Adiposity Measures and Risk of Cardiovascular Disease

David Wormser

Hughes Hall

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This dissertation is submitted for the degree of Doctor of Philosophy

For my parents

SUMMARY

Background Despite several decades of research, the relevance of body fat and body fat distribution to the risk of cardiovascular disease remains unclear. This thesis aims to investigate associations of body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with risk of first-onset cardiovascular disease under a range of different circumstances.

Methods This thesis used individual records from the Emerging Risk Factors Collaboration to calculate risk ratios, and measures of discrimination and reclassification. 118 prospective studies, involving 1,064,541 participants without known history of cardiovascular disease, had information on BMI at baseline examination. 58 of these studies, involving 221,934 participants, had additional information on waist and hip circumference at baseline examination. Serial measurements made in 42,300 participants from 12 studies with concomitant information on these adiposity measures enabled quantification of within-person variability in BMI, WC and WHR.

Results Cross-sectional analyses demonstrated that although the correlations of adiposity measures differed with one another, BMI, WC and WHR were similarly and importantly associated with mediating cardiovascular risk factors, such as blood pressure, fasting glucose and lipids. Within-person variability was lower in BMI (regression dilution ratio: 0.96) than in WC (0.88) and WHR (0.66). The variability of adiposity measures was not materially influenced by several characteristics, although the variability of WHR varied somewhat by sex, diabetes status and baseline WHR values. 1,064,541 individuals with information on BMI recorded 161,903 deaths or non-fatal cardiovascular outcomes during 15.0 million person-years of follow-up. In analyses adjusted for age, sex and smoking status, BMI had positive and nearly $\log_e$-linear associations with coronary heart disease and ischaemic stroke (except at BMI values below 20 kg/m^2), which were largely explained by the intermediate risk factors noted above. The association between BMI and non-vascular mortality was curvilinear. Data on 221,934 individuals with complete information on weight, height, and waist and hip circumference (14,297 incident cardiovascular outcomes; 1.87 million person-years of follow-up) demonstrated that BMI, WC and WHR were substantially and similarly related to risk of coronary heart disease and ischaemic stroke. For cardiovascular risk prediction, additional information on BMI, WC or WHR to a prediction model containing conventional risk factors did not importantly improve risk discrimination, nor classification of participants to risk categories of predicted 10-year risk.

Conclusions BMI, WC and WHR are similarly associated with risk of cardiovascular disease, with much of the risk explained by intermediate risk factors. These clinical measures of adiposity do not importantly improve cardiovascular risk prediction when additional information is available on blood pressures, history of diabetes and lipids.

CONTENTS

Note: Relevant tables, figures and references are provided at the end of each chapter.

PREFACE

The aim of this thesis was to investigate in detail the association of clinical measures of adiposity, such as body-mass index, waist circumference and waist-to-hip ratio, with risk of cardiovascular disease. During my doctoral studies, I have also conducted research on adult stature and risk of cause-specific mortality and vascular morbidity, which is presented in the appendix.

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

ACKNOWLEDGMENTS

Although the work described in this dissertation is my own, it would not have been possible without the support and effort of a number of individuals. I would like to thank my primary supervisor, Dr Angela Wood, and co-supervisors, Professor John Danesh and Dr Stephen Kaptoge, who provided guidance and support throughout my PhD. Dr Angela Wood and Professor John Danesh provided comments on each chapter.

A number of other people have contributed to the work presented in this thesis, and their contributions are gratefully acknowledged. In particular, I would like to thank all members of the Cardiovascular Epidemiology Unit, especially Emanuele Di Angelantonio for his medical guidance, Pei Gao for her statistical support, and Matthew Walker and Sarah Watson for their data management support. Special thank also to Gary Whitlock, University of Oxford, for sharing his expertise on adiposity. I would also like to thank family and friends for their support and encouragement over the last three years.

Details are provided below of my role and the role of others in the analyses reported in each chapter of this thesis.

Chapter 1

I produced relevant tables and figures and drafted the text. Work published by other has been appropriately attributed. Sreenivasa Rao Kondapally Seshasai contributed to the section on the biological evidence linking adiposity with cardiovascular disease on pages 5-7. Parts of this chapter have been published previously (Wormser D, Seshasai SR, Ray KK. Obesity as a risk factor for cardiovascular disease. In: Purcell H, ed. *Non communicable chronic diseases, diabetes and obesity, a future clinical challenge*. London: National Services for Health Improvement; 2011). Reeta Gobin, Sreenivasa Rao Kondapally Seshasai and Kausik Ray commented helpfully.

Chapter 2

I conducted literature searches to identify relevant prospective studies with available data. I abstracted relevant study-level characteristics from published reports and wrote queries to resolve issues related to the individual-level data provided by each study. Data cleaning and additional query correspondence were done by Matthew Walker and Sarah Watson. A list of

collaborators who contributed individual data to the Emerging Risk Factors Collaboration (ERFC) is available at www.phpc.cam.ac.uk. I am a member of the ERFC coordinating centre. Professor John Danesh is the principal investigator of the ERFC. Parts of this chapter were previously published in *Eur J Epidemiol 2007*. Stephen Kaptoge commented helpfully.

Chapter 3

I wrote the analysis plan that prespecified the statistical analyses used, conducted all analyses, and drafted all tables, figures and text. Statistical methods of individual participant meta-analyses of cross-sectional correlates were developed by a team of statisticians and epidemiologists led by Stephen Kaptoge, and were previously published in *Am J Epidemiol 2007*. I used STATA programs written by Stephen Kaptoge and Philip Perry, making modifications to adapt to my analyses as required. Parts of this chapter were previously published in *Lancet 2011*, of which I am the first author. Stephen Kaptoge and Reeta Gobin commented helpfully.

Chapter 4

I devised analysis strategies to assess the within-person variability of adiposity measures, conducted the analyses, produced the relevant tables and figures, and drafted the text. Statistical methods for assessment of within-person variability in individual participant meta-analyses were developed by a team of statisticians and epidemiologists led by Angela Wood and Ian White. I wrote the STATA programs to conduct the analyses. Angela Wood developed the algebraic framework of within-person variability in ratios and provided statistical advice. Findings on within-person variability in adiposity measures have been previously published in *Lancet 2011*, of which I am the first author. Parts of this chapter (ie, the extent of within-person variability in calculated variables) is also being prepared for publication. Ian White and Simon Thompson contributed statistical expertise on within-person variation in ratios.

Chapter 5

I wrote the analysis plan, conducted the analysis, produced relevant tables and figures, and drafted the text. The statistical methods were developed by a team of statisticians and epidemiologists, including (in alphabetical order) Emanuele Di Angelantonio, John Danesh, Sebhat Erquo, Stephen Kaptoge, Sarah Lewington, Lisa Pennells, Philip Perry, Simon Thompson, Ian White and Angela Wood. I used STATA programs developed by Stephen Kaptoge and Philip Perry, making modifications to adapt to my analyses as required. I wrote

my own new STATA programs to conduct certain aspects of the analyses. Angela Wood, Stephen Kaptoge and Pei Gao provided statistical advice. Garry Whitlock and Naveed Sattar contributed expertise on investigations of body-mass index in the ERFC. Stephen Kaptoge and Emanuele Di Angelantonio commented helpfully.

Chapter 6

I wrote the analysis plan, conducted the analysis, produced relevant tables and figures, and drafted the text. The statistical methods were developed by a team of statisticians and epidemiologists. I used STATA programs developed by Stephen Kaptoge and Philip Perry, making modifications to adapt to my analyses as required. I wrote my own new STATA programs to conduct certain aspects of the analyses. Angela Wood, Stephen Kaptoge and Pei Gao provided statistical advice. Parts of this chapter were previously published in *Lancet 2011*, of which I am the first author. Jorge Kizer, Debbie Lawlor, Børge Nordestgaard, Paul Ridker, Veikko Salomaa, June Stevens, Mark Woodward, Naveed Sattar, Rory Collins and Gary Whitlock contributed expertise on investigations of adiposity measures in the ERFC. Emanuele Di Angelantonio, Stephen Kaptoge, Alex Thompson, Nadeem Sarwar and Simon Thompson commented helpfully.

Chapter 7

I wrote the analysis plan, conducted the analysis, produced relevant tables and figures, and drafted the text. Statistical methods for risk prediction in a multi-study setting were developed by a team of statisticians and epidemiologists led by Lisa Pennells, Angela Wood and Stephen Kaptoge. I used STATA programs developed by Stephen Kaptoge. Angela Wood, Stephen Kaptoge and Pei Gao provided statistical advice. Parts of this chapter were previously published in *Lancet 2011*, of which I am the first author. Jorge Kizer, Debbie Lawlor, Børge Nordestgaard, Paul Ridker, Veikko Salomaa, June Stevens, Mark Woodward, Naveed Sattar, Rory Collins and Gary Whitlock contributed expertise on investigations of adiposity measures in the ERFC. Emanuele Di Angelantonio, Stephen Kaptoge, Lisa Pennells, Alex Thompson, Nadeem Sarwar and Simon Thompson commented helpfully.

Chapter 8

I produced the relevant table and drafted the text. Preliminary analyses on adipocytokines and risk of coronary heart disease in the Reykjavik Study were performed by Nadeem Sarwar et al. Vilmundur Gudnason is the principal investigator of the Reykjavik Study.

Appendix 2

I conducted the analysis and produced the relevant table. With input from Angela Wood, I drafted the text. Ian White and Simon Thompson commented helpfully. This appendix, together with parts of **Chapter 4**, is being prepared for publication.

Appendix 3

I wrote the analysis plan, conducted the analysis, produced relevant tables and figures, and drafted the text. The statistical methods were developed by a team of statisticians and epidemiologists. I used STATA programs developed by Stephen Kaptoge and Philip Perry, making modifications to adapt to my analyses as required. I wrote my own new STATA programs to conduct certain aspects of the analyses. Angela Wood and Stephen Kaptoge provided statistical advice. Aaron Folsom, George Davey-Smith and Frank Hu contributed expertise on investigations of body stature in the ERFC. Stephen Kaptoge, Emanuele Di Angelantonio, Pei Gao and Adam Butterworth commented helpfully. This chapter is being prepared for publication and has therefore benefited from the feedback of the collaborating investigators.

List of abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
APCSC	Asia Pacific Cohort Studies Collaboration
Apo-AI	Apolipoprotein AI
Apo-B	Apolipoprotein B
BMI	Body-mass index
BRAVE	Bangladesh Risk of Acute Vascular Events
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DXA	Dual-Energy X-Ray Absorptiometry
EPIC	European Prospective Investigation into Cancer
ERFC	Emerging Risk Factors Collaboration
FEV_1	Forced expiratory volume in one second
HDL	High density lipoprotein
HR	Hazard ratio
ICAM	Intercellular adhesion molecule
IDI	Integrated discrimination improvement
IL	Interleukin
IQR	Inter-quartile range
LDL	Low density lipoprotein
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
MI	Myocardial infarction
NCICC	National Cancer Institute Cohort Consortium
NEFA	Non-esterified fatty acids
NRI	Net reclassification improvement
OR	Odds ratio
PAI	Plasminogen activator inhibitor
PHS	Physicians' Health Study
PROMIS	Pakistan Risk of Myocardial Infarction Study
PSC	Prospective Studies Collaboration
RDR	Regression dilution ratio
ROS	Reactive oxygen species
RR	Risk ratio
SBP	Systolic blood pressure
SD	Standard deviation
TNF	Tumour necrosis factor
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoprotein
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
WHS	Women's Health Study

CHAPTER 1: Introduction

Summary

Although the mortality rate of cardiovascular disease has decreased in many European countries and in North America during the past 50 years, cardiovascular disease is still the leading cause of death worldwide, responsible for over 17 million annual deaths. At the same time, there has been a dramatic increase in the prevalence of obesity, resulting in more than 1 billion overweight adults and 300 million obese worldwide. Excess body fat has been associated with metabolic perturbations and an increased risk of cardiovascular disease and other chronic diseases in numerous epidemiological studies. Although adiposity has been recognised as a major cardiovascular risk factor, the relative importance of overall adiposity versus body fat distribution is still unclear. Body-mass index (BMI) is an indirect measure of overall adiposity, while waist circumference (WC) and waist-to-hip ratio (WHR) are surrogates of abdominal adiposity. This thesis aims to characterise more reliably than has previously been possible the associations of BMI, WC and WHR with cardiovascular disease under a range of different circumstances through re-analysis of individual participant data from prospective observational studies. This chapter describes the biology of adiposity, reviews the current evidence on the relationship between clinical measures of adiposity and cardiovascular disease, and outlines the aims of the thesis.

Background

Despite the reduction in the cardiovascular mortality rate in many European countries and in North America in recent decades, cardiovascular disease is still the leading cause of death worldwide, including the UK.[1-3] According to World Health Organization estimates from 2004, about one third of all global deaths can be attributed to cardiovascular disease.[4] It is estimated that worldwide 7.2 million people die annually from coronary heart disease and 5.7 million people from stroke.[5] In the USA in 2007, one in every 2.9 deaths resulted directly from cardiovascular disease and one in every 6 deaths from coronary heart disease.[6] In the UK, cardiovascular disease accounted for almost 200,000 deaths in 2008. About half of these cardiovascular deaths were from coronary heart disease and more than a quarter were from stroke.[3] In the UK in 2008, the yearly overall costs of cardiovascular disease alone are estimated to be nearly £31 billion, including the direct costs of health care, indirect losses to productivity and other informal care costs.[3] Equivalent figures for the EU and the USA are around €169 billion and $287 billion, respectively.[6,7]

The objectives of this chapter are to describe the biology of adiposity, review the current evidence on the relationship between clinical measures of adiposity and cardiovascular disease, and outline the aims of the thesis.

Cardiovascular disease

The term *cardiovascular disease* embraces all disorders that affect the cardiovascular system, such as coronary heart disease, cerebrovascular disease/stroke, heart failure and other vascular diseases.[8] Most types of cardiovascular disease involve chronic pathologic processes that lead to acute outcomes, such as myocardial infarction or sudden cardiac death. Coronary heart disease, also called ischaemic heart disease or coronary artery disease, is the most common form of cardiovascular disease, and refers to a group of related syndromes resulting from myocardial ischemia – an imbalance between the capacity of the coronary vessels to supply sufficient blood flow and the myocardial oxygen demand.[8-10] The basic clinical manifestations of coronary heart disease are stable angina, acute coronary syndrome (including myocardial infarction and unstable angina), heart failure, arrhythmia and sudden cardiac death.[8-10] Stroke refers to an interruption of the blood supply to any part of the brain. Ischaemic stroke (the most common type) results from an obstruction in the blood vessels, while haemorrhagic stroke occurs when a weakened blood vessel ruptures and bleeds into the surrounding tissue.[11] Because of the complex anatomy of the brain and its vasculature, the

clinical manifestations of stroke are highly variable, but commonly include inability to move one or more limbs on one side of the body, or to understand or formulate speech.[12]

Both coronary heart disease and ischaemic stroke are almost always caused by atherosclerotic narrowing of arteries due to progressive accumulation of lipids and fibrous elements in lesions within the arterial wall (**Figure 1.1**).[10,13,14] Following endothelial damage or dysfunction, which may be stimulated by factors such as smoking and type II diabetes, low-density lipoprotein (LDL) cholesterol particles enter the arterial wall where they are oxidised by macrophages and smooth muscle cells. Additional mono-nuclear cells such as monocytes are attracted to the site of damage, where they engulf LDL cholesterol and become foam cells.[10,13,14] Accumulation of foam cells and proliferation of smooth muscle cells results in growth of the plaque. Apoptosis, matrix degradation and release of inflammatory mediators generate a vulnerable plaque with a thin fibrous cap and a lipid-rich core. If the cap ruptures, contact between core molecules and coagulation factors in the blood results in formation of a thrombus that can cause acute occlusion of the vessel.[13-16] Either progressive or acute occlusion of the artery may lead to impeded blood flow, ischaemia, and infarction of the cardiac or cerebral tissue.[10,13,14]

Risk factors for cardiovascular disease

Over the last 50 years, more than 300 risk factors have been correlated to the occurrence of coronary heart disease and stroke, although most of them are of uncertain causal relevance.[1] In addition to the known non-modifiable risk factors, such as age and family history of cardiovascular disease, epidemiological and other studies have indentified a range of modifiable cardiovascular risk factors, including smoking, diabetes, and elevated blood pressure and cholesterol levels.[17-20] Because of these insights, improved strategies for primary and secondary prevention, as well as prognosis and treatment regimes have been developed that have contributed to a reduction in cardiovascular morbidity and mortality in many countries.[21-25] However, these established risk factors do not entirely explain coronary heart disease incidence[26] and existing interventions do not entirely eliminate cardiovascular risk.[24,27,28]

Adiposity

Obesity or adiposity is generally defined as a condition of abnormal or excessive fat accumulation, which results in an impairment of physical or psychological health.[29,30] The World Health Organization criteria define overweight as a body-mass index (BMI) of at least 25 kg/m^2 and obesity as a BMI of at least 30 kg/m^2 (**Table 1.1**).[31] Over the past few decades, there has been a dramatic increase in the prevalence of obesity, resulting in more than 1 billion overweight adults and 300 million obese worldwide (**Figure 1.2**).[1,32,33] In the United States, the prevalence of obesity more than doubled between 1960 and 2004, rising from 15.0% to 31.1% in adult men and from 15.1% to 33.2% in adult women.[34,35] In 2007-2008, the prevalence of obesity was 32.2% among men and 35.5% among women.[36] In the majority of European countries, the proportion of obese individuals increased by about 10% to 40% in the last ten years.[31] Estimates of the prevalence of obesity vary considerably, ranging from 4.0% to 28.3% in men and from 6.2% to 36.5% in women.[37] The highest prevalences were observed in regions of Italy and Spain in both sexes, as well as in Portugal, Poland, the Czech Republic, Romania, and Albania in Women. The lowest prevalences were observed in regions of France and Austria. Overall, Western and Northern Europe showed a lower prevalence of obesity compared to Eastern Europe and Mediterranean countries (**Figure 1.3**).[37] England has observed a particularly dramatic increase in prevalence. The proportion of obese adults increased from 13.2% in 1993 to 23.7% in 2006 for men and from 16.4% in 1993 to 24.2% in 2006 for women.[38] In the UK, the yearly direct cost of overweight and obesity is estimated to be around £3.2 billion, representing around 5% of the costs of the National Health Service.[39] Equivalent figures for the USA are $61 billion.[40]

Excess body fat has been linked with cardiovascular disease and other chronic diseases in various epidemiological studies.[41] Obesity is a heterogeneous disorder that is closely associated with metabolic perturbations. It impacts unfavourably on the prevalence of cardiovascular risk factors, such as impaired glucose tolerance, type II diabetes, hypertension, and dyslipidemia – all important contributors to the processes underlying the development of atherosclerosis.[42,43] Adipose tissue in the abdominal region, particularly in the visceral area, has been suggested to be an important risk factor for a range of metabolic abnormalities, which impact cardiovascular morbidity and mortality.[44-47] In light of the epidemiological evidence, the American Heart Association and the American Diabetes Association have called for action and have reclassified obesity as a major modifiable risk factor.[48-50]

Biological evidence linking adiposity with cardiovascular disease

Current understanding of the biology of adipose tissue suggests that this is not merely a repository for excess body fat but, instead, a dynamic organ involved in various metabolic processes capable of affecting several organs and physiological systems in the body. There is increasing evidence to suggest that the adverse effects of excess body fat are mediated through the interplay of several factors (**Figure 1.4**) including: increases in the fat mass *per se*, its pattern of distribution and the physiological consequences thereof; alterations in lipid metabolism; insulin resistance; inflammation; activation of the coagulation cascade; endocrine and paracrine effects of adipose tissue; increased oxidative stress; and the co-occurrence of other cardiovascular risk factors with obesity.[51,52]

An increased whole body fat mass, in particular abdominal fat, has been linked to increased fat content of the liver and the deposition of fat in ectopic areas such as the heart, blood vessels and the kidneys, resulting in impaired function of these organs due either to mechanical effects or to the intracellular deposition of lipids and consequent cellular damage (lipotoxicity).[51,52] This is particularly important in peripheral vessels where periadventitial fat deposition has been shown to increase arterial stiffness – a phenomenon compounded by the release of growth factors from adipose cells which leads to vascular smooth muscle cell growth.[51] Adiposity also results in increased cardiac output, increased peripheral vascular resistance, increased effort of breathing and reduced functional reserve volume of the lung with important cardio-respiratory consequences.[52] In Pickwickian syndrome (seen in severe obesity) there is, additionally, a restrictive type of lung defect with hypoventilation.

However, perhaps even more important than the mechanical consequences of obesity are the physiological and metabolic perturbations it causes. Obesity, in particular visceral adiposity, leads to several qualitative and quantitative changes in lipid metabolism, a phenomenon compounded by the close proximity of abdominal fat to the liver. The increased lipolytic state of obesity is responsible for the delivery of large amounts of non-esterified fatty acids (NEFAs) to the liver where they are converted to triglyceride-rich very low density lipoprotein (VLDL) particles and, by the action of cholesteryl ester transfer protein (CETP), to triglyceride-rich LDL cholesterol particles. CETP activity is upregulated in obesity, as is hepatic lipase activity. By contrast, lipoprotein lipase (LPL) enzyme activity is reduced. The net result of these changes is the characteristic dyslipidemia of obesity: increased VLDL, triacylglycerols, triglyceride and small dense LDL particles and decreased high density lipoprotein (HDL) concentrations.[51]

Small dense LDL particles are highly atherogenic due to their ability to penetrate endothelial fenestrations and reach the subendothelial spaces where they are taken up by the macrophage scavenger receptor (rather than LDL receptor) setting off a series of events that lead to the development of atherosclerotic plaques.[43,51] Furthermore, an increased production of reactive oxygen species (ROS) in obesity leads to the oxidation of LDL particles (ox-LDL) that are in turn taken up by macrophages of the arterial wall, also contributing to atheroma formation.[51] In addition to these direct proatherogenic effects of obesity, there are several indirect effects of the dyslipidemic state. For instance, increased NEFA levels impair endothelium-dependent vasodilation (as a consequence of reduced endothelial nitric oxide production), increase myocardial stress (through increased oxygen demand of cardiomyocytes and an impairment in their contractile function), and contribute to the insulin-resistant state of adiposity.[51] On the other hand, reduced HDL-cholesterol levels along with reduced HDL particle size have been shown *in vitro* to be less efficient in reducing oxidative stress.[43] Thus, both direct and indirect effects of lipid dysregulation may be responsible for the atherosclerosis and vascular complications of obesity.

One of the principal consequences of excess body fat (especially abdominal fat) is the development of insulin resistance and related metabolic effects. Insulin resistance in the liver and peripheral tissues results in glucose intolerance, excess production of NEFAs, increased production of small dense LDL and reduced clearance of apolipoprotein-B and triacylglycerol-rich lipoproteins, as well as delayed clearance of VLDL.[51] As described earlier, small dense LDL particles are highly atherogenic and, together with other abnormalities characteristic of insulin resistance syndromes, contribute to the excess burden of atherosclerosis in obesity. Besides, insulin resistance has also been shown to cause direct injury to cardiomyocytes leading to reduced glucose uptake and impaired contractile function thereof.[51] Additionally, insulin resistance is also associated with the release of several adipocytokines, which have important biological effects (see below).

In addition to fat cells (adipocytes), which constitute the major cell type, adipose tissue is also composed of macrophages, fibroblasts and other cells which appear in increased proportions in obesity. These cells produce cytokines, inflammatory mediators and procoagulant substances which are closely linked to the atherosclerotic process. Some of these molecules (like TNF-α, IL-1β and IL-6) stimulate the liver to generate additional bioactive substances including: (a) inflammatory markers (e.g. IL-8, IL-10, IL-15, complement factors B, D, C3, and

C-reactive protein [CRP]); (b) procoagulant substances (e.g. PAI-1, P-selectin, VCAM-1, ICAM-1, fibrinogen, tissue factor, von Willebrand factor and factor VII); (c) adipocytokines; and (d) vasoactive substances (e.g. angiotensinogen).[43,51,53] Increased circulating levels of some of these markers (such as TNF-α and IL-6) are associated with insulin resistance, increased CRP production and stimulation of the hypothalamic-pituitary-adrenal axis and, in combination with increased clotting factor levels and fibrinogen levels as well as decreased fibrinolysis, result in vascular injury and atherothrombosis.[53]

As stated previously, adipose tissue exerts endocrine and paracrine functions through the production of several adipocytokines. In obese individuals, increased levels of *leptin*, a molecule which influences food intake and energy expenditure, have been implicated in insulin resistance, atherogenesis, increased platelet aggregation and vascular thrombosis.[51] Raised leptin levels also activate the central sympathoregulatory pathways resulting in hypertension and vascular damage.[43,53] Leptin may also play a role in vascular calcification – a marker of coronary atherosclerosis.[51] Whilst adiposity leads to increased leptin levels, it produces an opposite effect on adiponectin concentrations. Adiponectin has been associated with several beneficial effects such as improvements in insulin sensitivity of the liver and peripheral organs,[51,53] anti-inflammatory effects, inhibition of the expression of intercellular adhesion molecules such as ICAM-1, VCAM-1 and E-selectin, and inhibition of foam cell formation within the atheroma as a result of inhibition of MMP enzyme activity.[51] Thus, reduced levels of adiponectin in obesity result in an increased propensity for atherothrombosis. Other biologically important mediators secreted in increased amounts in obesity include visfatin, angiotensinogen, ACE, angiotensin II and VEGF.[43,51,53] *Visfatin* is correlated with visceral fat depots and is believed to exert insulin-mimetic functions and promote adipogenesis.[51] Angiotensinogen, ACE and angiotensin II exert a vasoconstrictive influence on the vascular smooth muscle whilst VEGF promotes vascular smooth muscle cell proliferation and growth, resulting in vasculopathy and hypertension.[43,51,53]

An important consequence of the aforementioned phenomena related to adiposity is the development of other co-morbid conditions like type II diabetes and hypertension among overweight and obese individuals. Insulin resistance, activation of the renin-angiotensin system and sympathetic nervous system, decreased endothelium-dependent vasoreactivity and further augmentation of arterial thickness by VEGF are amongst the factors incriminated in the development of these additional cardiovascular risk factors in obesity.

Measurement of adiposity

Various methods exist for accurate measurement of the amount and distribution of body fat. Traditional methods, such as underwater weighing (densitometry) and isotope dilution (hydrometry), calculate body composition based on a two-compartment model that divides body weight into fat mass and fat-free mass.[54] Multi-compartment models that directly measure bone mineral, fat, protein and other components provide more accurate measurement of body composition.[54] For instance, the Dual-Energy X-Ray Absorptiometry (DXA) is a frequently used technique to estimate body composition in clinical studies.[55] It provides accurate measurements of the three components (fat mass, fat-free mass and bone mineral density) for the whole body, as well as for specific body regions. Imaging methods are considered the most accurate technique for measuring body composition and ascertaining fat distribution at the tissue-organ level.[56] Computer tomography and magnetic resonance imaging produce high-resolution images of selected tissue and organs to accurately quantify percentage body fat, and visceral and subcutaneous fat.[57] Although these techniques are highly reproducible and accurate, they are very expensive and time consuming and therefore may not currently suitable for clinical settings and most large-scale epidemiological studies (although UK Biobank, a prospective study of 500,000 people, may be an exception). For this reason, most studies measure weight, height and other anthropometric variables to assess amount and distribution of body fat. The following two sections discuss the properties of BMI, waist circumference (WC) and waist-to-hip ratio (WHR).

Body-mass index

BMI, defined as the ratio of weight in kilograms to the square of height in metres, represents a simple, but crude index that is widely used to indirectly estimate overall or general adiposity (without taking into account fat distribution). Overall adiposity has been generally expressed as a percentage of body fat (100×fat mass/total mass).[58] The validity of BMI has been demonstrated by various studies, as BMI correlates with percentage body fat that was assessed by superior techniques.[59-61] BMI values are considered age and sex independent.[31] BMI is recommended as the most useful epidemiological measure of obesity by the World Health Organization.[31] Their guidelines define BMI between 18.5 and 24.9 kg/m^2 as normal, 25 kg/m^2 or higher as overweight and 30 kg/m^2 or higher as obese (**Table 1.1**).[31]

Although BMI correlates well with body fat and predicts cardiovascular outcomes, the measure itself has some major limitations. BMI cannot distinguish between fat mass and lean (fat-free) mass, leading to potentially substantial differences in percentages of fat mass between individuals with similar BMI.[31,57] BMI values do not correspond to the same degree of fatness across the different populations because of ethnic variation in body composition. For instance, the percentage of body fat tends to be higher in whites than in blacks for a given BMI. Studies have shown that, although black individuals generally have higher BMI values compared with white individuals, the percentage of body fat as assessed by DXA is similar in blacks and whites.[59,62] By contrast, the percentage of body fat is generally higher in Asian than in Caucasian populations for a given BMI.[63] Asians have been shown to be at increased risk of type II diabetes and cardiovascular disease at BMI values lower than the existing World Health Organization cut-off point for overweight (ie, ≥25 kg/m^2).[64] However, because there were no clear cut-points for overweight and obesity in all Asian populations, the World Health Organization expert consultation decided not to lower the BMI cut-points for Asians.[64] Moreover, for a given BMI, body fat varies considerably between men and women.[59,65,66] Because men develop more lean body mass, especially bone mass and skeletal muscle, the percentage of body fat is generally higher in women than in men for the same BMI.[57,67] Also, BMI estimates lose reliability in persons of extreme heights and with very muscular builds.[29] Among older individuals, body fat estimated by BMI can be considerably erroneous due to some increase in fat mass and substantial loss of lean body mass during the aging process.[58,59,68,69] Thus, the interpretation of BMI as a measure of body fatness among an elderly population may be even more complex.

Waist circumference and waist-to-hip ratio

Location of body fat or body fat distribution has been recognised to be associated with several obesity-related diseases.[70] There is growing evidence that android obesity (ie, excess fat mass in the upper part of the body, such as the abdomen) is more strongly linked with metabolic abnormalities, which could subsequently lead to cardiovascular disease, than gynecoid obesity (ie, fat accumulation in the lower part of the body, such as the hips and thighs).[57,71,72] Particularly, visceral adipose tissue in the abdominal region is believed to be more metabolically active than other fat depots, such as abdominal subcutaneous fat.[73]

Waist circumference (WC) and waist-to-hip ratio (WHR; defined as the ratio of circumference in waist to hip), are indirect measures of fat mass in the abdominal or central body region. Although these measures take into account body fat distribution and have been validated, they have been criticised for failing to distinguish between abdominal visceral fat and abdominal subcutaneous fat.[47,57,73-75] WC is commonly measured at the midpoint between the lowest rib margin and the iliac crest, at the level of the umbilicus, or at the narrowest WC.[76] Hip circumference is typically measured at the maximal circumference over the buttocks.[57] While the interpretation of WC is straightforward (ie, WC is simply a proxy of abdominal fat), the interpretation of WHR is a bit more complex. Higher values of WHR can be due to both increased abdominal fat mass (ie, reflected in higher WC) and/or reduced gluteofemoral muscle or fat mass (ie, reflected in lower hip circumference).[57,73] Because the risk associated with particular values of WC or WHR differs across ethnic populations and sex, no cut-points are available globally.[31]

Epidemiological evidence linking adiposity with cardiovascular disease

Overall adiposity and cardiovascular risk

Several key publications in recent years have reported on the association between overall adiposity, as measured by BMI, and risk of cardiovascular disease. These large-scale observational studies have varied considerably with regard to their study design and participant characteristics, and used different methodologies to collate data. The INTERHEART study, the largest multinational case-control study of acute myocardial infarction to date which involved data on approximately 12,000 cases and 15,000 controls from 52 countries, reported modest and graded associations between BMI and myocardial infarction.[46] These relations, however, disappeared after adjusting for potential confounders (such as smoking, physical activity, alcohol consumption, diet and psychosocial factors) and potential mediating risk factors (such as apolipoprotein-AI and -B, hypertension and diabetes). Since results based on case-control studies, however robust they may be, have inherent limitations such as biases due to selection bias and reverse causality, findings from prospective study designs are generally considered more informative. Data from the prospective Physicians' Health Study (PHS),[77] involving 16,332 men and 1,505 cardiovascular events, and the Women's Health Study (WHS),[77] involving 32,700 women and 414 cardiovascular events, showed that higher BMI levels are generally associated with an increased risk of cardiovascular disease, even after controlling for several potential confounders, such as age, smoking, physical activity, ethnicity, alcohol

consumption and family history.[A] A systematic review of prospective cohort studies reporting on the association between BMI and coronary heart disease risk has shown both positive and J-shaped associations (ie, the risk being greatest at the extremes of BMI with a graded, non-linear increase in risk above the optimum) between BMI and risk of coronary heart disease.[78] Among the larger studies included in this review, the average increase in coronary heart disease risk for each 2 kg/m^2 higher BMI was 14%.

Although systematic reviews and literature-based meta-analyses offer useful summary data on various exposure-disease associations, they have some limitations (**Chapter 1** on page 14). Individual participant data meta-analyses overcome these deficiencies by pooling subject-level data from various studies and by applying uniform methods for their analyses. For example, the Asia Pacific Cohort Studies Collaboration (APCSC) pooled data from 33 cohort studies from the Asia-Pacific region with information on 310,000 participants and 3,332 stroke and 2,073 coronary events.[79] Age, sex and smoking adjusted findings of the APCSC have shown a continuous, positive and significant association between baseline BMI and risk of ischaemic stroke, haemorrhagic stroke and coronary heart disease, with each 2 kg/m^2 lower level of BMI associated with a 12% (95% confidence interval [CI] 9% to 5%) lower risk of ischaemic stroke, 8% (95% CI 4% to 12%) lower risk in haemorrhagic stroke and 11% (95% CI 9% to 13%) lower risk of coronary heart disease. More recently, the Asia Cohort Consortium BMI Project, a collaboration with more than 1.1 million participants from 19 cohorts in Asia, showed that underweight in Asians was associated with a substantially increased risk of death, including death from cardiovascular disease.[80] The Prospective Studies Collaboration (PSC) investigated the association between BMI and cause-specific mortality, by pooling primary data from 57 prospective studies with 900,000 participants from Western populations.[41] After controlling for age, sex and smoking status, BMI and death from coronary heart disease were positively and strongly associated throughout the BMI range from 20 to 40 kg/m^2. In the BMI range 25 to 50 kg/m^2, each 5 kg/m^2 higher baseline BMI level was associated with about 40% higher risk of death from coronary heart disease, while in the lower BMI range (15 to 25 kg/m^2) each 5 kg/m^2 higher baseline BMI level was associated with about 22% higher risk of death

[A] PHS and WHS are sex-specific prospective cohort studies. Compared to the reference category (22.5 to 24.9 kg/m^2), the adjusted relative risk for cardiovascular disease for men in PHS was 0.83 (95% CI 0.55-1.24) in the lowest BMI category (BMI<20 kg/m^2) and 2.12 (95% CI 1.36-3.30) in the highest BMI category (BMI ≥35 kg/m^2).[77] Corresponding relative risk ratios in the WHS were 0.89 (95% CI 0.54-1.02) in the lowest BMI category and 2.11 (95% CI 1.46-3.05) the highest BMI category.[77]

from coronary heart disease. In this study, the optimal BMI range as regards stroke mortality was between 22.5 and 25 kg/m^2. As for coronary heart disease, each 5 kg/m^2 higher BMI level in the higher BMI range (25 to 50 kg/m^2) was associated with about 40% increase in stroke mortality. Despite a positive relationship between BMI and systolic blood pressure across all values, there was no evidence of a positive association between BMI and stroke in the lower BMI range (15 to 25 kg/m^2). The flattening of the association with stroke mortality at lower BMI values was not removed after excluding participants who had ever smoked. A large meta-analysis with individual records from 388,622 individuals from 26 Western cohort studies with 18,000 coronary events, demonstrated that the adverse affects of adiposity are partially mediated by blood pressure and cholesterol levels.[81] The relative risk for coronary heart disease per 5 kg/m^2 higher baseline BMI reduced from 1.29 (95% CI 1.22-1.35), after adjustment for age, sex, smoking status and physical activity, to 1.16 (95% CI 1.11-1.21) after further adjustment for baseline values of systolic blood pressure and total cholesterol. Because it lacked information on diabetes, other lipids and inflammatory markers, however, this study could not investigate whether the effect of BMI on coronary heart disease is independent from such intermediate risk factors.

Overall versus abdominal obesity

Although recent studies have shown that abdominal adiposity, as measured by WC or WHR, may be even more important in determining cardiovascular risk rather than overall obesity, these findings, however, have been inconsistent. **Table 1.2** summarises the key features of prospective studies that reported on the association between overall adiposity (as assessed by BMI) and abdominal adiposity (as assessed by WC or WHR) with cardiovascular disease. 19 prospective cohort studies[77,82-99] and one meta-analysis,[100] involving individual participant data from essentially general populations (ie, participants not selected on the basis of having cardiovascular or other chronic disease at baseline examination), reported adjusted associations between different measures of adiposity and cardiovascular risk. Overall, these findings show that central or abdominal adiposity is an important indicator of cardiovascular risk. For instance, the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk), involving more than 2,300 incident coronary heart disease cases in almost 23,000 participants, reported adjusted relative risk estimates of 1.83 (95% CI 1.37-1.93) in men and 2.20 (95%CI 1.67-2.90) in women, when comparing people in the upper versus lower quintiles of baseline WHR.[83] When similar comparisons were made for BMI, the corresponding relative risks were 1.63 (95% CI 1.38-1.91) for men and 1.73 (95% CI 1.37-2.20) for women. By

contrast, the PHS reported somewhat stronger associations with BMI than with WHR.[77] Compared to the reference category (22.5 to 24.9 kg/m^2), the relative risk for cardiovascular disease after adjusting for several confounders was 2.25 (95% CI 1.36-3.30) in the highest BMI category. Corresponding estimates for WHR were 1.64 (95% CI 1.07-2.52), when compared to the reference category (0.89 to <0.94). Similar findings were observed in the WHS.[77] The 10-country EPIC prospective study, a European prospective study involving 350,000 participants and 15,000 deaths (of which the aforementioned EPIC-Norfolk study was a part) showed that both general and abdominal adiposity are associated with the risk of death, including cardiovascular disease.[89]

By comparison, WHR in the INTERHEART study showed a strong continuous positive association with acute myocardial infarction.[46] The odds ratios with increasing WHR quintile were greater than the odds ratios associated with increasing BMI quintiles. Because the associations with WHR and WC remained significant even after adjustment for various cardiovascular risk factors (while BMI became non-significant), the authors suggested that abdominal adiposity, as assessed by WHR or WC, may act through biological mechanisms that differ from known risk factors. However, powerful examination of the associations of BMI, WC and WHR with such possible intermediate risk factors is currently lacking, making it difficult to understand the biological pathways underlying these associations. After adjustment for age, sex and geographical region, odds ratios per one standard deviation higher baseline WHR and WC were 1.37 (95% CI 1.34-1.41) and 1.19 (95% CI 1.16-1.22), respectively. The corresponding odds ratio for one standard deviation higher baseline BMI was 1.10 (95% CI 1.07-1.13).

In summary, there is no conclusive evidence on whether clinical measures of abdominal adiposity are more strongly associated with cardiovascular outcomes than is BMI, a measure of overall adiposity. These uncertainties may explain why national and international guideline statements have provided differing recommendations about the value of assessment of clinical measures of adiposity for prediction of cardiovascular disease in primary prevention.[101] Recommendations range from omission of adiposity measures to their inclusion as additional screening tests to their formal inclusion as risk factors in prediction models. For example, whereas the World Health Organization[31] and the US National Heart, Lung and Blood Institute[102] recommend BMI measurement as well as assessment of WC in people with a BMI between 25.0 and 34.9 kg/m^2, several commonly-used cardiovascular risk scores omit

adiposity measures (eg, Framingham, SCORE, PROCAM, Reynolds), but others include BMI (eg, QRISK).[103]

Individual participant data meta-analysis

Meta-analysis is a statistical tool that combines results from similar studies in order to provide a pooled estimate. This technique can reduce bias, enhance precision, reduce exaggeration, assess consistency of results and help prioritise research.[104] Literature-based meta-analysis does this by pooling aggregated data from published studies of similar methodology and quality. However, this method has several potential important shortcomings. It cannot provide (i) precise analyses of risk marker-disease associations under a range of different circumstances (including assessment of any interactions); (ii) reliable characterisation of the shape of exposure-risk relationship; (iii) consistent approaches to adjustment for confounding factors; or (iv) detailed investigation of heterogeneity by both study and individual-level characteristics. These limitations can be overcome by performing an individual participant data meta-analysis, in which individual data from relevant studies are combined and re-analysed in order to obtain a reliable estimate of the associations between exposure and disease outcome. This method has several advantages, including the following: ability to adjust in a consistent manner for common potential confounders across the separate studies, ability to explore heterogeneity by both individual and study-level characteristics, ability to investigate hypotheses not addressed in the original publication, ability to include non-published information, ability to extend and update follow-up information, and ability to check and harmonise data from different sources and, thus, to use common outcome and exposure definitions.[105-107] Individual participant meta-analyses are, therefore, considered the gold standard of systematic review.

Thesis outline

The aims of this thesis are: (i) to assess precisely any lifestyle and biological correlates of BMI, WC and WHR; (ii) to determine the long-term within-person variability in BMI, WC and WHR; (iii) to characterise in detail the association of BMI with risk of first-ever vascular disease and cause-specific mortality (including investigation of the shape of any dose-response relationships; assessment of the role of confounders and biological mediators; exploration of potential sources of diversity); (iv) to characterise (and compare) in detail the associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke in participants

with concomitant information on weight, height, and waist and hip circumference, and (v) to investigate the ability of BMI, WC and WHR to predict cardiovascular disease.

Chapter 2 describes the methods used to establish the Emerging Risk Factors Collaboration (ERFC), an individual participant meta-analysis with data from up to 121 prospective epidemiological studies of cardiovascular disease. It also describes the design of the analysis in the ERFC focused on the 118 studies with information on BMI only (**Chapter 5** is based on data from this subset) and the 58 studies with concomitant information on BMI, WC and WHR (**Chapters 3, 4, 6** and **7** are based on data from this subset). **Chapter 3** reports the cross-sectional correlates of BMI, WC and WHR with several conventional cardiovascular risk factors and other characteristics recorded in the ERFC. **Chapter 4** reports on the long-term within-person variability of BMI, WC and WHR using data on serial measurements available in the ERFC. **Chapter 5** reports on shape, magnitude, specificity and mediation of associations of BMI with future risk of coronary heart disease, stroke and cause-specific mortality in the ERFC. **Chapter 6** reports on shape, magnitude, specificity and mediation of associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke. **Chapter 7** reports on the incremental predictive ability of BMI, WC and WHR for cardiovascular risk prediction. **Chapter 8** summarises the findings of the thesis, discusses strengths and limitations, and makes suggestions for future work. **Appendix 1** lists the publications I have authored during my doctoral studies. **Appendix 2** describes the rationale for using for some of the statistical analyses conducted. **Appendix 3** reports findings from a research project on adult height and risk of vascular disease and death, undertaken during my doctoral studies. **Appendix 4** lists the acronyms of the studies contributing to the ERFC.

Chapter 1 – References

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Table 1.1 Classification of adult underweight, overweight and obesity according to body-mass index (BMI)

Classification	BMI (kg/m^2)
Underweight	**<18.5**
Severe thinness	<16.00
Moderate thinness	16.00-16.99
Mild thinness	17.00-18.49
Normal range	**18.50-24.99**
Overweight	**≥25.00**
Pre-obese	25.00-29.99
Obese	**≥30.00**
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	≥40.00

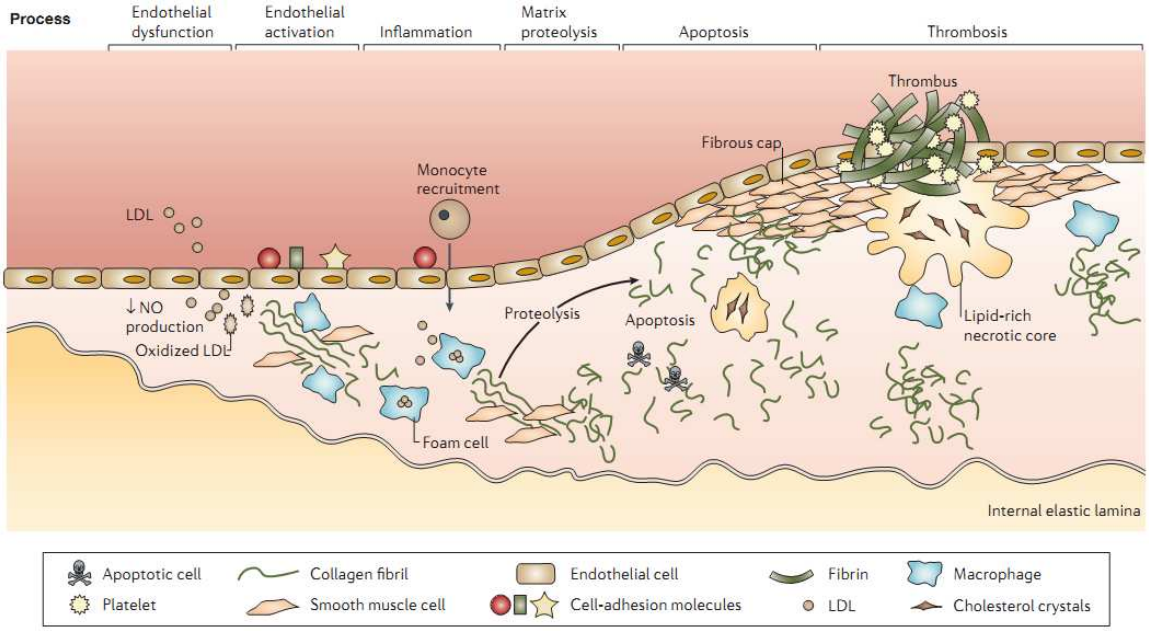
Source: World Health Organization Consultation of Obesity. Obesity: Preventing and Managing the Global Epidemic. Division of Non-communicable Disease. 2000. Geneva, World Health Organization.

Table 1.2 Prospective studies reporting cardiovascular risks with BMI, WC and WHR in approximately general populations

Study	Author, Year of publication (Reference)	Location	Endpoint	No of participants	No of events	Follow-up (years)	Direction of associations			Comments
							BMI	WC	WHR	
Thailand	Aekplakorn et al., 2007 (80)	Thailand	CHD death, nonfatal MI	2 536	66	17	↑	↑	→	Similar associations for WC and BMI
APCSC	Asia Pacific Cohort Studies Collaboration, 2006 (98)	Asia & Australia	CHD death, nonfatal MI	45 988	601	6	↑	↑↑	↑↑	Similar associations for WC and WHR
EPIC-Norfolk	Canoy et al., 2007 (81)	UK	CHD death, nonfatal MI	22591	2600	9.1	↑	↑↑	↑↑	Similar associations for WC and WHR
ARIC	Folsom et al., 1998 (82)	US	CHD death, nonfatal MI	14 040	398	6.2	↑	NA	↑↑	Associations with WHR were particularly stronger in women
PHS	Gelber et al., 2008 (75)	US	CVD death, nonfatal MI, nonfatal ischaemic stroke	16 332	1505	14.2	↑↑	↑↑	↑	Similar associations for WC and BMI
WHS	Gelber et al., 2008 (75)	US	CVD death, nonfatal MI, nonfatal ischaemic stroke	32 700	414	5.5	↑↑	↑↑	↑	Similar associations for WC and BMI
PRIME	Gruson et al., 2009 (83)	France/Northern Ireland	CHD death, nonfatal MI	10 602	659	10	↑	↑↑	↑↑	Similar associations for WC and WHR
KIHD	Lakka et al., 2002 (84)	Finland	CHD death, nonfatal MI	1 346	123	10.6	↑	↑	↑	Similar associations for all three adiposity measures
BWHHS	Lawlor et al., 2006 (85)	UK	CHD death, nonfatal MI	3589	194	4.4	↑	↑↑	↑↑	Similar associations for WC and WHR
EPIC	Pischon et al., 2008 (87)	Europe	CVD	359 387	3443	9.7	↑	↑	↑	All three measures were associated with CVD, although no direct comparison was done
GOTO13	Larsson et al., 1984 (88)	Sweden	CHD death, nonfatal MI	792	91	13	→	NA	↑	
GOTOW	Lapidus et al., 1984 (86)	Europe	CHD death, nonfatal MI	1462	73	12	↑	↑↑	↑↑	Similar associations for WC and WHR
MDC	Li et al., 2006 (89)	Sweden	CHD deaths, nonfatal MI and ischaemic stroke	27007	1100	7	(↑)↑↑*	NA	(↑↑)↑*	Analyses were stratified by sex
IWHS	Prineas et al., 1993 (90)	US	CHD death	32 898	115	4	↑	↑↑	↑↑	Similar associations for WC and WHR
NHS	Rexrode et al., 1998 (91)	US	CHD death, nonfatal MI	44 702	320	8	NA	↑	↑	Similar associations for WC and WHR
HPFS	Rimm et al., 1995 (92)	US	CHD death, nonfatal MI, CAS	29 122	420	3	↑↑	NA	↑	
Finland	Silventoinen at al., 2003 (93)	Finland	CHD death, nonfatal MI	11 510	386	-	→	→	→	
HBS	Terry et al., 1992 (94)	US	CHD death	84 910	1347	23	↑	NA	↑	Similar associations for BMI and WHR
ARFPS	Welborn et al. 2003 (95)	Australia	CVD death	9 206	81	11	→	↑↑	↑↑	Similar associations for WC and WHR
WLH	Yang et al., 2008 (96)	Sweden	CHD death, nonfatal MI	48 052	256	12	↑	↑↑	↑↑	Similar associations for WC and WHR
SWHS	Zhang et al., 2004 (97)	China	CHD death, nonfatal MI	67 334	70	2.5	↑	↑↑	↑↑	Similar associations for WC and WHR

Key: ↑, study reported positive association; ↑↑, study reported stronger positive association compared to that of other adiposity measure(s); →, study reported no significant association; APCSC, Asia Pacific Cohort Studies Collaboration; ARFPS, Australian Risk Factor Prevalence Study; ARIC, Atherosclerosis Risk in Communities Study; BMI, body-mass index; BWHHS, British Women's Heart and Health Study; CAS, coronary artery surgery; CHD, coronary heart disease; EPIC, European Prospective Investigation Into Cancer and Nutrition; GOTO43, Gothenburg Study 1943; GOTOW, Population Study of Women in Gothenburg; HBS, Harvard Build Study; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women's Health Study; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; MDC, Malmo Diet and Cancer; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physicians' Health Study; PRIME, Prospective Epidemiological Study of Myocardial Infarction; SWHS, Shanghai Women's Health Study; WHR, waist-to-hip ratio; WLH, Women's Lifestyle and Health Cohort Study; WHS, Women's Health Study; NA, not available.
*Associations of WHR are stronger in women, while association of BMI stronger in men.

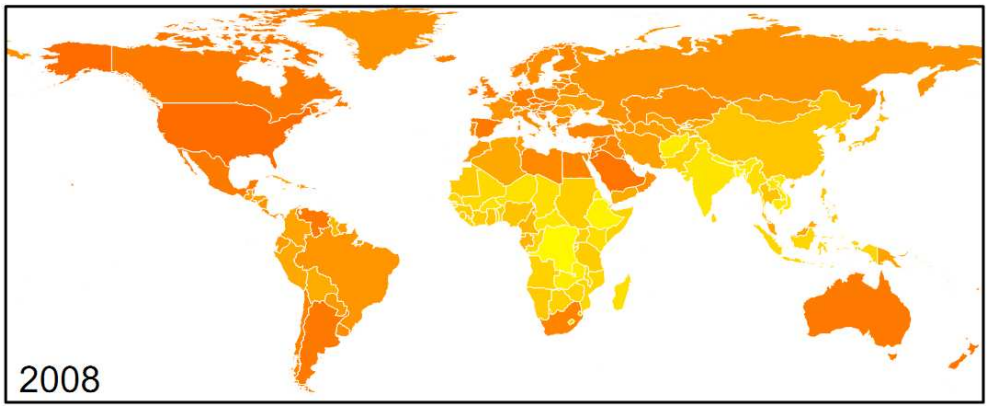
Figure 1.1 Plaque formation during atherosclerosis



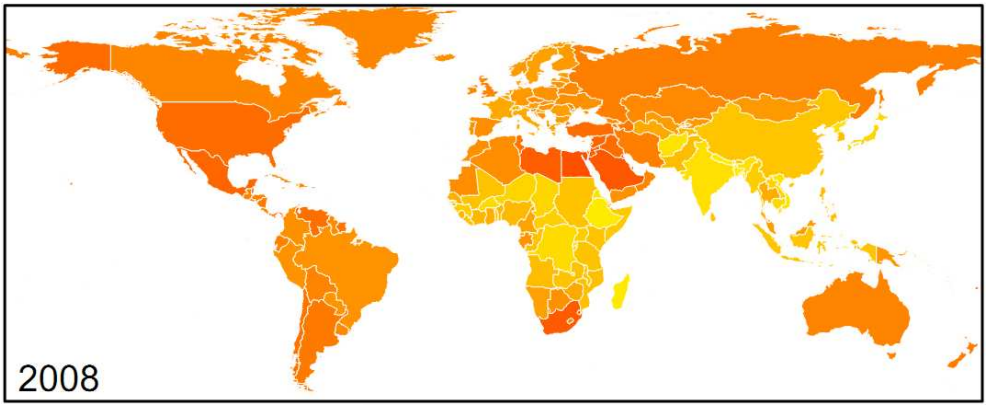
Source: Watkins H et al. *Nat Rev Genet*. 2006;7(3):163-173

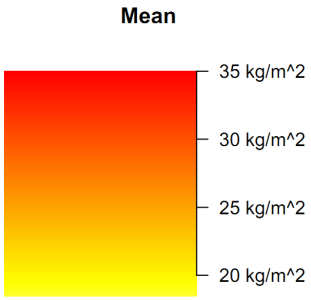
Figure 1.2 Age-standardised mean BMI values in men (panel A) and in women (panel B) worldwide in 2008

(A) Men



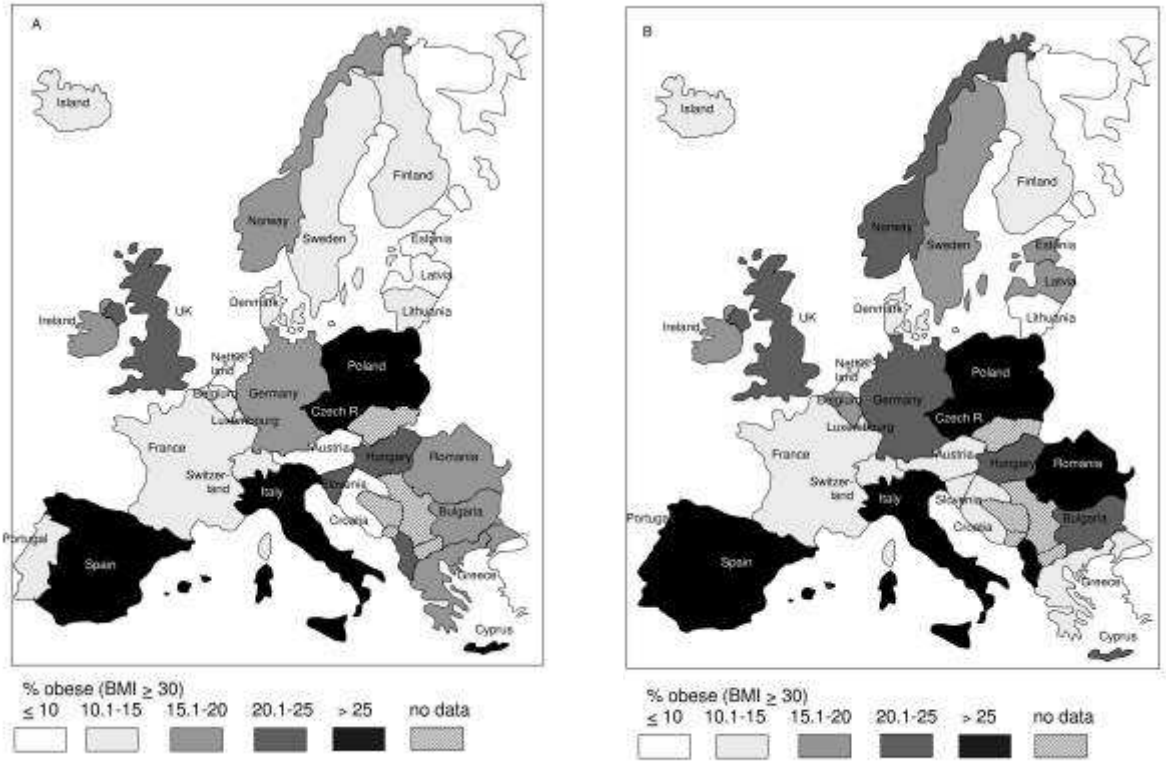
(B) Women





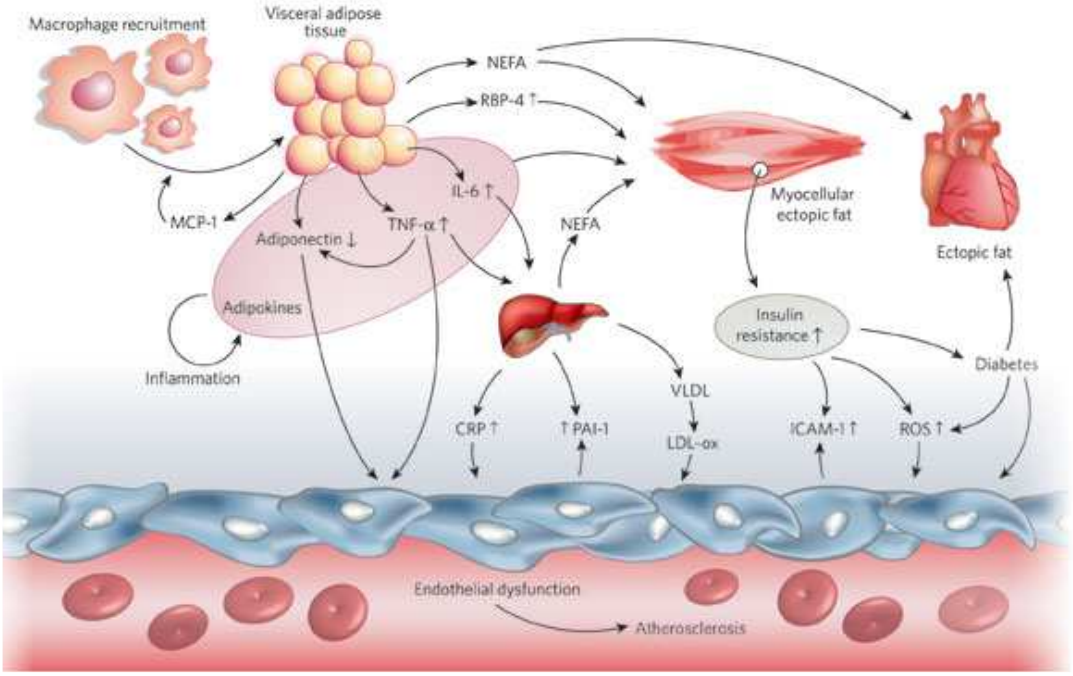
Source: Finucane et al. *Lancet* 2011;377:557-567

Figure 1.3 Regional variation in prevalence of obesity (BMI ≥30 kg/m^2) in men (panel A) and women (panel B) in Europe



Source: Berghöfer et al. *BMC Public Health*. 2008;8:200

Figure 1.4 Interplay between visceral adipose tissue and other pathways in the pathogenesis of atherosclerotic vascular disease



Source: Van Gaal et al. *Nature*. 2006;444:875

CHAPTER 2: The Emerging Risk Factors Collaboration

Summary

The Emerging Risk Factors Collaboration (ERFC) is an individual participant data meta-analysis of 121 prospective studies with information on lipid, inflammatory and/or metabolic markers, other established risk factors and characteristics, as well as major cardiovascular morbidity and/or cause-specific mortality. This chapter describes the methods used to establish the ERFC, and the data available for analyses on clinical measures of adiposity. 118 studies, involving more than 1 million participants with no known history of cardiovascular disease, had information on body-mass index, age and sex at baseline examination. 58 of these studies, involving more than 220,000 participants, had additional information on waist and hip circumference at baseline examination. Analysis of individual data from these studies in a meta-analysis should help to characterise more reliably and precisely than previously possible the association of adiposity measures with vascular and non-vascular outcomes under a range of different circumstances.

Background

Many prospective observational studies have reported on the associations between clinical measures of adiposity and subsequent risk of coronary heart disease and/or other cardiovascular outcomes.[1-24] However, individual studies have generally not been large enough to reliably characterise important features of these associations, including (i) reliably characterising the shape of any dose-response relationship; (ii) precisely estimating the magnitude of risk marker-disease association; or (iii) quantifying any potential variation of the association by levels of various relevant characteristics, such as by age groups or sex. Literature-based meta-analyses are primarily based on published data and, as described in **Chapter 1** on page 14, have some important limitations.

Re-analysis of individual data from a comprehensive set of relevant prospective studies can help to overcome the limitations of individual studies and literature-base meta-analyses. The Emerging Risk Factors Collaboration (ERFC) was set up to facilitate detailed evaluation of the association of emerging and established risk factors with cardiovascular disease. By October 2010, it involved individual participant data on over 1.3 million participants from 121 cohorts in predominantly Western populations (**Figure 2.1**).[3,5,8,14,25-112] The ERFC builds on and complements two existing collaborative meta-analyses of individual data from prospective studies of cardiovascular disease. The Prospective Studies Collaboration (PSC) consists of approximately 1 million participants from 61 cohort studies.[113] It is also based on studies from predominantly Western populations and thus, involves a number of the same cohorts as in the ERFC. But, whereas the ERFC collected data on lipid, inflammatory and metabolic markers and recorded both major cardiovascular morbidity and cause-specific mortality, the PSC focused principally on blood pressure,[114] total cholesterol[115] and body-mass index (BMI)[116] (without any information on abdominal adiposity, ie, waist and hip circumference) in relation to cause-specific mortality. The Asia Pacific Cohort Studies Collaboration (APCSC), involving 44 cohorts with 600,000 participants from mostly East Asian populations, recorded data on lipids and other markers in relation to cardiovascular morbidity and mortality.[117] However, as the APCSC involves mostly East-Asian participants who tend to have much lower incidence of coronary heart disease than Western participants, it has so far recorded only a small fraction of the incident coronary outcomes available in either the ERFC or the PSC. As the ERFC, the APCSC collected information on both overall and abdominal adiposity.[21] Because body composition differs between Western and East-Asian populations, however, findings from the APCSC may not be generalisable to Western individuals.[118] The overlap between these three

collaborations is small. Whereas approximately 20% of the data in the ERFC overlap with the PSC, there is virtually none between the ERFC and the APCSC.

This chapter presents the objectives of the ERFC, the methods of study identification, data collection and study management, a brief overview of the statistical methods, and a summary of the available data on adiposity measures. The majority of the information presented has previously been published as a protocol for the ERFC.[119]

Objectives of the Emerging Risk Factors Collaboration

The primary objectives of the collaboration were: (i) to assess, in people without known cardiovascular disease at baseline examination, the age and sex-specific associations of major lipids (ie, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol, and triglyceride), inflammatory markers (eg, C-reactive protein [CRP]) and other risk cardiovascular risk factors (eg, adiposity measures or diabetes) in relation to first-ever confirmed non-fatal myocardial infarction or coronary death, before and after taking into account within-person variability; (ii) to determine to what extent any associations with coronary heart disease are independent of possible confounding factors; (iii) to assess any joint effects (ie, effect modification) with established and emerging risk factors; (iv) to determine any incremental predictive value of these markers for cardiovascular disease, either separately or in combination, beyond that provided by established risk factors; and (v) to enable detailed exploration of potential sources of heterogeneity for each marker, involving both study-level characteristics (such as geographical region or study design) and individual-level characteristics (such as age, sex and levels of several established risk factors). Secondary objectives included: (i) investigating associations of these markers in relation to other vascular and non-vascular conditions; (ii) examining the cross-sectional correlates of these markers; and (iii) quantifying long-term within-person variability for each marker over time.

Identification of relevant studies and collection of data

Selection criteria and identification of studies

The initial focus of the collaboration was on circulating lipid markers (such as triglyceride, LDL and HDL cholesterol, lipoprotein(a) [Lp(a)] and apolipoprotein-AI and -B) and circulating markers of inflammation (such as CRP, albumin and leukocyte count). In 2009, the ERFC agreed to extend the collaboration to analyses to adiposity and other metabolic markers in relation to vascular disease and cause-specific morality.. Studies with information on relevant

markers were identified either in previously published meta-analyses, with additional studies indentified through updated computer-assisted literature searches of databases, scanning of reference lists, hand-searching of relevant journals and correspondence with authors of relevant studies. Prospective studies (reported variously as observational cohort studies, trials or analyses of nested case-control studies or case-cohort subsets) were eligible to participate in the ERFC if the following criteria were met: (i) data were available from baseline for at least one of the relevant markers; (ii) at least one year of follow-up; (iii) participants were selected from population-based samples (ie, were not selected on the basis of having previous cardiovascular diseases); and (iv) information on cause-specific mortality and/or major cardiovascular morbidity was collected during follow-up. Studies were prioritised for inclusion if they were known to have recorded at least 20,000 person-years at risk. Studies with data on adiposity measures were prioritised for inclusion if information on anthropometric indicators was measured by a trained person rather than self-reported. All, except two of the contacted studies agreed to provide data on adiposity measures to the ERFC.

Baseline covariates and characteristics recorded

Data were sought from investigators for each individual on lipids, inflammatory and metabolic markers and other characteristics recorded at the baseline survey and at any subsequent surveys during follow-up to enable study-specific correction for regression dilution.[120,121] **Table 2.1** lists the core variables that were sought (where available) from the initial baseline examination. Information on categorical variables, such as alcohol consumption status, physical activity and smoking status, has been systematically re-coded to maximise comparability amongst studies. Similarly, data from all subsequent resurvey examination were sought. Collection of data on sex, age at baseline and at the disease event (or at last follow-up) enabled age and sex-specific analyses. Data have been collected on features of study design (eg, population sampling framework, geographical location: **Tables 2.2-2.3**), blood storage and handling conditions, and measurement methods (eg, methods to assess waist and hip circumference: **Table 2.4**) used to help to characterise baseline evidence of coronary disease.

Outcome studied

For each individual, data have been sought on any of the following outcomes and their dates of occurrence: non-fatal coronary heart disease; non-fatal stroke; cause-specific mortality (or at least occurrence of fatal coronary heart disease and fatal stroke) and other cardiovascular outcomes. Precise details of the diagnostic criteria used for the definition of cases were sought

from each study (as were data on the completeness of follow-up in the prospective studies). Analyses were based on events classified according to codings from the *International Classification of Diseases* to at least three digits (outcome definitions are provided in **Table 2.5**) or, when unavailable, on study-specific classification systems. Attribution of death refers to the primary cause provided (or in its absence, the underlying cause provided) on death certificates. Non-fatal events that occurred on the same day were ranked as described in **Table 2.6**, and only the highest ranked event contributed to the primary analysis.

Data transfer and checking

Data were transferred from the individual studies to the coordinating centre using machine-readable formats convenient to the collaborator(s). Data were accepted in whatever format they were originally coded and stored by the study investigators. The data obtained from each participating study have been checked for internal consistency by the coordinating centre and any queries referred back, in confidence, to the study collaborator(s). Data were converted to a standard format for incorporation into a central database to be used for combined analyses. The content of the data were unchanged by this process, and computer-generated detailed summary tabulations based on the converted data were returned to each collaborator for review and confirmation. **Figure 2.2** describes the steps involved in data sharing, checking and ratification.

Study management

Confidentiality of data provided

The data provided from each study remain entirely the property of the principal investors of that study, and were held in strict confidence by the coordinating centre. Anonymous data on individual participants in each of the studies were stored securely on the computer database at the coordinating centre. The database at the coordinating centre is protected by two firewalls and a password-entry system accessible only to designated staff working under the supervision of the study coordinator. Only the coordinating centre has direct access to the combined dataset, and investigators retain the right to withdraw their data from some or all of the meta-analyses.

Ethical approval

The ERFC was approved by the Cambridge Ethics Review Committee (Cambridgeshire, UK). In addition, each of the studies included has previously received local institutional review board approval and consent from participants.

Statistical methods

Details of the statistical analyses have been published.[122] Briefly, the principal analyses adopted by the ERFC involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random effects meta-analysis. Most of these study-specific estimates were based on Cox proportional-hazards regression models, stratified, where appropriate, by sex and trial arm. Detailed descriptions of relevant statistical methods are provided in **Chapter 3** (cross-sectional correlates), **Chapter 4** (within-person variability), **Chapters 5-6** (associations with disease risk) and **Chapter 7** (risk prediction).

Summary of data available

Summary of data available on body-mass index

By October 2010, 121 prospective studies of cardiovascular disease, involving 1.3 million participants, had shared individual records. 118 of these studies, involving 1,064,541 participants, had information at baseline on weight and height (hence BMI), after exclusion of participants with known history of cardiovascular disease (ie, myocardial infarction, angina, stroke or other cardiovascular events) at initial ("baseline") examination (**Figure 2.3**). Three studies participating in the ERFC were not included in the BMI analysis because they did not have information on BMI at baseline survey,[123] had no follow-up time,[124] or a prior history of disease.[31] Overall, the mean (SD) age at baseline was 55 (9) years. 560,793 (53%) participants were male, 686,407 (64%) were from studies based in Europe, 321,840 (30%) from North America, 32,630 (3%) from Japan, 17,322 (2%) from Australia and 6,342 (1%) from the Caribbean (**Table 2.2**). Median year of baseline survey was 1986 (IQR 1977-1992). After excluding implausible BMI values (ie, the 18 participants with BMI above 100 kg/m^2), the overall distribution of BMI was approximately normal with mean (SD) of 26 kg/m^2 (4.1). Most studies sampled participants from population registers (eg, general practitioner lists, electoral roll lists) or in workplaces (**Table 2.2**). For 856,633 (80%) of the participants, height and weight were measured using standardised protocols; for the remainder, height and weight were self-reported (**Table 2.2**). Concomitant information was available on BMI, age, sex, smoking status

(current versus not current), systolic blood pressure (SBP), history of diabetes (yes versus no), and total cholesterol in 572,114 participants from 101 studies. 306,371 participants from 76 studies had additional information on HDL cholesterol and triglyceride. Repeat measurements were available on a total of 354,564 participants from 66 studies. 79 of the 118 contributing studies involved medical records, autopsy findings and other supplementary sources. 77 studies used definitions of myocardial infarction based on World Health Organization criteria. 58 studies reported diagnosis of strokes on the basis of brain imaging, and attributed stroke subtype.

Available data on body-mass index, waist circumference and waist-to-hip ratio

Fifty-eight[3,5,8,14,28,29,32,33,35,36,38-42,45,50,51,53-55,57,59,61-63,66,69-73,78,80,81,85,90,93-95,97,98,100,101,105,107,108,108] of the 118 studies, involving 221,934 participants without known history of cardiovascular disease at initial baseline examination, also had data on waist and hip circumference at baseline (**Figure 2.3**). The dataset was restricted to participants with concomitant information on weight, height and waist and hip circumference to allow direct comparisons between BMI, waist circumference (WC) and waist-to-hip ratio (WHR). 155,938 (70%) of these participants also had data on smoking status, SBP, history of diabetes, and total and HDL cholesterol. Resurvey data were available on 42,300 participants from 12 studies with concomitant information on weight and height, and waist and hip circumference at baseline examination and at resurvey. 43 of the 58 contributing studies involved medical records, autopsy findings and other supplementary sources to help classify deaths. 50 studies used definitions of myocardial infarction based on World Health Organization criteria. 43 studies reported diagnosis of strokes on the basis of brain imaging, and attributed stroke subtype. Four studies[14,45,62,108] provided self-reported height and weight and three studies[14,62,108] reported self-reported waist and hip circumference (**Table 2.4**). Weight and height was generally measured with participants dressed in light clothes and no shoes (**Table 2.4**). A majority of studies measured waist circumference either at the midway between lower rib margin and the iliac crest or at the umbilical level. Hip circumference was generally measured at the maximum circumference over the buttocks (**Table 2.4**). Mean (SD) age of participants at baseline was 58 (9) years, 97,745 (44%) were men, 129,326 (58%) were in Europe, 73,707 (33%) were in North America, 9,204 (4%) were in Australia and 9,697 were in Japan (**Table 2.3**). Median year of baseline survey was 1994 (IQR 1991-1998). After excluding participants with implausible adiposity values (ie, the 12 participants with BMI values above 100 kg/m^2, WC values above 250 cm or WHR values above 2.5), adiposity measures in the 58 studies were approximately normally

distributed (mean [SD]: 27 kg/m^2 [4.56] for BMI, 91 cm [12.6] for WC and 0.90 [0.083] for WHR), with higher WC and WHR values in men than in women (**Figure 2.4**). The distributions of adiposity measures were broadly similar across studies (**Figure 2.5**).

Conclusion

The ERFC is a collaboration of prospective studies that have recorded information on adiposity measures and other cardiovascular risk markers, as well as on cardiovascular morbidity and/or cause-specific mortality. Over 1 million people in 118 studies without known cardiovascular disease at baseline had complete information on baseline BMI, age and sex. 58 of the 118 studies, involving more than 220,000 participants, had additional information on baseline waist and hip circumference. Analysis of individual data from these studies in a meta-analysis should help to characterise more reliably and precisely than previously possible the association of adiposity measures with vascular and non-vascular outcomes under a range of different circumstances.

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Table 2.1 List of core variables sought in the Emerging Risk Factors Collaboration

From baseline examination

- Date of baseline survey
- A unique (but anonymous) identifier
- Date of birth (or age at baseline) and sex
- A unique identifier for case-control matched sets for studies in which controls are 'individually matched' to cases

Baseline survey (biochemistry, clinical measurements etc. made at the initial examination)

- Ethnicity
- Smoking and alcohol use (current / ex / never; amount / duration etc.)
- Use of cardiovascular medications (current and past use, in as much detail as possible, including anti-hypertensive drugs, 'statins', fibrates) and other medications (e.g. hypoglycemic agents, hormone replacement therapy) – also, treatment allocation made in randomized controlled trials
- Use of postmenopausal hormone therapy or oral contraceptives
- Prior history of coronary heart disease (in particular myocardial infarction and angina), stroke, transient ischemic attack (TIA), peripheral vascular disease (PVD) and diabetes
- Systolic and diastolic blood pressure
- Weight, height, waist and hip circumference
- Physical activity and socio-economic status
- Total, high- and low-density lipoprotein cholesterol (including particle size and numbers, where available); triglycerides; lipoprotein (a); apolipoprotein-AI and -B (including information about fasting status at time blood samples were taken); lipoprotein-associated phospholipase A_2 mass and activity levels
- Inflammatory markers (including C-reactive protein, fibrinogen, albumin, interleukin-6 and the leucocyte count)
- Creatinine, uric acid
- Haemostatic factors (including von-Willebrand factor, fibrin D-dimer)
- Metabolic factors (including fasting glucose, post load glucose, glycosylated hemoglobin and insulin)

From re-survey examinations

- The unique (but anonymous) identifier used for baseline visit
- Date of the visit (or, if not available, age at visit)
- Data on baseline items that were collected at repeat surveys (particularly established risk factors and other biochemical markers)

Non-fatal events during follow-up

- Myocardial infarction and date of MI
- Stroke (including subtype if available: e.g. ischaemic / haemorrhagic) and date of stroke
- Other subsidiary cardiovascular outcomes: e.g. angina, PVD, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PCTA), congestive heart failure
- Dates of censoring for end of follow-up for non-fatal events

Fatal events during follow-up

- Date last known to be alive (if not recorded as dead)
- Date of death (or, if not available, age at death)
- Underlying cause of death (preferably coded according to some specified version of the three-digit International Classification of Diseases (ICD); but if a three-digit ICD code is not available then whatever code the study already uses)
- Date of censoring for end of follow-up for fatal cases

Table 2.2 Some baseline characteristics of 118 prospective studies providing information on BMI to the ERFC

Study abbreviation	Country	Year(s) of baseline survey	Population source	Sampling	Measurement of height and weight	Total subjects	BMI (kg/m^2) mean (sd)	Age at survey (yrs) mean (sd)	Male (%)
Cohort studies									
AMORIS	Sweden	1987-1991	Screening	Complete	Assessed	58082	25 (4)	46 (10)	33334 (57)
ARIC	USA	1987-189	Households	Random	Assessed	14600	28 (5)	54 (6)	6302 (43)
ATENA[b]	Italy	1994-1996	General population	Random	Assessed	4741	27 (4)	50 (7)	0 (0)
ATS_SAR[c]	Italy	1983-1984	Combination or other	Complete & random	Assessed	4263	27 (5)	46 (8)	2065 (48)
ATTICA	Greek	2001	General population	Random	Assessed	1577	27 (4)	51 (11)	808 (51)
AUSDIAB	Australia	1999-2000	NR	NR	Assessed	9260	27 (5)	53 (13)	4110 (44)
BHS	Australia	1969-1978	Electoral rolls	Complete	Assessed	5992	25 (4)	45 (16)	2829 (47)
BRHS	UK	1978-1979	GP/Health service lists	Random	Assessed	6809	25 (3)	50 (6)	6809 (100)
BRUN	Italy	1990	General population	Random	Assessed	817	25 (4)	58 (11)	398 (49)
BUPA	UK	1976-1980	GP/Health service lists	Complete	Assessed	20885	25 (3)	47 (8)	20885 (100)
BWHHS	UK	1999-2000	General population	Random	Assessed	2796	27 (5)	68 (5)	0 (0)
CAPS	UK	1980-1982	Electoral rolls	Random	Assessed	2133	26 (4)	52 (5)	2133 (100)
CASTEL	Italy	1983-1985	Screening	Complete	Assessed	2499	26 (4)	73 (5)	951 (38)
CHARL	USA	1960-1961	Households	Random	Assessed	2031	25 (5)	50 (11)	952 (47)
CHS1[a]	USA	1989-1990	GP/Health service lists	Random	Assessed	3883	26 (5)	72 (5)	1491 (38)
CHS2[a]	USA	1993	GP/Health service lists	Random	Assessed	482	29 (5)	72 (5)	181 (38)
COPEN	Denmark	1992-1993	General population	Random	Assessed	8186	26 (4)	58 (15)	3508 (43)
DISCO[c]	Italy	1984-1987	Combination or other	Complete & random	Assessed	1923	28 (5)	50 (11)	843 (44)
DRECE	Spain	1991	General population	Random	Assessed	2819	26 (5)	41 (11)	1357 (48)
DUBBO	Australia	1988-1989	Electoral rolls	Complete	Assessed	2070	26 (4)	68 (7)	866 (42)
EAS	Scotland	1987-1988	GP/Health service lists	Random	Assessed	1036	25 (4)	64 (6)	515 (50)
EMOFRI[b]	Italy	1995-1996	General population	Complete	Assessed	360	26 (4)	55 (6)	176 (49)
EPESEBOS	USA	1988-1989	General population	Complete	Self-reported	757	27 (5)	77 (4)	263 (35)
EPESEIOW	USA	1988	General population	Random	Assessed	1225	27 (5)	78 (5)	368 (30)
EPESENCA	USA	1992-1993	General population	Random	Self-reported	1017	27 (5)	77 (5)	337 (33)
EPESENHA	USA	1988	General population	Complete	Self-reported	593	26 (4)	78 (5)	228 (38)
ESTHER	Germany	2001	GP list	Complete	Assessed	8160	28 (4)	62 (7)	3447 (42)
FINE_FIN	Finland	1989	Combination or other	Complete	Assessed	275	26 (4)	77 (5)	275 (100)
FINE_IT	Italy	1985	General population	Random	Assessed	461	26 (4)	72 (4)	461 (100)
FINRISK92	Finland	1992	General population	Random	Assessed	5279	26 (4)	46 (10)	2448 (46)
FINRISK97	Finland	1997	General population	Complete & random	Assessed	6395	27 (4)	51 (11)	3170 (50)
FRAMOFF	USA	1992-1993	General population	Complete	Assessed	3399	27 (5)	54 (10)	1547 (46)
GOH	Israel	1970-1971	General population	Random	Assessed	5558	25 (4)	43 (8)	2693 (48)
GOTO13	Sweden	1967	General population	Complete	Assessed	765	25 (3)	54 (2)	765 (100)
GOTO33	Sweden	1984	General population	Complete	Assessed	733	26 (3)	51 (0)	733 (100)
GOTO43	Sweden	1993	General population	Complete	Assessed	773	26 (3)	50 (0)	773 (100)
GOTOW	Sweden	1969	General population	Random	Assessed	1425	24 (4)	47 (6)	0 (0)
GREPCO[c]	Italy	1980	Combination or other	Complete & random	Assessed	794	25 (4)	44 (8)	0 (0)
GRIPS	Germany	1982	Occupational	Complete	Assessed	5785	26 (3)	48 (5)	5785 (100)
GUBBIO[c]	Italy	1983-1985	Combination or other	Complete & random	Assessed	3408	27 (4)	55 (13)	1515 (44)
HBS	Finland	1986	Occupational	NR	Assessed	1300	26 (3)	60 (4)	1300 (100)
HELSINAG	Finland	1989	General population	Random	Assessed	424	25 (4)	79 (4)	108 (25)
HISAYAMA	Japan	1988	General population	Complete	Assessed	2575	23 (3)	59 (12)	1087 (42)
HONOL	USA	1991-1992	GP/Health service lists	Complete	Assessed	2523	23 (3)	78 (4)	2523 (100)
HOORN	Netherlands	1990-1991	General population	Random	Assessed	2230	27 (4)	61 (7)	982 (44)
HPFS	USA	1986	Occupational	Complete	Self-reported	47788	26 (3)	54 (10)	47788 (100)
IKNS	Japan	1990-1992	Screening	Complete	Assessed	8047	23 (3)	58 (10)	3302 (41)
ISRAEL	Israel	1963	Occupational	Complete	Assessed	7702	25 (3)	49 (7)	7702 (100)
KARELIA	Finland	1972	General population	Random	Assessed	10784	26 (4)	41 (10)	5199 (48)
LASA	Netherlands	1992-1993	General population	Random	Assessed	1856	27 (4)	69 (9)	839 (45)
MALMO	Sweden	1978-1983	Screening	Random	Assessed	32483	25 (4)	46 (7)	21913 (67)
MATISS83[b]	Italy	1983-1984	General population	Random	Assessed	2562	28 (4)	51 (10)	1202 (47)
MATISS87[b]	Italy	1986-1987	General population	Random	Assessed	2116	29 (5)	52 (10)	937 (44)
MATISS93[b]	Italy	1993-1995	General population	Random	Assessed	1215	28 (5)	49 (9)	588 (48)
MCVDRFP	Netherlands	1988-1990	General population	Random	Assessed	23169	25 (4)	42 (10)	10727 (46)
MESA	USA	2001	General population	Random	Assessed	6768	28 (5)	62 (10)	3190 (47)
MICOL[c]	Italy	1985-1986	Combination or other	Complete & random	Assessed	19394	26 (4)	51 (10)	10859 (56)
MOGERAUG1	Germany	1984-1985	General population	Random	Assessed	871	28 (3)	54 (6)	871 (100)
MOGERAUG2	Germany	1989-1990	General population	Random	Assessed	3963	27 (4)	53 (12)	1949 (49)
MOGERAUG3	Germany	1997-1995	General population	Random	Assessed	3373	28 (4)	55 (10)	1664 (49)
MONFRI86[b]	Italy	1986	General population	Random	Assessed	1408	27 (4)	49 (9)	691 (49)
MONFRI89[b]	Italy	1989	General population	Random	Assessed	1344	26 (4)	49 (8)	666 (50)
MONFRI94[b]	Italy	1994	General population	Random	Assessed	1294	26 (4)	49 (8)	630 (49)
MONICA[c]	Italy	1983-1986	Combination or other	NR	Assessed	3661	27 (4)	49 (9)	1830 (50)
MORGEN	Netherlands	1994-1996	General population	Random	Assessed	17736	26 (4)	46 (9)	8060 (45)
MOSWEGOT	Sweden	1986-1994	General population	Random	Assessed	4158	25 (4)	47 (11)	1974 (47)

Table 2.2 cont'd Some baseline characteristics of 118 prospective studies providing information on BMI to the ERFC

Study abbreviation	Country	Year(s) of baseline survey	Population source	Sampling	Measurement of height and weight	Total subjects	BMI (kg/m^2) mean (sd)	Age at survey (yrs) mean (sd)	Male (%)
MRCOLD	UK	1996-1997	GP/Health service lists	Complete	Assessed	10145	26 (4)	80 (4)	3825 (38)
NCS1	Norway	1976-1977	General population	Complete	Assessed	24199	25 (4)	42 (4)	11914 (49)
NCS2	Norway	1975	General population	Complete	Assessed	13056	25 (3)	42 (4)	6654 (51)
NCS3	Norway	1974	General population	Complete	Assessed	10029	25 (4)	42 (4)	5203 (52)
NFR[c]	Italy	1980	Combination or other	Complete & random	Assessed	3088	26 (3)	55 (5)	3088 (100)
NHANESI	USA	1972-1973	General population	Cluster	Assessed	9356	26 (5)	50 (16)	3646 (39)
NHANESIII	USA	1990	General population	Cluster	Assessed	12436	27 (5)	54 (16)	5754 (46)
NHS	USA	1976	Occupational	Complete	Self-reported	118622	24 (4)	43 (7)	0 (0)
NPHSI	UK	1974-1977	Occupational	Complete	Assessed	1389	25 (3)	52 (7)	1389 (100)
NPHSII	UK	1990-1991	GP/Health service lists	Complete	Assessed	2964	26 (4)	57 (3)	2964 (100)
NSHS	Canada	1995	GP/Health service lists	Random	Assessed	1612	27 (6)	54 (15)	768 (48)
OB43[c]	Italy	1984	Combination or other	Complete & random	Assessed	3611	27 (4)	47 (8)	1735 (48)
OSAKA	Japan	1991-1994	Combination or other	NR	Assessed	12398	23 (3)	52 (10)	8430 (68)
OSLO	Norway	1972-1973	General population	Complete & random	Assessed	17253	25 (3)	44 (6)	17253 (100)
OYABE	Japan	1988	Screening	Complete	Assessed	5087	23 (3)	57 (11)	1567 (31)
PARIS1	France	1968-1971	Occupational	Complete	Assessed	7072	26 (3)	47 (2)	7072 (100)
PREVEND	Netherlands	1997-1998	NR	NR	Assessed	7387	26 (4)	50 (12)	3589 (49)
PRHHP	Caribbean	1966-1968	General population	Complete	Assessed	6342	25 (4)	54 (6)	6342 (100)
PRIME	France / NI	1992-1993	General population	Quota	Assessed	9581	27 (3)	55 (3)	9581 (100)
PROCAM	Germany	1981-1986	Occupational	Complete	Assessed	20163	26 (4)	44 (10)	14603 (72)
QUEBEC	Canada	1985	General population	Random	Assessed	967	26 (4)	56 (7)	967 (100)
RANCHO	USA	1984-1985	Households	Complete	Assessed	1785	25 (4)	68 (11)	739 (41)
REYK	Iceland	1970-1980	General population	Complete	Assessed	16771	25 (4)	52 (9)	8037 (48)
RF2[c]	Italy	1978	Combination or other	Complete & random	Assessed	5431	26 (4)	44 (9)	2549 (47)
ROTT	Netherlands	1991-1993	General population	Complete	Assessed	4750	26 (4)	68 (8)	1801 (38)
SHHEC	UK	1986-1989	GP/Health service lists	Random	Assessed	13529	26 (4)	49 (8)	6585 (49)
SHS	USA	1990-1991	General population	Complete	Assessed	4145	31 (6)	56 (8)	1620 (39)
SPEED	UK	1979-1981	GP/Health service lists	Complete	Assessed	2123	26 (3)	55 (4)	2123 (100)
TARFS	Turkey	1990-1998	Households	Random	Assessed	3383	27 (5)	46 (13)	1680 (50)
TOYAMA	Japan	1996	Occupational	NR	Assessed	4523	23 (3)	46 (7)	2907 (64)
TROMSØ	Norway	1986-1994	Households	Complete	Assessed	22037	24 (4)	43 (14)	10414 (47)
ULSAM	Sweden	1971-1972	General population	Complete	Assessed	2284	25 (3)	50 (1)	2284 (100)
USPHS2	USA	1996-1999	General population	Complete	Self-reported	10716	25 (3)	64 (8)	10716 (100)
VHMPP	Austria	1986-1992	Screening	Complete	Assessed	120611	25 (4)	48 (14)	55100 (46)
VITA	Italy	1994-1996	General population	Random	Assessed	8983	25 (4)	51 (8)	4027 (45)
WHITEI	UK	1997	Occupational	Complete	Assessed	4007	25 (3)	76 (5)	4007 (100)
WHITEII	UK	1986-1987	Occupational	Complete	Assessed	10200	25 (4)	45 (6)	6805 (67)
ZARAGOZA	Spain	1994	GP/Health service lists	Complete	Assessed	2838	29 (5)	59 (12)	1175 (41)
ZUTE	Netherlands	1990	General population	Random	Assessed	391	26 (3)	76 (4)	391 (100)
Clinical trials									
AFTCAPS	USA	1991-1993	Screening	Complete	Assessed	6605	27 (3)	58 (7)	5608 (85)
ALLHAT	USA/Canada/ Puerto Rico/US Virgin Islands	1994	Individuals with hypertension	NR	Assessed	28063	30 (6)	66 (8)	13758 (49)
LEADER	UK	1994-1998	GP/Health service lists	Complete	Assessed	927	26 (4)	68 (9)	927 (100)
MRFIT	USA	1974-1976	Screening	Complete	Assessed	12840	28 (3)	47 (6)	12840 (100)
PROSPER	Scotland/Ireland/ Netherland	1998-1999	Screening	Complete	Assessed	3252	27 (4)	75 (3)	1350 (42)
TPT	UK	1989-1991	GP/Health service lists	Complete	Assessed	22715	27 (4)	56 (7)	22715 (100)
WHS	USA	1994-1995	Occupational	Complete	Assessed	27479	26 (5)	55 (7)	0 (0)
WOSCOPS	UK	1989-1991	Screening	Complete	Assessed	6191	26 (3)	55 (6)	6191 (100)
Nested case-control studies									
EPICNOR	UK	1993-1998	GP/Health service lists	Complete	Assessed	1424	27 (4)	66 (8)	966 (68)
FIA	Sweden	1985-1999	General population	Random	Assessed	2636	26 (4)	54 (7)	2128 (81)
GLOSTRUP	Denmark	1976-1984	General population	Random	Assessed	207	26 (4)	51 (9)	168 (81)
USPHS	USA	1982	Occupational	Complete	Self-reported	936	25 (3)	60 (9)	936 (100)
WHIHABPS	USA	1994	General population	Complete	Assessed	1212	27 (6)	68 (6)	0 (0)
TOTAL						**1064541**	**26 (4.1)**	**55 (9.4)**	**560793 (53)**

[a]CHS included an original cohort (here termed CHS1) and a supplemental African-American cohort (here termed CHS2), which were analysed separately; [b]Progetto CUORE was analysed as 8 different studies (ie, ATENA, EMOFRI, MATISS83, MATISS87, MATISS93, MONFRI86, MONFRI89 and MONFRI94); [c]RIFLE Study was analysed as 9 different studies (ie, ATS_SAR, DISCO, GREPCO, GUBBIO, MICOL, MONICA, NFR, OB43 and RF2); Study acronyms are provided in Appendix 4. Abbreviations: Assessed = weight and height were assessed by a trained person; Self-reported = weight and height were measured by the subject itself; NR = information not reported. Summaries were based on participants without history of cardiovascular disease.

