Adiposity, major plasma biomarkers and the risk of cardiovascular diseases and mortality in Chinese adults

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A thesis submitted for the degree of Doctor of Philosophy

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Abstract

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Background: Uncertainty remains on the associations of adiposity with stroke types and subtypes. Moreover, the role of adiposity on cardiovascular disease (CVD) and non-CVD mortality remains to be clarified among certain population subgroups (e.g., those with diabetes). Reliable assessment of these associations is particularly important in China, where mean levels of adiposity and rates of CVD, especially stroke, differ importantly from those in Western populations.

Methods: In 2004-08 the China Kadoorie Biobank recruited >512,000 adults (41% men, mean age 52.0 years) from 10 diverse areas in China, recording, during 10-years' follow-up, 16,898 CVD deaths, 46,712 incident cases of ischaemic stroke (IS) and 10,775 intracerebral haemorrhage (ICH) events. A nested case-control study of ~12,000 incident strokes and ~6000 controls measured 18 plasma biomarkers. Multiple linear regression was used to examine cross-sectional associations of adiposity with blood pressure and plasma biomarkers. In prospective analyses, Cox regression was used to estimate adjusted (for confounders, i.e., age, sex, study area, smoking, alcohol, education and physical activity) hazard ratios (HRs) for each disease associated with body mass index (BMI) and other adiposity measures (e.g., waist circumference) and, among a subset of participants, with plasma biomarkers. The percentage of excess risk attenuated after adjustment for mediators was estimated using HRs.

Results: The overall mean (SD) BMI at baseline was 23.6 (3.2) kg/m^2. Adiposity was positively associated with blood pressure and adverse plasma biomarker profiles. Each 1 SD higher BMI was associated with 5.1 mmHg higher SBP, 0.2 mmol/L higher random plasma glucose (RPG), 0.1 mmol/L higher LDL-cholesterol, 0.1 mmol/L lower HDL-cholesterol, 0.2 log mg/L higher log high-sensitivity C-reactive protein and 3.0 u/L higher alanine aminotransferase. There was a log-linear positive association of BMI with IS (HR=1.19 [95% CI 1.18-1.20] per 1 SD higher BMI, adjusted for confounders), and main IS subtypes (lacunar: 1.21 [1.19-1.23]; non-lacunar: 1.24 [1.22-1.28]). Approximately half of the BMI-IS association was explained through baseline SBP (HR reduced from 1.19 to 1.10). Accounting for intra-individual variation in SBP suggested that about three quarters of the BMI-IS association is explained through usual SBP (reduced the HR to 1.05). Among a subset of individuals, major plasma biomarkers attenuated the HR of the association of BMI with IS to 1.04. For ICH, BMI showed no association at levels below 25.0 kg/m^2 (n=4485; 0.97 [0.93-1.02] per 1 SD higher) but a positive association at levels ≥25 kg/m^2 (n=2003; 1.20 [1.12-1.28]). Adjustments for baseline SBP and RPG reversed these associations, with an adjusted HR of 0.92 (0.89-0.94) per 1 SD higher BMI throughout the range examined. Further adjustment for selected plasma biomarkers among a subset of participants

attenuated the inverse association with ICH (n=3952; 0.95 [0.92-0.99]). Although there was a positive association of BMI with CVD incidence, there was a U-shaped association with CVD mortality, with the lowest risk at BMI 22.5 to <25.0 kg/m^2, similarly in those with (n=23,843) and without (n=422,871) diabetes at baseline. For other measures of adiposity, the associations with plasma biomarkers and disease risks were similar to those for BMI.

Conclusions: Among relatively lean Chinese adults, adiposity was positively associated with IS and its main subtypes, mainly through its effect on blood pressure. Given blood pressure, there was a strong inverse association of adiposity with ICH, which was attenuated towards the null after allowing for plasma biomarkers. The contrasting associations of adiposity with CVD incidence and mortality indicated poor survival following disease onset among those with lower BMI, in both individuals with and without diabetes.

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Statement of contribution to work

I was responsible for conceiving and developing the research questions addressed in this thesis. I performed all aspects of the literature reviews and planned and designed the analyses. I conducted all statistical analyses (some analyses used statistical programmes developed within the Clinical Trial Service Unit and Epidemiological Studies Unit of the Nuffield Department of Population Health). I produced all the tables and figures, interpreted the findings and wrote-up all aspects of the study presented in this thesis.

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List of abbreviations

ACC	Asian Cohort Consortium
ALT	Alanine aminotransferase
APCSC	Asia Pacific Cohort Studies Collaboration
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ARIC	Atherosclerosis Risk in Communities
AST	Aspartate aminotransferase
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CDC	Centre of Disease Control and Prevention
CKB	China Kadoorie Biobank
COPD	Chronic obstructive pulmonary disease
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit
CVD	Cardiovascular disease
DSP	Disease Surveillance Points
DXA	Dual-energy x-ray absorptiometry
eGFR	Estimated glomerular filtration rate
ERFC	Emerging Risk Factors Collaboration
FPG	Fasting plasma glucose
GGT	Gamma-glutamyl transferase
HC	Hip circumference
HDL	High-density lipoprotein
HIC	High-income countries
HS	Haemorrhagic stroke
hs-CRP	High-sensitivity C-reactive protein
ICH	Intracerebral haemorrhage
IHD	Ischaemic heart disease
IS	Ischaemic stroke
KOMERIT	Korean Metabolic Risk Factor
LDL	Low-density lipoprotein
LMIC	Low- and middle-income countries
MR	Mendelian randomization
NHIS	National Health Insurance Service
RDR	Regression dilution ratio
RPG	Random plasma glucose
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
TIA	Transient ischaemic attack
UKB	UK Biobank
WC	Waist circumference
WHR	Waist-to-hip ratio

Chapter 1. Introduction

1.1 Adiposity

1.1.1 Burden of adiposity

As a result of rapid social and lifestyle changes and economic growth, adiposity levels are increasing globally with significant implications for the global burden of disease.[1,2] Over the last four decades, the global age-standardised mean body mass index (BMI) increased from approximately 22.0 kg/m^2 to 24.0 kg/m^2.[3] Consequently, the proportion of the world's population classified as overweight (BMI: ≥25.0 to <30.0 kg/m^2) or obese (BMI: ≥30.0 kg/m^2) is estimated to have nearly tripled.[4] In 2016, 39% of adults (~2 billion) were classified as overweight and 13% (~600 million) as obese. It has been predicted that if recent trends continue, by 2025 approximately 20% of adults will be obese.[3] Moreover, excess adiposity was estimated to be directly or indirectly responsible for approximately 4 million adult deaths worldwide in 2015, thought mainly to be due to its association with conditions such as hypertension, diabetes and cardiovascular diseases (CVDs).[5]

Although, the prevalence of obesity is generally lower in low- and middle-income countries (LMICs) than in high-income countries (HICs), it has been estimated that over half of the individuals classified as obese worldwide are now living in LMICs.[6] For instance, in China about 5% (~60 million) of adults are classified as obese, accounting for approximately 10% of the world's obese individuals.[7] During the last three decades the largest increases in rates of obesity have been in HICs,[6] but in coming decades it is expected that the obesity rate will increase at the same or a

faster rate in LMICs. In most LMICs, although the prevalence of obesity is higher in urban than rural areas, the prevalence of obesity is increasing more rapidly in rural than in urban areas, particularly in East and South East Asian countries.[8] In China, between 1993 and 2011 the prevalence of obesity increased from 2.5% to 10.6% in rural areas and from 3.5% to 10.0% in urban areas.[9] In both HICs and LMICs women have higher prevalence of overweight/obesity than men, although this sex-difference is more pronounced in LMICs.[6] In China, between 1980 and 2015 the prevalence of overweight increased from 5.2% to 25.7% among men and from 9.3% to 22.8% among women.[5] In the same period, the prevalence of obesity increased from 0.3% to 5.0% among men, and from 0.9% to 5.5% among women.

1.1.2 Adiposity measures

Adipose tissue is a loose connective tissue composed mainly of adipocytes, endothelial cells and leukocytes, and acts as a site of energy storage.[10] The amount of adipose tissue in the body can be measured using various techniques. Gold-standard approaches include densitometry (e.g., underwater weighing) and imaging e.g., dual-energy x-ray absorptiometry (DXA), computed tomography and magnetic resonance imaging.[11] However, in most epidemiological studies adiposity is assessed using anthropometric measures, such as BMI, body fat percentage, waist circumference (WC), hip circumference (HC), and derivatives of these, reflecting their simplicity and cost effectiveness.

BMI is by far the most commonly used anthropometric measure, and is an index of body weight taking into account standing height. It is a widely used measure of general adiposity, but cannot distinguish between lean mass and fat mass.

Standardised BMI cut-points for BMI have been defined to classify individuals into various adiposity categories i.e., underweight, “normal” weight, overweight and obese (Table 1.1). Another general adiposity measure is body fat percentage. This can be measured either by using skinfold callipers or, more accurately, by using bioelectrical impedance analysis (BIA).[12] For a given BMI, individuals of Asian ethnicity tend to have higher body fat percentage than Caucasians, leading to the suggestion that different BMI cut-points should be used for different ethnic groups, and especially for Asian populations, in epidemiological studies (Table 1.1).[13] Both BMI and body fat percentage estimated using BIA correlate strongly with body fat percentage derived from DXA scans (correlation coefficient ~0.75 among men and ~0.85 among women).[14,15]

Central (or visceral or abdominal) adiposity refers to the adipose tissue located inside the abdominal cavity and surrounding organs such as the liver, kidneys and stomach,[16] which has been associated with a more adverse cardiometabolic profile.[17] Central adiposity measures (such as WC or waist-to-hip ratio [WHR]) are strongly correlated with general adiposity measures. However, they are more prone to measurement errors.[18] For example, although WC is reasonably strongly correlated with body fat percentage calculated by DXA (correlation coefficient ~0.75),[18,19] WHR correlates only moderately with body fat percentage estimated using this approach (correlation coefficient ~0.50).[19]

1.1.3 Adiposity and cardiometabolic traits

Adipose tissue acts not only as a site of energy storage, but also functions as an endocrine organ in its own right.[10] As such, it produces hormones (e.g., leptin, oestrogen, resistin),[20] inflammatory biomarkers,[21] fatty acids and adipocytokines.[22]

These products of adipose tissue have multiple effects in the body, including on cardiometabolic health. For example, higher levels of adipose tissue are associated with higher levels of insulin resistance,[23,24] renal dysfunction, higher blood pressure,[25] deranged liver metabolism (which can, in turn, lead to dyslipidaemia[22]), and endothelial dysfunction.[26] These cardiometabolic traits have been associated with higher risk of diseases, such as CVD.[27-39] Visceral adipose tissue is more metabolically active than subcutaneous adipose tissue and may additionally be particularly harmful since its products (e.g., adipocytokines, fatty acids and other substances) drain directly into the portal vein, and therefore may have more instant and stronger effects, including on liver metabolism and insulin resistance.[22]

A few previous studies have attempted to quantify the associations of adiposity with major cardiometabolic traits (e.g. lipids and lipoproteins, glucose). These observational studies have suggested that excess adiposity is associated with higher blood pressure,[40,41] dysglycaemia,[42,43] dyslipidaemia (high low-density lipoprotein [LDL] cholesterol and triglycerides levels, and low high-density lipoprotein [HDL] cholesterol levels),[44-48] and inflammation,[49-56] as well as with impaired renal[57-62] and liver[63-65] function. Subsequent Mendelian randomization (MR) studies have confirmed the causality of all of these associations (hypertension,[66] diabetes,[67,68] inflammation[69] and impaired liver function[70]), with the exception of that between adiposity and lower renal function. However, the mediating role of those cardiometabolic traits on the association of adiposity with major diseases, such as CVD, has not been fully investigated or understood.

1.2 Burden of cardiovascular diseases

CVD, referring to diseases of the heart and blood vessels, is the major cause of premature death globally.[71] In 2016, CVD, mainly ischaemic heart disease (IHD) and stroke, accounted for approximately 18 million deaths, representing over 30% of all global deaths.[71] Over three quarters of CVD deaths worldwide occur in LMICs, with about one fifth of these deaths in China (~4 million deaths). Of the CVD deaths in China, approximately 1.9 million deaths are due to stroke.

There are three major pathohistological types of stroke, namely, ischaemic stroke (IS), intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). IS occurs when there is an occlusion or stenosis of an artery supplying the brain, causing reduction in the blood flow (ischaemia). Haemorrhagic stroke (HS) refers to a bleed in the brain; when the bleeding occurs directly from an artery directly into an intraparenchymal region of the brain it is termed an ICH, and when bleeding occurs into the space surrounding the brain it is a SAH. IS and ICH can be further divided into subtypes according to the underlying pathology or the site within the brain that is affected. The main subtypes of IS are lacunar, large artery occlusion and cardioembolic stroke. Lacunar IS is the result from occlusion in small perforating arteries (small infarcts) supplying deep brain structures.[72] Large artery occlusion is referring to occlusion of a brain artery or branch cortical artery typically from atherosclerosis. Cardioembolic stroke is the result of occlusion in a brain blood vessel, from a material originating from the heart. Two main ICH subtypes are lobar and non-lobar (deep), based on the location of lesion. Lobar ICH is referring to bleeding in the brain located in one of the cerebral lobes (frontal, temporal, parietal, or occipital) and follows a “lobar” pattern. Non-lobar

ICH is referring to bleeding in basal ganglia, internal capsule, cerebellum or brain stem.

As well as the very high stroke incidence rate in Chinese, compared with Western, populations, the proportion of stroke events which are ICH is higher among Chinese populations.[73,74] It has been estimated that in China approximately 25% of total strokes are attributed to ICH,[75] whereas in Western population countries the proportion of ICH events was lower (9-13%).[76,77] In addition, the proportion of stroke events which are fatal differs between populations. For example, although the IS incidence rate is ~35% higher in China than the global average, the mortality to incidence ratio is lower (possibly reflecting the higher rate of brain imaging). In addition, although the ICH mortality rate in China decreased from 39% to 27% between 1990 and 2016, it remained twice the global average. As such, although in China the incidence rate of IS is about 4-fold higher than that of ICH, the number of deaths from these two stroke types are similar, reflecting the very high ICH case fatality rates.[78] Furthermore, there are important large regional variations in the incidence and mortality of stroke in China. For example, in north-east China, stroke incidence and mortality are approximately 2.5-fold and 1.5 -fold higher, respectively, than in south China.

1.3 Adiposity and the risk of cardiovascular diseases

Previous large prospective studies have shown that higher levels of adiposity are associated with higher risk of incident major CVD,[79] including IHD[80-83] and total stroke.[80,81] In addition, several MR studies have suggested that the association of adiposity with IHD is causal.[68,84,85] Evidence on the relationship of adiposity with

stroke types[80,86-96] and subtypes,[97-101] is more limited and less consistent, particularly for ICH.[91,95] In addition, what roles potential mediating factors, such as blood pressure and major cardiometabolic traits (e.g., lipids, inflammatory biomarkers), might play in these associations are poorly investigated and understood.

Evidence from previous prospective studies among the general population reported a J-shaped association between adiposity and all-cause and CVD mortality, with elevated levels of adiposity associated with higher risk of mortality.[82,102-107] Most of them also reported that the lowest risk of mortality was at BMI levels within the “normal” BMI range.[102,103,105,106] However, among individuals with established diseases, especially diabetes,[67,68] findings on the association of adiposity with mortality risks are conflicting.[108-119] Some studies of mainly Western populations suggest that overweight or obese individuals have lower mortality risk than their “normal” weight counterparts, leading to the notion of a so-called “obesity paradox”.[108-111,114,117,119] However, it is unclear whether this reflects a true effect of adiposity on mortality, or whether it is due to uncontrolled biases, such as reverse causality, or residual confounding. Moreover, there are inconsistent findings on the associations of adiposity with CVD mortality,[112,113,115,116,118] among individuals with diabetes, with particularly limited evidence from Chinese population studies, in which disease rates, levels of adiposity and management of diabetes and associated diseases differ importantly from those in most Western populations.

1.4 Aims and objectives of the thesis

In light of gaps in current evidence on the relationship of adiposity with stroke types and subtypes, and the mediating roles of cardiometabolic traits on those associations, as well the association of adiposity with mortality among individuals with diabetes, this thesis starts by identifying and assimilating findings from previous studies on both topics. Subsequently, it aims to investigate those associations using data from 0.5 million adults from the China Kadoorie Biobank (CKB).

The main objectives of this thesis are to:

1. Examine the associations of general and central adiposity with plasma biomarkers among ~18,000 CKB participants with available plasma biomarker data;
2. Examine the associations of plasma biomarkers with IS and ICH, among the same ~18,000 CKB participants;
3. Investigate the associations of general and central adiposity with IS and ICH and their subtypes among 0.5 million CKB participants;
4. Investigate the mediating roles of blood pressure and plasma biomarkers on the associations of adiposity with stroke types and subtypes;
5. Investigate the associations of adiposity with all-cause, CVD and other major cause-specific mortality among individuals with diabetes, comparing these with the same associations among individuals without diabetes.

Table 1.1. Adiposity classification according to BMI

Classification	BMI cut-offs (kg/m^2)	
	General population[a]	Asian population[b]
Underweight	<18.5	<18.5
Normal weight	18.5-24.9	18.5-22.9
Overweight	25.0-29.9	23.0-27.5
Obese	≥30.0	>27.5

[a]As recommended from the World Health Organization.[4] [b]Suggested Asian-specific BMI cut-offs.[13]
BMI: body mass index

Chapter 2. Literature review

This literature review summarises existing evidence from prospective studies on the associations of adiposity with major CVD, especially stroke types and subtypes (Chapter 5), and the association of adiposity with all-cause and CVD mortality, particularly among individuals with diabetes (Chapter 6). A formal review of literature examining the associations of plasma biomarkers with adiposity and with stroke types (the focus of Chapter 4) is not presented here, since the purpose of those analyses was largely to inform mediation analyses included in Chapter 5. However, a summary of relevant literature is presented in Chapter 4.

2.1 Adiposity and risk of stroke types and subtypes

Previous large prospective studies have extensively investigated the associations of adiposity with overall CVD, IHD and total stroke, and consistently reported higher levels of adiposity.[79-83] However, uncertainty remains on the association of adiposity with stroke types and subtypes; this is particularly true for HS and ICH.

2.1.1 Objectives

The available evidence on the prospective associations of adiposity with stroke types and subtypes is summarised and discussed in this literature review, which aims to highlight gaps in current knowledge to inform the analyses presented in Chapter 5 of this thesis.

2.1.2 Methodology and identified literature

The articles included in this literature review were identified using MEDLINE and Embase databases from their inception to July 1, 2019, and were limited (for practical reasons) to English language articles. Tables 2.1.1 and 2.1.2 show the detailed search terms used to identify articles investigating the association of adiposity with stroke types and subtypes, respectively. The process used to select articles is shown in Figures 2.1.1 and 2.1.2. In summary, articles were initially screened at title level (5768 articles for stroke types and 2993 for stroke subtypes), followed by the abstract level, to identify those investigating the association of adiposity with stroke types (n=113) or subtypes (n=23). Full-articles were then screened (42 articles for stroke types and 15 for stroke subtypes). Given the number of articles identified for the literature review for stroke types, and in an attempt to include studies providing the most robust evidence, meta-analyses were included only if based on individual participant data from prospective studies, and individual studies were included only if they had a prospective study design. Similarly, studies comprising <1500 IS events or <1000 HS or ICH events were excluded (n=25) to ensure inclusion only of studies with adequate power to provide robust evidence of the associations of adiposity with stroke types. Exclusion criteria based on the number of stroke events were not applied to the review of literature on the association of adiposity with stroke subtypes given the limited evidence available on this topic. A recently published CKB article investigating the association of adiposity with stroke types was excluded from the literature review, since similar findings using updated data are presented in Chapter 5 of this thesis.[120]

Ten studies investigating the association of adiposity with stroke types were identified for inclusion in the literature review, including three individual participant data meta-analyses[80,86-88] and seven prospective studies[89-95] (five East Asian[89,90,93-95] and two Western population[91,92] studies), which were mutually exclusive. Tables 2.1.3 and 2.1.4 summarise the study characteristics, and their main findings are presented in Tables 2.1.5-2.1.7. Five identified studies investigated the association of adiposity with stroke subtypes; their main characteristics and findings are presented in Table 2.1.8 and Tables 2.1.9 and 2.1.10, respectively.[97-101]

2.1.3 Association of adiposity with ischaemic stroke

All three identified individual participant data meta-analyses consistently reported positive log-linear[80,86-88] associations between BMI and IS at BMI levels >25.0 kg/m^2, but varied in whether this positive relationship continued down to lower BMI levels,[80,87] or whether the relationship was flat at lower levels.[86,88] The Emerging Risk Factors Collaboration (ERFC) individual participant data meta-analysis included ~89,400 individuals from predominantly Western population studies (n=21) and ~2400 IS events.[80] After adjustments for age, sex and smoking, among individuals without prior CVD there was a positive approximately log-linear association throughout the BMI range examined (20.0 to <35.0 kg/m^2), and each 1 SD (4.56 kg/m^2) higher BMI was associated with 20% higher risk of IS (HR 1.20 [95% CI 1.12-1.28]). This association was reported to be qualitatively similar after excluding individuals of non-European descent. The shape of the association of BMI with IS was similar among ~380,000 men (n=44 studies; 86% Asian population study participants) with ~1500 IS events from the Asia Pacific Cohort

Studies Collaboration (APCSC).[87] However, this study appeared to show a stronger relationship, with each 5 kg/m^2 higher usual BMI associated with 44% (HR 1.44 [95% CI 1.32-1.56]) higher risk of IS at BMI ≥20.0 kg/m^2 after adjustment for age. This apparently stronger association may in part reflect inclusion of individuals with prior CVD, lack of adjustment for smoking, and adjustment for intra-individual variation in BMI in the APCSC analyses. The same study reported that there was an apparent positive log-linear relationship between BMI and IS incidence at BMI levels >22.5 kg/m^2 among ~214,000 women (n=42 studies; 79% from Asian population studies; ~750 IS events), although they did not report the strength of the association.[88] The associations of BMI with IS among both men and women in the APCSC were similar among Asian and Australian/New Zealand populations.[87,88] At lower BMI levels, where the number of events was relatively small, there was no clear association between BMI and IS. Similarly, the Asian Cohort Consortium (ACC) study, which investigated the association of BMI with IS mortality among ~820,000 individuals (~5800 deaths) from East Asian studies (n=17), showed a J-shaped association throughout the BMI range examined (from 15 to ≤50 kg/m^2), with a positive and broadly log-linear association at BMI levels ≥25.0 kg/m^2 and no clear association at lower BMI levels.[86] Similar findings were observed in a sensitivity analysis excluding individuals with pre-existing CVD. Difference between studies may in part reflect different shapes of association of BMI with non-fatal and fatal IS. The ERFC study included only a small proportion of fatal IS (~5%),[80] while the APCSC study included a higher proportion of fatal IS (~20% and ~35% among men[87] and women,[88] respectively), and the ACC study included only fatal events.[86] The studies with lower proportions of fatal events tended to show a clear positive and log-linear association of BMI with IS

throughout the BMI range examined,[80,87] whereas the studies with higher proportions of fatal events reported no clear associations at lower BMI levels.[86,88]

There was a positive log-linear association of BMI with IS incidence throughout the BMI range examined in most of the individual prospective studies (one Western[91] and four East Asian[90,93-95] included in this literature review. The exceptions to this were one Western population study with small number of events,[92] and one East Asian population study which examined only IS mortality.[89] Of the seven individual prospective studies[89-95] identified that were not included in any of the individual participant data meta-analyses described above,[80,86-88] the largest Western population study was the Million Women Study, which included approximately 1.3 million women from the UK and ~10,000 IS events.[91] In that study, there was a positive log-linear association between BMI and IS incidence (after adjustments for age, region, smoking, alcohol, physical activity, height and socioeconomic status), and each 5 kg/m^2 higher BMI was associated with 21% (HR 1.21 [95% CI 1.18-1.23]) higher risk of IS.[91] After similar adjustments, a smaller Finnish study (~24,000 men and ~1300 IS)[92] and two large Korean studies (~440,000 non-smoking women with ~8700 IS[95] and ~235,000 men with ~4000 IS[90]), reported largely similar strengths of association of BMI with IS incidence, with 5-11% higher risks of IS per 1 kg/m^2 higher BMI. The largest study identified in this literature review was based on routine health data for ~22 million individuals from the Korean National Health Screening database.[93] This found a positive, approximately log-linear association of BMI with IS (~182,000 events) throughout the BMI range examined (from <17.1 to ≥30.0 kg/m^2), after adjustments for possible confounders. This study reported on the strength of the association of BMI with IS only after combined adjustments for potential confounders and

possible mediators (e.g., hypertension, diabetes and dyslipidaemia), whereas most previous studies reported the strength of the association separately adjusting for potential confounders only, and for potential confounders and mediators combined. Therefore, there was, unsurprisingly, a weaker association in this study (HR 1.03 [95% CI 1.03-1.04] per 1 SD [3.3 kg/m^2] higher BMI)[93] than in previous studies adjusting only for confounders,[90-92,95] mainly reflecting additional adjustments blood pressure and diabetes as potential mediators. In contrast to these positive log-linear associations of BMI with IS,[90-95] analyses among ~26,000 women (~1200 IS) in the previously described Finnish study, after adjustments for age, study year, smoking, alcohol, physical activity, socio-economic status and family history of stroke, showed no clear association throughout the BMI range examined (<18.5 to >30.0 kg/m^2), with the exception of women with BMI levels >30.0 kg/m^2, who experienced 41% (HR 1.41 [95% CI 1.21-1.64]) higher risk of incident IS than those with BMI 18.5 to <25.0 kg/m^2. The lack of association in that study likely reflects the smaller number of IS events (~1000 IS events), as compared to studies that reported a positive log-linear association (~3700[94] to 182,000[93] events).[90,91,93-95] A further study from Zhou et al, including ~212,000 Chinese men (~3700 IS deaths) reported little apparent association of BMI with IS mortality at BMI <25.0 kg/m^2 but a positive association at BMI ≥25.0 kg/m^2.[89] The inconsistency on the shape of the association between the study from Zhou et al[89] and most previous studies,[90-95] might reflect differences in the outcomes examined, since Zhou et al[89] investigated the association of BMI with IS mortality whereas the other studies focused on IS incidence.[90-93,95]

The effect of adjusting for possible mediators on the association of BMI with IS was investigated in two of the identified individual participant data meta-

analyses[80,86] and in several of the individual prospective studies.[90,92,94,95] The ACC study was the only one, however, to investigate the effects of individual possible mediators.[86] In that study, adjustment for hypertension, in addition to potential confounders (age, sex, smoking, alcohol, education, marital status, region, and history of cancer), attenuated the HR for IS mortality associated with BMI levels ≥25 kg/m^2, compared with 18.5 to <25.0 kg/m^2, from 1.28 (95% CI 1.11-1.48) to 1.13 (0.98-1.31). Adjustment for diabetes did not materially change the findings when compared with adjustment for potential confounding variables only. Other studies investigating the association of adiposity with IS incidence consistently reported that adjustments for possible mediators, including baseline blood pressure, diabetes-related variables and lipids, attenuated completely or partly the associations observed after adjustment only for confounders.[80,90,92,95] For instance, in the ERFC study, further adjustments for measured systolic blood pressure (SBP), diabetes, total cholesterol and HDL-cholesterol in addition to age, sex and smoking, attenuated the HR for IS from 1.20 (95% CI 1.12-1.28; adjusted for age, sex and smoking) to 1.06 (0.99-1.13) per 1 SD (4.56 kg/m^2) higher BMI.[80] Among a subset of individuals on whom the relevant data were available, subsequent separate adjustments for inflammatory biomarkers, such as fibrinogen (HR 1.06 [95% CI 0.99-1.13] among ~59,000 individuals [~1900 IS events]) and CRP (1.02 [0.95-1.10] among ~31,000 individuals [~1700 IS events]) did not significantly change the findings.[80] The Finnish study also reported that adjustments for baseline SBP, diabetes and cholesterol, in addition to age, study year, smoking, alcohol, physical activity, socio-economic status and family history of stroke, attenuated the strength of the association among men (from HR 1.05 [95% CI 1.04-1.07] to 1.02 [1.01-1.04]). Similarly, adjustments for baseline SBP, fasting

plasma glucose (FPG) and cholesterol partially attenuated the HR of BMI with IS incidence per 1 kg/m^2 from 1.05 (95% CI 1.05-1.06) to 1.03 (1.02-1.03) in the study of Korean non-smoking women from Park et al[95] and from 1.11 (1.09-1.12) to 1.06 (1.04-1.07) in Song et al's study of Korean men.[90] Likewise, a Chinese study from Bazzano et al, also reported that the association was partially attenuated after adjustments for baseline SBP and diabetes, however they did not report the strength of the association before or after adjustments for possible mediators.[94]

A small number of studies examined the association of central adiposity with IS, and reported similar associations to those of BMI.[80,92,93] For instance, in the ERFC study there was a positive log-linear association between central adiposity measures (WC and WHR) and IS, with the strength of the associations per 1 SD higher similar to those of BMI.[80] However, in contrast to the marked attenuation of the association of BMI with IS after adjustments for potential mediators, there was only partial attenuation of the association of central adiposity measures with IS. Specifically, the HR of WC and WHR with IS were reduced from 1.25 (95% CI 1.18-1.33) to 1.11 (1.05-1.17) and from 1.25 (1.18-1.33) to 1.14 (1.09-1.20), respectively. In the largest study included in this literature review, which was based on routine health data from ~22 million individuals from the Korean National Health Screening database, the strengths of the associations of BMI and WC with IS were similar after adjustments for potential confounders and possible mediators (e.g., hypertension, diabetes and dyslipidaemia) (HR 1.07 [95% CI 1.06-1.07] vs.1.03 [1.03-1.04] per 1 SD higher BMI and WC, respectively).[93] This latter study only reported, the strength of the association between adiposity and IS after adjustments for both potential confounders and possible mediators.

In summary, the majority of large individual participant data meta-analyses and individual prospective studies consistently reported a positive approximately log-linear association of BMI with IS incidence, throughout the BMI range examined.[80,87,90,91,93-95] After adjustments for potential confounders, the strength of the association was largely similar across different studies, with 5 kg/m^2 higher BMI associated with approximately 22% to 33% higher risk of incident IS.[80,86,90-95] After adjustment for possible mediators, including baseline SBP, diabetes and lipids, the excess risk of BMI with IS was attenuated to 7-16% per 5 kg/m^2 higher BMI.[80,90,92,95] None of these previous studies, however, accounted for measurement error or intra-individual variation in possible mediators, which may have led to an underestimation of their mediating effects. Moreover, the relevance of other potentially relevant mediators (e.g., markers of liver or renal function) was not investigated. In contrast, a few studies with either small numbers of IS events,[86,89,92] or high prevalence of fatal IS[88] reported a lack of association at lower BMI levels.

2.1.4 Association of adiposity with ischaemic stroke subtypes

All four identified prospective studies (two Western[98,100] and two East Asian[97,99] population studies) reporting on the association of adiposity with IS subtypes examined the association of BMI with lacunar IS. However, most of the associations reported in these studies were not statistically significant, probably due to the small number of events.[97-100] For instance, the Atherosclerosis Risk in Communities (ARIC) study, of ~13,500 participants (~140 lacunar IS events) from the US, reported that 1 SD (5.4 kg/m^2) higher BMI was associated with 12% (HR 1.12 [95% CI 0.95-1.31]) higher risk of lacunar IS, after adjustments for age, sex,

race, smoking, physical activity and alcohol intake.[100] Likewise, 1 kg/m^2 higher BMI was associated with 10% (HR 1.10 [95% CI 1.00-1.20]) higher risk of lacunar IS in a study of ~1600 Japanese adults (~170 lacunar IS events) after adjustment only for age.[99] Only a small number of studies investigated the effect of potential mediators in this relationship. [97,100] In the Japan Public Health Center-Based Prospective Study of ~88,800 individuals (~1290 lacunar IS events), after adjustments for hypertension, diabetes and dyslipidaemia, the initial positive approximately log-linear association of BMI with lacunar IS (adjusted for age, smoking, alcohol and physical activity) was slightly attenuated.[97] Among men, the HRs at BMI ≥30.0 kg/m^2 as compared to 23.0 to <25.0 kg/m^2 were attenuated from 1.68 (95% CI 1.08-2.62) to 1.51 (0.96-2.35), and among women from 2.08 (1.41-3.07) to 1.77 (1.19-2.63). The ARIC study was the only identified study to investigate the association of both general and central adiposity with lacunar IS, and after adjustments for potential confounders they reported positive log-linear associations of central adiposity measures (e.g., HR 1.37 [95% CI 1.12-1.66] per 1 SD higher WHR), but a null association of BMI (1.15 [0.98-1.34] per 1 SD higher).[100] These associations were completely attenuated after additional adjustments for possible mediators (e.g., SBP, diabetes, HDL-cholesterol, albumin) for both central adiposity (e.g., HR 0.94 [95% CI 0.76-1.17] per 1 SD higher WHR) and BMI (0.84 [0.69-1.01] per 1 SD higher).

The ARIC study was the only one to examine the association of adiposity with non-lacunar IS.[100] It reported a positive approximately log-linear association of adiposity with non-lacunar IS (~340 events), possibly stronger for central (e.g., HR 1.40 [95% CI 1.23-1.59] per SD higher WHR) than general (1.22 [1.10-1.35] per 1 SD higher BMI) adiposity. After adjustments for potential mediators the association

of WHR with non-lacunar IS was partially attenuated (HR 1.16 [95% CI 1.01-1.34] per SD higher), whereas the association of BMI was completely attenuated (1.00 [0.89-1.12] per SD higher).

In summary, this literature review clearly highlights that the existing evidence available on the relationship of adiposity with IS subtypes is very limited, with most studies including numbers of IS events which are far too small to allow reliable assessment of the shape or strength of the associations. In addition, there is a very limited understanding of factors mediating these associations.

2.1.5 Association of adiposity with haemorrhagic stroke

Two individual participant data meta-analyses,[86-88] and five separate cohort studies (one Western[91] and four East Asian[89,90,94,95] population studies) investigating the association of BMI with HS were identified for inclusion in this literature review. Among those studies, five investigated the association of adiposity with HS incidence,[87,88,90,91,94,95] and two with HS mortality.[86,89] The previously described Korean study from Park et al, including ~440,000 non-smoking women and ~4000 HS events, was the largest East Asian study examining the relationship of BMI with HS incidence. The authors reported a weak positive log-linear association of BMI with HS throughout the BMI range examined (from <18.5 to ≥32.0 kg/m^2), with 1 kg/m^2 higher BMI associated with 2% (1.02 [1.01-1.03]) higher risk of HS. Similar findings were reported in a Chinese prospective study[94] and in the APCSC individual participant meta-analysis (including 86% of participants from Asian population studies),[87,88] although both studies included a relatively smaller number of HS events as compared to the study from Park et al. None of these studies examined the associations of BMI

separately with fatal and non-fatal HS, as an attempt to investigate whether these associations are different, or affected by uncontrolled biases, given its high case-fatality rate of HS.[87,88,94,95] However, the studies included in this literature review did not report the proportion of fatal HS. An exception to this is the APCSC study, which reported that ~70% of HS events were fatal.[87,88] The other East Asian studies only reported the proportion of fatal total stroke events, which varied from ~25%[95] to ~50%.[94] Two studies included only individuals from East Asia investigated the association of BMI with HS mortality and they consistently reported that high BMI levels (>25.0 kg/m^2) were associated with higher risk of HS mortality, but that there was approximately flat association at lower BMI levels.[86,89] For instance, the previously described ACC individual participant meta-analysis (~6700 HS deaths) reported that individuals with BMI 27.5 to <30.0 kg/m^2 and 30.0 to <32.5 kg/m^2 had 24% (HR 1.24 [95% CI 1.14-1.36]) and 57% (1.57 [1.38-1.79]) higher risk of HS mortality than those with BMI 22.5 to <25.0 kg/m^2.[86] In the same study, individuals with BMI 17.5 to <20.0 kg/m^2 and 20.0 to <22.5 kg/m^2 had 5% (HR 1.05 [95% CI 0.96-1.27]) higher risk of IS and 8% (HR 0.92 [0.84-1.01]) lower risk of IS, respectively, as compared to those with BMI levels within the “normal” range. Similarly, a study of ~210,000 Chinese men (~3600 HS deaths) from Zhou et al, reported that individuals with BMI 25.0 to <27.5 kg/m^2 and ≥27.5 kg/m^2 had 16% (HR 1.16 [95% CI 1.02-1.33]) and 67% (1.67 [1.40-1.98]) higher risk of HS mortality, respectively, than those with BMI 20.0 to <22.5 kg/m^2. Individuals with BMI <18.5 kg/m^2 and 18.5-19.9 kg/m^2 had 5% (HR 1.05 [95% CI 0.95-1.16]) higher risk of IS and 7% (HR 0.93 [0.86-1.00]) lower risk of IS, respectively, than those with BMI 20.0 to 22.5 kg/m^2, consistent to ACC findings.[86]

The Million Women Study was the only identified Western population study that examined the association of BMI (self-reported) with HS incidence (~5900 events), but the proportion of fatal HS events was not reported.[91] After adjustments for potential confounders (age, region, smoking, alcohol, socioeconomic status, physical activity and height) there was a negative log-linear association, with each 5 kg/m^2 higher BMI associated with 11% (HR 0.89 [95% CI 0.86-0.92]) lower risk of HS.[91] This clearly contrasts with the positive log-linear associations reported in the previously described East Asian studies. [87,88,94,95] The authors of the Million Women Study speculated that the observed relationship of BMI with HS incidence in their study may reflect the inverse association of lipids (particularly LDL-related lipids) with HS, although they were not able to investigate the effect of lipids or other possible mediators (e.g., blood pressure, diabetes) on the association.[91] Of all of the studies included in this literature review, only three investigated the association of BMI with ICH, which is a subset of HS, and they generally reported similar associations to those with HS.[90,91,95]

A few studies have examined the combined mediating effect of baseline blood pressure, glucose and lipids on the association of BMI with incident HS. They consistently showed that the excess risk of HS associated with high BMI was explained mainly through those mediators.[90,94,95] For instance, Park et al's study of Korean women reported that adjustments for those variables (in addition to age, alcohol consumption and physical activity) completely attenuated the initial positive log-linear associations of BMI with HS (from HR 1.02 [95% CI 1.01-1.03] to 1.00 [0.98-1.01] per 1 kg/m^2) and ICH (from 1.02 [1.01-1.03] to 0.99 [0.98-1.00]), throughout the BMI range examined. Similar findings were reported in two East Asian population prospective studies, although these included smaller numbers of

HS and ICH cases.[90,94] In addition, the ACC individual participant data meta-analysis examined separately the mediating effects of hypertension and diabetes.[86] They reported that the initial association between BMI and HS mortality (after adjustment for age, sex, smoking, alcohol, education, marital status, region, and history of cancer) was completely attenuated after additional adjustment for hypertension, but separate adjustment for diabetes had a more limited effect.

In summary, the few studies that investigated the association of BMI with HS mortality consistently reported a null association at lower BMI levels but a positive association at higher BMI levels.[86,89] For HS incidence, Asian population studies reported positive approximately log-linear associations of BM with HS incidence,[87,88,90,94,95] whereas the one Western population study investigating this relationship reported an inverse log-linear association.[91] Few studies have examined the effect of potential mediators on the association of BMI with HS incidence, but those that did consistently reported that the initial associations (after adjustment for relevant confounders) were completely attenuated after additional adjustments for blood pressure, glucose and lipids.[90,94,95] This literature review highlights the need for better evidence from large prospective studies to clarify the association of general and central adiposity measures with HS, and more specifically with ICH incidence and mortality, including the role of possible mediators.

2.1.6 Association of adiposity with haemorrhagic stroke subtypes

Evidence on the association of BMI with HS subtypes is much more limited, with just one small nested case-control study identified. That US-based study included

188 individuals with lobar ICH, 196 with non-lobar ICH and 388 controls. Based on primary care data, after adjustment for age, sex, smoking, alcohol intake, and history of IHD, hypertension, diabetes, and hyperlipidaemia, there was a U-shaped association of BMI with both lobar and non-lobar ICH, with lowest risks at BMI levels of 18.5 to <30.0 kg/m^2 and 18.5 to < 25.0 kg/m^2, respectively. The relevance of central adiposity and the effect of possible mediators on the associations were not reported.

2.1.7 Limitations of the existing evidence and implications for future study

Despite previous large studies consistently demonstrating positive associations of BMI with IS incidence,[80,86,90-95] these studies have important limitations. Firstly, only a few studies investigated the associations of central adiposity with IS.[80,92,93,100] Secondly, evidence on the association of adiposity with IS subtypes is extremely limited, and derived only from small studies.[97-100] Thirdly, the few studies that examined the effect of potential mediators on the association of adiposity with IS[80,86,90,94,95] and IS subtypes,[97] mainly focused on the combined mediating effect of limited potential mediators (e.g., blood pressure, diabetes and lipids). Finally, these previous studies did not attempt to account for measurement error or intra-individual variation in potential mediators, which might lead to underestimation of their effects.

Previous studies examining the association of BMI with HS incidence reported conflicting findings, possibly reflecting a number of limitations.[87,88,90,91,94,95] Firstly, only a small number of studies investigated the association of BMI with ICH, as opposed to the less specific HS.[90,91,95] In addition, despite the high HS case-

fatality rate, none of the previous studies investigated the association of adiposity with fatal and non-fatal ICH separately, which could help assess whether the association are different or affected by uncontrol biases. With the exception of one study,[94] previous studies did not clarify the quality of diagnosis of HS cases (e.g., the extent of availability of neuro-imaging data to support diagnosis).[90,91,95] Furthermore, evidence on the association of BMI with ICH subtypes is particularly limited, and derived from just one small Western population study. Only few studies investigated the effect of possible mediators on the association of adiposity with HS, and those that did focused only on a small range of mediators,[90,94,95] and none investigated the effect of possible mediators on the association with ICH subtypes. Finally, there is also lack of evidence on the relevance of central adiposity with ICH and ICH subtypes.

Large-scale population-based studies including larger numbers of well-phenotyped stroke events, confirmed using imaging data, are needed to enable more reliable estimates of the associations of adiposity (both general and central) with stroke types and subtypes. This is perhaps particularly important in Chinese populations where the rates of ICH are much higher, and mean BMI levels are lower, as compared with more widely studied Western populations. Moreover, robust investigation of the effects of major potential mediators, such as blood pressure, as well as more novel potential mediators (e.g., inflammatory markers, renal and liver function biomarkers) is needed to provide a better understanding of these associations, and of possible approaches to mitigate adiposity-associated risks.

2.2 Adiposity and mortality among individuals with diabetes

The associations of adiposity with all-cause and CVD mortality have been extensively investigated in the general population.[82,102-107] The two largest individual-participant data meta-analyses of general population studies, including predominantly Western population studies, have demonstrated J-shaped associations of BMI with both all-cause and CVD mortality, with the lowest risk within the "normal" BMI range i.e., 18.5 to <25.0 kg/m^2.[102,106] Large prospective Asian general population-based studies among Chinese[103] and Indian[105] populations have similarly reported J-shaped associations of BMI with all-cause and CVD mortality, with the lowest risk of mortality at BMI levels again within the "normal" BMI range. In contrast with these comparatively well-established and consistent associations in the general population, findings from previous studies investigating such associations among individuals with prior diseases, such as diabetes, are less clear.

2.2.1 Objectives

This literature review seeks to provide a comprehensive critical appraisal and summary of published literature examining the prospective associations of adiposity with all-cause and CVD mortality among the general diabetes population. On the basis of this, it aims to highlight gaps in current knowledge, thereby informing the analyses presented in Chapter 6 of this thesis.

2.2.2 Methodology and identified literature

The search was conducted using MEDLINE and Embase databases. The detailed search terms used, and processes for selecting articles for inclusion in the review, are summarised in Table 2.2.1 and Figure 2.2.1, respectively. After using the search terms mentioned in Table 2.2.1, 5240 English language articles were identified on November 1, 2018. The titles of those articles were screened, followed by review of the abstracts of 67 relevant articles to identify those reporting on the association of adiposity with all-cause mortality among individuals with diabetes. Finally, the full texts of 48 articles were reviewed. Individual studies were excluded if they were included in identified meta-analyses (n=17), if they had a non-prospective study design (n=2), or if they included <1000 all-cause mortality deaths (n=18) to ensure robust estimates. One additional article was identified in weekly repeats of the search, undertaken until July 1, 2019. Based on this search methodology, 12 studies examining the association of adiposity with all-cause or CVD mortality among individuals with diabetes were included in this literature review, including five meta-analyses[109,110,114,117,119] and seven prospective studies.[108,111-113,115,116,118] Detailed characteristics of these studies are presented in Tables 2.2.2 and 2.2.3, and summaries of their main results are presented in Tables 2.2.4 and 2.2.5.

2.2.3 Association of adiposity with all-cause mortality among individuals with diabetes

The five identified meta-analyses (all published data meta-analyses)[109,110,114,117,119] and seven individual prospective studies (two Western[108,111] and five East

Asian[112,113,115,116,118] population studies) investigated the association of BMI with all-cause mortality among individuals with diabetes. The substantial body of evidence provided by these previous large prospective studies is reasonably consistent regarding the shape of the association, including across different ethnic groups, showing *reverse* J-shaped,[109-112,115,118] J-shaped[108] or U-shaped[114,119] associations of BMI with all-cause mortality. However, the findings are less consistent regarding the adiposity levels associated with the lowest mortality risk.

A published data meta-analysis by Chang et al, including ~386,000 individuals (~40,000 deaths) from mainly Western population cohort studies, found a *reverse* J-shaped association of BMI with all-cause mortality.[109] Compared with individuals with a BMI in the "normal" range (BMI 18.5 to <25.0 kg/m^2), underweight individuals (BMI <18.5 kg/m^2) had an approximately 60% (HR 1.59 [95% CI 1.32-1.91]) higher risk of all-cause mortality, while individuals classified as overweight (BMI 25.0 to <30.0 kg/m^2) had 14% (0.86 [0.78-0.96]) lower risk of all-cause mortality. Individuals with more extreme BMI levels were not associated with excess risk of all-cause mortality. For instance, the HRs among individuals with BMI 30.0 to <35.0 kg/m^2 and ≥35.0 kg/m^2 were 0.88 (95% CI 0.78-1.00) and 0.99 (0.84-1.16), respectively, as compared to those with BMI in the "normal" range. All studies included in the meta-analysis adjusted for age, sex and traditional vascular risk factors (e.g., smoking, alcohol) as a minimum, with some studies adjusting for additional factors including comorbid diseases, and duration and complications of diabetes. Three further published data meta-analyses included many of the same individual studies,[110,114,119] and unsurprisingly, therefore, showed broadly consistent findings to those of Chang et al.[109] Separate analysis of data from two East Asian studies included in Kwon et al's published data meta-analysis,

comprising ~92,700 individuals with type 2 diabetes, also showed a *reverse* J-shaped association, similar to that seen in the full (U-shaped association), predominantly Western, study population.[114] However, the lowest all-cause mortality risk was at a lower BMI level (22.0 to <23.0 kg/m^2 vs 28.0 to <30.0 kg/m^2) in these East Asian population analyses as compared to the full study population. A further smaller published data meta-analysis from Liu et al, included ~160,000 individuals with type 2 diabetes from predominantly Western population studies, and ~15,000 deaths. This study suggested higher BMI was associated with a lower risk of all-cause mortality, with no evidence of excess mortality risk at the upper end of the BMI range. Compared with individuals with a BMI in the "normal" range, overweigh and obese individuals had 19% (HR 0.81 [95% CI 0.74-0.90]) and 28% (0.72 [0.63-0.81]) lower risk of all-cause mortality, respectively, with no separate investigation of the risk among individuals with more extreme obesity.

A recent report from Jenkins et al, based on data from ~24,000 individuals with type 2 diabetes from the UK Biobank (UKB), reported a *reverse* J-shaped association between BMI and all-cause mortality (~1700 deaths) after exclusion of the first year of follow-up and adjustments for age, smoking, education, socioeconomic status and chronic diseases history.[111] Compared with individuals with BMI levels of 22.5 to <25.0 kg/m^2, underweight individuals (BMI <18.5 kg/m^2) had approximately 4-fold (HR 4.18 [95% CI 2.04-8.57]) higher risk of all-cause mortality, while individuals with BMI levels of 30.0 to <40.0 kg/m^2 had 22% (0.78, 0.65-0.95) lower mortality risk. The lowest mortality risk was at BMI levels within the obese range, regardless of smoking status, although it was somewhat more pronounced among current smokers, compared with previous and never smokers. The UKB study was the only study that also investigated the association of central

adiposity measures (WC and WHR) and body fat percentage with all-cause mortality, and showed similar associations to those of BMI. The other identified Western population study included only ~10,000 individuals with type 2 diabetes from Salford, UK, who were identified through routine data. This study reported all findings by smoking status, in an attempt to reduce confounding, and is described in more detail below.[108]

The Korean Metabolic Risk Factor (KOMERIT) study, based on routine health service data for ~900,000 individuals (~134,000 deaths) with diabetes, was by far the largest East Asian population study investigating the association of BMI with all-cause mortality.[115] After adjustments for age, sex, smoking, alcohol and physical activity, there was a *reverse* J-shaped association between BMI and all-cause mortality. The lowest mortality risk was seen at BMI levels of 25.0 to <30.0 kg/m^2, whereas the highest risk was seen at BMI levels <17.5 kg/m^2. Two further East Asian studies[112,118] similarly showed *reverse* J-shaped associations, with the lowest mortality risk at BMI levels within the overweight range, similar to the KOMERIT study.[115] The Kailuan occupational cohort study, of ~11,500 Chinese hospital employees with type 2 diabetes (~1250 deaths), found a null association between BMI and all-cause mortality at BMI <28.0 kg/m^2 after adjustments for age, sex, smoking, history of prior diseases (e.g., stroke, myocardial infarction [MI], hypertension and cancer), SBP and FPG.[116] However, individuals with BMI ≥28.0 kg/m^2 had 19% lower risk of all-cause mortality (HR 0.81 [95% CI 0.69-0.95]) than those with BMI 18.5 to <24.0 kg/m^2. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, including ~1500 deaths among ~3900 individuals with self-reported diabetes, reported a null association between BMI and all-cause mortality at BMI levels ≥23.0 kg/m^2, but individuals with BMI <20.0 kg/m^2

experienced the highest risk of mortality (HR 1.35 [95% CI 1.16-1.57]) as compared to those with BMI 20.0 to <23.0 kg/m^2, after adjustments for age, sex and lifestyle and diabetes-related (e.g., diabetes treatment and family history) factors. The less clear associations in these two smaller East Asian studies might reflect the smaller number of deaths among their study populations.[113,116]

Several studies have investigated the effect of age on the association of BMI with all-cause mortality, reporting mixed findings.[108,110,114-118] The KOMERIT study[115] showed that the higher risk of mortality at low BMI levels (<17.5 kg/m^2) was more pronounced among younger individuals with diabetes.[115] Similarly, one published data meta-analysis[117] and two individual East Asian population studies[116,118] reported higher excess mortality risk at the lower end of the BMI spectrum among younger individuals. In contrast, two other published data meta-analyses[110,114] and one Western population study[108] reported that the higher risk of mortality at low BMI was similar across age groups. All studies investigating the association of BMI with all-cause mortality by age group broadly consistently reported that BMI levels associated with the lowest mortality risk were similar across different age groups.[108,110,114-118]

Some studies made attempts to address the possible influence of reverse causality or confounding on the observed associations of BMI with all-cause mortality risk. This included excluding the first few years of follow-up and/or restricting analyses to never smokers. All individual prospective studies that excluded the first few (one to five) years of follow-up reported that the findings remained unchanged.[108,111,113,115,116] However, the published data meta-analysis from Kwon et al reported that the lower risk at BMI levels within the obese range

was less pronounced among studies with longer (≥10 years) follow-up.[114] The observed effects of smoking on the association of BMI with all-cause mortality differed between studies. Although some studies showed similar associations in smoking status stratified analyses,[110,112,115] others reported that smoking was an effect modifier.[108,111,114] Kwon et al, for example, observed no association of BMI with all-cause mortality when analyses were restricted to never smokers,[114] whilst the UKB[111] and Salford[108] studies found evidence of differing findings according to smoking status. The UKB study reported that the lowest risk of mortality was at lower BMI levels among never-smokers as compared to ever-smokers (22.5 to <25.0 kg/m^2 vs. 30.0 to <35.0 kg/m^2).[111] Likewise, the Salford study reported that, after adjustment for age and sex, the lowest risk of mortality was at BMI 22.5 to <25.0 kg/m^2 among never-smokers (~420 deaths), but at 25.0 to <35.0 kg/m^2 among ever-smokers (~760 deaths).[108] In addition, in both of these studies, the excess risk of mortality at low BMI levels was more pronounced among ever- than never-smokers.[108,111] The authors of these two studies suggested that smoking is an effect modifier on the association between BMI and all-cause mortality, given that smoking is inversely associated with BMI and is a risk factor for mortality

In summary, the majority of these previous studies examining the association of BMI with all-cause mortality reported *reverse* J-shaped,[109-112,115,118] or U-shaped[114,119] associations among individuals with diabetes, with the highest mortality risk seen at the lower end of the BMI range, irrespective of the overall mean BMI levels. All Western population studies consistently reported that the lowest risk of mortality was at BMI levels between 25.0 kg/m^2 and <35.0 kg/m^2,[108-111,114,117,119] leading to the notion of the so-called “obesity paradox” (i.e., overweight and/or obese individuals experiencing lower risks of mortality than their

"normal" weight counterparts). The findings from East Asian population studies were less consistent. However, the three larger studies did reasonably consistently report that the lowest risk of mortality was at BMI levels between 25.0 kg/m^2 and < <30.0 kg/m^2.[112,115,118] Exclusion of the first few years of follow-up consistently did not change the findings,[108,111,113,115,116] but there were conflicting findings regarding the influence of smoking status.[108,110-112,114,115]

2.2.4 Association of adiposity with CVD mortality among individuals with diabetes

The association of BMI with CVD mortality among individuals with diabetes was examined in three identified published data meta-analyses studies[114,117,119] and in four individual prospective studies (three East Asian population studies[112,113,118] and one Western population study[111]) (Tables 2.2.2 and 2.2.4). Overall, the findings of these studies were somewhat inconsistent. Two published meta-analyses of predominantly Western population studies reported a U-shaped association between BMI and CVD mortality among individuals with type 2 diabetes, with the lowest risk at BMI levels within the obese range.[114,119] A meta-analysis from Zaccardi et al, including ~98,000 individuals and ~4300 CVD deaths, found the lowest CVD mortality risk to be among individuals with a BMI of ~27.0 kg/m^2.[119] Likewise, Kwon et al's published data meta-analysis[114] of ~93,000 individuals (many of whom were also included in Zaccardi et al's study[119]) showed that the lowest CVD mortality risk was at BMI levels of 29.0 to <31.0 kg/m^2. In contrast, a published data meta-analysis from Liu et al including ~7000 individuals found a flat association between BMI and CVD mortality throughout the BMI range

examined (<18.0 kg/m^2 to ≥30.0 kg/m^2), possibly reflecting the small number of CVD deaths (~1200).

The previously described UKB study reported a U-shaped association of BMI with CVD mortality among individuals with diabetes. The lowest mortality risk was at BMI levels of 33.0 to <35.0 kg/m^2.[111] All three identified East Asian population individual prospective studies that examined the association between BMI and CVD mortality among individuals with type 2 diabetes reported no associations.[112,113,118] This included Xu et al's study, which was the largest of these East Asian population studies, involving ~ 53,000 Chinese individuals (~1850 CVD deaths) with type 2 diabetes.[118] Among men, they reported no association throughout the BMI range examined. However, among women, when compared to those with BMI 18.5 to <25.0 kg/m^2, there was a higher mortality risk among those with BMI <18.5 kg/m^2 (HR 1.49 [95% CI 1.15-1.93]), but similar risk among those with BMI >25.0 kg/m^2. Xu et al's findings possibly reflect the small number of deaths, particularly at higher end of BMI spectrum.

The association of central adiposity measures with CVD mortality among individuals with diabetes was not investigated in any of the identified studies. Likewise, attempts to control for reverse causality were limited in these studies. Only the UKB study examined the effect of smoking on the association of BMI with CVD mortality, and reported that the obesity paradox, which is referring to the phenomenon where individuals classified as overweigh/obese have lower risk of CVD mortality than their "normal" weight counterparts, was more pronounced among current smokers than among never-smokers. [111]

In summary, the largest Western population studies consistently reported U-shaped associations between BMI and CVD mortality among individuals with diabetes, with the lowest risk was at BMI levels between 27.0 and <31.0 kg/m^2.[111,114,119] Findings from individual Asian prospective studies were less clear.[112,113,116,118]

2.2.5 Limitations of the evidence and implications for future study

Although the association of adiposity with all-cause mortality among individuals with type 2 diabetes has been investigated in multiple prospective studies, including several large meta-analyses and individual cohorts, these studies have multiple limitations, and gaps in understanding of these associations remain. Firstly, the associations of adiposity measures other than BMI with all-cause mortality were investigated in only one identified study,[111] focusing on a Western population, and no identified studies investigated their associations with CVD mortality. Secondly, attempts to control for reverse causality and residual confounding were limited in many studies, particularly those investigating the association with CVD mortality. Those that did investigate these factors showed largely conflicting findings.[108,110,111,113-115] Thirdly, previous studies which did attempt to control for reverse causality as a result of pre-existing diseases, did not exclude diseases developed during follow-up. Finally, previous studies did not compare the association of adiposity with CVD mortality and incidence among individuals with diabetes, which could provide a better understanding of whether the obesity paradox reflects an association with survival or also with disease incidence.

These limitations indicate the need for large prospective studies investigating the association of a variety of adiposity measures with all-cause and cause-specific, particularly CVD, mortality, and robustly examining the potential influence of reverse causality and potentially important confounding e.g., by using information on prior diseases, on diseases developed during the follow-up period and on other relevant factors (e.g. smoking). Such larger-scale evidence would enable clarification of the levels of general and central adiposity associated with the lowest risk of mortality, and whether this differs according to ethnicity, sex or age. Moreover, comparisons are needed of the association of adiposity with mortality and with incident disease.

Table 2.1.1. Adiposity and risk of stroke types literature review search terms

	Search terms	
Adiposity	obes$.mp	lean mass.mp
	obesity	Body Composition
	Body Image	adiposity paradox.mp
	overweight$.mp	obesity paradox.mp
	Body Mass Index	Waist-Height ratio
	BMI.mp	Waist-Hip ratio
	Body Weight	Waist Circumference
	fat mass.mp	waist.mp
Stroke types	ischemia	hemorrhage
	isch?emi$.mp	Cerebral h?emorrhage.mp
	intracerebral.mp	Cerebral hemorrhage
	h?emorrhage.mp	
Prospective studies	cohort stud$.mp	Longitudinal Studies
	cohort studies.mp	longitudinal.mp
	Cohort Studies	Prospective Studies
	case cohort stud$.mp	prospective.mp
	nested case control study.mp	cohort analysis.mp
	cohort anal$.mp	longitudinal study.mp
	Follow-Up Studies	prospective study.mp
	follow up stud$.mp	Biobank.mp

Table 2.1.2. Adiposity and risk of stroke subtypes literature review search terms

	Search terms	
Adiposity	obes$.mp	lean mass.mp
	obesity	Body Composition
	Body Image	adiposity paradox.mp
	overweight$.mp	obesity paradox.mp
	Body Mass Index	Waist-Height ratio
	BMI.mp	Waist-Hip ratio
	Body Weight	Waist Circumference
	fat mass.mp	waist.mp
Stroke subtypes	ischemia	intracerebral.mp
	isch?emi$.mp	h?amorrhage.mp
	lacunar.mp	Cerebral h?emorrhage.mp
	lacunar infarct.mp	Cerebral hemorrhage
	non-lacunar.mp	lobar.mp
		deep lobar.mp
		non-lobar.mp
Prospective studies	cohort stud$.mp	Longitudinal Studies
	cohort studies.mp	longitudinal.mp
	Cohort Studies	Prospective Studies
	case cohort stud$.mp	prospective.mp
	nested case control study.mp	cohort analysis.mp
	cohort anal$.mp	longitudinal study.mp
	Follow-Up Studies	prospective study.mp
	follow up stud$.mp	Biobank.mp

Table 2.1.3. Characteristics of individual participant data meta-analyses examining the association of adiposity with stroke types

Study	Geographical location (no. of studies)	No. of participants (% of women)	Mean (SD) age, years	Adiposity measurements	Mean duration of follow-up, years	Outcomes (no. of events or deaths)
ACC[86]	China (n=4) Taiwan (n=2) Singapore (n=1) Korea (n=2) Japan (n=8)	820,439 (52)	53 (N/S)	BMI: measured or self-reported	9.7	IS (5771 deaths) HS (6758 deaths)
APCSC men[87] **and women**[88]	Asia (n=35) Australia or New Zealand (n=9)	600,443 (36)	Men: 52 (N/S) Women: 46 (N/S)	BMI: measured or self-reported	Men: 9.4 Women: 7.2	IS (men: 1448 events women: 749 events) HS (men: 1341 events women: 560 events)
ERFC[80]	Europe (n=11) USA (n=7) Japan (n=3)	89,413 (56)	58 (9)	BMI, WC, WHR: measured or self-reported	N/S	IS (2582 events)

ACC: Asian Cohort Consortium, APCSC: Asia Pacific Cohort Studies Collaboration, BMI: body mass index, ERFC: Emerging Risk Factors Collaboration, HS: haemorrhagic stroke, IS: ischaemic stroke, N/S: not stated, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.1.4. Characteristics of individual Western and East Asian population prospective studies examining the association of adiposity with stroke types

First author's name (year of baseline survey)	Geographical location	No. of participants (% of women)	Mean (SD) age, years	Adiposity measurements	Mean duration of follow-up, years	Outcomes (no. of events or deaths)
Kroll[91] **(1996-2001)**	UK	1,277,129 (100)	57 (5)	BMI: self-reported	11.7	IS (9993 events) HS (5852 events) ICH (2790 events)
Hu[92] **(1972-1977)**	Finland	49,996 (52)	N/S	BMI, WC, WHR: measured	19.5	IS (2554 events)
Cho[93] **(2009-2012)**	Korea	21,749,261 (N/S)	N/S	BMI and WC: measured	5.4	IS (181,637 events)
Park[95] **(1992-1995)**	Korea	439,582 (100)	N/S	BMI: measured	13.0	IS (8696 events) HS (3953 events) ICH (2522 events)
Song[90] **(1986-1990)**	Korea	234,863 (0)	N/S	BMI: measured	N/S	IS (3981 events) ICH (1806 events)
Zhou[89] **(1990-1991)**	China	212,000 (0)	54.1 (N/S)	BMI: measured	10.0	IS (1231 deaths) HS (3609 deaths)
Bazzano[94] **(1999-2000)**	China	154,736 (N/S)	N/S	BMI: measured	8.3	IS (3715 events) HS (2482 events)

BMI: body mass index, HS: Haemorrhagic stroke, ICH: intracerebral haemorrhage, IS: Ischaemic stroke, N/S: not stated, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.1.5. Key findings of individual participant data meta-analyses examining the association of adiposity with stroke type

Study	IS (HR, 95% CI)	HS (HR, 95% CI)	Adjustment	Sub-group analyses	Exclusions
ACC[86]	**BMI, kg/m^2** <15.0: 1.51 (0.71-3.23) 15.0-17.4: 1.16 (0.89-1.50) 17.5-19.9: 1.05 (0.90-1.22) 20.0-22.4: 0.92 (0.84-1.01) 22.5-24.9: Reference 25.0-27.4: 1.21 (1.07-1.37) 27.5-29.9: 1.25 (1.02-1.52) 30.0-32.4: 2.00 (1.63-2.45) 32.5-34.9: 2.00 (1.33-3.01) 35.0-50.0: 1.71 (1.14-2.58)	**BMI, kg/m^2** <15.0: 1.37 (0.91-2.07) 15.0-17.4: 1.05 (0.90-1.23) 17.5-19.9: 1.12 (0.91-1.38) 20.0-22.4: 0.99 (0.90-1.09) 22.5-24.9: Reference 25.0-27.4: 1.00 (0.90-1.11) 27.5-29.9: 1.28 (1.12-1.47) 30.0-32.4: 1.58 (1.27-1.95) 32.5-34.9: 2.08 (1.41-3.08) 35.0-50.0: 2.70 (1.44-5.05)	Age, sex, region, smoking, alcohol, SES, marital status, cancer	Age, smoking	First 3 years of follow-up Prior CVD[b]
APCSC men[87] and women[88]	**Per 5 kg/m^2 higher BMI** **Men:** 1.30 (1.12-1.52) **BMI ≥25.0 kg/m^2 vs. 18.5-24.9 kg/m^2** **Women:** 1.23 (1.01-1.51)	**Per 5 kg/m^2 higher BMI** **Men:** 1.08 (0.89-1.34) **BMI ≥25.0 kg/m^2 vs. 18.5-24.9 kg/m^2** **Women:** 0.75 (0.57-0.98)	Age, smoking, SBP, TC	Men: N/S Women: N/S	N/S
ERFC[80]	**Basic adjustments** **Per 1[a] SD higher** **BMI:** 1.20 (1.12-1.28) **WC:** 1.25 (1.18-1.33) **WHR:** 1.25 (1.18-1.32) **Additional adjustments** **Per 1[a] SD higher** **BMI:** 1.06 (0.99-1.13) **WC:** 1.11 (1.05-1.17) **WHR:** 1.14 (1.09-1.20)	N/S	**Basic:** Age, sex, smoking **Additional:** SBP, diabetes, TC, HDL-C	Age, sex	Prior CVD

[a]4.56 kg/m^2 for BMI, 12.6 cm for WC, 0.083 cm for WHR. [b] Sensitivity analysis.
ACC: Asian Cohort Consortium, APCSC: Asia Pacific Cohort Studies Collaboration, BMI: body mass index, CVD: cardiovascular disease, ERFC: Emerging Risk Factors Collaboration, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, HS: haemorrhagic stroke, IS: ischaemic stroke, N/S: not stated, SBP: systolic blood pressure, SES: socioeconomic status, TC: total cholesterol, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.1.6. Key findings of individual Western population prospective studies examining the association of adiposity with stroke types

First author's name	IS (HR, 95% CI)	HS (HR, 95% CI)	Adjustment	Sub-group analysis	Exclusions
Kroll[91]	**BMI, kg/m²**	**BMI, kg/m²**	Age, area, smoking, alcohol, physical activity, height and SES	Age Follow-up Treatment of hypertension, diabetes, cholesterol	Prior CVD
	<22.5: 1.00 (0.95-1.06)	<22.5: 1.00 (0.95-1.06)			
	22.5-24.9: 0.98 (0.94-1.02)	22.5-24.9: 0.86 (0.82-0.90)			
	25.0-27.4: 1.05 (1.01-1.10)	25.0-27.4: 0.81 (0.76-0.85)			
	27.5-29.9: 1.25 (1.19-1.32)	27.5-29.9: 0.79 (0.74-0.85)			
	≥30.0: 1.49 (1.43-1.55)	≥30.0 0.74 (0.70-0.79)			
Hu[92]	**Basic adjustments**		**Basic:** Age, study year, smoking, alcohol, physical activity, SES, family history of stroke **Additional**: SBP, total cholesterol, and diabetes	Sex Smoking Follow-up	Prior CVD
	Men **BMI, kg/m²**				
	<18.5: 0.49 (0.07-3.50)				
	18.5-24.9: Reference				
	25.0-29.9: 1.27 (1.12-1.44)				
	≥30.0: 1.70 (1.45-2.00)				
	Women **BMI, kg/m²**				
	<18.5: 1.81 (0.97-3.40)				
	18.5-24.9: Reference				
	25.0-29.9: 1.11 (0.96-1.28)				
	≥30.0: 1.41 (1.21-1.64)				
	Additional adjustments				
	Men **BMI, kg/m²**				
	<18.5: 0.54 (0.08-3.83)				
	18.5-24.9: Reference				
	25.0-29.9: 1.17 (1.03-1.33)				
	≥30.0: 1.42 (1.21-1.67)				
	Women **BMI, kg/m²**				
	<18.5: 1.81 (0.96-3.40)				
	18.5-24.9: Reference				
	25.0-29.9: 1.06 (0.92-1.23)				
	≥30.0: 1.23 (1.05-1.44)				

BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio, HS: haemorrhagic stroke, IS: ischaemic stroke, SES: socioeconomic status, SBP: systolic blood pressure.

