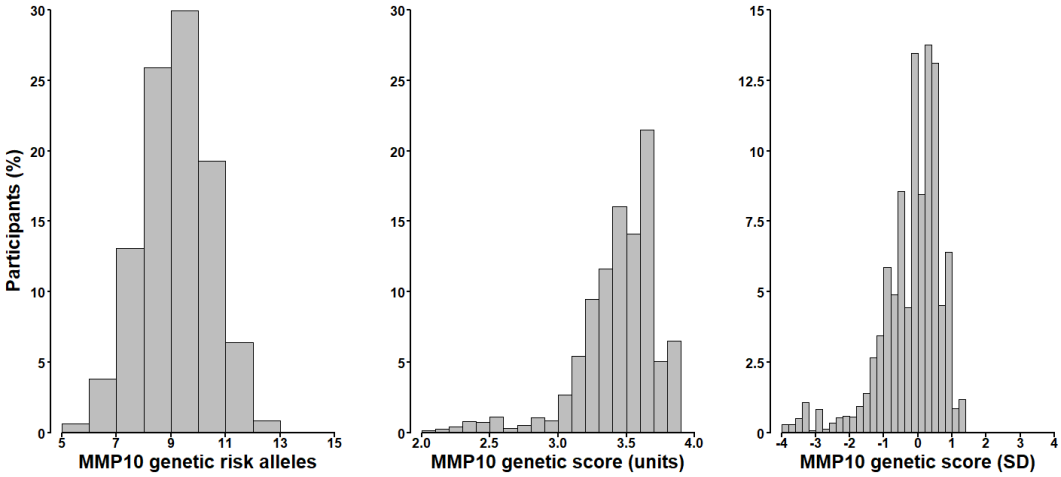
I.12.15. MMP10 (Matrix metalloproteinase-10) genetic score

Six variants were included in the MMP10 genetic score (**Appendix Table I.28**). The median F-stat for included variants was 102 (range 30 to 625). The proportion of variance explained was 8.5%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.45**).

Appendix Table I.28: Variants included in MMP10 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs3129886	6	HLA-DRA	C	T	0.071	0.75
rs486055	11	MMP10	C	T	0.340	0.84
rs17860955	11	MMP10	T	C	1.100	0.98
rs35054791	11	MMP12	TA	T	0.120	0.37
rs55930209	11	MMP8	C	A	0.260	0.96
rs601338	19	FUT2	A	G	0.120	0.50

Variants oriented so that effect allele is associated with greater MMP10 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, MMP10 - Matrix metalloproteinase-10, UKB – UK Biobank.



Appendix Figure I.45: Distribution of MMP10 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Matrix metalloproteinase-10 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher MMP10. MMP10 - Matrix metalloproteinase-10, SD – standard deviation.

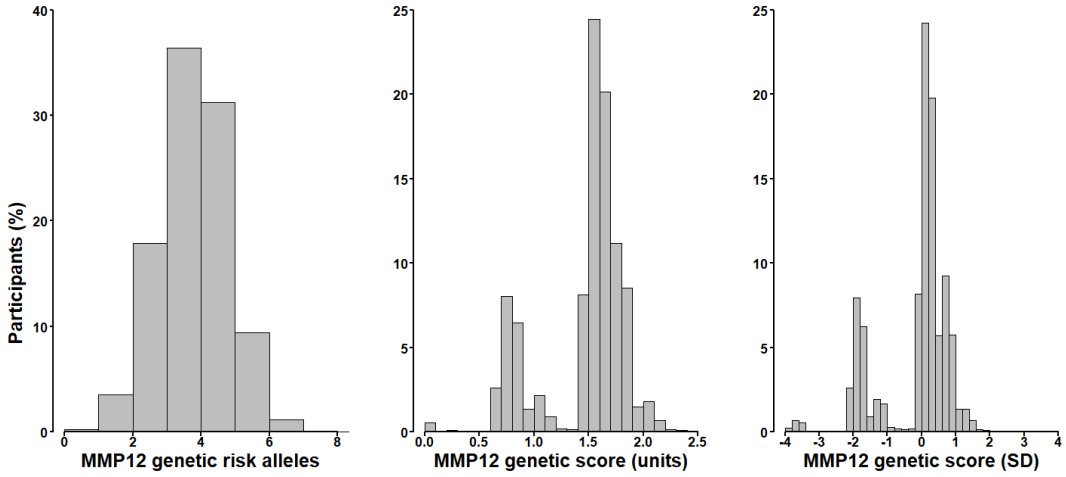
I.12.16. MMP12 (Matrix metalloproteinase-12) genetic score

Six variants were included in the MMP12 genetic score (**Appendix Table I.29**). The median F-stat for included variants was 99 (range 30 to 3,025). The proportion of variance explained was 16.3%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.46**).

Appendix Table I.29: Variants included in MMP12 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs72981675	11	MMP3	C	T	0.707	0.88
rs72987587	11	DCUN1D5	G	T	0.210	0.06
rs111850229	11	MMP13	T	C	0.270	0.04
rs185686655	11	MMP13	T	C	0.270	0.06
rs117953762	13	DACH1	C	T	0.250	0.02
rs12975366	19	LILRB5	T	C	0.080	0.61

Variants oriented so that effect allele is associated with greater MMP12 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, MMP12 - Matrix metalloproteinase-12, UKB – UK Biobank.



Appendix Figure I.46: Distribution of MMP12 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Matrix metalloproteinase-12 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher MMP12. MMP12 - Matrix metalloproteinase-12, SD – standard deviation.

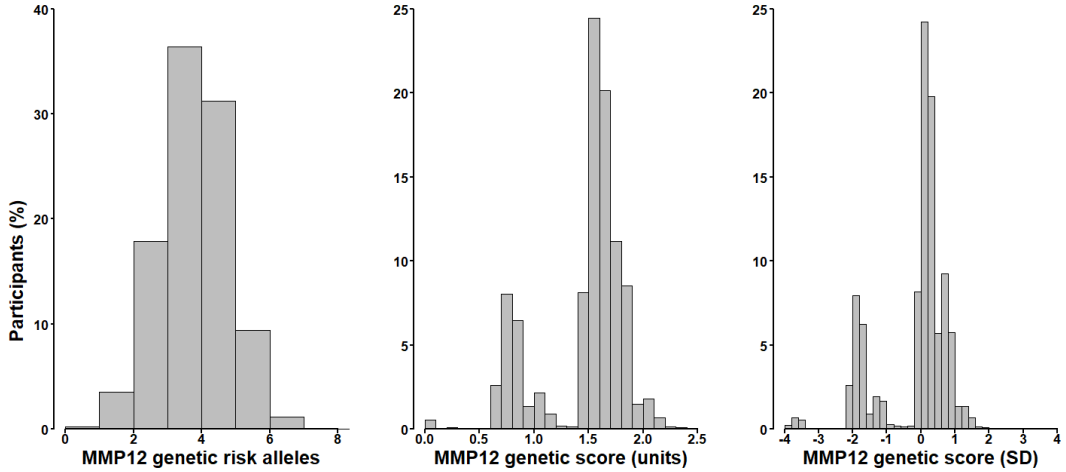
I.12.17. PTX3 (Pentraxin-related protein PTX3) genetic score

Five variants were included in the PTX3 genetic score (**Appendix Table I.30**). The median F-stat for included variants was 51 (range 35 to 1,044). The proportion of variance explained was 9.5%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.47**).

Appendix Table I.30: Variants included in PTX3 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs869463	3	C3orf22	A	G	0.170	0.25
rs9859018	3	VEPH1	A	G	0.100	0.27
rs11130319	3	NEK4	A	T	0.071	0.62
rs60515336	3	VEPH1	C	T	0.220	0.96
rs35524242	10	ITIH2	A	G	0.840	0.95

Variants oriented so that effect allele is associated with greater PTX3 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, PTX3 - Pentraxin-related protein PTX3, UKB – UK Biobank.



Appendix Figure I.47: Distribution of PTX3 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Pentraxin-related protein PTX3 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher PTX3. PTX3 - Pentraxin-related protein PTX3, SD – standard deviation.

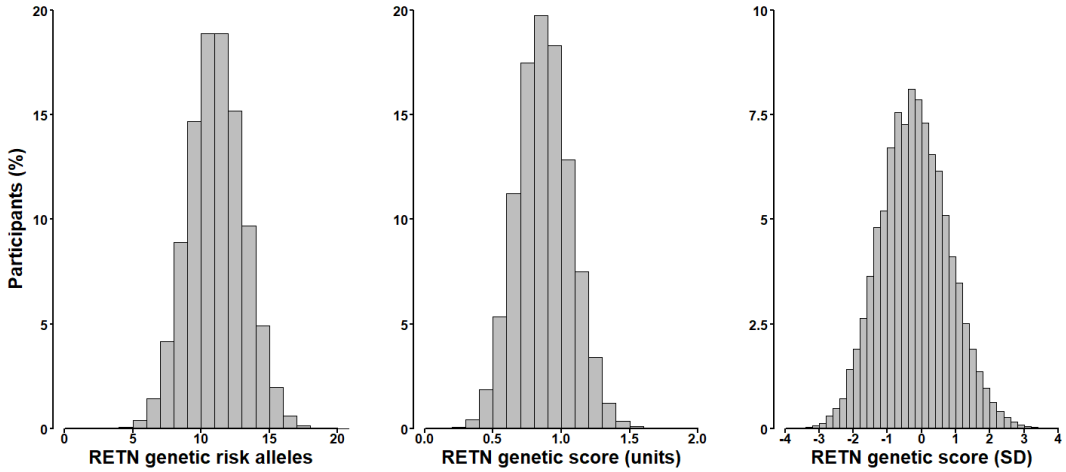
I.12.18. RETN (Resistin) genetic score

Twelve variants were included in the RETN genetic score (**Appendix Table I.31**). The median F-stat for included variants was 48 (range 30 to 156). The proportion of variance explained was 4.0%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.48**).

Appendix Table I.31: Variants included in RETN genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs199752470	1	EVI5	A	AG	0.096	0.1
rs7589428	2	THADA	A	G	0.063	0.49
rs17405635	2	ZFP36L2	A	G	0.08	0.26
rs6775731	3	RPN1	C	T	0.063	0.7
rs2239619	6	TRAM2	C	A	0.053	0.39
rs73008259	6	SF3B5	A	G	0.19	0.04
rs77691416	6	PLAGL1	A	C	0.12	0.91
rs445	7	CDK6	C	T	0.085	0.9
rs10103048	8	GSDMC	A	C	0.06	0.41
rs3087852	17	PSMD3	G	A	0.086	0.54
rs3745367	19	RETN	A	G	0.12	0.26
rs10401670	19	MCEMP1	T	C	0.15	0.43

Variants oriented so that effect allele is associated with greater RETN in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, RETN – Resistin, UKB – UK Biobank.



Appendix Figure I.48: Distribution of RETN variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Resistin genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher RETN. RETN – Resistin, SD – standard deviation.

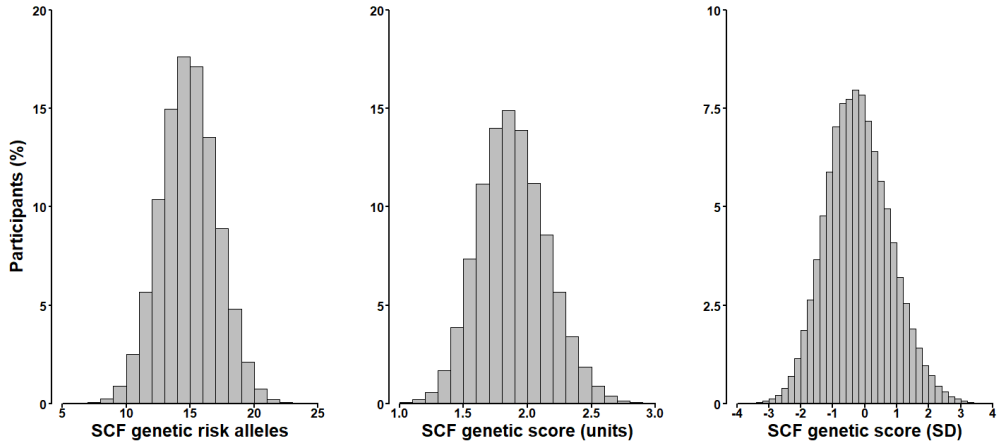
I.12.19. SCF (Stem Cell Factor) genetic score

Sixteen variants were included in the RETN genetic score (**Appendix Table I.32**). The median F-stat for included variants was 40 (range 30 to 584). The proportion of variance explained was 7.5%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.49**).

Appendix Table I.32: Variants included in SCF genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs822928	1	IRF2BP2	C	A	0.066	0.54
rs705379	7	PON1	A	G	0.072	0.47
rs2980888	8	TRIB1	C	T	0.070	0.70
rs579459	9	ABO	T	C	0.079	0.80
rs2740488	9	ABCA1	A	C	0.110	0.73
rs4149307	9	ABCA1	T	C	0.097	0.17
rs174528	11	MYRF	C	T	0.060	0.38
rs964184	11	ZPR1	C	G	0.082	0.86
rs11608458	12	DUSP6	C	T	0.070	0.36
rs45617141	15	ADAL	T	G	0.260	0.98
rs4986970	16	LCAT	A	T	0.200	0.97
rs12149545	16	CETP	A	G	0.130	0.31
rs73593810	16	CENPT	T	C	0.160	0.11
rs380267	19	LILRB2	G	A	0.120	0.22
rs6073958	20	PLTP	C	T	0.290	0.20
rs11569334	20	CD40	C	T	0.150	0.04

Variants oriented so that effect allele is associated with greater SCF in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, SCF – Stem Cell Factor, UKB – UK Biobank.



Appendix Figure I.49: Distribution of SCF variants in the UK Biobank population. *Histograms demonstrating the distribution of Stem Cell Factor genetic score values and alleles in the UK Biobank population (n=339,214). Risk alleles defined as those associated with higher SCF. SCF – Stem Cell Factor, SD – standard deviation.*

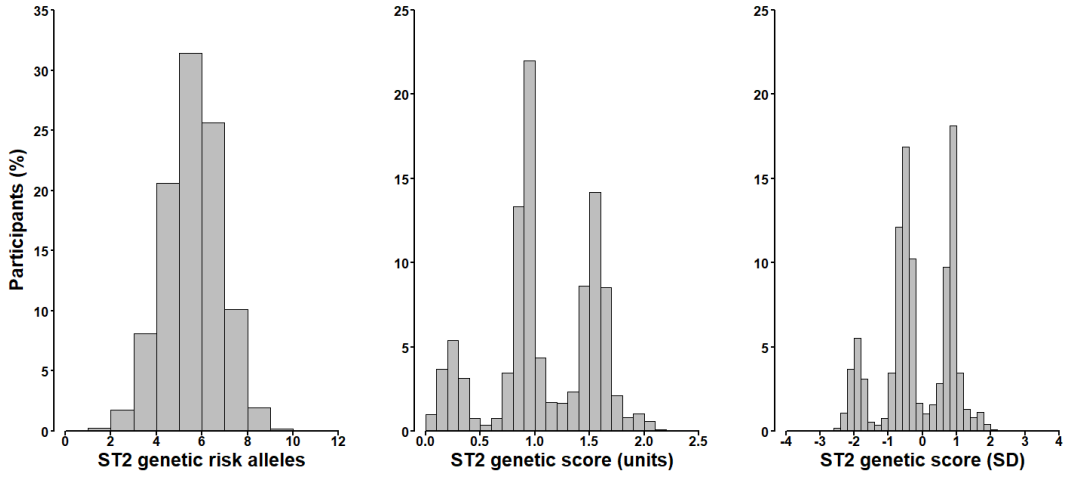
I.12.20. ST2 (ST2 protein) genetic score

Six variants were included in the ST2 genetic score (**Appendix Table I.33**). The median F-stat for included variants was 54 (range 33 to 5,456). The proportion of variance explained was 22.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.50**).

Appendix Table I.33: Variants included in ST2 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs2460382	2	MGAT5	G	A	0.077	0.23
rs7604529	2	IL1R1	A	G	0.100	0.84
rs13020553	2	IL1RL1	C	G	0.650	0.62
rs35518360	4	SLC39A8	T	A	0.120	0.08
rs635634	9	ABO	C	T	0.080	0.82
rs11603123	11	KIRREL3	A	G	0.380	0.03

Variants oriented so that effect allele is associated with greater ST2 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, ST2 – ST2 protein, UKB – UK Biobank.



Appendix Figure I.50: Distribution of ST2 variants in the UK Biobank population (n=339,214).

Histograms demonstrating the distribution of ST2 protein genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher ST2. SD – standard deviation, ST2 – ST2 protein.

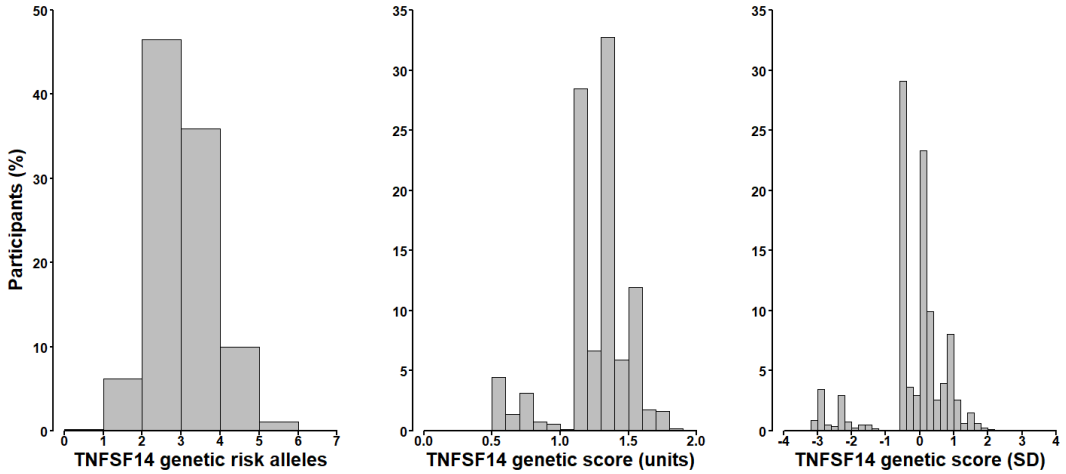
I.12.21. TNFSF14 (Tumour Necrosis Factor Ligand Superfamily Member 14) genetic score

Four variants were included in the TNFSF14 genetic score (**Appendix Table I.34**). The median F-stat for included variants was 112 (range 54 to 635). The proportion of variance explained was 5.9%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.51**).

Appendix Table I.34: Variants included in TNFSF14 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs344560	19	TNFSF14	C	T	0.630	0.95
rs413141	19	C3	A	G	0.160	0.14
rs7259081	19	NLRP12	T	A	0.200	0.25
rs138811446	19	TNFSF14	T	C	0.220	0.05

Variants oriented so that effect allele is associated with greater TNFSF14 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, TNFSF14 – Tumour Necrosis Factor Ligand Superfamily Member 14, UKB – UK Biobank.



Appendix Figure I.51: Distribution of TNFSF14 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Tumour Necrosis Factor Ligand Superfamily Member 14 genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher TNFSF14. SD – standard deviation, TNFSF14 – Tumour Necrosis Factor Ligand Superfamily Member 14.

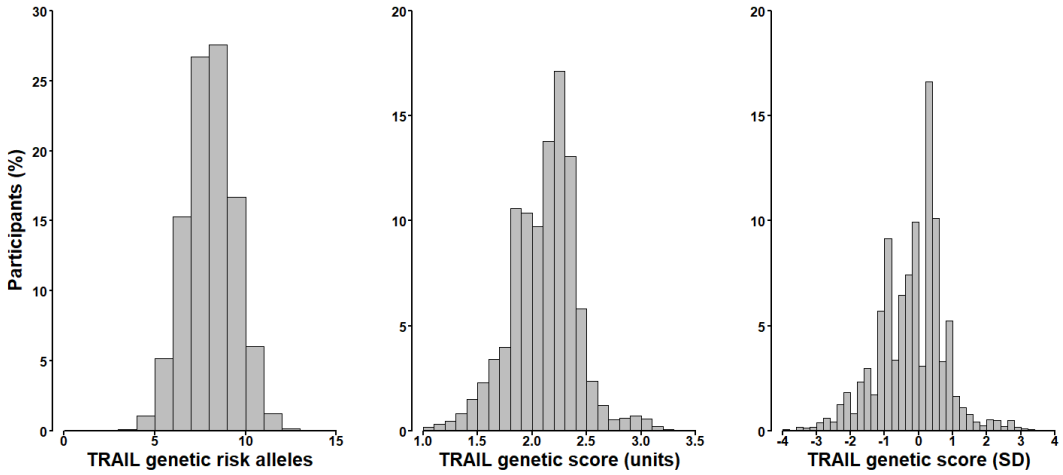
I.12.22. TRAIL (Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand) genetic score

Eight variants were included in the TRAIL genetic score (**Appendix Table I.35**). The median F-stat for included variants was 121 (range 48 to 448). The proportion of variance explained was 8.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.52**).

Appendix Table I.35: Variants included in TRAIL genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs35617250	1	CFH	T	C	0.110	0.2
rs232001	3	TNFSF10	C	G	0.090	0.36
rs2304456	3	KNG1	T	G	0.260	0.89
rs142552223	3	TNFSF10	G	A	0.470	0.96
rs28929474	14	SERPINA1	T	C	0.660	0.02
rs8178824	17	APOH	T	C	0.260	0.03
rs673408	18	MEP1B	A	G	0.086	0.54
rs4760	19	PLAUR	A	G	0.360	0.85

Variants oriented so that effect allele is associated with greater TRAIL in the original genome-wide associations study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, TRAIL – Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand, UKB – UK Biobank.



Appendix Figure I.52: Distribution of TRAIL variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher TRAIL. SD – standard deviation, TRAIL – Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand.

