# Adiposity and Coronary Heart Disease in the UK Biobank: A Prospective Cohort Study of 500 000 adults

Nuffield Department of Population Health

**Deborah E. Malden, BSc(Hons) MSc**

Trinity College, Oxford

Thesis submitted for the degree of Doctor of Philosophy
Hilary Term 2020

For my family

## ABSTRACT

**Background** Excess adiposity is a known risk factor for coronary heart disease (CHD). However, the underlying mechanisms have not been fully elucidated, and the relevance of different adiposity phenotypes remains unclear.

**Methods** The UK Biobank is a prospective study of 500 000 adults enrolled between 2006 and 2010 across the UK. Correlates of adiposity at baseline were explored for established and emerging cardiovascular risk factors. Cox regression analyses were used to obtain adjusted hazard ratios (HRs) for the associations of usual levels of body-mass index (BMI), body fat %, trunk fat % , waist circumference (WC), waist-to-height ratio (WHTR) and waist-to-hip ratio (WHR), or with genetically elevated BMI-adjusted WHR (WHRadjBMI) and BMI with incident CHD.

**Results** Among 455 148 participants without prior cardiovascular disease, 13 114 first-ever CHD events occurred over a mean follow-up period of 8 years. Measurement error and within-person variability was less extreme for BMI (regression dilution ratio: 0.92) than other measures, particularly WHR (0.66). Adiposity measures were closely correlated with each other at baseline, as well as with a number of socio-demographic, lifestyle and biological characteristics. In analyses adjusted for age, sex, socio-economic status, smoking and alcohol consumption, increasing usual levels of adiposity (i.e. corrected for regression dilution) were positively and log-linearly associated with CHD risk across all measures. Associations were notably stronger for central adiposity, particularly WHR (HR per usual SD 1.34, 95% CI 1.31-1.38) compared with BMI (1.24, 1.22-1.26). The relevance of usual WHR to CHD was particularly strong among women (1.41, 1.35-1.48), and remained strongly associated with CHD after adjustment for BMI. The observed prospective associations were partially mediated by blood pressure, lipids and insulin resistance, which explained at least half of the observed excess risk. Additional adjustment for glomerular filtration rate, liver enzymes and inflammatory markers completely attenuated associations with all measures except WHTR and WHR, which remained independently associated with CHD risk. Genetically elevated adiposity measures were associated with CHD risk (HR per SD higher WHRadjBMI: 1.31, 1.11 – 1.55; BMI: 1.22, 1.06 - 1.41), and with cardiometabolic traits.

**Conclusion** Adiposity measures demonstrated strong, positive and approximately log-linear associations with CHD risk, with no evidence of threshold effects within the ranges studied in this UK population. Central body fat distribution was associated with higher CHD risk compared with BMI and likely involves distinct and independent mechanisms.

## Acknowledgements

I would like to thank the UK Biobank participants, supporting staff and steering committee for producing the UK Biobank resource which will benefit population health for generations to come. I would also like to thank my funders, the Medical Research Council, without whom I would not have been able to undertake this research.

There are a few people who I could not have managed without. Firstly, I would like to thank my parents, Leah and Nick Malden, my brother Stephen Malden and my sister Hannah Pumphrey for their unwavering support throughout my degree(s). My supervisors Professor Sarah Lewington, Dr Benjamin Lacey, Professor Jonathan Emberson and Dr Derrick Bennett have each been a tremendous support throughout. Not only have they succeeded in supporting me through the timely completion of this thesis, but they have gone to extraordinary lengths to allow me to pursue my passion for a career in applied epidemiology. I would also like to thank Professor Jane Armitage for supporting my career from the beginning and encouraging my passion for impact in public health. To my wonderful friends Emilia Michalak, Rebecca Matthews, Dr Katherine Collett, Richard Lu and Dr Katherine Newell - thank you for making me laugh for four years. I owe a special thanks to William Cahill for his support when it mattered most. I would also like to thank the Oxford W1 volleyball team for making Oxford a truly special place.

Last but not least, to the many colleagues and collaborators from around the world with whom I have had the pleasure of working with, particularly my brilliant colleagues at the World Health Organization country office in Papua New Guinea who taught me that anything is achievable in public health.

## Statement of contribution to work

I drafted the text and produced all tables and figures presented in the current thesis. All analysis was conducted by myself, and I produced the pre-specified analysis plans for **Chapters 4 to 8** with advice from my supervisors Sarah Lewington, Jonathan Emberson, Ben Lacey and Derrick Bennet**.** I used SAS programs developed by Paul Sherliker and Alison Offer for some analyses, modifying them where required to adapt to UK Biobank data. To produce some of the figures presented in the current thesis, I used R packages developed by Matthew Arnold. I was the Principal Investigator for the UK Biobank application (no. 31461) and I drafted the project application and managed all aspects of the data access throughout. The research presented in **Chapter 6** has been published previously (Malden, D, Lacey, B., Emberson, J., Karpe,F., Allen, N., Bennett, D., and Lewington., S. Body Fat Distribution and Systolic Blood Pressure in 10,000 Adults with Whole-Body Imaging: UK Biobank and Oxford BioBank. *Obesity;* 2019), for which I was first author. I drafted the text, and Jonathan Emberson, Sarah Lewington, Ben Lacey, Fredrik Karpe, Naomi Allen and Derrick Bennett provided advice on the pre-specified analysis plan.

## Table of Contents

**ABSTRACT** ..... **i**
**Acknowledgements** ..... **ii**
**Statement of contribution to work** ..... **iii**
**List of presentations and awards** ..... **viii**
**List of abbreviations** ..... **ix**
**List of Tables** ..... **xi**
**List of Figures** ..... **xiii**

**CHAPTER 1: Introduction** ..... **1**
**Chapter summary** ..... **1**
**1.1 Coronary heart disease (CHD)** ..... **2**
1.1.2 Pathophysiology ..... 2
1.1.3 Risk factors for CHD ..... 3
**1.2 Adiposity** ..... **4**
1.2.1 Epidemiology of overweight and obesity ..... 4
1.2.2. Adiposity and CHD ..... 4
1.2.3 Central adiposity versus general adiposity ..... 6
1.2.4 Current therapies directed towards weight loss ..... 8
**1.3 Adiposity measures** ..... **9**
1.3.1 Direct measures ..... 9
1.3.2 Indirect measures ..... 10
**1.4 Genetics and adiposity** ..... **11**
1.4.1 Genetically elevated adiposity ..... 11
1.4.2 Genetically elevated adiposity and CHD risk ..... 12
**1.5 Study Setting** ..... **13**
**1.6 Thesis objectives** ..... **14**
**CHAPTER 1 Tables and figures** ..... **15**

**CHAPTER 2: Literature review** ..... **27**
**Chapter summary** ..... **27**
**2.1 Objectives** ..... **28**
**2.2 Search strategy** ..... **28**
**2.3 Prospective evidence** ..... **28**
2.3.1 Search results ..... 28
2.3.2 Body-Mass Index ..... 29
2.3.3 Central adiposity and body fat distribution measures ..... 32
2.3.4 Effect modification ..... 34
2.3.5 Intermediate factors ..... 35
**2.4 Summary of observational evidence: major inconsistencies, gaps in current evidence and implications for future research** ..... **35**
2.4.1 Strength and shape of the association between BMI and CHD risk ..... 35
2.4.2 The relevance of alternative adiposity measures to CHD risk beyond BMI ..... 36
2.4.3 Intermediate factors underlying adiposity-related CHD risk ..... 37
2.4.4 Addressing uncertainties surrounding observational associations between adiposity and CHD risk using the UK Biobank ..... 37
**2.5 Mendelian randomisation evidence** ..... **39**
2.5.1 Background ..... 39
2.5.2 Search results ..... 39
**2.6 Summary of genetic evidence: major inconsistencies, gaps in current evidence and implications for future research** ..... **41**
**2.7 Conclusion** ..... **42**
**Chapter 2 Tables and figures** ..... **43**

**CHAPTER 3: Overall study design and methods ..... 52**
**Chapter summary ..... 52**
**3.1. The UK Biobank ..... 53**
3.1.1 Overall study design and recruitment ..... 53
3.1.2 Baseline assessment procedures ..... 53
3.1.3 Resurvey and imaging visits ..... 55
3.1.4 Imaging procedures ..... 55
3.1.5 Study outcome and follow-up procedures ..... 56
**3.2 Oxford Biobank ..... 57**
3.2.1 Overall study design and recruitment ..... 57
3.2.2 Baseline survey ..... 57
3.2.3 Imaging procedures ..... 57
**3.3 General statistical methods ..... 58**
3.3.1 Selection of variables and variable derivation ..... 58
3.3.2 Exclusions ..... 59
**3.4 Baseline characteristics ..... 59**
**Chapter 3 Tables and Figures ..... 61**

**CHAPTER 4: Baseline correlates of adiposity measures ..... 70**
**Chapter summary ..... 70**
**4.1. Background ..... 71**
**4.2. Statistical methods ..... 73**
4.2.1 Overall study design and study population ..... 73
4.2.2 Cross-sectional analysis ..... 73
4.2.3 Graphical representation ..... 73
**4.3 Results ..... 74**
4.3.1 Correlations between adiposity measures at baseline ..... 74
4.3.2 Adiposity and demographic characteristics ..... 74
4.3.3 Adiposity and lifestyle factors ..... 75
4.3.4 Adiposity and prevalence of diabetes and hypertension ..... 76
4.3.5 Adiposity measures and blood-based risk factors for CHD ..... 76
**4.4 Discussion ..... 78**
4.4.1 Main findings ..... 78
4.4.2 Adiposity measures ..... 79
4.4.3 Demographic and lifestyle correlates of adiposity at baseline ..... 79
4.4.4 Adiposity and self-reported hypertension and diabetes ..... 81
4.4.5 Adiposity and blood pressure ..... 82
4.4.6 Adiposity and blood-based biomarkers ..... 83
4.4.7 Strengths and potential limitations ..... 86
**4.5 Conclusion ..... 87**
**Chapter 4 Tables and Figures ..... 88**

**CHAPTER 5: Within-person variability between adiposity measures ..... 112**
**Chapter summary ..... 112**
**5.1 Background ..... 113**
**5.2 Statistical methods ..... 114**
5.2.1 Graphical representation of within-person variability ..... 114
5.2.2 Estimating within-person variability of adiposity measures ..... 114
5.2.3 Determinants of within-person variability ..... 115
**5.3 Results ..... 116**
5.3.1. Resurvey population characteristics ..... 116
5.3.2 Repeat adiposity measures in the UK Biobank ..... 116
5.3.3 Quantifying within-person variability across adiposity measures in the UK Biobank ..... 116

5.3.4 Investigating secular trends ....117
5.3.5 Determinants of with-in person variability ....117
**5.4 Discussion....118**
5.4.1 Within-person variability of selected adiposity measures ....118
5.4.2 Estimating the RDR: A comparison of methods and method selection ....119
5.4.3 Validity of findings and underlying assumptions ....119
5.4.4 Study strengths and potential limitations ....120
**5.5 Conclusion ....121**
**Chapter 5 Figures and tables ....122**

**CHAPTER 6: Imaging study of body composition and systolic blood pressure in the UK Biobank and Oxford Biobank ....131**
**Chapter summary ....131**
**6.1 Background....132**
**6.2 Statistical methods....133**
6.2.1 Exclusions and variable derivation ....133
6.2.2 Cross-sectional analysis ....133
**6.3 Results....134**
6.3.1 Baseline characteristics ....134
6.3.2 Body composition with increasing levels of BMI, WC and WHR ....134
6.3.3 Body composition, body size and systolic blood pressure....135
**6.4 Discussion....136**
**6.5 Conclusion ....138**
**Chapter 6 Tables and Figures ....139**

**CHAPTER 7: Prospective associations between adiposity and coronary heart disease in the UK Biobank ....145**
**Chapter summary ....145**
**7.1 Background....146**
**7.2 Statistical analysis....147**
7.2.1 Within-person variability and correction for regression dilution bias....147
7.2.2 Association shape: CHD risk at increasing levels of adiposity ....147
7.2.3 Association magnitude: CHD risk per SD-unit increasing adiposity ....148
7.2.4 Effect modification ....148
7.2.5 Effect mediators....148
7.2.6 Sensitivity analysis....149
**7.3 Results....150**
7.3.1 Adiposity measures and CHD risk ....150
7.3.3 Sub-group analysis ....150
7.3.4 Independence of adiposity measures ....151
7.3.5 Effect mediators....151
7.3.6 Sensitivity analysis....151
**7.4 Discussion....152**
7.4.1 Association shape and magnitude....152
7.4.1 Effect modification ....153
7.4.2 Intermediate factors ....155
7.4.3 Strengths and limitations ....157
**7.5 Conclusion ....158**
**Chapter 7 Tables and Figures ....159**

**CHAPTER 8: Genetic associations between adiposity traits and coronary heart disease in the UK Biobank ..... 181**
**Chapter summary ..... 181**
**8.2 Genetic study protocol and statistical methods ..... 184**
8.2.1 Genotyping ..... 184
8.2.2 Genetic quality control procedures and exclusions ..... 184
8.2.3 SNP selection and construction of genetic risk scores for elevated adiposity ..... 184
8.2.3.1 Genetic risk scores for BMI ..... 185
8.2.3.2 Genetic risk score for WHRadjBMI ..... 186
8.2.4 GRS associations with adiposity traits and cardiovascular risk factors ..... 186
8.2.5 MR analysis ..... 186
8.2.6 Sensitivity analyses ..... 187
8.2.7 Power calculations ..... 188
**8.3 Results ..... 189**
8.3.1 Baseline characteristics ..... 189
8.3.2 Genetic associations of individual variants and genetic risk scores with adiposity ..... 189
8.3.4 Genetic associations of adiposity traits with DXA imaging compartments ..... 190
8.3.3 Genetic associations of adiposity traits and risk factors for CVD ..... 190
8.3.4 Causal genetic associations of adiposity traits and CHD ..... 192
8.3.5 Sensitivity analyses ..... 192
**8.4 Discussion ..... 193**
8.4.1 Main findings ..... 193
8.4.4 Validity of the MR causal estimates: MR assumptions ..... 198
8.4.5 Study strengths and limitations ..... 199
**8.5 Conclusion ..... 201**
**Chapter 8 Tables and Figures ..... 202**

**CHAPTER 9: Overall conclusions ..... 223**
**Chapter summary ..... 223**
**9.1 Main findings ..... 224**
9.1.1 Cross-sectional correlates of adiposity measures at baseline ..... 224
9.1.2 Within-person variability of adiposity measures ..... 224
9.1.3 Adiposity measures, body fat distribution and blood pressure ..... 225
9.1.4 Adiposity measures and CHD risk ..... 225
9.1.5 Genetically elevated adiposity and CHD risk ..... 226
**9.2. Biological mechanisms ..... 226**
**9.3 Strengths and limitations of the current study ..... 227**
**9.4 Implications for population health ..... 228**
9.4.1 Enhanced CHD risk prediction scores ..... 228
9.4.2 Obesity prevention will require multi-sectorial population-level interventions ..... 229
9.4.3 Improved estimates of the global burden of obesity ..... 230
**9.5 Implications for future research ..... 230**
9.5.1 The need for diverse population studies ..... 230
9.5.2 Future genetic studies on adiposity and CHD risk ..... 231
9.5.3 Future research targeted at central body fat distribution ..... 231
**9.6 Conclusion ..... 232**

**References ..... 233**
**Appendix ..... 253**

## List of presentations and awards

### Poster presentations

**Adiposity markers and myocardial infarction in the UK Biobank: A prospective cohort study of 450 000 adults** — 12/09/2017, Oxford
Li Ka Shing Foundation East-West Alliance Symposium

**Adiposity and incident MI in the UK Biobank** — 14/09/2017, Oxford
British Heart Foundation Centre for Research Excellence Symposium

**Adiposity and Ischaemic Heart Disease in the UK Biobank: A prospective cohort study of 500 000 men and women** — 23/05/2018, Vienna
European Congress on Obesity

**Adiposity and Ischaemic Heart Disease in the UK Biobank: A prospective study of 500 000 men and women** — 21/06/2018, Oxford
Medical Research Council - Doctoral Training Programme Symposium

**Watching our waistline: Waist circumference is a better predictor of coronary heart disease risk than BMI** — 19/09/2018, Oxford
Oxford open doors event (Public engagement)

**Body fat distribution and blood pressure in 10 000 adults with whole-body imaging: UK Biobank and Oxford Biobank** — 15/04/2018, Edinburgh
44th Adipose Tissue Discussion Group conference

### Oral presentations

**Adiposity measures and Ischaemic Heart Disease in the UK Biobank** — 28/02/2018, Oxford
NIHR Biomedical Research Centre Obesity Networking Event

**Adiposity and Ischaemic Heart Disease: Recent findings from the UK Biobank** — 02/07/2018, Oxford
Oxford Metabolic Health Inaugural Symposium

**Coronary heart disease in relation to general and central adiposity in the UK Biobank: A cohort study of 500 000 men and women** — 27/08/2018, Munich
European Society of Cardiology Congress

**Body composition and Blood Pressure in 10 000 UK Adults: Recent findings from the UK Biobank and Oxford Biobank** — 29/03/2019, Oxford
BRC Obesity Theme Networking Event

**Observational and genetic associations of adiposity measures with CHD risk in the UK Biobank: A prospective cohort study of 500 000 adults** — 30/01/2020, Oxford
NIHR BRC Obesity Theme Networking Event

### Awards

**ESC Moderated best poster award** for the session 'Latest registry data on coronary disease outcomes' — 27/08/2018, Munich

**Moderated DPhil poster prize,** Nuffield Department of Population Health, University of Oxford — 02/10/2018, Oxford

## List of abbreviations

| | |
|---|---|
| **ACC** | Asia Cohort Consortium |
| **AMI** | Acute myocardial infarction |
| **Apo-A** | Apolipoprotein A |
| **Apo-B** | Apolipoprotein B |
| **BF%** | Body fat percentage |
| **BIA** | Bio-electrical impedance analysis |
| **BMI** | Body-mass index |
| **BW** | Body weight |
| **BP** | Blood pressure |
| **CCHS** | Copenhagen City Heart Study |
| **C+C4D** | CARDIoGRAMplusC4D Consortium |
| **CETP** | Cholesterol Ester Transport Protein |
| **CGPS** | Copenhagen General Population Study |
| **CHD** | Coronary heart disease |
| **CI** | Confidence intervals |
| **CKB** | China Kadoorie Biobank |
| **CRP** | C-reactive protein |
| **CT** | Computer tomography |
| **CVD** | Cardiovascular disease |
| **DAG** | Directed acyclic graph |
| **DALY** | Disability Adjusted Life Years |
| **DBP** | Diastolic blood pressure |
| **DXA** | Dual x-ray absorptiometry |
| **EGCUT** | Estonian biobank study |
| **ENGAGE** | European Network for Genetic and Genomic Epidemiology Consortium |
| **ERFC** | Emerging Risk Factors Collaboration |
| **FFA** | Free fatty acid |
| **FFM** | Fat-free mass |
| **FHS** | Framingham Heart Study |
| **FM** | Fat mass |
| **GBD** | Global Burden of Disease study |
| **GBMRFC** | The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration |
| **GRS** | Genetic risk score |
| **GWAS** | Genome-wide association study |
| **HbA1c** | Haemoglobin A1c |
| **HDL** | High density lipoprotein |
| **HES** | Hospital Episode Statistics |
| **HFSS** | High fat, sugar and salt |
| **HL** | Hepatic Lipase |
| **HR** | Hazard ratio |
| **IPD** | Individual participants data |
| **LDL** | Low density lipoprotein |
| **Lp (a)** | Lipoprotein (a) |
| **LVH** | Left ventricular hypertrophy |
| **MET** | Metabolic equivalent of task |
| **MI** | Myocardial infarction |
| **MR** | Mendelian randomization |
| **MWS** | Million Women Study |
| **NAFLD** | Non-alcoholic fatty liver disease |
| **NEFA** | Non-esterified fatty acids |
| **NHS** | National Health Service |
| **NIH** | National Institutes of Health |

| | |
|---|---|
| **NIH-AARP** | National Institutes of Health American Association of Retired Persons Diet and Health Study |
| **OR** | Odds ratio |
| **PC** | Principal components |
| **PCA** | Principal component analysis |
| **PSC** | Prospective Studies Collaboration |
| **R** | Resistance |
| **RR** | Relative risk |
| **RDB** | Regression dilution bias |
| **RDR** | Regression dilution ratio |
| **SBP** | Systolic blood pressure |
| **SD** | Standard deviation |
| **SE** | Standard error |
| **SES** | Socio-economic status |
| **SMC** | Smooth Muscle Cell |
| **SNP** | Single nucleotide polymorphism |
| **VAT** | Visceral Adipose Tissue |
| **VLDL** | Very low-density lipoprotein |
| **WC** | Waist circumference |
| **WHO** | World Health Organization |
| **WHR** | Waist-to-hip ratio |
| **WHRadjBMI** | Waist-to-hip ratio adjusted for BMI |
| **WHTR** | Waist-to-height ratio |
| **$X_c$** | Reactance |
| **Z** | Impedance |

## List of Tables


| No. | Description | Page |
|---|---|---|
| **1.1** | A comparison between adiposity measures | 16 |
| **2.1** | Literature review search terms | 44 |
| **2.2** | Summary of prospective studies identified in literature review | 47 |
| **2.3** | Key findings of studies investigating the association between BMI and CHD | 48 |
| **2.4** | Key findings of studies investigating the association between central adiposity measures (WC, WHR and WHTR) and CHD | 50 |
| **2.5** | Summary of Mendelian randomization studies identified in literature review | 51 |
| **3.1** | ICD-10 codes used to define incident Coronary Heart Disease (CHD) | 64 |
| **3.2** | Selected socio-demographic characteristics in 455 148 participants aged 40 - 69 without cardiovascular disease at baseline, by sex | 66 |
| **3.3** | Selected body size and adiposity characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex | 67 |
| **3.4** | Selected lifestyle characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex | 68 |
| **3.5** | Selected biological and medical characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex | 69 |
| **4.1** | Partial correlation coefficients between adiposity measures at baseline, by sex | 90 |
| **4.2** | Mean adiposity across selected demographic variables at baseline among men | 93 |
| **4.3** | Mean adiposity across selected demographic variables at baseline among women | 94 |
| **4.4** | Mean adiposity across selected categorical variables at baseline, by sex | 99 |
| **5.1** | Baseline characteristics in full study population versus resurveyed population | 123 |
| **5.2** | Change in adiposity from baseline to a repeat measurement, by age and sex | 126 |
| **5.3** | Regression dilution ratios (95% CI) for adiposity and body size measures, estimated using three separate methods | 129 |
| **5.4** | Regression dilution ratios* (95% CI) for adiposity measures, separately according to selected categorical variables at baseline | 130 |
| **6.1** | Baseline characteristics in the Oxford Biobank and UK Biobank imaging studies combined, by sex | 140 |
| **6.2** | Mean change in DXA-derived body fat compartments per SD higher usual levels of BMI, WC and WHR, by sex | 142 |
| **7.1** | ICD10 and Operation codes for primary outcome in the current study | 161 |
| **8.1** | Basic information on loci associated with BMI in GIANT | 206 |

| | | |
|---|---|---|
| **8.2** | Basic information on loci associated with WHRadjBMI | 208 |
| **8.3** | Selected baseline characteristics of the study population used in the genetic analyses | 209 |
| **8.3** | Associations of weighted genetic risk scores for WHRadjBMI with established cardiovascular risk factors, socio-economic and lifestyle factors in the UK Biobank study | 217 |
| **8.4** | Regression coefficients for associations of CHD with genetic variants included in genetic risk scores for BMI and WHRadjBMI in the UK Biobank using MR Egger, weighted median and inverse-variance weighted methods | 221 |

## List of Figures


| No. | Description | Page |
|---|---|---|
| **1.1** | Processes leading to atherosclerosis within blood vessels | 17 |
| **1.2** | Age-standardize prevalence of overweight or obesity among adults (aged >20 years) in Europe, between 1980 and 2015 | 18 |
| **2.1** | Study selection procedure for systematic search 1: Prospective studies | 45 |
| **2.2** | Study selection procedure for systematic search 2: MR studies | 46 |
| **3.1** | Recruitment pattern and baseline assessment sites of the UK Biobank, 2006 - 2010 | 62 |
| **3.2** | DXA body composition image of a 56-year-old male with BMI 34.7kg/$m^2$ | 63 |
| **3.3** | Flow diagram of UK Biobank study population inclusion criteria for each analysis | 65 |
| **4.1** | Established and emerging pathways involved in the association between adiposity and CHD | 89 |
| **4.2** | Mean increase in adiposity measure per increasing fifth of baseline BMI, by sex | 91 |
| **4.3** | Mean adiposity by five-year age group and sex | 92 |
| **4.4** | Mean adiposity by ethnicity and sex | 95 |
| **4.5** | Mean adiposity by geographical location and sex | 96 |
| **4.6** | Mean prevalence of obesity across UK recruitment centers as defined by conventional thresholds of anthropometry, by sex | 97 |
| **4.7** | Mean prevalence of obesity across UK recruitment centers as defined by conventional thresholds of anthropometry, by sex | 98 |
| **4.8** | Daily alcohol consumption and current smoking prevalence with increasing levels of adiposity at baseline, by sex | 100 |
| **4.9** | Self-reported versus screen-detected diabetes prevalence at baseline with increasing levels of adiposity, by sex | 101 |
| **4.10** | Baseline adiposity and systolic blood pressure before and after removing participants on blood pressure-lowering medication | 102 |
| **4.11** | Baseline adiposity and diastolic blood pressure before and after excluding participants on blood pressure-lowering medication | 103 |
| **4.12** | Cross-sectional associations of baseline adiposity with LDL-C and HDL-C in the UK Biobank, by sex | 104 |
| **4.13** | Cross-sectional associations of baseline adiposity with Apo-lipoprotein A and Apo-lipoprotein B, by sex | 105 |
| **4.14** | Cross-sectional associations of baseline adiposity with total cholesterol and triglyceride levels, by sex | 106 |
| **4.15** | Cross-sectional associations of baseline adiposity with Lp(a) levels in the UK Biobank, by sex | 107 |
| **4.16** | Cross-sectional associations between baseline adiposity and markers of type-2 diabetes mellitus, by sex | 108 |
| **4.17** | Cross-sectional associations between baseline adiposity and inflammatory markers in the UK Biobank, by sex | 109 |
| **4.18** | Glomerular filtration rate (GFR) with increasing levels of adiposity among men and women without prior cardiovascular disease at recruitment in the UK Biobank | 110 |

| | | |
|---|---|---|
| **4.19** | Cross-sectional associations between baseline adiposity and liver enzyme levels in the UK Biobank, by sex | 111 |
| **5.1** | Age- and sex-adjusted mean adiposity at resurvey vs. baseline values in the same individuals | 125 |
| **5.2** | The effect of ageing between baseline and resurvey adiposity variables in the same individuals | 127 |
| **5.3** | Mean baseline and re-survey values in groups defined by fifths of baseline adiposity in re-survey population | 128 |
| **6.1** | Mean DXA-derived measures of body composition with increasing levels BMI, WC and WHR, by sex | 141 |
| **6.2** | DXA-derived measures of body composition versus systolic blood pressure (SBP) after additional adjustment for all other mutually exclusive body fat compartments, by study and sex | 143 |
| **6.3** | Anthropometric measures of adiposity versus systolic blood pressure (SBP), with and without further adjusting for DXA-derived measures of body composition, by sex | 144 |
| **7.1** | Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity measures in the UK Biobank | 162 |
| **7.2** | Hazard Ratios (95% CI) for CHD with increasing *usual* levels of adiposity, by sex | 163 |
| **7.3** | Hazard Ratios (95% CI) for CHD per SD higher *usual* adiposity levels, by sex | 164 |
| **7.4** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **men** by selected categorical characteristics at baseline | 165 |
| **7.5** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **women** by selected categorical characteristics at baseline | 166 |
| **7.6** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **men** by selected categorical characteristics at baseline | 167 |
| **7.7** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **women** by selected categorical characteristics at baseline | 168 |
| **7.8** | Hazard Ratios (95% CI) for CHD with increasing levels of BMI, WC and WHR, independently of other measures | 169 |
| **7.9** | Hazard Ratios (95% CI) per SD increasing usual BMI, WC and WHR before and after adjusting for general and central adiposity measures, by sex | 170 |
| **7.10** | Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of WC and WHR stratified by thirds of BMI, by sex | 171 |
| **7.11** | Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of BMI stratified by thirds of WC and WHR, by sex | 172 |
| **7.12** | Hazard Ratios (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c | 173 |
| **7.13** | Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c, by sex | 174 |
| **7.14** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity, with adjustment for baseline values of potential intermediate risk factors among **men** | 175 |
| **7.15** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher usual adiposity, with adjustment for baseline values of potential intermediate risk factors among **women** | 176 |
| **7.16** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after various exclusions | 177 |
| **7.17** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after various exclusions | 178 |

| | | |
|---|---|---|
| **7.18** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after adjusting for potential confounders | 179 |
| **7.19** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after adjusting for potential confounders | 180 |
| **8.1** | Directed acyclic graph illustrating the association between genetically elevated adiposity and coronary heart disease | 203 |
| **8.2** | Flow diagram of BMI-associated variant selection process | 204 |
| **8.3** | BMI-associated SNPs in GIANT identified as pleiotropic for other adiposity phenotypes to significance $p<5x10^{-8}$ | 205 |
| **8.4** | Flow diagram of WHRadjBMI-associated variant selection process | 207 |
| **8.5** | Comparison of effect sizes of BMI related SNPs in GIANT and UK Biobank study | 210 |
| **8.6** | Comparison of effect sizes of WHRadjBMI related SNPs in GIANT and UK Biobank | 211 |
| **8.7** | Weighted genetic risk score (GRS) for increasing BMI using 34 SNPs: distribution and mean BMI with increasing levels of GRS among men and women in the UK Biobank | 212 |
| **8.8** | Weighted genetic risk score (GRS) for increasing WHRadjBMI: distribution and mean BMI with increasing levels of GRS among men and women in the UK Biobank | 213 |
| **8.9** | Mean increase in body size and adiposity per SD increasing Genetic risk scores for BMI and WHRadjBMI, by sex | 214 |
| **8.10** | Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for BMI, by sex | 215 |
| **8.11** | Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for WHR adjusted for BMI (WHRadjBMI), by sex | 216 |
| **8.12** | Weighted genetic risk scores (GRS) for WHRadjBMI and BMI versus mutually exclusive DXA-derived variables of regional body composition | 218 |
| **8.13** | Association of increasing fifths of genetic risk scores for BMI and WHRadjBMI with coronary heart disease* risk in the UK Biobank | 219 |
| **8.14** | A comparison of Hazard Ratios (95% CI) for CHD risk with observed and genetically elevated BMI and WHRadjBMI | 220 |
| **8.15** | Regression and funnel plots for MR assumption investigations | 222 |

# CHAPTER 1: Introduction

## Chapter summary

Coronary heart disease (CHD) is the leading cause of death worldwide, despite recent advances in treatment and prevention strategies employed by many Western countries. Obesity, or excess adiposity, is an established risk factor involved in the pathogenesis of CHD, although the underlying mechanisms have not been fully elucidated. Moreover, it is unclear whether regional adiposity is a better indicator of CHD risk than general adiposity, and hence uncertainty remains surrounding the most relevant anthropometric measure of obesity for CHD risk prediction in contemporary populations. The objectives of this chapter are to: i) describe briefly the existing research into CHD; ii) identify current uncertainties; iii) describe the physiological aetiology thought to underlie the enhanced risk of CHD observed at higher levels of adiposity; and iv) provide a background and rationale for the thesis objectives. Body-mass index (BMI) is the most commonly used measure of general adiposity in epidemiological studies, and measures of central adiposity include waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHTR). Bio-electrical impedance analysis (BIA) is relatively inexpensive and may be superior to anthropometric measures when estimating adiposity. However, contemporary, large-scale evidence is lacking for a direct comparison of adiposity-related CHD risk associated with each measure, and the utility of BIA measures in contemporary populations is unclear. Recent advances in genetic epidemiology have allowed us to investigate the causal associations between adiposity and CHD risk. However, to date, studies have been unable to reliably compare the genetic and observational prospective associations between multiple independent adiposity measures and CHD risk in the same study population. This thesis aims to describe the observational and genetic associations between six commonly used adiposity measures and CHD more reliably than has been previously possible using data from the UK Biobank.

## 1.1 Coronary heart disease (CHD)

### *1.1.1 Epidemiology*

CHD, also referred to as ischaemic heart disease (IHD), is the most common form of cardiovascular disease (CVD) worldwide, and has been the leading cause of death for over 15 years. Global deaths caused by CHD have risen by 17% from 2005 to 2015.[1] Furthermore, this trend is expected to continue with the shift in global age structures (ageing populations) accompanying the current epidemiological transition. Despite age-standardised mortality from CHD declining in the UK over the past decade,[2, 3] CHD remains the greatest contributor to country-wide deaths. Results from the World Health Organization 'multinational MONItoring of trends and determinants in Cardiovascular disease (MONICA)' project, where data from 37 populations were collected each covering a 10-year period between 1979 and 1996 suggested that UK regions had some of the highest rates of CHD events across the 27 included countries,[4] with only a handful of European countries surpassing the UK CHD prevalence rates in 2016.[5] The economic burden of CHD and related CVD events in the UK is substantial, costing the National Health Service an estimated ~£9 billion in 2017.[6]

### *1.1.2 Pathophysiology*

The major manifestations of CHD include myocardial infarction (MI), chronic stable angina pectoris, acute coronary syndrome and sudden cardiac death. In combination with ischaemic stroke, these are collectively termed atherosclerotic conditions due to their postulated shared underlying pathophysiology. In brief, atherosclerosis is the process of gradual accumulation of an atherosclerotic plaque within lesions of part of the arterial wall in response to endothelial cell damage (**Figure 1.1**). An atherosclerotic plaque is composed of inflammatory cells, cellular debris, smooth muscle cells (SMCs), cholesterol and cholesterol ester, overlain by a fibrous cap. Low-density lipoprotein (LDL) cholesterol particles can migrate into the arterial wall where they are oxidised by macrophages and SMCs. A cascade of inflammatory processes can respond starting with migration of mono-nuclear cells such as monocytes to the site of damage, where they transform into foam cells.[7] Accumulation of foam cells and proliferation of SMCs leads to plaque growth, whilst cellular apoptosis, and continued release of inflammatory mediators gradually reduce the integrity of the fibrous cap. Over time, a variety of factors accelerate this process such as type II diabetes, smoking, and high serum cholesterol through their metabolic or chemically induced stress effects on the endothelium layer. A vulnerable plaque can undergo a number of processes*; i)* it may spontaneously lyse; *ii)* it could remain and subsequently become incorporated into the artery wall (further narrowing

the lumen) or; *ii)* the fibrous cap could tear, exposing the lipid-rich core underneath to the bloodstream, leading to the formation of an intraluminal coronary thrombus, and potential occlusion of the artery. Complete blockage of the coronary artery through this process leads to a symptomatic acute coronary event, or an MI.[8] In the majority of fatal MI cases, there are often several bouts of asymptomatic coronary thrombus that have been incorporated into the arterial wall prior to the final coronary event.[9]

### *1.1.3 Risk factors for CHD*

CHD is considered a highly complex disease, depicted by its multitude of varied and most likely inter-dependent risk factors. Studies of migrant populations indicate a strong environmental component to the development of CVD.[10] However, in some countries, for example in the case of migrants from South Asia to Western countries, the CHD incidence in established migrant populations exceeds those in the host country, implying that CHD risk is likely in part due to genetic susceptibility.[11]

More than 300 risk factors for CHD have been identified, including smoking, hypertension, hyperlipidaemia, adiposity, alcohol consumption, physical inactivity, psychological factors and diets which are high in fat, sugar and salt (HFSS).[12] There are also marked and unexplained differences in adiposity-related CHD risk between sex, ethnicity, socio-economic class and geographical location that are not fully accounted for by traditional risk factors alone.[13-16] Nevertheless, it is believed that an individual's risk of CHD is dominated by five major modifiable risk factors: *i)* cigarette smoking; *ii)* alcohol consumption; *iii)* raised blood pressure*; iv*) raised cholesterol; and *v)* obesity.[12] Accordingly, these risk factors are typically incorporated into global risk scores used as the foundation for guidelines and prevention strategies in developed countries, a concept first introduced in 1991 using data from the Framingham Heart Study.[17,18] However, altering these traditional risk factors in individuals does not completely attenuate the risk of CHD.[19] Furthermore, some of the identified risk factors are difficult to modify through current therapeutic strategies such as behavioural interventions. For these reasons, continued research into novel, specific and potentially modifiable risk factors for CHD in large contemporary populations remains critical.

## 1.2 Adiposity

### *1.2.1 Epidemiology of overweight and obesity*

The most commonly used method for measuring adiposity is body-mass index (BMI), defined as body weight in kilograms divided by the square of height in metres (i.e. kg/m$^2$). Originally developed during the 19th century, BMI became the preferred adiposity measure in the 1970s when data from the Seven Countries study suggested that BMI predicted adiposity-related complications.[20] For all ethnicities except Asian populations, the World Health Organization (WHO) and the National Institutes of health (NIH) have defined overweight as BMI values between 25.0 and 29.9 kg/m$^2$; and obesity as BMI ≥30.0 kg/m$^2$ (BMI≥35 kg/m$^2$ is defined as morbid obesity). The worldwide prevalence of obesity has increased dramatically over a relatively short period of time. In 2014, almost 40% of adults across the world were categorized as overweight and 13% were obese, which is double the prevalence in 1980. No single nation has reported a decrease in obesity rates over the past 33 years.[21] Historically, the prevalence of overweight in the UK was one of the highest in Europe (**Figure 1.2**), with over half of UK adults aged over 20 years categorised as overweight or obese in 1980,[22] and only a handful of European countries surpassing the UK overweight prevalence in 2015. Importantly, obesity and overweight have been established as risk factors for a variety of chronic diseases, including site-specific cancers, stroke and other non-coronary vascular diseases, type II diabetes, psychological disorders and a variety of musculoskeletal disorders, which together contribute to a colossal economic burden.[23-26] Indeed it has been postulated that obesity is leading to overall reductions in life expectancies in the US (something not seen for many decades), with the potential to overtake cigarette smoking as the leading modifiable risk factor for premature mortality.[27-30]

### *1.2.2. Adiposity and CHD*

Adipose tissue is a complex, multicellular endocrine organ, with the primary cell type, adipocytes, profoundly influencing the function of many organ systems by secreting a diverse array of metabolites. Adipocytes have fundamental roles in glucose homeostasis, insulin sensitivity, inflammation and lipid metabolism.[31] Consequently, the adverse effect of excess adipose tissue on CHD risk could involve the combined effect of several factors, eventually contributing to endothelial dysfunction.

However, the majority of the effect of adiposity on CHD risk is thought to be mediated through hypertension, enhanced insulin resistance and hypercholesterolemia, as evidenced by large-

scale prospective studies.[32] Obesity is associated with altered lipid metabolism, termed dyslipidaemia, which is characterised by increased levels of circulating low-density lipoprotein (LDL) cholesterol, triacylglycerols and total cholesterol, and reduced high-density lipoprotein (HDL) cholesterol levels. In obese subjects, the production and secretion of non-esterified fatty acids (NEFAs) is enhanced, which is later converted to triglyceride-rich very low-density lipoprotein (VLDL) particles in the liver by hepatic lipase (HL), and then further broken down by cholesteryl ester transfer protein (CETP) to triglyceride-rich LDL cholesterol particles. Both HL and CETP are upregulated in obesity, whereas the activity of lipoprotein lipase (the enzyme responsible for the reverse reaction) is attenuated. This process is likely to be more profound in abdominal obesity due to the close proximity of adipose tissue to the liver. Another pathway which contributes to endothelial dysfunction in obesity is insulin resistance, which is thought to be a consequence of several of the mechanisms discussed here, including increased levels of NEFAs, lipotoxicity and disturbances in adipokine secretion.[33] The hypothesized mechanisms by which obesity may influence blood pressure include peripheral vascular resistance or renal sodium retention.[34-36] Additionally, although the mechanisms are unclear, it is postulated that visceral fat exerts independent effects on blood pressure, possibly involving abnormal renin-angiotensin-aldosterone regulation and sympathetic nervous system activation.[37-40]

However, previous studies have demonstrated that the association between excess adiposity and CHD risk is independent beyond these traditional risk factors.[41] A number of potential physiological mechanisms could explain this observation, including an obesity-induced state of low-grade inflammation, endothelial dysfunction, haemostatic imbalance favouring coagulation, impaired endothelial vasodilatory responses and reduced heart rate variability due to withdrawal of vagal activity and sympathetic pre-dominance.[33, 42] Alternatively, the observed excess risk could be due to the residual effects of biological variation or imprecision in the measurement of known mediators.

Among many other metabolites, adipocytes produce the hormone leptin, a bioactive substance involved in the control of satiety and energy expenditure, with further atherogenic properties. Obesity is associated with elevated circulating leptin levels, which can lead to insulin resistance and other metabolic complications. Leptin also enhances platelet aggregation,[43] promoting angiogenesis and re-modelling of the vasculature, which in turn induces proliferation of vascular SMCs. Hence, leptin is one example whereby obesity could contribute to the narrowing of atherosclerotic arteries beyond traditional risk factors.[44]

Researchers have also postulated that some of the adverse effects of obesity could be the result of structural changes in response to increased total blood volume and cardiac output.[45] Structural changes in response to such haemodynamic changes could include left ventricular hypertrophy (LVH),[46,47] cardiac arrhythmias, concentric remodelling, concentric LVH,[48] left atrial enlargement, abnormal diastolic filling[45, 49] and complex ventricular arrhythmias, ultimately exerting adverse effects on diastolic and systolic function of the heart and potentiating the risk of cardiac events.[50] Similarly, structural changes could result from the physical size of fat deposits, ultimately affecting tissue function. Examples include the infiltration of fat deposits to the liver and ectopic areas such as the heart muscle, kidneys and even blood vessels often accompanying increases in whole body fat mass. As well as exerting a mechanical strain on the affected organs, infiltration of fat cells have metabolic consequences such as lipotoxicity following intracellular lipid deposition, a process which eventually leads to irreversible cell damage and subsequent tissue dysfunction.[51]

Although recent improvements in treatment strategies for intermediate risk factors have reduced the mortality rate of CHD in western Europe and North America over the past 50 years,[52] reports of pooled estimates from several prospective cohort studies such as the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (GBMRFC) have estimated that less than half (46%) of obesity-related CHD risk is mediated through raised blood pressure and/or raised cholesterol or glucose levels.[24] Additionally, it remains unclear whether overweight or obesity are associated with impaired responses to lipid-lowering and anti-hypertensive therapy.[53-54] Therefore, it is critical to continue research into the aetiological mechanisms underlying adiposity-related CHD risk, to reveal the remaining excess CHD risk associated with increasing adiposity after accounting for known modifiable risk factors and to identify further modifiable obesity-related risk factors. As well as potentially revealing novel therapies, this knowledge will also inform decision makers of the cost implications and health consequences arising from the management of risk factors for CHD at the population level. This is particularly important and timely, given the current and expected rise in global obesity rates.[55]

### *1.2.3 Central adiposity versus general adiposity*

Despite BMI being recognised as a major risk factor for CHD, it is estimated that over 40% of deaths attributed to raised BMI are occurring in individuals who are not obese,[56] and results from recent genetic Mendelian Randomisation (MR) studies suggest that central adiposity is independently associated with cardiovascular risk beyond general adiposity.[57, 58] Therefore,

further research into superior markers of adiposity-related disease risk which surpass BMI at the population level has the potential to contribute to earlier disease treatment and prevention.

Abdominal adiposity, also referred to as visceral or central adiposity, is characterised by increased visceral adipose tissue (VAT) surrounding the intra-abdominal organs, and is thought to be the most aetiologically relevant component of adiposity for the development of cardiovascular disease.[59,60] Compared with fat stored elsewhere, VAT appears more strongly associated with a cluster of metabolic perturbations predisposing to CHD including insulin resistance, type 2 diabetes, hypercholesterolemia and fatty-liver disease,[61-63] as well as cardiovascular events and all-cause mortality.[64-66]

Furthermore, despite similar overall weight loss, surgical reduction in intra-abdominal adipose tissue is associated with improved oral glucose tolerance, insulin sensitivity, and fasting plasma glucose, while surgical removal of large quantities of peripheral subcutaneous adipose tissue has relatively little effect.[67, 68] In a study quantifying the levels of visceral adiposity versus subcutaneous and liver fat through CT imaging, visceral fat was the only independent predictor of all-cause mortality.[66] Furthermore, large and robust studies attempting to measure visceral adiposity through indirect measures such as waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHTR) have since confirmed a strong relationship between central adiposity and cardiovascular risk, independently of general adiposity measures such as BMI.[69] However, exactly how much of the excess risk associated with visceral fat is not accounted for when measuring BMI remains unclear.

Although unclear, the independent effect of VAT on cardiovascular risk is thought to involve similar mechanisms to general adiposity, although the effect of VAT is exacerbated by a few key characteristics. Firstly, the close proximity of VAT to the portal vein allows free fatty acids and lipolysis-activating adipocytokines to drain directly into the liver, subsequently enhancing the susceptibility of the liver to hepatic insulin resistance.[37, 38, 40] Insulin resistance and hyperinsulinemia may increase sympathetic activity and sodium tubular reabsorption in the kidneys,[39] resulting in increased blood volume and raised blood pressure. Additionally, VAT is also thought to express distinct biological properties and responses to obesity as compared with body fat stored elsewhere, which may heighten cardiovascular risk.[70] For example, VAT is associated with enhanced hormone-sensitive lipase rates and is less responsive to the anti-lipolytic effects of insulin compared with subcutaneous adipocytes. Furthermore, VAT also produces less adiponectin, known to increase insulin sensitivity.[71] A key underlying mechanism could involve the limited capacity for adipocyte hypertrophy in adipocytes within the visceral regions. Upon reaching a critical size, adipocytes outgrow their blood supply and

hypoxic adipocytes undergo apoptosis, releasing inflammatory mediators which can reduce insulin sensitivity and lead to sympathetic nervous system activation. In addition, VAT cell lines are also more susceptible to hypoxia-induced apoptosis compared with subcutaneous adipocytes.[72] However, there is uncertainty about the contribution of each of these pathways to VAT-related CHD risk.

In contrast, subcutaneous adipose tissue has distinct biological properties, and is often associated with favourable lipid and glucose profiles, as well as overall reductions in cardiovascular risk.[73, 74] However, with reference to cardiovascular risk factors, there is some evidence suggesting that the effects of subcutaneous fat on cardiovascular risk factors are location-dependent,[75-78] but large-scale research investigating whether subcutaneous fat is protective or simply less harmful than fat stored elsewhere is lacking. Importantly, body fat distribution is also dependent on other characteristics such as ethnicity, age and sex, which themselves are established as strong risk factors for cardiovascular disease. Hormones in particular are closely related to body fat distribution, but also independently affect known risk factors such as insulin resistance.[79]

Despite epidemiological evidence suggesting the relevance of central adiposity to CHD risk, our current knowledge of the underlying biological mechanisms remains incomplete. Furthermore, although it is assumed that fat mass is the most hazardous component of body weight, evidence is lacking for the associations of fat-free mass with cardiovascular risk factors. To better understand why specific adiposity traits exert different effects on metabolic health and subsequent CHD risk, research would benefit from large-scale prospective studies with accurate information on adiposity measures and biomarkers, as well as available genetic and imaging data, such as the UK Biobank.[80]

### *1.2.4 Current therapies directed towards weight loss*

Bariatric surgery has proven the most effective intervention for weight loss, achieving around 20-30% loss of body weight after 6 months, with a small number of long-term follow-up studies suggesting an overall reduction in the incidence of type II diabetes and MI, as well as reductions in overall and cardiovascular mortality.[81,82] However, surgery is associated with a risk of complications, and is not scalable, particularly given the increasing prevalence of obesity. Although intensive lifestyle interventions are cost-effective, easy to implement, and have now been shown to achieve modest weight loss of approximately 10% of total body weight,[83, 84] long-term follow-up studies suggest that weight loss achieved through lifestyle

interventions is generally not sustained due to intrinsic adaptation mechanisms, as well as the influence of obesogenic environments.[85, 86]

Current efforts to use pharmacotherapy for weight loss have focused on satiety signalling mechanisms and insulin secretion. Work has progressed furthest on glucagon-like peptide-1 receptor agonists, with clinical trials reporting a fairly consistent weight loss of around 4-6 kilograms.[87] However, despite the consistent trends observed between increasing adiposity and CHD risk in observational and genetic epidemiological studies, to date no large randomised clinical trial has managed to successfully reduce the risk of CHD with sustained weight loss. The Lorcaserin CAMELLIA-TIMI 61 trial was the first pharmaceutical trial to demonstrate sustained weight-loss of almost 2.8 kg and cardiovascular safety after 3.3 years,[88] however full follow-up has not yet been completed. Continued research using large and detailed population studies has the potential to enhance our current understanding of the underlying mechanisms in order to identify potential novel therapeutic targets.

### 1.3 Adiposity measures

When quantifying associations between adiposity and risk of CHD, imprecise measurements and biological variation of adiposity could lead to systematic under-estimations of the burden of obesity-related disease in contemporary populations. To improve our current understanding of the underlying mechanisms of total and regional body fat accumulation, it is important to accurately and reliably measure body composition and regional adipose tissue. Currently, there are a number of direct and indirect methods for estimating body composition, each of which are summarised in Table 1.1 and will be described individually in greater depth below.

#### *1.3.1 Direct measures*

Recent technologies have been developed to allow for direct estimation of total and regional adipose tissue. Although VAT is thought to be the most aetiologically relevant component of adiposity, currently only computed tomography (CT) and magnetic resonance imaging (MRI) can provide direct measures of cross-sectional areas or volumetric measures[89]. CT technology involves making X-ray measurements from different projection angles around the body to produce multiple 2D high resolution images which are then analysed by software to estimate the adipose tissue with a large amount of accuracy. However, the major limitation with CT technology is the exposure to radiation. MRI is a powerful imaging tool that uses the distinct magnetic resonance properties of tissues to distinguish adipose from non-adipose tissue. Although this technology does not require radiation exposure, it involves creating a very

powerful magnetic field, skilled training staff and a large amount of time, severely limiting its scalability for use in large-scale research or population risk stratification. Despite these disadvantages, however, MRI technology is still considered the 'gold standard' technique for accurate and reliable assessment of body composition.

Another technique used to quantify regional adiposity is dual-energy x-ray absorptiometry (DXA), which is safer and quicker than MRI or CT imaging technologies due to the low-dose of ionizing radiation required.[90] DXA technology estimates fat and fat-free mass by measuring the absorption of X-ray photons at two low-dose frequencies of radiation. In addition to the practical advantages, DXA imaging has low precision errors for both total and regional body fat estimates when compared to MRI estimates.[91]

*1.3.2 Indirect measures*

Techniques such as DXA and MRI are not feasible for clinical risk assessment. Thus, there is a need for a simple, non-invasive method to estimate regional fat storage in contemporary populations, particularly visceral fat accumulation. Currently, the most widely used adiposity measure for estimating obesity-related disease-risk is BMI, which does not delineate fat from fat-free mass, nor does it account for differences in body fat distribution. Alternative measures include WC and WHR which have stronger associations with CVD risk compared with BMI, particularly among women.[14]

Bioelectrical impedance analysis (BIA) is an alternative, rapid and inexpensive method of estimating body fat percentage. BIA measures the opposition of body tissues to the flow of a small alternating current. Conductance is mainly determined by the volume of water in the body, which is almost entirely found in fat-free mass (FFM). Impedance measurements therefore allow for an estimation of the total volume of FFM and, by difference with body weight (BW), fat mass (FM) and body fat percentage (body fat % = ((BW – FFM)/BW) x 100). However, despite being validated and cross-validated within and between population subgroups previously,[92-95] the accuracy as well as the clinical relevance of bioimpedance is unclear. The adiposity-related CHD risk associated with BIA measures compared with conventional anthropometric measures of adiposity has not been investigated in a large contemporary population.

Importantly, the majority of previous studies which compared CHD risk across multiple adiposity measures have estimated the prospective CHD risk associated with adiposity levels measured at a single point in time ("baseline"), which may not accurately reflect the true

underlying levels (so-called “usual” level of exposure) of anthropometric measures over a prolonged period because of within-person variability (i.e. both random measurement errors and short-term biological variability). Consequently, relating single baseline measures to disease risk may lead to associations with usual levels being systematically underestimated, a phenomenon termed regression dilution bias (RDB).[96] Three methods are commonly used to correct for RDB using repeat exposure measurements on an approximately representative subset of participants a few years later (described in greater depth in **Chapter 5**). However, each method relies on a number of assumptions, and often no rationale is explicitly stated for the choice of correction method used. A full assessment of within-person variability associated with different adiposity measures using a single, contemporary large-scale study would allow for accurate comparisons of disease risk across adiposity measures, and can contribute to a greater understanding of adiposity-related associations in future research.

The Emerging Risk Factors Collaboration (ERFC) meta-analysis including over 140 000 participants across 39 studies has undertaken the most robust assessment of within-person variability across adiposity measures, after which investigators reported continuous positive associations of similar magnitude between different adiposity measures (BMI, WC and WHR) and CHD risk.[16] However, there was unexplained heterogeneity of within-person variability between studies, possibly owing to differences in study characteristics or protocols. To date, no single large-scale prospective study has compared the adiposity-related CHD risk between usual levels of BMI, WC, WHR, WHTR and BIA-derived adiposity measures in a contemporary UK population.

## 1.4 Genetics and adiposity

### *1.4.1 Genetically elevated adiposity*

The secular trend of increasing obesity across the world could be attributed to a multitude of factors, including; i) a profound change in the quality, quantity and source of food consumed; ii) a continual reduction in physical activity; or iii) a possible adaptation of the micro-biota which encourages appetite stimulation and hence enhanced dietary intake. The relative importance of energy expenditure versus energy intake has been the subject of controversy in the field,[97-99] however, it is generally accepted that a combination of distal factors have contributed to an enhanced societal ‘obesogenic environment’ with a subsequent shift in energy balance across the entire global population.[100]

However, despite the clear role of the obesogenic environment, twin studies provide consistent evidence for a strong influence of genetics on the observed variation in adiposity between individuals.[101-103] The estimated heritability of obesity is 40- 70%. Over the past 12-15 years, the creation of large-scale genetic mapping consortia, together with vast improvements in genotyping technology have enabled the discovery of over 400 genetic variants associated with obesity through hypothesis-free genome-wide association studies (GWAS).[104] However, together these common variants explain only a small proportion (~6%) of the total variability of obesity. Hence, since common variation is thought to account for over 20% of the variation of BMI, most of the heritability of obesity remains unexplained.[105] In agreement with results from recent weight loss trials discussed above, the majority of obesity-associated variants discovered to date provide strong support for the involvement of the central nervous system, indicating the importance of neurological appetite regulation to obesity as opposed to metabolic mechanisms.[105] However, recent studies investigating potential gene-environment interactions have identified novel loci which support the involvement of additional mechanisms underlying obesity susceptibility such as oxidative stress, glucose metabolism, lipid homeostasis and angiogenesis.[106, 107]

The pathophysiological response to adiposity also varies substantially between individuals, particularly in relation to known risk factors for CVD.[108] Recent GWAS have identified 47 novel common loci that influence body fat distribution independently of BMI in European populations,[109, 110] which may offer a partial explanation for the observed variation in cardio-metabolic factors between obese individuals.[111]

### *1.4.2 Genetically elevated adiposity and CHD risk*

The rapidly evolving field of genetic epidemiology has led to the development of MR studies, which utilise SNPs identified in GWAS as instrumental variables (IVs) for exposures of interest when estimating risk factor-disease associations (discussed in depth in **Chapters 2** & **8**).[112, 113] By design (given certain assumptions), estimates derived from MR studies represent unbiased and causal associations.[114] MR techniques are a useful tool to identify causal risk factor-disease associations as they can overcome some of the inherent limitations of observational epidemiological research such as confounding, measurement error and reverse causality.[114, 115]

Recent MR studies have confirmed a causal relationship for general and central adiposity with both all-cause and cardiovascular mortality,[116-118] as well as incident CHD risk.[58, 119, 120] However, causal estimates derived from MR studies are usually much larger than estimates

reported from observation studies.[121] However, importantly, MR estimates describe the combined risk associated with lifetime exposure to increased adiposity, and therefore these studies do not necessarily depict the risk associated with adiposity in middle age, but do give unbiased estimates of the true direction of risk factor-disease associations.[114] Furthermore, MR can also be used to identify independent associations between different traits which are commonly correlated in observational studies, such as specific adiposity traits.

Therefore, given that continued research is required to investigate the extent to which general adiposity and body fat distribution contribute independently to CHD risk through potentially unrelated but modifiable mechanisms, both observational and genetic epidemiological techniques have the potential to reveal mechanisms underlying obesity-related CHD. To date, no single study has had sufficient power to investigate both using the same study population.

### 1.5 Study Setting

The UK Biobank study is a large prospective cohort study of approximately 500 000 UK participants aged 40-70. The study is uniquely positioned to address some of the uncertainties alluded to in the present Chapter. Initiated in 2006 (recruitment between 2006 and 2010), the UK Biobank aims to investigate the relevance of a variety of exposures to different health outcomes, with a long-term goal of improving the prevention, diagnosis and treatment of common diseases in middle and old age.[80] The UK Biobank has detailed phenotyping of biological characteristics such as genetics and blood-based biomarkers on all participants, and planned imaging data on a sub-set of 100 000 participants (imaging data currently available in a subset of ~5 000) as part of the largest population imaging project to date. The UK Biobank also has robust information on lifestyle habits and well-defined, accurately adjudicated disease outcomes,[122] including over 13 000 first-ever CHD events. Additionally, full repeat baseline assessments were conducted on a representative subset of approximately 20 000 participants during 2012-2013 allowing the estimation of, and correction for, regression dilution bias between adiposity traits. Together with the large sample size, these characteristics make the UK Biobank the largest in-depth prospective cohort to date, allowing for a comprehensive investigation of adiposity-related CHD risk with considerably greater accuracy than has been previously possible.

### 1.6 Thesis objectives

The primary aim of this thesis is to describe the associations of commonly used measures of adiposity with risk of CHD in the UK Biobank using both observational and genetic epidemiological techniques. The main observational analyses will include six commonly used adiposity measures (BMI, body fat %, trunk fat %, WC, WHTR and WHR) and will take into account prior disease, potential confounding, within-person variability and reverse causality. Secondary aims include:

- Summarising the current epidemiological evidence from large-scale prospective and genetic studies for the association between adiposity and CHD risk (**Chapter 2**).
- Describing the main cross-sectional determinants of each of the selected adiposity measures in the UK Biobank, to identify potential confounders (**Chapter 4**).
- Assessing the within-person variability of the selected adiposity measures, to correct associations for regression dilution (**Chapter 5**).
- Investigating potential aetiological mechanisms underlying adiposity-related CHD risk by assessing cross-sectional associations between DXA-derived regional body composition estimates and blood pressure in a combined subset of UK Biobank and Oxford Biobank participants (**Chapter 6**).
- Assessing whether associations between adiposity and CHD risk differ by important demographic and lifestyle characteristics (**Chapter 7**).
- Assessing the extent to which the relationships between selected adiposity measures and CHD risk can be explained by established and emerging potential intermediate factors (**Chapter 7**).
- Assessing the causal nature of observed associations of adiposity measures with CHD using MR approaches (**Chapter 8**).

## CHAPTER 1 Tables and figures

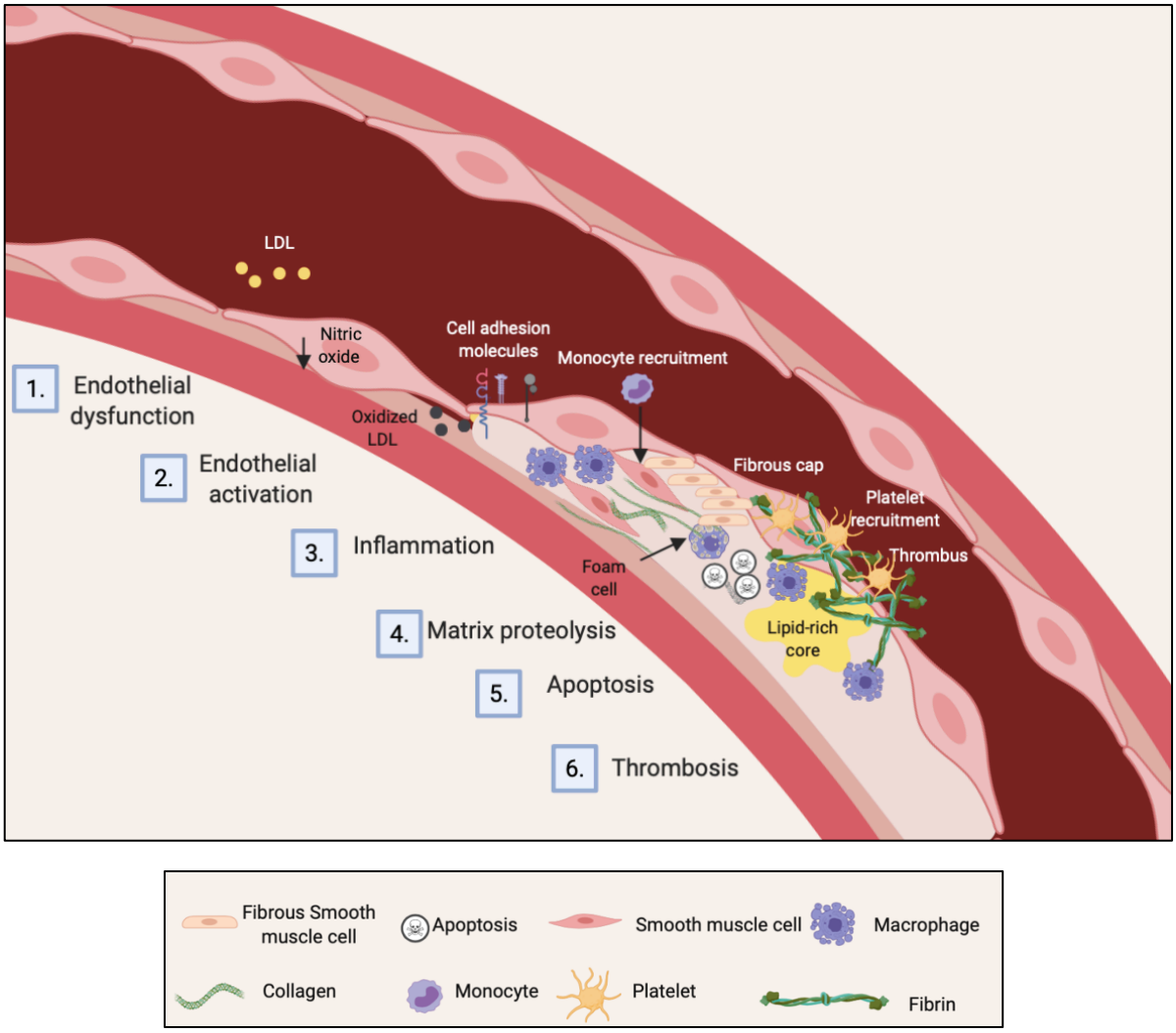

| Figure/Table | Title |
|---|---|
| **Table 1.1** | A comparison between adiposity measures |
| **Figure 1.1** | Processes leading to atherosclerosis within blood vessels |
| **Figure 1.2** | Age-standardize prevalence of overweight or obesity among adults (aged >20 years) in Europe, between 1980 and 2015 |

**Table 1.1** A comparison between adiposity measures

| Method | Major assumptions | Accuracy* | Reproducibility/ long-term stability | Inexpensive | No skilled training required | Safe | Portable | Regional estimate | Quick | Large-scale Observational evidence for IHD risk | Genetic markers exist | Large-scale genetic evidence for IHD risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **INDIRECT:** | | | | | | | | | | | | |
| **BMI** | The majority of body weight is stored as fat | * | *** | ***** | ***** | ***** | ***** | * | ***** | ***** | ***** | ***** |
| **WC** | Subcutaneous and visceral adipose tissue are equally distributed in all participants | * | ** | ***** | ***** | ***** | ***** | *** | ***** | *** | **** | ***** |
| **WHR** | Subcutaneous and visceral adipose tissue are equally distributed in all participants | * | * | ***** | ***** | ***** | ***** | *** | ***** | *** | **** | **** |
| **WHTR** | Subcutaneous and visceral adipose tissue are equally distributed in all participants | * | ** | ***** | ***** | ***** | ***** | *** | ***** | ** | * | *** |
| **BIA** | Hydration fraction, Validated on large representative sample, Population specific, | * | **** | ***** | ***** | ***** | ***** | *** | ***** | * | ** | ** |
| **DIRECT:** | | | | | | | | | | | | |
| **DXA** | Assumptions related to body size, sex and frame | **** | **** | ** | ** | *** | ** | **** | ** | * | ** | * |
| **MRI** | Assumptions related to magnetic properties of tissue | **** | *** | * | *** | **** | * | ***** | * | * | * | * |

*Accuracy was defined as the ability to quantify adipose tissue. BMI = Body-mass index; WC= Waist circumference; WHR= Waist-to-height ratio; WHR= Waist-to-hip ratio; BIA= Bio-electrical impedance analysis; DXA = Dual-energy x-ray absorptiometry imaging; MRI = Magnetic resonance imaging.

**Figure 1.1** Processes leading to atherosclerosis within blood vessels




LDL = Low-density lipoprotein.

**Figure 1.2.** Age-standardized prevalence of overweight or obesity among adults aged >20 years in Europe between 1980 and 2015

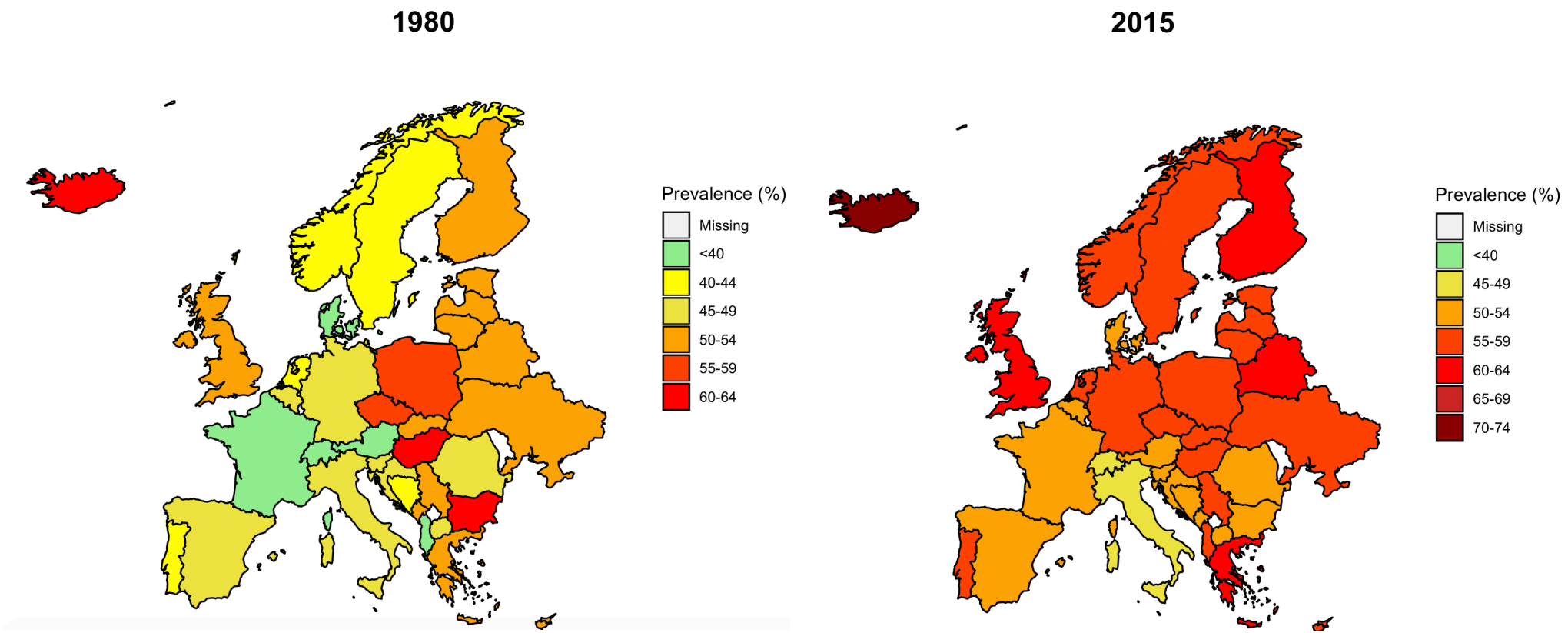



Figure produced in R (version 3.5.2) using data from the Global Burden of Disease (GBD) Study 2017.[22]

## CHAPTER 2: Literature review

### Chapter summary

This chapter reviews the current evidence on the observational and genetic associations between adiposity measures and CHD risk is unclear, and evidence from large-scale studies has not been reviewed recently. In the current chapter, MEDLINE and Embase were searched for large-scale studies (defined as ≥100 000 participants) investigating the prospective association between adiposity and CHD and for MR studies investigating the association between genetically elevated adiposity and CHD. Study population characteristics, outcomes, adjustments, exclusions, and reported associations were summarised. Twenty-three published articles met the inclusion criteria, including seventeen reports on the prospective observational associations (six meta-analyses; ten prospective studies) and seven MR studies. Of the observational studies, thirteen reported continuous positive associations between increasing adiposity and CHD risk, three studies demonstrated J-shaped associations and one study observed no association. Overall, each 5-unit ($kg/m^2$) higher BMI was associated with approximately 20-40% higher risk of CHD events in prospective studies. Most studies assessed the association of BMI with CHD risk, and of the few studies investigating the associations of CHD risk with other adiposity measures, most did not correct for within-person variability. Additionally, many of the identified meta-analyses were unable to adequately control for important confounders. In general, the reported genetic associations between adiposity and CHD risk were directionally concordant, but stronger than observational associations. Large-scale evidence that directly compares the risk of CHD across different adiposity measures is limited to a few prospective studies and summary-level MR studies.

## 2.1 Objectives

The objectives of this literature review were to summarise the published literature on the relevance of adiposity to CHD risk, to critically appraisal the literature, and to identify areas where data from UK Biobank could build on existing evidence to address the aims of the current thesis. Included in this chapter is a summary of the main findings reported from both large-scale prospective observational studies and MR studies, followed by a critical appraisal and discussion of the body of evidence.

## 2.2 Search strategy

Three individual searches were undertaken using MEDLINE and Embase databases. Databases were searched up to September 25$^{th}$, 2019 for studies reporting the prospective association between adiposity and CHD. Only reports with 100,000 or more participants were included in the review. For MR studies, databases were searched up to September 20$^{th}$, 2019 for studies investigating associations between genetically elevated adiposity and CHD. For all searches, adiposity (or related terms) must have appeared in the title as the major focus of each article. Reference lists of included studies were hand-searched to ensure the inclusion of key studies. Keywords and MeSH terms used to conduct the searches are summarised in **Table 2.1**. Of 5 907 observational studies originally identified in the original search, 49 full-text articles were screened for eligibility and a total of 16 studies met the full inclusion criteria (**Figure 2.1**). Of 1 768 MR studies originally identified in the original search, 83 full-text articles were screened for eligibility and a total of seven studies met the full inclusion criteria (**Figure 2.2**). Study population characteristics, outcomes, adjustments, exclusions, and reported associations (quoted as HRs with corresponding 95% Cis, unless otherwise stated) were summarised and discussed. Studies were classified by size, as defined by the maximum number of CHD cases included, as this is thought to directly influence the precision of relative risk estimates. Studies were described in chronological order according to year of publication.

## 2.3 Prospective evidence

### *2.3.1 Search results*

After meeting the inclusion criteria, seventeen reports describing the prospective association between adiposity and CHD risk were identified, including six meta-analyses and eleven large-scale prospective observational studies (**Table 2.2**). Although study protocols varied, the included studies consisted of large sample sizes with robust study designs and consideration of major biases. In general, despite the differences in study populations,

protocols and adjustment for confounders, the included studies provided consistent evidence for a positive association between increasing adiposity and CHD risk, although the exact shape and magnitude of effect size differed slightly between studies. Of the seventeen observational studies identified, the majority used BMI as the only measure of adiposity, most were conducted predominantly in Western populations,[14, 16, 123-128] five were in Asian populations,[129-133] and four were global meta-analyses.[1, 24, 134, 135] In three of the large-scale meta-analyses included study populations overlapped slightly,[1, 24, 134] however each investigated different questions regarding adiposity-related CHD risk which were relevant to the objectives of this thesis, and therefore the results of each were included in the current review. Additionally, three of the identified large-scale cohort studies were also included in the meta-analysis conducted by the Global BMI Mortality Collaboration.[14, 125, 128] However, these individual studies additionally investigated the CHD risk associated with central adiposity or body fat distribution measures in combination with BMI (including WC, WHR and WHTR), and therefore they were each considered separately. Similarly, two articles reported on the Million Women Study (MWS)[124, 125]; both were included as they investigated the CHD risk associated with different adiposity measures. Mean follow-up ranged from 7.1 years (UK Biobank[14]) to 25.7 years (Crump *et al*., 2017[126]).

### *2.3.2 Body-Mass Index*

#### *2.3.2.1 Western populations and global meta-analyses*

Eleven identified reports of large-scale cohort studies investigated the association between BMI and CHD,[14, 123, 125-128, 130-133] of which six described BMI-related CHD risk among predominantly Western populations.[14, 123, 125-128] In general, results presented by the included studies demonstrated that each 5-unit increase in BMI was associated with between 20 and 40% higher risk of CHD, at least in the upper BMI ranges (i.e. above 25kg/m$^2$).

The National Institutes of Health American Association of Retired Persons Diet and Health Study (NIH-AARP) including over 220 000 older US adults observed a strong positive association of CHD mortality with BMI, after excluding current smokers and individuals with extremely low BMI values (<18.5kg/m$^2$).[1] In this study, obesity (BMI≥30kg/m$^2$) was associated with more than double the risk of CHD mortality (RR 2.38, 2.07-2.73) compared with normal BMI (defined by WHO as BMI in the range 18.5-25 kg/m$^2$). Similarly, the UK MWS including over 1.2 million women followed up for over nine years demonstrated a log-linear association with incident (first-ever) CHD endpoints after excluding the first four years of follow-up.[125] In this study, after excluding participants at baseline with chronic disease and adjusting for a

range of potential confounders, each 5-unit increase in BMI was associated with 23% increase in the risk of incident CHD (1.23, 95% CI: 1.22-1.25) throughout the BMI range examined.

A study of over 140 000 Norwegian adults followed up for incident acute myocardial infarction (AMI) over 11.5 years also found positive associations with increasing levels of measured BMI. After excluding participants with known vascular disease and those taking anti-hypertensive medication, HRs for participants in the highest versus lowest levels (highest 40% versus lowest 60%) of BMI ranged from 1.28 (1.16-1.41) to 1.66 (1.37-2.01) across age groups and sex categories. Similarly, in a large cohort study including over 1.5 million Swedish military conscripts and over 38 000 events, positive associations were observed with increasing BMI and risk of incident CHD.[126] In this study, each 5-unit higher BMI was associated with a 40% increased risk of CHD (1.40, 1.34-1.47). A large record linkage study investigated the association between increasing BMI and risk of fatal CHD events in more than 3.6 million UK adults by linking primary care data to national mortality registration data.[123] A total of 55 180 CHD deaths occurred over an average follow-up period of 12 years. Increasing BMI was positively associated with CHD death, and overweight participants (BMI ranges 25- 30kg/$m^2$) were at approximately 10% increased risk of CHD death (1.11, 11.08 – 1.14) compared with normal weight participants (BMI 18.5 – 25kg/$m^2$). An early analysis of the UK Biobank population investigated the association between increasing BMI and risk of AMI in 479 610 UK adults without cardiovascular disease at recruitment.[14] In this study, one SD higher BMI was associated with approximately 28% (23-32%) and 22% (17-28%) increased risk of incident AMI after 7 years among men and women, respectively.

In general, the identified large-scale meta-analyses reported similar positive associations with BMI and CHD risk as observed in single studies. The Prospective Studies Collaboration (PSC) meta-analysis of 57 studies using data from over 850 000 participants took care to limit the impact of reverse causality in the main analysis of BMI and CHD mortality by excluding the first five years of follow-up, participants with low BMI (<15kg/$m^2$), and those with self-reported vascular disease at baseline.[135] Using this approach, the PSC demonstrated a positive and roughly log-linear relationship between BMI and CHD mortality throughout the BMI range of 20-40kg/$m^2$, with the lowest risk occurring at about 20-22.5 after adjusting for sex, age and smoking status. In upper BMI ranges, (25-50kg/$m^2$), each 5-unit higher BMI was associated with approximately 39% (34 - 44%) greater risk of CHD death. Similarly, the ERFC,[16] a meta-analysis of individual participant data (IPD) from more than 140 000 individuals predominantly from Western populations revealed a dose-response association between BMI and risk of incident CHD in those with BMI≥20kg/$m^2$, of approximately 29% increased risk of CHD per SD

increasing BMI (4.56kg/m$^2$), roughly equivalent to a 32% increase in CHD risk per 5-unit increasing BMI (1.32, 1.24-1.41).

The GBMRFC collaboration conducted an individual participant analysis of 97 prospective studies using data from 1.8M participants without prior CVD to investigate CHD risk over an average follow-up period of 13 years. [24] In this study, 5kg/m$^2$ higher BMI was associated with approximately 27% higher risk of incident CHD (1.27, 1.23- 1.31), with no apparent threshold at which lower BMI values were no longer associated with lower risk of CHD. Another large meta-analysis investigating the association between BMI and incident CHD events in over 1.1 million adults from 32 studies across Europe, North America, Asia and the Pacific displayed an approximate 20-30% increase in risk of all CHD events among men (1.28, 1.22- 1.40) and women (1.22, 1.16-1.28) per 5-unit higher BMI, also displaying no indication of a J-shaped association with increasing CHD risk at lower BMI values.[134] The most recent large-scale meta-analysis conducted by the Global BMI Mortality Collaboration used IPD from 239 prospective studies and over 10 million participants to investigate the association between BMI and cause-specific CVD mortality.[1] In this large global meta-analysis, a J-shaped association was observed between increasing BMI and risk of CHD death. Importantly, to limit reverse causality, analysis was restricted to 3.6 million never smokers without known CVD and the first 5 years of follow-up were excluded. Overall, participants with a BMI of approximately 22.5kg/m$^2$ were at the lowest risk of CHD death, above which a 5 kg/m$^2$ higher BMI was associated with over 40% increased risk of fatal CHD (1.42, 1.35 -1.49).

*2.3.2.2 Asian populations*

Overall, of the large-scale studies restricted to Asian populations, the majority demonstrated slightly stronger but directionally consistent adiposity-related CHD risk estimates compared with Western populations, although results from individual identified studies were less consistent, particularly for South Asian populations. Five large-scale studies were identified in Asian populations, including two prospective studies using national health insurance data in South Korea,[131, 133] one prospective study of Chinese men,[130] one large prospective study of 0.5M South Asians,[132] and one pooled meta-analysis of 20 prospective cohorts in East and South Asia conducted by the Asia Cohort Consortium (ACC).[129] In over 220 000 Chinese participants conducted, the Chinese Academy of Preventative Medicine study demonstrated a J-shaped association with increasing BMI and risk of CHD death after exclusion of early follow-up events and participants who self-reported smoking or prior CVD at baseline.[130] In the upper BMI range, however, each 5-unit increase in BMI was associated with a similar approximately 30% increased risk of CHD death as compared to Western cohorts (1.33, 1.16-

1.54). In contrast, a cohort study conducted by the Asian Continental Group including over 120 000 participants from South Korea observed a much stronger 93% increased risk of incident CHD events (1.93, 1.76 – 2.10) per 5 kg/m$^2$ higher BMI, with no indication of increased risk at lower BMI values.[133] A more recent large-scale prospective study using National Health Insurance data from over 2.6 million South Korean adults observed a 30% increased risk of incident CHD per 5-unit increasing BMI, as observed in Western cohorts (Men: 1.27 , 1.26-1.29; Women: 1.29, 1.23-1.36).[131] However, the analysis also adjusted for systolic blood pressure, total cholesterol and fasting serum glucose, all of which are likely to be on the causal pathway.

In contrast, in a large study conducted in Chennai, India, including more than 500 000 South Asians and over 12 500 cardiac deaths obtained through verbal autopsy, BMI was not associated with cardiac death.[132] This observation persisted after the exclusion of events occurring during early follow-up years, participants in higher SES groups, ever smokers and after adjustment for age, education, SES, smoking and alcohol consumption.

The Asia Cohort Consortium (ACC) meta-analysis also observed similar BMI-related CHD risk among Asian participants as compared with Western populations.[129] In this large-scale individual participant meta-analysis of over 1.1 million participants from 20 studies over 9.7 years, a BMI of ≥25 kg/m$^2$ appeared associated with approximately one-third higher risk of CHD mortality (1.33, 95% CI 1.21-1.46) compared with normal BMI (18.5 -24.9 kg/m$^2$).

*2.3.3 Central adiposity and body fat distribution measures*

Although most of the identified reports used BMI as the single measure of adiposity, five also reported on measurements of waist and hip circumferences, including four reports of large-scale cohort studies,[14, 124, 127, 128] and one meta-analysis,[16] all of which were conducted in predominantly Western populations.

The NIH-AARP study compared associations between self-reported WC and BMI on CHD mortality using conventional cut-points defined by WHO in over 220 000 non-smokers with BMI values ≥18.5kg/m$^2$ after adjustment for age, sex and ethnicity.[128] The HRs with increasing WC were roughly one third weaker than the HRs associated with increasing BMI categories. Participants in the highest category of WC (women: ≥88cm; men≥102cm) were at approximately 64% higher risk of CHD death (1.64, 1.38-1.95) compared with individuals in the lowest category of WC (women:<80cm; men:<94cm), whereas the highest category of BMI

(≥35 kg/m$^2$) was associated with more than double the risk of CHD death (2.38, 2.07-2.73) compared with normal or underweight BMI (≤25 kg/m$^2$).

Conversely, three more recent large-scale single observational studies observed generally consistent evidence for an independent effect of central adiposity on CHD risk beyond BMI. In the MWS, self-reported WC showed a strong, positive association with incident CHD which was independent of BMI in over 450 000 women without prior vascular disease at baseline after an average of 5.1 years with full adjustment for region, smoking status, alcohol consumption, exercise and socio-economic status (SES).[124] In this study, a 10cm increase in WC was associated with a 39% increased risk of CHD (1.39, 1.28-1.52) among women with BMI<25kg/m$^2$ but a 97% increased risk (1.97, 1.84 - 2.12) among women with BMI≥30kg/m$^2$. Similarly, a large study conducted by Egeland and colleagues comparing the risk of incident AMI associated with increasing levels of BMI, WC and WHR in 140 000 Norwegian participants observed stronger associations for central markers of adiposity (WC and WHR) compared with BMI, however this was only observed among women.[127] In this study, raised BMI and WHR (top 40% vs. bottom 60%) were each associated with approximately 50% increased risk of incident AMI among men (1.49, 1.32-1.68), whereas risk of AMI more than doubled among women in the top 40% of the WHR distribution compared with women in the bottom 60% (2.16, 1.71, 2.72). By comparison, women within the top 40% of the distribution of BMI had approximately 66% higher risk compared to those in the bottom 60% (1.66, 1.37-2.01). In an earlier analysis of the UK Biobank, differences in the strength of association with risk of AMI were also observed across four measures of adiposity (BMI, WC, WHTR and WHR).[14] Per sex-combined SD higher adiposity, WHR (SD: 0.09) was associated with the greatest excess risk of AMI, and the weakest association was observed with increasing BMI (SD: 4.76 kg/m$^2$), particularly among women whereby increasing WHR was associated with approximately 50% higher risk of CHD versus approximately 20% for BMI (WHR: 1.49, 1.39-1.59; BMI: 1.22, 1.17-1.28).

Importantly, none of these studies adequately accounted for within-person variability, meaning that reported magnitudes of the associations were likely underestimated due to RDB, particularly for central adiposity measures.[136] In the meta-analysis of over 140 000 participants conducted by the ERFC, per SD increase, BMI, WC and WHR were each associated with a similar roughly 30% increased risk of incident CHD (1.29 [1.22-1.37] for BMI; 1.32 [1.24-1.40] for WC; 1.30 [1.22-1.38] for WHR).[16] This analysis of IPD corrected for within-person variability for each of the different adiposity measures using reproducibility estimates from a subset of 63 821 participants. When observing the associations with increasing WC and WHR within

categories of BMI, each central adiposity marker remained positively associated with CHD risk.

*2.3.4 Effect modification*

The majority of identified studies investigated effect modification of adiposity-related CHD risk by sex, including the three global meta-analyses.[16, 134, 135] In the PSC meta-analysis, the risk of CHD mortality for every 5-unit increase in BMI was slightly higher among men than women (HR 1.42 vs. 1.35),[135] which was also observed for incident CHD in the global meta-analysis conducted by Magraw-Chaffin and colleagues (1.28 vs. 1.22).[134] However, no difference in BMI-related CHD risk was observed between men and women in the ERFC meta-analysis (1.26 vs. 1.24).[16] Individual large-scale prospective studies also displayed inconsistent evidence for effect modification by sex. Two large studies found no difference between BMI-associated CHD risk among men and women,[128, 131] one observed higher BMI-related CHD risk among men,[133] and two studies investigating the sex-difference across measures of adiposity observed no major differences in the BMI-associated CHD risk between men and women, but did observe a stronger effect of central measures (WC, WHR and WHTR) with CHD risk among women.[14, 127] The remaining studies did not estimate effect modification by sex,[1, 24, 123, 129] or analyses were solely among men[126, 130] or women.[124, 125]

Most of the included studies investigated the adiposity-related CHD risk across baseline age categories.[14, 16, 24, 125, 127, 129-131, 134, 135] In general, the risk of CHD associated with adiposity appeared larger at younger compared with older ages at baseline. In studies comparing across adiposity measures, this observation was consistent across measures.[14, 16, 124, 127] In the ERFC meta-analysis, the relative excess risk of CHD associated with BMI, WC and WHR was three to four times stronger between 40–59 years compared with older ages (≥70 years).[16] However, when interpreting potential effect modification by age-group, it is important to note that the absolute excess risk is much greater at older ages.

A number of included studies restricted analysis to fatal events only,[1, 123, 128, 130, 135, 136] and in general, these studies observed stronger associations between increasing BMI and CHD death compared with studies investigating incident CHD. However, three studies investigated the association between adiposity and CHD risk separately for non-fatal and fatal events.[24, 125, 134] In the MWS of over 1.2 million UK women followed up for CHD events occurring over nine years, a J-shaped association was observed with fatal events with a nadir at approximately 21kg/m$^2$, however a continuous log-linear association was observed with non-fatal events after excluding the first four years of follow-up.[125] However, in two large global

meta-analysis conducted by the GBMRFC and Mongraw-Chaffin colleagues, BMI-related CHD risk was not materially different between fatal and all incident events.[24, 134] Importantly, however, for these large-scale meta-analyses, event adjudication methods were likely inconsistent between included single studies.

*2.3.5 Intermediate factors*

Seven of the included large-scale observational studies attempted to estimate the adiposity-related CHD risk mediated through conventional cardiovascular risk factors, including four meta-analyses[16, 24, 129, 135] and three large-scale cohorts.[127, 130, 131] In all of these studies, SBP or hypertension, together with self-reported diabetes or fasting glucose levels and cholesterol levels (either LDL, HDL or total cholesterol) at baseline explained the majority of the observed adiposity-related CHD risk. Two studies investigated effect mediation across different adiposity measures, including the large cohort study conducted by Egeland and colleagues and the ERFC meta-analysis.[16, 127] Both studies observed a consistent independent effect of WHR on MI and CHD risk beyond SBP, total cholesterol and self-report diabetes, whereas BMI-related risk was substantially attenuated after adjusting for these risk factors.[127,16] With the exception of the ERFC meta-analysis, which reported a further attenuation of associations after additionally adjusting for C-reactive protein (CRP) and fibrinogen, no identified large-scale observational study investigated more than three conventional cardiovascular risk factors and all previous studies adjusted for baseline measures of intermediate factors only.

## 2.4 Summary of observational evidence: major inconsistencies, gaps in current evidence and implications for future research

*2.4.1* Strength and shape of the association between BMI and CHD risk

The exact strength and shape of the association between increasing BMI and CHD risk was not consistent across included studies, with CHD risk ranging between 20% and 40% per 5-unit increasing BMI and five studies either reporting a J-shaped at lower levels of BMI, or a null association.[1, 130, 134, 136] However, many included studies were unable to assess the full shape of the association because underweight participants were excluded. Importantly, Asian participants in the included studies had markedly lower mean BMI values (21-23kg/m$^2$) compared with Western cohorts (24-27kg/m$^2$), and therefore Western cohorts may lack power to quantify disease risk at low BMI values. Additionally, a few studies did not exclude all participants with vascular disease at baseline and therefore the observed associations at lower BMI values could be impacted by reverse causality.[128, 134]

Additionally, despite the large statistical power, uncertainty surrounding the strength of the relationship between adiposity and CHD risk may have arisen as a result of measurement error. Many studies used either self-reported adiposity or a combination of self-reported and measured adiposity.[1, 16, 24, 124, 125, 129, 130, 134, 135] Although generally the validity of self-reported BMI is high, previous reports have suggested a self-reported BMI may be systematically over-estimated at the lower tails of the distribution and underestimated at the upper tails of the distribution, particularly among women.[137, 138] If true, then the measured range of BMI values would be narrower than the true range, potentially leading to biased estimates away from the null. Furthermore, CHD was adjudicated differently between studies, with some studies relying solely on mortality registry data for CHD death,[1, 123, 128, 130, 135] and others using routine hospital data to capture non-fatal events. Of the studies that restricted analyses to CHD deaths, three reported a J-shaped association with increasing BMI and CHD risk,[1, 125, 135] suggesting that case fatality rates are higher in both lean and obese individuals than in those with a BMI within the normal or overweight range. The underlying reasons behind this observation are unclear, and whether the difference in CHD risk between fatal and incident events persists across different adiposity measures is not well established.

Whereas most cohort studies were able to account for a range of potential confounders in the analyses, a number did not account for important potential confounders (such as alcohol, smoking habits or socio-economic characteristics),[126, 127] and the included meta-analyses had a minimal set of adjustments (age, sex and smoking).[1, 16, 24, 134, 135] Additionally, the majority of study populations were not contemporary, with only two studies having recruited participants within the last decade.[14, 134]

### *2.4.2 The relevance of alternative adiposity measures to CHD risk beyond BMI*

Although some large-scale evidence exists to suggest a greater relevance of central adiposity (assessed via WC or WHR) to CHD risk beyond BMI, these findings were limited to a handful of studies included in this review. Furthermore, the results were inconsistent, with a lack of evidence for direct comparisons of adiposity-related CHD across standardised adiposity measures. For example, although WC and WHR showed a strong continuous association with CHD risk which surpassed BMI-associated CHD risk in three large-scale single studies,[14, 124, 127] the ERFC meta-analysis refutes this finding, demonstrating very little difference in the ability of each adiposity measure to predict CHD risk.[16] However, unexplained heterogeneity was observed between included studies in the ERFC, and other studies investigated CHD risk across multiple adiposity measures identified in the current review did not correct for within-person variability between measures. Therefore, further research is required to accurately

compare adiposity-related CHD risk across standardised adiposity measures after considering within-person variability in large contemporary populations. Additionally, of the large-scale studies identified, no study has investigated the relevance of measures of adiposity from newer technologies such as bioelectrical impedance analysis (BIA), for estimating adiposity-associated CHD risk.

### *2.4.3 Intermediate factors underlying adiposity-related CHD risk*

Of the studies with available biomarker data, the majority demonstrated that the adverse effects of BMI on CHD risk were at least partially mediated by blood pressure, insulin resistance and cholesterol.[16, 24, 127, 129, 131, 133, 135] However, there is not yet a clear understanding of how much excess adiposity-related CHD risk is mediated by each pathway. Investigating to what extent the adverse effects of high BMI might be mitigated by targeting these metabolic indicators will aid resource allocation and disease prevention efforts. The largest study to investigate this was the GBMRFC collaboration meta-analysis, which observed a 46% attenuation of BMI-associated CHD risk after adjustment for these three mediators. However, the variables used in adjusted analyses and measuring protocols differed across included studies, making it difficult to interpret the results. The ERFC meta-analysis was the only study identified which investigated potential intermediate factors other than blood pressure, insulin resistance or cholesterol, and therefore evidence is lacking for a full investigation into biological pathways underlying adiposity-related CHD in contemporary populations.[16] Furthermore, it is unclear whether abdominal adiposity, as assessed via WC and WHR, acts through biological mechanisms to increase CHD risk that are distinct from known risk factors, or whether they differ from intermediate factors underlying BMI-related CHD risk, as the ERFC was the only study identified which investigated intermediate factors across adiposity measures.[16]

### *2.4.4 Addressing uncertainties surrounding observational associations between adiposity and CHD risk using the UK Biobank*

A number of features makes the UK Biobank ideally suited to address some of these uncertainties. The UK Biobank has sufficient numbers of well-adjudicated incident events to investigate CHD risk across a wide distribution of adiposity, and by important population sub-groups, such as by sex. Therefore, given the uncertainties identified in the current review, the UK Biobank presents a unique opportunity to assess the shape and strength of the association between BMI and CHD risk with greater accuracy and detail than previously possible. Furthermore, with standardised measurements at baseline and repeat surveys, the UK

Biobank is the largest study to allow the investigation into comparisons between usual levels of other simple adiposity measures such as WC, WHR, WHTR or BIA and CHD risk beyond BMI with full correction for regression dilution. Furthermore, recently released biomarker data includes markers of organ function and emerging intermediate factors underlying adiposity-related CHD risk such as kidney function, liver function and systemic inflammation. Investigating the contribution of additional biological pathways to adiposity-related CHD risk beyond known intermediate factors has the potential to substantially improve our understanding of the biological mechanisms underlying adiposity-related CHD risk.

## 2.5 Mendelian randomisation evidence

### *2.5.1 Background*

An unavoidable limitation of observational studies is that associations may be confounded by unknown factors, or affected by reverse causality and other biases such as regression dilution, which inherently hinder the ability to determine causality underlying associations between risk factors and disease.[112] An additional challenge when separating the independent effects of general and central adiposity measures in observational studies is the high degree of correlation between adiposity measures. Hence, it is not possible to decipher the CHD risk which can be directly attributed to obesity through observational evidence alone, particularly given that obesity is a complex disorder resulting from a complex interplay of physiological, environmental and socio-economic determinants. In principle, RCTs and MR studies can overcome these limitations, because confounding factors are assumed to be randomly distributed across exposed and unexposed study participants.[139] Over the past decade, several large genetic consortia have made valuable contributions to our understanding of genetic factors and the causal role of single-nucleotide polypeptides (SNPs) predisposing certain traits in the prediction of CHD and other complex diseases. Several MR studies have confirmed the causal role of adiposity phenotypes, specifically BMI, WC and WHR in the development of CHD.[119, 140] However, large-scale evidence for these genetic associations has not been recently reviewed.

### *2.5.2 Search results*

Overall, seven published MR reports were identified investigating the association between genetically elevated adiposity traits and CHD (**Table 2.5**).[116, 119-121, 140-143] All identified studies consisted of a two-sample study design, three of which used summary-level data from over 180 000 individuals in the Coronary Artery Disease Genome-Wide Replication And Meta-analysis plus Coronary Artery Disease Genetics Consortium (C+C4D) meta-analysis with up to 65 055 cases of CHD.[119, 120, 140]

#### *2.5.2.1 Body-Mass Index*

Six of the identified MR studies investigated associations between genetically elevated BMI and CHD risk.[116, 119-121, 141, 142] The largest study investigated the CHD risk associated with a genetic risk score (GRS) combining 97 SNPs independently associated with BMI in a meta-analysis of IPD from 14 studies and summary-level data from the C+C4D consortia.[119] Overall,

in more than 220 000 participants and 65 000 CHD events, one SD genetically elevated BMI was associated with 36% higher odds of CHD (OR:1.36, 95% CI: 1.22-1.52). Using the same GRS for BMI, another summary-level MR study including over 80 000 individuals and over 20 000 cases of CHD from the C+C4D meta-analysis observed a similar increase in odds of CHD per SD genetically elevated BMI (1.37, 1.15 - 1.63).[120] In these studies, the GRS' for BMI explained between 1.7% and 1.9% of the total variance of BMI.

In a two-sample MR study conducted by Holmes et al. (2014) using IPD from over 6000 cases and more than 20 000 controls, 14 SNPs were combined in a weighted GRS which explained slightly less (approximately 0.8%) of the total variance of BMI.[116] In this study, 1 kg/m$^2$ genetically elevated BMI was associated with a slightly higher risk of CHD, although the study lacked power (OR 1.01, 0.94 – 1.08). In the same study, when these results were combined in a fixed effects meta-analysis with two other published MR studies, comprising a total of 219 423 individuals and 27 465 CHD events, the inverse-variance weighted OR of CHD per 1-kg/m$^2$ genetically elevated BMI remained non-significant at 1.04 (0.97-1.12). Another two-sample MR consisting of IPD from over 75 000 study participants in Copenhagen observed 52% increased odds of CHD (1.52, 1.12-2.05) per 4 kg/m$^2$ genetically elevated BMI as predicted by a weighted GRS consisting of three SNPs (FTO, MC4R and TMEM18).[121] The effect of genetically elevated BMI was much stronger than the observational association between BMI and CHD in the same study population (1.26, 1.19-1.43 per 4kg/m$^2$ higher BMI). Similarly, in the ENGAGE consortium consisting of IPD on over 3000 cases and 22 000 controls, an unweighted GRS of 32 SNPs for increasing BMI was associated with over double the odds of CHD compared with similar increases in observed BMI (OR per SD genetically elevated BMI: 1.47, 1.04-2.07 versus HR per SD higher BMI: 1.20, 1.12-1.28), although the uncertainty was much larger for MR analysis.[142]

*2.5.2.2 WC and WHR*

Whilst most of the identified studies used BMI as the primary measure of adiposity, four studies compared the CHD risk across different genetically elevated adiposity phenotypes (WC, HC or WHRadjBMI),[119, 120, 141, 142] and one study investigated waist-to-hip ratio adjusted for BMI (WHRadjBMI) as the primary adiposity measure.[140] As previously discussed, the largest study conducted by Dale and colleagues used a two-sample approach to investigate the associated risk of CHD with both BMI and WHR adjusted for BMI (WHRadjBMI) by combining IPD from 14 studies with summary-level data from the C+C4D cosortia.[119] In this study, per SD genetically elevated WHRadjBMI as predicted by a GRS of 49 SNPs was associated with 1.48 (1.28-1.71) higher odds of CHD, which is slightly larger than the CHD risk predicted for a

similar genetically increased BMI (1.36, 1.22-1.52). Emdin and colleagues used a similar approach by combining summary level data from the C+C4D meta-analysis with IPD on a subset of 111 986 UK Biobank participants (for whom early-release genetic data was available) to investigate the overall association between WHRadjBMI and CHD risk.[140] A total of 60 801 CHD events occurred in C+C4D, 5639 of which occurred in UKB. A weighted GRS consisting of 48 SNPs corresponding to one SD genetically elevated WHRadjBMI was associated with 46% higher odds of CHD (1.46, 1.32-1.62).

### 2.6 Summary of genetic evidence: major inconsistencies, gaps in current evidence and implications for future research

In general, the identified MR studies included in this literature review support a causal role for both central and general adiposity on the risk of CHD, however there were a number of limitations in previous MR studies, mostly attributed to their summary-level study designs and lack of IPD.

The largest study to comprehensively assess the causal roles of general and central adiposity traits on CHD risk to date was a combined meta-analysis using IPD from 14 prospective studies and summary-level data from the C+C4D consortium conducted by Dale and colleagues.[119] However, the MR estimates for associations with CHD were largely based on summary data, and a full investigation of the linear relationships between BMI or WHRadjBMI and CHD would require access to IPD in all studies. Furthermore, the investigators were unable to compare between observational and genetic estimates from within the same study population, and therefore the extent to which observational associations between different adiposity measures and risk of CHD are real or an artefact of different associations in different populations remains unclear. Another limitation of previous large-scale MR studies and the reliance on summary-level data is the lack of available information on cardiometabolic traits, which would allow for a full investigation into the mechanisms underlying adiposity-related CHD risk.

Additionally, previous MR studies have not currently had sufficient numbers of events to allow the observational and genetic associations between adiposity and CHD risk to be assessed using the same statistical modelling approach. Therefore, the use of different study populations and different statistical methods for the comparison of observational and genetic associations (usually logistic regression for genetic associations and Cox regression for observational associations) means that observational and genetic associations may not be directly comparable.

Although a useful tool for assessing causality, MR studies are not free of assumptions and potential biases. Importantly, single polymorphisms do not account for much variability within individual complex traits,[144] particularly for complex traits like BMI, which can cause weak instrument bias.[145] As a result of weak instrument bias, associations are often biased towards the null in the two sample setting. This can be overcome by assessing the combined effects of multiple genetic variants on an outcome of interest. But, despite the seven identified studies investigating the effect of a combination of multiple adiposity-associated SNPs on CHD risk, the largest amount of variability of an adiposity trait explained by a GRS was 2.6%.[120] However, genetic variation in BMI increases as the prevalence of obesity increases, and hence obesity genes are expressed more aggressively under the influence of an obesity-promoting environment. Therefore, investigating associations with obesity-predisposing genes in a contemporary, overweight population could enhance statistical power and contribute to a better understanding of susceptibility to complex diseases such as CHD.[146]

## 2.7 Conclusion

The evidence included in this review clearly demonstrates a positive association between adiposity and CHD risk in the overwhelming majority of large-scale observational studies. However, a number of uncertainties remain, including: *i)* the exact shape and magnitude of the association between adiposity and CHD, particularly between men and women, ethnic groups and incident/ fatal event type; *ii)* whether BMI could be superseded by more informative measures of adiposity for CHD risk; and *iii)* how much of the excess adiposity-related CHD risk can be attributed to potentially modifiable risk factors in contemporary populations. Whilst previous genetic MR studies have demonstrate directionally concordant associations between adiposity and CHD risk, the majority of large-scale studies are limited by a lack of IPD to allow for a detailed investigation into*: i)* the shape of genetic associations*; ii)* the direct comparison of observational and genetic evidence in the same population, using the same statistical methods; and *iii)* a comprehensive investigation into the genetic relevance of general and central adiposity on cardiometabolic traits. The UK Biobank study is uniquely advantaged by the availability of data which surpasses previous studies, including full genetic information on 0.5M adults, and hence provides an unparalleled opportunity to address some of these uncertainties, allowing for the most robust investigation into CHD risk associated with adiposity to date.