Table 2.1.7. Key findings of individual East Asian population prospective studies examining the association of adiposity with stroke types

First author's name	IS (HR, 95% CI)	HS (HR, 95% CI)	Adjustment	Sub-group analyses	Exclusions
Cho[93]	**BMI, kg/m^2** <18.5: 0.95 (0.93-0.98) 18.5-22.9: Reference 23.0-24.9: 1.01 (0.99-1.02) 25.0-29.9: 1.04 (1.03-1.06) ≥30.0: 1.12 (1.10-1.15) **WC[a]** Level 1: 0.91 (0.90-0.92) Level 2: 0.97 (0.96-0.99) Level 3: Reference Level 4: 1.03 (1.01-1.04) Level 5: 1.07 (1.05-1.09) Level 6: 1.11 (1.08-1.14)	-	Age, sex, smoking, alcohol, physical activity, SES, hypertension, diabetes, dyslipidaemia, COPD, and cancer	Sex	Prior CVD <20 years of age
Park[95]	**Per 1 kg/m^2 higher BMI** **Basic adjustments** 1.05 (1.05-1.06) **Additional adjustments** 1.03 (1.02-1.03)	**Per 1 kg/m^2 higher BMI** **Basic adjustments** 1.02 (1.01-1.03) **Additional adjustments** 1.00 (0.98-1.00)	**Basic:** Age, alcohol, physical activity **Additional:** SBP, FPG, serum cholesterol	Age Smoking	Prior CVD, diabetes, cancer, liver and respiratory disease BMI <16.0 First 2 years of follow-up
Song[90]	**Per 1 kg/m^2 higher BMI** **Basic adjustments** 1.11 (1.09-1.12) **Additional adjustments** 1.06 (1.04-1.07)	**Per 1 kg/m^2 higher BMI[b]** **Basic adjustments** 1.07 (1.05-1.09) **Additional adjustments** 1.02 (1.00-1.04)	**Basic:** Age, smoking, alcohol, physical activity, SES **Additional:** Blood pressure, glucose, cholesterol	N/S	Prior CVD

[a]WC: level 1: men <80 cm and women <75 cm, level 2: men 80 to 84.9 cm and women 75 to 79.9 cm, level 3: men 85 to 89.9 cm and women 80 to 84.9 cm, level 4: men 90 to 94.9 cm and women 85 to 89.9 cm, level 5: men 95 to 99.9 cm and women 90 to 94.9 cm, level 6: men ≥100 cm and women ≥95 cm. [b]These HRs refer to the association of BMI with ICH.
BMI: body mass index, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, FPG: fasting plasma glucose, HR: hazard ratio, HS: haemorrhagic stroke, IS: ischaemic stroke, MI: myocardial infarction, N/S: not stated, SBP: systolic blood pressure, SES: socioeconomic status, WC: waist circumference.

Table 2.1.7. (Continued) Key findings of individual East Asian population prospective studies examining the association of adiposity with stroke types

First author's name	IS (HR, 95% CI)	HS (HR, 95% CI)	Adjustment	Sub-group analyses	Exclusions
Zhou[89]	**BMI, kg/m^2**	**BMI, kg/m^2**	Age, area, smoking, and alcohol	Smoking Duration of follow-up	Prior CVD
	<18.5: 0.89 (0.73-1.08)	<18.5: 1.05 (0.95-1.16)			
	18.5-19.9: 0.92 (0.80-1.05)	18.5-19.9: 0.93 (0.86-1.00)			
	20.0-22.4: 1.00 (0.91-1.10)	20.0-22.4: 1.00 (0.95-1.05)			
	22.5-24.9: 0.94 (0.83-1.06)	22.5-24.9: 1.06 (0.99-1.14)			
	25.0-27.4: 1.16 (0.94-1.43)	25.0-27.4: 1.16 (1.02-1.33)			
	≥27.5: 1.67 (1.28-2.19)	≥27.5 1.67 (1.40-1.98)			
Bazzano[94]	**Basic adjustments**	**Basic adjustments**	**Basic:** Age, sex, area, smoking, alcohol, physical activity, SES **Additional:** SBP, diabetes	Age Sex Smoking	N/S
	BMI, kg/m^2	**BMI, kg/m^2**			
	<18.5: 0.76 (0.66-0.86)	<18.5: 1.00 (0.89-1.13)			
	18.5-24.9: Reference	18.5-24.9: Reference			
	25.0-29.9: 1.60 (1.48-1.72)	25.0-29.9: 1.18 (1.06-1.31)			
	≥30.0: 1.89 (1.66-2.16)	≥30.0: 1.54 (1.27-1.87)			
	Additional adjustments	**Additional adjustments**			
	BMI, kg/m^2	**BMI, kg/m^2**			
	<18.5: 0.89 (0.78-1.02)	<18.5: 1.18 (1.04-1.33)			
	18.5-24.9: Reference	18.5-24.9: Reference			
	25.0-29.9: 1.31 (1.21-1.41)	25.0-29.9: 0.95 (0.85-1.05)			
	≥30.0: 1.31 (1.14-1.49)	≥30.0: 1.06 (0.87-1.29)			

BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio, HS: haemorrhagic stroke, IS: ischaemic stroke, N/S: not stated, SBP: systolic blood pressure, SES: socioeconomic status.

Table 2.1.8. Characteristics of individual prospective studies examining the association of adiposity with stroke subtypes

First author's name (year of baseline survey)	Geographical location	No. of participants (% of women)	Mean (SD) age, years	Anthropometric measurements	Duration of follow-up, years	Outcomes (no. of events)
Li[97] (1990-1994)	Japan	88,756 (52)	N/S	BMI: self-reported	Median: 20	Lacunar IS (1290)
Yatsuya[100] (1987-1989)	USA	13,549 (56)	53.9 (N/S)	BMI, WC, WHR: measured	Median: 16.9	Lacunar IS (138) Non-lacunar IS (338)
Tanizaki[99] (1961)	Japan	1621 (56)	Men: 56 (9) Women: 57 (12)	BMI: measured	32	Lacunar IS (167)
Lioutas[98] (1948 and 1971)	USA	472 (49)	74 (10)	BMI: measured	N/S	Lacunar IS (118)
Biffi[101] (2004-2009)	USA	772 (N/S)	N/S	BMI: measured	N/S	Lobar ICH (188) Non-lobar ICH (196)

BMI: body mass index, ICH: intracerebral haemorrhage, IS: ischaemic stroke, N/S: not stated, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.1.9. Key findings of individual prospective studies examining the association of adiposity with IS subtypes

First author's name	Lacunar IS (RR, 95% CI)	Non-lacunar IS (RR, 95% CI)	Adjustment	Sub-group analysis	Exclusions
Li[97]	**Men** **BMI, kg/m²** <19.0: 0.58 (0.38-0.90) 19.0-20.9: 1.03 (0.83-1.29) 21.0-22.9: 0.89 (0.74-1.08) 23.0-24.9: Reference 25.0-26.9: 1.16 (0.94-1.44) 27.0-29.9: 1.26 (0.97-1.63) ≥30.0: 1.68 (1.08-2.62) **Women** **BMI, kg/m²** <19.0: 0.55 (0.32-0.92) 19.0-20.9: 0.71 (0.51-0.98) 21.0-22.9: 0.72 (0.55-0.94) 23.0-24.9: Reference 25.0-26.9: 0.97 (0.74-1.28) 27.0-29.9: 1.53 (1.15-2.03) ≥30.0: 2.08 (1.41-3.07)	-	Age, smoking, alcohol, physical activity	Sex	Prior CVD or cancer
Yatsuya[100]	**Basic adjustments** **Per 1 SD[a] higher** **BMI**: 1.15 (0.98-1.34) **WC**: 1.24 (1.06-1.45) **WHR**: 1.37 (1.12-1.66) **Additional adjustments** **Per 1 SD[a] higher** **BMI**: 0.84 (0.69-1.01) **WC**: 0.88 (0.73-1.06) **WHR**: 0.94 (0.76-1.17)	**Basic adjustments** **Per 1 SD[a] higher** **BMI:** 1.22 (1.10-1.35) **WC:** 1.29 (1.16-1.43) **WHR:** 1.40 (1.23-1.59) **Additional adjustments** **Per 1 SD[a] higher** **BMI**: 1.00 (0.89-1.12) **WC**: 1.05 (0.93-1.18) **WHR**: 1.16 (1.01-1.34)	**Basic:** Age, sex, race, smoking, cigarette years, alcohol,l SES, physical activity **Additional:** SBP, antihypertensive medication, diabetes, HDL-C, albumin, von Willebrand factor	N/S	N/S
Tanizaki[99]	**Per 1 kg/m² higher BMI** 1.10 (1.00-1.20)	**-**	Age	N/S	N/S
Lioutas[98]	**BMI kg/m²:** <20 vs. ≥20: 0.29 (0.04-2.34) <25 vs. ≥25: 1.61 (0.93-2.77) <30 vs. ≥30: 1.87 (1.13-1.08)	**-**	Age, time between clinical assessment and stroke	N/S	N/S

[a]SD BMI:5.4 kg/m², WC:13.9 cm, WHR:0.078.
BMI: body mass index, CVD: cardiovascular disease, N/S: not stated, RR: relative risk, SBP: systolic blood pressure, IS: ischaemic stroke, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.1.10. Key findings of individual prospective study examining the association of adiposity with ICH subtypes

First author's name	Lobar ICH (OR, 95% CI)	Non-Lobar ICH (OR, 95% CI)	Adjustment	Sub-group analysis	Exclusions
Biffi[101]	**BMI, kg/m^2** <18.5: 1.21 (0.61-2.38) 18.5-24.9: Reference 25.0-30.0: 0.95 (0.61-1.47) >30.0: 1.00 (0.57-1.75)	**BMI, kg/m^2** <18.5: 1.76 (1.14-2.73) 18.5-24.9: Reference 25.0-30.0: 1.40 (0.81-2.44) >30.0: 1.75 (1.12-2.72)	Age, sex, smoking, alcohol, hypertension, diabetes, coronary artery disease, hyperlipidaemia	Sex	N/S

BMI: body mass index, N/S: not stated, OR: odds ratios.

Figure 2.1.1. Flow chart of selection process for articles included in adiposity and risk of stroke types literature review

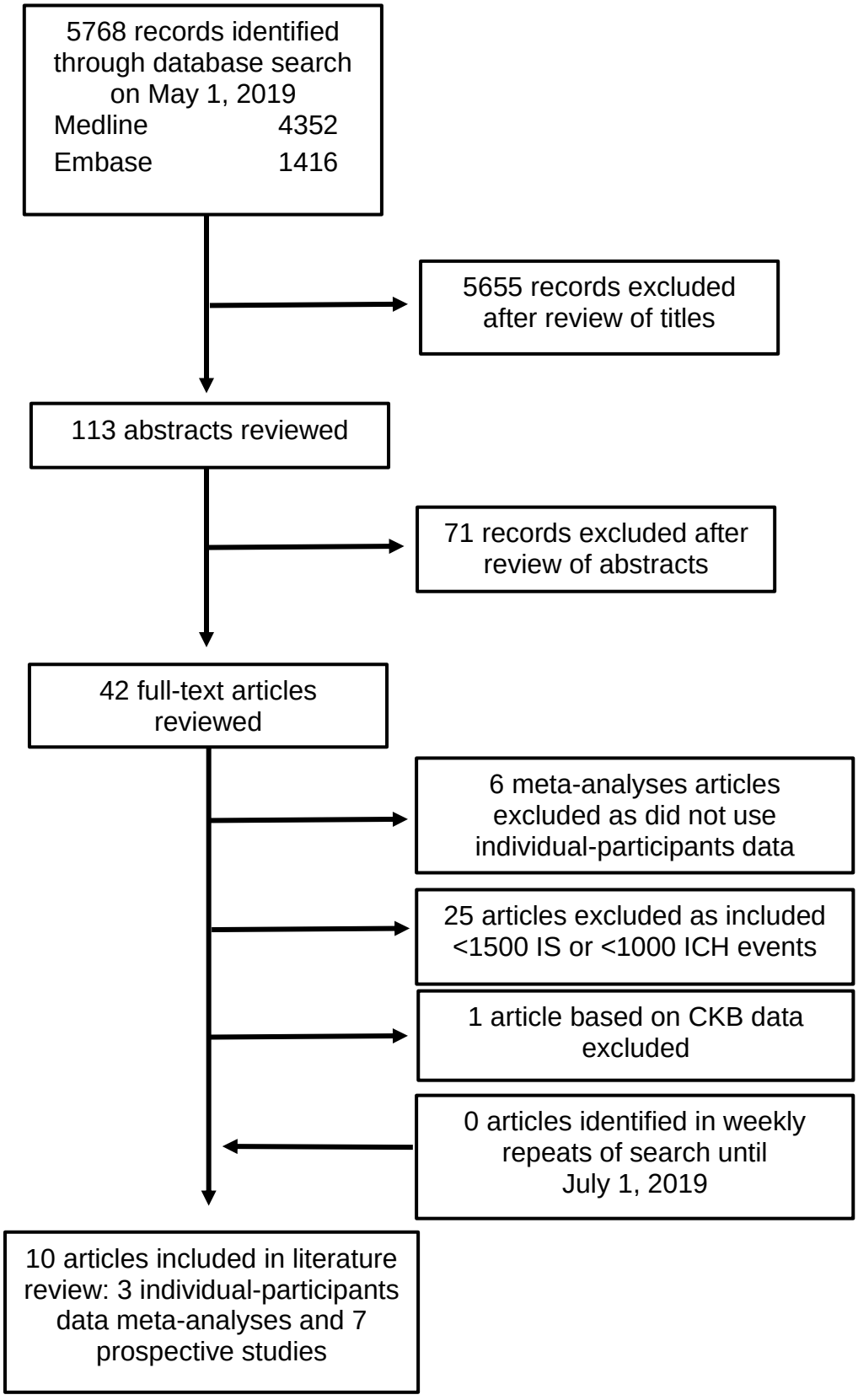


Figure 2.1.2. Flow chart of selection process for articles included in adiposity and risk of stroke subtypes literature review

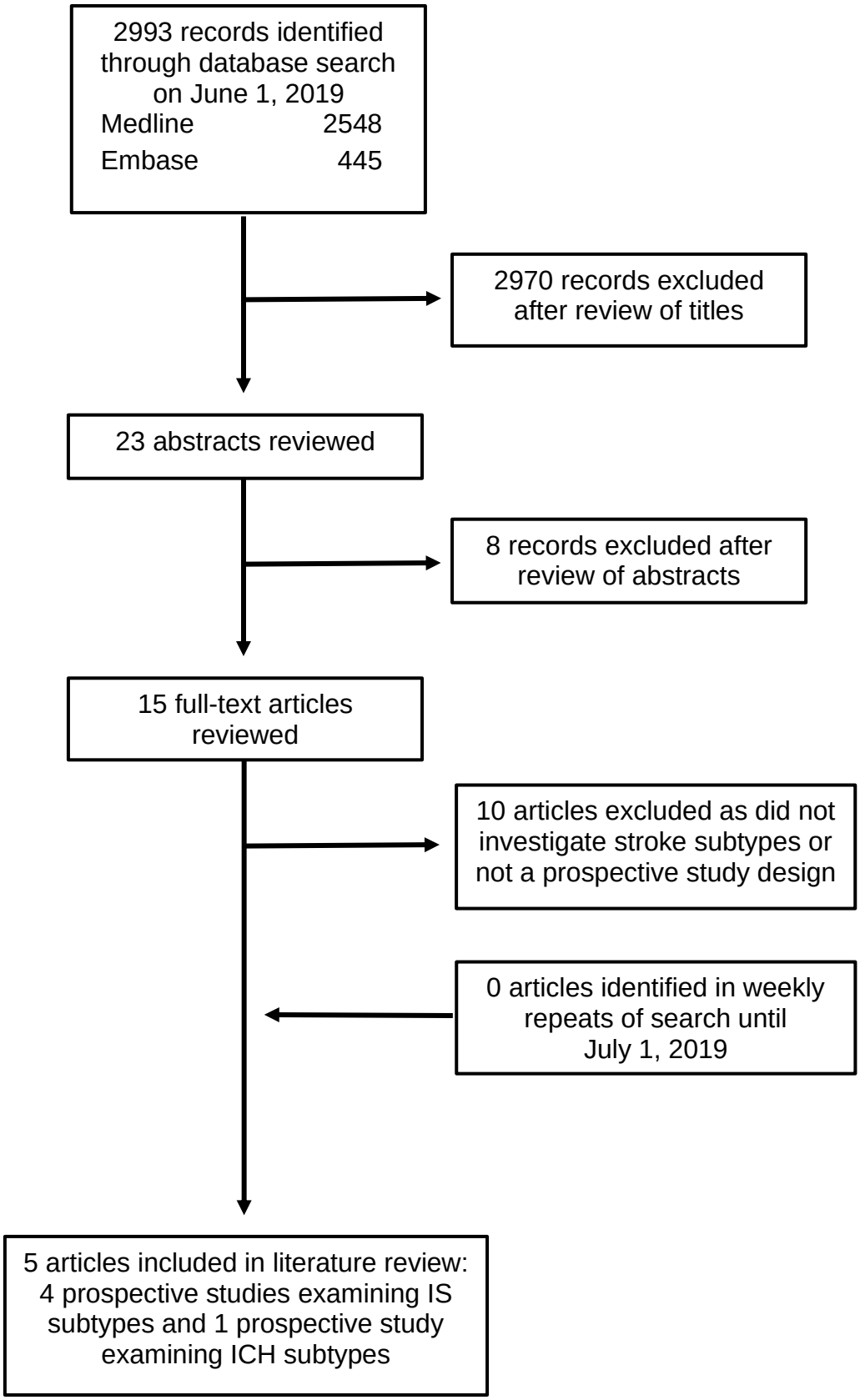


Table 2.2.1. Adiposity and risk of mortality among individuals with diabetes literature review search terms

	Search terms	
Adiposity	obes$.mp	Body Composition
	obesity	adiposity paradox.mp
	overweight$.mp	obesity paradox.mp
	Body Mass Index	Waist-Height ratio
	BMI.mp	Waist-Hip ratio
	Body Weight	Waist Circumference
	fat mass.mp	waist.mp
	lean mass.mp	
Mortality	mortal$.mp	Cerebrovascular Disorders
	Mortality	cerebrovascular.mp
	mortality.mp	cerebrovascular disease.mp
	Mortality, Premature	Myocardial Ischemia
	mortalities.mp	myocardial.mp
	death$.mp	Myocardial Infarction
	Death	coronary heart disease.mp
	Cause of Death	Coronary Disease
	stroke.mp	coronary disease.mp
	Stroke	
Diabetes	diabetes mellitus.mp	diabet$.mp
	Diabetes Mellitus	type 2 diabetes mellitus.mp
	Diabetes Mellitus, Type 2	
	T2DM.mp	
Prospective studies	cohort stud$.mp	Longitudinal Studies
	cohort studies.mp	longitudinal.mp
	Cohort Studies	Prospective Studies
	case cohort stud$.mp	prospective.mp
	nested case control study.mp	cohort analysis.mp
	cohort anal$.mp	longitudinal study.mp
	Follow-Up Studies	prospective study.mp
	follow up stud$.mp	Biobank.mp

Table 2.2.2. Characteristics of published data meta-analyses examining the association of adiposity with mortality among individuals with diabetes

First author's name	Geographical location (no. of studies)	No. of participants (% women)	Age, years	Adiposity measurements	Duration of follow-up, years	Outcomes (no. of studies / deaths)
Kwon[114]	Europe (n=8) USA (n=4) East Asia (n=2) Iran (n=1) Multinational (n=1)	445,125 (N/S)	N/S	BMI: measured (n=13); self-reported (n=3)	N/S	ACM (16 / N/S) CVD (4 / N/S)
Zaccardi[119]	Europe (n=10) USA (n=7) East Asia (n=2) Iran (n=1) Multinational (n=1)	414,587 (N/S)	Range: 40-77	BMI: measured or self-reported	Range: 2.7 to 15.9	ACM (18 / 61,889) CVD (6 / 4470)
Chang[109]	Europe (n=7) USA (n=6) East Asia (n=1) Multinational (n=2)	385,925 (N/S)	N/S	BMI: measured or self-reported	Range: 2.7 to 16.0	ACM (16 / N/S)
Gao[110]	Europe (n=9) USA (n=8) East Asian (n=1) Iran (n=1) Israel (n=1)	250,016 (N/S)	N/S	BMI: measured or self-reported	Range: 2.9 to 16.7	ACM (N/S)
Liu[117]	Europe (n=4) USA (n=3) East Asia (n=1) Israel (n=1)	161,984 (N/S)	N/S	BMI: measured (n=3); self-reported (n=2); medical records (n=4)	Range: 3.7 to 15.0	ACM (13 / N/S) CVD (3 / N/S)

ACM: all-cause mortality, BMI: body mass index, CVD: cardiovascular disease, N/S: not stated.

Table 2.2.3. Characteristics of individual prospective studies examining the association of adiposity with mortality among individuals with diabetes

First author's name (year of baseline survey)	Geographical location	No. of participants (% women)	Age, years	Adiposity measurements	Duration of follow-up, years	Outcomes (no. of deaths)
Lee[115] (2001-2004)	Korea	905,877 (37.2)	Mean: 44.4	BMI: measured	Mean: 10.5	ACM (134,081)
Xu[118] (2004-2014)	China	52,763 (53.2)	Mean: Men: 60.7 Women: 62.0	BMI: self-reported	Mean: 6.0	ACM (4777) CVD (1848)
Kim[112] (2002-2010)	Korea	N/S	Mean: 47.1	BMI: measured	Mean: 7.91	ACM (2361) CVD (367)
Jenkins[111] (2006-2010)	UK	23,842 (N/S)	Range: 40-69	BMI, WC, WHR and BFP: measured	Mean: 7.8	ACM (1723) CVD (N/S)
Kubota[113] (1988-1990)	Japan	3851 (45.1)	Range: 40-79	BMI: measured	Range: 19 to 21	ACM (1457) CVD (445)
Liu[116] (2006-2007)	China	11,449 (16.9)	Mean: 56.6	BMI: measured	Mean: 7.25	ACM (1254)
Badrick [108] (N/S)	UK	10,464 (43.3)	Mean: 67.5	BMI: medical records	Mean: 8.7	ACM (1211)

ACM: all-cause mortality, BFP: body fat percentage, BMI: body mass index, CVD: cardiovascular disease, N/S: not stated, WC: waist circumference, WHR: waist-to-hip ratio.

Table 2.2.4. Key findings of published data meta-analyses examining the association of adiposity with mortality among individuals with diabetes

First author's name	All-cause mortality		CVD mortality		Adjustment	Subgroup analyses	Exclusions
	Shape	**HR (95% CI)**	**Shape**	**HR (95% CI)**			
Kwon[114]	U-shaped	N/S	U-shaped	N/S	Varied	Age Sex Smoking Duration of follow-up Study location	N/S
Zaccardi[119]	U-shaped	N/S	U-shaped	N/S	Varied	Sex	N/S
Chang[109]	Reverse J-shaped	**BMI, kg/m^2** <18.5: 1.59 (1.32-1.91) 18.5-24.9: Reference 25.0-29.9: 0.86 (0.78-0.96) 30.0-34.9: 0.88 (0.78-1.00) >35.0: 0.99 (0.84-1.16)	-	-	Varied	Sex	N/S
Gao[110]	Reverse J-shaped	**BMI, kg/m^2** 18.5-24.9: Reference 25.0-29.9: 0.82 (0.74-0.91) >30.0: 0.87 (0.75-1.00)	-	-	Varied	Age Sex Smoking Follow-up Incidence of diabetes	N/S
Liu[117]	Inverse	**BMI, kg/m^2** 18.5-24.9: Reference 25.0-29.9: 0.81 (0.74-0.90) ≥30.0: 0.72 (0.63-0.81)	-	**BMI, kg/m^2** 18.5-24.9: Reference 25.0-29.9: 0.89 (0.66-1.20) ≥30.0: 0.77 (0.54-1.10)	Varied	Age Sex Study location	BMI <18.5 kg/m^2

All studies used random-effect meta-analyses.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio, N/S: not stated.

Table 2.2.5. Key findings of individual prospective studies examining the association of adiposity with mortality among individuals with diabetes

First author's name	All-cause mortality			CVD mortality			Adjustment	Subgroup analyses	Exclusions
	Shape		HR (95% CI)	Shape		HR (95% CI)			
Lee[115]	**BMI:** reverse J-shaped	**BMI, kg/m²**	Newly-diagnosed/prevalent diabetes:	-		-	Age, sex, smoking, alcohol and physical activity	Age Sex Smoking Duration of follow-up No prior diseases (cancer, heart disease, stroke)	Weight <30.0 kg Height <130 cm (for age <55 years) or <110 cm (for age ≥55 years) BMI ≥50.0 kg/m²
		<17.5:	2.64(2.52.-2.77**)/**3.22(3.03-3.42)						
		17.5-18.9:	1.98(1.09-2.15)/2.38(2.28-2.49)						
		19.0-20.4:	1.69(1.64-1.75)/1.86(1.79-1.92)						
		20.5-21.9:	1.44(1.40-1.48)/1.45(1.41-1.49)						
		22.0-23.4:	1.22(1.19-1.25)/1.23(1.20-1.27)						
		23.5-24.9:	1.08(1.05-1.10)/1.09(1.06-1.12)						
		25.0-26.4:	Reference						
		26.5-27.9:	0.97(0.94-1.00)/0.98(0.94-1.01)						
		28.0-29.4:	0.99(0.95-1.03)/0.95(0.91-0.99)						
		29.5-30.9:	1.05(1.00-1.11)/1.03(0.97-1.08)						
		≥31.0:	1.17(1.11-1.23)/1.08(1.02-1.14)						
Xu[118]	**BMI:** reverse J-shaped	**BMI, kg/m²**	Men/Women	**-**	**BMI, kg/m²**	Men/Women	Age at diabetes diagnosis, hypertension, cancer, family history of diabetes	Age Duration of follow-up	Deaths within 3 months of diabetes diagnosis
		<18.5:	1.29(1.07-1.55)/1.41(1.19-1.68)		<18.5:	1.29(0.93-1.79)/1.49(1.15-1.93)			
		18.5-24.9:	Reference		18.5-24.9:	Reference			
		25.0-29.9:	0.87(0.79-0.95)/ 0.94(0.86-1.03)		25.0-29.9:	0.94(0.81-1.09)/0.91(0.78-1.05)			
		≥30.0:	1.02(0.81-1.29)/1.13(0.93-1.36)		≥30.0:	1.21(0.84-1.75)/1.01(0.74-1.37)			
Kim[112]	**BMI:** reverse J-shaped	**BMI, kg/m²**		**-**	**BMI, kg/m²**		Age, sex, smoking, SES	Age Smoking	First 2 years of follow-up Prior cancer, CVD
		<18.5:	2.22 (1.70-2.89)		<18.5:	1.34 (0.60-3.02)			
		18.5-19.9:	1.73 (1.36-2.21)		18.5-19.9:	1.74 (0.87-3.48)			
		20.0-21.4:	1.30 (1.04-1.62)		20.0-21.4:	1.41 (0.76-2.63)			
		21.5-22.9:	1.21 (0.90-1.49)		21.5-22.9:	1.14 (0.66-1.98)			
		23.0-24.9:	Reference		23.0-24.9:	Reference			
		25.0-26.49:	0.80 (0.63-1.01)		25.0-26.49:	1.03 (0.54-1.98)			
		26.5-27.9:	0.79 (0.59-1.08)		26.5-27.9:	0.79 (0.36-1.73)			
		28.0-29.9:	0.81 (0.57-1.14)		28.0-29.9:	0.79 (0.27-2.30)			
		30.0-32.4:	0.98 (0.57-1.69)		30.0-32.4:	1.20 (0.15-9.76)			
		≥32.5:	1.02 (0.42-2.47)		≥32.5:	1.17 (0.19-7.27)			

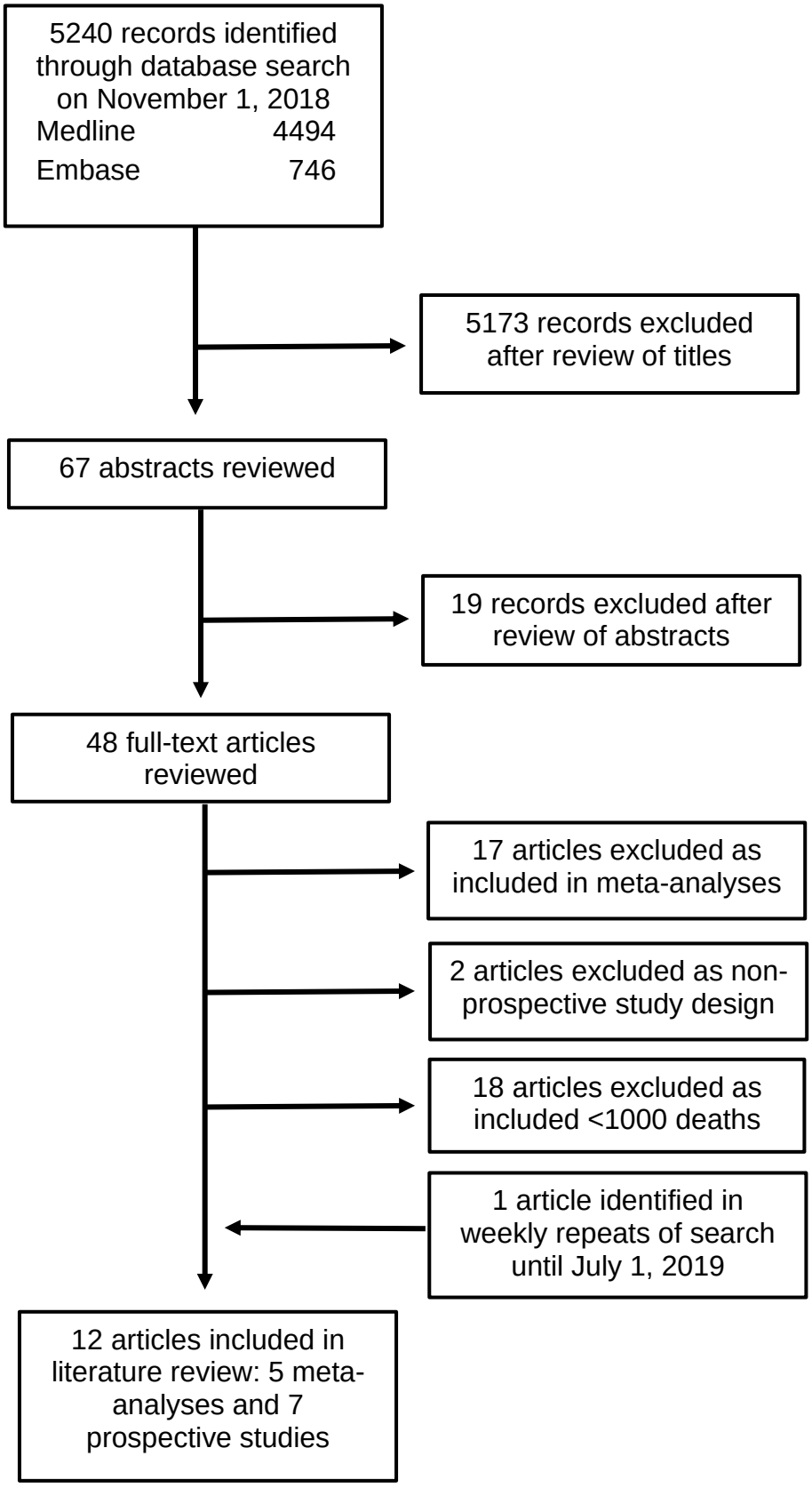
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio, SES: socioeconomic status.

Table 2.2.5. (Continued) Key findings of individual prospective studies examining the association of adiposity with mortality among individuals with diabetes

First author's name	All-cause mortality		CVD mortality		Adjustment	Subgroup analyses	Exclusions
	Shape	HR (95% CI)	Shape	HR (95% CI)			
Jenkins[111]	**BMI**: reverse J-shaped	**BMI, kg/m²**: < 18.5: 4.18(2.04-8.57) 18.40-22.4: 1.20(0.88-1.64) 22.50-24.9: Reference 25.00-29.9: 0.82(0.68-1.00) 30.00-39.9: 0.78(0.65-0.95) ≥40.0: 0.96(0.76-1.20)	**BMI**: J-shaped	N/S	Age, smoking, SES, education, and prior diseases (renal failure, liver failure, heart failure, dementia and cancer)	Sex Smoking Duration of follow-up	N/S
	WC: U-shaped	N/S					
	WHR: U-shaped	N/S					
	BFP: J-shaped	N/S					
Kubota[113]	**-**	**BMI, kg/m²** <20.0: 1.35(1.16-1.57) 20.0–22.9: Reference 23.0–24.9: 0.96(0.83-1.11) ≥25.0: 0.96(0.83-1.10)	**-**	**BMI, kg/m²**: <20.0: 1.40(1.05-1.85) 20.0–22.9: Reference 23.0–24.9: 1.11(0.86-1.43) ≥25.0: 1.10(0.86-1.41)	Age, sex, smoking, alcohol, physical activity, hypertension, diabetes treatment, family history of diabetes, mental stress, sleep duration, energy intake	Age Smoking Duration of follow-up	Prior diseases (CVD, cancer, renal disease, TB)
Liu[116]	**-**	**BMI, kg/m²** <18.5: 1.50(0.96-2.33) 18.5-23.9: Reference 24.0-27.9: 0.83(0.73-1.95) ≥28.0: 0.81(0.69-0.95)	-	-	Age, sex, FPG, smoking, SBP, history of hypertension, stroke, cancer and MI	Age Duration of follow-up No prior cancer	N/S
Badrick[108]	**BMI**: J-shaped	**BMI, kg/m²**: Never smokers/Ever smokers 18.5- 22.4: 1.23(0.81-1.86)/1.34(0.98-1.83) 22.5–24.9: Reference 25.0–29.9: 1.08(0.78-1.50)/0.74(0.59-0.92) 30.0–34.9: 1.12(0.79-1.60)/0.72(0.56-0.92) 35–39.9: 1.45(0.95-2.21)/1.09(0.81-1.46) ≥40.0: 2.87(1.84-4.49)/1.48(1.03-2.11)	-	-	Age, sex	Age Duration of follow-up Smoking No prior CVD, cancer	N/S

BMI: body mass index, BFP: body fat percentage, CVD: cardiovascular diseases, FPG: fasting plasma glucose, HR: hazard ratio, MI: myocardial infarction, N/S: not stated, SBP: systolic blood pressure, SES: socioeconomic status, TB: tuberculosis, WC: waist circumference, WHR: waist-to-hip ratio.

Figure 2.2.1. Flow chart of selection process for articles included in adiposity and risk of mortality among individuals with diabetes literature review



Chapter 3. China Kadoorie Biobank methods and study population

3.1 Study design

The CKB is a large blood-based prospective cohort study of over 0.5 million men and women, from 10 diverse areas of China.[121] The aim of the study is to provide reliable estimates of the associations of established and emerging risk factors with chronic diseases and mortality.[122] This section describes the data collection through detailed questionnaires, physical examinations and blood samples at baseline, and at repeat surveys, and the ongoing follow-up for cause-specific morbidity and mortality.

The study was established by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) of the University of Oxford and the China Centre for Disease Control and Prevention (CDC) in 2004. Oxford University and China CDC and the 10 study areas' local ethics committees provided ethics approval prior to commencement of the study.

3.2 Study population

The baseline survey took place between June 25, 2004, and July 15, 2008 in 10 (five urban and five rural) diverse locations across China (Figure 3.1). The study areas were chosen from China's nationally representative Disease Surveillance Points (DSP) to ensure geographic and socioeconomic diversity, additionally taking account of variation in disease patterns and exposures, population stability, quality of death and disease registries, and local commitment and capacity. In

each area, all permanent non-disabled residents aged 35-74 years were identified through official residential records, and were invited to attend a temporary assessment centre by letter (accompanied by a study information leaflet), delivered door-to-door by local community leaders or health workers following extensive publicity campaigns.

The estimated population response rate for the study was approximately 30%, ranging from 26% to 38% in rural areas and from 16% to 50% in urban areas. Although CKB was not designed to be representative of the Chinese population as a whole, the large size and diversity of the study population are such that the various associations demonstrated would be expected to be generalisable to the Chinese adult population.

3.3 Baseline survey

Eligible residents were invited to attend local assessment centres, and their eligibility to participate in the study was confirmed on arrival using their national identification card. Those slightly outside of the target age range were encouraged to participate. All eligible participants provided informed, written consent prior to participation, including permission to monitor their health through local clinics, hospitals and official disease registration systems, and for long-term storage of blood for anonymised and non-specified medical research. Participants were provided with feedback on their physical measurements and on-site blood tests by a medically-qualified member of study staff.

During the baseline survey, each participant moved through 10 stations in the assessment centre, and, on average, the visit lasted 60-75 minutes in total. Each

participant was interviewed by a member of study staff, using a laptop-based electronic questionnaire developed for the study. Software was used to detect, and bring to the attention of the interviewer, missing or extreme answers/values, logic errors or inconsistencies. Data were collected on demographic characteristics, socioeconomic status (such as household income, education, occupation), lifestyle (such as smoking, alcohol, physical activity and diet), family and personal medical history (such as doctor-diagnosed IHD, stroke/transient ischaemic attack [TIA], hypertension, cancer, chronic obstructive pulmonary disease [COPD] or diabetes), mental health and, for women, reproductive history. Participants who reported certain prior doctor-diagnosed diseases were asked follow-up questions about age at diagnosis and current medication use.

A 10ml non-fasting (except in Zhejiang, where participants were asked to fast prior to their attendance at the assessment centre) venous blood sample was collected into an ethylenediaminetetraacetic acid vacutainer (BD Hemogard™, BD, Franklin Lakes, New Jersey, USA), and the time passed since participants last ate was recorded. Random plasma glucose (RPG) levels were tested immediately using the Johnson & Johnson SureStep Plus Meter (LifeScan, Milipitas, CA). Participants with a RPG level ≥7.8 mmol/L and <11.1 mmol/L were asked to return for a fasting plasma glucose (FPG) test the following day. The samples were kept at 0-4°C with ice packs for a few hours and were then transferred to a local study laboratory, centrifuged and aliquoted into four cryovials. The cryovials were stored at -40°C for 3-4 months. The aliquots of plasma were subsequently transported to Oxford for long-term storage, and the buffy coat samples were transported to Beijing for long-term storage at -80°C.

Physical measurements were undertaken using standard instruments and protocols. Anthropometric measurements were undertaken with participants wearing light clothing, but without shoes. Standing and sitting height were measured to the nearest 0.1 cm using a portable stadiometer. Weight was measured using a body composition analyser (TANITA-TBF-300GS; Tanita Inc., Tokyo, Japan), with subtraction of the weight of clothing (typically 0.5 kg in summer, 1.0 kg in spring/autumn and 2.0-2.5 kg in winter). WC and HC were measured to the nearest 0.1 cm, using a non-stretchable tape. WC was measured midway between the lowest rib and the iliac crest; if it was not possible to identify these landmarks, measurement was made at 1.0 cm above the umbilicus. HC was measured around the maximum circumference of the buttocks. WC and HC were measured over underclothing or, if they were measured over clothes, 1.0-2.0 cm and 1.0-2.5 cm (typically, 1.0 cm if measured over a skirt and 2.5 cm if over trousers), respectively, were subtracted from the measurements. Bio-impedence was measured using the TANITA-TBF-300GS body composition analyser, using foot-to-foot BIA to measure body fat percentage. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). WHR was calculated as the ratio of WC to HC. Fat body mass was calculated as the product of body fat percentage divided by 100 and weight. Lean body mass was calculated by subtracting fat body mass from weight. Additional physical measurements included lung function, heart rate and blood pressure. Blood pressure was measured using a daily-calibrated LifeSource UA-779 digital sphygmomanometer (A&D Instruments; Abingdon, UK) after participants had rested in a sitting position for at least 5 minutes. Two blood pressure measurements were taken; if the

difference between the SBP measurements was >10 mmHg, a third measurement was taken and the last two recorded.

In order to ensure high quality data collection, all standard operating procedures were tested in a pilot study, and all equipment and materials used for the baseline survey were supplied centrally. Regional coordinating centre staff underwent training, which included instruction in practical procedures for conducting the survey, communication skills and the operation and maintenance of equipment. Overall, 354 staff participated in the collection of baseline data, and 95% of data were collected by 201 staff. Each staff member had a unique study identification number that was used prior to entering data on to the laptop to enable monitoring and identification of entries from each staff member. Multiple quality control procedures were undertaken, including regular central monitoring of data, blood processing times and recruitment, regular site visits by regional CDC staff and by CDC and CTSU staff (six monthly and annually, respectively). Within a few weeks of the baseline survey, an ~3% randomly selected sample of participants was invited to participate in a quality control survey. This involved recompletion of the baseline survey questionnaire and some repeat physical measurements.

3.4 Nested case-control study

A nested case-control study of incident stroke types included 5504 IS events, 5559 ICH events, 1907 MI, 483 SAH cases, 880 fatal IHD cases and 10,033 healthy controls. Participants with self-reported doctor-diagnosed IHD, stroke, TIA, cancer or statin use at baseline were excluded from the full CKB cohort, prior to participant selection. ICH cases comprised all such events identified by the

censoring date (January 1, 2014). Of the approximately 25,000 incident IS cases identified by the censoring date, 5504 IS cases that had deoxyribonucleic acid (DNA) extracted and occurring at ≤ 71 years of age were randomly selected. Controls were selected from participants who were free of any specified or unspecified type of stroke, MI or other IHD by the censoring date, and who had DNA extracted and available DNA concentration data. ICH cases were ranked in descending order according to date of event. Possible controls were identified for each ICH case matching for sex, year of birth and study area among participants followed-up and surviving to the date of the case's ICH event. A prioritisation score for each possible control was developed taking into account participation in 1st and 2nd resurveys, and two controls were selected for each ICH case. Controls were randomly selected among individuals matching for region, sex and closest year of birth. The same controls were used for both ICH and IS cases.

Biochemistry measurements were available for the youngest ~1,200 ICH cases, ~1200 IS cases, ~1000 MI cases, ~1200 controls, and ~300 participants included in the nested case control study, with matching baseline and resurvey samples with available 100µl/120µl aliquots. Of the remaining ~20,000 individuals included in the nested case-control study, ~13,000 randomly selected participants had biochemistry measurements. In total, 17 biochemistry measurements were assayed at the Wolfson Laboratory (CTSU, Oxford), using baseline plasma samples among a subset of ~18,000 participants. These are broadly grouped into the following five categories: lipids and lipoproteins, inflammatory biomarkers, renal function biomarkers, liver function biomarkers and other biomarkers (Table 3.1). Lipids and lipoproteins (except LDL-cholesterol, HDL-cholesterol) were assayed using Beckman-Coulter AU680 clinical chemistry analysers (Beckman-

Coulter, UK). LDL-cholesterol and HDL-cholesterol were assayed using N-geneous reagents, calibrations and settings (Genzyme Diagnostics, UK). The laboratory staff were blinded to case and control status and sample batches were measured randomly. The estimated glomerular filtration rate (eGFR), which is a derived renal function biomarker, was calculated using the 4-variable Modification of Diet in Renal Disease equation.[123]

To maximise the follow-up time, the disease status (e.g., IS case, ICH case or control) was re-identified by extending the censoring date to January 1, 2017 (censoring date used for this thesis). A number of previously identified controls developed IS and ICH events. In addition, a number of IS and ICH cases were re-classified as controls, mainly due to the initial linkage errors. Following this re-identification, plasma biomarkers were available for 5488 IS events, 4521 ICH events, 1060 MI, 143 SAH cases, 344 fatal IHD cases and 6542 healthy controls (from hereon in referred to as the CKB biochemistry cohort) (Table 3.2).

3.5 Resurveys

Periodic resurveys are conducted every 4-5 years, and include a randomly selected sample (using cluster random sampling with clinics in each of the study areas as the sampling unit) of ~5% of surviving participants. Resurveys were undertaken in 2008 and 2013-14, collecting the same data as at baseline with certain enhancements, and using the same procedures as used during the baseline survey. In the first resurvey (2008), 24,760 participants were invited to participate, and 19,788 participated (79.9% response rate). In the second resurvey

(2013-14), 33,073 participants were invited to participate, with 25,011 of them attending the resurvey (75.6% response rate).

The resurveys allow assessment of within-person variation in exposures (e.g. anthropometric measures or blood pressure) caused by measurement errors and short-term variation in individual's exposure levels. Single exposure measurements at baseline might not reflect the true or "usual" level of the exposure, resulting in under- or over-estimation of the true association between the exposure and disease of interest. Repeat exposure measurements in an individual will tend to fluctuate around their usual exposure level, and can be used to correct for potential "regression dilution" bias, to estimate the association of usual exposure levels with disease outcomes.[124] Moreover, the repeat interview and physical measurements enable quality control and assessment of the consistency of the data.

3.6 Follow-up and outcome adjudication

Participants are followed-up in all 10 study areas for cause-specific morbidity and mortality. In all areas, mortality is monitored through China CDC's DSP system, with annual checks against local residential and administrative records. Detailed information from death certificates is entered into a database by regional CDC staff, cross-checked by local CKB staff. For the few deaths without recent medical attention, standardised verbal autopsy procedures are used to determine probable cause of death.

Information on incident disease events is obtained from linkage to electronic health insurance records and, in eight study areas (Harbin, Suzhou, Liuzhou, Sichuan,

Gansu, Henan, Zhejiang, and Hunan), from disease registries for certain diseases (including stroke and IHD, diabetes and cancer). Qingdao has a cancer registry, but not stroke, IHD or diabetes registries. Information on ICD-10 coded hospitalisations, and coded examination and treatment procedures is available from national health insurance databases for more than 98% of CKB participants across all study areas.

Underlying causes of death and disease are coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)[125] by trained staff, blinded to baseline information. Detailed outcome validation has been completed (e.g., for diabetes) or is underway to improve the disease phenotype of all reported events of four major diseases (stroke, IHD, cancer, chronic kidney disease), and 1000 randomly selected cases of other diseases (e.g., diabetes and COPD).

The main outcomes examined in this thesis were IS (ICD-10 code I63) and ICH (ICD-10 code I61). For approximately 85% of non-fatal (on the day of the event) stroke events (~42,000 events) the medical records were successfully retrieved. Of these, ~90% had evidence of stroke in their medical records, of which, in turn, ~85% had evidence of primary stroke (stroke as the main diagnosis). Approximately 80% of non-fatal primary stroke events (~27,000) as the main diagnosis, were confirmed on during the adjudication process by senior stroke physicians and neurologists using neuroimaging. The adjudication process mainly focused on non-fatal stroke events (on the day of the event), since the retrieval rate for medical records of fatal stroke events was very poor. Brain imaging and medical records were used to classify adjudicated stroke events by their

pathologic types. The adjudication process is described in detail in Appendix Note A.1. Confirmed IS events with infarct diameter <15 mm reported on brain imaging were classified as lacunar IS. Confirmed IS events were otherwise classified as non-lacunar IS. Confirmed ICH events were sub-classified as lobar or non-lobar according to the location of the defining lesion, determined from radiological reporting. ICH events with the lesion in one or more of the frontal, temporal, parietal or occipital lobes of brain, and with no lesion in any other location, were classified as lobar ICH. ICH events in which the lesion was identified as being in a deep region of the brain, the cerebellum or the brain stem, but with no lesion in any other location, were classified as non-lobar ICH. A small number of confirmed ICH cases with lesions in both lobar and non-lobar areas were excluded from the adjudication process.

3.7 Baseline characteristics of China Kadoorie Biobank participants

Overall, 512,715 participants (including a few slightly outside the target 35-74 year age range) were recruited to CKB and completed the baseline survey, of whom 59.0% (302,510) were women and 44.1% (226,182) were living in urban areas. The number of participants recruited from each of the 10 study areas ranged from 29,686 in Haikou to 63,356 in Henan (Table 3.3). The overall mean (SD) age was 52.0 (10.6) years, with men being slightly older than women (Table 3.4). The prevalence of men reporting no formal education was lower than among women (8.9% and 25.3%, p<0.001). Also, a markedly higher proportion of men than women were current regular smokers (men 61.1% and women 2.4%, p<0.001) and current regular alcohol drinkers (men 38.2% and women 2.5%, p<0.001; Table 3.5). The mean (SD) daily physical activity level was 22.0 (13.1) metabolic

equivalent of task (MET) hours/day in men and 20.4 (10.5) MET hours/day in women.

Overall, at baseline, 11.6% of individuals reported doctor-diagnosed hypertension (men 11.3%, women 11.9%), 3.2% reported diabetes (men 2.9%, women 3.3%), 3.0% IHD (men 2.7%, women 3.2%) and 1.7% stroke/TIA (men 2.3%, women 1.3%). Men had a slightly higher mean (SD) SBP level than women (132.8 [19.1] mmHg and 129.9 [19.7]) mmHg, respectively, $p<0.001$; Table 3.6), whereas men and women had similar mean RPG levels (6.0 [2.3] mmol/L and 6.1 [2.3] mmol/L respectively, $p<0.001$). On average, men were about 10.0 cm taller and 7.5 kg heavier than women, but the two sexes had similar mean BMI levels (men 23.4 [3.1] kg/m^2 and women 23.8 [3.3] kg/m^2, $p<0.001$). According to general population BMI cut-offs, 27.7% of men and 28.9% of women were classified as overweight, and 2.9% of men and 4.7% of women were classified as obese. When Asian-specific BMI cut-offs were used, 41.4% and 11.1% of men, and 42.6% and 13.9% of women, were classified as overweight and obese, respectively. Men had slightly higher mean WC than women (82.0 [9.1] cm vs. 79.1 [9.0] cm, respectively, $p<0.001$), whereas women had higher mean HC than men (91.1 [6.2] cm vs. 90.7 [5.9] cm, respectively, $p<0.001$). Women's mean body fat percentage was approximately 10% higher than men's (32.1 [6.9] vs. 22.0 [5.8] %, respectively, $p<0.001$).

3.8 Baseline characteristics of the China Kadoorie Biobank nested case-control study population

Selected baseline characteristics of the 18,098 participants included in the nested-case control study and with available blood biochemistry data are presented in Table 3.7. Individuals with blood biochemistry data were older (57.0 [SD 10.2] vs. 52.0 [10.6] years, $p<0.001$), included a lower proportion of women (49.2% vs. 59.0%, $p<0.001$) and urban residents (29.9% vs. 44.1%, $p<0.001$), had a higher prevalence of self-reported doctor-diagnosed hypertension (18.7% vs. 11.6%, $p<0.001$), and a higher mean SBP (142.2 [24.6] vs. 131.1 [19.5], $p<0.001$) than the overall CKB population. There were some statistically significant differences in the mean values of anthropometric measures between the nested case control study and total study populations, but these differences were generally not clinically significant. Both baseline and first resurvey biomarker measurements were available for ~300 individuals, and both baseline and second resurvey biomarker measurements were available for ~900 individuals.

3.9 Baseline characteristics of the China Kadoorie Biobank resurvey populations

Selected baseline characteristics of the 19,786 and 25,239 participants included in the first and second resurveys, respectively, and comparisons of these baseline characteristics with those among the whole CKB population are presented in Table 3.8. There were some statistically significant differences in selected baseline characteristics, but these were, again, not generally clinically significant.

Table 3.1. Plasma biomarkers available in CKB

Plasma biomarker category	Plasma biomarkers
Lipids and lipoproteins	Low-density lipoprotein cholesterol
	High-density lipoprotein cholesterol
	Triglycerides
	Total cholesterol
	Apolipoprotein A1
	Apolipoprotein B
Inflammatory biomarkers	High-sensitivity C-reactive protein
	Albumin
	Fibrinogen
Renal function biomarkers	Creatinine
	Cystatin C
	Estimated glomerular filtration rate
Liver function biomarkers	Alanine aminotransferase
	Aspartate aminotransferase
	Gamma-glutamyl transferase
Other	Random plasma glucose
	Uric acid
	Vitamin D

Table 3.2. Disease status at censoring in 2014 and 2017 among individuals with blood biochemistry data

Disease status in 2017	Disease status in 2014						
	IS	ICH	Control	MI	SAH	Fatal IHD	Total
IS	5032	50	358	36	2	10	5488
ICH	7	4438	66	3	6	1	4521
Control	211	398	5897	5	21	10	6542
MI	59	16	21	963	0	1	1060
SAH	1	3	3	0	136	0	143
Fatal IHD	44	7	32	1	3	257	344
Total	5354	4912	6377	1008	168	279	18,098

ICH: intracerebral haemorrhage, IHD: ischaemic heart disease, IS: ischaemic stroke, MI: myocardial infarction, SAH: subarachnoid stroke

Table 3.3. Participant recruitment by study area and sex

Study area	Men (n=210,205)		Women (n=302,510)	
	n	**%**	**n**	**%**
Urban				
Qingdao	15624	7.4	19884	6.6
Harbin	23252	11.1	34304	11.3
Haikou	10794	5.1	18892	6.3
Suzhou	22363	10.6	30896	10.2
Liuzhou	19321	9.2	30852	10.2
Total	**91354**	**43.5**	**134828**	**44.6**
Rural				
Sichuan	21315	10.1	34371	11.4
Gansu	19298	9.2	30589	10.1
Henan	27841	13.2	35515	11.7
Zhejiang	24027	11.4	33677	11.1
Hunan	26370	12.5	33530	11.1
Total	**118851**	**56.5**	**167682**	**55.4**

Table 3.4. Baseline demographic and socioeconomic characteristics and medical history of participants by sex

Characteristic[a]	Men, % (n=210,205)	Women, % (n=302,510)
Age (years)		
30-59	70.2	75.6
60-69	20.3	17.6
70-79	9.5	6.9
Mean (SD)	*52.9 (10.8)*	*51.5 (10.4)*
Marital status		
Married with spouse	92.9	89.0
Widowed, separated or divorced	5.6	10.8
Never married	1.5	0.2
Highest level of education		
No formal a school	8.9	25.3
Primary school	33.4	31.4
Middle school	32.4	25.4
High school	17.5	13.5
College or university	7.9	4.4
Annual household income (Yuan/year)		
<2500	2.9	3.1
2500-4999	6.3	7.1
5000-9999	16.8	19.6
10,000-19,999	28.3	29.6
20,000-34,999	25.4	24.2
≥35,000	20.2	16.5
Self-reported doctor-diagnosed disease		
IHD	2.7	3.2
Stroke/TIA	2.3	1.3
Diabetes	2.9	3.3
Hypertension	11.3	11.9
Chronic kidney disease	1.3	1.6
Chronic hepatitis/cirrhosis	1.7	0.8
Cancer	0.5	0.5

[a]Standardised to the age (5-year groups) and study area (where appropriate).
IHD: ischaemic heart disease, TIA: transient ischaemic attack.

Table 3.5. Baseline lifestyle and dietary characteristics of participants by sex

Characteristic[a]	Men, % (n=210,205)	Women, % (n=302,510)
Smoking		
Never regular	14.4	94.9
Occasional	11.2	1.8
Ex-regular	13.3	0.9
Current regular	61.1	2.4
Alcohol consumption		
Never regular	20.4	63.6
Occasional	37.7	33.5
Ex-regular	3.8	0.4
Current regular	38.2	2.5
Physical activity (MET hours/day)		
<10	25.7	22.3
10-14.9	14.3	21.7
≥15	60.0	56.0
Mean (SD)	*22.0 (13.1)*	*20.4 (10.5)*
Regular consumption of foodstuffs[b]		
Fresh fruits	23.0	31.8
Fresh vegetables	98.3	98.3
Meat	51.6	44.1
Poultry	1.7	1.0
Fish/seafood	9.5	8.5
Soybean	10.7	9.3
Dairy products	11.0	12.6
Fresh eggs	25.7	23.6
Rice	70.6	72.4
Wheat	50.1	45.2

[a]Standardised to the age (5-year groups) and study area structure of the study population (where appropriate). [b]Regular consumption refers to consumption ≥ 4 days/week.
MET: metabolic equivalent of task.

Table 3.6. Baseline physical measurements and plasma glucose by sex

Characteristic[a]	Men (n=210,205)	Women (n=302,510)
Blood pressure and plasma glucose, mean (SD)		
SBP, mmHg	132.8 (19.1)	129.9 (19.7)
DBP, mmHg	79.2 (11.1)	76.8 (10.6)
RPG,[b] mmol/L	6.0 (2.3)	6.1 (2.3)
Anthropometric measures, mean (SD)		
Standing height, cm	165.2 (5.7)	154.1 (5.3)
Sitting height, cm	88.4 (3.3)	83.2 (3.1)
Weight,[c] kg	64.2 (9.7)	56.7 (8.8)
BMI,[d] kg/m^2	23.4 (3.1)	23.8 (3.3)
WC, cm	82.0 (9.1)	79.1 (9.0)
HC, cm	90.7 (5.9)	91.1 (6.2)
WHR	0.90 (0.06)	0.87 (0.07)
Body fat percentage[c]	22.0 (5.8)	32.1 (6.9)
Fat body mass,[c] kg	14.6 (5.6)	18.7 (6.5)
Lean body mass,[c] kg	49.6 (5.5)	38.0 (3.7)
Classification in adiposity categories, %		
General population BMI cut-offs		
Underweight (<18.5 kg/m^2)	4.5	4.3
Normal range (18.5-24.9 kg/m^2)	64.9	62.1
Overweight (25.0-29.9 kg/m^2)	27.7	28.9
Obese (≥30.0 kg/m^2)	2.9	4.7
Asian population BMI cut-offs		
Underweight (<18.5 kg/m^2)	4.5	4.3
Normal weight (18.5-22.9 kg/m^2)	43.0	39.2
Overweight (23.0-27.5 k,g/m^2)	41.4	42.6
Obese (≥27.5 kg/m^2)	11.1	13.9
WC cut-offs[e]		
Normal range	88.9	57.7
Abdominal obese grade 1	8.8	26.0
Abdominal obese grade 2	2.3	16.3

[a]Standardised to the age (5-year groups) and study area structure of the study population (where appropriate).
[b]Data missing for 8341 participants. [c]Data missing for 2 participants. [d]Data missing for 240 participants.
[e]Normal range for men ≤94cm and for women ≤80cm, abdominal obesity grade 1 for men 94.1-102.0 cm and for women 80.1-88.0 cm, and abdominal obesity grade 2 for men >102cm and for women >88cm.
BMI: body mass index, DBP: diastolic blood pressure, HC: hip circumference, SBP: systolic blood pressure, RPG: random plasma glucose, WC: waist circumference, WHR: waist-to-hip ratio.

Table 3.7. Baseline characteristics of the entire study population and of participants with blood biochemistry data included in nested-case control study

Characteristic	Full study population, % (n=512,715)	Nested-case control study population, % (n=18,098)	p-value[a]
Age (years), mean (SD)	52.0 (10.6)	57.0 (10.2)	<0.001
Women, %	59.0	49.2	<0.001
Living in urban area, %	44.1	29.9	<0.001
≥ 6 years of education, %	49.2	38.3	<0.001
Regular alcohol consumption, %	16.7	19.2	<0.001
Regular smoker, %	32.4	41.3	<0.001
Self-reported prevalent disease, %			
Diabetes	3.2	4.6	<0.001
Hypertension	11.6	18.7	<0.001
Chronic kidney disease	1.5	1.5	0.9
Chronic hepatitis/cirrhosis	1.2	1.1	0.3
Physical measurements and RPG, mean (SD)			
SBP, mmHg	131.1 (19.5)	142.2 (24.6)	<0.001
DBP, mmHg	77.8 (10.8)	81.8 (13.0)	<0.001
RPG,[b] mmol/L	6.1 (2.3)	6.4 (3.0)	<0.001
Standing height, cm	158.7 (5.5)	158.5 (5.6)	0.1
Weight, kg	59.8 (9.1)	59.4 (9.3)	0.9
BMI,[c] kg/m^2	23.7 (3.2)	23.6 (3.2)	0.006
WC, cm	80.3 (9.0)	81.0 (9.4)	<0.001
HC, cm	90.9 (6.1)	90.4 (6.2)	0.045
WHR	0.90 (0.06)	0.89 (0.07)	0.020
Body fat percentage[d]	28.0 (6.5)	26.6 (6.6)	<0.001
Fat body mass,[d] kg	17.0 (6.2)	16.2 (6.2)	<0.001
Lean body mass,[d] kg	42.7 (4.6)	43.2 (4.8)	<0.001

[a]Comparison with the full CKB cohort. [b]Data missing for 8341 participants at baseline survey and for 212 participants at nested-case control study. [c]Data missing for 2 participants at baseline survey and for 1 participant at nested-case control study. [d]Data missing for 240 participants at baseline survey and for 26 participants at nested-case control study.

BMI: body mass index, DBP: diastolic blood pressure, HC: hip circumference, MET: metabolic equivalent of task, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference, WHR: waist-to-hip ratio.

Table 3.8. Baseline characteristics of the study population at baseline survey and resurvey participants

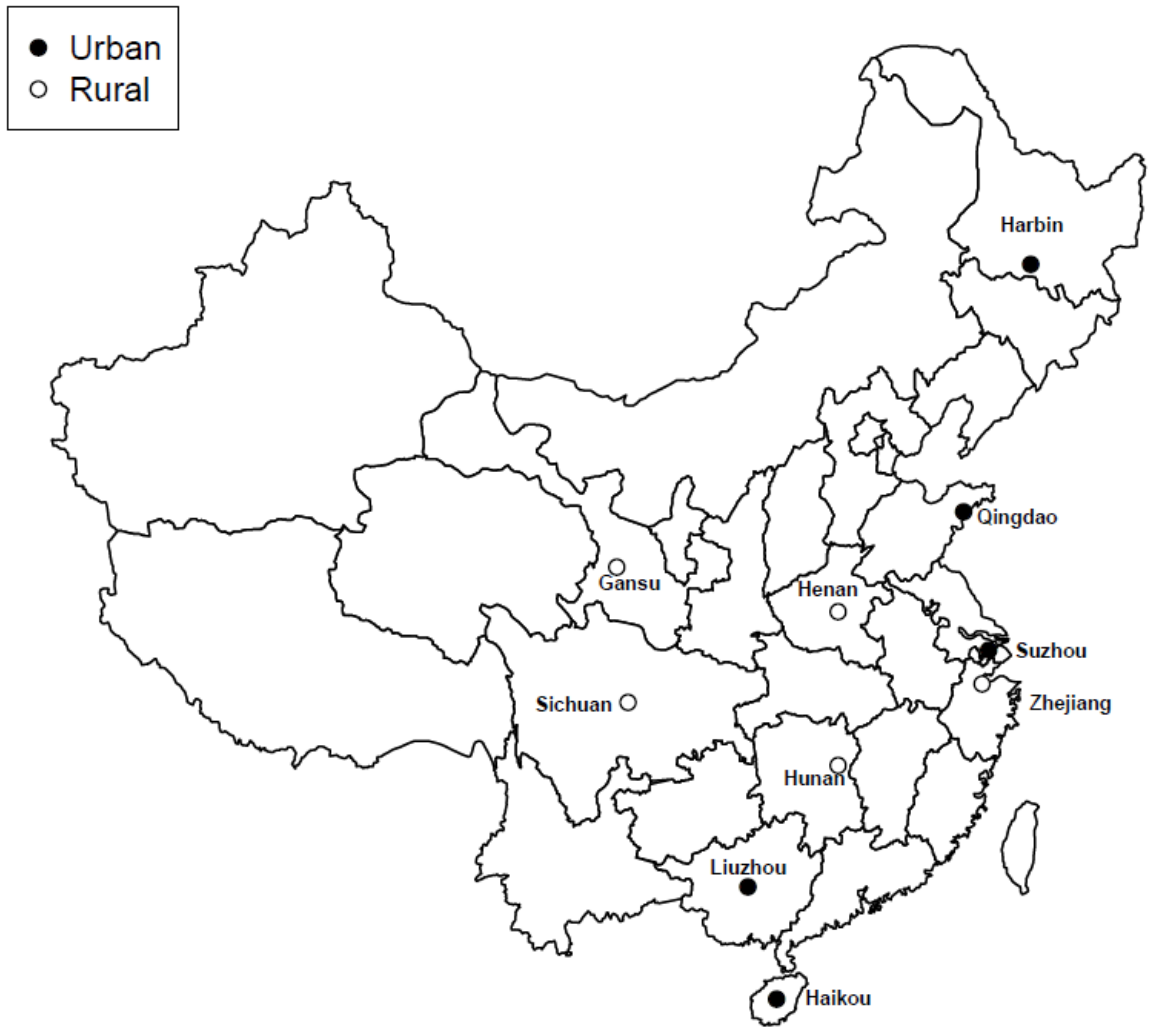
Characteristic	Participants				
	Baseline survey, % (n=512,715)	First resurvey (n=19,786)		Second resurvey (n=25,239)	
		%	p-value[a]	%	p-value[a]
Age (years), mean (SD)	52.0 (10.6)	52.0 (10.4)	0.1	51.6 (10.0)	<0.001
Women, %	59.0	60.7	<0.001	61.7	0.016
Living in urban area, %	44.1	41.3	<0.001	43.4	<0.001
≥ 6 years of education, %	49.2	47.6	<0.001	47.3	0.1
Regular alcohol consumption, %	16.7	16.3	0.1	16.2	<0.001
Regular smoker, %	32.4	30.9	<0.001	30.1	0.1
Self-reported disease, %					
IHD	3.0	3.4	0.002	2.9	0.1
Stroke/TIA	1.7	1.6	0.2	1.1	<0.001
Diabetes	3.2	3.1	0.9	2.6	<0.001
Hypertension	11.6	11.3	0.1	10.5	<0.001
Chronic kidney disease	1.5	1.2	<0.001	1.2	0.002
Chronic hepatitis/cirrhosis	1.2	1.1	0.1	1.0	0.003
Cancer	0.5	0.6	0.3	0.4	0.2
Physical measurements and RPG, mean (SD)					
SBP (mmHg)	131.1 (19.5)	132.2 (19.8)	<0.001	131.0 (19.2)	<0.001
RPG[b] (mmol/L)	6.1 (2.3)	5.9 (2.2)	<0.001	5.9 (2.1)	<0.001
Standing height (cm)	158.7 (5.5)	158.5 (5.4)	0.4	158.3 (5.4)	0.007
Weight (kg)	59.8 (9.1)	59.8 (9.0)	0.4	59.7 (9.0)	0.004
BMI[c] (kg/m^2)	23.7 (3.2)	23.7 (3.2)	0.2	23.7 (3.2)	0.3
WC (cm)	80.3 (9.0)	79.8 (8.8)	0.1	79.5 (8.7)	<0.001
HC (cm)	90.9 (6.1)	90.6 (6.0)	0.018	90.3 (5.9)	0.043
WHR	0.90 (0.06)	0.88 (0.06)	0.4	0.88 (0.06)	<0.001
Body fat percentage[d]	28.0 (6.5)	28.4 (6.5)	0.023	28.3 (6.4)	0.036
Fat body mass[d] (kg)	17.0 (6.2)	17.3 (6.2)	<0.001	17.2 (6.1)	0.5
Lean body mass[d] (kg)	42.7 (4.6)	42.5 (4.5)	0.011	42.4 (4.5)	<0.001

[a]Comparison with the baseline survey participants; [b]Data missing for 8341 participants at baseline survey, for 374 participants at first resurvey and for 331 participants at second resurvey. [c]Data missing for 2 participants at baseline survey and for 1 participant at first and second resurvey. [d]Data missing for 240 participants at baseline survey, for 4 participants at first resurvey and for 6 participants at second resurvey.