Table 2.3 Some baseline characteristics of the 58 prospective studies providing concomitant information on BMI, WC and WHR to the ERFC

Study abbreviation	Country	Year(s) of baseline survey	Population source	Sampling	No of subjects	BMI (kg/m^2) mean (sd)	WC (cm) mean (sd)	WHR mean (sd)	Age (yrs) mean (sd)	Male (%)
Cohort studies										
ARIC	USA	1987-1989	Households	Random	14383	28 (5)	97 (14)	0.92 (0.08)	54 (6)	6213 (43)
ATENA[b]	Italy	1993-1996	Electoral rolls	Random	4741	27 (4)	85 (10)	0.82 (0.07)	50 (7)	0 (0)
ATTICA	Greece	2001	General population	Random	1503	27 (4)	93 (14)	0.88 (0.11)	51 (11)	769 (51)
AUSDIAB	Australia	1999-2000	NR	NR	9204	27 (5)	91 (14)	0.87 (0.09)	53 (13)	4079 (44)
BRHS	UK	1998-2000	GP/Health service lists	Random	3466	27 (4)	97 (10)	0.95 (0.06)	68 (5)	3466 (100)
BRUN	Italy	1990	General population	Random	817	25 (4)	87 (11)	0.89 (0.07)	58 (11)	398 (49)
BWHHS	UK	1999-2001	General population	Random	2779	27 (5)	85 (12)	0.81 (0.07)	68 (5)	0 (0)
CAPS	UK	1990-1993	Electoral rolls	Random	1062	27 (4)	93 (10)	0.93 (0.06)	62 (4)	1062 (100)
CHARL	USA	1987-1989	Households	Random	428	27 (5)	95 (13)	0.94 (0.08)	71 (7)	179 (42)
CHS1[a]	USA	1989-1990	GP/Health service lists	Random	3881	26 (5)	93 (13)	0.92 (0.09)	72 (5)	1489 (38)
CHS2[a]	USA	1992-1993	GP/Health service lists	Random	480	29 (5)	99 (15)	0.94 (0.07)	72 (5)	181 (38)
COPEN	Denmark	1992-1994	General population	Random	8166	26 (4)	87 (13)	0.87 (0.10)	58 (15)	3502 (43)
DRECE	Spain	2006	General population	Random	497	28 (4)	95 (13)	0.92 (0.11)	57 (11)	222 (45)
EMOFRI[c]	Italy	1995-1996	General population	Random	360	26 (4)	91 (11)	0.90 (0.07)	55 (6)	176 (49)
EPESENCA	USA	1992-1993	General population	Random	1001	27 (5)	93 (13)	0.88 (0.08)	77 (5)	333 (33)
FINRISK92	Finland	1992	General population	Random	5276	26 (4)	88 (13)	0.86 (0.10)	46 (10)	2446 (46)
FINRISK97	Finland	1997	General population	Random	6382	27 (4)	90 (13)	0.87 (0.09)	52 (11)	3167 (50)
FRAMOFF	USA	1998-2000	General population	Complete	2685	28 (5)	99 (14)	0.94 (0.08)	60 (9)	1183 (44)
GOH	Israel	1999-2005	General population	Random	634	28 (5)	99 (11)	1.03 (0.12)	70 (7)	305 (48)
GOTO13	Sweden	1967	General population	Complete	756	25 (3)	87 (9)	0.93 (0.05)	54 (0)	756 (100)
GOTO33	Sweden	1983-1984	General population	Complete	729	26 (3)	95 (9)	0.93 (0.06)	51 (0)	729 (100)
GOTO43	Sweden	1993-1994	General population	Complete	762	26 (3)	95 (9)	0.99 (0.06)	50 (0)	762 (100)
GOTOW	Sweden	1968-1969	General population	Random	1401	24 (4)	74 (9)	0.74 (0.05)	47 (7)	0 (0)
HBS	Finland	1986	Occupational	NR	1268	26 (3)	97 (9)	0.97 (0.06)	60 (4)	1268 (100)
HISAYAMA	Japan	1988	General population	Complete	2515	23 (3)	81 (9)	0.91 (0.07)	59 (11)	1068 (42)
HOORN	Netherlands	1990-1991	General population	Random	2226	27 (4)	91 (11)	0.89 (0.09)	61 (7)	979 (44)
IKNS	Japan	1990-1993	Screening	Complete	1942	24 (3)	83 (9)	0.90 (0.07)	59 (10)	830 (43)
LASA	Netherlands	1992-1993	General population	Random	1806	27 (4)	97 (11)	0.94 (0.08)	69 (8)	827 (46)
MATISS83[b]	Italy	1993-1996	Electoral rolls	Random	1317	29 (4)	94 (10)	0.91 (0.09)	61 (9)	614 (47)
MATISS87[b]	Italy	1993-1996	Electoral rolls	Random	1077	29 (4)	94 (11)	0.91 (0.09)	58 (9)	510 (47)
MATISS93[b]	Italy	1993-1995	Electoral rolls	Random	1206	28 (5)	91 (11)	0.91 (0.08)	49 (9)	579 (48)
MESA	USA	2001	General population	Random	6768	28 (5)	98 (14)	0.93 (0.08)	62 (10)	3190 (47)
MOGERAUG2	Germany	1989-1990	General population	Random	3934	27 (4)	90 (12)	0.87 (0.08)	53 (12)	1935 (49)
MOGERAUG3	Germany	1994-1995	General population	Random	3368	28 (4)	92 (12)	0.88 (0.09)	55 (10)	1663 (49)
MONFRI89[b]	Italy	1989	Electoral rolls	Random	1330	26 (4)	88 (12)	0.87 (0.09)	49 (8)	658 (49)
MONFRI94[b]	Italy	1994	Electoral rolls	Random	1291	26 (4)	90 (12)	0.88 (0.09)	49 (8)	627 (49)
MORGEN	Netherlands	1993-1997	General population	Random	17707	26 (4)	88 (12)	0.86 (0.09)	46 (9)	8046 (45)
MOSWEGOT	Sweden	1985-1995	General population	Random	4132	25 (4)	85 (12)	0.86 (0.09)	47 (11)	1966 (48)
MRCOLD	UK	1995-1998	GP/Health service lists	Complete	9933	26 (4)	90 (12)	0.88 (0.08)	80 (4)	3747 (38)
NHANESIII	USA	1988-1993	General population	Cluster	10450	27 (6)	95 (14)	0.93 (0.09)	53 (16)	4859 (46)
NSHS	Canada	1995	GP/Health service lists	Random	1608	27 (6)	90 (15)	0.87 (0.10)	54 (15)	765 (48)
OSAKA	Japan	1992-1997	Combination or other	NR	717	23 (3)	84 (8)	0.90 (0.05)	49 (7)	602 (84)
PREVEND	Netherlands	1997-1998	NR	NR	7368	26 (4)	89 (13)	0.88 (0.09)	50 (12)	3583 (49)
PRIME	France/N. Ireland	1991-1993	General population	Quota	9563	27 (3)	95 (10)	0.96 (0.06)	55 (3)	9563 (100)
RANCHO	USA	1984-1986	Households	Complete	1784	25 (4)	85 (12)	0.84 (0.09)	68 (11)	739 (41)
ROTT	Netherlands	1990-1993	General population	Complete	4607	26 (4)	90 (11)	0.90 (0.09)	68 (8)	1752 (38)
SHHEC	UK	1989-1995	GP/Health service lists	Random	3489	26 (5)	86 (13)	0.85 (0.10)	49 (11)	1625 (47)
SHS	USA	1989-1991	General population	Complete	4135	31 (6)	105 (15)	0.95 (0.06)	56 (8)	1615 (39)
TARFS	Turkey	1998	Households	Random	2559	28 (5)	93 (12)	0.89 (0.09)	49 (12)	1270 (50)
TOYAMA	Japan	1996	Occupational	NR	4523	23 (3)	78 (9)	0.85 (0.07)	46 (7)	2907 (64)
TROMSØ	Norway	1994-1995	Households	Complete	1573	26 (4)	91 (11)	0.87 (0.08)	60 (10)	811 (52)
ULSAM	Sweden	1991-1994	General population	Complete	962	26 (3)	94 (9)	0.94 (0.05)	71 (1)	962 (100)
WHITEII	UK	1991-1993	Occupational	Complete	7862	25 (4)	85 (11)	0.87 (0.09)	49 (6)	5414 (69)
WHS	USA	1999-2001	Occupational	Complete	24138	27 (5)	89 (14)	0.83 (0.08)	60 (7)	0 (0)
Nested case-control studies										
EPICNOR	UK	1993-1997	GP/Health service lists	Complete	1417	27 (4)	93 (11)	0.90 (0.08)	66 (8)	960 (68)
HPFS	USA	1996	Occupational	Complete	394	26 (4)	99 (10)	0.96 (0.06)	66 (8)	394 (100)
NHS	USA	1986	Occupational	Complete	372	25 (4)	81 (11)	0.79 (0.07)	58 (6)	0 (0)
WHIHABPS	USA	1994	General population	Complete	1200	27 (6)	86 (13)	0.82 (0.09)	68 (6)	0 (0)
TOTAL					**221934**	**27 (4.56)**	**91 (12.6)**	**0.90 (0.08)**	**58 (9)**	**97745 (44)**

[a]CHS included an original cohort (here termed CHS1) and a supplemental African-American cohort (here termed CHS2), which were analysed separately. [b]Progetto CUORE was analysed as 7 different studies (ie, ATENA, EMOFRI, MATISS83, MATISS87, MATISS93, MONFRI89 and MONFRI94). Study acronyms are provided in Appendix 4**.** Abbreviation: NR = information not reported. Summaries were based on participants without history of cardiovascular disease.

Table 2.4 Description of methods used to assess adiposity measures in the 58 studies providing concomitant information on BMI, WC and WHR

Study abbreviation	Measurement of height & weight	Measurement of waist & hip	Assessment of height & weight	Assessment of waist circumference	Assessment of hip circumference
ARIC	Assessed	Assessed	participant wearing a scrub suit and no shoes	umbilical level	around the maximum buttocks
ATENA	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
ATTICA	Assessed	Assessed	light undergarments and no shoes	midway between lower rib margin and the iliac crest	around the maximum buttocks
AUSDIAB	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
BRHS	Assessed	Assessed	light undergarments and no shoes	midway between lower rib margin and the iliac crest	largest circumference below the waist
BRUN	Assessed	Assessed	measured after an overnight fast, subjects wearing only undergarments.	umbilical level	at greater trochanters
BWHHS	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	largest circumference below the waist
CAPS	Assessed	Assessed	NA	narrowest point between the costal line and the iliac crest	at greater trochanters
CHARL	Assessed	Assessed	light clothing and no shoes	umbilical level	at greater trochanters
CHS1	Assessed	Assessed	NA	umbilical level	maximum hip circumference
CHS2	Assessed	Assessed	NA	umbilical level	maximum hip circumference
COPEN	Assessed	Assessed	light clothing or underwear and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
DRECE	Assessed	Assessed	NA	NA	NA
EMOFRI[c]	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
EPESENCA	Self-reported	Assessed	NA	umbilical level	NA
EPICNOR	Assessed	Assessed	no shoes	smallest circumference between the ribs and iliac crest	maximum circumference between the iliac crest and the crotch
FINRISK92	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
FINRISK97	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
FRAMOFF	Assessed	Assessed	light clothing and no shoes	umbilical level	NA
GOH	Assessed	Assessed	light clothing and no shoes	one finger width above superior iliac crest	At groin level
GOTO13	Assessed	Assessed	wearing underpants	umbilical level	at the level of the anterior iliac crest
GOTO33	Assessed	Assessed	after an overnight fast, indoor clothing, and 0.8 kg deducted from the recorded weight	umbilical level	at the level of the anterior iliac crest
GOTO43	Assessed	Assessed	after an overnight fast, indoor clothing, and 0.8 kg deducted from the recorded weight	umbilical level	at the level of the anterior iliac crest
GOTOW	Assessed	Assessed	no shoes	midway between lower rib margin and the iliac crest	widest point between hip and buttock
HBS	Assessed	Assessed	without shoes and shirt	umbilical level	at the level of the anterior iliac crest
HISAYAMA	Assessed	Assessed	light clothing and no shoes	umbilical level	Around the buttocks, 4cm below the anterior superior iliac spine
HOORN	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	widest level over the greater trochanters
HPFS	Self-reported	Self-reported	NA	umbilical level	largest circumference between the waist and thighs
IKNS	Assessed	Assessed	light clothing and no shoes	umbilical level	maximum circumference over the buttocks
LASA	Assessed	Assessed	light clothing	midway between lower rib margin and the iliac crest	widest level over the greater trochanters
MATISS83	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MATISS87	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MATISS93	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MESA	Assessed	Assessed	light clothing and no shoes	umbilical level	NA
MOGERAUG2	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MOGERAUG3	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MONFRI89	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MONFRI94	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MORGEN	Assessed	Assessed	indoor clothing and no shoes	midway between lower rib margin and the iliac crest	at the level of the greater trochanters
MOSWEGOT	Assessed	Assessed	light clothing and no shoes after at least 4 h of fasting	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
MRCOLD	Assessed	Assessed	light undergarments and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks and below the iliac crest
NHANESIII	Assessed	Assessed	paper shirt and pants and foam slippers	at level with the iliac crest at the end of a normal expiration	maximum circumference over the buttocks
NHS	Self-reported	Self-reported	NA	umbilical level	largest circumference around hips (including buttocks)
NSHS	Assessed	Assessed	light clothing and no shoes	at the point of noticeable waist narrowing	at the level of the symphysis pubis and the greatest gluteal protuberance
OSAKA	Assessed	Assessed	light clothing and no shoes	umbilical level	maximum circumference over the buttocks
PREVEND	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
PRIME	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	above the buttocks
RANCHO	Assessed	Assessed	indoor clothing and no shoes	at the bending point (the natural indentation when bending sideways)	largest girth below the waist
ROTT	Assessed	Assessed	no shoes and heavy outer garments	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
SHHEC	Assessed	Assessed	NA	NA	NA
SHS	Assessed	Assessed	light clothing and no shoes	umbilical level	at the maximum protrusion of gluteal muscles
TARFS	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	at the level of the greater trochanters
TOYAMA	Assessed	Assessed	light clothing and no shoes	midway between lower rib margin and the iliac crest	maximum circumference over the buttocks
TROMSØ	Assessed	Assessed	light clothing and no shoes	umbilical level	at the widest point at the hips
ULSAM	Assessed	Assessed	NA	midway between lower rib margin and the iliac crest	measured over the widest part
WHIHABPS	Assessed	Assessed	light clothing and no shoes	at the natural waist or narrowest part of the torso	maximum circumference over the buttocks
WHITEII	Assessed	Assessed	NA	midway between lower rib margin and the iliac crest	at the level of the greater trochanters
WHS	Self-reported	Self-reported	NA	umbilical level	maximum circumference between the umbilicus and the thigh

Study acronyms are provided in Appendix 4**.** Abbreviations: Assessed = anthropometric marker was assessed by a trained person; Self-reported = anthropometric marker was measured by the subject itself; NA = information not available.

Table 2.5 Definition of endpoints in the ERFC

Endpoint	ICD-10 codes
All cardiovascular*	G45, I01, I03-I82, I87, I95-I99, F01, Q20-2Q28, R96
Coronary heart disease (CHD)*	I20-I25
Myocardial infarction	I21, I22
All cerebrovascular*	F01, I60-I69
Ischaemic stroke*	I63
Haemorrhagic stroke*	I61
Subarachnoid stroke*	I60
Unclassified stroke†*	I64
Other vascular deaths	Remainder of cardiovascular disease (fatal)
Cardiac dysrhythmia	I47-I49
Hypertensive disease	I10-I15
Pulmonary embolism	I26
Ill-defined descriptions and complications of the dearth disease	I51
Sudden death	R96
Aortic aneurysm	I71
Heart failure	I50
Peripheral vascular disease	I73-I74, I77-I78
Other	Remainder of vascular
All cancer	C00-C97, D00-D48
Oral	C00-C14
Colorectum	C18-C21
Oesophagus	C15
Stomach	C16
Liver	C22
Pancreas	C25
Lung	C34
Prostate	C61
Ovary	C56
Bladder	C67
Haematological	C81-C96
Endocrine & nervous	C69-C75
Melanoma	C43
Connective tissue	C40-C42, C45-C49
Breast (female)	C50
Other/unspecified	Remainder of cancer/ unspecified to ERFC
All non-cancer, non-vascular	A00-A99, B00-B99, D50-D99,E00-E99, F00, F02-F99, G00-G44, G46-G99, H00-H99, I00, I02, I83-I86, I88-I89, J00-J99, K00-K99, L00-L99, M00-M99, N00-N99, O00-O99, P00-P99, Q00-Q18, Q30-Q99, S00-S99, T00-T99, U04, V00-V99, W00-W99, X00-X99, Y00-Y99, Z00-Z99
All external cause	S00-S99, T00-T98, U04, V01-V99, W00-W99, X00-X99, Y00-Y98, Z00-Z99
Falls	W00-W19
Intentional self-harm	X60-X84
Infections	A00-A99, B00-B14, B20-B99
Diabetes mellitus	E10-E14
Mental disorders	F04-F99
Alzheimer's disease and related conditions	F00, F02, F03, G30-G32
Liver disease	B15-B19, K70-K77
Respiratory system disease	J00-J99
Pneumonia	J12-J18
COPD and related conditions	J40-J47
Digestive system disease (except liver)	K00-K69, K78-K93
Renal disease	N00-N19
Other/unspecified	Remainder of non-cancer, non-vascular/ unspecified to ERFC
Deaths of unknown cause or ill-defined cause	R00-R96, R97-R99 and non-vascular deaths defined according to study-specific read-codes for mortality, and not standard ICD codes.
All-cause mortality	A00-Y89

Attribution of deaths refers to the primary cause (or, in its absence the underlying cause) provided by individual studies. Corresponding ICD-6, 7, 8 or 9 codes were used for studies that recorded outcomes using earlier ICD versions. *includes both fatal and non-fatal events; †Unclassified stroke was defined by the ICD codes stated, or as strokes nor specified as ischaemic or haemorrhagic by study-specific codes.

Table 2.6 Order of priority for any non-fatal events that occurred on the same day

Rank	Type	Sub-type
1	MI	Definite
2	MI	Acute
3	MI	ST elevated
4	MI	non-ST elevated
5	MI	General
6	Coronary	CHD (general)
7	Stroke	Ischaemic
8	Stroke	Haemorrhagic
9	Stroke	definite general
10	Stroke	General
11	MI	non-transmural
12	Stroke	sub-arachnoid
13	MI	during surgery
14	MI	Silent
15	MI	Probable
16	Stroke	probable general
17	MI	Possible
18	Stroke	possible general
19	TIA	General
20	Angina	Unstable
21	MI	Suspect
22	Angina	definite general
23	Angina	General
24	Stroke	suspect general
25	Surgery	CABG
26	Surgery	angioplasty (PTCA)
27	Surgery	revascularisation
28	Surgery	cardiovascular
29	Angina	Stable
30	MI	Old
31	Angina	Possible
32	Coronary	coronary insufficiency (definite)
33	Coronary	coronary insufficiency (possible)
34	Coronary	cardiac arrest
35	Coronary	heart failure
36	Coronary	Arrhythmia
37	PVD	General
38	PVD	definite general
39	PVD	probable general
40	PVD	possible general
41	PVD	suspect general
42	Surgery	Amputation
43	Surgery	vascular surgery
44	Coronary	other heart disease
45	Coronary	General
46	Other	thromb/embolism
47	Other	ulcer/gangrene
48	Other	other CV
49	Other	other non-CV
50	Diabetes	General
51	Cancer	General
52	Surgery	General
53	Other	General

Figure 2.1 Map of countries participating in the ERFC

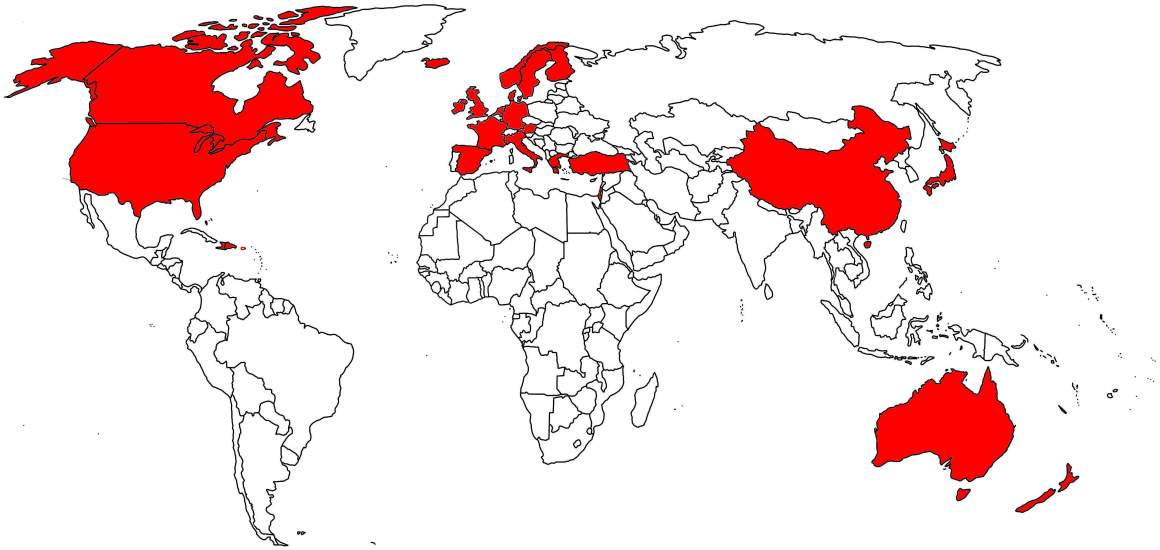


Figure 2.2 Sequence of data sharing, cleaning and ratification in the ERFC

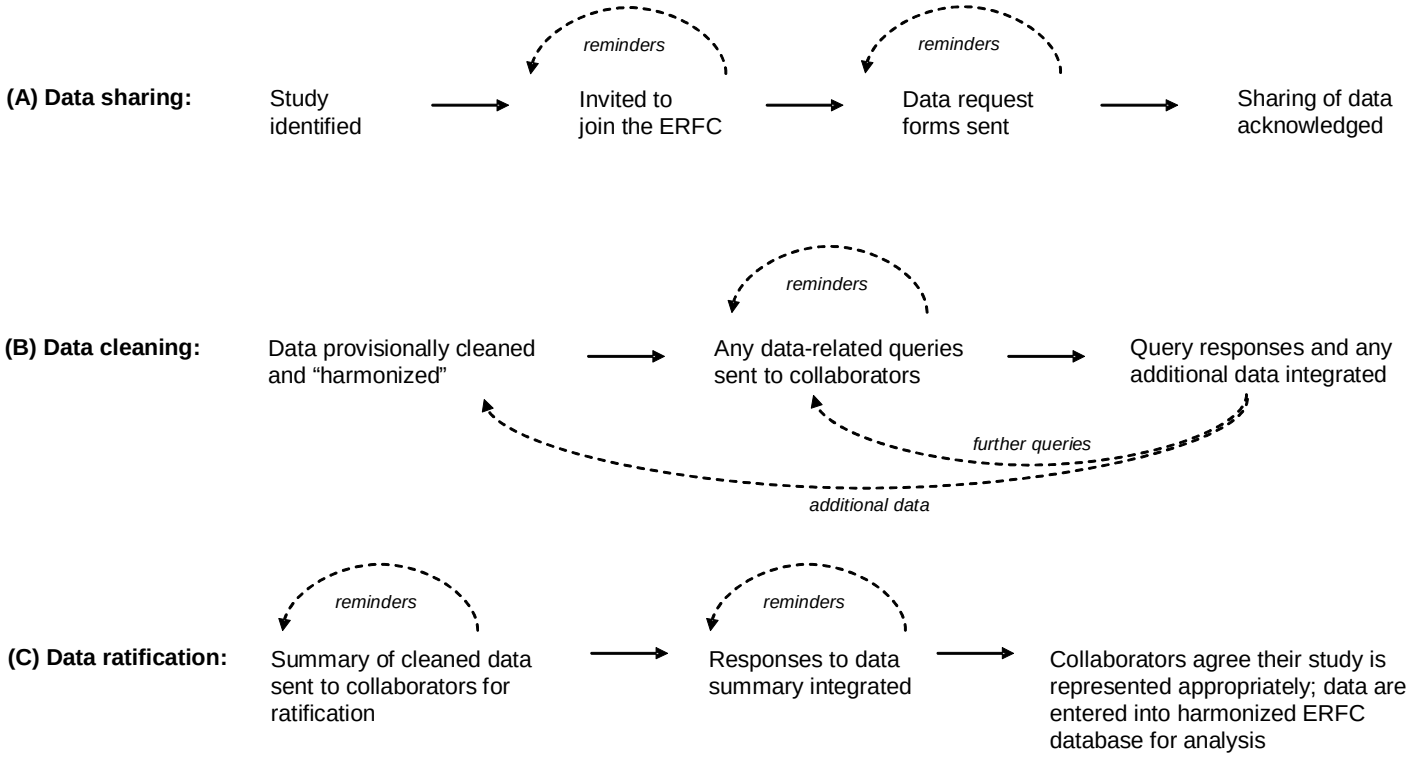


Figure 2.3 Flow diagram of available data on adiposity measures in the ERFC

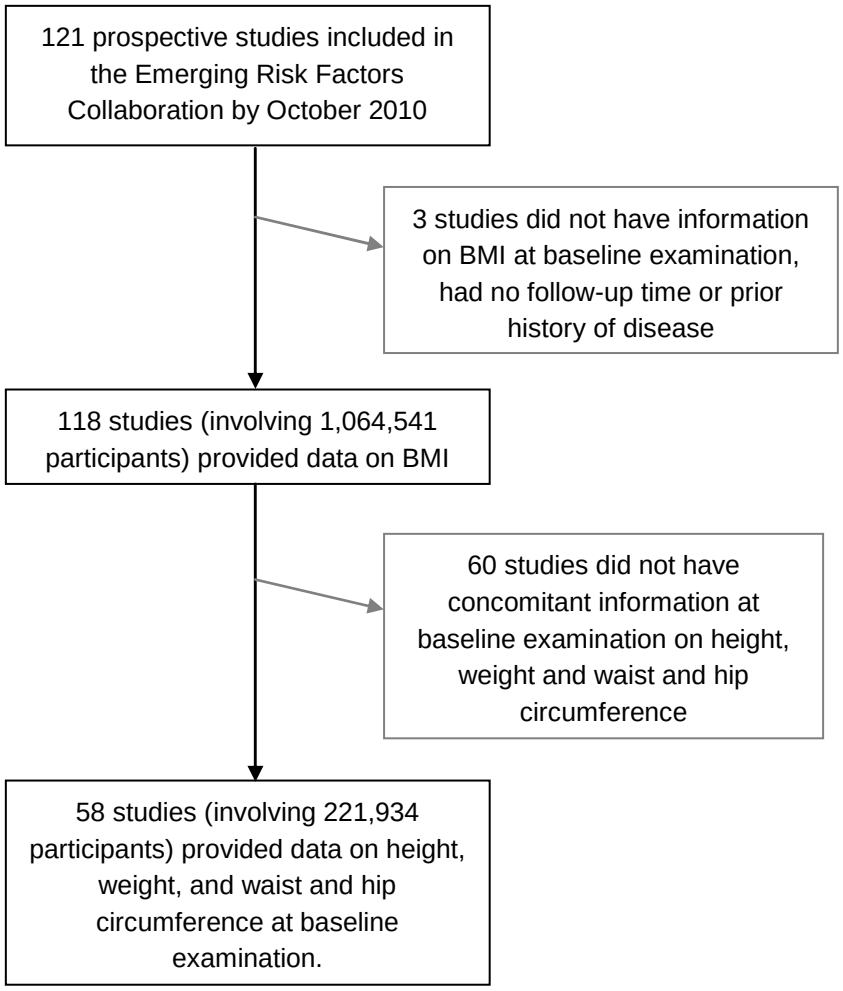
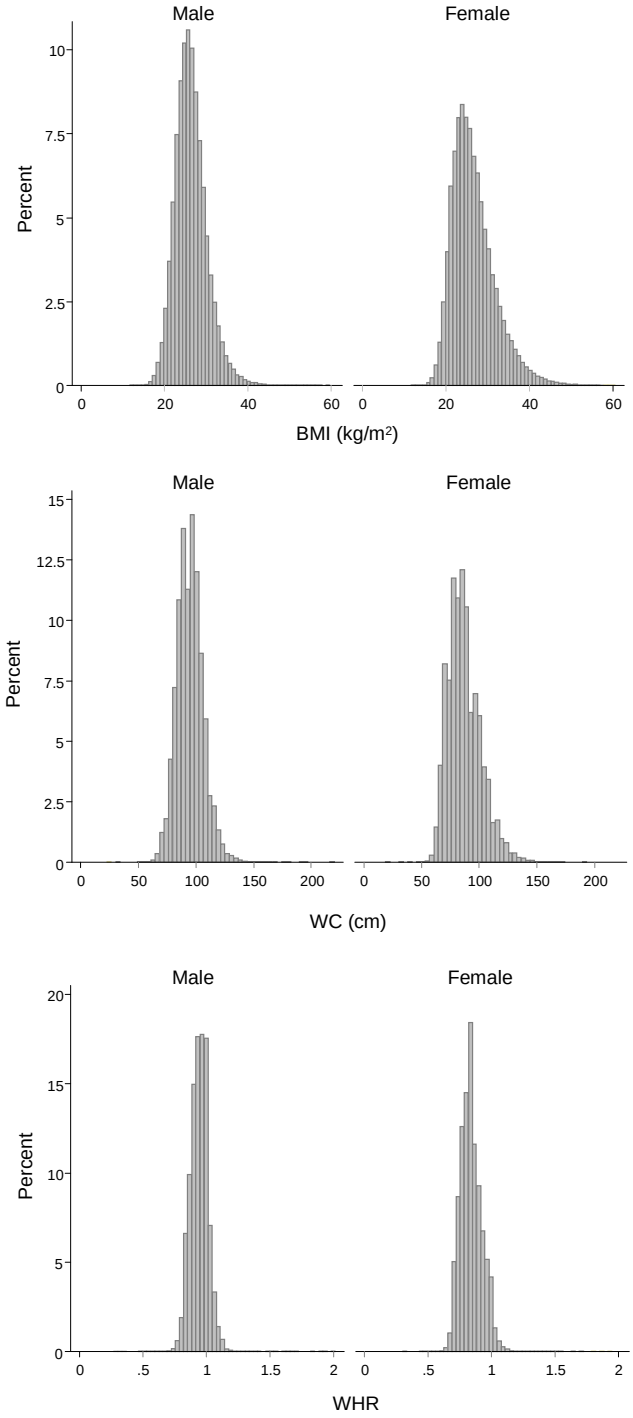
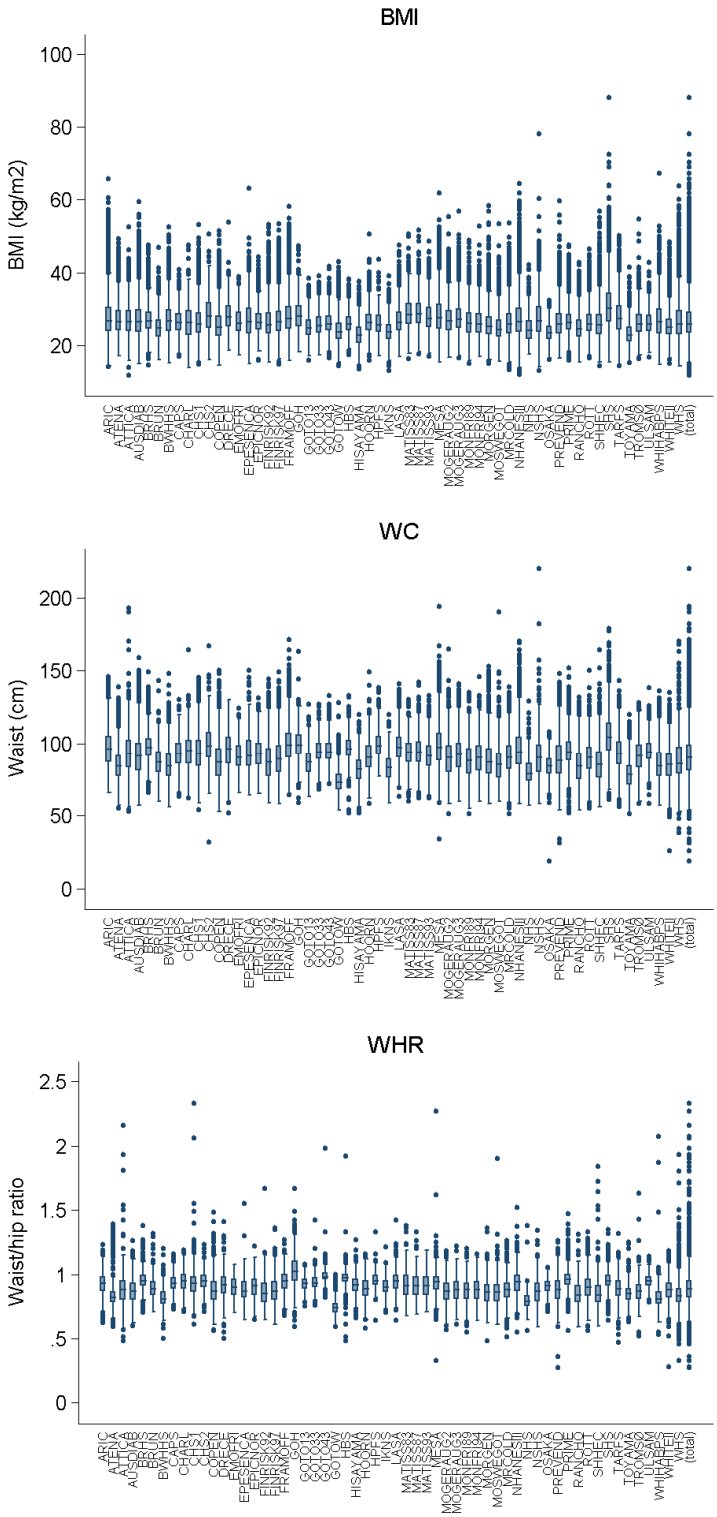


Figure 2.4 Sex-specific distributions of baseline BMI, WC and WHR across the 58 studies providing concomitant information on BMI, WC and WHR



Mean (SD) in men and women, respectively, were 26.4 kg/m^2 (3.8) and 26.6 kg/m^2 (5.0) for BMI, 94.9cm (10.5) and 86.6 cm (12.9) for WC, and 0.95 (0.064) and 0.84 (0.075) for WHR.

Figure 2.5 Study-specific box plots of baseline BMI, WC and WHR in the 58 studies providing concomitant information on BMI, WC and WHR



CHAPTER 3: Cross-sectional correlates of adiposity measures

Summary

The adverse effects of excess body fat on cardiovascular disease are believed to be mediated through the complex interplay of several well-established and putative risk factors, such as increased blood pressure levels, alterations in lipid metabolism, insulin resistance and potentially inflammation. This chapter reports on the cross-sectional associations of body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with several biochemical, lifestyle and other characteristics in 221,934 participants without known cardiovascular disease at baseline examination in the Emerging Risk Factors Collaboration. The data demonstrate that there were approximately linear and strong associations between BMI and WC, and WHR and WC, and only moderately strong correlations between BMI and WHR. These adiposity measures had broadly similar and approximately linear associations with cardiovascular risk factors, such as blood pressure, fasting glucose and inflammatory markers, and slightly curvilinear associations with lipid markers. In both males and females, BMI, WC and WHR were most strongly associated with blood pressure, high-density lipoprotein cholesterol, triglyceride, C-reactive protein and interleukin-6. Overall, adiposity measures were higher in individuals of non-European descent, in physically inactive people, in people with diabetes and people with low levels of education. Whereas mean BMI and WC values were somewhat lower in current smokers and current alcohol drinkers, mean WC and WHR values were higher in males than in females. These findings demonstrate that although the correlations between the three clinical measures of adiposity differ, BMI, WC and WHR are similarly and importantly associated with blood pressure, fasting glucose, lipids and inflammatory markers. This result supports the importance of intermediate risk factors on the pathway between excess body fat and cardiovascular disease. Furthermore, the findings suggest possible scope for confounding by lifestyle factors in observational studies of associations of adiposity measures with disease risk.

Background

As discussed in **Chapter 1** on pages 5-7, the adverse effects of excess body fat on cardiovascular disease are believed to be mediated through the complex interplay of several well-established and putative risk factors, such as increased blood pressure levels, alterations in lipid metabolism, insulin resistance and inflammation. In obesity, adipose tissue, particularly visceral fat in the abdominal region, is thought to promote lipolysis and resistance to insulin, which leads to increased levels of non-esterified fatty acids that are toxic to the liver, causing decreased insulin clearance, increased glucose production and dyslipidemia.[1,2] Moreover, adipose tissue releases inflammatory cytokines (eg, interleukin 6 [IL-6] and tumour necrosis factor-α [TNF-α]), which stimulate the liver to generate additional bioactive markers that are associated with insulin resistance and increased C-reactive protein (CRP).[1,3,4] The production of leptin by adipose tissue has also been implicated in insulin resistance and hypertension due to the activation of the central sympathoregulatory pathways.[1] Because of these relationships, body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) are likely to be strongly correlated with blood pressure, fasting glucose, lipids and inflammatory markers.[5,6]

Several epidemiological studies have reported on the cross-sectional association of adiposity measures with lipids, inflammatory markers and other characteristics.[7-12] These studies have, however, generally been underpowered to quantify reliably the magnitude, or to characterise the shape of any association. Furthermore, because they have often lacked concomitant measurement of height, weight, waist and hip circumference, it has been difficult to compare directly the cross-sectional associations with BMI, WC and WHR.

This chapter reports on the cross-sectional associations of BMI, WC and WHR with biochemical, lifestyle and other factors in 221,934 participants without known cardiovascular disease at baseline examination from 58 prospective studies in the Emerging Risk Factors Collaboration (ERFC). Reliable characterisation of these relationships with various factors will help to (i) determine the extent to which adiposity measures provide related information; (ii) better understand the biological pathways of the underlying association between adiposity and cardiovascular disease, and (iii) identify potential sources of confounding in epidemiological studies of associations of adiposity measures with disease risk.

Methods

Study design

Details of study selection, data collection and harmonisation in the ERFC have been described in **Chapter 2**. Briefly, the current analysis involved individual records from 58 prospective studies with complete information on age, sex, weight, height, and waist and hip circumference.

Statistical analysis

Descriptive statistics were calculated for a range of covariates measured at baseline examination of the 58 contributing studies. Continuous variables were summarised by pooling within-study means by random effects meta-analysis and categorical variables were summarised as raw counts and proportions.

The statistical methods used for the analysis of cross-sectional correlates of adiposity measures generally followed those used by the Fibrinogen Studies Collaboration.[13] Associations with blood pressure, lipids, inflammatory markers and other characteristics were calculated in relation to BMI, WC and WHR. For continuous variables, correlation coefficients were pooled across studies by random effects meta-analysis of study-specific Fisher's Z-transformed partial correlation coefficients (adjusted for age and sex).[13] So, for each study $s = 1 \ldots S$, Fisher's Z-transformed correlation coefficient Z_s and its standard error σ_s are given by

$$Z_s = 0.5 * \log_e \frac{1+r_s}{1-r_s} \qquad \text{and} \qquad \sigma_s = \frac{1}{\sqrt{n_s - 3}}, \qquad (3.1)$$

where r_s is the study-specific correlation coefficient and n_s the number of participants in study s. The Fisher's Z-transformed correlation coefficients Z_s were subsequently combined over studies using random effects meta-analysis (ie, allowing for heterogeneity between studies)[14] – see model (5.2) from **Chapter 5** on page 112 for more details. The pooled Z-transformed correlation coefficient Z^c was then back transformed, using following equation

$$r^c = \frac{\exp(2 * Z^c) - 1}{\exp(2 * Z^c) + 1}, \qquad (3.2)$$

where r^c is the combined correlation coefficient of r_s. Positively skewed variables (eg, triglyceride, lipoprotein(a) [Lp(a)], CRP) were $\log_e$-transformed to approximate the normal distribution.

The magnitude of association between adiposity measures and risk factors was estimated by regressing each risk factor on the relevant adiposity measure using linear mixed models adjusted for age, sex and study, allowing for between-study heterogeneity at the study level. The regression model for studies $s = 1 \ldots S$, and individuals $i = 1 \ldots n_s$, with risk factor Y_{si}, exposure of interest E_{si} and other covariates X_{si} can be written as

$$Y_{si} = \alpha_s + (\beta + u_s)E_{si} + \lambda X_{si} + \varepsilon_{si}, \qquad (3.3)$$

where $u_s \sim N(0, \sigma_u^2)$, $\varepsilon_{si} \sim N(0, \sigma_e^2)$ and β is the parameter of interest, being the change in risk factor per unit increase in exposure, adjusted for covariates X_{si}. Between-study heterogeneity in the estimated association β is represented by σ_u^2. In order to directly compare associations between adiposity measures, standardised regression coefficients were calculated by multiplying the regression coefficient from the mixed model by the standard deviation of the relevant adiposity measure. For associations with categorical variables, values of adiposity measures were Z-transformed (ie, standardised) to a mean 0 and a standard deviation of 1 to allow meaningful comparisons across adiposity measures. Associations were calculated by linear mixed models as described in (3.3), except that corresponding adiposity measures were regressed on categorical variables (in contrast to the previous model, where continuous risk factors were the dependent variables). Subsidiary analyses were further adjusted for smoking status, alcohol consumption, physical activity and education.

Shapes of the cross-sectional associations of adiposity measures with several continuous risk factors were assessed using a linear mixed model that included random effects at the study level.[13] Risk factors were standardised to allow meaningful graphical presentation. To allow assessment of the shape of association without imposing *a priori* any particular relationship, relevant adiposity measure was divided into tenths based on the overall distribution in males and females combined and fitted in the regression models as dummy variables. Model (3.3) was extended to include the fixed effects: study, age, age^2, sex, age$\times$sex, age$^2\times$sex, adiposity-tenth, adiposity-tenth$\times$age and adiposity-tenth$\times$sex (where $\times$ denotes an

interaction), and to allow the coefficient adiposity-tenth (entered as a continuous variable) to vary randomly across studies. Coefficients that were allowed to vary randomly across studies in subsidiary analyses were: age, age^2 and adiposity-tenth (entered as a continuous variable). From each fitted mixed model, overall adjusted means and 95% confidence intervals (CIs) of the continuous risk factor by sex within tenths of relevant adiposity measure were obtained with age fixed at 50 years (age was adjusted to 65 years in supplementary analyses). These adjusted means (95% CI) were plotted against the mean value of the relevant adiposity measure within each tenth to assess the shape of association. An inverse-variance weighted polynomial was superimposed across adjusted means to better investigate the shape of the association.

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Table 3.1 provides descriptive summaries of baseline characteristics of the participants included in the current analysis. Complete information on age, sex, weight, height, and waist and hip circumference were available on 221,934 participants in 58 studies without known history of cardiovascular disease at baseline examination. 155,938 of these participants also had data on smoking status, systolic blood pressure (SBP), history of diabetes, and total and high-density lipoprotein (HDL) cholesterol. Mean (SD) age of participants at baseline was 58 years (9), 124,189 (56%) were women.

Associations between adiposity measures

Figure 3.1 (panel A) shows that BMI, WC and WHR had broadly similar distributions across studies. For BMI, the studies with the lowest and highest BMI values had means of 22.9 kg/m^2 and 30.9 kg/m^2, respectively. For WC, the studies with the lowest and highest WC values had means of 74 cm (study consisting of females only) and 105 cm (study consisting of males only), respectively. For WHR, the studies with the lowest and highest WHR values had means of 0.74 (study consisting of females only) and 1.03, respectively. **Figure 3.1** (panel B) shows mean values of adiposity measure by sex in 5-year age bands. Overall, mean values of adiposity measures generally increased with age until about 55-75 years, then flattened or declined at older ages. Adiposity measures were continuously and approximately linearly associated with one another across the range of values in both sexes (**Figure 3.2**). Correlation

coefficients adjusted for age and sex were 0.85 (95% CI 0.84-0.86) between BMI and WC, 0.43 (95% CI 0.40-0.45) between BMI and WHR and 0.70 (95% CI 0.68-0.72) between WC and WHR. In studies comprising both males and females, these correlates were broadly similar in men and women, except for the correlation between BMI and WHR which was somewhat lower in women than in men (**Table 3.2**). Overall, BMI values were 4.06 kg/m^2 and 2.21 kg/m^2 higher per one standard deviation greater WC and WHR, respectively; WC values were 10.05 cm and 9.50 cm higher per one standard deviation greater BMI and WHR, respectively; and WHR values were 0.03 and 0.05 higher per one standard deviation greater BMI or WC, respectively (**Table 3.3**).

Associations of adiposity measures with categorical variables

Overall, mean WC and WHR values were significantly lower in women than men (mean differences: 7.95 cm for WC and 0.10 for WHR), whereas mean BMI values were similar in both sexes (**Table 3.4**). Mean WC and WHR values were significantly lower in non-white men compared to white men, while non-white women had significantly higher mean values for all adiposity measures compared to white women (**Table 3.5**). Overall BMI and WC values were significantly lower in current smokers than in ex- or never smokers (overall mean differences: 0.95 kg/m^2 for BMI and 1.49 cm for WC) (**Table 3.4**). By contrast, overall WHR values were slightly higher in current smokers than in other people (although such differences were not statistically significant in analyses done in men and women separately; **Table 3.5**). Furthermore, current alcohol drinkers had lower BMI and WC values than ex- or never alcohol drinkers (overall mean differences: 0.59 kg/m^2 for BMI and 1.01 cm for WC), while no significant differences were observed for WHR (**Table 3.4**). Moreover, in both sexes, mean values of adiposity measures were significantly higher in people with a history of diabetes compared to those without (overall mean differences: 1.96 kg/m^2 for BMI; 5.81 cm for WC; and 0.03 for WHR), in physically inactive compared to physically active individuals (overall mean differences: 0.69 kg/m^2 for BMI; 2.31 cm for WC; and 0.01 for WHR), and in people with no, or primary schooling only, compared to those with a tertiary education (overall mean differences: 1.31 kg/m^2 for BMI; 3.04 cm for WC; and 0.02 for WHR) (**Tables 3.4-3.5**). Qualitatively similar results to those above were observed in analyses with further adjustment for smoking status, alcohol consumption, physical activity and education (**Table 3.6**).

Associations of adiposity measures with blood pressure and fasting glucose

Figure 3.3 plots mean blood pressure and fasting glucose values by sex against mean values in tenths of adiposity measures, suggesting positive and approximately linear associations across the full range of values observed. Age and sex adjusted correlates of blood pressure were slightly weaker with WHR (r = 0.15 for both SBP and diastolic blood pressure [DBP]) than with BMI (r = 0.22 for SBP; r = 0.25 for DBP) or WC (r = 0.21 for SBP; r = 0.23 for DBP). Age and sex adjusted differences in SBP and DBP, respectively, per one standard deviation higher adiposity measure were 4.4 mmHg and 3.0 mmHg with BMI, 4.4 mmHg and 2.9 mmHg with WC and 3.4 mmHg and 2.1 mmHg with WHR (**Table 3.3**). Associations with fasting glucose were broadly similar across adiposity measures, but slightly weaker than those with blood pressure (**Figure 3.3**). Associations were broadly similar in males and females (**Table 3.2**).

Associations of adiposity measures with lipid markers

Adiposity measures had curvilinear and positive associations with total cholesterol, non-HDL cholesterol, triglyceride and apolipoprotein-B; negative associations with HDL cholesterol and apolipoprotein-AI; and no association with Lp(a) (**Figures 3.4-3.5**). Correlations of adiposity measures with these markers were the strongest for triglyceride (r = 0.28 for BMI; r = 0.31 for WC; r = 0.28 for WHR) and HDL cholesterol (r = -0.26 for BMI; r = -0.28 for WC; r = -0.21 for WHR). There were somewhat less strong correlations with non-HDL cholesterol (r = 0.16 for BMI; r = 0.17 for WC; r = 0.16 for WHR); apolipoprotein-AI (r = -0.17 for BMI; r = -0.17 for WC; r = -0.13 for WHR); and apolipoprotein-B (r = 0.14 for BMI; r = 0.15 for WC; r = 0.14 for WHR); and weaker correlations with total cholesterol (r = 0.07 for BMI; r = 0.07 for WC; r = 0.09 for WHR). Differences in non-HDL and HDL cholesterol and the geometric mean of triglyceride, respectively, per one standard deviation higher adiposity measure were: 0.19 mmol/l, -0.11 mmol/l, 1.17 mmol/l with BMI; 0.21 mmol/l, -0.12 mmol/l, 1.19 mmol/l with WC; and 0.22 mmol/l, -0.10 mmol/l, 0.19 mmol/l with WHR (**Table 3.3**). Associations were broadly similar across adiposity measures and sex (**Tables 3.2-3.3**).

Associations of adiposity measures with inflammatory markers

Adiposity measures demonstrated continuous and approximately linear associations with CRP, fibrinogen, leukocyte count and IL-6, and no association with albumin (**Figure 3.6**). Among these associations assessed, CRP (r = 0.29 for BMI; r = 0.30 for WC; r = 0.22 for WHR) and IL-6 (r = 0.24 for BMI; r = 0.25 for WC; r = 0.18 for WHR) were the strongest correlates. Associations were modest with fibrinogen (r = 0.15 for BMI; r = 0.16 for WC; r = 0.12 for WHR),

and weak with leukocyte count (r = 0.09 for BMI; r = 0.11 for WC; r = 0. 12 for WHR). Associations were broadly similar across adiposity measures (**Table 3.3**), but somewhat stronger in women than in men (**Table 3.2**).

In analyses restricted to participants with complete information on relevant covariates, age and sex adjusted correlation coefficients between adiposity measures and continuous variables were similar to those that were further adjusted for smoking status, alcohol consumption, physical activity and education (data not shown).

Discussion

This meta-analysis of individual data on 221,934 participants from 58 prospective studies without known cardiovascular disease at baseline examination quantified the cross-sectional correlates of BMI, WC and WHR with several established and emerging cardiovascular disease risk factors, in more detail and with greater precision than has previously been possible. Overall, there were approximately linear and strong associations between BMI and WC, and WHR and WC, and only moderately strong correlations between BMI and WHR. All three measures of adiposity showed continuous and approximately linear associations with blood pressure, fasting glucose and inflammatory markers, and slightly curvilinear associations with lipid markers. Despite suggestions that visceral fat is more metabolically active than other fat depots,[15] correlations with these intermediate risk factors on the pathway between excess body fat and cardiovascular disease were broadly similar for BMI, WC and WHR. In both males and females, BMI, WC and WHR were most strongly associated with blood pressure, HDL cholesterol, triglyceride, CRP and IL-6. Overall, adiposity measures were significantly higher in individuals of non-European descent, in physically inactive people, in people with a history of diabetes and in people with low levels of education. Whereas mean BMI and WC values were somewhat lower in current smokers and current alcohol drinkers, mean WC and WHR values were higher in males than in females.

Adiposity measures

The current analysis showed strong positive and approximately linear correlations between BMI and WC, and WHR and WC for both men and women, while there were only moderately strong correlations between BMI and WHR for both sexes. Consistent with the European Prospective Investigation into Cancer[16] (EPIC), a large prospective cohort study with more than 350,000 participants from 9 countries, the association between BMI and WHR was

somewhat stronger in men than in women. The current data suggest that BMI, WC and WHR may provide related but somewhat distinct information on adiposity. BMI correlates strongly with total fat mass, while WHR correlates well with abdominal fat mass.[17,18] Therefore, the strong correlation of WC with both BMI and WHR suggests that WC may capture information on body fat distribution, as well as on total body fatness.

Age, sex and ethnicity

In keeping with previous studies,[19-21] the present data demonstrate that mean values of adiposity measures generally increased with the age of participants until about 55-75 years, then flattened or declined in participants at older ages. The observed reduction of BMI values may be explained by a relatively greater loss of lean body mass than gain in fat mass at older ages.[22,23] As expected, mean BMI values were similar in males and females, while there were large sex differences in WC and WHR, with higher values in men than in women. The similarity in BMI values in both sexes is in contrast to the findings of a large cross-sectional study involving 150,000 men and women living in Mexico City, which observed much higher BMI values in women than in men.[24] The majority of participants in the ERFC are of European ancestry, hence relatively little information was available on other ethnicities. The current analysis combined all participants of non-European ancestry into one single category that consisted predominantly of black (37%) and East-Asian (36%) participants. Because body composition varies between different ethnicities, the interpretation of the observed differences is difficult. East-Asians are known to have generally lower values in adiposity measures compared to people of European ancestry.[25-27] By contrast, several studies have reported higher adiposity measure values in black women than in white women, while adiposity measure values were generally lower in black men compared to white men.[25,26,28-32] Such sex differences in the black population might explain the opposing associations observed for non-white men and non-white women in the current analysis.

Smoking, alcohol consumption, physical activity and socioeconomic status

The present data demonstrate that overall BMI and WC values were lower in current smokers than in ex- and never smokers. By contrast, overall WHR values were slightly lower in ex- and never smokers than in current smokers, even after adjustment for alcohol consumption, physical activity and education. The current data are supported by the findings of several studies.[21,33-44] The biological mechanisms of such differences in adiposity measures are unclear. It has been suggested that increased androgenicity may mediate the effect of smoking

on the distribution of body fat, leading to a relatively greater deposition of adipose tissue in the abdominal region compared to the gluteofemoral area.[38,43] Consistent with findings from the Prospective Studies Collaboration (PSC),[19] overall BMI values were lower in alcohol drinkers than in alcohol abstainers. Whereas overall WC values were also lower in current alcohol drinkers, no significant differences were observed in overall WHR values between current drinkers and ex- or never drinkers. Given that alcohol is high in calories, these findings may be surprising, as values of adiposity measures would be expected to be higher in alcohol drinkers. Further investigation of possible mechanisms is needed. Values of adiposity measures were lower in physically active people than in less active participants. Previous studies have suggested that increased physical activity is related to reductions in abdominal adiposity, however not necessarily in BMI.[45-48] The mechanism by which physical activity reduces obesity, in particular abdominal adiposity, is not fully understood but it is believed to be related to a relative increase in lipolysis in subcutaneous abdominal adipose tissue.[47] BMI, WC and WHR values tended to be higher in persons with low socioeconomic status (as indicated by the level of education reached). Consistent with previous findings,[49-51] the inverse association between socioeconomic status and adiposity measures was stronger in women than in men in the current analysis. Possible explanations for the sex differences are still unknown. Education is an indicator of acquisition of beliefs and knowledge.[52] It has been suggested that people with higher education are more likely to integrate healthy behaviours into their everyday lives than people with less education.[53] This may provide an explanation as to why people with higher socioeconomic status have lower adiposity measure values.

Blood pressure, fasting glucose and diabetes

BMI, WC and WHR were linearly and positively correlated with blood pressure levels, although the correlation of WHR was somewhat weaker. The positive relationship between adiposity and blood pressure is well established, however the underlying biological mechanisms are poorly understood.[54,55] It has been suggested that in overweight and obese persons the complex interaction of several metabolic and neurohormonal pathways, such as the rennin-angiotensin-aldosterone and sympathetic nervous systems, leads to increased peripheral vascular resistance.[55-58] Contrary to previous suggestions that measures of abdominal adiposity are more strongly related to diabetes,[59] BMI, WC and WHR were similarly and positively correlated with fasting glucose, and were all significantly higher in people with a history of diabetes. Obesity is associated with insulin resistance which, in combination with impaired pancreatic β-cell function, leads to hyperglycaemia and type II diabetes.[60]

Lipid markers

BMI, WC and WHR were similarly associated with lipid markers, with particularly strong correlates for non-HDL cholesterol and triglyceride. It has been postulated that obesity, in particular visceral adiposity, promotes the release of non-esterified fatty acids which are converted by enzymes in the liver into triglyceride-rich very low density lipoprotein (VLDL) particles and, by the action of cholesterol ester transfer protein (CETP), into triglyceride-rich low density lipoprotein (LDL) cholesterol particles (VLDL plus LDL comprise non-HDL cholesterol).[1,61] This also explains the observed correlation with apolipoprotein-B, as this apolipoprotein is specifically incorporated into non-HDL cholesterol particles. The up-regulation of CETP leads simultaneously to a decrease in HDL particles and hence apolipoprotein-AI, which may explain the inverse correlation with adiposity measures.[1,61]

Inflammatory markers

Adiposity measures were positively correlated with inflammatory markers, such as CRP, IL-6, fibrinogen and white cell count. These findings are consistent with the suggestion that obesity induces low-grade inflammation. As described in **Chapter 1** on pages 5-7, adipose tissue, composed of adipocytes, macrophages and other cells, releases several cytokines and inflammatory markers, such as TNF-α, IL-6 and IL-1β, which stimulate the liver to produce CRP and other inflammatory markers.[1,3,4] However, the relevance of inflammation for the pathogenesis of cardiovascular disease is still unclear, as discussed in detail in **Chapter 5** on page 121.

Strength and limitations

The general strengths and limitations of the ERFC are described in more detail in **Chapter 8**. Briefly, the present analysis provides the most precise, reliable and comprehensive assessment of the cross-sectional correlates of BMI, WC and WHR in up to 221,934 adults from 58 prospective studies with concomitant information on weight, height, and waist and hip circumference. In contrast to some previous investigations, the present meta-analysis should have minimised any impact of pre-existing cardiovascular diseases, because it involved only participants without known cardiovascular disease. Subsidiary findings excluding participants with death or a cardiovascular event during the first five years of follow-up were very similar to the overall findings, further limiting the scope of any "reverse association" biases due to subclinical or unreported disease. Because the present analyses were restricted to data available to the ERFC, it was not possible to investigate the association with dietary factors

(eg, calorie intake), cytokines (eg, TNF-α and other interleukins), or hormone concentrations (eg, leptin or adiponectin). The impact of any measurement error in adiposity measures or correlates on the associations was not assessed. Because within-person variability of WHR is larger than that of WC and BMI (**Chapter 4**), the observed associations with WHR may be somewhat underestimated. But as all analyses of error-prone traits were restricted to measurements taken at the same time as adiposity measures, the impact of any temporal trend (such as within-person variability through time) should have been minimised.

Conclusion

Although the correlations between clinical measures of adiposity differed, BMI, WC and WHR were similarly and importantly associated with blood pressure, fasting glucose and lipids. This finding highlights the importance of these intermediate risk factors on the pathway between excess body fat and cardiovascular disease. Furthermore, adiposity measures were correlated with age, smoking status and other lifestyle characteristics (such as alcohol consumption, physical activity and socioeconomic status), suggesting possible scope for confounding in observational studies of associations of adiposity measures with disease risk.

Chapter 3 – References

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Table 3.1 Summary of data available on BMI, WC, WHR and other covariates

	No of studies	No of participants	Mean (SD) or %
Adiposity measures			
BMI (kg/m^2)	58	221934	27 (4.56)
WC (cm)	58	221934	91 (12.6)
WHR	58	221934	0.90 (0.083)
Age at survey (yrs)	58	221934	58 (9)
BP and fasting glucose			
Systolic BP (mmHg)	53	191170	135 (20)
Diastolic BP (mmHg)	53	191112	80 (11)
Fasting glucose (mmol/l)	34	85330	5.6 (1.8)
Lipid markers			
Total cholesterol (mmol/l)	53	179735	5.80 (1.10)
Non-HDL cholesterol (mmol/l)	50	174024	4.40 (1.12)
HDL cholesterol (mmol/l)	50	174095	1.40 (0.40)
Log_e triglyceride (mmol/l)	47	146974	0.31 (0.53)
Apo AI (g/l)	17	63156	1.53 (0.30)
Apo B (g/l)	16	62347	1.13 (0.30)
Log_e Lp(a) (mg/dl)	15	55520	2.45 (1.17)
Inflammatory markers			
Fibrinogen (µmol/l)	28	97608	8.7 (2.1)
Log_e CRP (mg/l)	30	67483	0.66 (1.08)
Albumin (g/l)	19	64230	43 (3)
Log_e leukocyte count (x10^9 per l)	18	61522	1.82 (0.28)
Log_e Interleukin 6 (ng/l)	8	24290	0.57 (0.64)
Categorical variables			
Sex	58	221934	
Female		124189	56%
Male		97745	44%
Ethnicity	44	145882	
Non-white		28956	20%
White		116926	80%
Smoking status	58	219092	
Current		52261	24%
Not current		166831	76%
Alcohol status	47	195186	
Current		110199	56%
Not current		84987	44%
Physical activity	26	81707	
Active		26659	33%
Not active		55048	67%
History of diabetes	56	203849	
Yes		13899	7%
No		189950	93%
Level of education reached	33	125162	
Tertiary		34013	27%
Secondary		64186	51%
No schooling/Primary		26963	22%

Table 3.2 Correlations (95% CI) of BMI, WC and WHR with several continuous variables, stratified by sex

	BMI		WC		WHR	
	Males	Females	Males	Females	Males	Females
Adiposity measures						
BMI (kg/m^2)	-	-	0.86 (0.85, 0.87)	0.84 (0.82, 0.85)	0.52 (0.49, 0.54)	0.37 (0.34, 0.41)
Waist circumference (cm)	0.86 (0.85, 0.87)	0.84 (0.82, 0.85)	-	-	0.73 (0.71, 0.76)	0.71 (0.69, 0.74)
Waist/hip ratio	0.52 (0.49, 0.54)	0.37 (0.34, 0.41)	0.73 (0.71, 0.76)	0.71 (0.69, 0.74)	-	-
Age at survey (yrs)	-0.01 (-0.05, 0.03)	0.10 (0.06, 0.15)	0.10 (0.05, 0.14)	0.19 (0.16, 0.23)	0.16 (0.12, 0.21)	0.23 (0.20, 0.25)
BP and fasting glucose						
Systolic BP (mmHg)	0.19 (0.17, 0.22)	0.25 (0.22, 0.28)	0.21 (0.19, 0.24)	0.27 (0.24, 0.30)	0.20 (0.17, 0.23)	0.22 (0.19, 0.24)
Diastolic BP (mmHg)	0.26 (0.23, 0.28)	0.26 (0.24, 0.29)	0.24 (0.21, 0.27)	0.25 (0.22, 0.27)	0.18 (0.14, 0.21)	0.15 (0.12, 0.18)
Fasting glucose (mmol/l)	0.16 (0.14, 0.17)	0.22 (0.19, 0.24)	0.18 (0.16, 0.19)	0.24 (0.22, 0.26)	0.16 (0.14, 0.18)	0.20 (0.17, 0.23)
Lipid markers						
Total cholesterol (mmol/l)	0.11 (0.08, 0.13)	0.09 (0.06, 0.12)	0.10 (0.08, 0.13)	0.11 (0.08, 0.15)	0.11 (0.08, 0.14)	0.14 (0.11, 0.16)
Non-HDL cholesterol (mmol/l)	0.19 (0.17, 0.21)	0.18 (0.15, 0.21)	0.19 (0.16, 0.21)	0.21 (0.18, 0.24)	0.17 (0.14, 0.20)	0.21 (0.18, 0.24)
HDL cholesterol (mmol/l)	-0.27 (-0.28, -0.25)	-0.26 (-0.28, -0.25)	-0.26 (-0.27, -0.24)	-0.28 (-0.30, -0.26)	-0.19 (-0.21, -0.17)	-0.22 (-0.25, -0.20)
Log_e triglycerides (mmol/l)	0.30 (0.28, 0.32)	0.28 (0.25, 0.32)	0.31 (0.29, 0.33)	0.34 (0.31, 0.37)	0.28 (0.25, 0.30)	0.32 (0.28, 0.35)
Apo AI (g/l)	-0.17 (-0.19, -0.15)	-0.16 (-0.19, -0.14)	-0.16 (-0.19, -0.13)	-0.17 (-0.20, -0.14)	-0.12 (-0.15, -0.08)	-0.13 (-0.16, -0.09)
Apo B (g/l)	0.16 (0.12, 0.20)	0.14 (0.08, 0.21)	0.17 (0.13, 0.22)	0.18 (0.11, 0.24)	0.16 (0.11, 0.21)	0.19 (0.14, 0.25)
Log_e Lp(a) (mg/dl)	-0.03 (-0.06, -0.01)	0.03 (-0.02, 0.08)	-0.05 (-0.08, -0.02)	0.02 (-0.03, 0.06)	-0.06 (-0.10, -0.01)	0.00 (-0.03, 0.04)
Inflammatory markers						
Log_e CRP (mg/l)	0.21 (0.17, 0.26)	0.37 (0.33, 0.41)	0.26 (0.22, 0.30)	0.37 (0.33, 0.41)	0.25 (0.21, 0.29)	0.24 (0.21, 0.27)
Fibrinogen (µmol/l)	0.09 (0.06, 0.12)	0.25 (0.22, 0.28)	0.14 (0.10, 0.17)	0.26 (0.23, 0.29)	0.16 (0.13, 0.19)	0.18 (0.15, 0.21)
Albumin (g/l)	0.03 (-0.01, 0.07)	-0.09 (-0.14, -0.03)	-0.01 (-0.05, 0.03)	-0.09 (-0.14, -0.04)	-0.03 (-0.07, 0.01)	-0.03 (-0.06, -0.01)
Log_e leukocyte count (x10^9 per l)	0.06 (0.04, 0.07)	0.09 (0.07, 0.12)	0.10 (0.08, 0.12)	0.10 (0.08, 0.13)	0.13 (0.10, 0.16)	0.10 (0.07, 0.13)
Log_e Interleukin 6 (ng/l)	0.18 (0.13, 0.22)	0.33 (0.25, 0.41)	0.21 (0.16, 0.27)	0.34 (0.26, 0.41)	0.22 (0.17, 0.27)	0.23 (0.16, 0.29)

Sex-specific correlation coefficients were calculated using studies comprising both male and female participants.

Table 3.3 Cross-sectional associations of BMI, WC and WHR with various continuous variables

	Difference (95% CI) in row variables per 1-SD higher level of adiposity measures[¶]		
	BMI (kg/m^2)	**WC (cm)**	**WHR**
Adiposity measures			
BMI (kg/m^2)	-	4.06 (3.95, 4.17)	2.21 (2.05, 2.38)
WC (cm)	10.05 (9.85, 10.26)	-	9.50 (9.08, 9.91)
WHR	0.03 (0.03, 0.03)	0.05 (0.05, 0.06)	-
BP and fasting glucose			
Systolic BP (mmHg)	4.40 (4.00, 4.81)	4.41 (4.02, 4.80)	3.37 (3.08, 3.67)
Diastolic BP (mmHg)	2.95 (2.60, 3.31)	2.93 (2.59, 3.27)	2.09 (1.83, 2.35)
Fasting glucose (mmol/l)	0.29 (0.26, 0.32)	0.33 (0.28, 0.37)	0.29 (0.22, 0.36)
Lipid markers			
Total cholesterol (mmol/l)	0.09 (0.06, 0.11)	0.09 (0.07, 0.12)	0.12 (0.10, 0.14)
Non-HDL-cholesterol (mmol/l)	0.19 (0.16, 0.22)	0.21 (0.18, 0.24)	0.22 (0.19, 0.25)
HDL-cholesterol (mmol/l)	-0.11 (-0.11, -0.10)	-0.12 (-0.12, -0.11)	-0.10 (-0.11, -0.09)
Log_e triglycerides (mmol/l)	0.16 (0.14, 0.18)	0.18 (0.17, 0.20)	0.18 (0.16, 0.19)
Apo AI (g/l)	-0.05 (-0.06, -0.04)	-0.05 (-0.06, -0.04)	-0.04 (-0.06, -0.03)
Apo B (g/l)	0.05 (0.03, 0.06)	0.05 (0.04, 0.07)	0.05 (0.03, 0.07)
Log_e Lp(a) (mg/dl)	0.01 (-0.02, 0.04)	-0.01 (-0.04, 0.01)	-0.04 (-0.07, -0.01)
Inflammatory markers			
Fibrinogen (µmol/l)	0.33 (0.27, 0.39)	0.35 (0.28, 0.41)	0.30 (0.24, 0.37)
Log_e CRP (mg/l)	0.33 (0.29, 0.37)	0.36 (0.32, 0.40)	0.31 (0.26, 0.35)
Albumin (g/l)	-0.11 (-0.25, 0.03)	-0.10 (-0.22, 0.03)	0.02 (-0.06, 0.10)
Log_e leukocyte count (x10^9 per l)	0.03 (0.02, 0.03)	0.03 (0.03, 0.04)	0.04 (0.03, 0.05)
Log_e Interleukin 6 (ng/l)	0.15 (0.11, 0.19)	0.16 (0.12, 0.21)	0.14 (0.10, 0.19)

[¶]Change in row variable (adiposity measure or potential mediating risk factor) per 1-SD higher BMI, WC or WHR, adjusted for age and sex, pooled across studies using random effects meta-analysis. SDs were 4.56 kg/m^2 for BMI, 12.6 cm for WC and 0.083 for WHR.

Table 3.4 Cross-sectional associations of Z-transformed values of BMI, WC and WHR with various categorical variables and age at baseline

	Difference (95% CI) in Z-score of adiposity measures per 1-SD higher level in row variable or compared to reference category ‡		
	BMI (kg/m^2)	**WC (cm)**	**WHR**
Age at survey (yrs)	0.02 (-0.02, 0.06)	0.11 (0.08, 0.14)	0.15 (0.12, 0.17)
Categorical variables			
Sex			
Female	0.04 (-0.04, 0.11)	-0.63 (-0.74, -0.52)	-1.15 (-1.27, -1.03)
Male	Reference	Reference	Reference
Ethnicity			
Non-white	0.24 (0.13, 0.35)	0.10 (0.00, 0.20)	0.10 (0.01, 0.18)
White	Reference	Reference	Reference
Smoking status			
Current	-0.21 (-0.24, -0.18)	-0.12 (-0.15, -0.09)	0.05 (0.02, 0.07)
Not current	Reference	Reference	Reference
Alcohol status			
Current	-0.13 (-0.17, -0.09)	-0.08 (-0.12, -0.04)	-0.02 (-0.05, 0.01)
Not current	Reference	Reference	Reference
History of diabetes			
Yes	0.43 (0.37, 0.49)	0.46 (0.40, 0.52)	0.36 (0.32, 0.41)
No	Reference	Reference	Reference
Physical activity			
Active	-0.15 (-0.28, -0.03)	-0.18 (-0.30, -0.06)	-0.16 (-0.24, -0.08)
Not active	Reference	Reference	Reference
Level of education reached			
Tertiary	-0.29 (-0.34, -0.23)	-0.24 (-0.29, -0.19)	-0.26 (-0.30, -0.21)
Secondary	-0.17 (-0.21, -0.13)	-0.14 (-0.18, -0.11)	-0.13 (-0.16, -0.10)
No schooling/Primary	Reference	Reference	Reference

‡Difference in mean Z-score of adiposity measure per 1-SD higher levels of the row variable or compared to reference category, adjusted for age and sex, pooled across studies using random effects meta-analysis. Differences by sex were not adjusted for sex. To obtain the original scale of adiposity measures, Z-scores have to be multiplied by the standard deviation (SD) of relevant adiposity measure. SDs were 4.56 kg/m^2 for BMI, 12.6 cm for WC and 0.083 for WHR.

Table 3.5 Cross-sectional associations of Z-transformed values of BMI, WC and WHR with various categorical variables, stratified by sex

	Difference (95% CI) in Z-score of adiposity measures compared to reference category					
	BMI (kg/m^2)		WC (cm)		WHR	
	Males	Females	Males	Females	Males	Females
Ethnicity						
Non-white	-0.01 (-0.06, 0.03)	0.48 (0.29, 0.66)	-0.23 (-0.31, -0.14)	0.34 (0.15, 0.54)	-0.16 (-0.31, -0.01)	0.23 (0.09, 0.36)
White	Reference	Reference	Reference	Reference	Reference	Reference
Smoking status						
Current	-0.18 (-0.21, -0.14)	-0.29 (-0.33, -0.24)	-0.13 (-0.17, -0.10)	-0.20 (-0.25, -0.15)	-0.00 (-0.03, 0.02)	-0.01 (-0.05, 0.03)
Not current	Reference	Reference	Reference	Reference	Reference	Reference
Alcohol status						
Current	-0.03 (-0.06, 0.00)	-0.24 (-0.30, -0.18)	-0.01 (-0.04, 0.02)	-0.22 (-0.27, -0.16)	0.01 (-0.02, 0.04)	-0.14 (-0.19, -0.10)
Not current	Reference	Reference	Reference	Reference	Reference	Reference
History of diabetes						
Yes	0.32 (0.25, 0.38)	0.61 (0.52, 0.69)	0.35 (0.30, 0.41)	0.68 (0.61, 0.76)	0.31 (0.26, 0.37)	0.57 (0.50, 0.64)
No	Reference	Reference	Reference	Reference	Reference	Reference
Physical activity						
Active	-0.11 (-0.19, -0.02)	-0.24 (-0.48, -0.01)	-0.20 (-0.29, -0.10)	-0.22 (-0.42, -0.01)	-0.19 (-0.26, -0.13)	-0.17 (-0.31, -0.02)
Not active	Reference	Reference	Reference	Reference	Reference	Reference
Education reached						
Vocat/Uni	-0.16 (-0.22, -0.09)	-0.52 (-0.63, -0.40)	-0.19 (-0.25, -0.12)	-0.51 (-0.61, -0.40)	-0.32 (-0.40, -0.24)	-0.43 (-0.52, -0.34)
Secondary	-0.09 (-0.13, -0.04)	-0.33 (-0.41, -0.24)	-0.13 (-0.17, -0.08)	-0.33 (-0.39, -0.26)	-0.17 (-0.23, -0.11)	-0.28 (-0.32, -0.23)
Primary	Reference	Reference	Reference	Reference	Reference	Reference

Analyses were restricted to studies comprising both male and female participants. Difference (95% CI) in mean Z-score of adiposity measure compared to reference category, adjusted for age, pooled across studies using random effects meta-analysis. To obtain the original scale of adiposity measures, Z-scores have to be multiplied by the standard deviation (SD) of relevant adiposity measure. SDs were 4.56 kg/m^2 for BMI, 12.6 cm for WC and 0.083 for WHR.

Table 3.6 Cross-sectional associations of Z-transformed values of BMI, WC and WHR with various categorical variables, adjusted for potential confounders

	Difference (95% CI) in Z-score of adiposity measures compared to reference category					
	BMI (kg/m^2)		WC (cm)		WHR	
	Adjusted for age and sex	Further adjusted for potential confounders[†]	Adjusted for age and sex	Further adjusted for potential confounders[†]	Adjusted for age and sex	Further adjusted for potential confounders[†]
Sex						
Female	-0.04 (-0.14, 0.05)	-0.10 (-0.19, -0.02)	-0.78 (-1.02, -0.54)	-0.82 (-1.06, -0.59)	-1.30 (-1.51, -1.09)	-1.32 (-1.53, -1.11)
Male	Reference	Reference	Reference	Reference	Reference	Reference
Race						
Non-white	0.40 (0.09, 0.70)	0.33 (0.04, 0.62)	0.26 (0.09, 0.44)	0.18 (0.01, 0.34)	0.05 (-0.11, 0.20)	-0.01 (-0.19, 0.18)
White	Reference	Reference	Reference	Reference	Reference	Reference
Smoking status						
Current	-0.21 (-0.27, -0.15)	-0.22 (-0.28, -0.17)	-0.09 (-0.14, -0.05)	-0.10 (-0.15, -0.06)	0.07 (0.03, 0.10)	0.05 (0.02, 0.08)
Not current	Reference	Reference	Reference	Reference	Reference	Reference
Alcohol status						
Current	-0.19 (-0.26, -0.12)	-0.14 (-0.21, -0.08)	-0.13 (-0.20, -0.06)	-0.10 (-0.16, -0.03)	-0.05 (-0.10, -0.00)	-0.03 (-0.08, 0.01)
Not current	Reference	Reference	Reference	Reference	Reference	Reference
History of diabetes						
Yes	0.50 (0.40, 0.60)	0.46 (0.36, 0.55)	0.51 (0.42, 0.60)	0.48 (0.39, 0.57)	0.42 (0.34, 0.50)	0.40 (0.33, 0.47)
No	Reference	Reference	Reference	Reference	Reference	Reference
Physical activity						
Active	-0.22 (-0.34, -0.11)	-0.22 (-0.33, -0.10)	-0.25 (-0.37, -0.13)	-0.24 (-0.37, -0.11)	-0.19 (-0.29, -0.09)	-0.17 (-0.27, -0.07)
Not active	Reference	Reference	Reference	Reference	Reference	Reference
Level of education						
Tertiary	-0.31 (-0.38, -0.24)	-0.31 (-0.37, -0.24)	-0.26 (-0.32, -0.21)	-0.26 (-0.31, -0.20)	-0.28 (-0.33, -0.22)	-0.26 (-0.31, -0.21)
Secondary	-0.22 (-0.27, -0.17)	-0.21 (-0.26, -0.15)	-0.16 (-0.21, -0.12)	-0.15 (-0.19, -0.11)	-0.14 (-0.18, -0.10)	-0.13 (-0.17, -0.09)
No schooling/Primary	Reference	Reference	Reference	Reference	Reference	Reference

[†]Potential confounders are smoking status, alcohol status, physical activity and education.

Analysis is restricted to participants with complete information on height, weight, waist and hip circumference, smoking status, alcohol consumption, physical activity and education. Difference in mean Z-score of adiposity measure compared to reference category, adjusted as shown, pooled across studies using random effects meta-analysis. To obtain the original scale of adiposity measures, Z-scores have to be multiplied by the standard deviation (SD) of relevant adiposity measure. Differences by sex were not adjusted for sex. SDs were 4.56 kg/m^2 for BMI, 12.6 cm for WC and 0.083 for WHR.