**Chapter 2 Tables and figures**


| Figure/Table | Title |
|---|---|
| **Table 2.1** | Literature review search terms |
| **Figure 2.1** | Study selection procedure for systematic search 1: Prospective studies |
| **Figure 2.2** | Study selection procedure for systematic search 2: MR studies |
| **Table 2.2** | Summary of prospective studies identified in literature review |
| **Table 2.3** | Key findings of studies investigating the association between BMI and CHD |
| **Table 2.4** | Key findings of studies investigating the association between central adiposity measures (WC, WHR and WHTR) and CHD |
| **Table 2.5** | Summary of Mendelian randomization studies identified in literature review |

**Table 2.1** Literature review search terms

| Search criteria | Search terms (MeSH terms, or keyword searches) and time period |
|---|---|
| Adiposity | Adiposity OR anthropometry OR waist hip ratio OR WHR OR waist hip ratio OR body fat distribution OR body composition OR waist circumference OR hip circumference OR body mass index OR body mass OR impedance OR body fat OR fat mass OR obesity OR central obesity OR central adiposity OR visceral adiposity OR central fat distribution OR abdominal fat OR abdominally obesity OR abdominally obese |
| CHD | Cardiovascular disease OR heart infarction OR coronary heart disease OR ischemic heart disease OR myocardial infarction OR Coronary heart disease OR arterial disease OR vascular disease OR coronary event OR ischemic event OR coronary OR ischemia OR cardiac arrest OR atherosclerotic disease OR atherosclerosis OR atherosclerotic heart disease OR acute coronary syndrome OR coronary arterial disease |
| Study design | **Search 1:** Prospective OR longitudinal OR cohort OR observational<br>**Search 2:** Mendelian randomization OR genetic OR genetic association OR Mendelian OR gene OR allele OR genetics OR causal variant OR variant OR single nucleotide polymorphism OR SNP OR genetic association OR loci OR locus OR population genetics OR genome OR genetically predisposed OR genetically susceptible |
| Time period | 1974 – present |
| Source | Embase, MEDline |

**Figure 2.1** Study selection procedure for systematic search 1: Prospective studies

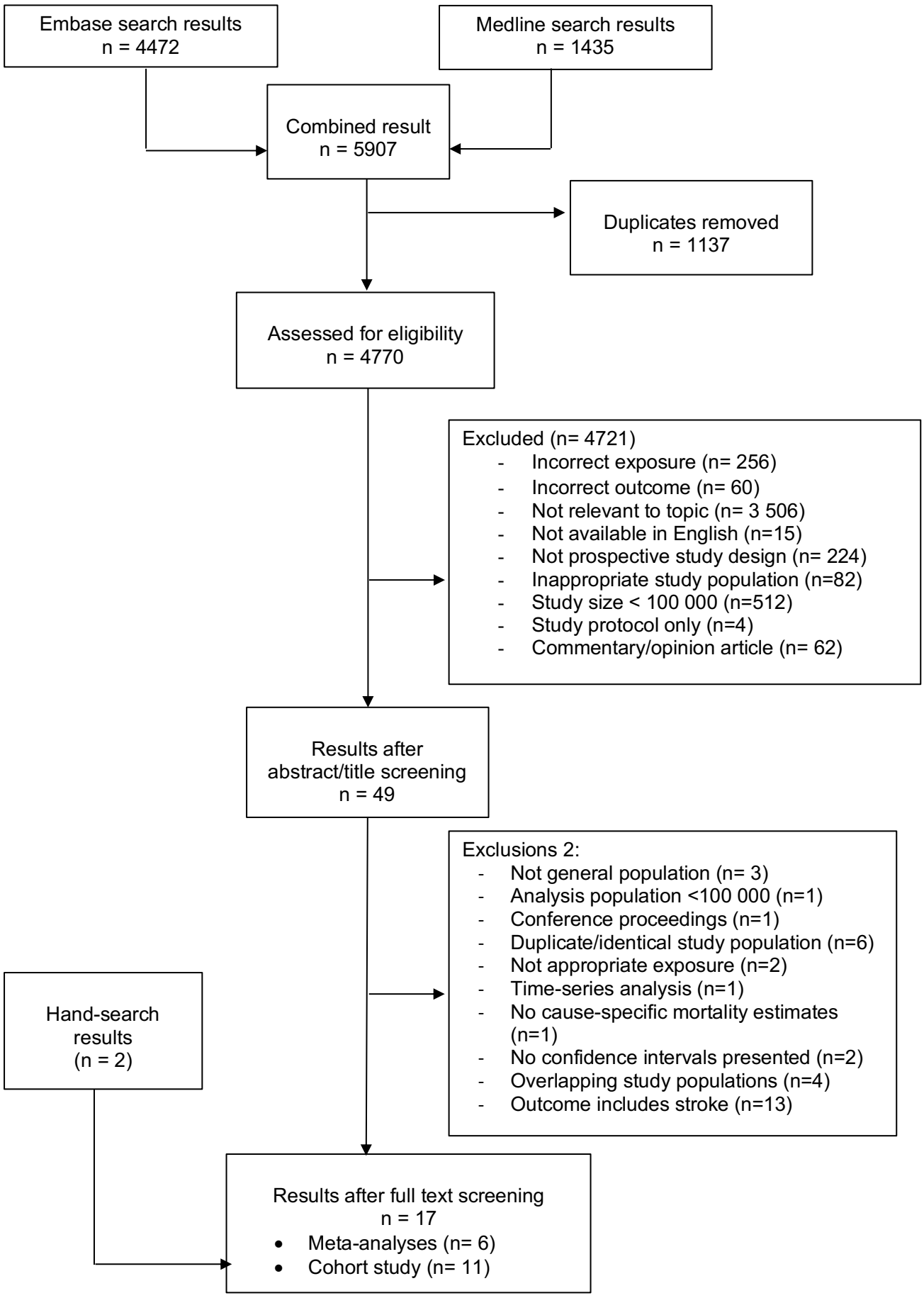


**Figure 2.2** Study selection procedure for systematic search 2: Mendelian randomisation studies

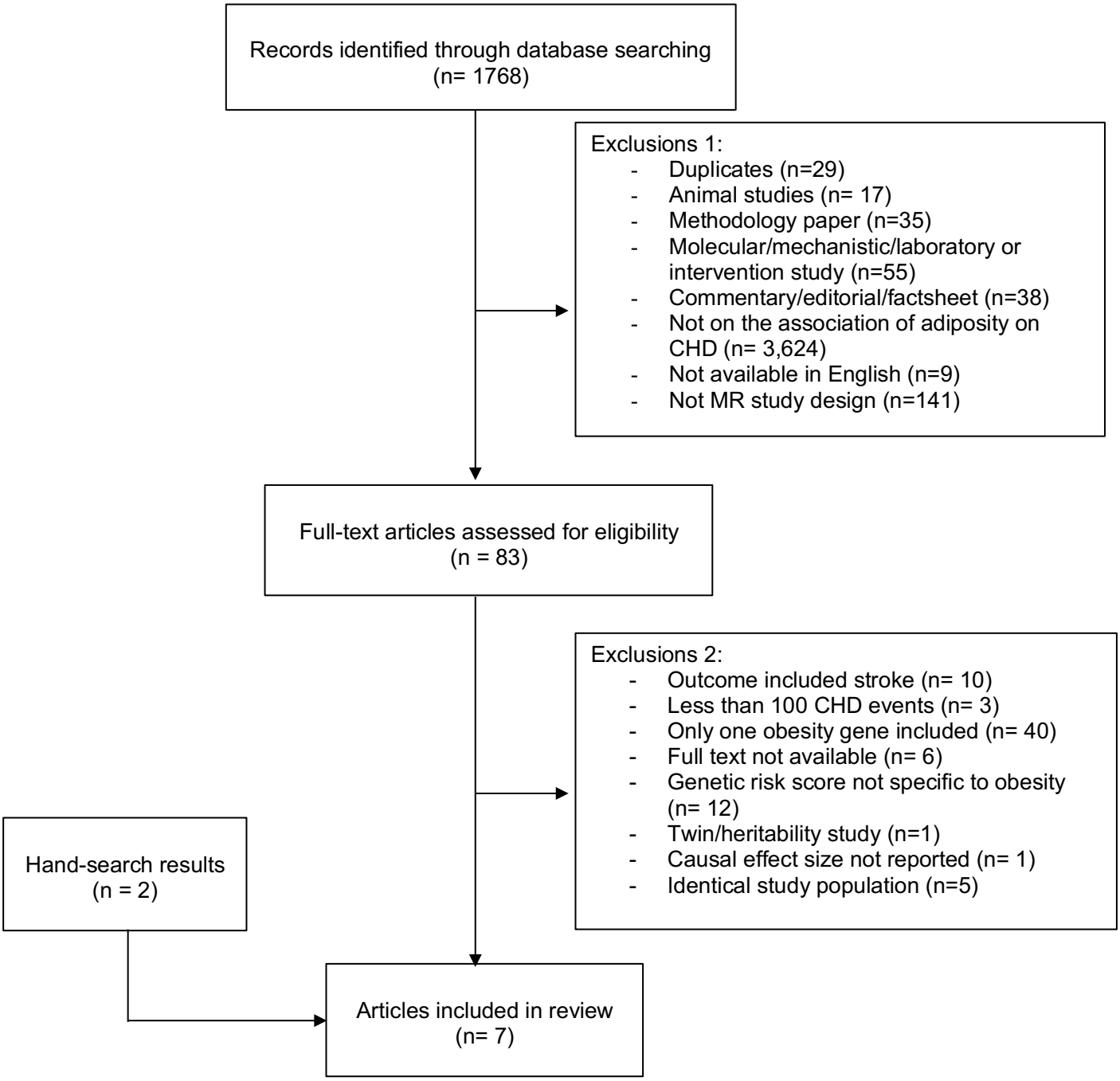


**Table 2.2** Summary of prospective studies identified in literature review, by number of study participants

| Study/Consortia | Region | Recruitment period | No. of participants (% Men) | Median/Mean, [IQR/range]/SD follow-up (years) | Adiposity marker(s) | Method of measurement | Median/Mean/ Range ([IQR]/SD) age, years | Mean (SD) BMI (kg/m$^2$), WC (cm), WHR |
|---|---|---|---|---|---|---|---|---|
| **Meta-Analyses:** | | | | | | | | |
| Global BMI Mortality Collaboration[1] (2016) | Global (Mostly western) | 1958 -- 2010 | 3.6M (43.2%) | 13.7 [ IQR: 11.4-14.7] | BMI | Measured & self-report w/ validation study | 53.1 (8.9) | 25.2 (3.9) |
| Global Burden of Metabolic risk factors for chronic disease collaboration[24] (2014) | Global (Mostly western) | 1948 – 2005 | 1.8M (40%) | 13.3 [range: 2.7-57.5] | BMI | Measured & self-report | Range: 18-99 | NR |
| Mongraw-Chaffin et al. (2015)[134] | Europe, Asia, North America, Pacific region | 1961 – 2006 | 1.2 M (55%) | Range: 3.4 – 34 | BMI | Measured & self-report | Range: 20 – 107 | NR |
| Asia Cohort Consortium (2013)[129] | East Asia & South Asia | 1963 – 2006 | 1.1M (48%) | 9.7 (range: 3.2 – 22) | BMI | Measured & self-report | 53.4 | 22.8 (3.6) |
| Prospective Studies Collaboration (2009)[135] | USA, Europe, Asia, Australia | 1975 – 1985 | 894 576 (61%) | 8 (SD 6) | BMI | Measured & Self-report | 46 (11) | 24.8 (3.8) |
| The Emerging Risk Factors Collaboration (2011)[16] | Europe, USA, Australia, Japan | 1967 – 2005 | 143 710 (44%) | 7.9 (range: 2.9 to 14.7) | BMI, WC, WHR | >90% Measured (sensitivity analysis comparison study) | 58 (9) | WC: 91 (12.6)<br>WHR:0.9 (0.083)<br>BMI: 27 (4.56) |
| **Prospective Cohorts:** | | | | | | | | |
| Bhaskaran et al. (2017)[123] | UK | 1989 – 2010 | 3 632 674 (45·3%) | 12·7 (5·5) | BMI | Measured | 36·9 [26·6–52·4] | NR |
| Korean National Health Insurance Service (Choi et al. 2018)[131] | South Korea | 2004 – 2005 | 2 611 450 (69%) | 9.9 | BMI | Measured | M: 35.1(4.8)<br>F: 32.5 (6.3) | 23.2 (3.2) |
| Crump et al., (2017)[126] | Sweden | 1969 – 1997 | 1 547 407 (100%) | 25.7 | BMI | Measured | 18 | 21.8 (3.0) |
| The Chennai prospective study (2018)[132] | India | 1998 – 2001 | 500 810 (55%) | 11 (3) | BMI | Measured | 45 (9) | 23.2 (3.8) |
| The Million Women Study (2013)[124, 125] | UK | 1996 – 2001 | 1 178 439 (0%) | 9 | BMI | Self-report, with internal validation | 56 (4.8) | 26.1 (4.6) |
| | | | 489 419 (0%) | 5.1 | WCadjBMI | | 60 (4.9) | BMI: 25.5(4)<br>WC: 75 (9.9) |
| UK Biobank (2018)[14] | UK | 2006 – 2010 | 479 610 (45%) | 7.1 | BMI, WC, WHR, WHTR | Measured | 56 (8.1) | M: 27.8 (4.2)<br>F: 27.0 (5.2) |
| The NIH-AARP Diet and Health Study (2011)[128] | USA | 1995 – 1996 | 225 712 (NR) | 10 | BMI, WC | Self-measured | M = 62.9 (5.3)<br>F = 71.7 (5.3) | NR |
| Chinese Academy of Preventative Medicine study (2006)[130] | China | 1990 – 1991 | 222 246 (100%) | 10 | BMI | Self-report, w/ internal validation study | Mean: 54 | 21.7 |
| Egeland et al. (2016)[127] | Norway | 1994 – 2003 | 140 789 (48%) | 11.5 (SD 2.8) | BMI, WC, WHR | Measured | <60: 41 (9.0)<br>≥60: 70 (7.0) | NR |
| Asian continental ancestry group (2005)[133] | South Korea | 1990 – 1992 | 133 740 (67%) | 9 | BMI | Measured | M: 44.8 (6.7)<br>F: 42.1 (6.0) | M: 23.4 (2.3)<br>F: 22.3 (2.3) |

NR = not reported; BMI = body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; SD = standard deviation.

**Table 2.3** Key findings of studies investigating the association between BMI and CHD

| Study/Consortia | Outcome definition | No. of CHD events | | | Exclusions and sensitivity analyses | Adjustments | Reported association | |
|---|---|---|---|---|---|---|---|---|
| | | Fatal | Non-fatal | Incident CHD | | | Shape | Hazard/Risk Ratio (95% CI) |
| **Meta-Analyses:** | | | | | | | | |
| Global BMI Mortality Collaboration (2016) | CHD | 54 872 | NR | NR | Ever smokers, prior disease, 5 years FU | Age & sex (ethnicity in sensitivity analysis) | J-shaped | Per 5-unit increase: 1.42 (1.35 - 1.49) |
| Global Burden of Metabolic risk factors for chronic diseases collaboration (2014) | CHD | NR | NR | 57 161 | Medical history of CHD or stroke, BMI<20kg/m$^2$, observed effect of length of FU | Age, sex, smoking as minimum adjustments (additional adjustment in some studies) | Positive | Per 5-unit increase: 1·27 (95% CI 1·23–1·31)<br>Versus. normal BMI:<br>i) Overweight: 1·26 (1·22–1·30)<br>ii) Obese: 1.69 (1.58-1.81) |
| Mongraw-Chaffin et al. (2015) | CHD | NR | 4 549 | 37 488 | First 3 years FU (current smokers in sensitivity analysis), most studies removed prevalent CVD | **IPD**: Age, smoking, multiple different covariates (study-specific) | Positive (J-shaped in women) | Per 5-unit increase:<br>Men= 1.28 (1.22 - 1.40)<br>Women= 1.22 (1.16– 1.28) |
| Asia Cohort Consortium (2013) | CHD | 14 411 | NR | NR | First 3 years FU, known history of CVD or stroke | **IPD:** Age, sex, smoking, alcohol, education, marital status, urban residence | Positive | Versus normal BMI (18.5-24.9):<br>Low BMI (15-18.4): 1.09 (0.81-1.45)<br>High BMI (≥25): 1.33 (1.21-1.46) in East Asians. Similar for South Asians. |
| Prospective Studies Collaboration (2009) | CHD | 10 208 | NR | NR | BMI<15, BMI≥50, history of heart disease or stroke, 5 years FU (Sensitivity analysis: ever smokers & first 15 years FU) | **IPD:** study, sex, age groups, smoking status. No RDB needed. | Positive | Per 5-unit increase (in upper BMI range, 25-50): 1.39 (1.34-1.44) |
| The Emerging Risk Factors Collaboration (2011) | CHD | NR | NR | 5 427 | Ever smokers, known CVD at baseline, first 5 & 10yrs FU, BMI<20 | **IPD**: Age, sex smoking (additionally, BL intermediate risk factors- SBP, HDL levels, DMT2 history) | Positive | Per SD increase: 1.29 (1.22-1.37) |
| **Prospective cohorts:** | | | | | | | | |
| Bhaskaran et al. (2017) | CHD | 55 108 | NR | NR | Sensitivity: 5 years FU, ever smokers, BL Cancer or CVD | Age, deprivation, calendar year, diabetes, alcohol status, and stratified for gender | Positive | RR versus 18.5-25 kg/m$^2$:<br>BMI <18.5: 1.09 (0.98-1.21)<br>Overweight (BMI 25-30 kg/m2): 1.11 (1.08-1.14)<br>Obese (BMI >30 kg/m2): 1.57 (1.51 – 1.62) |
| Crump et al., (2017) | CHD | NR | NR | 38 142 | Prior medical records of IHD, Sensitivity analysis of smoking (unmeasured) using assumed distribution) | Aerobic fitness, muscular strength, BMI, family history of CHD, education & SES | Positive | Per 5-unit increase: IRR 1.40 (1.34 – 1.47) |
| Korean National Health Insurance Service (NHIS), Choi et al. (2018) | CHD | NR | NR | 30 372 | Previous diagnosis of CHD, Subgroup analysis within strata of confounders | Age, household income, physical activity, alcohol consumption, smoking, SBP, glucose, cholesterol and charlson comorbidity index | Positive | Per 5-unit increase:<br>Men: 1.27 (1.26-1.29)<br>Women: 1.29 (1.23-1.36) |
| The Million Women Study (2013) | CHD | 2 431 | 30 034 | NR | Excluded history of cancer, heart disease, stroke, first 4yr FU | Region, smoking, age, alcohol, exercise & SES | Positive (incident)<br>J-shaped (fatal) | Versus BMI 22.5-24.9:<br>Incident CHD:<br>i) BMI<20= RR 0.89 (0.83-0.94)<br>ii) BMI≥35= RR 1.85 (1.78-1.92)<br>iii) per 5-unit increase: HR 1.23 (1.22-1.25)<br>Fatal CHD:<br>i) BMI<20= RR 1.27 (1.06-1.53)<br>ii) BMI≥35= RR 2.84 (2.51- 3.21) |

**Table 2.3** Continued

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| The Chennai prospective study (2018) | Cardiac mortality | 12 504 | NR | NR | 2 years FU, known chronic disease at BL, missing or out-of-range BMI or BP | Age, sex, education, SES, smoking and alcohol consumption | No association | BMI ranges 30 – 35kg/$m^2$ versus BMI ranges 15 -20kg/$m^2$: HR 1.11 (Non-significant) |
| UK Biobank (2018) | AMI | NR | NR | 5 710 | 2 years FU (sensitivity analysis), known CVD at BL | Age, Townsend deprivation index, and smoking status | Positive | Per SD increasing:<br>BMI: 1.22, 1.17-1.28 (women) and 1.28, 1.23- 1.32 (men)<br>WC: 1.35, 1.28-1.42 (women) and 1.28, 1,23- 1.33 (men)<br>WHR: 1.49, 1.39 – 1.59 (women) and 1.36, 1.30 – 1.43 (men)<br>WHTR:1.34, 1.27 – 1.40 (women) and 1.33, 1.28-1.38 (men) |
| Egeland et al. (2016) | AMI | NR | NR | 4 653 | Known vascular disease, current or past anti-hypertensive use | Age, smoking | Positive | Top 2 vs. bottom 3 quintiles:<br>Men<60 years: 1.49 (1.35-1.65)<br>Men≥60 years: 1.28 (1.16-1.41)<br>Women<60 years: 1.66 (1.37-2.01)<br>Women≥60 years: 1.23 (1.08- 1.40) |
| The NIH-AARP Diet and Health Study (2011) | CHD | 4 073 | NR | NR | Current smokers (sensitivity analysis: BMI <18.5kg/$m^2$ as proxy for current illness) | Age, sex, ethnicity | Positive | BMI: vs. Normal and underweight:<br>i) BMI≥25=RR 1.08 (0.99-1.18)<br>ii) BMI≥35: RR 2.38 (2.07-2.73). |
| Chinese Academy of Preventative Medicine study (2006) | CHD | 1 942 | NR | NR | Known CHD or stroke at BL (Sensitivity: first 3yr FU and ever smokers) | Area, age, smoking & alcohol | J-shaped | Per 5-unit increase:<br>RR 1.33 (1.16-1.54) |
| Asian continental ancestry group (2005) | CHD | NR | NR | 1 899 | 3 years FU, CVD, Liver disease of cancer at BL, BMI<18kg/$m^2$ | Age, sex, smoking, alcohol, exercise & insurance premiums | Positive | Per 5-unit increase: 1.93 (1.76- 2.10)<br>BMI≥30 Versus BMI 18.5-24.9: 4.37(2.48-7.69) |

FU = Follow-up; BL = baseline; AMI = acute myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; NR = not reported; BMI = body-mass index; IPD= individual participant data; SD =standard deviation; SES= socio-economic status; BP = blood pressure

**Table 2.4** Key findings of studies investigating the association between central adiposity measures (WC, WHR and WHTR) and CHD

| Study/Consortia | Outcome definition | No. of CHD events | | | Exclusions and sensitivity analyses | Adjustments | Reported association | |
|---|---|---|---|---|---|---|---|---|
| | | Fatal | Non-fatal | Incident CHD | | | Shape | Hazard/Risk Ratio (95% CI) |
| **Meta-Analyses:** | | | | | | | | |
| The Emerging Risk Factors Collaboration (2011) | CHD | NR | NR | 5259 | Known CVD at BL, first 5 & 10yrs FU, BMI<20 | **IPD**: Age, sex smoking (additionally, BL intermediate risk factors- SBP, HDL levels, DMT2 history) | Positive | Per SD increase:<br>i) BMI: HR 1.29 (1.22-1.37)<br>ii) WC: HR 1.32 (1.24-1.40)<br>iii) WHR: HR 1.30 (1.22-1.38). |
| **Prospective cohorts:** | | | | | | | | |
| The Million Women Study (MWS) | CHD | NR | NR | 10,998 | Excluded vascular disease and cancer at BL and 1yr FU | Region, smoking, alcohol, exercise & SES | Positive | WC≥80cm relative to <70cm in:<br>i) BMI<25= RR 1.39 (1.28-1.52)<br>ii) BMI 25-29.9= RR 1.57 (1.48-1.68) iii) BMI≥30= RR 1.97 (1.84-2.12) |
| UK Biobank (2018) | AMI | NR | NR | 5 710 | 2 years FU, known CVD at BL | Age, Townsend deprivation index, and smoking status | Positive | HR per SD increasing:<br>BMI: 1.22, 1.17-1.28 (women) and 1.28, 1.23- 1.32 (men)<br>WC: 1.35, 1.28-1.42 (women) and 1.28, 1,23- 1.33 (men)<br>WHR: 1.49, 1.39 – 1.59 (women) and 1.36, 1.30 – 1.43 (men)<br>WHTR:1.34, 1.27 – 1.40 (women) and 1.33, 1.28-1.38 (men) |
| Egeland et al. (2016) | AMI | NR | NR | 4,653 | Known vascular disease at BL, current or past anti-hypertensive use | Age, smoking | Positive | Top 2 vs. bottom 3 quintiles:<br>Men<60 years: 1.49 (1.32-1.68)<br>Men≥60 years: 1.24 (1.10-1.38)<br>Women<60 years: 2.16 (1.71-2.71)<br>Women≥60 years: 1.23 (1.06-1.42) |
| The NIH-AARP Diet and Health Study (2011) | CHD | 4,073 | NR | NR | Current smokers (sensitivity analysis: BMI <18.5 as proxy for current illness) | Age, sex, ethnicity | Positive | WC: top group (≥96cm [w], ≥118cm [m]) vs. bottom group (<80[women], <94[men]): RR= 1.64 (1.38-1.95) |

FU = Follow-up; BL = baseline; AMI = acute myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; HR = hazard ratio; NR = not reported; BMI = body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; IPD= individual participant data; SD =standard deviation.

**Table 2.5** Summary of Mendelian randomization studies identified in literature review

| Ref. | Study population | N | Study design | Mean age, years (SD) [study] | Ancestry | Adiposity trait | Variants included in genetic risk score (reference) [weighting] | Variance of adiposity explained (F-statistic) | CHD events | Hazard/Risk/Odds Ratio (95% CI) per 1 SD increase | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Observational association | Genetic association |
| **Dale et al. (2017)[119]** | C+C4D [48 studies] | 228 952 | Two-sample, summary-level & IPD of 14 studies | NR | European | BMI<br>WHRadjBMI | BMI: 97 SNPs<br>WHRadjBMI: 49 SNPs [weighted] | BMI: 1.7%<br>WHRadjBMI: 0.7% | 66 842<br>(3 716 from IPD analysis) | NR | Per SD genetically elevated:<br>BMI: OR1.36 (1.22-1.52)<br>WHRadjBMI: OR 1.48 (1.28-1.71) |
| **Emdin et al. (2017)[140]** | C+C4D [48 studies];<br>UK Biobank | 184 305;<br>111 986 (IPD) | Two-sample summary-level & IPD | 57 (8) [UK Biobank] | European | WHRadjBMI | 48 SNPs [weighted] | 1.5% (F=1713) | 66 440 | NR | OR 1.46 (1.32, 1.62) |
| **Holmes et al. (2014)[116]** | 7 cohort studies | 26 193 | Two-sample summary-level & IPD | 60 (range:17-100) | European | BMI | 14 SNPs [weighted] | 0.8% (F=237) | 6 073 | Per 1kg/m$^2$ higher BMI:<br>OR 1.02 (1.01, 1.02) | Per 1kg/m$^2$ genetically elevated BMI:<br>OR 1.01 (0.94,1.08) |
| | Additional meta-analysis of 7 studies | | | NR | European | BMI | 14 SNPs [ weighted] | NR | 27 465 | NR | Meta-analysis: OR 1.04 (0.97-1.12) |
| **Zhang et al. (2017)[120]** | C+C4D [22 studies] | 86 995 | Two-sample, summary-level | NR | European | BMI<br>HC<br>HCadjBMI<br>WC<br>WCadjBMI<br>WHR<br>WHRadjBMI | BMI: 68 SNPs<br>HC: 52 SNPs<br>HCadjBMI: 73SNPs<br>WC: 41 SNPs<br>WCadjBMI: 63 SNPs<br>WHR: 28 SNPs<br>WHRadjBMI: 36 SNPs [weighted] | BMI = 1.9%<br>HC = 1.8%<br>HCadjBMI = 2.6%<br>WC = 1.2%<br>WCadjBMI = 1.7%<br>WHR = 0.7%<br>WHRadjBMI = 1.1% | 22 233 | NR | Per SD (BMI: 4.77kg/m$^2$; HC: 8.46cm; WC: 12.52cm; WHR: 0.074) increasing:<br>BMI = OR 1.37 (1.15 - 1.63)<br>HC = OR 1.10 (0.89 – 1.36)<br>HCadjBMI = OR 0.83 (0.71 – 0.96)<br>WC = OR 1.39 (1.06 – 1.84)<br>WCadjBMI = OR 0.90 (0.72 – 1.91)<br>WHR = OR 1.46 (1.17 – 1.91)<br>WHRadjBMI = OR 1.42 (1.12 – 1.81) |
| **Nordestgaard et al. (2012)[121]** | CGPS, CCHS | 75 627 | Two-sample, IPD | 57 to 60 across studies (range: 40-70) | European | BMI | 3 SNPs | 0.28kg/m$^2$ higher BMI per allele | 11 056 | OR 1.26 (1.19, 1.34) per 4kg/m$^2$ higher BMI | OR = 1.52 (1.12, 2.05) per 4kg/m$^2$ genetically elevated BMI |
| **Elosua et al. (2016)[141]** | MIGen; FHS; FINRISK 1997; FINRISK 2002; EGCUT | 23 836 | Two-sample MR, IPD | 47.9 (13.3) – 54.61 (9.8) | European | BMI<br>WC | BMI: 81 SNPs<br>WC: 41 SNPs | NR | 3 905 | NR | Per allele:<br>BMI: OR= 1.08 [1.04, 1.13]<br>WC: OR= 1.06 [1.02,1.11] |
| **Hägg et al. (2015)[142]** | ENGAGE consortium [9 studies] | 22 193 | Two-sample MR, IPD | 49.5 (12.2) | European | BMI | 32 SNPs [unweighted] | 0.03 SD increase in BMI per allele (F= 484) | 3 062 | HR 1.20 (1.12, 1.28) | OR 1.47 (1.04, 2.07) per SD genetically elevated BMI |

SNP = Single nucleotide polymorphism; CHD = coronary heart disease; OR = odds ratio; MR = mendelian randomization; NR = not reported; BMI = body-mass index; WC = waist circumference; HC = hip circumference; WHR = waist-to-hip ratio; WCadjBMI = WC adjusted for BMI; HCadjBMI = HC adjusted for BMI ; WHRadjBMI = WHRadjBMI; IPD = individual participant data; SD = standard deviation; C+C4D = CARDIoGRAMplusC4D Consortium; CGPS = Copenhagen General Population Study; CCHS = Copenhagen City Heart Study; FHS = Framingham Heart Study; EGCUT = Estonian Biobank study; ENGAGE = European Network for Genetic and Genomic Epidemiology consortium.

# CHAPTER 3: Overall study design and methods

## Chapter summary

The UK Biobank is the most detailed and comprehensive large-scale prospective study to date. The current thesis uses a fraction of the resources available in the UK Biobank to investigate the observational and genetic epidemiological associations of adiposity-related CHD risk. The current chapter summarises the UK Biobank protocol where it is of particular relevance to the present study, including overall study design, baseline assessment procedures, repeat assessments and imaging protocols. Similarly, a brief description of the Oxford Biobank is included as this study was additionally included in **Chapter 6**. Finally, baseline exclusions and variable derivations used in the main analyses are described in the current chapter, as well as baseline characteristics of the study population used in the primary analysis (**Chapters 4, 7 & 8**). Further information on statistical methods which are relevant to particular thesis objectives are reported in subsequent chapters, where appropriate.

## 3.1. The UK Biobank

### *3.1.1 Overall study design and recruitment*

The UK Biobank study is a large observational study of over 500 000 UK participants aged 40-70 years. Participants were identified from National Health Service (NHS) registers, and invited to one of 20 assessment centres around the UK. Recruitment took place from March 2006 to September 2010 (**Figure 3.1**). The UK Biobank was initiated with the aim to investigate the importance of a vast variety of exposures in relation to different health outcomes, with a long-term goal of improving the prevention, diagnosis and treatment of diseases of middle and old age. The study protocol, baseline assessment and population characteristics are described in greater depth elsewhere.[122, 147] Ethics approval for the UK Biobank was granted by the North West Multi-Centre Research Ethics Committee in May 2006. All participants provided informed written consent to take part in the study. The UK Biobank application number for this research is 31461.

### *3.1.2 Baseline assessment procedures*

Following informed consent, participants self-reported lifestyle exposures, medical history and treatments before undergoing more detailed standardised assessments including adiposity and blood pressure measurements.

#### *3.1.2.1 Measurement of BMI, WC and WHR*

Total body weight was measured using a Tanita BC-418 MA body composition analyser (Tanita Corporation, Arlington Heights, IL), and the results were automatically uploaded onto the UK Biobank database. Body weight was measured to the nearest 0.1kg. For all body measurements, participants were asked to wear light clothing and remove their shoes. Standing height was measured using a Seca 202 Height measure, to the nearest centimetre (Seca, Hamburg, Germany). Once measured, each participant's height was entered manually into the database by a trained research nurse. Implausible values were flagged with a warning message. BMI was calculated as the ratio of weight to height squared. WC was measured using a Seca (Seca GMBH, Germany) non-stretchable sprung measuring tape whilst the participant was in an orthostatic position. The waist was identified as the natural indent at the midpoint between the lateral iliac crest and lowest rib, in accordance with the protocol used in other large-scale epidemiological studies.[148] If this natural indent could not be identified, the umbilicus was identified and the circumference was instead measured at this point. WC was measured after the participant was instructed to slowly breathe out. HC was measured

immediately after WC measurements were taken whilst the participant was standing in the same orthostatic position. HC was defined as the level of maximum posterior extension of the buttocks. WC and HC were manually entered into the computer in centimetres. WHR was calculated as the ratio of WC/HC. WHTR was calculated as the ratio of WC/height.

*3.1.2.2 Bio-impedance measurements*

BIA variables were measured using the Tanita BC-418 MA analyser. The procedure involved participants standing with bare feet on the analyser's footpads whilst holding onto metal conductor hand grips. The device estimates body composition using a constant current source with a high frequency current (50Hz, 500μA). Eight electrodes were positioned so that the electric current was supplied from electrodes situated on each sole of the feet close to the toes and near the fingertips of each hand. The voltage was measured on the heel of both feet and the palm of both hands. This method allowed for the measurement of arm, leg, whole body and trunk impedance separately by sequentially alternating the current through each of the electrodes.[149] Estimations were recorded in 0.1kg increments, and percentage fat was recorded in 0.1% increments.Resistance (R) and reactance ($X_C$) were both measured to the nearest Ohm, and were subsequently used to derive impedance ($Z = (R^2 + X_C^2)^{1/2}$). The impedance index was used as a measure of total body conductive volume (impedance index = $Height^2/Z$). The in-built body composition prediction equations used by the Tanita bc-418 scale have not been released by the manufacturer. However, for the present analysis, it was assumed that the formulae had been derived from a population with similar characteristics to the UK Biobank study population.

*3.1.2.3 Blood pressure*

Blood pressure was measured twice after the participant had been at rest for at least 5 minutes in the seated position by using a digital sphygmomanometer (Omron 705 IT; OMRON Healthcare Europe B.V., Hoofddorp, Netherlands) with a suitably sized cuff; the average of the two blood pressure measures was used throughout.

*3.1.241 Biomarker measurements*

During baseline assessment, approximately 45 ml of blood samples were collected. Samples were immediately stored in the appropriate aliquots for long-term storage – approximately 250 000 samples were stored in an automated -80℃ working archive, and approximately 250 000 samples were stored in a manual liquid nitrogen back-up archive. At a later date (between 2014 and 2017), a range of biochemistry measures were performed on the blood samples at a central laboratory. All samples were predominantly processed using custom-designed industrial-scale automation systems to generate about 25 000 sample aliquots per day.

Overall, 36 biochemistry markers were selected for assay in all 500 000 participants, including cholesterol levels and markers of inflammation, liver function, kidney function and insulin sensitivity. Further details of the measurements and the assay procedures are provided online by the UK Biobank.[150]

### *3.1.3 Resurvey and imaging visits*

A repeat survey of the full baseline assessment was conducted on a representative subset of approximately 20 000 participants during 2012-2013 to allow for the correction of the 'time-dependent' effects of RDB. From 2013 onwards, participants residing within a reasonable distance from one of three imaging centres were invited to attend a whole-body DXA and MRI imaging visit. Data were available for a total of 5170 participants at the time of writing, which will increase to 100 000 by 2022, making UKB the largest imaging study to date.

### *3.1.4 Imaging procedures*

Total mass and regional body fat mass were estimated using the GE Lunar iDXA densitometer (Madison, WI, USA). Daily quality control protocols were used to check the machine's calibration and to ensure long-term stability. As defined by the manufacturer, fat mass referred to total lipid mass, including phospholipids, organ lipids, marrow and subcutaneous adipose. Variables of interest from the scan that were used in the analysis included total fat mass, total fat free mass, android fat mass, gynoid fat mass, and visceral fat mass. The android region was defined as the lower trunk area bounded by two lines: a lower boundary across the top of the pelvis and an upper boundary of 20% of the distance between the iliac crest and the neck, just underneath the ribs. The gynoid region was also defined by two additional automatically placed lines. The upper line was placed at 1.5 times the height of the android region below the pelvic line, and the lower line was defined such that the distance between the two gynoid lines was twice the height of the android region (**Figure 3.2**).

Visceral fat was estimated using a proprietary algorithm defined in greater depth elsewhere.[151, 152] Briefly, android fat can be further subdivided into visceral and subcutaneous fat. The two layers are separated non-uniformly around the abdominal cavity. X-ray attenuation by DXA software determined the edge of the body and the outer edge of the abdominal cavity and used the distance between these two points to determine the width of the subcutaneous fat layer along the lateral extent of the abdomen. Similarly, anteroposterior abdominal thickness was estimated using the dual-energy attenuation spectrum information. These parameters, together with empirically derived geometric constants, were then used to estimate

subcutaneous android adipose tissue. Subsequently, VAT mass was computed by subtracting android subcutaneous adipose tissue from the total android fat mass.

### *3.1.5 Study outcome and follow-up procedures*

After undergoing the baseline assessment, study participants were linked to electronic health databases including Hospital Episode Statistics (HES), disease registries and Office for National Statistics cause of death data for accurate and specific outcome ascertainment. Algorithms were designed to provide additional adjudication of MI and stroke events (using HES records and operational codes) prior to the start of the study to ensure the exclusion of participants who had experienced a previous MI or stroke which was not self-reported. Similarly, HES records were used to obtain details of non-fatal incident coronary heart disease events. The main outcome used in the present study was first-ever incident coronary heart disease. ICD-10 codes used to define the outcome in the present analysis included: incident acute MI (I21.0-121.4, I21.9), subsequent MI (I22.0, I22.1, I22.8, I22.9), with additional ICD-10 codes for incident chronic ischaemic heart diseases (I25.6, I25.8, I25.9), complications following acute MI (I23.0-I23.6, I23.8), unspecified acute ischaemic heart disease (I24.9), chronic ischaemic heart disease (I25.6, I25.8, I25.9), operational codes (OPCS) for coronary artery disease related procedures (K40-K50, K75) and all fatal coronary events (I20-I25). A detailed list of ICD-10 and OPCS codes used in the current analysis is provided in **Table 3.1**.

## 3.2 Oxford Biobank

### *3.2.1 Overall study design and recruitment*

In 1999, the Oxford Biobank study recruited 5425 adults aged 29-55 years without known chronic disease from the general population of Oxfordshire, UK.[153] Participants were selected randomly from the NHS register and invited to undertake a whole-body DXA imaging scan (GE Lunar iDXA densitometer). The study was approved by the Oxford Ethics Committee, and all participants gave consent to participate in the study.

### *3.2.2 Baseline survey*

As in UK Biobank, participants provided information on demographic factors, lifestyle and medical history; and had measurements taken by trained healthcare professionals, including height, weight, waist and hip circumference at baseline assessment. WC and HC measurements were recorded to a standard operating procedure based on the WHO Steps manual (http://www.who.int/chp/ steps/manual/en/) to ensure reproducible measurements. A sub-study of the between-observer variability was performed, and the between-observer coefficient of variation for HC was 1.1% (95% confidence interval (CI) was 0.9–1.4%) and 1.8% (95% CI 1.4–2.1%) for WC. Blood pressure was measured four times using a digital sphygmomanometer (Omron M3, OMRON Healthcare Europe B.V. Kruisweg, Hoofddorp) with the participants at rest in the seated position for at least 5 minutes. The mean of the final three blood pressure measures was used in the present study (**Chapter 6**).

### *3.2.3 Imaging procedures*

As in UK Biobank, body composition was assessed using GE Lunar iDXA machine, which used the same method to calculate regional body composition as described previously (*Section 3.1.4*). All DXA measurements were recorded on a single GE Lunar DXA scanner operated by trained staff according to standard operating procedure. The machine was re-calibrated every morning with scanning using a GE Lunar calibration phantom. Scans were not performed unless calibration passed the quality control.

## 3.3 General statistical methods

### *3.3.1 Selection of variables and variable derivation*

#### *3.3.1.1 Categorical variables at baseline*

Selected demographic and lifestyle characteristics at baseline assessment were categorised into groups: age category (5-year age groups); qualification attainment (Higher education, A/AS-level, GCSE/O-level, other qualification, no qualifications); UK region (ten regions); ethnicity (White, Chinese, South Asian, Black, Mixed ethnicity, other); Townsend Deprivation Index (equal fifths); smoking status (current, former, never); and alcohol consumption (daily, at least weekly, less than weekly, never). Participants with missing information on each covariate were assigned to a separate category for analysis.

#### *3.3.1.2 Additional variables at baseline assessment*

For cross-sectional comparisons, blood pressure was categorised into meaningful clinical categories: SBP (<100, 100-119, 120-139, 140-159, ≥160 mmHg); DBP (<60, 60-69, 70-79, 80-89, ≥90 mmHg). Self-reported physical activity was categorised into <10, 10-49.9, ≥50 MET hours/week based on a formula used for UK Biobank previously.[154] Similarly, hours of self-reported sedentary activity were categorised into the following daily averages: <3 hours; 3-6 hours; and ≥7 hours.

#### *3.3.1.3 Biomarkers*

In addition to blood pressure, the following blood-based biomarkers at baseline were included in cross-sectional analyses with adiposity measures and were considered as potential mediating factors underlying adiposity-related CHD risk. The decision to include selected biomarkers was based on theoretical importance: insulin sensitivity (Hemoglobin A1c levels [HbA1c], non-fasting glucose and self-reported type II diabetes diagnosis); lipid levels (total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-c], apo-lipoprotein A [ApoA], apo-lipoprotein B [ApoB] and triglycerides [TG]); estimated glomerular filtration rate (eGFR), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; Liver enzyme activity (Alkaline Phosphatase [ALP] and Gamma Glutamyl-transferase [GGT]); and inflammatory markers (Albumin and C-reactive protein [CRP]). Additionally, Lipoprotein(a) [Lp(a)] was included in cross-sectional analyses, but, as has been observed elsewhere,[16] Lp(a) was not associated with adiposity at baseline and therefore was not included as a potential intermediate factor in subsequent analyses. Each biomarker was categorised into sex-specific tenths. Prior to analysis, CRP, Lp(a) and GGT were log-transformed to achieve approximately normal distributions.

*3.3.1.4 Imaging variables*

Mutually exclusive compartments of total body fat were derived from the standard regions estimated by the GE Lunar iDXA densitometer (*Section 3.1.4*). Subcutaneous android fat was calculated by subtracting VAT from the total android fat mass. For subsequent analyses, total body fat was classified into four mutually exclusive compartments: VAT mass, subcutaneous android fat, subcutaneous gynoid fat and other fat mass. Other fat mass was defined as the combined fat mass contained within both legs and arms, and the remaining trunk region.

*3.3.2 Exclusions*

Of the 502 678 participants who attended baseline assessment, participants who had withdrawn at the time of writing (n = 56), or were aged <40 or >69 years (n = 2425), or had missing or outlying/implausible values for selected anthropometric traits at baseline (n = 12 952) were excluded from the analysis (**Figure 3.3, Appendix 3.1**). Cut-offs for outlying and implausible values were decided for each measure based on sex-specific adiposity distributions and previous studies in similar contemporary populations.[155] To avoid reverse causality, individuals who reported a previous diagnosis of MI, stroke, peripheral vascular disease, heart failure, transient ischemic attack or angina at baseline survey were also excluded (n = 29 145), as were individuals with a previous admission to hospital for stroke or CHD identified in their medical records (n= 2894). For specific analyses assessing associations between adiposity and blood pressure, participants who reported using blood pressure lowering medication were also excluded (n= 79 361). Participants who were genetically related (n = 66 821) were excluded from all genetic analyses, as were participants who were not of European ancestry (n = 28 120) or who lacked genetic information (n = 13 644).

**3.4 Baseline characteristics**

**Table 3.2** describes the socio-demographic characteristics of participants included in the main analyses. The study population consisted of a total of 455 148 individuals without a history of CVD who had complete information on adiposity measures at baseline survey. The mean age at baseline was 56.1(SD 8) years old, and 44.2% (n= 200 639) were male. According to the self-reported baseline surveys, 94% of the study population were ethnically white and 57% of study participants had achieved at least A-level qualifications. **Tables 3.3 & 3.4** summarise the anthropometric characteristics, lifestyle habits and health status of the study population at baseline survey. On average, men were taller and larger with respect to mean BMI, WC, WHR and WHTR compared with women (**Table 3.3**). However, women had approximately 50%

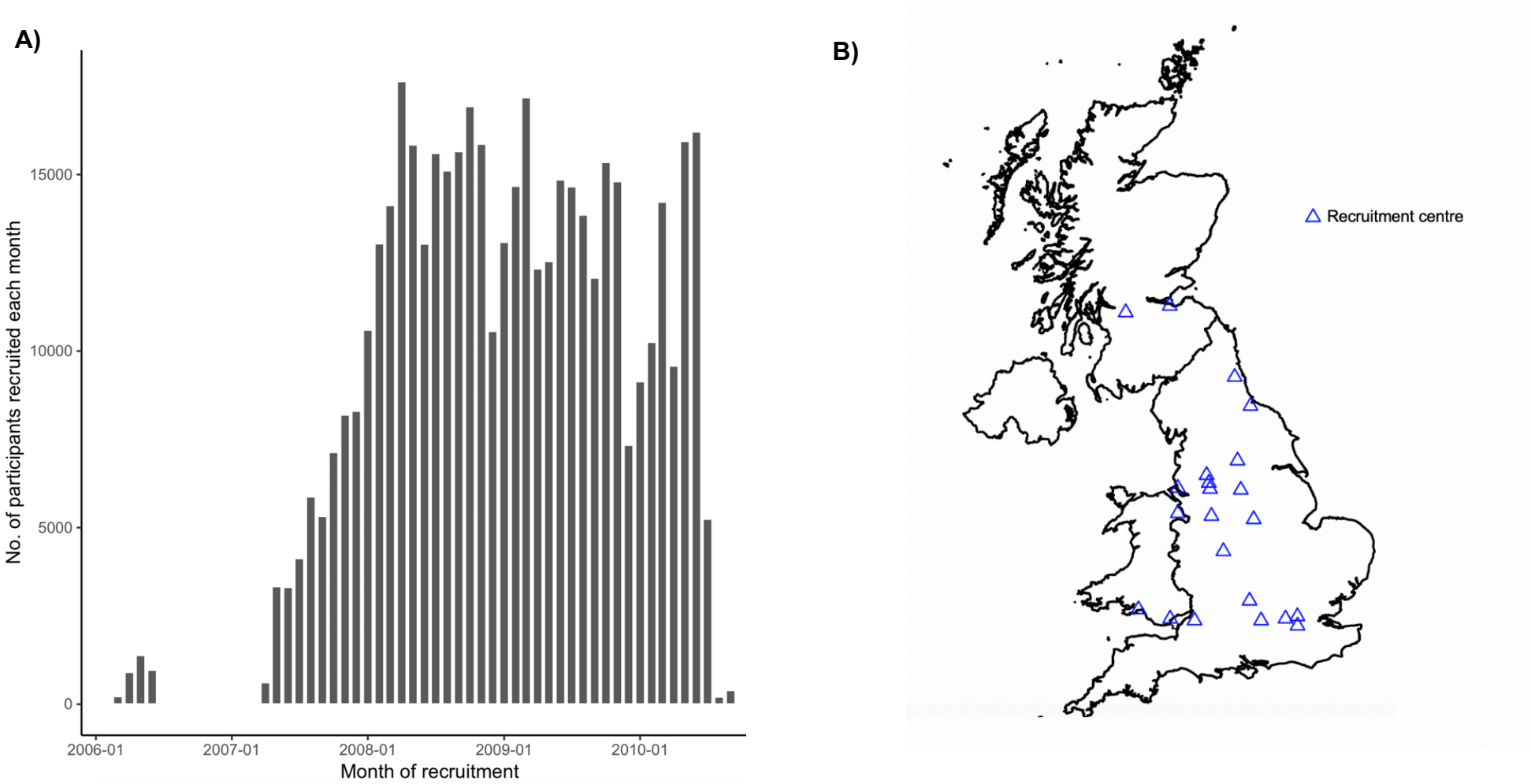
more body fat compared with men. Proportionally, fewer women consumed alcohol regularly or smoked compared with men (**Table 3.4**). On average, men exercised more regularly, or with greater intensity, compared with women (25% higher self-reported weekly METs), but a larger proportion of men were also sedentary for ≥7 hours per day compared with women (26% and 14% in men and women, respectively). Average SBP in men was 6 mmHg higher (141 mmHg) than in women (135 mmHg), and DBP was approximately 4 mmHg higher in men (85 mmHg) than in women (81 mmHg).

Biomarkers and clinical characteristics also varied by sex (**Table 3.5**). Doctor-diagnosed diabetes and hypertension were more prevalent among men at baseline survey compared with women (4.8% vs. 2.5% for diabetes; 27% vs. 22% for hypertension in men and women, respectively) . Almost 20% of men were on blood pressure-lowering medication versus 16% of women. Similarly, proportionally more men were on statin therapy compared with women (16% of men versus 10% of women). In general, women had higher mean levels of circulating total cholesterol (5.91 mmol/L in women; 5.59 mmol/L in men), most of which was explained by higher levels of HDL-C among women compared with men (1.60 vs. 1.29 mmol/L, respectively). Women and men had similar levels of circulating LDL-C (3.65 vs. 3.56 mmol/L, respectively). Correspondingly, Apo-A and Apo-B showed similar sex differences to HDL-C and LDL-C, respectively. Women also had raised levels of ALP and CRP compared with men. Conversely, men had higher levels of TG and GGT compared with women. Men and women had similar levels of non-fasting glucose, HbA1c, Lp(a), albumin and eGFR.

**Chapter 3 Tables and Figures**

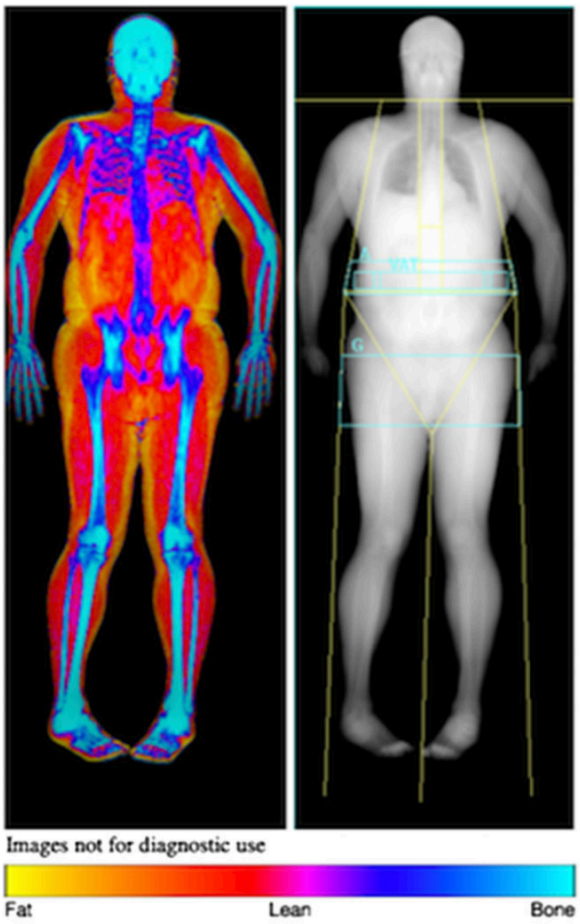

| Figure/Table | Title |
|---|---|
| **Figure 3.1** | Recruitment pattern and baseline assessment sites of the UK Biobank, 2006 - 2010 |
| **Figure 3.2** | DXA body composition image of a 56-year-old male with BMI 34.7kg/m2 |
| **Table 3.1** | ICD-10 codes used to define incident Coronary Heart Disease (CHD) |
| **Figure 3.3** | Flow diagram of UK Biobank study population inclusion criteria for each analysis |
| **Table 3.2** | Selected socio-demographic characteristics in 455 148 participants aged 40 - 69 without cardiovascular disease at baseline, by sex |
| **Table 3.3** | Selected body size and adiposity characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex |
| **Table 3.4** | Selected lifestyle characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex |
| **Table 3.5** | Selected biological and medical characteristics in 455 148 participants aged 40 -69 without cardiovascular disease at baseline, by sex |

**Figure 3.1** UK Biobank recruitment dates and recruitment site locations, 2006 - 2010




Recruitment patterns represent the monthly recruitment numbers of those participants included in the main analyses: those without missing/outlying adiposity values or a previous diagnosis of cardiovascular disease at baseline assessment. The blue circles in B) represent the location of each recruitment centre.

**Figure 3.2.** DXA body composition image of a 56-year-old male with BMI 34.7kg/m$^2$



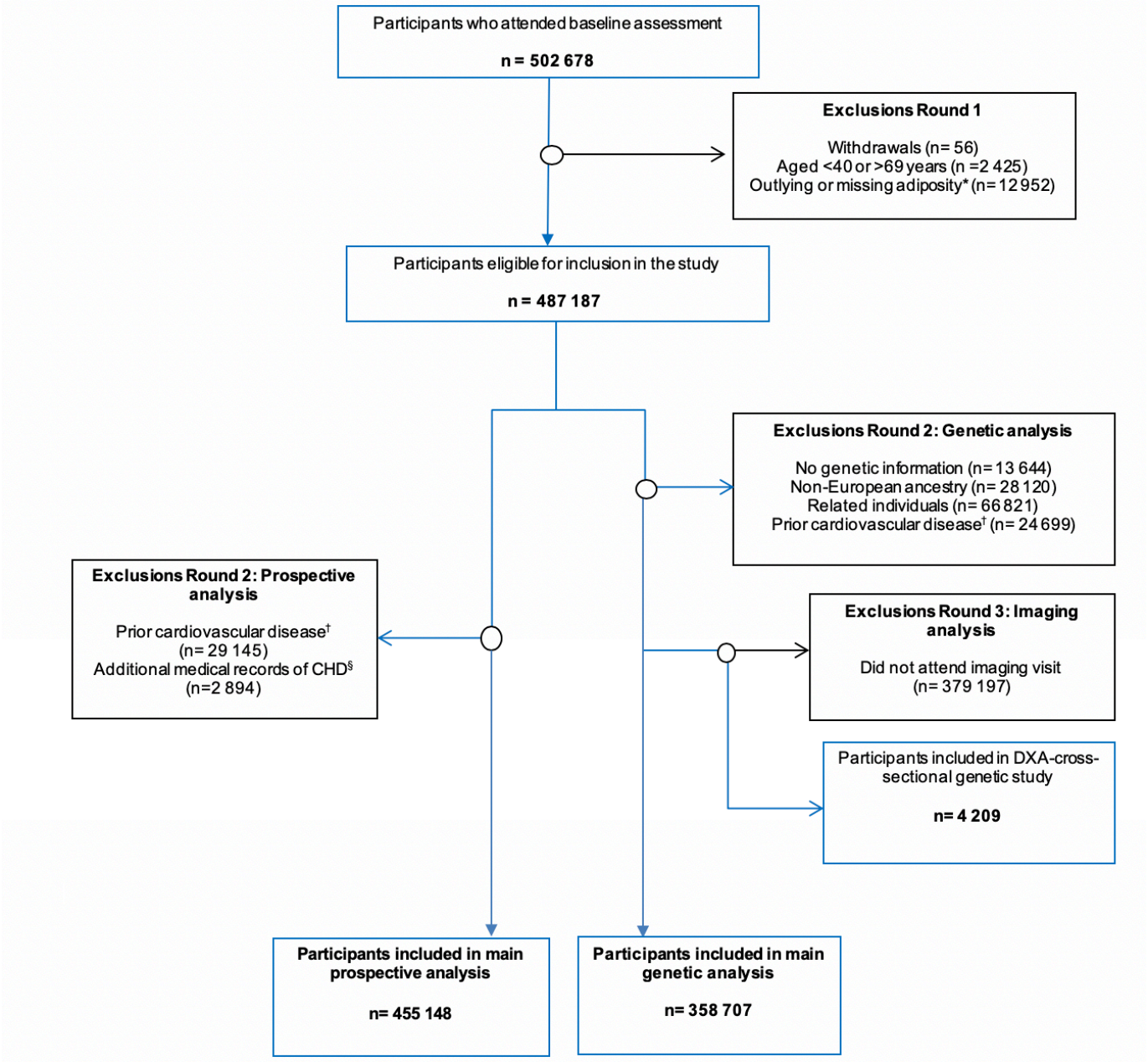

Source: Shepherd, *Clinical Reviews in Bone and Mineral Metabolism*, 2016; 14:201[156]

**Table 3.1** ICD-10 and operational codes used to define incident Coronary Heart Disease (CHD)

| Self-reported disease category | ICD-10/OPCS Category | ICD-10 code & definition | No. of Incident events occurring during follow-up |
|---|---|---|---|
| • Angina pectoris* | **I20** | I20.0 Unstable angina | 0 fatal (1 805 incident) |
| | | I20.1 Angina pectoris with documented spasm | 0 Fatal (98 incident) |
| | | I20.8 Other forms of angina pectoris | 0 Fatal (455 incident) |
| | | I20.9 Angina pectoris, unspecified angina | 4 fatal (7061 incident) |
| • Acute myocardial infarction | **I21** | I21.0 Acute transmural myocardial infarction of anterior wall | 925 |
| | | I21.1 Acute transmural myocardial infarction of inferior wall | 972 |
| | | I21.2 Acute transmural myocardial infarction of other sites | 113 |
| | | I21.3 Acute transmural myocardial infarction of unspecified site | 106 |
| | | I21.4 Acute subendocardial myocardial infarction | 1 071 |
| | | I21.9: Acute myocardial infarction, unspecified | 2 669 |
| • Subsequent myocardial infarction | **I22** | I22.0 Subsequent myocardial infarction of anterior wall | 6 |
| | | I22.1 Subsequent myocardial infarction of inferior wall | 13 |
| | | I22.8 Subsequent myocardial infarction of other sites | 0 |
| | | I22.9 Subsequent myocardial infarction of unspecified site | 57 |
| • Certain current complications following acute myocardial infarction | **I23** | I23.0 Haemopericardium as current complication following acute myocardial infarction; | 0 |
| | | I23.1 Atrial septal defect as current complication following acute myocardial infarction; | 1 |
| | | I23.2 Ventricular septal defect as current complication following acute myocardial infarction; | 7 |
| | | I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction; | 1 |
| | | I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction; | 0 |
| | | I23.5 Rupture of papillary muscle as current complication following acute myocardial infarction; | 2 |
| | | I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction; | 4 |
| | | I23.8 Other current complications following acute myocardial infarction | 10 |
| • Other acute ischaemic heart diseases | **I24** | I24.9 Acute ischaemic heart disease, unspecified (excl. ischaemic heart disease (chronic) NOS) | 749 |
| • Chronic ischaemic heart disease | **I25** | I25.6 Silent myocardial ischaemia | 5 |
| | | I25.8 Other forms of chronic ischaemic heart disease - Any condition in I21-I22 and I24.- specified as chronic | 1 548 |
| | | I25.9 Chronic ischaemic heart disease, unspecified -Ischaemic heart disease (chronic) NOS | 6 394 |
| • **Operations**: coronary heart disease | **K40*** | Saphenous vein graft replacement of coronary artery | 1 562 |
| | **K41*** | Other autograft replacement of coronary artery | 101 |
| | **K42*** | Allograft replacement of coronary artery | 0 |
| | **K43*** | Prosthetic replacement of coronary artery | 3 |
| | **K44*** | Other replacement of coronary artery | 17 |
| | **K45*** | Connection of thoracic artery to coronary artery | 1 633 |
| | **K46*** | Other bypass of coronary artery | 0 |
| | **K49*** | Transluminal balloon angioplasty of coronary artery | 230 |
| | **K50*** | Other therapeutic transluminal operations on coronary artery | 353 |
| | **K75*** | Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery | 5 691 |
| Total | | | **13 114** |

*Angina was included in the study outcome if the event was fatal only. For all other ICD-10 codes, first-ever events were included in the study outcome whether fatal or non-fatal.

**Figure 3.3** Flow diagram of UK Biobank study population inclusion criteria for each analysis




DXA= Dual-energy X-ray Absorptiometry imaging. *Thresholds for implausible/outlying adiposity values are summarised in **Appendix 3.1.** †Self-reported prior cardiovascular disease was defined as a previous doctor's diagnosis of the following conditions: Myocardial infarction, heart failure, stroke, trans-ischemic attack, angina or peripheral vascular disease at baseline. §Participants were excluded if electronic medical records indicated a history of the coronary events: revascularisation operations, diagnosis with Myocardial infarction, acute and chronic ischaemic heart disease.

**Table 3.2** Selected socio-demographic characteristics in 455 148 participants aged 40 - 69 without cardiovascular disease at baseline, by sex

| Characteristic | Men (n= 200 639) | Women (n= 254 509) | All (n= 455 148) |
|---|---|---|---|
| **Age, years** | | | |
| 40-44 | 11% | 11% | 11% |
| 45-49 | 14% | 14% | 14% |
| 50-54 | 15% | 16% | 16% |
| 55-59 | 18% | 19% | 18% |
| 60-64 | 23% | 24% | 24% |
| 65-69 | 18% | 16% | 17% |
| Mean (SD) | 56.2 (8.2) | 56.1 (7.9) | 56.1 (8.0) |
| **Ethnicity** | | | |
| White | 94% | 94% | 94% |
| Chinese | 0% | 0% | 0.3% |
| South Asian | 2% | 2% | 2% |
| Black | 2% | 2% | 2% |
| Mixed | 0% | 1% | 1% |
| Other | 1% | 1% | 1% |
| Prefer not to answer | 1% | 0% | 0.5% |
| **Highest qualification completed** | | | |
| No qualifications | 15% | 16% | 16% |
| GCSE/O-Level | 24% | 29% | 27% |
| AS/A-Level | 10% | 12% | 11% |
| Higher education | 48% | 42% | 44% |
| Prefer not to answer | 2% | 2% | 2% |
| **UK Region** | | | |
| London | 14% | 14% | 14% |
| South East | 9% | 9% | 9% |
| South West | 9% | 9% | 9% |
| East Midlands | 7% | 7% | 7% |
| West Midlands | 9% | 8% | 9% |
| Yorkshire & Humber | 15% | 15% | 15% |
| North West | 16% | 15% | 16% |
| North East | 11% | 11% | 11% |
| Wales | 4% | 4% | 4% |
| Scotland | 7% | 7% | 7% |

Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment (**Figure 3.3; Appendix 3.1**)

**Table 3.3** Selected body size and adiposity characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex

| Characteristic | Men (n= 200 639) | Women (n= 254 509) | All (n= 455 148) |
|---|---|---|---|
| **Height (cm)** | | | |
| <160 | 1% | 31% | 18% |
| 160 - 169 | 13% | 52% | 35% |
| 170 - 179 | 48% | 13% | 28% |
| ≥180 | 29% | 0.1% | 13% |
| Mean (SD) | 175.8 (6.8) | 162.6 (6.3) | 168.4 (9.3) |
| **BMI (kg/m²)** | | | |
| <18.5 | 0% | 1% | 0% |
| 18.5 - 24.9 | 26% | 40% | 33% |
| 25 - 29.9 | 50% | 37% | 43% |
| 30 - 34.9 | 19% | 15% | 17% |
| 35 - 40 | 4% | 5% | 5% |
| ≥40 | 1% | 2% | 2% |
| Mean (SD) | 27.7 (4.1) | 27.0 (5.1) | 27.3 (4.7) |
| **Body fat percentage (%)** | | | |
| <15 | 4% | 0.5% | 2% |
| 15 - 24.9 | 44% | 5% | 22% |
| 25 - 34.9 | 47% | 35% | 41% |
| ≥35 | 4% | 60% | 35% |
| Mean (SD) | 25.0 (5.7) | 36.5 (6.8) | 31.4 (8.5) |
| **Waist circumference (cm)** | | | |
| <70 | 0% | 9% | 5% |
| 70 - 79 | 4% | 31% | 19% |
| 80 - 89 | 22% | 31% | 27% |
| 90 - 99 | 38% | 18% | 27% |
| ≥100 | 35% | 12% | 22% |
| Mean (SD) | 96.5 (11.0) | 84.4 (12.3) | 89.7 (13.2) |
| **Waist-to-hip ratio** | | | |
| <0.7 | 0.5% | 3% | 2% |
| 0.7 - 0.79 | 1% | 40% | 23% |
| 0.8 - 0.89 | 28% | 45% | 38% |
| 0.9 - 0.99 | 55% | 11% | 30% |
| ≥1.0 | 15% | 1% | 7% |
| Mean, (SD) | 0.93 (0.06) | 0.82 (0.07) | 0.87 (0.09) |
| **Waist-to-height ratio** | | | |
| <0.45 | 4% | 19% | 12% |
| 0.45 - 0.49 | 50% | 50% | 50% |
| 0.50 - 0.54 | 27% | 16% | 21% |
| 0.55 - 0.59 | 13% | 9% | 11% |
| ≥0.6 | 7% | 7% | 7% |
| Mean (SD) | 0.55 (0.06) | 0.52 (0.08) | 0.53 (0.07) |
| **Trunk fat percentage** | | | |
| <15 | 4% | 1% | 2% |
| 15 - 24.9 | 29% | 11% | 19% |
| 25 - 34.9 | 56% | 41% | 47% |
| ≥35 | 11% | 47% | 31% |
| Mean (SD) | 27.4 (6.5) | 34.0 (7.6) | 31.1 (7.9) |

Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment (**Figure 3.3; Appendix 3.1**)

**Table 3.4** Selected lifestyle characteristics in 455 148 participants aged 40-69 without cardiovascular disease at baseline, by sex

| Characteristic | Men (n= 200 639 ) | Women (n= 254 509 ) | All (n= 455 148) |
|---|---|---|---|
| **Smoking status** | | | |
| Current | 12% | 9% | 10% |
| Former | 37% | 31% | 34% |
| Never | 51% | 60% | 56% |
| **Weekly alcohol consumption** | | | |
| Daily drinker | 26% | 16% | 20% |
| Regular drinker | 53% | 47% | 49% |
| Occasional drinker | 16% | 28% | 22% |
| Never drinker | 6% | 9% | 8% |
| **Physical activity level (MET-hr/wk)** | | | |
| <10 | 23% | 24% | 23% |
| 10 - 49.9 | 47% | 47% | 47% |
| ≥50 | 22% | 18% | 20% |
| Missing/prefer not to say | 8% | 12% | 10% |
| Mean (SD) | 41.3 (57.7) | 33.7 (41.6) | 37.1 (49.6) |
| **Sedentary time (hr/day)** | | | |
| <3 | 12% | 19% | 16 % |
| 3 - 6 | 60% | 64% | 62% |
| ≥7 | 26% | 14% | 19% |
| Missing/prefer not to say | 2% | 3% | 3% |
| Mean (SD) | 5.3 (2.7) | 4.4 (2.1) | 4.8 (2.4) |
| **Systolic blood pressure (mmHg)** | | | |
| <100 | 0.5% | 1% | 1% |
| 100 - 119 | 9% | 21% | 16% |
| 120 - 139 | 42% | 41% | 41% |
| 140 - 169 | 35% | 26% | 30% |
| ≥160 | 14% | 11% | 12% |
| Mean (SD) | 141 (17) | 135(19) | 138 (19) |
| **Diastolic blood pressure (mmHg)** | | | |
| <60 | 0.5% | 1% | 1% |
| 60 - 69 | 6% | 12% | 9% |
| 70 - 79 | 26% | 35% | 31% |
| 80 - 89 | 39% | 34% | 36% |
| ≥90 | 29% | 18% | 23% |
| Mean, (SD) | 85 (10) | 81 (10) | 82 (10) |

Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment (**Figure 3.3; Appendix 3.1**)

**Table 3.5** Selected biological and medical characteristics in 455 148 participants aged 40 -69 without cardiovascular disease at baseline, by sex

| Characteristic | Men (n= 200 639 ) | | Women (n= 254 509 ) | | All (n= 455 148) | |
|---|---|---|---|---|---|---|
| | N | %/Mean (SD) /Median [IQR]* | N | %/Mean (SD) /Median [IQR]* | N | %/Mean (SD) /Median [IQR]* |
| **Diagnosed conditions (%)** | | | | | | |
| Hypertension | 54 186 | 27% | 54 826 | 22% | 109 012 | 24% |
| Diabetes | 9 680 | 4.8% | 6 473 | 2.5% | 16 153 | 3.6% |
| **Medication use (%)** | | | | | | |
| Cholesterol-lowering therapy | 32 901 | 16% | 25 894 | 10% | 58 795 | 13% |
| Blood pressure-lowering therapy | 39 415 | 20% | 39 946 | 16% | 79 361 | 17% |
| **Levels of biomarkers, mean (SD)** | | | | | | |
| Cholesterol (mmol/L) | 188884 | 5.59 (1.09) | 237602 | 5.91 (1.11) | 426486 | 5.77 (1.11) |
| HDL cholesterol (mg/L) | 174472 | 1.29 (0.31) | 215887 | 1.60 (0.38) | 390359 | 1.46 (0.38) |
| LDL cholesterol (mg/L) | 188477 | 3.56 (0.83) | 237219 | 3.65 (0.86) | 425696 | 3.61 (0.85) |
| Triglycerides (mmol/L) | 188683 | 1.98 (1.16) | 237474 | 1.54 (0.85) | 426157 | 1.74 (1.02) |
| Apolipoprotein A (g/L) | 174206 | 1.43 (0.23) | 213946 | 1.64 (0.27) | 388152 | 1.55 (0.27) |
| Apolipoprotein B (g/L) | 187572 | 1.05 (0.23) | 236778 | 1.04 (0.24) | 424350 | 1.04 (0.24) |
| Lp(a)* (nmol/L) | 151200 | 19.4 [51.4] | 190977 | 22.1 [52.0] | 342177 | 21.1 [52.4] |
| Non-Fasting Glucose (mmol/L) | 174355 | 5.15 (1.32) | 215717 | 5.05 (1.03) | 390072 | 5.09 (1.2) |
| HbA1c (mmol/mol) | 187607 | 36.1 (7.1) | 236016 | 35.6 (5.71) | 423623 | 35.8 (6.3) |
| eGFR (mL/min/1.73 m²) | 188639 | 90.6 (13.5) | 237322 | 90.6 (13.99) | 425961 | 90.6 (13.8) |
| Alkaline Phosphatase, U/L | 188881 | 81.8 (24.5) | 237623 | 84.4 (27.19) | 426504 | 83.3 (26.1) |
| Gamma Glutamyltransferase,U/L* | 188761 | 32.8 [26.0] | 237501 | 21.2 [15.4] | 426262 | 26.3 [22.5] |
| Albumin (g/L) | 174574 | 45.6 (2.6) | 215967 | 45.0 (2.6) | 390541 | 45.3 (2.6) |
| CRP* (mg/L) | 188387 | 1.26 [1.83] | 237197 | 1.35 [2.27] | 425584 | 1.33 [2.10] |

*Skewed distributions. Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment (**Figure 3.3; Appendix 3.1**)

## CHAPTER 4: Baseline correlates of adiposity measures

### Chapter summary

Although it is believed that adiposity-related CHD risk is mediated mostly through adverse effects on blood pressure, lipids and insulin resistance, the majority of the excess risk remains unexplained after adjustment for these factors. Many other potential mediating factors have been largely unexplored in previous large cohort studies, including inflammation, liver function and glomerular filtration rate. This chapter investigates the cross-sectional associations between baseline adiposity measures (BMI, Body fat %, Trunk fat %, WC, WHTR and WHR) and set of lifestyle, demographic and biological factors, among 455 148 UK Biobank participants aged 40-69 years without cardiovascular disease or missing adiposity measures at baseline. All six selected adiposity measures were strongly, positively and approximately linearly correlated with each other, and each was associated with the selected demographic, lifestyle and cardiometabolic traits at baseline. However, there were some important differences between the associations of general and central adiposity measures with some characteristics, and particularly between WHR and BMI, which showed contrasting associations with current smoking and alcohol consumption. The selected adiposity measures at baseline were similarly associated with blood-based cardiometabolic traits, providing further evidence for the potential roles of blood pressure, cholesterol, and insulin resistance underlying adiposity-related CHD risk, and providing the first large-scale evidence for the potential role of emerging intermediate factors such as inflammatory markers, and liver and kidney function.

## 4.1. Background

As previously discussed in **Chapter 1**, the mechanisms underlying adiposity-related CHD risk remain unclear, although it is thought that the large majority of risk is mediated through blood pressure, insulin resistance and cholesterol.[24, 116, 157, 158] However, uncertainty surrounds the extent to which these pathways contribute to adiposity-mediated CHD risk, and whether the relevance of these pathways differ between general and central adiposity measures is also contested.

Excess adiposity produces a number of pathophysiological disturbances, including enhanced sympathetic nervous system activation, increased leptin secretion, enhanced angiotensin-aldosterone production and hyperinsulinemia. Together, these are thought to result in renal salt retention, which acts in conjunction with a state of increased peripheral resistance to raise blood pressure in obesity.[34, 35] However, the relevance of central adiposity to this process is largely unknown. Additionally, the enhanced lipolysis accompanying excess adipose tissue increases the levels of non-esterified fatty acids, resulting in liver toxicity and reduced insulin clearance.[159] The resulting increase in glucose production, insulin resistance and dyslipidaemia are further complications which are commonly treated in obese individuals. Although these processes are thought to be potentiated in central obesity, this has yet to be confirmed with large-scale observational and genetic studies in contemporary populations.

Several of these factors are likely inter-related and could have effects on other pathways with the potential to influence CHD risk (**Figure 4.1**). The independent contribution of these factors and the relevance of emerging cardiovascular risk factors have not been studied in detail using large and contemporary cohort studies. Furthermore, there is lack of evidence for the cross-sectional associations of different adiposity measures with potential intermediate factors underlying adiposity-related CHD risk. In previous observational studies, the association between adiposity and CHD risk cannot be fully explained by blood pressure, cholesterol and insulin resistance alone,[24] and it is unclear whether the remaining excess risk is due to incomplete adjustment resulting from measurement error or biological variation, or whether it is attributed to emerging intermediate factors which are potentially modifiable. In particular, there is growing evidence for the relevance of chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD) to CVD and all-cause mortality, both of which are associated with obesity.[160-162] However, whether these associations are causal and independent of the known factors underlying adiposity-related CHD risk remains unclear, and there is a lack of evidence for the relevance of central adiposity to liver and kidney function.

Importantly, adiposity is a complex trait, and is associated with an array of lifestyle, demographic and genetic factors through pathways that are not fully understood but may contribute substantially to CHD risk.[163] Before interpreting the prospective associations between adiposity and CHD risk, it is important to investigate the associations between potential confounders and adiposity traits at baseline.

A number of large-scale studies have assessed the correlations between adiposity and lifestyle, demographics and known risk factors for CHD, however most were limited by small sample size, a lack of information on potentially novel cardiovascular risk factors, or measurement error arising as a result of using different study protocols.[16, 24] Additionally, most studies lacked information on medication use, and therefore associations may in part be influenced by treatment effects. Furthermore, the majority of studies were unable to investigate the correlates of different measures of adiposity, particularly adiposity measures derived from newer technology such as BIA.

The UK Biobank is the largest single study to date with a variety of biomarkers available to assess the relevance of pathways such as inflammation, liver and kidney function, blood pressure, cholesterol, insulin resistance to adiposity-related CHD risk using standardised measures in a contemporary population. Therefore, this Chapter aims to examine cross-sectional correlates of each of the selected adiposity measures at baseline, to identify potential confounders and mediating pathways underlying adiposity-related CHD risk.

## 4.2. Statistical methods

### *4.2.1 Overall study design and study population*

The study design and exclusion criteria were explained in detail in **Chapter 3**. In brief, participants with no history of CVD at baseline assessment and with complete and plausible information on adiposity measures were included in the analysis. Additionally, in analyses of blood pressure, participants who self-reported using blood pressure lowering medication were excluded. The baseline characteristics of the study population used in the majority of cross-sectional analyses were summarised in **Chapter 3** (**Section 3.4**)**.**

### *4.2.2 Cross-sectional analysis*

Mean (SD) values of selected adiposity measures across levels of demographic, lifestyle and biological characteristics at baseline were calculated. To observe the shape of any association, mean (95% CI) adiposity or risk factor levels in tenths of each adiposity measure were calculated separately for men and women. Means were adjusted for age, region, education, ethnicity, deprivation index, smoking status and alcohol consumption, where appropriate, using a direct standardisation technique. Partial correlation coefficients were calculated for each cross-sectional comparison after adjusting for the same covariates. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

### *4.2.3 Graphical representation*

Although adiposity measures were analysed in groups defined by the deciles of sex-specific distributions, to allow meaningful comparisons across adiposity measures, levels of risk factors and mean adiposity measures were standardised, with each of the axes corresponding to SD differences from the overall mean value among men and women combined. In each plot, the area of the plotting symbol is proportional to the amount of statistical information that it represents (i.e. inversely proportional to the variance of the point estimate). Plots were created in R version 3.5.2 or STATA version 16.0.

## 4.3 Results

### *4.3.1 Correlations between adiposity measures at baseline*

Adiposity measures were positively and approximately linearly associated with each other across the entire range among men and women (**Figure 4.2**). **Table 4.1** shows the adjusted partial correlation coefficients between each measure of adiposity explored in the present study. After adjusting for important confounders, BMI was particularly highly correlated with body fat %, trunk fat %, WC and WHTR in both men and women (all r>0.8), however BMI was less strongly correlated with WHR, particularly among women. Comparing top and bottom fifth of the sex-specific BMI distributions, there was approximately 2-2.5 SD differences in WC, WHTR and Body fat%, whereas across the same groups of BMI, there was only an approximately 1.5 SD difference in WHR (**Figure 4.3**). Correlations with other markers of adiposity were generally lower for WHR and trunk fat %.

### *4.3.2 Adiposity and demographic characteristics*

**Tables 4.2** and **4.3** describe the mean adiposity levels observed at different levels of selected baseline demographic characteristics among men and women, respectively. On average, mean adiposity levels were higher in participants who were older, of non-White ethnicity, and in more deprived participants with lower education.

Among women, mean adiposity increased linearly with age for all measures, with 65 to 69 year olds displaying on average 0.8kg/$m^2$ higher mean BMI, 3.1% higher body fat, 4.1cm wider WC, 3.1% higher trunk fat percentage, 0.03 larger WHR and WHTR than those aged 40-44 years (**Figure 4.4**). Except for BMI, mean adiposity levels among men increased similarly with age. Mean BMI increased until approximately 55-59 years, above which mean BMI appeared to fall slightly. Across all age groups, men had higher levels of WC, WHR and WHTR than women. Mean BMI was similar between men and women at all ages. Mean adiposity levels also varied across ethnic groups after adjusting for socio-economic factors (**Figure 4.5**). Compared to participants of White ethnicity, men and women of South Asian ethnicity had lower general adiposity but raised central adiposity levels at baseline. However, participants of Black ethnicity had raised general adiposity levels, but only Black women had raised central adiposity levels compared with women of White ethnicity. Compared with other ethnicities, Chinese men and women had consistently lower mean levels of adiposity across all measures, although this was less marked for body fat distribution measures (WHR and WHTR).

Similarly, adiposity distributions varied by UK region (**Figure 4.6**). In general, mean adiposity was highest among participants recruited in Wales and lowest in those recruited from London and the South East. When comparing across adiposity measures, average prevalence of obesity or raised central adiposity levels varied between assessment centres. For example, despite relatively high prevalence of obesity (BMI≥30kg/$m^2$) in Scotland (Glasgow: 24.4%, Edinburgh: 21.8%) compared with regions in England, the prevalence of WHR values above the WHO-defined cut-point for 'high risk' (WHR> 94cm and >80cm for men and women, respectively) was slightly lower in Scotland compared with England (**Figure 4.7**).

*4.3.3 Adiposity and lifestyle factors*

**Table 4.4** displays the associations of baseline adiposity with lifestyle factors among men and women. In general, alcohol consumption was greatest at the lower ranges of adiposity. At all levels of adiposity, the percentage of men who reported alcohol consumption at least daily was about 10% higher in women, however men and women showed similar patterns of alcohol consumption with increasing adiposity (**Figure 4.8**). Daily drinking was more common in individuals at the lower ranges of general adiposity measures, but the prevalence of daily drinkers was similar across the WHR distribution. Similarly, the prevalence of current smokers was higher at the lower ranges of all adiposity measures except for WHR, which was positively associated with smoking prevalence. For example, whereas current smoking prevalence among women in the top tenth of BMI was approximately half that of women in the bottom tenth of BMI (7% vs. 12%, respectively), the prevalence of current smokers in the top tenth of WHR was approximately double that of the bottom tenth of WHR (10% vs. 5%, respectively). Although smoking prevalence was higher in men, there were similar associations between current smoking and levels of BMI and WHR as in women. Conversely, the prevalence of former smokers increased approximately linearly with increasing adiposity across all measures, which was more extreme among men (**Appendix 4.1**).

Adiposity was also strongly associated with physical activity levels. Mean adiposity increased linearly with decreasing self-reported METs/week of physical activity, and with increasing categories of sedentary hours, in both women and men (**Table 4.4**). The observed differences in mean adiposity at baseline between the lowest and highest category of sedentary hours (<3 vs. ≥7 hours) were approximately 3kg/m2 for BMI and 0.05 for WHR. Self-reported physical activity categories (MET/week) were also associated with differences in adiposity from the lowest (≤10 MET/wk) to the highest (≥50 MET/wk) category across all measures: 0.9kg/m2 and 1.4kg/m2 for BMI; 4.5cm and 4.3 for WC; and 0.02 and 0.01 for WHR among men and women, respectively.

*4.3.4 Adiposity and prevalence of diabetes and hypertension*

Both self-reported and screen-detected diabetes displayed strong and curvilinear associations with increasing adiposity. After adjusting for potential confounders, men had consistently higher prevalence of screen-detected and self-reported diabetes at any given level of each adiposity measure, except WC and WHR, for which diabetes prevalence was similar or somewhat higher among women (**Figure 4.9**). The same was true for self-reported hypertension (**Appendix 4.2**), although this was partly explained by difference in treatment between men and women, as men had slightly higher prevalence of screen-detected hypertension compared to women at similar levels of WC and WHR after participants on blood pressure medication were excluded (**Appendix 4.3**).

*4.3.5 Adiposity measures and blood-based risk factors for CHD*

*4.3.5.1 Adiposity measures and blood pressure*

Sex-specific mean SBP and DBP values at baseline are plotted by tenths of each adiposity measure in **Figures 4.10 and 4.11,** before and after excluding participants on blood pressure medication. In general, the result suggested a positive and approximately linear relationship with increasing blood pressure across the full range of observed values for each adiposity measure. Associations became stronger and more linear after excluding participants on blood pressure-lowering medication, the effect of which was more pronounced for SBP than DBP. Of the six selected adiposity measures, BMI had the strongest correlation with SBP (r= 0.17 and 0.19 for men and women, respectively). Although these correlations were increased to r=0.19 and r=0.21 for men and women, respectively, after excluding participants on BP lowering therapy, the association was still slightly curvilinear, with a slight plateau at the upper ranges of BMI. Similar (albeit weaker) trends were observed for WC, WHTR and WHR. Overall, adjusted correlates of adiposity with DBP were stronger than with SBP (**Figure 4.11)**.

*4.3.5.2 Adiposity measures and blood lipids*

**Figures 4.12 to 4.14** show the mean levels of particular blood lipid measures with increasing sex-specific tenths of adiposity measures for men and women at baseline. ApoB, LDL cholesterol and total cholesterol levels were only weakly positively associated with increasing adiposity, with an apparent threshold beyond which higher levels of adiposity were associated with lower levels of ApoB, LDL cholesterol and total cholesterol. ApoA and HDL cholesterol displayed strong and approximately linear inverse associations with increasing adiposity

across each measure, decreasing by approximately 1 SD between the top and the bottom tenths of each sex-specific distribution of adiposity. Excluding participants on statin therapy increased the strength of associations between adiposity and ApoB but did not change associations with ApoA (**Appendix 4.4**). Triglyceride levels displayed strong, positive and approximately linear associations with all markers of adiposity, increasing by approximately one SD between the bottom and the top tenth of the adiposity distribution among both men and women (**Figure 4.14**). Associations did not vary substantially for ApoA, ApoB, LDL, HDL or total cholesterol between adiposity measures, however WHR was a markedly stronger predictor of triglycerides, particularly among women. Lp(a) was not strongly associated with any adiposity marker (**Figure 4.15**).

*4.3.5.3 Adiposity and glycaemic control*

Adiposity was strongly and positively associated with increasing mean levels of both non-fasting glucose and HbA1c. In general, correlations with adiposity measures were stronger for HbA1c than non-fasting blood glucose **(Figure 4.16**). Mean levels of non-fasting glucose were similarly positively associated with all measures of adiposity, ranging from approximately 4.9mmol/L among the bottom tenths of adiposity to approximately 5.2-5.6mmol/L in the top tenths of adiposity among men and women. Similarly, there was about a ¾ SD difference in HbA1c levels between the top and bottom tenths of the sex-specific distribution across all adiposity measures, from approximately 34 to 39 mmol/mol, however the associations were somewhat weaker for body fat and trunk fat % compared to other measures.

*4.3.5.4 Adiposity and inflammatory markers*

Adiposity measures showed continuous and generally curvilinear associations with blood-based markers of inflammation (**Figure 4.17**). Associations were positive for CRP and particularly strong among women, for which an increase from the bottom to the top tenth of sex-specific adiposity distributions was associated with an approximate 1.75 SD CRP increase, compared with an observed 1 SD CRP increase among men. An exception was WHR, which demonstrated similar associations with increasing CRP among men and women (r among men: 0.13; women: 0.18). Increasing adiposity demonstrated inverse and curvilinear associations with albumin levels across each adiposity measure, however, this association was only approximately half as strong for WHR as with the other measures. For markers of central adiposity (WC) and body fat distribution (WHR and WHTR), the inverse association between increasing adiposity and lower albumin was approximately linear among men and women. However, for BMI, body fat % and trunk fat %, albumin levels increased or remained

constant until approximately the highest third of adiposity, at which point higher adiposity was associated with lower albumin.

*4.3.5.5 Adiposity measures glomerular filtration rate*

Increasing adiposity was strongly and inversely associated with glomerular filtration rate (**Figure 4.18**). This association was approximately linear and was slightly stronger among women than men for all measures except WHR. Compared with women in the bottom tenth, women in the top tenths of BMI, trunk fat %, body fat % , WC and WHTR had approximately 10 mL/min/1.73m$^2$ lower eGFR (approximately 0.75 SD difference), whereas those in the top tenth of the WHR distribution had approximately 4 mL/min/1.73m$^2$ (<0.25 SD difference) lower eGFR values. Although slightly weaker, correlations were similar among men.

*4.3.5.6 Adiposity and circulating liver enzymes*

Adiposity measures demonstrated continuous and approximately linear associations with both of the selected biomarkers of liver function (**Figure 4.19**). Correlations with ALP were generally lower for increasing adiposity among men compared with women (r ranging from 0.04 to 0.08 for men; 0.173 to 0.194 for women). Among women, correlations with ALP were lower for WHR (r=0.127) compared with other measures (r=0.173 to 0.204), whereas BMI was the weakest predictor of ALP among men (r=0.040) compared with other adiposity measures (r=0.063 to 0.080). Similar associations were observed between increasing adiposity levels and GGT concentrations, however men had higher concentrations of GGT at all levels of adiposity, and in general associations with increasing GGT were stronger for men compared to women across all markers of adiposity. Associations with GGT did not vary substantially by adiposity measure.

## 4.4 Discussion

*4.4.1 Main findings*

The current study, consisting of 455 148 UK Biobank participants without known cardiovascular disease at baseline, is the largest study to date to investigate the cross-sectional correlates of six adiposity measures with known and emerging risk factors for CHD. The size and standard protocol used in this study enabled comparisons of the cross-sectional associations between different adiposity measures and cardiovascular risk factors with greater accuracy and detail than previously possible.

Although adiposity measures displayed strong, positive and approximately linear associations with each other, WHR was least correlated with the other measures, particularly among women. Importantly, correlations with adiposity varied by a number of potential confounding factors. In general, adiposity was positively associated with physical inactivity, previous smoking, non-European ethnicity, and deprivation, and inversely associated with alcohol consumption and education attainment. However, compared with other measures, WHR showed opposing associations for lifestyle factors, including current smoking and alcohol consumption.

Adiposity measures demonstrated similar positive and mostly linear associations with blood pressure, triglycerides, inflammatory markers and liver enzymes, but inverse associations with ApoA and HDL levels. Associations for adiposity measures with ApoB, LDL and total cholesterol were approximately curvilinear. Overall, the strongest associations with increasing adiposity levels were observed for HDL cholesterol, triglycerides and HbA1c. In general, adiposity measures were similarly associated with selected biomarkers at baseline, with the exception of triglyceride levels (for which WHR was a stronger predictor), or blood pressure, albumin and CRP, which were each more strongly correlated with general adiposity measures. Men and women displayed approximately similar associations between adiposity and each of the selected biomarkers, with the exception of CRP, ALP and eGFR, for which women had stronger associations compared with men.

### *4.4.2 Adiposity measures*

The age-adjusted correlation coefficients between each adiposity measure align with those reported previously.[16, 164-166] Across the six selected adiposity measures, the weakest associations were observed for WHR which is consistent with findings presented elsewhere, including the ERFC meta-analysis and the European Prospective Investigation of Cancer, each including over 200 000 participants.[16, 167] The observed weaker correlations with WHR compared with other measures provides further evidence for WHR representing a distinct phenotype of adiposity, with potential corresponding independent effects on disease risk.

### *4.4.3 Demographic and lifestyle correlates of adiposity at baseline*

All measures were strongly and importantly correlated with demographic and lifestyle characteristics, many of which have the potential to confound prospective associations with CHD risk. Consistent with previous large-scale studies, the increase in BMI appeared to level off at older ages,[168, 169] whilst increasing WHR persisted across the full distribution of age categories indicating a change in body fat distribution with increasing age.[170, 171] The positive

relationship between age and adiposity is well established, as is the apparent more persistent rise in central adiposity measures with age such as WC and WHR than BMI.[169, 172] However, this has not been demonstrated previously with as much accuracy and power as the current study. Differences in fat distribution at older ages could result from lifestyle changes, natural remodelling and muscle loss with age, or could be an early indication of declining health.[171] This is an important factor to consider when estimating disease risk, particularly for WHR (~0.05 difference between top and bottom age bands), as age represents the strongest risk factor for CHD. Lower SES was also associated with excess adiposity. It is widely acknowledged that obesity is influenced by a multitude of factors clustered around social class such as housing conditions, economic stability, access to healthcare and other social factors, together broadly termed the social determinants of health,[163] and many previous studies have found similar increases across social class indicators, including in the UK Biobank previously.[173] Previous MR studies have also confirmed a causal role of genetically elevated BMI and social class, confirming results from the current study.[174]

Adiposity is also known to vary by ethnicity, and previous large-scale studies in diverse populations have also observed higher adiposity levels among Black participants and South Asians compared with White participants.[16] As the UK Biobank study population was 94% white, the lack of non-White participants limits the interpretation of comparisons between ethnic groups.

Adiposity was also strongly related to smoking, alcohol consumption and physical activity levels in the current study, as has been reported elsewhere.[175] Current smokers had higher WHR values compared with non-smokers. Although this has been described previously,[176, 177] the mechanisms underlying this are not clear. It has been hypothesised that regular smoking could alter the distribution of body fat through hormonal affects; previous studies have noted higher circulating levels of 'central adiposity-favouring' androgen levels in smokers compared with non-smokers.[178, 179] Another explanation could be that smoking is associated with reduced physical activity and enhanced sedentary lifestyle, both of which were also highly correlated with central adiposity. Furthermore, lower physical activity levels among smokers may reduce abdominal obesity through the preferential utilization of visceral or abdominal fat over subcutaneous fat depots, as has been shown elsewhere.[180] It could also be the case that, as smoking is strongly related to other lifestyle factors such as diet or SES, there is some residual confounding underlying its association with adiposity.

Conversely, an inverse association was observed between markers of general adiposity and smoking in the current study. This has been observed previously,[181, 182] and although the mechanisms are yet to be elucidated, it is thought to involve reduced appetite, reduced energy expenditure and altered lipoprotein lipase activity in adipose tissue. Former smokers had raised levels of adiposity across all measures, which has also been observed previously. Smoking cessation has been linked with increased appetite,[177] however the mechanisms underlying this observation are also not yet fully understood.

In line with the findings presented elsewhere,[16, 157] there was an increased prevalence of daily alcohol consumers at the lower ranges of adiposity which was consistently observed for all measures except WHR. The inverse associations between adiposity and alcohol consumption are unexpected given the calorie density of alcohol, and the mechanisms underlying this relationship are not well understood. Reductions in alcohol consumption could indicate the onset of chronic ill health,[183, 184] and many chronic conditions are implicated with obesity. Furthermore, alcohol abuse is positively related to income and other SES factors in the general population,[185] and therefore the observed inverse association between general adiposity and alcohol consumption may be due to residual confounding. Indeed, recent MR studies have confirmed a causal association between long-term alcohol consumption and increased BMI.[186-190] There is a lack of evidence for the relevance of genetically elevated central adiposity to alcohol consumption using MR techniques.

*4.4.4 Adiposity and self-reported hypertension and diabetes*

All measures showed similar positive and curvilinear associations with increasing prevalence of type II diabetes. This contradicts the findings of a number of studies which have previously observed stronger correlations for central adiposity (measured via WC) than BMI.[191-194] However, other large-scale studies agree with the current study.[16, 195] Although not yet fully understood, insulin resistance in obesity occurs due to receptor impairments resulting from elevated FFA, hyperinsulinemia and increased cytokines.[159] Whether this process is exacerbated in central obesity due to the closer proximity of adipocytes to the pancreas is still debated. In the current study, adiposity measures showed approximately similar patterns of association with increasing prevalence of hypertension at higher levels of all adiposity measures regardless of treatment effects, however the correlation with WHR was notably weaker. Although this was also shown in the ERFC meta-analysis,[16] this study was unable to observe treatment-naïve associations.

*4.4.5 Adiposity and blood pressure*

Although the association between adiposity and blood pressure has been widely observed in many large-scale observational epidemiological studies,[196, 197] the mechanisms are not fully elucidated, and associations between measures of central adiposity or body fat distribution are less widely studied. Although strongly correlated across all measures, there were marked differences in the observed association magnitude between adiposity measures and SBP. This is consistent with findings from other large-scale studies, including the ERFC,[16, 198] and is an important indication of potential differences in biological mechanisms underlying adiposity-related CHD. It is thought that general adiposity raises blood pressure through a combination of peripheral vascular resistance, renal sodium retention, abnormal renin-angiotensin-aldosterone regulation and sympathetic nervous system activation[34-36, 199] - the latter is thought to be exacerbated in central adiposity due to distinct biological properties of visceral adipose tissue which are not fully understood.[37-40] Possible mechanisms underlying mechanisms are discussed in greater depth in **Chapter 6**.

Importantly, associations were not completely linear, and the observed increases in SBP and DBP appeared to plateau at upper ranges of BMI, even after removing participants on BP lowering therapy. This finding contrasts with the findings of a number of large-scale observational studies, including the PSC and ERFC meta-analyses,[16, 157, 199, 200] within which there was no adiposity level beyond which further increases were not associated with further increases in blood pressure. However, few large-scale studies have had sufficient power to investigate blood pressure at the upper ranges of BMI (i.e. BMI 35- 45 kg/m$^2$).[200] There could be several explanations for the apparent plateau at upper adiposity ranges, including measurement error, true physiological responses or behavioural changes. As per the UK Biobank protocol, blood pressure readings were measured using small, medium and large cuff sizes if participants arm circumferences were 17 – 22 cm, 22 – 32 cm and 32 – 42 cm, respectively, and therefore this observation could also result from systematic differences in blood pressure measurements. Indeed, inappropriate cuff size is the most common error in blood pressure measurement and can lead to considerable systematic errors in BP readings by approximately 1- 6 mmHg when inappropriate cuff sizes are used.[201] Another explanation could be that participants in the upper ranges of adiposity could have altered their lifestyle or medication use as a result of clinical advice. A recent MR study by confirmed a non-linear causal association between genetic instruments for increasing BMI and SBP in the UK Biobank, supporting the causality of a plateau in BP levels at the upper ranges of adiposity.[202] In 2016, SBP was the leading modifiable risk factor attributing to disability adjusted life years (DALYs), and BMI was the fastest growing modifiable risk factor, with attributable DALYs rising

by 26-31% from 2006 to 2016.[136] Therefore, it is important to further investigate the association between adiposity and SBP.

### *4.4.6 Adiposity and blood-based biomarkers*

Although it is likely that adiposity-related CHD risk is mediated through intermediate factors such as lipoprotein levels, blood pressure, glucose levels, and inflammation,[24, 196, 197, 203] the relative contribution of these factors as well as the relevance of other factors such as liver or kidney function has not been studied in detail in large contemporary cohort studies. Furthermore, there is lack of evidence of the cross-sectional associations of different adiposity measures with intermediate factors underlying adiposity-related CHD risk. Together, this evidence will provide insight to delineate which of the intermediate variables from obesity to CHD are likely to be mediators.

#### *4.4.6.1 Lipids*

In line with previous evidence, adiposity measures were strongly correlated with most lipid levels, particularly HDL cholesterol and triglyceride levels. In line with previous evidence, in the upper ranges of all adiposity measures, on average participants had elevated serum triglyceride, Apo B, and LDL cholesterol levels, and reduced HDL cholesterol and Apo A – collectively termed dyslipidaemia.[204] The correlation coefficients were similar to those reported in the ERFC meta-analysis, in which the coefficients ranged from 0.01 for Lp(a) to -0.28 for HDL cholesterol across BMI, WHR and WC.[16] However, the ERFC was unable to investigate treatment effects by removing participants on statin therapy, which removed part of the curvilinear relationship with ApoB, improving the correlation coefficient (r) by at least 0.1 across all measures in the current study. Also similar to the results reported by the ERFC, selected adiposity measures showed similar patterns of association with lipid levels in the current study with the exception of triglyceride's which were more strongly correlated with WHR, WC and WHTR compared with other adiposity measures, specifically among women. Although there is a lack of evidence for the relevance of different adiposity measures to lipid metabolism, the association between BMI and lipids has been reported on widely using large-scale observational studies.[24, 157, 158] Moreover, MR studies have confirmed a causal association between BMI and increasing levels of HDL cholesterol, triglyceride's and total cholesterol.[116, 119, 140]

The mechanisms responsible for the observed dyslipidaemia in the upper ranges of adiposity are thought to result from a combination of the enhanced free fatty acid delivered to the liver

from increased adipose tissue, insulin resistance and a pro-inflammatory state. Specifically, triglyceride's are markedly higher in obesity due to the enhanced availability of FFAs for triglyceride synthesis in the liver,[205-207] which is confirmed by the results presented in the current study and others.[16] Furthermore, triglyceride's were also more tightly correlated with central adiposity compared with general adiposity measures among women in the current study, providing stronger evidence for a greater relevance of visceral adiposity to dyslipidaemia compared with general adiposity.[208] It is thought that visceral adiposity potentiates triglyceride production in the liver due to its closer proximity and other distinct biological characteristics such as enhanced lipolipase activity or reduced adiponectin levels.[209] However, reasons for the sex differences although previously observed are largely unknown. The observed inverse associations with adiposity measures and HDL cholesterol and ApoA is thought to arise partly as a result of adiposity-mediated up-regulation of CETP.[210]

*4.4.6.2 Insulin resistance*

Similar positive associations with adiposity were observed with increasing markers of insulin resistance (non-fasting glucose and HbA1c). This is consistent with the results observed in the ERFC, however the ERFC investigated non-fasting glucose levels only and therefore may be affected by measurement error to a greater extent than HbA1c levels.[211] Although the molecular mechanism by which adiposity causes insulin resistance is unclear, inflammation resulting from dyslipidaemia, the possible inhibitory effects of fatty acid oxidation on glucose oxidation, and enhanced adipokine secretion are all thought to contribute to insulin resistance.[212] Associations were similar between central adiposity measures and general adiposity measures for HbA1c or non-fasting glucose levels in the current study. As discussed previously, these results contradict those presented by other studies whereby centrally obese individuals appear more predisposed to insulin resistance and type II diabetes than generally obese individuals.[213-217] The underlying mechanisms thought to potentiate type II diabetes in obesity are not fully elucidated and likely involve many different biological pathways,[159] however the heightened release of NEFAs has been suggested as the single most critical factor in modulating insulin sensitivity, particularly in centrally obese subjects.[218, 219] It is thought that NEFAs compete with glucose for substrate oxidation leading to diminished downstream insulin-receptor signalling.[220]

However, more recently, mechanisms which are independent of NEFAs have been proposed to mediate adiposity-related insulin resistance, including the enhanced production of cytokines and pro-inflammatory mediators in obesity.[221, 222] Additionally, the downregulation of adiponectin also plays a role in insulin resistance through reduced fatty acid oxidation.[223, 224]

Furthermore, adipocyte-derived 'signals' such as retinol binding protein-4 may contribute to the pathogenesis of type II diabetes by predisposing to insulin resistance independently of other mechanisms.[225]

*4.4.6.3 Inflammatory markers*

In the current study, most selected adiposity measures were similarly associated with approximately linear increases in CRP and decreases in albumin, confirming the results of previous studies,[226-228] and agreeing with the hypothesis that adiposity is associated with a state of systemic inflammation.[229] Obesity-related inflammation is thought to result from an enhanced infiltration of macrophages into adipose tissue, releasing cytokines, inflammatory mediators and procoagulant substances which have independent effects on atherosclerosis, or secondary effects via the liver to secrete bioactive substances which contribute to the development of atherosclerosis through a variety of pathways, including insulin resistance. It has been postulated that central adiposity may be a more important driver of obesity-related inflammation than general adiposity due to enhanced production of cytokines and close proximity to the liver.[230] Previous studies describing the relationships between adiposity measures and CRP have observed generally stronger correlations for central adiposity measures than BMI.[230] However, as in the ERFC, in the current study WHR was less strongly correlated with each marker of inflammation, contradicting this theory. A possible reason could be that central adiposity measures such as WC or WHR are not sensitive measures of visceral fat, which was illustrated in the Framingham Heart Study comparing CRP associations between adiposity measures using both imaging techniques and anthropometric measures.[231] Additionally, women appeared more susceptible to obesity-related inflammation compared with men across all adiposity measures, and although this has been observed previously,[231] potential mechanisms underlying sex differences are poorly understood.