BMI: body mass index, DBP: diastolic blood pressure, HC: hip circumference, IHD: ischaemic heart disease, MET: metabolic equivalent of task, RPG: random plasma glucose, SBP: systolic blood pressure, TIA: transient ischaemic attack, WC: waist circumference, WHR: waist-to-hip ratio.

Figure 3.1. Map of China with locations of the China Kadoorie Biobank study areas

Map produced by Dr Hongchao Pan, CTSU University of Oxford



Chapter 4. Association of plasma biomarkers with adiposity and with stroke types

Previous studies have suggested that excess adiposity is associated with higher risks of IHD[80-82] and stroke.[80,81] Moreover, the findings of MR studies support a causal relationship of adiposity with IHD.[68,84,85] However, evidence derived from MR studies in regard to the nature of the relationship of adiposity with stroke types is conflicting.[68,84,85,126] A few studies supported that the association of adiposity with IS is likely to be causal[68,84] but others not,[85,126] whereas for HS the evidence is limited.[68,85] In addition, the underlying mechanisms of those relationships are incompletely understood. Therefore, analyses investigating the mediating effects of cardio-metabolic risk factors, such as blood pressure, lipids, inflammation, renal and liver function, and glycaemia, on the association of adiposity with CVD outcomes are needed. Such studies may enable better understanding of the mechanisms underlying these associations, and inform future strategies for disease prevention. However, such mediation analyses are clearly dependent on robust understanding of the associations of adiposity with cardio-metabolic risk factors, and of the associations of those same risk factors with stroke types.

The first part of this chapter (sub-chapter 4.1) investigates the cross-sectional associations of adiposity with blood pressure, and various plasma biomarkers (e.g., lipids, glucose, renal and liver function biomarkers). In the second part of this chapter (sub-chapter 4.2), the prospective associations of those plasma biomarkers with IS and ICH are investigated. These two sets of analyses will be used to inform analyses examining the mediating effects of these blood pressure

and these plasma biomarkers on the associations of adiposity with stroke types (Chapter 5).

4.1 Associations of general and central adiposity with plasma biomarkers

4.1.1 Background

Adipose tissue is a major site of energy storage in the body. In addition, it serves a complex metabolic role, influencing a range of pathophysiological pathways, including those involved in lipid[44-48] and glucose[127-129] metabolism, inflammatory processes,[49-56] and renal[57-62,130,131] and liver[63-65] function. Much existing evidence on the association of adiposity with markers of these mechanisms and pathways is derived from studies of Western populations, in which high proportions of individuals are overweight or obese. Furthermore, the majority of previous studies have focused on general adiposity measures, predominantly BMI. This indicates the need for better understanding of these associations at the lower end of the adiposity spectrum, and of the relationships of central adiposity with markers of these pathways, since visceral adipose tissue is proposed to be more metabolically active.[22] This is particularly relevant to certain groups, such as East Asian populations, in whom there is a lower prevalence of overweight and obesity, but greater propensity to central adiposity, than in more widely-studied Caucasian populations.[3] Furthermore, given known sex-differences in the amount and distribution of adipose tissue (with a greater tendency towards visceral adipose tissue deposition among men), it is of interest to investigate sex-differences in the associations of adiposity with plasma biomarkers.[132]

This sub-chapter aims to address some of these gaps in current understanding using data from CKB. The objectives are to examine the associations of measures of general and central adiposity with plasma biomarkers, and to investigate whether these associations differ by sex or other major participant characteristics.

4.1.2 Methods

4.1.2.1 Study population

4.1.2.1.1 Summary of study design

Analyses are based on participants from the CKB biochemistry cohort, described in detail in Section 3.4. In summary, a nested case-control study was designed to investigate CVD, including ~15,000 participants who experienced a variety of CVD endpoints (e.g., IS, ICH, SAH, MI, fata IHD), as well as ~10,000 healthy controls. Out of the ~25,000 individuals included in the nested case-control study, plasma biomarker data were available for a subset of ~18,000 participants, constituting the CKB biochemistry cohort. A detailed list of all measured and derived plasma biomarkers is provided in Section 3.4. Analyses for this sub-chapter were restricted to controls included in the CKB biochemistry cohort (n=6542) (from hereon in referred to as the CKB control biochemistry cohort).

4.1.2.1.2 Exclusions

Controls with missing or invalid data for any plasma biomarker (other than fibrinogen and vitamin D, which were available among a smaller sub-set) (n=832), or those with missing adiposity (BMI or body fat percentage, n=9) or RPG (n=67) data were excluded. Following these exclusions, 5634 participants remained for

inclusion in these analyses. A further 2174 and 2288 participants with missing biomarker data were excluded from analyses examining the associations of adiposity with fibrinogen and vitamin D, respectively, leaving 3460 and 3346 participants for inclusion in these analyses.

4.1.2.2 Adiposity measure definitions

The associations of two general (BMI, body fat percentage) and two central (WC, WHR) adiposity measures were examined. The definitions and methods used to assess these adiposity measures are described in detail in Section 3.3.

4.1.2.3 Plasma biomarkers

The analyses focused on 18 plasma biomarkers, which were grouped into five categories: lipids and lipoproteins, inflammatory biomarkers, renal and liver function biomarkers and "other" plasma biomarkers (RPG, uric acid and vitamin D) (Table 3.1).

4.1.2.4 Selection of effect modifiers

According to the known biological relationships of both adiposity and plasma biomarkers, the following variables were identified as potential effect modifiers: smoking,[133-138] alcohol,[135,138-142] SBP, and self-reported hypertension[40,143-145] or diabetes [146-148] at baseline.

4.1.2.5 Statistical analysis

The distribution of each of the plasma biomarkers was examined (Figure B.1-B.3). Given the skewed distribution, and consistent with other studies,[51] natural log transformation was performed for high-sensitivity C-reactive protein (hs-CRP) prior to analysis. The quantile rank values of each adiposity measure were used to create quintiles separately among men and women. The mean values and prevalence of selected baseline characteristics were calculated across these sex-specific quintiles of BMI, WC, WHR and body fat percentage, adjusted for age (5-year groups), sex and study area. The main analyses focused on the BMI and WC, the two most widely used general and central, respectively, adiposity measures. As sensitivity analyses, and for comparison reasons, the associations of WHR and body fat percentage with plasma biomarkers were also estimated. Pearson correlation coefficients between adiposity measures and biomarkers were calculated using residuals adjusted for age (5-year groups) and study area in sex-specific analyses, and additionally for sex in combined analyses.

For analyses examining adiposity measures as categorical variables, adjusted means of baseline plasma biomarkers were calculated for each sex-specific adiposity quintile using multiple linear regression, adjusted for age (5-year groups) and study area. In sex-combined analyses, the mean values of plasma biomarkers were estimated separately among men and women (as described above) and then the weighted average, based on the number of men and women, of those values was estimated. The adjusted mean values of each plasma biomarker were plotted against the mean levels of the adiposity measure for each quintile, together with the 95% CIs. Effect modification of the associations between adiposity measures

and plasma biomarkers was assessed by performing separate analyses within each level of the possible effect modifier, and comparing the resulting strengths of association per 1 SD higher adiposity measure.

Plasma biomarkers were regressed on levels of each adiposity measure as a continuous variable using multiple linear regression, adjusted for age (5-year groups) and study area. For visual comparison of the associations of general and central adiposity measures with plasma biomarkers, the t-values of each of the individual associations were plotted using a Manhattan style plot.

All statistical analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). All plots were produced using JASPER, an R package developed within CTSU, in R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

4.1.3 Results

In this subset of CKB participants, the mean (SD) age was 57.4 (1.4) years, 47.2% were women and 23.1% lived in urban areas (Table 4.1.1). The mean BMI overall was 23.0 (3.1) kg/m^2, and was slightly higher among women than men (23.4 [SD 3.1] vs. 22.6 [3.5] kg/m^2), and in urban than rural areas (24.2 [3.4] vs. 22.6 [3.3] kg/m^2). Overall, 26.3% of participants were overweight and 2.9% were obese. Men with lower BMI were more likely to be regular smokers. Moreover, individuals with lower BMI were less likely to have diabetes. There was a positive linear association between BMI and blood pressure; each 1 SD higher BMI (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) was associated with 5.1 mmHg higher SBP and 2.4 mmHg higher DBP, similar to the association observed in the whole CKB

cohort (Figure 4.1.1). WC showed largely similar associations with baseline characteristics (Table 4.1.2), including blood pressure (Figure 4.1.1). BMI, body fat percentage and WC were strongly inter-correlated, similarly among men and women ($r>0.75$; Table 4.1.3). In addition, BMI and WC were correlated with most plasma biomarkers ($-0.3<r<0.3$) (Table 4.1.4).

4.1.3.1 Lipids and lipoproteins

Figure 4.1.2 shows the associations of BMI and WC with plasma lipids and lipoproteins. In this and other similar figures, the x- and y-axes are presented on an SD scale, with the y-axis length equivalent to approximately ±1 SD from the mean plasma biomarker level. BMI was positively and broadly linearly associated with LDL-related biomarkers (LDL-cholesterol and apolipoprotein B [ApoB]) and triglycerides, and negatively and approximately linearly associated with HDL-related biomarkers (HDL-cholesterol and apolipoprotein A1 [ApoA1]) (Figure 4.1.2). Similar associations were observed with other adiposity measures (Figures 4.1.2, B.4 and B.5). For a given BMI, all lipid and lipoprotein concentrations were slightly higher among women than among men. The levels of LDL-related biomarkers were much higher in urban than in rural areas at a given adiposity level, whereas HDL-related biomarkers were similar in urban and rural areas (Figure 4.1.3). For a given BMI, the mean levels of most lipids tended to be higher at older ages (Figure 4.1.4) and among individuals with higher blood pressure (Figure 4.1.5). The strength of the associations of BMI with lipids and lipoproteins were generally similar across population subgroups, e.g., defined by sex (Figure 4.1.2 and Table 4.1.5), urban/rural residence (Figure 4.1.3 and Table 4.1.6), age (Figure 4.1.4), SBP (Figures 4.1.5), and prior-diseases (Figure B.6 and B7), and,

among men, by smoking and alcohol status (Figure B.8 and B9). An exception to this was LDL-cholesterol (and related biomarkers), which showed a stronger association with BMI in rural than in urban areas (0.14 [SE 0.01] vs. 0.07 [0.02] mmol/L per 1 SD higher BMI; Table 4.1.6).

4.1.3.2 Inflammatory biomarkers

Among women, there were reasonably linear, positive associations of BMI with log hs-CRP, and fibrinogen throughout the BMI range examined (Figure 4.1.6). However, among men, although there were similar positive associations at BMI levels >22.5 kg/m^2, at lower BMI levels there was no clear association with log hs-CRP and an inverse association of BMI with fibrinogen (giving an overall U-shape). The associations among men remained largely unchanged in analyses undertaken separately among ever- and never-smokers (Figure B.10). For a given BMI, fibrinogen levels were higher among women and in rural areas as compared to men and urban areas, respectively (Figures 4.1.6 and 4.1.7), and levels of both hs-CRP and fibrinogen were higher at older ages (Figure 4.1.8). There was a positive linear association between BMI and albumin, somewhat stronger among men than women (0.47 [SE 0.05] vs. 0.18 [0.05] g/L, per 1 SD higher BMI; Figure 4.1.6 and Table 4.1.5). Women and younger individuals had higher albumin levels than men and older individuals, respectively, at a given BMI. The levels of all three inflammatory biomarkers examined were higher among individuals with higher blood pressure at a given BMI. There were no notable differences in the associations of BMI with inflammatory biomarkers across other subgroups studied (Figures 4.1.9 and B.11-B13), and other adiposity measures showed largely similar associations to those of BMI (Figures 4.1.6, B.14 and B.15).

4.1.3.3 Renal function biomarkers

Higher BMI levels were associated with a declining renal function profile (Figure 4.1.6). There was a positive association of BMI with creatinine, stronger among men than women (1.70 [SE 0.33] vs. 0.33 [0.33] umol/L, per 1 SD higher BMI) (Table 4.1.5). Among men, there was no clear association between BMI and cystatin C. Among women, however, although there was a flat association at BMI levels <22.5. kg/m^2, there was a positive association at higher BMI levels (0.02 [SE 0.02] mg/L per 1 SD higher BMI). There was a negative linear association of BMI with eGFR, which was slightly stronger among men than women (3.61 [SE 0.40] vs. 1.92 [0.42] ml/min/1.73m^2). Similar trends of BMI with renal biomarkers were seen in other population subgroups (e.g., by alcohol consumption among men and by diabetes, hypertension status at baseline) (Figures B.11-B.13) and the associations of other adiposity measures with renal biomarkers were similar to those of BMI (Figures 4.1.6, B.14 and B.15). At a given BMI, individuals living in urban areas appeared to have lower renal function than those living in rural areas, when assessing renal function through creatinine and eGFR. However, the opposite was observed when renal function was assessed using cystatin C levels, i.e., cystatin C levels were higher in rural areas (Figure 4.1.7). For a given BMI, men had higher levels of creatinine and cystatin C than women, and renal function, as assessed by all three biomarkers, appeared to be higher among younger individuals (Figure 4.1.8) and those with SBP <120 mmHg (Figure 4.1.9).

4.1.3.4 Liver function biomarkers

The concentrations of all three liver function biomarkers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT]) were higher among men than women at a given BMI (Figure 4.1.10). ALT and AST levels were also higher, at a given level of adiposity, in rural than in urban areas (Figure 4.1.11). Among men, at given BMI levels there was no clear difference in ALT and AST levels between ever- and never-regular alcohol drinkers, but GGT concentrations were consistently higher at all BMI levels among ever- than never-regular alcohol drinkers (Figure B.16). There were positive, reasonably linear, associations of BMI with ALT and GGT, but no clear association between BMI and AST (Figure 4.1.10). The strengths of these associations of BMI with biomarkers of liver function were similar across the subgroups examined (Figures 4.1.10-4.1.13 and B.16-B.19). The associations of other adiposity measures with liver function biomarkers were similar to those of BMI (Figures 4.1.10, B.20 and B.21).

4.1.3.5 Other biomarkers

For a given BMI, RPG levels were slightly lower among men than women (Figure 4.1.10), in younger individuals (Figure 4.1.12) and in individuals with SBP <120 mmHg (Figure 4.1.13). BMI was positively associated with RPG, and the shape and strength of the association was similar across all subgroups examined (Figures 4.1.10-4.1.13). The associations of central adiposity measures (WC and WHR) and body fat percentage with RPG were similar to those of BMI (Figures 4.1.10, B.20 and B.21).

At a given BMI level, uric acid levels were higher among men than women (Figure 4.1.10), among those living in urban areas (Figure 4.1.11), and among older individuals (Figure 4.1.12). Among men, uric acid levels were higher with ever-regular, compared with never-regular, alcohol consumption (Figure B.16). There was a strong positive linear association of BMI with uric acid. The trend of this association was stronger in men than women (19.42 [SE 1.34] vs. 16.69 [1.20] umol/L per 1 SD higher BMI) (Figure 4.1.10 and Table 4.1.5), and in urban than rural areas (21.27 [1.89] vs. 17.59 [1.04] umol/L) (Figure 4.1.11 and Table 4.1.6). There was no clear difference in trend across other subgroups examined (Figures 4.1.12 and 4.1.13 and B.16-B.19), and the associations of other adiposity measures with uric acid were similar to those of BMI (Figures B.20 and B.21).

Vitamin D levels were higher among men than women, in individuals with lower SBP and in older individuals at a given level of adiposity (Figure 4.1.10). There was an inverse association of BMI with vitamin D, which was moderately stronger among men than women (0.54 [SE 0.17] vs. 0.21 [0.13] ng/ml, per 1 SD higher BMI) (Figure 4.1.10 and Table 4.1.5), but similar across the other subgroups examined (Figures 4.1.11-4.1.13). Also, the associations of other adiposity measures with vitamin D were similar to that of BMI (Figures 4.1.10, B.20 and B.21).

Figure 4.1.14 provides a visual comparison of t-values from the individual associations of measures of BMI, WC and WHR with the plasma biomarkers studied, by sex. The strength of the associations of the three adiposity measures with most of the plasma biomarkers were generally comparable. Among men, the strongest positive associations of all adiposity measures were with triglycerides,

ApoB and uric acid. The strongest negative associations were with HDL-cholesterol, ApoA1 and eGFR. Although, the strength of the associations of BMI with plasma biomarkers differed slightly when compared with those of central adiposity measures, the observed differences are unlikely to be clinically significant. For instance, BMI was moderately more strongly associated with albumin (0.47 [SE 0.05] per 1 SD higher BMI), than were central adiposity measures (0.39 [0.05] and 0.18 [0.04] g/L per 1 SD higher WC and WHR respectively) (Table 4.1.5). However, central adiposity measures showed moderately stronger associations than BMI with GGT (4.74 [SE 0.99], 6.25 [0.98] and 6.15 [0.86] u/L per 1 SD higher BMI, WC and WHR, respectively). Among women, triglycerides, hs-CRP and uric acid showed the strongest positive associations with adiposity, while the strongest negative associations were again with HDL-cholesterol, ApoA1 and eGFR. The associations of central adiposity measures with RPG and GGT were moderately stronger than those of BMI among women.

4.1.4 Discussion

The presented analyses are among the most detailed investigations of the associations of adiposity with plasma biomarkers in an East Asian population. Findings from CKB showed that excess adiposity is associated with largely adverse biomarker profiles, including dyslipidaemia, higher levels of glycaemia, and inflammatory and liver function biomarkers, and lower renal function. General and central adiposity measures showed largely comparable associations with the biomarkers studied.

The primary aim of this sub-chapter is to explore these associations of adiposity measures with plasma biomarkers in order to inform subsequent investigation of the possible mediating roles of these biomarkers in the association of adiposity with stroke types (Chapter 5). In addition, the availability of data on the same anthropometric measures and plasma biomarkers among UKB participants provides unique opportunity for comparisons with the observed associations in CKB, and for understanding of similarities and differences between these two diverse study populations. Discussion of the presented CKB findings therefore includes comparison with findings of similar analyses among approximately 300,000 UKB participants. The UKB study design and methods are described in detail elsewhere,[149] and a summary is provided in Appendix Note B.1, along with a description of the statistical methods used in these analyses.

4.1.4.1 Lipids and lipoproteins

In CKB, higher levels of adiposity were associated with higher concentrations of LDL-related biomarkers and triglycerides, and with lower levels of HDL-related biomarkers, consistent with previous studies.[44-48] Although the concentrations of all lipids and lipoproteins were higher among women than men for a given adiposity level (consistent with a previous study of ~4000 Chinese adults from Jiangxi province) there were no clear sex-differences in the strengths of the associations of adiposity with these biomarkers. Urban-rural differences were observed in the relationship of adiposity with LDL-related biomarkers in CKB. Although, for a given BMI, the concentrations of these biomarkers were consistently higher in urban than in rural areas (possibly reflecting socioeconomic, dietary or occupational differences[150]), the associations were stronger in rural areas. To my knowledge,

none of the previous East Asian studies have examined these associations separately in urban and rural areas. However, a study of ~33,000 individuals from Malawi found similar urban-rural differences in the association of BMI with LDL-cholesterol.[151]

In CKB, the BMI range examined was between approximately 18.0 to 30.0 kg/m^2, whereas for UKB, it was from approximately 22.0 to 35.0 kg/m^2. Likewise, the WC range examined in CKB was from 65 to 90 cm, and in UKB was from 70 to 120 cm. In addition, in UKB the mean BMI (men 27.4 [SD 4.1] kg/m^2 and women 26.7 [5.1] kg/m^2) and WC (men 95.6 [SD 10.9] cm and women 83.6 [12.2] cm) levels were higher as compared to mean BMI (men 23.4 [3.1] kg/m^2 and women 22.6 [3.5] kg/m^2) and WC (men 79.9 [SD 9.5] cm and women 78.5 [9.5] cm) in CKB. For a given BMI, CKB participants had lower concentrations of lipids and lipoproteins than UKB participants (Figure 4.1.2 and 4.1.15). Within the BMI range common to both study populations, the strength of the associations of BMI with lipids and lipoproteins was similar in the two study populations (Tables 4.1.5 and B.2). However, at the upper ends of the UKB BMI (≥31.0 kg/m^2) and WC (≥82.0 and ≥95.0 cm for women and men, respectively) ranges, there was an inverse association of adiposity with LDL-cholesterol. In CKB, evidence of the association of BMI with LDL-cholesterol at BMI ≥31.0 kg/m^2 is limited given the BMI distribution of the study population. However, in CKB at WC ≥82.0 and ≥95.0 cm among women and men, respectively, there was a positive linear association between BMI and LDL-cholesterol, in contrast with the inverse association observed in UKB at those WC levels. This CKB observation is similar to findings reported by the Strong Heart Study of ~1500 American Indians (BMI range approximately from 18.0 to 70.0 kg/m^2).[46] The inverse association at high adiposity

levels in UKB might reflect metabolic consequences of more frequent use of statins or other lipid-modification therapies among individuals with the highest BMI levels in the UKB population (although efforts were made to exclude individuals on statins, this is susceptible to misreporting and may not have excluded individuals using other lipid-lowering agents in the absence of statin therapy).

4.1.4.2 Inflammatory biomarkers

Excess adiposity is known to be associated with chronic low-grade inflammation, both through direct release of inflammatory mediators from adipose tissue and through stimulation of hepatic synthesis of inflammatory markers such as CRP.[21] The associations of BMI with hs-CRP and fibrinogen among women in CKB are consistent with these mechanisms. Higher hs-CRP concentrations at higher BMI were also seen among women in UKB (Figure 4.1.16) and in previous studies.[49-56] However, consistent with other trans-ethnic comparisons, the association of BMI with hs-CRP was slightly stronger in UKB than in CKB (0.56 log mg/L per 1 SD [5.1 kg/m^2] higher vs. 0.34 log mg/L per 1 SD [3.5 kg/m^2] higher; Table A.2). These ethnic-differences may reflect lifestyle (e.g., dietary[152]) differences or differenced in the BMI.

Among CKB men, there were similar positive associations of BMI with hs-CRP and fibrinogen at BMI ≥23.0 kg/m^2, but flat and inverse associations of BMI with hs-CRP and fibrinogen, respectively, at lower BMI levels. This contrasts with the positive association of BMI with hs-CRP among men in UKB throughout the full BMI range examined, and with similar associations of BMI with hs-CRP and fibrinogen, in previous studies.[49-56] These inconsistent findings might again reflect

differences in the adiposity levels examined, since few previous studies have been able to precisely estimate the relationship of BMI with inflammatory biomarkers at such low BMI levels as in CKB.[52,53,56] In order to investigate the possibility that the inverse association with fibrinogen at low BMI levels among men in CKB might reflect the high prevalence of smoking in this population,[153-155] the associations were re-examined after excluding ever-smokers. However, the associations remained unchanged in these analyses. Another, possible explanation for these findings might be reverse causality due to pre-existing diseases associated with weight loss and with inflammation. When analyses were repeated excluding individuals with a prior history of major diseases (diabetes, hypertension) the findings did not change, although these diseases are not expected to be associated with weight lost and the number of individuals included in these analyses was too small to draw any firm conclusions.

In CKB, there was a positive linear association of adiposity with albumin, which may be considered as a marker of inflammation or nutritional status, among both men and women. In contrast, among UKB women there was an inverse association between BMI and albumin throughout the full BMI range examined. Among UKB men, there was no apparent association at BMI <32.0 kg/m^2 and an inverse association at BMI >32.0 kg/m^2 (Figure 4.1.16). Although evidence from previous general population studies is limited, a small study of 122 outpatients from a hospital in the USA reported that obesity is associated with lower levels of albumin, similar to the UKB findings. The inconsistency in the findings between study populations might reflect differences in adiposity ranges studied, or the association of fat-rich diets with both excess weight and lower albumin levels.[156]

4.1.4.3 Renal function biomarkers

In CKB, higher adiposity levels were associated with lower renal function, as assessed by creatinine and eGFR. These findings were qualitatively consistent with those in UKB within the overlapping adiposity ranges (Figure 4.1.16), and with those reported in many previous studies.[57-62] However, the strength of the association of BMI with eGFR was slightly stronger in CKB than in UKB, particularly among men (-3.6 vs. -1.35 ml/min/1.73m^2 per 1 SD higher BMI). A recent individual participant data meta-analysis, including over five million participants, similarly showed a slightly stronger inverse association of BMI with GFR in Asian, (~1.1 million individuals) compared with Western, populations.[61] These ethnic-differences might reflect poorer control of blood pressure[157] and diabetes[158,159] among Asian populations, since it has been suggested that blood pressure,[40] diabetes[146] and inflammation[60] may mediate the association of adiposity with renal impairment. However, in CKB, additional adjustments for diabetes, SBP and hs-CRP did not materially change the findings (data not shown).

In CKB, there was no clear association of BMI with cystatin-C throughout the BMI range examined among men, or at the lower end of the BMI range among women. In contrast, UKB data (Figure 4.1.16) and previous small Western[130] and Chinese[131] population studies have shown a positive association between BMI and cystatin-C among both men and women. Associations of WHR and body fat percentage with cystatin-C in CKB were more consistent with these findings from UKB and previous studies.[130,131] These differences in the associations of different adiposity measures with cystatin C have been shown previously. Specifically, a

small East Asian study of ~300 individuals suggested that body fat percentage and WHR are the best adiposity measures for predicting cystatin-C. These differences may reflect limitations of cystatin C and creatinine as measures of renal function, since both are known to be influenced by different aspects of body size and adiposity, such as muscle mass.[62,160] In addition, higher creatinine levels tend to be associated with higher meat consumption and muscle mass, and may therefore be less well correlated with renal function.[62,161]

4.1.4.4 Liver function biomarkers

In CKB, higher levels of BMI were associated with higher levels of ALT and GGT. These findings are somewhat consistent with those from UKB (Figure 4.1.17) and from previous studies.[63-65] Higher levels of adiposity may be accompanied by deposition of excess fat in the liver which, in turn, has the potential to induce hepatic dysfunction. The relatively flat association of BMI with AST in CKB is consistent with the association in UKB and another Western population study[65] and may reflect AST's lower specificity as a marker of liver function, when compared with ALT and GGT.[162,163]

4.1.4.5 Other biomarkers

Findings from CKB, suggesting a positive linear association of adiposity with RPG, are consistent with current understanding of the role of adipose tissue in promoting insulin resistance, which, in turn, leads to higher glucose levels. Similar strengths of association of BMI/adiposity with RPG were observed in CKB and UKB. However, at a given BMI, RPG levels in CKB were higher than in UKB. This could reflect a true biological difference between the study populations, or could reflect

uncontrolled confounding e.g., by fasting time. In CKB, the associations of central adiposity measures with RPG were stronger than those of general adiposity measures, consistent with the results from UKB (Figure 4.1.17) and previous studies.[42,43] A possible explanation for this might be the strong correlation of central adiposity measures with visceral adiposity, which is thought to be more metabolically active, and metabolically harmful, than subcutaneous adipose tissue. For example, fatty acids, produced by visceral fat, drain directly into the portal vein, resulting in a more instant and stronger effect e,g, on insulin resistance.[22]

In CKB, there was a positive association between BMI and uric acid levels. These findings are consistent with the associations observed in UKB (Figure 4.1.17) and in previous studies.[164,165] In CKB, there were no clear sex-differences in the strength of the association (19.42 vs. 16.69 umol/L per 1 SD higher BMI), similar to UKB findings (23.13 vs. 26.42 umol/L per 1 SD higher BMI in men and women, respectively).

In the presented CKB analyses, high levels of adiposity were associated with lower levels of vitamin D, consistent with findings from UKB (Figure 4.1.17) and from a large meta-analysis including ~65,000 individuals. It is suggested that, since vitamin D is fat-soluble, its storage in adipose tissue reduces its bioavailability in blood.[166] In CKB, the association of BMI with vitamin D was slightly stronger among men than women (-0.95 vs. -0.34 ng/ml, per 1 SD higher BMI), and, at a given BMI, men had higher levels of vitamin D. However, such sex-differences were not observed in UKB, possibly reflecting ethnic-differences in typical lifestyle and occupational factors.

4.1.4.6 Strengths and limitations

The presented analyses of the associations of adiposity with plasma biomarkers in CKB have several strengths. These include investigation of a uniquely wide range of reliably-measured adiposity markers and plasma biomarkers, and the highly diverse study population. Moreover, the relatively lean study population, compared with Western studies, facilitated uniquely precise estimates of the associations at the lower end of the adiposity range. The value of this is highlighted by parallel analyses of UKB data, which enabled investigation of potential ethnic-differences. Finally, comprehensive sub-group analyses were carried out.

However, the cross-sectional study design limits inferences that can be made, particularly due to the potential for reverse causality. In addition, CKB plasma biomarker data were available only among a relatively small subset of the study population, limiting the power of subgroup investigations. Finally, the plasma biomarkers were measured using non-fasting blood samples, which might affect the observed associations of some plasma biomarkers (e.g., glucose, triglycerides). However, additional adjustment for fasting time did not materially change the findings.

4.2 Associations of plasma biomarkers with stroke types

4.2.1 Background

The pathophysiology of IS and ICH are incompletely understood. This is particularly true for ICH, since relatively few studies are adequately powered to study this less common stroke type. Through investigating the association of adiposity with the risk of stroke types, and the mediating roles of major plasma biomarkers in those associations in large-scale population-based studies, such as CKB, an improved understanding on pathophysiology of these stroke types may be achieved.

In previous observational epidemiological studies, higher levels of total cholesterol[27,96] and LDL-cholesterol,[167] and lower levels of HDL-cholesterol,[28,38,167,168] have been found to be associated with higher risks of IS. Studies have also suggested that inflammation,[29-31] impaired renal function,[32-34] dysglycaemia[35,36] and higher levels of uric acid are associated with higher risks of IS. However, this evidence is derived from mainly Western population studies, and the generalisability to other populations, with differing levels and distributions of plasma biomarkers, is unclear. In addition, given the lower proportion of HS and ICH in more widely-studied Western populations, as compared to East Asian populations,[73,74] the evidence on the associations of plasma biomarkers with these stroke types is limited and frequently derived from small studies (<1200 events) with limited power.[27,28,31,33,35,36,38,169-171]

This sub-chapter seeks to characterise the association of a range of plasma biomarkers with the risk of stroke types, overall and by various baseline

characteristics, using data from CKB. This will inform subsequent mediation analyses of the adiposity-stroke association.

4.2.2 Methods

4.2.2.1 Study population

4.2.2.1.1 Summary of study design

These analyses are based on the CKB biochemistry cohort. This included individuals from the nested case-control study of CVD (~25,000 individuals) for whom blood biochemistry data were available (~18,000 individuals). More detailed descriptions of the nested case-control study and CKB biochemistry cohort are provided in Section 3.4.

4.2.2.1.2 Exclusions

After excluding 1891 participants with missing or invalid biomarker data (except fibrinogen and vitamin D, which were measured in a smaller subset) and 131 with missing adiposity (BMI and body fat percentage, n=14) or RPG (n=117) data, 14,529 participants remained for inclusion in the analyses. This included 4943 IS cases, 3952 ICH cases and 5634 controls. In analyses examining the associations of fibrinogen and vitamin D, additional missing biomarker data necessitated further exclusions, leaving 9376 and 9112 participants, respectively.

4.2.2.2 Plasma biomarkers definitions

Analyses focused on the same 18 plasma biomarkers included in sub-chapter 4.1, and detailed in Section 3.4 and Table 3.1.

4.2.2.3 Outcome definitions

Data on stroke outcomes were obtained from death certificates, China CDC disease reporting systems and from the national health insurance system (Section 3.7). The main stroke types examined were IS (ICD-10 code I63) and ICH (ICD-10 code I61). Analyses were restricted to first events of any stroke type occurring between the ages of 35 and 79 years, with censoring at the first stroke event, 80 years of age or loss to follow-up.

4.2.2.4 Selection of confounders and effect modifiers

The following variables were identified as potential confounders or effect modifiers in the associations of plasma biomarkers with stroke types, based on a priori knowledge of their biological relationships: age, sex, study area, education,[172,173] smoking,[133-135,138,155,174,175] alcohol[138-140,142,176-178] and physical activity.[62,179,180]

4.2.2.5 Statistical analysis

Consistent with the approach adopted in sub-chapter 4.1, prior to analysis, hs-CRP was log transformed because of its skewed distribution. The mean values and prevalence of selected baseline characteristics were calculated separately among IS cases, ICH cases and controls, adjusted, where appropriate, for age (5-year groups), sex and study area.

Cox proportional hazards models, with time since baseline as the timescale, were used to estimate HRs for IS and ICH by plasma biomarkers, stratified by age-at-risk (5-year age groups), sex, and study area, and adjusted for education (no

formal education, primary school, middle school, high school, college/university), smoking (never, occasional, ex-regular, current regular), alcohol intake (never, occasional intake, ex-regular, reduced intake, weekly intake) and physical activity (metabolic equivalent of task [MET] hours per day). The plasma biomarkers were categorised into quintiles, to ensure reasonable numbers of participants in each category and enable comparisons between plasma biomarkers. The floating absolute risk method was used to estimate group-specific 95% CIs for each log HR to enable comparisons between any two categories (rather than just pairwise comparisons with the reference category).[181] The HR for IS and ICH per 1 SD higher in plasma biomarkers were estimated overall and across baseline characteristics (e.g., age, sex, area, SBP). For comparison of the strengths of the associations across baseline characteristics the χ^2 values for trend and heterogeneity were also calculated. Sensitivity analyses additionally adjusted for fasting time, SBP and BMI as continuous variables. The proportional hazards assumption was tested by examining the HRs for the first four and subsequent years of follow-up (and showed no strong evidence of departure).

All statistical analyses were conducted in SAS version 9.4. Cox regression was conducted using a SAS macro previously developed within CTSU. All plots were produced using JASPER, an R package developed within CTSU, in R version 3.3.

4.2.3 Results

Overall, 4943 and 3952 participants with first IS and ICH events, respectively, and 5634 controls were included in the current analyses (Table 4.2.1). Individuals with ICH were older and had higher mean SBP than individuals with IS and controls,

while individuals with IS were more likely to live in urban areas, and to have diabetes, more years of education and higher levels of adiposity. Controls were more physically active than participants with IS or ICH.

4.2.3.1 Lipids and lipoproteins

Figures 4.2.1 and 4.2.2 show the associations of lipids and lipoproteins with stroke types. In this and other similar figures throughout this sub-chapter, the lengths of the x-axes are equivalent to approximately ±1 SD from the mean of the relevant plasma biomarker. Concentrations of LDL-related biomarkers were positively and log-linearly associated with the risk of IS, with no evidence of a threshold within the biomarker ranges examined (Figures 4.2.1 and 4.2.2). Each 1 SD (0.7 mmol/L) higher LDL-cholesterol was associated with a 13% (HR 1.13 [95% CI 1.10-1.16]) higher risk of IS, and there was a very similar association of ApoB (1.12 [1.08-1.15] per 1 SD [21.2 mg/dL]) (Figure 4.2.3). There was a positive approximately log-linear relationship of triglycerides with IS (HR 1.06 [95% CI 1.04-1.09] per 1 SD [1.5 mmol/L] higher). HDL-cholesterol levels were inversely and broadly log-linearly associated with IS, with each 1 SD (0.3 mmol/L) higher HDL-cholesterol associated with 7% lower risk of IS (HR 0.93 [95% CI 0.90-0.96]). In contrast, there was no clear association between ApoA1 and IS.

Both LDL-related biomarkers were inversely and log-linearly associated with the risk of ICH (Figures 4.2.1 and 4.2.2). The strength of the associations of LDL-cholesterol (HR 0.94 [95% CI 0.90-0.97] per 1 SD higher) and ApoB (0.90 [0.86-0.93] per 1 SD higher) with ICH were similar (Figure 4.2.3). The association between triglycerides and ICH was inverse log-linear, with a 6% lower risk (HR

0.94 [95% CI 0.91-0.98]) per 1 SD higher. There was no clear evidence of an association between HDL-related biomarkers and the risk of ICH.

The association of LDL-cholesterol with IS was stronger among individuals living rural than in urban areas ($p_{heterogeneity}$=0.005) (Figure 4.2.4). Sex-differences were observed in the associations of triglycerides, with a stronger relationship with both stroke types among women than among men ($p_{heterogeneity}$≤0.001) (Figure 4.2.5). The associations of the lipids and lipoproteins examined with stroke types were broadly similar across other population subgroups examined (Figure 4.2.4-4.2.6 and B.22 and B.23). Moreover, for all lipids and lipoproteins, the findings were unchanged by additional adjustments for baseline SBP (Figure 4.2.7) and BMI (Figure 4.2.8). An exception to this was the strength of the association of triglycerides with ICH, which became slightly stronger after adjustments for baseline SBP (HR from 0.94 [95% CI 0.91-0.98] to 0.89 [0.85-0.92]).

4.2.3.2 Inflammatory biomarkers

There was a clear positive log-linear relationship between log hs-CRP and the risk of IS (HR 1.10 [95% CI 1.07-1.14] per 1 SD [1.2 log mg/L] higher) but a J-shaped association with ICH (Figure 4.2.3 and 4.2.9). Fibrinogen was positively, approximately log-linearly associated with IS, but there was no clear association with ICH. Albumin levels were inversely and broadly log-linearly associated with both stroke types; each 1 SD higher albumin (2.8 g/L) was associated with 6% (HR 0.94 [95% CI 0.91-0.97]) and 12% (0.88 [0.85-0.91]) lower risks of IS and ICH, respectively. The associations of all three inflammatory biomarkers with stroke types were similar across subgroups examined (Figures 4.2.10-4.2.12), and

additional adjustments for baseline SBP (Figure 4.2.7) and BMI (Figure 4.2.8) did not change the associations.

4.2.3.3 Renal function biomarkers

Lower renal function, represented by higher levels of creatinine and cystatin C and lower eGFR, was associated with higher risk of both stroke types (Figure 4.2.13). Among these renal biomarkers, cystatin-C showed the strongest associations with IS (HR 1.08 [95% CI 1.05-1.11] per 1 SD [0.3 mg/L] higher) and ICH (1.21 [1.18-1.24]) with a positive log-linear association throughout the range examined (Figure 4.2.3). There was a strong inverse log-linear association of eGFR with ICH among individuals with eGFR <108 ml/min/1.73m^2 (below the third quintile), but a weak positive association at higher eGFR levels. There was a flat association between creatinine with ICH at creatinine <70.0 umol/L (bottom fourth quintiles), whereas higher creatinine levels were associated with higher risk of ICH.

Differences in the strength of the associations of renal biomarkers with ICH were observed across some population subgroups (Figures 4.2.14-4.2.16). This included a stronger association of cystatin-C among individuals with diabetes compared to those without ($p_{heteroheneity}$<0.001) (Figure 4.2.14), and a stronger association of creatinine in urban than in rural areas ($p_{heteroheneity}$<0.001), and among individuals with diabetes than those without ($p_{heteroheneity}$<0.001) (Figure 4.2.15). Additional adjustments for baseline SBP (Figure 4.2.7) and BMI (Figure 4.2.8) had little effect on the relationships of all three renal function biomarkers with IS and ICH, and there were no clear differences in the strength of

associations of renal biomarkers with IS across the population subgroups examined (Figure 4.2.14).

4.2.3.4 Liver function biomarkers

There was a weak inverse log-linear association between AST and IS (HR 0.92 [95% CI 0.88-0.97] per 1 SD [16.6 u/L] higher AST) (Figure 4.2.17). In contrast, below the fifth quintiles ALT (≤23.6 u/L) and GGT (≤27.4 u/L), there were positive log-linear relationships with the risk of IS, with a flattening off of the risk at higher levels. There were no clear associations of any liver function biomarkers examined with the risk of ICH. The associations between liver function biomarkers and IS (Figure 4.2.18) and ICH (Figure B.24) were largely similar across different baseline characteristics, and they remained largely unchanged after additional adjustments for baseline SBP (Figure 4.2.7) and BMI (Figure 4.2.8).

4.2.3.5 Other biomarkers

Higher levels of RPG were associated with higher risk of IS (HR 1.12 [95% CI 1.09-1.15] per 1 SD [3.0 mmol/L] higher), and, to a lesser extent, with higher risk of ICH (1.09 [1.05-1.13]) (Figures 4.2.3 and 4.2.19). There was a positive association of uric acid levels with both stroke types, with a modestly stronger association with ICH (HR 1.13 [95% CI 1.09-1.18] per 1 SD [82.8 umol/L]) than with IS (1.08 [1.04-1.11]). The associations of both RPG (Figure B.25) and uric acid (Figure B.26) were similar across baseline characteristics. There was no clear association of vitamin D concentration with either IS or ICH.

4.2.4 Discussion

In this Chinese population there were positive associations of glycaemia, inflammation and uric acid concentration with risk of both IS and ICH, and higher risk of both stroke types among individuals with lower renal function. High levels of LDL-cholesterol, triglycerides and liver enzymes (e.g., ALT and GGT), and lower levels of HDL-cholesterol were associated with higher risk of IS only. The risk of ICH was higher among individuals with lower levels of LDL-related biomarkers and triglycerides. These findings are discussed below in the context of previous literature, additionally reflecting on how they will inform subsequent analyses investigating the mediating roles of the investigated plasma biomarkers in the associations of adiposity with stroke types.

4.2.4.1 Lipids and lipoproteins

The associations of lipids and lipoproteins with stroke types using CKB data were recently published,[182] but these analyses are included here for completeness and to inform the subsequent mediation analyses (Chapter 5). The shapes and strengths of the associations between lipid biomarkers and IS in CKB (positive and inverse log-linear associations of LDL-related biomarkers and HDL-cholesterol, respectively) are largely consistent with previous Western[28,168] and East Asian[167] population studies. However, the APCSC individual participant data meta-analysis of ~80,000 individuals from 25 cohort studies showed no evidence of an association between HDL-cholesterol and IS (~270 events), possibly due to the small number of events.[38] In CKB, after adjustment for age, sex, study area, education, smoking, alcohol and physical activity, each 1 SD (0.7 mmol/L) higher

LDL-cholesterol was associated with 13% (HR 1.13 [95% CI 1.10-1.16]) higher risk of IS. After similar adjustments, an individual participant data meta-analysis of ~270,000 individuals from China (~5000 IS events), reported a comparable risk, with each 1 mmol/L higher LDL-cholesterol associated with 8% higher risk of IS (1.08 [95% CI 1.04-1.11]).[167] The ERFC individual participant data meta-analysis of ~300,000 individuals from Europe and North America, reported a slightly stronger association of non-HDL-cholesterol with IS (n=2500, 1.21 [95% CI 1.14-1.28] per 1 SD [1.1 mmol/L] higher), possibly reflecting the minimal adjustments for potential confounding factors (age and sex only) in this study.[28] Previous Western[28,168] and East Asian[167] population studies reported an inverse log-linear association of HDL-cholesterol with IS and a positive log-linear association of triglycerides with IS, with association strengths comparable to those in CKB.[28,167,168] The stronger association of LDL-cholesterol with IS in rural than in urban areas in CKB may reflect lower awareness and less frequent management of dyslipidaemia in rural China.[183]

In CKB, there were inverse associations of LDL-related biomarkers with ICH, with a slightly stronger association of ApoB than of LDL-cholesterol. These findings are somewhat consistent with a previous MR study suggesting that ApoB is a stronger risk factor for CVD, particularly IHD, than LDL-cholesterol.[184] Previous prospective studies,[28,38,167,185] including the previously described individual participant data meta-analysis of ~270,000 Chinese (~2000 HS events),[167] and a published data meta-analysis of 1.4 million individuals (~8000 HS events)reported null associations between LDL-cholesterol and HS. Although in CKB, elevated levels of triglycerides were associated with lower risk of ICH, the individual participant data meta-analysis of ~270,000 Chinese adults reported no association.[167] The

lack of association between LDL-cholesterol[167,185] and triglycerides[167] observed in previous studies is not fully understood, but might reflect adjustment for potential mediators, such as blood pressure, in these studies, although, in CKB, adjustments for SBP did not change the findings. The flat association between HDL-cholesterol and ICH in CKB was also reported in the meta-analysis of 1.4 million individuals.[185]

4.2.4.2 Inflammatory biomarkers

Although, the associations of inflammatory biomarkers, specifically hs-CRP and fibrinogen, with stroke types using CKB data were recently published,[186] these findings are included in this chapter to inform the subsequent mediation analyses (Chapter 5). In CKB, there were positive log-linear associations of hs-CRP with IS and ICH, suggesting inflammation is associated with higher risk of both stroke types. After similar adjustments to those in CKB, analyses based on ~160,000 individuals in the ERFC individual participant data meta-analysis also showed a positive log-linear association between CRP and IS.[187] However, the strength of the association in ERFC was slightly stronger (HR 1.27 [95% CI 1.15-1.40] per 1 SD [1.1 log mg/L] higher usual log CRP vs. 1.10 [1.07-1.14] per 1 SD [1.2 log mg/L] higher log hs-CRP). This inconsistency in the strength of the association might reflect ethnic-differences, although a previous meta-analysis reported a similar strength of association between hs-CRP and IS in Asian and non-Asian population studies.[29] To my knowledge, only one previous study has reported on the association of hs-CRP with risk of HS. This showed no clear association, possibly reflecting the relatively small number of HS events included (~700 events).[29] Moreover, a small number of MR studies have reported that there is no

evidence that the CRP-IS association is causal,[188,189] but, to my knowledge, no MR studies have investigated the association of CRP with ICH.

Fibrinogen levels were positively and log-linearly associated with the risk of IS in CKB, but there was a U-shaped association with ICH. The Fibrinogen Studies Collaboration (FSC), an individual participant meta-analysis including ~150,000 individuals from 31 Western populations studies, reported a positive log-linear association of usual fibrinogen levels with both IS (~1300 events) and ICH (~400 events).[31] The difference between CKB and the FSC in the shape of the association of fibrinogen with ICH might again reflect the relatively small number of HS events included in the FSC, as compared to CKB.

There is very limited previous evidence on the association of albumin with risk of stroke types. However, the inverse association with IS in CKB is consistent with findings from the Northern Manhattan Study, which included ~3000 individuals and ~270 IS events.[30] To my knowledge there is no evidence from previous studies on the association of albumin with ICH in the general population. However, as an indicator of both inflammation[190] and poor nutritional status, the observed inverse association in CKB could be consistent with the proposed pathophysiology of ICH (i.e., rupture of vessels in the brain).[191]

4.2.4.3 Renal function biomarkers

Lower renal function was associated with higher risk of IS in CKB. Previous studies, assessing renal function mainly through eGFR, have reported similar shapes and strengths of association as were seen in CKB.[33,34] Evidence on the associations of cystatin C and creatine with stroke types is limited, and reported

largely in studies including only small numbers of IS events (<300).[192,193] In CKB, the association of cystatin C with IS was approximately two-fold stronger than the associations of the other two renal function biomarkers investigated. This seems consistent with findings from the Cardiovascular Health Study of elderly (≥65 years of age) individuals from the US, which reported a stronger association of cystatin-C than creatinine with total stroke (~400 events), but lacked data to investigate the association with stroke types.[194]

In CKB, lower renal function was also associated with a higher risk of ICH, again with a stronger association of cystatin C as compared to the other two renal function biomarkers. The strong inverse association between eGFR and ICH at eGFR <108 ml/min/1.73/m^2 in CKB could suggest that lower renal function is associated with higher risk of ICH only among individuals with eGFR levels below the "normal" range (< 90 ml/min/1.73/m^2). Previous studies also reported similar findings, but included smaller numbers of HS events (<1600).[33,193] For instance, the previously described large published data meta-analysis of 83 studies reported that individuals with GFR <60 ml/min/1.73m^2 had 39% (1.39 [0.96-1.86]) higher risk of HS than those with GFR >60 ml/min/1.73m^2.[33] Evidence from previous studies on the associations of cystatin C and creatinine with ICH is limited.

4.2.4.4 Liver function biomarkers

The liver is involved in a wide range of metabolic pathways, including lipid and glucose metabolism and inflammatory pathways. Liver dysfunction may influence CVD risk through such pathways, or through other less clearly defined mechanisms. In CKB, higher levels of ALT and GGT, were associated with higher

risk of IS. Consistent with CKB findings, the National Health Insurance Service (NHIS) nationwide population-based cohort of ~16 million Koreans also reported that higher levels of GGT were associated with higher risk of IS (~270,000 events). However, the NHIS study, and another Korean study of ~110,000 men (~1700 IS events), found no association between ALT and IS.[170,195] In CKB there was an inverse log-linear association between AST and IS, but the two previously described studies (NHIS and the Korean study of ~110,000 men) reported no association between AST and IS.[170,195] The inconsistent findings might reflect differences in adjustment levels, since previous studies adjusted for blood pressure, FPG, and lipids, in addition to major confounding factors adjusted for in the CKB analyses.[170,195]

In CKB there were no associations between liver function biomarkers and ICH, which is in contrast to findings from previous studies.[170,196] The NHIS National Sample Cohort study of ~450,000 Koreans, reported that elevated levels of GGT were associated with higher risk of ICH (~1000 events). Similarly, the previously described Korean study of ~100,000 men, reported that high levels of ALT and AST were associated with higher risk of ICH (~700 events).[170] There are no clear explanations for the differences in the findings between CKB and these other two Korean studies.[170,196]

4.2.4.5 Other biomarkers

There was a positive association of RPG with IS and ICH (throughout the RPG range examined, from 4.0 to 10.0 mmol/L), consistent with previous published findings from the whole CKB cohort.[197] Previous studies also reported that higher

levels of glucose were associated with higher risk of stroke types.[35,36] However, analyses based on ~700,000 individuals in the ERFC showed that only high levels (>8.0 mmol/L) of FPG were associated with higher risk of IS (~1750 events).[36] Consistent with the CKB findings for ICH, a large community-based cohort study of ~95,000 participants from Kailuan in China, reported that high (≥5.3 mmol/L) levels of FPG were associated with higher risk of ICH (~800 events).[35]

In CKB, high levels of uric acid were associated with higher risk of both IS and ICH. Likewise, a meta-analysis of seven prospective studies (six Western population and one East Asian population) reported that elevated levels of uric acid were associated with higher risk of IS and ICH.[198] The strengths of the associations of uric acid with stroke types were comparable between CKB (for IS HR 1.08 [95% CI 1.04-1.11] and for ICH 1.13 [1.09-1.18] per 1 SD [82.8 umol/L] higher uric acid) and this meta-analysis (for IS 1.13 [1.08–1.17] among men and 1.12 [1.06–1.18] among women, and for HS 1.05 [0.97–1.14] among men and 1.07 [1.01–1.14] among women per 59.5 umol/L higher uric acid). The underlying mechanisms by which uric acid might contribute to risk of stroke are not fully understood. However, the relationship might reflect the strong association between uric acid and hypertension,[199] one of the major risk factors for stroke,[200] although CKB findings did not change after additional adjustments for baseline SBP.

In this Chinese population, there was no association of vitamin D with either IS or ICH. A recent published data meta-analysis of 19 studies (15 cohort studies, three case control studies and one randomised clinical trial) similarly reported no association of vitamin D levels with risk of ICH (~460 events), but did find that

lower vitamin D levels were associated with a higher risk of IS (~3600 events).[201] However, the vitamin D range examined in that previous study was not described, and might differ from that in CKB, possibly explaining the inconsistent findings. Furthermore, a previous MR study suggested there is no causal association between low levels of vitamin D and IS.[202]

4.2.4.6 Strengths and limitations

As described in Section 4.1.4.6, the strengths of CKB include the diverse study population and availability of information on a novel range of plasma biomarkers. In addition, the completeness of follow-up, the high proportion of stroke types reliably diagnosed using neuroimaging, and the larger numbers of IS and ICH events captured in CKB than in most previous studies, ensure CKB can provide uniquely reliable risk estimates. Moreover, the ranges of some plasma biomarkers studied appear to differ between East Asian populations, such as in CKB, and more widely studied Western populations. This allows unique insights into the associations of these biomarkers, and is perhaps particularly relevant to lipids and lipoproteins.

However, CKB has limitations. The plasma biomarkers were available only among a subset of CKB participants, limiting the power to undertake detailed subgroup analyses. In addition, the associations of plasma biomarkers with stroke subtypes were not investigated because of the small number of stroke subtypes included in the CKB nested-case control study. Repeat measurements of plasma biomarkers in CKB were available among a subset of ~300 participants from the first resurvey (~2.5 years after baseline), and ~900 participants from the second resurvey (~6.3

years after baseline). However, these data were not used to estimate or account for intra-individual variation in biomarker concentrations in the presented analyses, because of the small number of individuals with repeated measurements. This may have resulted in under- or over-estimation of the strength of the association of biomarkers with stroke risk.

4.3 Conclusion

The findings presented in sub-chapter 4.1 provide evidence of the cross-sectional associations of general and central adiposity measures with a range of plasma biomarkers. In this relatively lean Chinese population, high levels of general and central adiposity were associated with adverse lipid profiles, inflammation, lower renal and liver function, higher levels of glycaemia and uric acid, and lower levels of vitamin D. The analyses presented in sub-chapter 4.2, demonstrate associations of these same biomarkers with stroke types, in particular showing associations of dyslipidaemia, inflammation, lower renal function, and higher glucose and uric acid levels with higher risks of IS and ICH. In addition, although no clear associations were shown between liver function biomarkers and risk of ICH, elevated levels of ALT and GGT, and lower levels of AST, were associated with higher risk of IS.

The main purpose of the analyses presented in this chapter was to inform the mediation analyses included in Chapter 5, which attempt to understand factors mediating the associations of adiposity with stroke types. MacKinnon et al described four criteria that should be met in reaching a conclusion that a variable (e.g., a plasma biomarker) acts as a mediator in the association between an

exposure (e.g. adiposity) and outcome (e.g. stroke). The current chapter investigated two of these criteria, specifically the existence of significant relationships between the exposure and potential mediating variables (adiposity and plasma biomarkers in sub-chapter 4.1), and between the potential mediating variables and outcome (after adjustment for the exposure of interest) (plasma biomarkers and stroke types in sub-chapter 4.2). In sub-chapter 4.1, both general and central adiposity measures were associated with all plasma biomarkers investigated. In sub-chapter 4.2, most plasma biomarkers, with the exception of ApoA1, creatinine and vitamin D, were associated with IS, both before and after adjustment for BMI. Likewise, most plasma biomarkers were associated with ICH before and after adjustments for BMI, with the exception of HDL-cholesterol, ApoA1, ALT and vitamin D. As such, these findings suggest that all of the investigated plasma biomarkers, with the exception of ApoA1, creatinine and vitamin D for IS and ApoA1, ALT and vitamin D for ICH, fulfil the two described criteria and that they could therefore be considered potential mediators of the relationships of adiposity with stroke types.

The remaining two criteria described by MacKinnon et al - that a significant relationship exists between the exposure and the outcome, and that that association is attenuated after accounting for the potential mediator - are examined in Chapter 5. The analyses presented in sub-chapter 4.2 are essential in informing assessment of the latter criterion. For example, information on the shape of the associations of the plasma biomarkers with stroke types, and on possible effect modifiers of these associations will inform how those plasma biomarkers are included in the mediation model. For example, according to findings presented in sub-chapter 4.2, there were approximately log-linear associations between many

plasma biomarkers and stroke types, suggesting that those plasma biomarkers should be considered as linear terms in the mediation model. However, there were non-log-linear associations of ALT and GGT with both stroke types, and of eGFR, fibrinogen, creatinine and AST with ICH. In light of these findings, it will be essential to consider the inclusion of these biomarkers as categorical variables in the mediation model. Information on how the associations of the plasma biomarkers with IS and ICH differ by baseline characteristics (e.g., sex, urban/rural residence) can be used to understand the potential need for inclusion of interaction terms in the mediation model. For example, as described, the associations of triglycerides with both stroke types were stronger among women than men, and the association of LDL-cholesterol with IS was stronger in rural than in urban areas in CKB, and the impact of these differences will be examined in Chapter 5. Using these insights gained from the presented analyses to ensure development of the most appropriate mediation model will enable more robust understanding of the factors mediating the associations of adiposity with stroke types.

Table 4.1.1. Baseline characteristics of participants by BMI

Characteristic[a]	BMI quintile[b]					Overall
	1	2	3	4	5	
No. of participants	1131	1127	1125	1123	1128	5634
Mean BMI (SD), kg/m^2	19.0 (1.0)	21.2 (0.5)	22.8 (0.5)	24.4 (0.6)	27.6 (1.9)	23.0 (3.1)
Age and socioeconomic factors						
Mean age (SD), years	57.8 (1.5)	57.6 (1.4)	57.5 (1.4)	57.6 (1.5)	57.5 (1.4)	57.4 (1.4)
Women, %	46.8	47.5	47.1	47.5	46.8	47.2
Urban, %	22.0	21.1	21.8	22.1	22.4	23.1
≥ 6 years of education, %	33.6	31.0	33.6	33.1	35.7	34.2
Lifestyle factors						
Men ever-regular smoker[c], %	80.2	78.3	72.4	69.6	72.6	74.8
Women ever-regular smoker[c], %	5.4	4.9	2.8	4.5	6.1	4.6
Men ever-regular drinker[d], %	33.7	31.5	36.1	30.8	35.4	33.3
Women ever-regular drinker[d], %	2.9	1.9	2.0	2.6	3.7	2.5
Mean physical activity (SD), MET-h/day	19.3 (12.4)	19.9 (11.7)	19.6 (11.4)	18.0 (12.1)	17.8 (10.4)	19.0 (11.1)
Medical history and health status, %						
Diabetes[e]	2.1	3.1	5.2	6.0	7.0	4.8
Hypertension[f]	4.8	7.7	9.9	12.9	19.6	11.0
Chronic kidney disease[f]	0.5	1.1	1.4	1.0	1.6	1.1
Chronic liver disease[f]	1.8	0.7	1.1	0.5	1.5	1.0
Self-rated poor health	11.0	10.2	9.7	9.6	9.6	9.9
Adiposity measures, mean (SD)						
Standing height, cm	158.3 (6.0)	158.2 (5.8)	158.4 (6.0)	158.3 (5.9)	158.6 (5.7)	158.4 (5.6)
Weight, kg	47.7 (4.4)	53.1 (4.2)	57.2 (4.4)	61.4 (4.8)	69.6 (7.0)	57.9 (8.9)
WC, cm	69.5 (5.1)	74.6 (4.7)	78.5 (4.9)	83.0 (5.1)	90.9 (7.2)	79.2 (9.0)
WHR	0.84 (0.002)	0.87 (0.002)	0.89 (0.002)	0.91 (0.002)	0.95 (0.002)	0.89 (0.001)
Body fat percentage	18.1 (3.1)	22.4 (3.2)	25.2 (3.4)	28.3 (3.8)	33.2 (4.9)	25.4 (6.3)
Blood pressure, mean (SD)						
SBP, mmHg	128.7 (19.3)	132.7 (18.9)	134.5 (20.2)	137.6 (21.6)	142.6 (20.2)	134.9 (20.0)
DBP, mmHg	74.4 (11.0)	75.9 (10.5)	77.0 (10.5)	78.7 (11.5)	81.0 (11.1)	77.3 (10.9)

[a]Adjusted for age (5-year groups), sex and study area (where appropriate). [b] Sex-specific quintiles. [c]Participants were classified as ever-regular smokers if they answered "on most days" or "daily or almost every day" to either "How often do you smoke tobacco now?" or "In the past, how frequently did you smoke?". [d]Participants were classified as ever-regular alcohol drinkers if they answered "usually at least once a week" to the question "During the past 12 months, how often did you drink alcohol?" or they answered yes to the question "In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?". [e]Participants were classified as having diabetes if they answered yes to the question "Has a doctor ever told you that you had diabetes?" or if they had a random plasma glucose level ≥7.0 mmol/L if time since last food was ≥8 hours, or ≥11.1 mmol/L if time since last food was <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. [f]Self-reported doctor diagnosis.

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MET-h/day: metabolic equivalent of task hours per day, WC: waist circumference, WHR: waist-to-hip ratio.

Table 4.1.2. Baseline characteristics of participants by waist circumference

Characteristic[a]	WC quintile[b]					Overall
	1	2	3	4	5	
No. of participants	1128	1127	1125	1126	1128	5634
Mean WC (SD), cm	67.3 (3.0)	73.7 (1.5)	78.6 (1.4)	83.7 (1.7)	92.7 (5.2)	79.2 (9.0)
Age and socioeconomic factors						
Mean age (SD), years	57.6 (1.5)	57.4 (1.4)	57.5 (1.4)	57.5 (1.4)	57.7 (1.5)	57.4 (1.4)
Women, %	47.1	47.7	47.0	47.1	46.7	47.2
Urban, %	21.4	21.6	22.2	22.3	22.2	23.1
≥ 6 years of education, %	31.8	32.9	33.8	33.1	35.0	34.2
Lifestyle factors						
Men ever-regular smoker[c], %	80.2	78.3	72.4	69.6	72.7	74.8
Women ever-regular smoker[c], %	5.4	4.9	2.8	4.5	6.1	4.6
Men ever-regular drinker[d], %	33.7	31.5	36.1	30.8	35.4	33.3
Women ever-regular drinker[d], %	2.9	1.9	2.0	2.6	3.7	2.5
Mean physical activity (SD), MET-h/day	20.2 (13.0)	19.5 (11.7)	19.2 (11.2)	18.5 (11.1)	17.5 (10.8)	19.0 (11.1)
Medical history and health status, %						
Diabetes[e]	1.6	2.2	3.4	7.4	8.7	4.8
Hypertension[f]	4.9	6.6	10.6	13.2	19.2	11.0
Chronic kidney disease[f]	0.6	1.2	1.0	0.9	1.6	1.1
Chronic liver disease[f]	1.3	1.1	0.7	0.6	1.8	1.0
Self-rated poor health	11.4	9.0	10.3	10.9	8.8	9.9
Adiposity measures, mean (SD)						
Standing height, cm	156.8 (6.4)	157.3 (5.6)	158.7 (5.5)	158.6 (5.6)	160.5 (5.6)	158.4 (5.6)
Weight, kg	48.2 (4.6)	53.1 (4.6)	57.4 (4.7)	61.1 (5.3)	69.5 (7.3)	57.9 (8.9)
BMI, kg/m^2	19.5 (1.7)	21.4 (1.7)	22.7 (1.6)	24.2 (1.8)	27.0 (2.6)	23.0 (3.1)
WHR	0.81 (0.001)	0.86 (0.001)	0.89 (0.001)	0.92 (0.001)	0.96 (0.001)	0.89 (0.001)
Body fat percentage	18.8 (4.1)	22.6 (4.1)	25.0 (3.9)	27.9 (4.4)	32.5 (5.7)	25.4 (6.3)
Blood pressure, mean (SD)						
SBP, mmHg	129.3 (19.2)	132.2 (19.1)	134.6 (19.4)	137.7 (21.3)	141.0 (19.7)	134.9 (20.0)
DBP, mmHg	74.7 (10.5)	75.8 (10.3)	77.1 (10.7)	79.2 (11.0)	80.3 (10.7)	77.3 (10.9)

[a]Adjusted for age (5-year groups), sex and study area (where appropriate). [b] Sex-specific quintiles. [c]Participants were classified as ever-regular smokers if they answered "on most days" or "daily or almost every day" to either "How often do you smoke tobacco now?" or "In the past, how frequently did you smoke?". [d]Participants were classified as ever-regular alcohol drinkers if they answered "usually at least once a week" to the question "During the past 12 months, how often did you drink alcohol?" or they answered yes to the question "In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?". [e]Participants were classified as having diabetes if they answered yes to the question "Has a doctor ever told you that you had diabetes?" or if they had a random plasma glucose level ≥7.0 mmol/L if time since last food was ≥8 hours, or ≥11.1 mmol/L if time since last food was <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. [f]Self-reported doctor diagnosis.

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MET-h/day: metabolic equivalent of task hours per day, WC: waist circumference, WHR: waist-to-hip ratio.

Table 4.1.3. Correlation coefficients between adiposity measures

		WC	WHR	Body fat percentage	Lean mass	Fat mass
BMI	**Men:**	0.86	0.64	0.80	0.62	0.88
	Women:	0.83	0.55	0.88	0.49	0.93
	All:	0.84	0.59	0.84	0.55	0.90
WC	**Men:**	0.83	0.74	0.65	0.83	
	Women:	0.81	0.79	0.50	0.84	
	All:	0.82	0.76	0.58	0.83	
WHR	**Men:**	0.59	0.36	0.61		
	Women:	0.57	0.26	0.55		
	All:	0.58	0.32	0.58		
Body fat percentage	**Men:**	0.27	0.95			
	Women:	0.21	0.95			
	All:	0.23	0.95			
Lean mass	**Men:**	0.50				
	Women:	0.43				
	All:	0.45				

Pearson correlation coefficients, adjusted for age (5-year groups), sex and study area (where appropriate).
BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio.

