

**ADIPOSITY AND CAUSE-SPECIFIC MORTALITY
IN THE MEXICO CITY PROSPECTIVE STUDY**

DPhil Thesis

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Abstract

Background: Previous studies have reported conflicting results about the associations of adiposity with risk of all-cause mortality in Hispanic populations. Moreover, the relevance of different markers of adiposity for cause-specific mortality may differ between Hispanic and other populations.

Methods: Between 1998 and 2004, 159 755 adults aged ≥ 35 years from Mexico City were enrolled into a prospective study. Follow-up for cause-specific mortality was until 1st January 2018. Cox regression was used to estimate the relative risks (RRs) of death from specific causes associated with general adiposity (total body mass [BMI] and fat mass index [FMI]) and with abdominal adiposity (waist circumference, waist-hip ratio [WHR], and waist-height ratio [WHtR]), both overall and independently of each other, after adjustment for confounders. To minimise bias from reverse causation, the main analyses excluded those with screen-detected or diagnosed diabetes, other chronic diseases, and deaths in the first 5 years of follow-up. Excess attributable mortality and survival curves were derived from the RRs combined with national mortality rates.

Results: Among those aged 35-89 years when recruited, mean (standard deviation [SD]) BMI was 29.5 (4.9) kg/m² and 34% were obese (>30 kg/m²). Both BMI and FMI had J-shaped associations with all-cause mortality, whereas waist circumference, WHR and WHtR were all linearly and positively related to mortality throughout the ranges studied. Each 5 kg/m² higher BMI above 25 kg/m² was associated with 32% higher risk of death at ages 40-74 years, chiefly due to a 38% higher risk of death from vascular or metabolic diseases. Across the full ranges, 1 SD higher levels of the adiposity markers were associated with 21% higher mortality at ages 40-74 years for BMI, 22% higher mortality for FMI, 25% higher mortality for waist circumference, 17% higher mortality for WHR, and 26% higher mortality for WHtR. For deaths from a vascular or metabolic cause, these estimates were 29%, 31%, 32%, 24% and 37%, respectively. Adjustment of BMI, WHR and WHtR for other markers of adiposity resulted in only a modest attenuation of the strength of the associations of these markers with mortality. By contrast, adjustment of waist circumference for the other markers of adiposity

strengthened its association with mortality. Similarly, after adjustment for lean mass index, the association of FMI with all-cause mortality was strengthened. The various adiposity markers also displayed associations with several non-vascular non-metabolic causes of death. In particular, all of the adiposity markers were strongly related to death from respiratory and infective causes, but none were strongly associated with cancer mortality. Associations were broadly similar in men and women, somewhat stronger at younger than at older ages, and consistent according to levels of other confounders. Sensitivity analyses replicated the results of the main findings. Among those with diabetes, adiposity (particularly BMI) was *inversely* related to mortality, reflecting a reversal of causality caused by weight loss resulting from poor glycaemic control. The excess mortality associated with BMI above 30 kg/m² compared with BMI below 25 kg/m² accounted for 14% of all vascular and metabolic deaths. Applying the findings to current national Mexican death rates, compared with a BMI of 25 kg/m² life expectancy from age 40 years was reduced by about 3 years at a BMI of 30 kg/m², but by almost 10 years at a BMI of 40 kg/m².

Conclusions: Consistent with findings in Western populations, both general, and especially, abdominal adiposity, were strongly predictive of all-cause and cause-specific mortality in this Mexican cohort, thereby refuting the ‘Hispanic obesity paradox’. The failure of previous studies of Hispanic populations to detect such associations is likely due to their failure to account for reverse causality bias (arising from weight loss due to poorly controlled diabetes). Further studies are needed to elucidate the causal relevance of the associations with different markers of adiposity, and to determine the mechanisms underlying such associations.

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List of Abbreviations

BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
FM	Fat Mass
FMI	Fat Mass Index
HbA1c	Glycosylated haemoglobin
HC	Hip circumference
HDL-c	High Density Lipoprotein Cholesterol
Ht	Height
ICD-10	International Classification of Disease 10 th edition
LDL-c	Low Density Lipoprotein Cholesterol
LM	Lean Mass
LMI	Lean Mass Index
RDR	Regression dilution ratio
RR	Death Rate Ratio
SE	Standard error
SD	Standard deviation
TG	Triglycerides
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-hip ratio
WHtR	Waist-height ratio

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S70	Relevance of each 11.3 cm higher baseline waist circumference (full ranges) to mortality at ages 40–74 years, with progressive adjustment for baseline confounders, among those with HbA1c $< 7\%$, without diabetes or other chronic disease, and after exclusion of the first 5 years of follow-up
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Chapter 1: Introduction

1.1 Background

Adiposity is one of the chief determinants of morbidity and premature mortality,¹ and overweight and obesity (defined by body-mass index [BMI] ≥ 25 or ≥ 30 kg/m², respectively²) have been estimated to account for about 4 million deaths per year worldwide.³ In the last three decades, the prevalence of obesity has increased, and continues to increase in many populations throughout the world, particularly in Latin-America.⁴ Yet, excess adiposity is largely avoidable, and public health interventions worldwide have defined targets to reduce the prevalence of obesity by 50%, in order to reduce the subsequent risks associated with excess premature deaths by 2025.⁵ But the forecasts in achieving such targets are pessimistic, with little evidence of success to date, as addressing the obesity epidemic requires a sustained multi-factorial preventive approach.⁶

The determinants of excess adiposity are complex, as are the consequences of adiposity for multiple comorbidities, and excess mortality from vascular, metabolic (i.e., diabetes), as well as other chronic diseases.⁷ Although the worldwide mortality rates for vascular-metabolic diseases have decreased substantially over the last five decades by 17% per decade,⁸ vascular mortality remains the global leading cause of premature death, accounting for over 17.5 million deaths annually.⁹ A study comparing changes in vascular-metabolic risk factors (e.g., BMI, cholesterol and blood-pressure), with changes in vascular-metabolic deaths between 1980 and 2009 in 26 industrialised countries, demonstrated reductions in mortality (associated with reductions in levels

of traditional risk factors), but reported that Mexico was a country where the mortality rates did not decline.¹⁰ In 2014, Mexico was ranked as the 5th most severe obese population in the world and the 2nd most severe obese population in Latin-America (after USA, China, Russia and Brazil), with 22.9% of male and 20.3% of female adults estimated to have a BMI ≥ 30 kg/m² (and 5.5% and 12.9%, respectively, with a BMI ≥ 35 kg/m²).¹¹ In 2016, chronic kidney disease, diabetes, ischaemic heart disease and stroke, were estimated as the leading causes of death from non-communicable disease in Mexico.⁹ Paradoxically, however, three studies of Mexican general-populations have reported no associations of overweight or obesity with all-cause mortality.¹²⁻¹⁴ The findings of the latter studies were controversial. In addition, excess adiposity and prevalence of diabetes (partly mediating some of the excess risk of death from vascular, renal and several non-metabolic causes¹⁵), have doubled between 1975 and 2016 in Latin America.^{11,16}

This chapter provides a summary of the epidemiology of adiposity, highlights the major differences between recent large studies of adiposity and mortality in diverse populations, identifies unresolved questions for the Mexican population, and outlines the aims of this thesis.

1.2 The definition and epidemiology of adiposity

Adipose tissue is distributed subcutaneously and viscerally, and when it accumulates excessively around organs it becomes particularly hazardous.¹⁷ Excess adiposity associated with obesity is generally defined as disproportionate body weight for a given height. Depending where the excess adiposity is stored, either general or abdominal, or at other sites, excess adiposity results in higher risks of specific

diseases.¹⁷ It is generally thought that the effects of excess adiposity on vascular-metabolic mortality are largely mediated by the effects on blood pressure, LDL-c, glucose, and insulin resistance.⁶ However, hormone-associated mechanisms have also been proposed to mediate some of the excess risks associated with mortality from certain cancers, or in the case of respiratory mortality, mechanical restriction due to excess abdominal adiposity on lung function.¹⁷

The aetiology of excess adiposity and its distribution in the body is multi-factorial, and involves genetic, life-course factors (e.g., birth-weight, diet, physical activity), biological factors (e.g., gut microbiota, parity, menopause), and socio-economic factors (e.g., education, health awareness, income).¹⁷ The physiopathology of excess adiposity is influenced by excess energy balance, either from excess caloric intake, or a reduced energy expenditure.¹⁸⁻²⁴ The biological processes involved are complex, and are largely regulated by leptin, adiponectin and resistin.¹⁷ The heterogeneity of different body-fat configurations and ectopic fat deposition are also influenced by the presence of genetic variants (e.g., including common variants at the *MC4R*, *TFA2BP*, *TMEM18* *Lep*, *Pomc*, *BDNF*, *DNAH10*, *PLXND1* genes, and the *FTO* locus).²⁵⁻²⁷

The association of excess adiposity with poor health has been long recognised, but understanding of the consequences of obesity has evolved over time, facilitated by advances in genetic determinants of different markers of adiposity. For instance, Hippocrates first reported that sudden death was more common “among those naturally fat than in the lean”.²⁸ In 1777, Lavoisier discovered the role of combustion in energy balance, with subsequent applications to the combustion of fat in humans. One century later, Quetelet outlined the concept of body size with what is known today

as the body-mass index, which remains one of the most commonly used ‘instruments’ to guide clinical decisions in modern medicine.²⁸ The advent of modern imaging technology in the 20th century, has enabled detailed characterisation of different types of adipose tissues,²⁹ and assessment of their differential importance for various diseases. These include, for example, the associations of epicardial fat with arrhythmias,³⁰ the association of liver fat with coronary heart disease, or that of high liver fat with type 2 diabetes (DM).²⁹ The most commonly used methods for clinical assessment of adiposity (most of which are also applied in contemporary epidemiological research), are summarised in **Table 1.1**.

The emergence of obesity as a major global health issue has stimulated research both on the effects of excess adiposity on premature deaths and life expectancy, as well as on the causal pathways that link adiposity and various diseases. New approaches, such as genetic epidemiology, have enabled reliable assessment of the causal associations of different adiposity traits with a wide range of diseases, using polygenic risk-scores and Mendelian Randomisation (MR) techniques.³¹⁻³³ More recently, direct and genetic markers of body-composition have clarified that general fat mass (FM), lean mass (LM), visceral fat, and subcutaneous fat, appear to have distinct associations with vascular-metabolic traits and specific causes of death.^{32,34-36} **Table 1.2** provides an overview of the interpretation of the statistical modelling of various adiposity markers in relation to disease and mortality risk assessment at a population level.

Table 1.1: Summary of gold-standard measurements for assessing adiposity

Method	Description	Strengths and limitations
Anthropometry	Employs physical measurements of different characteristics of the human body associated with general and abdominal adiposity and with body-fat distributions. Includes markers of height, weight, body mass index, waist and hip circumferences and their ratio, and skinfold thickness.	Convenient (rapid, inexpensive, reproducible), reliable markers for general and abdominal adiposity, reasonable for risk-prediction in otherwise healthy young adults and for public health guidance, but cannot easily distinguish fat from lean mass, visceral from subcutaneous fat, or trunk from leg fat distributions. Can be used to reasonably predict general body composition using ethnic-specific equations validated with direct markers from DXA/CT scan, and biomarkers.
Bioelectrical Impedance Analyses	Determines the resistance to the flow of an electric current through the human body, from which the total body water is initially estimated, and subsequently, total fat mass [FM] is calculated on the basis of the constant hydration of fat-free [lean] mass [LM].	Convenient, requires portable equipment and standardised equations, but reproducibility is influenced by hydration status, pre-existing diseases, and body structure. Gives more accurate measures of the two body-mass compartments (i.e., FM and LM) than those derived from anthropometric equations, but less precise (or informative) compared to direct markers from body imaging as it cannot accurately distinguish visceral from subcutaneous fat, or trunk from leg fat. It also measures total skeletal and smooth muscle mass, bone mass and body water.
Densitometry	Determines body density as mass per-unit of body volume, using air displacement plethysmography or underwater weighing, from which total fat mass is subsequently estimated.	Time consuming, requires major and active participant cooperation. Somewhat complicated manoeuvre, standardised techniques are unsuitable for older adults and less feasible for use in large-scale research.
Imaging methods	Estimate total FM, bone mineral and muscle mass from Dual-energy X-ray Absorptiometry [DXA], subcutaneous and visceral fat from Magnetic Resonance [MRI] or Computer Tomography [CT].	Relatively safe and highly reproducible, the MRI/CT are the gold standard for accurate and precise measurement of different body fat depots, but it is expensive. Superior to DXA, it accurately measures subcutaneous, visceral, android and gynoid fat tissues, ectopic liver fat, trunk and leg muscle mass.

Sources: González-Muniesa et al, Obesity, Nature reviews Disease primers 2017; 3:17034. F. Hu, Obesity Epidemiology, 2008, Chapter 5 (Adapted with permission from Copyright Oxford University Press). Linge et al, Body Composition Profiling in the UK Biobank Imaging Study, Obesity 2018; 26:1785-95. TANITA, Body Composition Analyser Manual, 2013.

Table 1.2 Combinations of different adiposity measures used to predict consequences of adiposity on disease risk

Adiposity Model	Correlations between markers	Interpretation of the various combinations of adiposity markers
Weight + Ht	Ht is weakly correlated with weight, moderately correlated with LM, and not correlated with FM.	Weight (given Ht) is a marker of general FM.
BMI + Ht	Not correlated.	BMI is a marker of general adiposity standardised to Ht. Ht is a surrogate of pre-adult nutrition.
Ht-adjusted weight + Ht	Not correlated.	Height-adjusted weight is a marker of general adiposity. Ht is a surrogate of pre-adult nutrition.
BMI + WC	Highly correlated.	WC is a marker of abdominal adiposity; BMI (given WC) is complicated to interpret, as it reflects muscle rather than FM, especially in the elderly.
BMI + WHR	Moderately correlated.	BMI is a marker of general adiposity (given abdominal and gluteal body-fat distributions).
WHR + BMI	Moderately correlated.	WHR is a marker of body-fat distributions and an indicator of excess abdominal adiposity (given gluteal fat), over and above general adiposity for a given Ht.
WC + HC	Moderately correlated.	WC is a marker of abdominal adiposity (subcutaneous and visceral). HC (given WC) encapsulates gluteo-femoral fat, muscle, and bone structure.
WC + HC + BMI	Highly correlated.	WC is a marker of subcutaneous and visceral abdominal adiposity (given gluteal muscle and bone, and general LM).
WHtR + weight + HC	WHtR, HC and FM are moderately correlated. WHtR and LM are not.	WHtR is a marker of abdominal adiposity standardised to Ht (given LM and gluteo-femoral fat, muscle and bone).
Changes in weight + in WC	Highly correlated.	Change in WC represents changes in body-fat distributions. Change in weight (holding WC constant) reflects change in LM (e.g., in the elderly, weight loss is largely due to muscle loss).
FM + LM + Ht	FM and LM, and Ht and LM are moderately correlated. Ht and FM are not correlated.	FM is a marker of general adiposity (e.g., total visceral, subcutaneous, and ectopic adiposity, including mostly, but not only, abdominal fat), given muscle mass and Ht; LM is a marker of muscle mass, body water and bone mass. The model is equivalent to FM%, FMI (kg/m ²), FM-LM ratio.
LM + FM + Ht	As above.	LM represents general fat-free mass (muscle, bone, water), given general adiposity and Ht.
FM + WHR + LM	WHR is not correlated with FM or LM.	FM is a marker of adiposity over and above the abdominal and gluteo-femoral fat distributions; a proxy for other adipose depots (e.g., ectopic organ-tissue, leg).

Ht=Height; BMI: Body Mass Index; WC=Waist Circumference; HC=Hip Circumference; WHR=Waist-Hip ratio; WHtR=Waist-Ht ratio; FM=Fat Mass; LM= Lean Mass. FMI=Fat Mass Index. Adapted with permission from F. Hu, Obesity Epidemiology, 2008, Chapter 5, Copyright Oxford University Press. Models of body composition are based on the references to chapters 1 and 2.

1.3 Adiposity and risk assessment in different populations

From a population-health perspective, epidemiological studies have shown that anthropometric and body-fat characteristics vary between populations,^{28,37} but the overall hazards associated with excess adiposity at levels of BMI ≥ 25 kg/m² are largely similar in most populations.³⁸⁻⁴¹ However, the relevance of body-fat distributions is more heterogeneously associated with risk of different diseases (e.g., with opposing associations of waist and hip circumference to vascular-metabolic diseases),^{40,42,43} and are more informative at a given BMI than when considered individually.^{44,45}

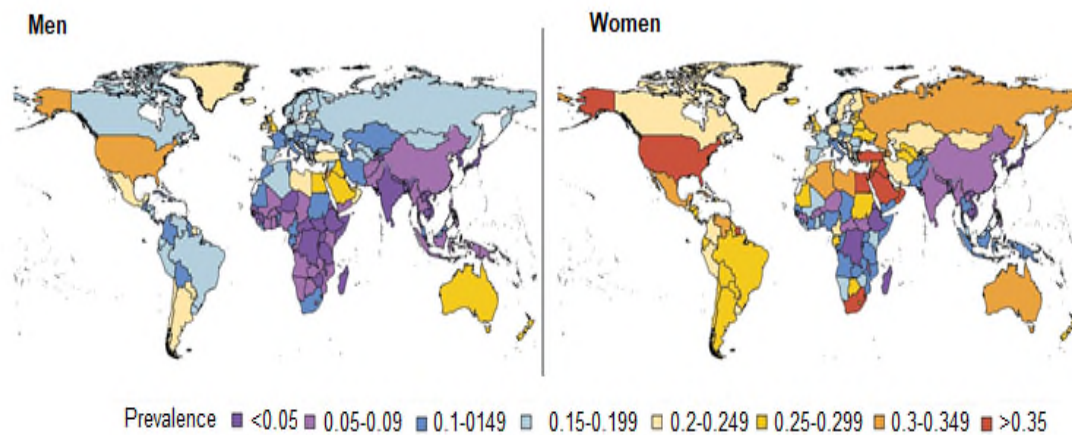
Moreover, several relatively small studies, involving ethnically-diverse populations suggest that the risk of vascular-metabolic traits starts at different levels of general or abdominal adiposity in different populations.⁴⁶ For instance, Asians (who are generally lean), have higher absolute risks of cardiovascular disease and type 2 diabetes at BMI values lower than 25 kg/m², while among Mexicans (who are more adipose), vascular risk appears to be 'lowest' at 30-35 kg/m²,^{47,48} or gradually lower with higher levels of total fat-mass percentage.⁴⁹ Such findings led to the adoption of 'population-appropriate thresholds' for the assessment of vascular-metabolic risk associated with different conventional markers of adiposity in clinical practice.⁵⁰⁻⁵² Such discrepant findings resulted in differences between clinical guidelines and risk prediction models, ranging from inclusion (i.e., QRISK, Framingham) to omission (i.e., Globorisk, Predict) of adiposity markers as additional screening tools.⁵³⁻⁵⁶ In 2008, the World Health Organisation (WHO) Expert Consultation on Waist Circumference and WHR, re-emphasised the appropriateness of population-specific cut-offs for BMI, and recommended that further studies are needed to define population-specific cut-offs for

abdominal markers of adiposity in certain populations. In particular, they highlighted the limited available evidence on adiposity and disease among Hispanic populations (who have a high prevalence of obesity).⁵⁷ Subsequently, appreciation of the importance of adequate statistical power for increasing the reliability of risk estimates for different disease outcomes and mortality, has challenged the interpretation of small studies. This prompted large-scale prospective cohorts with prolonged duration of follow-up, to reliably assess the shape and strength of the associations of different markers of adiposity with disease outcomes in different populations. Importantly, such studies found no evidence of any 'threshold' levels below which lower levels of adiposity was not associated with lower vascular-metabolic risk^{34,58} (either when considered alone or for a given level of BMI).^{40,44}

1.4 Adiposity prevalence, trends and associated mortality

Recent estimates from 68.5 million adults showed that, between 1980 and 2015, the prevalence of obesity doubled in over 70 countries and continued to increase elsewhere. The estimated prevalence of adult obesity varies between countries (**Figure 1.1**). In 2015, Mexico had relatively high rates of obesity, with 23.4% (95% CIs 21.6-24.3) of men and 32.7% (31.9-33.4) of women aged 20 years or more, estimated to have a BMI ≥ 30 kg/m², respectively.³ These rates demonstrate a substantial increase compared with those estimated in 1980s (e.g., 13.6; [12.9-14.4] in men, and 20.5; [20.0-21.2] in women, respectively). By comparison, adult obesity in the United States, increased from 10.7% in men and 15.0% in women in 1980s, to 30.7% and 35.5% in 2015, respectively, while in India, the increase ranged from 1.2% in men and 2.1% in women in 1980s, to 4.6% and 7.0% in 2015, respectively.³

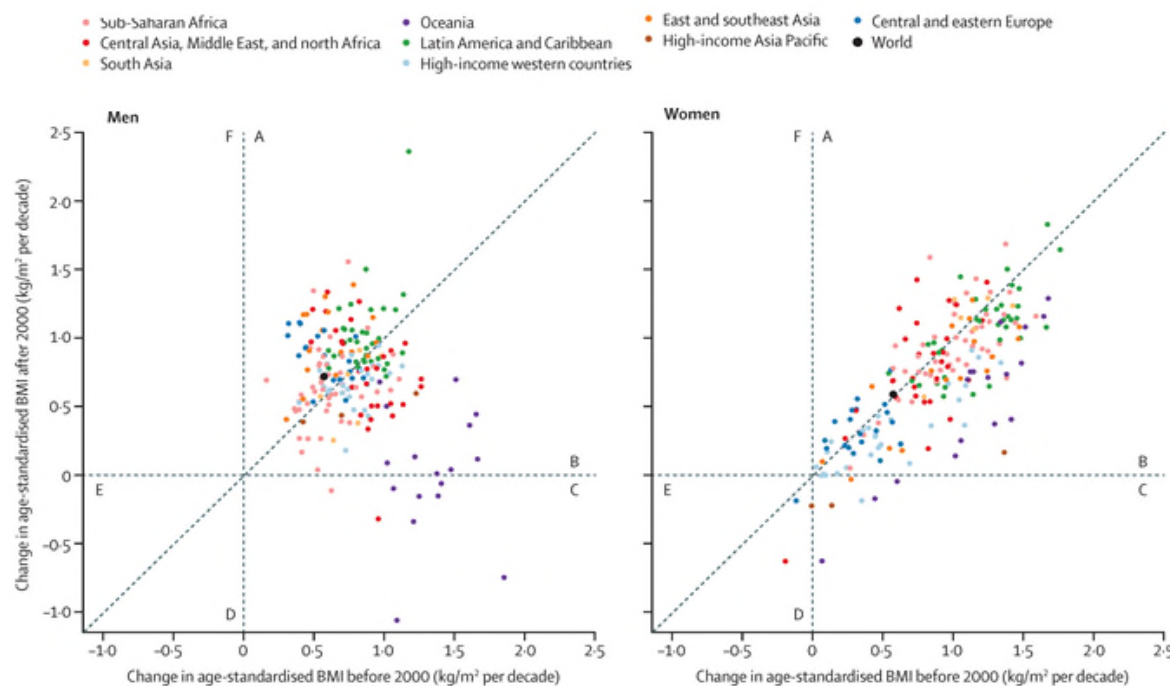
Figure 1.1: Age-standardised worldwide prevalence of obesity by sex in 2015



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The rate at which the prevalence of obesity increased worldwide, varies between countries, between men and women, and by different calendar-periods. For instance, estimates from 19.2 million adults from 200 countries, demonstrates that in most Western populations, the age-standardised mean BMI has increased more slowly

Figure 1.2: Worldwide changes in age-standardised mean BMI

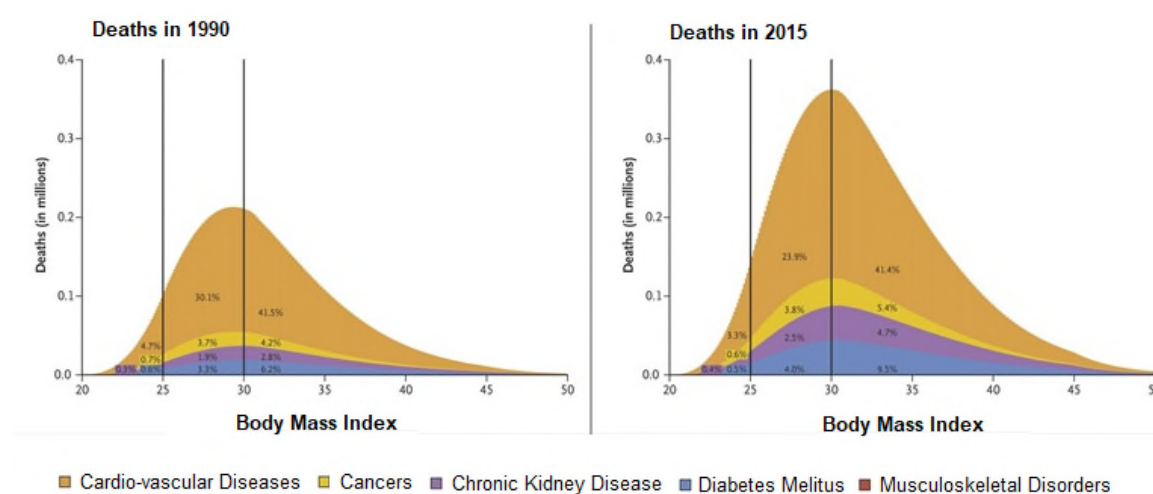


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after 2000 than it had before 2000 (**Figure 1.2; A,B**). By comparison, in most of Latin-America, the age-standardised mean BMI increased more rapidly after 2000 than it had before 2000 among men, while in women, the increase was more rapid before 2000.¹¹ These patterns suggest that the full health consequences of excess adiposity in Latin-America are still to emerge.

The global mortality rates from vascular causes (and other obesity-related disease) have decreased steeply between 1970 and 2010, including in most low and middle-income countries.⁸ Nonetheless, recent estimates suggest that the worldwide consequences of increases in obesity are associated with increasing proportion of the absolute mortality rates from major chronic diseases (i.e., from vascular, renal or diabetic causes; **Figure 1.3**). Recent estimates from the Global Burden of Disease 2015 suggest that more than two-thirds of the deaths related to high BMI worldwide are from vascular causes.³

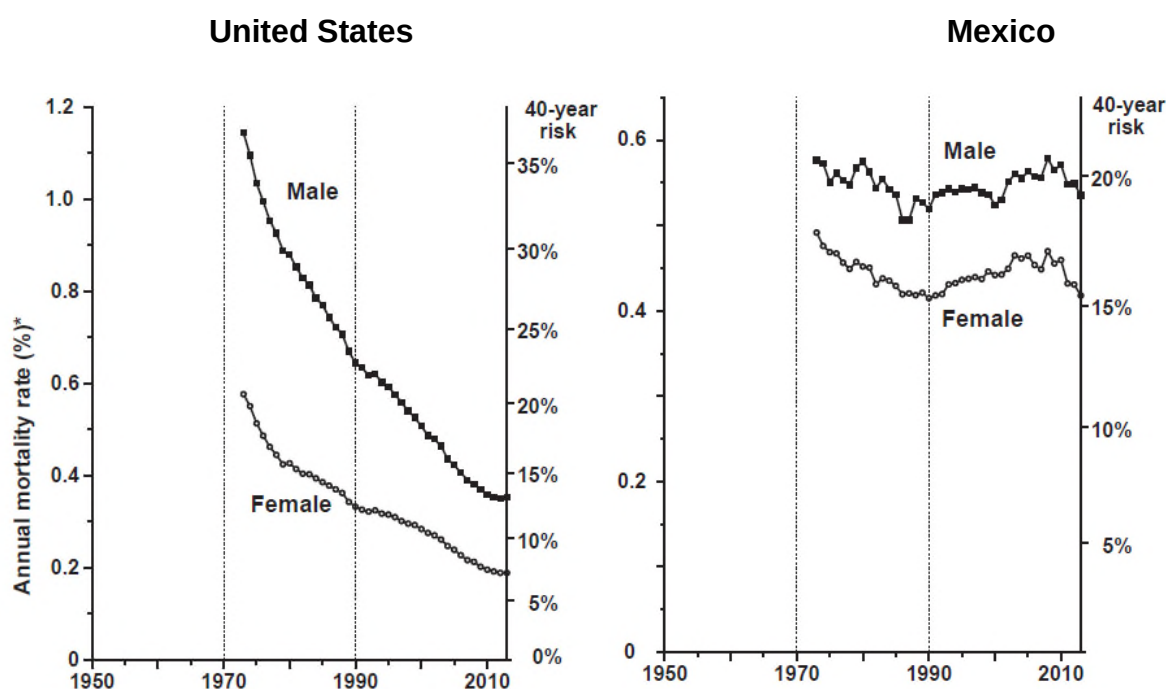
Figure 1.3: Global mortality associated with BMI in 1990 and in 2015, by cause



Absolute risk estimates are in millions. The vertical lines mark the boundaries for overweight (25-29 kg/m²) and obesity (>30 kg/m²). Reproduced with permission from the N Engl J Med 2017; 377:13-27, Copyright Massachusetts Medical Society.

Compared to most countries where vascular and other metabolic deaths declined, the Mexican rates for premature mortality from vascular, renal and diabetic causes remained remarkably high between 1973 and 2013 (**Figure 1.4**).¹⁵ Importantly, access to treatments for blood pressure and diabetes, which account for an important proportion of premature vascular-metabolic deaths among Mexicans,^{15,59} became a national priority at the beginning of the 21st century.^{60,61} While improvements in provision of blood pressure lowering medication have already been achieved,⁶² the impact of recent policies for diabetes will not be known for some years.⁶³ Meanwhile, the prevalence and intensity of smoking, which account for most of the preventable deaths worldwide, are lower among Mexicans compared with other populations,^{64,65} yet, the expected effects of smoking on excess mortality are likely to increase in future years.^{66,67} Therefore, the persistently high vascular-metabolic mortality rates in

Figure 1.4: 1973-2013 mortality rates from vascular, renal and diabetic disease at ages 35-74 years in USA and in Mexico



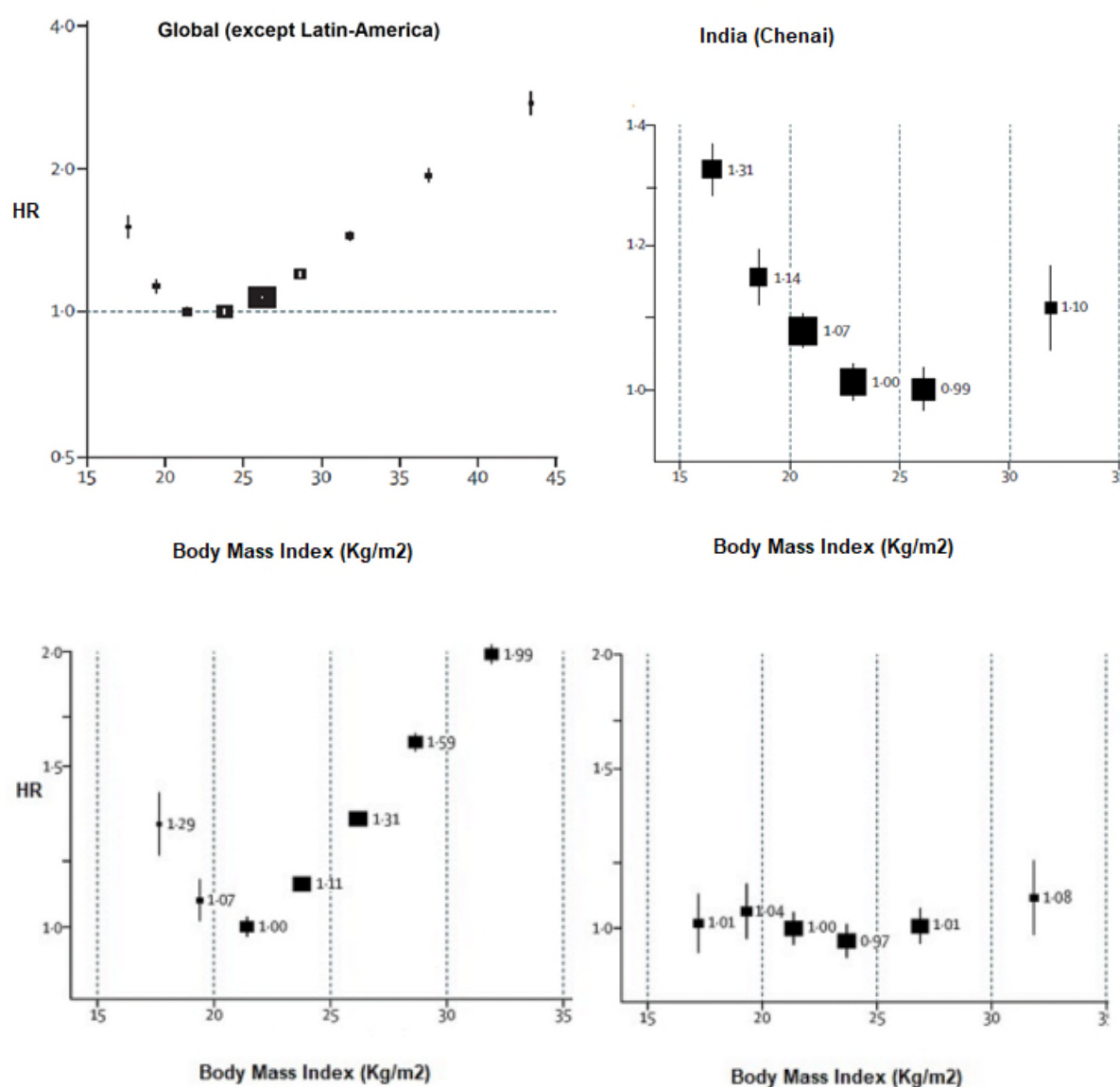
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Mexico,^{68,69} have prompted further research of the relevance of excess adiposity for premature death.

1.5 Adiposity and mortality in different populations

Recent studies of adiposity and premature mortality highlighted some major qualitative differences between populations, some of which are summarised in **Figure 1.5**.

Figure 1.5: Comparison of all-cause mortality (top) and vascular mortality (bottom) versus BMI at ages 35-69 years in different populations



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A large meta-analysis involving individual-data from 239 prospective studies mostly from high-income countries, demonstrated that among 4 million never-smokers without prior chronic diseases, who survived more than 5 years after baseline, each additional 5 kg/m² among those with a BMI $\geq$ 25 kg/m², was associated with about 31% higher risk of all-cause mortality, and 42% higher risk of vascular mortality.³⁸ These findings were similar to a previous analysis of individual data of 0.9 million adults from 57 studies included in the Prospective Studies Collaboration.³⁹ In contrast, another meta-analysis, involving 0.7 million never-smoking Asians without prior disease, who survived more than 3 years, found that BMI $\geq$ 25 kg/m² was associated with a substantial excess risk of death only in East Asians, but not among South-Indians.⁷⁰ Similarly, a recent study of 0.4 million never-smoking adults from South India, who had no previous disease and survived for at least 2 years, found that BMI was approximately unrelated to vascular mortality (**Figure 1.5**).⁷¹ The precise reasons for the differences in associations of BMI with mortality between Indian and Western populations are not fully understood, but may reflect the higher ratios of fat to lean mass at the lower ranges of BMI, or effects of sub-clinical disease associated with pathological weight loss, or the counter-balancing adverse effects of BMI on blood pressure, or other correlates of low BMI, including low socioeconomic status (poverty) and delayed effects of early life events.

Furthermore, in two recent meta-analyses of prospective studies of Mexican adults (17,000 and 39,000 respectively), BMI above 25 kg/m² (i.e., overweight or obesity) , compared with normal weight (BMI 18.5 to 25 kg/m²), was not associated with higher all-cause mortality (Hazard Ratio [HR] 0.8; 95% CIs 0.6-0.9), while BMI<18.5 kg/m² was (HR=2.2; 1.4-3.5).^{13,14} Importantly, the non-Hispanic studies minimised bias from

pre-existing disease by restricting analyses to those without known chronic diseases, but the Mexican studies did not allow for the possible impact of “reverse causality” (whereby low BMI can be a consequence of disease). Additional studies that limit the effects of reverse causality are therefore needed to clarify the relevance of excess adiposity to mortality in Mexican populations.

Furthermore, until more recently, large-scale research employed convenient anthropometric markers of adiposity. However, BMI values for example, do not correspond to a similar degree of excess adiposity compared to DXA values of specific adipose tissues, because body-composition varies by sex, age, or in different ethnic groups.⁷² Men, for instance, tend to have a higher percentage of skeletal muscle and bone-mass for a given BMI, while women, tend to have a higher percentage of body-fat.²⁸ Furthermore, it was recognised that the relevance of BMI to mortality is confounded not only by greater percentages of fat mass between individuals with similar BMI, but also by muscle mass in young adults, sarcopenia in the elderly, or higher fat-to-lean mass ratio [FLMR] at otherwise low levels of BMI in some populations (e.g., South-Asians).²⁸ As the association of BMI with mortality may differ between populations with substantially lower mean BMI, or among those with high body-fat and a small stature (e.g., Asians, Mexicans),²⁸ direct measures of fat-composition are likely to be particularly informative. However, in large studies with a long follow-up it is difficult to obtain direct measures of subcutaneous, muscular or organ-specific adiposity, as they require assessment from bio-impedance, dual-energy X-ray, or computer tomography. Consequently, most epidemiological studies lack such data, and analyses are restricted to conventional anthropometric markers of general or abdominal adiposity (with the exception of the recent enhancements from

the UK Biobank).

Two very recent studies of 51,529 North-Americans and 10,329 Mexican-Americans compared the relevance of BMI, WHtR and measured fat and lean mass [LM] from DXA to mortality, and described monotonic positive associations of fat mass [FM] with all-cause and diabetic mortality. However, among Hispanics, increasing FM was inversely associated with vascular mortality.^{35,36} The Mexican report did not specify how pre-existing disease was accounted for, and the sample size was small for statistical stability. Furthermore, the independent value of each marker of body composition given other adiposity markers (i.e., how lean mass affects the relevance of fat mass, or that of waist circumference) has not been investigated. Additional and larger studies to address such questions in Mexican populations are therefore needed to reliably assess the overall and independent relevance of body composition to mortality from different causes.

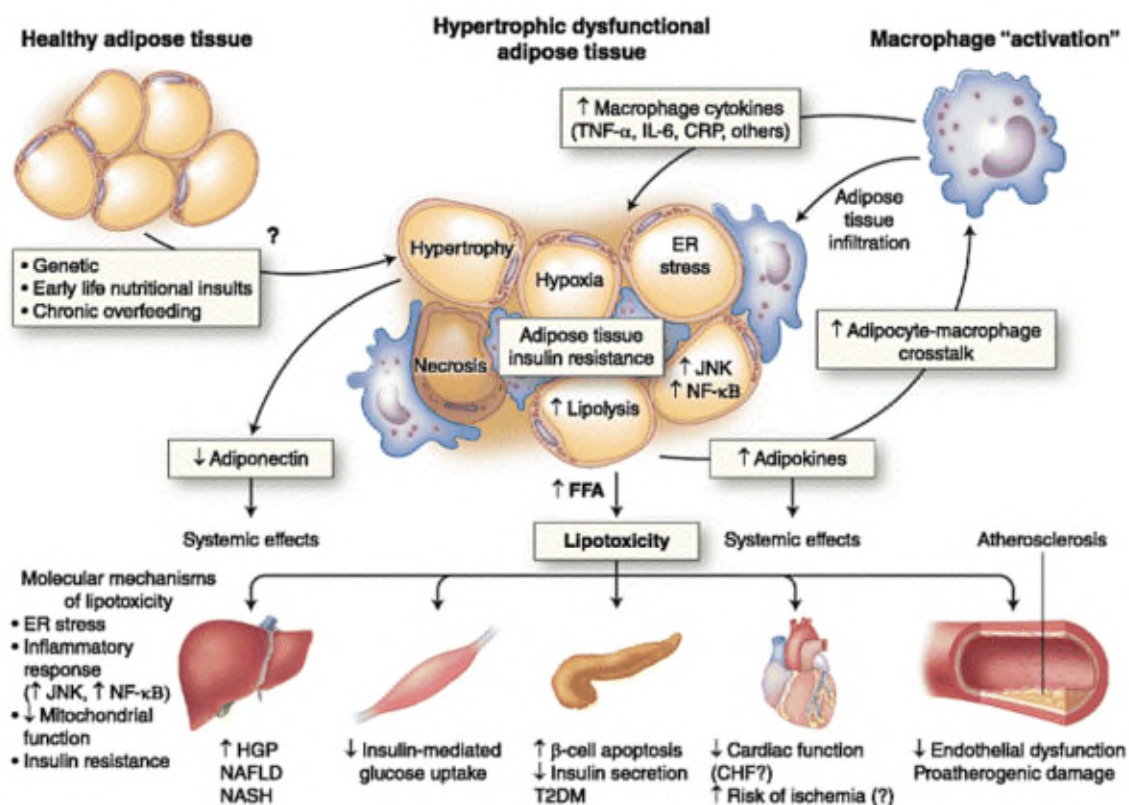
1.6 Adiposity, mediating risk-factors and vascular-metabolic diseases

Large Mendelian Randomisation (MR) studies have demonstrated that genetic variants associated with different adiposity traits are causally associated with several vascular and non-vascular diseases (including some neoplasms).^{7,32} It is believed that the hazardous effects of adiposity are largely mediated through higher levels of blood-pressure, circulating lipids, glucose and biomarkers of the liver and renal function, or through inflammation (**Figure 1.6**).⁷³⁻⁷⁵

The consequent biological perturbations are complex and more hazardous with excess abdominal adiposity in the visceral regions. They include: sub-optimal liver

function, increased insulin resistance, glucose intolerance, concentrations of adipocytokines, interleukins, small dense LDL particles, non-esterified fatty-acids and pro-coagulation factors, and reduced clearance of apolipoprotein-B, triglycerides and very-low density lipids.⁷⁶ Subsequently, these perturbations results in vascular damage through the development of atherosclerotic plaques in the blood vessels, vascular calcification, atherothrombosis, uncontrolled levels of glucose, and damage of the renal vasculature, among others.¹⁷

Figure 1.6: Adiposity associated metabolic dysregulation



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While genetic estimates have been largely limited (until very recently) to crude markers of adiposity, previous observational and physiological evidence also suggested that

different body-fat distributions, such as the opposite relevance of waist and hip circumferences, are more important to vascular-metabolic risk than the relevance of general adiposity alone. At a population level, a meta-analysis of 1 million European adults has demonstrated that given BMI, the WHR is of substantial additional relevance to cardio-vascular and total mortality risk prediction, but the risk-estimates for an equivalent increase throughout the full ranges of general or abdominal adiposity were not reported.⁴⁰ Such observational evidence was complemented by mechanistic studies which explain that the different structure and function of adipocytes, together with the different lipid and inflammatory cytokines characterising the abdominal-gynoid fat distribution, are the 'vectors' for increase in vascular-metabolic risk.^{44,77,78} Furthermore, a meta-analysis involving 0.2 million adults from 58 prospective cohorts (largely Caucasian) limited to *non-fatal* ischaemic vascular events, reported that each SD higher levels of usual adiposity were associated with an increased risk of 23% (95% CI: 17–29%) for BMI, 27% (20–33%) for waist circumference, and 25% (19–31%) for WHR. These estimates were largely explained by the intermediate effects of blood pressure, diabetes, and the ratio of HDL-c to total cholesterol, in the case of BMI, but they only partially explained the effects of abdominal adiposity, as a substantial excess risk still persisted after accounting for these mediators.⁴⁴

Among Mexicans, mortality rates from renal and diabetic causes are substantially higher compared to those in other populations,¹⁵ and elevated HbA1c confers a substantially greater risk among adults with diabetes from Mexico City,⁵⁹ than those in other populations⁷⁹ (e.g., the death RR at a HbA1c<9% was 3.3 for IHD, 2.6 for stroke, and 15.8 for renal failure, and twice as large again above 9%). But, the relevance of other adiposity-associated mediators to different causes of death has not been

systematically assessed in Mexicans, and whether their importance to specific diseases differs from those described in Caucasian or Asian populations.

Nuclear Magnetic Resonance (NMR) technologies now enable measurement of multiple metabolites which could be used to more finely characterise differences in *metabolomic pathways* through which excess fat mass or abdominal adiposity mediate the excess risks for mortality from vascular-metabolic diseases (versus lean mass or BMI alone). For instance, an MR study of 12,600 Caucasian adults characterised the *metabolomic profile* for gain in BMI with 82 biomarkers, and demonstrated that very large very-low-density lipoproteins were more hazardous than large HDL-c, as are most fatty acids (except for polyunsaturated fatty acids), or leptin but not adiponectin.⁷³ No Mexican studies to date have explored the *mediating risk factors* of various adiposity markers in relation of specific disease, using novel biomarker assays.

1.7 Aims of this thesis

The primary aim of this thesis was to reliably assess the shape and strength of the associations of different markers of adiposity, including predicted body-fat composition, to mortality from specific causes among 150,000 adults from the Mexico City Prospective Study (MCPS), an established blood-based cohort study with over 15 years of mortality follow-up, after taking account of reverse causality bias. Furthermore, the thesis examined the role of selected traditional mediators through which different markers of adiposity may increase the risk of mortality from vascular-metabolic causes (ie, cardiac, stroke sub-types, renal, diabetic, and hepatic diseases among those with/out diabetes). In particular, the thesis assessed the additional relevance of established risk factors, specifically, HbA1c, blood pressure, HDL-c, non

HDL-c and triglycerides.^{77,78,80-83}

1.8 Outline of thesis

The aims of this thesis were:

1. To describe the baseline characteristics of the study population by different levels of general and abdominal markers of adiposity, and to assess the correlates of such adiposity markers.
2. To assess the within-person variability of different adiposity markers over a period of about 15 years, using resurvey data collected between 2015 and 2019 in a subset of 10,000 individuals (in order to correct for regression dilution bias in sensitivity analyses).
3. To use the resurvey data (which included bio-impedance estimates of adiposity) to assess how well external Mexican-specific equations (from direct markers of body composition)²⁸ can predict *measured* fat and lean mass in the MCPS participants, and apply these equations (or modifications of them) to all the participants at baseline, to assess their relevance to mortality.
4. To compare the overall shape and strength of different markers of adiposity (including BMI, predicted fat mass index, waist circumference, the waist-hip ratio and the ratio of waist to height), to mortality from all and specific causes, with a focus on premature deaths from vascular-metabolic disease, before and after excluding individuals with previously diagnosed or un-diagnosed diabetes.
5. To assess the extent to which the relevance of different markers of adiposity to mortality were explained by selected established mediators (i.e., HbA1c, blood pressure and selected lipids), in a subset of participants with available biomarkers.

Chapter 2 summarises the findings from a systematic literature review, aiming: 1) to identify previous Mexican studies of adiposity and mortality, and to compare findings

with those from other populations; and 2) to summarise important differences in the relevance of different markers of adiposity to cause-specific mortality. **Chapter 3** summarises the design and the methodology of the Mexico City Prospective Study, and the statistical methods used in this thesis. It includes the selection, assessment and follow-up of the study population, definitions of exposures and their long-term repeatability, confounders, mediators, and the mortality endpoints. **Chapter 4** describes the baseline characteristics of the study population in relation to different adiposity markers, the characteristics of those resurveyed, the estimates of within-person variability over a 15-year interval, and the agreement between direct versus predicted markers of body-mass composition. It includes the cross-sectional associations of each adiposity marker with diabetes and selected vascular-metabolic mediators (HbA1c, SBP, DBP, HDL-c, non HDL-c and triglycerides). **Chapter 5** describes the shape and the strength of the risks of general adiposity (i.e. BMI) with total and cause-specific mortality, before and after different strategies to minimize reverse causality (including interactions with age-at-risk and pre-existing diabetes). It includes population-attributable fractions and absolute differences in survival. **Chapter 6** describes the shape and the strength of the predicted body-mass composition (FMI given LMI) to total and cause-specific mortality. **Chapter 7** describes the shape and the strength of abdominal markers of adiposity (mostly waist circumference and WHR) with total and cause-specific mortality. Chapters 5 to 7 explore, in addition, the potential mechanisms underlying the increased risks of death from specific vascular-metabolic causes associated with adiposity, by describing the relative ability of selected mediators (above) to predict mortality from the selected causes. **Chapter 8** summarises the key findings of the thesis, including the strengths, limitations, relevance for clinical practice and for public health, and further research.

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Chapter 2: Literature review of previous studies of adiposity and cause-specific mortality

2.1 Background

Large prospective studies of randomly selected individuals recruited from the general population in different countries are needed for reliable assessment of the relevance of adiposity to specific causes of death. Many such prospective studies have previously assessed the relevance of different markers of either general or central adiposity (mostly BMI, WC, WHR), or of body-composition (mostly fat and lean mass), to risk of death from major causes (e.g., vascular, neoplastic, diabetic, or pulmonary diseases). Most of the available evidence from prospective studies of adiposity and cause-specific mortality (and meta-analyses of such studies) has accrued from either European, North-American or Asian populations. However, little evidence is available from large prospective studies conducted in Latin-American populations where the prevalence of obesity has increased substantially in the recent decades¹ and where morbidity patterns appear to differ importantly compared with Western or Asian populations.^{2 3} For example, the Global BMI Mortality Collaboration Report included individual participant data from 239 prospective studies, none of which were from Latin-America.⁴ Hence, there is a need for more evidence about the relevance of adiposity to specific causes of death in contemporary Latin-American populations.

2.2 Systematic searches and literature review

A systematic search and literature review was undertaken using the Cochrane Collaboration methodology⁵ between December 2016 and May 2017, and updated regularly thereafter. The aims of this systematic review were to identify relevant

studies of associations of adiposity with mortality in Mexicans, and to compare findings with other Caucasian, Asian, other Latin-American or Mexican-American population-based studies.

Generic systematic searches, unrestricted to any specific language or year of publication, were conducted using MEDLINE (via PubMed), EMBASE (via OVID), and the SCIELO Libraries for Mexican Journals, and the World Health Organisation (WHO) Virtual Library for South-America (LILACS). In addition, the reference lists of previous meta-analyses were screened to identify additional potentially eligible studies otherwise not identified by the literature search. Conversely, smaller individual studies included in meta-analyses were not presented separately, unless they provided additional information on different adiposity markers or specific causes of death.

Details of the search strategy are provided in **Supplementary Tables S1 and S2**. The Medical Subject Heading (MeSH) terms were standardised to capture identical information in all the four databases, and combined both free text and truncated terms in order to capture the specific populations of interest, markers of adiposity (i.e, all anthropometric markers for body size, abdominal adiposity and body-fat composition and distribution), mortality outcomes, and prospective cohorts involving general populations. Additional terms for 'overweight', 'weight change', 'vital statistics', 'death', 'fatal events' from 'vascular-metabolic' or 'any causes' were included in alternative searches for comparison. The Boolean operators 'AND', 'OR' and 'NOT' were used to combine the MesH terms within and between the search blocks. The search options were somewhat limited for the Latin-American specific resources for which the MesH terms had to be more strategically selected. The identified reports were imported,

managed and archived using EndNote (version X9.1). A summary of the systematic literature review is provided in **Figure 2.1**.

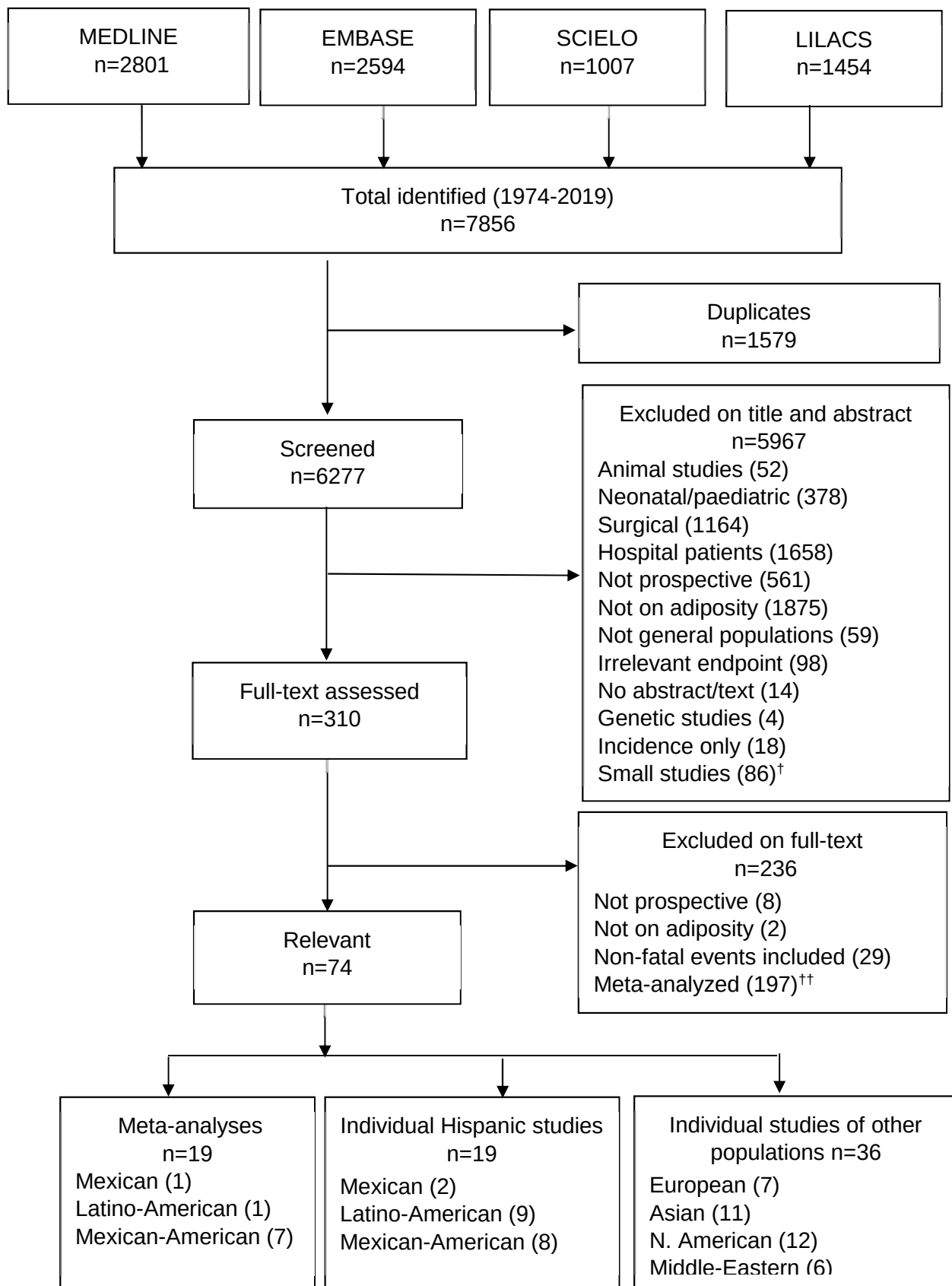
2.3 Selection criteria for studies of interest

Selected details of individual studies were abstracted and summarised using modified Cochrane,⁵ MOOSE⁶ and Newcastle-Ottawa criteria for non-randomised studies.⁷ The chief emphasis was on prospective rather than retrospective studies, and on general population studies of adults rather than hospital or patient-based studies of specific diseases or obesity-related interventions (e.g., bariatric surgery). Moreover, genetic studies of adiposity, those describing trends of adiposity and mortality over time, and those involving only non-fatal events as an outcome were also excluded. To ensure that reliable evidence from large-enough studies is assessed, studies of Latin-American populations were included regardless of their size, but studies done elsewhere were only included if they involved at least 100,000 individuals (or 10,000 individuals for studies that included direct markers of body composition).

2.4 Exclusions based on titles and abstracts

The reasons for exclusion based on title and abstract screening were: animal studies (n=52), neonatal or paediatric studies (n=378), surgical or hospital-based studies (n=2822), retrospective or cross-sectional (n=547) and non-epidemiological studies (n=14; mostly opinion letters on prevention, guidelines or state-of-the art reviews), studies of disease incidence (n=18), those in which adiposity was genetically defined (n=4), or considered as a confounder, mediator (eg, of diet or physical exercise), or just one component of multi-factorial predictive indices (e.g., for vascular risk)

Figure 2.1: PRISMA Flowchart of the identified studies



[†] N<100,000 individuals for studies of anthropometry; N<10,000 individuals for studies of DXA or BIA.

^{††} Previously included in the Global BMI Collaboration and/or Aune et al., unless different adiposity exposures or mortality outcomes were investigated. Last updated July 2019.

(n=1875), irrelevant endpoints (n=98; e.g., trends or trajectories of obesity, suicidal or HIV mortality, pregnancy-associated fatalities), lack of abstract or inability to retrieve the full text (n=14) and studies with a sample size smaller than *a-priori* defined (n=86 involving less than 100,000 adults in anthropometric studies, or less than 10,000 adults in studies of DXA or BIA).

2.5 Exclusions based on full-text reports

Further studies were excluded after full inspection of the remaining reports (n=310) when details were not obvious from the abstract. Reasons included summaries on selected themes (n=8; e.g., gender differences and disease-specific adiposity-associated risk), non-fatal events as a major component of the outcome, in addition to mortality (n=29), and small studies or small meta-analyses subsequently included in larger meta-analyses (n=197).

2.6 Overview of identified studies

A total of 6277 unique reports published between 1974 and mid-2019 were identified after carefully designed identical searches using all four library sources. Of those, 5967 did not meet the general criteria of interest and were excluded at the first screening. Of the remaining, 236 studies were further excluded after detailed assessment of their relevance to the aim of this review. A total of 74 relevant studies remained, including 19 meta-analyses (of individual or summary data, of which only one was from Mexico), 19 Hispanic studies (of which only two were from Mexico), and 36 individual studies from other populations (**Figure 2.1**). **Supplementary Tables S3-S6** provide a summary of all these studies, grouped by the adiposity markers of interest (43 studies of general adiposity, 2 studies of abdominal adiposity, 4 studies of body

composition, and 25 comparative studies of various markers).

The vast majority of these studies recorded information on prior diagnoses of cardiovascular, neoplastic, or respiratory diseases at baseline, and excluded participants with known chronic diseases, in addition to deaths that occurred in the first 2 to 10 years of follow-up (in order to minimise reverse causality bias). However, the criteria used for pre-existing or pre-clinical diseases varied considerably. In particular, most studies did not exclude those with previously diagnosed diabetes (perhaps because it is considered to be a major mediator of the effect of adiposity on mortality). While some studies assessed the relevance of adiposity to mortality separately in those with and without diabetes, none excluded individuals with screen-detected diabetes from their analyses. A few studies assessed the relevance of abdominal adiposity at different levels of BMI, some addressed residual confounding from smoking by restricting analyses to never-smokers, and a few assessed gender or ethnic-specific associations. Some studies mutually adjusted for adiposity-specific mediators (in particular glucose, lipids, renal and inflammatory biomarkers), or for adiposity-associated morbidities (e.g., diabetes, cardiovascular diseases, or clinical dyslipidaemia).

Of the meta-analyses, the vast majority used a random-effects approach. Only a few large studies, such as the Prospective Studies Collaboration⁸ and the Global BMI Collaboration⁴ re-analysed the individual participant data obtained from the contributing studies. This approach allowed harmonisation of the categorisation of adiposity markers and covariates of interest for more direct comparisons of their relevance to different causes of death across multiple scenarios.

2.7 Summary of the studies of general adiposity

A total of 13 meta-analyses of general adiposity (largely BMI) and mortality were Identified, and of those, only one included Latin-American populations exclusively (S3).

Several very large meta-analyses including data from 240 individual epidemiological studies involving a total of 0.3-30 million individuals, have been conducted to compare the shape and the strength of the associations of BMI to mortality from all-causes, and from major specific causes (mostly cardiovascular, neoplastic, respiratory, renal, and their sub-types). These aimed to 'establish' the BMI ranges for 'lower risk' in different populations of never-smokers with no history of chronic diseases at recruitment, and to a lesser extent, obesity-attributable population risk and survival. Importantly, from all the individual studies included in these meta-analyses, only one study was from Mexico, and seven were from Mexican North-American populations.

In addition to meta-analyses, 20 cohorts of 0.5 to 11.5 million individuals complemented the evidence in other non-Hispanic populations (including Asian [China/India/Korea], European [Austria/Sweden/UK], Middle Eastern [Israel], or N. American [USA/Canada] populations; S3). Another 10 individual studies involving Hispanic populations, were largely from the USA, with only one study from Mexico, one included Pima Indians, and only 2 were from other Latin-American countries.

Almost all the studies identified reported that BMI had a J-shaped association with all-cause, cardiovascular, and neoplastic mortality, with an apparent 'lower risk' at a BMI of 22.5 kg/m² in adults^{4,9} and at about 18.5 kg/m² in adolescents¹⁰ without prior history

of disease, who survived for at least 2 to 5 years. Importantly, the overall associations were stronger in never than in ever smokers, when adolescent versus adult BMI was considered, and with selected diseases. For example, compared to those with a BMI of 20-25 kg/m², those with a BMI >30 kg/m² had up to 18-fold higher risks for diabetic mortality,¹¹ up to 5-fold higher risks for ischaemic cardiac mortality,¹² and a more modest, 2 to 4-fold higher risk for cancer of the breast, liver, prostate or kidney regions.¹³ In contrast, inverse J-shaped associations were reported for general adiposity and risk of mortality from chronic lung disease¹⁴ and, in South-Asian populations, for all-cause and stroke mortality.^{15,16,17}

A selection of the most informative studies of BMI and mortality involving non-Mexican populations are summarised in **Table 2.1**. Estimates from the Global BMI Collaboration, the US National Cancer Institute Cohort Consortium, and the Prospective Studies Collaboration, demonstrated that in meta-analyses of individual-level data from multi-ethnic adult populations aged 35 years or more, each 5 unit higher level of BMI above 25 kg/m² was, on average, associated with a 30% higher risks of death from any cause, 40-50% higher risks of death from cardiovascular or respiratory causes, and a 20% higher risk of death from any type of cancer.^{4,8,18} However one major meta-analysis restricted to Asian populations from the Asia Cohort Consortium BMI Project, found that among 0.7 million never-smokers aged 18 years or more who had survived more than 3 years, BMI above 25 kg/m² was associated with substantially higher mortality only in East Asians, and not in South Asians.¹⁵

These findings have subsequently been replicated by a recent study of 0.4 million

Table 2.1: Selected studies of BMI and mortality involving non-Mexican populations, by study size

Author (year) Study type	Recruitment period (Follow-up)	No. of participants (age, years) No. of deaths	Confounders	Exclusions		Adiposity (mean, SD)† Mortality	Summary Findings	
				Prior disease	FU		Shape (lower risk)	HR (95%CI)
The Global BMI (2016) Meta-analysis	1958-2010 (13.7 yrs)	3.9 M (35-89 yrs) 385,879 deaths	Age, sex, ethnicity	CVD, stroke, cancer, emphysema	5 yrs	BMI (25.2±3.9) All-cause CHD Stroke	J-shape (~22.5 kg/m ²) J-shape J-shape	per 5-units 1.3 (1.3-1.3) 1.4 (1.3-1.5) 1.4 (1.3-1.5)
deGonzalez (2010) Meta-analysis	1976-2002 (10 yrs)	1.4 M (19-84 yrs) 160,087 deaths	Age, study, physical activity, drinking, education, marital status	Chronic diseases	5 yrs	BMI (26.3) All-cause	J-shape (20-25 kg/m ²)	per 5-units 1.3 (1.3-1.3)
Zheng (2011) Meta-analysis	1984-2006 (9.2 yrs)	1.1 M (18+ yrs) 120,700 deaths	Age, sex, education, cohort, exercise, smoking residence, marital status	CVD, stroke, cancer	3 yrs	BMI (22.9±3.6) All-cause EA All-cause SA CVD EA CVD SA	Inverse J-shape (22.5-25 kg/m ²) U-shape Null	>25 kg/m ² 1.1 (1.0-1.1) 1.0 (0.7-1.4) 1.1 (1.0-1.1) 1.0 (0.7-1.4)
Chen (2013) Meta-analysis	To 2008 (9.7 yrs)	1.1 M (53.4 yrs) 49,000 deaths	Age, sex, education, exercise, smoking, drinking, residence, marital status	Cancer	3 yrs	BMI (25.2±3.9) CVD CHD Stroke	U-shape J-shape inverse J-shape	>25 kg/m ² 1.2 (1.1-1.3) 1.3 (1.2-1.5) 1.1 (0.9-1.2)
Gajalakshmi (2018) Asia (India)	1998-2015 (17 yrs)	0.5 M (35-69 yrs) 29,519 deaths	Age, sex, smoking, drinking, education, SES, SBP	MI, stroke, cancer TB, asthma	2 yrs	BMI (23.2±3.8) All-cause Cardiac/Stroke Renal	inverse J-shape (20-25 kg/m ²) Null Null	NR

Studies were selected on size, completeness of information, individual data analyses (as opposed to meta-analyses of estimates from other studies), rigour, and relevant differences in findings (further details are included on the Supplementary Tables S3-6). Results are selective on mortality from all or vascular-metabolic causes (cardiac, cerebrovascular, diabetic, renal or liver disease). Continuous estimates are for measured BMI (in kg/m²) above the nadir. Studies 1 and 2 excluded ever smokers.

M=millions; CVD=Cardiovascular Disease; CHD=Coronary Heart Disease; MI=Myocardial Infarction; TB=Tuberculosis; NR=Not Reported; SA=South Asians; EA=East Asians. † Detailed summary statistics given if reported.

adults living in South India and followed-up for 17 years, which also found that among never-smokers who had no prior history of chronic diseases and survived more than 2 years, BMI was approximately *unrelated* to cardiovascular mortality, despite BMI being log-linearly related to blood-pressure, and blood pressure being log-linearly related to cardiac and stroke mortality.¹⁶

Several Latin-American studies (n=11) also assessed BMI-associated mortality. The largest such studies included meta-analyses of the US National Surveys (n=38,810), individual prospective studies (n=16,798), or Mexican-specific smaller studies (n=8,415). Such studies typically found no evidence that higher BMI measured in middle age was associated with higher mortality (**Table 2.2**).¹⁹⁻²² The findings differ markedly from studies conducted in Caucasians or most Asian populations, and have been referred to as '*the Hispanic obesity paradox*'.²³⁻²⁶ However, these Hispanic studies had a relatively short duration of follow-up (9-13 years), and most did not exclude individuals with previous medical histories, nor deaths within the first few years of follow-up. A single study of 2,628 Pima Indians from Arizona, which did exclude individuals with pre-existing diabetes, reported U and J-shaped associations of BMI with all-cause and cardiovascular mortality, respectively, with a 'lower' risk at a baseline BMI of 30-35 kg/m²,²⁷ and compared to this group, a 2-fold higher risk for all-cause mortality at a BMI ≥40 kg/m². Among those with diabetes, the risk for cardiovascular mortality was 1.2-fold at a BMI <25 kg/m², and a 3.4-fold at a BMI ≥40 kg/m² (compared to those with a BMI of 30-35 kg/m², and when duration of diabetes, and insulin therapy were accounted for). However, the statistical reliability was very low, given that only 55 cardio-vascular cases were available. A more recent study

Table 2.2: Selected studies of BMI and mortality including Mexican populations, by study size

Author (year) Study type	Recruitment period (Follow-up)	No. of participants (age, years) No. of deaths	Confounders	Exclusions		Adiposity (mean, SD) Mortality	Summary Findings	
				Prior disease	FU		Shape (lower risk)	HR (95%CI)
Mehta (2013) USA Hispanics	1997-2006 (8.9 yrs)	38,810 (18+ yrs) 1461 deaths	Age-attained, sex smoking, exercise	No	No	BMI All-cause	Null	NR
Fontaine (2012) USA Hispanics	1965-2006 (13 yrs)	16,798 (18-80 yrs) 5186 deaths	Age-attained, sex, smoking	No	No	BMI All-cause	inverse J-shape	NR
Howell (2017) USA Hispanics	1988-2010 (22 yrs)	10,641 (26+ yrs) 1196 deaths	Age, sex, smoking	No	No	BMI (29.9±6) All-cause CVD Diabetes	Positive Non-linear Positive	NR
Kumar (2015) Mexico	2001-2012 (11 yrs)	8415 (50+ yrs) 1067 deaths	Age, sex, smoking, comorbidities, education, marital status	No	5 yrs	BMI (26.3±5.3) All-cause	inverse J-shape (~25 kg/m ²)	NR
AlSnih (2002) USA Hispanics	1993-1999 (5 yrs)	3050 (65+ yrs) 507 deaths	Age, education, smoking, handgrip, medical history, timed walk, marital status	No	No	BMI All-cause	inverse J-shape	NR
Hanson (1995) USA Pima Indians	1965-1990 (8.1 yrs)	2628 (30+ yrs) 249 deaths	Age, sex, FU time, year at entry, smoking	Diabetes	No	BMI (31.0) All-Cause CVD	U-shape (30-35 kg/m ²) J-shape	NR

Conventions as per table 2.1. Studies 1 and 3 included 58% Mexicans. Study 1 excluded ever smokers. Studies 3 and 6 excluded pregnant women.

which included 6,242 young Mexican-Americans from the National Health and Nutrition Examination Surveys (NHANES) who were followed-up for 22 years, showed variable associations with different causes. For instance, among those who gained weight from 20 kg/m² to more than 35 kg/m², this study described a log-linear higher risk for vascular and all-causes of death, but not for deaths from diabetes. Specifically, compared to those with a BMI of 18.5 to 24.9 kg/m² (reference group with a HR of 1), those with a BMI above 35 kg/m² had a 1.7-fold higher risk for cardiovascular mortality and a 3.6-fold higher risk for all-cause mortality, respectively.²⁸

2.8 Summary of the studies of abdominal adiposity

Studies of abdominal adiposity alone were rare (**S4**). One multi-ethnic North-American study of 170,000 adults from the NIH-AARP Diet and Health Cohort without chronic disease at assessment followed-up for over 12 years, reported a 10% lower risk of all-cause mortality with low abdominal adiposity in men, and a 20% lower risk in women.²⁹ Levels of abdominal adiposity were defined by the WHO gender-specific cut-offs for self-measured waist circumference (<102 cm in men, and <88 cm in women, validated with technician-measures in a sub-set of the participants). Furthermore, the estimates were made in the context of other life-style characteristics. One other North-American study of nearly 105,000 adults from the Cancer Prevention Study II Nutrition Cohort who were followed-up for 9 years, reported positive associations of waist circumference with mortality from cardiovascular, neoplastic, respiratory, and all-causes combined. Despite prior diseases and early deaths not being excluded in this particular study, the associations were approximately log-linear, and above a BMI of 25 kg/m², each 10 cm higher waist circumference was associated with a 20% higher risk for mortality from all-causes in men, and a 10% higher risk in women,

respectively.³⁰

2.9 Summary of the studies of body composition

A single Latin-American study, two North-American studies, and one Asian study assessed the relevance of different body-fat depots (i.e., total, visceral, subcutaneous, and their central or peripheral distributions), to all-cause and specific mortality from cardiovascular or neoplastic causes. The markers from DXA, CT scan, or derived from anthropometric equations, were heterogeneously associated with mortality (**S5**). Generally, direct markers of percent fat mass (FM) or visceral fat, demonstrated largely positive associations with deaths from all-causes, with a 2-fold relative risk at the top 3rd or 4th of the distributions, compared to those in the lowest percentiles (considered to be at no risk, or a HR of 1).

In one North-American study of over 9,000 adults aged 20 years or more from NHANES, without chronic diseases, who survived for at least one year, and had been followed-up for nearly 9 years, the associations of increased percentage of fat mass with all-cause, and with cardiovascular mortality, were J-shaped (**Table 2.3**). For instance, those in the 4th quartile of the FM distributions had a 1.5-fold higher risk of death from any cause, compared to those in the 2nd quartile, and a 2.2-fold higher risk of cardiovascular mortality, respectively.³¹ In one study of over 36,600 Korean adults, which did not account for pre-existing medical histories or deaths occurring in the first years of follow-up, the increase of the ratio of visceral to subcutaneous fat (VSR) routinely measured by CT scan, was positively associated with all-cause mortality, while the increase in subcutaneous fat area (SFA) was inversely associated with mortality from all-causes.³² For instance, those in the top third of the distribution of the

Table 2.3: Selected studies of body composition and mortality, by study size

Author (year) Study type	Recruitment period (Follow-up)	No. of participants (age, years) No. of deaths	Confounders	Exclusions		Adiposity (mean, SD) Mortality	Summary Findings	
				Prior disease	FU		Shape (lower risk)	HR (95%CI)
Lee (2018) Asia (Korea)	2007-2015 (5.7 yrs)	36,656 (45-65 yrs) 253 deaths	Age, sex, glucose, BMI, WC, HDL-c, CRP, triglycerides, albumin, haemoglobin, muscle- mass, proteinuria, medication	No	No	All-cause TFM (15.8±5 kg) VSFA SFA	Negative Positive Negative	NR NR NR
Zong (2016) N. America (USA)	1999-2006 (8.8 yrs)	9,471 (20+ yrs) 683 deaths	Age, sex, ethnicity, smoking, drinking, exercise, education, income, marital status, family medical history	Diabetes, CVD, COPD, cancer, asthma, mental conditions	1 yr	All-cause TFM (33.1±.07%) Trunk FM (kg) Leg FM (kg) CVD TFM Trunk FM Leg FM	J-shape J-shape J-shape inverse J-shape U-shape U-shape	NR NR NR NR NR NR

Conventions as per tables 2.1-3. HDL-c=High Density Lipoprotein Cholesterol; CRP=C-Reactive Protein; WC=Waist circumference; T/FM=Total/Fat Mass; VSFA=Visceral to Subcutaneous Fat area ratio; SFA=Subcutaneous Fat Area. FM was measured by Computer Tomography in Study 1 and by Dual X-Ray Absorptiometry (DXA) in Study 2.

VSR had a 2-fold higher risk of all-cause mortality compared to those in the lowest third, but the statistical credibility was limited, as only 253 deaths were available.

2.10 Summary of the comparative studies of different adiposity markers

A total of 25 studies (including 6 meta-analyses, 7 Latin-American and one Mexican-American study, among other cohorts), assessed mortality risk with multiple markers of adiposity (**S6**). Adiposity was considered in various ways, as dichotomous exposures, WHO modified categories, or equal percentiles, which complicated direct comparisons of the results of different studies. Continuous estimates were also calculated differently, with most (but not all) studies assessing risk per one SD or per 5-units higher levels of markers of general body mass and composition, or of abdominal adiposity. In general, even among those without prior history of chronic diseases, the estimates of observed fat mass, WHR and waist-height ratio for all and different cardio-metabolic causes of death, varied importantly by sex and the way in which adiposity was grouped (i.e., binary or continuous).

Overall, in meta-analyses or individual studies which assessed various disease outcomes, BMI displayed largely positive, but non log-linear associations, with mortality from all or specific causes, while fat mass and different markers of abdominal adiposity were more often positively and log-linearly associated with risk from the same causes throughout the ranges studied (**Table 2.4**),³³⁻³⁶ and irrespective of ethnicity.³³ By contrast, most Latin-American studies reported inverse J-shaped associations with mortality from any cause, and only one recent study of Mexicans from NHANES showed log-linear, very weak, positive associations of BMI, fat mass, waist circumference and WHtR, with cardiovascular, diabetic or all-cause mortality

Table 2.4: Selected studies of multiple adiposity markers and mortality including non-Mexican populations, by study type and size

Author (year) Study type	Recruitment period (Follow-up)	No. of participants (age, years) No. of deaths	Confounders	Exclusions		Adiposity (mean, SD) Mortality	Summary Findings	
				Prior disease	FU		Shape (lower risk)	HR (95%CI)
Pischon (2008) Meta-analysis	1992-2000 (9.7 yrs)	359,387 (25-70 yrs) 14,723 deaths	Age, study, smoking drinking, education, exercise, height	cancer, CHD, stroke	5 yrs	<u>All-cause/CVD</u> BMI WC WHR	J-shape (20-24.9 kg/m ²) Positive Positive	NR
Dhalwani (2018) Europe (UK)	2006-2010 (7 yrs)	0.5 M (40-69 yrs) 13,896 deaths	Age, sex, smoking, ethnicity, SES, MET, drinking, diet, handgrip strength, medication, CVD, cancer, diabetes duration	CVD, cancer	2 yrs	<u>All-cause</u> BMI (No DM) WC (No DM) BMI (DM) WC (DM) <u>CVD</u> BMI (No DM) WC (No DM) BMI (DM) WC (DM)	inverse J-shape (18.5-25 kg/m ²) U-shape inverse J-shape inverse J-shape U-shape J-shape U-shape inverse J-shape	NR
Kim (2017) Europe (UK)	2006-2010 (7 yrs)	0.5 M (40-69 yrs) 8287 deaths	Age, sex, ethnicity, smoking, exercise drinking, grip strength Townsend index employment, diet, statin, HRT, pulse rate	heart attack, cancer, COPD stroke	2 yrs	<u>CVD (Men)</u> BMI WC FM (%) <u>CVD (Women)</u> BMI WC FM	Positive Positive Positive Positive J-shape (80-88 cms) inverse J-shape	NR
Park (2018) Asia (Korea)	2002-2013 (5.6 yrs)	465,629 (40-89 yrs) 5,469 deaths	Age, sex, smoking, drinking, exercise, income	CVD, cancer diabetes hypertension	No	<u>All-cause/CVD</u> BMI (23.2±3.4) WC (80.5±8.9) WHtR (0.5±0.06) WWI (8.1±0.6) ABSI (10.4±0.8)	J-shape J-shape J-shape J-shape J-shape	NR

Conventions as per tables 2.1-4. SES=Socio-economic status; MET=Metabolic Equivalent Task; HRT=Hormone Replacement Therapy; COPD=Chronic Obstructive Pulmonary Disease; DM=Diabetes Mellitus; WHR=Waist-hip ratio; WHtR=Waist-height ratio; WWI=Weight-adjusted-waist index (cm/ $\sqrt{\text{kg}}$); ABSI=Anthropometric Body Shape Index (cm*kg^{5/6}/m^{2/3}). FM was measured by DXA in Study 3.

(e.g., HRs<1.1 per 1 SD higher level throughout the ranges of the exposures; **Table 2.5**).³⁷ In one carefully conducted study of nearly 40,000 North-American male adults from the Health Professionals Follow-up Study, who had no chronic diseases and survived for at least 2 years, DXA-measured lean mass displayed a U-shaped association with mortality from all causes or from cardiovascular causes, even after exclusion of those with extreme leanness.³² Importantly, studies which only partially accounted for pre-existing or pre-clinical diseases (i.e., selective exclusions of one or the other, or less than 5 years of follow-up), often reported non-linear associations of body-fat with mortality.^{32,37-40} One contemporary large study investigated mortality risk after stratification for diabetes in 0.5 million individuals from the UK Biobank, without other known diseases who survived for at least 2 years, and described U- or inverse J-shaped associations of BMI and of waist circumference with all or cardiovascular causes of death, even among those without known diabetes at baseline (**Table 2.4**).⁴¹

2.11 Mexican studies in context

While a large body of research has been conducted, and focused on clarifying the shapes and the 'lower risk ranges' of BMI and other anthropometric markers of adiposity in many populations, only a few studies have examined such effects in Latin-American populations (limited to only 0.16% of the total global population included in the 74 identified reports). A vast majority of these data were collected between 1960 and 2010, before the prevalence of obesity increased more significantly worldwide. A few small contemporary cohorts have recently investigated the relevance of body composition in addition to convenient anthropometric markers of adiposity, but they have not matured sufficiently to estimate cause-specific associations reliably. Mexico was ranked 5th in order of severity among the most obese populations worldwide in

Table 2.5: Selected studies of multiple adiposity markers and mortality including Mexican and Mexican-American populations, by study size

Author (year) Study type	Recruitment period (Follow-up)	No. of participants (age, years) No. of deaths	Confounders	Exclusions		Adiposity (mean, SD) Mortality	Summary Findings	
				Prior disease	FU		Shape (lower risk)	HR (95%CI)
Lee (2018) N. America (USA)	1987-2012 (21.4 yrs)	38,006 (40+ yrs) 12,356 deaths	Age, sex, ethnicity, smoking, drinking, residency, height, exercise, energy intake, family medical histories	CVD, cancer	2 yrs	<u>All-cause</u> BMI (25.4) FM (kgs) LM (kgs) <u>CVD</u> BMI FM (kgs) LM (kgs)	J-shape (22.5-25 kg/m ²) Positive U-shape (56 kgs) J-shape (22.5-25 kg/m ²) Positive U-shape	per SD 1.2 (1.1-1.2) 1.2 (1.2-1.3) 0.9 (0.8-0.9) NR 1.7 (1.5-1.9) NR
Howell (2018) Mexican (USA)	1999-2010 (11 yrs)	10,329 (26+ yrs) 1423 deaths	Age, sex, smoking	No	No	<u>All-cause</u> BMI (28.1±5.6) WC (94.6±13.5) WHtR (0.58±0.08) FM (31.5±9.7%) FM (23.9±10.1 kgs) LM (51±11.5 kgs) <u>CVD</u> BMI WC WHtR FM (%) FM (kgs) LM (kgs) <u>Diabetes</u> BMI WC WHtR FM (%) FM (kgs) LM (kgs)	Positive Positive Positive Positive Null Null Positive Positive Positive Negative Null Positive Positive Positive Positive Null Negative	per 5-units 1.0 (1.0-1.1) 1.0 (1.0-1.1) 1.1 (1.0-1.1) 1.1 (1.0-1.2) 1.0 (1.0-1.1) 1.0 (0.9-1.0) 1.1 (0.9-1.4) 1.1 (1.0-1.1) 1.1 (1.0-1.2) 0.9 (0.7-1.2) 1.0 (0.8-1.3) 1.2 (1.0-1.5) 1.2 (1.0-1.5) 1.1 (1.0-1.2) 1.3 (1.1-1.5) 1.2 (1.0-1.5) 1.0 (0.9-1.3) 0.9 (0.7-1.2)

Conventions as per tables 2.1-5. F/LM from DXA. Study 1 excluded women and those with FM<2.5/>10th centile or BMI<12.5/>60 kg/m², study 2 pregnancy.

2014.⁴² However, there was limited available evidence from previous studies conducted in Mexico. The only large collection of Mexican-American populations involved 40,000 middle-aged adults, and reported no excess risk of death associated with levels of BMI higher than 25 kg/m². In contrast, a smaller study, involving 10,000 young adults, reported positive associations of BMI, abdominal adiposity, or predicted body-composition, with death from cardio-metabolic causes. Thus, the lack of available evidence for the effect of adiposity on mortality in one of the most adipose populations in the world, has prompted the so called '*Hispanic obesity paradox*'. This highlights the need for further research to reliably establish the relevance of different markers of adiposity to different causes of death in Hispanic populations. The aims of this thesis are to clarify the associations of various markers of adiposity with premature mortality in a Hispanic population, using data from 150,000 adults who were enrolled in one of the largest contemporary Mexican cohorts.

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Chapter 3: Methods

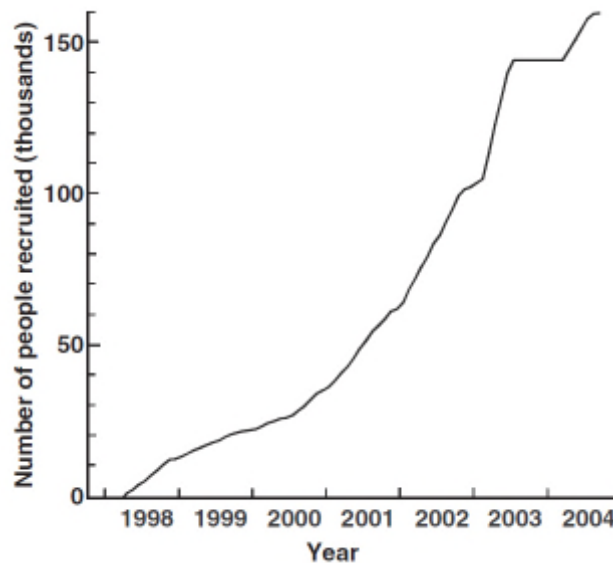
This chapter describes the design and methods used in the Mexico City Prospective Study (MCPS), including recruitment, baseline and resurvey assessments, mortality follow-up, and the epidemiological and statistical methods used for analysis in this thesis.

3.1 Study design, procedures and follow-up

3.1.1 Target population and recruitment of participants

This prospective cohort study was designed to examine the preventable causes of premature mortality in a large sample of middle-aged adults living in Mexico City.¹ Two districts with relatively stable populations and contrasting socio-economic characteristics were selected, one more affluent [Coyoacán] and one less affluent [Iztapalapa]. Between 1995 and 1997, all the households in both districts were mapped in a census fashion, through door-to-door interviews, and the identifiable characteristics of potentially eligible participants (age, sex, and address) were ascertained and recorded. Between 1998 and 2004, 112,333 targeted households were systematically visited, and of those, 106,059 (94%) yielded 159,755 potentially eligible participants. All of the consenting adults aged 35 years or greater were recruited and assessed at their homes. A total of 52,644 men and 107,111 women were enrolled (representing a '*household response-rate*' of 94%, and an average of 1.5 participants per household; Figure 3.1).

Figure 3.1 Cumulative recruitment of participants



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3.1.2 Baseline assessments

Trained nurses used an interview-administered *standardised questionnaire* to record detailed information on socio-demographic, lifestyle and health characteristics (details on Table 3.1), and also collected measurements of anthropometry and blood-pressure. All participants had blood samples collected for long-term storage in liquid nitrogen.

Physical measurements were recorded using a standard protocol, with the participants wearing light clothing (i.e., after removing jackets and sweaters), using standard equipment that was calibrated every two weeks. Standing height without shoes was measured (to the nearest 0.1 cm) using wooden triangles and wall-fixed non-stretchable tapes, with the feet flat on an even floor, and the head kept in the Frankfort-Plane position. Weight was measured to the nearest 0.1 kg using portable scales

(analogue scales between 1998-2003, but electronic scales between 2003-2004) placed on an even floor. Waist and hip circumferences were measured to the nearest 0.1 cm (over light shirts or trousers), using non-stretchable tapes. Waist circumference was measured at the midpoint between the iliac crest and the costal margin, while hip circumference was measured around the femoral epicondyles.

Table 3.1: Survey questionnaires

Information collected	Baseline	Resurvey
Socio-demographic		
• Date of birth	-	✓
• Age	✓	✓
• Sex	✓	✓
• Residence	✓	✓
• Income (household, personal)	✓	✓
• Educational achievement	✓	✓
• Occupation	✓	✓
Lifestyle		
• Smoking (passive, active status and amount)	✓	✓
• Alcohol use (status, type, frequency)	✓	✓
• Physical exercise (status, frequency, amount)	✓	✓
• Diet (fruits/vegetables, fried foods; cooking oil)	✓	✓
• Sleep duration	✓	-
Health		
• Healthcare insurance (provider)	✓	✓
• Doctor-diagnosed disease (type, year)	✓	✓
• Medication use in the last year (name)	✓	✓
• Diabetes (diagnosis, medication, interventions)	-	✓
• Reproductive history (menopause, parity, age at first pregnancy and first sexual relationship, oophorectomy, hormone replacement therapy,	✓	✓
• Mental health (cognition and memory)	-	✓

Systolic and diastolic blood pressure were measured in the seated position, three times (at three minute intervals) to the nearest 1 mmHg, using a standard mercury

sphygmomanometer recalibrated monthly, with an appropriate sized-cuff for the arm circumference.

Data were entered into handheld devices that were programmed to automatically query implausible values before being uploaded these daily into the study database. A Microwand 32ES barcode optical reading device (Hand Held Products) was used during the first survey stages (April 1998-November 2001), and a SPT 500 personal digital assistant with palm operating system (Symbol) thereafter (November 2001-December 2004).

3.1.3 Blood collection, storage and assays

Participants provided a 10 mL non-fasting blood sample, collected in EDTA vacutainers pre-labelled with bar-coded unique IDs, subsequently scan-linked to each participant's electronic file. Samples were stored in cool boxes during each working day, before transportation to a central laboratory in Mexico City, for overnight storage at 4°C. On the following day, the plasma and buffy coat were separated after centrifugation (15 minutes at 2100g and 4°C), and subsequently stored at -80°C before shipment on dry ice to Oxford (UK), where samples were stored long-term over liquid nitrogen.

Glycosylated haemoglobin levels (HbA1c) were measured with HA-8180 analysers (Arkray), using validated high-performance liquid chromatography, with calibrators traceable to standards specified by the International Federation of Clinical Chemistry (IFCC). Values were expressed in IFCC units of millimoles per mole, subsequently

converted to Diabetes Control and Complications Trial HbA1c percentages (calculated as $\text{millimoles/mole} \times 0.0915 + 2.15$).²

3.1.4 Resurvey of 10,000 surviving participants

Between 1st of June 2015 and 27th of February 2019, 29,011 households were selected at random for resurvey, from which 8,278 (29%) households provided a total of 10,144 original study participants who were still alive. A total of 3,044 men and 7,100 women consented to participate and were revisited systematically to assess repeat questions and assessments identical to those at baseline, assessment of within-person variability in selected risk factors over time, and some ‘enhancements’ (see below).

Participants were visited at home by trained nurses and doctors who applied a standard protocol similar to that used at baseline. The procedures included a face-to-face standardised questionnaire (details in **Table 3.1**), collection of a 10 mL non-fasting blood sample, measurement of anthropometry (height, weight, waist and hip circumferences), and measurement of systolic and diastolic blood pressure (using digital monitors [Model UA-767 Plus BT]). Further enhancements included bio-impedance and spirometry assessments, additional information on medical history, treatment for diabetes, diet, cognitive function, and in a sub-set, collection of 50 mL of urine.

Bio-impedance was analysed using a TANITA SC-240MA analyser scale calibrated weekly, which estimated body-mass composition using a two-compartmented model that divided body weight into fat and lean mass, including estimates of skeletal muscle,

bone mass and total body-water. The scales were placed on an even floor and participants stood on the scale, while wearing light clothing, and without socks, with their feet placed on the two electrode plaques. Values for age, sex and height were manually typed into the device, and the total body mass (in kgs) was estimated based on the principle of resistance to an alternative electrical current, as a function of the tissue composition measured between the two electrodes (where the resistance increases in proportion to the extent of fat mass, and was lower among leaner individuals).³ To minimise data entry errors, the bio-impedance measurements were automatically imported into password-protected electronic tablets (Samsung Galaxy 10.1), and linked to the other participants' questionnaire data collected. For quality control, screen-shots of the results screens were recorded, and random checks confirmed the accuracy of the data linkage.

3.1.5 Mortality follow-up and adjudication

Mexico has a comprehensive system for registration of deaths,⁴ with almost all the adult deaths being medically certified⁵ according to the WHO International Classification of Diseases 10th Revision [ICD-10]⁶, and only a small proportion attributed to unknown causes.

Follow-up of the study participants for cause-specific mortality was conducted through use of a Soundex probabilistic linkage algorithm to the Mexican Electronic Death Register (*Sistema Epidemiológico y Estadístico de las Defunciones*), based on name, age, and place of death. A subset of probable matches was subsequently confirmed by visits to the participant's homes. Validation of 7,000 matched deaths confirmed the reliability of the death certification process in over 95% of the cases. As of January

2018, 23,539 medically certified deaths were reliably identified, and the relevant information included date and place of death, name and ICD-coded underlying and contributory causes of death, duration with known disease, and medical certification at the time of death. Study clinicians then reviewed and, if necessary, recoded the underlying cause of death (for example, accepting diabetes as the underlying cause only for deaths due to acute diabetic crises, and recoding other such deaths to an appropriate alternative cause, often vascular, renal, or infection, based on the information recorded in parts 1 and 2 of the certificate).⁷ Any deaths attributed primarily to a risk factor (e.g., hypertension or hypercholesterolemia) were also re-attributed to an appropriate alternative underlying disease (e.g., vascular).

3.1.6 Funding and ethics approval

The study was funded by the Mexican Health Ministry, the Mexican National Council of Science and Technology, the Wellcome Trust (058299/Z/99), the Medical Research Council, and the British Heart Foundation. Ethics approval was obtained from the Mexican National Council of Science and Technology, the Mexican Ministry of Health (143300410D0020/153300912X3548/2015; FMED/CI/RGG/083/2017), and the University of Oxford (135/2014). All study participants provided written informed consent to participate in the baseline assessment and resurvey.

3.2 Epidemiological methods

This section describes the epidemiological concepts addressed in this thesis, including exposures, confounders, mediators, disease and mortality outcomes, and the statistical methods used to assess the associations of interest.

3.2.1 Definition and classification of adiposity exposures

General adiposity was defined by body-mass index (BMI) and fat-mass index (FMI), where BMI was estimated as body weight in kilograms divided by the square of height in meters [kg/m^2], and the sum of FMI and LMI equaled BMI. The BMI and FMI provide a proxy of total adiposity for a given height, whereas LMI provided a proxy for the total of muscle, bone and water-mass for a given height, used only to estimate the independent relevance of FMI to mortality risk given fat-free mass.

Weight reflects both fat and lean mass, but these were not measured at baseline. However, equations exist, allowing for such estimates to be predicted from age, sex, weight, and waist circumference. For instance, Mexican-specific equations developed by the National Health and Nutrition Examination Survey [NHANES] estimated fat and lean mass, and tested the agreement between predicted body composition from anthropometry-derived equations versus direct measures from DXA.^{8,9} For the purposes of this thesis, the following NHANES algorithms were applied to estimate fat and lean mass in all men and women at baseline:

- $$\text{FM}_{\text{Men}} (\text{kgs}) = -18.592 - (0.009 \times \text{age} [\text{yr}]) - (0.080 \times \text{height} [\text{cm}]) + (0.226 \times \text{weight} [\text{kg}]) + (0.387 \times \text{waist} [\text{cm}]) + 0.080 \quad (3.1)$$

- $$\text{FM}_{\text{Women}} (\text{kgs}) = 11.817 + (0.041 \times \text{age} [\text{yr}]) - (0.199 \times \text{height} [\text{cm}]) + (0.610 \times \text{weight} [\text{kg}]) + (0.044 \times \text{waist} [\text{cm}]) + 0.388 \quad (3.2)$$

- $$\text{LM}_{\text{Men}} (\text{kgs}) = 19.363 + (0.001 \times \text{age} [\text{yr}]) + (0.064 \times \text{height} [\text{cm}]) + (0.756 \times \text{weight} [\text{kg}]) - (0.366 \times \text{waist} [\text{cm}]) - 0.066 \quad (3.3)$$

- $$\text{LM}_{\text{Women}} (\text{kgs}) = -10.683 - (0.039 \times \text{age} [\text{yr}]) + (0.186 \times \text{height} [\text{cm}]) + (0.383 \times \text{weight} [\text{kg}]) - (0.043 \times \text{waist} [\text{cm}]) - 0.359 \quad (3.4)$$

Using the bio-impedance data available at resurvey assessment, the agreement between '*equation-predicted*' and '*bio-impedance estimated*' fat and lean mass was assessed using sex-specific Pearson correlation coefficients.

Given that body-mass includes, but cannot distinguish between general and abdominal adiposity or the dominant distributions of adiposity around the waist and hips, markers of central adiposity were of particular interest, specifically, waist and hip circumferences, their ratio, and the waist-height ratio. Waist circumference (measured in cm) was considered a proxy of subcutaneous and visceral abdominal fat (including ectopic liver fat and interstitial depots). Hip circumference (HC, measured in cm) was considered a proxy of subcutaneous gluteal fat (albeit inclusive of gluteal muscle and hip bones), used only to estimate the independent relevance of waist circumference to mortality risk at a given HC. The waist-hip ratio (WHR) was considered a marker of body-shape and excessive distribution of abdominal adiposity relative to gluteo-femoral adiposity. The waist-height ratio (WHtR) was considered a marker of excessive abdominal adiposity for a given height.

For comparison with other major studies, the BMI was *initially defined* using the WHO categories of ≥ 18.5 to < 22.5 kg/m², ≥ 22.5 to < 25 kg/m² (reference), ≥ 25 to < 30 kg/m² (overweight), ≥ 30 to < 35 kg/m² (obesity grade 1), ≥ 35 to < 40 kg/m² (obesity grade 2), and ≥ 40 to ≤ 60 kg/m² (obesity grade 3), further divided by 22.5 and 27.5 kg/m², given that two-thirds of the cohort were classified as 'normal' or 'overweight'. For comparison, all other markers of adiposity were *initially considered as prevalence-matched* groups equivalent to BMI, based on the respective baseline distributions (of FMI, waist circumference, WHR and WHtR, respectively), so that the proportion of the

cohort in each group, was the same as for each BMI group. *Thereafter*, for comparison with other major meta-analyses, the markers of adiposity were classified in five equal-sized groups of the sex-specific distributions at baseline (with the bottom and the top groups further divided into two groups corresponding to the top and bottom 10% of the distributions). Furthermore, adiposity was also assessed as a *continuous exposure* in which death risk ratios per one standard deviation [SD] higher *observed* or *usual levels*, were calculated as the average of the sex-specific SD (as described in the **Prospective Analyses Section** below). This allows estimates for different adiposity markers to be directly compared (one SD equalled 4.71 kg/m² of BMI, 2.78 kg/m² of FMI, 10.88 cm of WC, 0.061 units of WHR and 0.071 units of WHtR of the baseline values; see **S48** for the corresponding usual values, and **Figure 4.5** in **Chapter 4** for the corresponding values used in cross-sectional analyses at ages 35-89 years). Analyses of BMI and mortality assessed relative risks per 5 kg/m² higher measured BMI (e.g., clinical definition), and some analyses additionally assessed RRs per 1 SD higher BMI, chiefly for comparison of effects with those of higher FMI per 1 SD (e.g., epidemiological definition).

3.2.2 Extreme values and handling of missing data

Values of the various adiposity exposures and associated mediators (SBP and HbA1c), were considered plausible based on *a priori* knowledge and assessment of the distributions. Adiposity was considered plausible for values within the ranges of 35-250 kgs for weight, 120-200 cms for height, 60-180 cms for WC, 70-180 cms for HC, and from those, derived BMI within 18.5-60 kg/m², derived WHR and WHtR within 0.5-1.5 units, respectively, and predicted FM and LM within 3 SDs of the sex-specific distributions (i.e., 1.8-49.9 kg of FM in men, 1.1-51.4 kg of FM in women, 32.8-67.7 kg

of LM in men and 23.1-66.8 kg of LM in women, respectively). No imputations were applied for missing data.

3.2.3 Classification of prevalent diseases at recruitment

Previously-diagnosed diseases at baseline included self-reported chronic diseases, specifically, hypertension, diabetes, cardiac or cerebrovascular cases, renal disease, any type of cancer, cirrhosis of the liver, or emphysema. Diabetes was of particular interest for this thesis, and it was defined as either doctor-diagnosis or regular use of any anti-diabetic medications (insulin, sulphonylureas and biguanides) for at least one year before recruitment into the study. Screen-detected (or undiagnosed) diabetes was conservatively defined as no previous doctor diagnosis but a glycosylated haemoglobin [HbA1c] of 7% or higher.

3.2.4 Classification of causes of death

Among specific causes of death, vascular-metabolic diseases were, of particular interest. Disease outcomes were classified into specific underlying (rather than contributory) causes of death according to the ICD-10 codes (4th digit) recorded on the death certificates (Details of adjudication methods are as described in the section ***Mortality follow-up and adjudication***), These causes of death were classified into the following major categories: vascular, renal, metabolic, neoplastic, respiratory, infective, external, or ill-defined diseases [see **S8** for the defining ICD-10 codes]. The vascular causes were further subdivided into ischaemic and other cardiac deaths, stroke types (ischaemic and haemorrhagic, including intra-cerebral and subarachnoid haemorrhage, or unknown), and other circulatory deaths (peripheral arterial disease [PAD], and thromboembolism). The renal causes were sub-divided into acute and

chronic kidney disease, and other urinary diseases. The metabolic causes were sub-divided into acute glycaemic crises, and diseases of the liver, pancreas, and the biliary tract. The neoplastic causes were sub-divided by tumour site (e.g., cancers of the breast, endometrium, cervix, ovary, prostate, lung, oesophagus/stomach, colon/other, hepato-biliary, pancreas, urinary tract or haematological causes). The respiratory causes were sub-divided into chronic respiratory diseases [COPD] and other infections of the lung (i.e., TB and pneumonia). The infective causes included gastric and other major infections (mostly from helicobacter pylori, septicaemia, and HIV). The remaining causes included any deaths otherwise not classified in any of the groups above, non-medical causes (e.g., from violence), and ill-defined ICD-codes. In this thesis, the combination of any vascular, renal or metabolic causes are referred to as *vascular-metabolic deaths*, and the combination of any respiratory, neoplastic, or infective causes, *non-vascular-metabolic causes of death*.

3.2.5 Confounders

A confounder is an extraneous factor independently associated with both the outcome and the exposure of interest (but not as a result of it), which accounts wholly or partially for the observed effect of an exposure on disease status.¹⁹ The following confounders were considered based on *a priori* knowledge: age, sex, district of residence (Coyoàcan or Iztapalapa [more/less affluent, respectively]), level of education achieved (university or college, high school, elementary school, other type), self-reported leisure-time physical exercise (none, up to twice weekly, at least three times weekly), smoking status and amount of tobacco use (never, former, current but not daily, and daily [<10 or ≥ 10 cigarettes/day]), and drinking status (never, former, and current [any amount]). Residual confounding which cannot be fully 'excluded' by

multivariable adjustment of the selected characteristics was assessed separately for different age-at-risk categories and smoking, as described in **Section 3.4** below.

3.2.6 Mediators and effect modifiers

Mediators are specific characteristics associated with an exposure (as a result of it), which are intermediate in the causal chain between an exposure and disease outcome.¹⁹ It is generally believed that the association of adiposity with excess mortality from specific causes is mediated through several biological factors, which are on the causal pathway, including blood pressure, glucose, lipids, renal, liver, or inflammatory biomarkers. In this thesis, the effects of SBP and HbA1c were assessed as possible mediators between adiposity and cause-specific mortality, and in a subset, HDL-c, non HDL-c and triglycerides were also assessed among 12,706 men and 22,238 women with data available. (The correlation between NMR-measured lipids and biochemistry-measured lipids was assessed in 217 participants with available data, without diabetes or other chronic disease at baseline.)

Effect modifiers are characteristics which alter the magnitude or the direction of an association between an exposure and a disease.¹⁹ Based on *a priori* knowledge, age-at-risk (in the bands of 40-59 years, 60-74 years, and 75-89 years), sex, and previously diagnosed diabetes, were considered as the most likely effect modifiers in this thesis. In addition, the potential effect modification by the strata of all other confounders (residential district, education, physical activity, smoking and drinking status) was also assessed.

3.2.7 Reverse causality bias

Some diseases are associated with pathological *weight-loss* or *weight-gain* preceding a diagnosis (e.g., cancers, diabetes), or during severe stages of disease (e.g., decompensated cirrhosis of the liver, advanced renal failure).^{26,27} Such alterations of the general levels of adiposity as a consequence (rather than a cause) of a disease, is defined as *reverse causality bias*, and unless accounted for, it may distort the *true causal relevance* of adiposity for mortality from specific causes. Based on *a priori* evidence and preliminary univariate analyses from the present study, the possibility that adiposity levels were altered by presence of pre-existing diseases (e.g., cross-sectional and prospective ‘inverse’ associations of adiposity with mortality among those with chronic disease at the time adiposity was measured), previously-diagnosed diabetes, vascular or chronic kidney disease, liver cirrhosis, cancer, and emphysema, were considered to be possible sources of reverse causality bias.

For example, in this cohort, the mean levels of BMI at baseline were similar in those with and without previously-diagnosed diabetes, but among those *without* a diagnosis, BMI was strongly predictive of the prevalence of diabetes ~14 years later.⁷ Moreover, among those *with* previously-diagnosed diabetes, BMI was *inversely* related to blood levels of glycated haemoglobin (a proxy for levels of blood glucose over the past few months),²⁸ suggesting reverse causality from un-diagnosed or uncontrolled diabetes (both leading to weight loss prior to recruitment). Consequently, participants with previously-diagnosed or treated or screen-detected diabetes (e.g., HbA1c $\geq 7\%$) were considered to be subject to reverse causality bias, and excluded from the main analyses (but included in some other analyses in order to demonstrate the magnitude of this bias). The potential distortion by other pre-existing diseases on the association

of baseline levels of adiposity with mortality, was assessed with and without inclusion of medical histories at baseline (above), and of deaths that occurred during different follow-up periods (e.g., the first 5-10 years), in order to assess the potential impact of pre-clinical diseases. In addition to diabetes, previous-diagnoses of any other diseases outlined above and deaths in the first 5 years of follow-up were also excluded from the main analyses in this thesis.

3.3 Statistical methods

This section describes the statistical methods used to assess the cross-sectional associations of the different markers of adiposity with vascular-metabolic risk factors and pre-existing disease at recruitment, and the prospective associations of adiposity with cause-specific mortality (including mediation analyses of blood pressure, HbA_{1c}, and selected lipids). The cross-sectional analyses included participants at ages 35-89 years, whereas the primary analyses of mortality assessed premature death at ages 40-74 years (given exclusion of the first 5 years of follow-up), with some analyses also conducted for deaths at ages 75-89 years. Unless otherwise indicated, the main analyses excluded participants with an HbA_{1c} level of 7% or higher at recruitment, and those with previously-diagnosed diabetes, vascular disease, renal disease, cancer, liver cirrhosis, and emphysema, those who had missing or extreme values for any anthropometry measure (1.4% of otherwise eligible participants), missing or implausible covariate data (0.1% of otherwise eligible participants), and those aged 90 years or older at recruitment. In addition, those who had uncertain vital status at the end of follow-up (1.5% of otherwise eligible participants) and deaths that occurred in the first 5 years of follow-up were excluded from prospective analyses. (A summary of exclusions is provided in **Table 4.1 of Chapter 4.**) All analyses in this thesis were

conducted with STATA v14.2 and R v3.5.3 (www.r-project.org).

3.3.1 Cross-sectional analyses of adiposity

The sex-specific distributions of each of the adiposity markers were first assessed graphically, using histograms, box-plots, and summary statistics (e.g., means, standard deviations [SDs], medians, interquartile ranges [IQRs], and ranges). The concordance between different adiposity markers was summarised using Pearson coefficients calculated separately in men and women.

For each of the five markers of general and abdominal adiposity (and also for height), mean levels (and 95% confidence intervals [CIs]) for each of the five-equally sized age-groups of men and five-equally sized age-groups of women, were calculated with regression models and plotted against the mean age in each group (with the area of the squares inversely proportional to the variance). For visual comparability of the adiposity-specific patterns, each Y-axis extends over 1 SD above and below the mean of each marker.

The *sex-specific associations* between adiposity at *baseline* and socio-demographic characteristics, lifestyle characteristics, physical and biological measures, and medical history (e.g., hypertension, diabetes, and regular use of any anti-hypertensive, anti-thrombotic and lipid-lowering medications), were initially described by increasing levels of BMI defined by the *WHO-modified groups* (as described in the section on **Adiposity Exposures** above), and for the other markers of adiposity, by *BMI-prevalence-matched groups* (such that the proportion of the participants in each group corresponds to that of BMI), and summarized using descriptive statistics (i.e., means

for continuous variables and proportions for categorical variables).