*4.4.6.4 Liver enzymes and glomerular filtration rate*

ALP and GGT showed positive and approximately linear associations with increasing adiposity across all measures, although ALP showed weaker correlations among men compared with women for all markers except WHR. ALP and GGT are commonly raised in non-alcoholic fatty liver disease (NAFLD),[161] which is a common hepatic manifestation of the metabolic syndrome, including obesity.[232-234] However, despite large observational evidence suggesting that adiposity is strongly associated with NAFLD, the underlying mechanisms and the relative influence of general adiposity and body fat distribution is uncertain.[235] Visceral adipose tissue is thought to play a particularly crucial role in NAFLD by enhancing inflammation and cellular FFA transport. Together, these are thought to cause a cascade of reactions which divert

accumulated triglycerides away from adipose tissue and towards other metabolic organs such as the liver.[236, 237] Therefore, results from the present study are somewhat surprising, given that WHR was less correlated with liver enzymes compared with the other measures of adiposity.

The findings presented in the current study also provide evidence for an association between adiposity (particularly general adiposity) and kidney function, as has been observed in smaller population studies.[238] Although unclear, this is thought to arise as a result of ectopic fat build up in excess adiposity, eventually leading to interferences in organ function.[239]

*4.4.7 Strengths and potential limitations*

The availability, completeness and accuracy of a variety of established and emerging cardiovascular risk factors and demographic characteristics, coupled with the large sample size contribute to the robust study design of the UK Biobank which allows for the investigation of correlates of adiposity with greater accuracy than has been previously possible. A major strength of the current study is the ability to investigate potential treatment effects underlying associations with adiposity – an important consideration when interpreting cross-sectional associations in a contemporary population where a potentially substantial proportion are taking medication (17% were on blood pressure and 12% were on statins in the current study). This has not been possible to this scale previously. Additionally, the UK Biobank has available data on new and emerging cardiovascular risk factors such as eGFR and liver enzymes which have not yet been investigated in relation to adiposity with precision at scale.

However, when interpreting the results of the current study, there are a number of potential limitations which must be acknowledged. Firstly, the pathophysiological mechanisms underpinning dyslipidaemia, insulin resistance and inflammation are complex, inter-related and not fully understood. Therefore, it is not possible to quantify the effects of adiposity on one pathway when they are highly inter-linked. For example, in severe insulin resistance, the insulin induced stimulation of lipoprotein lipase may be reduced, which would also decrease the clearance of triglyceride rich lipoproteins, exacerbating dyslipidemia.[240] Likewise, although both general and central adiposity measures were similarly associated with blood-based biomarkers, it is possible that each has distinct and independent pathophysiological mechanisms of effect; however it is not possible to reveal these effects through cross-sectional comparisons alone since adiposity measures are also highly correlated. However, these problems are unavoidable and ubiquitous across epidemiological research. Moreover, adiposity measures showed clear associations with most demographic and lifestyle

characteristics at baseline, evidencing the complex nature of adiposity in a contemporary UK population. Therefore, residual confounding is likely. Fortunately, however, another strength of the UK Biobank is the availability of genetic data on 0.5M participants, allowing for the first time the ability to complement observational associations with genetic associations to assess the causal relevance of associations within the same population at scale (**Chapter 8**).

Ideally, cross-sectional comparisons should be corrected for short-term within-person variability (**Chapter 5**), for which statistical methods have been developed.[241, 242] This may have been an underlying explanation for weaker associations observed with WHR compared with other measures for some of the cardiometabolic traits. However, since cross-sectional comparisons use measures recorded at a single time point, large amounts of variability are likely minimal.

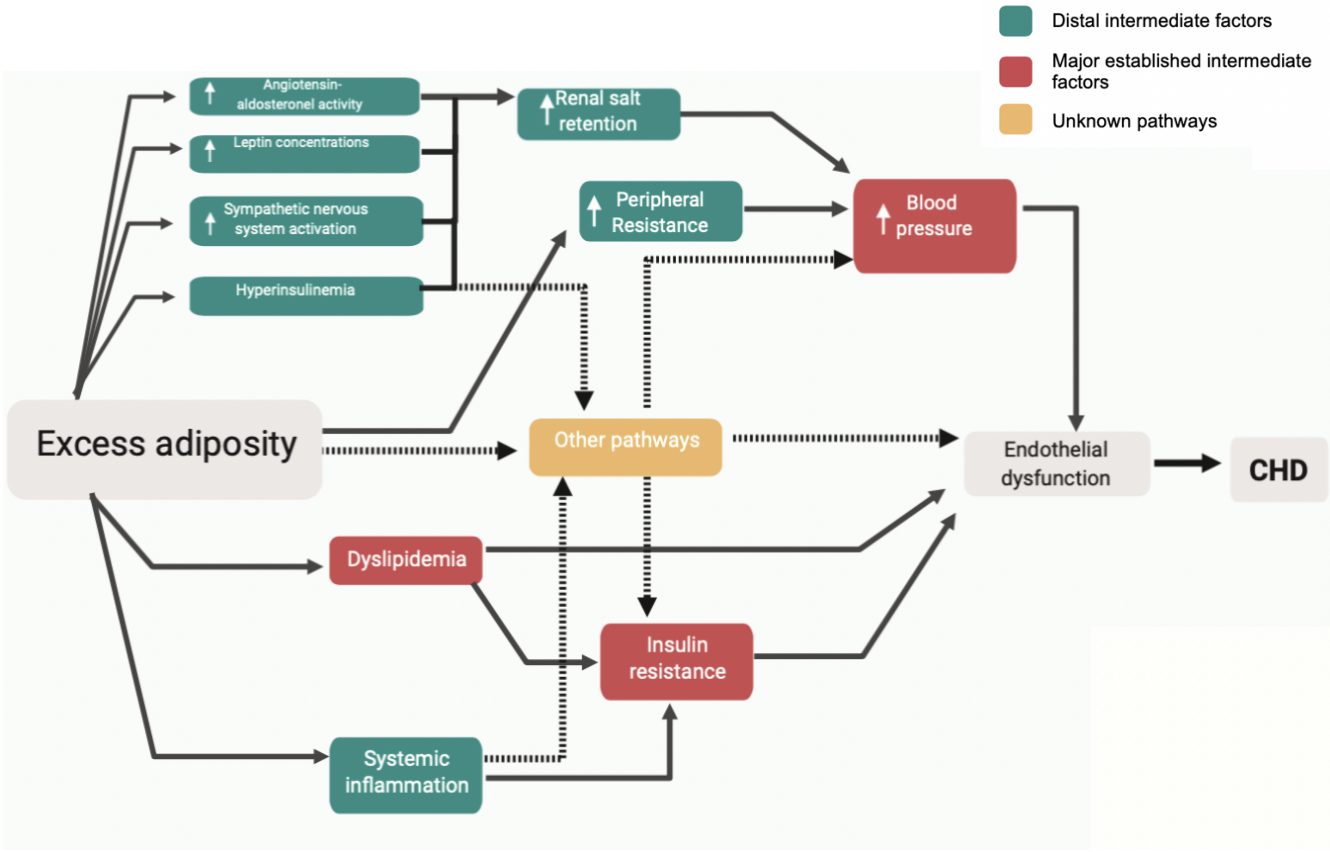
### 4.5 Conclusion

In summary, all six adiposity measures were strongly correlated with each other and with various socio-demographic, lifestyle and biological characteristics at baseline. Although in general, associations were similar between adiposity measures, there were important differences between general and central adiposity measures for some characteristics, in particular between WHR and BMI, which showed contrasting associations with current smoking and alcohol consumption, for example. Furthermore, there were unexplained sex differences in adiposity correlates at baseline, and therefore it is important to investigate adiposity-related CHD risk separately for men and women. The selected adiposity measures at baseline were similarly associated with blood-based cardiometabolic traits, providing further evidence for the potential roles of blood pressure, cholesterol, insulin resistance and inflammation underlying adiposity-related CHD risk, and highlighting some potential emerging intermediate factors such as kidney and liver function.

**Chapter 4 Tables and Figures**


| Figure/Table | Title |
|---|---|
| **Figure 4.1** | Established and emerging pathways involved in the association between adiposity and CHD |
| **Table 4.1** | Partial correlation coefficients between adiposity measures at baseline, by sex |
| **Figure 4.2** | Mean increase in adiposity measure per increasing fifth of baseline BMI, by sex |
| **Table 4.2** | Mean adiposity across selected demographic variables at baseline among men |
| **Table 4.3** | Mean adiposity across selected demographic variables at baseline among women |
| **Figure 4.3** | Mean adiposity by five-year age group and sex |
| **Table 4.4** | Mean adiposity across selected categorical variables at baseline, by sex |
| **Figure 4.4** | Mean adiposity by ethnicity and sex |
| **Figure 4.5** | Mean adiposity by geographical location and sex |
| **Figure 4.6** | Mean prevalence of obesity across UK recruitment centres as defined by conventional thresholds of anthropometry, by sex |
| **Figure 4.7** | Mean prevalence of obesity across UK recruitment centres as defined by conventional thresholds of anthropometry, by sex |
| **Figure 4.8** | Daily alcohol consumption and current smoking prevalence with increasing levels of adiposity at baseline, by sex |
| **Figure 4.9** | Self-reported versus screen-detected diabetes prevalence at baseline with increasing levels of adiposity, by sex |
| **Figure 4.10** | Baseline adiposity and systolic blood pressure before and after removing participants on blood pressure-lowering medication |
| **Figure 4.11** | Baseline adiposity and diastolic blood pressure before and after excluding participants on blood pressure-lowering medication |
| **Figure 4.12** | Cross-sectional associations of baseline adiposity with LDL-C and HDL-C in the UK Biobank, by sex |
| **Figure 4.13** | Cross-sectional associations of baseline adiposity with Apo-lipoprotein A and Apo-lipoprotein B, by sex |
| **Figure 4.14** | Cross-sectional associations of baseline adiposity with total cholesterol and triglyceride levels, by sex |
| **Figure 4.15** | Cross-sectional associations of baseline adiposity with Lp(a) levels in the UK Biobank, by sex |
| **Figure 4.16** | Cross-sectional associations between baseline adiposity and markers of type-2 diabetes mellitus, by sex |
| **Figure 4.17** | Cross-sectional associations between baseline adiposity and inflammatory markers in the UK Biobank, by sex |
| **Figure 4.18** | Glomerular filtration rate (GFR) with increasing levels of adiposity among men and women without prior cardiovascular disease at recruitment in the UK Biobank |
| **Figure 7.19** | Cross-sectional associations between baseline adiposity and liver enzyme levels in the UK Biobank, by sex |

**Figure 4.1** Established and emerging pathways involved in the association between adiposity and CHD



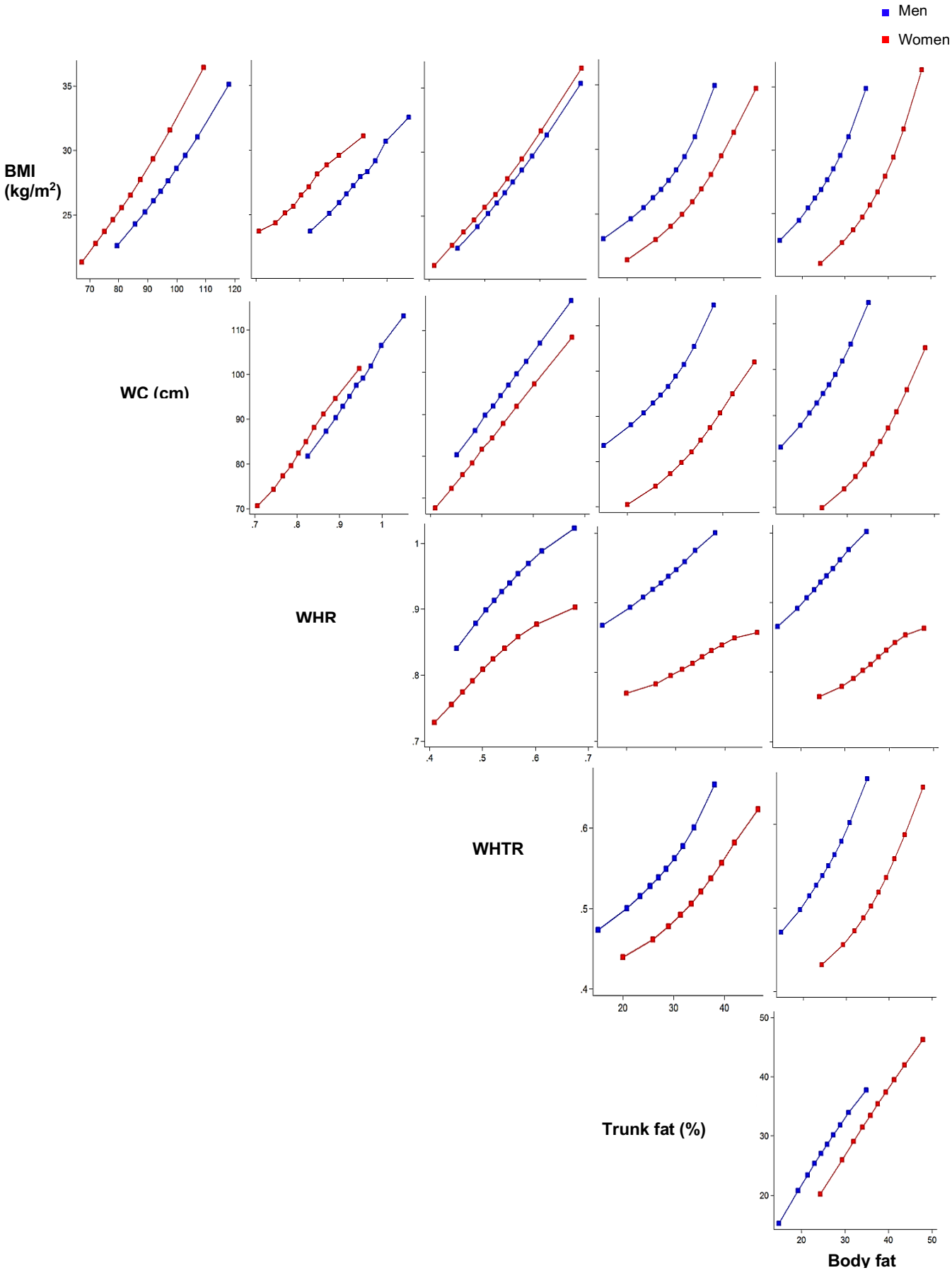

CHD = coronary heart disease. Solid lines represent established pathways and dotted lines represent unknown or emerging pathways from adiposity to endothelial dysfunction and subsequent.

**Table 4.1** Partial correlation coefficients between adiposity measures at baseline, by sex

| | | Body fat % | | WC | | WHR | | WHTR | | Trunk fat % | | HC | | Height | | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **BMI** | Men: | 0.803 | Men: | 0.876 | Men: | 0.600 | Men: | 0.889 | Men: | 0.767 | Men: | 0.816 | Men: | -0.035 | Men: | 0.884 |
| | Women: | 0.852 | Women: | 0.872 | Women: | 0.448 | Women: | 0.883 | Women: | 0.758 | Women: | 0.887 | Women: | -0.091 | Women: | 0.918 |
| **Body fat %** | | | Men: | 0.790 | Men: | 0.610 | Men: | 0.810 | Men: | 0.987 | Men: | 0.679 | Men: | -0.055 | Men: | 0.699 |
| | | | Women: | 0.812 | Women: | 0.437 | Women: | 0.787 | Women: | 0.979 | Women: | 0.818 | Women: | 0.047 | Women: | 0.831 |
| **WC** | | | | | Men: | 0.796 | Men: | 0.943 | Male: | 0.761 | Men: | 0.829 | Men: | 0.171 | Men: | 0.870 |
| | | | | | Women: | 0.743 | Women: | 0.966 | Female: | 0.749 | Women: | 0.822 | Women: | 0.073 | Women: | 0.862 |
| **WHR** | | | | | | | Men: | 0.808 | Men: | 0.591 | Men: | 0.324 | Men: | -0.028 | Men: | 0.530 |
| | | | | | | | Women: | 0.743 | Women: | 0.391 | Women: | 0.227 | Women: | -0.055 | Women: | 0.403 |
| **WHTR** | | | | | | | | | Men: | 0.779 | Men: | 0.731 | Men: | -0.164 | Men: | 0.724 |
| | | | | | | | | | Women: | 0.696 | Women: | 0.771 | Women: | -0.188 | Women: | 0.768 |
| **Trunk fat %** | | | | | | | | | | | Men: | 0.651 | Men: | -0.054 | Men: | 0.667 |
| | | | | | | | | | | | Women: | 0.765 | Women: | 0.163 | Women: | 0.784 |
| **HC** | | | | | | | | | | | | | Men: | 0.296 | Men: | 0.871 |
| | | | | | | | | | | | | | Women: | 0.151 | Women: | 0.907 |
| **Height** | | | | | | | | | | | | | | | Men: | 0.430 |
| | | | | | | | | | | | | | | | Women: | 0.303 |

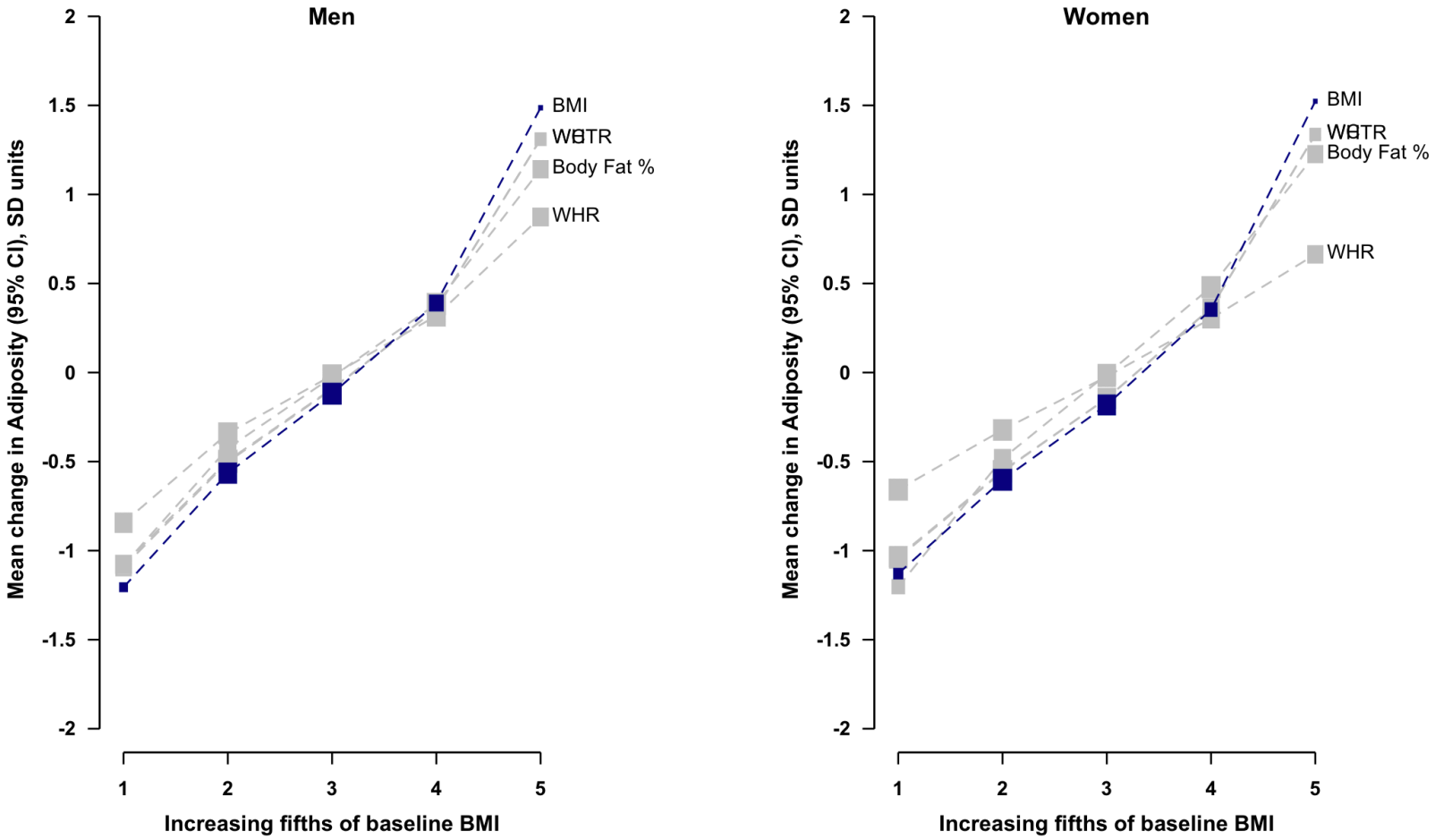
Pearson partial correlations were adjusted for age group (5-year groups), region (10 groups), educational (5 groups), ethnicity (7 groups), deprivation (fifths), alcohol consumption (5 groups) and smoking (3 groups). Analysis excludes participants with a history of cardiovascular disease and those with outlying/implausible or missing adiposity variables at baseline assessment.

**Figure 4.2** Mean change in adiposity with increasing tenths of each adiposity measure




BMI: Body-mass Index; WC: Waist circumference; WHTR: Waist-to-height ratio; WHR: Waist-to-hip-ratio

**Figure 4.3** Mean increase in adiposity measure per increasing fifth of baseline BMI, by sex




· BMI: Body-mass Index; WC: Waist circumference; WHTR: Waist-to-height ratio; WHR: Waist-to-hip-ratio. Mean (95% CI) values were directly standardised to age at baseline (5-year groups), education (5 groups), deprivation (fifths), region (10 groups), ethnicity (7 groups), alcohol consumption (5 groups) and smoking habits (3 groups). Axes represent +/- 2 standard deviations (SD) from the sex-specific value of each adiposity measure. Analysis excluded participants with a history of diagnosis of cardiovascular disease or outlying/missing adiposity variables at baseline.

**Table 4.2** Mean adiposity across selected demographic variables at baseline among men

| | | General adiposity | | Central adiposity | | | |
|---|---|---|---|---|---|---|---|
| **Characteristic** | **N** | **BMI (kg/m$^2$)** | **Body fat (%)** | **Trunk fat (%)** | **WC (cm)** | **WHR** | **WHTR** |
| **Age, years** | | | | | | | |
| 40 - 44 | 22973 | 27.4 (4.2) | 23.2 (5.6) | 25.4 (6.4) | 94.2 (10.8) | 0.91 (0.06) | 0.53 (0.06) |
| 45 - 49 | 27731 | 27.6 (4.2) | 23.9 (5.6) | 26.2 (6.4) | 95.2 (11.0) | 0.92 (0.06) | 0.54 (0.06) |
| 50 - 54 | 30583 | 27.8 (4.2) | 24.7 (5.6) | 27.0 (6.4) | 96.4 (11.2) | 0.93 (0.06) | 0.55 (0.06) |
| 55 - 59 | 35832 | 27.8 (4.2) | 25.2 (5.7) | 27.6 (6.5) | 97.0 (11.1) | 0.94 (0.06) | 0.55 (0.06) |
| 60 - 64 | 47061 | 27.7 (4.0) | 25.7 (5.5) | 28.2 (6.4) | 97.3 (10.8) | 0.94 (0.06) | 0.56 (0.06) |
| 65 - 69 | 36459 | 27.6 (3.8) | 26.3 (5.5) | 28.8 (6.4) | 97.5 (10.6) | 0.95 (0.06) | 0.56 (0.06) |
| **Highest qualification** | | | | | | | |
| Higher education | 96518 | 27.3 (3.9) | 24.5 (5.6) | 26.8 (6.5) | 95.5 (10.7) | 0.93 (0.06) | 0.54 (0.06) |
| AS/A-Level | 20980 | 27.6 (4.1) | 24.8 (5.6) | 27.3 (6.5) | 96.4 (10.9) | 0.93 (0.06) | 0.55 (0.06) |
| GCSE/O-Level | 48340 | 28.0 (4.1) | 25.3 (5.5) | 27.6 (6.3) | 97.1 (11.0) | 0.94 (0.06) | 0.55 (0.06) |
| Other | 31009 | 28.4 (4.3) | 26.6 (5.7) | 28.9 (6.5) | 98.7 (11.4) | 0.95 (0.06) | 0.57 (0.07) |
| Missing | 3792 | 27.9 (4.2) | 25.4 (5.8) | 27.8 (6.6) | 97.6 (11.2) | 0.94 (0.06) | 0.56 (0.06) |
| **Region** | | | | | | | |
| London | 27223 | 27.3 (4.1) | 24.5 (5.8) | 27.1 (6.6) | 95.8 (11.2) | 0.93 (0.07) | 0.54 (0.06) |
| South East | 17568 | 27.2 (3.9) | 24.0 (5.6) | 26.2 (6.5) | 97.0 (10.5) | 0.93 (0.06) | 0.55 (0.06) |
| South West | 17242 | 27.4 (4.0) | 24.1 (5.7) | 26.2 (6.6) | 96.0 (11.0) | 0.93 (0.06) | 0.54 (0.06) |
| East Midlands | 13534 | 27.7 (4.0) | 24.8 (5.7) | 27.1 (6.5) | 97.3 (11.0) | 0.93 (0.06) | 0.55 (0.06) |
| West Midlands | 18903 | 27.9 (4.1) | 25.5 (5.6) | 27.8 (6.3) | 97.0 (11.1) | 0.94 (0.06) | 0.55 (0.06) |
| Yorkshire & Humber | 29640 | 27.8 (4.0) | 25.1 (5.6) | 27.5 (6.5) | 97.2 (11.0) | 0.94 (0.06) | 0.55 (0.06) |
| North West | 31396 | 27.9 (4.2) | 25.6 (5.7) | 28.0 (6.4) | 96.2 (11.1) | 0.93 (0.06) | 0.55 (0.06) |
| North East | 22918 | 28.0 (4.1) | 25.6 (5.5) | 28.0 (6.2) | 96.5 (10.5) | 0.93 (0.06) | 0.55 (0.06) |
| Wales | 8392 | 28.2 (4.2) | 25.8 (5.7) | 28.1 (6.4) | 97.7 (11.0) | 0.94 (0.06) | 0.56 (0.06) |
| Scotland | 13823 | 27.6 (4.1) | 25.4 (5.6) | 27.8 (6.4) | 95.0 (10.7) | 0.92 (0.06) | 0.54 (0.06) |
| **Ethnicity** | | | | | | | |
| White | 188832 | 27.7 (4.1) | 25.0 (5.7) | 27.4 (6.5) | 96.6 (11.0) | 0.93 (0.06) | 0.55 (0.06) |
| South Asian | 4338 | 26.9 (3.7) | 25.9 (5.0) | 28.6 (5.6) | 95.1 (10.1) | 0.95 (0.06) | 0.56 (0.06) |
| Black | 3097 | 28.3 (4.2) | 25.2 (5.6) | 27.5 (6.4) | 94.4 (10.8) | 0.91 (0.06) | 0.54 (0.06) |
| Chinese | 541 | 25.1 (3.0) | 21.1 (4.9) | 23.6 (6.1) | 87.3 (8.5) | 0.90 (0.06) | 0.52 (0.05) |
| Mixed | 998 | 27.6 (4.4) | 24.4 (6.0) | 26.6 (6.8) | 94.7 (11.4) | 0.92 (0.07) | 0.54 (0.07) |
| Other ethnicity | 1737 | 27.8 (3.9) | 25.1 (5.5) | 27.6 (6.2) | 95.4 (10.6) | 0.93 (0.06) | 0.56 (0.06) |
| Missing | 1096 | 27.8 (4.3) | 25.1 (6.0) | 27.5 (6.9) | 96.9 (11.6) | 0.94 (0.07) | 0.56 (0.07) |
| **Deprivation index (fifths)** | | | | | | | |
| One (most affluent) | 40447 | 27.5 (3.7) | 24.8 (5.4) | 27.1 (6.2) | 96.0 (10.2) | 0.93 (0.06) | 0.54 (0.06) |
| Two | 40082 | 27.6 (3.9) | 24.9 (5.5) | 27.2 (6.3) | 96.2 (10.5) | 0.93 (0.06) | 0.55 (0.06) |
| Three | 39466 | 27.7 (4.0) | 25.1 (5.6) | 27.4 (6.4) | 96.6 (10.7) | 0.93 (0.06) | 0.55 (0.06) |
| Four | 39379 | 27.8 (4.2) | 25.1 (5.7) | 27.4 (6.6) | 96.7 (11.2) | 0.93 (0.06) | 0.55 (0.06) |
| Five (least affluent) | 41002 | 27.9 (4.6) | 25.4 (6.1) | 27.8 (6.9) | 97.0 (12.0) | 0.94 (0.07) | 0.56 (0.07) |

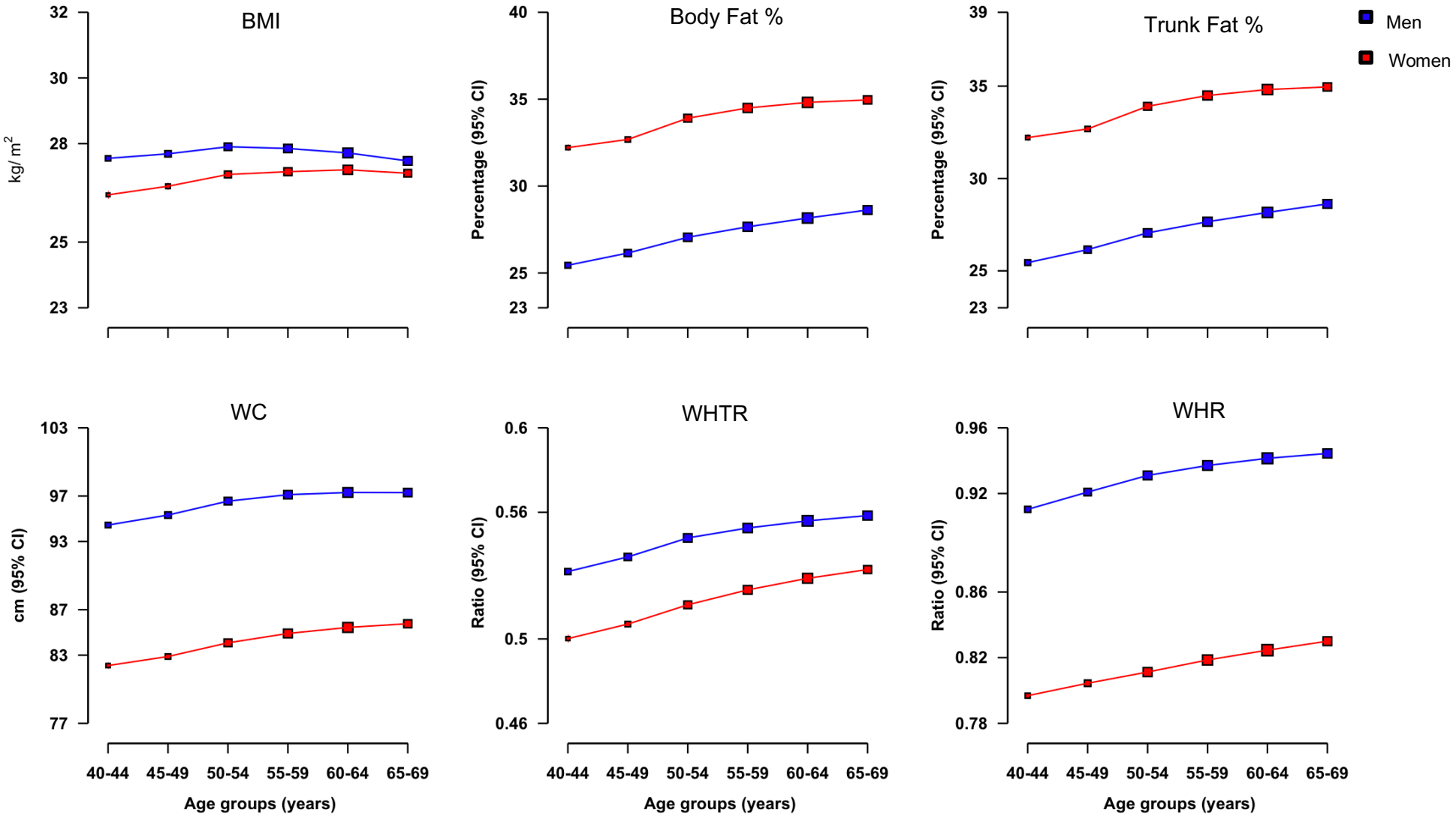
Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment. BMI= Body-mass Index; WC= waist circumference; WHR= Waist-to-hip ratio; WHTR= Waist-to-height ratio.

**Table 4.3** Mean adiposity across selected demographic variables at baseline among women

| | | General adiposity | | Central adiposity | | | |
|---|---|---|---|---|---|---|---|
| | N | BMI (kg/m$^2$) | Body fat (%) | Trunk fat (%) | WC (cm) | WHR | WHTR |
| **Age, years** | | | | | | | |
| 40 - 44 | 26727 | 26.4 (5.3) | 34.6 (7.2) | 32.1 (8.2) | 81.9 (12.3) | 0.80 (0.07) | 0.50 (0.08) |
| 45 - 49 | 35453 | 26.6 (5.3) | 35.1 (7.1) | 32.6 (8.0) | 82.7 (12.4) | 0.80 (0.07) | 0.51 (0.08) |
| 50 - 54 | 41402 | 27.0 (5.2) | 36.2 (6.9) | 33.8 (7.8) | 84.0 (12.5) | 0.81 (0.07) | 0.52 (0.08) |
| 55 - 59 | 47848 | 27.1 (5.1) | 36.8 (6.7) | 34.4 (7.5) | 84.8 (12.4) | 0.82 (0.07) | 0.52 (0.08) |
| 60 - 64 | 61141 | 27.2 (4.9) | 37.3 (6.4) | 34.9 (7.3) | 85.4 (12.0) | 0.82 (0.07) | 0.53 (0.08) |
| 65 - 69 | 41938 | 27.2 (4.6) | 37.6 (6.2) | 35.1 (7.0) | 85.9 (11.6) | 0.83 (0.07) | 0.53 (0.07) |
| **Highest qualification** | | | | | | | |
| Higher education | 106033 | 26.5 (4.9) | 35.7 (6.9) | 33.3 (7.7) | 83.2 (12.0) | 0.81 (0.07) | 0.51 (0.08) |
| AS/A-Level | 30220 | 26.7 (5.0) | 35.9 (6.8) | 33.5 (7.7) | 83.5 (12.1) | 0.81 (0.07) | 0.51 (0.08) |
| GCSE/O-Level | 73111 | 27.2 (5.1) | 36.9 (6.6) | 34.4 (7.5) | 84.8 (12.3) | 0.82 (0.07) | 0.52 (0.08) |
| Other | 40440 | 28.1 (5.1) | 38.3 (6.3) | 35.8 (7.3) | 87.3 (12.3) | 0.84 (0.07) | 0.55 (0.08) |
| Missing | 4705 | 27.6 (5.3) | 37.2 (6.8) | 34.6 (7.7) | 86.5 (12.6) | 0.83 (0.07) | 0.54 (0.08) |
| **Region** | | | | | | | |
| London | 35944 | 26.5 (5.1) | 35.7 (7.0) | 33.2 (7.8) | 84.1 (12.5) | 0.82 (0.07) | 0.52 (0.08) |
| South East | 23005 | 26.4 (4.8) | 35.2 (6.8) | 32.6 (7.6) | 84.5 (12.0) | 0.81 (0.07) | 0.52 (0.08) |
| South West | 22904 | 26.6 (5.0) | 35.8 (6.8) | 33.2 (7.6) | 83.5 (12.2) | 0.81 (0.07) | 0.51 (0.08) |
| East Midlands | 17301 | 27.0 (5.1) | 36.4 (6.7) | 33.9 (7.5) | 85.4 (12.3) | 0.82 (0.07) | 0.53 (0.08) |
| West Midlands | 21263 | 27.4 (5.2) | 37.0 (6.7) | 34.5 (7.5) | 85.1 (12.8) | 0.82 (0.07) | 0.53 (0.08) |
| Yorkshire & Humber | 37589 | 27.0 (5.0) | 36.8 (6.8) | 34.6 (7.8) | 84.6 (12.1) | 0.81 (0.07) | 0.52 (0.08) |
| North West | 38345 | 27.3 (5.1) | 37.2 (6.6) | 34.7 (7.5) | 84.4 (12.2) | 0.82 (0.07) | 0.52 (0.08) |
| North East | 29209 | 27.3 (5.0) | 37.1 (6.5) | 34.6 (7.4) | 84.6 (12.0) | 0.82 (0.07) | 0.52 (0.08) |
| Wales | 10585 | 27.6 (5.3) | 37.4 (6.7) | 34.8 (7.6) | 85.8 (12.5) | 0.82 (0.07) | 0.53 (0.08) |
| Scotland | 18364 | 26.9 (5.0) | 36.8 (6.8) | 34.4 (7.8) | 82.8 (11.9) | 0.81 (0.07) | 0.51 (0.08) |
| **Ethnicity** | | | | | | | |
| White | 240091 | 26.9 (5.0) | 36.4 (6.8) | 34.0 (7.6) | 84.3 (12.2) | 0.82 (0.07) | 0.52 (0.08) |
| South Asian | 4170 | 27.2 (4.8) | 37.7 (6.1) | 35.0 (7.2) | 86.2 (11.4) | 0.85 (0.07) | 0.55 (0.08) |
| Black | 4205 | 30.2 (5.8) | 39.6 (6.5) | 37.0 (7.4) | 91.1 (13.0) | 0.84 (0.07) | 0.56 (0.08) |
| Chinese | 934 | 23.5 (3.5) | 30.2 (5.9) | 26.8 (7.0) | 76.4 (8.9) | 0.81 (0.06) | 0.49 (0.06) |
| Mixed | 1738 | 27.1 (5.4) | 36.2 (7.1) | 33.5 (8.0) | 84.2 (12.8) | 0.82 (0.07) | 0.52 (0.08) |
| Other ethnicity | 2375 | 27.7 (5.6) | 36.7 (7.3) | 33.9 (8.3) | 85.9 (12.8) | 0.83 (0.07) | 0.54 (0.08) |
| Missing | 996 | 27.9 (5.6) | 37.1 (6.8) | 34.4 (7.5) | 86.8 (12.7) | 0.83 (0.07) | 0.54 (0.08) |
| **Deprivation index (fifths)** | | | | | | | |
| One (most affluent) | 50519 | 26.4 (4.6) | 35.9 (6.5) | 33.5 (7.4) | 82.9 (11.4) | 0.81 (0.07) | 0.51 (0.07) |
| Two | 50781 | 26.6 (4.7) | 36.2 (6.5) | 33.8 (7.4) | 83.5 (11.7) | 0.81 (0.07) | 0.51 (0.07) |
| Three | 51456 | 26.8 (4.9) | 36.4 (6.6) | 34.0 7.5.) | 84.0 (11.9) | 0.81 (0.07) | 0.52 (0.08) |
| Four | 51537 | 27.1 (5.2) | 36.6 (6.9) | 34.1 (7.7) | 84.9 (12.5) | 0.82 (0.07) | 0.52 (0.08) |
| Five (least affluent) | 49914 | 27.9 (5.8) | 37.3 (7.2) | 34.8 (7.2) | 86.8 (13.4) | 0.83 (0.07) | 0.54 (0.09) |

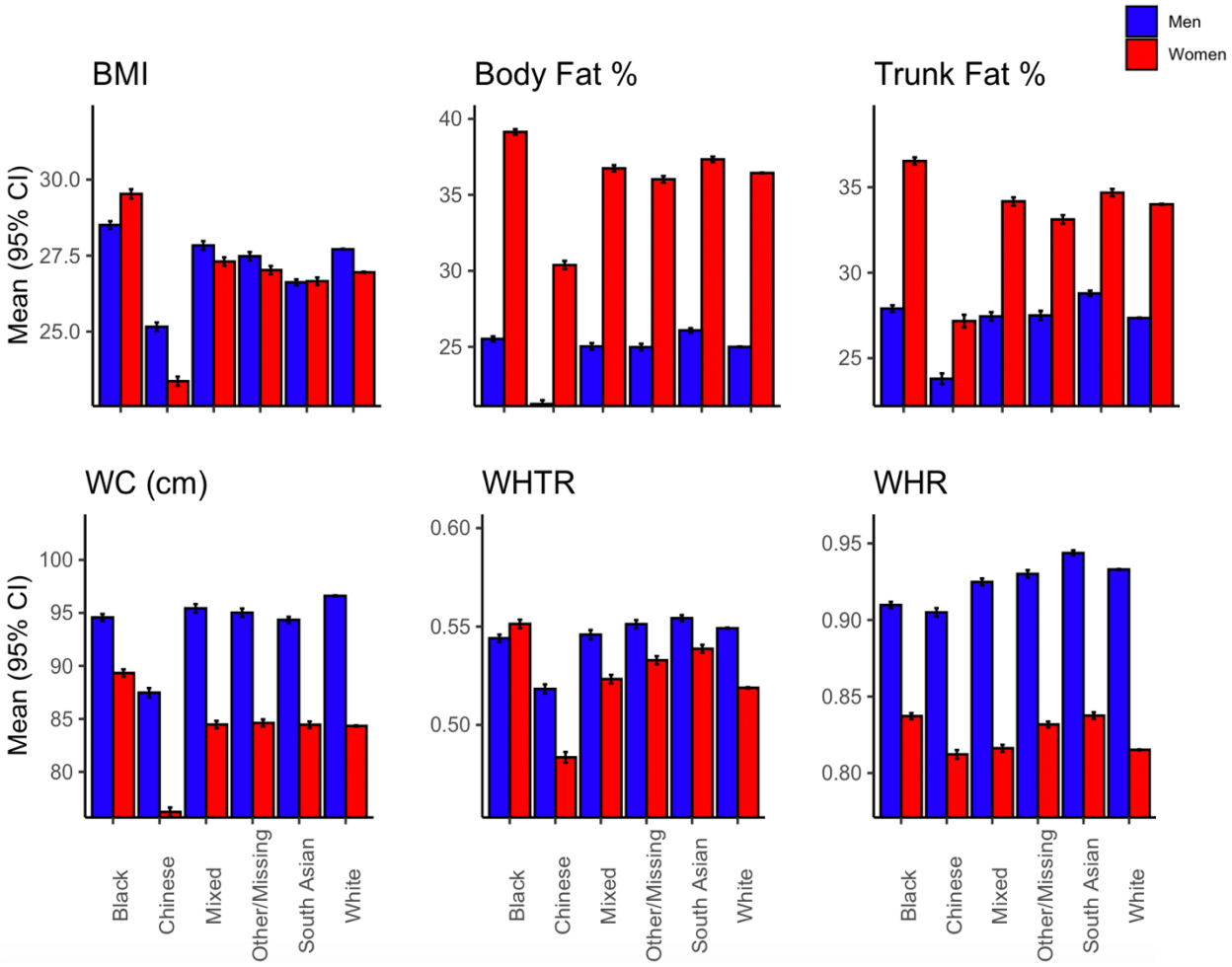
Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment. BMI= Body-mass Index; WC= waist circumference; WHR= Waist-to-hip ratio; WHTR= Waist-to-height ratio.

**Figure 4.4** Mean adiposity by five-year age group and sex



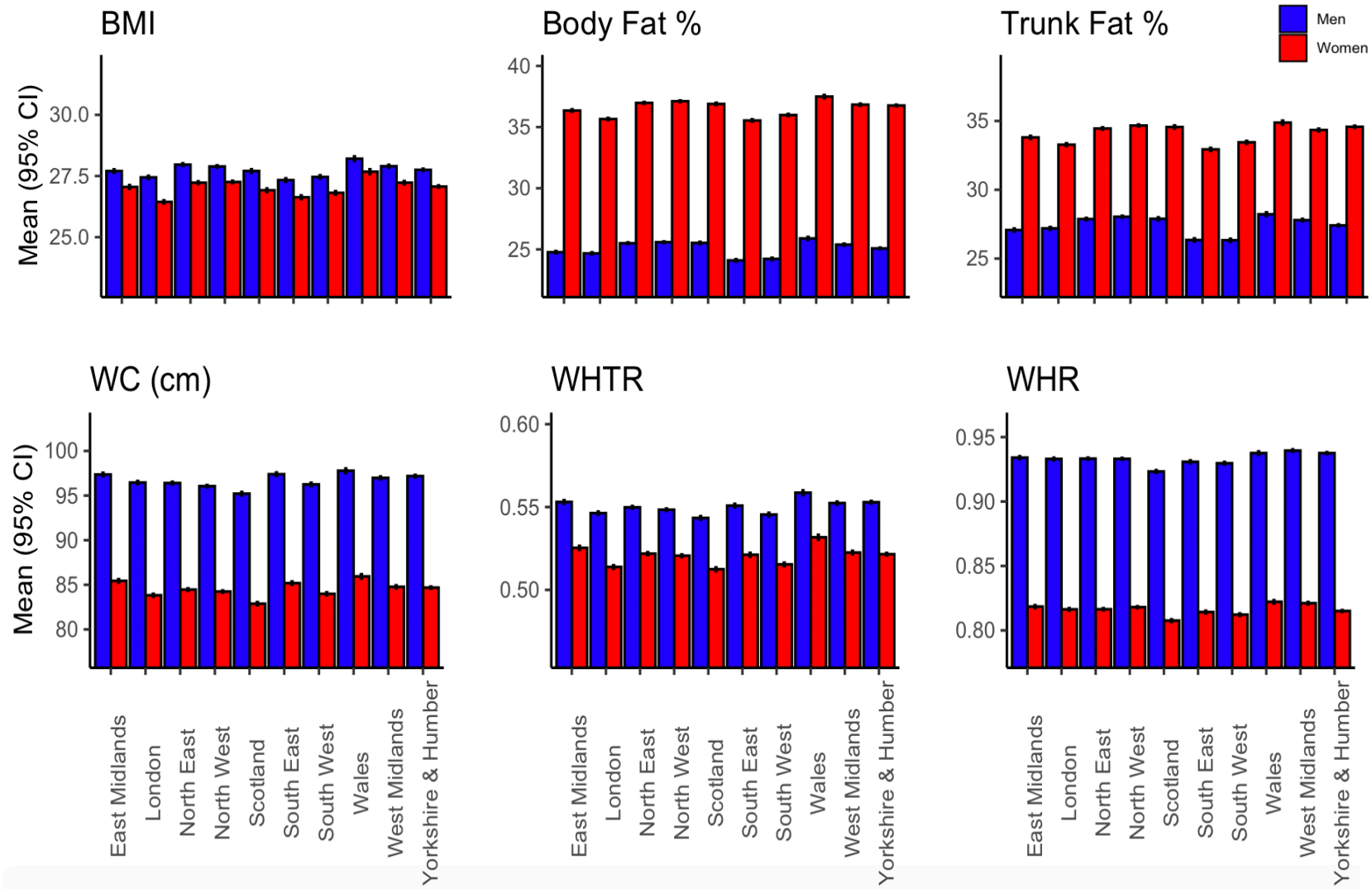

BMI= Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio. Points represent mean adiposity levels and corresponding 95% confidence intervals. Estimates are directly standardised to UK region, qualification attainment, deprivation index, smoking and alcohol consumption. Y-Axes were standardised to represent the average ±3 standard deviations from average of mean adiposity levels among men and women.

**Figure 4.5** Mean adiposity by ethnicity and sex



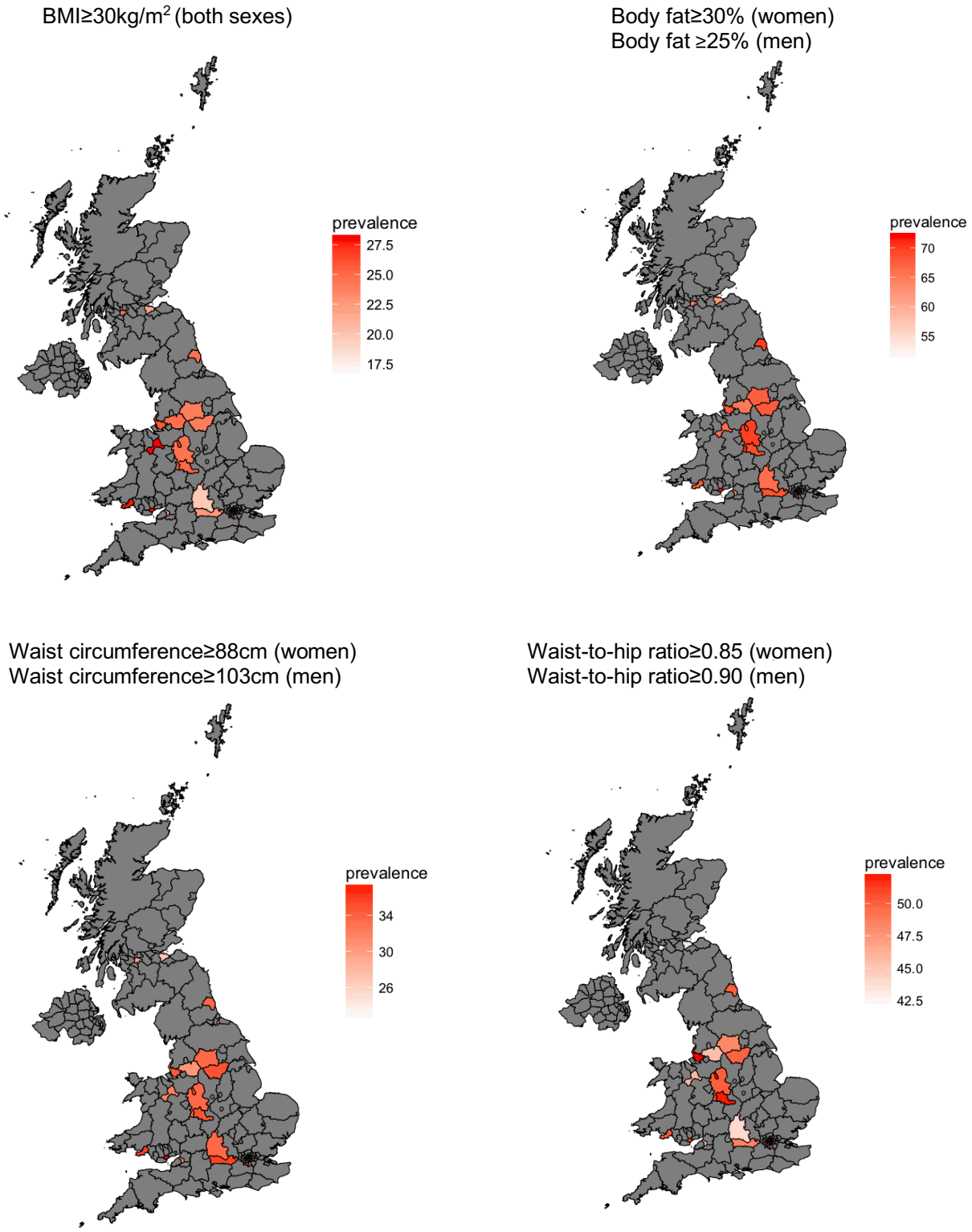

BMI= Body-mass index; WC = waist circumference; WHR= waist-to-hip ratio; WHTR= Waist-to-height ratio. Mean values (95% confidence intervals) represent the mean levels of adiposity per ethnic group among men and women without cardiovascular disease or missing/outlying adiposity measures at baseline. Estimates are directly standardised to age (5-year groups) UK region, qualification attainment, deprivation index, smoking habits and alcohol consumption. Y-axes are standardised to represent ±1 standard deviation from the average of mean adiposity values among men and women combined.

**Figure 4.6** Mean adiposity by geographic location and sex




BMI= Body-mass index; WC = waist circumference; WHR= waist-to-hip ratio; WHTR= Waist-to-height ratio. Mean values (95% confidence intervals) represent the mean levels of adiposity per ethnic group among men and women without cardiovascular disease or missing/outlying adiposity measures at baseline. Estimates are directly standardised to age (5-year groups), ethnicity, qualification attainment, deprivation index, smoking habits and alcohol consumption. Y-axes are standardised to represent ±1 standard deviation from the average of mean adiposity values among men and women combined.

**Figure 4.7** Mean prevalence of obesity across UK recruitment centers as defined by conventional thresholds of anthropometry, by sex



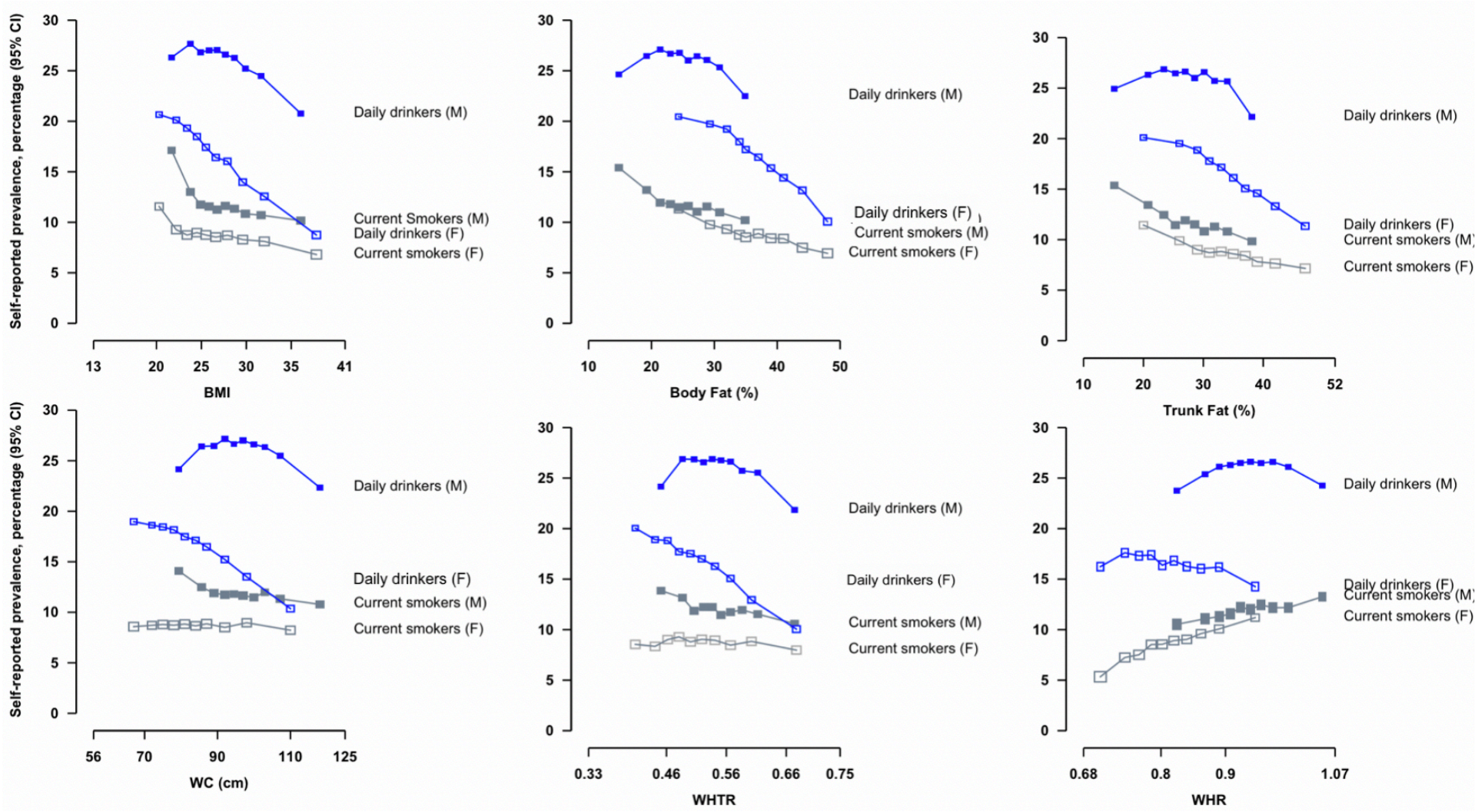

Thresholds are based on WHO definition of obesity, or where this was not available, the WHO recommended thresholds for optimum health were used. Analysis was restricted to participants with no missing or implausible adiposity variables at baseline, and those who did not self-report cardiovascular disease at baseline survey. Prevalence estimates were directly standardised to age at baseline (5-year groups), education (5 groups), ethnicity (7 groups), deprivation (5 groups), smoking (3 groups) and alcohol consumption (4 groups).

**Table 4.4** Mean adiposity across selected categorical variables at baseline, by sex

| | N | BMI (kg/m$^2$) | Body fat (%) | Trunk fat (%) | WC (cm) | WHR | WHTR |
|---|---|---|---|---|---|---|---|
| **MEN** | 200 639 | 27.7 (4.1) | 25.0 (5.7) | 27.4 (6.5) | 96.5 (11.0) | 0.93 (0.06) | 0.55 (0.06 |
| **Smoking habits** | | | | | | | |
| Current smoker | 24 360 | 27.2 (4.2) | 24.4 (5.9) | 26.6 (6.8) | 95.8 (11.2) | 0.94 (0.06) | 0.55 (0.06) |
| Former smoker | 73 878 | 28.2 (4.1) | 26.0 (5.5) | 28.4 (6.3) | 98.3 (10.9) | 0.94 (0.06) | 0.56 (0.06) |
| Never smoker | 101 417 | 27.4 (4.0) | 24.5 (5.6) | 26.8 (6.5) | 95.4 (10.8) | 0.92 (0.06) | 0.54 (0.06) |
| Missing | 984 | 28.4 (4.4) | 26.3 (5.9) | 28.8 (6.8) | 98.9 (11.7) | 0.95 (0.06) | 0.57 (0.06) |
| **Alcohol consumption** | | | | | | | |
| At least daily | 51 325 | 27.3 (3.7) | 24.9 (5.5) | 27.2 (6.3) | 96.2 (10.3) | 0.93 (0.06) | 0.55 (0.06) |
| Once to four times/week | 105 433 | 27.7 (4.0) | 25.0 (5.6) | 27.4 (6.4) | 96.4 (10.7) | 0.93 (0.06) | 0.55 (0.06) |
| Less than once a week | 31 709 | 28.2 (4.6) | 25.3 (6.1) | 27.6 (6.9) | 97.4 (12.2) | 0.94 (0.07) | 0.56 (0.07) |
| Never | 11 735 | 27.8 (4.6) | 25.4 (6.1) | 27.8 (6.9) | 96.9 (12.3) | 0.94 (0.07) | 0.56 (0.07) |
| Missing | 437 | 28.0 (4.8) | 25.5 (6.4) | 27.9 (7.3) | 97.7 (12.1) | 0.95 (0.07) | 0.57 (0.07) |
| **Physical Activity (MET/week )** | | | | | | | |
| Low, 0– <10 | 45 645 | 28.3 (4.4) | 26.3 (5.6) | 28.8 (6.3) | 98.9 (11.5) | 0.95 (0.06) | 0.56 (0.07) |
| Moderate, 10– <50 | 93 758 | 27.4 (3.9) | 24.7 (5.5) | 27.1 (6.4) | 95.8 (10.5) | 0.93 (0.06) | 0.54 (0.06) |
| High, ≥50 | 44 322 | 27.4 (3.8) | 24.1 (5.6) | 26.2 (6.5) | 94.8 (10.5) | 0.93 (0.06) | 0.54 (0.06) |
| Missing | 16 914 | 28.4 (4.6) | 26.0 (6.0) | 28.4 (6.8) | 98.6 (12.0) | 0.95 (0.07) | 0.56 (0.07) |
| **Sedentary Activity (hrs/week )** | | | | | | | |
| Low, <3 | 24 004 | 26.1 (3.6) | 22.5 (5.7) | 24.6 (6.7) | 94.2 (10.1) | 0.91 (0.06) | 0.52 (0.06) |
| Moderate, 3 - 6 | 119 554 | 27.5 (3.9) | 24.8 (5.5) | 27.2 (6.3) | 96.0 (10.5) | 0.93 (0.06) | 0.55 (0.06) |
| High, ≥7 | 52 154 | 28.8 (4.4) | 26.6 (5.6) | 29.1 (6.2) | 99.4 (11.5) | 0.95 (0.06) | 0.57 (0.07) |
| Missing | 4 927 | 28.3 (4.5) | 26.0 (5.9) | 28.4 (6.7) | 98.0 (11.8) | 0.95 (0.07) | 0.57 (0.07) |
| **WOMEN** | 254 509 | 27.0 (5.1) | 36.5 (6.8) | 34.0 (7.6) | 84.4 (12.3) | 0.82 (0.07) | 0.52 (0.08) |
| **Smoking habits** | | | | | | | |
| Current smoker | 22 128 | 26.6 (5.0) | 35.8 (7.0) | 33.2 (7.9) | 84.7 (12.4) | 0.83 (0.07) | 0.52 (0.08) |
| Former smoker | 79 010 | 27.3 (5.0) | 37.0 (6.7) | 34.6 (7.5) | 85.4 (12.3) | 0.82 (0.07) | 0.53 (0.08) |
| Never smoker | 152 177 | 26.9 (5.1) | 36.3 (6.8) | 33.9 (7.6) | 83.8 (12.2) | 0.81 (0.07) | 0.52 (0.08) |
| Missing | 1 194 | 28.2 (5.3) | 37.8 (7.3) | 35.1 (7.3) | 87.8 (12.6) | 0.84 (0.07) | 0.55 (0.08) |
| **Alcohol consumption** | | | | | | | |
| At least daily | 41 477 | 25.7 (4.2) | 35.1 (6.5) | 32.7 (7.4) | 82.3 (10.9) | 0.81 (0.07) | 0.51 (0.07) |
| Once to four times/week | 119 138 | 26.6 (4.6) | 36.1 (6.6) | 33.7 (7.5) | 83.3 (11.5) | 0.81 (0.07) | 0.51 (0.07) |
| Less than once a week | 70 573 | 28.1 (5.6) | 37.7 (6.9) | 35.2 (7.7) | 86.6 (13.3) | 0.82 (0.07) | 0.54 (0.08) |
| Never | 22 819 | 28.1 (5.8) | 37.7 (7.2) | 35.1 (8.1) | 87.0 (13.8) | 0.83 (0.07) | 0.54 (0.09) |
| Missing | 502 | 28.2 (5.6) | 37.5 (6.9) | 34.6 (7.7) | 88.2 (13.3) | 0.85 (0.08) | 0.55 (0.09) |
| **Physical Activity (MET/week)** | | | | | | | |
| Low, 0– <10 | 60 321 | 27.8 (5.4) | 37.8 (6.7) | 35.5 (7.5) | 86.6 (12.9) | 0.82 (0.07) | 0.53 (0.08) |
| Moderate, 10– <50 | 120 249 | 26.6 (4.8) | 36.0 (6.6) | 33.5 (7.5) | 83.4 (11.7) | 0.81 (0.07) | 0.51 (0.07) |
| High, ≥50 | 44 620 | 26.2 (4.5) | 35.0 (6.7) | 32.4 (7.6) | 82.3 (11.3) | 0.81 (0.07) | 0.51 (0.07) |
| Missing | 29 319 | 28.3 (5.7) | 38.1 (6.9) | 35.6 (7.8) | 87.5 (13.3) | 0.83 (0.07) | 0.54 (0.08) |
| **Sedentary Activity (hrs/week )** | | | | | | | |
| Low, <3 | 47 291 | 25.4 (4.5) | 34.0 (6.7) | 31.4 (7.7) | 80.3 (11.1) | 0.80 (0.07) | 0.50 (0.07) |
| Moderate, 3 - 6 | 163 415 | 27.0 (4.9) | 36.6 (6.6) | 34.2 (7.5) | 84.4 (12.0) | 0.82 (0.07) | 0.52 (0.08) |
| High, ≥7 | 36 015 | 28.8 (5.6) | 38.9 (6.6) | 36.5 (7.4) | 88.6 (13.2) | 0.83 (0.07) | 0.55 (0.08) |
| Missing | 7 788 | 28.3 (5.5) | 38.2 (6.7) | 35.5 (7.6) | 87.8 (0.07) | 0.84 (0.07) | 0.55 (0.08) |

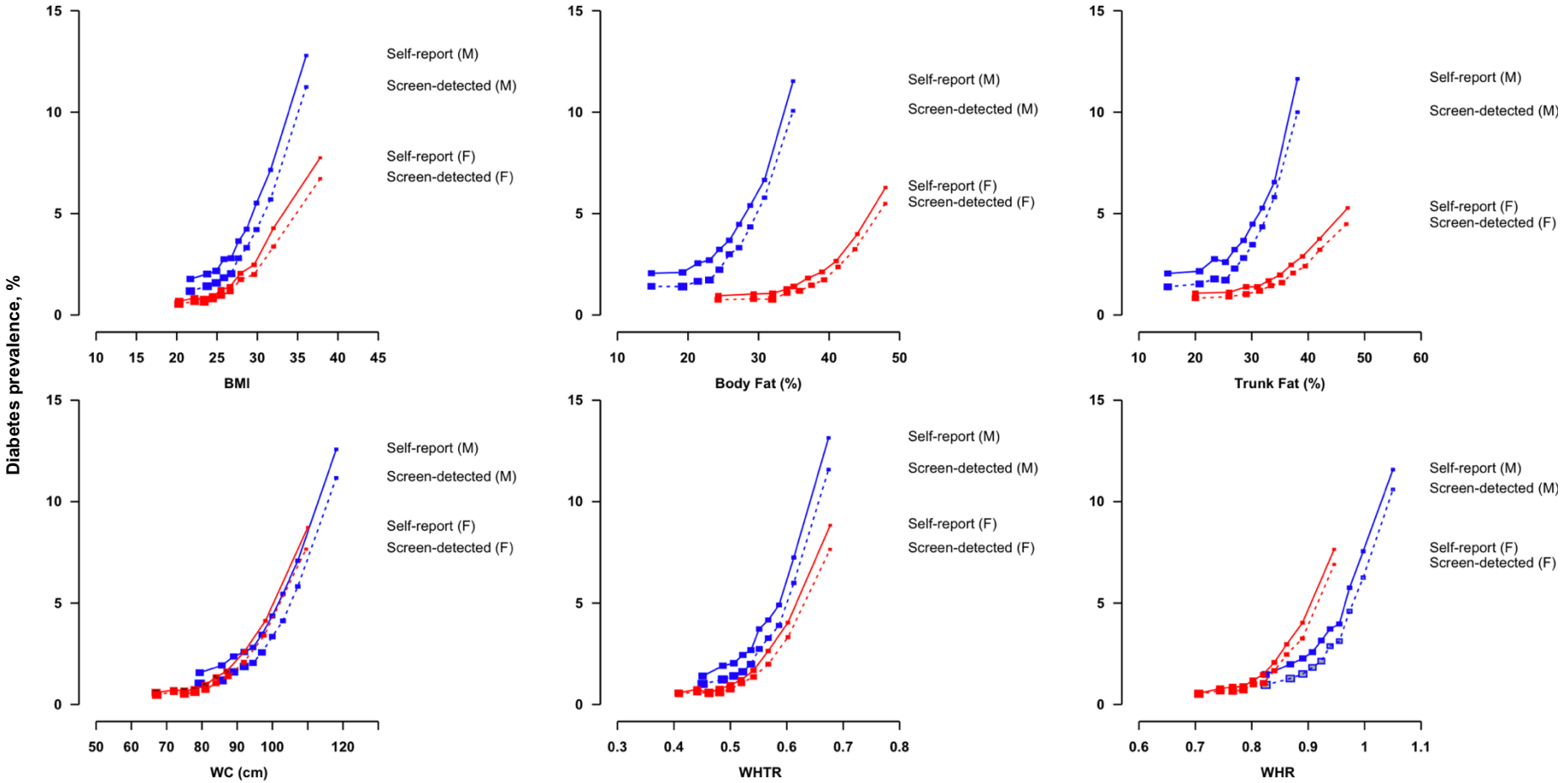
Participants were restricted to those without missing or outlying adiposity, and those without prior self-reported or medical history of cardiovascular disease at baseline assessment. BMI= Body-mass Index; WC= waist circumference; WHR= Waist-to-hip ratio; WHTR= Waist-to-height ratio; MET = Metabolic equivalent of task.

**Figure 4.8** Daily alcohol consumption and current smoking prevalence with increasing levels of adiposity at baseline, by sex



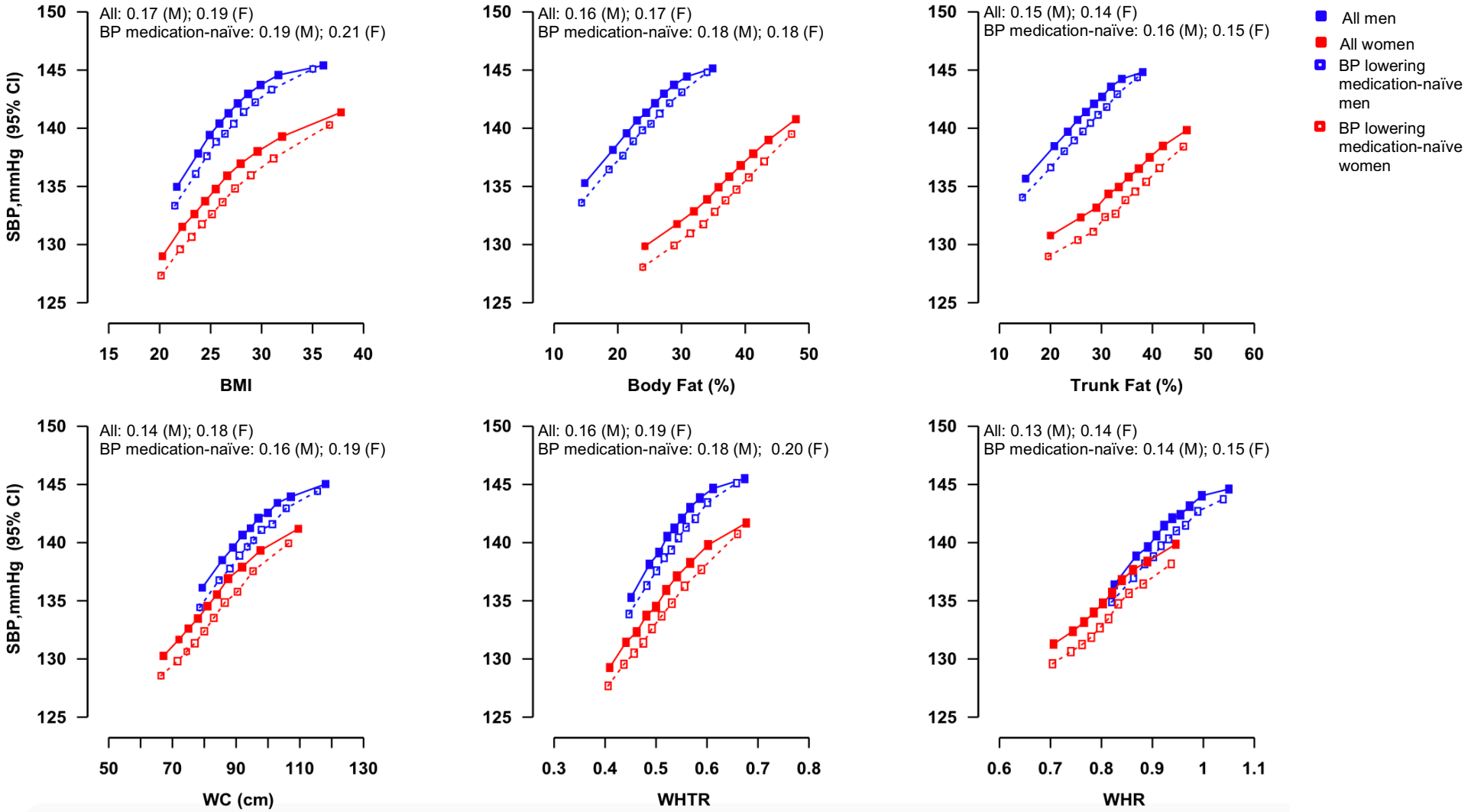

BMI= Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio. Points represent prevalence of self-reported daily alcohol consumption and current smoking habits, with corresponding 95% confidence intervals. Estimates are directly standardised to age (5-year groups), UK region, qualification attainment, ethnicity, deprivation index, smoking habits and alcohol consumption, where appropriate. X-axes are standardised to represent ±3 standard deviations from the average of mean adiposity values among men and women.

**Figure 4.9** Self-reported versus screen-detected diabetes prevalence* at baseline with increasing levels of adiposity, by sex



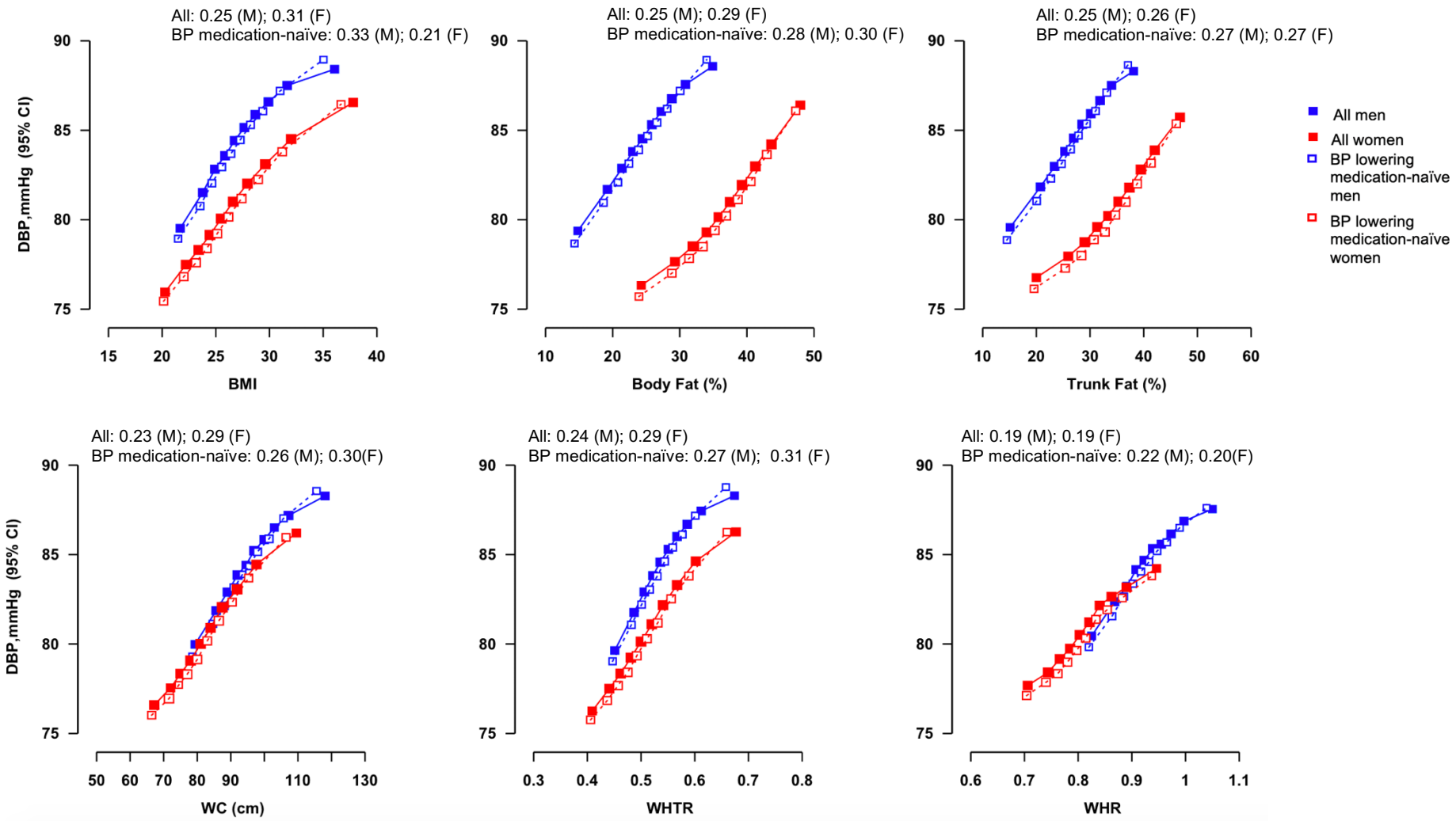

BMI= Body-mass index; WC = waist circumference; WHR= waist-to-hip ratio; WHTR= Waist-to-height ratio. Points represent prevalence of self-reported and screen-detected type II diabetes and corresponding 95% confidence intervals among UK Biobank men (M) and women (F) without cardiovascular disease or missing/outlying adiposity measures at baseline. Estimates are directly standardised to age (5-year groups) UK region, qualification attainment, ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males and females combined, adjusted for the same covariates. X-axes are standardised to represent ±3 standard deviations from the average of mean adiposity values among men and women.
*Screen-detected type II diabetes was defined as a HbA1c greater then 48mmol/mol (6.5%).

**Figure 4.10** Baseline adiposity and systolic blood pressure before and after removing participants on blood pressure-lowering medication



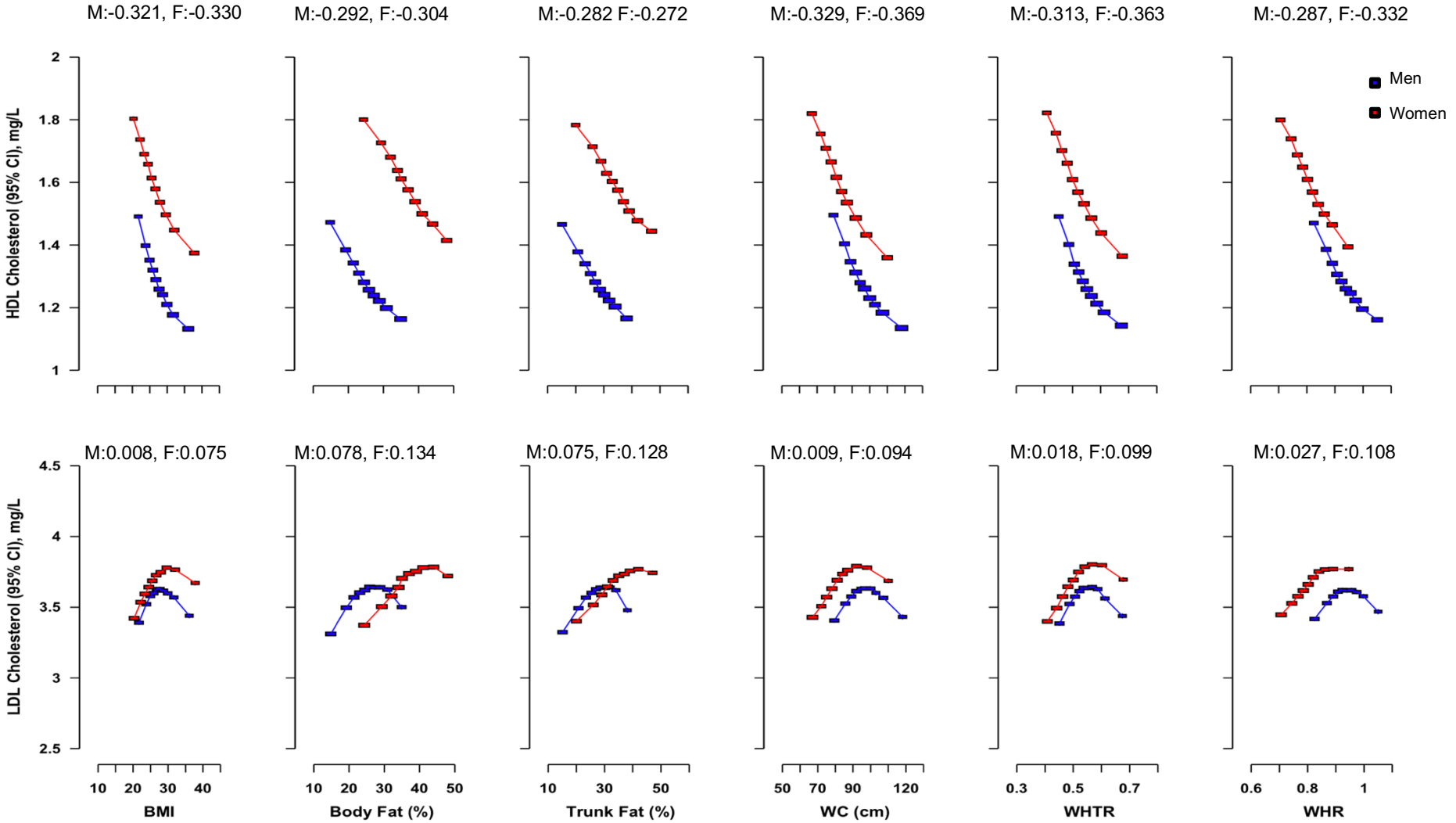

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio; SBP = systolic blood pressure; M= Male; F = Female. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males and females combined, adjusted for the same covariates. Analyses were restricted to 454 217 individuals without missing adiposity or SBP or history of cardiovascular disease at baseline, with additional exclusions of participants self-reporting use of blood pressure-lowering treatment (n = 78 430). Y-axes are standardised to represent ±0.5SD from the average of mean SBP among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.11** Baseline adiposity and diastolic blood pressure before and after excluding participants on blood pressure-lowering medication



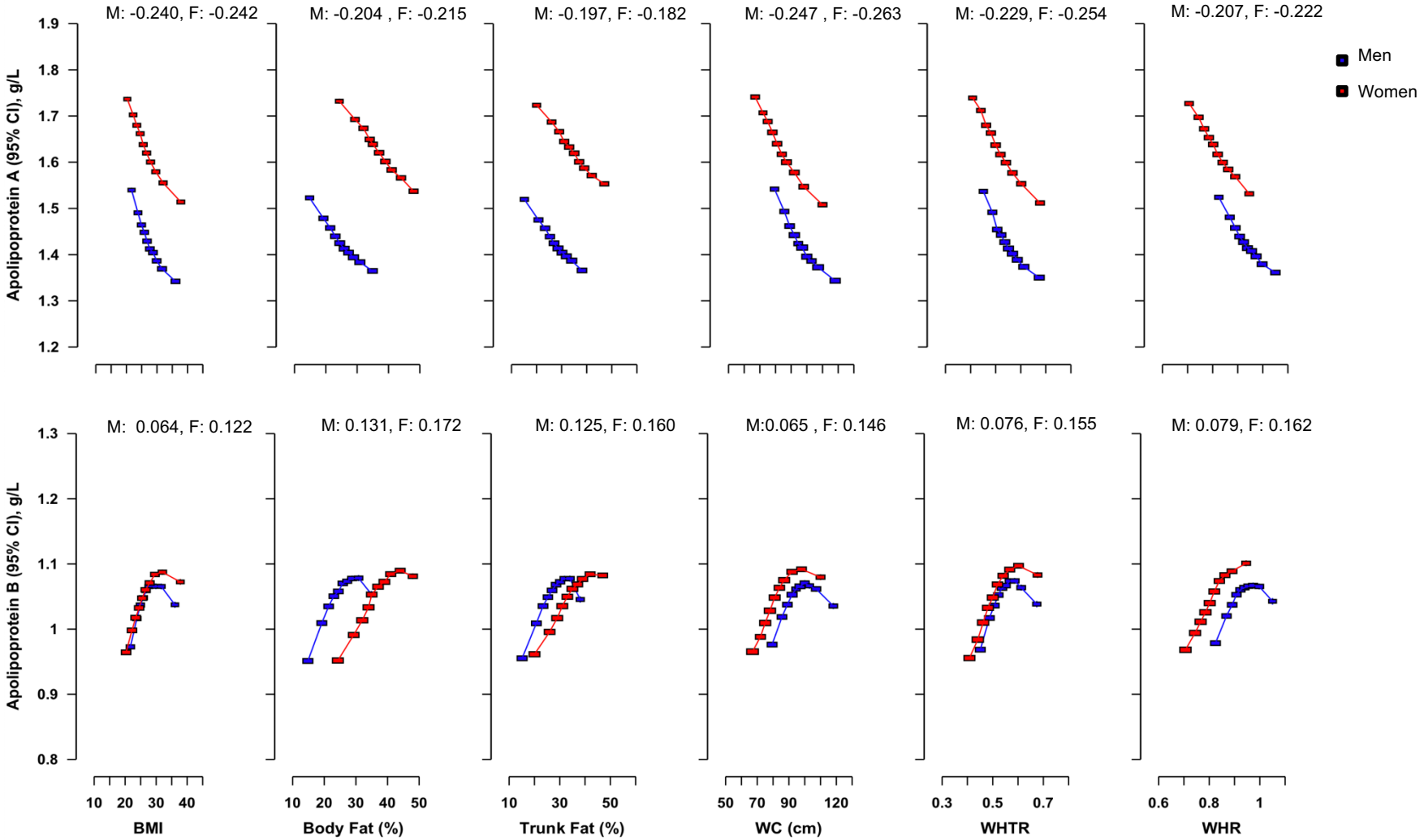

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio; DBP = systolic blood pressure; M= Male; F = Female. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males and females combined, adjusted for the same covariates. Analyses were restricted to 454 217 individuals without missing adiposity or SBP or a previous history of cardiovascular disease at baseline, with additional exclusions of participants self-reporting use of blood pressure-lowering treatment (n = 78 430). Y-axes are standardised to represent ±0.5SD from the average of mean DBP among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.12** Cross-sectional associations of baseline adiposity with LDL-C and HDL-C in the UK Biobank, by sex



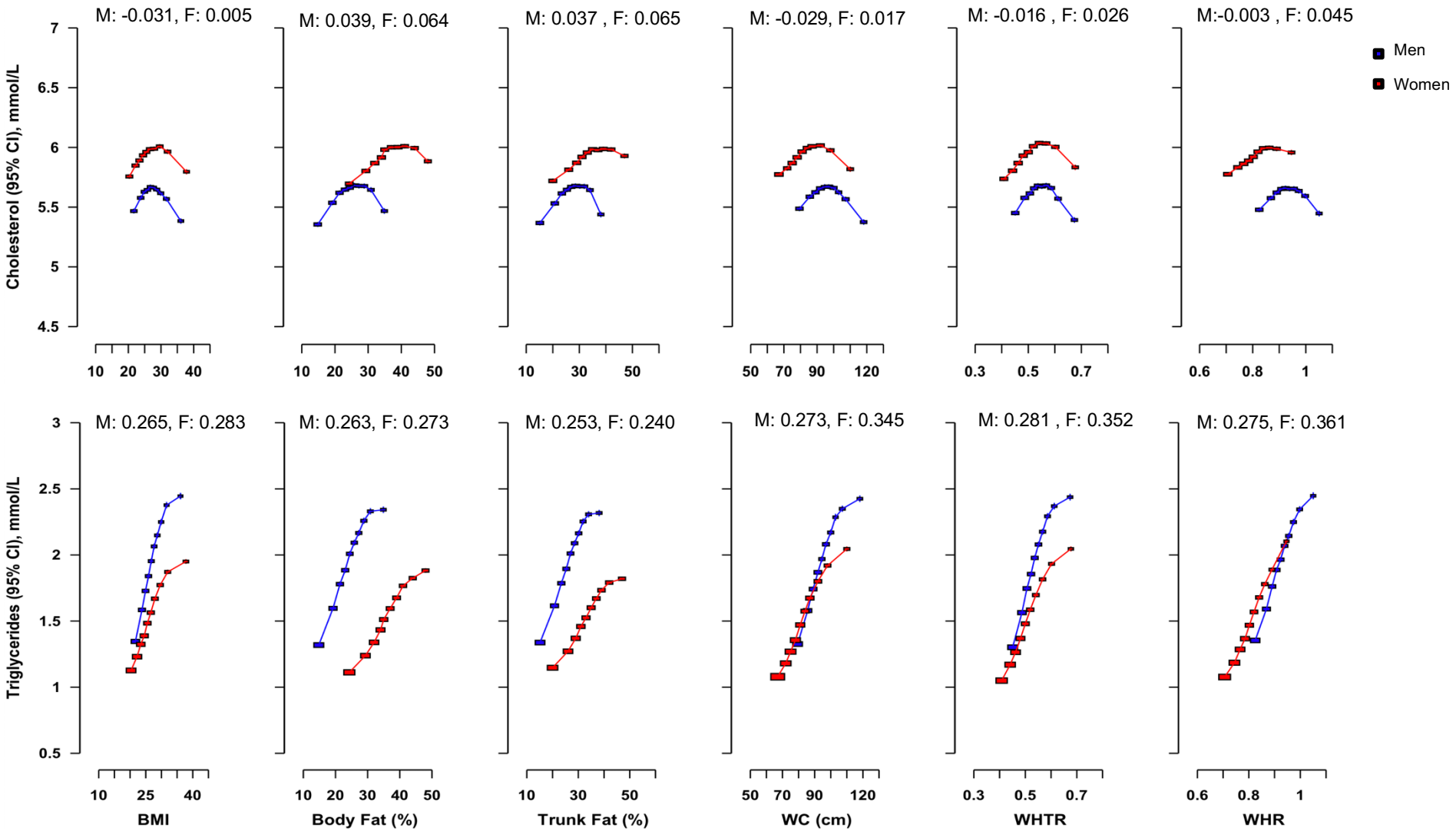

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio; HDL = High-density lipoprotein; LDL= Low-density lipoprotein. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean cholesterol levels among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.13** Cross-sectional associations of baseline adiposity with Apo-lipoprotein A and Apo-lipoprotein B, by sex



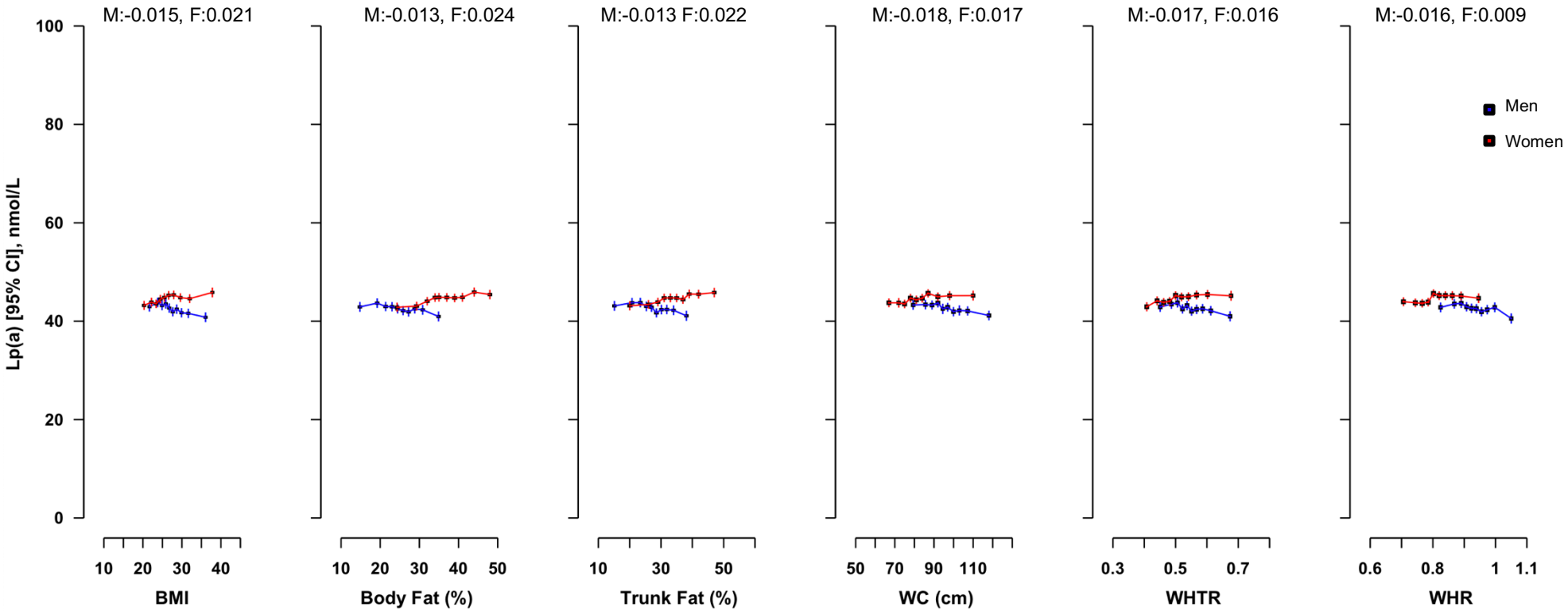

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables or history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean cholesterol levels among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.14** Cross-sectional associations of baseline adiposity with total cholesterol and triglyceride levels, by sex



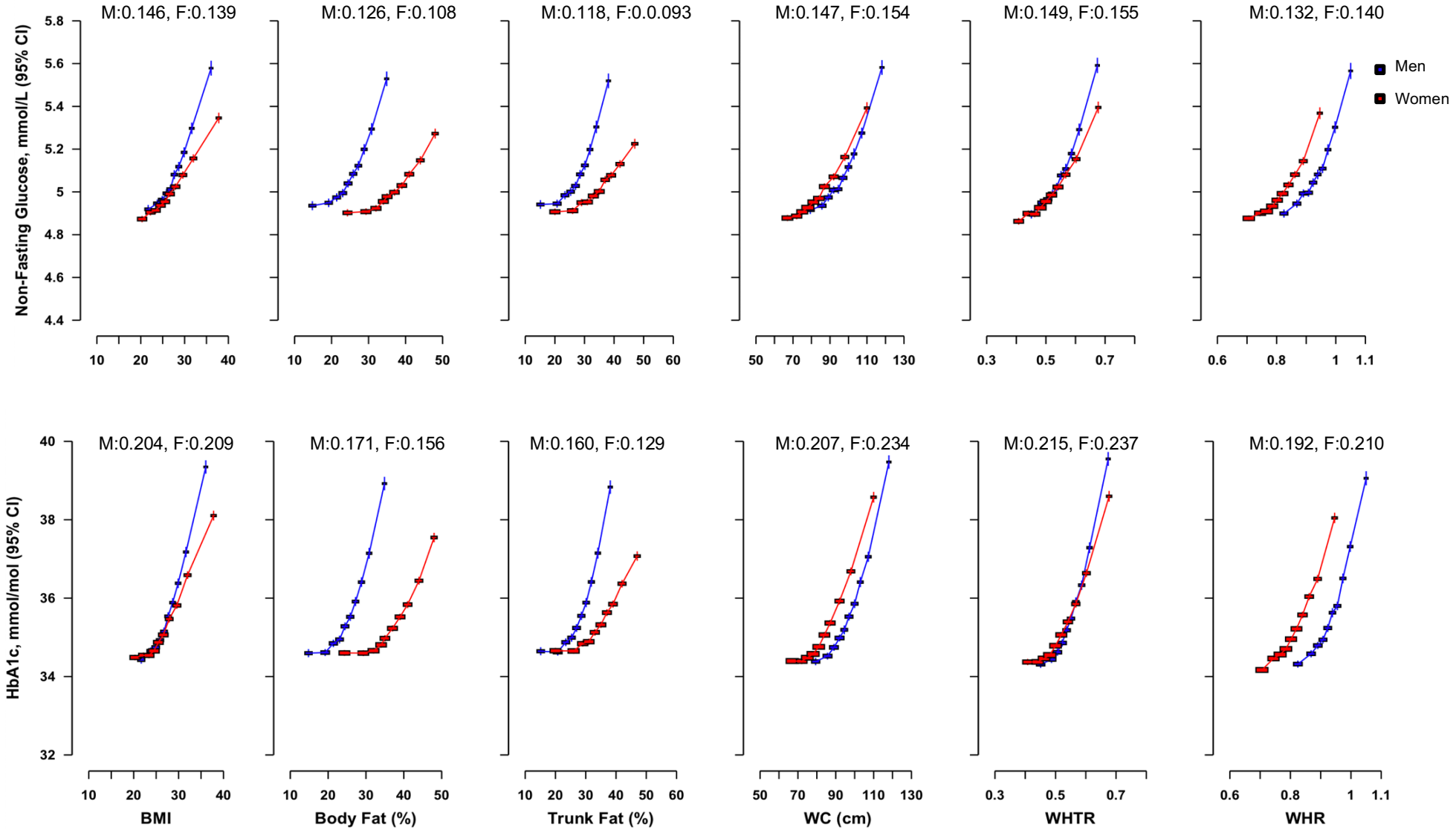

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean biomarker levels among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.15** Cross-sectional associations of baseline adiposity with Lp(a) levels in the UK Biobank, by sex



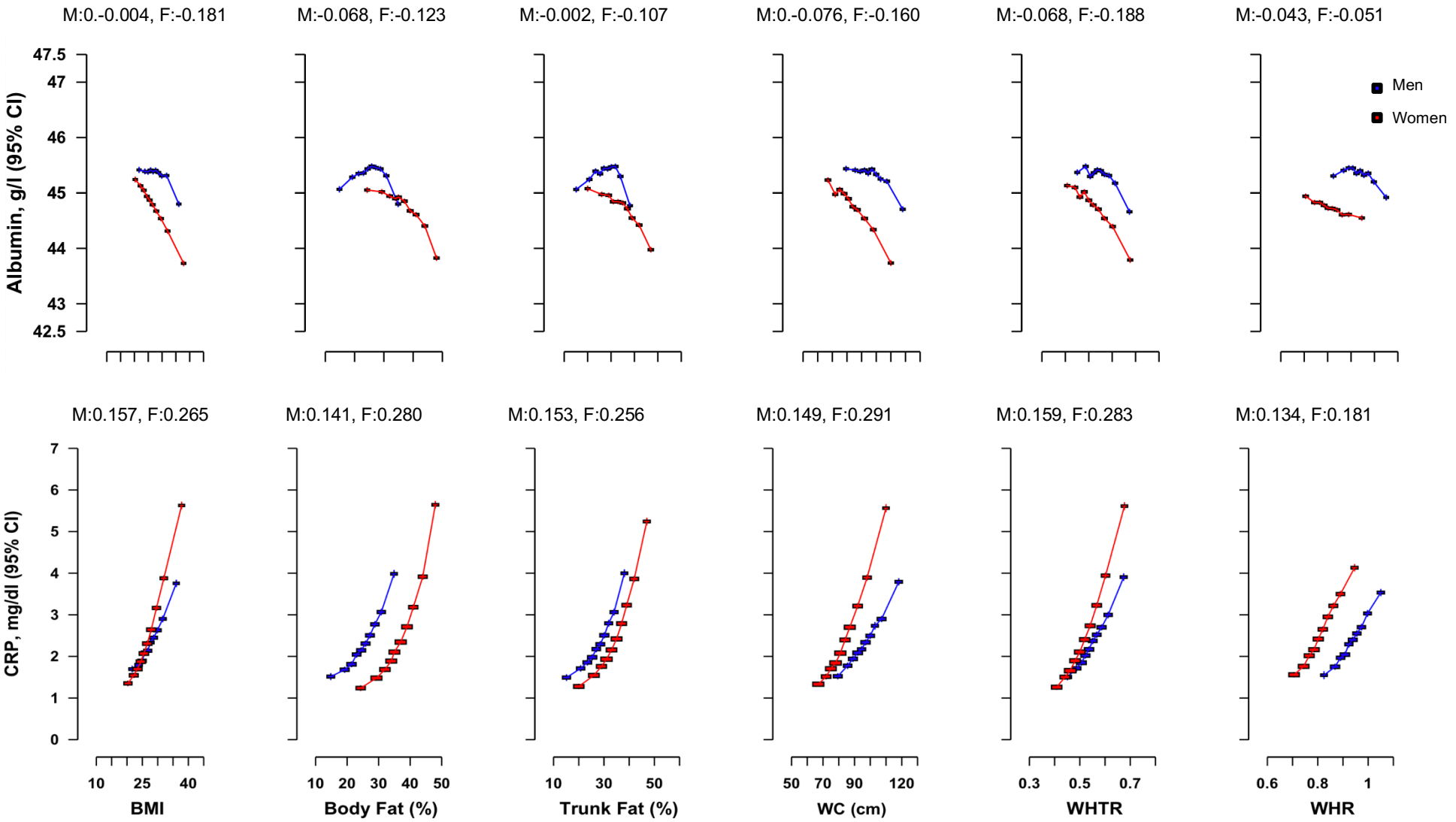

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio; Lp(a) = Lipoprotein (a). Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean lipoprotein (a) levels among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.16** Cross-sectional associations between baseline adiposity and markers of type-2 diabetes mellitus, by sex



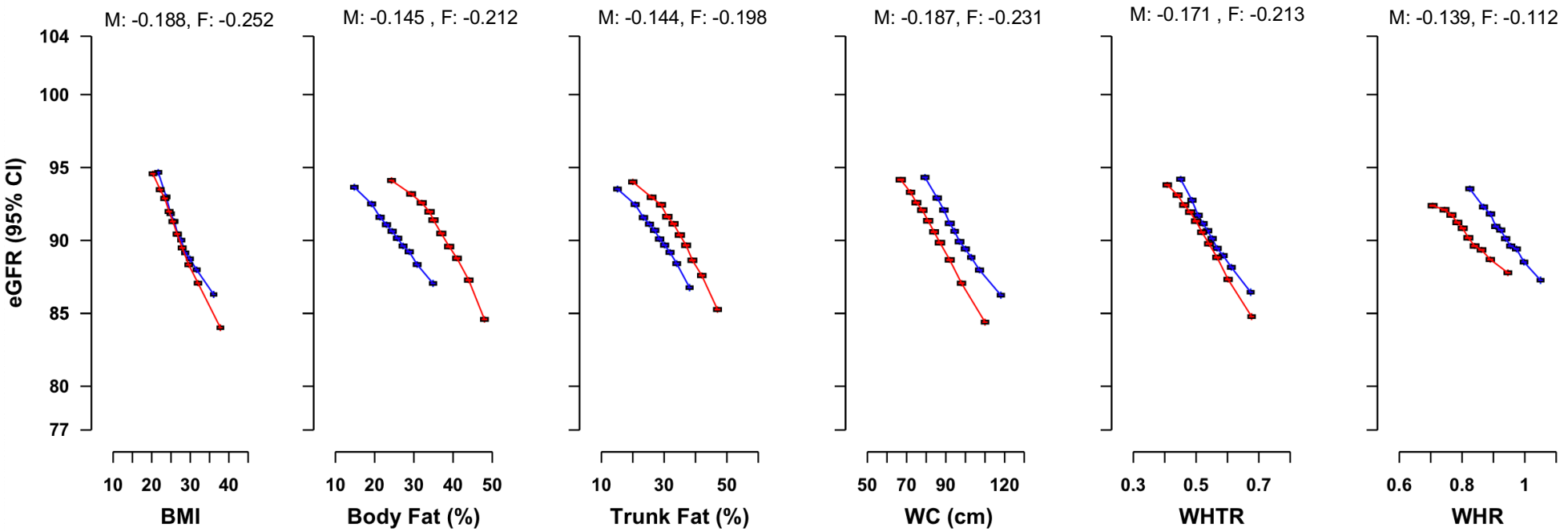

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1/2SD from the average of mean baseline values among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women.