Table 4.1.4. Correlation coefficients between adiposity measures, blood pressure and plasma biomarkers

		SBP	DBP	LDL-cholesterol	HDL-cholesterol	Triglycerides	Total cholesterol	ApoA1	ApoB	Log hs-CRP	Albumin	Fibrinogen	Creatinine	Cystatin C	eGFR	ALT	AST	GGT	RPG	Uric acid	Vitamin D
BMI	**Men:**	0.23	0.20	0.22	-0.30	0.32	0.21	-0.19	0.31	0.16	0.18	-0.01	0.09	0.01	-0.17	0.15	-0.01	0.10	0.11	0.27	-0.09
	Women:	0.26	0.22	0.16	-0.27	0.27	0.13	-0.16	0.23	0.30	0.06	0.07	0.02	0.10	-0.09	0.19	0.06	0.12	0.11	0.26	-0.05
	All:	0.25	0.21	0.19	-0.29	0.30	0.17	-0.18	0.27	0.23	0.12	0.03	0.06	0.05	-0.13	0.17	0.02	0.10	0.11	0.26	-0.07
WC	**Men:**	0.20	0.19	0.19	-0.29	0.36	0.20	-0.17	0.29	0.19	0.15	0.00	0.10	0.03	-0.15	0.15	0.00	0.12	0.13	0.29	-0.10
	Women:	0.23	0.19	0.15	-0.29	0.31	0.14	-0.17	0.24	0.32	0.08	0.09	0.05	0.14	-0.10	0.18	0.05	0.14	0.17	0.29	-0.06
	All:	0.21	0.19	0.17	-0.29	0.34	0.17	-0.17	0.27	0.25	0.11	0.04	0.07	0.08	-0.13	0.16	0.01	0.12	0.15	0.29	-0.08
SBP	**Men:**	0.71	0.09	-0.01	0.13	0.13	0.04	0.12	0.07	0.22	0.02	0.07	0.02	-0.08	0.09	0.08	0.08	0.07	0.06	-0.07	
	Women:	0.72	0.09	-0.03	0.15	0.13	0.04	0.13	0.11	0.22	0.02	0.04	0.04	-0.06	0.05	0.03	0.05	0.07	0.05	-0.06	
	All:	0.71	0.09	-0.02	0.14	0.13	0.04	0.13	0.09	0.22	0.02	0.06	0.03	-0.07	0.07	0.06	0.06	0.07	0.06	-0.07	
DBP	**Men:**	0.10	-0.01	0.11	0.14	0.03	0.14	0.09	0.21	0.09	0.10	0.05	-0.10	0.08	0.06	0.10	0.00	0.09	-0.04		
	Women:	0.10	-0.04	0.14	0.13	0.03	0.14	0.11	0.22	0.02	0.02	0.03	-0.06	0.06	0.03	0.04	0.02	0.07	-0.02		
	All:	0.10	-0.02	0.12	0.13	0.03	0.14	0.10	0.21	0.06	0.06	0.04	-0.08	0.07	0.05	0.07	0.01	0.08	-0.03		
LDL-cholesterol	**Men:**	0.01	0.13	0.85	-0.01	0.91	0.07	0.23	0.13	0.01	-0.05	-0.07	0.04	-0.08	-0.01	-0.01	0.06	-0.11			
	Women:	0.16	0.08	0.86	0.13	0.90	0.10	0.18	0.12	0.01	-0.03	-0.02	0.07	0.00	0.06	0.05	0.07	-0.09			
	All:	0.08	0.10	0.86	0.05	0.90	0.09	0.21	0.13	0.01	-0.05	-0.05	0.05	-0.05	0.02	0.02	0.06	-0.10			
HDL-cholesterol	**Men:**	-0.28	0.26	0.88	-0.10	-0.16	0.05	-0.13	-0.06	-0.12	0.06	-0.07	0.06	0.06	-0.10	-0.13	0.07				
	Women:	-0.40	0.32	0.86	-0.01	-0.17	0.05	-0.07	-0.04	-0.15	0.01	-0.09	-0.03	-0.05	-0.08	-0.18	0.06				
	All:	-0.33	0.29	0.87	-0.06	-0.16	0.05	-0.11	-0.05	-0.13	0.03	-0.08	0.02	0.02	-0.09	-0.15	0.06				
Triglycerides	**Men:**	0.40	-0.08	0.22	0.08	0.18	0.02	0.05	0.02	-0.05	0.17	0.08	0.25	0.12	0.22	-0.14					
	Women:	0.32	-0.16	0.23	0.14	0.14	0.00	0.05	0.10	-0.06	0.14	0.06	0.18	0.19	0.26	-0.13					
	All:	0.36	-0.11	0.22	0.11	0.16	0.01	0.05	0.05	-0.06	0.16	0.07	0.23	0.15	0.24	-0.14					
Total cholesterol	**Men:**	0.30	0.83	0.06	0.30	0.09	0.02	-0.07	-0.07	0.08	-0.01	0.12	0.00	0.09	-0.11						
	Women:	0.35	0.84	0.08	0.25	0.08	0.02	-0.02	-0.06	0.08	0.01	0.12	0.08	0.10	-0.10						
	All:	0.32	0.84	0.07	0.28	0.09	0.02	-0.05	-0.07	0.08	0.00	0.12	0.04	0.09	-0.11						
ApoA1	**Men:**	-0.07	-0.18	0.10	-0.19	-0.07	-0.12	0.05	-0.02	0.09	0.15	-0.07	-0.05	0.02							
	Women:	0.01	-0.13	0.10	-0.08	-0.05	-0.10	-0.01	-0.03	0.00	0.00	-0.03	-0.08	0.01							
	All:	-0.04	-0.16	0.10	-0.14	-0.06	-0.11	0.02	-0.02	0.06	0.10	-0.05	-0.06	0.02							
ApoB	**Men:**	0.14	0.28	0.16	0.05	-0.03	-0.10	0.07	-0.07	0.05	0.01	0.12	-0.11								
	Women:	0.17	0.24	0.16	0.05	0.02	-0.08	0.09	0.00	0.09	0.09	0.15	-0.11								
	All:	0.15	0.26	0.16	0.05	0.00	-0.09	0.08	-0.05	0.06	0.05	0.14	-0.11								
Log hs-CRP	**Men:**	-0.12	0.53	0.09	0.17	-0.04	0.08	0.04	0.14	0.10	0.14	-0.05									
	Women:	-0.07	0.45	0.13	0.23	-0.10	0.10	0.04	0.18	0.16	0.27	-0.01									
	All:	-0.09	0.50	0.10	0.19	-0.07	0.09	0.04	0.15	0.13	0.19	-0.03									
Albumin	**Men:**	-0.11	0.01	-0.11	-0.09	0.09	-0.02	-0.01	-0.05	0.11	-0.02										
	Women:	-0.06	-0.02	-0.08	-0.07	0.10	0.04	0.06	-0.03	0.07	0.01										
	All:	-0.08	0.00	-0.10	-0.08	0.09	0.00	0.02	-0.04	0.09	-0.01										
Fibrinogen	**Men:**	0.07	0.13	-0.04	0.01	-0.04	0.01	-0.03	0.00	0.03	-0.02										
	Women:	0.09	0.17	-0.06	0.09	0.11	0.09	0.02	0.12	-0.02											
	All:	0.08	0.15	-0.05	0.04	0.00	0.01	0.01	0.07	-0.02											
Creatinine	**Men:**	0.79	-0.83	0.00	-0.03	0.01	0.02	0.35	0.07												
	Women:	0.72	-0.69	-0.01	0.03	0.03	0.04	0.42	0.07												
	All:	0.76	-0.76	-0.01	-0.01	0.02	0.03	0.38	0.07												
Cystatin C	**Men:**	-0.55	0.02	0.00	0.05	0.00	0.33	0.09													
	Women:	-0.53	0.04	0.09	0.07	0.01	0.51	0.08													
	All:	-0.54	0.03	0.03	0.05	0.00	0.40	0.09													
eGFR	**Men:**	0.00	0.04	0.00	-0.02	-0.38	-0.07														
	Women:	-0.01	-0.04	-0.01	-0.05	-0.44	-0.10														
	All:	0.00	0.01	0.00	-0.03	-0.41	-0.08														
ALT	**Men:**	0.72	0.39	0.07	0.11	0.00															
	Women:	0.78	0.45	0.05	0.15	0.00															
	All:	0.73	0.41	0.06	0.12	0.00															
AST	**Men:**	0.52	0.03	0.06	0.01																
	Women:	0.33	-0.03	0.12	0.05																
	All:	0.47	0.01	0.08	0.02																
GGT	**Men:**	0.09	0.17	-0.03																	
	Women:	0.10	0.12	-0.03																	
	All:	0.09	0.15	-0.03																	
RPG	**Men:**	-0.02	-0.01																		
	Women:	0.02	-0.03																		
	All:	0.00	-0.02																		
Uric acid	**Men:**	0.03																			
	Women:	0.05																			
	All:	0.04																			

Pearson correlation coefficients, adjusted for age (5-year) groups, sex and study area (where appropriate).
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, BMI: body mass index, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference.

Table 4.1.5. Plasma biomarker increments per 1 SD higher BMI and waist circumference by sex

Plasma biomarkers	Men		Women	
	Estimate[a] (SE) per 1 SD higher BMI	Estimate[a] (SE) per 1 SD higher WC	Estimate[a] (SE) per 1 SD higher BMI	Estimate[a] (SE) per 1 SD higher WC
Lipids and lipoproteins				
LDL-cholesterol, mmol/L	0.14 (0.01)	0.12 (0.01)	0.11 (0.01)	0.09 (0.01)
HDL-cholesterol, mmol/L	-0.09 (0.01)	-0.09 (0.01)	-0.08 (0.01)	-0.08 (0.01)
Triglycerides, mmol/L	0.50 (0.03)	0.56 (0.03)	0.37 (0.03)	0.40 (0.03)
Total cholesterol, mmol/L	0.18 (0.02)	0.17 (0.02)	0.13 (0.02)	0.11 (0.02)
ApoA1, mg/dL	-4.53 (0.42)	-3.87 (0.42)	-3.15 (0.38)	-3.39 (0.38)
ApoB, mg/dL	5.98 (0.36)	5.77 (0.36)	4.56 (0.37)	4.32 (0.37)
Inflammatory				
Log hs-CRP, log mg/L	0.20 (0.02)	0.23 (0.02)	0.34 (0.02)	0.36 (0.02)
Albumin, g/L	0.47 (0.05)	0.39 (0.05)	0.18 (0.05)	0.14 (0.05)
Fibrinogen, g/L	-0.01 (0.01)	0.01 (0.01)	0.03 (0.01)	0.03 (0.01)
Renal function				
Creatinine, umol/L	1.70 (0.33)	1.70 (0.32)	0.33 (0.33)	0.77 (0.33)
Cystatin C, mg/L	-0.001 (0.003)	0.003 (0.003)	0.012 (0.002)	0.016 (0.002)
eGFR, ml/min/1.73m^2	-3.61 (0.40)	-3.27 (0.40)	-1.92 (0.42)	-2.00 (0.42)
Liver function				
ALT, u/L	2.71 (0.34)	2.73 (0.34)	2.81 (0.28)	2.44 (0.28)
AST, u/L	-0.26 (0.39)	-0.14 (0.39)	0.69(0.24)	0.47 (0.24)
GGT, u/L	4.74 (0.99)	6.25 (0.98)	4.20 (0.66)	4.06 (0.66)
Other				
RPG, mmol/L	0.24 (0.04)	0.28 (0.04)	0.28 (0.05)	0.45 (0.05)
Uric acid, umol/L	19.42 (1.34)	21.49 (1.32)	16.69 (1.20)	17.63 (1.19)
Vitamin D, mg/ml	-0.54 (0.17)	-0.58 (0.17)	-0.21 (0.13)	-0.27 (0.14)

[a]Adjusted for age (5-year groups) and study area. The estimates of plasma biomarkers per 1 SD higher adiposity measures were estimated using sex-specific SDs. SD of BMI 3.1 for men and 3.3 for women, WC SD 9.5 for men and women.

ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, BMI: body mass index, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose, WC: waist circumference.

Table 4.1.6. Plasma biomarker increments per 1 SD higher BMI and waist circumference in urban and rural areas

Plasma biomarkers	Urban		Rural	
	Estimate[a] (SE) per 1 SD higher BMI	Estimate[a] (SE) per 1 SD higher WC	Estimate[a] (SE) per 1 SD higher BMI	Estimate[a] (SE) per 1 SD higher WC
Lipids and lipoproteins				
LDL-cholesterol, mmol/L	0.07 (0.02)	0.07 (0.02)	0.14 (0.01)	0.12 (0.01)
HDL-cholesterol, mmol/L	-0.08 (0.01)	-0.09 (0.01)	-0.09 (0.01)	-0.08 (0.01)
Triglycerides, mmol/L	0.43 (0.05)	0.56 (0.05)	0.45 (0.02)	0.47 (0.02)
Total cholesterol, mmol/L	0.10 (0.03)	0.11 (0.03)	0.18 (0.01)	0.16 (0.01)
ApoA1, mg/dL	-3.71 (0.53)	-3.96 (0.54)	-3.80 (0.34)	-3.38 (0.33)
ApoB, mg/dL	3.90 (0.56)	4.28 (0.57)	5.88 (0.29)	5.54 (0.29)
Inflammatory				
Log hs-CRP, mg/L	0.29 (0.03)	0.31 (0.03)	0.27 (0.02)	0.29 (0.02)
Albumin, g/L	0.17 (0.06)	0.16 (0.07)	0.40 (0.04)	0.34 (0.04)
Fibrinogen, g/L	0.03 (0.02)	0.03 (0.02)	0.02 (0.01)	0.03 (0.01)
Renal function				
Creatinine, umol/L	1.17 (0.33)	1.24 (0.34)	1.03 (0.29)	1.23 (0.28)
Cystatin C, mg/L	0.016 (0.004)	0.021 (0.004)	0.008 (0.003)	0.014 (0.003)
eGFR, ml/min/1.73m^2	-1.87 (0.49)	-1.98 (0.51)	-3.22 (0.35)	-2.96 (0.34)
Liver function				
ALT, u/L	2.80 (0.37)	2.99 (0.38)	2.82 (0.27)	2.67 (0.27)
AST, u/L	0.68 (0.32)	0.68 (0.32)	0.06 (0.29)	0.10 (0.28)
GGT, u/L	5.60 (1.03)	6.17 (1.05)	4.47 (0.73)	5.37 (0.71)
Other				
RPG, mmol/L	0.24 (0.07)	0.35 (0.07)	0.27 (0.04)	0.36 (0.04)
Uric acid, umol/L	21.27 (1.89)	23.03 (1.93)	17.59 (1.04)	19.03 (1.00)
Vitamin D, mg/ml	-0.82 (0.30)	-0.87 (0.30)	-0.71 (0.19_	-0.77 (0.19)

[a]Adjusted for age (5-year groups), sex and study area. The estimates of plasma biomarkers per 1 SD higher adiposity measures were estimated using sex-specific SDs. SD of BMI 3.1 for men and 3.3 for women, WC SD 9.5 for men and women.

ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase BMI: body mass index, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose, WC: waist circumference.

Figure 4.1.1. Association of BMI and WC with blood pressure, by sex

Mean values adjusted for age (5-year groups) and study area, by sex. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of the adiposity measures and the ±1S and ±2S represent 1 and 2 SD from the mean, respectively.
BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, WC: waist circumference.

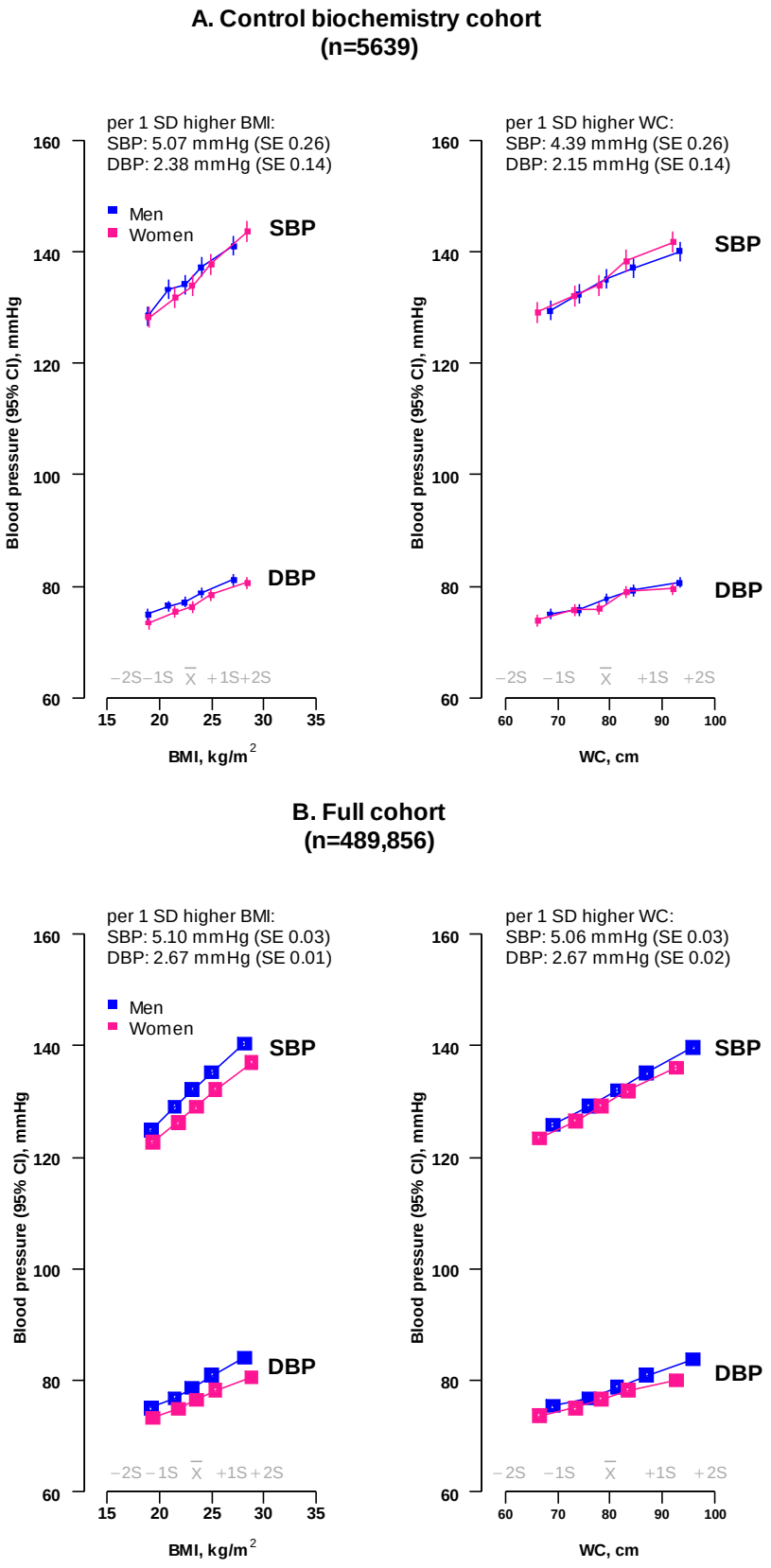


Figure 4.1.2. Association of BMI and WC with lipids and lipoproteins by sex

Mean values adjusted for age (5-year groups) and study area, by sex. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WC: waist circumference.

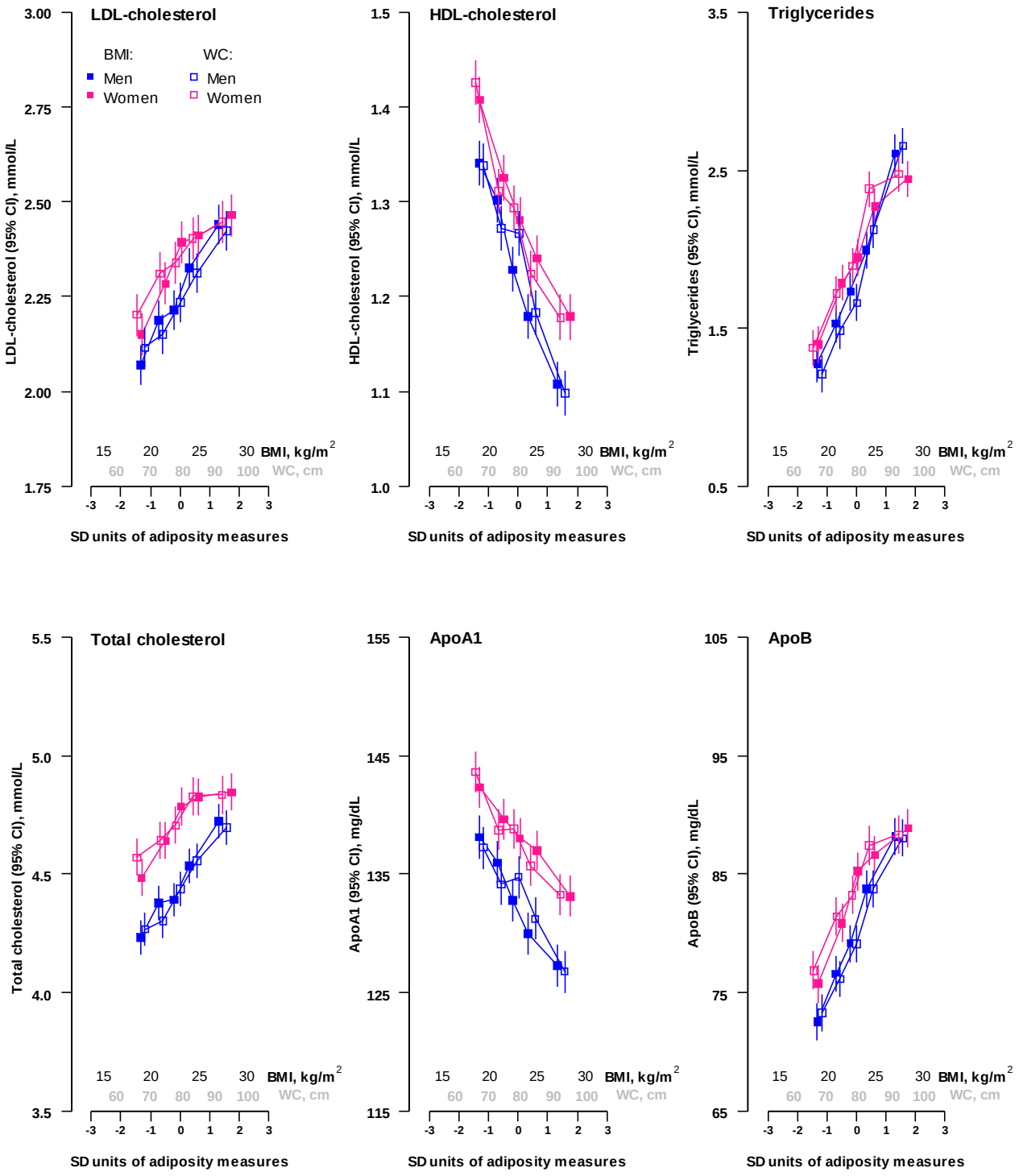


Figure 4.1.3. Association of BMI with lipids and lipoproteins in urban and rural areas

Mean values represent weighted-average of sex specific means adjusted for age (5-year groups) and study area, separately in urban and rural areas. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WC: waist circumference.

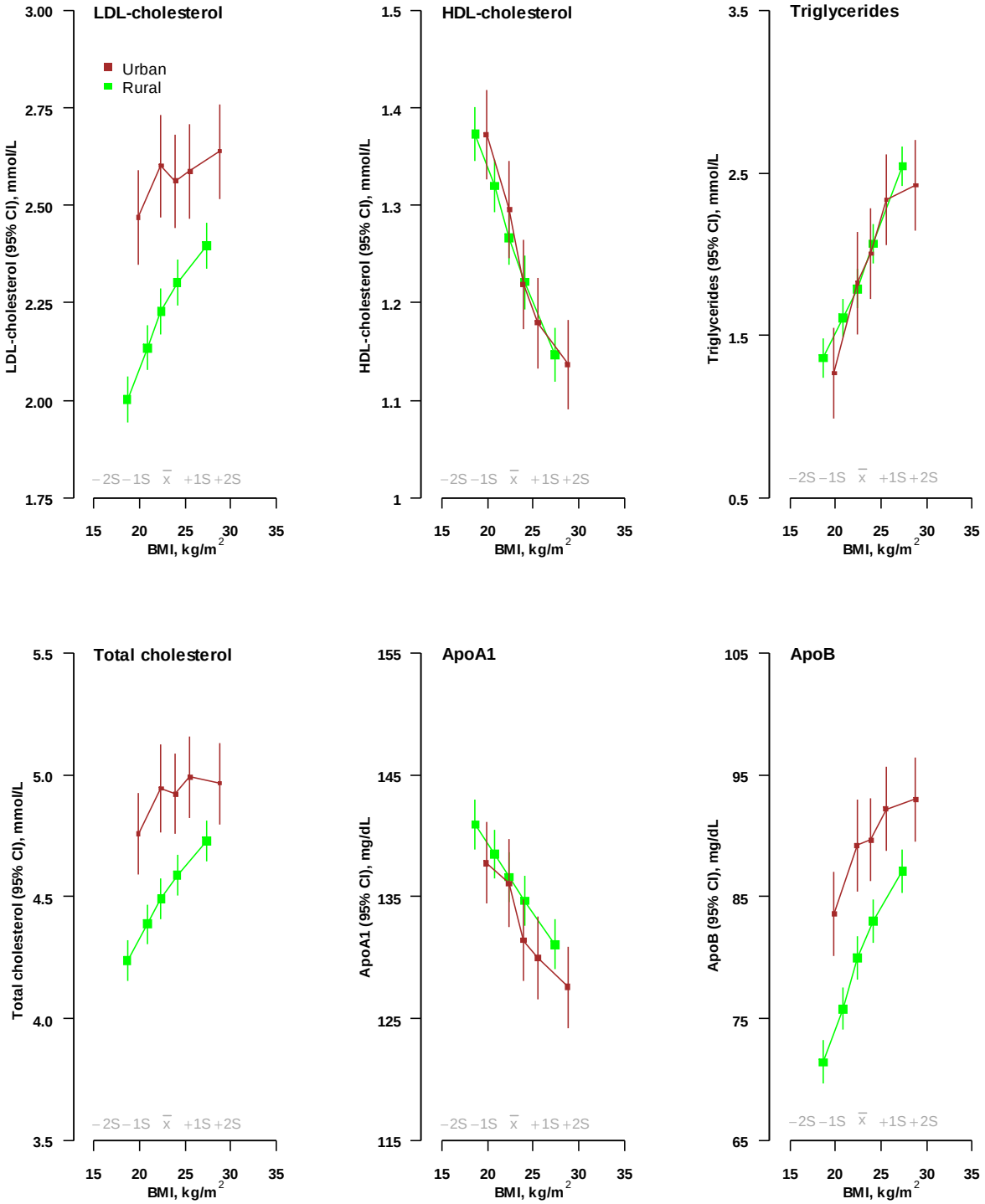


Figure 4.1.4. Association of BMI with lipids and lipoproteins by age

Mean values represent weighted-average of sex specific means adjusted for age (5-year groups) and study area, across age groups. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WC: waist circumference.

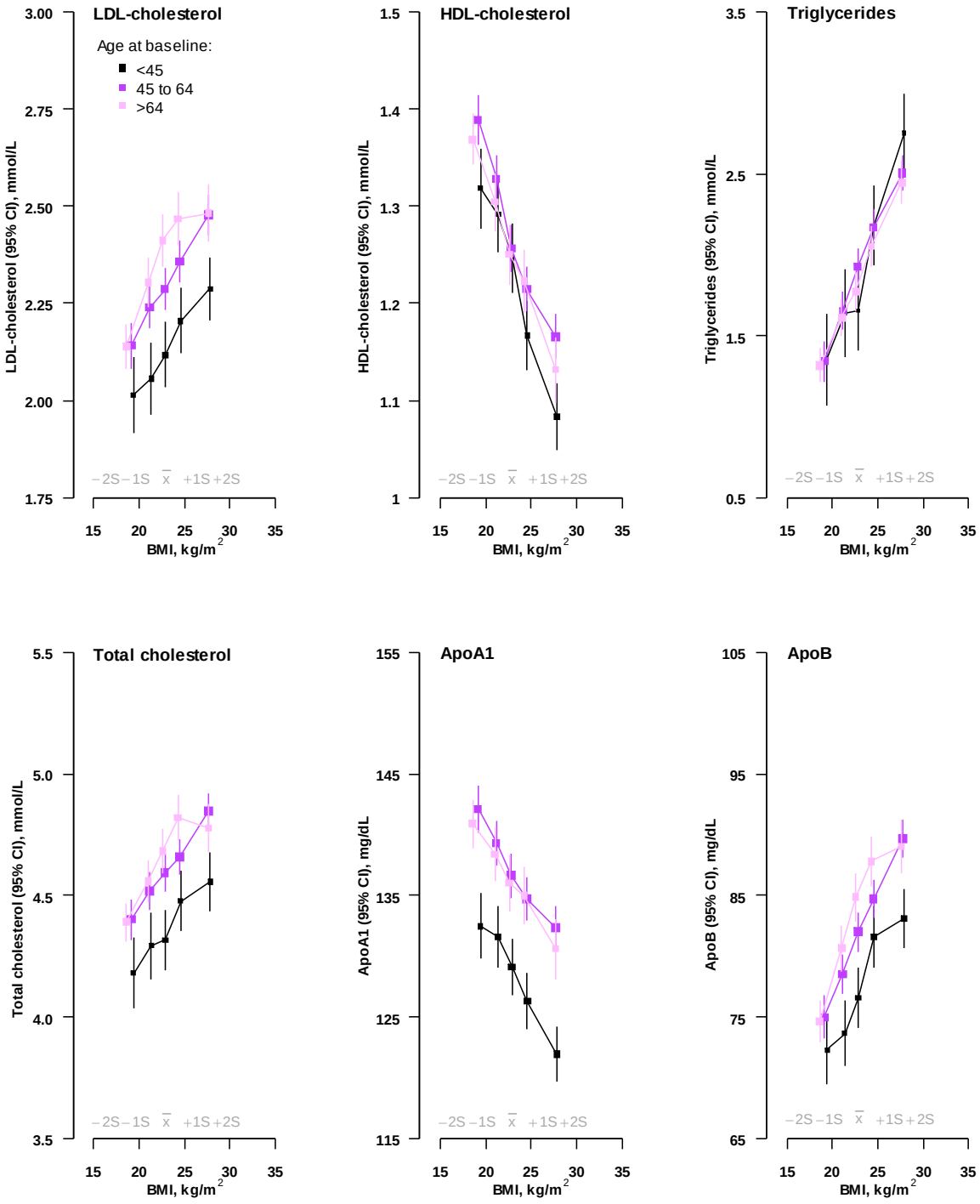


Figure 4.1.5. Association of BMI with lipids and lipoproteins by systolic blood pressure

Mean values represent weighted-average of sex specific means adjusted for age (5-year groups) and study area, across SBP groups. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WC: waist circumference.

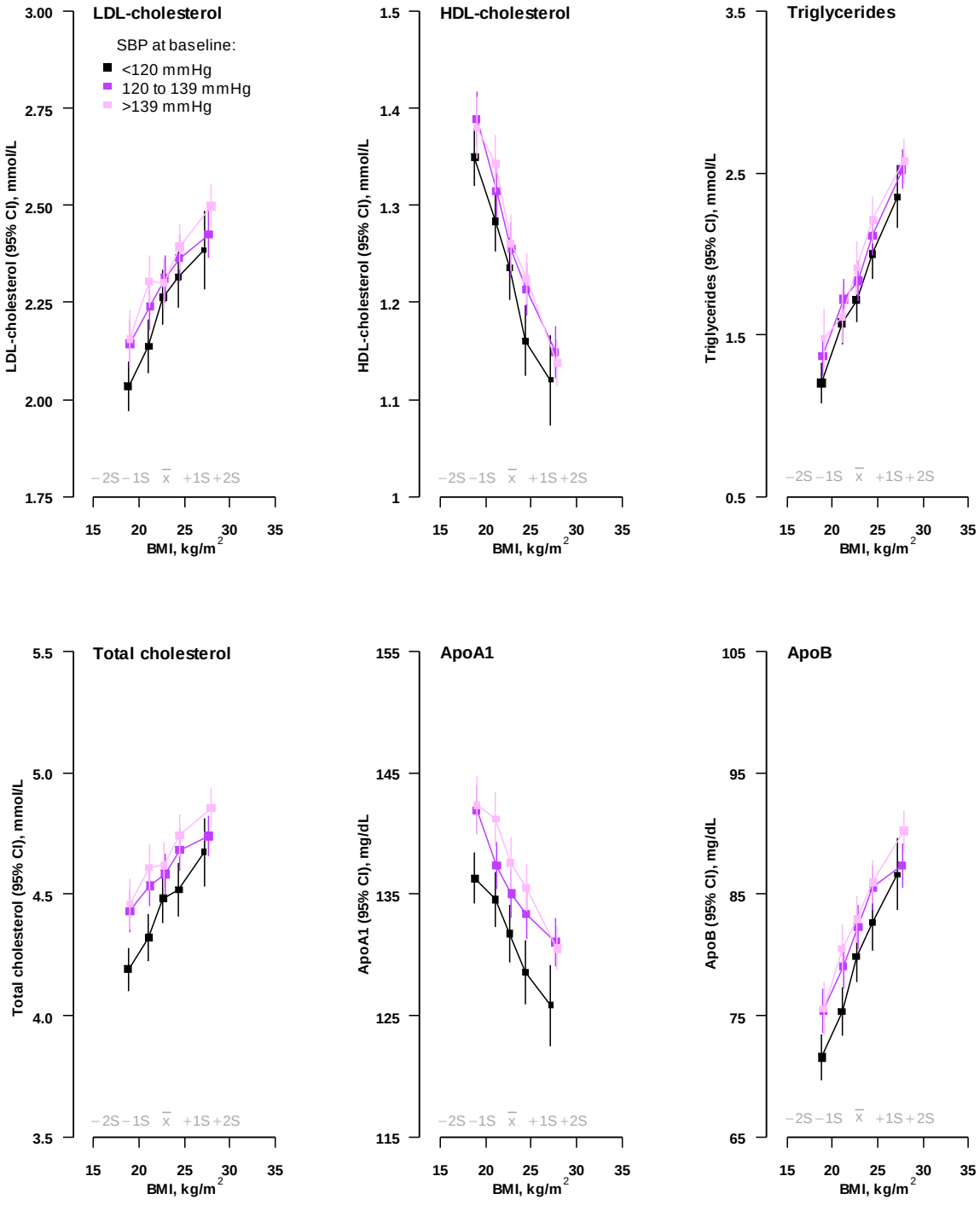


Figure 4.1.6. Association of BMI and WC with inflammatory and renal function biomarkers by sex

Conventions as Figure 4.1.2.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L.
Fibrinogen data were available for 3460 participants.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, WC: waist circumference.

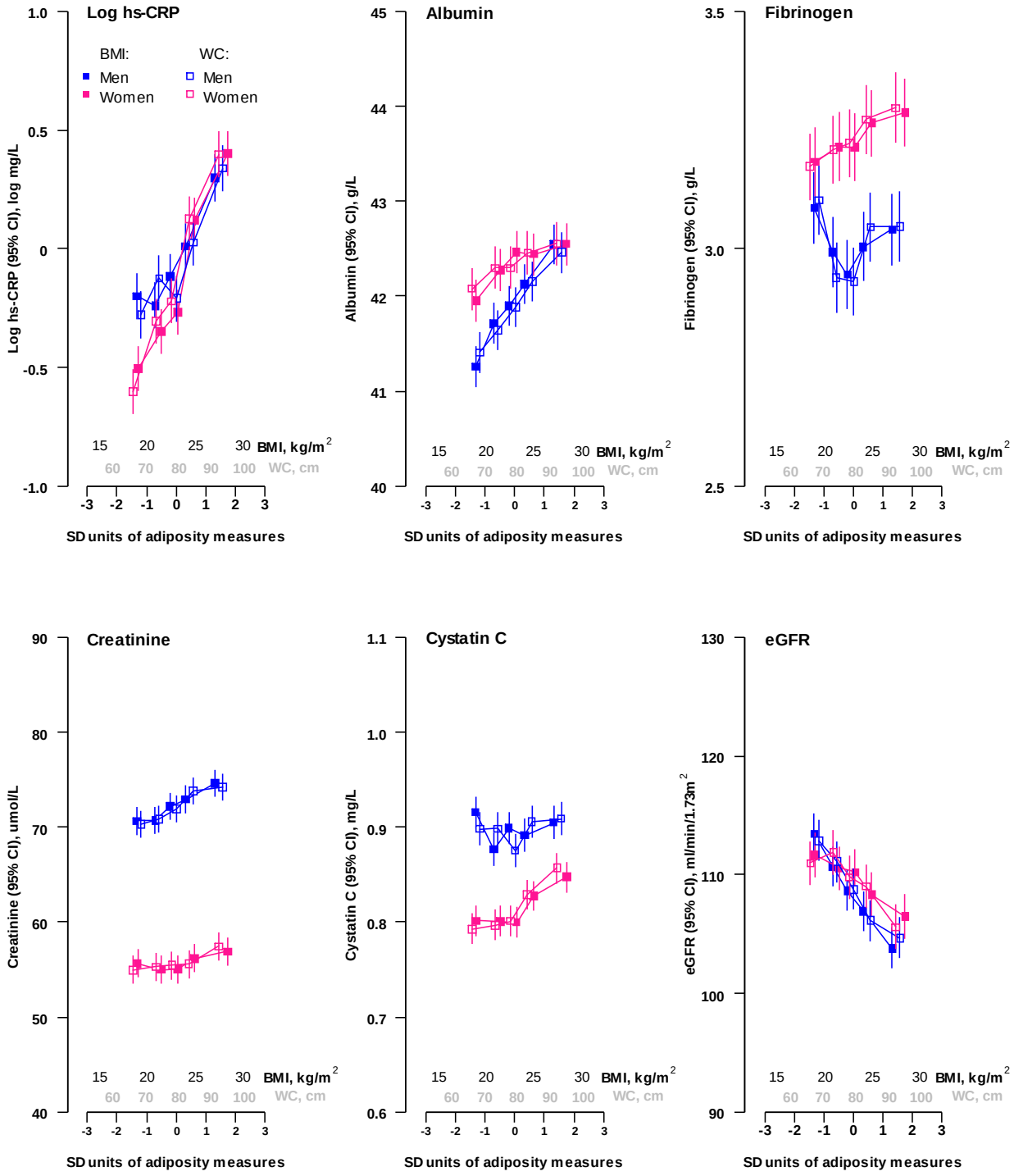


Figure 4.1.7. Association of BMI with inflammatory and renal function biomarkers in urban and rural areas

Conventions as Figure 4.1.3.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L.
Fibrinogen data were available for 3460 participants.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

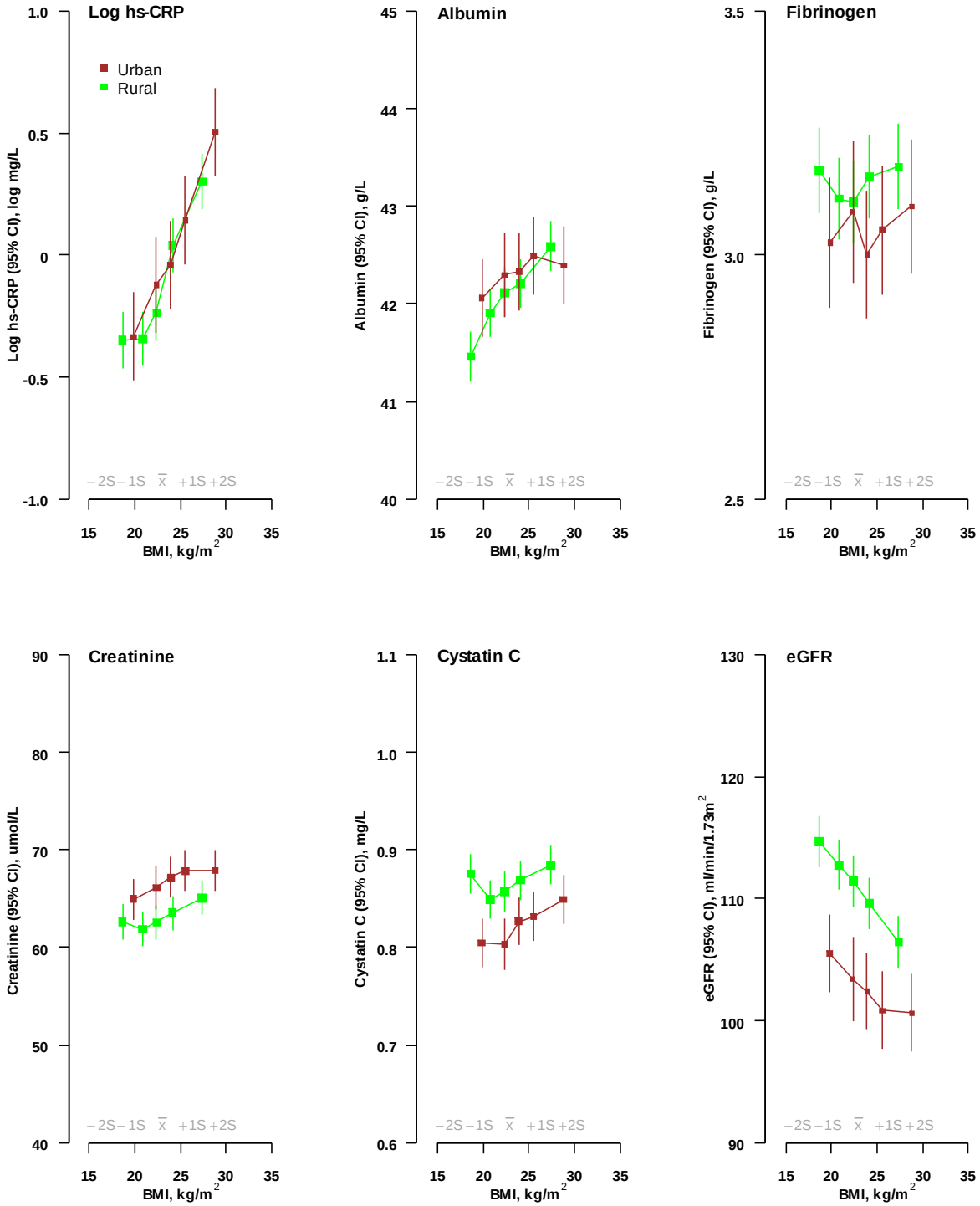


Figure 4.1.8. Association of BMI with inflammatory and renal function biomarkers by age

Conventions as Figure 4.1.4.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L.
Fibrinogen data were available for 3460 participants.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

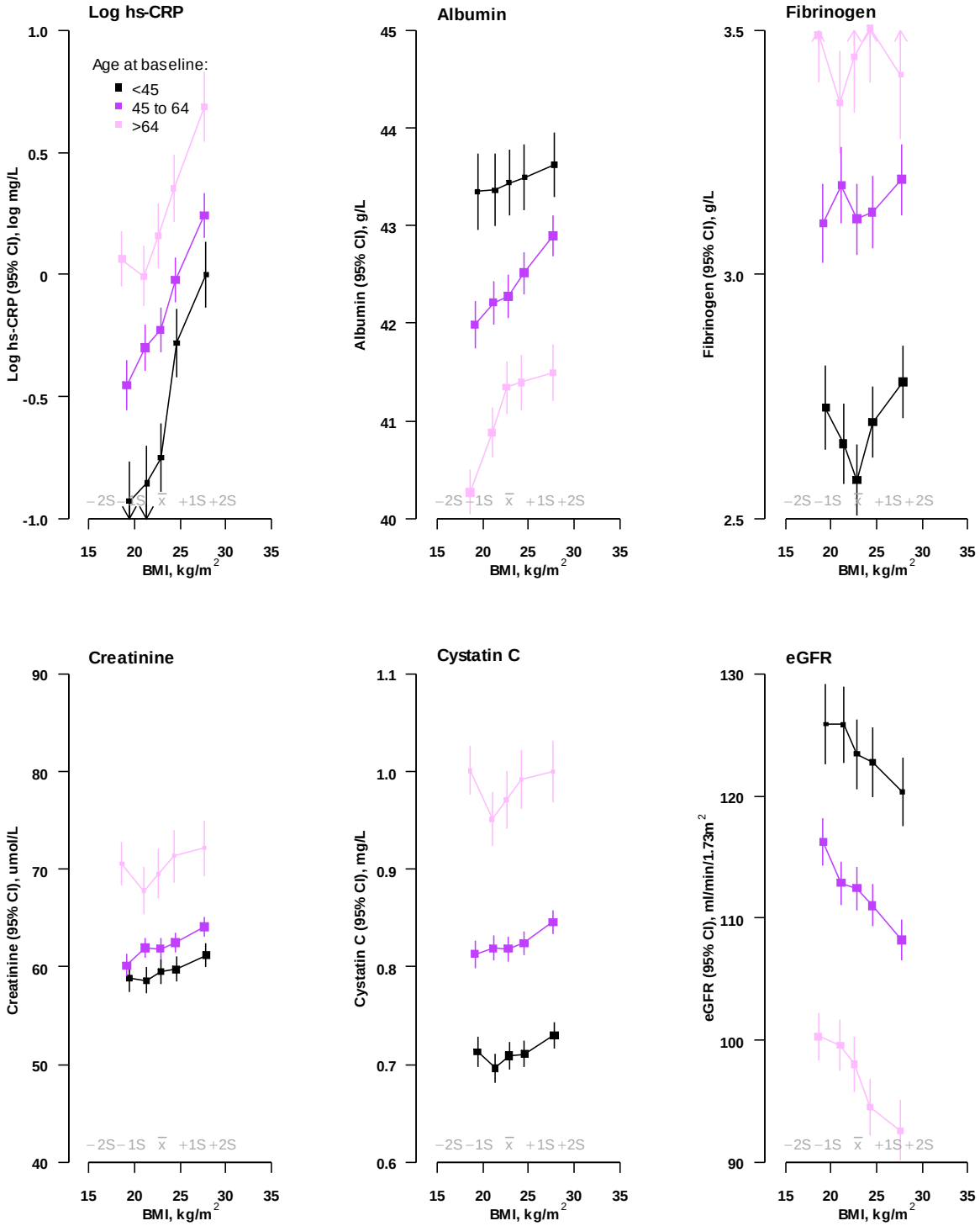


Figure 4.1.9. Association of BMI with inflammatory and renal function biomarkers by systolic blood pressure

Conventions as Figure 4.1.5.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L.
Fibrinogen data were available for 3460 participants.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, SBP: systolic blood pressure.

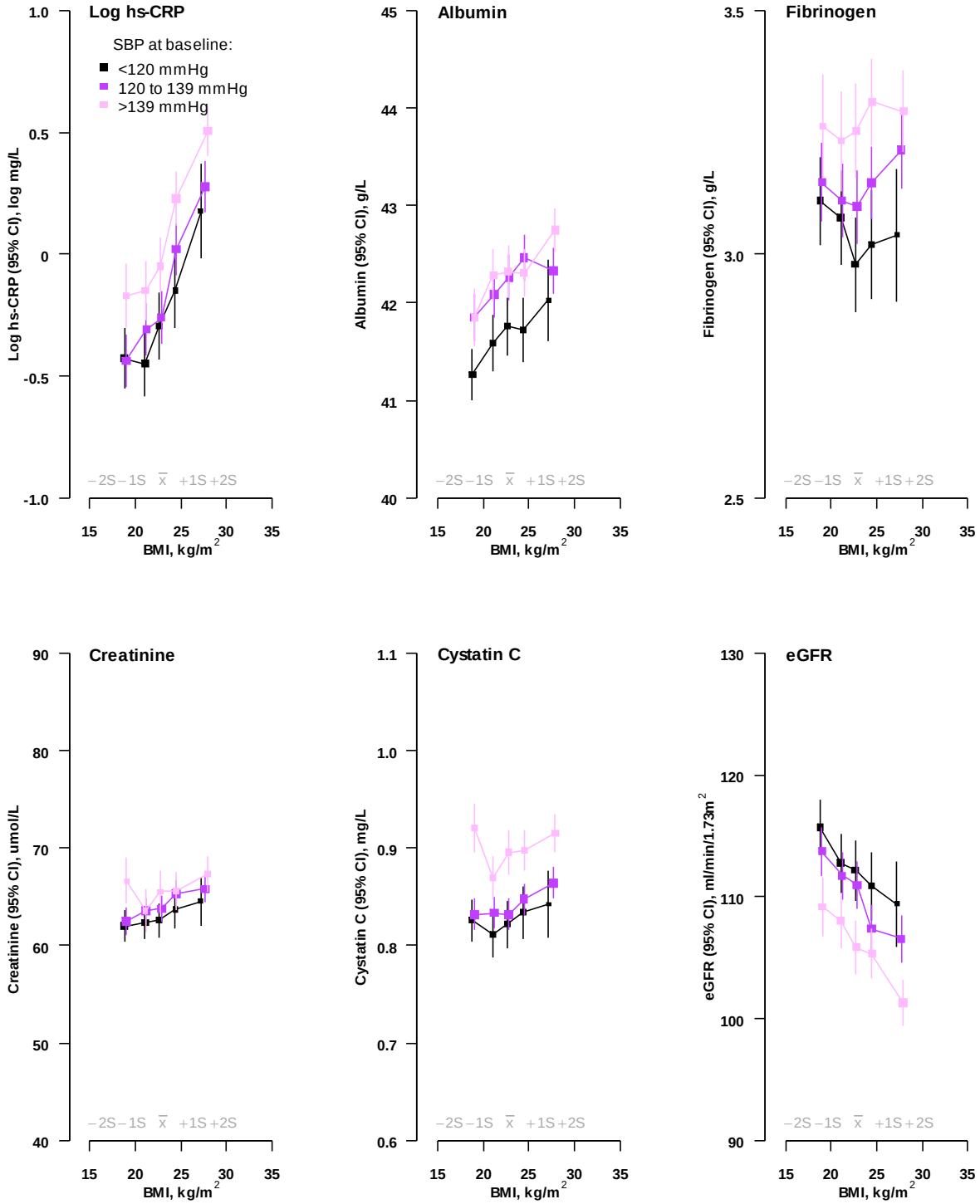


Figure 4.1.10. Association of BMI and WC with liver function and other plasma biomarkers by sex

Conventions as Figure 4.1.2.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml.
Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, WC: waist circumference.

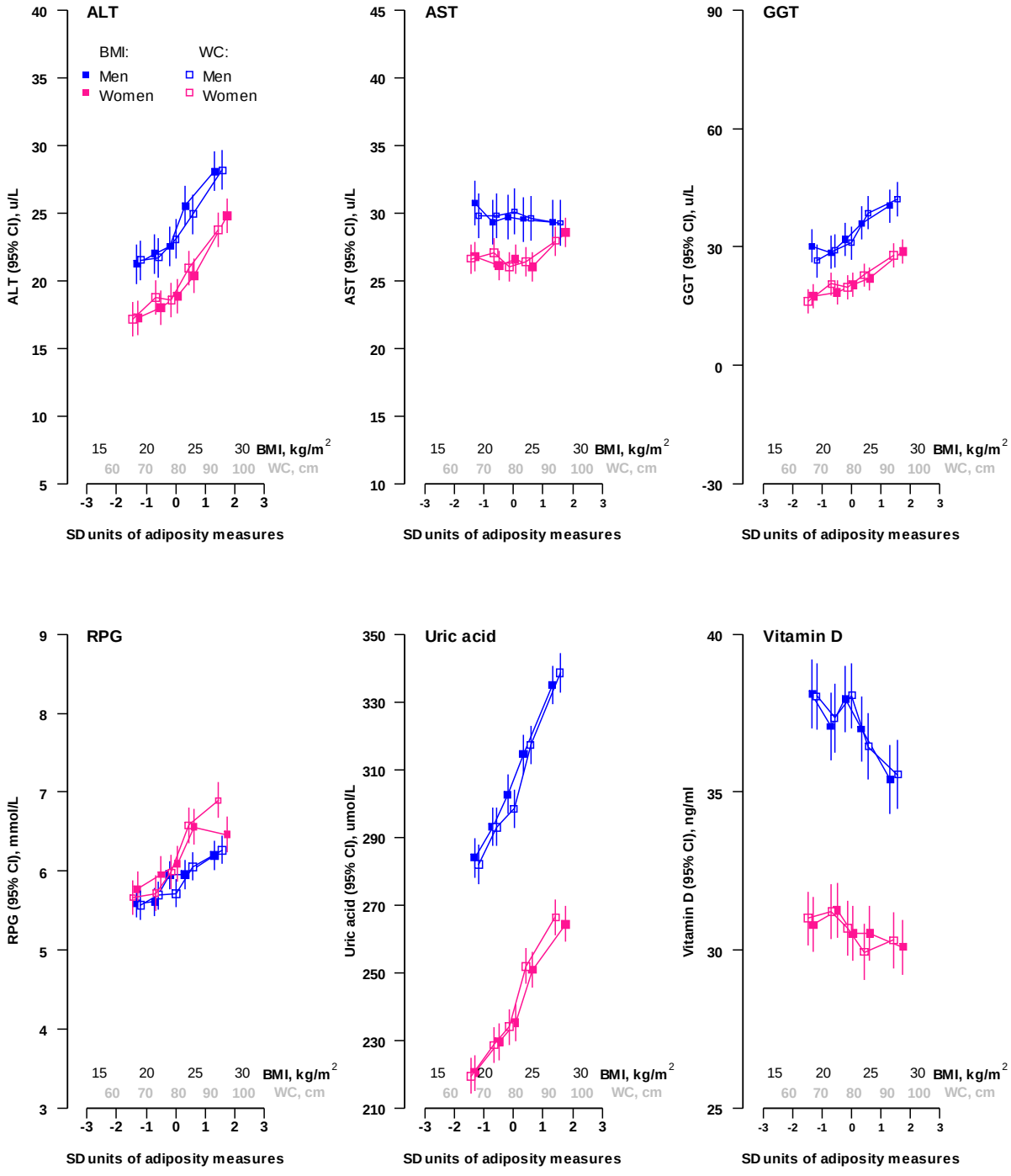


Figure 4.1.11. Association of BMI with liver function and other plasma biomarkers in urban and rural areas

Conventions as Figure 4.1.3.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml.
Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase.

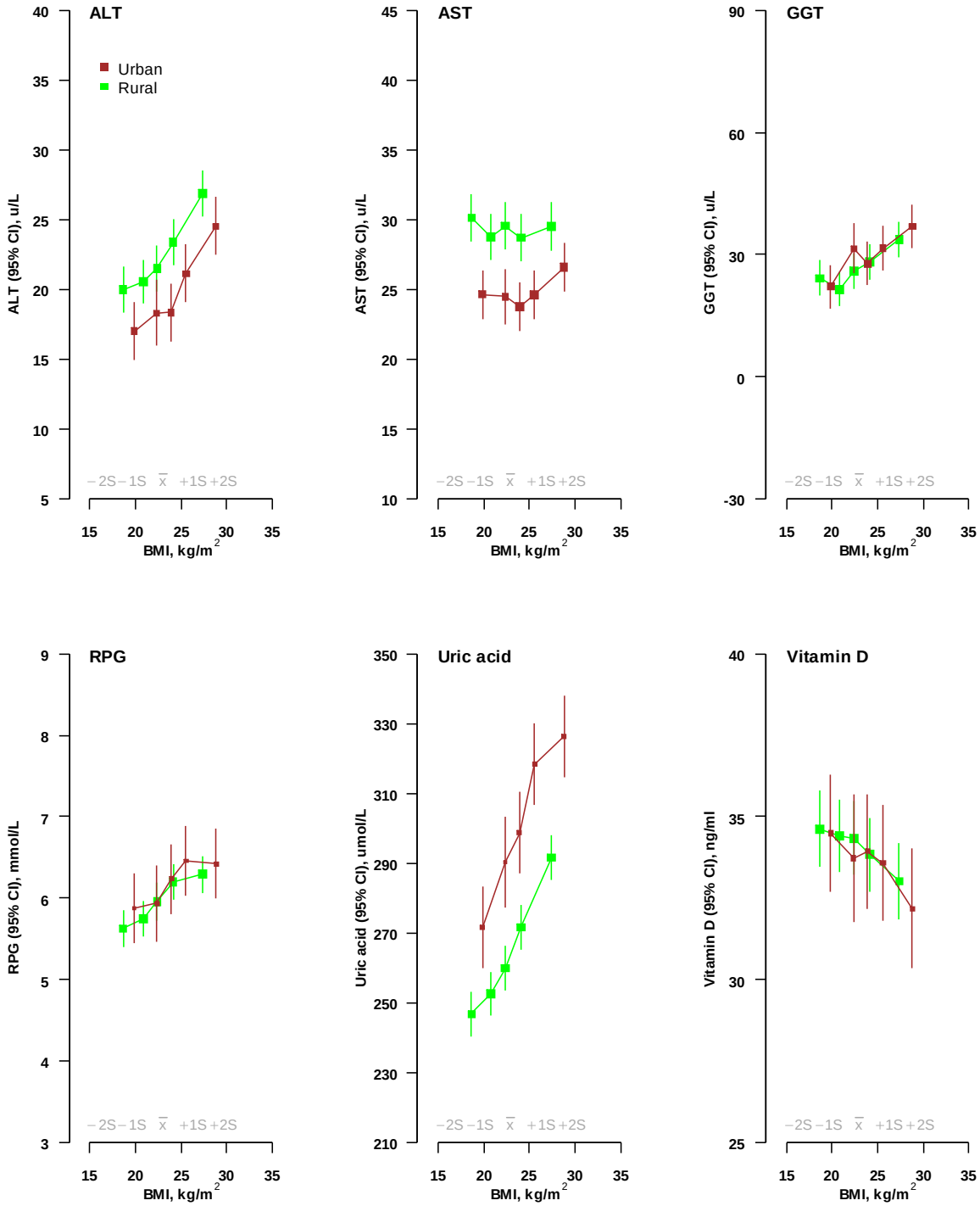


Figure 4.1.12. Association of BMI with liver function and other plasma biomarkers by age

Conventions as Figure 4.1.4.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml.
Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase.

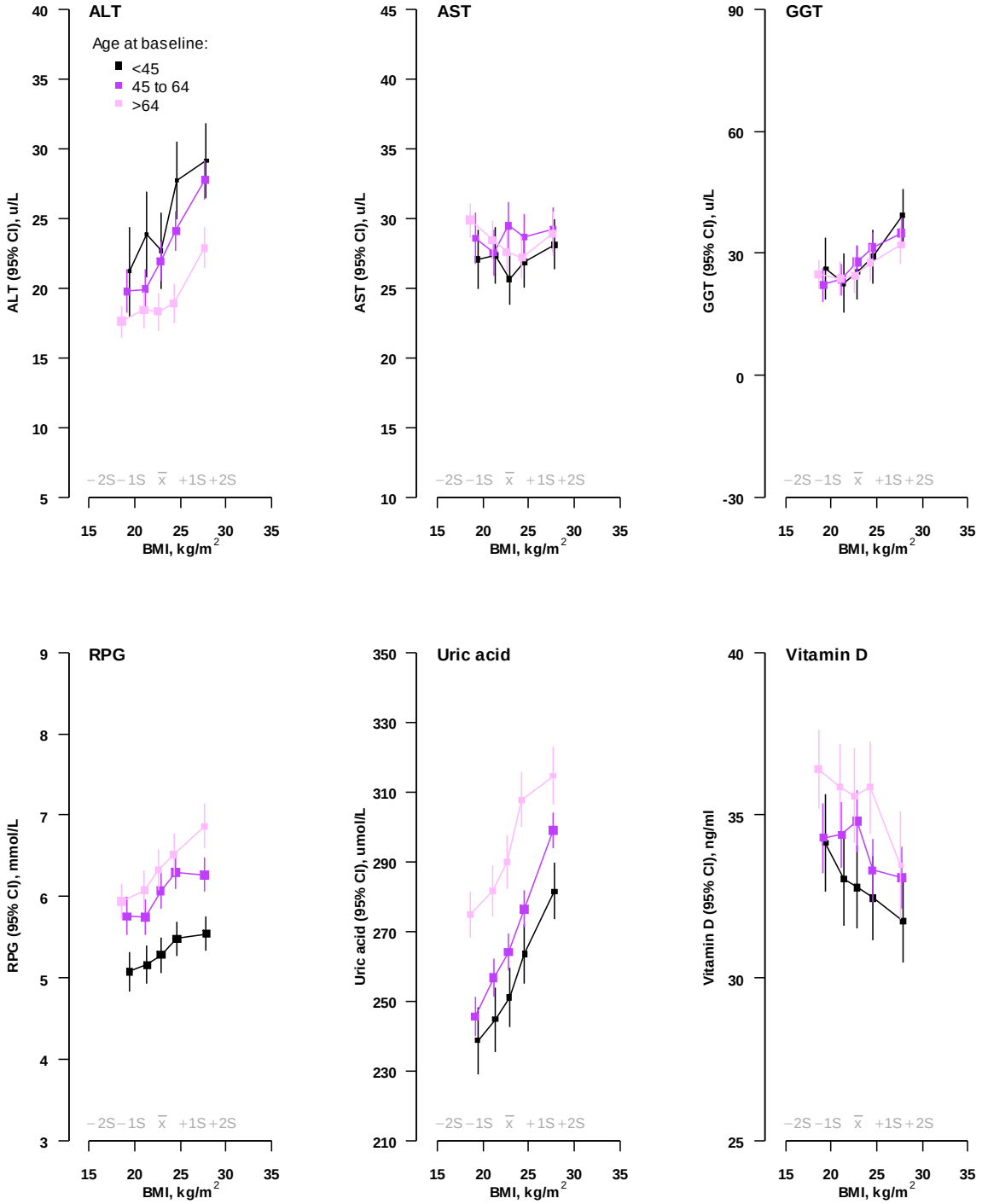


Figure 4.1.13. Association of BMI with liver function and other plasma biomarkers by systolic blood pressure

Conventions as Figure 4.1.5.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml.
Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, SBP: systolic blood pressure.

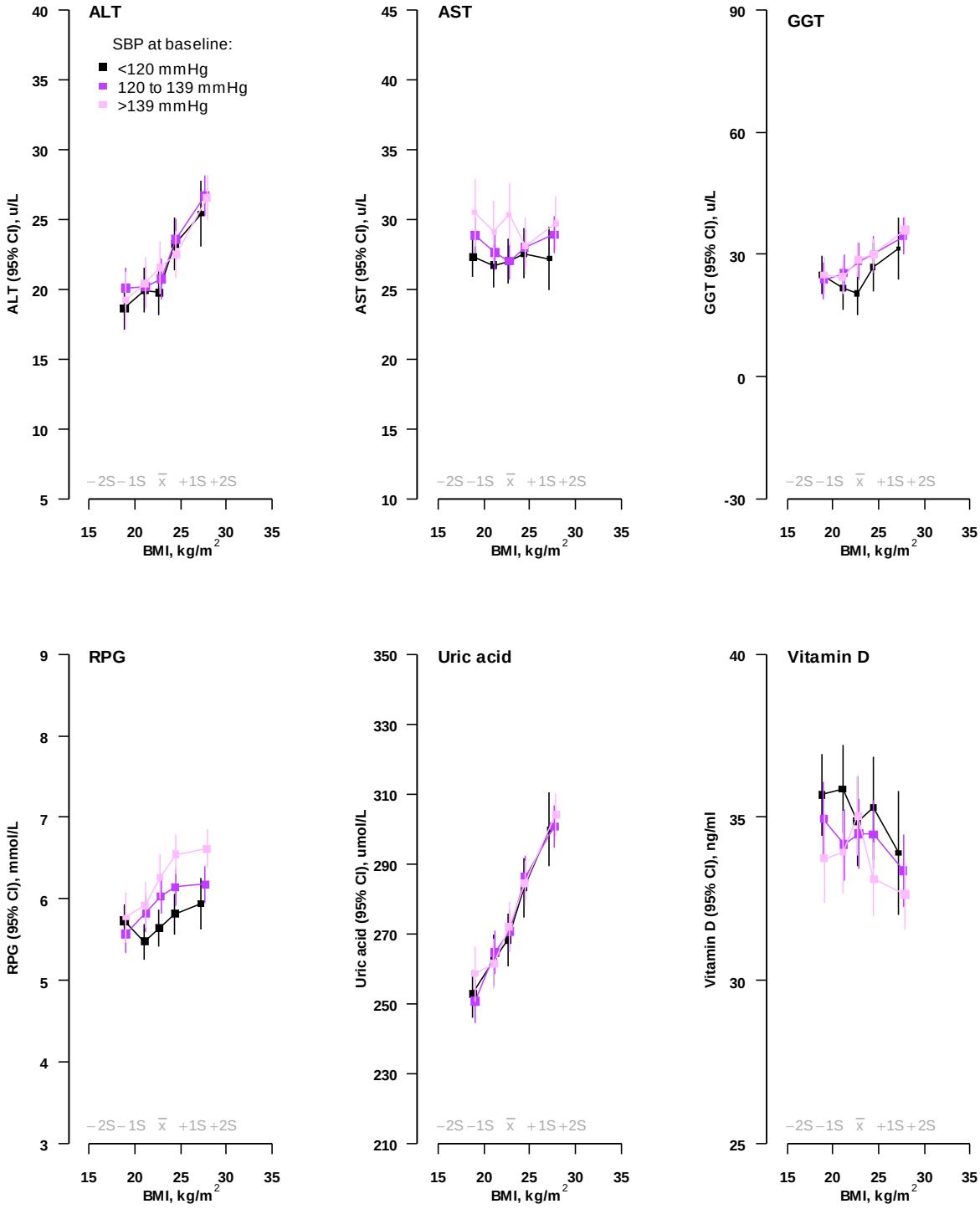


Figure 4.1.14. Manhattan style plot of t-values for the associations between general and central adiposity measures and plasma biomarkers by sex

T-values were extracted from the association of each plasma biomarker with adiposity measures using generalised linear models adjusted for age (5-year groups) and study area, by sex. Adjustment for multiple testing was performed using Bonferroni correction method (grey dashed lines). The plasma biomarkers (x-axis) were ordered according to the t-value (descending order) from the association with BMI and the black solid line represents t-values of the association between BMI and plasma biomarkers, separately in men and women. Vitamin D data were available for 3346 participants. Fibrinogen data were available for 3460 participants.
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase; BMI: body mass index, eGFR: estimate glomerular filtration rate, GGT: gamma glutamyl transferase, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose, WC: waist circumference, WHR: waist-to-hip ratio.

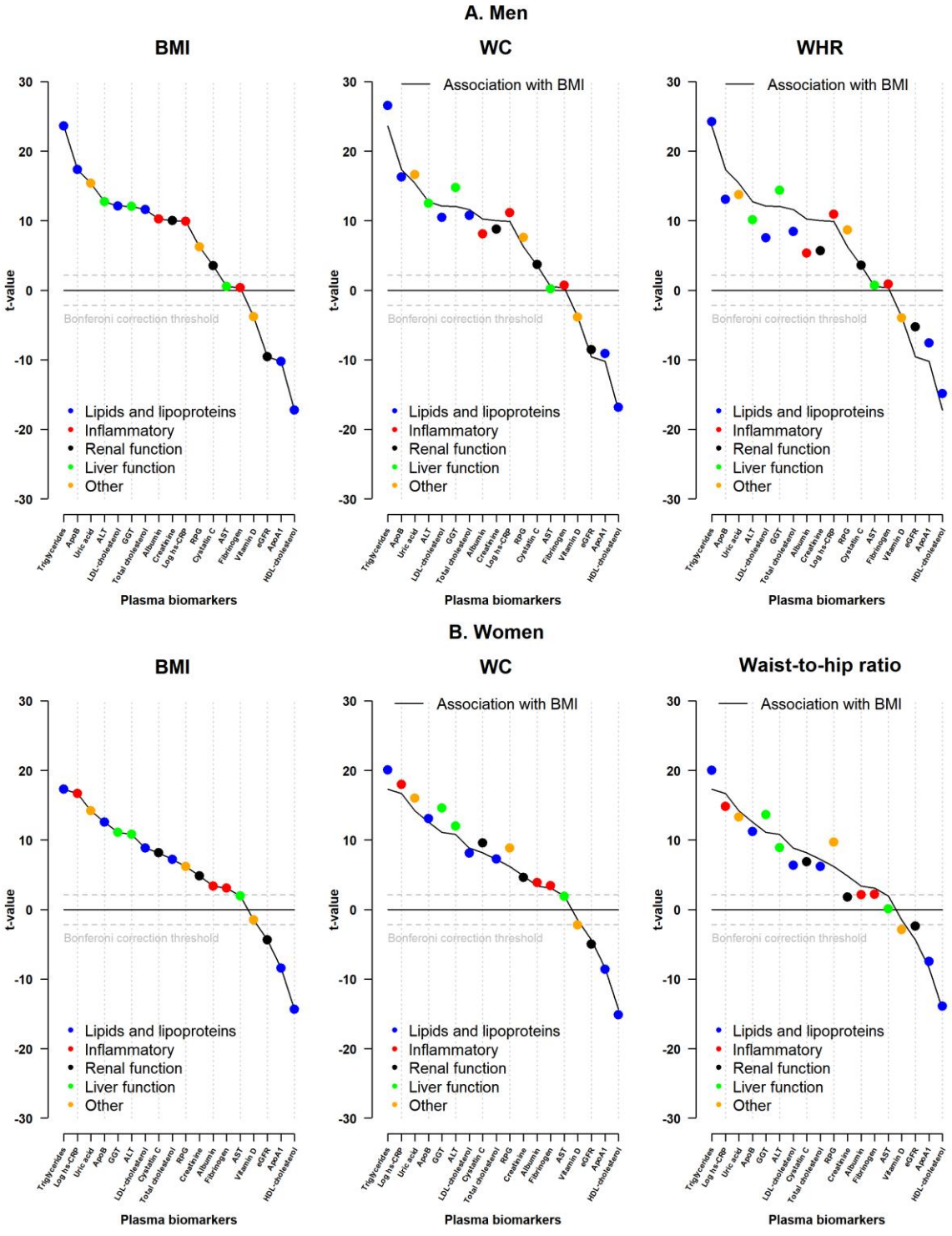


Figure 4.1.15. Association of BMI and WC with lipids and lipoproteins by sex in UKB

Mean values adjusted for age (5-year groups) and recruitment centre, by sex. Each closed square represents the mean value. The vertical lines indicate 95% Cis. The length of y-axis is the same (in absolute levels) as in CKB figures, with the exception of HDL-related biomarkers where the length of x-axis is double the length as compared to CKB figures. Mean (SD) of plasma biomarkers: ApoA1: 154.4 (27.1) mg/dL, ApoB: 104.1 (20.1) mg/dL, HDL-cholesterol: 1.5 (0.4) mmol/L, LDL-cholesterol: 3.6 (0.7) mmol/L, total cholesterol: 5.8 (0.9) mmol/L, triglycerides: 1.7 (0.9) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WC: waist circumference.