Subsequently, the *shapes of the associations* between each marker of adiposity (BMI, FMI, waist circumference, WHR and WHtR classified by the ten equal-sized groups of the sex-specific distributions) and various traditional vascular-metabolic risk factors at baseline (HbA1c, SBP, DBP, HDL-c, non HDL-c, and triglycerides), were assessed with regression models stratified by sex, and adjusted for age, district, education, physical exercise, alcohol or smoking status and amount. The associations of general adiposity *independent* of abdominal adiposity and vice-versa, were then assessed with further adjustment for the other markers of adiposity (for instance BMI given WHR, FMI given LMI, waist circumference given BMI and HC, and WHtR given weight and HC). The adjusted means with their 95% CIs were plotted across the group-specific means of each adiposity marker on the X-axes, extended across 3 SDs (from -1 SD below, to +2 SDs above the mean).

Furthermore, the *strength of the associations* of continuous levels of each of the adiposity markers with HbA1c, blood-pressure and selected lipids at baseline, was assessed with similar regression models. The overall and sex-specific mean levels of HbA1c, SBP, DBP, HDL-c, non HDL-c, and triglycerides associated with each 1 SD higher general and central adiposity (corresponding to 4.7 kg/m² BMI, 3.7 kg/m² FMI, 11.2 cm waist circumference, and 0.1 units of WHR and WHtR, respectively; see **Figure 4.5** of **Chapter 4** for the sex-specific values), were summarised using forest-plots including the mean estimates and their 95% CIs, before and after adjustment for the other markers of adiposity. To minimise reverse causality bias, the exclusions listed at the beginning of this section applied, and in addition, those who were regularly

taking any anti-hypertensive medication at baseline assessment were also excluded. Sensitivity analyses assessed the associations of adiposity with previously-diagnosed diabetes at baseline and at resurvey (with adiposity defined for convenience by the five equally-sized groups of the sex-specific distributions).

3.3.2 Prospective analyses of adiposity and cause-specific mortality

The primary analyses assessed the shape and strength of the *associations* of each of the adiposity markers with *premature mortality* (between ages 40 to 75 years) from *all, vascular-metabolic and non-vascular-metabolic causes*. Cox regression models with age-attained and follow-up time (by the time an event occurred, or in the absence of death, at censoring) as underlying time-scales, yielded the hazard ratios (HR) for specific causes associated with general (BMI) and abdominal adiposity (WC, WHtR), including predicted body-mass composition (FMI) and body-fat distributions (WHR), *overall and independent of each other marker*. To *limit the effects of reverse causality bias*, participants with prior disease (as specified in the section on **Reverse causality** above) and deaths in the first 5 years of follow-up were excluded from the main analyses. In this thesis these hazard ratios are referred to as *Death Rate Ratios* (RRs).

3.3.3 Proportional Hazard Assumptions

To examine the dependency of the death RRs on follow-up time, RRs were estimated separately for deaths occurring at <5, 5 to <10, and ≥10 years after recruitment. However, even if the mortality rate ratios in different time periods do differed (indicating a violation of the assumptions), the log RRs from the Cox model over the overall follow-up period, still provide useful descriptive statistic, for it can be thought of as the weighted average of the *log mortality rate ratios* in different time periods.

3.3.4 Censoring approach

Participants who did not die during the age-at-risk period under investigation were *censored* at the end of that period (e.g., on their 75th birthday for analyses of deaths at ages 40 to <75 years), or at the end of follow-up (January 1st, 2018). In analyses of cause-specific mortality, participants who died from a cause other than that being analysed were censored at their date of death.

3.3.5 Mortality analyses by age-at-risk

Multivariable Cox proportional hazard models assessed mortality risk. Because adjustment for age does not fully remove the associated confounding, and because age-attained at the time of death is more important than age at baseline, age was stratified by 5-years intervals of the age-attained at the time of the event, or for those who did not die, at right censoring (i.e., *age-at-risk*). The Cox models used a Lexis expansion,^{31,32} which allowed for concomitantly accounting for age-at-risk and the follow-up time-intervals spent in each Lexis cell,²⁰⁻²² adiposity exposures and covariates. The model calculates the baseline hazard of a participant at a given follow-up time $t-t_0$, and the slope denoting the $\log_e HR$ between participants with increased levels of adiposity relative to the reference group, adjusted for the confounding effects of the covariates.^{22,29} Analyses were stratified by 5-years age-at-risk categories, and mutually adjusted for sex, recreational physical activity, smoking, drinking, highest education achieved, and district of residence (considered in the categories described in the section on **Confounders** above).

3.3.6 Shapes of associations

To *compare* the shapes of the associations of adiposity with total and cause-specific

mortality (from any vascular-metabolic and any non-vascular-metabolic causes combined, as well as from the different major component diseases; detailed in the section on **Classification of causes of death** above), the *observed levels of adiposity at baseline* were classified in two ways: as *prevalence-matched groups* (detailed in the section on **Adiposity Exposures** above), and as *five equal-sized groups of the sex-specific distributions*, with the bottom and the top fifths further divided into two tenths. The relative risk for each group compared with the bottom group, was estimated and presented with *group-specific 95% CIs*, which ascribes an appropriate variance to the log of the RR in every group, including the reference and allows for comparisons of the death RRs between any two groups.³³ The adjusted estimates were plotted on a log-scale against the *observed levels of each adiposity marker* across the x-axes corresponding to the same number of SDs (from -1 SD below, to +2 SD above the mean, enabling direct comparison of the slopes), and centred at the group-specific means of each marker.

3.3.7 Strengths of associations

To investigate *the average strength of the associations* of each marker of adiposity with total and cause-specific mortality, subsequent analyses included *observed levels of adiposity as continuous variables* (specifically, per 5 kg/m² of BMI <25 kg/m² and ≥25 kg/m², and for all other markers, per 1 SD throughout the full ranges studied, corresponding to 4.71 kg/m² BMI, 2.78 kg/m² FMI, 6.99 kg FM, 10.88 cm waist circumference, 0.061 units WHR and 0.071 units WHtR). Continuous estimates included sex-specific and age-specific death RRs for all-cause mortality and for any vascular-metabolic mortality at ages 40-59 years, 60-74 years, and 75-89 years, and cause-specific death RRs at ages 40-74 years. The RRs associated with each

adiposity marker were calculated throughout the full ranges studied, both *overall and independent of each other marker*, with the same adjustments described for the categorical analyses above. From those RRs, the absolute risks of death were subsequently estimated as *population attributable fractions* [PAF] associated with the excess risks of cause-specific mortality due to a BMI ≥ 30 kg/m². The PAFs were calculated as the sum of the fraction of deaths *attributable* to a BMI of 30-39 kg/m² and of 40+ kg/m², respectively, as **[no. events*(RR-1)/RR] (3.5)**, where RR is the cause-specific risk associated with each level of excess BMI relative to the group with 20-25 kg/m², as a proportion of all deaths (example as per footnote of **S39**).

3.3.8 Assessment of possible effect modification

Effect modification was assessed for each adiposity marker (as a continuous variable) by strata of each of the confounders included. Furthermore, the *degree of confounding to mortality risk* from all, vascular-metabolic and non-vascular-metabolic causes, was assessed by step-wise analyses of each confounder, with the material changes in the strength of the associations summarized by the *Wald chi-square statistic* calculated as **(-2)*logLR** [likelihood ratio].

3.3.9 Assessment of possible effect mediators

The excess risk of premature mortality from vascular-metabolic causes (including of any vascular, cardiac and stroke deaths, and renal or acute diabetic deaths) associated with the various markers of adiposity explained by the mediating effects of SBP, HbA1c, HDL-c, non HDL-c and triglycerides, was assessed using identical Cox models described above but additionally adjusted for *observed levels of each of these mediators* at baseline (grouped by the five-equally sized groups of the sex-specific

distributions). From those, the incremental relative importance of each mediator considered, to predict mortality risk at ages 40-75 years was subsequently estimated as $(-2) \cdot \log LR$ (relative to the estimates from the Cox model before adjustment for each mediator).

3.3.10 Estimation of effects of adiposity on survival

The death RRs describe the *relative* impact of various markers of adiposity on mortality, but not the *absolute* excess risks of premature death. To estimate what the RRs for mortality per BMI increase from this cohort would imply for the dependence on BMI of the probability of survival, calculations assumed that the 2016 Mexican National death rates correspond to those in a population with an average BMI similar to that observed in this cohort. Firstly, the sex-specific five-yearly death probabilities from 40 to 44 years up until 70 to 75 years of age, were extracted from the WHO Mexican National Mortality Rates in 2016.³⁵ Assuming a general population mean BMI of 29 kg/m², the corresponding RRs for all-cause mortality at ages 40-75 years in a population with a mean BMI of x kg/m² higher (or lower) than 29 kg/m², would then differ from the national death rates by a factor of $RR^{x/5}$ (or its inverse). That factor represents the average increase in RR for all-cause mortality per 5 kg/m² higher level of observed BMI (>25 kg/m²) in this cohort. The age and sex-specific percent probabilities for survival **[S]** from ages 40 to 75 years associated with 5 kg/m² higher BMI in the ranges of <25, 25-29, 30-34, 35-39 and 40-50 kg/m², respectively, were then calculated as **100 - [(1- S_{BMI})*100] (3.6).**

3.4 Sensitivity analyses

Supplementary analyses assessed mortality risks associated with adiposity *stratified*

by the presence of diagnosed or screen-detected diabetes, and with *inclusion* of well-controlled previously-diagnosed diabetes at baseline (i.e., HbA1c <7%). Residual confounding due to smoking was also assessed for specific-causes of death by subgroup analyses of never-smokers, based on the evidence from other studies, showing that heavy smokers had lower weight on average than non-smokers, while those who quit smoking often gain weight.²³⁻²⁵

Mortality analyses with correction for regression dilution bias

One bias that is often overlooked in prospective studies relating risk factors assessed at recruitment to disease risk decades later, is *regression dilution bias*, which arises when a component of the total variation in a baseline exposure represents “within” rather than “between” person variation.¹⁷ Such bias can substantially underestimate the true relevance of long-term, *usual* levels of risk factors to disease, and can be easily corrected for by estimating the extent of the within-person variation (termed as ‘*regression dilution ratios*’ [RDRs]), by resurveying a subset of the survivors.^{17,18} The degree of such variations might differ between exposures (for instance, height and BMI are more stable over time, whereas waist circumference and WHR are less repeatable),¹⁰⁻¹⁶ can be attributed to short-term random errors (i.e., technician-dependent measurement error of waist circumference), or long-term within-person variation (i.e., intended or pathological weight loss).

In this thesis, the repeat anthropometry at re-survey were used to estimate the average *long-term within-person variability* and the *usual levels* of adiposity among 6383 participants aged 35-75 years, without doctor-diagnosed or screen-detected diabetes or other chronic disease at baseline (i.e., similar to the sub-set included in

the main analyses of mortality; the general characteristics of those participants at resurvey versus baseline were compared in **S16**). The *RDRs* for each adiposity marker was quantified through the *MacMahon-Peto ratio* of the ranges of the mean adiposity levels within each fifth of the baseline levels of each marker at resurvey (x_2), relative to the mean levels in the corresponding groups at baseline (x_1).³⁰ From those, the *mid-follow-up time-point* was modelled (details in **S14**), to allow for the fact that the majority of the deaths included occurred before the resurvey, and the repeated measures were taken 10-years later compared to other studies. For comparison, alternative *RDRs* used *Spearman non-parametric rank correlations* and *Rosner regression equations* (**S13**). The *Spearman method* provided the correlation coefficient r_s as an estimate of the *RDR*, and the *Rosner method* provided the slope of the regression line (β) as an estimate of the *RDR*.²⁹ The stability and variability of those *RDRs* were subsequently compared with the MacMahon *RDRs* within strata of the baseline characteristics (age, sex, residential district, education level, smoking, drinking, and physical exercise).

The MacMahon-Peto method was ultimately *used for correcting the risk-estimates for mortality*, given its flexibility and precision over the other methods. The death *RRs* were estimated for *predicted levels of usual* adiposity considered as continuous variables per one *usual SDs* higher levels of each marker. The expected usual levels of adiposity exposures used in the Cox models, were calculated as $u=M + r[b-M]$ (3.8; where M is the average of the sex-specific mean adiposity levels at baseline, r is the adiposity-specific *mid-point RDR*, and b is the observed adiposity level at baseline), further divided by one *usual SD* calculated as $s^* = \sqrt{r \times s}$ (3.9; where s is the average of the baseline *SDs* in men and in women).³⁴ This approach allows for *comparison of the death RRs given equivalent differences* in usual levels of adiposity (specifically,

4.31 kg/m² BMI, 2.67 kg/m² FMI, 1.84 kg/m² LMI, 10.03 cm waist circumference, 8.83 cm HC, 0.05 units WHR and 0.05 units WHtR).

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Chapter 4: Cross-sectional results

Abstract

Adiposity, in general, and abdominal adiposity in particular, have been associated with higher levels of vascular-metabolic risk factors, including higher levels of blood lipids, blood pressure, glucose and diabetes. Population-specific thresholds for general and central markers of adiposity have been proposed for the prediction of vascular-metabolic disease risk, but the evidence from Hispanic populations is limited. This chapter investigates the prevalence and correlates of overweight and obesity among 145,659 adults from the Mexico City Prospective Study, and the cross-sectional associations of five markers of adiposity (BMI, FMI, waist circumference, WHR and WHtR) to diabetes, HbA1c, blood pressure and selected lipids (HDL-c, non HDL-c and triglycerides), among participants without pre-existing chronic diseases at baseline assessment. In this Mexican population, 34% of the participants had a BMI ≥ 30 kg/m² at recruitment. All markers of general and abdominal adiposity were continuously and linearly related to mean levels of HbA1c and blood pressure, in both men and women, and with no threshold levels. General and abdominal adiposity was inversely associated with HDL-c and non HDL-c, and strongly, positively, associated with triglycerides, in both men and women. Each 1 SD higher adiposity level was associated with about 0.10% higher HbA1c, 3 mmHg higher SBP, 2 mmHg higher DBP (except for WHR), 0.02 mmol/L lower HDL-c, 0.02 mmol/L higher non-HDL-c, and 0.10 mmol/L higher triglycerides. Central, but not general adiposity, was continuously and linearly associated to previously-diagnosed or screen-detected diabetes. The relevance of general adiposity to lipids, HbA1c and blood pressure

was largely independent of abdominal adiposity, whereas much of the relevance of abdominal adiposity to blood pressure and triglycerides, but not to HbA1c, HDL-c and non-HDL-c, was explained by general adiposity. In conclusion, in this Mexican population, abdominal adiposity was a stronger independent predictor of diabetic-risk than general adiposity, while general adiposity was a stronger independent predictor of blood pressure than abdominal adiposity, in both men and women, with no evidence of 'threshold' effects. General and abdominal adiposity were independently and similarly associated to HDL-c and non HDL-c, while general adiposity (particularly BMI), was a stronger independent predictor of triglycerides, in both men and women.

4.1 Background

Adiposity^{1,2} and its vascular-metabolic consequences, such as elevated lipid levels,³ blood pressure,⁴ or glucose,^{5,6} are major, yet modifiable, risk factors for cardiovascular and metabolic diseases.^{7,8} The prevalence of obesity, diabetes and hypertension, have continued to increase in the last decade,⁹⁻¹¹ continuing to account for substantial excess risks of premature death and disability in most populations.¹²

Body mass index (BMI) and the waist-hip ratio (WHR) are convenient markers of general and abdominal adiposity used in epidemiological studies and in clinical practice, given their causal associations with lipids, diabetes risk, and blood pressure, as suggested by Mendelian randomisation studies¹³⁻¹⁷ and clinical trials of weight-loss interventions.^{18,19} Nonetheless, previous studies have reported conflicting results about the importance of general versus central adiposity with different vascular-metabolic risk factors. For example, some studies have found BMI to be more strongly related to blood pressure

than waist circumference or the WHR,^{20,21} others reported opposite findings,²²⁻²⁴ while other studies have reported similar associations of BMI and the waist-height ratio (WHtR) with blood pressure.^{21,25} By contrast, these and a few additional studies have unanimously reported that waist circumference^{23,24,26,27} and WHtR were more strongly related to risk of diabetes than BMI,^{21,25} except for one meta-analysis that reported similar associations of BMI, waist circumference, WHR and WHtR with risk of incident diabetes.²⁸

For example, a contemporary study of 0.5 million mostly lean Chinese adults, estimated that systolic blood pressure (SBP) increased by about 8 mmHg for each 5 kg/m² higher BMI,²⁰ an association that was somewhat greater than those reported in studies conducted a few decades ago in Western populations included in the Prospective Studies Collaboration (PSC).¹ In the latter Chinese study, the risk of incident diabetes was 2-fold greater for each 9.5 cm higher waist circumference,²⁹ consistent with that seen in the European Prospective Investigation into Cancer and Nutrition (EPIC) study,³⁰ but somewhat stronger than that reported in meta-analyses of previous studies conducted in different Western populations.²⁸ While the studies of the associations of adiposity with diabetes included screen-detected cases in addition to self-reported doctor-diagnosed cases, none have apparently investigated the associations of adiposity with circulating levels of HbA1c or glucose per se. This aspect warrants further investigation in diverse populations, including Mexicans, among whom diabetes and high levels of HbA1c are common.³¹

The effects of adiposity on risk of vascular metabolic disease are complex, and involve

the mediating effects of lipids, which likely play a causal role in these associations. Findings from previous studies of adiposity and lipids have consistently demonstrated inverse associations of adiposity levels with HDL-c and positive associations with non HDL-c. For instance, among nearly 1 million adults from 57 cohorts in the Prospective Studies Collaboration, each 5 kg/m² higher BMI was associated with 0.15 mmol/L lower HDL-c and 0.45 mmol/L higher non HDL-c.¹ A recent Mendelian Randomization study of almost 13,000 young adults from prospective cohorts demonstrated that each 1 kg/m² higher BMI was causally associated with 0.05 SDs lower HDL-c, 0.05 SDs higher non HDL-c and 0.07 SDs higher levels of triglycerides, and that weight gain was associated with an increase in the levels of these lipids, while weight loss causes a decrease.³² Another MR study involving nearly 35,000 European adults estimated that each 1 kg/m² higher genetic BMI associated with 0.02 mmol/L lower HDL-c, 0.04 mmol/L lower LDL-c, and 0.82% higher triglycerides.¹⁵ Among nearly 112,000 adults from the UK Biobank, 1 SD increase in genetic WHR at a given BMI was causally associated with 0.39 SDs lower HDL-c, 0.16 SDs higher LDL-c and 0.42 SDs higher triglyceride levels.¹⁷

Beyond lipids, the hazardous effects of excess adiposity on cardio-metabolic risk likely involve several inter-related biological processes of other established cardiovascular risk factors. As discussed in **Chapter 1 (section1.6)**, the visceral fat stored in the abdominal region is likely to be associated with increased lipolysis and resistance to insulin, consequent increase in blood levels of fatty acids and liver enzymes, and ultimately, with excesses of circulating glucose and low-density cholesterol. In particular, excess glucose and lipids are frequently associated with elevated levels of plasma creatinine and systolic

blood pressure. Furthermore, the excess adipose tissues in the abdominal area manufacture inflammatory cytokines, which promote the increase in plasma levels of C-reactive protein.³³⁻³⁶ By contrast, the excess adipose tissue stored in the gluteo-femoral region is involved in the stimulation of high-density cholesterol and other enzymes (including through indirect effects on their synthesis in the liver and intestines), that attenuate the hazards of visceral fat.^{37,38} Because of these processes, BMI, WHR, and in particular the waist circumference, are often associated with increased levels of blood lipids,¹ glucose and other markers of insulin regulation, in addition to high levels of blood pressure^{20,39} and inflammatory biomarkers.^{40,41}

Based on the evidence from previous, albeit mostly small, studies suggesting that different markers of adiposity may be differentially related to different vascular or metabolic risk factors, the World Health Organisation (WHO) and the International Federation of Diabetes (IFD) have recommended population-specific cut-offs for various markers of adiposity, for predicting risk of vascular disease and diabetes in clinical practice.²⁷ Furthermore, in 2008, the WHO Expert Consultation on waist circumference and WHR, highlighted the need for re-assessing existing “adiposity cut-off points” for specific populations, and a particular need for evidence on the assessment of diabetes risk among Hispanic populations.²⁷ As varying levels of adiposity and its associated vascular-metabolic risk factors change over time, both between and within populations,^{9,42} updated estimates from contemporary cohorts are necessary.

This chapter describes the study population included in this thesis, and quantifies the

prevalence and correlates of overweight and obesity among 145,659 men and women aged 35-89 at recruitment. It examines the cross-sectional relevance of two measures of general adiposity (body-mass index [BMI] and predicted fat-mass index [FMI]) and three measures of abdominal adiposity (waist circumference [WC], waist-hip ratio [WHR], and waist-height ratio [WHtR]), to diabetes, HbA1c, systolic and diastolic blood pressures [SBP, DBP], previously-diagnosed hypertension, and selected lipids (HDL-c and non HDL-c and triglycerides). The shape and the strength of these associations were assessed using regression models adjusted for confounders. To limit the effects of measurement error, very extreme or implausible values of adiposity, HbA1c, blood pressure or lipids, were excluded (details on **Table 4.1**). To minimise the effects of reverse causality bias, those previously diagnosed with vascular, respiratory, or chronic kidney disease, cancer, and cirrhosis of the liver, at the time of the recruitment in the Mexico City Prospective Study, were also excluded. In addition, analyses of adiposity with HbA1c, blood pressure and lipids, also excluded those with diabetes (previously-diagnosed or screen-detected), as well as those regularly taking blood pressure-lowering medications in the last year (except for analyses of HbA1c).

4.2 Exclusions and complete information of interest

Of the 159,755 participants recruited into the study, 8135 had a history of diagnosed major chronic diseases (other than diabetes) at the time of the recruitment, and were excluded, together with a further 5961 who were aged >90 years or had implausible or missing data (1.5%), leaving 145,659 eligible for analysis (47,657 men and 98,002 women; **Table 4.1**).

Of those, 18,981 (13%) participants had previously-diagnosed or treated diabetes, a further 8396 (7%) had a HbA1c $\geq 7\%$ suggestive of un-diagnosed diabetes, leaving 39,787 men and 82,020 women for analyses of adiposity with risk of diabetes. Of those, a further 5092 were taking antihypertensive medication, leaving 36,331 men and 70,438 women aged 35–89 years, for analyses of adiposity with vascular risk factors. Among those, a subset of 10,065 men and 16,424 women aged 35–89 years also had NMR assays, and were included in analyses of adiposity with selected lipids.

4.3 General baseline characteristics of study participants

Among the 47,657 men and 98,002 women eligible for analyses, mean age was 52 ± 13 years, 60% resided in the less affluent district (Iztapalapa) of Mexico City selected for the study, 50% of men and 36% of women completed secondary or higher levels of education, and 30% of men and 19% of women did regular leisure-time physical activity (**Table 4.2**). Smoking prevalence was 50% in men and 23% in women (based on reported current use of tobacco at recruitment in the study), while the prevalence of drinking was higher, with 74% of the study participants reporting current use of alcohol at recruitment.

Mean systolic (SBP) and diastolic blood pressures (DBP) were 127 ± 17 mmHg and 83 ± 10 mmHg respectively, with largely similar values in men as in women. The prevalence of self-reported doctor-diagnosed hypertension was higher in women than in men (23% vs 14%, respectively; **Table 4.2**). Mean levels of glycosylated haemoglobin were also comparable in men and in women ($6.1 \pm 1.7\%$), as was the proportion of those with reported doctor-diagnosed (13%) or un-diagnosed diabetes (7%). The regular use of

essential medications for vascular risk was somewhat higher among women than men for blood pressure lowering drugs (17% vs 10%, respectively), while the use of anti-thrombotics (mostly aspirin) or lipid lowering medications was low (2% and 0.5%, respectively), both in men as in women. The baseline characteristics of those with available measures of lipids were similar to those described above, except for the prevalence of un-diagnosed diabetes being lower (3%) and the majority residing in the most affluent district (Coyoacán; **S9**). Mean levels of traditional lipids were 1.0 ± 0.2 mmol/L for HDL-c, 2.5 ± 0.7 mmol/L for non HDL-c, and 1.5 ± 0.5 mmol/L for triglycerides, largely comparable in men and in women.

4.4 Adiposity-associated baseline characteristics of study participants

Among the 145,659 participants eligible for analyses, adiposity measures were reasonably normally distributed (**S10**). The mean (SD) BMI was 29 ± 5 kg/m², FMI 11 ± 4 kg/m², waist circumference 94 ± 11 cm, HC 105 ± 11 cm, WHR 0.91 ± 0.07 and WHtR 0.60 ± 0.08 , and 34% had a BMI >30 kg/m² (e.g., classified as obese). The levels of BMI and FMI increased with age, both in men and in women, but modestly decreased after the age of 60 years (**Figure 4.1**). The levels of abdominal adiposity (including waist circumference, WHR, and WHtR) increased steeply with increasing age until age 80 years and over, in both men and women. General adiposity, particularly predicted FMI, was somewhere higher in women than in men, while waist circumference and WHR, were slightly higher in men compared to women.

4.5 Correlates between different adiposity markers

General and abdominal adiposity were correlated with each other, and the strengths of these correlations varied with sex and the different markers of adiposity (**Table 4.3**). Predicted fat and lean mass among those without diabetes or other chronic disease at recruitment, correlated well with the direct measures from Bio-Impedance Analyses [BIA] (all $r > 0.84$; **Figure 4.2**), and displayed good predictive agreement, particularly among men (**S11**). In both men and women, weight, waist circumference and HC were all highly correlated (each pairwise correlation coefficient > 0.70). By contrast, height was only weakly positively correlated with waist and hip circumferences in women, but nearly uncorrelated in men. BMI and WHR were weakly correlated with each other in women ($r = 0.21$), but somewhat more strongly correlated in men ($r = 0.42$). Both BMI and predicted FMI were more strongly correlated with waist circumference, both in men and in women ($r > 0.80$), than with WHR, particularly among women ($r = 0.20$). In both men and women, BMI was highly correlated with both predicted FMI and predicted LMI ($r > 0.90$), but its correlation was stronger with predicted total fat mass ($r > 0.9$) than with predicted total lean mass ($r > 0.7$), likely due to the stronger association between predicted LM and height. Predicted FMI and LMI at baseline were highly correlated with each other, both in men ($r = 0.76$) and women ($r = 0.97$), even in those aged less than 75 years (**S12.1**), while the correlations between directly-measured FMI and LMI from the BIA among those re-surveyed 15 years later, were more modest ($r = 0.35$ in men and $r = 0.55$ in women; **S12.2**). These differences were likely related to the greater degree of overlap and variability between the sex-specific BIA-measured FMI and LMI at re-survey, compared to the lack of overlap and little variability (particularly among women), between the sex-specific

predicted FMI and LMI at baseline.

4.6 Repeatability of adiposity markers over time

Repeat measurements of adiposity among 6,383 participants without known disease at baseline and complete information recorded after an interval of 15 years, showed agreement by different methods (e.g., Spearman, Rosner, MacMahon-Peto; **S13**). The 'mid-point' estimated regression dilution ratios were 0.89 for BMI, 0.92 for predicted FMI, 0.85 for waist circumference, 0.74 for WHR, and 0.87 for WHtR (**S14**), and did not vary much depending on the baseline characteristics (**S15**). Furthermore, the general characteristics of the participants re-surveyed 15 years later, were largely similar to the baseline characteristics (**S16**), except for the use of tobacco and alcohol (which decreased from 30% to 13%, and from 75% to 52%, respectively), and for diagnosed and treated hypertension and diabetes (which increased from 19% to 44%, and from 9% to 32%, respectively, likely due to the ageing of the cohort).

4.7 Adiposity and confounders

The univariate associations between increasing levels of each of the adiposity markers of interest with age, sex, district of residence, education attained, smoking status, frequency of leisure-time physical activity and alcohol consumption are summarised on **Tables 4.2, 4.4 and S17-S20**.

Age and sex

On average, between ages 35 and 89 years, mean height was 165 ± 7 cm in men and

151±6 cm in women, mean weight was 76±13 kg in men and 68±13 kg in women, and mean BMI was 27.8±4.1 kg/m² in men and 29.2±4.9 kg/m² in women (**Table 4.2**). At every age, mean BMI and predicted FMI were lower in men compared to women, but mean waist circumference was higher among men compared to women (**Figure 4.1**). The WHR and WHtR increased with age in both sexes, and on average, WHR was higher among men compared to women (0.96±0.06 versus 0.87±0.07), while WHtR was slightly lower among men than in women (0.58±0.06 versus 0.61±0.08).

Smoking, alcohol consumption, physical activity and socioeconomic status

Throughout the ranges studied (BMI 18.5-60 kg/m², waist circumference 60-180 cm, and WHR 0.5-1.5), those with higher levels of adiposity were less likely to live in the wealthier of the two districts (Coyoacán), less likely to be physically active, and less likely to have been educated to college or university level (**Tables 4.4; S17-S20**). Use of tobacco or alcohol were not strongly associated with level of adiposity. These univariate associations suggest that socio-economic characteristics and lifestyle are likely to confound the relevance of adiposity to risk of vascular or metabolic diseases. Therefore, the multi-variable analyses for mediators in the following sections are estimated with adjustment for baseline age, sex, residential district, level of education achieved, leisure-time physical activity, smoking status and alcohol consumption.

4.8 Adiposity and selected mediators

Levels of HbA1c and diabetes, blood pressure, and lipids, in groups defined by baseline BMI, are shown in **Table 4.4** and **Table 4.5** (**S17-S20** show the patterns for the other

markers of general or abdominal adiposity). **Figures 4.4 to 4.13** show the relevance of the five markers of general and abdominal adiposity (BMI, predicted FMI, waist circumference, WHR and WHtR), with seven major vascular-metabolic risk-factors: diabetes, HbA1c, SBP, DBP, HDL-c, non HDL-c, and triglycerides (see **Figure S21** for the distribution of these mediators), after adjustment for confounders. The associations are presented both before and after adjustment for other markers of adiposity (e.g. general adiposity given abdominal adiposity, and vice versa), and in a comparable manner (e.g., slopes across the deciles or quintiles of the sex-specific distributions of each adiposity marker extended across ± 2 SD, and for continuous associations, the average increase in each mediator is presented per 1 SD higher level of each adiposity marker). Results are also given separately for men and women (**S22-S26**).

4.8.1 Associations of adiposity with HbA1c and diabetes

Among all women without chronic disease at baseline other than diabetes, mean HbA1c increased from $6.0 \pm 1.9\%$ at a BMI of 18.5-25 kg/m² to $6.4 \pm 1.6\%$ at a BMI of 40-60 kg/m², but in men mean HbA1c was similar at all levels of BMI (**Table 4.4**). Similar univariate associations were observed for predicted FMI and abdominal adiposity across *BMI-prevalence-matched* levels of all other markers studied among men, whereas among women, associations were somewhat stronger, particularly with increased levels of WHR, from $5.5 \pm 1.1\%$ at 0.51-0.81 units of WHR versus $6.7 \pm 2.1\%$ at 1.00-1.49 units of WHR, respectively (**S19**). By contrast, the prevalence of previously-diagnosed diabetes decreased with increase in BMI in men, from 15% at a BMI of 18.5-25 kg/m² to 10% at a BMI of 40-60 kg/m², and in women, the prevalence of previously-diagnosed diabetes was

similar at all levels of BMI (**Table 4.4**). By comparison, the prevalence of un-diagnosed diabetes increased from 6% at a BMI of 18.5-25 kg/m² to 10% at a BMI of 40-60 kg/m², with similar associations among men and women. Similar univariate associations with un-diagnosed diabetes were observed for predicted FMI and abdominal adiposity across *BMI-prevalence-matched* levels of all other markers studied (**S17-S20**), whereas the associations of FMI and abdominal adiposity with previously-diagnosed diabetes were somewhat stronger among women, particularly with increased levels of WHR, from 5% at 0.51-0.81 units of WHR to 25% at 1.00-1.49 units of WHR, respectively (**S19**).

After adjustment for age, sex, socioeconomic and lifestyle characteristics, abdominal adiposity at recruitment was positively and linearly associated with previously-diagnosed or screen-detected diabetes (**Figure 4.3**), while general adiposity was ‘apparently’ unrelated to diabetes, both in men and in women (**S22**). However, among participants without (diagnosed or screen-detected) diabetes at recruitment who were resurveyed 15 years later, baseline BMI strongly predicted the prevalence of (diagnosed or screen-detected) diabetes at resurvey, to a degree comparable to waist circumference or the WHR (about a 4-fold increase in prevalence over fifths of the distribution of baseline adiposity; **Figure 4.3**). These findings suggest that in this Mexican population, history of diabetes at recruitment or elevated levels of HbA1c among those undiagnosed, alter the levels of adiposity at baseline, hence, the multivariable analyses and results reported in the following sections, exclude participants with both diagnosed or screen-detected diabetes at recruitment.

Relevance of adiposity to HbA1c in those without diabetes

Among those without previously-diagnosed or screen-detected diabetes at recruitment, the two markers of general adiposity, BMI and FMI, were both positively, and linearly, associated with HbA1c (**Figure 4.4**) after adjustment for age, sex, socioeconomic and lifestyle characteristics, with each 1 SD higher level of adiposity being associated with about a 0.10% higher HbA1c (**Figure 4.5**). Associations were consistent in women and in men, and additional adjustment of BMI for WHR, and of FMI for LMI, did not materially affect the shape or the strength of the overall associations. Similarly, all three markers of abdominal adiposity (WC, WHR and WHtR) were positively and linearly related to HbA1c. The strength of the overall associations for waist circumference and WHtR were similar to those seen for BMI and FMI, both in women and in men, whereas the associations for WHR were half as strong (**Figures 4.4, 4.5 and S23**). Adjustment for general adiposity and HC had little effect on the associations with WHtR, while for WHR and waist circumference, additional adjustment for BMI and HC (respectively), reduced the magnitude of the association by about one third (from 0.05% per 1 SD higher WHR [95% CI 0.05-0.06] to 0.03% [0.03-0.03], and from 0.10% per 1 SD higher waist circumference [0.10-0.10] to 0.06% [0.06-0.07], respectively; **Figure 4.5**).

4.8.2 Associations of adiposity with blood pressure

Among the participants without chronic disease at baseline other than diabetes, mean SBP increased with higher levels of adiposity, from 125±16 mmHg at a BMI of 18.5-25 kg/m² to 138±17 mmHg at a BMI of 40-60 kg/m² in men, and from 122±17 mmHg to 135±16 mmHg in women, while the increases in DBP with BMI were 82±10 mmHg at a

BMI of 18.5-25 kg/m² to 91±11 mmHg at a BMI of 40-60 kg/m² in men, and from 79±10 mmHg to 89±10 mmHg in women (**Table 4.4**). These univariate associations were similar with FMI and abdominal adiposity across *BMI-prevalence-matched* ('equivalent') levels of all the markers studied (**S17-S20**). As expected, given their associations with both SBP and DBP, the associations of *general and abdominal* adiposity with self-reported previously-diagnosed hypertension were strong and positive. In men, such a diagnosis increased from 9% at a BMI of 18.5-25 kg/m² to 27% at a BMI of 40-60 kg/m², while for women it increased from 14% at a BMI of 18.5-25 kg/m² to 40% at a BMI of 40-60 kg/m² (**Table 4.4**). Similar sex-specific increases in prevalent hypertension at recruitment were observed across the various *BMI prevalence-matched* levels of all the other markers of adiposity (**S17-S20**).

Relevance of adiposity to SBP in those without diabetes

Among those without previously-diagnosed or screen-detected diabetes at recruitment, the two markers of *general* adiposity (BMI and FMI), were both positively and linearly associated with SBP after adjustment for confounders (**Figure 4.6**), with each 1 SD higher level of adiposity being associated with about a 3 mmHg higher SBP (**Figure 4.7**), and no threshold levels below which lower general or abdominal adiposity was not associated with lower SBP, in both men and women (**S24**). For both BMI and FMI the association was somewhat greater in women than in men. Adjustment for WHR had little effect on the association seen with BMI, reducing its magnitude from 2.96 mmHg per 1 SD (95% CI 2.88-3.04) to 2.78 mmHg per 1 SD (2.70-2.87). Adjustment of FMI for lean mass index reduced its overall association from 2.87 mmHg per 1 SD (2.79-2.95) to 2.47 mmHg per

1 SD (2.32-2.62; **Figure 4.7**). Similarly, all three markers of *abdominal* adiposity (WC, WHR and WHtR) were also positively and linearly related to SBP (**Figure 4.6**), in both men and women (**S24**), with no threshold levels. The strength of the associations for WC and WHtR were similar to those observed for BMI and FMI (again with a larger association seen in women than in men), while the strength of the association for each 1 SD higher WHR was only about half as large (1.37 mmHg higher SBP [1.28-2.95]; **Figure 4.7**). However adjustment for other markers of adiposity considerably reduced the magnitude of the associations seen for the markers of abdominal adiposity. For example, for WC, further adjustment for BMI and HC reduced the association from 2.87 mmHg per 1 SD (2.78-2.95) to 1.77 mmHg per 1 SD (1.62-1.92), while for WHR, adjustment for BMI reduced the association from 1.37 mmHg per 1 SD (1.28-1.46) to 0.59 mmHg per 1 SD (0.50-0.68).

Relevance of adiposity to DBP in those without diabetes

Among those without previously-diagnosed or screen-detected diabetes at recruitment, the overall and independent relevance of the different markers of adiposity to DBP, after adjustment for confounders, was similar to that for SBP (**Figure 4.8**), with no threshold levels below which lower general or abdominal adiposity was not associated with lower DBP, in both men and women (**S25**). On average, each 1 SD higher adiposity marker was associated with about a 2 mmHg higher DBP, again with the exception of WHR which was only half as strongly related to DBP (0.90 mmHg per 1 SD [0.84-0.97]; **Figure 4.9**). Similarly to SBP, additional adjustment for other markers of adiposity had little effect on the association seen for BMI, a modest effect for FMI, and a substantial effect for each of

the three markers of abdominal adiposity.

4.8.3 Associations of adiposity with selected lipids

Among the participants without chronic disease at baseline other than diabetes, mean HDL-c and non HDL-c did not appear to vary with higher levels of general or abdominal adiposity, while mean triglycerides increased from 1.4 ± 0.4 mmol/L at a BMI of 18.5-25 kg/m² to 1.6 ± 0.4 mmol/L at a BMI of 40-60 kg/m² in men, and from 1.3 ± 0.4 mmol/L to 1.5 ± 0.4 mmol/L in women (**Table 4.5**). These univariate associations were similar with FMI and abdominal adiposity across *BMI-prevalence-matched* levels of all the markers studied. Among these without diabetes or other chronic disease at baseline, lipid assays from the NMR correlated well with those from traditional biochemistry (all $r > 0.77$; **Table 4.6**). Furthermore, the correlation of different lipid types measured by the NMR, was good between total cholesterol, non HDL-c and LDL-c ($r > 0.95$), moderate between non HDL-c and triglycerides ($r = 0.36$), and weak between lipids, HbA1c, SBP and DBP ($r < 0.2$; **Table 4.7**).

Relevance of adiposity to selected lipids in those without diabetes

Among those without previously-diagnosed or screen-detected diabetes at recruitment, and after adjustment for confounders, the two markers of general adiposity, BMI and FMI, were both inversely associated with HDL-c, positively associated with non-HDL-cholesterol, and strongly, positively and approximately linearly associated with triglycerides (**Figure 4.10**). Each 1 SD higher level of adiposity was associated with about a -0.02 mmol/L non HDL-c, about a 0.02 mmol/L HDL-c, and about a 0.10 mmol/L

triglycerides (**Figure 4.11**), with similar estimates in women and in men. Additional adjustment of BMI for WHR, and of FMI for LMI, did not materially affect the shape (**Figure 4.12**) or the strength of the overall associations for HDL-c and non HDL-c, but did reduce the magnitude of the association with triglycerides by half (**Figure 4.13**). The overall associations of all three markers of abdominal adiposity (WC, WHR and WHtR) to HDL-c, non HDL-c and triglycerides were similar in shape and strength to those seen for BMI and FMI, both in women and in men (**Figure 4.12**). Adjustment for general adiposity had little effect on the associations of abdominal adiposity with HDL-c and non HDL-c, but reduced the magnitude of the associations with triglycerides by about one third (from 0.10 [0.09-0.10] per 1 SD higher waist circumference to 0.06 [0.05-0.07], and from 0.08 [0.08, 0.09] per 1 SD higher WHR to 0.05 [0.04, 0.05], respectively; **Figure 4.12**).

4.9 Strength and limitations

These are the first comprehensive analyses of adiposity with vascular-metabolic risk factors in a contemporary Mexican population, showing associations of multiple markers of adiposity with multiple vascular or metabolic risk factors. These analyses minimised the effects of reverse causality bias from pre-existing chronic diseases, and in particular, undiagnosed and uncontrolled diabetes and long-term use of anti-diabetic treatment or use of blood pressure-lowering medication at the time adiposity markers were measured. Carefully collected and replicate measures of anthropometry and blood-pressure measured directly (rather than self-reported) by medical staff following a standardised protocol, together with standardised laboratory measures of HbA1c and lipids across the cohort, are a particular strength. Furthermore, the possibility of reasonably predicting fat

and lean mass from Mexican-specific equations is novel, and enabled assessment of the relevance of FMI independent of LMI beyond BMI. While other measures of adiposity from body imaging (through Dual-Energy X-ray Absorptiometry or Magnetic Resonance) could further disentangle the relevance of visceral fat versus muscle mass or other fat depots to vascular-metabolic risk,⁴³ such measures are difficult to collect in large studies conducted in low- or middle-income countries where resources for research are more limited.

4.10 Conclusions

In this contemporary Mexican cohort, adiposity was extremely common, it was strongly inversely associated with physical activity and positively associated with HbA1c, blood pressure, non HDL-c and triglycerides. General adiposity was more strongly associated with blood pressure than abdominal adiposity, while abdominal, but not general adiposity, was more strongly associated with diagnosed or screen-detected diabetes, with no suggestion of any threshold levels. Furthermore, both general and abdominal adiposity associated *inversely* with HDL-c and *positively* with non HDL-c and triglycerides. These findings suggest that among those without chronic disease or diabetes at recruitment, adiposity is strongly associated to vascular-metabolic disease risk, and HbA1c, blood pressure and lipids, partially mediate the relevance of adiposity with risk of such diseases in this Mexican population. By contrast, the lack of an association between BMI and diabetes prevalence at baseline is indicative of substantial reverse causality, the impact of which will now be examined in the next chapter. The consequences of general and abdominal adiposity for risk of overall and cause-specific mortality, including those

mediated through HbA1c, SBP and selected lipids among those without previously-diagnosed or screen-detected diabetes or other chronic disease at baseline, are assessed in the subsequent chapters of this thesis.

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Table 4.1: Data exclusions with counts

TOTAL NUMBER OF PARTICIPANTS	N=159,755
Details of the exclusions applied	n
Age ≥ 90 (or missing) at recruitment	854
Prior chronic disease [†] (other than diabetes)	8135
Uncertain mortality ^{††}	2401
Height <120 OR >200 cms (or missing)	2231
Weight <35 OR >250 kgs (or missing)	2114
WC <60 OR >180 cms (or missing)	2311
HC <70 OR >180 cms (or missing)	2273
BMI <18.5 OR ≥ 60 (or missing)	3044
WHR <0.5 OR >1.5 (or missing)	2184
District of residence, level of education achieved, use of tobacco or alcohol, any leisure-time physical activity (missing)	263
Excluded for any of the above reasons*	14,096
No. of participants aged 35-89 at baseline eligible for analyses**	145,659

WC: waist circumference; HC: hip circumference; BMI: body mass index; WHR: waist-hip ratio; Of all participants with a BMI of 15-60 Kg/m², 782 (0.5%) had a BMI of 15 to 18.5 kg/m².

[†] Self-reported previously-diagnosed vascular or chronic kidney disease, cancer, cirrhosis of the liver, or emphysema.

^{††} As of 01 January 2018. Unreliable probabilistic matching, did not satisfy all criteria.

* A total of 2,426 (1.5%) participants had missing data on any of the variables listed in the table, of which 1.4% (n=2,172) were missing anthropometric measures.

** Of all the participants eligible for analyses, 18,981 (13.03%) had previously- diagnosed diabetes or were taking any anti-diabetic medications at the time of the recruitment, and among those un-diagnosed with diabetes, 4870 (3.3%) had a glycosylated haemoglobin [HbA1c] $\geq 7\%$ (classified as screen-detected diabetes). A sub-set of 145,519 participants also had measured systolic blood-pressure [SBP] (in the ranges of 80-250 mmHg at a pulse-pressure ≤ 15 mmHg), and 141,754 had measured HbA1c (in the ranges of 3-19%). Of those with complete information on both SBP and HbA1c, 34,985 (24.7%) participants have been diagnosed or treated for diabetes or had a HbA1c $\geq 7\%$, or were taking anti-hypertensive medication at baseline assessment, leaving 106,769 men and women eligible for cross-sectional analyses of interest. A sub-set of 34,944 participants without chronic disease also had complete assays of NMR metabolites of interest (specifically, serum cholesterol, non/HDL-c and triglycerides), of which 4,984 had previously-diagnosed or screen-detected diabetes, leaving 29,960 men and women eligible for mediation analyses.

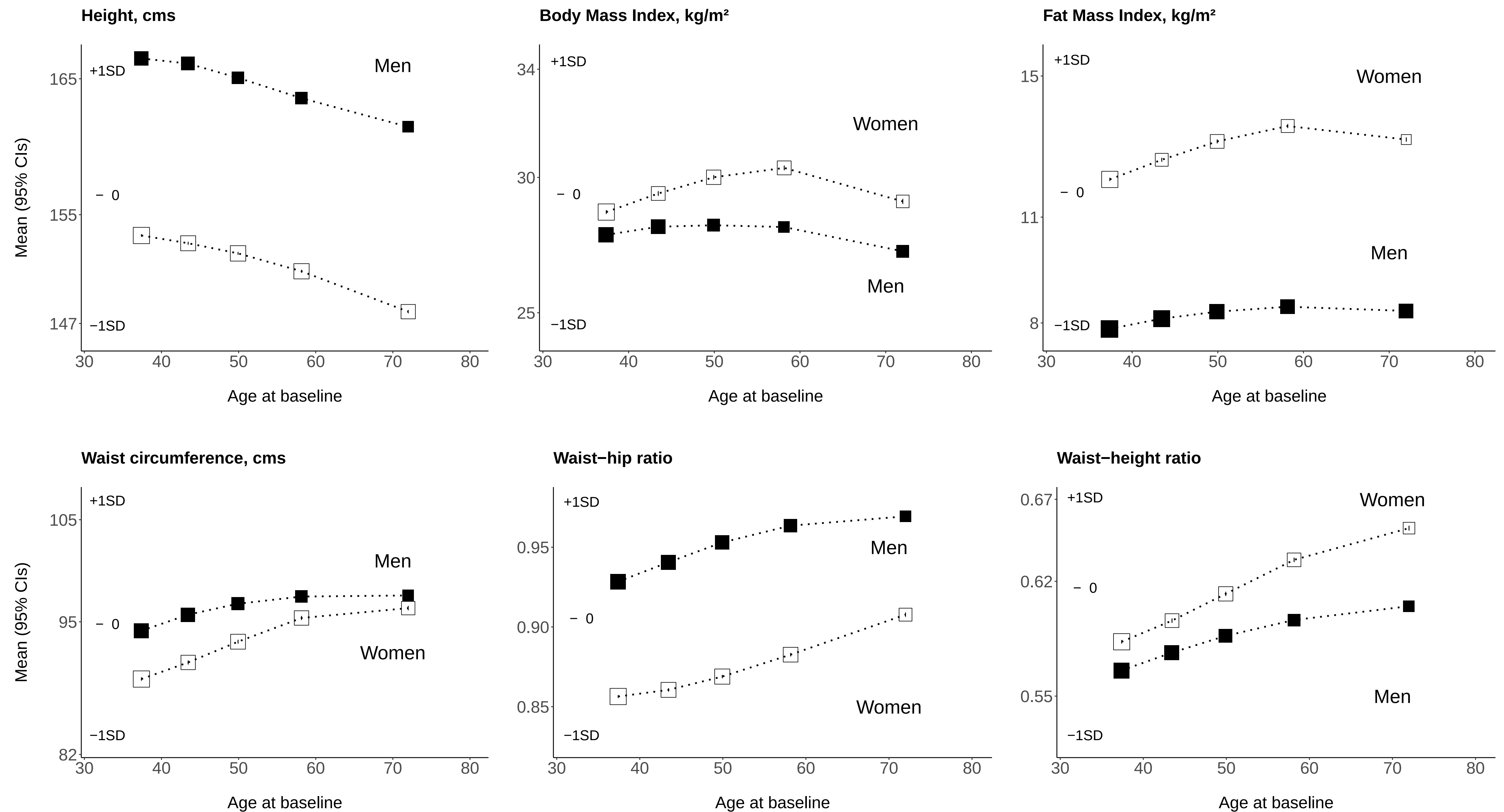
Table 4.2: Baseline characteristics of 47,657 men and 98,002 women aged 35-89 years, without prior chronic disease (other than diabetes) at recruitment

	Men	Women	All
N	47,657	98,002	145,659
Age, years	52 (13)	51 (13)	52 (13)
Socio-economic and lifestyle			
Resident of Coyoacán	20,510 (43%)	37,356 (38%)	57,866 (40%)
University/college educated	23,936 (50%)	35,166 (36%)	59,102 (41%)
Current tobacco use	23,654 (50%)	22,487 (23%)	46,141 (32%)
Current alcohol use	40,447 (85%)	67,887 (69%)	108,334 (74%)
Regular leisure-time physical activity	14,260 (30%)	18,290 (19%)	32,550 (22%)
Anthropometry and derived markers of adiposity			
Height, cm	165 (7)	151 (6)	156 (9)
Weight, kg	76 (13)	68 (13)	70 (13)
WC, cm	96 (10)	93 (12)	94 (11)
HC, cm	101 (8)	106 (11)	105 (11)
BMI, kg/m ²	28 (4)	30 (5)	29 (5)
WHR	0.95 (0.06)	0.88 (0.07)	0.91 (0.07)
WHtR	0.59 (0.06)	0.62 (0.08)	0.60 (0.08)
FM, kg	22 (6)	30 (8)	27 (8)
FMI, kg/m ²	8.2 (2.28)	13 (3.35)	11.4 (3.76)
Blood pressure			
SBP, mmHg	129 (16)	127 (17)	127 (17)
DBP, mmHg	84 (10)	82 (10)	83 (10)
Previously-diagnosed hypertension	6,609 (14%)	22,470 (23%)	29,079 (20%)
Diabetes and HbA1c[†]			
Previously-diagnosed diabetes*	6,178 (13%)	12,803 (13%)	18,981 (13%)
Un-diagnosed diabetes**	2,981 (7%)	5,415 (6%)	8,396 (7%)
HbA1c %	6.1 (1.7)	6.1 (1.7)	6.1 (1.7)
HbA1c (median, IQR)	5.5 (5.3-5.9)	5.5 (5.3-6.0)	5.5 (5.3-6.0)
Medication use			
Any antihypertensive	4,892 (10%)	16,472 (17%)	21,364 (15%)
Any antithrombotic	1,055 (2%)	2,583 (3%)	3,638 (2%)
Any lipid lowering	257 (0.5%)	483 (0.5%)	740 (0.5%)

Mean (SD) or n (column %) shown, unless otherwise specified. [†]Glycosylated haemoglobin.

*Includes those taking any anti-diabetic medication. **Those with a HbA1c ≥7% among those without previously-diagnosed diabetes. Exclusions and conventions as per table 4.1.

Figure 4.1: Cross-sectional age and sex-specific levels of anthropometry and markers of adiposity among 47,657 men and 98,002 women aged 35–89 years, without previously-diagnosed chronic disease (other than diabetes) at recruitment



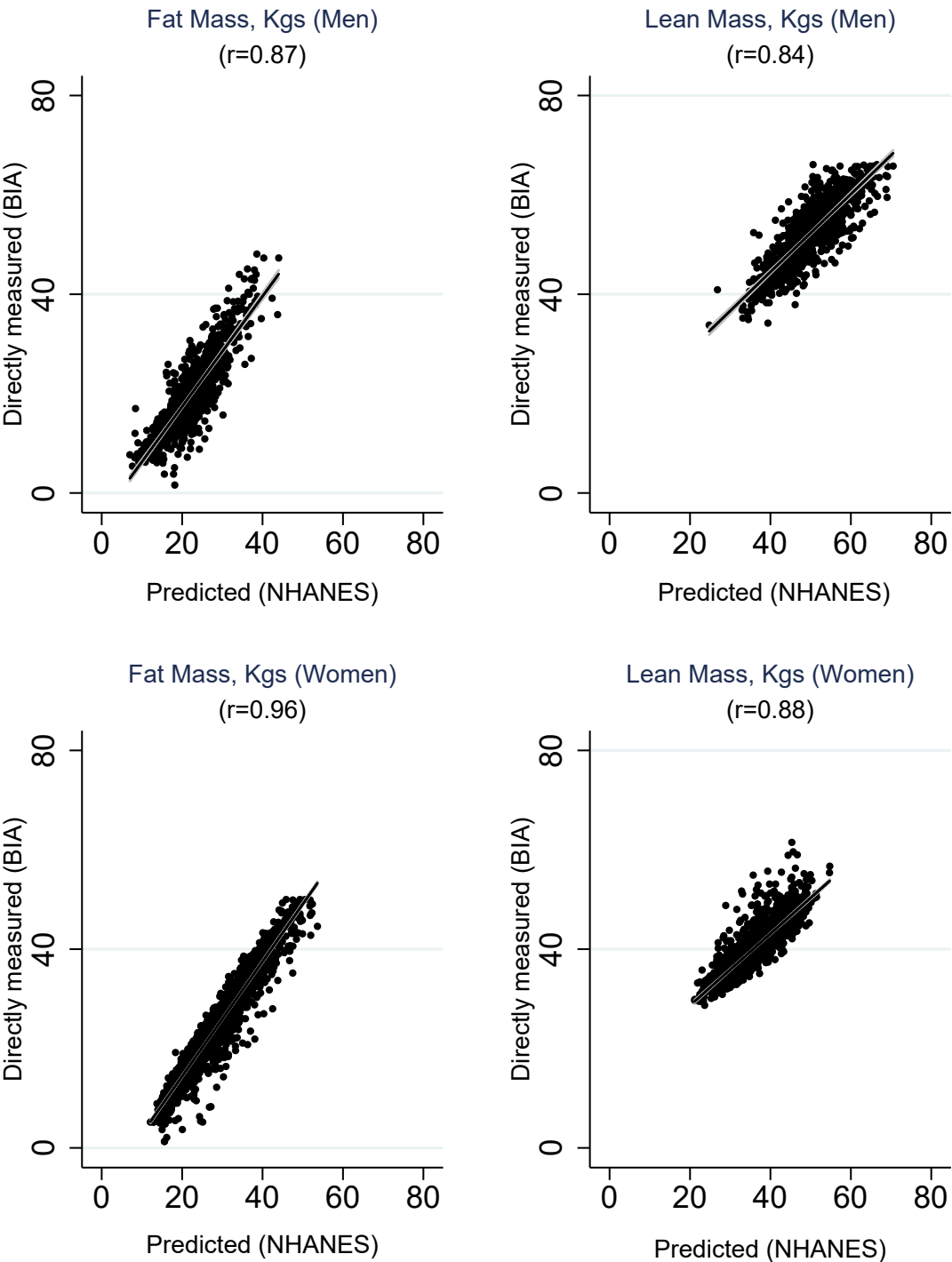
Anthropometric and adiposity markers defined within five equally-sized groups of the sex-specific distributions. Y-axes extend 1SD above and below the mean of each marker. Square sizes are inversely proportional to the variance. Exclusions as per table 4.1.

Table 4.3: Pearson correlation coefficients of baseline anthropometric markers of adiposity among 47,657 men and 98,002 women aged 35-89 years, without chronic disease (other than diabetes) at recruitment

	Height	Weight	BMI	FMI	LMI	FM	LM	WC	HC	WHR	
Weight	0.48	Men									
	0.35	Women									
	0.48	Both									
BMI	-0.04	0.86	Men								
	-0.10	0.89	Women								
	-0.16	0.79	Both								
FMI	-0.06	0.79	0.94	Men							
	-0.15	0.86	0.99	Women							
	-0.47	0.47	0.87	Both							
LMI	0.00	0.81	0.93	0.74	Men						
	-0.01	0.92	0.98	0.96	Women						
	0.41	0.84	0.66	0.20	Both						
FM	0.24	0.92	0.90	0.95	0.72	Men					
	0.17	0.98	0.96	0.95	0.95	Women					
	-0.17	0.70	0.91	0.94	0.36	Both					
LM	0.61	0.94	0.71	0.55	0.78	0.72	Men				
	0.60	0.95	0.72	0.67	0.79	0.87	Women				
	0.81	0.79	0.32	-0.14	0.87	0.13	Both				
WC	0.17	0.80	0.81	0.94	0.56	0.97	0.55	Men			
	0.00	0.77	0.81	0.84	0.74	0.84	0.59	Women			
	0.14	0.78	0.77	0.61	0.61	0.72	0.46	Both			
HC	0.29	0.81	0.76	0.77	0.63	0.84	0.68	0.79	Men		
	0.13	0.85	0.84	0.84	0.82	0.88	0.74	0.81	Women		
	-0.03	0.71	0.83	0.79	0.44	0.86	0.25	0.74	Both		
WHR	-0.06	0.34	0.42	0.62	0.15	0.59	0.09	0.69	0.11	Men	
	-0.19	0.12	0.21	0.27	0.11	0.21	-0.01	0.58	-0.01	Women	
	0.24	0.30	0.16	-0.04	0.38	0.04	0.39	0.60	-0.09	Both	
WHtR	-0.22	0.60	0.82	0.96	0.55	0.86	0.30	0.92	0.67	0.71	Men
	-0.31	0.61	0.80	0.85	0.70	0.74	0.37	0.95	0.73	0.61	Women
	-0.32	0.52	0.81	0.79	0.40	0.76	0.08	0.89	0.72	0.46	Both

Exclusions and conventions as per table 4.1. In addition to the key markers of adiposity investigated in the thesis, the table also includes the markers used in subsequent analyses with mutual adjustments.

Figure 4.2: Correlates between predicted versus direct markers of body-mass composition among 1221 men and 2933 women age 35-89 years, without diabetes or other disease at resurvey



Pearson correlations between predicted markers from Mexican-specific NHANES equations versus direct measures from the Bio-Impedance Analysis (BIA). Formulae:
 FM men = -18.592-(0.009*age)-(0.080*height)+(0.226*weight)+(0.387*waist)+0.080
 FM women = 11.817+(0.041*age)-(0.199*height)+(0.610*weight)+(0.044*r_waist)+0.388
 LM = weight-FM. Exclusions as per table 4.1, values outside 3 SDs, or mean differences between BIA and predicted values <-10 (for women) or >20 (for men; 58 participants).

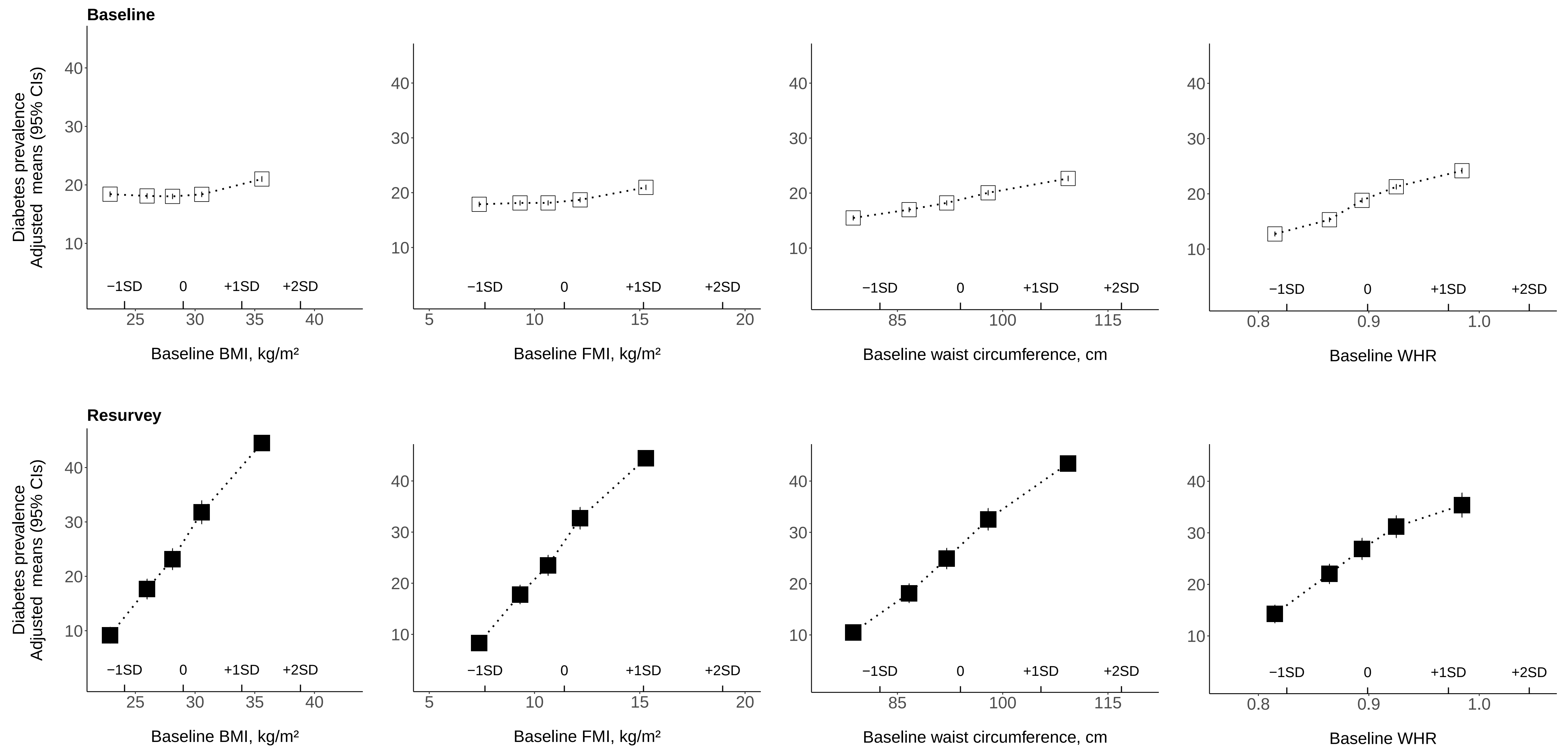
Table 4.4: Baseline characteristics by BMI of 47,657 men and 98,002 women aged 35-89 years without prior chronic disease (other than diabetes)

	MEN by BMI (kg/m ²)					WOMEN by BMI (kg/m ²)				
	18.5 - 24.9	25 - 29.9	30 - 34.9	35 - 39.9	40 - 60	18.5 - 24.9	25 - 29.9	30 - 34.9	35 - 39.9	40 - 60
N	11,106	23,398	10,661	2,015	477	17,621	39,443	27,255	10,002	3,681
Age, years	54 (14)	52 (13)	52 (12)	51 (11)	48 (11)	51 (14)	51 (13)	52 (12)	51 (11)	51 (11)
Socio-economic and lifestyle										
Resident of Coyoacán	5283 (48%)	10210 (44%)	4139 (39%)	703 (35%)	175 (37%)	7975 (45%)	15661 (40%)	9405 (35%)	3176 (32%)	1139 (31%)
University/college educated	5533 (50%)	11992 (51%)	5168 (48%)	988 (49%)	255 (53%)	8040 (46%)	14979 (38%)	8310 (30%)	2814 (28%)	1023 (28%)
Leisure physical activity	3432 (31%)	7462 (32%)	2853 (27%)	414 (21%)	99 (21%)	4017 (23%)	8171 (21%)	4332 (16%)	1330 (13%)	440 (12%)
Current tobacco use	5924 (53%)	11372 (49%)	5148 (48%)	969 (48%)	241 (51%)	4553 (26%)	9172 (23%)	5809 (21%)	2140 (21%)	813 (22%)
Current alcohol use	9443 (85%)	19833 (85%)	9042 (85%)	1722 (85%)	407 (85%)	11969 (68%)	27487 (70%)	18919 (69%)	6917 (69%)	2595 (70%)
Anthropometry and derived markers of adiposity										
Height, cm	165 (7)	165 (7)	164 (7)	164 (7)	164 (9)	152 (7)	152 (6)	151 (6)	151 (6)	150 (6)
Weight, kg	63 (7)	74 (7)	86 (8)	99 (10)	117 (15)	54 (6)	63 (6)	73 (7)	84 (8)	99 (11)
WC, cm	87 (7)	95 (6)	104 (7)	115 (8)	127 (12)	81 (7)	90 (7)	99 (8)	107 (8)	118 (10)
HC, cm	94 (5)	100 (5)	107 (6)	114 (7)	126 (12)	95 (6)	103 (6)	111 (7)	120 (8)	132 (11)
BMI, kg/m ²	23 (2)	27 (1)	32 (1)	37 (1)	43 (3)	23 (2)	28 (1)	32 (1)	37 (1)	43 (3)
WHR	0.92 (0.06)	0.95 (0.05)	0.98 (0.06)	1.00 (0.06)	1.01 (0.08)	0.85 (0.07)	0.88 (0.06)	0.89 (0.06)	0.89 (0.06)	0.89 (0.07)
WHtR	0.53 (0.04)	0.58 (0.04)	0.64 (0.04)	0.70 (0.05)	0.77 (0.06)	0.53 (0.05)	0.59 (0.05)	0.65 (0.05)	0.71 (0.06)	0.78 (0.07)
FM, kg	16 (3)	22 (3)	28 (4)	35 (4)	43 (7)	20 (3)	27 (3)	33 (3)	40 (4)	50 (6)
FMI, kg/m ²	5.7 (1.1)	7.9 (1.04)	10.3 (1.1)	12.9 (1.26)	16.1 (2.01)	8.7 (1.03)	11.7 (0.99)	14.6 (0.97)	17.8 (0.95)	21.9 (2.17)
Blood pressure										
SBP, mmHg	125 (16)	128 (15)	131 (15)	135 (16)	138 (17)	122 (17)	125 (17)	129 (16)	132 (16)	135 (16)
DBP, mmHg	82 (10)	84 (9)	86 (10)	89 (10)	91 (11)	79 (10)	82 (10)	84 (10)	86 (10)	88 (10)
Diagnosed hypertension	988 (9)	3069 (13)	1964 (18%)	457 (23%)	131 (27%)	2520 (14)	7800 (20)	7336 (27%)	3334 (33%)	1480 (40%)
Diabetes										
Previously-diagnosed †	1646 (15%)	2960 (13%)	1280 (12%)	246 (12%)	46 (10%)	2293 (13%)	4976 (13%)	3609 (13%)	1380 (14%)	545 (15%)
Un-diagnosed ††	595 (6%)	1340 (7%)	784 (8%)	214 (12%)	48 (11%)	833 (5%)	1978 (6%)	1566 (7%)	725 (8%)	313 (10%)
HbA1c (median, IQR)	5.4 (5.2-5.8)	5.5 (5.3-5.9)	5.6 (5.4-6.1)	5.8 (5.4-6.3)	5.8 (5.5-6.4)	5.4 (5.1-5.7)	5.5 (5.3-5.9)	5.6 (5.4-6.1)	5.7 (5.4-6.3)	5.9 (5.5-6.5)
Medication use										
Any antihypertensives	767 (7%)	2280 (10%)	1423 (13%)	321 (16%)	101 (21%)	1945 (11%)	5681 (14%)	5350 (20%)	2384 (24%)	1112 (30%)
Any antithrombotics	203 (2%)	525 (2%)	265 (2%)	45 (2%)	17 (4%)	426 (2%)	928 (2%)	779 (3%)	321 (3%)	129 (4%)
Any lipid lowering	43 (0.4%)	137 (0.6%)	61 (0.6%)	14 (0.7%)	2 (0.4%)	78 (0.4%)	216 (0.5%)	134 (0.5%)	43 (0.4%)	12 (0.3%)

Mean (SD) or n (column %) shown, unless otherwise specified. † Includes those taking anti-diabetic medications. †† Those with measured HbA1c ≥7% .

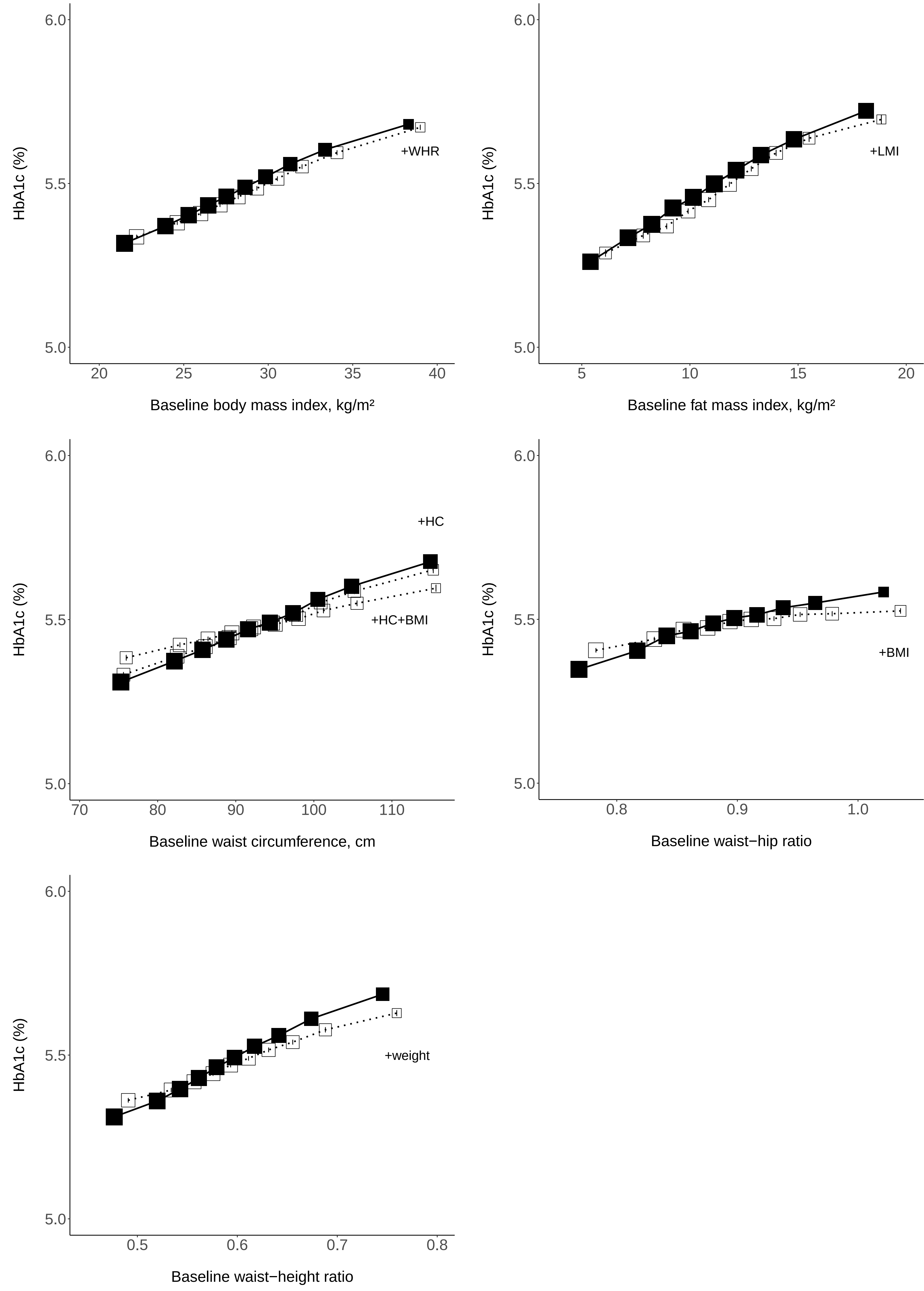
Exclusions and conventions as per Table 4.1.

Figure 4.3: Associations of general and abdominal adiposity markers at baseline, with diabetes at baseline (top) and at resurvey (bottom)



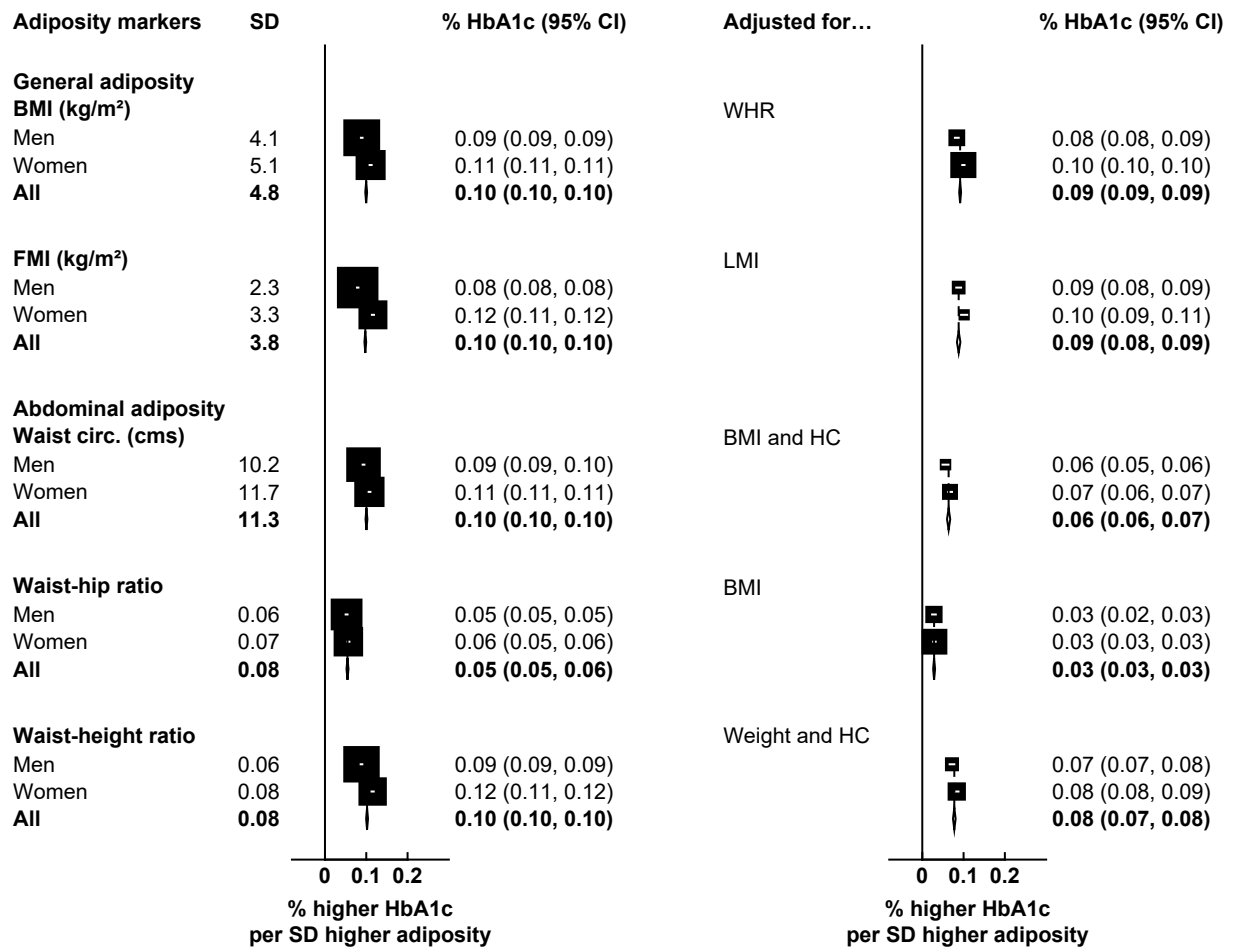
Means and 95% CIs were estimated with regression models adjusted for age, sex, district, education, physical exercise, alcohol or smoking status and amount. Adiposity was defined by five equally-sized groups of the sex-specific distributions. Diabetes refers to doctor-diagnosis and/or use of antidiabetic medications or a HbA1c $\geq 7\%$. Baseline analyses excluded other medical histories (as per table 4.1; N=145,660). Resurvey analyses are in a sub-sample of 9545 recruits without diabetes or other chronic disease at baseline, who were followed-up 15 years later. The plotted estimates are centred at the mean. Square sizes are inversely proportional to the variance. Each X-axis range is equivalent in terms of the number of the SDs of the adiposity markers. BMI = Body Mass Index; FMI = Fat Mass Index; WHR = Waist-hip ratio.

Figure 4.4: Cross-sectional associations of general and abdominal markers of adiposity and glycosylated haemoglobin (HbA1c) among 39,787 men and 82,020 women aged 35–89 years, without diabetes or other chronic disease at recruitment



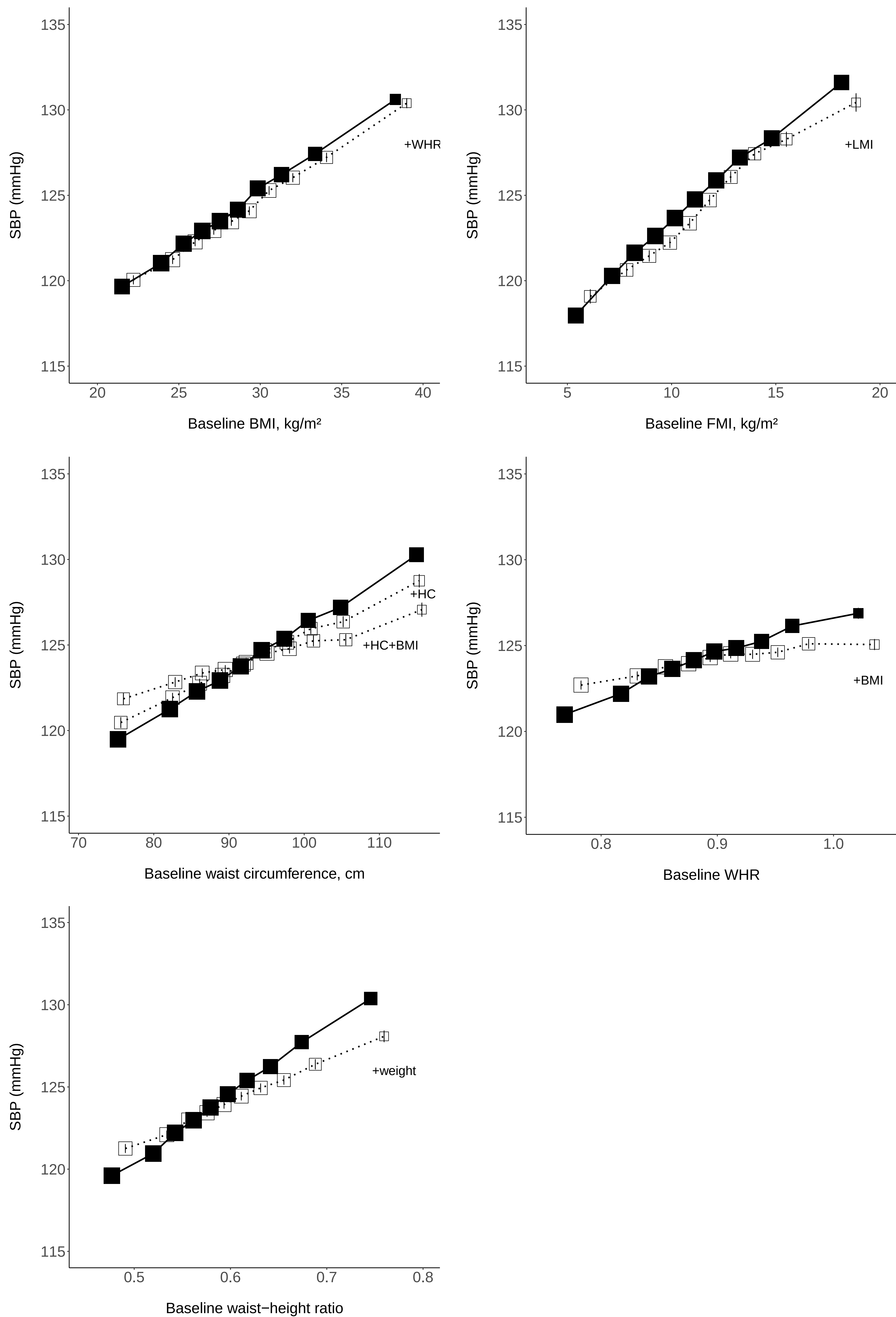
Means and 95% confidence intervals (CIs) from regression models adjusted for age, sex, district, education, physical exercise, alcohol and smoking. Adiposity defined by the deciles of the sex-specific distributions. Black squares show the overall associations of each adiposity marker, white squares show the associations with additional adjustments as stated in the plot. Exclusions as per table 4.1, and in addition, previously-diagnosed or treated diabetes, and HbA1c $\geq 7\%$. Plotted estimates are centered at the mean, with square sizes inversely proportional to the variance and the vertical lines for the 95% CIs. BMI=body mass index; LMI=lean mass index; WHR=waist-hip ratio; HC=hip circ.

Figure 4.5. Overall and sex-specific relevance of adiposity markers to glycosylated haemoglobin (HbA1c) among 39,787 men and 82,020 women aged 35-89 years, without diabetes or other chronic disease at recruitment, before and after additional adjustment for other adiposity markers



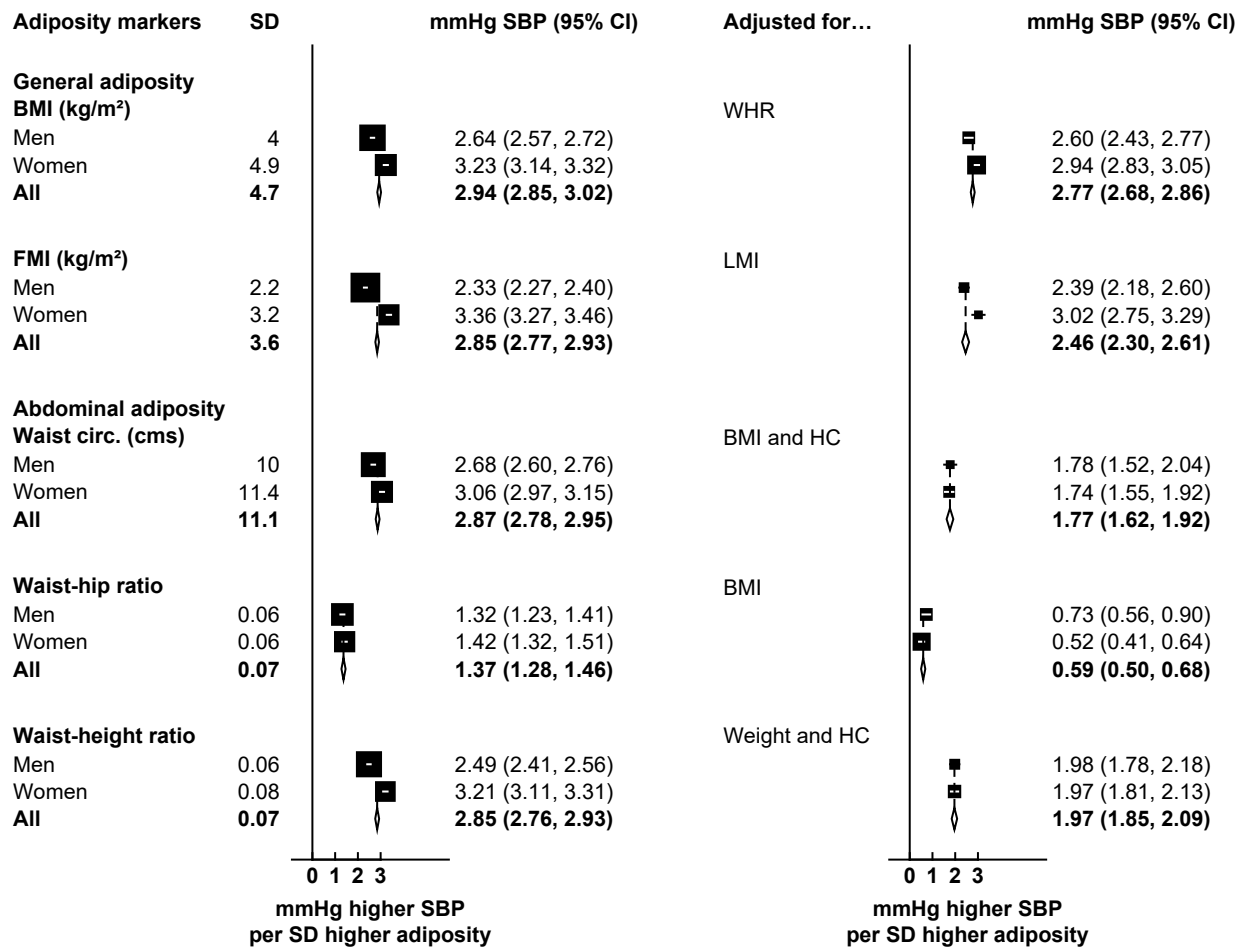
Estimates represent the increase in % HbA1c associated with each standard deviation [SD] higher adiposity level, adjusted for age, sex, district, education, physical exercise, alcohol and smoking status. For the additional adjustments stated on the plot, adiposity markers were accounted for by the five equally sized groups of the sex-specific distributions. The area of each square is inversely proportional to the amount of statistical information. Values in parentheses are 95% confidence intervals (CIs). Each diamond represents the inverse variance-weighted average of the two estimates above it. Exclusions and conventions as per figure 4.4

Figure 4.6: Cross-sectional associations of general and abdominal markers of adiposity and systolic blood pressure (SBP) among 36,331 men and 70,438 women aged 35–89 years, without diabetes or other chronic disease at recruitment



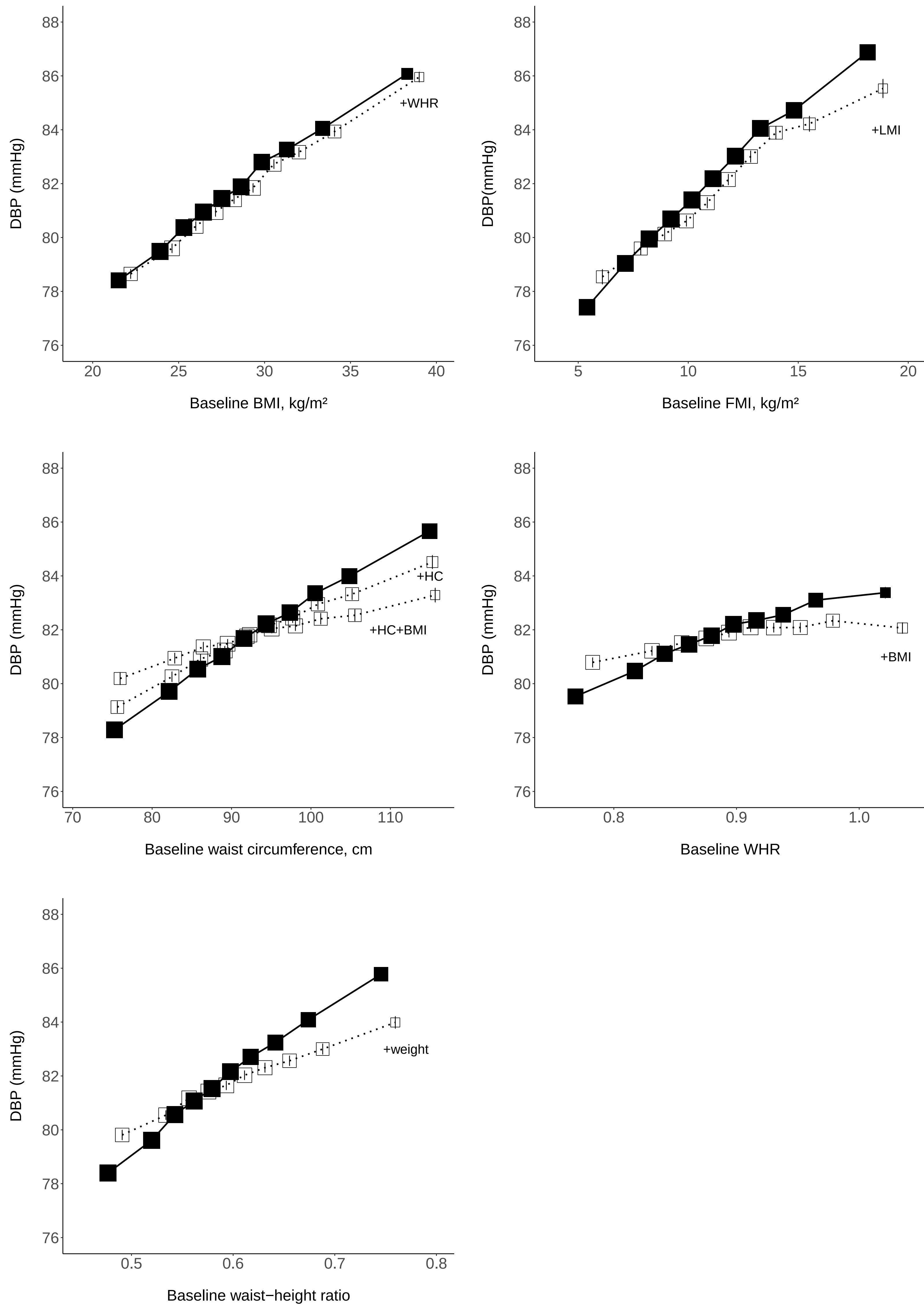
Analyses as per Figure 4.4, with further exclusion of those taking any anti-hypertensive treatment at baseline.

Figure 4.7. Overall and sex-specific relevance of adiposity markers to systolic blood pressure (SBP) among 36,331 men and 70,438 women aged 35-89 years, without diabetes or other chronic disease at recruitment, before and after additional adjustment for other adiposity markers



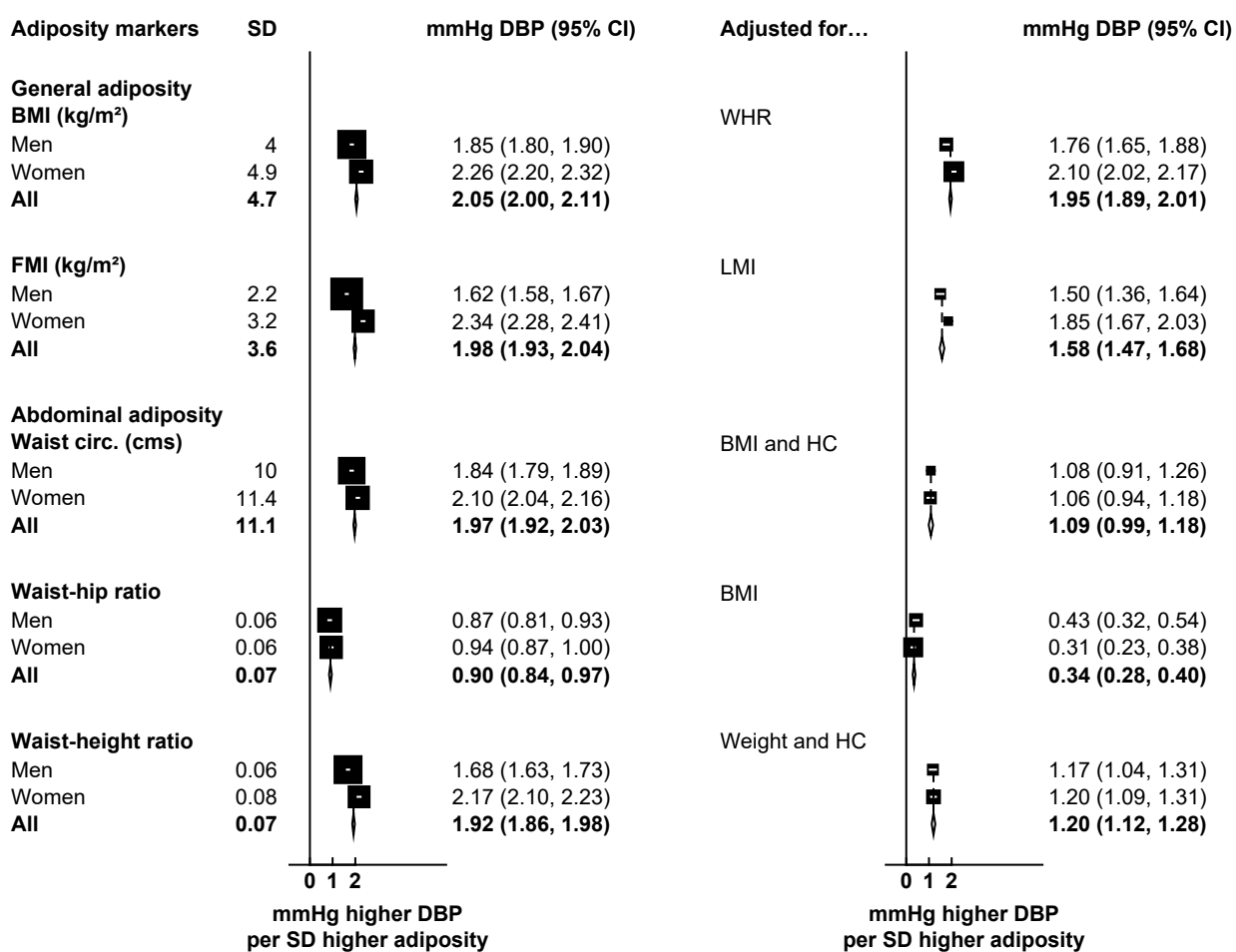
Analyses and conventions as per Figure 4.5.

Figure 4.8: Cross-sectional associations of general and abdominal markers of adiposity and diastolic blood pressure (DBP) among 36,331 men and 70,438 women aged 35–89 years, without diabetes or other chronic disease at recruitment



Analyses as per Figure 4.6.

Figure 4.9. Overall and sex-specific relevance of adiposity markers to diastolic blood pressure (DBP) among 36,331 men and 70,438 women aged 35-89 years, without diabetes or other chronic disease at recruitment, before and after additional adjustment for other adiposity markers



Analyses and conventions as per Figure 4.5.

Table 4.5: Baseline levels of selected lipids by levels of adiposity among 12,706 men and 22,238 women aged 35-89 years without prior chronic disease (other than diabetes) and complete information on NMR assays

	Men			Women		
	HDL-c	non-HDL-c	Triglycerides	HDL-c	non-HDL-c	Triglycerides
	Mean (SD)			Mean (SD)		
General adiposity						
BMI (kg/m²)						
18.5 - 24.9	1.0 (0.2)	2.5 (0.7)	1.4 (0.4)	1.1 (0.2)	2.5 (0.7)	1.3 (0.4)
25 - 29.9	1.0 (0.2)	2.5 (0.7)	1.6 (0.4)	1.1 (0.2)	2.5 (0.7)	1.5 (0.4)
30 - 34.9	0.9 (0.1)	2.5 (0.7)	1.7 (0.5)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
35 - 39.9	0.9 (0.2)	2.5 (0.7)	1.7 (0.4)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
40 - 60	0.9 (0.2)	2.4 (0.5)	1.6 (0.4)	1.0 (0.2)	2.4 (0.5)	1.5 (0.4)
FMI (kg/m²)						
1.9 - 7.8	1.0 (0.2)	2.5 (0.7)	1.4 (0.4)	1.1 (0.2)	2.5 (0.7)	1.3 (0.4)
7.9 - 12.2	1.0 (0.2)	2.5 (0.7)	1.6 (0.4)	1.1 (0.2)	2.5 (0.7)	1.5 (0.4)
12.3 - 15.9	0.9 (0.1)	2.5 (0.7)	1.7 (0.4)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
16.0 - 19.3	0.9 (0.2)	2.5 (0.6)	1.7 (0.5)	1.0 (0.2)	2.5 (0.6)	1.6 (0.4)
19.4 - 32.2	0.9 (0.2)	2.5 (0.6)	1.6 (0.4)	1.0 (0.2)	2.5 (0.6)	1.5 (0.4)
Abdominal adiposity						
Waist circ. (cm)						
60 - 84.9	1.0 (0.2)	2.5 (0.7)	1.4 (0.4)	1.1 (0.2)	2.5 (0.7)	1.3 (0.4)
85 - 96.9	1.0 (0.2)	2.5 (0.7)	1.6 (0.4)	1.1 (0.2)	2.5 (0.7)	1.5 (0.4)
97 - 107.9	0.9 (0.2)	2.5 (0.7)	1.7 (0.4)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
108 - 117.9	0.9 (0.2)	2.5 (0.6)	1.7 (0.5)	1.1 (0.2)	2.5 (0.6)	1.6 (0.4)
118 - 168	1.0 (0.2)	2.5 (0.6)	1.6 (0.4)	1.0 (0.2)	2.5 (0.6)	1.6 (0.4)
Waist-hip ratio						
0.54 - 0.84	1.0 (0.2)	2.5 (0.7)	1.5 (0.5)	1.1 (0.2)	2.5 (0.7)	1.3 (0.4)
0.85 - 0.92	1.0 (0.2)	2.5 (0.7)	1.6 (0.4)	1.1 (0.2)	2.5 (0.7)	1.5 (0.4)
0.93 - 0.99	1.0 (0.2)	2.5 (0.7)	1.7 (0.5)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
1.00 - 1.03	0.9 (0.2)	2.4 (0.7)	1.7 (0.5)	1.1 (0.2)	2.4 (0.7)	1.6 (0.4)
1.04 - 1.47	1.0 (0.2)	2.5 (0.6)	1.6 (0.5)	1.1 (0.2)	2.5 (0.6)	1.6 (0.4)
Waist-height ratio						
0.38 - 0.54	1.0 (0.2)	2.5 (0.7)	1.4 (0.4)	1.1 (0.2)	2.5 (0.7)	1.3 (0.4)
0.55 - 0.62	1.0 (0.2)	2.5 (0.7)	1.6 (0.4)	1.1 (0.2)	2.5 (0.7)	1.5 (0.4)
0.63 - 0.70	0.9 (0.2)	2.5 (0.7)	1.7 (0.5)	1.1 (0.2)	2.5 (0.7)	1.6 (0.4)
0.71 - 0.77	0.9 (0.1)	2.5 (0.6)	1.7 (0.5)	1.1 (0.2)	2.5 (0.6)	1.6 (0.4)
0.78 - 1.08	1.0 (0.2)	2.5 (0.6)	1.5 (0.4)	1.0 (0.2)	2.5 (0.6)	1.5 (0.4)

Conventions and exclusions as per table S9. Adiposity markers grouped by sex-specific BMI equivalent-prevalence.

Table 4.6: Pearson correlation coefficients of biochemistry versus NMR markers of selected lipids among 85 men and 132 women aged 35-89 years, without diabetes* or other chronic disease at baseline

Biochemistry	NMR metabolites				
	Cholesterol	LDL-c	non-HDL-c	HDL-c	Triglycerides
Cholesterol	0.78	0.70	0.76	0.23	0.41
LDL-c	0.79	0.82	0.81	0.10	0.19
non-HDL-c	0.76	0.71	0.80	0.02	0.54
HDL-c	0.21	0.09	0.00	0.77	-0.38
Triglycerides	0.00	-0.16	0.06	-0.19	0.80

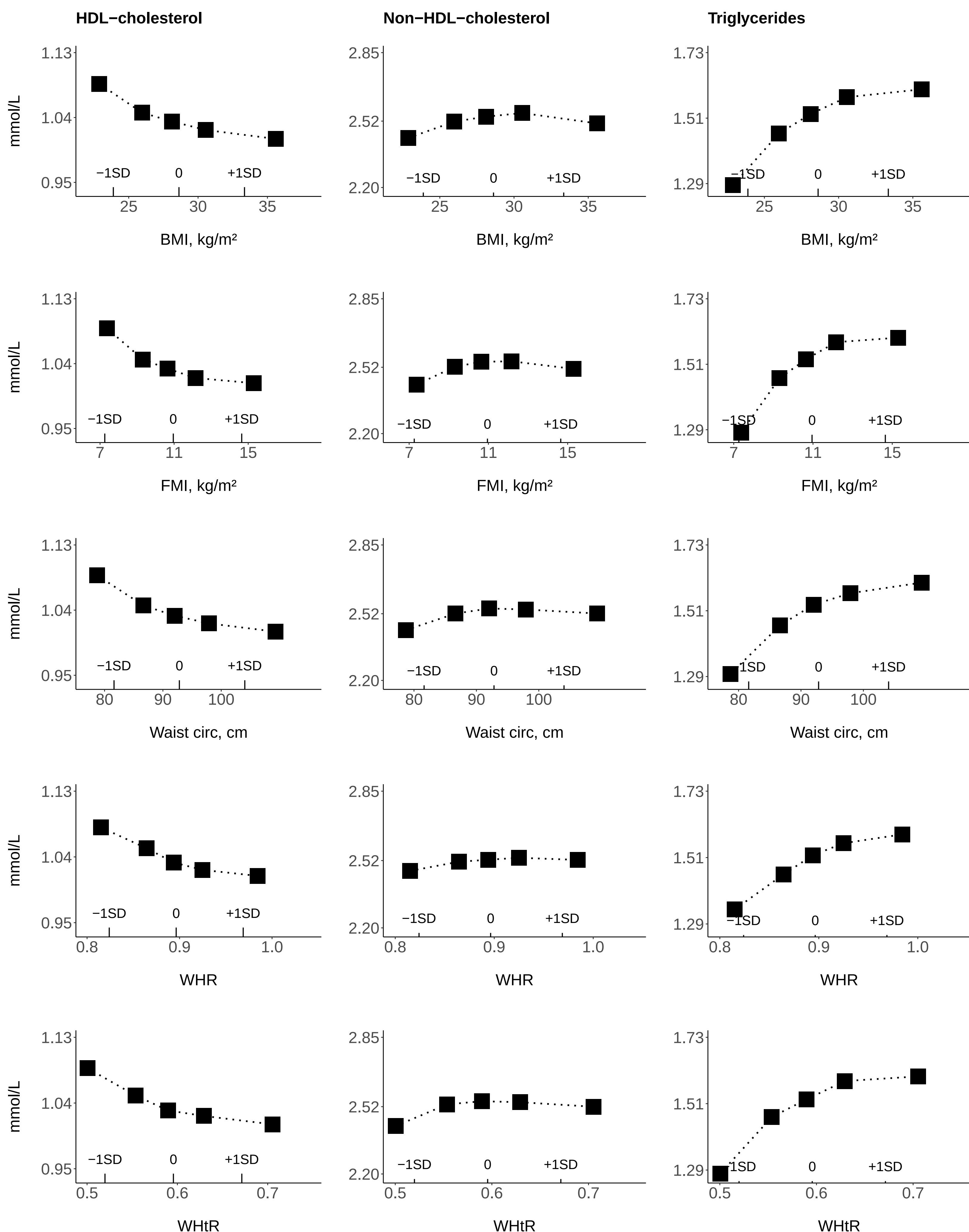
Biochemistry was available only in a subset, as specified in the title. *Diabetes defined as previously diagnosed, treated, or screen detected. Exclusions as per Table 4.1 and in addition 33 participants with diabetes, and 9 participants with assays measurements greater than 3 SDs from the mean. LDL-c=low-density cholesterol; HDL-c=high-density cholesterol.

Table 4.7: Pearson correlation coefficients of selected lipids and vascular-metabolic traits of adiposity among 10,898 men and 19,062 women aged 35-89 years, without diabetes or other chronic disease at baseline

	Cholesterol	LDL-c	non-HDL-c	HDL-c	Triglyc.	HbA1c	SBP	
LDL-c	0.95	Men						
	0.95	Women						
	0.95	Both						
non-HDL-c	0.97	0.96	Men					
	0.97	0.97	Women					
	0.97	0.97	Both					
HDL-c	0.36	0.20	0.14	Men				
	0.43	0.25	0.19	Women				
	0.43	0.25	0.18	Both				
Triglycerides	0.14	-0.05	0.20	-0.21	Men			
	0.35	0.21	0.43	-0.17	Women			
	0.27	0.13	0.36	-0.23	Both			
HbA1c	0.03	-0.01	0.04	-0.03	0.18	Men		
	0.15	0.13	0.18	-0.07	0.26	Women		
	0.09	0.07	0.12	-0.05	0.20	Both		
SBP	-0.07	-0.10	-0.07	0.02	0.10	0.10	Men	
	0.05	0.02	0.06	-0.04	0.19	0.23	Women	
	0.03	0.01	0.04	-0.02	0.12	0.19	Both	
DBP	-0.05	-0.07	-0.05	0.00	0.10	0.11	0.79	Men
	0.05	0.03	0.07	-0.05	0.15	0.18	0.80	Women
	0.04	0.02	0.05	-0.04	0.13	0.14	0.76	Both

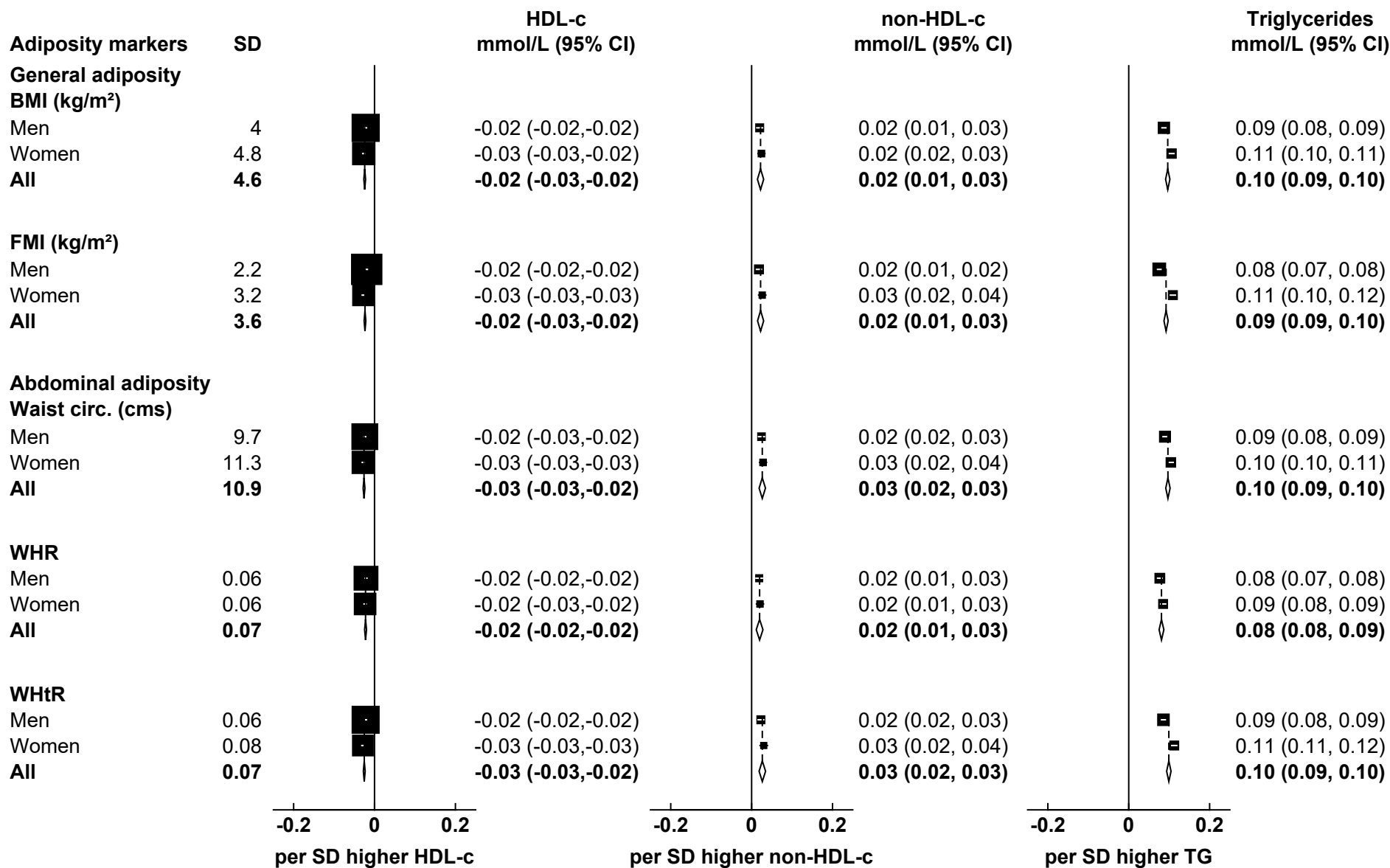
Exclusions as per table 4.1 restricted to those with complete information on NMR assays.