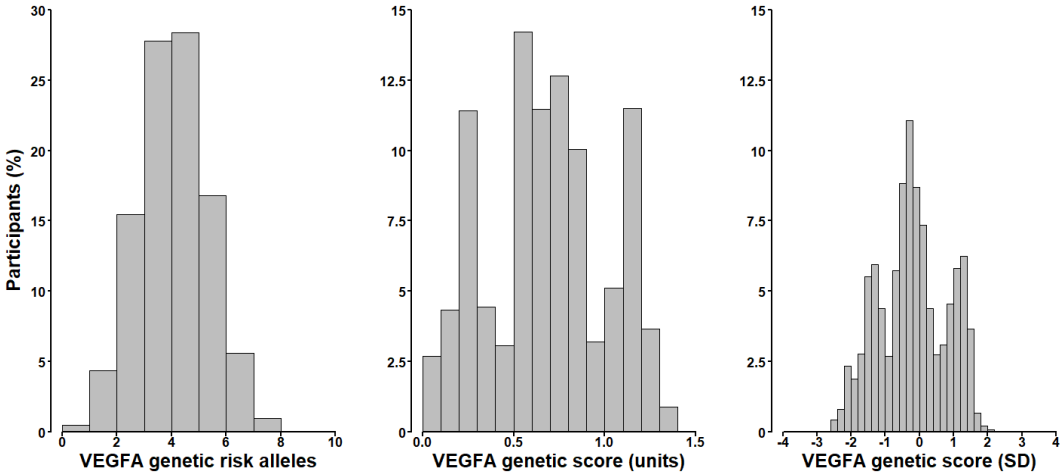
I.12.23. VEGFA (Vascular Endothelial Growth Factor A) genetic score

Four variants were included in the VEGFA genetic score (**Appendix Table I.36**). The median F-stat for included variants was 101 (range 29 to 1,406). The proportion of variance explained was 11.5%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.53**).

Appendix Table I.36: Variants included in VEGFA genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs61818787	1	BRINP3	C	T	0.086	0.19
rs6921438	6	C6orf223	G	A	0.450	0.51
rs6993770	8	ZFPM2	A	T	0.150	0.71
rs10822155	10	JMJD1C	A	C	0.075	0.41

Variants oriented so that effect allele is associated with greater VEGFA in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank, VEGFA – Vascular Endothelial Growth Factor A.



Appendix Figure I.53: Distribution of VEGFA variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Vascular Endothelial Growth Factor A genetic score values and alleles in the UK Biobank population. Risk alleles defined as those associated with higher VEGFA. SD – standard deviation, VEGFA – Vascular Endothelial Growth Factor A.

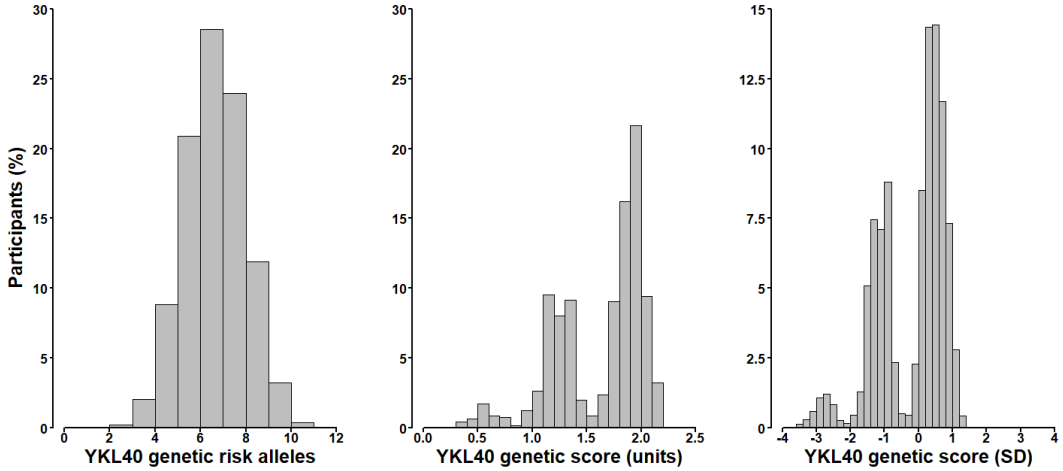
I.12.24. YKL40 (Chitinase-3-Like Protein 1) genetic score

Five variants were included in the YKL40 genetic score (**Appendix Table I.37**). The median F-stat for included variants was 57 (range 29 to 4,489). The proportion of variance explained was 18.8%. Risk alleles for selected variants were normally distributed in UKB (**Appendix Figure I.54**).

Appendix Table I.37: Variants included in YKL40 genetic score

RSID	Chr	Nearest gene	Effect allele	Other allele	Weighting for score	EAF (UKB)
rs4950931	1	CHI3L1	A	G	0.670	0.8
rs1260326	2	GCKR	T	C	0.071	0.39
rs62140201	2	C2orf91	G	A	0.210	0.97
rs28601761	8	TRIB1	C	G	0.120	0.59
rs339969	15	RORA	C	A	0.075	0.38

Variants oriented so that effect allele is associated with greater YKL40 in the original genome-wide association study. Ordered by chromosome. Chr – Chromosome; EAF – effect allele frequency, UKB – UK Biobank, YKL40 – Chitinase-3-Like Protein 1.



Appendix Figure I.54: Distribution of YKL40 variants in the UK Biobank population (n=339,214).
Histograms demonstrating the distribution of Chitinase-3-Like Protein 1 genetic score values and risk alleles in the UK Biobank population. Risk alleles defined as those associated with higher YKL40. SD – standard deviation, YKL40 – Chitinase-3-Like Protein 1.

Appendix J - Effect of individual variants included in genetic scores in UK Biobank

J.1. Effect of body mass index variants on body mass index and risk of atrial fibrillation in UK Biobank

For the 348 variants making up the BMI genetic score, the beta and standard error values for baseline BMI and AF in UKB are displayed in **Appendix Table J.1** and **Appendix Figure J.1**.

Appendix Table J.1: Variants included in the body mass index genetic score

RSID	Effect Allele	Other Allele	BMI		AF	
			Beta	SE	Beta	SE
rs2229616	C	T	0.120	0.009	0.020	0.031
rs7550711	T	C	0.064	0.008	0.014	0.027
rs13107325	T	C	0.054	0.005	0.025	0.017
rs663129	A	G	0.053	0.003	0.013	0.010
rs13021737	G	A	0.052	0.003	0.034	0.012
rs9332817	G	C	0.048	0.008	-0.024	0.027
rs543874	G	A	0.048	0.003	0.010	0.011
rs10066835	T	C	0.046	0.011	-0.049	0.038
rs6265	C	T	0.042	0.003	0.017	0.011
rs10182181	G	A	0.036	0.003	-0.014	0.009
rs2304607	G	A	0.036	0.004	0.006	0.013
rs208015	T	C	0.036	0.005	0.039	0.017
rs12189178	T	C	0.035	0.007	0.030	0.024
rs9931164	A	G	0.034	0.009	0.000	0.032
rs6938239	G	A	0.033	0.004	0.029	0.013
rs17238110	A	G	0.033	0.009	0.009	0.030
rs11672660	C	T	0.032	0.003	0.002	0.011
rs2230590	C	T	0.032	0.003	0.004	0.009
rs3814883	T	C	0.030	0.003	0.029	0.009
rs3810291	A	G	0.029	0.003	0.012	0.009
rs12420725	G	A	0.029	0.006	0.043	0.019
rs10938397	G	A	0.029	0.003	0.005	0.009
rs1475774	A	G	0.029	0.009	0.050	0.029
rs3734572	C	T	0.028	0.006	0.006	0.021
rs12446632	G	A	0.028	0.004	-0.012	0.012
rs40067	G	A	0.028	0.003	-0.003	0.012

rs7124681	A	C	0.028	0.003	-0.011	0.009
rs13329567	C	T	0.028	0.003	0.019	0.011
rs2820311	G	A	0.028	0.003	0.015	0.009
rs7138803	A	G	0.027	0.003	0.018	0.009
rs7560871	A	G	0.027	0.005	0.001	0.017
rs12429545	A	G	0.027	0.004	0.010	0.013
rs10962549	T	C	0.027	0.003	0.026	0.012
rs11659764	T	A	0.027	0.006	-0.048	0.019
rs10499276	T	C	0.026	0.004	0.017	0.013
rs17806379	C	T	0.026	0.003	0.010	0.011
rs17302346	C	T	0.026	0.009	-0.028	0.031
rs498240	G	A	0.025	0.005	0.025	0.017
rs7187776	G	A	0.025	0.003	0.011	0.009
rs4516268	C	A	0.025	0.003	0.014	0.011
rs17207196	C	T	0.025	0.003	0.033	0.009
rs7899106	G	A	0.025	0.006	-0.015	0.020
rs8016859	C	G	0.025	0.007	0.048	0.022
rs12577642	T	A	0.025	0.003	0.017	0.009
rs9688431	T	C	0.025	0.005	0.022	0.019
rs12411886	A	C	0.025	0.005	0.057	0.016
rs1412235	C	G	0.024	0.003	0.008	0.009
rs7144011	T	G	0.024	0.003	0.013	0.011
rs2033529	G	A	0.024	0.003	0.025	0.010
rs17681451	G	A	0.023	0.005	0.020	0.016
rs12147845	T	C	0.023	0.004	0.029	0.014
rs16906845	G	A	0.023	0.006	0.027	0.019
rs1178060	A	G	0.023	0.004	-0.020	0.012
rs3819299	T	G	0.023	0.006	-0.006	0.019
rs13191362	A	G	0.023	0.004	-0.002	0.013
rs12364470	G	T	0.023	0.003	0.025	0.012
rs12098284	T	C	0.023	0.004	0.029	0.013
rs11611246	T	G	0.022	0.003	-0.006	0.011
rs4671328	T	G	0.022	0.003	-0.001	0.009
rs7871866	C	G	0.022	0.004	0.021	0.012
rs845084	A	G	0.022	0.003	0.025	0.010
rs7444298	A	G	0.022	0.003	0.011	0.010
rs10460960	A	G	0.022	0.004	-0.017	0.014
rs7730898	A	G	0.022	0.003	-0.017	0.010
rs1884897	G	A	0.021	0.003	-0.002	0.009
rs1431659	A	G	0.021	0.003	0.001	0.010
rs3803286	A	G	0.021	0.003	-0.008	0.009
rs6474945	G	T	0.021	0.003	0.016	0.009
rs6545714	G	A	0.021	0.003	0.010	0.009
rs1106908	G	A	0.021	0.003	0.003	0.009
rs16907751	C	T	0.021	0.004	0.023	0.015
rs7531656	A	G	0.021	0.003	-0.014	0.009
rs7531118	C	T	0.021	0.003	0.026	0.009
rs4981693	A	G	0.020	0.003	-0.010	0.010
rs17014375	G	T	0.020	0.004	0.022	0.013
rs6443750	C	T	0.020	0.003	-0.003	0.011
rs7102454	C	T	0.020	0.003	0.006	0.009
rs2075650	A	G	0.020	0.004	-0.021	0.012
rs12042959	A	G	0.020	0.004	-0.026	0.012
rs901630	C	T	0.020	0.003	0.010	0.009
rs6019482	C	T	0.020	0.003	0.018	0.012
rs4986044	C	T	0.020	0.003	0.006	0.009
rs17757975	T	C	0.020	0.004	-0.018	0.012
rs6786582	C	T	0.020	0.003	-0.013	0.010

rs8016771	G	T	0.019	0.005	0.042	0.016
rs8081039	T	C	0.019	0.005	0.011	0.019
rs12964689	A	G	0.019	0.003	0.019	0.009
rs12035349	G	A	0.019	0.004	0.014	0.013
rs4841659	T	C	0.019	0.003	-0.015	0.009
rs329124	A	G	0.019	0.003	0.038	0.009
rs329651	T	G	0.019	0.003	0.004	0.011
rs12448738	C	A	0.019	0.004	0.022	0.013
rs6710871	A	G	0.019	0.004	0.023	0.013
rs16932761	G	A	0.019	0.003	-0.002	0.010
rs1927790	C	T	0.019	0.003	0.001	0.009
rs28350	A	G	0.019	0.003	0.024	0.011
rs2282231	T	C	0.019	0.003	0.029	0.011
rs11079849	C	T	0.018	0.003	-0.001	0.009
rs11583122	T	C	0.018	0.005	0.017	0.016
rs13321566	G	A	0.018	0.003	0.002	0.012
rs7919	C	A	0.018	0.003	0.013	0.009
rs7557796	T	C	0.018	0.003	0.005	0.009
rs7181610	A	T	0.018	0.004	0.012	0.012
rs10467530	C	G	0.018	0.004	-0.009	0.013
rs7601895	C	G	0.018	0.003	-0.010	0.009
rs10920678	A	G	0.018	0.003	0.017	0.009
rs12939549	A	G	0.018	0.003	0.003	0.009
rs1951455	C	T	0.018	0.003	0.011	0.010
rs10971712	C	T	0.018	0.004	-0.043	0.014
rs17522122	T	G	0.018	0.003	0.007	0.009
rs11866815	C	T	0.018	0.003	0.008	0.010
rs11496125	T	C	0.018	0.003	-0.001	0.009
rs9630985	C	A	0.017	0.003	0.015	0.009
rs967605	C	T	0.017	0.003	-0.002	0.012
rs3887080	A	G	0.017	0.004	0.006	0.013
rs1862451	A	G	0.017	0.003	0.017	0.010
rs217671	G	A	0.017	0.003	0.006	0.010
rs2000746	A	G	0.017	0.003	0.016	0.010
rs9595908	T	C	0.017	0.003	0.012	0.009
rs13263601	C	A	0.017	0.003	-0.005	0.009
rs2611742	C	T	0.017	0.003	0.006	0.009
rs6463489	T	C	0.017	0.004	0.014	0.014
rs2781668	T	C	0.017	0.003	0.018	0.012
rs7243357	T	G	0.017	0.003	0.006	0.012
rs3753549	C	T	0.017	0.004	-0.001	0.013
rs4077093	T	G	0.017	0.003	-0.009	0.011
rs1333423	A	T	0.017	0.003	0.008	0.010
rs427943	C	A	0.017	0.003	0.014	0.009
rs6548221	A	G	0.017	0.003	0.004	0.011
rs7211567	C	T	0.017	0.003	-0.004	0.011
rs1048932	C	A	0.017	0.003	0.016	0.009
rs4518345	G	A	0.016	0.003	0.001	0.010
rs2170382	T	C	0.016	0.004	0.008	0.014
rs284227	C	T	0.016	0.003	0.000	0.010
rs12514473	T	C	0.016	0.003	0.008	0.010
rs12575252	G	C	0.016	0.003	0.011	0.009
rs17608150	T	C	0.016	0.005	0.031	0.016
rs12448257	A	G	0.016	0.003	0.029	0.011
rs1477887	G	A	0.016	0.003	0.017	0.009
rs3826705	C	T	0.016	0.004	0.023	0.014
rs9291467	T	C	0.016	0.003	0.006	0.009
rs6448587	A	C	0.016	0.003	0.009	0.012

rs12888545	G	A	0.016	0.003	-0.008	0.010
rs9538141	A	G	0.016	0.003	0.005	0.009
rs2479958	A	G	0.016	0.003	0.001	0.009
rs7217226	G	T	0.016	0.003	0.030	0.009
rs17551974	C	A	0.016	0.003	0.005	0.011
rs7083450	T	C	0.016	0.004	-0.038	0.012
rs355777	C	G	0.016	0.003	0.004	0.009
rs12422552	G	C	0.016	0.003	0.000	0.010
rs39654	G	A	0.016	0.003	0.019	0.009
rs7903146	C	T	0.016	0.003	0.010	0.010
rs2154297	C	T	0.016	0.003	0.000	0.010
rs2653365	C	T	0.016	0.003	0.051	0.011
rs756717	G	A	0.015	0.003	-0.024	0.009
rs853679	A	C	0.015	0.003	0.007	0.012
rs1552717	A	T	0.015	0.004	-0.008	0.013
rs977540	A	G	0.015	0.003	0.015	0.010
rs905938	C	T	0.015	0.003	0.045	0.010
rs2836961	C	A	0.015	0.003	-0.021	0.009
rs11753081	T	G	0.015	0.003	-0.002	0.012
rs4820408	T	G	0.015	0.003	0.009	0.009
rs2875762	C	G	0.015	0.003	0.020	0.010
rs29938	C	T	0.015	0.003	0.001	0.009
rs2283093	T	C	0.015	0.003	0.003	0.011
rs7334078	T	C	0.015	0.003	-0.001	0.010
rs1852006	G	A	0.015	0.003	-0.006	0.009
rs3768486	G	A	0.015	0.003	0.012	0.011
rs1819844	A	G	0.015	0.003	0.005	0.012
rs10929925	C	A	0.015	0.003	0.024	0.009
rs9979651	G	C	0.014	0.005	-0.030	0.017
rs6564360	G	A	0.014	0.003	-0.014	0.011
rs6888159	C	G	0.014	0.003	-0.010	0.009
rs1048365	T	C	0.014	0.004	-0.018	0.012
rs2190788	T	G	0.014	0.003	0.030	0.009
rs450231	G	A	0.014	0.003	-0.013	0.010
rs11736228	A	T	0.014	0.003	0.015	0.010
rs1241986	G	A	0.014	0.004	-0.003	0.012
rs7206608	G	C	0.014	0.003	0.006	0.009
rs1865341	T	C	0.014	0.003	0.016	0.010
rs1941697	A	G	0.014	0.003	-0.005	0.009
rs2192158	A	G	0.014	0.003	0.014	0.009
rs2733287	C	A	0.014	0.003	-0.002	0.009
rs1323068	G	A	0.014	0.003	-0.002	0.009
rs1452075	T	C	0.014	0.003	0.002	0.010
rs6922214	G	A	0.014	0.004	0.009	0.012
rs17636031	C	T	0.014	0.003	0.012	0.010
rs1000096	C	T	0.014	0.003	0.033	0.009
rs1625427	T	C	0.014	0.003	-0.001	0.009
rs6477694	C	T	0.014	0.003	0.002	0.009
rs1437929	A	G	0.014	0.003	-0.001	0.010
rs403656	A	G	0.014	0.004	-0.012	0.012
rs1003081	T	C	0.014	0.003	0.001	0.009
rs6577584	G	T	0.014	0.003	-0.017	0.009
rs9827072	G	A	0.014	0.004	0.004	0.015
rs17096552	G	A	0.014	0.004	-0.002	0.013
rs1454148	T	C	0.014	0.003	-0.018	0.010
rs10773049	C	T	0.014	0.003	-0.004	0.009
rs827092	T	C	0.014	0.003	0.001	0.009
rs2030342	T	C	0.014	0.003	-0.003	0.009

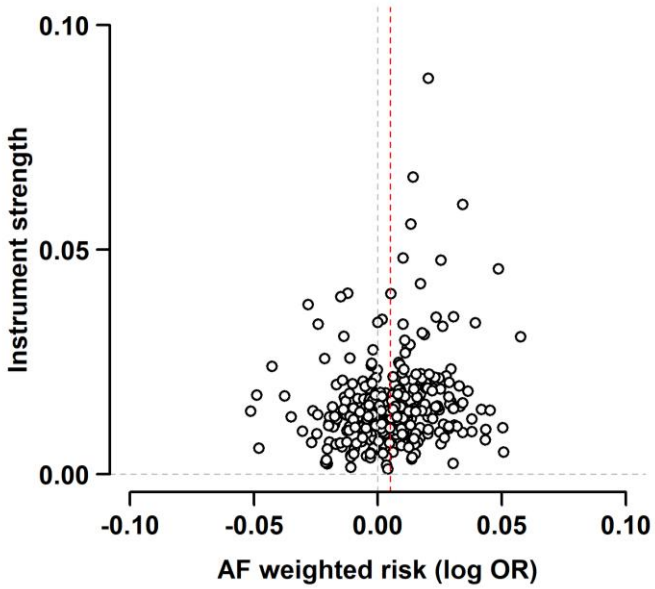
rs1937684	A	T	0.014	0.003	0.006	0.009
rs3844598	G	A	0.014	0.003	-0.020	0.009
rs12731372	T	C	0.013	0.003	-0.009	0.010
rs7181498	T	C	0.013	0.003	0.009	0.009
rs934515	A	G	0.013	0.004	-0.003	0.014
rs9507983	C	T	0.013	0.003	-0.005	0.009
rs6804842	G	A	0.013	0.003	0.036	0.009
rs9349239	A	G	0.013	0.003	-0.020	0.009
rs1436343	G	A	0.013	0.003	0.038	0.009
rs7777102	G	A	0.013	0.004	0.025	0.013
rs954018	G	A	0.013	0.003	-0.004	0.010
rs881301	C	T	0.013	0.003	0.005	0.009
rs10745785	C	T	0.013	0.003	0.004	0.009
rs11150911	A	C	0.013	0.003	-0.005	0.010
rs12035149	G	C	0.013	0.003	0.005	0.011
rs3849570	A	C	0.013	0.003	0.008	0.009
rs159032	T	C	0.013	0.003	0.002	0.010
rs9571687	C	A	0.013	0.003	-0.007	0.009
rs13047416	C	G	0.013	0.003	0.019	0.009
rs13227658	C	T	0.013	0.003	0.013	0.009
rs1285245	G	C	0.013	0.003	0.008	0.009
rs1038088	G	T	0.013	0.003	0.008	0.009
rs3807566	G	T	0.013	0.003	0.020	0.009
rs6804181	A	T	0.013	0.003	-0.011	0.012
rs17197116	C	T	0.013	0.005	-0.005	0.016
rs13417156	C	T	0.013	0.003	-0.001	0.009
rs903959	A	T	0.013	0.003	-0.013	0.009
rs9603697	T	C	0.013	0.003	0.008	0.009
rs13290794	G	A	0.012	0.003	0.003	0.009
rs4969387	G	C	0.012	0.003	0.006	0.010
rs11115176	T	C	0.012	0.003	0.017	0.010
rs892261	C	T	0.012	0.003	0.015	0.009
rs13203153	G	A	0.012	0.003	-0.006	0.011
rs9362662	A	G	0.012	0.003	0.009	0.009
rs17105272	T	C	0.012	0.003	-0.020	0.009
rs4886869	G	A	0.012	0.003	-0.020	0.009
rs9299	T	C	0.012	0.003	0.001	0.009
rs4372836	T	C	0.012	0.003	0.011	0.009
rs3822683	A	G	0.012	0.003	-0.019	0.011
rs6767619	C	G	0.012	0.003	-0.001	0.009
rs10083803	C	T	0.012	0.003	-0.002	0.010
rs587230	A	G	0.012	0.003	-0.011	0.012
rs17446091	C	T	0.012	0.003	0.017	0.011
rs7425440	T	C	0.012	0.003	0.002	0.011
rs2425857	A	G	0.012	0.003	0.008	0.009
rs9615905	T	C	0.012	0.003	0.010	0.009
rs825680	A	T	0.012	0.003	-0.006	0.009
rs12922346	C	G	0.012	0.003	-0.003	0.010
rs254428	T	G	0.012	0.003	0.010	0.009
rs7683836	G	A	0.012	0.003	0.014	0.009
rs6919443	G	A	0.012	0.003	0.001	0.009
rs2357760	A	G	0.012	0.003	0.011	0.009
rs2459359	C	G	0.012	0.006	-0.003	0.019
rs8070454	C	T	0.012	0.003	-0.009	0.009
rs7941030	C	T	0.012	0.003	0.002	0.009
rs6877851	G	C	0.012	0.003	0.014	0.010
rs2228213	G	A	0.012	0.003	0.034	0.009
rs6786125	G	C	0.012	0.003	0.007	0.011