Figure 3.1 Mean values of adiposity measure according to studies (panel A) and within 5-year age bands adjusted for studies (panel B)

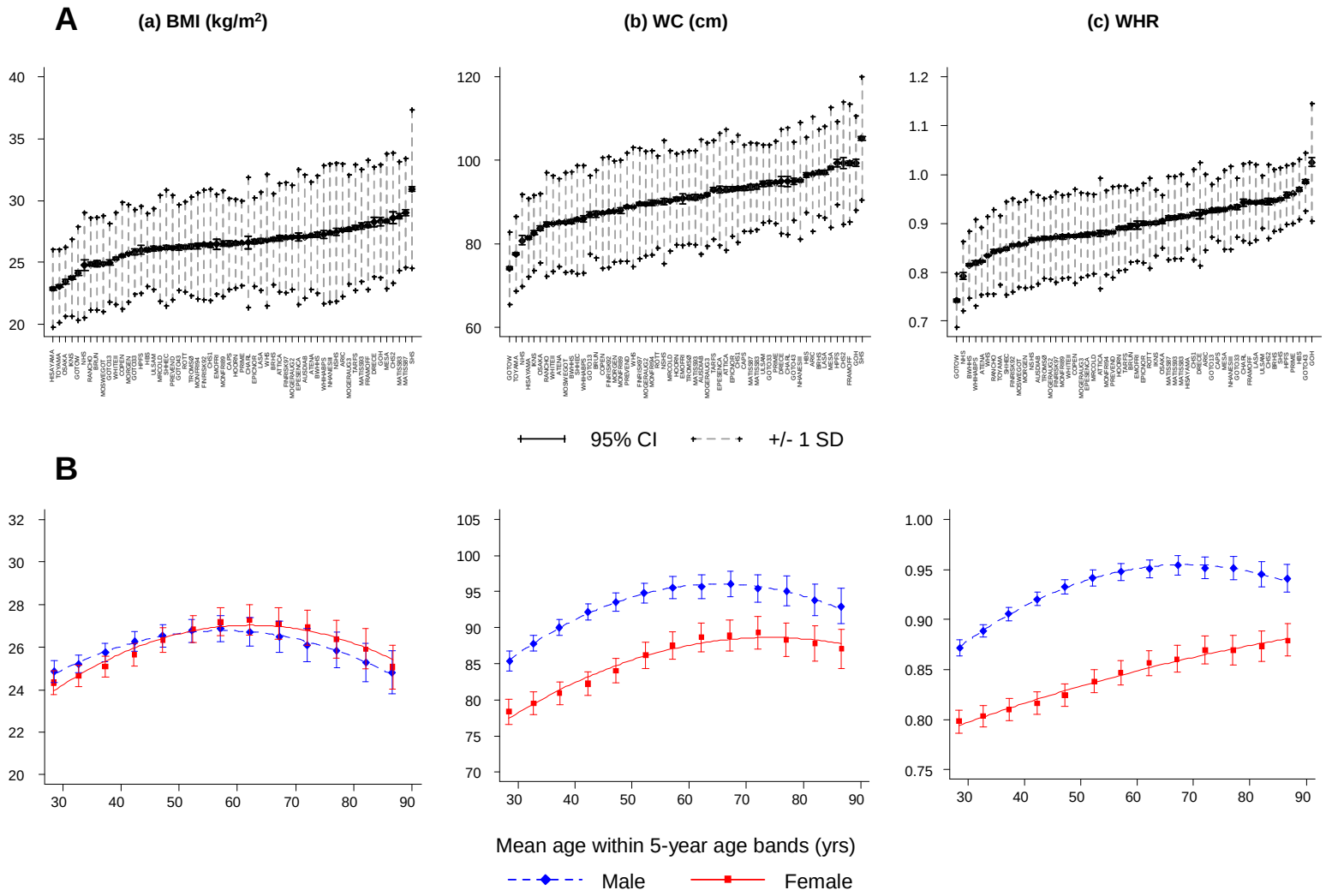
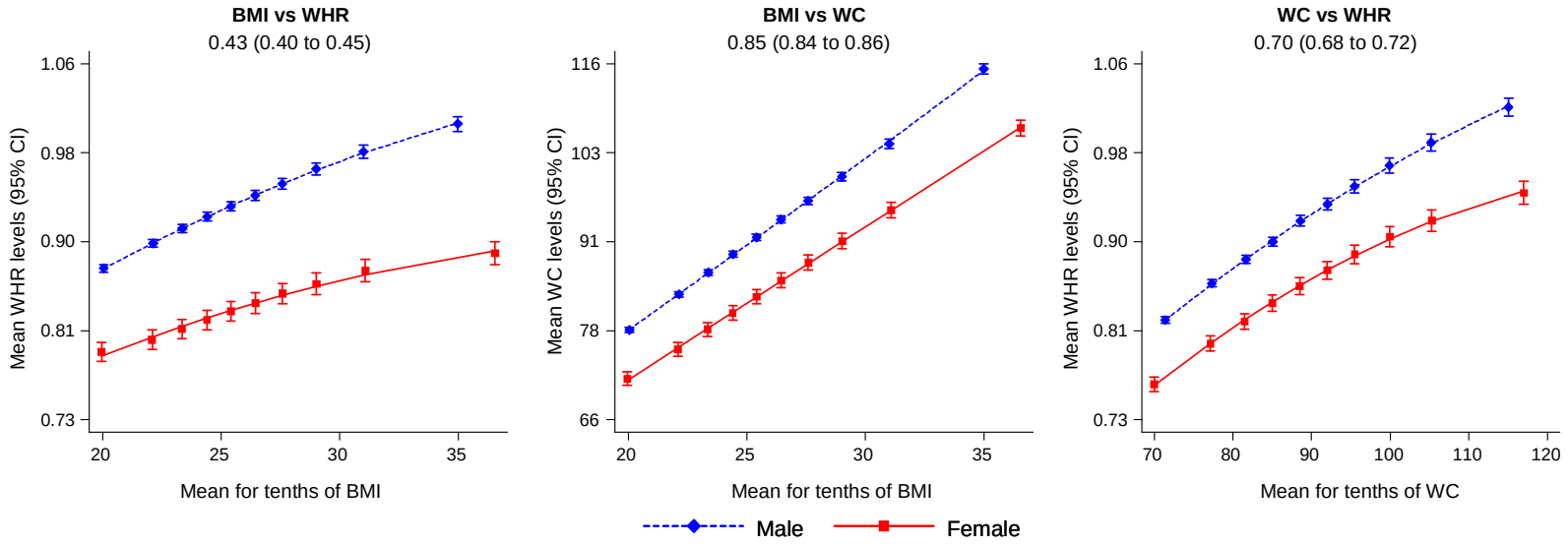
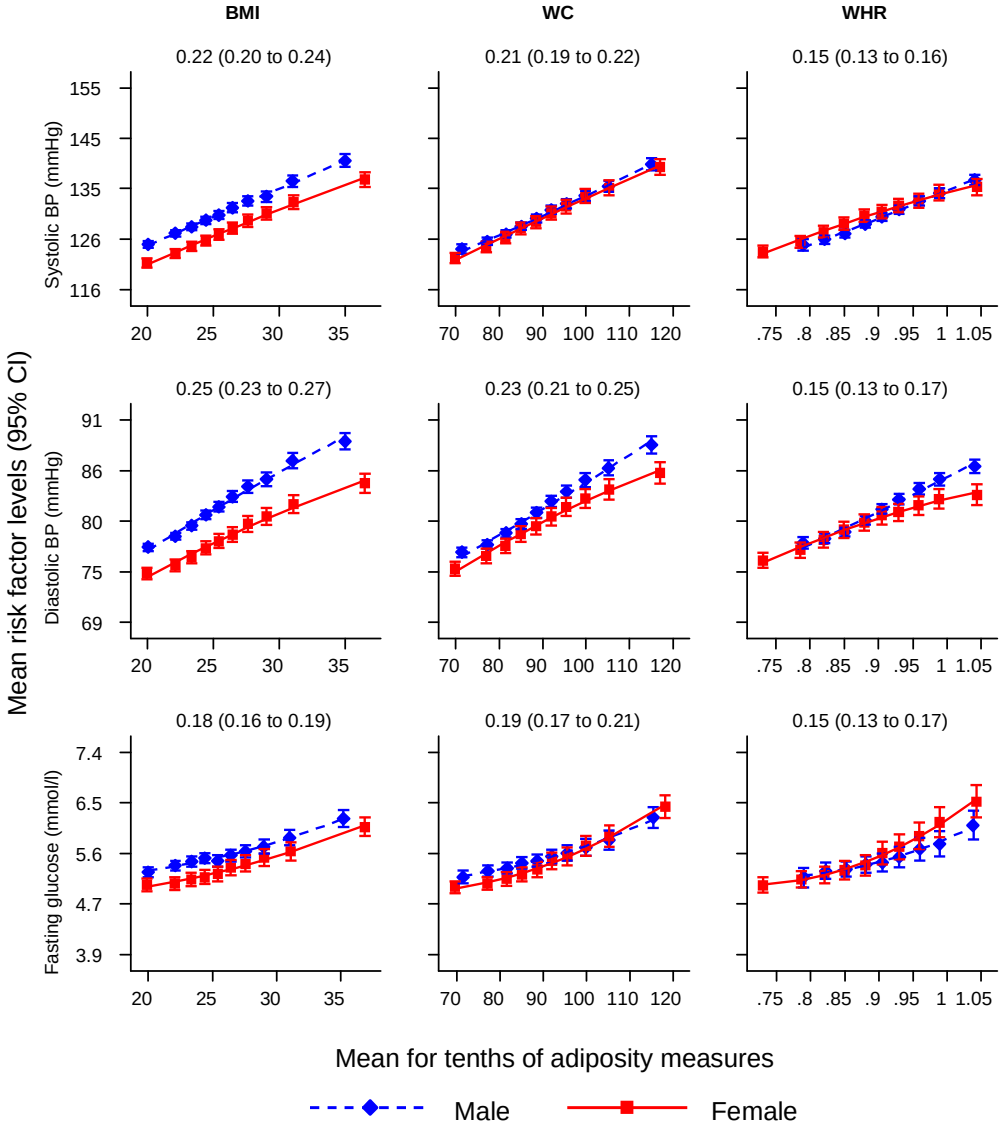


Figure 3.2 Cross-sectional associations between values of adiposity measures with each other



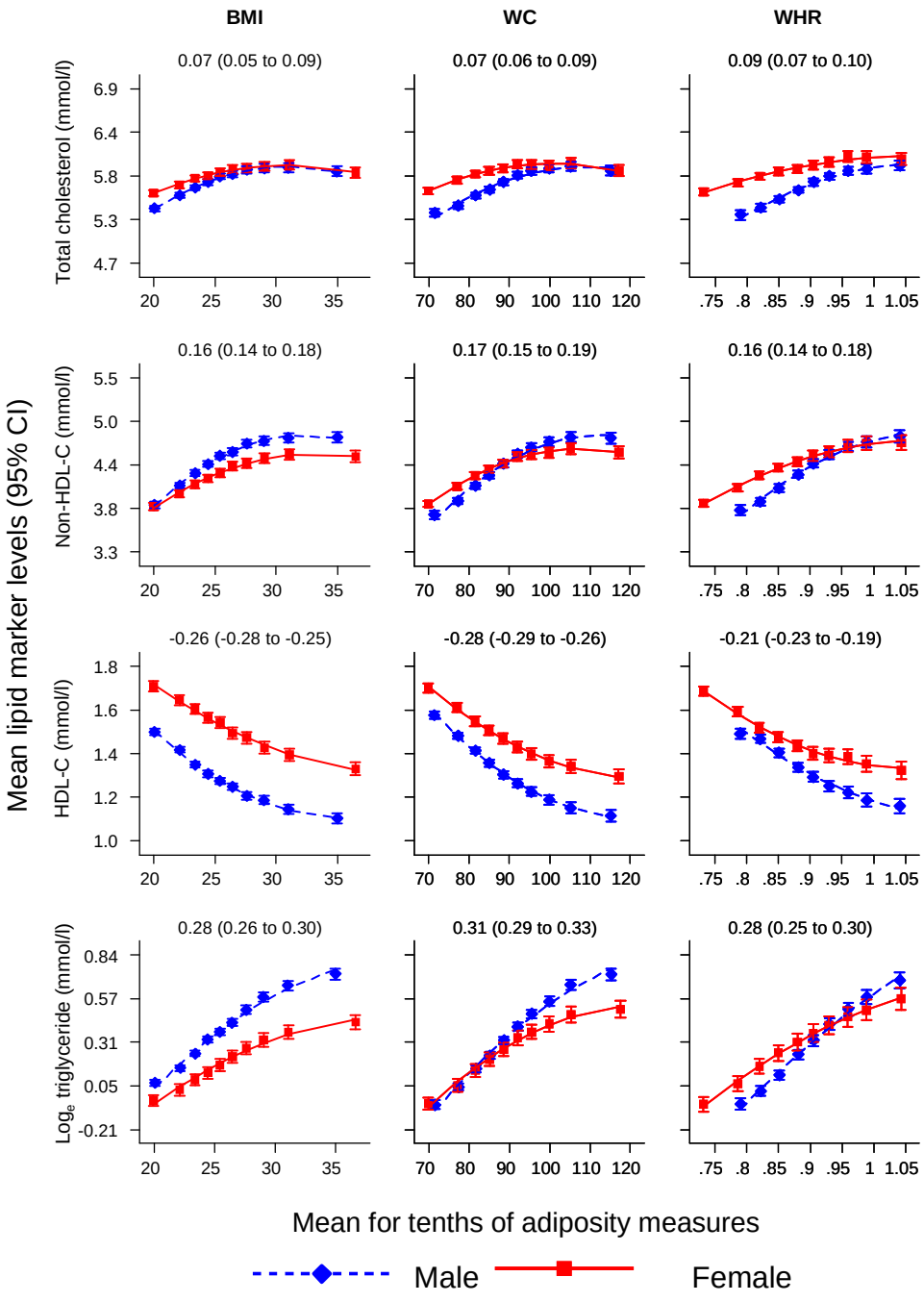
Mean adiposity measure values were adjusted to age 50 years. The values presented above each figure correspond to the age and sex adjusted partial correlation coefficient (95% CI) between adiposity measures in males and females combined. Y-axes are standardised to correspond to SD differences.

Figure 3.3 Cross-sectional associations of adiposity measures with blood pressure and fasting glucose



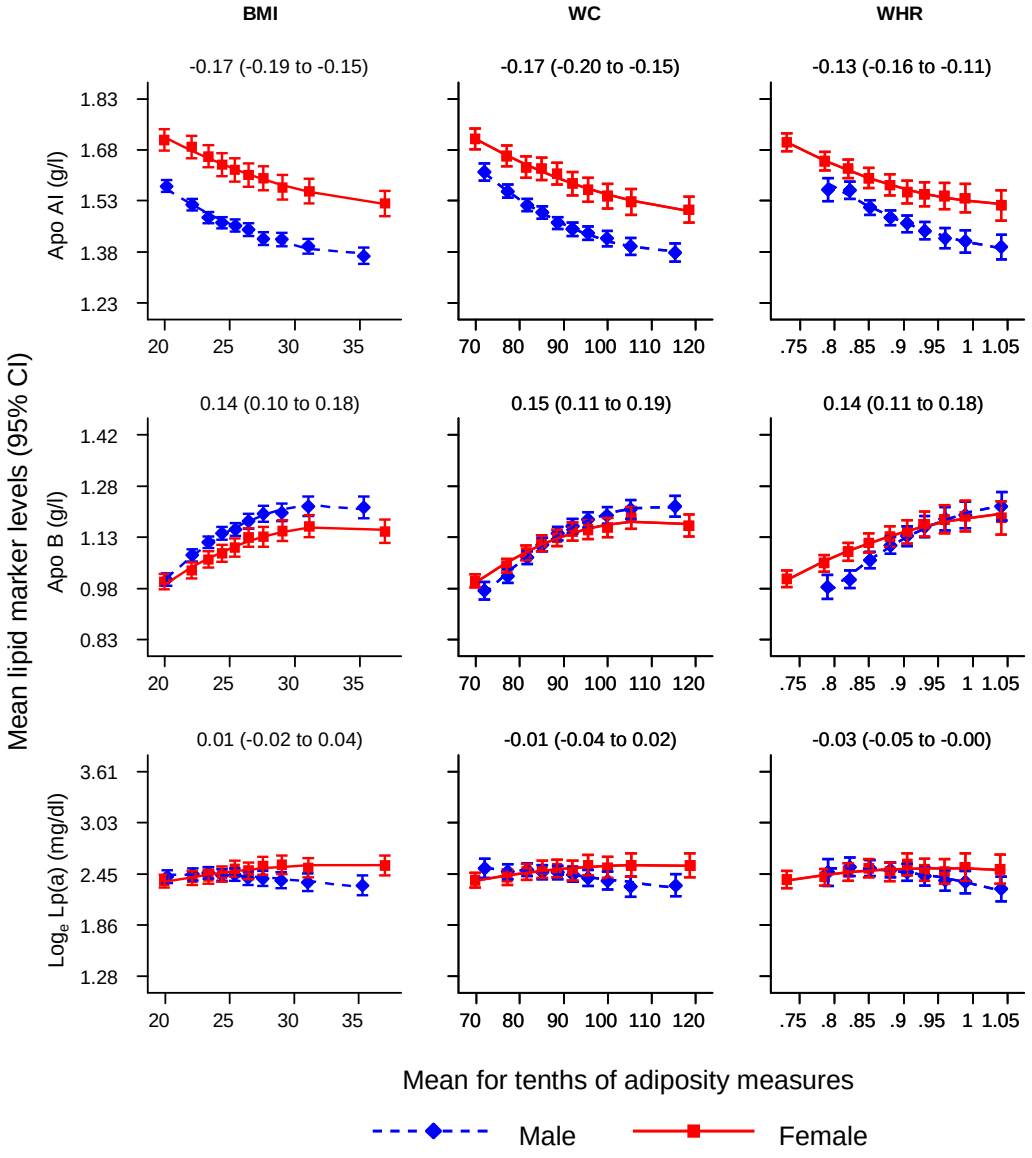
Mean risk factor values were adjusted to age 50 years. The values presented above each figure correspond to the age and sex adjusted partial correlation coefficient (95% CI) between adiposity measures and BP/fasting glucose in males and females combined. Y-axes are standardised to correspond to ½-SD differences.

Figure 3.4 Cross-sectional associations of adiposity measures with lipid markers



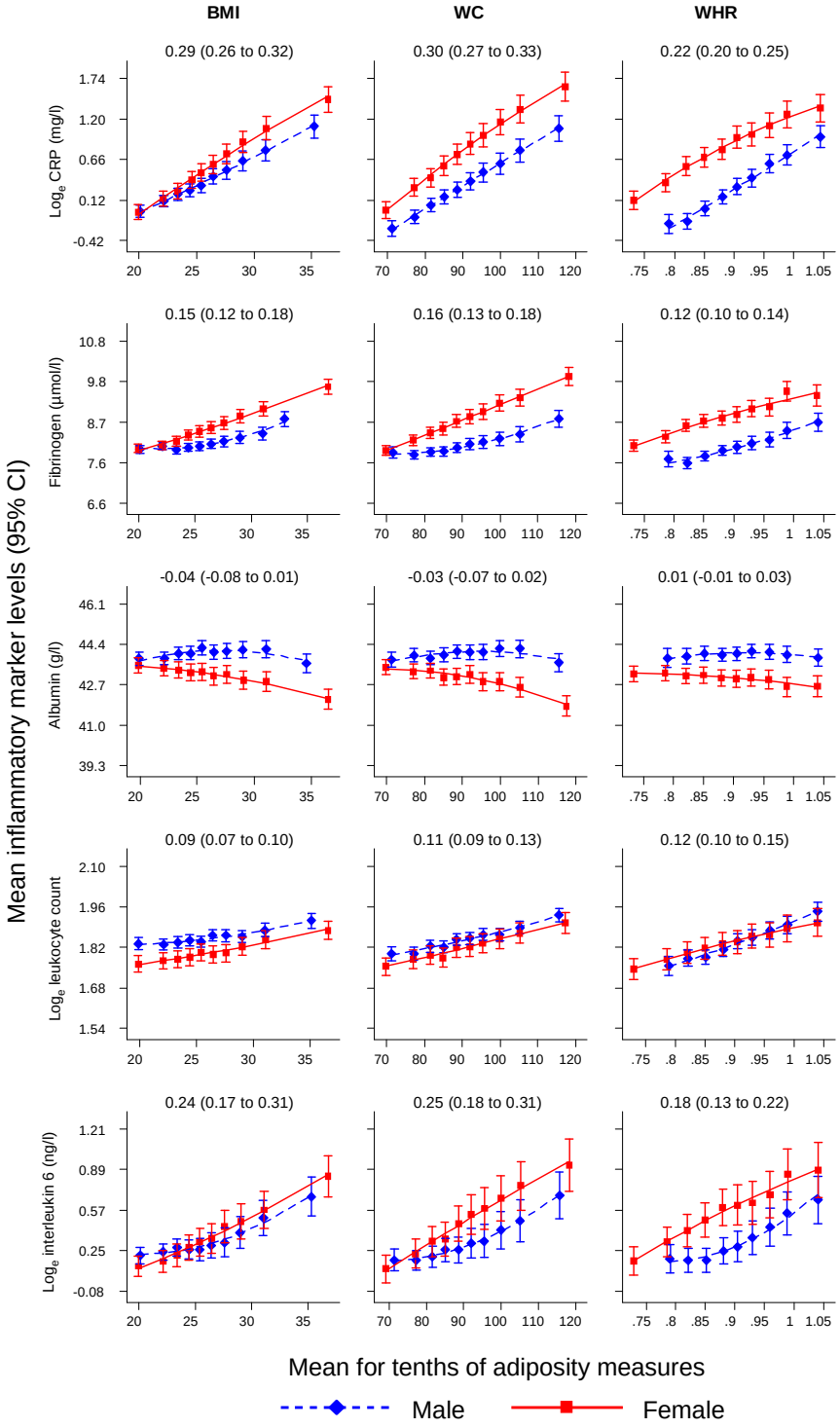
Mean risk factor values were adjusted to age 50 years. The values presented above each figure correspond to the age and sex adjusted partial correlation coefficient (95% CI) between adiposity measures and lipid markers in males and females combined. Y-axes are standardised to correspond to ½-SD differences.

Figure 3.5 Cross-sectional associations of adiposity measures with apolipoproteins and Lp(a)



Mean risk factor values were adjusted to age 50 years. The values presented above each figure correspond to the age and sex adjusted partial correlation coefficient (95% CI) between adiposity measures and apolipoproteins/Lp(a) in males and females combined. Y-axes are standardised to correspond to ½-SD differences.

Figure 3.6 Cross-sectional associations of adiposity measures with inflammatory markers



Mean risk factor values were adjusted to age 50 years. The values presented above each figure correspond to the age and sex adjusted partial correlation coefficient (95% CI) between adiposity measures and inflammatory markers in males and females combined. Y-axes are standardised to correspond to ½-SD differences.

CHAPTER 4: Within-person variability in adiposity measures

Summary

Within-person variability in risk factors can bias aetiological associations with disease risk. While within-person variability in directly measured risk factors has been extensively studied, less is known about within-person variability in calculated risk factors, such as sums or ratios, of measured variables. This chapter illustrates the extent of within-person variability in calculated variables and reports on such variability in body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR), using data on over 79,000 serial measurements taken on average of 6 years apart in over 42,000 participants from 12 prospective studies. Within-person variability was assessed by the regression dilution ratio (RDR). The findings show that the extent of within-person variability in calculated risk factors can be considerably larger (or smaller) than the within-person variability in its components. Furthermore, the present data demonstrate that the reproducibility (ie, low within-person variability) of BMI (RDR 0.96 [95% confidence interval [CI] 0.94-0.98]) is superior to that of WC (RDR 0.88 [95% CI 0.86-0.91]) and WHR (RDR 0.66 [95% CI 0.59-0.72]). The within-person variability in adiposity measures is not materially influenced by several characteristics, although the RDR of WHR varies somewhat by sex, diabetes status and baseline WHR values. These findings suggest that the degree of underestimation of the magnitude of association with disease risk is smaller for BMI than for WC and WHR in analyses using baseline values.

Background

Epidemiological analyses often aim to estimate the aetiological association between error-free levels of risk factors and the likelihood of disease. Because most risk factors are measured with error and are subject to fluctuations within individuals, analyses that use only one single measurement of a risk factor may produce biased estimates of such associations.[1,2] Such bias can be caused by technical measurement error and/or within-person variation.[3,4] These sources of variability are classed together as "within-person variability" in the present chapter. In regression analyses with only a single risk factor, within-person variability leads to an underestimation of the true magnitude of the association between long-term average levels of the risk factor and disease (regression dilution bias),[5,6] whereas in analyses with multiple error-prone risk factors the association may be either over- or underestimated.[7] Various methods have been proposed to quantify and to correct the effect of within-person variability in aetiological associations estimated from a single measurement of the risk factor.[2,8]

While within-person variability in directly measured risk factors (eg, blood pressure[9] or fibrinogen[10]) has been extensively studied, less is known about within-person variability in calculated risk factors, such as sums and differences (eg, change in height) or ratios (eg, body-mass index [BMI] or waist-to-hip ratio [WHR]) of measured variables. This chapter will show that the extent of within-person variability in calculated risk factors can often appear higher or lower than expected in comparison to the within-person variability in the components that comprise the calculated risk factor.

Current information on variability in adiposity measures is mostly based on studies conducted in a small number of individuals over a short time period (<6 months).[11-14] A relatively small study with repeat measurements taken over three years in almost 2,000 participants, investigated long-term within-person variability in adiposity ratios and anthropometric indicators by use of the intra-class correlation coefficient.[15] The findings of that study suggested that the within-person variability in BMI is lower than that of waist circumference (WC) and WHR.

The objectives of this chapter are to (i) illustrate the extent of within-person variability in calculated variables; (ii) produce reliable estimates that quantify the within-person variability of BMI, WC and WHR; and (iii) identify important determinants of such variability. This chapter reports data from 79,145 serial measurements made in 42,300 participants from 12 studies in the Emerging Risk Factors Collaboration (ERFC).

Methods

Study design

Details of data on adiposity measures in the ERFC are given in **Chapter 2**. Briefly, the current analysis involves individual records from 12 prospective studies. A total of 42,300 participants without known history of cardiovascular disease at the initial ("baseline") examination had concomitant information on height, weight, waist and hip circumference at baseline examination and at resurvey.

Regression dilution ratios

The within-person variability in adiposity ratios and anthropometric indicators was quantified by the regression dilution ratio (RDR).[5,9,10] The RDR estimates the extent to which an individual's adiposity measurements vary around a long-term average adiposity level. The assumption is that knowledge of the long-term average level of an adiposity measure would completely capture the risk of disease associated with that adiposity measure.[16]

The RDR is a ratio of the between-person variance over the total-variance (= between-person variance + within-person variance).[17] Values of the RDR close to one suggest a small degree of within-person variability, and values closer to zero imply greater levels of within-person variability. Using *Rosner's regression approach*,[8] RDRs were estimated by regressing a repeat measurement of adiposity measures on their baseline values. Study and resurvey-specific RDRs were estimated from separate linear regression models in each study and at each resurvey. So, for each study $s = 1 \ldots S$, with individuals $i = 1 \ldots n_s$, and repeat measurements $r = 1 \ldots r_{si}$, the model can be written as

$$E_{sir} = \alpha_{sr} + \beta_{sr} E_{si} + \varepsilon_{sir}, \qquad (4.1)$$

where $\varepsilon_{sir} \sim N(0, \sigma^2_{sr})$ and β_{sr} is the study and resurvey-specific RDR. E_{sir} and E_{si} represent repeat and baseline measurements of adiposity measure E, respectively. α_{sr} represents the study and resurvey-specific intercept. Overall RDRs were estimated from a single linear mixed model of the repeat measurement on the baseline measurement, adjusted for study and resurvey (to allow for general differences in mean levels between studies and at different resurveys) and with allowance for between-study heterogeneity in the RDR and between-

person heterogeneity in mean levels (to account for multiple repeat measurements per individual).

The overall RDR was obtained using the following model

$$E_{sir} = \alpha_{sr} + (\beta + u_s)E_{si} + w_{si} + \varepsilon_{sir}, \qquad (4.2)$$

where $u_s \sim N(0,\sigma_u^2)$, $w_{si} \sim N(0,\sigma_w^2)$ and $\varepsilon_{sir} \sim N(0,\sigma_e^2)$. Between-study heterogeneity on the estimated RDR value β is represented by σ_u^2. The parameters σ_w^2 and σ_e^2 represent individual-specific and residual variation, respectively. Overall within and between-person variances were estimated from a further single linear mixed model, using all baseline and resurvey measurements as the dependent variable, adjusted for study and resurvey.

Adjusting RDR for covariates

To assess the impact of confounders (or mediators) on the RDR of adiposity measures, baseline covariates X_{si} (eg, age, sex, smoking status, systolic blood pressure [SBP], high-density lipoprotein [HDL] and non-HDL cholesterol, and $\log_e$ triglyceride) were included progressively in regression model (4.2) as fixed coefficient terms. The adjusted Rosner regression model is given by

$$E_{sir} = \alpha_{sr} + (\beta + u_s)E_{si} + \lambda X_{si} + w_{si} + \varepsilon_{sir}, \qquad (4.3)$$

where $u_s \sim N(0,\sigma_u^2)$, $w_{si} \sim N(0,\sigma_w^2)$ and $\varepsilon_{sir} \sim N(0,\sigma_e^2)$. β represents the overall RDR, adjusted for covariates X_{si}.

Determinants of variability

Investigation of potential determinants of variability (ie, time since baseline, age, sex, smoking status, history of diabetes, SBP, HDL and non-HDL cholesterol, BMI, WC and WHR) was done by fitting an interaction term between baseline values of the determinant and the relevant adiposity measure in regression model (4.2), also allowing for additional study random effects.

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Within-person variability in calculated variables

Whereas the within-person variability of WHR is considerably greater than that of waist and hip circumference, the within-person variability of BMI is similar to that of its components (see below section *Extent of within-person variability in adiposity measures*). The following two sections, therefore, investigate possible explanations why the within-person variability of ratios can be larger than expected in comparison to the within-person variability of the components.

Within-person variability in ratios – algebraic formula

Assume the classical additive measurement error models for two correlated normally distributed variables T_1 and T_2 in a single study,

$$
\begin{aligned}
Q_{1i} &= a_1 + T_{1i} + e_{1i} \\
Q_{2i} &= a_2 + T_{2i} + e_{2i} \\
\text{where } &\begin{bmatrix} T_{1i} \\ T_{2i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}\right) \\
\text{and } &\begin{bmatrix} e_{1i} \\ e_{2i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \upsilon_1^2 & \tau\upsilon_1\upsilon_2 \\ \tau\upsilon_1\upsilon_2 & \upsilon_2^2 \end{bmatrix}\right).
\end{aligned}
$$

Q_{1i} and Q_{2i} represent the observed variables measured with error for individual *i*. Within and between-person variances for Q_1 are represented by υ_1^2 and σ_1^2 respectively, and likewise for Q_{2i}. The parameter ρ represents the correlation between the error-free values T_1 and T_2, whereas the parameter τ represents the correlation between the within-person errors of T_1 and T_2, which is often assumed to be zero.

The RDRs for Q_1 and Q_2 are simply

$$\text{RDR}(Q_1) = \frac{\sigma_1^2}{\sigma_1^2 + \upsilon_1^2} \qquad \text{and} \qquad \text{RDR}(Q_2) = \frac{\sigma_2^2}{\sigma_2^2 + \upsilon_2^2}.$$

Now suppose one is interested in the calculated variable T_2-T_1. For example, T_1 and T_2 may be true measures of height at two subsequent ages and one is interested in the change in growth as an exposure. In this case, one may expect $\mu_1<\mu_2$, similar between-person variances σ_1^2

and σ_2^2, a strong correlation ρ, and similar but uncorrelated within-person variances υ_1^2 and υ_2^2.

The within and between-individual variances for the observed difference Q_2-Q_1 are given by

$$\text{within - indiviudal variance}\,(Q_2 - Q_1) = \upsilon_1^2 + \upsilon_2^2 - 2\tau\upsilon_1\upsilon_2$$
$$\text{between - individual variance}\,(Q_2 - Q_1) = \sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2$$
$$\text{RDR}(Q_2 - Q_1) = \frac{\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2}{(\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2) + (\upsilon_1^2 + \upsilon_2^2 - 2\tau\upsilon_1\upsilon_2)}.$$

The value of the between-person variance is important here. If T_1 and T_2 are similarly distributed with equal variances (say σ^2) then the between-person variance for Q_2-Q_1 is simply $2\sigma^2 - 2\rho\sigma^2$, which becomes close to zero as the correlation ρ approaches 1. It is unlikely that the within-individual variance for Q_2-Q_1 will similarly shrink, as τ is typically closer to 0. This can result in a relatively larger within-person variance and consequently low RDR in the calculated variable. For example, there is relatively large within-person variability in measures of growth change in comparison to the within-person variability in height measures.

The algebraic forms for the within and between-person variances are simple for summations and differences of variables. For ratios of variables, say $R = T_2^* / T_1^*$, it is easier to consider its $\log_e$-transformation, $\log_e R = \log_e T_2^* - \log_e T_1^*$, to which the above equations can be applied (replacing T with $\log_e T^*$) under assumption of normality. Below it is illustrated how the RDRs of Q_1+Q_2 and Q_2-Q_1 vary with the crucial parameters ρ, τ and comparative variances of T_1 and T_2.

Numerical results

Figure 4.1 displays the calculated RDRs for Q_1+Q_2 and Q_2-Q_1, under the scenarios (i) RDR(Q_1)=RDR(Q_2) equal to 0.95, 0.80 and 0.60, (ii) ρ varying from -1 to 1 and (iii) ratios of the between-person variances σ_1^2 and σ_2^2 equal to 1, 0.75, 0.5 and 0.25. First, it is assumed that there is no correlation between the within-person errors (ie, $\tau = 0$). Under these scenarios, the RDR(Q_2-Q_1) (dotted line) decreases with higher correlation ρ because of the reduction in the between-person variance and the increase in the relative within-person variance. The decline

in RDR$(Q_2$-$Q_1)$ becomes particularly important with ρ in the positive range. Depending on the RDRs of Q_1 and Q_2, the decrease can occur mainly at high correlations ρ or stretch also over lower correlations. For instance, for RDR(Q_1)=RDR(Q_2)=0.95, ρ>0.8 leads to a sudden drop in the RDR(Q_2-Q_1), while for lower RDRs of Q_1 and Q_2, the RDR$(Q_2$-$Q_1)$ decreases earlier and less remarkably. Greater discrepancy in the distributions of T_1 and T_2 attenuates that effect by limiting the RDR(Q_2-Q_1) to decrease beyond a certain boundary value. A similar, but reversed situation is observed for RDR(Q_1+Q_2) (dashed line).

Figure 4.2 plots the calculated RDRs for Q_1+Q_2 and Q_2-Q_1, under the scenarios (i) RDR(Q_1)=RDR(Q_2) equal to 0.95, 0.80 and 0.60, (ii) ρ varying from -1 to 1 and (iii) τ equal to 0, 0.3, 0.6 and 0.9. The variances are now assumed to be equal $\sigma_1^2 = \sigma_2^2$. RDR(Q_2-Q_1) declines with higher correlation ρ. However, RDR(Q_2-Q_1) becomes more stable with increasing τ, except at very high values of ρ.

These numerical findings provide a useful insight for the observed RDRs of adiposity measures presented below.

Extent of within-person variability in adiposity measures

Available data from repeat measurements in the ERFC

Baseline characteristics of studies and participants with concomitant repeat measurements on weight, height, waist and hip circumference are summarised in **Table 4.1**. A total of 42,300 out of 58,271 participants in 12 studies had one or more repeat measurements, and 21,360 participants from 4 studies had more than two repeats. The participants with repeat measurements were not formally random samples from each cohort, although in general they were selected with the intention of being fairly representative of all individuals in the cohorts of interest. Individuals with repeat measurements of adiposity measures generally had somewhat higher baseline adiposity measures, were younger and were more likely to be non-smokers than individuals in the same studies without repeats (data not shown). A total of 79,145 repeat measurements were available derived from 18 different resurvey times spanning between 2 to 10 years after the baseline survey. The mean time interval between baseline and repeat was 5.9 years (**Table 4.2** panel B). Mean (SD) values of adiposity measures among those with repeats were generally similar at baseline and follow-up resurveys (**Table 4.2**). For instance, the overall mean values (SD) at baseline examination were 27 kg/m^2 (5.0) for BMI, 92 cm (13)

for WC and 0.90 (0.08) for WHR. Corresponding overall mean values (SD) at resurvey were 27 kg/m^2 (5.2) for BMI, 94 cm (14) for WC and 0.91 (0.08) for WHR.

Regression dilution ratios for adiposity measures

Overall unadjusted RDRs of adiposity measures, combined across studies and time intervals, were 0.96 (95% confidence interval [CI] 0.93-0.98) for BMI, 0.72 (95% CI 0.65-0.80) for WHR and 0.87 (95% CI 0.85-0.90) for waist-to-height ratio (WHtR) (**Figure 4.3**). Corresponding RDRs of components of these ratios were 0.87 (95% CI 0.85-0.90) for WC, 0.90 (95% CI 0.86-0.93) for hip circumference, 0.99 (95% CI 0.99-1.00) for height and 0.97 (95% CI 0.96-0.98) for weight. There was considerable heterogeneity between the study and resurvey-specific RDRs of WHR, with RDRs ranging from 0.48 to 0.87. The total heterogeneity between RDRs had a standard deviation of 0.04 (95% CI 0.02-0.06) with BMI, 0.04 (95% CI 0.03-0.07) with WC and 0.13 (95% CI 0.08-0.19) with WHR.

Illustration of the extent of within-person variability in adiposity ratios

Correlations and ratios of the between-person variances for the components of BMI, WHR and WHtR are shown in **Table 4.3**. Overall, waist and hip circumference were more strongly correlated than either waist circumference and height or weight and height. Additionally, the errors for waist and hip circumference were strongly correlated, which is likely to be due to the same measuring procedure for waist and hip circumference. **Figure 4.4** illustrates that studies with low RDRs of WHR had generally lower RDRs of waist and hip circumference, larger ratios of variances for $\log_e$ waist and hip circumference, and higher correlations between waist and hip circumference. There was large between-study variation in the correlations between waist and hip circumference and the ratios of between-person variances of $\log_e$ waist and hip circumference, resulting in the observed heterogeneity in the RDRs of WHR.

Determinants of within-person variability in adiposity measures

Adjusting for potential confounders and mediators

While the overall RDRs of BMI and WC remained virtually unchanged after adjustment for sex, the RDR decreased to 0.66 (95% CI 0.59-0.74) for WHR (**Table 4.4**). The within-person variability of adiposity measures did not materially change upon further adjustment for baseline values of age, smoking status, SBP, history of diabetes, and HDL and non-HDL cholesterol (**Table 4.4**).

Time trends in RDRs

The length of the time between baseline and repeat measurement did not materially affect within-person variability of BMI and WC (**Table 4.5**) (although the time trend was formally significant, the overall RDR of WC did not vary materially with time interval). The within-person variability of WHR decreased with time since baseline, with the overall RDRs of 0.76 (95% CI 0.69-0.84) at 1 year, 0.67 (95% CI 0.59-0.75) at 5 years and 0.58 (95% CI 0.50-0.66) at 10 years (**Table 4.5**). However, these findings were dominated by the ARIC study (as seen from the decline in RDRs of ARIC [ie, the three biggest data markers] over time in **Figure 4.3**). After excluding the ARIC study, the decline over time in the overall RDR of WHR was not significant anymore (-0.01 [95% CI -0.03 to 0.01] for the RDR time trend per 5-year change).

Predictors of variability

The variability in BMI and WC was not materially affected by age, sex, smoking status, baseline SBP, HDL and non-HDL cholesterol (**Table 4.6**) (although some formally significant interactions with these variables were observed, the RDRs did not vary materially). There was some evidence that within-person variability of WHR was somewhat greater in women than in men and in people with a history of diabetes than in those without such a history. Similarly, there was evidence that the within-person variability of WHR was greater at higher baseline WHR values (**Table 4.6**). The non-linear relationship between baseline WHR and repeat measurements was reduced but not removed on $\log_e$-transformation of WHR. The overall RDR for $\log_e$ WHR, adjusted for age and sex, was 0.65 (95% CI 0.58-0.72), with the standard deviation of the total heterogeneity of 0.12 (95% CI 0.08-0.18).

RDR for other cardiovascular risk factors

To compare the within-person variability for adiposity measures with that of other cardiovascular risk factors, estimates were calculated using repeat information in up to 42,300 participants with complete information on BMI, WC and WHR. The age and sex adjusted RDRs were 0.57 (95% CI 0.52-0.62) for SBP, 0.75 (95% CI 0.69-0.80) for HDL cholesterol, 0.63 (95% CI 0.59-0.67) for non-HDL cholesterol and 0.66 (95% CI 0.60-0.72) for $\log_e$ triglyceride (**Figure 4.5**).

Discussion

This chapter presented data on serial measurements of adiposity measures from 42,300 participants in 12 prospective studies, providing the most comprehensive and detailed assessment of long-term within-person variability in adiposity measures. Furthermore, the current chapter illustrated the extent of within-person variability in calculated risk factors. The data demonstrate that the within-person variability of BMI is lower than that of WC and WHR. The within-person variability in adiposity measures is not materially influenced by several individual-level characteristics, although the RDR of WHR varies somewhat by sex and diabetes status, and is somewhat lower at higher baseline WHR values. This chapter has also shown that for given regression dilution ratios in two directly measured risk factors, the effect of within-person variability in corresponding calculated variables depends mostly on the strength of correlations and similarity of the between-person variances of the directly measured risk factors.

The current data demonstrate that the reproducibility (ie, low within-person variability) of BMI (RDR 0.96) is superior to that of WC (RDR 0.88) or WHR (RDR 0.66), suggesting that for long-term epidemiological studies of disease outcomes, regression dilution bias is less important for BMI than for WC or WHR. While the length of time between baseline and repeat measurement did not materially affect the variability of BMI and WC, the RDR of WHR decreased somewhat with longer follow-up. This suggestion should, however, be interpreted carefully, because only a few studies provided more than one repeat per individual. The observed findings are highly dependent on the data of the ARIC study. Indeed, the apparent time trend in the variability of WHR was abolished when the ARIC study was excluded from the analysis. Therefore, further studies are required to investigate this time trend, as corrections for regression dilution bias require stronger assumptions when RDRs vary substantially over time.[16]

The variability of adiposity measures was not materially influenced by several individual characteristics, such as age, smoking status, blood pressure and lipids, although the variability in WHR was somewhat greater in females than in males and in people with a history of diabetes than in those without such a history. The current data showed that the within-person variability in WHR increased at higher baseline WHR values, suggesting that there is a non-linear relationship between baseline and repeats of WHR. This increase in variability is probably due to the difficulty in measuring accurately WHR in obese people. As increasing WHR values are continuously associated with risk of cardiovascular disease (**Chapter 6**) and

as the RDR of WHR is lower at higher WHR values, use of an overall RDR may underestimate the true aetiological association.[10] To allow for the non-linear relationship between repeats of WHR measures, regression calibration models[1] can be used to assess the association between WHR and disease risk. Because there was considerable between-study heterogeneity in the RDRs of WHR, the observed differences in RDRs should, however, be interpreted carefully, as it is uncertain how much these observed differences are due to study differences rather than true differences in sex, diabetes status and levels of baseline WHR.

The estimated RDRs of BMI and WC were unaffected by adjustment for age at baseline, sex and other established risk factors, suggesting that unadjusted RDRs for correcting relative risks associated with BMI and WC may generally be used. The RDR of WHR reduced somewhat upon adjustment for sex, but otherwise the RDR did not materially change with further adjustments. Using an unadjusted RDR to estimate the adjusted underlying association of WHR with disease risk will underestimate the true association.

The current analysis has also shown that for given regression dilution biases in directly measured risk factors, the effect of within-person variability in corresponding calculated variables depends on the strength of correlations and the similarity of the between-person variances of the directly measured risk factors. The overall RDR of WHR was considerably lower than that of BMI, WHtR and its components. The main explanation for this finding is that overall waist and hip circumference are more strongly correlated and have – at least for some studies – more similar between-person variances than height and weight or waist circumference and height, respectively. Study and resurvey-specific correlations and between-person variances of waist and hip circumference varied considerably across studies, explaining the observed heterogeneity in the RDRs of WHR.

The limitations of regression dilution methods for correction for within-person variability are well-known.[10] Firstly, regression dilution correction methods assume that the confounders (and mediators) are perfectly measured.[17] As these factors are generally measured with error, correction methods would need to be extended for such analyses, for example, using a *multivariate* Rosner regression model.[2] This approach has been implemented for analyses on associations of adiposity with disease risk (**Chapters 5-6**). Secondly, regression dilution correction methods assume that disease risk depends on a single underlying error-corrected exposure level. In a more realistic model with time-dependent true underlying exposure,

regression dilution corrections are valid if disease risk depends only on current true underlying exposure, or if RDRs are constant over life course.[16] Except possibly for WHR, there was no important time trend in RDRs over a 10-year time span, suggesting the corrections are likely to be appropriate for adiposity measures. Thirdly, the observed exposure-disease association may reflect residual bias due to unmeasured confounders (eg, dietary intake or physical activity) rather than being causal associations. Corrections for the extent of within-person variability amplify the effect of such non-causal associations with no epidemiological value.[18]

Conclusion

The extent of within-person variability in calculated risk factors can be considerably larger (or smaller) than the within-person variability in its components. The present data demonstrate that the reproducibility of BMI is superior to that of WC and WHR. The within-person variability of adiposity measures is not materially influenced by several characteristics, although the RDR of WHR varies somewhat by sex, diabetes status and baseline WHR values. These findings suggest that the degree of underestimation of the magnitude of association with disease risk is smaller for BMI than for WC and WHR in analyses using baseline values.

Chapter 4 – References

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Table 4.1 Characteristics of studies and individuals with serial measurements of adiposity measures

		Among individuals with at least one repeat											
						Baseline mean (SD)							
Study	**No of individuals with baseline values**	**No of individuals**	**No of re-surveys**	**No of individuals with >2 repeats**	**Male %**	**Age (yrs)**	**WC (cm)**	**Hip (cm)**	**Height (cm)**	**Weight (kg)**	**WHR**	**WHtR**	**BMI (kg/m^2)**
ARIC	14383	13414	3	12065	43	54 (6)	97 (14)	105 (10)	168 (9)	78 (17)	0.92 (0.08)	0.57 (0.08)	28 (5)
AUSDIAB	9204	5280	1	-	44	53 (11)	91 (14)	105 (10)	169 (9)	77 (16)	0.86 (0.09)	0.54 (0.08)	27 (5)
CHS1	3881	3265	1	-	38	72 (5)	93 (13)	101 (9)	164 (9)	72 (14)	0.92 (0.09)	0.57 (0.08)	26 (4)
COPEN	8166	4332	1	-	42	54 (13)	86 (13)	99 (8)	169 (10)	73 (14)	0.86 (0.09)	0.51 (0.07)	25 (4)
EPICNOR	1417	792	1	-	67	65 (8)	92 (11)	103 (7)	168 (9)	75 (12)	0.90 (0.08)	0.55 (0.06)	27 (3)
HOORN	2226	1359	1	-	45	60 (7)	90 (10)	102 (6)	169 (9)	75 (11)	0.88 (0.09)	0.53 (0.06)	26 (3)
IKNS	1942	86	1	-	83	63 (8)	83 (8)	91 (6)	158 (7)	59 (8)	0.92 (0.06)	0.53 (0.06)	23 (3)
LASA	1806	1124	2	707	44	70 (7)	97 (11)	103 (8)	167 (9)	75 (12)	0.94 (0.08)	0.58 (0.07)	27 (4)
MESA	6768	6373	3	6002	48	62 (10)	98 (14)	106 (11)	167 (10)	79 (17)	0.93 (0.08)	0.59 (0.09)	28 (5)
RANCHO	1784	882	1	-	40	65 (10)	84 (12)	100 (8)	167 (10)	70 (14)	0.83 (0.09)	0.50 (0.06)	25 (4)
SHS	4135	3482	2	2586	37	56 (8)	106 (15)	111 (13)	165 (9)	84 (18)	0.95 (0.06)	0.64 (0.10)	31 (6)
TARFS	2559	1911	1	-	50	47 (11)	93 (12)	105 (10)	163 (9)	74 (13)	0.89 (0.09)	0.57 (0.08)	28 (5)
Overall	**58271**	**42300**	**-**	**21360**	**44**	**61 (9)**	**92 (13)**	**103 (10)**	**166 (9)**	**74 (16)**	**0.90 (0.08)**	**0.56 (0.08)**	**27 (5.0)**

Appendix 4 lists study acronyms.

Table 4.2 Comparison of means and standard deviations (SD) of adiposity measures, grouped by study, between baseline measurements (panel A) and repeat measurements (panel B)

A Baseline measurements

Study	No of individuals	WC		Hip		Height		Weight		WHR		WHtR		BMI	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ARIC	13414	97	14	105	10	168	9	78	17	0.92	0.08	0.57	0.08	28	5.3
AUSDIAB	5280	91	14	105	10	169	9	77	16	0.86	0.09	0.54	0.08	27	4.8
CHS1	3265	93	13	101	9	164	9	72	14	0.92	0.09	0.57	0.08	26	4.4
COPEN	4332	86	13	99	8	169	10	73	14	0.86	0.09	0.51	0.07	25	4.0
EPICNOR	792	92	11	103	7	168	9	75	12	0.9	0.08	0.55	0.06	27	3.4
HOORN	1359	90	10	102	6	169	9	75	11	0.88	0.09	0.53	0.06	26	3.3
IKNS	86	83	8	91	6	158	7	59	8	0.92	0.06	0.53	0.06	23	3.1
LASA	1124	97	11	103	8	167	9	75	12	0.94	0.08	0.58	0.07	27	4.1
MESA	6373	98	14	106	11	167	10	79	17	0.93	0.08	0.59	0.09	28	5.4
RANCHO	882	84	12	100	8	167	10	70	14	0.83	0.09	0.5	0.06	25	3.6
SHS	3482	106	15	111	13	165	9	84	18	0.95	0.06	0.64	0.10	31	6.3
TARFS	1911	93	12	105	10	163	9	74	13	0.89	0.09	0.57	0.08	28	5.1
Overall	**42300**	**92**	**13**	**103**	**10**	**166**	**9**	**74**	**16**	**0.90**	**0.08**	**0.56**	**0.08**	**27**	**5.0**

Table 4.2 con't Comparison of means and standard deviations (SD) of adiposity measures, grouped by study, between baseline measurements (panel A) and repeat measurements (panel B)

B Repeat measurements

Study	No of individuals	Mean time (yrs)	WC		Hip		Height		Weight		WHR		WHtR		BMI	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ARIC	13079	2.9	98	14	106	10	168	9	79	17	0.92	0.08	0.58	0.09	28	5.4
	11841	6.0	100	14	107	11	168	9	80	17	0.94	0.07	0.6	0.09	28	5.6
	10787	8.9	102	14	107	11	168	9	81	17	0.95	0.07	0.61	0.09	29	5.6
AUSDIAB	5280	5.0	93	14	106	10	168	10	78	16	0.88	0.09	0.55	0.08	28	5.1
CHS1	3265	2.9	97	13	102	10	164	9	71	14	0.94	0.08	0.59	0.08	27	4.5
COPEN	4332	9.4	89	13	102	8	169	10	74	15	0.87	0.09	0.53	0.07	26	4.3
EPICNOR	792	3.8	93	11	104	8	168	9	76	13	0.89	0.08	0.55	0.06	27	3.8
HOORN	1359	6.4	93	11	102	8	169	9	76	12	0.91	0.08	0.55	0.06	27	3.6
IKNS	86	3.7	85	8	90	5	158	7	58	8	0.94	0.07	0.54	0.06	23	3.0
LASA	931	3.1	95	11	103	9	166	9	74	13	0.92	0.09	0.57	0.07	27	4.2
	900	6.1	97	11	103	8	166	9	75	12	0.94	0.08	0.58	0.07	27	4.2
MESA	6091	1.6	98	14	105	11	166	10	78	17	0.93	0.08	0.59	0.09	28	5.5
	5868	3.2	98	14	105	11	166	10	78	17	0.93	0.08	0.59	0.09	28	5.5
	5698	4.8	99	15	106	12	166	10	78	18	0.94	0.07	0.6	0.09	28	5.6
RANCHO	882	8.3	86	13	101	9	166	10	70	15	0.85	0.09	0.52	0.07	25	4.0
SHS	3268	3.9	107	15	112	14	164	9	84	19	0.96	0.06	0.65	0.10	31	6.5
	2775	7.9	106	15	112	14	164	9	84	19	0.95	0.07	0.65	0.10	31	6.6
TARFS	1911	9.2	96	12	105	11	162	10	77	14	0.92	0.09	0.6	0.08	30	5.3
Overall		**5.9**	**94**	**14**	**103**	**11**	**166**	**9**	**75**	**16**	**0.91**	**0.08**	**0.57**	**0.09**	**27**	**5.2**

Appendix 4 lists study acronyms.

Table 4.3 Overall correlations and comparative distributions of components of WHR, WHtR and BMI

T_2/T_1	Correlation (95% CI) of measures between subjects	Correlation (95% CI) of within-subjects errors	$SD_{Log\ T2}$	$SD_{Log\ T1}$	$Var_{Log\ T1}/Var_{Log\ T2}$
Waist/hip ratio	0.810 (0.806, 0.813)	0.574 (0.569, 0.578)	0.131	0.090	0.47
Waist/height ratio	0.227 (0.198, 0.217)	-0.084 (-0.091, -0.077)	0.131	0.056	0.18
BMI (Weight/Height^2)	0.524 (0.516, 0.531)	0.050 (0.043, 0.057)	0.199	0.112	0.32

Abbreviations: SD = standard deviation; Var = variance.

Table 4.4 Regression dilution ratios (95% CI) for BMI, WC, WHR and WHtR, progressively adjusted for baseline values of conventional risk factors

Adjusted for baseline levels of	**Body-mass index**	**Waist circumference**	**Waist/hip ratio**	**Waist/height ratio**
Unadjusted	0.97 (0.94, 0.98)	0.88 (0.85, 0.90)	0.72 (0.64, 0.80)	0.88 (0.86, 0.91)
Sex	0.96 (0.34, 0.98)	0.88 (0.86, 0.91)	0.66 (0.59, 0.74)	0.88 (0.86, 0.91)
plus age	0.96 (0.94, 0.98)	0.89 (0.86, 0.91)	0.66 (0.59, 0.73)	0.89 (0.87, 0.92)
plus smoking status	0.96 (0.94, 0.98)	0.89 (0.86, 0.91)	0.66 (0.59, 0.73)	0.89 (0.87, 0.92)
plus systolic blood pressure	0.97 (0.95, 0.99)	0.89 (0.87, 0.92)	0.66 (0.58, 0.73)	0.89 (0.87, 0.92)
plus history of diabetes	0.97 (0.95, 0.99)	0.89 (0.87, 0.92)	0.65 (0.58, 0.72)	0.89 (0.87, 0.92)
plus Non-HDL cholesterol	0.97 (0.95, 0.99)	0.89 (0.87, 0.92)	0.65 (0.57, 0.72)	0.89 (0.87, 0.92)
plus HDL cholesterol	0.97 (0.95, 0.99)	0.89 (0.86, 0.91)	0.63 (0.56 (0.70)	0.89 (0.87, 0.92)

Analyses were restricted to participants with complete information on age, sex, systolic blood pressure, smoking status, history of diabetes and non-HDL and HDL cholesterol (75731 repeats in 40023 individuals in 11 studies).

Table 4.5 Regression dilution ratios for BMI, WC, WHR and WHtR at different time points since baseline measurement

	Body-mass index	Waist circumference	Waist/hip ratio	Waist/height ratio
Overall RDR (95% CI)	0.96 (0.94, 0.98)	0.88 (0.86, 0.91)	0.66 (0.59, 0.72)	0.88 (0.85, 0.91)
RDR (95% CI) time trend per 5 year change	-0.013 (-0.029, 0.001)	-0.040 (-0.062, -0.018)	-0.093 (-0.111, -0.076)	-0.015 (-0.034, 0.002)
RDR (95% CI) at 1 year	0.97 (0.97, 0.98)	0.92 (0.90, 0.96)	0.76 (0.69, 0.84)	0.90 (0.87, 0.93)
RDR (95% CI) at 5 years	0.96 (0.95, 0.98)	0.89 (0.86, 0.92)	0.67 (0.59, 0.75)	0.88 (0.85, 0.92)
RDR (95% CI) at 10 years	0.95 (0.92, 0.98)	0.85 (0.80, 0.90)	0.58 (0.50, 0.66)	0.87 (0.83, 0.91)

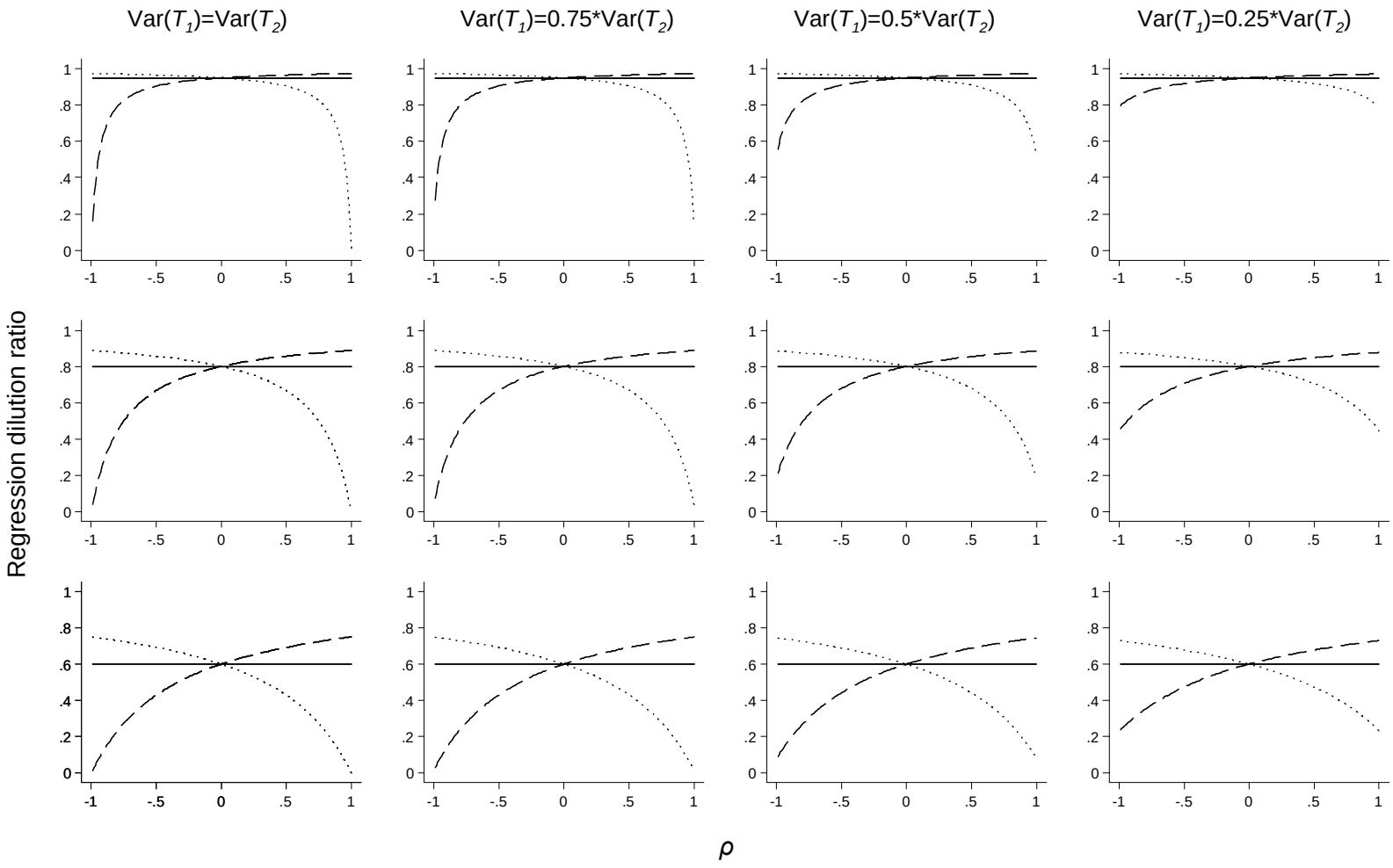
Analyses were adjusted for age at baseline and sex.

Table 4.6 Regression dilution ratios for BMI, WC and WHR by levels of several individual-level characteristics at baseline

Baseline characteristics	BMI		WC		WHR	
	RDR (95% CI)	Interaction p-value	RDR (95% CI)	Interaction p-value	RDR (95% CI)	Interaction p-value
Age at baseline (yrs)						
40-59	0.97 (0.94, 0.99)		0.89 (0.87, 0.92)		0.68 (0.61, 0.75)	
60-69	0.95 (0.93, 0.98)		0.87 (0.85, 0.90)		0.64 (0.57, 0.72)	
70+	0.94 (0.91, 0.96)	<0.001	0.87 (0.84, 0.90)	0.003	0.62 (0.55, 0.69)	<0.001
Per 8.76 years increase	-0.013 (-0.017, -0.008	<0.001	-0.013 (-0.018, -0.007)	<0.001	-0.026 (-0.032, -0.021)	<0.001
Sex						
Males	0.96 (0.94, 0.98)		0.89 (0.86, 0.92)		0.68 (0.61, 0.75)	
Females	0.96 (0.94, 0.98)	0.647	0.86 (0.83, 0.89)	<0.001	0.58 (0.51, 0.65)	<0.001
Smoking status						
Current	0.95 (0.92, 0.97)		0.87 (0.85, 0.90)		0.68 (0.61, 0.74)	
Not current	0.96 (0.94, 0.98)	0.016	0.89 (0.86, 0.91)	0.026	0.65 (0.58, 0.72)	0.037
History of diabetes						
Yes	0.91 (0.89, 0.94)		0.86 (0.83, 0.89)		0.58 (0.51, 0.64)	
No	0.97 (0.95, 0.99)	<0.001	0.89 (0.86, 0.91)	<0.001	0.66 (0.59, 0.72)	<0.001
Systolic blood pressure						
<116 mmHg	0.98 (0.96, 1.00)		0.89 (0.87, 0.92)		0.68 (0.60, 0.75)	
116-132 mmHg	0.97 (0.94, 0.99)		0.89 (0.86, 0.91)		0.65 (0.58, 0.73)	
≥133 mmHg	0.95 (0.92, 0.97)	<0.001	0.88 (0.86, 0.91)	0.1226	0.63 (0.56, 0.71)	<0.001
Per 19.5 mmHg increase	-0.010 (-0.015, -0.007)	<0.001	-0.006 (-0.011, -0.002)	0.008	-0.018 (-0.023, -0.013)	<0.001
Non-HDL cholesterol						
<3.6 mmol/l	0.97 (0.95, 0.99)		0.89 (0.86, 0.92)		0.67 (0.60, 0.74)	
3.6-4.53 mmol/l	0.97 (0.95, 0.99)		0.89 (0.86, 0.92)		0.65 (0.58, 0.72)	
≥4.54 mmol/l	0.95 (0.93, 0.97)	<0.001	0.86 (0.83, 0.89)	<0.001	0.62 (0.55, 0.69)	<0.001
Per 1.09 mmol/l increase	-0.010 (-0.014, -0.006)	<0.001	-0.012 (-0.017, -0.008)	<0.001	-0.016 (-0.022, -0.011)	<0.001
HDL cholesterol						
<1.15 mmol/l	0.95 (0.93, 0.97)		0.88 (0.85, 0.91)		0.62 (0.56, 0.69)	
1.15-1.49 mmol/l	0.96 (0.94, 0.98)		0.87 (0.84, 0.90)		0.62 (0.55, 0.69)	
≥1.50 mmol/l	0.98 (0.96, 1.00)	<0.001	0.88 (0.85, 0.91)	0.115	0.65 (0.58, 0.72)	<0.001
Per 0.41 mmol/l increase	0.014 (0.010, 0.019)	<0.001	0.000 (-0.004, 0.005)	0.886	0.007 (0.001, 0.013)	0.015
Body-mass index						
<24.8 kg/m^2	0.98 (0.96, 1.01)		0.79 (0.74, 0.83)		0.62 (0.55, 0.69)	
24.8-28.7 kg/m^2	0.96 (0.93, 1.00)		0.74 (0.69, 0.78)		0.61 (0.54, 0.68)	
≥28.8 kg/m^2	0.94 (0.92, 0.97)	<0.001	0.82 (0.77, 0.86)	<0.001	0.57 (0.50, 0.64)	<0.001
Per 4.56 kg/m^2 increase	NA	NA	-0.014 (-0.022, -0.006)	<0.001	-0.037 (-0.042, -0.031)	<0.001
Waist circumference						
<87 cm	0.97 (0.93, 1.01)		0.86 (0.83, 0.89)		0.58 (0.51, 0.65)	
88-99 cm	0.94 (0.90, 0.98)		0.89 (0.86, 0.93)		0.55 (0.48, 0.63)	
≥100 cm	0.94 (0.89, 0.98)	<0.001	0.89 (0.87, 0.92)	0.023	0.53 (0.46, 0.61)	<0.001
Per 13.3 cm increase	-0.003 (-0.010, 0.004)	0.371	NA	NA	-0.026 (-0.032, -0.020)	<0.001
Waist/hip ratio						
<0.88	0.97 (0.95, 1.00)		0.98 (0.94, 1.02)		0.68 (0.62, 0.74)	
0.88-0.95	0.95 (0.93, 0.98)		0.96 (0.93, 1.00)		0.70 (0.63, 0.77)	
≥0.96	0.95 (0.92, 0.97)	<0.001	0.90 (0.86, 0.94)	<0.001	0.51 (0.44, 0.57)	<0.001
Per 0.08 increase	-0.012 (-0.016, -0.008)	<0.001	-0.010 (-0.017, -0.002)	0.010	NA	NA

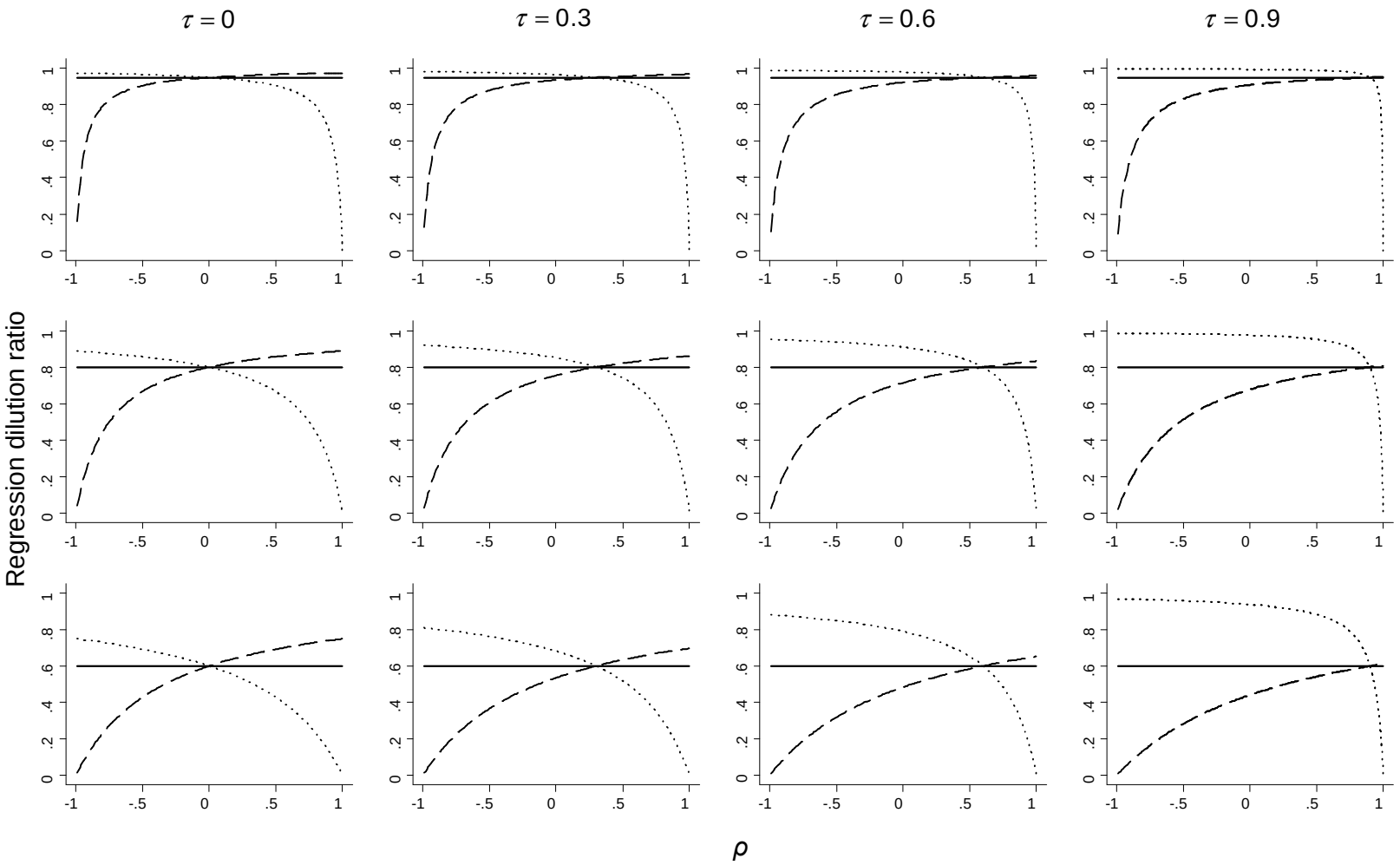
Analyses were adjusted for age at baseline and sex. Continuous variables were divided intro thirds based on the overall distribution in males and females combined.

Figure 4.1 Changes in regression dilution ratios according to correlation ρ and different ratios of comparative between-person variances of components



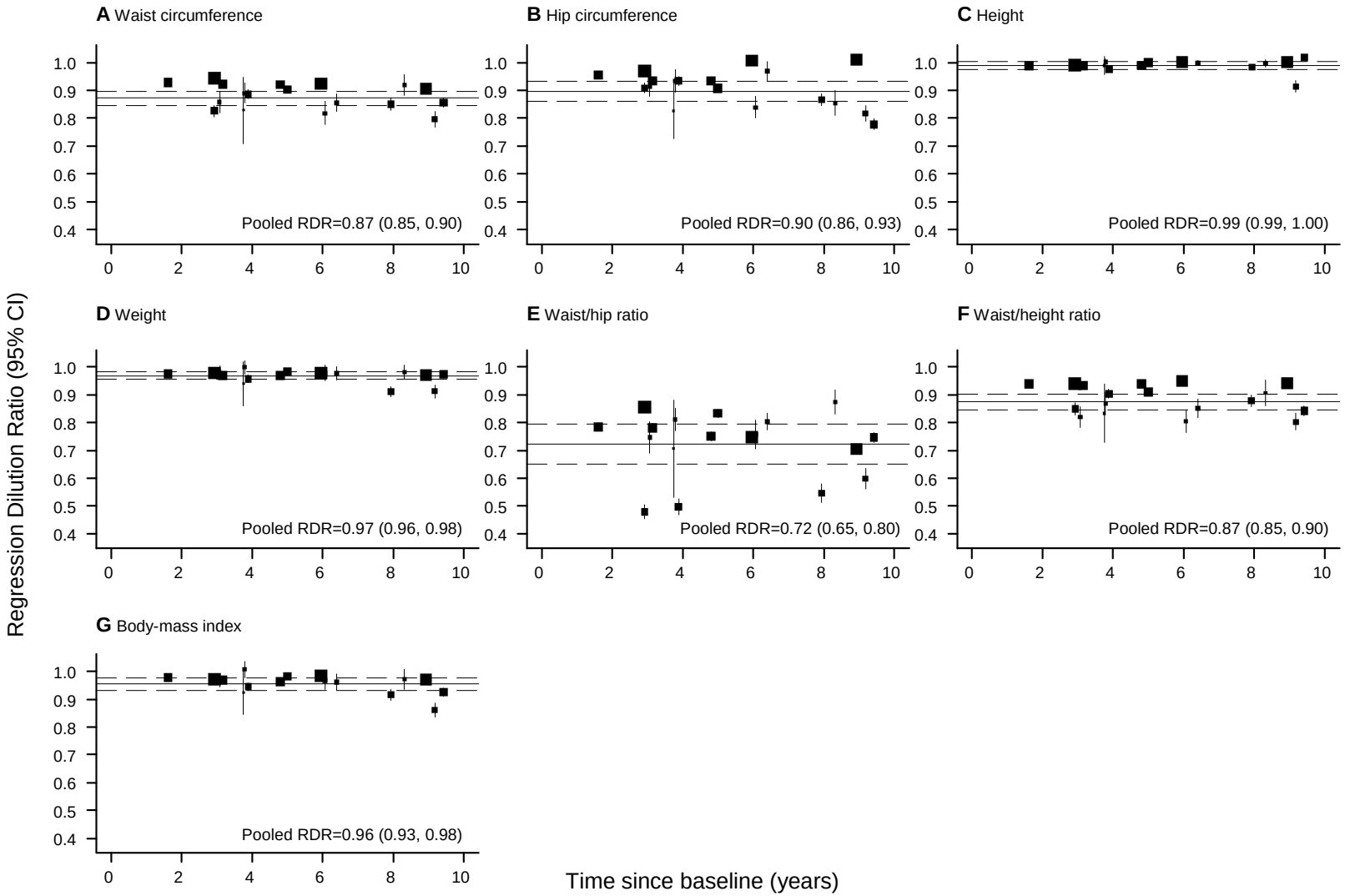
Regression dilution ratios (RDRs) for Q_1+Q_2 (dashed line) and Q_2-Q_1 (dotted line) shown for RDR(Q_1) = RDR(Q_2) = 0.95 (top row), = 0.8 (middle row), = 0.6 (bottom row) (solid lines). Assumption: τ = 0

Figure 4.2 Changes in regression dilution ratios according to correlation ρ and different correlations of within-person errors of components



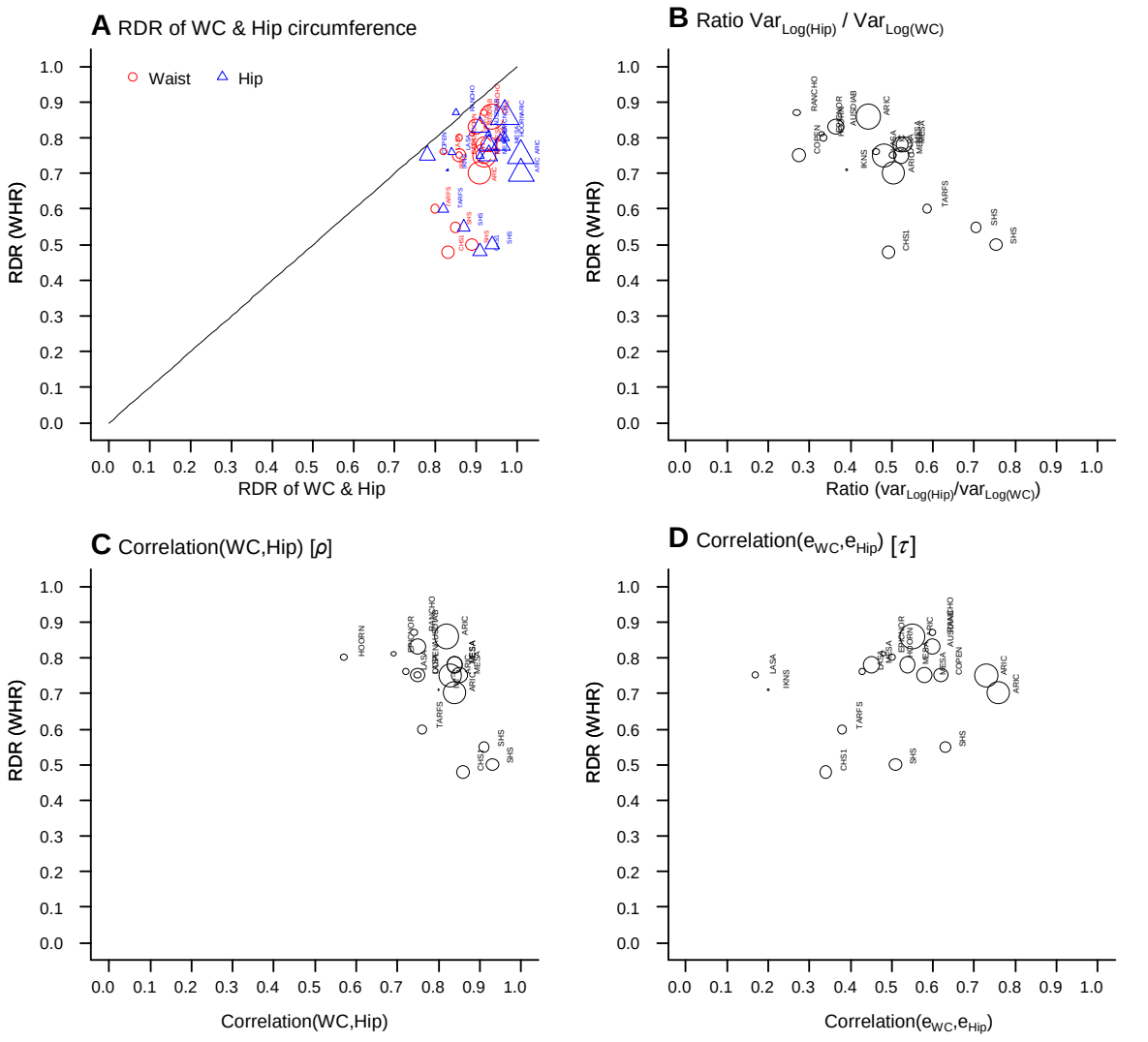
Regression dilution ratios (RDRs) for Q_1+Q_2 (dashed line) and Q_2-Q_1 (dotted line) shown for RDR(Q_1) = RDR(Q_2) = 0.95 (top row), = 0.8 (middle row), = 0.6 (bottom row) (solid lines). Assumption: Var(T_2) = Var(T_1)

Figure 4.3 Unadjusted regression dilution ratios for adiposity measures and anthropometric indicators plotted against time since baseline measurement by study



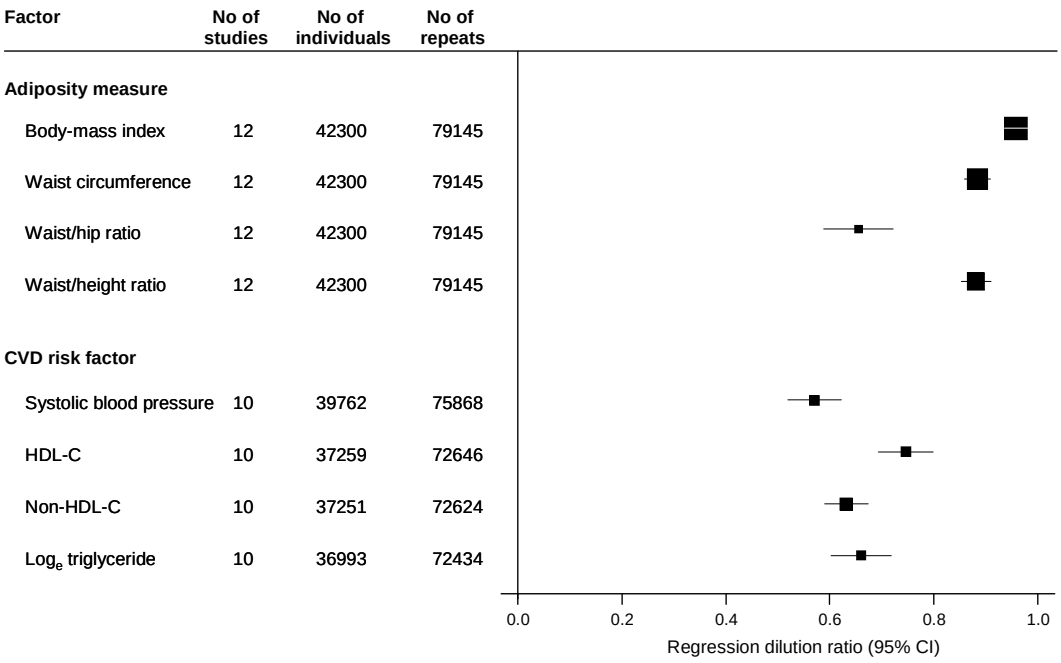
The sizes of data markers are proportional to the inverse of the variance of the regression dilution ratios (RDRs).

Figure 4.4 Unadjusted study and resurvey-specific regression dilution ratios of WHR by influential properties of waist and hip circumference



Panel A shows the study and resurvey-specific RDRs of WHR according to individual RDRs of waist and hip circumference. Panel B shows RDRs of WHR according to the comparative between-person variances of $\log_e$ waist and $\log_e$ hip circumference. Panel C shows the RDRs of WHR according to the correlation ρ of waist and hip circumference. Panel D shows the RDRs of WHR according to the correlations of within-person errors τ of waist and hip circumference. The sizes of data markers are proportional to the inverse of the variance in panel A and proportional to number of individuals in panel B, C and D.

Figure 4.5 Age and sex adjusted regression dilution ratios for adiposity measures and different cardiovascular risk factors



CHAPTER 5: Associations of body-mass index with risk of coronary heart disease, stroke, and cause-specific mortality

Summary

Although various prospective studies and collaborative analyses have reported on the associations of body-mass index (BMI) with coronary heart disease, stroke and/or non-vascular outcomes, the aetiological relevance of these relationships is still unclear. For instance, it is uncertain how much of the effect of BMI on disease risk can be accounted by confounders and biological mediators; whether associations with cardiovascular disease differ importantly at different levels of such risk factors, and how the shape of associations is characterised in associations with site-specific cancers and non-vascular conditions other than cancer. This chapter reports prospective analyses of individual participant data from over 1 million participants without known history of cardiovascular disease in 118 prospective studies, based mostly in Western countries. During 15.0 million person-years at risk, there were 31,909 non-fatal myocardial infarctions or strokes and 129,994 deaths. In analyses adjusted for age, sex and smoking status, and excluding participants with BMI values below 20 kg/m^2, there were approximately $\log_e$-linear associations with risk of coronary heart disease, ischaemic stroke and all cardiovascular mortality. Risk ratios per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status, were 1.31 (95% confidence interval [CI] 1.26-1.36) for coronary heart disease and 1.23 (95% CI 1.18-1.29) for ischaemic stroke. These associations were largely explained by long-term average levels of mediating risk factors, such as blood pressure, history of diabetes and lipids. Risk ratios for coronary heart disease were significantly greater in some groups at lower absolute risk – ie, in people without history of diabetes, at early middle age and at lower-than-average systolic blood pressure. Across the full range of BMI values, BMI had curvilinear associations with all-cause mortality, including most site-specific cancers and non-vascular conditions not attributed to cancer. In participants with BMI values of 25 kg/m^2 or higher, BMI was positively associated with a range of non-vascular mortality outcomes. Particularly strong relationships were observed with risk of death from diabetes and renal disease. By contrast, among participants with BMI values below 25 kg/m^2, the negative association of BMI was predominantly due to the strong negative associations with respiratory disease and cancers of the lung and upper aerodigestive tract. These inverse associations were much stronger in smokers than in never smokers. In participants with BMI values of 25 kg/m^2 or higher, associations of BMI with non-vascular mortality attenuated somewhat after accounting for long-term levels of the intermediate factors noted above.

Background

Although several large prospective studies[1-10] and individual participant data meta-analyses of observational studies in Western[11-13] and Asian[14-16] populations have reported on associations of body-mass index (BMI) with risk of coronary heart disease, stroke and/or non-vascular mortality, the aetiological relevance of these relationships remains uncertain. Because previous studies involved a moderate number of outcomes,[2] relied on self-reported weight and height,[2,12] and/or lacked measurement of mediating and other established risk factors,[10-12] it is uncertain how much of the effect of BMI on disease risk can be accounted by confounders and biological mediators, such as blood pressure, diabetes, lipids, inflammation, alcohol consumption, physical activity and socioeconomic indicators; whether associations with cardiovascular disease differ importantly at different levels of such risk factors, and how the shape of associations is characterised in associations with site-specific cancers and non-vascular conditions other than cancer. Furthermore, two relatively small studies[17,18] have suggested that BMI is more strongly related to fatal cardiovascular disease than non-fatal cardiovascular disease. Previous collaborative analyses,[10-12] however, were not able to evaluate this suggestion, because they did not record non-fatal outcomes.

The objective of this chapter is to produce reliable estimates of the associations of BMI with subsequent risk of coronary heart disease, stroke and cause-specific mortality, incorporating adjustment for potential confounders and biological mediators using data from the Emerging Risk Factors Collaboration (ERFC).[19]

Methods

Study design

Details of study selection, data collection and harmonisation have been described in **Chapter 2**. Briefly, the current analyses included individual participant data on BMI from 118 prospective studies involving 1,064,541 participants without known history of cardiovascular disease at the initial ("baseline") examination. The general characteristics of these studies, including methods for measurement of weight and height, were described in **Chapter 2**.

Analytical approach

Associations of BMI were assessed in relation to fatal or first-ever non-fatal coronary heart disease or stroke and cause-specific mortality, including deaths from vascular disease, cancer, and non-vascular conditions not attributed to cancer, as well as to further subdivisions of these

outcomes. Analyses involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random effects meta-analysis.[20] The main analyses were based on Cox proportional-hazards regression models, estimated for each study separately. The Cox models were stratified, where appropriate, by sex and trial arm.[21] The Cox proportional hazards model for each study $s = 1 \ldots S,$ with strata $k = 1 \ldots K_s$ (for most studies $K_S = 2$ just for two sexes) and individuals $i = 1 \ldots n_s$, with exposure of interest E_{si} and other covariates X_{si}, can be written as

$$\log_e(h_{ski}(t \mid E_{si}, X_{si})) = \log_e h_{0sk}(t) + \beta_s E_{si} + \gamma_s X_{si}, \qquad (5.1)$$

where $h_{ski}(t \mid E_{si}, X_{si})$ is the hazard at time *t* after baseline, $h_{0sk}(t)$ is the baseline hazard at time *t*, and β_s the parameter of interest, being the $\log_e$ hazard ratio per unit increase in the exposure of study *s*, adjusted for confounding and/or mediating effects of the covariates X_{si}. The estimated $\log_e$ hazard ratios were subsequently combined over studies using random effects meta-analysis (ie, allowing for heterogeneity between studies).[22] The random effects meta-analysis model with variance v_s for the estimate β_s is given by

$$\begin{aligned} \hat{\beta}_s &= \beta_s + \varepsilon_s, \quad \text{where} \quad \varepsilon_s \sim N(0, v_s) \\ \beta_s &= \beta + \eta_s, \quad \text{where} \quad \eta_s \sim N(0, \tau^2). \end{aligned} \qquad (5.2)$$

β represents the pooled $\log_e$ hazard ratio and the variance τ^2 represents the extent of heterogeneity between studies.[23] Parallel analyses were conducted using fixed-effect models.[11,24-26]

Participants contributed only their first non-fatal outcome or death recorded at age 40 years or older (ie, deaths preceded by non-fatal coronary heart disease or stroke were not included in the analyses). The assumptions of proportionality of hazards were evaluated within each study by including an interaction term between exposure and time since baseline measurement.[20] Study-specific interaction terms were then pooled by random effects meta-analysis across studies to provide the average interaction term and corresponding test statistic. A significant correlation between time and $\log_e$ hazard ratio would indicate that the proportional hazards assumption is violated. The proportional hazards assumptions were satisfied.

For the five contributing "nested" case-control studies within prospective cohorts, odds ratios were calculated with logistic regression models.[27] Provided the disease is relatively rare, hazard ratios and odds ratios were assumed to approximate the same relative risk and are collectively described as "risk ratios".[28] The risk ratios were combined as described in (5.2).

To avoid over-fitting of the statistical models, studies with fewer than five incident cases of an outcome were excluded from the analysis of that particular outcome. Risk ratios were initially adjusted for age, sex and smoking status only. To explore confounding and potential biological pathways underlying associations, risk ratios were further adjusted for systolic blood pressure (SBP), history of diabetes, total and high-density lipoprotein (HDL) cholesterol, triglyceride, C-reactive protein (CRP), fibrinogen, alcohol consumption, or socioeconomic indicators (ie, educational attainment and occupational category). To limit potential bias due to pre-existing disease (ie, reverse causality), the first five years of follow-up were excluded in analyses involving associations with non-vascular outcomes and BMI values below 25 kg/m^2 (see Results).

Heterogeneity and reporting biases

Between-study heterogeneity in $\log_e$ risk ratio was estimated by calculating the Q statistic for testing heterogeneity and its corresponding transformation to the I^2 statistic for quantifying the extent of heterogeneity

$$Q = \sum \frac{1}{v_s + \tau^2}(\hat{\beta}_s - \beta)^2 \qquad \text{and} \qquad I^2 = \frac{Q-(S-1)}{Q} x100\%, \qquad (5.3)$$

where S represents the number of studies.[29,30] Confidence intervals for the I^2 statistic were calculated as recommended by Higgins and Thompson.[30] The I^2 statistic describes the percentage of variance in the estimated $\log_e$ risk ratios from each study that is attributable to between-study variation as opposed to sampling variation. Values of I^2 close to 0 correspond to lack of heterogeneity. Potential bias from small study effects was assessed by funnel plots and use of Egger's test for publication bias.[31]

Shape of associations

To characterise shapes of associations, study-specific risk ratios calculated within categories of baseline BMI values were pooled on a $\log_e$ scale by multivariate random effects meta-analysis and plotted against mean BMI values within each category.[32,33] BMI categories were defined as multiples of 2.5 kg/m^2 (ie, <20, 20 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30.0, 30.0 to <32.5, 32.5 to <35.0, 35.0 to <37.5, 37.5 to <40.0, ≥40.0 kg/m^2). 95% confidence intervals (CIs) were estimated from floated variances that reflect the amount of information underlying each group (including the reference group).[34] This allows the values to be compared informatively between any pair of exposure categories, rather than only with the arbitrary chosen reference group. In the figures presented, sizes of data markers are proportional to the inverse of the variance of the $\log_e$ risk ratios. Because associations with vascular outcomes were nearly $\log_e$-linear (except at low values of BMI: see Results), regression coefficients were calculated to estimate the risk ratios associated with 5 kg/m^2 higher baseline BMI in participants with baseline BMI values of 20 kg/m^2 or higher. Because association with non-vascular conditions (and all-cause mortality) were curvilinear (with the lowest risk ratios at about 22.5 to 27.5 kg/m^2), risk ratios of these outcomes were estimated within two ranges of baseline BMI – (i) in participants with BMI values below 25 kg/m^2 and (ii) in participants with BMI values of 25 kg/m^2 or higher. Associations with non-vascular mortality outcomes were approximately $\log_e$-linear in these two ranges of baseline BMI.

Effect modification

Effect modification by individual characteristics, such as age or other risk markers, was assessed using within-study information.[35,36] Using a two-stage approach, study-specific interaction estimates δ_s for the potential effect modifier X_{si} were estimated using model (5.4) and subsequently combined by random effects meta-analysis, as described in (5.2).

$$\log_e(h_{ski}(t \mid E_{si}, X_{si})) = \log_e h_{0sk}(t) + \beta_s E_{si} + \gamma_s X_{si} + \delta_s E_{si} X_{si}. \qquad (5.4)$$

The overall interaction term was then based on only within-study information. Model (5.4) was further extended to include adjustments for other confounders, such as age and smoking status. Effect modification at the study-level, such as geographical region or study design, were assessed entirely on between-study comparisons using random effects meta-regression.[37]

Using the estimates of β_s from model (5.1), model (5.2) was extended to include a study-level covariate X_s, so that

$$\hat{\beta}_s = \beta_s + \varepsilon_s, \quad \text{where} \quad \varepsilon_s \sim N(0, \nu_s)$$
$$\beta_s = \beta + \delta_B X_s + \eta_s, \quad \text{where} \quad \eta_s \sim N(0, \tau^2). \qquad (5.5)$$

δ_B is the between-study interaction term allowing for between-study variance τ^2. Effect modifications with variables that can have both within-study and between-study information (eg, sex or ethnicity) depending on the individual study, were based on within-study information only. Differences between associations with coronary deaths and non-fatal myocardial infarction were examined in competing risk models.[38]

Within-person variability

As discussed in **Chapter 4**, within-person variability in exposures can underestimate the true magnitude of exposure-disease association,[39,40] while within-person variability in confounders can bias the association in either direction.[41] To take into account the impact of within-person variability in BMI and potential confounders and biological mediators, regression dilution ratios (RDRs) were calculated by use of regression calibration models that allow for between-study and between-individual heterogeneity.[23,42] For each error-prone variable, the regression calibration model with studies $s = 1 \ldots S$, individuals $i = 1 \ldots n_s$, and repeat measurements $r = 1 \ldots r_{si}$, can be written as

$$E_{sir} = \alpha_{sr} + (\beta + u_s)E_{si} + \lambda X_{si} + w_{si} + \varepsilon_{sir}, \qquad (5.6)$$

where $u_s \sim N(0, \sigma_u^2)$, $w_{si} \sim N(0, \sigma_w^2)$ and $\varepsilon_{sir} \sim N(0, \sigma_e^2)$. E_{sir} and E_{si} represent repeat and baseline measurements of the error-prone variable, respectively, and X_{si} represents other baseline covariates. Between-study heterogeneity on the estimated RDR value β is represented by the variance σ_u^2. The parameters σ_w^2 and σ_e^2 represent individual-specific and residual variation, respectively. The regression calibration model shown in (5.6) was used to predict conditional expectations of long-term average ("usual") levels of BMI (and potential confounders and intermediate risk factors), which were then used in assessments of associations with disease risk.[23,43,44]

Censoring for outcomes

For participants who had multiple events (eg, two coronary events at separate time points, or a coronary event followed by another type of event such as a stroke or death from cancer), analyses in the ERFC focused on first events (**Chapter 2**). Thus, in analysis of coronary heart disease events, participants were followed until their first coronary event, or censored at the time of other non-fatal cardiovascular events, such as stroke, or death from other causes. The rationale for this was that major cardiovascular events, such as first non-fatal myocardial infarction or stroke, may lead to lifestyle and other modifications (eg, medication use) that may alter levels of risk factors and so disrupt the association between risk factors and subsequent disease risk. Subsidiary analyses were done for fatal outcomes without censoring previous non-fatal outcomes.

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Characteristics of the 118 studies contributing to the analyses are summarised in **Table 2.2** in **Chapter 2** on pages 45-46 and in **Tables 5.1-5.2**. Mean (SD) age at baseline of the 1,064,541 participants without known history of cardiovascular disease at baseline was 56 (9) years; 47% were women. Participants were mainly from Europe (63%), North America (30%) or Japan (3%). During 15.0 million person-years at risk (median 13.5 years to first outcome), there were a total of 161,903 deaths or major non-fatal vascular outcomes, comprising: 20,150 non-fatal myocardial infarctions, 23,210 coronary deaths, 11,759 non-fatal and 8,586 fatal strokes; 12,088 deaths from other vascular diseases, 45,643 deaths from cancer, 30,684 deaths from non-vascular non-cancer cause and 9,783 deaths of unknown or ill-defined cause (**Table 5.2**).