**Figure 4.17** Cross-sectional associations between baseline adiposity and inflammatory markers in the UK Biobank, by sex



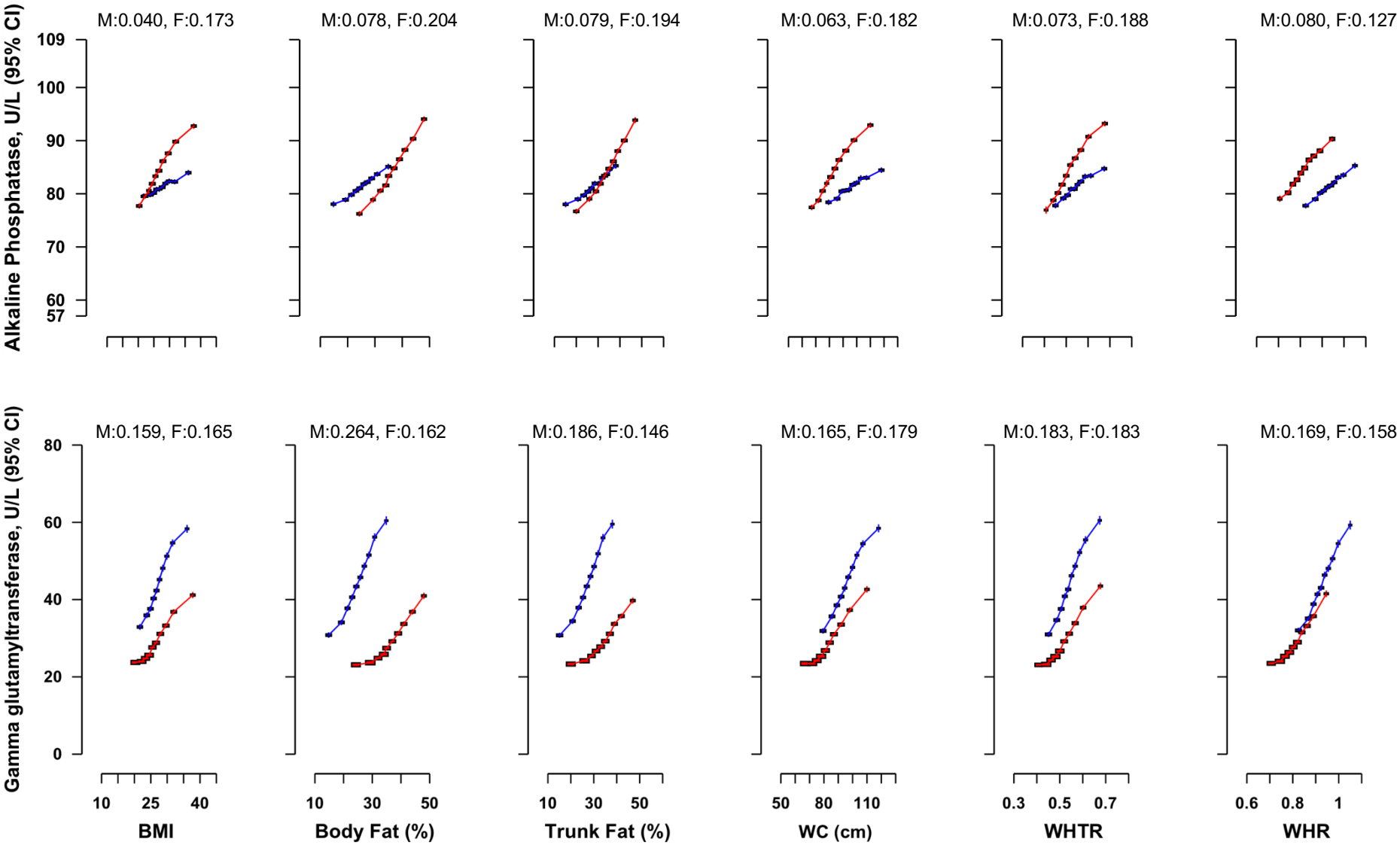

BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio; CRP = C-reactive protein. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean inflammatory markers among men and women combined. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

**Figure 4.18** Glomerular filtration rate (GFR) with increasing levels of adiposity among men and women without prior cardiovascular disease at recruitment in the UK Biobank




GFR estimates were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Mean GFR estimates (95% CI) were directly standardised to age (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Y-axes were standardised to represent 1 SD from the average of sex-specific mean values of GFR, and X-axes are standardised to represent ±3SDs from the average of sex-specific mean values of adiposity. Analysis was restricted to those participants with no history of diagnosis with cardiovascular disease.

**Figure 4.19** Cross-sectional associations between baseline adiposity and liver enzyme levels in the UK Biobank, by sex




BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region, qualification attainment , ethnicity, deprivation index, smoking habits and alcohol consumption. The values presented above each figure correspond to the partial correlation coefficient between adiposity measures in males (M) and females (F) combined, adjusted for the same covariates. Analyses were restricted to individuals without missing adiposity or biomarker variables at baseline, and those without a history of cardiovascular disease at baseline. Y-axes are standardised to represent ±1SD from the average of mean liver enzymes among men and women combined.

## CHAPTER 5: Within-person variability between adiposity measures

### Chapter summary

Prospective epidemiological associations can be systematically underestimated by 'regression dilution bias' (RDB), arising as a result of imprecise measurements or short-term biological variability (collectively termed within-person variability) in the risk factor of interest. Within-person variability is known to affect adiposity measures, particularly ratios, which complicates comparisons across measures in prospective analyses. However, RDB in adiposity measures has not been assessed at scale in a single study. This Chapter assesses the within-person variability of six measures of adiposity: BMI, BIA-derived body fat % and trunk fat %, WC, WHTR and WHR using three methods (Rosner's, self-correlation and MacMahon-Peto) of quantifying the regression dilution ratio (RDR) in 18 737 resurveyed UK Biobank participants. Each adiposity trait was associated with some degree of within-person variability, but it was more extreme for ratio measures, particularly WHR (RDR 0.66) compared with BMI (RDR 0.92) or single measures such as WC (RDR 0.82). The three methods discussed in the current chapter provide similar estimates of RDR across adiposity measures. RDRs did not vary substantially by baseline characteristics such as age, sex or demographic factors. RDB should be considered when investigating and interpreting prospective epidemiological associations with adiposity, particularly for WHR, which will be underestimated by approximately one third if uncorrected for RDB.

## 5.1 Background

As discussed previously, the majority of studies assessing disease risk associated with different adiposity measures have not taken into account their respective errors in measurement and biological variation. Most previous studies use the adiposity measures at baseline survey as the main exposure, which typically underestimates the true associations between long-term average (or "usual") levels of a particular risk factor with disease risk – a phenomenon termed regression dilution bias (RDB).[96, 242, 243] RDB arises from a combination of random measurement error, short-term biological variability and longer-term within-person variability.[244] Therefore, given the likelihood that each of these factors varies substantially between adiposity measures, it is difficult to make accurate comparisons of epidemiological associations across adiposity measures which are not corrected for RDB. There are a number of methods available to correct for RDB in the analyses,[242, 243, 245, 246] however each is associated with certain caveats, or relies on different assumptions. Despite this, often no rationale is explicitly stated for the choice of RDB correction method and little attention is paid to the assumptions made and related imprecision introduced making such corrections.

To date, the most in-depth investigation comparing the within-person variability associated with different adiposity measures was conducted by the ERFC, who investigated the RDB associated with three adiposity measures (BMI, WC and WHR) in sub-set of 42 300 participants from 12 prospective studies with full information on repeat measurements of adiposity across follow-up.[16, 247] However, a key limitation was the unexplained heterogeneity in RDRs between studies, which may have been due to differences in study protocols or cohort effects. Furthermore, this study only investigated RDB associated with four commonly used adiposity measures in the analysis, and therefore the within-person variability of BIA measures remains unknown. The UK Biobank has available information on resurveyed baseline measurements using identical protocols in a large subset of participants approximately five years after baseline assessment.

The aim of this Chapter is to examine the within-person variability associated with BMI, body fat%, trunk fat %, WC, WHTR and WHR from baseline to resurvey examination using three commonly used methods for RDB correction, taking into account assumptions and providing a rationale for use in prospective analyses.

## 5.2 Statistical methods

### *5.2.1 Graphical representation of within-person variability*

For graphical representation of within-person variability across adiposity measures, mean adiposity at baseline was plotted against the mean of each adiposity measure at resurvey approximately 4.7 years later. Mean adiposity at resurvey was estimated separately for each baseline adiposity group (tenths) using linear regression, adjusted for sex and age (5-year age groups). When plotted, the middle six categories were combined into three categories resulting in seven estimates of adiposity. All plots were created in R using the 'Jasper' package (CTSU, Oxford).

### *5.2.2 Estimating within-person variability of adiposity measures*

All commonly used methods of RDB correction involve calculating the regression dilution ratio (RDR) as an estimate of the between-person variability as a proportion of total variability (i.e. between plus within-person variability), which can be used as a correction factor in subsequent analyses by assuming that uncorrected estimates are underestimating disease risk by a factor of 1/RDR.[246, 248] The same RDR is also used to correct the standard error (SE) so that confidence intervals reflect the uncertainty of the estimated effect size between the usual levels of a risk factor and the outcome of interest. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

#### *5.2.2.1 Method 1: MacMahon-Peto method (non-parametric)*

First described in 1990,[246] the MacMahon-Peto non-parametric method involves calculating the RDR as the ratio of differences between repeat exposure and baseline measurements across equal groups defined by baseline risk factor distributions. Groups are defined by equal fifths of each adiposity measure at baseline, specifically in resurveyed participants. The mean adiposity levels are then calculated separately in the same groups at resurvey, and the absolute differences in mean levels between the top and bottom fifths are calculated at both time points. The ratio of these 'inter-quintile range' values is used as an estimate of the regression dilution ratio ($RDR_{MP}$), defined as:

$$RDR_{MP} = \frac{w_{RS}^{U} - w_{RS}^{L}}{w_{BL}^{U} - w_{BL}^{L}}$$

Where $w^{U}$ and $w^{L}$ refer to the top and bottom fifths with respect to adiposity measures 'w' at either baseline (BL) and resurvey (RS), specifically in groups defined by equal fifths of each

adiposity measure at baseline in resurveyed participants. There are a number of advantages to using this method of RDB correction. Firstly, it is intuitively appealing as estimates are based mostly on information from the tails or extremes of the risk factor distribution, which is an intuitive reflection of the extent of 'regression to the mean'. Also, being non-parametric, this method relies on fewer assumptions compared with parametric methods. However, there are several drawbacks to this method. Firstly, dividing the data into fifths may over-simplify the variability associated with a risk factor of interest, as not all of the information is utilised by this method. Furthermore, the choice of equal categories is arbitrary, and using tenths or fifths will produce slightly different RDR estimates. This was investigated in the current analysis by comparing the RDR estimates when using equal tenths instead of fifths, to investigate potential heterogeneity between RDRs when using arbitrary groupings (**Appendix 5.3 & 5.4**).

#### *5.2.2.3 Method 2: Rosner's regression (parametric)*

Rosner's regression technique uses a parametric linear approximation method which assumes a linear relationship between baseline and resurvey measurements. This method also carries the additional assumptions of linear regression analysis, including independence and homoscedasticity of residuals.[242] RDRs are estimated for each adiposity variable by regressing values of resurvey measurements on baseline measurements. A strength of this method is that the RDR can be adjusted for potential confounders (in the current analysis, RDRs were adjusted for adjusted for sex and 5-year age category). A potential limitation of this method is the arbitrary decision to regress the second measurement on the first.

#### *5.2.2.4 Method 3: Self-correlation method (parametric)*

A self-correlation method approach can be employed using Pearson's partial correlation coefficients (*r*) between baseline and re-survey measurements. The *r* represents the RDR and can be used in a similar way as the two previous methods to account for RDB in prospective analyses. This method assumes a similar constant variance between baseline and resurveyed estimates of adiposity. If this assumption is met, this method should provide similar estimates of the RDRs obtained by other parametric methods. An advantage of this method is that estimates will be less susceptible to random variation than ratio methods. However, non-parametric methods are thought to be superior over longer periods of follow-up.[243]

### *5.2.3 Determinants of within-person variability*

RDRs were compared across categories of selected categorical baseline characteristics using the self-correlation method.

## 5.3 Results

### *5.3.1. Resurvey population characteristics*

Resurvey assessment took place in three centres within two regions (Newcastle and Cheadle). Compared with the full study population, the individuals who took part in the resurvey assessment were slightly older at baseline, more likely to be White (98%), less likely to smoke (4% current smokers versus 10%) and had slightly lower levels of all adiposity variables (**Table 5.1**). All six selected adiposity markers were similarly distributed at baseline and re-survey assessment (**Appendix 5.1 & 5.2**).

### *5.3.2 Repeat adiposity measures in the UK Biobank*

When plotted against resurvey measurements in groups defined by the quintiles of baseline adiposity distributions with the top and bottom fifths further split into two groups, each of the selected adiposity measures displayed at least some degree of regression to the mean (**Figure 5.1**).

**Table 5.2** displays the mean values of the selected adiposity measures at baseline, along with the mean differences between baseline and resurvey measurements by 5-year age group in 18,737 participants who attended resurvey assessment. All measures increased from baseline to resurvey in both sexes, except BMI at ages 55 to 59, and 60 to 64 among women, within which BMI slightly declined (by -0.07 and -0.04kg/m$^2$, respectively) over this time period. For BMI and WHR, in general, larger mean differences were observed between baseline and resurvey measurements at younger ages. In contrast, mean levels of WC increased from baseline to resurvey to a slightly greater extent in older ages compared with younger ages, particularly WC (mean differences among those aged 44 to 49 versus 64 to 69 years at baseline: 1.20 cm and 1.80 cm among men; 2.16 cm and 2.35 cm among women), suggesting an increasing tendency towards central body fat distribution with increasing age. This overall trend persisted in sex-combined analysis (**Figure 5.2**).

### *5.3.3 Quantifying within-person variability across adiposity measures in the UK Biobank*

Upon dividing the resurvey population into five equal groups defined by baseline adiposity distribution, mean BMI at baseline ranged from 21.7 kg/m$^2$ in the bottom fifth to 33.5 kg/m$^2$ in the top fifth, whereas mean BMI across the same groups at resurvey ranged from 22.0 kg/m$^2$ to 33.1 kg/m$^2$ (**Figure 5.3**). This narrowing range was observed across all adiposity measures, representing a regression to the mean upon repeat measurement. When comparing baseline with resurvey means, the ratio of ranges between the top and bottom categories were lower

for central adiposity measures, particularly WHR, compared with BMI and body fat. The RDR's calculated via MacMahon's method ranged from 0.61 for WHR to 0.94 for BMI (**Table 5.3**). Estimated within-person variability was slightly greater for WHR when using the Mac-Mahon Peto method to estimate RDRs compared with other methods (RDR = 0.61 for MacMahon-Peto versus 0.63 and 0.66 for Rosner's and self-correlation methods, respectively). However, for other adiposity measures, the estimates of RDR were not materially different between the different methods. For all measures, Rosner's method demonstrated very slightly higher RDR estimates than the self-correlation method with a slight difference of approximately ±0.01/0.02.

*5.3.4 Investigating secular trends*

In the current study, over ~4.7 years from baseline to resurvey, overall mean adiposity increased only marginally for BMI, body fat % and trunk fat %, whereas there was a marked secular trend for increasing WC, WHR and WHTR across follow-up whereby participants who were aged, say, 47 years at resurvey had higher values of WC, WHR and WHTR than those who were aged 47 years at baseline (**Figure 5.2**).

*5.3.5 Determinants of with-in person variability*

The RDR's of each selected adiposity measure from baseline to resurvey were similar among men and women (**Table 5.3**), with the MacMahon Peto method displaying the greatest variation of RDRs between men and women **(Appendix 5.6 & 5.7**). Although there was some evidence for greater within-person variability at younger ages for BMI and WHR with RDRs strengthening by approximately 0.01 per decade older age (**Table 5.4**)**,** overall RDRs did not materially change with age. Furthermore, very little difference in RDR was observed across categories of educational attainment, ethnicity, smoking habits, physical activity or alcohol consumption at baseline.

## 5.4 Discussion

This chapter describes findings from the largest single study to investigate RDB across six adiposity markers. The present study investigated three statistical methods for estimating within-person variability associated with adiposity measures. There were a number of important findings presented in this chapter which are of particular relevance to epidemiological research of adiposity-related disease.

### *5.4.1 Within-person variability of selected adiposity measures*

In the current study, all six selected adiposity measures were associated with some degree of within-person variability. However, the observed within-person variability was substantially greater for WHR than other measures, regardless of the method used to quantify the RDR. This finding supports the results from previous studies concluding that ratios in particular are associated with greater variability than their components.[247, 249] Therefore, RDB must be considered in future investigations that compare associations between adiposity measures, otherwise adiposity-related disease risk will be systematically underestimated to a greater extent for composite or ratio-based measures whereby the components are not stable over time, such as WHR and WHTR. Risk factor-outcome associations are an important consideration when defining public health priorities and making high-level funding decisions; therefore, failing to account for RDB can lead to severe underestimations of population attributable fractions to risk factors, and the likely benefits of interventions.[250, 251] Therefore, the results from the current study justifies the necessity of careful consideration of RDB in future analysis which involves estimating the population attributable fractions of adiposity measures, without which, a clear understanding of the potential benefits of population-level interventions targeted at obesity may not be realised.

The RDRs presented in the current chapter are similar to those observed in the ERFC meta-analysis for BMI (RDR 0.96), WHTR (0.87), WC (0.87) and WHR (RDR 0.72).[16, 247] However, the ERFC was a meta-analysis, and the authors noted some between-study heterogeneity which may have arisen as a result of cohort effects or differences in study protocols. The comparability between the ERFC and UK Biobank supports the idea that within-person variability of selected adiposity measures can in theory be universally applied to any population.[252] This approach has proven useful previously for studies that did not conduct resurveys.[130] These findings have important implications for the interpretation of adiposity-related disease risk, since prospective associations will be underestimated for adiposity measures that are not corrected for RDB. The majority of large-scale studies do not correct

for RDB in the analyses, and therefore, the majority of large-scale observational evidence for adiposity-related CHD risk (summarised in **Chapter 2)** has underestimated associations, particularly for WHR.

### *5.4.2 Estimating the RDR: A comparison of methods and method selection*

Whether using MacMahon-Peto, Rosner's or self-correlation methods, very little material changes in RDR estimates were observed across adiposity measures, except for WHR which was associated with greater variability using the MacMahon-Peto method compared with the other methods. Importantly, MacMahon-Peto method does not use all of the available data.

Provided that the distributional assumptions are met, the parametric methods are thought to be superior methods of correcting for RDB.[243] The results from this study indicate that methods which rely on arbitrary groupings such as the MacMahon-Peto method have the potential to alter the RDR estimates and subsequent prospective associations. Rosner's method also involves the arbitrary decision of regressing the resurvey on baseline estimates. Furthermore, as an additional statistical consideration, a ratio of two normally distributed variables, such as WHR, is not strictly normally distributed, potentially violating assumptions of the additive measurement error model.[247, 253] In comparison with Rosner's method, correlation-based methods avoid arbitrary decisions, have fewer assumptions, and have been found to produce superior estimates of RDB.[243] Therefore, although the differences in RDRs derived from Rosner's and the self-correlation method were subtle and unlikely to affect the prospective associations, the self-correlation method was the chosen method for RDB correction in subsequent analyses (**Chapters 6 & 7**).

### *5.4.3 Validity of findings and underlying assumptions*

RDB correction methods have a number of shared assumptions, including the assumption that the resurvey population is approximately representative of the entire population at baseline, and that each population has similar distributions of exposures. Although the resurveyed population was not entirely representative of the baseline population, the distributions of each adiposity measure were similar in the current study. The almost exact agreement between the RDR estimates presented in the current study with those reported by the ERFC also suggests that these estimates of within-person variability are generalisable to other populations, at least among predominantly western populations. Furthermore, it is assumed that errors in the exposure measurement are the result of random (unbiased) within-person error as opposed to systematic (biased) within-person error and are independent of disease risk. The RDRs presented in the current study did not vary substantially by other

categories of baseline characteristics, including sex, ethnicity, education, smoking, alcohol or physical activity level. However, the within-person variability was slightly enhanced at younger ages, specifically for central adiposity. This could represent a true shift towards central body fat distribution in middle age, which has been observed previously, perhaps in part due to menopause.[169, 172] However, since the RDR captures both true and random fluctuations over time, the validity of the present findings are likely unaffected.

When correcting for RDB, there is no agreed optimal time interval between baseline and repeat measures within the literature. However, it is thought that this interval should be sufficiently large to capture true long-term biological variation as well as short-term measurement error, but generally RDRs decrease with time.[247] Previous reports have suggested that the assessment of variation in an exposure over a four-year period is sufficient to enable estimation of usual levels over the first decade of follow-up.[96, 250] The current study provides further evidence to support this, since when comparing mean adiposity values between baseline, resurvey (after ~4.7 years) and imaging visits (after ~7.2 years), the majority of the observed within-person variability was captured at the first resurvey (**Appendix 5.5**). Additionally, the apparent secular trend for increasing adiposity observed in the current study may be an indication of cohort effects due to differences in the length of exposure to obesogenic environments or the influence of early life factors. Importantly, changes in time-trends throughout the life-course could affect the validity of RDRs.[254] However, the interval between the baseline and subsequent resurveys is likely too short to allow for reliable investigations into cohort effects.

### *5.4.4 Study strengths and potential limitations*

This study has a number of strengths. First, it is the largest single study to investigate RDB across six adiposity markers to date. Furthermore, the current study was the first to investigate the within-person variability associated with BIA-derived adiposity measures. However, a number of limitations must be considered when interpreting the results from the current chapter. Firstly, despite other methods for RDB correction described in the literature,[243] it was decided *a priori* to compare three methods. However, although these three methods are commonly used and widely cited, due to a lack of evidence, no clear consensus exists as to the superiority of one method with respect to adiposity measures. Additionally, these results were based on a subset of less than 20 000 participants with complete information at resurvey who are not completely representative of the fill 0.5M cohort at baseline. Representativeness of the resurvey population is a fundamental assumption underpinning the methods described in this chapter, and therefore this may have slightly impacted the results. Furthermore, only

one repeat measure was used per participant. However, in 1925 participants who had undertaken repeat surveys on two separate occasions (again at imaging visit approximately 7.2 years after baseline), the majority of within-person variability was captured at the first resurvey assessment in these individuals (**Appendix 5.5**).

The limitations of regression dilution correction methods have been discussed at length elsewhere.[243, 245] However, owing to the robust study design of the UK Biobank, a number of these could be over-come in the present analysis. Firstly, each method assumes that determinants of RDB are accurately measured. However, in the current analysis and in previous studies,[247] age and sex were the only factors for which a slight difference in RDR was observed, which can be reasonably assumed to be accurately measured. The self-correlation method was selected for subsequent analyses. However, whilst this method assumes an additive non-differential measurement error model across adiposity distributions, the MacMahon or other non-parametric methods which place a greater emphasis on the tails of each distribution may be preferred. Lastly, RDB correction is thought to enhance associations when exposure-disease relationships are dominated by residual confounding. However, previous MR studies have confirmed a causal association between adiposity measures and CHD, which limits the possibility of the association largely existing as a result of residual confounding.[119, 140]

### 5.5 Conclusion

This study was the largest single study to comprehensively investigate the within-person variability associated with six commonly used adiposity measures, to quantify the RDB underlying adiposity-related disease risk. In summary, WHR was associated with substantially greater levels of within-person variability compared with BMI, WHTR, WC and BIA-derived measures. The three methods discussed in the current chapter provide similar estimates of RDR. These findings have important implications for future research since without correcting for within-person variability, direct comparisons between adiposity measures and prospective disease risk are likely inaccurate.

## Chapter 5 Figures and tables


| Figure/Table | Title |
|---|---|
| **Table 5.1** | Baseline characteristics in full study population versus resurveyed population |
| **Figure 5.1** | Age- and sex-adjusted mean adiposity at resurvey vs. baseline values in the same individuals |
| **Table 5.2** | Change in adiposity from baseline to a repeat measurement, by age and sex |
| **Figure 5.2** | The effect of ageing between baseline and resurvey adiposity variables in the same individuals |
| **Figure 5.3** | Mean baseline and re-survey values in groups defined by fifths of baseline adiposity in re-survey population |
| **Table 5.3** | Regression dilution ratios (95% CI) for adiposity and body size measures, estimated using three separate methods |
| **Figure 5.4** | Regression dilution ratios* (95% CI) for adiposity measures, separately according to selected categorical variables at baseline |

**Table 5.1** Baseline characteristics in full study population versus resurveyed population

| | Baseline population | | | Resurvey population | | |
|---|---|---|---|---|---|---|
| | **Males** | **Females** | **All** | **Males** | **Females** | **All** |
| **N** | 200 639 | 254 509 | 455 148 | 8,909 | 9,828 | 18,737 |
| **Age, years** | | | | | | |
| 40-44 | 11% | 11% | 11% | 8% | 8% | 8% |
| 45-49 | 14% | 14% | 14% | 10% | 12% | 11% |
| 50-54 | 15% | 16% | 16% | 14% | 16% | 15% |
| 55-59 | 18% | 19% | 18% | 22% | 24% | 23% |
| 60-64 | 23% | 24% | 24% | 29% | 27% | 28% |
| 65-69 | 18% | 16% | 17% | 18% | 13% | 15% |
| Mean (SD) | 56.2 (8.2) | 56.1 (7.9) | 56.1 (8.0) | 57.3 (7.5) | 56.4 (7.2) | 56.8 (7.4) |
| **Ethnicity** | | | | | | |
| White | 94% | 94% | 94% | 98% | 98% | 98% |
| Chinese | 0.2% | 0.4% | 0.3% | 0% | 0% | 0% |
| South Asian | 2% | 2% | 2% | 1% | 1% | 1% |
| Black | 2% | 2% | 2% | 0% | 0% | 0% |
| Mixed | 0.4% | 1% | 1% | 0% | 0% | 0% |
| Other | 1% | 1% | 1% | 1% | 0% | 0% |
| Prefer not to answer | 1% | 0.3% | 0.5% | 0% | 0% | 0% |
| **Highest qualification** | | | | | | |
| No qualifications | 15% | 16% | 16% | 9% | 8% | 8% |
| GCSE/O-Level | 24% | 29% | 27% | 20% | 24% | 23% |
| AS/A-Level | 10% | 12% | 11% | 12% | 13% | 12% |
| Higher education | 48% | 42% | 44% | 57% | 52% | 54% |
| Prefer not to answer | 2% | 2% | 2% | 3% | 3% | 3% |
| **UK Region** | | | | | | |
| London | 14% | 14% | 14% | 0% | 0% | 0% |
| South East | 9% | 9% | 9% | 0% | 0% | 0% |
| South West | 9% | 9% | 9% | 0% | 0% | 0% |
| East Midlands | 7% | 7% | 7% | 0% | 0% | 0% |
| West Midlands | 9% | 8% | 9% | 8% | 7% | 7% |
| Yorkshire & Humber | 15% | 15% | 15% | 28% | 27% | 28% |
| North West | 16% | 15% | 15% | 64% | 65% | 65% |
| North East | 11% | 11% | 11% | 0% | 0% | 0% |
| Wales | 4% | 4% | 4% | 0% | 0% | 0% |
| Scotland | 7% | 7% | 7% | 0% | 0% | 0% |
| **Height (cm)** | 175.8 (6.8) | 162.6 (6.3) | 168.4 (9.3) | 176.1 (6.6) | 163.0 (6.2) | 169.2 (9.1) |
| **BMI (kg/m²)** | 27.7 (4.1) | 27.0 (5.1) | 27.3 (4.7) | 27.2 (3.9) | 26.4 (4.8) | 26.8 (4.4) |
| **Body fat percentage** | 25.0 (5.7) | 36.5 (6.8) | 31.4 (8.5) | 24.6 (5.6) | 36.0 (6.6) | 30.6 (8.4) |
| **Waist circumference (cm)** | 96.5 (11.0) | 84.4 (12.3) | 89.7 (13.2) | 94.9 (10.7) | 82.4 (11.6) | 88.4 (12.8) |

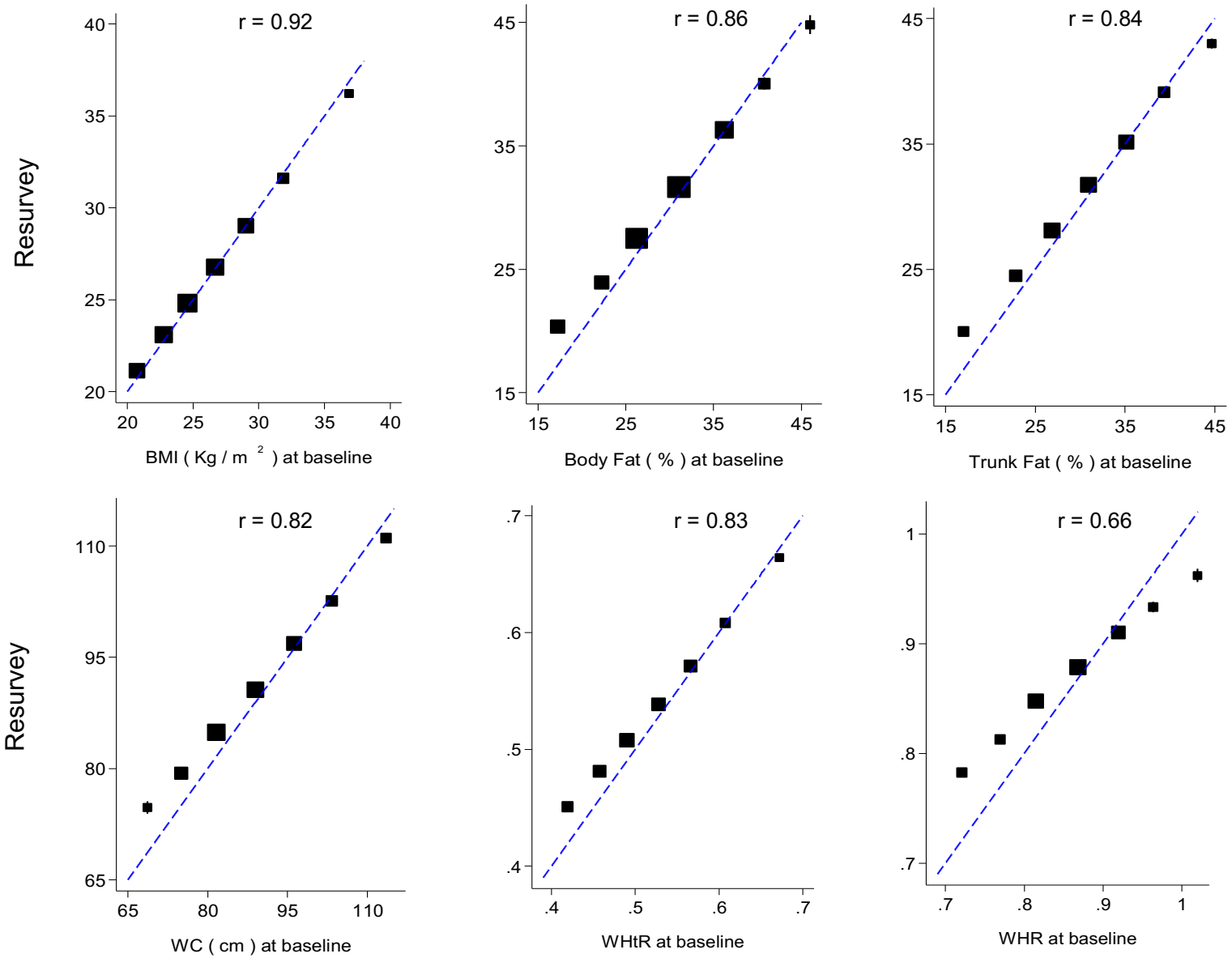
Analyses was restricted to participants with complete information on adiposity at baseline (and re-survey), and without known cardiovascular disease at baseline

**Table 5.1** Baseline characteristics in full study population versus resurveyed population

| | Baseline population | | | Resurvey population | | |
|---|---|---|---|---|---|---|
| | **Males** | **Females** | **All** | **Males** | **Females** | **All** |
| **Waist-to-hip ratio** | 0.93 (0.06) | 0.82 (0.07) | 0.87 (0.09) | 0.92 (0.06) | 0.81 (0.07) | 0.86 (0.09) |
| **Waist-to-height ratio** | 0.55 (0.06) | 0.52 (0.08) | 0.53 (0.07) | 0.54 (0.06) | 0.51 (0.07) | 0.52 (0.07) |
| **Trunk fat percentage** | 27.4 (6.5) | 34.0 (7.6) | 31.1 (7.9) | 26.9 (6.4) | 33.7 (7.5) | 30.5 (7.8) |
| **Smoking status** | | | | | | |
| Current | 12% | 9% | 10% | 5% | 4% | 4% |
| Former | 37% | 31% | 34% | 40% | 31% | 35% |
| Never | 51% | 60% | 56% | 55 | 65% | 60% |
| **Weekly alcohol** | | | | | | |
| Daily drinker | 26% | 16% | 20% | 27% | 18% | 22% |
| Regular drinker | 53% | 47% | 49% | 55% | 51% | 53% |
| Occasional drinker | 16% | 28% | 22% | 14% | 25% | 20% |
| Never drinker | 6% | 9% | 8% | 4% | 6% | 5% |
| **Physical activity (MET hr/wk)** | | | | | | |
| Low, <10 | 23% | 24% | 23% | 24% | 24% | 24% |
| Moderate, 10-49.9 | 47% | 47% | 47% | 48% | 49% | 48% |
| High, ≥50 | 22% | 18% | 20% | 20% | 15% | 18% |
| Missing | 8% | 12% | 10% | 8% | 12% | 10% |
| Mean (SD) | 41.3 (57.7) | 33.7 (41.6) | 37.1 (49.6) | 37.2 (50.9) | 31.0 (37.0) | 34.0 (44.4) |
| **Systolic blood pressure (mmHg)** | | | | | | |
| <100 | 0.5% | 1% | 1% | 0% | 1% | 1% |
| 100 - 119 | 9% | 21% | 16% | 8% | 22% | 15% |
| 120 - 139 | 42% | 41% | 41% | 43% | 41% | 42% |
| 140 - 169 | 35% | 26% | 30% | 35% | 26% | 30% |
| ≥160 | 14% | 11% | 12% | 13% | 10% | 12% |
| Mean (SD) | 141.1 (17.3) | 135.2 (19.2) | 137.8 (18.6) | 142.4 (18.0) | 136.4 (19.8) | 139.2 (19.2) |
| **Diastolic blood pressure (mmHg)** | | | | | | |
| <60 | 0.5% | 1% | 1% | 0% | 1% | 1% |
| 60 - 69 | 6% | 12% | 9% | 6% | 13% | 10% |
| 70 - 79 | 26% | 35% | 31% | 28% | 37% | 33% |
| 80 - 89 | 39% | 34% | 36% | 39% | 32% | 36% |
| ≥90 | 29% | 18% | 23% | 26% | 16% | 21% |
| Mean (SD) | 84.5 (9.9) | 80.8 (10.0) | 82.4 (10.1) | 83.7 (10.2) | 79.7 (10.3) | 81.6 (10.5) |
| **Diagnosed conditions** | | | | | | |
| **Hypertension, %** | 27.0% | 21.5% | 24.0% | 24.7 %) | 18.7 % | 21.6 %) |
| **Diabetes, %** | 4.8% | 2.5% | 3.6% | 18.9%) | 1.8 % | 2.7 % |

Analyses was restricted to participants with complete information on adiposity at baseline (and re-survey), and without known cardiovascular disease at baseline

**Figure 5.1** Age- and sex-adjusted mean adiposity at resurvey vs. baseline values in the same individuals



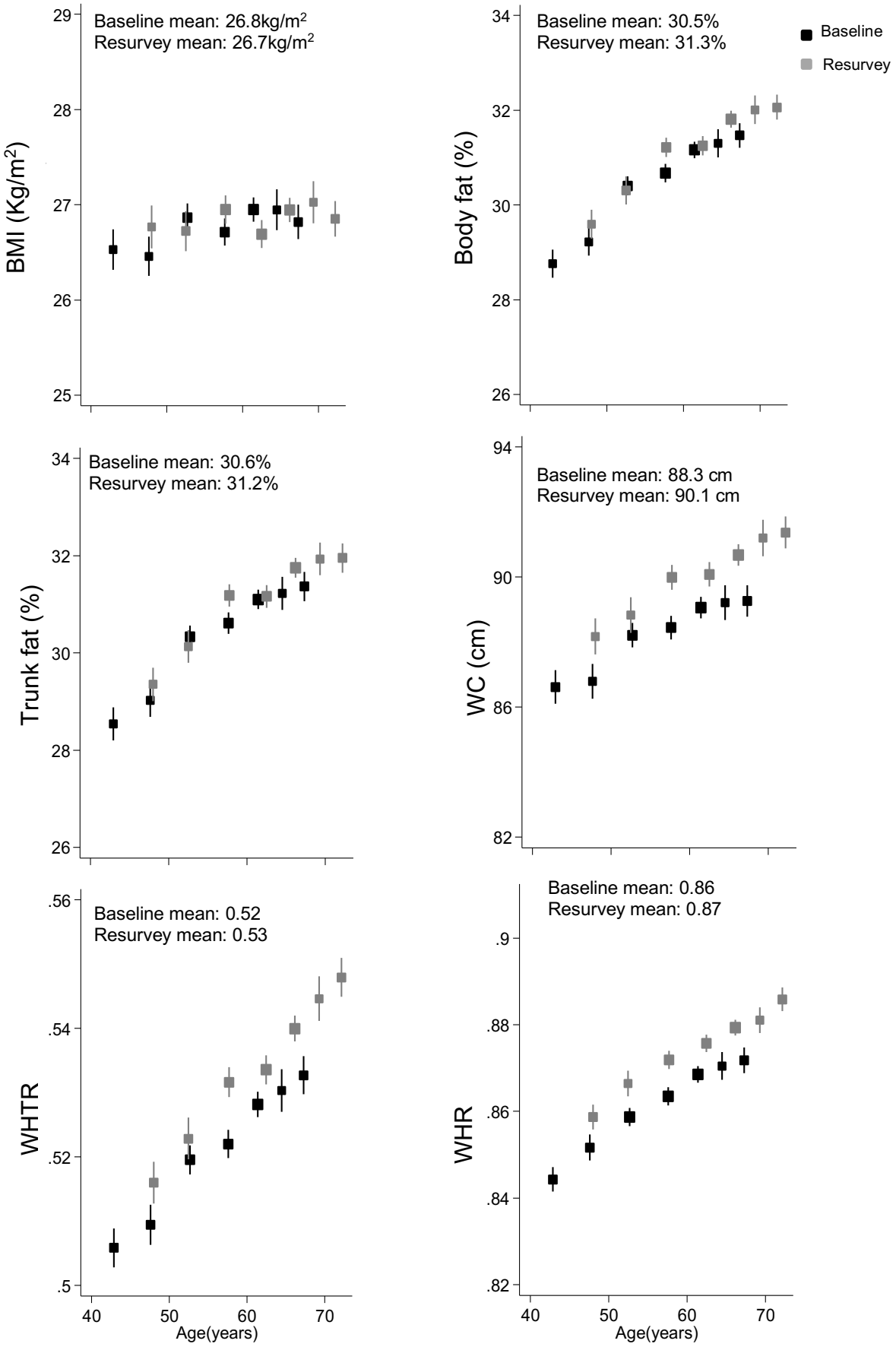

Point estimates represent the mean adiposity values (95% CI) at baseline and re-survey by age group, adjusted for region (three groups), education (five groups), deprivation (fifths) and sex, where appropriate. Analyses was restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline. Dotted line represents r= 1.0; a shallow shape indicated regression dilution.

**Table 5.2** Change in adiposity from baseline to a repeat measurement, by age and sex

| | Baseline Population (n=455 148) | | | | | | | | Resurvey population (n=18,737) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Baseline values, 2006-2010 | | | | | | | | Difference at resurvey, 2013-2014 | | | | | |
| | Mean Age | No. | Mean Adiposity | | | | | | Mean Age | No. | Mean Adiposity | | | | | | Mean Age | Mean Difference (SE) | | | | |
| | | | BMI (kg/m$^2$) | BF (%) | TF (%) | WC (cm) | WHR | WHtR | | | BMI (kg/m$^2$) | BF (%) | TF (%) | WC (cm) | WHR | WHtR | | BMI (kg/m$^2$) | BF (%) | TF (%) | WC (cm) | WHR | WHtR |
| **Male** | | | | | | | | | | | | | | | | | | | | | | | |
| **40-44** | 42.3 | 22973 | 27.4 | 23.2 | 25.4 | 94.2 | 0.91 | 0.53 | 42.3 | 716 | 27.1 | 22.9 | 25.0 | 93.1 | 0.90 | 0.52 | 47.4 | 0.21 (0.07) | 0.95 (0.12) | 0.99 (0.15) | 1.20 (0.25) | 0.012 (0.002) | 0.008 (0.001) |
| **45-49** | 47.0 | 27731 | 27.7 | 23.9 | 26.2 | 95.2 | 0.92 | 0.54 | 47.1 | 926 | 27.1 | 23.4 | 25.7 | 93.5 | 0.91 | 0.53 | 52.0 | 0.13 (0.05) | 1.01 (0.10) | 1.11 (0.12) | 1.51 (0.22) | 0.012 (0.002) | 0.010 (0.001) |
| **50-54** | 52.0 | 30583 | 27.8 | 24.7 | 27.0 | 96.4 | 0.93 | 0.55 | 52.1 | 1212 | 27.2 | 24.1 | 26.5 | 94.5 | 0.92 | 0.54 | 57.1 | 0.08 (0.04) | 0.91 (0.09) | 1.03 (0.10) | 1.38 (0.19) | 0.010 (0.001) | 0.009 (0.001) |
| **55-59** | 57.0 | 35832 | 27.8 | 25.2 | 27.6 | 97.0 | 0.94 | 0.55 | 57.2 | 1926 | 27.3 | 24.7 | 27.1 | 95.1 | 0.92 | 0.54 | 62.1 | 0.09 (0.03) | 0.93 (0.07) | 1.02 (0.08) | 1.59 (0.15) | 0.011 (0.001) | 0.011 (0.001) |
| **60-64** | 61.9 | 47061 | 27.7 | 25.7 | 28.2 | 97.4 | 0.94 | 0.56 | 61.9 | 2550 | 27.3 | 25.1 | 27.5 | 95.7 | 0.93 | 0.55 | 66.7 | 0.09 (0.03) | 1.06 (0.06) | 1.21 (0.07) | 1.37 (0.13) | 0.007 (0.001) | 0.010 (0.001) |
| **65-69** | 66.8 | 36459 | 27.6 | 26.3 | 28.8 | 97.6 | 0.95 | 0.56 | 66.7 | 1592 | 27.0 | 25.3 | 27.7 | 95.2 | 0.93 | 0.55 | 71.6 | 0.08 (0.03) | 1.07 (0.07) | 1.29 (0.09) | 1.80 (0.15) | 0.011 (0.001) | 0.013 (0.001) |
| **Female** | | | | | | | | | | | | | | | | | | | | | | | |
| **40-44** | 42.3 | 26727 | 26.3 | 34.5 | 32.1 | 81.9 | 0.80 | 0.50 | 42.3 | 780 | 25.9 | 34.1 | 31.7 | 80.4 | 0.79 | 0.49 | 47.5 | 0.37 (0.08) | 0.81 (0.14) | 0.75 (0.16) | 2.16 (0.27) | 0.018 (0.002) | 0.014 (0.002) |
| **45-49** | 47.1 | 35453 | 26.6 | 35.1 | 32.6 | 82.7 | 0.80 | 0.51 | 47.1 | 1155 | 25.9 | 34.3 | 31.9 | 80.7 | 0.80 | 0.49 | 52.1 | 0.30 (0.06) | 1.01 (0.11) | 0.97 (0.14) | 2.29 (0.22) | 0.017 (0.002) | 0.015 (0.001) |
| **50-54** | 52.1 | 41402 | 27.0 | 36.2 | 33.8 | 83.9 | 0.81 | 0.52 | 52.2 | 1612 | 26.4 | 35.9 | 33.7 | 82.2 | 0.80 | 0.50 | 57.1 | 0.13 (0.05) | 0.80 (0.08) | 0.78 (0.11) | 2.22 (0.18) | 0.016 (0.001) | 0.015 (0.001) |
| **55-59** | 57.1 | 47848 | 27.1 | 36.9 | 34.4 | 84.8 | 0.82 | 0.52 | 57.1 | 2334 | 26.3 | 36.1 | 33.9 | 82.6 | 0.81 | 0.51 | 62.0 | -0.07(0.04) | 0.33 (0.07) | 0.20 (0.09) | 1.62 (0.15) | 0.013 (0.001) | 0.011 (0.001) |
| **60-64** | 61.9 | 61141 | 27.2 | 37.3 | 34.9 | 85.5 | 0.82 | 0.53 | 61.8 | 2680 | 26.6 | 36.6 | 34.4 | 83.0 | 0.81 | 0.51 | 66.6 | -0.04(0.04) | 0.32 (0.06) | 0.19 (0.08) | 1.95 (0.13) | 0.014 (0.001) | 0.014 (0.001) |
| **65-69** | 66.8 | 41938 | 27.2 | 37.6 | 35.2 | 86.0 | 0.83 | 0.53 | 66.6 | 1276 | 26.7 | 37.0 | 34.6 | 83.9 | 0.82 | 0.52 | 71.5 | 0.05 (0.04) | 0.24 (0.09) | 0.06 (0.12) | 2.35 (0.19) | 0.015 (0.002) | 0.017 (0.001) |
| **All*** | 56.1 (8.0) | 455148 | 27.3 | 31.5 | 31.1 | 89.7 | 0.87 | 0.53 | 56.8 | 18575 | 27.0 | 31.0 | 30.6 | 88.5 | 0.85 | 0.52 | 61.8 | 0.08 (0.01) | 0.75 (0.02) | 0.75 (0.03) | 1.77 (0.05) | 0.013(0.0004) | 0.012 (0.0003) |

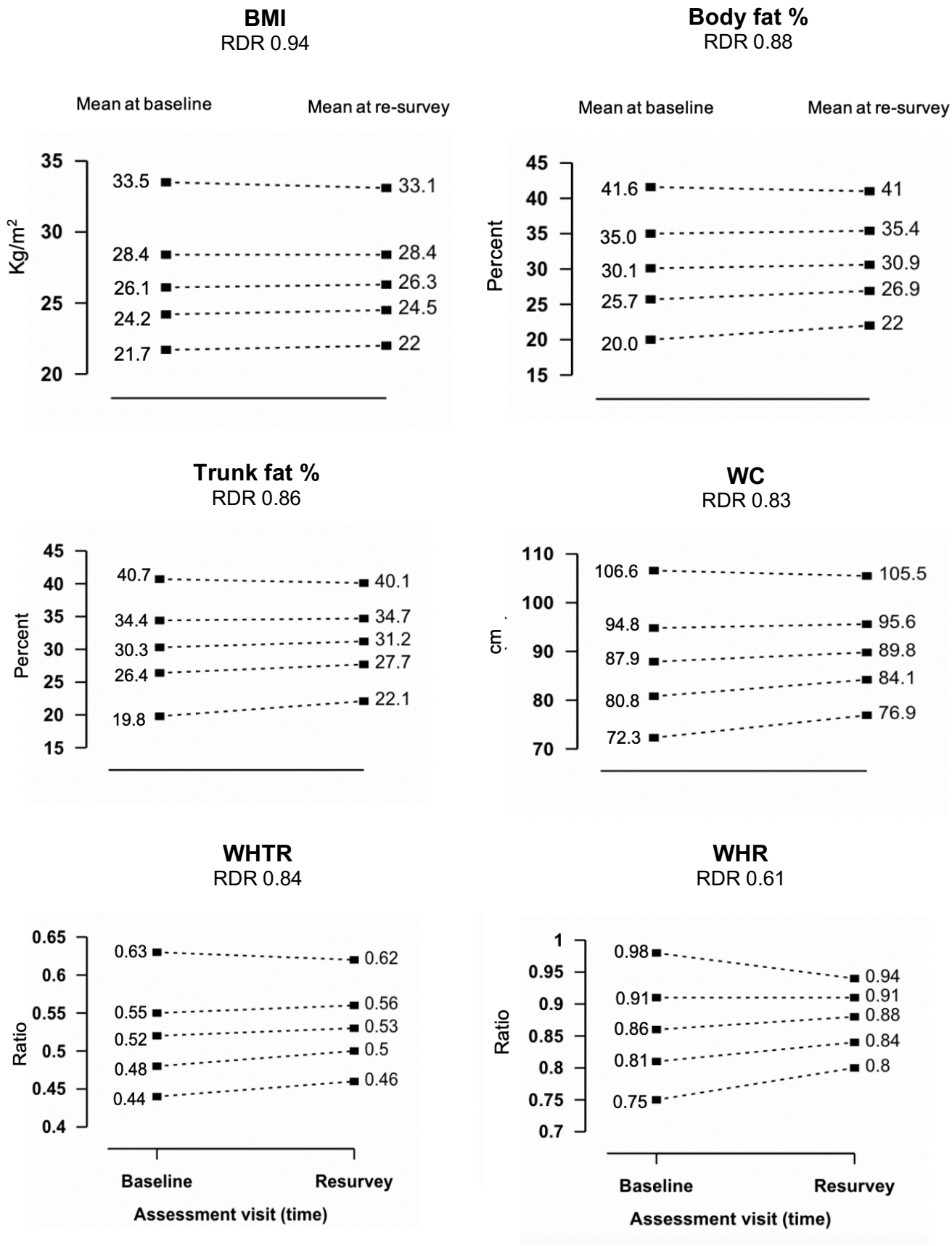
*Adjusted for sex and region. Analyses were restricted to participants with complete information on adiposity (and re-survey) assessment, and without cardiovascular disease at baseline.

**Figure 5.2** The effect of ageing between baseline and resurvey adiposity variables in the same individuals




BMI= Body-mass index; WC= waist circumference; WHTR= waist-to-height ratio; WHR= waist-to-hip ratio. Point estimates represent equal tenths of the age distribution, and the middle six tenths were combined, resulting in seven estimates. Estimates (95% CI) values were adjusted for region and sex. Analyses was restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline.

**Figure 5.3** Mean baseline and re-survey values in groups defined by fifths of baseline adiposity in re-survey population




BMI= Body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; RDR = regression dilution ratio. Analyses were restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline. RDRs were calculating using the MacMahon-Peto method.

**Table 5.3** Regression dilution ratios (95% CI) for adiposity and body size measures, estimated using three separate methods

| | RDR Rosner's method | | | RDR Intra-class correlation method | | | RDR Peto-MacMahon method | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Men*** | **Women*** | **All†** | **Men*** | **Women*** | **All†** | **Men** | **Women** | **All** |
| **Height** | 0.98 | 0.98 | 0.98 | 0.99 | 0.99 | 0.99 | 0.98 | 0.98 | 0.98 |
| **Weight** | 0.95 | 0.93 | 0.94 | 0.94 | 0.93 | 0.93 | 0.94 | 0.94 | 0.94 |
| **Body mass index** | 0.95 | 0.94 | 0.94 | 0.93 | 0.92 | 0.92 | 0.94 | 0.94 | 0.94 |
| **Body fat** | 0.87 | 0.88 | 0.87 | 0.86 | 0.87 | 0.86 | 0.87 | 0.88 | 0.88 |
| **Trunk fat** | 0.85 | 0.84 | 0.84 | 0.84 | 0.84 | 0.84 | 0.85 | 0.84 | 0.84 |
| **Waist Circumference** | 0.83 | 0.85 | 0.84 | 0.82 | 0.82 | 0.82 | 0.82 | 0.86 | 0.83 |
| **Hip Circumference** | 0.83 | 0.89 | 0.87 | 0.79 | 0.83 | 0.82 | 0.81 | 0.89 | 0.86 |
| **Waist-to-height ratio** | 0.83 | 0.87 | 0.85 | 0.82 | 0.83 | 0.83 | 0.82 | 0.90 | 0.84 |
| **Waist-to-hip ratio** | 0.64 | 0.62 | 0.63 | 0.67 | 0.66 | 0.66 | 0.65 | 0.63 | 0.61 |

*Adjusted for age; †Adjusted for age and sex; Analyses was restricted to participants with complete information on adiposity at baseline (and re-survey), and without known cardiovascular disease at baseline

**Table 5.4** Regression dilution ratios* (95% CI) for adiposity measures, separately according to selected categorical variables at baseline

| | N | BMI (kg/m$^2$) | Body Fat % | Trunk Fat % | WC | WHTR | WHR |
|---|---|---|---|---|---|---|---|
| **Age, years** | | | | | | | |
| 40-49 | 4 901 | 0.92 | 0.86 | 0.84 | 0.82 | 0.83 | 0.65 |
| 50-59 | 9 481 | 0.93 | 0.86 | 0.83 | 0.82 | 0.82 | 0.66 |
| 60-69 | 2 865 | 0.94 | 0.88 | 0.84 | 0.84 | 0.84 | 0.67 |
| **Ethnicity** | | | | | | | |
| White | 18 285 | 0.92 | 0.86 | 0.84 | 0.82 | 0.84 | 0.66 |
| Other | 452 | 0.93 | 0.86 | 0.83 | 0.81 | 0.81 | 0.65 |
| **Highest qualification completed** | | | | | | | |
| College degree | 10 171 | 0.93 | 0.87 | 0.84 | 0.82 | 0.82 | 0.66 |
| Less than college education | 8 492 | 0.92 | 0.86 | 0.83 | 0.82 | 0.82 | 0.66 |
| **Smoking status** | | | | | | | |
| Current | 781 | 0.91 | 0.83 | 0.81 | 0.82 | 0.82 | 0.66 |
| Former | 6 686 | 0.92 | 0.85 | 0.83 | 0.82 | 0.82 | 0.66 |
| Never | 11 236 | 0.93 | 0.87 | 0.84 | 0.82 | 0.83 | 0.65 |
| **Weekly alcohol consumption** | | | | | | | |
| Daily drinker | 4 175 | 0.93 | 0.87 | 0.84 | 0.818 | 0.82 | 0.65 |
| Regular drinker | 9 881 | 0.92 | 0.86 | 0.84 | 0.809 | 0.81 | 0.65 |
| Occasional drinker | 3 668 | 0.91 | 0.86 | 0.83 | 0.828 | 0.83 | 0.67 |
| Never drinker | 1 011 | 0.92 | 0.87 | 0.83 | 0.850 | 0.85 | 0.67 |
| **Physical activity level (MET-hr/wk)** | | | | | | | |
| Low, <10 | 4 440 | 0.92 | 0.86 | 0.84 | 0.82 | 0.83 | 0.65 |
| Moderate, 10 - 49.9 | 9 003 | 0.93 | 0.86 | 0.83 | 0.81 | 0.82 | 0.65 |
| High, ≥50 | 3 278 | 0.92 | 0.84 | 0.83 | 0.81 | 0.81 | 0.64 |
| Missing/prefer not to say | 1 859 | 0.92 | 0.85 | 0.82 | 0.83 | 0.84 | 0.69 |

*Calculated using the self-correlation method. Analyses were restricted to participants without known cardiovascular disease at baseline, and with complete information on adiposity and confounders at baseline and re-survey.

# CHAPTER 6: Imaging study of body composition and systolic blood pressure in the UK Biobank and Oxford Biobank

## Chapter summary

Adiposity is known to be associated with blood pressure, but uncertainty remains about the relevance of the distribution of excess weight to blood pressure levels. This Chapter combines individual participant imaging data from the UK Biobank and the Oxford Biobank. Both studies had similar protocols for baseline assessments, which included body size measurements (height, weight, WC, hip circumference and SBP), and imaging using whole-body Dual-energy X-ray Absorptiometry (DXA). Multiple linear regression was used to relate SBP to anthropometric adiposity measures (BMI, WC and WHR) and DXA-derived measures of regional body fat (subcutaneous android fat, visceral android fat, subcutaneous gynoid fat, and other fat mass). Repeat measures of anthropometric variables were used to correct these associations for measurement error. After exclusions, 10 260 participants remained. Mean age was 48.6 (SD 9.8) years, 55% were women and 96% were of White ethnicity. SBP was positively associated with DXA-derived measures of visceral android fat (3.2 mmHg per SD in men, 2.8 mmHg in women) and fat-free mass (1.92 mmHg among men and 1.64 mmHg among women), but there was no evidence of an association with subcutaneous android or gynoid fat. Mean differences in SBP (men/women, mmHg) per SD higher BMI (2.9/3.2) was slightly greater than per SD higher WC (2.7/3.1) or WHR (2.5/2.4). These associations were unchanged following adjustment for fat-free mass, but adjustment for visceral android fat completely eliminated associations with WC and WHR, and more than halved the association with BMI. The results presented in the current chapter suggest that visceral fat is the primary etiological component of central and general adiposity underlying the development of adiposity-related hypertension.

## 6.1 Background

Adiposity is an established risk factor for vascular disease, and this association is known to be mediated in part by raised blood pressure. RCTs of weight loss interventions (and MR studies of blood pressure in relation to adiposity-related genetic variants) support the causality of the relationship between adiposity and blood pressure,[81, 116, 255] but the underlying mechanisms are not fully understood. In particular, the relevance of regional fat mass to blood pressure is not known.

Previous studies of adiposity and blood pressure have mostly used indirect measures of adiposity, such as BMI, WC or WHR. The etiological relevance of general adiposity (as measured by BMI) and central adiposity (as measured by WC or WHR) have been inferred from these findings. However, these measures are highly correlated and associated with differing degrees of measurement error, which complicates comparisons between measures.[16] Direct measures of body composition that accurately quantify regional fat distribution (such as DXA imaging scans) can overcome these limitations. However, it has only recently become feasible to conduct large-scale studies with whole-body imaging scans, and therefore evidence for the independent associations between regional body composition and blood pressure is, to date, limited to a handful of small-scale studies.[256-260]

The aim of this Chapter is to examine the cross-sectional associations of SBP with DXA-derived measures of regional fat mass, using two large-scale imaging studies (UK Biobank and Oxford Biobank).[80, 261] This will allow an investigation into the etiological relevance of regional fat mass to SBP levels, and an assessment of the extent to which the observed associations of SBP with commonly-used anthropometric measures of adiposity (BMI, WC and WHR) are explained by their association with various regional fat depots.

## 6.2 Statistical methods

### *6.2.1 Exclusions and variable derivation*

A meta-analysis of the individual results from the UK Biobank and Oxford Biobank was performed. After excluding those with missing or extreme values of adiposity measures or blood pressure (n=335), 10 260 participants from both studies were available for analysis (**Appendix 6.1**). All analyses were performed separately for men and women, and were adjusted for age (5-year groups) and socioeconomic factors (education [College/University degree, other professional qualification, work-based qualification, A-Level or equivalent, O-Level or equivalent and no qualifications] in UK Biobank participants and occupation [professional/managerial, skilled, skilled manual, partly skilled manual, unskilled and unemployed] in Oxford Biobank participants).

### *6.2.2 Cross-sectional analysis*

The interrelationships between DXA-derived measures of regional body fat and commonly used anthropometric measures of adiposity (BMI, WC and WHR) were described using Pearson's partial correlation coefficient (r). Linear regression was used to estimate the mean differences in each DXA-derived measure of body composition (regional fat mass and total fat-free mass) per 1 SD difference in the usual levels of each anthropometric measure of adiposity. After excluding participants on blood pressure lowering therapy (n= 657), linear regression was also used to relate SBP to each DXA-derived measure of body composition (with mutual adjustment for the other DXA-derived measures) and to each anthropometric measure of adiposity (with and without further adjustment for selected DXA-derived measures of body composition); these analyses were further adjusted for height (sex-specific fifths) and alcohol consumption (5 groups), based on theoretical importance and significant contributions to the model.

The linear associations of each anthropometric adiposity measure with DXA measures or blood pressure were corrected for measurement error by dividing the beta coefficient (and SE) by the RDR, as estimated by the correlation between measures at imaging and resurvey (2.1 years prior to imaging) in 2 063 UK Biobank participants (**Appendix 6.2**). This technique has been described in greater depth elsewhere[262] and in **Chapter 5**. Upon correction for this RDB, estimates reflect the associations between 'usual' adiposity levels and DXA measures or SBP. Similarly, the 'usual SD' of each anthropometric measure was obtained from the measured SD through multiplication by $\sqrt{r}$. Potential sources of bias were explored by conducting various

sensitivity analyses, the results of which are presented in the Supplementary appendix. To observe the effects of blood pressure lowering medication and prevalent vascular disease, the main analysis was repeated including individuals who self-reported taking blood pressure lowering medication. Similarly, the effect of further confounding by lifestyle factors was explored by additionally adjusting for smoking habits and physical activity. Furthermore, due to slightly skewed distributions for some of the DXA-derived body composition variables, analyses were repeated using log-transformed DXA-derived variables. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). All plots were created in R using the 'Jasper' package (CTSU, Oxford)

## 6.3 Results

### *6.3.1 Baseline characteristics*

After exclusions, 10 260 participants contributed to the main analyses (**Table 6.1**). Mean age was 49.2 (SD 10.1) and 48.0 (SD 9.5) years among men and women, respectively. On average, participants in the UK Biobank imaging sub-study were approximately 20 years older than those in the Oxford Biobank (**Appendix 6.3**). Almost all (96%) were of White ethnicity and over half were of professional occupation in both sexes. Among men, 8% were current smokers and 27% consumed alcohol daily, whereas among women, 6% were current smokers and 13% consumed alcohol daily. On average, men had higher BMI, WC and WHRs than women. The difference in weight between men and women (approximately 15 kilograms) was almost entirely due to differences in fat-free mass. The distribution of body fat also differed between sexes, with men having on average less subcutaneous fat in android and gynoid regions, but over twice the amount of visceral android fat (1.4 kg in men vs 0.6 kg in women).

### *6.3.2 Body composition with increasing levels of BMI, WC and WHR*

BMI was strongly correlated with WC (r=0.87 in men and 0.86 in women), and both measures were less strongly correlated with WHR (r=0.45-0.80; **Appendix 6.4**). For DXA-derived measures of body composition, subcutaneous android fat was strongly correlated with subcutaneous gynoid fat (r=0.81 in men and 0.85 in women) and there were more modest correlations of these variables with visceral android fat (r=0.46-0.72). Fat-free mass was only weakly correlated with DXA-derived measures of regional body fat mass (r=0.28-0.53).

BMI, WC and WHR were all associated with approximately linear increases in body fat across all compartments (**Figure 6.1**), however the strength of association varied across each anthropometric measure (**Table 6.2; Appendix 6.5**). BMI and WC had approximately similar,

strong associations with increasing mass across all body compartments, and on average, WHR had the weakest association with increasing regional mass per SD increment. However, strengths of the associations with visceral fat were similar for each of the anthropometric measures of adiposity.

*6.3.3 Body composition, body size and systolic blood pressure*

**Figure 6.2** summarises the sex-specific and study-specific associations of DXA-derived measures of body composition with SBP. After additional adjustment for other mutually exclusive body fat compartments and total fat-free mass, VAT remained strongly and independently associated with an approximately 3-4mmHg raised SBP in both men and women (3.16 mmHg per SD in men and 2.81 mmHg per SD in women). Similarly, fat-free mass also appeared independently associated with raised SBP (1.92 mmHg per SD in men and 1.64 mmHg per SD in women). In contrast, there was no evidence that either subcutaneous android or gynoid fat were associated with SBP. 'Other fat' was positively associated with SBP in women only (2.11 mmHg per SD).

The associations with SBP were not materially altered when participants taking blood pressure lowering medication were included in the analyses, except for the relation with visceral android fat, which was strengthened (**Appendix 6.6**). In addition, the associations were not materially altered after further adjustment for smoking and physical activity (**Appendix 6.7**). With the exception of slightly shallower associations with SBP for increasing visceral android fat among women, log-transformation of each body composition variable did not impact associations (**Appendix 6.8**). Overall, there was little evidence of significant heterogeneity in the findings between the two studies.

For both men and women, SBP was positively related to each of the anthropometric measures of adiposity (**Figure 6.3**). These associations were largely unaltered after adjustment for fat-free mass, but further adjustment for visceral android fat more than halved the associations with BMI, and almost completely removed the associations with WC and WHR and SBP. Additional adjustment for other fat depots did not significantly alter associations**.**

## 6.4 Discussion

This report on two large-scale imaging studies quantifies the associations of blood pressure with regional fat mass and fat-free mass, and indicates that much of the relation between blood pressure and commonly used anthropometric measures of adiposity are explained by their correlation with visceral fat. In both men and women, blood pressure was positively associated with visceral fat and fat-free mass, but there was no evidence of an association with subcutaneous android or gynoid fat after adjustment for other fat compartments. The strengths of the associations with visceral fat were similar for each of the anthropometric measures of adiposity, but the associations with some of the other body components were notably weaker with WHR.

Several previous imaging studies (mostly using DXA or MRI scans) have described the associations between blood pressure and regional fat mass or fat-free mass.[256-260] Consistent with the present report, these studies describe strong positive associations with visceral fat, but the findings for subcutaneous fat and lean body mass are more variable, with some describing positive associations,[257, 258] and others negative.[256, 259, 260] Most studies made some adjustment for total fat mass but not for the range of mutually exclusive depots of fat and fat-free mass as in the present study. Furthermore, the size of these studies did not allow the strengths of these associations to be quantified reliably.

The relation between blood pressure and the anthropometric measures of adiposity used in the present report have been well described in previous studies.[35, 198, 199, 263-265] The strengths of the associations of blood pressure with BMI and WC in the present report are similar to those described in other populations of European origin (recent studies indicate these associations may be stronger in East Asian populations[199]). In contrast, the associations with WHR are somewhat stronger than most previous studies, perhaps reflecting the effect of correction for measurement error in this study, which was greater for WHR than for the other measures, and which has been rarely accounted for in other studies. Similarly, the few studies that have reported the relation between anthropometric measures of adiposity and regional fat mass, without correction for measurement error, have reported stronger associations of BMI and WC with visceral fat mass than with WHR. In the present study, however, there was no evidence of difference between these measures in their relationship with visceral fat.

The associations of blood pressure with each of the anthropometric measures of adiposity were strongly attenuated when adjusting for visceral android fat, with complete attenuation of

the associations with central adiposity (WC and WHR). This indicates that the relation between central adiposity and blood pressure is mediated largely by visceral android fat (or some correlate of visceral fat) and suggests there are additional mechanisms by which general adiposity (as measured by BMI) may influence blood pressure. Visceral fat is known to have distinct biological properties as compared with body fat stored elsewhere, but the mechanisms by which it may influence blood pressure are not clear; potential mechanisms involve abnormal renin-angiotensin-aldosterone regulation and sympathetic nervous system activation.[37-40] The hypothesized mechanisms by which general adiposity may influence blood pressure, in addition to its effects shared by central adiposity, include peripheral vascular resistance or renal sodium retention.[34-36, 199] The positive relation between fat-free mass and blood pressure was unexpected, but has been reported in other populations.[266]

The key strengths of the present study include: its large sample size; the high-quality measurements of body composition, blood pressure and potential confounders; and the repeated surveys in a subset of UK Biobank participants to allow correction for within-person variability of adiposity variables (but not of DXA measures). A potential limitation of this study was the inability of DXA imaging technology to quantify ectopic fat within internal organs (such as the heart and liver) as there is some evidence that this is correlated with metabolic disease, independently of total visceral fat.[267, 268] Also, the body fat compartments used in the present study may contain a mixture of adipose tissues with differing biological characteristics (for example, deep layers of subcutaneous fat are considered to have similar properties to visceral fat) but it was not possible to assess this in the present study.[70] The UK Biobank study has the potential to address some of these issues (e.g. detailed characterization of adiposity using MRI scans) and investigate the relation of body composition to vascular disease and other risk factors, such as diabetes and lipid fractions.

Some of the observed variability of anthropometric measures may reflect real temporal variation in addition to measurement error. However, similar self-correlations were observed between baseline and imaging visit (~7 years apart [**Appendix 6.2**]) compared to resurvey and imaging visits (~2 years apart), indicating that real long-term variability is unlikely to account for much of the observed variability between measures. There were no repeat measurements available from the Oxford Biobank, so it was assumed that the within-person variability in UK Biobank participants was comparable to that of Oxford Biobank; whereas ideally repeat measurements in both studies would have been used.[16]

## 6.5 Conclusion

Adiposity is an established risk factor for vascular disease, and this association is known to be mediated in part by blood pressure, diabetes and blood lipids.[269] The findings presented in the current Chapter support the primary importance of visceral fat (or some correlates thereof) in the relation between adiposity and blood pressure, in contrast to an apparent lack of an independent association with subcutaneous android and gynoid fat. It also found a strong relation between fat-free mass and blood pressure that requires further investigation. After correction for within-person variability, the associations with visceral fat were similar for each of the anthropometric measures of adiposity, and the relation between these measures and blood pressure was largely explained by their correlation with visceral fat. Overall, these findings suggest that visceral fat is the primary etiological component of both central and general adiposity underlying the development of adiposity-related hypertension.

**Chapter 6 Tables and Figures**

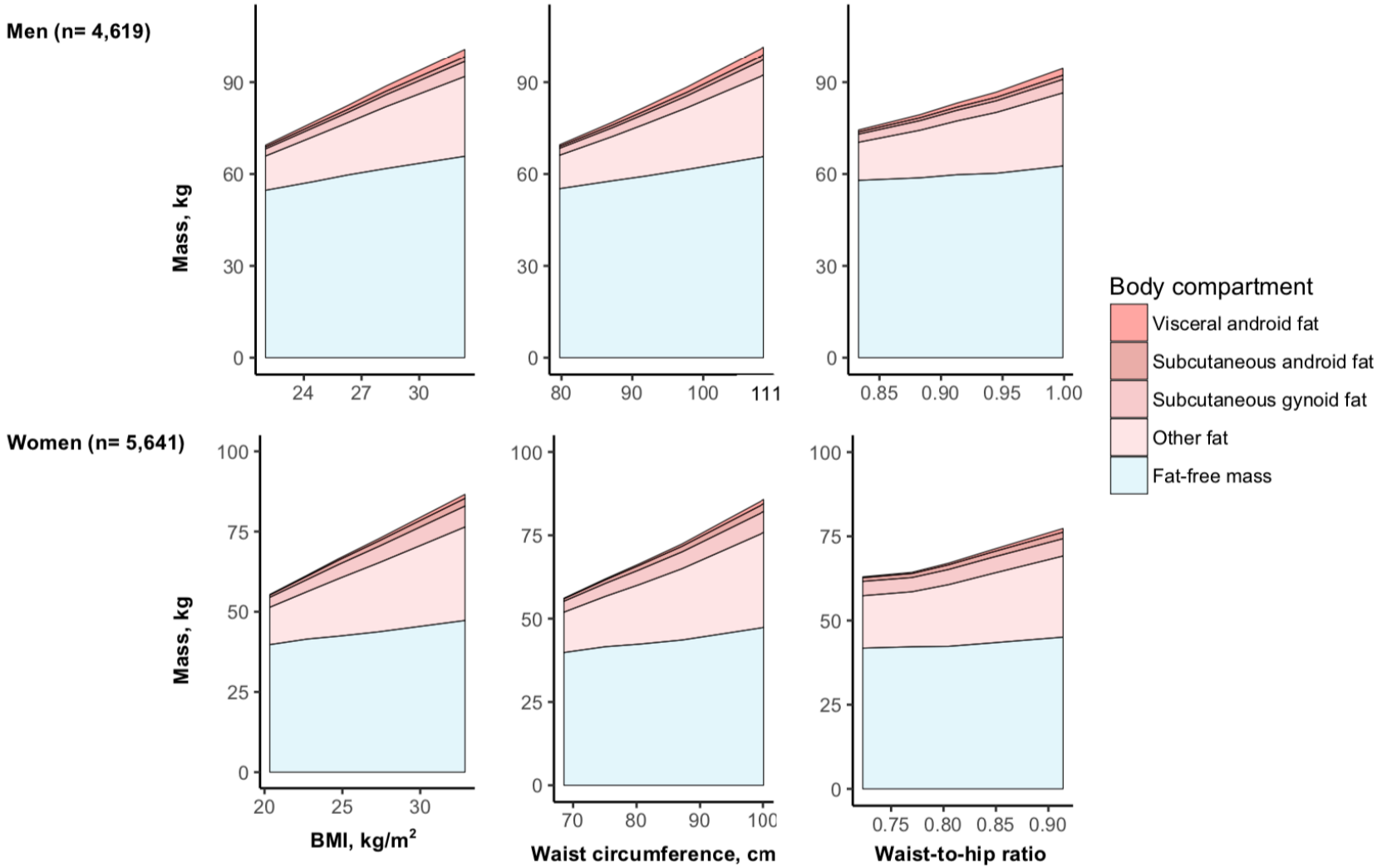

| Figure/Table | Title |
|---|---|
| **Table 6.1** | Baseline characteristics in the Oxford Biobank and UK Biobank imaging studies combined, by sex |
| **Figure 6.2** | Mean DXA-derived measures of body composition with increasing levels BMI, WC and WHR, by sex |
| **Table 6.2** | Mean change in DXA-derived body fat compartments per SD higher usual levels of BMI, WC and WHR, by sex |
| **Figure 6.2** | DXA-derived measures of body composition versus SBP after additional adjustment for all other mutually exclusive body fat compartments, by study and sex |
| **Figure 6.3** | Anthropometric measures of adiposity versus systolic blood pressure (SBP), with and without further adjusting for DXA-derived measures of body composition, by sex |

**Table 6.1** Baseline characteristics in the Oxford Biobank and UK Biobank imaging studies combined, by sex

| | Men (n=4 619) | Women (n=5 641) |
|---|---|---|
| **Demographic characteristics** | | |
| Mean age, years (SD) | 49.2 (10.1) | 48.0 (9.5) |
| White, n (%) | 4 448 (96%) | 5 419 (96%) |
| Professional occupation, n (%) | 2 966 (64%) | 3 170 (56%) |
| Current smoker, n (%) | 368 (8%) | 347 (6%) |
| Daily drinker, n (%) | 1 229 (27%) | 722 (13%) |
| **Anthropometry, mean (SD)** | | |
| Height, cm | 177.5 (6.8) | 164.1 (6.4) |
| Weight, kg | 84.1 (13.2) | 68.9 (12.7) |
| BMI, kg/m$^2$ | 26.7 (3.8) | 25.6 (4.6)) |
| Waist circumference, cm | 93.1 (10.2) | 82.3 (11.6) |
| Hip circumference, cm | 101.6 (6.9) | 101.2 (9.4) |
| Waist-to-hip ratio | 0.91 (0.06) | 0.81 (0.07) |
| **DXA measures, mean (SD)** | | |
| Fat-free mass, kg | 59.9 (7.2) | 42.9 (5.2) |
| Fat mass, kg | 23.8 (8.4) | 25.6 (9.3) |
| Visceral fat | 1.4 (0.9) | 0.6 (0.5) |
| Subcutaneous android fat | 1.0 (0.5) | 1.4 (0.7) |
| Subcutaneous gynoid fat | 3.5 (1.2) | 4.6 (1.5) |
| Other fat | 17.8 (6.2) | 19.0 (6.9) |
| **Blood pressure, mean (SD)** | | |
| Systolic, mmHg | 134.0 (16.0) | 124.5 (18.0) |
| Diastolic, mmHg | 79.8 (9.5) | 75.3 (9.7) |

DXA = Dual energy X-ray Absorptiometry. Those with missing or outlying anthropometry, DXA and blood pressure variables (see **Appendix 6.1**)

**Figure 6.1** Mean DXA-derived measures of body composition with increasing levels BMI, WC and WHR, by sex



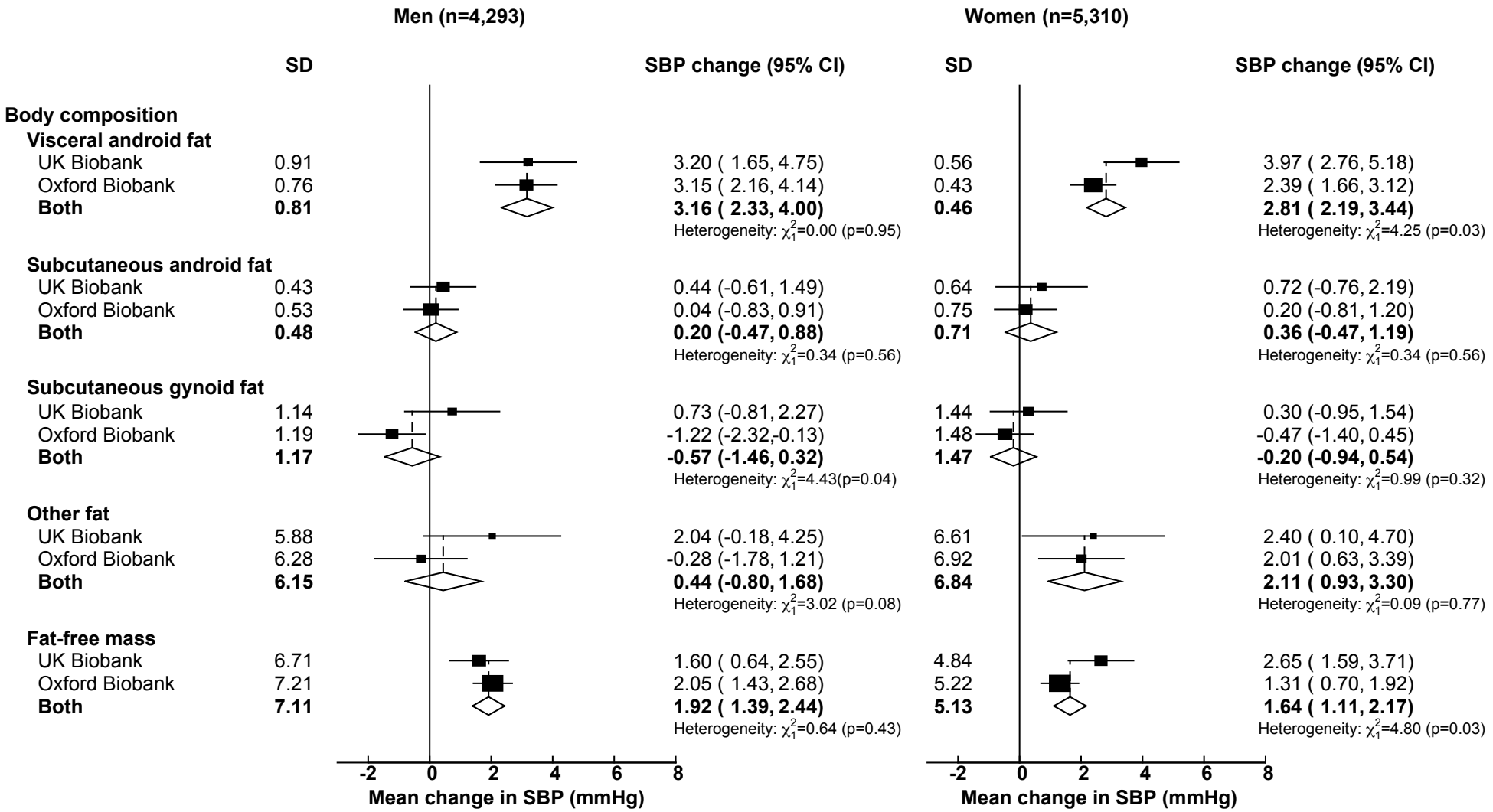

DXA = Dual energy X-ray Absorptiometry. Participants with missing or outlying anthropometry, DXA and blood pressure variables were excluded (**Appendix 6.1**).

**Table 6.2** Mean change in DXA-derived body fat compartments per SD higher usual levels of BMI, waist circumference and waist-to-hip ratio, by sex

| Adiposity measure | Men (n=4619) | | | Women (n= 5641) | | |
|---|---|---|---|---|---|---|
| | SD | Mean change (kg) | 95% CI | SD | Mean change (kg) | 95% CI |
| **BMI** | 3.7 | | | 4.5 | | |
| Visceral android fat | | 0.74 | 0.72 - 0.76 | | 0.44 | 0.43 – 0.46 |
| Subcutaneous android fat | | 0.33 | 0.32 - 0.34 | | 0.62 | 0.61 – 0.70 |
| Subcutaneous gynoid fat | | 1.00 | 0.98 - 1.02 | | 1.29 | 1.26 – 1.31 |
| Other fat | | 5.56 | 5.47 - 5.64 | | 6.53 | 6.46 – 6.59 |
| Fat-free mass | | 4.11 | 3.95 - 4.28 | | 2.83 | 2.72 – 2.94 |
| **Waist circumference** | 9.5 | | | 10.7 | | |
| Visceral android fat | | 0.73 | 0.72 – 0.75 | | 0.43 | 0.42 – 0.44 |
| Subcutaneous android fat | | 0.38 | 0.37 - 0.39 | | 0.64 | 0.63 – 0.65 |
| Subcutaneous gynoid fat | | 1.09 | 1.07 – 1.11 | | 1.19 | 1.16 – 1.22 |
| Other fat | | 6.10 | 6.02 – 6.19 | | 6.56 | 6.47 – 6.65 |
| Fat-free mass | | 4.08 | 3.90 – 4.27 | | 2.97 | 2.85 – 3.09 |
| **Waist-to-hip ratio** | 0.05 | | | 0.06 | | |
| Visceral android fat | | 0.72 | 0.70 – 0.75 | | 0.36 | 0.35 – 3.38 |
| Subcutaneous android fat | | 0.28 | 0.27 – 0.30 | | 0.39 | 0.37 – 0.41 |
| Subcutaneous gynoid fat | | 0.79 | 0.76 - 0.83 | | 0.43 | 0.38 – 0.48 |
| Other fat | | 5.17 | 4.99 – 5.34 | | 3.99 | 3.78 – 4.19 |
| Fat-free mass | | 2.04 | 1.79 – 2.29 | | 1.47 | 1.31 – 1.63 |

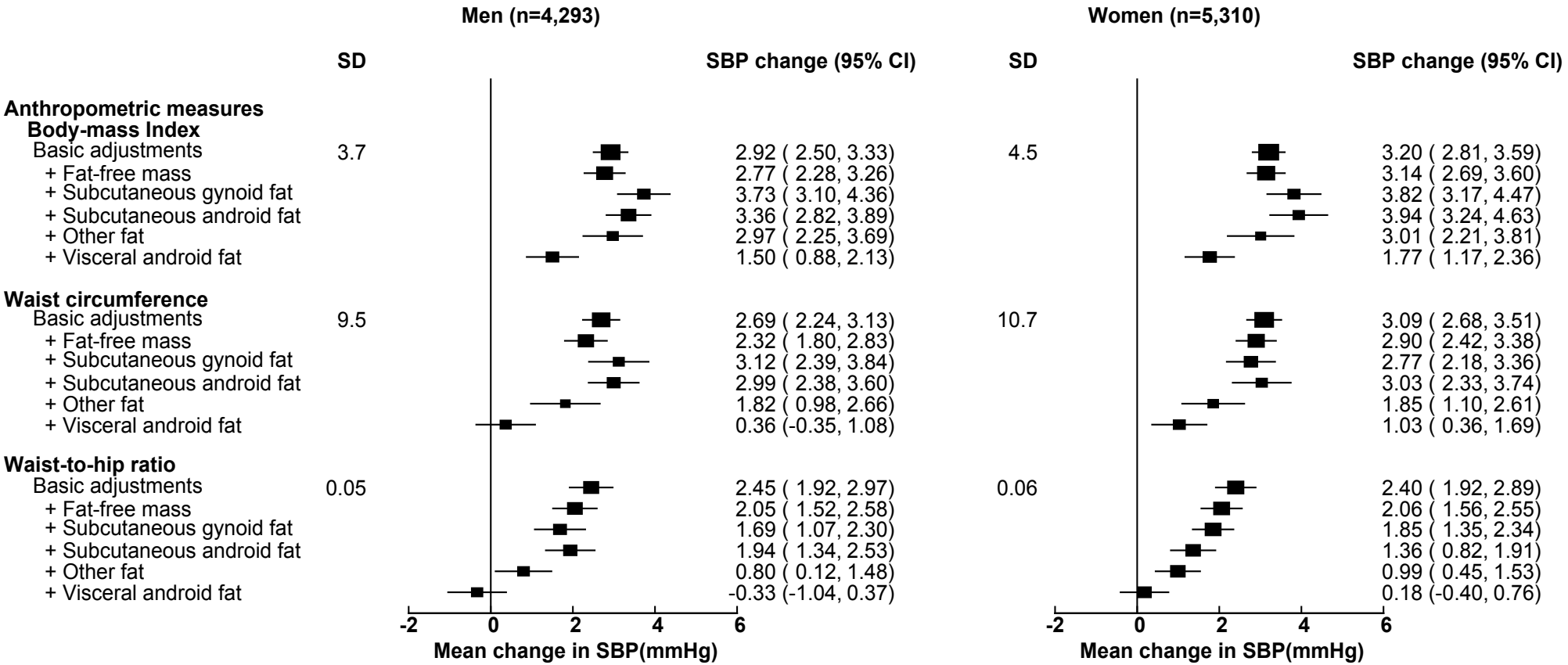
DXA= Dual energy X-ray Absorptiometry. Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in **Appendix 6.1**.

**Figure 6.2** DXA-derived measures of body composition versus SBP after additional adjustment for all other mutually exclusive body fat compartments, by study and sex




Results presented as the mean change in SBP per standard deviation (SD) increase in DXA-derived body composition variable, adjusted for age (5-year groups), height (sex-specific fifths), education/occupation (6 groups) and alcohol consumption (5 groups). Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in **Appendix 6.1**, with further exclusion of those on blood pressure lowering medication.

**Figure 6.3** Anthropometric measures of adiposity versus SBP, with and without further adjusting for DXA-derived measures of body composition, by sex




DXA= Dual energy X-ray Absorptiometry. Results presented as the mean change in SBP per standard deviation (SD) increase in anthropometric measure of adiposity, adjusted for age (5-year groups), education/occupation (6 groups) and alcohol consumption (5 groups). Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in Appendix 6.1., with further exclusion of those on blood pressure lowering medication.

## CHAPTER 7: Prospective associations between adiposity and coronary heart disease in the UK Biobank

### Chapter summary

Adiposity is a major risk factor for CHD, but most studies use indirect markers of general adiposity such as BMI. There is no clear consensus on which adiposity measure best predicts CHD risk in a contemporary UK population, and the extent to which excess adiposity-related CHD risk could be prevented through established and emerging cardiovascular risk factors remains unknown. This Chapter uses 455 148 UK Biobank participants aged 40-69 years without prior vascular disease or missing adiposity values at baseline. Cox regression analysis produced combined and sex-specific HR for incident CHD with increasing usual levels of BMI, Body fat %, Trunk fat %, WC, WHTR and WHR after adjustment for potential confounders. The independent effects of these measures were explored, as well as effect modification by selected characteristics, and potential mediating factors. A total of 13 114 incident CHD events occurred over a follow-up period of 8 years. Each adiposity measure displayed positive and approximately log-linear associations with subsequent CHD risk, with stronger associations for measures of adiposity distribution than for general adiposity after correcting for RDB. The HR per SD higher usual levels of adiposity ranged from 1.24 (1.22 – 1.26) for BMI to 1.34 (1.31 – 1.38) for WHR. The relevance of usual WHR to CHD was particularly strong among women (1.41, 1.35 - 1.48), and remained strongly associated with CHD after adjustment for BMI (1.25, 1.22 - 1.28). The observed prospective associations were partially mediated by blood pressure, lipids and insulin resistance, which together explained most of the observed excess risk. Additional adjustment for markers of glomerular filtration rate, liver function and inflammation resulted in near-complete removal of associations for all measures except WHTR and WHR, which remained independently associated with CHD risk.

## 7.1 Background

Excess adiposity is a leading risk factor for CHD in the UK and globally.[270] The majority of evidence for adiposity-related CHD risk comes from large-scale epidemiological studies investigating the effects of BMI. Despite being a reasonably predictive measure of general adiposity, BMI does not directly quantify fat mass, nor does it indicate body fat distribution. Furthermore, there is growing evidence that visceral adiposity may be more aetiologically relevant than general adiposity to CHD.[271] Therefore, other commonly-used measures of body fat distribution, such as WC, WHTR, WHR or bio-electrical impedance analysis (BIA) could be superior to BMI when identifying high-risk individuals for CHD.[198, 272] However, their relevance to CHD risk beyond BMI remains unclear, and currently these measures are not utilized for CHD risk prediction at the population level. In particular, previous validation studies of BIA have been very small (n<1000), and the relevance of this technology to CHD risk beyond other measures has not been assessed using large-scale studies.

Previous large-scale prospective cohort studies have not allowed a direct comparison of the associations of CHD risk with a wide range of established and emerging measures of adiposity, including BMI, WC, WHR, WHTR and BIA estimates of body composition. To date, the most reliable evidence for the association between adiposity and CHD risk is from meta-analyses of large-scale prospective studies. ERFC meta-analysis of 58 prospective studies using IPD for 220 000 participants, reported strong, positive and approximately log-linear associations of incident CHD risk with BMI, WC and WHR. Each measure was associated with similar approximately 30% higher risk of CHD per usual SD higher adiposity level (HR for BMI: 1.32, 1.24-1.41; WC: 1.32, 1.24 – 1.40; WHR: 1.30, 1.22 -1.38).[273] However, unlike individual studies, meta-analyses are not able to conduct as detailed an assessment for confounding and other biases (e.g. accounting for within-person variability in exposures using the same study population). A number of large prospective studies have indicated that measures of central adiposity (such as WC and WHR) have stronger associations than BMI with CHD risk,[124, 127, 167] however there is a lack of large-scale evidence for the relevance of WHTR and BIA-derived adiposity measures to CHD risk.

In summary, uncertainty remains surrounding the relevance of common measures of general and central adiposity to CHD risk and the underlying mechanisms remain unclear. This Chapter has three primary aims: i) to describe the relation of BMI, BIA-derived body fat%, trunk fat %, WC, WHTR and WHR with risk of CHD in the UK Biobank, with careful consideration for confounding, measurement error and other potential sources of bias; ii) to assess whether the associations differ across important population sub-groups; and iii) to

explore whether these associations are independent beyond established and emerging intermediate factors such as blood pressure, insulin resistance, dyslipidaemia, systemic inflammation, liver and kidney function.

## 7.2 Statistical analysis

Hazard ratios (HR) and corresponding 95% confidence intervals (CI) for higher adiposity on the risk of incident CHD events were calculated using Cox proportional-hazards regression analysis. Where appropriate, regression models were stratified by 5-year age-at-risk, region and sex, and were further adjusted for education, deprivation index, ethnicity, smoking and alcohol consumption. Decisions on covariate adjustments were based on theoretical importance as evidenced by previous studies,[124, 157, 163, 167] and clear evidence for CHD-related factors which had displayed clear cross-sectional associations with adiposity measures at baseline (**Chapter 4**). The statistical improvement of the model after progressive adjustment was explored for each confounding factor, and potential confounders which did not impact on the exposure-disease association were not included as confounders in the main analysis. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). All plots were created in R using the 'Jasper' package (CTSU, Oxford)

### *7.2.1 Within-person variability and correction for regression dilution bias*

The RDR produced by the Pearson's partial correlation coefficient method (parametric) was used to correct for RDB in the main analysis.[254] The decision to use this self-correlation method to estimate the RDR was based on previous analyses (**Chapter 5**). The estimated log(HR) for baseline measures (and their corresponding standard errors) were divided by the RDR, a statistical technique described previously.[262] Similarly, the 'usual SD' of each adiposity measure was obtained from the baseline SD through multiplication by $\sqrt{r}$. For graphical representation of HR (95% CI) with increasing usual levels of adiposity, estimates were plotted against the mean adiposity value at resurvey within groups defined by baseline tenths (or fifths) of adiposity.

### *7.2.2 Association shape: CHD risk at increasing levels of adiposity*

To investigate and compare the shapes of associations between adiposity measures and CHD risk, HRs were plotted in tenths defined by the overall baseline adiposity measurements. When plotted, consecutive pairs of the middle six tenths were combined to create the middle three fifths, and all estimates were plotted against the mean value at resurvey within each baseline group to represent 'usual' levels of adiposity as discussed previously (**Chapter 5**). For meaningful graphical comparisons, x-axes were standardised between plots to represent

±3 SDs from the overall mean value. For sex-specific analyses, the reference group was the lowest tenth of adiposity among women. All 95% confidence intervals were estimated to represent the group-specific variance, including the reference group.[155, 274, 275]

### *7.2.3 Association magnitude: CHD risk per SD-unit increasing adiposity*

Where HRs were approximately log-linear, CHD risk was estimated per usual SD higher adiposity level, thereby allowing for direct comparisons of the magnitude of the association between adiposity measures. All analyses investigating association magnitude between adiposity and CHD risk were performed separately for men and women, based on previous evidence of effect modification by sex.[14] Therefore, sex-specific usual SDs were used for all sex-specific analyses. Joint effects and independence between adiposity measures were investigated by comparing HRs with increasing BMI (per SD usual levels) before and after adjusting for central adiposity measures (WC, WHR and WHTR) and vice versa.

### *7.2.4 Effect modification*

To investigate the consistency of adiposity-related CHD risk (per usual SD unit) across the study population, the associated HRs were compared across important population subgroups. These subgroups were decided *a priori* based on theoretical importance and previous evidence of effect modification identified in the literature search (**Chapter 2**), including age-at-risk categories (40-49; 50-59; 60-69;70-79), Ethnicity (White; non-White), UK region (England; Scotland; Wales) and education attainment (College educated; not college educated). Heterogeneity between subgroups was assessed using standard Chi-squared tests for Heterogeneity. Similarly, Chi-squared tests for trend were used to assess if the HRs differed meaningfully according to any given subgroups.

### *7.2.5 Effect mediators*

Potential intermediate factors underlying adiposity-related CHD risk were included in the Cox proportional hazard regression models sequentially by order of theoretical importance according to the literature[24, 116, 140, 157, 247] and significant contribution to the model. To allow for a direct comparison with previous large-scale evidence,[24, 247] possible combinations of SBP, HbA1c, self-reported type II diabetes, lipids (including Apo A, Apo B, LDL and HDL cholesterol) and inflammatory markers (including CRP and albumin) were included in the analysis. Additional potential mediators included in the present analysis that have not been previously investigated in large-scale studies included eGFR (estimated using the CKD-EPI equation) and liver enzymes (ALP and GGT).

*7.2.6 Sensitivity analysis*

A variety of sensitivity analyses were performed to assess the potential for known biases underlying prospective associations between adiposity and CHD risk. Previous literature has suggested a difference in adiposity-related associations between fatal and non-fatal CHD events.[124] Therefore, an analysis was performed using CHD death as the endpoint. Additionally, to investigate possible effects of reverse causality, HRs for the first half of follow-up were compared with final half of follow-up (approximately four years each). To investigate potential treatment effects, HRs were also compared among participants who did not report taking blood pressure-lowering medication at baseline. Lastly, to explore the impact of smoking habits and alcohol consumption, additional sensitivity analyses were conducted excluding ever-drinkers and ever-smokers.

## 7.3 Results

### *7.3.1 Adiposity measures and CHD risk*

During a median of 8 years, 13 114 first-ever CHD events occurred (**Table 7.1**), including 817 fatal events. Most CHD events (n= 8970) occurred in men. After adjusting for potential confounders, all six adiposity measures displayed strong, positive and approximately log-linear associations with incident CHD (**Figure 7.1**). In general, associations with CHD risk were stronger for measures of central adiposity than for general adiposity. Compared with those in the bottom tenth of the distribution, the HR for those in the top tenth ranged from 2.30 (95% CI: 2.20 – 2.41) for BMI to 3.37 (95% CI: 3.23 – 3.50) for WHR. When stratified by sex, the HRs per SD were stronger among women for all measures, although men were at greater absolute risk of CHD at all levels of adiposity **(Figure 7.2)**.

Per SD higher usual levels (**Figure 7.3**), central adiposity measures displayed the strongest associations with CHD risk, and WHR in particular was associated with over a third greater excess risk of CHD than BMI (HR per usual SD: 1.34 for WHR versus 1.24 for BMI). HRs were larger for women than men, particularly for body fat % (HR per usual SD higher body fat %: 1.32 [1.27 – 1.37] among women versus 1.24 [1.21 – 1.27] among men) and body fat distribution measures (HR per SD increasing WC: 1.36 vs. 1.24; WHTR: 1.38 vs. 1.27; and WHR: 1.41 vs. 1.31 for women vs. men), all of which showed statistically significant effect modification by sex ($p_{Het}$<0.01).

### *7.3.3 Sub-group analysis*

**Figures 7.4 to 7.7** display the sex-specific HRs for CHD per usual SD higher adiposity measure by categories of age, ethnicity, region and education. Associations were not affected by age-at-risk, and although there was a general trend for higher relative risk of CHD at younger ages, the confidence intervals mostly overlapped, with only WHR among women showing a significant linear trend towards lower relative risks at older ages ($p_{Trend}$ = 0.03). Although the confidence intervals were wide, the HR for higher WHR was stronger among men of non-White ethnicity compared with White men (HR per SD usual level: 1.51, 1.33- 1.71 and 1.31, 1.28 -1.35, $p_{Het}$= 0.04) which was not observed among women or for any other adiposity measure. Whether participants achieved higher education or whether they were recruited from Scotland, England or Wales did not materially affect adiposity-related CHD risk.

*7.3.4 Independence of adiposity measures*

The association between BMI and CHD was approximately halved after adjusting for WHR and WC in sex-combined analyses (**Figure 7.8**). Conversely, associations of WC and WHR with CHD risk were only partially explained by general adiposity measures (BMI or Body fat%). In sex-stratified analyses, adjusting for WC removed the association between BMI and CHD risk among women (HR per SD increasing BMI: 1.27, 1.23 – 1.31 and 1.02, 0.96 – 1.08 before and after adjusting for WC, respectively), but only partially attenuated the association among men (**Figure 7.9**). Associations with WHR were partly explained by BMI among both men and women. Conversely, BMI explained the majority of WC-related CHD risk among men, whereas the association between WC and CHD risk was unchanged in women after adjusting for BMI. Across thirds of BMI, increasing thirds of WHR remained associated with a linear increase in CHD risk, as did WC. However, given that adiposity measures are correlated, there was a lack of power to assess this relationship in participants in the top third of BMI and bottom third of WC and vice versa (**Figure 7.10**). Increasing thirds of WHR remained associated with increasing CHD risk within thirds of BMI (**Figure 7.11**).

*7.3.5 Effect mediators*

All six adiposity measures remained positively associated with CHD risk after adjusting for blood pressure, lipids and insulin resistance, however associations were more than halved across all measures (**Figure 7.12**). When stratified by sex, in general, associations with general and central adiposity measures were similarly attenuated in men and women after adjusting for these potential mediating factors (**Figure 7.13**). After additional adjustment for liver enzymes, eGFR and inflammatory markers, associations with CHD were completed attenuated for BMI, body fat %, trunk fat % and WC among both men and women, whereas WHTR and WHR remained independently associated with CHD risk (**Figures 7.14 & 7.15**).

*7.3.6 Sensitivity analysis*

Associations were largely unaltered when analyses were repeated in never smokers, never drinkers, participants without self-reported diabetes, and in participants who did not report using blood pressure-lowering medication at baseline assessment (**Figures 7.16 & 7.17**). Slightly stronger associations were observed for central adiposity measures (WC, WHTR and WHR) with fatal CHD among men (**Figure 7.16**), but there was insufficient power to assess this in women (**Figure 7.17**). HRs did not appreciably differ after omission of the first four years of follow-up, or after additional adjustment for physical activity (**Figures 7.18 & 7.19**).