rs559267	G	A	0.012	0.003	0.009	0.009
rs11844682	G	C	0.012	0.003	-0.002	0.009
rs980329	C	T	0.012	0.003	-0.004	0.010
rs1928295	T	C	0.012	0.003	0.009	0.009
rs8033510	T	C	0.012	0.003	-0.005	0.009
rs2425241	C	T	0.012	0.005	-0.003	0.016
rs7607351	T	C	0.012	0.003	0.009	0.009
rs329277	G	T	0.012	0.003	-0.002	0.009
rs331949	C	T	0.012	0.003	0.014	0.009
rs9540493	A	G	0.011	0.003	0.016	0.009
rs2307022	A	G	0.011	0.003	0.010	0.009
rs10923724	C	T	0.011	0.003	0.001	0.009
rs12443621	G	A	0.011	0.003	0.000	0.009
rs629443	T	G	0.011	0.003	-0.007	0.010
rs6442021	C	T	0.011	0.003	0.003	0.009
rs1403846	T	C	0.011	0.003	0.010	0.012
rs273697	G	A	0.011	0.003	0.015	0.009
rs1452134	C	T	0.011	0.003	0.008	0.009
rs7209235	G	A	0.011	0.003	-0.002	0.010
rs7123876	C	T	0.011	0.003	-0.014	0.010
rs3736485	A	G	0.011	0.003	-0.001	0.009
rs10867256	C	T	0.011	0.003	0.005	0.009
rs483752	T	C	0.011	0.003	-0.015	0.010
rs2275426	A	G	0.011	0.003	0.012	0.009
rs17080319	T	C	0.011	0.004	-0.003	0.013
rs17591778	A	G	0.011	0.003	-0.007	0.010
rs1853639	G	A	0.011	0.003	-0.004	0.009
rs10989568	A	G	0.011	0.003	0.007	0.009
rs13201877	G	A	0.011	0.004	0.000	0.013
rs10168197	G	C	0.011	0.003	-0.008	0.011
rs4936671	C	G	0.011	0.003	0.015	0.009
rs223051	T	C	0.011	0.003	-0.008	0.009
rs972540	G	A	0.011	0.003	0.008	0.010
rs765332	G	T	0.011	0.004	0.034	0.014
rs4524456	G	A	0.010	0.003	0.014	0.009
rs4796243	G	A	0.010	0.003	0.013	0.010
rs13041173	G	A	0.010	0.003	-0.003	0.009
rs10146527	T	C	0.010	0.003	-0.003	0.009
rs6879326	C	T	0.010	0.003	0.003	0.009
rs2731222	A	C	0.010	0.003	0.007	0.010
rs1866510	C	T	0.010	0.003	0.020	0.009
rs775731	C	T	0.010	0.003	0.001	0.009
rs573455	G	A	0.010	0.003	0.007	0.009
rs6818414	C	T	0.010	0.003	0.015	0.009
rs9475173	A	G	0.010	0.003	0.029	0.009
rs7313924	C	G	0.010	0.003	-0.025	0.010
rs762147	G	A	0.010	0.003	0.004	0.010
rs8567	G	A	0.009	0.003	-0.001	0.009
rs3772934	T	C	0.009	0.003	0.000	0.010
rs1205106	G	A	0.009	0.003	0.020	0.009
rs12776880	A	T	0.009	0.003	0.008	0.010
rs4515655	C	T	0.009	0.003	0.003	0.009
rs12625413	C	T	0.009	0.003	-0.017	0.009
rs884282	C	T	0.009	0.003	0.001	0.009
rs10876418	C	T	0.009	0.003	-0.004	0.010
rs12694021	A	C	0.009	0.003	0.010	0.009
rs4985155	A	G	0.009	0.003	-0.005	0.009
rs2440885	A	G	0.009	0.003	0.004	0.009

rs12713433	T	C	0.009	0.003	-0.027	0.011
rs7710595	A	C	0.008	0.003	0.032	0.009
rs6843738	G	A	0.008	0.003	-0.035	0.009
rs3800649	A	G	0.008	0.003	0.005	0.010
rs2534760	T	A	0.008	0.003	-0.011	0.010
rs6495252	T	C	0.008	0.003	-0.008	0.009
rs7117238	G	A	0.008	0.003	-0.010	0.012
rs487060	T	C	0.007	0.003	0.013	0.009
rs6061162	T	C	0.007	0.004	0.011	0.015
rs580438	T	C	0.007	0.003	-0.018	0.009
rs6490055	G	A	0.007	0.003	-0.012	0.010
rs6803870	T	C	0.007	0.003	0.043	0.012
rs968972	A	G	0.007	0.003	0.012	0.009
rs7692088	C	G	0.007	0.003	0.014	0.009
rs4342060	C	T	0.006	0.003	-0.021	0.011
rs2252300	T	A	0.006	0.003	-0.011	0.011
rs2160077	A	G	0.006	0.003	-0.009	0.009
rs497417	T	A	0.006	0.003	-0.011	0.011
rs10769165	C	T	0.006	0.003	0.005	0.009
rs12207241	G	A	0.006	0.003	-0.001	0.009
rs8069296	C	T	0.006	0.003	-0.004	0.011
rs160401	T	C	0.005	0.003	0.008	0.010
rs10459012	A	C	0.004	0.003	-0.002	0.011
rs3829849	T	C	0.004	0.003	-0.001	0.009
rs919433	A	G	0.004	0.003	0.027	0.009
rs10203277	A	G	0.003	0.004	-0.011	0.013
rs346722	C	T	0.003	0.004	0.001	0.013
rs11803119	A	T	0.001	0.010	-0.051	0.035
rs12039524	G	A	-0.001	0.003	-0.021	0.012
rs7702514	T	C	-0.002	0.003	0.003	0.011
rs12458	T	A	-0.004	0.003	0.030	0.009
rs6060151	G	T	-0.006	0.003	-0.003	0.009

Betas are effect estimates per effect allele for body mass index and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for body mass index residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for body mass index in UK Biobank. AF – atrial fibrillation, BMI – body mass index, SE – standard error

1



Appendix Figure J.1: Funnel plot of variants in body mass index genetic score. *Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in the body mass index genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.*

1

2

J.2. Effect of waist circumference variants on waist circumference and risk of atrial fibrillation in UK Biobank

For the 37 variants making up the WC genetic score, the beta and standard error values for baseline WC and AF in UKB are displayed in **Appendix Table J.2** and **Appendix Figure J.2**.

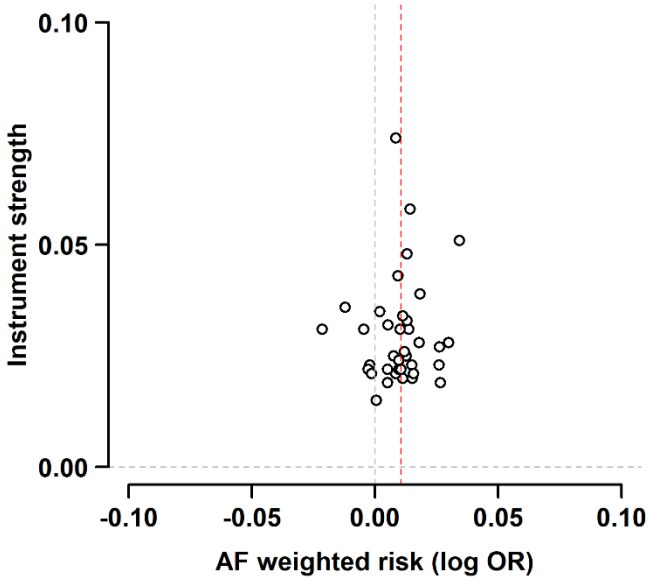
Appendix Table J.2: Variants included in the waist circumference score

RSID	Effect Allele	Other Allele	WC		AF	
			Beta	SE	Beta	SE
rs1558902	A	T	0.064	0.003	0.008	0.009
rs7550711	T	C	0.055	0.008	0.014	0.027
rs6567160	C	T	0.048	0.003	0.013	0.010
rs6755502	C	T	0.043	0.003	0.034	0.012
rs943005	T	C	0.036	0.003	0.018	0.012
rs633715	C	T	0.036	0.003	0.009	0.011
rs10767658	C	G	0.031	0.003	0.014	0.009
rs7498665	G	A	0.029	0.003	0.011	0.009
rs2112347	T	G	0.028	0.003	0.013	0.009
rs1516725	C	T	0.026	0.004	-0.005	0.013
rs2287019	C	T	0.024	0.003	0.002	0.011
rs7138803	A	G	0.024	0.003	0.018	0.009
rs2293576	G	A	0.024	0.003	0.005	0.009
rs10938397	G	A	0.023	0.003	0.005	0.009
rs806794	A	G	0.023	0.003	-0.003	0.010
rs7144011	T	G	0.023	0.003	0.013	0.011
rs4776970	A	T	0.023	0.003	0.015	0.009
rs3810291	A	G	0.023	0.003	0.012	0.009
rs10968576	G	A	0.022	0.003	0.008	0.009
rs2531992	G	A	0.022	0.004	0.030	0.012
rs2075650	A	G	0.022	0.004	-0.021	0.012
rs12429545	A	G	0.020	0.004	0.010	0.013
rs9400239	C	T	0.019	0.003	0.010	0.010
rs16996700	T	C	0.019	0.003	0.015	0.010
rs3127553	G	A	0.019	0.003	-0.002	0.009
rs6545714	G	A	0.018	0.003	0.010	0.009
rs2325036	A	C	0.018	0.003	0.026	0.009
rs7531118	C	T	0.018	0.003	0.026	0.009
rs12446632	G	A	0.017	0.004	-0.012	0.012
rs10840100	G	A	0.016	0.003	0.011	0.009
rs929641	A	G	0.013	0.003	-0.002	0.009
rs3849570	A	C	0.012	0.003	0.008	0.009
rs6163	A	C	0.011	0.003	0.026	0.009
rs2489623	C	A	0.011	0.003	0.005	0.009

rs7903146	C	T	0.010	0.003	0.010	0.010
rs7239883	G	A	0.010	0.003	0.016	0.009
rs2176040	A	G	0.002	0.003	0.001	0.009

Betas are effect estimates per effect allele for waist circumference and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for waist circumference residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for waist circumference in UK Biobank. AF – atrial fibrillation, SE- standard error, WC – waist circumference.

1



Appendix Figure J.2: Funnel plot of variants in waist circumference genetic score.

Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in waist circumference genetic score. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7. The red dotted line is the overall per-allele effect estimate.

2

J.3. Effect of waist circumference adjusted for body mass index variants on waist circumference adjusted for body mass index and risk of atrial fibrillation in UK Biobank

For the 46 variants making up the WCadjBMI genetic score, the beta and standard error values for baseline WCadjBMI and AF in UKB are displayed in **Appendix Table J.3** and **Appendix Figure J.3**.

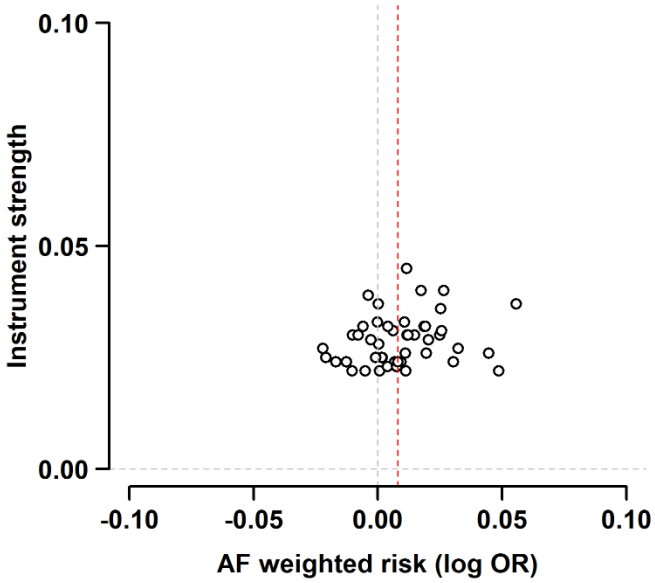
Appendix Table J.3: Variants included in the waist circumference adjusted for body mass index score

RSID	Effect Allele	Other Allele	WCadjBMI Beta	WCadjBMI SE	AF Beta	AF SE
rs4239436	G	A	0.045	0.003	0.026	0.011
rs1358980	T	C	0.039	0.003	-0.006	0.009
rs984222	G	C	0.038	0.003	-0.004	0.009
rs7536458	T	G	0.035	0.003	0.011	0.010
rs754133	A	G	0.035	0.003	-0.008	0.009
rs7162542	G	C	0.035	0.003	0.017	0.009
rs979012	T	C	0.034	0.003	-0.001	0.009
rs6556301	T	G	0.033	0.003	0.000	0.009
rs3116162	A	G	0.033	0.005	0.012	0.016
rs757608	A	G	0.032	0.003	0.011	0.009
rs17451107	T	C	0.032	0.003	0.012	0.009
rs1812175	G	A	0.032	0.003	0.018	0.012
rs1708299	A	G	0.032	0.003	0.015	0.010
rs11057397	C	T	0.031	0.003	0.049	0.009
rs3791675	C	T	0.031	0.003	0.025	0.010
rs1055144	T	C	0.029	0.003	0.000	0.011
rs12991495	T	C	0.029	0.003	0.032	0.009
rs13192994	C	A	0.029	0.004	0.056	0.014
rs3786897	G	A	0.029	0.003	0.001	0.009
rs606452	A	C	0.028	0.004	0.019	0.013
rs11205303	C	T	0.027	0.003	0.025	0.009
rs10990303	T	C	0.027	0.003	0.012	0.011
rs3843467	T	G	0.027	0.003	0.020	0.011
rs13083798	A	G	0.027	0.003	-0.017	0.009
rs395962	T	G	0.026	0.003	-0.010	0.009
rs4542783	T	C	0.025	0.003	0.009	0.009
rs2503111	A	G	0.025	0.003	0.002	0.009
rs780159	G	A	0.025	0.003	0.011	0.009
rs710841	T	C	0.024	0.003	0.045	0.010
rs1879529	G	T	0.022	0.003	0.019	0.010
rs10843151	G	A	0.022	0.003	0.006	0.009

rs806794	A	G	0.022	0.003	-0.003	0.010
rs4868126	G	T	0.022	0.003	0.004	0.009
rs10231365	T	C	0.020	0.003	0.007	0.009
rs8007661	C	T	0.019	0.003	0.008	0.009
rs10429950	C	T	0.019	0.003	0.025	0.010
rs2062708	C	T	0.019	0.003	0.000	0.012
rs7176527	C	T	0.018	0.003	0.004	0.011
rs7801581	T	C	0.018	0.003	-0.021	0.010
rs12493901	G	A	0.017	0.003	0.030	0.009
rs6772896	T	C	0.015	0.003	0.007	0.009
rs12330322	C	T	0.014	0.003	-0.022	0.011
rs615672	G	C	0.013	0.003	0.002	0.009
rs2637030	G	A	0.012	0.003	-0.010	0.009
rs1330	T	C	0.010	0.003	-0.005	0.009
rs741677	A	G	0.009	0.003	-0.013	0.009

Betas are effect estimates per effect allele for waist circumference adjusted for body mass index and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for WCadjBMI residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for WCadjBMI in UK Biobank. AF – atrial fibrillation, SE- standard error, WCadjBMI – waist circumference adjusted for body mass index.

1



Appendix Figure J.3: Funnel plot of variants in waist circumference adjusted for body mass index genetic score.

Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in WCadjBMI genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age2, sex, array, and principal components of ancestry 1-7.

2

J.4.Effect of fat mass variants on fat mass and risk of atrial fibrillation in UK Biobank

For the 157 variants making up the FM genetic score, the beta and standard error values for baseline FM and AF in UKB are displayed in **Appendix Table J.4** and **Appendix Figure J.4**.

Appendix Table J.4: Variants included in the fat mass score

	Effect	Other	Fat mass		AF	
RSID	Allele	Allele	Beta	SE	Beta	SE
rs76895963	G	T	0.079	0.010	0.179	0.032
rs11642015	T	C	0.064	0.003	0.008	0.009
rs76929617	A	G	0.055	0.007	0.026	0.023
rs11951885	C	T	0.051	0.009	0.045	0.029
rs6567160	C	T	0.048	0.003	0.013	0.010
rs62621197	C	T	0.045	0.007	0.098	0.025
rs13135092	G	A	0.044	0.005	0.030	0.016
rs76040172	G	A	0.042	0.006	-0.004	0.019
rs34517439	A	C	0.041	0.004	0.049	0.013
rs72892910	T	G	0.038	0.003	0.018	0.012
rs12140153	G	T	0.036	0.004	0.008	0.015
rs73622719	A	G	0.035	0.006	-0.030	0.020
rs55931203	T	C	0.035	0.003	0.015	0.011
rs6060455	G	A	0.034	0.007	0.007	0.025
rs1477290	C	T	0.033	0.004	0.006	0.013
rs11030119	A	G	0.033	0.003	0.013	0.009
rs7649970	T	C	0.032	0.004	0.023	0.013
rs61765651	C	T	0.031	0.003	0.026	0.011
rs1881505	T	C	0.030	0.006	-0.002	0.019
rs41313250	A	G	0.029	0.004	0.008	0.014
rs41310284	C	A	0.028	0.004	0.002	0.015
rs9843653	C	T	0.028	0.003	0.002	0.009
rs4477562	T	C	0.028	0.004	0.009	0.013
rs2370982	T	C	0.027	0.003	0.017	0.011
rs10938398	A	G	0.027	0.003	0.007	0.009
rs73041988	T	G	0.027	0.003	0.001	0.012
rs60572790	C	T	0.025	0.003	0.015	0.009
rs67844506	A	G	0.025	0.003	0.011	0.011
rs1516725	C	T	0.025	0.004	-0.005	0.013
rs62246314	A	G	0.025	0.004	0.011	0.014
rs55637757	C	T	0.025	0.004	-0.016	0.013
rs7845090	G	A	0.025	0.003	0.001	0.010
rs10153031	G	T	0.025	0.003	0.017	0.009
rs55714539	C	A	0.024	0.003	-0.002	0.009
rs2678204	G	T	0.024	0.003	0.016	0.009
rs79704991	T	G	0.024	0.004	0.017	0.013
rs62082913	G	A	0.024	0.004	-0.024	0.015
rs314279	C	A	0.024	0.004	-0.005	0.014