Associations with coronary heart disease, ischaemic stroke and other vascular outcomes

In analyses adjusted for age, sex, and smoking status only, there were J-shaped associations of baseline BMI with risk of coronary heart disease, ischaemic stroke and all vascular mortality across the range of values (**Figure 5.1**). To account for non-linear associations at lower values of BMI, further analyses excluded the 61,682 (5.8%) participants with BMI values below 20 kg/m^2. Log_e-linear associations of baseline BMI with various vascular outcomes per 5 kg/m^2 higher baseline BMI are shown in **Figure 5.2**. After adjustment for age, sex and smoking status, baseline BMI was significantly associated with all specific vascular outcomes, except

subarachnoid haemorrhage. Risk ratios per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking only, were 1.31 (95% CI 1.26-1.36) for coronary heart disease, 1.23 (95% CI 1.18-1.29) for ischaemic stroke, 1.16 (95% CI 1.08-1.26) for haemorrhagic stroke, 1.18 (95% CI 1.12-1.23) for unclassified stroke and 1.31 (95% CI 1.26-1.36) for all cardiovascular mortality. Particularly strong associations were also observed for hypertensive disease (RR 1.67 [95% CI 1.47-1.90]), pulmonary embolism (RR 1.63 [95% CI 1.45-1.84]), heart failure (RR 1.41 [95% CI 1.29-1.55]) and sudden death (RR 1.40 [95% CI 1.26-1.55]).

Risk ratios for coronary heart disease and ischaemic stroke reduced considerably after additional adjustment for baseline values of potential intermediate risk factors such as blood pressure, history of diabetes, lipids, CRP, fibrinogen, or fasting glucose (**Table 5.3**). For example, in analyses restricted to participants with complete information on relevant covariates, risk ratios – initially adjusted for age, sex and smoking status only and then further adjusted for baseline values of SBP, history of diabetes, HDL and non-HDL cholesterol, and triglyceride – were, respectively, 1.26 (95% CI 1.21-1.32) and 1.08 (95% CI 1.04-1.11) for coronary heart disease, and 1.24 (95% CI 1.19-1.29) and 1.07 (95% CI 1.02-1.11) for ischaemic stroke.

In regression dilution corrected analyses, the observed association between BMI and risk of coronary heart disease and ischaemic stroke was largely explained by long-term average levels of these potential intermediate risk factors (**Table 5.4** & **Figure 5.3**). For example, in analyses restricted to participants with complete information on relevant covariates, risk ratios – initially adjusted for age, sex and smoking status only and then further adjusted for usual levels of SBP, history of diabetes, HDL and non-HDL, triglyceride and CRP – were, respectively, 1.24 (95% CI 1.17-1.32) and 0.93 (95% CI 0.87-1.00) for coronary heart disease, and 1.19 (95% CI 1.10-1.29) and 0.92 (95% CI 0.84-1.00) for ischaemic stroke.

Among the contributing studies, between-study heterogeneity tended to decrease with increasing adjustment of risk ratios for intermediate risk factors. Risk ratios were not appreciably altered after further adjustment for potential confounding factors, such as alcohol consumption, physical activity or indicators of socioeconomic status (**Table 5.3**).

In analyses restricted to studies providing data on both outcomes, risk ratios were slightly stronger for coronary death (RR 1.33 [95% CI 1.27-1.40]) than for non-fatal myocardial infarction (RR 1.26 [95% CI 1.21-1.31], p=0.006 for the difference; **Figures 5.2** and **5.4**). The association with coronary death remained stronger compared to that with non-fatal myocardial infarction, even after further adjustment for biological, socioeconomic and behavioural risk factors (**Table 5.5**). Analyses involving fatal myocardial infarction rather than coronary death yielded similar results, albeit lower power (data not shown).

Qualitatively similar results to those reported here were also observed in analyses that excluded: the initial five years of follow-up (**Table 5.6** & **Figure 5.5**), current smokers (**Table 5.6** & **Figure 5.6**); participants who were not of European descent (**Table 5.6**); or the participants who had self-reported height and weight (rather than measured by a trained person) (data not shown); or participants known to be receiving lipid-lowering, blood pressure-lowering or other cardiovascular medication at baseline (data not shown). Risk ratios were also broadly similar using fixed-effect models (**Figures 5.7-5.8**) and after additional adjustment for cigarette pack-years (in addition to smoking status) (data not shown). There was no evidence of bias due to small studies (data not shown).

Risk ratios for coronary heart disease and ischaemic stroke associated with BMI were around three times stronger at ages 40-59 years than at 70 years or older (although the absolute risk is much higher at older ages; **Figure 5.9**), but risk ratios did not otherwise vary importantly by sex, ethnicity, geographical region, educational level, HDL and non-HDL cholesterol, triglyceride, CRP or fasting glucose (**Figures 5.9-5.10**). Associations with coronary heart disease were somewhat stronger in people without history of diabetes, but were similar by smoking status (**Figures 5.10-5.11**). Risk ratios for coronary heart disease were greater at lower-than-average SBP levels (**Figure 5.9**). Associations of BMI and risk of coronary death and non-fatal myocardial infarction separately were broadly similar in subgroups defined by sex, smoking status and age groups (**Figure 5.12**).

Associations with non-vascular mortality outcomes and all-cause mortality

In analyses adjusted for age, sex and smoking status only, there were curvilinear associations between baseline BMI and risk of all cancer mortality, all non-vascular non-cancer mortality, and all-cause mortality (**Figure 5.13**). Because risk ratios at low BMI values were potentially confounded by weight loss due to pre-existing disease (ie, reverse causality), further shape

analyses excluded the first five years of follow-up (**Figure 5.14** & Results below). For both sexes, the relative risks for all-cause mortality were lowest at about 22.5 to 25 kg/m^2 (**Figure 5.15**). Associations between baseline BMI and risk of death from cause-specific non-vascular outcomes are shown in **Figures 5.16-5.17**.

In participants with BMI values of 25 kg/m^2 or higher, the risk ratios per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status only, were 1.12 (95% CI 1.09-1.15) for all cancer mortality, 1.32 (95% CI 1.26-1.38) for all non-vascular non-cancer mortality and 1.26 (95% CI 1.23-1.29) for all-cause mortality (**Table 5.7**). These risk ratios were reduced after additional adjustment for baseline values of blood pressure, history of diabetes, lipids, CRP, fibrinogen or fasting glucose (**Table 5.8**). In regression dilution corrected analyses, long-term average levels of these biological risk factors reduced the risk ratios even further (data not shown). However, associations were not altered after additional adjustment for alcohol consumption, physical activity or indicators of socioeconomic status (**Table 5.8**). As regard to site-specific cancer deaths, in people with BMI values of 25 kg/m^2 or higher, baseline BMI was positively associated with cancers of the liver, oesophagus, pancreas, stomach, blood, colorectum, prostate, renal, endocrine and nervous systems, and breast (**Figure 5.18**). There were non-significant associations of BMI with some site-specific cancers (eg, melanoma, bladder, ovary and lung). Aside from cancer, baseline BMI was also positively associated with death due to diabetes mellitus, renal disease, digestive diseases, infections, liver disease, chronic obstructive pulmonary disease, external causes and mental disorders (**Figure 5.18**). There was modest heterogeneity among contributing studies (I^2 12% [95% CI 0% to 33%] for all cancer deaths and I^2 53% [95% CI 40% to 63%] for all deaths not attributed to vascular disease or cancer; **Table 5.7**). Findings were qualitatively similar after exclusion of the first five years of follow-up (**Table 5.9**).

In participants with BMI values below 25 k/m^2, baseline BMI was negatively associated with all cancer mortality, all non-vascular non-cancer mortality and all-cause mortality. Exclusion of the first five years of follow-up attenuated these associations (**Tables 5.7** and **5.9**), and hence, the results described below relate to analyses with such exclusions. In analyses adjusted for age, sex and smoking status, and restricted to participants with BMI values below 25 kg/m^2, the risk ratios per 5 kg/m^2 higher baseline BMI were 0.82 (95% CI 0.76-0.87) for all cancer mortality, 0.53 (95% CI 0.48-0.57) for all non-vascular non-cancer mortality and 0.74 (95% CI 0.70-0.78) for all-cause mortality (**Table 5.9**). Baseline BMI was negatively associated with risk of oral

cancer and cancers of the lung, oesophagus, stomach and ovary (**Figure 5.19**). There were strong inverse associations between baseline BMI and death due to respiratory disease, which remained even after exclusion of ten years of follow-up (**Figures 5.19-5.20**). Baseline BMI below 25 kg/m^2 was inversely associated with all other specific non-vascular non-cancer conditions, except with diabetes mellitus and liver disease (**Figure 5.19**). There was modest heterogeneity among contributing studies (I^2 34% [95% CI 13% to 50%] for all cancer deaths and I^2 49% [95% CI 33% to 61%] for all deaths not attributed to vascular disease or cancer; **Table 5.9**). Associations with non-vascular mortality outcomes were weakened in analyses restricted to never-smokers only (**Table 5.9**).

Qualitatively similar results to those reported here were observed in a range of subsidiary analyses, such as those that: were restricted to participants with measured (rather than self-reported) height and weight (data not shown), omitted participants of non European descent (**Table 5.9**); analysed associations with fatal outcomes without censoring previous non-fatal outcomes (**Table 5.10**); or used fixed effect models (data not shown).

Discussion

The current analysis of 1,064,541 participants in 118 prospective studies assessed the shape, specificity, magnitude and independence of associations of BMI with risk of vascular morbidity and cause-specific mortality. After exclusion of participants with BMI values below 20 kg/m^2, there were approximately $\log_e$-linear associations with risk of coronary heart disease and all cardiovascular mortality, although somewhat weaker associations were observed with stroke. The observed associations with coronary heart disease and ischaemic stroke were largely explained by long-term average levels of mediating risk factors, such as blood pressure, history of diabetes and lipids. Across the full range of BMI values, BMI had curvilinear associations with all-cause mortality, including most site-specific cancers and non-vascular conditions not attributed to cancer. In participants with BMI values of 25 kg/m^2 or higher, BMI was positively associated with a range of non-vascular mortality outcomes. Particularly strong relationships were observed with risk of death from diabetes and renal disease. By contrast, among participants with BMI values below 25 kg/m^2, the negative association of BMI was predominantly due to the strong negative associations with death due to respiratory disease and cancers of the lung and upper aerodigestive tract. In participants with BMI values of 25 kg/m^2 or higher, associations between BMI and non-vascular mortality attenuated somewhat after accounting for long-term average levels of intermediate factors noted above.

The current analysis has shown that the observed association of BMI with coronary heart disease and ischaemic stroke is largely explained by long-term average levels of blood pressure, history of diabetes, lipids and inflammatory markers. Because excess adiposity is a major determinant of these intermediate risk factors noted above (**Chapter 3**),[45] the current findings underscore the importance of controlling adiposity to help prevent coronary heart disease and stroke. For instance, effective interventions for weight loss have shown to reduce blood pressure levels, favourably affect the lipid profile and to increase insulin sensitivity.[45] While there is increasing evidence that blood pressure, lipids and diabetes contribute to the pathogenesis of cardiovascular disease, the role of inflammation is controversial.[46] For instance, a recent study with almost 200,000 participants used to principle of "Mendelian randomisation" to show that CRP itself is unlikely to be a causal factor for coronary heart disease.[47] Nevertheless, there is considerable evidence showing that other markers of inflammation may well contribute to cardiovascular disease.[46,48,49]

The current data also suggest the relevance of controlling intermediate risk factors by use of lipid-lowering or blood pressure-lowering medication for instance, in order to combat the detrimental vascular effects of overweight and obesity.[50-53] Furthermore, these data have shown that in participants with BMI values of 25 kg/m^2 or higher, the association between BMI and non-vascular conditions is partly mediated by such risk factors, suggesting that some of the adverse effects of BMI may be reversible for non-vascular mortality too. The associations of BMI with vascular and non-vascular outcomes were, however, not altered after adjustment for confounding factors, such as alcohol consumption, physical activity or socioeconomic indicators. In contrast to previous much smaller studies,[17,18] which observed much stronger associations of BMI with risk of fatal than non-fatal cardiovascular disease, BMI was only slightly more strongly related to coronary death than to non-fatal myocardial infarction in the current study. Although statistically significant, this difference is probably too small to have any meaningful clinical implications. Similar, but larger differential associations between fatal and non-fatal cardiovascular disease have been observed for other cardiovascular risk factors, such as diabetes[54] or CRP.[55,56]

There was strong modification of the effects of BMI by age, with about three-fold higher excess risk for coronary heart disease and ischaemic stroke with higher BMI in early middle age than at older ages. This finding must be interpreted appropriately, acknowledging that absolute

cardiovascular risk increases with age. Hence, studies that found greater risk ratios associated with BMI in younger compared to older adults have found the opposite relationship when age groups were compared using absolute risk differences rather than risk ratios.[57,58] Nevertheless, the weakening of the associations between BMI and cardiovascular disease risk at older ages might be due to the weaker associations at older ages of intermediate risk factors,[11] such as blood pressure[25] or cholesterol measures.[26] Also, BMI at older ages might be affected by loss of muscle mass.[59,60] Risk ratios for coronary heart disease were also significantly greater in some other groups at lower absolute risk of vascular disease – ie, in people without diabetes and at lower-than-average SBP. Further investigation is needed to identify possible mechanisms of such effect modification. Otherwise, there were no important modifications of the effect of BMI on risk of coronary heart disease and ischaemic stroke by other subgroups assessed.

The current analysis demonstrated curvilinear associations of BMI with risk of death from a range of site-specific cancers and non-vascular conditions other than cancer. In the BMI range of 25 kg/m^2 or higher, BMI was positively and moderately associated with mortality from cancers of the liver, oesophagus, pancreas, stomach, blood, and colorectum, and somewhat less strongly with cancers of the prostate, kidney, endocrine and nervous system, and breast. Aside from cancers, BMI was positively and strongly associated with mortality due to diabetes, renal disease and digestive diseases. There were moderately strong associations of BMI with death due to infections, liver disease, chronic obstructive pulmonary disease, external causes and mental disorders. In participants with BMI values below 25 kg/m^2, BMI was negatively and strongly associated with death from oral and lung cancer, and somewhat less strongly with mortality from cancers of the oesophagus, stomach and ovary. Among non-vascular non-cancer outcomes, there were strong inverse associations between BMI and death due to respiratory diseases. Although the relationship remained strong even after exclusion of the first ten years of follow-up, the observed inverse association might still be due to reverse causality, as chronic obstructive pulmonary disease can cause weight loss over many years.[11] In participants with BMI values below 25 k/m^2, BMI was also inversely associated with death due to infections, falls, Alzheimer's disease, renal disease, nervous system disorders, external causes, intentional self-harm, mental disorders and digestive diseases. The inverse associations weakened in analyses restricted to never-smokers. Because smoking is strongly related to outcomes, such as lung cancer or chronic obstructive pulmonary disease, the observed differences in the associations might be due to imprecisely measured confounding by

smoking (eg, smoking intensity). Further research is required to investigate the inverse associations with various outcomes among never-smokers. The observed findings are broadly consistent with those of the Prospective Studies Collaboration (PSC).[11] For instance, among participants with BMI values of 25 kg/m^2 or higher, the risk ratios for all-cause mortality and all cancer mortality were 1.26 and 1.12 per 5 kg/m^2 higher baseline BMI in the current study, compared to 1.29 and 1.10 in the PSC. Corresponding risk ratios in participants with BMI values below 25 kg/m^2 were 0.74 and 0.82 in the current study, compared to 0.79 and 0.82 in the PSC.

There was some between-study heterogeneity in the risk ratios, although it was only partly explained by the variables recorded here. Much of the inverse association of BMI with non-vascular outcomes in particiapants with low BMI values was explained by pre-existing disease and/or confounding (eg, smoking). Therefore, if the inverse association at low BMI is partly non-causal, the real optimum for BMI might be somewhat lower than the optimum observed in the current study.[11] The generalisability of the current findings, at least to Western populations, is supported by broadly consistent results across the 118 studies in 24 countries. As more than 90% of the participants were adults of European ancestry in high-income countries, the current study could not assess the effect of obesity on disease risk in children, or in adults of other ethnic groups or in low-income countries.[61-63]

Conclusion

BMI had positive and nearly $\log_e$-linear associations with coronary heart disease and ischaemic stroke (except at BMI values below 20 kg/m^2), which were largely explained by intermediate risk factors, such as blood pressure, diabetes and lipids. The association between BMI and non-vascular mortality was curvilinear.

Chapter 5 – References

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Table 5.1 Summary of data contributing to the analysis of BMI

Variable	No of studies	No of subjects	Mean (SD) or %
BMI (kg/m^2)	118	1064541	26 (4)
Age at survey (yrs)	118	1064541	56 (9)
BP and fasting glucose			
SBP (mmHg)	114	823757	136 (19)
DBP (mmHg)	114	825230	82 (11)
Fasting glucose (mmol/l)	57	301749	5.5 (1.6)
Lipid markers			
Total cholesterol (mmol/l)	114	807182	5.9 (1.1)
Non-HDL-C (mmol/l)	97	448087	4.49 (1.12)
HDL-C (mmol/l)	97	448500	1.34 (0.37)
Log_e triglyceride (mmol/l)	96	656203	0.33 (0.52)
Inflammatory markers			
Log_e CRP (mg/l)	48	136455	0.66 (1.11)
Fibrinogen (µmol/l)	45	222258	9.2 (2.1)
Categorical veriables			
Sex	118	1064541	
Female		503748	47%
Male		560793	53%
Ethnicity	89	506969	
East Asian		36925	7%
Black		26042	5%
Other		10380	2%
White		433622	86%
Smoking status	117	988239	
Current		305761	31%
Not current		682478	69%
Alcohol status	89	506600	
Current		325398	64%
Not current		181202	36%
History of diabetes	105	781253	
Yes		38652	5%
No		742601	95%
Physical activity	60	325038	
Active		126770	39%
Not active		198268	61%
Education	58	334746	
Tertiary		90389	27%
Secondary		164903	49%
Primary		65659	20%
No schooling		13795	4%
Occupation or job	56	345571	
Other		47100	14%
Office		116753	34%
Manual		93101	27%
Not working		88617	26%

Table 5.2 Summary of events of individual studies with complete information on BMI, age and sex

Study abbreviation	All cardiovascular disease*	All cardiovascular deaths	Coronary heart disease*	Non-fatal myocardial infarction	Coronary death	All cerebrovascular disease*	Ischaemic stroke*	Haemorrhagic stroke*	Subarachnoid heamorrhage*	Unclassified stroke*	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer deaths	Oral	Colorectal	Colon	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Endometrial	Bladder	Renal	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer non-vascular deaths	All external causes	Infections	Diabetes mellitus	Mental disorder	Nervous system disorder	Liver disease	Pneumonia	COPD & related conditions	Digestive system disorders (excl. liver)	Renal disease	Death of unknown cause or ill-defined cause	All-cause mortality
Cohorts																																																		
AMORIS	3677	734	2011	1583	428	1421	938	212	120	135	11	12	26	3	60	27	4	1390	13	174	118	23	60	32	108	221	111	38	5	27	61	123	61	43	19	92	707	230	35	30	43	84	61	33	65	48	8	46	2877
ARIC	1643	427	875	675	200	565	456	56	33	16	21	51	12	0	13	13	7	692	6	58	44	11	14	7	45	228	31	20	2	18	12	68	21	7	16	61	352	55	24	28	10	33	20	11	75	20	15	36	1507
ATENA[b]	30	9	18	17	1	4	1	2	1	0	2	3	0	0	1	0	0	22	0	0	0	0	1	1	4	4	0	2	0	1	1	3	0	0	0	4	8	4	0	0	0	1	2	0	0	0	0	1	40
ATS_SAR[c]	34	34	21	0	21	8	0	1	1	6	0	0	0	0	1	0	0	56	1	5	4	0	2	4	3	14	0	2	0	1	1	5	5	0	0	4	30	12	0	0	0	1	4	2	2	2	3	4	124
ATTICA	30	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	1	0	0	0	0	0	0	0	0	0	0	50
AUSDIAB	181	138	65	24	41	47	14	7	2	18	6	16	2	0	0	18	2	106	1	12	6	3	1	0	3	13	9	2	0	1	1	6	11	1	2	2	139	5	25	19	9	17	4	12	4	3	5	54	437
BHS	931	931	519	0	519	221	23	21	4	144	14	22	9	0	37	35	9	547	6	83	67	12	23	6	22	87	60	16	3	17	15	47	18	13	6	34	478	53	4	38	28	63	11	32	106	45	22	17	1973
BRHS	1857	775	1214	674	540	516	7	13	10	475	7	5	12	0	50	11	8	745	11	84	52	34	45	20	29	248	62	0	0	39	18	39	23	6	2	0	305	33	5	4	6	28	18	44	95	27	8	134	1959
BRUN	101	56	54	23	31	40	24	15	0	0	0	0	4	0	3	0	0	68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	55	12	2	0	3	1	2	22	5	5	1	1	180
BUPA	1505	1505	1012	0	1012	254	31	37	12	145	3	14	23	0	94	30	2	1383	11	189	137	72	67	21	86	287	158	0	0	48	50	132	64	32	15	0	618	115	12	4	35	91	50	61	92	56	30	37	3543
BWHHS	197	30	90	77	13	91	0	1	0	90	0	1	3	0	4	1	2	116	1	13	10	3	7	1	6	18	0	10	4	6	0	5	4	0	1	14	69	4	2	1	1	12	3	10	12	8	0	3	218
CAPS	291	152	251	139	112	18	3	3	1	9	0	4	7	0	3	1	1	127	1	18	15	5	12	1	5	46	4	0	0	3	3	8	5	1	1	0	63	11	1	0	2	4	5	3	21	7	2	0	342
CASTEL	521	521	95	0	95	107	0	0	0	107	0	0	29	74	0	216	0	278	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	299	0	59	0	0	0	28	0	37	0	0	18	1116
CHARL	950	585	522	223	299	264	30	34	5	186	32	21	11	0	11	13	5	297	4	26	22	14	16	2	14	88	20	1	3	5	5	17	9	3	2	19	282	17	16	32	12	17	17	36	43	34	16	60	1224
CHS1[a]	1116	271	593	380	213	467	368	62	0	37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	809	1080
CHS2[a]	111	29	56	33	23	49	40	5	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	67	96
COPEN	1371	352	513	472	41	592	368	73	16	122	10	22	26	13	15	58	0	529	7	47	40	21	13	9	31	141	31	17	3	22	7	28	11	6	5	44	642	58	41	28	25	44	30	135	80	47	18	150	1673
DISCO[c]	12	12	9	0	9	3	1	1	0	1	0	0	0	0	0	0	0	11	0	2	2	0	0	0	0	3	0	2	0	1	0	1	0	0	0	0	6	3	0	1	0	0	2	0	0	0	0	0	29
DRECE	29	29	15	0	15	6	0	1	0	4	0	1	1	0	0	2	0	63	2	12	10	1	4	1	5	13	1	1	1	2	0	3	1	1	2	6	42	5	3	5	0	6	6	1	6	3	0	0	134
DUBBO	541	135	283	220	63	192	76	20	3	87	4	0	5	0	6	28	0	169	2	18	11	3	3	2	8	28	16	4	1	6	5	18	2	1	0	7	169	24	12	1	9	16	6	26	24	14	8	18	491
EAS	169	80	82	41	41	68	0	3	2	60	1	2	1	0	4	3	0	126	1	17	12	6	9	1	5	33	14	3	0	1	1	7	0	1	0	8	70	2	2	0	5	11	0	12	16	6	3	8	284
EMOFRI[b]	8	4	2	2	0	3	2	1	0	0	3	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	1	9
EPESEBOS	91	35	38	30	8	26	17	6	2	1	19	0	2	0	0	1	0	22	0	3	3	2	2	1	1	2	4	0	0	0	1	1	0	2	0	0	26	3	2	0	1	2	0	6	1	2	4	8	91
EPESEIOW	152	68	57	33	24	58	22	6	2	26	12	2	1	0	1	14	0	23	0	1	1	1	0	1	3	5	2	1	0	2	0	3	0	0	0	3	46	5	6	1	0	1	3	8	3	2	7	25	162
EPESENCA	120	46	48	28	20	50	30	5	0	15	12	0	0	0	0	7	0	34	0	5	5	1	1	0	1	14	5	0	1	1	0	2	0	0	0	0	33	5	4	1	0	2	1	9	2	3	3	16	129
EPESENHA	87	51	21	17	4	21	10	2	0	9	31	1	0	0	0	4	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	20	2	2	0	0	1	2	7	2	1	1	20	94
ESTHER	243	22	88	77	11	151	3	1	1	146	0	0	0	0	2	0	0	55	1	6	4	1	1	1	5	17	2	1	0	1	0	3	3	1	2	3	17	1	1	2	0	2	2	0	3	4	0	7	101
FINE_FIN	111	62	70	33	37	29	8	1	0	16	0	2	2	0	0	4	0	39	0	5	3	0	2	0	1	13	11	0	0	0	1	3	0	0	0	0	44	9	1	4	8	2	0	11	5	2	0	1	146
FINE_IT	210	142	67	18	49	104	4	5	0	85	1	5	0	2	1	19	1	108	2	22	15	2	11	3	5	17	19	0	0	6	3	7	5	0	1	0	47	15	0	1	0	3	4	5	4	9	1	32	329
FINRISK92	296	60	150	119	31	124	84	36	1	0	1	1	6	2	1	4	0	82	1	8	3	2	9	4	6	17	3	3	2	0	2	2	5	2	3	10	101	47	5	0	2	7	6	13	1	7	4	1	244
FINRISK97	224	59	109	75	34	95	75	19	1	0	0	2	10	0	1	2	0	69	1	5	3	3	6	3	6	12	4	3	0	0	3	6	3	2	0	4	79	29	5	1	2	2	4	21	3	5	0	2	209
FRAMOFF	207	21	127	114	13	72	62	8	2	0	0	0	0	0	0	0	0	135	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	79	0	0	0	0	0	0	0	0	0	0	34	269
GOH	593	593	277	0	277	134	2	12	3	72	66	13	9	15	4	19	4	334	8	43	33	3	19	10	24	39	15	9	1	8	3	33	17	1	2	26	322	45	19	46	15	17	20	16	42	29	28	692	1941
GOTO13	369	43	213	211	2	116	0	1	0	115	0	0	6	5	3	18	0	115	1	14	5	7	8	3	8	18	24	0	0	4	8	6	2	3	1	0	50	2	2	1	8	4	6	14	5	4	1	43	251
GOTO33	44	22	27	14	13	8	0	0	0	8	2	0	2	0	0	0	0	27	1	3	3	0	6	0	1	7	2	0	0	0	1	2	1	0	0	0	29	9	0	1	7	4	2	2	2	0	0	3	81
GOTO43	42	4	28	27	1	12	9	1	1	1	0	0	0	0	1	0	0	16	0	0	0	0	1	0	0	3	0	0	0	0	2	4	3	0	1	0	4	2	0	0	0	0	2	0	0	0	0	1	25
GOTOW	369	131	148	94	54	179	0	0	0	179	0	0	0	0	0	0	0	154	0	0	0	0	0	0	0	14	0	15	0	0	0	19	0	1	0	17	116	82	25	0	0	0	0	0	0	0	0	6	407
GREPCO[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	5
GRIPS	449	47	299	299	0	103	0	0	0	103	0	0	13	17	3	10	0	108	2	18	11	0	11	3	6	34	3	0	0	5	1	10	7	1	1	0	69	30	4	0	0	2	7	3	3	16	3	1	225
GUBBIO[c]	107	107	69	0	69	29	11	2	1	13	0	2	1	0	0	0	1	95	2	8	7	1	12	9	5	12	3	5	0	2	0	8	3	0	3	9	34	15	0	0	0	3	6	2	5	0	0	3	239
HBS	131	131	87	0	87	27	0	0	0	27	0	0	0	0	0	0	0	158	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	112	27	0	0	0	0	0	0	0	0	0	10	411
HELSINAG	106	106	42	0	42	41	21	3	0	3	2	2	7	0	3	1	2	38	0	3	2	1	4	1	3	4	2	1	0	3	0	2	0	0	0	2	72	2	0	0	12	2	0	42	1	6	1	15	231
HISAYAMA	356	76	77	67	10	220	148	49	21	0	1	10	2	0	12	2	2	154	1	19	14	4	22	25	11	30	2	2	0	0	0	12	3	0	0	2	154	23	7	0	0	3	13	42	11	19	5	2	386
HONOL	314	110	156	114	42	133	12	40	2	75	3	4	1	0	7	0	1	182	3	17	12	9	28	1	9	41	29	0	0	0	2	26	2	0	2	0	156	18	7	6	37	17	1	16	27	8	1	87	535
HOORN	171	69	73	60	13	53	3	4	0	46	11	0	3	13	4	12	0	85	1	9	8	3	6	2	5	19	3	4	0	2	2	2	4	0	0	2	18	5	1	0	1	0	0	6	3	0	1	40	212

Table 5.2 con't Summary of events of individual studies with complete information on BMI, age and sex

Study abbreviation	All cardiovascular disease[a]	All cardiovascular deaths	Coronary heart disease[a]	Non-fatal MI	Coronary death	All cerebrovascular disease[a]	Ischaemic stroke[a]	Haemorrhagic stroke[a]	Subarachnoid heamorrhage[a]	Unclassified stroke[a]	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer deaths	Oral	Colorectal	Colon	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Endometrial	Bladder	Renal	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer non-vascular deaths	All external causes	Infections	Diabetes mellitus	Mental disorder	Nervous system disorder	Liver disease	Pneumonia	COPD & related conditions	Digestive system disorders (excl. liver)	Renal disease	Death of unknown cause or ill-defined cause	All-cause mortality
HPFS	4424	4424	2575	0	2575	740	100	129	37	176	57	14	45	354	146	206	12	4400	67	477	422	141	95	68	342	782	649	0	0	179	137	719	209	127	45	0	3604	668	154	86	326	799	128	307	382	198	184	362	12790
IKNS	495	154	84	37	47	344	158	71	25	90	2	0	1	0	3	57	0	297	4	24	15	12	72	27	32	18	7	1	0	3	0	10	3	2	1	4	250	59	6	4	3	0	14	88	11	13	17	59	760
ISRAEL	987	987	723	0	723	264	0	0	0	264	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1544	2531
KARELIA	3136	987	1983	1387	596	931	69	48	40	768	22	21	41	3	18	44	3	692	9	46	24	12	54	22	38	156	20	28	11	9	30	69	19	11	9	55	825	238	40	22	27	54	27	238	38	48	23	13	2517
LASA	54	0	34	34	0	20	0	0	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	536	536
MALMO	2418	1185	2047	1233	814	143	36	49	21	16	6	6	17	1	46	18	3	1274	27	108	70	25	69	21	91	335	74	38	5	36	50	106	59	36	19	52	667	169	14	25	51	61	87	45	93	53	7	163	3289
MATISS83[b]	336	196	83	47	36	99	26	10	3	57	71	11	1	0	0	54	0	90	1	3	2	0	2	3	1	12	0	0	0	0	0	6	3	0	3	2	60	9	0	9	3	5	11	3	6	3	4	65	411
MATISS87[b]	175	95	45	22	23	58	9	8	2	39	36	3	0	1	1	27	0	46	0	2	2	0	3	1	1	7	1	1	0	0	0	1	2	0	2	0	33	11	0	1	2	1	4	0	1	2	5	33	207
MATISS93[b]	31	13	14	11	3	7	1	2	1	3	4	1	0	0	0	5	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	1	0	1	0	1	1	0	0	1	2	5	29
MCVDRFP	457	457	197	0	197	97	15	31	14	32	19	8	8	8	16	27	4	852	8	82	59	23	32	6	48	247	26	27	5	12	15	60	19	18	16	97	358	70	13	23	13	41	22	19	73	45	8	113	1780
MESA	173	21	83	69	14	84	68	13	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	122	143
MICOL[c]	150	150	105	0	105	33	7	3	0	20	0	0	3	0	3	0	2	248	5	25	22	5	20	15	16	75	2	7	1	3	5	16	10	4	5	14	94	20	0	3	0	3	41	4	8	6	3	24	516
MOGERAUG1	108	61	79	47	32	5	0	2	0	2	0	0	5	2	2	10	1	40	1	7	4	1	5	1	3	8	1	0	0	1	2	1	2	0	0	0	25	7	0	2	3	2	1	3	4	2	0	0	126
MOGERAUG2	129	66	104	63	41	7	1	1	1	3	0	1	4	1	0	8	0	77	3	14	10	0	4	2	6	16	2	4	2	1	4	6	2	1	1	5	53	11	2	2	7	3	7	2	10	5	2	3	199
MOGERAUG3	36	25	18	11	7	5	2	1	0	2	0	3	2	0	0	3	0	20	1	5	4	0	1	1	1	2	1	1	0	0	1	3	2	0	0	0	9	2	0	1	2	0	1	1	0	0	0	0	54
MONFRI86[b]	107	62	28	20	8	25	14	4	2	5	44	0	2	1	1	4	0	41	0	0	0	1	2	3	0	5	0	0	0	0	1	1	1	0	0	1	22	6	0	1	0	1	5	1	0	1	2	42	167
MONFRI89[b]	82	43	28	22	6	20	10	5	0	5	23	0	2	0	1	6	0	16	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	23	4	1	0	0	0	6	2	0	3	1	18	100
MONFRI94[b]	40	13	11	11	0	17	6	7	1	2	9	0	0	1	1	0	0	7	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	7	1	0	0	0	0	3	1	0	1	0	13	40
MONICA[c]	38	38	28	0	28	8	0	1	0	5	0	0	0	0	0	0	0	45	0	2	1	1	8	4	0	10	0	2	0	1	5	1	1	1	0	1	17	5	0	0	0	0	3	0	2	1	2	0	100
MORGEN	149	149	77	0	77	24	3	10	7	4	4	2	3	4	6	5	0	317	6	32	22	10	10	5	23	80	8	10	1	6	7	19	7	4	6	33	95	25	7	5	4	12	9	5	9	8	0	26	587
MOSWEGOT	280	67	143	104	39	117	66	17	18	15	2	0	7	0	2	1	1	109	1	10	8	1	5	3	7	15	6	5	1	0	1	10	5	1	4	16	56	14	1	1	6	9	3	0	10	5	2	4	236
MRCOLD	2636	2636	1148	0	1148	843	52	61	13	519	62	50	47	0	92	170	47	1386	15	165	107	56	69	30	63	219	141	25	11	62	22	89	11	15	16	98	2077	83	59	50	45	334	17	540	293	252	44	210	6309
NCS1	548	548	375	0	375	67	9	17	26	12	5	13	2	43	12	8	0	560	10	76	49	8	37	3	29	75	13	32	9	4	15	69	32	15	4	49	247	89	7	21	10	19	16	9	31	11	5	83	1438
NCS2	280	280	193	0	193	28	2	7	11	6	5	8	1	20	4	1	1	327	5	66	44	3	27	1	13	44	12	18	3	8	12	17	18	12	3	30	143	61	3	7	11	11	8	10	9	4	4	54	804
NCS3	465	465	287	0	287	86	8	24	22	23	6	19	0	38	5	3	0	286	5	19	12	1	31	5	22	62	6	25	4	4	12	18	10	1	1	25	142	45	4	4	17	14	9	4	25	7	2	96	989
NFR[c]	124	124	90	0	90	27	2	9	1	11	0	0	1	0	4	0	0	151	1	12	7	3	14	8	4	39	8	0	0	7	4	17	6	3	3	0	41	13	0	0	0	1	15	3	2	4	2	15	331
NHANESI	1757	1112	930	330	600	499	135	46	18	274	48	58	11	1	20	38	5	702	6	92	71	18	26	14	37	143	55	15	3	23	15	74	15	7	4	63	636	82	41	49	27	31	33	88	110	60	31	52	2502
NHANESIII	854	854	471	0	471	171	0	0	0	171	0	43	0	0	14	50	0	542	74	0	0	8	17	17	26	144	53	7	0	3	0	50	4	8	0	32	624	71	37	57	0	45	38	64	95	5	20	12	2032
NHS	5247	5247	2290	0	2290	1341	23	106	654	235	152	15	101	345	150	219	155	10367	101	965	765	97	158	91	614	2212	0	726	279	116	184	1079	370	163	85	2216	6320	924	257	331	1126	552	374	274	471	379	89	1495	23429
NPHSI	196	88	154	85	69	23	0	0	0	23	0	0	0	0	0	0	0	85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	0	0	0	0	0	0	0	0	0	0	3	216
NPHSII	297	56	194	175	19	73	39	7	7	20	0	4	2	16	6	0	0	117	1	21	15	11	9	2	6	26	5	0	0	2	3	12	4	3	2	0	25	5	1	0	0	3	4	1	7	2	0	3	201
NSHS	87	40	24	0	24	51	1	1	1	48	5	0	0	0	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40
OB43[c]	24	24	15	0	15	8	1	1	1	4	0	0	0	0	1	0	0	36	1	6	6	0	0	2	2	5	0	0	1	3	0	3	1	0	2	5	14	2	0	0	0	0	3	0	4	3	1	3	77
OSAKA	261	106	42	26	16	144	57	27	16	44	1	3	0	1	4	62	0	220	3	15	8	9	37	30	18	10	7	5	0	2	1	10	7	0	0	6	146	22	11	1	8	2	17	43	6	12	9	155	627
OSLO	2613	2613	1604	0	1604	379	56	79	29	170	35	51	15	119	158	61	5	2016	46	310	184	42	125	23	115	504	225	0	0	47	60	179	74	51	22	0	1073	182	29	67	60	106	98	90	226	101	27	188	5890
OYABE	198	57	26	0	26	141	88	30	22	1	0	7	0	0	0	19	0	181	0	7	0	7	46	5	11	28	0	0	0	0	0	4	0	0	0	2	97	26	7	1	0	3	7	34	5	5	0	41	376
PARIS1	601	601	341	0	341	100	0	0	0	100	0	0	0	0	0	0	0	918	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	479	150	0	0	0	0	0	0	0	153	0	83	2081
PREVEND	219	71	146	124	22	31	0	17	7	7	3	1	2	1	10	5	1	180	3	23	21	4	12	1	8	42	8	1	1	8	8	7	3	2	3	10	42	12	0	3	2	5	3	2	7	4	0	13	306
PRHHP	384	245	213	125	88	84	54	20	3	5	0	28	4	24	8	0	1	159	9	12	8	18	29	0	4	24	15	0	0	1	1	18	4	0	1	0	181	76	12	7	4	9	39	6	6	8	3	9	594
PRIME	208	37	146	129	17	42	33	6	0	3	0	0	0	17	0	0	0	99	3	15	9	4	4	3	4	29	2	0	0	2	3	8	6	1	2	0	34	24	0	0	0	2	3	1	1	1	1	15	185
PROCAM	741	301	486	367	119	106	77	22	0	7	4	0	13	97	8	13	0	440	15	56	29	6	25	10	33	97	22	0	0	13	0	43	17	0	0	28	206	64	21	0	6	5	22	48	7	10	2	50	997
QUEBEC	43	10	31	28	3	5	0	0	0	5	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	31	41
RANCHO	507	113	222	219	3	185	0	1	0	175	9	16	1	0	5	10	5	173	0	21	18	2	3	0	11	36	28	3	3	6	4	20	4	6	1	10	200	10	7	6	31	21	7	40	22	15	4	1	487
REYK	4538	2510	3249	2028	1221	768	183	162	45	243	45	52	78	12	71	82	6	2424	22	281	226	43	182	44	173	532	202	68	13	64	92	169	93	20	38	199	1656	77	62	41	15	360	27	276	278	130	35	92	6682
RF2[c]	90	90	64	0	64	18	2	7	0	8	0	0	2	0	1	0	0	149	4	12	9	1	10	9	10	27	3	4	1	1	4	7	10	3	6	20	53	15	0	3	2	1	14	2	2	3	4	28	320
ROTT	652	441	244	211	33	144	38	23	3	63	1	0	3	55	21	77	2	450	3	69	51	14	15	5	29	92	27	6	5	18	11	46	11	3	17	43	319	43	19	0	1	117	6	34	44	28	8	169	1379
SHHEC	682	182	459	325	134	184	56	21	21	81	2	4	2	2	7	3	1	405	7	48	27	17	17	10	21	122	12	8	1	6	9	18	13	5	3	36	152	11	21	6	5	8	18	25	27	11	1	26	765
SHS	784	311	451	303	148	214	8	10	0	190	24	12	6	4	2	15	4	224	5	17	13	4	7	15	14	39	8	5	1	1	15	28	4	0	1	15	609	89	34	154	29	6	124	36	31	27	18	19	1163
SPEED	353	194	252	98	154	77	66	2	1	5	1	2	5	0	9	0	0	205	4	30	16	8	15	0	6	69	11	0	0	7	7	13	6	1	0	0	77	11	1	1	1	7	3	12	22	4	4	1	477

Table 5.2 con't Summary of events of individual studies with complete information on BMI, age and sex

Study abbreviation	All cardiovascular disease*	All cardiovascular deaths	Coronary heart disease*	Non-fatal MI	Coronary death	All cerebrovascular disease*	Ischaemic stroke*	Haemorrhagic stroke*	Subarachnoid heamorrhage*	Unclassified stroke*	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer deaths	Oral	Colorectal	Colon	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Endometrial	Bladder	Renal	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer non-vascular deaths	All external causes	Infections	Diabetes mellitus	Mental disorder	Nervous system disorder	Liver disease	Pneumonia	COPD & related conditions	Digestive system disorders (excl. liver)	Renal disease	Death of unknown cause or ill-defined cause	All-cause mortality
TARFS	316	255	217	53	164	62	1	0	0	61	0	0	2	12	1	11	0	35	0	4	4	0	2	2	1	3	1	0	0	0	0	0	1	0	0	1	25	7	0	2	1	4	0	0	3	1	0	174	489
TOYAMA	92	8	34	33	1	51	24	17	10	0	0	0	0	0	0	4	0	28	1	2	2	0	7	4	0	6	1	1	0	0	0	4	0	0	2	0	15	10	0	0	0	1	2	1	0	0	1	32	83
TROMSØ	1877	281	1009	889	120	727	537	88	45	52	13	12	1	30	28	19	2	592	9	76	59	14	39	9	37	127	42	27	8	12	12	54	15	10	11	28	354	82	12	7	13	54	12	35	66	33	8	34	1261
ULSAM	996	252	593	446	147	316	195	56	19	41	3	10	7	0	18	13	3	394	3	35	18	12	22	11	32	65	85	0	0	16	16	29	12	9	2	0	203	49	6	11	3	29	10	13	31	22	6	7	856
USPHS2	643	104	310	282	28	259	217	40	0	2	0	0	0	38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	688	792
VHMPP	3281	3281	1683	0	1683	783	81	122	24	443	61	60	45	1	57	184	34	2297	45	264	193	30	184	69	149	460	135	76	15	55	67	172	87	40	19	181	1284	363	4	98	42	115	164	69	169	127	34	67	6929
VITA	66	21	38	30	8	19	15	2	1	1	5	0	0	0	1	1	0	44	2	3	3	1	2	4	3	7	1	0	0	3	1	4	4	1	0	3	17	6	0	2	0	1	4	0	1	1	0	4	86
WHITEI	473	473	218	0	218	141	19	14	4	75	12	7	6	0	40	20	4	400	2	50	41	19	13	3	20	62	84	0	0	22	5	43	11	5	3	0	348	9	9	7	10	44	5	114	47	31	11	14	1235
WHITEII	348	94	316	254	62	10	2	2	2	4	0	2	4	0	3	1	1	160	2	23	17	7	7	2	7	15	6	6	2	3	8	13	8	5	3	21	72	25	2	1	0	10	10	4	7	4	1	3	329
ZARAGOZA	100	24	50	35	15	50	9	0	0	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	24
ZUTE	124	56	57	37	20	39	1	1	0	34	2	0	1	0	8	14	0	56	0	4	3	2	4	0	6	10	10	0	0	5	0	4	1	1	0	0	32	2	2	1	2	2	1	6	7	4	2	17	161
SUBTOTAL	67607	42242	37732	15763	21969	18065	5585	2229	1426	7323	1078	765	739	1401	1359	2158	354	44162	632	4584	3383	949	2004	789	2611	8935	2675	1344	412	1007	1058	4011	1502	723	452	3775	30160	5082	1240	1379	2199	3417	1834	3266	3515	2299	838	9646	126210
Clinical trials																																																	
AFTCAPS	191	26	147	143	4	23	22	0	0	1	0	0	0	12	0	0	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	4	0	0	0	0	0	0	0	0	0	0	57
ALLHAT	1666	6	1124	1119	5	542	0	0	0	542	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	11
LEADER	181	95	99	36	63	66	51	3	0	12	1	0	1	0	3	6	3	49	1	4	1	2	2	2	1	25	2	0	0	2	2	2	0	0	0	0	32	0	4	0	1	0	1	11	5	4	0	7	183
MRFIT	896	256	767	583	184	80	5	4	8	61	8	7	6	0	5	0	0	141	6	10	8	5	9	2	7	62	4	0	0	2	4	9	3	5	1	0	84	50	1	1	0	3	11	3	4	7	0	3	484
PROSPER	395	88	266	201	65	115	0	0	0	115	0	0	0	0	0	0	0	113	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	42	0	0	0	0	0	0	0	0	0	0	0	243
TPT	1638	585	1213	776	437	337	187	37	19	93	5	3	17	0	30	15	1	787	11	84	51	37	47	7	31	246	66	0	0	27	30	38	33	4	6	0	189	40	7	1	4	20	2	29	50	16	4	22	1583
WHS	606	93	237	229	8	288	241	26	19	2	0	0	0	52	0	0	0	373	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	159	46	0	0	0	0	0	0	31	0	0	0	625
WOSCOPS	447	80	368	297	71	70	0	0	0	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	105	185
SUBTOTAL	6020	1229	4221	3384	837	1521	506	70	46	896	14	10	24	64	38	21	4	1481	18	98	60	44	58	11	39	333	72	0	0	31	36	49	36	9	7	0	524	141	12	2	5	23	14	43	90	27	4	137	3371
Nested case-control studies																																																	
EPICNOR	-	-	481	257	224	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FIA	-	-	611	469	142	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GLOSTRUP	-	-	70	54	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
USPHS	-	-	245	223	22	-	153	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WHIHABPS	-	-	-	-	-	-	606	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUBTOTAL	-	-	1407	1003	404	-	759	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL	**73627**	**43471**	**43360**	**20150**	**23210**	**19586**	**6850**	**2299**	**1472**	**8219**	**1092**	**775**	**763**	**1465**	**1397**	**2179**	**358**	**45643**	**650**	**4682**	**3443**	**993**	**2062**	**800**	**2650**	**9268**	**2747**	**1344**	**412**	**1038**	**1094**	**4060**	**1538**	**732**	**459**	**3775**	**30684**	**5223**	**1252**	**1381**	**2204**	**3440**	**1848**	**3309**	**3605**	**2326**	**842**	**9783**	**129581**

Study acronyms are provided in Appendix 4**.**

*Includes both fatal and non-fatal events.

[a]CHS included an original cohort (here termed CHS1) and a supplemental African-American cohort (here termed CHS2), which were analysed separately.

[b]Progetto CUORE was analysed as 8 different studies (ie, ATENA, EMOFRI, MATISS83, MATISS87, MATISS93, MONFRI86, MONFRI89 and MONFRI94).

[c]RIFLE Study was analysed as 9 different studies (ie, ATS_SAR, DISCO, GREPCO, GUBBIO, MICOL, MONICA, NFR, OB43 and RF2).

Table 5.3 Risk ratios for coronary heart disease and ischaemic stroke per 5 kg/m^2 higher baseline BMI, adjusted for baseline values of biological, socioeconomic and behavioural risk factors

	Coronary heart disease			Ischaemic stroke		
Progressive adjustment	**No of cases**	**RR (95% CI)**	**I^2 (95% CI)**	**No of cases**	**RR (95% CI)**	**I^2 (95% CI)**
Age, sex & smoking	26198	1.30 (1.26 to 1.35)	74 (68 to 78)	4496	1.23 (1.18 to 1.29)	10 (0 to 35)
Plus systolic blood pressure	26198	1.21 (1.18 to 1.25)	56 (45 to 65)	4496	1.13 (1.09 to 1.17)	0 (0 to 31)
Plus history of diabetes	26198	1.19 (1.16 to 1.23)	59 (48 to 67)	4496	1.09 (1.05 to 1.13)	0 (0 to 31)
Plus total cholesterol	26198	1.17 (1.14 to 1.21)	52 (39 to 62)	4496	1.09 (1.05 to 1.13)	0 (0 to 31)
Additional adjustment						
Lipids						
Age, sex & smoking	12137	1.26 (1.21 to 1.32)	61 (49 to 70)	3460	1.24 (1.19 to 1.29)	0 (0 to 36)
Plus conventional risk factorsl[†]	12137	1.16 (1.12 to 1.20)	39 (18 to 54)	3460	1.09 (1.05 to 1.14)	0 (0 to 36)
Plus non-HDL-C, HDL-C & $\log_e$ triglyceride[‡]	12137	1.08 (1.04 to 1.11)	26 (0 to 45)	3460	1.07 (1.02 to 1.11)	0 (0 to 36)
Inflammatory markers						
Age, sex & smoking	7458	1.23 (1.17 to 1.29)	41 (13 to 60)	2218	1.20 (1.11 to 1.30)	32 (0 to 61)
Plus conventional risk factorsl[†]	7458	1.14 (1.08 to 1.19)	39 (10 to 59)	2218	1.09 (1.01 to 1.18)	31 (0 to 61)
Plus $\log_e$ CRP	7458	1.06 (1.01 to 1.12)	40 (12 to 60)	2218	1.05 (0.97 to 1.13)	28 (0 to 59)
Age, sex & smoking	7112	1.28 (1.22 to 1.34)	53 (33 to 67)	2515	1.25 (1.17 to 1.33)	24 (0 to 53)
Plus conventional risk factorsl[†]	7112	1.16 (1.11 to 1.21)	38 (9 to 58)	2515	1.09 (1.03 to 1.14)	1 (0 to 43)
Plus fibrinogen	7112	1.13 (1.08 to 1.18)	38 (8 to 57)	2515	1.07 (1.02 to 1.12)	0 (0 to 43)
Fasting glucose						
Age, sex & smoking	12527	1.26 (1.20 to 1.33)	71 (61 to 78)	2116	1.22 (1.12 to 1.32)	32 (0 to 58)
Plus conventional risk factorsl[†]	12527	1.14 (1.10 to 1.19)	43 (19 to 60)	2116	1.08 (1.01 to 1.15)	9 (0 to 42)
Plus fasting glucose	12527	1.13 (1.09 to 1.18)	42 (18 to 59)	2116	1.07 (0.99 to 1.15)	15 (0 to 47)
Lifestyle factors						
Age, sex & smoking	16415	1.28 (1.22 to 1.34)	75 (68 to 81)	3230	1.20 (1.15 to 1.26)	11 (0 to 41)
Plus education	16415	1.27 (1.21 to 1.32)	74 (66 to 80)	3230	1.20 (1.15 to 1.25)	0 (0 to 38)
Age, sex & smoking	14964	1.35 (1.31 to 1.40)	46 (25 to 61)	1848	1.29 (1.22 to 1.36)	0 (0 to 41)
Plus occupation/job	14964	1.35 (1.30 to 1.39)	46 (24 to 61)	1848	1.29 (1.22 to 1.36)	0 (0 to 41)
Age, sex & smoking	20435	1.28 (1.24 to 1.33)	62 (53 to 70)	4185	1.23 (1.18 to 1.29)	11 (0 to 37)
Plus alcohol consumption	20435	1.28 (1.24 to 1.32)	61 (51 to 70)	4185	1.22 (1.17 to 1.28)	9 (0 to 35)
Age, sex & smoking	15851	1.36 (1.30 to 1.42)	61 (47 to 71)	1921	1.25 (1.16 to 1.35)	28 (0 to 54)
Plus physical activity	15851	1.35 (1.30 to 1.41)	59 (45 to 70)	1921	1.24 (1.16 to 1.34)	26 (0 to 53)

[†]Systolic blood pressure, history of diabetes and total cholesterol.
[‡]Total cholesterol was not included in further adjustments.
Risk ratios were adjusted as shown, and stratified, where appropriate, by sex and trial arm. Analyses were restricted to subsets with complete information and BMI values ≥20kg/m^2.

Table 5.4 Risk ratios for coronary heart disease and ischaemic stroke per 5 kg/m^2 higher usual levels of BMI, adjusted for usual levels of potential intermediate risk factors

	RR (95% CI)	I^2 (95% CI)	RR (95% CI)	I^2 (95% CI)
Coronary heart disease	**68 studies & 12137 cases**		**29 studies & 3961 cases**	
Adjusted for age, sex and smoking	1.29 (1.24 to 1.35)	60 (48 to 69)	1.24 (1.17 to 1.32)	33 (0 to 57)
Plus systolic blood pressure	1.18 (1.14 to 1.23)	36 (14 to 52)	1.15 (1.09 to 1.22)	21 (0 to 50)
Plus history of diabetes	1.14 (1.09 to 1.18)	41 (21 to 56)	1.10 (1.04 to 1.17)	25 (0 to 52)
Plus non-HDL-cholesterol	1.10 (1.06 to 1.15)	40 (20 to 55)	1.07 (1.01 to 1.14)	26 (0 to 53)
Plus HDL-cholesterol	1.06 (1.01 to 1.10)	47 (30 to 60)	1.01 (0.95 to 1.08)	32 (0 to 57)
Plus $\log_e$ triglyceride	1.04 (1.01 to 1.08)	18 (0 to 40)	1.02 (0.95 to 1.08)	28 (0 to 54)
Plus $\log_e$ CRP			0.93 (0.87 to 1.00)	28 (0 to 55)
Ischaemic stroke	**40 studies & 3460 cases**		**14 studies & 1764 cases**	
Adjusted for age, sex and smoking	1.27 (1.21 to 1.32)	0 (0 to 36)	1.19 (1.10 to 1.29)	26 (0 to 61)
Plus systolic blood pressure	1.11 (1.06 to 1.16)	0 (0 to 36)	1.07 (0.99 to 1.16)	19 (0 to 56)
Plus history of diabetes	1.04 (0.99 to 1.09)	0 (0 to 36)	1.01 (0.93 to 1.10)	23 (0 to 59)
Plus non-HDL-cholesterol	1.03 (0.97 to 1.09)	14 (0 to 42)	1.01 (0.93 to 1.11)	28 (0 to 62)
Plus HDL-cholesterol	1.02 (0.97 to 1.07)	0 (0 to 36)	1.02 (0.91 to 1.14)	45 (0 to 71)
Plus $\log_e$ triglyceride	1.02 (0.98 to 1.07)	0 (0 to 36)	1.00 (0.91 to 1.09)	25 (0 to 60)
Plus $\log_e$ CRP			0.92 (0.84 to 1.00)	13 (0 to 51)

Risk ratios (RRs) were adjusted as shown, and stratified, where appropriate, by sex and trial arm. Analyses were restricted to BMI values ≥20kg/m^2.

Table 5.5 Risk ratios for coronary deaths and non-fatal myocardial infarction (MI) per 5 kg/m^2 higher baseline BMI, adjusted for baseline values of biological, socioeconomic and behavioural risk factors

	Coronary deaths			Non-fatal MI		
Progressive adjustment	**No of cases**	**RR (95% CI)**	**I^2 (95% CI)**	**No of cases**	**RR (95% CI)**	**I^2 (95% CI)**
Age, sex & smoking	6298	1.33 (1.26 to 1.40)	43 (23 to 58)	12928	1.27 (1.22 to 1.31)	48 (31 to 62)
Plus systolic blood pressure	6298	1.23 (1.17 to 1.29)	31 (6 to 50)	12928	1.20 (1.16 to 1.24)	37 (15 to 54)
Plus history of diabetes	6298	1.20 (1.14 to 1.26)	30 (4 to 49)	12928	1.18 (1.13 to 1.22)	42 (21 to 57)
Plus total cholesterol	6298	1.19 (1.14 to 1.25)	26 (0 to 46)	12928	1.16 (1.12 to 1.20)	36 (12 to 53)
Additional adjustment						
Lipids						
Age, sex & smoking	2836	1.32 (1.23 to 1.41)	39 (13 to 57)	7266	1.25 (1.19 to 1.31)	48 (26 to 63)
Plus conventional risk factorsl[†]	2836	1.20 (1.12 to 1.28)	30 (0 to 51)	7266	1.15 (1.10 to 1.20)	31 (1 to 52)
Plus non-HDL-C, HDL-C & $\log_e$ triglyceride[‡]	2836	1.13 (1.06 to 1.21)	26 (0 to 49)	7266	1.06 (1.02 to 1.11)	26 (0 to 49)
Inflammatory markers						
Age, sex & smoking	1936	1.29 (1.17 to 1.43)	40 (6 to 61)	4963	1.21 (1.14 to 1.29)	45 (14 to 64)
Plus conventional risk factorsl[†]	1936	1.19 (1.07 to 1.32)	39 (4 to 61)	4963	1.12 (1.05 to 1.19)	40 (6 to 62)
Plus $\log_e$ CRP	1936	1.10 (0.98 to 1.24)	45 (15 to 64)	4963	1.06 (0.99 to 1.12)	39 (5 to 61)
Age, sex & smoking	1781	1.34 (1.23 to 1.47)	44 (16 to 62)	4505	1.27 (1.20 to 1.34)	41 (11 to 60)
Plus conventional risk factorsl[†]	1781	1.21 (1.11 to 1.32)	36 (4 to 58)	4505	1.16 (1.10 to 1.22)	33 (0 to 56)
Plus fibrinogen	1781	1.17 (1.07 to 1.28)	38 (6 to 59)	4505	1.13 (1.07 to 1.19)	34 (0 to 56)
Fasting glucose						
Age, sex & smoking	3485	1.35 (1.25 to 1.46)	54 (31 to 70)	6984	1.21 (1.15 to 1.27)	44 (13 to 64)
Plus conventional risk factorsl[†]	3485	1.22 (1.14 to 1.30)	35 (0 to 59)	6984	1.12 (1.09 to 1.16)	0 (0 to 41)
Plus fasting glucose	3485	1.21 (1.13 to 1.30)	35 (0 to 59)	6984	1.12 (1.08 to 1.15)	0 (0 to 41)
Lifestyle factors						
Age, sex & smoking	4481	1.28 (1.21 to 1.36)	41 (11 to 61)	10595	1.25 (1.19 to 1.32)	71 (60 to 80)
Plus education	4481	1.27 (1.20 to 1.35)	39 (7 to 60)	10595	1.27 (1.20 to 1.35)	39 (7 to 60)
Age, sex & smoking	4250	1.37 (1.30 to 1.44)	24 (0 to 51)	7065	1.32 (1.26 to 1.38)	32 (0 to 56)
Plus occupation/job	4250	1.36 (1.29 to 1.43)	24 (0 to 51)	7065	1.31 (1.25 to 1.37)	31 (0 to 55)
Age, sex & smoking	4932	1.34 (1.27 to 1.43)	46 (26 to 61)	11160	1.26 (1.21 to 1.31)	47 (27 to 61)
Plus alcohol consumption	4932	1.34 (1.26 to 1.42)	45 (25 to 60)	11160	1.25 (1.21 to 1.30)	46 (26 to 60)
Age, sex & smoking	3655	1.41 (1.32 to 1.49)	25 (0 to 52)	7542	1.27 (1.21 to 1.33)	41 (8 to 62)
Plus physical activity	3655	1.39 (1.31 to 1.48)	27 (0 to 53)	7542	1.27 (1.20 to 1.33)	38 (4 to 60)

[†]Systolic blood pressure, history of diabetes and total cholesterol.
[‡]Total cholesterol was not included in further adjustments.
Risk ratios were adjusted as shown, and stratified, where appropriate, by sex and trial arm. Analyses were restricted to studies contributed data to both outcomes and BMI values ≥20kg/m^2.

Table 5.6 Supplementary analyses for coronary heart disease and ischaemic stroke per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status

Description of supplementary analysis	Outcome	No of cases	RR (95% CI)	I^2 (95% CI)
Excluding 5 years of follow-up	Coronary heart disease	27519	1.36 (1.30 to 1.42)	81 (77 to 84)
	Ischaemic stroke	3335	1.26 (1.19 to 1.33)	22 (0 to 45)
Excluding current smokers	Coronary heart disease	24975	1.31 (1.25 to 1.36)	80 (77 to 83)
	Ischaemic stroke	4809	1.25 (1.21 to 1.30)	4 (0 to 28)
Excluding non-European descents	Coronary heart disease	36985	1.31 (1.26 to 1.37)	72 (64 to 78)
	Ischaemic stroke	4474	1.24 (1.18 to 1.29)	11 (0 to 36)

Risk ratios were adjusted for age at baseline and smoking status and stratified, where appropriate, by sex and trial arm. Analyses were restricted to BMI values ≥20kg/m^2.

Table 5.7 Risk ratios for major causes of death per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status

	BMI <25kg/m^2			BMI ≥25kg/m^2		
Cause of death	**No of deaths**	**RR (95% CI)**	**I^2 (95% CI)**	**No of deaths**	**RR (95% CI)**	**I^2 (95% CI)**
All cancer deaths	22500	0.75 (0.70 to 0.81)	50 (37 to 61)	20870	1.12 (1.09 to 1.15)	12 (0 to 33)
All non-cancer non-vascular deaths	15446	0.48 (0.45 to 0.53)	57 (45 to 66)	13702	1.32 (1.26 to 1.38)	53 (40 to 63)
Death of unknown cause or ill-defined cause	4581	0.64 (0.57 to 0.73)	42 (18 to 59)	4756	1.21 (1.14 to 1.28)	21 (0 to 44)
All-cause mortality	60638	0.68 (0.65 to 0.72)	67 (60 to 73)	63628	1.26 (1.23 to 1.29)	64 (56 to 71)

Risk ratios were adjusted as shown, and stratified, where appropriate, by sex and trial arm.

Table 5.8 Risk ratios for all cancer mortality, non-vascular non-cancer mortality and all-cause mortality per 5 kg/m^2 higher baseline BMI in the BMI range ≥25kg/m^2, adjusted for baseline values of biological, socioeconomic and behavioural risk factors

	All cancer deaths			All non-cancer non-vascular deaths			All-cause mortality		
Progressive adjustment	**No of deaths**	**RR (95% CI)**	**I^2 (95% CI)**	**No of deaths**	**RR (95% CI)**	**I^2 (95% CI)**	**No of deaths**	**RR (95% CI)**	**I^2 (95% CI)**
Age, sex & smoking	10497	1.12 (1.08 to 1.16)	6 (0 to 29)	6448	1.34 (1.26 to 1.42)	47 (31 to 60)	32631	1.27 (1.23 to 1.31)	59 (48 to 67)
Plus systolic blood pressure	10497	1.11 (1.07 to 1.15)	11 (0 to 34)	6448	1.29 (1.22 to 1.36)	39 (19 to 54)	32631	1.22 (1.18 to 1.25)	48 (34 to 59)
Plus history of diabetes	10497	1.10 (1.06 to 1.14)	10 (0 to 33)	6448	1.25 (1.18 to 1.33)	41 (23 to 55)	32631	1.20 (1.16 to 1.23)	52 (39 to 62)
Plus total cholesterol	10497	1.10 (1.06 to 1.14)	11 (0 to 33)	6448	1.24 (1.17 to 1.32)	43 (25 to 57)	32631	1.19 (1.16 to 1.23)	53 (40 to 63)
Additional adjustment									
Lipids									
Age, sex & smoking	4489	1.11 (1.06 to 1.15)	0 (0 to 32)	2944	1.35 (1.24 to 1.47)	57 (42 to 69)	13128	1.24 (1.19 to 1.29)	45 (26 to 59)
Plus conventional risk factors[†]	4489	1.09 (1.04 to 1.14)	4 (0 to 29)	2944	1.28 (1.17 to 1.40)	60 (45 to 70)	13128	1.19 (1.14 to 1.23)	47 (30 to 60)
Plus non-HDL-C, HDL-C & $\log_e$ triglyceride[‡]	4489	1.07 (1.02 to 1.12)	2 (0 to 24)	2944	1.28 (1.16 to 1.41)	60 (46 to 71)	13128	1.17 (1.12 to 1.22)	44 (25 to 58)
Inflammatory markers									
Age, sex & smoking	1990	1.06 (0.99 to 1.14)	0 (0 to 44)	1370	1.26 (1.15 to 1.38)	10 (0 to 44)	6945	1.21 (1.15 to 1.27)	24 (0 to 50)
Plus conventional risk factors[†]	1990	1.05 (0.98 to 1.13)	0 (0 to 44)	1370	1.21 (1.11 to 1.31)	0 (0 to 45)	6945	1.17 (1.12 to 1.22)	19 (0 to 47)
Plus $\log_e$ CRP	1990	1.01 (0.94 to 1.09)	0 (0 to 44)	1370	1.15 (1.06 to 1.25)	0 (0 to 45)	6945	1.11 (1.05 to 1.16)	21 (0 to 48)
Age, sex & smoking	2968	1.08 (1.01 to 1.15)	17 (0 to 46)	2066	1.34 (1.20 to 1.50)	59 (41 to 72)	8766	1.23 (1.17 to 1.30)	54 (34 to 68)
Plus conventional risk factors[†]	2968	1.06 (0.99 to 1.13)	19 (0 to 48)	2066	1.26 (1.12 to 1.42)	63 (46 to 74)	8766	1.17 (1.11 to 1.24)	55 (36 to 69)
Plus fibrinogen	2968	1.03 (0.96 to 1.10)	24 (0 to 50)	2066	1.21 (1.08 to 1.36)	59 (40 to 72)	8766	1.14 (1.08 to 1.20)	55 (36 to 69)
Fasting glucose									
Age, sex & smoking	4498	1.13 (1.08 to 1.18)	0 (0 to 38)	3094	1.32 (1.20 to 1.45)	54 (32 to 69)	14075	1.26 (1.20 to 1.32)	61 (46 to 72)
Plus conventional risk factors[†]	4498	1.10 (1.05 to 1.15)	0 (0 to 38)	3094	1.23 (1.12 to 1.34)	51 (26 to 67)	14075	1.18 (1.12 to 1.24)	57 (40 to 69)
Plus fasting glucose	4498	1.09 (1.04 to 1.14)	0 (0 to 38)	3094	1.20 (1.10 to 1.32)	48 (23 to 66)	14075	1.16 (1.11 to 1.22)	54 (36 to 67)
Lifestyle factors									
Age, sex & smoking	5883	1.08 (1.04 to 1.13)	12 (0 to 40)	4380	1.29 (1.21 to 1.38)	52 (31 to 66)	18252	1.22 (1.18 to 1.27)	58 (43 to 69)
Plus education	5883	1.08 (1.03 to 1.13)	13 (0 to 41)	4380	1.28 (1.19 to 1.37)	53 (32 to 67)	18252	1.22 (1.17 to 1.26)	60 (46 to 71)
Age, sex & smoking	6427	1.09 (1.05 to 1.13)	0 (0 to 35)	3891	1.35 (1.28 to 1.44)	22 (0 to 47)	20359	1.27 (1.23 to 1.30)	27 (0 to 49)
Plus occupation/job	6427	1.09 (1.05 to 1.13)	0 (0 to 35)	3891	1.34 (1.26 to 1.42)	19 (0 to 45)	20359	1.26 (1.22 to 1.30)	27 (0 to 49)
Age, sex & smoking	8832	1.09 (1.05 to 1.13)	9 (0 to 32)	6228	1.29 (1.22 to 1.37)	47 (30 to 60)	27709	1.29 (1.22 to 1.37)	47 (30 to 60)
Plus alcohol consumption	8832	1.09 (1.05 to 1.13)	7 (0 to 31)	6228	1.28 (1.21 to 1.36)	45 (28 to 59)	27709	1.28 (1.21 to 1.36)	45 (28 to 59)
Age, sex & smoking	7117	1.13 (1.09 to 1.17)	0 (0 to 34)	4318	1.34 (1.25 to 1.44)	45 (21 to 61)	20633	1.30 (1.26 to 1.35)	53 (36 to 66)
Plus physical activity	7117	1.12 (1.08 to 1.17)	0 (0 to 34)	4318	1.33 (1.24 to 1.43)	43 (19 to 60)	20633	1.30 (1.25 to 1.35)	52 (34 to 65)

[†]Systolic blood pressure, history of diabetes and total cholesterol. [‡]Total cholesterol was not included in further adjustments.
Risk ratios were adjusted as shown, and stratified, where appropriate, by sex and trial arm. Analyses were restricted to subsets with complete information.

Table 5.9 Risk ratios per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status

Description of supplementary analysis	Outcome	BMI <25kg/m^2			BMI ≥25kg/m^2		
		No of deaths	RR (95% CI)	I^2 (95% CI)	No of deaths	RR (95% CI)	I^2 (95% CI)
Excluding 5 years of follow-up	All cancer deaths	18678	0.82 (0.76 to 0.87)	34 (13 to 50)	16567	1.14 (1.11 to 1.18)	20 (0 to 40)
	All non-cancer non-vascular deaths	12901	0.53 (0.48 to 0.57)	49 (33 to 61)	11309	1.31 (1.26 to 1.38)	42 (24 to 56)
	Respiratory disease	4257	0.40 (0.35 to 0.45)	40 (15 to 57)	2918	1.20 (1.10 to 1.32)	40 (17 to 57)
	All-cause mortality	49769	0.74 (0.70 to 0.78)	58 (47 to 66)	51108	1.29 (1.25 to 1.32)	58 (47 to 66)
Including never-smokers only	All cancer deaths	5809	0.94 (0.84 to 1.05)	24 (0 to 45)	6257	1.13 (1.10 to 1.17)	0 (0 to 28)
	Lung cancer	329	0.86 (0.57 to 1.30)	19 (0 to 57)	293	1.06 (0.88 to 1.26)	0 (0 to 58)
	All non-cancer non-vascular deaths	4261	0.61 (0.54 to 0.69)	27 (0 to 48)	4531	1.32 (1.24 to 1.42)	43 (24 to 58)
	Respiratory disease	861	0.47 (0.38 to 0.58)	20 (0 to 50)	861	1.08 (0.96 to 1.22)	16 (0 to 47)
	All-cause mortality	16787	0.80 (0.74 to 0.86)	37 (18 to 52)	20405	1.28 (1.24 to 1.33)	49 (35 to 60)
Excluding non-European descents	All cancer deaths	21382	0.76 (0.70 to 0.82)	53 (39 to 63)	20095	1.13 (1.10 to 1.16)	8 (0 to 30)
	All non-cancer non-vascular deaths	14464	0.49 (0.45 to 0.54)	52 (39 to 63)	12819	1.33 (1.28 to 1.39)	32 (12 to 48)
	All-cause mortality	57242	0.70 (0.66 to 0.73)	64 (56 to 71)	60700	1.28 (1.25 to 1.30)	51 (38 to 61)

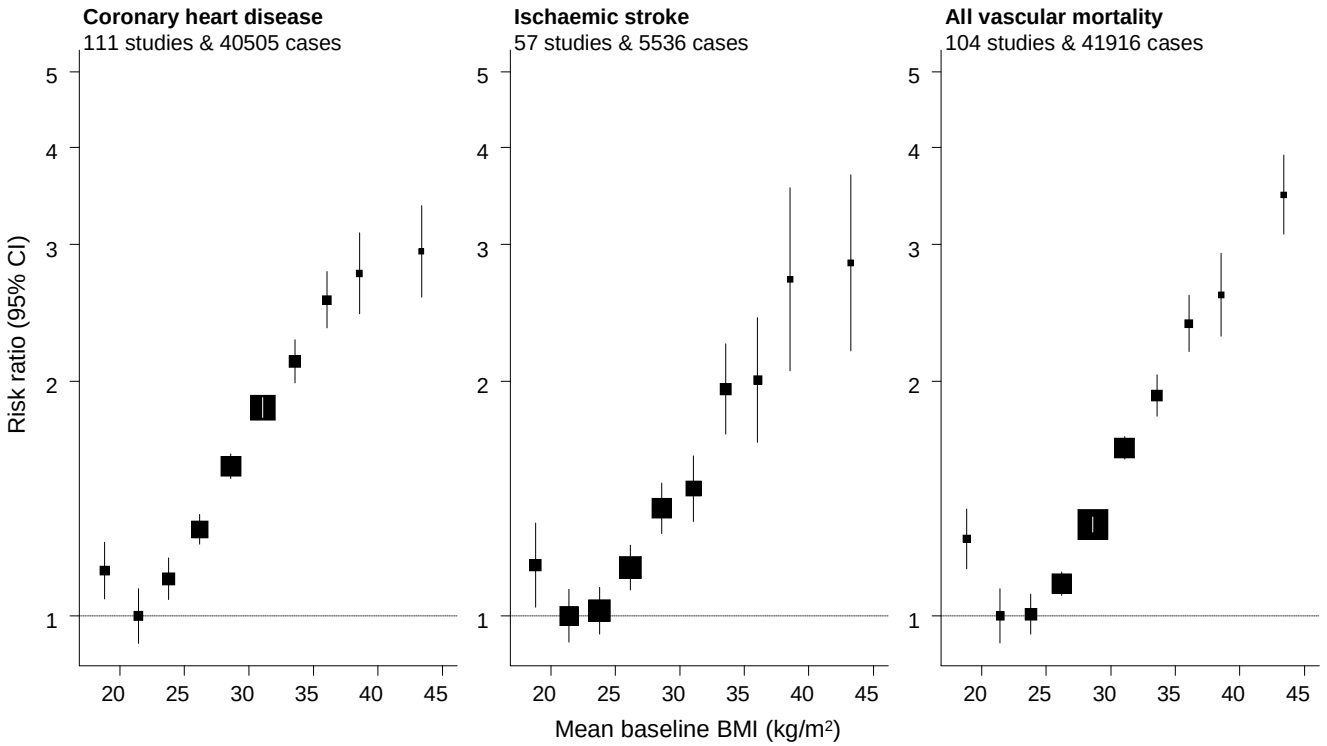
Risk ratios (RRs) were adjusted for age at baseline and smoking status and stratified, where appropriate, by sex and trial arm.

Table 5.10 Risk ratios for all cancer mortality, non-cancer non-vascular mortality and all-cause mortality per 5 kg/m^2 higher baseline BMI without censoring for previous non-fatal outcomes, adjusted for age, sex and smoking status

	BMI <25kg/m^2			BMI ≥25kg/m^2		
Cause of death	**No of deaths**	**HR (95% CI)**	**I^2 (95% CI)**	**No of deaths**	**HR (95% CI)**	**I^2 (95% CI)**
All cancer deaths	19732	0.83 (0.77 to 0.88)	36 (15 to 52)	23158	1.11 (1.08 to 1.14)	21 (0 to 40)
All non-cancer non-vascular deaths	14012	0.55 (0.51 to 0.60)	49 (33 to 61)	15804	1.30 (1.25 to 1.36)	54 (41 to 64)
All-cause mortality	55704	0.76 (0.73 to 0.80)	52 (39 to 63)	75505	1.25 (1.22 to 1.28)	73 (68 to 78)

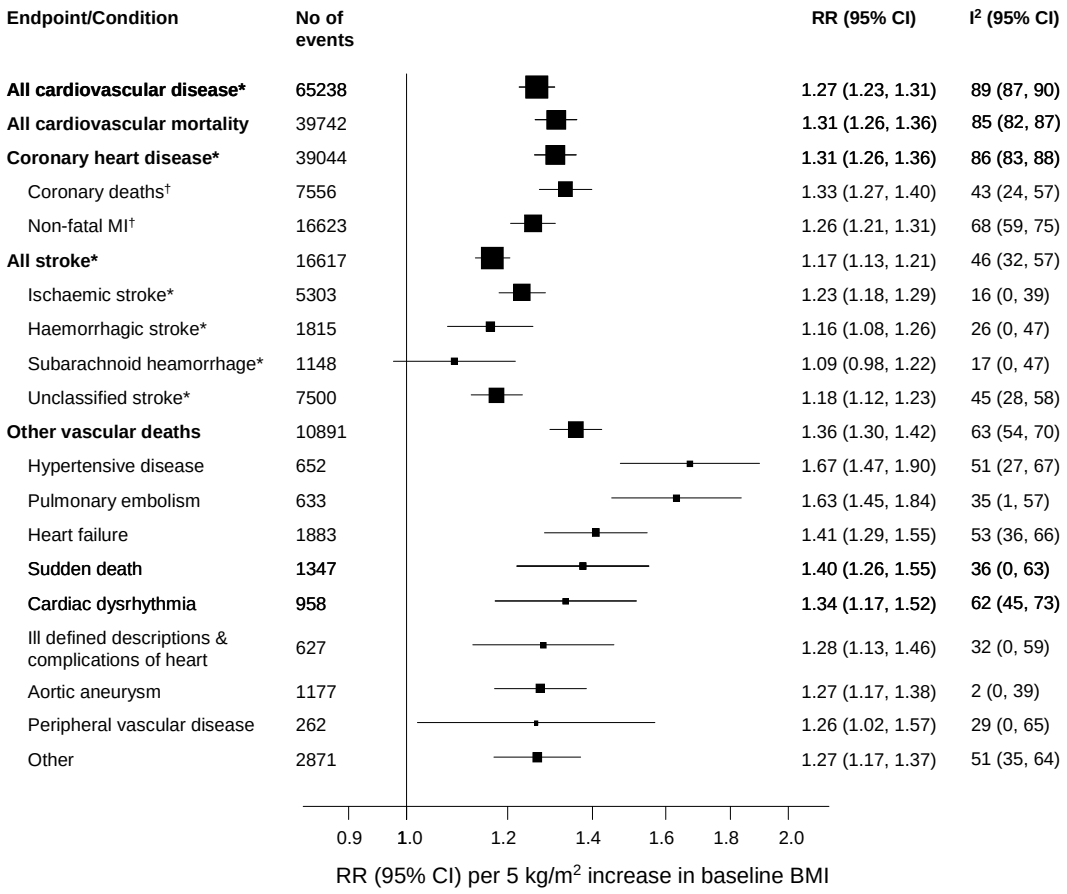
Analyses involving participants with BMI below 25 kg/m^2 excluded the first five years of follow-up. Risk ratios were adjusted for age and smoking, and stratified, where appropriate, by sex and trial arm.

Figure 5.1 Risk ratios for coronary heart disease, ischaemic stroke and all vascular mortality across categories of baseline BMI, adjusted for age, sex and smoking status



Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Reference groups are the second category (ie, 20 to <22.5 kg/m^2).

Figure 5.2 Risk ratios for vascular outcomes per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status (in participants with BMI values of 20kg/m^2 or higher)

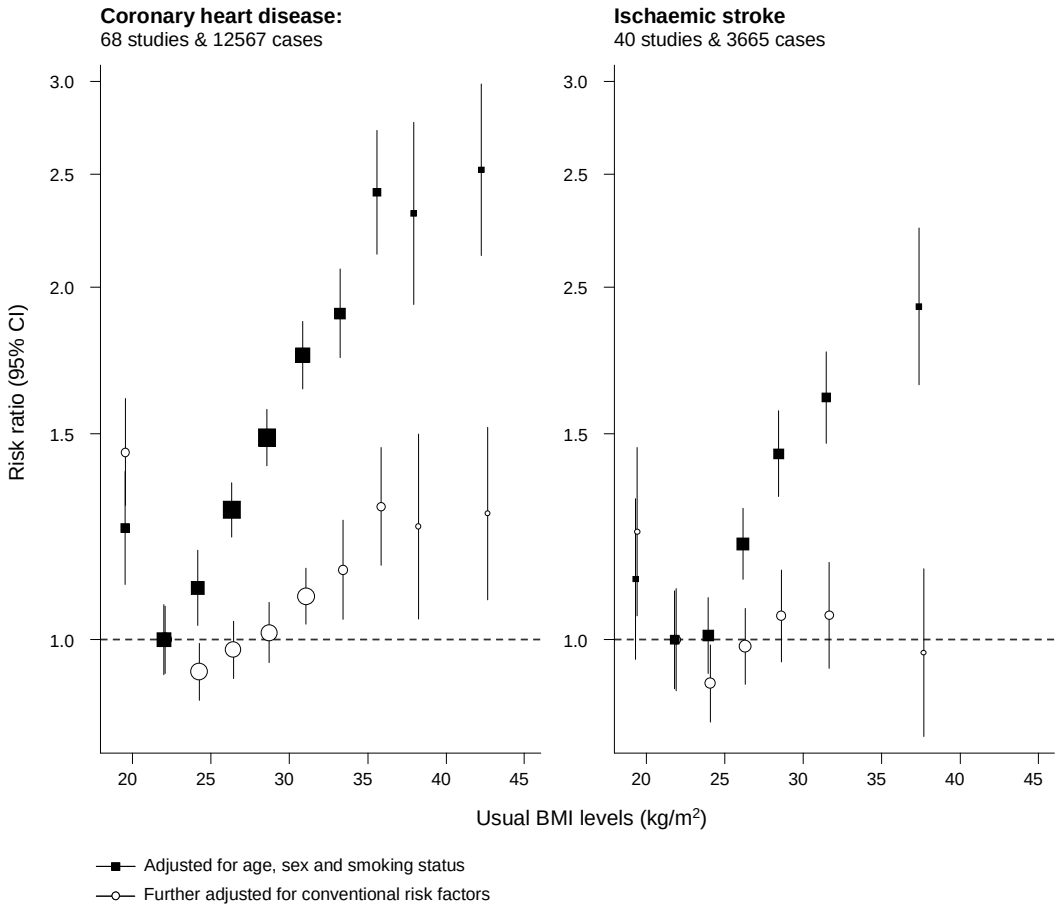


*Includes both fatal and non-fatal events.
†Restricted to studies contributing to both outcomes.

Causes of other vascular deaths are ordered by their strength of association. Risk ratios (RRs) were adjusted for age at baseline and smoking status and stratified, where appropriate, by sex and trial arm. Analyses were restricted to participant with BMI values ≥20 kg/m^2. There was evidence of heterogeneity in risk ratios between different vascular outcomes (P-value for heterogeneity <0.001). P-value = 0.006 for test of difference between associations with coronary deaths and non-fatal myocardial infarction (MI).

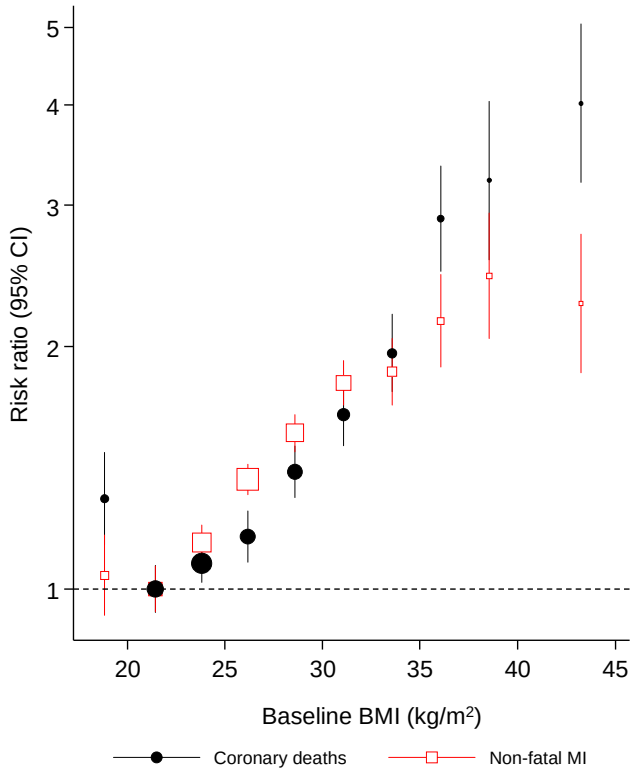
For comparison with results in Chapter 6, risk ratios per 4.56 kg/m^2 were 1.28 (95% CI 1.23-1.32) for coronary heart disease and 1.21 (95% CI 1.16-1.26) for ischaemic stroke.

Figure 5.3 Risk ratios for coronary heart disease and ischaemic stroke across categories of usual levels of BMI



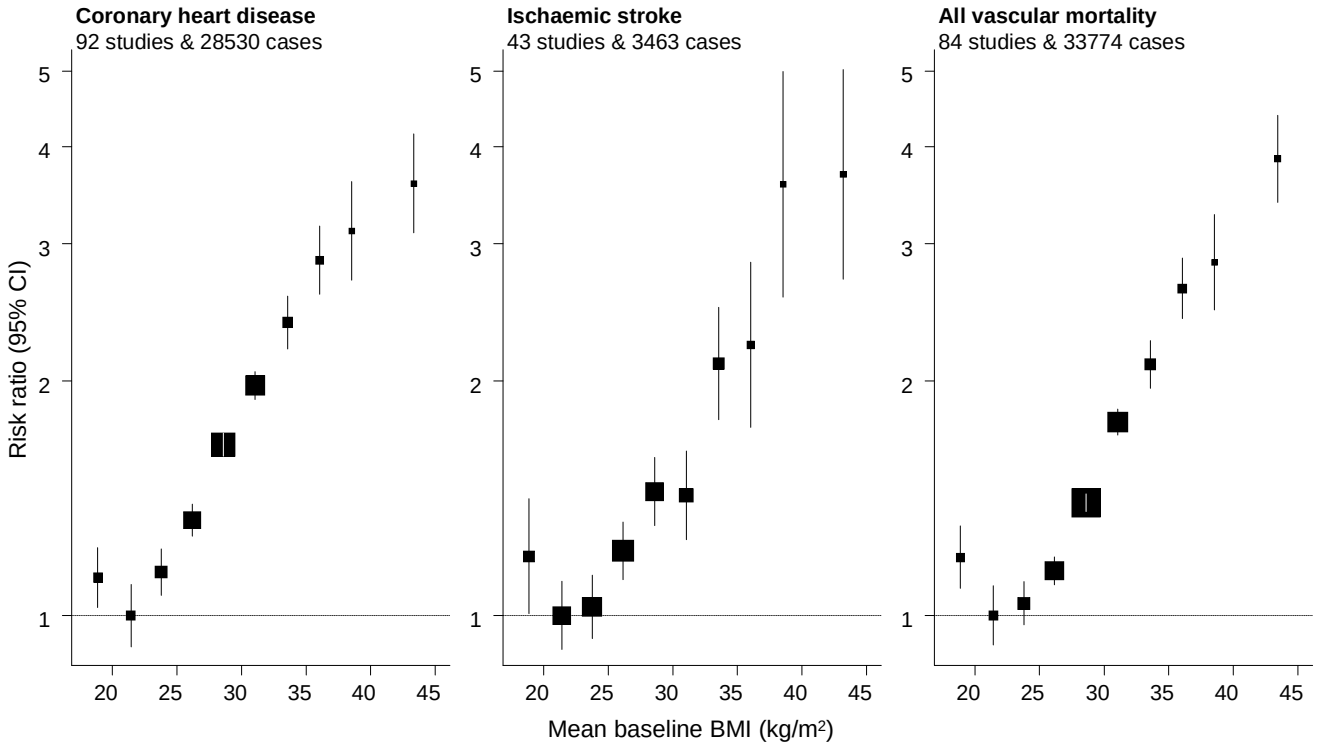
Regression analyses were stratified, where appropriate, by sex and trial arm. Values with further adjustments were adjusted for age, sex and usual levels of smoking status, SBP, history of diabetes, total and HDL cholesterol, and $\log_e$ triglyceride. Reference groups are the second category (ie, 20 to <22.5 kg/m^2).