## 7.4 Discussion

This study has characterised the associations between six commonly used adiposity measures and CHD risk in greater detail and with greater precision than has been previously possible. The results presented in this Chapter suggest a greater relevance of central adiposity compared to general adiposity for CHD risk. Therefore, BMI could be superseded by measures of adiposity which are more informative of CHD risk at the population level, including BIA-based adiposity measures. Of the large-scale studies identified in the literature review comparing associations of CHD risk between multiple indices of adiposity (**Chapter 2**), the current study includes the largest number of incident CHD events, which is twice the number of events included in the ERFC meta-analysis and an early analysis of AMI in the UK Biobank.[14, 247] Furthermore, this is the largest study to assess the association between BIA-based measures of body composition and CHD risk to date.

### *7.4.1 Association shape and magnitude*

The results presented in the current study are broadly consistent with most studies identified in the literature review, showing a positive association with increasing adiposity and CHD risk, with no evidence for a threshold of effect throughout the entire range of adiposity.[14, 24, 123, 127-129, 131, 133, 247] The current study had the advantage of available HES records to capture all previous MI or stroke events at baseline rather than relying on self-reported prior disease. Therefore, the accurate exclusion of baseline disease in the current analysis avoided reverse causality. In an early analysis of the UK Biobank, initially a J-shaped association with increasing BMI and a composite outcome of all fatal CVD events was observed before removing participants with baseline disease, reinforcing the importance of controlling for reverse causality.[249] The results presented in the current study provide further justification for the importance of preventing adiposity-related CHD risk by reducing the entire distribution of adiposity at a population level, as there was no evidence of an adverse effect on CHD risk at the lower ranges of each adiposity measure.[276] However, when considering this approach, it is important to acknowledge possible harmful effects of very low BMI values, particularly as previous evidence has suggested an apparent association with many fatal health outcomes, self-harm and interpersonal violence.[123]

Results from the current study contrast with observations from the ERFC meta-analysis of 58 prospective studies using IPD on over 220 000 participants which observed similar magnitudes of associations for CHD with increasing BMI, WC and WHR of roughly 30% per SD increase in adiposity.[273] However, the authors noted unexplained heterogeneity of the

adiposity-CHD associations between included studies, most likely from differing protocols, cohort effects (study populations were recruited at different times) or other study-specific characteristics. Indeed, a more recent analysis of ERFC data limited to 12 studies, observed associations with CHD risk were more consistent with the HRs presented in the current study for usual levels of BMI, WC, WHTR and WHR.[247] Similarly, the log-linear positive associations for CHD risk observed with increasing BMI, WC, WHTR and WHR were consistent with an early analysis of UK Biobank data investigating adiposity-related AMI risk (HR per 1 SD increasing adiposity: 1.28 and 1.22 for BMI; 1.28 and 1.35 for WC; 1.33 and 1.34 for WHTR; 1.36 and 1.49 for WHR among men and women, respectively).[14] Similarly, the greater relevance of central adiposity measures to CHD and CVD risk compared with general adiposity has been observed elsewhere.[124, 127, 128, 277]

Moreover, body fat distribution and general adiposity measures were separately and independently associated with incident CHD in the current study. This has been demonstrated elsewhere,[124, 127] and suggests that central adiposity measures such as WC and WHR could provide additional information beyond BMI for improved CHD risk prediction at the population level (discussed in greater detail in **Chapter 9**).[278] The mechanisms underlying the apparent greater relevance of central adiposity to CHD risk compared with general adiposity have been discussed in depth in **Chapter 1** (*Section 1.2.3*), however it is thought to involve the metabolic effects of visceral fat in particular.[61-63]

### *7.4.1 Effect modification*

The main results were generally consistent with other large-scale studies comparing adiposity-related CHD risk across different measures, however previous studies have lacked power to reliably describe adiposity-CHD associations across important population sub-groups. As a result, current evidence is inconsistent for effect modification of BMI-related CHD, and there is a lack of large-scale evidence for effect modification of CHD risk associated with central adiposity and BIA-derived adiposity measures.

#### *7.4.1.1 Sex differences*

When stratified by sex, the relevance of central adiposity to CHD in the current study was particularly strong among women compared with men. This finding is consistent with sex-differences observed previously for central adiposity in the handful of large-scale studies identified with sufficient power to investigate this (one of which is an early analysis of UK Biobank study participants).[14, 127] However, the current study is the largest study to investigate effect modification of central adiposity-related CHD risk by sex, including over twice the number of CHD events as previous large-scale studies.[14, 124, 127, 273] In the current study, BMI-

related CHD risk did not differ between men and women. This finding is also consistent with previous studies, including the ERFC,[273] three other large-scale meta-analyses,[134, 157, 279] and four other large-scale prospective studies.[14, 127, 128, 131]

Although not fully understood, there could be a number of explanations for the observed sex-differences for central adiposity. Firstly, a stronger effect of central adiposity among women could be the result of different body fat distribution patterns among men and women. For example, 1-SD higher WHR among women would represent a greater absolute increase in WC (and hence, likely visceral fat) compared with 1-SD higher WHR among men simply because women have larger hips. However, studies which investigate the effects of specific fat depots such as VAT on metabolic mediators such as insulin resistance have also found a greater susceptibility to the effects of central adiposity and VAT on metabolic risk factors among women compared with men.[280-282] Therefore, the observed sex difference could be the result of a true biological susceptibility to the effects of central adiposity among women compared with men.

However, it is important to acknowledge that at all levels of adiposity, men were at greater absolute risk of CHD, which, given the results described in the current study may in part be explained by their 'unfavourable' central body fat distribution relative to women. In particular, gluteo-femoral adipose tissues may play a key role in determining the level of central adiposity and hence the susceptibility to cardiometabolic consequences of adiposity. Recent RCTs have suggested that peripheral fat storage could protect from the expansion of central fat depots among women.[283] Therefore, the increased susceptibility to CHD observed for central body fat distribution measures among women could be the result of a reduction in 'cardio-protective' gluteo-femoral fat depots rather than adverse effects of visceral adipose tissue.

Although the reasons are unclear, given the results presented in the current study, when investigating adiposity-related CHD risk, it is important to stratify analyses by sex otherwise associations will be dominated by men (who experience the majority of CHD events) and associations among women will be masked.

#### *7.4.1.2 Age*

In contrast to the ERFC and others,[14, 124, 127, 134, 273] the current analysis did not observe clear stronger associations with CHD risk at younger ages, although slightly stronger associations were observed for women at younger ages compared with older age groups, particularly for central adiposity. However, there were very few events in this subgroup of the study population

(n=106), and the results must be interpreted with caution. Importantly, age is the strongest risk factor for CHD risk, and therefore this increase in absolute risk of CHD across age groups must be considered when interpreting effect modification by age in relation to CHD relative risks. It has also been suggested that the accuracy of adiposity measures, particularly BMI, could be compromised in older individuals due to the characteristic loss of muscle mass,[284] which could in part explain the observed weaker associations in older age groups. However, weaker associations with CHD risk in the upper categories of age-at-risk were also observed for body fat % and trunk fat % in the current study, contesting this. Importantly, older age groups are also likely to suffer from reverse causation due to the increased prevalence of chronic conditions which may affect weight such as sarcopenia or dementia.[285]

#### *7.4.1.3 Fatal versus non-fatal events*

The findings presented in the current study suggest that case fatality is greater at upper ranges of central adiposity, specifically among men. However, there were very few fatal CHD events among women (n=184), and therefore there was a lack of statistical power to precisely assess the impact of event type among women in the current study.

These results are consistent with the ERFC meta-analysis and two other large-scale meta-analyses which observed slightly stronger or no change in BMI-CHD associations with coronary death compared with incident CHD.[24, 134, 286] The MWS observed much stronger BMI-CHD associations for fatal (n = 2431) compared with incident CHD events (n= 32 465). This enhanced effect of adiposity on CHD severity has also been described in smaller studies with fewer events.[287-289] None of these studies investigated the effects of different adiposity measures on fatal and non-fatal events, and therefore the UK Biobank is the largest study to date to directly compare the adiposity-related CHD risk across the six selected adiposity measures separately for incident and fatal CHD events. Underlying explanations for the observed greater effect of central adiposity on CHD mortality in the current study are unclear, however the confidence intervals were wide. The case fatality rate of CHD is low in contemporary populations and the UK Biobank will require further years of follow-up to capture large numbers of fatal CHD events.

### *7.4.2 Intermediate factors*

The phenotypic detail of the UK Biobank has the potential to provide novel insights into intermediate pathways underlying adiposity-related CHD risk with greater accuracy than previous large-scale studies. Although speculated previously, the involvement of liver and

kidney function underlying adiposity-related CHD risk has not been investigated in large-scale prospective studies.

Consistent with previous RCT, laboratory and epidemiological evidence,[290, 291] the prospective associations in the current study were chiefly mediated by baseline measures of blood pressure, lipids and insulin resistance, which together explained over half of the observed excess CHD risk across all selected measures of adiposity. These results were similar to those reported by the GBMRFC study where 46% of the observed excess risk of CHD attributed to BMI was explained by blood pressure, cholesterol, and markers of glycaemia in a large meta-analysis of individuals participant data from over 1.8 million individuals across 97 studies.[24] Also similar to the current study, the ERFC meta-analysis found that at least half of the observed CHD risk associated with BMI, WC and WHR was explained by baseline values of blood pressure, history of diabetes, and total and HDL cholesterol.[286, 292] In the current study, additional markers of eGFR, liver function and inflammation completely attenuated associations with all measures except WHTR and WHR, which remained independently associated with CHD risk. These findings suggest that body fat distribution may be contributing to CHD risk through alternative mechanisms compared with general adiposity that are distinct from established risk factors.

This finding suggests that clinical or public health interventions aimed at controlling lipids, blood pressure or glucose tolerance could largely address the excess risk of CHD associated with obesity. The mechanisms through which each of these metabolic mediators act to increase adiposity-related CHD risk is complex but well-established; thought to involve a number of interconnected pathways discussed in depth in **Chapter 4,** including*: i)* sympathetic nervous system activation, angiotensin-aldosterone activity, and hyperinsulinemia contributing to hypertension; and *ii)* dyslipidaemia and systemic inflammation contributing to insulin resistance.[293] However, the current study suggests that additional targets to reduce inflammation, or enhance liver and kidney function could also contribute to further reductions in adiposity-related CHD risk at the population level. Despite the postulated involvement of various morphological adaptations in organ structure and haemodynamic function which is thought to occur in obesity, the contribution of these factors had not been assessed in a large-scale epidemiological study to date. Ectopic fat storage in the kidneys can impair their function, contributing to increased CHD risk in excess adiposity through a variety of pathways including renal salt retention and subsequent hypertension.[239, 293] However, adjusting for eGFR similarly attenuated associations across all adiposity measures. This finding is perhaps surprising given that abdominal obesity is thought to exacerbate renal salt retention since it is directly related to intra-abdominal pressure.[294] Similarly, excess adiposity has been linked with ectopic fat

storage in the liver, which is thought to contribute to many of the metabolic perturbations accompanying obesity, including inflammation, dyslipidaemia and insulin resistance.[293]

Results from the current study suggest that a small proportion of excess CHD risk associated with body fat distribution measures (particularly WHR) were unexplained by baseline measurements of selected cardiometabolic traits. Therefore, WHR may act through mechanisms which were unrelated to established risk factors for CHD. Recent MR studies have confirmed the apparent distinct effects of central adiposity on cardiometabolic traits.[119, 140] Future higher-powered MR studies on a variety of cardiometabolic traits will reveal the independent effects of WHR beyond BMI (**Chapter 8**). Although poorly understood, there could be a number of possible explanations underlying this observation, including 'indirect' mechanisms such as structural changes resulting from visceral adipose tissue expansion and resulting organ damage.[295]

Importantly, whilst overall the findings present in the current study suggest that a significant proportion of the adiposity-related CHD risk could be mitigated by targeting potentially modifiable intermediate factors, it is likely that a larger proportion of CHD risk could be explained by long-term average levels of each intermediate risk factors.[241, 247, 273, 292] However, the validity of methods to correct for long-term measurement error in intermediate factors are uncertain, and therefore this was not undertaken.[254]

### *7.4.3 Strengths and limitations*

The present study included participants from a single large UK population, which reduced the potential for heterogeneity of societal and person-specific factors between different populations which is often unavoidable in large meta-analyses,[157, 273, 279] but maintained the size and length of follow-up required to observe clear exposure-outcome associations. Additionally, the availability of accurately adjudicated events, and standardised measurements of exposures, confounders and potential mediating factors together contribute to a level of phenotypic detail which surpasses all previous studies. Combined with the ability to investigate and infer causality behind observational associations using genetic information (**Chapter 8**), this makes the UK Biobank the ideal platform to conduct a comprehensive investigation into the effect of adiposity on disease risk in a contemporary population.

However, there is still potential for a number of limitations which are ubiquitous across observational epidemiological research. Firstly, the relationship between BMI and CHD risk is commonly affected by reverse causality. However, in the present study, associations

appeared unaffected by follow-up time (**Figures 7.16 & 7.17**), and careful consideration was taken to ensure all participants with prior CVD at baseline were excluded, including prevalent angina as an additional precaution, which was not included in the main outcome (**Chapter 3**). The additional use of HES records for outcome adjudication also likely enhanced the precision of the reported disease risk estimates.[296] Furthermore, whilst the ability to correct for RDB between adiposity measures was a particular strength of the current study, the observed RDR estimates could still be susceptible to imprecision due to the limitations and assumptions of within-person variability estimates discussed previously (**Chapter 5**).[254]

Finally, the UK Biobank cohort lacks ethnic diversity. Although the subgroup analysis demonstrated slightly stronger associations of (hence, suggesting enhanced susceptibility to) adiposity-related CHD risk in non-White compared to White ethnic groups in the current study, this result must be interpreted with caution given the small number of events occurring in non-White ethnic groups.

### 7.5 Conclusion

In summary, all six selected adiposity measures demonstrated strong, positive and approximately log-linear associations with CHD risk throughout the observable range of adiposity, with no evidence of threshold effects. Central adiposity measures displayed the strongest associations with CHD risk, particularly WHR, and appeared particularly relevant among women compared with men. Body fat distribution may act through distinct and independent mechanisms compared with general adiposity, beyond known and emerging cardiometabolic risk factors.

**Chapter 7 Tables and Figures**

| Figure/Table | Title |
|---|---|
| **Table 7.1** | ICD10 and Operation codes for primary outcome in the current study |
| **Figure 7.1** | Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity measures in the UK Biobank |
| **Figure 7.2** | Hazard Ratios (95% CI) for CHD with increasing *usual* levels of adiposity, by sex |
| **Figure 7.3** | Hazard Ratios (95% CI) for CHD per SD higher *usual* adiposity levels, by sex |
| **Figure 7.4** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **men** by selected categorical characteristics at baseline |
| **Figure 7.5** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **women** by selected categorical characteristics at baseline |
| **Figure 7.6** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **men** by selected categorical characteristics at baseline |
| **Figure 7.7** | Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **women** by selected categorical characteristics at baseline |
| **Figure 7.8** | Hazard Ratios (95% CI) for CHD with increasing levels of BMI, WC and WHR, independently of other measures |
| **Figure 7.9** | Hazard Ratios (95% CI) per SD increasing usual BMI, WC and WHR before and after adjusting for general and central adiposity measures, by sex |
| **Figure 7.10** | Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of WC and WHR stratified by thirds of BMI, by sex |
| **Figure 7.11** | Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of BMI stratified by thirds of WC and WHR, by sex |
| **Figure 7.12** | Hazard Ratios (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c |
| **Figure 7.13** | Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c, by sex |
| **Figure 7.14** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity, with adjustment for baseline values of potential intermediate risk factors among **men** |
| **Figure 7.15** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher usual adiposity, with adjustment for baseline values of potential intermediate risk factors among **women** |
| **Figure 7.16** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after various exclusions |
| **Figure 7.17** | Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after various exclusions |

**Figure 7.18** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after adjusting for potential confounders

**Figure 7.19** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after adjusting for potential confounders

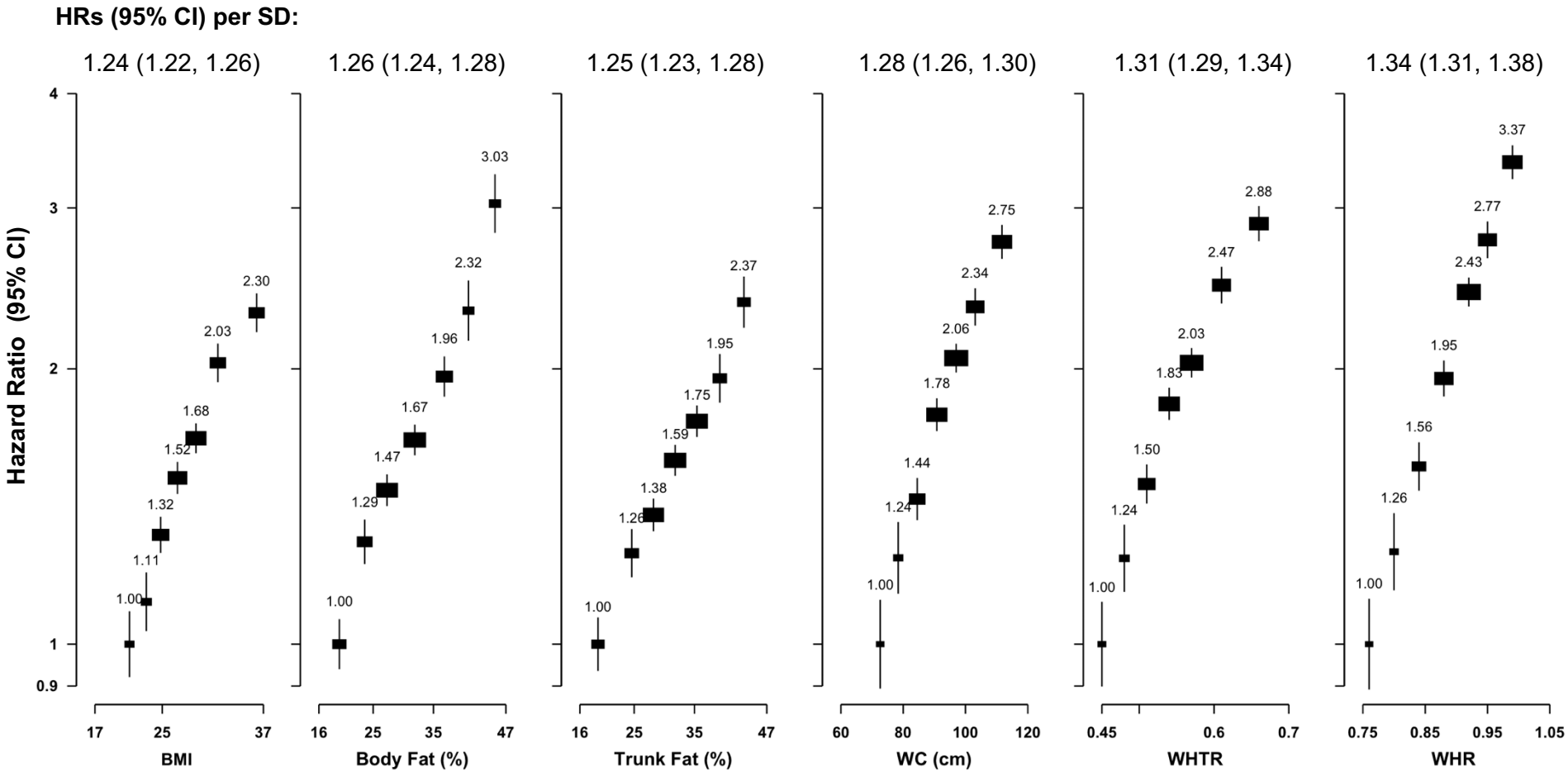
---

**Table 7.1**ICD10 and Operation codes for primary outcome in the current study

| Self-reported disease category | ICD-10/OPCS Category | ICD-10/OPCS code & definition | No. of events occurring during follow-up |
|---|---|---|---|
| • Angina pectoris* | **I20** | I20.0 Unstable angina | 0 fatal (1 805 incident) |
| | | I20.1 Angina pectoris with documented spasm | 0 Fatal (98 incident) |
| | | I20.8 Other forms of angina pectoris | 0 Fatal (455 incident) |
| | | I20.9 Angina pectoris, unspecified angina | 4 fatal (7061 incident) |
| • Acute myocardial infarction | **I21** | I21.0 Acute transmural myocardial infarction of anterior wall | 925 |
| | | I21.1 Acute transmural myocardial infarction of inferior wall | 972 |
| | | I21.2 Acute transmural myocardial infarction of other sites | 113 |
| | | I21.3 Acute transmural myocardial infarction of unspecified site | 106 |
| | | I21.4 Acute subendocardial myocardial infarction | 1 071 |
| | | I21.9 Acute myocardial infarction, unspecified | 2 669 |
| • Subsequent myocardial infarction | **I22** | I22.0 Subsequent myocardial infarction of anterior wall | 6 |
| | | I22.1 Subsequent myocardial infarction of inferior wall | 13 |
| | | I22.8 Subsequent myocardial infarction of other sites | 0 |
| | | I22.9 Subsequent myocardial infarction of unspecified site | 57 |
| • Certain current complications following acute myocardial infarction | **I23** | I23.0 Haemopericardium as current complication following acute myocardial infarction; | 0 |
| | | I23.1 Atrial septal defect as current complication following acute myocardial infarction; | 1 |
| | | I23.2 Ventricular septal defect as current complication following acute myocardial infarction; | 7 |
| | | I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction; | 1 |
| | | I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction; | 0 |
| | | I23.5 Rupture of papillary muscle as current complication following acute myocardial infarction; | 2 |
| | | I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction; | 4 |
| | | I23.8 Other current complications following acute myocardial infarction | 10 |
| • Other acute ischaemic heart diseases | **I24** | I24.9 Acute ischaemic heart disease, unspecified (excl. ischaemic heart disease (chronic) NOS) | 749 |
| • Chronic ischaemic heart disease | **I25** | I25.6 Silent myocardial ischaemia | 5 |
| | | I25.8 Other forms of chronic ischaemic heart disease - Any condition in I21-I22 and I24.- specified as chronic | 1 548 |
| | | I25.9 Chronic ischaemic heart disease, unspecified -Ischaemic heart disease (chronic) NOS | 6 394 |
| • **Operations**: coronary heart disease | **K40*** | Saphenous vein graft replacement of coronary artery | 1 562 |
| | **K41*** | Other autograft replacement of coronary artery | 101 |
| | **K42*** | Allograft replacement of coronary artery | 0 |
| | **K43*** | Prosthetic replacement of coronary artery | 3 |
| | **K44*** | Other replacement of coronary artery | 17 |
| | **K45*** | Connection of thoracic artery to coronary artery | 1 633 |
| | **K46*** | Other bypass of coronary artery | 0 |
| | **K49*** | Transluminal balloon angioplasty of coronary artery | 230 |
| | **K50*** | Other therapeutic transluminal operations on coronary artery | 353 |
| | **K75*** | Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery | 5 691 |
| Total | | | **13 114** |

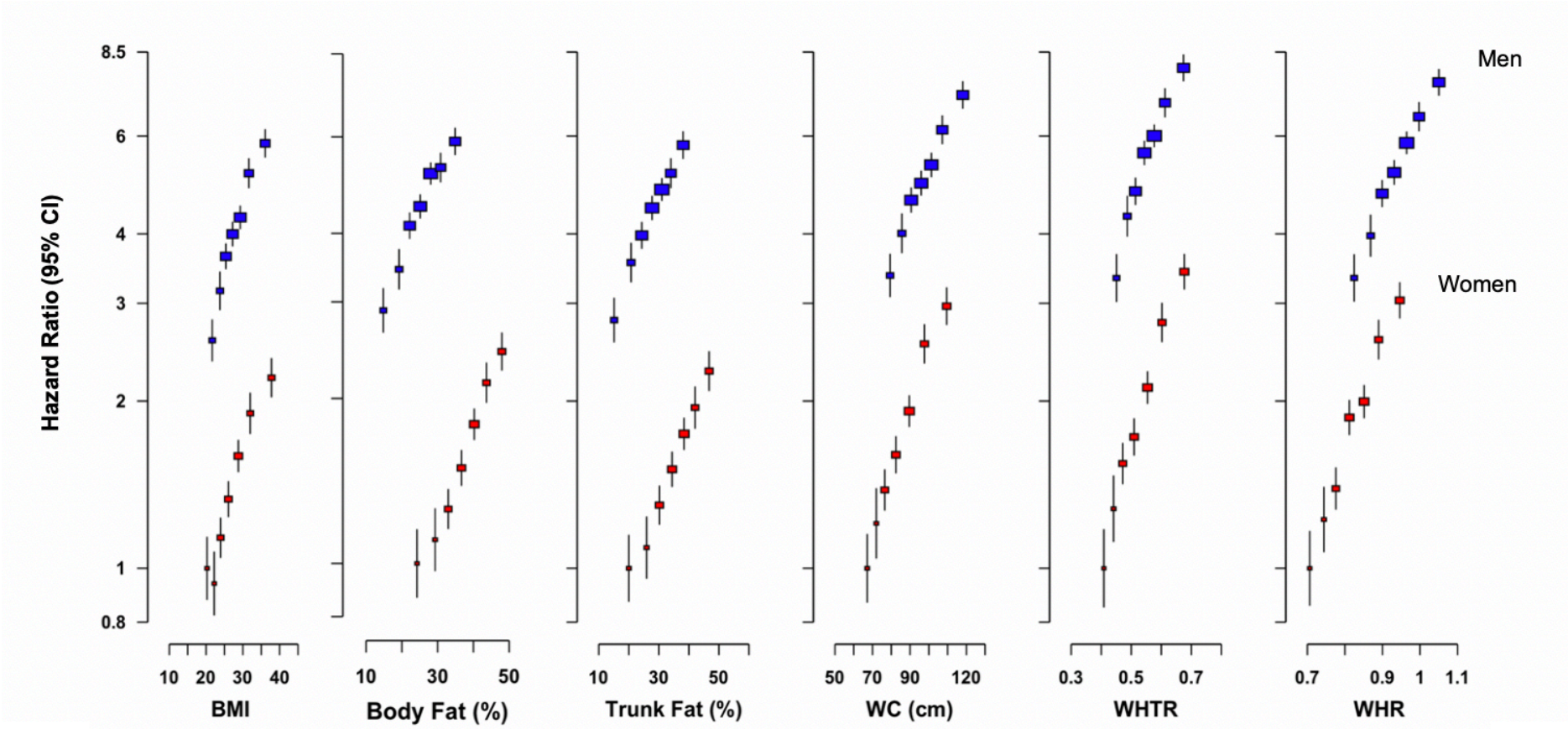
*Angina was included in the study outcome if the event was fatal only. For all other ICD-10 codes, first-ever events were included in the study outcome whether fatal or non-fatal.

**Figure 7.1** Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity measures in the UK Biobank



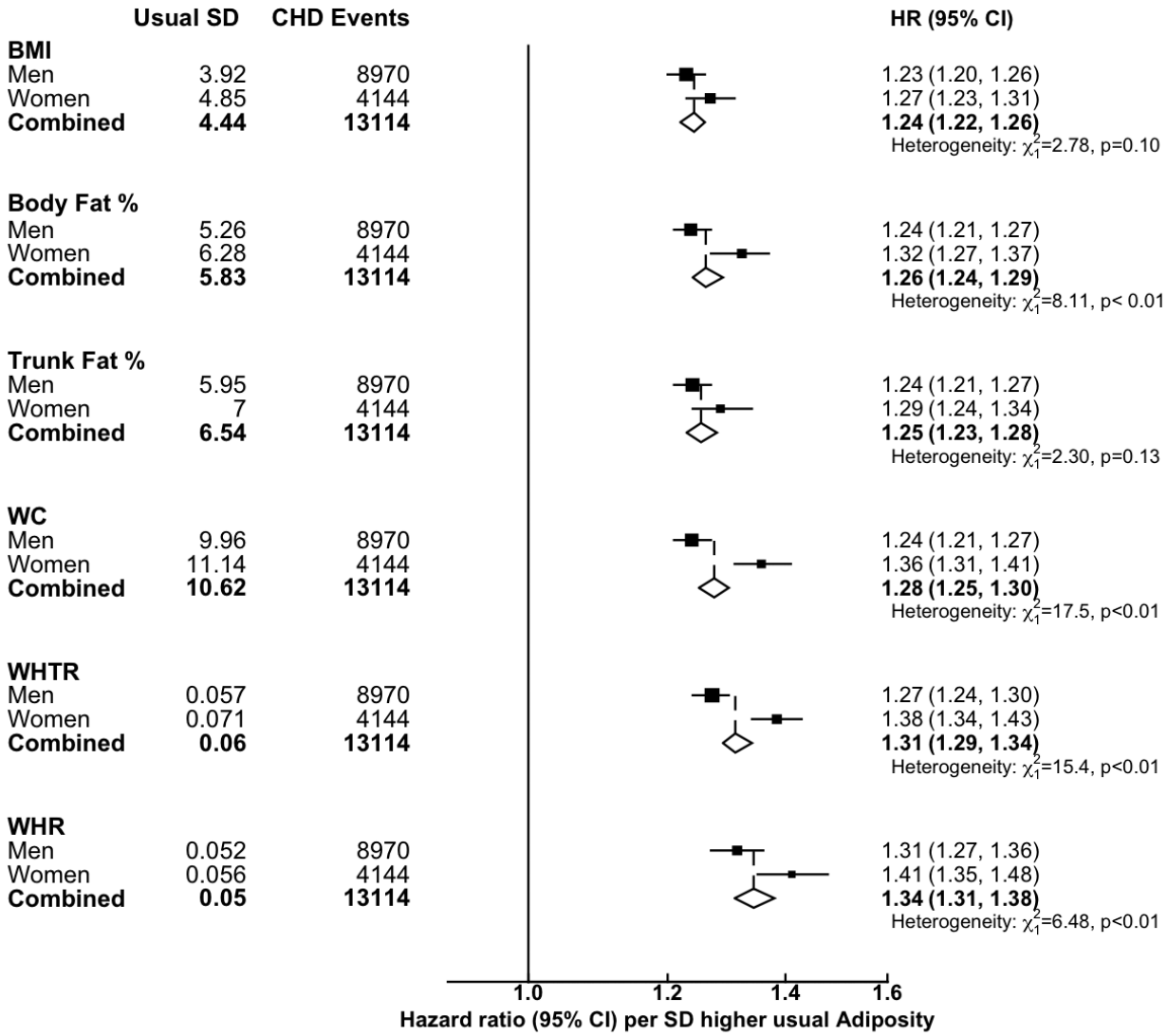

BMI: Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio; WHR= Waist-to-hip ratio. Hazard ratios (95% CI) were stratified by UK region (10 regions), and were further adjusted for age-at-risk (5-year groups), education, social deprivation, ethnicity, smoking and alcohol consumption. Groups correspond to tenths, and the middle three fifths, based on the distribution of each adiposity measure at baseline among men and women. Areas of point estimates are inversely proportional to the variance of the log risk. 95% CIs for group-specific risks reflect uncertainty in the log for each risk estimate. Analysis was restricted to those participants without a history of cardiovascular disease or missing/implausible adiposity measures at baseline (n=455 148).

**Figure 7.2** Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity, by sex



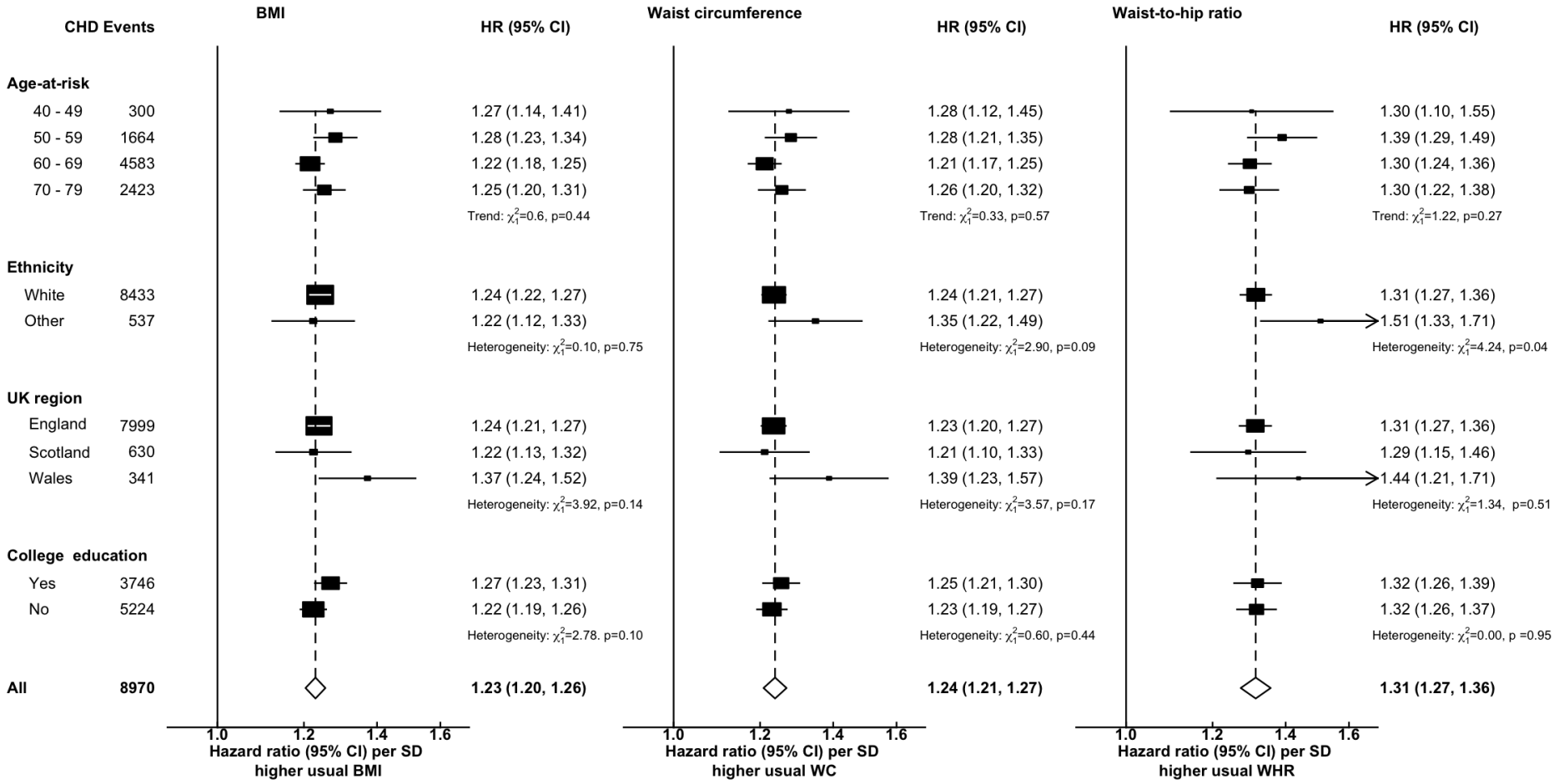

BMI: Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio; WHR= Waist-to-hip ratio. Hazard ratios (95% CI) were stratified by UK region (10 regions), with further adjustment for age-at-risk (5-year groups), education, social deprivation, ethnicity, smoking and alcohol consumption. Groups correspond to the bottom and top two tenths, and the middle three fifths, based on the distribution of each adiposity measure at baseline among men and women. Reference groups were the bottom tenth among women. X-axes represent approximately ±3SDs of the average sex-specific mean value. Areas of point estimates are inversely proportional to the variance of the log risk. 95% CIs for group-specific risks reflect uncertainty in the log risk for each estimate. Analysis was restricted to those participants without a history of cardiovascular disease or missing/implausible adiposity measures at baseline (n=455 148).

**Figure 7.3** Hazard Ratio (95% CI) for CHD per SD higher *usual* adiposity levels, by sex



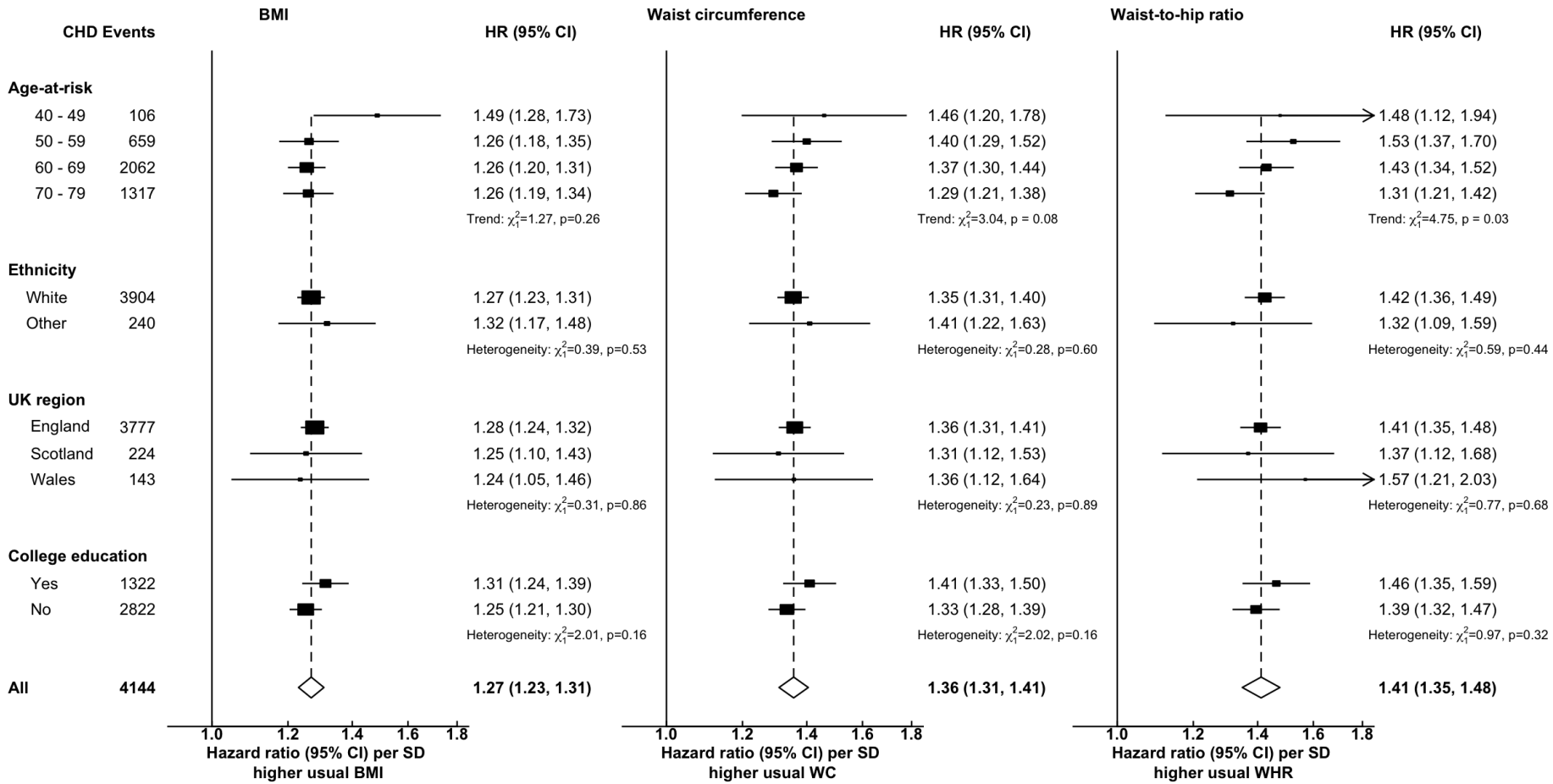

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline (n=455 148).

**Figure 7.4** Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **men** by selected categorical characteristics at baseline



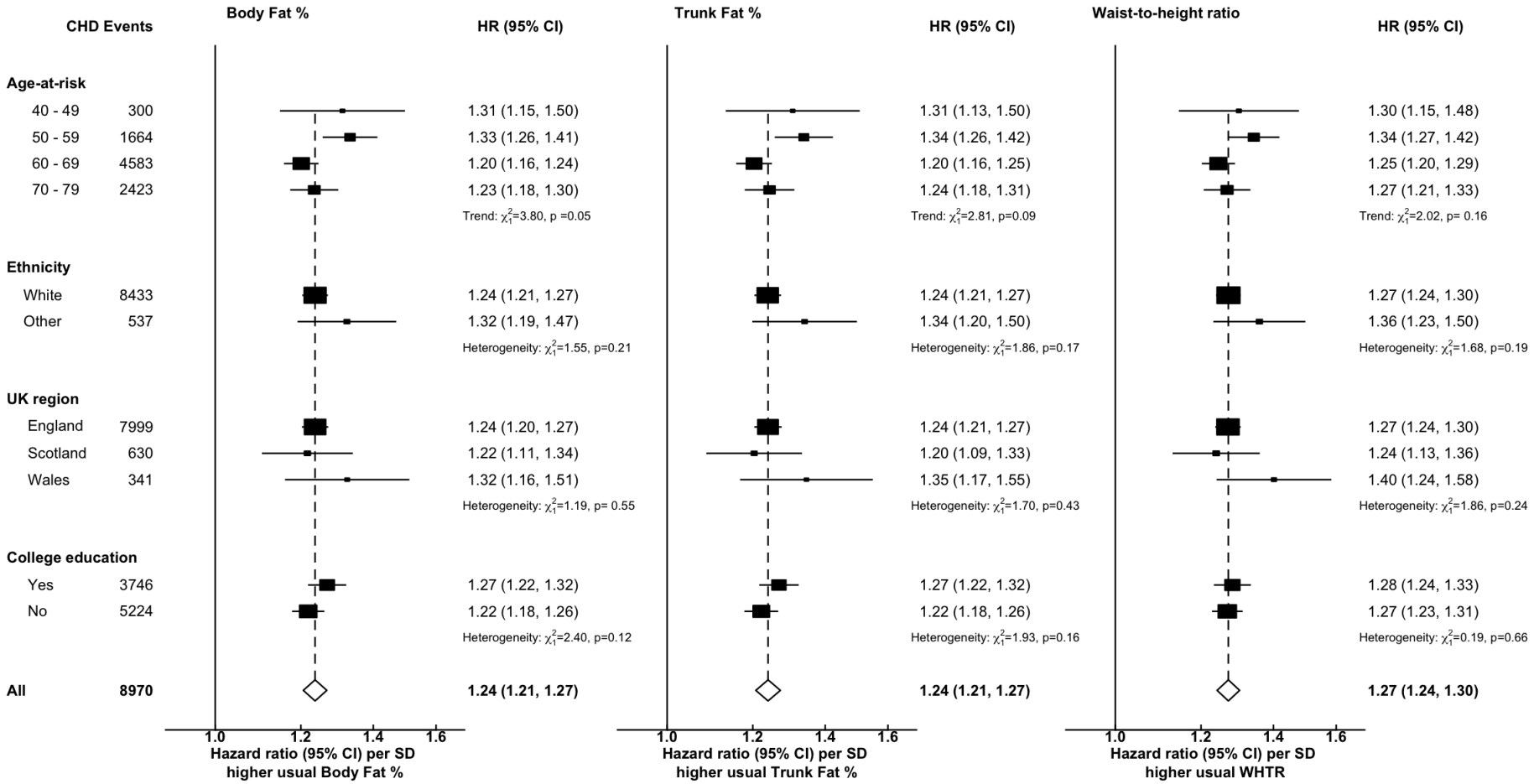

BMI= Body-mass Index; WC= Waist circumference; WHR= Waist-to-hip-ratio. Where appropriate, hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline.

**Figure 7.5** Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of BMI, WC and WHR among **women** by selected categorical characteristics at baseline



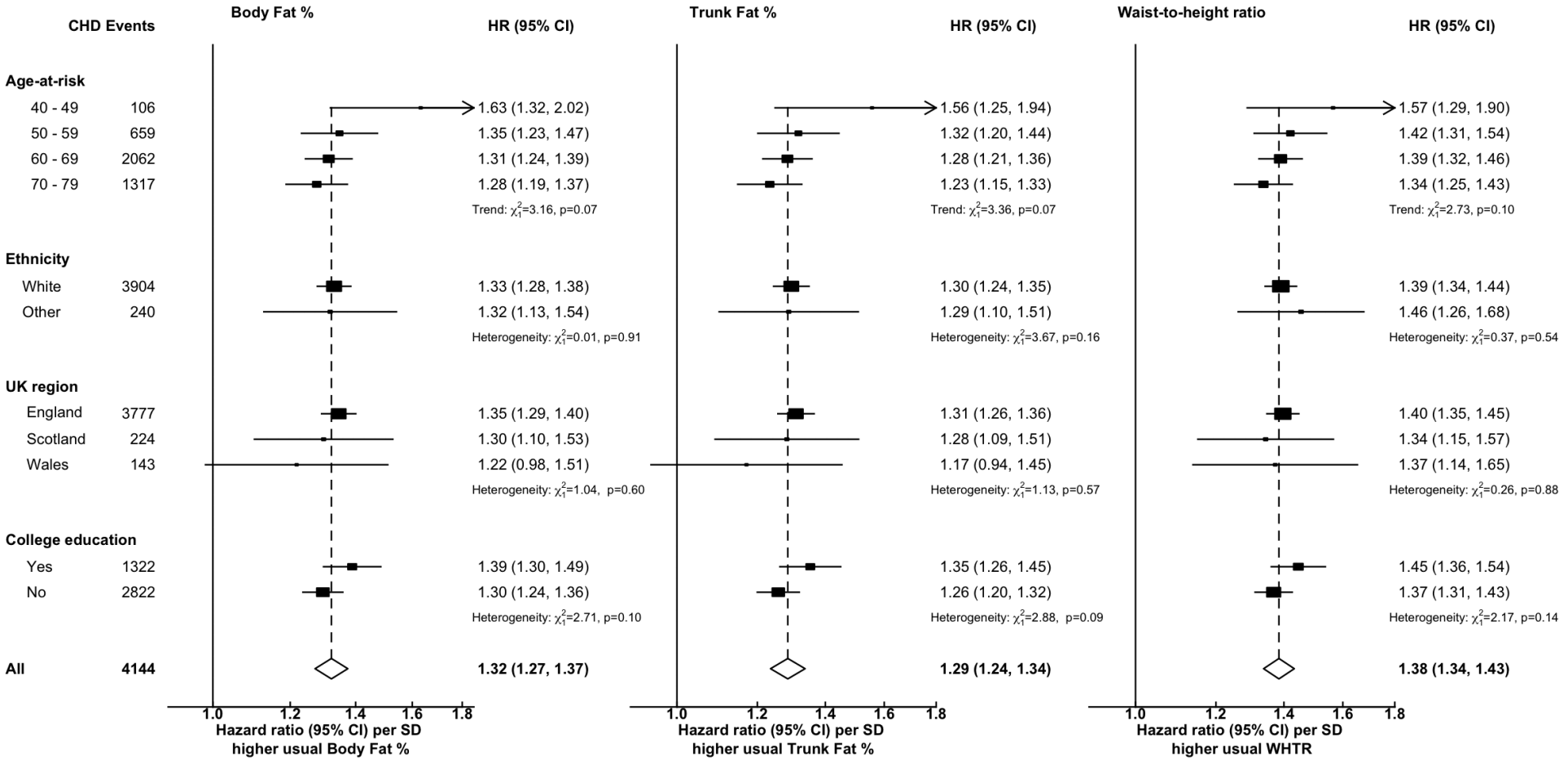

BMI= Body-mass Index; WC= Waist circumference; WHR= Waist-to-hip-ratio. Where appropriate, hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline.

**Figure 7.6** Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **men** by selected categorical characteristics at baseline



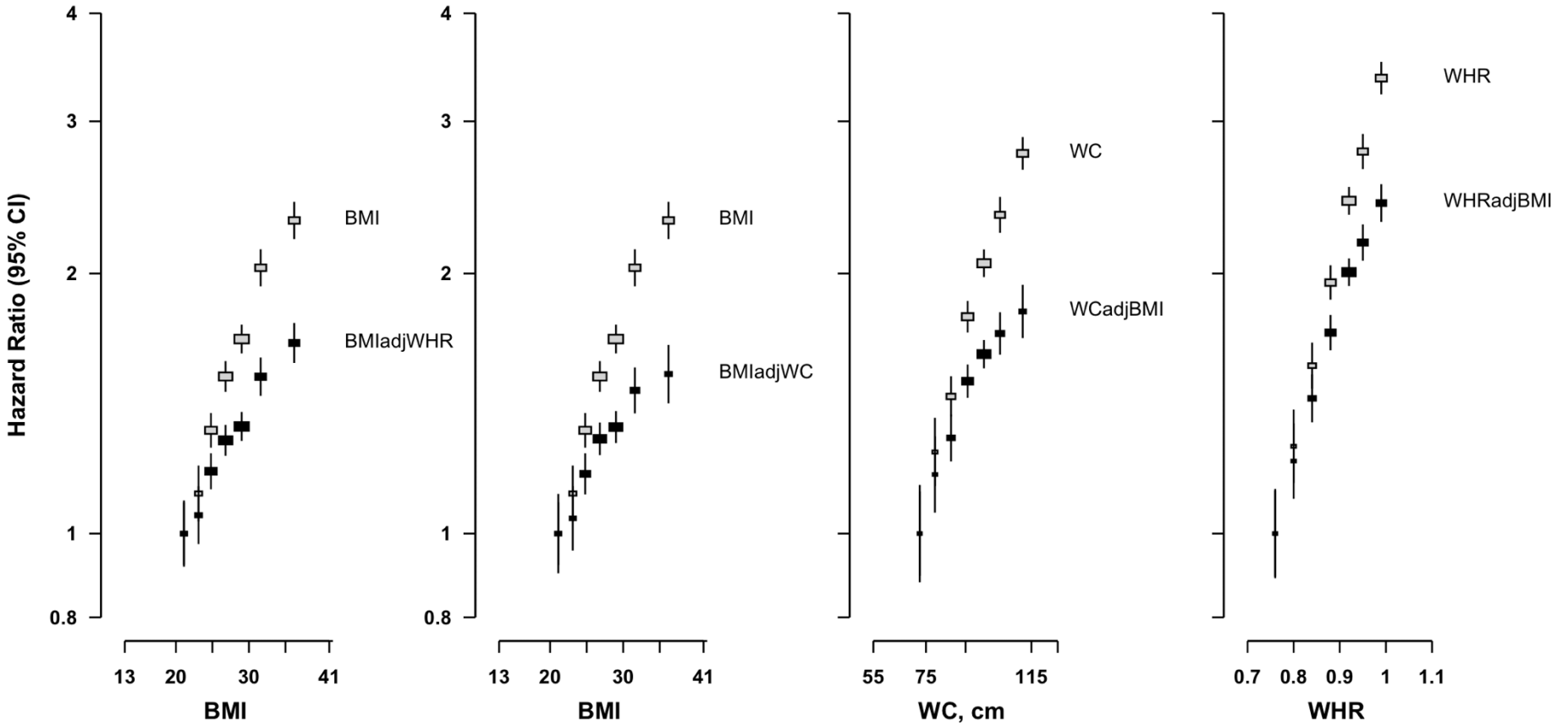

WHTR= Waist-to-height-ratio. Where appropriate, hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline.

**Figure 7.7** Hazard Ratios (95% CI) for coronary heart disease per SD higher *usual* levels of Body Fat %, Trunk Fat % and WHTR among **women** by selected categorical characteristics at baseline



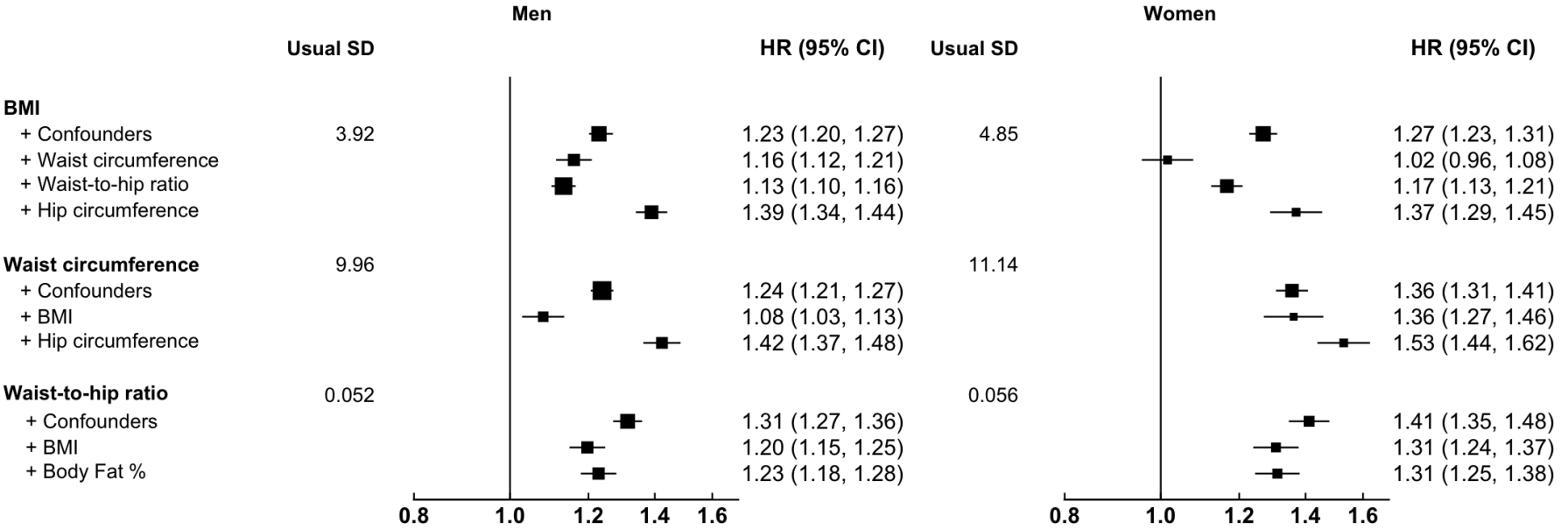

WHTR= Waist-to-height-ratio. Where appropriate, hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline.

**Figure 7.8** Hazard Ratios (95% CI) for CHD with increasing levels of BMI, WC and WHR, independently of each other




BMI: Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio; WHR= Waist-to-hip ratio. Hazard ratios (95% CI) were stratified by UK region (10 regions), and were further adjusted for age-at-risk (5-year groups), education, social deprivation, ethnicity, smoking and alcohol consumption. Groups correspond to tenths, and the middle three fifths, based on the distribution of each adiposity measure at baseline among men and women. X-axes represent approximately ±3SDs of the average sex-specific mean value. Areas of point estimates are inversely proportional to the variance of the log risk. 95% CIs for group-specific risks reflect uncertainty in the log for each risk estimate. Analysis was restricted to those participants without a history of cardiovascular disease or missing/implausible adiposity measures at baseline (n=455 148).

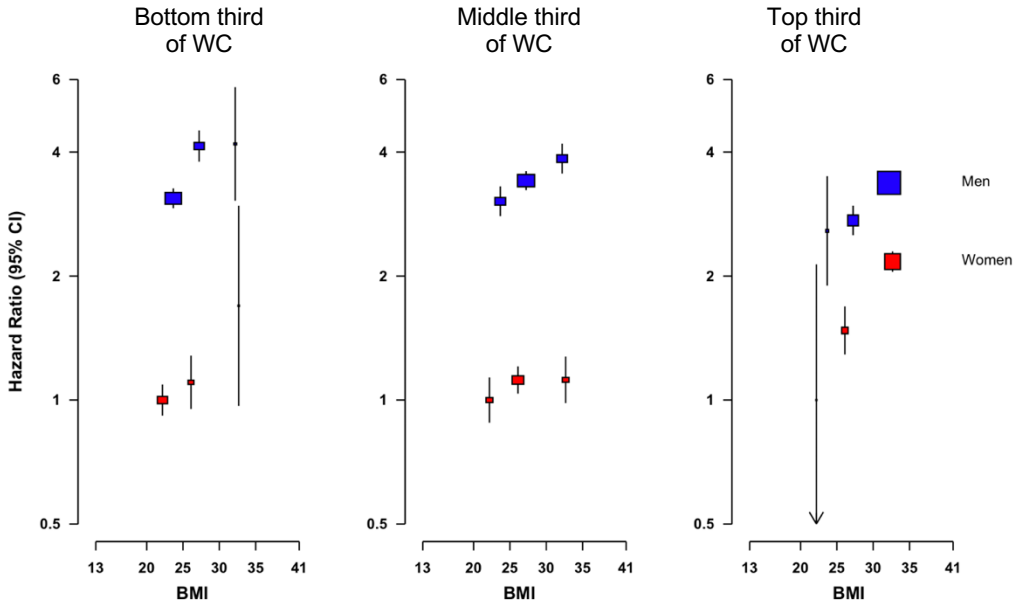
**Figure 7.9** Hazard Ratio (95% CI) per SD increasing usual BMI, WC and WHR before and after adjusting for general and central adiposity measures, by sex



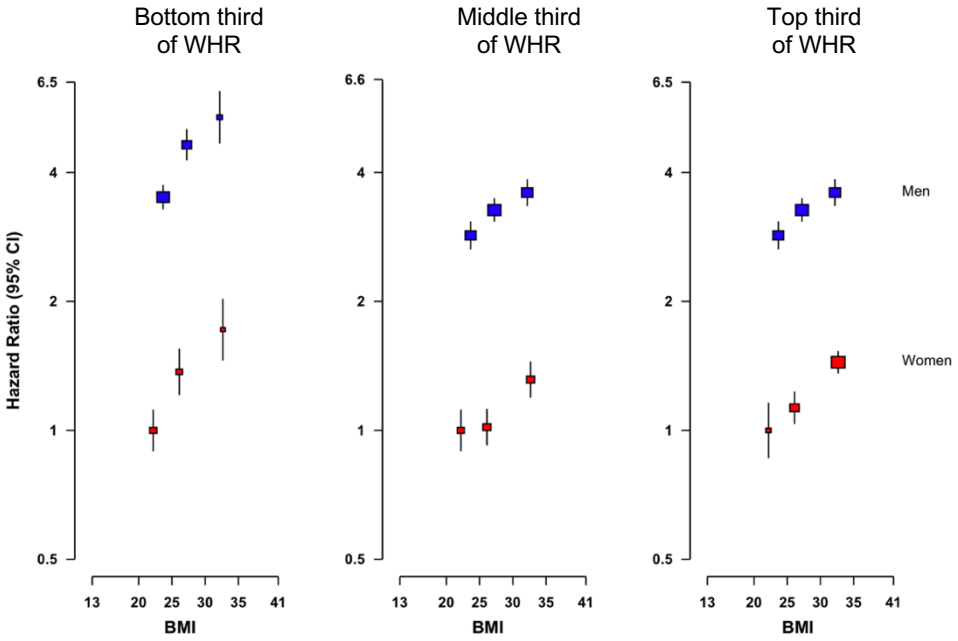

BMI= Body-mass Index. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity (7 groups), smoking (3 groups), alcohol (4 groups) and were stratified by sex and UK region (10 regions). For BMI, WC and WHR, first results were adjusted for confounders only, then other adiposity measures were each adjusted for separately. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data and those who did not self-report doctor-diagnosed cardiovascular disease at baseline.

**Figure 7.10** Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of WC and WHR stratified by thirds of BMI, by sex

**1. a) Hazard Ratio by thirds of BMI according to WC thirds**



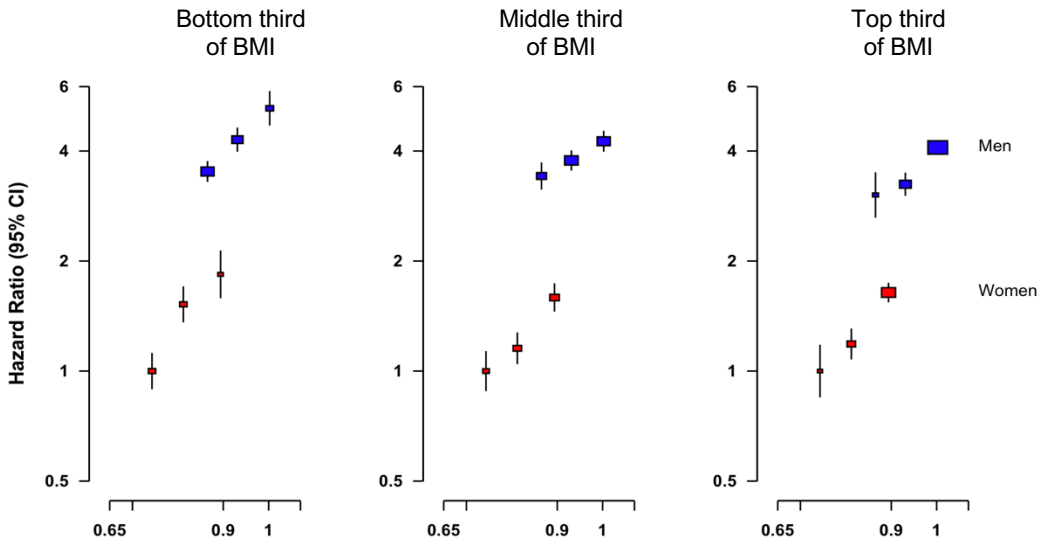

**B) Hazard Ratio by thirds of BMI according to WHR thirds**



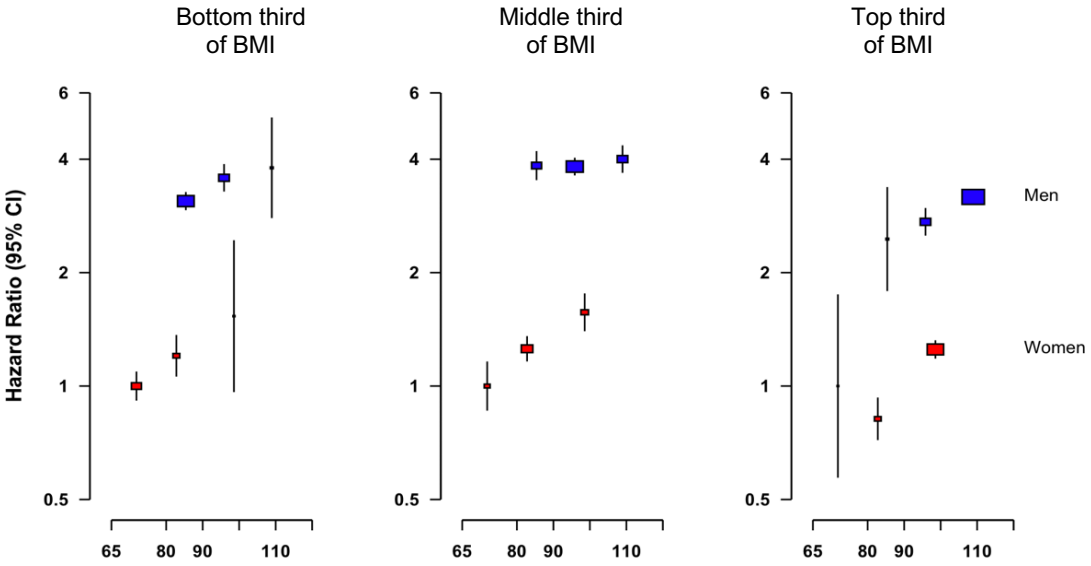

BMI= Body-mass Index; WC= Waist circumference; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. X-axes represent approximately ±3SDs of the average sex-specific mean value. Areas of point estimates are inversely proportional to the variance of the log risk. Analysis was restricted to those participants with complete adiposity data at baseline and who did not have cardiovascular disease at baseline (n=455 148).

**Figure 7.11** Hazard Ratios (95% CI) for coronary heart disease at increasing thirds of BMI stratified by thirds of WC and WHR, by sex

**A) Hazard Ratio by thirds of WHR according to BMI thirds**

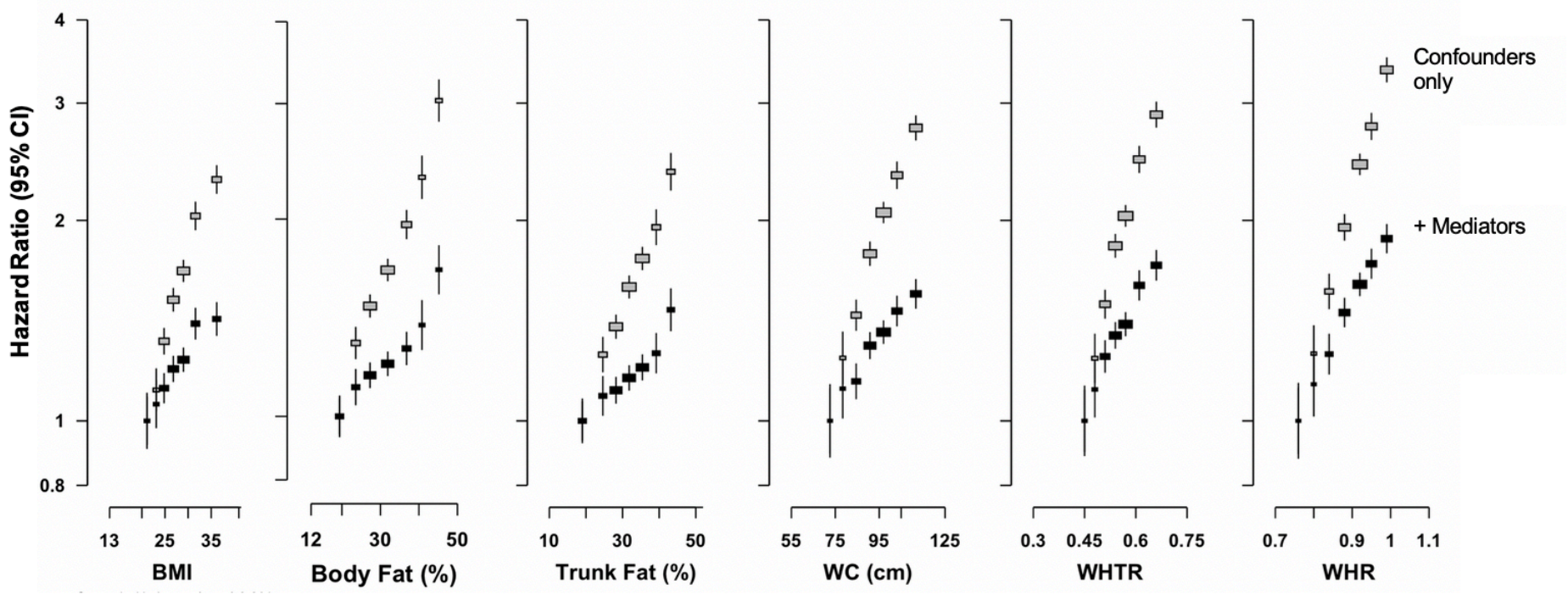



**B) Hazard Ratio by thirds of WC (cm) according to BMI thirds**



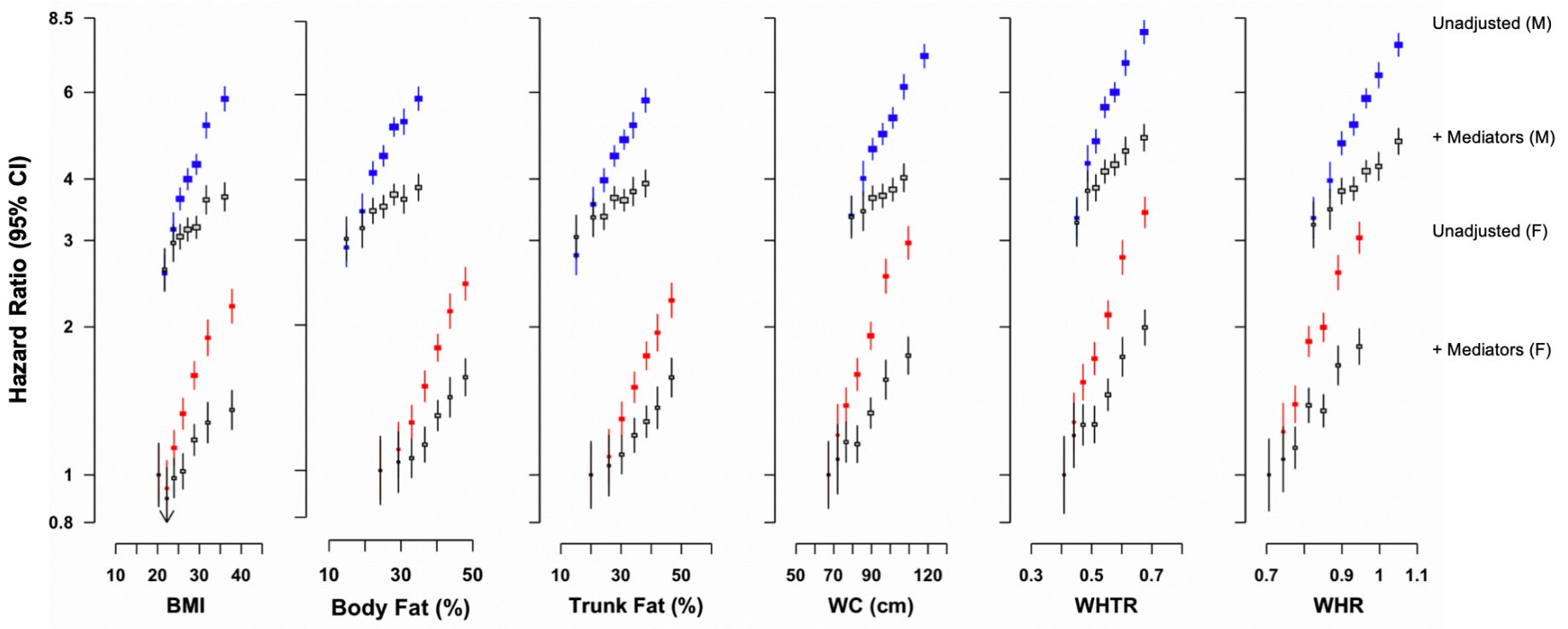

BMI= Body-mass Index; WC= Waist circumference; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. X-axes represent approximately ±3SDs of the average sex-specific mean value. Areas of point estimates are inversely proportional to the variance of the log risk. Analysis was restricted to those participants with complete adiposity data at baseline and who did not have cardiovascular disease at baseline (n=455 148).

**Figure 7.12** Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c



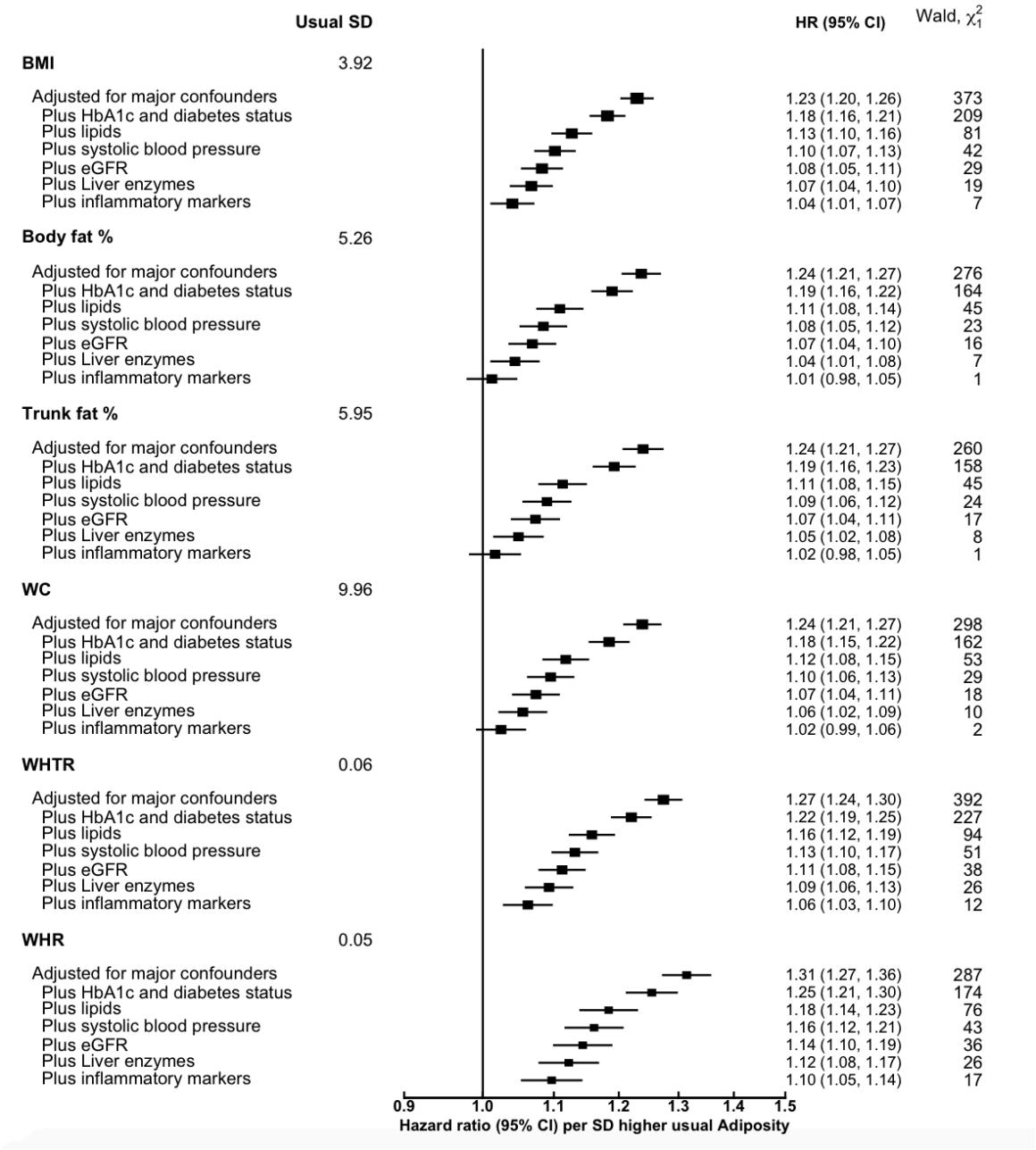

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Groups were defined by tenths of the adiposity distribution among men and women combined, and the reference groups were the lowest tenth. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education (5 groups), deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by sex and UK region. Additional adjustments were sex-specific tenths of the following: lipids (Low-density lipoprotein, High-density lipoprotein, Apo-lipoprotein A, Apo-lipoprotein B), systolic blood pressure, type II diabetes self-reported doctor's diagnosis and HbA1c. Areas of point estimates are inversely proportional to the variance of the log risk. Analysis was restricted to those participants with complete adiposity and biomarker data and without cardiovascular disease at baseline (n=455 148).

**Figure 7.13** Hazard Ratio (95% CI) for CHD with increasing *usual* levels of adiposity, before and after adjusting for blood pressure, cholesterol, diabetes status and HbA1c, by sex



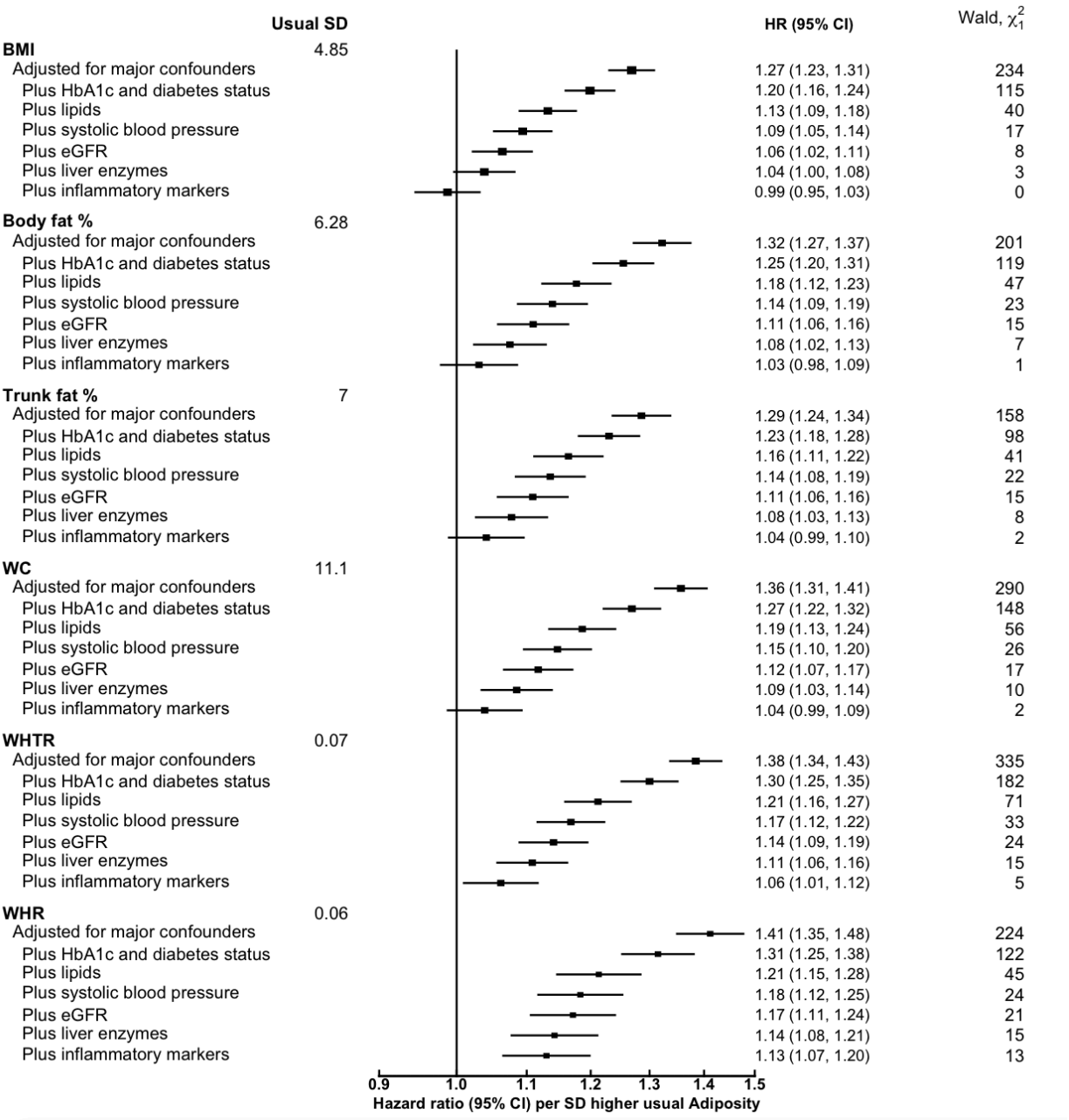

BMI: Body-mass index; WC = waist circumference; WHTR= Waist-to-height ratio; WHR= Waist-to-hip ratio. Hazard ratios (95% CI) were stratified by UK region (10 regions), with further adjustment for age-at-risk (5-year groups), education, social deprivation, ethnicity, smoking, alcohol consumption, systolic blood pressure, lipids, self-reported type II diabetes and HbA1c, where appropriate. Groups correspond to the bottom and top two tenths, and the middle three fifths, based on the distribution of each adiposity measure at baseline among men and women. Reference groups were the bottom tenth of adiposity among women. X-axes represent ±3SDs of the average sex-specific mean value. Areas of point estimates are inversely proportional to the variance of the log risk. 95% CIs for group-specific risks reflect uncertainty in the log for each risk estimate. Analysis was restricted to those participants without a history of cardiovascular disease or missing/implausible adiposity measures at baseline (Table A1).

**Figure 7.14** Hazard Ratio (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity, with adjustment for baseline values of potential intermediate risk factors among **men**



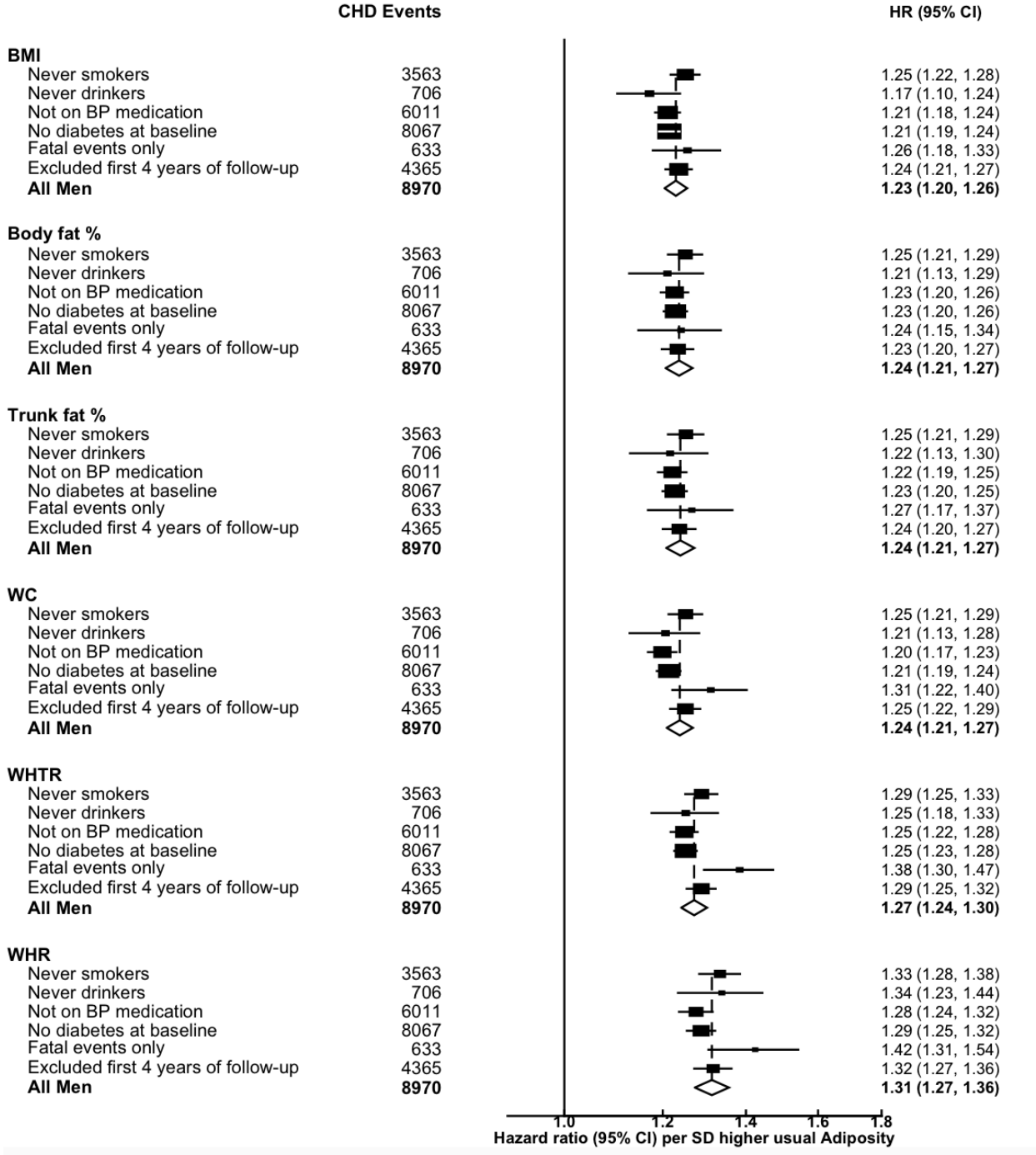

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity and biomarker data and those who did not have cardiovascular disease at baseline.

**Figure 7.15** Hazard Ratio (95% CI) for coronary heart disease per 1-SD higher usual adiposity, with adjustment for baseline values of potential intermediate risk factors among **women**



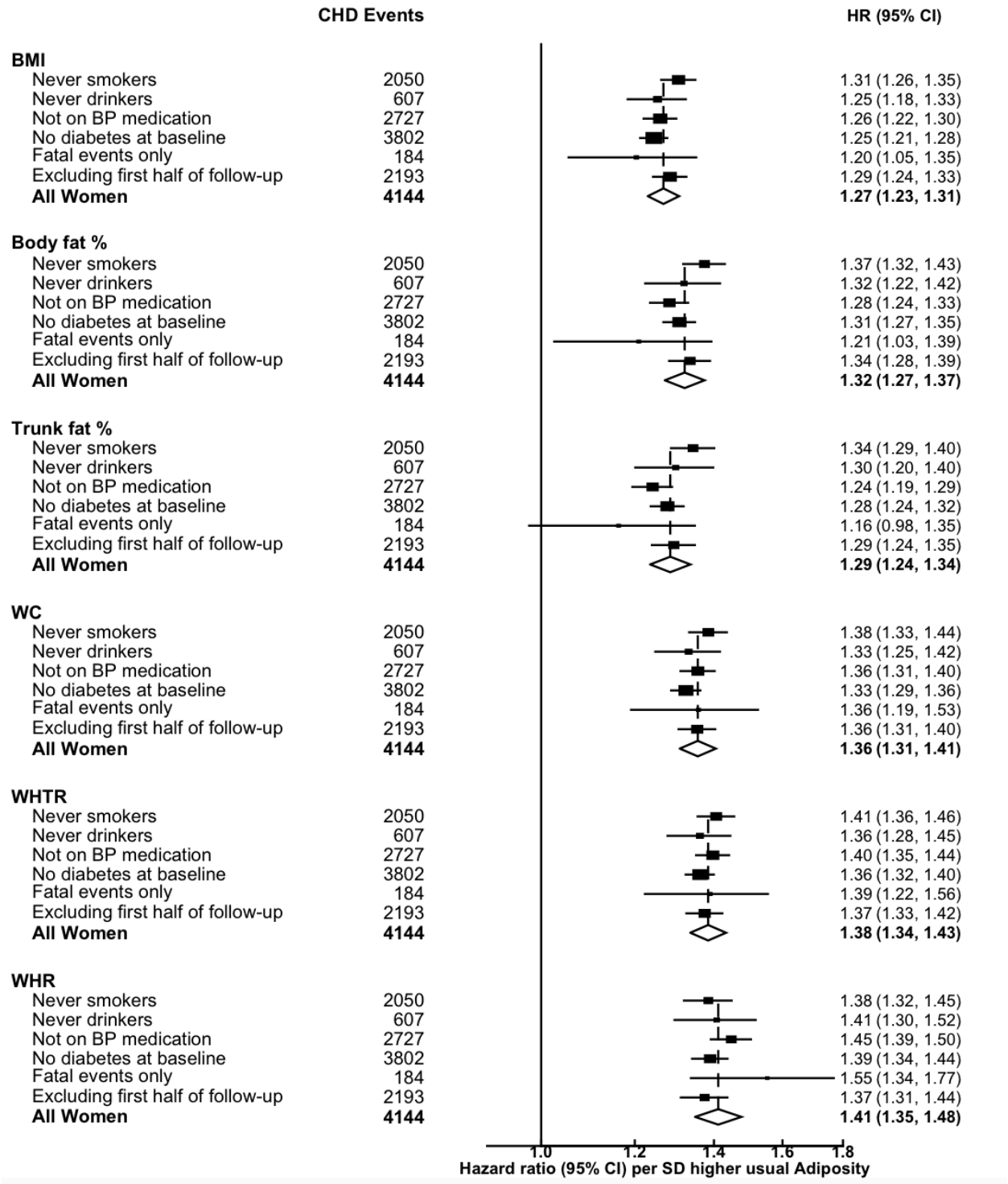

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity and biomarker data and those who did not have cardiovascular disease at baseline.

**Figure 7.16** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after various exclusions



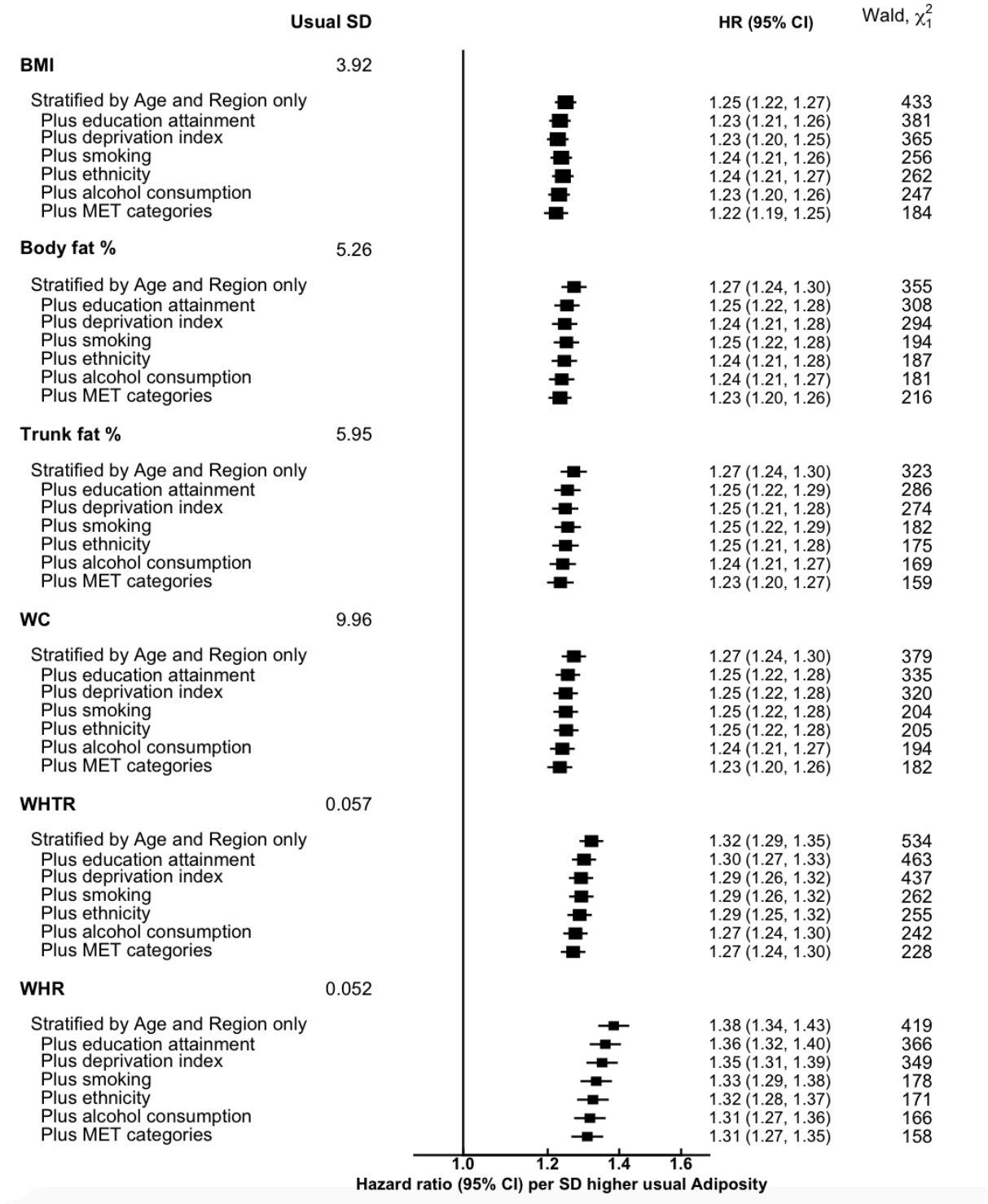

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity and biomarker data (where appropriate), and those who did not have cardiovascular disease at baseline.

**Figure 7.17** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after various exclusions



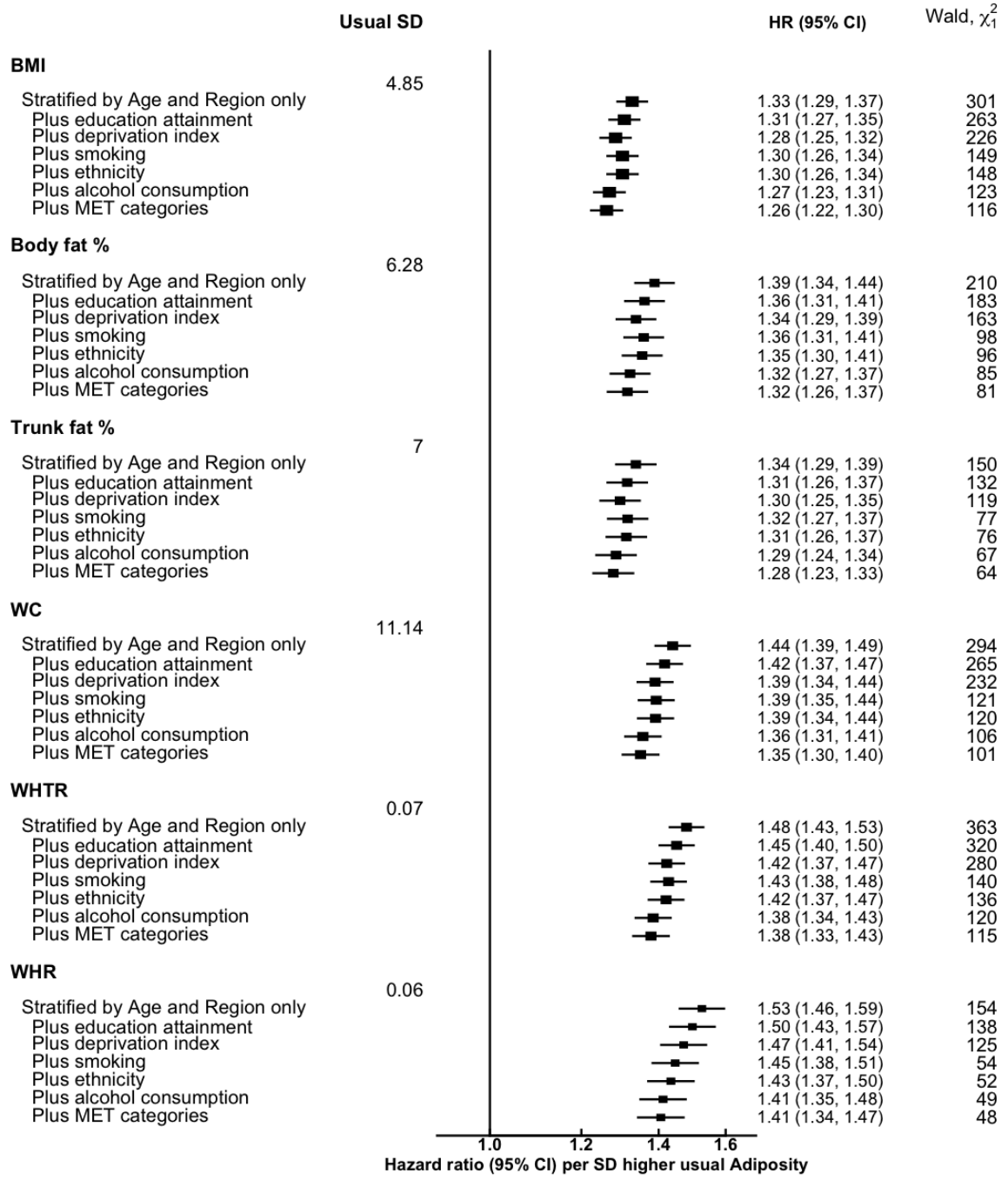

BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity and biomarker data (where appropriate), and those who did not have cardiovascular disease at baseline.

**Figure 7.18** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **men** before and after adjusting for potential confounders




BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data at baseline and who did not have cardiovascular disease at baseline.

**Figure 7.19** Hazard Ratios (95% CI) for coronary heart disease per 1-SD higher *usual* adiposity in **women** before and after adjusting for potential confounders




BMI= Body-mass Index; WC= Waist circumference; WHTR =Waist-to-height ratio; WHR= Waist-to-hip-ratio. Hazard ratios (95% CI) were adjusted for age-at-risk (5-year groups), education, deprivation index (fifths), ethnicity, smoking, alcohol and were stratified by UK region. Areas of point estimates are inversely proportional to the variance of the log risk. Usual SDs were calculated by multiplication of baseline SD by √RDR. Analysis was restricted to those participants with complete adiposity data at baseline and who did not have cardiovascular disease at baseline.

## CHAPTER 8: Genetic associations between adiposity traits and coronary heart disease in the UK Biobank

### Chapter summary

Observational studies have suggested that the relevance of body fat distribution to CHD is independent of general adiposity. However, previous MR studies have been underpowered to complement observational evidence with an assessment of the causal relevance of adiposity on CHD risk and cardiometabolic factors using the same study population. This chapter investigates the causal relevance of two independent adiposity phenotypes, BMI and WHR adjusted for BMI (WHRadjBMI), to cardiometabolic trats and CHD risk in the UK Biobank. Cox regression analysis was used to produce hazard ratios per 1-SD higher genetically elevated BMI and WHRadjBMI using genetic risk scores (GRS) for each trait. Similarly, associations of each GRS with cardiometabolic traits was assessed using linear regression analysis. An externally weighted GRS for BMI restricted to 34 variants specifically associated with BMI, and a GRS for elevated WHRadjBMI comprising 47 SNPs were each associated with elevated risk of CHD, however genetically elevated WHRadjBMI appeared particularly relevant to CHD risk (HR 1.41, 1.27 – 1.56) compared with BMI (1.37, 0.94 – 1.98). When the GRS for BMI was expanded to include SNPs associated with other adiposity traits to genome-wide significance (WC, HC and WHR), the association with CHD risk had enhanced precision but was directionally concordant (1.22, 1.06 – 1.41). Genetically elevated BMI was associated with socio-demographic factors and other confounders at baseline. Both genetically elevated BMI and WHRadjBMI were associated with similar raised blood pressure and hbA1c levels. BMI was additionally associated with reduced kidney function and systemic inflammation, whereas WHRadjBMI appeared protective against these factors and was more closely related to dyslipidaemia (raised LDL cholesterol, raised TG and lowered HDL cholesterol). The genetic associations were consistent with the observational associations of adiposity traits with CHD (p for heterogeneity>0.05; **Chapter 7**). The evidence summarised in this chapter suggests that BMI and WHR depict two separate and mutually exclusive aspects of adiposity, with clear differences in their associated metabolic perturbations.

## 8.1 Background

The observational associations between adiposity measures and CHD risk presented in **Chapter 7** were consistent with previous large-scale studies, suggesting central adiposity measures have stronger associations with CHD risk.[124, 127, 128, 247, 277] However, inherent biases such as reverse causation, confounding and measurement error are ubiquitous and often unavoidable in observational studies. Furthermore, adiposity measures are correlated, and each is associated with different degrees of within-person variability, which complications comparisons of observational associations with disease risk across measures. Therefore, it is not possible to assess the independent causal relevance of adiposity measures and CHD risk using observational studies alone, and hence the causal relevance of central adiposity beyond general adiposity to CHD risk is still debated.

In the absence of large-scale RCTs, MR approaches can overcome some of the common drawbacks of traditional observational epidemiology. MR studies use genetic variation in the form of single nucleotide polymorphisms (SNPs) or a GRS comprising multiple SNPs as a proxy instrumental variable (IV) for an exposure of interest, which, given a number of assumptions, can provide unbiased and unconfounded causal estimates of exposure-outcome associations (such as the associations between adiposity traits and CHD risk, **Figure 8.1**).[139, 297] Furthermore, in contrast to observed adiposity traits, genetic IVs can be tailored to represent specific and distinct adiposity phenotypes. For example, recent GWAS have identified WHR adjusted for BMI (WHRadjBMI) SNPS that are independently associated with body fat distribution (as measured via WHR) beyond BMI.[109, 110]

The causal relevance of genetically elevated BMI and WHRadjBMI with CHD risk has been confirmed previously using MR techniques (see **Chapter 2**).[116, 119-121, 140-142] However, as yet, the majority of previous studies investigating the relevance of genetically elevated BMI to CHD risk include SNPs which are also associated with other markers of adiposity (including markers of body fat distribution, such as WC, HC, WHTR and WHR) to genome-wide significance ($p<5x10^{-8}$). Therefore, there is a lack of evidence for the distinct causal associations of BMI with CHD risk independently of other adiposity phenotypes.

Furthermore, due to a lack of genetic information in large longitudinal cohorts, the majority of previous MR studies have used summary-level study designs for the primary analysis, with a handful including a sub-set of IPD. There are a number of limitations to this approach:

**i)** To date, no previous study has had sufficient numbers of CHD events among participants with genetic information to reliably assess the genetic relevance of adiposity traits on CHD risk using the same population. Therefore, the use of different study populations and statistical methods (usually logistic regression for genetic associations and Cox regression for observational associations) could mean that observational and genetic associations reported in previous studies may not be directly comparable. Cox regression analysis can also be used to calculate MR-derived risk estimates using genetic variants in place of observed risk factor variables,[118] and although this technique is a relatively new concept in genetic epidemiology, it relies on similar assumptions to logistic regression.[298]

ii) The primary use of summary-level data has meant that previous studies have been unable to undertake a detailed assessment of the linear associations between adiposity-related CHD risk, particularly at low levels of BMI or WHR, for which previous observational studies have presented conflicting evidence of a J-shape with disease risk.[299]

iii) The lack of large-scale population studies with available data on both genetic and cardiometabolic traits has limited the ability to study the potential intermediate pathways underlying genetic associations between adiposity and CHD risk previously.[119, 140]

For the first time, with full genetic data available in a large and contemporary prospective cohort study and with a sufficient numbers of CHD events, the UK Biobank allows a direct comparison between observational and genetic associations of adiposity traits with CHD risk using the same study population. The current chapter uses genetic variants which are associated with two distinct adiposity phenotypes – general adiposity (BMI) and body fat distribution (WHRadjBMI) - as IVs in an MR analysis of CHD risk in the UK Biobank.

## 8.2 Genetic study protocol and statistical methods

### *8.2.1 Genotyping*

Using the blood samples collected at baseline assessment, all participants in the UK Biobank were genotyped in 106 batches with an 800 000 SNP CHiP panel. Roughly 50 000 participants were genotyped using Affymetrix UK BiLEVE Axiom array, and 440 000 were genotyped using an Affymetrix UK Biobank Axiom array. Over 96M SNPs were imputed using two reference panels: i) a combined panel of both UK10K the 1000 Genomes Phase 3 reference panels[300]; and ii) the Haplotype Reference Consortium (HRC) panel.[301] For SNPs imputed on both panels, the HRC was used. The UK Biobank derived genomic principal components (PCA), and the first ten PCs were used in the analyses to limit population stratification.