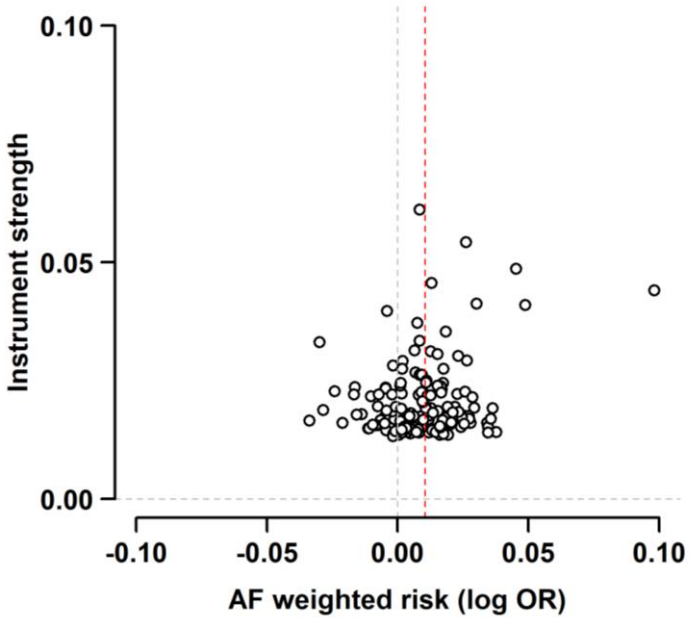
rs13174863	G	A	0.023	0.004	0.017	0.012
rs9471333	C	T	0.023	0.003	0.012	0.009
rs62104483	A	G	0.023	0.003	0.009	0.009
rs11781222	T	C	0.023	0.004	0.013	0.013
rs17770336	T	C	0.023	0.003	0.008	0.009
rs7238896	G	A	0.022	0.004	0.028	0.013
rs2494196	A	C	0.022	0.003	0.001	0.010
rs4876611	G	A	0.022	0.003	0.023	0.010
rs9320823	C	T	0.022	0.003	0.009	0.009
rs4981693	A	G	0.022	0.003	-0.010	0.010
rs55726687	A	G	0.022	0.003	-0.007	0.011
rs6857	C	T	0.022	0.003	-0.017	0.012
rs62025854	G	T	0.022	0.003	0.026	0.010
rs6452788	G	A	0.021	0.003	0.011	0.010
rs10787738	T	C	0.021	0.003	0.011	0.010
rs6545714	G	A	0.021	0.003	0.010	0.009
rs236660	C	T	0.020	0.003	0.036	0.009
rs2192527	G	A	0.020	0.003	0.020	0.009
rs2181375	G	A	0.020	0.003	0.011	0.009
rs10172196	A	G	0.020	0.003	0.015	0.010
rs704061	C	T	0.020	0.003	0.023	0.009
rs3803286	A	G	0.020	0.003	-0.008	0.009
rs4671328	T	G	0.020	0.003	-0.001	0.009
rs10128597	G	A	0.020	0.003	0.013	0.010
rs56288810	G	A	0.019	0.003	-0.004	0.011
rs12578952	A	G	0.019	0.003	0.026	0.010
rs4785955	T	G	0.019	0.003	0.027	0.011
rs10490530	G	A	0.019	0.004	0.029	0.013
rs2439823	G	A	0.019	0.003	0.022	0.009
rs1017529	A	C	0.019	0.003	0.012	0.012
rs28642975	A	G	0.019	0.003	0.013	0.009
rs12037698	G	A	0.019	0.004	-0.029	0.012
rs4673617	T	C	0.019	0.003	0.010	0.010
rs12477088	T	C	0.019	0.003	0.012	0.009
rs1834144	C	A	0.019	0.003	0.005	0.009
rs62178054	T	C	0.019	0.003	0.024	0.009
rs9321191	T	C	0.019	0.003	0.021	0.011
rs10492229	T	C	0.019	0.003	-0.034	0.010
rs16895130	G	A	0.019	0.003	0.012	0.010
rs2979655	G	T	0.018	0.004	-0.002	0.012
rs217672	C	A	0.018	0.003	0.006	0.010
rs73225274	G	A	0.018	0.004	0.001	0.013
rs7171864	A	G	0.018	0.003	-0.016	0.009
rs1886558	A	G	0.018	0.003	0.004	0.009
rs1426371	G	A	0.018	0.003	0.000	0.010
rs35343344	C	A	0.018	0.003	0.019	0.010
rs10259620	A	G	0.018	0.003	-0.004	0.011
rs2474896	T	C	0.018	0.003	0.018	0.009
rs1783541	T	C	0.018	0.003	-0.014	0.011
rs67536595	C	T	0.018	0.003	0.004	0.011
rs208477	T	C	0.018	0.003	-0.001	0.011
rs10195808	A	G	0.018	0.003	0.006	0.009
rs6686901	C	T	0.018	0.003	0.036	0.009
rs60898782	A	G	0.017	0.003	0.027	0.011
rs1218822	A	G	0.017	0.003	0.012	0.009
rs17014332	C	T	0.017	0.003	0.009	0.011
rs4709745	C	T	0.017	0.003	-0.008	0.010

rs6031847	T	C	0.017	0.003	0.006	0.010
rs1731260	T	G	0.017	0.003	-0.007	0.009
rs845084	A	G	0.017	0.003	0.025	0.010
rs1441264	A	G	0.017	0.003	-0.005	0.009
rs76095247	A	C	0.017	0.003	-0.010	0.010
rs62259475	A	G	0.017	0.003	0.003	0.009
rs17256211	G	A	0.017	0.003	0.020	0.009
rs12619178	C	T	0.017	0.003	0.004	0.009
rs13156484	G	A	0.017	0.003	0.016	0.009
rs61903695	G	A	0.017	0.003	-0.005	0.010
rs854917	C	T	0.017	0.003	0.021	0.010
rs12339822	G	A	0.017	0.003	-0.006	0.009
rs2289379	C	T	0.017	0.003	0.025	0.009
rs6893495	T	C	0.017	0.003	-0.021	0.011
rs11714279	G	A	0.017	0.003	0.015	0.010
rs1427325	A	C	0.017	0.003	0.008	0.009
rs7934638	A	G	0.016	0.003	0.017	0.010
rs2418507	T	C	0.016	0.003	0.001	0.009
rs10873302	T	C	0.016	0.003	-0.011	0.010
rs1373349	C	T	0.016	0.003	0.028	0.009
rs10947793	A	G	0.016	0.003	0.034	0.009
rs12583517	G	T	0.016	0.003	0.008	0.010
rs11856579	G	A	0.016	0.003	0.007	0.010
rs10216829	A	G	0.016	0.003	-0.006	0.010
rs10829932	C	T	0.016	0.003	-0.007	0.010
rs12330631	C	T	0.016	0.003	-0.001	0.009
rs9847186	G	A	0.016	0.003	0.034	0.009
rs1891215	C	T	0.016	0.003	0.013	0.009
rs329118	C	T	0.016	0.003	0.038	0.009
rs7701886	G	A	0.016	0.003	0.008	0.009
rs12222235	C	T	0.015	0.003	-0.005	0.009
rs815163	T	C	0.015	0.003	0.016	0.009
rs11780222	A	C	0.015	0.003	-0.003	0.010
rs59104534	T	C	0.015	0.003	0.024	0.010
rs4794222	A	G	0.015	0.003	0.035	0.010
rs11782074	T	G	0.015	0.003	-0.011	0.009
rs3759094	C	T	0.015	0.003	0.017	0.009
rs6127658	C	T	0.015	0.003	0.005	0.010
rs10820852	C	A	0.015	0.003	0.017	0.010
rs6029180	G	A	0.015	0.003	-0.001	0.009
rs8132491	G	A	0.015	0.003	0.016	0.010
rs1458156	T	C	0.015	0.003	-0.002	0.009
rs35014268	C	A	0.015	0.003	0.001	0.010
rs9610311	C	T	0.015	0.003	0.002	0.010
rs12218858	T	C	0.015	0.003	0.000	0.009
rs7925100	A	G	0.015	0.003	0.007	0.009
rs4398538	T	C	0.015	0.003	0.009	0.009
rs7503604	C	A	0.014	0.003	0.008	0.009
rs75983170	G	T	0.014	0.003	0.003	0.009
rs249612	T	C	0.014	0.003	0.016	0.010
rs894347	A	G	0.014	0.003	0.002	0.009
rs1470749	G	T	0.014	0.003	0.019	0.009
rs11968025	G	T	0.014	0.003	0.000	0.009
rs2016469	A	G	0.014	0.003	0.004	0.009
rs1342395	A	C	0.014	0.003	0.005	0.009
rs4072917	A	G	0.014	0.003	0.015	0.009
rs2869950	C	T	0.014	0.003	0.007	0.009

rs1857883	A	G	0.014	0.003	0.012	0.009
rs11655587	C	T	0.014	0.003	0.006	0.009
rs301806	T	C	0.014	0.003	-0.002	0.009
rs529200	G	A	0.014	0.003	0.017	0.009
rs11001963	T	C	0.014	0.003	0.016	0.009

Betas are effect estimates per effect allele for fat mass and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for fat mass residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for fat mass in UK Biobank. AF – atrial fibrillation, SE-standard error.

1



Appendix Figure J.4: Funnel plot of variants in fat mass genetic score.
Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in FM genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

2

3

J.5. Effect of lean mass variants on lean mass and risk of atrial fibrillation in UK Biobank

For the 222 variants making up the LM genetic score, the beta and standard error values for baseline LM and AF in UKB are displayed in **Appendix Table J.5** and **Appendix Figure J.5**.

Appendix Table J.5: Variants included in the lean mass score

	Effect	Other	Lean mass		AF	
RSID	Allele	Allele	Beta	SE	Beta	SE
rs76895963	G	T	0.167	0.010	0.179	0.032
rs78378222	G	T	0.137	0.012	0.032	0.039
rs33966734	C	A	0.128	0.011	0.072	0.040
rs76227980	C	T	0.097	0.009	0.029	0.031
rs58280444	A	G	0.094	0.016	0.068	0.052
rs62621812	A	G	0.076	0.009	-0.048	0.032
rs9128	T	C	0.076	0.012	-0.012	0.043
rs56238630	T	C	0.075	0.008	0.027	0.027
rs66922415	G	A	0.074	0.003	0.015	0.010
rs2744965	T	C	0.064	0.004	0.028	0.013
rs55872725	T	C	0.062	0.003	0.008	0.009
rs62621197	C	T	0.061	0.007	0.098	0.025
rs72656010	T	C	0.061	0.004	0.022	0.013
rs72704611	C	T	0.058	0.011	0.010	0.038
rs34517439	A	C	0.058	0.004	0.049	0.013
rs7559547	T	C	0.055	0.003	0.033	0.012
rs7663887	C	A	0.052	0.004	0.016	0.012
rs3118903	G	A	0.052	0.003	0.005	0.011
rs17024393	C	T	0.050	0.008	0.017	0.027
rs11564039	T	C	0.049	0.009	0.036	0.030
rs1355603	C	T	0.047	0.003	0.019	0.012
rs62064921	C	T	0.047	0.007	0.000	0.023
rs73175572	G	A	0.046	0.004	0.019	0.014
rs76520574	C	T	0.045	0.007	0.003	0.023
rs55681913	C	T	0.045	0.004	0.053	0.014
rs42044	G	T	0.045	0.003	-0.041	0.010
rs6505216	G	T	0.045	0.003	0.024	0.011
rs7235010	A	G	0.044	0.003	0.027	0.011
rs28457693	G	A	0.043	0.004	0.025	0.014
rs76364830	G	A	0.042	0.005	0.070	0.019
rs74494415	C	T	0.042	0.007	0.048	0.023
rs11568828	T	C	0.041	0.004	-0.024	0.015
rs9350850	C	T	0.041	0.005	0.005	0.016
rs7129320	G	A	0.038	0.003	0.025	0.012
rs76798800	T	G	0.037	0.003	0.044	0.010
rs3798519	C	A	0.036	0.003	0.016	0.011
rs3731321	T	C	0.035	0.003	0.007	0.012
rs2885697	G	T	0.035	0.003	0.029	0.009

rs6874142	G	T	0.034	0.004	0.037	0.014
rs35506085	G	A	0.033	0.003	0.018	0.011
rs62515437	T	G	0.033	0.003	0.047	0.010
rs78870364	C	T	0.033	0.006	-0.005	0.021
rs11160601	T	C	0.032	0.004	0.013	0.015
rs74411434	T	C	0.032	0.005	0.044	0.017
rs12713004	G	A	0.031	0.003	0.017	0.010
rs67674827	T	C	0.031	0.003	0.030	0.010
rs76098726	C	T	0.031	0.005	0.000	0.016
rs12378054	T	C	0.031	0.005	0.014	0.016
rs244711	T	C	0.030	0.003	0.003	0.010
rs2633266	C	T	0.030	0.004	0.022	0.014
rs6088638	C	T	0.030	0.003	-0.002	0.012
rs4477562	T	C	0.030	0.004	0.009	0.013
rs34776209	C	T	0.030	0.003	0.013	0.010
rs4073717	G	T	0.029	0.003	0.018	0.011
rs6096886	A	G	0.029	0.003	0.014	0.011
rs757558	G	T	0.029	0.004	0.034	0.012
rs2539999	C	T	0.029	0.003	0.034	0.010
rs6995599	C	T	0.029	0.003	0.023	0.010
rs11014285	A	G	0.029	0.003	0.007	0.012
rs8066863	A	G	0.029	0.004	0.024	0.014
rs11030119	A	G	0.029	0.003	0.013	0.009
rs76513770	T	C	0.029	0.004	0.015	0.013
rs10514136	A	G	0.029	0.003	0.041	0.010
rs7156335	C	T	0.028	0.004	-0.016	0.015
rs73052033	T	C	0.028	0.003	-0.003	0.011
rs11717749	T	C	0.028	0.004	0.011	0.014
rs61732778	A	G	0.028	0.005	0.051	0.017
rs12209223	A	C	0.028	0.004	0.063	0.014
rs55760822	G	T	0.027	0.005	0.008	0.016
rs61628776	A	G	0.027	0.004	0.018	0.013
rs35288270	T	C	0.027	0.004	0.024	0.013
rs1864193	C	A	0.027	0.004	0.007	0.013
rs73619441	T	G	0.027	0.004	0.013	0.013
rs1390498	A	G	0.026	0.003	0.017	0.010
rs3853252	A	G	0.026	0.003	0.000	0.009
rs11187838	A	G	0.026	0.003	-0.005	0.009
rs78964719	T	G	0.026	0.005	0.037	0.017
rs10202845	A	G	0.026	0.004	0.010	0.014
rs2319817	A	G	0.026	0.004	0.025	0.014
rs6762578	A	G	0.026	0.003	0.015	0.011
rs58670122	A	G	0.025	0.004	0.004	0.013
rs3818416	C	A	0.025	0.003	0.017	0.010
rs12879423	G	A	0.025	0.003	0.018	0.009
rs2842385	G	A	0.025	0.003	-0.003	0.011
rs7230581	A	G	0.025	0.003	0.015	0.012
rs73163931	G	A	0.025	0.004	0.028	0.014
rs6800021	A	G	0.025	0.003	0.005	0.009
rs12072845	G	A	0.025	0.003	0.011	0.009
rs11880992	A	G	0.024	0.003	0.007	0.009
rs247008	G	A	0.024	0.003	0.001	0.009
rs11747434	C	T	0.024	0.003	0.008	0.010
rs1347247	G	A	0.024	0.005	0.017	0.016
rs9379084	G	A	0.024	0.004	0.014	0.014
rs1474055	T	C	0.023	0.004	0.006	0.014
rs10434434	A	C	0.023	0.004	0.023	0.012

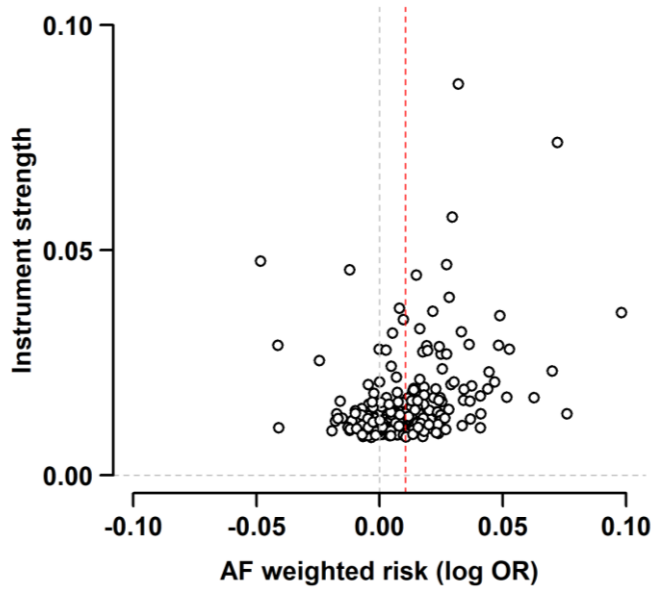
rs9894577	G	A	0.023	0.003	0.004	0.009
rs55726687	A	G	0.023	0.003	-0.007	0.011
rs12344584	A	G	0.023	0.005	0.076	0.016
rs2252720	C	T	0.023	0.003	0.023	0.009
rs7137828	T	C	0.023	0.003	-0.010	0.009
rs33967909	A	G	0.023	0.003	0.013	0.011
rs676105	C	T	0.023	0.003	0.012	0.010
rs7218001	A	C	0.022	0.003	-0.017	0.011
rs12900116	T	C	0.022	0.003	0.003	0.009
rs1984119	T	C	0.022	0.003	0.020	0.010
rs73013411	A	C	0.022	0.004	0.008	0.013
rs2678204	G	T	0.022	0.003	0.016	0.009
rs4128460	A	G	0.022	0.003	0.016	0.011
rs1926034	A	G	0.022	0.003	0.024	0.009
rs57635800	A	G	0.022	0.003	0.010	0.010
rs12540011	A	G	0.022	0.003	0.007	0.010
rs703593	A	G	0.021	0.003	0.015	0.009
rs73601548	T	C	0.021	0.004	-0.010	0.014
rs4858697	G	A	0.021	0.003	0.037	0.009
rs34045288	T	C	0.021	0.003	0.024	0.009
rs2592831	C	T	0.021	0.003	0.025	0.009
rs514328	A	G	0.021	0.004	-0.007	0.014
rs11907497	C	T	0.021	0.003	-0.015	0.010
rs2900208	A	C	0.021	0.003	0.005	0.009
rs343935	C	T	0.021	0.004	0.010	0.012
rs2158045	T	C	0.021	0.003	0.015	0.009
rs7849060	C	T	0.021	0.003	0.041	0.010
rs668871	T	C	0.021	0.003	0.013	0.009
rs11578046	G	A	0.021	0.003	0.015	0.009
rs61765651	C	T	0.021	0.003	0.026	0.011
rs2508710	T	G	0.021	0.003	-0.011	0.011
rs11042717	T	C	0.021	0.003	-0.018	0.009
rs7910211	C	T	0.021	0.004	-0.017	0.012
rs34776495	G	A	0.021	0.003	-0.002	0.009
rs2455561	T	G	0.021	0.003	0.004	0.009
rs57790054	G	A	0.021	0.003	-0.007	0.010
rs4804090	C	T	0.021	0.003	-0.005	0.009
rs3778157	C	T	0.020	0.003	0.016	0.012
rs663112	T	C	0.020	0.004	0.018	0.012
rs1967315	A	G	0.020	0.003	-0.003	0.010
rs7072873	C	T	0.020	0.003	-0.005	0.009
rs13186522	T	C	0.020	0.003	0.006	0.009
rs3809570	A	C	0.020	0.003	0.005	0.010
rs2396348	T	C	0.020	0.003	0.003	0.010
rs7141420	T	C	0.020	0.003	0.017	0.009
rs1541597	T	G	0.019	0.003	0.013	0.011
rs7255927	G	A	0.019	0.003	-0.003	0.010
rs62370476	G	A	0.019	0.003	0.019	0.011
rs3923783	C	A	0.019	0.003	0.014	0.011
rs14976	T	C	0.019	0.003	-0.002	0.010
rs5752989	G	A	0.019	0.003	0.002	0.009
rs60804050	G	A	0.019	0.003	0.010	0.010
rs2075060	A	G	0.019	0.003	0.005	0.009
rs7229520	G	A	0.019	0.003	-0.041	0.009
rs4752689	A	G	0.019	0.003	0.013	0.009
rs3795503	T	C	0.018	0.003	0.007	0.009
rs2102278	G	A	0.018	0.003	0.004	0.009

rs7845090	G	A	0.018	0.003	0.001	0.010
rs7396827	T	C	0.018	0.003	0.009	0.009
rs11709402	G	A	0.018	0.003	0.010	0.010
rs29938	C	T	0.018	0.003	0.001	0.009
rs73228208	A	G	0.018	0.003	0.006	0.011
rs475591	C	T	0.018	0.003	0.024	0.009
rs2413592	G	A	0.018	0.003	-0.007	0.010
rs12422933	A	C	0.018	0.003	0.033	0.010
rs7208285	G	A	0.018	0.003	0.020	0.009
rs2979655	G	T	0.018	0.003	-0.002	0.012
rs4895917	C	T	0.017	0.003	-0.001	0.009
rs4985148	A	C	0.017	0.003	-0.004	0.009
rs983399	C	T	0.017	0.003	0.000	0.009
rs71414738	T	C	0.017	0.003	0.008	0.011
rs7278123	A	G	0.017	0.003	0.014	0.011
rs4888153	A	G	0.017	0.003	0.041	0.010
rs357501	A	G	0.017	0.003	0.009	0.009
rs181895	A	G	0.017	0.003	0.011	0.009
rs4143843	C	T	0.017	0.003	0.009	0.009
rs246177	T	C	0.017	0.003	0.027	0.009
rs8019890	A	C	0.017	0.003	0.008	0.009
rs11589536	A	C	0.017	0.003	0.021	0.009
rs10746837	G	A	0.017	0.003	0.014	0.009
rs9295	A	G	0.017	0.003	0.016	0.010
rs68156080	A	G	0.017	0.003	0.009	0.010
rs632224	A	G	0.017	0.003	0.014	0.009
rs2115459	T	C	0.017	0.003	0.010	0.009
rs10202701	T	C	0.017	0.003	-0.002	0.009
rs1927635	C	T	0.017	0.003	0.013	0.009
rs62129346	T	C	0.017	0.003	0.014	0.010
rs10811901	A	G	0.017	0.003	-0.012	0.009
rs254963	A	G	0.016	0.003	0.004	0.009
rs1692584	C	T	0.016	0.003	0.004	0.009
rs8107967	A	G	0.016	0.003	0.004	0.009
rs705159	A	G	0.016	0.003	0.010	0.009
rs7220854	C	T	0.016	0.003	-0.005	0.009
rs501332	A	G	0.016	0.003	-0.019	0.010
rs2870132	C	A	0.016	0.003	-0.006	0.010
rs11707955	C	T	0.016	0.003	0.000	0.009
rs7184768	A	G	0.016	0.003	-0.005	0.009
rs4819021	T	C	0.016	0.003	0.000	0.009
rs662115	T	C	0.016	0.003	0.018	0.009
rs755481	G	T	0.016	0.003	-0.009	0.009
rs8133137	G	A	0.016	0.003	0.023	0.009
rs310802	T	C	0.015	0.003	-0.007	0.010
rs1528450	C	T	0.015	0.003	0.014	0.009
rs10076828	A	G	0.015	0.003	0.024	0.010
rs6563808	T	C	0.015	0.003	0.004	0.010
rs10139746	A	G	0.015	0.003	0.009	0.009
rs1837367	A	G	0.015	0.003	0.007	0.009
rs11783086	C	T	0.015	0.003	0.004	0.009
rs6755489	A	G	0.015	0.003	-0.001	0.010
rs35651070	G	A	0.015	0.003	0.019	0.012
rs2866719	T	C	0.015	0.003	0.011	0.009
rs877041	A	G	0.015	0.003	0.004	0.009
rs4270917	C	T	0.015	0.003	0.000	0.009
rs12986369	A	G	0.015	0.003	0.010	0.009

rs58403320	G	A	0.015	0.003	-0.013	0.011
rs4778918	T	C	0.015	0.003	0.010	0.009
rs10231036	G	A	0.015	0.003	0.017	0.009
rs10091194	G	A	0.014	0.003	0.004	0.009
rs1004030	T	C	0.014	0.003	0.001	0.009
rs174047	G	T	0.014	0.003	-0.003	0.009
rs17806016	A	G	0.014	0.003	0.007	0.009
rs7590946	T	C	0.014	0.003	-0.007	0.009
rs11196169	A	G	0.014	0.003	-0.006	0.009
rs6902789	A	G	0.014	0.003	-0.012	0.009
rs7812293	T	C	0.014	0.003	0.013	0.009
rs7649884	A	G	0.014	0.003	-0.002	0.009
rs7624087	C	T	0.014	0.003	0.011	0.009
rs6719296	A	G	0.014	0.003	-0.005	0.009

Betas are effect estimates per effect allele for lean mass and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for lean mass residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for lean mass in UK Biobank. AF – atrial fibrillation, SE – standard error.