Figure 5.4 Risk ratios for coronary deaths and non-fatal myocardial infarction (MI) by categories of baseline BMI, restricted to studies providing data on both outcomes



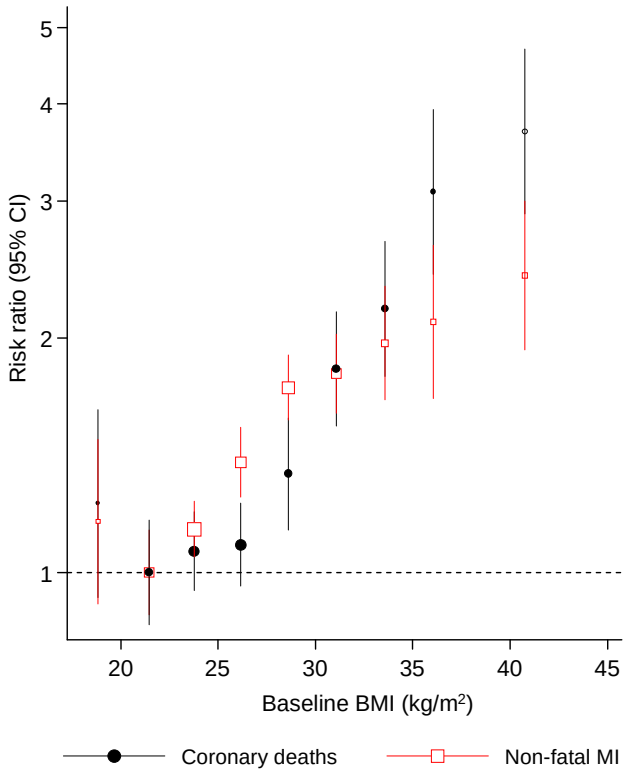
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Analyses involved 62 studies with 7853 coronary deaths and 15649 non-fatal MIs. Reference groups are the second category (ie, 20 to <22.5 kg/m^2).

Figure 5.5 Risk ratios for coronary heart disease, ischaemic stroke and all vascular mortality across categories of baseline BMI, after excluding the first five years of follow-up



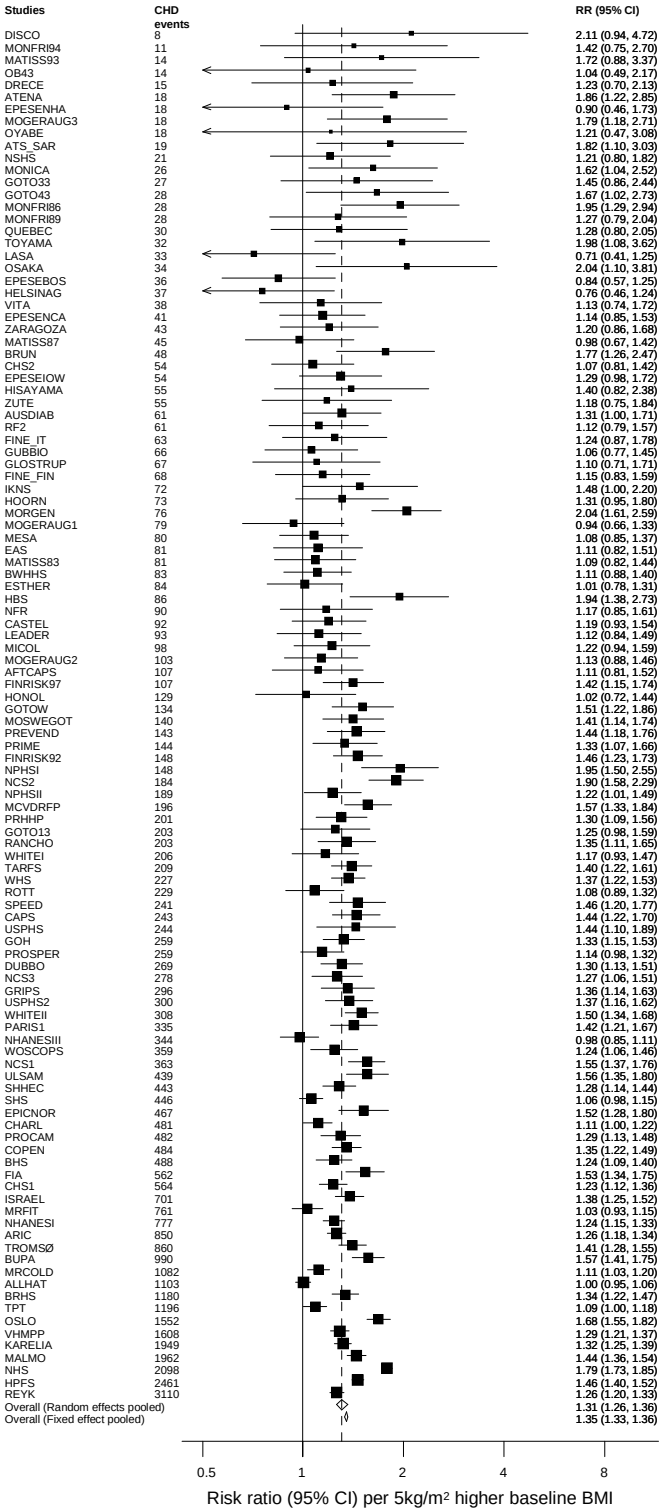
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Reference groups are the second category (ie, 20 to <22.5 kg/m^2).

Figure 5.6 Risk ratios for coronary deaths and non-fatal myocardial infarction (MI) by categories of baseline BMI, restricted to studies providing data on both outcomes and on never-smokers only



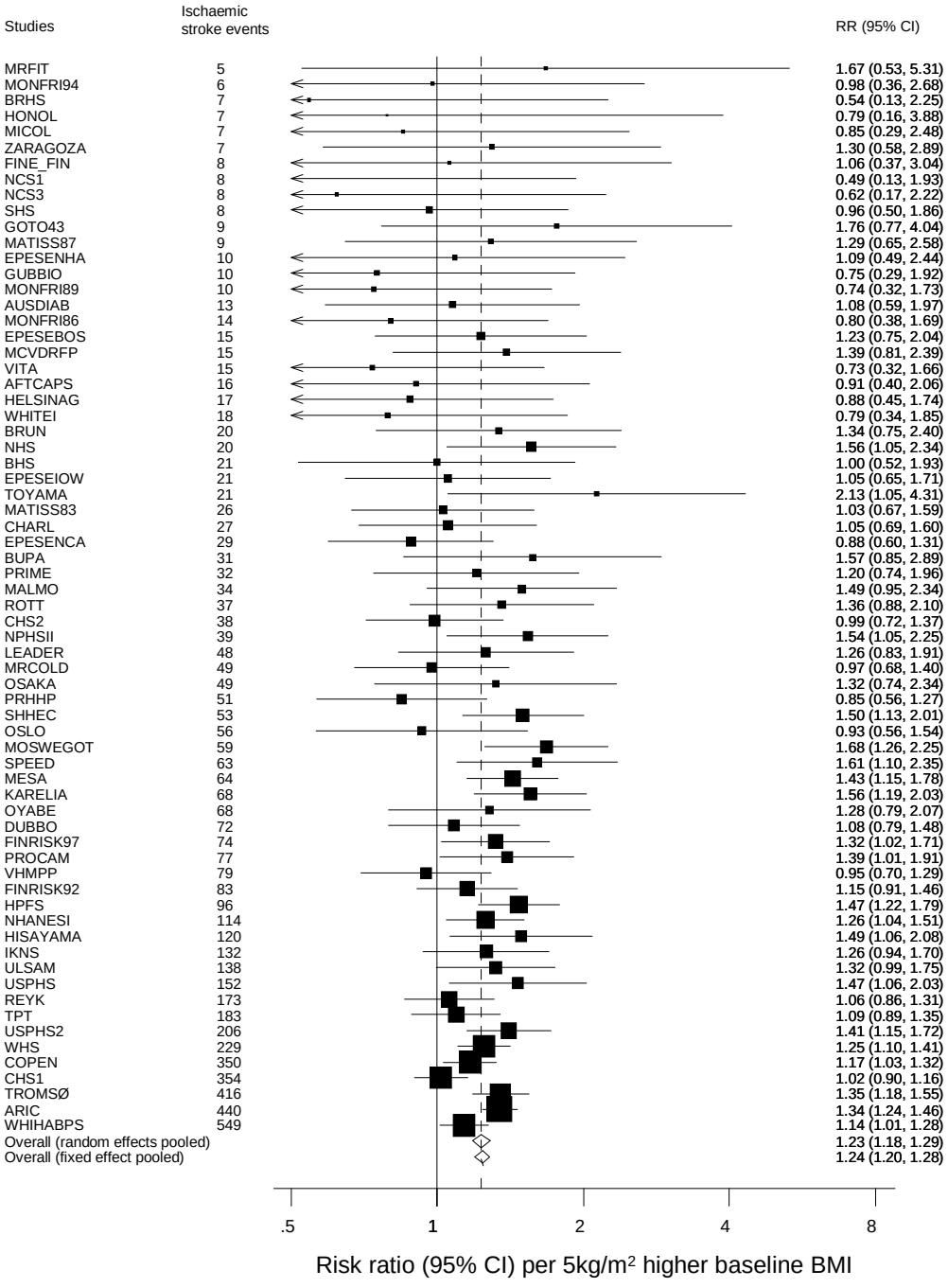
Analyses were adjusted for age, and stratified, where appropriate, by sex and trial arm. Analyses involved 30 studies with 1696 coronary deaths and 3051 non-fatal MIs. Reference groups are the second category (ie, 20 to <22.5 kg/m^2).

Figure 5.7 Study-specific risk ratios for coronary heart disease per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status



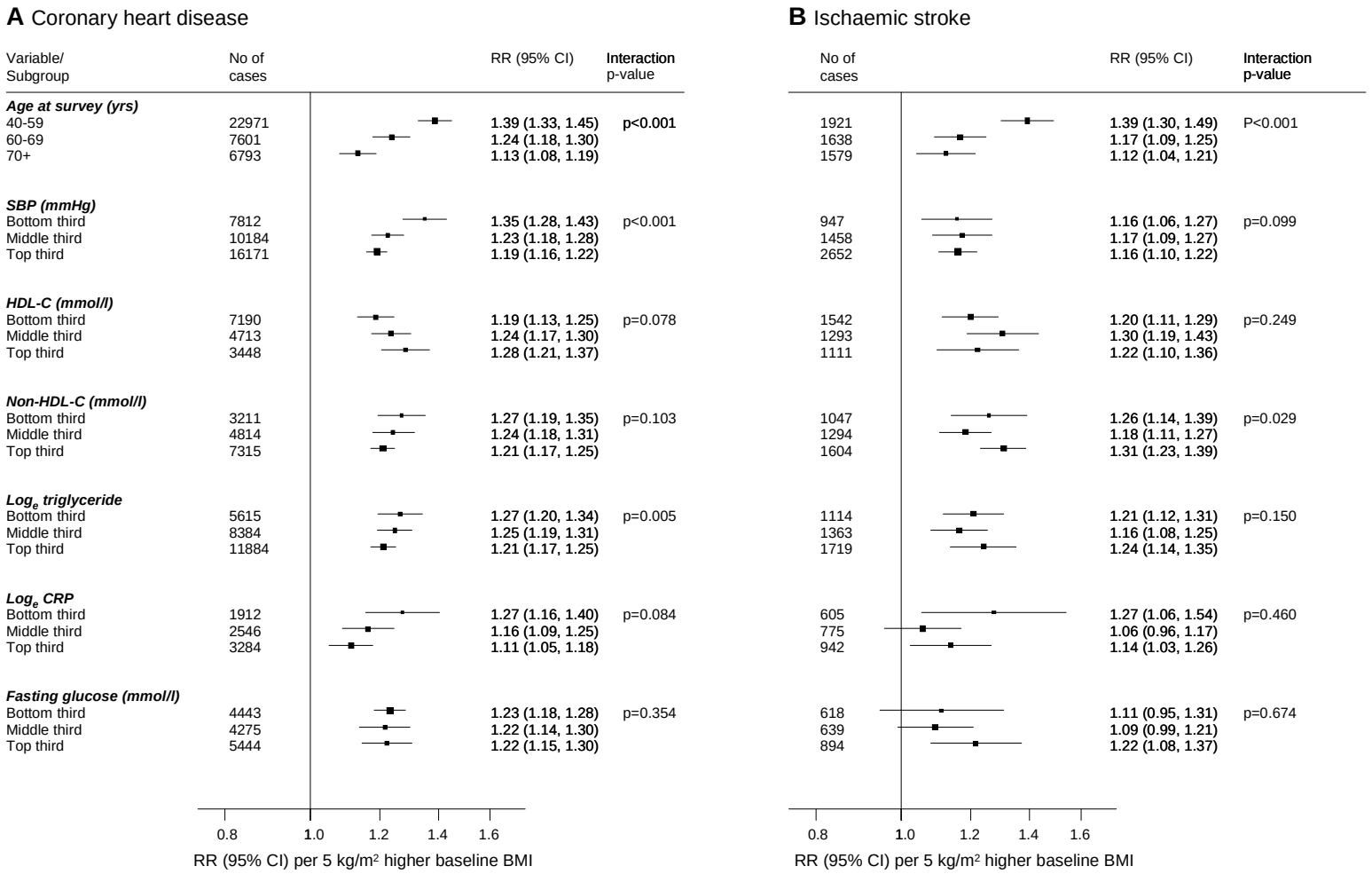
Analyses were restricted to participants with BMI values ≥20 kg/m^2.

Figure 5.8 Study-specific risk ratios for ischaemic stroke per 5 kg/m^2 higher baseline BMI, adjusted for age, sex and smoking status



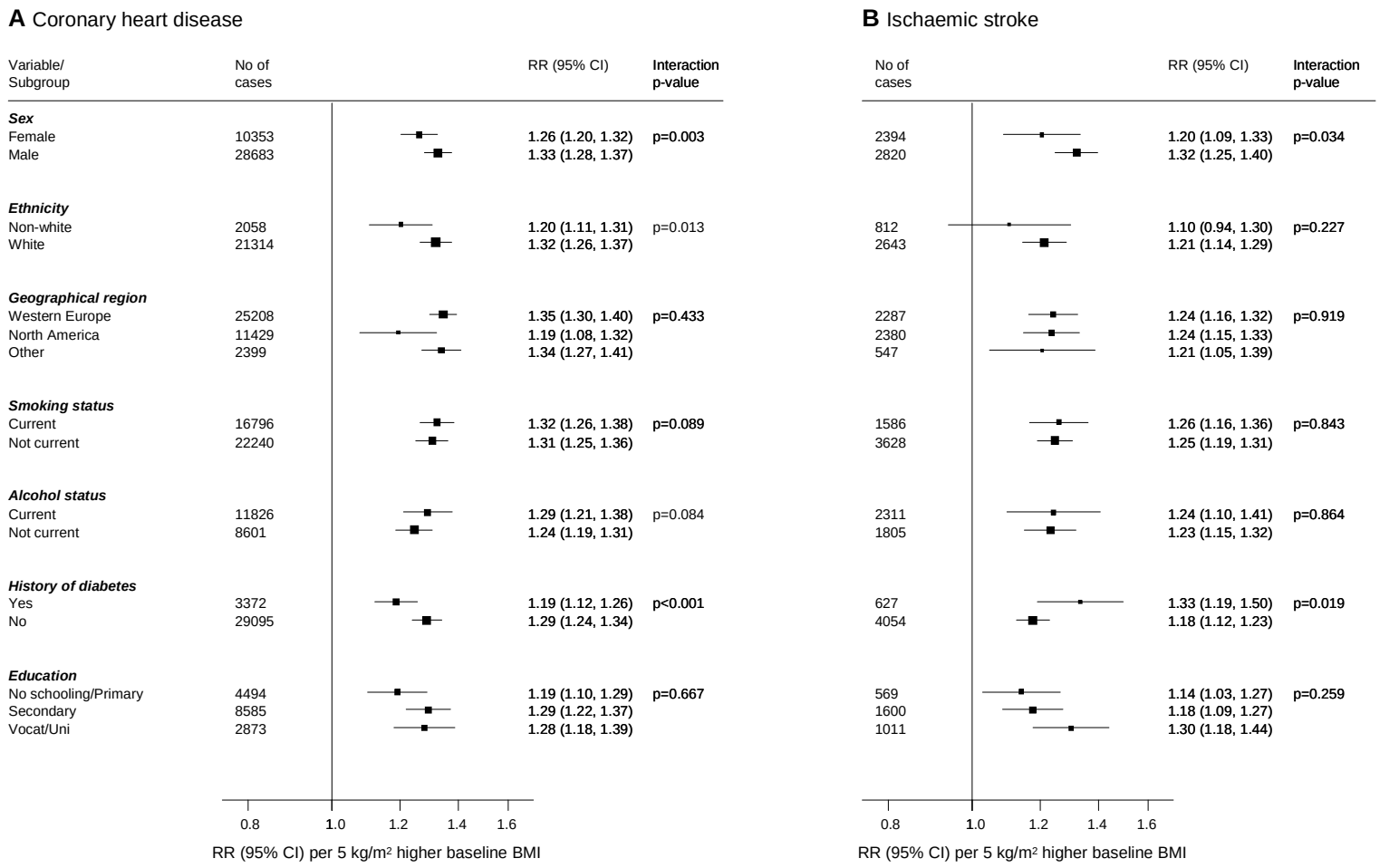
Analyses were restricted to participants with BMI values ≥20 kg/m^2.

Figure 5.9 Risk ratios for coronary heart disease and ischaemic stroke per 5 kg/m^2 higher baseline BMI, according to various characteristics of continuous variables



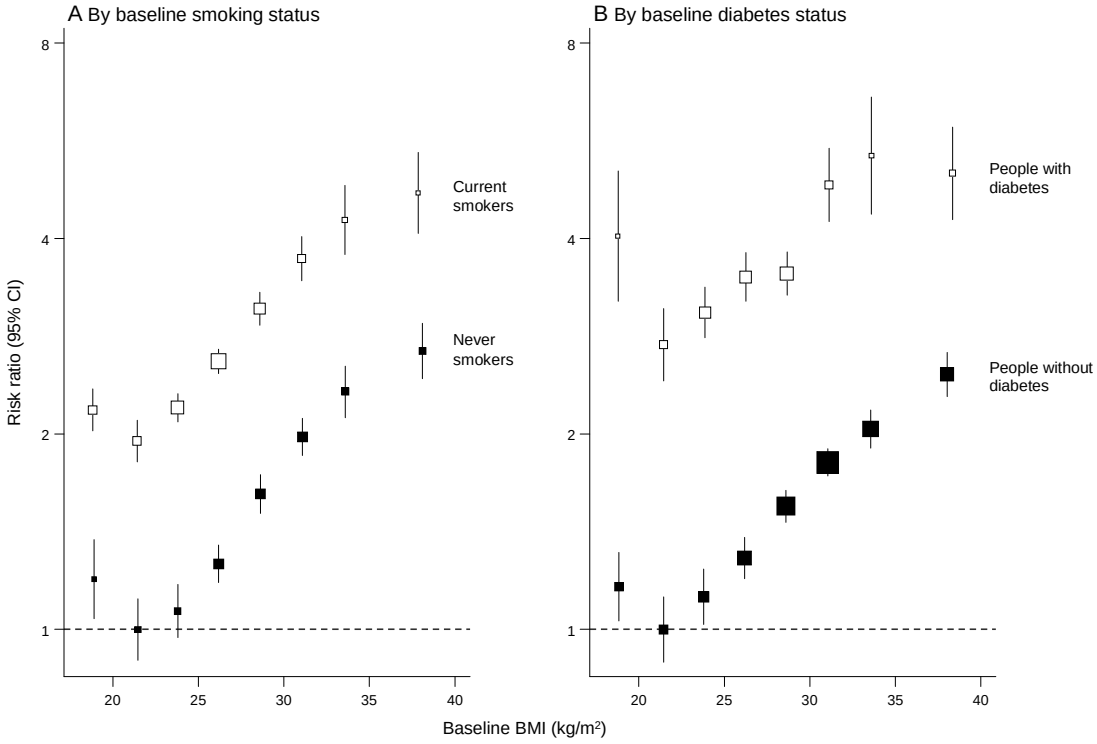
Risk ratios were adjusted for age and smoking, and stratified, where appropriate, by sex and trial arm. Analyses involved baseline values of BMI and interaction variables. Analyses were restricted to participants with BMI values ≥20 kg/m^2. P-values for interaction were calculated from analyses using continuous variable, where appropriate.

Figure 5.10 Risk ratios for coronary heart disease and ischaemic stroke per 5 kg/m^2 higher baseline BMI, according to various characteristics of categorical variables



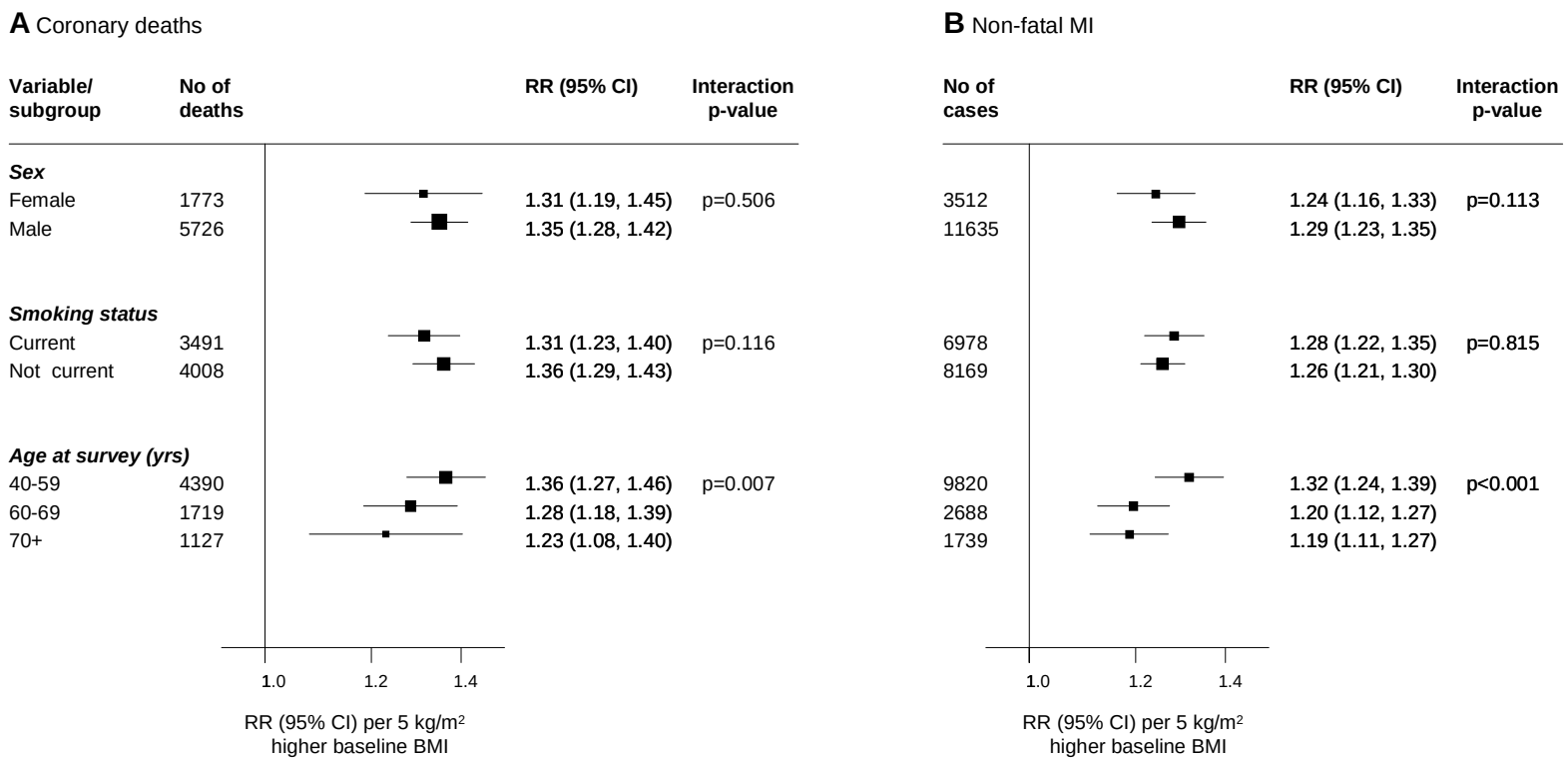
Risk ratios were adjusted for age and smoking, and stratified, where appropriate, by sex and trial arm. Analyses were restricted to participant with BMI values ≥20 kg/m^2.

Figure 5.11 Risk ratios for coronary heart disease by baseline smoking and diabetes status



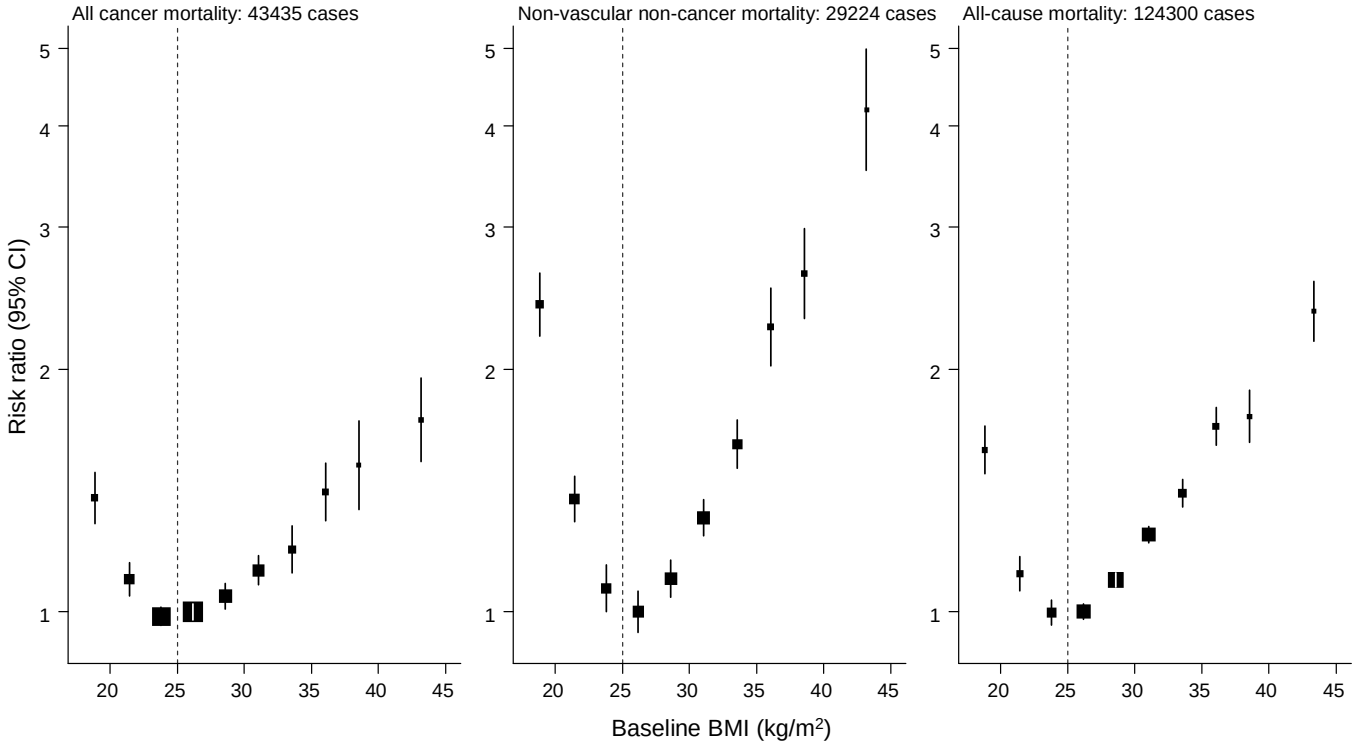
Analysis by baseline smoking status was based on 279,473 current smokers and 389,196 never smokers from 96 studies with 26609 cases. Analysis by baseline diabetes status was based on 42,913 people with diabetes and 714,442 people without diabetes from 95 studies with 32573 cases.

Figure 5.12 Risk ratios for coronary deaths and non-fatal myocardial infarction (MI) per 5 kg/m^2 higher baseline BMI, according to sex, smoking status and age at baseline



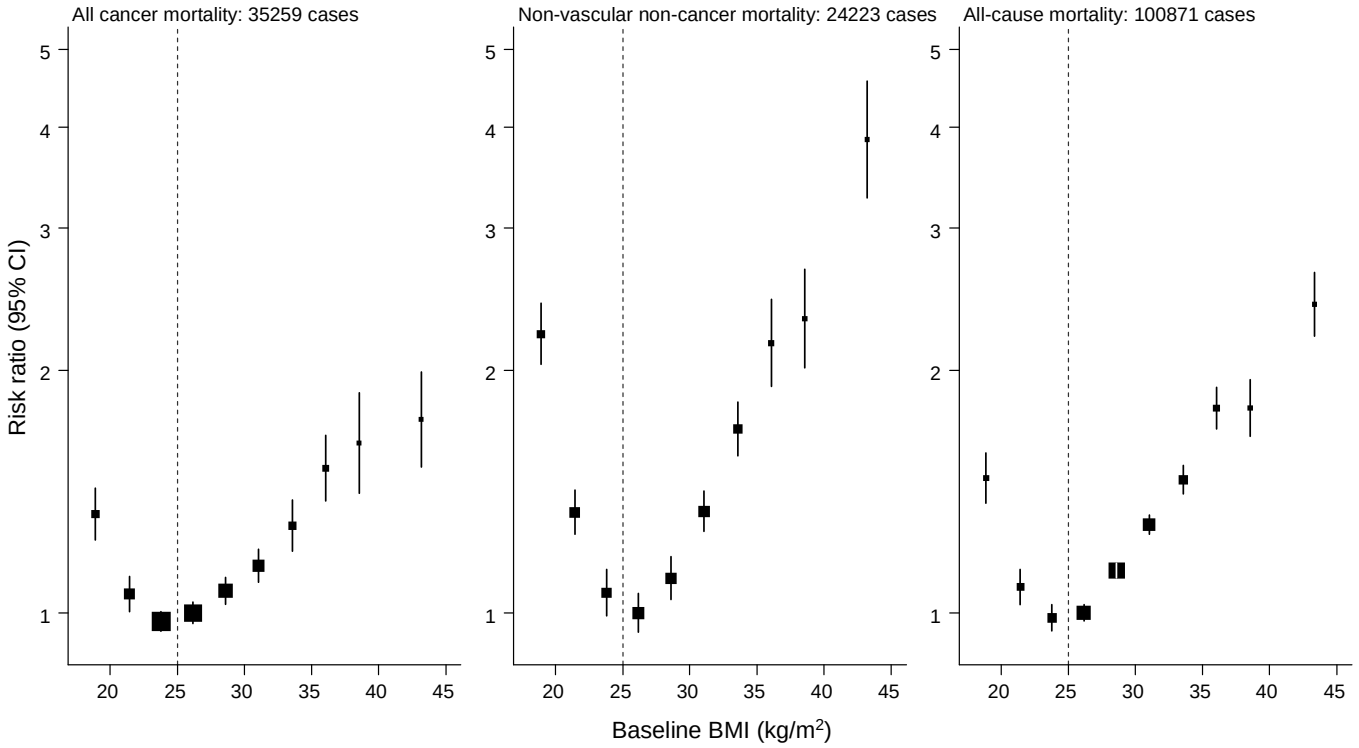
Analyses were restricted to studies providing data to both outcomes. Risk ratios were adjusted for age and smoking, and stratified, where appropriate, by sex and trial arm. Analyses involved baseline values of BMI and interaction variables. Analyses were restricted to participant with BMI values ≥20 kg/m^2. P-values for interaction were calculated from analyses using continuous variable, where appropriate.

Figure 5.13 Risk ratios for all cancer mortality, non-vascular non-cancer mortality and all-cause mortality across categories of baseline BMI, adjusted for age, sex and smoking status



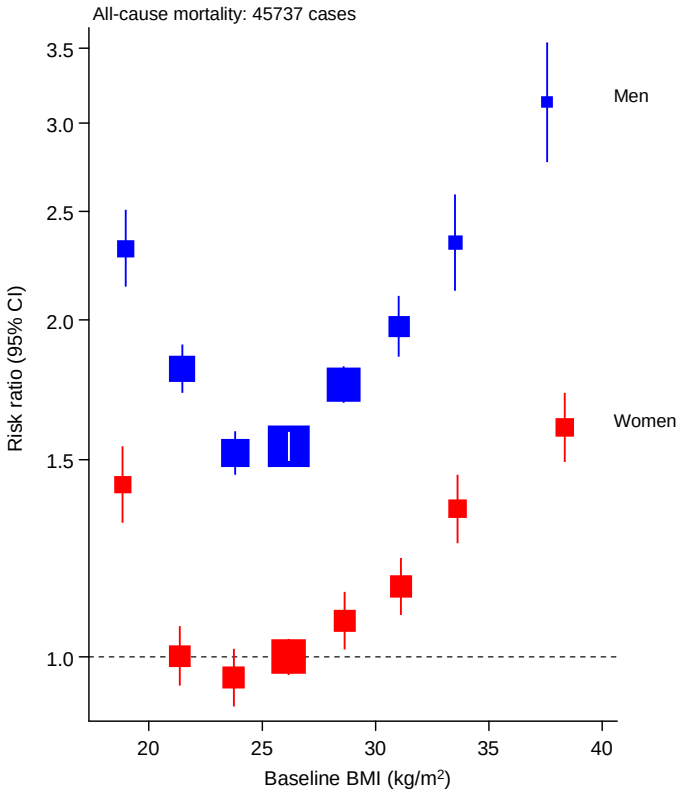
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2).

Figure 5.14 Risk ratios for all cancer mortality, non-vascular non-cancer mortality and all-cause mortality across categories of baseline BMI, after excluding the first five years of follow-up.



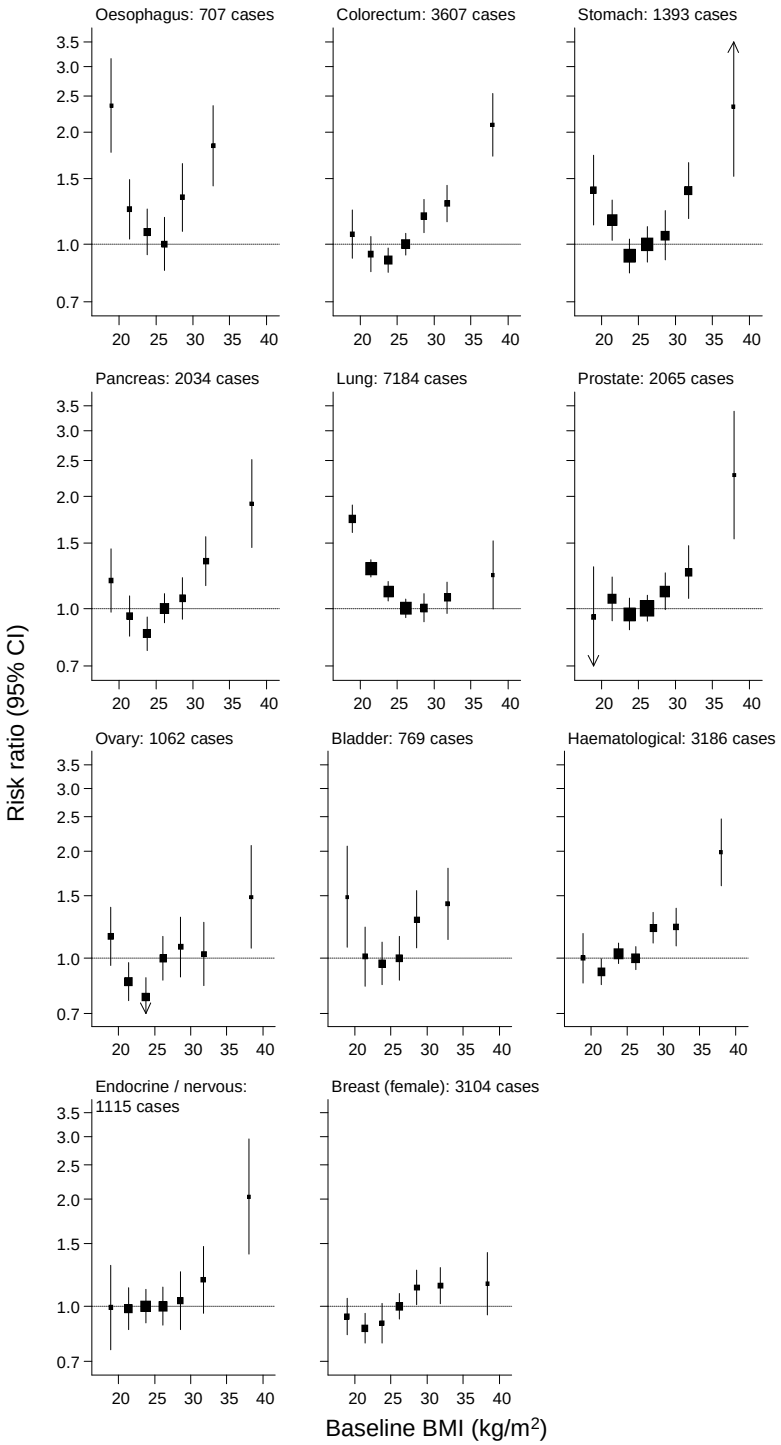
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Analyse excluded participants with less than 5 years. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2).

Figure 5.15 Risk ratios for all-cause mortality across categories of baseline BMI, among men and women



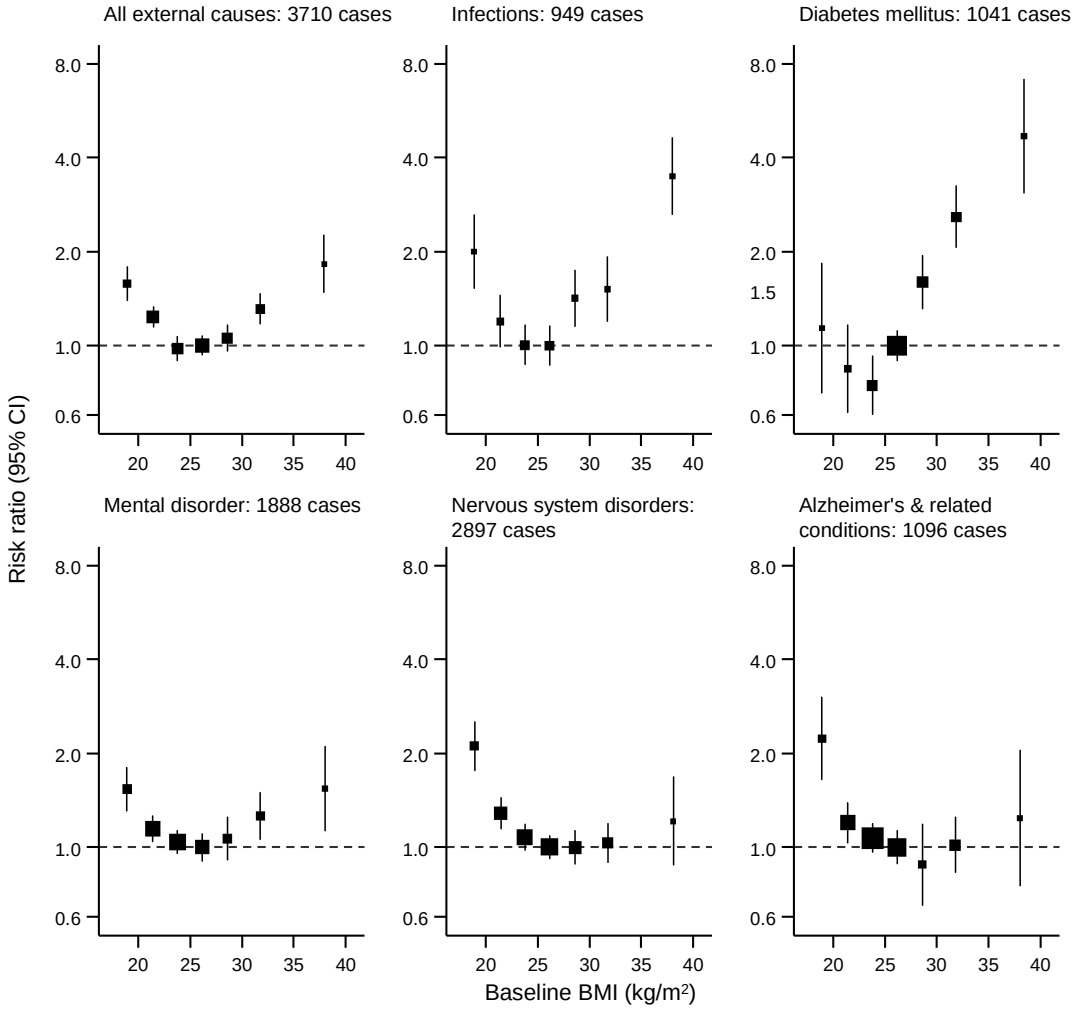
Analysis was restricted to studies contributing information on both men and women. Analysis was adjusted for age and smoking status, and stratified, where appropriate, by trial arm. Analyse excluded participants with less than five years of follow-up. Reference group is the category including the mean BMI value in women (ie, 25 to <27.5 kg/m^2 in women).

Figure 5.16 Risk ratios for site-specific cancer mortality across categories of baseline BMI



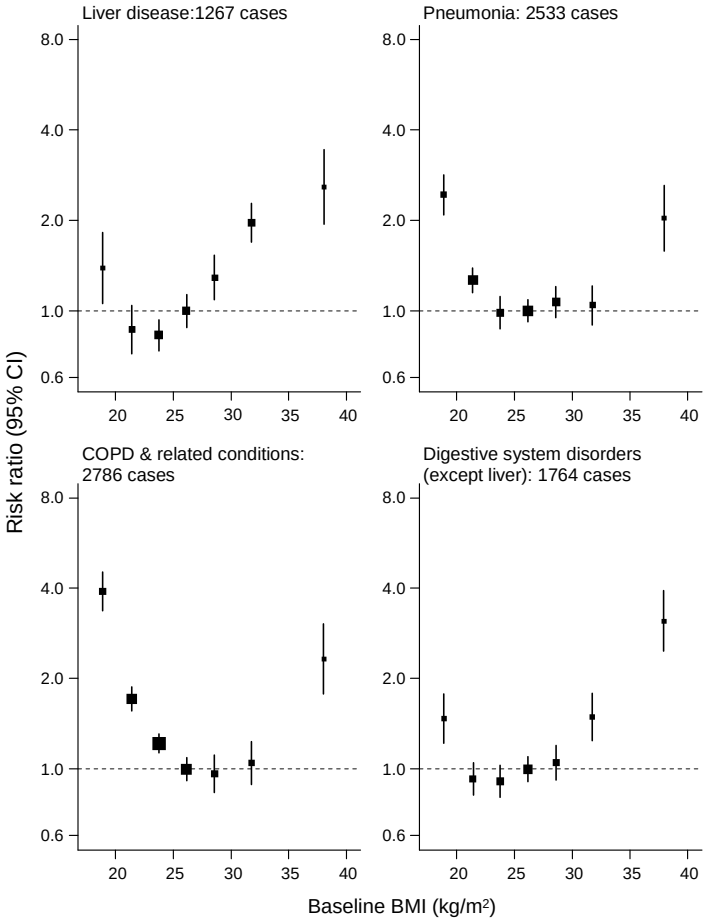
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Analyses excluded participants with less than five years of follow-up. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2). Other cancer outcomes are not shown, because there were generally too few deaths to characterise reliably shape of associations.

Figure 5.17A Risk ratios for non-vascular non-cancer specific mortality across categories of baseline BMI



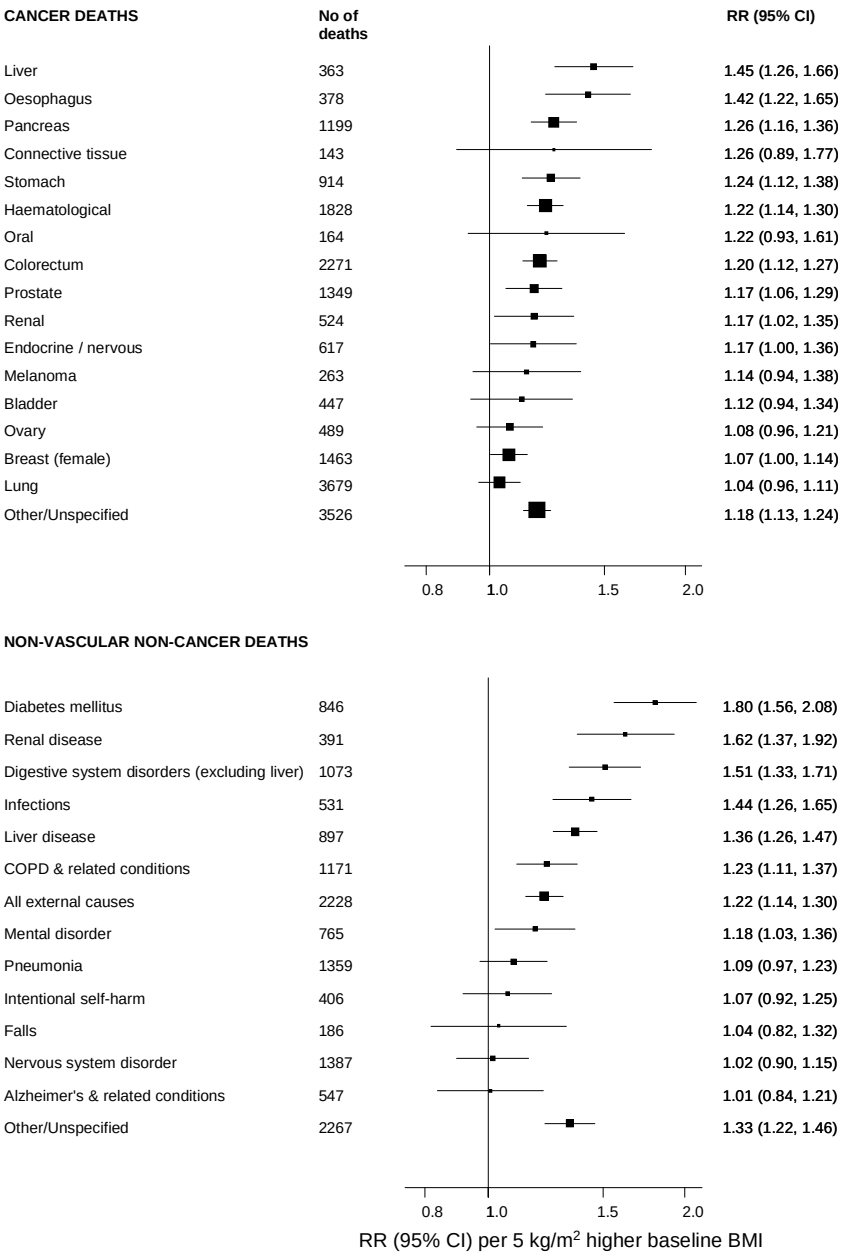
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Analyses excluded participants with less than five years of follow-up. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2). Other non-vascular non-cancer outcomes are not shown, because there were generally too few deaths to characterise reliably shape of associations.

Figure 5.17B Risk ratios for non-vascular non-cancer specific mortality outcomes across categories of baseline BMI



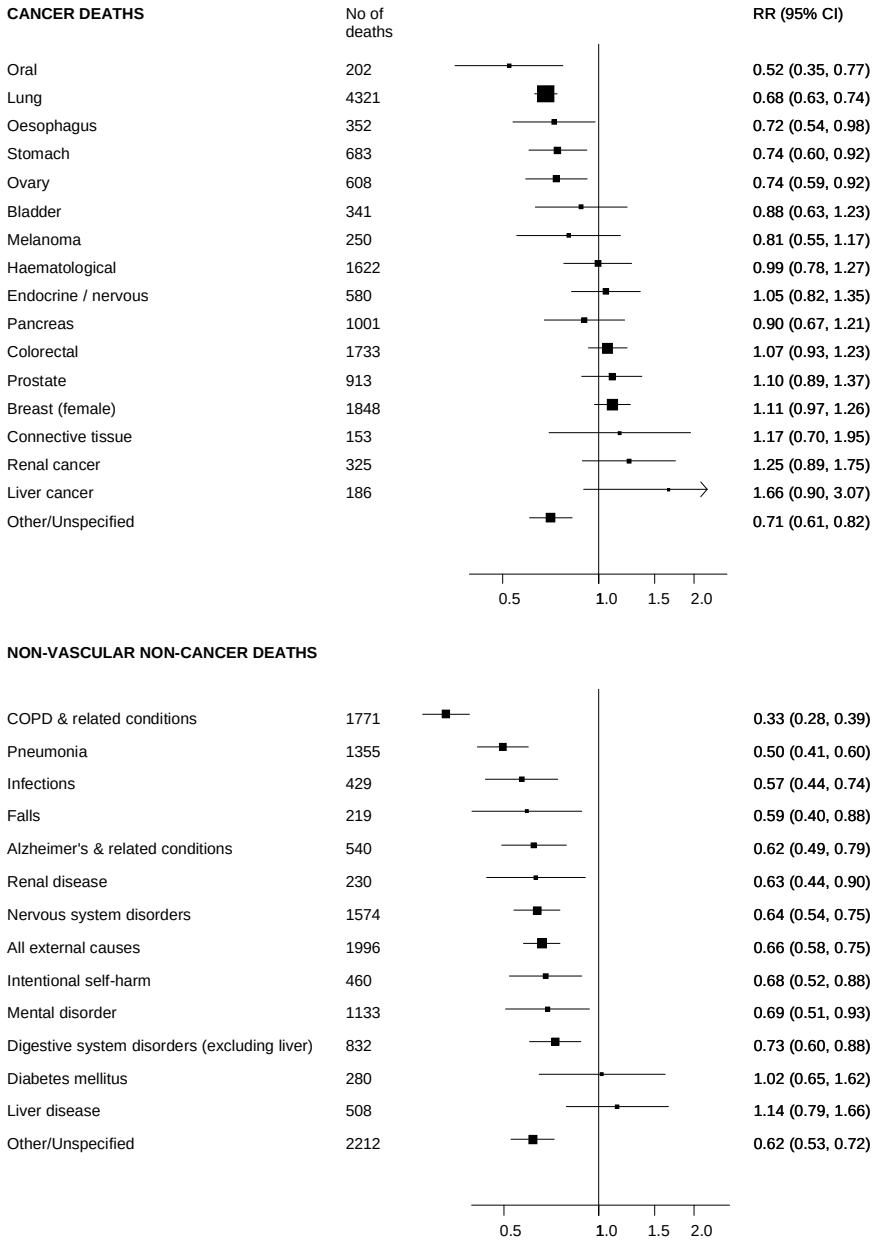
Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Analyses excluded participants with less than five years of follow-up. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2). Other non-vascular non-cancer outcomes are not shown, because there were generally too few deaths to characterise reliably shape of associations.

Figure 5.18 Risk ratios for cause-specific non-vascular mortality outcomes per 5 kg/m^2 higher baseline BMI in the BMI range ≥25kg/m^2



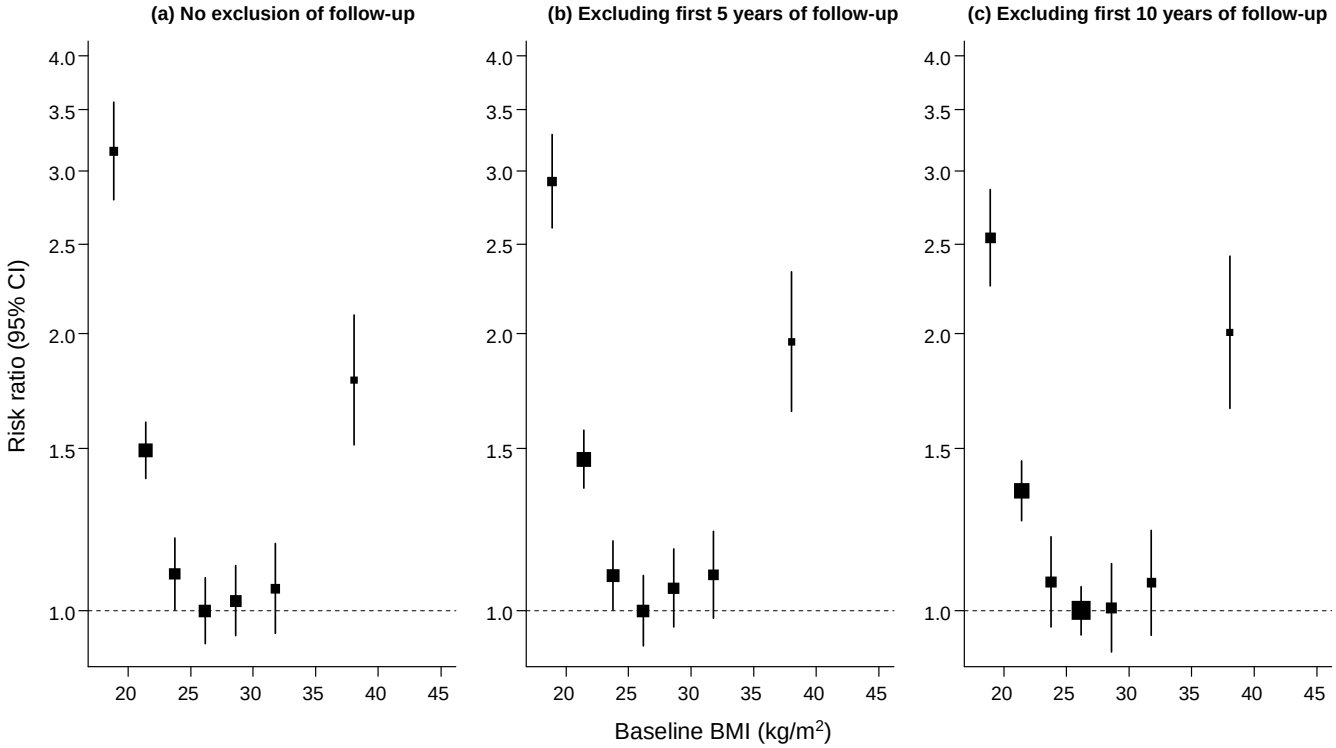
With the exception of "Other/Unspecified", causes of deaths are presented in descending order of their estimated risk ratios (RRs). All analyses are adjusted for age and smoking status, and stratified by sex and trial arm. There was evidence of heterogeneity in risk ratios between different cancer sites and between different non-cancer non-vascular causes of death (P-value for heterogeneity <0.001 for both).

Figure 5.19 Risk ratios for cause-specific non-vascular mortality per 5 kg/m^2 higher baseline BMI in the BMI range <25kg/m^2, after excluding the first five years of follow-up



Analyses excluded the first five years of follow-up. With the exception of "Other/Unspecified", causes of deaths are presented in ascending order of their estimated risk ratios (RRs). All analyses are adjusted for age and smoking status, and stratified by sex and trial arm. There was evidence of heterogeneity in risk ratios between different cancer sites and between different non-cancer non-vascular causes of death (P-value for heterogeneity <0.001 for both).

Figure 5.20 Risk ratios for death due to respiratory disease across categories of baseline BMI, (a) without exclusion of follow-up or excluding (b) the first five years of follow-up or (c) the first ten years of follow-up



Analyses were restricted to 42 studies involving 7906 deaths in (a), 6861 deaths in (b) and 5282 deaths in (c). Analyses were adjusted for age and smoking status, and stratified, where appropriate, by sex and trial arm. Reference group is the category including the mean BMI value (ie, 25 to <27.5 kg/m^2).

CHAPTER 6: Associations of adiposity measures with risk of coronary heart disease and ischaemic stroke

Summary

Although several epidemiological studies have reported on the associations of body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with risk of cardiovascular disease, the relative importance of overall versus abdominal adiposity is still unclear. A large retrospective case-control study has reported that baseline measurement of WHR is three times more strongly associated with risk of acute myocardial infarction than is BMI, recommending that WHR replaces BMI as the principal clinical measure of adiposity. After reliably characterising the association of BMI with cardiovascular morbidity and cause-specific mortality in **Chapter 5**, this chapter reports prospective analyses of individual records from 221,934 participants in 58 mostly Western prospective studies with complete information on BMI, WC and WHR, and without known history of cardiovascular disease at baseline examination. During 1.87 million person-years at risk, there were 11,196 first-ever non-fatal and fatal coronary heart disease and ischaemic stroke outcomes. In analyses adjusted for age, sex and smoking status only, nearly $\log_e$-linear associations were observed between BMI, WC and WHR, and risk of coronary heart disease and ischaemic stroke across the range of values, except at low BMI values. After excluding participants with BMI values below 20 kg/m^2, age, sex and smoking status adjusted risk ratios for coronary heart disease and ischaemic stroke were broadly similar with BMI, WC and WHR. These risk ratios reduced considerably, after further adjustment for intermediate risk factors, such as blood pressure, history of diabetes, total and high-density lipoprotein cholesterol. The effect of abdominal adiposity on the risk of coronary heart disease and ischaemic stroke was largely independent of BMI. The risk ratios were about three-to-four fold stronger in participants at early middle age than at older ages, but otherwise did not vary materially by sex, method of adiposity assessment (ie, self-reported versus assessed by a trained person) and other characteristics recorded. These findings refute previous recommendations to adopt WHR instead of BMI as the principal clinical measure of adiposity.

Background

Although several epidemiological studies have reported on the associations of body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with risk of coronary heart disease,[1-24] the relative importance of overall versus abdominal adiposity is still unclear (**Chapter 1**). A large retrospective case-control study has reported that baseline measurement of WHR is three times more strongly associated with risk of acute myocardial infarction than is BMI, recommending that WHR replaces BMI as the principal clinical measure of adiposity.[23] Prospective studies have, however, been unable to evaluate reliably this suggestion because most involved a moderate number of incident vascular disease outcomes,[2,4,21,25] relied only on self-reported adiposity measures,[4] lacked measurement of both BMI and abdominal adiposity in the same participants,[26-28] and/or lacked measurement of lipids and other established risk factors.[9,27] Moreover, previous studies were unable to investigate whether measures of abdominal adiposity are more strongly related to risk of ischaemic stroke than is BMI, primarily because there has been a paucity of published information.[21,29-31] Because of these limitations, previous prospective studies with concomitant data on weight, height, waist and hip circumference were not able to examine reliably the magnitude of associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke; characterise the shape of any dose-response relationship; explore the degree to which associations can be explained by correlations with other cardiovascular risk factors (notably intermediate risk factors; **Chapter 3**); or assess whether associations differ importantly under different circumstances, such as at different levels of BMI, in different age groups, or by sex. Consequently, the relevance of clinical measures of adiposity to the vascular disease aetiology remains uncertain, and important aspects of its epidemiology have yet to be characterised in detail.

The objective of this chapter is to produce reliable estimates of the associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke under different circumstances, incorporating adjustment for potential confounders and biological mediators using data from the Emerging Risk Factors Collaboration (ERFC).[32]

Methods

Study design

Details of study selection, data collection and harmonisation have been described in **Chapter 2**. Briefly, the current analysis involves individual records from 58 prospective studies. A total of 221,934 participants without known history of cardiovascular disease at the initial ("baseline") examination had information on height, weight, and waist and hip circumference. 155,938 (70%) of these participants also had data on smoking status, history of diabetes, systolic blood pressure (SBP), and total and high-density lipoprotein (HDL) cholesterol.

Analytical approach

The statistical methods have been described in detail in **Chapter 5** on pages 111-116. The principal measures of adiposity studied were BMI, WC and WHR. Associations of these measures were assessed in relation to fatal or first-ever coronary heart disease and ischaemic stroke. Analyses involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random effects meta-analysis.[33] Hazard ratios were calculated using Cox proportional-hazards regression models stratified by sex.[34] The proportional hazards assumptions were met. Participants contributed only first non-fatal outcome or death recorded at age 40 years or older (ie, deaths preceded by non-fatal coronary event or stroke were not included). For the four contributing individually-matched nested case-control studies within prospective cohorts, odds ratios were calculated with conditional logistic regression models. Provided the disease is relatively rare, hazard ratios and odds ratios were assumed to approximate the same relative risk and are collectively described as "risk ratios".[35] The incidence of coronary heart disease and ischaemic stroke is higher than that of many endpoints reported in **Chapter 5**. Therefore, to avoid over-fitting of the statistical models, studies with fewer than ten incident cases (rather than five cases) of an outcome were excluded from the analysis of that particular outcome.

Shape analysis

To characterise shapes of associations, study-specific risk ratios calculated within overall quantiles (ie, quantile groups defined across all studies) of baseline adiposity values were pooled on a $\log_e$ scale by multivariate random effects meta-analysis and plotted against mean values of the relevant adiposity measure within each quantile.[36,37] Whereas shape analysis in relation to coronary heart disease were based on deciles, corresponding analyses with ischaemic stroke used quintiles only, since there were considerably fewer incident stroke events than coronary events. 95% confidence intervals (CIs) were estimated from floated

variances that reflect the amount of information underlying each group (including the reference group).[38] Because associations were nearly $\log_e$-linear (except at low values of BMI: see Results), regression coefficients were calculated to estimate the risk ratios associated with one standard deviation (SD) higher baseline values: 4.56 kg/m^2 higher BMI, 12.6 cm higher WC and 0.083 higher WHR, thereby allowing for direct comparisons between adiposity measures. Risk ratios with clinically defined categories of BMI and WC in combination were also calculated.[39] Risk ratios were initially adjusted for age, sex and smoking status only. To explore potential biological pathways underlying associations, risk ratios were further adjusted for SBP, history of diabetes, total and HDL cholesterol. Effect modification was investigated with formal tests of interaction, and p-values for interaction were calculated with continuous variables, when appropriate. Diversity between studies was investigated by grouping studies by recorded characteristics and meta-regression. Extent of heterogeneity was indicated by the I^2 statistic.[40,41]

Within-person variability

Correction for within-person variability in adiposity measures and in potential confounders and biological mediators was achieved by use of conditional expectations of long-term average ("usual") levels of adiposity measures and potential confounders and mediators predicted from Rosner regression calibration models,[42,43] and used in assessments of associations with disease risk. As described in **Appendix 2**, regression coefficients were calculated to estimate the risk ratios associated with 1-SD higher usual levels adjusted for age, sex and smoking status: 4.36 kg/m^2 higher BMI, 10.98 cm higher WC and 0.059 higher WHR. These SDs in usual levels remained unchanged after further adjustment for intermediate risk factors (ie, SBP, history of diabetes, and total and HDL cholesterol). Sensitivity analyses involved regression calibration models allowing variability of WHR to vary by sex, history of diabetes and baseline WHR values (**Chapter 4**).

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Characteristics of individual studies are summarised in **Table 2.3** in **Chapter 2** on page 47 and in **Table 6.1**. Mean (SD) age of participants at baseline was 58 (9) years, 124,189 (56%) were women, and 129,326 (58%) were in Europe, 73,707 (33%) were in North America, 9,204 (4%) were in Australia and 9,697 (4%) were in Japan. During 1.87 million person-years at risk (median 5.7 years to first outcome, IQR 3.0-9.0), there were 8,290 coronary heart disease outcomes (4,982 non-fatal myocardial infarctions and 3,308 coronary deaths) and 2,906 incident ischaemic stroke outcomes (2,764 non-fatal and 142 fatal outcomes).

Associations with coronary heart disease

In analyses adjusted for age, sex and smoking status only, there were nearly $\log_e$-linear associations of BMI, WC and WHR and risk of coronary heart disease, except at low BMI values (**Figure 6.1**). These associations were similar when clinically defined categories of BMI and WC were combined (**Figure 6.2**). To account for the non-linear association at low BMI values, further analyses excluded the 9,355 participants (4%) with BMI values below 20 kg/m^2. In analyses restricted to participants with complete information on relevant covariates, risk ratios for coronary heart disease per one standard deviation higher baseline values – initially adjusted for age, sex and smoking status only, and then further adjusted for baseline values of intermediate risk factors (ie, SBP, history of diabetes and total and HDL cholesterol) – respectively, were 1.29 (95% CI 1.22-1.37) and 1.11 (95% CI 1.05-1.17) with BMI, 1.32 (95% CI 1.24-1.40) and 1.12 (95% CI 1.06-1.19) with WC, and 1.30 (95% CI 1.22-1.38) and 1.14 (95% CI 1.09-1.18) with WHR (**Table 6.2**). Risk ratios for coronary heart disease reduced even more after additional adjustment for C-reactive protein (CRP) (**Table 6.3**). In regression dilution corrected analyses, long-term average levels of blood pressure, diabetes and lipids accounted for more than two-thirds of the coronary risk associated with adiposity measures (**Table 6.4**). The proportion in risk reduction was possibly somewhat larger for BMI than for WHR (ie, 74% risk reduction for BMI versus 62% risk reduction for WHR). Among the contributing studies, heterogeneity between studies tended to decrease after adjustment of risk ratios for intermediate risk factors (**Table 6.2**).

Associations with ischaemic stroke

Associations with ischaemic stroke were approximately $\log_e$-linear, with possible attenuation at low BMI values (**Figure 6.1**). After exclusion of participants with BMI values below 20 kg/m^2, age, sex and smoking status adjusted risk ratios for ischaemic stroke with BMI, WC and WHR

were broadly similar to those for coronary heart disease (**Table 6.2**). Risk ratios for ischaemic stroke per one standard deviation higher baseline values – initially adjusted for age, sex and smoking status only and then further adjusted for baseline values of intermediate risk factors – respectively, were 1.20 (95% CI 1.12-1.28) and 1.06 (95% CI 0.99-1.13) with BMI, 1.25 (95% CI 1.18-1.33) and 1.11 (95% CI 1.05-1.17) with WC, and 1.25 (95% CI 1.18-1.32) and 1.14 (95% CI 1.09-1.20) with WHR (**Table 6.2**). Risk ratios for ischaemic stroke reduced even more after additional adjustment for CRP (**Table 6.3**). In regression dilution corrected analyses, blood pressure, diabetes and lipids accounted for at least half of the association between adiposity measures and ischaemic stroke (**Table 6.4**). The proportion in risk reduction was possibly somewhat larger for BMI than for WHR (ie, 89% risk reduction for BMI versus 53% risk reduction for WHR). Between-study heterogeneity tended to decrease after adjustment of risk ratios for intermediate risk factors (**Table 6.2**).

Sensitivity analyses

Qualitatively similar results to those reported here were also observed in analyses that excluded: the initial five or ten years of follow-up, current smokers; participants who were not of European descent; or the 29,905 participants who had only self-reported adiposity measures (**Table 6.5**); the few studies with the most discrepant findings (**Figure 6.3**); or the 21,139 participants known to be receiving lipid-lowering, blood pressure-lowering or other cardiovascular medication at baseline (data not shown). Risk ratios were also broadly similar using fixed-effect models (**Figure 6.3**) and after additional adjustment for: cigarette pack-years (in addition to smoking status), alcohol consumption or measures of socioeconomic status (data not shown). The risk ratio with WHR corrected for regression dilution was somewhat higher when regression calibration models were allowed to vary by sex, history of diabetes and baseline WHR (data not shown). Risk ratios with waist-to-height ratio (WHtR) were similar to those of WC because of the strong correlation between WC and WHtR (r = 0.95, 95% CI 0.94-0.96) (**Table 6.2**). There was no evidence of bias due to small studies (**Figure 6.4**).

Assessment of joint effects

Risk ratios for coronary heart disease and ischaemic stroke associated with adiposity measures were around three-to-four times stronger at ages 40-59 years than at older than 70 years, but similar in men and women (**Figures 6.5-6.6**). Risk ratios for coronary heart disease were possibly higher at lower-than-average systolic blood pressure, but otherwise did not vary importantly by baseline levels of smoking status, history of diabetes, HDL and non-HDL

cholesterol, CRP or ethnicity (**Figure 6.7**). Risk ratios for coronary heart disease with BMI and WC were similar at different triglyceride levels, but risk ratios with WHR were somewhat stronger at lower-than-average triglyceride levels (**Figures 6.7-6.8**). There were no important variations in risk ratios of studies using self-reported adiposity measures values versus adiposity measures assessed by a trained person, or with other features recorded at the study-level (**Figure 6.7**).

Combined analyses of adiposity measures

Further analyses investigated joint effects and independence between adiposity measures. Risk ratios with WC and WHR were generally similar at different BMI levels and slightly reduced after adjustment for BMI (**Table 6.6** & **Figures 6.5** and **6.9**). For example, risk ratios for coronary heart disease – initially adjusted for age, sex and smoking status, and then additionally adjusted for BMI – respectively, were 1.31 (95% CI 1.24-1.37) and 1.23 (95% CI 1.15-1.32) with WC, and 1.29 (95% CI 1.23-1.35) and 1.21 (95% CI 1.16-1.26) with WHR (**Table 6.6**). Corresponding risk ratios for ischaemic stroke were 1.26 (95% CI 1.19-1.33) and 1.26 (95% CI 1.16-1.36) with WC, and 1.25 (95% CI 1.19-1.32) and 1.18 (95% CI 1.13-1.24) with WHR (**Table 6.6**). By contrast, associations with BMI reduced considerably and disappeared after adjustment for WHR or WC, respectively (**Table 6.6**).

Discussion

The current analysis of individual data from 221,934 people without initial cardiovascular disease in 58 mostly Western prospective studies assessed the shape, specificity and independence of associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke. These data demonstrate that: (i) BMI, WC and WHR have nearly $\log_e$-linear associations with risk of coronary heat disease and ischaemic stroke (after exclusion of the 4% of people with BMI values below 20 kg/m^2); (ii) BMI and measures of abdominal adiposity each have a similar magnitude of association with risk of coronary heart disease; (iii) excess adiposity is broadly similarly related to risk of coronary heart disease and ischaemic stroke; (iv) much of the risk of coronary heart disease and ischaemic stroke is explained by intermediate risk factors such as blood pressure, history of diabetes, and total and HDL cholesterol; (v) measures of abdominal adiposity increase cardiovascular risk largely independent of BMI; and (vi) age strongly modifies the impact of adiposity on coronary heart disease and ischaemic stroke.

Contrary to a report from INTERHEART[23] (a large case-control study with 12,000 cases of first myocardial infarction and 14,000 controls) that WHR is three times more strongly related to myocardial infarction than is BMI, the current analysis has shown that BMI, WC and WHR each have a similar strength of association with cardiovascular disease risk, arguing against the idea of replacing BMI with WC or WHR as the principal measure of adiposity in clinical practice. Whereas INTERHEART observed an odds ratio for myocardial infarction of only 1.12 per 5 kg/m^2 higher baseline BMI, the corresponding risk ratio for coronary heart disease was 1.32 in the current analysis. This discrepancy might be due to the greater susceptibility of retrospective studies of acute myocardial infarction to some biases (eg, selection biases, reverse causality) than long-term prospective studies of people without an initial history of cardiovascular disease. Because visceral fat is believed to be more metabolically active than other fat depots such as subcutaneous fat,[44-46] abdominal adiposity measures such as WC and WHR are expected to be more strongly associated with metabolic abnormalities and cardiovascular disease risk than is BMI, since BMI is a measures of general adiposity. However, the current findings indicate that BMI, WC and WHR each have similar associations with risk of coronary heart disease and ischaemic stoke. This might be due to the fact that these measures of abdominal adiposity are poor surrogates of visceral adiposity, as they do not distinguish visceral adipose tissue from abdominal subcutaneous adipose tissue, which is only possible by use of imaging techniques.[44,47] The similarity of effect of adiposity on coronary heart disease and ischaemic stroke contrasts with results previously reported for pro-atherogenic lipids (which are four times more strongly related to coronary heart disease than ischaemic stroke[48]) and systolic blood pressure (which is more strongly related to ischaemic stroke than coronary heart disease[49]). The current data, therefore, highlight the potential importance of reducing adiposity for both coronary heart disease and ischaemic stroke.

The current analysis has shown that at least half of the risk with coronary heart disease and ischaemic stroke associated with adiposity measures is explained by baseline values of blood pressure, history of diabetes, and total and HDL cholesterol – with an even larger proportion of this risk explained by long-term average levels of these intermediate risk factors. The findings observed for BMI in this chapter are very similar to those observed in **Chapter 5**, which involves five times more participants. The proportion in risk reduction was possibly somewhat larger for BMI than for WHR. Nevertheless, as discussed in **Chapter 5**, the current findings underscore the importance of controlling adiposity to help prevent coronary heart disease and stroke, as well as potential added benefits of controlling these intermediate risk factors to

combat the detrimental vascular effects of overweight and obesity.[50] The current findings have shown that the effect of abdominal adiposity on risk of coronary heart disease and ischaemic stroke is largely independent of BMI and not modified by BMI. However, the association of BMI with these outcomes was reduced and even disappeared after adjustment for WC or WHR, respectively, suggesting that these measures of abdominal adiposity provide useful information on cardiovascular disease beyond that of BMI. Furthermore, the risk ratios were not greatly different between studies using self-reported adiposity measures and adiposity measures assessed by a trained person, or different locations of WC assessment. By contrast, there was a strong modification of the effects of adiposity by age, with three-to-four higher excess risk for coronary heart disease and ischaemic stroke in early middle age than at older ages. Possible explanations of that interaction have been discussed in **Chapter 5**. Otherwise, there were no important modifications of the effect of adiposity on risk of coronary heart disease and ischaemic stroke by subgroups assessed.

The data in this chapter are likely to represent a substantial proportion of available data from prospective studies of overall and abdominal adiposity and incident disease risk, at least in Western populations, and include data from several studies that have not previously reported such associations. The data complements previous analyses of large prospective studies. In contrast with the Prospective Studies Collaboration[26] (PSC) and the National Cancer Institute Cohort Consortium[27] (NCICC) which lacked information on WC and WHR, the ERFC had concomitant data for each participant on BMI, WC and WHR. In contrast with NCICC and the European Prospective Investigation into Cancer[9] (EPIC) which lacked information on lipids, the ERFC had concomitant information on lipids, blood pressure and other conventional risk factors. Whereas the PSC, NCICC and EPIC all lacked non-fatal cardiovascular outcomes, the ERFC involved fatal or first-onset non-fatal myocardial infarctions and ischaemic stokes recorded during 1.87 million person-years at risk. Whereas the EPIC aggregated cardiovascular outcomes, the ERFC reported associations with coronary heart disease and ischaemic stroke separately. There was some heterogeneity in risk ratios with adiposity measures. However, the generalisability of the current findings, at least to Western populations, is supported by broadly consistent results across 58 cohorts in 17 countries. Although the analysis could only use a fifth of the coronary events available in the previous chapter, the current findings with BMI were consistent with those observed in **Chapter 5**. For instance, the risk ratio for coronary heart disease, adjusted for age, sex and smoking status, was 1.31 per 5 kg/m^2 higher baseline BMI in **Chapter 5**, while the corresponding risk ratio was

1.32 in the current chapter. Contrary to previous suggestions,[51-53] WHtR was associated to a similar extent with risk of coronary heart disease and ischaemic stroke as were other clinical measures of adiposity. As most of the participants in this study were of European descent, further studies are needed in people of non-European descent.[21,54,55]

Conclusion

Excess adiposity is substantially and similarly related to risk of coronary heart disease and ischaemic stroke. BMI, WC and WHR each have a similar magnitude of associations with risk of coronary heart disease and ischaemic stroke, with much the risk explained by intermediate risk factors, such as blood pressure, history of diabetes, total and HDL cholesterol. These findings refute previous recommendations to adopt WHR instead of BMI as the principal clinical measure of adiposity.

Chapter 6 – References

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Table 6.1 Descriptive summaries, grouped by study, of individuals with concomitant information on BMI, WC, WHR, age and sex

	Total No. with Weight, Height, Waist & Hip measured	Age (yrs) mean (sd)	Male (%)	BMI (kg/m^2) mean (sd)	WC (cm) mean (sd)	WHR mean (sd)	Follow-up (yrs) median (5th & 95th percentiles)	Coronary heart diseae (CHD) events	All CHD deaths	Non-fatal MI events	Ischaemic stroke events	Ischaemic stroke deaths	Non-fatal ischaemic stroke events
Cohort studies													
ARIC	14383	54 (6)	6213 (43)	28 (5)	97 (14)	0.92 (0.08)	14.0 (4.9 to 15.7)	865	198	667	455	2	453
ATENA[b]	4741	50 (7)	0 (0)	27 (4)	85 (10)	0.82 (0.07)	6.7 (5.2 to 8.1)	18	1	17	1	0	1
ATTICA	1503	51 (11)	769 (51)	27 (4)	93 (14)	0.88 (0.11)	5.0 (5.0 to 5.0)	0	0	0	0	0	0
AUSDIAB	9204	53 (13)	4079 (44)	27 (5)	91 (14)	0.87 (0.09)	5.0 (4.8 to 8.5)	65	41	24	13	2	11
BRHS	3466	68 (5)	3466 (100)	27 (4)	97 (10)	0.95 (0.06)	5.0 (1.9 to 5.0)	160	92	68	3	3	0
BRUN	817	58 (11)	398 (49)	25 (4)	87 (11)	0.89 (0.07)	15.3 (3.9 to 15.5)	54	31	23	24	9	15
BWHHS	2779	68 (5)	0 (0)	27 (5)	85 (12)	0.81 (0.07)	7.3 (3.2 to 8.4)	89	13	76	0	0	0
CAPS	1062	62 (4)	1062 (100)	27 (4)	93 (10)	0.93 (0.06)	3.1 (1.8 to 3.3)	29	16	13	0	0	0
CHARL	428	71 (7)	179 (42)	27 (5)	95 (13)	0.94 (0.08)	11.8 (1.3 to 12.9)	56	28	28	2	2	0
CHS1[a]	3881	72 (5)	1489 (38)	26 (5)	93 (13)	0.92 (0.09)	12.1 (1.9 to 12.9)	593	213	380	368	0	368
CHS2[a]	480	72 (5)	181 (38)	29 (5)	99 (15)	0.94 (0.07)	9.1 (1.7 to 9.5)	56	23	33	40	0	40
COPEN	8166	58 (15)	3502 (43)	26 (4)	87 (13)	0.87 (0.10)	13.2 (2.7 to 14.9)	509	41	468	368	3	365
DRECE	497	57 (11)	222 (45)	28 (4)	95 (13)	0.92 (0.11)	1.5 (1.5 to 1.5)	0	0	0	0	0	0
EMOFRI[b]	360	55 (6)	176 (49)	26 (4)	91 (11)	0.90 (0.07)	6.8 (6.5 to 7.2)	2	0	2	2	0	2
EPESENCA	1001	77 (5)	333 (33)	27 (5)	93 (13)	0.88 (0.08)	4.0 (1.4 to 4.6)	45	17	28	30	1	29
FINRISK92	5276	46 (10)	2446 (46)	26 (4)	88 (13)	0.86 (0.10)	11.8 (7.1 to 11.9)	150	31	119	84	0	84
FINRISK97	6382	52 (11)	3167 (50)	27 (4)	90 (13)	0.87 (0.09)	6.8 (6.0 to 6.9)	109	34	75	75	0	75
FRAMOFF	2685	60 (9)	1183 (44)	28 (5)	99 (14)	0.94 (0.08)	5.2 (3.1 to 7.0)	51	4	47	24	0	24
GOH	634	70 (7)	305 (48)	28 (5)	99 (11)	1.03 (0.12)	3.9 (0.3 to 6.9)	0	0	0	0	0	0
GOTO13	756	54 (0)	756 (100)	25 (3)	87 (9)	0.93 (0.05)	23.5 (5.0 to 30.5)	211	2	209	0	0	0
GOTO33	729	51 (0)	729 (100)	26 (3)	95 (9)	0.93 (0.06)	12.8 (5.8 to 13.1)	27	13	14	0	0	0
GOTO43	762	50 (0)	762 (100)	26 (3)	95 (9)	0.99 (0.06)	10.0 (7.9 to 10.7)	28	1	27	9	1	8
GOTOW	1401	47 (7)	0 (0)	24 (4)	74 (9)	0.74 (0.05)	32.2 (8.7 to 32.7)	147	54	93	0	0	0
HBS	1268	60 (4)	1268 (100)	26 (3)	97 (9)	0.97 (0.06)	20.5 (6.0 to 20.5)	85	85	0	0	0	0
HISAYAMA	2515	59 (11)	1068 (42)	23 (3)	81 (9)	0.91 (0.07)	14.0 (3.2 to 14.0)	77	10	67	146	1	145
HOORN	2226	61 (7)	979 (44)	27 (4)	91 (11)	0.89 (0.09)	8.8 (3.7 to 9.9)	73	13	60	3	3	0
IKNS	1942	59 (10)	830 (43)	24 (3)	83 (9)	0.90 (0.07)	7.1 (4.1 to 14.6)	11	5	6	23	2	21
LASA	1806	69 (8)	827 (46)	27 (4)	97 (11)	0.94 (0.08)	9.9 (1.8 to 10.4)	33	0	33	0	0	0
MATISS83[b]	1317	61 (9)	614 (47)	29 (4)	94 (10)	0.91 (0.09)	8.7 (3.7 to 9.7)	20	3	17	13	0	13
MATISS87[b]	1077	58 (9)	510 (47)	29 (4)	94 (11)	0.91 (0.09)	8.5 (5.0 to 9.5)	12	5	7	4	0	4
MATISS93[b]	1206	49 (9)	579 (48)	28 (5)	91 (11)	0.91 (0.08)	8.3 (7.0 to 9.3)	14	3	11	1	0	1
MESA	6768	62 (10)	3190 (47)	28 (5)	98 (14)	0.93 (0.08)	4.8 (2.5 to 5.2)	83	14	69	68	0	68
MOGERAUG2	3934	53 (12)	1935 (49)	27 (4)	90 (12)	0.87 (0.08)	7.9 (2.3 to 8.4)	102	41	61	1	1	0
MOGERAUG3	3368	55 (10)	1663 (49)	28 (4)	92 (12)	0.88 (0.09)	3.0 (1.8 to 3.6)	18	7	11	2	2	0
MONFRI89[b]	1330	49 (8)	658 (49)	26 (4)	88 (12)	0.87 (0.09)	13.6 (6.6 to 13.7)	28	6	22	10	0	10
MONFRI94[b]	1291	49 (8)	627 (49)	26 (4)	90 (12)	0.88 (0.09)	8.5 (7.2 to 8.8)	11	0	11	5	0	5
MORGEN	17707	46 (9)	8046 (45)	26 (4)	88 (12)	0.86 (0.09)	10.8 (8.5 to 13.1)	77	77	0	3	3	0
MOSWEGOT	4132	47 (11)	1966 (48)	25 (4)	85 (12)	0.86 (0.09)	12.9 (7.6 to 18.6)	141	39	102	65	3	62
MRCOLD	9933	80 (4)	3747 (38)	26 (4)	90 (12)	0.88 (0.08)	8.7 (1.2 to 11.7)	1118	1118	0	52	52	0
NHANESIII	10450	53 (16)	4859 (46)	27 (6)	95 (14)	0.93 (0.09)	8.8 (4.2 to 11.7)	320	320	0	0	0	0
NSHS	1608	54 (15)	765 (48)	27 (6)	90 (15)	0.87 (0.10)	9.7 (3.7 to 10.0)	24	24	0	1	1	0
OSAKA	717	49 (7)	602 (84)	23 (3)	84 (8)	0.90 (0.05)	7.7 (3.9 to 16.8)	4	2	2	3	0	3
PREVEND	7368	50 (12)	3583 (49)	26 (4)	89 (13)	0.88 (0.09)	8.2 (6.7 to 8.9)	145	22	123	0	0	0
PRIME	9563	55 (3)	9563 (100)	27 (3)	95 (10)	0.96 (0.06)	5.2 (5.0 to 7.3)	145	17	128	33	0	33
RANCHO	1784	68 (11)	739 (41)	25 (4)	85 (12)	0.84 (0.09)	14.2 (2.0 to 18.1)	222	3	219	0	0	0
ROTT	4607	68 (8)	1752 (38)	26 (4)	90 (11)	0.90 (0.09)	11.9 (3.2 to 14.1)	235	33	202	37	37	0
SHHEC	3489	49 (11)	1625 (47)	26 (5)	86 (13)	0.85 (0.10)	10.0 (4.8 to 10.0)	119	44	75	26	0	26
SHS	4135	56 (8)	1615 (39)	31 (6)	105 (15)	0.95 (0.06)	12.4 (2.1 to 14.3)	449	147	302	8	8	0
TARFS	2559	49 (12)	1270 (50)	28 (5)	93 (12)	0.89 (0.09)	9.0 (2.0 to 10.0)	102	68	34	1	1	0
TOYAMA	4523	46 (7)	2907 (64)	23 (3)	78 (9)	0.85 (0.07)	12.7 (7.8 to 12.8)	34	1	33	24	0	24
TROMSØ	1573	60 (10)	811 (52)	26 (4)	91 (11)	0.87 (0.08)	11.1 (2.6 to 11.3)	146	18	128	78	0	78
ULSAM	962	71 (1)	962 (100)	26 (3)	94 (9)	0.94 (0.05)	12.2 (2.3 to 14.9)	137	43	94	83	0	83
WHITEII	7862	49 (6)	5414 (69)	25 (4)	85 (11)	0.87 (0.09)	7.6 (3.8 to 8.2)	167	22	145	1	1	0
WHS	24138	60 (7)	0 (0)	27 (5)	89 (14)	0.83 (0.08)	4.7 (3.0 to 5.6)	115	4	111	117	0	117
SUBTOTAL	218551	58 (9)	96391 (44)	27 (4.56)	91 (12.6)	0.90 (0.08)	7.9 (2.9 to 14.7)	7531	3047	4484	2306	138	2168
Nested case-control studies													
EPICNOR	1417	66 (8)	960 (68)	27 (4)	93 (11)	0.90 (0.08)	7.1 (2.2 to 9.3)	479	224	255	-	-	-
HPFS	394	66 (8)	394 (100)	26 (4)	99 (10)	0.96 (0.06)	4.0 (0.8 to 4.0)	129	21	108	-	-	-
NHS	372	58 (6)	0 (0)	25 (4)	81 (11)	0.79 (0.07)	12.0 (5.2 to 12.0)	151	16	135	-	-	-
WHIHABPS	1200	68 (6)	0 (0)	27 (6)	86 (13)	0.82 (0.09)	6.8 (1.2 to 9.3)	-	-	-	600	4	596
SUBTOTAL	3383	64 (7)	1354 (40)	26 (4.46)	90 (11.8)	0.87 (0.08)	6.9 (1.5 to 12.0)	759	261	498	600	4	596
TOTAL	**221934**	**58 (9)**	**97745 (44)**	**27 (4.56)**	**91 (12.6)**	**0.90 (0.08)**	**7.9 (2.9 to 14.7)**	**8290**	**3308**	**4982**	**2906**	**142**	**2764**

[a]CHS included an original cohort (here termed CHS1) and a supplemental African-American cohort (here termed CHS2), which were analysed separately; [b]Progetto CUORE was analysed as 7 different studies (ie, ATENA, EMOFRI, MATISS83, MATISS87, MATISS93, MONFRI89 and MONFRI94); Study acronyms are provided in Appendix 4**.**

Table 6.2 Associations of baseline values of adiposity measures with coronary heart disease and ischaemic stroke risk, adjusted for baseline values of potential confounders and intermediate risk factors

	Adjusted for age, sex and smoking		Adjusted for age, sex, smoking and intermediate risk factors[†]	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Coronary heart disease (39 studies, 143710 individuals & 5259 cases)				
Body-mass index	1.29 (1.22 to 1.37)	65 (52 to 75)	1.11 (1.05 to 1.17)	45 (20 to 62)
Waist circumference	1.32 (1.24 to 1.40)	64 (50 to 75)	1.12 (1.06 to 1.19)	49 (25 to 65)
Waist/hip ratio	1.30 (1.22 to 1.38)	65 (51 to 75)	1.14 (1.09 to 1.18)	14 (0 to 42)
Waist/height ratio	1.34 (1.27 to 1.42)	64 (49 to 74)	1.15 (1.09 to 1.21)	43 (17 to 61)
Ischaemic stroke (21 studies, 85169 individuals & 2431 cases)				
Body-mass index	1.20 (1.12 to 1.28)	39 (0 to 64)	1.06 (0.99 to 1.13)	26 (0 to 57)
Waist circumference	1.25 (1.18 to 1.33)	21 (0 to 54)	1.11 (1.05 to 1.17)	9 (0 to 43)
Waist/hip ratio	1.25 (1.18 to 1.32)	21 (0 to 53)	1.14 (1.09 to 1.20)	0 (0 to 47)
Waist/height ratio	1.27 (1.18 to 1.35)	33 (0 to 61)	1.13 (1.05 to 1.22)	32 (0 to 61)

[†]Intermediate risk factors were systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Risk ratios (RRs) are presented per 4.56 kg/m^2 higher BMI, 12.6 cm higher WC, 0.083 higher WHR and 0.075 higher WHtR (1-SD higher baseline values). RRs were adjusted as shown, and stratified, where appropriate by sex. Analyses were restricted to participants with BMI values ≥20kg/m^2.