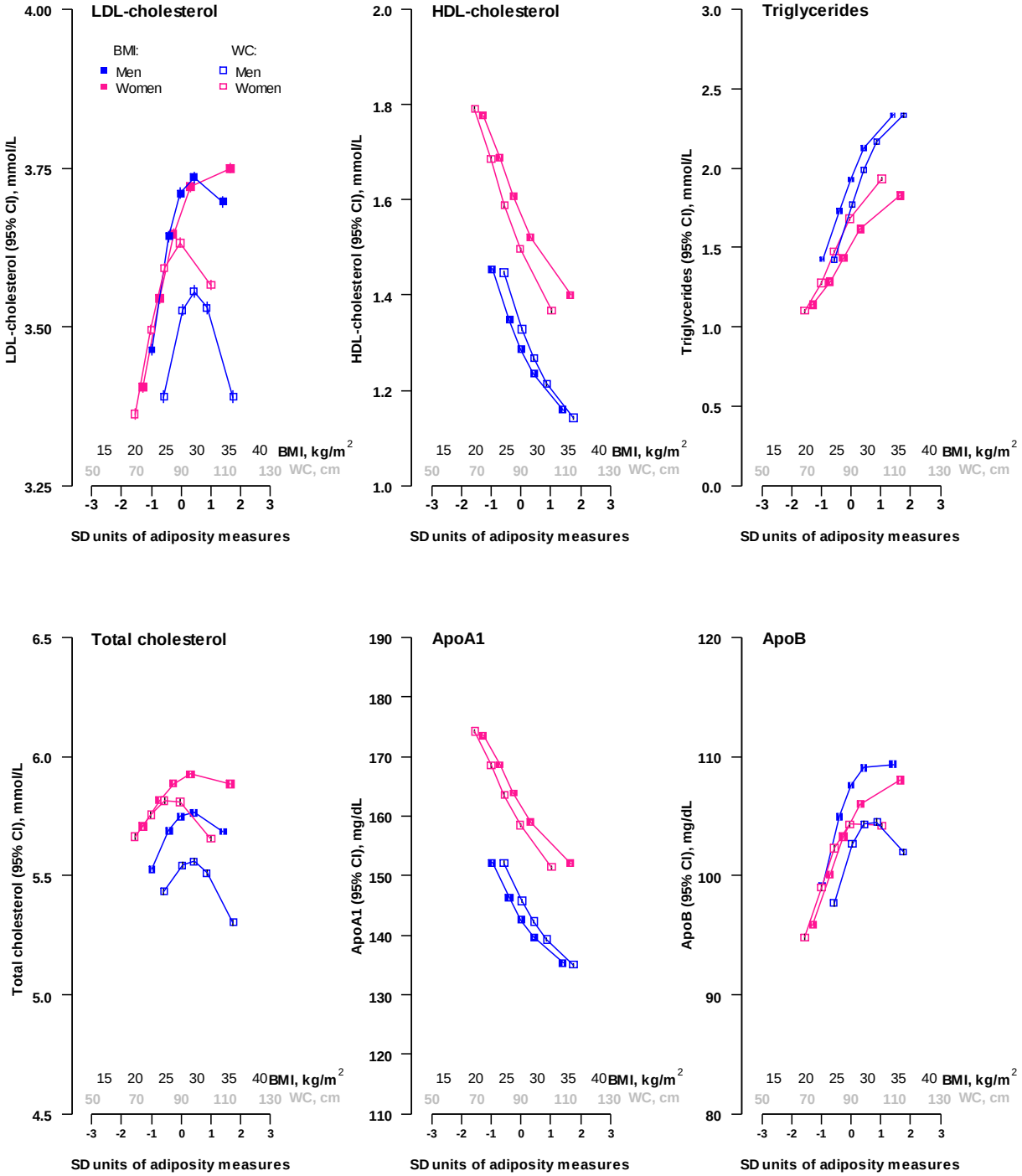


Figure 4.1.16. The association of BMI and WC with inflammatory and renal function biomarkers by sex, in UKB

Mean values adjusted for age (5-year groups) and recruitment centre, by sex. Each closed square represents the mean value. The length of y-axis is the same (in absolute levels) as in CKB figures, with the exception Cystatin C where the length of x-axis is double the length as compared to CKB figures. Mean (SD): albumin: 45.2 (2.6), creatinine: 71.4 (15.5), cystatin C: 0.9 (0.2), eGFR: 93.1 (16.9), log hs-CRP: 0.3 (1.1).
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, WC: waist circumference.

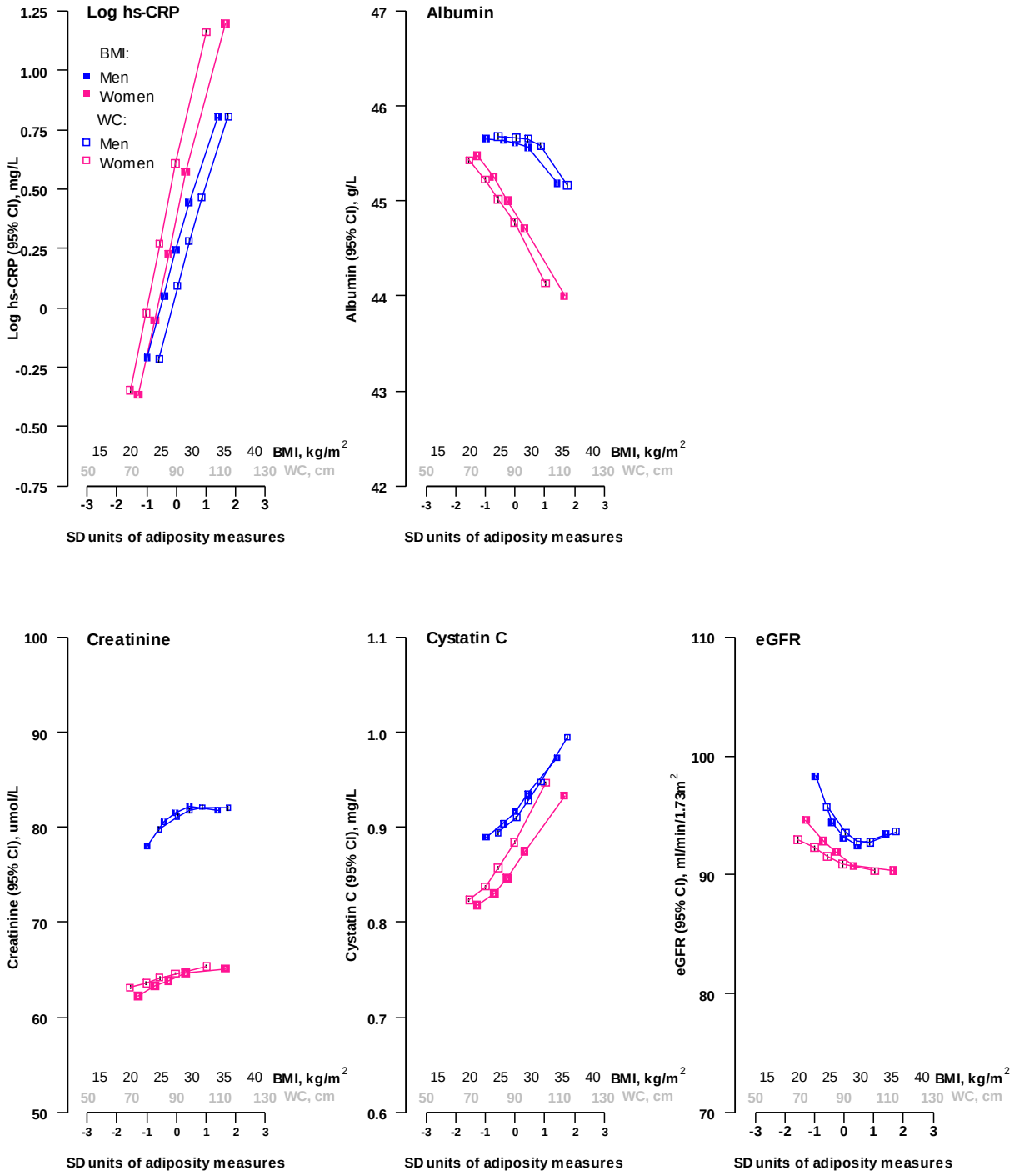


Figure 4.1.17. The association of BMI and WC with liver function and other plasma biomarkers by sex, in UKB

Mean values adjusted for age (5-year groups) and recruitment centre, by sex. Each closed square represents the mean value. The vertical lines indicate 95% Cis. The length of y-axis is the same (in absolute levels) as in CKB figures, with the exception uric acid where the length of x-axis is double the length as compared to CKB figures. Mean (SD): ALT: 22.7 (14.2) u/L, AST: 25.7 (10.7) u/L, GGT: 34.8 (38.6) u/L, RPG: 5.0 (0.9) mmol/L, uric acid: 303.0 (78.4) umol/L, vitamin D: 48.3 (21.1) ng/ml. ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, RPG: random plasma glucose, WC: waist circumference.

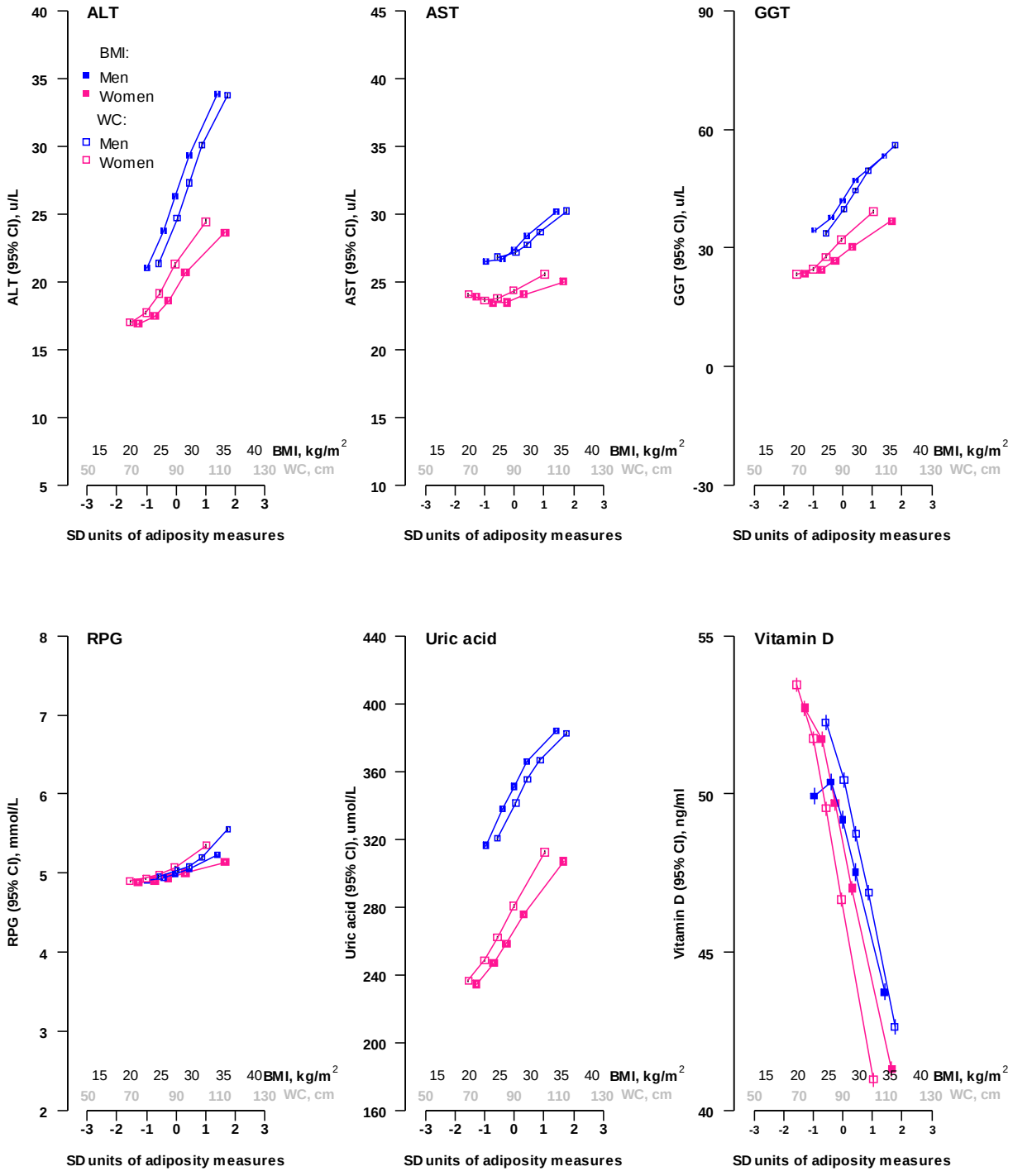


Figure 4.1.18. Manhattan style plot of t-values for the association between general and central adiposity measures and plasma biomarkers by sex, in UKB

T-values were extracted from the association of each plasma biomarker with adiposity measure using generalised linear models adjusted for age (5-year groups) and recruitment centre, by sex. Adjustment for multiple testing was performed using Bonferroni correction method (grey dashed lines). The plasma biomarkers (x-axis) were ordered according to the t-value (descending order) from the association with BMI and the black solid line represents t-values of the association between BMI and plasma biomarkers, separately in men and women.
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase; BMI: body mass index, eGFR: estimate glomerular filtration rate, GGT: gamma glutamyl transferase, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose, WC: waist circumference, WHR: waist-to-hip ratio.

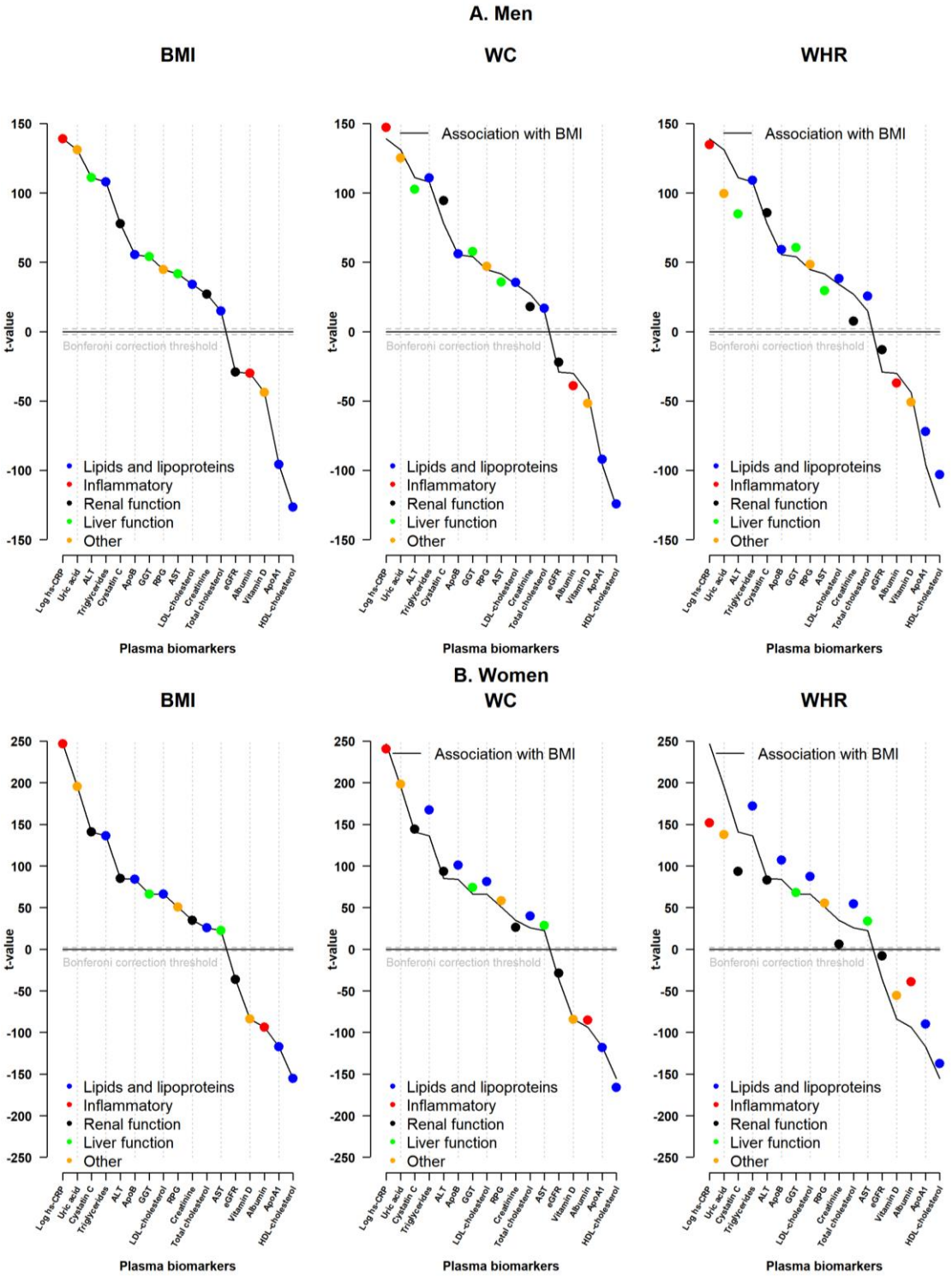


Table 4.2.1. Baseline characteristics of participants in the nested case-control study

Characteristic[a]	IS cases	ICH cases	Controls
No. of participants	4943	3952	5634
Age and socioeconomic factors			
Mean age (SD), years	54.4 (9.3)	59.4 (10.2)	57.4 (1.4)
Female, %	53.9	47.2	47.2
Urban, %	45.5	22.2	23.1
≥6 years of education, %	52.2	29.2	34.2
Lifestyle factors			
Male ever-regular smokers, %	76.9	75.8	74.8
Female ever-regular smokers, %	4.0	5.2	4.6
Male ever-regular drinkers, %	38.1	35.4	33.3
Female ever-regular drinkers, %	3.1	3.2	2.5
Mean physical activity (SD), MET-h/day	17.8 (11.3)	17.4 (11.4)	19.0 (11.1)
Physical measurements, mean (SD)			
SBP, mmHg	141.8 (23.8)	153.1 (26.8)	134.9 (20.0)
DBP, mmHg	82.9 (12.4)	86.5 (14.0)	77.3 (10.9)
BMI, kg/m^2	24.4 (3.3)	23.2 (3.3)	23.0 (3.1)
WC, cm	82.9 (9.3)	80.4 (9.6)	79.2 (9.0)
WHR	0.90 (0.06)	0.90 (0.07)	0.89 (0.001)
Body fat percentage	28.8 (6.5)	25.6 (6.8)	25.4 (6.3)
Medical history and health status, %			
Diabetes	6.4	4.1	4.8
Hypertension	21.5	25.9	11.0
Chronic kidney disease	2.4	1.4	1.1
Chronic liver disease	1.2	1.3	1.0

[a]Adjusted for age (5-year groups), sex and study area (where appropriate).
BMI: body mass index, DBP: diastolic blood pressure, ICH: intracerebral haemorrhage, IS: ischaemic stroke, SBP: systolic blood pressure, MET-h/day: metabolic equivalent of task hours per day, WC: waist circumference, WHR: waist-to-hip ratio.

Figure 4.2.1. Associations of lipids with ischaemic stroke and intracerebral haemorrhage

The HRs of stroke types by baseline plasma biomarker values (quintiles), are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. HRs are plotted against mean baseline plasma biomarker levels in each quintile. Squares represent the HR with area inversely proportional to the variance. Vertical lines represent the corresponding 95% CI.
HDL-cholesterol: high-density lipoprotein cholesterol, HR: hazard ratio, LDL-cholesterol: low-density lipoprotein cholesterol.

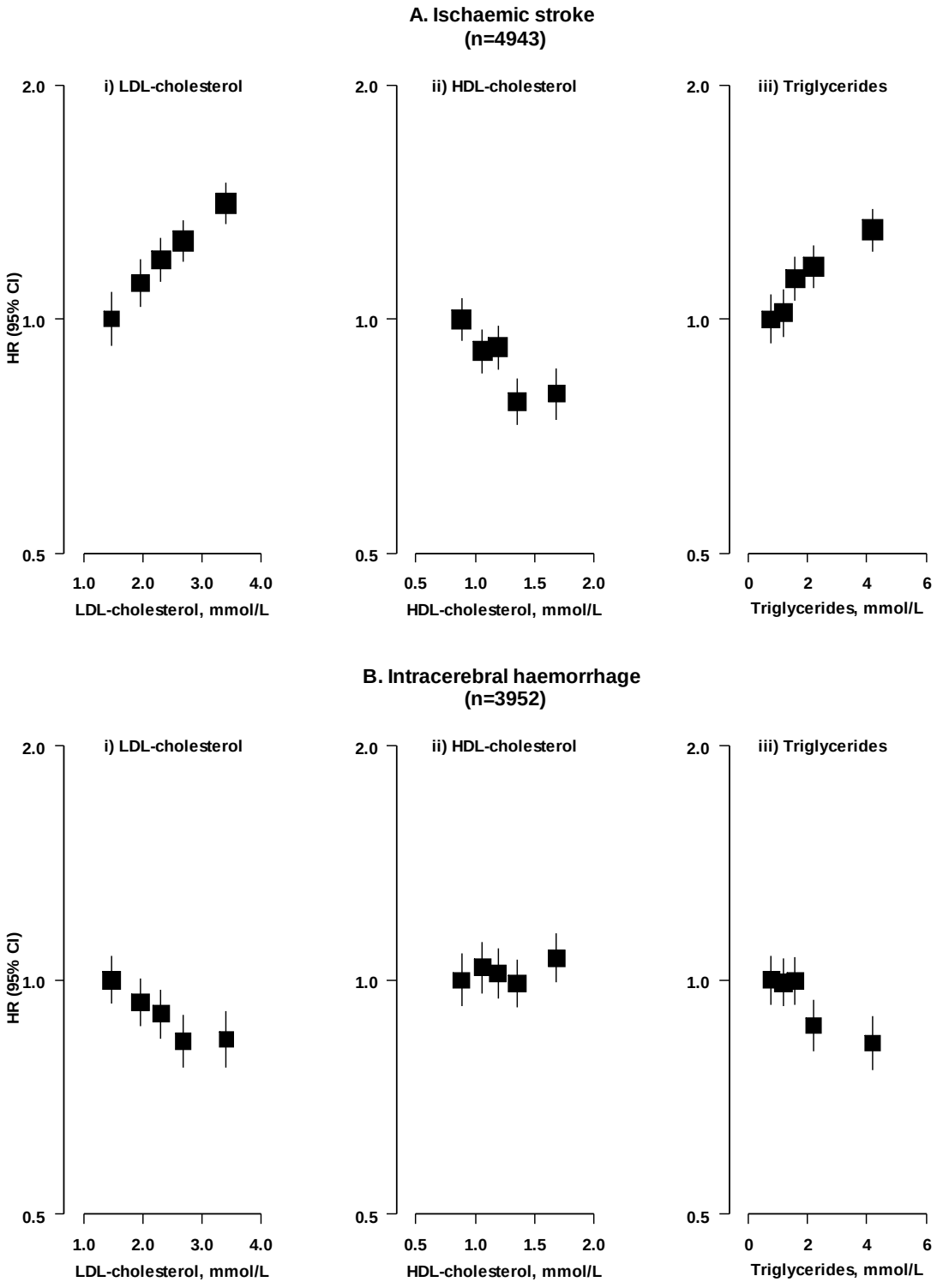


Figure 4.2.2. Associations of total cholesterol and lipoproteins with ischaemic stroke and intracerebral haemorrhage

Conventions as Figure 4.2.1.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, HR: hazard ratio.

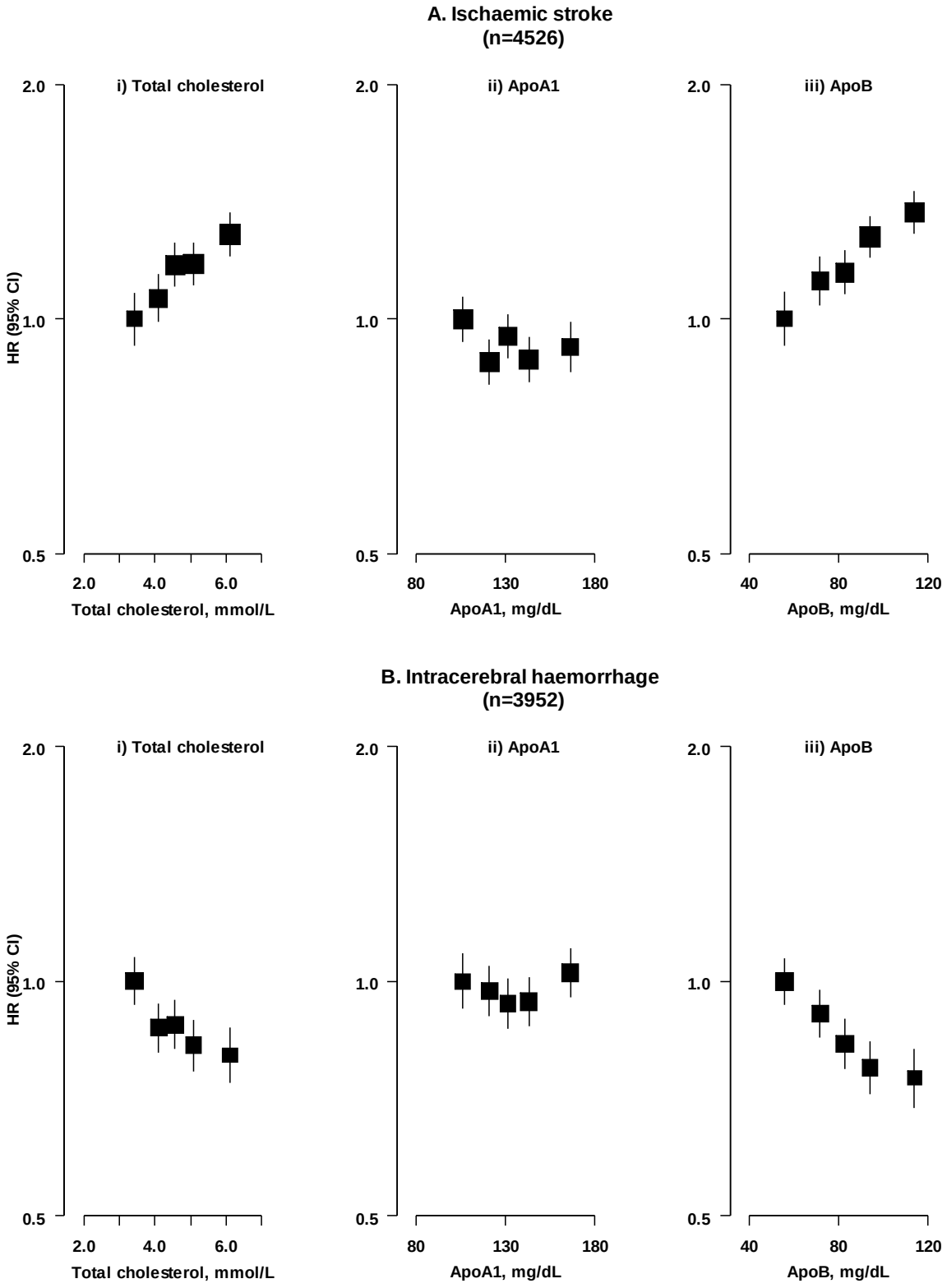


Figure 4.2.3. Associations per SD higher of plasma biomarkers with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types per 1 SD higher of plasma biomarkers, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. Squares represent the HR with area inversely proportional to the variance. Horizontal lines represent the corresponding 95% CIs.
Fibrinogen, 2283 IS events and 1936 ICH events; Vitamin D, 2209 IS events and 1880 ICH events.
SD of plasma biomarkers albumin: 2.8 g/L, ALT: 17.4 u/L, ApoA1: 22.1 mg/dL, ApoB: 21.2 mg/dL, AST: 18.2 u/L, creatinine: 26.5 umol/L, cystatin C: 0.3 mg/L, eGFR: 25.2 ml/min/1.73m^2, fibrinogen: 0.8 g/L, GGT: 71.6 u/L, HDL-cholesterol: 0.3 mmol/L, LDL-cholesterol: 0.7 mmol/L, log hs-CRP: 1.2 log mg/L, RPG: 3.0 mmol/L, total cholesterol: 1.0 mmol/L, triglycerides: 1.5 mmol/L, uric acid: 82.8 umol/L.
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose.

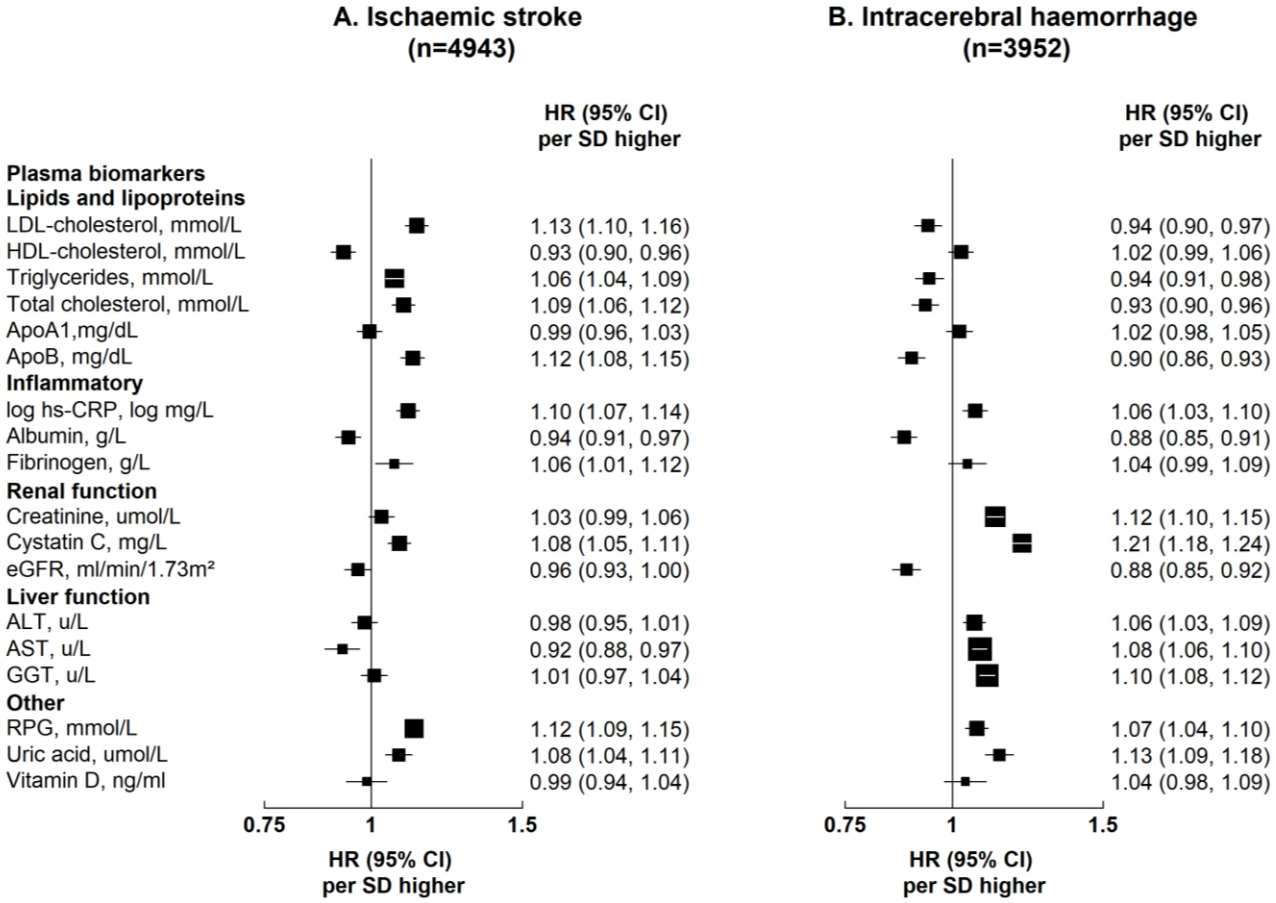


Figure 4.2.4. Associations per SD higher LDL-cholesterol with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types per 1 SD (0.7 mmol/L) higher LDL-cholesterol, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (except where it is the variable of interest). Participants were classified as ever-regular smokers if they answered “on most days” or “daily or almost every day” to either “How often do you smoke tobacco now?” or “In the past, how frequently did you smoke?”. Participants were classified as ever-regular alcohol drinkers if they answered “usually at least once a week” to the question “During the past 12 months, how often did you drink alcohol?” or they answered yes to the question “In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?”. Participants were classified as having diabetes if they answered yes to the question “Has a doctor ever told you that you had diabetes?” or if they had a random plasma glucose level ≥7.0 mmol/L if time since last food was ≥8 hours, or ≥11.1 mmol/L if time since last food was <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. Squares represent the HR with area inversely proportional to the variance. Horizontal lines represent the corresponding 95% CIs. The diamond represents the overall HR and its 95% CI.
BMI: body mass index, HR: hazard ratio, LDL-cholesterol: low-density lipoprotein cholesterol, SBP: systolic blood pressure.

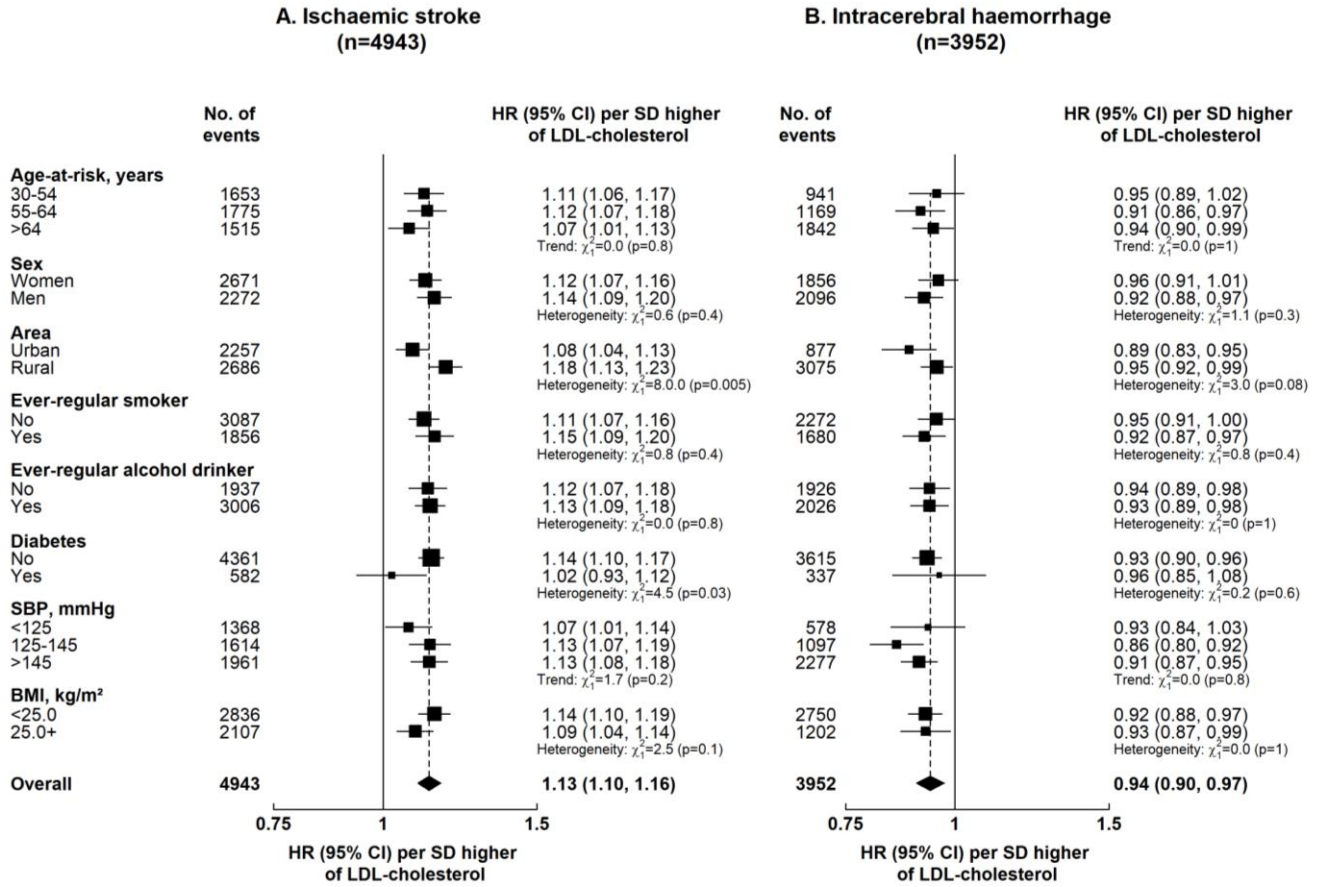


Figure 4.2.5. Associations per SD higher triglycerides with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (1.5 mmol/L) higher of triglycerides. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

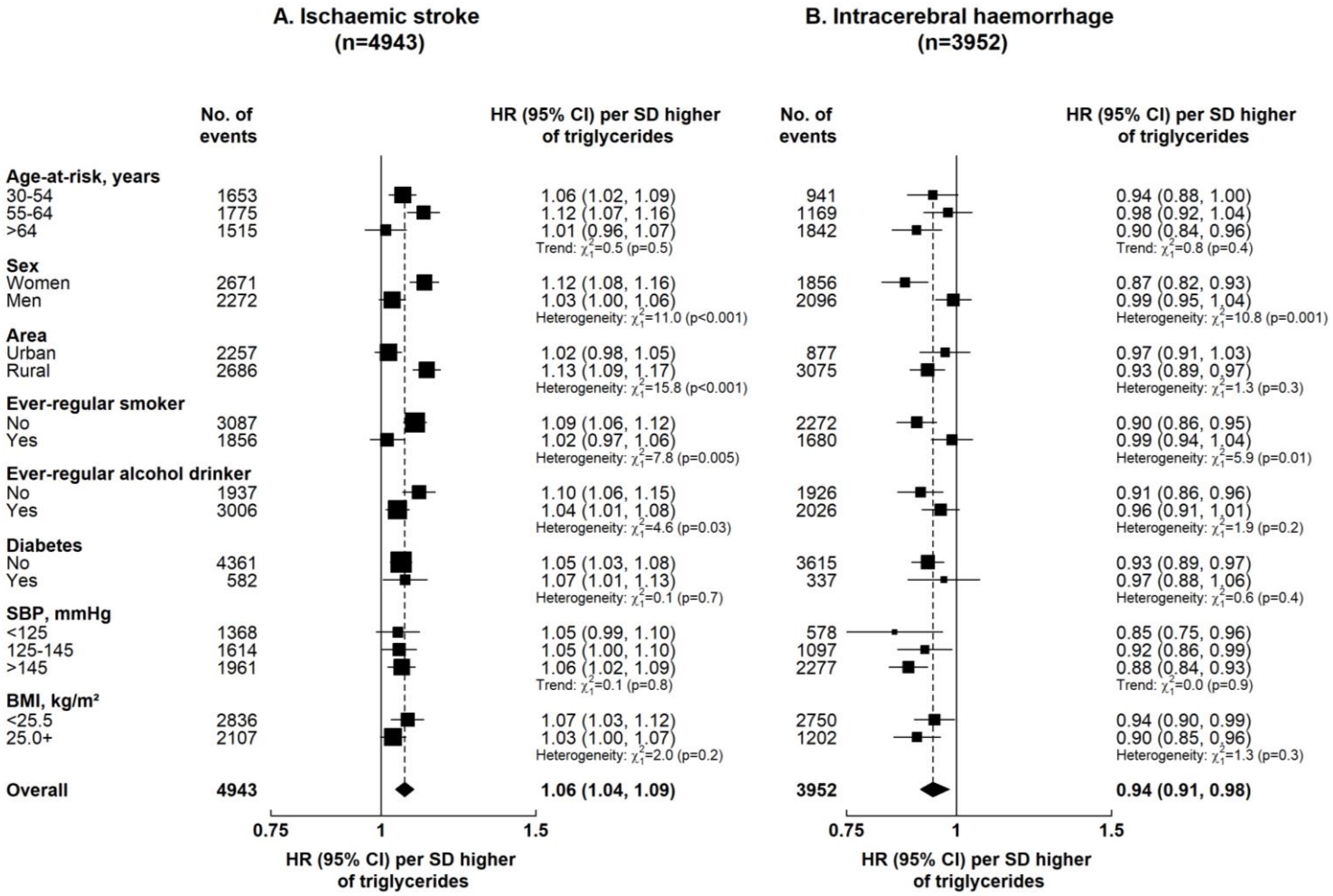


Figure 4.2.6. Associations per SD higher of HDL-cholesterol with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (1.5 mmol/L) higher of HDL-cholesterol. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, HDL-cholesterol: high-density lipoprotein cholesterol, SBP: systolic blood pressure.

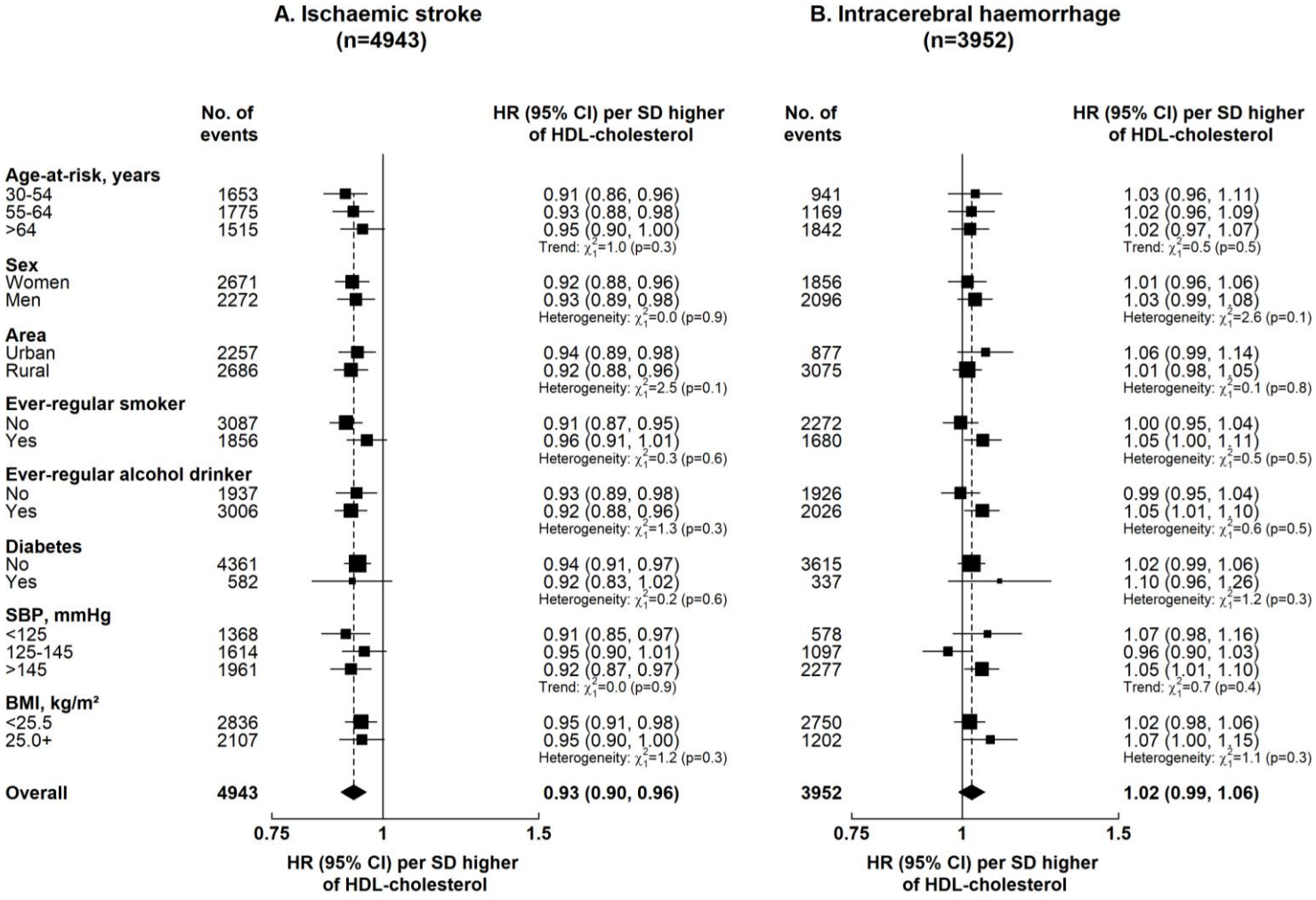


Figure 4.2.7. Associations per SD higher of plasma biomarkers with ischaemic stroke and intracerebral haemorrhage additionally adjusted for baseline SBP

The HRs for stroke types per 1 SD higher of plasma biomarkers, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol, physical activity and baseline SBP. Squares represent the HR with area inversely proportional to the variance. Horizontal lines represent the corresponding 95% CIs. Fibrinogen, 2283 IS events and 1936 ICH events. Vitamin D, 2209 all IS events and 1880 all ICH events.
SD of plasma biomarkers albumin: 2.8 g/L, ALT: 17.4 u/L, ApoA1: 22.1 mg/dL, ApoB: 21.2 mg/dL, AST: 18.2 u/L, creatinine: 26.5 umol/L, cystatin C: 0.3 mg/L, eGFR: 25.2 ml/min/1.73m^2, fibrinogen: 0.8 g/L, GGT: 71.6 u/L, HDL-cholesterol: 0.3 mmol/L, LDL-cholesterol: 0.7 mmol/L, log hs-CRP: 1.2 log mg/L, RPG: 3.0 mmol/L, total cholesterol: 1.0 mmol/L, triglycerides: 1.5 mmol/L, uric acid: 82.8 umol/L.
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose.

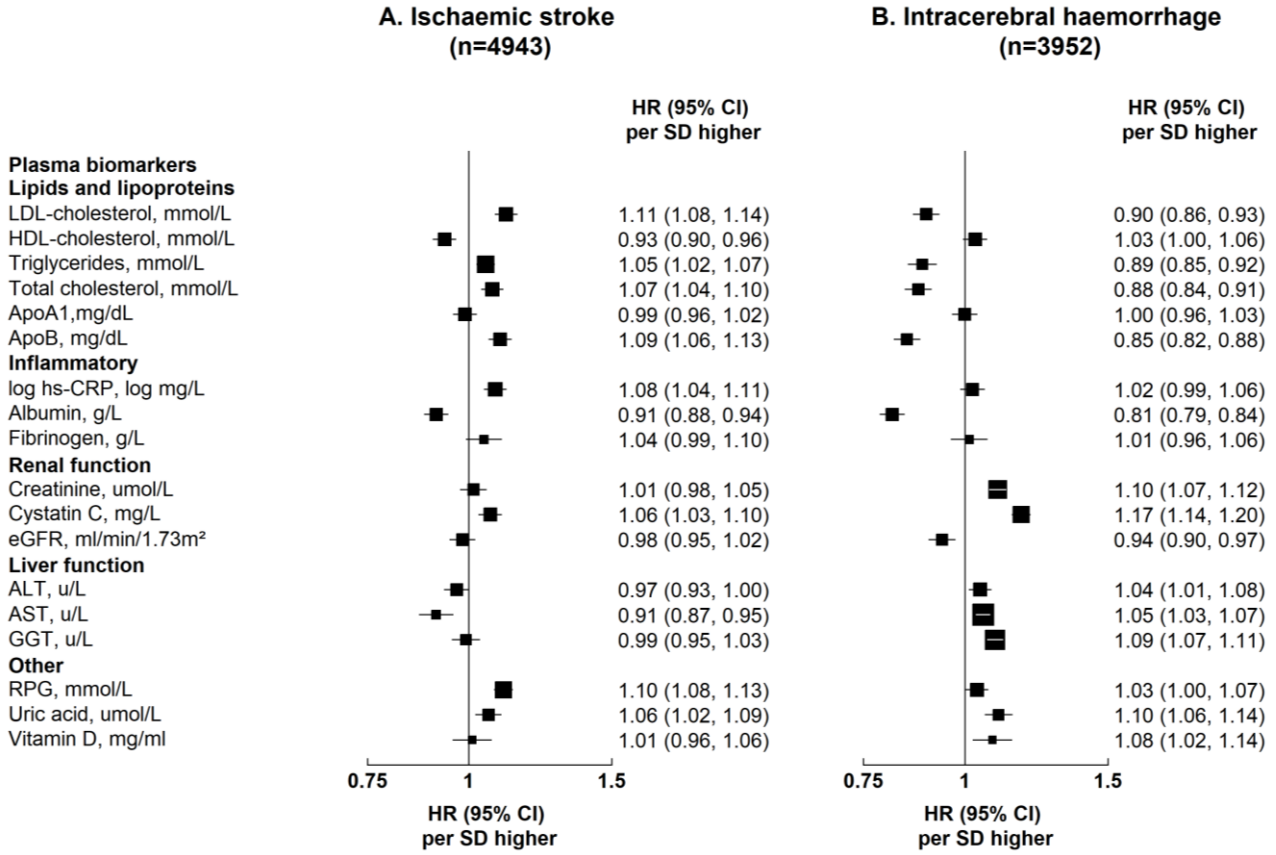


Figure 4.2.8. Associations per SD higher of plasma biomarkers with ischaemic stroke and intracerebral haemorrhage additionally adjusted for baseline BMI

The HRs for stroke types per 1 SD higher of plasma biomarkers, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol, physical activity and measured BMI. Squares represent the HR with area inversely proportional to the variance. Horizontal lines represent the corresponding 95% CIs. Fibrinogen, 2283 IS events and 1936 ICH events. Vitamin D, 2209 all IS events and 1880 all ICH events.
SD of plasma biomarkers albumin: 2.8 g/L, ALT: 17.4 u/L, ApoA1: 22.1 mg/dL, ApoB: 21.2 mg/dL, AST: 18.2 u/L, creatinine: 26.5 umol/L, cystatin C: 0.3 mg/L, eGFR: 25.2 ml/min/1.73m^2, fibrinogen: 0.8 g/L, GGT: 71.6 u/L, HDL-cholesterol: 0.3 mmol/L, LDL-cholesterol: 0.7 mmol/L, log hs-CRP: 1.2 log mg/L, RPG: 3.0 mmol/L, total cholesterol: 1.0 mmol/L, triglycerides: 1.5 mmol/L, uric acid: 82.8 umol/L.
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, RPG: random plasma glucose.

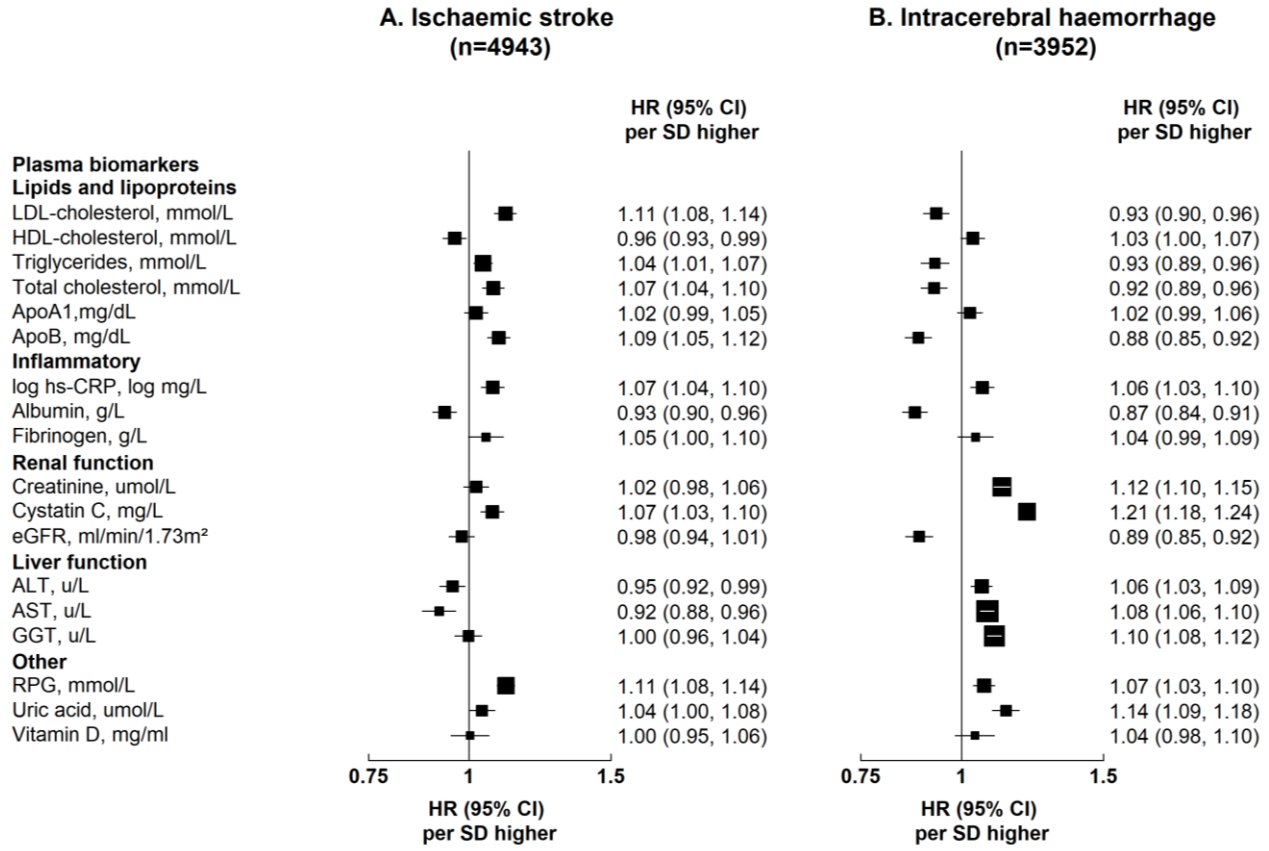


Figure 4.2.9. Associations of inflammatory biomarkers with ischaemic stroke and intracerebral haemorrhage

Conventions as Figure 4.2.1.
Analysis for fibrinogen, 2283 IS and 1936 ICH events.
HR: hazard ratio, hs-CRP: high-sensitivity C-reactive protein.

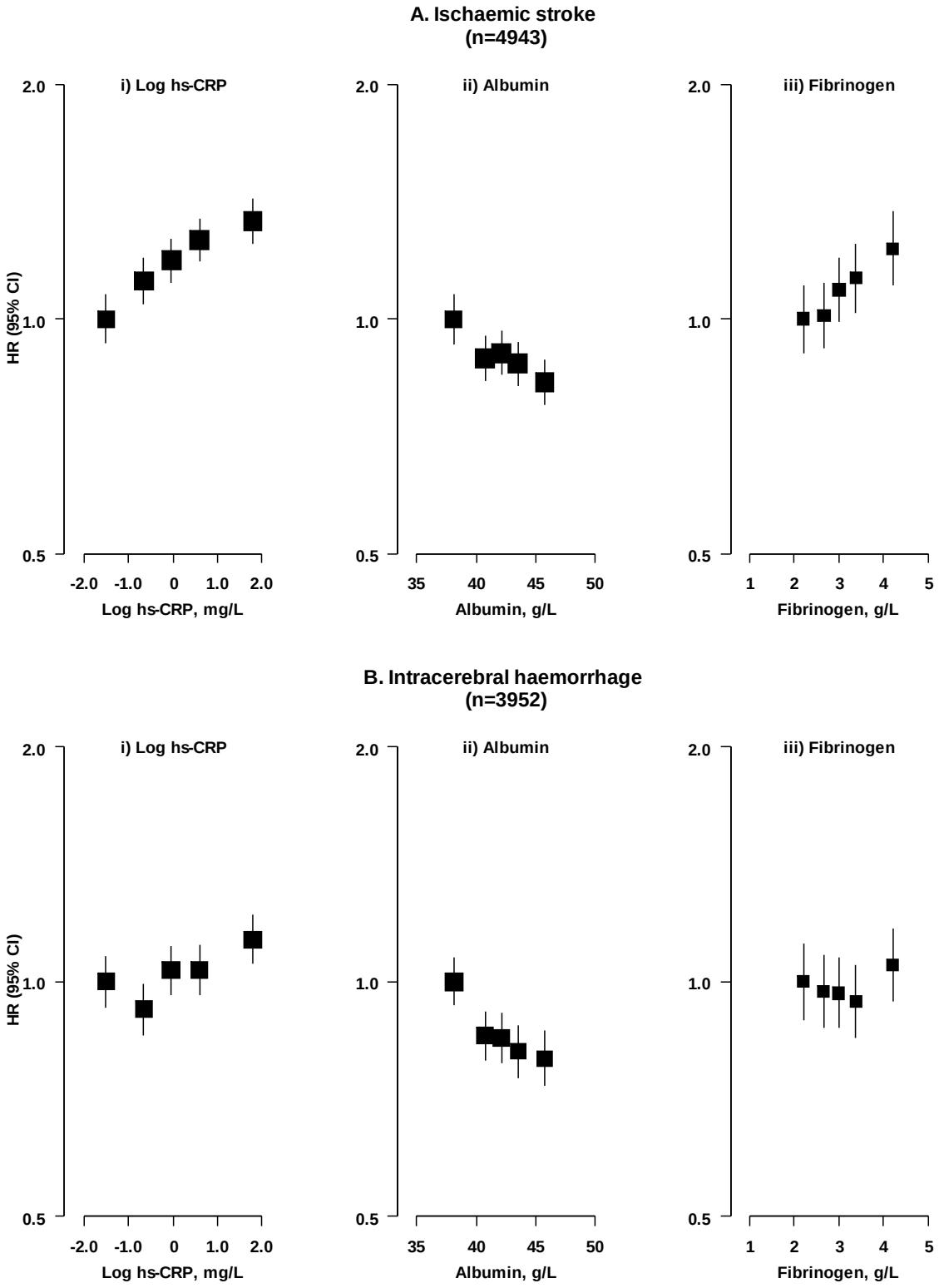


Figure 4.2.10. Associations per SD higher of log hs-CRP with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (1.2 log mg/L) higher of log hs-CRP. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, hs-CRP: high-sensitivity C-reactive protein, SBP: systolic blood pressure.

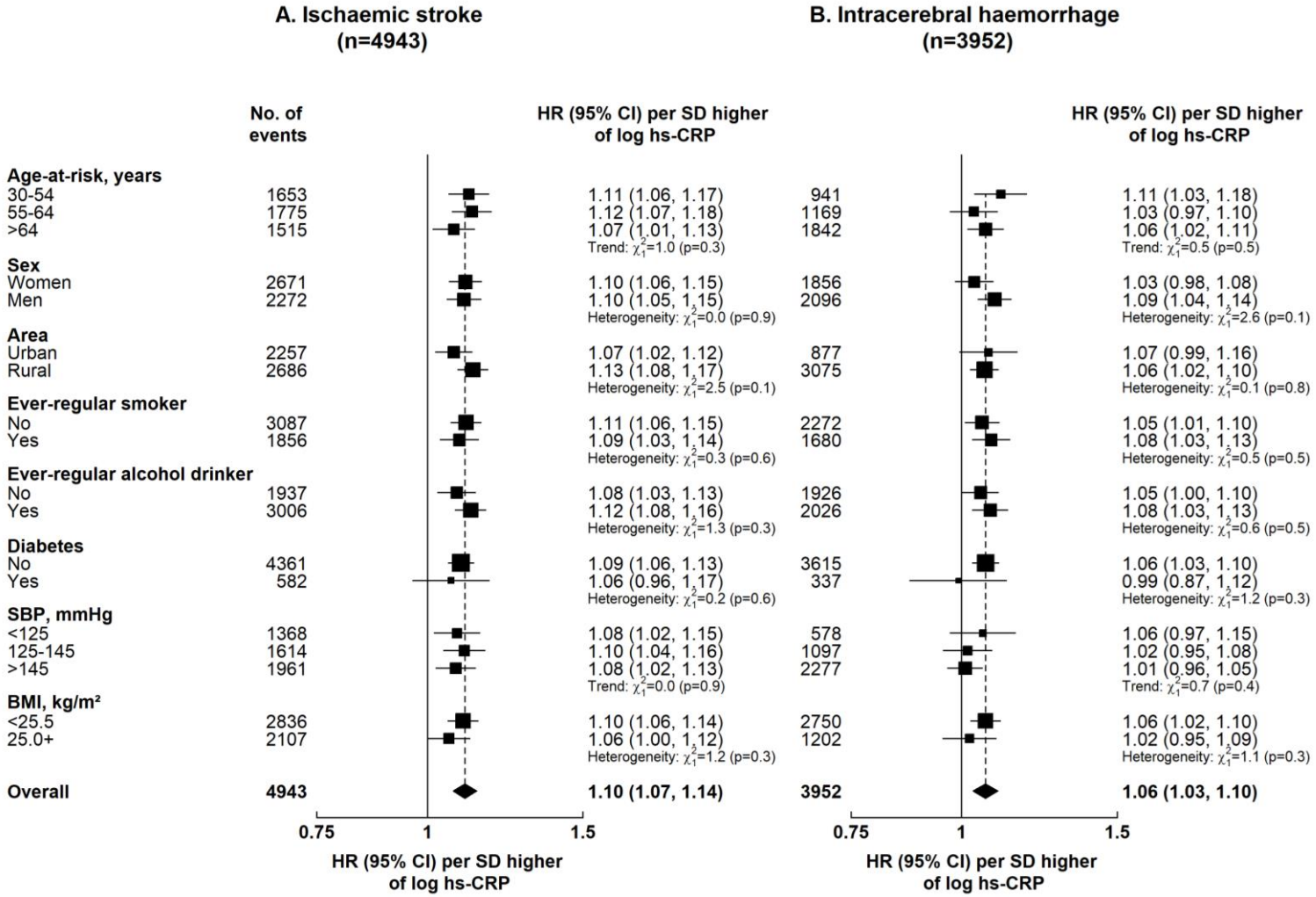


Figure 4.2.11. Associations per SD higher of albumin with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (2.8 g/L) higher of albumin. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

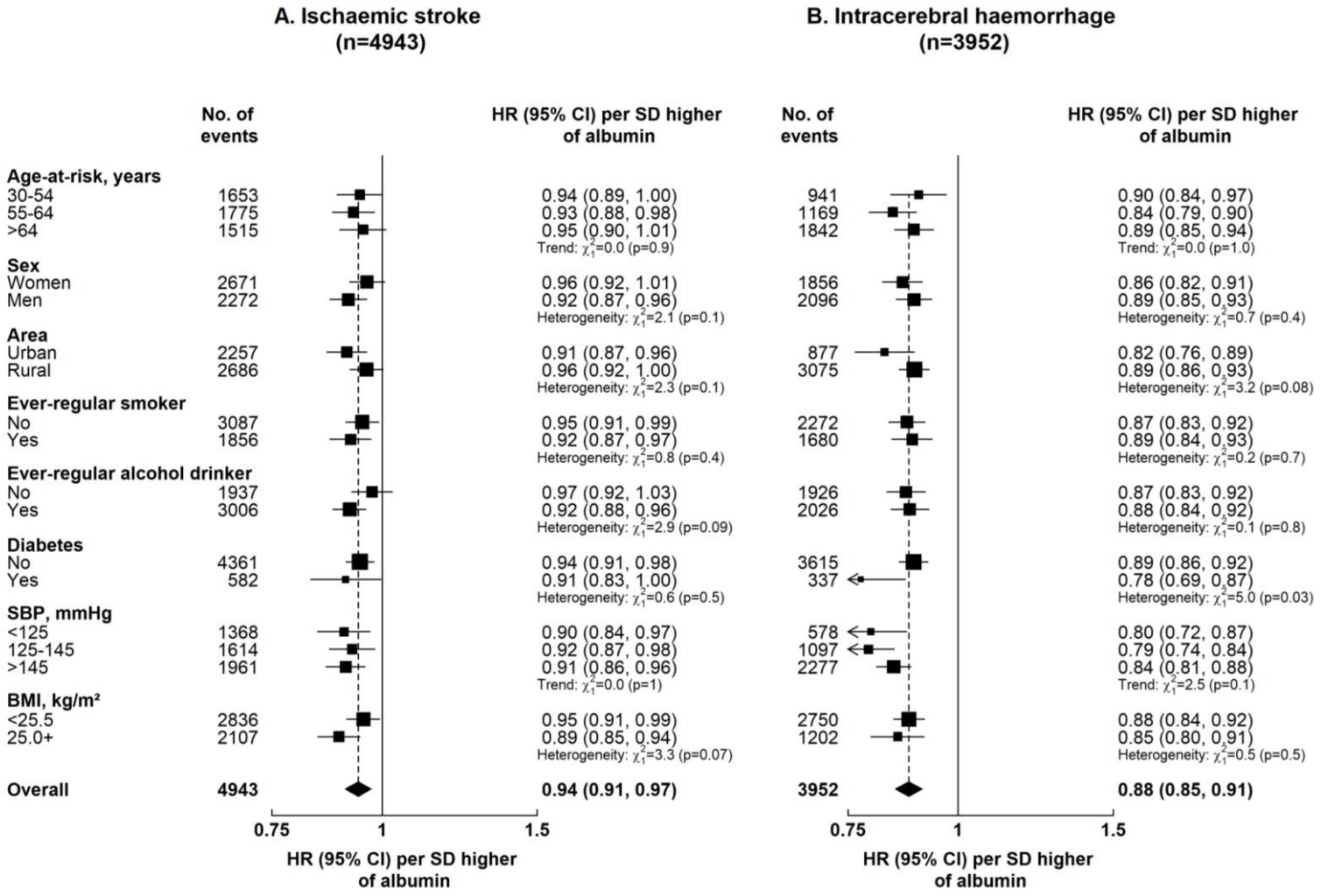


Figure 4.2.12. Associations per SD higher of fibrinogen with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (0.8 g/L) higher of fibrinogen. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

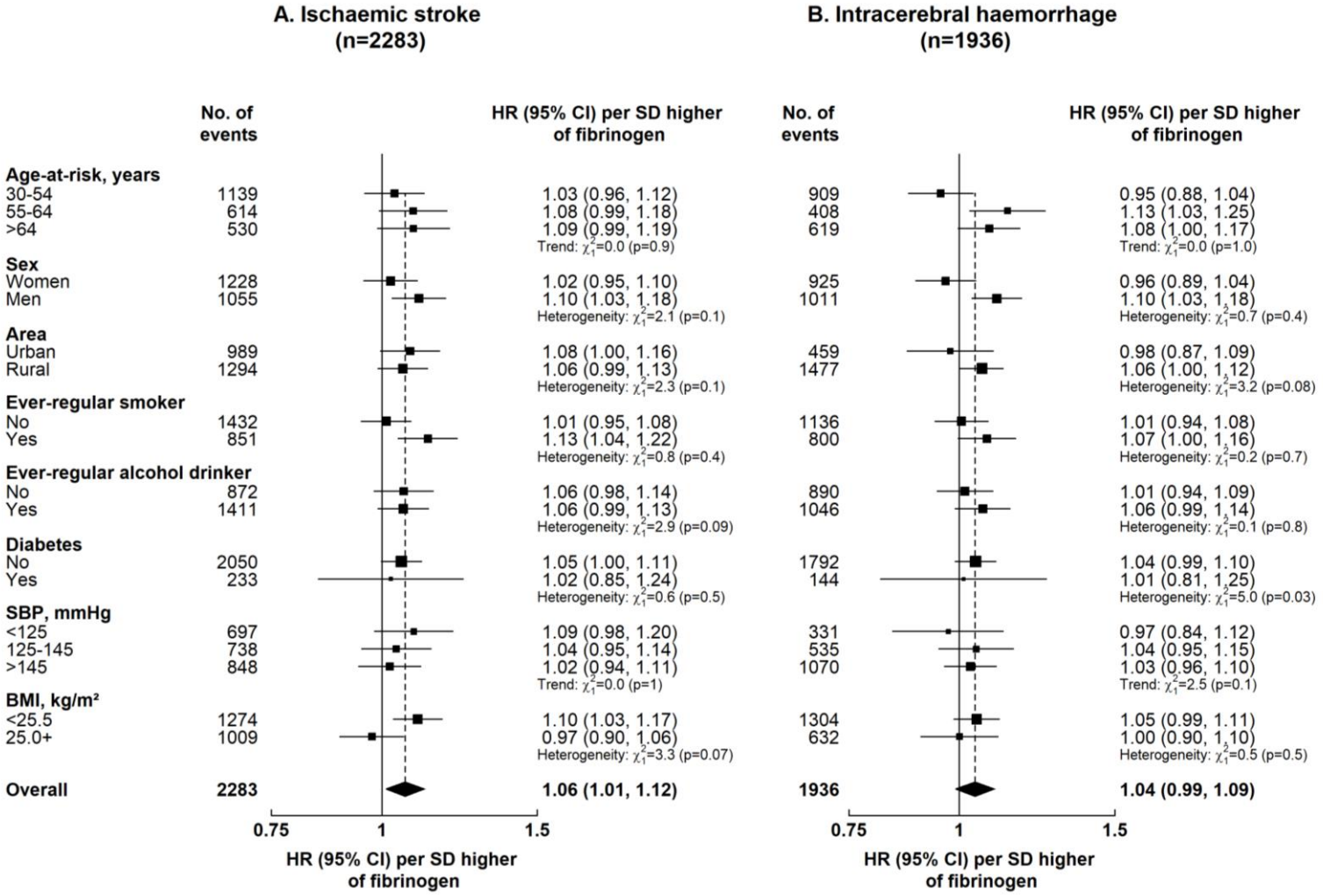


Figure 4.2.13. Associations of renal function biomarkers with ischaemic stroke and intracerebral haemorrhage

Conventions as Figure 4.2.1.
eGFR: estimated glomerular filtration rate, HR: hazard ratio.