1



Appendix Figure J.5: Funnel plot of variants in lean mass genetic score.
Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in lean mass genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

2

J.6. Effect of C-reactive protein variants on C-reactive protein and atrial fibrillation in UK Biobank

For the 255 variants making up the CRP genetic score, the beta and standard error values for baseline log-CRP and AF in UKB are displayed in **Appendix Table J.6** and **Appendix Figure J.6**.

Appendix Table J.6: Variants included in the C-reactive protein score

RSID	Effect Allele	Other Allele	Log-CRP		AF	
			Beta	SE	Beta	SE
rs147711004	G	A	0.191	0.007	-0.027	0.023
rs17616063	A	G	0.127	0.005	0.009	0.017
rs149624078	C	T	0.119	0.011	0.036	0.039
rs1800961	C	T	0.106	0.007	-0.017	0.025
rs28929474	C	T	0.100	0.009	0.060	0.031
rs11208685	A	T	0.096	0.003	-0.014	0.011
rs75460349	A	C	0.096	0.008	-0.030	0.029
rs531479718	C	CAA	0.087	0.002	0.050	0.009
rs4656241	C	T	0.084	0.003	-0.014	0.011
rs61946383	A	G	0.081	0.003	0.026	0.009
rs55707100	T	C	0.080	0.008	-0.029	0.029
rs1260326	T	C	0.074	0.003	-0.007	0.009
rs149394327	C	G	0.058	0.007	0.112	0.025
rs11047224	G	C	0.055	0.007	-0.042	0.024
rs77738620	C	T	0.054	0.012	0.032	0.042
rs77704739	T	C	0.047	0.006	-0.014	0.022
rs7012637	A	G	0.047	0.002	0.009	0.009
rs2207132	A	G	0.046	0.007	-0.015	0.025
rs1801272	A	T	0.046	0.008	0.006	0.028
rs6734238	G	A	0.044	0.003	0.004	0.009
rs12239046	C	T	0.039	0.003	0.008	0.009
rs58542926	T	C	0.038	0.005	0.000	0.017
rs11868378	G	A	0.037	0.003	-0.013	0.012
rs11666245	G	A	0.034	0.006	0.028	0.021
rs469882	A	C	0.034	0.003	-0.003	0.011
rs4817984	C	A	0.033	0.003	0.013	0.010
rs56821385	C	T	0.033	0.007	0.010	0.026
rs4647725	T	C	0.033	0.003	-0.019	0.012
rs2289852	G	A	0.033	0.005	0.038	0.019
rs2239222	G	A	0.032	0.003	-0.014	0.009
rs17138478	A	C	0.032	0.004	0.029	0.013
rs6519133	T	C	0.032	0.003	-0.020	0.009
rs3768321	T	G	0.032	0.003	0.049	0.011
rs4018180	G	A	0.032	0.005	0.051	0.018
rs1037170	T	C	0.031	0.003	0.007	0.010
rs1800973	A	C	0.031	0.005	0.001	0.018
rs62618693	C	T	0.031	0.006	0.023	0.021

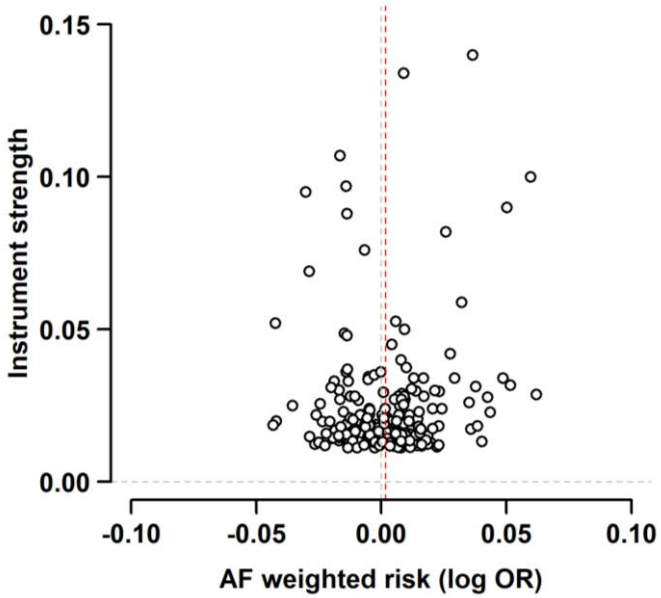
rs11667234	A	C	0.030	0.006	0.014	0.021
rs1490384	C	T	0.030	0.002	0.009	0.009
rs6486122	T	C	0.030	0.003	0.021	0.009
rs75229905	T	C	0.029	0.004	-0.014	0.013
rs339969	A	C	0.029	0.003	0.017	0.009
rs16988471	C	A	0.028	0.006	-0.005	0.021
rs200733118	A	C	0.028	0.005	0.017	0.018
rs1688043	C	T	0.027	0.005	0.012	0.018
rs11772470	G	A	0.027	0.003	-0.017	0.012
rs10868852	A	C	0.027	0.007	-0.005	0.026
rs687339	C	T	0.026	0.003	-0.036	0.011
rs12231235	G	A	0.026	0.002	-0.012	0.009
rs4988483	A	C	0.026	0.005	0.042	0.019
rs1332328	T	C	0.026	0.003	0.009	0.009
rs72730950	A	G	0.026	0.005	0.009	0.017
rs55855238	C	T	0.026	0.003	0.005	0.009
rs6073958	T	C	0.025	0.003	-0.011	0.011
rs10095930	T	C	0.025	0.003	0.008	0.009
rs2429473	A	C	0.025	0.003	0.008	0.011
rs11790458	G	A	0.025	0.003	-0.024	0.012
rs1056441	C	T	0.024	0.003	0.008	0.009
rs2657896	C	T	0.024	0.003	-0.015	0.012
rs7756870	G	C	0.024	0.003	-0.026	0.009
rs145604770	G	A	0.023	0.006	0.062	0.023
rs28601761	C	G	0.023	0.003	0.002	0.009
rs1441169	A	G	0.023	0.002	0.010	0.009
rs6920220	A	G	0.023	0.003	0.007	0.010
rs9604045	G	T	0.023	0.003	0.015	0.011
rs2700938	C	T	0.023	0.003	0.002	0.009
rs1880241	A	G	0.023	0.002	0.007	0.009
rs3732356	G	T	0.023	0.005	-0.005	0.018
rs505922	C	T	0.022	0.003	0.024	0.009
rs6686560	A	G	0.022	0.004	-0.024	0.015
rs17056278	G	C	0.022	0.005	0.043	0.016
rs2280406	A	G	0.022	0.002	0.000	0.009
rs75265117	G	C	0.021	0.004	0.015	0.013
rs1545536	C	T	0.021	0.003	0.021	0.011
rs3808348	C	T	0.021	0.003	-0.008	0.011
rs74904971	C	A	0.021	0.004	0.009	0.014
rs7357754	G	A	0.021	0.002	-0.006	0.009
rs56094641	G	A	0.021	0.003	0.008	0.009
rs2161037	A	G	0.021	0.002	-0.013	0.009
rs11118625	A	G	0.021	0.003	0.002	0.010
rs2542153	C	T	0.021	0.002	-0.005	0.009
rs78428995	C	T	0.021	0.002	0.011	0.009
rs13028310	C	T	0.020	0.003	0.035	0.012
rs1886008	T	C	0.020	0.004	0.012	0.014
rs113585586	T	G	0.020	0.004	0.023	0.013
rs12459419	C	T	0.020	0.003	0.007	0.009
rs11928797	C	A	0.020	0.004	0.009	0.014
rs2307377	G	A	0.020	0.005	-0.005	0.016
rs7933202	A	C	0.020	0.003	0.001	0.009
rs76620584	A	G	0.019	0.004	0.001	0.015
rs552693039	T	T	0.019	0.003	-0.021	0.011
rs1292061	G	A	0.019	0.002	0.011	0.009
rs7103411	T	C	0.019	0.003	0.011	0.011
rs1800693	T	C	0.019	0.003	-0.006	0.009

rs34864350	G	A	0.019	0.005	-0.017	0.019
rs4714508	G	A	0.019	0.003	0.003	0.009
rs60037105	A	T	0.019	0.003	0.038	0.009
rs5017416	T	G	0.019	0.006	-0.009	0.021
rs35462231	A	T	0.019	0.003	0.014	0.011
rs166169	C	T	0.019	0.003	-0.007	0.012
rs11689543	T	A	0.019	0.003	-0.012	0.009
rs6792725	A	G	0.019	0.003	-0.005	0.010
rs11078597	T	C	0.019	0.003	-0.002	0.011
rs12927172	A	G	0.019	0.003	-0.014	0.009
rs73137144	A	G	0.019	0.003	-0.043	0.011
rs1905505	A	G	0.018	0.003	0.011	0.010
rs704017	A	G	0.018	0.002	0.015	0.009
rs17391694	T	C	0.018	0.004	0.036	0.013
rs6020459	C	T	0.018	0.003	-0.006	0.010
rs12929503	T	C	0.018	0.003	0.009	0.009
rs4764939	C	T	0.018	0.002	0.012	0.009
rs7084062	G	A	0.018	0.002	0.008	0.009
rs9611454	C	T	0.018	0.003	0.006	0.009
rs10871777	G	A	0.018	0.003	0.014	0.010
rs12132412	G	A	0.018	0.003	-0.015	0.009
rs34761529	C	T	0.018	0.003	0.008	0.011
rs4141632	A	G	0.017	0.003	-0.009	0.010
rs114947103	C	T	0.017	0.003	-0.008	0.012
rs562609617	G	G	0.017	0.003	-0.001	0.010
rs4418728	G	T	0.017	0.002	0.007	0.009
rs7127808	T	A	0.017	0.003	0.014	0.011
rs9738365	A	C	0.017	0.003	-0.006	0.010
rs7956514	G	T	0.017	0.003	-0.017	0.010
rs55981844	T	C	0.017	0.003	0.003	0.010
rs663015	C	T	0.017	0.003	0.005	0.009
rs1338071	C	G	0.017	0.003	0.001	0.010
rs12516176	C	T	0.017	0.003	0.009	0.010
rs10770829	T	C	0.017	0.003	0.005	0.011
rs1532085	A	G	0.017	0.003	0.010	0.009
rs2596937	C	T	0.017	0.003	0.007	0.011
rs59916403	T	G	0.017	0.003	0.003	0.009
rs750344	A	G	0.017	0.003	-0.022	0.010
rs12716972	G	A	0.017	0.002	0.022	0.009
rs174373	T	C	0.016	0.003	-0.004	0.011
rs6595549	G	C	0.016	0.003	-0.005	0.011
rs8072566	G	A	0.016	0.003	-0.011	0.011
rs4658403	C	T	0.016	0.003	0.001	0.012
rs10760691	G	A	0.016	0.003	-0.010	0.009
rs72799498	A	G	0.016	0.003	0.002	0.012
rs1869358	T	C	0.016	0.003	-0.018	0.010
rs28582591	A	G	0.016	0.003	0.011	0.012
rs4149349	C	C	0.016	0.003	-0.012	0.009
rs4690098	T	C	0.016	0.003	-0.003	0.010
rs2261790	C	T	0.016	0.002	-0.003	0.009
rs3935032	C	T	0.016	0.003	0.014	0.009
rs10924372	C	T	0.016	0.003	0.006	0.009
rs787488	A	G	0.016	0.003	0.011	0.010
rs570916461	A	AT	0.016	0.003	0.010	0.009
rs7539725	A	G	0.016	0.004	0.016	0.013
rs11653826	T	C	0.016	0.004	-0.042	0.015
rs11156891	T	A	0.015	0.003	-0.006	0.011

rs288183	T	G	0.015	0.003	-0.012	0.012
rs2956395	G	C	0.015	0.003	-0.014	0.009
rs4755720	C	T	0.015	0.003	0.007	0.009
rs142122735	C	C	0.015	0.003	-0.022	0.009
rs2161374	C	T	0.015	0.002	-0.006	0.009
rs385417	A	C	0.015	0.003	-0.019	0.009
rs113584870	G	A	0.015	0.003	-0.015	0.012
rs197419	C	A	0.015	0.003	0.009	0.009
rs1470560	A	G	0.015	0.003	0.023	0.009
rs62011286	G	A	0.015	0.003	-0.014	0.009
rs11708067	G	A	0.015	0.003	0.013	0.010
rs13294945	T	G	0.015	0.003	0.014	0.009
rs34284056	C	A	0.015	0.003	0.004	0.010
rs4354188	T	C	0.015	0.002	-0.005	0.009
rs56045434	G	C	0.015	0.003	-0.001	0.012
rs13066686	C	A	0.014	0.003	0.002	0.009
rs6925389	G	A	0.014	0.003	-0.029	0.009
rs146424514	A	G	0.014	0.003	0.011	0.012
rs4788095	C	T	0.014	0.003	0.009	0.009
rs7310135	T	C	0.014	0.002	0.006	0.009
rs583040	G	A	0.014	0.003	-0.009	0.009
rs72694393	G	T	0.014	0.002	-0.016	0.009
rs2156407	A	G	0.014	0.003	-0.017	0.010
rs13416992	A	C	0.014	0.003	0.011	0.009
rs10864088	G	A	0.014	0.003	0.011	0.010
rs4468667	G	A	0.014	0.003	0.019	0.010
rs12613751	G	A	0.014	0.003	0.006	0.009
rs12140498	C	T	0.014	0.003	0.011	0.011
rs123698	G	C	0.014	0.003	-0.010	0.009
rs73672511	G	T	0.014	0.004	0.020	0.013
rs12428361	C	T	0.014	0.003	-0.019	0.010
rs303429	C	T	0.014	0.003	0.010	0.009
rs7908825	G	C	0.014	0.002	0.040	0.009
rs2030291	A	T	0.014	0.003	-0.025	0.009
rs17417252	G	A	0.014	0.003	-0.005	0.010
rs12523793	G	A	0.014	0.003	-0.003	0.009
rs178826	T	C	0.014	0.002	0.002	0.009
rs2177382	G	A	0.013	0.003	-0.001	0.012
rs10831676	A	C	0.013	0.002	0.005	0.009
rs245767	G	A	0.013	0.003	-0.017	0.010
rs9905884	A	C	0.013	0.003	-0.011	0.010
rs10106298	A	G	0.013	0.003	-0.003	0.009
rs7662792	T	A	0.013	0.003	-0.001	0.009
rs930035	G	A	0.013	0.003	0.000	0.009
rs10880868	T	C	0.013	0.003	0.012	0.011
rs6443429	A	C	0.013	0.003	-0.012	0.009
rs59737437	C	T	0.013	0.003	-0.016	0.010
rs12620844	C	T	0.013	0.003	-0.004	0.009
rs7993752	C	A	0.013	0.003	0.008	0.009
rs1222209	C	A	0.013	0.003	-0.005	0.009
rs17098829	G	C	0.013	0.003	0.004	0.010
rs67890964	C	T	0.013	0.003	0.005	0.009
rs4246598	A	C	0.013	0.002	-0.003	0.009
rs12220	C	T	0.013	0.003	0.018	0.009
rs630372	A	G	0.013	0.003	0.008	0.010
rs11012732	G	A	0.013	0.003	-0.005	0.009
rs424539	G	C	0.013	0.003	0.014	0.009

rs189400382	G	A	0.013	0.003	-0.008	0.009
rs6993128	C	T	0.013	0.003	0.001	0.010
rs12621948	C	G	0.012	0.003	-0.001	0.010
rs3785568	T	C	0.012	0.003	-0.004	0.011
rs12270146	A	G	0.012	0.003	0.003	0.010
rs11217192	T	G	0.012	0.003	0.004	0.010
rs946551	C	T	0.012	0.003	0.000	0.010
rs994596	T	C	0.012	0.003	0.018	0.009
rs10497423	G	T	0.012	0.003	0.004	0.009
rs1635852	T	C	0.012	0.002	0.010	0.009
rs11054402	C	T	0.012	0.003	-0.009	0.009
rs2274782	T	C	0.012	0.003	-0.023	0.009
rs6775319	T	A	0.012	0.003	-0.003	0.010
rs6453434	T	G	0.012	0.003	0.006	0.009
rs1969066	A	G	0.012	0.003	0.006	0.010
rs112957492	T	C	0.012	0.003	-0.006	0.009
rs7455288	T	C	0.011	0.003	0.002	0.010
rs11711864	A	G	0.011	0.002	0.007	0.009
rs72712556	G	A	0.011	0.003	-0.001	0.009
rs10498240	A	C	0.011	0.003	-0.006	0.009
rs2239949	C	T	0.011	0.003	0.016	0.009
rs12191817	G	T	0.011	0.003	-0.002	0.009
rs17050272	A	G	0.011	0.002	-0.003	0.009
rs7801838	C	T	0.011	0.003	0.003	0.009
rs6768108	C	T	0.011	0.002	-0.010	0.009
rs2926851	T	C	0.011	0.002	0.011	0.009
rs10969334	C	A	0.011	0.003	0.008	0.009
rs9965184	A	T	0.011	0.003	0.003	0.009
rs10008492	T	C	0.011	0.003	0.004	0.009
rs11782130	T	G	0.011	0.003	-0.010	0.009
rs9977825	T	C	0.010	0.003	0.016	0.009
rs59427082	C	T	0.010	0.002	0.013	0.009
rs10027275	G	C	0.010	0.003	0.002	0.010
rs9788721	C	T	0.010	0.003	-0.007	0.009
rs11624418	A	G	0.010	0.003	-0.002	0.010
rs459625	T	C	0.010	0.002	0.011	0.009
rs68085814	G	A	0.010	0.003	0.004	0.010
rs12605964	T	C	0.010	0.003	-0.012	0.009
rs991946	T	C	0.009	0.002	-0.013	0.009
rs141936164	A	G	0.009	0.003	-0.003	0.009
rs17138528	T	C	0.009	0.003	-0.027	0.010
rs500812	T	G	0.009	0.003	-0.010	0.009
rs35415272	A	AAA	0.009	0.003	-0.003	0.009
rs6801781	A	G	0.009	0.003	0.003	0.010
rs6695390	T	G	0.008	0.002	0.011	0.009
rs6500446	A	G	0.008	0.002	0.007	0.009
rs10078214	A	C	0.008	0.003	0.020	0.010

Betas are effect estimates per effect allele for log-C-reactive protein and atrial fibrillation calculated from UK Biobank data. Effect estimates are calculated for log C-reactive protein residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for log C-reactive protein in UK Biobank. CRP – C-reactive protein, SE – standard error.



Appendix Figure J.6: Funnel plot of variants in C-reactive protein genetic score. *Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as per-allele log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in C-reactive protein genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.*

J.7. Effect of cis-C-reactive protein variants on C-reactive protein and atrial fibrillation in UK Biobank

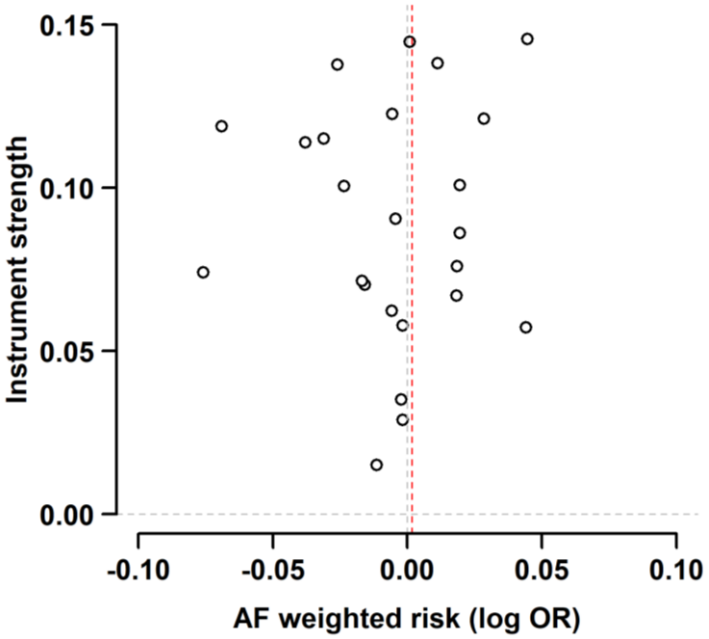
For the 28 variants making up the cis-C-reactive protein genetic score, the beta and standard error values for baseline log-CRP and AF in UKB are displayed in **Appendix Table J.7** and **Appendix Figure J.7**.

Appendix Table J.7: Variants included in the cis-C-reactive protein score

RSID	Effect Allele	Other Allele	Log-CRP		AF	
			Beta	SE	Beta	SE
rs11579148	C	T	0.300	0.012	-0.012	0.043
rs77013776	A	C	0.249	0.007	-0.018	0.023
rs3091244	A	G	0.214	0.005	0.011	0.019
rs7551731	T	C	0.167	0.003	0.000	0.009
rs188497920	G	A	0.155	0.013	0.045	0.044
rs116702045	G	A	0.134	0.007	0.001	0.024
rs12760385	G	A	0.126	0.009	-0.026	0.031
rs116247097	G	A	0.118	0.009	-0.006	0.030
rs58785319	ACACC	A	0.098	0.014	-0.069	0.050
rs115585839	T	G	0.098	0.009	-0.031	0.033
rs3093070	G	T	0.095	0.009	-0.038	0.030
rs113188187	T	C	0.095	0.008	0.028	0.029
rs151313645	C	A	0.082	0.003	-0.004	0.009
rs12094103	A	G	0.082	0.009	0.019	0.031
rs72698563	T	A	0.079	0.013	-0.076	0.044
rs12116869	T	C	0.078	0.008	0.018	0.029
rs200372148	G	GT	0.078	0.007	-0.024	0.024
rs547550247	C	A	0.073	0.006	-0.017	0.022
rs61821592	C	T	0.073	0.009	0.019	0.030
rs116073407	A	G	0.063	0.011	-0.016	0.037
1:159683234	G	GCGGGAGGTACCAGAGACAGAGACGTGGGGCCCATGCGGTGTAAAAAAC	0.059	0.010	0.044	0.036
rs116337989	A	G	0.056	0.010	0.018	0.036
rs2592904	T	C	0.050	0.003	-0.002	0.009
rs12026296	T	C	0.049	0.005	-0.006	0.016
rs11589667	C	T	0.030	0.003	-0.002	0.009
rs76769546	G	A	0.028	0.006	-0.002	0.020
rs368274510	T	C	0.013	0.003	-0.012	0.011
rs11265263	C	A	0.002	0.049	-0.292	0.151

Betas are effect estimates per effect allele for log-C-reactive protein and atrial fibrillation calculated from UKB data. Effect estimates are calculated for log C-reactive protein residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were

calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for log C-reactive protein in UKB. CRP – C-reactive protein, SE – standard error.