Table 6.3 Risk ratios for coronary heart disease and ischaemic stroke per 1-SD higher baseline BMI, WC and WHR values, with adjustment for baseline values of potential intermediate risk factors

Outcome / adjusted variables[†]	RR (95% CI)		
	Body-mass index	Waist circumference	Waist/hip ratio
Coronary heart disease			
(34 studies, 114083 participants & 4800 cases)			
Adjusted for age, sex and smoking	1.28 (1.21 to 1.36)	1.30 (1.23 to 1.37)	1.30 (1.22 to 1.38)
plus intermediate risk factors	1.10 (1.05 to 1.16)	1.11 (1.06 to 1.17)	1.14 (1.10 to 1.18)
plus $\log_e$ triglyceride	1.10 (1.05 to 1.15)	1.11 (1.06 to 1.16)	1.15 (1.11 to 1.19)
(21 studies, 50492 participants & 2854 cases)			
Adjusted for age, sex and smoking	1.26 (1.17 to 1.35)	1.28 (1.19 to 1.38)	1.28 (1.19 to 1.37)
plus intermediate risk factors	1.10 (1.02 to 1.18)	1.11 (1.03 to 1.20)	1.12 (1.07 to 1.17)
plus $\log_e$ C-reactive protein	1.04 (0.97 to 1.12)	1.05 (0.98 to 1.13)	1.08 (1.04 to 1.13)
(21 studies, 82557 participants & 3568 cases)			
Adjusted for age, sex and smoking	1.25 (1.16 to 1.34)	1.26 (1.17 to 1.35)	1.27 (1.18 to 1.37)
plus intermediate risk factors	1.08 (1.01 to 1.14)	1.08 (1.02 to 1.15)	1.13 (1.09 to 1.18)
plus fibrinogen	1.06 (1.00 to 1.12)	1.06 (1.00 to 1.12)	1.13 (1.09 to 1.18)
Ischaemic stroke			
(20 studies, 81017 participants & 2395 cases)			
Adjusted for age, sex and smoking	1.19 (1.11 to 1.28)	1.25 (1.18 to 1.33)	1.25 (1.18 to 1.33)
plus intermediate risk factors	1.06 (0.99 to 1.13)	1.11 (1.05 to 1.17)	1.15 (1.09 to 1.21)
plus $\log_e$ triglyceride	1.06 (0.99 to 1.13)	1.11 (1.05 to 1.18)	1.15 (1.09 to 1.21)
(12 studies, 30758 participants & 1656 cases)			
Adjusted for age, sex and smoking	1.16 (1.08 to 1.25)	1.21 (1.13 to 1.29)	1.22 (1.13 to 1.31)
plus intermediate risk factors	1.07 (0.98 to 1.16)	1.11 (1.03 to 1.20)	1.15 (1.06 to 1.25)
plus $\log_e$ C-reactive protein	1.02 (0.95 to 1.10)	1.11 (1.03 to 1.20)	1.13 (1.04 to 1.23)
(15 studies, 59328 participants & 1856 cases)			
Adjusted for age, sex and smoking	1.21 (1.12 to 1.31)	1.26 (1.18 to 1.34)	1.28 (1.17 to 1.39)
plus intermediate risk factors	1.08 (1.00 to 1.16)	1.12 (1.05 to 1.18)	1.17 (1.08 to 1.25)
plus fibrinogen	1.06 (0.99 to 1.13)	1.11 (1.05 to 1.17)	1.16 (1.08 to 1.24)

[†]Intermediate risk factors were systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Risk ratios (RRs) are presented per 4.56 kg/m^2 higher BMI, 12.6 cm higher WC and 0.083 higher WHR (ie, 1-SD higher baseline values). Analyses are restricted to participants with BMI values ≥20 kg/m^2 and complete information on age, sex, smoking status and intermediate risk factors plus triglyceride, CRP or fibrinogen in turn.

Table 6.4 Associations of usual levels of BMI, WC and WHR with coronary heart disease and ischaemic stroke risk, adjusted for usual levels of potential confounders and intermediate risk factors

	Adjusted for age, sex and smoking		Adjusted for age, sex, smoking and intermediate risk factors[†]	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Coronary heart disease (39 studies, 143710 individuals & 5259 cases)				
Body-mass index	1.30 (1.23 to 1.38)	66 (52 to 76)	1.07 (1.02 to 1.13)	40 (12 to 59)
Waist circumference	1.32 (1.25 to 1.41)	65 (50 to 75)	1.09 (1.03 to 1.15)	45 (20 to 62)
Waist/hip ratio	1.35 (1.26 to 1.44)	58 (40 to 71)	1.12 (1.07 to 1.17)	5 (0 to 33)
Ischaemic stroke (21 studies, 85169 individuals & 2431 cases)				
Body-mass index	1.20 (1.12 to 1.28)	42 (2 to 65)	1.02 (0.96 to 1.08)	20 (0 to 53)
Waist circumference	1.26 (1.18 to 1.34)	26 (0 to 57)	1.07 (1.02 to 1.13)	3 (0 to 49)
Waist/hip ratio	1.30 (1.23 to 1.37)	2 (0 to 48)	1.13 (1.06 to 1.20)	0 (0 to 47)

[†]Intermediate risk factors were systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Risk ratios (RRs) are presented per 4.36 kg/m^2 higher BMI, 10.98 cm higher WC and 0.059 higher WHR (ie, 1-SD higher usual levels). RRs were adjusted as shown, and stratified, where appropriate, by sex. Analyses were restricted to participants with BMI values ≥20kg/m^2.

Table 6.5 Age, sex and smoking status adjusted associations of baseline values of BMI, WC and WHR with coronary heart disease and ischemic stroke risk, under various exclusion circumstances

A Excluding data from first 5 years of follow-up

Adiposity measure	Coronary heart disease (36 studies, 123685 individuals & 4028 cases)		Ischaemic stroke (18 studies, 63356 individuals & 1479 cases)	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index	1.31 (1.23 to 1.39)	59 (40 to 71)	1.24 (1.13 to 1.35)	40 (0 to 66)
Waist circumference	1.36 (1.28 to 1.45)	56 (36 to 70)	1.27 (1.16 to 1.39)	42 (0 to 67)
Waist/hip ratio	1.31 (1.23 to 1.38)	51 (27 to 66)	1.24 (1.15 to 1.35)	36 (0 to 64)

B Excluding smokers

Adiposity measure	Coronary heart disease (45 studies, 147963 individuals & 5561 cases)		Ischaemic stroke (21 studies, 92594 individuals & 1985 cases)	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index	1.23 (1.16 to 1.29)	60 (44 to 71)	1.21 (1.13 to 1.30)	41 (0 to 65)
Waist circumference	1.27 (1.20 to 1.34)	62 (47 to 72)	1.24 (1.17 to 1.32)	22 (0 to 54)
Waist/hip ratio	1.24 (1.17 to 1.32)	22 (0 to 54)	1.23 (1.15 to 1.31)	21 (0 to 54)

C Excluding known participants of non-European descent

Adiposity measure	Coronary heart disease (47 studies, 178532 individuals & 6752 cases)		Ischaemic stroke (21 studies, 104996 individuals & 2130 cases)	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index	1.30 (1.23 to 1.37)	64 (51 to 74)	1.21 (1.13 to 1.29)	32 (0 to 60)
Waist circumference	1.29 (1.22 to 1.36)	64 (50 to 73)	1.25 (1.17 to 1.33)	35 (0 to 62)
Waist/hip ratio	1.33 (1.26 to 1.40)	65 (52 to 74)	1.26 (1.18 to 1.34)	24 (0 to 55)

D Excluding studies involving self-reported anthropometric measurements

Adiposity measure	Coronary heart disease (47 studies, 178300 individuals & 7391 cases)		Ischaemic stroke (23 studies, 98973 individuals & 2524 cases)	
	RR (95%CI)	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index	1.27 (1.21 to 1.34)	69 (59 to 77)	1.20 (1.13 to 1.29)	41 (3 to 64)
Waist circumference	1.30 (1.23 to 1.37)	67 (55 to 75)	1.25 (1.18 to 1.33)	32 (0 to 59)
Waist/hip ratio	1.29 (1.23 to 1.36)	65 (52 to 74)	1.25 (1.18 to 1.33)	27 (0 to 56)

Risk ratios (RRs) are presented per 4.56 kg/m^2 higher BMI, 12.6 cm higher WC and 0.08 higher WHR (ie, 1-SD higher baseline values). RRs were adjusted for age at baseline and smoking status and stratified, where appropriate, by sex. All analyses were restricted to participants with BMI values ≥20 kg/m^2.

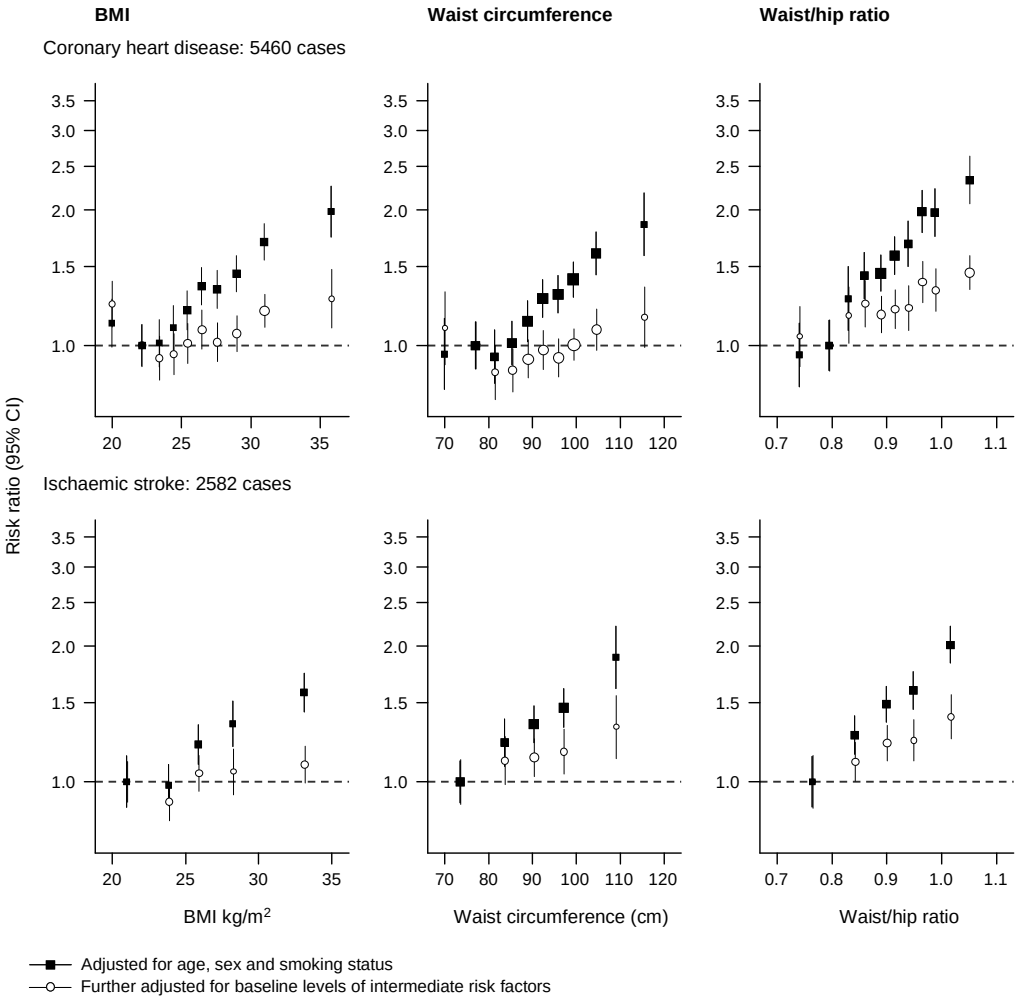
Table 6.6 Associations of baseline values of BMI, WC and WHR with coronary heart disease and ischaemic stroke risk, adjusted for baseline values of adiposity measures

Coronary heart disease (51 studies & 7750 cases)	1-SD	Adjusted for age, sex and smoking		Adjusted for age, sex, smoking and BMI (or WC for association with BMI)	
Adiposity measure		**RR (95%CI)**	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index*	4.56	1.27 (1.21 to 1.34)	67 (56 to 76)	1.06 (0.99 to 1.13)	37 (11 to 55)
Waist circumference	12.6	1.31 (1.24 to 1.37)	65 (53 to 74)	1.23 (1.15 to 1.32)	33 (6 to 53)
Hip circumference	9.44	1.16 (1.11 to 1.21)	47 (26 to 62)	0.87 (0.82 to 0.93)	28 (0 to 49)
Waist/hip ratio	0.08	1.29 (1.23 to 1.35)	3 (50 to 73)	1.21 (1.16 to 1.26)	37 (12 to 55)
Ischaemic stroke (25 studies & 2661 cases)		Adjusted for age, sex and smoking		Adjusted for age, sex, smoking and BMI (or WC for association with BMI)	
Adiposity measure	1-SD	**RR (95%CI)**	**I^2 (95% CI)**	**RR (95%CI)**	**I^2 (95% CI)**
Body-mass index†	4.56	1.21 (1.13 to 1.29)	44 (10 to 65)	1.00 (0.92 to 1.08)	0 (0 to 44)
Waist circumference	12.6	1.26 (1.19 to 1.33)	31 (0 to 58)	1.26 (1.16 to 1.36)	0 (0 to 44)
Hip circumference	9.44	1.13 (1.07 to 1.20)	31 (0 to 58)	0.91 (0.84 to 0.98)	0 (0 to 44)
Waist/hip ratio	0.08	1.25 (1.19 to 1.32)	20 (0 to 51)	1.18 (1.13 to 1.24)	0 (0 to 44)

*Associations with BMI were adjusted for WC. RR = 1.18 (1.13 to 1.24) after adjustment for age, sex, smoking and WHR.
†Associations with BMI were adjusted for WC. RR = 1.13 (1.07 to 1.20) after adjustment for age, sex, smoking and WHR.

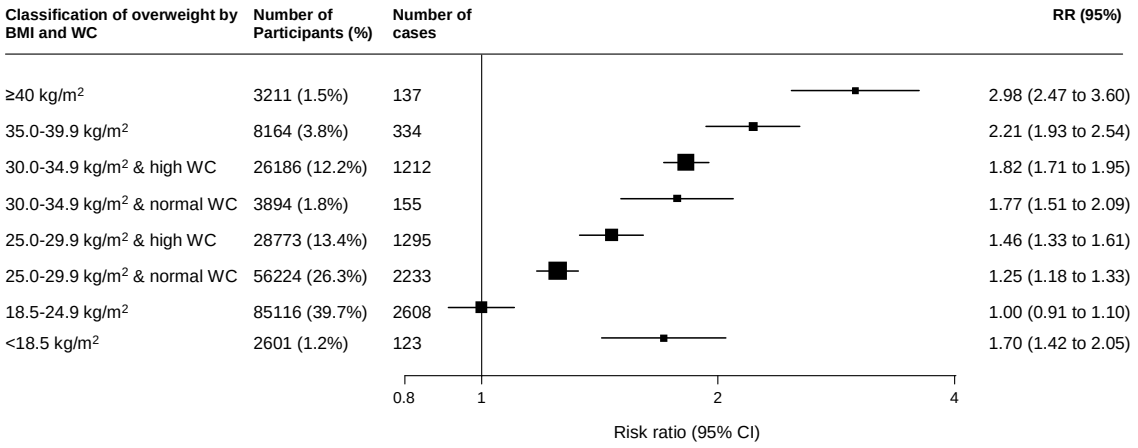
Risk ratios (RRs) are presented per 1-SD higher baseline values of adiposity measures. RRs were adjusted as shown, and stratified, where appropriate, by sex. Analyses were restricted to participants with BMI values ≥20kg/m^2.

Figure 6.1 Risk ratios for coronary heart disease and ischaemic stroke across quantiles of baseline BMI, WC and WHR



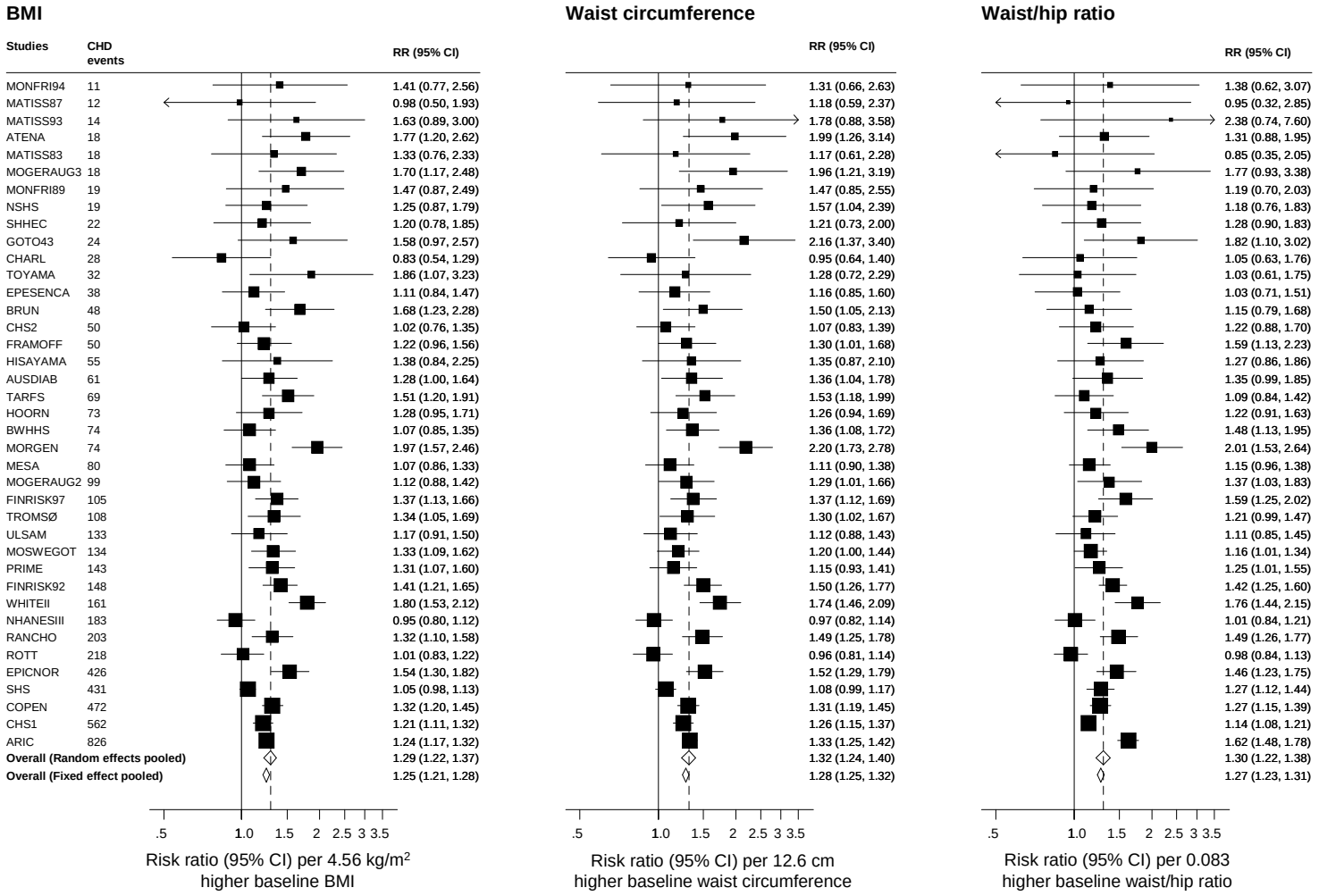
Regression analyses were stratified, where appropriate, by sex. Values with further adjustments were adjusted for age, smoking status, systolic blood pressure, history of diabetes and total and HDL cholesterol. Referent groups are the second deciles in the plots for coronary heart disease and the first quintiles in the plots for ischaemic stroke.

Figure 6.2 Risk ratios for coronary heart disease by clinically defined categories of baseline BMI and WC



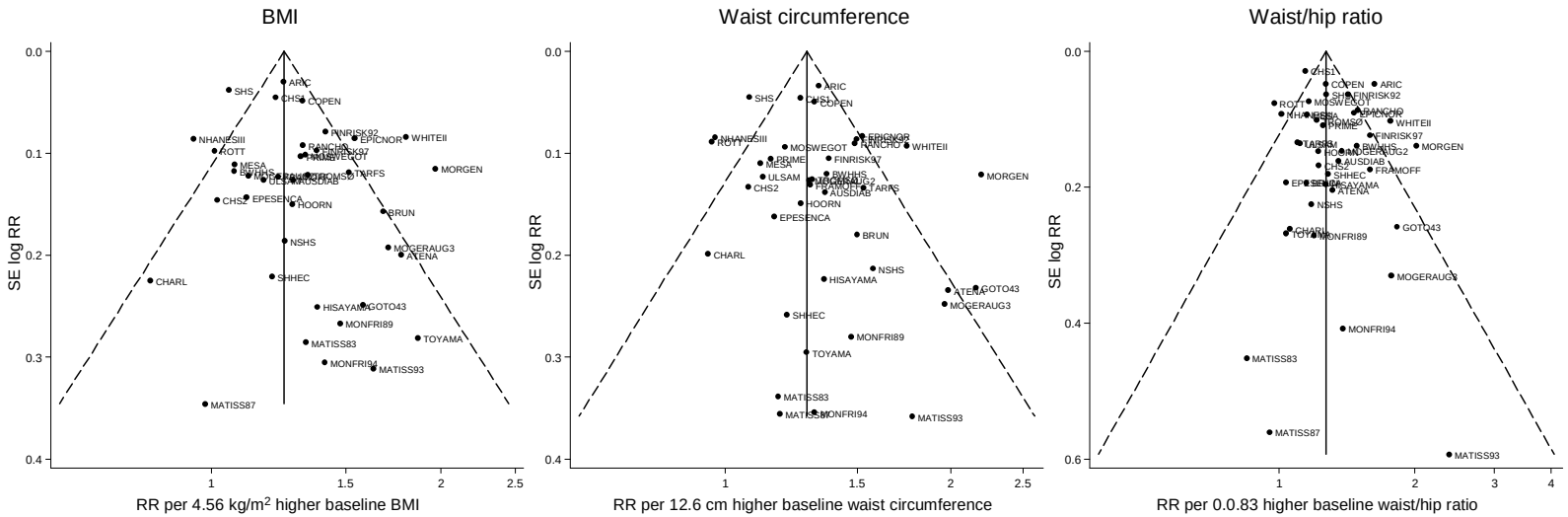
Analysis was based on 214,169 participants (involving 8097 cases) from 52 studies. Risk ratios were adjusted for age and smoking status, and stratified, where appropriate, by sex. High WC was defined as WC >102 cm in men and WC >88 cm in women.

Figure 6.3 Study-specific risk ratios for coronary heart disease per 1-SD higher baseline BMI, WC and WHR, adjusted for age, sex and smoking status



Analyses were restricted to participants with BMI values ≥20 kg/m^2 and complete information on age, sex, smoking status, history of diabetes, systolic blood pressure, and total and HDL cholesterol. In the BMI analysis, after excluding the 6 most discrepant studies (CHARL, MATISS87, NHANESIII, MORGEN, TOYOMA, WHITEII) the risk ratio was 1.26 (95% CI 1.20-1.33) and the I^2 was reduced to 45% (95% CI 17% to 64%). In the WC analysis, after excluding the 6 most discrepant studies (CHARL, NHANESIII, ROTT, ATENA, GOTO43, MORGEN) the risk ratio was 1.31 (95% CI 1.25-1.38) and the I^2 was reduced to 40% (95% CI 9% to 61%). In the waist/hip ratio analysis, after excluding the 6 most discrepant studies (MATISS83, MATISS87, ROTT, GOTO43, MATISS93, MORGEN) the risk ratio was 1.30 (95% CI 1.22-1.37) and the I^2 was reduced to 61% (95% CI 43% to 73%).

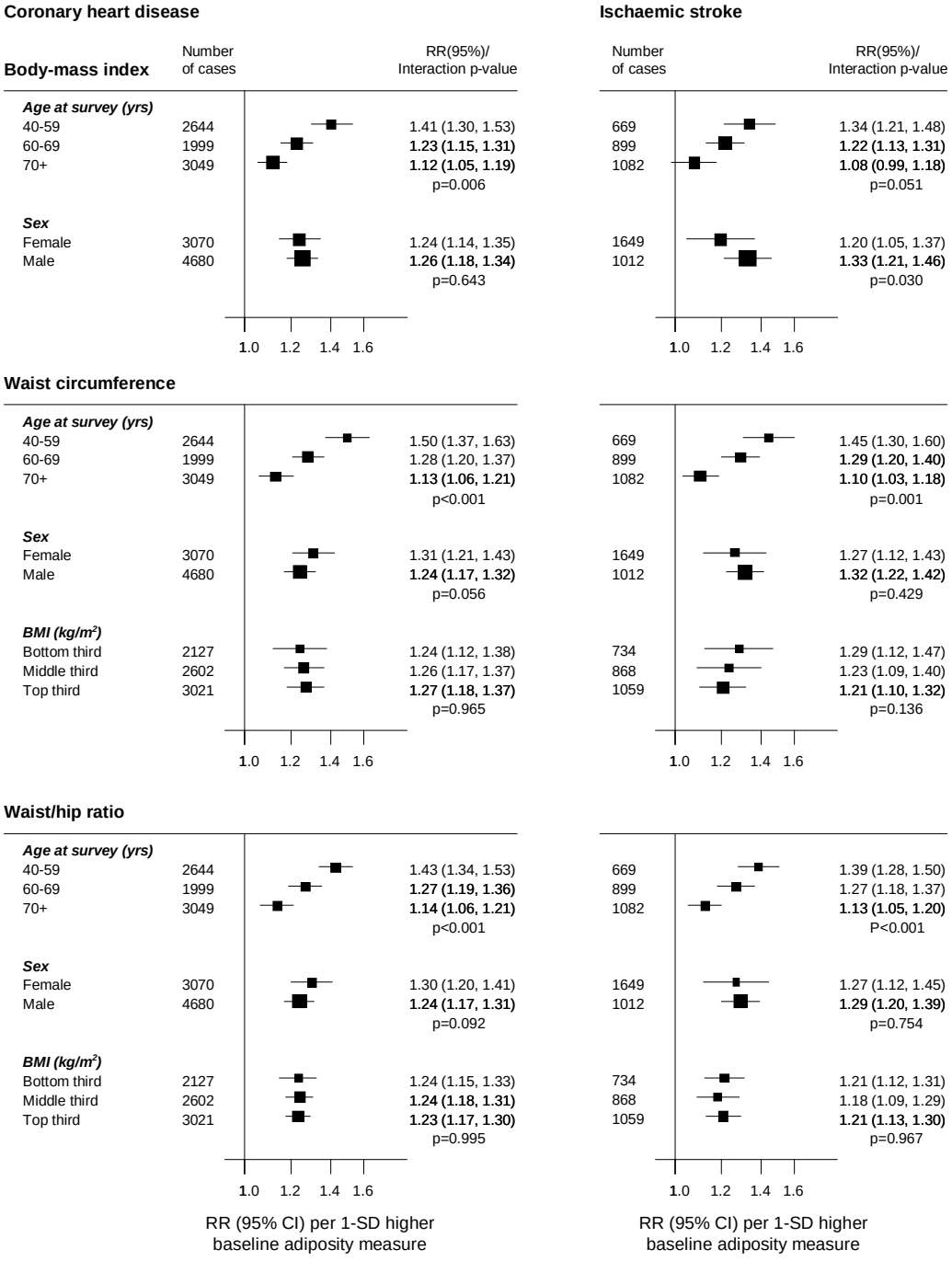
Figure 6.4 Funnel plots assessing potential bias from small-study effects in the meta-analysis of adiposity measures with coronary heart disease risk



Analyses were restricted to participants with BMI values ≥20 kg/m^2 and complete information on age, sex, smoking status, history of diabetes, systolic blood pressure, and total and HDL cholesterol.

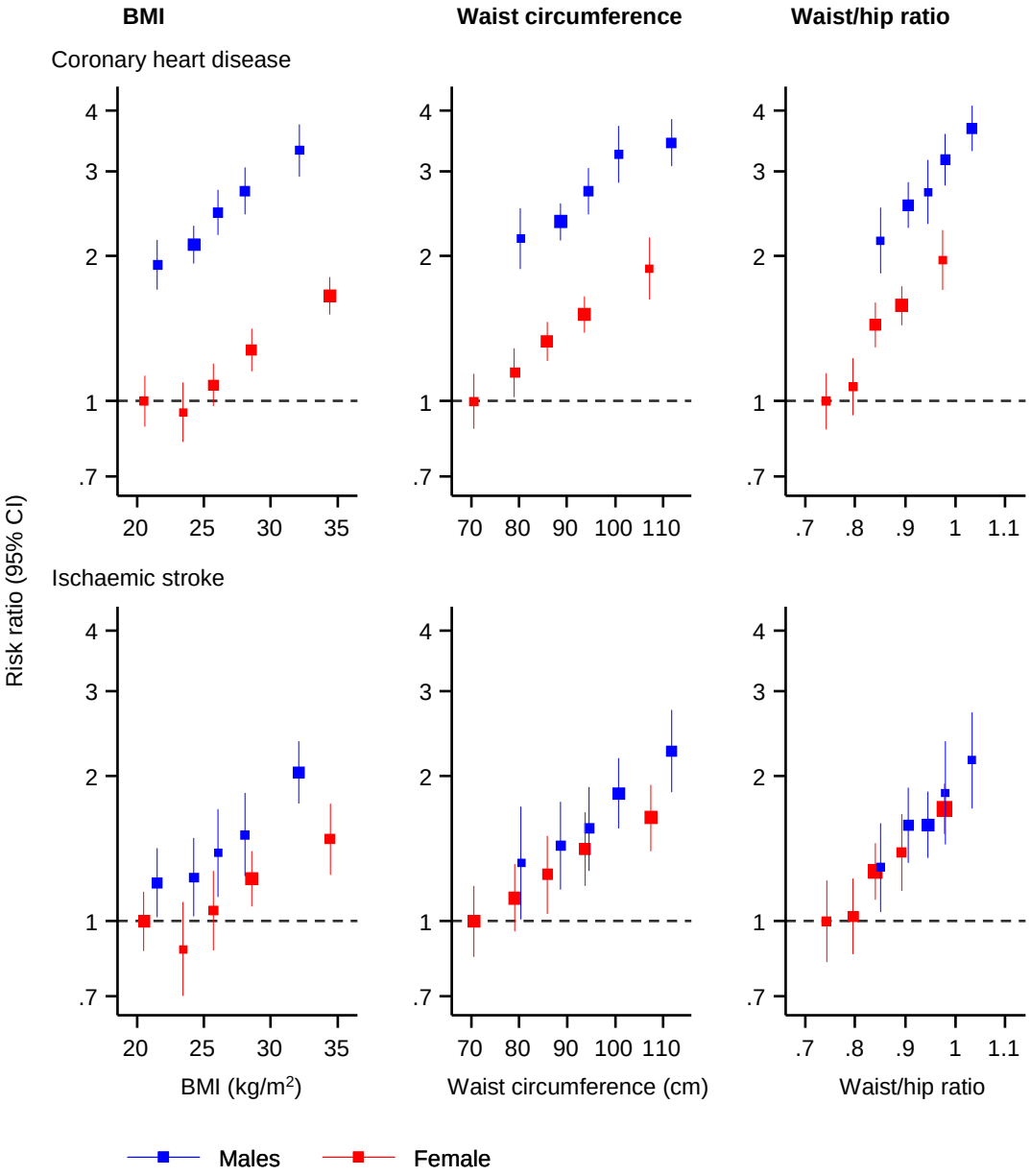
There was no evidence of bias from small-study effects for BMI (p = 0.123), waist circumference (p = 0.211) and waist/hip ratio (p = 0.414) using Egger's test from small-study effects.

Figure 6.5 Risk ratios for coronary heart disease and ischaemic stroke per 1-SD higher baseline BMI, WC and WHR, according age, sex and BMI at baseline



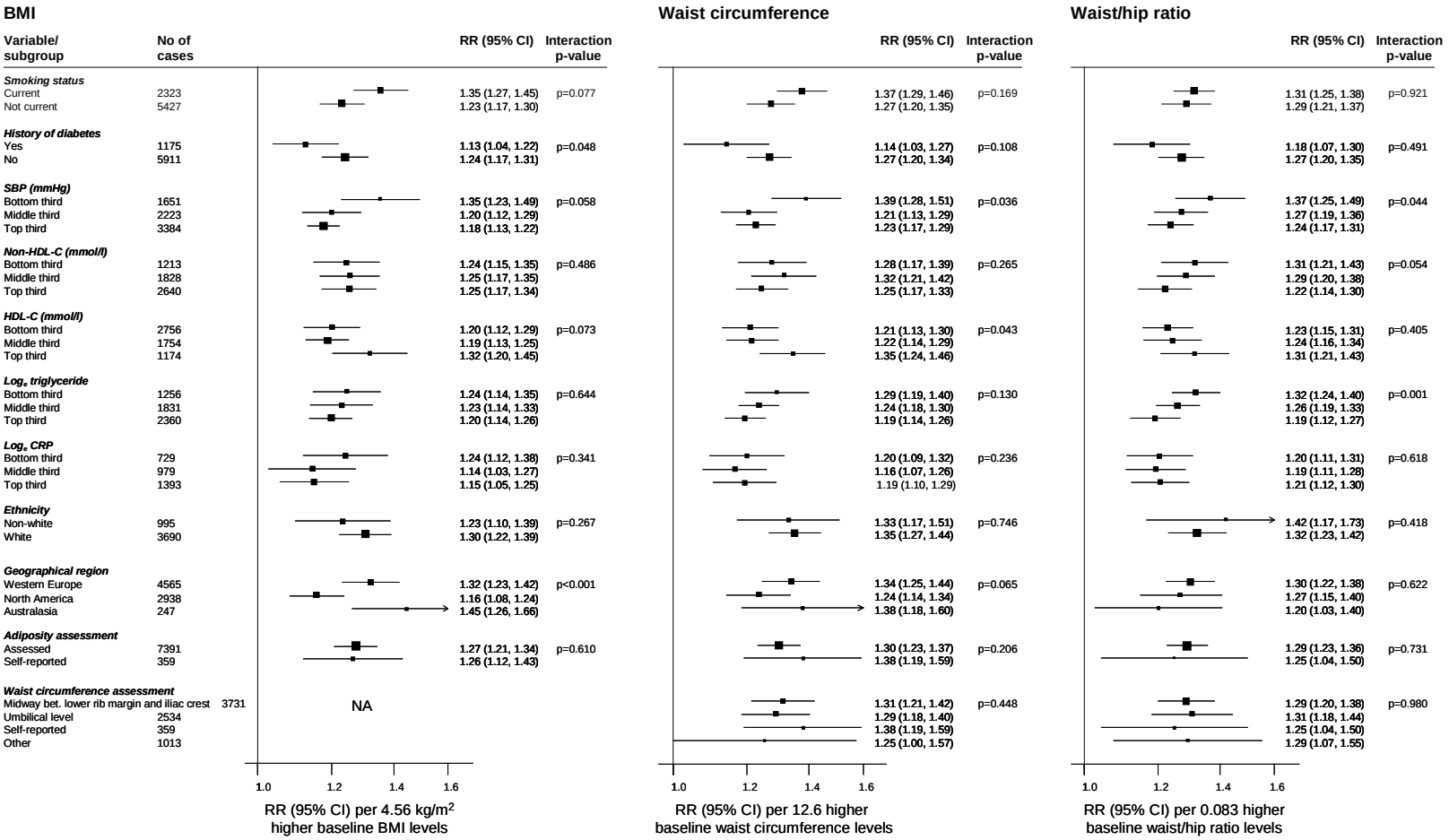
Risk ratios (RRs) are presented per 4.56 kg/m^2 higher BMI, 12.6 cm higher WC and 0.083 higher WHR (ie, 1-SD higher baseline values). Study-specific risk ratios were adjusted for age at baseline and smoking status, and stratified, where appropriate, by sex. Analyses were restricted to participants with BMI values ≥20 kg/m^2.

Figure 6.6 Risk ratios for coronary heart disease and ischaemic stroke across quintiles of baseline BMI, WC and WHR, among men and women



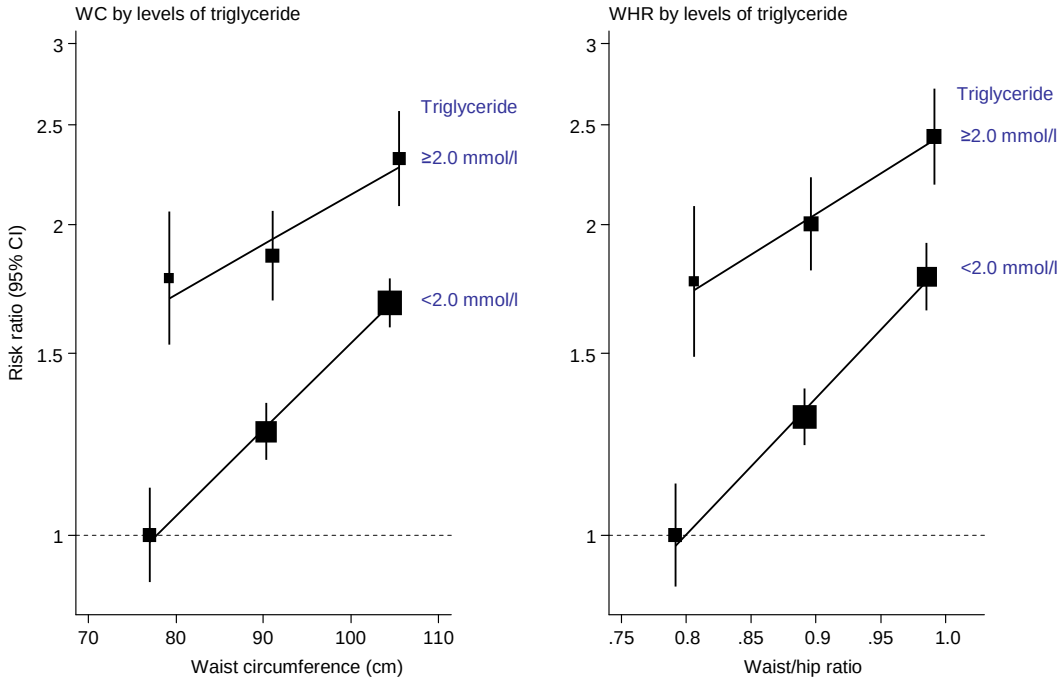
Analyses were restricted to studies with data on both males and females. Regression analyses were adjusted for age and smoking status. Referent groups are the first quintile in women in the plots.

Figure 6.7 Risk ratios for coronary heart disease per 1-SD higher baseline BMI, WC and WHR, according to several individual and study level characteristics



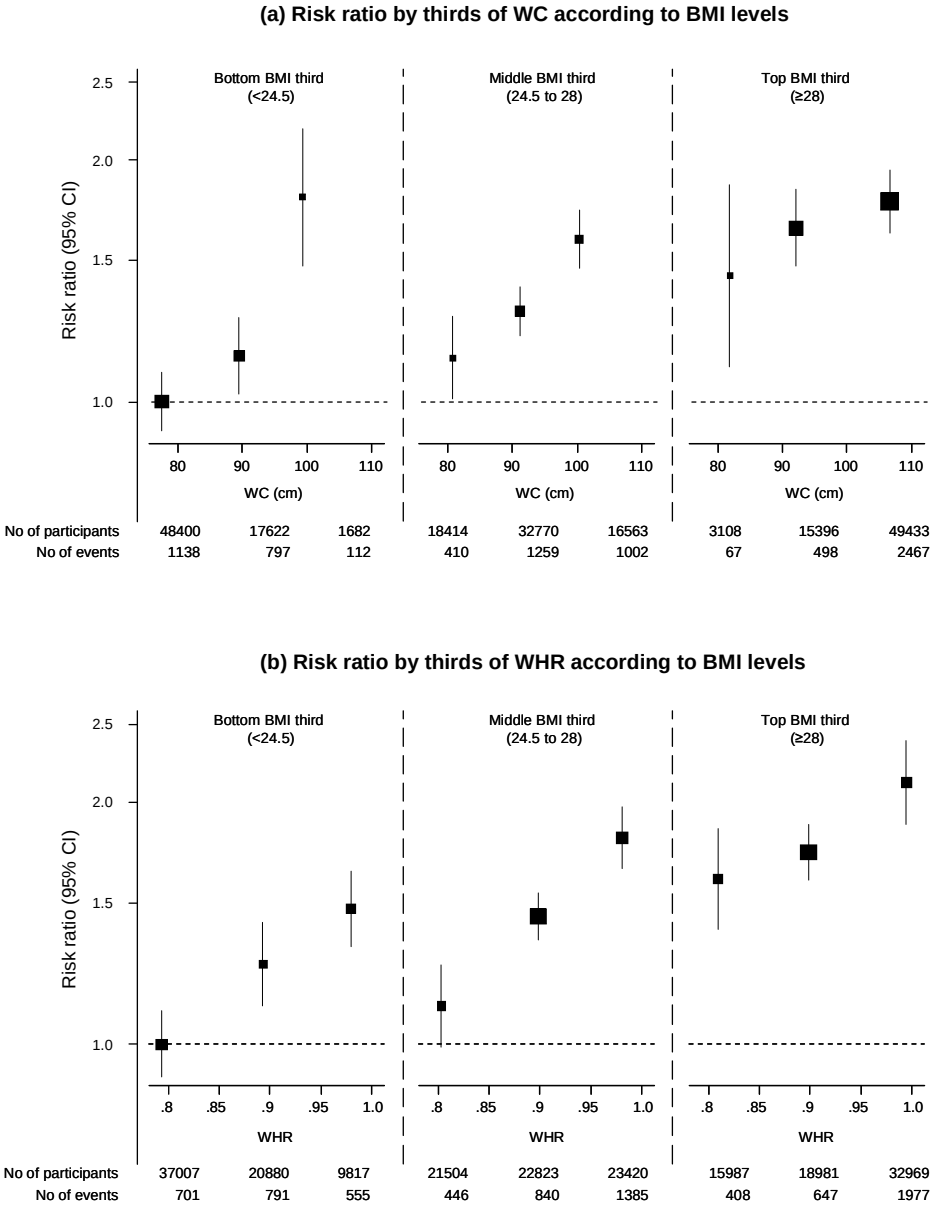
Study-specific risk ratios were adjusted for age and smoking status, and stratified, where appropriate, by sex. Analyses were restricted to participant with BMI values ≥20 kg/m^2.
Abbreviation: NA = not applicable.

Figure 6.8 Risk ratios for coronary heart disease across thirds of WC and WHR by baseline values of triglyceride



Analysis was based on 141,203 participants (involving 5684 cases) from 41 studies. Regression analyses were adjusted for age at baseline and smoking status, and stratified, where appropriate, by sex. Referent groups are the lowest third of WC or WHR in the lower level of triglyceride.

Figure 6.9 Risk ratios for coronary heart disease across thirds of WC and WHR, stratified by thirds of BMI



Analysis was based on 203,388 participants (involving 7750 cases) from 51 studies. Analyses were restricted to participants with BMI values ≥20kg/m^2. Risk ratios were adjusted for age at baseline and smoking status, and stratified, where appropriate, by sex. Reference groups are the lowest third of waist circumference or waist-to-hip ratio in the bottom third of BMI. Similar findings were observed with BMI categories were <25, 25-29.9 and ≥30 kg/m^2 using the full range of BMI values.

CHAPTER 7: Adiposity measures in cardiovascular disease risk prediction

Summary

Findings from a previous systematic review of 27 guideline statements showed substantial variation in recommendations about the value of inclusion of clinical measures of adiposity in risk scores for the primary prevention of cardiovascular disease in developed countries. Furthermore, a relatively small study suggested replacing assessment of lipid measures with that of adiposity measures in resource-limited settings where cholesterol testing is not feasible for cardiovascular disease risk assessment. This chapter reports on the incremental predictive ability of adiposity measures, assessed singly or in combination, under a wide range of circumstances in 144,795 healthy participants from the Emerging Risk Factors Collaboration. Additional information on body-mass index (BMI), waist circumference, and waist-to-hip ratio (WHR) to a cardiovascular disease risk prediction model containing conventional risk factors did not importantly improve risk discrimination, nor classification of participants to risk categories of predicted 10-year risk. Regarding the replacement of lipids with adiposity measures, the current data has shown that a combination of BMI and WHR provides only about one-quarter of the predictive information provided by total and high-density lipoprotein cholesterol combined. These findings indicates that for population-wide assessment of cardiovascular disease risk, simple adiposity measures provide little or no additional information about cardiovascular disease risk prediction given knowledge about risk factors used in standard risk scores. They also highlight the desirability of supporting the development of lipid assessment in resource-limited settings.

Background

For the prevention of cardiovascular disease, clinicians depend on risk scores that correctly and easily identify patients at high risk of cardiovascular disease, so that they can provide targeted preventative interventions.[1-3] Over the past three decades, many cardiovascular disease risk prediction models have been proposed, each including different risk factors.[4] While analyses of the type presented in **Chapters 5** and **6** involving measures of associations (such as relative risks) are informative for aetiological purposes, they do not directly assess the ability of a risk marker for cardiovascular disease risk prediction.[5-8] Therefore, specific measures (eg, measures of risk discrimination and reclassification) have been developed to assess the predictive accuracy of a risk maker.[1]

National and international guideline statements have provided differing recommendations about the value of assessment of clinical measures of adiposity for cardiovascular risk prediction in primary prevention.[4] Recommendations range from omission of adiposity measures to their inclusion as additional screening tests to their formal inclusion as risk factors in prediction models. For example, whereas the World Health Organization[9] and the US National Heart, Lung and Blood Institute[10] recommend body-mass index (BMI) measurement as well as assessment of waist circumference (WC) in people with a BMI between 25.0 and 34.9 kg/m^2, several commonly-used cardiovascular disease risk scores omit adiposity measures (eg, Framingham[11], PROCAM[12], SCORE[13], ASSIGN[14] or Reynolds[15]), but others include BMI (eg, QRISK[16]) (**Table 7.1**). Furthermore, some data suggest that BMI can serve as a simple alternative in settings where cholesterol testing is not feasible for cardiovascular disease risk assessment.[17] This suggestion, however, requires larger-scale evaluation, with inclusion of measures of abdominal adiposity.

This divergence in guideline recommendations noted above may reflect, in part, uncertainties in relation to data from previous studies. As described in **Chapter 1** on pages 10-13, previous prospective studies with assessment of BMI, WC and waist-to-hip ratio (WHR) in the same people have reported inconsistent findings regarding the relative importance of overall and abdominal adiposity to the risk of cardiovascular disease.[18-41] Furthermore, prospective studies of adiposity have often lacked concomitant measurement of lipids and other conventional risk factors. This feature has made it difficult for such studies to evaluate adiposity measures in the context of standard risk prediction scores.[26,42] Furthermore, because studies have often

reported on measures of association rather than on specific measures of predictive ability, they may not have been able to make an optimum assessment of predictive ability.[7,8]

The objective of this chapter is to quantify the incremental gain in predictive ability that can be attributed to addition of BMI, WC and WHR, singly or in combination, to cardiovascular risk prediction models under a wide range of circumstances, using data from the Emerging Risk Factors Collaboration (ERFC).[43]

Methods

Study design

Details of data on adiposity measures in the ERFC are given in **Chapter 2**. The current analysis involved individual records from 144,795 participants in 39 prospective cohort studies with the following features: (1) participants were not selected on the basis of having previous cardiovascular disease; (2) participants had BMI values of 20 kg/m^2 or higher; (3) concomitant information was provided at baseline on weight, height, waist and hip circumference, smoking status, systolic blood pressure (SBP), history of diabetes, and total and high-density lipoprotein (HDL) cholesterol; (4) individual studies recorded at least ten cardiovascular outcomes; and (5) at least 1 year of follow-up had been accrued.

Analyses involved participants with baseline BMI, WC and WHR plus conventional risk factors (ie, smoking status, SBP, history of diabetes, and total and HDL cholesterol). The study outcome was cardiovascular disease, defined as first-ever myocardial infarction or coronary death or any cerebrovascular disease event.

Risk prediction model

The risk prediction models were based on a Cox proportional regression model stratified by study and sex (ie, allowing for separate baseline hazards by study and sex), but common coefficients (ie, $\log_e$ hazard ratios) across studies.[44] For each stratum $k = 1 \ldots K$ (ie, distinct combinations of study and sex), with $i = 1 \ldots n_k$ individuals in stratum *K*, and baseline covariates X_i, the probability of surviving without a cardiovascular disease event to at least time *t* years after baseline is given by

$$S_{ki}(t \mid X_i) = S_{0k}(t)^{\exp(\beta X_i)}, \qquad (7.1)$$

where $S_{0k}(t)$ is the baseline survival at time *t*. The probability of a cardiovascular event within *t* years is given by

$$\Pr(T \le t \mid X_i, k) = 1 - S_{ki}(t \mid X_i) = 1 - S_{0k}(t)^{\exp(\beta X_i)}. \qquad (7.2)$$

Deaths from non-cardiovascular causes were censored. Parallel analyses involved multivariate random effects meta-analyses, allowing for between-study heterogeneity. The random effects model yielded similar point estimates for β but with wider confidence intervals. Since only the point estimates were necessary for making the absolute risk predictions and calculating measures of discrimination, the simpler stratified Cox proportional regression model was used for derivation of the risk prediction model. The models were fitted to data from all participants and then the predictive ability was assessed using measures of discrimination and reclassification.

Measures of discrimination

Discrimination refers to the ability of a risk prediction model to separate those who do and do not have the disease of interest.[7] Discrimination was assessed using Harrell's C-index for censored time-to-event data.[45,46] The C-index is the probability, that for a randomly selected pair of participants, the individual who develops cardiovascular disease first has the higher value of the linear predictor βX_i (ie, the worse prognosis).[46] A C-index of 0.5 indicates that the model has no discriminatory power (ie, the model does no better than chance alone), while a value of 1 implies perfect discrimination. It is estimated by examining within each stratum all possible pairs of participants for which the participant who has the shorter participation time fails. It classifies each pair as concordant (ie, matching in rank according to the magnitude of the linear predictor and the order of failure), discordant (ie, opposite in such ranking), or undecided (ie, tied in either category). The overall measures is given by

$$C = \frac{n_c + 0.5n_u}{n_c + n_d + n_u}, \qquad (7.3)$$

where n_c, n_d and n_u are the number of concordant, discordant and undecided pairs, respectively.

To deal with the multi-study structure of the data, the overall C-index was calculated in two stages, with estimation within each study separately before pooling results to obtain an overall average estimate. Within each study, pair-wise comparisons were constrained to allow only pairing of participants within the same strata (ie, concordance/discordance counts did not include comparison of males to females). So, for each study $s = 1,\ldots S$, the C-index $\hat{\theta}_s$ with variance $\hat{\sigma}^2_{\hat{\theta}s}$ was calculated, the variance being estimated using an efficient jackknife approach for rank statistics.[47]

Subsequently, the C-indices and corresponding variances were combined across studies using a weighted average:

$$\theta = \frac{\sum w_s \hat{\theta}_s}{\sum w_s} \qquad \text{and} \qquad \sigma_\theta = \sqrt{\frac{\sum w_s^2 \hat{\sigma}^2_{\hat{\theta}s}}{(\sum w_s)^2}}, \qquad (7.4; 7.5)$$

where w_s is the study-specific weight (ie, weighted according to the number of cardiovascular events in each study). Alternative weights were considered, including inverse-variance weights in fixed and random effects meta-analysis models.[48] However, weighting by the number of events in a study was considered the most appropriate, as it best matches the weighting applied across studies in the derivation of the original stratified Cox proportional regression model described in (7.1). As described in detail in **Chapter 5**, the extent of heterogeneity between studies was indicated by the I^2 statistic.[49,50]

To investigate the change in C-index on addition of a new risk factor, two risk prediction models were fitted, one model with the core risk factors only (eg, age, sex, smoking status, blood pressure, history of diabetes and lipids), and the second model with the core risk factors plus the new risk factor (eg, BMI). The C-index $\hat{\theta}_s$ for both models, their difference $\hat{\Delta}_s$, and corresponding jackknife standard errors[47] were calculated within each study. The study-specific C-index changes and the corresponding variances were then combined using models described in (7.4; 7.5), replacing θ with Δ. Between-study heterogeneity in C-index changes were quantified by the I^2 statistic.[49,50]

Risk reclassification

Risk reclassification was assessed by comparing the predicted 10-year cardiovascular disease risk from the model containing conventional risk factors to the predicted risk from models that contained also – either assessed separately or combined – BMI, WC and WHR. The 10-year risk predictions were calculated using model (7.2). Participants were placed into standard 10-year risk categories (0% to <5%, 5% to <10%, 10% to <20% and ≥20%) based on the Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP-III) guidelines,[51] and movement between risk categories on addition of adiposity measures was quantified by the Net Reclassification Improvement[52] (NRI) that summarises whether movement between risk categories is in the correct direction. The reclassification of individuals was deemed appropriate for cardiovascular disease cases occurring before 10 years moving up the risk categories, and for event free individuals at 10 years moving down the risk categories on addition of adiposity measures. The NRI and the corresponding standard error are given by

$$\text{NRI} = \left(\frac{\#\,\text{events}\uparrow}{\#\,\text{events}} - \frac{\#\,\text{events}\downarrow}{\#\,\text{events}}\right) + \left(\frac{\#\,\text{nonevents}\downarrow}{\#\,\text{nonevents}} - \frac{\#\,\text{nonevents}\uparrow}{\#\,\text{nonevents}}\right)$$

$$\text{and} \quad \sqrt{\frac{\hat{p}_{\text{up,events}} + \hat{p}_{\text{down,events}}}{\#\,\text{events}} + \frac{\hat{p}_{\text{up,nonevents}} + \hat{p}_{\text{down,nonevents}}}{\#\,\text{nonevents}}}, \qquad (7.6;7.7)$$

where $\hat{p}_{\text{up,events}}$ and $\hat{p}_{\text{down,events}}$ are probabilities of moving up or down a category among events calculated as $(\#\,\text{events}\uparrow/\#\,\text{events})$ and $(\#\,\text{events}\downarrow/\#\,\text{events})$ and likewise for $\hat{p}_{\text{up,nonevents}}$ and $\hat{p}_{\text{down,nonevents}}$ among non-events.

Because risk categories are inherently arbitrary, the Integrated Discrimination Improvement[52] (IDI) was also used, which estimates the average absolute improvement in predicted risk between different models. The IDI can be estimated as

$$\text{IDI} = (\bar{\hat{p}}_{\text{new,events}} - \bar{\hat{p}}_{\text{old,events}}) - (\bar{\hat{p}}_{\text{new,nonevents}} - \bar{\hat{p}}_{\text{old,nonevents}}), \qquad (7.8)$$

where $\bar{\hat{p}}_{\text{new,events}}$ and $\bar{\hat{p}}_{\text{old,events}}$ are the average estimated 10-year risks among events according to the new and the old model, respectively, and similarly for $\bar{\hat{p}}_{\text{new,nonevents}}$ and $\bar{\hat{p}}_{\text{old,nonevents}}$.

The standard error of the IDI is given by

$$\sqrt{(se_{events})^2 + (se_{nonevents})^2}, \qquad (7.9)$$

where se_{events} and $se_{nonevents}$ are the standard errors of the paired differences between new and old model-based predicted probabilities across all events and non-events, respectively.

In order to calculate 10-year risk predictions, studies with less than 10 year of follow-up and participants who were censored before 10 years were not able to contribute to the reclassification analyses, while individuals whose cardiovascular events occurred after 10 years were considered as non-cases.

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Information on age, sex, weight, height, waist and hip circumference, smoking status, SBP, history of diabetes, total and HDL cholesterol was available in 144,795 participants from 39 cohorts, yielding 8,347 first-onset cardiovascular disease outcomes (4,839 coronary heart disease and 3,508 cerebrovascular outcomes) during 1.3 million person-years at risk (median, 5.7 [IQR 3.0-9.0] years to first outcome). The baseline characteristics of the 144,795 participants were broadly similar to those participants from the larger dataset with information on age, sex, weight, height, and waist and hip circumference only (**Chapter 2**). **Table 7.2** shows adjusted hazard ratios for cardiovascular disease with baseline values of BMI, WC, WHR, total and HDL cholesterol and other conventional risk factors. In models with conventional risk factors plus one measure of adiposity, hazard ratios of adiposity measure were 1.07 (95% confidence interval [CI] 1.03-1.11) for BMI, 1.10 (95% CI 1.06-1.15) for WC and 1.12 (95% CI 1.08-1.15) for WHR. In models including conventional risk factors plus two adiposity measures (ie, BMI plus either WC or WHR), hazard ratios were, respectively, 0.97 (95% CI 0.92-1.02) and 1.13 (95% CI 1.07-1.20) for BMI and WC, and 1.04 (95% CI 1.00-1.08) and 1.11 (95% CI 1.07-1.14) for BMI and WHR.

Addition of adiposity measures to age and sex only

Compared to a risk prediction model containing age and sex only, addition of adiposity measures, whether assessed singly or in combination, achieved modest increases in C-index (**Figure 7.1**). The C-index increases with additional information of adiposity measures were 0.0051 (95% CI 0.0031-0.0072) with BMI, 0.0077 (95% CI 0.053-0.0100) with WC and 0.0102 (95% CI 0.0080-0.0125) with WHR. This translates, for example on addition of WHR to correct prediction of the order of cardiovascular disease events in an extra 102 pairs out of 10,000 pairs of participants screened (6,843 as opposed to 6,741 pairs per 10,000). By contrast, addition of conventional risk factors (ie, smoking status, SBP, history of diabetes, and total and HDL cholesterol) improved risk prediction more substantially, giving an increase in the C-index about five times greater than that seen on addition BMI and WHR together (0.0584 versus 0.0108). Compared to a risk prediction model containing age, sex and BMI, addition of WC or WHR significantly improved risk discrimination ($p<0.001$ for both). Broadly similar findings to those reported above were observed in analyses that used 10-year risk reclassification metrics (**Table 7.3**).

Replacement of total and HDL cholesterol with adiposity measures

When information on adiposity measures was added to a risk prediction containing non-lipid variables (ie, age, sex, smoking, systolic blood pressure and history of diabetes), WC and WHR significantly improved risk discrimination, however, less than did total and HDL cholesterol combined (**Figure 7.2**). For example, the incremental gain in predictive value provided by a combination of BMI and WHR was about one-quarter of the predictive gain provided by total and HDL cholesterol (C-index change of 0.0022 versus 0.0087). Additional information on BMI, WC or WHR, however, did not significantly change cardiovascular disease reclassification of participants to 10-year predicted risk categories (net reclassification improvement [NRI] of 0.17% [95% CI -0.57% to 0.91%], 0.13% [95% CI -0.71% to 0.97%], 0.52% [95% CI -0.33% to 1.38%], respectively), whereas total and HDL cholesterol combined did (NRI of 2.83 [95% CI 1.56% to 4.11%]; **Table 7.4**). Assessment of combinations of adiposity measures revealed no important improvement in risk discrimination (**Figure 7.2**) or reclassification (**Table 7.4**). Qualitatively similar results to those for risk discrimination were observed in analyses that assessed integrated discrimination improvement (**Table 7.4**).

Addition of adiposity measures to conventional risk factors

When information on lipids and other conventional risk factors was available, additional information on BMI, WC or WHR did not importantly change cardiovascular disease risk discrimination (C-index changes of -0.0001, -0.0001 and 0.0008, respectively; **Table 7.5**) nor reclassification of participants to 10-year predicted risk categories (NRIs of -0.19%, -0.05% and -0.05%, respectively; **Tables 7.5-7.6**). To assess any incremental gain in predictive ability provided by adiposity measures irrespective of the sequence of their addition to a risk model, the effect of one-at-a-time omission of each risk factor was assessed from a full model. The impact of omission of BMI and WC was nearly zero and that for WHR was small (**Figure 7.3**). This result applied in analyses that either included or omitted people with diabetes at baseline (**Figure 7.4**) and for a wide range of other circumstances (**Figure 7.5**). It was not possible to assess risk prediction at different ages because studies differed considerably in age distributions. Qualitatively similar results to those noted above were observed in analyses that assessed integrated discrimination improvement (**Table 7.5**). Whereas there was considerable between-study heterogeneity in the absolute values of the C-index (mainly reflecting the differing age distributions of contributing studies; **Figure 7.6**), there was only little between-study heterogeneity in C-index changes (**Figure 7.7**).

Discussion

In high-income countries, the common situation is for individuals to have information available on several conventional risk factors, including lipids. In this situation, the current analysis of individual data from a total of 144,795 people without a history of cardiovascular disease in 39 prospective cohort studies has shown that BMI, WC and WHR, assessed singly or in combination, do not importantly improve prediction of cardiovascular disease risk when additional information is available on blood pressure, history of diabetes and cholesterol measures. This is because much of the association between adiposity and cardiovascular disease is explained by these intermediate risk factors. This main finding does not, of course, diminish the importance of adiposity as a major modifiable determinant of cardiovascular disease. Because excess adiposity is major determinant of the intermediate risk factors, the findings in **Chapter 5** have underscored the importance of controlling adiposity to help prevent cardiovascular disease, as well as the relevance of controlling these intermediate risk factors to combat the detrimental vascular effects of overweight and obesity.[53] However, the findings of the current analysis indicate that for population-wide assessment of cardiovascular disease risk, simple adiposity measures provide little or no additional information about cardiovascular

disease risk prediction given knowledge about risk factors used in standard risk scores. Even so, there could be other reasons to include adiposity measures in risk assessment (such as promotion of behaviour change[54] or improvement of risk communication).

Previous smaller studies (and World Health Organization guidelines) have suggested that for situations in which there is no information on lipids for cardiovascular disease risk prediction (such as in resource-limited settings, where lipid measurement is not possible, too expensive, or inconvenient) assessment of simple adiposity measures can be used instead, with only a modest loss of predictive ability.[55-57] However, data from the current analysis indicate that a combination of BMI and WHR provides only about one-quarter of the predictive information provided by total and HDL cholesterol. This gain in assessment is equivalent to correct prediction of the order of cardiovascular disease outcomes in an extra 65 pairs out of 10,000 pairs of participants screened. This finding highlights, therefore, the desirability of supporting the development of lipid assessment in resource-poor settings in parallel with implementing interim strategies that dispense with this need.

The current analysis also assessed the predictive ability of adiposity measures for assessment of adiposity related cardiovascular disease risk, ignoring intermediate risk factors on the pathway between adiposity and cardiovascular disease. The findings indicate that adiposity measures significantly improve risk discrimination and risk reclassification (except the NRI for BMI) when taking into account information on age and sex only. However, the gain in risk discrimination is more than five times smaller than that achieved by measurement of intermediate risk factors (ie, SBP, history of diabetes and lipids) and smoking status. The analyses have also shown that WC and WHR further significantly improve risk discrimination in models including additionally BMI. Consistent with the findings from the European Prospective Investigation into Cancer[26] (EPIC), the current data suggest measurement of WC or WHR in addition of BMI for assessment of adiposity related cardiovascular disease risk.

The strength and potential limitations of the available data merit consideration. Compared to previous reports investigating the predictive ability of adiposity measures,[19,26,58-60] the current analysis had concomitant information on BMI, WC, WHR, lipids and other conventional risk factors and/or included several times more incident first-onset cardiovascular disease outcomes. Whereas previous analyses have often reported only on measures of association, the current analysis considered several measures of risk reclassification and discrimination,

and found broadly concordant results among them. Discrimination was assessed using the C-index, which acknowledges time-to-event data and makes allowance for censoring (in contrast to reclassification methods). However, this measure has been criticised of being insensitive to modest but potentially important improvements in predicted risk that fail to alter the ranking of predicted survival probabilities.[7] Furthermore, because the probability of correct ordering of risks may not be of great clinical relevance, some researchers consider the C-index inappropriate for the evaluation of risk markers.[61] The current analysis included reclassification analyses, which examine movement of participants between clinically relevant risk categories, upon addition of a new marker of interest to a risk model containing (conventional) risk factors.[15] Although reclassification metric are clinically more intuitive than discrimination methods, they are sensitive to the landmark time, number of risk categories, as well as choice of risk categories.[62] The current analysis quantified the incremental gain of adiposity measures in context of several conventional risk factors, as well as irrespective of the sequence of addition of risk factors to the model. Adiposity measures contributed relatively little to the heterogeneity in the results observed, which was mostly due to the differing age ranges across cohorts. The data showed that adiposity measures provide less predictive information than total and HDL cholesterol combined. Because this finding is based on data from adults from mostly European ancestry living in high-income countries, further study is needed in resource-limited settings.

Conclusions

Whether assessed singly or in combination, BMI, WC and WHR do not importantly improve cardiovascular disease risk prediction in Western people when additional information exists on blood pressure, history of diabetes and cholesterol measures. Because a combination of BMI and WHR provides only about one-quarter of the predictive information provided by total and HDL cholesterol, the development of lipid assessment should be supported in resource-poor settings.

Chapter 7 – References

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Table 7.1 Comparison of some features of commonly-used cardiovascular risk scores

	PROCAM 2002	**SCORE** 2003	**Reynolds** 2007 (Women), 2008 (Men)	**ASSIGN** 2007	**QRISK2** 2008	**Framingham** 2008
Derivation dataset						
Location	Germany	Europe	US	Scotland	England & Wales	US
Population source	Industrial employees (volunteer, not random)	General (mostly random)	Health service employees (volunteer, not random)	General (random)	GP (not random)	General (volunteer, random)
No of cohorts/centres	1 cohort	12 cohorts	2 controlled trials	1 cohort	531 centres	2 cohorts
No of participants	26975 (18460 men, 8515 women)	205178 (117098 men, 88080 women)	35282 (10724 men, 24558 women;)	13297 (6540 men, 6757 women)	2.3 M	8491 (3969 men, 4522 women)
Age range						
Age range	20-75	40-65	45-80	30-74	35-75	30-74
Marker currently used						
Age, sex, smoking & blood pressure	✓	✓	✓	✓	✓	✓
Interview based						
Ethnicity					✓	
Family history of CVD	✓			✓	✓	
History of diabetes	✓		✓	✓	✓	✓
Rheumatoid arthritis					✓	
Chronic renal disease					✓	
Atrial fibrillation					✓	
Socioeconomic status				✓	✓	
hsCRP			✓			
History of premature MI (parent<age 60)			✓			
HbA1c if diabetic			✓			
Physical measurements						
BMI					✓	
Lipid measurements						
Total cholesterol			✓	✓		✓
HDL-cholesterol	✓		✓	✓		✓
LDL-cholesterol	✓					
Total / HDL cholesterol ratio		✓			✓	
Triglyceride	✓					
Current treatment						
Antihypertensive					✓	✓
Outcome definition	Fatal / non-fatal MI	Fatal CVD	Fatal / non-fatal CVD	Fatal / non-fatal CVD	Fatal / non-fatal CVD	Fatal / non-fatal CVD

Table 7.2 Summary of available data and hazard ratios for cardiovascular disease with baseline values of risk factors

	Mean (SD) or No (%)	BMI	WC		WHR	
		HR (95% CI)[†]	HR (95% CI)[†]	HR (95% CI)[‡]	HR (95% CI)[†]	HR (95% CI)[‡]
Males		NA*	NA*	NA*	NA*	NA*
Age at survey (years)	57.29 (9.20)	1.99 (1.87, 2.12)	1.98 (1.86, 2.11)	1.97 (1.85, 2.09)	1.96 (1.84, 2.08)	1.97 (1.85, 2.09)
Current smokers	71538 (49.4)	1.86 (1.69, 2.04)	1.86 (1.70, 2.04)	1.84 (1.68, 2.02)	1.81 (1.66, 1.98)	1.84 (1.68, 2.02)
SBP (mmHg)	135.2 (19.6)	1.31 (1.27, 1.36)	1.30 (1.26, 1.35)	1.31 (1.26, 1.35)	1.30 (1.26, 1.35)	1.30 (1.26, 1.35)
History of diabetes	10508 (7.3)	1.97 (1.83, 2.13)	1.94 (1.80, 2.10)	1.97 (1.82, 2.13)	1.94 (1.80, 2.10)	1.94 (1.79, 2.10)
Total cholesterol (mmol/l)	5.79 (1.09)	1.17 (1.14, 1.21)	1.17 (1.14, 1.21)	1.17 (1.14, 1.21)	1.17 (1.14, 1.21)	1.17 (1.13, 1.20)
HDL cholesterol (mmol/l)	1.38 (0.40)	0.80 (0.76, 0.84)	0.81 (0.77, 0.85)	0.81 (0.77, 0.85)	0.81 (0.77, 0.85)	0.81 (0.77, 0.85)
BMI (kg/m^2)	26.94 (4.56)	1.07 (1.03, 1.11)	-	0.97 (0.92, 1.02)	-	1.04 (1.00, 1.08)
WC (cm)	91.5 (12.6)	-	1.10 (1.06, 1.15)	1.13 (1.07, 1.20)	-	-
WHR	0.90 (0.08)	-	-	-	1.12 (1.08, 1.15)	1.11 (1.07, 1.14)

[†]Hazard ratios (HRs) were adjusted, where appropriate, for age, sex, smoking status, systolic blood pressure, history of diabetes, total cholesterol, HDL cholesterol plus either BMI, WC or WHR.
[‡]Hazard ratios were adjusted, where appropriate, for age, sex, smoking status, systolic blood pressure, history of diabetes, total cholesterol, HDL cholesterol, BMI plus either WC or WHR.
*Models were stratified by sex.
Standard deviations (SDs) were calculated without excluding individuals with BMI values <20kg/m^2. Hazard ratios are presented per 1-SD measured level or compared to relevant reference category.

Table 7.3 Reclassification of 10-year predicted risk of cardiovascular disease after addition of adiposity measure(s) or conventional risk factors to a model including age and sex only

Reclassification (20 studies, 4777 cases, 43944 controls)	**NRI [%] (95% CI)**	**IDI (95% CI)**
Addition of adiposity measures		
BMI	0.55% (-0.42%, 1.53%)	0.0015 (0.0009, 0.0022)
WC	1.29% (0.17%, 2.42%)	0.0027 (0.0018, 0.0035)
WHR	2.66% (1.58%, 3.75%)	0.0029 (0.0021, 0.0037)
BMI & WC	1.11% (-0.02%, 2.23%)	0.0027 (0.0018, 0.0035)
BMI & WHR	2.56% (1.39%, 3.74%)	0.0036 (0.0026, 0.0045)
Weight & height	0.81% (-0.24%, 1.85%)	0.0021 (0.0014, 0.0026)
WC & hip	2.55% (1.33%, 3.77%)	0.0041 (0.0031, 0.0051)
Weight & height & WC & hip	2.93% (1.68%, 4.18%)	0.0048 (0.0038, 0.0059)
Addition of cardiovascular risk factors		
Non-lipid variables[‡]	15.30% (13.52%, 17.08%)	0.0275 (0.0250, 0.0301)
Conventional risk factors[¶]	17.36% (15.49%, 19.23%)	0.0334 (0.0306, 0.0362)

[‡]Smoking status, systolic blood pressure and history of diabetes.
[¶]Smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Model included age and was stratified by sex. Abbreviations: NRI = Net Reclassification Improvement; IDI = Integrated Discrimination Improvement.

Table 7.4 Reclassification of 10-year predicted risk of cardiovascular disease after addition of adiposity measure(s) or total and HDL cholesterol measures to a non-lipid-based model

	Body-mass index	Waist circumference	Waist/hip ratio	Body-mass index & Waist circumference	Body-mass index & Waist/hip ratio	Total & HDL cholesterol
Reclassification (20 studies, 4777 cases, 43944 controls)						
Participants who developed CVD at 10 years						
Appropriately reclassified	159 (3.33%)	201 (4.21%)	211 (4.42%)	205 (4.29%)	243 (5.09%)	509 (10.66%)
Inappropriately reclassified	137 (2.87%)	180 (3.77%)	189 (3.96%)	184 (3.85%)	217 (4.54%)	381 (7.98%)
No change	4481 (93.80%)	4777 (92.02%)	4377 (91.63%)	4388 (91.86%)	4317 (90.37%)	3887 (81.37%)
Participants event free at 10 years						
Appropriately reclassified	1033 (2.35%)	1402 (3.19%)	1572 (3.58%)	1435 (3.27%)	1735 (3.95%)	3095 (7.04)
Inappropriately reclassified	1161 (2.64%)	1538 (3.5%)	1544 (3.51%)	1533 (3.49%)	1752 (3..99%)	3027 (6.89%)
No change	41750 (95.01%)	41004 (93.31%)	40828 (92.91%)	40976 (93.25%)	40457 (92.06%)	37822 (86.07%)
NRI (95% CI)	0.17% (-0.57%, 0.91%)	0.13% (-0.71%, 0.97%)	0.52% (-0.33%, 1.38%)	0.22% (-0.63%, 1.06%)	0.51% (-0.41%, 1.42%)	2.83% (1.56%, 4.11%)
p-value	0.652	0.76	0.231	0.615	0.281	<0.0001
IDI (95% CI)	0.0005 (0.0001, 0.0010)	0.0012 (0.0006, 0.0018)	0.0019 (0.0012, 0.0026)	0.0013 (0.0007, 0.0019)	0.0019 (0.0012, 0.0027)	0.0059 (0.0046, 0.0072)
p-value	0.022	<0.001	<0.001	<0.001	<0.001	<0.0001

Non-lipid-based variables were age, smoking status, systolic blood pressure and history of diabetes. Model was stratified by sex. Abbreviations: NRI = Net Reclassification Improvement; IDI = Integrated Discrimination Improvement.

Table 7.5 Reclassification of 10-year predicted risk and changes in risk discrimination for cardiovascular disease after addition of adiposity measure(s) to a model including conventional risk factors

	Body-mass index	Waist circumference	Waist/hip ratio	Body-mass index & Waist circumference	Body-mass index & Waist/hip ratio
Discrimination (39 studies, 8347 cases, 144795 participants)					
Reference C-Index 0.7325 (0.7274, 0.7376)					
C-Index change (95% CI)	-0.0001 (-0.0005, 0.0002)	-0.0001 (-0.0006, 0.0005)	0.0008 (0.0001, 0.0014)	-0.0000 (-0.0005, 0.0006)	0.0006 (-0.0000, 0.0013)
p-value†	0.430	0.816	0.027	0.933	0.068
p-value‡	Ref	0.627	0.006	0.454	0.009
Reclassification (20 studies, 4777 cases, 43944 controls)					
Participants who developed CVD at 10 years					
Appropriately reclassified	68 (1.42%)	111 (2.32%)	132 (2.76%)	106 (2.22%)	141 (2.95%)
Inappropriately reclassified	73 (1.53%)	110 (2.30%)	136 (2.85%)	116 (2.43%)	142 (2.97%)
No change	4636 (97.05%)	4556 (95.37%)	4509 (94.39%)	4555 (95.35%)	4494 (94.08%)
Participants event free at 10 years					
Appropriately reclassified	507 (1.15%)	806 (1.83%)	1091 (2.48%)	856 (1.95%)	1111 (2.53%)
Inappropriately reclassified	545 (1.24%)	839 (1.91%)	1078 (2.45%)	847 (1.93%)	1116 (2.54%)
No change	42892 (97.61%)	42299 (96.26%)	41775 (95.06%)	42241 (96.12%)	41717 (94.93%)
NRI (95% CI)	-0.19% (-0.70%, 0.32%)	-0.05% (-0.69%. 0.58%)	-0.05% (-0.76%, 0.65%)	-0.19% (-0.83%, 0.45%)	-0.03% (-0.75%, 0.69%)
p-value	0.461	0.867	0.88	0.562	0.93
IDI (95% CI)	0.0001 (-0.0002, 0.0003)	0.0004 (0.0000, 0.0007)	0.0010 (0.0004, 0.0015)	0.0005 (0.0001, 0.0008)	0.0009 (0.0004, 0.0015)
p-value	0.654	0.043	<0.001	0.016	0.001

†p-value is for changes in C-index as compared with a model including conventional risk factors.
‡p-value is for changes in C-index as compared with addition of BMI alone.

Conventional risk factors include age, smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol. The number of individuals classified according to their predicted 10-year cardiovascular risk are reported in Table 7.6. Abbreviations: NRI = Net Reclassification Improvement; IDI = Integrated Discrimination Improvement.

Table 7.6 Reclassification of individuals between predicted 10-year cardiovascular disease risk categories upon addition of BMI, WC or WHR to a model including conventional risk factors

a) BMI

Model without BMI	Model with BMI				Reclassified into new risk categories	
	0-5%	5-10%	10-20%	>20%	Lower	Higher
0-5%						
Cases, n	528	12	0	0	0	12
Non-cases, n	24025	242	0	0	0	242
5-10%						
Cases, n	15	907	26	0	15	26
Non-cases, n	261	9058	189	0	261	189
10-20%						
Cases, n	0	28	1373	30	28	30
Non-cases, n	0	170	6669	114	170	114
>20%						
Cases, n	0	0	30	1828	30	0
Non-cases, n	0	0	76	3140	76	0
Total						
Cases, n	543	947	1429	1858	73	68
Non-cases, n	24286	9470	6934	3254	507	545

b) WC

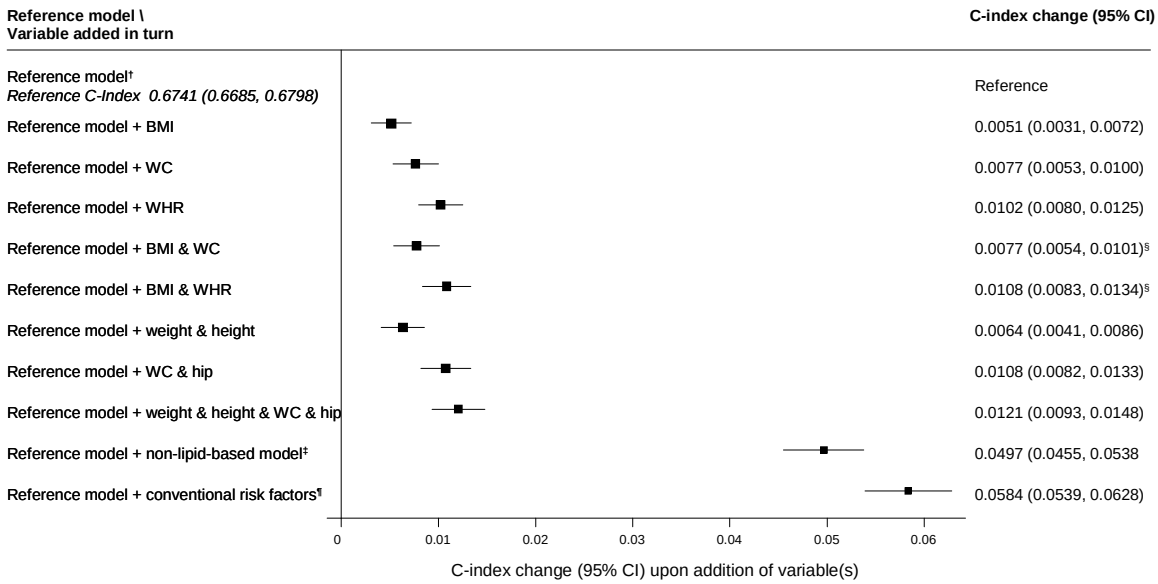
Model without WC	Model with waist circumference				Reclassified into new risk categories	
	0-5%	5-10%	10-20%	>20%	Lower	Higher
0-5%						
Cases, n	517	23	0	0	0	23
Non-cases, n	23902	365	0	0	0	365
5-10%						
Cases, n	20	895	33	0	20	33
Non-cases, n	400	8808	300	0	400	300
10-20%						
Cases, n	0	44	1332	55	44	55
Non-cases, n	0	264	6515	174	264	174
>20%						
Cases, n	0	0	46	1812	46	0
Non-cases, n	0	0	142	3074	142	0
Total						
Cases, n	537	962	1411	1867	110	111
Non-cases, n	24302	9437	6957	3248	806	839

c) WHR

Model without WHR	Model with waist/hip ratio				Reclassified into new risk categories	
	0-5%	5-10%	10-20%	>20%	Lower	Higher
0-5%						
Cases, n	512	28	0	0	0	28
Non-cases, n	23811	456	0	0	0	456
5-10%						
Cases, n	26	880	42	0	26	42
Non-cases, n	501	8627	378	2	501	380
10-20%						
Cases, n	0	48	1321	62	48	62
Non-cases, n	0	374	6337	242	374	242
>20%						
Cases, n	0	0	62	1796	62	0
Non-cases, n	0	0	216	3000	216	0
Total						
Cases, n	538	956	1425	1858	136	132
Non-cases, n	24312	9457	6931	3244	1091	1078

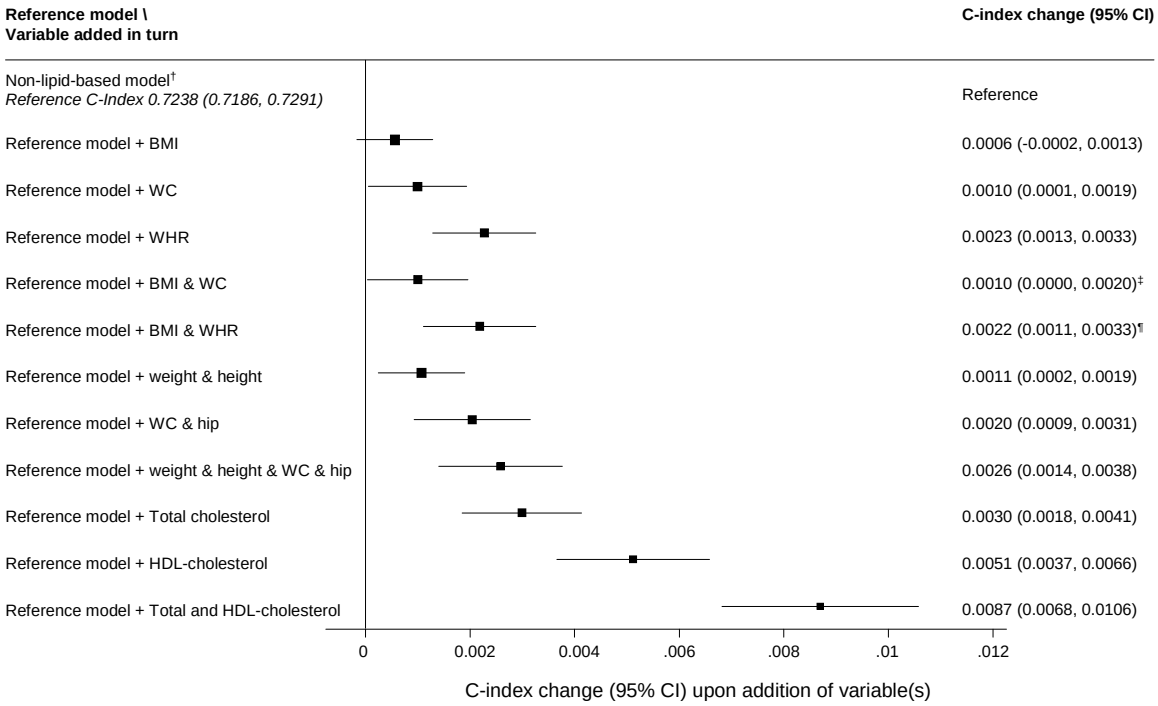
Conventional risk factors include age, smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol.

Figure 7.1 Changes in C-index for cardiovascular disease risk prediction on addition of adiposity measures or conventional risk factors to a model containing age and sex only



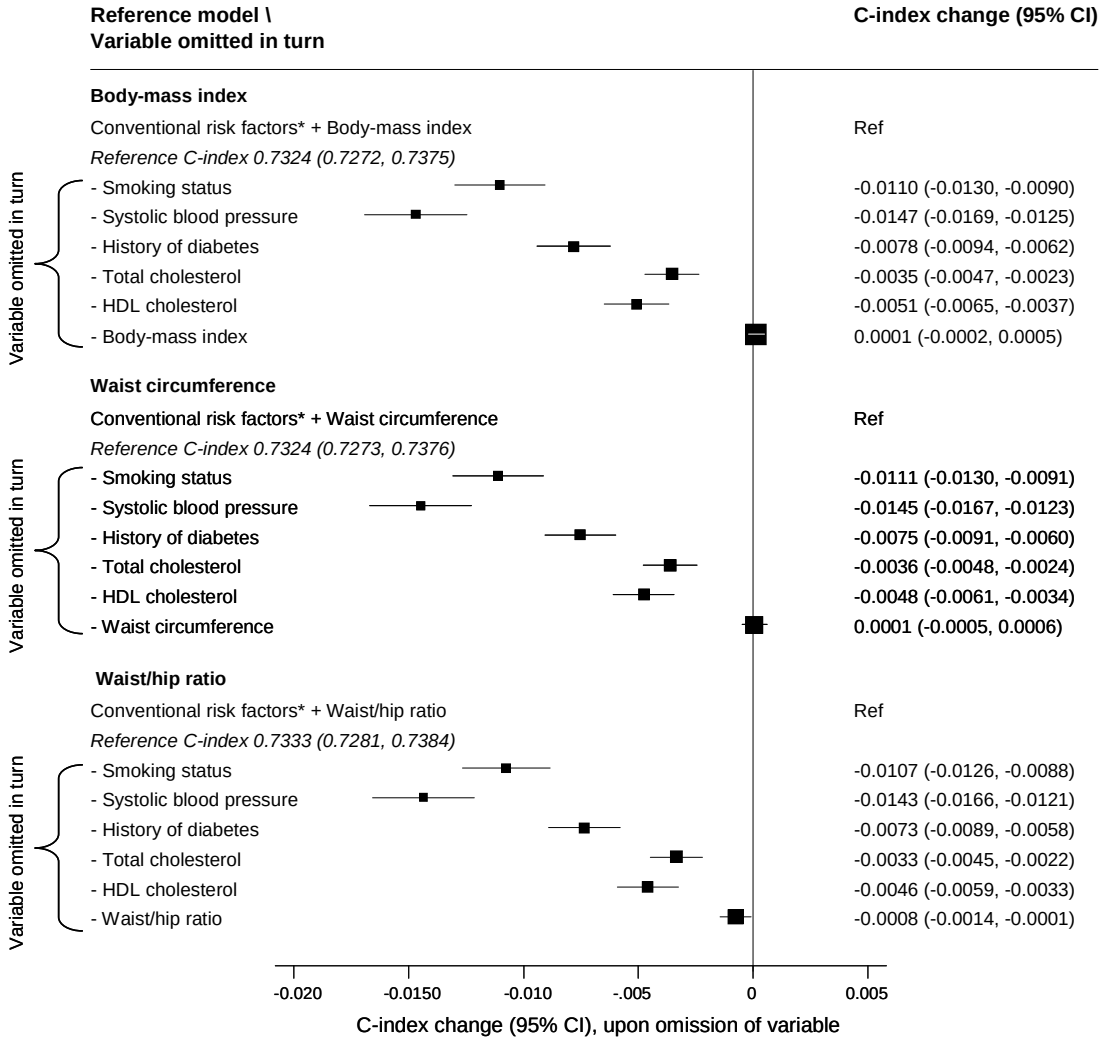
†Reference model includes age and is stratified by sex.
‡Smoking status, systolic blood pressure and history of diabetes.
¶Smoking status, systolic blood pressure, history of diabetes and total and HDL cholesterol.
§p<0.001 for change in C-index after addition of WC or WHR into the reference model plus BMI.