Figure 4.10: Cross-sectional associations of general and central markers of adiposity, and selected lipids among 10,065 men and 16,424 women aged 35–89 years, without diabetes or other chronic disease at recruitment, before adjustment for other markers of adiposity



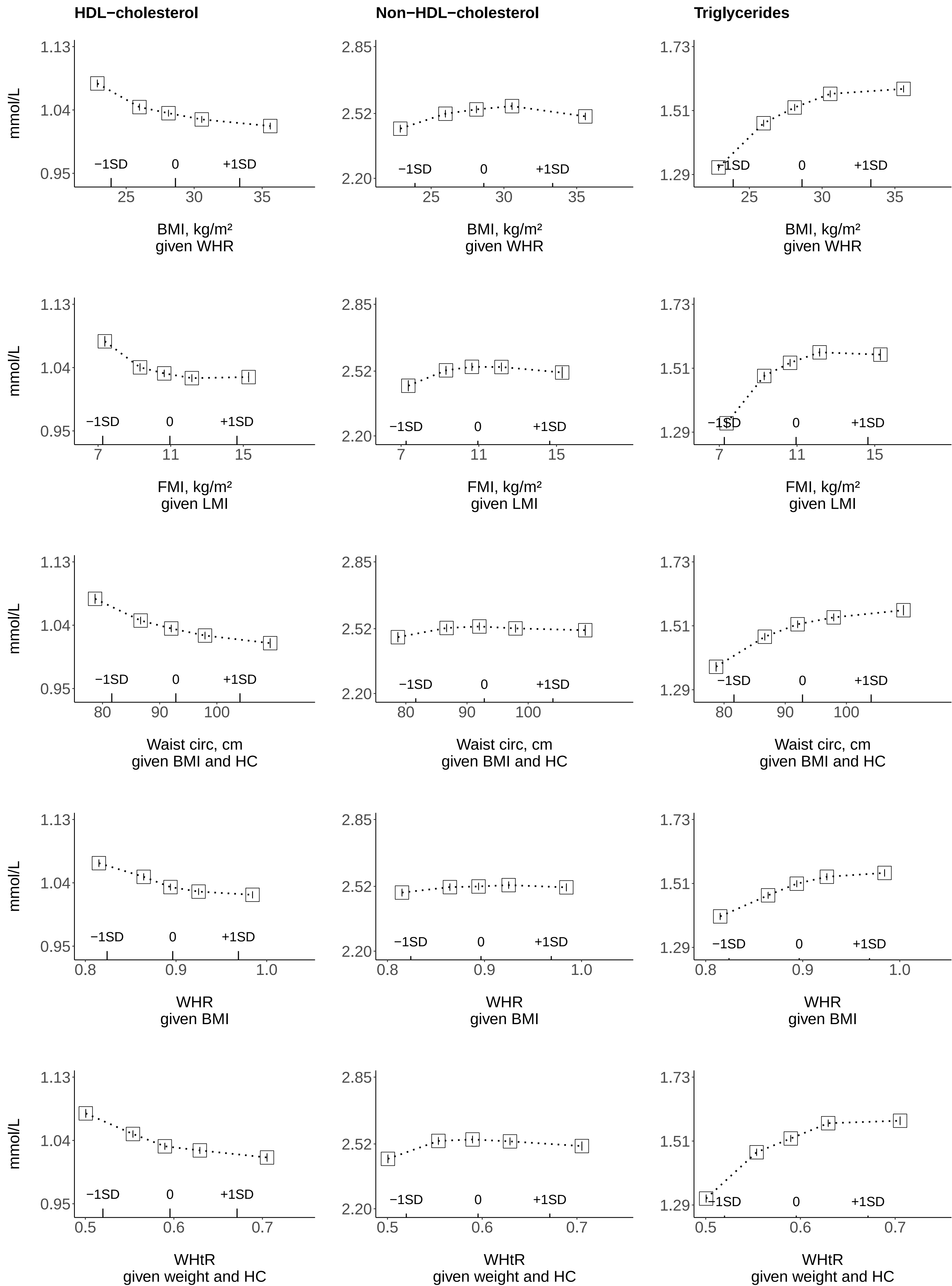
Analyses and conventions as per figure 4.6, now restricted to a sub-set of 26,489 participants with complete information on lipids from the NMR. Adiposity markers defined by five equally-sized groups of the sex-specific distributions. Y-axes extend 0.5 SDs above and below the mean level of each lipid marker.

Figure 4.11. Overall and sex-specific relevance of adiposity markers to selected lipids among 10,065 men and 16,424 women aged 35-89 years, without diabetes or other chronic disease at recruitment, before adjustment for other adiposity markers



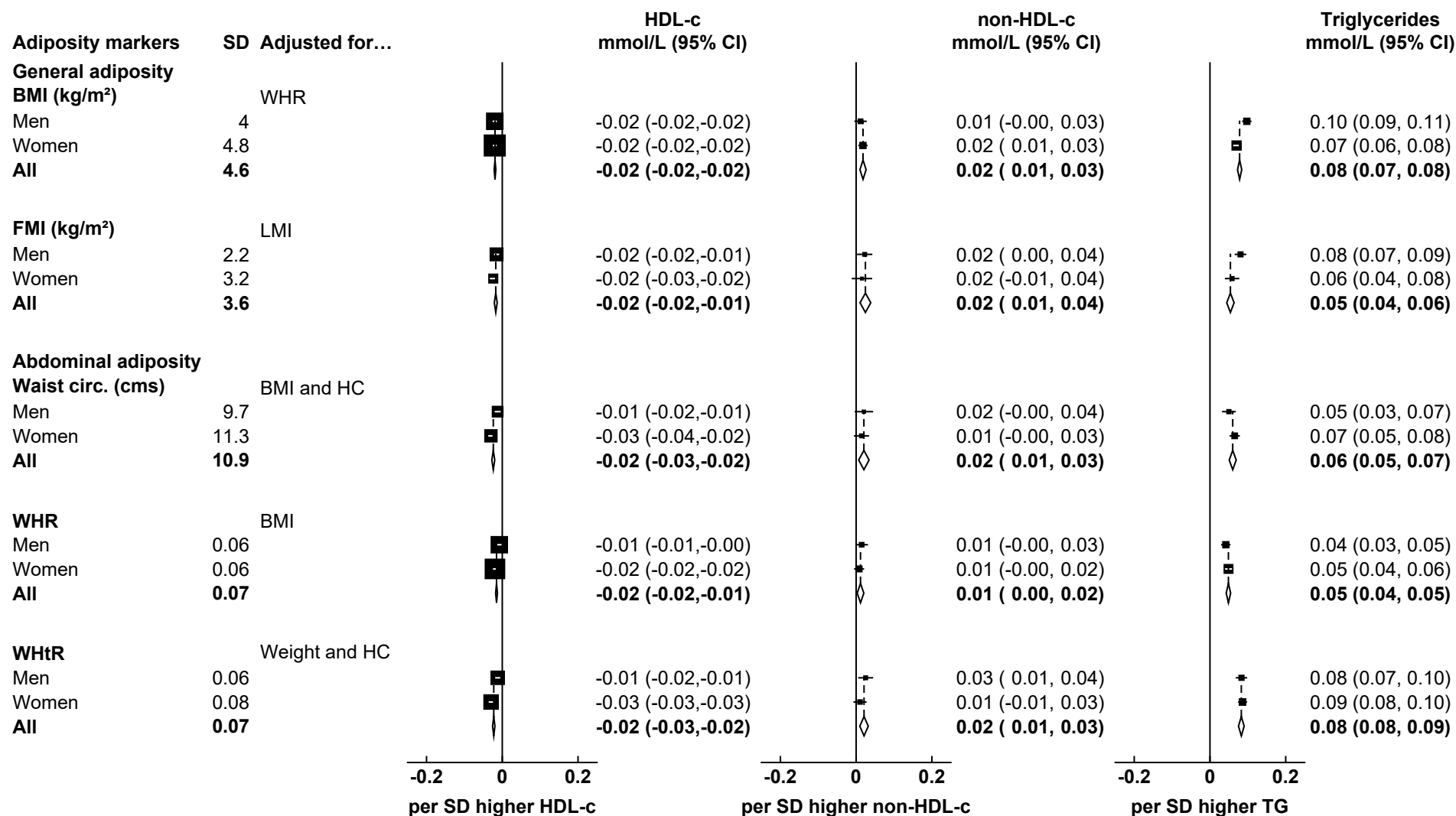
Analyses and conventions as per Figure 4.7, restricted to those with complete NMR assays.

Figure 4.12: Cross-sectional associations of general and central markers of adiposity and selected lipids among 10,065 men and 16,424 women aged 35–89 years, without diabetes or other chronic disease at recruitment, after adjustment for other adiposity markers



Analyses as per figure 4.10, with further adjustments for other markers of adiposity as indicated in the plot.

Figure 4.13. Independent and sex-specific relevance of adiposity markers to selected lipids among 10,065 men and 16,424 women aged 35-89 years, without diabetes or other chronic disease at recruitment, after adjustment for other adiposity markers



Analyses and conventions as per Figure 4.11, with additional adjustments for other markers of adiposity as indicated in the plot.

Chapter 5: BMI and mortality

Abstract

Body-mass index (BMI) above 25 kg/m² is associated with higher risks of death from vascular, metabolic, neoplastic, and other causes, but previous reports had suggested that in Hispanic populations, BMI was not associated with higher mortality rates. This was referred to as “*the Hispanic obesity paradox*”. This chapter examined the relevance of adiposity to 16-year mortality risk from specific causes among 145,659 Mexican adults aged 35 years and older at recruitment into the Mexico City Prospective Study, avoiding reverse causality biases. Participants with a glycosylated haemoglobin level of 7% or greater (suggestive of screen-detected diabetes in the absence of diagnosed cases of diabetes) and with previously-diagnosed diabetes, in addition to other chronic diseases at the baseline assessment of the adiposity markers, were excluded from the main analyses. Cox regression adjusted for confounders yielded mortality rate ratios (RRs) after at least 5 years of follow-up and before age 75 years. The association of BMI at baseline with all-cause mortality was J-shaped, with the minimum risk at 25 to <27.5 kg/m². Above 25 kg/m², each 5 kg/m² increase in BMI was associated with a 32% increase in all-cause mortality (RR=1.32; 95% CIs 1.24-1.36), including a 38% higher risk from vascular or metabolic causes (RR=1.38, 1.31-1.46). This association was stronger at ages 40 to <60 years (RR=1.40; 1.30-1.49) than at ages 60 to <75 years (RR=1.24; 1.17-1.31), but was not materially affected by sex, smoking, or other confounders. The associations of BMI with mortality was weakened only slightly by adjustment for WHR. Compared with a BMI of 25 kg/m², adult life expectancy from age 40 years was reduced by about 3 years at a BMI of 30 kg/m², but by nearly 10 years at a BMI of 40 kg/m². By contrast,

among those with previously-diagnosed or screen-detected diabetes, baseline BMI was *inversely* associated to mortality. In conclusion, in this contemporary Mexican population, BMI was strongly associated with premature mortality, with shapes and strength of associations comparable to those reported in other populations and no evidence of 'an obesity paradox'. Diabetes distorted the true relevance of BMI to mortality in this cohort.

5.1 Background

Excess adiposity accounts for substantial morbidity, disability and premature mortality.¹⁻⁴ Despite much public health attention, the worldwide evidence suggests that the prevalence of adiposity has increased substantially in recent years. In 2015, over 600 million adults were obese, and 4 million deaths were caused by BMI above 25 kg/m² of which, 40% occurred among individuals with a BMI above 30 kg/m².² Recent estimates from 189 prospective studies involving almost 4 million never-smoking Western, Australian and Asian adults without pre-existing diseases who survived for at least 5 years and were followed-up for nearly 15 years, demonstrated that all-cause mortality rates were minimal at a BMI of 20-25 kg/m², but increased steeply above 25 kg/m², with each 5 kg/m² higher BMI being associated with 31% higher all-cause mortality and 42% higher cardiovascular mortality.⁴ Since most of those studies were completed, the prevalence of obesity has increased in many countries, whereas vascular mortality has decreased. Further, the associations of BMI with mortality may be different in populations with substantially higher mean BMI than those originally studied, or in particular ethnic groups.⁵ For instance, another meta-analysis restricted to Asian countries found that among 0.7 million never smokers who had survived more than 3 years, above a BMI of 25 kg/m², additional increases in BMI

were associated with substantially higher mortality in East Asians but not in South Asians.⁶ Similarly, a recent study in South India among 0.4 million adults without previous disease who had survived longer than 2 years, found that BMI was approximately unrelated to vascular mortality.⁷ Studies of adiposity and mortality from Hispanic populations have reported conflicting results. A meta-analysis of 5 prospective studies involving 17,000 Hispanic adults, found no association between overweight or obesity and increased all-cause mortality.⁸ A second meta-analysis of 39,000 Hispanic adults from National Surveys showed that low, but not high BMI, was associated with higher all-cause mortality.⁹ Finally, a recent study of 10,000 Mexican-American adults from the National Health and Nutrition Survey (NHANES) study reported very weak associations of BMI with all-cause mortality, log-linear positive association of BMI with vascular or diabetic mortality, but inverse associations of percentage fat mass with vascular (but not diabetic) mortality.¹⁰ As detailed in **Chapter 2 (sections 2.7 and 2.11)**, none of the previous studies conducted in Hispanic populations investigated the possibility of low BMI being a consequence of pre-existing disease and the potential impact of such *reverse causality* on their findings. Such inverse J-shaped associations of adiposity with risk of mortality observed in small studies, have been referred to as '*the Hispanic obesity paradox*', hypothesizing that people with disease and high BMI 'tend to be better off' than people with disease and low BMI.^{11,12} Some expert views have argued that exclusion of individuals with pre-existing disease may induce bias in the assessment of adiposity in relation to mortality (for instance diabetes likely mediates the associations of adiposity with specific causes of death), and proposed that exclusion of medical histories not to be necessary in analyses of BMI and mortality.¹² However, the interplay between highly incident chronic diseases with adiposity levels and consequent mortality, has not been

thoroughly assessed in populations from low and middle-income countries where the management and prognosis of such diseases may differ from Western populations. Therefore, further studies involving a larger number of disease cases with prolonged follow-up are needed to clarify the '*true relevance*' of overweight and obesity to mortality in Hispanic populations. Such clarifications are important to guide local public health strategies to reduce levels of adiposity and their associated excess risks of mortality both in Mexico and in other Hispanic populations.

This chapter examines the relevance of BMI to cause-specific mortality among 145,659 men and women aged 35-89 years at recruitment into the Mexico City Prospective Study, who were followed-up for 16-years. As described in the **Methods chapter (Section 3.3)**, Cox models with age-at-risk and follow-up time as underlying time variables, assessed the overall, age, sex, and cause-specific relative risk of death, adjusted for traditional confounders, before and after excluding participants with previously-diagnosed and screen-detected diabetes (conservatively defined as HbA1c $\geq 7\%$ in the absence of a diagnosis), in addition to chronic disease at recruitment and deaths occurring during the first 5 years of follow-up.

For comparison with the previous major studies of mortality, BMI was defined clinically, by the WHO-modified categories of 18.5 to $<25 \text{ kg/m}^2$ (normal), 25 to $<30 \text{ kg/m}^2$ (overweight), 30 to $<35 \text{ kg/m}^2$ (obesity grade 1), 35 to $<40 \text{ kg/m}^2$ (obesity grade 2), and 40 to $<60 \text{ kg/m}^2$ (obesity grade 3), with the first 2 groups being further divided by 22.5 kg/m^2 and 27.5 kg/m^2 , respectively (given that two-thirds of the cohort were classified as normal or overweight). The shapes of the association with mortality risk were first assessed throughout the full ranges of BMI, then the continuous risk for

cause-specific mortality was estimated per additional 5 kg/m² higher BMI above 25 kg/m², both overall and independent of abdominal adiposity. The mediating effects of HbA1c, SBP, HDL-c and non HDL-c, and triglycerides were estimated in a subset with available information.

Sensitivity analyses included estimates by strata of confounders, *exclusion* of current or former smokers, *exclusion* of individuals with an HbA1c concentration of 6.5% to <7% (the clinical threshold for screen-detected diabetes), and *inclusion* of those with previously-diagnosed diabetes but good glycaemic control (conservatively defined as an HbA1c level <7%, given the general-population involved in the present study), and with usual (rather than baseline) levels of BMI. Heterogeneity for estimates within the strata of confounders and trends across ages were estimated by the chi² statistic.

5.2 Study participants and adiposity related characteristics

Of the 145,659 eligible participants aged 35-89 years, with complete data and without chronic diseases at baseline other than diabetes (the baseline characteristics of these participants are described in **Table 4.4** and **Sections 4.3 and 4.4 of Chapter 4**), 18,981 (13.03%) had previously-diagnosed diabetes at the time of the recruitment, and a further 4870 (3.3%) had a HbA1c of or above 7% (suggestive of undetected diabetes). Of all the 16,079 reliably identified deaths accrued by January 2018, 9110 (56.7%) occurred prematurely at ages 35-74 years (**S7**), and of those, 2818 (30.9%) occurred in the first 5 years of follow-up, of which 1369 (48.6%) were among those with previously-diagnosed diabetes. Of the 38,254 men and 80,162 women aged 35-89 years without diabetes (including screen-detected cases based on measured

HbA1c $\geq 7\%$), or other chronic disease at recruitment who survived for at least 5 years, 95,658 were aged 35-74 years and 22,758 were aged 75-89 years, and were included in the main analyses of mortality.

5.3 Illustration of reverse causality bias

For comparability with the previous major studies of BMI and mortality conducted in other populations^{1,4 13-15} and as described in the **Methods chapter (Section 3.2.7)**, individuals with a previous diagnosis of cancer, liver cirrhosis, vascular, respiratory, or chronic kidney diseases at the time of recruitment into the Mexico City Prospective Study were excluded from all analyses, in order to minimise the effects of reverse-causality bias in relation to adiposity-associated mortality. Residual bias was further investigated with and without exclusion of both previously-diagnosed and screen-detected diabetes (generally referred to as *diabetes* throughout the thesis). Likewise, the impact of including and excluding deaths occurring during the first 5 years of follow-up was also assessed. **Figures 5.1** and **5.2** illustrate the magnitude of such biases by showing the associations with and without these additional exclusions. Among those without chronic disease other than diabetes at recruitment and all years of follow-up, the associations of BMI with premature mortality from any cause would have been ‘U-shaped’, with a ‘lower’ mortality risk at a BMI of 27.5 to <30 kg/m² (**Figure 5.1**). However, stratification of analyses by diabetes at baseline revealed markedly different associations depending on the presence or absence of diabetes, with strongly inverse associations for premature mortality among those with diabetes (**Figure 5.2**). Among those with previously-diagnosed or screen-detected diabetes (but no other chronic disease at baseline), the association of BMI with mortality was *inverse J-shaped* with a ‘lower’ mortality risk at a BMI of 30 to <35 kg/m². By contrast, among those without

diabetes (or other chronic disease at recruitment), the association was *positive J-shaped* with a 'lower' mortality risk at a BMI of 27.5 to <30 kg/m². Among those who died within the first 5 years of follow-up, the patterns of these associations were comparable, but the differences among those with and without diabetes were more accentuated. After excluding deaths that occurred within the first 5 years of follow-up, the inverse associations among those with previously-diagnosed or screen-detected diabetes persisted, while among those without diabetes at recruitment, the mortality risk became much stronger across the full BMI range. Compared with associations in the first 5 years of follow-up, the death RR in the later years for all-cause mortality decreased from 1.56 to 1.08 for a BMI of 18.5 to <22.5 kg/m², increased from 0.77 to 0.98 for a BMI of 27.5 to <30 kg/m², and increased from 1.92 to 2.19 for a BMI of 40 to <60 kg/m² (all RRs relative to BMI in the range 22.5 to 25 kg/m²; **Figure 5.2**). Additional exclusion of the first 10 rather than 5 years of follow-up did not further strengthen the association of BMI with mortality in the overweight or obese BMI ranges of 25-27.5 kg/m² (**S27**).

Given that diabetes and high levels of HbA1c (both extremely common in this cohort), and deaths occurring during the first 5 years of follow-up exacerbate problems of reverse causality bias, participants with previously-diagnosed or screen-detected diabetes, as well as those who died within the first 5 years after recruitment, were ultimately excluded from the subsequent analyses of mortality presented in the following sections.

5.4 BMI and total mortality

Among participants without previously-diagnosed or screen-detected diabetes and

other chronic disease at baseline, who survived for at least 5 years after recruitment, BMI had a J-shaped association with premature mortality at ages 40-74 years throughout the full range of 18.5 to 60 kg/m², with a lower risk at 25-27.5 kg/m² (**Figure 5.3**). The relative risks (RR) of premature death from any cause for those with a BMI >40 kg/m² compared to those with a BMI of 22.5 to 25 kg/m² was 2.19 (95% confidence interval [CI] 1.90-2.54). Similar patterns were observed in men and in women, but men had a higher absolute risk of total mortality compared to women (**Figure 5.4**). The relevance of BMI to all-cause mortality was largely independent of abdominal adiposity, as adjustment for WHR only slightly attenuated the shapes of the association throughout the BMI ranges (**Figure 5.5**). On average, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 32% higher risk of death at ages 40-74 years (RR=1.32; 1.27-1.37). After adjustment for WHR, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 29% higher risk (RR=1.29; 1.24-1.34). In sensitivity analyses excluding ever smokers, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 37% higher mortality (RR=1.37; 1.30-1.44), while in analyses including those with well-controlled diabetes, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 30% higher mortality (RR=1.30; 1.25-1.35).

5.4.1 Age and sex-specific associations of BMI with total mortality

Analyses stratified by different age-at-risk bands, showed that the overall relevance of BMI to all-cause mortality was J-shaped at every age, but appeared stronger at ages 40-59 years than at ages 60-74 years (**S28**). Supplementary assessment of mortality risk at ages 75-89 years (aiming to compare estimates after additional exclusion of those with diabetes in this cohort, to those from the Global BMI Collaboration and the Prospective Studies Collaboration), showed a much weaker J-shaped association with

total mortality at this age compared to that observed at ages 40-59 years or 60-74 years, but the absolute mortality risks were greater after the age of 75 years compared to younger ages (**S28**). On average, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 42% higher mortality at ages 40-59 years (RR=1.42 95% CIs 1.33-1.51), a 27% higher mortality at ages 60-74 years (RR=1.27; 1.21-1.33), and only 21% higher mortality at ages 75-89 years (RR=1.21; 1.15-1.27; X^2 for trend=16.4, p-value=0.003; **Figure 5.6**). At every age, the estimates were broadly similar in men and in women, and were little affected by additional adjustment for abdominal adiposity. Given WHR, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 36% higher mortality at ages 40-59 years (RR=1.36; 1.28-1.45), a 25% higher mortality at ages 60-74 years (RR=1.25; 1.19-1.32), and a 21% higher mortality at ages 75-89 years, respectively (RR=1.21; 1.15-1.26; X^2 for trend=9.1, p-value=0.01; **Figure 5.6**).

5.5 Associations of BMI with cause-specific mortality

The non-linear association with total mortality described in **Section 5.4** above, was more accentuated for non-vascular and non-metabolic diseases (e.g. neoplastic, respiratory, infective, or external causes, including ill-defined diseases), than it was for vascular or metabolic causes (e.g., cardiac, cerebrovascular, other vascular, renal, acute diabetic crises, or hepatobiliary diseases; **Figure 5.3**). The RR of premature death among those with BMI >40 kg/m² compared to a BMI of 22.5 to 25 kg/m² was 2.64 (2.14-3.26) for all the vascular-metabolic causes combined, compared with 1.89 (1.55-2.30) for all the non-vascular-metabolic causes combined. Additional adjustment for WHR, only slightly attenuated the shapes of the associations with mortality from these causes (**Figure 5.5**), such that the RR for those with BMI >40 kg/m² versus a BMI of 22.5 to 25 kg/m² was 2.31 (1.78-3.01) for vascular-metabolic mortality and 1.75

(1.38-2.23) for non-vascular-metabolic mortality.

5.5.1 Age and sex-specific associations of BMI with vascular-metabolic mortality

Similar to all-cause mortality, the estimates of BMI with vascular-metabolic mortality stratified by age-at-risk were stronger at younger than at older ages. Specifically, the RR for vascular-metabolic deaths with each 5 kg/m² higher BMI above 25 kg/m² was 53% higher risk at ages 40-59 years (RR=1.53; 1.39-1.67), 32% higher risk at ages 60-74 years (RR=1.32; 1.23-1.41), and 24% higher risk at ages 75-89 years (RR=1.24; 1.17-1.33; X^2 for trend=13.2, p-value=0.001; **Figure 5.7**). These associations were broadly similar in men and women at every age, and largely independent of abdominal adiposity. Given WHR, each 5 kg/m² higher BMI above 25 kg/m² was associated with a 43% higher vascular-metabolic mortality at ages 40-59 years (RR=1.43; 1.30-1.58), a 30% higher mortality at ages 60-74 years (RR=1.30; 1.21-1.39), and a 24% higher mortality at ages 75-89 years (RR=1.24; 1.16-1.32; X^2 for trend=6.1, p-value=0.05; **Figure 5.7**).

5.5.2 BMI and mortality from specific vascular-metabolic causes

The shapes of the association of BMI (across the full ranges) with the different underlying causes of vascular or metabolic deaths at ages 40-74 years are shown in **Figure 5.8**, and the magnitude of associations for comparable differences in BMI are shown in **Table 5.1**. Strong, positive associations were observed for cardiac, cerebrovascular, renal or diabetic deaths (**Figure 5.8**). On average, each 5 kg/m² higher BMI above 25 kg/m² was associated with 38% higher risk of any vascular-metabolic deaths (RR=1.38; 95% CIs 1.31-1.46), including a 35% higher risk from any

vascular causes (RR=1.35; 1.25-1.45), and a larger, 56% higher risk from renal or diabetic causes (RR=1.56; 1.38-1.74). The risk of mortality associated with each 5 kg/m² higher BMI above 25 kg/m² was largely similar for the cardiac and cerebrovascular causes at ages 40-74 years (RR=1.33; 1.22-1.46 vs. 1.20; 1.03-1.40, respectively), as it was for the hepatobiliary causes (RR=1.34; 1.20-1.51; **Table 5.1**). Further adjustment for WHR attenuated these estimates only slightly (**S29**), such that the RRs per 5 kg/m² higher BMI above 25 kg/m² were 1.31 (1.22-1.41) for any vascular deaths, 1.30 (1.18-1.42) for cardiac deaths, 1.17 (1.00-1.37) for stroke deaths, 1.52 (1.35-1.72) for renal or diabetic deaths, and 1.27 (1.13-1.44) for hepatobiliary deaths, respectively (**S30**).

The cause-specific RRs associated with BMI were consistent (both above and below 25 kg/m²), when analyses were restricted to never-smokers (**Table 5.2**), excluded participants with an HbA1c level of 6.5% to <7% (**S31**), or included those with previously-diagnosed diabetes but good glycaemic control (defined as HbA1c levels below 7%; **S32**). Specifically, the death RRs with each 5 kg/m² higher BMI above 25 kg/m² among never smokers were 1.47 (1.36-1.58) for any vascular-metabolic causes at ages 40-74, 1.45 (1.31-1.59) for any vascular causes, 1.36 (1.20-1.54) for cardiac causes, 1.34 (1.10-1.64) for stroke, 1.66 (1.42-1.95) for renal or diabetic causes, and 1.34 (1.13-1.59) for hepatobiliary causes, respectively (**Table 5.2**). By comparison, the RRs after inclusion of those with well-controlled diabetes were 1.35 (1.28-1.42) for any vascular-metabolic deaths, 1.33 (1.24-1.42) for any vascular deaths, 1.32 (1.21-1.43) for cardiac deaths, 1.19 (1.02-1.38) for stroke deaths, 1.42 (1.27-1.59) for renal or diabetic deaths, and 1.34 (1.20-1.50) for hepatobiliary deaths, respectively (**S32**). Additional correction for regression dilution suggested somewhat stronger

associations of usual levels of BMI with the various causes of vascular-metabolic death (RRs were 1.40; 1.29-1.51 for any vascular deaths, 1.44; 1.35-1.53 for any vascular or metabolic deaths, 1.65; 1.44-1.88 for renal or acute diabetic deaths, and 1.37; 1.31-1.43 for deaths from any cause; **S36**).

5.5.3 Mediation effects of vascular and metabolic traits on vascular-metabolic mortality

Tables 5.3 and **5.4** show the risk of premature mortality for selected vascular, renal or diabetic causes of death at a given BMI, before and after additional adjustment for likely mediators. The RR for any vascular-metabolic deaths with each 5 kg/m² higher BMI above 25 kg/m², did not essentially alter after additional adjustment for HbA1c (RR changed from 1.39; 1.31-1.47 to 1.38, 1.30-1.46), and after adjustment for SBP, the mortality risk reduced modestly (from 1.39; 1.31-1.47 to 1.33; 1.26-1.41, **Table 5.3**). Similar changes in the magnitude of the associations (of about 1-2% after accounting for HbA1c, and of about 5-7% after accounting for SBP), were observed in analyses of BMI at a given WHR, for premature deaths from any vascular, ischaemic, or vascular-metabolic causes combined. For cerebrovascular deaths, the reduction in RR was somewhat larger, particularly at a given SBP (from 1.20; 1.02-1.40 to 1.09; 0.93-1.28, corresponding to a reduction in the Wald-chi² statistic from 5.0 to 1.1). For deaths from renal causes or diabetic crises, the reduction in RRs was also larger, both at a given SBP as well as at a given HbA1c (from 1.55; 1.38-1.65 to 1.46; 1.29-1.66, and to 1.48; 1.30-1.68, respectively, corresponding to a reduction in the Wald-chi² statistic from 50.4 to 35.2, and from 50.4 to 36.6, respectively).

Among the subset of 29,960 participants with additional measures of lipids, the

changes in the proportional hazards for vascular-metabolic deaths due to higher BMI appeared larger after adjustment for SBP than after adjustment for HbA1c (**Table 5.4**), both before and after further adjustment of BMI for WHR. Furthermore, in this subset, preliminary analyses with additional adjustment for HDL-c, non HDL-c, and triglycerides, did not appear to majorly change the magnitude of the associations of BMI with the various ischaemic, cerebrovascular or other vascular causes of death, and for renal or diabetic mortality, a small reduction in the RR was observed after accounting for HDL-c (from 1.47; 1.15-1.88 to 1.44; 1.13-1.84, corresponding to a change in the Wald- χ^2 statistic from 9.5 to 8.6).

5.5.4 BMI and mortality from specific non-vascular non-metabolic causes

Compared to vascular-metabolic mortality, the risks of premature mortality from other non-vascular or non-metabolic underlying causes associated with BMI were weaker, particularly for cancer deaths (**Figure 5.8**). On average, each 5 kg/m² higher BMI above 25 kg/m² was associated with 15% higher risk of neoplastic death (RR=1.15; 1.06-1.24), 47% higher risk of respiratory death (RR=1.47; 1.32-1.64), and 47% higher risk of death from infection (RR=1.47; 1.28-1.68; **Table 5.1**). The RRs for comparable increases in BMI were largely similar with the various cancer subtypes (**Figure 5.9**). The apparent hazards for urinary, gastro-intestinal or haematological cancers (as opposed to cancers of the breast, pancreas, hepatobiliary, or gynaecological sites), were based on very small number of cases and were not significantly different. Additional adjustment for WHR did not materially alter the findings for the various non-vascular-metabolic underlying causes of death (**S29**). For instance, the RRs for equivalent increases in BMI at a given WHR (**S30**) were 1.44 (1.28-1.61) for respiratory deaths, 1.42 (1.24-1.63) for infective deaths, and 1.14 (1.05-1.23) for

cancer deaths (largely driven by a higher risk for urinary cancers [RR=1.62; 1.13-2.23], gastro-intestinal cancers [RR=1.43; 1.11-1.84] and haematological cancers [RR=1.29; 1.02-1.61]; **S33**).

Similar to estimates for vascular-metabolic mortality, the RRs for the various non-vascular, non-metabolic underlying causes of premature death associated with higher BMI were consistent among never-smokers (**Table 5.2**), or after including those with well-controlled diabetes (**S32**). Specifically, the RRs for mortality at ages 40-74 among never smokers were 1.44 (1.24-1.67) for respiratory deaths, 1.55 (1.30-1.84) for infective deaths and 1.14 (1.06-1.23) for cancer deaths, (largely driven by higher mortality from gastro-intestinal cancers [RR=1.45; 1.05-1.99] and urinary cancers [RR= 1.69; 1.01-2.81], **S34**). By comparison, the RRs after inclusion of those with well-controlled diabetes were 1.43 (1.29-1.59) for respiratory deaths, 1.47 (1.29-1.67) for infective deaths, and 1.14 (1.06-1.23) for cancer deaths (also driven by a higher risk from urinary cancers [RR=1.62; 1.13-2.32] and gastro-intestinal cancers [RR=1.43; 1.11-1.84], **S35**). The effects of correction for regression dilution increased associations only slightly (**S36**).

5.6 Effect-modification of mortality risk by levels of confounders

The RRs of premature mortality from any-cause and from any vascular-metabolic cause associated with each 5 kg/m² higher BMI above 25 kg/m², were broadly similar irrespective of sex, district of residence, smoking status, level of education achieved, leisure-time physical activity, or alcohol intake (**Figures 5.10 and S37**). Step-wise multivariable adjustments for these confounders, indicated little differences in the risk estimates after adjustment for such confounders (**S38**).

5.7 BMI and survival

Applying the estimated relative risk of a 32% increased mortality per 5 kg/m² higher BMI above 25 kg/m² to the sex and age-specific current national death rates for Mexico, a BMI of 35 kg/m² (compared with 25 kg/m²), was associated with a reduction of about 3 years in life expectancy from age 40, while a BMI of 40 kg/m² was associated with a reduction of nearly 10 years (**Figure 5.11**). Furthermore, among women with a BMI of 40 kg/m², nearly 50% would have died by the age of 75 years, compared to about a 30%, among those with a BMI of 30 kg/m². Among men, the estimated loss in survival was somewhat more extreme, such that among men with a BMI of 40 kg/m², nearly 65% would have died by the age of 75 years, compared to about a 45%, among those with a BMI of 30 kg/m². The excess absolute risk attributed to a BMI >30 kg/m² accounted for 18% of all deaths from a vascular or metabolic cause at ages 40-74 years (including 16% of the cardiac deaths, 18% of the stroke deaths, 28% of the renal deaths, and 56% of the acute diabetic crises), and 11% of all deaths from a respiratory or an infective cause (**S39**).

5.8 Strengths and limitations

With direct rather than self-reported anthropometry, along with the aforementioned precautions against being substantially misled by reverse causality, this analysis could reliably assess the associations between mortality and BMI, separate and joint of the distributions of central adiposity. Although the study could not rule out some residual confounding, its major strengths include its size and duration, yielding many deaths for analysis, and the availability of information on a wide range of relevant risk factors (although only partially on lipids levels). A particular strength of this analysis includes associations of BMI with mortality among those with un-diagnosed diabetes in addition

to diagnosed diabetes, which allowed for careful control for reverse causality bias due to diabetes. Furthermore, these analyses allowed direct comparisons of mortality risk from specific causes for equivalent differences per 5 kg/m² BMI, which also allows for the present findings to be put in perspective with those from the largest studies from other populations.

Nevertheless, analyses were constrained by several limitations. First, data regarding the incidence of nonfatal diabetes, renal, vascular and other major disease were lacking. Second, identification of causes of death relied on death certificates; however, the main analyses focused on all-cause mortality or the aggregate of vascular-metabolic deaths. Third, too few cancer deaths occurred to enable a reliable investigation of site-specific cancers risk. Finally, as in many prospective studies, the participants were probably somewhat healthier than the general population, specifically because the analyses excluded those with diabetes or other chronic diseases at recruitment.

5.9 Conclusions

In contrast with previous studies conducted in Hispanic populations, the present results demonstrated that general adiposity was strongly associated with higher risks of death from all causes. The U-shaped association of BMI with mortality observed when pre-existing disease at recruitment and all years of follow-up were included was misleading, chiefly due to the strong inverse associations in participants with diabetes, and among those without diabetes, by the lack of an association with deaths during the first 5 years of follow-up. After excluding participants with diabetes, in addition to other pre-existing diseases, and the first 5 years of follow-up, the estimates from this

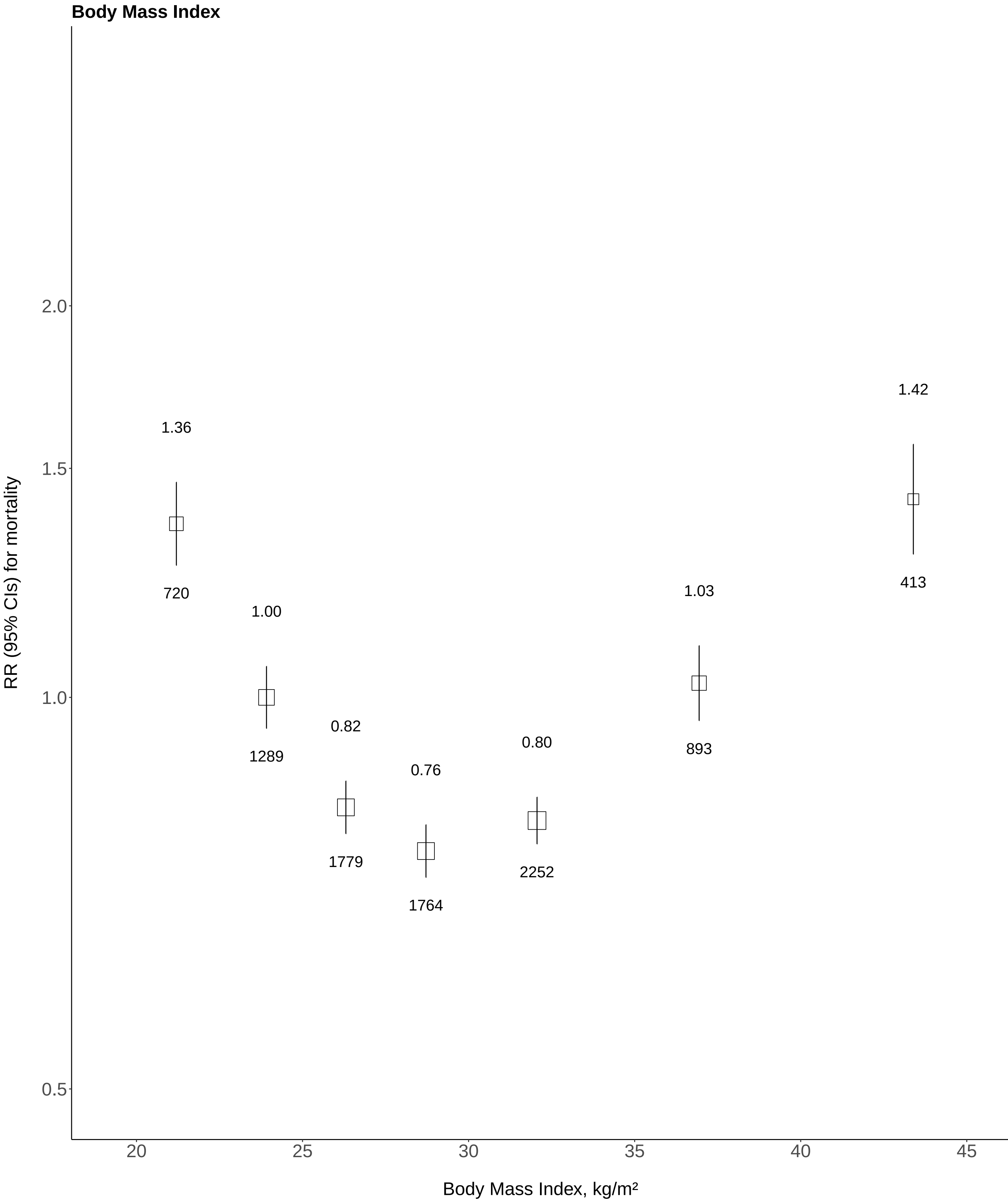
thesis are about 3-fold stronger compared to estimates from previous meta-analyses of Hispanics, with each 5 kg/m² higher BMI above 25 kg/m² being associated with a 32% higher relative risk of death from all causes, which was largely driven by a 38% higher risk of death from vascular and metabolic causes. These excess risks were independent of abdominal adiposity, so that, even after controlling for WHR, individuals with a BMI >40 kg/m² had a 2-fold higher death rate from all-causes and vascular-metabolic causes, compared with those with a BMI of 22.5 to <25 kg/m². Based on the current national death rates in Mexico, a BMI of 40 kg/m² was estimated to consequently reduce life expectancy among Mexicans by nearly 10 years. These findings are remarkably consistent with the previous reports in Western populations. However, the 'true' relevance of BMI to cause-specific mortality can be affected by lean mass, or may be less informative than the distribution of more hazardous fat depots, such as abdominal versus gluteo-femoral fat. The subsequent chapters in this thesis will assess the relevance of predicted fat mass index (analogous to BMI) and of several measures of abdominal adiposity for cause-specific mortality.

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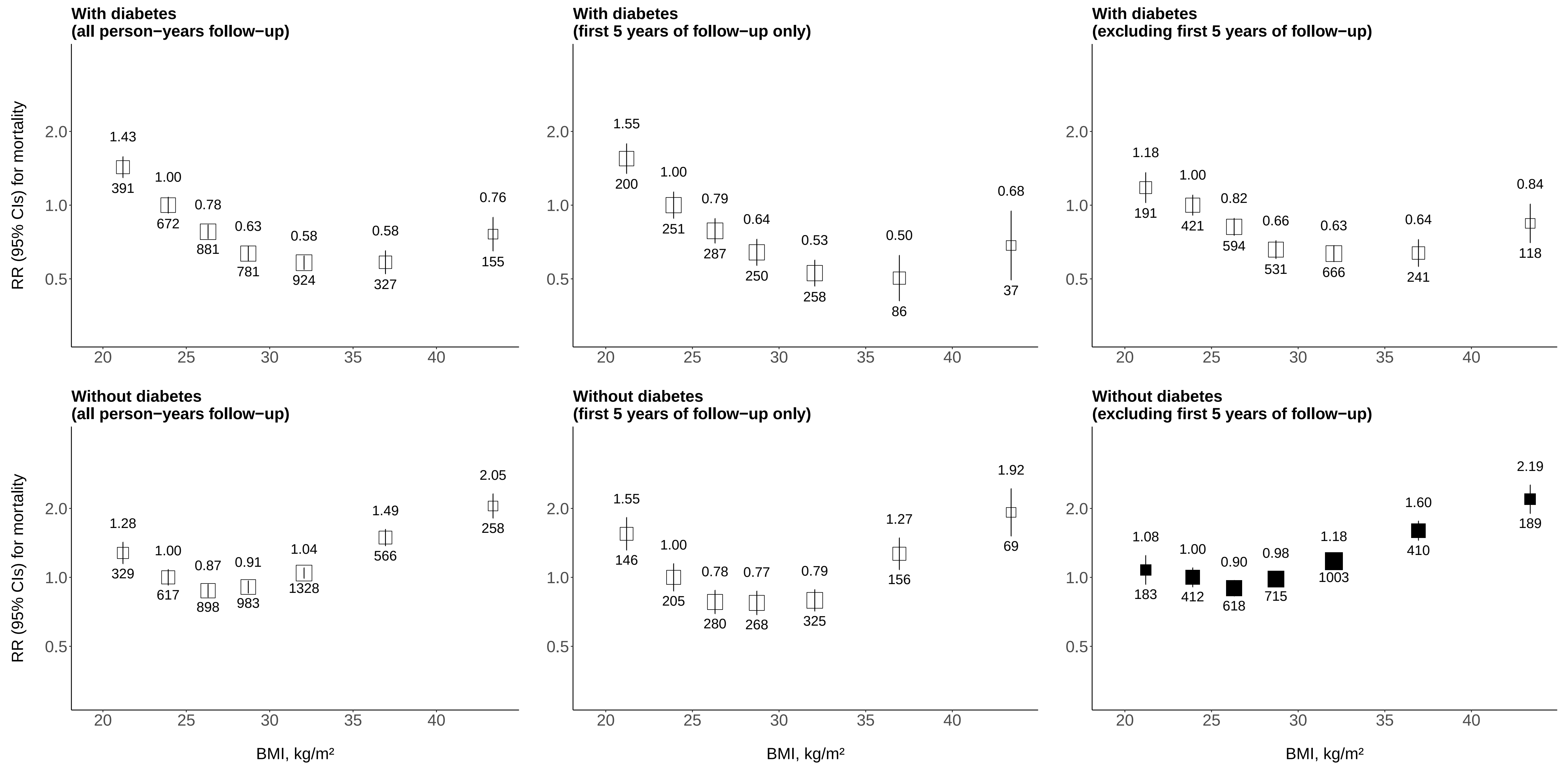
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Figure 5.1. Associations of BMI to all-cause mortality mortality at ages 35–74 years, including those with previously-diagnosed or screen-detected diabetes at baseline and all person-years of follow-up



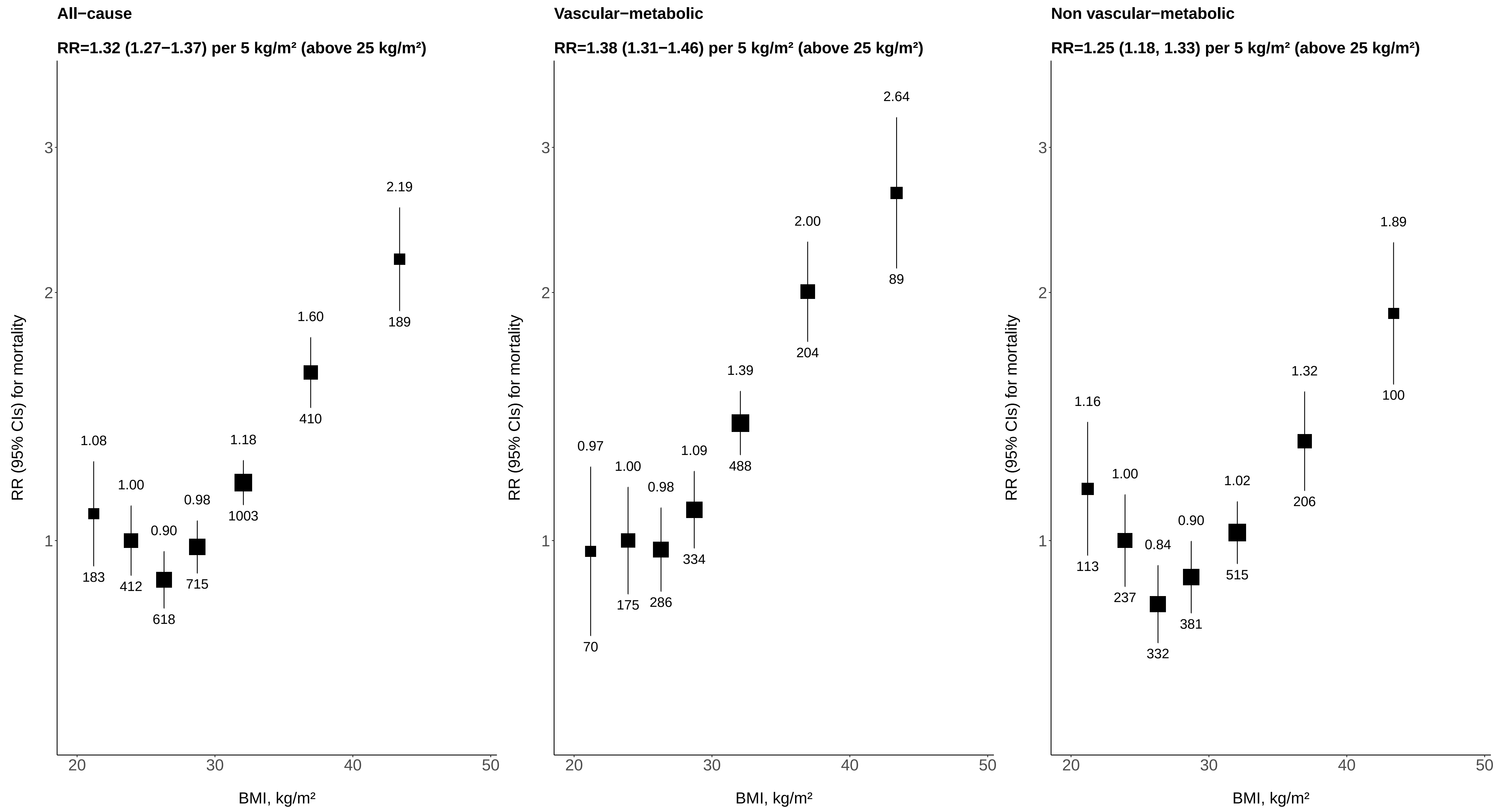
Cox models with age-attained and length of follow-up as underlying time-variables, stratified by age-at-risk (in 5-years ranges), and adjusted for sex, district, education, physical exercise, alcohol or smoking status and amount. BMI is grouped by modified WHO categories of 18.5 to <22.5 kg/m², 22.5 to <25 kg/m² (reference), 25 to <27.5 kg/m², 27.5 to <30 kg/m², 30 to <35 kg/m², 35 to <40 kg/m², and 40 to 60 kg/m². The plotted RRs are centred at the mean BMI in each group. The vertical lines through each point represent group-specific 95% CIs, with the area of each square inversely proportional to the amount of statistical information. For each group the RR is above the square and the number of deaths below. Analyses exclude participants with previously diagnosed chronic disease at baseline (ischaemic heart disease, stroke, chronic kidney disease , liver cirrhosis, cancer or emphysema), and those with missing data. Screen-detected diabetes defined as HbA1c of or above 7%. BMI = body mass index; RR= death rate ratio; CI = confidence intervals.

**Figure 5.2. Associations of BMI to all-cause mortality at ages 35–74 years,
in those with and without previously-diagnosed or screen-detected diabetes at baseline, by total and early follow-up**



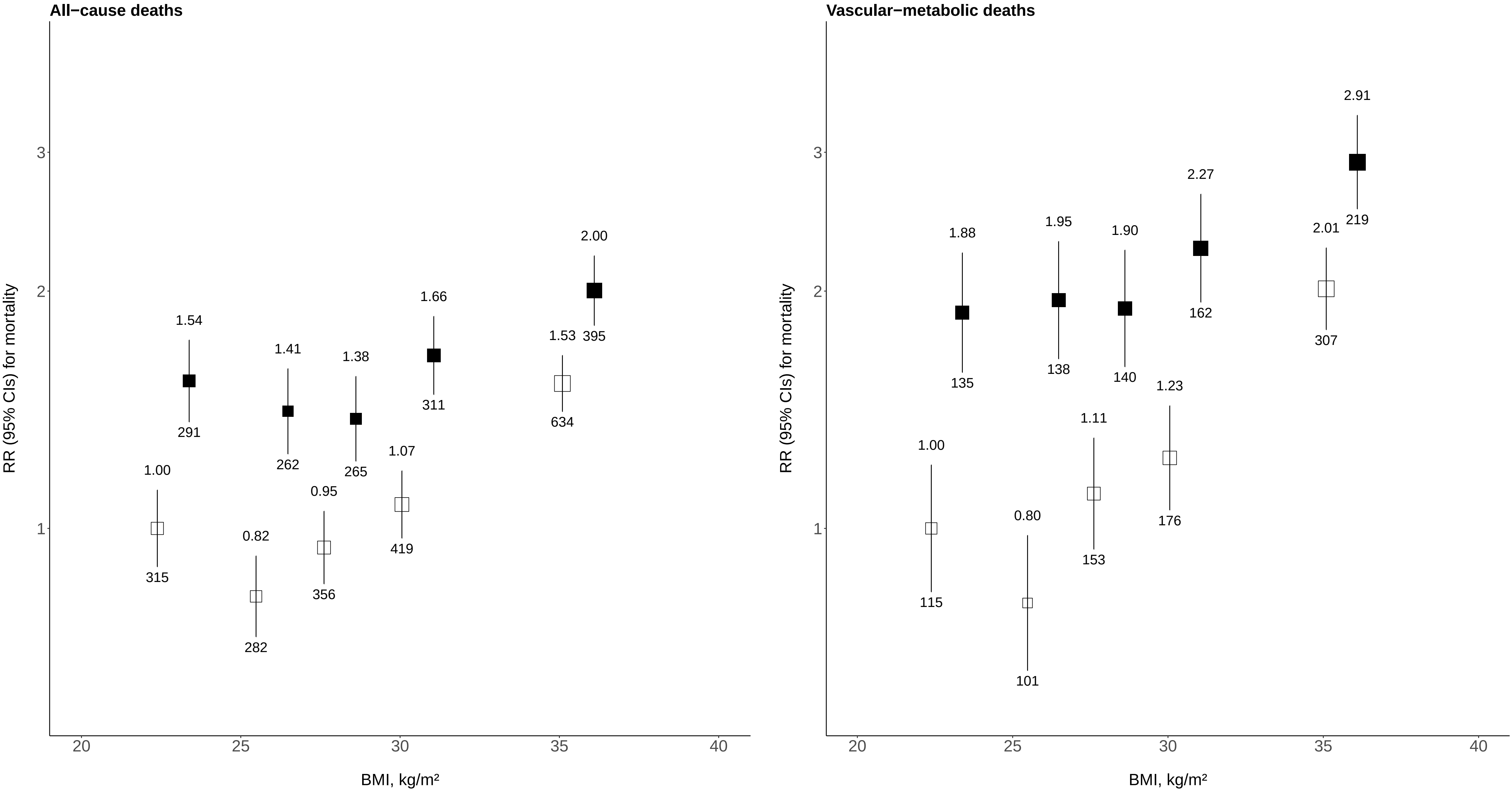
Analyses as per figure 5.1. Of all 9110 deaths included in analyses, 2818 occurred in the first 5-years of follow-up, of which 1369 were among those with diabetes.

Figure 5.3: Overall relevance of BMI to mortality at ages 40–74 years



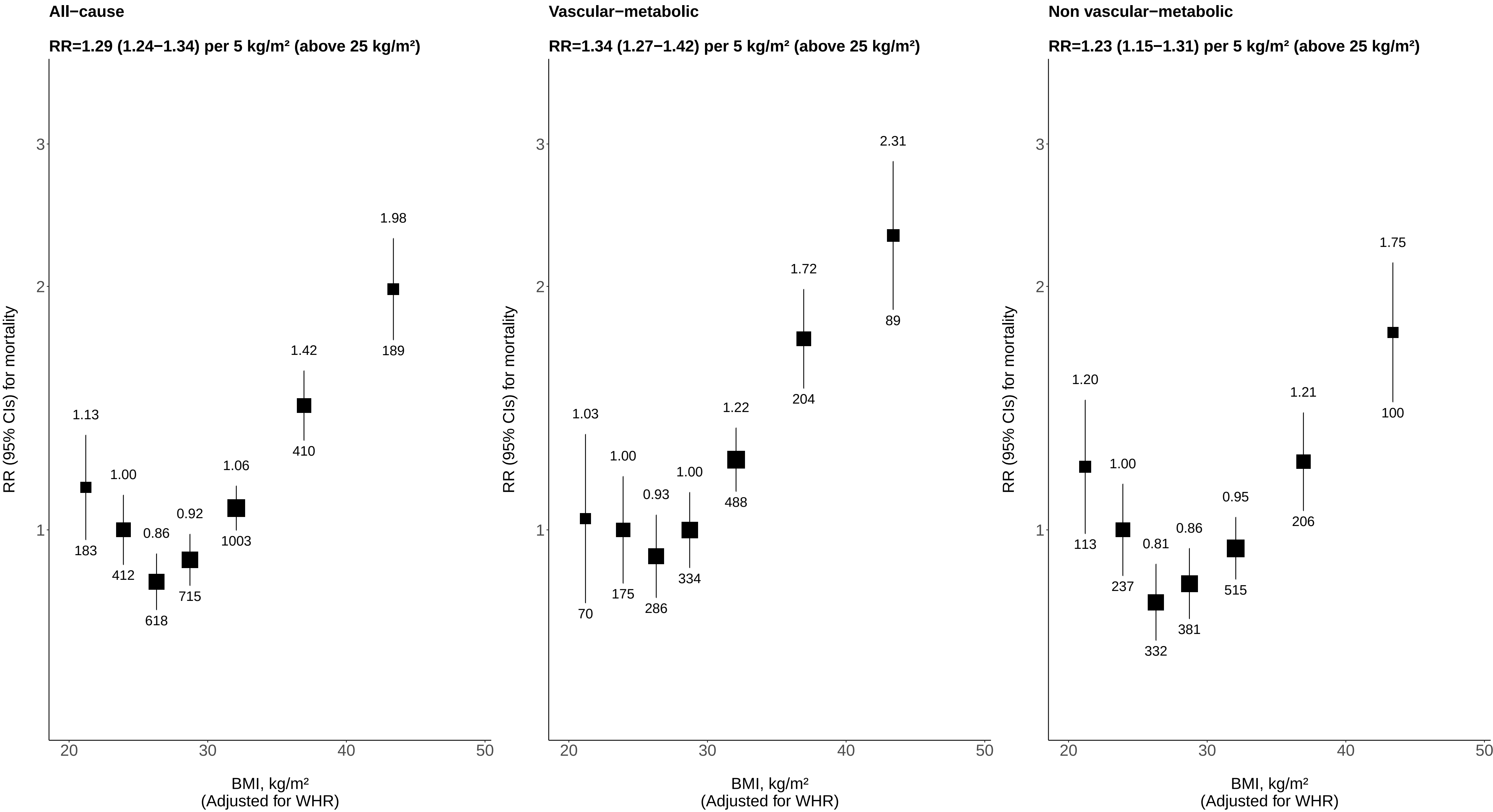
Analyses as per figure 5.1, now with previously-diagnosed or screen-detected diabetes and the first 5 years of follow-up excluded.

Figure 5.4: Sex-specific relevance of BMI to all-cause and vascular-metabolic mortality among men (black squares) compared to women (white squares), at ages 40–74 years



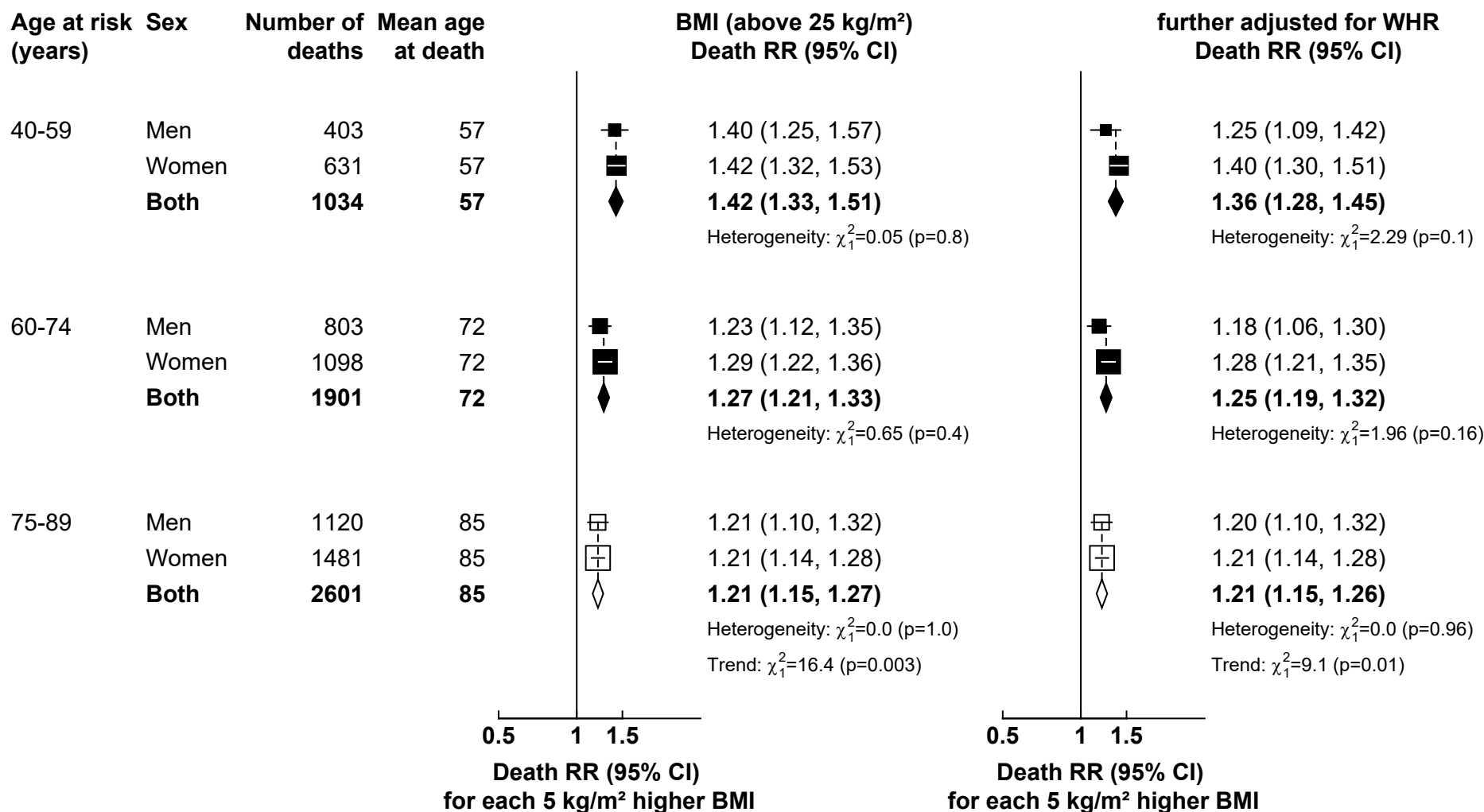
Analyses and conventions as per Figure 5.3. BMI grouped by five equally-sized groups of the sex-specific distributions at baseline.

Figure 5.5: Independent relevance of BMI to mortality at ages 40–74 years



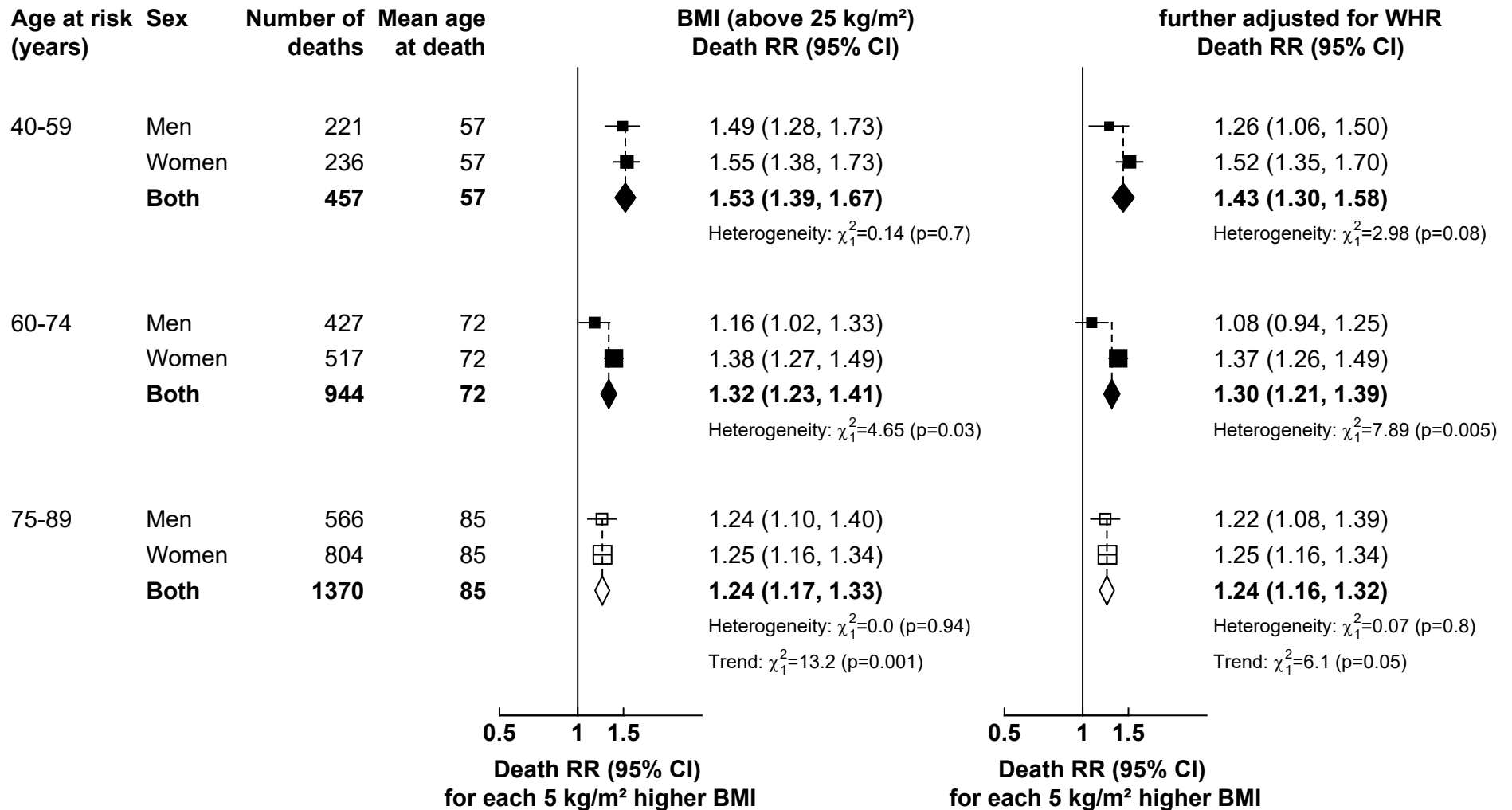
Analyses and conventions as per Figure 5.3, with additional adjustments as indicated in the plot.

Figure 5.6: Age and sex-specific relevance of BMI (above 25 kg/m²) to all-cause mortality



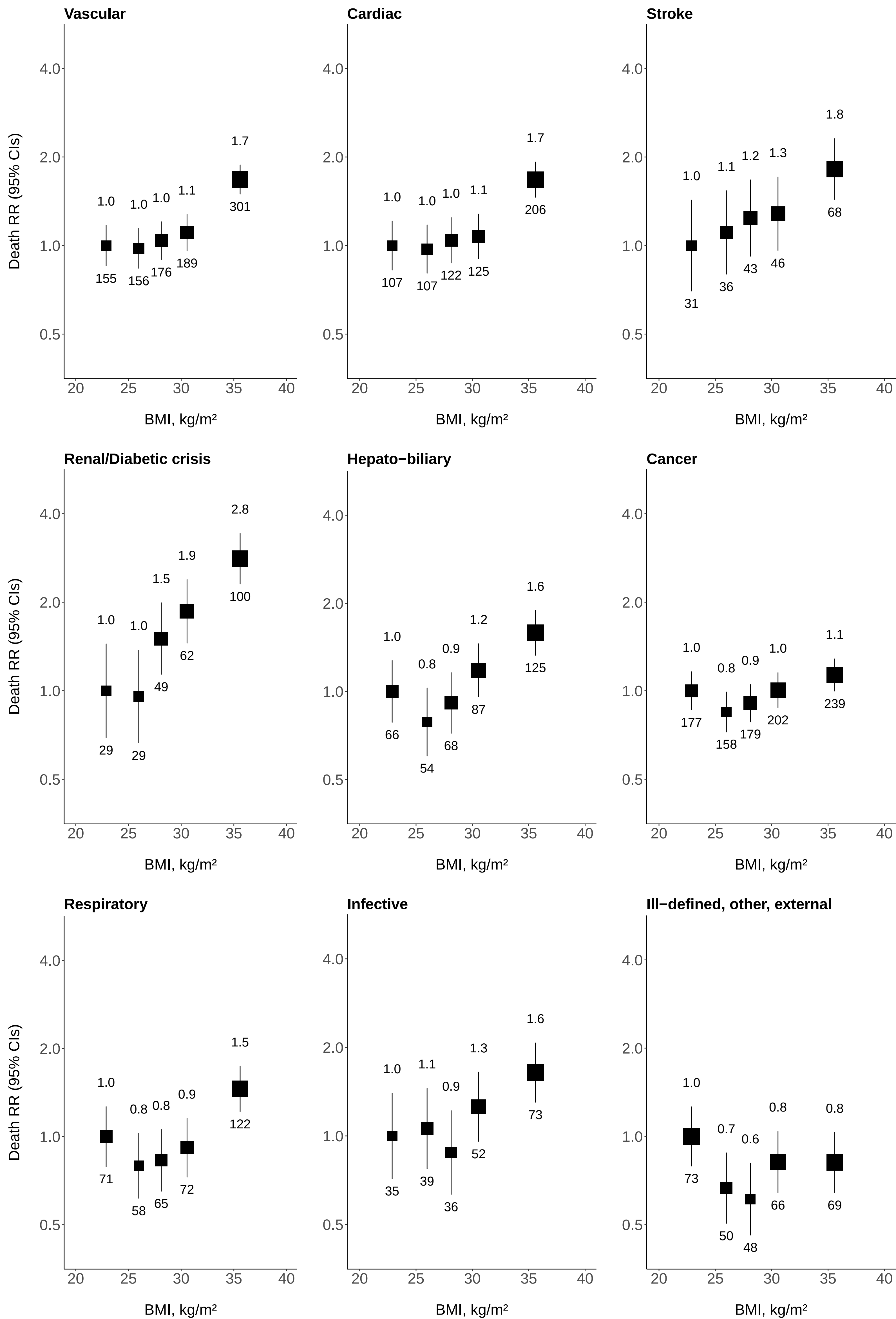
Analyses and conventions as per figure 5.3. Number of deaths corresponds to analyses of BMI above 25 Kg/m². Diamonds represent the values for men and women combined. The results for the oldest age group is left unshaded, for premature mortality at ages 40-74 years is of primary interest. The total number of deaths at ages 40-89 years was 6,859.

Figure 5.7: Age and sex-specific relevance of BMI (above 25 kg/m²) to vascular-metabolic mortality



Analyses and conventions as per figure 5.6. The total number of deaths at ages 35-89 years was 3,361.

Figure 5.8: Relevance of BMI to mortality from specific causes at ages 40–74 years



Analyses per Figure 5.3. BMI grouped by five-equally sized groups of the sex-specific distributions.

Table 5.1: BMI and cause-specific mortality at ages 40-74 years (excludes previously-diagnosed diabetes, those with HbA1c $\geq 7\%$, other chronic disease and the first 5 years of follow-up)

Cause death	BMI 18.5 to <25 kg/m ² n=20,636		BMI 25 to 60 kg/m ² n=108,293	
	No deaths	RR per 5 kg/m ² (95% CIs)	No deaths	RR per 5 kg/m ² (95% CIs)
Vascular				
Ischaemic Heart Disease	77	0.83 (0.40-1.75)	437	1.26 (1.14-1.40)
Other cardiac	25	0.84 (0.23-3.07)	128	1.53 (1.30-1.80)
Subtotal: any cardiac	102	0.83 (0.44-1.59)	565	1.33 (1.22-1.46)
Stroke	30	0.82 (0.25-2.66)	194	1.20 (1.03-1.40)
Other vascular	17	3.56 (0.55-22.99)	69	1.85 (1.51-2.27)
Subtotal: vascular	149	0.97 (0.56-1.66)	828	1.35 (1.25-1.45)
Metabolic				
Renal/Acute diabetic crises	29	0.45 (0.14-1.39)	240	1.56 (1.38-1.76)
Hepatobiliary	67	1.12 (0.48-2.60)	333	1.34 (1.20-1.51)
Subtotal: any vascular-metabolic	245	0.91 (0.60-1.38)	1401	1.38 (1.31-1.46)
Cancer				
Lung/Upper aero-digestive	29	0.55 (0.18-1.68)	68	1.10 (0.83-1.47)
Other cancer	141	1.06 (0.60-1.87)	717	1.15 (1.06-1.25)
Subtotal: any cancer	170	0.92 (0.55-1.53)	785	1.15 (1.06-1.24)
Other				
Respiratory	69	0.55 (0.26-1.16)	319	1.47 (1.32-1.64)
Infective	39	0.87 (0.30-2.52)	196	1.47 (1.28-1.68)
Other/III-defined/external	72	0.54 (0.26-1.13)	234	1.19 (1.03-1.38)
Total: all-cause	595	0.80 (0.61-1.04)	2935	1.32 (1.27-1.37)

Analyses and exclusions as per Figure 5.3.

Table 5.2: Baseline BMI (per 5 kg/m²) vs deaths at ages 40-74 years by cause, among never smokers

Cause death	BMI 18.5 to <25 kg/m ² n=8,939		BMI 25 to 60 kg/m ² n=51,765	
	No deaths	RR per 5 kg/m ² (95% CIs)	No deaths	RR per 5 kg/m ² (95% CIs)
Vascular				
Ischaemic Heart Disease	22	0.61 (0.16-2.39)	173	1.24 (1.06-1.45)
Other cardiac	13	0.27 (0.05-1.32)	69	1.63 (1.33-2.00)
Subtotal: any cardiac	35	0.44 (0.16-1.24)	242	1.36 (1.20-1.54)
Stroke	9	2.06 (0.16-27.14)	93	1.34 (1.10-1.64)
Other vascular	4	4.99 (0.06-434.98)	33	2.30 (1.82-2.91)
Subtotal: vascular	48	0.66 (0.26-1.67)	368	1.45 (1.31-1.59)
Metabolic				
Renal/Acute diabetic crises	11	0.29 (0.04-1.88)	104	1.66 (1.42-1.95)
Hepatobiliary	18	3.00 (0.43-21.07)	127	1.34 (1.13-1.59)
Subtotal: any vascular-metabolic	77	0.82 (0.38-1.76)	599	1.47 (1.36-1.58)
Cancer				
Lung/Upper aero-digestive	6	0.78 (0.05-12.69)	20	1.32 (0.85-2.04)
Other cancer	60	1.22 (0.49-2.99)	391	1.17 (1.06-1.30)
Subtotal: any cancer	66	1.17 (0.50-2.74)	411	1.18 (1.07-1.31)
Other				
Respiratory	28	0.67 (0.19-2.37)	154	1.44 (1.24-1.67)
Infective	9	1.03 (0.10-10.77)	100	1.55 (1.30-1.84)
Other/ill-defined/external	30	0.31 (0.10-0.96)	87	1.22 (0.98-1.52)
Total: all-cause	210	0.76 (0.48-1.21)	1351	1.37 (1.30-1.44)

Analyses and exclusions as per Table 5.1

Table 5.3: HbA1c and SBP mediated associations of BMI to mortality from major vascular-metabolic causes at ages 40-74 years

	BMI per 5 kg/m² (above 25 kg/m²)	Wald χ^2	Further adjusted for WHR	Wald χ^2
Any vascular-metabolic (n=1363)				
plus confounders*	1.39 (1.31-1.47)	136.3	1.35 (1.27-1.43)	106.0
plus HbA1c only [†]	1.38 (1.30-1.46)	122.4	1.34 (1.27-1.42)	97.6
plus SBP only [†]	1.33 (1.26-1.41)	99.0	1.30 (1.23-1.38)	77.3
Any vascular (n=805)				
plus confounders	1.36 (1.26-1.46)	68.2	1.33 (1.23-1.43)	54.6
plus HbA1c only	1.34 (1.24-1.45)	59.0	1.31 (1.22-1.42)	48.3
plus SBP only	1.29 (1.20-1.39)	45.6	1.27 (1.17-1.37)	36.5
Ischaemic Heart Disease (n=424)				
plus confounders	1.28 (1.15-1.43)	20.8	1.24 (1.11-1.39)	14.3
plus HbA1c only	1.27 (1.14-1.42)	17.8	1.23 (1.10-1.38)	12.5
plus SBP only	1.23 (1.11-1.38)	14.1	1.20 (1.07-1.34)	9.5
Any cerebrovascular (n=189)				
plus confounders	1.20 (1.02-1.40)	5.0	1.17 (0.99-1.37)	3.4
plus HbA1c only	1.18 (1.01-1.39)	4.1	1.16 (0.98-1.36)	2.9
plus SBP only	1.09 (0.93-1.28)	1.1	1.06 (0.90-1.26)	0.6
Renal/Diabetic crisis (n=235)				
plus confounders	1.55 (1.38-1.75)	50.4	1.52 (1.34-1.72)	42.9
plus HbA1c only	1.48 (1.30-1.68)	36.6	1.45 (1.28-1.65)	31.9
plus SBP only	1.46 (1.29-1.66)	35.2	1.44 (1.26-1.63)	30.2

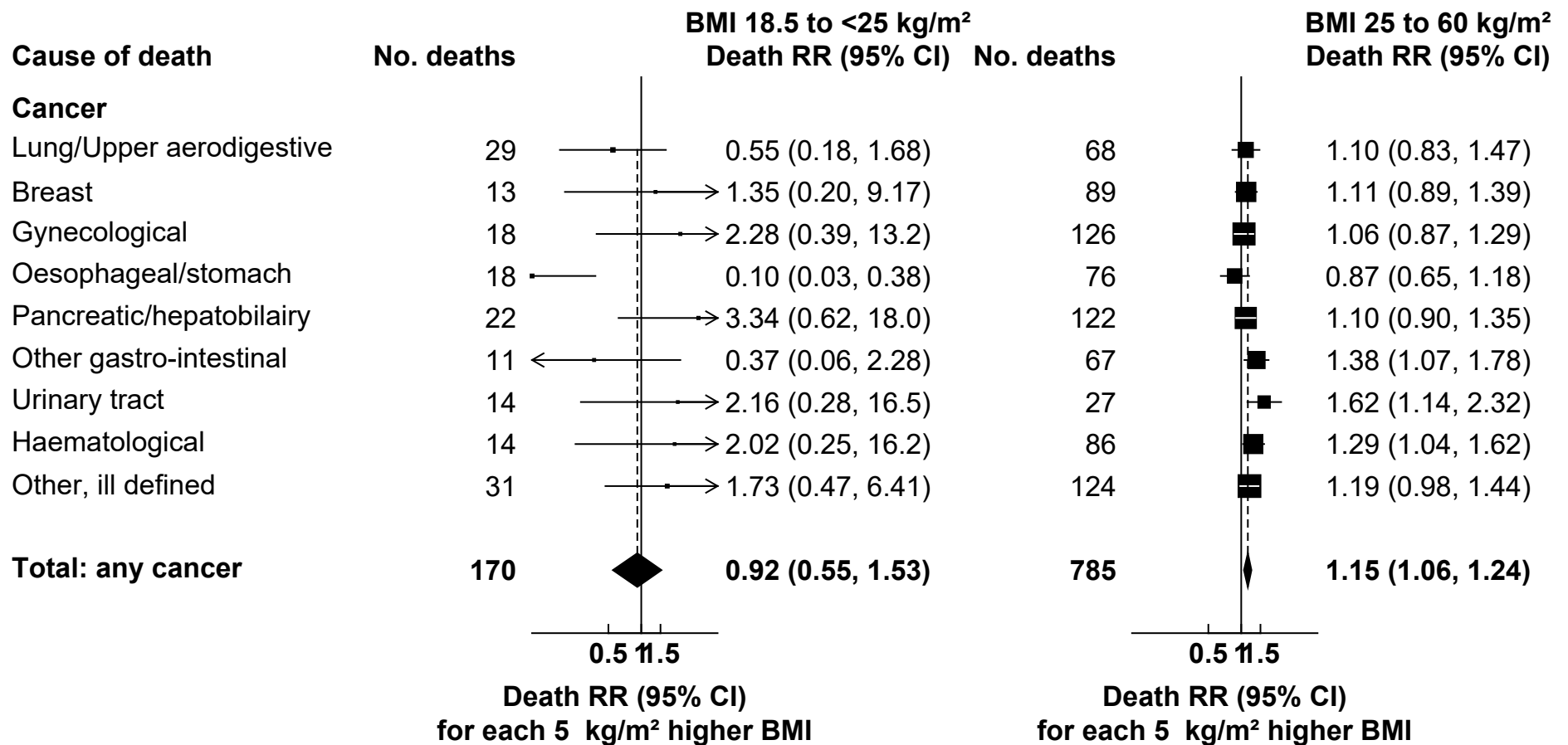
*As per Table 5.1, now restricted to those with complete measures of SBP and HbA1c. † Confounders-adjusted model, further adjusted for that mediator only. Chi-squared statistic calculated as $(-2) \times \log LR$ [likelihood ratio].

Table 5.4: Metabolic mediated associations of BMI (above 25 kg/m²) to major causes of vascular-metabolic mortality at ages 40-74 years

Mediator adjustment	Vascular-metabolic (n=376)	Wald X ²	Vascular (n=218)	Wald X ²	IHD (n=118)	Wald X ²	Stroke (n=51)	Wald X ²	Renal/Diabetic* (n=51)	Wald X ²
Overall										
per 5 kg/m ² [†]	1.39 (1.25-1.54)	35.6	1.35 (1.17-1.55)	17.2	1.19 (0.96-1.47)	2.6	1.54 (1.17-2.01)	9.8	1.47 (1.15-1.88)	9.5
plus HbA1c ^{††}	1.35 (1.21-1.51)	28.0	1.30 (1.12-1.50)	12.5	1.16 (0.93-1.44)	1.7	1.46 (1.10-1.93)	7.1	1.40 (1.09-1.81)	6.8
plus SBP ^{††}	1.33 (1.19-1.48)	25.7	1.29 (1.12-1.49)	11.8	1.13 (0.91-1.41)	1.3	1.40 (1.06-1.85)	5.5	1.37 (1.07-1.76)	6.1
plus HDL-c ^{††}	1.38 (1.24-1.53)	34.1	1.34 (1.16-1.54)	16.4	1.18 (0.96-1.46)	2.4	1.54 (1.18-2.02)	9.9	1.44 (1.13-1.84)	8.6
plus non HDL-c ^{††}	1.38 (1.24-1.54)	35.1	1.35 (1.17-1.55)	17.1	1.19 (0.97-1.47)	2.7	1.52 (1.16-1.99)	9.3	1.46 (1.15-1.86)	9.4
plus TG ^{††}	1.39 (1.25-1.55)	37.1	1.35 (1.17-1.56)	17.3	1.18 (0.95-1.46)	2.3	1.56 (1.19-2.04)	10.5	1.46 (1.15-1.87)	9.5
Independent of WHR										
per 5 kg/m ²	1.31 (1.17-1.47)	21.7	1.27 (1.10-1.48)	10.2	1.07 (0.86-1.35)	0.4	1.42 (1.07-1.89)	6.0	1.43 (1.11-1.84)	7.6
plus HbA1c	1.28 (1.14-1.44)	17.3	1.24 (1.06-1.44)	7.5	1.05 (0.84-1.32)	0.2	1.37 (1.02-1.83)	4.4	1.37 (1.05-1.78)	5.4
plus SBP	1.26 (1.13-1.42)	15.7	1.23 (1.05-1.43)	6.9	1.03 (0.82-1.30)	0.1	1.31 (0.97-1.76)	3.2	1.34 (1.04-1.74)	4.9
plus HDL-c	1.30 (1.16-1.46)	20.8	1.27 (1.09-1.47)	9.7	1.07 (0.85-1.34)	0.3	1.43 (1.08-1.91)	6.1	1.41 (1.09-1.81)	7.0
plus non HDL-c	1.30 (1.16-1.46)	21.3	1.27 (1.10-1.47)	10.0	1.08 (0.86-1.35)	0.4	1.41 (1.06-1.87)	5.6	1.42 (1.10-1.83)	7.5
plus TG	1.31 (1.17-1.47)	22.5	1.27 (1.10-1.48)	10.3	1.07 (0.85-1.34)	0.3	1.44 (1.09-1.91)	6.4	1.42 (1.10-1.82)	7.3

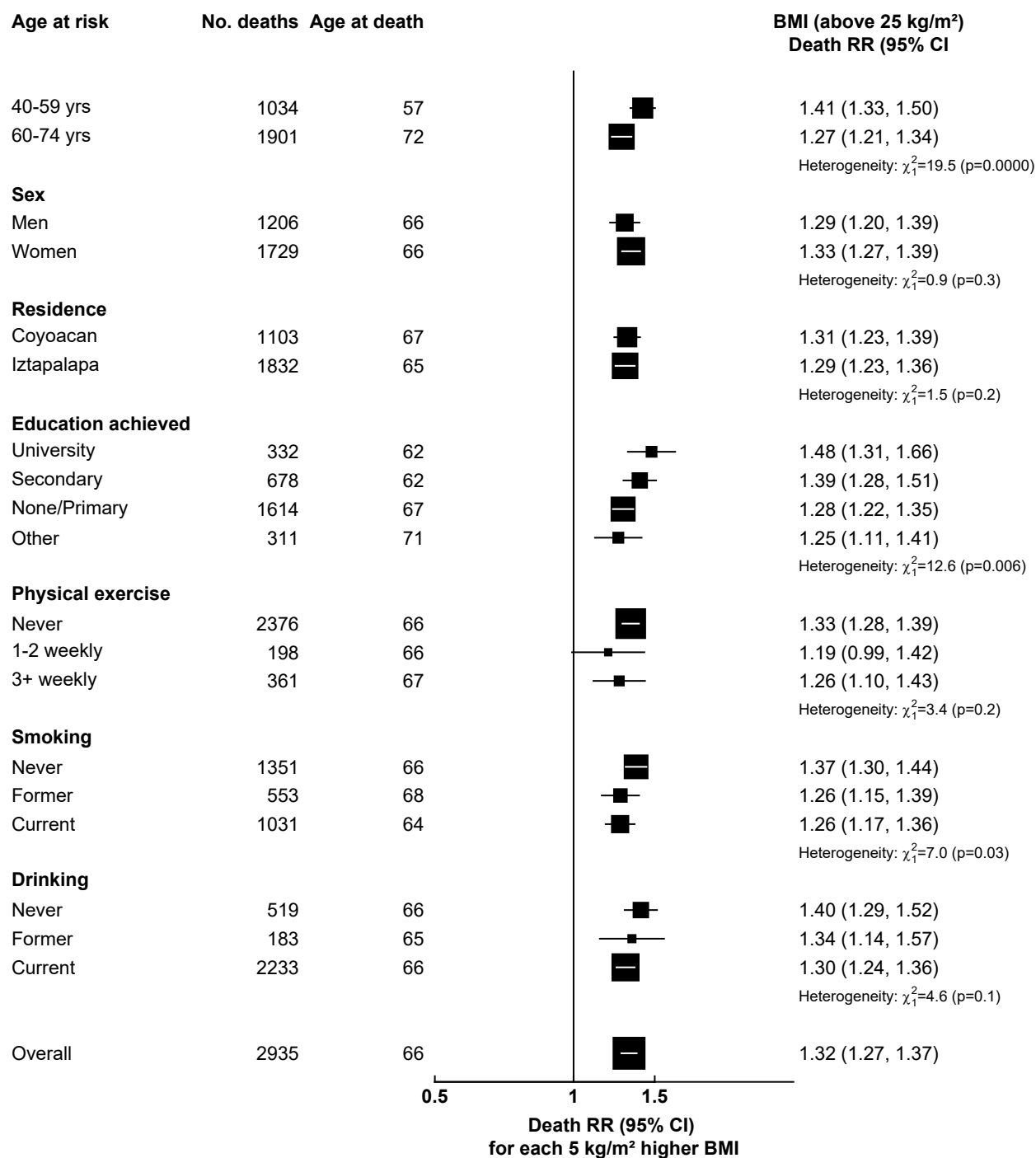
Analyses as per Table 5.3, now restricted to those with complete information on NMR lipids. [†]Main model adjusted for confounders. ^{††}Further adjustment of the main model for that mediator only. IHD=Ischaemic Heart Disease. *Refers to diabetic crises. SBP=systolic blood pressure; HbA1c=glycosylated haemoglobin; HDL-c= high-density cholesterol; TG=triglycerides.

Figure 5.9: Overall relevance of each 5 kg/m² higher BMI to cancer mortality at ages 40-74 years (previously-diagnosed or screen-detected diabetes, other chronic disease at baseline, and the first 5 years of follow-up excluded)



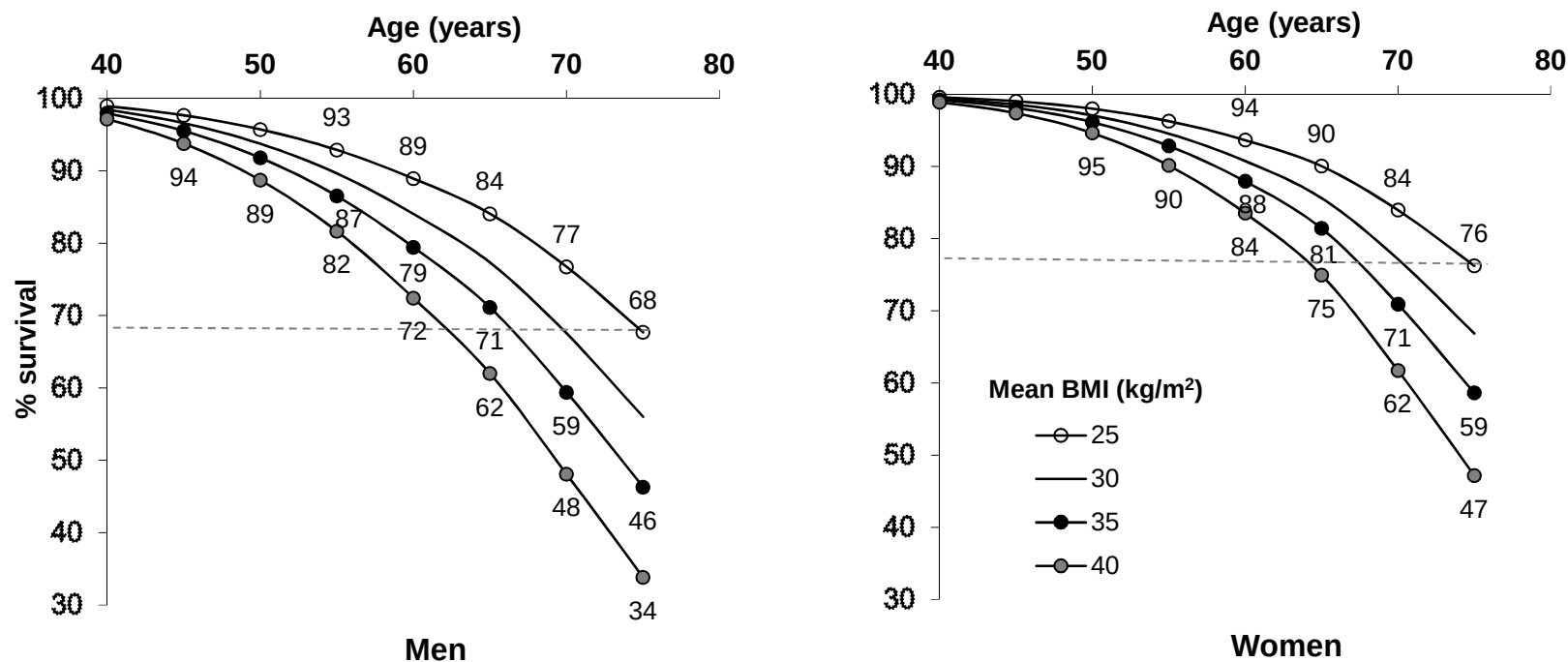
Analyses and conventions as per Figure 5.6., now restricted to ages 40-74 years.

Figure 5.10. Relevance of BMI (above 25 kg/m²) to all-cause mortality at ages 40-74 years, by strata of confounders



Analyses as per Figure 5.6, now restricted to those aged 40-74 years.

Figure 5.11: BMI versus expected survival from age 40 at 2016 Mexican mortality rates, at different BMI levels



Estimated effects of BMI on 40-year survival from age 40 years. The age- and sex-specific national death rates for Mexico for the year 2016 are assumed to correspond to a population with mean BMI 29 kg/m². The all-cause mortality death RR associated with BMI throughout the range ≥ 25 kg/m² is then applied to these rates to estimate death rates for the four groups shown: BMI < 25 kg/m²; BMI 30-34.9 kg/m² (i.e., grade 1 obesity, 26% of the study population, mean 32 kg/m²); BMI 35-39.9 kg/m² (i.e., grade 2 obesity, 8% of the study population, mean 37 kg/m²); and BMI 40-49.9 kg/m² (3% of the study population, mean 43 kg/m²).

Chapter 6: Predicted Fat Mass Index and mortality

Abstract

High levels of BMI are associated with higher risk of all-cause mortality, but the association throughout the full range of BMI is non-linear, including with mortality from vascular or metabolic causes. Total body mass reflects both fat and lean mass, which may have very different effects on disease-specific risk, and they might be more informative than BMI for assessing the 'true' relevance of excess adiposity to such diseases. Nonetheless, the evidence available on the association of fat mass with cause-specific mortality in Mexican populations is very limited. This chapter examined the relevance of predicted fat mass index (FMI), including at a given lean mass index (LMI) calculated analogous to BMI, to the 16-year risk of cause-specific mortality at ages 40-74 years, among 145,659 Mexican adults from the Mexico City Prospective Study. Among those with glycosylated haemoglobin (HbA1c) below 7%, without diabetes or other chronic diseases at baseline, who survived more than 5 years, predicted FMI had a positive J-shaped association with all-cause mortality at ages 40-74 years. However, after additional adjustment for predicted LMI, the association of FMI with mortality became stronger, and approximately log-linear. The risk of mortality was particularly strong for vascular or metabolic causes, with no threshold levels throughout the ranges of predicted FMI. Each 1 SD higher FMI was associated with 22% increased risk for all-cause mortality (RR=1.22; 95% CIs 1.18-1.25), including a 31% increased mortality from vascular-metabolic causes (RR=1.31; 1.26-1.37). At a given LMI, each 1 SD higher FMI was associated with 31% increased risk for all-cause mortality (RR=1.31; 1.24-1.37) and 40% increased mortality from a vascular-metabolic cause (RR=1.40; 1.31-1.50). The association of FMI with mortality was stronger at

ages 40 to <60 years (RR=1.29; 1.22-1.35) than at ages 60 to <75 years (RR=1.20; 1.15-1.24), and were not materially affected by sex, smoking, or other confounders. In conclusion, in this Mexican population, predicted FMI had strong positive effects on vascular, metabolic, and other causes of death. Mortality risk with FMI (given LMI) was stronger than mortality risk with BMI, with no evidence of a threshold throughout the ranges studied.

6.1 Background

BMI is a widely-used marker of adiposity in epidemiological studies, however its association with mortality is non-linear, including with vascular-metabolic deaths, even in large studies of never smokers with prolonged follow-up, which took account of pathological weight loss from pre-existing diseases.¹⁻⁴ It has been suggested that lean mass (LM) confounds the true relevance of fat mass (FM) to mortality, and separating the effects of FM from those of LM might explain the non-linear association of BMI with mortality.^{5,6} Indeed, a recent Mendelian Randomization study, involving 0.36 million adults from the UK Biobank demonstrated largely opposing effects of genetic FMI and genetic LMI (defined by 82 mutually exclusive single-nucleotide polymorphisms) with several vascular diseases. For example, each 1 kg/m² higher genetic FMI was associated with a 8% higher risk of coronary artery disease, a 22% higher risk of heart failure, and a 38% higher risk of ischemic stroke, whereas the risk associated with each 1 kg/m² higher genetic LMI was 1% higher for coronary artery disease, 8% lower for heart failure, and 25% lower for ischemic stroke, respectively.⁷ By contrast, the observational evidence from the same cohort suggests that among the UK Biobank participants without chronic disease at baseline who survived for at least 2 years and were followed for 7 years, bio-impedance (BIA) measured FM percentage was positively associated with all-cause

mortality, but its association with vascular mortality was inversely J-shaped in men and negative in women.⁸ While large genetic studies are preferable for reliably assessing the life-long consequences of body composition to specific causes of death, such studies are challenging to conduct in low or middle-income countries, for they require substantial resources. Therefore, observational epidemiology relying on more easily accessible markers of body composition from large prospective cohorts, often remains the only option for studying mortality associated risk in many populations.¹⁵ However, observational studies of body-composition and mortality are limited, compared to conventional studies of anthropometric markers of adiposity. In addition, the observational evidence on body composition and mortality have reported conflicting results, partly due to the relatively small sample-size of such studies, the different approaches for addressing reverse-causality bias, or due to differences in length of follow-up between studies (**S6** details the findings from the systematic literature review). For example, one recent study limited to 38,000 North-American men without vascular disease or cancer at recruitment, who survived for at least 10 years, and were followed for 21 years, showed linear positive associations of BIA-estimated total FM with all-cause and vascular mortality.⁹ By contrast, a smaller North-American study of 16,415 adults without chronic disease at baseline who survived for at least 5 years, and were followed for 19 years, described U-shaped associations of FM percentage with all-cause mortality in men, and J-shaped associations in women, with a 80% and a 20% higher risks of death above a total FM of 40%, respectively.¹⁰ Another study of 10,329 Mexican-Americans from the National Health Nutrition and Examination Survey, who were followed for 11 years, showed linear positive associations of BIA-measured FM with all-cause and diabetic mortality, but for cardiovascular deaths, the risk was inverse with higher FM percentage, yet positive with total FM.¹¹ In this study, each 5% higher FM was associated with a 6% higher risk for all

cause mortality, including a 20% higher risk for diabetic deaths, but a 9% lower risk for cardiovascular deaths. Nonetheless, this Mexican-American study was too small to reliably assess mortality risk, and in addition it failed to account for pre-existing medical diseases at the time body-composition was measured. Therefore, it remains unknown how the separate and joint relevance of different markers of body fat-mass compares to that of BMI in contemporary Mexican populations.

This chapter examined the relevance of total FMI, overall and independent of LMI, to mortality from vascular, metabolic and other specific causes, among 145,659 men and women aged 40-89 years, without diabetes or other chronic disease at baseline, who survived for more than 5 years since recruitment in the Mexico City Prospective Study (MCPS). FMI and LMI were calculated analogous to BMI, as indices standardised to height-squared (kg/m^2), such that their sum equals total BMI. As described in **Chapter 3 (Section 3.2.1)**, fat and lean mass were first predicted in all the participants, as a *function* of age, sex, height, weight and waist circumference, using Mexican-specific equations from the NHANES study. The predicted measures were subsequently 'validated' in the subset of participants with bio-impedance measures at resurvey in the MCPS cohort (see **Figure 4.2** in **chapter 4** for correlations). For analyses of mortality, predicted FMI was considered as a continuous exposure and was defined epidemiologically. The shapes of the associations of predicted FMI with mortality were assessed with the FMI grouped by the sex-specific quintiles of the baseline distributions, with the bottom and top groups further divided into two groups corresponding to the 10% of the distributions. (For comparing the shapes of the associations of FMI with those from BMI in chapter 5, some sensitivity analyses were conducted with predicted FMI grouped by the *BMI-matched-prevalence* of the WHO

recommended 'clinical' groups. Nonetheless, because large recent studies of body composition suggest that adiposity represents a *continuous risk*, modified quintiles of the exposure are preferable to fixed ranges). Cox models were conducted with the same adjustments as in chapter 5, with emphasis on premature deaths at ages 40-74 years, and some additional analyses at ages 75-89 years. The continuous risk for mortality with FMI was subsequently assessed per each 1 SD higher FMI throughout the full ranges, both overall and independent of predicted LMI. Analyses assessed the overall, age, sex and cause-specific risk, with adjustment for traditional confounders. Additionally, mortality risk with total fat mass (in kilograms), both overall and independent of total lean mass (in kilograms) and of height, was also assessed. Similar to the previous chapter, sensitivity analyses included estimates *restricted* to never-smokers, with *inclusion* of well-controlled diabetes, accounting for the additional effects of traditional vascular and metabolic mediators of adiposity, as well as correction for regression dilution.

6.2 Study participants and adiposity related characteristics

The participants included in the analyses of FMI and mortality were the same as in analyses of BMI (details in **Section 5.2 of Chapter 5**). Those with chronic disease at recruitment, other than diabetes, and incomplete data were excluded from all analyses. Assessment of reverse causality bias from previously-diagnosed or screen-detected diabetes, and inclusion of all years of follow-up involved 145,659 participants aged 35-89 years. Analyses among those without diabetes (or other chronic disease at baseline) who survived for at least 5 years after recruitment into the study, included 38,254 men and 80,162 women aged 40-89 years, of which 95,658 men and women aged 40-74 years were included in analyses of premature mortality.

On average, among those aged 35 and 89 years, mean predicted fat mass was 22 ± 6 kg in men and 30 ± 8 kg in women. Predicted total FMI represented 39.3% of the total BMI, and mean FMI was 8.2 ± 2.3 kg/m² in men and 13.2 ± 3.3 kg/m² in women. Throughout the ranges studied (FMI of 0.8-32.3 kg/m², **S10**), those with higher levels of FMI were less likely to live in the wealthier of the two districts (Coyoàcan), less likely to be physically active, less likely to smoke, and less likely to have been educated to college or university level (**S17**). In addition, those with higher levels of FMI had higher levels of abdominal adiposity and blood pressure, and were more likely to have undiagnosed diabetes, and among women (but not in men), more likely to have previously-diagnosed diabetes.

6.3 Illustration of reverse causality bias

The impact of previously-diagnosed or screen-detected diabetes at recruitment and of the deaths occurring during the first 5 years of follow-up on the associations of predicted FMI with mortality, was investigated similar to BMI (**Chapter 5, section 5.2**). Supplementary figures **S40** and **S41** show the subsequent biases and largely misleading conclusions, if no exclusions had been implemented. Similar to BMI, the association for predicted FMI with all-cause mortality when participants with diabetes and all years of follow-up were included, would have been ‘U-shaped’ (**S40**), due to the strongly inverse associations with mortality in participants with previously-diagnosed or screen-detected diabetes, and also by lack of an association with deaths during the first 5 years of follow-up among those without diabetes or other chronic disease at recruitment (diagnosed cancer, cirrhosis of the liver, vascular, respiratory, or chronic kidney disease; **S41**). Consequently, the following sections present the relevance of FMI to mortality after exclusion of those with diabetes in addition to other

chronic disease at recruitment, and of deaths that occurred during the first 5 years of follow-up.

6.4 FMI and total mortality

Predicted FMI was positively J-shaped associated with premature mortality from all-causes at ages 40-74 years, and after mutual adjustment for LMI, the association became stronger and approximately log-linear throughout the ranges (**Figure 6.1**). The patterns of these associations were somewhat stronger in women compared to men (**Figure 6.2**), including in analyses with residuals of FMI and LMI (**S42**). The RR for all-cause mortality comparing those in the top versus bottom tenth of the distributions of predicted FMI at baseline was 1.68 (95% CIs 1.45-1.94), and for a given amount of LMI, the corresponding RR was 2.33 (1.81-3.02). On average, each 1 SD higher FMI (corresponding to 2.78 kg/m²) was associated with a 22% higher risk of all-cause mortality at ages 40-74 years (RR=1.22; 1.18-1.25), a risk that strengthened after accounting for predicted LMI to 31% (RR=1.31; 1.24-1.37). By comparison, each 1 SD higher FM (corresponding to 6.99 kgs) was associated with a 21% higher risk of premature death from any cause (RR=1.21; 1.17-1.25), an association that strengthened after adjustment for LM (RR=1.32; 1.26-1.38), but attenuated slightly after additional adjustment for height (RR=1.29; 1.23-1.36). Each 1 SD higher FMI was associated with 26% increased mortality from any cause at ages 40-74 years among never smokers (RR=1.26; 1.21-1.31), and 20% increase in mortality after inclusion of those with well-controlled diabetes (RR=1.20; 1.16-1.23).

6.5 Age and sex-specific associations of FMI to total mortality

Similar to BMI, the relevance of FMI to all-cause mortality was stronger at ages 40-59

years and much weaker at ages 75-89 years, but the absolute risk for total mortality increased with age (**S28**). Across the full ranges of the predicted FMI, each 1 SD higher FMI was associated with 29% increased mortality risk at ages 40-59 years (RR=1.29 95% CIs 1.22-1.35), 20% increased mortality at ages 60-74 years (RR=1.20; 1.15-1.24), and 13% increased mortality at ages 75-89 years (RR=1.13; 1.09-1.17; X^2 for trend=18.05, p-value=0.001), with broadly similar estimates in men as in women at every age (**Figure 6.3**). After adjustment for predicted LMI, the mortality risk associated with each 1 SD higher FMI was 37% higher at ages 40-59 years (RR=1.37; 1.26-1.49), 27% higher at ages 60-74 years (RR=1.27; 1.19-1.36), and 18% higher at ages 75-89 years (RR=1.18; 1.11-1.25; X^2 for trend=8.61, p-value=0.01; **Figure 6.3**). Given the stronger associations of FMI with mortality risk at ages 40-74 years compared to mortality risk at ages 75-89 years, the next section focuses on premature mortality before the age of 75 years.

6.6 FMI and premature mortality from specific causes

FMI was strongly positively associated with mortality from any vascular or metabolic causes, with no evidence of a threshold throughout the ranges studied, whereas the association of FMI with mortality from other non-vascular or non-metabolic causes was U-shaped, and remained J-shaped even after adjustment for LMI (**Figure 6.1**). The RR for mortality comparing those in the top versus the bottom tenth of the distributions of predicted FMI at baseline was 3-fold higher for any vascular-metabolic causes (RR=3.13; 2.16-4.54), but less than 2-fold higher for any non-vascular, non-metabolic causes combined (1.81; 1.27-2.59). Alternative analyses of total FM in relation to vascular-metabolic and non-vascular-metabolic mortality at ages 40-74 years, showed similar patterns, including for estimates at a given total LM and height (**Figure 6.4**).