Appendix Figure J.7: Funnel plot of variants in cis-C-reactive protein genetic score.

Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as per-allele log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in cis-C-reactive protein genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

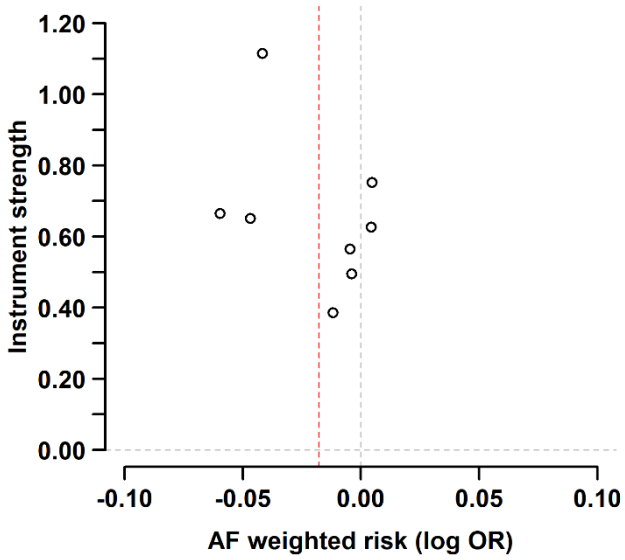
J.8. Effect of Interleukin 6-receptor variants on C-reactive protein and risk of atrial fibrillation in UK Biobank

For the eight variants making up the interleukin 6-recptor genetic score, the beta and standard error values for baseline log-CRP and AF in UKB are displayed in **Appendix Table J.8** and **Appendix Figure J.8**.

Appendix Table J.8: Variants included in the IL-6 receptor score

Variant RSID	Effect Allele	Other Allele	Log-CRP		AF	
			Beta	SE	Beta	SE
rs4129267	T	C	-0.090	0.003	-0.042	0.009
rs116805289	A	C	-0.057	0.008	0.004	0.029
rs139952834	C	T	-0.052	0.012	-0.047	0.040
rs3766924	C	T	-0.045	0.003	-0.012	0.011
rs79925547	T	C	-0.044	0.011	0.005	0.038
rs61806853	C	T	-0.038	0.006	-0.004	0.020
rs76518735	A	C	-0.035	0.009	-0.005	0.032
rs149551556	C	T	-0.024	0.010	-0.060	0.035

Betas are effect estimates per effect allele for log-C-reactive protein and atrial fibrillation calculated from UKB data. Effect estimates are calculated for log C-reactive protein residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for log C-reactive protein in UKB. AF- atrial fibrillation, IL – interleukin, SE – standard error.



Appendix Figure J.8: Funnel plot of variants in interleukin-6 receptor genetic score.

Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as per-allele log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in interleukin-6 receptor genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

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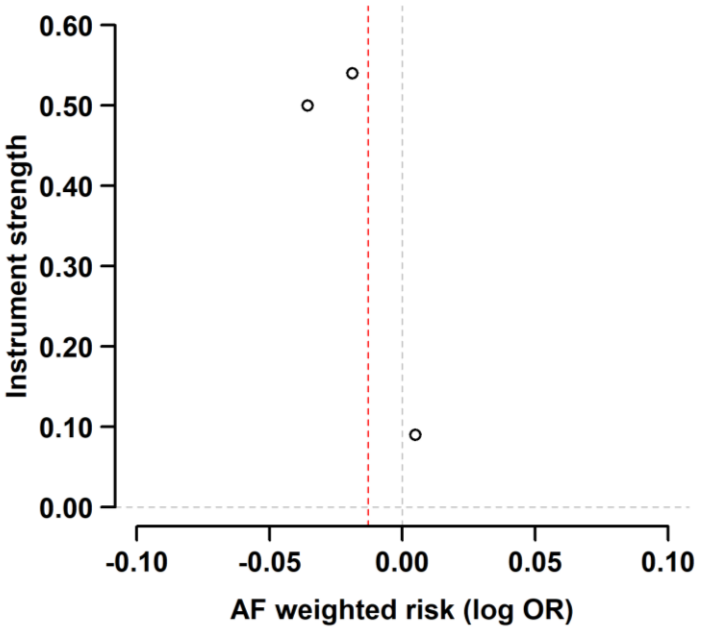
J.9. Effect of CD40 variants on C-reactive protein and risk of atrial fibrillation in UK Biobank

For the three variants making up the CD40 genetic score, the beta and standard error values for baseline log-CRP and AF in UKB are displayed in **Appendix Table J.9** and **Appendix Figure J.9**.

Appendix Table J.9: Variants included in the CD40 receptor score

Variant RSID	Effect Allele	Other Allele	Log-CRP		AF	
			Beta	SE	Beta	SE
rs41282788	C	G	-0.006	0.008	-0.019	0.029
rs4810485	G	T	-0.003	0.003	0.005	0.009
rs4801216	C	T	-0.002	0.003	-0.036	0.010

Betas are effect estimates per effect allele for log-C-reactive protein and atrial fibrillation calculated from UKB data. Effect estimates are calculated for log C-reactive protein residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for log C-reactive protein in UKB. AF – atrial fibrillation, CRP – C-reactive protein, SE – standard error.



Appendix Figure J.9: Funnel plot of variants in CD40 genetic score.
Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as per-allele log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in CD40 genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

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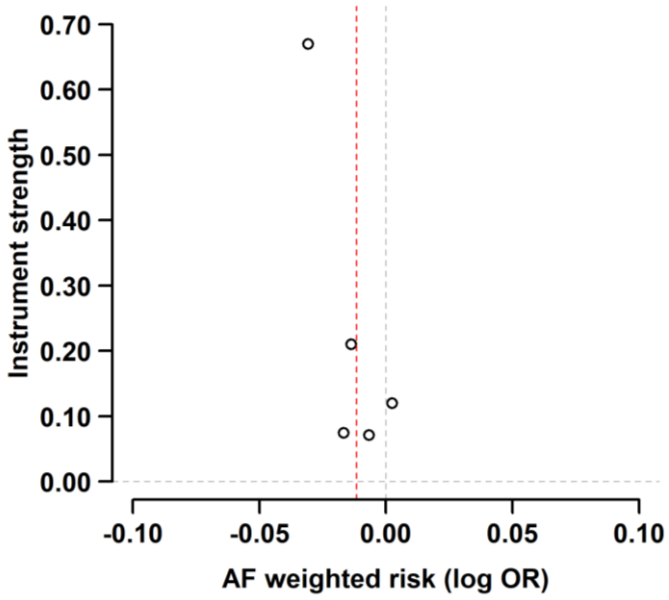
J.10. Effect of YKL40 variants on C-reactive protein and risk of atrial fibrillation in UK Biobank

For the five variants making up the YKL40 genetic score, the beta and standard error values for baseline log-CRP and AF in UKB are displayed in **Appendix Table J.10** and **Appendix Figure J.10**.

Appendix Table J.10: Variants included in the YKL40 receptor score

			Log-CRP		AF	
RSID	**Effect Allele**	**Other Allele**	**Beta**	**SE**	**Beta**	**SE**
rs1260326	T	C	0.076	0.003	-0.007	0.009
rs28601761	C	G	0.024	0.003	0.002	0.009
rs4950931	A	G	-0.003	0.003	-0.031	0.011
rs62140201	G	A	-0.014	0.008	-0.014	0.026
rs339969	C	A	-0.028	0.003	-0.017	0.009

Betas are effect estimates per effect allele for log-C-reactive protein and atrial fibrillation calculated from UKB data. Effect estimates are calculated for log C-reactive protein residuals using linear regression models adjusted for sex, age, age^2, array, and principal components of ancestry 1-7. Effect estimates for atrial fibrillation were calculated using logistic regression adjusting for the same covariates. Variants are ordered from largest to smallest effect size for log C-reactive protein in UKB. AF – atrial fibrillation, CRP – C-reactive protein, SE – standard error.

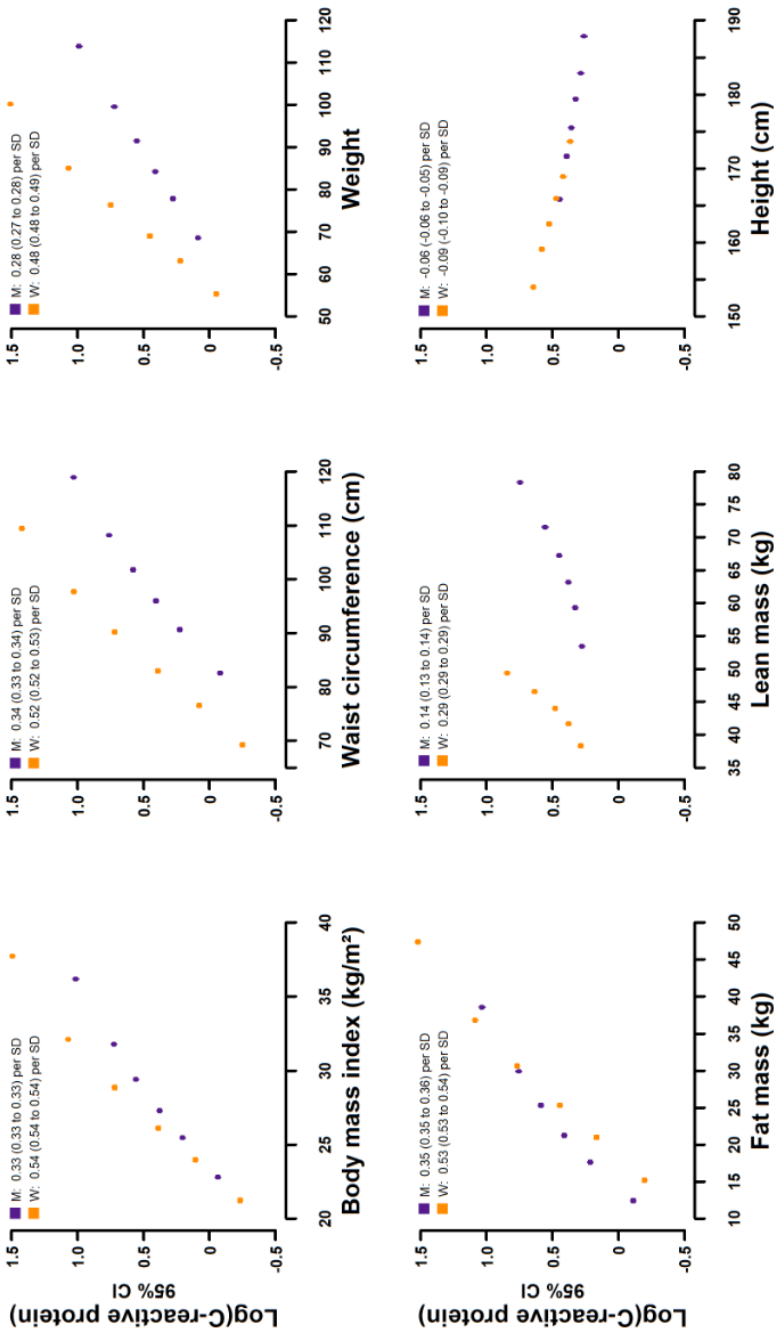


Appendix Figure J.10: Funnel plot of variants in YKL40 genetic score.
Funnel plot showing individual variant effects on atrial fibrillation (AF) expressed as per-allele log odds ratio (OR) estimates from UK Biobank data vs. strength of the variant in YKL40 genetic score. The red dotted line is the overall per-allele effect estimate. ORs were adjusted for age, age^2, sex, array, and principal components of ancestry 1-7.

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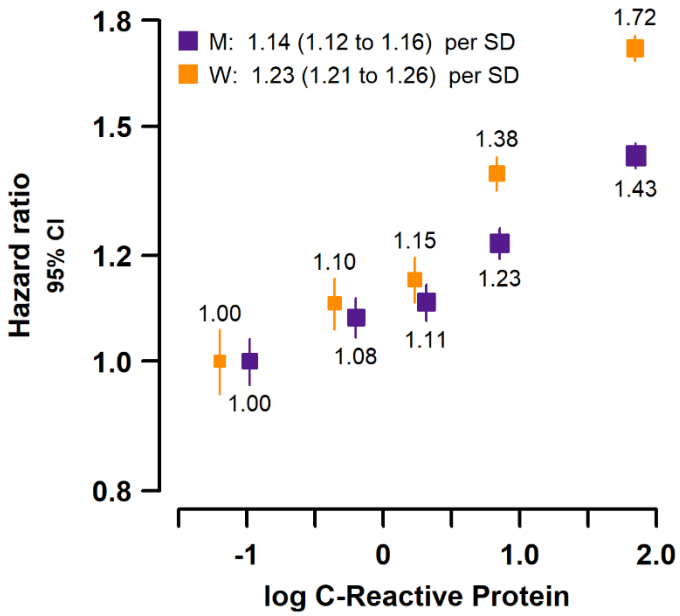
Appendix K - Chapter 8 supplementary figures

This appendix contains supplementary materials relating to **Chapter 8** of this thesis.

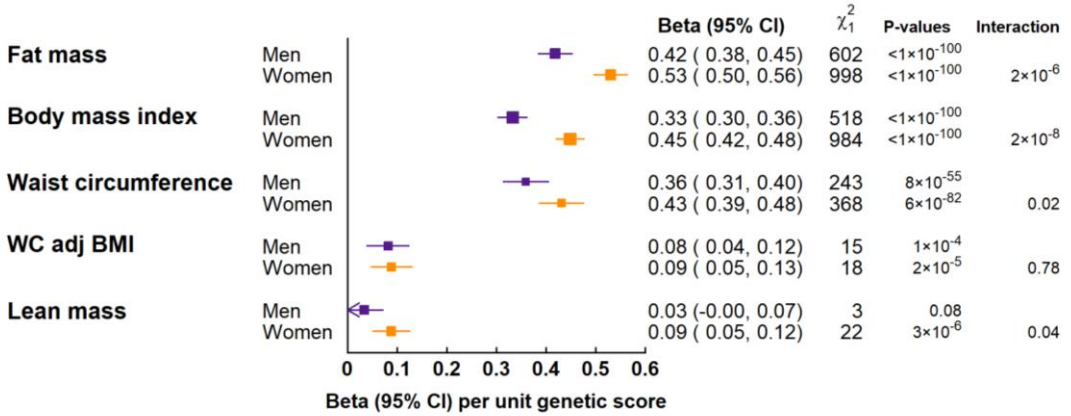


Appendix Figure K.1: Association of anthropometric measures and baseline log-C-reactive protein in men and women.

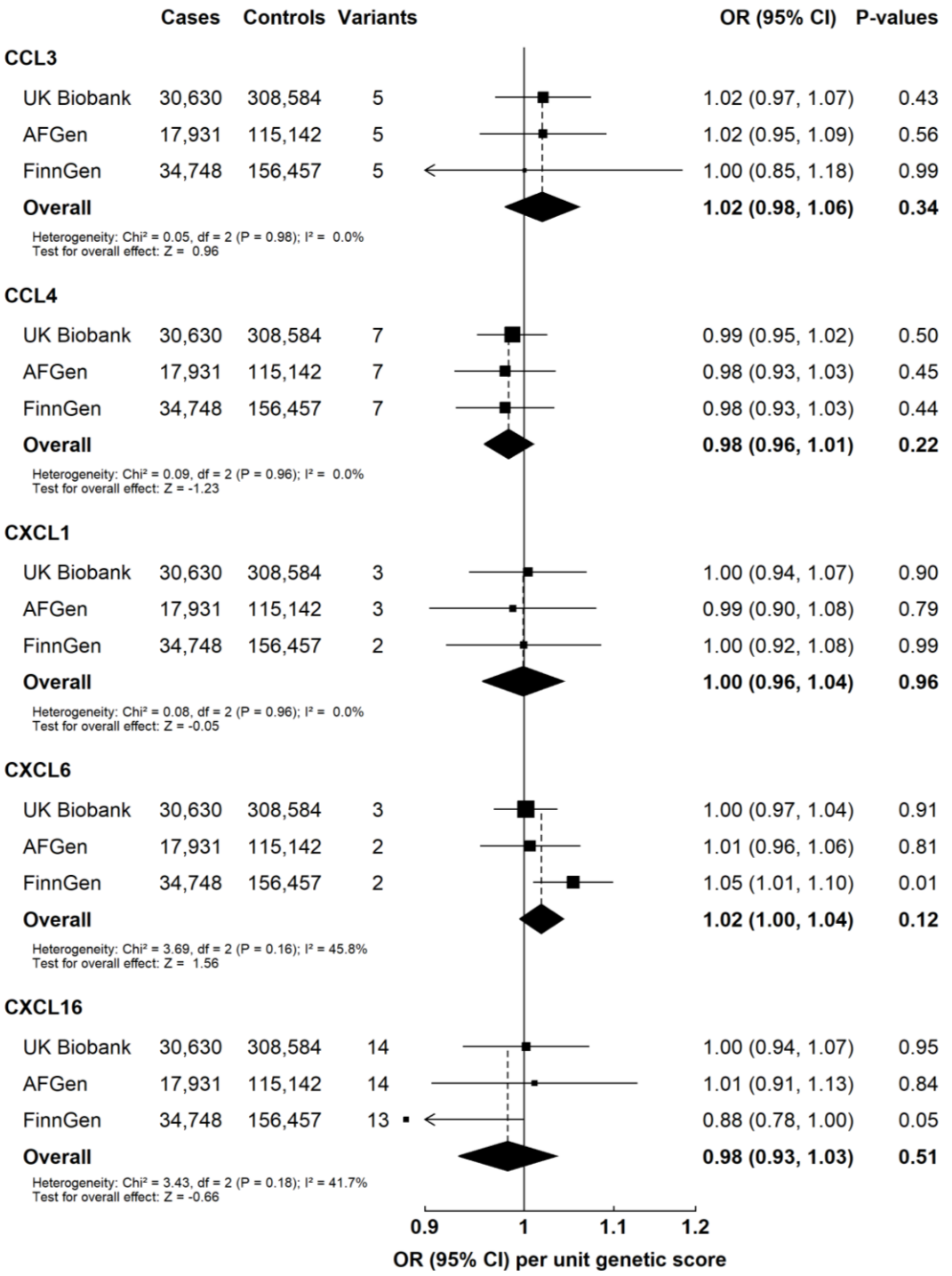
Mean log-CRP levels for each group determined using least-squares method adjusting for age, sex, alcohol, smoking, deprivation, and ethnicity. For each category, the area of the square is inversely proportional to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The lowest four groups each comprise 20% of the sample with the highest two groups each comprising 10% of the sample. Displayed separately in men (purple) and women (orange). CRP – C-reactive protein



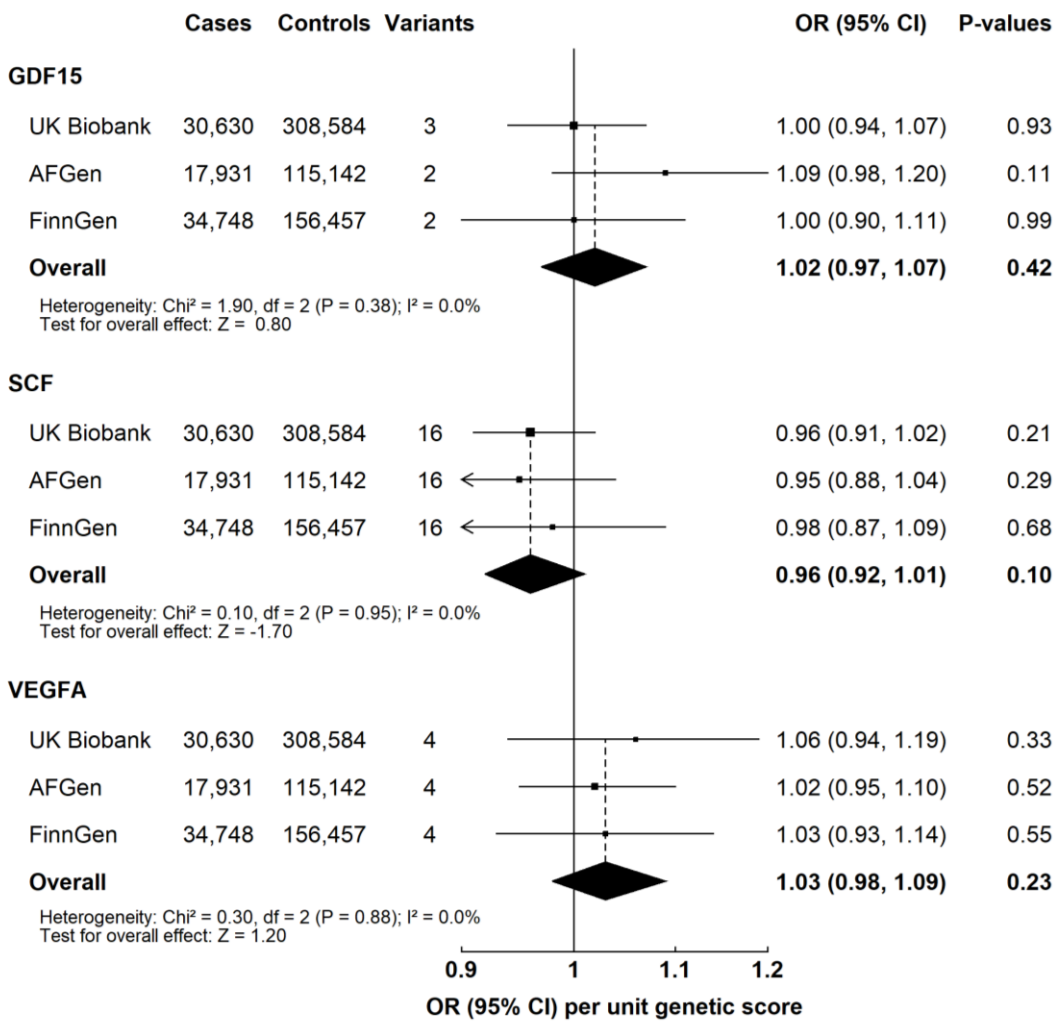
Appendix Figure K.2: Association between baseline log-C-reactive protein and atrial fibrillation in UK Biobank by sex.
Hazard ratios (HR) were adjusted for age, sex, ethnicity, smoking, alcohol, and deprivation in UK Biobank participants (n=446,838) and displayed in men (purple) and women (orange). For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars). The groups each comprised 20% of the sample in men and women separately. Hazard ratios shown above each square for women and below for men. SD – standard deviation



Appendix Figure K.3: Association between genetically predicted adiposity traits and log-C-reactive protein in men and women (n=308,490).
Effect estimates (beta) were adjusted for sex, age, age^2, genotyping array, and principal components of ancestry 1-7 and scaled per unit increase in genetic score for each adiposity measure. For each category, the area of the square is inversely proportional to the variance of the category-specific risk, which also determines the 95% confidence intervals (represented by error bars). WCadjBMI – waist circumference adjusted for body mass index.