Figure 7.2 Changes in C-index for cardiovascular disease risk prediction on addition of adiposity measures or lipid markers to a non-lipid-based model



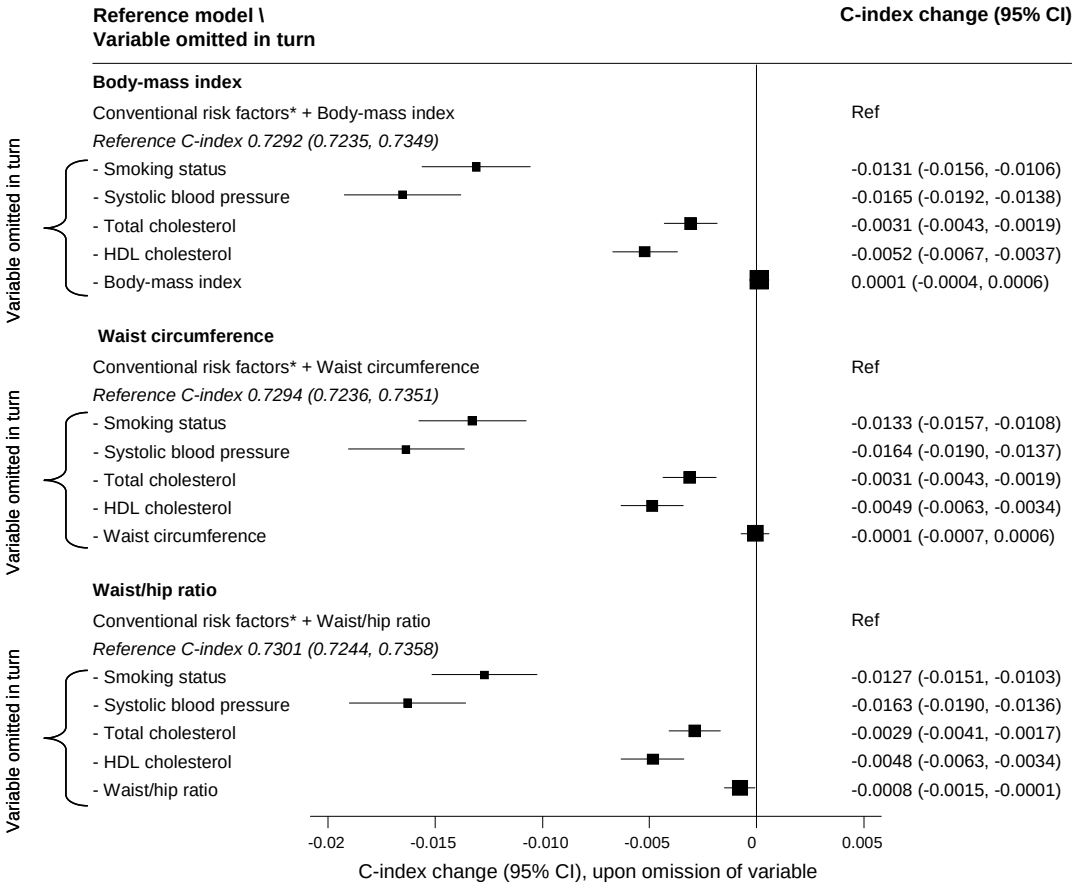
†Non-lipid-base model includes age, smoking status, systolic blood pressure and history of diabetes. Model was stratified by sex.
§p=0.175 for change in C-index after addition of WC into the reference model plus BMI.
¶p<0.001 for change in C-index after addition of WHR into the reference model plus BMI.

Figure 7.3 Changes in C-index for cardiovascular disease risk prediction on omission of individual risk factors from a full model containing conventional risk factors plus BMI, WC or WHR



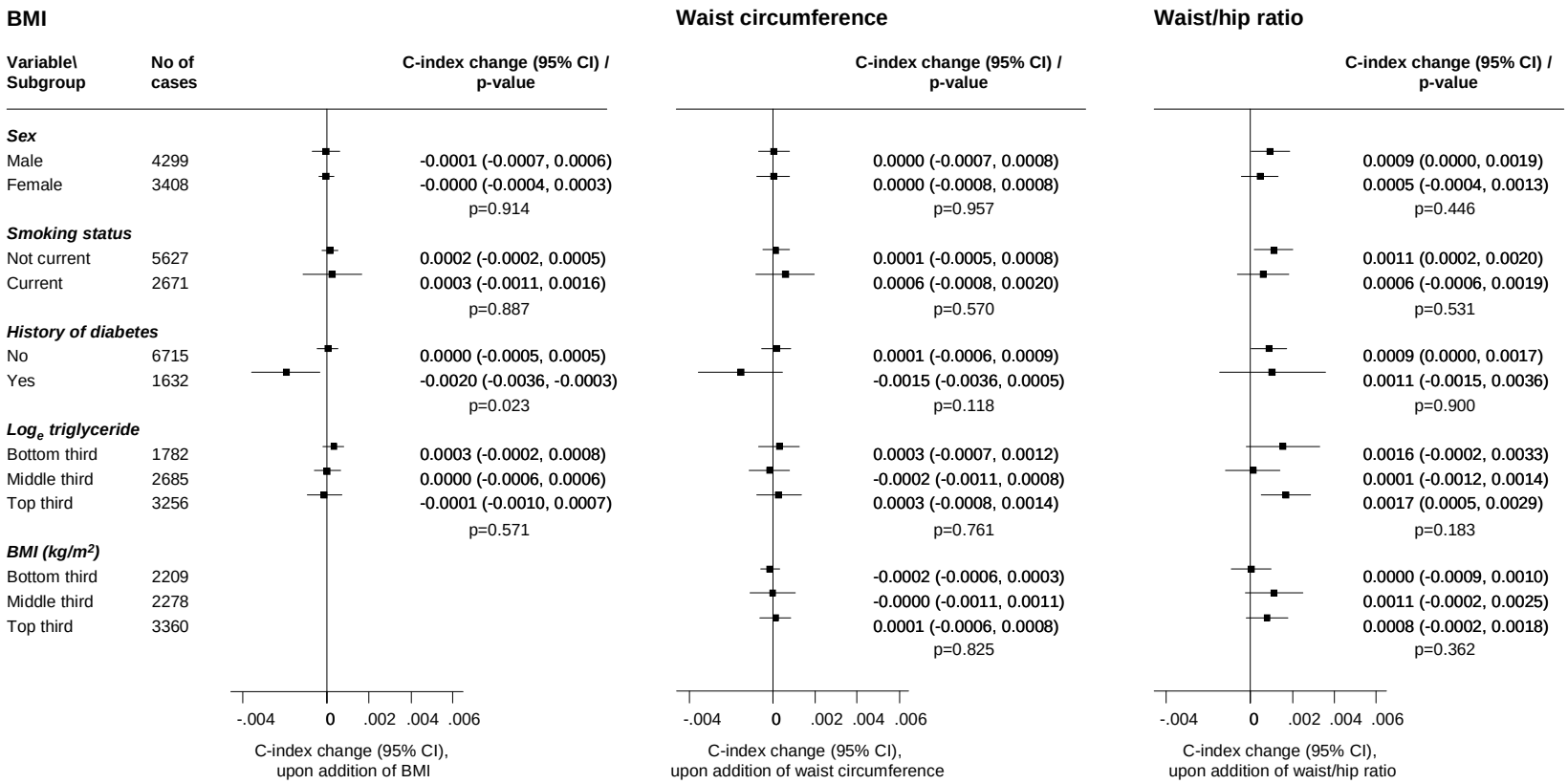
*Conventional risk factors include age, smoking status, systolic blood pressure, history of diabetes, and total and HDL cholesterol. Model was stratified by sex.

Figure 7.4 Changes in C-index for cardiovascular disease risk prediction on omission of individual risk factors from a full model containing conventional risk factors plus BMI, WC or WHR in participants without diabetes at baseline



*Conventional risk factors include age, smoking status, systolic blood pressure, and total and HDL cholesterol. Model was stratified by sex.

Figure 7.5 Changes in C-index for cardiovascular disease risk prediction upon addition of BMI, WC or WHR on top of conventional risk factors, according to different subgroups



Models contain all conventional risk factors (ie, age, systolic blood pressure, smoking status, history of diabetes, and total and HDL cholesterol) with and without inclusion of BMI, WC or WHR. Predictive ability added by BMI, WC or WHR is given, with a p-value testing the null hypothesis of no difference in effect between levels of each subgroup. Error bars indicate 95% confidence limits. In each case only studies with information on both subgroup levels are used. Not all studies used had full information across all subgroups levels, so comparisons across subgroups (eg, men versus smokers) are not reliable due to inclusion of between study differences.

Figure 7.6 Study-specific C-index for cardiovascular disease risk prediction in a model including conventional risk factors

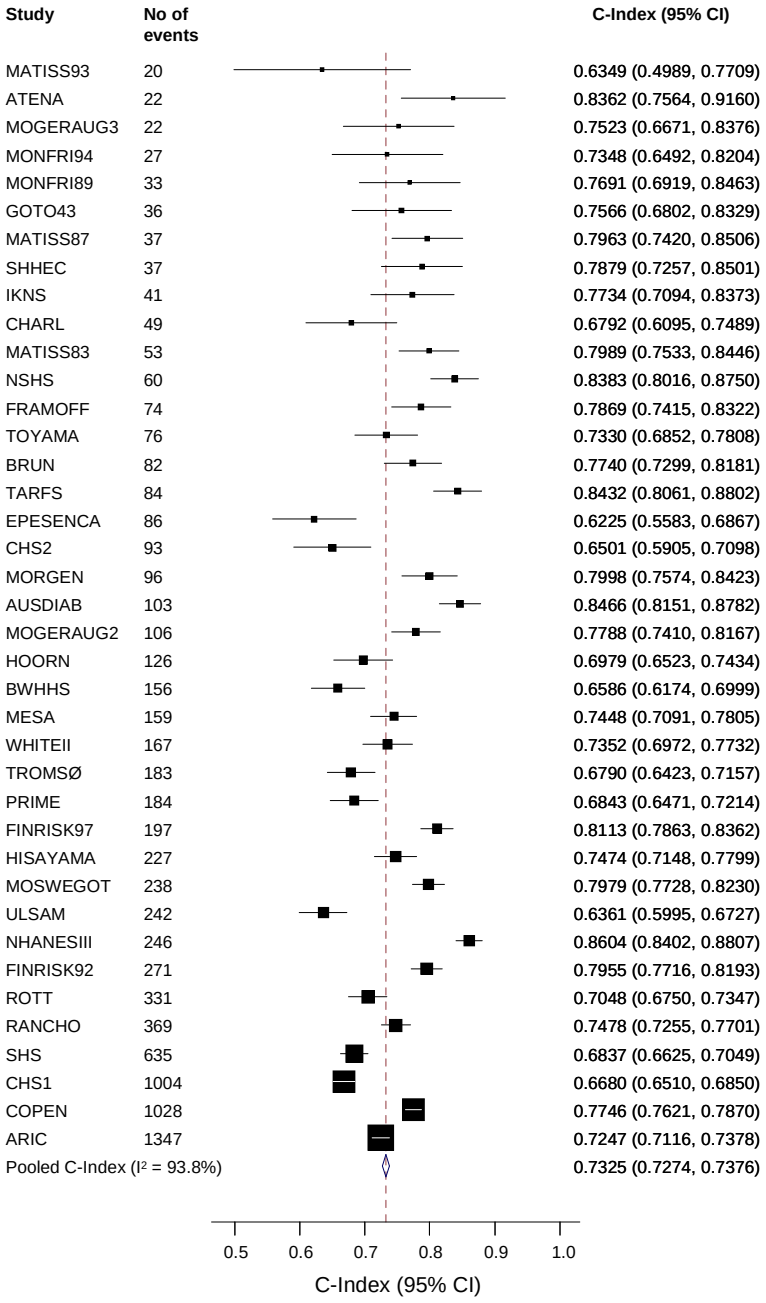
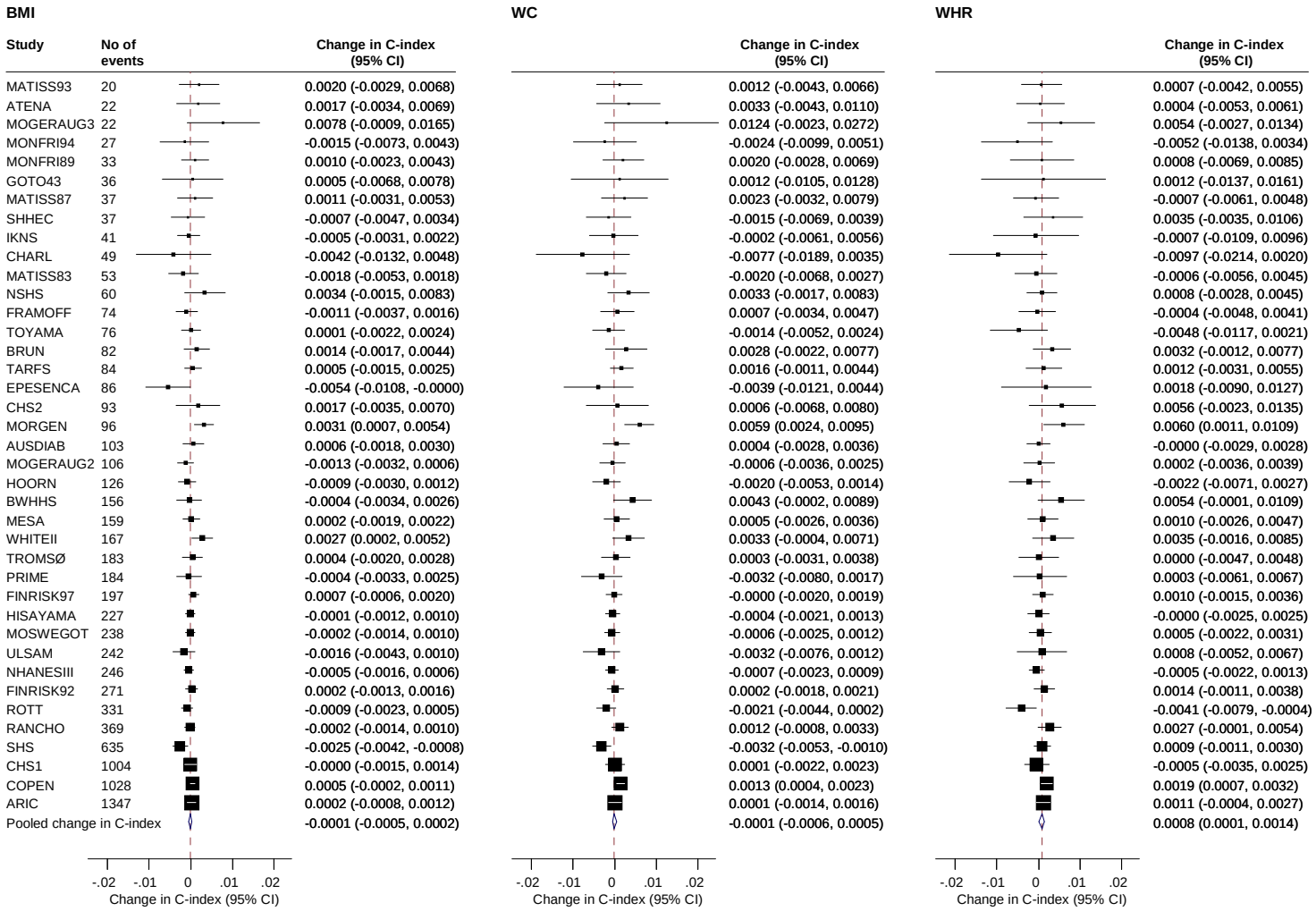


Figure 7.7 Study-specific changes in C-index for cardiovascular disease risk prediction after addition of BMI, WC or WHR to a model including conventional risk factors



I^2 (95% CI) for changes in C-index were 18% (0% to 45%) with BMI, 35% (4% to 56%) with WC and 1% (0% to 37%) with WHR.

CHAPTER 8: Discussion

This thesis used individual participant data from mostly Western prospective studies with information on body-mass index (BMI) and measures of abdominal adiposity, such as waist circumference (WC) and waist-to-hip ratio (WHR), in order to: (i) assess lifestyle and biological correlates of BMI, WC and WHR; (ii) determine the long-term within-person variability in BMI, WC and WHR; (iii) characterise in detail the association of BMI with risk of cardiovascular morbidity and cause-specific mortality under different circumstances in participants with information on BMI only; (iv) characterise in detail the associations of BMI, WC and WHR with risk of coronary heart disease and ischaemic stroke in participants with concomitant information on all three adiposity measures; and (v) investigate the ability of BMI, WC and WHR to predict cardiovascular disease. This final chapter summarises the main findings, discusses the strengths and limitations of the available data, and highlights further studies that are needed to clarify the relevance of adiposity to cardiovascular disease.

Summary of the principal findings

The Emerging Risk Factors Collaboration (ERFC) is an individual participant meta-analysis of more than 120 prospective epidemiological studies with information on lipids, inflammatory and/or metabolic markers, other cardiovascular risk factors, as well as major cardiovascular morbidity and/or cause-specific mortality (**Chapter 2**). 118 prospective studies, involving more than 1 million participants without known history of cardiovascular disease, had information on BMI at baseline examination. 58 of these studies, involving more than 220,000 participants had additional information on waist and hip circumference at baseline examination.

Cross-sectional correlates of adiposity measures

Analyses of individual records from up to 221,934 participants demonstrated that there were approximately linear and strong associations between BMI and WC (r = 0.85), and WHR and WC (r = 0.70), and only moderately strong correlations between BMI and WHR (r = 0.43) (**Chapter 3**). Adiposity measures had broadly similar and approximately linear associations with cardiovascular risk factors, such as blood pressure, fasting glucose and inflammatory markers, and slightly curvilinear associations with lipid markers. In both males and females, BMI, WC and WHR were most strongly associated with blood pressure, high-density lipoprotein (HDL) cholesterol, triglyceride, C-reactive protein (CRP) and interleukin-6 (IL-6). Overall, adiposity measures were higher in individuals of non-European descent, physically

inactive people, people with diabetes, and people with low levels of education. Whereas mean BMI and WC values were somewhat lower in current smokers and current alcohol drinkers, mean WC and WHR values were higher in males than in females. These findings demonstrate that although the correlations between clinical measures of adiposity differ, BMI, WC and WHR are similarly and importantly associated with blood pressure, fasting glucose, lipids and inflammatory markers. This finding highlights the importance of intermediate risk factors on the pathway between excess body fat and cardiovascular disease. Furthermore, the findings suggest possible scope for confounding by lifestyle factors in observational studies of associations of adiposity measures with disease risk.

Within-person variability in adiposity measures

The findings in **Chapter 4** showed that the extent of within-person variability in calculated risk factors can be considerably larger (or smaller) than the within-person variability in its components. Furthermore, analyses of data on over 79,000 serial measurements of BMI, WC and WHR taken on average of 6 years apart in over 42,000 participants from 12 prospective studies demonstrated that the reproducibility in BMI (regression dilution ratio [RDR] 0.96) was superior to that of WC (RDR 0.88) and WHR (RDR 0.66). The within-person variability in adiposity measures was not materially influenced by several characteristics (such as age, smoking status, blood pressure and lipids), although the RDR of WHR varied somewhat by sex, diabetes status and baseline WHR values. These findings suggest that the degree of underestimation of the magnitude of association with disease risk is smaller for baseline measures of BMI than for WC and WHR.

Associations of BMI with disease risk

Over 31,000 non-fatal myocardial infarctions or strokes and almost 130,000 deaths were recorded during approximately 15.0 million person-years at risk in more than 1 million participants from 118 prospective studies, mainly from Western populations (**Chapter 5**). In analyses adjusted for age, sex and smoking status, and excluding participants with BMI values below 20 kg/m^2, there were nearly log$_e$-linear associations with risk of coronary heart disease, ischaemic stroke and all cardiovascular mortality. Risk ratios per 5 kg/m^2 baseline BMI change, adjusted for age, sex and smoking status, were 1.31 (95% confidence interval [CI] 1.26-1.36) for coronary heart disease and 1.23 (95% CI 1.18-1.29) for ischaemic stroke. These associations were largely explained by long-term average levels of mediating risk factors, such as blood pressure, history of diabetes, lipids and inflammatory markers (although the causal

relevance of some inflammatory markers is uncertain). Risk ratios for coronary heart disease were significantly greater in some groups at lower absolute risk – ie, in people without history of diabetes, at early middle age and at lower-than-average systolic blood pressure (SBP). Across the full range of BMI values, BMI had curvilinear associations with all-cause mortality, including most site-specific cancers and non-vascular conditions not attributed to cancer. In participants with BMI values of 25 kg/m^2 or higher, particularly strong positive relationships were observed with risk of death from diabetes and renal disease. By contrast, among participants with BMI values below 25 kg/m^2, the negative association of BMI was predominantly due to the strong negative associations with death due to respiratory disease and cancers of the lung and upper aerodigestive tract.

Associations of adiposity measures with risk of coronary heart disease and ischaemic stroke

A large multinational retrospective case-control study has reported that WHR is three times more strongly associated to risk of acute myocardial infarction than is BMI, suggesting that WHR should replace BMI as the principal clinical measure of adiposity.[1] However, in prospective analyses that involved 221,934 individuals with concomitant information on height, weight, waist and hip circumference, there were nearly log_e-linear associations between BMI, WC and WHR, and risk of coronary heart disease and ischaemic stroke across the range of values, except at low BMI (**Chapter 6**). After excluding participants with BMI values below 20 kg/m^2, age, sex and smoking status adjusted risk ratios for coronary heart disease and ischaemic stroke were broadly similar for one standard deviation change of BMI, WC and WHR. These risk ratios reduced considerably after further adjustment for intermediate risk factors, such as SBP, history of diabetes, total and HDL cholesterol. Whereas these risk factors explained coronary risk to a similar extent, the risk reduction for ischaemic stroke was mainly due to blood pressure. The effect of abdominal adiposity on the risk of coronary heart disease and ischaemic stroke was largely independent of BMI. The risk ratios were about three-to-four fold stronger in participants at early middle age than at older ages, but otherwise did not vary materially by sex, method of adiposity assessment (ie, self-reported versus assessed by a trained person) and other characteristics recorded. These findings refute previous recommendations to adopt WHR instead of BMI as the principal clinical measure of adiposity.

Adiposity measures in risk prediction

National and international guidelines have provided differing recommendations about the value of clinical measures of adiposity for prediction of cardiovascular risk in primary prevention.[2] Recommendations range from omission of adiposity measures, to inclusion of such measures as additional screening tests, to formal inclusion of such measures as risk factors in prediction models. Furthermore, it has been suggested to replace assessment of lipid measures with that of adiposity measures in resource-limited settings where cholesterol testing is not feasible for cardiovascular disease risk assessment.[3] In analyses of 114,795 healthy participants with concomitant information on weight, height, waist and hip circumference, lipids and other conventional risk factors, BMI, WC and WHR did not importantly improve risk discrimination, nor classification of participants to risk categories of predicted 10-year risk when information was available lipids and other conventional risk factors (**Chapter 7**). Regarding the replacement of lipids with adiposity measures, the results have shown that a combination of BMI and WHR provides only about one-quarter of the predictive information provided by total and HDL cholesterol. These findings indicate that for population-wide assessment of cardiovascular disease risk, simple adiposity measures provide little or no additional information about cardiovascular disease risk prediction given knowledge about risk factors used in standard risk scores. They also highlight the desirability of supporting the development of lipid assessment in resource-limited settings.

Strengths and limitation of current data

The findings of this thesis differ from previous reports on adiposity measures and cardiovascular risk in several important ways that enhance its scientific value and accuracy. First, the dataset is large; the data compass 118 prospective studies with information on BMI at baseline examination and 58 prospective studies with complete information on weight, height, and waist and hip circumference at baseline examination, thereby reducing scope for random error and avoiding undue emphasis on the results of any particular study. Second, in contrast to previous individual participant data meta-analyses,[4-6] the dataset has concomitant information on BMI, WC, WHR and conventional risk factors, allowing reliable examination of the predictive ability of BMI, WC and WHR in context of standard risk scores. Third, harmonisation of individual records has enhanced consistency across studies, allowed use of common outcome definitions and consistent approaches to adjustment for potential confounders and biological mediators. Fourth, individuals with known history of cardiovascular disease were excluded from the analysis, limiting any effects of clinically evident disease on

weight or abdominal adiposity (ie, minimising any reverse causality). Fifth, use of data on several individuals with repeat measurements has allowed investigation of within-person variability in adiposity measures (and other covariates). Sixth, the dataset has enabled to reliably examine associations with coronary heart disease, ischaemic stroke and non-vascular conditions, and to explore the degree to which any associations can be explained by potential confounders and biological mediators. Seventh, the data has allowed detailed investigation of potential sources of heterogeneity, including comparison of associations at different levels of BMI and other cardiovascular risk factors. Finally, the analyses have used more appropriate statistical methods, including use of consistent within-study comparisons and incorporation of potential between-study heterogeneity into risk estimates.

The limitations of the current data also merit consideration. Although analyses were restricted to individuals without known history of cardiovascular disease at baseline examination, and subsidiary analyses excluded the first five years of follow-up, residual biases (ie, reverse association) may still remain because of subclinical or unreported prevalent disease. Second, not all studies recorded all possible variables of interest. For instance, only a fifth of the participants with data available on BMI had also concomitant information on waist and hip circumference. Statistical methods such as multiple imputation techniques in meta-analytical settings are under development, but beyond the scope of this thesis.[7] Third, despite the consistency of the results across studies in many countries, participants in the ERFC were predominantly from Western populations. Future studies should also investigate whether the current findings can be generalised to people from other ethnic groups or from low-income countries.[8] Fourth, because the ERFC had only information on the severity of adiposity, this thesis could not assess the impact of the duration of adiposity on intermediate risk factors and disease risk. Furthermore, additional studies are needed to better understand to what extent obesity, particularly in children and young adults, relates to the development of intermediate risk factors and cardiovascular disease in adulthood. Fifth, despite the large size of the dataset, this thesis could not examine associations of BMI, WC and WHR with cause-specific mortality. Future prospective studies will be required to examine whether measures of abdominal adiposity have different associations with risk of death from specific cancer sites and other non-vascular conditions than has BMI. Sixth, this thesis considered single measurements of adiposity measures for cardiovascular risk prediction. Future studies should also investigate the relevance of changes in body size for prediction of subsequent cardiovascular disease. Seventh, any preferential diagnosis of cardiovascular disease in people who were overweight

or obese may have tended to overestimate associations. Eighth, the ERFC had information only on adiposity estimated indirectly by anthropometric indicators. Large studies are needed that concurrently assess several additional adiposity markers not assessed in the current analyses, including direct measures of abdominal adiposity or skinfold thickness,[9] as well as circulating concentrations of adipocytokines.[10,11] Lastly, because the current findings are based on observational data they cannot, of course, establish any causal relationships of adiposity with cardiovascular disease.

Ongoing and future studies

Further clarification of the role of clinical measures of adiposity for non-vascular conditions

It has been suggested that measures of abdominal adiposity (eg, WC or WHR) are more strongly associated with risk of death from some cancers and other non-vascular conditions than is BMI.[5,12-20] Because previous studies generally have had limited numbers of specific outcomes, adjusted inconsistently for confounders and mediators, or reported on adiposity measures in relation to one (or few) selected or aggregated conditions only, there is a need for adequately powered, standardised assessment of associations of BMI, WC and WHR with the risk of death from a broad range of causes. The ERFC will therefore extend analyses to adiposity measures in relation to risk of cause-specific mortality. In order to obtain adequate statistical power, I will identify new relevant prospective studies with available data and invite them to join the ERFC, as well as ask current ERFC collaborators whether they would like to provide further data on adiposity measures and/or cause-specific mortality.

Further clarification on the role of other adiposity measures

Although the current analyses indicated that BMI and measures of abdominal adiposity, such as WC and WHR, are each associated with risk of cardiovascular disease, these relationships may have been underestimated due to imprecise assessment of body fat and body composition by these indirect measures of adiposity. Several other methods of measurement of overall body fatness and body fat distribution have been proposed for large-scale epidemiological studies. Skinfold measures the thickness of the skin and subcutaneous fat mass which can be used to estimate overall body fatness.[21] Because most research on skinfold thickness has been focused on children and young adults, less is known on the association of skinfold thickness with cardiovascular disease risk in adults. Larger subscapular skinfold has been associated with greater risk of coronary heart disease in previous studies,[22] but it is uncertain how skinfold measures relate to cardiovascular disease compared to other

measures of adiposity.[23,24] Existing population-based prospective studies could help to address such uncertainties. For example, triceps, subscapular and abdominal skinfolds, as well as weight, height and WC have been measured in 19,000 initially healthy participants in the prospective Reykjavik Study. This study was initiated in 1967 and indentified participants resident in Reykjavik, Iceland, through population registers.[25] All participants were monitored subsequently for cause-specific mortality and cardiovascular morbidity, with a loss of follow-up of only about 0.6% to date. To enable assessment of any confounding and mediation, the study collected data on a range of cardiovascular risk factors, such smoking, blood pressure, lipids and inflammatory markers. Analyses of such data should help to examine the association of skinfold thickness with risk of cardiovascular disease, and to compare it with that of other adiposity measures.

As discussed in **Chapter 1** on page 8, Dual-energy X-ray Absorptiometry (DXA) measures total and regional body composition, including the estimation of fat-free mass, fat mass and bone mineral content.[26] The most accurate methods available to measure body composition at the tissue level are imaging methods, such as magnetic resonance imaging and computed tomography. It has been suggested that visceral adipose fat depot is more strongly associated with metabolic disease risk than are other fat depots.[27-32] While WC and WHR are reasonably good markers of abdominal adiposity, they have been criticised for being poor surrogates of visceral adiposity, as they may not distinguish visceral adipose tissue from abdominal subcutaneous adipose tissue, which is only possible by use of imaging techniques.[33,34] However, such data from large-scale epidemiological studies are currently lacking. Generation of new observational data with accurate measurement of body fat and body fat distribution will therefore provide new insights into the association of adiposity with cardiovascular disease. For example, adiposity is being assessed in 500,000 people aged 40 to 69 in the UK Biobank study.[35] This prospective study is a major medical research initiative with the aim of improving the prevention, diagnosis and treatment of a wide range of conditions, such as cancer, cardiovascular disease or dementia. Following piloting in 2005-2006, UK Biobank started recruiting participants with detailed information on lifestyle, environment and genes in 2008. While weight, height, waist and hip circumference are measured in all participants, UK Biobank also measures amount and distribution of body fat in approximately 100,000 participants using DXA and imaging methods.[36] New data from this study should substantially advance understanding of body fat distribution with risk of cardiovascular disease, as well as non-vascular conditions.

Further clarification of biomarkers of adiposity

As discussed in detail in **Chapter 1** on pages 5-7, adipocytokines released by adipose tissue are believed to be involved in development of atherosclerosis via inflammatory processes.[37] Available data from prospective studies on adipocytokines and cardiovascular disease risk, however, are sparse.[10,11,38,39] For instance, only a few studies, involving a total of about 1,300 coronary disease cases, have reported associations of adiponectin and/or leptin levels with risk of coronary heart disease, yielding largely inconsistent findings.[40-46] Observational data on adipocytokines from large population-based studies should help to better understand mechanisms by which adiposity increases cardiovascular risk. For instance, adiponectin and leptin have been measured in a nested case-control study within the prospective Reykjavik Study. 1,917 participants had a coronary event during follow-up; 3,618 controls (frequency-matched to cases with respect to calendar year of recruitment, sex and age) were free from coronary heart disease at the end of the study period. In preliminary analyses, lower adiponectin was associated with a greater risk of coronary heart disease, even after adjustment for several conventional risk factors, including BMI (**Table 8.1**). By contrast, leptin levels were not associated with risk of coronary heart disease. Such analyses on adiponectin, leptin and possibly other adipocytokines should advance understanding of the biological pathways through which the adverse vascular effects of excess body fat are mediated.

Further clarification on the role of adiposity measures in other ethnic groups

Since most previous studies were conducted in participants from Western populations,[4-6] less is known about the relationship between adiposity measures and risk of cardiovascular disease in other ethnic groups, such as South-Asians. The Pakistan Risk of Myocardial Infarction Study (PROMIS) and the Bangladesh Risk of Acute Vascular Events (BRAVE) study are two case-control studies based in South Asia. PROMIS has already collected information on BMI, WC and WHR, and several other established and emerging risk factors in 10,000 individuals with first-ever acute myocardial infarction and 10,000 controls.[47] Furthermore, it measured around 45,000 genetic markers using Illumina "cardiochip" array, and performed a genomewide association scan (GWAS) in 20,000 individuals using the Illumina 610-Quad array. Since Pakistan generally has a high prevalence of obesity and high rates of cardiovascular disease, this study should provide complementary insights into the relevance of adiposity to cardiovascular disease as compared with studies in European populations. BRAVE is a new global vascular research initiative that is currently in the pilot phase. The target of the study is to recruit at least 10,000 individuals with a first-ever confirmed myocardial infarction, and

10,000 patients with computer tomography-confirmed stroke events, and one control per case. BRAVE will collect information on various cardiovascular risk factors, including BMI, WC and WHR. Contrary to observations from Western and East Asian populations, a recent prospective study has shown that higher BMI is not associated with greater risk of death in Bangladeshis.[48] BRAVE should provide further insights into the relationship of adiposity measures with cardiovascular disease in the Bangladeshi population

Besides studies in South Asians, there are other large prospective studies, such as the Kadoorie Study and the Mexico City Study that may provide complementary information on the role of adiposity measures to the risk of cardiovascular disease.[49,50] The Kadoorie Study of Chronic Disease in China (KSCDC) is a prospective blood-based study, involving 500,000 middle aged adults in 10 different parts of China.[49] The Mexico City Prospective Study recruited about 150,000 men and women in order to assess the associations of established and new risk factors with risk of cause-specific deaths in Mexico City.[50] Both studies collected information on height, weight, waist and hip circumferences and other established and emerging risk factors to enable detailed investigation of the association of adiposity measures with risk vascular and non vascular mortality outcomes in non-Western populations.

Further clarification on the role of adiposity in children and young adults

Evidence on the impact of the duration of obesity on the risk of mortality is sparse.[51] Furthermore, it is unclear to what extent body fatness and body distribution in adolescence relates to the development of intermediate risk factors and to increased cardiovascular risk, and whether such risk is independent of adiposity in adulthood.[52-54] Birth cohorts, such as the Avon Longitudinal Study of Parents and Children (ALSPAC),[55,56] should address such uncertainties in the future. ALSPAC is a longitudinal population based birth cohort that recruited 14,000 pregnant women with expected delivery between 1991 and 1992. Since then, all offspring are monitored and invited regularly for follow-up examinations to obtain detailed information on various characteristics, including body composition. Such data collected throughout the life course should help to better understand the relevance adiposity in childhood or young adults for the development of cardiovascular disease in later life.[57]

Conclusion

BMI, WC and WHR each have similar magnitudes of association with risk of cardiovascular disease. This argues against previous suggestions to adopt WHR instead of BMI as the principal clinical measure of adiposity. Furthermore, these adiposity measures do not importantly improve cardiovascular risk prediction when additional information exists on blood pressure, history of diabetes and cholesterol measures. To investigate the relevance of adiposity to cardiovascular disease, large studies are needed that concurrently assess several additional adiposity markers, including direct measures of abdominal adiposity or skinfold thickness, as well as circulating concentrations of adipocytokines.

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Table 8.1 Associations of baseline levels of adiponectin, leptin and BMI with coronary heart disease risk in the Reykjavik Study

Adiposity marker	Adjusted for age, sex and period	Adjusted for age, sex, period and conventional risk factors	Adjusted for age, sex, period, conventional risk factors and inflammatory markers	Adjusted for age, sex, period, conventional risk factors, inflammatory markers and BMI
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Log_e adiponectin[†]	1.24 (1.10-1.41)	1.24 (1.09-1.41)	1.22 (1.06-1.41)	1.18 (1.02-1.36)
Log_e leptin	1.20 (1.04-1.37)	1.13 (0.98-1.31)	1.07 (0.92-1.26)	0.95 (0.79-1.14)
BMI	1.40 (1.25-1.56)	1.30 (1.15-1.46)	1.22 (1.07-1.39)	NA

Odds ratios (OR) are presented per two standard deviations higher baseline values in adiposity markers. "Period" refers to calendar year of recruitment. Conventional risk factors are smoking status, systolic blood pressure, history of diabetes and total cholesterol. Inflammatory markers are C-reactive protein, interleukin 6 and albumin.
[†]Odd ratios are presented per two standard deviations lower adiponectin.

APPENDIX 1: List of publications authored during PhD

Published or in press

1. The Emerging Risk Factors Collaboration. **Wormser D**, Kaptoge S, Di Angelantonio E et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet.* 2011;377:1085-1095.

2. **Wormser D**, Di Angelantonio E, Sattar N, Collins S, Thompson S, Danesh J. Body-mass index, abdominal adiposity, and cardiovascular risk – Authors' reply. *Lancet.* 2011;378:228.

3. The Emerging Risk Factors Collaboration (member of coordinating centre). Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med.* 2011;364:829-841.

4. The Emerging Risk Factors Collaboration (member of the coordinating centre). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375:2215-2222.

5. Saleheen D, Alexander M, Rasheed A, **Wormser D** et al. Association of the 9p21.3 locus with risk of first-ever myocardial infarction in Pakistanis: case-control study in South Asia and updated meta-analysis of Europeans. *Arterioscler Thromb Vasc Biol.* 2010;30:1467-1473.

6. **Wormser D**, Seshasai SR, Ray KK. Obesity as a risk factor for cardiovascular disease. In: Purcell H, ed. *Non communicable chronic diseases, diabetes and obesity, a future clinical challenge*. London: National Services for Health Improvement. (In press)

Submitted or in preparation

7. The Emerging Risk Factors Collaboration. **Wormser D**, Di Angelantonio E, Kaptoge S et al. Adult stature and risk of cause-specific death and vascular morbidity in 1 million people: individual-participant meta-analysis. (Submitted)

8. The Emerging Risk Factors Collaboration (member of coordinating centre). Assessment of C-reactive protein or fibrinogen to predict cardiovascular disease. (Submitted)

9. IL6R Genetics Consortium and Emerging Risk Factors Collaboration (member of the coordinating centre). Interleukin-6 receptor pathways and coronary heart disease. (Submitted)

10. The Emerging Risk Factors Collaboration (member of the writing committee). Lipid-related markers and cardiovascular disease prediction. (Submitted)

11. **Wormser D**, Wood AM et al. Within-person variability in calculated variables: estimating the aetiological association between adiposity measures and risk of coronary heart disease. (In preparation)

12. The Emerging Risk Factors Collaboration. Associations of established and emerging risk factors with coronary heart disease, ischaemic stroke and haemorrhagic stroke. (In preparation)

APPENDIX 2: Rationale for using standard deviation changes in long-term average levels for comparing aetiological associations of risk factors with different degrees of within-person variability

Introduction

The extent of within-person variability may be of importance when taking into account regression dilution bias and making direct comparisons of the strength of association with outcome of risk factors with different degrees of within-person variability. **Chapter 6** compares the magnitudes of association of adiposity measures, such as body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with risk of cardiovascular disease. Such comparisons are straightforward when the effect of within-person variability is ignored (ie, analyses using measured ["baseline"] values). Assuming $\log_e$-linear relationships with cardiovascular disease risk, associations are generally compared per standard deviation changes in baseline values of adiposity measures.[1] Because of different degrees of within-person variability in adiposity measures, however, the interpretation of these findings becomes more complicated when associations are also corrected for regression dilution bias and use of baseline standard deviation as unit to compare associations may be inappropriate.

Using data on adiposity measures from the Emerging Risk Factors Collaboration (ERFC), this appendix shows how to compare magnitudes of associations of risk factors with different degrees of within-person variability taking into account regression dilution bias.

Methods

Details of data on adiposity measures in the ERFC are given in **Chapter 2**. The current analysis involved individual records from 42,300 participants from 12 prospective studies with the following features: (1) participants were not selected on the basis of having previous cardiovascular disease; (2) concomitant information was provided on height, weight, waist and hip circumference at initial ("baseline") examination and at resurvey; and (3) at least 1 year of follow-up had been accrued.

The statistical methods have been described in detail in **Chapter 5** on pages 111-116. Risk ratios for BMI, WC and WHR were calculated in relation to first-ever non-fatal or fatal coronary heart disease. To investigate the impact of different degrees of within-person variability in adiposity measures on these associations, risk ratios were corrected for regression dilution

bias and presented per one standard deviation higher baseline and long-term average ("usual") levels. Correction for the effect of within-person variability in adiposity measures was achieved by use of conditional expectations of long-term average levels of adiposity measures adjusted for age, sex and smoking status, which were predicted from the Rosner regression calibration models.[2,3] Usual levels of adiposity ratios were estimated by regressing repeat measurements of adiposity ratios on the baseline values of the ratios. Analyses involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random effects meta-analysis.[4] Evidence of heterogeneity was indicated by the I^2 statistic.[5]

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Concomitant baseline and repeat information on height, weight, and waist and hip circumference were available in 42,300 participants from 12 prospective studies, among whom there were 3,484 coronary events. Without correction for regression dilution bias, risk ratio of coronary heart disease per one standard deviation higher baseline BMI, WC and WHR were broadly similar (**Table A2.1**). Similar results were observed in analyses that corrected for regression dilution bias and calculated risk ratios per one standard deviation changes in usual levels of adiposity measures. In such corrected analyses that calculated risk ratios per one standard deviation higher baseline adiposity measure, however, coronary heart disease was distinctly more strongly associated with WHR than with BMI or WC.

Discussion

Risk ratios for coronary heart disease per one standard deviation higher usual levels of BMI, WC and WHR are similar, but quite different conclusions could be drawn had the regression-dilution-corrected associations been presented per standard deviation of baseline levels. This contrast is worthy of further thought. The objectives of many aetiological studies are to estimate associations between usual levels of risk factors and the likelihood of disease, expressed as risk of ratios for some appropriate unit change in the risk factors. For continuous variables, the measure of unit change is often chosen as a standard deviation in the observed baseline risk factor, which allows (i) direct comparisons of risk associations for several baseline risk factors measured on different scales, uncorrected for within-person variability, and (ii)

direct comparisons of risk associations for a single risk factor before and after correction for within-person variability. It is arguable, however, whether use of baseline standard deviation as the unit of change for comparison between different risk factors would be valid after correction for within-person variability. Correcting for within-person variability in a single risk factor can be viewed as shrinking the observed distribution of the risk factor to its true usual distribution, and the degree of shrinkage will depend on the extent of within-person variability. Thus, for risk factors with substantial within-person variability, the standard deviation for the usual levels could be much smaller than the standard deviation of the observed baseline levels. Given the aetiological objectives, it is more appropriate to present the risk of ratios per standard deviation change in the usual levels to allow a direct comparison of risk associations between usual levels of several risk factors with different degrees of within-person variability, such as presented for the different adiposity measures. These results may closely resemble the risk associations uncorrected for within-person variability, as one might expect from using smaller unit changes that counteract the effect of correcting for regression dilution bias. Further statistical investigations are warranted in this area.

Conclusion

Aetiological associations of risk factors with different degrees of within-person variability should be compared per standard deviation changes in usual levels in analyses corrected for regression dilution.

Appendix 2 – References

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3. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med.* 2009;28:1067-1092.
4. Emerging Risk Factors Collaboration. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol.* 2010;39:1345-1359.
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Table A2.1 Associations of BMI, WC, WHR and waist-to-height ratio (WHtR) with coronary heart disease risk, with and without correction for within-person variability

	Baseline levels			Usual levels					RDR
Coronary heart disease (12 studies & 3351 cases)	**1-SD (BL)**	**RR (95%CI)**	**I^2 (95% CI)**	**1-SD (BL)**	**RR (95%CI)**	**1-SD (UL)**	**RR (95%CI)**	**I^2 (95% CI)**	
Body-mass index	4.95	1.26 (1.17 to 1.37)	69 (44 to 83)	4.95	1.29 (1.18 to 1.40)	4.76	1.28 (1.17 to 1.38)	69 (45 to 83)	0.96 (0.94, 0.98)
Waist circumference	13.29	1.30 (1.20 to 1.40)	64 (33 to 81)	13.29	1.35 (1.23 to 1.47)	11.65	1.30 (1.20 to 1.40)	65 (34 to 81)	0.88 (0.86, 0.91)
Waist/hip ratio	0.084	1.30 (1.18 to 1.44)	79 (65 to 88)	0.084	1.50 (1.29 to 1.74)	0.061	1.34 (1.20 to 1.50)	79 (65 to 88)	0.66 (0.59, 0.72)
Waist/height ratio	0.080	1.31 (1.21 to 1.42)	66 (38 to 82)	0.080	1.37 (1.25 to 1.50)	0.071	1.32 (1.22 to 1.43)	67 (39 to 82)	0.88 (0.85, 0.91)

Risk ratios (RRs) and regression dilution ratios (RDRs) were adjusted for age, sex and smoking status. Analyses were restricted to participants with BMI values ≥20kg/m^2. Abbreviations: BL = baseline levels; UL = usual levels.

APPENDIX 3: Adult stature and risk of cause-specific death and vascular morbidity in 1 million people

Summary

The extent to which adult stature, a biomarker of the interplay of genetic endowment and early-life experiences, is related to risk of diseases of late-onset is uncertain. This appendix reports prospective analyses of individual participant data from over 1 million participants in 121 studies with more than 170,000 deaths or major non-fatal vascular outcomes. The data demonstrate that for people born between 1900 and 1960, mean adult height increased by 0.5 to 1.0 cm with each successive decade of birth. After adjustment for age, sex, smoking status and year of birth, risk ratios per 6.5 cm greater height were 0.97 (95% confidence interval [CI] 0.96-0.99) for death from any cause, 0.94 (95% CI 0.93-0.96) for death from vascular causes, 1.04 (95% CI 1.03-1.06) for death from cancer and 0.92 (95% CI 0.90-0.94) for death from other causes. Height was negatively associated with death from coronary disease, stroke subtypes, heart failure, stomach and oral cancers, chronic obstructive pulmonary disease, mental disorders, liver-disease and external causes. In contrast, height was positively associated with death from ruptured aortic aneurysm, pulmonary embolism, melanoma, and cancers of the pancreas, endocrine and nervous systems, ovary, breast, prostate, colorectum, blood and lung. At the two extremes, risk of melanoma death was 25% higher per 6.5 cm increment in height, whereas risk of death from chronic obstructive pulmonary disease was 15% lower. Risk ratios were not appreciably altered after further adjustment for adiposity, blood pressure, lipids, inflammation, diabetes mellitus, alcohol consumption or socioeconomic indicators. These findings demonstrate that adult stature has multiple opposing relationships with death from vascular, neoplastic, respiratory and other causes, independent from major risk factors.

Background

Because adult stature is a widely available biomarker that reflects the interplay of genetic endowment and various early-life experiences and exposures (such as fetal, dietary, social and psychological circumstances),[1-5] the study of height could reveal insights into patterns of shared and differing early determinants of major diseases of later life. Previous studies have suggested that there is a weakly negative association between adult height and death from any cause, which is mainly due to the well-established inverse association between stature and risk of coronary disease.[6-9] However, previous studies have been underpowered to consider associations of adult height with other common vascular outcomes (such as stroke subtypes, heart failure, pulmonary embolism or ruptured aortic aneurysm)[10,11] and with a broad range of nonvascular causes, such as site-specific cancers and nonvascular diseases other than cancer, such chronic obstructive pulmonary disease.[12-15] Furthermore, studies have not been able to combine adequate statistical power with characterisation of a range of risk factors that could be mediators (or confounders) of relationships between height and late-onset diseases, such as markers of blood lipids, blood pressure, inflammation, dysglycemia and socioeconomic indicators.

The objective of this appendix is to provide estimates of any independent associations of baseline adult height with the risk of cause-specific death (as well as major vascular morbidity) by analysing data from 1,085,949 people who were at risk for a total of 16.1 million person-years.

Methods

Study design

The current analyses focus on individual participant data on adult height from 121 prospective studies that also had information on age and sex at baseline, that did not select participants on the basis of having previous chronic disease, that recorded cause-specific mortality and/or vascular morbidity (ie, non-fatal myocardial infarction or stroke) using clearly defined criteria; and that accrued more than 1 year of follow-up. Details of the contributing study are presented **Table A3.1** and corresponding study acronyms are in **Appendix 4**. There were 1,085,949 participants who had no known history of cardiovascular disease at the baseline examination. For 875,782 (81%) of the participants, height was measured using standardised protocols; for the remainder, height was self-reported (**Table A3.1**). In registering fatal outcomes, all contributing studies used coding from the *International Classification of Diseases* to at least 3

digits or study-specific classification systems, and ascertainment was based on death certificates. Attribution of death refers to the primary cause (or, in its absence, the underlying cause) provided. 80 of the 121 contributing studies also involved medical records, autopsy findings and other supplementary sources to help classify deaths. 78 studies used standard definitions of myocardial infarction based on World Health Organization criteria. 59 studies reported diagnosis of strokes on the basis of typical clinical features and brain imaging and attributed stroke subtype.

Statistical analyses

The statistical methods have been described in detail in **Chapter 5** on pages 111-116. Height was normally distributed and the pooled within-study standard deviation (SD) was 6.5 cm for both males and females. Associations of height were assessed in relation to fatal or first-ever non-fatal coronary disease or stroke and cause-specific mortality, including deaths from vascular disease, cancer, and nonvascular conditions not attributed to cancer, as well as to further subdivisions of these outcomes. Participants contributed only the first non-fatal outcome or death recorded at age 40 years or older (ie, deaths preceded by non-fatal coronary disease or stroke were not included). Subsidiary analysis was done for fatal outcomes without censoring of previous non-fatal outcomes. Analyses involved a two-stage approach with estimates of association calculated separately within each study before pooling across studies by random effects meta-analysis.[16] Hazard ratios were calculated using Cox proportional-hazards regression models stratified by decades of year of birth, and, where appropriate, by sex and trial arm.[17] The proportional hazards assumptions were satisfied. For the six contributing "nested" case-control studies within prospective cohorts, odds ratios were calculated with logistic regression models. Provided the disease is relatively rare, hazard ratios and odds ratios were assumed to approximate the same relative risk and are collectively describe as "risk ratios".[18] To avoid over-fitting of the statistical models, studies with fewer than five incident cases of an outcome were excluded from the analysis of that particular outcome.

To assess the shape of association, study and sex-specific risk ratios calculated within quantiles of baseline values of height were pooled on a $\log_e$ scale by multivariate random effects meta-analysis and plotted against mean height values within each quantile. 95% confidence intervals (CIs) were estimates from variances attributed to the groups to reflect the amount of information within each group (including the reference group).[19]

When associations were approximately $\log_e$-linear, regression coefficients were calculated to estimate the risk ratio per one standard deviation greater baseline height. Parallel analyses were done in males and females separately. Unless specified otherwise, risk ratios were adjusted for age, sex, year of birth and smoking status only. To explore confounding and potential biological pathways underlying associations, risk ratios were further adjusted for systolic blood pressure (SBP), history of diabetes, body-mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), total and high density lipoprotein (HDL) cholesterol, triglyceride, C-reactive protein (CRP), fibrinogen, alcohol consumption, or socioeconomic indicators (ie, educational attainment and occupational category) and raw lung function (ie, forced expiratory volume in one second [FEV_1] unstandardised for age or height). Evidence of heterogeneity was indicated by the I^2 statistic.[20] Subsidiary analyses were corrected for regression dilution in height and covariates,[21,22] using serial measurement in 355,391 participants from 67 cohorts (mean interval: 5.5 years).

All analyses were performed using Stata release 11 (StataCorp LP, College Station, Texas USA).

Results

Characteristics of the contributing studies are shown in **Table A3.1**. Among the 1,085,949 participants included, the mean (SD) age at baseline was 55 (10) years; 48% were women. Most participants were in Europe (60%) or North America (33%). Median year of baseline survey was 1986 (IQR 1976-1992). Although mean height varied across studies, SDs were similar across studies (**Figure A3.1**). Overall mean (SD) height was 173 (6.5) cm in men and 160 (6.5) cm in women. For both sexes, mean height decreased with age, but increased by 0.5 to 1.0 cm per decade of birth between 1900 and 1960 (**Figure A3.2**). 619,984 of the participants had information on smoking status, SBP, diabetes, BMI and total cholesterol.

At baseline, there were modest and positive correlations of height with body weight, waist and hip circumference and FEV_1, but weakly negative correlations with blood pressure, lipids and inflammatory markers (**Table A3.2** panel A & **Figure A3.3**). On average, people of white European ancestry were 8.46 cm (95% CI 7.48 to 9.44 cm) taller than East-Asians, alcohol drinkers were 0.64 cm (95% CI 0.44 to 0.85 cm) taller than non-drinkers, people without diabetes were 0.34 cm (95% CI 0.20 to 0.49 cm) taller than those with diabetes, people with more education were 5.09 cm (95% CI 4.54 to 5.63 cm) taller than others, and people with

office jobs were 1.55 cm (95% CI 1.27 to 5.63 cm) taller than manual workers (**Table A3.2** panel B).

As would be expected for a trait that is stable in middle-aged people, the regression dilution ratio for adult height, adjusted for age, sex and year of birth, was close to 1.0, ie, 0.96 (95% CI 0.95-0.97; **Figure A3.4**) during a mean interval of about 6 years.

During 16.1 million person-years at risk (median 11.5 years to first outcome), there were a total of 174,374 deaths or major non-fatal vascular outcomes, comprising: 19,768 non-fatal myocardial infarctions, 26,102 coronary deaths and 161 unspecified coronary events; 11,757 non-fatal and 9534 fatal strokes; 13,345 deaths from other vascular diseases, 49,722 deaths from cancer, 34,527 deaths from non-vascular non-cancer causes, and 9,458 deaths of unknown or ill-defined cause (**Table A3.3**). The overall association of height with death from any cause was weakly inverse and possibly curvilinear (**Figure A3.5**).

Height and cardiovascular diseases

There were continuous inverse associations for the risk of each of coronary disease and stroke across the range of baseline height values, with possible attenuation at higher values (**Figures A3.5-A3.6**). Crude rates of coronary disease per 1000 person-years in the bottom and top fifths of baseline height distribution, respectively, were 5.6 and 2.9 in men and 2.6 and 0.9 in women. Associations of baseline height with vascular outcomes are shown in **Figure A3.7**. After adjustment for age, sex, smoking status and birth year, risk ratios per one standard deviation higher baseline height were 0.93 (95% CI 0.91-0.94) for coronary disease, 0.94 (95% CI 0.90-0.97) for ischaemic stroke, 0.90 (95% CI 0.85-0.95) for haemorrhagic stroke, 0.91 (95% CI 0.84-0.98) for subarachnoid haemorrhage, 0.95 (95% CI 0.92-0.98) for unclassified stroke and 0.94 (95% CI 0.89-0.99) for death from heart failure. In contrast, the corresponding risk ratios were 1.12 (95% CI 1.03-1.21) for pulmonary embolism and 1.12 (95% CI 1.05-1.20) for ruptured aortic aneurysm (**Figure A3.7**). Risk ratios were not appreciably altered after additional adjustment for blood pressure, diabetes, lipids, CRP, fibrinogen, BMI, WC, WHR, alcohol consumption or indicators of socioeconomic status (**Tables A3.4-A3.5**). However, risk ratios became non-significant after adjustment for FEV_1. Risk ratios for coronary disease and stroke appeared to become more extreme with later decade of birth, but risk ratios did not vary materially by the other characteristics recorded (**Figure A3.8**).

Height and cancer mortality and non-vascular non-cancer mortality

Height was continuously and positively associated with total cancer mortality (**Figure A3.5** and **Figure A3.9**), though inversely associated with death from oral and stomach cancers. As regards other site-specific cancers, height was positively associated with death from melanoma, and cancers of the pancreas, endocrine and nervous systems, breast, ovary, prostate, colorectum, blood and lung (**Figure A3.10**). Risk ratios for breast cancer mortality were similar across age-at-risk groups (**Figure A3.11**). With the exception of adjustment for FEV_1 (which accentuated risk ratios for total cancer mortality), adjustment for several major risk factors for chronic disease did not appreciably vary risk ratios for cancer death (**Table A3.4-A3.5**). There were non-significant associations of height with some site-specific cancers (eg, liver, connective tissue, oesophagus and bladder). For every 6.5 cm greater height, risk ratios were 0.84 (95% CI 0.80-0.89) for chronic obstructive pulmonary disease, 0.89 (95% CI 0.83-0.96) for mental disorders, 0.89 (95% CI 0.84-0.93) for liver disease, 0.96 (95% CI 0.92-1.00) for death from external causes and 0.96 (95% CI 0.92-1.00) for pneumonia (**Figure A3.10** and **Figure A3.12**).

Sensitivity analyses

Qualitatively similar results to those reported here were observed in a range of subsidiary analyses, such as those that: restricted attention to participants with measured (rather than self-reported) height (data not shown); omitted the initial five years of follow-up, current smokers, participants of non-European descent (**Table A3.5**); included fatal outcomes without censoring previous non-fatal outcomes (**Table A3.6**); used fixed effect (**Figure A3.12**) or sex-specific (**Table A3.5**) models; or corrected concurrently for regression dilution in height and in potential confounders and mediators (data not shown).

Discussion

The current analysis of individual participant data from more than 1 million people demonstrated that, whereas the risk of death from any cause is 3% lower per 6.5 cm increment in height, disaggregation of this overall association reveals stronger and opposing relationships with death from a variety of vascular, neoplastic, respiratory and other causes, independent from major risk factors. At the two extremes, the risk of death from melanoma is about 25% higher per 6.5 cm increment in height, whereas the risk of death from chronic obstructive pulmonary disease is about 15% lower for the same difference in height. Because the disease associations of height were not appreciably altered after adjustment for long-term levels of

smoking, adiposity, blood pressure, lipids, diabetes and inflammation, it reduces the likelihood that such factors are major mediators of the associations in this study. Hence, the results of our study suggest that variations in adult stature (and, by implication, the determinants of height) have pleiotropic effects on major diseases of later life. Furthermore, the current data demonstrate that mean adult height in developed countries has increased by 0.5 to 1.0 cm per decade for those born between 1900 and 1960.[6,13] Consequently, although height is 80 to 90% heritable,[23,24] these population-wide increases in height have most likely been due to non-genetic factors.

The current data showed that taller people have a lower risk of death from coronary disease, major pathological subtypes of stroke, heart failure, oral and gastric cancers, chronic obstructive pulmonary disease, mental disorders, liver diseases and external causes. Some of these conditions have been previously associated with height.[6,25-28] For example, the inverse association between height and coronary disease has been proposed to be due to taller people having larger coronary vessel diameters, elevated insulin-like growth factors and/or greater lung capacity.[6,11,29,30] The last of these mechanisms is supported by the current data, since the association of height and coronary disease was markedly attenuated after adjustment for FEV_1 (though this interpretation is complicated by the fact that lung function is itself strongly correlated with body size). In contrast with earlier less powerful studies, the current study demonstrated negative associations of similar magnitude between adult stature and risk of major pathological subtypes of stroke, a pattern that differs from the differential associations previously observed of certain conventional risk factors (eg, pro-atherogenic lipids[31]) with stroke subtypes. The negative association observed between height and death from gastric cancer is consistent with the known relevance to this malignancy of *Helicobacter pylori* infection, acquisition of which is related to poorer socioeconomic circumstances in childhood.[11,32]

In contrast with the negative associations observed between height and death from coronary disease and stroke, there were positive associations between adult stature and risk of death from pulmonary embolism (which could be due to greater propensity to venous thrombosis owing to greater venous surface area or more venous valves in taller people[33]) and ruptured aortic aneurysm (which could be due to longer arteries being more prone to rupture[34]). The current data also indicate that taller people have greater risk of death from several common malignancies. For some cancers, it has been proposed that because taller people have larger

organs, they have greater numbers of cells at risk of malignant transformation and/or proliferation.[35] For breast and other hormone-related cancers, it has been proposed that taller people have tumour-inducing biochemical alterations[6,12] and/or genes linked with both skeletal growth and cancer risk.[36]

The current study has several strengths. These include the large sample size (174,374 deaths or major non-fatal vascular outcomes recorded during more than 16 million person-years at risk), standardised approaches to adjust for potential confounding factors, serial assessment of risk factors in 355,000 participants, extended period of follow-up and information about a variety of disease outcomes. Furthermore, the current study investigated several factors that could mediate associations of height and disease. The current study minimised potential bias by involving data from only prospective cohort studies. The generalisability of the current findings to populations in economically developed Western countries is supported by broadly consistent results across 121 prospective cohorts in 24 countries. Due to the wide age ranges and periods of recruitment of the participants in our study, the current study was able to quantify reliably the trend toward increasing height in successive birth cohorts.

Despite this study's strengths, residual bias could persist due to unmeasured or imprecisely measured confounding factors (eg, dietary factors and socioeconomic factors, respectively). Apart from for coronary disease and stroke, the current study studied only fatal outcomes. Future studies will seek to investigate whether height-related genetic loci[5] are associated with the height-related diseases identified in this report, and to determine whether ethnic or geographical variation in genetic make-up could explain the current results. However, the scope for the latter explanation has been reduced because more than 90% of the participants in this study were of white European descent. Further studies are also needed to investigate more specific early-life exposures[6] in relation to adult-onset diseases. Although the associations observed of height with major disease are generally too weak to inform disease prediction, the current results suggest avenues for new aetiological insights.

Conclusion

Adult stature, which is an indicator of the interplay of genetic and early-life factors, has opposing relationships with a variety of vascular, neoplastic, respiratory and other causes, independent from major risk factors. These data underscore the pleiotropy and potential importance of early-life influences on major adult-onset diseases.

Appendix 3 – References

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Table A3.1 Characteristics of individuals studies with complete information on height, age and sex

Study design/ study[a]	Total No. with height measured	Country	Measurement of height	Height (cm) mean (sd)		Age at survey (yrs) mean (sd)	Male (%)	Follow-up (yrs) median (5th & 95th percentiles)
				Males	Females			
AFTCAPS	6605	USA	Assessed	179 (7)	164 (6)	58 (7)	5608 (85)	5.1 (4.3 to 6.7)
ALLHAT	28087	USA/Canada/Puerto Rico/US Virgin Islands	Assessed	174 (9)	160 (9)	66 (8)	13775 (49)	4.4 (0.8 to 6.7)
AMORIS	58117	Sweden	Assessed	178 (7)	165 (6)	46 (10)	33287 (57)	13.2 (6.6 to 17.0)
ARIC	14604	USA	Assessed	176 (7)	162 (6)	54 (6)	6303 (43)	14.0 (5.0 to 15.7)
ATENA	4750	Italy	Assessed	-	156 (6)	50 (7)	0 (0)	6.7 (5.2 to 8.1)
ATS_SAR	4264	Italy	Assessed	165 (7)	153 (6)	46 (8)	2066 (48)	8.7 (5.7 to 8.7)
ATTICA	1533	Greek	Assessed	174 (7)	162 (7)	51 (11)	786 (51)	5.0 (5.0 to 5.0)
AUSDIAB	8794	Australia	Assessed	176 (7)	162 (7)	53 (12)	3873 (44)	5.0 (4.9 to 8.5)
BHS	5991	Australia	Assessed	174 (7)	161 (6)	45 (16)	2829 (47)	26.3 (7.1 to 33.2)
BRHS	6810	UK	Assessed	173 (7)	-	50 (6)	6810 (100)	24.5 (4.7 to 25.4)
BRUN	817	Italy	Assessed	172 (7)	160 (6)	58 (11)	398 (49)	20.2 (3.9 to 20.5)
BUPA	20889	UK	Assessed	177 (7)	-	47 (8)	20889 (100)	23.7 (11.3 to 26.7)
BWHHS	2797	UK	Assessed	-	159 (6)	68 (5)	0 (0)	7.3 (3.1 to 8.4)
CAPS	2134	UK	Assessed	171 (6)	-	52 (5)	2134 (100)	13.0 (4.0 to 13.0)
CASTEL	2504	Italy	Assessed	168 (7)	155 (6)	73 (5)	955 (38)	11.2 (2.4 to 14.0)
CHA	34250	USA	Assessed	176 (7)	163 (7)	41 (13)	19894 (58)	32.0 (11.6 to 35.6)
CHARL	2031	USA	Assessed	175 (7)	162 (6)	50 (11)	952 (47)	24.1 (3.5 to 39.9)
CHS1	3787	USA	Assessed	173 (6)	159 (6)	72 (5)	1441 (38)	12.1 (2.0 to 12.9)
CHS2	464	USA	Assessed	173 (7)	160 (7)	72 (5)	173 (37)	9.1 (1.9 to 9.5)
COPEN	8197	Denmark	Assessed	176 (7)	163 (7)	58 (15)	3509 (43)	13.2 (2.7 to 14.9)
DISCO	1925	Italy	Assessed	165 (7)	154 (6)	50 (11)	843 (44)	5.5 (5.5 to 9.5)
DRECE	2818	Spain	Assessed	170 (8)	158 (6)	41 (11)	1360 (48)	16.4 (15.5 to 16.6)
DUBBO	2071	Australia	Assessed	173 (6)	160 (6)	68 (7)	867 (42)	14.1 (1.8 to 14.9)
EAS	1036	Scotland	Assessed	173 (7)	160 (6)	64 (6)	515 (50)	15.2 (2.8 to 15.8)
EMOFRI	360	Italy	Assessed	174 (6)	161 (6)	55 (6)	176 (49)	6.8 (6.5 to 7.2)
EPESEBOS	770	USA	Self-reported	170 (8)	157 (7)	77 (4)	263 (34)	4.0 (1.1 to 4.5)
EPESEIOW	1229	USA	Assessed	171 (8)	157 (8)	78 (5)	369 (30)	4.8 (1.6 to 4.9)
EPESENCA	1025	USA	Self-reported	173 (7)	158 (6)	77 (5)	338 (33)	4.0 (1.3 to 4.6)
EPESENHA	606	USA	Self-reported	172 (8)	160 (6)	78 (5)	230 (38)	4.4 (1.5 to 4.7)
EPICNOR	1426	UK	Assessed	173 (7)	159 (6)	66 (8)	967 (68)	7.1 (2.2 to 9.3)
ESTHER	8164	Germany	Assessed	174 (7)	162 (6)	62 (7)	3447 (42)	5.0 (2.0 to 5.9)
FIA	2509	Sweden	Assessed	176 (7)	162 (6)	54 (8)	2026 (81)	4.2 (0.5 to 9.6)
FINE_FIN	278	Finland	Assessed	169 (7)	-	77 (5)	278 (100)	6.9 (1.1 to 10.0)
FINE_IT	461	Italy	Assessed	166 (7)	-	72 (4)	461 (100)	9.8 (1.9 to 21.4)
FINRISK92	5776	Finland	Assessed	176 (7)	162 (6)	44 (11)	2667 (46)	16.9 (7.9 to 16.9)
FINRISK97	7224	Finland	Assessed	175 (7)	162 (6)	49 (12)	3538 (49)	11.8 (6.7 to 11.9)
FLETCHER	686	New Zealand	Assessed	175 (7)	162 (6)	52 (14)	545 (79)	5.6 (2.2 to 6.4)
FRAMOFF	2711	USA	Assessed	175 (7)	161 (6)	60 (9)	1192 (44)	5.2 (3.1 to 7.0)
FUNAGATA	2751	Japan	Assessed	161 (7)	150 (6)	57 (12)	1208 (44)	10.2 (4.7 to 12.0)
GLOSTRUP	210	Denmark	Assessed	175 (7)	162 (8)	50 (9)	171 (81)	4.5 (0.5 to 10.5)
GOH	5647	Israel	Assessed	168 (7)	157 (7)	43 (8)	2750 (49)	29.0 (11.9 to 36.0)
GOTO13	769	Sweden	Assessed	175 (6)	-	54 (2)	769 (100)	23.3 (4.5 to 30.5)
GOTO33	733	Sweden	Assessed	178 (6)	-	51 (0)	733 (100)	12.8 (5.8 to 13.1)
GOTO43	775	Sweden	Assessed	178 (7)	-	50 (0)	775 (100)	11.0 (7.9 to 11.7)
GOTOW	1425	Sweden	Assessed	-	164 (6)	47 (6)	0 (0)	32.2 (10.6 to 32.7)
GREPCO	794	Italy	Assessed	-	159 (6)	44 (8)	0 (0)	7.9 (7.7 to 8.4)
GRIPS	5785	Germany	Assessed	175 (6)	-	48 (5)	5785 (100)	9.8 (4.8 to 10.0)
GUBBIO	3412	Italy	Assessed	167 (7)	155 (6)	55 (13)	1515 (44)	8.4 (5.6 to 9.4)
HBS	1300	Finland	Assessed	177 (6)	-	60 (4)	1300 (100)	20.5 (6.0 to 20.5)
HELSINAG	432	Finland	Assessed	172 (5)	159 (6)	79 (4)	109 (25)	9.1 (1.9 to 11.0)
HISAYAMA	2576	Japan	Assessed	162 (6)	149 (6)	59 (12)	1088 (42)	14.0 (3.2 to 14.0)
HONOL	2530	USA	Assessed	162 (6)	-	78 (4)	2530 (100)	6.2 (1.4 to 7.6)
HOORN	2231	Netherlands	Assessed	176 (7)	163 (6)	61 (7)	983 (44)	8.8 (3.6 to 9.9)
HPFS	48810	USA	Self-reported	178 (7)	-	54 (10)	48810 (100)	20.2 (6.2 to 21.9)
IKNS	8048	Japan	Assessed	167 (7)	150 (6)	58 (10)	3302 (41)	11.1 (5.1 to 18.6)
ISRAEL	7826	Israel	Assessed	172 (7)	-	49 (7)	7826 (100)	23.3 (7.9 to 23.9)
KARELIA	10784	Finland	Assessed	173 (6)	159 (6)	41 (10)	5199 (48)	36.7 (6.7 to 36.9)
KIHD	2063	Finland	Assessed	162 (6)	-	53 (5)	2063 (100)	20.1 (3.0 to 24.1)
LASA	1861	Netherlands	Assessed	174 (7)	162 (6)	69 (9)	839 (45)	9.8 (1.5 to 10.4)
LEADER	927	UK	Assessed	172 (7)	-	68 (9)	927 (100)	4.2 (0.9 to 6.2)
MALMO	32486	Sweden	Assessed	177 (7)	164 (6)	46 (7)	21916 (67)	18.2 (7.9 to 22.6)

Table A3.1 con't Characteristics of individuals studies with complete information on height, age and sex

Study design/ study[a]	Total No. with height measured	Country	Measurement of height	Height (cm) mean (sd)		Age at survey (yrs) mean (sd)	Male (%)	Follow-up (yrs) median (5th & 95th percentiles)
				Males	Females			
MATISS83	2562	Italy	Assessed	164 (6)	154 (6)	51 (10)	1202 (47)	18.7 (6.8 to 19.5)
MATISS87	2117	Italy	Assessed	165 (6)	153 (6)	52 (10)	937 (44)	15.6 (6.8 to 16.2)
MATISS93	1214	Italy	Assessed	167 (6)	155 (6)	49 (9)	587 (48)	8.3 (7.1 to 9.3)
MCVDRFP	23169	Netherlands	Assessed	177 (7)	165 (7)	42 (10)	10727 (46)	16.8 (13.6 to 18.9)
MESA	6768	USA	Assessed	174 (8)	160 (7)	62 (10)	3190 (47)	4.8 (2.5 to 5.2)
MICOL	19401	Italy	Assessed	169 (7)	157 (7)	51 (10)	10865 (56)	5.9 (4.5 to 7.1)
MOGERAUG1	871	Germany	Assessed	172 (6)	-	54 (6)	871 (100)	13.0 (3.6 to 13.4)
MOGERAUG2	3974	Germany	Assessed	173 (7)	161 (7)	53 (12)	1953 (49)	7.9 (2.3 to 8.4)
MOGERAUG3	3378	Germany	Assessed	173 (7)	160 (6)	55 (10)	1667 (49)	3.0 (1.8 to 3.6)
MONFRI86	1413	Italy	Assessed	172 (7)	160 (6)	49 (9)	695 (49)	16.7 (7.6 to 16.9)
MONFRI89	1346	Italy	Assessed	172 (6)	160 (6)	49 (8)	666 (49)	13.6 (7.5 to 13.7)
MONFRI94	1294	Italy	Assessed	173 (7)	161 (6)	49 (8)	630 (49)	8.5 (8.0 to 8.8)
MONICA	3663	Italy	Assessed	170 (7)	158 (6)	49 (9)	1830 (50)	6.5 (2.1 to 10.5)
MORGEN	17737	Netherlands	Assessed	178 (7)	165 (7)	46 (9)	8060 (45)	10.8 (8.5 to 13.1)
MOSWEGOT	4170	Sweden	Assessed	178 (7)	166 (6)	47 (11)	1983 (48)	13.9 (7.6 to 19.6)
MRCOLD	10233	UK	Assessed	169 (7)	155 (7)	80 (4)	3861 (38)	8.7 (1.2 to 11.7)
MRFIT	12846	USA	Assessed	176 (7)	-	47 (6)	12846 (100)	6.9 (4.4 to 7.8)
NCS1	24201	Norway	Assessed	176 (6)	163 (6)	42 (4)	11915 (49)	16.1 (13.5 to 16.7)
NCS2	13056	Norway	Assessed	176 (6)	163 (5)	42 (4)	6654 (51)	17.2 (12.8 to 17.8)
NCS3	10029	Norway	Assessed	173 (7)	160 (6)	42 (4)	5203 (52)	18.1 (12.1 to 18.8)
NFR	3102	Italy	Assessed	169 (6)	-	55 (5)	3102 (100)	10.2 (6.1 to 11.2)
NHANESI	9355	USA	Assessed	174 (7)	161 (6)	50 (16)	3646 (39)	19.0 (4.0 to 21.1)
NHANESIII	14658	USA	Assessed	175 (8)	161 (7)	50 (18)	6765 (46)	14.4 (4.0 to 17.7)
NHS	119546	USA	Self-reported	-	164 (6)	43 (7)	0 (0)	28.6 (12.0 to 30.3)
NPHSI	1389	UK	Assessed	172 (7)	-	52 (7)	1389 (100)	14.6 (4.4 to 18.6)
NPHSII	2965	UK	Assessed	174 (7)	-	57 (3)	2965 (100)	8.3 (3.4 to 10.4)
NSHS	1651	Canada	Assessed	174 (7)	160 (7)	54 (15)	790 (48)	9.7 (3.7 to 10.0)
OB43	3618	Italy	Assessed	169 (7)	157 (7)	47 (8)	1737 (48)	7.5 (5.1 to 9.1)
OSAKA	12379	Japan	Assessed	167 (6)	152 (6)	52 (10)	8414 (68)	10.2 (3.9 to 18.8)
OSLO	17257	Norway	Assessed	178 (7)	-	44 (6)	17257 (100)	29.5 (10.9 to 30.5)
OYABE	5088	Japan	Assessed	161 (7)	149 (6)	57 (11)	1568 (31)	10.4 (5.3 to 10.6)
PARIS1	7073	France	Assessed	174 (5)	-	47 (2)	7073 (100)	22.9 (7.6 to 26.1)
PREVEND	6934	Netherlands	Assessed	179 (7)	167 (7)	50 (11)	3380 (49)	7.6 (4.7 to 8.2)
PRHHP	6344	Caribbean	Assessed	165 (7)	-	54 (6)	6344 (100)	8.3 (5.2 to 12.0)
PRIME	9581	France / NI	Assessed	173 (7)	-	55 (3)	9581 (100)	5.2 (5.0 to 7.3)
PROCAM	20174	Germany	Assessed	175 (7)	163 (7)	44 (10)	14608 (72)	10.0 (3.9 to 18.9)
PROSPER	3253	Scotland/Ireland/Netherland	Assessed	173 (7)	159 (7)	75 (3)	1351 (42)	3.2 (1.1 to 3.8)
QUEBEC	988	Canada	Assessed	171 (7)	-	56 (7)	988 (100)	5.3 (3.4 to 5.6)
RANCHO	1785	USA	Assessed	175 (7)	161 (6)	68 (11)	739 (41)	14.2 (2.0 to 18.1)
REYK	16814	Iceland	Assessed	177 (6)	163 (6)	52 (9)	8046 (48)	24.7 (6.3 to 37.1)
RF2	5433	Italy	Assessed	169 (7)	157 (7)	44 (9)	2551 (47)	13.7 (11.3 to 14.1)
ROTT	4751	Netherlands	Assessed	175 (7)	162 (7)	68 (8)	1801 (38)	12.0 (3.1 to 14.2)
SHHEC	13533	UK	Assessed	173 (7)	160 (6)	49 (8)	6587 (49)	10.0 (6.3 to 10.0)
SHS	4148	USA	Assessed	173 (6)	160 (6)	56 (8)	1622 (39)	12.4 (2.0 to 14.3)
SPEED	2126	UK	Assessed	172 (7)	-	55 (4)	2126 (100)	16.7 (3.3 to 18.2)
TARFS	3287	Turkey	Assessed	169 (7)	156 (7)	46 (13)	1636 (50)	12.9 (2.3 to 17.6)
TOYAMA	4523	Japan	Assessed	168 (6)	154 (6)	46 (7)	2907 (64)	12.7 (7.8 to 12.8)
TROMSØ	21861	Norway	Assessed	177 (7)	164 (6)	43 (14)	10326 (47)	18.8 (5.1 to 19.3)
ULSAM	2284	Sweden	Assessed	176 (6)	-	50 (1)	2284 (100)	28.0 (6.5 to 35.9)
USPHS	936	USA	Self-reported	178 (7)	-	60 (9)	936 (100)	0.0 (0.0 to 0.0)
USPHS2	10716	USA	Self-reported	179 (8)	-	64 (8)	10716 (100)	10.9 (4.9 to 11.5)
VHMPP	120581	Austria	Assessed	174 (7)	162 (6)	48 (14)	55110 (46)	13.1 (2.2 to 16.7)
VITA	8996	Italy	Assessed	174 (7)	162 (6)	51 (8)	4031 (45)	3.3 (1.7 to 5.3)
WHIHABPS	1222	USA	Assessed	-	161 (6)	68 (6)	0 (0)	6.8 (1.2 to 9.3)
WHITEI	4019	UK	Assessed	174 (7)	-	76 (5)	4019 (100)	8.2 (2.0 to 8.4)
WHITEII	10201	UK	Assessed	176 (7)	162 (7)	45 (6)	6805 (67)	12.4 (4.9 to 14.1)
WHS	27758	USA	Self-reported	-	164 (6)	55 (7)	0 (0)	10.2 (8.4 to 10.8)
WOSCOPS	6192	UK	Assessed	172 (7)	-	55 (6)	6192 (100)	4.8 (2.9 to 6.0)
ZARAGOZA	2920	Spain	Assessed	165 (7)	153 (7)	59 (12)	1205 (41)	5.1 (3.8 to 5.1)
ZUTE	391	Netherlands	Assessed	173 (7)	-	76 (4)	391 (100)	8.6 (1.0 to 10.1)
TOTAL	**1085949**			**173 (6.5)**	**160 (6.5)**	**55 (10)**	**563692 (52)**	**13.7 (3.3 to 30.1)**

[a]Appendix 4 lists study acronyms. Abbreviations: Assessed = height was assessed using standardised protocol; Self-reported = height was measured by the subject itself.

Table A3.2 Summary of data available and associations with height

A

	Summary of available data on height			Difference (95% CI) in row variables per 1-SD (6.5cm) higher height values[†]
	No of studies	No of subjects	Mean (SD) or %	
Height (cm)	121	1085949	167 (6.5*)	-
Physical measurements				
BMI (kg/m^2)	121	1081839	26 (4)	-0.32 (-0.35 to -0.28)
Weight (kg)	121	1081839	73 (13)	4.82 (4.74 to 4.91)
Waist circumference (cm)	54	176957	90 (12)	1.40 (1.29 to 1.50)
Hip circumference (cm)	50	174252	101 (9)	1.86 (1.76 to 1.96)
Waist-to-hip ratio	50	174150	0.89 (0.08)	-0.003 (-0.003 to -0.002)
SBP (mmHg)	117	840352	136 (19)	-0.31 (-0.41 to -0.22)
DBP (mmHg)	117	841842	82 (11)	0.14 (0.09 to 0.20)
Fasting glucose (mmol/l)	62	313423	5.5 (1.6)	-0.01 (-0.02 to 0.00)
FEV_1 (l/1min)	10	72480	2.75 (0.77)	0.21 (0.19 to 0.24)
Lipid markers				
Total cholesterol (mmol/l)	117	824332	5.8 (1.1)	-0.05 (-0.06 to -0.04)
LDL cholesterol (mmol/l)	13	61006	3.67 (0.87)	-0.04 (-0.05 to -0.02)
Non-HDL cholesterol (mmol/l)	100	452696	4.48 (1.11)	-0.04 (-0.05 to -0.03)
HDL cholesterol (mmol/l)	100	453106	1.34 (0.37)	-0.01 (-0.01 to -0.00)
Log_e triglyceride (mmol/l)	99	661385	0.33 (0.52)	-0.01 (-0.01 to -0.01)
Apo AI (g/l)	30	124035	1.47 (0.27)	-0.01 (-0.01 to -0.00)
Apo B (g/l)	31	126523	1.10 (0.28)	-0.01 (-0.02 to -0.02)
Log_e Lp(a) (mg/dl)	31	104007	2.29 (1.25)	-0.00 (-0.02 to 0.01)
Inflammatory markers				
Log_e CRP (mg/l)	49	138177	0.64 (1.10)	- 0.04 (-0.05 to -0.03)
Fibrinogen (µmol/l)	46	201724	9.3 (2.1)	-0.08 (-0.10 to -0.07)
Albumin (g/l)	39	150324	43 (4)	-0.01 (-0.04 to 0.01)
Log_e leukocyte count(x10^9/l)	37	135340	1.84 (0.27)	-0.02 (-0.02 to -0.01)
Log_e Interleukin 6 (ng/l)	10	19417	0.47 (0.66)	-0.02 (-0.03 to 0.00)

*Same pooled standard deviation (SD) in males and females.
†Change in row variable per 1-SD (6.5 cm) higher height levels, adjusted for age, sex and year of birth, pooled across studies using random effects meta-analysis.

Table A3.2 con't Summary of data available and associations with height

B

	Summary of available data on height			Difference (95% CI) in height per 1 SD higher level of row variable or compared to reference category (cm)‡
	No of studies	No of subjects	Mean (SD) or %	
Age at survey (yrs)	121	1085949	55 (10)	-1.48 (-1.60 to -1.36)
Sex	121	1085949		
Female		522257	48%	-12.9 (-13.0 to -12.7)
Male		563692	52%	Reference
Ethnicity	93	549459		
East Asian		39800	7%	-8.46 (-9.44 to -7.48)
Black		29895	5%	-0.30 (-1.12 to 0.52)
Other		11369	2%	-5.28 (-6.14 to -4.42)
White		468395	85%	Reference
Smoking status	120	1010302		
Current		315789	31%	-0.01 (-0.10 to 0.08)
Not current		694513	69%	Reference
Alcohol status	92	511895		
Current		325781	64%	0.64 (0.44 to 0.85)
Not current		186114	36%	Reference
History of diabetes	110	833766		
Yes		39106	5%	-0.34 (-0.49 to -0.20)
No		794660	95%	Reference
Level of education reached	61	374737		
Tertiary		106396	28%	5.09 (4.54 to 5.63)
Secondary		187779	50%	3.64 (3.19 to 4.09)
Primary		66758	18%	2.05 (1.62 to 2.47)
No schooling		13804	4%	Reference
Occupation or job	59	360531		
Office		127181	35%	1.55 (1.27 to 1.84)
Not working		90013	25%	0.26 (-0.11 to 0.62)
Other		47468	13%	0.87 (0.48 to 1.25)
Manual		95869	27%	Reference

‡Change in height levels per 1 standard deviation (SD) higher levels of row variables or compared to reference category, adjusted for age, sex and year of birth, pooled across studies using random effects meta-analysis.