The association of FM at a given LM appeared stronger than that of FMI at a given LMI, but additional adjustment for height ultimately attenuated the strength of the associations, such that the RR for vascular-metabolic mortality with higher FM adjusted for LM (comparing those in the top versus bottom 10% of the distributions), decreased from 3.90 (2.84-3.35) to 2.91 (2.05-4.12), (which was largely comparable to the RRs observed for FMI at a given LMI). By contrast, the relevance of FM to mortality from any non-vascular, non-metabolic causes did not materially alter after accounting for LM and for height. Furthermore, analyses stratified by different levels of BMI, showed no evidence that among those with a low BMI in this cohort, the relevance of FM or FMI to vascular-metabolic mortality (after accounting for LM or LMI) is stronger than among those with a higher BMI (**S43, S44**).

6.6.1 Age and sex-specific associations of FMI to vascular-metabolic mortality

The associations of FMI with vascular-metabolic mortality were somewhat stronger in women compared to men (**Figures 6.5, S42**), and stronger at younger than at older ages (**Figure 6.6**). Specifically, each 1 SD higher FMI was associated with 39% increased vascular-metabolic mortality at ages 40-59 years (RR=1.39; 1.29-1.49), 28% increased mortality at ages 60-74 years (RR=1.28; 1.21-1.35), and 18% increased mortality at ages 75-89 years (RR=1.18; 1.12-1.24; X^2 for trend=14.4, p-value=0.0007). After adjustment for LMI, each 1 SD higher FMI was associated with 39% increased vascular-metabolic mortality at ages 40-59 years (RR=1.39; 1.23-1.56), 38% increased mortality at ages 60-74 years (RR=1.38; 1.26-1.51), and 27% increased mortality at ages 75-89 years (RR=1.27; 1.17-1.37; X^2 for trend=2.4, p-value=0.3). Given that the associations of FMI to mortality are much stronger before age 75 years than at older ages, the following sections present the findings for

premature mortality from various causes at ages 40-74 years.

6.6.2 FMI and specific mortality from vascular or metabolic causes

The relevance of FMI to mortality varied with the different underlying causes of death (**Figure 6.7** shows the shapes of these associations). Predicted FMI was associated positively with mortality from specific vascular or metabolic diseases, and after adjustment for LMI, the relevance of FMI to premature mortality from cardiac, cerebrovascular, renal disease, acute diabetic crises, and hepatobiliary causes appeared stronger and log-linear, with no evidence of a threshold (**Figure 6.8**). Each 1 SD higher FMI (corresponding to 2.78 kg/m² at baseline), was associated with a 31% (RR=1.31; 1.26-1.37) higher risk for premature mortality from any vascular-metabolic causes, including a 48% higher risk for renal or acute diabetic causes of death (RR=1.48; 1.34-1.63), and a 28% higher risk for any hepatobiliary causes (RR=1.28; 1.17-1.40). For all the vascular causes combined, a 1 SD higher FMI was associated with a 27% increased mortality at ages 40-74 years (RR=1.27; 1.20-1.35) which was largely similar for the various component diseases, including a 25% higher risk from any cardiac deaths (RR=1.25; 1.17-1.34) and a 20% higher risk from any cerebrovascular deaths (RR=1.20; 1.07-1.34; **Figure 6.9**). For comparison, the mortality risk associated with each 1 SD higher BMI (4.71 kg/m²) across the full ranges was 29% higher for any vascular-metabolic causes (RR=1.29; 1.23-1.35) and 26% higher for any vascular causes (RR=1.26; 1.19-1.33), and slightly attenuated at a given WHR, specifically, 24% higher for any vascular-metabolic causes (RR=1.24; 1.18-1.30), and 22% for any vascular causes combined (RR=1.22; 1.14-1.29).

The estimates with total FM, both overall and at a given LM and height, were largely

similar to those with total FMI (**S45**). On average, each SD higher total FM (corresponding to 6.99 kgs) was associated with a 27% higher risk for any vascular or metabolic deaths combined (RR=1.27; 1.21-1.33), a more extreme risk for premature death from renal or acute diabetic causes (RR=1.49; 1.35-1.64), and a more modest risk for premature death from hepatobiliary causes (RR=1.20; 1.10-1.32). The risk of higher FM with any vascular deaths was 23% (RR=1.23; 1.16-1.31), and it was broadly comparable for premature death from stroke and cardiac causes (RR=1.15; 1.02-1.30 and 1.22; 1.14-1.31, respectively). After adjustment for total LM, the risk for vascular-metabolic mortality with higher total FM nearly doubled (RR=1.36; 1.22-1.52 for cardiac causes, 1.58; 1.31-1.91 for stroke, 1.57; 1.35-1.83 for renal or diabetic causes, and 1.41; 1.22-1.62 for hepatobiliary causes). Further adjustment for height attenuated these RRs slightly (**S45**).

The death RRs for vascular-metabolic causes associated with higher FMI were consistent when analyses were restricted to never-smokers (1.36; 1.28-1.44, **Table 6.1**), and somewhat weaker after including those with previously diagnosed diabetes but good glycaemic control based on HbA1c levels below 7% (1.26; 1.21-1.31, **S47**). Specifically, the RRs for mortality at ages 40-74 years among never smokers were 1.34 (1.25-1.45) for any vascular deaths, 1.25 (1.13-1.38) for cardiac deaths, 1.34 (1.15-1.56) for stroke deaths, 1.52 (1.33-1.73) for renal or diabetic deaths, and 1.28 (1.12-1.46) for hepatobiliary deaths. By comparison, the RRs after inclusion of those with well-controlled diabetes were 1.24 (1.18-1.31) for any vascular deaths, 1.23 (1.15-1.32) for cardiac deaths, 1.16 (1.04-1.30) for stroke deaths, 1.30 (1.19-1.42) for renal or diabetic deaths, and 1.27 (1.16-1.39) for hepatobiliary deaths.

The effects of correction for regression dilution were minimal, as the associations of usual levels of FMI with the various causes of death were largely unaltered (**S48 and S49**). Before adjustment for LMI, higher usual FMI was associated with somewhat lower mortality risk, compared to estimates for equivalent increases in usual BMI above 25 kg/m². However, compared with the effects of usual BMI across the full ranges, the RRs with usual FMI accounted for LMI were slightly higher. For instance, the death RR with each 4.31 kg/m² usual BMI (equivalent to 1 usual SD) across the full ranges, was 1.25 (1.19-1.31) for any vascular-metabolic causes, and 1.18 (1.14-1.22) for all-causes, while the RR with each 2.67 kg/m² usual FMI (equivalent to 1 usual SD) across the full ranges, was 1.32 (1.27-1.38) for any vascular-metabolic causes, and 1.23 (1.19-1.27) for all-causes, respectively (**S48**). After additional adjustment of FMI for LMI, these associations were nearly twice as strong (specifically, the RRs were 1.42; 1.32-1.53 for vascular-metabolic deaths, and 1.32; 1.25-1.39 for deaths from any cause; **S49**).

6.6.3 Mediation effects of traditional vascular and metabolic traits on vascular-metabolic mortality

Tables 6.2 and 6.3 show the death RRs for the major vascular, renal or acute diabetic causes of premature mortality at a given FMI, before and after additional account for traditional mediators (HbA1c, blood pressure and selected lipids). Overall, the RR for any vascular-metabolic deaths with higher FMI were largely unaltered after adjustment for HbA1c, and after adjustment for SBP, the RR reduced modestly (from 1.31; 1.26-1.37 to 1.26; 1.21-1.32, consistent with comparable reductions in the Wald chi²-statistic from 152.7 to 107.3; **Table 6.2**). Similar changes in the magnitude of the associations (of 1-2 % reduction in mortality risk after accounting for HbA1c, and of 4-

6% reduction after accounting for SBP), were observed for deaths from any vascular or ischaemic causes, and also for estimates of FMI at a given LMI. For deaths from cerebrovascular and renal or acute diabetic causes, the reduction in RR appeared more pronounced after accounting for SBP (from 1.19; 1.06-1.34 to 1.10; 0.97-1.24, and from 1.48; 1.34-1.63 to 1.41; 1.27-1.56, respectively, corresponding to reductions in the Wald χ^2 -statistic from 8.6 to 2.2, and from 61.2 to 44.2, respectively; **Table 6.2**). Additional adjustment for HbA1c also suggested somewhat larger reductions in the RRs for renal or acute diabetic deaths, when compared to those for ischaemic, cerebrovascular or other vascular causes (from 1.48; 1.34-1.62 to 1.42; 1.29-1.57, corresponding to reductions in the Wald χ^2 -statistic from 61.2 to 46.3).

Analyses among participants with additional measures of lipids showed comparable changes in the proportional hazards due to FMI after additional adjustment for HbA1c or SBP (**Table 6.3**), both before and after account for LMI. In this subset, preliminary analyses with additional adjustment for HDL-c, non HDL-c, and triglycerides, did not essentially alter the magnitude of the associations of FMI with premature death from any vascular-metabolic, ischaemic, cerebrovascular, or other vascular causes. A small reduction in mortality risk from renal or acute diabetic causes was observed after accounting for HDL-c (from 1.46; 1.21-1.76 to 1.43; 1.19-1.73, corresponding to a reduction in the Wald- χ^2 statistic from 15.9 to 14.4; **Table 6.3**). These findings were broadly consistent in analyses of FMI adjusted for LMI. In addition small reductions in the RRs with FMI at a given LMI were observed for mortality from ischaemic and renal or acute diabetic causes after additional adjustment for triglycerides (from 1.26; 0.96 to 1.65 to 1.23; 0.93-1.61, and from 1.58; 1.18-2.11 to 1.55; 1.15-2.07, respectively,

corresponding to a reduction in the Wald- χ^2 statistic from 2.8 to 2.2, and from 9.6 to 8.5, respectively).

6.6.4 FMI and mortality from specific non-vascular, non-metabolic causes

The association of FMI with premature mortality was weak for neoplastic causes, and non-linear for respiratory and infective causes (**Figure 6.7**). After adjustment for LMI, these associations became stronger and log-linear, both for respiratory and infective mortality, with no evidence of a threshold, while associations with cancer mortality reversed (**Figure 6.8**). Across the full ranges studied, each 1 SD higher FMI was associated with a 30% higher risk for respiratory mortality (RR=1.30; 1.19-1.41), a 29% higher risk for infective mortality (RR=1.29; 1.19-1.41), and a 7% higher risk for neoplastic mortality (RR=1.07; 1.01-1.14, **Figure 6.9**), which was broadly similar for the various cancer subtypes (**Figure 6.10**). After adjustment for LMI, each 1SD higher FMI was associated with 56% increased mortality from respiratory causes (RR=1.56; 1.37-1.78), 58% increased mortality from infective causes (RR=1.58; 1.40-1.79), and 4% lower neoplastic mortality (RR=0.96; 1.84-1.08, **Figure 6.9**). Again, the LMI-adjusted RRs per 1 SD higher FMI were comparable for most cancer subtypes, but appeared somewhat larger for breast cancer (RR=1.36; 0.96-1.93), and inverse with cancer of the stomach and oesophagus (RR=0.61; 0.41-0.91; **Figure 6.10**).

The estimates for mortality risk from specific cancers, respiratory and infective causes with total FM, both overall and at a given LM and height, were largely similar to those for total FMI (**S45-46**). On average, each 1 SD higher total FM (corresponding to 6.99 kgs) was associated with a 12% higher risk for any neoplastic deaths (RR=1.12; 1.06-1.19) and a 28% higher risk for infective deaths (RR=1.28; 1.18-1.39; **Figure 6.10**).

Additional adjustment for total LM, nearly doubled the RRs with equivalent increases in total FM for infective and respiratory causes (RR=1.59, 1.41-1.79 and 1.56, 1.37-1.77, respectively), but attenuated the RRs for cancer mortality importantly (RR=0.95; 0.86-1.05), with the largest changes in the magnitude of the associations observed for cancer of the oesophagus or stomach (from 0.87; 0.71-1.08 to 0.76; 0.54-1.06) and cancers of the lung or upper aero-digestive sites (from 0.96; 0.78-1.18 to 0.76; 0.54-1.05; **S46**). Further adjustment for height (in addition to total LM) appeared to strengthen the association of total FM to mortality from breast cancer (from 1.04; 0.76-1.42 to 1.31; 0.95-1.80), but did not materially alter the associations seen for the other cancer subtypes. Sensitivity analyses showed consistent results among never smokers (**Table 6.1**) and after inclusion of those with well-controlled diabetes (**S47**). Furthermore, the estimates for non-vascular-metabolic mortality risks were largely unaltered by correction for regression dilution (**S48 and S49**).

6.7 Effect-modification of mortality risk by levels of confounders

The RRs of premature mortality from any cause and from vascular-metabolic causes associated with each 1 SD higher FMI (given LMI) were similar within each age range, in men as in women, and were not materially affected by district of residence, level of education achieved, leisurely physical exercise, smoking status or drinking (**S50, S51**). Similarly, step-wise analyses for each of the confounders considered, indicated virtually no difference in the relative risk estimates for deaths associated with higher FMI after progressive adjustment for such confounders (**S52**) once age and sex were accounted for. By contrast, additional adjustment of FMI for LMI substantially strengthened the RR for all-cause mortality importantly (from 22% to 31%), and also the RR for vascular-metabolic mortality (from 31% to 40%).

6.8 Strengths and limitations

The present study is the largest analysis to comprehensively assess the association of predicted fat mass index with premature mortality from various causes of premature death in a contemporary Mexican population. This chapter employs a novel approach, by applying Mexican-specific anthropometric equations that reasonably predict fat and lean mass in a very large study in which measurement of DXA or bio-impedance analysis would have been logistically challenging to obtain. This approach extended previous analyses of BMI, and in particular, clarified that lean mass index obscures the 'true' association of FMI with mortality risk (particularly at the lower ranges of the distributions). The present findings therefore explain that the apparent non-linear associations of BMI with mortality is due to the confounding effects of LMI on mortality risk, for the association of FMI to mortality is otherwise nearly log-linear.

The additional strengths of this analysis include age and sex-specific mortality RR estimates, risks estimates for many vascular as well as non-vascular diseases and various cancer subtypes, and careful account of the impact of diabetes. Finally, the availability of repeat anthropometric measures enabled to assess the variability of the predicted FMI over time and to estimate mortality risk with usual, rather than baseline levels of the predicted levels of adiposity, although this adjustment barely had an effect, because the estimated RDR is (presumably) close to a value of 1. However, this analysis is importantly limited by the fact that predicted FM and LM are not accurate measures of the actual body-mass composition, as more precise measures from DXA would have been. The correlations between the bio-impedance measures and the NHANES predicted markers used in the present analysis were high, giving some confidence that the estimates from this analysis are reasonable indicators of what the

true associations would have been, should direct measures of body composition would have been available. Therefore, while the present findings are likely to be relevant for other Mexican adults, they might not be generalizable to other populations, particularly those with different body-compositions (i.e., Indians, Caucasians, Chinese). Finally, genetic markers of body composition and additional biomarker measures of lipid subtypes, renal, and liver function in the entire cohort, would have enabled further assessment mechanisms by which excess fat mass causes mortality from different diseases.

6.9 Conclusions

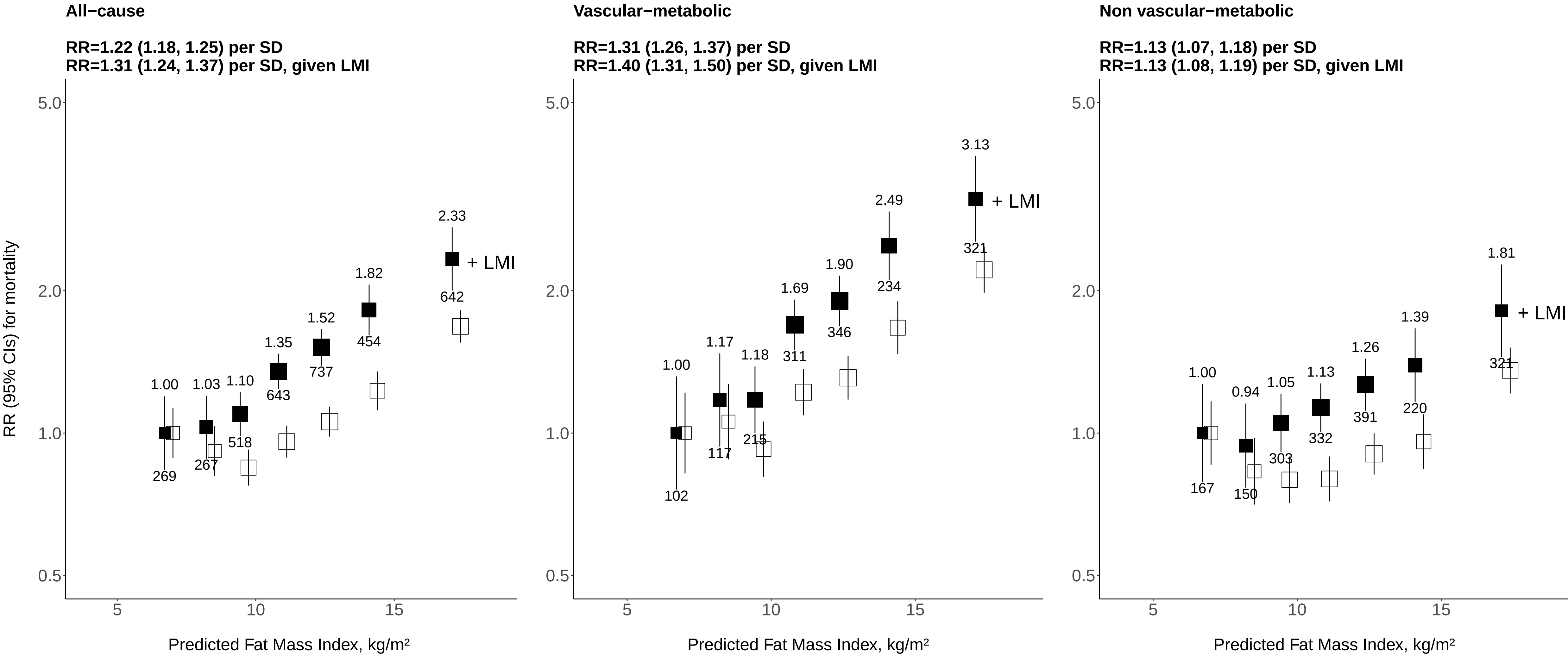
In this Mexican population, fat mass index (analogous to BMI) had strong positive effects on premature mortality, particularly from vascular, renal, and other metabolic causes. At a given LMI, the association of FMI to mortality was approximately log-linear, with no evidence for a threshold throughout the ranges studied. By contrast, in those with diabetes, weight loss (likely caused by poor glycaemic control, which is common in this cohort), substantially biased the associations seen with higher FMI. Among those without diabetes or other chronic disease at baseline, who survived for more than 5 years, each 1 SD higher FMI at a given LMI, was associated with 31% higher mortality from any causes, chiefly due to a 40% increased risk of death from vascular or metabolic causes. After controlling for LMI, individuals in the top 10% of the distribution of FMI had a 2-fold higher death rate from all-causes, and a 3-fold higher death rate from vascular-metabolic causes, compared with those in the bottom 10% of the distribution. These associations are stronger compared to the effects of BMI on mortality described in the previous chapter, and demonstrate that LMI confounds the true association of FMI (and implicitly of BMI) to mortality in this Mexican

population. The present findings further strengthen the evidence against previous suggestions of a 'Hispanic obesity paradox', and demonstrate that easily predictive markers of FMI are of substantial additional relevance.

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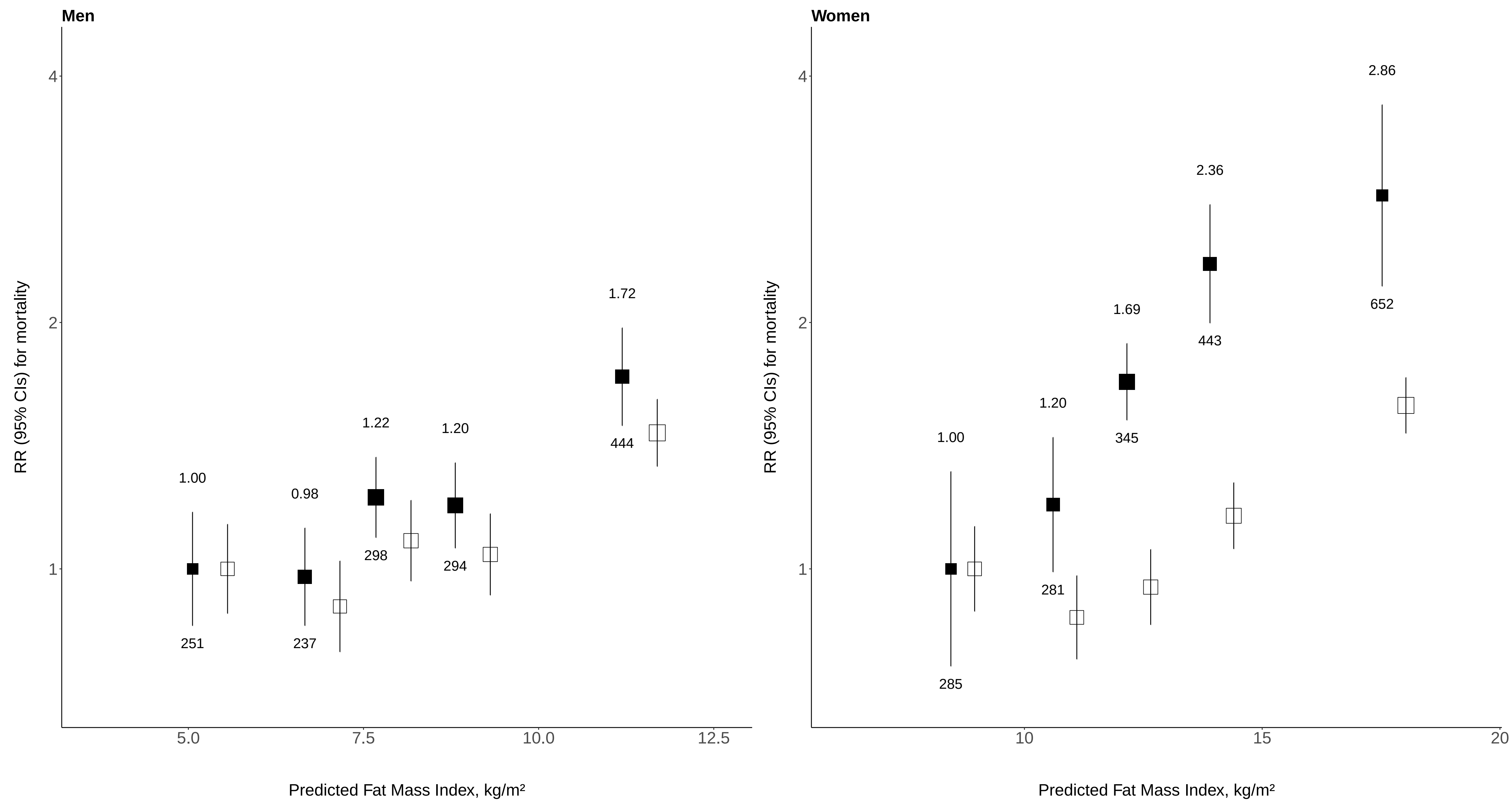
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Figure 6.1: Relevance of predicted FMI to mortality at ages 40–74 years
(those with HbA1c $\geq 7\%$, diabetes, other chronic disease at baseline, and the first 5 years of follow-up excluded)



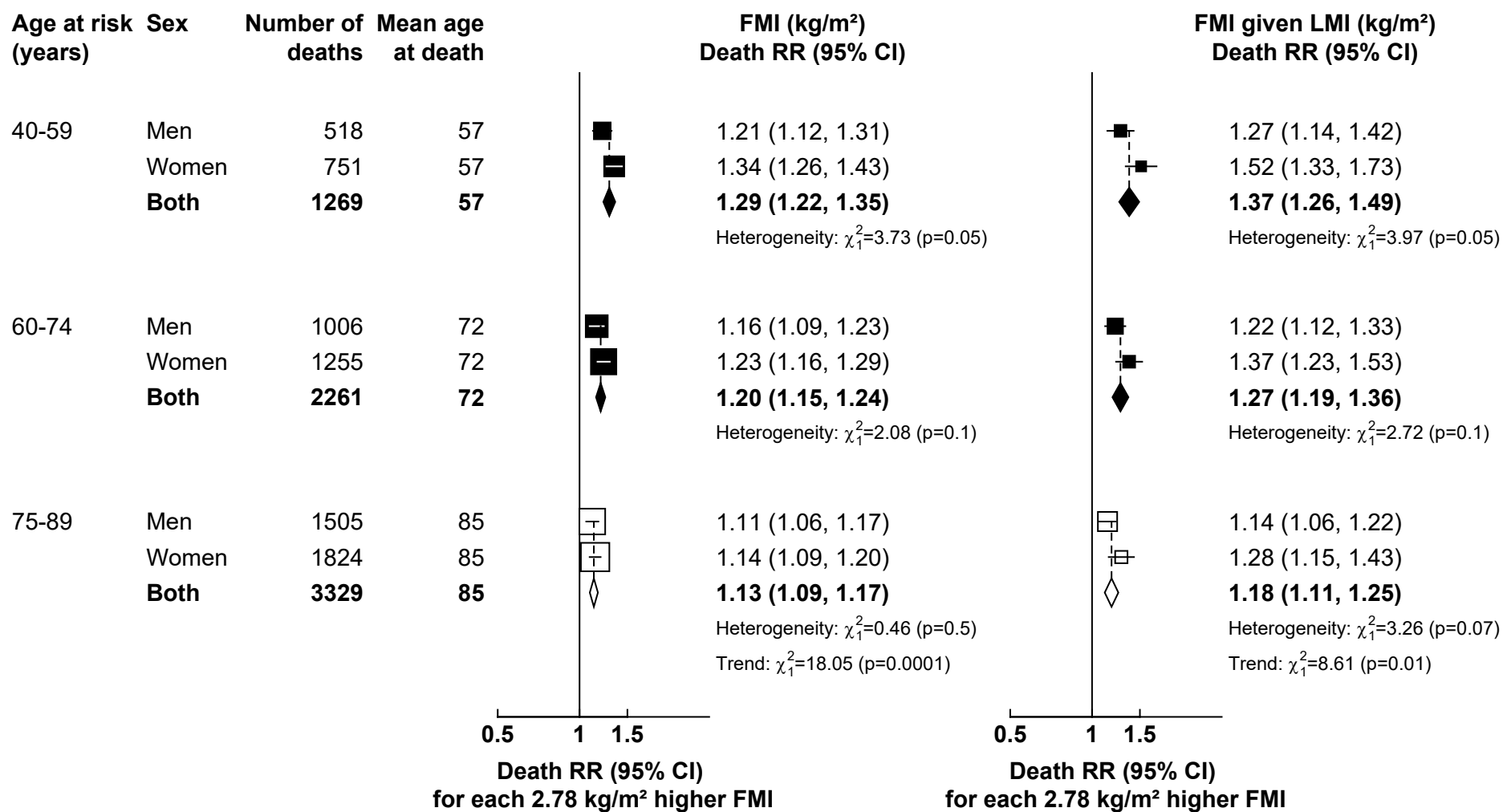
Fat Mass Index (FMI) and Lean Mass Index (LMI) were calculated analogous to BMI, from predicted fat and lean mass (details in footnote of Fig.4.2). The RRs shown above each square, are estimated with Cox models, accounting for age-attained and length of follow-up as underlying time-variables, adjusted for age (in 5-years bands), sex, district, education, physical exercise, alcohol or smoking status and amount. Adiposity markers are considered as sex-specific percentiles of 10% (reference), 20%, 40%, 60%, 80% and 90%, respectively. Each axis corresponds to the same number of SDs of the adiposity markers. The plotted RRs are centred at the mean. Square sizes are inversely proportional to the variance. Exclusions as per Table 4.1 (chapter 4), with the additional criteria specified in the title. Diabetes refers to previous diagnose or use of any anti-diabetic medication.

Figure 6.2: Sex-specific relevance of predicted FMI to all-cause mortality at ages 40–74 years



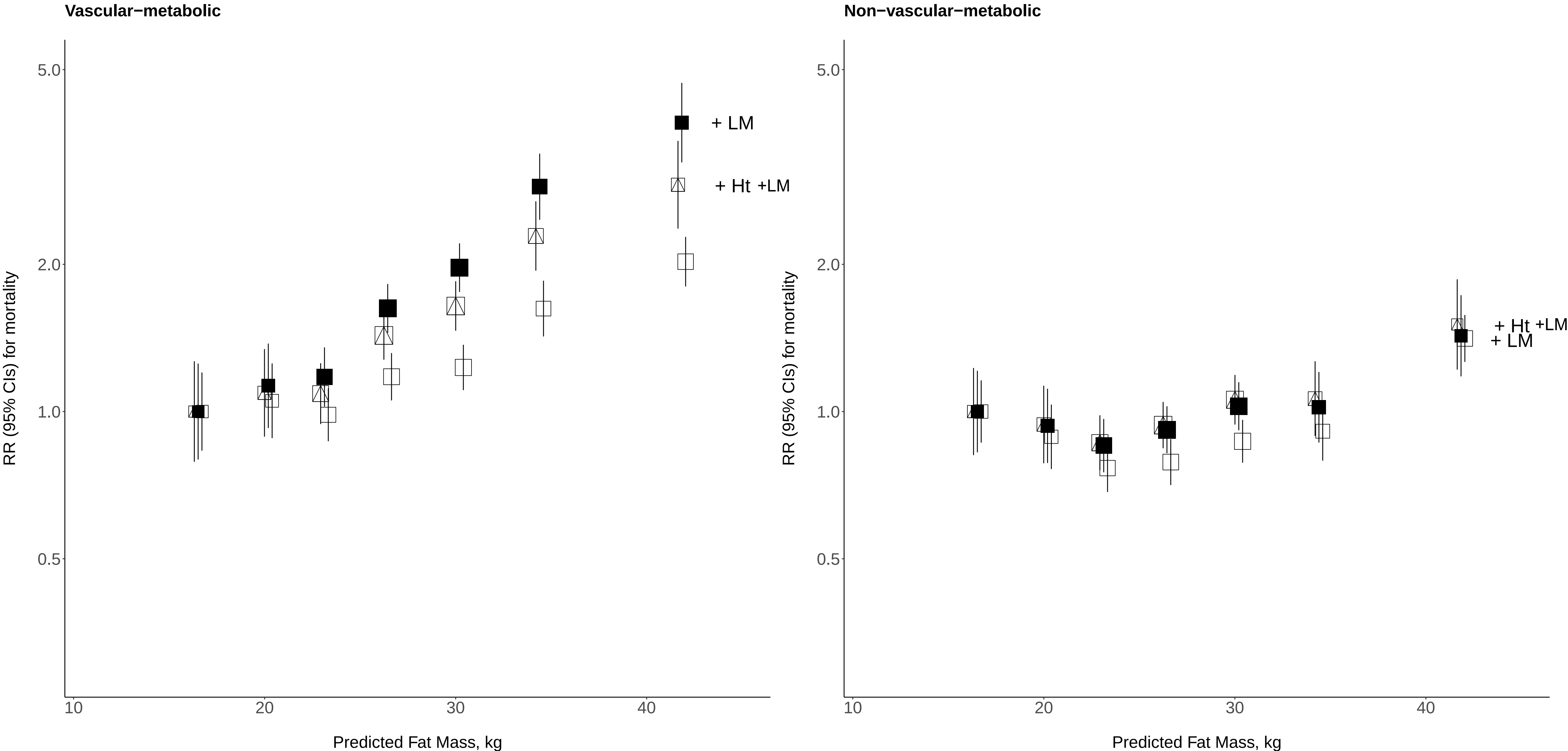
Analyses and conventions as per Figure 6.1. Adiposity markers grouped by five equally-sized groups of the sex-specific distributions at baseline. White squares represent overall associations, dark squares represent independent associations after further adjustment for LMI.

Figure 6.3: Overall and independent age and sex-specific relevance of FMI to all-cause mortality



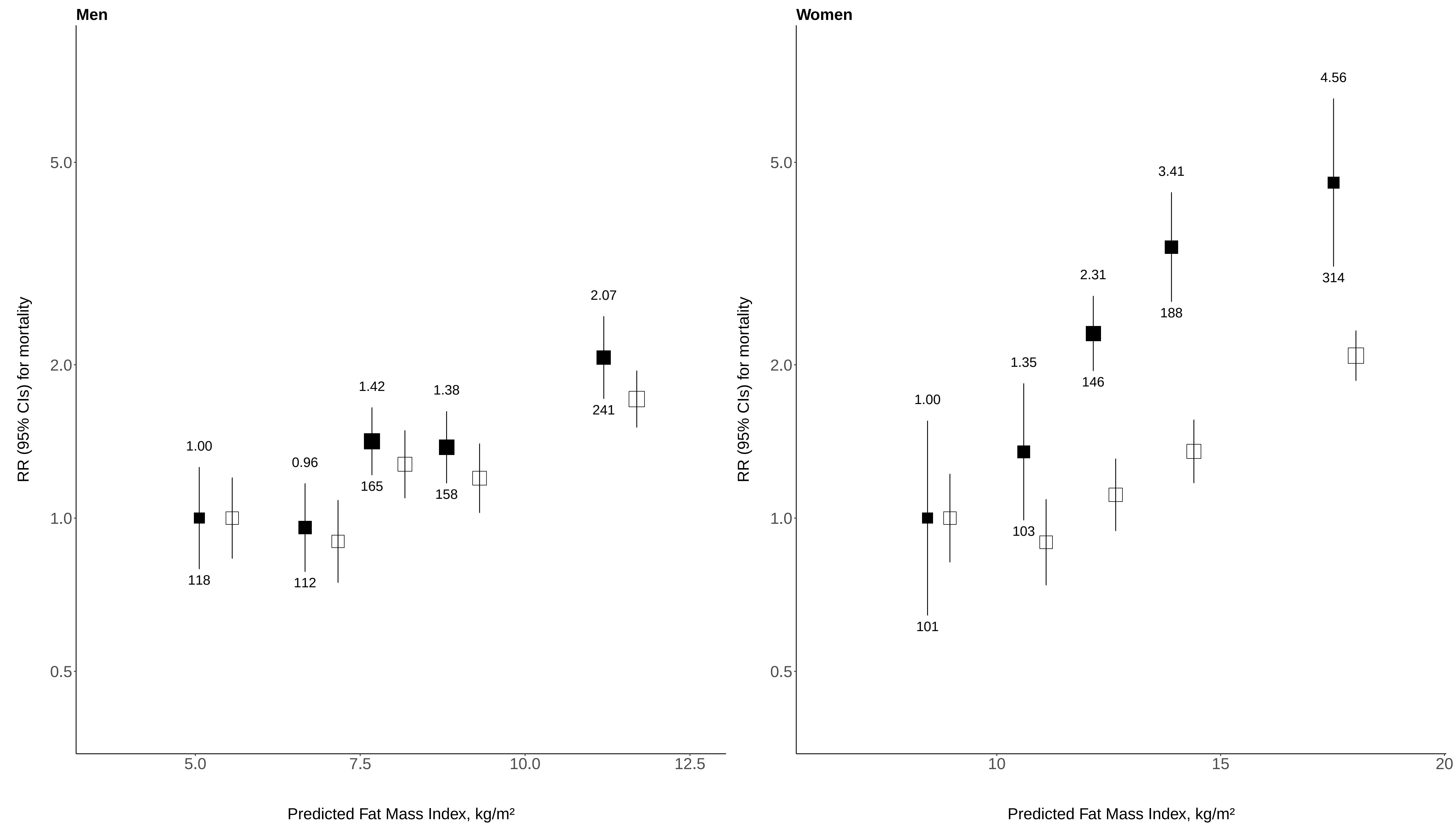
Analyses and conventions as per figure 6.1. Diamonds represent the values for men and women combined. The results for the oldest age group is left unshaded, as premature mortality at ages 40-74 years is of most interest. FMI = Fat Mass Index; LMI = Lean Mass Index.

Figure 6.4: Relevance of predicted fat mass to vascular-metabolic and non vascular-metabolic mortality at ages 40–74 years (diabetes, HbA1c $\geq 7\%$, other chronic disease at baseline, and first 5 years of follow-up excluded)



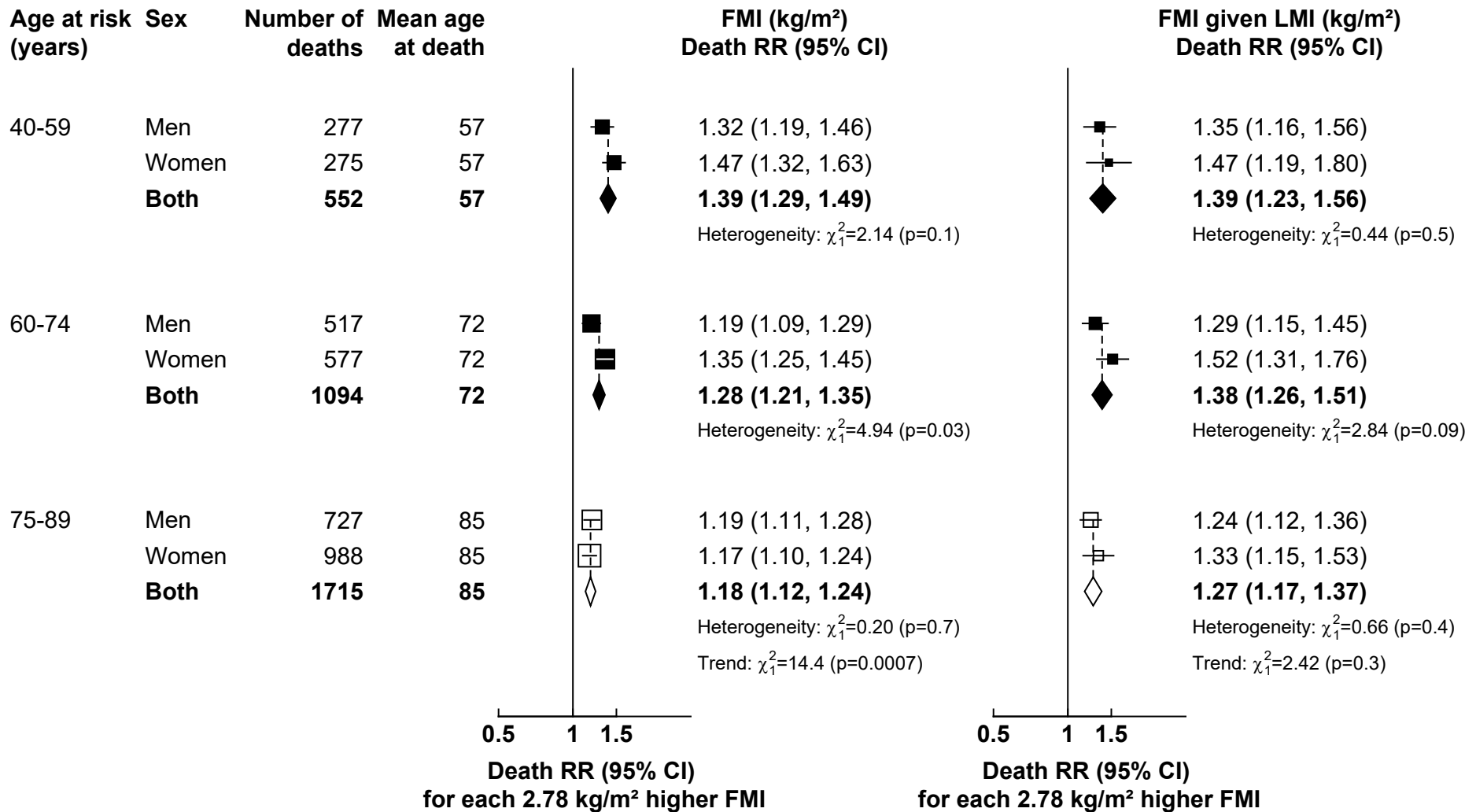
Analyses as per Figure 6.1. White squares represent overall associations of FMI irrespective of LMI and height. Dark squares represent the independent associations of FMI adjusted for LMI and for height, as indicated in the plots. FM = Fat Mass; LM = Lean Mass; Ht= Height.

Figure 6.5: Sex-specific relevance of predicted FMI to vascular-metabolic mortality at ages 40–74 years



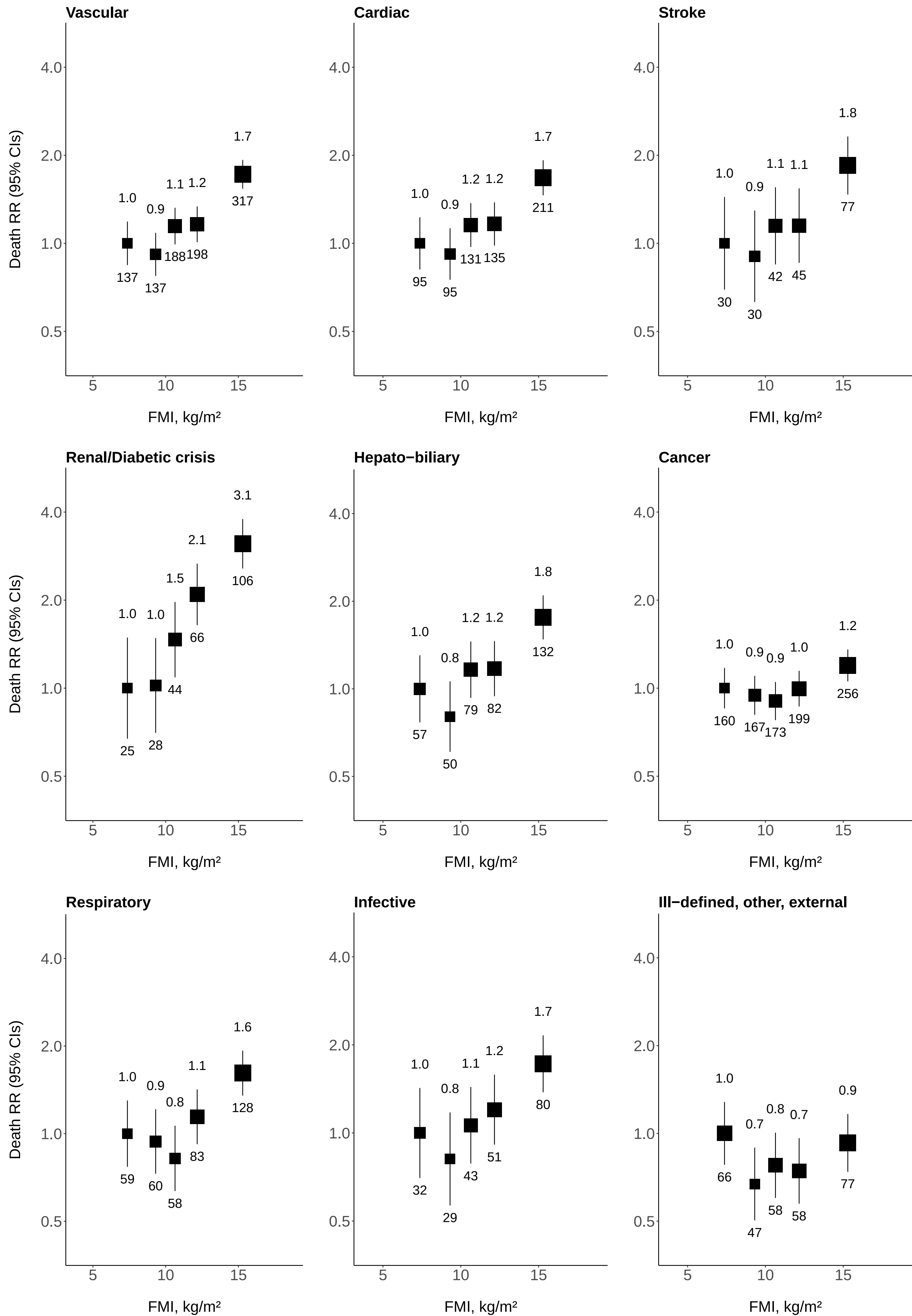
Analyses and conventions as per Figure 6.2.

Figure 6.6: Overall and independent age and sex-specific relevance of FMI to vascular-metabolic mortality



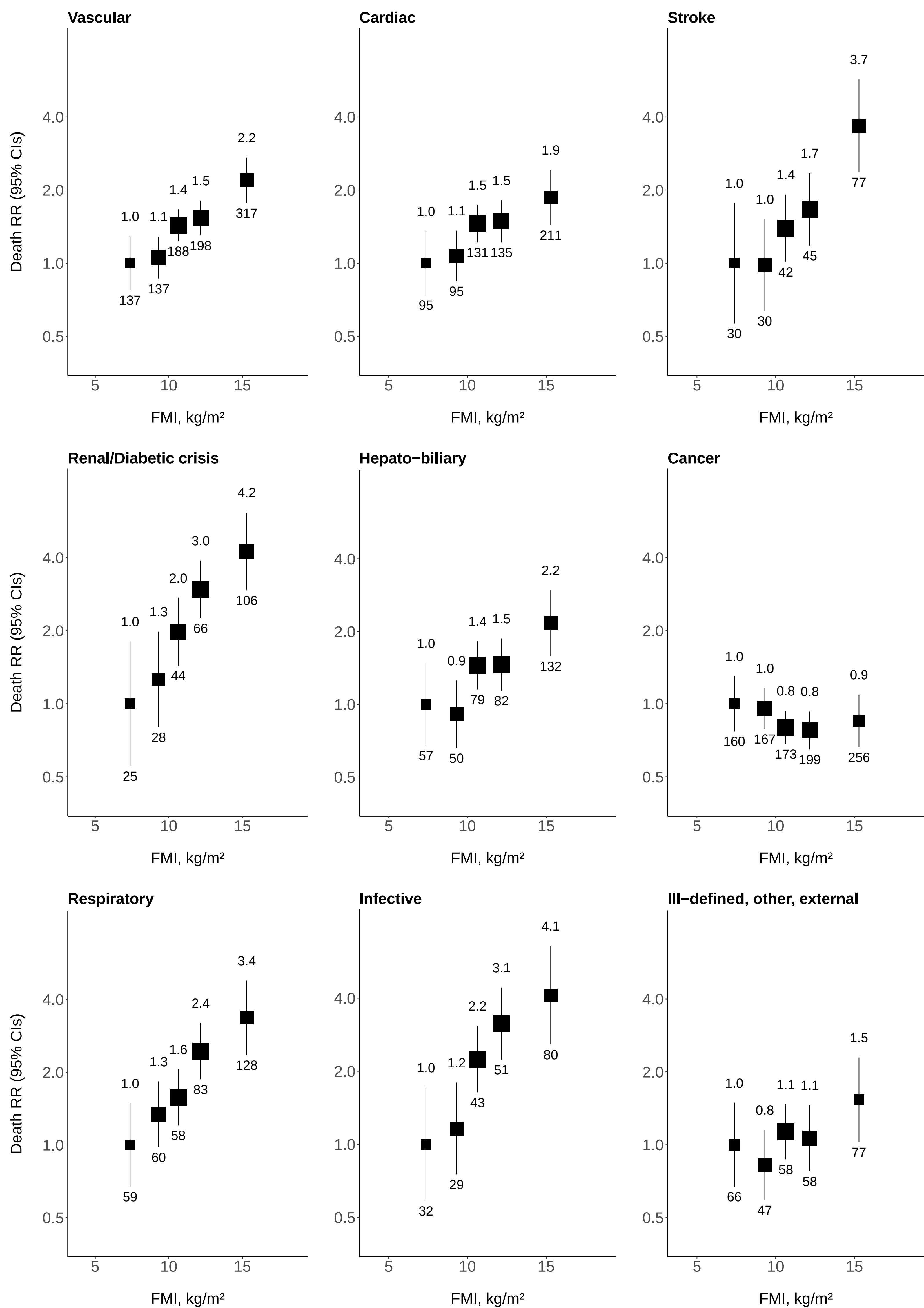
Analyses and conventions as per Figure 6.3.

Figure 6.7: Relevance of FMI to mortality from specific causes at ages 40–74 years



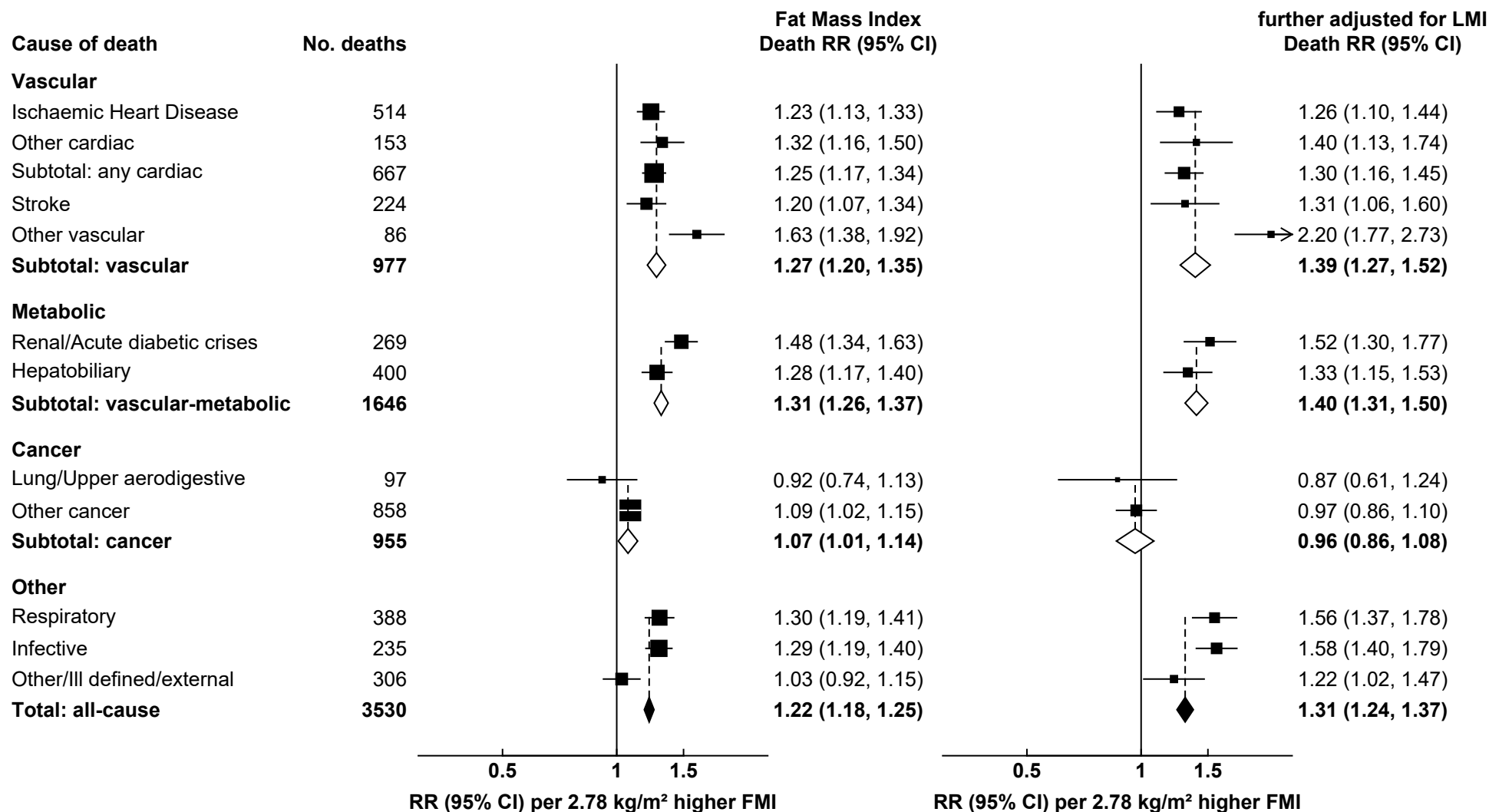
Analyses per Figure 6.1. FMI grouped by five equally-sized groups of the sex-specific distributions at baseline.

Figure 6.8: Independent relevance of FMI (given LMI) to mortality from specific causes at ages 40–74 years



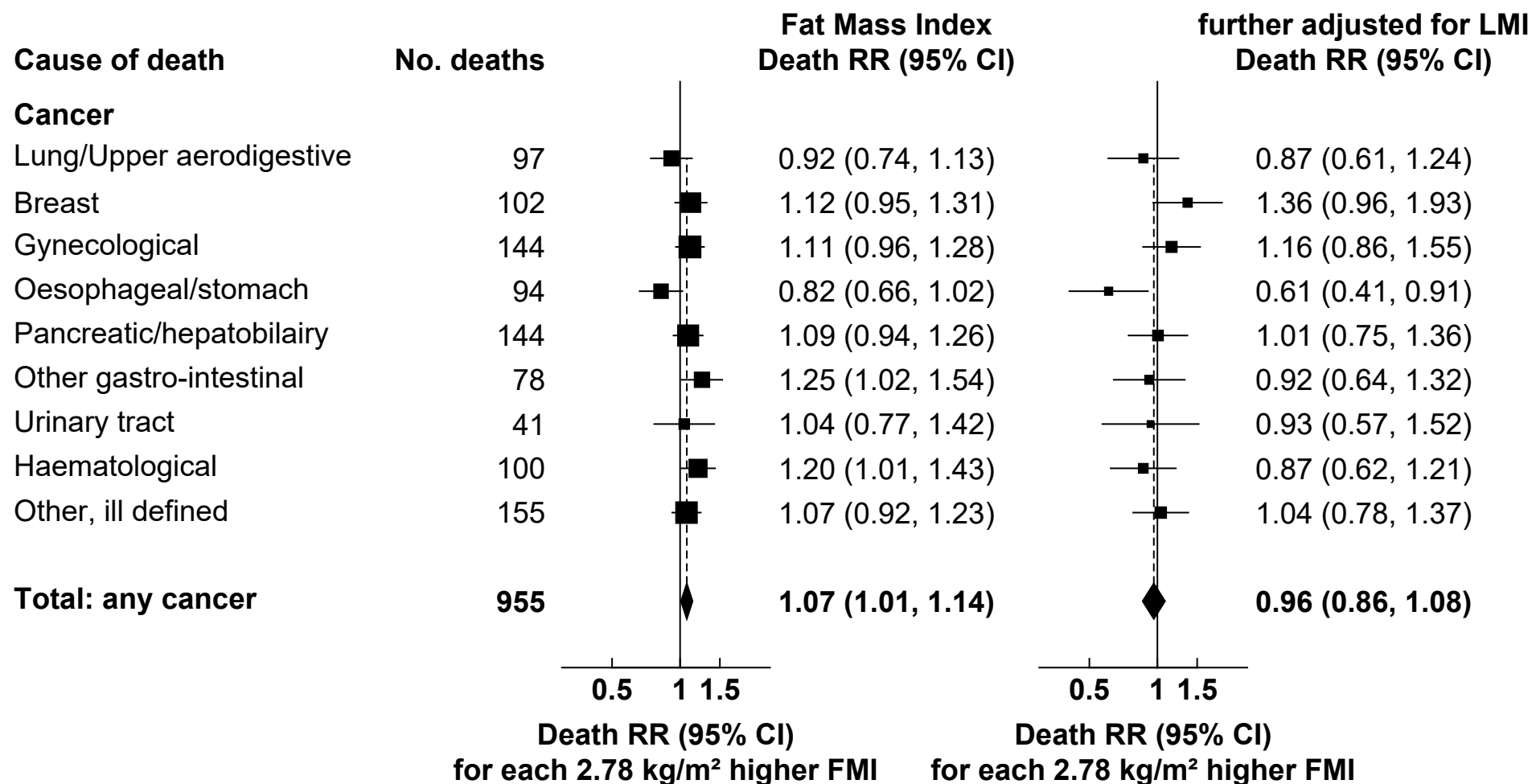
Analyses per Figure 6.7.

Figure 6.9: FMI and cause-specific mortality at ages 40-74 years



Analyses as per Figure 6.1. Death rate ratios (RR) were estimated for comparable differences of 1 standard deviation (SD) of the predicted FMI calculated as the average of the sex-specific SDs at baseline. The markers further adjusted for (as indicated in the plot), were grouped by five equally-sized groups of the sex-specific distributions at baseline. For comparison, the RRs associated with each 1 SD higher BMI (4.71 kg/m²) across the full ranges were 1.26 (1.19-1.33) for any vascular causes, 1.29 (1.23-1.35) for any vascular-metabolic causes, 1.08 (1.02-1.15) for any cancers, and 1.21 (1.17-1.24) for all-causes. The RRs per 1SD higher BMI at a given WHR across the full ranges were, 1.22 (1.14-1.29) for any vascular causes, 1.24 (1.18-1.30) for any vascular-metabolic causes, 1.07 (1.01-1.14) for any cancers, and 1.17 (1.14-1.21) for all-causes, respectively.

Figure 6.10. FMI and cancer-specific mortality at ages 40-74 years



Analyses and conventions as per Figure 6.8.

Table 6.1: Overall associations of FMI with deaths at ages 40-74 years by cause, among never smokers

Cause death	Fat Mass Index, kg/m ²	
	No deaths	RR per 1SD (95% CIs)
Vascular		
Ischaemic Heart Disease	195	1.20 (1.07-1.36)
Other cardiac	82	1.35 (1.14-1.59)
Subtotal: any cardiac	277	1.25 (1.13-1.38)
Stroke	102	1.34 (1.15-1.56)
Other vascular	37	2.02 (1.66-2.45)
Subtotal: vascular	416	1.34 (1.25-1.45)
Metabolic		
Renal/Acute diabetic crises	115	1.52 (1.33-1.73)
Hepatobiliary	145	1.28 (1.12-1.46)
Subtotal: any vascular-metabolic	676	1.36 (1.28-1.44)
Cancer		
Lung/Upper aero-digestive	26	1.05 (0.75-1.49)
Breast	74	1.15 (0.95-1.38)
Gynaecological	79	1.18 (0.99-1.42)
Oesophageal/stomach	45	0.71 (0.52-0.96)
Pancreatic/hepatobiliary	76	1.03 (0.84-1.26)
Other gastro-intestinal	38	1.38 (1.07-1.78)
Urinary tract	15	1.13 (0.72-1.76)
Haematological	44	1.26 (1.00-1.59)
Other/III-defined	80	1.15 (0.95-1.38)
Subtotal: any cancer	477	1.12 (1.03-1.21)
Other		
Respiratory	182	1.28 (1.14-1.44)
Infective	109	1.37 (1.23-1.51)
Other/III-defined/external	117	0.99 (0.83-1.17)
Total: all-cause	1561	1.26 (1.21-1.31)

Excludes those with HbA1c ≥7%, previously-diagnosed diabetes or other chronic disease at recruitment and the first 5 years of follow-up.

Table 6.2: HbA1c and SBP mediated associations of FMI to major vascular-metabolic causes of death at ages 40-74 years

	FMI per 2.78 kg/m ²	Wald χ^2	further adjusted for LMI	Wald χ^2
Vascular-metabolic (n=1,600)				
plus confounders*	1.31 (1.26-1.37)	152.7	1.40 (1.30-1.50)	87.1
plus HbA1c only [†]	1.31 (1.25-1.37)	138.7	1.39 (1.30-1.49)	83.7
plus SBP only [†]	1.26 (1.21-1.32)	107.3	1.36 (1.26-1.46)	70.7
Any vascular (n=950)				
plus confounders	1.28 (1.21-1.35)	72.7	1.39 (1.27-1.53)	49.4
plus HbA1c only	1.26 (1.19-1.34)	61.5	1.38 (1.26-1.51)	45.6
plus SBP only	1.22 (1.15-1.29)	45.9	1.34 (1.22-1.47)	38.1
Ischaemic Heart Disease (n=499)				
plus confounders	1.23 (1.14-1.34)	25.3	1.25 (1.10-1.44)	10.8
plus HbA1c only	1.22 (1.12-1.33)	21.6	1.24 (1.09-1.43)	9.9
plus SBP only	1.19 (1.09-1.29)	15.7	1.21 (1.06-1.39)	7.7
Any cerebrovascular (n=219)				
plus confounders	1.19 (1.06-1.34)	8.6	1.31 (1.06-1.61)	6.5
plus HbA1c only	1.17 (1.04-1.32)	6.6	1.29 (1.05-1.60)	5.8
plus SBP only	1.10 (0.97-1.24)	2.2	1.22 (0.99-1.51)	3.4
Renal/Diabetic crisis (n=264)				
plus confounders	1.48 (1.34, 1.62)	61.2	1.52 (1.30, 1.78)	27.5
plus HbA1c only	1.42 (1.29-1.57)	46.3	1.48 (1.26-1.74)	23.4
plus SBP only	1.41 (1.27-1.56)	44.2	1.47 (1.26-1.73)	22.6

*As per Figure 6.9, now restricted to 33,441 men and 71,655 women with complete measures of SBP and HbA1c. †Confounders-adjusted model, further adjusted for that mediator only. FMI= Fat Mass Index; LMI = Lean Mass Index. HbA1c = Glycosylated haemoglobin; SBP = Systolic Blood Pressure.

Table 6.3: Metabolic mediated associations of FMI (full-ranges) to major causes of vascular-metabolic mortality at ages 40-74 years

Mediator adjustment	Vascular-metabolic (n=450)	Wald χ^2	Vascular (n=262)	Wald χ^2	IHD (n=139)	Wald χ^2	Stroke (n=62)	Wald χ^2	Renal/Diabetic* (n=75)	Wald χ^2
Overall										
per 1SD [†]	1.31 (1.21-1.43)	43.3	1.27 (1.14-1.41)	19.5	1.19 (1.02-1.39)	4.9	1.38 (1.13-1.70)	9.8	1.46 (1.21-1.76)	15.9
plus HbA1c ^{††}	1.29 (1.18-1.40)	34.0	1.23 (1.10-1.37)	13.6	1.16 (0.99-1.37)	3.4	1.32 (1.06-1.63)	6.3	1.41 (1.16-1.71)	12.1
plus SBP ^{††}	1.27 (1.16-1.38)	30.4	1.22 (1.09-1.36)	12.4	1.14 (0.97-1.34)	2.5	1.27 (1.03-1.57)	4.8	1.40 (1.15-1.69)	11.5
plus HDL-c ^{††}	1.31 (1.21-1.42)	42.9	1.27 (1.14-1.41)	19.0	1.19 (1.01-1.39)	4.6	1.41 (1.15-1.73)	10.7	1.43 (1.19-1.73)	14.4
plus non HDL-c ^{††}	1.31 (1.21-1.42)	42.3	1.27 (1.14-1.41)	19.5	1.19 (1.02-1.39)	4.9	1.38 (1.13-1.69)	9.4	1.45 (1.20-1.74)	15.4
plus TG ^{††}	1.32 (1.22-1.43)	44.6	1.27 (1.14-1.41)	19.1	1.17 (1.00-1.37)	3.7	1.39 (1.13-1.71)	10.0	1.46 (1.21-1.76)	16.0
Independent of LMI										
per 1SD	1.41 (1.23-1.62)	25.3	1.41 (1.18-1.69)	14.0	1.26 (0.96-1.65)	2.8	1.71 (1.26-2.34)	11.5	1.58 (1.18-2.11)	9.6
plus HbA1c	1.39 (1.21-1.59)	22.3	1.37 (1.15-1.65)	11.7	1.23 (0.94-1.62)	2.2	1.64 (1.19-2.25)	9.4	1.55 (1.16-2.07)	8.6
plus SBP	1.37 (1.20-1.57)	20.9	1.37 (1.14-1.64)	11.2	1.21 (0.92-1.60)	1.9	1.63 (1.18-2.25)	8.9	1.53 (1.14-2.05)	8.0
plus HDL-c	1.40 (1.22-1.60)	24.0	1.40 (1.17-1.67)	13.2	1.24 (0.94-1.62)	2.4	1.75 (1.27-2.40)	12.0	1.54 (1.16-2.06)	8.6
plus non HDL-c	1.40 (1.22-1.60)	24.1	1.40 (1.17-1.68)	13.5	1.25 (0.95-1.64)	2.6	1.70 (1.25-2.32)	11.3	1.56 (1.17-2.08)	9.2
plus TG	1.40 (1.23-1.60)	24.3	1.40 (1.17-1.67)	13.3	1.23 (0.93-1.61)	2.2	1.72 (1.26-2.35)	11.6	1.55 (1.15-2.07)	8.5

[†] Analyses as per Table 6.2, showing estimates per each 2.78 kg/m² higher FMI across the full ranges, adjusted for confounders, now restricted to 29,960 participants with complete information on NMR measured lipids. ^{††} Further adjustment of the main model for that mediator only. IHD=Ischaemic Heart Disease.

*Refers to diabetic crises. HbA1c=glycosylated haemoglobin; SBP=systolic blood pressure; HDL-c= high-density cholesterol; TG=triglycerides.

Chapter 7: Abdominal adiposity and mortality

Abstract

Abdominal adiposity is associated with higher risks of mortality from vascular, metabolic, neoplastic, and other causes, but results of previous studies conducted in Hispanic populations have been conflicting. This chapter compares the relevance of waist circumference, waist-hip ratio (WHR) and waist-height ratio (WHtR) to premature mortality among 145,659 Mexican adults who were followed for 16-years. After adjustment for confounding factors and controlling for the effects of reverse causality bias, abdominal adiposity was strongly, positively associated with mortality at ages 40-74 years, with no threshold levels. Comparing the top versus bottom tenth of the distribution, the RR for all-cause mortality was 1.91 (95% CI 1.65-2.22) for waist circumference, 1.79 (1.52-2.11) for WHR, and 2.01 (1.71-2.36) for WHtR. By comparison, the RR for vascular-metabolic mortality was 2.45 (1.94-3.09) for waist circumference, 2.19 (1.70-2.83) for WHR and 2.72 (2.13-3.47) for WHtR. The corresponding death RRs with each 1 standard deviation (SD) higher levels of each of these markers of abdominal adiposity were 1.25 (1.21-1.38), 1.17; (1.14-1.21) and 1.26 (1.22-1.30) for mortality from any cause, and 1.32 (1.26-1.38), 1.24 (1.18-1.30) and 1.37 (1.31-1.43), for mortality from vascular or metabolic causes, respectively. Mutual adjustment for other markers of general (eg, BMI) or gluteo-femoral adiposity (eg, hip circumference) strengthened the relevance of waist circumference to mortality risk. In those with diabetes (among whom poor glycaemic control was common), weight loss substantially biased the associations of mortality with waist circumference. In conclusion, in this Mexican population, waist circumference had strong positive effects on vascular, metabolic, and other causes of death, independent of BMI. In

contrast with previous studies conducted in Hispanic populations, the present findings demonstrate that abdominal obesity is particularly hazardous, and given BMI, the waist circumference and the WHR remain of substantial additional relevance to mortality.

7.1 Background

Several large prospective studies have shown that abdominal adiposity is more hazardous than general adiposity, being positively and linearly associated with mortality from vascular and other causes,¹⁻⁷ irrespective of ethnicity.² However, other studies have reached different conclusions.⁸⁻¹¹ Nonetheless, direct comparisons of the results of different observational studies of abdominal adiposity are constrained somewhat by the selection of different markers of adiposity, different approaches to how those markers are analysed (e.g, categorical or continuous), and varying approaches to limit the effects of reverse causality bias due to pre-existing disease (details on **Chapter 2**, pages 39 and 42-46, and Supplementary Tables **S4** and **S6**).

A meta-analysis of 359,387 adults without chronic disease at recruitment from 9 countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC), reported strong linear positive associations of waist circumference and of WHR (but not of hip circumference) with all-cause mortality (n=14,724), with each 5 cm higher waist circumference (at a given BMI), being associated with a 17% higher risk of mortality in men and a 13% higher risk in women, while each 0.1 higher WHR (at a given BMI), was associated with a 34% higher risk of mortality in men and a 24% higher risk in women, respectively.⁴ These associations appeared somewhat stronger in current smokers than in never smokers, and for neoplastic than for vascular deaths in men, while in women, the RRs were stronger for vascular than for neoplastic

deaths.⁴ In a cohort of 156,624 postmenopausal women from 40 centres in the Women's Health Initiative Study, waist circumference above 88 cm at a BMI of 18.5-24.9 kg/m², was associated with higher risk of mortality from vascular, neoplastic and all-causes combined (n=43,838), but at a given waist circumference below 88 cm, a BMI above 30 kg/m² was unrelated to risk of mortality from cardio-vascular and all-causes, while the risk with neoplastic mortality was 10% lower, compared to those with a lower BMI for the same levels of waist circumference.⁵ Another North-American study of 105,000 adults from the Cancer Prevention Study II Nutrition Cohort followed for 9 years, reported linear positive associations of waist circumference with mortality from vascular, neoplastic, respiratory and all-causes combined (n=14,647), with each 10 cm higher levels of waist circumference above a BMI of 25 kg/m² being associated with a 20% higher risk for mortality from any cause in men, and a 10% higher risk in women, respectively.¹ Another individual-data meta-analysis of 221,934 adults without cardiovascular diseases at baseline assessment in 58 prospective studies conducted in 17 (mostly high-income) countries, also reported strong linear positive associations of waist circumference and of WHR with cardiovascular events (n=14,297), with a 26% higher risk per each 1 SD higher abdominal adiposity above a BMI of 20 kg/m² (corresponding to 12.6 cm of waist circumference and 0.083 units of WHR, respectively).⁷ These associations, which included non-fatal and fatal events, were largely similar irrespective of gender, smoking status, or history of diabetes at the time adiposity markers were measured.

By contrast to these largely positive findings, a recent study of 0.5 million adults from the UK Biobank (UKB) who survived for at least 2 years, investigated the impact of diabetes on the relevance of abdominal adiposity to mortality over 6.9 years of follow-

up, and showed U- and J-shaped associations of waist circumference with cardiovascular, neoplastic and all-cause mortality (n=13,896), even among participants without diabetes or other chronic disease at baseline, while among those with pre-existing diabetes, these non-linear associations were even more accentuated.⁸ However, a recent Mendelian randomisation (MR) study of the UKB population reported strong positive associations of genetically-determined waist-hip ratio (at a given BMI) with risk of premature death from coronary artery disease, ischaemic stroke, diabetes, liver disease, renal failure or other non-vascular or non-metabolic diseases, highlighting the causal relevance of central adiposity for such diseases.¹²

Most observational studies of central adiposity and mortality conducted in Hispanic populations have been limited and conflicting, as most such studies have failed to show positive associations of central adiposity with mortality,⁹⁻¹¹ with the exception of one recent study of 10,329 Mexican-Americans from the National Health and Nutrition Examination Surveys (NHANES) in which only weak positive associations between both waist circumference and waist-height ratio with vascular or metabolic causes of death were reported (e.g., RRs <1.1 throughout the ranges).¹³ Although this study had a follow-up of 11 years, the total number of deaths was low (n=1,423) and analyses included participants with prior chronic diseases and deaths occurring during the early years of follow-up, which could have confounded the true associations of abdominal adiposity with mortality.¹⁴

This chapter investigated the separate and combined relevance of three markers of abdominal adiposity (waist circumference, WHR and WHtR), to mortality from various

causes among 145,659 men and women aged 40-89 years who had no chronic disease (other than diabetes) at recruitment in the Mexico City Prospective Study, and survived for at least 5 years from the time adiposity markers were measured at baseline assessment. Reverse causality bias from pre-existing or screen-detected diabetes was assessed similar to previous analyses described in Chapters 5 and 6. The primary analyses were restricted to premature deaths occurring at ages 40-75 years, but some analyses were also conducted for deaths at older ages (among 22,758 adults aged ≥ 75 to < 90 years).

Similar to chapter 6, and for comparison with analyses of predicted body-composition, the markers of abdominal adiposity were considered as continuous exposures defined epidemiologically (rather than by fixed “clinical thresholds”). The linear associations of abdominal adiposity with mortality were first assessed with the adiposity markers classified as five equally-sized groups of the sex-specific distributions at baseline (with the bottom and the top groups being further divided into two groups corresponding to the top and the bottom 10% of the distributions). The continuous relevance of abdominal adiposity to cause-specific mortality was subsequently assessed per each 1 SD higher levels throughout the ranges of the various markers, and in addition, independent of general adiposity (i.e., BMI, or total weight, for analyses of WHtR) or independent of gluteo-femoral adiposity (ie, hip circumference for analyses of waist circumference). Sensitivity analyses assessed death RRs among never smokers, and with inclusion of those with well-controlled diabetes (defined by HbA1c levels $< 7\%$), and with usual (rather than baseline) levels of the adiposity markers. Finally, the mediating effects of HbA1c, SBP, HDL-c, non HDL-c and triglycerides was estimated in a subset with available information (similar to chapter 6).

7.2 Study participants and adiposity related characteristics

The participants included in various analyses of abdominal adiposity with mortality were the same as those in analyses of BMI and FMI (as detailed in **Sections 2 of Chapters 5 and 6**). Among the 145,659 participants aged 35-89 years (without chronic disease at baseline, except for diabetes), mean waist circumference was 96 ± 10 cm in men and 93 ± 12 cm in women, mean WHR 0.95 ± 0.06 in men and 0.88 ± 0.07 in women, and mean WHtR 0.59 ± 0.06 in men and 0.62 ± 0.08 in women (**Table 4.2, chapter 4**). Throughout the ranges studied (waist circumference of 60.0-179.2 cm, WHR of 0.5-1.5 units, and WHtR of 0.4-1.2 units; **S10**), those with higher levels of abdominal adiposity had higher levels of general adiposity, and therefore, similar socio-demographic and health characteristics to those with higher BMI or predicted FMI (as described in the previous chapters). Specifically, those with higher abdominal adiposity were less likely to live in the wealthier of the two districts (Coyoàcan), less likely to have university or college education, less likely to be physically active, and less likely to smoke (**S18-S20**). In addition, those with higher levels of abdominal adiposity had higher levels of blood pressure and were more likely to have un-diagnosed or diagnosed diabetes, and more likely to use anti-hypertensive or antithrombotic medications, but not lipid-lowering medications.

7.3 Illustration of reverse causality bias

Reverse causality bias was assessed as previously described in the **Methods chapter (section 3.2.7)**, and using a similar approach to analyses of BMI and FMI (**Chapters 5 and 6, sections 5.3. and 6.3, respectively**). Supplementary figures **S40, S53 and S54** illustrate the biases that would have resulted if exclusions of diabetes, other previously-diagnosed chronic diseases, and deaths occurring during the first 5 years

of follow-up, had not been implemented. The WHR would have remained linearly and positively associated with mortality throughout the ranges studied, but for waist circumference, the association would have been misleading and strikingly J-shaped. This observation was qualitatively different from the findings in the main analyses (**Figures 7.1 and 7.2**), chiefly due to a strong inverse association of abdominal adiposity with all-cause mortality in individuals with previously-diagnosed or screen-detected diabetes, combined with a J-shaped association during the first 5 years of follow-up in individuals without diabetes (**S53**).

7.4 Abdominal adiposity and total mortality

At ages 40-74 years, abdominal adiposity was positively associated with all-cause mortality, with approximately log-linear associations observed for waist-hip ratio and waist-height ratio, and a J-shaped association with waist circumference (**Figure 7.1**). Comparing the top versus bottom tenth of each distribution, the all-cause mortality RR was 1.91 (95% CI 1.65-2.22) for waist circumference, 1.79 (1.39-2.06) for the waist-hip ratio, and 2.01 (1.71-2.36) for the waist-height ratio. The RRs corresponding to each 1 SD higher level of each one of the adiposity markers (corresponding to 10.88 cms of waist circumference, 0.061 units of WHR, and 0.071 units of WHtR), were 1.25 (95% CIs 1.21-1.28) for waist circumference, 1.17 (1.14-1.21) with WHR, and 1.26 (1.22-1.30) for WHtR.

After adjustment of central adiposity for general adiposity (eg, BMI or total weight) and the distributions of body-fat (e.g, waist circumference at a given hip circumference, indicative of visceral abdominal adiposity relative to gluteo-femoral adiposity), the associations of waist circumference and of waist-height ratio with premature mortality

from all-causes were more extreme, while the associations of waist-hip ratio were attenuated (**Figure 7.2**). Given the other markers of adiposity, the RRs corresponding to a 1 SD higher level of abdominal adiposity, were 1.32 (95% CIs 1.25-1.38) for waist circumference, 1.14 (1.10-1.18) for WHR, and 1.29 (1.24-1.35) for WHtR.

7.5 Age and sex-specific associations of abdominal adiposity with total mortality

The associations of abdominal adiposity with all-cause mortality were broadly consistent in subgroup analyses at different ages and by sex (**S28, S55**). At every age, the overall relevance of waist circumference and of WHR to all-cause mortality was positive throughout the ranges studied, albeit the associations were stronger at ages 40-59 years compared to ages 60-74 years, and it attenuated at ages 75-90 years, but the absolute risks were greater at older than at younger ages (**S28**). Each 1 SD higher waist circumference was associated with a 30% increased mortality at ages 40-59 years (RR=1.30; 95% CIs 1.23-1.36), 22% increased mortality at ages 60-74 years (RR=1.22; 1.17-1.27), and 14% increased mortality at ages 75-89 years (RR=1.14; 1.10-1.18; χ^2 for trend=17.82, p-value=0.0001; **S56**). By comparison, the each 1 SD higher WHR was associated with 23% increased mortality at ages 40-59 years (RR=1.23; 1.16-1.29), 15% increased mortality at ages 60-74 years (RR=1.15; 1.10-1.20), and 2% increased mortality at ages 75-89 years (RR=1.02; 0.99-1.06; χ^2 for trend=40.49, p-value<0.00001; **S56**). The age-specific mortality risks per each SD higher WHtR were identical to the RRs for higher waist circumference, and somewhat stronger compared to the estimates for higher WHR, particularly for mortality at ages 40-74 years (**S56**). At every age, these mortality risks were broadly similar in women compared to men, for all the three markers of abdominal adiposity (**S56**). After

adjustment for general and gluteo-femoral adiposity, the age and sex-specific associations of waist circumference with all-cause mortality at ages 40-74 years strengthened modestly, those of WHR weakened modestly, and those of WHtR remained largely unaffected (**S57**).

Given that the associations of abdominal adiposity with mortality were stronger at younger than at older ages, the next section focuses on premature deaths at ages 40-74 years.

7.6 Abdominal adiposity and premature mortality from specific causes

At ages 40-74 years, all three markers of abdominal adiposity were strongly and positively associated with mortality from vascular or metabolic causes, with no evidence of a threshold throughout the ranges studied (**Figure 7.3**). The RRs for any vascular-metabolic deaths (from cardiac, cerebrovascular, renal, hepatobiliary, or acute diabetic causes) comparing those in the top versus the bottom tenth of the distributions were 2.42 (1.92-3.04) for waist circumference, 2.18 (1.69-2.82) for WHR, and 2.63 (2.05-3.37) for WHtR, respectively. After accounting for general or gluteo-femoral adiposity, the overall associations of waist circumference and of WHtR to vascular-metabolic deaths became particularly strong throughout the full ranges, whereas the relevance of WHR attenuated (**Figure 7.4**), such that the RRs comparing those at the top versus the bottom tenth of the distributions were 3.22 (2.23-4.63) for waist circumference, 1.87 (1.43-2.43) for WHR, and 3.35 (2.46-4.57) for WHtR. Furthermore, analyses stratified by different levels of BMI, showed no evidence that among those with a low BMI in this cohort, the relevance of abdominal adiposity to vascular-metabolic mortality is stronger than among those with a higher BMI (**S61**,

S44).

By contrast, of the three markers of abdominal adiposity studied, only the WHR was positively log-linearly associated with mortality from any non-vascular or non-metabolic causes combined (**Figure 7.5**). However, given levels of general or gluteo-femoral adiposity, the relevance of waist circumference and of WHtR to mortality from any non-vascular-metabolic causes strengthened importantly throughout the ranges (**Figure 7.6**), such that the RRs, comparing those at the top versus the bottom tenths of the distributions were 2.13 (1.54-2.95) for waist circumference, 1.52 (1.21-1.90) for WHR and 1.65 (1.25-2.18) for WHtR.

7.6.1 Age and sex-specific associations of abdominal adiposity to vascular-metabolic mortality

Similar sex-specific associations were observed for premature mortality from any vascular or metabolic causes (**S58**), and across ages, the associations were somewhat stronger at younger than at older ages (**S59**). Specifically, each 1 SD higher waist circumference was associated with 38% increased vascular-metabolic mortality at ages 40-59 years (RR=1.38; 1.28-1.48), 29% increased mortality at ages 60-74 years (RR=1.29; 1.21-1.36), and 18% increased mortality at ages 75-89 years (RR=1.18; 1.13-1.24; X^2 for trend 12.74; p-value 0.002; **S59**). Similar patterns were observed for WHR, as well as for WHtR. Specifically, the age-specific RRs with higher WHR decreased from 1.32 to 1.04 for deaths at ages 40-60 years vs deaths at ages 75-98 years, respectively (X^2 for trend 34.15; p-value <0.00001). Similarly, the age-specific RRs with higher WHtR, decreased from 1.44 to 1.18 for deaths at ages 40-60 years vs deaths at ages 75-98 years, respectively (X^2 for trend 23.13; p-value

<0.00001). These age-specific patterns were consistent independent of general or gluteo-femoral adiposity (**S60**).

7.6.2 Abdominal adiposity and specific mortality from vascular or metabolic causes

The relevance of abdominal adiposity to mortality from ischaemic, cerebrovascular, hepatobiliary, renal or acute diabetic causes was largely similar, with no evidence of a threshold throughout the ranges (see **Figures 7.7- 7.9** for the shapes of the overall associations, and supplementary figures **S62-S64** for cause-specific associations independent of other markers of adiposity). Across the ranges of the three markers studied, the RR for premature mortality from any vascular-metabolic causes associated with each 1 SD higher levels of abdominal adiposity was 1.32 (95% CIs 1.26-1.38) for waist circumference, 1.24 (1.18-1.30) for WHR, and 1.37 (1.31-1.43) for WHtR. For each adiposity marker, the death RRs were broadly comparable for cardiac, cerebrovascular, other vascular, and hepatobiliary causes of death (**Figure 7.10**), but larger for deaths from renal causes or acute diabetic crises, particularly with waist circumference (1.51; 1.36–1.67). After adjustment for other markers of general or gluteo-femoral adiposity, the RRs for any vascular-metabolic deaths became more extreme with waist circumference (1.36; 1.27-1.47) and with WHtR (1.44; 1.36-1.54), while the RRs for WHR attenuated (1.18; 1.12-1.24; **Table 7.1**). These mutually-adjusted RRs were similar for the various vascular component diseases of premature death, and remained stronger for renal or acute-diabetic causes.

The estimates for vascular-metabolic deaths were consistent in analyses restricted to never-smokers (the RRs were 1.41; 1.32-1.51 for waist circumference, 1.20; 1.12-1.29

for WHR, and 1.46; 1.37-1.56 for WHtR; **Table 7.2**), and after including participants with previously diagnosed diabetes but good glycaemic control given HbA1c below 7% (the RRs were 1.28; 1.22-1.33 for waist circumference, 1.23; 1.17-1.28 for WHR, and 1.32; 1.27-1.38 for WHtR; **S65**). Again, the estimates among never smokers and among those with well-controlled diabetes, were comparable for the various vascular, hepatobiliary, renal or acute diabetic causes of premature mortality.

The effects of correction for regression dilution for death risk from any vascular-metabolic causes were modest and comparable for all the markers studied (**S48**), including for estimates after adjustment for general or gluteo-femoral adiposity (**S49**), as well as for the various component diseases. Specifically, the RRs for premature mortality from such causes with usual waist circumference strengthened by 3% compared to estimates without correction for such bias (from 1.32; 1.26-1.38 to 1.35; 1.29-1.42; **S48**). Similar changes in the magnitude of the association were estimated for usual levels of WHR and WHtR (the RRs strengthened from 1.24; 1.18-1.30 to 1.28; 1.21-1.35, and from 1.37; 1.31-1.43 to 1.40; 1.34-1.47, respectively).

7.6.3 Mediation effects of traditional vascular and metabolic traits on vascular-metabolic mortality

Tables 7.3 to 7.6 show the death RRs for major vascular, renal or acute diabetic causes of premature mortality with higher levels of abdominal adiposity, before and after adjustment for traditional mediators (HbA1c, blood pressure, HDL-c, non HDL-c and triglycerides).

Additional account for HbA1c did not essentially alter the strength of the associations

with vascular-metabolic deaths, except for WHtR (the RRs reduced from 1.37; 1.31-1.44 to 1.32; 1.26-1.39 for WHtR, from 1.32; 1.26-1.38 to only 1.31; 1.25-1.38 for waist circumference, and from 1.23; 1.18-1.29 to only 1.22; 1.17-1.28 for WHR; **Table 7.3**). Similar changes were observed for the associations of abdominal adiposity at a given HbA1c with mortality from any vascular, cardiac, and cerebrovascular causes (reduction in RRs by 1-4%), and somewhat more pronounced reductions in mortality risk from renal causes or acute diabetic crises (from 1.50; 1.35-1.67 to 1.45; 1.30-1.61 for waist circumference, and from 1.51; 1.36-1.67 to 1.45; 1.30-1.62 for WHtR, corresponding to changes in the Wald- χ^2 statistics from 58.7 to 44.0, and from 57.8 to 43.4, respectively).

Additional account for SBP also appeared to have virtually no effect on the strengths of the associations for vascular-metabolic mortality, except for waist circumference (the RRs reduced from 1.32; 1.26-1.38 to 1.27; 1.21-1.33 for waist circumference, and from 1.23; 1.18-1.29 to only 1.21; 1.15-1.27 for WHR, while the RRs of 1.37; 1.31-1.44 for WHtR remained unchanged; **Table 7.3**). The degree of change in the magnitude of these associations due to additional account for SBP (of about 5% reduction in the death RRs), were largely comparable for any vascular, cardiac, renal or acute diabetic deaths, but importantly greater for stroke deaths (the RRs reduced by 10%, from 1.24; 1.10-1.41 to 1.14; 1.01-1.30 for waist circumference, and from 1.32; 1.17-1.49 to 1.22; 1.07-1.38 for WHtR, corresponding to changes in the Wald- χ^2 statistics from 11.8 to 8.8, and from 19.6 to 9.3, respectively). After additional adjustment for general or gluteo-femoral adiposity, the effects of HbA1c and of SBP on mortality risk from the various vascular or metabolic causes appeared more modest.

In the subset of participants with additional measures of lipids, the additional relevance of HbA1c and SBP to mortality from specific vascular, renal, or metabolic causes, was largely consistent for all markers of abdominal adiposity (**Tables 7.4-7.6**). In this subset, additional account for HDL-c, non HDL-c, and triglycerides, had virtually no apparent effect on the associations of waist circumference, WHR or WHtR with premature deaths from any vascular, ischaemic, or cerebrovascular causes, both before and after adjusting for other markers of general or gluteo-femoral adiposity. However, a modest reduction was observed for mortality from renal or acute diabetic causes with waist circumference after accounting for HDL-c (the RRs reduced from 1.43; 1.16-1.75 to 1.40; 1.14-1.72, and from 1.66; 1.19-2.30 to 1.61; 1.16-2.24 after further adjustment for BMI and hip circumference, which corresponded to changes in the Wald-chi² statistic from 11.5 to 10.1, and from 9.1 to 7.9, respectively, **Table 7.4**). Comparable changes (of about 3% decrease in the RRs) were observed for the mortality risk with WHR and WHtR at a given HDL-c.

7.6.4 Abdominal adiposity and premature mortality from specific non-vascular or non-metabolic causes

The overall and independent relevance of abdominal adiposity to premature mortality from specific non-vascular-metabolic causes was largely comparable to that for vascular-metabolic causes, but importantly weaker for deaths from neoplastic causes (**Figures 7.7- 7.9** and **S62-S64**). At ages 40-74 years, the overall death RRs for any non-vascular or non-metabolic causes combined (from neoplastic, respiratory, infective, external, or other unknown or ill-defined medical causes) with each 1 SD higher levels of abdominal adiposity appeared modest (RR, 95% CIs 1.18; 1.12-1.24 for waist circumference, 1.13; 1.07-1.18 for WHR, and 1.15; 1.10-1.21 for WHtR;

Figure 7.5), largely due to the lack of an association with mortality from cancer of the lung or upper aero-digestive sites, and mortality from external or unknown causes (**Figure 7.10**).

For the composite of any non-vascular non-metabolic causes of death, the RR per 1 SD levels of abdominal adiposity given general or gluteo-femoral adiposity, was 1.28 (1.19–1.38) for waist circumference, 1.12 (1.06–1.17) for WHR, and 1.14 (1.06–1.22) for WHtR, respectively (**Figure 7.6**). Waist circumference was strongly and positively associated with mortality from infective causes (RR=1.42; 1.26-1.58) and respiratory causes (RR=1.36; 1.24, 1.49), whereas the association with neoplastic mortality was much weaker (RR=1.11; 1.04-1.18; **Figure 7.10**), irrespective of the cancer subtype (**Figure 7.11**). Compared to estimates for waist circumference, the death RRs for comparable differences in WHR were more modest (RRs were 1.29; 1.15-1.45 for infective causes, 1.26; 1.15-1.38 for respiratory causes, and 1.06; 0.99-1.13 neoplastic causes, respectively), whereas the estimates for WHtR were largely similar (RRs were 1.44; 1.29-1.61 for infective causes, 1.40; 1.27-1.53 for respiratory causes, and 1.05; 0.99-1.12 for neoplastic causes, respectively; **Figure 7.10**). At a given BMI and hip circumference, the RRs associated with higher waist circumference or higher WHtR became stronger for mortality from respiratory and infective causes (RRs >1.6 and >1.5, respectively), while the associations with neoplastic mortality were largely unaffected by these additional adjustments (**Tables 7.1 and 7.7**).

The death RRs for the various non-vascular or non-metabolic specific diseases were consistent in analyses restricted to never-smokers (**Table 7.2**), and after including participants with previously-diagnosed diabetes but good glycaemic control given

HbA1c below 7% (**S65**). The effects of correction for regression dilution for each of the three markers of abdominal adiposity assessed strengthened the RRs modestly (**S48, S49**).

7.7 Effect-modification of mortality risk by levels of confounders

The RRs of premature mortality from any-cause associated with each 1 SD higher abdominal adiposity were broadly similar irrespective of district of residence, level of education achieved, leisurely physical activity, or alcohol intake (**S67-S69**). Similarly, step-wise multivariable adjustments for confounders indicated little differences in the risk estimates after adjustment for such confounders, except for the district of residence which appeared to explain 3-5% of the associations of abdominal adiposity with either total, vascular-metabolic, or non-vascular-metabolic mortality (**S70-S72**).

7.8 Strengths and limitations

In addition to the strengths and limitations already highlighted in the corresponding sections for analyses of general adiposity with mortality in chapters 5 and 6, the present analyses extend to markers of interest less explored before (ie, the waist-height ratio), using standardised, directly-measured anthropometry (rather than self-reports). Furthermore, while the effects of waist circumference and WHR on vascular mortality have been investigated previously, this study adds estimates for site-specific cancers in a previously-understudied population.

Nevertheless, the present study had several limitations, including lack of imaging measures of visceral adipose tissues, and lack of bioassays levels of lipids, renal and liver function, which could have enabled to explore the mechanisms underlying the

associations of abdominal adiposity relative to gluteo-femoral adiposity, with mortality from the various specific causes. Such additional information would have permitted to detect any specific differences in disease-specific mediators for premature deaths, and would have perhaps elucidated the apparent similarity of the observed associations identified through the present analyses. Furthermore, the present estimates likely under-estimate the true risks, given that data on incident diseases was lacking at the time this thesis was conducted. Finally, these analyses were the first to show that pre-existing diabetes distorted the relevance of waist circumference (but not of WHR) to mortality risk. However, despite the comprehensive strategy to ameliorate reverse-causality bias and the effects of residual confounding, alternative strategies, such as Mendelian Randomisation, would have been desirable, yet, beyond the scope of this thesis.

7.9 Conclusions

In this Mexican population, abdominal adiposity had strong positive effects on mortality. Higher levels of abdominal adiposity were a major risk factor for premature death, particularly from vascular, renal, and other metabolic causes, with no evidence for a threshold throughout the ranges studied. The present study also demonstrated that in those with diabetes, weight loss (likely caused by poor glycaemic control) substantially biased the association seen with waist circumference, but did not affect the relevance of WHR to mortality. Each 1 SD higher waist circumference was associated with a 25% higher risk of death from all causes, chiefly due to a 32% higher risk of death from vascular-metabolic causes (or in the case of WHtR, a 37% higher risk). These excess risks were largely independent of general and gluteo-femoral adiposity, so that, even after controlling for BMI and HC, individuals in the top 10% of

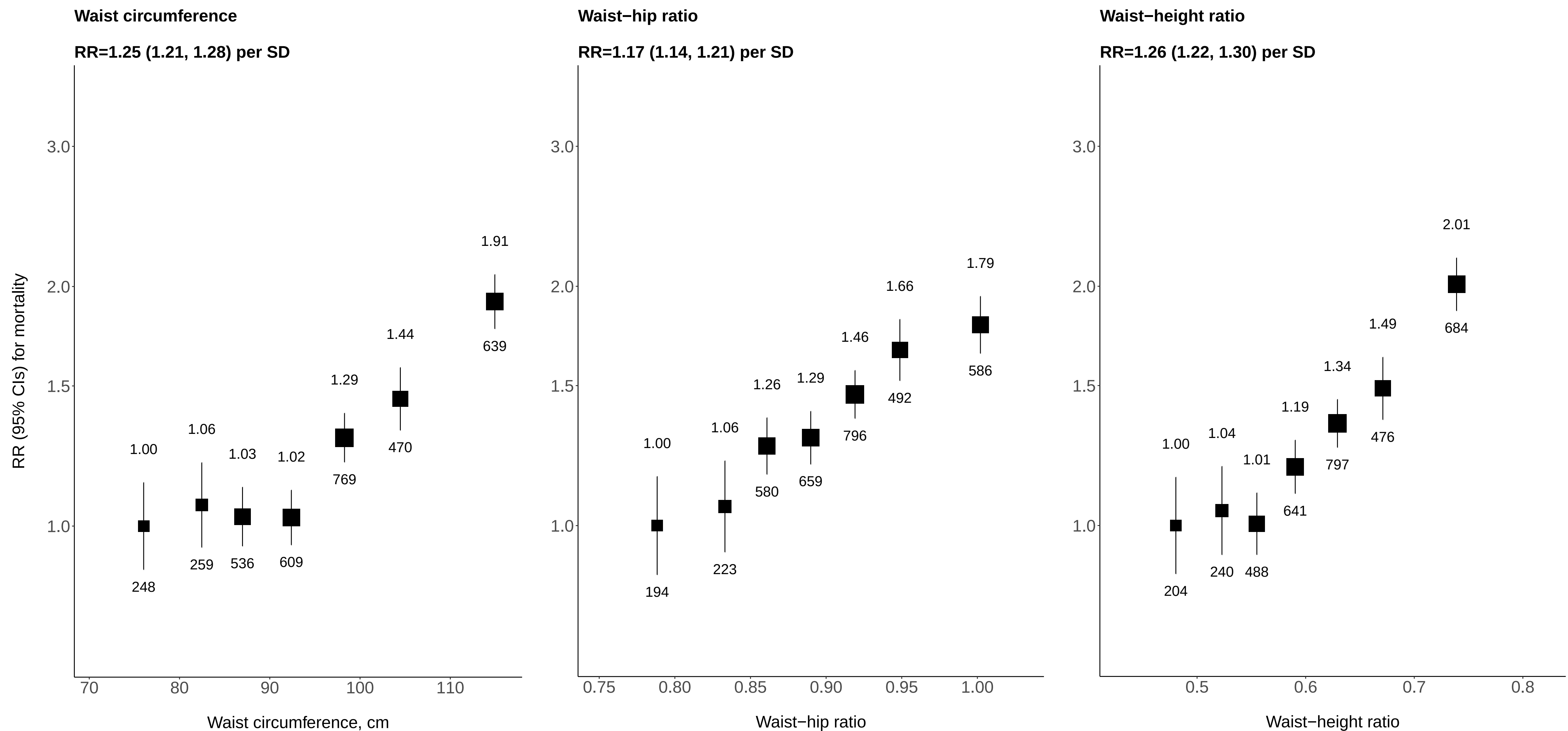
the distributions of waist circumference had a 2.5-fold higher death rate from all-causes, and a 3-fold higher death rate from vascular-metabolic causes, compared with those in the bottom 10% of the distributions. The findings from this study are importantly stronger compared to the most recent results from the Mexican-American participants in the NHANES survey, because the present analyses excluded those with pre-existing or un-detected diabetes, in addition to other chronic disease at the time baseline levels of adiposity were measured. In addition, the findings from this study ultimately demonstrate that given BMI, the WHR remains of substantial additional relevance to mortality risk, suggesting that abdominal obesity is particularly hazardous.

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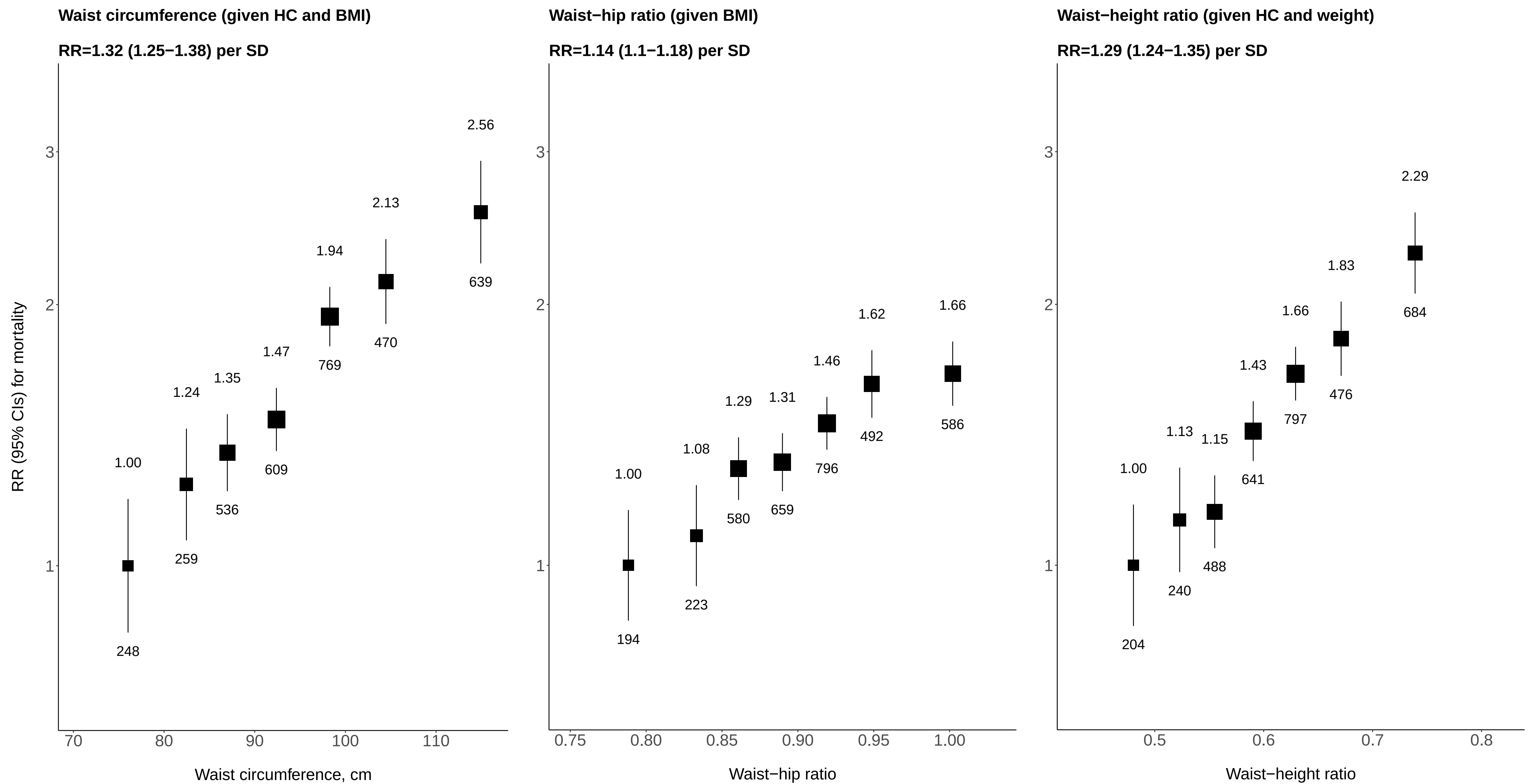
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Figure 7.1: Overall relevance of waist circumference, WHR and WHtR to all-cause mortality at ages 40–74 years (diabetes, those with HbA1C $\geq 7\%$, and the first 5 years of follow-up excluded)



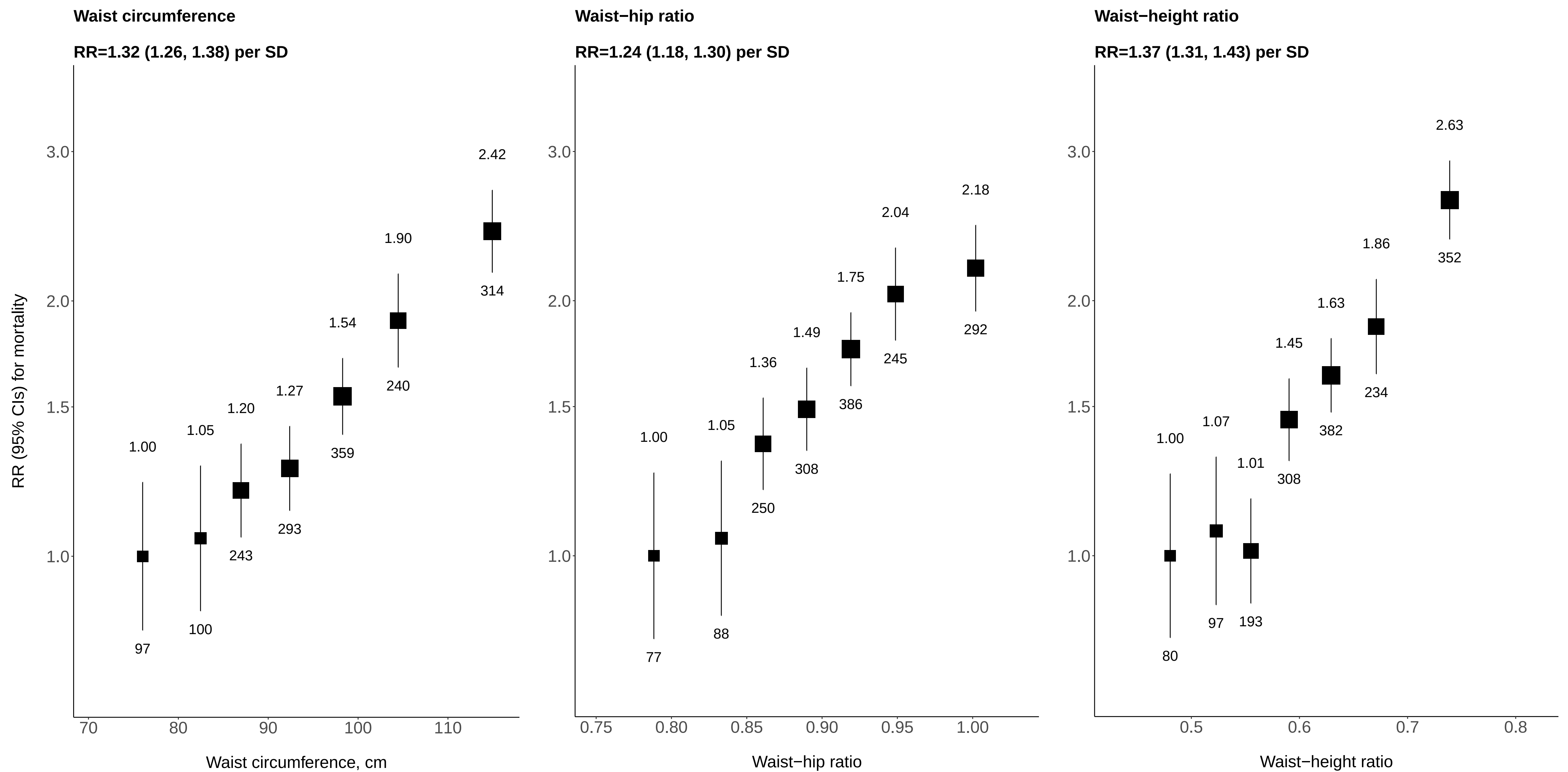
Adiposity markers are considered as sex-specific percentiles of 10% (reference), 20%, 40%, 60%, 80% and 90%, respectively. The RRs shown above each square, are estimated with Cox models, accounting for age-attained and length of follow-up as underlying time-variables, adjusted for age (in 5-years bands), sex, district, education, physical exercise, alcohol or smoking status and amount. Each axis corresponds to the same number of SDs of the adiposity markers. The plotted RRs are centred at the mean. Square sizes are inversely proportional to the variance. Exclusions as per Table 4.1 (Chapter 4), with the additional criteria specified in the title. Diabetes refers to previous diagnose or use of any anti-diabetic medication.

**Figure 7.2: Independent relevance of waist circumference, WHR and WHtR to all-cause mortality at ages 40–74 years
(excluding diagnosed diabetes, those with HbA1C $\geq 7\%$, and the first 5 years of follow-up)**



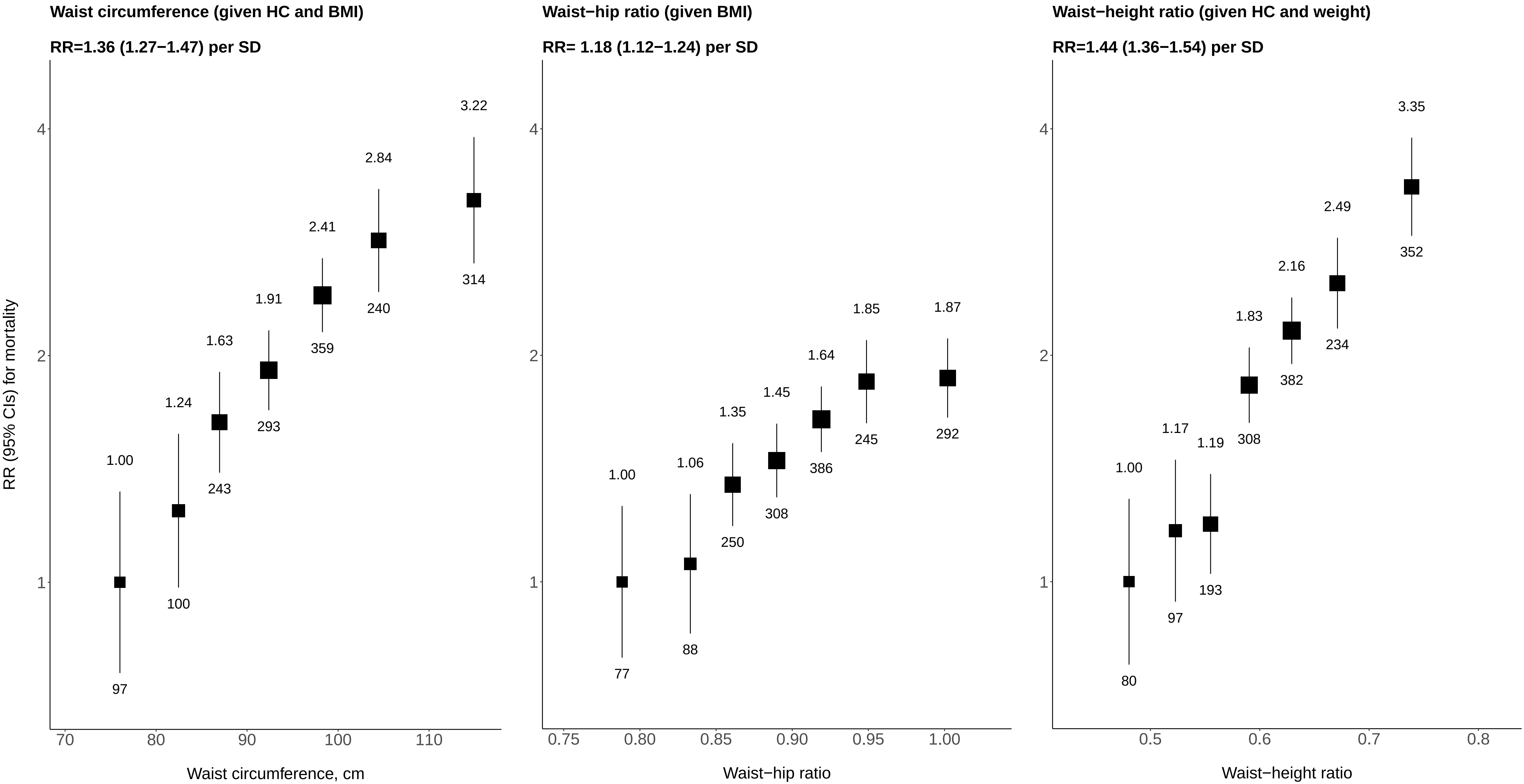
Analyses and conventions as per figure 7.1.