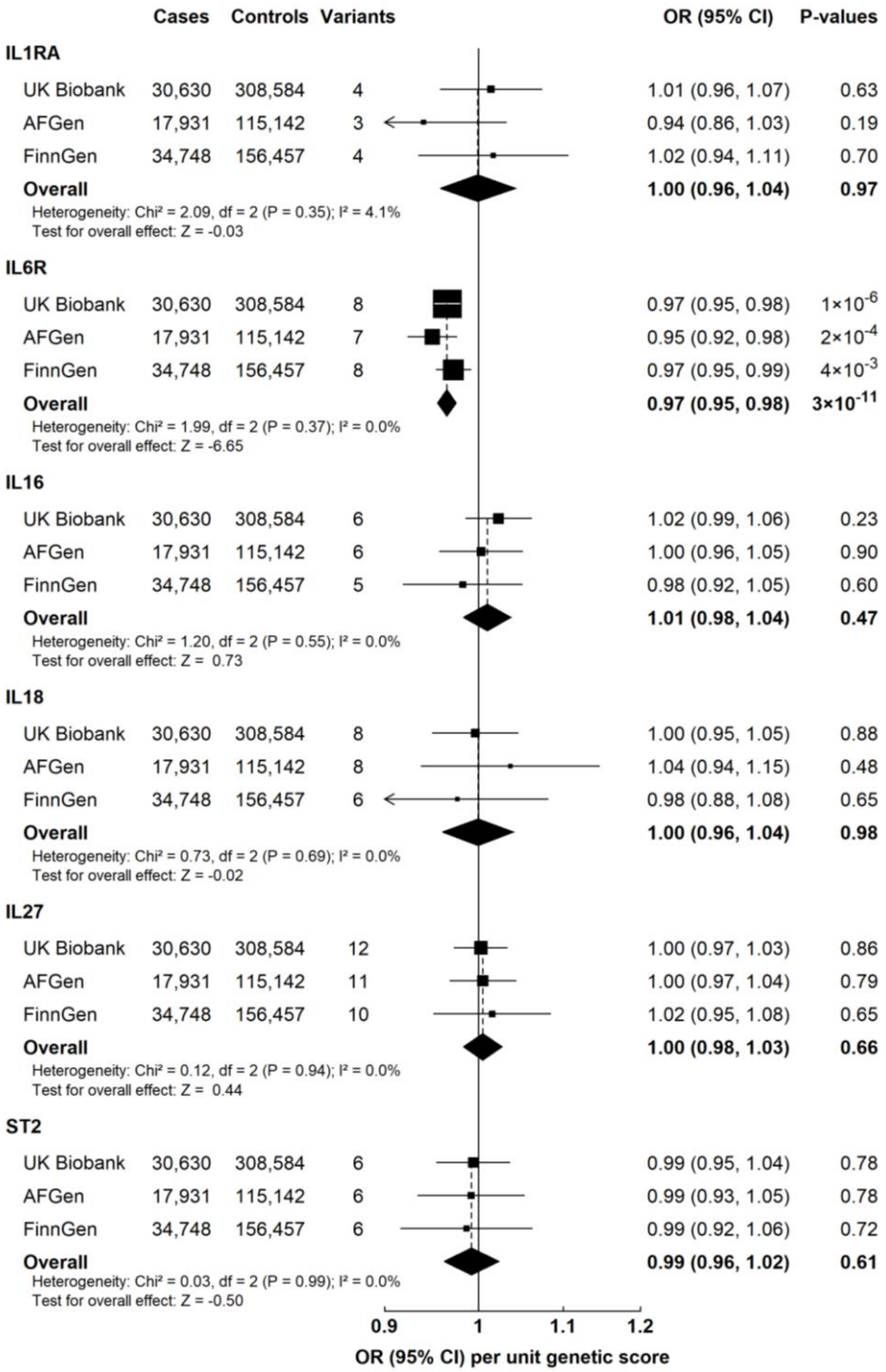


Appendix Figure K.4: Meta-analysis of causal effect of genetically predicted inflammatory proteins (chemokines) on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. CCL – C-C motif chemokine, CXCL – C-X-C motif chemokine.



Appendix Figure K.5: Meta-analysis of causal effect of genetically predicted inflammatory proteins (growth factors) on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. GDF – growth/differenation factor, SCF – stem cell factor, VEGF – vascular endothelial growth factor

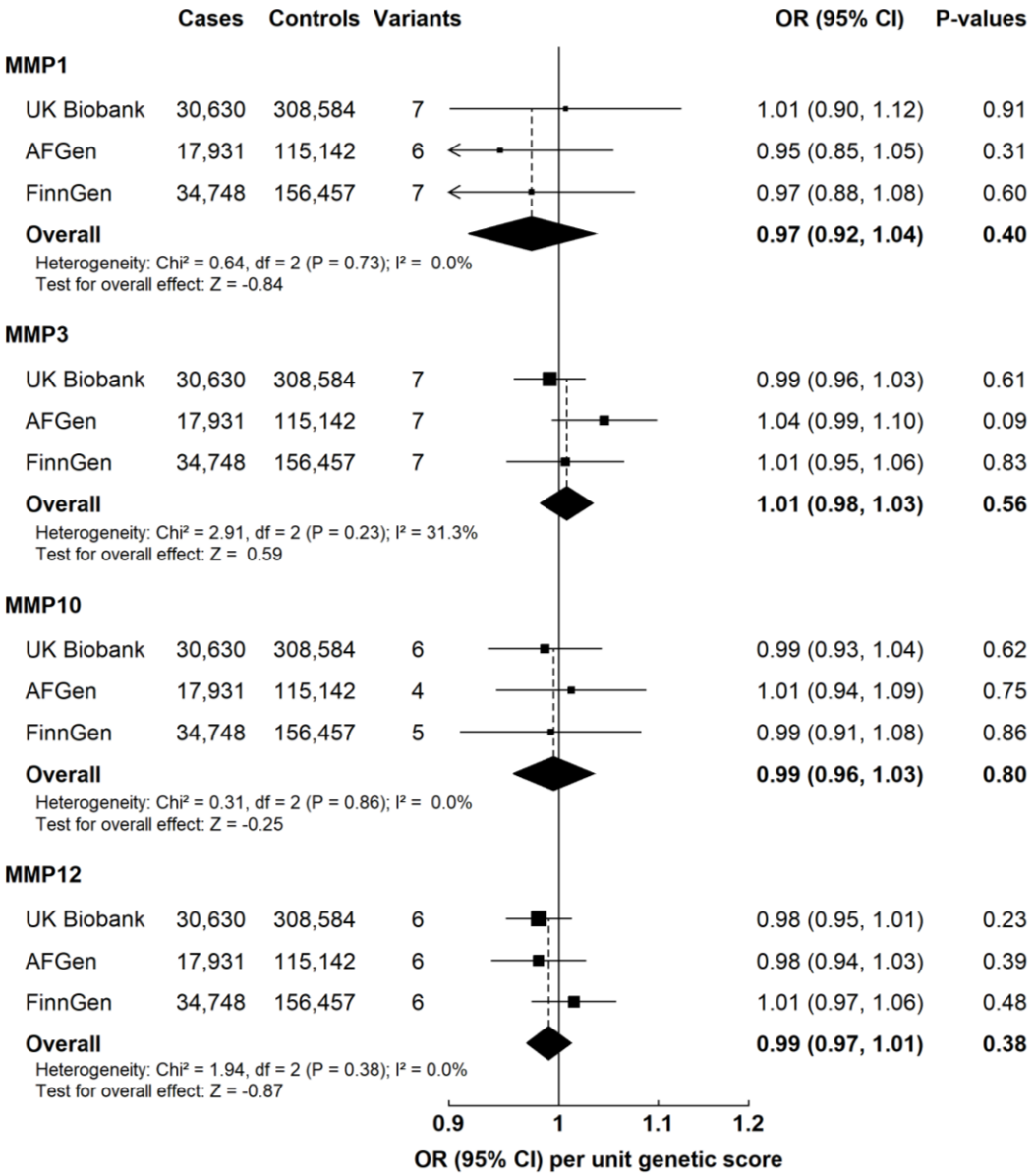
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Appendix Figure K.6: Meta-analysis of causal effect of genetically predicted inflammatory proteins (interleukins) on risk of atrial fibrillation.

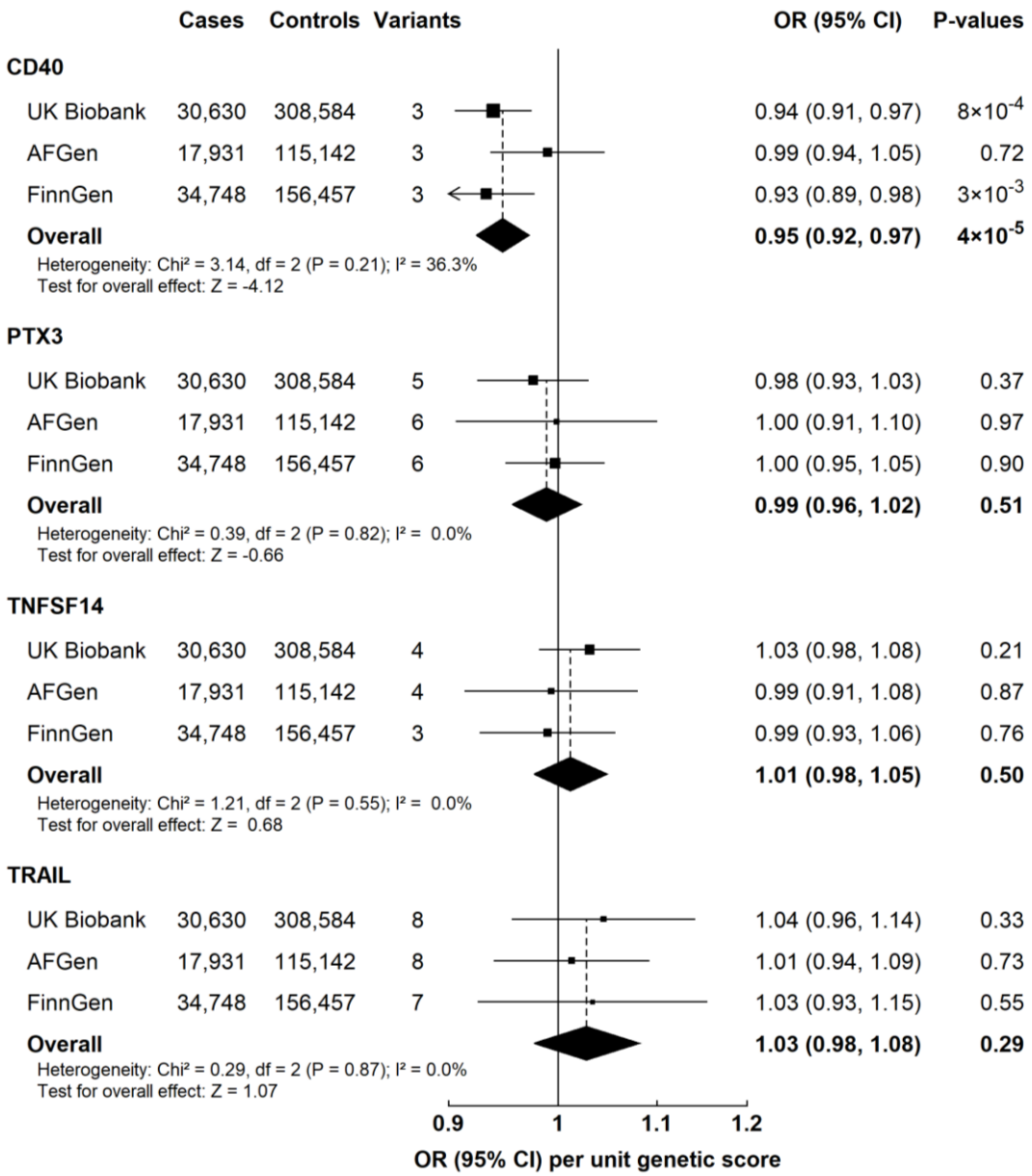
Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. UK Biobank, AFGen, and FinnGen ORs were calculated using inverse variance weighted methods. IL – interleukin, ST2 – ST protein.

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Appendix Figure K.7: Meta-analysis of causal effect of genetically predicted inflammatory proteins (matrix metalloproteinase) on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. UK Biobank, AFGen, and FinnGen ORs were calculated using inverse variance weighted methods. MMP – matrix metalloproteinase.

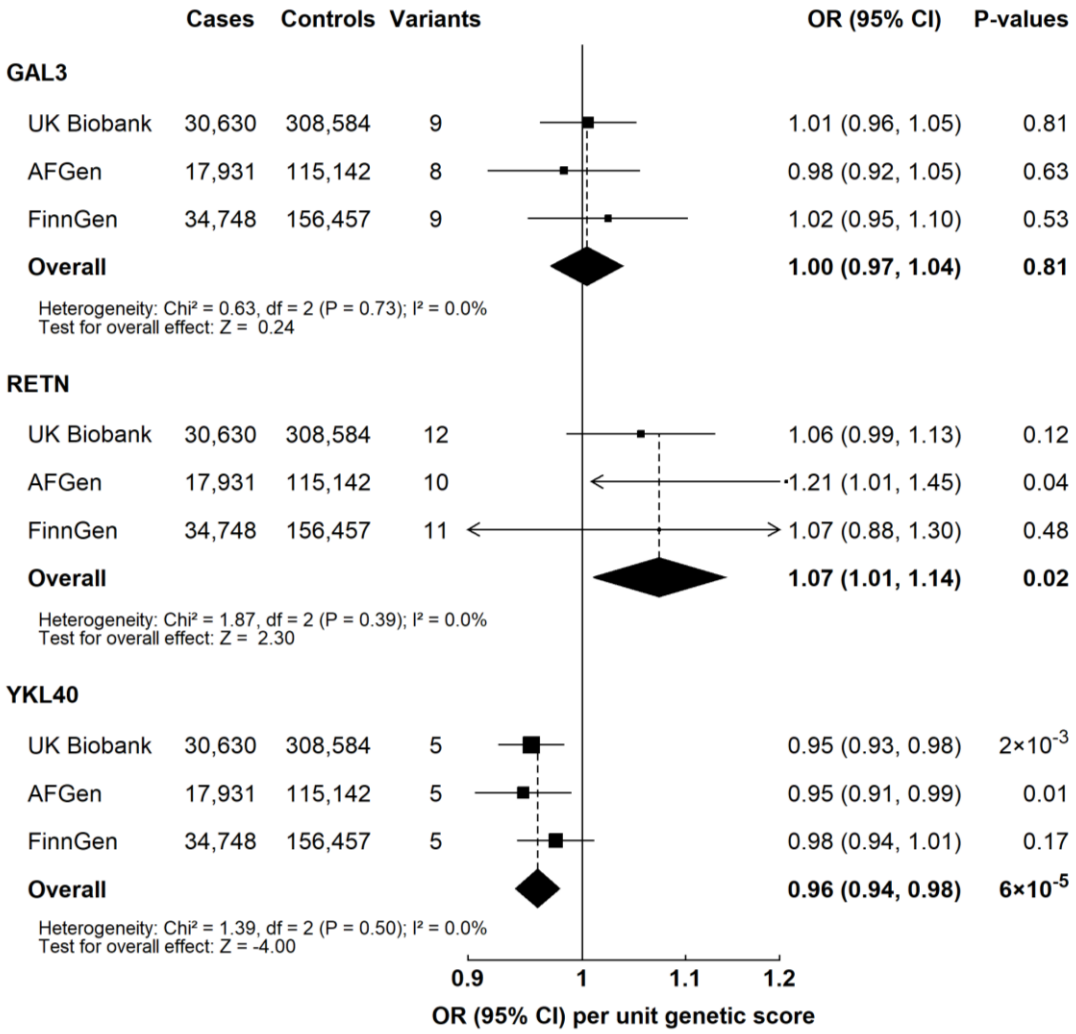
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Appendix Figure K.8: Meta-analysis of causal effect of genetically predicted inflammatory proteins (Tumour Necrosis Factor-related) on risk of atrial fibrillation.

Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. CD40 – Tumour necrosis factor receptor superfamily member 5, PTX3 – pentraxin-related protein 3, TNFSF14 – TNF ligand superfamily member 14, TRAIL – TNF-related apoptosis-inducing ligand

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Appendix Figure K.9: Meta-analysis of causal effect of genetically predicted inflammatory proteins (others) on risk of atrial fibrillation.
Boxes represent point estimates of effect per unit higher inflammatory protein score, with sizes inversely proportional to their variance which also define the 95% confidence intervals (95%CI, represented by error bars). Diamond represent meta-analysis estimates. UK Biobank, AFGen, and FinnGen odds ratios (ORs) were calculated using inverse variance weighted methods. UK Biobank, AFGen, and FinnGen ORs were calculated using inverse variance weighted methods. GAL – galectin-3, RETN – resistin, YKL40 – chitinase-3-like protein 1.

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Appendix L - Chapter 9 supplementary tables and figure

Appendix Table L.1: Read Codes used to identified 5,032 cases from primary care records

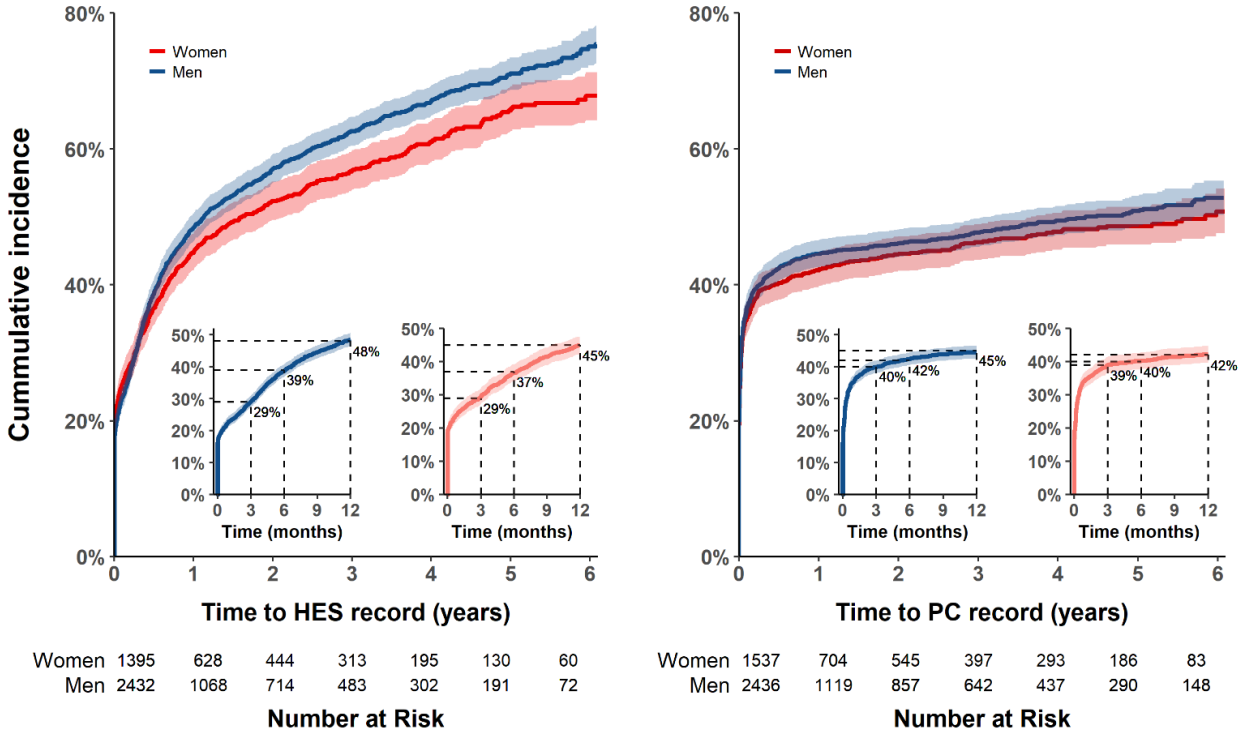
Read code description	n (%)	Read Code Version 2	Read Code Version 3	
Atrial fibrillation	2,904 (57.7)	G5730	G5730	
Paroxysmal atrial fibrillation	953 (18.9)	G5732	Xa2E8	
Atrial fibrillation and flutter	390 (7.8)	G573.	G573.	
Atrial flutter	270 (5.4)	G5731	G5731	
Atrial fibrillation monitoring	149 (3.0)	662S.	XaIIT	*
Direct current cardioversion	58 (1.2)	7L1H0	7L1H0	
H/O: atrial fibrillation	39 (0.8)	14AN.	XaDv6	*
Atrial fibrillation resolved	31 (0.6)	212R.	XaLFz	*
Referral to atrial fibrillation clinic	28 (0.6)	8HTy.	XaXrZ	*
Atrial fibrillation annual review	26 (0.5)	6A9..	XaMGD	
Percutaneous transluminal ablation of atrioventricular node	21 (0.4)	79340	79340	
Atrial fibrillation monitoring administration	20 (0.4)	9Os..	XaMDF	*
Paroxysmal atrial flutter	18 (0.4)	G5736	XaaUH	
Rapid atrial fibrillation	18 (0.4)	-	XaEga	
Persistent atrial fibrillation	17 (0.3)	G5735	XaOfa	
Atrial fibrillation and flutter NOS	16 (0.3)	G573z	G573z	
External cardioversion NEC	10 (0.2)	7L1H1	XE0Jj	
Permanent atrial fibrillation	9 (0.2)	G5734	XaOft	
Excepted from atrial fibrillation quality indicators: Patient unsuitable	7 (0.1)	9hF0.	XaLFi	*
Percutaneous transluminal ablation of atrial wall for atrial flutter	7 (0.1)	793M1	XaMmc	
Controlled atrial fibrillation	5 (<0.1)	-	Xa7nI	
Electrical cardioversion NOS	5 (<0.1)	-	Xa3ru	
History of atrial flutter	5 (<0.1)	14AR.	XaNRA	*
Atrial fibrillation monitoring first letter	4 (<0.1)	9Os0.	XaMDG	*
Lone atrial fibrillation	4 (<0.1)	-	X202R	
Atrial fibrillation monitoring verbal invite	3 (<0.1)	9Os3.	XaMDK	*
Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC	3 (<0.1)	793M3	XaMrB	
Chemical cardioversion	2 (<0.1)	7L1H8	XaOfF	