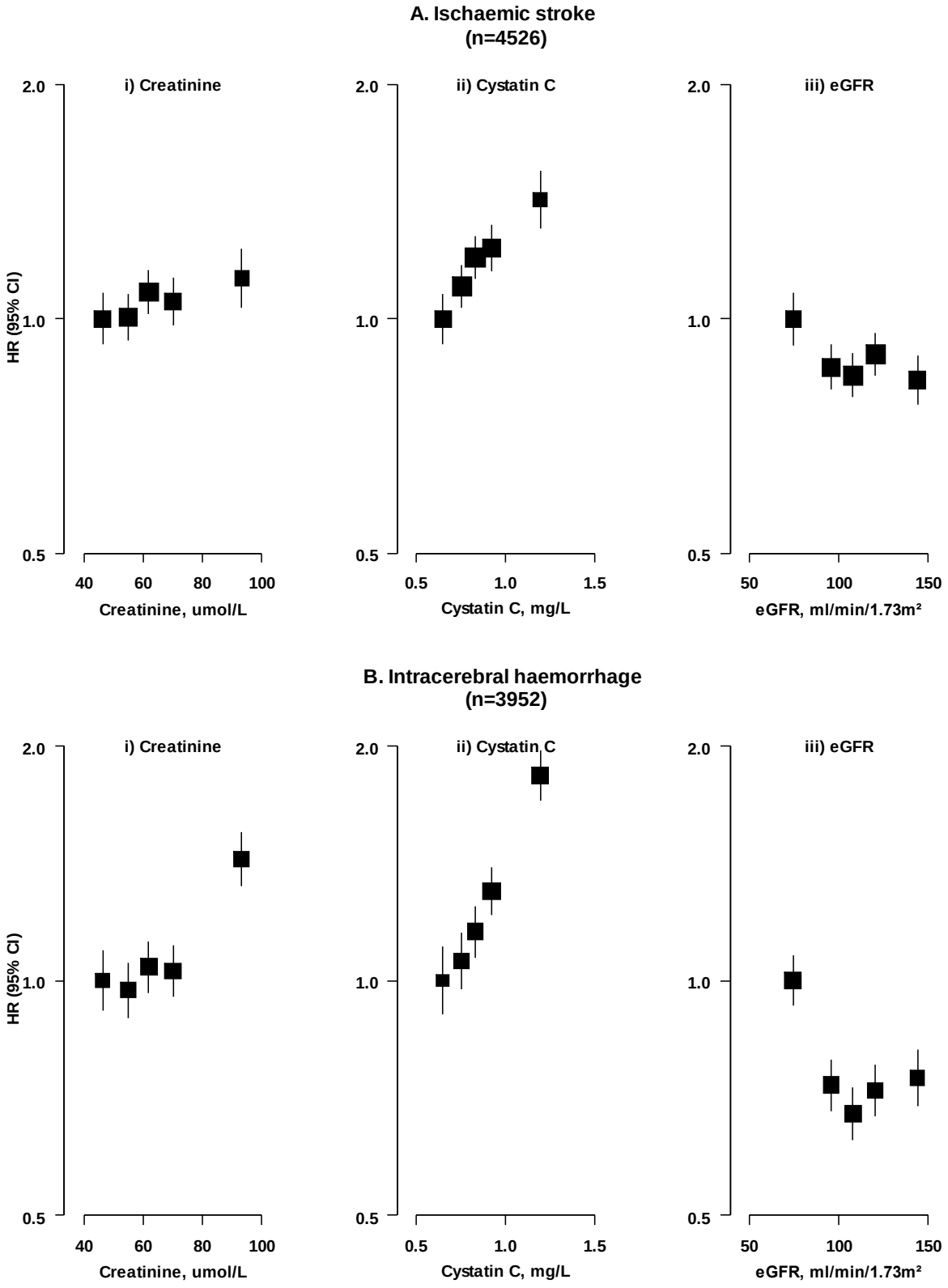


Figure 4.2.14. Associations per SD higher of cystatin C with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (0.3 mg/L) higher of cystatin C. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

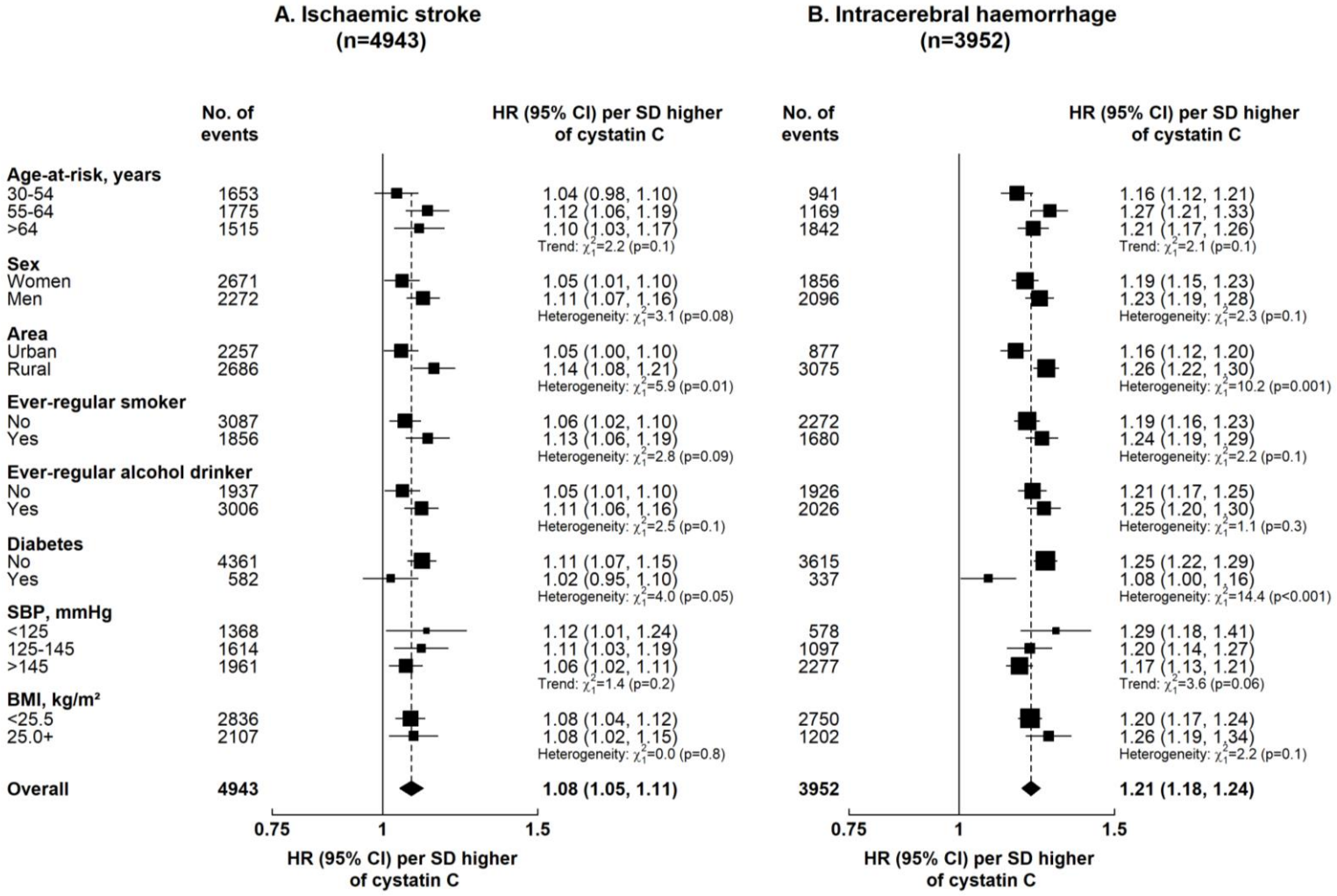


Figure 4.2.15. Associations per SD higher of creatinine with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (26.5 mg/L) higher of creatinine. Conventions as Figure 4.2.4.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

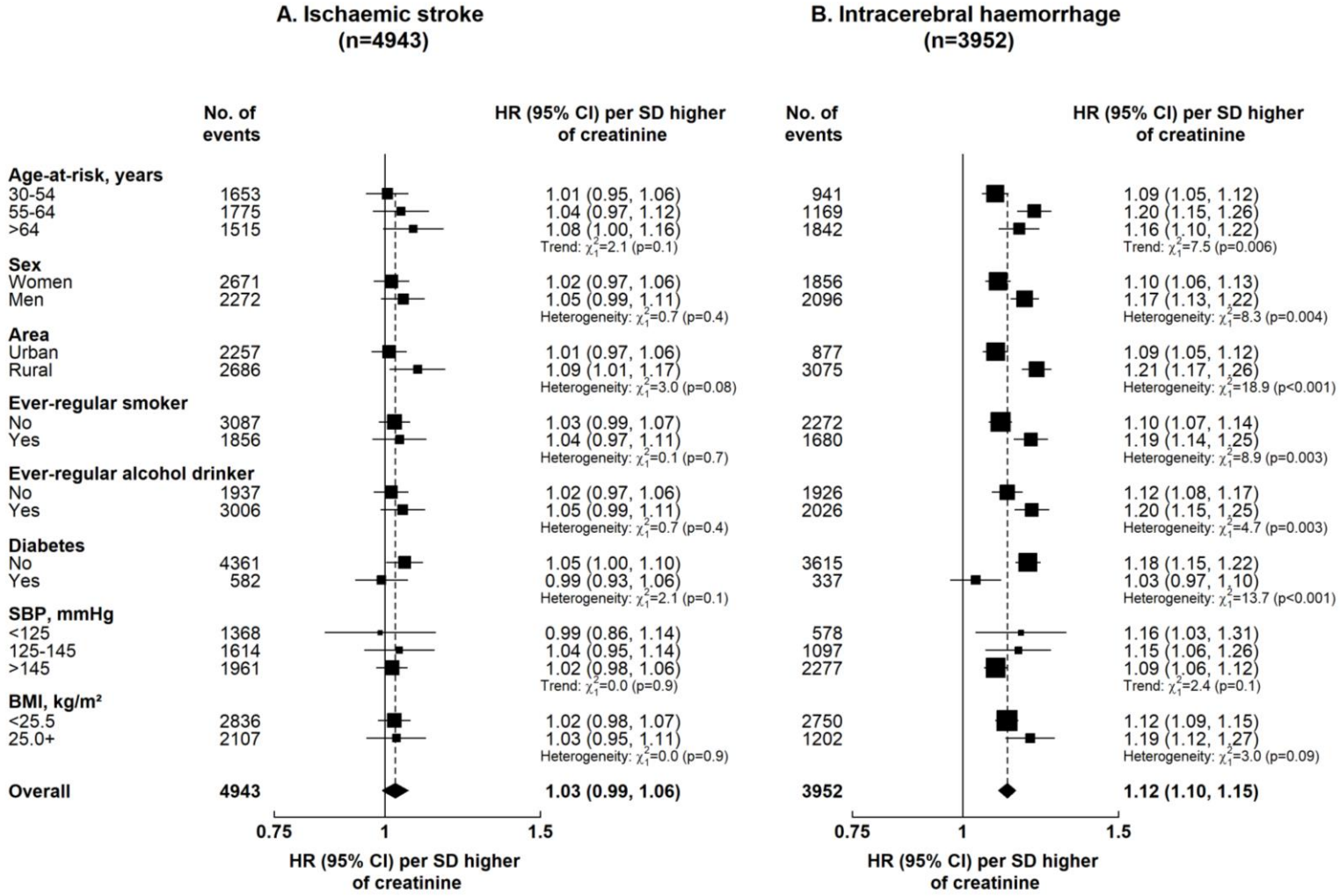


Figure 4.2.16. Associations per SD higher of eGFR with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types were estimated per 1 SD (25.2 ml/min/1.73m^2) higher of eGFR. Conventions as Figure 4.2.4.
BMI: body mass index, eGFR: estimated glomerular filtration rate, HR: hazard ratio, SBP: systolic blood pressure.

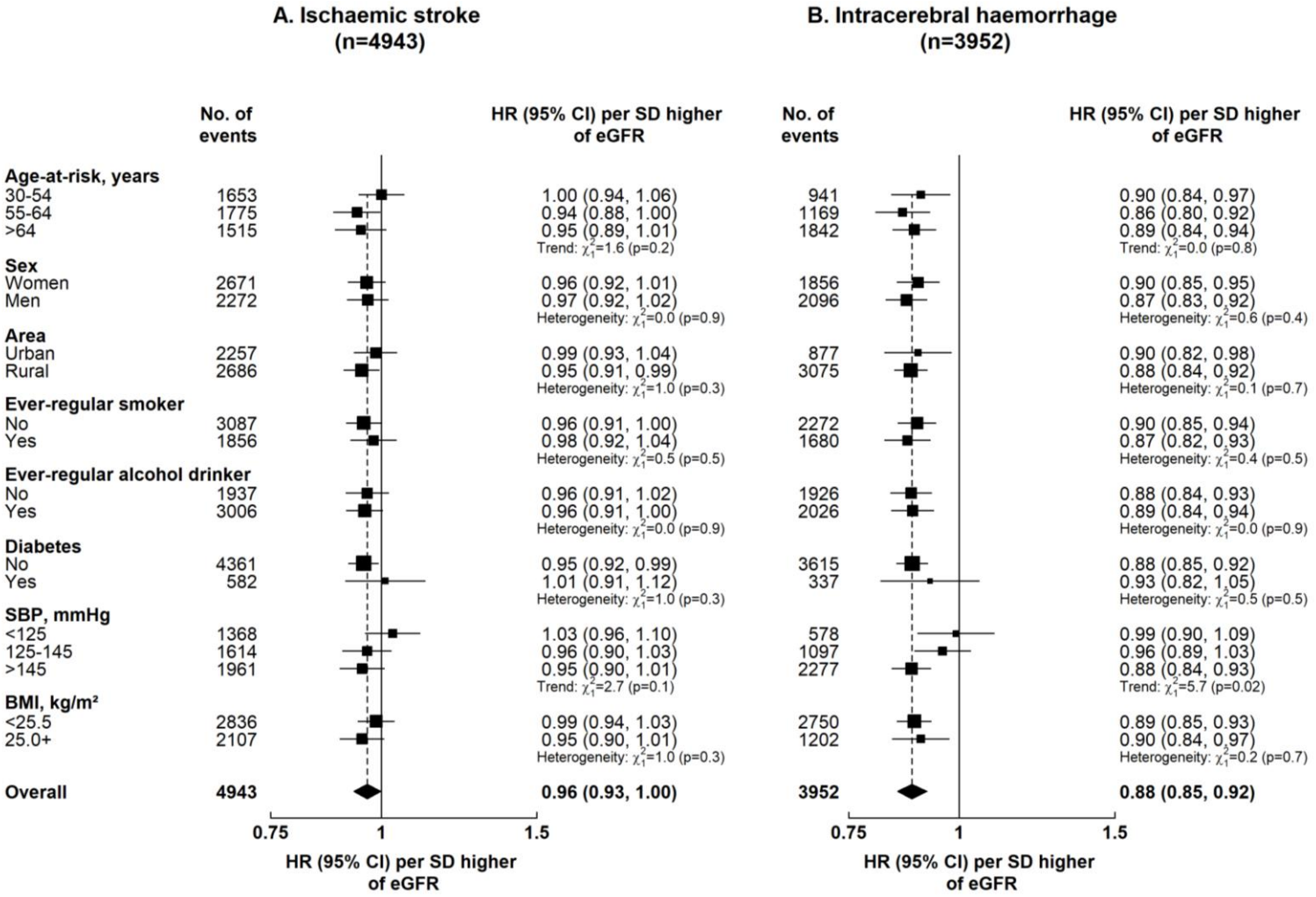


Figure 4.2.17. Associations of liver function biomarkers with ischaemic stroke and intracerebral haemorrhage

Conventions as Figure 4.2.1.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: Gamma glutamyl transferase, HR: hazard ratio.

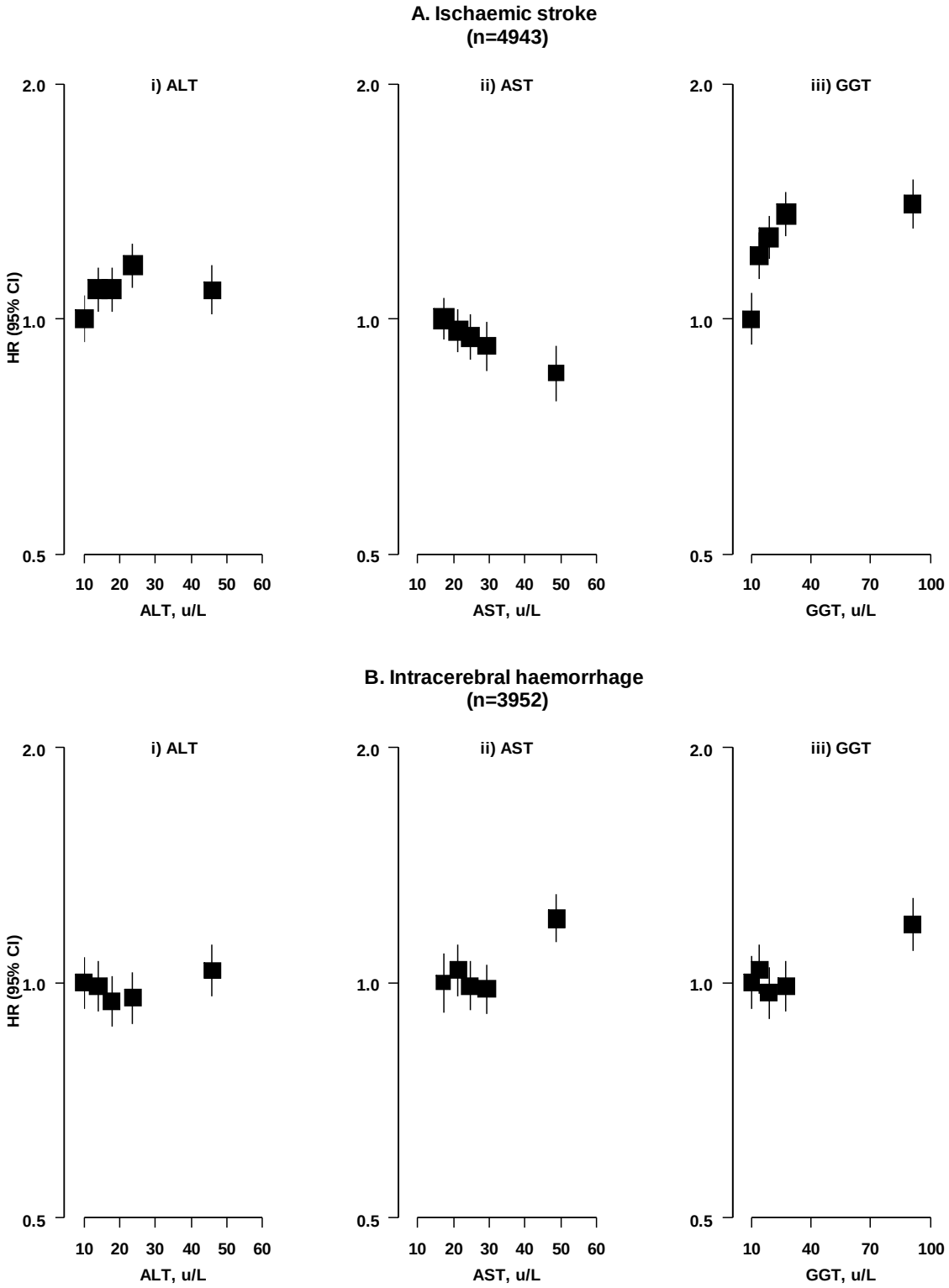


Figure 4.2.18. Associations per SD higher of liver function biomarkers with ischaemic stroke

The HRs for stroke types were estimated per 1 SD higher of liver function biomarkers. SDs of liver function biomarkers ALT: 17.4 u/L, AST: 18.2 u/L, GGT: 71.6 u/L. Conventions as Figure 4.2.4.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: Gamma glutamyl transferase, HR: hazard ratio, SBP: systolic blood pressure.

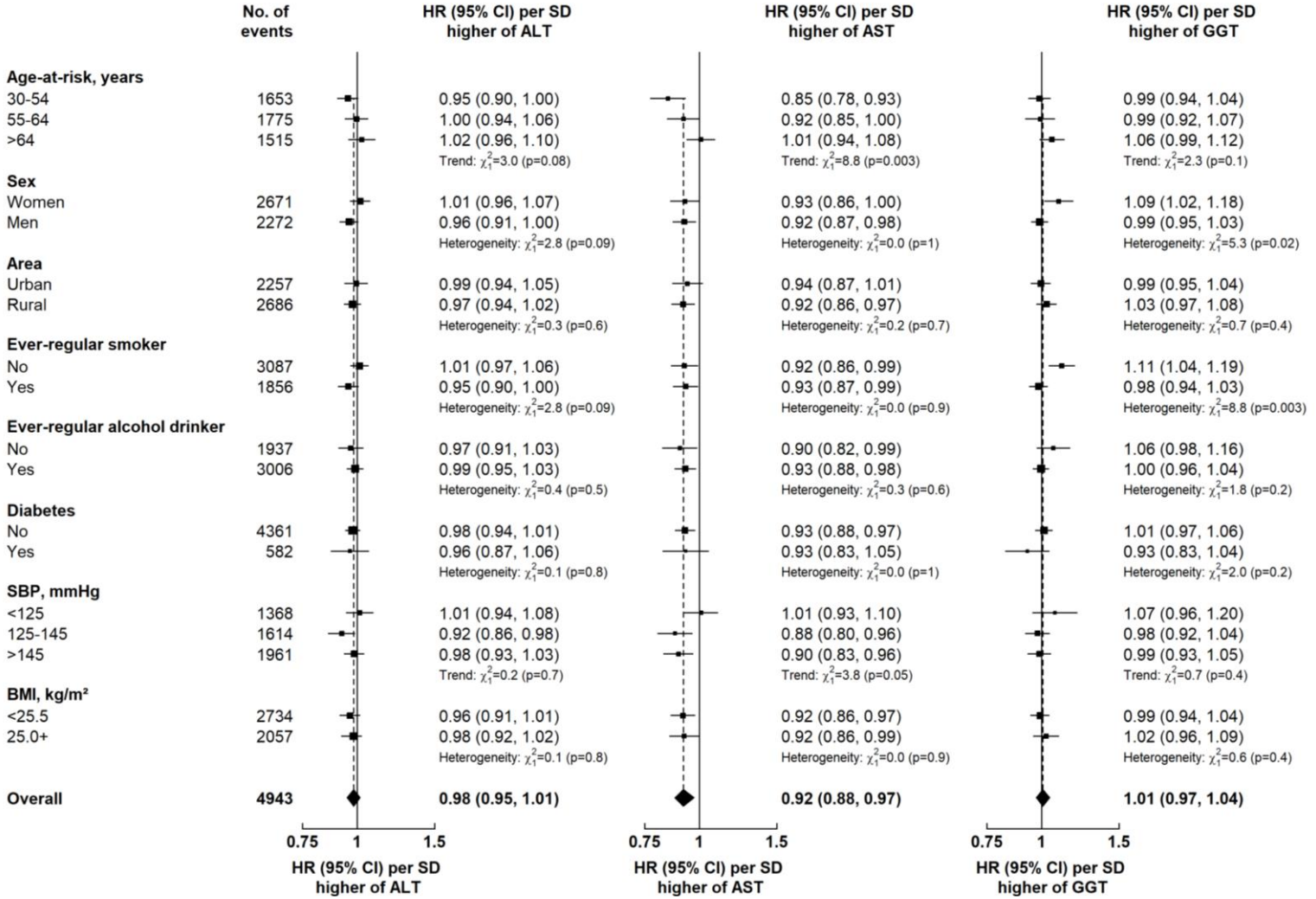
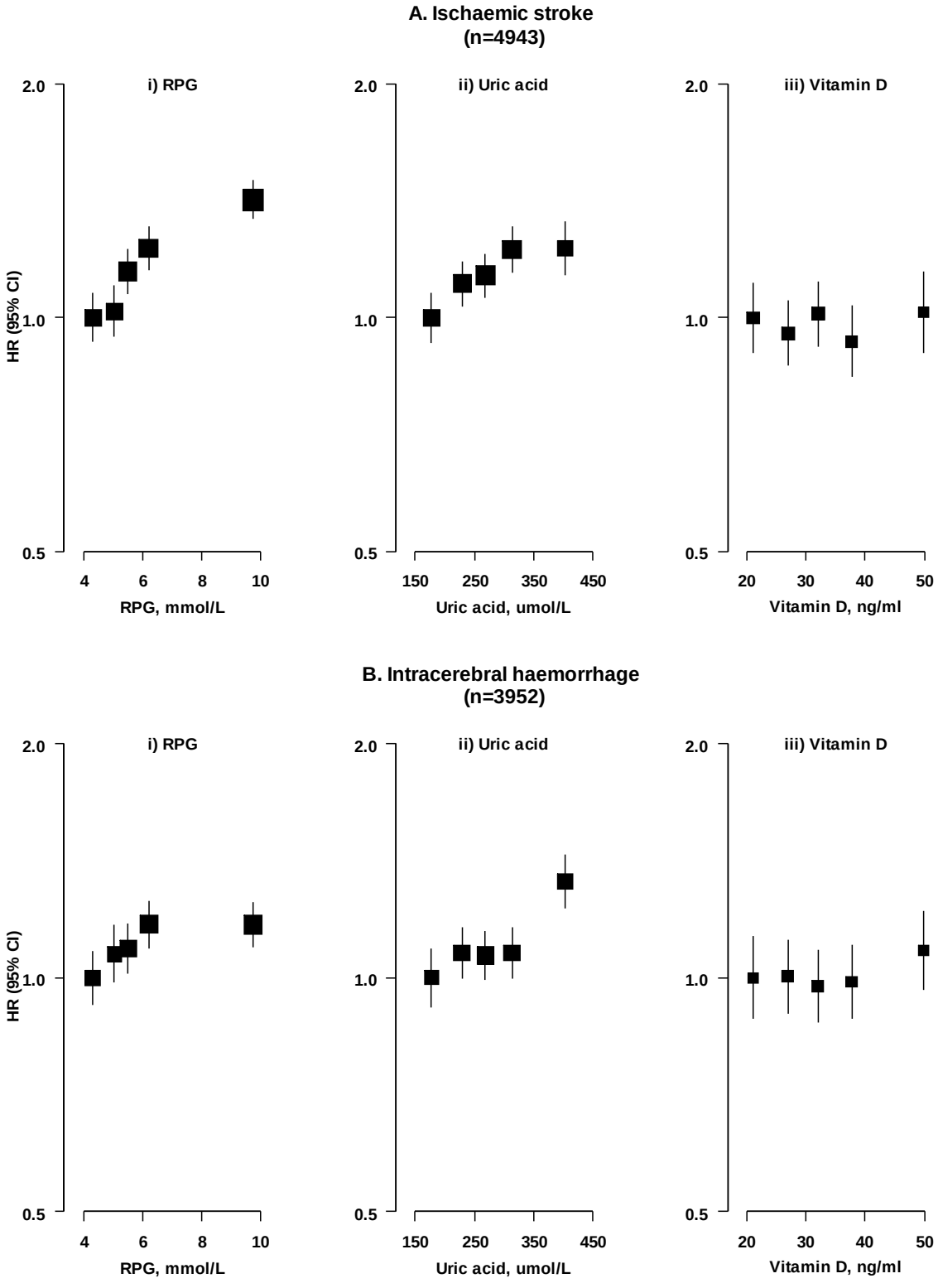


Figure 4.2.19. Associations of random plasma glucose, uric acid and vitamin D with ischaemic stroke and intracerebral haemorrhage

Conventions as Figure 4.2.1.
Analysis for vitamin D, 2209 IS and 1880 ICH events.
HR: hazard ratio, RPG: random plasma glucose.



Chapter 5. Adiposity and the risk of stroke types and subtypes

5.1 Background

The proportion of the population classified as overweight or obese is increasing globally, including in LMICs such as China.[3] Excess adiposity is associated with elevated levels of blood pressure[40] and glucose,[146] and with unfavourable changes in lipid profiles (e.g., higher LDL-cholesterol and triglycerides, and lower HDL-cholesterol).[44-48] These changes can in turn lead to an increased risk of major CVD, including IHD - the leading cause of death worldwide[203] - and stroke. Indeed, it has been estimated that one fifth of total stroke cases in China are attributable to elevated levels of adiposity.[204] However, uncertainty remains on the relevance of adiposity to stroke types and subtypes, and its indirect effect through possible mediators, such as blood pressure and major plasma biomarkers.

Existing evidence on the association of BMI with IS, including evidence from CKB,[120] is fairly consistent in showing higher risk of IS at higher BMI levels.[80,86-88,90,91,93-96] The limited evidence available on the association of BMI with subtypes of IS has also shown positive associations of BMI with lacunar[97-100] and non-lacunar[100] IS. However, previous studies examining these associations with IS subtypes included only small numbers of events (<1300 lacunar IS and <400 non-lacunar IS), limiting the ability to draw robust conclusions. Previous evidence on the association of BMI with HS is limited, to some extent, by inconsistencies in endpoint definitions. Some studies use the term HS to refer to ICH and SAH combined,[91,94,95] while others use it to refer to ICH and other non-traumatic intracranial haemorrhage.[87,88] Since these constituent conditions (e.g., ICH, SAH,

other non-traumatic intracranial haemorrhage) may have differing pathophysiologies, combining them as a single entity may obscure important risk factor associations or mediating pathways. Prior investigations of the association of BMI with HS incidence have variably reported positive,[87,88,90,94,95] or inverse[91] approximately log-linear associations throughout the BMI ranges examined. Studies that investigated the relationship between BMI and HS mortality reported a or null associations at lower BMI levels but a positive association at higher BMI levels.[86,89] Previous published analyses based on CKB data showed a null association of BMI with the risk of ICH (~5400 events) at BMI levels <25.0 kg/m^2, but a positive association at BMI levels ≥25.0 kg/m^2. Furthermore, only one small Western population study - a nested case-control study - has examined the association of BMI with ICH subtypes (e.g., lobar and non-lobar). The inconsistency in the findings of these studies, particularly for HS, may reflect the relatively small number of events, or misclassification of stroke types due to limited availability of brain imaging in many studies.[80,86-89,91,92,95] Moreover, few previous studies investigated the association of central adiposity with stroke types,[80,92,93] and even fewer with stroke subtypes.[100]

The mechanisms through which adiposity is associated with the risk of stroke types and subtypes are not fully understood. Factors such as blood pressure, dysglycaemia, dyslipidaemia, inflammation, renal impairment or hepatic dysfunction may mediate these associations, but robust evidence supporting such hypotheses is lacking. An individual-participant data meta-analysis, including 1.8 million individuals, reported that blood pressure, glucose and lipids together explained ~95% of the BMI-associated risk of total stroke. Furthermore, of these three factors, blood pressure was found to be the most important mediator, alone

explaining ~65% of the risk of total stroke. A number of studies have also reported that the associations of BMI with stroke types[80,90,92,94,95] and subtypes[97] are mediated, either completely or partially, through these same potential mediators. However, none of these studies investigated the effects of these mediators individually, nor did they account for intra-individual variation or measurement error in these variables. Previous analyses based on CKB data showed that, after adjustment for SBP, there was an inverse association of BMI with ICH (~5400 events), although low BMI was associated with lower blood pressure, and lower blood pressure was associated with lower risk of ICH. It remains unclear, therefore, if low adiposity itself, or other factors associated with lower levels of adiposity, might increase the risk of ICH, counteracting the effect of low blood pressure.

Given the patterns of obesity observed in East Asian, including Chinese, populations, and the differing CVD profiles (including higher rates of stroke and a greater proportion of HS events) as compared to Western populations, it is of interest to investigate the association of adiposity with stroke types and subtypes in the CKB study population, as well as factors mediating these associations. The objectives of this chapter are to examine the association of measures of general (BMI and body fat percentage) and central (WC, WHR) adiposity with stroke types and subtypes, overall and by baseline characteristics (e.g., age, sex), and to investigate the mediating roles of blood pressure and plasma biomarkers in these associations.

5.2 Methods

5.2.1 Study population

5.2.1.1 Summary of study design

Analyses for this chapter involve ~0.5 million participants from the CKB study, described in detail in Section 3.1. The analyses excluded individuals with prior self-reported IHD, stroke or TIA at baseline (n=23,129), and those with missing data for adiposity measures (n=225) or RPG (n=8150). Following these exclusions, 481,211 participants remained. The potential mediating roles of blood pressure and RPG in the association of adiposity with stroke types and subtypes were investigated in the same study population.

Analyses examining the mediating roles of additional plasma biomarkers in the association of adiposity with stroke types are based on data from the CKB biochemistry cohort, as described in Section 3.4. Data on 18 plasma biomarkers, including lipids and lipoproteins, inflammatory biomarkers and renal and liver function biomarkers, were available for ~18,000 individuals. The mediating roles of fibrinogen and vitamin D were not examined due to the limited number of individuals for whom data were available. In addition, the mediating role of total cholesterol was not examined, since the roles of its main components (i.e., LDL-cholesterol and HDL-cholesterol) were examined. Following these exclusions, 14,529 participants (4943 individuals with IS, 3952 individuals with ICH and 5634 controls) with valid data available for all 15 remaining plasma biomarkers remained for inclusion in these analyses.

5.2.2 Adiposity measures

The methods used to assess measures of general (BMI, body fat percentage) and central (WC, WHR) adiposity during the baseline survey and resurveys are described in detail in Section 3.3.

5.2.3 Outcome definitions

Data on stroke outcomes were obtained from death certificates, disease registries and from the national health insurance system (Section 3.7). The main stroke types examined were incident IS (ICD-10 code I63) and ICH (ICD-10 code I61), including both adjudicated and non-adjudicated events. Analyses were restricted to first events of any stroke type occurring between the ages of 35 and 79 years. Participants were censored at the time of the first stroke event, death from any cause or loss to follow-up, or at 80 years of age. Additional analyses examined fatal (death with 28 days of the first stroke event) and non-fatal IS and ICH separately.

Adjudicated stroke events and the main pathological stroke subtypes, such as lacunar and non-lacunar IS, and lobar and non-lobar ICH, were also examined separately. The adjudication processes and definition of the stroke subtypes is described in detail in Section 3.6 and Appendix Note A.1.

5.2.4 Selection of confounders

The following baseline variables were identified as potential confounders of the association of adiposity with stroke types and subtypes, based on a priori

knowledge: age, sex, study area, education,[172,173,205] smoking,[136,174,206] alcohol consumption[139,142,177] and physical activity.[179,180,207,208]

5.2.5 Statistical analyses

Adiposity measures were categorised into five groups based on sex-specific quintile cut-points, ensuring reasonable numbers of participants and stroke events in each group, and enabling comparisons between adiposity measures. The mean values and prevalence of selected baseline characteristics were calculated by the BMI categories, adjusted, where appropriate, for age (5-year groups), sex and study area.

Cox proportional hazards models, with time since baseline as the timescale, were used to estimate HRs for the associations of adiposity measures with IS, ICH and their subtypes (lacunar and non-lacunar IS, and lobar and non-lobar ICH), stratified by age-at-risk (5-year age groups), sex, and study area, and adjusted for education (no formal education, primary school, middle school, high school, college/university), smoking (never, occasional, ex-regular, current regular), alcohol intake (never, occasional intake, ex-regular, reduced intake, weekly intake) and physical activity (metabolic equivalent of task [MET] hours per day). In analyses examining adiposity measures as categorical variables, the floating absolute risk method was used to estimate group-specific 95% CIs for each HR. This enables comparisons between any two categories, rather than just pairwise comparisons with the reference category. The HRs per sex-specific SD higher in BMI were estimated overall and across strata of other baseline characteristics (e.g., age, sex, area), and χ^2 values for trend and heterogeneity were calculated.

As described by MacKinnon et al, a causal steps approach can be used in mediation analyses. This requires four criteria to be met in order to establish the presence of mediation, specifically, within the context of the mediation analyses presented herein, the presence of: 1) a significant association of adiposity with stroke types/subtypes; 2) a significant association of adiposity with the potential mediating variable (e.g., SBP, plasma biomarkers); 3) a significant relationship of the mediating variable with the risk of stroke types/subtypes in a model also including the adiposity (e.g., BMI); and 4) a larger coefficient relating adiposity to the risk of stroke types/subtypes in a model not including the potential mediating variable than in one including the potential mediating variable. The methods used to investigate step 1 are described above, and analyses addressing steps 2 and 3 are presented in sub-chapters 4.1 and 4.2, respectively. The individual effects of plasma biomarkers fulfilling steps 2 and 3, in addition to SBP and RPG, on the associations of adiposity with stroke types, were investigated among individuals included in the CKB biochemistry cohort. The change in the strength of the association of BMI with stroke types after including the selected plasma biomarker was assessed using the χ_1^2 from the likelihood ratio test. The combination of plasma biomarkers most strongly predicting the risk of stroke types, given SBP and RPG, was investigated using stepwise regression with a significance level for entry and exit of 0.018 (Bonferroni correction for multiple testing of 14 biomarkers). The percentage reduction in the χ_1^2 value for BMI and in the log HR[209] after adjustments for additional terms, addressed the final step (step 4) in the mediation analyses. In addition, given the observed non-log-linear associations of some plasma biomarkers with stroke types (e.g., ALT, GGT) (sub-chapter 4.2), the effect of those plasma biomarkers on the relationships of adiposity with stroke types was

investigated both using linear and categorical terms. Moreover, given the observed effect modification by sex and urban/rural residence in the associations of other plasma biomarkers (e.g., LDL-cholesterol, ApoB, albumin) with stroke types (sub-chapter 4.2), the effects of sex and urban-rural interactions with those plasma biomarkers were investigated in the final model of the stepwise regression.

The self-correlation coefficients of adiposity measures, blood pressure and RPG were estimated using measurements from the baseline survey and two periodic resurveys (Section 3.5) among a subset of ~20,000 participants. The self-correlation coefficients for SBP were used as a regression dilution ratio (RDR) to correct prospective analyses for biases resulting from measurement error or intra-individual variation, which can lead to underestimation the effect of potential mediators on the association of adiposity with stroke. Adjustment for regression dilution bias was used in investigation of the associations of SBP with stroke types and subtypes, and in the mediation analyses including SBP. To adjust for regression dilution bias, and therefore obtain HRs for "usual" levels of SBP, the log HRs for the associations of baseline SBP were divided by the RDR (0.63). In the analyses investigating the mediating role of SBP as a covariate in the association of BMI with stroke types and subtypes, the log HR adjusted for usual SBP was estimated as follows: the difference between the log HRs derived from models with and without adjustment for baseline SBP was divided by the RDR and the outcome of that was added to the log HR derived from the model without adjustment for SBP.[105]

$$\log HR_{usual\ SBP} = \log HR_{without\ adj.\ for\ SBP} + \frac{(\log HR_{with\ adj.\ for\ SBP} - \log HR_{without\ adj.\ for\ SBP})}{RDR}$$

For comparison purposes, the effect of baseline and usual SBP was also investigated in the association of other adiposity measures (e.g., WC, WHR, body fat percentage). Adjustment for regression dilution bias was only considered for SBP, because it's effect on the association of adiposity with stroke types was more marked than the effects of the plasma biomarkers. Moreover, correcting multiple covariates (e.g., plasma biomarkers) for measurement error requires multiple estimates of correlation coefficients between each of the covariates at baseline and resurvey (e.g., correlation matrix) which it would not be possible to accurately estimate given that repeat measurements for plasma biomarkers were available among only a small number of participants (<900 in the first resurvey and ~1100 in the second resurvey).[210,211] In addition, these methods rely on assumptions (such as linearity) that cannot easily be confirmed.

The proportional hazards assumption was tested by examining the HRs for the first 4 and subsequent years of follow-up (and showed no strong evidence of departure). Sensitivity analyses, attempting to control for reverse causality by excluding the first five years of follow-up and restricting the analyses to never smokers, were conducted. In addition, analyses involving plasma biomarkers were additionally adjusted for fasting time.

All statistical analyses were conducted in SAS version 9.4. Cox regression was conducted using a SAS macro previously developed within CTSU. All plots were produced using JASPER, an R package developed within CTSU, in R version 3.3.

5.3 Results

5.3.1 Baseline characteristics

Among the 481,211 individuals included in this analysis, the mean (SD) age at baseline was 51.6 (10.6) years and 284,535 (59.1%) were women (Table 5.1). The associations between sex-specific BMI quintiles and baseline characteristics were similar in this CKB population to those in the subset of 5449 CKB control individuals from the CKB control biochemistry cohort described in sub-chapter 4.1. The overall mean BMI was 23.6 (SD 3.2) kg/m^2 (women: 23.8 [3.3]; men: 23.4 [3.1] kg/m^2) and 28.4% (women: 29.0%; men: 27.6%) and 3.9% (women: 4.6%; men: 2.8%) of participants were classified as overweight and obese, respectively. BMI was positively associated with all other anthropometric and adiposity measurements studies. BMI, WC and body fat percentage were highly intercorrelated (r>0.80) (Table 5.2). There was a high degree of self-correlation for adiposity measures, particularly for BMI, body fat percentage and WC (r: 0.78-0.93; Table 5.3). The self-correlation for plasma biomarkers varied from 0.21 to 0.85 (Table 5.4).

During a median (IQR) 9.3 (8.2-10.1) years of follow-up (up to January 2017), 47,230 first stroke events were recorded at ages-at-risk 35-79 years. Over 85% of first stroke events were classified into a stroke type, including 33,755 IS events (861 [2.5%] fatal), and 6488 ICH events (2979 [45.9%] fatal). To date, 17,392 (51.5%) IS events have been adjudicated, of which 10,866 (62.5%) were lacunar IS and 6526 (37.5%) were non-lacunar IS. Of the 1462 (22.5%) ICH cases adjudicated, 246 (16.8%) were lobar ICH and 1216 (83.2%) were non-lobar ICH.

5.3.2 Ischaemic stroke and its subtypes

Throughout the BMI range examined (approximately 18.0 to 30.0 kg/m^2), there was a positive log-linear association between BMI and incident IS (Figure 5.1). Each 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI was associated with 19% higher risk of all incident IS (HR 1.19 [95% CI 1.18-1.20]). There was a slightly stronger association with overall adjudicated IS than with non-adjudicated IS (1.23 [1.21-1.25] vs 1.16 [1.14-1.18], $p_{heterogeneity}$<0.0001). The strength of the associations of BMI with non-lacunar IS and lacunar IS were similar (HR 1.24 [95% CI 1.22-1.28] vs 1.21 [1.19-1.23], $p_{heterogeneity}$=0.1). There was a U-shaped association of BMI with the small proportion of IS events that were fatal (861 events); BMI levels of 22.3 to 24.3 kg/m^2 were associated with the lowest risk of fatal IS (Figure 5.2).

The association of BMI with IS was modestly stronger among men than women (HR 1.23 [95% CI 1.21-1.25] vs.1.17 [1.15-1.18] per 1 SD higher BMI, $p_{heterogeneity}$<0.0001; Figures 5.3 and 5.4). This was driven by a stronger association of BMI with lacunar IS among men (HR 1.27 [95% CI 1.23-1.31] vs. 1.17 [1.14-1.20]; $p_{heterogeneity}$<0.0001), with no clear sex-difference in the association with non-lacunar IS (1.25 [1.21-1.30] in men vs 1.24 [1.20-1.28] in women). There were positive approximately log-linear associations of BMI with IS and IS subtypes across all age-at-risk groups examined, and, at a given BMI, the risk of IS and IS subtypes was higher among older individuals (Figure 5.5). Although, the strength of the associations for all IS and non-lacunar IS were broadly similar across ages, the association of BMI with risk of lacunar IS was slightly stronger among younger individuals (age-at-risk 30-59 years) as compared

to older individuals (age-at-risk >69 years) (HR 1.29 vs. 1.13, $p_{heterogeneity}$<0.0001). Associations of BMI with IS and IS subtypes were similar in urban and rural areas and across the 10 study areas (Figure 5.6 and 5.7), and remained largely unchanged after excluding the first 5 years of follow-up and, separately, ever-regular smokers (Figure 5.8 and 5.9).

Usual SBP was strongly positively and log-linearly associated with IS and IS subtypes (Figure 5.10). After adjusting for regression dilution bias in SBP, using a regression dilution factor of 0.63 (Table 5.3), each 1 SD higher usual SBP (19.3 mmHg), was associated with a 70% higher risk of all IS (HR 1.70, 95% CI 1.67-1.72). The association was stronger with non-lacunar IS than with lacunar IS (HR 2.02 [95% CI 1.96-2.09] vs. 1.60 [1.55-1.64], $p_{heterogeneity}$<0.0001). Although there was also a positive log-linear association of RPG with IS, the strength of the association was considerably weaker than that of usual SBP (HR 1.14 [95% CI 1.13-1.14] per 1 SD [2.2 mmol/L] higher RPG; Figure 5.11). RPG was also positively associated with non-lacunar IS (HR 1.17 [95% CI 1.15-1.19] per 1 SD higher), but the association with lacunar IS was less clear.

The positive log linear associations of BMI with IS and IS subtypes were substantially attenuated when adjusted for SBP in addition to potential confounders. After adjustment for baseline SBP, the HR per 1 SD higher BMI was reduced by 47% (95% CI 24-50%), from 1.19 (95% CI 1.18-1.20) to 1.10 (1.09-1.11). After correcting for measurement error or intra-individual variation in SBP, to adjust for usual SBP, the HR was attenuated by 74% (70-78%), to 1.05 (95% CI 1.04-1.06). This suggests that a large proportion of the association of BMI with IS was mediated through SBP (Figure 5.12 and Table 5.5). Further adjustment for

RPG, in addition to usual SBP, had only a small effect (HR 1.04 [95% CI 1.03-1.05]). The effects of baseline SBP, usual SBP, and RPG on the association of BMI with IS subtypes were similar to the effects on the association with all IS. Other adiposity measures, including body fat percentage, WC and WHR, showed similar associations with IS and IS subtypes after adjustment for potential confounders (Figures 5.13-5.15). Adjustment for baseline SBP, reduced the IS HR per 1 SD higher WC and WHR by ~20%, whereas it reduced the HR per 1 SD higher body fat percentage by ~40%, similar to the findings for BMI. Likewise, adjustment for usual, rather than measured, SBP, attenuated the associations of central adiposity measures with all IS by ~40%, whereas it reduced the associations of general adiposity measures by ~70%. Given usual SBP, the effect of adjustment for RPG on the associations of other adiposity measures with IS and IS subtypes was modest.

Data on plasma biomarkers were available for the CKB biochemistry cohort of 14,529 participants (4943 IS events). Among these individuals, after adjustment for potential confounders, there was a moderately weaker association of BMI with incident IS (HR 1.13 [95% CI 1.10-1.16]) than was observed in the full CKB cohort (1.19 [1.18-12.20]; Figures 5.16 and 5.1). In this population subset, the HR was attenuated to 1.08 (95% CI 1.05-1.11) after additional adjustment for baseline SBP. Given baseline SBP, the risk prediction of incident IS was improved slightly more after adjustment for RPG as compared to adjustment for diabetes at baseline (likelihood ratio test χ_1^2=48.1 vs. χ_1^2=42.9). Also, the HR of the association of BMI with IS (adjusted for baseline SBP) was reduced slightly to 1.07 (95% CI 1.04-1.10) after additional adjustment for RPG (the base model).

Among all biomarkers examined, additional separate adjustments for ApoB, LDL-cholesterol, HDL-cholesterol, log hs-CRP and uric acid reduced the HR from 1.07 to 1.06 and the value of χ_1^2 (for BMI obtained from the likelihood ratio test between the model with the additional term and the base model) from ~22.0 to ~14.0. The other plasma biomarkers examined had less effect on the association of BMI with IS.

The plasma biomarkers that improved the fit (reduction in the χ_1^2 of the model) of the base model (adjusted for possible confounders, baseline SBP and RPG) of the association of BMI with IS were LDL-cholesterol, albumin, HDL-cholesterol, AST and uric acid. Their subsequent effects on the HR of BMI with IS are presented in Figure 5.17. Given baseline SBP and RPG, LDL-cholesterol was the first plasma biomarker selected into the model (using a stepwise regression), and it reduced the HR from 1.07 to 1.06 and the value of χ_1^2 for BMI by 34%, from 21.9 to 14.5. Further adjustment for albumin made little change to the findings. However, subsequent adjustment for HDL-cholesterol reduced the HR to 1.04 and the χ_1^2 value for BMI by about 50%, to 7.1. Additional adjustment for AST and uric acid had little effect on the HR (1.04) and the χ_1^2 value for BMI was reduced to 4.6. In total, additional adjustments for baseline SBP, RPG, LDL-cholesterol, albumin, HDL-cholesterol, AST and uric acid attenuated the strength of the association of BMI with IS from 1.13 (only adjusted for potential confounders) to 1.04 per 1 SD higher BMI. The net effect of LDL-related terms (the sum of the product of the parameter estimates of LDL-related biomarkers, derived from the fully adjusted stepwise models included in Figures 5.17 and 5.18, and the actual values of those biomarkers) in the final model derived from the stepwise regression was in the direction of higher LDL-cholesterol and ApoB being associated with higher risk of

IS (Table C.1). After adjusting SBP for regression dilution bias, 1 SD higher BMI was associated with 2% (HR 1.02 [95% CI 0.98-1.05]) higher risk of IS (Figure 5.17). In the model included all of the plasma biomarkers selected from the stepwise regression model, including relevant urban/rural-interaction (for LDL-cholesterol) made no difference in the findings (Figure C.1). Moreover, additional adjustments for fasting time did not change the findings. The potential mediating effects of plasma biomarkers (other than RPG) on the association of BMI with IS subtypes were not examined because of the small stroke subtype event numbers.

5.3.3 Intracerebral haemorrhage and its subtypes

There was no clear association between BMI and all ICH incident events at BMI levels <25.0 kg/m^2 (Figure 5.1). However, individuals with a BMI ≥25.0 kg/m^2 experienced 19% (HR 1.19 [95% CI 1.13-1.26]) higher risk of ICH than individuals with BMI 22.5-25.0 kg/m^2. Approximately 75% of all ICH events were non-adjudicated, mainly reflecting the high case-fatality rate of ICH, and the low rate of retrieval of medical records for fatal events. Therefore, the associations of BMI with non-adjudicated ICH and fatal ICH were similar to that with all ICH (Figures 5.1 and 5.2). However, among the adjudicated ICH events, there was a positive log-linear association between BMI and non-lobar ICH throughout the BMI range examined; each 1 SD higher BMI was associated with 14% higher risk (HR 1.14 [95% CI 1.08-1.21]) (Figure 5.1). However, there was no clear association of BMI with lobar ICH, but the number of events included was small. There was a positive broadly log-linear association of BMI with non-fatal ICH (Figure 5.2).

The associations of BMI with ICH and its subtypes appeared to be largely similar among men and women (Figure 5.3 and 5.4). There were positive associations of BMI with all ICH, non-adjudicated ICH and non-lobar ICH among younger ages (age-at-risk 35-69). Among the oldest participants (age-at-risk 70-79 years), however, there were U-shaped associations with all ICH and non-adjudicated ICH (Figure 5.5). Attempts to control for residual confounding and reverse causality, by restricting the analyses to never-smokers and by excluding the first 5 years of follow-up, did not materially alter the overall (Figures 5.8-5.9) or age-specific findings (Figures C.2 and C.3). The associations of BMI with ICH and ICH subtypes were similar in urban and rural areas (Figure 5.6) and across the 10 study areas (Figure 5.7).

The positive log linear association of usual SBP with all ICH (HR 2.55, 95% CI [2.48-2.63] per 1 SD higher usual SBP), was stronger than the association observed with all IS (Figure 5.10). Usual SBP was more strongly associated with adjudicated ICH (HR 3.20 [95% CI 3.00-3.40]) than with non-adjudicated ICH (2.24 [2.20-2.28], $p_{heterogeneity}$<0.001). Among the adjudicated ICH events, there was a significantly stronger association of usual SBP with non-lobar (HR 3.33 [95% CI 3.12-3.56]) than with lobar (2.32 [1.98-2.73]) ICH ($p_{heterogeneity}$<0.001). RPG was weakly positively associated with all ICH and non-adjudicated ICH (1.12 [1.10-1.14] and 1.13 [1.11-1.15], respectively; Figure 5.11). There were no clear associations of RPG with adjudicated lobar or non-lobar ICH outcomes, although this may, in part, reflect the relatively small numbers of adjudicated ICH events.

The associations of BMI with ICH and ICH subtypes were reversed after additional adjustment for baseline SBP (Figure 5.12 and Table 5.6). Assuming a log-linear

association of BMI with all ICH, the HR per 1 SD higher BMI was reduced from 1.08 (95% CI 1.05-1.11) to 0.92 (0.89-0.94). Additional adjustments for usual SBP reduced the HR further to 0.84 (95% 0.81-0.85). In addition to usual SBP, further adjustment for baseline RPG had only a small effect on the HR of all ICH (HR 0.83 [95% CI 0.81-0.85]). Adjustments for baseline and usual SBP, and subsequent adjustments for RPG had similar effects on the association of BMI with adjudicated and non-adjudicated ICH. The associations of body fat percentage and WC with ICH and ICH subtypes were similar to the associations of BMI, before and after adjustments for SBP and RPG (Figures 5.13 and 5.14). However, after adjustments for potential confounders, there was a positive approximately log-linear association of WHR with ICH and ICH subtypes overall (Figure 5.15). In sex-specific analyses there were flat associations of WHR with ICH and ICH subtypes at lower WHR (≤0.87), but individuals with higher WHR levels had higher risks of ICH and ICH subtypes, for both sexes (Figure C.4). Additional adjustment for baseline SBP attenuated the sex-combined associations of WHR with ICH and ICH subtypes towards the null, and adjustment for usual SBP reversed the associations (Figure 5.15).

In the CKB biochemistry cohort of 14,529 participants, there was no association at BMI levels <25 kg/m^2, and a positive association at higher BMI levels, similar to the relationship observed in the full study cohort (Figure 5.1 and 5.16). After additional adjustment for baseline SBP this association was reversed (0.91 [0.88-0.94]) (Figure 5.16), similar to the effect of adjustment for baseline SBP on the association in the full CKB cohort. Further adjustments for diabetes and/or RPG had no effect on the HR. For consistency, the individual effects of potential mediators on the association of BMI with ICH were compared to the base model

(adjustments for possible confounders, baseline SBP and RPG). Additional separate adjustments for ApoB and triglycerides reduced the value of χ_1^2 (for BMI) from 31.1 to 12.1 and 14.9, respectively and attenuated the HR of the base model from 0.91 to 0.94 and 0.93, respectively. Separate adjustments for LDL-cholesterol and albumin reduced the value of χ_1^2 (for BMI) from 31.1 to ~21.0, and slightly attenuated the HR towards the null (from 0.91 to 0.92).

The subsequent effects on the HR of BMI with ICH of the plasma biomarkers (albumin, cystatin C, GGT, LDL-related biomarkers, creatinine, triglycerides and uric acid) that improved the fit of the base model (adjusted for possible confounders, baseline SBP and RPG) in a stepwise regression are presented in Figure 5.17. Given the potential confounders, baseline SBP and RPG, albumin was the first plasma biomarkers included in the model; it reduced the value of χ_1^2 for BMI by ~31%, from 31.1 to 21.4, and slightly attenuated the HR towards the null (from 0.91 to 0.92). Further subsequent adjustments for cystatin C and GGT had no effect on the HR for the association between BMI and ICH. Additional adjustments for LDL-related biomarkers reduced the χ_1^2 value for BMI from 21.4 to 8.4 and attenuated the HR to 0.95. Further adjustments for creatinine, and uric acid slightly attenuated the HR to 0.95 and adjustment for triglycerides to 0.96. Overall, adjustments for potential confounders, baseline SBP, RPG, LDL-cholesterol, albumin, HDL-cholesterol, ApoA1, ApoB and AST, attenuated the inverse association of BMI with ICH towards the null. In the final model from the stepwise regression, the net effect of LDL-related terms was in the direction of higher LDL-cholesterol and ApoB being associated with lower risk of ICH (Table C.1). Further adjustments for usual SBP reduced the HR of ICH to 0.89. Additional adjustments for sex interactions and fasting time made negligible difference to the

strength of the BMI and all ICH incidence association (Figure C.1). The above selected plasma biomarkers had similar effects on the associations of BMI with fatal and non-fatal ICH, with the exception of LDL-related biomarkers, which had a more marked effect for non-fatal ICH (Figure 5.18). This may reflect a somewhat stronger effect of LDL-terms on non-fatal ICH than on fatal ICH (Table C.1). Again, the small number of ICH subtypes events did not allow investigation of the role of plasma biomarkers in the association of BMI with ICH subtypes.

5.4 Discussion

The presented analyses provide the most detailed, large-scale description of the association of adiposity (both general and central) with stroke types and subtypes. Moreover, they carefully assess the potential mediating roles of blood pressure, glucose and other major plasma biomarkers in the associations of adiposity with stroke. There were strong positive log-linear associations of adiposity with IS and IS subtypes, with baseline SBP accounting for about half of the observed associations. Additional adjustments for RPG and other major plasma biomarkers (LDL- and HDL-related biomarkers, albumin and AST) further, but incompletely, attenuated the associations. However, after accounting for intra-individual variation and measurement error in SBP, the association was completely attenuated. For ICH, the association with adiposity was totally different, despite a strong positive association of adiposity with blood pressure and a strong positive association of blood pressure with ICH risk. For total ICH, the risk did not start to rise with increasing BMI until a BMI level of approximately 25 kg/m^2. Above this level, although there was a positive log-linear association of BMI with ICH risk, the strength of the association was much weaker than that for IS, and than that

expected based on the association of adiposity with blood pressure and of blood pressure with ICH. Further analyses showed the shape of the association appeared to differ by ICH subtypes, with a positive log-linear association for non-lobar ICH throughout the range of BMI examined. Additional adjustment for baseline SBP reversed the associations of BMI with ICH and ICH subtypes. Further adjustments for plasma biomarkers attenuated the HRs for ICH somewhat towards the null; the most marked effect was observed in adjusting the association of BMI with non-fatal ICH for LDL-related biomarkers.

5.4.1 Ischaemic stroke and its subtypes

Similar to findings from the present analyses, previous large prospective Western[91,92] and East Asian[90,93-95] population studies, and individual participant data meta-analyses of prospective studies,[80,86-88] reported positive log-linear associations between BMI and IS. After adjustments for potential confounders (e.g., age, smoking, alcohol, physical activity and socioeconomic status), but not known mediators (e.g., blood pressure, diabetes and lipids), most previous studies reported strengths of association of BMI with IS[80,86,90-95] similar to those described in CKB (HR 1.19 [95% CI 1.18-1.20] per 1 SD [3.1 kg/m^2 for men and 3.3 kg/m^2 for women] higher BMI, 33,755 events). The BMI-IS association was approximately as expected given the strong positive associations of BMI with SBP, and of SBP with IS, observed in CKB. Each 1 SD higher BMI, corresponding to 8.1 mmHg higher usual SBP, would be expected to be associated with 14% higher risk of IS (HR 1.14 [95% CI 1.13-1.14]). To enable between study comparisons, the strength of the associations of BMI with IS incidence in previous studies are presented here per 3 kg/m^2 higher BMI (the approximate SD for BMI in CKB), after adjustments for

possible confounders. The Million Women Study of ~1.3 million women from UK found that each 3 kg/m^2 higher BMI was associated with 12% (HR 1.12 [95% CI 1.10-1.13]) higher risk of IS (~10,000 events).[91] After similar adjustments to those in the Million Women Study, a large study of ~400,000 non-smoking Korean women (~8700 IS events) reported a strength of association (HR 1.16 [95% CI 1.16-1.19] per 3 kg/m^2) similar to that in both the Million Women Study[91] and CKB.

In the full CKB cohort, adjustment for baseline SBP, in addition to potential confounders, reduced the HR of the association of BMI with IS incidence by 47%, from 1.19 to 1.10. Adjustment for usual, rather than baseline, SBP reduced the HR further, to 1.05. None of the previous studies investigated separately the mediating role of SBP on the association of BMI with IS incidence. Instead, the studies that examined the effect of possible mediators (blood pressure, lipids and glucose) focused on their overall combined effects.[80,90,92,95] Furthermore, none of these studies accounted for intra-individual variation or measurement error in SBP, likely underestimating the mediating effect of SBP. Similar to CKB findings, the previously described study of ~400,000 non-smoking women from Korea showed that after adjustments for baseline SBP, FPG and cholesterol, the HR of BMI with IS incidence was attenuated by ~40% (HR per 3 kg/m^2 from 1.16 to 1.09). The ERFC meta-analysis of 221,934 individuals from 58 prospective studies of predominantly Western populations, reported that additional adjustments for baseline SBP, diabetes, total cholesterol and HDL-cholesterol in examination of the association of BMI with IS reduced the HR per 3 kg/m^2 higher BMI from 1.13 to 1.04.[80] Although the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group's meta-analysis (including 1.8 million individuals form 97 prospective studies) did not examine stroke types, it investigated the mediating

roles of blood pressure, cholesterol and glucose in the association of BMI with total stroke (~31,000 events), including comparing these between populations.[81] These analyses showed comparable mediating effects of these factors in Asian and Western populations,[81] consistent with the largely similar findings of analyses examining the effects of mediating factors on the association of BMI with IS in the predominantly Western population ERFC[80] and the East Asian populations included in CKB and the study of non-smoking women in Korea.[95] ERFC was the only previous study that investigated the possible mediating effect of inflammatory biomarkers, specifically CRP and fibrinogen. In a subset of the population with available data, adjustment for CRP resulted in attenuation of the HR of the association of BMI with IS from 1.06 to 1.01. However, separate adjustment for fibrinogen had no effect on the HR. Findings from the CKB biochemistry cohort suggested that adjustments for baseline SBP, RPG and major plasma biomarkers (LDL- and HDL-related biomarkers, albumin and AST) reduced the HR for the association of BMI with IS from 1.13 to 1.04. However, after adjustment for usual SBP, in addition to those same possible mediators, the association of BMI with IS was completely attenuated (HR 1.00). These findings highlight a major strength of CKB in enabling adjustment for regression dilution bias in the major mediator (SBP), in contrast with all previous studies. Moreover, these findings highlight not just the importance of SBP, RPG and lipids as potential mediators of the association of BMI with IS, but also the potential importance of albumin (a marker of, among other things, inflammation and nutritional status) and AST (a marker of liver function, muscle damage and myocardial injury[163]), although they have not been established to have a causal association with IS.

In CKB, the shape and the strength of the associations of BMI with IS subtypes, i.e., lacunar and non-lacunar IS, were similar to those with all IS. The few previous studies that have investigated the association of BMI with IS subtypes have focused mainly on lacunar IS.[97-100] These have consistently reported positive, but non-significant, associations, reflecting the small number of lacunar IS events included in these studies (approximately ten times fewer than in CKB).[97-100] The ARIC study of 13,549 individuals from the USA is the only study to have investigated the association of BMI with both lacunar (~140 events) and non-lacunar (~340 events) IS.[100] This study reported a positive approximately log-linear association of BMI with non-lacunar IS (HR 1.12 [95% CI 1.10-1.35] per 3 kg/m^2 higher BMI) and lacunar IS (1.08 [0.99-1.18]), largely similar to CKB findings. In that US population, the proportions of individuals classified as overweight and obese were 37% and 24%, respectively, much higher than in CKB (28% and 4.0%, respectively). In CKB, adjustment for usual SBP and baseline RPG combined explained 67% and 83% of the initial HR (adjusted for age, sex, study area, education, smoking, alcohol and physical activity) of BMI with lacunar IS and non-lacunar IS, respectively. In the ARIC study, additional adjustments for SBP, HDL-cholesterol, diabetes and albumin explained all of the association of non-lacunar IS (HR from 1.12 [95% CI 1.05-1.18] to 1.00 [0.94-1.06], per 3 kg/m^2) and lacunar IS (HR from 1.08 [0.99-1.18] to 0.91 [0.81-1.01]). However, the study included only about 1/100th and 1/20th the number of lacunar IS and non-lacunar IS events, respectively, as the present analyses in CKB, which provide the most robust evidence to date on the association of BMI with IS subtypes.

Few previous studies additionally investigated the association of other adiposity measures with IS[80,92,93] and IS subtypes.[100] Similar to the present findings in CKB,

previous studies reported that, after adjustment for potential confounders, the shape and strength of the associations of central adiposity measures (WC and WHR) with IS incidence[80,93] and IS subtypes,[100] were broadly similar to those of BMI. To my knowledge, CKB is the first study to provide evidence on the association of body fat percentage with IS and IS subtypes, and it showed similar associations to the other adiposity measures studied. In the present study, additional adjustments for SBP attenuated the associations of both general and central adiposity measures with IS and IS subtypes. However, the attenuation of the HR was more marked for general than for central adiposity measures. This might reflect the stronger association of general, as compared to central, adiposity measures with SBP.[40] Consistent with CKB, the ERFC study showed that adjustments for baseline SBP, diabetes, total- and HDL-cholesterol had smaller effects on the HR for central adiposity measures than for BMI.[80] For instance, after adjustments for those four possible mediators the HR of the association of WC, WHR and BMI with IS was reduced by ~56%, ~44% and ~70%, respectively. The previously described ARIC study was the only one that investigated the association of both general (BMI) and central (WC and WHR) adiposity measures with IS subtypes.[100] Similar to the CKB findings, they reported a positive log-linear association of all three adiposity measures with IS subtypes before and after adjustments for potential mediators (baseline SBP, HDL-cholesterol, diabetes and albumin). However, in the ARIC study, the number of events (~140 lacunar IS and ~380 non-lacunar IS) was too small to draw any robust conclusion. To date, only ERFC and ARIC investigated the effect of mediators on the association of central adiposity measures with IS[80] and IS subtypes.[100] Both were Western population studies and, to my knowledge, the present analyses in CKB are the first to

investigate the effect of mediators on the association of central adiposity with IS and IS subtypes in an East Asian population. Also, the ERFC[80] and ARIC[100] studies included smaller numbers of IS and IS subtype events as compared to CKB. Furthermore, they did not adjust for measurement error or intra-individual variation in SBP.