**Figure 7.3: Overall relevance of waist circumference, WHR and WHtR to vascular-metabolic mortality at ages 40–74 years
(those with HbA1C $\geq 7\%$, diabetes, other chronic disease at recruitment and the first 5 years of follow-up excluded)**



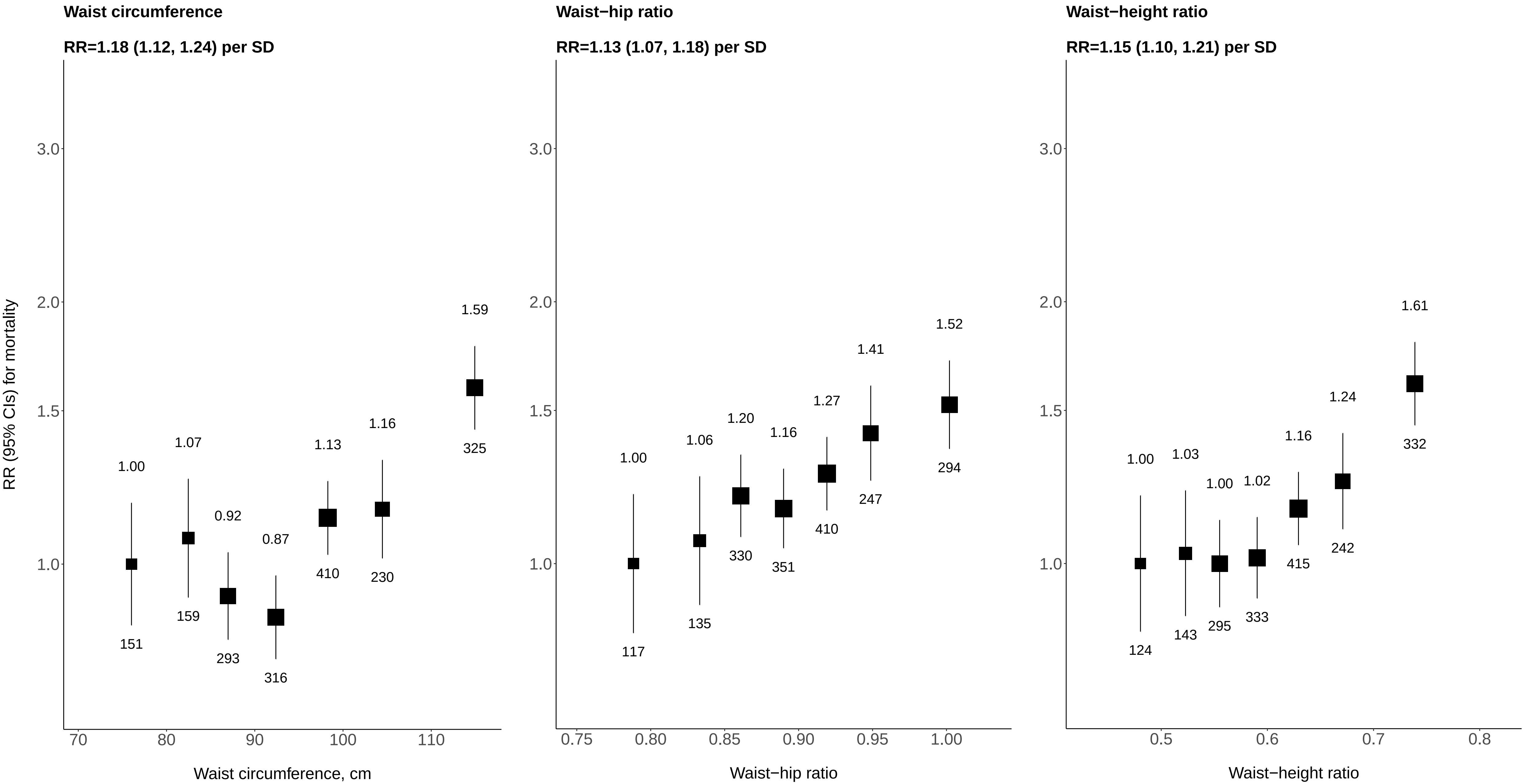
Analyses and conventions as per figure 7.1.

Figure 7.4: Independent relevance of waist circumference, WHR and WHtR to vascular-metabolic mortality at ages 40–74 years (excluding diagnosed diabetes, those with HbA1C $\geq 7\%$, and the first 5 years of follow-up)



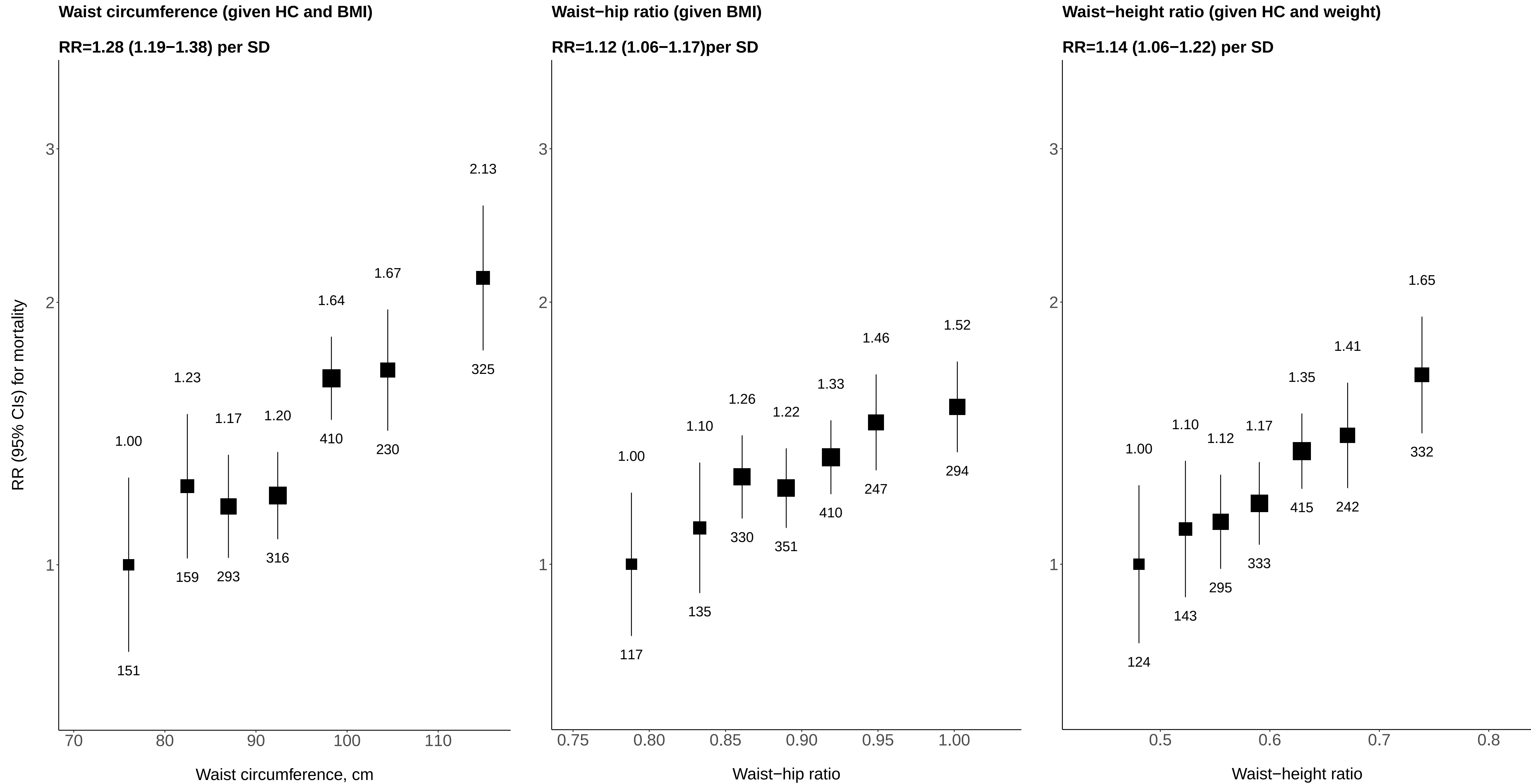
Analyses and conventions as per figure 7.1.

Figure 7.5: Overall relevance of waist circumference, WHR and WHtR to non vascular-metabolic mortality at ages 40–74 years (diabetes, those with HbA1C >=7%, and the first 5 years of follow-up excluded)



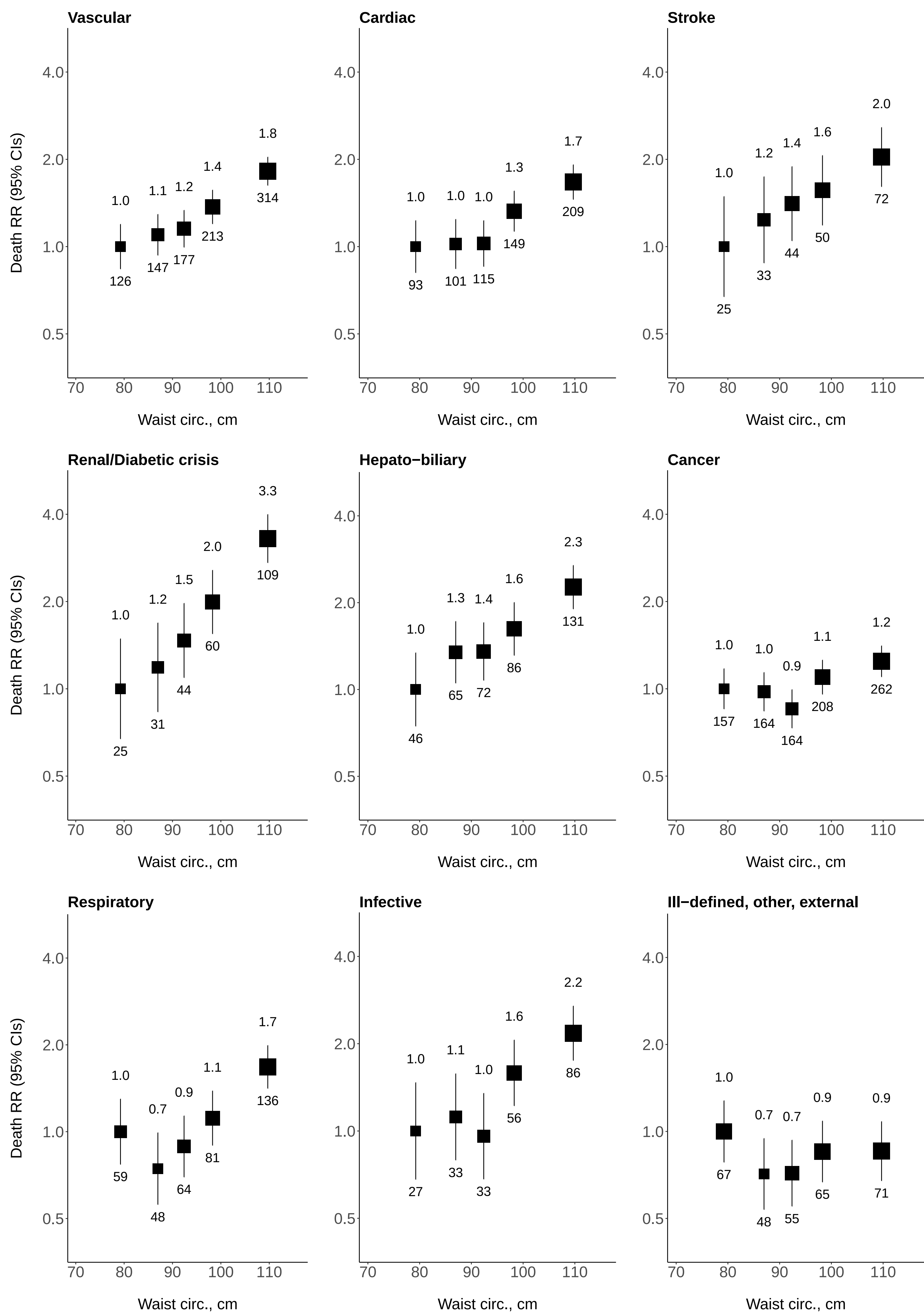
Analyses and conventions as per figure 7.1.

Figure 7.6: Independent relevance of waist circumference, WHR and WHtR to non vascular-metabolic mortality at ages 40–74 years (excluding diagnosed diabetes, those with HbA1C $\geq 7\%$, and the first 5 years of follow-up)



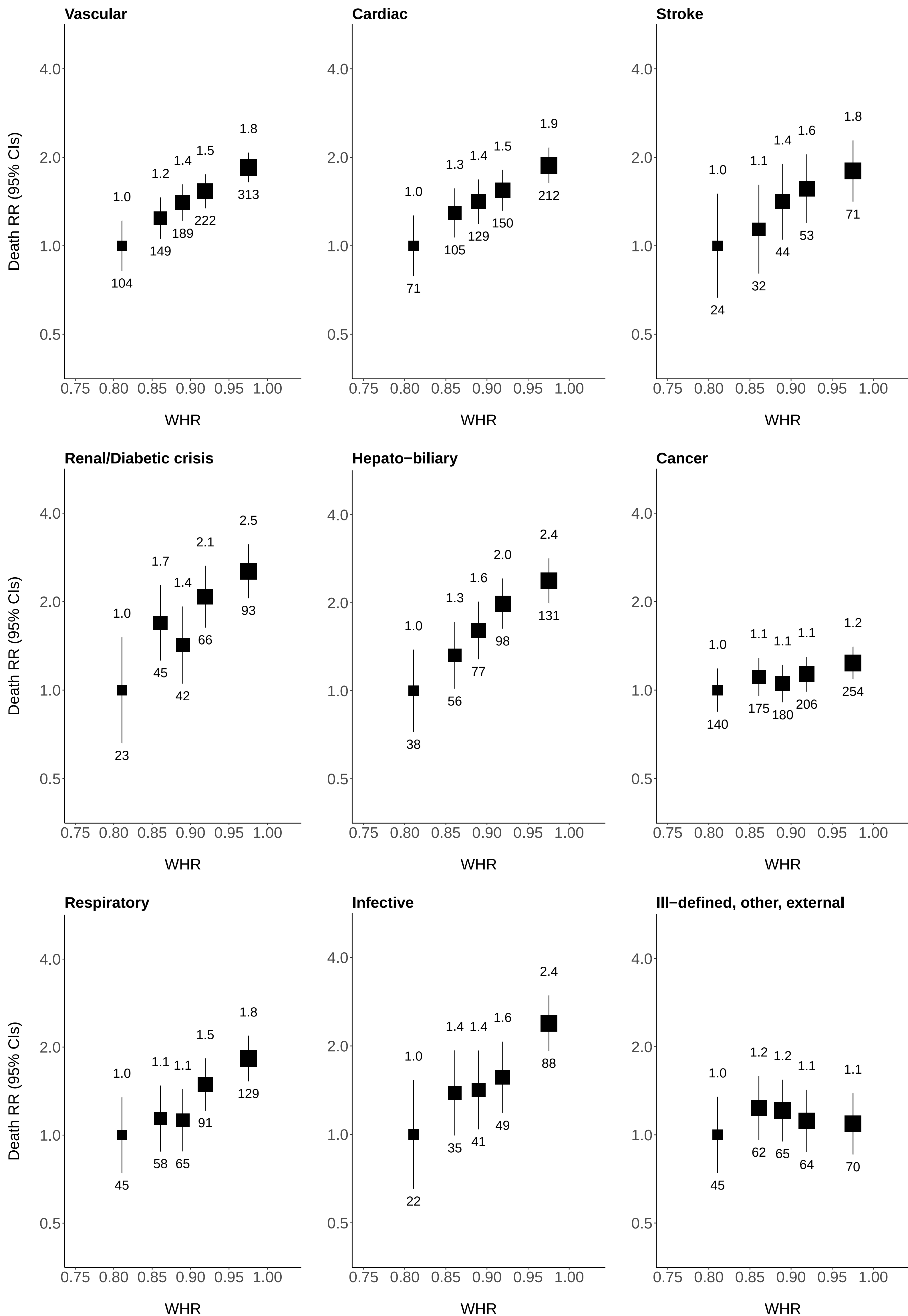
Analyses and conventions as per figure 7.1.

Figure 7.7: Overall relevance of waist circumference to mortality from specific causes at ages 40–74 years



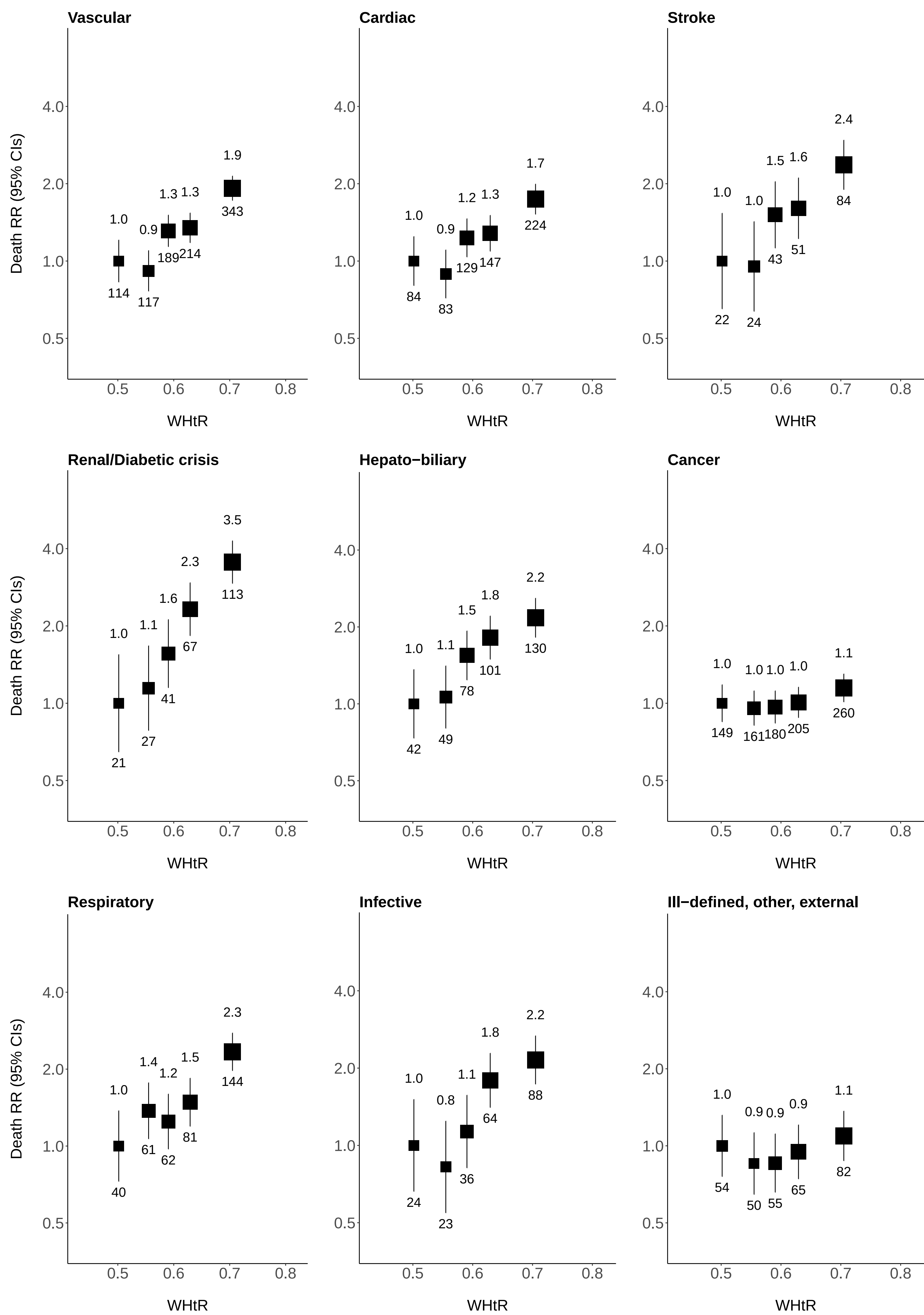
Analyses per Figure 7.1. Adiposity markers grouped by five equally-sized groups of the sex-specific distributions at baseline.

Figure 7.8: Overall Relevance of WHR to mortality from specific causes at ages 40–74 years



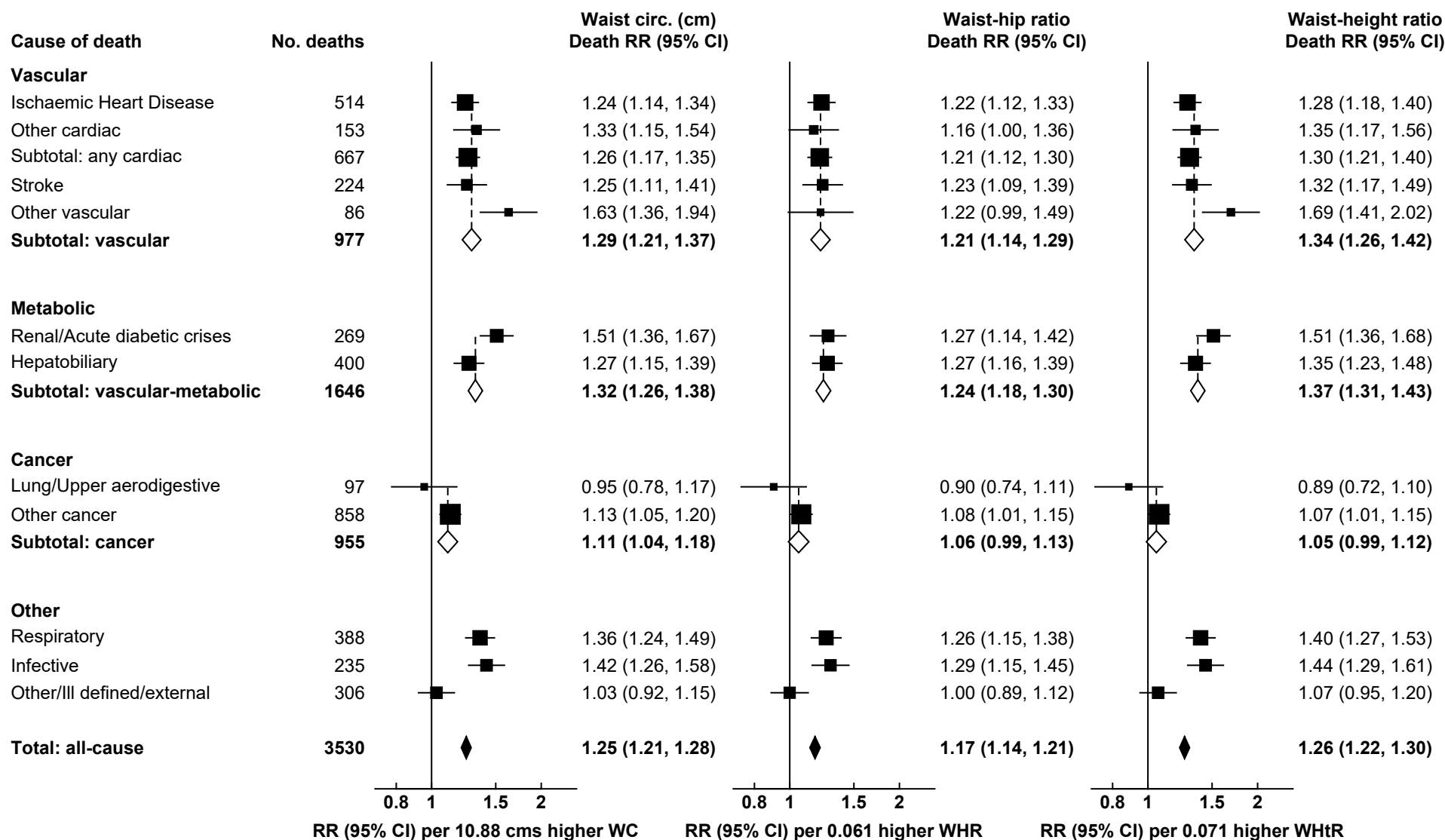
Analyses per Figure 7.7.

Figure 7.9: Overall relevance of waist–height ratio to mortality from specific causes at ages 40–74 years



Analyses per Figure 7.1. Adiposity markers grouped by five equally-sized groups of the sex-specific distributions at baseline.

Figure 7.10. Overall relevance of waist circumference, WHR and WHtR to mortality at ages 40-74 years, by cause
(those with HbA1C $\geq 7\%$, diabetes, and the first 5 years of follow-up excluded)



Analyses as per Figure 7.1. Death rate ratios (RR) were estimated for comparable differences of 1 standard deviation (SD) of the adiposity markers, calculated as the average of the sex-specific SDs at baseline. The other adiposity markers further adjusted for (as indicated in the plot), were grouped by five equally-sized groups of the sex-specific distributions at baseline. WC = Waist circumference; WHR = Waist-hip ratio; WHtR = Waist-height ratio.

Table 7.1: Independent associations of waist circumference, WHR and WHtR with deaths at ages 40-74 years, by cause

Cause death	further adjusted for...	No. deaths	Waist circ. (cm)	WHR	WHtR
			BMI and HC	BMI	HC and weight
			RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Vascular					
Ischaemic Heart Disease		514	1.29 (1.13-1.49)	1.18 (1.08-1.29)	1.37 (1.22-1.54)
Other cardiac		153	1.32 (1.05-1.67)	1.12 (0.95-1.31)	1.35 (1.11-1.65)
Subtotal: any cardiac		667	1.30 (1.16-1.47)	1.16 (1.07-1.26)	1.37 (1.24-1.51)
Stroke		224	1.26 (1.03-1.55)	1.19 (1.04-1.35)	1.49 (1.26-1.76)
Other vascular		86	1.97 (1.54-2.51)	1.18 (0.96-1.46)	1.78 (1.40-2.25)
Subtotal: vascular		977	1.36 (1.23-1.50)	1.17 (1.10-1.25)	1.44 (1.32-1.56)
Metabolic					
Renal/Acute diabetic crises		269	1.43 (1.21-1.69)	1.16 (1.03-1.31)	1.41 (1.22-1.64)
Hepatobiliary		400	1.31 (1.13-1.53)	1.22 (1.10-1.34)	1.48 (1.31-1.68)
Subtotal: vascular-metabolic		1646	1.36 (1.27-1.47)	1.18 (1.12-1.24)	1.44 (1.36-1.54)
Cancer					
Lung/Upper aero-digestive		97	0.95 (0.67-1.35)	0.93 (0.75-1.15)	0.78 (0.58-1.05)
Other cancer		858	1.12 (1.00-1.25)	1.06 (0.99-1.14)	0.97 (0.88-1.06)
Subtotal: cancer		955	1.10 (0.99-1.22)	1.05 (0.98-1.12)	0.95 (0.87-1.04)
Other					
Respiratory		388	1.61 (1.40-1.84)	1.23 (1.12-1.36)	1.57 (1.39-1.78)
Infective		235	1.60 (1.35-1.89)	1.26 (1.11-1.42)	1.52 (1.30-1.77)
Other/III-defined/external		306	1.12 (0.93-1.36)	1.02 (0.90-1.15)	1.13 (0.96-1.32)
Total: all-cause		3530	1.32 (1.25-1.38)	1.14 (1.1-1.18)	1.29 (1.24-1.35)

Analyses as per figure 7.10, with further adjustments for other adiposity markers, as indicated. BMI= Body Mass Index; HC=Hip circumference.

Table 7.2: Overall associations of waist circumference, WHR and WHtR with deaths at ages 40-74 years by cause, among never smokers

		Waist circ. (cm)	WHR	WHtR
Cause death	No. deaths	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Vascular				
Ischaemic Heart Disease	195	1.23 (1.08-1.40)	1.16 (1.01-1.33)	1.28 (1.13-1.46)
Other cardiac	82	1.43 (1.18-1.73)	1.18 (0.96-1.46)	1.46 (1.21-1.77)
Subtotal: any cardiac	277	1.29 (1.15-1.44)	1.17 (1.04-1.31)	1.34 (1.20-1.49)
Stroke	102	1.39 (1.17-1.66)	1.22 (1.02-1.47)	1.48 (1.25-1.74)
Other vascular	37	2.15 (1.72-2.68)	1.32 (0.99-1.76)	2.21 (1.76-2.77)
Subtotal: vascular	416	1.39 (1.28-1.52)	1.20 (1.09-1.31)	1.45 (1.33-1.58)
Metabolic				
Renal/Acute diabetic crises	115	1.63 (1.40-1.89)	1.19 (1.00-1.42)	1.59 (1.37-1.85)
Hepatobiliary	145	1.29 (1.11-1.51)	1.24 (1.07-1.45)	1.38 (1.19-1.59)
Subtotal: vascular-metabolic	676	1.41 (1.32-1.51)	1.20 (1.12-1.29)	1.46 (1.37-1.56)
Cancer				
Lung/Upper aero-digestive	26	1.00 (0.68-1.47)	0.78 (0.53-1.16)	1.07 (0.74-1.55)
Other cancer	451	1.16 (1.06-1.26)	1.06 (0.96-1.16)	1.10 (1.01-1.21)
Subtotal: cancer	477	1.15 (1.05-1.25)	1.04 (0.95-1.14)	1.10 (1.01-1.20)
Other				
Respiratory	182	1.40 (1.23-1.60)	1.24 (1.08-1.42)	1.42 (1.25-1.62)
Infective	109	1.57 (1.34-1.85)	1.18 (0.98-1.41)	1.56 (1.33-1.83)
Other/III-defined/external	117	0.98 (0.82-1.18)	1.02 (0.85-1.23)	1.02 (0.85-1.22)
Total: all-cause	1561	1.30 (1.25-1.37)	1.14 (1.09-1.2)	1.31 (1.26-1.37)

Analyses as per Figure 7.10.

Table 7.3: HbA1c and SBP mediated associations of waist circumference, WHR and WHtR to major vascular-metabolic causes of death at ages 40-74 years

	Waist circ. (cm)	Wald χ^2	WHR	Wald χ^2	WHtR	Wald χ^2
Vascular-metabolic (n=1,600)						
plus confounders*	1.32 (1.26-1.38)	144.3	1.23 (1.18-1.29)	77.5	1.37 (1.31-1.44)	186.5
plus HbA1c only [†]	1.31 (1.25-1.38)	130.4	1.22 (1.17-1.28)	69.6	1.32 (1.26-1.39)	138.9
plus SBP only [†]	1.27 (1.21-1.33)	102.0	1.21 (1.15-1.27)	60.6	1.37 (1.31-1.43)	172.4
plus adiposity marker**	1.36 (1.26-1.47)	65.8	1.17 (1.12-1.23)	39.8	1.44 (1.36-1.54)	132.0
plus HbA1c only	1.36 (1.26-1.46)	63.7	1.17 (1.11-1.23)	38.4	1.44 (1.35-1.53)	127.5
plus SBP only	1.33 (1.23-1.43)	55.5	1.16 (1.11-1.22)	35.3	1.41 (1.32-1.50)	112.4
Any vascular (n=950)						
plus confounders	1.29 (1.22-1.37)	70.9	1.21 (1.14-1.29)	38.3	1.34 (1.27-1.42)	94.6
plus HbA1c only	1.28 (1.20-1.36)	60.0	1.20 (1.13-1.28)	32.8	1.33 (1.25-1.41)	82.6
plus SBP only	1.23 (1.16-1.31)	45.6	1.18 (1.11-1.26)	28.2	1.29 (1.21-1.37)	65.3
plus adiposity marker	1.37 (1.24-1.51)	39.5	1.17 (1.09-1.25)	21.9	1.44 (1.33-1.56)	76.9
plus HbA1c only	1.36 (1.23-1.50)	37.1	1.16 (1.09-1.24)	20.4	1.43 (1.32-1.55)	71.6
plus SBP only	1.33 (1.20-1.46)	31.9	1.16 (1.08-1.23)	18.7	1.40 (1.29-1.52)	62.9
Ischaemic Heart Disease (n=499)						
plus confounders	1.24 (1.14-1.35)	24.9	1.22 (1.12-1.33)	20.4	1.29 (1.18-1.40)	33.7
plus HbA1c only	1.23 (1.13-1.34)	21.3	1.21 (1.11-1.32)	18.3	1.24 (1.14-1.35)	23.0
plus SBP only	1.19 (1.09-1.30)	15.7	1.19 (1.09-1.30)	15.5	1.28 (1.17-1.39)	29.7
plus adiposity marker	1.30 (1.13-1.50)	13.1	1.17 (1.07-1.29)	11.6	1.36 (1.21-1.53)	26.5
plus HbA1c only	1.29 (1.12-1.49)	12.4	1.17 (1.07-1.28)	11.2	1.36 (1.20-1.53)	24.9
plus SBP only	1.27 (1.10-1.46)	10.6	1.16 (1.06-1.27)	10.1	1.33 (1.18-1.49)	21.5
Any cerebrovascular (n=219)						
plus confounders	1.24 (1.10-1.41)	11.8	1.24 (1.09-1.40)	11.4	1.32 (1.17-1.49)	19.6
plus HbA1c only	1.23 (1.08-1.39)	9.6	1.23 (1.08-1.39)	10.0	1.30 (1.15-1.48)	16.9
plus SBP only	1.14 (1.01-1.30)	8.8	1.19 (1.05-1.36)	7.4	1.22 (1.07-1.38)	9.3
plus adiposity marker	1.28 (1.04-1.57)	5.3	1.20 (1.05-1.36)	7.1	1.51 (1.28-1.78)	23.2
plus HbA1c only	1.27 (1.03-1.57)	5.0	1.19 (1.04-1.36)	6.8	1.49 (1.26-1.77)	21.6
plus SBP only	1.21 (0.98-1.49)	3.2	1.18 (1.03-1.34)	5.7	1.43 (1.20-1.69)	16.8
Renal/Diabetic crisis (n=264)						
plus confounders	1.50 (1.35-1.67)	58.7	1.27 (1.13-1.42)	16.9	1.51 (1.36-1.67)	57.8
plus HbA1c only	1.45 (1.30-1.61)	44.0	1.23 (1.09-1.38)	11.9	1.45 (1.30-1.62)	43.4
plus SBP only	1.43 (1.29-1.59)	42.6	1.23 (1.10-1.38)	12.6	1.44 (1.29-1.60)	42.4
plus adiposity marker	1.42 (1.19-1.68)	16.0	1.16 (1.02-1.31)	5.4	1.40 (1.21-1.63)	20.0
plus HbA1c only	1.38 (1.16-1.64)	13.4	1.14 (1.01-1.29)	4.2	1.36 (1.17-1.58)	16.3
plus SBP only	1.38 (1.16-1.63)	13.3	1.14 (1.01-1.29)	4.6	1.36 (1.17-1.59)	16.1

*Analyses per Figure 7.10, showing estimates per 1SD higher marker of abdominal adiposity across the full ranges, adjusted for confounders, now restricted to 33,441 men and 71,655 women with complete measures of SBP and HbA1c. † Further adjustment of the main model for that mediator only.

** Waist circ. adjusted for BMI and hip circ., WHR adjusted for BMI, WHtR adjusted for hip circ. and weight.

Table 7.4: Metabolic mediated associations of waist circumference to major causes of vascular-metabolic mortality at ages 40-74 years

Mediator adjustment	Vascular-metabolic (n=450)	Wald χ^2	Vascular (n=262)	Wald χ^2	IHD (n=139)	Wald χ^2	Stroke (n=62)	Wald χ^2	Renal/Diabetic* (n=75)	Wald χ^2
Overall										
per 1SD [†]	1.34 (1.23-1.46)	43.5	1.32 (1.18-1.48)	23.4	1.53 (1.23-1.89)	14.7	1.53 (1.23-1.89)	14.7	1.43 (1.16-1.75)	11.5
plus HbA1c ^{††}	1.31 (1.20-1.43)	34.7	1.28 (1.14-1.44)	17.3	1.46 (1.16-1.83)	10.7	1.46 (1.16-1.83)	10.7	1.37 (1.11-1.69)	8.3
plus SBP ^{††}	1.29 (1.18-1.41)	31.5	1.27 (1.13-1.42)	16.1	1.40 (1.12-1.74)	8.6	1.40 (1.12-1.74)	8.6	1.35 (1.10-1.67)	8.0
plus HDL-c ^{††}	1.33 (1.22-1.45)	42.5	1.32 (1.17-1.47)	22.6	1.56 (1.25-1.94)	15.8	1.56 (1.25-1.94)	15.8	1.40 (1.14-1.72)	10.1
plus non HDL-c ^{††}	1.33 (1.22-1.45)	43.2	1.32 (1.18-1.47)	22.9	1.52 (1.22-1.88)	14.3	1.52 (1.22-1.88)	14.3	1.41 (1.15-1.74)	10.9
plus TG ^{††}	1.34 (1.23-1.47)	44.4	1.32 (1.18-1.48)	22.7	1.54 (1.24-1.91)	15.0	1.54 (1.24-1.91)	15.0	1.43 (1.16-1.76)	11.7
Independent of BMI and hip circ.										
per 1SD	1.39 (1.20-1.60)	43.5	1.38 (1.15-1.67)	11.4	1.70 (1.21-2.37)	9.5	1.70 (1.21-2.37)	9.5	1.66 (1.19-2.30)	9.1
plus HbA1c	1.37 (1.18-1.58)	34.7	1.36 (1.12-1.64)	10.0	1.66 (1.18-2.34)	8.4	1.66 (1.18-2.34)	8.4	1.62 (1.17-2.26)	8.2
plus SBP	1.35 (1.17-1.57)	31.5	1.35 (1.12-1.63)	9.6	1.60 (1.14-2.25)	7.5	1.60 (1.14-2.25)	7.5	1.60 (1.15-2.23)	7.8
plus HDL-c	1.38 (1.19-1.59)	42.5	1.38 (1.14-1.66)	11.0	1.74 (1.24-2.45)	10.1	1.74 (1.24-2.45)	10.1	1.61 (1.16-2.24)	7.9
plus non HDL-c	1.38 (1.19-1.60)	43.2	1.38 (1.14-1.66)	11.1	1.69 (1.21-2.36)	9.4	1.69 (1.21-2.36)	9.4	1.65 (1.18-2.30)	8.6
plus TG	1.39 (1.20-1.60)	44.4	1.38 (1.14-1.67)	11.2	1.71 (1.22-2.39)	9.7	1.71 (1.22-2.39)	9.7	1.65 (1.19-2.31)	8.8

[†] Analyses as per Table 7.3, showing estimates from the main model adjusted for confounders, now restricted to 29,960 participants with complete information on NMR measured lipids. ^{††} Further adjustment of the main model for that mediator only. IHD=Ischaemic Heart Disease. *Refers to diabetic crises. HbA1c=glycosylated haemoglobin; SBP=systolic blood pressure; HDL-c= high-density cholesterol; TG=triglycerides.

Table 7.5: Metabolic mediated associations of WHR to major causes of vascular-metabolic mortality at ages 40-74 years

Mediator adjustment	Vascular-metabolic (n=450)	Wald χ^2	Vascular (n=262)	Wald χ^2	IHD (n=139)	Wald χ^2	Stroke (n=62)	Wald χ^2	Renal/Diabetic* (n=75)	Wald χ^2
Overall										
per 1SD	1.33 (1.22-1.45)	40.2	1.33 (1.19-1.49)	24.2	1.39 (1.20-1.62)	18.5	1.45 (1.18-1.79)	12.2	1.38 (1.12-1.70)	9.4
plus HbA1c	1.31 (1.20-1.43)	34.6	1.31 (1.16-1.47)	20.2	1.36 (1.17-1.59)	15.3	1.42 (1.14-1.77)	10.0	1.35 (1.09-1.67)	7.7
plus SBP	1.30 (1.19-1.42)	32.4	1.30 (1.16-1.46)	19.4	1.38 (1.18-1.61)	16.9	1.38 (1.12-1.71)	8.8	1.34 (1.08-1.66)	7.3
plus HDL-c	1.33 (1.22-1.45)	40.8	1.33 (1.19-1.49)	24.9	1.39 (1.19-1.61)	18.5	1.47 (1.19-1.82)	13.0	1.35 (1.10-1.66)	8.0
plus non HDL-c	1.33 (1.22-1.45)	41.4	1.33 (1.19-1.49)	24.8	1.39 (1.20-1.61)	18.7	1.45 (1.17-1.78)	12.1	1.37 (1.11-1.69)	8.9
plus TG	1.34 (1.22-1.46)	42.1	1.33 (1.19-1.49)	24.4	1.38 (1.18-1.60)	16.9	1.45 (1.18-1.79)	12.2	1.40 (1.14-1.72)	10.3
Independent of BMI and hip circ.										
per 1SD	1.27 (1.15-1.39)	23.7	1.28 (1.14-1.45)	16.1	1.36 (1.16-1.60)	13.7	1.40 (1.12-1.74)	8.98	1.29 (1.02-1.62)	4.7
plus HbA1c	1.25 (1.14-1.38)	21.5	1.27 (1.13-1.44)	14.9	1.35 (1.14-1.58)	12.6	1.39 (1.11-1.75)	8.2	1.28 (1.02-1.61)	4.4
plus SBP	1.26 (1.14-1.39)	22.4	1.27 (1.12-1.43)	14.6	1.36 (1.15-1.60)	13.4	1.36 (1.09-1.69)	7.5	1.27 (1.01-1.60)	4.1
plus HDL-c	1.27 (1.15-1.39)	24.2	1.28 (1.14-1.45)	16.7	1.35 (1.15-1.59)	13.8	1.42 (1.13-1.77)	9.4	1.26 (1.00-1.59)	3.9
plus non HDL-c	1.27 (1.15-1.39)	24.2	1.28 (1.14-1.45)	16.5	1.36 (1.16-1.59)	13.9	1.40 (1.12-1.74)	8.9	1.28 (1.02-1.62)	4.4
plus TG	1.27 (1.16-1.40)	25.3	1.28 (1.14-1.45)	16.6	1.35 (1.15-1.59)	13.4	1.39 (1.12-1.73)	8.8	1.31 (1.04-1.64)	5.3

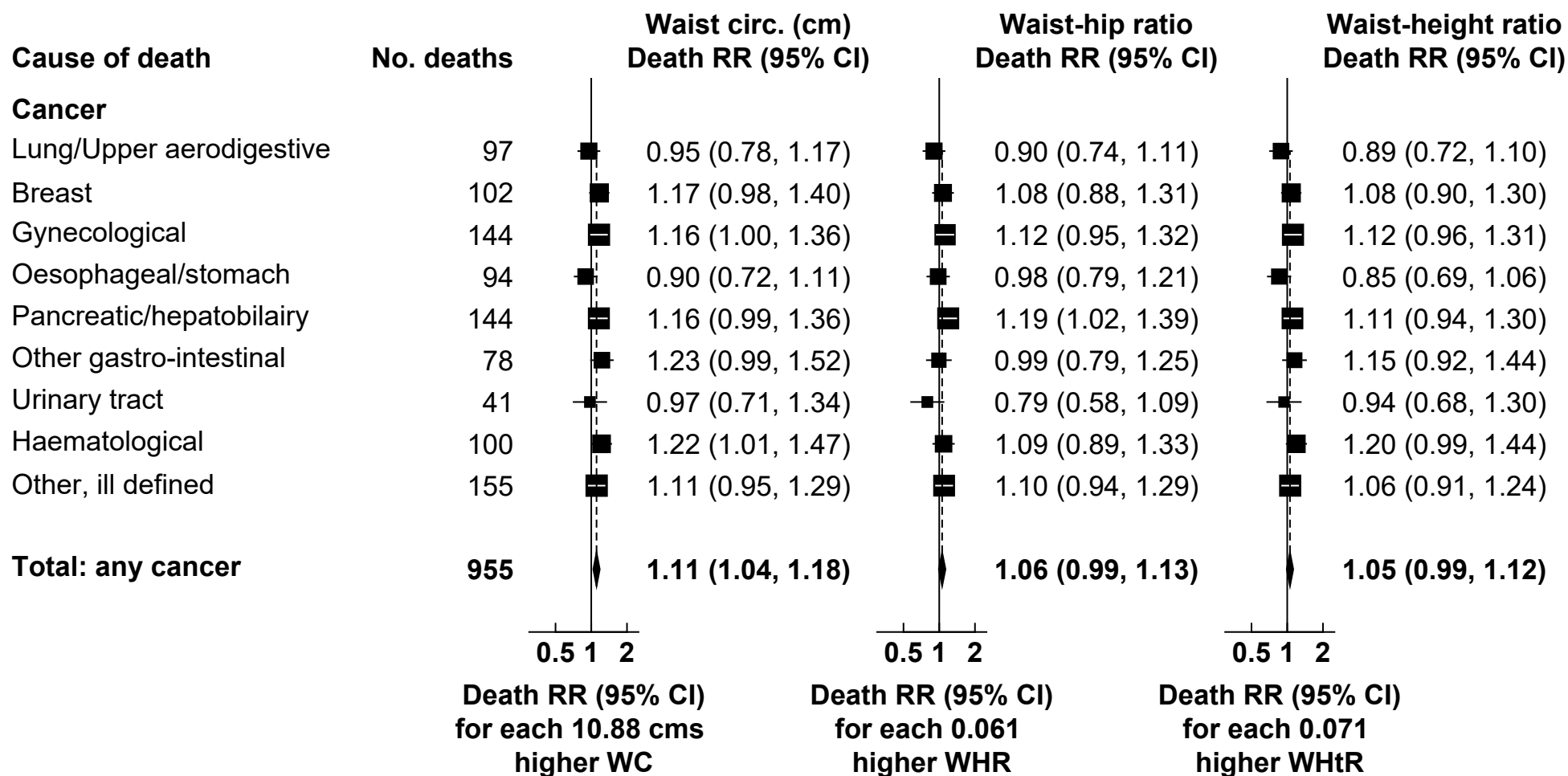
Analyses as per Table 7.4, restricted to those with complete information on NMR lipids. IHD=Ischaemic Heart Disease. *Refers to diabetic crises. HbA1c=glycosylated haemoglobin; SBP=systolic blood pressure; HDL-c= high-density cholesterol; TG=triglycerides.

Table 7.6: Metabolic mediated associations of WHtR to major causes of vascular-metabolic mortality at ages 40-74 years

Mediator adjustment	Vascular-metabolic (n=450)	Wald χ^2	Vascular (n=262)	Wald χ^2	IHD (n=139)	Wald χ^2	Stroke (n=62)	Wald χ^2	Renal/Diabetic* (n=75)	Wald χ^2
Overall										
per 1SD	1.33 (1.22-1.46)	43.5	1.38 (1.23-1.54)	31.1	1.31 (1.12-1.54)	10.9	1.62 (1.31-1.72)	19.9	1.55 (1.27-1.90)	18.3
plus HbA1c	1.31 (1.20-1.44)	34.7	1.32 (1.18-1.48)	22.6	1.26 (1.07-1.48)	7.4	1.49 (1.20-1.85)	12.7	1.49 (1.21-1.83)	13.9
plus SBP	1.30 (1.19-1.42)	31.5	1.34 (1.19-1.50)	24.0	1.29 (1.09-1.52)	8.9	1.55 (1.24-1.94)	15.1	1.50 (1.22-1.85)	14.4
plus HDL-c	1.33 (1.22-1.45)	42.5	1.37 (1.23-1.53)	30.4	1.30 (1.11-1.52)	10.4	1.65 (1.33-2.04)	21.1	1.53 (1.25-1.87)	16.6
plus non HDL-c	1.33 (1.22-1.45)	41.7	1.37 (1.23-1.54)	30.8	1.31 (1.11-1.53)	10.8	1.61 (1.31-1.99)	19.7	1.55 (1.27-1.89)	18.2
plus TG	1.34 (1.23-1.46)	44.4	1.38 (1.23-1.54)	30.5	1.28 (1.09-1.51)	9.0	1.63 (1.32-2.02)	20.2	1.56 (1.27-1.91)	18.5
Independent of BMI and hip circ.										
per 1SD	1.27 (1.16-1.40)	19.5	1.44 (1.23-1.69)	20.5	1.44 (1.15-1.80)	10.3	1.87 (1.39-2.50)	17.6	1.92 (1.46-2.53)	21.9
plus HbA1c	1.27 (1.15-1.39)	19.5	1.40 (1.19-1.64)	16.7	1.42 (1.13-1.78)	9.3	1.76 (1.31-2.38)	13.9	1.86 (1.41-2.46)	19.2
plus SBP	1.26 (1.15-1.39)	19.5	1.40 (1.20-1.65)	17.1	1.39 (1.11-1.75)	8.2	1.80 (1.33-2.43)	14.8	1.88 (1.42-2.49)	19.8
plus HDL-c	1.27 (1.16-1.40)	19.5	1.44 (1.23-1.68)	20.5	1.43 (1.15-1.78)	10.0	1.91 (1.42-2.57)	18.3	1.89 (1.43-2.49)	20.4
plus non HDL-c	1.27 (1.16-1.40)	19.5	1.44 (1.23-1.69)	20.7	1.44 (1.15-1.80)	10.4	1.86 (1.39-2.49)	17.6	1.92 (1.45-2.53)	21.4
plus TG	1.28 (1.16-1.41)	19.5	1.44 (1.23-1.68)	20.4	1.41 (1.13-1.77)	9.1	1.87 (1.40-2.51)	17.6	1.94 (1.47-2.55)	21.9

Analyses as per Table 7.4, restricted to those with complete information on NMR lipids. IHD=Ischaemic Heart Disease. *Refers to diabetic crises. HbA1c=glycosylated haemoglobin; SBP=systolic blood pressure; HDL-c= high-density cholesterol; TG=triglycerides.

Figure 7.11. Overall relevance of waist circumference, WHR and WHtR to cancer mortality at ages 40-74 years, by type (those with HbA1C $\geq 7\%$, diabetes at baseline, and the first 5 years of follow-up excluded)



Analyses as per Figure 7.10.

Table 7.7: Independent associations of waist circumference, WHR and WHtR with cancer deaths at ages 40-74 years, by subtype

		Waist circ. (cm)	WHR	WHtR
further adjusted for...		BMI and HC	BMI	HC and weight
Cancer deaths	No deaths	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Lung/Upper aero-digestive	97	0.95 (0.67-1.35)	0.93 (0.75-1.15)	0.78 (0.58-1.05)
Breast	102	1.16 (0.84-1.59)	1.05 (0.86-1.28)	0.87 (0.67-1.14)
Gynaecological	144	1.25 (0.96-1.63)	1.10 (0.93-1.30)	1.08 (0.86-1.36)
Oesophageal/stomach	94	0.99 (0.68-1.44)	1.02 (0.82-1.27)	0.81 (0.60-1.10)
Pancreatic/hepatobiliary	144	1.15 (0.88-1.50)	1.17 (0.99-1.38)	1.03 (0.82-1.29)
Other gastro-intestinal	78	0.95 (0.65-1.39)	0.91 (0.71-1.16)	0.86 (0.63-1.19)
Urinary tract	41	0.87 (0.51-1.48)	0.83 (0.59-1.15)	0.78 (0.50-1.22)
Haematological	100	1.05 (0.76-1.45)	1.02 (0.83-1.26)	1.04 (0.80-1.37)
Other/III-defined	155	1.21 (0.95-1.56)	1.10 (0.94-1.30)	1.02 (0.82-1.26)
Subtotal: any cancer	955	1.10 (0.99-1.22)	1.05 (0.98-1.12)	0.95 (0.87-1.04)

Analyses as per figure 7.11, with further adjustments for other adiposity markers, as indicated.

Table 7.8: Overall associations of waist circumference, WHR and WHtR with cancer deaths at ages 40-74 years, among never smokers

Cancer deaths	No. deaths	Waist circ. (cm)	WHR	WHtR
		RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Lung/Upper aero- digestive	26	1.00 (0.68-1.47)	0.78 (0.53-1.16)	1.07 (0.74-1.55)
Breast	74	1.18 (0.96-1.47)	1.03 (0.81-1.30)	1.09 (0.88-1.35)
Gynaecological	79	1.27 (1.04-1.56)	1.14 (0.92-1.42)	1.24 (1.01-1.51)
Oesophageal/stomach	45	0.75 (0.55-1.04)	0.90 (0.66-1.22)	0.71 (0.52-0.98)
Pancreatic/hepatobiliary	76	1.07 (0.86-1.34)	1.18 (0.95-1.46)	1.02 (0.82-1.27)
Other gastro-intestinal	38	1.34 (1.01-1.78)	0.92 (0.66-1.29)	1.24 (0.92-1.67)
Urinary tract	15	1.01 (0.61-1.67)	0.80 (0.47-1.34)	0.97 (0.58-1.62)
Haematological	44	1.41 (1.09-1.83)	1.26 (0.96-1.65)	1.38 (1.06-1.78)
Other/III-defined	80	1.14 (0.92-1.40)	1.00 (0.80-1.25)	1.12 (0.91-1.38)
Subtotal: any cancer	477	1.15 (1.05-1.25)	1.04 (0.95-1.14)	1.10 (1.01-1.20)

Analyses as per Figure 7.10.

Chapter 8: Discussion

This thesis used individual participant data from the Mexico City Prospective Study with measures of general adiposity, specifically, body-mass index (BMI) and predicted fat-mass index (FMI), and measures of abdominal adiposity, specifically, waist circumference (WC), waist-hip ratio (WHR), and waist-height ratio (WHtR) in order to: (1) assess the lifestyle correlates of adiposity and compare the strength of the associations of each marker with traditional metabolic and vascular mediators of adiposity; (2) determine the long-term within-person variability of these adiposity markers; (3) comprehensively assess and compare the association of these adiposity markers with risk of cause-specific mortality; and (4) investigate the additional relevance of selected mediators of adiposity to mortality from vascular or metabolic causes. This chapter reviews the key findings of the thesis, with their strengths and limitations, highlights the novel aspects and implications for future research needed to complement the findings, and discusses the likely relevance for clinical practice and public health.

8.1 Summary of key findings from cross-sectional analyses

The Mexico City Prospective Study is a contemporary cohort of nearly 160,000 adults recruited in the early 2000s, with information on anthropometric markers of adiposity, lifestyle characteristics, medical history, vascular and metabolic risk factors such as measured blood pressure and biomarkers of glucose and lipids, as well as cause-specific mortality during 16 years since enrollment (**Chapter 3**).

8.1.1. Cross-sectional correlates of adiposity markers

Analyses of individual data on 145,659 participants aged 35-89 years showed that nearly a third had a BMI above 30 kg/m² (ie, were obese). All adiposity markers increased steeply with age, up to 60 years of age, after which the association flattened, except for WHR and WHtR which increased with age up to 89 years both in men and in women (**Chapter 4**). Cross-sectional analyses showed high correlations between all markers of adiposity ($r > 0.60$), except for BMI and WHR ($r = 0.16$; **Chapter 4**). Adiposity levels at baseline were strongly and inversely associated with regular leisure-time physical activity and education achieved, were modestly lower among current smokers, but were not associated with drinking habits. These findings suggest possible confounding by lifestyle factors in observational studies of adiposity and disease-specific mortality.

8.1.2 Within-person variability in adiposity markers

The findings in Chapter 4 showed that the extent of within-person variability in adiposity markers was relatively modest. Analyses of serial measurements of BMI, WC and WHR recorded in 6,000 participants without known disease about 15 years apart demonstrated high reproducibility of all the markers of adiposity assessed. Assuming a linear relationship between the RDR and the duration over which it is estimated, the '*mid-point RDR*' estimate was 0.74 for WHR and > 0.85 for all other adiposity markers. These estimates were comparable with those from nearly 60 prospective studies of general populations,¹ and somewhat weaker than estimates obtained from a shorter duration of follow-up from Chinese populations.² The extent of within-person variability in adiposity markers was similar irrespective of age, sex,

socio-demographic and lifestyle characteristics. Overall, the degree of underestimation of the strength of associations with risk of death through the use of baseline adiposity markers in analyses, is likely to be relatively small (albeit somewhat larger for WHR).

8.1.3 Associations of adiposity and selected vascular-metabolic risk factors

Among the participants without diabetes or other chronic disease, and not taking antihypertensive medication at recruitment, all adiposity markers had strong log-linear associations with HbA1c and blood pressure, and curvi-linear associations with the selected lipids, positive with HDL-c and triglycerides, and inverse with non HDL-c (**Chapter 4**). The markers of general adiposity were most strongly predictive of high blood pressure, whereas markers of abdominal adiposity were most strongly predictive of HbA1c and diabetes, with no evidence of any threshold level below which lower adiposity was not associated with lower levels of these risk factors. The findings highlight the partial mediating role of these metabolic and vascular risk factors on the pathways through which excess adiposity mediates vascular or metabolic disease risk and subsequent mortality. Furthermore, the associations between adiposity and HDL-c, non HDL-c and triglycerides, support the hypothesis of adiposity being causally associated with vascular-metabolic diseases.

8.1.3.1 Associations of adiposity with diabetes risk

A striking finding from this thesis is that while adiposity was associated with higher levels of HbA1c, higher BMI was not associated with diabetes prevalence at baseline, but 16-years later, those with extreme levels of BMI at baseline had a 4-

fold higher prevalence of diagnosed diabetes compared to those with lower levels of BMI (**Chapter 4**). These observations differ from previous findings in most populations which showed positive associations of excess adiposity with diabetes. However, the '*prospective*' findings from this thesis are consistent with the evidence from the Prospective Studies Collaboration (PSC) in which obesity increased the prevalence of diabetes almost 5-fold over the full BMI range.³ Other prospective analyses of BMI and waist circumference among 0.5 million lean Chinese from the China Kadoorie Biobank (CKB), also demonstrated a log-linear association between elevated adiposity at age 25 years and incident diabetes, with each 1 SD higher usual adiposity being associated with nearly a doubling in the risk of diabetes, but a more modest risk after mutual adjustment for each other marker (e.g., a 1.3-fold higher for BMI and 1.5-fold higher for waist circumference).⁴ Similar estimates were reported by the European Prospective Investigation on Cancer and Nutrition (EPIC) and the InterAct Consortium.⁵⁻⁷

The analyses from this thesis showed largely positive associations of adiposity with HbA1c at baseline, and estimated that each 1 SD higher general adiposity was associated with 0.1% higher HbA1c, whereas the association with each 1 SD higher abdominal adiposity was only half as strong. The associations of BMI and of FMI with HbA1c remained largely unaffected by additional account for abdominal adiposity, whereas for a given amount of general adiposity, the associations of WC and of WHR weakened by about a third. Observational studies of adiposity and glycosylated haemoglobin, to compare with, are rare. Meanwhile, the genetic evidence on the effects of adiposity on biomarker-signatures of diabetes is somewhat heterogeneous, whereas genetic studies of type 2 diabetes are

unanimously positive. For instance, several studies among over 0.2 million participants from the UK Biobank (UKB),⁸⁻¹⁰ the ENGAGE Consortium¹¹ and 8 other cohorts,¹² confirmed a causal association of genetically-instrumented BMI, WHR, or BMI-adjusted-WHR with fasting insulin, whereas findings were conflicting for HbA1c, fasting glucose, and 2-hours oral tolerance test to glucose, some suggesting causal associations, others not. Only one study of 67,553 genotyped Europeans from the ENGAGE Consortium reported a 0.2% (95% CI 0.01-0.4) higher HbA1c with each SD genetically-elevated BMI,¹¹ which are twice as strong compared to the estimates from this thesis. By comparison to these genetic estimates, the magnitude of the effects observed in the present Mexican cohort were modest, likely due to the exclusion of both screen-detected diabetes and pre-diagnosed cases, as well as lack of accounting for incident disease and the life-long effects of excess adiposity otherwise captured by the genetic analyses.

By contrast to most biomarker studies, the genetic studies of adiposity and type 2 diabetes showed stronger causal associations with genetically-elevated WHR (odd ratios [OR] of 1.57; 95% CIs 1.34-1.83), than with genetically-elevated BMI (1.27; 1.18–1.36), including for BMI-adjusted-WHR (1.77; 1.57-2.00).¹² Only one study of 14 cohorts included in the CARDIoGRAMplus, MEGASTROKE and the DIAGRAM collaborations estimated that the causal effects of 97 BMI-associated SNPs on the incidence of diabetes were stronger than those of 47 WHR-associated SNPs (adjusted for BMI), (ORs of 1.98; 1.41-2.78 versus 1.82; 1.38-2.42, respectively).¹³ Nonetheless, the most recent study from nearly 0.5 million adults from the UKB involving 567 BMI-associated SNPs and 324 WHR-associated SNPs, concluded that the causal effect of genetically-elevated WHR on mortality from type 2 diabetes

decreased after adjustment for genetically-elevated BMI (from an OR of 3.62; 3.32-3.95 to 2.10; 1.96-2.26), whereas the causal effect of genetically-elevated BMI remained strong after adjustment for genetically-elevated WHR (3.18; 2.97-3.39).⁸ The discrepant results between the relevance of abdominal versus general adiposity in these genetic analyses are not fully understood, and the proposed mechanisms of diabetes are complex, including high insulin resistance or insulin tolerance due to impaired liver enzymes.^{14,15}

The findings from this thesis support the hypothesis that excess adiposity in general, and abdominal adiposity in particular, causes elevated levels of glucose in the blood and consequent development of diabetes, but among Mexican adults with pre-existing diabetes, poor glycaemic control (characteristic in the present cohort) results in pathological weight loss, distorting the 'true association' of adiposity with diabetes risk.

8.1.3.2 Associations of adiposity with blood pressure

In this cohort, each 1 SD higher unit of general adiposity (corresponding to 4.7 kg/m² of BMI and 3.7 kg/m² of FMI) was associated with a 3 mmHg higher SBP and a 2 mmHg higher DBP. For a given amount of general adiposity, any marker of abdominal adiposity studied in this thesis was less strongly related to blood pressure. These findings differ to some extent from previous observations in other populations. For instance, in a meta-analysis of 900,000 individuals from mostly Western populations with moderate levels of adiposity recruited during the second half of the 20th century, each 5 kg/m² higher BMI was associated with about a 5 mmHg higher SBP,³ while in a more contemporary study of 500,000 mostly lean

Chinese adults, each 5 kg/m² higher BMI was associated with about a 8 mmHg higher SBP.¹⁶ The estimates from this Mexican population with very high levels of general and abdominal adiposity were more modest, possibly due to differences in other risk factors. For example, in China, the dietary intake of sodium (estimated by 24 hours urinary excretion) is higher than in Mexico¹⁷ or other Western populations.^{18,19} Since dietary sodium predicts SBP independently of BMI,^{20,21} variation in sodium intake may partly account for between-population differences. Alternatively, different methodologies for the measurement of blood pressure or central anthropometry by different studies, might also contribute. For instance, by contrast with the use of automated devices to measure blood pressure in the CKB study,¹⁶ blood pressure at entry into the Mexico City study (as for most other cohorts in the meta-analysis above), relied on the use of manual sphygmomanometers, which are subject to observer-dependent random errors and digit preference.²¹

The cross-sectional estimates obtained from this Hispanic population were nonetheless broadly comparable with estimates obtained by Mendelian-randomisation studies of adiposity and vascular-metabolic traits. For example, a study of 14 BMI-associated SNPs from 34,500 adults from 8 European population-based cohorts, reported that each 1 kg/m² genetically-elevated BMI increased SBP by 0.7 (95% CIs 0.2-1.2) mmHg.¹² Similarly, a study of the FTO polymorphism in over 145,000 participants from 30 mostly Caucasian cohorts, reported that each 1 kg/m² genetically-elevated BMI was associated with a 0.9 (0.5–1.3) mmHg higher SBP and a 0.6 (0.6–0.7) mmHg higher DBP.²² Similarly, among over 0.6 million adults from the UK Biobank, EPIC and the Fenland cohorts, each 1 SD genetically-elevated waist circumference was associated with a 3.0 (2.0-4.0) mmHg higher SBP

and a 2.0 (1.0- 2.0) mmHg higher DBP, respectively,⁹ whereas each SD of 48 WHR-associated SNPs (adjusted for BMI) was associated with a 2.1 (1.2-3.0) mmHg higher SBP and a 1.3 (0.8 to 1.8) mmHg higher DBP.¹⁰

The results from this thesis therefore support the hypothesis generated by previous studies that, in Mexican adults, general adiposity may be more relevant to blood pressure than the location of the adipose tissue per se.^{23,24} Furthermore, the present findings are also consistent with those from 500,000 Chinese adults showing little association between abdominal adiposity and blood pressure independent of BMI, and no suggestion of threshold levels.² However, some studies in other populations have reported that while general and abdominal adiposity both predict the development of hypertension,²⁵ markers of abdominal adiposity may be more discriminatory than markers of general adiposity.²⁶ Proposed mechanisms underlying the associations of adiposity with blood pressure are complex, and include dysfunctional adipose tissue promoting activation of the sympathetic nervous system and the renin-angiotensin-aldosterone pathways, and adiponectin deficiency reducing nitric oxide production and increasing systemic inflammation and oxidative stress.^{23,24}

8.1.3.3 Associations of adiposity with selected lipids

On average, each 1 SD higher level of general or abdominal adiposity were associated with a 0.02 to 0.03 mmol/L lower HDL-c, a 0.02 to 0.03 mmol/L higher non HDL-c, and a 0.08 to 0.10 mmol/L higher triglycerides. Mutual adjustment for other markers of adiposity did not alter these associations, except for triglycerides. In particular, higher FMI, WC and WHR, were independently associated with 0.05 to

0.06 mmol/L higher levels of triglycerides (**Chapter 4**). By comparison, observational analyses from nearly 1 million Western adults from 57 cohorts in the PSC collaboration, suggest stronger cross-sectional associations between BMI and traditional lipids from biochemistry than those observed in the present cohort. Specifically, in the PSC, each 5 kg/m² higher BMI in the range of 15-30 kg/m² was associated with 0.15 mmol/L lower HDL-c and 0.45 mmol/L higher non HDL-c.³ The results from this cohort also appeared 2 to 5-fold weaker compared to estimates from over 220,000 adults from 58 prospective studies in the Emerging Risk Factors Collaboration (ERFC), in which each 1 SD higher BMI was associated with 0.19 mmol/L higher non HDL-c, 0.11 mmol/L lower HDL-c and 0.16 mmol/L higher triglycerides, and each 1 SD higher waist circumference or WHR were associated with 0.21 mmol/L higher non HDL-c, 0.12 mmol/L lower HDL-c and 0.18 mmol/L higher triglycerides, respectively.¹ These differences could be due to the exclusion of those with screen-detected diabetes in the present cohort. However, the estimates from the present cohort are largely comparable with those from analyses of NMR-metabolites among nearly 13,000 young European adults, which estimated that each 1 kg/m² higher BMI is observationally associated with 0.04 SDs higher non HDL-c, 0.06 SDs lower HDL-c, and 0.08 SDs higher triglycerides, and causally associated with 0.05 SDs higher non HDL-c, 0.04 SDs lower HDL-c, and 0.07 SDs higher triglycerides, with largely similar estimates for waist circumference.²⁷ A larger MR analysis of nearly 35,000 European adults of whom 13% had type 2 diabetes showed broadly similar estimates to those from this thesis; specifically, each 1 kg/m² genetically-elevated BMI was causally associated with 0.02 mmol/L lower HDL-c and 0.81 mmol/L higher triglyceride levels.¹²

8.2 Summary of key findings from analyses of mortality

In this Mexican study, both general and abdominal adiposity were strongly and independently related to mortality. Both measured BMI and estimated FMI (which was reasonably predictable from age, sex, and other anthropometric variables), had a J-shaped association with all-cause mortality, but at a given amount of lean mass index (LMI), the association of FMI to mortality became approximately log-linear, and particularly strong for vascular-metabolic causes of death (**Chapters 5 and 6**). Nonetheless, the chief finding of the present thesis is that the association of BMI and predicted FMI with mortality would have been *U-shaped* before excluding participants with pre-existing diabetes (in addition to other chronic disease at baseline). This association was *qualitatively distorted* by the ‘*strongly inverse*’ associations with mortality risk among participants with screen-detected or diagnosed diabetes at the time adiposity markers were measured. After exclusion of those with diabetes, the association of BMI and predicted FMI with mortality became *positively J-shaped*, illustrating how *misleading* analyses of general adiposity with mortality could be, should exclusion of diabetes not apply. In Mexico, poorly controlled diabetes is common, results in weight loss,^{28,29} and as demonstrated in this thesis, failure to adequately control for it can ultimately result in *spurious inverse associations* between BMI, FMI and mortality in those with diabetes. The approach of minimising the *reverse causality bias* by excluding participants with diabetes from the main analyses in this thesis (in addition to other chronic diseases and early deaths), led to remarkably consistent *qualitative* results with previous findings from Western populations in the Global BMI Collaboration,³⁰ the PSC,³ the ERFC¹ and the EPIC studies.³¹ Thus, the present results refuted the claim of an ‘*Hispanic obesity paradox*’ suggested by previous analyses in Hispanic populations which did not

account for pre-existing disease resulting in low but no overweight or abdominal obesity being associated with higher risk of all-cause mortality,³²⁻³⁷ or by a recent large US study reporting that for a given waist circumference, BMI appeared to be unrelated to mortality.³⁸ Furthermore, this thesis highlighted the resulting 10-year reduction in life expectancy associated with a BMI of 40 kg/m² compared with a BMI of 25 kg/m² in this Mexican population (**Chapter 5**), which is also comparable with the estimates from Western populations.

One other major finding from this thesis was to clarify that at a given amount of LMI, predicted FMI is log-linearly associated to premature mortality from cardiac, cerebrovascular, renal or acute diabetic crises, as well as hepatobiliary, respiratory and infective causes throughout the whole ranges, whereas there was no indication of higher mortality from cancer (**Chapter 6**). These findings are also consistent with those from other populations that reported continuous positive associations of predicted fat mass with all-cause and specific mortality.^{39,40} Nonetheless, some previous studies of body-mass relying on insufficient number of events from specific causes lead to heterogeneous findings, including J- or U-shaped associations of higher fat mass with mortality risk.^{34,41,42} Again, these *qualitative differences* between studies likely reflect the play of chance due to small sample sizes, and differential account for pre-existing disease or follow-up time-lags.

In addition to clarifying the associations of general adiposity with mortality in this Mexican population, the present analyses also demonstrated that waist circumference had particularly strong positive effects on mortality, and additional

account for BMI and HC, showed no threshold level below which lower waist circumference was not associated with lower mortality risk (**Chapter 7**). These findings suggest that abdominal adiposity is particularly hazardous and of substantial relevance for predicting mortality risk in Mexicans, in addition to general adiposity. Given the *dose-response* relevance of abdominal adiposity to mortality in this Mexican population, the present findings do not support the recommendations from the World Health Organisation (WHO) for the use of '*clinically informative thresholds*' in the assessment of vascular-metabolic risk.⁴³

8.2.1 Associations of adiposity with premature mortality from specific causes

At ages 40-74 years, each 5 kg/m² higher BMI *above* 25 kg/m² was associated with a 32% higher risk of death, chiefly due to a 38% higher risk of death from vascular or metabolic diseases (**Chapter 5**). Throughout the *full ranges* of the adiposity markers studied, the relevance of FMI and of abdominal adiposity to mortality was stronger than that of BMI, in particular after accounting for other markers of adiposity. Each 4.71 kg/m² higher BMI, 2.78 kg/m² higher FMI, 10.9 cm higher waist circumference, 0.06 units higher WHR, and 0.07 units higher WHtR (corresponding to comparable differences of 1 SD of the sex-specific distributions of each marker at baseline), were associated, respectively, with a 21%, 22%, 25%, 17% and 26% higher risk of mortality from all-causes, and a 29%, 31%, 32%, 24% and 37% higher risk of mortality from vascular-metabolic causes (**Chapters 6-7**). The relevance of general and abdominal adiposity to mortality was broadly independent of each other, such that after mutual adjustment for other markers, the mortality risk from any cause with each 1 SD higher level of adiposity was 17% higher for BMI, 31% higher for FMI, 32% higher for waist circumference, 14% higher for WHR and 29% higher for WHtR.

By comparison, the mutually-adjusted risk of vascular-metabolic mortality was 24% higher for BMI, 40% higher for FMI, 36% higher for waist circumference, 18% higher for WHR, and 44% higher for WHtR. The relevance of abdominal adiposity to vascular-metabolic mortality was particularly strong for mortality from renal causes and acute diabetic crises, as each 1 SD higher abdominal adiposity throughout the full ranges was associated with a 30% to 50% higher risks of premature death from such disease. By contrast, the negative association of BMI with mortality below 25 kg/m² was largely due to strong negative associations due to mortality from renal or acute diabetic causes, respiratory disease and cancers of the lung and upper-aero-digestive sites.

The *quantitative* estimates for mortality risk from this Mexican population were remarkably consistent to the observational estimates for BMI or abdominal adiposity reported from Caucasian populations in the Global BMI Collaboration,³⁰ the PSC,³ the ERFC¹ and the EPIC studies³¹ which accounted for reverse causality bias from pre-existing diseases. However, compared to previous studies in other Hispanic populations, the estimated risks for vascular-metabolic mortality reported in the present thesis are about 4-fold greater,^{32,34,37,44} which may reflect small sample sizes of such studies, failure to investigate the impact of low waist circumference due to pre-existing disease and differences in mortality risk by length of follow-up. Compared to the mortality risk estimated to be caused by genetically-elevated WHR in British adults, the percentage increase in mortality risk associated with 1 SD differences in anthropometrically-elevated WHR from this cohort appear more modest, respectively, 27% for cardiac causes (versus 74% in the UKB), 28% for cerebrovascular causes (versus 34% in the UKB), 23% for renal causes (versus 60%

in the UKB), 64% for diabetic causes (versus 262% in the UKB), and 31% for hepatobiliary causes (versus 162% in the UKB).⁸ These differences remained after additional adjustment for BMI, may reflect the residual confounding from measurement error of the waist and hip circumferences in the observational estimates and the life-time harm of excess abdominal adiposity measured by genetic markers (as opposed to adult measurement of adiposity). Indeed, findings from 2.3 million participants aged 17 years at the time baseline adiposity was measured, have shown greater effects of extreme adiposity with cardiovascular and other metabolic outcomes,^{45,46} suggesting that the mortality estimates from this thesis could be underestimated.

The findings on FMI and vascular mortality at a given LMI from this thesis are broadly comparable with two observational North-American studies which included Mexicans. One study described log-linear associations of fat mass (FM) with total and vascular mortality independent of lean mass (LM), with each 1 SD higher FM resulting in a 20% increase in all-cause mortality and a 70% increase in vascular mortality.³⁹ The second study showed positive associations of DXA-measured FM percentage with mortality from all-causes or diabetes, yet null associations with vascular mortality,³⁴ but the sample size was limited to just over 10,000 adults and the effect of pre-existing disease on body composition could not be assessed reliably. A recent genetic study among 0.5 million adults from the UK Biobank demonstrated causal associations of genetically-elevated FMI with 9 vascular diseases, but negative associations of genetically-elevated LMI with the same diseases, and some heterogeneity in the effect of each 1 kg/m² higher genetic FMI, ranging between 8% and 46% higher risk of various vascular diseases.⁴⁰ In this British study, the FMI and the LMI instruments congregated 82

mutually-exclusive SNPs for each marker of body composition, an approach that overcomes the limitations of genetic BMI which could contain SNPs common to either measure of body composition. While the findings from this thesis cannot be directly compared to those from the UKB because of the limited numbers of individual vascular diseases accrued, the overall genetic effects on vascular outcomes for comparable increases in FMI were twice as strong in the UKB compared to the observational estimates from this cohort. These differences could also reflect the less precise proxy derived for FMI (and LMI) in this thesis as opposed to the unbiased instrumental variables available in the UKB, but also chiefly because genetic FMI reflects life-long effects, including those from excess adiposity in childhood and adolescence, which were not available in this Mexican study.

In addition to mortality from vascular or metabolic causes to which excess adiposity is likely causally associated with, this thesis extended estimates to respiratory, infective, and neoplastic causes of death (**Chapters 5-7**). The percent increase in mortality risk from respiratory or infective causes associated with each 1SD higher adiposity was somewhat stronger with abdominal adiposity than with general adiposity, and broadly similar to estimates for vascular-metabolic mortality, ranging from 30% to 59%. By contrast, the mortality risk from cancer was more modest, ranging from 5% to 11%, which was broadly similar for the different cancer subtypes, although the number of specific events were too small to reliably assess these specific associations. Again, these findings were consistent with those from European populations in the Global BMI Collaboration³⁰ and the EPIC study.³¹ While higher levels of abdominal adiposity (relative to gluteo-femoral adiposity) are associated with higher levels of unfavourable lipids, inflammatory and cytokine

profiles, explaining the higher risk of cardiovascular and metabolic diseases,^{14,15} the mechanisms underlying the associations between adiposity and fatal infections, chronic respiratory diseases or neoplasms are not fully understood. Genetic studies of adiposity with non-vascular, non-metabolic diseases to compare with are limited, and show heterogeneous findings. For example, recent estimates from 0.4 million adults from the UK Biobank confirmed that genetically-elevated WHR is causally associated with a 50% higher risk of mortality from chronic obstructive pulmonary disease,⁸ one MR study of genetically-elevated WHR demonstrated a 60% increased risk of colorectal cancer (with apparent no effects on other cancer subtypes),⁴⁷ while MR studies of genetically-elevated BMI demonstrated a 30% higher risk of ovarian and lung cancers,⁴⁸ almost 20% higher risk of stomach and oesophageal cancers, but a 30% lower risk of breast cancer.⁴⁹

8.2.2 Mediators of adiposity and mortality risk from specific causes

Analyses from this thesis showed that the reduction in the RRs for mortality with higher adiposity after additional adjustment for selected lipids at baseline were relatively modest, particularly with non HDL-c and triglycerides (**Chapters 5-7**). Accounting for higher SBP, however, reduced the percentage increase in mortality risk from cardiac, cerebrovascular or renal and diabetic causes by 3% to 13%, whereas reductions in percentage mortality risk from such causes were more modest after accounting for HbA1c (3% to 7%) or for HDL-c (1% to 3%). The ERFC showed that the combined relevance of BMI and of WHR to major vascular diseases, represents only a quarter of the additional predictive value of total cholesterol and HDL-c,¹ suggesting a stronger mediation effect of lipids than that observed in this thesis. Lipids assays in the present cohort were obtained from the NMR platform, in

the ERFC, from biochemistry. However, the NMR and biochemistry markers in the present analysis correlated highly, suggesting that any remaining quantitative or qualitative differences between platforms would not have materially affected the present estimates. Therefore, the most likely reason for the observed differences between studies could be due to the exclusion of both screen-detected and diagnosed diabetes in this thesis.

8.3 Strengths and limitations

The chief strengths of the present analysis include the measures undertaken to control for reverse causality bias (specifically, exclusion of those with previously-diagnosed diabetes and deaths occurring in the first 5 years of follow up), the large number of participants and prolonged duration of follow-up (resulting in a large number of deaths), and a range of sensitivity analyses that supported the consistency of the main findings and conclusions. This thesis studied commonly used anthropometric markers of adiposity, but other markers (directly measured and calculated), including body imaging (through Dual-Energy X-ray Absorptiometry or Magnetic Resonance Imaging) could further distinguish the differential relevance of adipose tissues to mortality from specific causes and the mediating effects of lipids versus diabetes or blood-pressure.⁵⁰ Such measures are, however, difficult to collect in large prospective studies in low or middle-income countries where resources for research are more limited. Furthermore, the availability of multiple measures (rather than self-reports) of general and abdominal adiposity enabled direct comparisons of death rates from multiple outcomes with equivalent differences in levels of adiposity. Another unique feature of the present analysis is the inclusion of predicted body-mass composition, which extended estimates of mortality risk beyond BMI, making

the present study the largest of this kind. In addition, serial assessments of BMI and WHR enabled additional estimates of mortality risk with long-term (rather than baseline) levels of adiposity, although the differences would have been rather small due to the high reproducibility of the markers studied. Therefore, this thesis significantly extends the available evidence on Mexican-Americans from the NHANES study,³⁹ given that the present analysis included 15-fold more participants. It also extends the evidence from the Global BMI Consortium,³⁰ the PSC,³ and the EPIC meta-analyses,³¹ which lacked data from any Mexican population. Furthermore, analyses of predicted FMI demonstrated that markers of body-mass composition are easily predictable, and help overcoming the confounding from LMI in traditional analyses of BMI. Finally, the present findings on the importance of abdominal adiposity in addition to general adiposity add to the previous evidence from the INTERHEART study, one of the first to highlight the use of WHR instead of BMI as the principal clinical measure of adiposity in a multi-ethnic context.⁵¹

Nevertheless, the present study was constrained by several limitations, including lack of non-fatal events, MRI data on body composition and visceral adiposity, and full-cohort profiling with biomarkers of lipid classes, renal, and liver function, which would have enabled assessing mechanisms by which adiposity causes excess mortality from different diseases. Furthermore, information on mortality relied on linkage to electronic register for vital statistics and death certificates, but in Mexico, such data proved accurate in validation studies.⁵² The limited cases of stroke and cancer subtypes, or acute versus chronic cardiac and renal diseases limited the possibility of better understanding heterogeneity of associations between finer phenotypes, or to reliably assess associations among never smokers. Furthermore,

knowledge of adiposity levels in childhood and adolescence might have resulted in larger deaths RRs with increase in adiposity levels, but such data were not available. Similarly, lack of information on age at menopause and the insufficient number of vascular-metabolic or neoplastic events accrued limited assessment of disease-specific differences in risk by pre and post-menopausal status, but the age-stratified analyses of mortality in women after the age of 60 years could be considered proxies for post-menopausal effects, although that age-band would have excluded early menopause cases.

8.4 Clinical relevance of the present findings

Consistent with the findings from the Global BMI Collaboration, the PSC, and the EPIC study, the key findings from this thesis reinforced that in this Mexican population, general and abdominal adiposity were independently related to vascular, renal, metabolic, respiratory, infective and neoplastic causes of premature death. In contrast to the J-shaped association of BMI with mortality, FMI was approximately log-linearly related to mortality from such causes (independent of LMI). Furthermore, the present analysis indicated that from all the five markers of adiposity studied, abdominal fat distribution was more strongly associated with premature mortality from these causes than general adiposity, with no threshold levels throughout the ranges studied. The present findings are particularly relevant in the context of the previous recommendations by the 2008 World Health Organization Expert Consultation on waist circumference and WHR,⁴³ which highlighted a need for clinically-informative adiposity cut-off points for Hispanic populations. This uniquely large Mexican study provides no support for the use of adiposity-specific cut-offs for assessing vascular, metabolic or other major chronic disease risk in clinical practice

in Mexico. Furthermore, most of the existing screening tools for vascular risk-prediction in general populations (e.g. Framingham, PROCAM, Reynolds) omit convenient measures of adiposity, and favour the superior predictive value of plasma lipids.^{53,54} Yet, the WHO recommended that in resource-limited settings where laboratory facilities are unavailable, the use of BMI remains desirable.⁵³ The findings from this thesis showed that while the strength of the association of abdominal adiposity with vascular-metabolic and other mortality appears largely similar to that of BMI above 25 kg/m², across the full ranges of the adiposity markers studied, abdominal adiposity is more strongly associated with mortality risk than BMI, hence the use of BMI would underestimate the true risks of interest in a Mexican population. Meanwhile, waist circumference and WHtR were highly correlated with BMI or with FMI (**Chapter 4**), and mutually-adjusted estimates could be susceptible to collinearity. As the WHR is less correlated with BMI or FMI, suggesting that the WHR may be preferable to BMI, but perhaps not to FMI, as predicted FMI is also a function of waist circumference (**Chapter 3**). In addition, the results from this thesis show that the long-term reproducibility of predicted FMI appeared higher to that of BMI (mid-point RDRs of 0.84 versus 0.78) and the long-term reproducibility of WHtR appeared higher to that of waist-circumference or WHR (15-years RDRs 0.75 versus 0.70 and 0.48; **Chapter 4**). Also, BMI and waist circumference were more sensitive to reverse causality bias from initial diseases (compared to WHR), prompting questions about the suitability of the different adiposity markers for assessment of mortality risk. The present findings therefore suggest the need for complementary markers of both general and abdominal adiposity, including FMI and WHtR, for together they can enhance our understanding of long-term mortality risk in Mexican adults with a low or normal BMI. Currently, Mexican clinicians are guided largely by

risk-calculators developed in other populations,⁵⁴ as the only Mexican-specific charts developed more recently by Globorisk, relies on survey data from less than 4,500 Mexicans and extrapolations from Western populations.⁵⁵ As the relevance of BMI to vascular-metabolic risk differs majorly among those with diabetes in this Mexican population compared to other populations, the findings from this thesis suggest that other markers of adiposity should be considered when developing Mexican-specific risk-calculators for vascular and other causes of death, including for example, prediction algorithms for renal, diabetic and liver diseases.

8.5 Public health relevance of the present findings

The results of the present study provide reliable local evidence to guide public health strategies to reduce mean levels of adiposity and prevent premature deaths in Mexican populations. Excess adiposity is a major cause of diabetes and high blood pressure, which are major causes of premature death and disability, accounting for at least one third of deaths in Mexico at ages 40-74 years.^{28,29,56} In 2013, Mexico introduced the National Strategy for the control of overweight, obesity and diabetes,⁵⁷ followed in 2016 by a declaration of obesity and diabetes as 'national emergencies'.⁵⁸ As a result, current health care strategies focus on improvements in health education and promotion of physical activity, taxation of high sugar drinks, and calorie-dense foods, together with early identification and monitoring of major risk factors and improvements in the quality of care for patients diagnosed with diabetes. As the results from this thesis suggest, moderate population-wide reductions in average levels of adiposity, could lead to substantial reductions in morbidity, and of nearly 20% of the excess vascular-metabolic mortality due to a BMI above 30 kg/m² (including 30% of the renal deaths and 18% of the stroke deaths),

and up to 10-years gain in life expectancy among middle-aged Mexicans (**Chapter 5**). The current findings are also relevant for other Hispanic populations, including many millions of Mexican-Americans, not least because they refute previous suggestions⁶ of any 'obesity paradox' among Hispanics.

8.6 Conclusions

Overall, in this Mexican population with high levels of obesity, both general and abdominal adiposity were major, independent risk factors for premature death from many causes. The findings were comparable with those reported in other Western populations, thereby refuting the 'Hispanic obesity paradox'. The findings from this thesis also suggest that FMI may be preferable to BMI for assessing the 'true hazards', as adjusted analyses overcome the confounding from high LMI among very fit or physically active individuals with a high BMI. The present findings also highlight the particularly hazardous effects of abdominal adiposity for risk of premature deaths from vascular or metabolic causes, suggesting that measures of abdominal adiposity remain of important additional relevance to markers of general adiposity. Despite the similarities of the results from this thesis with those from previous large meta-analyses which took account of pre-existing diseases or with some genetic studies, biomarker and genetic studies of the present cohort are needed to establish the causal associations of adiposity markers with specific causes of death, and the mechanisms through which adiposity is associated to various disease.

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S1: The structure of the strategic searches for literature review

Populations	Location	Study type	Exposure	Outcome/Endpoint
hispanic [MeSH]† <u>Inclusive of</u> Hispanic Americans Latino Mexican American population [MeSH]† <u>Inclusive of</u> general and adult population Mexic* hispanic* latino* “Mexican-American” “populations” Selective exclusions neonat* newborn infant* child*	Americas [MeSH]± <u>Inclusive of</u> Caribbean West Indies Central America Gulf of Mexico North America Latin America South America Canada United States Greenland Mexico Cuba Brasil Colombia Argentina Perú Venezuela Chile Ecuador* Guatemala Haití Bolivia Dominica Honduras Paraguay Nicaragua El Salvador Costa Rica Panamá	Cohort Studies± [MeSH] <u>Inclusive of</u> follow-up cohort longitudinal prospective retrospective Cohort analysis† [MeSH] <u>inclusive of</u> cohort studies, design or analyses Prospective Study† [MeSH] <u>inclusive of</u> prospective studies, design or method Longitudinal Study† [MeSH] <u>inclusive of</u> longitudinal evaluation or studies Biobank*††	Body Weights and Measures[MeSH]± <u>Inclusive of</u> body size body fat distribution adiposity body height body weight body mass index BMI Waist-Hip Ratio WHR Waist Circumference Hip Circumference Waist-Height ratio Anthropometric parameters [MeSH]† <u>Inclusive of</u> weight, height Waist, hip, abdominal circumferences WHR WHtR Weight /height ratio Body mass /BMI, fat, size Fat/free mass (and others: leg length, neck, head, tight, arm circumferences) Obesity[MeSH]± <u>Inclusive of</u>	mortality[MeSH]± <u>inclusive of</u> cause of death fatal outcome premature mortality excess mortality standardised mortality ratio mortality rate death rate (and some age-specific terms or hospital mortality) mortality[MeSH]† <u>inclusive of</u> excess mortality premature mortality mortality rate standardised mortality ratio (and some cause or populations specific terms) fatality[MeSH]† <u>inclusive of</u> <u>death</u> <u>fatal outcome</u> <u>fatal case</u> "mortality" [Subheading] ± <u>inclusive of:</u> survival and death rate mortalidad

	Puerto Rico Uruguay Jamaica Trinidad Tobago Guyana Surinam Bahamas Belize North America [MeSH]† <u>Inclusive of</u> the USA Canada and Mexico South and Central America[MeSH]† <u>Inclusive of</u> Latin America and all the individual countries and islands in South and Central America "Mezo America"		abdominal obesity benign obesity morbid obesity Obesity[MeSH]† <u>Inclusive of</u> adiposity adipose tissue body weight excess overweight Body Weight Changes [MeSH]± <u>Inclusive of</u> weight change weight gain weight loss body fat [MeSH]† <u>Inclusive of</u> body fat and composition adiposity thin* fat* obes* adipos* abdominal fat* body fat overweight "extreme* /morbid / severe* /increasing* obesity" exp weight gain/ † exp weight reduction/ † exp weight change/†	death "non-fatal" non-fatal.mp. "all-cause mortality" "total mortality" "heart disease" "vascular disease" "metabolic disease" "ischaemic heart disease" "coronary disease" stroke cerebrovascular cardiovascular diabetes

± PubMed/MEDLINE specific

† OVID/EMBASE specific

†† Since 2018

S2: Selected searches and identified articles for inclusion

1. <u>MEDLINE via PubMed (since 1980)</u> www.pubmed.com	2. <u>EMBASE via OVID (since 1974)</u> http://ovidsp.tx.ovid.com/
<u>Search #1 “Adiposity and mortality in Hispanics”</u> (("Americas"[MeSH] OR Mexic* OR hispanic* OR latino*)) AND ((cohort OR prospective OR biobank*)) AND (("Body Weights and Measures"[MeSH] OR "Obesity"[MeSH] OR adipos* OR overweight OR obesity)) AND (("mortality"[MeSH] OR "mortality"[Subheading] OR death OR mortality)) NOT (neonat* OR newborn OR animal) <u>Search #2 “Meta-analyses of adiposity studies”</u> (("Body Weights and Measures"[MeSH]) OR "Obesity"[MeSH] OR adipos*)) AND (((("mortality"[MeSH Subheading] OR "death" OR "fatal*" OR "non-fatal*")) AND ("Cohort Studies"[MeSH])) AND ("review" OR "meta-analysis")) NOT (infant* OR child* OR neonat* OR newborn) <u>Search #3 “ Adiposity and mortality in extreme populations”</u> (("adult populations" OR "adults")) AND (("extreme*" OR "morbid" OR "severe*" OR "increasing*")) AND (("Body Weights and Measures"[MeSH] OR "Obesity"[MeSH] OR adipos* OR overweight OR fatness OR thinness OR “body fat*” OR "weight gain" OR "weight change" OR “weight loss”) AND (("mortality"[MeSH] OR "mortality"[Subheading] OR "death"	<u>Search #1 “Adiposity and mortality in Hispanics”</u> (exp "south and central america"/ or exp North America/ or exp hispanic/) AND (exp cohort analysis/ or exp prospective study/ or exp longitudinal study/) AND (exp "anthropometric parameters"/ or exp obesity/) AND (exp mortality/ or exp fatality) NOT (newborn/ OR neonat.mp.) <u>Search #2 “Meta-analyses of adiposity studies”</u> (exp "anthropometric parameters"/ OR exp obesity/) AND (exp mortality/ or exp fatality) AND (exp cohort analysis/) AND ("review"/ or meta-analysis/) NOT (newborn/ or neonat.mp. or infant*.mp. or child/) <u>Search #3“ Adiposity and mortality in extreme populations”</u> adult/ AND (extreme or morbid or severe or increasing).mp. AND (exp "anthropometric parameters"/ or exp obesity/ or exp body fat/ or exp weight gain/ or fatness.mp. or exp weight change/) AND (exp mortality/ or exp fatality

Search #4[†] “Large studies of adiposity and mortality” ((cohort OR prospective OR biobank) AND ("Body Weights and Measures"[MeSH] OR "Obesity"[MeSH] OR obesity OR adipos* OR overweight) AND ("mortality"[MeSH] OR "mortality"[Subheading] OR "death" OR mortality)) NOT (neonat* OR newborn OR animal)	Search #4[†] “Large studies of adiposity and mortality” (exp "anthropometric parameters"/ or exp obesity/ or obesity.mp. or adiposity.mp.) AND (exp mortality/ or mortality.mp. or exp fatality/ AND (cohort.mp. or prospective.mp. or biobank.mp.) NOT (newborn/ or neonat.mp. or infant*.mp. or child/)
3. SCIELO - Virtual Library of Mexican and other South American Journals (since 1985) http://search.scielo.org/	4. LILACS – The Virtual Library of the World Health Organisation of South and Central-American Journals (since 1982) http://lilacs.bvsalud.org/en/
(cohort OR longitudinal OR prospective OR biobank[†]) AND (obes* OR adipos* OR overweight OR fat* OR thin* OR waist* OR weight* OR hip*) AND (mortal* OR death OR fatal*) AND NOT (newborn OR neonat* OR animal)	(cohort OR longitudinal OR prospective OR biobank[†]) AND (obes* OR adipos* OR overweight OR fat* OR thin* OR waist* OR weight* OR hip*) AND (mortal* OR death OR fatal*) AND NOT (newborn OR neonat* OR animal)

† Term/search added since 2018, to specifically capture emerging biobank-named cohorts.