Appendix Table L.1: Read Codes used to identified 5,032 cases from primary care records

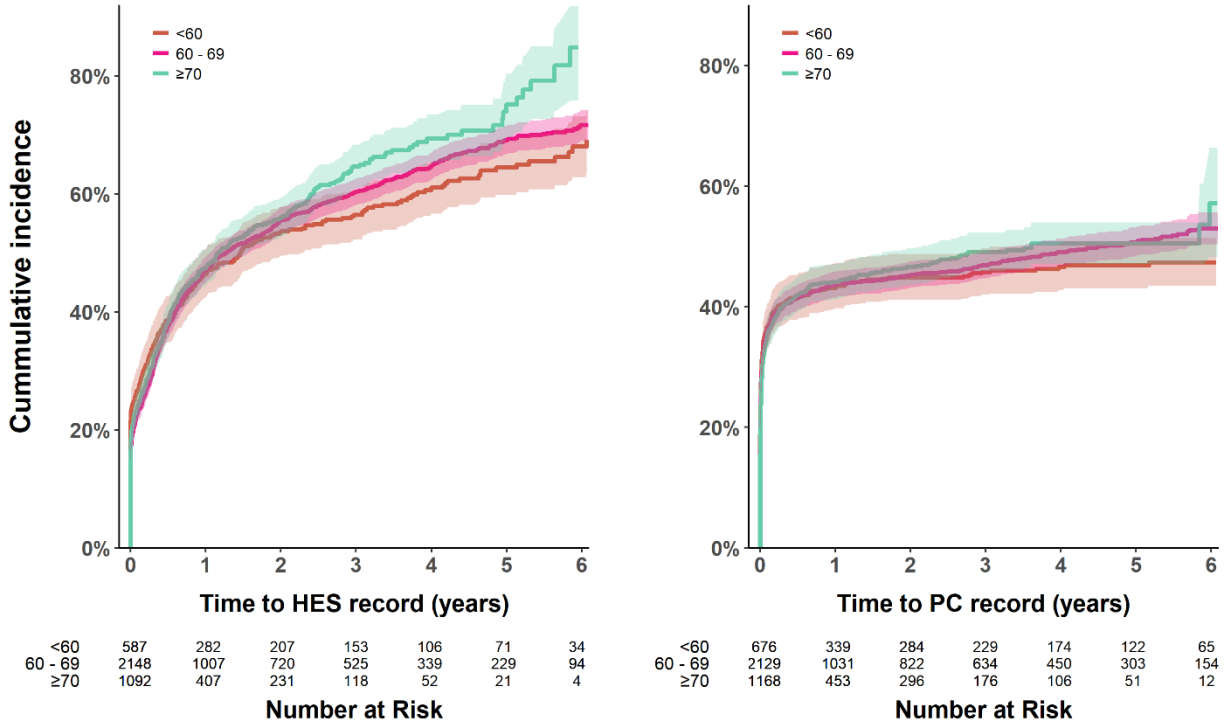
Read code description	n (%)	Read Code Version 2	Read Code Version 3	
Percutaneous transluminal ablation of pulmonary vein to left atrium conducting system	2 (<0.1)	793M0	XaMmd	
Atrial fibrillation care pathway	1 (<0.1)	8CMW2	XaZdc	*
Atrial fibrillation monitoring telephone invite	1 (<0.1)	9Os4.	XaMFn	*
Atrial fibrillation monitoring third letter	1 (<0.1)	9Os2.	XaMDI	*
Direct current defibrillation	1 (<0.1)	-	XaBdb	
Excepted from atrial fibrillation quality indicators: Informed dissent	1 (<0.1)	9hF1.	XaLFj	*
Non-rheumatic atrial fibrillation	1 (<0.1)	G5733	X202S	
Percutaneous transluminal ablation of atrial wall NEC	1 (<0.1)	79348	XaMrA	
Percutaneous transluminal internal cardioversion NEC	1 (<0.1)	793M2	XaMmb	

Read codes with identical descriptions are combined. Read codes with no records extracted from the primary care dataset have not been displayed. * Read codes identified through key-word search.

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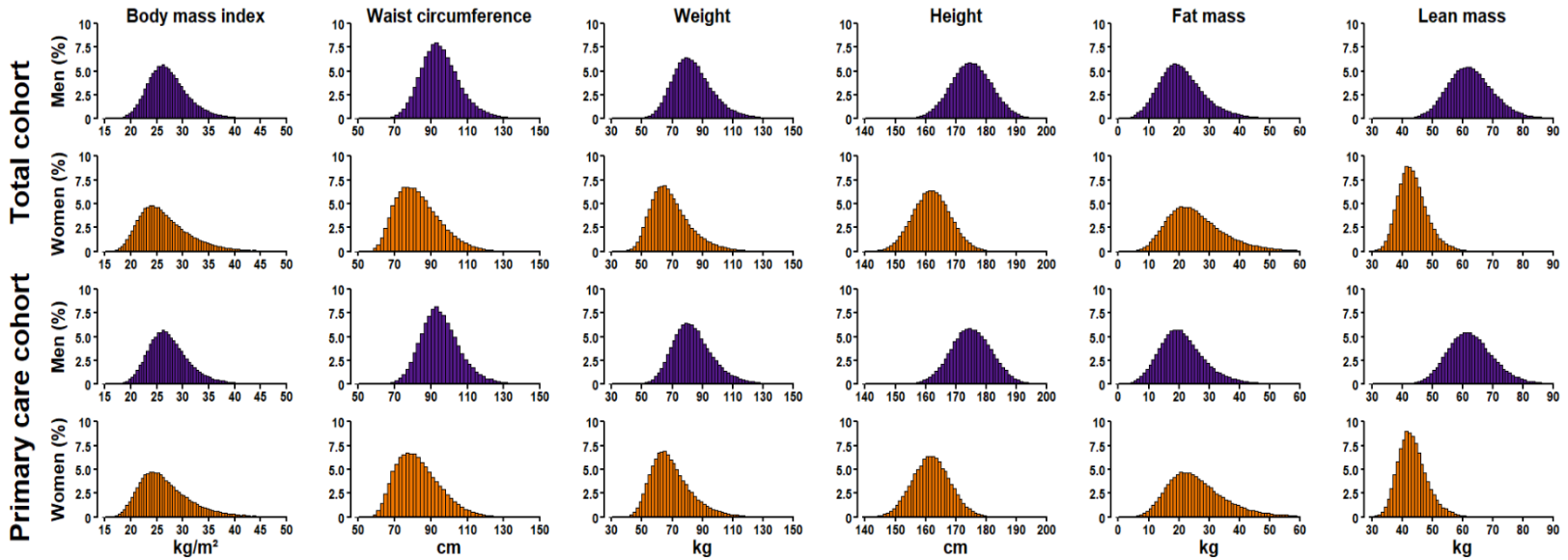


Appendix Figure L.1: Time from atrial fibrillation ascertainment to identification in an alternate source by sex. *Cumulative incidence plots showing years to subsequent hospital episode statistic atrial fibrillation ascertainment for those first identified in primary care (left, n=3,827) and years to subsequent primary care atrial fibrillation ascertainment for those first identified in hospital episode statistics (right, n=3,973) stratified by sex. Individuals without a subsequent ascertainment in the alternative source are censored. Inset plots show individuals identified within one year for men and women separately. Values below the x-axis are numbers at risk. Analyses exclude participants who had a prior ascertainment in the alternate source. HES – hospital episode statistics, PC – primary care*

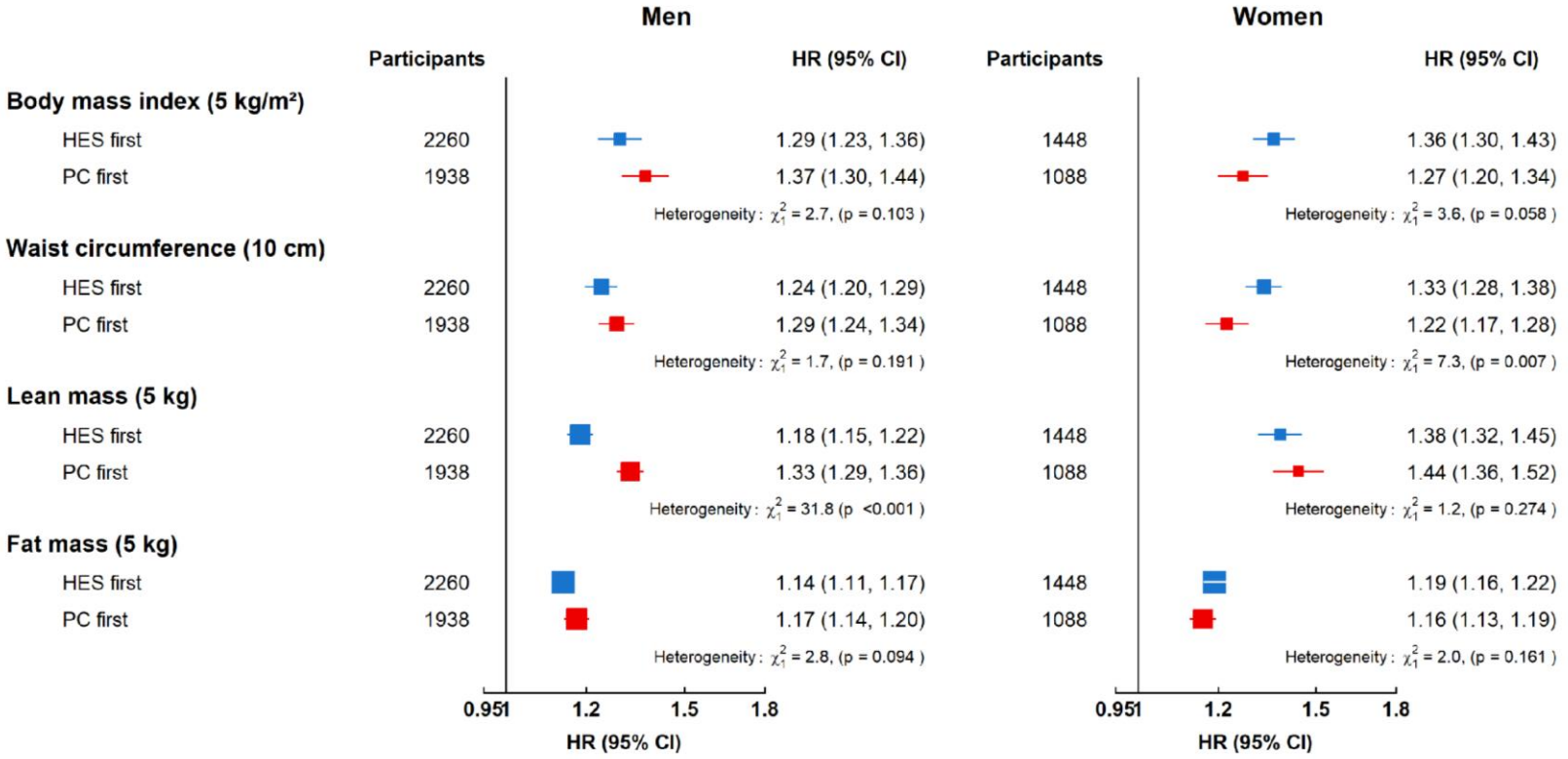


Appendix Figure L.2: Time from atrial fibrillation ascertainment to identification in alternate source by age at ascertainment.

Cumulative incidence plots showing years to subsequent hospital episode statistics atrial fibrillation ascertainment for those first identified in primary care (left, n=3,827) and years to subsequent primary care atrial fibrillation ascertainment for those first identified in hospital episode statistics (right, n=3,973) stratified by participant age at first atrial fibrillation ascertainment. Individuals without a subsequent ascertainment in the alternative source are censored. Inset plots show individuals identified within one year for men and women separately. Values below the x-axis are numbers at risk. Analyses exclude participants who had a prior ascertainment in the alternate source. HES – hospital episode statistics, PC – primary care.

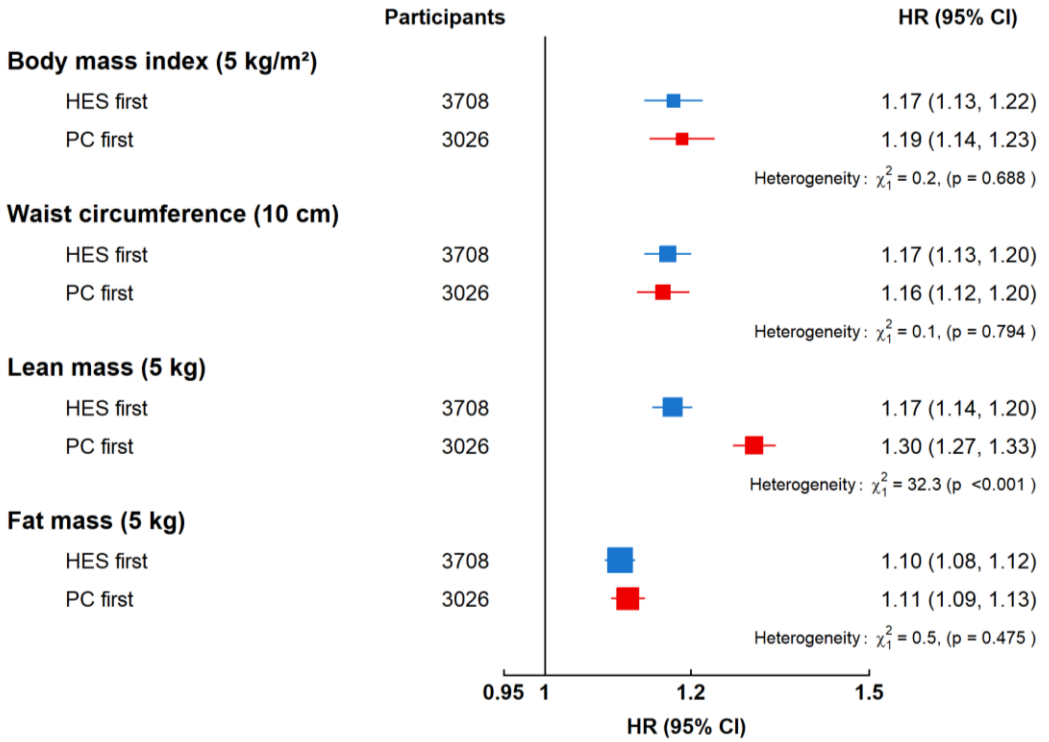


Appendix Figure L.3: Histograms of anthropometric measures split between men and women.
Women are displayed in orange and men are displayed in purple. The total cohort includes all participants in UK Biobank with appropriate anthropometric measures (see ***Chapter 4****). The primary care sub-set includes 218,272 participants in whom primary care data and appropriate anthropometric measures are available.*



Appendix Figure L.4: Anthropometric measures and risk of atrial fibrillation by source of first atrial fibrillation record split by participant sex.

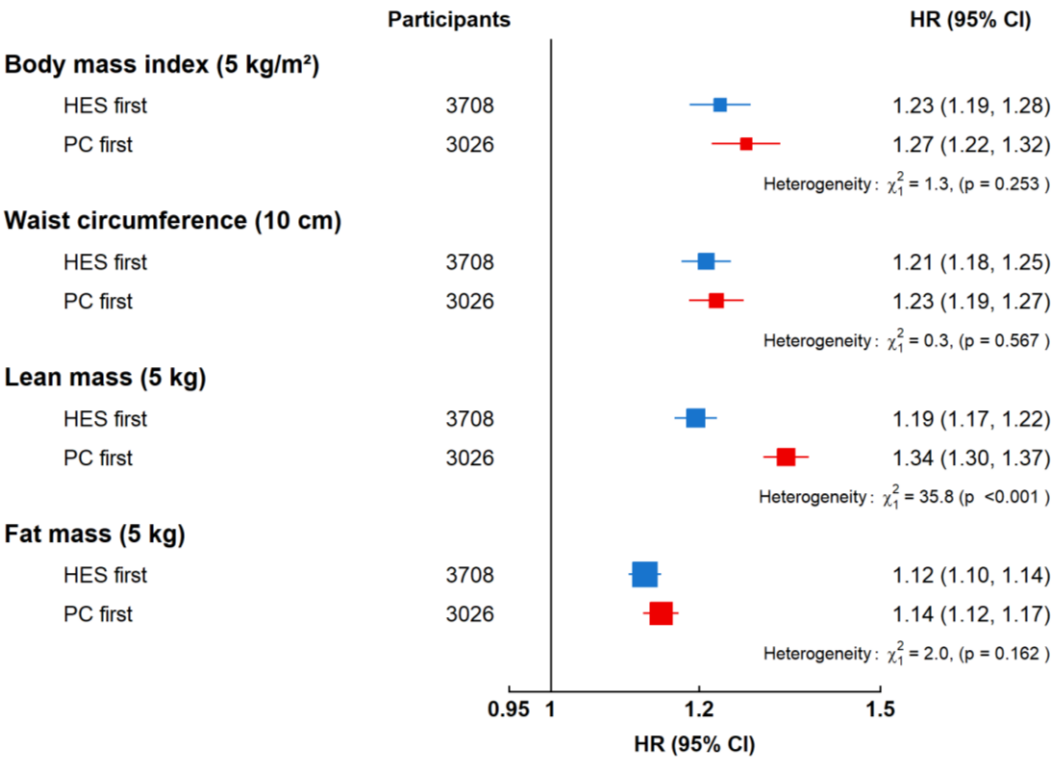
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars).



Appendix Figure L.5: Anthropometric measures and risk of atrial fibrillation by source of first atrial fibrillation record adjusted for baseline disease and healthcare utilisation.

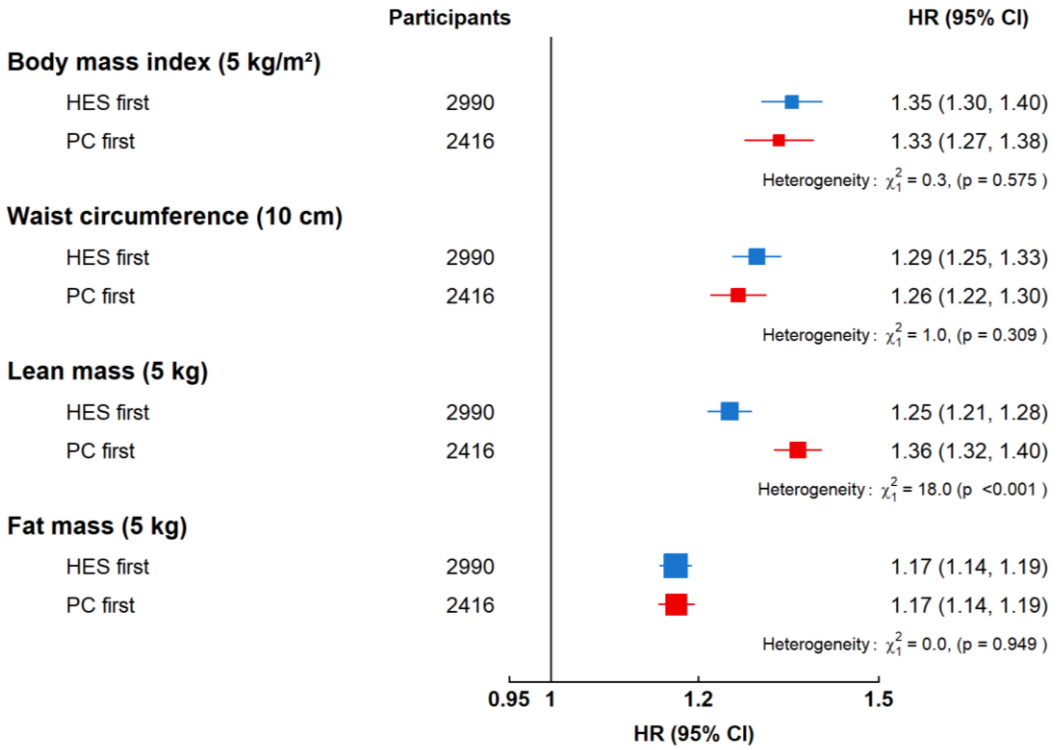
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, alcohol, baseline cardiovascular disease (coronary heart disease, hypertension, heart failure, stroke, and diabetes), hospital admissions, and primary care encounters. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (95%CI, represented by error bars).

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Appendix Figure L.6: Anthropometric measures and risk of atrial fibrillation by source of first AF record adjusted for diet, and physical activity.
Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, alcohol, weekly metabolic equivalent of task (MET) hours, processed meat consumption, and bread consumption. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars).

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Appendix Figure L.7: Anthropometric measures and risk of atrial fibrillation by source of first atrial fibrillation record with participants censored within the first two years removed.

Hazard ratios (HR) were adjusted for age, sex, ethnicity, deprivation, smoking, and alcohol. Participants censored within two years of enrolment were removed. For each category, the area of the square is inversely proportion to the variance of the category-specific log risk, which also determines the 95% confidence intervals (represented by error bars).

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