### *8.2.2 Genetic quality control procedures and exclusions*

The UK Biobank performed internal quality control (QC) on the SNPs prior to inclusion in the present study. Samples failed QC if they had one or more of the following: i) duplicate samples; ii) genetic call rates were below 98%; iii) genetic and self-reported sex were not concordant; iv) outlying heterozygosity after adjusting for PCs; or v) participant withdrew consent. Additionally, samples were excluded if sex effects, array effects, batch effects, plate effects or departures from the Hardy-Weinberg equilibrium were detected. On average, over 7 000 SNPs failed QC per batch.[122] Similarly, related individuals (3$^{rd}$ degree or closer) were also excluded (n= 66 821), as estimated via a Kinship-based INference for Genome-wide association studies (KING) coefficient between all pairs of study participants.[302] Participants who were not of European descent (n= 28 120) were excluded to limit the effects of population stratification. A total of 383 406 unrelated UK Biobank participants of European Ancestry, aged 40-69 years, without missing or outlying adiposity at baseline, passed genetic QC and were therefore eligible for inclusion in genetic analysis. Of these, 24 699 participants had a previous history of cardiovascular disease and were therefore excluded to allow for a direct comparison with observational risk estimates (**Chapter 3**, **Figure 3.3**). Therefore, a total of 358 707 participants were included in the current analysis.

### *8.2.3 SNP selection and construction of genetic risk scores for elevated adiposity*

To investigate the causal relevance and independent effects of general and central adiposity on CHD risk, SNPs were selected for inclusion into three GRSs for elevated adiposity: i) a

restricted GRS for BMI (34-SNP GRS-BMI); ii) an unrestricted GRS for BMI (75-SNP GRS-BMI); and iii) a GRS for WHR adjusted for BMI (47-SNP GRS-WHRadjBMI).

Genetic instruments for each adiposity phenotype were constructed using the estimated effect sizes from published GWAS of independent discovery populations.[297], SNPs were selected from the published GWAS of The Genetic Investigation of ANthropometric Traits (GIANT) consortia – an international Collaboration set up to combine genome-wide association studies for the discovery of genetic loci which modify human body size and weight. Discovery GWAS were either based on Hapmap-imputed SNPs (~2.8 M SNPs) or on genotyped Metabochip SNPs (~190 K SNPs). Alleles included in each GRS were weighted by effect sizes published by the GIANT consortia, and it was assumed that per allele effects were additive on selected adiposity traits.[303] The genetic effect estimates on BMI and WHRadjBMI in GIANT were obtained from inverse-variance weighted (IVW) meta-analyses of study-specific genetic effect estimates on BMI or WHRadjBMI, respectively. For the purposes of the current analyses, only estimates from sex-combined, European ancestry meta-analysis were used, including up to 322,154 participants from 114 studies for BMI, and 210 088 participants from 101 studies for WHRadjBMI.[105, 110]

SNPs were excluded from GRSs if they were in high linkage disequilibrium (LD) with other SNPs for the same selected adiposity trait. The population-specific measures of LD were calculated from 1000Genome Project (Phase 3, Version 5), using data from publicly available reference haplotypes of European populations (British). The LD statistics included: D prime (D') - an indicator of allelic segregation for two genetic variants, ranging from 0 to 1 with higher values indicating tight linkage of alleles and R squared ($R^2$) - a measure of correlation of alleles for two genetic variants. $R^2$ values range from 0 to 1 with higher values indicating a higher degree of correlation. The threshold chosen for 'high LD' was $R^2$>0.2 to remove correlated variants that would otherwise contribute minimal additional information.[304]

*8.2.3.1 Genetic risk scores for BMI*

Locke et al (2015) discovered 97 SNPs which were associated ($p<5x10^{-8}$) with BMI in the GIANT consortia, of which 77 SNPs were genome-wide significant in analysis restricted to participants of European ancestry.[105] A recent GWAS conducted by Yengo et al. (2018) discovered 941 SNPs associated with BMI to genome-wide significance using a combination of UK Biobank and GIANT study populations.[104] However, these SNPs were not included in the present analysis because of the potential to over-estimate the proportion of variance explained for BMI when discovery and analysis populations overlap.[305] Of the 77 SNPs

identified in GIANT, two SNPs were found to be in high LD (**Figure 8.2**; **Appendix 8.1**), and 41 SNPs had significant pleotropic effects ($p<5x10^{-8}$) on other adiposity measures (WC, HC or WHR) as reported in the GIANT consortium (**Figure 8.3**). Therefore, 34 SNPs were combined in an externally weighted 'restricted' GRS which was more specific to genetically elevated BMI (34-SNP GRS-BMI) and the weighted effects of 75 SNPs were combined to produce an 'unrestricted' GRS for elevated BMI which included SNPs also associated with WC,HC and WHR to genome-wide significance (75-SNP GRS-BMI). Basic information on the included SNPs is summarised in **Table 8.1.**

*8.2.3.2 Genetic risk score for WHRadjBMI*

Using the same criteria as for GRS-BMI SNP selection, 82 SNPs were identified from two independent GWAS of GIANT consortium data (**Figure 8.4**).[109, 110] However, each study discovered slightly different SNPs for genetically elevated BMI due to differences in study protocols. Where two SNPs were in high LD, the SNP with the largest reported effect size from each study was included in the current analysis (**Table 8.2**). As no pleiotropic associations for BMI were observed for WHRadjBMI-associated SNPs to genome-wide significance (**Appendix 8.2)**, all 47 identified SNPs were used to construct the GRS for WHRadjBMI, weighted by the effect sizes as reported in GIANT, as described previously.

*8.2.4 GRS associations with adiposity traits and cardiovascular risk factors*

To assess the strength of association with adiposity traits, each GRS was divided into sex-specific fifths, and general linear regression was used to estimate the mean adiposity levels (and 95% CIs) at increasing fifths of GRS separately for men and women. General linear regression was used to assess associations per 1-unit higher GRS for elevated adiposity with continuous cardiovascular risk factors at baseline such as blood pressure, lipids, HbA1c, inflammatory markers, eGFR, GGT and ALP. Similarly, logistic regression was used to estimate the odds of binary characteristics at baseline per 1-unit increase in GRS. All genetic associations between adiposity and cardiovascular risk factors were stratified by sex, and adjusted for age at baseline, age$^2$, the first ten PCA components, batch number and array type.

*8.2.5 MR analysis*

For a direct comparison with the observational estimates described in **Chapter 7**, Cox proportional hazards regression was used to produce HRs for CHD risk per unit higher GRS, representing approximately 1-SD increase in adiposity trait as defined by GIANT. Therefore,

as in **Chapter 7** the date of diagnosis was used to calculate time-to-event since recruitment, with follow-up censored at the last date of available health records. An instrumental variable ratio estimate method was used to scale results to represent the effect size per observed SD higher adiposity trait in the current study[118]:

$$\beta_{IV}=(\beta_{YZ}/\beta_{XZ})x \text{ Usual SD}$$

where $\beta_{IV}$ is the IV causal estimate of the association between adiposity trait (BMI or WHRadjBMI) and CHD ; $\beta_{YZ}$ is the ln(HR) of CHD with each 1-unit increase in a GRS (Z) derived from the Cox proportional hazards model; and $\beta_{XZ}$ is the change in adiposity trait (X) with each unit increase in the GRS (Z). To allow for a direct comparison with the observational associations presented in **Chapter 7**, each estimate per 1-unit increasing adiposity was multiplied by the 'usual' SD. Exponentiating $\beta_{IV}$ yielded an MR estimate of the HR of CHD per usual SD increase. SEs were also scaled, via the same method. As per risk factor associations, the associations of each GRS with CHD risk were stratified by sex, and adjusted for age-at-risk, age$^2$, the first ten PCA components, batch number and array type. Genetic association estimates were interpreted based on point estimates, CIs and p-values. Heterogeneity between observational and genetic estimates were assessed using Cochran's Q test.[306]

*8.2.6 Sensitivity analyses*

To satisfy the MR assumptions, a number of sensitivity analyses were performed. Firstly, to investigate whether GRSs were independent of confounders (**Figure 8.1**), the impact of covariates on each GRS was assessed separately. It is possible that socio-economic factors are associated with both adiposity and CHD through true causal mechanisms.[174] Therefore, associations of weighted GRSs for BMI and WHRadjBMI with the main socio-economic factors identified as potential confounders in **Chapter 7** were assessed using linear regression for continuous traits and logistic regression for binary traits. Possible confounders included education, UK region, deprivation index, smoking habits and alcohol consumption.

Secondly, to assess the validity of the second assumption that genetic variants are only associated with the exposure of interest, the validity of each genetic variant included in the GRSs as IVs for each adiposity trait was assessed using MR Egger regression, IVW and weighted median approaches.[297, 307-309] MR Egger is a modified version of IVW meta-analysis,[308] and when applied to MR analyses, the slope provides an estimate of the average causal effect and the intercept provides an estimate of the average pleiotropic effect across all genetic variants. In addition, plots of GRS-exposure vs. GRS-outcome effect sizes and

funnel plots were created for each adiposity trait. For funnel plots, the IV strength (the absolute effect size on adiposity divided by the standard error) was plotted against the precision of individual estimates (ln(HR)divided by the predicted SD increase in adiposity for each genetic variant).[310]

GRS-risk factor associations and MR analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). Sensitivity analysis with IVW, weighted median and MR Egger methods were performed using R version 3.5.1 (The R Foundation for Statistical Computing), with the R package 'MendelianRandomization'. All plots were created in R using the 'Jasper' package (CTSU, Oxford).

*8.2.7 Power calculations*

Power and sample size estimations were calculated using publicly available R code specifically designed for MR.[311] The current study had sufficient power to assess the associations with 75-SNP GRS-BMI among men and women combined (approximately 83% power to investigate the causal effects of BMI on CHD, assuming effect size of HR 1.40, 10 000 events and type I error rate of 5%), however there was only approximately 63% and 27% power for 47-SNP WHRadjBMI GRS or 34-SNP BMI GRS, respectively (**Appendix 8.3**). It was decided a priori that given the weak genetic instruments, sex-specific estimates would lack power, and therefore were not included in the main results.

## 8.3 Results

### *8.3.1 Baseline characteristics*

Despite the exclusion of approximately 100 000 participants at baseline who were genetically related, of non-European ancestry or lacked genetic information, the genetic analysis study population included 358 707 participants with similar proportions across age groups, education levels and UK recruitment regions at baseline compared with the study population included in the main observational analysis described in **Chapter 7** (**Table 8.3**). Similarly, prospective and genetic populations had approximately similar proportions of participants across groups of lifestyle characteristics, and similar mean levels of adiposity and blood pressure.

### *8.3.2 Genetic associations of individual variants and genetic risk scores with adiposity*

All variants included in the restricted 34-SNP GRS-BMI and the unrestricted 75-SNP GRS-BMI were positively associated with BMI in the UK Biobank (**Figure 8.5**), and there was no evidence of significant heterogeneity in reported effect sizes between the UK Biobank and GIANT. Likewise, effect sizes were approximately similar between UK Biobank and GIANT studies for individual variants included in the 47-SNP GRS-WHRadjBMI (**Figure 8.6**).

Externally weighted scores for genetically elevated BMI (34-SNP GRS-BMI) and WHRadjBMI (47-SNP GRS-WHRadjBMI) were each robustly associated with linear increases in BMI and WHR, respectively, among men and women (**Figures 8.7 & 8.8**). The 34-SNP GRS-BMI explained a total of 0.26% of the variation in BMI across the study population and the 47-SNP GRS-WHRadjBMI explained a total of 0.76% of variation in WHR. The unrestricted GRS for BMI (75-SNP GRS-BMI) explained substantially more variance in BMI than the restricted score (1.5%). F-statistics for all scores indicated strong instruments (34-SNP GRS-BMI: 935; 75-SNP GRS-BMI: 5 518; 47-SNP WHRadjBMI: 2 758).

Per 1-unit increase in GRS, BMI increased by 0.80 (0.78, 0.82) SD units and 0.65 (0.61, 0.69) for 75-SNP GRS-BMI and 34-SNP GRS-BMI, respectively (**Figure 8.9**). A similar 1-unit increasing 47-SNP GRS-WHRadjBMI was associated with an average increase in WHR of 0.50 SD units (0.48, 0.52). The restricted GRS for BMI was slightly inversely associated with height by approximately -0.05 SD units per 1-unit higher GRS (95% CI -0.07- 0.02), which was not observed for the unrestricted GRS for BMI (0.01, -0.01- 0.02). All three GRSs were associated with other body size and adiposity traits (weight, BMI, Body Fat %, WC, HC, WHTR and WHR) in the current study. Although the restricted GRS for BMI was strongly and positively associated with all other adiposity traits, these associations were about 0.15 SD

units weaker than associations with the unrestricted GRS for BMI (75-SNP GRS-BMI). After body weight, the next strongest association with GRS-BMI was observed for HC (0.55, 0.51-0.59 and 0.71, 0.69 – 0.73 per 1-unit increasing GRS for 34-SNP GRS-BMI and 75-SNP GRS -BMI, respectively). The weakest association with GRS-BMI was observed for WHR (0.18, 0.15 – 0.21 and 0.27, 0.25 – 0.27 for 34-SNP- and 75-SNP GRS-BMI, respectively). By contrast, each 1-unit increase in externally weighted GRS-WHRadjBMI was strongly and inversely associated with over one third lower HC (SD units: -0.37, -0.39, -0.34) and was slightly inversely associated with general adiposity (-0.12 for body weight, -0.16 for BMI and -0.08 for body fat %). In general, however, weaker correlations were observed between GRS-WHRadjBMI and other adiposity measures compared with the GRSs for BMI.

The shape and magnitude of associations with adiposity traits at increasing fifths of 34-SNP GRS-BMI did not differ between men and women (**Figure 8.10**). However, across increasing fifths of the distribution of GRS-WHRadjBMI, the strength of GRS-WHRadjBMI as a genetic instrument for WHR was at least twice as strong among women compared with men (mean difference [SD units] in WHR between top to bottom fifths of GRS-WHRadjBMI: 0.2 and 0.4 among men and women, respectively, **Figure 8.11**).

*8.3.4 Genetic associations of adiposity traits with DXA imaging compartments*

In a sub-set of study participants (n = 4902), it was possible to examine the associations of increasing GRS for adiposity traits with DXA body fat compartments (definitions of compartments as in **Chapter 6**). In general, both 34-SNP GRS-BMI and GRS-WHRadjBMI were associated with similar higher levels of in visceral android fat, fat-free mass and subcutaneous android fat at increasing fifths of each GRS (**Figure 8.12**). However, whereas increasing fifths of 34-SNP GRS-BMI were associated with higher levels of body fat across all compartments, the GRS-WHRadjBMI was inversely associated with gynoid fat, which was approximate 0.2 SD units higher at the top fifth of GRS-WHRadjBMI compared to the bottom fifth.

*8.3.3 Genetic associations of adiposity traits and risk factors for CVD*

There was evidence for positive genetic associations with markers of SES (increasing deprivation scores and odds for less than 10 years of education) per unit increase in 34-SNP and 75-SNP GRS-BMI (**Table 8.4**). Similarly, on average, per unit increase in GRS for BMI, participants were approximately 20% less likely to consume alcohol daily and approximately 20% more likely to have ever smoked. These associations were slightly stronger for the unrestricted GRS-BMI compared with restricted GRS-BMI. There was no evidence for similar associations with selected SES characteristics and genetically elevated WHRadjBMI.

In the UK Biobank, GRS-BMI associations were apparent for blood pressure when using the unrestricted GRS for BMI (per 1 unit increasing 75-SNP GRS-BMI: 0.95mmHg [0.58 – 1.32] for SBP and 0.88mmHg [0.67, 1.09] for DBP). However, there was no evidence for an association between the restricted GRS-BMI and blood pressure (per 1 unit increasing 34-SNP GRS-BMI: -0.15 mmHg [-0.86 – 0.56] for SBP and 0.32 mmHg [-0.08, 0.73] for DBP). Positive associations were observed between genetically elevated WHRadjBMI and blood pressure (SBP per 1-unit increasing GRS-WHRadjBMI: 0.65mmHg, 0.23 – 1.07).

Associations with other mediators were similar between 34-SNP GRS-BMI and 75-SNP GRS-BMI, with the exception of ALP, which was more closely correlated with the restricted GRS (1.50 U/L, 0.42 – 2.56 for 34-SNP GRS-BMI versus. 1.21 U/L, 0.66 – 1.77 for 75-SNP GRS-BMI), and HbA1c, which was stronger for the unrestricted GRS-BMI (0.92 mmol/mol, 0.79 - 1.05 for 75-SNP GRS-BMI versus 0.71 mmol/mol, 0.46 – 0.96 for 34-SNP GRS-BMI), although confidence intervals were much wider for the restricted GRS. WHRadjBMI was also associated with HbA1c, although this association was only half as strong as that observed for the unrestricted GRS-BMI (per unit increasing GRS-WHRadjBMI: 0.45mmol/mol, 0.30 – 0.60).

There was no evidence for a significant association between increasing GRS-BMI (restricted or unrestricted scores) and LDL cholesterol, whereas positive associations were observed between GRS-WHRadjBMI and LDL cholesterol. One-unit increases in GRSs for BMI and WHRadjBMI were inversely associated with HDL cholesterol (approximately 0.10 mg/L), and positively associated with HbA1c and Triglycerides. Triglycerides were more tightly correlated with GRS-WHRadjBMI (0.33 mmol/L, 0.31, 0.35) compared with GRS-BMI (0.11 mm/L, 0.09 – 0.13 and 0.11 mm/L, 0.07 – 0.15 for 75-SNP and 34-SNP GRS-BMI, respectively). Log(GGT) was positively associated with genetically elevated WHRadjBMI (per 1-unit increasing GRS-WHRadjBMI: 0.09 U/L, 0.08 – 0.11), but was not associated with genetically elevated BMI. In contrast, restricted and unrestricted GRS-BMI scores were positively related to ALP but GRS-WHRadjBMI was not.

Similarly, genetically elevated WHRadjBMI and BMI demonstrated opposing associations with inflammatory markers. Whereas genetically elevated BMI displayed strong positive associations with log(CRP) levels, and (slightly weaker) inverse associations with albumin, a similar 1-unit higher GRS-WHRadjBMI was not associated with CRP levels, but displayed a strong positive association with albumin levels (0.26 g/L, 0.19- 0.36, $p=5.43 \times 10^{-14}$).

*8.3.4 Causal genetic associations of adiposity traits and CHD*

Genetically elevated BMI and WHRadjBMI were associated with higher risk of CHD in the current study population, which appeared approximately linear across the predicted ranges of adiposity (**Figure 8.13**). Although less precise, risk of CHD was directionally consistent when using the restricted 34-SNP GRS-BMI (HR 1.37, 0.94 – 1.98) compared with the unrestricted 75-SNP GRS-BMI (HR 1.22, 1.06 - 1.41 per SD genetically elevated BMI, **Figure 8.14**). A similar SD genetically elevated WHRadjBMI was associated with a slightly higher risk of CHD (HR 1.31, 1.11 – 1.55), which was slightly stronger than the observed risk of CHD with genetically elevated BMI or observational associations for WHRadjBMI. However, given the weak instruments used in the current study, confidence intervals overlapped, and no significant heterogeneity was observed between the observational and genetic associations for either BMI or WHRadjBMI ($p_{het}$>0.05).

*8.3.5 Sensitivity analyses*

For individual SNPs included in the 75-SNP GRS-BMI and GRS-WHRadjBMI, the observed intercepts from MR-Egger regression slopes did not reach statistical significance, indicating a lack of evidence for directional pleiotropy (**Figure 8.15**). For WHRadjBMI SNPs, the slope of the IVW regression was 0.237 (95% CI 0.038 – 0.436) which was similar to the slope for MR-Egger regression (0.253, -0.252 – 0.759), indicating no directional pleiotropy. However, the intercept for 34-SNP GRS-BMI was marginally significant, indicating some directional pleiotropy. Funnel plots showed a lack of asymmetry of log(HR) estimates for individual SNPs included in 75-SNP GRS-BMI and GRS-WHRadjBMI, but asymmetry for 34-SNP GRS-BMI, indicating the presence of directional pleiotropy for this score.

## 8.4 Discussion

### *8.4.1 Main findings*

This chapter provides robust evidence for the genetic associations of two distinct adiposity phenotypes, general adiposity (BMI) and body fat distribution (WHRadjBMI), with established and emerging cardiovascular risk factors and CHD risk. The current study is the largest MR study to directly compare the observational and genetic associations with CHD risk within the same study population using genetic instruments which were carefully constructed to represent specific adiposity phenotypes. Furthermore, the data-rich UK Biobank resource allowed, for the first time, an investigation into the shape of the genetic associations between adiposity traits and CHD risk by splitting the GRSs into fifths, whereby previous studies have been limited by a lack of IPD.

The findings from this study confirm an approximately log-linear causal association between body fat distribution (measured via WHR) and risk of CHD which is independent of BMI-related CHD risk. The current study also provided evidence for differential mechanistic pathways implicated with each genetically elevated adiposity phenotype. Together, these findings suggest that general adiposity and central body fat distribution are distinct traits which likely act through independent biological mechanisms to influence cardiovascular risk factors and CHD risk.

### *8.4.2 Comparison of findings to previous MR studies*

A total of seven previous large-scale MR studies (n>100 000) investigating the genetic associations of adiposity and CHD risk were identified in the literature review (**Chapter 2**).[116, 119-121, 140-142] Consistent with the findings presented in the current chapter, all previous MR studies have identified positive associations with genetically elevated adiposity and CHD risk. Four of the identified large-scale MR studies assessed the genetic associations of body fat distribution (as measured via WHRadjBMI or WC) with CHD risk,[119, 120, 140, 141] the majority of which used summary-level statistics from the CARDIoGRAMplusC4D Consortium (C+C4D).[119, 120, 140] Only three of the identified large-scale studies investigated the genetic relevance of BMI or WHRadjBMI on cardiometabolic traits.[116, 119, 140]

#### *8.4.2.1 Body-mass Index*

In the current study, each SD genetically elevated BMI was associated with an approximate 20-30% increased risk of CHD regardless of whether the genetic instrument included SNPs associated with other adiposity traits to genome-wide significance. Although overall genetic

estimates for CHD risk were less precise, there was no evidence for heterogeneity between observational and genetic associations.

In general, these findings are consistent with previous MR reports, providing further evidence to support the causal role of general adiposity on CHD risk. Two of the identified previous large-scale MR studies used summary-level statistics from C+C4D to assess the impact of genetically elevated BMI on CHD risk.[119, 120] The C+C4D consortium is a large collaborative study designed to investigate the genetic components of CHD using comprehensive genome-wide association meta-analysis approaches.[312] C+C4D includes more than 60 000 cases and 120 000 controls. Dale and colleagues (2017) combined C+C4D outcomes with 3,716 additional CHD events using IPD from 14 prospective cohort studies, and reported an approximately 36% increased risk of CHD associated with 1-SD genetically elevated BMI (OR 1.36, 1.33 – 1.52).[119] Zhang and colleagues (2017) also reported similar causal estimates of 37% higher odds of CHD per 4.8 kg/m$^2$ genetically elevated BMI as estimated by an externally weighted GRS consisted of 68 SNPs, using 22 233 CHD cases and over 60 000 controls from the C+C4D consortia.[120]

A few smaller MR studies with available IPD have reported similar increases in CHD risk ranging between approximately 20% to 52% per SD genetically elevated BMI using various GRSs for BMI.[116, 121, 141, 142] However, two of these studies lacked power to observe statistical significance using IPD alone which was likely to be due to insufficient numbers of CHD events and the weak GRSs for BMI.[116, 142]

Only two of the identified MR studies included sensitivity analyses to remove pleiotropic SNPs which were also associated with other adiposity traits to genome-wide significance.[116, 120] The results were consistent with the results presented in the current study, with an overall loss of power and precision but consistent directional effects. This observation indicates an independent causal role of general adiposity on CHD risk beyond other adiposity phenotypes.

#### *8.4.2.2 WHR adjusted for BMI*

In the current study, 1-SD genetically elevated WHRadjBMI was associated with approximately 30% higher risk of CHD (HR 1.31, 1.11 – 1.55), which is stronger than the association with genetically elevated BMI, and slightly stronger than observed WHRadjBMI. However, there was no evidence of significant heterogeneity between observational and genetic associations of WHRadjBMI with CHD risk. Three of the MR studies identified in **Chapter 2** have reported associations with WHRadjBMI on CHD risk, all of which use a two-sample approach including summary-level outcome data from the C+C4D consortia.[119, 120, 140]

The combined two-sample summary-level MR study conducted by Dale *et al.* (2017) with ~3 000 additional CHD events from IPD reported 48% increased odds of CHD (OR 1.48, 1.28 – 1.71) per 1SD genetically elevated WHRadjBMI compared with 36%(OR 1.36, 1.22 – 1.52) genetically elevated BMI.[119] Emdin at al. (2017) also reported a similar 46% increased odds of CHD (OR 1.46, 1.32 – 1.62) per SD genetically elevated WHRadjBMI using a summary-level approach but with the additional inclusion of IPD from the first 111 986 genotyped UK Biobank participants (contributing almost 6 000 additional CHD events).[140] However, due to the limited number of CHD cases, no comparisons were made between observational and genetic associations using the same study population, as has been possible in the current study. An MR analysis conducted by Zhang et al (2017) including more than 22 000 cases and 60 000 controls from C+C4D, also demonstrated that 1-SD genetically elevated BMI was associated with 37% higher odds of CHD (OR 1.37, 1.15 – 1.63) whereas WHRadjBMI displayed a stronger association with CHD risk (OR 1.42, 1.12 – 1.81), consistent with the current study.

However, with sufficient outcome and genetic data, the current study confirmed, for the first time, approximately log-linear associations between adiposity traits (BMI and WHRadjBMI) and CHD risk to complement the observational associations in the same study population using the same statistical methods. Therefore, the present study provides the most robust evidence to date for genetically elevated body fat distribution and general adiposity each increasing CHD risk independently of each other. In line with this theory, each adiposity phenotype was characterised by a slightly different body composition profile; WHR with a reduction of gynoid fat, and BMI an increase in total fat, including gynoid fat. Importantly, variants associated with each trait also differ in their proposed mechanistic actions – whereby, in general BMI-associated SNPs are linked with neuronal pathways and WHRadjBMI are linked with metabolic pathways.[313] Together these results provide further evidence to suggest that BMI and WHRadjBMI are distinct and mutually exclusive adiposity phenotypes which should both be considered as risk factors for CHD risk.

*8.4.2.3 Adiposity and socio-demographic factors*

The present study is the largest single study with available information on SES markers at scale, allowing a full assessment of the potential effect of confounding factors on associations between genetically elevated adiposity and CHD risk. Importantly, genetically elevated BMI displayed strong associations with lifestyle and SES characteristics. This finding agrees with those observed previously in large-scale Phenome-Wide Association Studies (PheWAS), suggesting that there are common genetic variants between BMI and smoking,[121, 314] alcohol

consumption,[121] and other markers of SES.[116, 174] However, previous evidence for similar pleiotropic effects of SNPs only associated with BMI and not body fat distribution is sparse. In the current study, WHRadjBMI was not associated with any of the selected SES characteristics. This contrasts with the findings presented by one of the previous large-scale MR studies conducted by Dale et al (2017),[119] which observed causal associations for WHRadjBMI with smoking. However, as this study was restricted by a lack of IPD there may have been inconsistencies in the measurements of potential confounding factors. In line with the current study, Emdin and colleagues (2017) found no association between WHRadjBMI and any of the potential confounding factors investigated.[140]

*8.4.2.4 Adiposity and cardiometabolic traits*

A small number of previous large-scale MR studies have investigated the genetic associations between BMI and various cardiometabolic traits.[116, 119, 140] Just one of the identified MR studies compared genetic associations between BMI and WHRadjBMI with cardiometabolic risk factors (Dale *et al.,* 2017).[119] Although this study found similar associations to those presented in the current study for elevated cardiometabolic traits with increasing adiposity, sample sizes were limited by a lack of available biomarker data in included studies to investigate associations with continuous cardiometabolic traits in finer resolution, such as blood pressure (n=~30 000), inflammatory markers (n=~14 000), triglycerides (n=~30 000), e-GFR ( n=~10 000) and glycaemic traits (n=~20 000). With full genetic information and available data on cardiometabolic traits for over 300 000 participants, the current study is the largest genetic study to investigate the association between adiposity traits and cardiometabolic biomarkers to date. Therefore, results from the current study reveal important novel insights into pathways contributing to adiposity-related cardiometabolic perturbations.

In the present study, there were some clear differences in the genetic associations between adiposity traits and blood-based biomarkers. Firstly, LDL cholesterol was not associated with either GRS for increasing BMI, but was strongly and positively associated with genetically elevated WHRadjBMI. Additionally, although genetically elevated WHRadjBMI and BMI were each associated with lower HDL and raised triglyceride levels, associations were over three times stronger for WHRadjBMI. This agrees with the few large-scale studies investigating the genetic relevance of BMI and WHRadjBMI on lipid levels,[116, 119, 140] and with cross-sectional observational evidence (**Chapter 4**), suggesting that body fat distribution is more tightly correlated with dyslipidaemia compared with BMI.

Genetic associations between adiposity traits also differed somewhat with respect to blood pressure. In contrast to previous MR studies which have observed stronger genetic

associations for WHRadjBMI and SBP compared with BMI,[119] the unrestricted 75-SNP GRS-BMI and GRS-WHRadjBMI were associated with similarly elevated SBP and DBP values in the present study. However, associations with 75-SNP GRS-BMI and SBP could be attributed to elevated levels of other adiposity phenotypes (such as WHR), since 75-SNP GRS-BMI was less specific to BMI and the genetic association between BMI and SBP was removed when the restricted 34-SNP GRS-BMI was used, suggesting that adiposity-related hypertension may be attributed to central adiposity. This has not been assessed previously at scale using a specific GRS for BMI.

In the present study, positive associations were observed between all GRSs and HbA1c, providing further evidence for the causal role of adiposity on glucose intolerance and insulin resistance. In contrast, the MR study conducted by Dale and colleagues (2017) observed no association with genetically elevated WHRadjBMI and non-fasting glucose.[119] However, non-fasting glucose is a less sensitive measure of glycaemic control compared with HbA1c levels. Emdin et al (2017) observed significantly higher log-transformed fasting insulin levels and non-fasting glucose levels per 1-SD genetically elevated WHRadjBMI in over 100 000 UK Biobank participants, but BMI was not assessed.[140] Similarly, Holmes et al. (2014) observed associations between a 14 SNP GRS-BMI and fasting glucose levels but did not assess WHRadjBMI.[116]

Genetically elevated BMI was associated with significantly lower albumin levels and higher CRP levels, consistent with the observational associations presented in **Chapter 4 & 7** and other studies.[315, 316] The chronic state of inflammation often observed in obesity is thought to have arisen through hypertrophy of adipocytes and resulting hypoxia, eventually leading to cell death and the production of proinflammatory cytokines.[317, 318] However, in contrast, WHR was not associated with CRP and appeared protective against reductions in albumin in the current study. This was also observed by Dale and colleagues, where WHRadjBMI increased albumin levels by approximately 0.17 SD units (-0.04, 0.39) although there was a lack of power in this study (n= ~17 000) and so this result was non-significant. Albumin has historically been used as a marker of starvation,[319] but it is also raised in states of systemic inflammation and kidney disease.[320] This apparent protective effect of genetically elevated WHRadjBMI could be the result of specific biological properties of adipose tissue found in different depots during periods of energy surplus. For example, recent evidence has suggested that for poorly understood reasons, subcutaneous fat cannot expand through hyperplasia past a certain point, leading to either their rupture or macrophage invasion with the release of pro-inflammatory adipokines.[321] This way, by measuring essentially a decrease in subcutaneous fat storage (i.e. HC), perhaps WHR confers a protective effect on inflammation. Alternatively,

this apparent protective effect of GRS-WHRadjBMI on systemic inflammation could be an artefact of the slight inverse association with BMI observed in the present study. However, as this is the first study with the ability to assess the genetic relevance of body fat distribution on markers of inflammation at scale, these results should be interpreted as hypothesis-generating.

Different associations were also observed between adiposity phenotypes for GGT and ALP levels, with genetically elevated BMI showing strong positive associations with ALP and non-significant associations with log(GGT), and genetically elevated WHRadjBMI showing strong positive associations with log(GGT) and a lack of association with ALP. Since ALP and GGT are both indicators of liver function, this contrast is somewhat surprising. However, ALP and GGT are associated with slightly different pathways. For example, despite the tendency for both enzymes to increase in liver disease, raised ALP is an additional indicator of bone disease. Therefore, these results may suggest a possible effect of BMI on bone disease, and a possible independent effect of WHRadjBMI on liver function. None of the identified large-scale MR studies have investigated the genetic associations of adiposity on GGT and ALP. However, a few smaller studies have found similar evidence for a causal association between genetically elevated BMI and higher levels of GGT, although they generally lacked power.[315, 322]

The current study provides the first large-scale genetic evidence for a causal effect of BMI on a reduction in kidney function as measured via eGFR, which remained significant for the restricted 34-SNP GRS-BMI. In contrast, the previous MR study conducted by Dale and colleagues (2017) did not observe an association between GRS-BMI and eGFR, however this study had insufficient power to assess this association robustly (n=~10 000).[119] Additionally, in contrast to the current study, two large MR studies observed no significant association between genetically elevated WHRadjBMI and eGFR.[119, 140] However, the slight positive association with WHRadjBMI and eGFR observed in the current study could also be the result of the inverse association between GRS-WHRadjBMI and BMI. It has been hypothesised that the adverse effect of general adiposity on kidney function can arise as a result of an infiltration fat storage in the kidneys which can impair their function.[239, 293]

### *8.4.4 Validity of the MR causal estimates: MR assumptions*

The validity of the MR approach used in the present study relies on a number of important assumptions. First, it requires a strong link between SNPs included as IVs and the exposure of interest (assumption 1 in **Figure 8.1**). The genetic instruments used in the present study, although explaining only a small percentage of variation, were all significantly associated with

the adiposity traits of interest, and had F statistics over 900, indicating that the genetic instruments were strong with negligible weak instrument bias. Second, MR assumes the absence of directional pleiotropy, that is, it assumes that the genetic variants used as IVs affect the outcome through the exposure and not through other pathways or confounding factors (**Figure 8.1**). Pleiotropy can be vertical (i.e. downstream of BMI) or horizontal (i.e. genetically associations with traits that are on separate pathways to BMI). Although not directly testable, the pleiotropy assumption was explored by comparing MR estimates derived from IVW, MR Egger and weighted Median approaches. Whilst each method is associated with different assumptions itself, the general concordance of estimates derived from each measure is thought to reinforce the validity of the results.[310] This was true for WHRadjBMI and in general for GRS-BMI scores in the present study, where in general slopes were concordant (although with a loss of precision, for 34-SNP GRS-BMI in particular) across each method used. However, MR Egger was not directionally consistent for 34-SNP GRS-BMI or 75-SNP-GRS, suggesting the presence of horizontal pleiotropy, possibly through the observed associations with the SES factors mentioned above. For the 75-SNP GRS-BMI, however, there was a lack of evidence for the intercept differing from zero, suggesting that the observed horizontal pleiotropy was unlikely to have affected the result.

### *8.4.5 Study strengths and limitations*

The present study presents with a number of strengths. Firstly, it was the largest study to date with sufficient genetic and prospective outcome data on a single study population which allowed for the first time: *i)* an investigation into the shape of associations between different adiposity phenotypes and CHD risk (at least across the range of adiposity predicted by each GRS); *ii)* a comparison of genetic and observational associations of adiposity phenotypes with CHD in a single population; *iii)* the use of consistent statistical modelling for both observational and genetic associations (i.e. Cox regression analysis); and *iv)* a detailed investigation into the genetic relevance of two distinct adiposity phenotypes on the largest number of cardiometabolic traits to date.

However, the current study has a number of potential limitations, many of which are widely recognised as unavoidable in genetic studies. Firstly, the validity of the MR approach used in the present study relies on a number of key assumptions (*Section 8.4.4*). Importantly, GRS-BMI was associated with SES factors in the current study, including smoking, education, deprivation index and daily alcohol consumption, which suggests that the observed associations between GRS-BMI and CHD could in part be attributed to residual confounding by SES (hence, violating a key MR assumption). Additionally, WHRadjBMI was inversely

associated with BMI, which could introduce collider bias.[323] However, in this example, the inverse association with BMI will likely bias estimates with WHRadjBMI towards the null.

The GRSs used in the current study were weak instruments and explained little variation in adiposity traits (0.26 - 1.51%), partly due to the two-sample study design which limited the use of newly discovered SNPs for adiposity traits.[104] It is also possible that the additional 20 SNPs discovered in non-European populations may have strengthened the GRS for BMI. However, a similar proportion of variation in BMI was explained by the unrestricted 75-SNP GRS-BMI in the current study as has been discovered previously in the UK Biobank using 97 SNPs for BMI,[202] suggesting that the additional SNPs also discovered in non-European populations do not contribute much additional information to GRSs. Indeed, it is widely recognised that the great majority of the estimated heritability of adiposity remains unexplained, despite the ever-increasing resolution of our knowledge of the genome.[324] A limitation to genetic investigations of complex traits is the likelihood of a vast array of processes at the genomic level, including gene-environment interactions, epistasis (the phenomenon whereby one polymorphism's effect on a trait depends on other polymorphisms present in the genome) and genomic imprinting (the phenomenon by which genomes 'recognise' parental genetic modifications and reprogram development accordingly, effectively allowing offspring to inherit genetic alterations from their parent or grandparent).[325] As our understanding of the genome expands, these processes (and likely others as yet undiscovered) continue to emerge as potential explanations for 'missing heritability'.[326] Currently, GWAS are not designed to capture these interactions at scale, and therefore it may not be possible to quantify the true genetic effects of increasing adiposity on disease risk using current technology. Therefore, although MR is a useful tool for causal inference at scale, until there is a full understanding of genomic processes, the results from MR studies should be interpreted with caution.

In the present study, despite using a restricted GRS for increasing BMI, the 34-SNP GRS-BMI was still correlated with WHR (although less than the expanded GRS). Therefore, it remains difficult to separate the causal effects of general and central adiposity using genetic and observational epidemiological methods currently. Future studies would benefit from investigating risk factor- and disease-associations with GRS-BMI which include SNPs discovered in a population after adjusting for body fat distribution measures, as has been done for WHRadjBMI SNPs.[110]

A shortfall of the UK Biobank is the lack of ethnic diversity, which limits the applicability of research findings to other populations. There is a continued need to explore the relevance of

adiposity measures to CHD in large numbers of non-White ethnic groups,[327] particularly as these individuals may have enhanced susceptibility to adiposity-related CHD.[328]

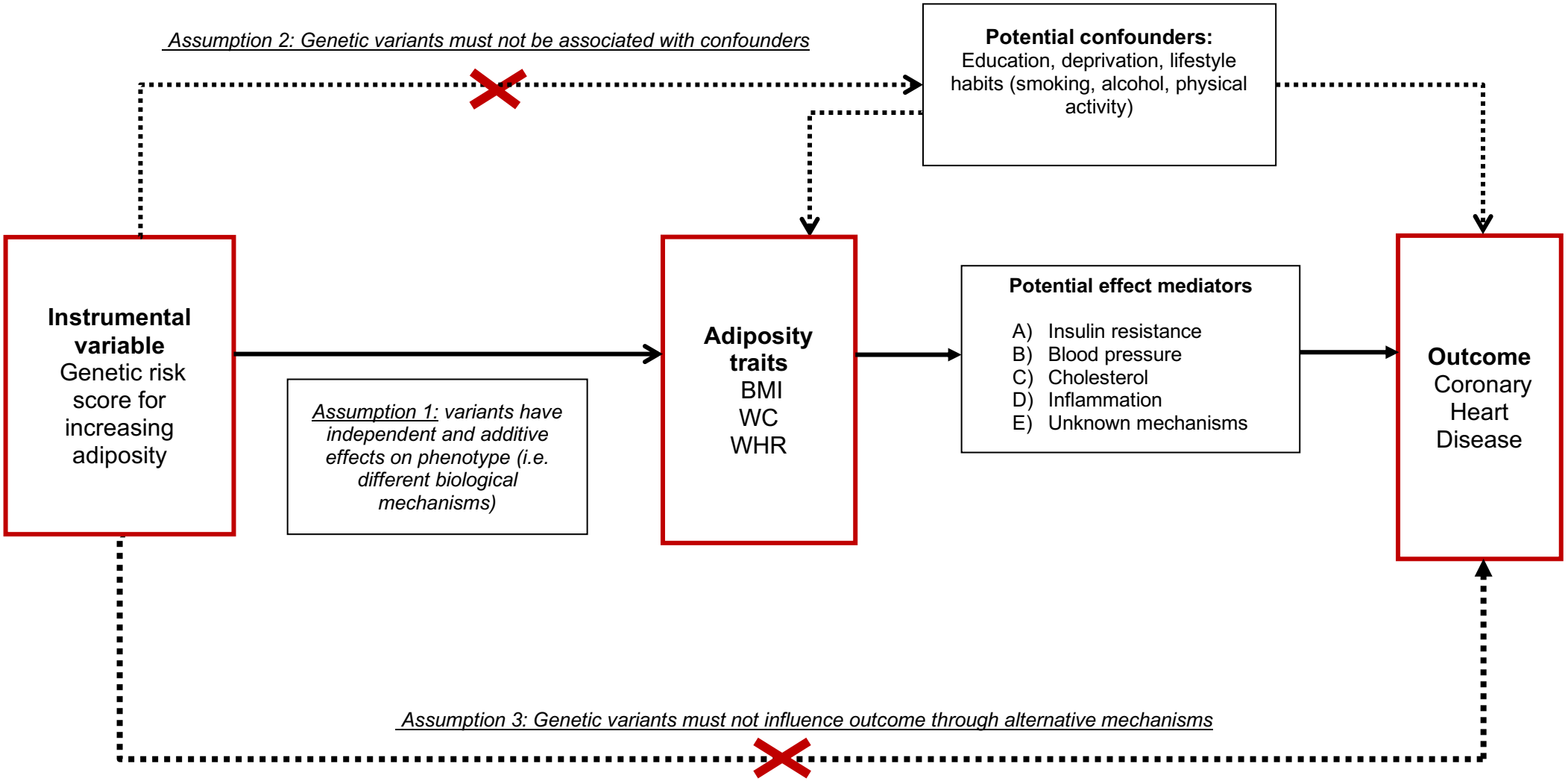
### 8.5 Conclusion

The current study used MR techniques to estimate the causal associations of independent BMI and WHRadjBMI GRSs with cardiometabolic traits and CHD risk. In accordance with the observational estimates presented in **Chapter 7**, genetically elevated WHRadjBMI was associated with a higher risk of CHD risk compared with BMI. Each genetically elevated adiposity phenotype was also independently associated with a vast array of cardiometabolic traits. Whereas both adiposity phenotypes were similarly associated with insulin resistance and blood pressure, body fat distribution was more closely associated with dyslipidaemia, and general adiposity appeared more closely linked with inflammation and kidney function. Given the evidence summarised in this Chapter, it is clear that both BMI and WHR depict two separate and mutually exclusive aspects of adiposity: general adiposity, and body fat distribution, respectively, with clear and distinct differences in their associated metabolic perturbations and subsequent influence on CHD risk. Therefore, each should be considered separately as CHD risk factors.

**Chapter 8 Tables and Figures**

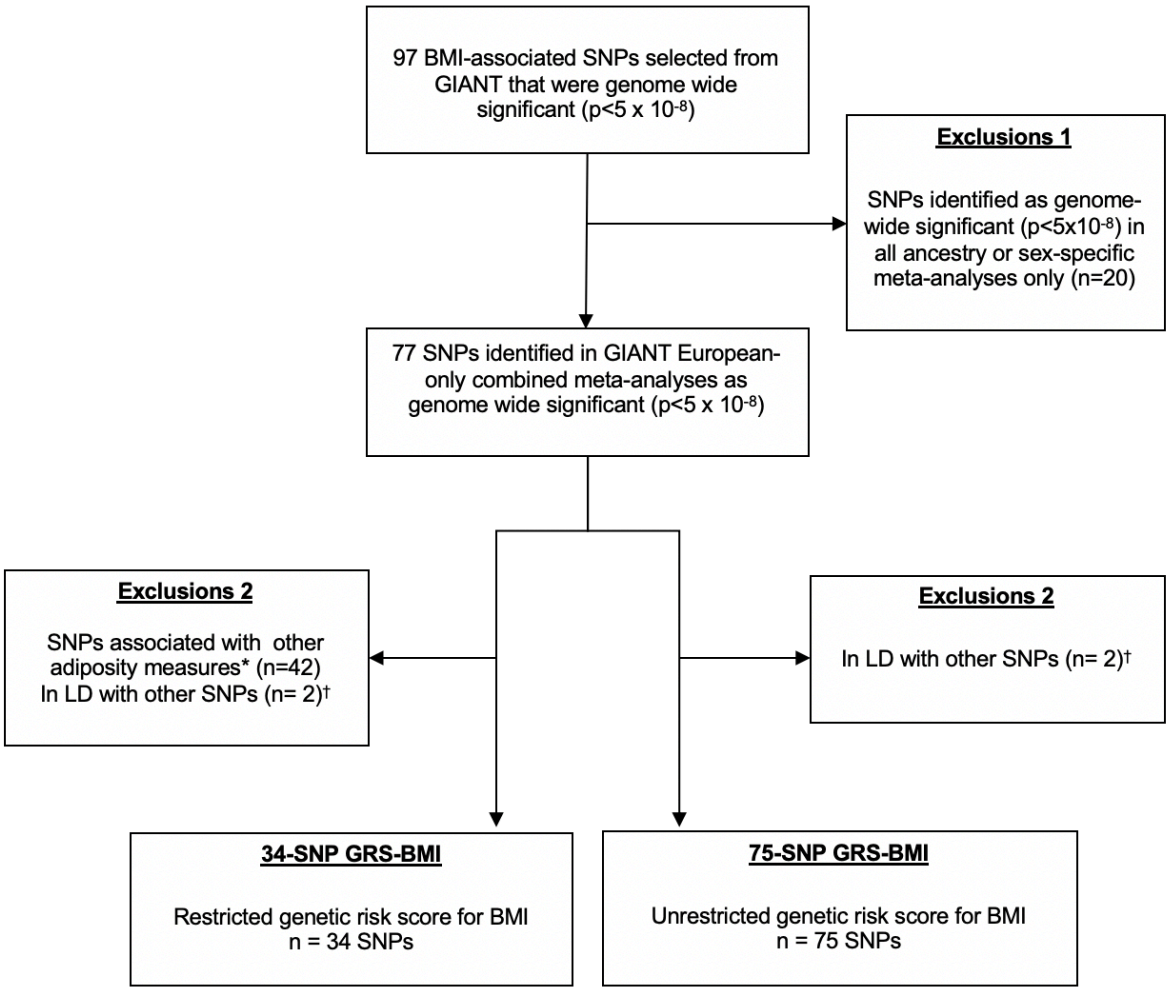

| Figure/Table | Title |
|---|---|
| **Figure 8.1** | Directed acyclic graph illustrating the association between genetically elevated adiposity and coronary heart disease |
| **Figure 8.2** | Flow diagram of BMI-associated variant selection process |
| **Figure 8.3** | BMI-associated SNPs in GIANT identified as pleiotropic for other adiposity phenotypes to significance $p<5x10^{-8}$ |
| **Table 8.1** | Basic information on loci associated with BMI in GIANT |
| **Figure 8.4** | Flow diagram of WHRadjBMI-associated variant selection process |
| **Table 8.2** | Basic information on loci associated with WHRadjBMI |
| **Table 8.3** | Selected baseline characteristics of the study population used in the genetic analyses |
| **Figure 8.5** | Comparison of effect sizes of BMI related SNPs in GIANT and UK Biobank study |
| **Figure 8.6** | Comparison of effect sizes of WHRadjBMI related SNPs in GIANT and UK Biobank |
| **Figure 8.7** | Weighted genetic risk score (GRS) for increasing BMI using 34 SNPs: distribution and mean BMI with increasing levels of GRS among men and women in the UK Biobank |
| **Figure 8.8** | Weighted genetic risk score (GRS) for increasing WHRadjBMI: distribution and mean BMI with increasing levels of GRS among men and women in the UK Biobank |
| **Figure 8.9** | Mean increase in body size and adiposity per SD increasing Genetic risk scores for BMI and WHRadjBMI, by sex |
| **Figure 8.10** | Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for BMI, by sex |
| **Figure 8.11** | Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for WHR adjusted for BMI (WHRadjBMI), by sex |
| **Table 8.3** | Associations of weighted genetic risk scores for WHRadjBMI with established cardiovascular risk factors, socio-economic and lifestyle factors in the UK Biobank study |
| **Figure 8.12** | Weighted genetic risk scores (GRS) for WHRadjBMI and BMI versus mutually exclusive DXA-derived variables of regional body composition |
| **Figure 8.13** | Association of increasing fifths of genetic risk scores for BMI and WHRadjBMI with coronary heart disease* risk in the UK Biobank |
| **Figure 8.14** | A comparison of Hazard Ratios (95% CI) for CHD risk with observed and genetically elevated BMI and WHRadjBMI |
| **Table 8.4** | Regression coefficients for associations of CHD with genetic variants included in genetic risk scores for BMI and WHRadjBMI in the UK Biobank using MR Egger, weighted median and inverse-variance weighted methods |
| **Figure 8.15** | Regression and funnel plots for MR assumption investigations |

**Figure 8.1** Directed acyclic graph (DAG) illustrating the association between genetically elevated adiposity and coronary heart disease



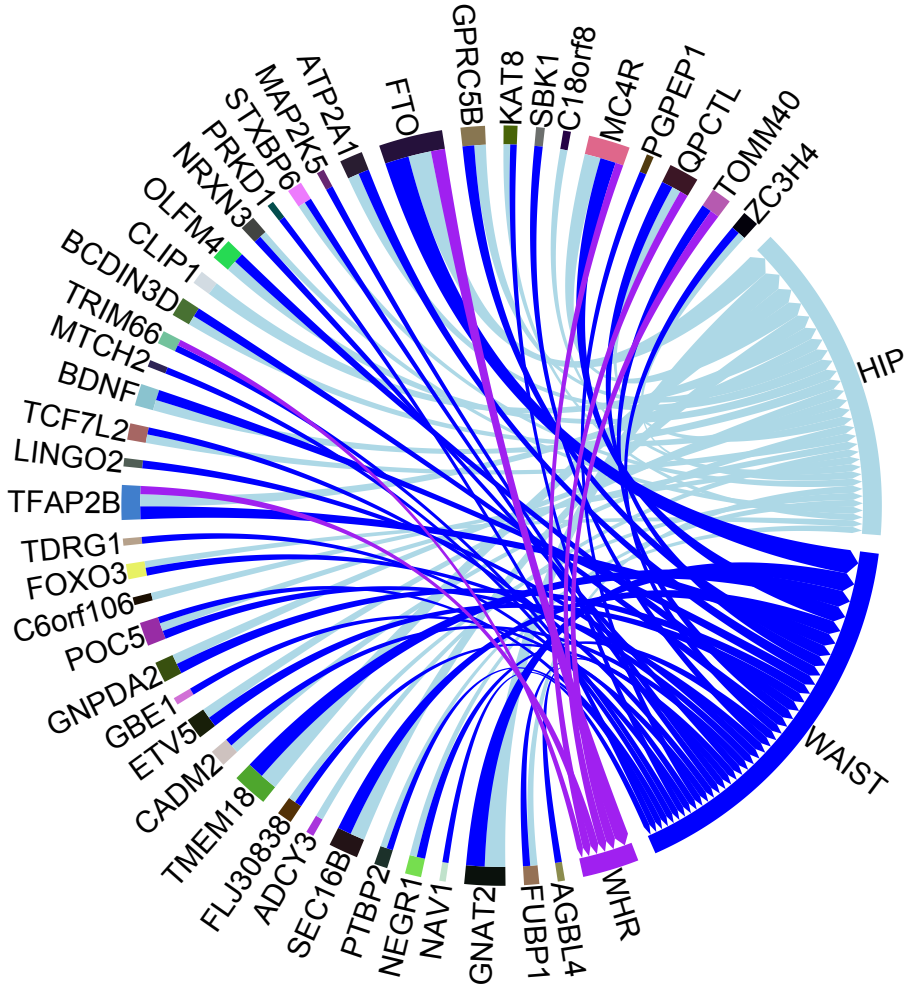

WC= waist circumference; WHR = waist-to-hip ratio; BMI = Body-mass index

**Figure 8.2** Flow diagram of BMI-associated variant selection process




BMI= Body-mass index; SNP= Single nucleotide polymorphism; GIANT= Genetic investigation of anthropometric traits consortium; LD= Linkage disequilibrium. *Significant pleiotropy was defined as an association to significance level $p<5x10^{-8}$ as reported in the GIANT consortium. †SNPs were defined as being in LD if R-squared >0.2.

**Figure 8.3** BMI-associated SNPs in GIANT identified as pleiotropic for other adiposity phenotypes to significance $p<5x10^{-8}$



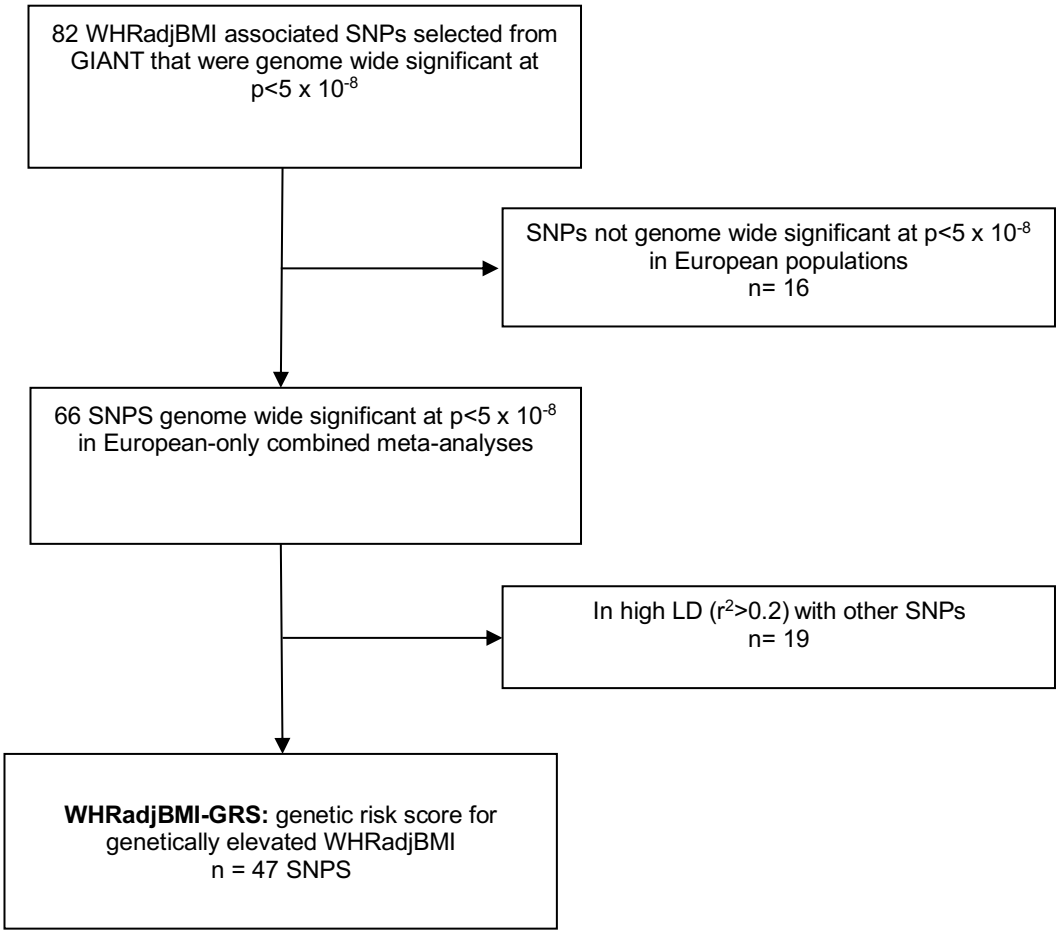

WHR = Waist-to-hip ratio. Lines represent associations between individual loci and each adiposity phenotype as reported in GIANT meta-analysis (Locke et al., 2015). Lines were weighted by the reported effect size in GIANT. Labels correspond to the nearest identified gene of each single nucleotide polymorphism.

**Table 8.1** Basic information on loci associated with BMI in GIANT

| | SNP | Chr | Position | Nearest gene | EA | OA | Beta | SE | EAF | Variance explained | Significant Pleiotropic traits | LD | BMI-GRS 1? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | rs543874 | 1 | 176,156,103 | *SEC16B* | G | A | 0.048 | 0.004 | 0.193 | 0.072% | WC, HC | | |
| 2. | rs3101336 | 1 | 72,523,773 | *NEGR1* | C | T | 0.033 | 0.003 | 0.613 | 0.053% | WC, HC | | |
| 3. | rs12566985 | 1 | 74,774,781 | *FPGT-TNNI3K* | G | A | 0.024 | 0.003 | 0.446 | 0.029% | | | Y |
| 4. | rs17024393 | 1 | 109,956,211 | *GNAT2* | C | T | 0.066 | 0.009 | 0.040 | 0.033% | WC, HC | | |
| 5. | rs11165643 | 1 | 96,696,685 | *PTBP2* | T | C | 0.022 | 0.003 | 0.583 | 0.023% | WC, HC | | |
| 6. | rs12401738 | 1 | 78,219,349 | *FUBP1* | A | G | 0.021 | 0.003 | 0.352 | 0.020% | WC, HC | | |
| 7. | rs657452 | 1 | 49,362,434 | *AGBL4* | A | G | 0.023 | 0.003 | 0.394 | 0.025% | WC, | | |
| 8. | rs2820292 | 1 | 200,050,910 | *NAV1* | C | A | 0.020 | 0.003 | 0.555 | 0.019% | WC, | | |
| 9. | rs11583200 | 1 | 50,332,407 | *ELAVL4* | C | T | 0.018 | 0.003 | 0.396 | 0.015% | | Y | |
| 10. | rs13021737 | 2 | 622,348 | *TMEM18* | G | A | 0.060 | 0.004 | 0.828 | 0.103% | WC, HC | | |
| 11. | rs10182181 | 2 | 25,003,800 | *ADCY3* | G | A | 0.031 | 0.003 | 0.462 | 0.047% | HC | | |
| 12. | rs1016287 | 2 | 59,159,129 | *FLJ30838* | T | C | 0.023 | 0.003 | 0.287 | 0.021% | WC, HC | | |
| 13. | rs2121279 | 2 | 142,759,755 | *LRP1B* | T | C | 0.025 | 0.004 | 0.152 | 0.015% | | | Y |
| 14. | rs7599312 | 2 | 213,121,476 | *ERBB4* | G | A | 0.022 | 0.003 | 0.724 | 0.019% | | | Y |
| 15. | rs11126666 | 2 | 26,782,315 | *KCNK3* | A | G | 0.021 | 0.003 | 0.283 | 0.017% | | | Y |
| 16. | rs1528435 | 2 | 181,259,207 | *UBE2E3* | T | C | 0.018 | 0.003 | 0.631 | 0.015% | | | Y |
| 17. | rs11688816 | 2 | 62,906,552 | *EHBP1* | G | A | 0.017 | 0.003 | 0.525 | 0.015% | | | Y |
| 18. | rs1516725 | 3 | 187,306,698 | *ETV5* | C | T | 0.045 | 0.005 | 0.872 | 0.045% | WC, HC | | |
| 19. | rs13078960 | 3 | 85,890,280 | *CADM2* | G | T | 0.030 | 0.004 | 0.196 | 0.028% | WC, HC | | |
| 20. | rs2365389 | 3 | 61,211,502 | *FHIT* | C | T | 0.020 | 0.003 | 0.582 | 0.019% | | | Y |
| 21. | rs16851483 | 3 | 142,758,126 | *RASA2* | T | G | 0.048 | 0.008 | 0.066 | 0.029% | | | Y |
| 22. | rs6804842 | 3 | 25,081,441 | *RARB* | G | A | 0.019 | 0.003 | 0.575 | 0.017% | | | Y |
| 23. | rs3849570 | 3 | 81,874,802 | *GBE1* | A | C | 0.019 | 0.003 | 0.359 | 0.016% | WC, | | |
| 24. | rs10938397 | 4 | 44,877,284 | *GNPDA2* | G | A | 0.040 | 0.003 | 0.434 | 0.079% | WC, HC | | |
| 25. | rs13107325 | 4 | 103,407,732 | *SLC39A8* | T | C | 0.048 | 0.007 | 0.072 | 0.030% | | | Y |
| 26. | rs17001654 | 4 | 77,348,592 | *SCARB2* | G | C | 0.031 | 0.005 | 0.153 | 0.024% | | | Y |
| 27. | rs11727676 | 4 | 145,878,514 | *HHIP* | T | C | 0.036 | 0.006 | 0.910 | 0.021% | | | Y |
| 28. | rs2112347 | 5 | 75050998 | *POC5* | T | G | 0,026 | 0.003 | 0.629 | 0.032% | WC | | |
| 29. | rs2207139 | 6 | 50,953,449 | *TFAP2B* | G | A | 0.045 | 0.004 | 0.177 | 0.058% | WC, HC | | |
| 30. | rs205262 | 6 | 34,671,142 | *C6orf106* | G | A | 0.022 | 0.004 | 0.273 | 0.019% | HC | | |
| 31. | rs13191362 | 6 | 162,953,340 | *PARK2* | A | G | 0.028 | 0.005 | 0.879 | 0.016% | | | Y |
| 32. | rs2033529 | 6 | 40,456,631 | *TDRG1* | G | A | 0.019 | 0.003 | 0.293 | 0.015% | WC, | | |
| 33. | rs9400239 | 6 | 109,084,356 | *FOXO3* | C | T | 0.019 | 0.003 | 0.688 | 0.015% | WC, HC | | |
| 34. | rs1167827 | 7 | 75,001,105 | *HIP1* | G | A | 0.020 | 0.003 | 0.553 | 0.020% | | | Y |
| 35. | rs2245368 | 7 | 76,446,079 | *PMS2L11* | C | T | 0.032 | 0.006 | 0.180 | 0.030% | | | Y |
| 36. | rs17405819 | 8 | 76,969,139 | *HNF4G* | T | C | 0.022 | 0.003 | 0.700 | 0.021% | | | Y |
| 37. | rs2033732 | 8 | 85,242,264 | *RALYL* | C | T | 0.019 | 0.004 | 0.747 | 0.014% | | | Y |
| 38. | rs10968576 | 9 | 28,404,339 | *LINGO2* | G | A | 0.025 | 0.003 | 0.320 | 0.027% | WC, | | |
| 39. | rs1928295 | 9 | 119,418,304 | *TLR4* | T | C | 0.019 | 0.003 | 0.548 | 0.018% | | | Y |
| 40. | rs4740619 | 9 | 15,624,326 | *C9orf93* | T | C | 0.018 | 0.003 | 0.542 | 0.016% | | | Y |
| 41. | rs10733682 | 9 | 128,500,735 | *LMX1B* | A | G | 0.017 | 0.003 | 0.478 | 0.015% | | | Y |
| 42. | rs6477694 | 9 | 110,972,163 | *EPB41L4B* | C | T | 0.017 | 0.003 | 0.365 | 0.014% | | | Y |
| 43. | rs7903146 | 10 | 114,748,339 | *TCF7L2* | C | T | 0.023 | 0.003 | 0.713 | 0.022% | WC, HC | | |
| 44. | rs17094222 | 10 | 102,385,430 | *HIF1AN* | C | T | 0.025 | 0.004 | 0.211 | 0.021% | | | Y |
| 45. | rs11191560 | 10 | 104,859,028 | *NT5C2* | C | T | 0.031 | 0.005 | 0.089 | 0.015% | | | Y |
| 46. | rs7899106 | 10 | 87,400,884 | *GRID1* | G | A | 0.040 | 0.007 | 0.052 | 0.015% | | | Y |
| 47. | rs11030104 | 11 | 27,641,093 | *BDNF* | A | G | 0.041 | 0.004 | 0.792 | 0.056% | WC, HC | | |
| 48. | rs3817334 | 11 | 47,607,569 | *MTCH2* | T | C | 0.026 | 0.003 | 0.407 | 0.033% | WC, | | |
| 49. | rs4256980 | 11 | 8,630,515 | *TRIM66* | G | C | 0.021 | 0.003 | 0.646 | 0.020% | WHR, WC | | |
| 50. | rs12286929 | 11 | 114,527,614 | *CADM1* | G | A | 0.022 | 0.003 | 0.523 | 0.023% | | | Y |
| 51. | rs2176598 | 11 | 43,820,854 | *HSD17B12* | T | C | 0.020 | 0.004 | 0.251 | 0.015% | | | Y |
| 52. | rs7138803 | 12 | 48,533,735 | *BCDIN3D* | A | G | 0.032 | 0.003 | 0.384 | 0.047% | WC, HC | | |
| 53. | rs11057405 | 12 | 121,347,850 | *CLIP1* | G | A | 0.031 | 0.006 | 0.901 | 0.017% | HC | | |
| 54. | rs12429545 | 13 | 53,000,207 | *OLFM4* | A | G | 0.033 | 0.005 | 0.133 | 0.026% | WC, HC | | |
| 55. | rs12016871 | 13 | 26,915,782 | *MTIF3* | T | C | 0.030 | 0.005 | 0.203 | 0.029% | | | Y |
| 56. | rs7141420 | 14 | 78,969,207 | *NRXN3* | T | C | 0.024 | 0.003 | 0.527 | 0.028% | WC, HC | | |
| 57. | rs11847697 | 14 | 29,584,863 | *PRKD1* | T | C | 0.049 | 0.008 | 0.042 | 0.019% | | | Y |
| 58. | rs12885454 | 14 | 28,806,589 | PRKD1 | C | A | 0.0207 | 0.0033 | 0.642 | 0.020% | WC | | |
| 59. | rs10132280 | 14 | 24,998,019 | *STXBP6* | C | A | 0.023 | 0.003 | 0.682 | 0.023% | WC, HC | | |
| 60. | rs16951275 | 15 | 65,864,222 | *MAP2K5* | T | C | 0.031 | 0.004 | 0.784 | 0.033% | WC, | | |
| 61. | rs3736485 | 15 | 49535902 | DMXL2 | A | G | 0.0176 | 0.0031 | 0.454 | 0.015% | | | Y |
| 62. | rs1558902 | 16 | 52,361,075 | *FTO* | A | T | 0.082 | 0.003 | 0.415 | 0.325% | WHR, WC, HC | | |
| 63. | rs3888190 | 16 | 28,796,987 | *ATP2A1* | A | C | 0.031 | 0.003 | 0.403 | 0.046% | WC, HC | | |
| 64. | rs12446632 | 16 | 19,842,890 | *GPRC5B* | G | A | 0.040 | 0.005 | 0.865 | 0.038% | WC, HC | | |
| 65. | rs758747 | 16 | 3,567,359 | *NLRC3* | T | C | 0.023 | 0.004 | 0.265 | 0.020% | | | Y |
| 66. | rs9925964 | 16 | 31,037,396 | *KAT8* | A | G | 0.019 | 0.003 | 0.620 | 0.017% | WC, HC | | |
| 67. | rs2650492 | 16 | 28,240,912 | *SBK1* | A | G | 0.021 | 0.004 | 0.303 | 0.018% | WC, | Y | |
| 68. | rs12940622 | 17 | 76,230,166 | *RPTOR* | G | A | 0.018 | 0.003 | 0.575 | 0.016% | | | Y |
| 69. | rs1000940 | 17 | 5,223,976 | *RABEP1* | G | A | 0.019 | 0.003 | 0.320 | 0.016% | | | Y |
| 70. | rs6567160 | 18 | 55,980,115 | *MC4R* | C | T | 0.056 | 0.004 | 0.236 | 0.111% | WHR, WC, HC | | |
| 71. | rs7243357 | 18 | 55,034,299 | *GRP* | T | G | 0.022 | 0.004 | 0.812 | 0.014% | | | Y |
| 72. | rs1808579 | 18 | 19,358,886 | *C18orf8* | C | T | 0.017 | 0.003 | 0.534 | 0.014% | HC, | | |
| 73. | rs2287019 | 19 | 50,894,012 | *QPCTL* | C | T | 0.036 | 0.004 | 0.804 | 0.041% | WHR, WC, HC | | |
| 74. | rs3810291 | 19 | 52,260,843 | *ZC3H4* | A | G | 0.028 | 0.004 | 0.666 | 0.036% | WC, HC | | |
| 75. | rs2075650 | 19 | 50,087,459 | *TOMM40* | A | G | 0.026 | 0.005 | 0.848 | 0.017% | WHR, WC | | |
| 76. | rs29941 | 19 | 39,001,372 | *KCTD15* | G | A | 0.018 | 0.003 | 0.669 | 0.015% | | | Y |
| 77. | rs17724992 | 19 | 18,315,825 | *PGPEP1* | A | G | 0.019 | 0.004 | 0.746 | 0.014% | WC | | |

SNP= Single nucleotide polymorphism; Chr= Chromosome number; EA= Effect allele; OA= Other Allele; EAF = Effect Allele Frequency; SE= Standard Error; BMI-GRS1= Restricted 34-SNP genetic risk score for increasing BMI used in the current study. Effect sizes represent the standard deviation increase in BMI per additional effect allele in the GIANT consortium. SNPs were identified in European populations only, were not in Linkage Disequilibrium with each other, and had no pleiotropic effects on WC, WHR or HC to the threshold significance level of $p=5x10^{-8}$ as reported in GIANT (Locke et al., 2015).

**Figure 8.4** Flow diagram of waist-to-hip ratio adjusted for BMI (WHRadjBMI) -associated variant selection process used in the current study




BMI= Body-mass index; SNP= Single nucleotide polymorphism; GIANT= Genetic investigation of anthropometric traits consortium; LD= Linkage disequilibrium. *Significant pleiotropy was defined as an association to significance level $p<5x10^{-8}$ as reported in the GIANT consortium (Shungin et al., 2015).

**Table 8.2** Basic information on 47 loci associated with WHRadjBMI used in the present analyses

| SNP | Chr | Position | Nearest gene | EA | OA | Beta | P-value | EAF | Analysis | Significant effects on WC and HC $p<5x10^{-8}$ | Reference | No. of participants |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2645294 | 1 | 119376110 | TBX15-WARS2 | T | C | 0.0312 | 1.69E-19 | 0.5797 | Primary | WCadjBMI | Shungin et al., 2015 | 209808 |
| rs905938 | 1 | 153258013 | DCST2 | T | C | 0.0249 | 7.34E-10 | 0.7427 | Primary | | Shungin et al., 2015 | 207867 |
| rs10919388 | 1 | 168639127 | GORAB | C | A | 0.0239 | 3.18E-09 | 0.7226 | Primary | | Shungin et al., 2015 | 181049 |
| rs714515 | 1 | 170619613 | DNM3-PIGC | G | A | 0.027 | 4.38E-15 | 0.4285 | Primary | HCadjBMI | Shungin et al., 2015 | 203401 |
| rs2820443 | 1 | 217820132 | LYPLAL1 | T | C | 0.0349 | 5.26E-21 | 0.7167 | Primary | HCadjBMI, HC | Shungin et al., 2015 | 209975 |
| rs1385167 | 2 | 66054152 | MEIS1 | G | A | 0.0293 | 1.85E-09 | 0.1475 | Primary | | Shungin et al., 2015 | 206619 |
| rs10195252 | 2 | 165221337 | GRB14-COBLL1 | T | C | 0.027 | 5.87E-15 | 0.5926 | Primary | HCadjBMI, HC | Shungin et al., 2015, Heid et al., 2010 | 209395 |
| rs1569135 | 2 | 187823643 | CALCRL | A | G | 0.0213 | 5.61E-10 | 0.5297 | Primary | | Shungin et al., 2015 | 209906 |
| rs17819328 | 3 | 12464342 | PPARG | G | T | 0.0208 | 2.43E-09 | 0.4317 | Primary | HCadjBMI | Shungin et al., 2015 | 208809 |
| rs2276824 | 3 | 52612526 | PBRM1 | C | G | 0.0236 | 3.17E-11 | 0.4342 | Primary | | Shungin et al., 2015 | 208901 |
| rs2371767 | 3 | 64693298 | ADAMTS9 | G | C | 0.0363 | 1.59E-20 | 0.7247 | Primary | WCadjBMI, HC | Shungin et al., 2015 | 194506 |
| rs6784615 | 3 | 52481466 | NISCH-STAB1 | T | | 0.043 | 3.84E-10 | 0.941 | Primary | | Heid et al., 2010 | 109,028 |
| rs10804591 | 3 | 130816923 | PLXND1 | A | C | 0.0245 | 6.57E-09 | 0.795 | Primary | HCadjBMI | Shungin et al., 2015 | 209921 |
| rs17451107 | 3 | 158280303 | LEKR1 | T | C | 0.0256 | 1.14E-12 | 0.6145 | Primary | WCadjBMI | Shungin et al., 2015 | 207795 |
| rs9991328 | 4 | 89932144 | FAM13A | T | C | 0.0185 | 4.45E-08 | 0.4882 | Primary | | Shungin et al., 2015 | 209925 |
| rs303084 | 4 | 124286398 | SPATA5-FGF2 | A | G | 0.0232 | 3.88E-08 | 0.7961 | Primary | | Shungin et al., 2015 | 209941 |
| rs7705502 | 5 | 173253421 | CPEB4 | A | G | 0.0271 | 4.66E-14 | 0.3278 | Primary | WCadjBMI | Shungin et al., 2015 | 209827 |
| rs6556301 | 5 | 176460183 | FGFR4 | T | G | 0.0221 | 2.58E-08 | 0.3573 | Primary | WCadjBMI | Shungin et al., 2015 | 178874 |
| rs1294410 | 6 | 6683751 | LY86 | C | T | 0.0309 | 2.03E-18 | 0.6329 | Primary | HCadjBMI, HC | Shungin et al., 2015 | 209830 |
| rs7759742 | 6 | 32489714 | BTNL2 | A | T | 0.0226 | 4.41E-11 | 0.511 | Primary | | Shungin et al., 2015 | 208263 |
| rs1358980 | 6 | 43872529 | VEGFA | T | C | 0.0392 | 3.11E-27 | 0.4676 | Primary | WCadjBMI | Shungin et al., 2015 | 206862 |
| rs1936805 | 6 | 127493809 | RSPO3 | T | C | 0.0425 | 3.56E-35 | 0.5109 | Primary | HCadjBMI,WCadjBMI | Shungin et al., 2015 | 209859 |
| rs10245353 | 7 | 25825139 | NFE2L3 | A | C | 0.0348 | 8.41E-16 | 0.1998 | Primary | WCadjBMI | Shungin et al., 2015 | 210008 |
| rs7801581 | 7 | 27190296 | HOXA11 | T | C | 0.0265 | 3.68E-10 | 0.2424 | Primary | WCadjBMI | Shungin et al., 2015 | 195215 |
| rs12679556 | 8 | 72676782 | MSC | G | T | 0.0268 | 2.14E-11 | 0.2475 | Primary | WCadjBMI | Shungin et al., 2015 | 203826 |
| rs10991437 | 9 | 106775741 | ABCA1 | A | C | 0.0311 | 1.02E-08 | 0.1135 | Primary | | Shungin et al., 2015 | 209941 |
| rs11231693 | 11 | 63619188 | MACROD1-VEGFB | A | G | 0.0411 | 4.48E-08 | 0.0624 | Primary | | Shungin et al., 2015 | 198072 |
| rs10842707 | 12 | 26362631 | ITPR2-SSPN | T | C | 0.0324 | 4.4E-16 | 0.2318 | Primary | | Shungin et al., 2015 | 210023 |
| rs1443512 | 12 | 52628951 | HOXC13 | A | C | 0.0283 | 6.94E-13 | 0.2373 | Primary | | Shungin et al., 2015, Heid et al.,2010 | 209980 |
| rs4765219 | 12 | 123006063 | CCDC92 | C | A | 0.0284 | 1.56E-15 | 0.668 | Primary | | Shungin et al., 2015 | 209807 |
| rs8042543 | 15 | 29495555 | KLF13 | C | T | 0.0263 | 1.16E-09 | 0.7824 | Primary | | Shungin et al., 2015 | 208255 |
| rs8030605 | 15 | 54291890 | RFX7 | A | G | 0.0304 | 8.77E-09 | 0.1415 | Primary | | Shungin et al., 2015 | 208374 |
| rs1440372 | 15 | 64820205 | SMAD6 | C | T | 0.0244 | 1.13E-10 | 0.7097 | Primary | | Shungin et al., 2015 | 207447 |
| rs4646404 | 17 | 17360924 | PEMT | G | A | 0.0266 | 1.36E-11 | 0.6653 | Primary | | Shungin et al., 2015 | 198196 |
| rs12608504 | 19 | 18250135 | JUND | A | G | 0.0219 | 8.79E-10 | 0.355 | Primary | WCadjBMI | Shungin et al., 2015 | 209990 |
| rs4081724 | 19 | 38516786 | CEBPA | G | A | 0.0347 | 7.38E-12 | 0.8512 | Primary | | Shungin et al., 2015 | 207418 |
| rs979012 | 20 | 6571374 | BMP2 | T | C | 0.0273 | 3.34E-14 | 0.3425 | Primary | WCadjBMI | Shungin et al., 2015 | 209941 |
| rs224333 | 20 | 33487376 | GDF5 | G | A | 0.0202 | 2.57E-08 | 0.6232 | Primary | HCadjBMI, HC | Shungin et al., 2015 | 208025 |
| rs6090583 | 20 | 44992238 | EYA2 | A | G | 0.0224 | 6.17E-11 | 0.48 | Primary | | Shungin et al., 2015 | 209435 |
| rs2294239 | 22 | 27779477 | ZNRF3-KREMEN1 | A | G | 0.0252 | 7.24E-13 | 0.5866 | Primary | WCadjBMI | Shungin et al., 2015 | 209454 |
| rs12143789 | 1 | 119298677 | TBX15 | C | G | 0.0244 | 7.55E-09 | 0.2055 | Secondary | | Shungin et al., 2015 | 209874 |
| rs12489828 | 3 | 52542054 | NT5DC2 | G | T | 0.0227 | 7.11E-11 | 0.5488 | Secondary | WCadjBMI | Shungin et al., 2015 | 204485 |
| rs13083798 | 3 | 52624788 | PRBM1 | A | G | 0.0227 | 4.09E-11 | 0.4903 | Secondary | WCadjBMI | Shungin et al., 2015 | 209128 |
| rs459193 | 5 | 55842508 | ANKRD55 | A | G | 0.0259 | 1.58E-11 | 0.2645 | Secondary | WCadjBMI | Shungin et al., 2015 | 209952 |
| rs72959041 | 6 | 127496586 | RSPO3 | A | G | 0.1252 | 2.86E-22 | 0.0575 | Secondary | WCadjBMI | Shungin et al., 2015 | 65066 |
| rs2071449 | 12 | 52714278 | HOXC4-HOXC6 | A | C | 0.0276 | 2.99E-14 | 0.3692 | Secondary | WCadjBMI | Shungin et al., 2015 | 206953 |
| rs863750 | 12 | 123071397 | ZNF664 | T | C | 0.0258 | 7.37E-14 | 0.5932 | Secondary | | Shungin et al., 2015 | 209371 |

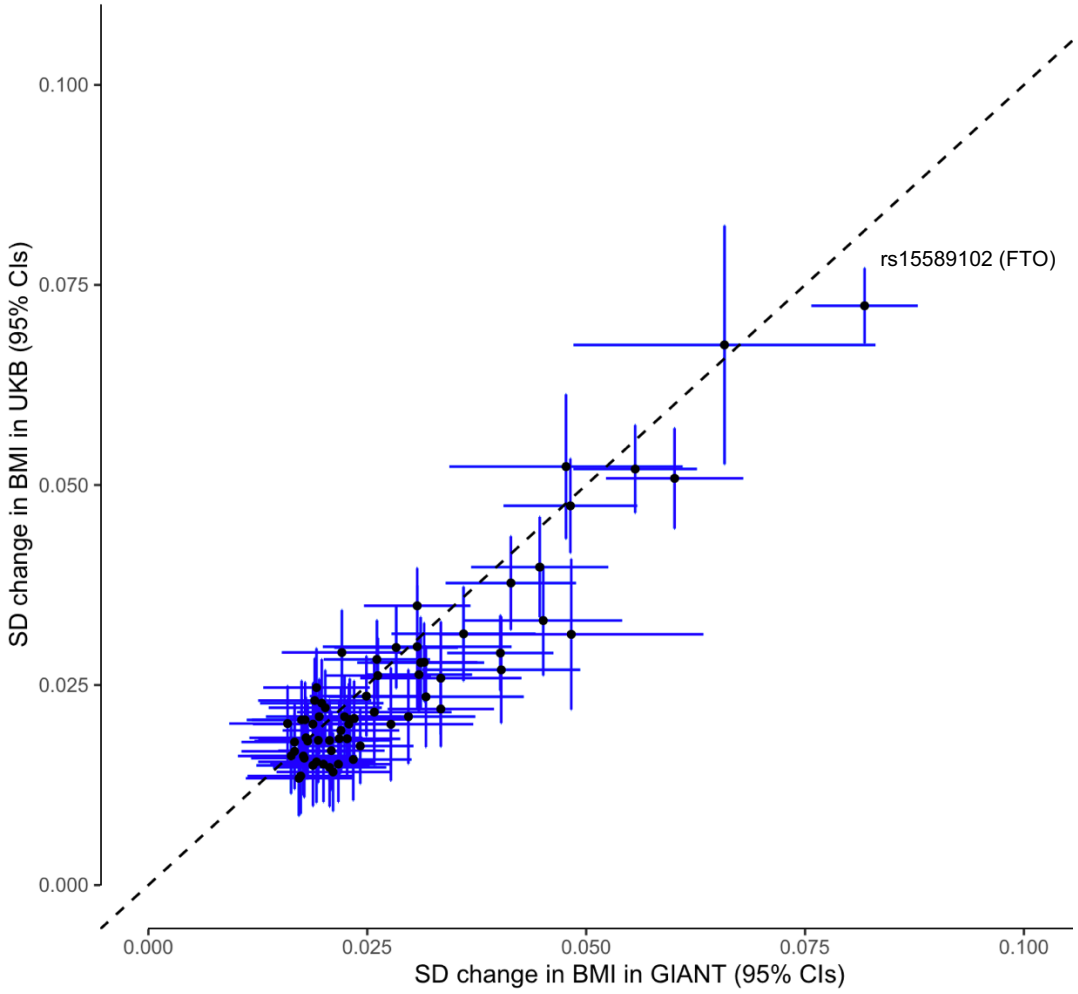
Chr=Chromosome number; EA= Effect allele; OA= Other Allele; EAF = Effect Allele Frequency; GRS 1= genetic risk score 1: Conservative/non-pleiotropic risk score; GRS 2: Liberal/pleiotropic risk score. Effect sizes represent the standard deviation increase in WHRadjBMI per additional effect allele in the GIANT consortium.

**Table 8.3** Selected baseline characteristics of the study population used in the genetic analyses compared with study population used in main prospective analysis (**Chapter 7**)

| | Main analysis population | | | Genetic population | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Men** | **Women** | **All** | **Men** | **Women** | **All** |
| **N** | 200 639 | 254 509 | 455 148 | 159442 | 199265 | 358707 |
| **Age, years** | | | | | | |
| 40-44 | 11% | 11% | 11% | 11% | 10% | 10% |
| 45-49 | 14% | 14% | 14% | 13% | 14% | 13% |
| 50-54 | 15% | 16% | 16% | 15% | 16% | 16% |
| 55-59 | 18% | 19% | 18% | 18% | 18% | 19% |
| 60-64 | 23% | 24% | 24% | 24% | 25% | 24% |
| 65-69 | 18% | 16% | 17% | 19% | 17% | 18% |
| Mean (SD) | 56.2 (8.2) | 56.1 (7.9) | 56.1 (8.0) | 56.4 (8.1) | 56.3 (7.9) | 56.3 (8.0) |
| **Ethnicity** | | | | | | |
| White | 94% | 94% | 94% | 100% | 100% | 100% |
| None-white | 6% | 6% | 6% | 0% | 0% | 0% |
| **Highest qualification** | | | | | | |
| No qualifications | 15% | 16% | 16% | 16% | 15% | 15% |
| GCSE/O-Level | 24% | 29% | 27% | 30% | 24% | 27% |
| AS/A-Level | 10% | 12% | 11% | 12% | 11% | 12% |
| Higher education | 48% | 42% | 44% | 42% | 48% | 45% |
| Prefer not to answer | 2% | 2% | 2% | 3% | 1% | 1% |
| **UK Region** | | | | | | |
| London | 14% | 14% | 14% | 12% | 13% | 13% |
| South East | 9% | 9% | 9% | 9% | 10% | 10% |
| South West | 9% | 9% | 9% | 9% | 9% | 9% |
| East Midlands | 7% | 7% | 7% | 7% | 7% | 7% |
| West Midlands | 9% | 8% | 9% | 9% | 8% | 9% |
| Yorkshire & Humber | 15% | 15% | 15% | 15% | 15% | 15% |
| North West | 16% | 15% | 15% | 15% | 15% | 15% |
| North East | 11% | 11% | 11% | 11% | 11% | 11% |
| Wales | 4% | 4% | 4% | 4% | 4% | 4% |
| Scotland | 7% | 7% | 7% | 7% | 8% | 7% |
| **Adiposity and body size** | | | | | | |
| Height (cm) | 175.8 (6.8) | 162.6 (6.3) | 168.4 (9.3) | 175.8 (6.8) | 162.6 (6.3) | 168.4 (9.3) |
| BMI (kg/m²) | 27.7 (4.1) | 27.0 (5.1) | 27.3 (4.7) | 27.7 (4.1) | 26.9 (5.1) | 27.3 (4.7) |
| Body fat percentage | 25.0 (5.7) | 36.5 (6.8) | 31.4 (8.5) | 25.0 (5.7) | 36.4 (6.8) | 31.4 (8.5) |
| Waist circumference (cm) | 96.5 (11.0) | 84.4 (12.3) | 89.7 (13.2) | 96.6 (11.0) | 84.2 (12.2) | 89.7 (13.2) |
| Waist-to-hip ratio | 0.93 (0.06) | 0.82 (0.07) | 0.87 (0.09) | 0.93 (0.06) | 0.82 (0.07) | 0.87 (0.09) |
| Waist-to-height ratio | 0.55 (0.06) | 0.52 (0.08) | 0.53 (0.07) | 0.55 (0.06) | 0.52 (0.08) | 0.53 (0.07) |
| Trunk fat percentage | 27.4 (6.5) | 34.0 (7.6) | 31.1 (7.9) | 27.4 (6.5) | 33.9 (7.6) | 31.1 (7.9) |
| **Smoking status** | | | | | | |
| Current | 12% | 9% | 10% | 12% | 9% | 10% |
| Former | 37% | 31% | 34% | 38% | 32% | 34% |
| Never | 51% | 60% | 56% | 50% | 59% | 55% |
| **Weekly alcohol consumption** | | | | | | |
| Daily drinker | 26% | 16% | 20% | 27% | 17% | 21% |
| Regular drinker | 53% | 47% | 49% | 54% | 48% | 51% |
| Occasional drinker | 16% | 28% | 22% | 15% | 27% | 22% |
| Never drinker | 6% | 9% | 8% | 5% | 8% | 6% |
| **Physical activity (MET-hr/wk)** | | | | | | |
| Low, <10 | 23% | 24% | 23% | 23% | 24% | 23% |
| Moderate, 10-49.9 | 47% | 47% | 47% | 48% | 48% | 48% |
| High, ≥50 | 22% | 18% | 20% | 22% | 18% | 20% |
| Missing/prefer not to say | 8% | 12% | 10% | 8% | 11% | 9% |
| **Blood pressure, mmHg** | | | | | | |
| Systolic blood pressure | 141.1 (17.3) | 135.2 (19.2) | 137.8 (18.6) | 141.3 (17.3) | 135.2 (19.1) | 137.9 (18.6) |
| Diastolic blood pressure | 84.5 (9.9) | 80.8 (10.0) | 82.4 (10.1) | 84.5 (9.9) | 80.7 (10.0) | 82.4 (10.1) |
| **Diagnosed conditions** | | | | | | |
| Hypertension, % | 27.0% | 21.5% | 24.0% | 27.0% | 21.0% | 23.7% |
| Diabetes, % | 4.8% | 2.5% | 3.6% | 4.4% | 2.2% | 3.2% |

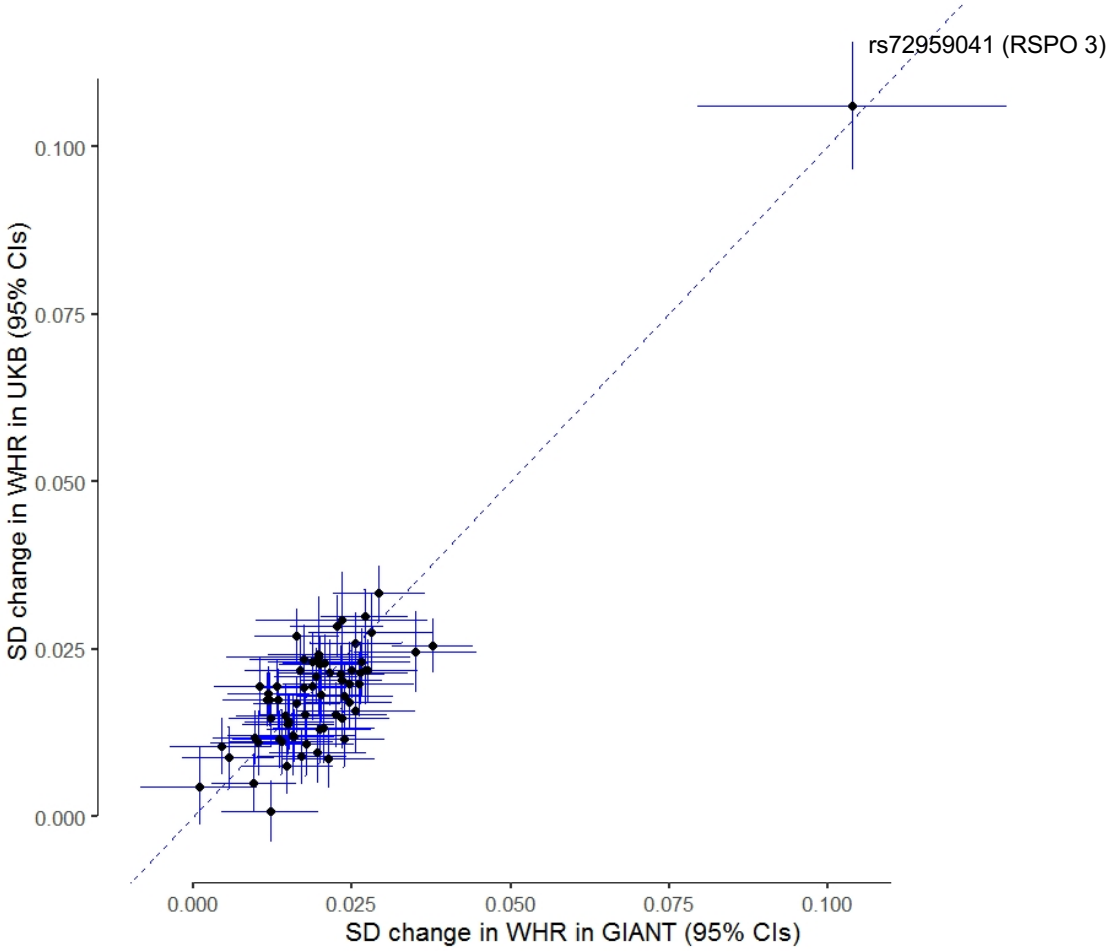
MET= Metabolic equivalent of task units. Observational study population included individuals without prior cardiovascular disease or missing/outlying adiposity values at baseline .Genetic study population included unrelated individuals of European descent, without prior cardiovascular disease or missing/outlying adiposity values at baseline.

**Figure 8.5** Comparison of effect sizes of BMI-associated variants in GIANT and UK Biobank



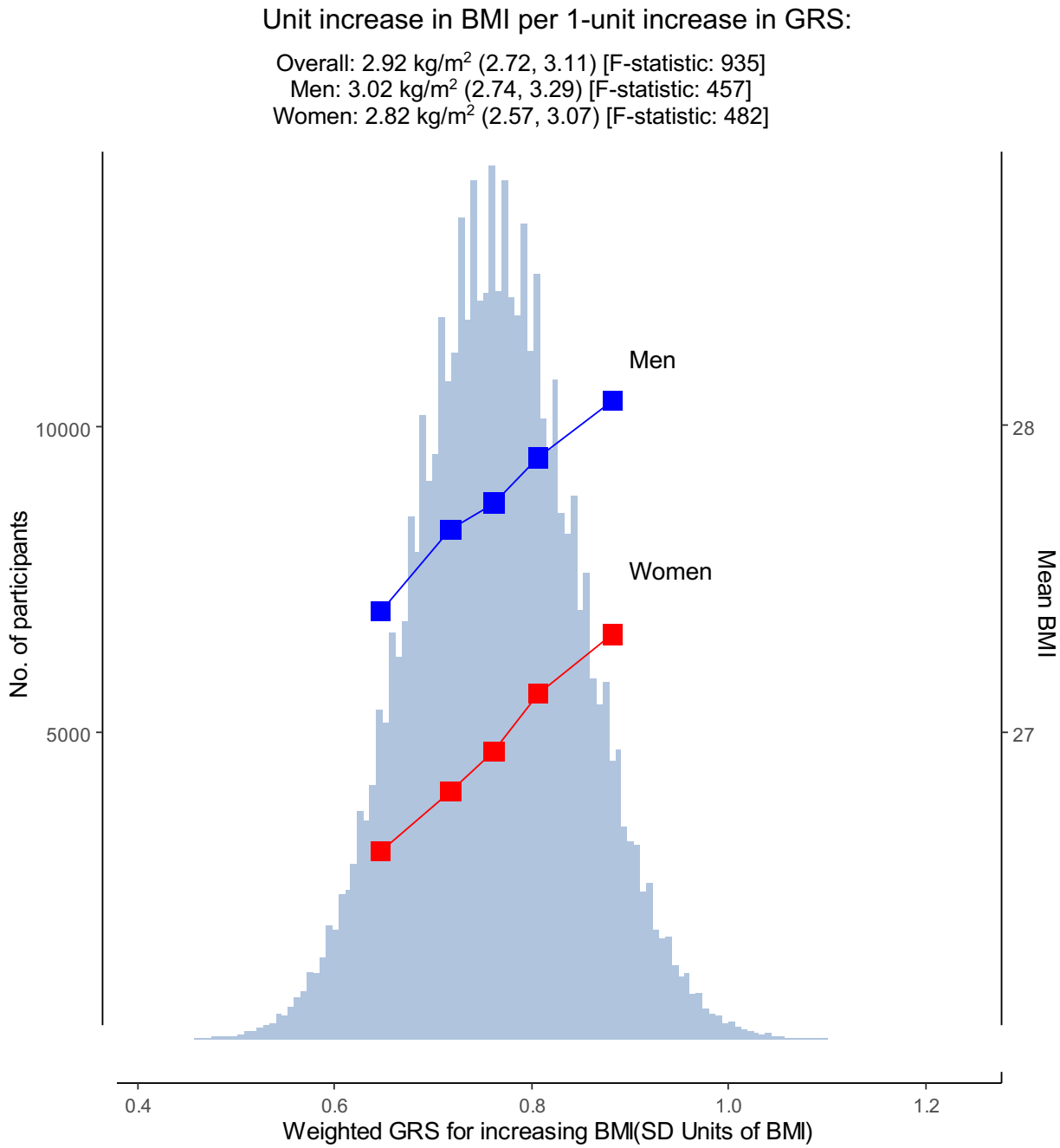

UKB = UK Biobank; SD= standard deviation; BMI = Body-mass index. Effect sizes represent the SD increase in BMI per additional BMI-increasing allele in the GIANT and UKB studies. The analyses were performed by region/study separately, and adjustments were made for sex and age at baseline. Overall estimates from GIANT were combined through inverse-variance weighted meta-analysis. Horizontal lines represent the 95% confidence intervals of the effect estimates in the GIANT study, while the vertical lines represent the corresponding confidence intervals in UKB.

**Figure 8.6** Comparison of effect sizes of WHRadjBMI-associated SNPs on WHR in GIANT and the UK Biobank



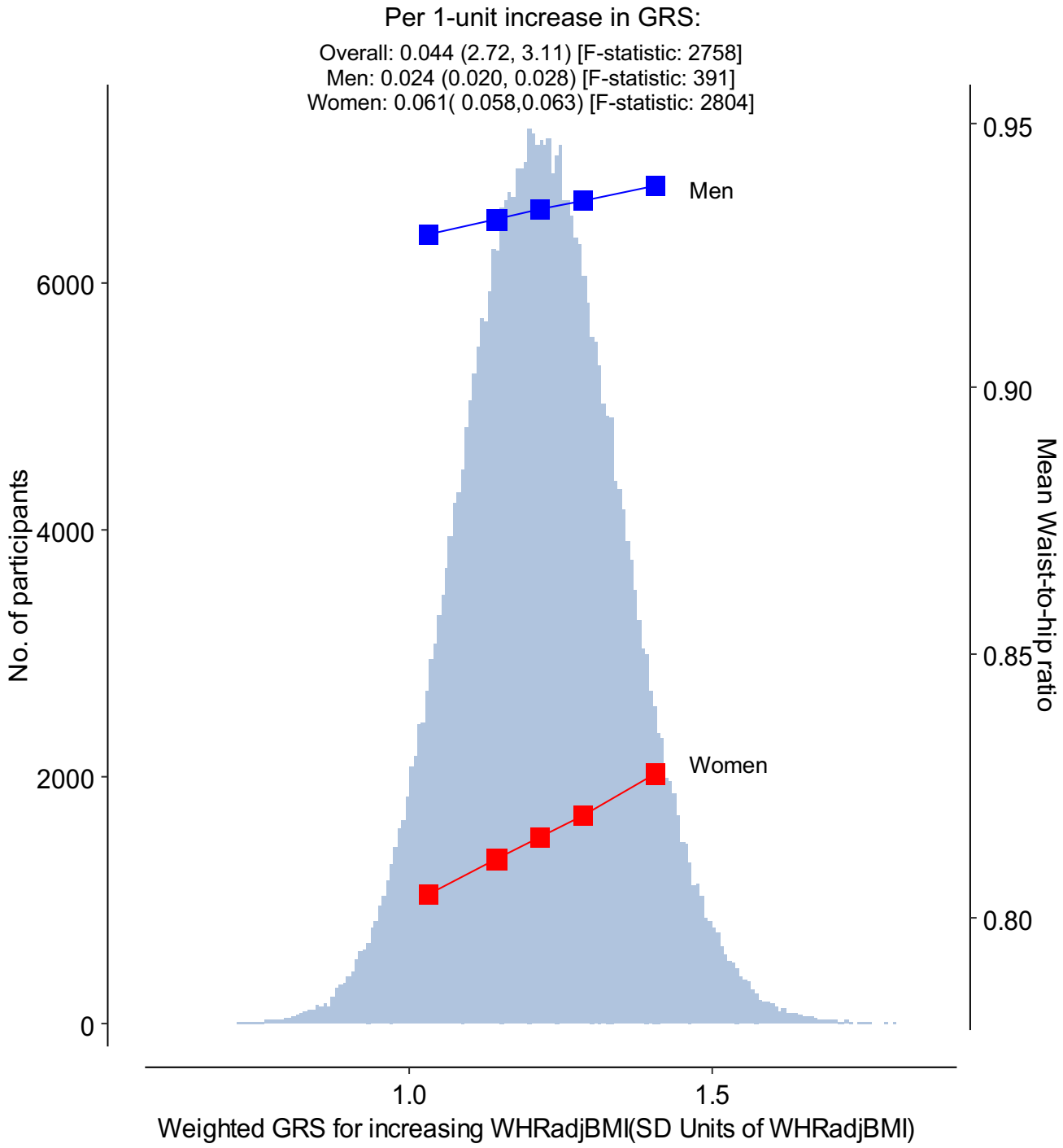

Effect sizes represent the standard deviation (SD) increase in WHR per additional WHRadjBMI-increasing allele in the GIANT and UK Biobank (UKB) studies. The analyses were performed by region/study separately, and adjustments were made for sex in GIANT analysis, and additionally for age at baseline (5-year groups) analyses of UK Biobank participants. A total of 68 WHRadjBMI-associated SNPs were included in the analyses as identified by Shungin et al. (2015). Overall estimates were combined through inverse-variance weighted meta-analysis. Horizontal lines represent the 95% confidence intervals (CIs) of the effect estimates in the GIANT study. Vertical lines represent the 95% confidence intervals (CIs) of the effect estimates in the UKB study. Top hit corresponds to rs72959041 (gene: RSPO 3) in both studies. Analyses were conducted in unrelated individuals of European ancestry in the UK Biobank with no missing or outlying adiposity variables and full genetic information at baseline survey (n=383 406).