S3: Published studies of BMI and mortality, by study size

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Summary findings				
					Prior disease	FU	Adiposity (mean, SD)† Mortality	HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)	
1	Aune (2016) Meta-analysis	1950 - 2015	30.3 M (18+ yrs) All-cause (37 M) Studies included (230) Hispanic (4)	Age, smoking, education, exercise, drinking, family disease	Any chronic	10 yrs	BMI†† All-cause	NR NR	NR	J-shape ~22.5	per 5 1.3 (1.2-1.3)
2	Shen (2017) Meta-analysis	2000 - 2015 (3-28 yrs)	15.1 M (NR) Neoplastic (272K) Studies included (15) Hispanic (NR)	Age, sex, smoking, ethnicity, education, SES, drinking	NR	NR	BMI†† Lung cancer	NR NR	NR	non-linear Negative	per 5 0.9 (0.9-0.9)
3	Kim (2017) Asia (Korea)	2005-2015 (5.2 yrs)	11.5 M (20+ yrs) All-cause (212,704)	Age, sex, smoking, drinking, exercise, diabetes, cancer, hypertension, dyslipidaemia, income	Cancer, other chronic disease	No	BMI†† (27.1±3.2) All-cause % Weight change Normal-Obesity Obesity-Normal No weight change	-15 ±5 20+ Positive Negative U-shape	2.6 (2.5-2.7) 1.00 1.8 (1.7-1.9)	NR	NR
4	Global BMI (2016) Meta-analysis	1958 - 2010 (13.7 yrs)	3.9 M (53 yrs) Specific (385,879) Studies included (239) Hispanic (0)	Age, sex, ethnicity smoking	Any chronic	5 yrs	BMI (25.2±3.9) All-cause CHD Stroke Respiratory Neoplastic	NR NR	NR	J-shape ~22.5	per 5 1.4 (1.3-1.5) 1.4 (1.3-1.5) 1.4 (1.3-1.5) 1.4 (1.3-1.5) 1.2 (1.2-1.2)
5	Twig (2014) Middle-East (Israel)	1967 - 2011 (40 yrs)	2.3 M (21+ yrs) All-cause (18,530)	Age, sex, birth year, SES, height	Cancer, CVD diabetes , mental , trauma	2 yrs	BMI (21.6±3.4) All-cause Men Women	5-24th <3rd 97th + <3rd 95th +	1.0 1.1 (1.0-1.2) 1.9 (1.7-2.1) 1.1 (0.9-1.4) 2.2 (1.5-3.0)	J-shape J-shape J-shape	NR NR

†Adiposity was measured, unless otherwise specified. Summary statistics given if reported. †† Includes self-reports. BMI= Body Mass Index in kg/m². Continuous estimates are per specific units unless otherwise specified. Lower risk refers to the nadir in kg/m². SES=Socio-economic status; CHD=Chronic Heart Disease; CVD=Cardiovascular Disease; DM=Diabetes Mellitus; NR= Not reported; Studies included refer to the total of individual studies meta-analysed; Hispanic refers to Mexican or other Latino-American populations.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
6	Twig (2017) Middle-East (Israel)	1967-2011 FU 40 yrs	2.3 M (17+ yrs.) Vascular (3178)	Age, sex, year birth, SES, height	No		BMI†† (21.6±3.4)	22-25	1.00	NR	per 1-unit
							Hypertensive	30 +	8.0 (3.7–17.2)		1.2 (1.1-1.2)
							HF	30 +	5.4 (2.3–15.2)		1.1 (1.0-1.2)
							CM	30 +	4.0 (1.7–9.3)		1.1 (1.1-1.2)
							Pulm. Embolism	30 +	3.0 (0.9–9.8)		1.1 (1.0-1.2)
							Cardiac arrest/VF	30 +	3.7 (2.6–6.5)		1.1 (1.1-1.1)
							Arterial	30 +	2.7 (0.8–8.7)		1.1 (1.0-1.2)
							Any CVD	30 +	4.1 (3.4–4.9)		1.1 (1.1-1.1)
							FU				
							10 yrs	30 +	2.1 (0.8-5.3)		
7	Twig (2016) Middle-East (Israel)	1967 - 2011 (40 yrs)	2.3 M (17+ yrs) Specific (32,127)	Age, sex, birth year, SES, height	N/A	N/A	BMI (21.6±3.4)	5-24th	1.0		per z-score
							All-cause	95th +	1.7 (1.6-1.8)	J-shape	1.5 (1.5-1.6)
							All CVD	95th +	3.5 (2.9-4.1)	J-shape	
							All Non-CVD	95th +	1.5 (1.4-1.6)	J-shape	
							CHD	95th +	4.9 (3.9-6.1)	Positive	
							Stroke	95th +	2.6 (1.7-4.1)	J-shape	
							Sudden	95th +	2.1 (1.5-2.9)	J-shape	
							0-10 yrs FU	95th +	2.0 (1.1-3.9)		
							30-40 yrs FU	95th +	4.1 (3.1-5.4)		
8	Twig (2016) Middle-East (Israel)	1967 - 2011 (40 yrs)	2.3 M (17+ yrs) Metabolic (481)	Age, sex, birth year, SES, height	Diabetes	No	BMI (21.6±3.4)	5-24th	1.0		
							DM	50-74th +	1.6 (1.1-2.3)	J-shape	NR
								85-94th	8.0 (5.7-11.3)		
								95th +	17.2 (12.0-25.0)		
9	Twig (2018) Middle-East (Israel)	1967 - 2011 (40 yrs)	2.3 M (17+ yrs) Renal (226)	Age, sex, birth year , education, country of birth	DM, kidney hypertension, rheumatic	No	BMI (21.6±3.4)	18.5-22	1.0	J-shape	per 1
							CKD	<18.5	0.9 (0.5-1.6)	~18.6	1.1 (1.1-1.2)
								30+	1.2 (1.1-1.2)		

Conventions as above. DM= Diabetes Mellitus, BP=Blood Pressure; MI=Myocardial Infarction; IHD=Ischaemic Heart Disease; CM=Cardiomyopathy; VF=Ventricular Fibrillation

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
10	Furer (2018) Middle-East (Israel)	1967 - 2011 (NR)	2.2 M (17+ yrs) Specific (32,127)	Age, sex, birth year, residential SES, education, country	Any medical diagnosis	30 yrs	BMI	18-22	1.0		NR
							CVD	<18	1.0 (0.9-1.1)	Positive	
							Men	30+	5.4 (4.6-6.3)		
							Women	<18	0.7 (0.5-1.0)	Positive	
								30+	3.9 (2.5-6.1)		
							No-CVD	<18	1.0 (1.0-1.1)	J-shape	
							Men	30+	1.5 (1.4-1.6)		
11	Robertson (2019) Europe (Sweden)	1969 - 2005 (27 yrs)	1.6 M (17+ yrs) Vascular (4477)	Age, year, centre, DM, BP, CHD	MI, IHD, CM women	N/A	BMI (21.9±3.0)	18.5-20	1.0		per 1
							CM	<18.5	1.1 (0.9-1.3)	Positive	1.1 (1.1-1.2)
							dilated	35+	8.1 (5.8-11.4)		
							hypertrophic	<18.5	1.0 (0.7-1.5)	Positive	1.1 (1.1-1.1)
								35+	2.3 (0.7-7.2)		
							alcohol/drug	<18.5	1.0 (0.7-1.5)	non-linear	1.1 (1.1-1.1)
								35+	7.2 (3.1-16.6)		
12	deGonzalez (2010) Meta-analysis	1976 - 2002 (10 yrs)	1.4 M (19-84 yrs) All-cause (160,087) Studies included (19) Hispanic (0)	age, study, physical activity, drinking, education, marital status	CVD, cancer	5 yrs	BMI (26.3.)	15-18.4	1.7 (1.5-2.1)	J-shape	per 5
							All-cause	18.5-19	1.2 (1.0-1.4)	(20-24.9)	1.3 (1.3-1.3)
								22-22.4	1.0 (0.9-1.1)		
								22.5-24	1.0		
								25-27.4	1.1 (1.0-1.1)		
								27.5-29	1.2 (1.1-1.3)		
								30-34	1.4 (1.3-1.6)		
								35-39	1.7 (1.5-1.9)		
								40-49	2.3 (1.9-2.7)		
13	Cao (2010) Meta-analysis	1980 - 2009 (NR)	1.2 M (NR) Neoplastic (6788) Studies included (5) Hispanic (NR)	NR	cancer	No	BMI	NR	NR	NR	per 5
							Prostate cancer				1.2 (1.1-1.3)

Conventions as above.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
14	Chen (2013) Meta-analysis	To 2008 (9.7 yrs)	1.1 M (53.4 yrs) Vascular (49, 184) Studies included (20) Hispanic (0)	Age, sex, education exercise, smoking drinking, residence, marital status	Cancer	3 yrs	BMI	18.5-24	1.0		
							CVD (E Asians)	25+	1.2 (1.1-1.3)	NR	NR
							CVD (S Asians)	25+	1.1 (0.9-1.2)	NR	
							CHD (EA)	25+	1.3 (1.2-1.5)	U-shape	
							CHD (SA)	25+	1.1 (1.0-1.3)	J-shape	
							Stroke (EA)	25+	1.1 (0.9-1.2)	inverse J	
							Stroke (SA)	25+	0.9 (0.8-1.2)	inverse J	
							IS (EA)	25+	1.2 (1.0-1.4)	NR	
							HS (SA)	25+	1.0 (0.8-1.3)	NR	
15	Zheng (2011) Meta-analysis	1984 - 2006 (9.2 yrs)	1.1 M (18+ yrs) Vascular (120,700) Studies included (19) Hispanic (0)	Age, sex, education, residence, cohort marital status smoking	CVD, stroke, cancer	3 yrs	All-cause	22.6-26	1.0		
							BMI (22.9±3.6)	<15	2.8 (1.9-4.1)	inverse-J	1.2 (1.1–1.2)
							E. Asians	35+	1.5 (1.3-1.7)		1.1 (1.0–1.1)
								<15	2.1 (1.8-2.6)	inverse-J	1.2 (1.0–1.4)
							S. Asians	35+	1.3 (0.7-2.3)		1.0 (0.7–1.3)
							CVD	<15	1.4 (1.2-1.6)	U-shape	N/A
							E. Asians	35+	1.5 (1.3-1.7)		
								<15	1.0 (0.8-1.2)	Null	N/A
							S. Asians	35+	1.0 (0.6-2.0)		
16	Gajalakshmi (2018) Asia (India)	1998 - 2015 (17 yrs)	0.5 M (35-69 yrs) Specific (29,519)	Age, sex, smoking, drinking, education, SES, BP	MI, stroke, cancer, TB, asthma	2 yrs	BMI (23.2±3.8)	22.5-25	1.0		N/A
							All-medical	15-18.5	1.5 (NR)	inverse J	
								30-35	1.0 (NR)		
							Cardiac	15-18.5	1.1 (1.0-1.3)	Null	
								30-35	1.1 (1.1-1.2)		
							Stroke	15-18.5	1.1 (0.9-1.3)	Null	
								30-35	1.2 (1.0-1.5)		
							Neoplastic	15-18.5	1.5 (1.4-1.6)	inverse J	
								30-35	1.2 (1.1-1.3)		
							Renal	15-18.5	1.0 (0.8-1.3)	J-shape	
								30-35	1.3 (1.1-1.6)		
							TB	15-18.5	2.5 (2.3-3.0)	inverse J	
								30-35	0.8 (0.6-1.5)		

Conventions as above. IS=Ischaemic Stroke; HS=Haemorrhagic Stroke; N/A=Not Applicable. TB=Tuberculosis.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
17	Lee (2018) Asia (Korea)	2002 - 2013 (14 yrs)	496,390 (40-89 yrs) Neoplastic (5,469)	Age, sex, smoking, drinking, exercise income, family history cholesterol, Charleston Index, aspirin, oral contraceptives	Cancer	No	BMI (23.2±3.4)	<18.6	1.1 (0.6-1.9)	inverse J	NR
							Oesophagus	≥30	0.3 (0.0-2.0)	18.5-22	
							Colorectal	<18.6	1.2 (0.8-1.8)	inverse J	NR
								≥30	2.3 (1.4-3.8)		
							Liver	<18.6	0.8 (0.5-1.1)	inverse J	NR
								≥30	2.0 (1.4-2.9)		
							Gallbladder	<18.6	0.8 (0.4-1.5)	inverse J	NR
								≥30	2.0 (1.0-3.9)		
							Pancreas	<18.6	0.8 (0.5-1.4)	J-shape	NR
								≥30	1.4 (0.7-2.7)		
							Prostate	<18.6	1.2 (0.6-2.3)	J-shape	NR
								≥30	2.9 (1.1-7.1)		
							Kidney	<18.6	0.6 (0.1-2.6)	J-shape	NR
								≥30	3.8 (1.3-11.0)		
18	Milajerdi (2018) Meta-analysis	1974 - 2017 (2-30 yrs)	258,379 (NR) Cardiac (13,201) Studies included (16) Hispanic (0)	study-specific	Heart failure	2 wks.	BMI	<18	1.0		NR
							pre-HF	40+	1.2 (0.6-2.4)	Positive	
							post-HF	40+	0.7 (0.6-0.8)	Negative	
19	Bethea (2014) Meta-analysis	1982 - 2008 (5-20 yrs)	239,597 (55 yrs) Neoplastic (898) Studies included (7) Hispanic (0)	Age, sex, smoking, education, drinking, exercise marital status	NR	5 yrs	BMI††	18.5-24	1.0	Positive	per 5
							Pancreatic	25-29	1.1 (0.9-1.3)		1.1 (1.0-1.2)
							cancer	30-34	1.2 (1.0-1.6)		
								35+	1.3 (1.0-1.8)		
20	Smith (2008) Meta-analysis	1980-2000 (10 yrs)	221,194 (40-79 yrs) Neoplastic (7804) Studies included (25) Hispanic (0)	Age, sex, region, smoking, drinking,	Cancer, poor health	5 yrs	BMI (27.1)	20-22.5	1.0		per 5
							EC	<20	1.2 (1.1-1.3)	Negative	0.7 (0.6-0.9)
								>25	0.7 (0.5-0.9)		
							SC	NR	NR	NR	0.7 (0.6-0.9)
							AC	NR	NR	NR	1.5 (1.4-1.8)

Conventions as above. HF=Heart Failure; SP=sarcopenic; EC=Oesophageal Cancer; SC=Squamous cells cancer; AC=Adenocarcinomas.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
21	Hozawa (2018) Meta-analysis	1987 - 2005 (10 yrs)	179,987 (40-89 yrs) All-cause (17,166) Studies included (13) Hispanic (0)	Age, sex, smoking, study	Any history Cholesterol≥4 ever smoking	5 yrs	BMI (23.2±3)	20-22.5 <19 >30	1.0 ~1.4 (NR) ~1.7 (NR)	Non-linear 20-25	NR
22	Yang (2010) Asia (China)	1990-2016 (15 yrs)	221,194 (40-79 yrs) Respiratory (2960)	Age, area, smoking, drinking, education, biomass exposure, diet	Respiratory, abnormal lung function (LF)	5 yrs	BMI (21.7±2.7) Low LF Normal LF	<18.5 18.5-19 20-22.4 22.5-24 25+ <18.5 18.5-19 20-22.4 22.5-24 25+ 0.8 (NR)	3.2 (NR) 2.1 (NR) 1.6 (NR) 1.4 (NR) 1.2 (NR) 1.3 (NR) 1.1 (NR) 1.0 (NR) 0.8 (NR) 0.8 (NR)	Negative Negative	per 5 1.3 (1.2-1.4) NR
23	Zhou (2010) Asia (China)	1990 - 2006 (15 yrs)	220,000 (40-79 yrs) Vascular (2764)	Age, smoking education, drinking	CVD	3 yrs	BMI (21.7±2.7) IHD	<20 20+	1.1 (NR) 1.0 (NR)	J-shape	per 5 1.2 (1.9-1.5)
24	Yang (2009) Asia (China)	1990 - 2016 (15 yrs)	217,180 (40-79 yrs) Neoplastic (2145)	Age, area, smoking, drinking, education, biomass exposure, diet	Respiratory	3 yrs	BMI (21.7±2.7) Lung cancer Smokers Non-smokers	20-22.4 <18.5 18.5-19 22.5-24 25+ <18.5 18.5-19 22.5-24 25+ 1.3 (NR)	1.0 (NR) 1.3 (NR) 1.3 (NR) 1.0 (NR) 0.7 (NR) 1.6 (NR) 1.1 (NR) 1.2 (NR) 1.3 (NR)	Negative Null	per 5 0.7 (0.6-0.8) N/A
25	Chen (2006) Asia (China)	1990 - 2002 (10 yrs)	212,000 (40-79 yrs) Vascular (5766)	Age, area, smoking drinking	Cardiac, stroke	3 yrs	BMI (21.7±2.7) IHD Non-smokers	20-21 <18 26+ <18 26+ 1.5 (1.2-1.7)	1.0 1.1 (0.9-1.4) 1.4 (1.2-1.7) 1.1 (0.9-1.4)	J-shape ~20-22 Positive	per 2 1.1 (1.1-1.2) NR

Conventions as above.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
26	Zhou (2008) Asia (China)	1990 - 2002 (10 yrs)	212,000 (40-79 yrs) Vascular (5766)	Age, area, smoking drinking	Cardiac, stroke	3 yrs	BMI (21.7±2.7)	20-22.4	1.0		per 2.5
							Stroke	<18.5 27.5+	1.1 (0.9-1.1) 1.6 (1.4-1.9)	Positive	NR
							Non-smokers		NR	Positive	1.2 (1.1-1.2)
							Current-smokers		NR	Negative	
							HS	<18.5 27.5+	1.1 (0.9-1.2) 1.7 (1.4-2.0)	J-shape	1.1 (1.1-1.2)
							IS	<18.5 27.5+	0.9 (0.7-1.1) 1.7 (1.3-2.2)	Positive	1.2 (1.1-1.4)
							US	<18.5 27.5+	1.0 (0.8-1.2) 1.5 (1.0-2.1)	Positive	NR
27	Klenk (2009) Europe (Austria)	1985 - 2006 (15 yrs)	184,697 (26-57 yrs) Specific (15,557)	Age, smoking status, occupation	None	3 yrs	BMI (41.7±15.4)	22.0-24	1.0		
							All-cause (Men)	<18.5 35+	2.6 (2.2-3.0) 2.1 (1.4-1.8)	U-shape ~22-25	NR
							CVD		NR	U-shape	NR
							Cancer		NR	U-shape	NR
							Respiratory		NR	inverse J ~30	NR
							All-cause (Wom)	<18.5 35+	1.4 (1.2-1.6) 1.6 (1.4-1.8)	U-shape ~22-25	NR
							CVD		NR	J-shape	NR
							Cancer		NR	U-shape	NR
							Respiratory		NR	inverse J ~22-25	NR
							28	Song (2016) Meta-analysis	1976 - 2012 (15.5 yrs)	173,229 (30-75 yrs) Specific (35,358) Studies included (2) Hispanic (0)	Age, sex, height, exercise, ethnicity, amount smoked, family cancer endoscopy, multivitamins, hormonal med, mammography, med. exam, drinking, diet aspirin
All-cause											
Lean	stable	1.0	NR	N/A							
Increase	moderate	1.0 (1.0-1.1)									
Increase	marked	1.3 (1.2-1.3)									
Medium	stable/inc	1.0 (1.0-1.1)									
Heavy	stable/incr	1.5 (1.4-1.6)									
CVD											
Increase	moderate	1.0 (1.0-1.2)	NR	N/A							
Increase	marked	1.6 (1.5-1.8)									
Medium	stable/inc	1.1 (1.0-1.2)									
Heavy	stable/incr	2.0 (1.9-2.8)									

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Summary findings				
					Prior disease	FU	Adiposity (mean, SD)† Mortality	HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)	
28	Song (2016) Meta-analysis						<u>Cancer</u>				
							Increase	moderate	1.0 (1.0-1.1)	NR	N/A
							Increase	marked	1.1 (1.0-1.2)		
							Medium	stable/inc	1.0 (1.0-1.2)		
							Heavy	stable/incr	1.2 (1.1-1.4)		
							<u>Body shape†† (Men)</u>				
							All-cause				
							Increase	moderate	1.0 (1.0-1.1)	NR	N/A
							Increase	marked	1.1 (1.1-1.2)		
							Medium	stable/inc	1.1 (1.0-1.1)		
							Heavy	stable/incr	1.2 (1.1-1.2)		
							<u>CVD</u>				
							Increase	moderate	1.1 (1.0-1.2)	NR	N/A
							Increase	marked	1.3 (1.2-1.4)		
							Medium	stable/inc	1.2 (1.1-1.3)		
							Heavy	stable/incr	1.3 (1.2-1.5)		
							<u>Cancer</u>				
							Increase	moderate	1.0 (0.9-1.1)	NR	N/A
							Increase	marked	1.1 (0.9-1.2)		
							Medium	stable/inc	1.0 (0.9-1.1)		
							Heavy	stable/incr	1.1 (0.9-1.3)		
29	Chen (2012) Asia (China)	1990 - 2006 (15 yrs)	142,214 (40-79 yrs) Specific (17,800)	Age-at-risk, smoking education, drinking, area	Any chronic	5 yrs	BMI (21.8±2.5)	20-22.5	1.0	U-shape	per 5
							All-cause	15-17.5	1.1 (0.9-1.2)	~22.5-25	1.3 (1.1-1.4)
								35+	0.8 (0.3-1.7)		
							Vascular	NR	NR	J-shape	1.5 (1.3-1.8)
							CHD	30+	1.5 (1.3-1.8)	J-shape	1.5 (1.1-1.9)
							Stroke	30+	1.8 (1.6-2.5)	J-shape	1.6 (1.4-1.9)
							Hypertensive	30+	1.5 (0.8-2.5)	J-shape	2.0 (1.2-3.4)
							DM, renal, hepatic	NR	NR	NR	1.5 (1.0-2.3)
							Neoplastic	NR	NR	NR	0.9 (0.8-1.2)
							Liver cancer	30+	1.1 (0.8-1.6)	U-shape	1.1 (0.7-1.8)
							Lung cancer	30+	0.8 (0.6-1.3)	Negative	0.9 (0.6-1.4)
							Stomach cancer	30+	0.9 (0.6-1.5)	U-shape	1.0 (0.6-1.5)
							UAD cancer	30+	0.6 (0.4-1.2)	Null	0.9 (0.5-1.5)
							COPD	30+	0.8 (0.6-1.3)	Negative	1.0 (0.7-1.3)

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
30	Rosella (2019) N. America (Canada)	2000 - 2010 (5.5 yrs)	149,262 (18-90 yrs) All-cause (16,929)	Age, sex, income, comorbidity score	pregnancy	No	BMI	18.5-20	1.0		
							All-cause	<18.5	4.2 (3.7-4.7)	U-shape	NR
							Men	35+	2.1 (1.6-2.7)		
							Women	<18.5 35+	1.6 (1.5-1.8) 1.4 (1.2-1.7)	U-shape	NR
31	Hong (2016) Asia (Korea)	2004 - 2012 (23 yrs)	113,478 (55+ yrs) Neoplastic (3478)	Age, income, smoking, drinking, exercise	Cancer	2 yrs	BMI† † (23.6 ±2.7)	25-27.4	1.0		per 5
							All cancers	30+	1.0 (0.7-1.5)	inverse J	1.3 (1.0-1.6)
							Oral&Larynx	30+	3.4 (0.4-29.0)	U-shape	1.8 (0.3-10.3)
							Oesophagus	27.5+	0.8 (0.2-2.7)	inverse J	0.7 (0.1-3.6)
							Stomach	30+	0.7 (0.2- 2.2)	inverse J	1.3 (0.7-2.3)
							Large intestine	30+	1.7 (0.7-4.3)	U-shape	1.0 (0.5-2.0)
							Liver	30+	1.4 (0.7-2.8)	U-shape	1.4 (1.0-2.1)
							Gallbladder	30+	0.9 (0.1-6.4)	Non-linear	1.6 (0.7-4.1)
							Pancreas	30+	1.3 (0.3-5.7)	Non-linear	0.9 (0.3-2.4)
							Lung	30+	1.0 (0.4-2.4)	inverse J	1.6 (1.0-2.4)
							Prostate	30+	2.8 (0.3-23.1)	Positive	0.7 (1.2-4.3)
							Kidney	27.5+	0.4 (0.0-3.2)	inverse J	0.0 (0.0-0.1)
							Bladder	27.5+	0.4 (0.0-3.1)	inverse J	0.7 (0.1-4.6)
							NHL	27.5+	1.4 (0.5-3.9)	Non-linear	0.7 (0.2-3.4)
							Leukaemia	27.5+	2.5 (0.8-8.0)	Positive	2.9 (0.9-9.1)
32	Adams (2014) N. America (USA)	1995 - 2009 (12.5 yrs)	109,947 (50-70 yrs) All-cause (12,000)	Age, sex, ethnicity, smoking, drinking, exercise, education, study	No	No	BMI (20.7±1.4)	18.5-<22.5	1.0		
							All-cause	<18.5	1.2 (1.0-1.5)	J-shape	NR
								22.5-24	1.1 (1.1-1.2)		
								25-27.4	1.5 (1.3-1.6)		
								27.5-30	2.1 (1.9-2.4)		
								30+	2.6 (12.3-3.0)		
							gain>25.0	<25.0	1.0	N/A	N/A
							Age 50 yrs		1.3 (1.2-1.4)		
33	Mehta (2013) USA (Hispanics)	1997 - 2006 (8.9 yrs)	38,810 (18+ yrs) All-cause (1461) Mexicans (59%)	Age-attained , sex, smoking, exercise	No	No	BMI	18.5-<25	1.0		
							age 60+	<18.5	2.2 (1.4-3.5)	inverse J	NR
								25-<30	0.8 (0.6-0.9)		
								35+	0.7 (0.6-0.9)		
							age <60	as above	NR	Positive	NR

Conventions as above. COPD=Chronic Obstructive Pulmonary Disease; NHL=Non-Hodgkin Lymphoma; UAD=Upper Aero-Digestive.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality		Summary findings		
					Prior disease	FU			HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
34	Fontaine (2012) Meta-analysis	1965 - 2006 (13 yrs)	16,798 (18+ yrs) All-cause (5186) Studies included (5) Hispanic (5)	Age, sex, smoking	No	No	BMI	18.5-<25	1.0		
							All-cause	<18.6	1.6 (1.2-2.3)	inverse J	NR
							18-<60 yrs	25-<30	0.7 (0.6-0.9)		
								30-<35	1.1 (0.9-1.3)		
								35+	1.0 (0.8-1.4)	inverse J	NR
							60-<70 yrs	<18.5	1.4 (1.1-1.9)		
								25-<30	1.0 (1.0-1.1)		
								30-<35	0.9 (0.8-1.1)		
								35+	0.8 (0.7-1.0)		
							>70 yrs	<18.5	1.3 (1.0-1.6)	inverse J	NR
								25-<30	0.9 (0.8-0.9)		
								30-<35	0.9 (0.8-1.0)		
	PRHHP Latin-America (Puerto-Rico)	1965 -1980 (12 yrs)	5,187 (35-79 yrs) All-cause (2619)	Age, sex, smoking	CHD	No	18-<60 yrs	<18.5	1.5 (1.1-2.2)	U-shape	NR
								25-<30	1.0 (0.8-1.1)		
								30-<35			
								35+	1.3 (0.7-2.5)	J-shape	NR
							60-<70 yrs	<18.5	1.4 (1.0-1.8)		
								25-<30	1.1 (1.0-1.2)		
								30-<35	1.2 (1.0-1.4)		
								35+	1.6 (0.9-2.8)	inverse J	NR
							>70 yrs	<18.5	1.6 (1.1-2.4)		
								25-<30	1.0 (0.8-1.3)		
								30-<35	1.2 (0.9-1.7)		
								35+	1.4 (0.4-4.3)	non-linear	NR
	NHANES iii USA (Hispanics)	1988 -1994 (15 yrs)	5,182 (24 yrs) All-cause (840)	Age, sex, smoking	No	No	18-<60 yrs	25-<30	0.8 (0.5-1.4)		
								30-<35			
								35+	0.9 (0.4-2.2)	J-shape	NR
							60-<70 yrs	<18.5	1.0 (0.2-6.3)		
								25-<30	1.2 (0.5-3.2)		
								30-<35	1.4 (0.5-3.9)	inverse J	NR
								35+	1.0 (0.3-3.1)		
							>70 yrs	<18.5	1.5 (0.9-2.5)		
								25-<30	0.8 (0.6-1.3)		
								30-<35	0.7 (0.4-1.4)		
								35+	1.0 (0.3-2.7)		

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality		Summary findings		
					Prior disease	FU			HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
34	SAHS Mexican (USA)	1979 - 2000 (14 yrs)	2,758 (18+ yrs) All-cause (923)	Age, sex, smoking	No	No	All-cause	<18.6	2.0 (0.5-8.3)	inverse J	NR
							BMI	25-<30	1.0 (0.7-1.3)		
							18-<60 yrs	30-<35	1.0 (0.7-1.4)		
								35+	1.0 (0.7-1.4)		
							60-<70 yrs	<18.6	2.5 (1.0-6.3)	inverse J	NR
								25-<30	1.1 (0.8-1.4)		
								30-<35	0.9 (0.6-1.4)		
								35+	1.2 (0.8-1.7)		
							>70 yrs	<18.5	1.9 (0.4-8.0)	Negative	NR
								25-<30	1.1 (0.7-1.6)		
	HEPESE Mexican (USA)	1995 - 1996 (12 yrs)	1,882 (60+ yrs) All-cause (385)	Age, sex, smoking	No	No		30-<35	0.8 (0.5-1.3)		
								35+	0.9 (0.6-1.6)		
							60-<70 yrs	<18.5	NR	inverse J	NR
								25-<30	0.4 (0.3-0.5)		
								30-<35	1.0 (0.8-1.1)		
								35+	0.7 (0.6-0.9)		
							>70 yrs	<18.5	0.9 (0.6-1.4)	Null	NR
								25-<30	0.8 (0.8-0.9)		
								30-<35	0.9 (0.8-1.0)		
								35+	0.6 (0.5-0.8)		
	SALSA Mexican (USA)	1998 - 2006 (9 yrs)	1,625 (60+ yrs) All-cause (419)	Age, sex, smoking	No	No	60-<70 yrs	<18.5	NR		
								25-<30	0.9 (0.5-1.3)	J-shape	NR
								30-<35	0.8 (0.5-1.5)		
								35+	1.4 (0.8-2.6)		
							>70 yrs	25-<30	0.7 (0.5-0.9)	inverse J	NR
								30-<35	0.6 (0.4-0.8)		
								35+	0.9 (0.6-1.2)		

Conventions as above. (Continuation of previous report.)

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
35	Howell (2017) USA (Hispanics)	1988 - 2010 (22 yrs)	6,242 (NR) (26+ yrs) Specific (1196) Mexicans (58.6%)	Age, sex, smoking	Pregnancy	No	BMI†† (29.9±6)	18.5-<25	1.0		
							All-cause	25-<30	1.2 (0.9–1.7)	Positive	NR
								30-<35	2.5 (1.7–3.6)		
								35+	3.6 (1.1–11.1)		
							CVD	25-<30	0.5 (0.2–1.3)	Non-linear	NR
								30-<35	0.7 (0.2–3.6)		
								35+	1.7 (0.2–18.5)		
							DM	25-<30	0.9 (0.3–3.1)	Positive	NR
								30-<35	5.9 (1.2–29.7)		
								35+	3.2 (0.26–40.0)		
							Neoplastic	25-<30	1.3 (0.5–3.2)	Non-linear	NR
								30-<35	2.4 (0.6–9.0)		
								35+	1.1 (0.1–7.7)		
36	Crespo (2002) Latin-America (Puerto-Rico)	1962 - 1965 (NR)	9,824 (NR) All-cause (NR)	Age, education, smoking, residence, hypertension, cholesterol, exercise	CHD	3 yrs	BMI	<18.5	1.0	Null	NR
							All-cause	18.5-<25	0.7 (0.6-0.8)		
								25-<30	0.6 (0.5-0.7)		
								30+	0.5 (0.5-0.6)		
37	Kumar (2015) Mexico	2001 - 2012 (11 yrs)	8,415 (50+ yrs) All-causes (1067)	Age, sex, smoking comorbidities marital status education	No	5 yrs (NR)	BMI††	18.5-<25	1.0	inverse J	NR
							All-cause	<18.5	1.3 (1.0-1.7)		
								25-<30	0.8 (0.7-1.0)		
								30-<35	0.9 (0.7-1.0)		
								35+	0.9 (0.7-1.2)		
38	AlSnih (2002) USA (Hispanics)	1993 - 1999 (5 yrs)	3,050 (65+ yrs) All-cause (507)	Age, education, smoking, handgrip strength , timed walk, disability, medical history, marital status	No	No	BMI	22-<26	1.0	inverse J	NR
							All-cause (Men)	<22	0.9 (0.6–1.5)		
								26-<30	0.7 (0.5–1.0)		
								≥30	0.7 (0.4–1.0)	inverse J	NR
							All-cause (Wom)	<22	1.4 (0.9–2.2)		
								26-<30	0.9 (0.6–1.2)		
								≥30	0.6 (0.4–0.9)		

Conventions as above.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
39	Hanson (1995) USA (Pima Indians)	1965 - 1990 (8.1 yrs)	2,628 (30+ yrs) Specific (249)	Age, sex, smoking. year at entry, FU	DM pregnancy	No	BMI (30.1)	30-<35	1.0		
							All-Cause	<25	1.5 (1.0-2.2)	U-shape	NR
								25-<30	1.0 (0.7-1.5)		
								>35-40	1.2 (0.8-1.9)		
								40+	1.9 (1.2-3.1)		
							CVD	<25	1.2 (0.5-2.7)	J-shape	NR
								25-<30	0.9 (0.4-1.9)		
								>35-40	0.7 (0.2-2.3)		
								40+	1.5 (0.4-5.8)		
							Other medical	<25	1.4 (0.9-2.2)	J-shape	NR
40	Amador (2006) USA (Hispanics)	NR (7 yrs)	1,749 (65+ yrs) All-cause (NS)	Age, smoking, marital status, handgrip strength , timed walk, BMI, disability, medical history, education	NS	NS	Weight	5% lost	1.3 (1.1-1.7)	N/A	NR
							All-Cause	5% gain	0.8 (0.6-1.0)		
41	Ottenbacher (2012) USA (Hispanics)	1993 - 1999 (3 yrs)	948 (75+ yrs) All-cause (NS)	Socio-demographic, BMI, low income, smoking, activities, depression, comorbidities, cognitive function	No	No	BMI	30+	0.7 (0.4–1.1)	NR	NR
							All-Cause				
42	Espinoza (2013) USA (Hispanics)	1992 - 1996 (8.2 yrs)	751 (65+ yrs) All-cause (NS)	Age, sex, frailty, DM, income, cognition, depression, comorbidities education	No	No	BMI	30+	1.0 (1.0-1.0)	N/A	NR
							All-Cause				
43	Beleigoli (2012) Latin-America (Brazil)	1997 - 2007 (6.9 yrs)	578 (60+ yrs) All-causes (140)	Age, sex, smoking, BMI, income, exercise education, DM, BP, ECG, BP, cholesterol creatinine, anti-hypertensive	No	No	Weight	5% lost	1.5 (1.0-2.2)	N/A	NR
							All-Cause	5% gain	1.6 (1.0-2.7)		

S4: Published studies of abdominal adiposity and mortality, by study size

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality		Summary findings		
					Prior disease	FU			HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
1	Behrens (2013) N. America (USA)	1996-2009 (12.5 yrs)	170,672 (51-71 yrs) All-cause (20,000)	Age, sex, smoking, education, diet drinking, HC,	CVD, Cancer DM, emphysema,	No	WC††				
							All-cause		1.0	NR	NR
							Men	<102 cms	0.9 (0.8-0.9)		
							Women	<88 cms	0.8 (0.8-0.9)		
2	Jacobs (2010) N. America (USA)	1992 - 2006 (9 yrs)	104,843 (50+ yrs) Specific (14,647)	Age, ethnicity, education, exercise, smoking, height drinking, marital status, HRT	No	No	All-cause	By BMI††			per 10
							WC††	25-30	1.5 (1.2-1.8)	Positive	1.2 (1.1-1.2)
							Men	30+	1.7 (1.3-2.3)	Positive	1.2 (1.1-1.3)
							Women	25-30	1.8 (1.4-2.2)	Positive	1.1 (1.1-1.2)
								30+	1.3 (1.0-1.6)	Positive	1.1 (1.1-1.2)
							WC††	<90/<75	1.0		
							Men	120+	2.0 (1.7-2.4)	Positive	NR
							Women	110+	2.4 (2.0-2.8)	Positive	NR
							CVD				
							Men	120+	1.4 (1.2-1.6)	Positive	NR
							Women	110+	1.9 (1.6-2.4)	Positive	NR
							Cancer				
							Men	120+	1.2 (1.0-1.3)	Positive	NR
							Women	110+	1.3 (1.1-1.6)	Positive	NR
							Respiratory				
							Men	120+	1.1 (0.8-1.4)	Positive	NR
							Women	110+	1.2 (0.8-1.7)	Positive	NR

†Adiposity was measured, unless otherwise specified. Summary statistics given if reported. †† Includes self-reports. BMI= Body Mass Index in kg/m².

WC=Waist Circumference; HC=Hip Circumference; HRT=Hormone Replacement Therapy; CVD=Cardio-vascular Disease; DM=Diabetes Mellitus; NR= Not reported.

Study 2 excluded individuals who lost >4.5 kgs of weight or gained >11.3 kgs of weight.

S5: Published studies of body composition and mortality, by study size

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Summary findings				
					Prior disease	FU	Adiposity (mean, SD)† Mortality	HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)	
1	Lee (2018) Asia (Korea)	2007 - 2015 (5.7 yrs)	36,656 (45-65 yrs) All-cause (253)	Age, sex, glucose, triglycerides, HDL-C, haemoglobin, CRP albumin, proteinuria, WC, BMI, MM medication use	No	No	TFM (15.8±5)				
							<u>All-cause</u>	Q1	1.0		
							SFA	Q3	0.7 (0.4-1.1)	Negative	NR
							VSR	Q3	1.9 (1.2-3.2)	Positive	NR
							TFM				
							Q1	SFA (Q3)	1.1 (0.5-2.4)	Negative	NR
							Q2	SFA (Q3)	0.4 (0.1-1.6)	Negative	NR
							Q3	SFA (Q3)	0.6 (0.2-1.5)	Negative	NR
							Q4	SFA (Q3)	0.3 (0.1-0.7)	Negative	NR
2	Brown (2017) N. America (USA)	1988 - 1994 (18.8 yrs)	10,642 (18+ yrs) Specific (3531)	Age, sex, drinking, smoking, diet, exercise	Cardiac, MI, DM cancer	No	adVAT (181±0.7)				
							<u>All-cause</u>	Q1	1.0	Positive	NR
								Q5	2.2 (1.4–3.3)		
							<u>CVD</u>	Q5	2.6 (0.8–8.5)	Non-linear	NR
							<u>Cancers</u>	Q5	3.3 (1.5–7.2)	Non-linear	NR
3	Zong (2016) N. America (USA)	1999 - 2006 (8.8 yrs)	9,471 (20+ yrs) Specific (683)	Age, sex, ethnicity, education, smoking, drinking, exercise, marital status, income, family medical history	DM, CVD, cancer COPD, asthma mental	1 yr	TFM% (33.1±0.7)				
							<u>All-cause</u>	Q2	1.0		
							TFM%	Q4	1.5 (1.1-2.0)	J-shaped	NR
							Trunk FM	Q4	1.3 (1.0-1.9)	J-shaped	NR
							Leg FM	Q4	1.3 (1.0-1.8)	J-shaped	NR
							<u>CVD</u>				
							TFM%	Q4	2.2 (1.2-4.3)	inverse J	NR
							Trunk FM	Q4	1.9 (1.2-4.3)	U-shaped	NR
							Leg FM	Q4	1.5 (0.8-2.9)	U-shaped	NR
							<u>Cancer</u>				
							TFM%	Q4	1.8 (1.0-3.1)	J-shaped	NR
							Trunk FM	Q4	1.4 (0.7-2.6)	J-shaped	NR
							Leg FM	Q4	1.3 (0.7-2.3)	inverse J	NR

†Adiposity was measured, unless otherwise specified. Summary statistics given if reported. †† Includes self-reports. NR= Not reported; N/A=Not Applicable

SFA= Subcutaneous Fat Area, VSR=Visceral:Subcutaneous Fat area ratio, T/FM=Total/Fat mass; adVAT= Anthropometrically-defined Visceral Adipose Tissues (cm²)

MM=Muscle Mass. Study 1 employed Computer Tomography (CT) scan. Study 3 employed Dual X-Ray Absorptiometry (DXA).

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality	Summary findings		
					Prior disease	FU		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
4	deSantana (2019) Latin-America (Brazil)	NR (4 yrs)	839 (65+ yrs) All-cause (132)	Age, sex, smoking, exercise, drinking, diabetes, falls, CVD, Vit.D, albumin, calcium, hypertension	No	No				per 100g VAT
							<u>All-cause</u>			per 1kg/m ² FMI
							VAT	NR	NR	1.6 (1.3-2.1)
							FMI	NR	NR	0.6 (0.4-0.7)
							LMM	NR	NR	14.8 (5.1-42.7)
							<u>CVD</u>			
							VAT	NR	NR	1.6 (1.3-2.1)
							FMI	NR	NR	0.6 (0.4-0.7)
							LMM	NR	NR	14.8 (5.1-42.7)

Conventions as above. VAT=Visceral Adipose Tissue, FMI=Fat Mass Index; LMM=Low Muscle Mass. Study 4 employed Dual X-Ray Absorptiometry (DXA).

S6: Published studies of multiple adiposity measures and mortality, by study size

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Summary findings				
					Prior disease	FU	Adiposity (mean, SD)† Mortality	HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)	
1	Teras (2014) Meta-analysis	1955 - 2002 (18-85 yrs)	1.5 M (NR) Neoplastic (1388) Studies included (20) Hispanic (0)	Age, smoking education, exercise drinking, family disease	Cancer	5 yrs	Any cancer	<18.5	1.2 (0.7-2.1)	J-shape	per 5
							BMI††	18.5-21	1.0 (0.8-1.3)	(~22)	1.2 (1.1-1.3)
								21-23	1.0		per 1
								23-25	1.2 (1.0-1.5)		1.1 (1.0-1.1)
								25-27.5	1.1 (0.9-1.4)		
								27.5-30	1.2 (1.0-1.5)		
								30-35	1.5 (1.1-2.0)		
								35+	1.1 (1.0-1.2)		
							WC	<90	1.0	Positive	per 5
								90-100	1.3 (1.0-1.6)		1.1 (1.0-1.1)
								100-110	1.3 (1.0-1.7)		
								110+	1.5 (1.1-2.0)		
							WHR	<0.9	1.0	Null	per 0.1
								0.9-0.95	1.0 (0.8-1.2)		1.0 (0.9-1.2)
								0.95-1.0	1.1 (0.8-1.5)		
								1.0+	1.1 (0.8-1.4)		
2	Genkinger (2015) Meta-analysis	1995 - 2015 (NR)	1.0 M (18+ yrs) Neoplastic (5181) Studies included (20) Hispanic (0)	Age, sex, BMI, WC	NR	NR	Pancreatic	<23	1.0	NR	per 5
							cancer	23-25	1.2 (1.1-1.2)		1.2 (1.1-1.2)
							BMI	25-27.4	1.4 (1.2-1.5)		
								27.5-30	1.5 (1.2-1.8)		
								30+	1.4 (1.1-1.8)		
								gain			1.0 (1.0-1.1)
							WC	NR	NR	NR	per 10
											1.1 (1.0-1.1)
							WHR	NR	NR	NR	per 0.1
											1.1 (1.0-1.2)

†Adiposity was measured, unless otherwise specified. Summary statistics given if reported. †† Includes self-reports. NR= Not reported; BMI=Body Mass Index in kg/m²; WC=Waist circumference in cms; WHR=Waist:Hip ratio in cms. Lower risk refers to the nadir of the specific measure. Continuous estimates are per adiposity-specific units (i.e. kg/m² for BMI, cms for WC, etc.) unless otherwise specified. Studies included refer to the total individual studies meta-analysed; Hispanic refers to Mexican or other Latino-American populations. The reference groups apply throughout, unless otherwise specified.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
3	Karahalios (2017) Meta-analysis	1995 - 2015 (NR)	872,466 (NR) Specific (66,016) Studies included (26) Hispanic (0)	Age, sex, BMI, smoking, exercise education, SES, drinking, ethnicity medical histories (only in some)	No	6 yrs	All-cause	stable	1.0		per 7.5
							Weight (kgs)	loss	NR	U-shape	1.4 (1.3-1.6)
								gain	NR	U-shape	1.1 (1.0-1.3)
							CVD	loss	NR	NR	1.5 (1.3-1.7)
								gain	NR	NR	1.2 (1.1-1.4)
							Cancer	loss	NR	NR	1.2 (1.0-1.5)
								gain	NR	NR	1.0 (1.0-1.1)
							WC (cms)	loss	NR	NR	1.3 (1.1-1.5)
4	Carmienke (2013) Meta-analysis	1981 - 2003 (5-24 yrs)	689,465 (18+ yrs) All-cause (48,000) Studies included (18) Hispanic (0)	Varied from none to multiple&complex	NR	5 yrs	All-cause	24.9	1.0		
							BMI	30+	1.0 (1.0-1.1)	U-shape	NR
								35+	1.3 (1.2-1.3)		
							WC	80-95	1.0	J-shape	NR
								105-120	1.5 (1.3-1.6)		
							WHR	0.8-0.95	1.0	Positive	NR
								0.9-1.1	1.5 (1.4-1.6)		
							WHtR	Q5	1.3 (1.1-1.7)	Positive	NR
5	Kim (2017) Europe (UK)	2006 - 2010 (7 yrs)	0.5 M (40-69 yrs) All-cause (8287)	Age, sex, ethnicity, smoking, exercise drinking, grip strength Townsend index employment status statin, HRT use, meat consumption pulse rate	heart attack, cancer, COPD, stroke	2 yrs	<u>All-cause</u>				
							<u>BMI</u>	18.5-25	1.0		
							Men	35+	1.51 (1.2-1.9)	Positive	NR
							Women	35+	1.6 (1.3-2.0)	J-shape (25-30)	
							<u>WC</u>	<94\<80	1.0		
							Men	102+	1.3 (1.2-1.5)	Positive	
							Women	88+	1.3 (1.1-1.4)	J-shape (80-88)	
							<u>FM (%)</u>	<20\<30	1.0		
							Men	25+	1.1 (0.9-1.3)	Positive	
							Women	33+	1.1 (0.9-1.2)	Positive	
							<u>CVD</u>				
							BMI (Men)	35+	2.5 (1.7-3.7)	Positive	
							BMI (Wom)	35+	1.9 (1.2-2.9)	J-shape (30-35)	
							WC (Men)	102+	1.5 (1.2-2.0)	J-shape (80-88)	
							WC (Wom)	88+	1.5 (1.1-2.1)	J-shape (80-88)	
							FM (% , Men)	25+	1.2 (0.9-1.7)	inverse J	
							FM (% , Wom)	33+	0.9 (0.6-1.4)	Negative	

Conventions as above. FM=Fat Mass; CVD= Cardiovascular Disease; COPD= Chronic Obstructive Pulmonary Disease; SES=Socio=Economic Status; HRT=Hormone Replacement.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
6	Dhalwani (2018) Europe (UK)	2006 - 2010 (7 yrs)	0.5 M (40-69 yrs) Specific (12,096)	Age, sex, ethnicity, smoking, SES, MET, drinking, diet, handgrip strength, CVD, cancer, DM duration medication use	CVD, cancer	2 yrs	All-cause	18.5-22.9	1.0		
							BMI (No DM)	<18.6	2.3 (1.9-2.7)	inverse-J	NR
							40+	1.3 (1.1-1.4)		(25-30)	
							BMI (DM)	<18.6	2.5 (1.2-4.9)	inverse-J	
							40+	0.9 (0.8-1.1)		(25-30)	
							WC (No DM)	Q6	1.2 (1.1-1.4)	U-shape (~81)	
							WC (DM)	Q6	0.8 (0.7-0.9)	inverse-J (~81)	
							CVD	<18.6	2.0 (1.5-3.0)	U-shape	
							BMI (No DM)	40+	2.0 (1.5-2.5)	(25-30)	
							BMI (DM)	<18.6	4.0 (1.3-11.5)	inverse-J	
							40+	1.1 (0.9-1.5)		(25-30)	
							WC (No DM)	Q6	1.5 (1.4-1.6)	J-shape (~81)	
							WC (DM)	Q6	1.2 (1.0-1.3)	inverse J (~81)	
							Cancer	<18.6	1.5 (1.1-1.9)	U-shape	
							BMI (No DM)	40+	1.1 (0.9-1.5)	(18.5-25)	
							BMI (DM)	<18.6	0.7 (0.1-5.0)	non-linear	
							40+	0.7 (0.4-1.0)		(<18.5)	
							WC (No DM)	Q6	1.2 (1.1-1.4)	J-shape (~81)	
							WC (DM)	Q6	0.9 (0.8-1.0)	Negative	
7	Park (2018) Asia (Korea)	2002 - 2013 (5.6 yrs)	465,629 (40-89 yrs) Specific (5469)	Age, sex, smoking, drinking, exercise income	CVD, cancer DM, hypertension	No	All-cause/CVD	23-25	1.0		
							BMI (23.2±3.4)	<18.5	2.6 (2.3-2.8)	J-shape	NR
								≥32.5	1.4 (1.1-1.8)		
							WC (80.5±8.9)	<64	2.2 (1.9-2.6)	J-shape	
								78.6-84.8	1.0		
								≥103	0.8 (0.7-1.1)		
							WHtR (0.5±0.06)	<0.4	2.0 (1.7-2.4)	J-shape	
								0.48-0.51	1.0		
								≥0.63	1.0 (0.9-1.2)		
							WWI (8.1±0.6)	<8.83	1.5 (1.2-2.0)	J-shape	
								9.89-10.34	1.0		
								≥12.11	1.8 (1.6-2.0)		
							ABSI (10.4±0.8)	<6.95	1.4 (1.1-1.7)	J-shape	
								7.72-8.04	1.0		
								≥9.13	2.6 (2.0-2.5)		

Conventions as above. MET=Metabolic Equivalent Task; DM=Diabetes Mellitus; WHtR=Waist:Height ratio; WWI=Weight-adjusted-waist index in cm/√kg;
ABSI=Body Shape Index in cm*kg5/6/m2/3.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
8	Farmer (2019) Europe (UK)	2006 - 2010 (5.1 yrs)	452,931 (40-69 yrs) Vascular (11,336)	Age, sex, smoking, ethnicity, depravation, drinking, exercise DM	CVD	4 yrs	All-cause				
							Opt BMI/HGS	<30/<25	1.0	N/A	N/A
							Obese/non-SP	>30/>25	1.3 (1.2-1.3)		
							SP/non-obese	<25/<30	1.1 (1.0-1.1)		
							SP Obesity	<25/>30	1.4 (1.3-1.5)		
							<u>CVD</u>			N/A	N/A
							Obese/non-SP	>30/>25	1.5 (1.3-1.6)		
							SP/non-obese	<25/<30	1.7 (1.4-1.9)		
							SP Obesity	<25/>30	1.8 (1.4-2.2)		
							<u>All-cause</u>				
							Opt WHR/HGS	<0.9/<25	1.0	N/A	N/A
							Obese/non-SP	>0.9/>26	1.2 (1.2-1.3)		
							SP/non-obese	<25/<0.9	1.4 (1.3-1.5)		
							SP Obesity	<25/>0.9	1.5 (1.4-1.7)		
							<u>CVD</u>			N/A	N/A
							Obese/non-SP	>0.9/>26	1.4 (1.3-1.6)		
							SP/non-obese	<25/<0.9	1.7 (1.4-2.1)		
							SP Obesity	<25/>0.9	2.0 (1.7-2.4)		
9	Pischon (2008) Meta-analysis	1992 - 2000 (9.7 yrs)	359,387 (25-70 yrs) Specific (14,723) Studies included (9) Hispanic (0)	age, study, smoking drinking, education, exercise, height	cancer, CHD, stroke	5 yrs	<u>All-cause</u>	23.5-25	1.0		
							<u>BMI</u>	<18.5	2.3 (1.8-2.9)	J-shape	NR
							Men	35+	1.9 (1.7-2.2)	(20-24.9)	
							Women	<18.5	1.7 (1.4-2.0)		
								35+	1.6 (1.5-1.8)		
							<u>WC</u>	<86/<70	1.0	Positive	
							Men	102+	2.0 (1.8-2.3)		
							Women	89+	1.8 (1.6-2.0)		
							<u>WHR</u>	<.89/<.73	1.0	Positive	
							Men	0.99+	1.7 (1.5-1.8)		
							Women	0.85+	1.5 (1.4-1.7)		
							<u>Vascular</u>				
							<u>BMI</u>	<18.5	1.8 (1.2-2.9)	J-shape	
							Men	35+	2.6 (1.9-3.7)	(20-24.9)	
							Women	<18.5	1.1 (0.7-1.7)		
								35+	3.3 (2.2-4.9)		

Conventions as above. Opt=Optimal; CHD=Coronary Heart Disease; HGS=Hand Grip Strength; SP=Sarcopenia defined in kgs.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality	Summary findings		
					Prior disease	FU		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
9	Pischon (2008) Meta-analysis						<u>Vascular</u>			
							WC Men	102+	1.8 (1.4-2.3)	Positive
							WC Women	89+	2.3 (1.7-3.2)	
							WHR Men	0.99+	1.3 (1.1-1.6)	Positive
							WHR Women	0.85+	1.7 (1.4-2.2)	
							<u>Neoplastic</u>			
							BMI Men	<18.5	1.2 (0.7-2.0)	J-shape (20-24.9)
								35+	1.2 (1.0-1.6)	
							BMI Women	<18.5	1.2 (0.8-1.6)	
								35+	1.4 (1.1-1.7)	
							WC Men	102+	1.9 (1.5-2.4)	Positive
							WC Women	89+	1.3 (1.0-1.6)	
							WHR Men	0.99+	1.6 (0.9-3.0)	Positive
							WHR Women	0.85+	1.2 (1.1-1.4)	
							<u>COPD</u>	23.5-25	1.0	J-shape 20-24.9
							BMI Men	<18.5	6.5 (3.6-12.0)	
								35+	1.5 (1.3-1.8)	
							BMI Women	<18.5	4.7 (2.6-8.6)	
								35+	1.6 (0.8-2.9)	Positive
							WC Men	102+	6.7 (3.6-12.0)	
							WC Women	89+	2.9 (1.5-5.7)	Positive
							WHR Men	0.99+	3.3 (2.1-5.2)	
							WHR Women	0.85+	3.3 (1.9-5.8)	

Conventions as above (Continuation form the previous section).

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
10	Leitzman (2011) N. America (USA)	1996 - 2005 (9 yrs)	225,712 (50-71 yrs) Specific (20,977)	Age, sex, ethnicity, smoking, drinking,	No	No	All-cause	18.5-24.9	1.0	J-shape	NR
							BMI††	35+	1.7 (1.6-1.8)	(25 -30)	
							WC††	<80/94	1.0	Positive	
								96/118+	1.7 (1.5-1.8)		
							<u>Diabetes/Kidney</u>				
							BMI	35+	4.8 (3.6-6.3)	Positive	
							WC	96/118+	2.4 (1.7-3.5)	Positive	
							<u>CVD</u>				
							BMI	35+	2.4 (2.1-2.6)	Positive	
							WC	96/118+	1.4 (1.2-1.6)	Positive	
							<u>CHD</u>				
							BMI	35+	2.4 (2.1-2.7)	Positive	
							WC	96/118+	1.6 (1.4-1.9)	Positive	
							<u>Any Cancer</u>				
							BMI	35+	1.2 (1.1-1.4)	Positive	
							WC	96/118+	1.4 (1.2-1.6)	Positive	
							<u>Lung Cancer</u>				
							BMI	35+	0.9 (0.7-1.2)	Negative	
							WC	96/118+	1.8 (1.6-2.1)	Positive	
							<u>COPD</u>				
							BMI	35+	1.2 (0.9-1.6)	J-shape	
							WC	96/118+	2.8 (1.9-3.9)	Positive	
11	Chen (2017) N. America (USA)	1993 - 2008 (15 yrs)	161,808 (50–79 yrs) All-cause (18,320)	Age, study, race, exercise, smoking, drinking, income, medical history, HRT use, education, marital status	No	No	All-cause	18.5-24.9	1.0		NR
							<u>BMI</u>	<18.5	1.7 (1.0-2.9)	J-shape	
							African-American	40+	1.4 (1.1-1.7)		
							Hispanic	<18.5	3.5 (1.3-9.6)	J-shape	
								40+	2.4 (1.6-3.7)		
							Caucasian	<18.5	1.7 (1.4-1.9)	J-shape	
								40+	1.4 (1.3-1.6)		
							<u>WC</u>	80-89	1.0		
							African-American	<79	0.9 (0.7-1.0)	Positive	
								115+	1.7 (1.4-2.1)		
							Hispanic	<79	1.0 (0.7-1.3)	Positive	
								115+	2.3 (1.4-3.7)		
							Caucasian	<79	1.0 (0.9-1.0)	Positive	
								115+	1.7 (1.6-1.9)		

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
12	Bowman (2017) Europe (UK)	2006 - 2010 (6.5 yrs)	130,743 (60-69 yrs) Vascular (2974)	Age, sex, education, smoking, drinking	Cancer heart failure dementia	2 yrs	CAD	18.5-25	1.0		
							BMI	30-35	1.3 (1.1-1.4)	NR	NR
							WHR	<.91/<.79	1.0	NR	
							(Men/Women)	>0.96/0.85	1.3 (1.2-1.5)		
							BMI	WHR			
							18.5-25	>0.96/0.85	1.3 (1.1-1.6)	Non-linear	
							25-30	>0.96/0.85	1.4 (1.2-1.6)	Negative	
30-35	>0.96/0.85	1.5 (1.3-1.7)	Positive								
13	Padwal (2016) N. America (Canada)	1999 - 2015 (5.5 yrs)	54,440 (40+ yrs) All-cause (5949)	Age, aggregate diagnosis score ethnicity, income, residency, drinking, COPD	No	No	All-Cause	Q3 (25-27)	1.0	J-shape	NR
							BMI	Q1 (<22.5)	1.5 (1.4–1.6)	(~27)	
							Women	Q5 (31+)	1.0 (0.9–1.1)		
							Men	Q1 (<22.5)	1.3 (1.0–1.5)	U-shape	
								Q5 (31+)	1.1 (0.9–1.4)	(~27)	
							FM%				NR
							Women	Q1 (<25)	1.4 (1.2–1.5)	inverse J	
								Q5 (38+)	1.1 (1.0–1.2)	(~32)	
							Men	Q1 (<25)	1.2 (1.0–1.5)	J-shape	
								Q5 (38+)	1.4 (1.2–1.7)	(~30)	
14	Lee (2018) N. America (USA)	1987 - 2012 (21.4 yrs)	38,006 (40+ yrs) Specific (12,356)	Age, sex, ethnicity, height, smoking, residency, drinking, exercise, energy intake, family medical histories	CVD, cancer	10 yrs	All-cause	22.5-25	1.0	J-shape	per SD
							BMI (25.4)	<18.6	1.7 (1.3-2.3)	(22.5-25)	1.2 (1.1-1.2)
								35+	2.3 (2.0–2.6)		
							FM	Q1	1.0		
								Q5	1.35 (1.3-1.5)	Positive	1.2 (1.2-1.3)
							LM	Q5	0.97 (0.9-1.0)	U-shape	0.9 (0.8-0.9)
							CVD			(~55)	
							BMI	<18.6	1.4 (0.9-2.4)	J-shape	NR
								35+	2.7 (2.1–3.4)	(22.5-25)	
							FM	Q5	1.67 (1.5-1.9)	Positive	1.7 (1.5-1.9)
LM	Q5	1.11 (1.0-1.2)	U-shape	NR							
			(~60)								

Conventions as above. CAD=Coronary Artery Disease. FM=Fat Mass; LM=Lean Mass from DXA. Study 14 excluded those with a FM<10th centile and a BMI<12.5/>60 kg/m².

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
15	Franceschini (2015) USA (Hispanics)	1993 - 1998 (11.6 yrs)	20,117 (50+ yrs) Renal (3104) Hispanic (20%)	Age, smoking, eGFR, education, ethnicity, region, study, BP, DM, treatments	No	3 yrs	BMI (29.8±6.2)	18.5-<25	1.0		
							ESRD	25-<30	1.0 (0.9-1.0)	J-shape	1.0 (1.0-1.1)
								30+	1.2 (1.1-1.3)		
							WC (90±13.8)	<=88cm	1.0	NR	1.0 (1.0-1.1)
								>88cm	1.4 (1.3-1.5)		
16	Dong (2018) N. America (USA)	1988 - 2011 (19 yrs)	16,415 (18-89 yrs) All-cause (4999)	Age, sex, ethnicity, education, smoking, drinking, exercise, hypertension income	Any medical histories	5 yrs	<u>All-cause (Men)</u>		1.0		
							FM% (25.5±6.1)	<1	1.5 (1.2-1.9)	U-shape	NR
								40+	1.8 (1.1-2.7)		
							WHR (0.96±.08)	0.9-1.0	1.0		
								<85	1.5 (1.1-2.0)	inverse J	NR
								1.10+	1.2 (1.0-1.4)		
							<u>All-Cause (Wom)</u>				
							FM% (37.8±7.4)	<1	2.1 (1.5-3.0)	J-shape	NR
								40+	1.2 (1.0-1.4)		
							WHR (0.88±.08)	<80	0.8 (0.6-1.0)	Positive	NR
								1.05+	1.1 (0.9-1.4)		
17	Koch (2008) Latin-America (Chile)	1998 - 2006 (8 yrs)	13,054 (NR) All-causes (670)	Age, smoking, family CVD, DM, income, drinking, dyslipidaemia	No	No	<u>All-cause (Men)</u>				
							BMI (26.7±4.3)	>30	0.8 (0.6-1.1)	N/A	NR
							WC (91.5±12.6)	102+	1.3 (0.9-1.7)		
							WHR (.9±.09)	1+	0.9 (0.7-1.2)		
							WHt (.55±.08)	0.55+	2.4 (1.6-3.5)		
							<u>All-Cause (Wom)</u>				
							BMI (27.7±5.1)	>30	0.9 (0.7-1.3)		
							WC (87.6±12.9)	88+	1.3 (1.0-1.8)		
							WHR (0.86±.1)	0.85+	1.5 (1.2-2.2)		
							WHt (.57±.09)	0.55+	1.6 (1.1-2.3)		
18	Abramowitz (2018) N. America (USA)	1999 - 2011 (9.3 yrs)	11,687 (20+ yrs) All-cause (1,819)	Age, sex, ethnicity smoking, education, exercise	Heart disease DM, cancer eGFR<30	2 yrs	All-cause	18.5-25	1.2 (1.0-1.3)	U-shape	
							BMI	25-30	1.0	(~25)	NR
								30-40	1.2 (1.0-1.4)		
							Low MM	<25 BMI	1.3 (1.1-1.5)	J-shape	
								25-30 BMI	1.5 (1.2-1.9)	(~25)	
								30-40 BMI	2.6 (1.2-5.5)		

Conventions as above. ESRD=End Stage Renal Disease; GFR=Glomerular Filtration Rate in mL/min/1.73m²; DM=Diabetes Mellitus; BP=Blood Pressure; FM=Fat Mass from DXA. MM=Muscle Mass from DXA.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)†		Summary findings		
					Prior disease	FU	Mortality		HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
19	Howell (2018) USA (Mexicans)	1999 - 2010 (11 yrs)	10,329 (26+ yrs) Specific (1,423)	Age, sex, smoking	No	No	All-cause	N/A	N/A		per 5
							BMI (28.1±5.6)			Positive	1.0 (1.0-1.1)
							WC (94.6±13.5)			Positive	1.0 (1.0-1.1)
							WHtR (0.58±0.08)			Positive	1.1 (1.0-1.1)
							FM (%) (31.5±9.7)			Positive	1.1 (1.0-1.2)
							FM (kg) (23.9±10.1)			Null	1.0 (1.0-1.1)
							LM (kg) (51±11.5)			Null	1.0 (0.9-1.0)
							<u>CVD</u>				
							BMI			Positive	1.1 (0.9-1.4)
							WC			Positive	1.1 (1.0-1.1)
							WHtR			Positive	1.1 (1.0-1.2)
							FM (%)			Negative	0.9 (0.7-1.2)
							FM (kg)			Null	1.0 (0.8-1.3)
							LM (kg)			Positive	1.2 (1.0-1.5)
							<u>Diabetes</u>				
							BMI			Positive	1.2 (1.0-1.5)
							WC			Positive	1.1 (1.0-1.2)
							WHtR			Positive	1.3 (1.1-1.5)
							FM (%)			Positive	1.2 (1.0-1.5)
							FM (kg)			Null	1.1 (0.9-1.3)
							LM (kg)			Negative	0.9 (0.7-1.2)
20	Suemoto (2015) Latin-America (Brazil)	2000 - 2010 (6.5 yrs)	2,441 (75+ yrs) All-cause (621)	Age, sex, smoking, diet, exercise, SES education, drinking occupation, frailty, marital status, yr. study arthritis, depression	CHD, stroke, cancer, DM	No	All-Cause	18.5-<20	1.5 (1.1-2.1)		
							BMI (27.0)	20-<25	1.0	inverse J	NR
								25-<30	0.8 (0.7-1.0)		
								30+	0.8 (0.6-1.1)		
							WC (95.0)	>95	1.1 (0.9–1.3)	N/A	
21	Rosero-Bixby (2012) Latin-America (Costa Rica)	2005 - 2010 (5 yrs)	2,313 (60+ yrs) All-cause (564)	Age, sex, HbA1c, BP, Lipids, CRP, stress hormones, smoking, cancer handgrip strength, peak flow	No	No	WHR	>0.87	1.0 (0.8–1.3)	N/A	
							All-cause				per SD
							BMI (26.9±5.2)	NR	NR	NR	0.9 (NR)
							WC (93.9±12.4)	NR	NR	NR	1.0 (NR)
							<u>CVD</u>				
							BMI (26.9±5.2)	NR	NR	NR	0.9 (NR)
							WC (93.9±12.4)	NR	NR	NR	1.8 (NR)

Conventions as above. HbA1c= Glycosylated Haemoglobin. Study 19 excluded pregnant women.

No.	Author (Publication)	Recruitment period (Follow-up)	No of participants (age, years) Deaths (No)	Confounders	Exclusions		Adiposity (mean, SD)† Mortality		Summary findings		
					Prior disease	FU			HR (95% CIs)	Shape (lower risk)	per-unit (95% CIs)
22	DeAlmeida (2019) Latin-America (Brazil)	2000 - 2010 (6.5 yrs)	1,504 (60+ yrs) All-causes (769)	Age, sex, smoking, exercise, diet, drinking, education, occupation, SES, marital status, disease depression, cognition	No	No	All-cause	<23	1.3 (1.1 –1.5)		
							BMI (26.3±0.17)	23-28	1.0	inverse J	NR
								28-30	1.1 (0.9-1.4)		
								30-35	1.0 (0.8–1.3)		
								35+	1.1 (0.7-1.6)		
							WC (0.72±0.16)	>91	1.0 (0.8-1.1)	N/A	NR
							WHR (0.94±.07)	>0.92	1.0 (0.9–1.2)	N/A	NR
							Triceps skinfold	low	1.3 (1.1-1.5)	N/A	NR
							Arm circ	<25th	1.4 (1.2-1.7)	N/A	NR
							Calf circ	low	1.3 (1.1-1.6)	N/A	NR
Arm MA	low	1.2 (1.0-1.6)	N/A	NR							
23	Beleigoli (2012) Latin-America (Brazil)	1997 - 2007 (8.9 yrs)	1,450 (60+ yrs) All-cause (521)		No	No	All-cause	<18.5	1.5 (1.0-1.9)		0.8 (0.8-0.9)
							BMI (24.8)	18.5-<25	1.0	inverse J	
								25-<30	0.8 (0.6-0.9)		
								35+	0.8 (0.6-1.1)		
							WC (90±11.0)	range	NR	NR	1.0 (1.0-1.1)
24	David (2017) Latin-America (Brazil)	1994 - 2009 (13 yrs)	236 (80+ yrs) Specific (234)	Age, sex, smoking, hypertension, DM cholesterol, creatinine	none, then, Renal Insuff GFR≤30	5 yrs	All-cause				
							BMI (26.3±4.8)	>27	1.0 (0.7-1.3)	NR	NR
								≥25	1.0 (0.7-1.5)		
							WC (90.2±11.7)	88/102	0.8 (0.6-1.2)	NR	NR
								80/94	0.9 (0.6-1.3)		
							WHt (.57±.07)		0.6 (0.4-1.0)	NR	NR
							WHR (.89±.07)		1.1 (0.5-1.6)	NR	NR
							CVD				
							BMI	>27	0.8 (0.5-1.3)	NR	NR
								≥25	0.8 (0.5-1.4)		
WC	88/102	0.6 (0.3-0.9)	NR	NR							
	80/94	0.7 (0.4-1.3)									
WHtR		0.6 (0.4-1.2)	NR	NR							
WHR		0.8 (0.5-1.4)	NR	NR							
25	Abar (2019) Meta-analysis	2002 - 2014 (1-31ys)	NR (18+ yrs) Neoplastic (8973) Studies included (19) Hispanic (0)	Age, sex, lifestyle (heterogeneous) by study	NR	NR	BMI				per 5
							Myeloma	NR	NR	Positive	1.2 (1.1-1.2)
							Leukaemia	NR	NR	Positive	1.2 (1.0-1.3)
							NHodgkin Lymph	NR	NR	Positive	1.1 (1.1-1.2)
							WC				
							NHodgkin Lymph	NR	NR	NR	1.1 (1.1-1.2)

S7: Underlying cause of death at ages 35-89 years by sex, among those with no prior chronic disease (except for diabetes)

	Including those with diabetes or HbA1c ≥7%					Excluding those with diabetes or HbA1c ≥7%				
Age-at-risk	35-74		75-89		35-89	35-74		75-89		35-89
Sex	Men	Women	Men	Women	All	Men	Women	Men	Women	All
Number of deaths	3,982	5,128	3,031	3,938	16,079	2,223	2,756	2,071	2,378	9,428
Vascular causes	1,176	1,376	1,074	1,576	5,202	628	722	726	976	3,052
Ischaemic heart disease	743	687	666	866	2,962	389	329	445	523	1,686
Other cardiac*	97	225	98	216	636	62	141	62	143	408
Ischaemic stroke	25	42	37	70	174	15	19	31	42	107
Haemorrhagic stroke	104	159	65	99	427	58	103	48	64	273
Other cerebrovascular	106	148	130	226	610	51	70	84	137	342
PAD**, Thromboembolism, other	101	115	78	99	393	53	60	56	67	236
Renal causes	644	891	328	443	2,306	121	166	153	167	607
Acute kidney injury	27	40	27	40	134	16	19	17	31	83
Chronic kidney disease	562	736	242	314	1,854	83	116	103	96	398
Other urinary	55	115	59	89	318	22	31	33	40	126
Metabolic causes	630	562	245	312	1,749	398	286	135	136	955
Acute glycaemic crises	154	203	103	136	596	28	36	20	25	109
Liver disease	421	285	110	132	948	336	203	92	84	715
Gallstone, biliary, pancreatic disease	55	74	32	44	205	34	47	23	27	131
Neoplastic causes	566	1,069	411	469	2,515	456	862	322	350	1,990
Cancer, upper aero-digestive	93	77	59	39	268	75	63	45	28	211
Cancer, non-upper aero-digestive	473	992	352	430	2,247	381	799	277	322	1,779
Respiratory causes	326	427	454	522	1,729	199	235	333	332	1,099
COPD, chronic lung disease	97	126	222	217	662	75	87	185	156	503
Respiratory infections	229	301	232	305	1,067	124	148	148	176	596
Infective causes***	246	383	244	300	1,173	121	190	179	189	679
External, other, Ill-defined	394	420	275	316	1,405	300	295	223	228	1,046

The figures shown in bold font represent sub-totals of specific causes accrued as of January 2018. Exclusions as per Table 4.1. *Includes heart failure, atrial fibrillation and sudden deaths. **PAD= Peripheral Arterial Disease. *** Includes gastric infections.

S8: List of clinician-adjudicated ICD-10 codes for leading or primary causes contributing to each component of the specific deaths at any age, independent of disease history reported at baseline

Vascular Causes	
Ischaemic heart disease	I200, I209-11, I219, I221, I229, I248-49, I251-52, I255, I258-59
Other cardiac	I011, I050-51, I059, I069, I071, I079-81, I091, I099-110, I119, I270, I272, I279, I289, I301, I309, I318-19, I330, I340, I348-51, I358-59, I369, I38X, I420-22, I426, I429, I441-43, I453, I460, I469, I471-72, I48X, I490, I499-501, I509, I518-19, Q210-11, Q213, Q225, Q231, Q248
Ischaemic stroke	I633-35, I638-39, I693
Haemorrhagic stroke	I600, I608-09, I61, I610, I612, I614-15, I618-20, I629, I690-91
Other cerebrovascular	F019, I669, I671-74, I678-79, I694, I698, I649, I64X
PAD, Thromboembolism	I830, I839, I872, I888, I890, I959, I99X, K550-52, K559, K761, E115, E145, I702, I709-10, I712-14, I718-19, I731, I739, I741, I749, I771, I779
Other vascular	I260, I269, I802-03, I822, I828-30, I839, I872, I888, I890, I959, I99X, K550-52, K559, K761
Renal causes	
Acute kidney injury	N002, N170, N179
Chronic kidney disease	E102, E112, E142, I120, I129-32, I139, N039, N049, N059, N119, N12X, N142, N180, N185, N189, N19X, N281, N289, Q612, Q619, Y841
Other urinary disease	N10X, N133, N139, N151, N200-02, N308, N360, N390, N398
Metabolic causes	
Acute glycemic crises	E100-11, E120, E140, E141, E162
Liver disease	B162, B169, B171, B181-82, B190, B199, D134, I850, I859, I864, K701-04, K709, K711, K720-21, K729, K739, K742-46, K750, K754, K759, K766-67, K769
Gallstone, biliary, pancreatic	K800-05, K810-11, K819-21, K823, K828-31, K852, K858-59, K85X, K861, K863, K868
Neoplastic causes	
Upper aero-digestive or lung	C009, C01X, C029, C049-50, C059, C069, C07X, C089, C109, C119, C139-40, C329, C33X, C340, C349, D380-1, D383
Non-upper aero-digestive nor lung	C159-60, C169-70, C179-81, C184, C187, C189, C19X-20X, C210, C220-21, C229, C23X, C240-41, C248-50, C252, C259-61, C269, C310, C319, C37X, C383-84, C402, C410-12, C414, C419, C438-39, C442, C444-45, C447, C449-51, C459, C469, C479-80, C482, C490, C492-93, C495, C499, C509, C519, C52X, C539, C541, C549, C55-6X, C609, C61X, C629, C64-5X, C679-80, C709-11, C717-19, C729, C73X, C741, C749, C751, C753, C759-65, C779-80, C786-88, C793-96, C798, C800, C809, C80X, C811, C817, C819, C822, C829, C833, C838-39, C844-5, C851, C857, C859, C880, C900-2, C910-11, C919-22, C924, C927, C929-30, C950, C959, C969, C97X, D371-72, D374, D376-77, D391, D410, D414, D419, D430-32, D440, D449, D483-4, D486-7, D489
Respiratory causes	
COPD, chronic lung disease	E840, E848, J399, J459, J40X, J42X, J46X-47X, J439-41, J448-49, J60X, J64X, J677, J679-80, J80X-81X, J841, J849, J90X, J939, J948, J960-61, J969, J980-81, J984-85, J988, Q311
Respiratory infections	A150, A162, A165, A169, B909, B206, B440-41, J039, J09, J150-51, J157, J159-82, J189, J209, J219, J22X, J391, J852, J869
Infective causes (exclude respiratory, includes gastric)	A060, A09X, A418-19, A480, A483, A810, A86X, B162, B169, B171, B181-2, B190, B199, B200-1, B206-8, B210, B227, B238, B24X, B373, B377, B690, B699, G009, G039, G049, G060, H440, I330, I38X, I011, I301, I309, H664, J039, J391, K359, K37X, K572, K578, K610-11, K630, K650, K658-59, K750, K830, K931, L021-4, L029, L031-2, L038-9, L088-9, L899, L89X, L905, L984, M009, M600, M725-6, M798, M861, M869, N719, N764, N739, Y405
Other, external, ill-defined causes	
Other medical	D181, D27X, D329, D361, D464, D467, D469, D471, D529-30, D539, D589, D594, D619, D649, D65X, D682, D691, D693-94, D696, D699, D70X, D739, E035, E039, E049, E059, E065, E230, E249, E271, E43X, E46X, E500, E509, E725, E835, E871, E875-76, E878, E889, F03X, F09X, F102, F329, G10X, G112, G121-22, G20X, G219, G309, G312, G319, G35X, G406, G409, G419, G439, G589, G610, G629, G700, G710, G809, G819, G822, G919, G931, G934-38, G951-52, G958-59, L100, L108-9, L511-12, L921, L97X, L989, M050, M068-9, M100, M109, M165, M189, M199, M259, M300, M311, M313, M319, M321, M329, M331, M348-50, M623, M729, M809, M819, M844, N40X, N768, N823, N939, N948, O622, O720
Ill-defined	E86X, E870, E872, R040, R048, R092, R100, R11X, R13X, R190, R568, R571, R578-79, R58X, R630, R688, R69X, R99X
External	S068, S720, T782, V029, V031, V041, V049, V051, V059, V099, V149, V182, V209, V299, V439, V489, V494, V499, V580-81, V719, V785, V878, V892, V899, W018, W068, W100, W105, W108, W119, W130, W134-35, W138-39, W170, W172, W174, W178, W18, W180-81, W184, W188-90, W194-95, W198-99, W206, W228, W250, W490, W557, W704, W744, W748, W780, W789, W799, W808, W849, W856, W87, W878, X09, X090, X094, X314, X360, X470, X53, X530, X539, X590, X598-99, X640, X680, X700, X708, X740, X780, X800, X910, X914, X928, X950, X954-55, X958-59, X990, X994, X998-99, Y040, Y044, Y048, Y084, Y090, Y099, Y14, Y159, Y200, Y239-40, Y265, Y330, Y334, Y340, Y344-45, Y348-49, Y405, Y579, Y609, Y834-35, Y838-39, Y846, Y86X, Y899

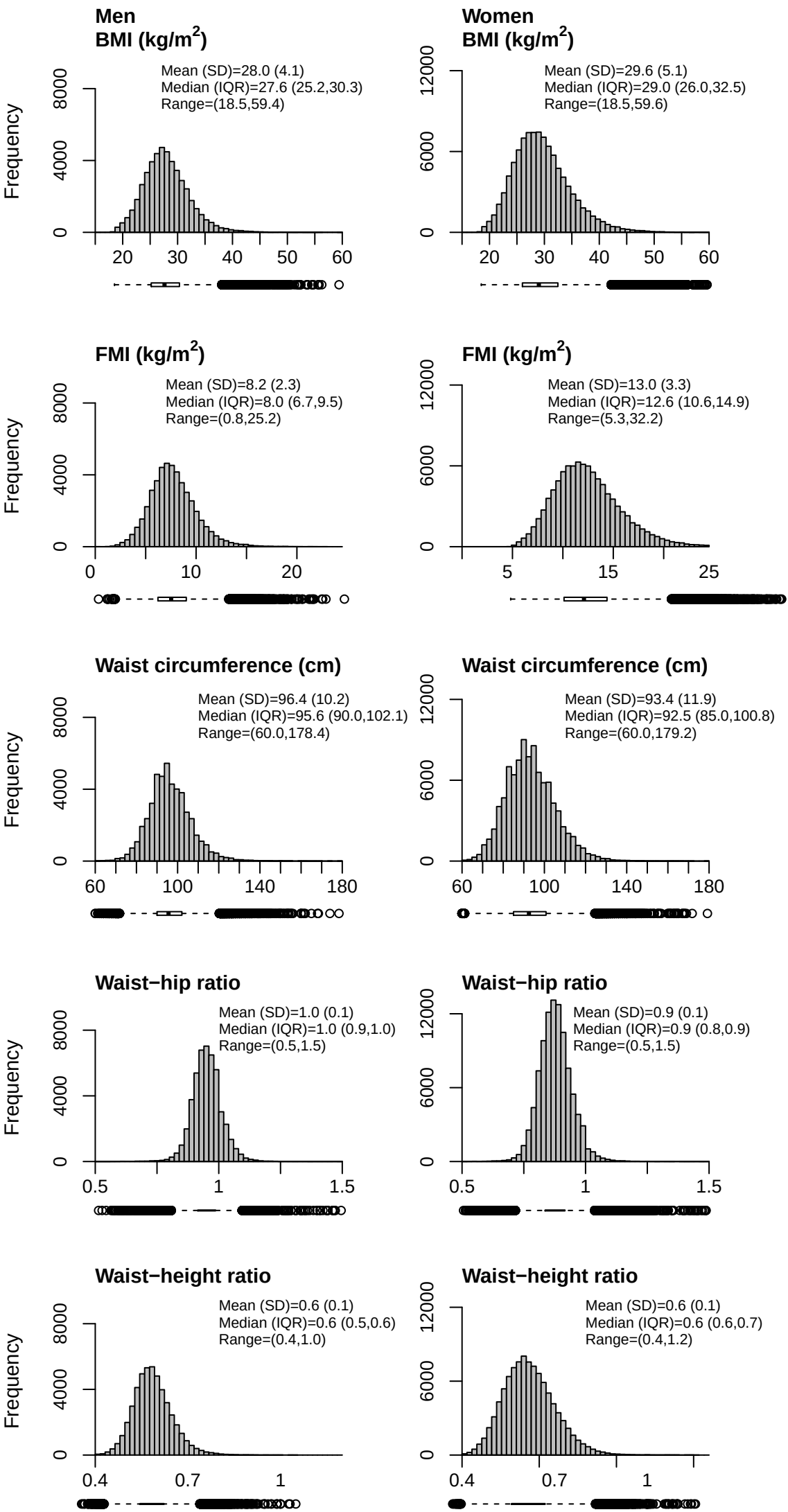
Reliably identified events accrued within the cohort through matching with The Mexican National Mortality Register.

S9: Baseline characteristics of 12,706 men and 22,238 women aged 35-89 years, without chronic disease (other than diabetes) and complete information on NMR assays

	Men	Women	All
N	12,706	22,238	34,944
Age, years	52 (13)	51 (12)	51 (12)
Socio-economic and lifestyle			
Resident of Coyoacán	11,540 (91%)	19,973 (90%)	31,513 (90%)
University/college educated	6,089 (48%)	7,359 (33%)	13,448 (38%)
Current tobacco use	6,502 (51%)	5,104 (23%)	11,606 (33%)
Current alcohol use	11,140 (88%)	16,025 (72%)	27,165 (78%)
Leisure-time physical activity	3,910 (31%)	4,098 (18%)	8,008 (23%)
Anthropometry and derived markers of adiposity			
Height, cm	164 (7)	151 (6)	156 (9)
Weight, kg	75 (12)	67 (12)	70 (13)
WC, cm	95 (10)	92 (12)	93 (11)
BMI, kg/m ²	28 (4)	29 (5)	29 (5)
WHR	0.95 (0.06)	0.87 (0.07)	0.90 (0.07)
WHtR	0.58 (0.06)	0.61 (0.08)	0.60 (0.08)
FM, kg	22 (6)	29 (8)	26 (8)
FMI, kg/m ²	8 (2.22)	13 (3.32)	11 (3.74)
Blood pressure			
SBP, mmHg	129 (16)	128 (18)	129 (17)
DBP, mmHg	85 (10)	83 (10)	84 (10)
Diagnosed hypertension	1,530 (12%)	4,875 (22%)	6,405 (18%)
Diabetes and HbA1c			
Previously-diagnosed diabetes	1,406 (11%)	2,508 (11%)	3,914 (11%)
Un-diagnosed diabetes	402 (4%)	668 (3%)	1,070 (3%)
HbA1c (median, IQR)	5.4 (5.2-5.7)	5.4 (5.2-5.8)	5.4 (5.2-5.8)
Selected lipids			
HDL-c, mmol/l††	1.0 (0.2)	1.1 (0.2)	1.0 (0.2)
Non-HDL-c, mmol/l	2.5 (0.7)	2.5 (0.7)	2.5 (0.7)
Triglycerides, mmol/l	1.6 (0.5)	1.5 (0.4)	1.5 (0.5)
Medication use			
Any antihypertensive	1,123 (9%)	3,612 (16%)	4,735 (14%)
Any antithrombotic	240 (2%)	508 (2%)	748 (2%)
Any lipid lowering	73 (0.6%)	135 (0.6%)	208 (0.6%)

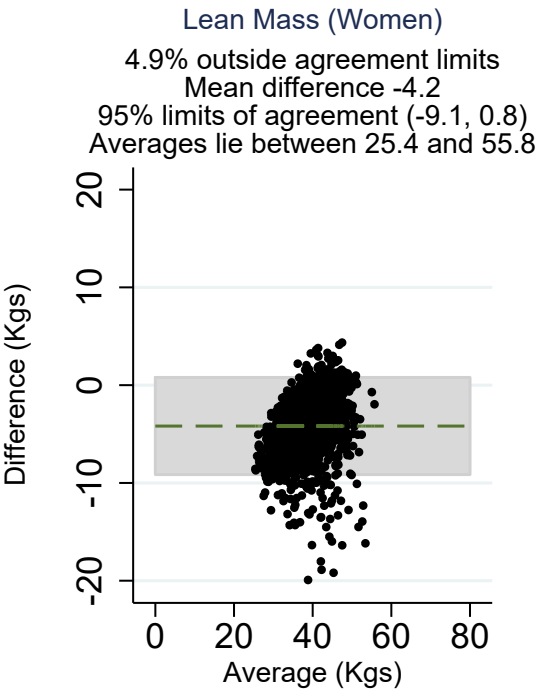
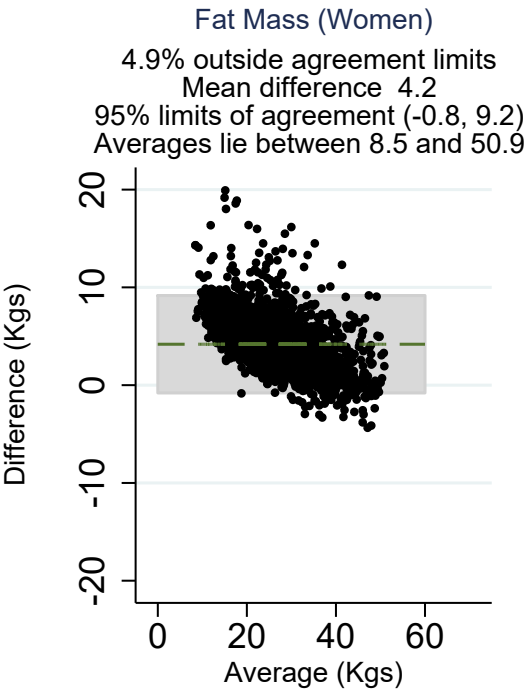
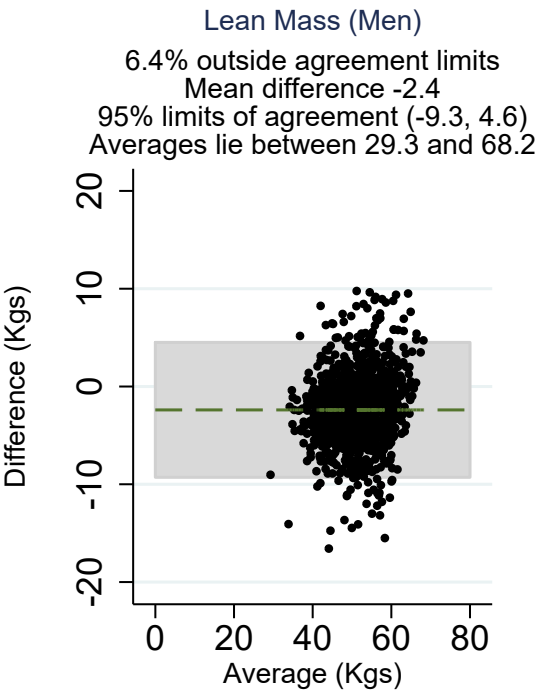
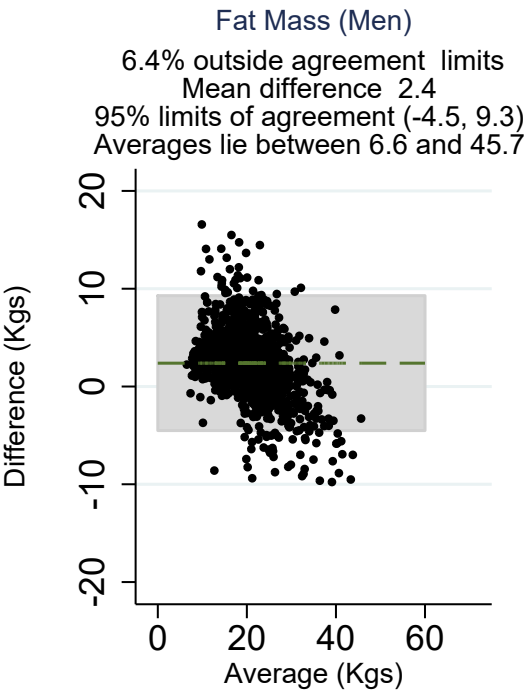
Conventions as per tables 4.1 and 4.2. † HDL-c=high-density cholesterol; ††LDL-c=low-density cholesterol; HbA1c levels were similar in men as in women (e.g. 5.9%±1.6%).

S10: Distributions of adiposity markers among 47,657 men and 98,002 women aged 35–89 years at baseline



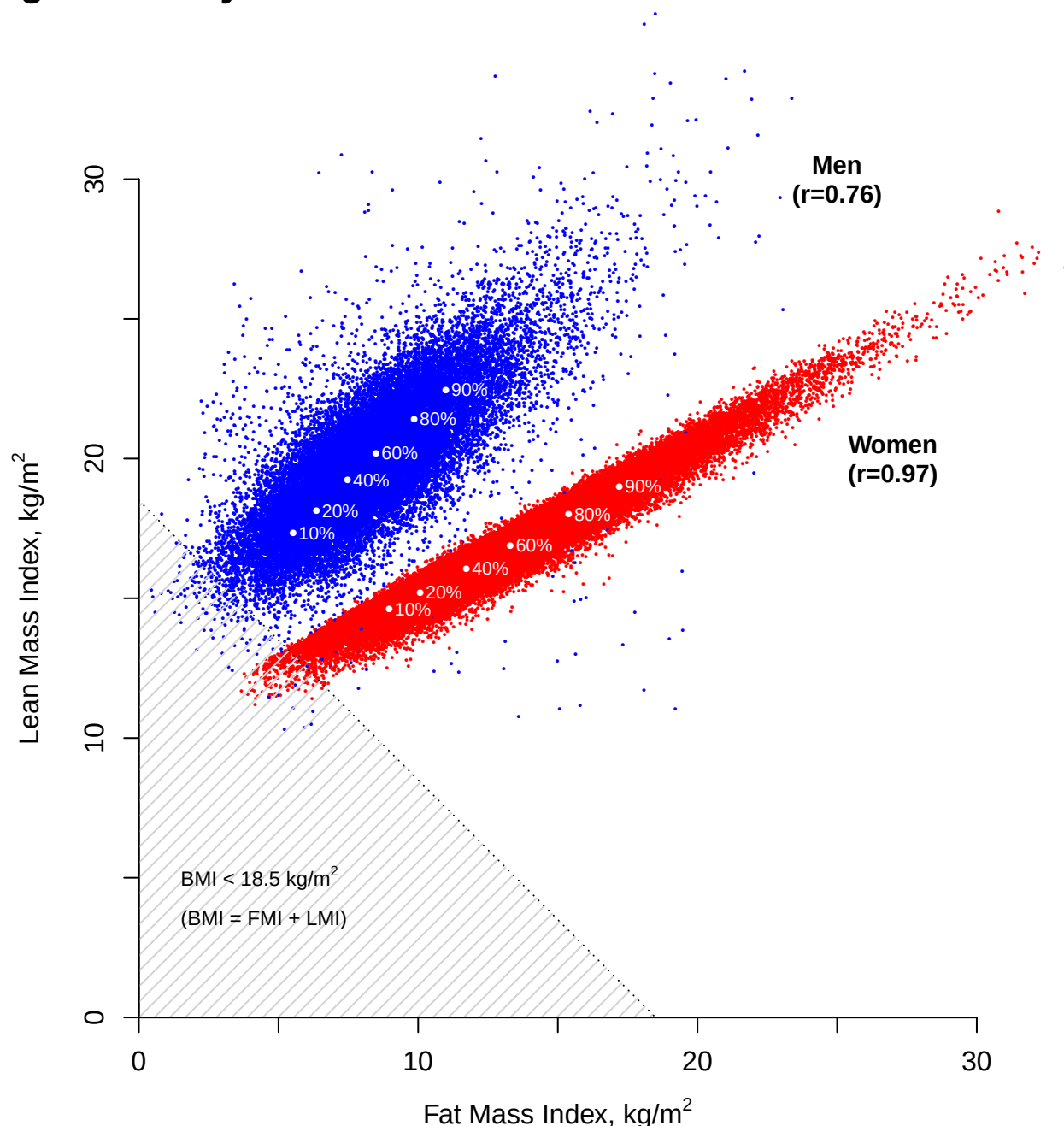
Exclusions as per table 4.1.

S11: Agreement between predicted versus directly-measured markers of fat and lean mass among 1221 men and 2933 women aged 35-89 years, without diabetes or other chronic disease at resurvey



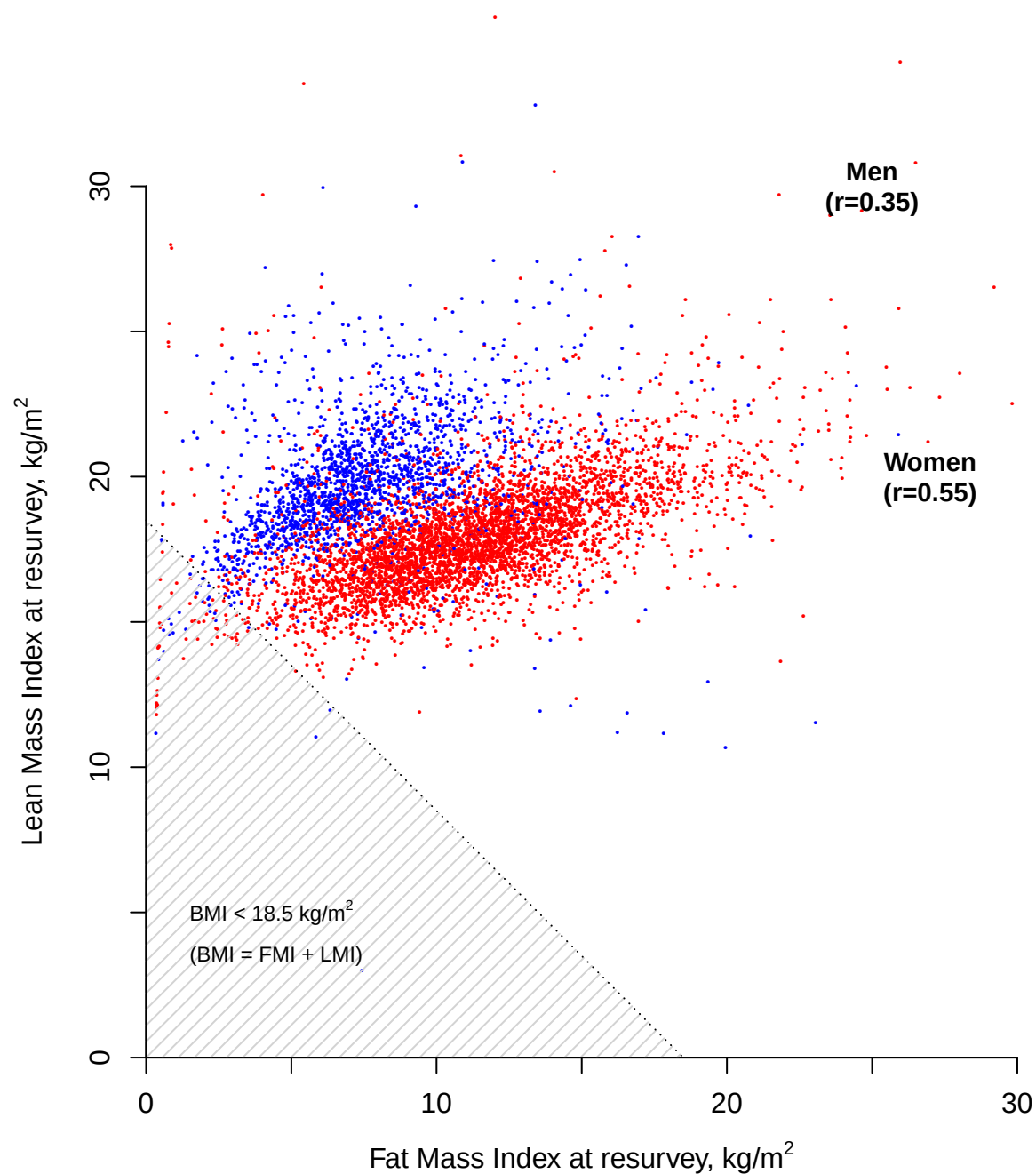
Bland-Altman plots between the differences of paired markers (y-axis) versus their average (x-axis). $y=0$ shows perfect agreement between predicted markers from Mexican-specific NHANES equations vs directly measured markers from Bio-Impedance Analysis (BIA). Equations and exclusions as per Figure 4.2.

S12.1: Predicted FMI versus LMI in men and women aged 35–74 years and without diabetes at recruitment



The grey shaded area corresponds to people with baseline BMI < 18.5 kg/m², who are excluded from the main analyses. The solid white points show, for both men and women, the 10th, 20th, 40th, 60th, 80th and 90th centiles of the FMI and LMI distributions (ie, the cutpoints used to define the 7 main groups in the prospective analyses). Ages 35–74 years was also chosen to further inform prospective analyses of mortality in chapter 6. FMI = Fat Mass Index; LMI = Lean Mass Index.

S12.2: Direct-measures of FMI versus LMI at resurvey (from BIA), in men and women aged 35–74 years and without diabetes at recruitment



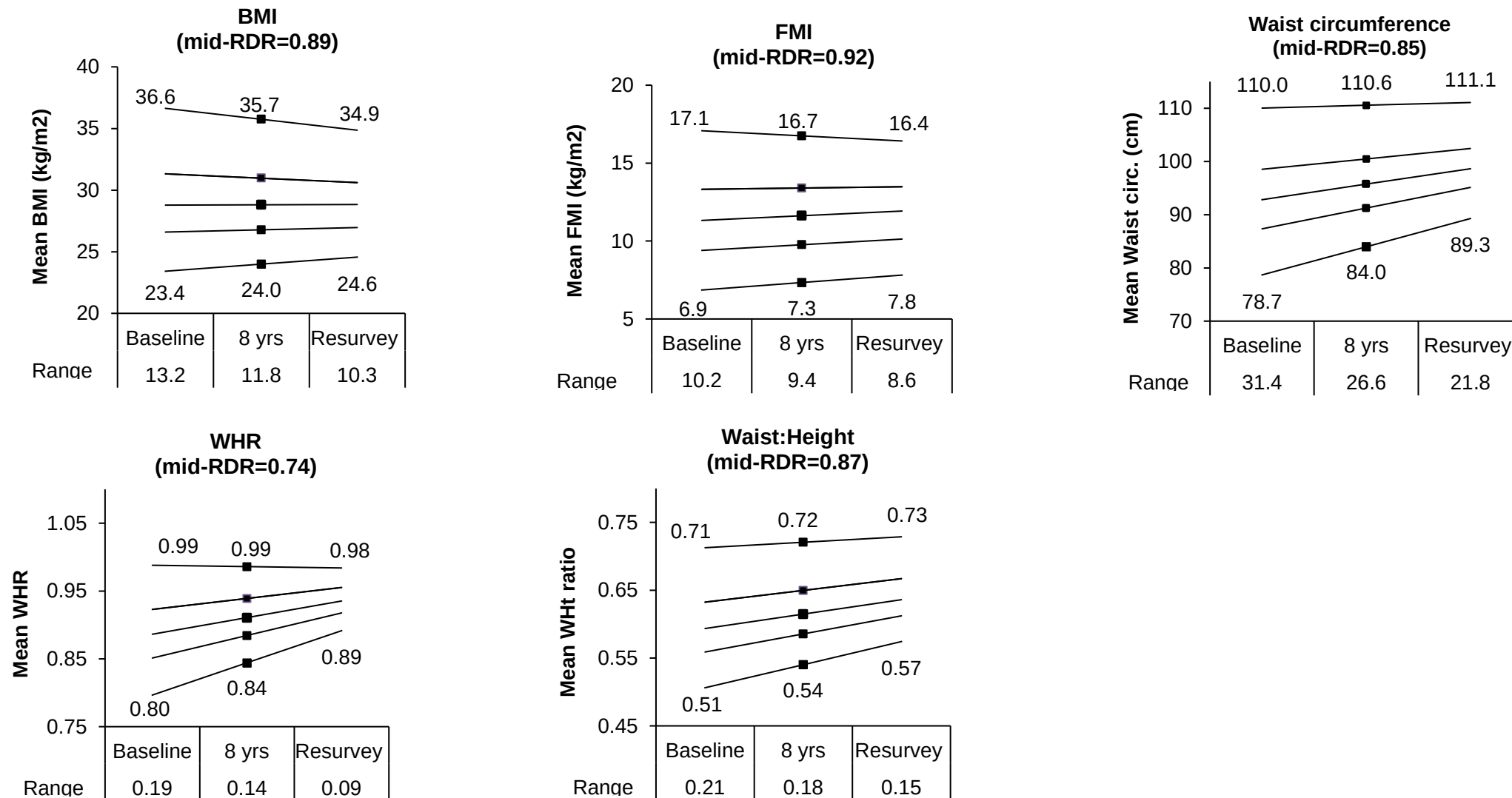
BIA = Bio-Impedance Analyser.

S13: Regression dilution correction factors for different anthropometric and adiposity markers, among 1,822 men and 4,561 women aged 35-74 years, estimated over ~15 years between the baseline and resurvey assessment

Correction factors			
Anthropometric and adiposity markers	Spearman*	Rosner**	MacMahon-Peto***
Height	0.93	0.93	0.93
Waist circ.	0.67	0.69	0.70
BMI	0.74	0.77	0.78
WHR	0.47	0.45	0.48
WHtR	0.69	0.74	0.75
FMI	0.82	0.84	0.84
FM	0.79	0.81	0.81

*Correlation coefficients. **Regression coefficients. ***The ratio of the follow-up to baseline ranges within quintiles of baseline measures, throughout the entire re-survey. Estimates are restricted to those with complete information on all measures at baseline and at resurvey. Other baseline exclusions are as per table 4.1, and in addition, those with diagnosed or treated diabetes, or with a HbA1c $\geq 7\%$ at baseline were also excluded (to inform main analyses of premature mortality presented in the following chapters). BMI=Body Mass Index; WHR=Waist-hip ratio; WHtR=Waist-height ratio; FMI=Fat Mass Index; FM=Fat Mass.

S14: Regression to the mean of adiposity markers between baseline and resurvey among 6,383 adults aged 35-74 years without diabetes or other chronic disease



Resurvey measurements were taken on average 15 years after baseline measurements. Mid-point ranges show the average estimates assuming a hypothetical resurvey ~8 years after the baseline. The mid-RDR represents the MacMahon-Peto estimate of the regression dilution calculated as the ratio of the ranges displayed at mid-point to those at baseline (for example, the mid-RDR for BMI was calculated as $(35.7-24.0)/(36.6-23.4)=0.89$), within fifths of the baseline markers. Each y-axis corresponds to the same number of SDs of each marker, to allow comparability of the degree of shrinkage. Means within the lower fifths are displayed at the bottom of each graph. Exclusions are as per table 4.1, and in addition, those aged 75 years or more, those with previously-diagnosed or treated diabetes, or a HbA1c $\geq 7\%$, were also excluded (to match analyses of premature mortality).

S15: Comparison of mid-point MacMahon-Peto* regression dilution ratios for BMI, FMI, waist circumference, WHR and WHtR by strata of confounders, estimated among 6,383 participants aged 35-74 years

			Regression dilution ratios				
Confounders		N	BMI	FMI	WC	WHR	WHtR
Overall		6383	0.89	0.92	0.85	0.74	0.87
Age (years)	35-44	2976	0.89	0.91	0.85	0.74	0.86
	45-54	2590	0.90	0.94	0.85	0.74	0.89
	55-64	817	0.89	0.94	0.83	0.71	0.84
Sex	Men	1822	0.90	0.89	0.85	0.64	0.85
	Women	4561	0.88	0.88	0.86	0.68	0.86
Residence	Coyoacán	3425	0.87	0.91	0.85	0.75	0.84
	Iztapalapa	2958	0.91	0.93	0.85	0.73	0.88
Education	University	970	0.92	0.95	0.84	0.75	0.87
	Secondary	1868	0.90	0.94	0.85	0.76	0.87
	Elementary	3125	0.89	0.92	0.85	0.73	0.87
	Other	420	0.86	0.95	0.86	0.70	0.86
Tobacco use	Never	3293	0.87	0.90	0.86	0.72	0.87
	Ever	972	0.92	0.96	0.85	0.73	0.87
	Current	2118	0.91	0.93	0.84	0.75	0.87
Alcohol use	Never	1176	0.86	0.89	0.86	0.74	0.91
	Ever	412	0.90	0.95	0.86	0.74	0.87
	Current	4795	0.90	0.92	0.84	0.74	0.87
Exercise	None	5065	0.89	0.92	0.85	0.74	0.87
	1-2/week	496	0.92	0.94	0.89	0.77	0.92
	3+/week	822	0.87	0.90	0.84	0.72	0.86

*The ratio of the mid-point (~8 years between baseline and resurvey) to baseline means, restricted to those with complete information on all markers of adiposity. Conventions and exclusions as per table 4.1, and in addition, those with diagnosed, treated or screen-detected diabetes at baseline.

S16: Baseline versus resurvey characteristics of 2864 men and 6681 women followed-up 15 years after recruitment

	Baseline			Resurvey		
	Men	Women	Both	Men	Women	Both
Age, years	52 (11)	51 (11)	51 (11)	68 (11)	67 (11)	67 (11)
Socio-economic and lifestyle						
Residents of Coyoacan	1604 (56%)	3448 (52%)	5052 (53%)	1604 (56%)	3448 (52%)	5052 (53%)
University/college educated	1281 (45%)	2092 (31%)	3373 (35%)	1301 (46%)	2354 (36%)	3655 (39%)
Current tobacco use	1477 (52%)	1348 (20%)	2825 (30%)	678 (24%)	591 (9%)	1269 (13%)
Current alcohol use	2466 (86%)	4660 (70%)	7126 (75%)	1765 (63%)	3157 (48%)	4922 (52%)
Regular leisure physical activity	853 (30%)	1130 (17%)	1983 (21%)	687 (24%)	1224 (19%)	1911 (20%)
Anthropometry and derived markers of adiposity						
Height, cm	164 (6)	151 (6)	155 (8)	162 (7)	150 (6)	154 (9)
Weight, kg	76 (12)	69 (12)	71 (13)	72 (13)	65 (13)	68 (14)
WC, cm	97 (10)	94 (12)	95 (11)	99 (11)	99 (12)	99 (12)
BMI, kg/m ²	28 (4)	30 (5)	29 (5)	27 (4)	29 (5)	29 (5)
WHR	1 (0.06)	0.9 (0.06)	0.9 (0.07)	1 (0.06)	0.9 (0.07)	0.9 (0.07)
WHtR	0.6 (0.06)	0.6 (0.08)	0.6 (0.08)	0.6 (0.07)	0.7 (0.08)	0.6 (0.08)
FM, kg	23 (6)	30 (8)	28 (8)	22 (7)	29 (8)	27 (8)
FMI, kg/m ²	8.4 (2.23)	13.2 (3.29)	11.7 (3.73)	8.5 (2.44)	13.1 (3.4)	11.7 (3.77)
Blood pressure						
SBP, mmHg	129 (15)	127 (16)	128 (16)	134 (22)	133 (23)	133 (22)
DBP, mmHg	85 (10)	83 (10)	84 (10)	80 (11)	79 (11)	80 (11)
Diagnosed hypertension	339 (12%)	1428 (21%)	1767 (19%)	1053 (37%)	3146 (47%)	4199 (44%)
Diabetes						
Previously-diagnosed	270 (9%)	635 (10%)	905 (9%)	844 (29%)	2178 (33%)	3022 (32%)
Un-diagnosed	164 (6%)	334 (6%)	498 (6%)	61 (3%)	134 (3%)	195 (3%)
HbA1c (median, IQR)	5.5 (5.3-5.8)	5.5 (5.3-5.9)	5.5 (5.3-5.9)	5.7 (5.4-6.4)	5.7 (5.4-6.5)	5.7 (5.4-6.5)
Medication use						
Any antihypertensives	238 (8%)	985 (15%)	1223 (13%)	972 (34%)	2770 (41%)	3742 (39%)
Any antithrombotics	47 (2%)	153 (2%)	200 (2%)	310 (11%)	719 (11%)	1029 (11%)
Any lipid lowering	13 (0.5%)	30 (0.4%)	43 (0.5%)	262 (9.1%)	503 (7.5%)	765 (8%)

Conventions and exclusions as per tables 4.1 and 4.5.

S17: Baseline characteristics by FMI of 47,657 men and 98,002 women aged 35-89 years without prior chronic disease (other than diabetes)

	Men by FMI (kg/m ²)					Women by FMI (kg/m ²)				
	0.8 - 6.5	6.6 - 9.3	9.4 - 12.0	12.1 - 14.8	14.9 - 25.2	5.3 - 9.9	10.0 - 13.1	13.2 - 16.4	16.5 - 19.6	19.7 - 32.2
N	11,106	23,398	10,661	2,015	477	17,621	39,443	27,255	10,002	3,681
Age, years	51 (13)	52 (13)	54 (13)	53 (12)	51 (12)	49 (13)	51 (13)	53 (12)	53 (12)	52 (11)
Socio-economic and lifestyle										
Resident of Coyoacán	5384 (48%)	10131 (43%)	4119 (39%)	713 (35%)	163 (34%)	8055 (46%)	15619 (40%)	9388 (34%)	3160 (32%)	1134 (31%)
University/college educated	6040 (54%)	12027 (51%)	4742 (44%)	905 (45%)	222 (47%)	8827 (50%)	14899 (38%)	7890 (29%)	2606 (26%)	944 (26%)
Current tobacco use	6114 (55%)	11458 (49%)	4950 (46%)	898 (45%)	234 (49%)	4871 (28%)	9209 (23%)	5616 (21%)	2013 (20%)	778 (21%)
Current alcohol use	9415 (85%)	19853 (85%)	9048 (85%)	1724 (86%)	407 (85%)	12140 (69%)	27432 (70%)	18848 (69%)	6881 (69%)	2586 (70%)
Leisure physical activity	3748 (34%)	7312 (31%)	2710 (25%)	397 (20%)	93 (19%)	4128 (23%)	8022 (20%)	4345 (16%)	1353 (14%)	442 (12%)
Anthropometry and derived markers of adiposity										
Height, cm	165 (7)	165 (7)	164 (7)	163 (7)	164 (9)	153 (7)	152 (6)	151 (6)	150 (6)	150 (6)
Weight, kg	64 (7)	75 (8)	85 (9)	97 (11)	113 (17)	54 (6)	64 (7)	73 (7)	84 (8)	98 (11)
WC, cm	85 (5)	95 (4)	106 (5)	117 (6)	131 (11)	80 (7)	90 (7)	99 (7)	108 (8)	118 (10)
HC, cm	94 (5)	100 (5)	107 (6)	115 (7)	126 (12)	95 (6)	102 (6)	111 (7)	120 (8)	132 (11)
BMI, kg/m ²	23 (2)	27 (2)	32 (2)	36 (2)	42 (5)	23 (2)	28 (1)	32 (2)	37 (1)	43 (3)
WHR	0.90 (0.05)	0.95 (0.05)	0.99 (0.05)	1.02 (0.06)	1.05 (0.11)	0.85 (0.07)	0.88 (0.06)	0.89 (0.06)	0.90 (0.07)	0.89 (0.07)
WHtR	0.51 (0.03)	0.58 (0.03)	0.64 (0.03)	0.71 (0.03)	0.80 (0.05)	0.52 (0.05)	0.59 (0.05)	0.66 (0.05)	0.72 (0.05)	0.79 (0.07)
FM, kg	15 (3)	22 (3)	28 (3)	35 (4)	44 (6)	20 (3)	27 (3)	33 (3)	40 (4)	49 (6)
FMI, kg/m ²	5.5 (0.89)	7.9 (0.76)	10.4 (0.75)	13.1 (0.76)	16.6 (1.67)	8.7 (0.98)	11.6 (0.93)	14.7 (0.91)	17.8 (0.89)	21.9 (2.15)
Blood pressure										
SBP, mmHg	124 (15)	128 (15)	132 (16)	136 (17)	138 (16)	121 (16)	125 (17)	129 (17)	132 (16)	136 (16)
DBP, mmHg	82 (10)	84 (9)	86 (10)	89 (11)	90 (11)	79 (10)	82 (10)	84 (10)	86 (10)	88 (10)
Diagnosed hypertension	813 (7%)	2970 (13%)	2181 (20%)	506 (25%)	139 (29%)	2109 (12%)	7648 (19%)	7632 (28%)	3524 (35%)	1557 (42%)
Diabetes										
Previously-diagnosed	1452 (13%)	2978 (13%)	1411 (13%)	284 (14%)	53 (11%)	1979 (11%)	4958 (13%)	3797 (14%)	1489 (15%)	580 (16%)
Un-diagnosed	555 (6%)	1339 (7%)	818 (9%)	222 (13%)	47 (11%)	810 (5%)	1969 (6%)	1565 (7%)	745 (9%)	326 (11%)
HbA1c (median, IQR)	5.4 (5.2-5.7)	5.5 (5.3-5.9)	5.7 (5.4-6.1)	5.8 (5.4-6.4)	5.9 (5.5-6.5)	5.4 (5.1-5.6)	5.5 (5.3-5.8)	5.6 (5.4-6.1)	5.8 (5.4-6.3)	5.9 (5.5-6.5)
Medication use										
Any antihypertensives	614 (6%)	2181 (9%)	1621 (15%)	374 (19%)	102 (21%)	1583 (9%)	5593 (14%)	5569 (20%)	2555 (26%)	1172 (32%)
Any antithrombotics	181 (2%)	511 (2%)	289 (3%)	56 (3%)	18 (4%)	399 (2%)	920 (2%)	786 (3%)	334 (3%)	144 (4%)
Any lipid lowering	43 (0.4%)	140 (0.6%)	61 (0.6%)	9 (0.4%)	4 (0.8%)	70 (0.4%)	223 (0.6%)	131 (0.5%)	46 (0.5%)	13 (0.4%)

Conventions and exclusions as per table 4.5. Adiposity grouped by equivalent-prevalences corresponding to each of the BMI groups in table 4.5.

S18: Baseline characteristics by waist circ. of 47,657 men and 98,002 women aged 35-89 years without prior chronic disease (other than diabetes)

	Men by waist circumference (cm)					Women by waist circumference (cm)				
	60-89.1	89.2-101.3	101.4-113.6	113.7-125.2	125.3-178.4	60-82	83-94	95-105	106-116.1	116.2-171.8
N	11,106	23,398	10,661	2,015	477	17,621	39,443	27,255	10,002	3,681
Age, years	50 (13)	52 (13)	54 (13)	54 (13)	52 (12)	47 (11)	50 (12)	54 (13)	54 (13)	52 (12)
Socio-economic and lifestyle										
Resident of Coyoacán	5269 (47%)	10066 (43%)	4255 (40%)	756 (38%)	164 (34%)	8660 (49%)	15154 (38%)	9290 (34%)	3174 (32%)	1078 (29%)
University/college educated	5970 (54%)	11892 (51%)	4865 (46%)	967 (48%)	242 (51%)	9290 (53%)	15035 (38%)	7485 (27%)	2423 (24%)	932 (25%)
Current tobacco use	6070 (55%)	11502 (49%)	4957 (46%)	900 (45%)	225 (47%)	5034 (29%)	9204 (23%)	5512 (20%)	1973 (20%)	765 (21%)
Current alcohol use	9426 (85%)	19904 (85%)	8993 (84%)	1718 (85%)	406 (85%)	12432 (71%)	27558 (70%)	18539 (68%)	6833 (68%)	2525 (69%)
Leisure physical activity	3813 (34%)	7183 (31%)	2747 (26%)	421 (21%)	96 (20%)	4416 (25%)	7917 (20%)	4194 (15%)	1319 (13%)	444 (12%)
Anthropometry and derived markers of adiposity										
Height, cm	163 (7)	165 (7)	166 (7)	167 (7)	168 (7)	152 (6)	151 (6)	166 (7)	167 (7)	168 (7)
Weight, kg	64 (8)	74 (8)	86 (9)	99 (10)	115 (17)	56 (7)	64 (8)	86 (9)	99 (10)	115 (17)
WC, cm	84 (4)	95 (3)	106 (3)	118 (3)	134 (9)	78 (4)	89 (3)	106 (3)	118 (3)	134 (9)
HC, cm	94 (5)	100 (5)	107 (6)	115 (7)	126 (12)	95 (6)	103 (6)	107 (6)	115 (7)	126 (12)
BMI, kg/m ²	24 (2)	27 (2)	31 (3)	35 (3)	41 (5)	24 (3)	28 (3)	32 (3)	36 (4)	41 (5)
WHR	0.90 (0.05)	0.95 (0.04)	0.99 (0.05)	1.03 (0.06)	1.07 (0.10)	0.82 (0.05)	0.87 (0.05)	0.91 (0.06)	0.92 (0.06)	0.94 (0.08)
WHtR	0.52 (0.03)	0.58 (0.03)	0.64 (0.03)	0.71 (0.04)	0.80 (0.06)	0.51 (0.04)	0.59 (0.03)	0.66 (0.03)	0.73 (0.04)	0.81 (0.06)
FM, kg	15 (3)	21 (2)	28 (3)	36 (3)	45 (5)	21 (4)	27 (4)	28 (3)	36 (3)	45 (5)
FMI, kg/m ²	5.7 (1.06)	8 (0.99)	10.3 (1.11)	12.8 (1.3)	16.1 (2)	9.3 (1.62)	11.9 (1.8)	10.3 (1.11)	12.8 (1.3)	16.1 (2)
Blood pressure										
SBP, mmHg	124 (15)	128 (15)	132 (16)	136 (16)	139 (16)	120 (16)	125 (16)	132 (16)	136 (16)	139 (16)
DBP, mmHg	82 (9)	84 (9)	86 (10)	89 (10)	91 (11)	79 (10)	82 (10)	86 (10)	89 (10)	91 (11)
Diagnosed hypertension	788 (7%)	2928 (13%)	2192 (21%)	554 (27%)	147 (31%)	1880 (11%)	7515 (19%)	7793 (29%)	3717 (37%)	1564 (42%)
Diabetes										
Previously-diagnosed	1361 (12%)	2973 (13%)	1471 (14%)	310 (15%)	63 (13%)	1326 (8%)	4577 (12%)	4375 (16%)	1805 (18%)	720 (20%)
Un-diagnosed	527 (5%)	1356 (7%)	834 (9%)	211 (12%)	53 (13%)	746 (5%)	1896 (5%)	1673 (7%)	740 (9%)	360 (12%)
HbA1c (median, IQR)	5.4 (5.2-5.7)	5.5 (5.3-5.9)	5.7 (5.4-6.2)	5.8 (5.4-6.4)	5.9 (5.5-6.5)	5.3 (5.1-5.5)	5.5 (5.3-5.8)	5.7 (5.4-6.2)	5.8 (5.4-6.4)	5.9 (5.5-6.5)
Medication use										
Any antihypertensives	578 (5%)	2139 (9%)	1647 (15%)	415 (21%)	113 (24%)	1357 (8%)	5448 (14%)	5739 (21%)	2742 (27%)	1185 (32%)
Any antithrombotics	174 (2%)	502 (2%)	298 (3%)	60 (3%)	21 (4%)	348 (2%)	953 (2%)	807 (3%)	334 (3%)	141 (4%)
Any lipid lowering	43 (0.4%)	137 (0.6%)	64 (0.6%)	12 (0.6%)	1 (0.2%)	78 (0.4%)	199 (0.5%)	140 (0.5%)	51 (0.5%)	15 (0.4%)

Conventions and exclusions as per S9.