5.4.2 Intracerebral haemorrhage and its subtypes

Findings from previous studies, mainly focused on the broader HS endpoint rather than ICH, have been inconsistent.[86-89,91,94,95] After adjustments for potential confounders, previous studies variably reported a positive[87,88,94,95] or an inverse log-linear[91] association between BMI and HS throughout the BMI range examined, or no association at BMI <25.0 kg/m^2 but a positive log-linear association at BMI ≥25.0 kg/m^2.[86,89] Three large studies (one Western population and two East Asian population study) have assessed the associations of BMI with ICH incidence, again with mixed findings.[90,91,95] For instance, the Million Women Study, after adjustments for potential confounders (age, study area, smoking, alcohol, physical activity, height and socioeconomic status), reported an inverse log-linear association between self-reported BMI and HS (~5900 events, HR 0.89 [95% CI 0.86-0.92]) throughout the BMI range examined (<22.5 to ≥30 kg/m^2).[91] They also reported an inverse association of BMI with ICH and SAH. However, the proportion of HS cases in the Million Women Study classified as SAH was notably high (53% vs. 47% ICH). This contrasts with CKB, in which 8% of HS cases were SAH and 92% were ICH, and with previous literature suggesting that the proportion of HS cases classified as SAH were 5-20% in East Asian population studies,[212,213] and 20-25% among Western population studies.[76,214] In contrast to

findings observed in Million Women study, a previously described study of ~440,000 non-smoking women from Korea reported that, after adjustments for age, smoking, alcohol and physical activity, there was a positive broadly log-linear association with both HS (~4000 events, HR 1.02 [95% CI 1.01-1.03] per 1 kg/m^2 higher BMI) and ICH (~2500 events, 1.02 [1.01-1.03]), throughout the BMI range examined (<18.5 to ≥32.0 kg/m^2).

In CKB, given the strong positive association of BMI with SBP, it could be expected that 1 SD higher BMI, corresponding to 8.1 mmHg higher usual SBP, would be associated with a HR of 1.26 (95% CI 1.25-1.27) for ICH. However, there was no association between BMI and ICH (6488 events) at BMI <25.0 kg/m^2, and a positive association at BMI levels ≥25.0 kg/m^2. At BMI <25.0 kg/m^2 there was no clear association of BMI with fatal ICH, but a weak positive association with non-fatal ICH. In analyses by age-at-risk, there was an inverse log-linear association between BMI and ICH incidence among older individuals at BMI <25.0 kg/m^2 but a positive approximately log-linear association among younger individuals throughout the BMI range examined. This suggests that the lack of association of BMI with risk of ICH at BMI levels <25.0 kg/m^2 for all ICH and fatal ICH might reflect reverse causality from undiagnosed disease or frailty, which are associated with lower BMI but higher risk of ICH. Possible misclassification of events due to limited availability of brain imaging in many previous studies might have affected their findings and explain some inconsistencies between studies.

Only East Asian studies have examined the effect of potential mediators, such as blood pressure, diabetes and lipids, on the association of BMI with HS or ICH, and they reported mixed findings.[90,94,95] The previously described large study of

~400,000 non-smoking Korean women reported that adjustments for baseline SBP, FPG and cholesterol, in addition to potential confounders, completely attenuated the initial positive log-linear associations of BMI with HS (from 1.02 [95% CI 1.01-1.03] to 1.00 [0.98-1.01] per 1 kg/m^2) and ICH (from 1.02 [1.01-1.03] to 0.99 [0.98-1.00]). Likewise, two smaller East Asian population studies reported that adjustments for baseline SBP, FPG and cholesterol,[90] or for baseline SBP and diabetes,[94] fully attenuated the associations of BMI with ICH and HS, respectively. In CKB, additional adjustments for baseline SBP reversed the initial positive association of BMI with ICH, and further adjustment for usual SBP strengthened the inverse association. A possible explanation for this phenomenon might be that other factors might increase the risk of ICH at low BMI, counteracting the beneficial effect of low SBP. This is demonstrated by findings in the CKB biochemistry cohort, where the inverse association between BMI and non-fatal ICH (given baseline SBP) was mainly explained through LDL-related biomarkers. This is consistent with findings from a recently published study, which suggested that the inverse association between LDL-cholesterol and ICH is likely to be causal.[182] For fatal-ICH the inverse association with BMI (given SBP) was slightly more marked than for non-fatal ICH, which might reflect a larger influence of reverse causality on fatal-ICH. In addition, LDL-related biomarkers explained only part of the HR of the association of BMI with fatal ICH, but they fully explained the association with non-fatal ICH.

The present analyses in CKB are the largest to date investigating the association of BMI with ICH subtypes. There was a positive broadly log-linear association of BMI with non-lobar ICH (1216 events), but unclear association with lobar ICH (246 events), the latter likely due to the small number of events. Additional adjustments

for usual SBP and RPG inverted the association of BMI with both ICH subtypes. Only one small longitudinal case-control study (188 lobar ICH, 196 non-lobar ICH and 388 controls), based on primary care data from the US, examined the association of BMI with ICH subtypes. It found a U-shaped association of BMI with lobar and non-lobar ICH after adjustments for potential confounders, hypertension and hyperlipidaemia.[101] The limited evidence on the association of BMI with ICH subtypes highlights the need for further evidence from CKB and other studies to enable reliable estimates of disease risk.

To my knowledge, the present analyses in CKB are the first East Asian study analyses investigating the association of different adiposity measures (WC, WHR, body fat percentage) with ICH, and the first ever analyses investigating the relevance of those measures on ICH subtypes. The associations of WC and body fat percentage with ICH and ICH subtypes were generally similar to the associations of BMI, both before and after adjustments for potential mediators. However, there was a positive, approximately log-linear association of WHR with ICH and ICH subtypes, after adjustments for potential confounders, but an inverse log-linear association after further adjustments for usual SBP and RPG. Although the findings for WHR are different from those of the other adiposity measures in sex-combined analyses, in analyses separately by sex the association was similar to the other adiposity measures. There was a null association between WHR and ICH at WHR <0.87 but a positive approximately log linear association at higher WHR levels, among men and women. Just one small study from Finland, including ~50,000 individuals, has examined the association of WC with HS (~700 events). This reported unclear associations, both before and after adjustments for SBP, diabetes and total cholesterol, likely reflecting the small number of events.[92]

5.4.3 Strengths and limitations

As described in Chapter 4, CKB has several strengths, including the large and diverse study population, the completeness of follow-up, and the wide-range of reliably-measured (as indicated by their high degrees of self-correlation) general and central adiposity measures at study baseline. Also, the wider range of plasma biomarkers available in CKB, as compared to previous studies, provided the opportunity to investigate the mediating role of a greater number of factors. The analyses presented adopted a robust approach to assessment of the role of potential mediators, including all recommended steps (Chapter 4 and 5), as described. CKB resurvey data allowed adjustments for RD to account for measurement error, particularly in SBP, which is the major mediator of the association of adiposity with stroke types and subtypes. In CKB, baseline SBP explained almost half of the log HR of BMI with IS, whereas usual SBP explained about three quarters. None of the previous studies accounted for intra-individual variation or measurement error in SBP, suggesting they might have underestimated the true effect of SBP in the association of BMI with stroke types and subtypes. Moreover, the high frequency of use of neuroimaging in China, in combination with the on-going stroke adjudication process in CKB, permits uniquely reliable estimates of the associations of adiposity, and other risk factors, with well-characterised stroke types and subtypes.

The presented CKB analyses also have several limitations. During the adjudication process, ~1% of stroke events initially reported as IS were subsequently adjudicated as ICH events, and ~3% of initially reported ICH events were adjudicated as IS. Therefore, some non-adjudicated IS events are likely to be ICH

and vice versa, which may explain the slightly weaker association of BMI with non-adjudicated IS as compared with adjudicated IS (HR 1.16 vs. 1.23 per 1 SD higher BMI). Moreover, a lower proportion of ICH events were adjudicated as compared to IS (~23% vs. ~52%), reflecting the lower retrieval rate of medical records for ICH than IS (~70% vs. ~90%), in turn due to the higher proportion of fatal ICH events as compared to IS events (~46% vs. ~3%). Furthermore, data are not yet available for all non-lacunar IS subtypes (e.g., cardioembolic and large artery stroke), precluding investigation of the associations of adiposity with these subtypes. However, the ongoing outcome adjudication process will provide more detailed stroke phenotyping data for future investigations. In addition, plasma biomarkers were available in only a subset of CKB participants. As a result of this, it was not possible to investigate the mediating effects of plasma biomarkers in the associations of adiposity with stroke subtypes and the extent of possible subgroup analyses was limited. Although repeated measurements for plasma biomarkers were collected in a small subset of participants during the resurveys (~300 individuals during first resurvey and ~900 individuals during second resurvey) adjustment for regression dilution bias was only considered for SBP (major mediator). The method for correcting for measurement error for multiple covariates is complex (e.g., correlation matrix), and given the limited repeat measurement data for plasma biomarkers, the estimates for the correlation matrix may not be accurate.[210,211] Moreover, the assumptions (e.g., linearity) of this method cannot easily be checked. The plasma assays were based on non-fasting blood samples, which might not capture the true mediating effect of some plasma biomarkers (e.g., RPG, triglycerides), although further adjustments for fasting time did not change the findings. Moreover, alternative glycaemic indicators, including fasting

or post-load plasma glucose, may have explained a greater proportion of the association of adiposity with stroke.[215] Finally, the mediating roles of blood pressure and plasma biomarkers in the association of adiposity with stroke types, was investigated using a single more conventional method. It may be of a value to repeat these mediation analyses using alternative methods such as that described by VanderWeele which separately estimates direct and indirect effects of adiposity on stroke types using a 2-stage regression.[216] However, two sets of analyses using overlapping data to investigate the mediating roles of blood pressure, glucose and cholesterol on the association of BMI with IHD, reported similar findings irrespective of which method was used.[81,217]

The presented analyses provide robust new evidence that high levels of adiposity are associated with higher risk of IS and IS subtypes in a population with relatively low BMI. Those associations appear to mainly be explained through SBP. Given baseline SBP, lipids and other plasma biomarkers slightly attenuated the association of BMI with IS. There was no association between adiposity and ICH at BMI levels within the "normal" range (BMI <25.0 kg/m^2), and even at BMI levels ≥25 kg/m^2 the positive association was much weaker than that expected given the association between adiposity and blood pressure and between blood pressure and overall ICH risk. There was, however, a positive association with non-lobar ICH through the full BMI range examined, possibly reflecting the notably strong association of usual SBP with non-lobar ICH. Given baseline SBP, there were strong inverse associations of adiposity with ICH and ICH subtypes. Those associations were attenuated towards the null after allowing for plasma biomarkers, and particularly for non-fatal ICH after allowing for LDL-related biomarkers. The lack of understanding of the causality of those associations,

particularly for ICH and ICH subtypes, highlights the need for future MR studies to assess those associations. Despite the potential health benefits derived from weight loss,[218] there are known challenges in achieving sustained weight loss through weight management interventions in the general population.[219,220] However, interventions to control the main mediators of the association between adiposity and stroke, such as hypertension[221,222] and dyslipidaemia,[223] which may be more sustainably, might contribute to lessen the adverse effect of excess adiposity on stroke. This clearly, however, does not diminish the importance of maintaining optimum bodyweight.

Table 5.1. Baseline characteristics by BMI quintiles

Characteristic[a]	BMI quintile[b]					Overall
	1	2	3	4	5	
No. of participants	96,224	94,692	97,726	94,213	98,356	481,211
Mean BMI (SD), kg/m²	19.3 (1.2)	21.6 (0.5)	23.3 (0.5)	25.2(0.6)	28.4 (2.1)	23.6 (3.2)
Age and socioeconomic factors						
Mean age (SD), years	52.5 (11.6)	50.9 (10.6)	51.2 (10.3)	51.6 (10.1)	51.8 (10.0)	51.6 (10.6)
Women, %	59.1	59.1	59.1	59.1	59.1	59.1
Urban, %	32.7	38.4	43.9	49.2	54.7	43.8
≥ 6 years of education, %	49.2	49.6	50.2	50.4	49.1	49.5
Lifestyle factors						
Men ever-regular smoker[c], %	79.7	76.4	73.6	71.1	70.6	74.4
Women ever-regular smoker[c], %	3.8	3.0	2.9	2.6	2.9	3.0
Men ever-regular drinker[d], %	35.5	37.6	37.3	37.1	37.0	37.0
Women ever-regular drinker[d], %	2.3	2.4	2.5	2.5	2.4	2.4
Mean physical activity (SD), MET-h/day	21.8 (13.2)	22.1 (12.0)	21.7 (11.6)	21.1 (11.9)	20.3 (12.8)	21.4 (11.7)
Medical history and health status, %						
Diabetes[e]	3.3	4.3	5.2	6.2	8.2	5.5
Hypertension[f]	4.3	6.5	9.1	12.3	18.0	9.9
Blood pressure lowering medication	1.4	2.3	3.3	4.6	7.0	3.6
Self-rated poor health	12.2	9.1	8.2	8.2	9.2	9.3
Adiposity measures, mean (SD)						
Standing height, cm	158.6 (6.4)	158.6 (5.7)	158.7 (5.5)	158.8 (5.5)	158.9 (6.0)	158.7 (5.5)
Weight, kg	48.8 (5.0)	54.6 (4.1)	58.9 (4.3)	63.7 (4.7)	71.9 (7.5)	85.3 (3.2)
WC, cm	69.6 (5.8)	75.3 (4.9)	79.6 (4.9)	84.3 (5.2)	91.6 (7.4)	80.1 (9.0)
WHR	0.83 (0.06)	0.86 (0.05)	0.88 (0.05)	0.91 (0.05)	0.93 (0.06)	0.88 (0.06)
Body fat percentage	20.1 (3.8)	24.6 (3.1)	27.8 (3.3)	31.0 (3.8)	35.9 (5.4)	27.9 (6.4)
Blood pressure and glucose, mean (SD)						
SBP, mmHg	123.6 (20.7)	127.5 (19.1)	130.3 (18.7)	133.5 (19.4)	138.2 (21.7)	130.7 (19.3)
DBP, mmHg	73.9 (11.6)	75.7 (10.6)	77.4 (10.5)	79.3 (10.7)	81.8 (12.1)	77.7 (10.7)
RPG, mmol/L	5.8 (2.5)	5.9 (2.3)	6.0 (2.3)	6.1 (2.4)	6.3 (2.7)	6.0 (2.2)

[a]Adjusted for age (5-year groups), sex and study area (where appropriate). [b] Sex-specific quintiles. [c]Participants were classified as ever-regular smokers if they answered "on most days" or "daily or almost every day" to either "How often do you smoke tobacco now?" or "In the past, how frequently did you smoke?". [d]Participants were classified as ever-regular alcohol drinkers if they answered "usually at least once a week" to the question "During the past 12 months, how often did you drink alcohol?" or they answered yes to the question "In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?".[e] Participants were classified as having diabetes if they answered yes to the question "Has a doctor ever told you that you had diabetes?" or if they had random plasma glucose level ≥7.0 mmol/L if time since last food ≥8 hours, or ≥11.1 mmol/L if time since last food <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. [f]Self-reported at baseline.

BMI: body mass index, DBP: diastolic blood pressure, MET-h/day: metabolic equivalent of task hours per day, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference, WHR: waist-to-hip ratio.

Table 5.2. Correlation coefficients of adiposity measures, blood pressure and random plasma glucose

		BMI	WC	WHR	Body fat percentage	SBP	DBP	RPG
BMI	**Men:**	0.87	0.62	0.81	0.23	0.29	0.09
	Women:	0.84	0.51	0.89	0.24	0.25	0.10
	All:	0.85	0.55	0.86	0.24	0.26	0.10
WC		**Men:**	0.80	0.75	0.20	0.26	0.13
		Women:	0.78	0.78	0.27	0.23	0.17
		All:	0.78	0.76	0.24	0.24	0.15
WHR			**Men:**	0.57	0.18	0.19	0.15
			Women:	0.50	0.27	0.18	0.20
			All:	0.53	0.24	0.19	0.18
Body fat percentage				**Men:**	0.20	0.30	0.05
				Women:	0.24	0.26	0.08
				All:	0.23	0.27	0.07
SBP					**Men:**	0.72	0.11
					Women:	0.72	0.14
					All:	0.72	0.13
DBP						**Men:**	0.03
						Women:	0.03
						All:	0.03

Pearson correlation coefficients, adjusted for age (5-year groups), sex and study area (where appropriate).
BMI: body mass index, DBP: diastolic blood pressure, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference, WHR: waist-to-hip ratio.

Table 5.3. Self-correlation of adiposity measures and blood pressure between baseline and resurveys

	Baseline and first resurvey[a] (n=18,475)	Baseline and second resurvey[b] (n=23,961)	Mean
Adiposity measures			
BMI	0.93	0.87	0.90
WC	0.84	0.78	0.81
WHR	0.68	0.59	0.64
Body fat percentage	0.90	0.80	0.85
Blood pressure			
SBP	0.70	0.55	0.63
DBP	0.66	0.53	0.60

Pearson correlation coefficients.
[a]2.5 years from baseline survey, [b]6.3 years from baseline survey.
BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, WC: waist circumference, WHR: waist-to-hip ratio.

Table 5.4. Self-correlation of plasma biomarkers between baseline and resurveys

Plasma biomarkers	Baseline and first resurvey		Baseline and second resurvey		Baseline and first or second resurvey[a]	
	No. individuals	Correlation coefficient (SE)	No. individuals	Correlation coefficient (SE)	No. individuals	Correlation coefficient (SE)
Lipids and lipoproteins						
LDL-cholesterol	328	0.75 (0.02)	880	0.63 (0.02)	1149	0.64 (0.02)
HDL-cholesterol	328	0.73 (0.03)	880	0.71 (0.02)	1149	0.70 (0.01)
Triglycerides	328	0.39 (0.05)	880	0.48 (0.03)	1149	0.45 (0.02)
Total cholesterol	328	0.72 (0.03)	880	0.62 (0.02)	1149	0.64 (0.02)
ApoA1	328	0.62 (0.03)	880	0.61 (0.02)	1149	0.62 (0.02)
ApoB	328	0.78 (0.02)	880	0.68 (0.02)	1149	0.70 (0.01)
Inflammatory biomarkers						
Log hs-CRP	328	0.53 (0.04)	880	0.47 (0.03)	1149	0.48 (0.02)
Albumin	206	0.65 (0.04)	807	0.42 (0.03)	976	0.46 (0.03)
Fibrinogen	116	0.47 (0.07)	268	0.46 (0.05)	377	0.46 (0.04)
Renal function biomarkers						
Creatinine	328	0.85 (0.02)	880	0.47 (0.03)	1149	0.49 (0.02)
Cystatin C	200	0.74 (0.03)	408	0.82 (0.02)	595	0.79 (0.02)
eGFR	328	0.76 (0.02)	880	0.75 (0.01)	1149	0.74 (0.01)
Liver function biomarkers						
ALT	328	0.36 (0.05)	880	0.36 (0.03)	1149	0.37 (0.03)
AST	328	0.25 (0.05)	880	0.21 (0.03)	1149	0.22 (0.03)
GGT	204	0.83 (0.02)	792	0.64 (0.02)	960	0.64 (0.02)
Other biomarkers						
RPG	18,403	0.53 (0.01)	23,825	0.39 (0.01)	28,197	0.48 (0.01)
Uric acid	204	0.77 (0.03)	618	0.70 (0.02)	796	0.72 (0.02)
Vitamin D	110	0.64 (0.06)	252	0.43 (0.05)	356	0.49 (0.04)

Pearson correlation coefficients.

[a]Among individuals with repeated plasma biomarkers measurements both at first and second resurvey, the self-correlation coefficients between baseline and resurvey were calculated using the first resurvey measurement.

ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, eGFR: estimated glomerular filtration rate, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, hs-CRP: high sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose.

Table 5.5. Association of baseline BMI with IS and IS subtypes, adjusted for random plasma glucose and SBP

	HR (95% CI) per 1 SD higher BMI			
	All	Adjudicated		Non-adjudicated
		Lacunar	Non-lacunar	
Men, no. of events	15,041	4617	3205	7219
Basic adjustments[a]	1.23 (1.21-1.25)	1.27 (1.23-1.31)	1.25 (1.21-1.30)	1.19 (1.16-1.22)
+ baseline SBP	1.11 (1.10-1.13)	1.16 (1.13-1.20)	1.11 (1.07-1.15)	1.09 (1.06-1.11)
+ usual SBP	1.05 (1.04-1.06)	1.10 (1.08-1.14)	1.04 (1.00-1.07)	1.04 (1.01-1.05)
+ RPG	1.05 (1.03-1.06)	1.10 (1.07-1.13)	1.03 (0.99-1.06)	1.02 (1.00-1.05)
Women, no. of events	18,714	6249	3321	9144
Basic adjustments[a]	1.17 (1.15-1.18)	1.17 (1.14-1.20)	1.24 (1.20-1.28)	1.14 (1.12-1.16)
+ baseline SBP	1.09 (1.07-1.11)	1.10 (1.07-1.13)	1.13 (1.09-1.16)	1.07 (1.05-1.09)
+ usual SBP	1.05 (1.03-1.07)	1.06 (1.03-1.09)	1.07 (1.03-1.09)	1.03 (1.01-1.05)
+ RPG	1.04 (1.02-1.06)	1.06 (1.02-1.09)	1.06 (1.02-1.09)	1.02 (1.00-1.05)
All, no. of events	33,755	10,866	6526	16,363
Basic adjustments[a]	1.19 (1.18-1.20)	1.21 (1.19-1.23)	1.24 (1.22-1.28)	1.16 (1.14-1.18)
+ baseline SBP	1.10 (1.09-1.11)	1.12 (1.10-1.15)	1.12 (1.09-1.15)	1.08 (1.06-1.10)
+ usual SBP	1.05 (1.04-1.06)	1.07 (1.05-1.11)	1.06 (1.02-1.08)	1.04 (1.02-1.06)
+ RPG	1.04 (1.03-1.05)	1.08 (1.05-1.10)	1.04 (1.02-1.07)	1.02 (1.01-1.04)

[a]Stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (where appropriate).
The HR (95% CI) per 1 SD higher BMI were estimated using sex-specific SDs (3.1 kg/m^2 for men and 3.3 kg/m^2 for women).
BMI: body mass index, RPG: random plasma glucose, SBP: systolic blood pressure.

Table 5.6. Association of baseline BMI with ICH and ICH subtypes, adjusted for random plasma glucose and SBP

	HR (95% CI) per 1 SD higher BMI			
	All	Adjudicated		Non-adjudicated
		Lobar	Non-lobar	
Men, no. of events	3428	135	653	2640
Basic adjustments[a]	1.09 (1.05-1.13)	0.99 (0.83-1.19)	1.18 (1.09-1.28)	1.07 (1.03-1.12)
+ baseline SBP	0.91 (0.88-0.95)	0.83 (0.69-1.00)	0.95 (0.87-1.03)	0.91 (0.87-0.95)
+ usual SBP	0.82 (0.79-0.86)	0.75 (0.62-0.90)	0.84 (0.76-0.91)	0.83 (0.79-0.86)
+ RPG	0.82 (0.79-0.85)	0.75 (0.61-0.91)	0.84 (0.77-0.91)	0.82 (0.78-0.86)
Women, no. of events	3060	111	563	2386
Basic adjustments[a]	1.07 (1.04-1.11)	1.16 (0.97-1.40)	1.11 (1.02-1.21)	1.06 (1.02-1.11)
+ baseline SBP	0.92 (0.89-0.96)	1.03 (0.86-1.25)	0.90 (0.83-0.98)	0.92 (0.89-0.96)
+ usual SBP	0.84 (0.81-0.88)	0.96 (0.80-1.17)	0.80 (0.74-0.87)	0.85 (0.82-0.88)
+ RPG	0.84 (0.81-0.87)	0.96 (0.80-1.17)	0.80 (0.73-0.87)	0.85 (0.81-0.88)
All, no. of events	6488	246	1216	5026
Basic adjustments[a]	1.08 (1.05-1.11)	1.07 (0.94-1.22)	1.14 (1.08-1.21)	1.07 (1.04-1.10)
+ baseline SBP	0.92 (0.89-0.94)	0.92 (0.81-1.06)	0.92 (0.87-0.98)	0.91 (0.89-0.94)
+ usual SBP	0.84 (0.81-0.85)	0.84 (0.74-0.98)	0.81 (0.77-0.87)	0.83 (0.81-0.86)
+ RPG	0.83 (0.81-0.85)	0.85 (0.74-0.97)	0.82 (0.77-0.87)	0.83 (0.81-0.86)

[a]Stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (where appropriate).
The HR (95% CI) per 1 SD higher BMI were estimated using sex-specific SDs (3.1 kg/m^2 for men and 3.3 kg/m^2 for women).
BMI: body mass index, RPG: random plasma glucose, SBP: systolic blood pressure.

Figure 5.1. Association of baseline BMI with stroke types and subtypes

The HRs for stroke types and subtypes by baseline BMI (sex-specific quintiles), are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. HRs are plotted against mean baseline BMI in each sex-specific quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The HR (95% CI) per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI is presented at the top of each figure. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively.
BMI: body mass index, HR: hazard ratio.

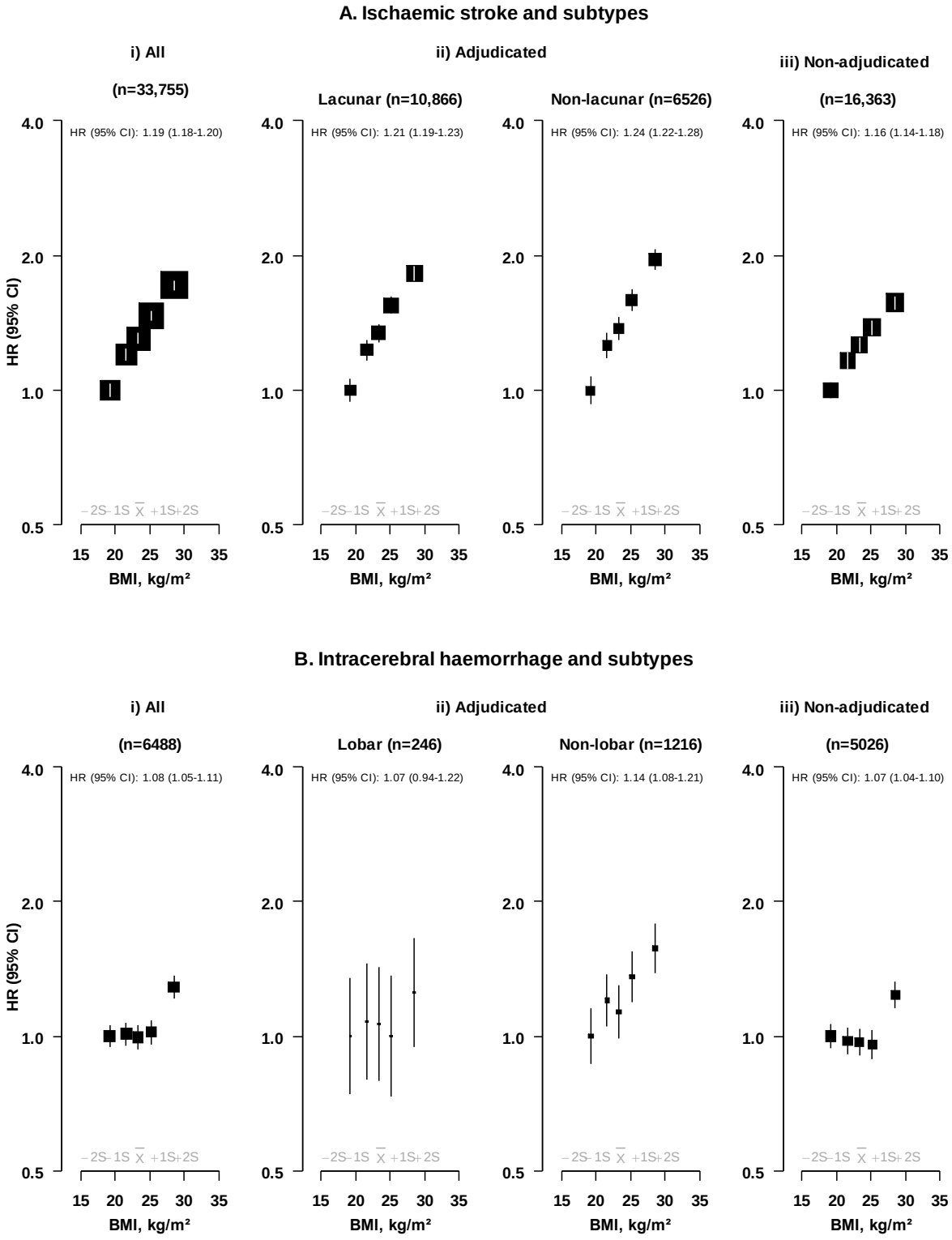


Figure 5. 2. Association of baseline BMI with fatal and non-fatal stroke types

Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

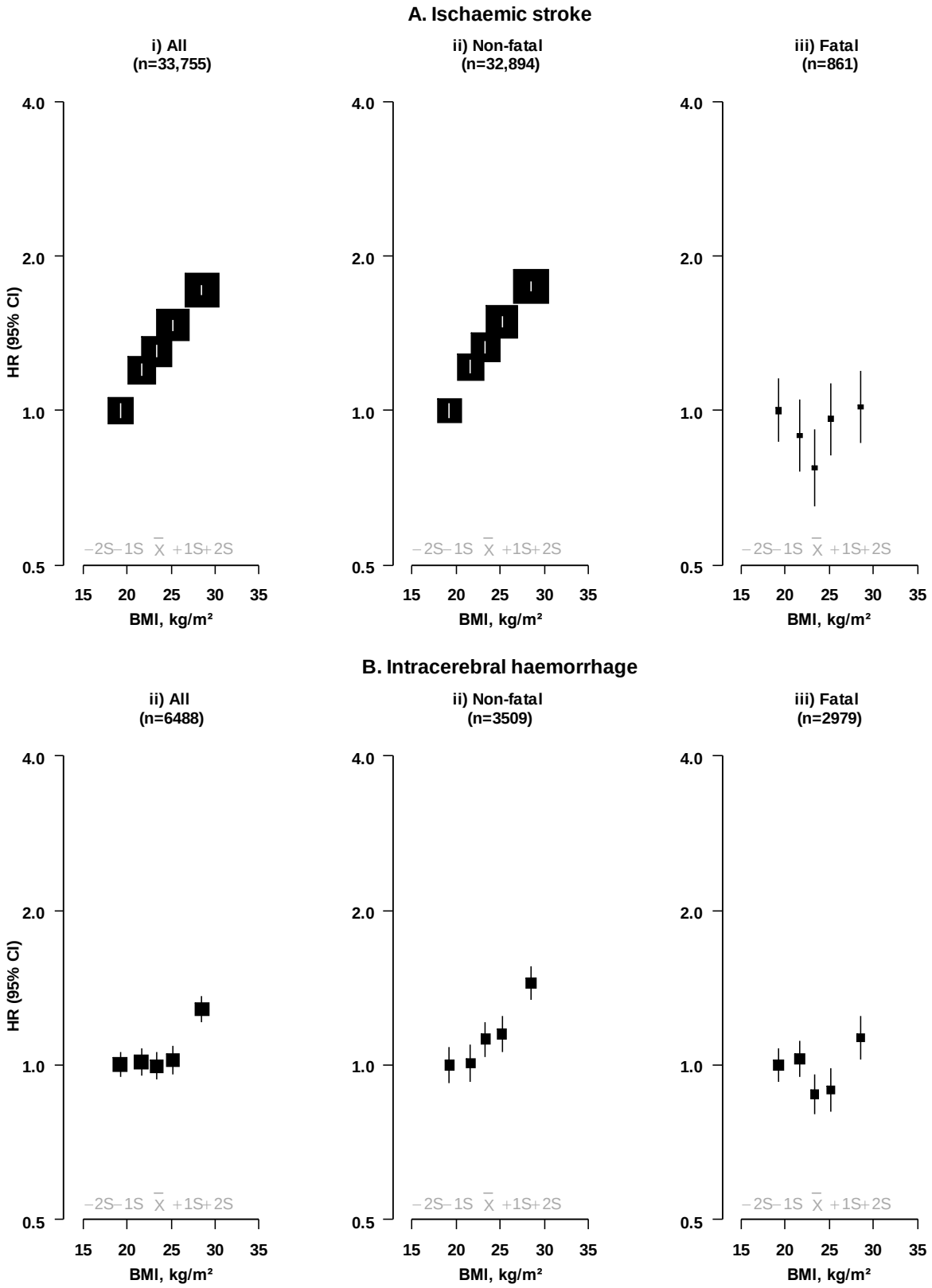


Figure 5.3. Association of baseline BMI with stroke types and subtypes by sex

Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

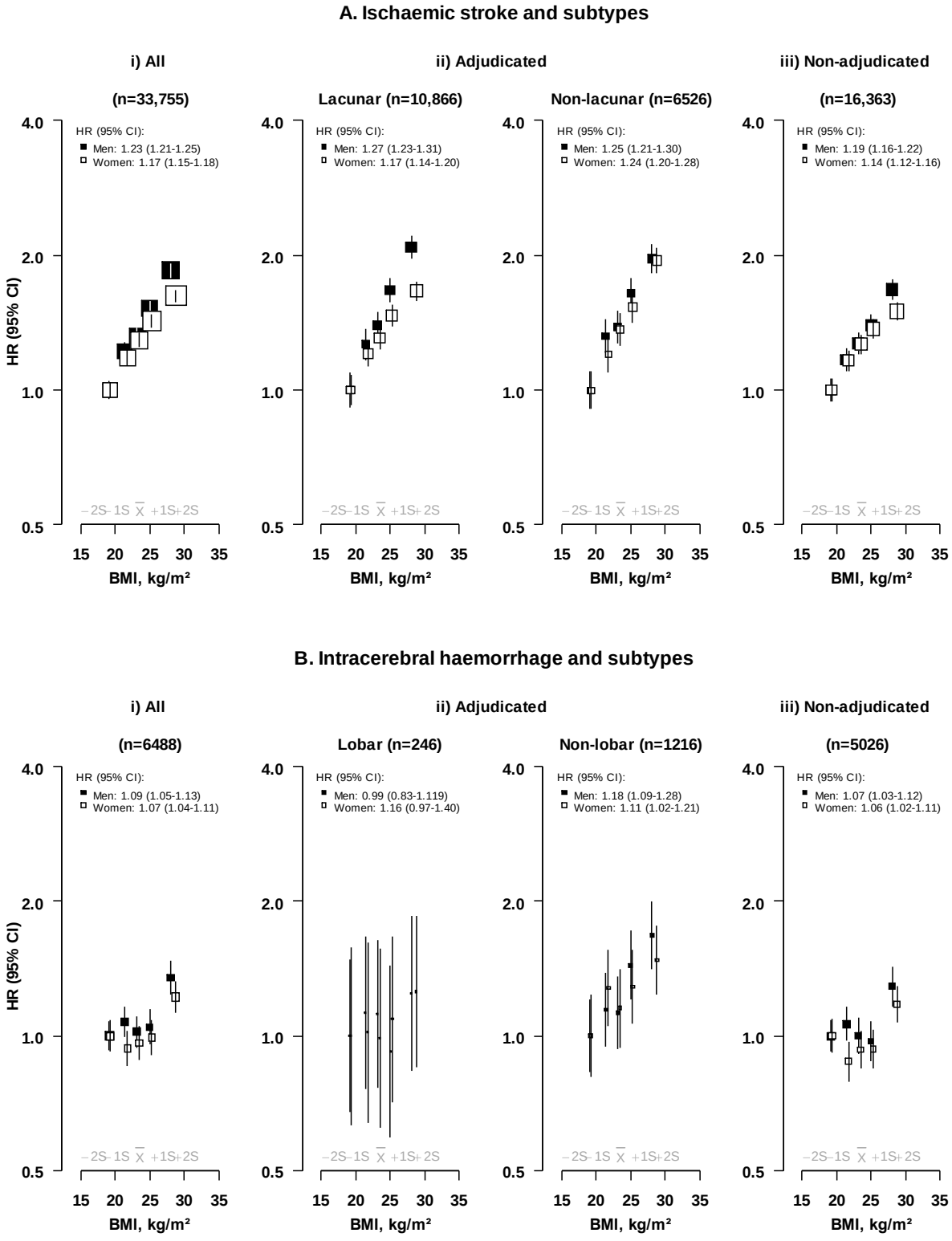


Figure 5.4. Association of baseline BMI with stroke types, by baseline characteristics

The HRs for stroke types per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI, are stratified by age-at-risk and sex, and adjusted for education, smoking, alcohol and physical activity (except where it is the variable of interest). Participants were classified as ever-regular smokers if they answered "on most days" or "daily or almost every day" to either "How often do you smoke tobacco now?" or "In the past, how frequently did you smoke?". Participants were classified as ever-regular alcohol drinkers if they answered "usually at least once a week" to the question "During the past 12 months, how often did you drink alcohol?" or they answered yes to the question "In the past, did you ever have a period of at least 1 year during which you usually drank some alcohol at least once a week?". Participants were classified as having diabetes if they answered yes to the question "Has a doctor ever told you that you had diabetes?" or if they had a random plasma glucose level ≥7.0 mmol/L if time since last food ≥8 hours, or ≥11.1 mmol/L if time since last food <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs. The dashed vertical lines indicate the overall HR, and diamonds indicate combined values and their 95% CIs.
BMI: body mass index. HR: hazard ratio.

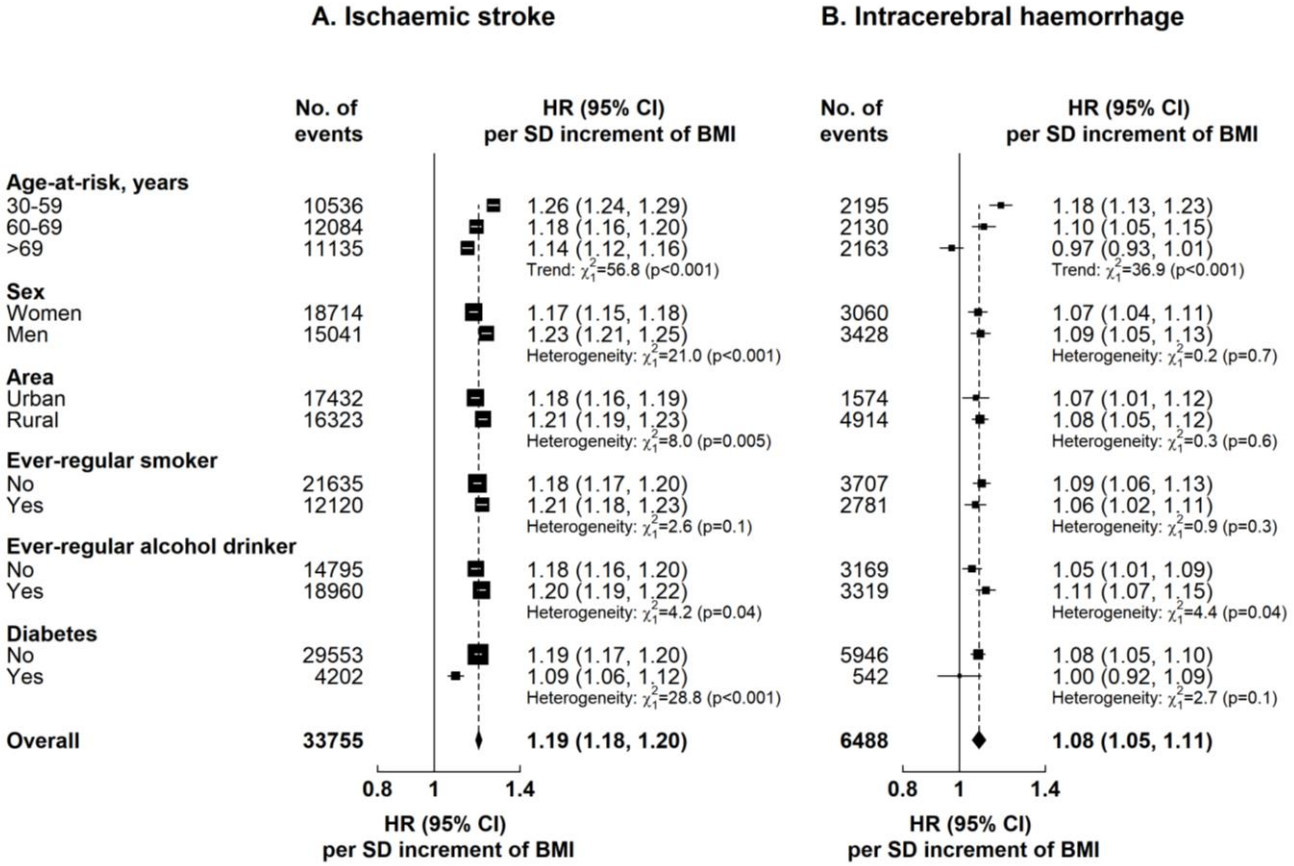


Figure 5.5. Association of baseline BMI with stroke types and subtypes, stratified by age-at-risk

The HRs for stroke types and subtypes by baseline BMI (sex-specific quintiles), are stratified by age-at-risk. Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

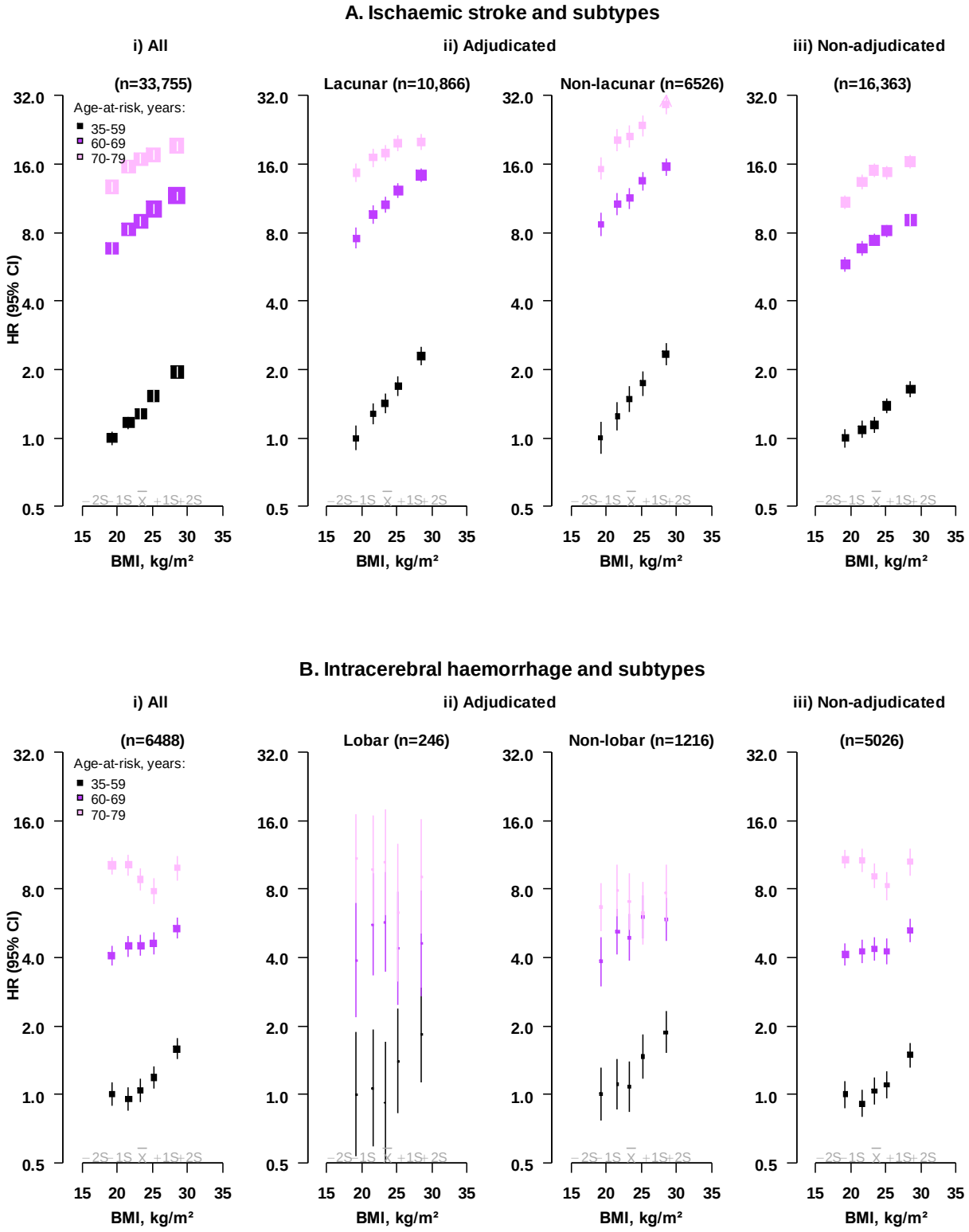


Figure 5.6. Association of baseline BMI with stroke types and subtypes in urban and rural areas

Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

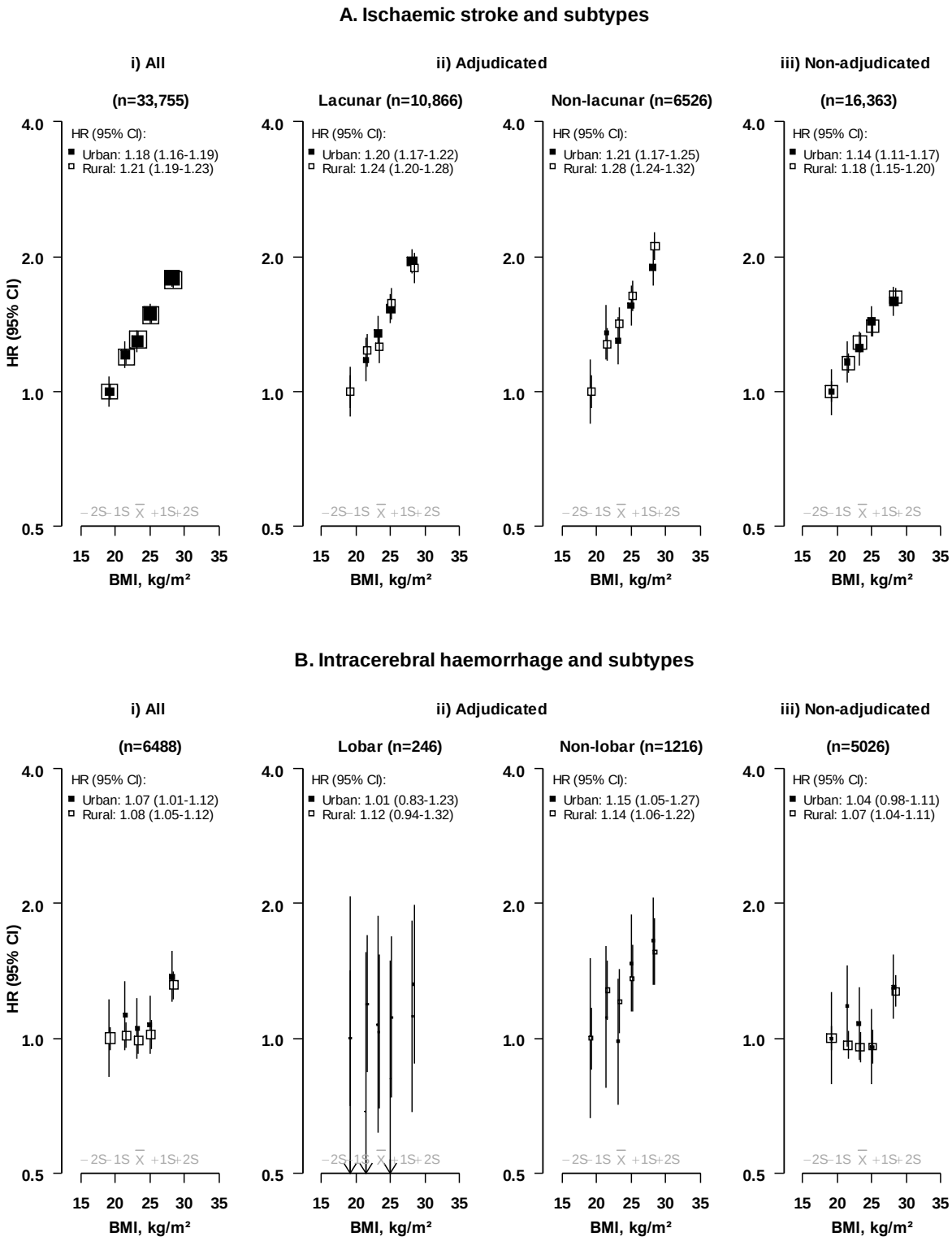


Figure 5.7. Association of baseline BMI with stroke types, by study area

The HRs for stroke types per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI, are stratified by age-at-risk and sex, and adjusted for education, smoking, alcohol and physical activity, separately in each study area. Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs. The dashed vertical lines indicate the overall HR for the five urban areas combined and the five rural areas combined. Diamonds indicate combined values and their 95% CIs.
BMI: body mass index, HR: hazard ratio.

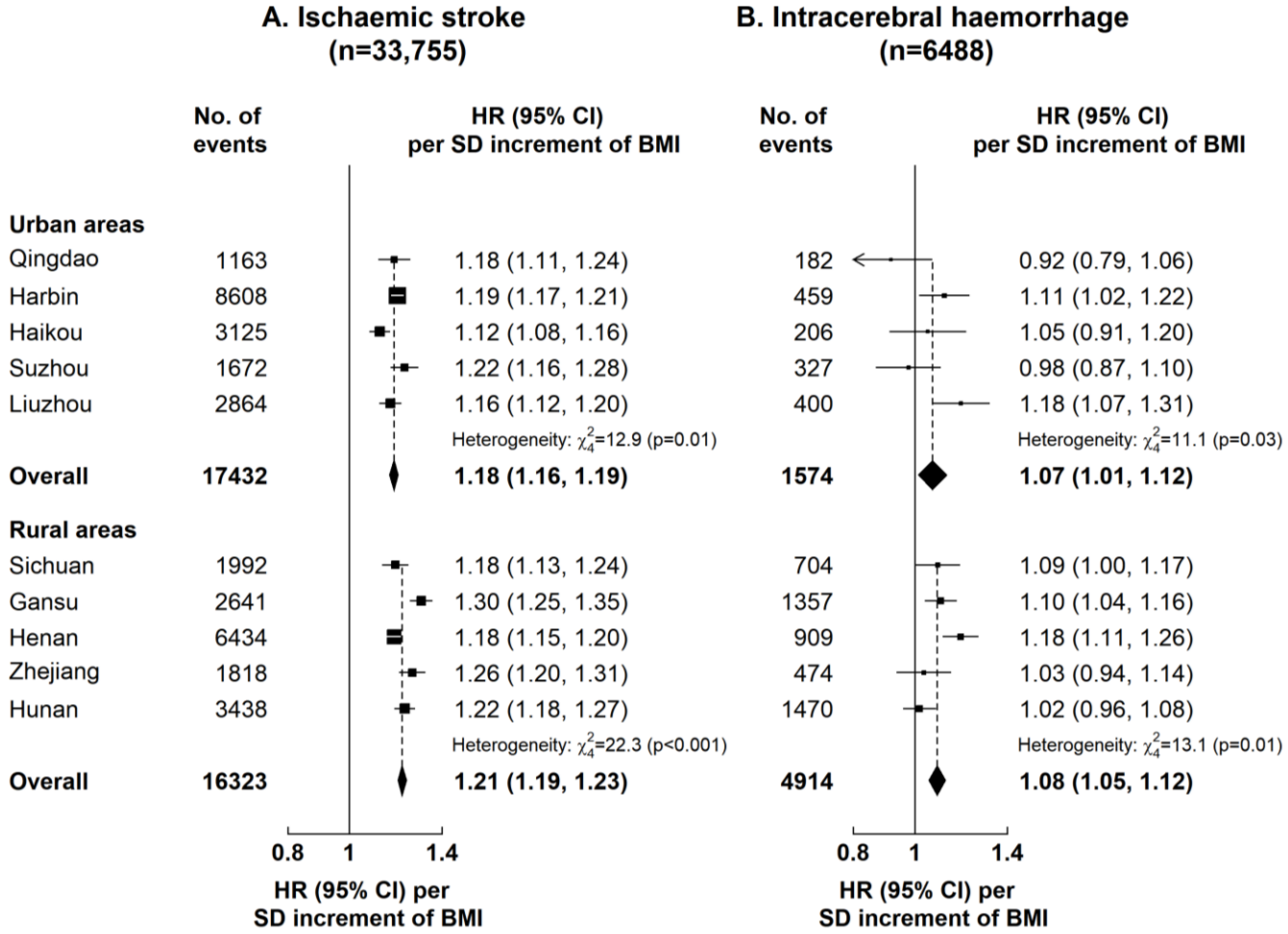


Figure 5.8. Association of baseline BMI with stroke types and subtypes, excluding the first five years of follow-up

Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

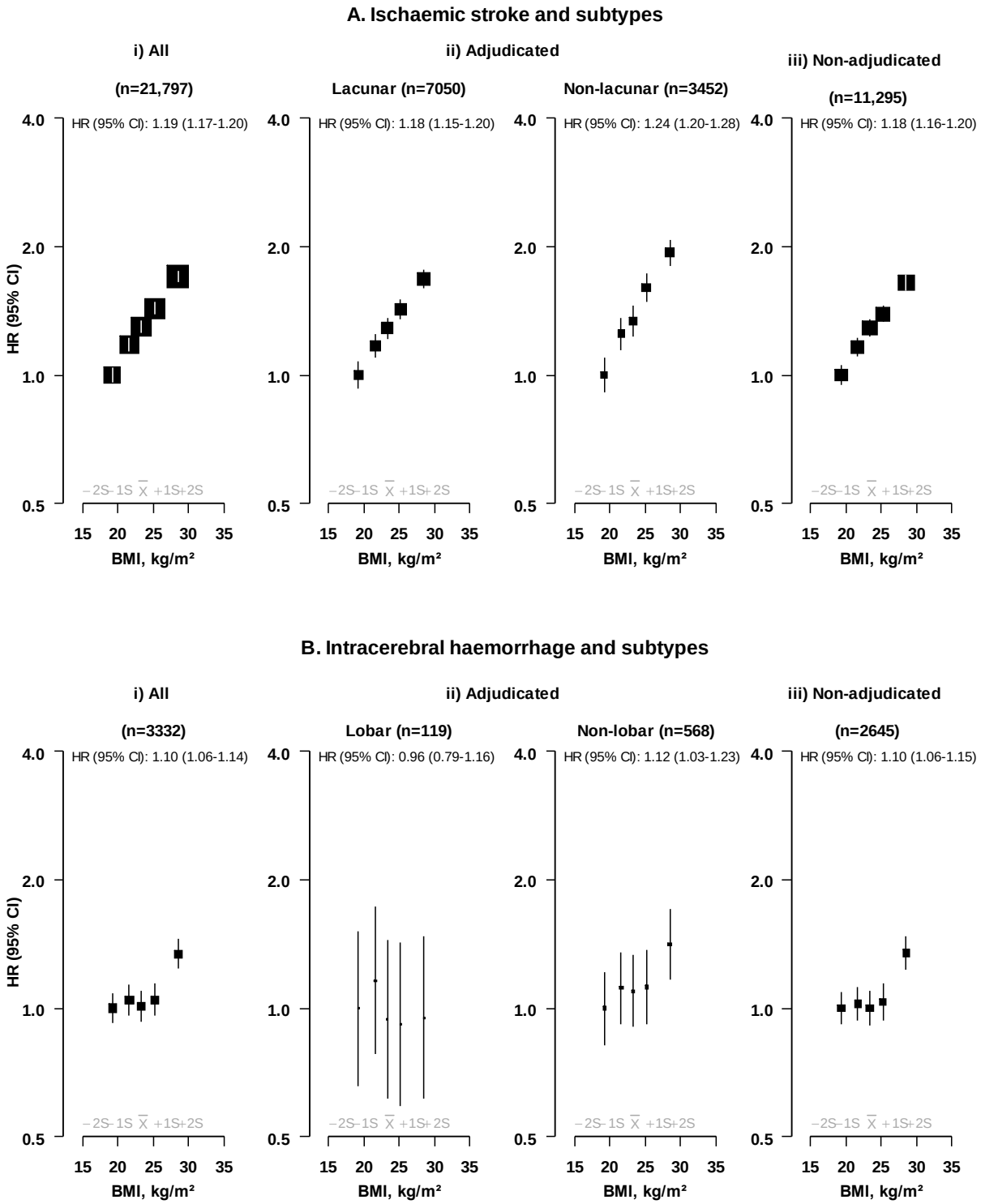


Figure 5.9. Association of baseline BMI with stroke types and subtypes among never-regular smokers

Conventions as Figure 5.1.
BMI: body mass index, HR: hazard ratio.

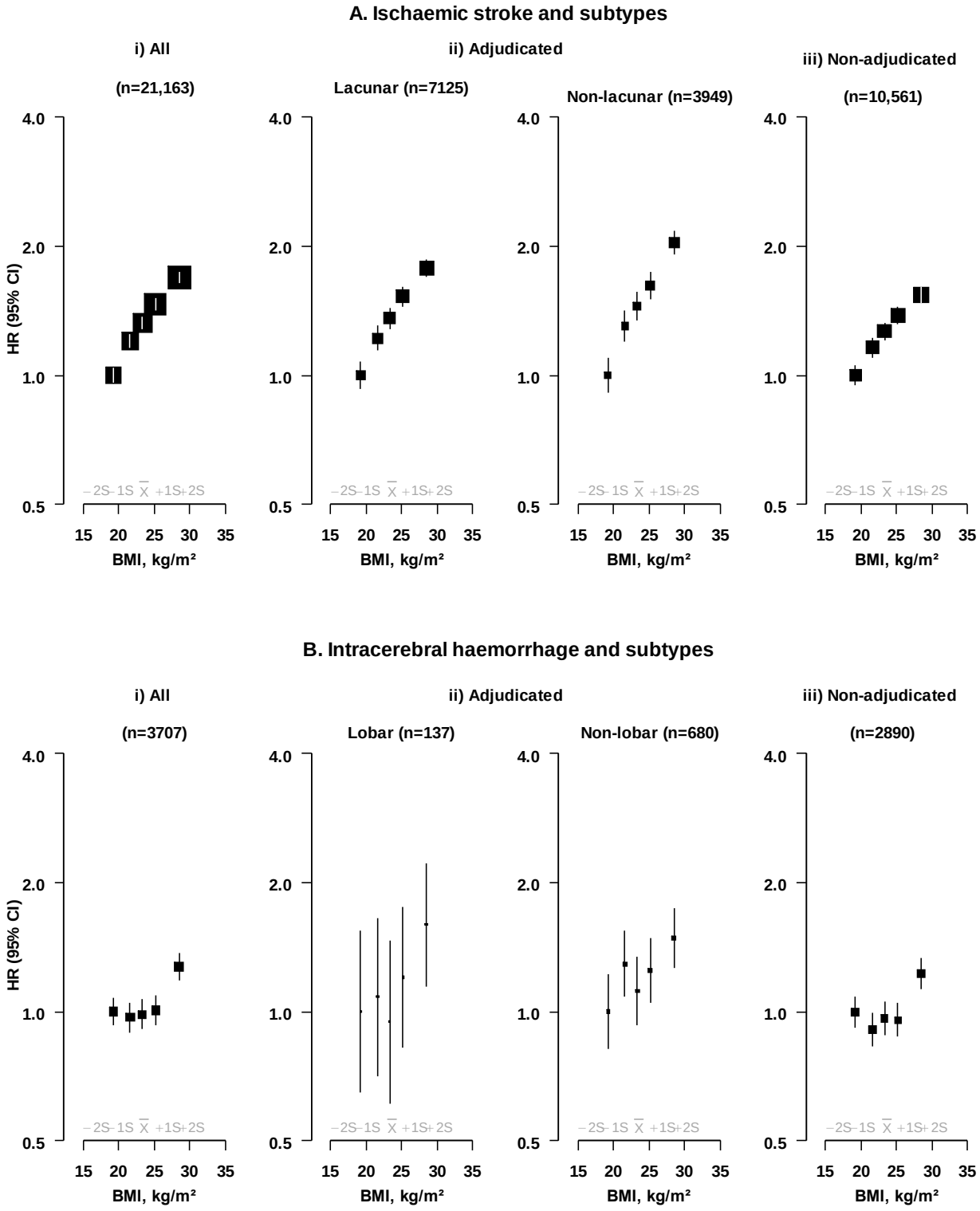
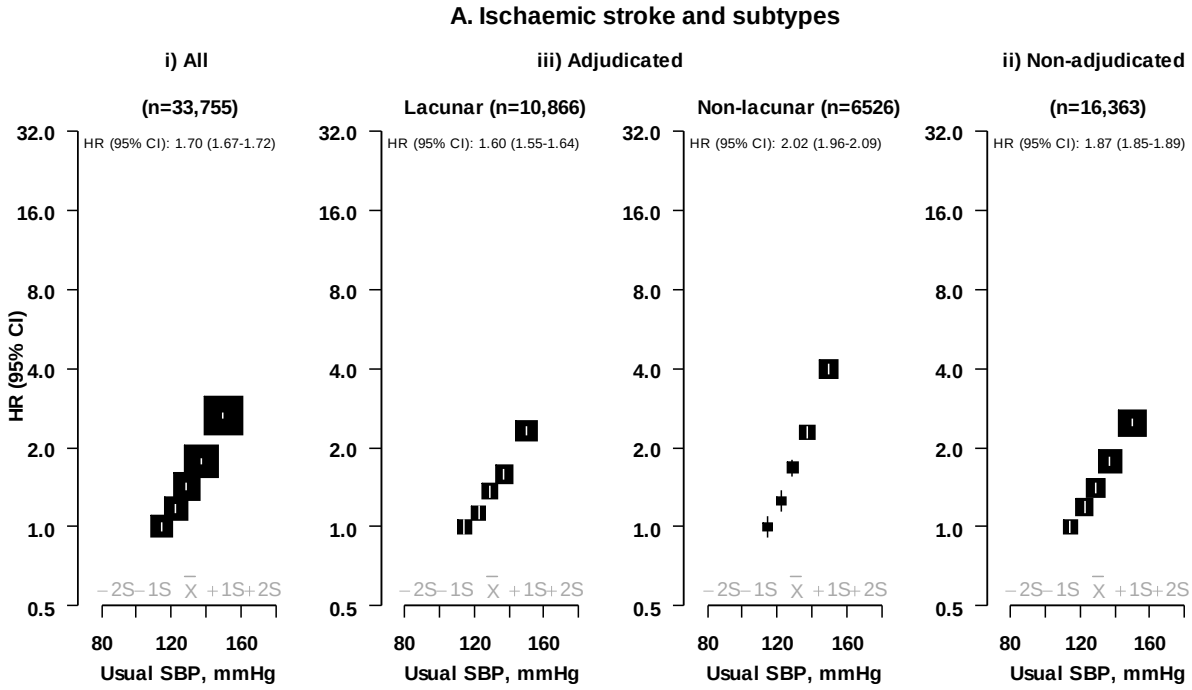


Figure 5.10. Association of usual SBP with stroke types and subtypes

The HRs for stroke types and subtypes by usual SBP (quintiles), are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. HRs are plotted against mean resurvey SBP in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The HR (95% CI) per 1 SD (19.3 mmHg) higher usual SBP is presented at the top of each figure. The $\bar{x}$ above the x-axis represents the mean value of SBP and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively
HR: hazard ratio, SBP: systolic blood pressure.



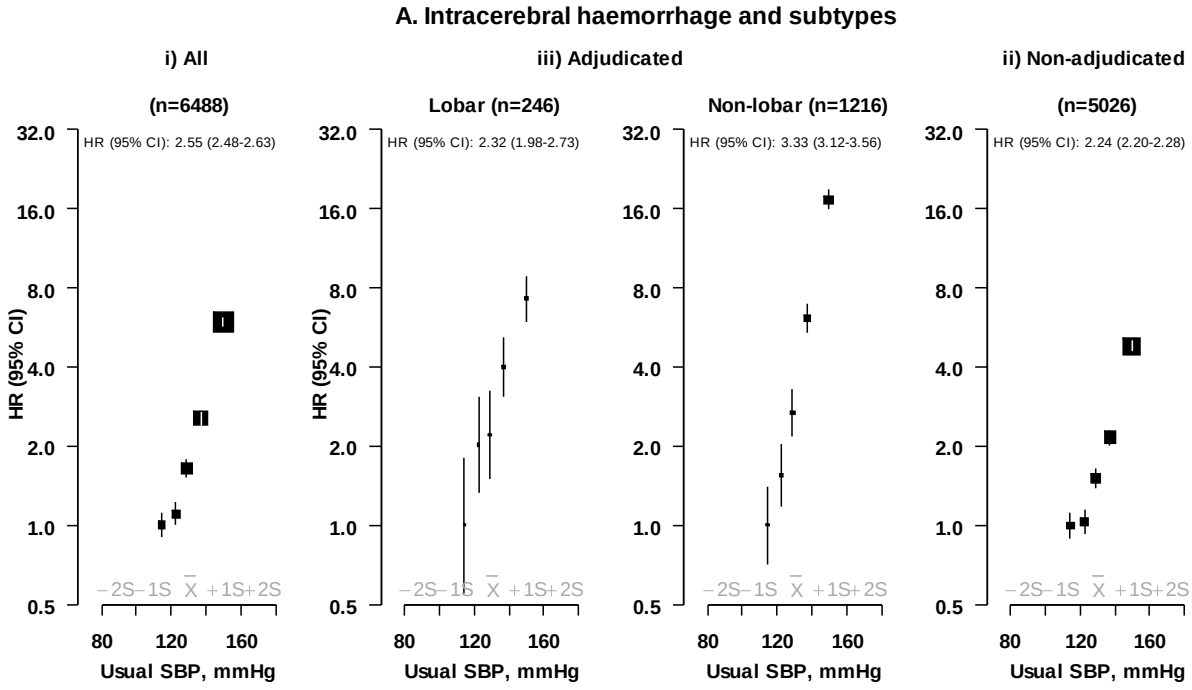


Figure 5.11. Association of baseline random plasma glucose with stroke

The HRs for stroke types and subtypes by baseline RPG (quintiles), are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. HRs are plotted against mean baseline RPG in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The HR (95% CI) per 1 SD (2.2 mmol/L) higher RPG is presented at the top of each figure. The $\bar{x}$ above the x-axis represents the mean value of RPG and the ±1S and ±2S represent 1 and 2 SD from the mean, respectively
HR: hazard ratio, RPG: random plasma glucose.