Table A3.3 Summary of events of individual studies with complete information on height, age and sex

Study design/ study[†]	Cardiovascular outcomes															Cancer deaths																				Non-cancer, non-cardiovascular deaths											Deaths of unkown or ill-defined cause[‡]	All-cause mortality
	All cardiovascular disease[*]	All vascular deaths	Coronary heart disease[*]	All stroke[*]	Ischaemic stroke[*]	Haemorrhagic stroke[*]	Subarachnoid heamorrhage[*]	Unclassified stroke[*]	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Ruptured aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer	Oral	Colorectal	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Bladder	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer, non-vascular	External causes	Infections	Diabetes mellitus	Mental disorders	Alzheimers & related conditions	Liver disease	Pneumonia	COPD & related conditions	Digestive system disorders (except liver)	Renal disease		
Cohort studies																																															
AMORIS	3710	745	2026	1435	950	213	120	136	11	12	27	3	61	28	5	1402	13	175	23	62	33	110	224	111	38	28	123	60	43	19	91	707	228	35	30	43	41	61	33	66	48	8	46	2900
ARIC	1644	427	876	565	456	56	33	16	21	51	12	0	13	13	7	692	6	58	11	14	7	45	228	31	20	18	68	21	7	16	61	352	55	24	28	10	7	20	11	75	20	15	36	1507
ATENA[b]	30	9	18	4	1	2	1	0	2	3	0	0	1	0	0	22	0	0	0	1	1	4	4	0	2	1	3	0	0	0	4	8	4	0	0	0	1	2	0	0	0	0	1	40
ATS_SAR[c]	34	34	21	8	0	1	1	6	0	0	0	0	1	0	0	56	1	5	0	2	4	3	14	0	2	1	5	5	0	0	4	30	12	0	0	0	0	4	2	2	2	3	4	124
ATTICA	30	30	0	0	0	0	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	1	0	0	0	0	0	0	0	0	0	0	50
AUSDIAB	136	76	80	40	12	2	5	17	3	1	1	0	3	2	3	116	0	16	3	1	1	6	22	2	3	2	10	13	7	5	8	60	10	1	4	0	9	2	1	13	4	3	36	288
BHS	931	931	519	221	23	21	4	144	11	22	9	0	37	38	9	547	6	83	12	23	6	22	87	60	16	17	47	18	13	6	34	478	53	4	38	28	41	11	32	106	45	22	17	1973
BRHS	1858	776	1215	516	7	13	10	475	7	5	12	0	50	11	8	745	11	84	34	45	20	29	248	62	0	39	39	23	6	2	0	305	33	5	4	6	5	18	44	95	27	8	134	1960
BRUN	151	80	66	63	43	19	0	0	0	0	7	0	5	9	0	83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	74	12	3	0	11	0	3	26	8	5	3	3	240
BUPA	1509	1509	1016	254	31	37	12	145	3	14	23	0	94	30	2	1383	11	189	72	67	21	86	287	158	0	48	132	64	32	15	0	618	115	12	4	35	16	50	61	92	56	30	37	3547
BWHHS	197	30	90	91	0	1	0	90	0	1	3	0	4	1	2	116	1	13	3	7	1	6	18	0	10	6	5	4	0	1	14	69	4	2	1	1	9	3	10	12	8	0	3	218
CAPS	291	152	251	18	3	3	1	9	0	4	7	0	3	1	1	127	1	18	5	12	1	5	46	4	0	3	8	5	1	1	0	63	11	1	0	2	1	5	3	21	7	2	0	342
CASTEL	522	522	95	107	0	0	0	107	0	0	29	74	0	217	0	278	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	299	0	59	0	0	0	28	0	37	0	0	18	1117
CHA	4820	4820	3000	786	116	154	39	375	119	126	62	3	88	174	32	3630	38	403	73	103	73	211	940	253	95	73	395	122	36	46	269	2774	346	195	146	114	181	184	323	436	177	105	389	11613
CHARL	950	585	522	264	30	34	5	186	32	21	11	0	11	13	5	297	4	26	14	16	2	14	88	20	1	5	17	9	3	2	19	282	17	16	32	12	5	17	36	43	34	16	60	1224
CHS1[a]	1066	258	571	443	346	62	0	35	0	0	0	0	0	0	0	385	0	41	7	13	10	24	95	33	13	6	41	9	2	0	25	392	47	19	1	69	48	8	45	33	37	16	11	1046
CHS2[a]	107	28	53	48	39	5	0	4	0	0	0	0	0	0	0	34	0	4	0	2	0	4	15	4	0	1	0	0	0	0	1	26	2	2	1	5	1	0	4	1	2	2	1	89
COPEN	1372	352	514	592	368	73	16	122	9	22	26	13	15	59	0	531	7	47	21	13	9	31	141	31	17	22	28	11	6	5	45	643	58	41	28	25	27	30	135	80	47	18	150	1676
DISCO[c]	12	12	9	3	1	1	0	1	0	0	0	0	0	0	0	11	0	2	0	0	0	0	3	0	2	1	1	0	0	0	0	6	3	0	1	0	0	2	0	0	0	0	0	29
DRECE	29	29	15	6	0	1	0	4	0	1	1	0	0	2	0	63	2	12	1	4	1	5	13	1	1	2	3	1	1	2	6	43	5	4	5	0	0	6	1	6	3	0	0	135
DUBBO	542	135	284	192	76	20	3	87	4	0	5	0	6	28	0	169	2	18	3	3	2	8	28	16	4	6	18	2	1	0	7	169	24	12	1	9	12	6	26	24	14	8	18	491
EAS	169	80	82	68	0	3	2	60	1	2	1	0	4	3	0	126	1	17	6	9	1	5	33	14	3	1	7	0	1	0	8	70	2	2	0	5	5	0	12	16	6	3	8	284
EMOFRI[b]	8	4	2	3	2	1	0	0	3	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	1	9
EPESEBOS	94	38	38	26	17	6	2	1	19	1	2	0	0	2	0	22	0	3	2	2	1	1	2	4	0	0	1	0	2	0	0	26	3	2	0	1	0	0	6	1	2	4	9	95
EPESEIOW	153	69	57	58	22	6	2	26	12	2	1	0	1	14	0	24	0	2	1	0	1	3	5	2	1	2	3	0	0	0	3	46	5	6	1	0	0	3	8	3	2	7	25	164
EPESENCA	122	47	49	51	30	6	0	15	12	0	0	0	0	7	0	35	0	5	1	1	0	1	14	5	0	1	3	0	0	0	0	33	5	4	1	0	0	1	9	2	3	3	11	126
EPESENHA	88	52	21	21	10	2	0	9	31	1	0	0	0	4	0	4	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	20	2	2	0	0	1	2	7	2	1	1	21	97
ESTHER	244	22	89	151	3	1	1	146	0	0	0	0	2	0	0	55	1	6	1	1	1	5	17	2	1	1	3	3	1	2	3	17	1	1	2	0	0	2	0	3	4	0	7	101
FINE_FIN	112	63	71	29	8	1	0	16	0	2	2	0	0	4	0	40	0	5	0	2	0	1	14	11	0	0	3	0	0	0	0	45	9	1	4	8	0	0	12	5	2	0	1	149
FINE_IT	210	142	67	104	4	5	0	85	1	5	0	2	1	19	1	108	2	22	2	11	3	5	17	19	0	6	7	5	0	1	0	47	15	0	1	0	2	4	5	4	9	1	32	329
FINRISK92	325	80	163	137	86	39	3	6	1	2	6	2	1	6	0	85	2	9	2	9	4	6	18	3	3	0	2	5	2	3	10	104	48	5	0	2	2	6	14	1	8	4	1	270
FINRISK97	259	69	121	109	76	19	1	13	0	2	11	0	1	10	0	70	1	5	3	6	3	6	12	5	3	0	6	3	2	0	4	80	29	5	1	2	0	4	22	3	5	0	2	221
FRAMOFF	77	4	52	25	24	1	0	0	0	0	0	0	0	0	0	51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	27	0	0	0	0	0	0	0	0	0	0	18	100
FUNAGATA	171	63	27	138	69	19	4	46	0	0	0	0	2	1	1	105	1	17	5	20	5	7	22	0	1	2	4	0	0	0	5	57	13	4	1	0	0	3	19	0	5	5	7	232
GOH	602	602	281	138	2	12	3	76	67	13	9	15	4	19	4	337	8	43	3	19	10	24	40	16	9	8	33	17	1	2	26	329	45	19	46	15	4	21	17	45	30	29	701	1969
GOTO13	373	43	217	116	0	1	0	115	0	0	6	5	3	18	0	115	1	14	7	8	3	8	18	24	0	4	6	2	3	1	0	50	2	2	1	8	0	6	14	5	4	1	43	251
GOTO33	44	22	27	8	0	0	0	8	2	0	2	0	0	0	0	27	1	3	0	6	0	1	7	2	0	0	2	1	0	0	0	29	9	0	1	7	0	2	2	2	0	0	3	81
GOTO43	47	4	29	16	12	1	1	2	0	0	0	0	1	0	0	16	0	0	0	1	0	0	3	0	0	0	4	3	0	1	0	4	2	0	0	0	0	2	0	0	0	0	1	25
GOTOW	369	131	146	178	2	0	0	175	2	0	0	0	1	1	1	154	0	1	0	1	0	0	14	0	15	0	19	0	1	0	19	118	76	21	1	0	4	0	2	2	1	0	4	407
GREPCO[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	5
GRIPS	449	47	299	103	0	0	0	103	0	0	13	17	3	10	0	108	2	18	0	11	3	6	34	3	0	5	10	7	1	1	0	69	30	4	0	0	0	7	3	3	16	3	1	225
GUBBIO[c]	109	109	71	29	11	2	1	13	0	2	1	0	0	0	1	95	2	8	1	12	9	5	12	3	5	2	8	3	0	3	9	35	15	0	0	0	0	6	2	5	0	1	3	242
HBS	131	131	87	27	0	0	0	27	0	0	0	0	0	0	0	158	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	112	27	0	0	0	0	0	0	0	0	0	10	411
HELSINAG	109	109	42	43	22	3	0	3	2	2	8	0	3	1	2	38	0	3	1	4	1	3	4	2	1	3	2	0	0	0	2	75	2	0	0	12	1	0	44	1	6	1	16	238
HISAYAMA	356	76	77	220	148	49	21	0	1	10	2	0	12	2	2	154	1	19	4	22	25	11	30	2	2	0	12	3	0	0	2	155	24	7	0	0	1	13	42	11	19	5	2	387
HONOL	314	110	156	133	12	40	2	75	3	4	1	0	7	0	1	183	3	17	9	28	1	9	41	30	0	0	26	2	0	2	0	158	18	7	7	37	0	1	17	27	8	1	88	539
HOORN	172	70	73	53	3	4	0	46	12	0	3	13	4	12	0	85	1	9	3	6	2	5	19	3	4	2	2	4	0	0	2	18	5	1	0	1	0	0	6	3	0	1	40	213
HPFS	4543	4543	2634	767	102	133	40	180	59	14	45	366	149	218	12	4527	70	499	145	99	68	355	804	667	0	181	740	211	130	45	0	3722	688	158	93	337	363	131	313	391	204	190	373	13165
IKNS	495	154	84	344	158	71	25	90	2	0	1	0	3	57	0	297	4	24	12	72	27	32	18	7	1	3	10	3	2	1	4	250	59	6	4	3	0	14	88	11	13	17	59	760
ISRAEL	1000	1000	732	268	0	0	0	268	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1572	2572
KARELIA	3273	1040	2036	971	71	48	40	804	16	25	41	3	18	89	3	695	9	46	12	54	22	38	156	20	28	9	70	19	11	9	55	840	239	42	22	27	27	27	244	41	49	23	12	2587

Table A3.3 con't Summary of events of individual studies with complete information on height, age and sex

Study design/ study[†]	Cardiovascular outcomes															Cancer deaths																Non-cancer, non-cardiovascular deaths											Deaths of unkown or ill-defined cause[‡]	All-cause mortality
	All cardiovascular disease*	All vascular deaths	Coronary heart disease*	All stroke*	Ischaemic stroke*	Haemorrhagic stroke*	Subarachnoid heamorrhage*	Unclassified stroke*	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Ruptured aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer	Oral	Colorectal	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Bladder	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer, non-vascular	External causes	Infections	Diabetes mellitus	Mental disorders	Alzheimers & related conditions	Liver disease	Pneumonia	COPD & related conditions	Digestive system disorders (except liver)	Renal disease		
KIHD	586	61	404	153	111	35	2	3	0	3	2	0	5	2	1	146	3	14	2	6	5	19	34	15	0	3	12	8	6	3	0	131	43	3	1	2	14	20	8	6	12	2	7	345
LASA	52	0	33	19	0	0	0	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	490	490
MALMO	2418	1185	2047	143	36	49	21	16	6	6	17	1	46	18	3	1274	27	108	25	69	21	91	335	74	38	36	106	59	36	19	52	667	169	14	25	51	10	87	45	93	53	7	163	3289
MATISS83[b]	336	196	83	99	26	10	3	57	71	11	1	0	0	54	0	90	1	3	0	2	3	1	12	0	0	0	6	3	0	3	2	60	9	0	9	3	2	11	3	6	3	4	65	411
MATISS87[b]	175	95	45	58	9	8	2	39	36	3	0	1	1	27	0	46	0	2	0	3	1	1	7	1	1	0	1	2	0	2	0	33	11	0	1	2	1	4	0	1	2	5	33	207
MATISS93[b]	31	13	14	7	1	2	1	3	4	1	0	0	0	5	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	1	0	1	0	0	1	0	0	1	2	5	29
MCVDRFP	457	457	197	97	15	31	14	32	19	8	8	8	16	27	4	852	8	82	23	32	6	48	247	26	27	12	60	19	18	16	97	358	70	13	23	13	12	22	19	73	45	8	113	1780
MESA	173	21	83	84	68	13	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	122	143
MICOL[c]	150	150	105	33	7	3	0	20	0	0	3	0	3	0	2	248	5	25	5	20	15	16	75	2	7	3	16	10	4	5	14	94	20	0	3	0	0	41	4	8	6	3	24	516
MOGERAUG1	108	61	79	5	0	2	0	2	0	0	5	2	2	10	1	40	1	7	1	5	1	3	8	1	0	1	1	2	0	0	0	25	7	0	2	3	1	1	3	4	2	0	0	126
MOGERAUG2	130	67	105	7	1	1	1	3	0	1	4	1	0	8	0	77	3	14	0	4	2	6	16	2	4	1	6	2	1	1	5	53	11	2	2	7	0	7	2	10	5	2	3	200
MOGERAUG3	36	25	18	5	2	1	0	2	0	3	2	0	0	3	0	21	1	5	0	2	1	1	2	1	1	0	3	2	0	0	0	9	2	0	1	2	0	1	1	0	0	0	0	55
MONFRI86[b]	108	62	28	26	14	5	2	5	44	0	2	1	1	4	0	41	0	0	1	2	3	0	5	0	0	0	1	1	0	0	1	22	6	0	1	0	1	5	1	0	1	2	42	167
MONFRI89[b]	82	43	28	20	10	5	0	5	23	0	2	0	1	6	0	16	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	23	4	1	0	0	0	6	2	0	3	1	18	100
MONFRI94[b]	39	13	10	17	6	7	1	2	9	0	0	1	1	0	0	7	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1	7	1	0	0	0	0	3	1	0	1	0	13	40
MONICA[c]	38	38	28	8	0	1	0	5	0	0	0	0	0	0	0	45	0	2	1	8	4	0	10	0	2	1	1	1	1	0	1	17	5	0	0	0	0	3	0	2	1	2	0	100
MORGEN	149	149	77	24	3	10	7	4	4	2	3	4	6	5	0	317	6	32	10	10	5	23	80	8	10	6	19	7	4	6	33	95	25	7	5	4	2	9	5	9	8	0	26	587
MOSWEGOT	307	67	155	132	75	19	22	15	2	0	7	0	2	1	1	109	1	10	1	5	3	7	15	6	5	0	10	5	1	4	16	56	14	1	1	6	5	3	0	10	5	2	4	236
MRCOLD	2661	2661	1159	850	54	61	14	522	64	50	48	0	94	171	47	1390	15	166	57	69	30	63	221	143	25	59	90	9	15	17	98	2120	100	65	50	46	262	17	547	296	254	46	201	6372
NCS1	548	548	375	67	9	17	26	12	5	13	2	43	12	8	0	560	10	76	8	37	3	29	75	13	32	4	69	32	15	4	49	247	89	7	21	10	1	16	9	31	11	5	83	1438
NCS2	280	280	193	28	2	7	11	6	5	8	1	20	4	1	1	327	5	66	3	27	1	13	44	12	18	8	17	18	12	3	30	143	61	3	7	11	0	8	10	9	4	4	54	804
NCS3	465	465	287	86	8	24	22	23	6	19	0	38	5	3	0	286	5	19	1	31	5	22	62	6	25	4	18	10	1	1	25	142	45	4	4	17	2	9	4	25	7	2	96	989
NFR[c]	125	125	91	27	2	9	1	11	0	0	1	0	4	0	0	151	1	12	3	14	8	4	39	8	0	7	17	6	3	3	0	41	13	0	0	0	1	15	3	2	4	2	15	332
NHANESI	1746	1104	926	493	132	46	18	272	48	58	11	1	20	38	5	701	6	92	18	26	14	37	143	55	15	23	74	15	7	4	62	634	82	40	49	27	9	33	88	110	59	31	51	2490
NHANESIII	1464	1464	794	280	0	0	0	280	0	76	0	0	18	104	0	915	110	0	17	36	27	44	249	81	16	9	75	10	11	0	63	1141	105	68	106	0	71	62	127	161	12	42	71	3591
NHS	5295	5295	2315	1350	24	106	657	236	1	15	103	347	151	374	157	10457	101	972	98	161	91	621	2230	0	733	118	1086	374	167	85	2231	6376	934	260	334	1138	0	379	276	476	383	89	1508	23636
NPHSI	196	88	154	23	0	0	0	23	0	0	0	0	0	0	0	85	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	0	0	0	0	0	0	0	0	0	0	3	216
NPHSII	298	57	195	73	39	7	7	20	0	4	2	16	6	0	0	117	1	21	11	9	2	6	26	5	0	2	12	4	3	2	0	25	5	1	0	0	1	4	1	7	2	0	3	202
NSHS	89	41	25	52	1	1	1	49	5	0	0	0	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	41
OB43[c]	24	24	15	8	1	1	1	4	0	0	0	0	1	0	0	36	1	6	0	0	2	2	5	0	0	0	3	3	1	0	2	5	14	2	0	0	0	0	3	0	4	3	1	3	77
OSAKA	261	106	42	144	57	27	16	44	1	3	0	1	4	62	0	220	3	15	9	37	30	18	10	7	5	2	10	7	0	0	6	146	22	11	1	8	0	17	43	6	12	9	155	627
OSLO	2615	2615	1604	379	56	79	29	170	36	51	15	119	159	61	5	2017	46	310	42	125	23	115	504	225	0	47	179	74	51	22	0	1072	182	29	66	60	15	98	90	226	101	27	188	5892
OYABE	198	57	26	141	88	30	22	1	0	7	0	0	0	19	0	181	0	7	7	46	5	11	28	0	0	0	4	0	0	0	2	97	26	7	1	0	0	7	34	5	5	0	41	376
PARIS1	480	480	195	100	4	30	5	49	22	4	0	25	8	3	4	918	32	37	37	19	4	24	120	16	0	18	35	18	1	12	0	465	150	2	4	9	1	80	4	6	71	0	218	2081
PRHHP	384	245	213	84	54	20	3	5	0	28	4	24	8	0	1	159	9	12	18	29	0	4	24	15	0	1	18	4	0	1	0	182	76	12	7	4	0	39	6	6	8	3	9	595
PRIME	208	37	146	42	33	6	0	3	0	0	0	17	0	0	0	99	3	15	4	4	3	4	29	2	0	2	8	6	1	2	0	34	24	0	0	0	0	3	1	1	1	1	15	185
PROCAM	741	301	486	106	77	22	0	7	4	0	13	97	8	13	0	441	15	56	6	25	10	33	97	23	0	13	43	17	0	0	28	206	64	21	0	6	3	22	48	7	10	2	49	997
QUEBEC	45	10	32	6	0	0	0	6	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	32	42
RANCHO	507	113	222	185	0	1	0	175	9	16	1	0	5	10	5	173	0	21	2	3	0	11	36	28	3	6	20	4	6	1	10	200	10	7	6	31	11	7	40	22	15	4	1	487
REYK	4550	2518	3258	768	183	162	45	243	47	52	78	12	71	82	6	2426	22	281	43	182	44	173	533	203	68	64	169	93	20	38	199	1663	77	62	41	15	217	27	278	281	130	35	91	6698
RF2[c]	90	90	64	18	2	7	0	8	0	0	2	0	1	0	0	149	4	12	1	10	9	10	27	3	4	1	7	10	3	6	20	53	15	0	3	2	1	14	2	2	3	4	28	320
ROTT	652	441	244	144	38	23	3	63	1	0	3	55	21	77	2	450	3	69	14	15	5	29	92	27	6	18	46	11	3	17	43	319	43	19	0	1	79	6	34	44	28	8	169	1379
SHHEC	683	182	460	184	56	21	21	81	2	4	2	2	7	3	1	405	7	48	17	17	10	21	122	12	8	6	18	13	5	3	36	152	11	21	6	5	2	18	25	27	11	1	26	765
SHS	785	312	451	214	8	10	0	190	24	12	6	4	2	15	4	224	5	17	4	7	15	14	39	8	5	1	28	4	0	1	15	611	89	34	155	29	0	124	36	31	27	19	19	1166
SPEED	355	196	254	77	66	2	1	5	1	2	5	0	9	0	0	205	4	30	8	15	0	6	69	11	0	7	13	6	1	0	0	77	11	1	1	1	2	3	12	22	4	4	1	479
TARFS	318	257	220	61	1	0	0	60	0	0	2	12	1	11	0	34	0	4	0	1	2	1	3	1	0	0	0	1	0	0	1	25	7	0	2	1	4	0	0	3	1	0	173	489
TOYAMA	92	8	34	51	24	17	10	0	0	0	0	0	0	4	0	28	1	2	0	7	4	0	6	1	1	0	4	0	0	2	0	15	10	0	0	0	0	2	1	0	0	1	32	83
TROMSØ	1875	281	1007	727	537	88	45	52	13	12	1	30	28	19	2	592	9	76	14	39	9	37	127	42	27	12	54	15	10	11	28	352	80	12	7	13	36	12	35	66	33	8	34	1259
ULSAM	996	252	593	316	195	56	19	41	2	10	7	0	18	14	3	394	3	35	12	22	11	32	65	85	0	16	29	12	9	2	0	203	49	6	11	3	17	10	13	31	22	6	7	856
USPHS2	643	104	310	259	217	40	0	2	0	0	0	38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	688	792
VHMPP	3277	3277	1683	781	81	122	24	442	61	60	45	1	57	184	34	2300	45	264	30	184	69	149	460	138	76	55	172	87	40	19	181	1282	362	4	96	42	20	165	69	170	127	34	64	6923
VITA	66	21	38	19	15	2	1	1	5	0	0	0	1	1	0	44	2	3	1	2	4	3	7	1	0	3	4	4	1	0	3	17	6	0	2	0	0	4	0	1	1	0	4	86

Table A3.3 con't Summary of events of individual studies with complete information on height, age and sex

Study design/ study[†]	Cardiovascular outcomes															Cancer deaths																Non-cancer, non-cardiovascular deaths											Deaths of unkown or ill-defined cause[‡]	All-cause mortality
	All cardiovascular disease*	All vascular deaths	Coronary heart disease*	All stroke*	Ischaemic stroke*	Haemorrhagic stroke*	Subarachnoid heamorrhage*	Unclassified stroke*	Cardiac dysrhythmia	Hypertensive disease	Pulmonary embolism	Sudden death	Ruptured aortic aneurysm	Heart failure	Peripheral vascular disease	All cancer	Oral	Colorectal	Oesophageal	Stomach	Liver	Pancreatic	Lung	Prostate	Ovarian	Bladder	Haematological	Endocrine & nervous	Melanoma	Connective tissue	Breast (female)	All non-cancer, non-vascular	External causes	Infections	Diabetes mellitus	Mental disorders	Alzheimers & related conditions	Liver disease	Pneumonia	COPD & related conditions	Digesive system disorders (except liver)	Renal disease		
WHITEI	473	473	218	141	19	14	4	75	12	7	6	0	40	20	4	403	2	50	19	13	3	20	63	85	0	22	43	11	5	3	0	351	9	9	7	10	17	5	114	48	31	12	14	1241
WHITEII	349	94	317	10	2	2	2	4	0	2	4	0	3	1	1	160	2	23	7	7	2	7	15	6	6	3	13	8	5	3	21	72	25	2	1	0	0	10	4	7	4	1	3	329
ZARAGOZA	100	24	50	50	9	0	0	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	24
ZUTE	124	56	57	39	1	1	0	34	2	0	1	0	8	14	0	56	0	4	2	4	0	6	10	10	0	5	4	1	1	0	0	32	2	2	1	2	0	1	6	7	4	2	17	161
SUBTOTAL	73792	47869	41363	19310	5875	2454	1483	7861	1062	921	809	1442	1470	2612	396	48855	742	5115	1084	2184	897	2935	10283	3038	1469	1111	4551	1667	782	514	4118	34150	5599	1484	1574	2419	1634	2159	3755	4099	2469	1002	9330	140204
Clinical trials																																											
AFTCAPS	191	26	147	23	22	0	0	1	0	0	0	12	0	0	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16	4	0	0	0	0	0	0	0	0	0	0	57
ALLHAT	1667	6	1124	543	0	0	0	543	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	11
LEADER	181	95	99	66	51	3	0	12	1	0	1	0	3	6	3	49	1	4	2	2	2	1	25	2	0	2	2	0	0	0	0	32	0	4	0	1	0	1	11	5	4	0	7	183
MRFIT	902	256	773	80	5	4	8	61	8	7	6	0	5	0	0	141	6	10	5	9	2	7	62	4	0	2	9	3	5	1	0	84	50	1	1	0	0	11	3	4	7	0	3	484
PREVEND	206	61	140	30	0	17	7	6	3	1	2	1	9	4	1	166	3	22	3	11	0	6	39	7	1	8	7	3	2	3	9	41	12	0	3	2	3	3	2	6	4	0	13	281
PROSPER	396	88	267	115	0	0	0	115	0	0	0	0	0	0	0	113	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	42	0	0	0	0	0	0	0	0	0	0	0	243
WHS	611	93	240	290	243	26	19	2	0	0	0	52	0	0	0	380	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	160	47	0	0	0	0	0	0	31	0	0	0	633
WOSCOPS	448	80	369	70	0	0	0	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	105	185
SUBTOTAL	4602	705	3159	1217	321	50	34	810	12	8	9	65	17	10	4	867	10	36	10	22	4	14	126	13	1	12	18	6	7	4	9	377	114	5	4	3	3	15	16	46	15	0	128	2077
Nested case-control studies																																											
EPICNOR	-	-	481	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FIA	-	-	551	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FLETCHER	-	-	161	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GLOSTRUP	-	-	71	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
USPHS	-	-	245	-	153	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WHIHABPS	-	-	-	-	611	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUBTOTAL	-	-	1509	-	764	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL	78394	48574	46031	20527	6960	2504	1517	8671	1074	929	818	1507	1487	2622	400	49722	752	5151	1094	2206	901	2949	10409	3051	1470	1123	4569	1673	789	518	4127	34527	5713	1489	1578	2422	1637	2174	3771	4145	2484	1002	9458	142281

*includes fatal and non-fatal events; [†]Appendix 4 lists study acronyms; [‡]Ill-defined causes of death were non-vascular deaths defined according to study-specific read-codes for mortality; [a]CHS included an original cohort (here termed CHS1) and a supplemental African-American cohort (here termed CHS2), which were analysed separately; [b]Progetto CUORE was analysed as 8 different studies (ie, ATENA, EMOFRI, MATISS83, MATISS87, MATISS93, MONFRI86, MONFRI89 and MONFRI94); [c]RIFLE Study was analysed as 9 different studies (ie, ATS_SAR, DISCO, GREPCO, GUBBIO, MICOL, MONICA, NFR, OB43 and RF2).

Table A3.4 Risk ratios of coronary heart disease, stroke and cancer mortality per 1-SD (6.5 cm) higher baseline height, adjusted for baseline levels of biological, socioeconomic and behavioural risk factors

	Coronary heart disease*			Stroke*			Cancer mortality		
Progressive adjustment	**No of participants**	**No of events**	**RR (95% CI)**	**No of participants**	**No of events**	**RR (95% CI)**	**No of participants**	**No of deaths**	**RR (95% CI)**
Age, sex and year of birth	615842	30893	0.92 (0.90 to 0.94)	600605	12726	0.92 (0.90 to 0.95)	548327	25195	1.04 (1.02 to 1.06)
Plus smoking status	615842	30893	0.92 (0.91 to 0.94)	600605	12726	0.92 (0.90 to 0.95)	548327	25195	1.05 (1.03 to 1.06)
Plus systolic blood pressure	615842	30893	0.93 (0.91 to 0.95)	600605	12726	0.94 (0.91 to 0.96)	548327	25195	1.05 (1.03 to 1.06)
Plus history of diabetes	615842	30893	0.93 (0.91 to 0.95)	600605	12726	0.94 (0.91 to 0.96)	548327	25195	1.05 (1.03 to 1.06)
Plus body-mass index	615842	30893	0.94 (0.92 to 0.96)	600605	12726	0.94 (0.91 to 0.96)	548327	25195	1.05 (1.03 to 1.07)
Plus total cholesterol	615842	30893	0.95 (0.93 to 0.97)	600605	12726	0.94 (0.91 to 0.96)	548327	25195	1.05 (1.03 to 1.06)
Additional adjustment									
Lipids									
Basic model†	315881	13448	0.95 (0.94 to 0.97)	304657	7295	0.95 (0.92 to 0.98)	280379	9037	1.04 (1.01 to 1.07)
Plus non-HDL-C, HDL-C & $\log_e$ triglyceride‡	315881	13448	0.95 (0.93 to 0.97)	304657	7295	0.95 (0.92 to 0.98)	280379	9037	1.04 (1.01 to 1.07)
Inflammatory markers									
Basic model†	126314	8473	0.93 (0.91 to 0.95)	117054	3659	0.98 (0.94 to 1.03)	97634	4483	1.05 (1.01 to 1.09)
Plus $\log_e$ CRP	126314	8473	0.94 (0.91 to 0.96)	117054	3659	0.99 (0.94 to 1.03)	97634	4483	1.05 (1.01 to 1.10)
Basic model†	179250	8020	0.94 (0.91 to 0.97)	171161	4392	0.95 (0.91 to 1.00)	166313	6226	1.04 (1.01 to 1.07)
Plus fibrinogen	179250	8020	0.95 (0.92 to 0.97)	171161	4392	0.96 (0.92 to 1.00)	166313	6226	1.04 (1.01 to 1.07)
Lifestyle factors & FEV_1									
Age, sex, smoking and year of birth	362636	20833	0.93 (0.91 to 0.95)	352052	8623	0.95 (0.92 to 0.98)	322527	15172	1.05 (1.02 to 1.07)
Plus education	362636	20833	0.94 (0.92 to 0.96)	352052	8623	0.96 (0.93 to 0.99)	322527	15172	1.06 (1.03 to 1.09)
Age, sex, smoking and year of birth	357759	15892	0.93 (0.91 to 0.95)	350935	7373	0.94 (0.91 to 0.96)	343381	12445	1.03 (1.01 to 1.05)
Plus occupation/job	357759	15892	0.93 (0.91 to 0.96)	350935	7373	0.94 (0.92 to 0.97)	343381	12445	1.04 (1.02 to 1.06)
Age, sex, smoking and year of birth	500367	22003	0.92 (0.90 to 0.93)	488113	11076	0.93 (0.91 to 0.95)	468497	17353	1.03 (1.01 to 1.05)
Plus alcohol consumption	500367	22003	0.92 (0.90 to 0.93)	488113	11076	0.93 (0.91 to 0.96)	468497	17353	1.03 (1.01 to 1.05)
Age, sex, smoking and year of birth	72208	6463	0.90 (0.87 to 0.93)	69139	1872	0.97 (0.93 to 1.02)	70858	5294	1.04 (0.99 to 1.10)
Plus FEV_1	72208	6463	0.98 (0.92 to 1.03)	69139	1872	1.03 (0.98 to 1.09)	70858	5294	1.13 (1.05 to 1.21)

*Includes both fatal and non-fatal events.
†All basic models were adjusted for age, sex, year of birth, smoking status, systolic blood pressure, history of diabetes, body-mass index and total cholesterol.
‡Total cholesterol was not included in further adjustments.

Risk ratios were adjusted as shown, and stratified by decades of year of birth and, where appropriate, by sex and trial arm.

Table A3.5 Risk ratios for major outcomes per 1-SD (6.5cm) higher baseline height, adjusted for age, sex, year of birth and smoking status

Description of supplementary analysis	Outcome	No of events	RR (95% CI)	I^2 (95% CI)
Excluding 5 years of follow-up	Coronary heart disease*	31680	0.93 (0.91 to 0.95)	44 (29 to 56)
	Stroke*	13590	0.93 (0.91 to 0.96)	47 (32 to 59)
	Cancer mortality	39346	1.05 (1.04 to 1.07)	18 (0 to 38)
Excluding current smokers	Coronary heart disease*	27290	0.92 (0.90 to 0.94)	45 (31 to 56)
	Stroke*	14182	0.94 (0.92 to 0.97)	40 (24 to 53)
	Cancer mortality	29029	1.04 (1.03 to 1.06)	11 (0 to 31)
	Lung	3164	1.07 (1.03 to 1.10)	0 (0 to 30)
	Respiratory disease	5435	0.93 (0.88 to 0.98)	54 (40 to 65)
Excluding non-European descents	Coronary heart disease*	40743	0.92 (0.91 to 0.94)	44 (29 to 55)
	Stroke*	16197	0.94 (0.91 to 0.96)	43 (28 to 55)
	Cancer mortality	45089	1.04 (1.03 to 1.06)	19 (0 to 38)
Restricted to men only	Coronary heart disease*	30958	0.93 (0.91 to 0.94)	39 (23 to 51)
	Stroke*	10227	0.93 (0.90 to 0.95)	34 (16 to 48)
	Cancer mortality	25875	1.04 (1.03 to 1.06)	4 (0 to 26)
	All cause-mortality	79763	0.97 (0.96 to 0.98)	56 (45 to 64)
Restricted to women only	Coronary heart disease*	12236	0.93 (0.90 to 0.95)	29 (5 to 46)
	Stroke*	8235	0.94 (0.91 to 0.98)	43 (24 to 57)
	Cancer mortality	21616	1.05 (1.02 to 1.07)	17 (0 to 39)
	All cause mortality	56968	0.97 (0.95 to 0.99)	59 (48 to 68)
Adjustment for waist circumference instead of BMI[†]	Coronary heart disease*	6043	0.93 (0.90 to 0.96)	14 (0 to 41)
	Stroke*	4016	0.95 (0.91 to 1.00)	32 (0 to 54)
	Cancer mortality	4950	1.04 (1.00 to 1.08)	28 (0 to 52)
Adjustment for waist/hip ratio instead of BMI[†]	Coronary heart disease*	5913	0.95 (0.92 to 0.98)	5 (0 to 33)
	Stroke*	3908	0.97 (0.92 to 1.02)	37 (5 to 58)
	Cancer mortality	4840	1.05 (1.00 to 1.09)	30 (0 to 53)

*Includes both fatal and non-fatal events.
[†]Analyses were additionally adjusted for systolic blood pressure, history of diabetes and total cholesterol.

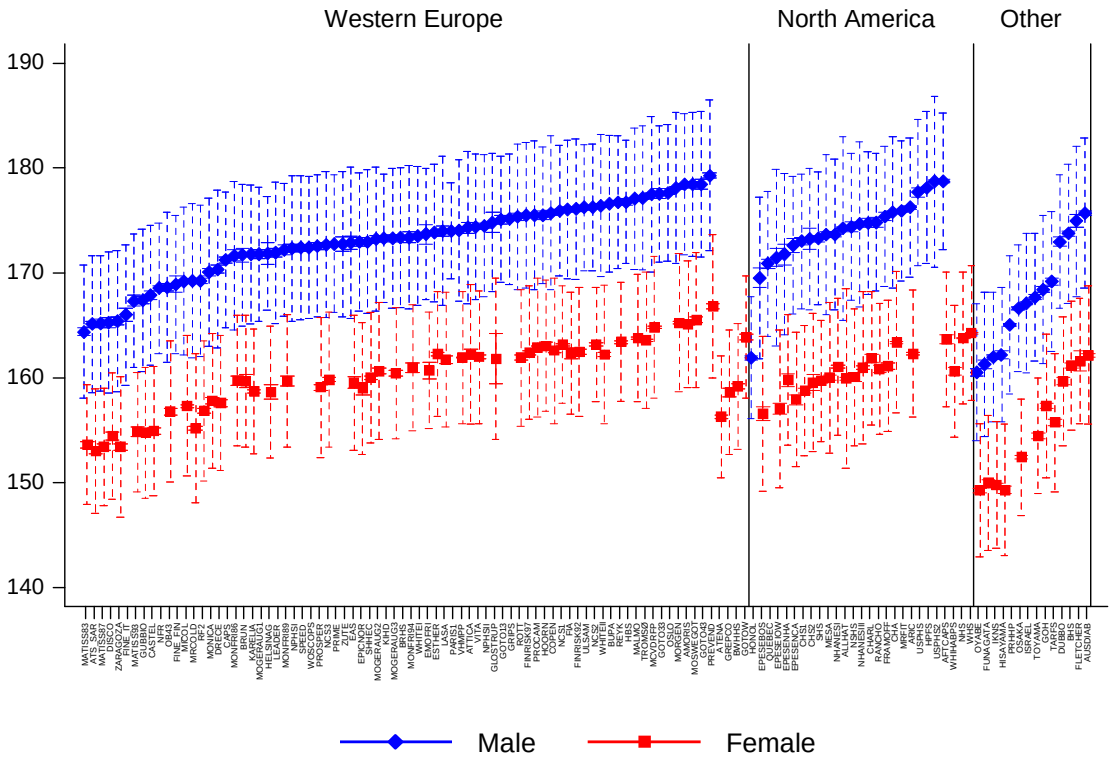
Risk ratios (RRs) were adjusted for age at baseline and smoking status and stratified by decades of year of birth and, where appropriate, by sex and trial arm.

Table A3.6 Risk ratios of cause-specific mortality without censoring for previous non-fatal outcomes per 1-SD (6.5 cm) higher baseline of height, adjusted for age, sex, year of birth and smoking status

Endpoint	No of deaths	RR (95%CI)	I^2 (95% CI)
All cardiovascular deaths	56989	0.94 (0.93 to 0.96)	61 (52 to 68)
Coronary deaths	30552	0.93 (0.91 to 0.95)	40 (24 to 52)
Stroke	11749	0.92 (0.89 to 0.95)	55 (43 to 64)
Ischaemic stroke	1662	0.90 (0.84 to 0.96)	27 (0 to 47)
Haemorrhagic stroke	1711	0.93 (0.87 to 1.00)	31 (3 to 51)
Subarachnoid haemorrhage	1145	0.90 (0.81 to 1.01)	38 (4 to 60)
Unclassified stroke	5123	0.93 (0.89 to 0.97)	38 (18 to 54)
Other vascular deaths			
Hypertensive disease	978	0.91 (0.83 to 1.00)	43 (15 to 61)
Heart failure	2970	0.94 (0.90 to 0.97)	6 (0 to 31)
Sudden death	1737	0.99 (0.93 to 1.05)	27 (0 to 55)
Cardiac dysrhythmia	1201	1.02 (0.95 to 1.09)	25 (0 to 49)
Peripheral vascular disease	361	0.99 (0.86 to 1.13)	17 (0 to 53)
Pulmonary embolism	780	1.12 (1.03 to 1.22)	16 (0 to 44)
Ruptured aortic aneurysm	1457	1.12 (1.05 to 1.19)	20 (0 to 46)
All cancer deaths	50926	1.04 (1.03 to 1.06)	18 (0 to 36)
Melanoma	693	1.25 (1.11 to 1.40)	41 (7 to 62)
Connective tissue	431	1.12 (1.01 to 1.24)	5 (0 to 37)
Pancreas	2889	1.09 (1.05 to 1.14)	9 (0 to 33)
Endocrine & nervous	1585	1.11 (1.05 to 1.16)	0 (0 to 33)
Breast (female)	4026	1.08 (1.04 to 1.11)	0 (0 to 34)
Bladder	1107	1.07 (0.98 to 1.17)	38 (11 to 57)
Liver	795	1.06 (0.96 to 1.16)	34 (3 to 55)
Ovary	1428	1.07 (1.01 to 1.13)	0 (0 to 38)
Prostate	3036	1.06 (1.02 to 1.11)	5 (0 to 31)
Colorectum	5116	1.06 (1.03 to 1.10)	16 (0 to 38)
Haematological	4481	1.05 (1.02 to 1.08)	0 (0 to 29)
Lung	10569	1.04 (1.02 to 1.07)	3 (0 to 24)
Oesophagus	1074	0.97 (0.90 to 1.04)	12 (0 to 40)
Stomach	2154	0.95 (0.91 to 1.00)	14 (0 to 38)
Oral	665	0.88 (0.81 to 0.96)	8 (0 to 40)
Other/Unspecified	9937	1.03 (1.01 to 1.05)	0 (0 to 25)
Non-vascular non-cancer deaths	37173	0.92 (0.90 to 0.94)	49 (37 to 60)
COPD & related conditions	4351	0.85 (0.81 to 0.89)	35 (13 to 52)
Mental disorders	2534	0.89 (0.83 to 0.96)	36 (8 to 56)
Liver disease	2066	0.88 (0.84 to 0.93)	16 (0 to 40)
Diabetes mellitus	1610	0.93 (0.88 to 0.99)	16 (0 to 45)
All external causes	5716	0.96 (0.93 to 1.00)	25 (0 to 43)
Infections	1517	0.96 (0.89 to 1.02)	25 (0 to 49)
Alzheimer's and related conditions	1763	0.97 (0.93 to 1.02)	0 (0 to 40)
Pneumonia	4176	0.95 (0.91 to 0.99)	24 (0 to 45)
Renal disease	1022	0.97 (0.91 to 1.03)	0 (0 to 37)
Intentional self-harm	1119	0.98 (0.89 to 1.07)	35 (0 to 57)
Digestive system disorders (except liver)	2584	0.99 (0.95 to 1.04)	15 (0 to 39)
Falls	574	1.12 (1.02 to 1.24)	12 (0 to 47)
Other/Unspecified	9182	0.96 (0.94 to 0.99)	6 (0 to 28)
Deaths of unknown or ill-defined cause	11033	0.96 (0.93 to 0.99)	43 (26 to 57)
All-cause mortality	156185	0.97 (0.96 to 0.98)	73 (67 to 78)

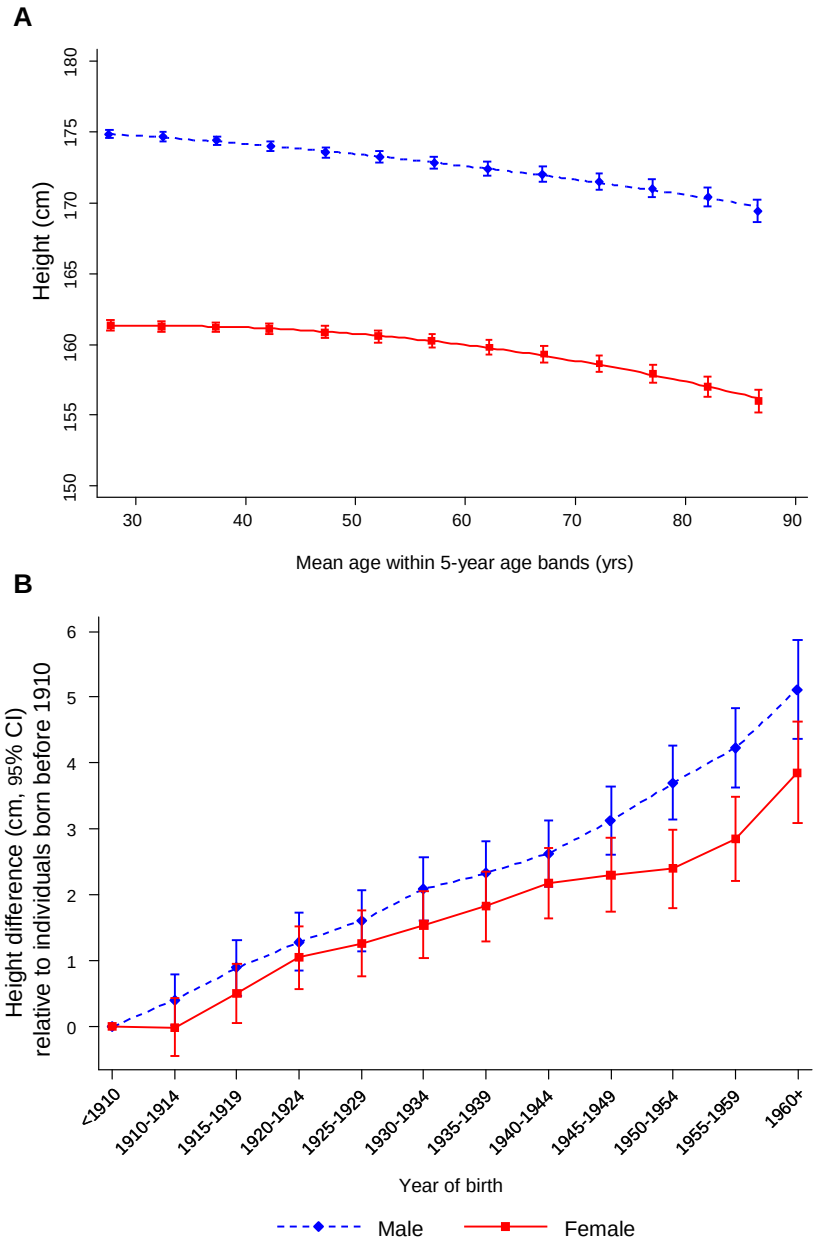
Risk ratios (RRs) are presented per 1-SD (6.5 cm) higher baseline height values. Risk ratios were adjusted for age and smoking and stratified by decades of year of birth and, where appropriate, by sex and trial arm.

Figure A3.1 Sex-specific mean baseline height values (95% CI, +/- 1-SD), by geographical region



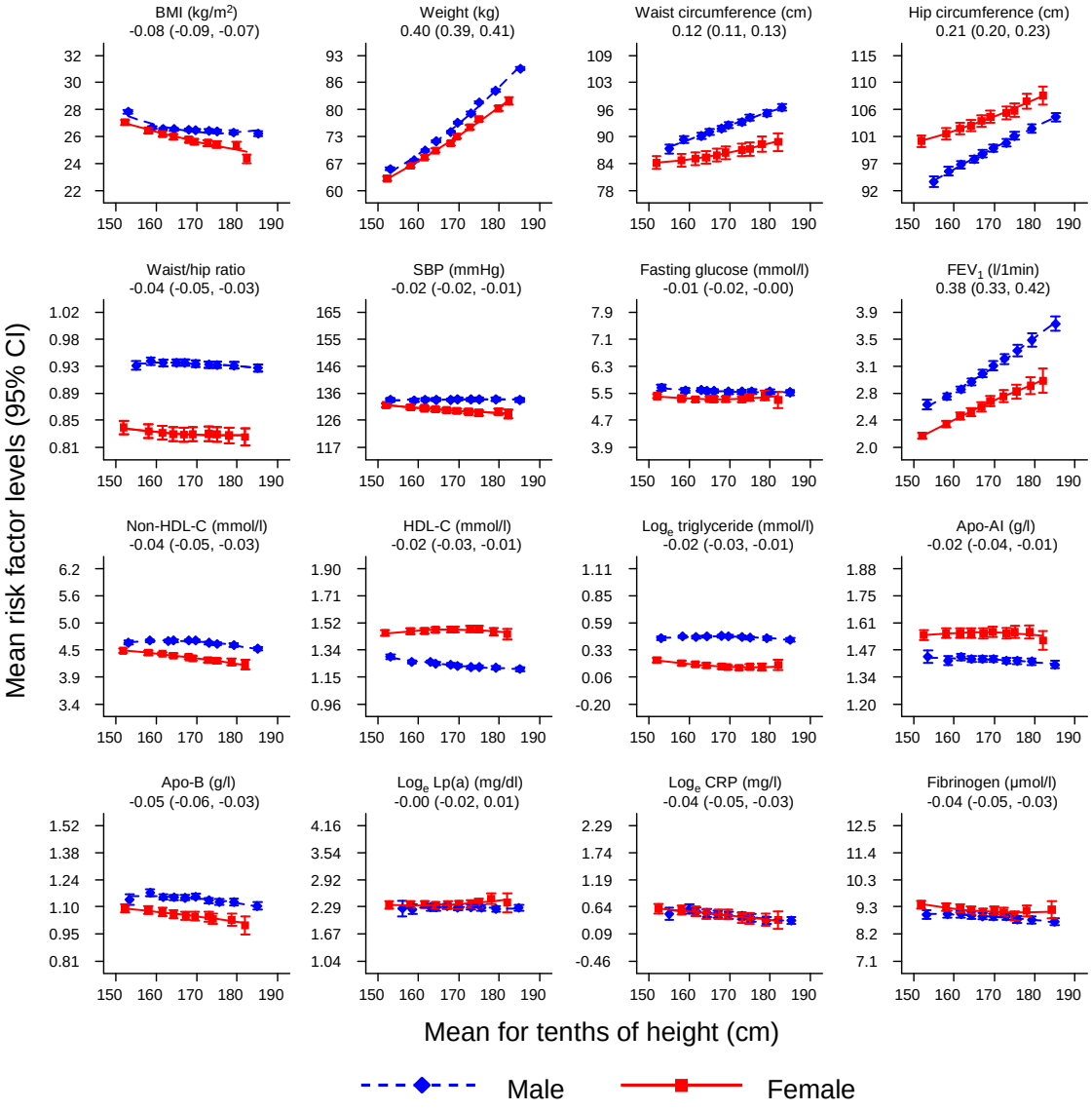
Appendix 4 lists study acronyms.

Figure A3.2 Mean baseline height within 5-year age bands (panel A) and differences in baseline height across calendar years relative to individuals born before 1910 (panel B)



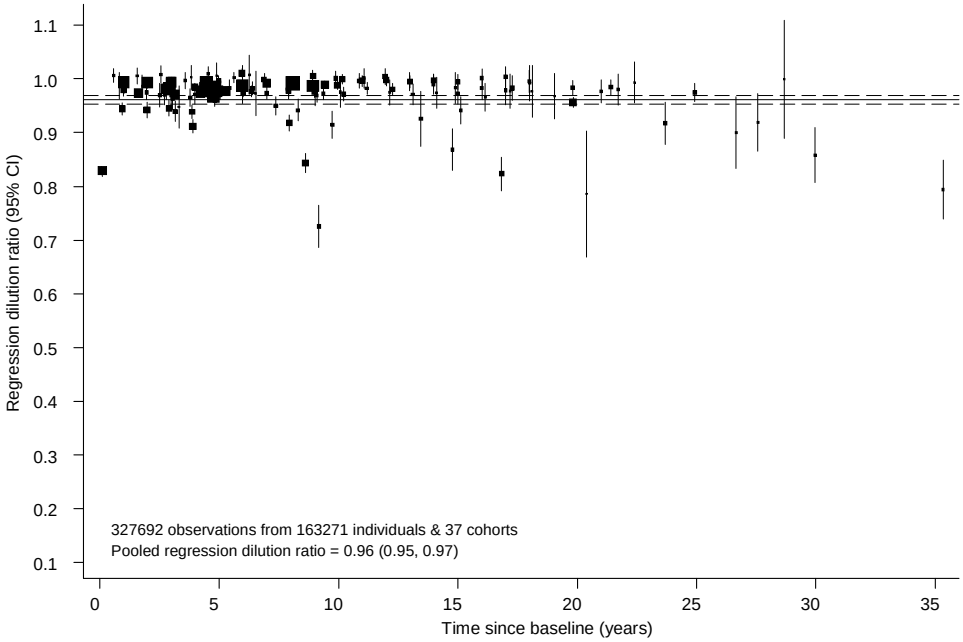
All analyses were adjusted for study. Also, mean baseline height values were adjusted for year of birth (panel A), and differences in baseline height were adjusted to age 50 years (panel B).

Figure A3.3 Cross-sectional associations between height and some continuous risk factors



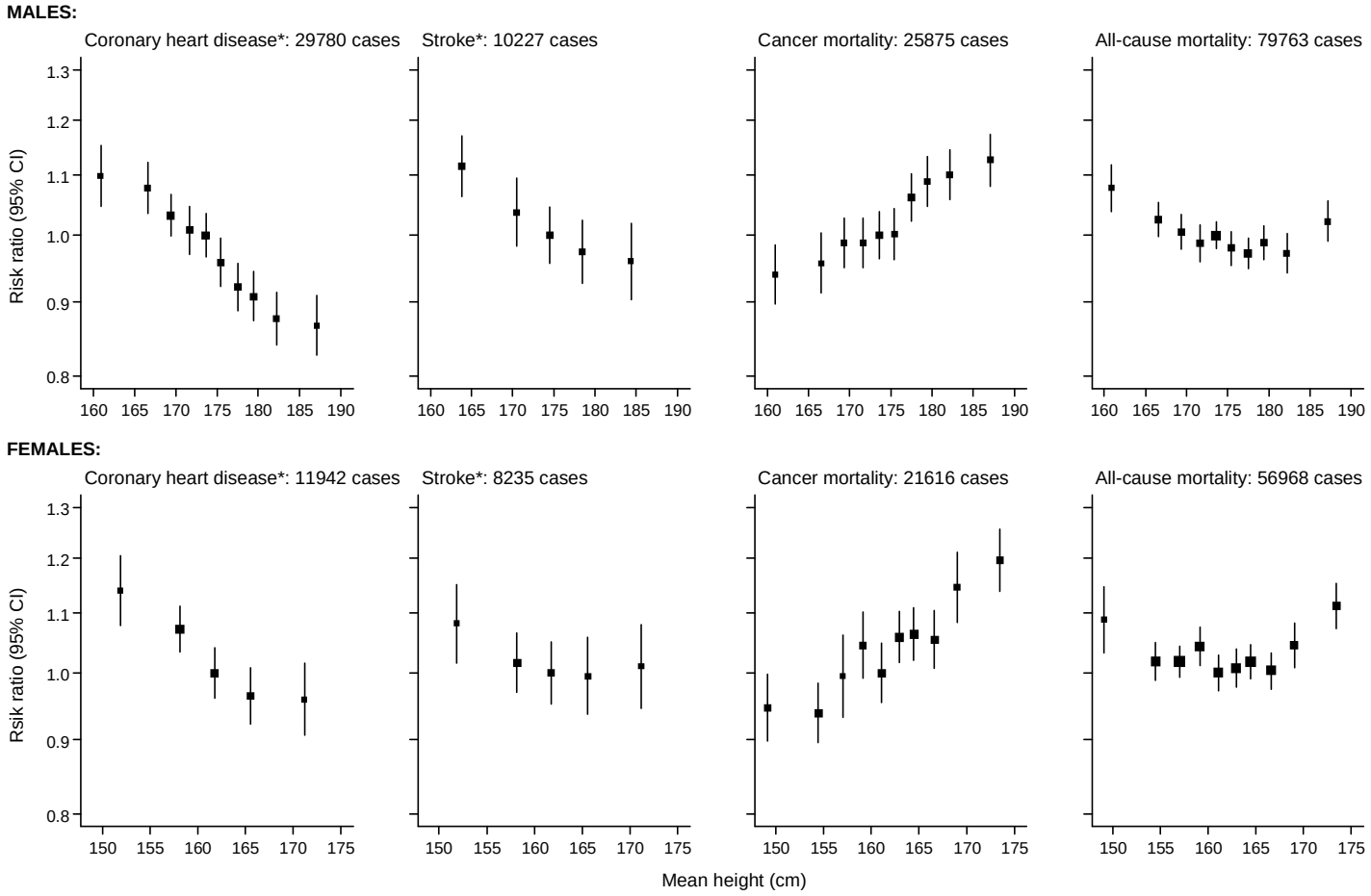
Mean risk factor levels were adjusted to age 50 years. The values above each figure correspond to the age, sex and birth year adjusted partial correlation coefficient (95% CI) between risk factor and height in males and females combined.

Figure A3.4 Regression dilution ratios for height plotted against time since baseline measurement by study



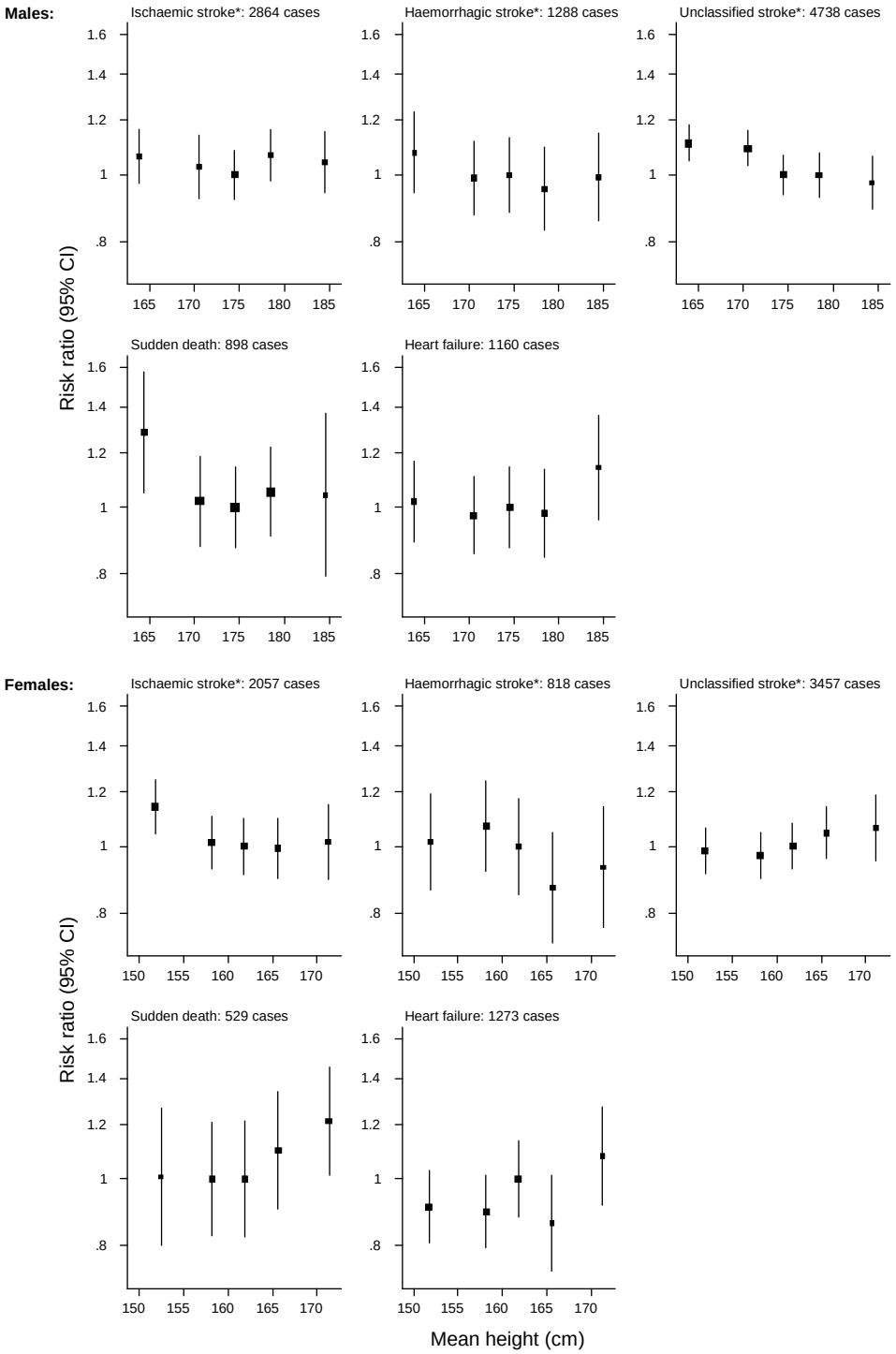
Analyses were adjusted for age at baseline, sex and decades of year of birth.

Figure A3.5 Risk ratios for coronary heart disease, stroke, cancer mortality and all-cause mortality across quantiles of baseline height, among males and females



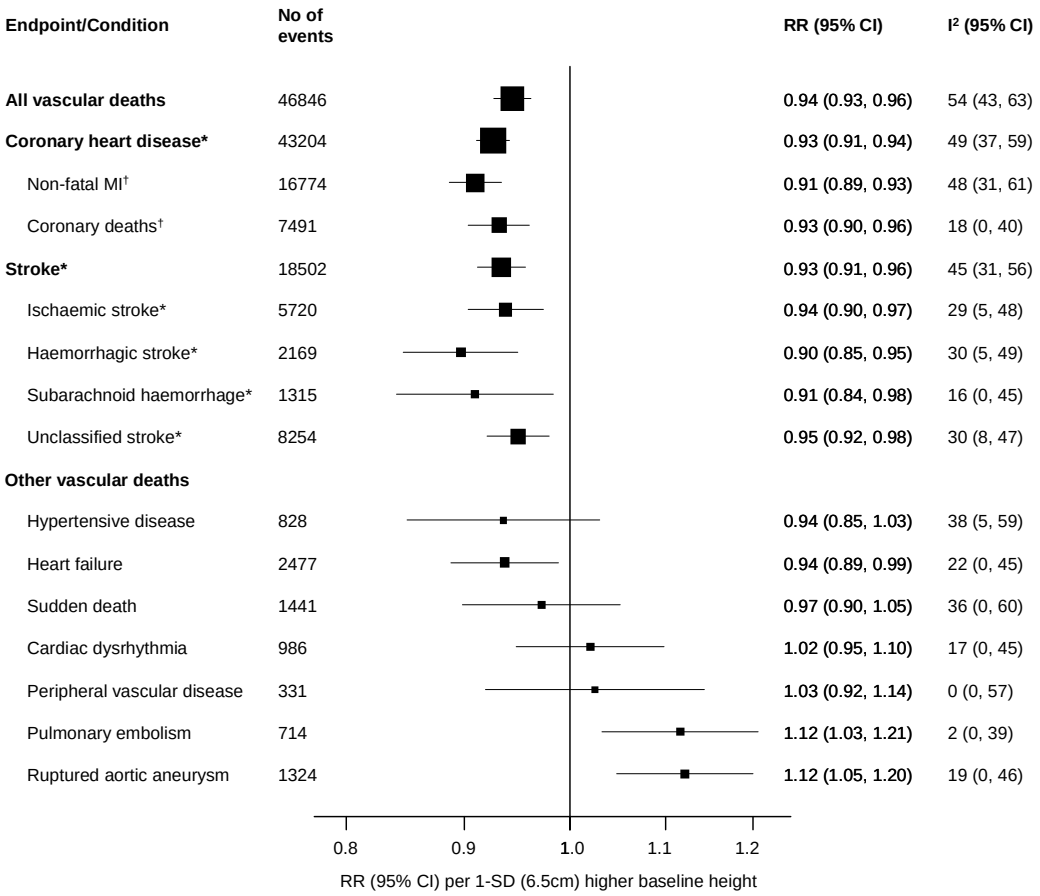
*Includes fatal and non-fatal events. Regression analyses were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by trial arm. Reference groups are the fifth deciles or third quintiles in the plots.

Figure A3.6 Risk ratios for vascular outcomes across quintiles of baseline height



*Includes fatal and non-fatal events. Regression analyses were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by trial arm. Reference groups are the third quintile of the plots. Other vascular outcomes are not shown, because there were generally too few deaths for each sex to characterise reliably shape of associations.

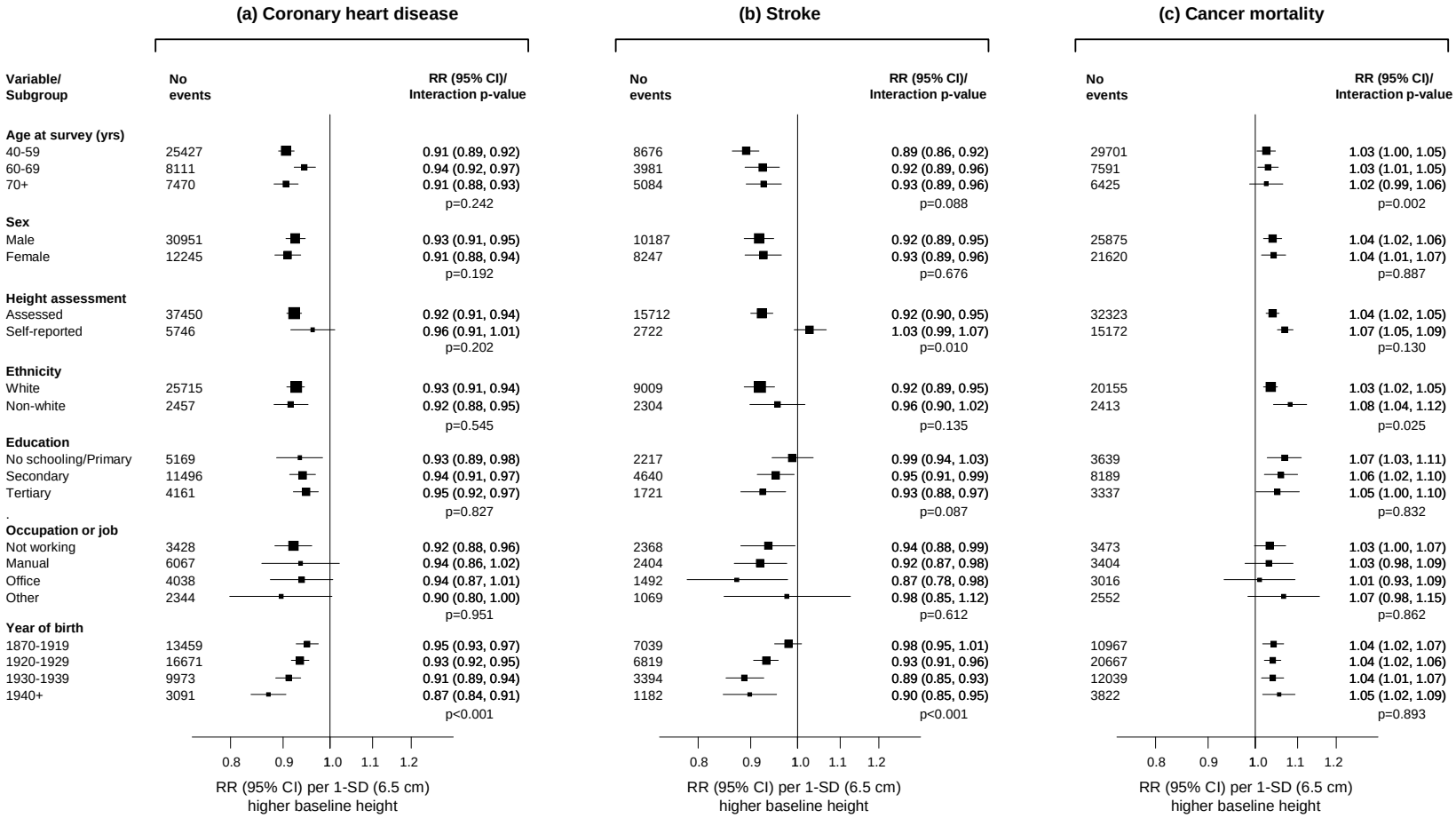
Figure A3.7 Risk ratios for vascular outcomes per 1-SD (6.5cm) higher baseline height, adjusted for age, sex, smoking and year of birth



*Includes both fatal and non-fatal events.
†Restricted to studies contributing to both outcomes.

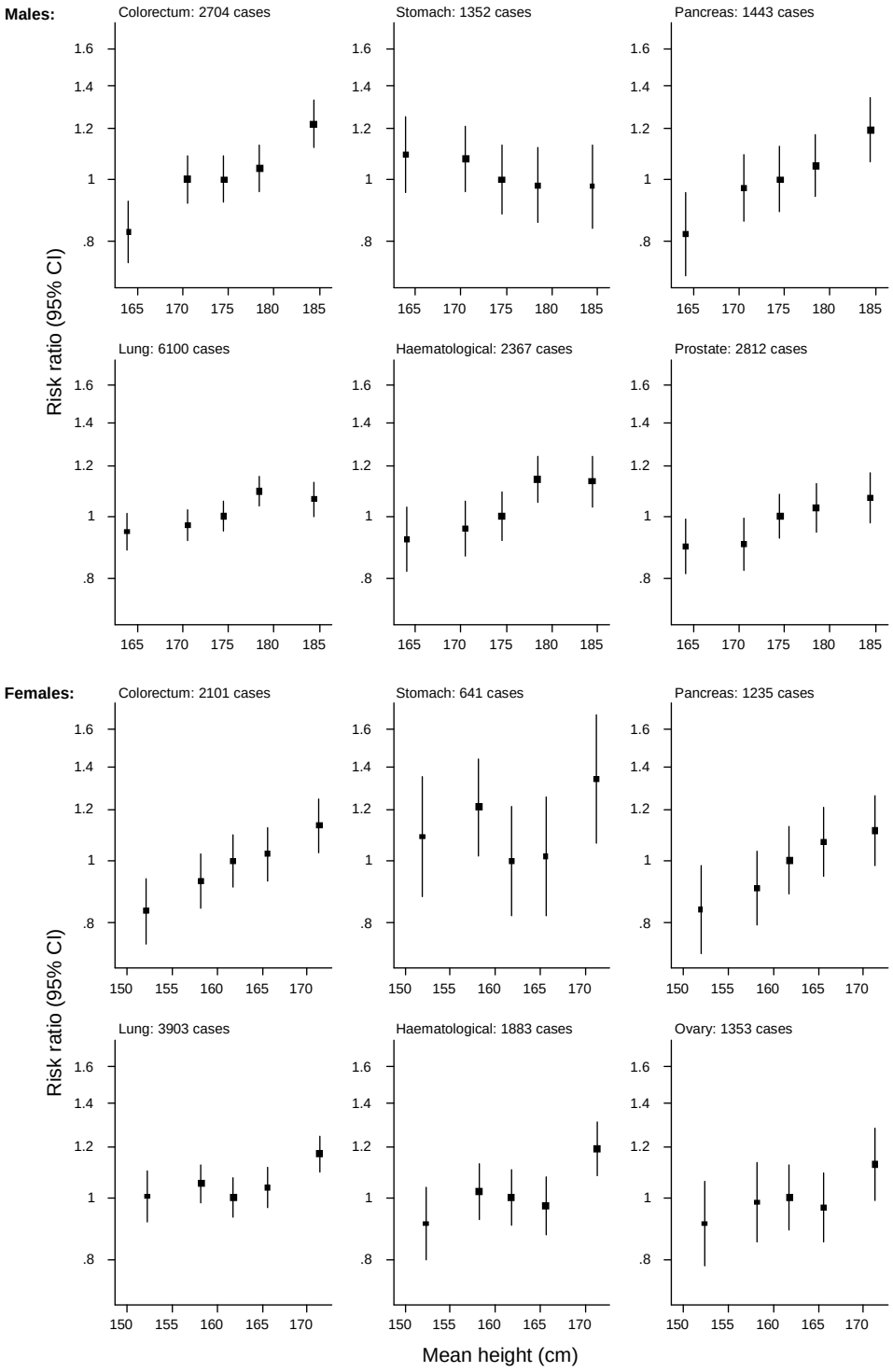
Causes of other vascular deaths are ordered by their strength of association. Risk ratios (RRs) were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by sex and trial arm. There was evidence of heterogeneity in risk ratios among vascular outcomes (P-value for heterogeneity <0.001).

Figure A3.8 Risk ratios for coronary heart disease, stroke and cancer mortality per 1-SD (6.5cm) higher baseline height, according to baseline levels of various characteristics



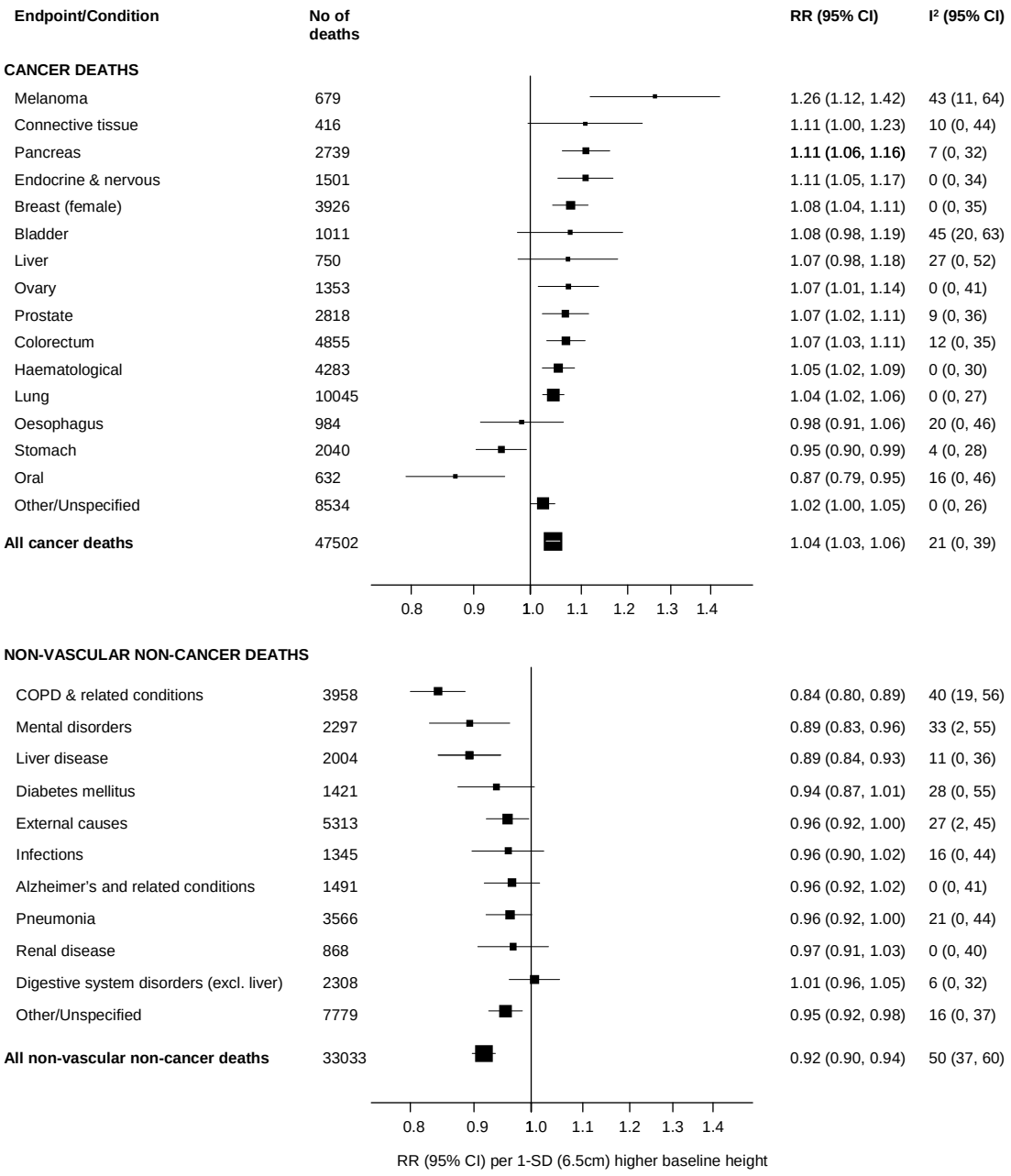
Risk ratios were adjusted for age at baseline and smoking status, and stratified by decades of year of birth, and, where appropriate, by sex and trial arm. Abbreviations: Assessed = height was assessed using standardised protocol; Self-reported = height was measured by the subject itself.

Figure A3.9 Risk ratios for site-specific cancer mortality across quintiles of baseline height



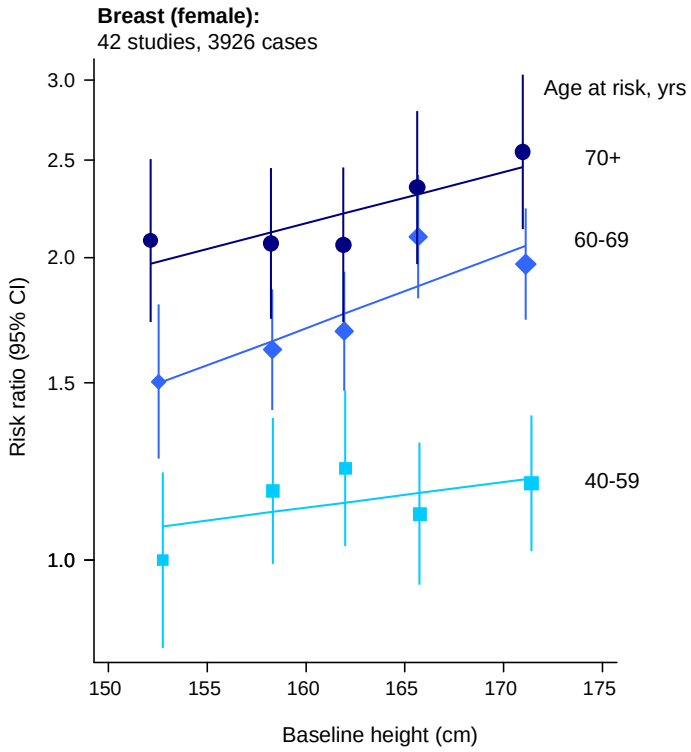
Regression analyses were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by trial arm. Reference groups are the third quintile of the plots. Other cancer outcomes are not shown, because there were generally too few deaths for each sex to characterise reliably shape of associations.

Figure A3.10 Risk ratios for cause-specific non-vascular mortality per 1-SD (6.5cm) higher baseline height, adjusted for age, sex, smoking and year of birth



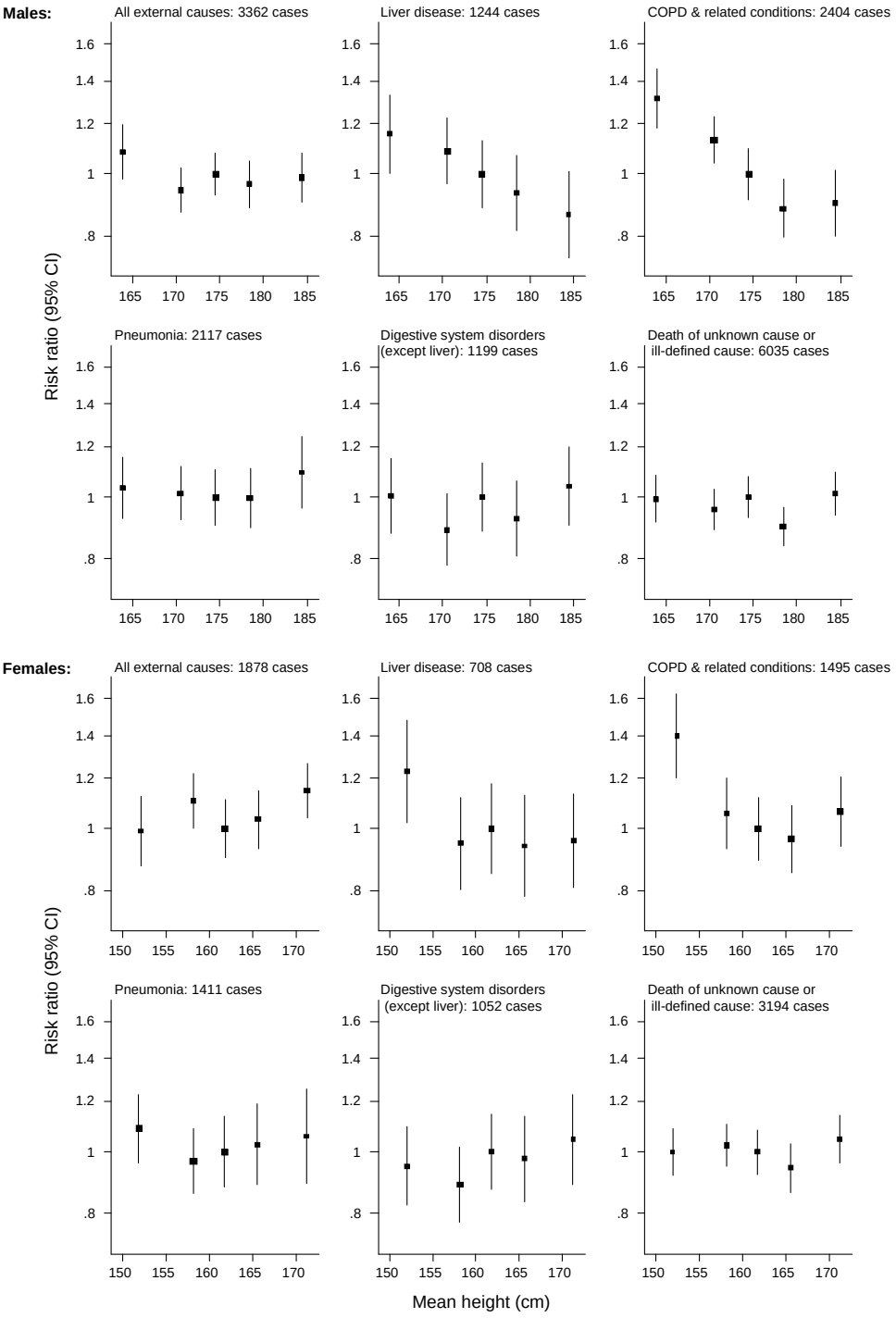
With the exception of the classifications "Other/Unspecified", causes of deaths are ordered by their strength of association. Risk ratios (RRs) were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by sex and trial arm. There was evidence of heterogeneity in risk ratios among cancer sites and among the non-vascular non-cancer causes of deaths (P-value for heterogeneity <0.001 for both comparisons). Risk ratio for all-cause mortality per 1-SD (6.5cm) was 0.97 (0.96-0.99), I^2 = 69% (63% to 75%) and for unknown or ill-defined cause was 0.96 (0.93-1.00), I^2 = 45% (27% to 58%).

Figure A3.11 Age-at-risk specific risk ratios for breast cancer mortality by fifth of baseline height, adjusted for year of birth and smoking status



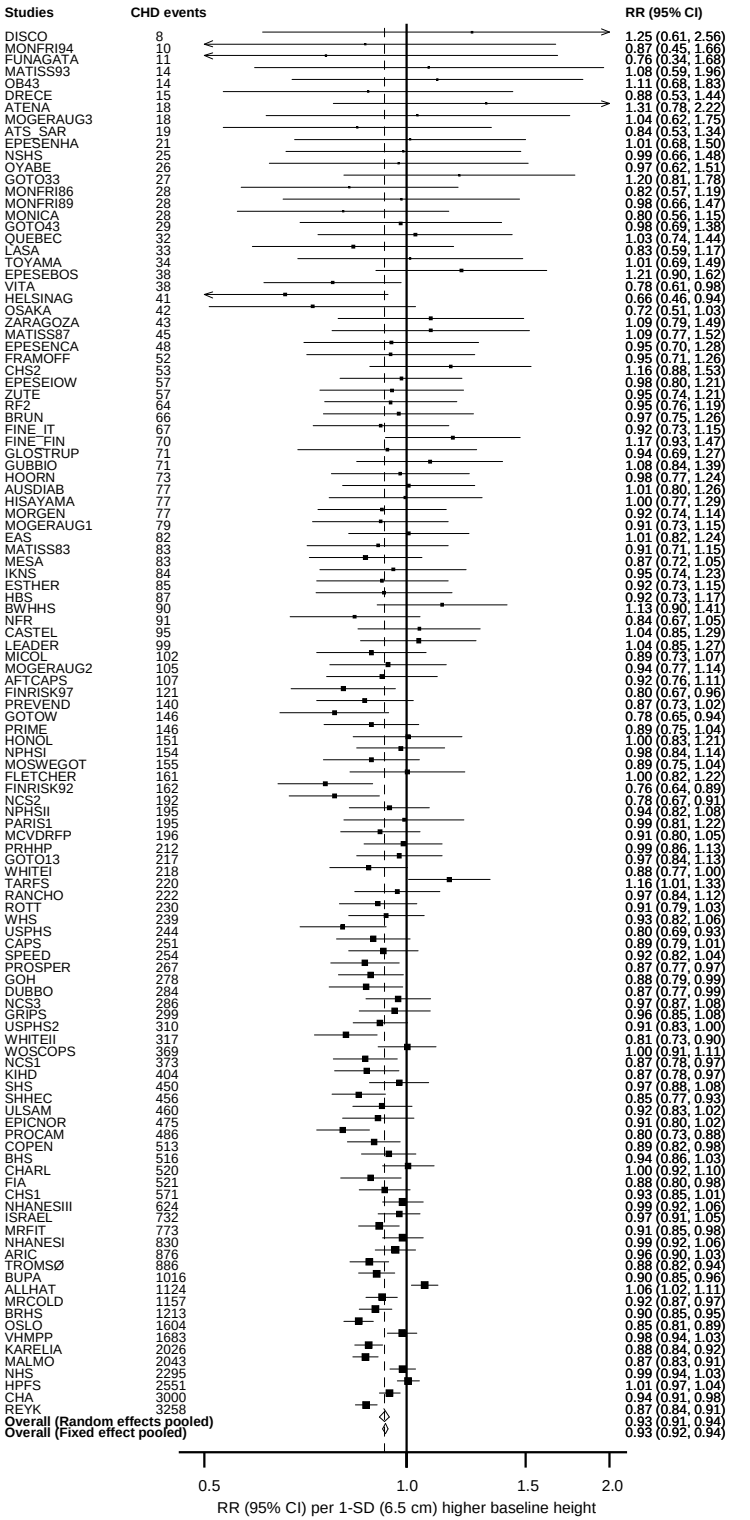
Risk ratios (RRs) were adjusted for smoking status and stratified by decades of year of birth and, where applicable, by trial arm. P-value for interaction between baseline height values and age-at-risk groups was 0.53.

Figure A3.12 Risk ratios for non-vascular non-cancer specific mortality across quintiles of baseline height



Regression analyses were adjusted for age at baseline and smoking status, and stratified by decades of year of birth and, where appropriate, by trial arm. Reference groups are the third quintile of the plots. Other outcomes are not shown, because there were generally too few deaths for each sex to characterise reliably shape of associations

Figure A3.13 Study-specific risk ratios for coronary heart disease per 1-SD (6.5cm) higher baseline height, adjusted for age, sex, year of birth and smoking status



I^2 = 49% (95% CI 37% to 59%).

APPENDIX 4: List of study acronyms

AFTCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; **ALLHAT**, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **AMORIS**, Apolipoprotein Related Mortality Risk Study; **ARIC**, Atherosclerosis Risk in Communities Study; **ATENA**, cohort of Progetto CUORE; **ATS_SAR,** cohort of Risk Factors and Life Expectancy Pooling Project; **ATTICA**, ATTICA Study; **AUSDIAB**, Australian Diabetes, Obesity and Lifestyle Study; **BHS**, Busselton Health Study; **BRHS**, British Regional Heart Study**;** **BRUN**, Bruneck Study; **BUPA**, BUPA Study; **BWHHS**, British Women's Heart and Health Study; **CaPS**, Caerphilly Prospective Study; **CASTEL**, Cardiovascular Study in the Elderly; **CHA**, Chicago Heart Association Study; **CHARL**, Charleston Heart Study; **CHS-1**, original cohort of the Cardiovascular Health Study; **CHS-2**, supplemental African-American cohort of the Cardiovascular Health Study; **COPEN**, Copenhagen City Heart Study; **DISCO**, cohort of Risk Factors and Life Expectancy Pooling Project; **CUORE**, Progetto CUORE; **DRECE**, Diet and Risk of Cardiovascular Disease in Spain; **DUBBO**, Dubbo Study of the Elderly; **EAS**, Edinburgh Artery Study; **EMOFRI**, part of CUORE; **EPESEBOS**, The Established Populations for the Epidemiologic Study of the Elderly Studies, Boston; **EPESEIOW**, The Established Populations for the Epidemiologic Study of the Elderly Studies, Iowa; **EPESENCA**, The Established Populations for the Epidemiologic Study of the Elderly Studies, North Carolina; **EPESENHA**, The Established Populations for the Epidemiologic Study of the Elderly Studies, New Haven; **EPICNOR,** European Prospective Investigation of Cancer Norfolk Study; **ESTHER**, Epidemiologische Studie zu Chancen der Verhutung und optimierten Therapie chronischer Erkrankungen in der alteren Bevolkerung; **FIA,** First Myocardial Infarction in Northern Sweden; **FINE-FIN**, Finland, Italy and Netherlands Elderly Study - Finland cohort; **FINE-IT**, Finland, Italy and Netherlands Elderly Study – Italian cohort; **FLETCHER**, Fletcher Challenge Blood Study; **FINRISK-92**, Finrisk Cohort 1992; **FINRISK-97**, Finrisk Cohort 1997; **FRAMOFF**, Framingham Offspring Study; **FUNAGATA**, The Funagata Study; **GLOSTRUP**, Research Centre for Prevention and Health; **GOH**, The Glucose Intolerance, Obesity and Hypertension Study; **GOTO13**, Goteborg Study 1913; **GOTO33**, Göteborg 1933 Study; **GOTO43**, Göteborg 1943 Study; **GOTOW**, Population Study of Women in Gothenburg, Sweden; **GREPCO,** cohort of Risk Factors and Life Expectancy Pooling Project; **GRIPS**, Göttingen Risk Incidence and Prevalence Study; **GUBBIO**, cohort of Risk Factors and Life Expectancy Pooling Project; **HBS**, Helsinki Businessmen Study; **HELSINAG**, Helsinki Aging Study; **HISAYAMA,** Hisayama Study; **HONOL**, Honolulu Heart Program; **HOORN**, Hoorn

Study; **HPFS**, Health Professionals Follow-up Study; **IKNS**, Ikawa, Kyowa, and Noichi Study; **ISRAEL**, Israeli Ischaemic Heart Disease Study;**KARELIA**, North Karelia Project; **KIHD**, Kuopio Ischaemic Heart Disease Study; **LASA**, Longitudinal Aging Study Amsterdam; **LEADER**, Lower Extremity Arterial Disease Event Reduction Trial; **MALMO**, Malmö Study; **MATISS-83**, cohort of Progetto CUORE; **MATISS-87**, cohort of Progetto CUORE; **MATISS-93**, cohort of Progetto CUORE; **MCVDRFP**, Monitoring of CVD Risk Factors Project; **MESA**, Multi-Ethnic Study of Atherosclerosis; **MICOL**, cohort of Risk Factors and Life Expectancy Pooling Project; **MOGERAUG1**, MONICA/KORA Augsburg Surveys S1; **MOGERAUG2**, MONICA/KORA Augsburg Surveys S2; **MOGERAUG3**, MONICA/KORA Augsburg Surveys S3; **MONFRI-86**, cohort of Progetto CUORE; **MONFRI-89**, cohort of Progetto CUORE; **MONFRI-94**, cohort of Progetto CUORE; **MONICA**, cohort of Risk Factors and Life Expectancy Pooling Project; **MORGEN**, Monitoring Project on Chronic Disease Risk Factors; **MOSWEGOT**, MONICA Göteborg Study; **MRCOLD**, MRC Study of Older People; **MRFIT**, Multiple Risk Factor Intervention Trial 1; **NCS 1, 2 and 3**, Norwegian Counties Studies; **NFR**, cohort of Risk Factors and Life Expectancy Pooling Project; **NHANES I**, First National Health and Nutrition Examination Survey; **NHANES III**, Third National Health and Nutrition Examination Survey; **NHS**, Nurses' Health Study; **NPHSI**, Northwick Park Heart Study I; **NPHSII**, Northwick Park Heart Study II; **NSHS**, Nova Scotia Health Survey; **OB43**, cohort of Risk Factors and Life Expectancy Pooling Project; **OSAKA**, Osaka Study; **OSLO**, Oslo Study; **OYABE**, Oyabe study; **PARIS1**, Paris Prospective Study I; **PREVEND**, Prevention of Renal and Vascular End Stage Disease Study; **PRHHP**, Puerto Rico Heart Health Program; **PRIME**, Prospective Epidemiological Study of Myocardial Infarction; **PROCAM**, Prospective Cardiovascular Münster Study; **PROSPER**, Prospective Study of Pravastatin in the Elderly at Risk; **QUEBEC**, Quebec Cardiovascular Study; **RANCHO**, Rancho Bernardo Study; **REYK**, Reykjavik Study; **RF2**, cohort of Risk Factors and Life Expectancy Pooling Project; **RIFLE**, Risk Factors and Life Expectancy Pooling Project; **ROTT**, The Rotterdam Study; **SHHEC**, Scottish Heart Health Extended Cohort; **SHS**, Strong Heart Study; **SPEED**, Speedwell Study; **TARFS**, Turkish Adult Risk Factor Study; **TOYAMA**, Toyama; **TROMSØ**, Tromsø Study; **ULSAM**, Uppsala Longitudinal Study of Adult Men; **USPHS**, U.S. Physicians Health Study; **USPHS2**, U.S. Physicians Health Study II; **VHMPP**, Vorarlberg Health Monitoring and Promotion Programme; **VITA**, Vicenza Thrombophilia and Athrosclerosis Project; **WHIHABPS**, Women's Health Initiative (Hormones and Biomarkers Predicting Stroke in Women); **WHITE I**, Whitehall I Study; **WHITE II**, Whitehall II Study; **WHS**, Womens Health Study; **WOSCOPS**, West of Scotland Coronary Prevention Study; **ZARAGOZA**, Zaragosa study; **ZUTE**, Zutphen Elderly Study