S19: Baseline characteristics by WHR of 47,657 men and 98,002 women aged 35-89 years without prior chronic disease (other than diabetes)

	Men by WHR					Women by WHR				
	0.51 - 0.910	0.91 - 0.97	0.98 - 1.04	1.05 - 1.10	1.11 - 1.50	0.51 - 0.81	0.82 - 0.88	0.89 - 0.94	0.95 - 0.99	1.00 - 1.49
N	11,106	23,398	10,661	2,015	477	17,621	39,443	27,255	10,002	3,681
Age, years	48 (12)	52 (12)	56 (12)	59 (13)	58 (13)	47 (10)	49 (11)	53 (13)	58 (13)	62 (14)
Socio-economic and lifestyle										
Resident of Coyoacán	5263 (47%)	10283 (44%)	4161 (39%)	674 (33%)	129 (27%)	8664 (49%)	15089 (38%)	9169 (34%)	3310 (33%)	1124 (31%)
University/college educated	6815 (61%)	12078 (52%)	4225 (40%)	660 (33%)	158 (33%)	9701 (55%)	15250 (39%)	7569 (28%)	2031 (20%)	615 (17%)
Current tobacco use	5840 (53%)	11643 (50%)	5069 (48%)	877 (44%)	225 (47%)	5130 (29%)	9360 (24%)	5697 (21%)	1746 (17%)	555 (15%)
Current alcohol use	9381 (84%)	19889 (85%)	9061 (85%)	1721 (85%)	395 (83%)	12812 (73%)	27588 (70%)	18637 (68%)	6517 (65%)	2333 (63%)
Leisure physical activity	4234 (38%)	6972 (30%)	2546 (24%)	409 (20%)	99 (21%)	4560 (26%)	7567 (19%)	4192 (15%)	1449 (14%)	522 (14%)
Anthropometry and derived markers of adiposity										
Height, cm	165 (7)	165 (7)	164 (7)	164 (7)	164 (8)	153 (6)	152 (6)	151 (6)	150 (7)	149 (7)
Weight, kg	70 (11)	76 (12)	80 (13)	85 (15)	88 (18)	65 (12)	68 (12)	69 (13)	69 (13)	67 (14)
WC, cm	87 (7)	96 (7)	103 (9)	110 (10)	117 (15)	83 (10)	92 (10)	98 (10)	103 (10)	107 (12)
HC, cm	100 (8)	101 (7)	103 (8)	103 (9)	101 (12)	105 (12)	107 (11)	107 (11)	106 (11)	102 (11)
BMI, kg/m ²	26 (3)	28 (4)	30 (4)	31 (5)	32 (6)	27 (5)	30 (5)	31 (5)	31 (5)	30 (5)
WHR	0.88 (0.04)	0.95 (0.02)	1.01 (0.02)	1.07 (0.02)	1.16 (0.07)	0.79 (0.03)	0.86 (0.02)	0.91 (0.02)	0.97 (0.01)	1.04 (0.06)
WHtR	0.53 (0.05)	0.58 (0.04)	0.63 (0.05)	0.67 (0.06)	0.72 (0.09)	0.54 (0.07)	0.60 (0.07)	0.65 (0.07)	0.68 (0.07)	0.72 (0.08)
FM, kg	17 (5)	22 (5)	26 (6)	30 (7)	33 (9)	27 (8)	30 (8)	31 (7)	31 (8)	31 (8)
FMI, kg/m ²	6.4 (1.73)	8.1 (1.74)	9.7 (2.05)	11 (2.28)	12.3 (3.15)	11.4 (3.29)	12.8 (3.23)	13.7 (3.19)	14 (3.24)	13.9 (3.28)
Blood pressure										
SBP, mmHg	125 (14)	128 (15)	132 (16)	135 (17)	135 (16)	122 (15)	125 (16)	129 (17)	132 (18)	133 (19)
DBP, mmHg	82 (9)	84 (10)	86 (10)	87 (11)	87 (10)	80 (10)	82 (10)	84 (10)	84 (10)	85 (11)
Diagnosed hypertension	885 (8%)	3058 (13%)	2054 (19%)	489 (24%)	123 (26%)	2500 (14%)	8037 (20%)	7361 (27%)	3238 (32%)	1334 (36%)
Diabetes										
Previously-diagnosed	941 (8%)	2960 (13%)	1803 (17%)	374 (19%)	100 (21%)	917 (5%)	4175 (11%)	4544 (17%)	2241 (22%)	926 (25%)
Un-diagnosed	514 (5%)	1417 (7%)	839 (9%)	178 (11%)	38 (10%)	760 (5%)	1877 (5%)	1766 (8%)	743 (10%)	259 (9%)
HbA1c (median, IQR)	5.4 (5.2-5.6)	5.5 (5.3-5.9)	5.7 (5.4-6.3)	5.8 (5.4-6.5)	5.8 (5.4-6.5)	5.4 (5.1-5.6)	5.5 (5.3-5.9)	5.6 (5.4-6.2)	5.8 (5.4-6.7)	5.8 (5.4-7)
Medication use										
Any antihypertensives	657 (6%)	2227 (10%)	1531 (14%)	383 (19%)	94 (20%)	1841 (10%)	5733 (15%)	5434 (20%)	2433 (24%)	1031 (28%)
Any antithrombotics	184 (2%)	505 (2%)	295 (3%)	56 (3%)	15 (3%)	412 (2%)	1037 (3%)	739 (3%)	259 (3%)	136 (4%)
Any lipid lowering	49 (0.4%)	122 (0.5%)	67 (0.6%)	18 (0.9%)	1 (0.2%)	67 (0.4%)	206 (0.5%)	136 (0.5%)	52 (0.5%)	22 (0.6%)

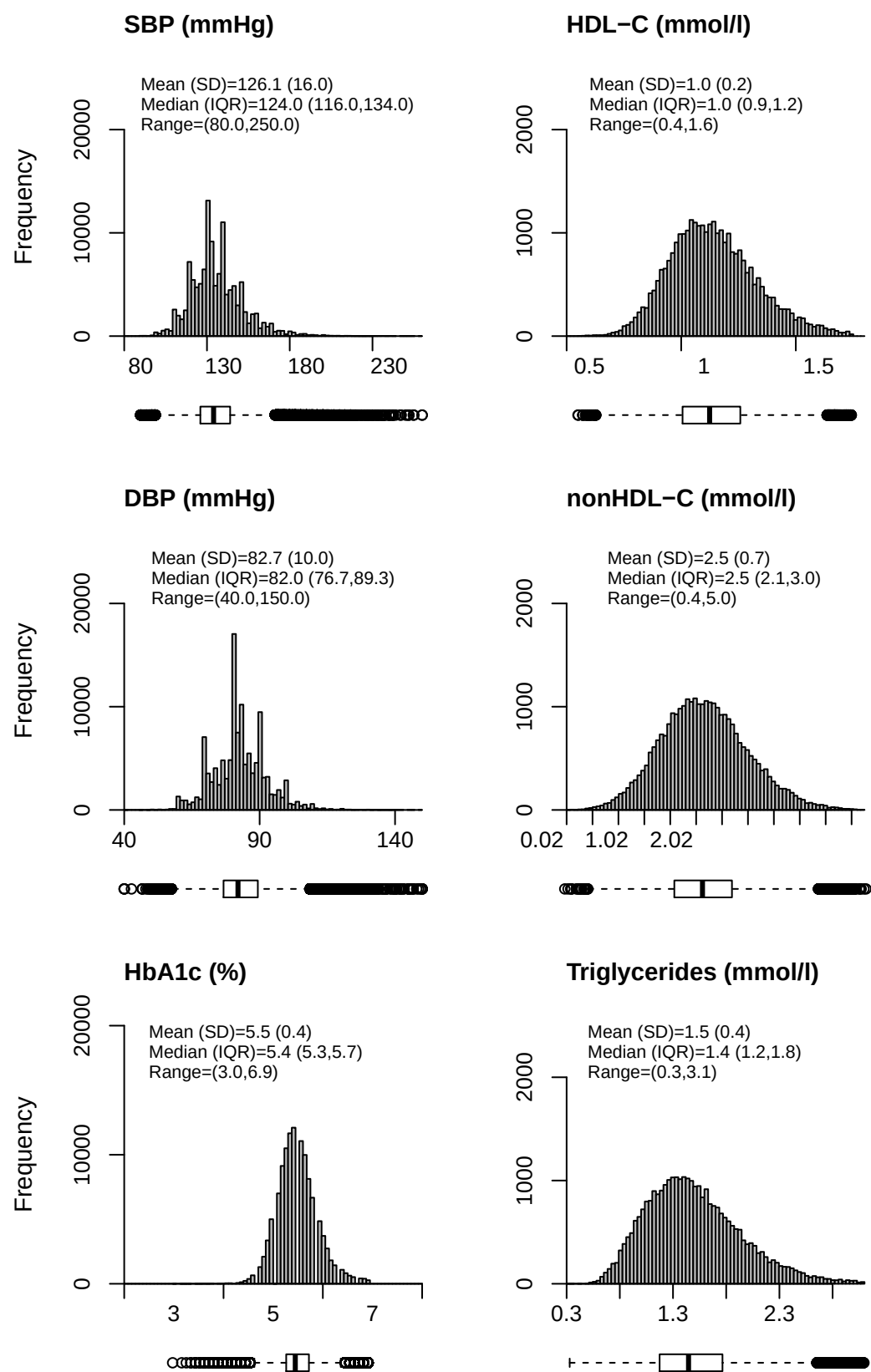
Conventions and exclusions as per S9.

S20: Baseline characteristics by WHtR of 47,657 men and 98,002 women aged 35-89 years without prior chronic disease (other than diabetes)

	Men by WHtR					Women by WHtR				
	0.36 - 0.53	0.54 - 0.61	0.62 - 0.68	0.69 - 0.75	0.76 - 1.05	0.37 - 0.53	0.54 - 0.62	0.63 - 0.70	0.71 - 0.77	0.78 -1.15
N	11,106	23,398	10,661	2,015	477	17,621	39,443	27,255	10,002	3,681
Age, years	48 (12)	52 (13)	56 (13)	56 (13)	55 (13)	46 (10)	50 (12)	56 (13)	56 (13)	55 (13)
Socio-economic and lifestyle										
Resident of Coyoacán	5407 (49%)	10135 (43%)	4095 (38%)	717 (36%)	156 (33%)	8666 (49%)	15270 (39%)	9219 (34%)	3098 (31%)	1102 (30%)
University/college educated	6800 (61%)	11946 (51%)	4222 (40%)	777 (39%)	191 (40%)	10402 (59%)	15358 (39%)	6805 (25%)	1937 (19%)	663 (18%)
Current tobacco use	6293 (57%)	11585 (50%)	4704 (44%)	859 (43%)	213 (45%)	5517 (31%)	9339 (24%)	5298 (19%)	1724 (17%)	609 (17%)
Current alcohol use	9391 (85%)	19864 (85%)	9077 (85%)	1708 (85%)	407 (85%)	12636 (72%)	27645 (70%)	18428 (68%)	6708 (67%)	2470 (67%)
Leisure physical activity	4068 (37%)	7139 (31%)	2575 (24%)	386 (19%)	92 (19%)	4791 (27%)	7833 (20%)	4010 (15%)	1266 (13%)	390 (11%)
Anthropometry and derived markers of adiposity										
Height, cm	167 (7)	165 (7)	163 (7)	162 (7)	162 (9)	155 (6)	152 (6)	150 (6)	149 (6)	148 (6)
Weight, kg	67 (9)	75 (10)	83 (11)	93 (14)	107 (19)	58 (8)	65 (9)	72 (11)	79 (13)	89 (16)
WC, cm	85 (5)	95 (5)	105 (5)	116 (6)	131 (11)	78 (5)	89 (5)	100 (5)	109 (5)	121 (9)
HC, cm	95 (6)	100 (6)	106 (7)	113 (8)	124 (13)	96 (6)	103 (7)	110 (9)	118 (10)	129 (12)
BMI, kg/m ²	24 (2)	27 (2)	31 (3)	36 (3)	41 (5)	24 (3)	28 (3)	32 (4)	35 (4)	41 (6)
WHR	0.90 (0.05)	0.95 (0.04)	0.99 (0.05)	1.03 (0.06)	1.07 (0.11)	0.81 (0.05)	0.87 (0.05)	0.91 (0.06)	0.93 (0.06)	0.95 (0.08)
WHtR	0.51 (0.03)	0.58 (0.02)	0.65 (0.02)	0.72 (0.02)	0.81 (0.05)	0.51 (0.03)	0.59 (0.02)	0.66 (0.02)	0.74 (0.02)	0.82 (0.05)
FM, kg	16 (3)	22 (4)	27 (4)	34 (5)	43 (7)	22 (4)	28 (5)	33 (6)	38 (7)	45 (9)
FMI, kg/m ²	5.6 (1.03)	7.9 (0.94)	10.3 (0.99)	13.0 (1.08)	16.3 (1.89)	9.3 (1.57)	11.9 (1.77)	14.4 (2.1)	17.0 (2.4)	20.4 (3.31)
Blood pressure										
SBP, mmHg	124 (14)	128 (15)	133 (16)	136 (17)	138 (16)	119 (15)	125 (16)	130 (17)	134 (17)	137 (17)
DBP, mmHg	82 (9)	84 (9)	86 (10)	88 (11)	90 (10)	78 (10)	82 (10)	84 (10)	86 (10)	88 (10)
Diagnosed hypertension	704 (6%)	2936 (13%)	2282 (21%)	549 (27%)	138 (29%)	1680 (10%)	7310 (19%)	8037 (29%)	3825 (38%)	1618 (44%)
Diabetes										
Previously-diagnosed	1224 (11%)	3037 (13%)	1538 (14%)	317 (16%)	62 (13%)	1049 (6%)	4561 (12%)	4510 (17%)	1921 (19%)	762 (21%)
Un-diagnosed	512 (5%)	1365 (7%)	858 (9%)	192 (11%)	54 (13%)	786 (5%)	1864 (5%)	1663 (7%)	768 (10%)	352 (12%)
HbA1c (median, IQR)	5.4 (5.2-5.6)	5.5 (5.3-5.9)	5.7 (5.4-6.2)	5.8 (5.5-6.5)	5.9 (5.5-6.5)	5.3 (5.1-5.5)	5.4 (5.3-5.8)	5.7 (5.4-6.2)	5.8 (5.5-6.5)	6 (5.6-6.8)
Medication use										
Any antihypertensives	514 (5%)	2125 (9%)	1733 (16%)	417 (21%)	103 (22%)	1230 (7%)	5232 (13%)	5895 (22%)	2869 (29%)	1246 (34%)
Any antithrombotics	163 (1%)	516 (2%)	293 (3%)	62 (3%)	21 (4%)	367 (2%)	930 (2%)	806 (3%)	342 (3%)	138 (4%)
Any lipid lowering	39 (0.4%)	140 (0.6%)	63 (0.6%)	12 (0.6%)	3 (0.6%)	69 (0.4%)	207 (0.5%)	141 (0.5%)	53 (0.5%)	13 (0.4%)

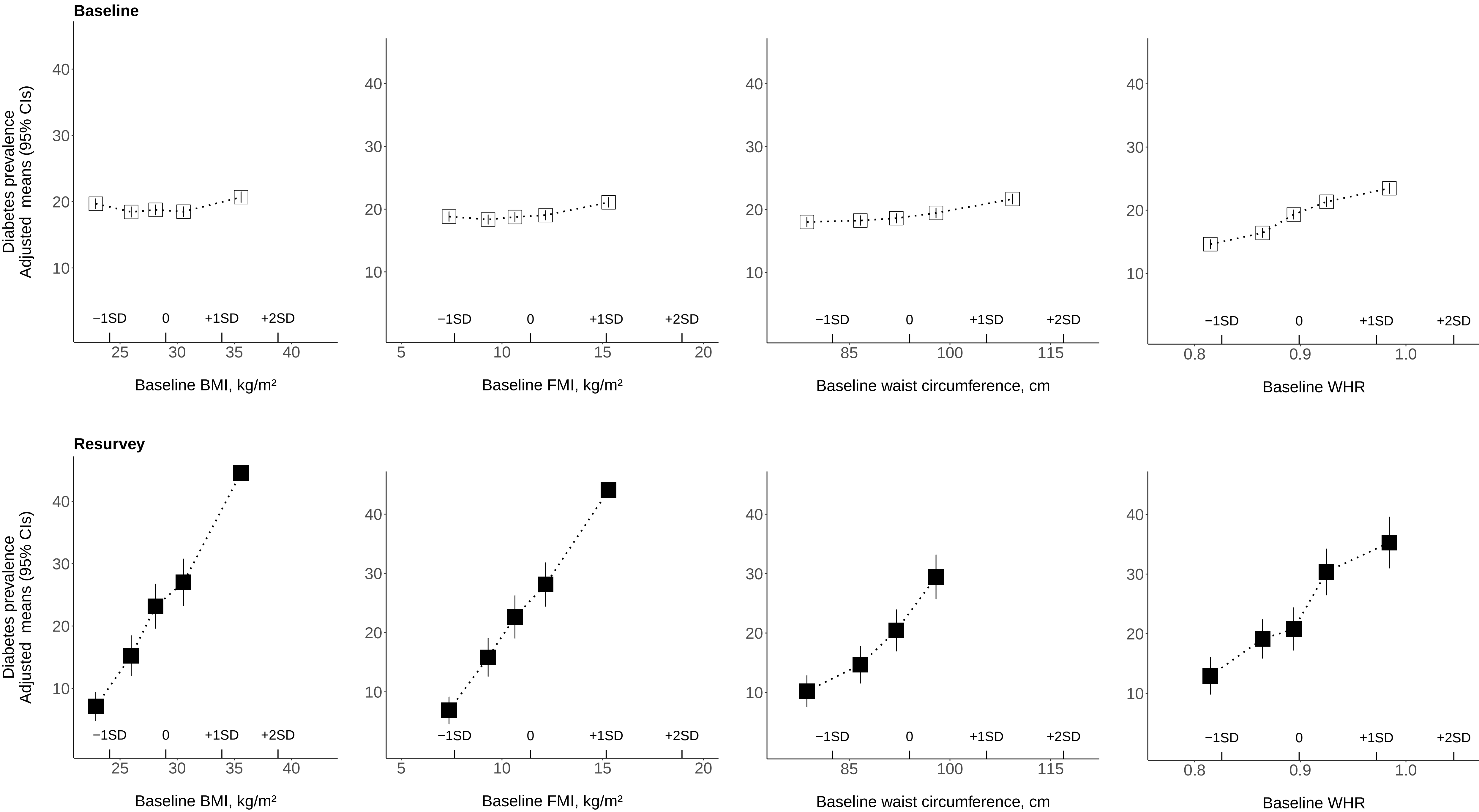
Conventions and exclusions as per S9.

S21: Distributions of selected mediators of adiposity among 12,706 men and 22,238 women aged 35–89 years at baseline



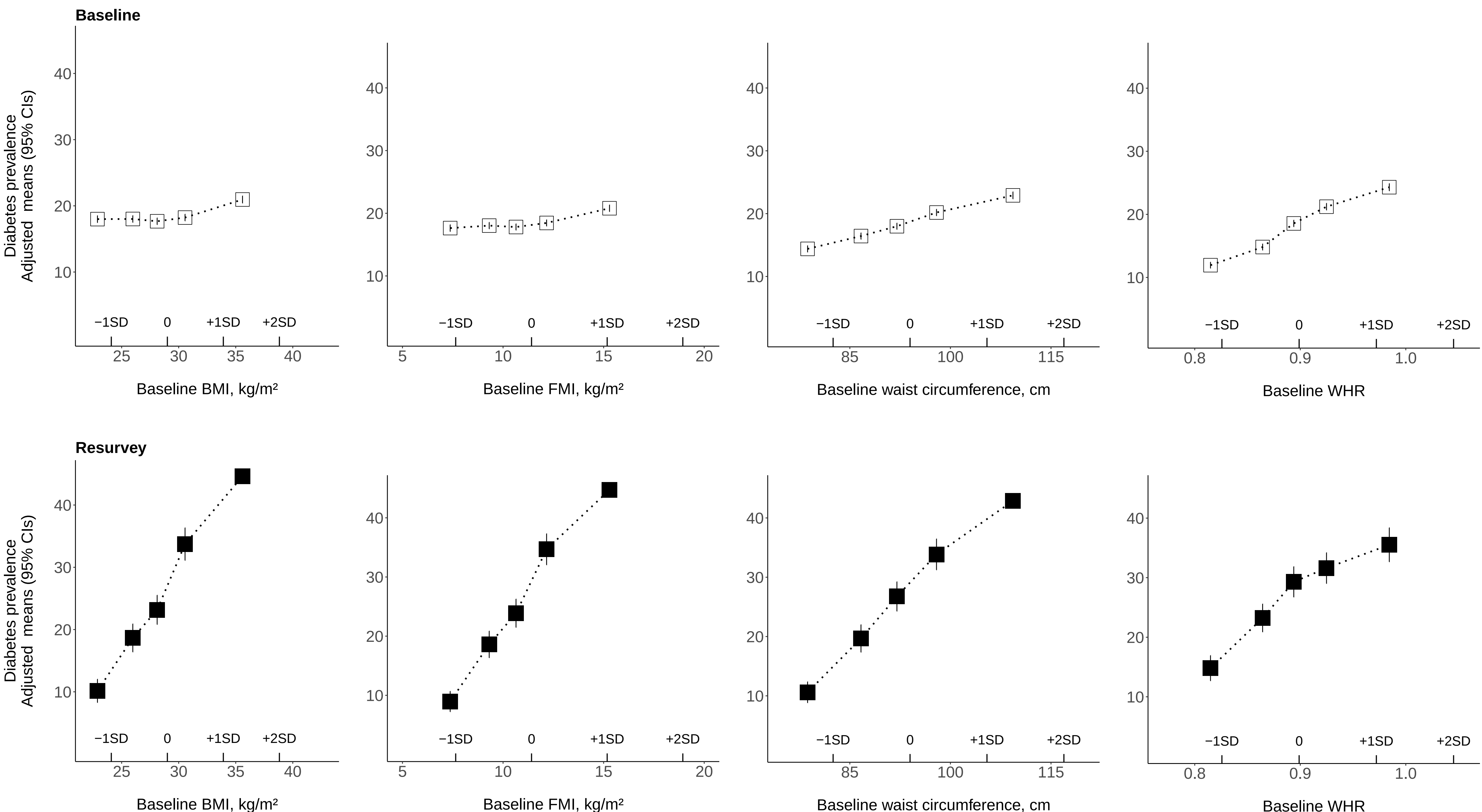
Exclusions as per table 4.1, restricted to participants with complete information on all the mediators.

S22.1: Associations of general and abdominal adiposity markers at baseline, with diabetes at baseline (top) and at resurvey (bottom), among men



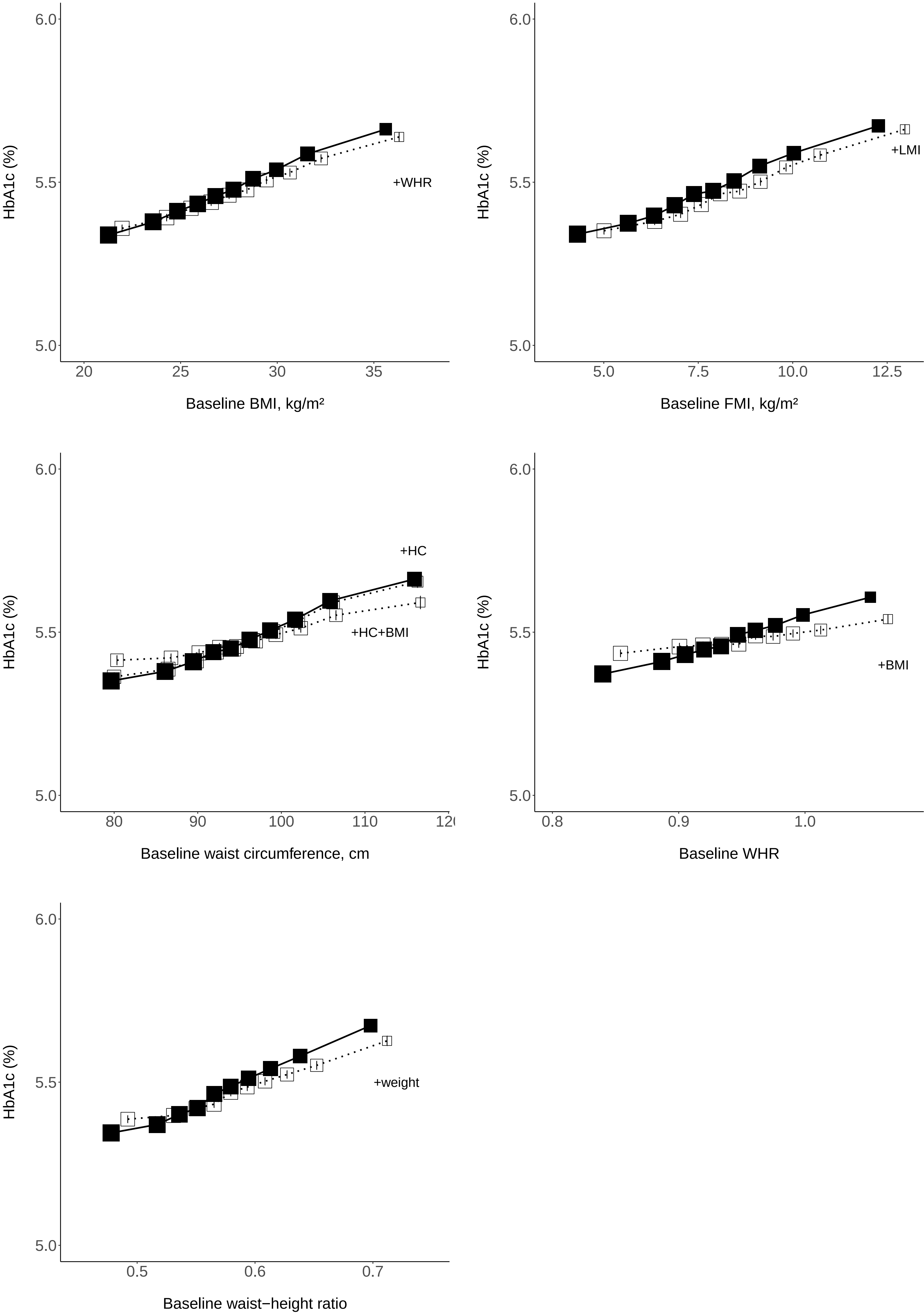
Analyses as per figure 4.3.

S22.2: Associations of general and abdominal adiposity markers at baseline, with diabetes at baseline (top) and at resurvey (bottom), among women



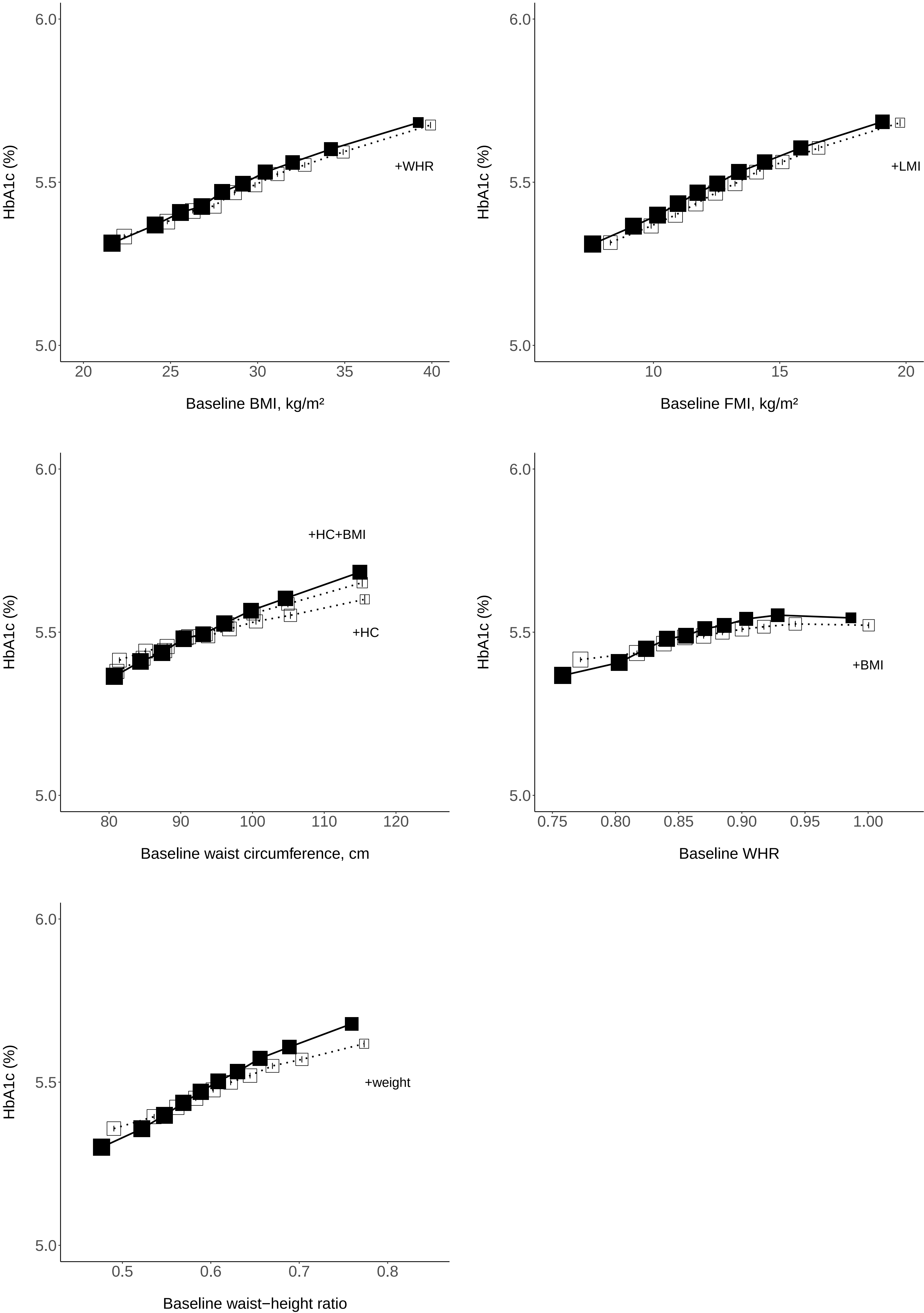
Analyses as per figure 4.3.

S23.1: Cross-sectional associations of general and central markers of adiposity and glycosylated haemoglobin (HbA1c) among 39,787 men aged 35–89 years, without diabetes or other chronic disease at recruitment



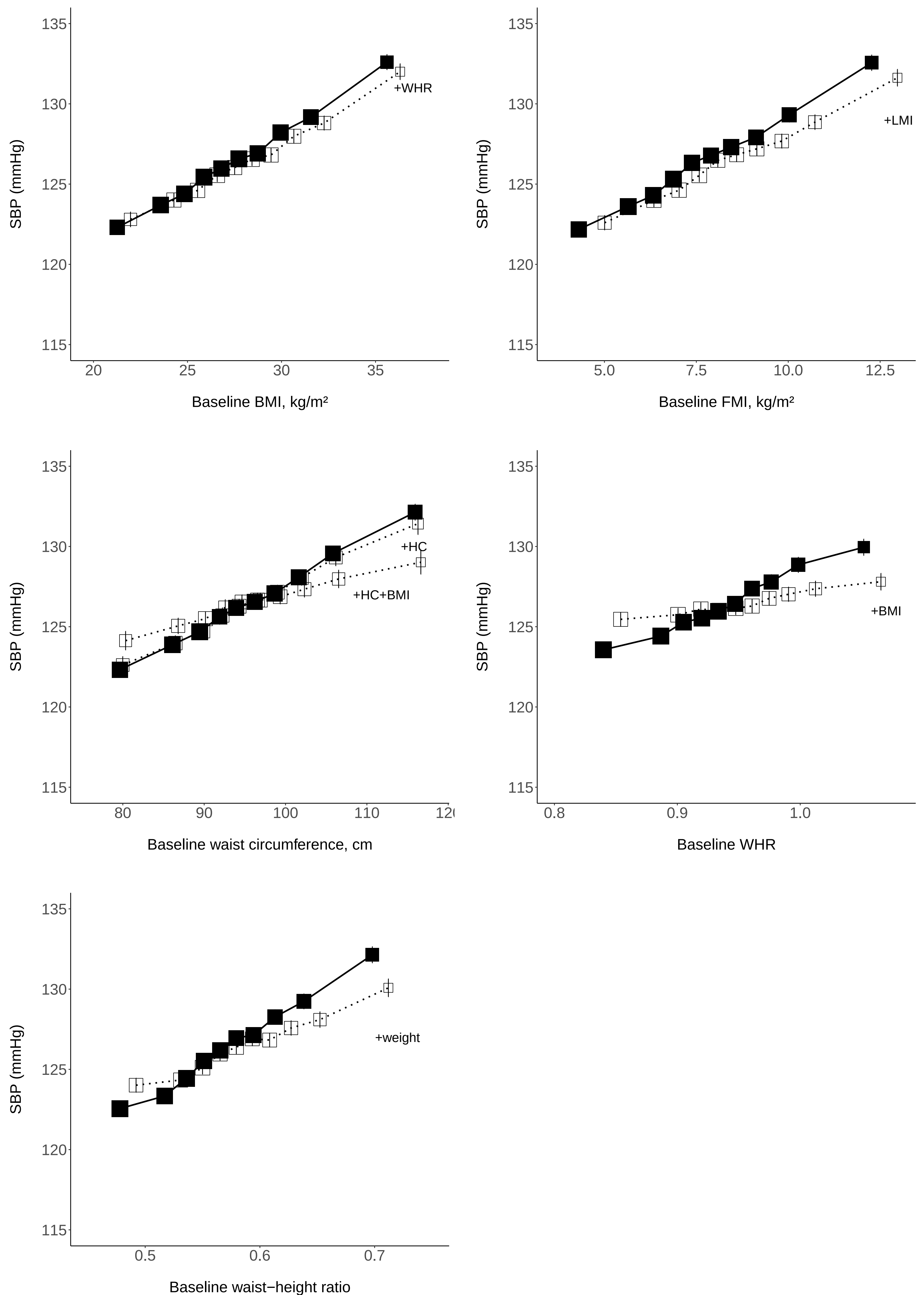
Analyses as per Figure 4.4.

S23.2: Cross-sectional associations of general and central markers of adiposity and glycosylated haemoglobin (HbA1c) among 82,020 women aged 35–89 years, without diabetes or other chronic disease at recruitment



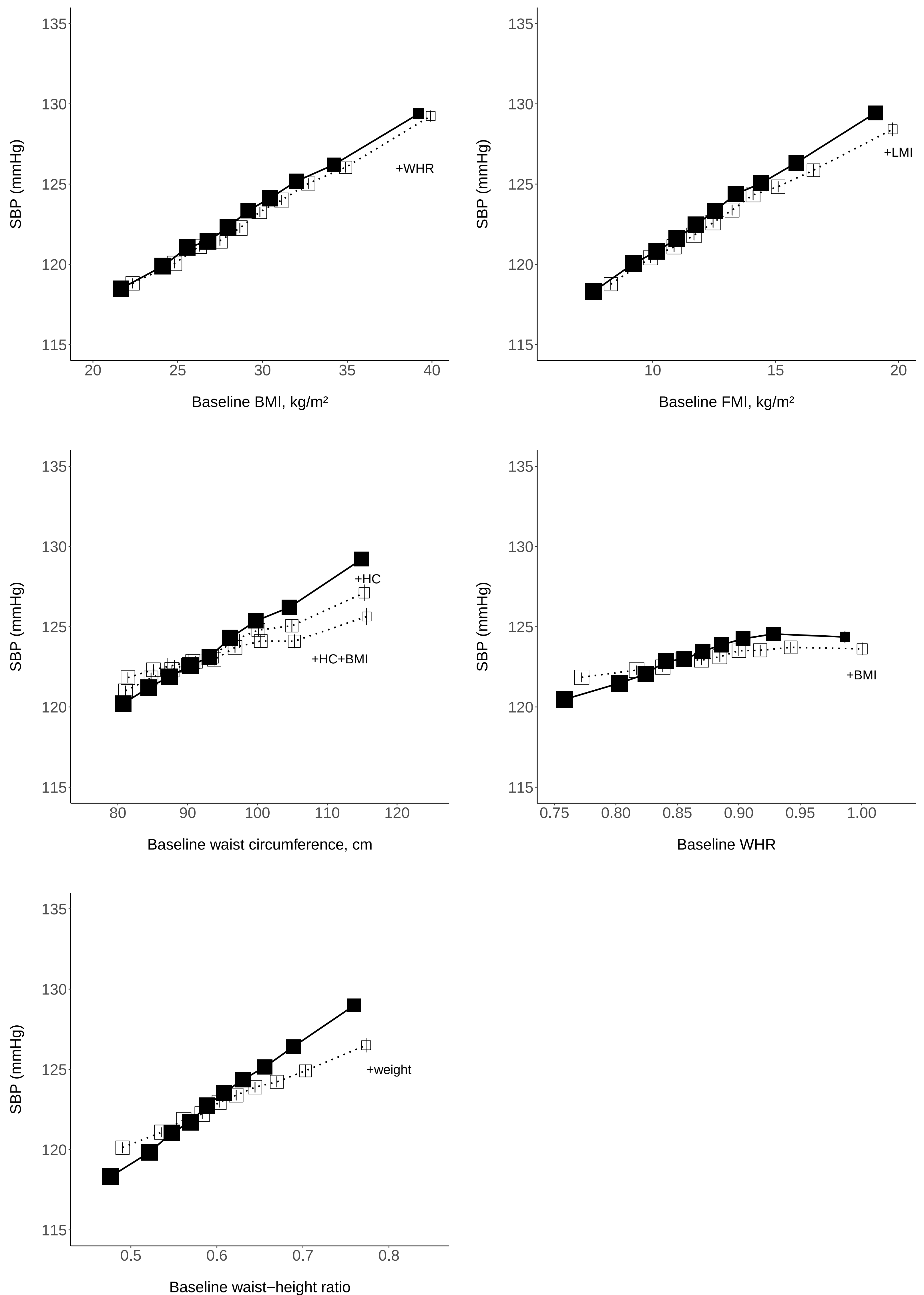
Analyses as per Figure 4.4.

S24.1: Cross-sectional associations of general and abdominal markers of adiposity and systolic blood pressure (SBP) among 36,331 men aged 35–89 years, without diabetes or other chronic disease at recruitment



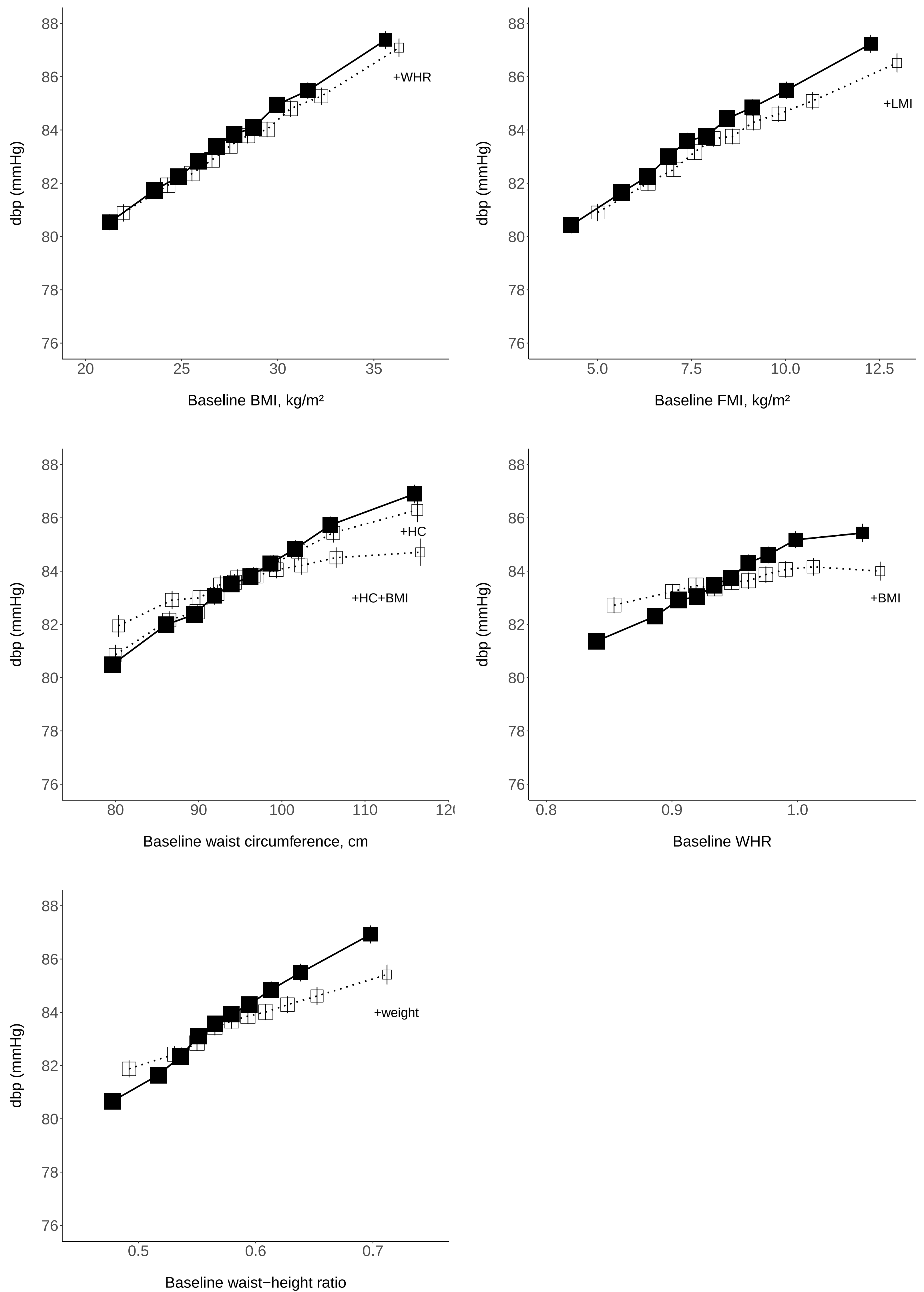
Analyses as per Figure 4.6.

S24.2: Cross-sectional associations of general and abdominal markers of adiposity and systolic blood pressure (SBP) among 70,438 women aged 35–89 years, without diabetes or other chronic disease at recruitment



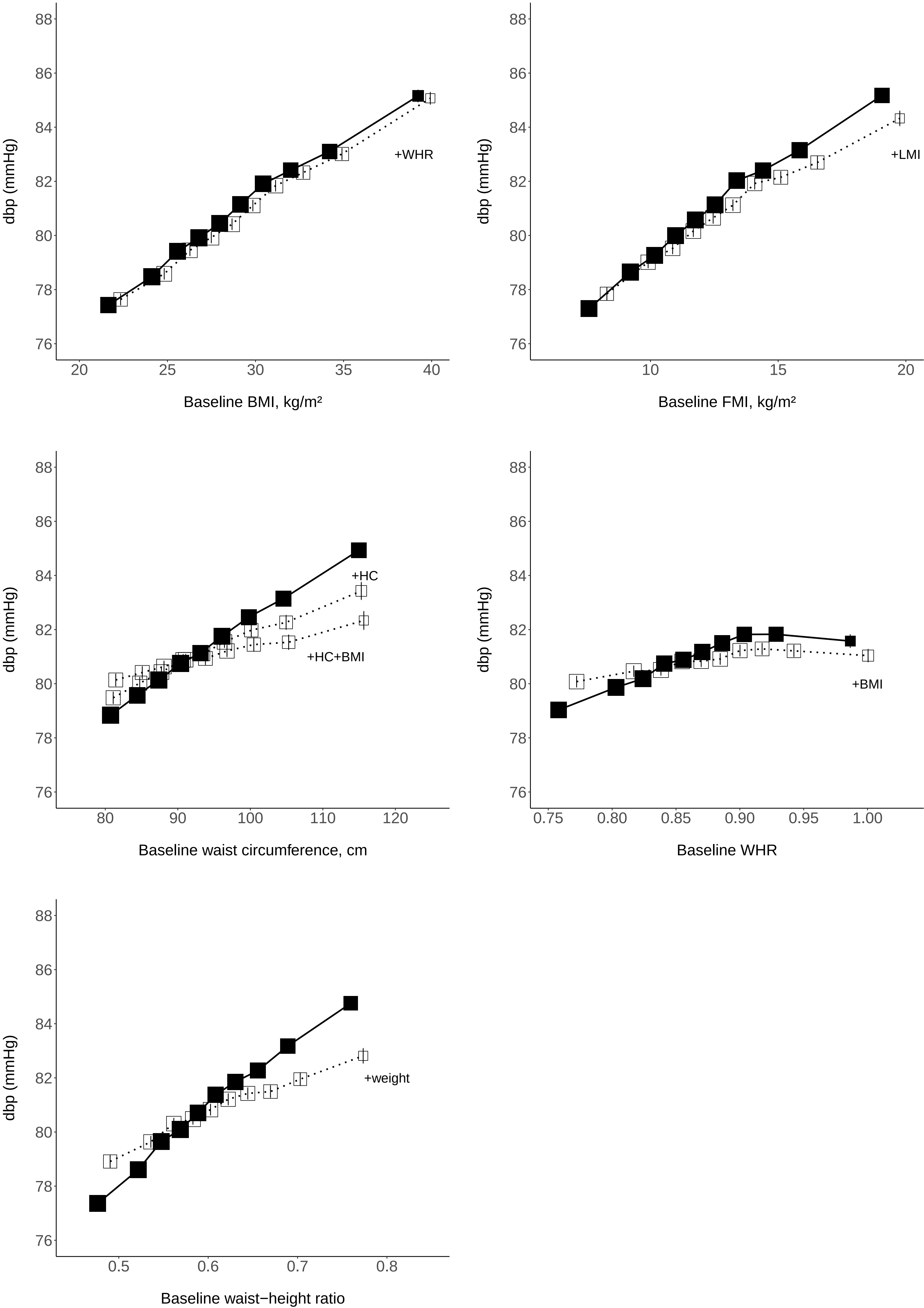
Analyses as per Figure 4.6.

S25.1: Cross-sectional associations of general and central markers of adiposity and diastolic blood pressure (DBP) among 36,331 men aged 35–89 years, without diabetes or other chronic disease at recruitment



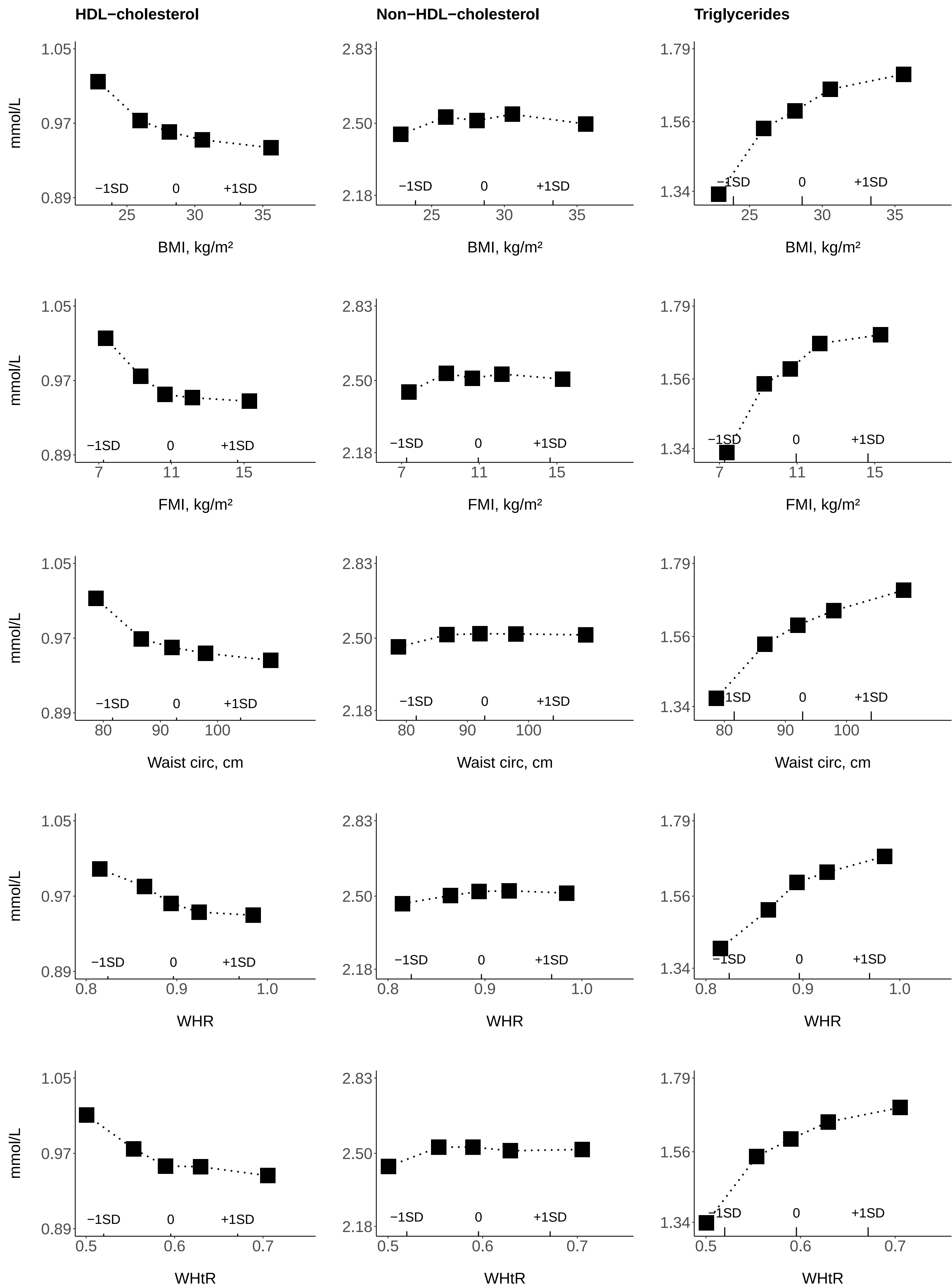
Analyses as per Figure 4.6.

S25.2: Cross-sectional associations of general and central markers of adiposity and diastolic blood pressure (DBP) among 70,438 women aged 35–89 years, without diabetes or other chronic disease at recruitment



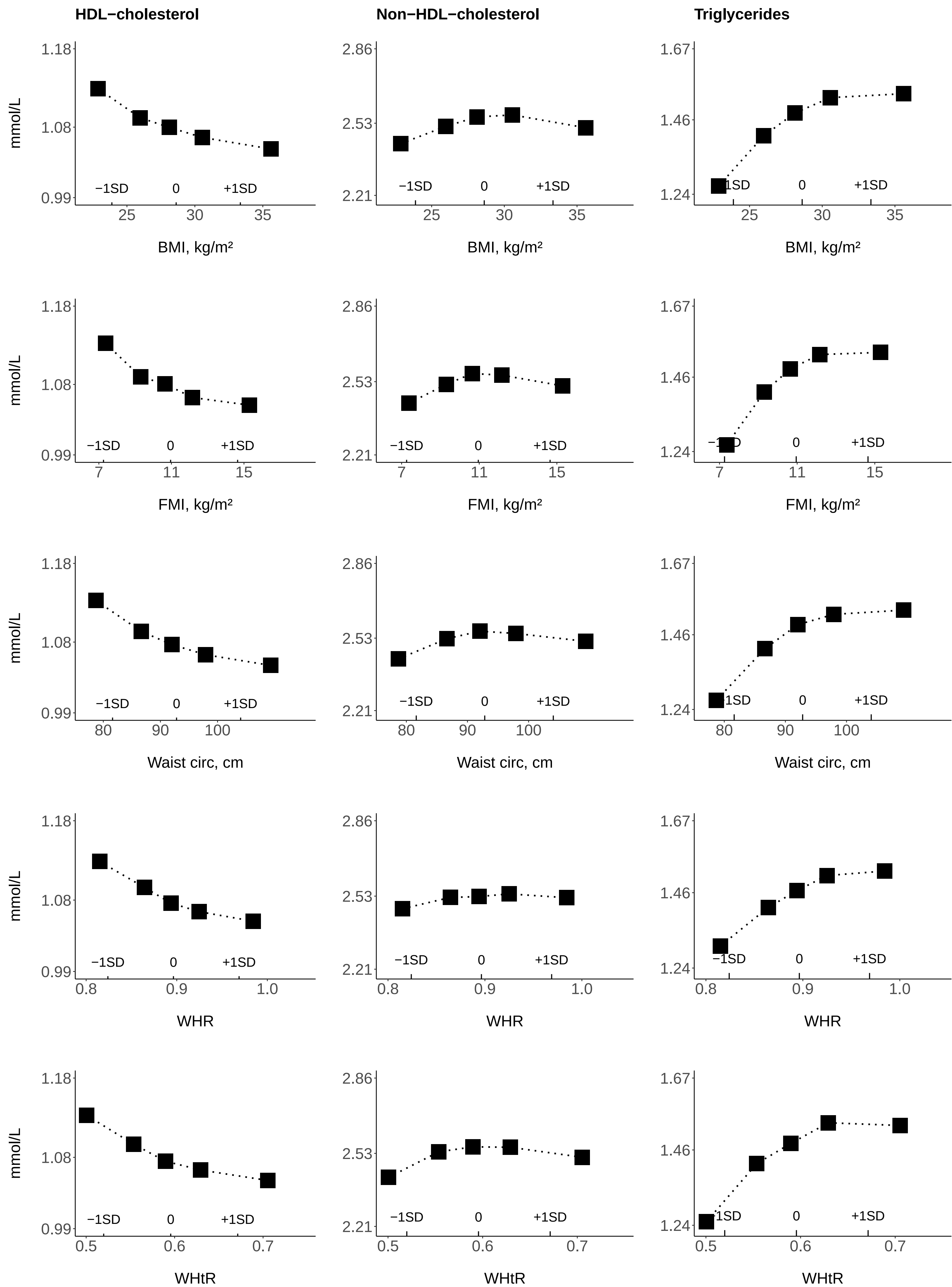
Analyses as per Figure 4.6.

S26.1: Cross-sectional associations of general and central adiposity markers and selected lipids among 10,065 men aged 35–89 years, without diabetes or other chronic disease at recruitment, before adjustment for other adiposity markers



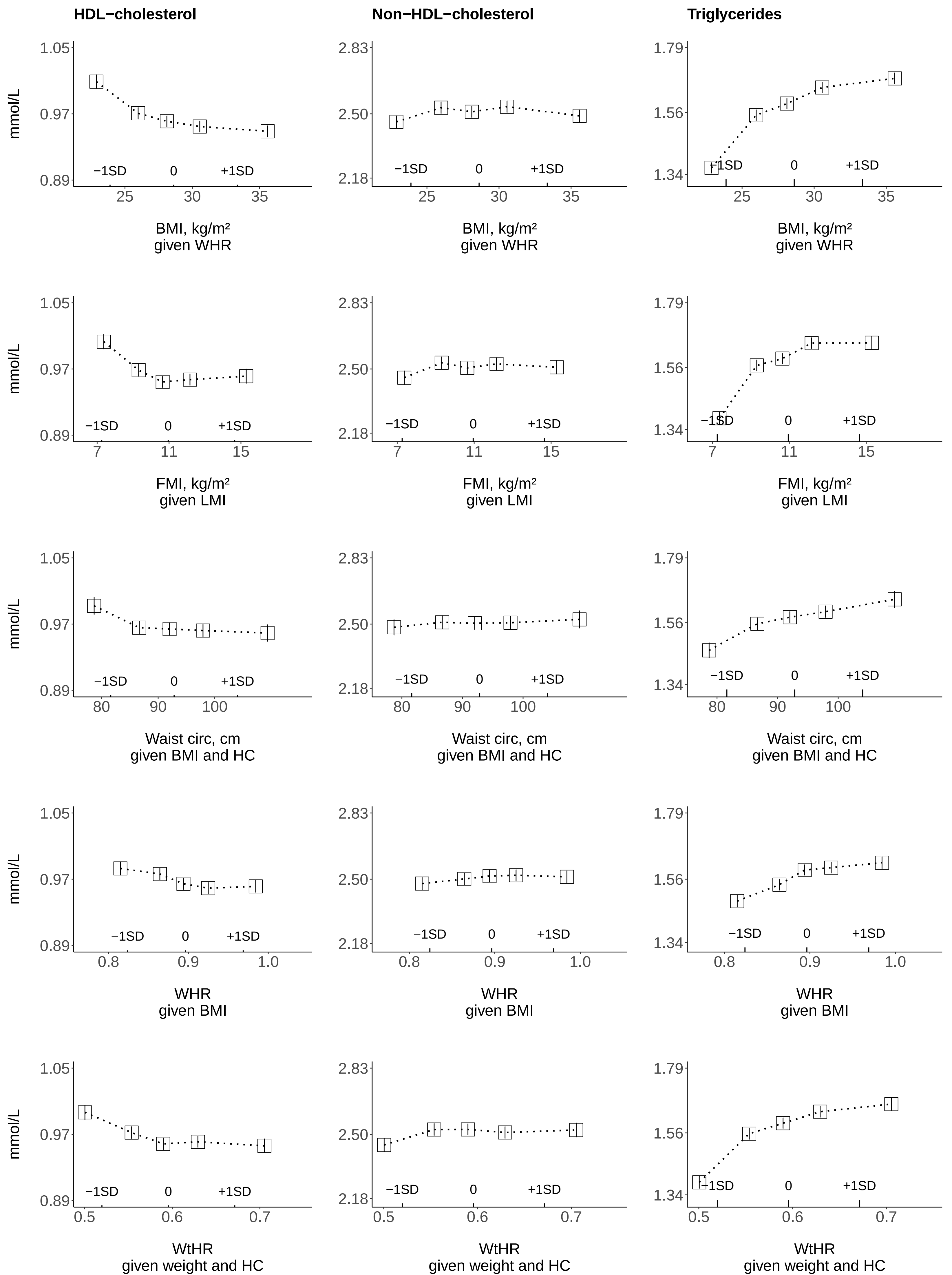
Analyses and conventions as per figure 4.10.

S26.2: Cross-sectional associations of general and central adiposity markers and selected lipids among 16,424 women aged 35–89 years, without diabetes or other chronic disease at recruitment, before adjustment for other adiposity markers



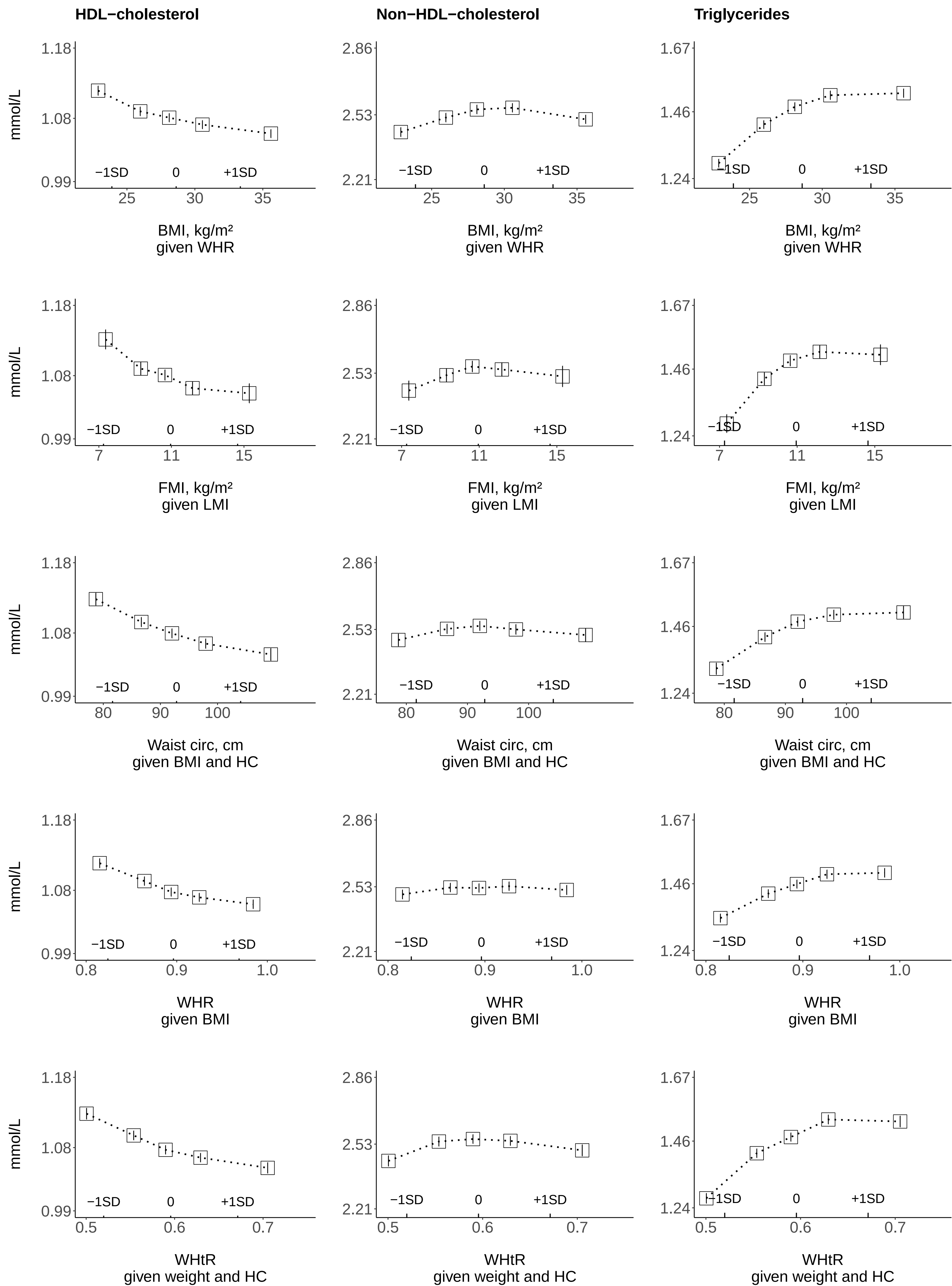
Analyses and conventions as per figure 4.10.

S26.3: Cross-sectional associations of general and central adiposity markers and selected lipids among 10,065 men aged 35–89 years, without diabetes or other chronic disease at recruitment, after adjustment for other adiposity markers



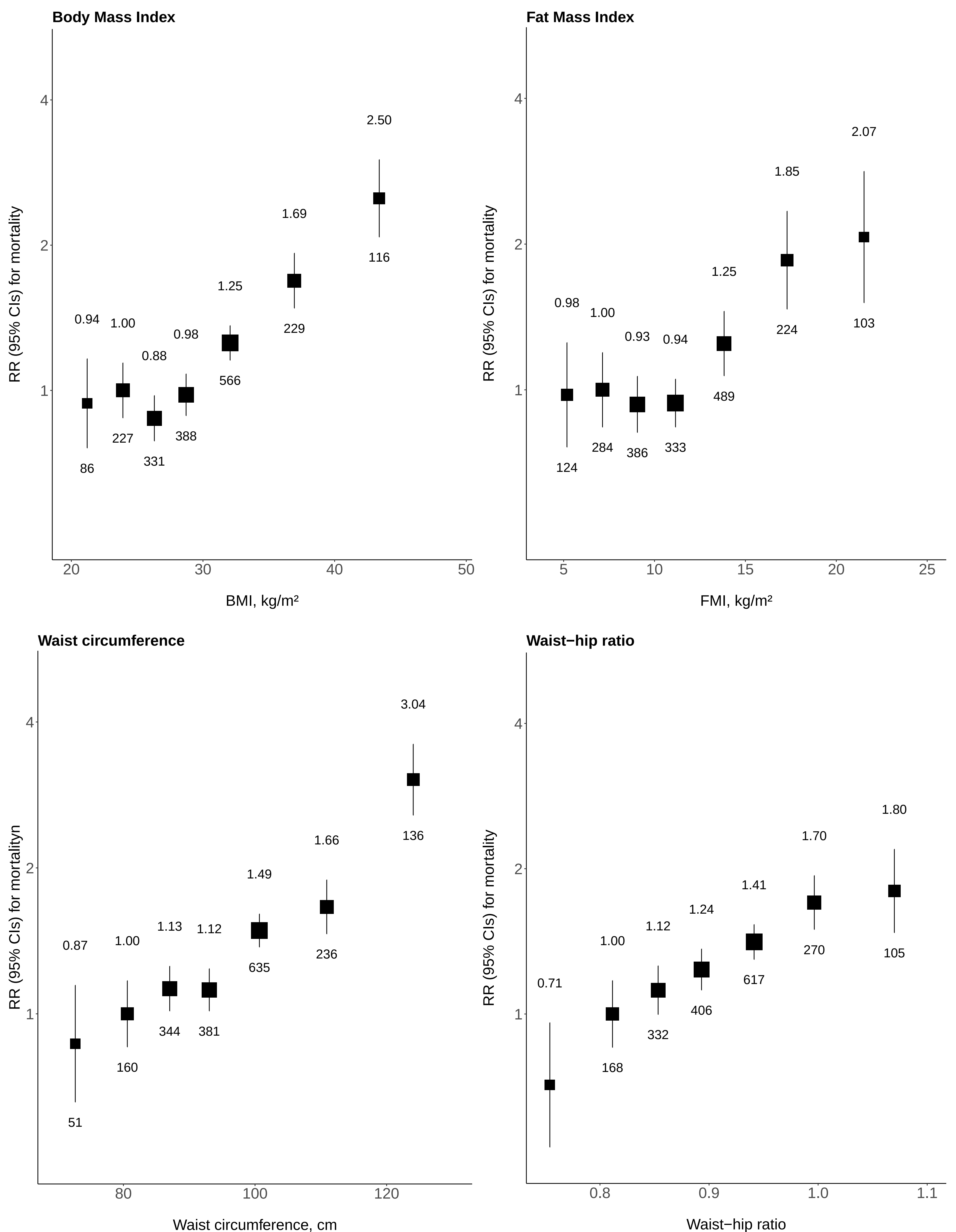
Analyses as per figure 4.11.

S26.4: Cross-sectional associations of general and central adiposity markers and selected lipids among 16,424 women aged 35–89 years, without diabetes or other chronic disease at recruitment, after adjustment for other adiposity markers



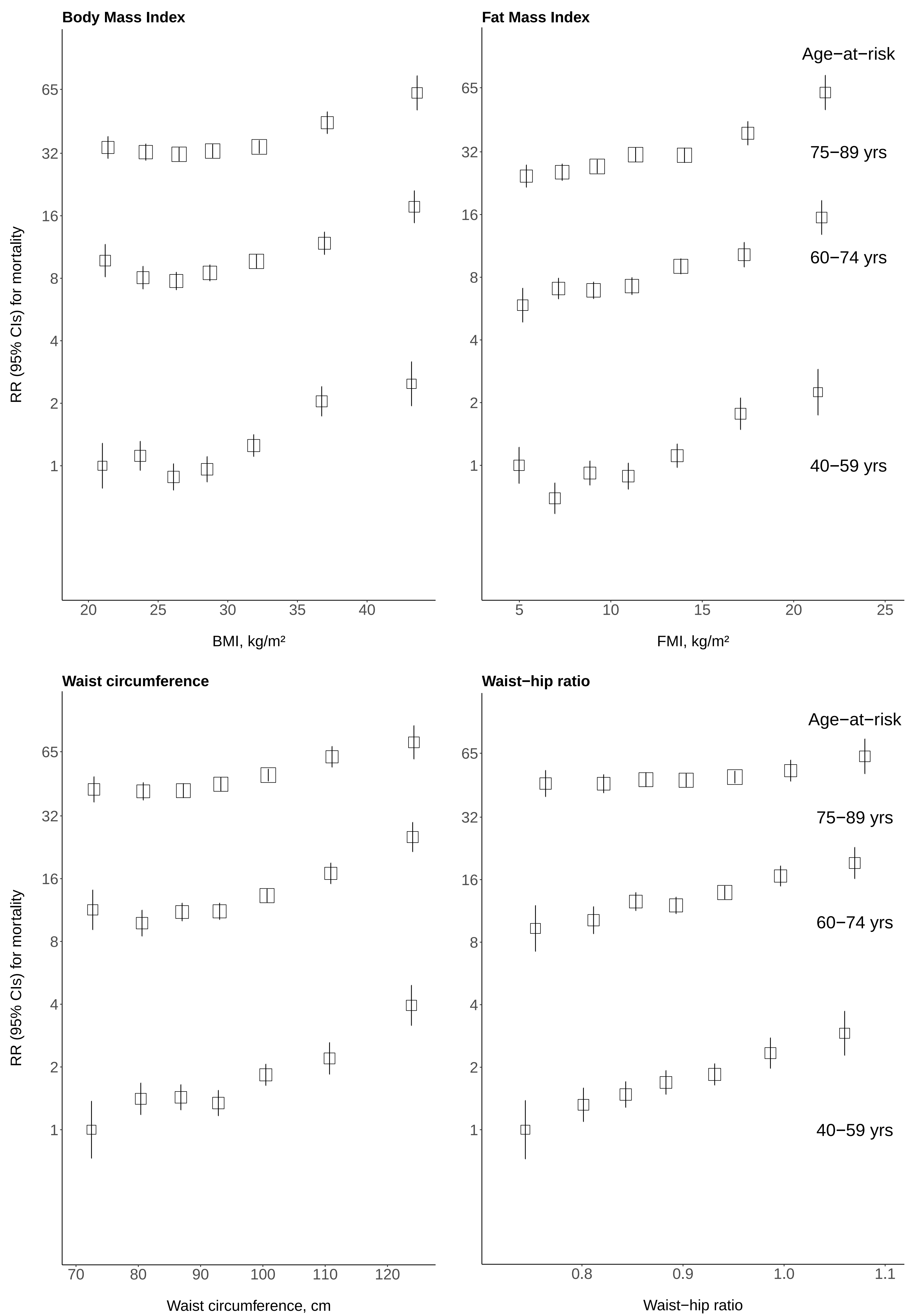
Analyses as per figure 4.11.

**S27: Relevance of BMI, FMI, waist circumference and WHR
to all-cause mortality at ages 50–74 years, after exclusion of the first 10 years of follow-up**



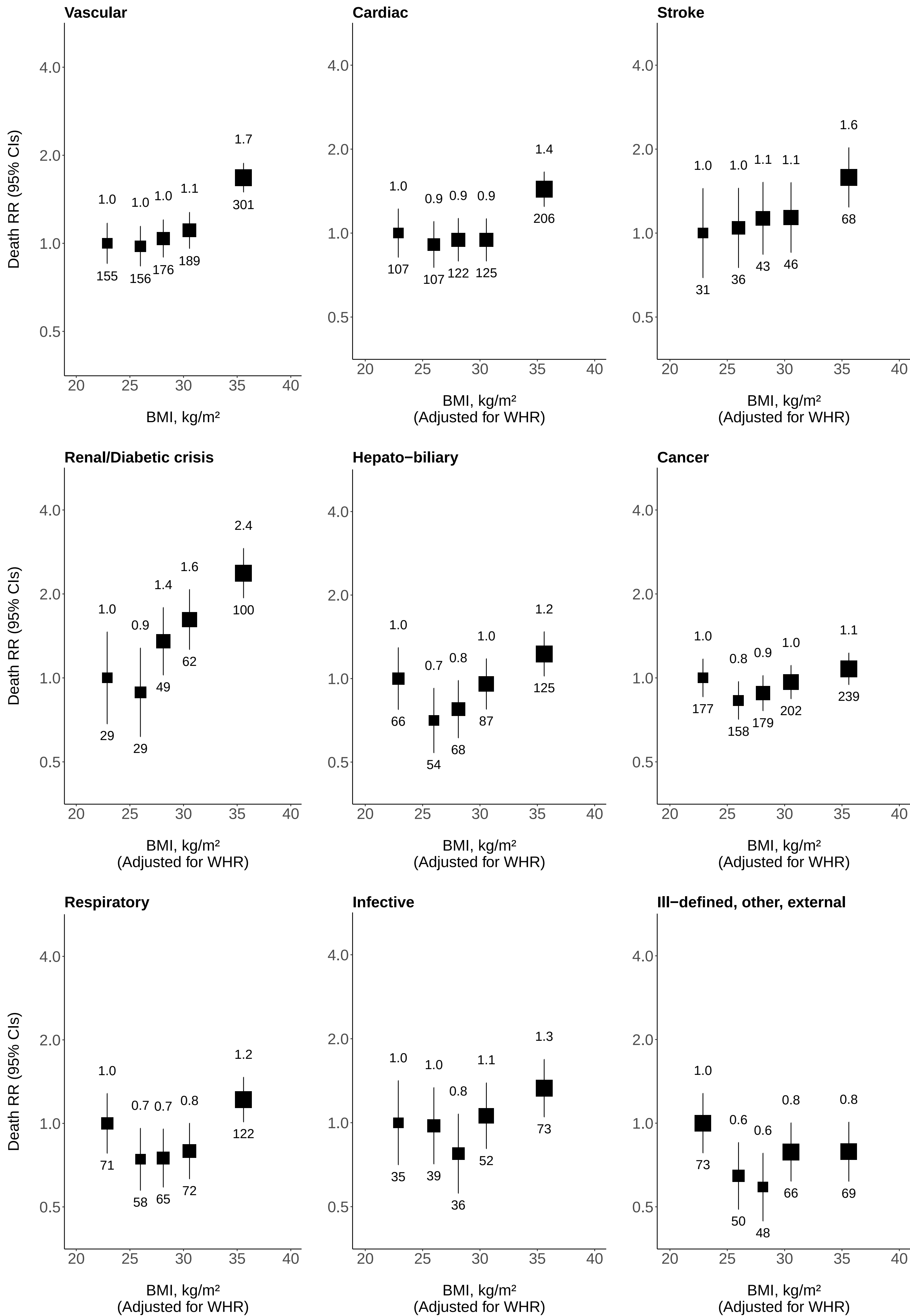
Analyses and conventions as per Figure 5.1. Of the 100,515 participants included, 1943 died from any cause.

S28. All-cause mortality versus BMI, FMI, waist circumference and WHR by age-at-risk among those without diabetes or other chronic disease at baseline (first 5 years of follow-up excluded)



Analyses as per Figure 5.1, now with previously-diagnosed, treated or screen-detected diabetes at baseline, and early follow-up excluded.

S29: Independent relevance of BMI to mortality from specific causes at ages 40–74 years



Analyses and conventions as per Figure 5.8., with additional adjustments as indicated in the plot.

S30: Baseline BMI (per 5 kg/m²) vs deaths at ages 40-74 years by cause, independent of WHR

	BMI 18.5 to <25 kg/m ² n=20,636		BMI 25 to 60 kg/m ² n=108,293	
Cause death	No deaths	RR per 5 kg/m ² (95% CIs)	No deaths	RR per 5 kg/m ² (95% CIs)
Vascular				
Ischaemic Heart Disease	77	0.77 (0.36-1.64)	437	1.22 (1.09-1.36)
Other cardiac	25	0.72 (0.19-2.67)	128	1.52 (1.29-1.79)
Subtotal: any cardiac	102	0.75 (0.39-1.45)	565	1.30 (1.18-1.42)
Stroke	30	0.68 (0.21-2.25)	194	1.17 (1.00-1.37)
Other vascular	17	2.91 (0.43-19.58)	69	1.83 (1.49-2.25)
Subtotal: vascular	149	0.85 (0.49-1.47)	828	1.31 (1.22-1.41)
Metabolic				
Renal/Acute diabetic crises	29	0.36 (0.11-1.16)	240	1.52 (1.35-1.72)
Hepatobiliary	67	0.96 (0.41-2.27)	333	1.27 (1.13-1.44)
Subtotal: any vascular-metabolic	245	0.78 (0.51-1.21)	1401	1.34 (1.27-1.42)
Cancer				
Lung/Upper aero-digestive	29	0.55 (0.17-1.73)	68	1.09 (0.81-1.46)
Other cancer	141	1.07 (0.60-1.91)	717	1.14 (1.05-1.24)
Subtotal: any cancer	170	0.92 (0.55-1.55)	785	1.14 (1.05-1.23)
Other				
Respiratory	69	0.43 (0.20-0.93)	319	1.44 (1.28-1.61)
Infective	39	0.61 (0.21-1.80)	196	1.42 (1.24-1.63)
Other/III-defined/external	72	0.53 (0.25-1.13)	234	1.18 (1.02-1.37)
Total: all-cause	595	0.72 (0.55-0.94)	2935	1.29 (1.24-1.34)

Analyses as per Table 5.1, now with additional adjustment for abdominal adiposity.

S31: Baseline BMI (per 5 kg/m²) vs deaths at ages 40-74 years, by cause (further excludes those with a HbA1c of 6.5-7%)

Cause death	BMI 18.5 to <25 kg/m ² n=20,561		BMI 25 to 60 kg/m ² n=106,526	
	No deaths	RR per 5 kg/m ² (95% CIs)	No deaths	RR per 5 kg/m ² (95% CIs)
Vascular				
Ischaemic Heart Disease	73	0.73 (0.35-1.56)	422	1.25 (1.12-1.40)
Other cardiac	25	0.85 (0.23-3.09)	121	1.49 (1.26-1.76)
Subtotal: any cardiac	98	0.76 (0.40-1.46)	543	1.31 (1.20-1.44)
Stroke	30	0.83 (0.25-2.68)	185	1.17 (0.99-1.38)
Other vascular	17	3.59 (0.55-23.23)	67	1.90 (1.55-2.33)
Subtotal: vascular	145	0.91 (0.53-1.57)	795	1.33 (1.23-1.43)
Metabolic				
Renal/Acute diabetic crises	29	0.45 (0.14-1.40)	227	1.56 (1.38-1.77)
Hepatobiliary	67	1.12 (0.48-2.62)	322	1.33 (1.18-1.49)
Subtotal: any vascular-metabolic	241	0.88 (0.57-1.34)	1344	1.37 (1.30-1.45)
Cancer				
Lung/Upper aero-digestive	29	0.56 (0.18-1.70)	67	1.09 (0.81-1.46)
Other cancer	137	1.07 (0.60-1.91)	691	1.15 (1.06-1.25)
Subtotal: any cancer	166	0.93 (0.55-1.55)	758	1.15 (1.06-1.24)
Other				
Respiratory	69	0.55 (0.26-1.17)	302	1.44 (1.28-1.61)
Infective	39	0.88 (0.30-2.53)	184	1.42 (1.23-1.64)
Other/III-defined/external	72	0.54 (0.26-1.13)	227	1.17 (1.01-1.36)
Total: all-cause	587	0.79 (0.60-1.03)	2815	1.30 (1.25-1.36)

Analyses as per Table 5.1, with the additional exclusions specified in the title.

S32: Baseline BMI (per 5 kg/m²) vs deaths at ages 40-74 years by cause (includes those with previously-diagnosed diabetes and HbA1c <7%)

Cause death	BMI 18.5 to <25 kg/m ² n=21,115		BMI 25 to 60 kg/m ² n=111,939	
	No deaths	RR per 5 kg/m ² (95% CIs)	No deaths	RR per 5 kg/m ² (95% CIs)
Vascular				
Ischaemic Heart Disease	90	0.61 (0.32-1.18)	492	1.25 (1.13-1.38)
Other cardiac	26	0.84 (0.23-2.99)	136	1.53 (1.31-1.79)
Subtotal: any cardiac	116	0.66 (0.36-1.18)	628	1.32 (1.21-1.43)
Stroke	36	0.97 (0.32-2.94)	207	1.19 (1.02-1.38)
Other vascular	18	2.24 (0.41-12.17)	74	1.80 (1.48-2.20)
Subtotal: vascular	170	0.80 (0.49-1.32)	909	1.33 (1.24-1.42)
Metabolic				
Renal/Acute diabetic crises	58	0.53 (0.23-1.20)	313	1.42 (1.27-1.59)
Hepatobiliary	71	1.27 (0.55-2.94)	349	1.34 (1.20-1.50)
Subtotal: any vascular-metabolic	299	0.81 (0.56-1.19)	1571	1.35 (1.28-1.42)
Cancer				
Lung/Upper aero-digestive	29	0.55 (0.18-1.67)	73	1.11 (0.84-1.46)
Other cancer	143	1.07 (0.60-1.89)	748	1.15 (1.06-1.24)
Subtotal: any cancer	172	0.93 (0.56-1.54)	821	1.14 (1.06-1.23)
Other				
Respiratory	74	0.52 (0.25-1.06)	354	1.43 (1.29-1.59)
Infective	43	0.82 (0.30-2.22)	215	1.47 (1.29-1.67)
Other/ill-defined/external	74	0.55 (0.27-1.14)	252	1.20 (1.04-1.37)
Total: all-cause	662	0.76 (0.59-0.98)	3213	1.30 (1.25-1.35)

Analyses as per Table 5.1, with the additional inclusions specified in the title.

S33: Baseline BMI (per 5 kg/m²) vs cancer subtypes at ages 40-74 years, independent of WHR (excludes previously-diagnosed diabetes and those with HbA1c ≥7%)

	BMI 18.5 to <25 kg/m ² n=20,636		BMI 25 to 60 kg/m ² n=108,293	
Cause death	No deaths	RR per 5 kg/m² (95% CIs)	No deaths	RR per 5 kg/m² (95% CIs)
Lung/Upper aero-digestive	29	0.55 (0.17-1.73)	68	1.09 (0.81-1.46)
Breast	13	1.49 (0.21-10.45)	89	1.10 (0.88-1.38)
Gynaecological	18	2.72 (0.46-16.14)	126	1.05 (0.85-1.28)
Oesophageal/stomach	18	0.09 (0.02-0.35)	76	0.84 (0.61-1.15)
Pancreatic/hepatobiliary	22	3.46 (0.63-19.07)	122	1.06 (0.86-1.31)
Other gastro-intestinal	11	0.29 (0.04-1.85)	67	1.43 (1.11-1.84)
Urinary tract	14	2.66 (0.34-20.93)	27	1.62 (1.13-2.32)
Haematological	14	2.02 (0.24-16.81)	86	1.29 (1.02-1.61)
Other, ill defined	31	1.57 (0.42-5.92)	124	1.18 (0.97-1.43)
Subtotal: any cancer	170	0.92 (0.55-1.55)	785	1.14 (1.05-1.23)

Analyses as per Table 5.1, now with additional adjustment for abdominal adiposity.

S34: Baseline BMI (per 5 kg/m²) vs cancer subtype at ages 40-74 years, among never smokers (excludes previously-diagnosed diabetes and those with HbA1c ≥7%)

	BMI 18.5 to <25 kg/m ² n=8,939		BMI 25 to 60 kg/m ² n=51,765	
Cause death	No deaths	RR per 5 kg/m² (95% CIs)	No deaths	RR per 5 kg/m² (95% CIs)
Lung/Upper aero-digestive	6	0.78 (0.05-12.69)	20	1.32 (0.85-2.04)
Breast	10	5.28 (0.36-77.23)	64	1.20 (0.93-1.54)
Gynaecological	8	16.98 (0.47-618)	71	1.15 (0.90-1.48)
Oesophageal/stomach	8	0.05 (0.01-0.35)	37	0.64 (0.40-1.04)
Pancreatic/hepatobiliary	13	2.47 (0.30-20.69)	63	1.12 (0.85-1.47)
Other gastro-intestinal	3	2.13 (0.02-192.28)	35	1.45 (1.05-1.99)
Urinary tract	4	0.23 (0.01-5.21)	11	1.69 (1.01-2.81)
Haematological	3	2.19 (0.03-150.1)	41	1.27 (0.93-1.72)
Other, ill defined	11	1.78 (0.19-16.81)	69	1.22 (0.95-1.56)
Subtotal: any cancer	66	1.17 (0.50-2.74)	411	1.18 (1.07-1.31)

Analyses as per Table 5.2.

S35: Baseline BMI (per 5 kg/m²) vs cancer subtypes at ages 40-74 years (includes those with previously-diagnosed diabetes and HbA1c <7%)

	BMI 18.5 to <25 kg/m ² n=21,115		BMI 25 to 60 kg/m ² n=111,939	
Cause death	No deaths	RR per 5 kg/m² (95% CIs)	No deaths	RR per 5 kg/m² (95% CIs)
Lung/Upper aero-digestive	29	0.55 (0.18-1.67)	73	1.11 (0.84-1.46)
Breast	13	1.34 (0.20-9.19)	92	1.14 (0.92-1.41)
Gynaecological	18	2.28 (0.39-13.24)	128	1.06 (0.87-1.30)
Oesophageal/stomach	18	0.10 (0.03-0.37)	83	0.88 (0.66-1.17)
Pancreatic/hepatobiliary	23	3.33 (0.64-17.37)	132	1.06 (0.87-1.29)
Other gastro-intestinal	12	0.43 (0.07-2.54)	71	1.39 (1.09-1.78)
Urinary tract	14	2.14 (0.28-16.21)	29	1.58 (1.11-2.24)
Haematological	14	2.02 (0.25-16.26)	87	1.28 (1.03-1.60)
Other, ill defined	31	1.73 (0.46-6.42)	126	1.18 (0.97-1.42)
Subtotal: any cancer	172	0.93 (0.56-1.54)	821	1.14 (1.06-1.23)

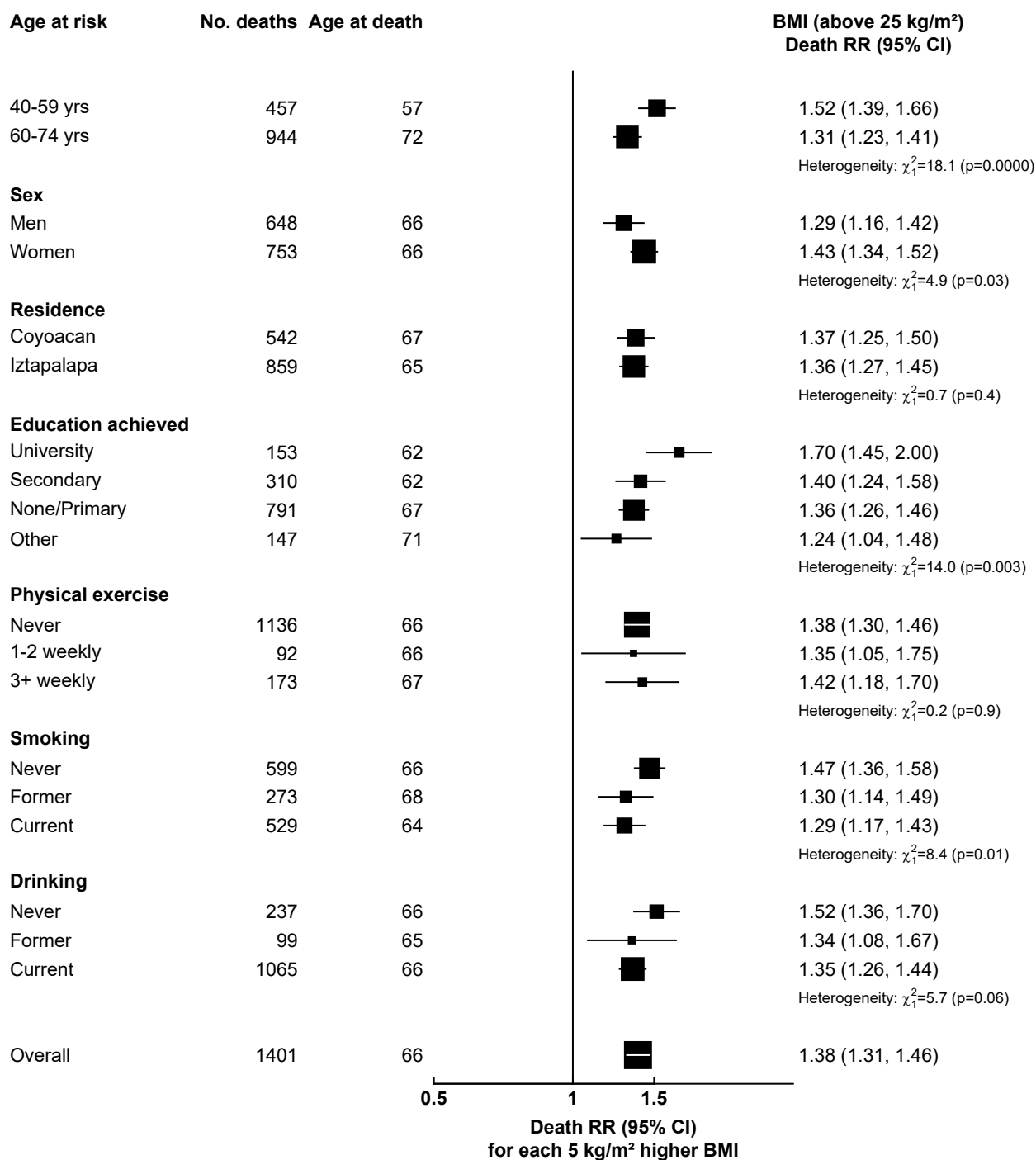
Analyses as per Table 5.1, with the additional inclusions specified in the title.

S36: Usual levels of BMI (above 25 kg/m²) versus cause-specific mortality at ages 40-74 years (excludes previously-diagnosed diabetes, those with HbA1c ≥7%, and the first 5 years of follow-up)

Cause of death	No. deaths	BMI per 5 kg/m ²	further adjusted for baseline WHR
Vascular			
Ischaemic Heart Disease	437	1.30 (1.15-1.47)	1.28 (1.13-1.44)
Other cardiac	128	1.61 (1.35-1.93)	1.59 (1.33-1.91)
Subtotal: any cardiac	565	1.38 (1.25-1.53)	1.36 (1.23-1.50)
Stroke	194	1.23 (1.03-1.46)	1.18 (0.99-1.41)
Other vascular	69	2.00 (1.59-2.51)	1.96 (1.55-2.47)
Subtotal: vascular	828	1.40 (1.29-1.51)	1.36 (1.25-1.48)
Metabolic			
Renal/Acute diabetic crises	240	1.65 (1.44-1.88)	1.61 (1.41-1.85)
Hepatobiliary	333	1.39 (1.22-1.58)	1.33 (1.17-1.53)
Subtotal: any vascular-metabolic	1401	1.44 (1.35-1.53)	1.40 (1.32-1.49)
Cancer			
Lung/Upper aero-digestive	68	1.12 (0.81-1.54)	1.09 (0.79-1.52)
Other cancer	717	1.17 (1.07-1.29)	1.17 (1.06-1.28)
Subtotal: any cancer	785	1.17 (1.07-1.28)	1.16 (1.06-1.27)
Other			
Respiratory	319	1.54 (1.36-1.74)	1.50 (1.32-1.70)
Infective	196	1.54 (1.32-1.79)	1.50 (1.28-1.75)
Other/III-defined/external	234	1.22 (1.03-1.43)	1.21 (1.02-1.43)
Total: all-cause	2935	1.37 (1.31-1.43)	1.34 (1.28-1.40)

Estimates represent death RRs for comparable sex-specific differences per 5 kg/m² usual increase in BMI above 25 kg/m², corrected for regression dilution ratios of 0.89. Adjustments for confounders, WHR, and exclusions are as per main analyses of mortality (details on the footnote of figures 5.1 and 5.2).

S37. Relevance of BMI (above 25 kg/m²) to vascular-metabolic mortality at ages 40-74 years, by strata of confounders



Analyses as per Figure 5.10.

S38. Association of each 5 kg/m² higher baseline BMI (above 25 kg/m²) to mortality at ages 40-74 years, with progressive adjustment for baseline confounders

Adjustment	All-cause			Vascular-metabolic			Non vascular-metabolic		
	Death RR (95% CI)	Wald-chi		Death RR (95% CI)	Wald-chi		Death RR (95% CI)	Wald-chi	
Age, sex	 1.36 (1.31, 1.41)	246		 1.42 (1.35, 1.50)	168		 1.29 (1.21, 1.37)	68	
plus smoking	 1.36 (1.31, 1.41)	255		 1.43 (1.35, 1.51)	174		 1.29 (1.22, 1.37)	70	
plus exercise	 1.35 (1.30, 1.40)	240		 1.42 (1.34, 1.49)	164		 1.28 (1.21, 1.36)	65	
plus drinking	 1.35 (1.30, 1.40)	241		 1.42 (1.34, 1.50)	166		 1.28 (1.21, 1.36)	65	
plus education	 1.35 (1.30, 1.40)	231		 1.41 (1.34, 1.49)	158		 1.28 (1.20, 1.36)	64	
plus residence	 1.32 (1.27, 1.37)	195		 1.38 (1.31, 1.46)	136		 1.25 (1.18, 1.33)	52	
	0.7 1 1.5 Death RR (95% CI)			0.7 1 1.5 Death RR (95% CI)			0.7 1 1.5 Death RR (95% CI)		

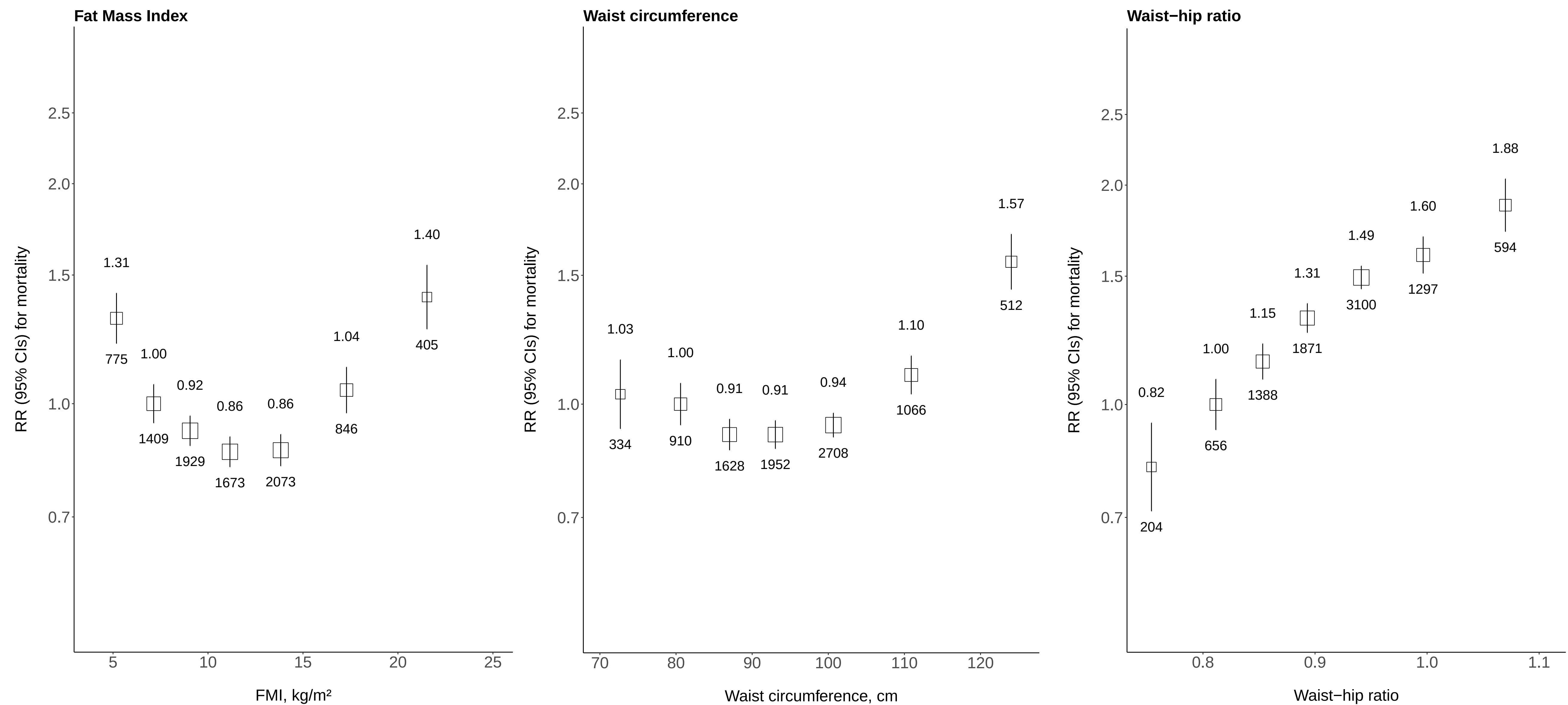
Analyses as per Table 5.1.

S39: Excess mortality from specific causes at ages 40-74 years associated with obese BMI (≥ 30 Kg/m²)

	Events	RR (95% CIs)	Events	RR (95% CIs)	Events	RR (95% CIs)	Events	RR (95% CIs)	Events	RR (95% CIs)	Mortality attributable to BMI $>30^*$
	BMI <20 kg/m ²		BMI 20-25 kg/m ²		BMI 25-29 kg/m ²		BMI 30-39 kg/m ²		BMI 40+ kg/m ²		
Any vasculo-metabolic	11	1.03 (0.57 - 1.85)	234	1.00	620	1.04 (0.96 - 1.13)	692	1.53 (1.42 - 1.65)	89	2.64 (2.14 - 3.26)	18%
Any vascular	8	1.20 (0.60 - 2.40)	141	1.00	378	1.06 (0.96 - 1.18)	399	1.47 (1.33 - 1.63)	51	2.51 (1.90 - 3.31)	16%
Any cardiac	6	1.34 (0.60 - 2.99)	96	1.00	262	1.08 (0.96 - 1.22)	270	1.49 (1.32 - 1.69)	33	2.48 (1.75 - 3.50)	16%
Any cerebrovascular	2	1.52 (0.38 - 6.11)	28	1.00	89	1.23 (1.00 - 1.52)	98	1.66 (1.35 - 2.04)	7	1.49 (0.71 - 3.14)	18%
Any kidney disease	2	1.85 (0.46 - 7.44)	24	1.00	77	1.23 (0.98 - 1.54)	97	1.94 (1.59 - 2.38)	17	4.28 (2.64 - 6.94)	28%
Any hepatobiliary	1	0.35 (0.05 - 2.52)	66	1.00	151	0.89 (0.76 - 1.05)	165	1.33 (1.14 - 1.56)	17	1.90 (1.17 - 3.07)	12%
Diabetes (glycaemic crisis)	0	...	3	1.00	14	1.92 (1.11 - 3.30)	31	5.69 (3.66 - 8.84)	4	10.18 (3.75 - 27.66)	56%
Any cancer	7	0.94 (0.45 - 1.97)	163	1.00	376	0.90 (0.81 - 0.99)	368	1.07 (0.96 - 1.18)	41	1.44 (1.06 - 1.96)	4%
Any respiratory	5	1.63 (0.68 - 3.94)	64	1.00	138	0.84 (0.71 - 1.00)	153	1.19 (1.01 - 1.40)	28	2.77 (1.90 - 4.04)	11%
Infective (excl. respiratory)	1	0.58 (0.08 - 4.10)	38	1.00	80	0.80 (0.64 - 1.00)	96	1.16 (0.94 - 1.42)	20	2.88 (1.84 - 4.51)	11%
External, ill-defined, other	5	1.59 (0.66 - 3.83)	67	1.00	119	0.71 (0.60 - 0.85)	104	0.81 (0.67 - 0.99)	11	1.16 (0.64 - 2.10)	-7%
All-Cause	29	1.11 (0.77 - 1.60)	566	1.00	1333	0.92 (0.87 - 0.97)	1413	1.25 (1.18 - 1.31)	189	2.14 (1.85 - 2.47)	11%

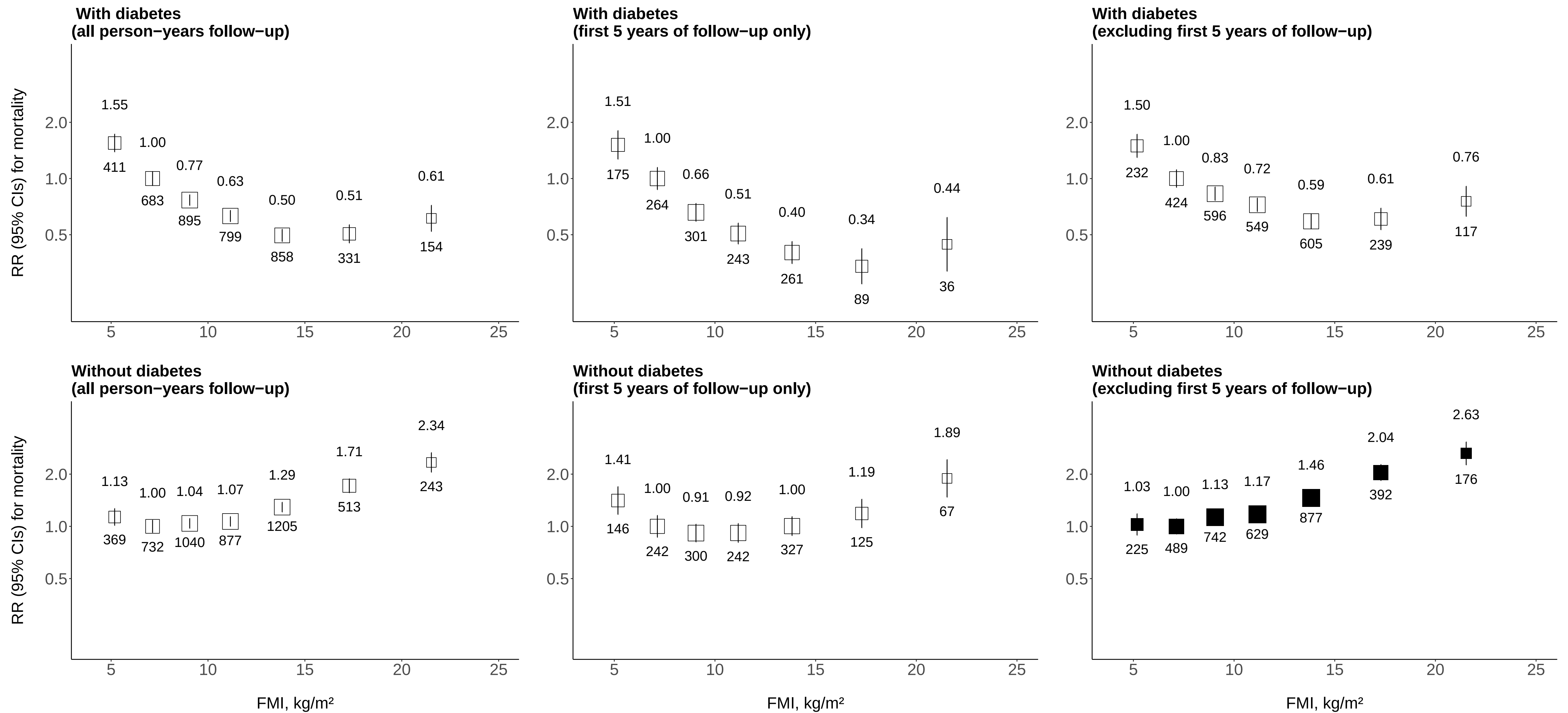
*The number of deaths attributable to the excess risk associated with BMI ≥ 30 kg/m² was calculated as the sum of the fraction of events in the population that is attributable to a BMI of 30-39 and 40-60 kg/m² respectively, as number of deaths attributable to the excess risk associated with that level of adiposity $\times (RR-1)/RR$, where the RR is the cause specific death RR for that group, relative to those with usual BMI of 20-25 kg/m². For example, the total vascular-metabolic mortality attributed to a BMI of 30 or more was estimated as $100 \times ([692 \times 0.53/1.53] + [89 \times 1.64/2.64]) / (1646)$.