**Figure 8.7** Weighted genetic risk score (GRS) for increasing BMI using 34 SNPs: distribution and mean BMI with increasing levels of GRS among men and women in the UK Biobank



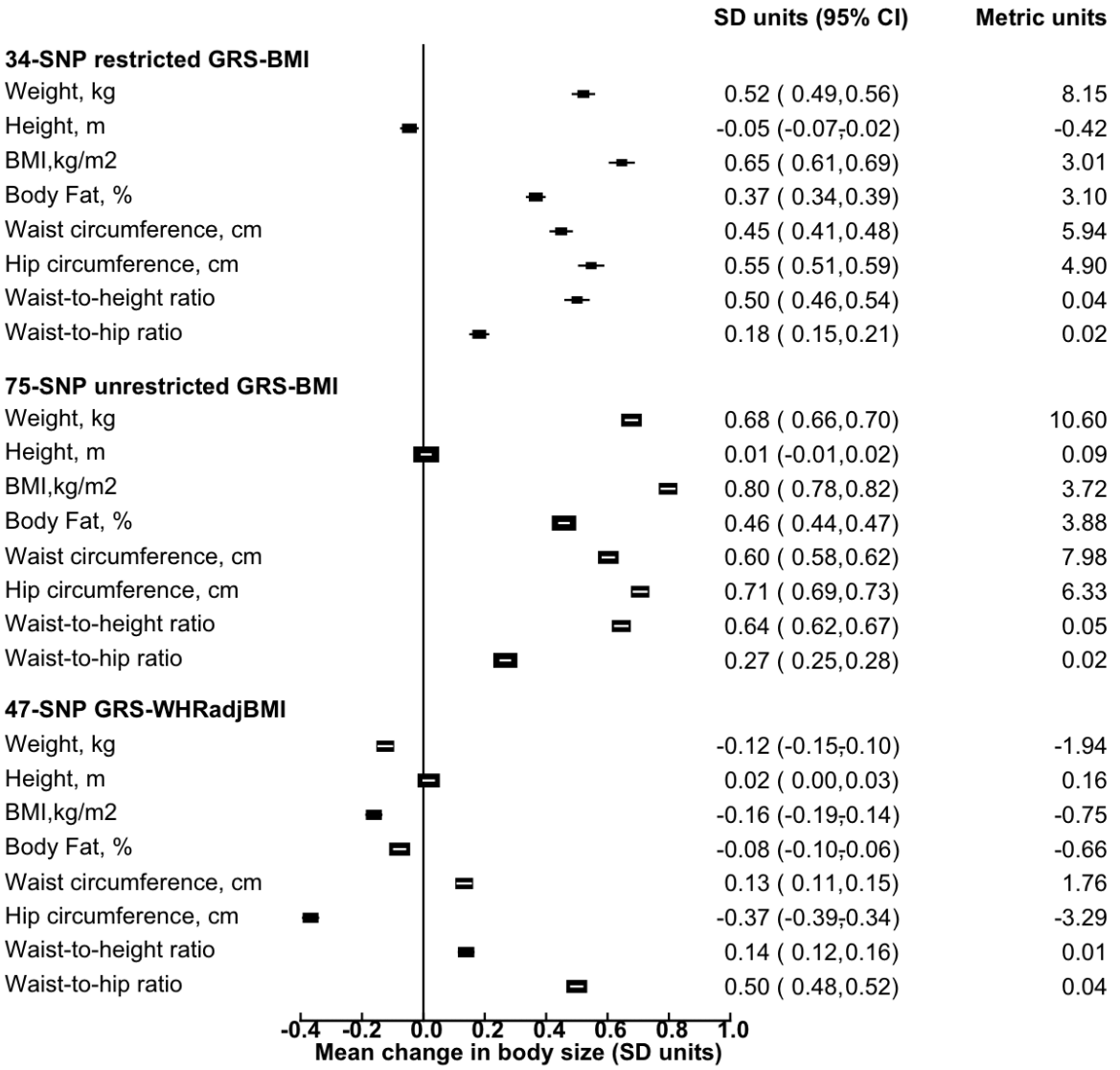

Mean (SD) values of BMI were directly standardised to age at baseline (5-year groups) and region (10 UK regions). The Genetic Risk Score (GRS) consisted of 34 SNPs which were associated with BMI to significance $p<5x10^{-8}$ in European populations and were not significantly associated with other adiposity traits, and showing no evidence of Linkage Disequilibrium ($R^2<0.2$) as reported by Locke et al., 2015. Values presented above the figure represent the unit increase in BMI per SD increasing GRS. Secondary Y-axis is standardised to represent ±0.5 standard deviations from the overall mean BMI in the UKB among men and women combined.

**Figure 8.8** Weighted genetic risk score (GRS) for increasing WHRadjBMI: distribution and mean WHR with increasing levels of GRS in the UK Biobank, by sex



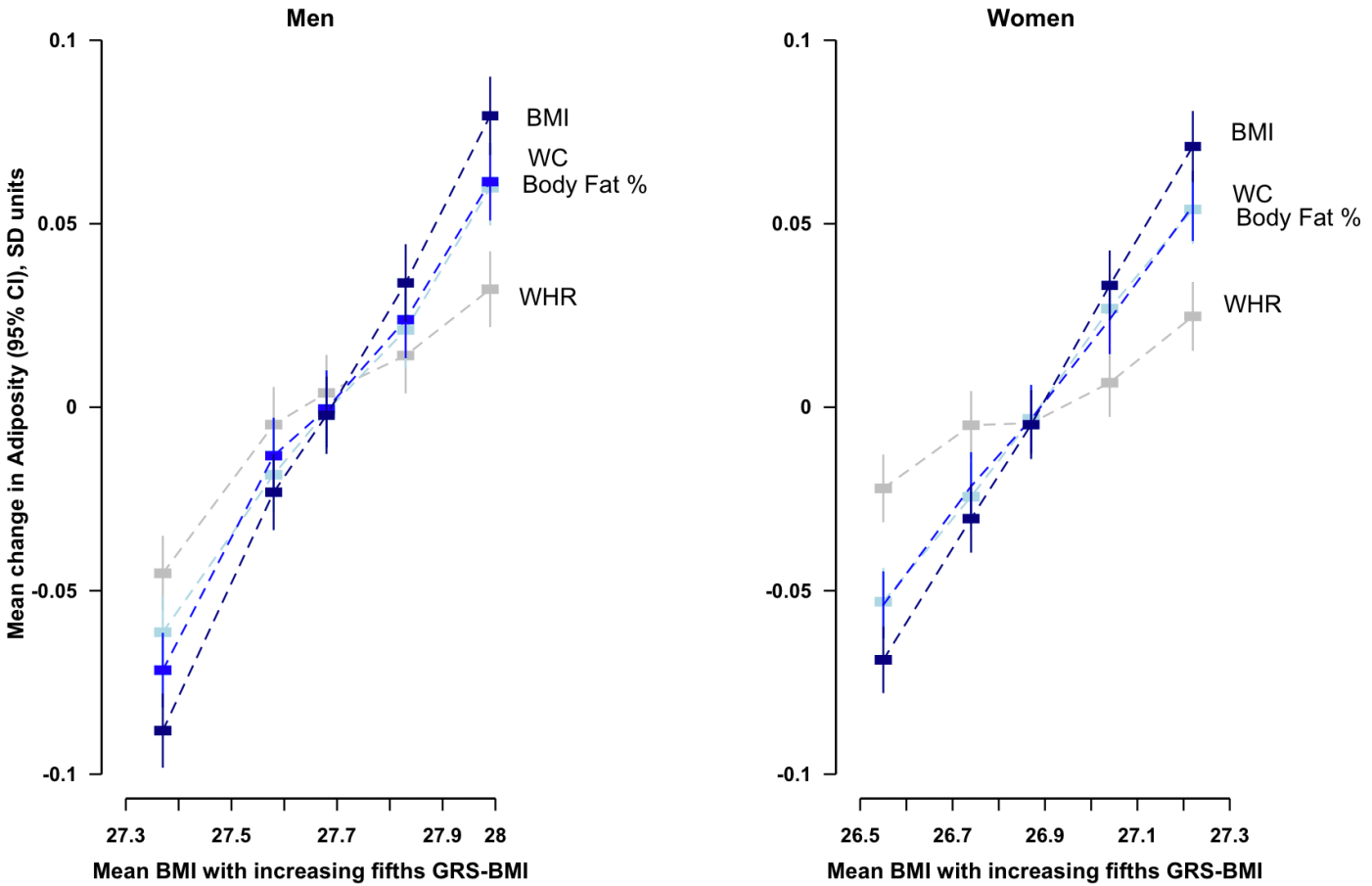

Mean (SD) values of WHR were directly standardised to age at baseline (5-year groups) and UK region (10 regions). The Genetic Risk Score (GRS) consisted of 47 SNPs associated with WHR to significance $p=5x10^{-8}$ in European populations, with no evidence of Linkage Disequilibrium ($r^2<0.2$) as reported by Shungin et al., 2015. Study population consists of those individuals who were not related to 3rd degree or closer, with no prior cardiovascular disease or outlying/missing adiposity measures at baseline.

**Figure 8.9** Mean increase in body size and adiposity per SD genetically elevated BMI and WHRadjBMI



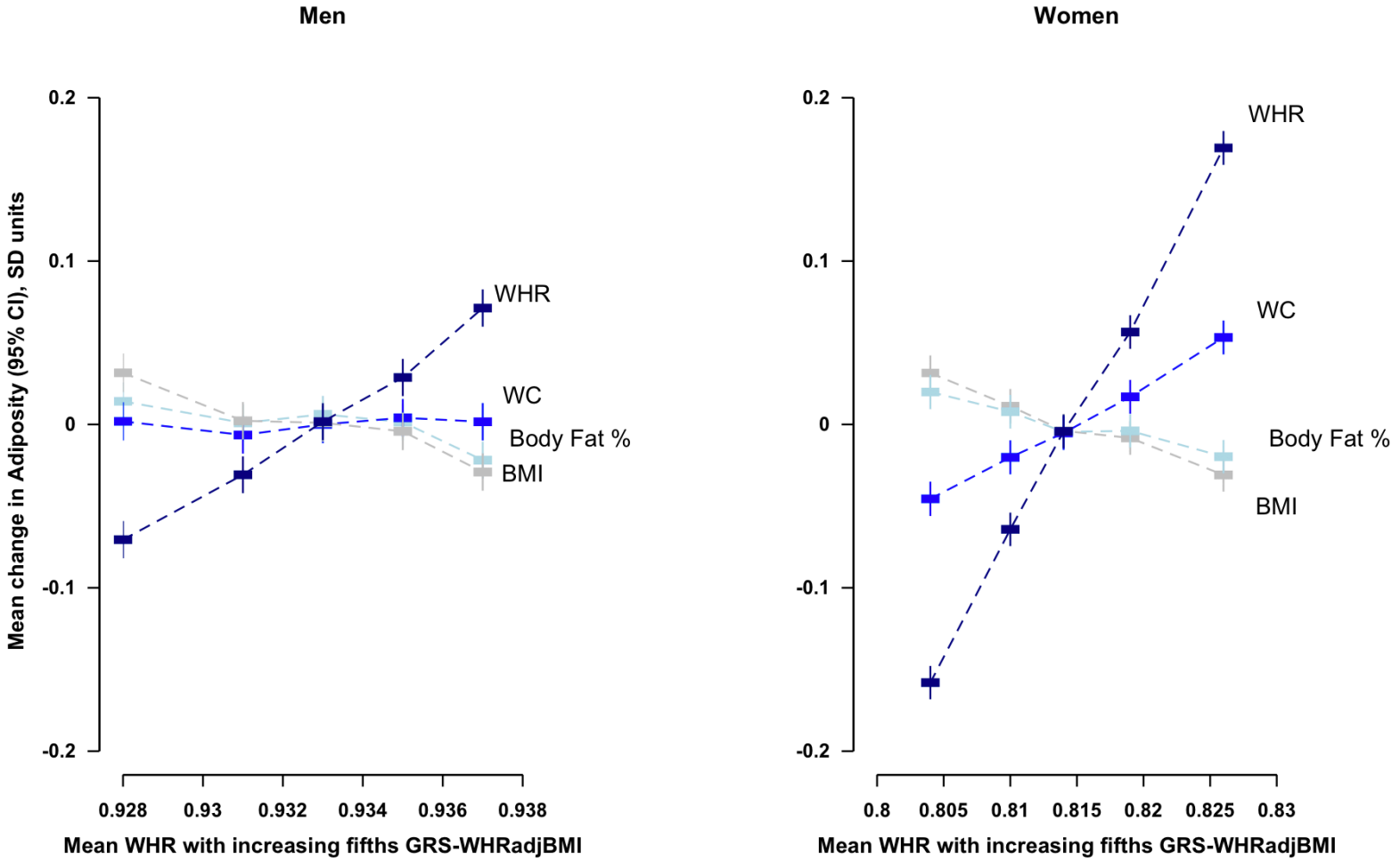

GRS= Genetic risk score; BMI= Body-mass index; WHRadjBMI = Waist-to-hip ration adjusted for BMI; SD= Standard deviation. The GRS for each adiposity trait include BMI GRS 1: 34 variants associated with only BMI to $p<5x10^{-8}$; BMI GRS 2: 75 variants additionally associated with WC, HC and WHR to $p<5x10^{-8}$; WHRadjBMI GRS: 47 variants associated with WHRadjBMI to $p<5x10^{-8}$ as reported previously in the GIANT consortia. The associations were adjusted for sex, UK region (10 regions) and age at baseline (5-year groups). Effect estimates represent the observed standard deviation increase in each adiposity/body size trait per unit increase in weighted genetic risk score (SD change in adiposity previously reported in discovery analyses). Analyses were restricted to unrelated individuals of European descent, with no self-reported cardiovascular disease or missing/outlying adiposity values at baseline.

**Figure 8.10** Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for BMI, by sex




Mean (SD) values were directly standardised to age at baseline (5-year groups) and region (10 UK regions). Axes are standardised to ±1 standard deviation (SD) from the sex-specific mean values for each adiposity trait. The genetic risk score (GRS) includes 34 SNPs identified in European population which were independently associated with BMI to significance threshold $p=5x10^{-8}$ with no evidence of linkage disequilibrium (LD) or pleiotropic effects to this significance threshold with other adiposity traits. Analysis was restricted to unrelated participants of European ancestry with complete genetic information and no cardiovascular disease at baseline.

**Figure 8.11** Mean adiposity at increasing fifths of weighted genetic risk score (GRS) for WHR adjusted for BMI (WHRadjBMI), by sex



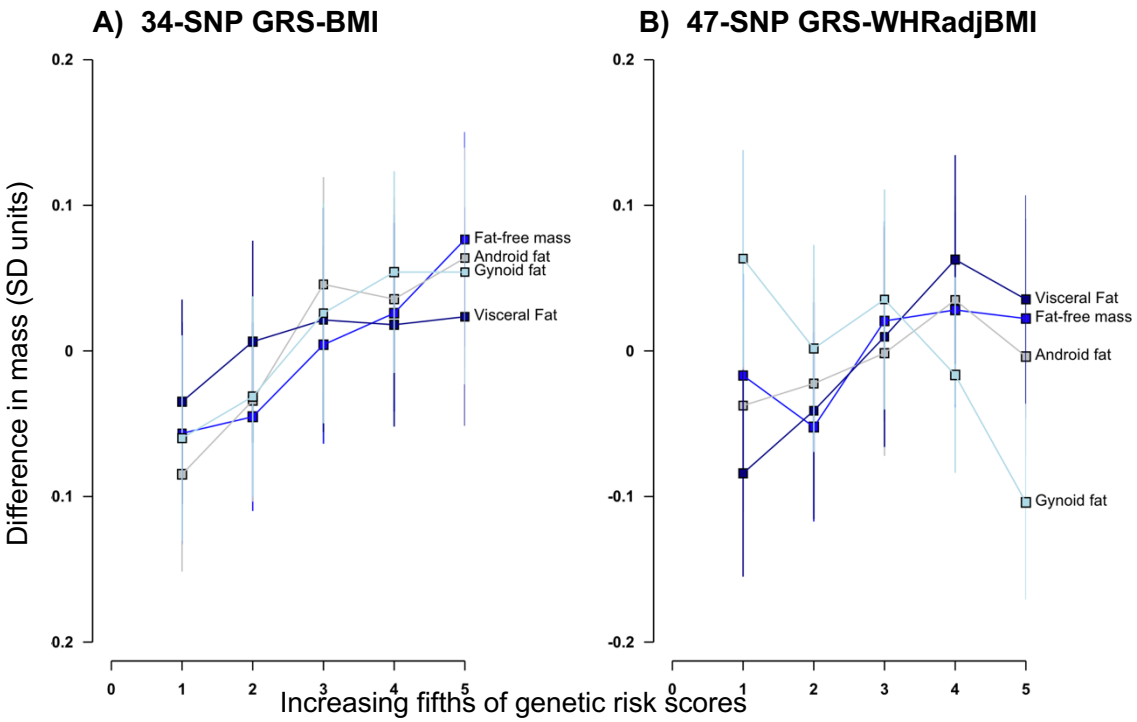

Mean (SD) values were directly standardised to age at baseline (5-year groups) and UK region (10 regions). Axes are standardised to ±0.2 standard deviation (SD) from the sex-specific mean values per adiposity trait at baseline. The genetic risk score (GRS) includes 47 SNPs identified in European populations which were not in linkage disequilibrium with other WHRadjBMI SNPs ($r^2$<0.2) as identified in Shungin et al., 2015. Analyses are restricted to unrelated individuals of European ancestry who did not report cardiovascular disease at recruitment and had no outlying/missing adiposity values.

**Table 8.4** Associations of weighted genetic risk scores for WHRadjBMI and BMI with established cardiovascular risk factors, socio-economic and lifestyle factors in the UK Biobank study

| | | Odds ratio/ Beta coefficient per 1-unit increasing GRS | | | | | |
|---|---|---|---|---|---|---|---|
| | | 34-SNP GRS-BMI | | 75-SNP GRS-BMI | | 47-SNP GRS-WHRadjBMI | |
| | N | Estimate (95% CI)* | P value | Estimate (95% CI)* | P value | Estimate (95% CI)* | P value |
| *Potential confounders* | | | | | | | |
| Townsend deprivation index | 358 274 | 0.13 (0.01, 0.25) | 0.030 | 0.12 (0.05, 0.18) | 0.0003 | -0.05 (-0.12, 0.02) | 0.16 |
| <High school education | 193401 vs. 161920 | 1.17 1.07, 1.27) | 0.0003 | 1.08 (1.03,1.12) | 0.0009 | 1.01 (0.96, 1.07) | 0.61 |
| Daily drinker | 76827 vs. 281875 | 0.83 (0.75 0.91) | 0.0002 | 0.73 (0.70, 0.77) | $9.34 \times 10^{-17}$ | 0.99 (0.95, 1.04) | 0.23 |
| Ever smoker | 159 894 vs. 198 808 | 1.16 (1.07, 1.27) | 0.0004 | 1.20 (1.15, 1.25) | $2.61 \times 10^{-31}$ | 0.99 (0.95, 1.04) | 0.78 |
| Physical activity, MET hrs/wk | 325 501 | 1.95 (-0.18, 4.1) | 0.07 | 0.27 (-0.83, 1.37) | 0.63 | 1.07 (-0.20, 2.34) | 0.10 |
| *Potential mediators* | | | | | | | |
| Systolic blood pressure, mmHg | 358 449 | -0.15(-0.86, 0.56) | 0.68 | 0.95 (0.58, 1.32) | $4.05 \times 10^{-7}$ | 0.65 (0.23, 1.07) | 0.003 |
| Diastolic blood pressure, mmHg | 358 449 | 0.32 (-0.08,0.73) | 0.12 | 0.88 (0.67, 1.09) | $1.48 \times 10^{-16}$ | 0.64 (0.39, 0.88) | $2.49 \times 10^{-7}$ |
| LDL cholesterol, mg/L | 341 372 | -0.021 (-0.06, 0.02) | 0.25 | -0.02 (-0.03, 0.00) | 0.09 | 0.11 (0.09, 0.13) | $7.65 \times 10^{-26}$ |
| HDL cholesterol, mg/L | 312 945 | -0.08 (-0.1, -0.07) | $7.45 \times 10^{-26}$ | -0.08 (-0.09, -0.07) | $1.15 \times 10^{-92}$ | -0.10 (-0.11, -0.09) | $2.45 \times 10^{-102}$ |
| Triglycerides, mmol/L | 341 732 | 0.11 (0.07, 0.15) | $5.73 \times 10^{-7}$ | 0.11 (0.09, 0.13) | $4.77 \times 10^{-24}$ | 0.33 (0.31, 0.35) | $3.39 \times 10^{-149}$ |
| HbA1c, mmol/mol | 341 732 | 0.71 (0.46, 0.96) | $2.76 \times 10^{-8}$ | 0.92 (0.79, 1.05) | $1.07 \times 10^{-43}$ | 0.45 (0.30, 0.60) | $4.91 \times 10^{-9}$ |
| Log(CRP), mg/L | 341 283 | 0.20 (0.15, 0.24) | $1.04 \times 10^{-18}$ | 0.20 (0.18, 0.22) | $4.43 \times 10^{-65}$ | -0.03 (-0.05, 0.00) | 0.04 |
| Albumin, g/L | 313 078 | -0.37 (-0.48,-0.26) | 0.006 | -0.41 (-0.47, -0.35) | $4.16 \times 10^{-43}$ | 0.26 (0.19, 0.32) | $5.34 \times 10^{-14}$ |
| Alkaline Phosphatase, U/L | 342 005 | 1.50 (0.42, 2.56) | $6.32 \times 10^{-3}$ | 1.21 (0.66, 1.77) | $1.91 \times 10^{-5}$ | -0.13 (-0.77, 0.50) | 0.69 |
| Log(GGT), U/L | 341 805 | -0.002 (-0.03, 0.2) | 0.88 | 0.01 (-0.00, 0.03) | 0.06 | 0.09 (0.08, 0.11) | $8.43 \times 10^{-35}$ |
| eGFR, mL/min/1.73m$^2$ | 341 563 | -1.00 (-1.53,-0.54) | $4.28 \times 10^{-5}$ | -1.03 (-1.28, -0.77) | $4.26 \times 10^{-15}$ | 0.71 (0.42, 1.00) | 0.0001 |

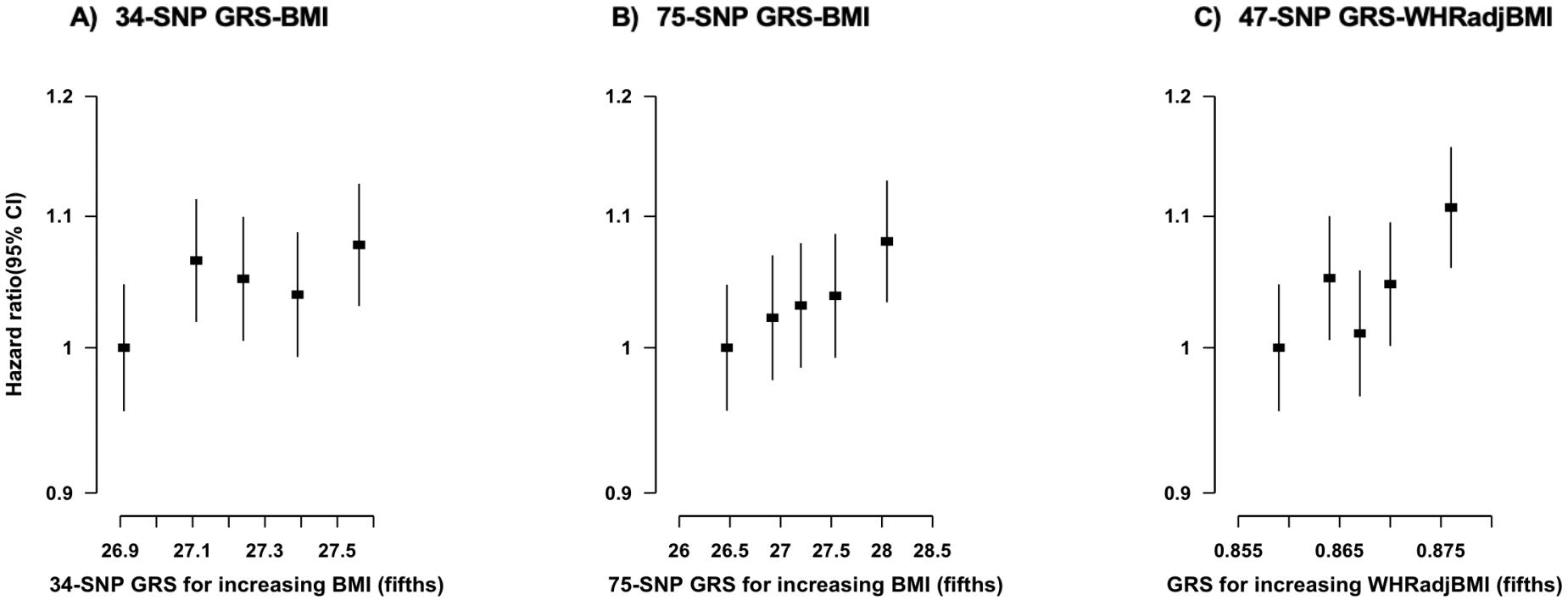
Genetic study population included unrelated individuals of European descent, without prior cardiovascular disease or missing/outlying adiposity values at baseline. The genetic risk scores (GRS) for each adiposity trait include 34 SNPs for genetically elevated BMI and 47 SNPs for WHRadjBMI, weighted by previously reported effect sizes (Locke et al., 2015 and Shungin et al., 2015). *Odds ratio for binary traits and beta coefficient for continuous traits (in native units) expressed per 1-unit increase in GRS for each adiposity phenotype. Causal estimates were adjusted for sex, age, first ten genomic principal components, genotyping array, batch number and age$^2$.

**Figure 8.12** Weighted genetic risk scores for BMI and WHRadjBMI with mutually exclusive DXA-derived compartments of body fat and fat-free mass in the UK Biobank



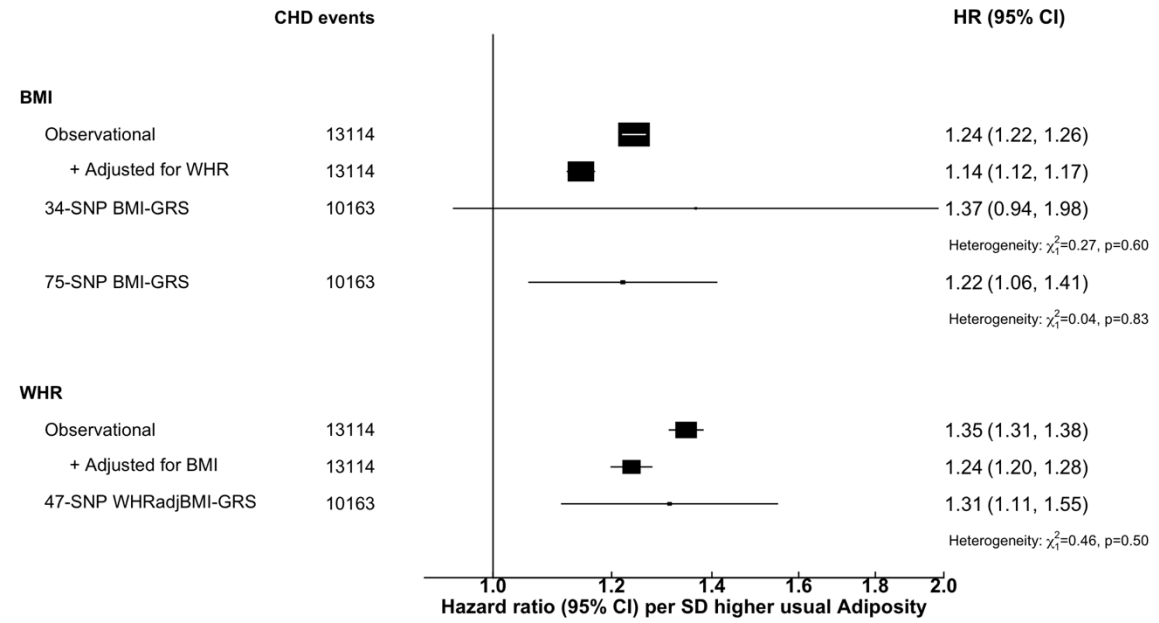

Mean (SD) values were directly standardised to age at baseline and UK region. Y-Axes were standardised to ±0.2 SD from the sex-specific mean values per DXA-derived body composition variable. The genetic risk scores (GRS) for each adiposity trait include: A) 34 SNPs for genetically elevated BMI; and B) 47 SNPs for WHRadjBMI, weighted by previously reported effect sizes (Locke et al., 2015 and Shungin et al., 2015). Analyses included 4 209 unrelated UK Biobank participants of European ancestry with complete genetic and imaging data.

**Figure 8.13** Association of increasing fifths of genetic risk scores for BMI and WHRadjBMI with coronary heart disease risk in the UK Biobank




SNP= single nucleotide polymorphism; GRS= Genetic risk score; BMI= body-mass index; WHR= Waist-to-hip ratio; WHRadjBMI = Waist-to-hip ratio adjusted for body mass index; 34-SNP GRS-BMI= Genetic risk score for elevated BMI comprising 34 SNPs specifically associated with BMI to genome-wide significance in GIANT; 75-SNP GRS-BMI= GRS for elevated BMI comprising 75 SNPs associated with BMI to genome-wide significance in GIANT; 47-SNP GRS-WHR= GRS for elevated WHR adjusted for BMI comprising 47 SNPs associated with WHRadjBMI in GIANT. GRSs for each adiposity trait include SNPs for genetically elevated BMI and WHRadjBMI weighted by previously reported effect sizes (Locke et al., 2015 and Shungin et al., 2015). Analyses were restricted to 358 707 unrelated participants of European ancestry, with complete genetic information, and without outlying/ missing adiposity variables or a history of cardiovascular disease at baseline. Associations were adjusted for the first ten genomic principal components, genotyping array, batch number, age-at-risk and age$^2$.

**Figure 8.14** Comparison of observational and genetic associations of BMI and WHRadjBMI with coronary heart disease




Observational analyses were restricted to 455 158 participants without outlying/ missing adiposity variables or a history of cardiovascular disease at baseline. Genetic analyses were restricted to 358 707 unrelated participants of European ancestry, with complete genetic information, and without outlying/ missing adiposity variables or a history of cardiovascular disease at baseline. Observational estimates were taken from **Chapter 7**. Genetic risk scores (GRS) were composed of the following single nucleotide polymorphisms (SNPs) discovered in European populations by the GIANT consortia: 34-SNP GRS-BMI = 34 SNPs associated with BMI, and not WHR, hip or waist circumference to genome-wide significance; 75-SNP GRS-BMI = 75 SNPs associated with BMI and other adiposity traits to genome-wide significance; GRS-WHRadjBMI = 47 SNPs associated with WHRadjBMI to genome-wide significance; All SNPs were weighted by the effect size as estimated in the GIANT consortia. Genetic analyses were stratified by sex and UK region, and were further adjusted for age-at-risk, age$^2$, the first ten principle components, batch number and array type. Overall estimates were reported for 1 SD usual increase in observed or genetically elevated adiposity, respectively. Heterogeneity was assessed between observational and genetic associations using Cochrane's Q test.

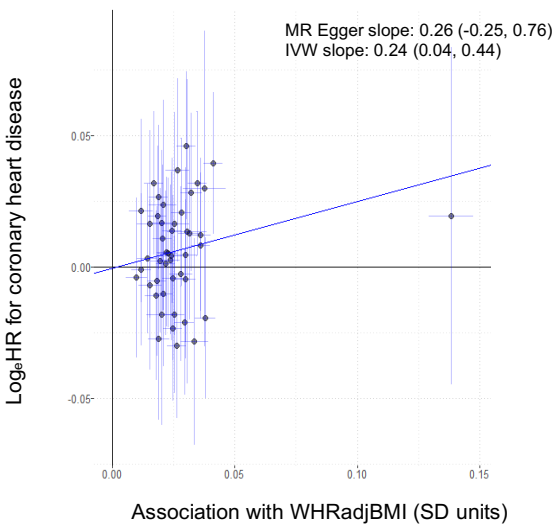
**Table 8.5** Regression coefficients for associations of CHD with genetic variants included in genetic risk scores for BMI and WHRadjBMI in the UK Biobank using MR Egger, weighted median and inverse-variance weighted methods

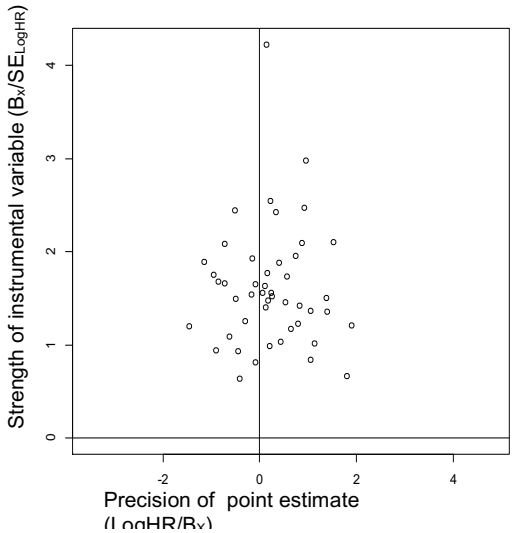
| Mendelian randomisation method | Risk of Coronary heart disease (n= 10 163 events) | |
|---|---|---|
| | Hazard Ratio (95% CI)* | P value |
| **47 WHRadjBMI-associated variants** | | |
| Inverse-variance weighted | 1.27 (1.04, 1.55) | 0.020 |
| Simple Median | 1.24 (0.93, 1.64) | 0.138 |
| Weighted median | 1.21 (0.91, 1.60) | 0.186 |
| MR-Egger regression | 1.29 (0.78, 2.14) | 0.326 |
| Intercept | 1.00 (0.99, 1.01) | 0.945 |
| **34 BMI-specific variants** | | |
| Inverse-variance weighted | 1.35 (0.98, 1.84) | 0.062 |
| Simple Median | 1.80 (1.05, 3.06) | 0.032 |
| Weighted median | 0.99 (0.62, 1.60) | 0.980 |
| MR-Egger regression | 0.63 (0.34, 1.30) | 0.209 |
| Intercept | 1.02 (1.00, 1.03) | 0.024 |
| **75 BMI-nonspecific variants** | | |
| Inverse-variance weighted | 1.18 (0.99, 1.36) | 0.085 |
| Simple Median | 1.29 (1.04,1.53) | 0.043 |
| Weighted median | 1.12 (0.90, 1.35) | 0.310 |
| MR-Egger regression | 0.96 (0.58, 1.34) | 0.844 |
| Intercept | 1.01 (1.00, 1.02) | 0.237 |

*Hazard Ratio (95% CI) expressed as the risk of coronary heart disease per 1-unit higher genetic risk score

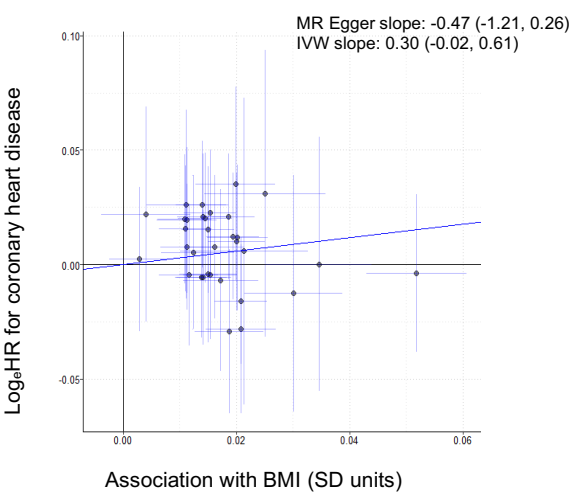
**Figure 8.15** MR Egger regression plots and funnel diagrams for genetic variants included in genetic risk scores for BMI and WHRadjBMI

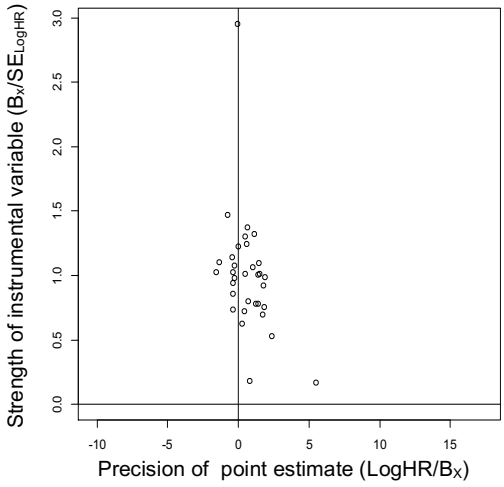
### B) 47-SNP WHRadjBMI-GRS



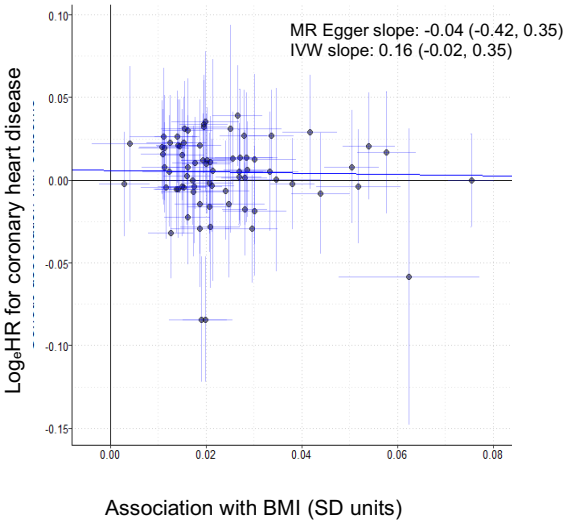



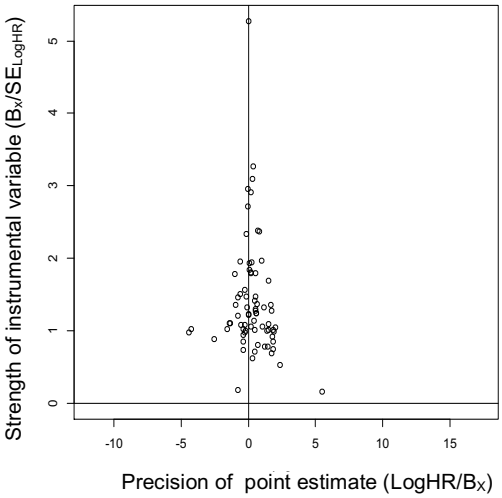

### A) 34-SNP BMI-GRS




### C) 75-SNP BMI-GRS



# CHAPTER 9: Overall conclusions

## Chapter summary

This thesis describes the associations between adiposity and CHD in greater detail than has previously been possible. Using data from over 450 000 UK adults without cardiovascular disease, this thesis investigated the following broad aims in relation to the association of CHD with BMI, WC, Body fat %, Trunk fat %, WHTR and WHR *: i)* to describe the baseline correlates of adiposity measures*; ii)* to summarise the long-term within-person variability of adiposity measures; *iii)* to investigate the relevance of body fat distribution to adiposity-related hypertension; *iv)* to investigate the observational associations between usual levels of each adiposity measure and CHD risk; *v)* to describe the genetic associations of BMI and WHR with CHD risk and likely intermediate factors; and *vi)* to investigate the extent to which the observational associations with adiposity are explained by both known and emerging intermediate factors. This Chapter summarises the main findings of the thesis, and interprets the results in the context of our current knowledge of the biological mechanisms underlying adiposity-related CHD risk. It also describes the major strengths and potential limitations of the present study, as well as the implications of the current findings for population health and future research.

## 9.1 Main findings

### *9.1.1 Cross-sectional correlates of adiposity measures at baseline*

The six selected adiposity measures were correlated with each other and with demographic, lifestyle and cardiometabolic traits at baseline (**Chapter 4**). However, in comparison to other adiposity measures, WHR was only moderately correlated with BMI, and in general displayed weaker associations with other traits at baseline (in part due to its greater within-person variability). The distribution of adiposity also varied slightly across subgroups of the study population. On average, adiposity levels were higher in men (except body fat % and trunk fat %), older age groups, non-White participants, participants with low levels of education, participants with higher deprivation scores, and in physically inactive participants. Although associations with each adiposity measure were directionally concordant for most traits, some important differences were observed for WHR. In particular, whilst higher adiposity values were generally observed in non-smokers and in non-drinkers, mean WHR was higher in current smokers compared with non-smokers, and WHR did not appear associated with alcohol consumption. These findings reinforce the importance of adjusting for confounding factors in observational associations with adiposity measures. Furthermore, each selected adiposity measure at baseline displayed similar associations with blood-based cardiometabolic traits, reinforcing the contributing roles of blood pressure, cholesterol, insulin resistance and inflammation in mediating adiposity-related CHD risk, and providing the first large-scale evidence for a potential role of emerging intermediate factors such as liver and kidney function.

### *9.1.2 Within-person variability of adiposity measures*

The findings in **Chapter 5** summarise the within-person variability of the six selected measures of adiposity in 18 737 resurveyed UK Biobank participants using three methods of quantifying the RDR: Rosner's, self-correlation and MacMahon-Peto, each of which relies on slightly different assumptions. All six adiposity traits were associated with some degree of within-person variability, but it was more extreme for WHR (RDR 0.66) and WC (RDR 0.82) compared with BMI (RDR 0.92). The three methods provided similar estimates of RDR across adiposity measures. RDRs did not vary substantially by baseline characteristics such as age, sex or demographic factors. In summary, RDB should be considered when investigating and interpreting prospective epidemiological associations with adiposity, particularly for WHR, which will be underestimated if left uncorrected for RDB. Although the choice of parametric or non-parametric methods did not materially alter the estimated RDRs, given the additional

assumptions required by Rosner's method, and the limited data used by the MacMahon-Peto method, the self-correlation method was used to correct for RDB in the current thesis.

### *9.1.3 Adiposity measures, body fat distribution and blood pressure*

**Chapter 6** combined individual participant imaging data from the UK Biobank and the Oxford Biobank to relate both usual adiposity levels (BMI, WC and WHR) and DXA-derived measures of regional body fat (subcutaneous android fat, visceral android fat, subcutaneous gynoid fat, and other fat mass) to SBP in 10 260 participants. DXA-derived measures of visceral android fat and fat-free mass were positively related to SBP (with 1 SD differences in mass associated, respectively, with about 3 mmHg and 2 mmHg higher SBP), but there was no evidence of an association with SBP of either subcutaneous android or gynoid fat. Mean differences in SBP (men/women, mmHg) per SD higher BMI (2.9/3.2 mmHg) were slightly greater than per SD higher WC (2.7/3.1 mmHg) or WHR (2.5/2.4 mmHg). These associations were unchanged following adjustment for fat-free mass, but adjustment for visceral android fat completely eliminated associations with WC and WHR, and more than halved the association with BMI. These findings suggest that visceral fat is the primary etiological component of central and general adiposity underlying the development of adiposity-related hypertension.

### *9.1.4 Adiposity measures and CHD risk*

Each adiposity measure displayed a strong, positive and approximately log-linear association with CHD risk in this large contemporary UK population (**Chapter 7**). There were no observed 'threshold' points at which higher levels of adiposity were no longer associated with higher CHD risk (within the adiposity ranges studied). Of the six selected adiposity measures, usual WHR was most strongly associated with CHD risk, with the strength of the association more than one third greater than that seen for BMI. The relationship of CHD risk with central adiposity and body fat distribution was particularly strong in women, among whom the strength of association for WHR was more than 50% greater than for BMI. The increased CHD risk associated with each adiposity measure was substantially accounted for by baseline insulin resistance, cholesterol levels and blood pressure; additional factors related to liver function, kidney function and inflammatory markers explaining the remainder of the excess risk associated with BMI, body fat %, trunk fat % and WC. By contrast, WHR and WHTR remained independently associated with CHD risk after adjustment for these factors.

*9.1.5 Genetically elevated adiposity and CHD risk*

**Chapter 8** used MR techniques to construct GRSs to estimate the causal effect of BMI and BMI-adjusted WHR (i.e., WHRadjBMI) on both cardiometabolic traits and CHD risk. These analyses included 358 707 unrelated participants with available genetic information and without baseline cardiovascular disease (or missing or outlying adiposity variables). Consistent with the observational analyses shown in **Chapter 7**, genetically elevated WHRadjBMI was associated with a greater increased risk of CHD than genetically elevated BMI. Both GRSs were independently associated with cardiometabolic traits: similar strengths of association seen for insulin resistance and blood pressure; a stronger association seen with dyslipidaemia for WHRadjBMI than for BMI; and a stronger association with inflammation and kidney function seen for BMI than for WHRadjBMI. These results provide further evidence to support the distinct effects of body fat distribution versus general adiposity on cardiometabolic perturbations and subsequent CHD risk.

## 9.2. Biological mechanisms

The results presented in **Chapters 4, 6, 7 & 8** of the current thesis provide further evidence for the adverse effects of raised adiposity on various cardiometabolic risk factors and CHD risk. Adiposity is an established risk factor for CHD.[12] The postulated biological mechanisms through which excess adiposity contributes to CHD risk have been discussed in depth previously (**Chapters 1, 4 & 7**). In brief, although the relationship between adiposity and CHD risk is complex and incompletely understood, the large majority is thought to be driven by elevated blood pressure, insulin resistance and dyslipidaemia.[24, 116, 293] The results from the current study support this hypothesis, as evidenced by the strong associations of adiposity measures with baseline blood pressure, markers of insulin resistance and cholesterol levels, as well as the observed attenuation of adiposity-related CHD risk after adjusting for these factors in prospective analysis (together explaining over 90% of the BMI-related CHD risk). However, compared with BMI, the observed adiposity-related CHD risk was stronger for central adiposity measures and particularly strong for WHR. The more profound effects of central adiposity on CHD risk are thought to be the result of the close proximity of adipose tissue to the liver and other internal organs which could exacerbate the cardiometabolic consequences of adiposity, including insulin resistance and dyslipidaemia.[37-39] However, the stronger association observed between WHR and CHD compared with WC, as well as its apparent distinct associations with baseline cardiometabolic traits and the excess WHR-related CHD risk beyond the selected cardiometabolic traits observed in the current study, suggest that central body fat distribution acts through distinct mechanisms to enhance CHD risk, independently of general adiposity. As discussed previously (**Chapter 1**), the exact

mechanisms underlying central body fat distribution and enhanced CHD risk remains unclear, but it could involve a protective effect of gynoid fat.[73, 74] Further research is required using detailed large-scale population studies to enhance our understanding of the underlying mechanisms of WHR-related CHD risk (*Section 9.5.3*).

### 9.3 Strengths and limitations of the current study

The current study represents the largest single study to investigate the observational and genetic associations of six commonly used adiposity measures with CHD risk. In addition to the large sample size, the standardised exposure measurements, the availability of repeat measurements, biomarkers, imaging and genetic data has allowed for the assessment of adiposity-related CHD risk in further detail, and with greater precision than has been possible previously. The most robust evidence for adiposity-related CHD risk to date comes from large meta-analyses of prospective studies,[16, 24, 134, 157] the majority of which have described strong, positive, and approximately log-linear associations of the established measures of adiposity with CHD previously. However, these previous studies mostly include only fatal CHD events, or only study the effects of BMI, and most were conducted several decades ago. The UK Biobank data in the current study has allowed an assessment of whether the shape and strength of these associations in the current UK population are consistent with those found in previous meta-analyses of prospective studies; whether alternative adiposity measures are more or less predictive of CHD than the established measures (particularly BIA-based measures, which have not been assessed previously in large-scale studies); whether associations of CHD risk with each adiposity measure differs importantly by age, sex, ethnicity, event type (fatal/non-fatal) or by other major subgroups of the UK population; whether differences in adiposity-related cardiometabolic perturbations could be attributed to body fat distribution; and, whether genetic associations are directionally concordant with observational associations in the same study population.

However, despite these strengths, it is important to acknowledge a number of potential limitations when interpreting the results presented in the current study. First, the UK Biobank is comprised of a contemporary middle-aged population residing in the UK with good access to healthcare services. Whilst this is particularly advantageous when conducting a long-term observational study by allowing accurate passive follow-up, it also carries a number of limitations. The lack of ethnic diversity in the UK Biobank limits the generalisability of the study findings to other non-White ethnic populations. Also, the case fatality of CHD in contemporary populations is very low, and therefore further follow-up is required to achieve accurate statistical power for the analysis of fatal CHD events, particularly among women. Furthermore,

in contemporary Western populations, such as the UK, which have been exposed to so-called 'obesogenic' environments for decades, on average, the distribution of BMI is shifted towards higher BMI values. Therefore, the current study lacks statistical power to investigate the risk of disease at low or very low levels of adiposity.

Additionally, although it is likely that the use of HES records reduced the number of participants included in the analysis with CVD who did not self-report CVD at baseline survey (particularly as participants with a diagnosis of angina at baseline were excluded), it is still possible that participants with sub-clinical CVD were included in the analysis and therefore may have contributed to reverse causality. Additionally, the strong associations of adiposity with lifestyle and demographic factors observed in the current thesis (**Chapter 4**), reinforce the complex social and environmental determinants of adiposity. Therefore, despite the robust nature of the data, residual confounding may still be present. However, a major strength of the current study was the ability to assess genetic associations in the same study population, which appeared directionally concordant with the observational estimates and are less likely to be affected by some of the major biases of convention observational studies, such as reverse causality and confounding.

## 9.4 Implications for population health

### *9.4.1 Enhanced CHD risk prediction scores*

The results from the current study suggest that central body fat distribution measures such as WC and WHR demonstrated stronger associations with CHD risk than BMI. However, whether WC or WHR could provide additional information beyond BMI for improved CHD risk prediction at the population level remains unclear. Risk prediction equations among people without previous evidence of CVD are an important disease prevention tool, as they help to identify individuals at highest absolute CHD risk who would therefore benefit most from earlier therapy with interventions which are proven effective for primary prevention[329, 330] such as statins,[331, 332] blood pressure lowering medication,[333] and lifestyle interventions.[334 335] Indeed, results from the present study suggested that the large majority of adiposity-related CHD risk can be explained by only a handful of intermediate factors, and therefore early intervention could help to prevent most primary CHD events. Many risk tools have been developed, most of which estimate an individual's 10-year absolute risk of CHD or CVD events from a set of measures which vary in complexity and applicability to general practice settings.[336-340] Of the current risk scores, only one (QRISK3)[339] includes a measure of adiposity. Despite several population studies describing independent effects of WHR and WC on CVD outcomes beyond BMI,[124, 127, 277] there is a lack of evidence for the contribution of these measures to CVD risk tools.

Pragmatic risk models which utilise simple measures such as body size instead of, say, lipid values, may be of greater value in many and low and middle-income countries as they do not rely on costly and time-consuming laboratory measurements. The need to develop simple CVD risk prediction tools is becoming increasingly important given the rising incidence of CVD in developing countries relative to developed countries.[136]

*9.4.2 Obesity prevention will require multi-sectorial population-level interventions*

The current study provides further evidence to suggest that there is no point at which lower levels of adiposity are not associated with lower CHD risk (at least down to the levels commonly seen in this UK population). Thus, public health interventions that aim to cause even a small downwards shift in mean adiposity levels at the population level could lead to substantial reductions in CHD.[276] No single country has so far successfully reduced the obesity prevalence or curbed the epidemic in any way however.[27]

Recent data suggests that obesity prevalence (as reflected by BMI >30 kg/m$^2$) will exceed 50% in the UK by 2030, impacting further on public health and costing an excess of £1.9 billion in additional annual healthcare costs.[341, 342] Therefore, obesity prevention strategies must be implemented. The current approach used by the UK government is to identify high-risk individuals (i.e. obese patients), and to treat obesity and its metabolic consequences with individual-based therapy; less than 5% of the NHS budget is spent on prevention.[343] Given the consistent association with CHD risk seen at all levels of adiposity, the results presented in the current study suggest that further benefits could be realised by identifying the distal and underlying causes of obesity and altering the whole distribution of risk at the population level.[276] Importantly, the current study demonstrated strong and robust associations between BMI and multiple indicators of social class. This provides further evidence to suggest that obesity prevention might be more effective if individual-based strategies were supplemented with population-level strategies targeted at the wider social determinants of health, such as living conditions, education, deprivation, social isolation and poor quality of the environment, as well as legal and fiscal interventions. Indeed there is mounting evidence that changes in individual behaviour can be achieved through a combination of societal, organisational, and individual efforts.[344, 345] Furthermore, by narrowing inequities, these interventions are likely to lead to a number of improvements in public health through downstream benefits on multiple risk factors for chronic disease, not just obesity or CHD.

*9.4.3 Improved estimates of the global burden of obesity*

Defining the burden of a disease is an important first step in resource allocation for public and global health. Obesity and its determinants are risk factors for three of the four leading causes of non-communicable diseases worldwide, and the global costs are thought to exceed $2 trillion annually in direct health-care costs and lost economic productivity.[346] However, current estimates are derived from meta-analyses of observational studies investigating the effect of BMI on disease risk, and no similar estimate has been used to quantify the global burden of body fat distribution. Results presented in the current thesis suggest that abdominal adiposity, independent of BMI, could be a major driver of the global CHD burden. Therefore, current estimates could be underestimating the global obesity-related disease burden, particularly for CHD. The present thesis also reinforces the importance of correcting for RDB, which, if unaccounted for can lead to severe underestimations of population attributable fractions, and the likely benefits of interventions, particularly for ratio-based measures such as WHR where its components are likely to vary over time.[247, 250, 251]

## 9.5 Implications for future research

*9.5.1 The need for diverse population studies*

Whilst the results of the current study highlight the importance of continued obesity research for the benefit of population health, one must be cognisant of the fact that the UK Biobank is a contemporary UK-based population study comprised of mostly White participants (94%). As discussed earlier (**Chapters 7 & 8**), although there is a lack of observational and genetic evidence for adiposity-related CHD, it is thought that non-White participants are particularly pre-disposed to the effects of adiposity, and possibly through excess accumulation of VAT.[347] Furthermore, the greatest absolute burden of CVD is occurring in developing regions where populations are predominantly non-White.[328] Despite this need, few large-scale studies have been established in predominantly non-White populations,[129-131, 133, 348-351] and of these, less than a handful have similarly detailed exposure and outcome measurements compared to the UK Biobank. A number of studies identified in Asian participants have produced similar estimates to the current study for CHD risk,[129, 130, 133] others observed null or J-shaped associations with CHD risk.[130, 132] Therefore, it is still unclear whether non-White ethnic groups have different patterns of adiposity-related CHD risk. Current genetic studies also lack ethnic diversity, with less than 15% of all participants included in current GWAS being of non-White ethnicity.[327] Therefore, future large-scale studies, such as the UK Biobank, which are capable

of observing both observational and genetic associations of adiposity measures with CHD risk among non-White ethnic groups, will derive further benefits to global health.

### *9.5.2 Future genetic studies on adiposity and CHD risk*

Genetic epidemiology is a rapidly evolving field, and future genetic analyses could address some of the specific limitations of the current study. As discussed previously in **Chapter 8**, it remains difficult to separate the causal effects of general and central adiposity using current genetic and observational epidemiological methods because previous GWAS have not identified SNPs for BMI which are entirely independent of central adiposity or body fat distribution (e.g. WHR). Therefore, it is not clear whether associations with GRS-BMI are partly due to SNPs which are influencing body fat distribution. Future analysis would benefit from identifying BMI-specific SNPs from a GWAS of BMI adjusted for WHR (BMIadjWHR).

Additionally, although the large sample size and available IPD in the current study allowed the ability to complement observational with genetic associations in the same study population (using the same statistical model), it was still limited by a lack of statistical information owing to the weak GRSs used as IVs. The GRSs only predicted a narrow range of adiposity in this study population, and the highest amount of variability explained by a GRS was 1.5%. Recent meta-analyses of GWAS studies involving UK Biobank, together with C+C4D, have identified further SNPs which increase the variability of BMI explained to around 6%.[104] Future analyses should afford the opportunity to re-examine the causal relevance of adiposity and CHD using additional variants for BMI and WHR, employing statistical approaches such as re-sampling methods to deal with overlapping populations in discovery and analysis populations.[352] Future genetic studies employing mediation analysis approaches would also be informative in dissecting direct or indirect effects of adiposity on CHD risk, particularly if GRSs for cardiometabolic traits are used.[353, 354]

### *9.5.3 Future research targeted at central body fat distribution*

The current thesis suggests that WHR is causally associated with CHD risk beyond BMI, however substantial focus of drug development or lifestyle interventions have been targeted towards reductions in BMI, with little effort towards development of therapies which might favourably alter body fat distribution. The UK Biobank resource offers an opportunity to expand our understanding of the biological mechanisms underlying body fat distribution and CHD risk through the use of DXA imaging, biomarker and genetic data. For example, future genetic studies investigating the mechanistic links between numerous SNPs and WHR could lead to

novel therapeutic strategies to reduce abdominal adiposity for CHD risk reduction. Similarly, building on the results presented in **Chapter 6**, further cross-sectional investigations which assess associations between mutually exclusive body fat compartments and a range of cardiometabolic traits other than blood pressure, could reveal further potentially modifiable factors underlying WHR-related CHD risk that could be amenable to intervention.

### 9.6 Conclusion

Usual levels of general adiposity measures (BMI and body fat %), central adiposity measures (WC and trunk fat %) and body fat distribution measures (WHTR and WHR) all demonstrated strong, positive and approximately log-linear associations with CHD risk, with no evidence of threshold effects within the ranges studied in this UK population. Associations were notably stronger for central adiposity, particularly WHR, compared with BMI. The relevance of WHR to CHD was particularly strong among women and remained strongly associated with CHD after adjustment for BMI. The observed prospective associations were partially mediated by blood pressure, lipids and insulin resistance, which explained at least half of the observed excess risk. Genetically elevated BMI and WHRadjBMI were independently associated with CHD risk and with cardiometabolic traits. Given the evidence summarised in the current thesis, it is clear that both BMI and WHR depict two separate and mutually exclusive aspects of adiposity – general adiposity and central body fat distribution – with clear differences in their associated metabolic perturbations and eventual effects on CHD risk. Therefore, each should be considered separately as risk factors for CHD. Future research would benefit from separating the genetic effects of the different measures of adiposity on CHD risk, investigating adiposity-related CHD risk in ethnically diverse populations, and developing population-level strategies which are targeted at both central and general adiposity.

## References


1. GBD. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1459-544.
2. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: Linked national database study. BMJ (Online). 2012; 344 (7842) (no pagination).
3. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. Heart. 1945; 102:1945-52.
4. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. Lancet. 1999; 353:1547-57.
5. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry. 1012; 5:987-1012.
6. Wilkins E WL, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European Cardiovascular Disease Statistics 2017 . European Heart Network 2017.
7. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001; 104:365-72.
8. Srikanth S, Ambrose JA. Pathophysiology of coronary thrombus formation and adverse consequences of thrombus during pci. Current Cardiology Reviews. 2012; 8:168-76.
9. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. Circulation. 2001; 103:934-40.
10. Jartti L, Ronnemaa T, Raitakari OT, Hedlund E, Hammar N, Lassila R, et al. Migration at early age from a high to a lower coronary heart disease risk country lowers the risk of subclinical atherosclerosis in middle-aged men. Journal of Internal Medicine. 2009; 265:345-58.
11. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis and cardiovascular disease between ethnic groups in Canada: the study of health assessment and risk in ethnic groups (SHARE). Indian heart journal. 2000; 52:Nov-Dec.
12. WHO. The cardiovascular disease atlas of risk factors. . The World Health Organisation; 2017 [27/04/2017]; Available from: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_03_risk_factors.pdf
13. Bell AC, Adair LS, Popkin BM. Ethnic differences in the association between body mass index and hypertension. American Journal of Epidemiology. 2002; 155:346-53.
14. Peters SAE, Bots SH, Woodward M. Sex differences in the association between measures of general and central adiposity and the risk of myocardial infarction: Results from the UK Biobank. Journal of the American Heart Association. 2018; 7.
15. Schmiegelow MD, Hedlin H, Mackey RH, Martin LW, Vitolins MZ, Stefanick ML, et al. Race and ethnicity, obesity, metabolic health, and risk of cardiovascular disease in postmenopausal women. Journal of the American Heart Association. 2015; 4.
16. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: Collaborative analysis of 58 prospective studies. The Lancet. 2011; 377:1085-95.

17. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. American Heart Journal. 1991; 121:293-8.
18. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837-47.
19. Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America. Bulletin of the World Health Organization. 2010; 88:120-30.
20. Keys A. Coronary heart disease in seven countries. 1970. Nutrition (Burbank, Los Angeles County, Calif). 1997:Mar 1997.
21. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, 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. The Lancet. 2014; 384:766-81.
22. GBD. Obesity and Overweight Prevalence 1980-2015: Institute for Health Metrics and Evaluation (IHME)2017.
23. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet. 2014; 384:755-65.
24. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1.8 million participants. The Lancet. 2014; 383:970-83.
25. Eckel RH, Kahn R, Robertson RM, Rizza RA. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. Circulation. 2006; 113:2943-6.
26. Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nature Medicine. 2006; 12:62-6.
27. Kitahara CM, Flint AJ, Berrington de Gonzalez A, Bernstein L, Brotzman M, MacInnis RJ, et al. Association between Class III Obesity (BMI of 40-59 kg/m<sup>2</sup>) and Mortality: A Pooled Analysis of 20 Prospective Studies. PLoS Medicine. 2014; 11 (7) (no pagination).
28. Manson JE, Bassuk SS. Obesity in the United States: A fresh look at its high toll. Journal of the American Medical Association. 2003; 289:229-30.
29. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. New England Journal of Medicine. 2005; 352:1138-45.
30. Sturm R, Wells KB. Does obesity contribute as much to morbidity as poverty or smoking? Public Health. 2001; 115:229-35.
31. Rutkowski JM, Stern JH, Scherer PE. The cell biology of fat expansion. Journal of Cell Biology. 2015; 208:501-12.
32. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, et al. Body-mass index and mortality in Korean men and women. New England Journal of Medicine. 2006; 355:779-87.
33. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006; 444:875-80.
34. Kalil GZ, Haynes WG. Sympathetic nervous system in obesity-related hypertension: Mechanisms and clinical implications. Hypertension Research. 2012; 35:4-16.
35. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertension Research. 2010; 33:386-93.
36. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association Scientific Statement on obesity and

heart disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006; 113:898-918.
37. Grassi G, Dell'Oro R, Facchini A, Trevano FQ, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. Journal of Hypertension. 2004; 22:2363-9.
38. Landsberg L. Insulin-mediated sympathetic stimulation: Role in the pathogenesis of obesity-related hypertension (or, how insulin affects blood pressure, and why). Journal of Hypertension. 2001; 19:523-8.
39. Moan A, Nordby G, Rostrup M, Eide I, Kjeldsen SE. Insulin sensitivity, sympathetic activity, and cardiovascular reactivity in young men. Am J Hypertens. 1995; 8:268-75.
40. Straznicky NE, Eikelis N, Lambert EA, Esler MD. Mediators of sympathetic activation in metabolic syndrome obesity. Current hypertension reports. 2008; 10:440-7.
41. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Archives of Internal Medicine. 2007; 167:1720-8.
42. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: An intuition toward cardiac autonomic alteration-a risk of CVD. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2017; 10.
43. Konstantinides S, Schafer K, Koschnick S, Loskutoff DJ. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. Journal of Clinical Investigation. 2001; 108:1533-40.
44. Singhal A, Farooqi S, Cole TJ, O'Rahilly S, Fewtrell M, Kattenhorn M, et al. Influence of leptin on arterial distensibility: A novel link between obesity and cardiovascular disease? Circulation. 1919; 106:1919-24.
45. Alpert MA. Obesity cardiomyopathy: Pathophysiology and evolution of the clinical syndrome. American Journal of the Medical Sciences. 2001; 321:225-36.
46. Otto ME, Belohlavek M, Khandheria B, Gilman G, Svatikova A, Somers V. Comparison of right and left ventricular function in obese and nonobese men. American Journal of Cardiology. 2004; 93:1569-72.
47. Mensah GA, Treiber FA, Kapuku GK, Davis H, Barnes VA, Strong WB. Patterns of body fat deposition in youth and their relation to left ventricular markers of adverse cardiovascular prognosis. American Journal of Cardiology. 1999; 84:583-8.
48. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH. Disparate Effects of Left Ventricular Geometry and Obesity on Mortality in Patients With Preserved Left Ventricular Ejection Fraction. American Journal of Cardiology. 2007; 100:1460-4.
49. Lavie CJ, Amodeo C, Ventura HO, Messerli FH. Left atrial abnormalities indicating diastolic ventricular dysfunction in cardiopathy of obesity. Chest. 1987; 92:1042-6.
50. Aurigemma GP, De Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. Circulation: Cardiovascular Imaging. 2013; 6:142-52.
51. Konige M, Wang H, Sztalryd C. Role of adipose specific lipid droplet proteins in maintaining whole body energy homeostasis. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2014; 1842:393-401.
52. Hunink MGM, Goldman L, Tosteson ANA, Mittleman MA, Goldman PA, Williams LW, et al. The recent decline in mortality from coronary heart disease, 1980-1990; The effect of secular trends in risk factors and treatment. Journal of the American Medical Association. 1997; 277:535-42.
53. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Hazen SL, Ntanios F, et al. Effects of Obesity on Lipid-Lowering, Anti-Inflammatory, and Antiatherosclerotic Benefits of Atorvastatin or Pravastatin in Patients With Coronary Artery Disease (from the REVERSAL Study). American Journal of Cardiology. 2006; 97:1553-7.

54. Bulbulia R, Bowman L, Wallendszus K, Collins R, Meade T, Sleight P, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: A randomised controlled trial. The Lancet. 2011; 378:2013-20.
55. Prentice AM. The emerging epidemic of obesity in developing countries. International Journal of Epidemiology. 2006; 35:93-9.
56. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. New England Journal of Medicine. 2017; 377:13-27.
57. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, Smith GD, et al. The effect of elevated body mass index on ischemic heart disease risk: Causal estimates from a mendelian randomisation approach. PLoS Medicine. 2012; 9 (5) (no pagination).
58. Emdin CA, Khera AV, Natarajan P, Klarin D, Zekavat SM, Hsiao AJ, et al. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. JAMA - Journal of the American Medical Association. 2017; 317:626-34.
59. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007; 116:39-48.
60. Ding J, Visser M, Kritchevsky SB, Nevitt M, Newman A, Sutton-Tyrrell K, et al. The association of regional fat depots withhypertension in older persons of white and African American ethnicity. Am J Hypertens. 2004; 17:971-6.
61. Gastaldelli A, Sironi AM, Ciociaro D, Positano V, Buzzigoli E, Giannessi D, et al. Visceral fat and beta cell function in non-diabetic humans. Diabetologia. 2005; 48:2090-6.
62. Lee YH, Lee SH, Jung ES, Kim JS, Shim CY, Ko YG, et al. Visceral adiposity and the severity of coronary artery disease in middle-aged subjects with normal waist circumference and its relation with lipocalin-2 and MCP-1. Atherosclerosis. 2010; 213:592-7.
63. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA Journal of the American Medical Association. 1150; 308:1150-9.
64. Kannel WB, Cupples LA, Ramaswami R, Stokes IJ, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. Journal of Clinical Epidemiology. 1991; 44:183-90.
65. Koster A, Murphy RA, Eiriksdottir G, Aspelund T, Sigurdsson S, Lang TF, et al. Fat distribution and mortality: The AGES-Reykjavik study. Obesity. 2015; 23:893-7.
66. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. Obesity (Silver Spring, Md). 2006; 14:336-41.
67. Klein S, Fontana L, Young L, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. New England Journal of Medicine. 2004; 350:2549-57.
68. Thorne A, Lonnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: Omentectomy in connection with adjustable gastric banding. International Journal of Obesity. 2002; 26:193-9.
69. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. JAMA. 1998; 280:1843-8.
70. Marinou K, Hodson L, Vasan SK, Fielding BA, Banerjee R, Brismar K, et al. Structural and functional properties of deep abdominal subcutaneous adipose tissue explain its association with insulin resistance and cardiovascular risk in men. Diabetes Care. 2014; 37:821-9.
71. Turer AT, Scherer PE. Adiponectin: Mechanistic insights and clinical implications. Diabetologia. 2012; 55:2319-26.

72. White UA, Tchoukalova YD. Sex dimorphism and depot differences in adipose tissue function. Biochimica et Biophysica Acta Molecular Basis of Disease. 1842; 3:377-92.
73. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. International Journal of Obesity. 2010; 34:949-59.
74. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: A case-control study. Lancet. 2005; 366:1640-9.
75. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. Journal of Clinical Investigation. 1995; 96:88-98.
76. Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. American Journal of Physiology Endocrinology and Metabolism. 2000; 278:E941-E8.
77. Misra A, Garg A, Abate N, Peshock RM, Stray-Gundersen J, Grundy SM. Relationship of anterior and posterior subcutaneous abdominal fat to insulin sensitivity in nondiabetic men. Obesity research. 1997; 5:93-9.
78. Wajchenberg BL. Subcutaneous and visceral adipose tissue: Their relation to the metabolic syndrome. Endocrine Reviews. 2000; 21:697-738.
79. Bjorntorp P. The regulation of adipose tissue distribution in humans. International Journal of Obesity. 1996; 20:291-302.
80. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Medicine. 2015; 12 (3) (no pagination).
81. Bohula EA, Wiviott SD, McGuire DK, Inzucchi SE, Kuder J, Im K, et al. Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients. New England Journal of Medicine. 2018; 26:26.
82. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. Journal of Internal Medicine. 2013; 273:219-34.
83. Ahern AL, Wheeler GM, Aveyard P, Boyland EJ, Halford JCG, Mander AP, et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. The Lancet. 2017; 389:2214-25.
84. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet. 2018; 391:541-51.
85. Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technology Assessment. 2004; 8.
86. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: Systematic review and meta-analyses of randomised controlled trials. BMJ. 2014; 348.
87. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obesity Science and Practice. 2017; 3:3-14.
88. Bohula EA, Wiviott SD, McGuire DK, Inzucchi SE, Kuder J, Im KA, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. New England Journal of Medicine. 1107; 379:1107-17.
89. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. British Journal of Radiology. 2012; 85:1-10.
90. Denton N, Karpe F. Measuring body composition and regional fat mass accurately. Practical Diabetes. 2016; 33:224-6.
91. Hind K, Oldroyd B, Truscott JG. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. European Journal of Clinical Nutrition. 2011; 65:140-2.

92. Ellegard L, Bertz F, Winkvist A, Bosaeus I, Brekke HK. Body composition in overweight and obese women postpartum: Bioimpedance methods validated by dual energy X-ray absorptiometry and doubly labeled water. European Journal of Clinical Nutrition. 2016; 70:1181-8.
93. Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. British Journal of Nutrition. 2000; 83:115-22.
94. Martinoli R, Mohamed EI, Maiolo C, Cianci R, Denoth F, Salvadori S, et al. Total body water estimation using bioelectrical impedance: A meta-analysis of the data available in the literature. Acta Diabetologica. 2003; 40:S203-S6.
95. Pietrobelli A, Morini P, Battistini N, Chiumello G, Nunez C, Heymsfield SB. Appendicular skeletal muscle mass: Prediction from multiple frequency segmental bioimpedance analysis. European Journal of Clinical Nutrition. 1998; 52:507-11.
96. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long- term follow-up of prospective studies. American Journal of Epidemiology. 1999; 150:341-53.
97. Hill JO, Peters JC. Commentary: Physical activity and weight control. International Journal of Epidemiology. 2013; 42:1840-2.
98. Luke A, Cooper RS. Physical activity does not influence obesity risk: Time to clarify the public health message. International Journal of Epidemiology. 1831; 42:1831-6.
99. Swinburn B. Commentary: Physical activity as a minor player in the obesity epidemic: What are the deep implications? International Journal of Epidemiology. 2013; 42:1838-40.
100. Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. Annals of Nutrition and Metabolism. 2015; 66:7-12.
101. Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. Journal of the American Medical Association. 1986; 256:51-4.
102. Turula M, Kaprio J, Rissanen A, Koskenvuo M. Body weight in the Finnish Twin Cohort. Diabetes Research and Clinical Practice. 1990; 10:S33-S6.
103. Wardle J, Carnell S, Haworth CMA, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. American Journal of Clinical Nutrition. 2008; 87:398-404.
104. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum Mol Genet. 2018; 27:3641-9.
105. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518:197-206.
106. Justice AE, Winkler TW, Feitosa MF, Graff M, Fisher VA, Young K, et al. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. Nature Communications. 2017; 8.
107. Qi Q, Chu AY, Kang JH, Huang J, Rose LM, Jensen MK, et al. Fried food consumption, genetic risk, and body mass index: Gene-diet interaction analysis in three US cohort studies. BMJ. 2014; 348.
108. Franks PW, Merino J. Gene-lifestyle interplay in type 2 diabetes. Current Opinion in Genetics and Development. 2018; 50.
109. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Ssteinthorsdottir V, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nature Genetics. 2010; 42:949-60.
110. Shungin D, Winkler T, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 2015; 518:187-96.
111. Rey-López JP, De Rezende, L.F., De Sá, T.H. & Stamatakis, E. . Is the Metabolically Health Obesity Phenotype an Irrelevant Artifact for Public Health? American Journal of Epidemiology. 2015; 182:737-41.

112. Smith GD, Timpson N, Ebrahim S. Strengthening causal inference in cardiovascular epidemiology through Mendelian randomization. Annals of Medicine. 2008; 40:524-41.
113. Wehby GL, Ohsfeldt RL, Murray JC. 'Mendelian randomization' equals instrumental variable analysis with genetic instruments. Statistics in Medicine. 2745; 27:2745-9.
114. Bennett DA, Holmes MV. Mendelian randomisation in cardiovascular research: An introduction for clinicians. Heart (no pagination), 2017. 2017; Date of Publication:June 08.
115. Delgado-Rodriguez M, Llorca J. Bias. Journal of epidemiology and community health. 2004; 58:635-41.
116. Holmes MV, Lange LA, Palmer T, Lanktree MB, North KE, Almoguera B, et al. Causal effects of body mass index on cardiometabolic traits and events: A Mendelian randomization analysis. American Journal of Human Genetics. 2014; 94:198-208.
117. Sun YQ, Burgess S, Staley JR, Wood AM, Bell S, Kaptoge SK, et al. Body mass index and all cause mortality in HUNT and UK Biobank studies: Linear and non-linear mendelian randomisation analyses. BMJ. 2019; 364.
118. Wade KH, Carslake D, Sattar N, Davey Smith G, Timpson NJ. BMI and Mortality in UK Biobank: Revised Estimates Using Mendelian Randomization. Obesity. 2018; 26:1796-806.
119. Dale CE, Fatemifar G, Palmer TM, White J, Prieto-Merino D, Zabaneh D, et al. Causal Associations of Adiposity and Body Fat Distribution with Coronary Heart Disease, Stroke Subtypes, and Type 2 Diabetes Mellitus: A Mendelian Randomization Analysis. Circulation. 2017; 135:2373-88.
120. Zhang X, Lv WQ, Qiu B, Zhang LJ, Qin J, Tang FJ, et al. Assessing causal estimates of the association of obesity-related traits with coronary artery disease using a Mendelian randomization approach. Scientific reports. 2018; 8.
121. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, Smith GD, et al. The effect of elevated body mass index on ischemic heart disease risk: Causal estimates from a mendelian randomisation approach. PLoS Medicine. 2012; 9.
122. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018; 562:203-9.
123. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. The Lancet Diabetes and Endocrinology. 2018; 6:944-53.
124. Canoy D, Cairns BJ, Balkwill A, Lucy Wright F, Green J, Reeves G, et al. Coronary heart disease incidence in women by waist circumference within categories of body mass index. European Journal of Preventive Cardiology. 2013; 20:759-62.
125. Canoy D, Cairns BJ, Balkwill A, Wright FL, Green J, Reeves G, et al. Body mass index and incident coronary heart disease in women: A population-based prospective study. BMC Medicine. 2013; 11.
126. Crump C, Sundquist J, Winkleby MA, Sundquist K. Interactive effects of obesity and physical fitness on risk of ischemic heart disease. International Journal of Obesity. 2017; 41:255-61.
127. Egeland GM, Igland J, Vollset SE, Sulo G, Eide GE, Tell GS. High population attributable fractions of myocardial infarction associated with waist-hip ratio. Obesity. 2016; 24:1162-9.
128. Leitzmann MF, Moore SC, Koster A, Harris TB, Park Y, Hollenbeck A, et al. Waist circumference as compared with body-mass index in predicting mortality from specific causes. PLoS ONE. 2011; 6.
129. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: Pooled analysis of prospective data from the Asia Cohort Consortium. BMJ. 2013; 347.
130. Chen Z, Yang G, Zhou M, Smith M, Offer A, Ma J, et al. Body mass index and mortality from ischaemic heart disease in a lean population: 10 year prospective study of 220 000 adult men. International Journal of Epidemiology. 2006; 35:141-50.

131. Choi S, Kim K, Kim SM, Lee G, Jeong SM, Park SY, et al. Association of Obesity or Weight Change With Coronary Heart Disease Among Young Adults in South Korea. JAMA Intern Med. 2018; 178:1060-8.
132. Gajalakshmi V, Lacey B, Kanimozhi V, Sherliker P, Peto R, Lewington S. Body-mass index, blood pressure, and cause-specific mortality in India: a prospective cohort study of 500 810 adults. The Lancet Global Health. 2018; 6:e787-e94.
133. Jee SH, Pastor-Barriuso R, Appel LJ, Sun I, Miller IER, Guallar E. Body mass index and incident ischemic heart disease in South Korean men and women. American Journal of Epidemiology. 2005; 162:42-8.
134. Mongraw-Chaffin ML, Peters SAE, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: A systematic review and meta-analysis of 95 cohorts with 1.2 million participants. The Lancet Diabetes and Endocrinology. 2015; 3:437-49.
135. PSC. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009; 373:1083-96.
136. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 1923; 392:1923-94.
137. Wright FL, Green J, Reeves G, Beral V, Cairns BJ, Million Women Study c. Validity over time of self-reported anthropometric variables during follow-up of a large cohort of UK women. BMC Med Res Methodol. 2015; 15:81.
138. Kuskowska-Wolk A, Karlsson P, Stolt M, Rossner S. The predictive validity of body mass index based on self-reported weight and height. International journal of obesity. 1989; 13:441-53.
139. Smith GD, Ebrahim S. 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease? International Journal of Epidemiology. 2003; 32:1-22.
140. Emdin CA, Khera AV, Natarajan P, Klarin D, Zekavat SM, Hsiao AJ, et al. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. JAMA Journal of the American Medical Association. 2017; 317:626-34.
141. Elosua R, Lluis-Ganella C, Subirana I, Havulinna A, Lall K, Lucas G, et al. Cardiovascular risk factors and ischemic heart disease. Circulation: Cardiovascular Genetics. 2016; 9:279-86.
142. Hagg S, Fall T, Ploner A, Magi R, Fischer K, Draisma HHM, et al. Adiposity as a cause of cardiovascular disease: A Mendelian randomization study. International Journal of Epidemiology. 2015; 44:578-86.
143. Lv WQ, Zhang X, Fan K, Xia X, Zhang Q, Liu HM, et al. Genetically driven adiposity traits increase the risk of coronary artery disease independent of blood pressure, dyslipidaemia, glycaemic traits. European Journal of Human Genetics. 1547; 26:1547-53.
144. Ioannidis JPA. Prediction of cardiovascular disease outcomes and established cardiovascular risk factors by Genome-wide association markers. Circulation: Cardiovascular Genetics. 2009; 2:7-15.
145. Hegele RA. Genetic prediction of coronary heart disease: Lessons from Canada. Scandinavian Journal of Clinical and Laboratory Investigation, Supplement. 1999; 59:153-67.
146. Rokholm B, Silventoinen K, Angquist L, Skytthe A, Kyvik KO, Sorensen TIA. Increased genetic variance of BMI with a higher prevalence of obesity. PLoS ONE. 2011; 6.
147. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Medicine. 2015; 12.

148. Ribeiro-Filho FF, Faria AN, Azjen S, Zanella MT, Ferreira SR. Methods of estimation of visceral fat: advantages of ultrasonography. Obesity research. 2003; 11:1488-94.
149. Bosy-Westphal A, Schautz B, Later W, Kehayias JJ, Gallagher D, Muller MJ. What makes a BIA equation unique? Validity of eight-electrode multifrequency BIA to estimate body composition in a healthy adult population. European Journal of Clinical Nutrition. 2013; 67:S14-S21.
150. UK Biobank Biomarker Project Companion Document to Accompany Serum Biomarker Data. UK Biobank 2019 [cited 2019]; Available from: http://biobank.ctsu.ox.ac.uk/showcase/docs/serum_biochemistry.pdf.
151. Ergun DL, Rothney MP, Oates MK, Xia Y, Wacker WK, Binkley NC. Visceral Adipose Tissue Quantification Using Lunar Prodigy. Journal of Clinical Densitometry. 2013; 16:75-8.
152. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity. 2012; 20:1313-8.
153. Karpe F, Vasan SK, Humphreys SM, Miller J, Cheeseman J, Dennis AL, et al. Cohort profile: The Oxford Biobank. International Journal of Epidemiology. 2018; 47.
154. Perez-Cornago A, Key TJ, Allen NE, Fensom GK, Bradbury KE, Martin RM, et al. Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. British Journal of Cancer. 2017; 117:1562-71.
155. Alegre-Diaz J, Herrington W, Lopez-Cervantes M, Gnatiuc L, Ramirez R, Hill M, et al. Diabetes and cause-specific mortality in Mexico City. New England Journal of Medicine. 2016; 375:1961-71.
156. Shepherd J. Evaluation of Sarcopenia by DXA. Clinical Reviews in Bone and Mineral Metabolism. 2016; 14:45-9.
157. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009; 373:1083-96.
158. Varbo A, Benn M, Smith GD, Timpson NJ, Tybjaerg-Hansen A, Nordestgaard BG. Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. Circulation Research. 2015; 116:665-73.
159. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444:840-6.
160. Astor BC, Hallan SI, Miller ER, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. American Journal of Epidemiology. 2008; 167:1226-34.
161. Brea A, Puzo J. Non-alcoholic fatty liver disease and cardiovascular risk. International Journal of Cardiology. 2013; 167:1109-17.
162. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA Journal of the American Medical Association. 2010; 303:423-9.
163. Foresight. Tackling Obesities: Future Choices. Obesity System Map. [database on the Internet]2007.
164. Cerhan JR, Moore SC, Jacobs EJ, Kitahara CM, Rosenberg PS, Adami HO, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. Mayo Clinic Proceedings. 2014; 89:335-45.
165. Hartz A, He T, Rimm A. Comparison of adiposity measures as risk factors in postmenopausal women. Journal of Clinical Endocrinology and Metabolism. 2012; 97:227-33.
166. Jacobs EJ, Newton CC, Wang Y, Patel AV, McCullough ML, Campbell PT, et al. Waist circumference and all-cause mortality in a large US cohort. Archives of Internal Medicine 170 (15) (pp 1293-1301), 2010. 2010; Date of Publication:August 9-23.

167. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. New England Journal of Medicine. 2008; 359:2105-20.
168. Droyvold WB, Nilsen TIL, Kruger O, Holmen TL, Krokstad S, Midthjell K, et al. Change in height, weight and body mass index: Longitudinal data from the HUNT Study in Norway. International Journal of Obesity. 2006; 30:935-9.
169. Vlassopoulos A, Combet E, Lean MEJ. Changing distributions of body size and adiposity with age. International Journal of Obesity. 2014; 38:857-64.
170. Santanasto AJ, Goodpaster BH, Kritchevsky SB, Miljkovic I, Satterfield S, Schwartz AV, et al. Body Composition Remodeling and Mortality: The Health Aging and Body Composition Study. The journals of gerontology Series A, Biological sciences and medical sciences. 2017; 72:513-9.
171. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: An update. Physiological Reviews. 2013; 93:359-404.
172. Hunter GR, Gower BA, Kane BL. Age Related Shift in Visceral Fat. Int. 2010; 8:103-8.
173. Sarkar C, Webster C, Gallacher J. Association between adiposity outcomes and residential density: a full-data, cross-sectional analysis of 419 562 UK Biobank adult participants. The Lancet Planetary Health. 2017; 1:e277-e88.
174. Tyrrell J, Jones SE, Beaumont R, Astley CM, Lovell R, Yaghootkar H, et al. Height, body mass index, and socioeconomic status: Mendelian randomisation study in UK Biobank. BMJ. 2016; 352.
175. Martinez JA. Body-weight regulation: Causes of obesity. Proceedings of the Nutrition Society. 2000; 59:337-45.
176. Komiya H, Mori Y, Yokose T, Tajima N. Smoking as a risk factor for visceral fat accumulation in Japanese men. Tohoku Journal of Experimental Medicine. 2006; 208:123-32.
177. Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. III. Effects of cigarette smoking. Journal of the American Medical Association. 1989; 261:1169-73.
178. Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. Clinical Endocrinology. 2005; 63:239-50.
179. Khaw KT, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. New England Journal of Medicine. 1988; 318:1705-9.
180. Ryder JW, Gilbert M, Zierath JR. Skeletal muscle and insulin sensitivity: pathophysiological alterations. Frontiers in bioscience : a journal and virtual library. 2001; 6.
181. Gordon T, Kannel WB, Dawber TR, McGee D. Changes associated with quitting cigarette smoking: the Framingham Study. American Heart Journal. 1975; 90:322-8.
182. Morris RW, Taylor AE, Fluharty ME, Bjorngaard JH, Asvold BO, Gabrielsen ME, et al. Heavier smoking may lead to a relative increase in waist circumference: Evidence for a causal relationship from a Mendelian randomisation meta-analysis. The CARTA consortium. BMJ Open. 2015; 5.
183. Ng Fat L, Cable N, Shelton N. Worsening of Health and a Cessation or Reduction in Alcohol Consumption to Special Occasion Drinking Across Three Decades of the Life Course. Alcoholism: Clinical and Experimental Research. 2015; 39:166-74.
184. Roerecke M, Rehm J. Ischemic heart disease mortality and morbidity rates in former drinkers: A meta-analysis. American Journal of Epidemiology. 2011; 173:245-58.
185. Grant BF. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: Results of the national longitudinal alcohol epidemiologic survey. Journal of Studies on Alcohol. 1997; 58:464-73.
186. Chen L, Smith GD, Harbord RM, Lewis SJ. Alcohol intake and blood pressure: A systematic review implementing a mendelian randomization approach. PLoS Medicine. 2008; 5:0461-71.

187. Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nature Genetics. 2011; 43:531-8.
188. Lawlor DA, Nordestgaard BG, Benn M, Zuccolo L, Tybjaerg-Hansen A, Davey Smith G. Exploring causal associations between alcohol and coronary heart disease risk factors: Findings from a mendelian randomization study in the copenhagen general population study. European Heart Journal. 2013; 34:2519-28.
189. Takagi S, Iwai N, Yamauchi R, Kojima S, Yasuno S, Baba T, et al. Aldehyde dehydrogenase 2 gene is a risk factor for myocardial infarction in Japanese men. Hypertension Research. 2002; 25:677-81.
190. Takeuchi F, Isono M, Nabika T, Katsuya T, Sugiyama T, Yamaguchi S, et al. Confirmation of ALDH2 as a major locus of drinking behavior and of its variants regulating multiple metabolic phenotypes in a Japanese population. Circulation Journal. 2011; 75:911-8.
191. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: The nurses' health study. American Journal of Epidemiology. 1997; 145:614-9.
192. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: The Iowa Women's Health Study. Archives of Internal Medicine. 2000; 160:2117-28.
193. Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Kostense PJ, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. The American journal of clinical nutrition. 2003; 77:1192-7.
194. Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans--a 7-year prospective study. Obesity research. 1997; 5:16-23.
195. Vazquez G, Duval S, Jacobs Jr DR, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: A meta-analysis. Epidemiologic Reviews. 2007; 29:115-28.
196. Havlik RJ, Hubert HB, Fabsitz RR, Feinleib M. Weight and hypertension. Annals of Internal Medicine. 1983; 98:855-9.
197. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. Journal of the American Medical Association. 1978; 240:1607-10.
198. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. Journal of Clinical Epidemiology. 2008; 61:646-53.
199. Zheng B, Collins R, Tian X, Chen J, Li L, Peto R, et al. Blood pressure in relation to general and central adiposity among 500 000 adult Chinese men and women. International Journal of Epidemiology. 2015; 44:1305-19.
200. Gnatiuc L, Alegre-Diaz J, Halsey J, Herrington WG, Lopez-Cervantes M, Lewington S, et al. Adiposity and Blood Pressure in 110 000 Mexican Adults. Hypertension. 2017; 69:608-14.
201. Sprafka JM, Strickland D, Gomez-Marin O, Prineas RJ. The effect of cuff size on blood pressure measurement in adults. Epidemiology. 1991; 2:214-7.
202. Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. Genetic Epidemiology. 2017; 41:341-52.
203. Bjorntorp P. 'Portal' adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis. 1990; 10:493-6.
204. Vekic J, Zeljkovic A, Stefanovic A, Jelic-Ivanovic Z, Spasojevic-Kalimanovska V. Obesity and dyslipidemia. Metabolism: Clinical and Experimental. 2019; 92.

205. Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, et al. Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. Journal of Clinical Lipidology. 2013; 7:304-83.
206. Klop B, Elte JWF, Cabezas MC. Dyslipidemia in Obesity: Mechanisms and Potential Targets. Nutrients. 2013; 5:1218-40.
207. Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological targeting of the atherogenic dyslipidemia complex: The next frontier in CVD prevention beyond lowering LDL cholesterol. Diabetes. 2016; 65:1767-78.
208. Bjornson E, Adiels M, Taskinen MR, Boren J. Kinetics of plasma triglycerides in abdominal obesity. Current Opinion in Lipidology. 2017; 28:11-8.
209. Christou GA, Kiortsis DN. Adiponectin and lipoprotein metabolism. Obesity Reviews. 2013; 14:939-49.
210. Lovren F, Teoh H, Verma S. Obesity and Atherosclerosis: Mechanistic Insights. Canadian Journal of Cardiology. 2015; 31:177-83.
211. Nathan DM, Balkau B, Bonora E, Borch-Johnsen K, Buse JB, Colagiuri S, et al. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. CPD Bulletin Clinical Biochemistry. 2010; 10:25-33.
212. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001; 409:307-12.
213. Cnop M, Landchild MJ, Vidal J, Havel PJ, Knowles NG, Carr DR, et al. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: Distinct metabolic effects of two fat compartments. Diabetes. 2002; 51:1005-15.
214. Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Kahn SE, Leonetti DL, et al. Preventing diabetes - Applying pathophysiological and epidemiological evidence. British Journal of Nutrition. 2000; 84:S173-S6.
215. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003; 46:3-19.
216. Liu L, Feng J, Zhang G, Yuan X, Li F, Yang T, et al. Visceral adipose tissue is more strongly associated with insulin resistance than subcutaneous adipose tissue in Chinese subjects with pre-diabetes. Current Medical Research and Opinion. 2018; 34:123-9.
217. Montague CT, O'Rahilly S. The perils of portliness: Causes and consequences of visceral adiposity. Diabetes. 2000; 49:883-8.
218. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes. 1997; 46:3-10.
219. Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YDI. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. Diabetes. 1988; 37:1020-4.
220. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet. 1963; 1:785-9.
221. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004; 145:2273-82.
222. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. Journal of Clinical Investigation. 2005; 115:1111-9.
223. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. Journal of Clinical Investigation. 2006; 116:1784-92.
224. Scherer PE. Adipose tissue: From lipid storage compartment to endocrine organ. Diabetes. 2006; 55:1537-45.

225. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005; 436:356-62.
226. Ajani UA, Ford ES, Mokdad AH. Prevalence of high C-reactive protein in persons with serum lipid concentrations within recommended values. Clinical Chemistry. 2004; 50:1618-22.
227. Klisic AN, Vasiljevic ND, Simic TP, Djukic TI, Maksimovic MZ, Matic MG. Association between C-reactive protein, anthropometric and lipid parameters among healthy normal weight and overweight postmenopausal women in Montenegro. Laboratory Medicine. 2014; 45:12-6.
228. Stepien M, Stepien A, Wlazel RN, Paradowski M, Banach M, Rysz J. Obesity indices and inflammatory markers in obese non-diabetic normo- and hypertensive patients: A comparative pilot study. Lipids in Health and Disease. 2014; 13.
229. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity & inflammation: The linking mechanism & the complications. Archives of Medical Science. 2017; 13:851-63.
230. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-Reactive Protein to Abdominal Adiposity. American Journal of Cardiology. 2010; 106:56-61.
231. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, 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; 116:1234-41.
232. Angulo P. Nonalcoholic fatty liver disease. Revista de gastroenterologia de Mexico. 2005; 3.
233. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: Analysis of the British Women's Heart and Health study and meta-analysis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2007; 27:2729-35.
234. Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol. 2007; 13:1579-84.
235. Pang Y, Kartsonaki C, Turnbull I, Guo Y, Chen Y, Clarke R, et al. Adiposity in relation to risks of fatty liver, cirrhosis and liver cancer: a prospective study of 0.5 million Chinese adults. Scientific reports. 2019; 9.
236. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. Journal of Clinical Endocrinology and Metabolism. 2008; 93:s74-s80.
237. Nahandi MZ, Khoshbaten M, Ramazanzadeh E, Abbaszadeh L, Javadrashid R, Shirazi KM, et al. Effect of non-alcoholic fatty liver disease on carotid artery intima-media thickness as a risk factor for atherosclerosis. Gastroenterol. 2014; 7:55-62.
238. Kovesdy CP, Furth SL, Zoccali C. Obesity and kidney disease: hidden consequences of the epidemic. Clinical nephrology. 2017; 87:163-72.
239. Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. International Journal of Obesity. 2004; 28:S58-S65.
240. Hirano T. Pathophysiology of diabetic dyslipidemia. Journal of Atherosclerosis and Thrombosis. 2018; 25:771-82.
241. Rosner B, Spiegelman D, Willett WC. Correction of logistic regression relative risk estimates and confidence intervals for measurement error: The case of multiple covariates measured with error. American Journal of Epidemiology. 1990; 132:734-45.
242. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. Statistics in Medicine. 1989; 8:1051-69.
243. Frost C, Thomson, S. Correcting for Regression Dilution Bias: Comparison of Methods for a Single Predictor Variable. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2000; 163.2 173-89.

244. Lewington S, Thomsen T, Davidsen M, Sherliker P, Clarke R. Regression dilution bias in blood total and high-density lipoprotein cholesterol and blood pressure in the Glostrup and Framingham prospective studies. European Journal of Cardiovascular Prevention and Rehabilitation. 2003; 10:143-8.
245. Berglund L. Regression dilution bias: Tools for correction methods and sample size calculation. Upsala Journal of Medical Sciences. 2012; 117:279-83.
246. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. Lancet. 1990; 335:765-74.
247. Wormser D, White IR, Thompson SG, Wood AM. Methodology within-person variability in calculated risk factors: Comparing the aetiological association of adiposity ratios with risk of coronary heart disease. International Journal of Epidemiology. 2013; 42:849-59.
248. Wood A. Regression dilution methods for meta-analysis: Assessing long-term variability in plasma fibrinogen among 27 247 adults in 15 prospective studies. International Journal of Epidemiology. 2006; 35:1570-8.
249. Iliodromiti S, Celis-Morales CA, Lyall DM, Anderson J, Gray SR, Mackay DF, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: A cohort study of 296 535 adults of white European descent. European Heart Journal. 2018; 39.
250. Emberson JR, Whincup PH, Morris RW, Walker M. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: Impact of regression dilution bias. European Heart Journal. 2003; 24:1719-26.
251. Iribarren C, Sharp D, Burchfiel CM, Sun P, Dwyer JH. Association of serum total cholesterol with coronary disease and all- cause mortality: Multivariate correction for bias due to measurement error. American Journal of Epidemiology. 1996; 143:463-71.
252. Whitlock G, Clark T, Vander Hoorn S, Rodgers A, Jackson R, Norton R, et al. Random errors in the measurement of 10 cardiovascular risk factors. European Journal of Epidemiology. 2001; 17:907-9.
253. Allison DB, Paultre F, Goran MI, Poehlman ET, Heymsfield SB. Statistical considerations regarding the use of ratios to adjust data. International Journal of Obesity. 1995; 19:644-52.
254. Frost C, White IR. The effect of measurement error in risk factors that change over time in cohort studies: Do simple methods overcorrect for 'regression dilution'? International Journal of Epidemiology. 2005; 34:1359-68.
255. Fall T, Hagg S, Magi R, Ploner A, Fischer K, Horikoshi M, et al. The Role of Adiposity in Cardiometabolic Traits: A Mendelian Randomization Analysis. PLoS Medicine. 2013; 10 (6) (no pagination).
256. Chandra A, Neeland IJ, Berry JD, Ayers CR, Rohatgi A, Das SR, et al. The relationship of body mass and fat distribution with incident hypertension: Observations from the dallas heart study. Journal of the American College of Cardiology. 2014; 64:997-1002.
257. Ding J, Visser M, Kritchevsky SB, Nevitt M, Newman A, Sutton-Tyrrell K, et al. The association of regional fat depots with hypertension in older persons of white and African American ethnicity. Am J Hypertens. 2004; 17:971-6.
258. Foy CG, Hsu FC, Haffner SM, Norris JM, Rotter JI, Henkin LF, et al. Visceral fat and prevalence of hypertension among African Americans and Hispanic Americans: Findings from the IRAS family study. Am J Hypertens. 2008; 21:910-6.
259. Vasan SK, Osmond C, Canoy D, Christodoulides C, Neville MJ, Di Gravio C, et al. Comparison of regional fat measurements by dual-energy X-ray absorptiometry and conventional anthropometry and their association with markers of diabetes and cardiovascular disease risk. International Journal of Obesity. 2018; 42:850-7.

260. Yano Y, Vongpatanasin W, Ayers C, Turer A, Chandra A, Carnethon MR, et al. Regional Fat Distribution and Blood Pressure Level and Variability: The Dallas Heart Study. Hypertension. 2016; 68:576-83.
261. Karpe F, Vasan SK, Humphreys SM, Miller J, Cheeseman J, Dennis AL, et al. Cohort profile: The Oxford Biobank. International Journal of Epidemiology. 2018; 47:21-g.
262. Clarke R, Emberson JR, Breeze E, Casas JP, Parish S, Hingorani AD, et al. Biomarkers of inflammation predict both vascular and non-vascular mortality in older men. European Heart Journal. 2008; 29:800-9.
263. Dorresteijn JAN, Visseren FLJ, Spiering W. Mechanisms linking obesity to hypertension. Obesity Reviews. 2012; 13:17-26.
264. Gnatiuc L, Alegre-Diaz J, Halsey J, Herrington WG, Lopez-Cervantes M, Lewington S, et al. Adiposity and Blood Pressure in 110000 Mexican Adults. Hypertension. 2017; 69:608-14.
265. Huxley R, James WPT, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, et al. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obesity Reviews. 2008; 9:53-61.
266. Bastawrous MC, Piernas C, Bastawrous A, Oke J, Lasserson D, Mathenge W, et al. Reference values for body composition and associations with blood pressure in Kenyan adults aged >=50 years old. European Journal of Clinical Nutrition. 2018:1-8.
267. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:15430-5.
268. Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: The Framingham heart study. Hepatology. 2010; 51:1979-87.
269. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: Systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. The Lancet. 2011; 377:568-77.
270. Bennett DA, Krishnamurthi RV, Barker-Collo S, Forouzanfar MH, Naghavi M, Connor M, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. Glob Heart. 2014; 9:107-12.
271. Hajer GR, Van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. European Heart Journal. 2008; 29:2959-71.
272. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. PLoS ONE. 2017; 12 (5) (no pagination).
273. Emerging Risk Factors C, Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011; 377:1085-95.
274. Chen Z, Peto R, Zhou M, Iona A, Smith M, Yang L, et al. Contrasting male and female trends in tobacco-attributed mortality in China: evidence from successive nationwide prospective cohort studies. The Lancet. 2015; 386:1447-56.
275. Easton DF, Peto J, Babiker AGAG. Floating absolute risk: An alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Statistics in Medicine. 1991; 10:1025-35.
276. Rose G. Sick individuals and sick populations. International Journal of Epidemiology. 1985; 14:32-8.
277. Yusuf PS, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet. 2004; 364:937-52.
278. Welborn TA, Dhaliwal SS. Preferred clinical measures of central obesity for predicting mortality. European Journal of Clinical Nutrition. 2007; 61:1373-9.

279. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388:1459-544.
280. De Mutsert R, Gast K, Widya R, De Koning E, Jazet I, Lamb H, et al. Associations of Abdominal Subcutaneous and Visceral Fat with Insulin Resistance and Secretion Differ between Men and Women: The Netherlands Epidemiology of Obesity Study. Metabolic Syndrome and Related Disorders. 2018; 16:54-63.
281. Langenberg C, Sharp SJ, Schulze MB, Rolandsson O, Overvad K, Forouhi NG, et al. Long-term risk of incident type 2 diabetes and measures of overall and regional obesity: The epic-interact case-cohort study. PLoS Medicine. 2012; 9.
282. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: Are there differences between men and women? The MONICA/KORA Augsburg Cohort Study. American Journal of Clinical Nutrition. 2006; 84:483-9.
283. Hernandez TL, Kittelson JM, Law CK, Ketch LL, Stob NR, Lindstrom RC, et al. Fat redistribution following suction lipectomy: Defense of body fat and patterns of restoration. Obesity. 2011; 19:1388-95.
284. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: The effect of diabetes, obesity, and other diseases. The Lancet Diabetes and Endocrinology. 2014; 2:819-29.
285. Berrigan D, Troiano RP, Graubard BI. BMI and mortality: the limits of epidemiological evidence. The Lancet. 2016; 388:734-6.
286. Wormser D. Adiposity measures and risk of Coronary Heart Disease: University of Cambridge; 2011.
287. Hotchkiss JW, Davies CA, Leyland AH. Adiposity has differing associations with incident coronary heart disease and mortality in the Scottish population: Cross-sectional surveys with follow-up. International Journal of Obesity. 2013; 37:732-9.
288. Logue J, Murray HM, Welsh P, Shepherd J, Packard C, Macfarlane P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. Heart. 2011; 97:564-8.
289. Rosengren A, Stegmayr B, Johansson I, Huhtasaari F, Wilhelmsen L. Coronary risk factors, diet and vitamins as possible explanatory factors of the Swedish north-south gradient in coronary disease: A comparison between two MONICA centres. Journal of Internal Medicine. 1999; 246:577-86.
290. Hardman AE. Physical activity, obesity and blood lipids. International Journal of Obesity. 1999; 23:S64-S71.
291. Higgins M, D'Agostino R, Kannel W, Cobb J. Benefits and adverse effects of weight loss: Observations from the Framingham study. Annals of Internal Medicine. 1993; 119:758-63.
292. Wormser D, Wood AM, Di Angelantonio E, Thompson SG, Danesh J. Metabolic mediators of body-mass index and cardiovascular risk. The Lancet. 2014; 383:2042-3.
293. Van Gaal LF. Mechanisms linking obesity with cardiovascular disease. Diabetes, Obesity and Metabolism. 2010; Conference:1st International Diabetes and Obesity Forum. Athens Greece. Conference Publication: (var.pagings). 12 (SUPPL. 1) (pp 21).
294. Hall JE. Mechanisms of abnormal renal sodium handling in obesity hypertension. Am J Hypertens. 1997; 10.
295. Bluher M, Laufs U. New concepts for body shape-related cardiovascular risk: Role of fat distribution and adipose tissue function. European Heart Journal. 2019; 40:2856-8.
296. Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. The Lancet Public Health. 2017; 2:e277-e85.

297. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. International Journal of Epidemiology. 2013; 42:1134-44.
298. Sun L, Bennett D, Walters RG, Hill M, Parish S, Millwood IY, et al. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. Nature Medicine. 2019; 25:569-74.
299. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories a systematic review and meta-analysis. JAMA Journal of the American Medical Association. 2013; 309:71-82.
300. Chou WC, Zheng HF, Cheng CH, Yan H, Wang L, Han F, et al. A combined reference panel from the 1000Genomes and UK10K projects improved rare variant imputation in European and Chinese samples. Scientific reports. 2016; 6.
301. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nature Genetics. 2016; 48:1279-83.
302. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics. 2010; 26:2867-73.
303. Clarke GM, Anderson CA, Pettersson FH, Cardon LR, Morris AP, Zondervan KT. Basic statistical analysis in genetic case-control studies. Nature Protocols. 2011; 6:121-33.
304. Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. American Journal of Human Genetics. 2015; 97:576-92.
305. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. Genetic Epidemiology. 2016; 40:597-608.
306. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal. 2003; 327:557-60.
307. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic Epidemiology. 2016; 40:304-14.
308. Bowden J, Smith GD, Burgess S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. International Journal of Epidemiology. 2015; 44:512-25.
309. Hartwig FP, Smith GD, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. International Journal of Epidemiology. 2017; 46:1985-98.
310. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. Epidemiology. 2017; 28:30-42.
311. Burgess S. Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. International Journal of Epidemiology. 2014; 43:922-9.
312. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nature Genetics. 2015; 47:1121-30.
313. Winkler TW, Gunther F, Hollerer S, Zimmermann M, Loos RJ, Kutalik Z, et al. A joint view on genetic variants for adiposity differentiates subtypes with distinct metabolic implications. Nature Communications. 2018; 9.
314. Wang T, Moon JY, Wu Y, Amos CI, Hung RJ, Tardon A, et al. Pleiotropy of genetic variants on obesity and smoking phenotypes: Results from the Oncoarray Project of The International Lung Cancer Consortium. PloS one. 2017; 12.
315. Fall T, Hagg S, Magi R, Ploner A, Fischer K, Horikoshi M, et al. The Role of Adiposity in Cardiometabolic Traits: A Mendelian Randomization Analysis. PLoS Medicine. 2013; 10.

316. Timpson NJ, Nordestgaard BG, Harbord RM, Zacho J, Frayling TM, Tybjaerg-Hansen A, et al. C-reactive protein levels and body mass index: Elucidating direction of causation through reciprocal Mendelian randomization. International Journal of Obesity. 2011; 35:300-8.
317. Netzer N, Gatterer H, Faulhaber M, Burtscher M, Pramsohler S, Pesta D. Hypoxia, oxidative stress and fat. Biomolecules. 2015; 5:1143-50.
318. Sikaris KA. The Clinical Biochemistry of Obesity-More Than Skin Deep. Heart Lung and Circulation. 2007; 16:S45-S50.
319. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, et al. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterology Report. 2016; 4:272-80.
320. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Characteristics Recommended for the Identification and Documentation of Adult Malnutrition (Undernutrition). Journal of the Academy of Nutrition and Dietetics. 2012; 112:730-8.
321. Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, Despres JP, Matsuzawa Y, Loos RJF, et al. Obesity. Nature Reviews Disease Primers. 2017; 3.
322. Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, et al. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on bmi. Diabetes. 2008; 57:1419-26.
323. Aschard H, Vilhjalmsson BJ, Joshi AD, Price AL, Kraft P. Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. American Journal of Human Genetics. 2015; 96:329-39.
324. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. 2009; 461:747-53.
325. Soubry A, Guo L, Huang Z, Hoyo C, Romanus S, Price T, et al. Obesity-related DNA methylation at imprinted genes in human sperm: Results from the TIEGER study. Clinical Epigenetics. 2016; 8.
326. Young AI. Solving the missing heritability problem. PLoS Genetics. 2019; 15.
327. Sirugo G, Williams SM, Tishkoff SA. The Missing Diversity in Human Genetic Studies. Cell. 2019; 177:26-31.
328. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing Epidemic of Coronary Heart Disease in Low- and Middle-Income Countries. Current Problems in Cardiology. 2010; 35:72-115.
329. Cooney MT, Dudina AL, Graham IM. Value and Limitations of Existing Scores for the Assessment of Cardiovascular Risk. A Review for Clinicians. Journal of the American College of Cardiology. 2009; 54:1209-27.
330. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2017.
331. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366:1267-78.
332. Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. New England Journal of Medicine. 2017; 377:1217-27.
333. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. The Lancet. 2016; 387:957-67.
334. Zhang X, Devlin HM, Smith B, Imperatore G, Thomas W, Lobelo F, et al. Effect of lifestyle interventions on cardiovascular risk factors among adults without impaired glucose tolerance or diabetes: A systematic review and meta-analysis. PLoS ONE [Electronic Resource]. 2017; 12:e0176436.

335. Collins R, Peto R, Hennekens C, Doll R, Bubes V, Buring J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet. 2009; 373:1849-60.
336. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Garcia FAR, et al. Statin use for the primary prevention of cardiovascular disease in adults: US preventive services task force recommendation statement. JAMA Journal of the American Medical Association. 1997; 316:1997-2007.
337. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. European Heart Journal. 2003; 24:987-1003.
338. D'Agostino Sr RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. Circulation. 2008; 117:743-53.
339. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: Prospective cohort study. BMJ. 2017; 357.
340. Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet. 2018; 391:1897-907.
341. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. American Journal of Preventive Medicine. 2012; 42:563-70.
342. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. The Lancet 378 (9793) (pp 815-825), 2011. 2011; Date of Publication:August 27-September 2.
343. McAlister FA, Robitaille C, Gillespie C, Yuan K, Rao DP, Grover S, et al. The impact of cardiovascular risk-factor profiles on blood pressure control rates in adults from Canada and the United States. Canadian Journal of Cardiology. 2013; 29:598-605.
344. Marteau TM, White M, Rutter H, Petticrew M, Mytton OT, McGowan JG, et al. Increasing healthy life expectancy equitably in England by 5 years by 2035: could it be achieved? The Lancet. 2019; 393:2571-3.
345. Colchero MA, Popkin BM, Rivera JA, Ng SW. Beverage purchases from stores in Mexico under the excise tax on sugar sweetened beverages: Observational study. BMJ. 2016; 352.
346. Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, et al. The Global Syndemic of Obesity, Undernutrition, and Climate Change: The Lancet Commission report. The Lancet. 2019; 393:791-846.
347. Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. The Journal of the Association of Physicians of India. 2009; 57.
348. Armas Rojas N, Lacey B, Lewington S, Varona Perez P, Burrett JA, Morales Rigau JM, et al. Cohort Profile: The Cuba Prospective Study. International Journal of Epidemiology. 2019; 48.
349. Chen Z, Chen J, Collins R, Peto R, Wu F, Li L, et al. China Kadoorie Biobank of 0.5 million people: Survey methods, baseline characteristics and long-term follow-up. International Journal of Epidemiology. 2011; 40:1652-66.
350. Gajalakshmi V, Peto R, Kanimozhi VC, Whitlock G, Veeramani D. Cohort profile: The Chennai prospective study of mortality among 500 000 adults in Tamil Nadu, South India. International Journal of Epidemiology. 2007; 36:1190-5.
351. Gnatiuc L, Alegre-Diaz J, Wade R, Ramirez-Reyes R, Tapia-Conyer R, Garcilazo-Avila A, et al. General and Abdominal Adiposity and Mortality in Mexico City: Prospective Study of 150 000 Adults. Annals of Internal Medicine. 2019; 13:13.
352. Angrist J, Imbens, G., & Krueger, A. Jackknife instrumental variables estimation. Journal of Applied Econometrics. 1999; 14:57-67.

353. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annual Review of Public Health. 2016; 37.
354. Burgess S, Thompson DJ, Rees JMB, Day FR, Perry JR, Ong KK. Dissecting causal pathways using mendelian randomization with summarized genetic data: Application to age at menarche and risk of breast cancer. Genetics. 2017; 207:481-7.

**Appendix**

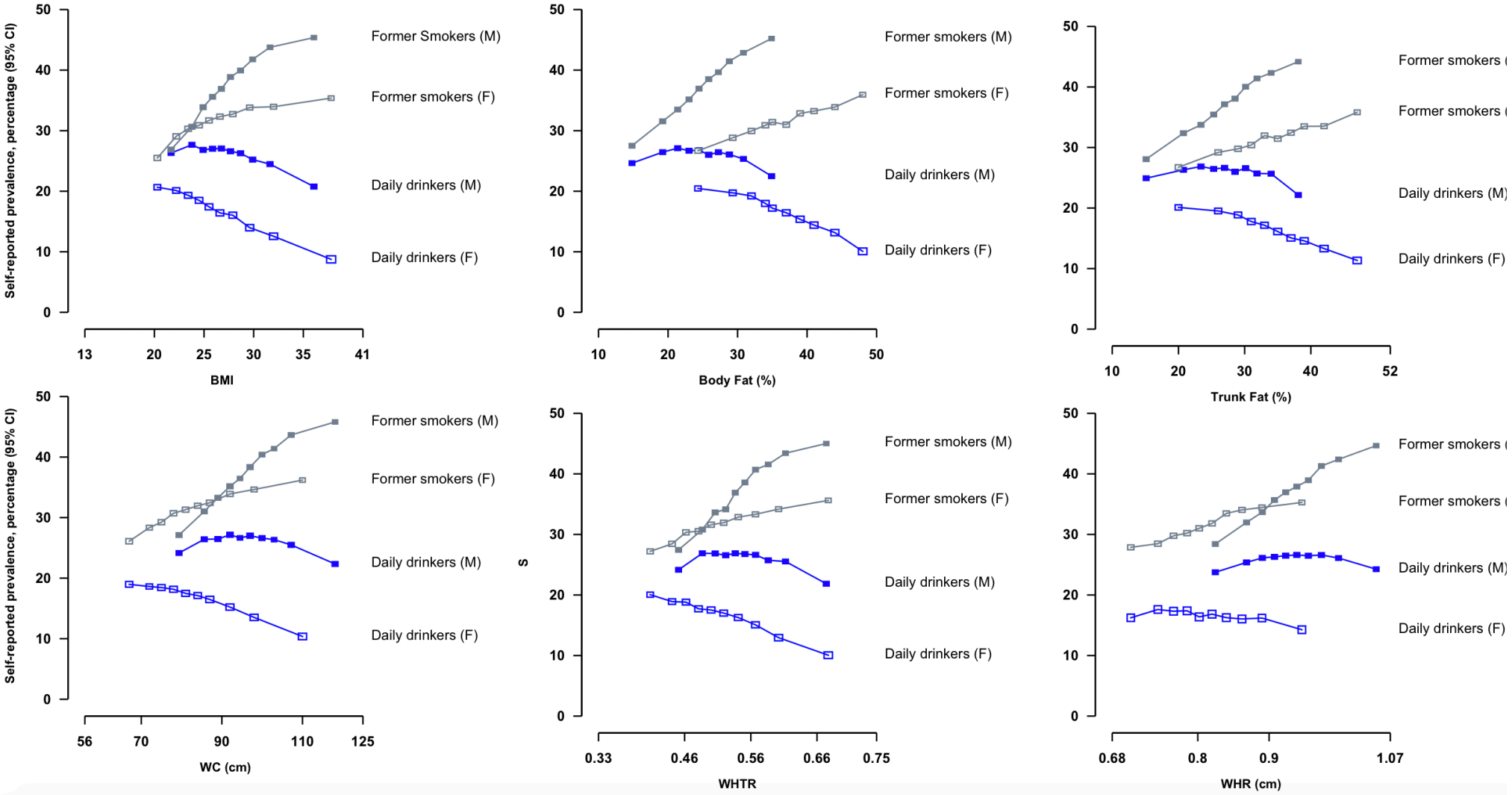

| No. | Title |
|---|---|
| **Appendix 3.1** | Summary of outlying, implausible and missing anthropometric variables in the UK Biobank |
| **Appendix 4.1** | Daily alcohol consumption and previous smoking prevalence with increasing levels of adiposity at baseline, by sex |
| **Appendix 4.2** | Self-reported versus screen-detected hypertension prevalence at baseline with increasing adiposity, by sex |
| **Appendix 4.3** | Self-reported versus screen-detected hypertension prevalence at baseline with increasing adiposity in a blood pressure medication naïve population, by sex |
| **Appendix 4.4** | Cross-sectional associations of baseline adiposity with Apo-lipoprotein A and Apo-lipoprotein B in a cholesterol-lowering treatment-naïve population |
| **Appendix 5.1** | Baseline versus resurvey distribution of adiposity measures among men |
| **Appendix 5.2** | Baseline versus resurvey distribution of adiposity measures among women |
| **Appendix 5.3** | Mean baseline & re-survey values in groups defined by baseline adiposity in resurveyed participants |
| **Appendix 5.4** | Difference between regression dilution ratios (RDRs) as estimated using MacMahon method at fifths and tenths of adiposity distributions |
| **Appendix 5.5** | Mean adiposity at baseline and resurvey in groups defined by fifths of baseline adiposity in 1 925 participants attending all three visits |
| **Appendix 6.1** | Exclusion criteria for participants included in analyses, by study |
| **Appendix 6.2** | Correlation coefficients between anthropometric measurements at imaging visit and resurvey assessments approximately 2.1 and 7.2 years prior |
| **Appendix 6.3** | Baseline characteristics by study |
| **Appendix 6.4** | Adjusted correlation coefficients between selected body size and composition variables |
| **Appendix 6.5** | BMI, waist circumference and waist-to-hip ratio versus body composition, by sex |
| **Appendix 6.6** | Mean change in systolic blood pressure (SBP) per 1 standard deviation (SD) higher DXA-derived body composition variable in 10,260 participants, by study and sex |
| **Appendix 6.7** | Mean change in systolic blood pressure (SBP) per 1 standard deviation (SD) higher regional body composition after further adjustment for smoking and physical activity, by sex |
| **Appendix 6.8** | Mean change in systolic blood pressure (SBP) per 1 standard deviation (SD) higher log-transformed body composition, by study and sex |
| **Appendix 6.9** | Mean change in systolic blood pressure (SBP) per 1 standard deviation (SD) higher anthropometric variable, with and without further adjustment for fat-free mass and visceral android fat, by sex |
| **Appendix 8.1** | Genetic instruments for BMI and WHRadjBMI in high linkage disequilibrium within the same chromosomes |
| **Appendix 8.2** | Pleiotropic effects of WHRadjBMI-associated SNPs on adiposity traits in GIANT |
| **Appendix 8.3** | Power of genetic instruments to detect hazard ratios per 1 SD genetically elevated adiposity trait, assuming 13 000 events, 350 000 participants and a type I error rate of 5% |

**Appendix 3.1** Summary of outlying, implausible and missing anthropometric variables in the UK Biobank

| Anthropometric variable | Men | | | | Women | | | | Total excluded |
|---|---|---|---|---|---|---|---|---|---|
| | Missing data (n) | Lower cut-off | Upper cut-off | Number outside of limits | Missing data (n) | Lower cut-off | Upper cut-off | Number outside of limits | |
| **Directly measured** | | | | | | | | | |
| Body weight (kg) | 1,401 | <45kg | ≥170kg | 107 | 1,353 | <40kg | ≥150kg | 226 | 3,087 |
| Height (cm) | 1,390 | <140cm | ≥200cm | 123 | 1,159 | <140cm | ≥185cm | 231 | 2,903 |
| Waist circumference(cm) | 1,065 | <65cm | ≥150cm | 213 | 1,078 | <55cm | ≥140cm | 190 | 2,546 |
| Hip circumference (cm) | 1,104 | <80cm | ≥145cm | 319 | 1,097 | <70cm | ≥150cm | 512 | 3,032 |
| **Derived** | | | | | | | | | |
| Body-mass index (kg/m$^2$) | 1,633 | <15 | ≥60 | 17 | 1,451 | <15 | ≥60 | 79 | 3,180 |
| Waist-to-hip ratio | 1,125 | <0.7 | ≥1.2 | 178 | 1,121 | <0.60 | ≥1.2 | 63 | 2,487 |
| Waist-to-height ratio | 1,437 | <0.35 | ≥0.9 | 72 | 1,250 | <0.35 | ≥0.90 | 179 | 2,938 |
| Body fat percentage (%) | 5,240 | <5% | ≥45% | 147 | 5,091 | <10% | ≥60% | 90 | 10,568 |
| Trunk fat percentage (%) | 5,124 | <5% | ≥50% | 759 | 5,256 | <10% | ≥60% | 881 | 12,020 |
| **Total excluded** | 5,628 | - | - | 1,162 | 5,380 | - | - | 1,146 | 12,952 |

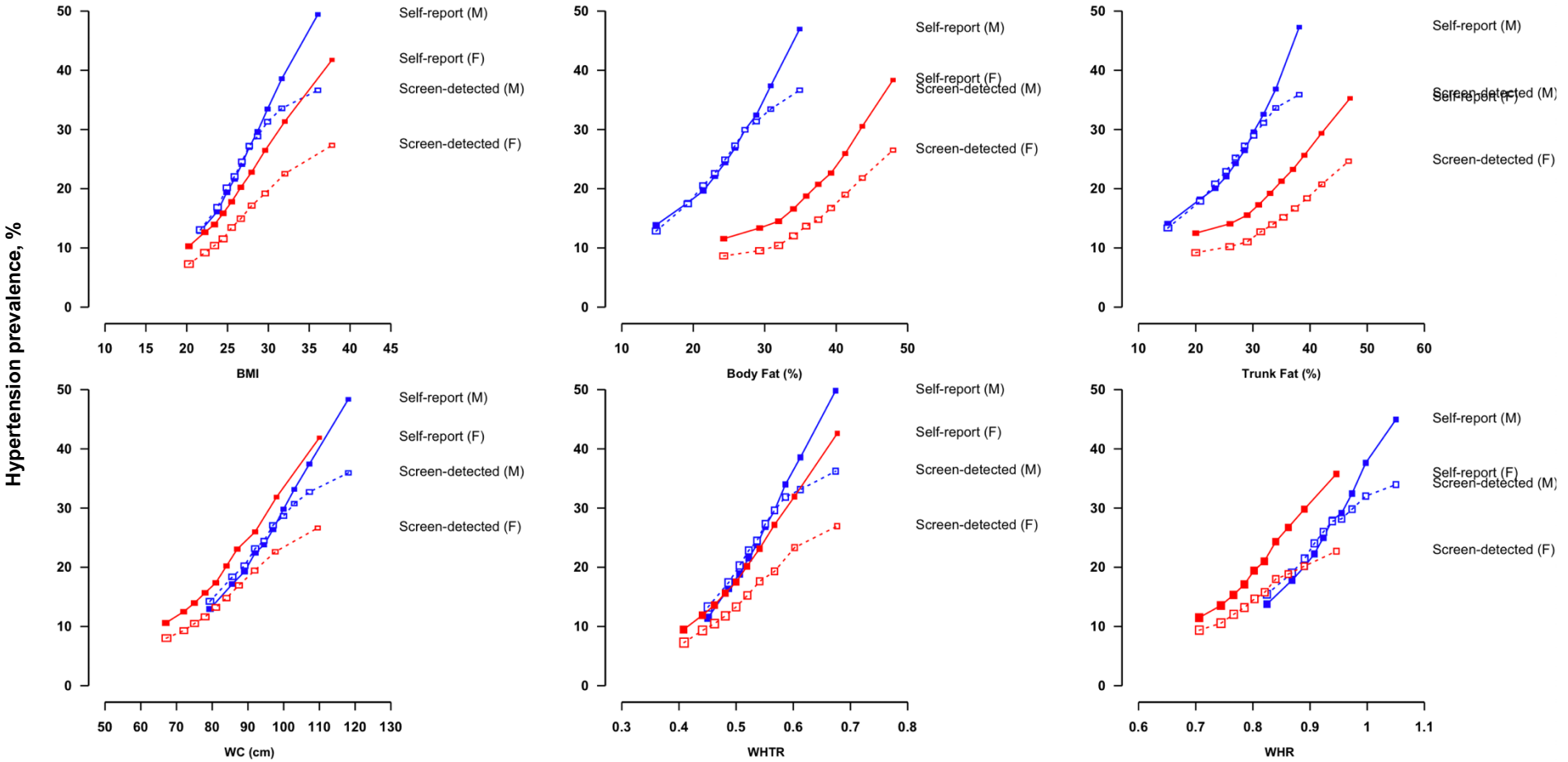
Table includes 500 222 adults aged 40-69 years at baseline assessment.

**Appendix 4.1** Daily alcohol consumption and previous smoking prevalence with increasing levels of adiposity at baseline, by sex



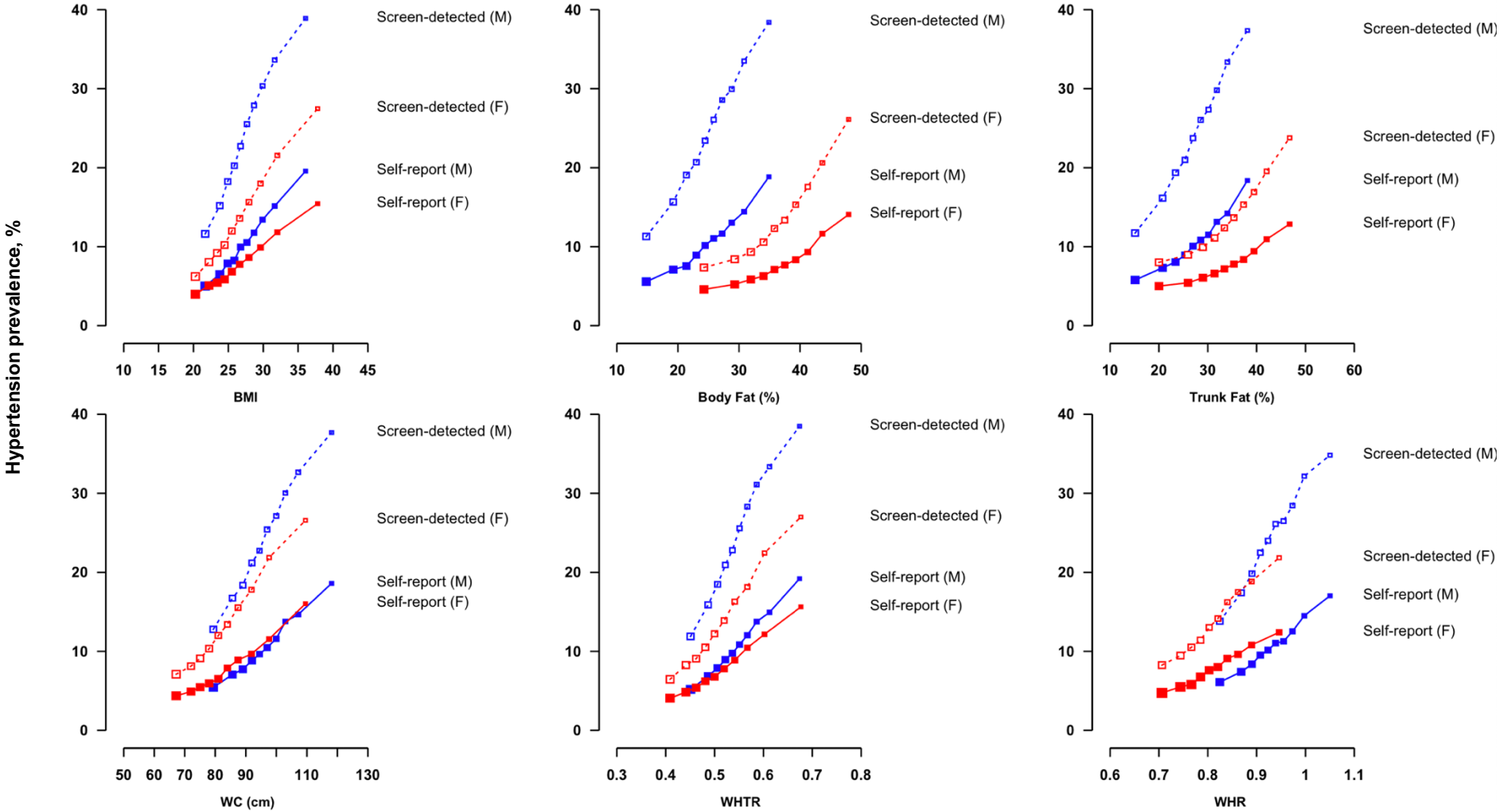

Mean prevalence shown; BMI=Body mass index; WC= Waist circumference; WHR= Waist:hip ratio;. Analyses excluded participants with a history of cardiovascular disease (Stroke, Myocardial infarction, Chronic heart failure, angina, transient ischemic attack, peripheral vascular disease), and those with extreme or implausible measures of adiposity. Mean values (95% Cis) were directly standardised to age group, region, ethnicity, educational attainment and quintile of townsend deprivation index.

**Appendix 4.2** Self-reported versus screen-detected* hypertension prevalence at baseline with increasing adiposity, by sex



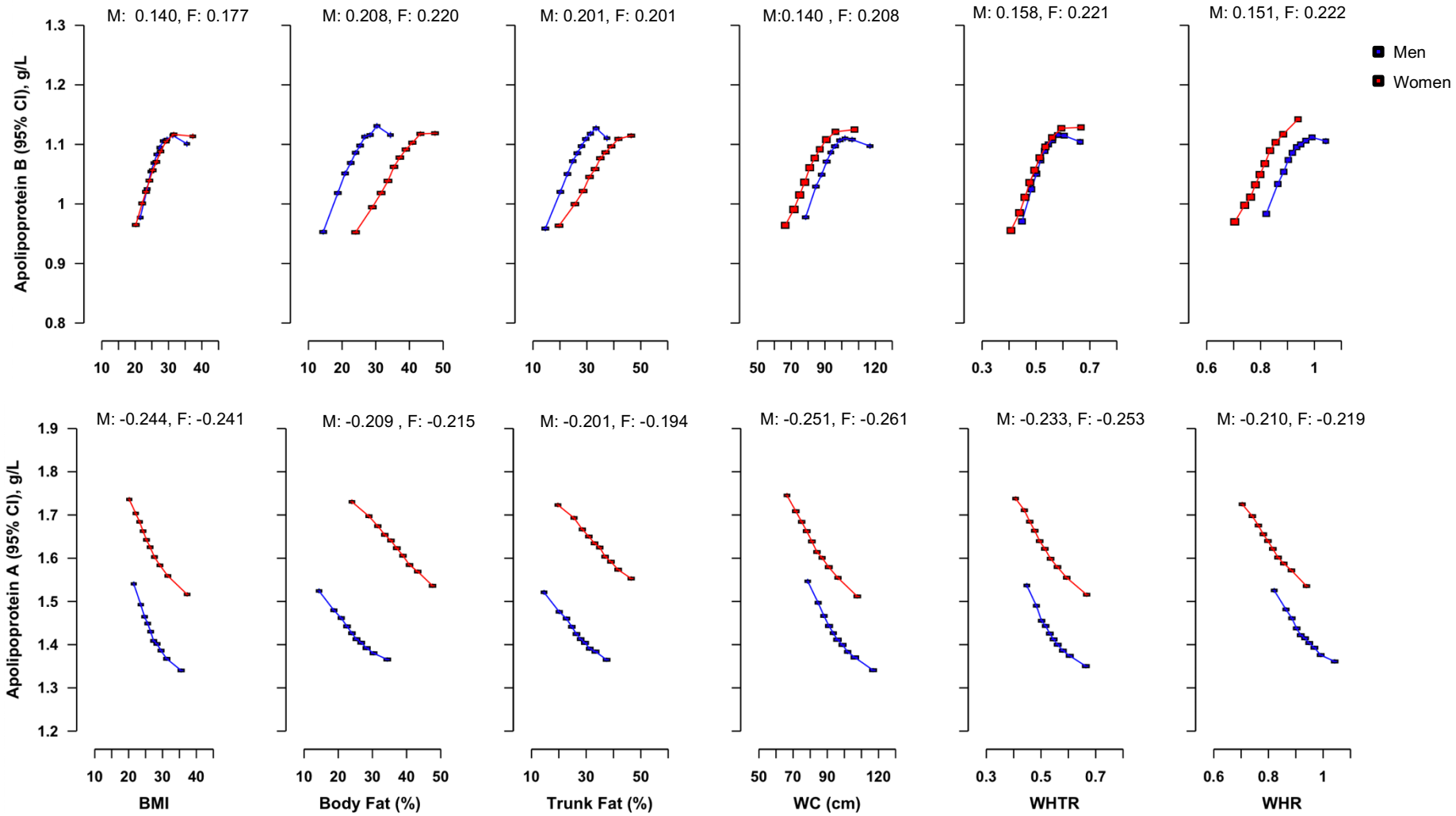

BMI= Body-mass index; WC = waist circumference; WHR= waist-to-hip ratio; WHTR= Waist-to-height ratio. Points represent prevalence of self-reported and screen-detected hypertension and corresponding 95% confidence intervals among UK Biobank men (M) and women (F) without cardiovascular disease, self-reported hypertension medication use or missing/outlying adiposity measures at baseline. Estimates are directly standardised to age (5-year groups), UK region, qualification attainment, ethnicity, deprivation index, smoking habits and alcohol consumption. X-axes are standardised to represent ±3 standard deviations from the average of mean adiposity values among men and women.
*Screen-detected hypertension was defined as blood pressure values above 140/90 mmHg.

**Appendix 4.3** Self-reported versus screen-detected* hypertension prevalence at baseline with increasing adiposity in a blood pressure medication naïve population, by sex



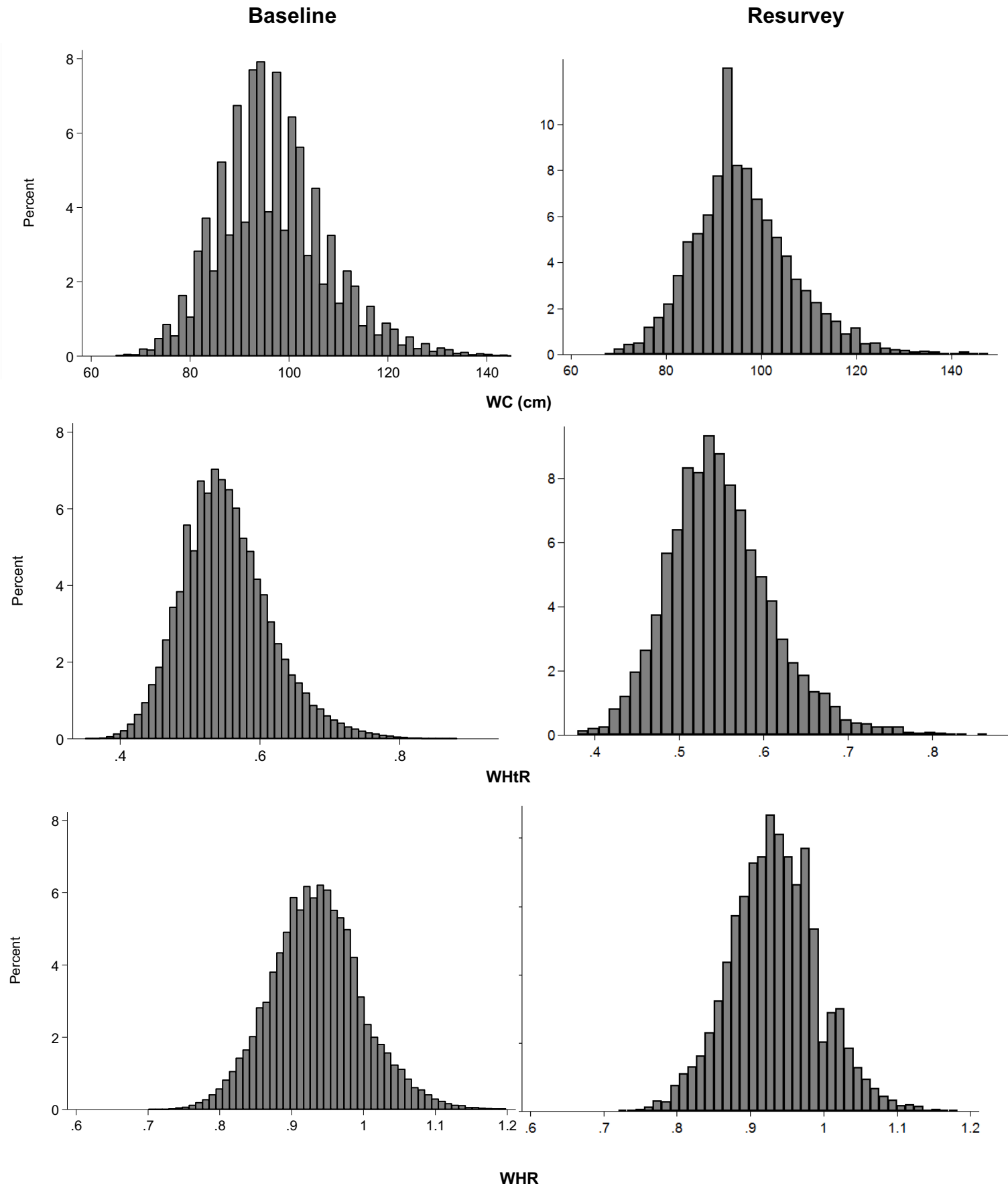

BMI= Body-mass index; WC = waist circumference; WHR= waist-to-hip ratio; WHTR= Waist-to-height ratio. Points represent prevalence of self-reported and screen-detected hypertension and corresponding 95% confidence intervals among UK Biobank men (M) and women (F) without cardiovascular disease, self-reported hypertension medication use or missing/outlying adiposity measures at baseline. Estimates are directly standardised to age (5-year groups), UK region, qualification attainment, ethnicity, deprivation index, smoking habits and alcohol consumption. X-axes are standardised to represent ±3 standard deviations from the average of mean adiposity values among men and women.
*Screen-detected hypertension was defined as blood pressure values above 140/90 mmHg.

**Appendix 4.4** Cross-sectional associations of baseline adiposity with Apo-lipoprotein A and Apo-lipoprotein B in a cholesterol-lowering treatment-naïve population

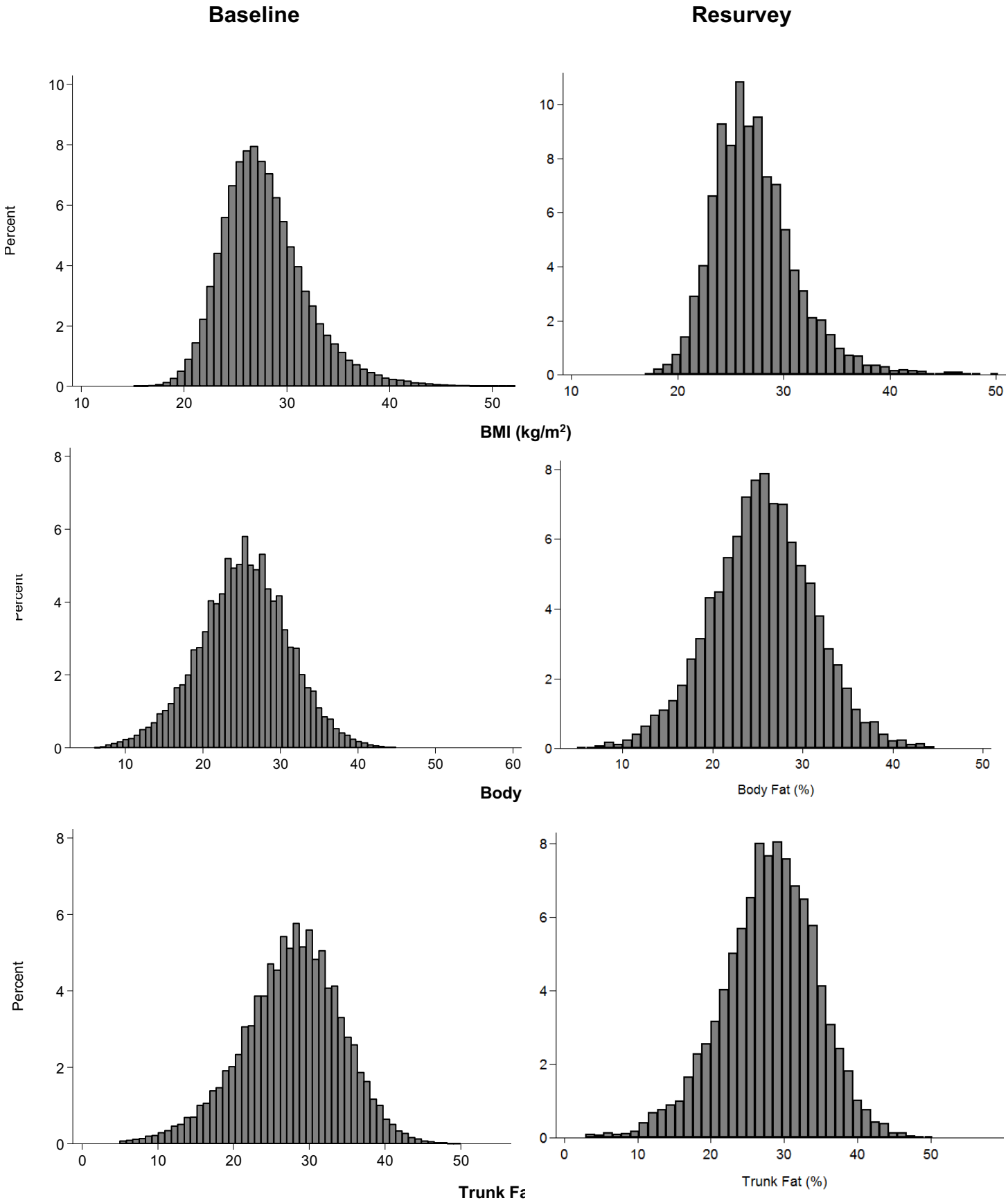



BMI= Body-mass index; WC= Waist circumference; WHTR = Waist-to-height ratio; WHR= Waist-to-hip ratio. Mean risk factor estimates (95% CI) were directly standardised to age group (5-year groups), UK region (10 regions), qualification attainment (5 groups), ethnicity (7 groups), deprivation index (fifths), smoking habits (3 groups) and alcohol consumption (4 groups). Analyses were restricted to 396 353 individuals without missing adiposity or biomarker variables or history of cardiovascular disease at baseline, with additional exclusions of participants self-reporting use of cholesterol-lowering treatment. Y-axes are standardised to represent ±1SD from the average of mean cholesterol levels among men and women. X-axes are standardised to represent approximately ±3SD from the average of mean adiposity values among men and women at baseline.

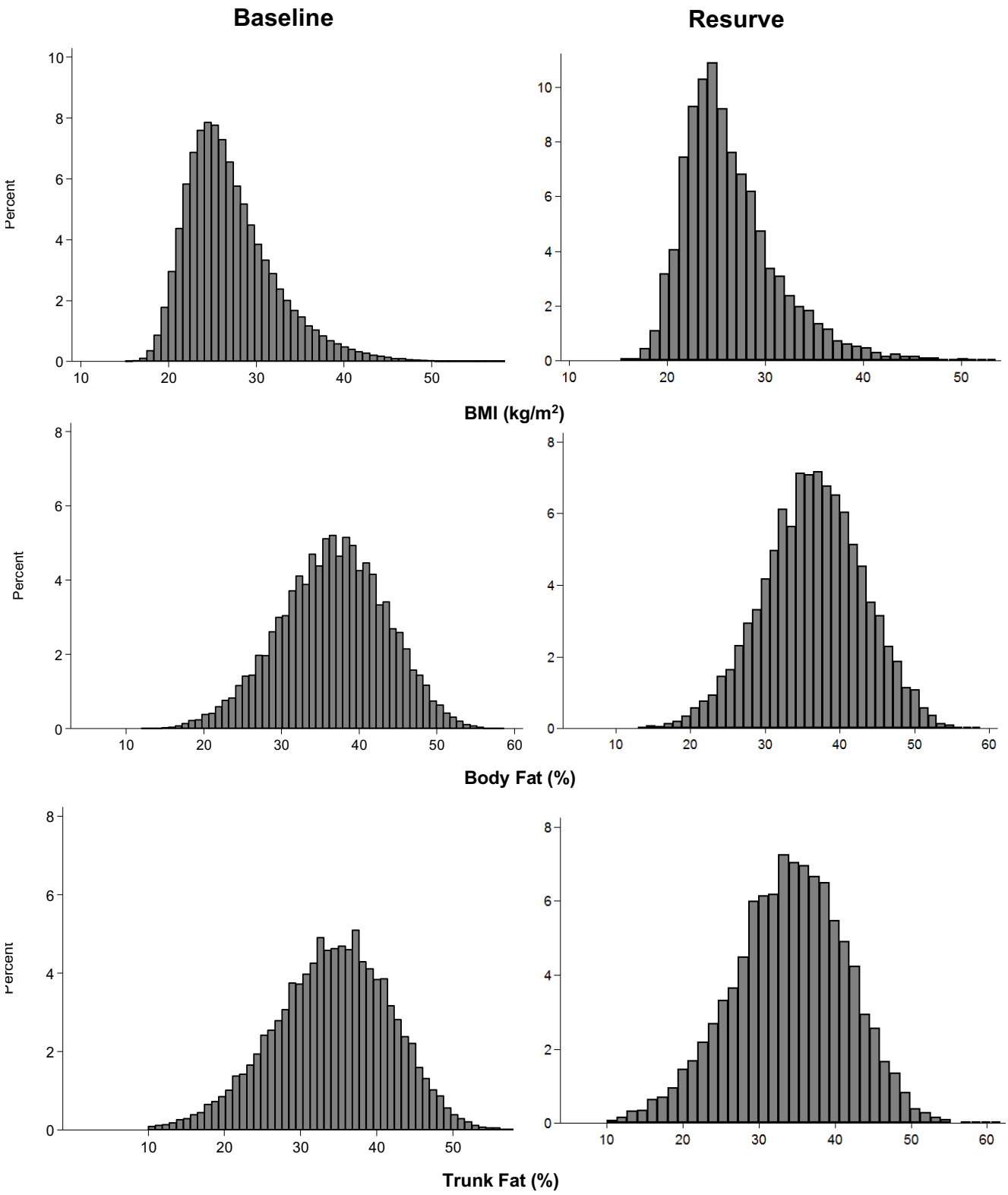
**Appendix 5.1** Baseline versus resurvey distribution of adiposity measures among men



**Appendix 5.1 continued** Baseline versus resurvey distribution of adiposity measures among men

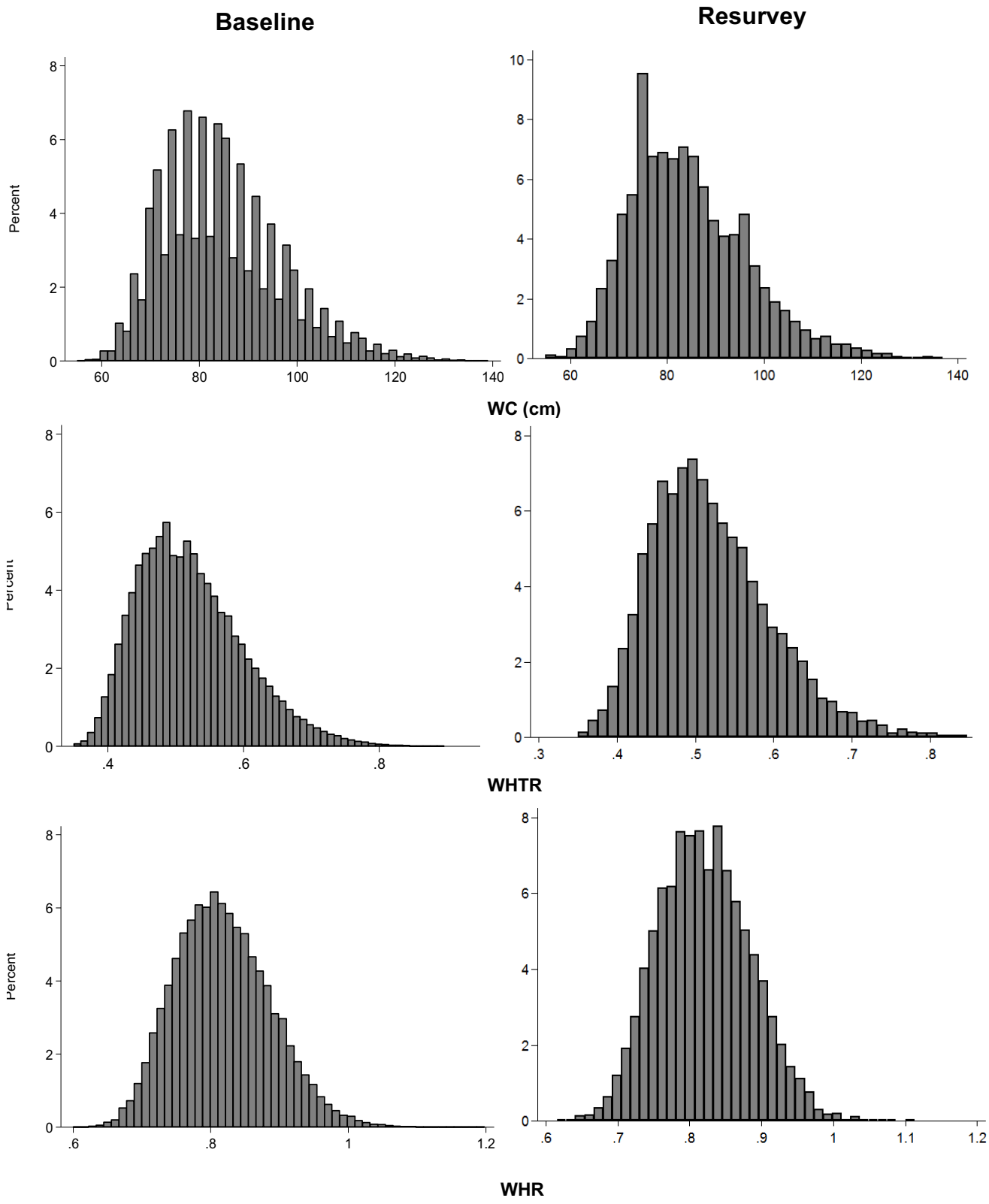


**Appendix 5.2** Baseline versus resurvey distribution of adiposity measures among women



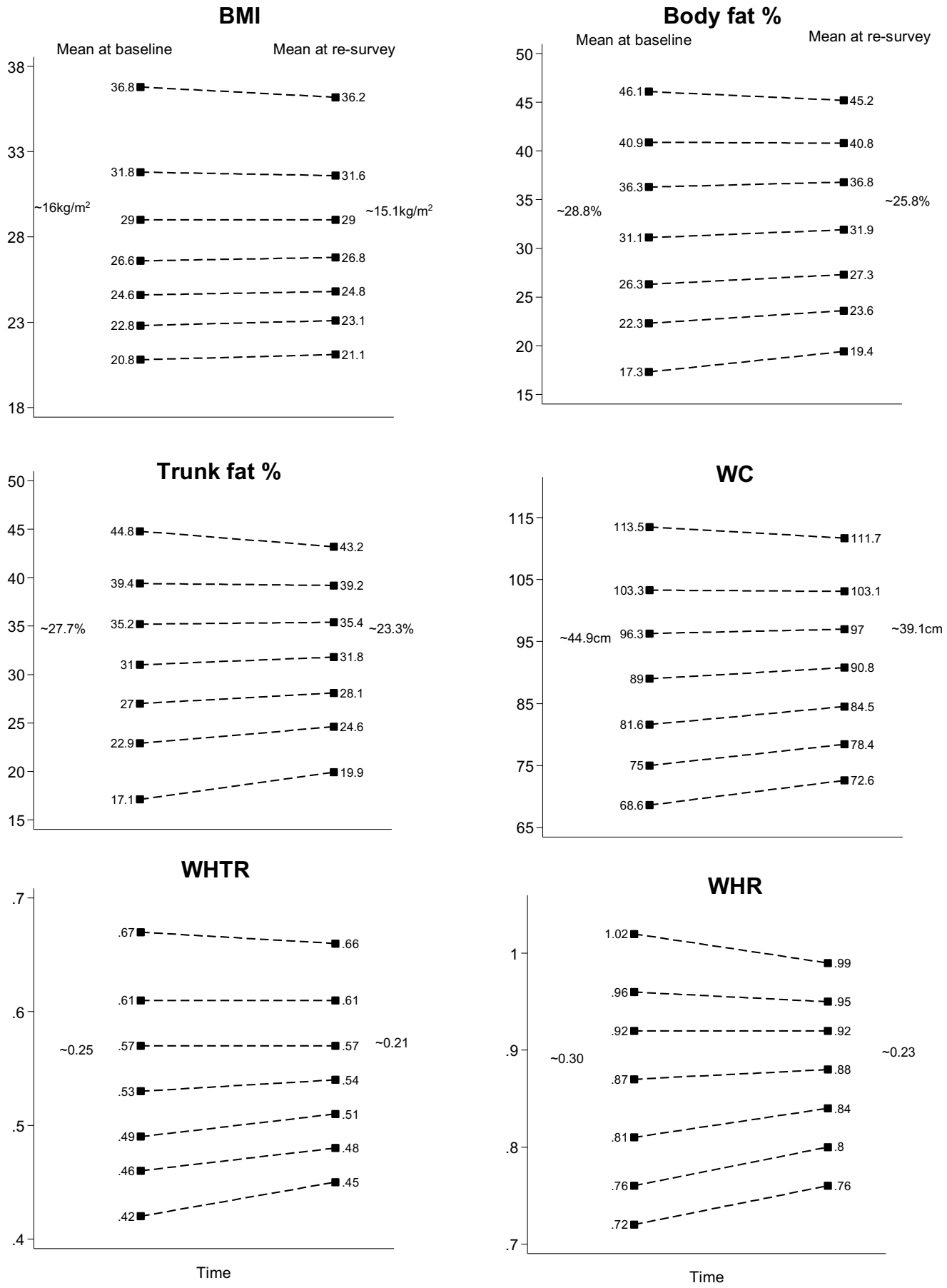

BMI= Body-mass index. Analyses were restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline.

**Appendix 5.2 continued** Baseline versus resurvey distribution of adiposity measures among women




WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio. Analyses were restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline.

**Appendix 5.3** Mean baseline & re-survey values in groups defined by baseline tenths of adiposity in resurveyed participants

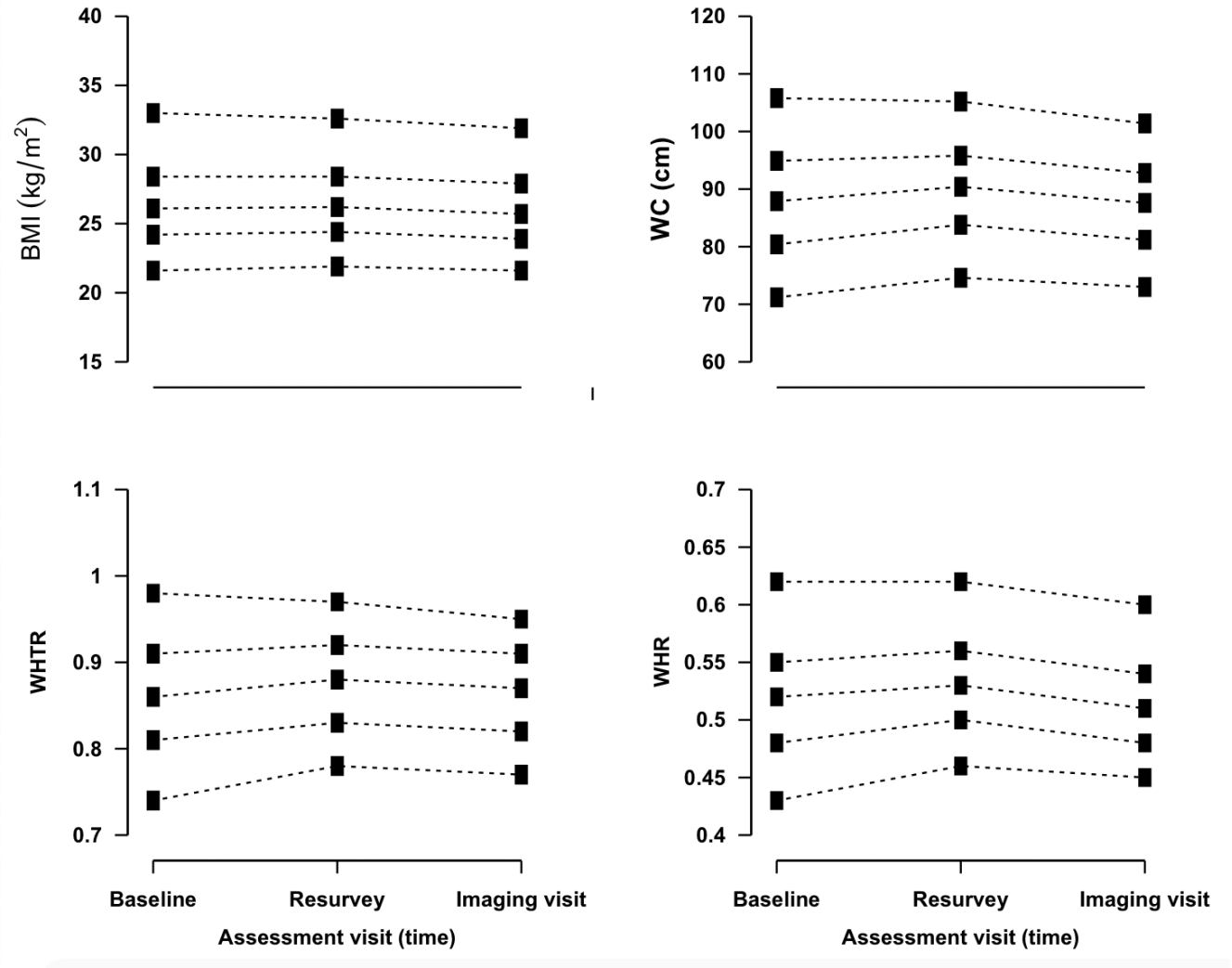



BMI= Body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; RDR = regression dilution ratio. Analyses were restricted to participants with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline. RDRs were calculating using the MacMahon-Peto method.

**Appendix 5.4** Difference between regression dilution ratios (RDRs) as estimated using MacMahon method at fifths and tenths of adiposity distributions

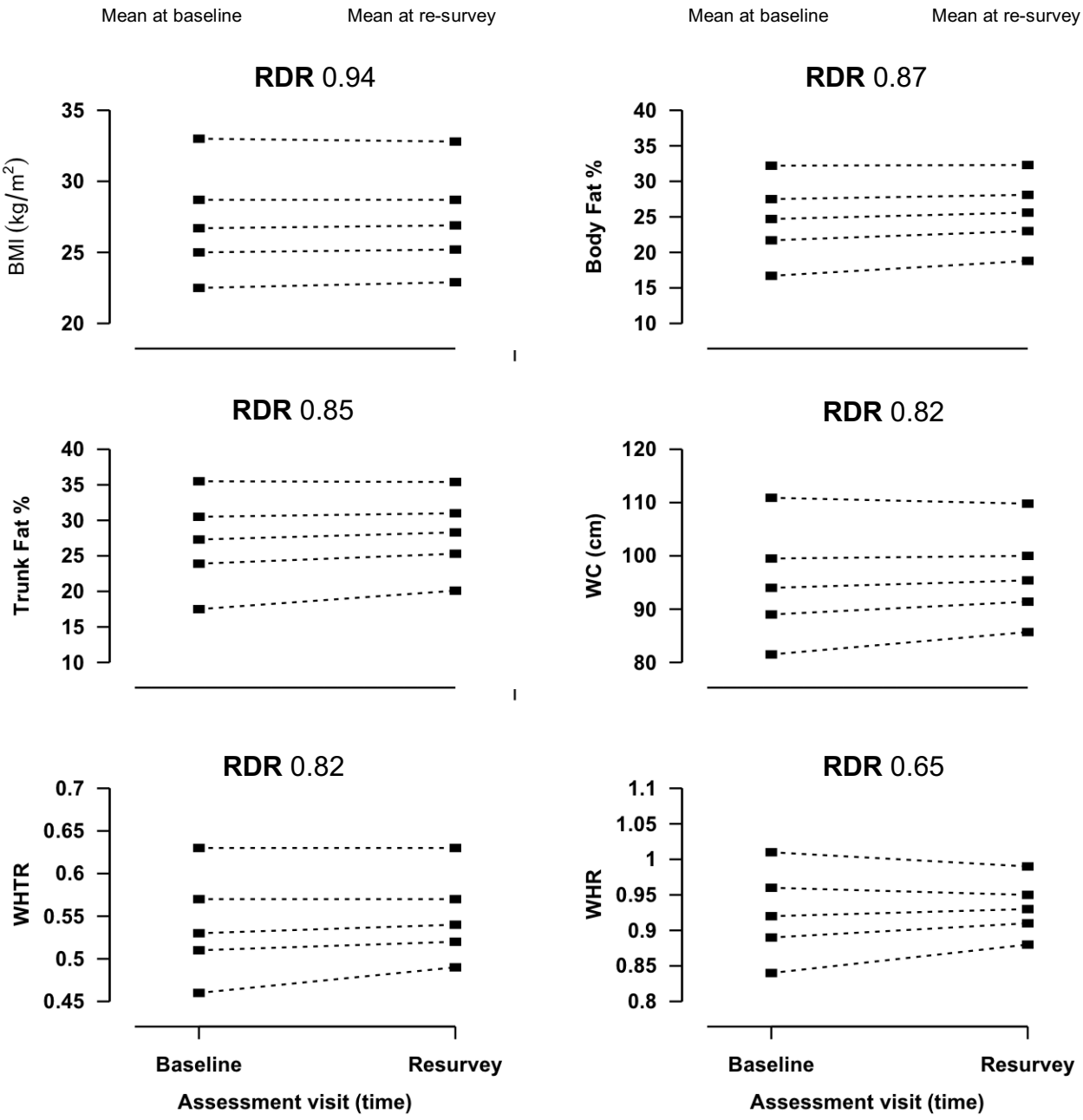
| | Regression dilution ratio (RDR) | | Difference in RDR |
|---|---|---|---|
| | Fifths | Tenths | |
| **Body mass index** | 0.94 | 0.94 | 0 |
| **Body fat** | 0.88 | 0.90 | +0.02 |
| **Trunk fat** | 0.86 | 0.84 | -0.02 |
| **Waist Circumference** | 0.83 | 0.87 | +0.04 |
| **Waist-to-height ratio** | 0.84 | 0.84 | 0 |
| **Waist-to-hip ratio** | 0.61 | 0.77 | +0.16 |

**Appendix 5.5** Mean adiposity at baseline and resurvey in groups defined by fifths of baseline adiposity in 1 925 participants attending all three visits



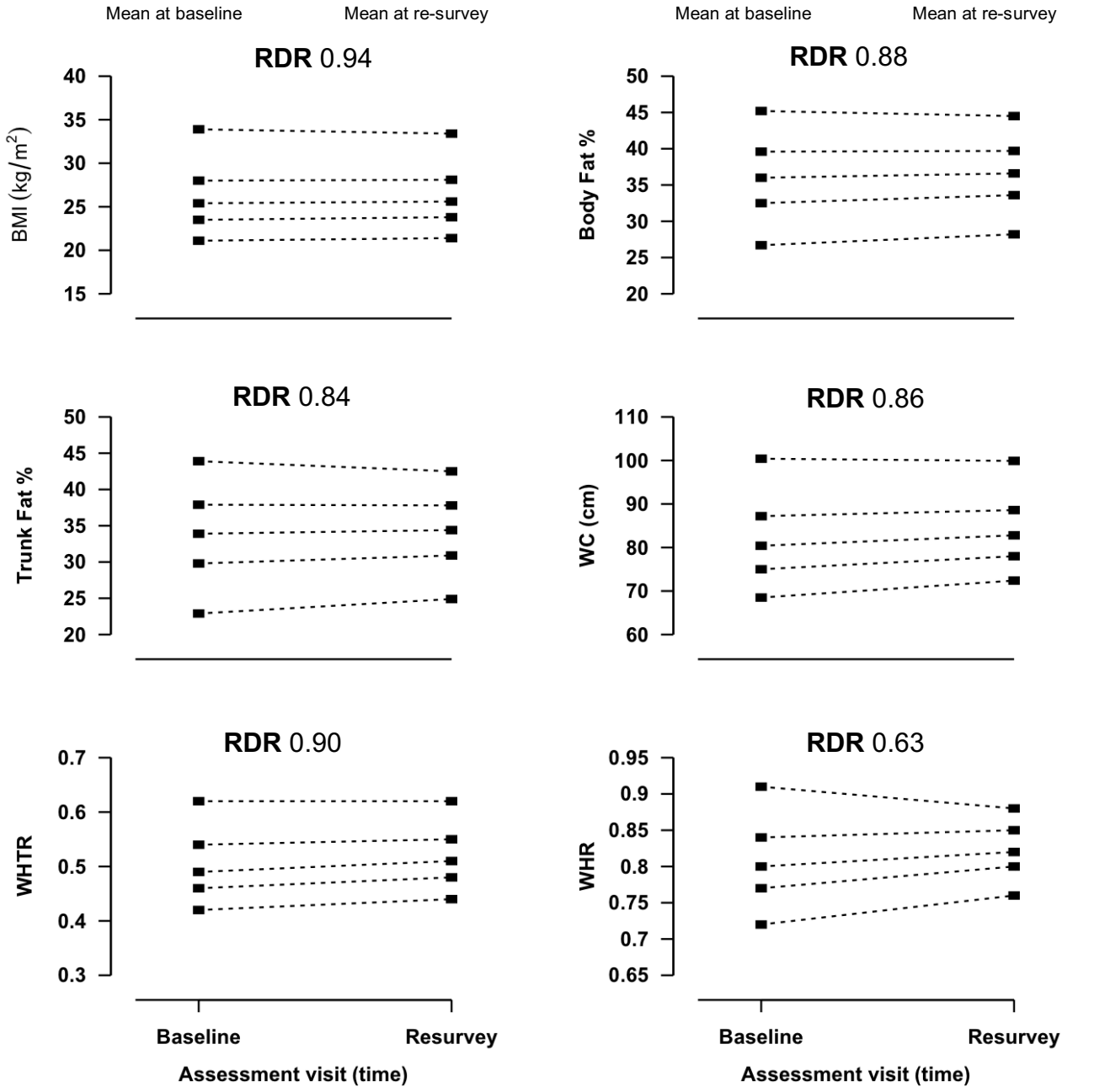

BMI= Body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; RDR = regression dilution ratio. Analyses were restricted to participants with complete information on adiposity at baseline, re-survey and imaging visits, and without known cardiovascular disease at baseline. RDRs were calculating using the MacMahon-Peto method.

**Appendix 5.6** Mean adiposity at baseline and resurvey in groups defined by fifths of baseline adiposity in men who attended resurvey assessment




BMI= Body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; RDR = regression dilution ratio. Analyses were restricted to men with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline. RDRs were calculating using the MacMahon-Peto method.

**Figure 5.7** Mean adiposity at baseline and resurvey in groups defined by fifths of baseline adiposity in men who attended resurvey assessment




BMI= Body-mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHTR = waist-to-height ratio; RDR = regression dilution ratio. Analyses were restricted to women with complete information on adiposity at baseline and re-survey, and without known cardiovascular disease at baseline. RDRs were calculating using the MacMahon-Peto method.

**Appendix 6.1** Exclusion criteria for participants of the Oxford Biobank (OBB) and UK Biobank (UKB) imaging studies

| | Men (n= 4 708) | | | | | | Women (n=5 887) | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Missing | | Lower limit | Upper limit | Outliers | | Missing | | Lower limit | Upper limit | Outliers | | OBB | UKB |
| | OBB | UKB | | | OBB | UKB | OBB | UKB | | | OBB | UKB | | |
| **Directly measured** | | | | | | | | | | | | | | |
| Body weight (kg) | 0 | 0 | <40kg | ≥170kg | 0 | 0 | 0 | 0 | <40kg | ≥150kg | 2 | 3 | 2 | 3 |
| Height (cm) | 0 | 10 | <140cm | ≥200cm | 6 | 0 | 4 | 11 | <140cm | ≥185cm | 7 | 2 | 17 | 23 |
| Waist circumference(cm) | 2 | 10 | <65cm | ≥150cm | 2 | 0 | 3 | 10 | <55cm | ≥140cm | 5 | 0 | 12 | 20 |
| Hip circumference (cm) | 2 | 10 | <80cm | ≥145cm | 1 | 1 | 4 | 10 | <70cm | ≥150cm | 7 | 0 | 14 | 21 |
| Body-mass index (kg/m$^2$) | 0 | 10 | <15 | ≥50 | 0 | 0 | 4 | 11 | <15 | ≥60 | 5 | 2 | 9 | 23 |
| Waist-to-hip ratio | 3 | 10 | <0.7 | ≥1.2 | 4 | 0 | 4 | 10 | <0.60 | ≥1.2 | 6 | 0 | 17 | 20 |
| **DXA measurements, kg** | | | | | | | | | | | | | | |
| Body fat | 0 | 0 | <3kg | ≥60kg | 8 | 10 | 0 | 0 | <3kg | ≥60kg | 26 | 8 | 34 | 18 |
| Subcutaneous android fat | 7 | 0 | <0.01kg | ≥5kg | 7 | 1 | 11 | 0 | <0.01kg | ≥5kg | 17 | 0 | 43 | 1 |
| Visceral android fat | 7 | 26 | <0.01kg | ≥5kg | 15 | 11 | 11 | 35 | <0.01kg | ≥5kg | 141 | 4 | 174 | 76 |
| Subcutaneous gynoid fat | 0 | 0 | <0.1kg | ≥15kg | 0 | 0 | 0 | 0 | <0.1kg | ≥15kg | 1 | 0 | 1 | 0 |
| Other fat | 7 | 0 | <2kg | ≥50kg | 2 | 0 | 0 | 0 | <2kg | ≥50 | 10 | 0 | 19 | 0 |
| **Systolic blood pressure** | 2 | 11 | <80mmHg | ≥240mmHg | 1 | 0 | 2 | 8 | <80mm Hg | ≥240mmHg | 3 | 0 | 8 | 19 |
| **Total excluded** | | | | | | | | | | | | | 198 | 137 |
| **Total included** | | | | | | | | | | | | | 5227 | 5033 |
| **Total combined** | | | | | | | | | | | | | | 10, 260 |

DXA =Dual energy X-ray Absorptiometry; OBB = Oxford BioBank; UKB= UK Biobank

**Appendix 6.2.** Correlation coefficients between anthropometry measures at imaging visit and resurvey assessments in the UK Biobank approximately 2.1 and 7.2 years prior

| | Self-correlation between 1st resurvey and imaging visit (~2.1 years after) | | | Self-correlation between baseline survey and imaging visit (~7.2 years after) | | |
|---|---|---|---|---|---|---|
| | **Men (n=1003)** | **Women (n=1060)** | **All (n=2063)*** | **Men (n=2390)** | **Women (n=2643)** | **All (n=5033)*** |
| **Height** | 0.99 | 0.99 | 0.99 | 0.98 | 0.98 | 0.98 |
| **Weight** | 0.96 | 0.95 | 0.96 | 0.93 | 0.91 | 0.92 |
| **Body mass index** | 0.95 | 0.95 | 0.95 | 0.91 | 0.91 | 0.91 |
| **Waist Circumference** | 0.83 | 0.84 | 0.84 | 0.79 | 0.81 | 0.80 |
| **Hip Circumference** | 0.80 | 0.86 | 0.84 | 0.78 | 0.82 | 0.80 |
| **Waist-to-hip ratio** | 0.63 | 0.65 | 0.64 | 0.62 | 0.65 | 0.64 |

*Adjusted for sex

**Appendix 6.3** Baseline characteristics by study

| | Oxford Biobank (n=5 227) | | UK Biobank (n=5 033) | |
|---|---|---|---|---|
| | **Men (n= 2 229)** | **Women (n= 2 998)** | **Men (n=2 390)** | **Women (n= 2 643)** |
| **Demographic characteristics** | | | | |
| Mean age, years (SD) | 41.5 (5.9) | 41.8 (6.1) | 63.2 (7.5) | 61.8 (7.5) |
| White, n (%) | 2 162 (97%) | 2 878 (96%) | 2 286 (96%) | 2 541 (96%) |
| Professional occupation, n (%) | 1 515 (68%) | 1 808 (60%) | 1 451 (61%) | 1 371 (52%) |
| Current smoker, n (%) | 240 (11%) | 249 (8%) | 128 (5%) | 98 (4%) |
| Daily drinker, n (%) | 670 (30%) | 343 (11%) | 559 (23%) | 379 (14%) |
| **Anthropometry, mean (SD)** | | | | |
| Height, cm | 179.2 (6.6) | 165.5 (6.2) | 176 (6.6) | 162 (6.3) |
| Weight, kg | 85.3 (13.6) | 69.3 (13.0) | 83.1 (12.7) | 68.5 (12.3) |
| BMI, kg/m$^2$ | 26.2 (3.9) | 25.0 (4.6) | 26.8 (3.6) | 26.0 (4.5) |
| Waist circumference, cm | 92.8 (10.9) | 82.5 (11.9) | 93.4 (9.4) | 82.1 (11.2) |
| Hip circumference, cm | 101.7 (7.1) | 101.3 (9.3) | 101.6 (6.8) | 101.1 (9.4) |
| Waist-to-hip ratio | 0.91 (0.07) | 0.81 (0.07) | 0.92 (0.05) | 0.81 (0.06) |
| **DXA measures, mean (SD)** | | | | |
| Fat-free mass, kg | 61.4 (7.3) | 43.9 (5.3) | 58.5 (6.8) | 41.8 (4.9) |
| Percentage body fat, % | | | | |
| Fat mass, kg | 22.9 (8.6) | 24.7 (9.4) | 24.6 (8.1) | 26.7 (9.1) |
| Visceral fat | 1.08 (0.76) | 0.43 (0.43) | 1.67 (0.91) | 0.78 (0.57) |
| Subcutaneous android fat | 1.10 (0.53) | 1.43 (0.75) | 0.98 (0.44) | 1.42 (0.64) |
| Subcutaneous gynoid fat | 3.40 (1.19) | 4.52 (1.48) | 3.54 (1.16) | 4.65 (1.45) |
| Other fat | 17.09 (6.27) | 18.20 (6.92) | 18.40 (5.96) | 19.80 (6.67) |
| **Blood pressure, mean (SD)** | | | | |
| Systolic, mmHg | 127.2 (12.3) | 116.6 (12.9) | 140.3 (16.6) | 133.4 (18.7) |
| Diastolic, mmHg | 79.0 (9.2) | 73.5 (9.2) | 80.6 (9.8) | 77.4 (9.9) |

DXA = Dual energy X-ray Absorptiometry; Those with missing or outlying anthropometry, DXA and blood pressure variables (see **Appendix 6.1**)

**Appendix 6.4** Adjusted correlation coefficients between selected body size and composition variables

| | | Anthropometry variables | | DXA variables | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **BMI** | **WHR** | **Fat-free mass** | **Visceral android fat** | **Subcutaneous android fat** | **Subcutaneous gynoid fat** | **Other fat** |
| **WC** | Men: | 0.87 | 0.80 | 0.54 | 0.80 | 0.71 | 0.83 | 0.90 |
| | Women: | 0.86 | 0.73 | 0.56 | 0.83 | 0.82 | 0.73 | 0.88 |
| **BMI** | | Men: | 0.62 | 0.58 | 0.79 | 0.67 | 0.81 | 0.88 |
| | | Women: | 0.45 | 0.56 | 0.77 | 0.85 | 0.85 | 0.93 |
| **WHR** | | | Men: | 0.24 | 0.67 | 0.47 | 0.52 | 0.66 |
| | | | Women: | 0.23 | 0.62 | 0.40 | 0.20 | 0.45 |
| **Fat-free mass** | | | | Men: | 0.37 | 0.28 | 0.41 | 0.43 |
| | | | | Women: | 0.39 | 0.49 | 0.52 | 0.53 |
| **Visceral android fat** | | | | | Men: | 0.46 | 0.72 | 0.87 |
| | | | | | Women: | 0.67 | 0.62 | 0.82 |
| **Subcutaneous android fat** | | | | | | Men: | 0.81 | 0.79 |
| | | | | | | Women: | 0.85 | 0.91 |
| **Subcutaneous gynoid fat** | | | | | | | Men: | 0.93 |
| | | | | | | | Women: | 0.91 |

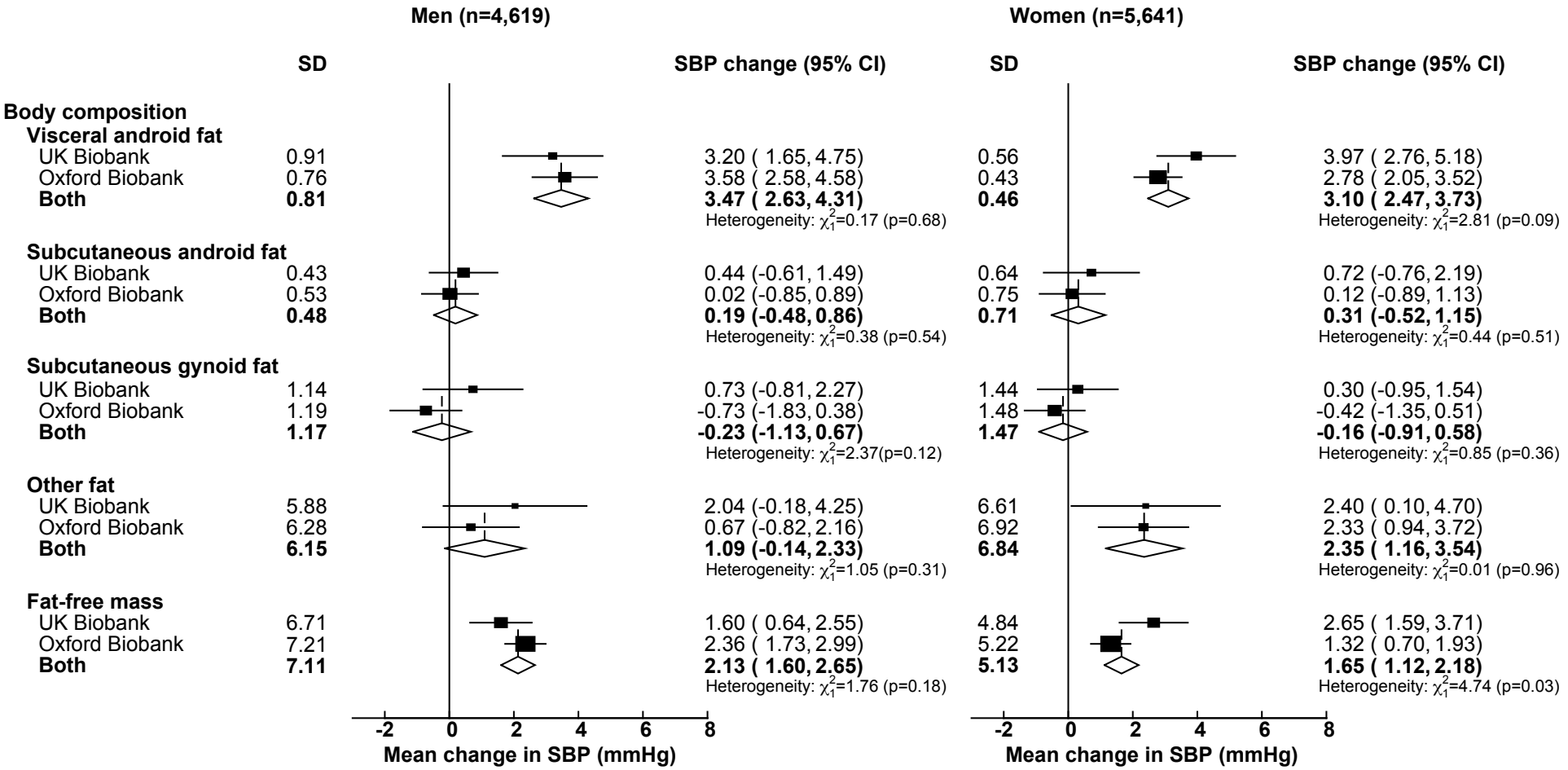
DXA=Dual energy X-ray Absorptiometry; Analyses in 10 260 participants (exclusions as in **Appendix 6.1**); Correlation coefficients were adjusted for age (5-year groups).

**Appendix 6.5** BMI, WC and WHR versus body composition, by sex

| | | | Age- and education-adjusted means (95% CI) | | | | |
|---|---|---|---|---|---|---|---|
| **Men (n=4,619)** | **Level** | **N** | **Visceral fat** | **Subcutaneous android fat** | **Subcutaneous gynoid fat** | **Other fat** | **Fat-free mass** |
| **BMI, kg/m²** | 22.01 | 923 | 0.58 (0.55- 0.60) | 0.65 (0.63- 0.68) | 2.33 (2.29- 2.37) | 11.19 ( 10.99- 11.38) | 54.68 (54.34- 55.02) |
| | 24.51 | 925 | 0.97 (0.94- 1.00) | 0.88 (0.86- 0.90) | 2.93 (2.89- 2.96) | 14.69 ( 14.51 -14.88) | 57.50 (57.14- 57.87) |
| | 26.29 | 923 | 1.29 (1.25- 1.32) | 1.01 (0.99- 1.03) | 3.32 (3.28- 3.37) | 17.10 ( 16.90 - 17.29) | 59.69 (59.31- 60.07) |
| | 28.26 | 924 | 1.69 (1.66- 1.73) | 1.17 (1.15- 1.19) | 3.89 (3.84- 3.94) | 20.20 ( 19.99- 20.41) | 61.76 (61.38- 62.15) |
| | 32.37 | 924 | 2.45 (2.40- 2.50) | 1.53 (1.50- 1.57) | 4.97 (4.89- 5.04) | 26.06 ( 25.72- 26.41) | 65.79 (65.33- 66.25) |
| **WC, cm** | 79.75 | 902 | 0.54 (0.52- 0.57) | 0.62 (0.60- 0.64) | 2.28 (2.24- 2.32) | 10.92 (10.73- 11.11) | 55.21 ( 54.82- 55.61) |
| | 87.20 | 843 | 0.95 (0.92- 0.97) | 0.87 (0.83- 0.87) | 2.88 (2.84- 3.92) | 14.46 (14.27- 14.65) | 57.78 ( 57.37- 58.20) |
| | 91.92 | 996 | 1.27 (1.24- 1.30) | 1.01 (0.99- 1.03) | 3.33 (3.29- 3.36) | 17.08 (16.91- 17.24) | 59.33 (58.98 - 59.68) |
| | 97.73 | 1005 | 1.70 (1.67- 1.73) | 1.17 (1.15- 1.19) | 3.89 (3.85- 3.94) | 20.20 (20.01- 20.38) | 61.47 ( 61.10- 61.84) |
| | 108.58 | 873 | 2.49 (2.44- 2.54) | 1.59 (1.56- 1.63) | 5.10 (5.02- 5.17) | 26.66 (26.32- 26.99) | 65.68 ( 65.21 - 66.16) |
| **WHR** | 0.83 | 924 | 0.65 (0.62- 0.68) | 0.73 (0.70- 0.76) | 2.65 (2.58- 2.72) | 12.43 ( 12.13- 12.73) | 57.93 ( 57.48- 58.39) |
| | 0.88 | 930 | 1.01 (0.97 - 1.05) | 0.95 (0.93- 0.98) | 3.13 (3.07- 3.19) | 15.54 ( 15.24 - 15.83) | 58.76 ( 58.32- 59.19) |
| | 0.91 | 923 | 1.32 (1.28- 1.36) | 1.06 (1.04- 1.09) | 3.47( 3.41- 3.54) | 17.56 ( 17.26- 17.85) | 59.77 ( 59.34- 60.20) |
| | 0.95 | 913 | 1.68 (1.64- 1.73) | 1.15 (1.12- 1.18) | 3.80 (3.73- 3.87) | 19.89 ( 19.57- 20.21) | 60.23 ( 59.78- 60.67) |
| | 1.00 | 929 | 2.27 (2.22- 2.33) | 1.37 (1.33- 1.41) | 4.40 (4.32- 4.48) | 23.89 ( 23.47- 24.30) | 62.61 ( 62.10- 63.12) |
| **Women (n=5,641)** | | | | | | | |
| **BMI, kg/m²** | 20.339 | 1128 | 0.19 ( 0.19- 0.20) | 0.71 ( 0.70- 0.73) | 3.11 ( 3.07- 3.15) | 11.64 (11.49- 11.79) | 39.74 (39.50- 39.97) |
| | 22.757 | 1128 | 0.31 ( 0.30- 0.32) | 1.05 ( 1.03- 1.06) | 3.78 ( 3.74- 3.82) | 14.81 (14.67- 14.95) | 41.49 (41.25- 41.74) |
| | 24.739 | 1128 | 0.48 ( 0.47- 0.50) | 1.35 ( 1.33- 1.37) | 4.41 ( 4.37- 4.46) | 17.87 (17.72- 18.02) | 42.39 (42.14- 42.63) |
| | 27.342 | 1129 | 0.72 ( 0.70- 0.74) | 1.69 ( 1.66- 1.71) | 5.11 ( 5.06- 5.17) | 21.51 (21.34- 21.68) | 43.75 (43.48- 44.01) |
| | 32.876 | 1128 | 1.26 (1.23 - 1.29) | 2.39 ( 2.36- 2.43) | 6.53 ( 6.45- 6.61) | 29.15 (28.84- 29.45) | 47.27 (46.97- 47.56) |
| **WC, cm** | 68.558 | 1171 | 0.19 ( 0.18- 0.20) | 0.73 ( 0.71 - 0.75) | 3.29 ( 3.25- 3.34) | 12.10 (11.94- 12.26) | 39.82 (39.58- 40.06) |
| | 75.085 | 1043 | 0.31 ( 0.30- 0.32) | 1.07 ( 1.05- 1.09) | 3.89 ( 3.84- 3.94) | 15.10 (14.93- 15.28) | 41.57 (41.31- 41.83) |
| | 80.441 | 1179 | 0.48 ( 0.47- 0.50) | 1.34 ( 1.32- 1.36) | 4.43 (4.37- 4.48) | 17.87 (17.68- 18.06) | 42.34 (42.10 - 42.57) |
| | 87.143 | 1093 | 0.71 ( 0.69- 0.73) | 1.68 ( 1.65- 1.70) | 5.05 (4.98 - 5.11) | 21.38 (21.15- 21.60) | 43.58 (43.32- 43.83) |
| | 100.102 | 1155 | 1.27 ( 1.24- 1.30) | 2.36 ( 2.32- 2.40) | 6.29 ( 6.20- 6.38) | 28.49 (28.15- 28.83) | 47.35 (47.06- 47.64) |
| **WHR** | 0.723 | 1133 | 0.27 (0.26- 0.29) | 1.08 (1.04- 1.11) | 4.26 ( 4.18- 4.35) | 15.56 (15.24- 15.87) | 41.80 (41.51 - 42.08) |
| | 0.77 | 1119 | 0.38 (0.36- 0.40) | 1.18 (1.15- 1.22) | 4.22 (4.14 - 4.30) | 16.34 (16.01- 16.68) | 42.19 (41.92 - 42.46) |
| | 0.805 | 1131 | 0.51 (0.49- 0.53) | 1.39 (1.35 - 1.42) | 4.50 ( 4.42- 4.59) | 18.33 (17.98- 18.68) | 42.32 (42.05- 42.60) |
| | 0.846 | 1130 | 0.72 (0.69- 0.74) | 1.59 (1.55- 1.63) | 4.79 ( 4.70- 4.88) | 20.56 (20.17- 20.94) | 43.34 (43.03- 43.64) |
| | 0.914 | 1128 | 1.09 (1.05- 1.13) | 1.93 (1.89- 1.98) | 5.16 ( 5.06- 5.25) | 24.08 (23.66 - 24.51) | 45.06 (44.74- 45.38) |

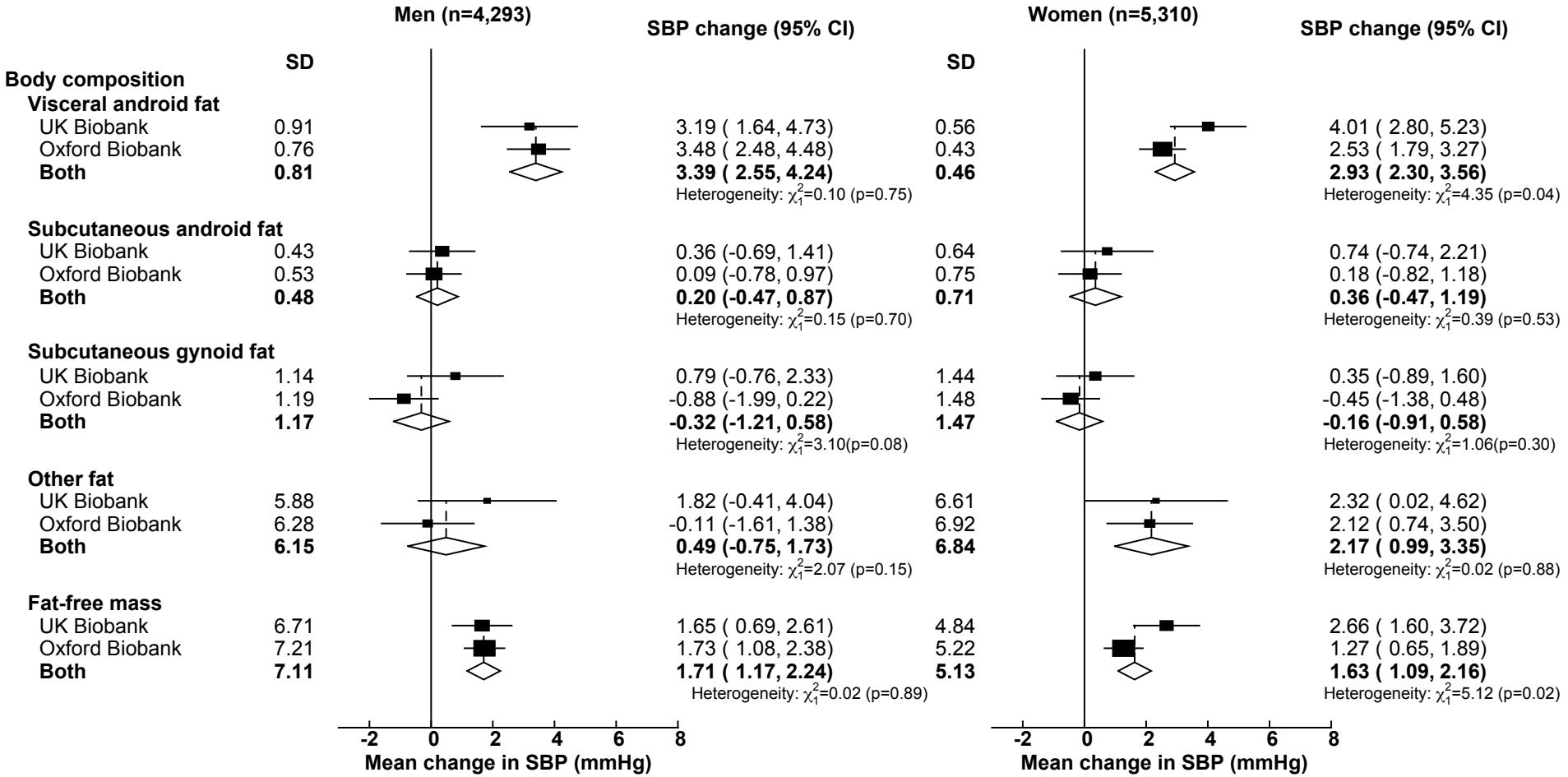
Means adjusted for age (5-year groups) and qualification attainment (5 groups). Analyses in 10 260 imaging participants; exclusions as **Appendix 6.1**

**Appendix 6.6** Mean change in SBP per SD higher DXA-derived body composition variable in 10 260 participants including those on blood pressure lowering medication, by study and sex



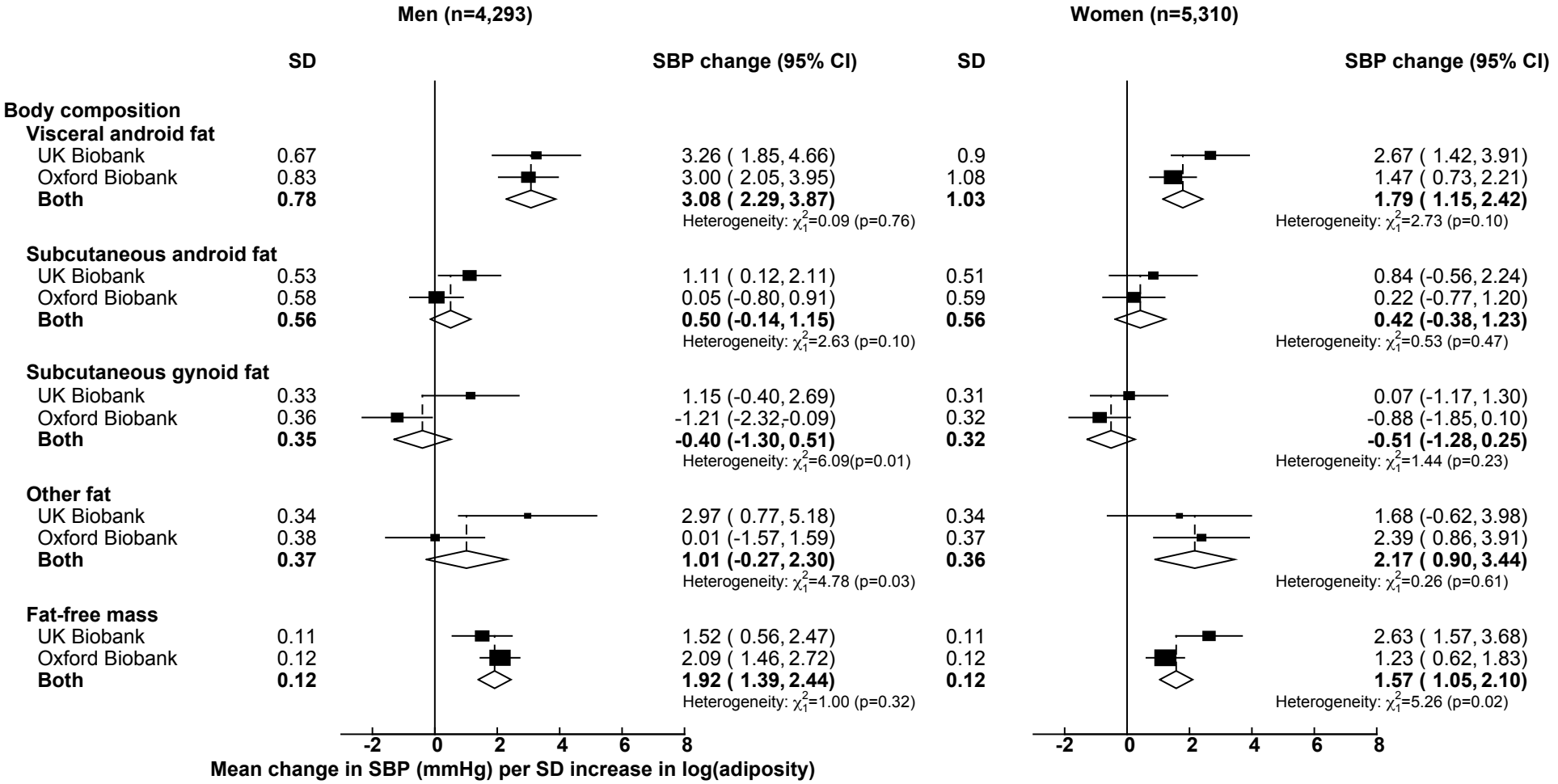

DXA = Dual energy X-ray Absorptiometry. Results presented as the mean change in SBP per standard deviation (SD) increase in DXA-derived body composition variable, adjusted for age (5-year groups), height (sex-specific fifths), education/occupation (6 groups) and alcohol consumption (5 groups). Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in Appendix 6.1.

**Appendix 6.7** Mean change in SBP per SD higher DXA-derived body composition variables after further adjustment for smoking and physical activity, by study and sex




DXA= Dual energy X-ray Absorptiometry. Results presented as the mean change in SBP per standard deviation (SD) increase in DXA-derived body composition variable, adjusted for age (5-year groups), height (sex-specific fifths), education/occupation (6 groups), alcohol consumption (5 groups), physical activity (5 groups) and smoking (4 groups). Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in Appendix 6.1, with further exclusion of those on blood pressure lowering medication.

**Appendix 6.8.** Mean change in SBP per SD higher log-transformed DXA-derived body composition variables, by study and sex




DXA= Dual energy X-ray Absorptiometry. Results presented as the mean change in SBP per standard deviation (SD) increase in the log-transformed DXA-derived body composition variable, adjusted for age (5-year groups), height (sex-specific fifths), education/occupation (6 groups) and alcohol consumption (5 groups). Weighted average of the study-specific SDs, with weights equal to 1 divided by the variance of the study-specific beta coefficient. Exclusions as in Appendix 6.1, with further exclusion of those on blood pressure lowering medication.

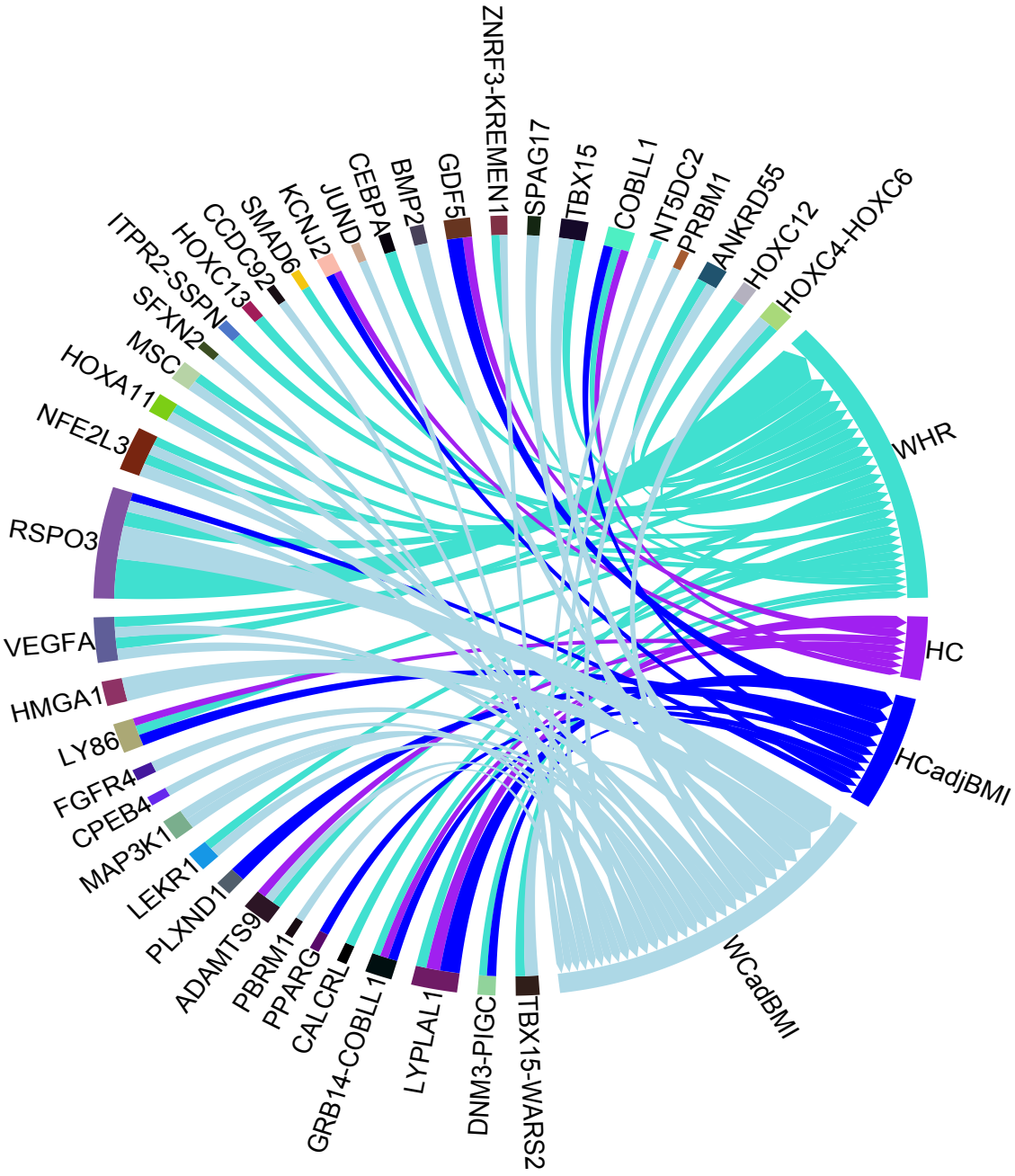
**Appendix 8.1** Genetic instruments for BMI and WHRadjBMI in high linkage disequilibrium within the same chromosomes*

| SNPS | Chromosome | D' | $R^2$ |
|---|---|---|---|
| **BMI** | | | |
| rs11583200 and rs657452 | 1 | 0.746 | 0.483 |
| rs3888190 and rs2650492 | 16 | 0.720 | 0.304 |
| **WHRadjBMI** | | | |
| rs1106529 and rs984222 | 1 | 0.904 | 0.488 |
| rs2645294 and rs1106529 | 1 | 0.965 | 0.465 |
| rs2645294 and rs984222 | 1 | 0.975 | 0.794 |
| rs714515 and rs1011731 | 1 | 1.000 | 1.000 |
| rs1128249 and rs10195252 | 2 | 1.000 | 0.911 |
| rs12692737 and rs10195252 | 2 | 0.973 | 0.729 |
| rs12692737 and rs1128249 | 2 | 0.974 | 0.802 |
| rs12692738 and rs10195252 | 2 | 1.000 | 0.403 |
| rs12692738 and rs1128249 | 2 | 1.000 | 0.442 |
| rs12692738 and rs12692737 | 2 | 1.000 | 0.523 |
| rs2371767 and rs6795735 | 3 | 1.000 | 0.495 |
| rs9687846 and rs3936510 | 5 | 1.000 | 0.968 |
| rs6861681 and rs7705502 | 5 | 1.000 | 1.000 |
| rs1294421 and rs1294410 | 6 | 1.000 | 0.934 |
| rs7759742 and rs2076529 | 6 | 0.945 | 0.586 |
| rs6905288 and rs998584 | 6 | 1.000 | 0.762 |
| rs1358980 and rs998584 | 6 | 0.977 | 0.854 |
| rs1358980 and rs6905288 | 6 | 0.973 | 0.646 |
| rs1936805 and rs11961815 | 6 | 0.956 | 0.304 |
| rs11961815 and rs9491696 | 6 | 0.747 | 0.207 |
| rs9491696 and rs1936805 | 6 | 1.000 | 0.896 |
| rs3902751 and rs10245353 | 7 | 1.000 | 0.780 |
| rs10245353 and rs1055144 | 7 | 1.000 | 1.000 |
| rs3902751 and rs1055144 | 7 | 1.000 | 0.780 |
| rs10842707 and rs718314 | 12 | 1.000 | 0.945 |
| rs10783615 and rs1443512 | 12 | 1.000 | 0.558 |
| rs4823006 and rs2294239 | 20 | 0.977 | 0.893 |

SNP=Single nucleotide polymorphism; BMI= Body-mass index; WHRadjBMI = Waist-to-hip ratio; LD= Linkage disequilibrium.

*The population-specific measures of linkage disequilibrium were calculated from 1000Genome Project (Phase 3, Version 5), using data from publicly available reference haplotypes of European populations (British). The linkage Disequilibrium statistics included: D prime (D') - an indicator of allelic segregation for two genetic variants, ranging from 0 to 1 with higher values indicating tight linkage of alleles and R squared ($R^2$) - a measure of correlation of alleles for two genetic variants. $R^2$ values range from 0 to 1 with higher values indicating a higher degree of correlation. $R^2$ is sensitive to allele frequency.

**Appendix 8.2** Pleiotropic effects of WHRadjBMI-associated SNPs on other adiposity phenotypes in GIANT




Lines represent associations between individual loci and each adiposity phenotype as reported in GIANT meta-analysis (Shungin *et al.,* 2015) . Lines were weighted by the reported effect size in GIANT. Labels correspond to the nearest identified gene of each single nucleotide polymorphism.

**Appendix 8.3** Power of genetic instruments to detect hazard ratios per SD genetically elevated adiposity trait, assuming 10 000 events and a type I error rate of 5%

| | Discovery population characteristics | | $R^2$ | Power (%) to detect hazard ratios for 1SD increasing adiposity of: | | | | |
|---|---|---|---|---|---|---|---|---|
| | Ancestry | Sample size | | 1.50 | 1.45 | 1.40 | 1.35 | 1.30 |
| 47-SNP GRS-WHRadjBMI | European | 210 088* | 0.76% | 69% | 63% | 54% | 45% | 36% |
| 34-SNP GRS-BMI (restricted) | European | 322 154† | 0.26% | 31% | 27% | 23% | 18% | 15% |
| 75-SNP GRS-BMI (unrestricted) | European | 322 154† | 1.51% | 94% | 89% | 83% | 74% | 62% |

SNP = Single Nucleotide Polymorphism. GRS= genetic risk score; BMI = body-mass index; WHRadjBMI = waist to hip ratio adjusted for BMI; SD= standard deviation. *From Shungin *et al.* (2015). †From Locke *et al.* (2015).