S40. Comparative associations of FMI, waist circumference and WHR to all-cause mortality at ages 35–74 years, including those with previously-diagnosed or screen-detected diabetes at baseline and all person-years of follow-up



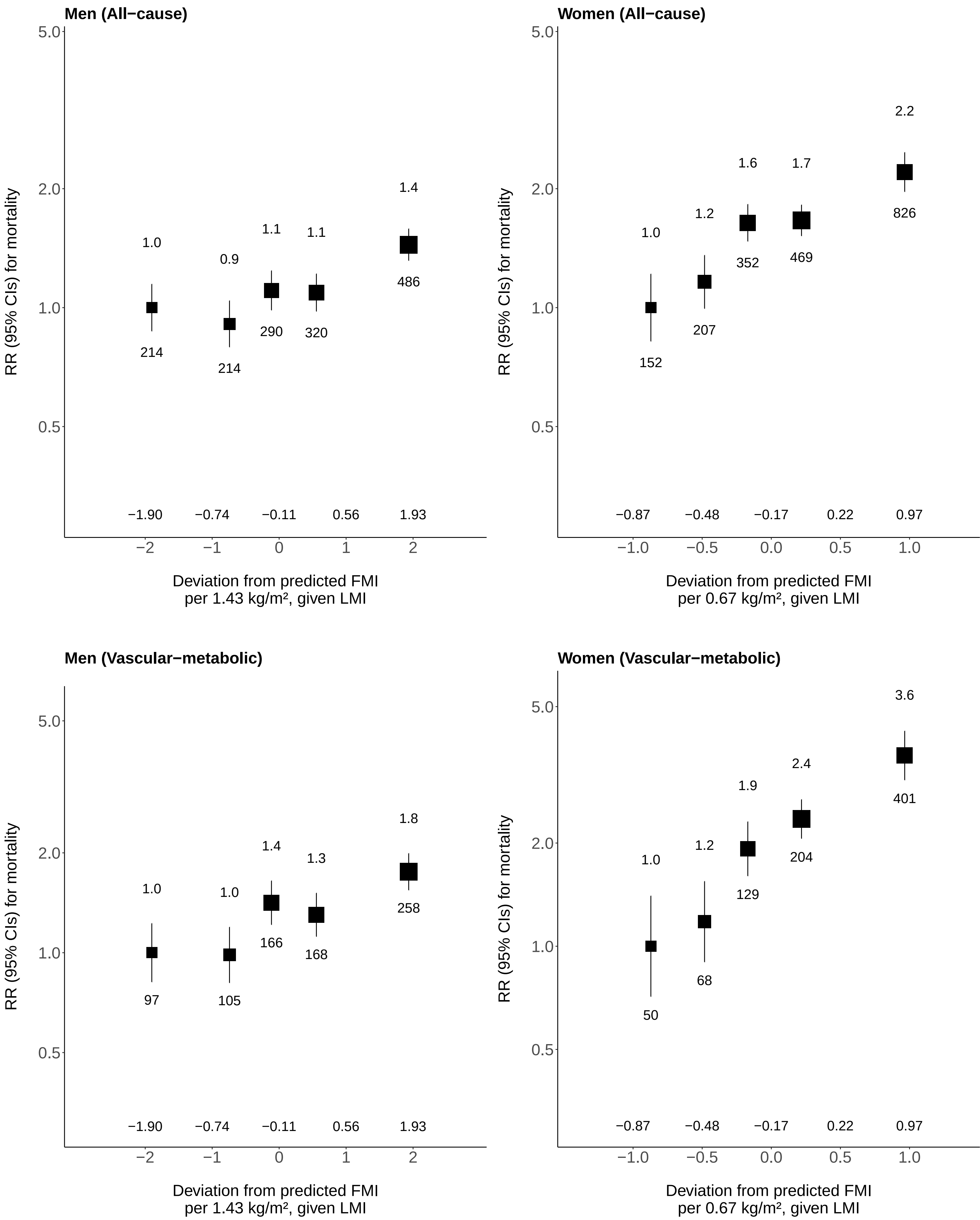
Analyses as per figure 5.1, except for diabetes history and the different follow-up exclusions.

**S41. Associations of predicted FMI to all-cause mortality at ages 35–74 years,
in those with and without previously-diagnosed or screen-detected diabetes at baseline, by total and early follow-up**



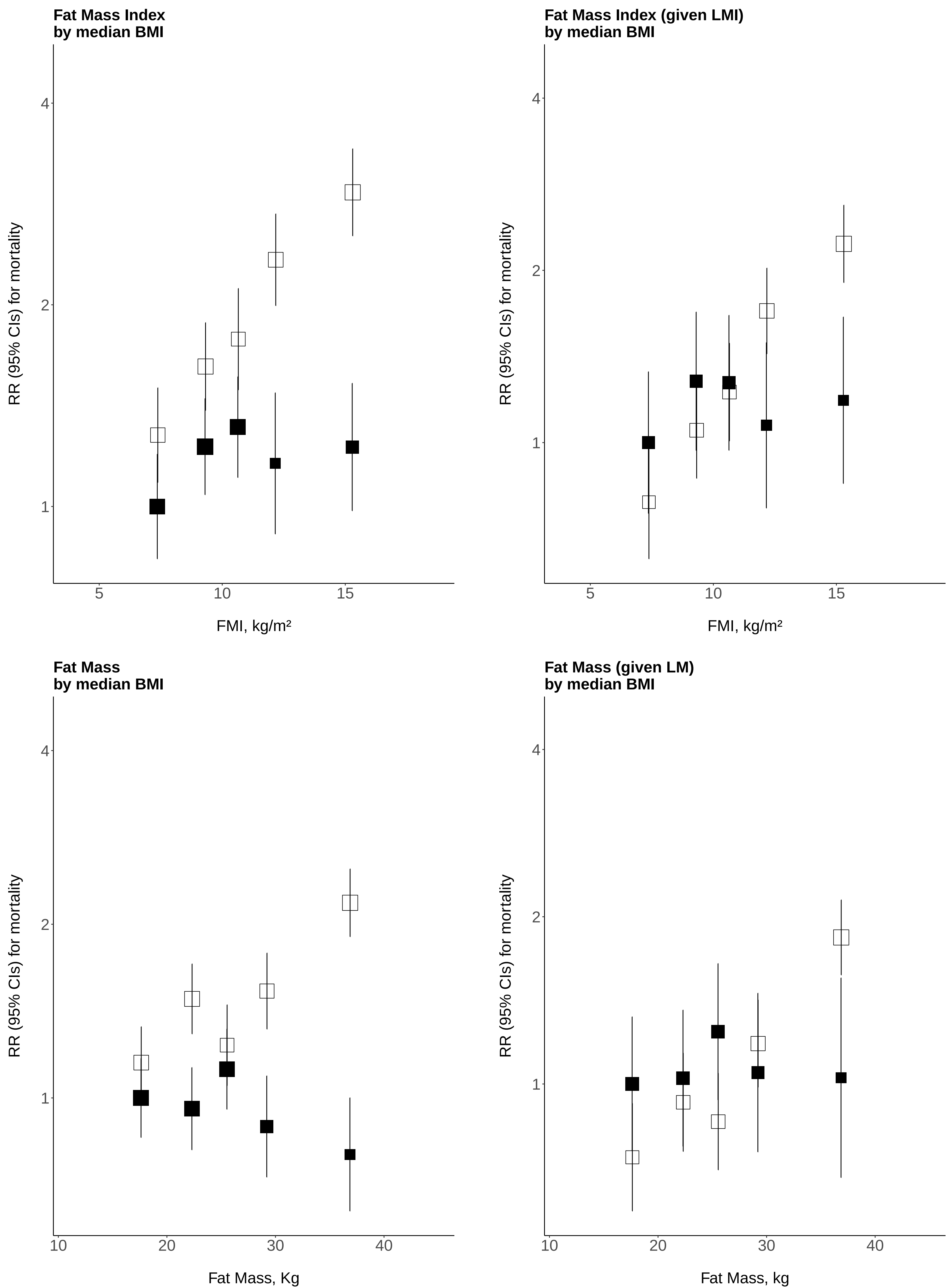
Analyses as per figure 5.2.

S42: Sex-specific relevance of predicted residuals of FMI to all-cause and vascular-metabolic mortality at ages 40–74 years



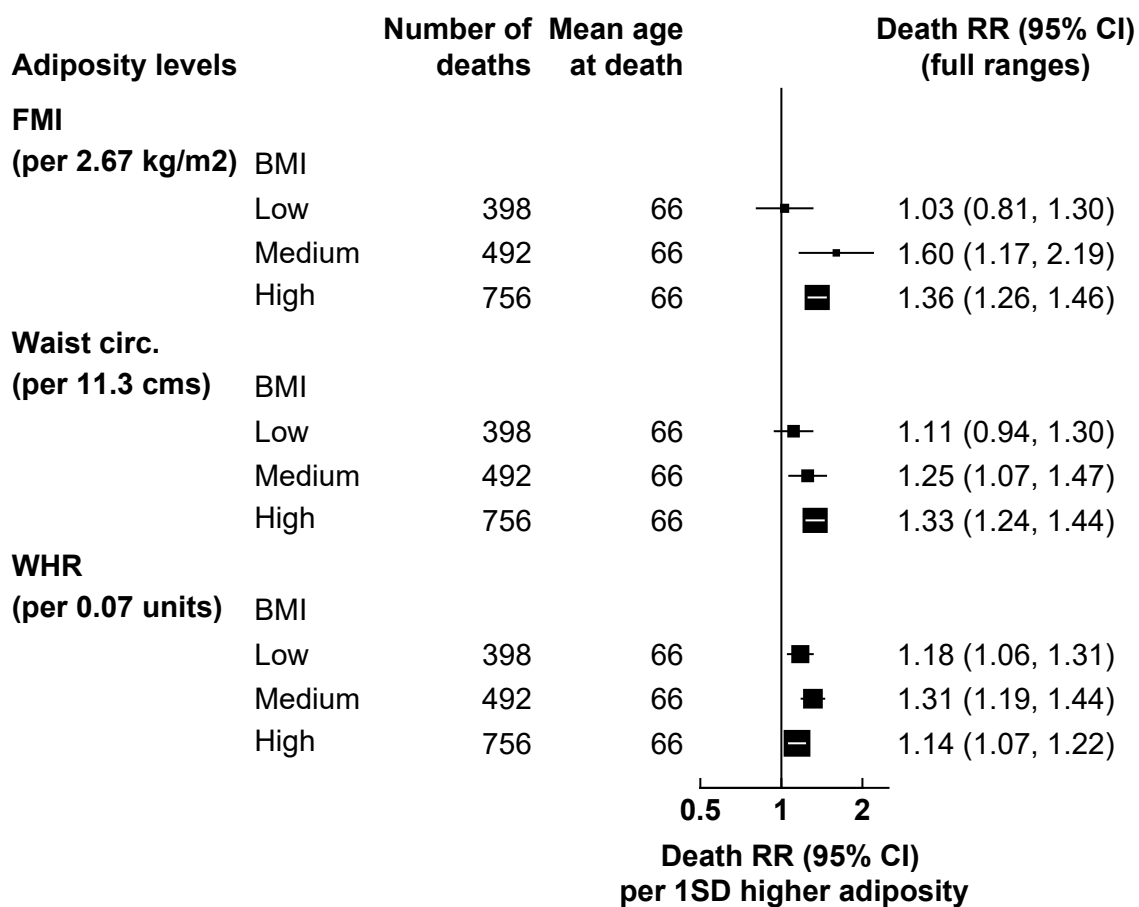
Analyses with residuals estimated from the regression of fat and lean mass indices, grouped by the 5-equal groups (quintiles) of the sex-specific distributions at baseline. X-axes extend over an equal degree of the deviations from the mean, as indicated in each plot. Conventions and exclusions as per figure 6.1.

S43: Relevance of predicted FMI and FM by median BMI, to vascular-metabolic mortality at ages40–74 years



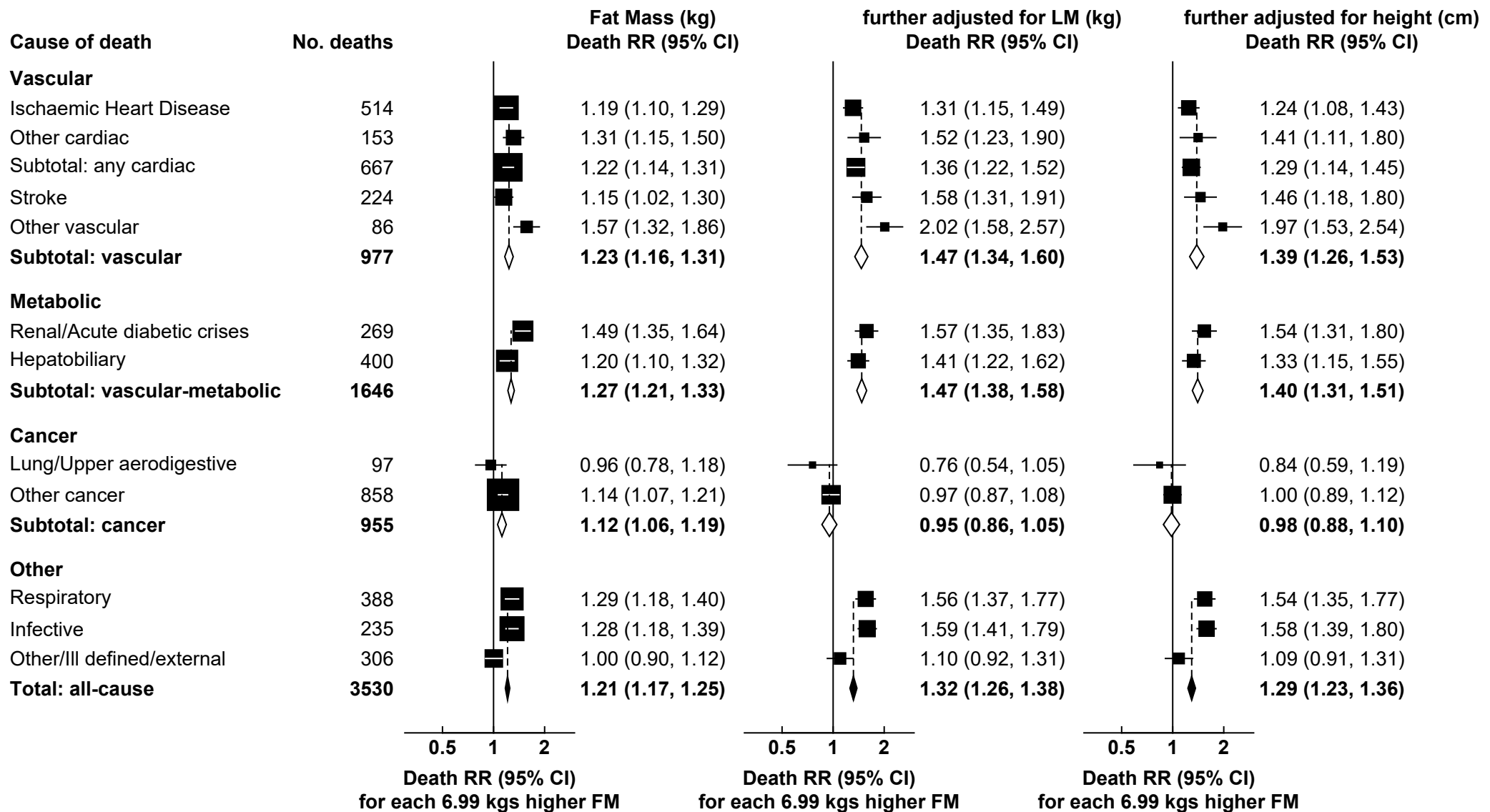
White squares represent the estimates for each adiposity marker above the median of BMI, as indicated in the plot. Analyses and conventions as per Figure 6.1.

S44: Relevance of equivalent sex-specific units of selected markers of adiposity to vascular-metabolic mortality at ages 40-74 years by different levels of BMI



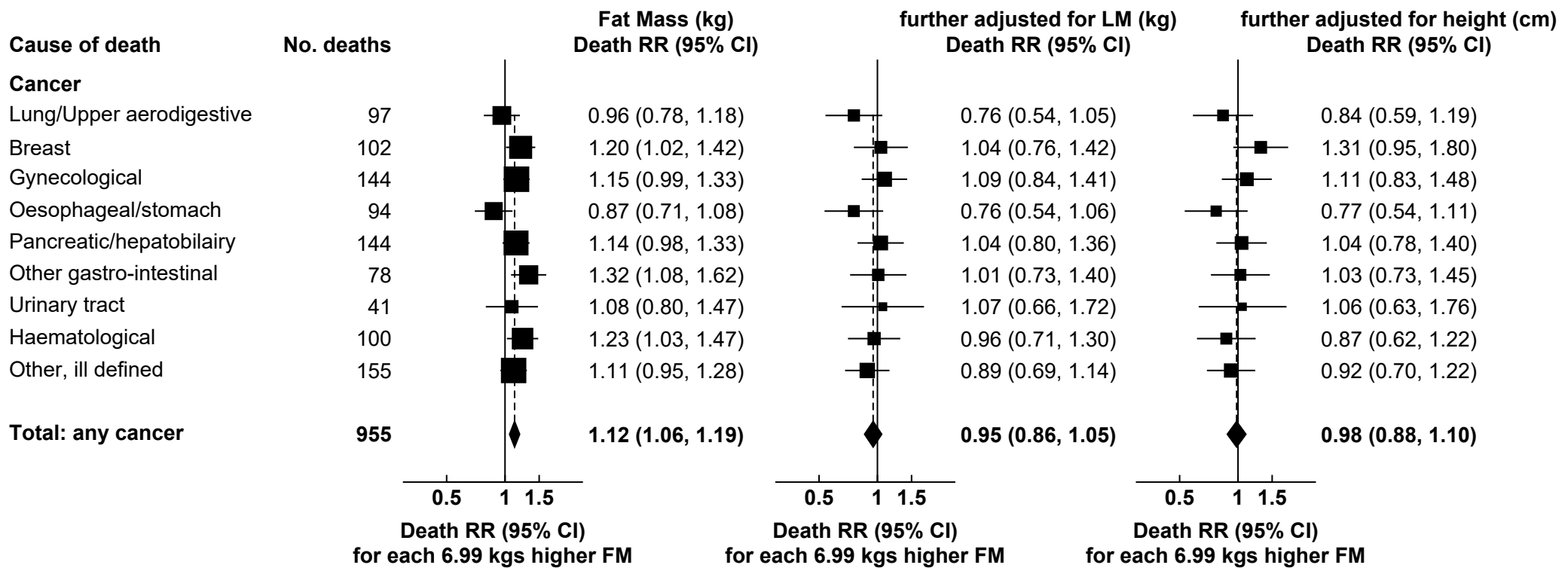
Analyses as per Figure 5.1. BMI levels represent the sex-specific tertiles of the baseline distributions, across the full ranges .

S45. Fat mass and cause-specific mortality at ages 40-74 years



Analyses as per Figure 6.8.

S46. Fat mass and cancer-specific mortality at ages 40-74 years



Analyses as per Figure 6.8.

**S47: Overall associations of FMI with deaths at ages 40-74 years by cause
(includes those with previously-diagnosed diabetes and HbA1c<7%)**

Cause death	Fat Mass Index, kg/m ²	
	No deaths	RR per 1SD (95% CIs)
Vascular		
Ischaemic Heart Disease	582	1.20 (1.11-1.30)
Other cardiac	162	1.32 (1.17-1.50)
Subtotal: any cardiac	744	1.23 (1.15-1.32)
Stroke	243	1.16 (1.04-1.30)
Other vascular	92	1.56 (1.33-1.84)
Subtotal: vascular	1079	1.24 (1.18-1.31)
Metabolic		
Renal/Acute diabetic crises	371	1.30 (1.19-1.42)
Hepatobiliary	420	1.27 (1.16-1.39)
Subtotal: any vascular- metabolic	1870	1.26 (1.21-1.31)
Cancer		
Lung/Upper aero-digestive	102	0.93 (0.76-1.14)
Breast	105	1.14 (0.98-1.33)
Gynaecological	146	1.11 (0.96-1.28)
Oesophageal/stomach	101	0.85 (0.69-1.05)
Pancreatic/hepatobiliary	155	1.06 (0.92-1.23)
Other gastro-intestinal	83	1.25 (1.03-1.53)
Urinary tract	43	1.04 (0.77-1.41)
Haematological	101	1.19 (1.00-1.42)
Other/III-defined	157	1.06 (0.92-1.23)
Subtotal: any cancer	993	1.07 (1.01-1.14)
Other		
Respiratory	428	1.27 (1.17-1.38)
Infective	258	1.28 (1.19-1.38)
Other/III-defined/external	326	1.05 (0.94-1.16)
Total: all-cause	3875	1.20 (1.16-1.23)

Excludes other chronic disease at baseline and the first 5 years of follow-up.

S48: Usual levels of general and central adiposity versus cause-specific mortality at ages 40-74 years (excludes previously-diagnosed diabetes, those with HbA1c $\geq 7\%$ and the first 5 years of follow-up)

Cause of death	No. deaths	BMI per 4.31 kg/m ²	FMI per 2.67 kg/m ²	Waist circ. per 10.03 cms	WHR per 0.05 units	WHtR per 0.05 units
Vascular						
Ischaemic Heart Disease	514	1.25 (1.13-1.39)	1.24 (1.14-1.35)	1.26 (1.15-1.38)	1.26 (1.15-1.39)	1.31 (1.20-1.43)
Other cardiac	153	1.51 (1.29-1.76)	1.34 (1.17-1.53)	1.36 (1.17-1.59)	1.19 (1.00-1.43)	1.38 (1.19-1.61)
Subtotal: any cardiac	667	1.32 (1.21-1.44)	1.27 (1.18-1.36)	1.28 (1.19-1.39)	1.25 (1.14-1.36)	1.33 (1.23-1.43)
Stroke	224	1.19 (1.03-1.39)	1.21 (1.07-1.36)	1.27 (1.11-1.46)	1.27 (1.10-1.47)	1.35 (1.18-1.53)
Other vascular	86	1.82 (1.49-2.21)	1.66 (1.40-1.97)	1.70 (1.40-2.06)	1.25 (0.99-1.59)	1.75 (1.45-2.12)
Subtotal: vascular	977	1.33 (1.24-1.43)	1.29 (1.21-1.36)	1.32 (1.23-1.40)	1.25 (1.17-1.35)	1.37 (1.28-1.46)
Metabolic						
Renal/Acute diabetic crises	269	1.54 (1.37-1.73)	1.50 (1.36-1.66)	1.56 (1.40-1.75)	1.33 (1.16-1.51)	1.56 (1.39-1.74)
Hepatobiliary	400	1.33 (1.19-1.49)	1.29 (1.18-1.42)	1.29 (1.17-1.43)	1.32 (1.18-1.47)	1.38 (1.25-1.52)
Subtotal: any vascular-metabolic	1646	1.37 (1.30-1.44)	1.32 (1.27-1.38)	1.35 (1.29-1.42)	1.28 (1.21-1.35)	1.40 (1.34-1.47)
Cancer						
Lung/Upper aero-digestive	97	1.10 (0.83-1.45)	0.91 (0.73-1.13)	0.95 (0.76-1.19)	0.89 (0.70-1.13)	0.88 (0.70-1.10)
Other cancer	858	1.15 (1.06-1.24)	1.09 (1.02-1.16)	1.14 (1.06-1.22)	1.09 (1.01-1.18)	1.08 (1.01-1.16)
Subtotal: any cancer	955	1.14 (1.06-1.24)	1.07 (1.01-1.14)	1.12 (1.04-1.20)	1.07 (0.99-1.15)	1.06 (0.99-1.13)
Other						
Respiratory	388	1.45 (1.31-1.61)	1.31 (1.20-1.43)	1.39 (1.26-1.54)	1.31 (1.17-1.46)	1.43 (1.30-1.57)
Infective	235	1.45 (1.27-1.65)	1.35 (1.21-1.51)	1.46 (1.29-1.65)	1.35 (1.18-1.54)	1.48 (1.31-1.67)
Other/III-defined/external	306	1.18 (1.03-1.36)	1.03 (0.92-1.16)	1.03 (0.91-1.17)	1.00 (0.87-1.14)	1.07 (0.95-1.21)
Total: all-cause	3530	1.31 (1.26-1.36)	1.23 (1.19-1.27)	1.27 (1.23-1.31)	1.20 (1.16-1.25)	1.28 (1.24-1.33)

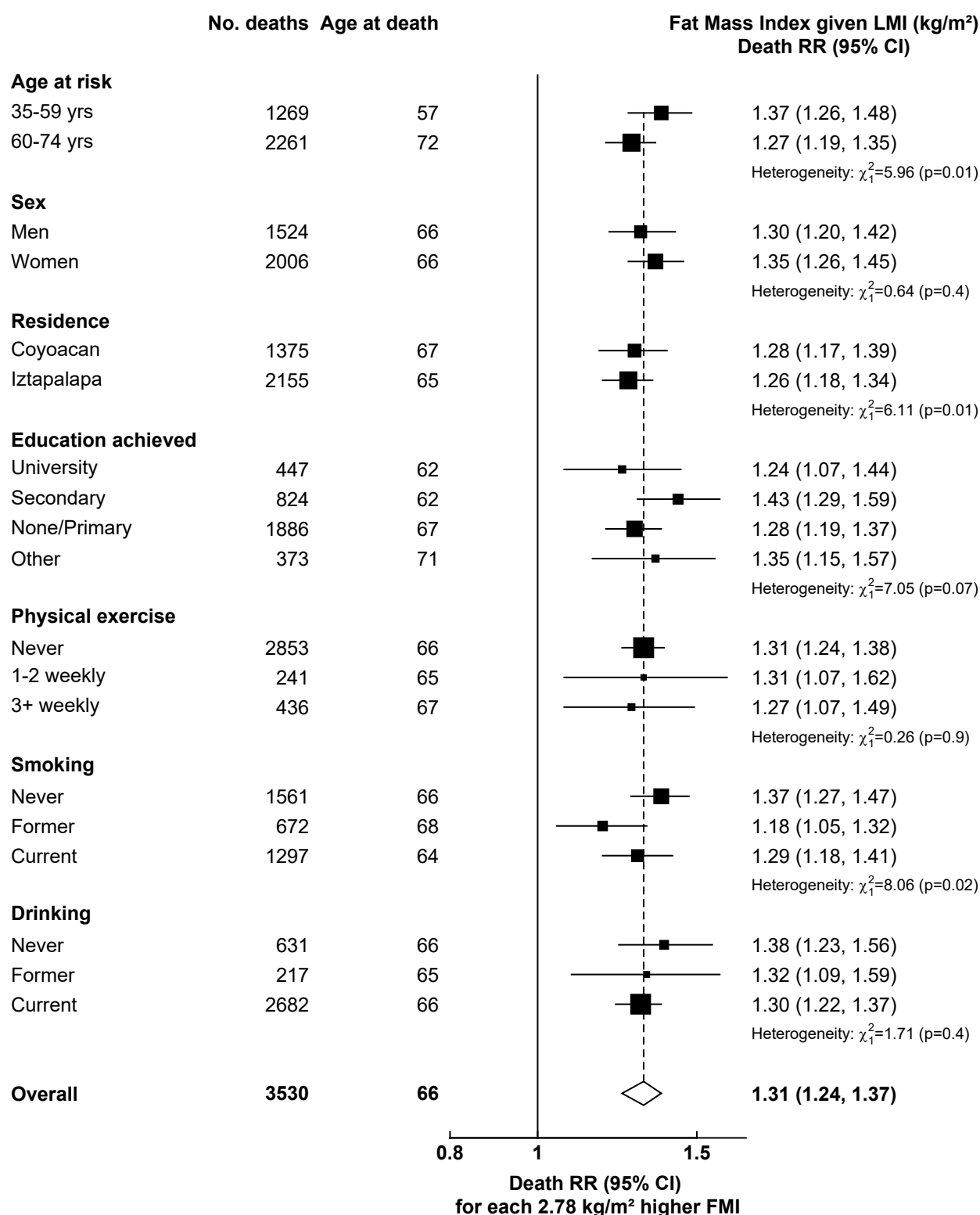
Estimates represent death RRs for comparable sex-specific differences per one usual SD increase for each adiposity marker across the full ranges studied (except for BMI, which included only those with 25 to 60 kg/m²), corrected for regression dilution ratios of 0.89 for BMI, 0.92 for FMI, 0.85 for WC, 0.74 for WHR and 0.88 for WHtR (calculated as the ratio of mid-point values at resurvey to baseline values). Adjustment for confounders and exclusions are as per main analyses of mortality (see details on the footnote of Figure 5.1). The RR for any vascular-metabolic deaths across the full ranges of BMI was 1.25 (1.19-1.31) and 1.18 (1.14-1.22) for any cause of death. BMI = Body Mass Index; FMI = Fat Mass Index; WHR = Waist-hip ratio; WHtR = Waist-height ratio.

S49: Independent relevance of usual levels of general and central adiposity to cause-specific mortality at ages 40-74 years (excludes previously-diagnosed diabetes, those with HbA1c $\geq 7\%$ and the first 5 years of follow-up)

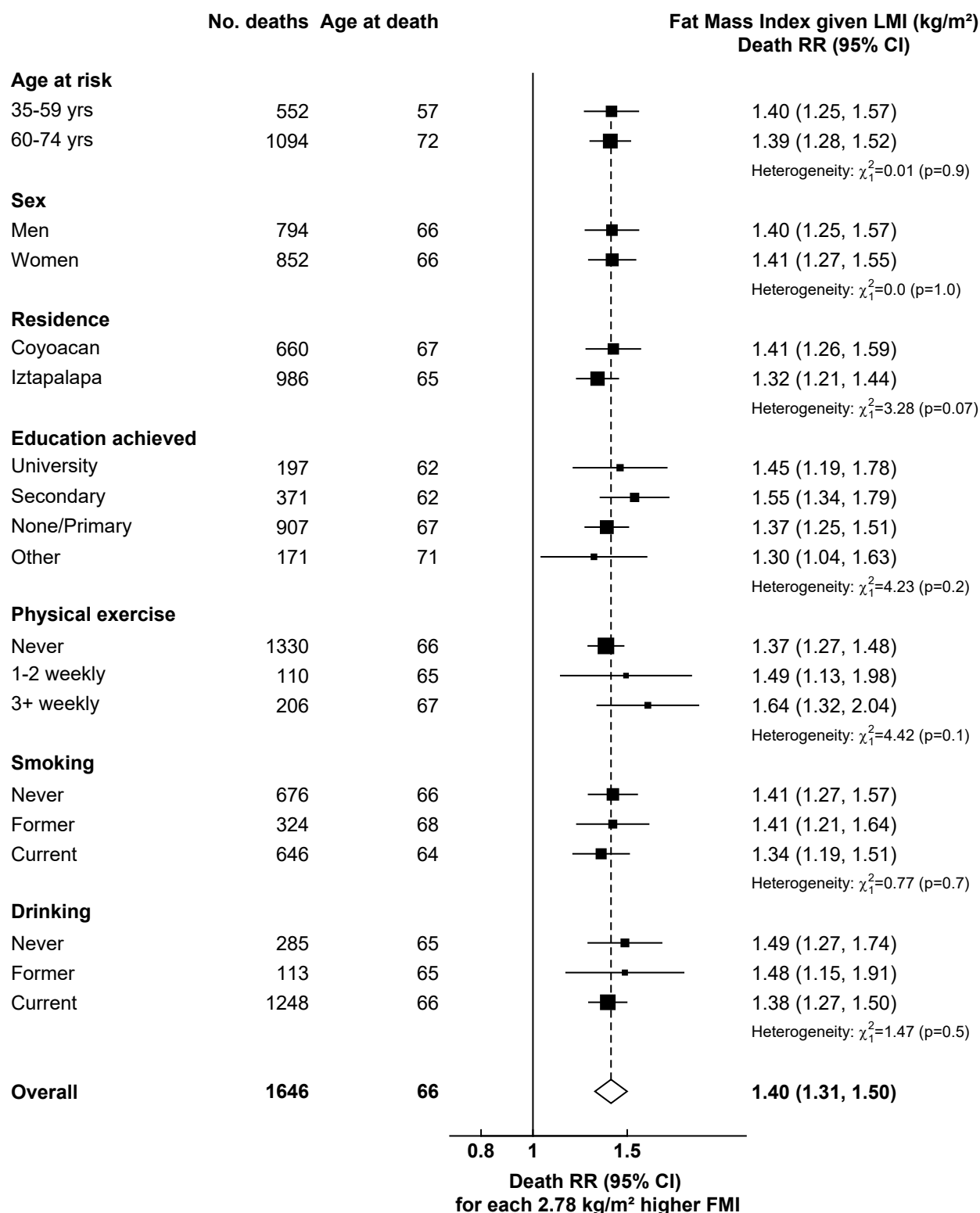
Cause of death	No. deaths	BMI per 4.31 kg/m ² (given WHR)	FMI per 2.67 kg/m ² (given LMI)	Waist circ. per 10.03 cms (given BMI, HC)	WHR per 0.05 units (given BMI)	WHtR per 0.05 units (given weight, HC)
Vascular						
Ischaemic Heart Disease	514	1.21 (1.09-1.35)	1.27 (1.11-1.46)	1.32 (1.14-1.54)	1.21 (1.09-1.34)	1.40 (1.24-1.59)
Other cardiac	153	1.50 (1.28-1.76)	1.42 (1.13-1.78)	1.35 (1.05-1.74)	1.14 (0.95-1.37)	1.38 (1.12-1.71)
Subtotal: any cardiac	667	1.29 (1.18-1.41)	1.31 (1.17-1.48)	1.33 (1.17-1.52)	1.19 (1.09-1.30)	1.40 (1.26-1.56)
Stroke	224	1.16 (1.00-1.36)	1.32 (1.07-1.63)	1.29 (1.03-1.61)	1.22 (1.05-1.42)	1.53 (1.28-1.83)
Other vascular	86	1.79 (1.47-2.19)	2.28 (1.81-2.85)	2.09 (1.60-2.72)	1.21 (0.95-1.55)	1.85 (1.44-2.38)
Subtotal: vascular	977	1.30 (1.21-1.40)	1.41 (1.28-1.55)	1.39 (1.26-1.55)	1.20 (1.11-1.29)	1.47 (1.35-1.61)
Metabolic						
Renal/Acute diabetic crises	269	1.50 (1.33-1.69)	1.55 (1.32-1.82)	1.47 (1.23-1.77)	1.19 (1.03-1.37)	1.45 (1.24-1.70)
Hepatobiliary	400	1.26 (1.12-1.42)	1.34 (1.16-1.56)	1.34 (1.14-1.59)	1.25 (1.12-1.41)	1.53 (1.33-1.75)
Subtotal: any vascular-metabolic	1646	1.33 (1.26-1.40)	1.42 (1.32-1.53)	1.40 (1.29-1.51)	1.21 (1.14-1.28)	1.48 (1.39-1.58)
Cancer						
Lung/Upper aero-digestive	97	1.09 (0.82-1.45)	0.86 (0.59-1.25)	0.95 (0.65-1.39)	0.92 (0.72-1.18)	0.77 (0.56-1.06)
Other cancer	858	1.13 (1.05-1.23)	0.97 (0.86-1.10)	1.13 (1.00-1.27)	1.07 (0.98-1.16)	0.96 (0.87-1.07)
Subtotal: any cancer	955	1.13 (1.05-1.22)	0.96 (0.86-1.08)	1.11 (0.99-1.25)	1.05 (0.97-1.14)	0.94 (0.86-1.04)
Other						
Respiratory	388	1.42 (1.27-1.58)	1.59 (1.39-1.83)	1.67 (1.44-1.94)	1.27 (1.14-1.43)	1.63 (1.43-1.85)
Infective	235	1.41 (1.23-1.61)	1.64 (1.38-1.95)	1.66 (1.39-1.99)	1.31 (1.13-1.50)	1.56 (1.33-1.84)
Other/III-defined/external	306	1.17 (1.02-1.36)	1.23 (1.02-1.49)	1.13 (0.92-1.39)	1.02 (0.89-1.18)	1.14 (0.96-1.35)
Total: all-cause	3530	1.28 (1.23-1.33)	1.32 (1.25-1.39)	1.35 (1.27-1.42)	1.16 (1.12-1.21)	1.32 (1.26-1.38)

Analyses as per S48. Estimates for each adiposity marker were further adjusted for other markers (as stated in the table) grouped as five-equal groups of the sex-specific distributions at baseline. The RR for vascular-metabolic deaths across the full ranges of BMI was 1.05 (0.97-1.13), and 1.05 (1.00-1.12) for any cause of death. LMI = Lean Mass Index; HC = Hip circumference.

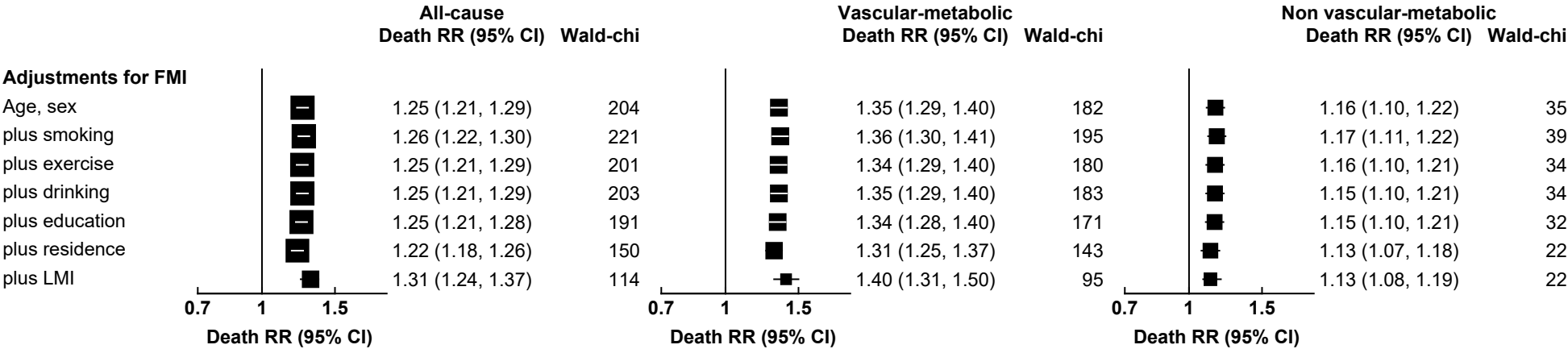
S50. Relevance of FMI to all-cause mortality at ages 40-74 years, by strata of confounders



S51. Relevance of FMI to vascular-metabolic mortality at ages 40-74 years, by strata of confounders

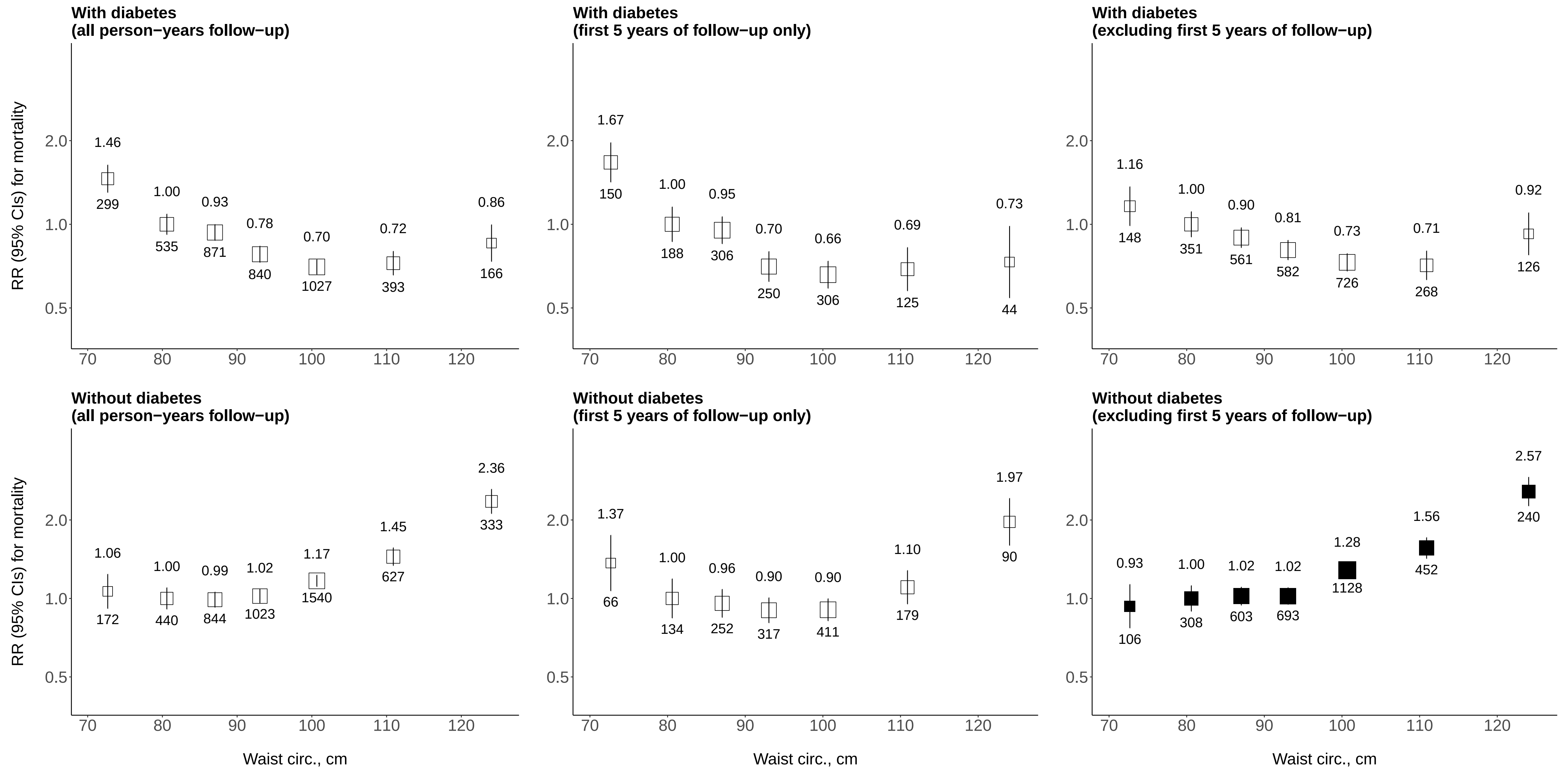


S52: Relevance of each 2.78 kg/m² higher FMI to mortality at ages 40-74 years, with progressive adjustment for baseline confounders



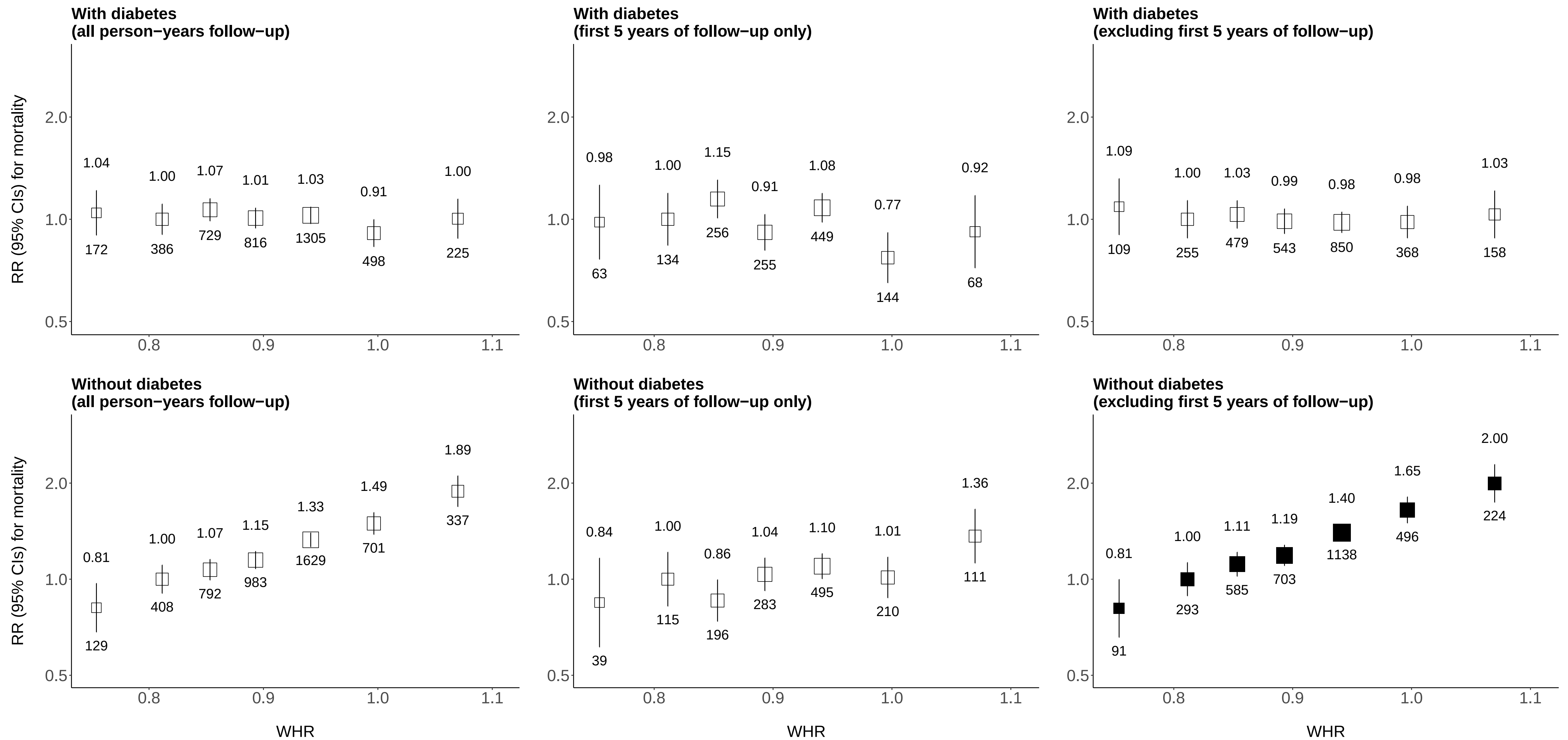
Analyses as per Figure 6.6.

**S53. Associations of waist circumference to all-cause mortality at ages 35–74 years,
in those with and without previously-diagnosed or screen-detected diabetes at baseline, by total and early follow-up**



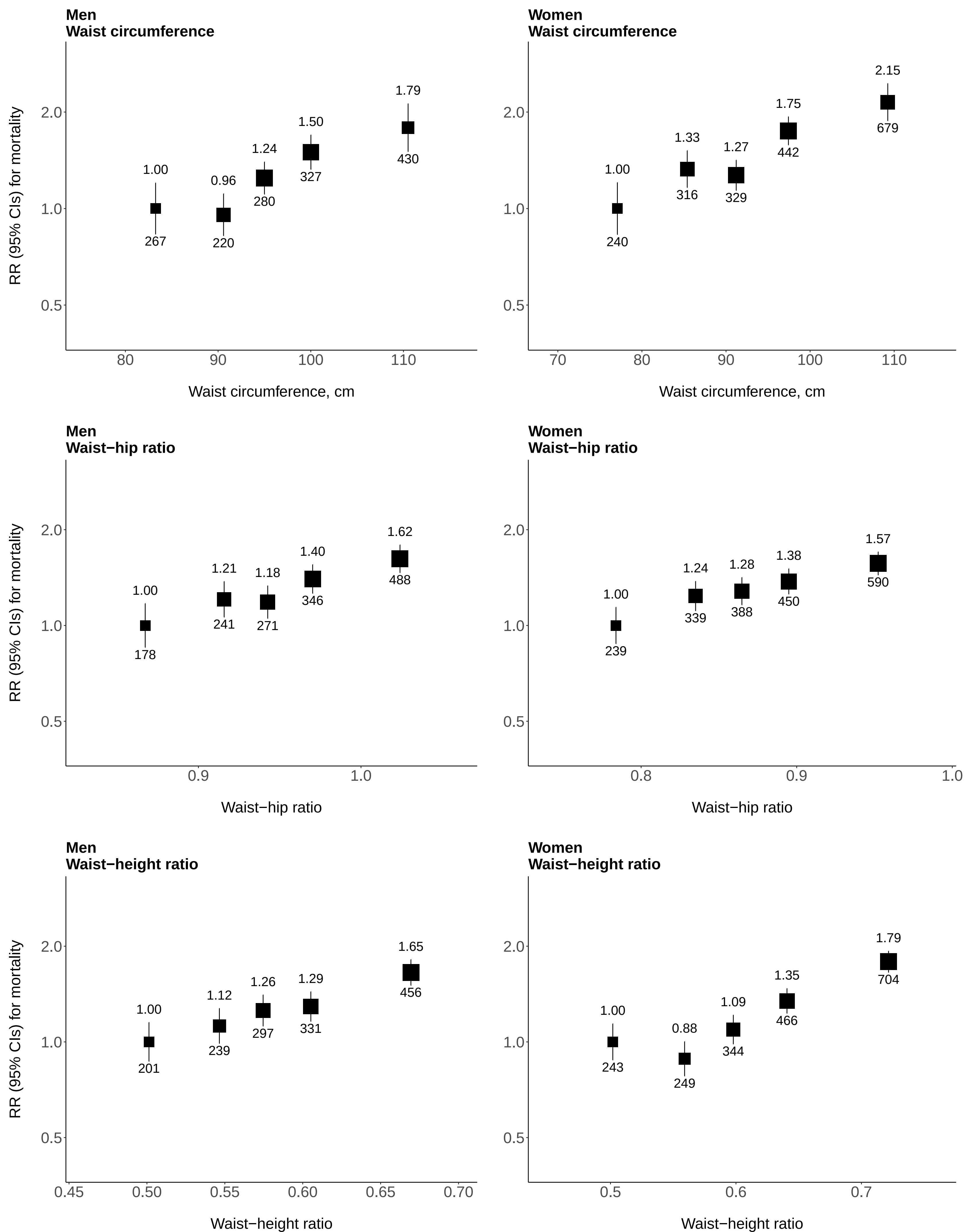
Analyses as per Figure 5.2 (chapter 5).

**S54. Associations of WHR to all-cause mortality at ages 35–74 years,
in those with and without previously-diagnosed or screen-detected diabetes at baseline, by total and early follow-up**



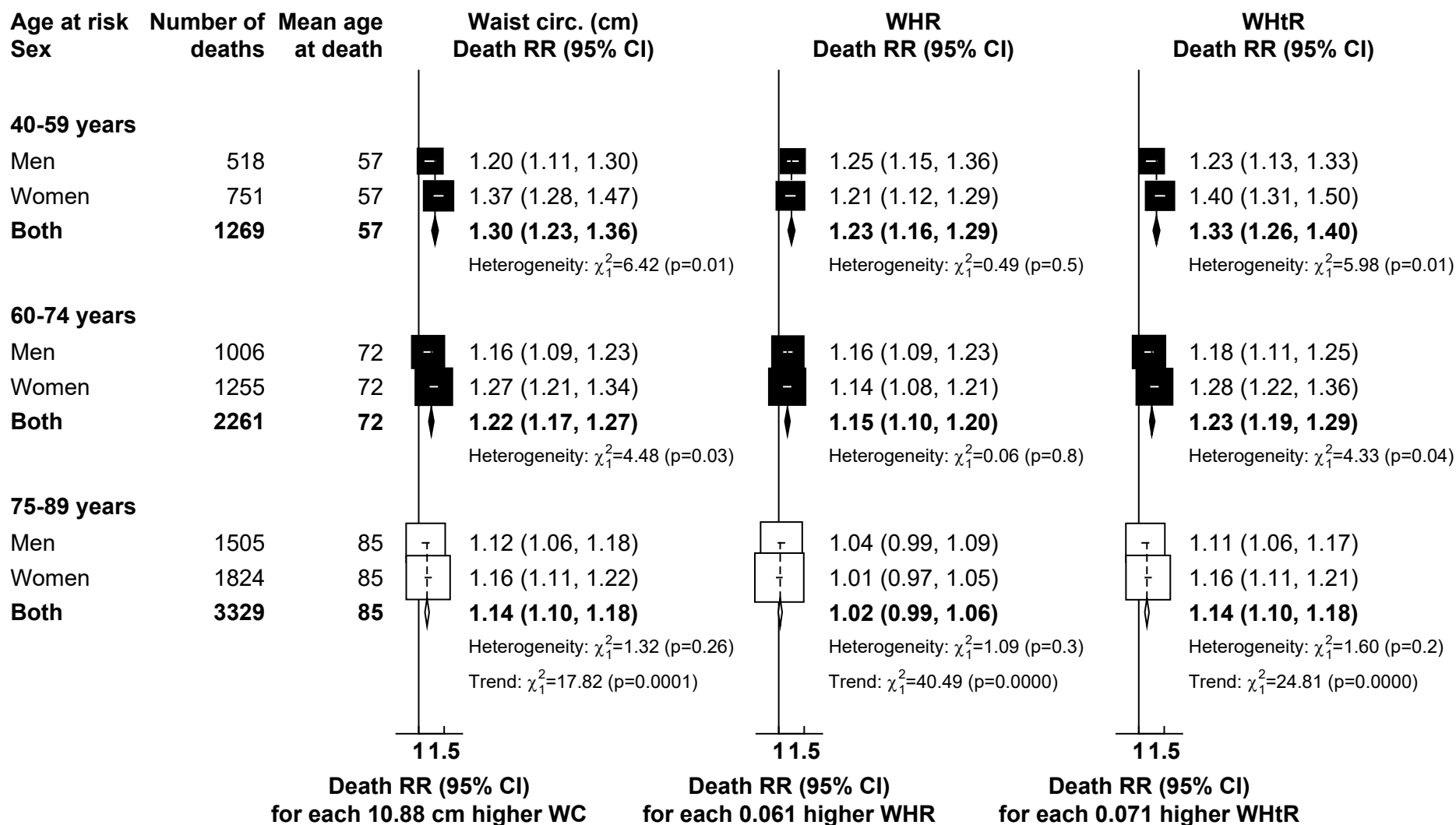
Analyses as per Figure 5.2 (chapter 5).

**S55: Sex-specific relevance of waist circumference, WHR and WHtR
to all-cause mortality at ages 40–74 years
(diabetes, those with HbA1C ≥7%, and the first 5 years of follow-up excluded)**



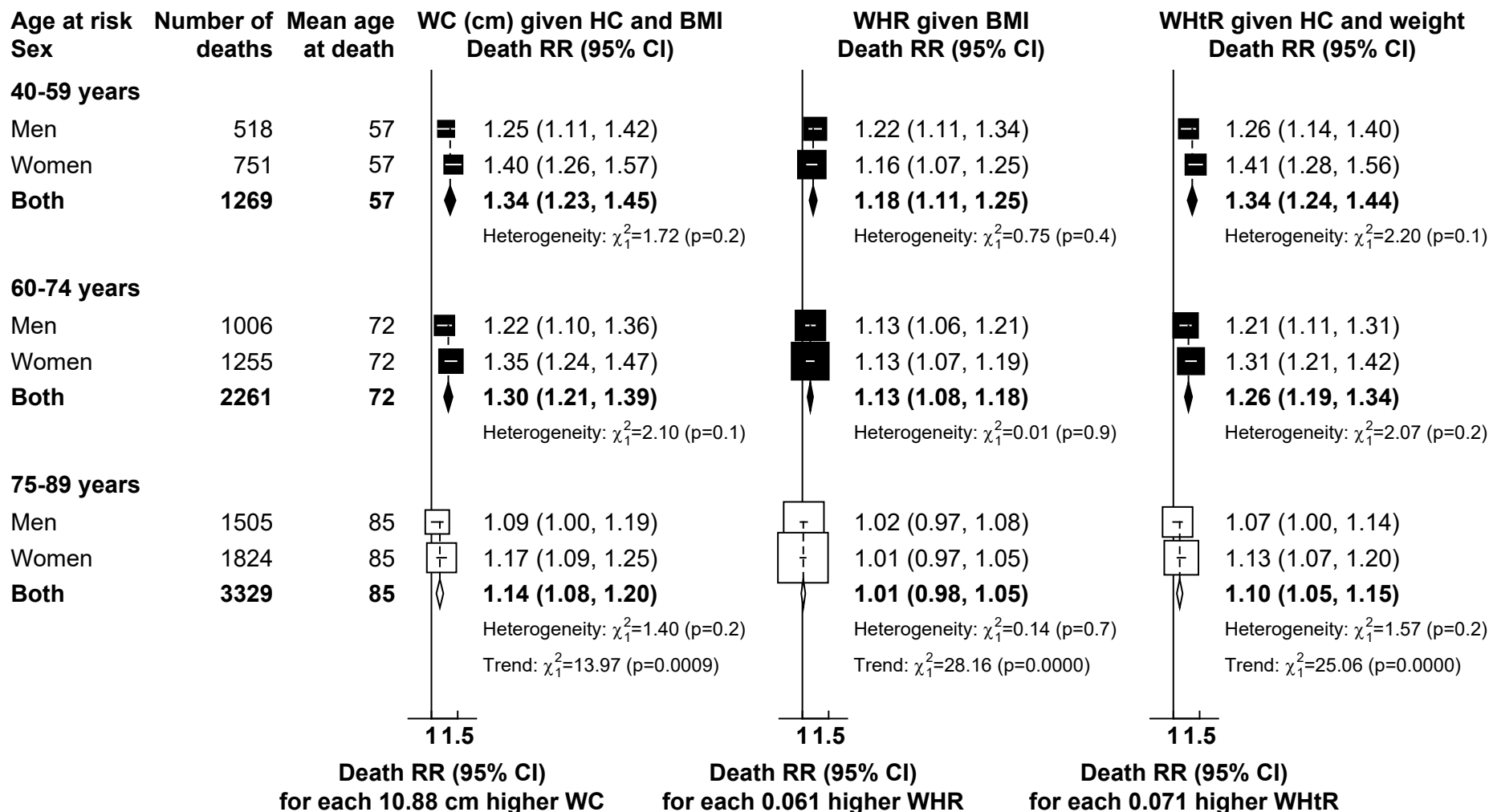
Analyses as per figure 7.1.

S56: Overall age and sex-specific relevance of waist circumference, WHR and WHtR to all-cause mortality



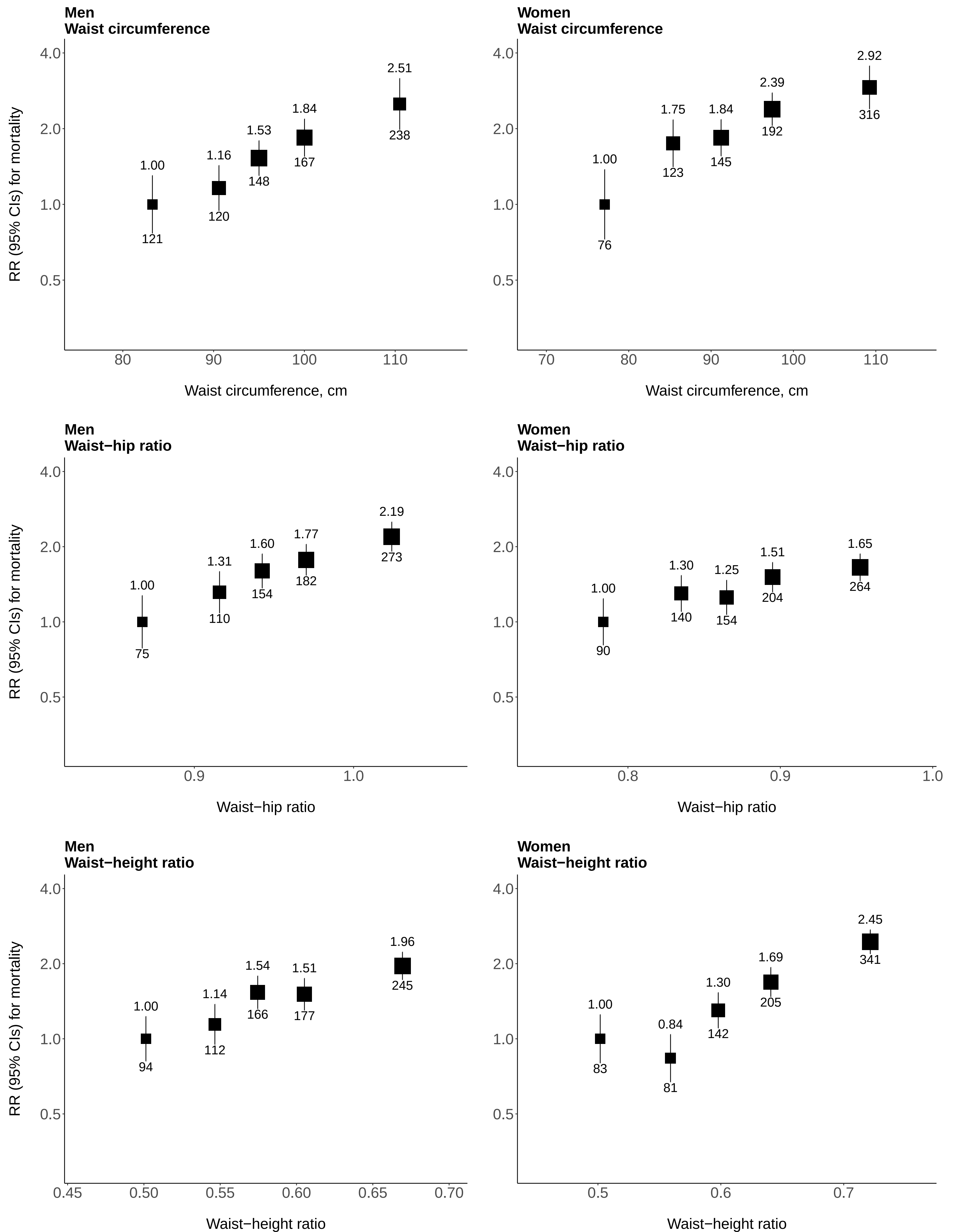
Analyses and conventions as per figure 7.1. Diamonds represent the values for men and women combined. The results for the oldest age group is left unshaded, as premature mortality at ages 40-74 years is of most interest.

S57: Independent age and sex-specific relevance of waist circumference, WHR and WHtR to all-cause mortality



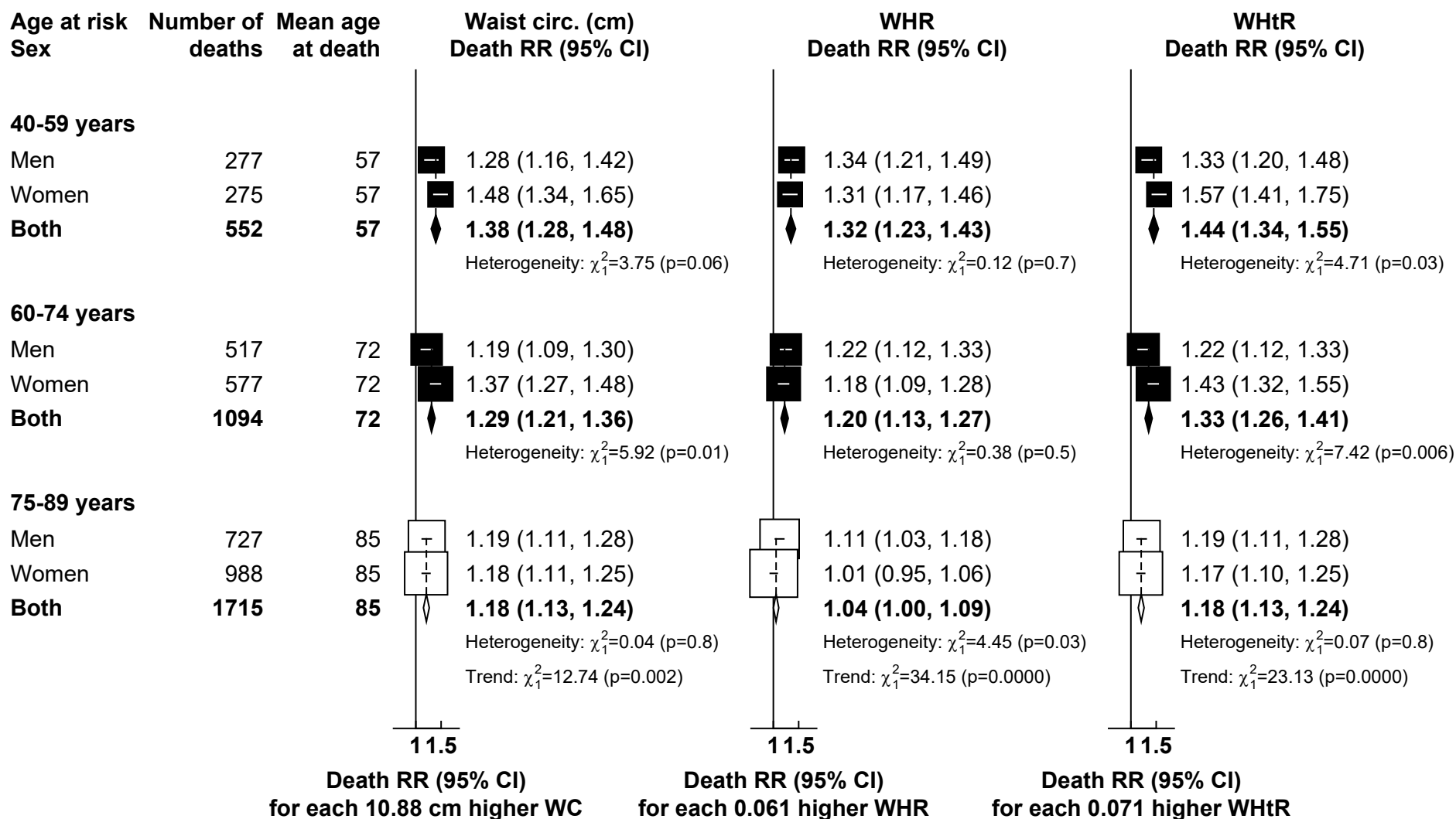
Analyses and conventions as per figure S56, with additional adjustment as indicate din the plot.

**S58: Sex-specific relevance of waist circumference, WHR and WHtR
to vascular-metabolic mortality at ages 40–74 years
(diabetes, those with HbA1C $\geq 7\%$, and the first 5 years of follow-up excluded)**



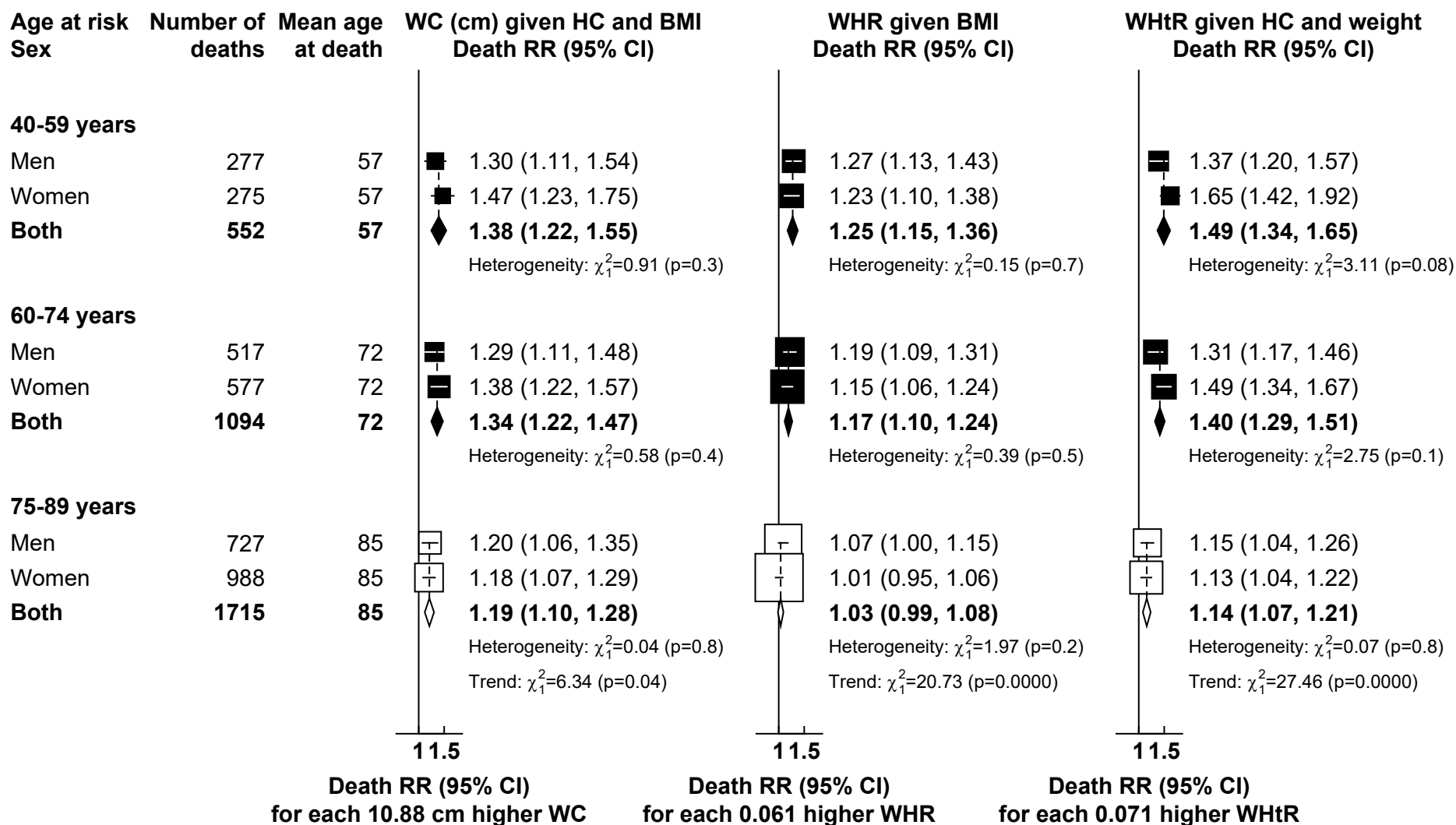
Analyses as per Figure 7.1.

S59: Overall age and sex-specific relevance of waist circumference, WHR and WHtR to vascular-metabolic mortality



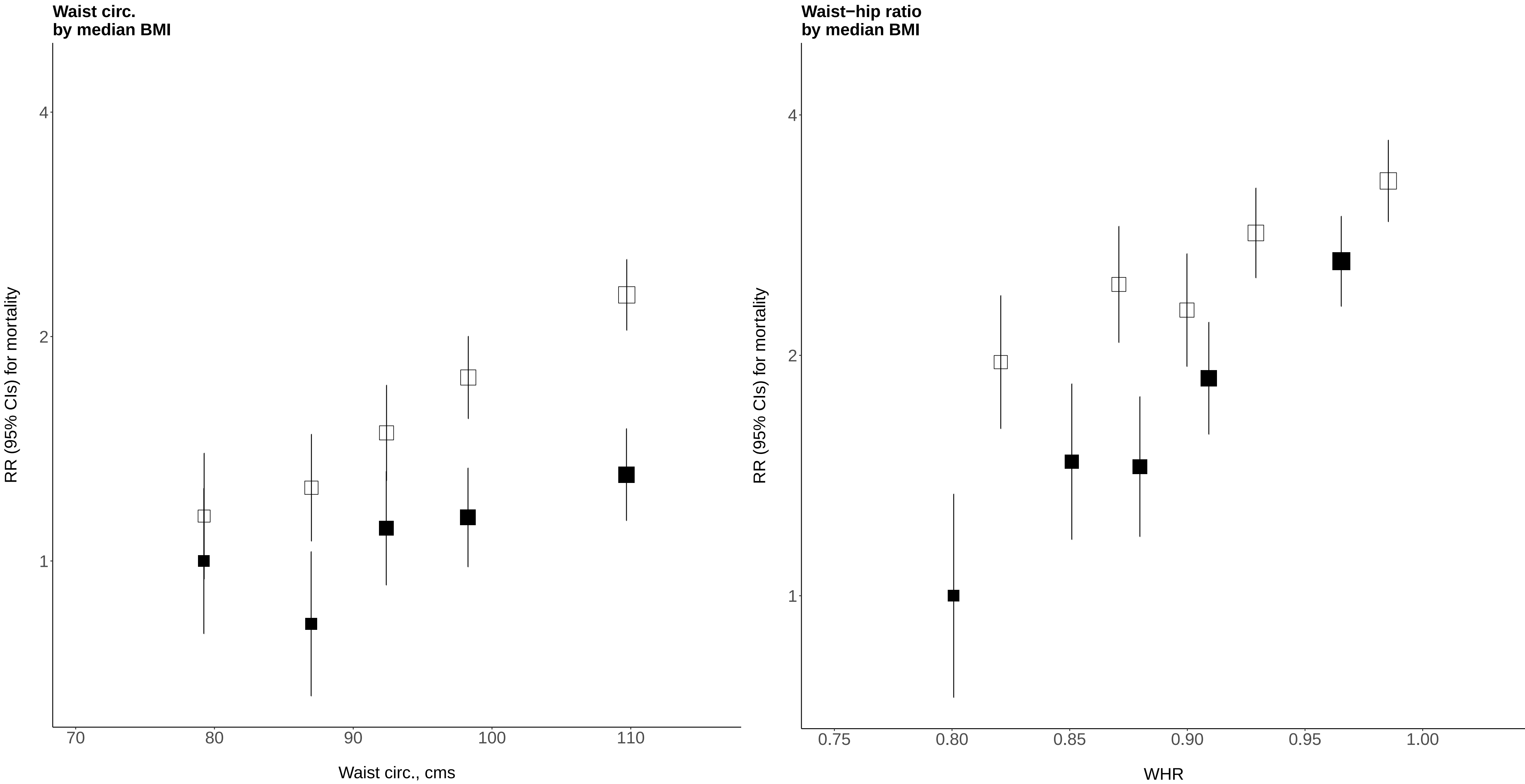
Analyses and conventions as per figure S56.

S60: Independent age and sex-specific relevance of waist circumference, WHR and WHtR to vascular-metabolic mortality



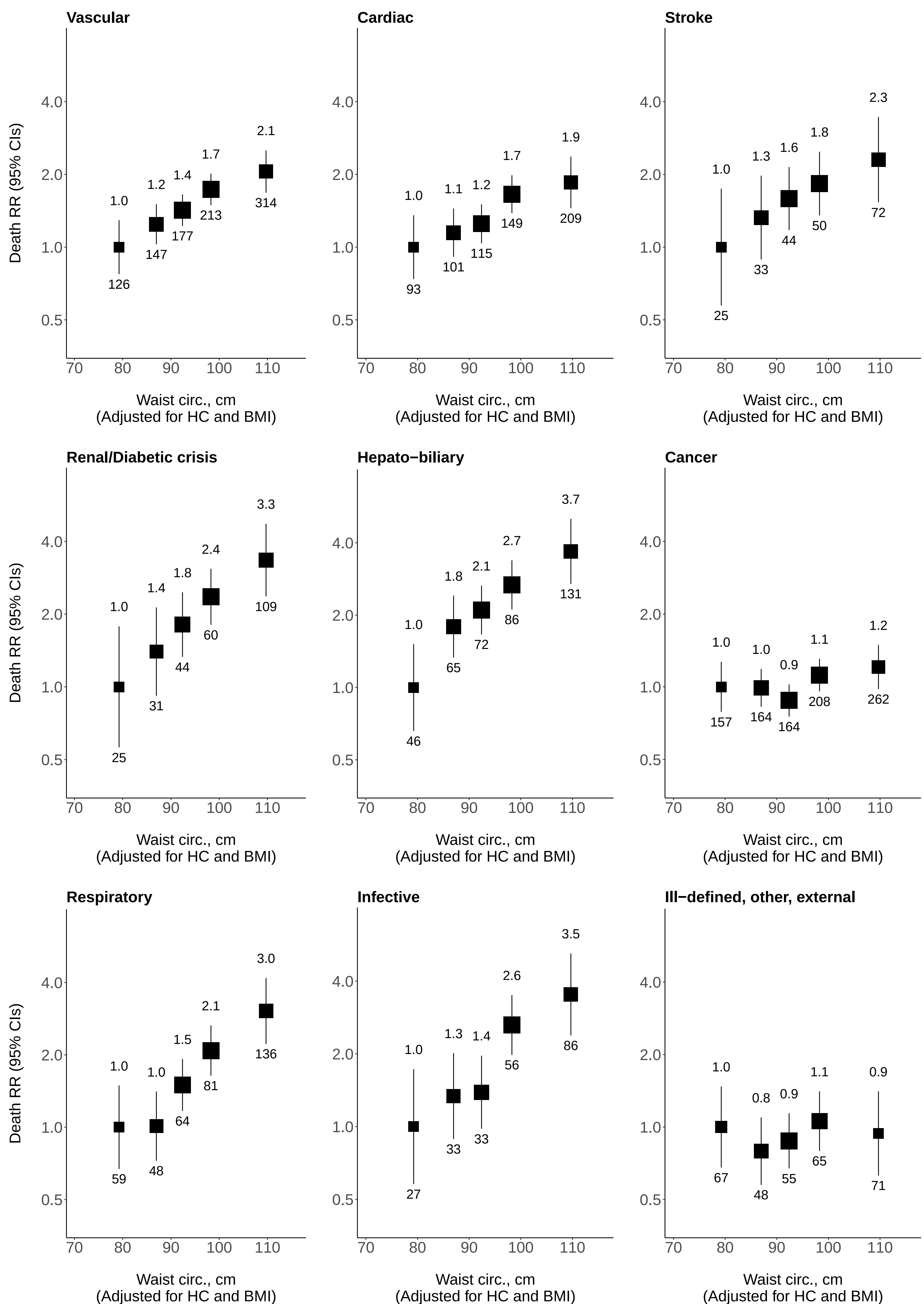
Analyses and conventions as per figure S56.

**S61: Relevance of selected markers of abdominal adiposity by median BMI, to vascular-metabolic mortality at ages 40–74 years
(excluding those with HbA1c $\geq 7\%$, diabetes, and the first 5 years of follow-up)**



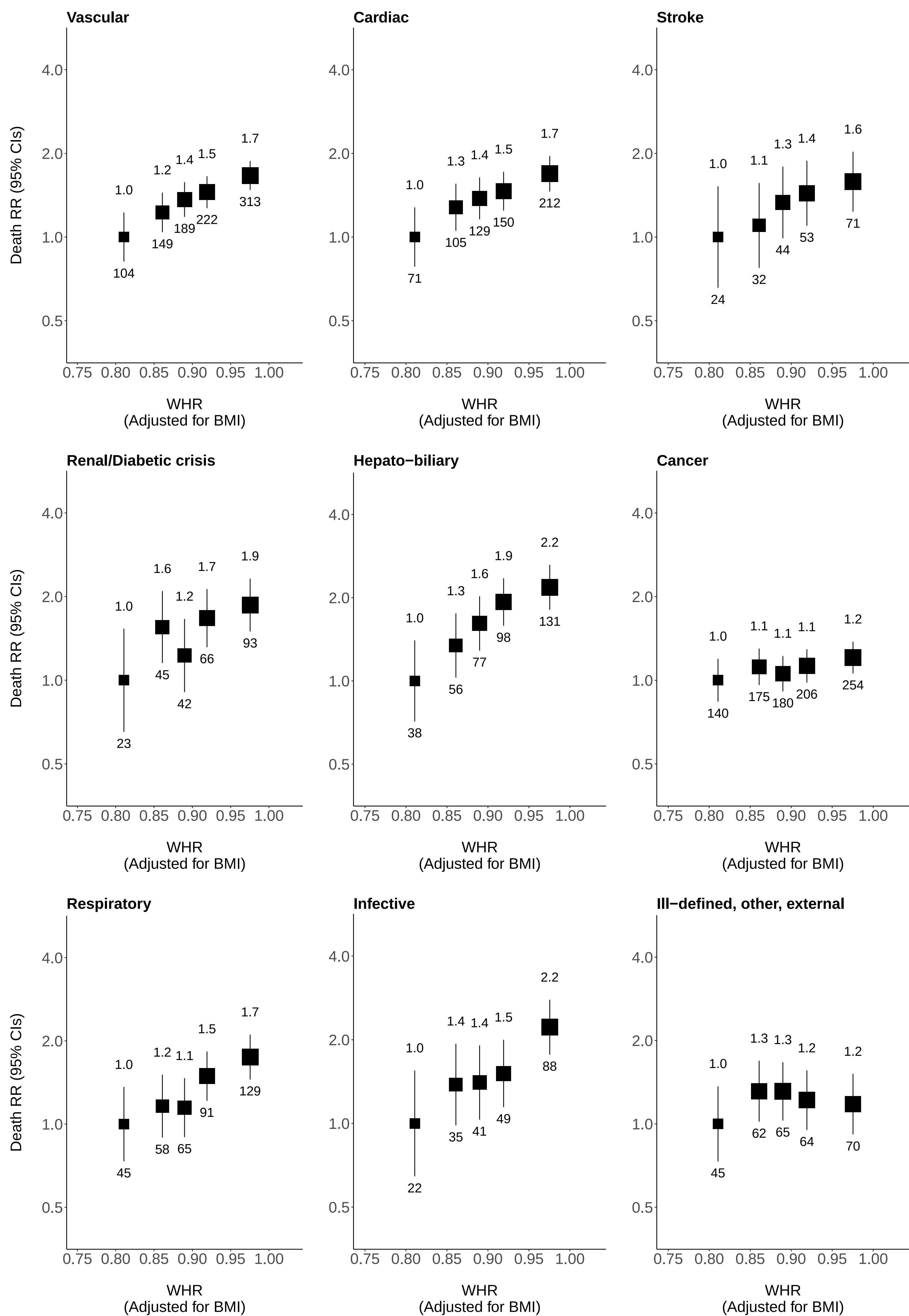
White squares represent the estimates for each adiposity marker above the median of BMI, as indicated in the plot. Analyses and conventions as per Figure 5.1.

S62: Independent relevance of waist circumference to mortality from specific causes at ages 40–74 years



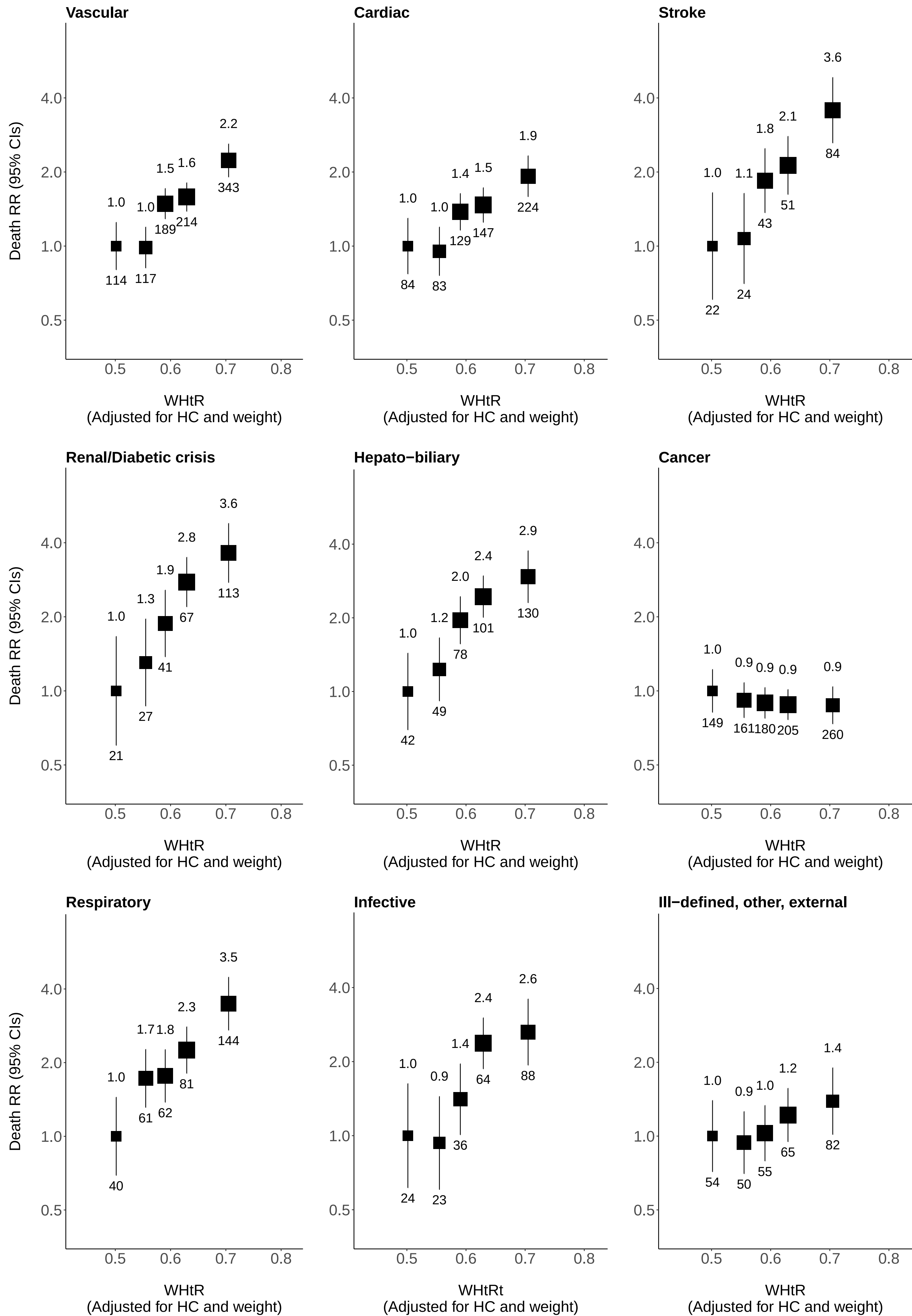
Analyses per Figure 7.7, with additional adjustments as indicated in the plot.

S63: Independent relevance of WHR to mortality from specific causes at ages 40–74 years



Analyses per Figure 7.7, with additional adjustments as indicated in the plot.

S64: Independent relevance of WHtR to mortality from specific causes at ages 40–74 years



Analyses per Figure 7.7, with additional adjustments as indicated in the plot.

S65: Overall associations of markers of waist circumference, WHR and WHtR with deaths at ages 40-74 years, by cause (includes diabetes and those with HbA1c <7% at baseline)

		Waist circ. (cm)		WHR	WHtR
Cause death	No. deaths	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Vascular					
Ischaemic Heart Disease	582	1.21 (1.12-1.31)	1.20 (1.11-1.30)	1.25 (1.15-1.35)	
Other cardiac	162	1.33 (1.15-1.53)	1.19 (1.02-1.38)	1.36 (1.18-1.56)	
Subtotal: any cardiac	744	1.24 (1.15-1.32)	1.20 (1.12-1.29)	1.27 (1.19-1.37)	
Stroke	243	1.22 (1.08-1.37)	1.22 (1.08-1.38)	1.28 (1.14-1.44)	
Other vascular	92	1.56 (1.30-1.86)	1.15 (0.94-1.41)	1.62 (1.36-1.93)	
Subtotal: vascular	1079	1.26 (1.19-1.33)	1.20 (1.13-1.27)	1.30 (1.23-1.38)	
Metabolic					
Renal/Acute diabetic crises	371	1.33 (1.21-1.46)	1.23 (1.12-1.36)	1.34 (1.22-1.48)	
Hepatobiliary	420	1.27 (1.16-1.40)	1.28 (1.17-1.40)	1.36 (1.24-1.49)	
Subtotal: vascular-metabolic	1870	1.28 (1.22-1.33)	1.23 (1.17-1.28)	1.32 (1.27-1.38)	
Cancer					
Lung/Upper aero-digestive	102	0.96 (0.79-1.17)	0.90 (0.74-1.10)	0.90 (0.73-1.11)	
Other cancer	891	1.12 (1.05-1.20)	1.07 (1.00-1.14)	1.07 (1.01-1.14)	
Subtotal: cancer	993	1.10 (1.04-1.17)	1.05 (0.99-1.12)	1.06 (0.99-1.12)	
Other					
Respiratory	428	1.35 (1.24-1.47)	1.27 (1.16-1.38)	1.38 (1.27-1.51)	
Infective	258	1.38 (1.24-1.54)	1.28 (1.14-1.43)	1.41 (1.26-1.57)	
Other/IlI-defined/external	326	1.04 (0.94-1.16)	1.00 (0.89-1.12)	1.08 (0.96-1.20)	
Total: all-cause	3875	1.23 (1.19-1.26)	1.17 (1.13-1.21)	1.24 (1.20-1.28)	

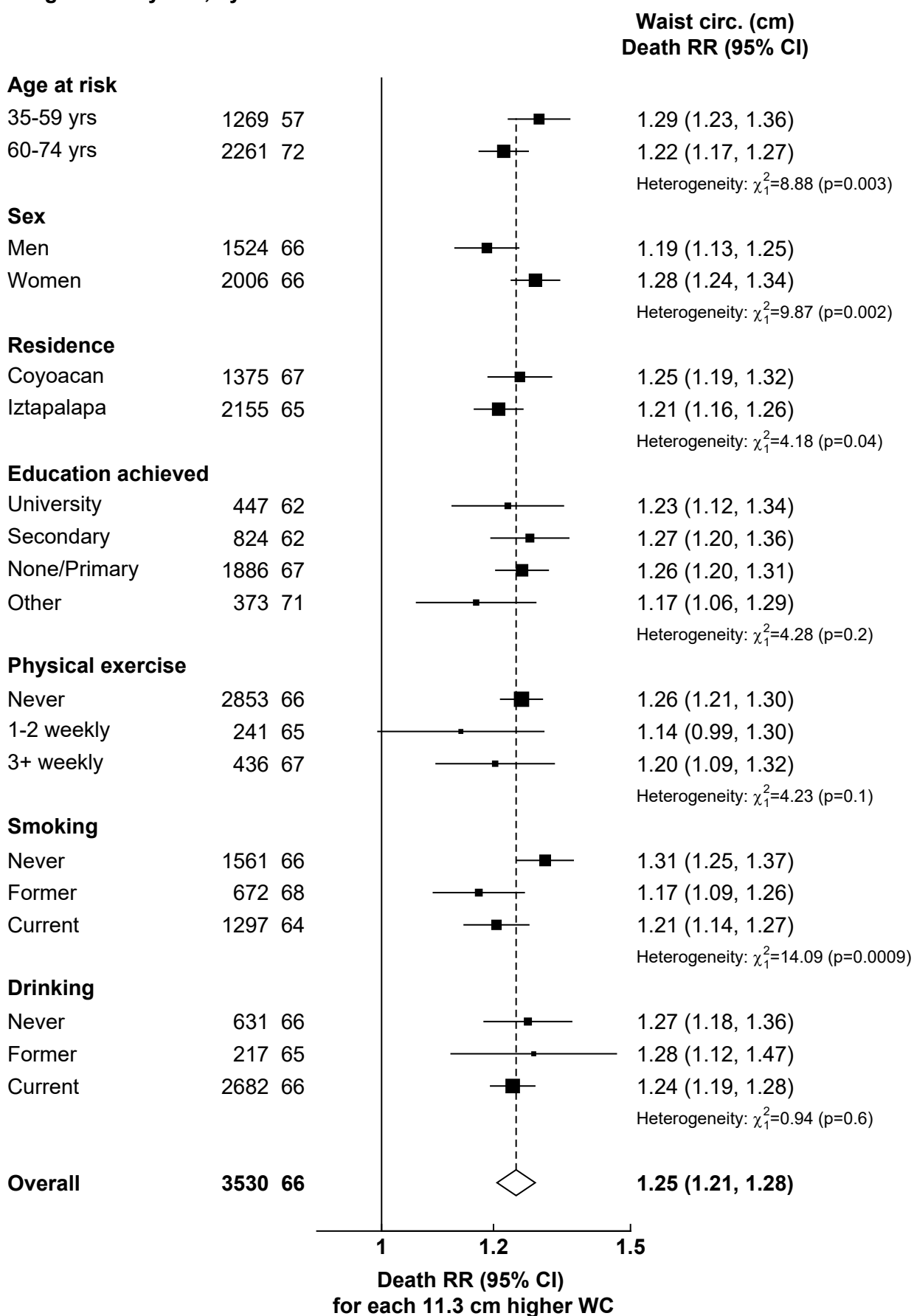
Analyses as per Figure 7.10, except for inclusion of those with well controlled diabetes.

S66: Overall associations of waist circumference, WHR and WHtR with cancer deaths at ages 40-74 years, by subtype (includes diabetes and those with HbA1c<7%)

Cancer deaths	No. deaths	Waist circ. (cm)	WHR	WHtR
		RR per 1SD (95% CIs)	RR per 1SD (95% CIs)	RR per 1SD (95% CIs)
Lung/Upper aero- digestive	102	0.96 (0.79-1.17)	0.90 (0.74-1.10)	0.90 (0.73-1.11)
Breast	105	1.20 (1.00-1.43)	1.09 (0.90-1.32)	1.10 (0.92-1.32)
Gynaecological	146	1.16 (0.99-1.35)	1.11 (0.94-1.30)	1.12 (0.96-1.30)
Oesophageal/stomach	101	0.91 (0.74-1.12)	0.97 (0.79-1.19)	0.87 (0.70-1.07)
Pancreatic/hepatobiliary	155	1.14 (0.98-1.32)	1.17 (1.01-1.37)	1.09 (0.93-1.27)
Other gastro-intestinal	83	1.22 (0.99-1.50)	0.98 (0.78-1.23)	1.16 (0.93-1.43)
Urinary tract	43	0.97 (0.71-1.32)	0.80 (0.59-1.09)	0.94 (0.68-1.29)
Haematological	101	1.22 (1.01-1.47)	1.10 (0.90-1.34)	1.20 (0.99-1.45)
Other/III-defined	157	1.10 (0.94-1.28)	1.10 (0.94-1.28)	1.05 (0.90-1.23)
Subtotal: any cancer	993	1.10 (1.04-1.17)	1.05 (0.99-1.12)	1.06 (0.99-1.12)

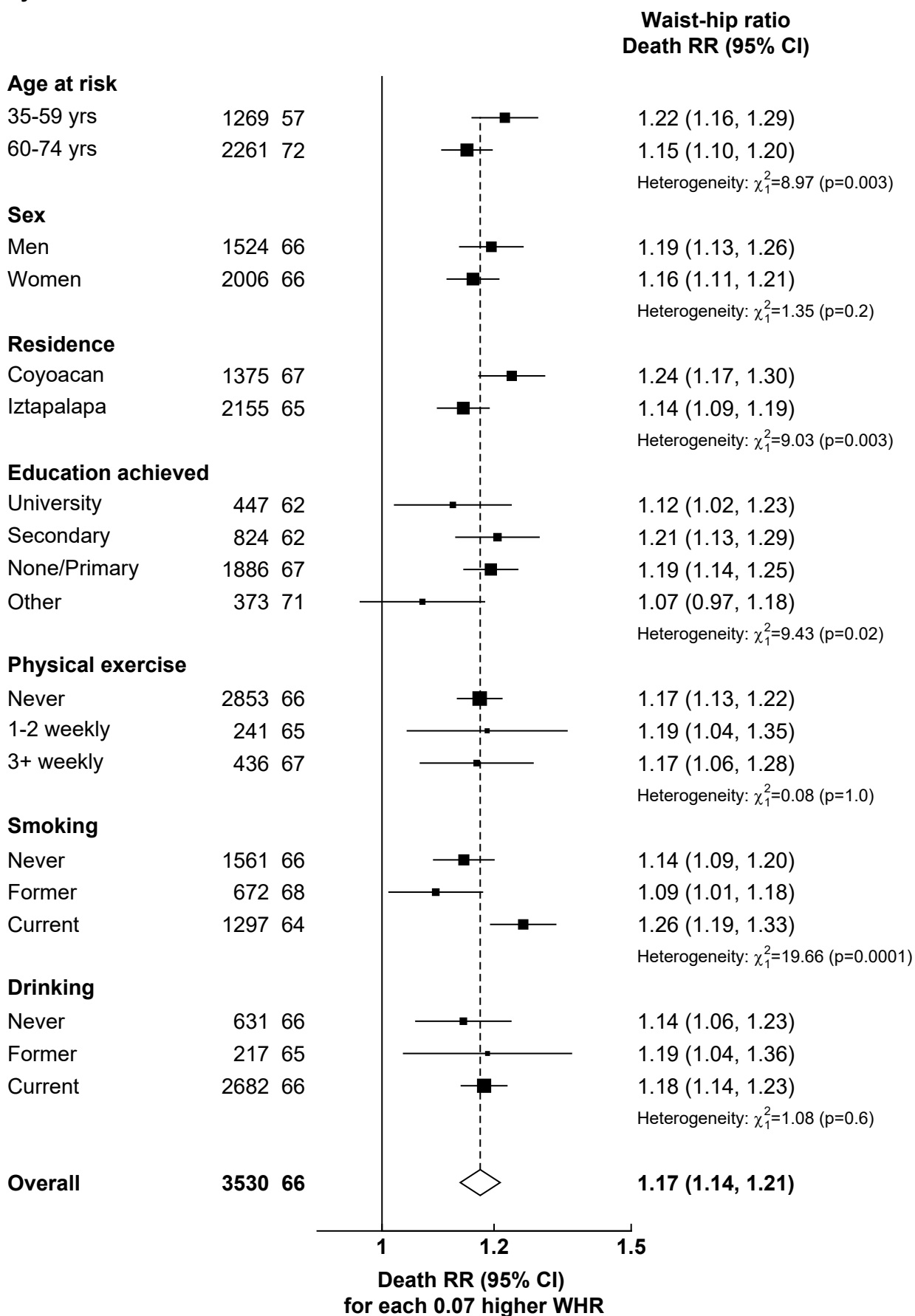
Analyses as per S63.

**S67. Relevance of waist circumference to all-cause mortality
at ages 40-74 years, by strata of confounders**



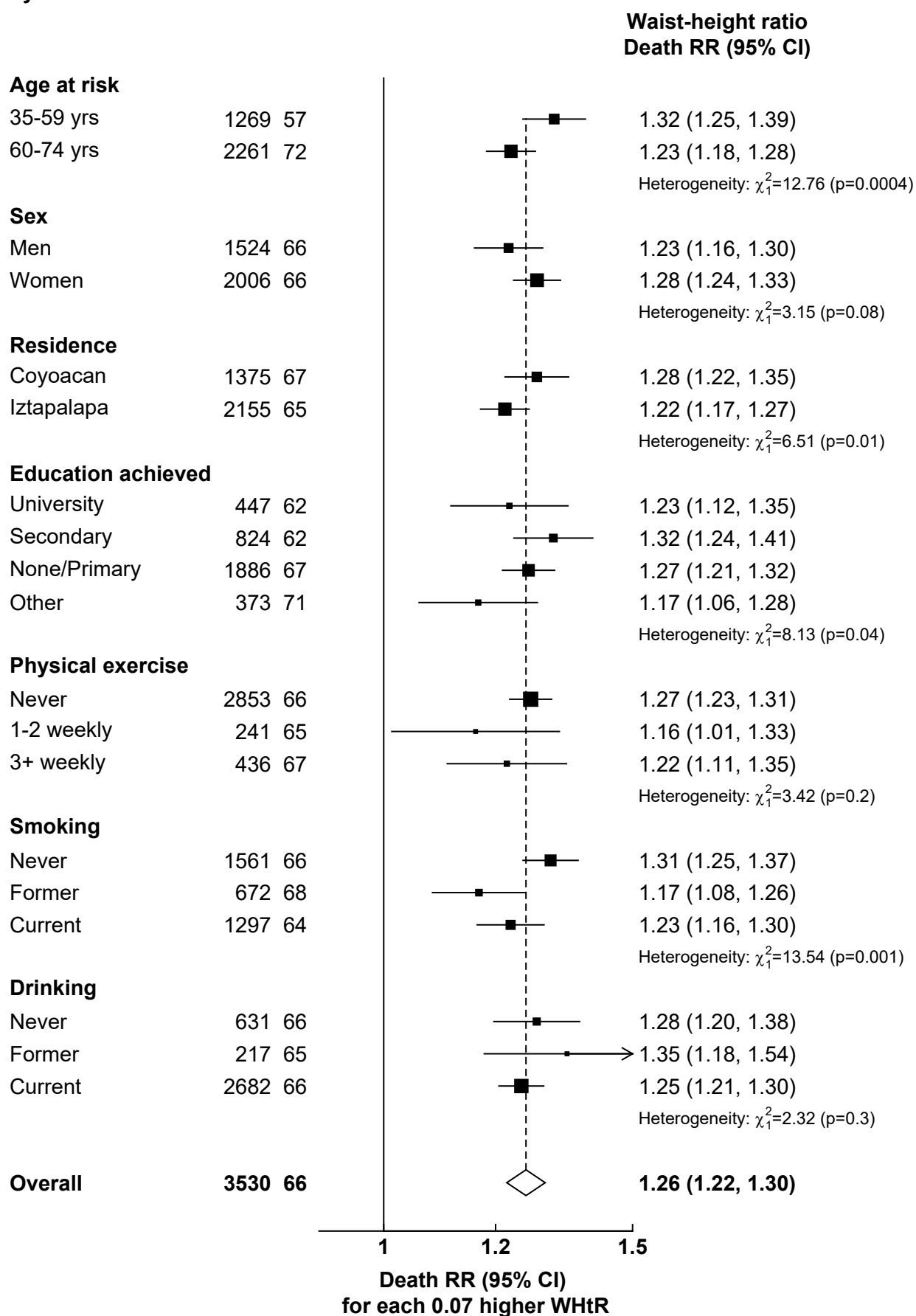
Analyses as per Figure 7.1.

S68. Relevance of waist-hip ratio to all-cause mortality at ages 40-74 years, by strata of confounders



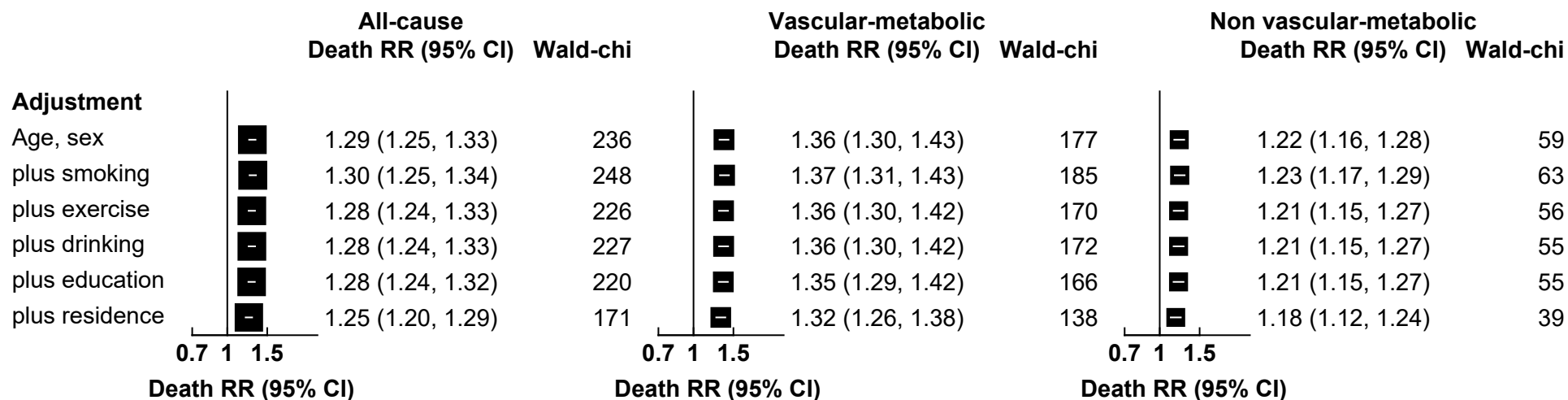
Analyses as per Figure 7.1.

S69. Relevance of waist-height ratio to all-cause mortality at ages 40-74 years, by strata of confounders



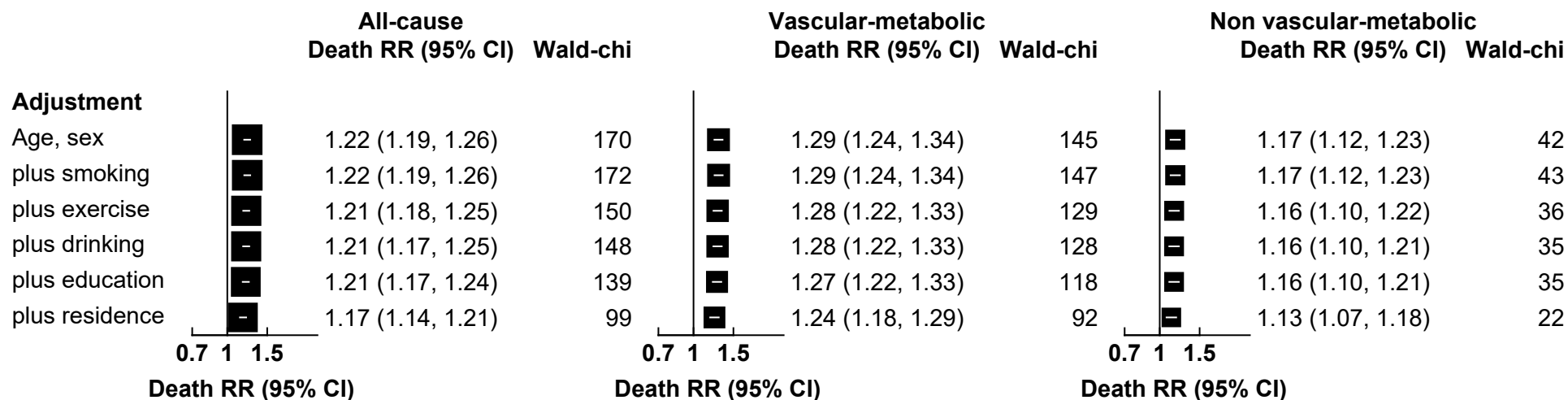
Analyses as per Figure 7.1.

S70. Relevance of each 11.3 cm higher baseline waist circumference (full ranges) to mortality at ages 40-74 years, with progressive adjustment for baseline confounders, among those with HbA1c <7%, without diabetes or other chronic disease, and after exclusion of the first 5 years of follow-up



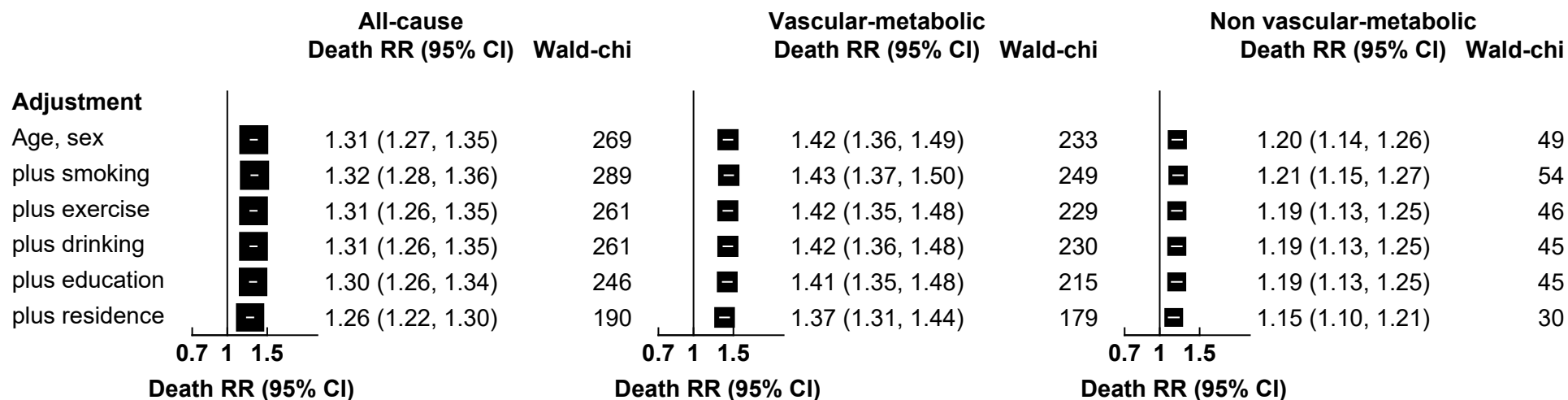
Analyses as per Figure 7.1.

S71. Relevance of each 0.07 higher baseline WHR (full ranges) to mortality at ages 40-74 years, with progressive adjustment for baseline confounders, among those with HbA1c <7%, without diabetes or other chronic disease and after exclusion of the first 5 years of follow-up



Analyses as per Figure 7.1.

S72. Relevance of each 0.07 higher baseline WHtR (full ranges) to mortality at ages 40-74 years, with progressive adjustment for baseline confounders, among those with HbA1c <7%, without diabetes or other chronic disease, and after exclusion of the first 5 years of follow-up



Analyses as per Figure 7.1.