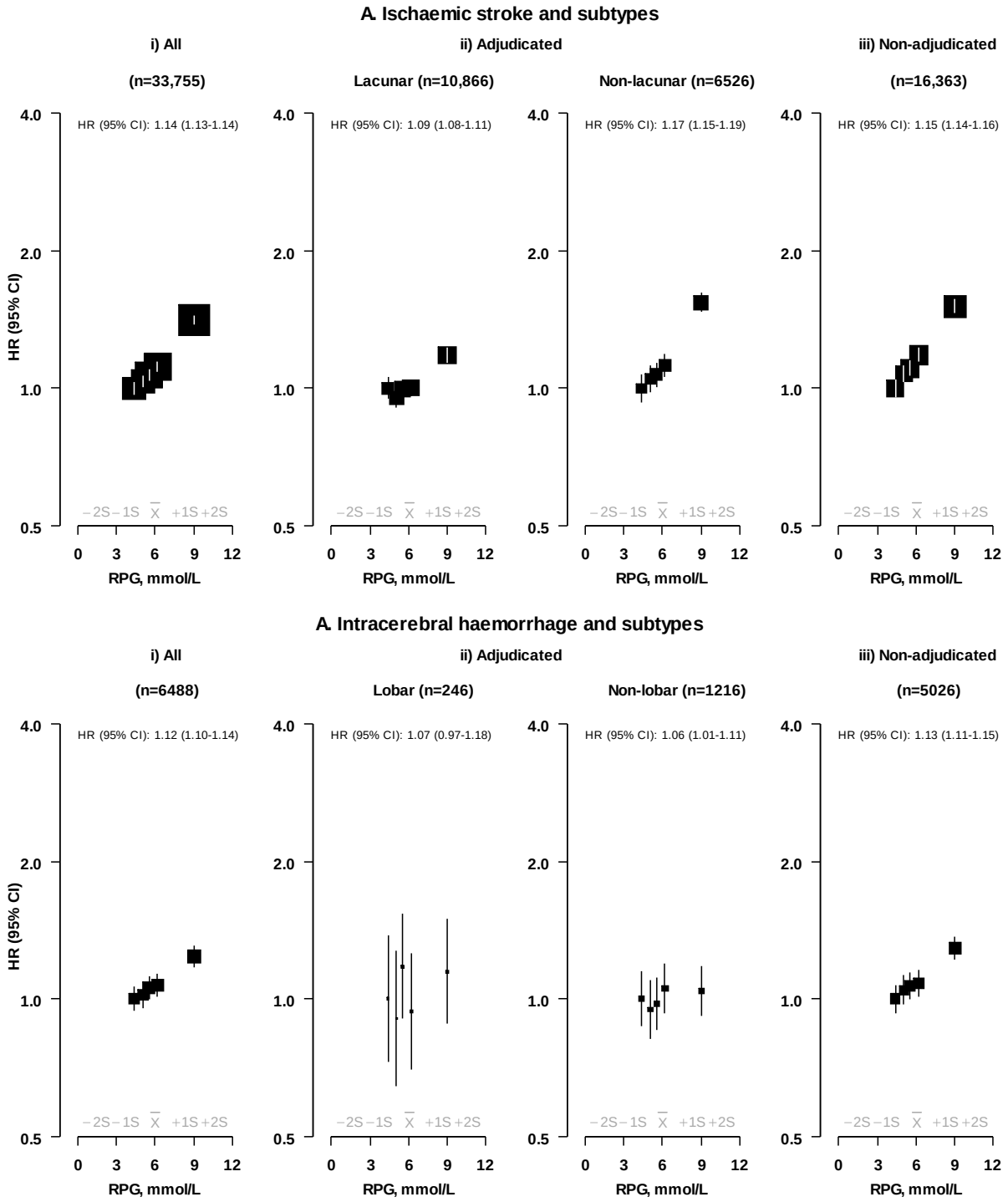


Figure 5.12. Association of baseline BMI with stroke types and subtypes, additionally adjusted for random plasma glucose and SBP

The HRs for stroke types and subtypes by baseline adiposity (sex-specific quintiles), are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (basic adjustments). Then they are subsequently adjusted for RPG, baseline SBP and usual SBP. HRs are plotted against mean baseline BMI in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The $\bar{x}$ above the x-axis represents RPG mean value and the +1S and +2S represent the 1 and 2 SD from the mean, respectively.
BMI: body mass index, HR: hazard ratio, RPG: random plasma glucose, SBP: systolic blood pressure.

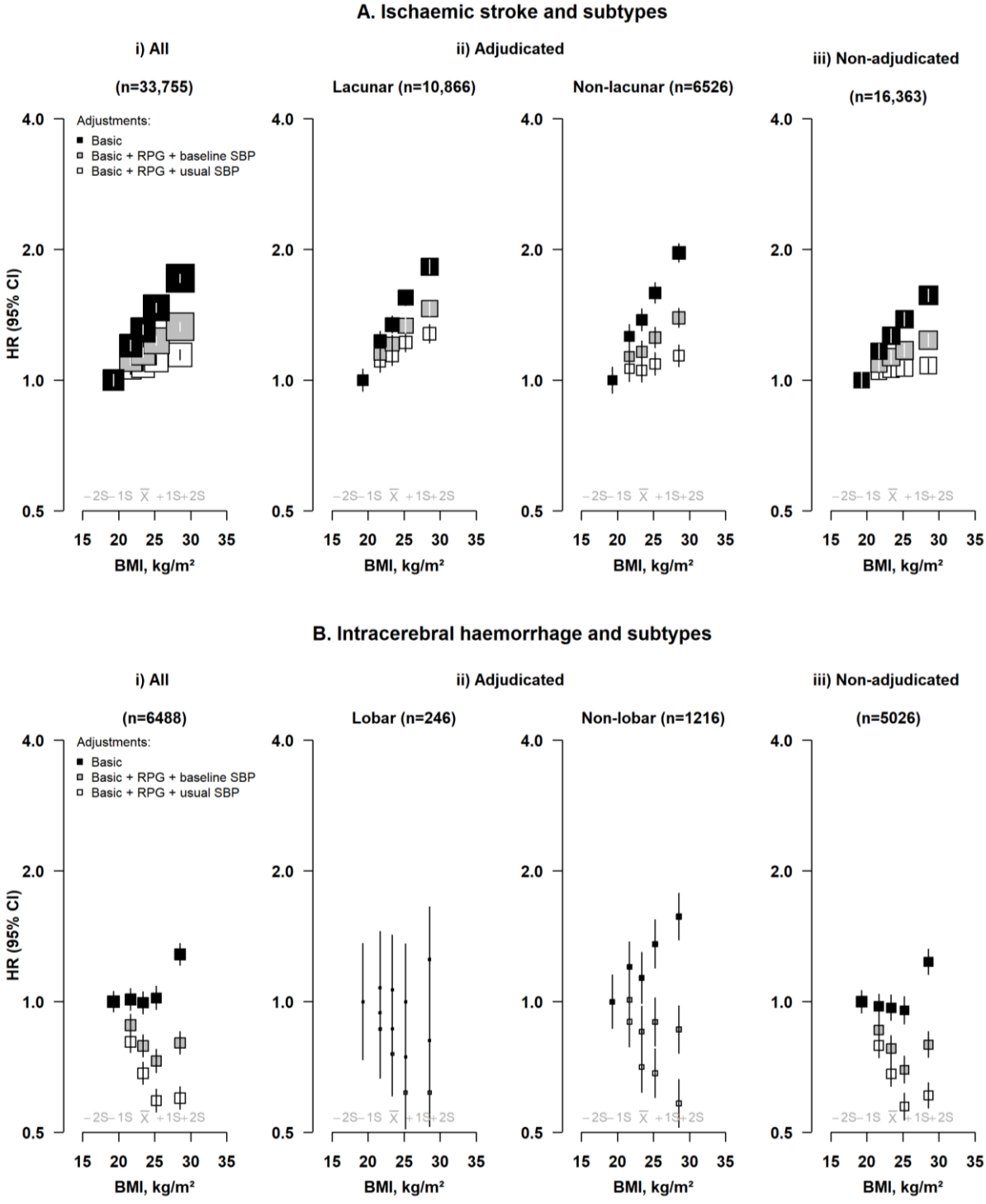


Figure 5.13. Association of baseline waist circumference with stroke types and subtypes

Conventions as Figure 5.12.
HR: hazard ratio, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference.

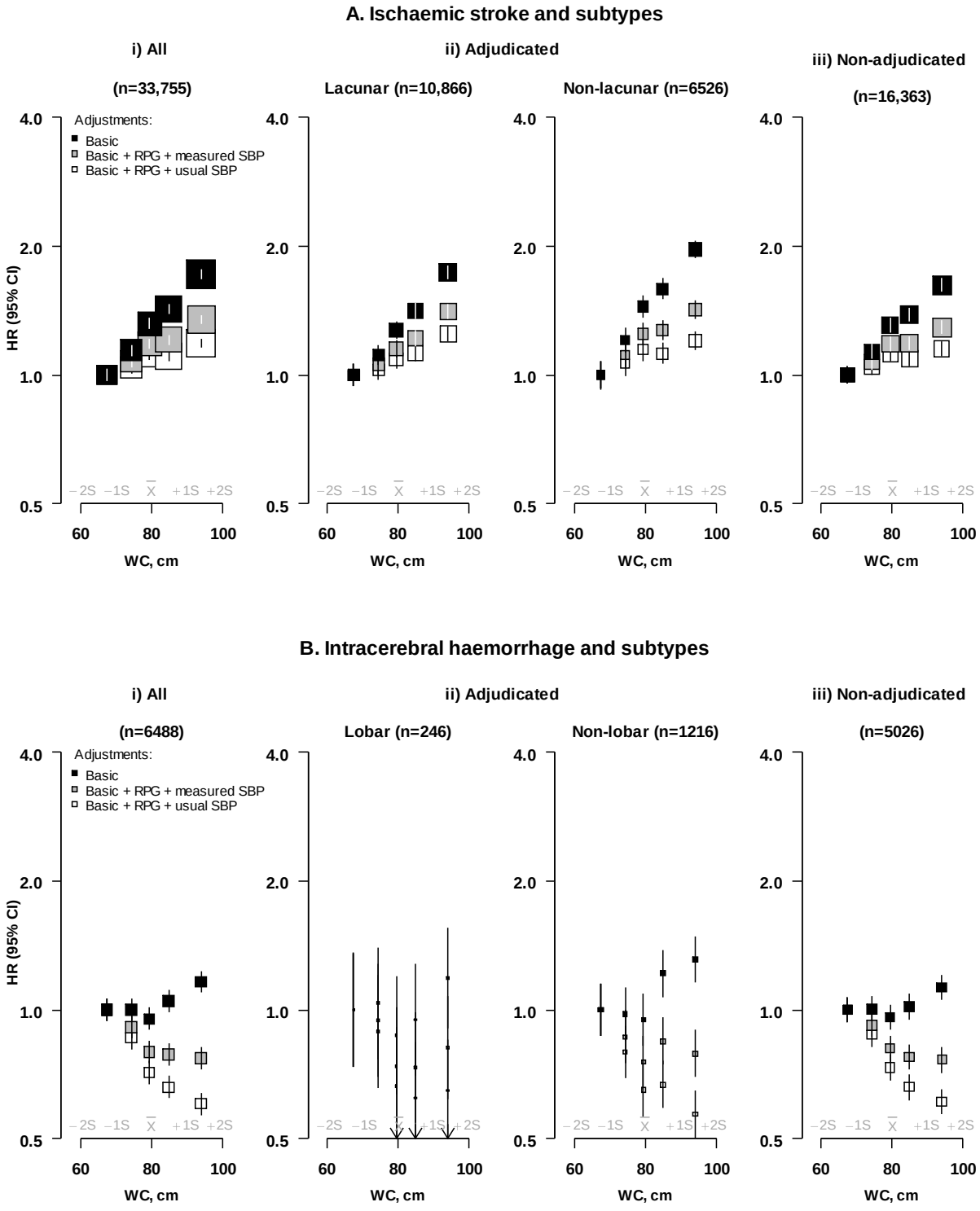


Figure 5.14. Association of baseline body fat percentage with stroke types and subtypes

Conventions as Figure 5.12.
HR: hazard ratio, RPG: random plasma glucose, SBP: systolic blood pressure.

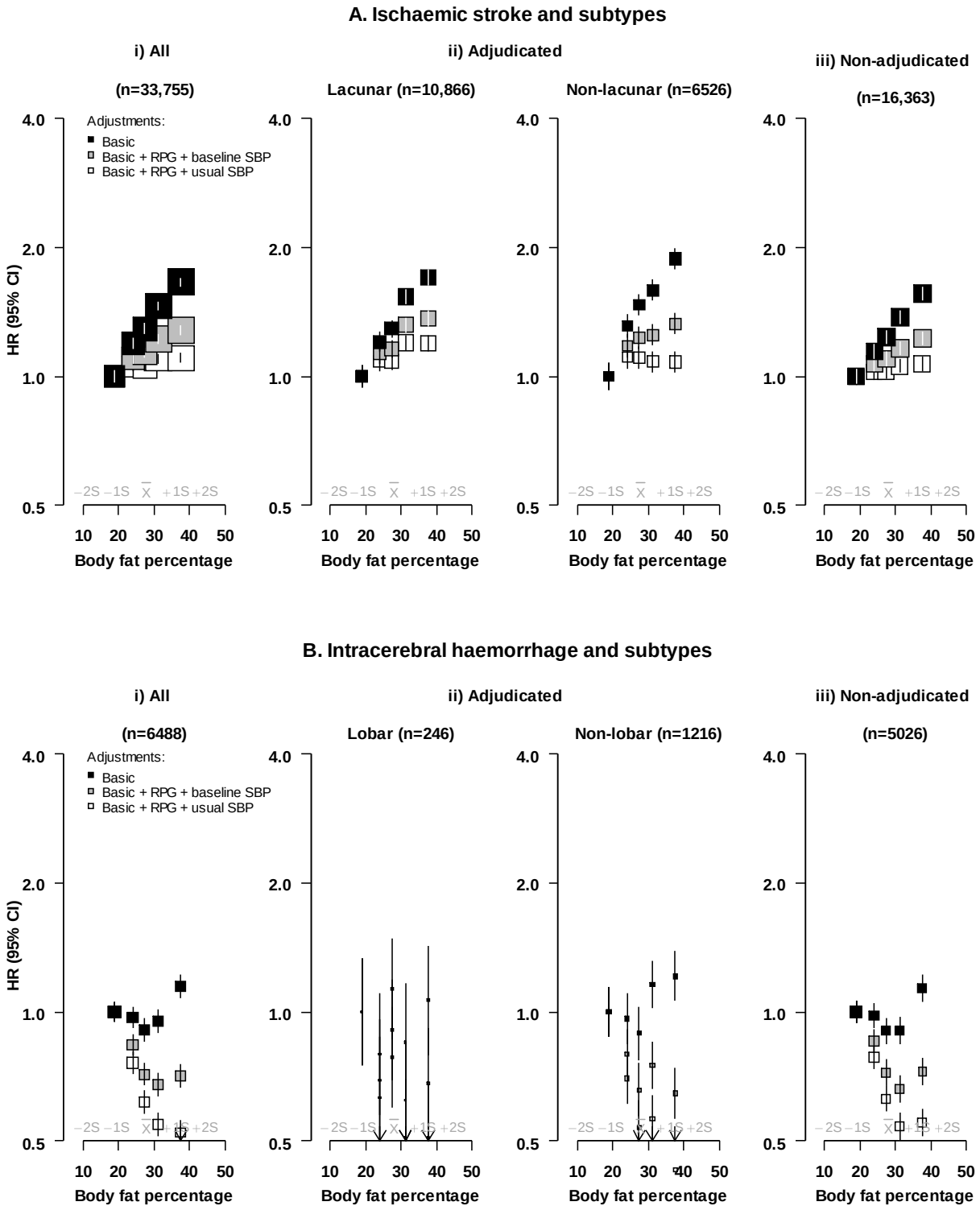


Figure 5.15. Association of baseline waist-to-hip ratio with stroke types and subtypes

Conventions as Figure 5.12.
HR: hazard ratio, RPG: random plasma glucose, SBP: systolic blood pressure, WHR: waist-to-hip ratio.

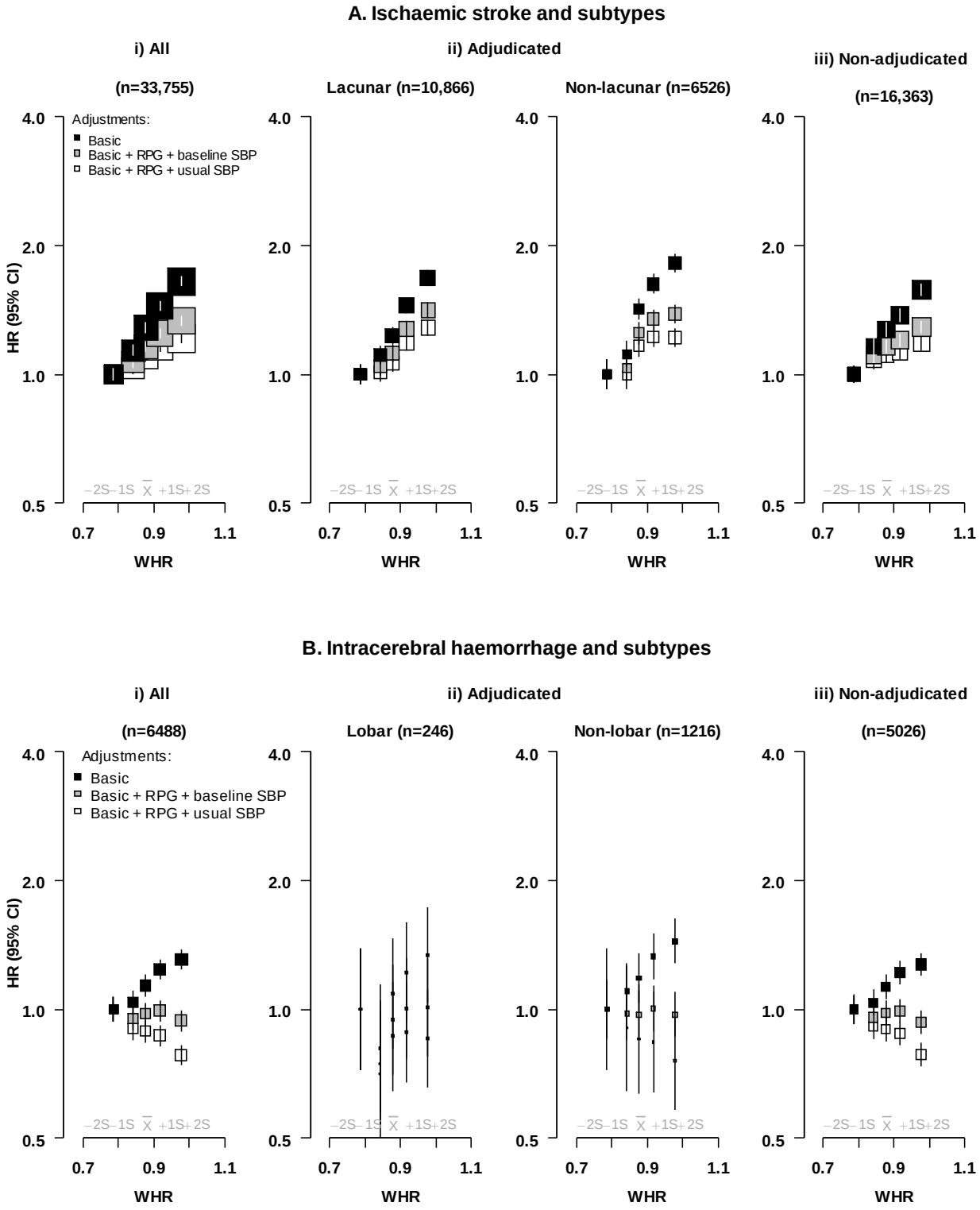


Figure 5.15. Association of baseline BMI with stroke types adjusted for different potential mediators among a subset of the CKB population (n=14,529)

The HRs for stroke types per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI. Basic adjustments were stratified by age-at-risk and sex, and adjusted for education, smoking, alcohol and physical activity. The Chi-squares are from the likelihood ratio test that compares the models with and without adjustments of the additional term (for measured values). The Chi-squares of the additional term have one degree of freedom for linear terms and four degrees of freedoms for categorical terms. Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs.

ALT: alanine amino transferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate amino transferase, BMI, body mass index, eGFR: estimated glomerular filtration rate, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, HR: hazard ratio, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein, RPG: random plasma glucose, SBP: systolic blood pressure.

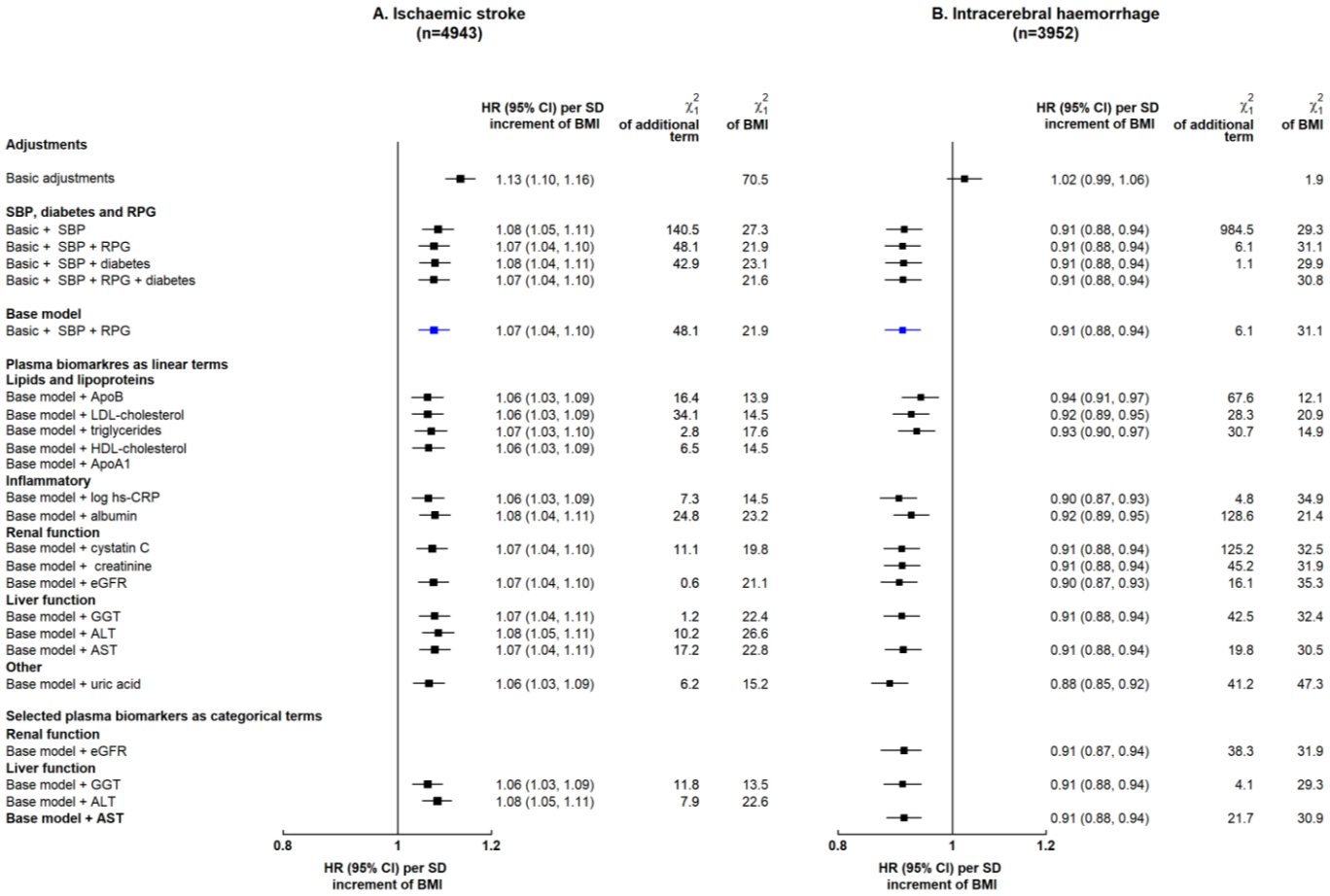


Figure 5.16. Association of baseline BMI with stroke types adjusted for selected potential mediators among a subset of the CKB population (n=14,529)

The left panel shows adjusted HRs for stroke types per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (basic adjustments). Then they are subsequently adjusted for usual SBP and RPG and major plasma biomarkers. HRs are plotted against mean baseline BMI in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The right panel shows HRs per 1 SD higher BMI, by subsequent adjustments for major plasma biomarkers. The Chi-squares are from the likelihood ratio test that compares the models with and without adjustments of the additional term (measured values). Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs.

ApoB: apolipoprotein B, AST: aspartate transferase, BMI: body mass index, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein, HR: hazard ratio, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose, SBP: systolic blood pressure.

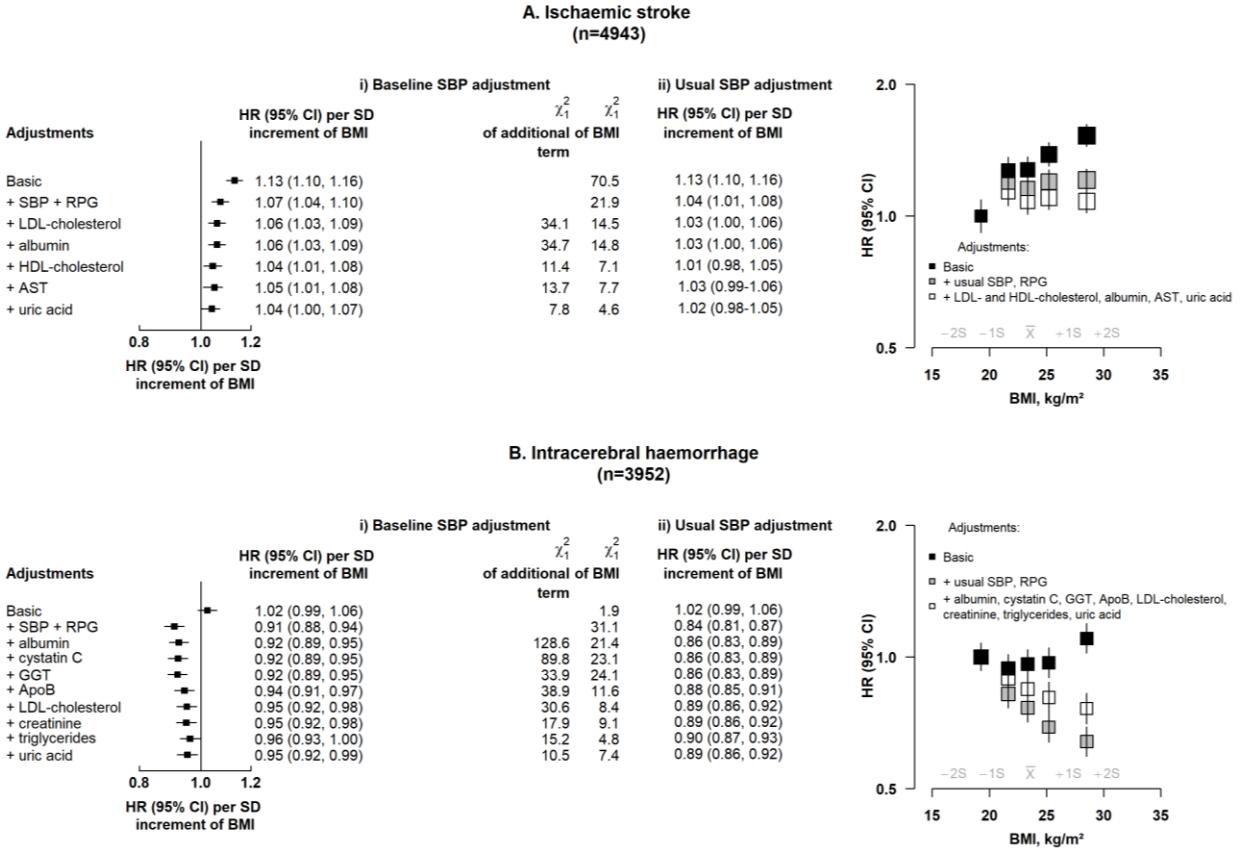
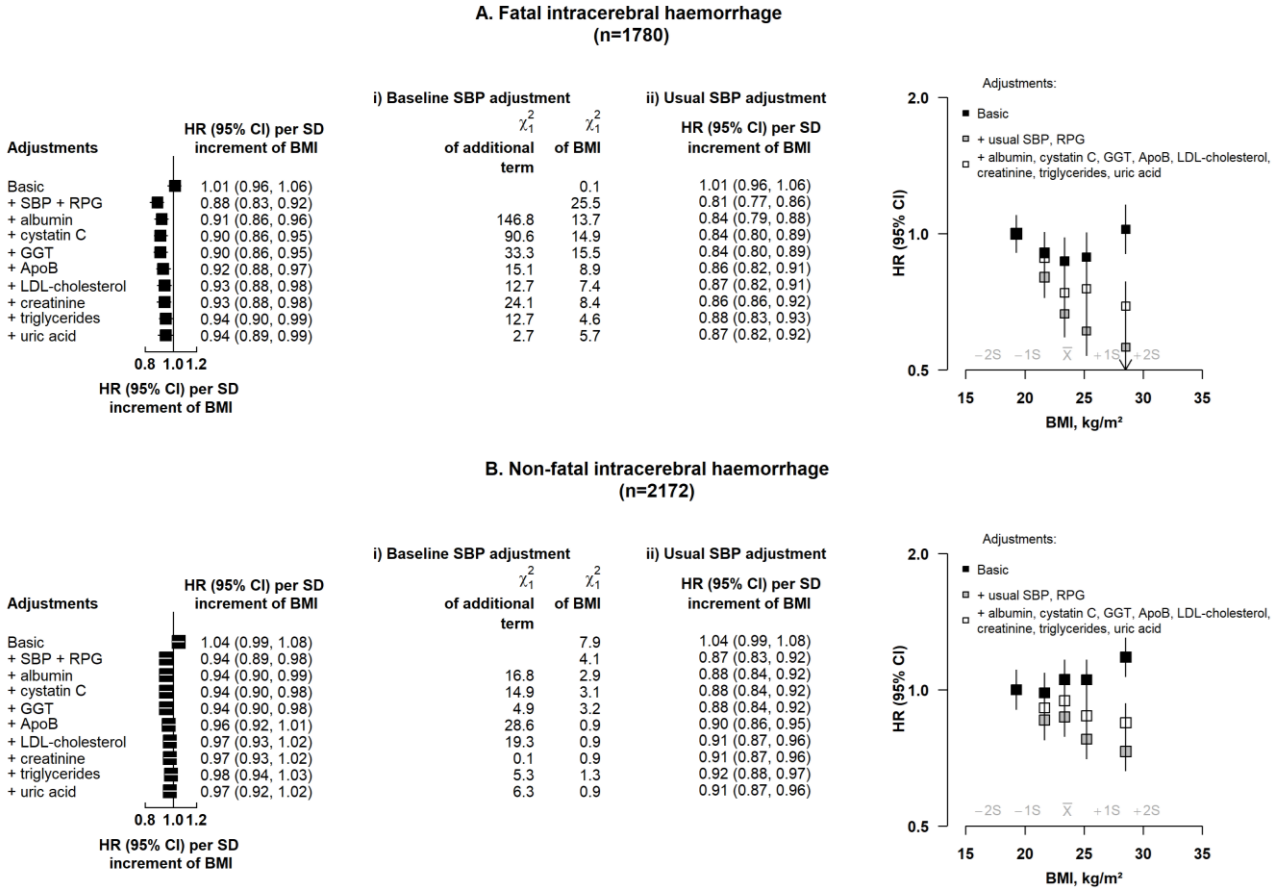


Figure 5.17. Association of baseline BMI with fatal and non-fatal intracerebral haemorrhage adjusted for selected potential mediators among a subset of the CKB population (n=14,529)

The left panel shows adjusted HRs for fatal and non-fatal ICH per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI, stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (basic adjustments). Then they are subsequently adjusted for usual SBP and RPG and major plasma biomarkers. HRs are plotted against mean baseline BMI in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The right panel shows HRs per 1 SD higher BMI, by subsequent adjustments for major plasma biomarkers. The Chi-squares are from the likelihood ratio test that compares the models with and without adjustments of the additional term (measured values). Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs.

ApoB: apolipoprotein B, BMI: body mass index, GGT: gamma glutamyl transferase, HR: hazard ratio, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose, SBP: systolic blood pressure.



Chapter 6. Adiposity and the risk of vascular and non-vascular mortality among individuals with and without diabetes

6.1 Background

Uncertainty remains not only regarding the relevance of adiposity to the incidence of certain major CVD, such as ICH (Chapter 5), but also the relevance of adiposity for vascular and non-vascular mortality. This applies particularly to individuals with existing chronic diseases, such as type 2 diabetes.[109,111,112,114,224-226] In the general population, studies have shown J-shaped[82,103,105-107] associations between BMI and all-cause mortality, with some observing that overweight or obese individuals have lower mortality risk than their "normal" weight counterparts.[104-107] However, it has been suggested that these observations may be due to uncontrolled biases, such as reverse causality, or residual confounding.[105,106] For example, previous general population studies demonstrated that the BMI levels associated with the lowest risk of mortality were shifted from the overweight/obese BMI range to the "normal" range after attempts to control for residual confounding and reverse causality.[105,106]

It is of interest to also understand the adiposity-mortality associations among individuals with pre-existing chronic conditions, particularly conditions caused by excess adiposity or resulting in weight changes, such as type 2 diabetes. Such understanding would help to inform appropriate disease management policies. As described in Section 2.2, the majority of previous large prospective studies among individuals with diabetes have reported U-shaped[109,112,114] or *reverse* J-shaped[111,115,116,225,226] associations between BMI and all-cause mortality, with the lowest risk seen at BMI levels between 25.0 and 40.0 kg/m^2. This has led to the

notion of a so-called “obesity paradox” in diabetes, whereby overweight/obese individuals with diabetes have lower mortality than their “normal” weight counterparts, despite the causal association between obesity and type 2 diabetes[67,68] and several major diseases, such as IHD.[227,228] However, it remains unclear whether this reflects a survival benefit of overweight/obesity following development of diabetes, or inadequate attempts to control for biases. For instance, studies among individuals with diabetes generally incompletely controlled for reverse causality or residual confounding.[109,111,114,116,224-226] In addition, previous studies focused only on BMI,[109,112,114-116] rather than other adiposity measures, or on all-cause,[109,115,116,226] rather than cause-specific, mortality. Furthermore, they did not examine the time course of death following disease onset, and few directly compared associations among individuals both with and without diabetes in the same population.

This chapter aims to investigate the association of a range of adiposity measures with total and cause-specific mortality among individuals both with and without diabetes using data from the CKB. The specific objectives of this chapter are to examine a) the association of adiposity with CVD, non-CVD and all-cause mortality; b) the association of BMI with CVD incidence and survival at different time points following disease onset; c) how these associations differ by baseline characteristics (e.g., age, sex, study area), and, among individuals with diabetes, by diabetes duration and treatment; d) the effect of smoking and prior diseases on these associations.

6.2 Methods

6.2.1 Study population

6.2.1.1 Summary of study design

The analyses included in this chapter are based on individuals in the ~0.5 million CKB cohort, which has been described in detail in Section 3.1.

6.2.1.2 Exclusions

Analyses were restricted to individuals without prior stroke/TIA (n=8884), IHD (n=15,472), cancer (n=2577), COPD (n=37,055) or tuberculosis (TB; n=7659), and those without missing adiposity measures (BMI and body fat percentage, n=240). Following these exclusions, 446,713 participants remained for inclusion in the current analyses.

6.2.2 Definition of prevalent diabetes

Prevalent diabetes was defined as having either self-reported or screen-detected diabetes at the time of the baseline survey. Self-reported diabetes refers to those who had a “yes” response to the question, “Has a doctor ever told you that you had diabetes?” Among individuals without self-reported diabetes, screen-detected diabetes was defined as having a RPG level ≥7.0 mmol/L with time since last food ≥8 hours, or ≥11.1 mmol/L with time since last food <8.0 hours, or a FPG level ≥7.0 mmol/L on subsequent testing.

6.2.3 Adiposity measures definitions

Anthropometric measurements were undertaken as described in Section 3.3. Analyses in this chapter focused on BMI, with other general and central adiposity measures (e.g., body fat percentage, fat body mass, lean body mass, WC and WHR) examined for comparison.

6.2.5 Outcome definitions

The main outcomes examined were all-cause mortality, CVD (ICD-10 code I00-I99) and non-CVD mortality, and their main components. For CVD mortality, the main components investigated included IHD, total stroke, IS and ICH, while for non-CVD mortality the main components examined included COPD, cancer, chronic kidney disease and diabetic ketoacidosis or coma (Table 6.1). For CVD, additional analyses examined fatal and non-fatal events separately. Fatal CVD was defined as death from any cause within 28 days following a first-ever CVD event, while non-fatal CVD was any first CVD event without death within 28 days.

6.2.4 Selection of confounders

Based on a priori knowledge of biological relationships, the following variables were identified as potential confounders in the association of adiposity with mortality: age, sex, study area, education,[172,205] smoking,[136,206] alcohol consumption[139,142,177] and physical activity.[179,180,207,208]

6.2.5 Statistical analyses

All analyses were performed separately for participants with and without diabetes at baseline. The mean values and prevalence of selected baseline characteristics were calculated across four BMI categories (cut-points: 18.5, 25.0 and 30.0 kg/m^2), adjusted, where appropriate, for age (5-year groups), sex and study area.

Cox proportional hazards models, with time since baseline to whichever came first out of death, loss to follow-up or end of the current follow-up cycle (January 2017) as the timescale, were used to estimate HRs for predefined mortality and disease outcomes by adiposity measures. The analyses were stratified by age-at-risk (5-year age groups), sex, and study area, and adjusted for education (no formal education, primary school, middle school, high school, college/university), smoking (never, occasional, ex-regular, current regular), alcohol intake (never, occasional intake, ex-regular, reduced intake, weekly intake) and physical activity (metabolic equivalent of task [MET] hours per day). Sex-specific quintiles were used as cut-offs to categorise adiposity measures into five groups, to enable direct comparisons of associations across different adiposity measures. The floating absolute risk method was used to estimate group-specific 95% CIs for each log HR to enable comparisons between any two categories (rather than just pairwise comparisons with the reference category).[181] The proportional hazards assumption was tested by examining the HRs for the first four and subsequent years of follow-up (and showed no strong evidence of departure).

The main analyses were repeated after excluding individuals who died during the first five years of follow-up and ever smokers. BMI-associated risks were compared

across strata of baseline characteristics, including sex, study area and age, separately in individuals with self-reported and screen-detected diabetes and, among individuals with self-reported diabetes, according to medication use and diabetes duration. Additional analyses investigated the association of BMI with fatal and non-fatal CVD, and cause-specific mortality. Sensitivity analyses further excluded individuals with poor self-rated health at baseline, other self-reported prior diseases at baseline (hypertension, cirrhosis/chronic hepatitis, chronic kidney disease), and diseases developed during follow-up (COPD, chronic kidney disease, chronic liver disease, gastrointestinal disease, cancer), in an attempt to control for reverse causality as comprehensively as possible. Additional analyses excluded individuals who developed diabetes during the follow-up period.

All statistical analyses were conducted in SAS version 9.4. Cox regression was conducted using a SAS macro previously developed within CTSU. All plots were produced using JASPER, an R package developed within CTSU, in R version 3.3.

6.3 Results

Among the 446,713 individuals without prior CVD, cancer, COPD or TB, 5.3% (n=23,842) had diabetes at baseline, with a similar prevalence of self-reported (n=11,995, 2.9%) and screen-detected (n=11,847, 2.7%) diabetes. Individuals with diabetes had higher mean (SD) BMI than those without diabetes (25.0 [3.4] vs 23.6 [3.1] kg/m^2 [p<0.0001]), and higher prevalence of overweight (BMI 25.0 to <30.0 kg/m^2) (40.8% vs 28.3% [p<0.0001]) and obesity (BMI ≥30.0 kg/m^2) (8.3% vs 3.7% [p<0.0001]). Participants with diabetes tended to be older and less physically active, and to have higher levels of central adiposity (assessed through WC and WHR) than

those without diabetes (p<0.0001 for all described comparisons) (Table 6.2). BMI was strongly positively associated with SBP. Individuals with lower BMI were more likely to be ever-regular smokers as compared to those with higher BMI levels, regardless of diabetes status. Among individuals without diabetes, there was a weak positive association between BMI and RPG levels, whereas the converse was true among those with diabetes. The prevalence of self-reported poor health was highest among underweight (BMI <18.5 kg/m^2) individuals both with and without diabetes.

During 4.4 million person-years of follow-up (mean, 9.2 years), 26,814 (6.0%) participants died at ages 35 to 79 years, including 3509 (14.7%) deaths among individuals with diabetes (Table 6.3). The proportion of total deaths due to CVD (9816 deaths, 36.6%) was slightly higher among individuals with diabetes than those without (41.0% vs 35.9%). The proportion of CVD deaths due to IHD was also slightly higher among those with diabetes as compared with individuals without diabetes (41.1% vs. 34.2%). In contrast, the proportion of CVD deaths due to any stroke was slightly lower among individuals with diabetes (41.3% vs. 47.5%). Overall, 109,005 first-ever CVD events were recorded during the same period of follow-up, including 9940 among those with diabetes and 99,065 among those without diabetes. Of the first-ever CVD events, 5557 were fatal (i.e., followed by death within 28 days of onset), including 718 among individuals with diabetes and 4839 among individuals without diabetes. A further 7994 first-ever CVD events were followed by death 28 days or more after onset (all-cause mortality post non-fatal CVD event), including 1424 among the population with diabetes and 6570 among those without diabetes.

Individuals with diabetes at baseline had significantly higher risk of developing CVD (HR 1.55 [95%CI 1.51-1.58]), and of dying from CVD (2.29 [2.17-2.43]), non-CVD causes (1.97, 1.88-2.07) or any cause (2.09 [2.02-2.17]). The diabetes-associated risks tended to be higher at lower BMI levels (Figure 6.1). Among those both with and without diabetes, there were strong positive and log-linear associations of BMI with risk of incident CVD events throughout the entire BMI range examined (approximately 18.0 to 30.0 kg/m^2), with the association moderately steeper among those without diabetes (HR 1.19 [95% CI 1.19-1.20] vs. 1.12 [1.10-1.14] per 1 SD [.1 kg/m^2 for men and 3.3 kg/m^2 for women] higher BMI; Figure 6.1). Largely similar associations were seen with cause-specific CVD mortality, but with a somewhat lower risk of ICH at low BMI, although the number of events was limited among individuals with diabetes (Figure 6.2).

For CVD mortality, the association with BMI was U-shaped, with lowest risk at BMI 22.5 to <25.0 kg/m^2 (Figure 6.1). Among those without diabetes, individuals with BMI <18.5 kg/m^2 and ≥25.0 kg/m^2 had HRs of 1.18 (95% CI 1.09-1.29) and 1.52 (1.38-1.68), respectively, compared with those with BMI 22.5 to <25.0 (reference group). Among individuals with diabetes, using the same reference group, the adjusted HR for those with BMI<18.5 kg/m^2 was 3.88 (95% CI 2.98-5.05), approximately two-fold higher than that associated with BMI 22.5 to <25.0 (2.20 [1.99-2.45]), while for those with BMI ≥25.0 kg/m^2 the HR was 2.85 (2.37-3.41).

For non-CVD mortality the association with BMI was a *reverse* J-shaped, regardless of diabetes status (Figure 6.1). Among individuals without diabetes, the lowest non-CVD mortality risk was seen at BMI 25.0 to <30.0 kg/m^2 (HR 0.94 [95% CI 0.91-0.97]), and the highest risk at BMI <18.5 kg/m^2 (1.75 [1.65-1.85]), compared with

individuals with BMI 22.5 to <25.0 (reference group). Among individuals with diabetes, underweight was associated with an approximately three-fold higher risk of non-CVD mortality compared to a BMI of 22.5 to 25.0 kg/m^2 (HR 5.88 [95% CI 4.94-7.01] vs. 1.93 [1.77-2.11]), with no excess non-CVD mortality risk among those who were overweight (1.68 [1.55-1.81]) or obese (1.79 [1.51-2.13]). A similar *reverse* J-shaped association was seen for COPD deaths, although the number of deaths was limited (Figure 6.3). In contrast, there appeared to be a weak inverse association of BMI with risk of cancer mortality (Figure 6.3). BMI was strongly inversely associated with the risk of mortality due to both diabetic ketoacidosis/coma and kidney disease among individuals with diabetes. Among those without diabetes, there were much less clear associations, probably at least partly due to the small number of deaths.

Since about two-thirds of all deaths were due to non-CVD mortality, the shape of the associations of BMI with all-cause mortality were similar to those with non-CVD mortality (Figure 6.1). The *reverse* J-shaped association with all-cause mortality was similar among individuals with and without diabetes, although the excess risk at low BMI was more extreme among individuals with diabetes. In that group, individuals with BMI levels 25.0 to <30.0 kg/m^2 had the lowest risk, whereas among those without diabetes the risk of all-cause mortality was similarly low among those with BMI levels of 22.5 to <25.0 kg/m^2 and 25.0 to <30.0 kg/m^2.

The associations of BMI with CVD and non-CVD mortality were similar among men and women (Figure D.1). However, the shapes of these association differed slightly between individuals living in urban and rural areas (Figure D.2). Among individuals with diabetes, the association between BMI and CVD mortality was *reverse* J-shaped in urban areas and U-shaped in rural areas. For non-CVD mortality, there

was a *reverse* J-shaped association with BMI in urban areas and a clearer inverse association in rural areas. The previously noted inverse association of BMI with non-CVD mortality at the lower end of the BMI range, was more extreme among younger individuals (<65 years) with diabetes compared with their older (≥65 years) counterparts (Figure 6.4).

The observed inverse associations of BMI with CVD and non-CVD mortality, and with fatal and non-fatal CVD at BMI <25.0 kg/m^2 remained largely unchanged when analyses were restricted to never smokers, or after excluding the first 5 years of follow-up. The only exception to this was some attenuation of the excess risk of non-CVD mortality among underweight individuals with diabetes (HR reduced from 5.88 [95% CI 4.94-7.01] to 3.69 [2.71-5.03]; Figures 6.5- 6.7) after excluding the first five years of follow-up. Further exclusion of participants with poor self-rated health at baseline, slightly attenuated the excess risk of both CVD and non-CVD mortality at low BMI, among individuals with diabetes (Table D.1 and D.2). Additional exclusions of individuals with prior self-reported doctor-diagnosed diseases at baseline (hypertension, chronic kidney disease and chronic liver diseases), with poor self-rated health at baseline, or who were hospitalised for major chronic diseases (COPD, chronic kidney disease, chronic liver disease, cancer) during follow-up, did not materially alter the associations (Figure 6.8). Moreover, exclusion of individuals who developed diabetes during follow-up also did not change the associations (Figure 6.9). Additional adjustment for baseline SBP attenuated the associations of BMI with CVD (HR from 2.85 to 1.12) and non-CVD (HR from 1.79 to 1.70) mortality at BMI levels >30.0 kg/m^2 among individuals with diabetes (Figure D.3). However, after this additional adjustment, the mortality risks from CVD and non-CVD became more extreme among underweight individuals with diabetes (HR increased from 3.88

to 4.12 and from 5.88 to 6.01, respectively). The associations between BMI and CVD, non-CVD and all-cause mortality remained after additional adjustments for baseline RPG, regardless diabetes status (Figure D.4). The shape of the associations of BMI with fatal and non-fatal CVD were similar among individuals with self-reported and screen-detected diabetes, but with slightly less extreme excess fatal CVD risk at low BMI among those with screen-detected diabetes (Figure 6.10). Among those with self-reported diabetes, the associations of BMI with mortality risks were similar across subgroups defined by diabetes medication use (taking insulin, taking oral hypoglycaemic agents or not taking medications) and by diabetes duration (Figures D.5 and D.6). However, the numbers of deaths in these subgroups were small.

Among individuals with diabetes, there was a strong log-linear positive association of WC (HR 1.15 [95% CI 1.13-1.18] per 1 SD (9.62) higher) and WHR (1.12 [1.10-1.14] per 1 SD (0.07) higher) with risk of incident CVD (Figure 6.11), similar to the association of BMI (1.12 [1.10-1.14] per 1 SD (3.2) higher; Figure 6.1). The shapes of the associations of adiposity measures other than BMI (WC, WHR, body fat percentage, lean body mass and fat body mass) with fatal CVD and all-cause mortality post non-fatal CVD event tended to be flatter than those of BMI, and the excess risk at low adiposity levels appeared less extreme (Figures 6.1, 6.11 and 6.12). Among individuals without diabetes, there were no clear associations of central adiposity measures (WC and WHR) with the risks of fatal CVD and all-cause mortality post non-fatal CVD event, in contrast with the U-shaped association of BMI.

6.4 Discussion

In this study, diabetes was strongly positively associated with mortality risk, with two-fold higher risk as compared with those without diabetes. There were U- and *reverse* J-shaped associations between BMI and CVD and non-CVD mortality, respectively, and these associations were generally shallower among those without diabetes. Regardless of diabetes status, individuals with BMI levels between 22.5 to <25.0 kg/m^2 and 25.0 to <30.0 kg/m^2 had the lowest CVD and non-CVD mortality risks, respectively. The *reverse* J-shaped association of adiposity with mortality persisted after extensive attempts to control for reverse causality and confounding. There were contrasting relationships of BMI with incident CVD events (log-linear) compared with fatal CVD and mortality post non-fatal CVD events (*reverse* J-shaped associations with a strong log-linear inverse association at BMI <25 kg/m^2).

6.4.1 Associations among individuals without diabetes

In CKB, among individuals without diabetes there was a U-shaped association between BMI and CVD mortality, with the lowest mortality risk at BMI 22.5 to <25.0 kg/m^2. In contrast, there were *reverse* J-shaped associations between BMI and both all-cause and non-CVD mortality, with the lowest risk at BMI levels 22.5 to <30.0 kg/m^2 and 25.0 to <30.0 kg/m^2, respectively. Many prospective studies or meta-analyses of such studies have previously reported on the associations of BMI with all-cause mortality, and, in general, have shown an approximately J-shaped,[82,102-107] associations. However, the BMI levels associated with the lowest mortality risk varied across different studies and populations, as well as with differing degrees of adjustment for potential confounders and for reverse causality. A 2013 meta-analysis

of 97 studies, including 2.88 million general population participants, observed that overweight individuals had lower mortality risk than their “normal” weight counterparts (HR 0.94 [95% CI 0.91-0.96] vs. 1.00), although this study did not attempt to control for biases. Those findings were reproduced in a large individual participant data meta-analysis, including 239 studies and 10.6 million participants from four continents (Asia, Australia and New Zealand, Europe and North America); when examining the association in the full study population, the lowest risk of mortality was found to be at BMI levels of 25.0 to <35.0 kg/m^2. However, after restricting analyses to never-smokers, and excluding individuals with pre-existing diseases (CVD, cancer and respiratory disease) and the first five years of follow-up, there was a positive association of BMI with risk of mortality at BMI levels >22.5 kg/m^2. This suggests that the insufficient attempts to control for reverse causality in the 2013 meta-analysis may have led to misleading findings. Likewise, a prospective study from Chennai in India (~0.5 million individuals and ~30,000 deaths) reported that the lowest risk of all-cause mortality was at lower BMI levels after restricting the analysis to never smokers (lowest mortality risk shifted from BMI 25.0 to <30.0 kg/m^2 to 22.5 to <25.0 kg/m^2).[105]

In contrast with these findings, a prospective study of ~220,000 Chinese men (~17,800 deaths) showed the lowest risk of all-cause mortality was at BMI 22.5 to <25.0 kg/m^2 among both never- and ever-smokers. In these findings and in the findings included in this thesis, the BMI levels associated with the lowest risk of mortality did not change after various attempts to control for residual confounding and reverse causality (excluding individuals who developed major chronic diseases during follow-up, excluding the first few years of follow-up and restricting the analyses to never smokers). The inconsistent findings between studies might reflect

differing distributions of diseases in the populations concerned, as the associations with all-cause mortality will be strongly influenced by the dominant causes of death in individual populations. Indeed, in the presented analyses, the *reverse* J-shaped association between BMI and all-cause mortality reflected the association of BMI with non-CVD mortality, given that about two-thirds of all deaths were attributed to non-CVD causes. Only few studies investigated the association of BMI with cause-specific mortality, including the Prospective Studies Collaboration (PSC) individual participant data meta-analysis of 57 prospective studies, involving ~900,000 adults from predominantly Western populations. It found a J-shaped association between BMI and all-cause mortality (~72,700 deaths), with an inverse association at BMI <22.5 kg/m^2, which was mainly due to strong inverse associations with respiratory diseases and lung cancer (~8,500 deaths) which were much stronger among smokers than non-smokers.

In addition, in this thesis there was a U-shaped association between BMI and CVD mortality, with the lowest risk of mortality at BMI 22.5 to <25.0 kg/m^2. Consistent with these findings, the previously described study from Chennai in India (~12,500 deaths)[105] and the study of ~220,000 Chinese men (~6,700 deaths) reported U- and J-shaped associations between BMI and CVD mortality, respectively, with an apparently optimal BMI of 22.5 to <25.0 kg/m^2. The presented CKB analyses also investigated the association of BMI with cause-specific CVD mortality outcomes, and found a flat association with stroke mortality at BMI <25.0 kg/m^2 (mainly driven by the association with ICH mortality which accounted for approximately three-quarters of stroke deaths) and a shallow U-shaped association with IHD mortality. The PSC reported approximately similar findings; there was no clear positive association with stroke mortality (~6000 deaths) and IHD mortality (~18,000 deaths) at the lower end

of the BMI range, but positive associations at BMI levels ≥22 kg/m^2. Although the PSC reported similar associations between BMI and IHD mortality in different populations, these were largely of European ancestry (e.g., European, Israeli, US and Australian), and they were not able to investigate this association separately in East Asian populations due to the small number of deaths in the relevant constituent studies.

6.4.2 Associations among individuals with diabetes

Among individuals with diabetes in CKB, there were U-shaped and *reverse* J-shaped associations between BMI and CVD mortality and all-cause mortality, respectively. The lowest risk of CVD mortality was at BMI levels of 22.5 to <25.0 kg/m^2, whereas for all-cause mortality it was at higher BMI levels (25.0 to <30.0 kg/m^2). Many large prospective studies, or meta-analyses comprising such studies, have examined the associations of adiposity with mortality among people with diabetes. These have generally reported *reverse* J-shaped,[109-112,115,118] or U-shaped[114,119] associations. Consistent with these shapes, underweight individuals in the current and most previous studies generally experienced greater excess mortality risk than individuals with BMI in the "normal" range.[109-112,115,118] However, the adiposity levels associated with the lowest mortality risk varied greatly between studies. Some studies found that "normal" weight individuals had higher mortality risk than their overweight[109,110,114,115,118] or obese[111] counterparts, leading to the notion of the so-called "obesity paradox". For instance, in a meta-analysis of 16 prospective studies of ~445,000 participants, predominantly from Western populations, there were U-shaped associations between BMI and all-cause and CVD mortality, broadly similar to the shapes observed in CKB, particularly for CVD mortality.[114] The BMI levels

(28.0 to <30.0 kg/m^2) associated with the lowest risk of all-cause and CVD mortality in that meta-analysis were slightly higher than in CKB (22.5 to <25.0 and 22.5 to <30.0 kg/m^2, respectively). In an attempt to control for biases, the study included additional analyses excluding individuals with prior disease and the first few years of follow-up, but the findings remained unchanged, consistent with CKB. A recent report, based on ~24,000 UKB participants with self-reported diabetes, showed a *reverse* J-shaped association between BMI and the risk of all-cause mortality (1723 deaths, mean follow-up 7.8 years), similar to CKB. Consistent with the predominantly Western population study meta-analysis, the UKB report also found that the BMI levels (women 34.1 kg/m^2, men 31.7 kg/m^2) associated with the lowest risk of all-cause mortality were higher as compared to CKB.[111]

Previous East Asian population studies consistently reported *reverse* J-shaped[112,113,115,118] or U- shaped[114] associations of BMI with all-cause mortality, but the range of BMI levels associated with the lowest mortality risk varied. A meta-analysis of two prospective studies in East Asian populations, involving 92,697 participants with diabetes, found a U-shaped association of BMI with all-cause mortality (27,191 deaths), with the lowest risk at a BMI within the “normal” range (22.0 to <23.0 kg/m^2),[114] similar to findings in CKB. While other East Asian studies consistently reported *reverse* J-shaped associations of BMI with all-cause mortality, the lowest mortality risk in these studies was, in contrast, among individuals with BMI levels within the overweight range.[112,113,115,118] For instance, the prospective KOMERIT study, based on routine health service data from Korea, reported the lowest all-cause mortality risk (~130,000 deaths during 10.5 years of follow-up) at BMI levels within the overweight range, among individuals with both newly-diagnosed (25.0 to <29.5 kg/m^2) and previously-diagnosed (26.5 to <29.5 kg/m^2)

diabetes.[115] As in CKB, that study also reported that the high risk of mortality at low BMI levels was slightly more pronounced among younger individuals, for reasons that were not entirely clear. It is possible, however, that individuals with onset of type 2 diabetes at a younger age may be more susceptible to complications of the disease (independent of diabetes duration) and, in turn, have a higher mortality risk, compared to those who develop diabetes at older ages.

Evidence derived from previous Western[111] and East Asian[112,113,118] population studies on the association of adiposity with CVD-mortality is limited, with frequently inadequate attempts to control for biases. These studies consistently reported J-shaped[111,118] or *reverse* J-shaped[112,113] associations of BMI with CVD mortality, largely consistent with association observed in the presented CKB analyses. However, most of these studies reported the lowest risk of CVD mortality at higher BMI levels (within the overweight range)[111,112,118] as compared to CKB. For instance, a study from Shanghai of 52,763 Chinese adults with diabetes showed that the lowest all-cause (4777 deaths during 6.0 years of follow-up) and CVD (1848 deaths) mortality risks were at BMI levels within the overweight range (25.0 to <30.0 kg/m^2).[118] However, this Shanghai study adjusted for, rather than excluded, prior diseases (e.g., cancer and hypertension) in the analyses, so the control for reverse causality may be more likely to be incomplete.

Differences between studies in the shape and the apparent optimal BMI may also reflect differences in study design, different balances of causal and reverse causal influences, variation in the timing of exposure measurement, or statistical considerations. For instance, previous studies measured BMI at different time points relative to diagnosis of diabetes, including before, at the time of[229] or after[111,115,225,230]

diagnosis. This could lead to misclassification, since diabetes treatments (or lack of treatment) can influence weight changes. However, in CKB, comparisons of the associations in self-reported diabetes (BMI measured after diagnosis) and screen-detected diabetes (BMI measured at the time of detection of diabetes), and investigations of the effects of diabetes treatment and duration among those with self-reported diabetes, showed little evidence of such biases. The association of adiposity with mortality during the first few years of follow-up might be more greatly affected by reverse causality, since deaths occurring during this time might be related to undiagnosed disease at the time of recruitment into the study, which may also have influenced adiposity levels. Indeed, a study among individuals with diabetes reported that the BMI levels associated with lowest mortality risk shifted to lower levels after excluding the first four years of follow-up,[231] whereas studies that excluded fewer years of initial follow-up (one to three years) largely reported no changes in the findings.[108,110,111,113-116,118,119] In addition, the majority of studies among individuals with diabetes[109,111,112,114-116] reported that the apparent obesity paradox was less evident in analyses excluding current or previous smokers, although a few studies reported that this did not change their findings.[224-226] In the present study, such attempts to control for reverse causality and confounding had little effect. Additional attempts to account for reverse causality by excluding individuals who developed major chronic diseases, including COPD, CKD, chronic liver disease and diabetes, during follow-up, also had little effect on the findings. Despite these extensive measures, residual biases and/or confounding may persist that could account for the excess mortality risk at low BMI in CKB e.g., due to incomplete capture of relevant chronic diseases or frailty. Inconsistency in the findings might also reflect variation in the level of adjustment for potential

confounders in studies, with the majority of previous studies adjusting for probable mediators of the association of BMI with mortality (e.g., pre-existing diseases, such as CVD, or blood pressure).[111,113,116,118] For example, in the presented CKB analyses, additional adjustments for baseline SBP attenuated the association of BMI with mortality at higher BMI levels, whereas at the lower end of the BMI range the association became slightly stronger.

Only a few studies have compared the association of BMI with mortality among individuals with and without diabetes.[111,115] Consistent with CKB, these studies reported that the excess risk at low BMI was more extreme among individuals with diabetes.[111,115] In CKB BMI levels associated with the lowest mortality risk were similar in individuals with and without diabetes. However, previous studies have found that the lowest mortality risk was at higher BMI levels among individuals with diabetes.[111,115] Although most prior studies have focused on either the general population or on individuals with diabetes, rather than both, comparisons of the findings of such studies might highlight differences in the BMI levels associated with the lowest mortality risk between individuals with and without diabetes. Western population studies both among the general population[82,102,104,106,107] and among individuals with diabetes,[108,109,111,114,117,119] have consistently reported that the BMI levels associated with the lowest risk of mortality varied greatly from “normal” to obese BMI ranges. Although, a number of these Western population studies (both in general population[106] or among individuals with diabetes[108,111]) reported that the BMI levels associated with the lowest risk of mortality were shifted from overweight/obese BMI range to “normal” range, after attempts to control for reverse causality and/or residual confounding. Asian population studies among individuals with diabetes[112,113,115,118] found the lowest mortality risk at higher BMI levels as compared

to general population Asian studies.[103,105] In contrast, the findings included in this thesis and from the previously described meta-analysis of two studies of 92,697 East Asian participants with diabetes,[114] reported that the lowest mortality risk was at BMI levels within the “normal” range, consistent with the findings from large Asian general population studies.[103,105] The inconsistency in the BMI levels associated with the lowest mortality risk between studies in both general population and among diabetes might reflect differences in statistical considerations including attempts to control for biases.

Collider bias may have influenced the described association of adiposity with mortality among individuals with diabetes.[232,233] Since the risk of developing diabetes is higher among individuals with excess adiposity (exposure)[67,68] and is influenced by risk factors for both adiposity and mortality (outcome) (e.g., smoking),[206] conditioning analyses examining the association of adiposity with mortality on diabetes might introduce selection biases.[234] This might also explain the obesity paradox observed in many studies among individuals with diabetes. Also, the characteristics of individuals who develop diabetes in the absence of overweight or obesity may differ from those who develop diabetes in the presence of overweight or obesity (e.g., varying levels of genetic predisposition, different diabetes types including possible secondary diabetes). As such, the excess mortality risk at low BMI might reflect the effect of risk factors for developing diabetes on mortality risk, rather than the effect of low adiposity levels per se.

To my knowledge, no previous studies have directly compared the association of BMI with CVD incidence, fatal CVD and mortality post non-fatal CVD events. In the present study, there was a positive log-linear association of BMI with CVD incidence

but a *reverse* J-shaped association with fatal CVD and with mortality post non-fatal CVD event, suggesting a possible adverse impact of low BMI on survival. Similarly, the low risk of CVD incidence at low BMI might reflect the protective effect of low blood pressure on CVD, since blood pressure is a major mediator on the association of adiposity with CVD, as discussed in Chapter 5. Despite extensive attempts to avoid reverse causality resulting from prior diseases, it may still be the case that low BMI is such an overriding indicator of poor or deteriorating health that this reverse causal effect remains. Further investigations of the association of adiposity with mortality in large populations including a relatively high proportion of lean individuals are needed to better understand this. It is possible that the excess mortality risk associated with low BMI reflects low lean, rather than low fat, body mass and associated frailty, with adverse impacts on survival following CVD events. This is supported by analyses using data from the CKB second resurvey (~25,000 individuals), which showed an inverse association between hand grip strength and all-cause mortality (Table D.3), since low hand grip strength could serve as a proxy for degree of frailty.[235].

Few previous studies have simultaneously investigated the association of multiple adiposity measures with mortality among individuals with diabetes.[111,236] In a study based on the UKB, there were approximately U-shaped associations of WC, WHR and body fat percentage with all-cause mortality but a *reverse* J-shaped association of BMI with all-cause mortality, among those with or without diabetes.[111] However, in CKB the associations of the same adiposity measures (WC, WHR and body fat percentage) with all-cause and CVD mortality were similar but more flat to the association of BMI. In CKB, bio-impedance was used to estimate lean and fat body mass; shallow *reverse* J-shaped associations of both measures with all-cause

mortality were observed, suggesting that both low lean and low fat body mass are associated with highest mortality risk. Further investigation, using accurate and direct measures of lean and fat mass (e.g., imaging), may help to further elucidate these observed associations.

6.4.3 Strengths and limitations

This study has several strengths, including the large study population, availability of information on a uniquely wide-range of reliably-measured adiposity measures, completeness of follow-up and availability of data on a wide range of cause-specific mortality endpoints. The relatively lean study population, compared with Western studies, enabled robust investigation of relationships at the lower end of the adiposity range. Moreover, the associations of adiposity with mortality were examined among individuals both with and without diabetes and, in the former group, separately among individuals with self-reported and screen-detected diabetes. Among those with diabetes, the potential influences of diabetes treatment, duration and management were also assessed. In addition, the effect of diabetes developed during follow-up was examined by excluding those individuals from the analysis. As such, the presented analyses represent one of the most comprehensive and detailed investigations of these associations among individuals with diabetes. Finally, comprehensive attempts were made to control for reverse causality, and to investigate the effects of additional adjustments for potential metabolic mediators, such as SBP and RPG, although these had little impact on the association of BMI with mortality.

However, the study has limitations. Firstly, it was not possible to differentiate between type 1 and type 2 diabetes. However, based on age at diagnosis (<30 years) and insulin use, <1% of individuals with diabetes were likely to have had type 1 diabetes. Therefore, the presented findings might not be relevant to individuals with type 1 diabetes. In addition, defining screen-detected diabetes predominantly on the basis of RPG levels would be expected to result in misclassification, likely failing to identify some cases of diabetes.[237] However, this would not be expected to substantially alter the observed findings. Furthermore, despite the extensive attempts to control for reverse causality, some may remain. For example, current follow-up feasibly permits exclusion only of the first 5 years of follow-up, which may be inadequate to reliably avoid reverse causality, and exclusion of individuals with potentially relevant diseases is likely incomplete. For example, dementia is associated with higher mortality risk, however it cannot be fully captured during follow-up in CKB, particularly during the preclinical phase in which individuals may start to lose weight. This may contribute to higher mortality risk at lower adiposity levels, and apparent protective effects of higher levels of adiposity. Finally, the analyses were based on single adiposity measurements and do not account for changes in weight during follow-up. However, based on repeat measurements among a subset of ~17,000 participants, on average 3.6 years after baseline, the self-correlation coefficient of BMI was 0.93, suggesting the impact of this on estimated risks would be limited. Furthermore, accounting for changes in weight during follow-up could increase susceptibility to reverse causality.

6.5 Conclusion

In conclusion, in this large prospective study of Chinese adults with relatively low mean levels of adiposity, the risk of incident CVD, particularly non-fatal CVD, was higher with higher BMI, from a level of approximately 18.5 kg/m^2 among individuals with or without diabetes. For CVD and non-CVD mortality, there were strong, apparently independent, U- and *reverse* J-shaped associations, respectively. Among individuals with and without diabetes, BMI levels of 22.5 to <25.0 kg/m^2 and 22.5 to <30.0 kg/m^2 were associated with the lowest CVD and non-CVD mortality, respectively, while those with a BMI of 22.5 to <25.0 kg/m^2 appeared to have the lowest mortality risk following any incident CVD event. The high risk of mortality at high BMI levels, and the contrasting associations between fatal and non-fatal CVD at low BMI, suggest that maintenance of a BMI within the range of 22.5 to <25.0 kg/m^2 (i.e., the upper end of the “normal weight” range) is an important indicator of health among people both with and without diabetes.

Table 6.1. ICD-10 codes for causes of death

Cause of death	ICD-10 codes
CVD	I00-I99
IHD	I20-I25
Stroke	I60-I61, I63-I64
IS	I63
ICH	I61
Non-CVD	
COPD	I26-I27, J41-J44
Cancer	C00-C97
Diabetic ketoacidosis or coma	E10.0, E11.0, E12.0,E13.0, E14.0, E10.1, E11.1, E12.1,E13.1, E14.1, E10.3, E11.3, E12.3,E13.3, E14.3, E10.4, E11.4, E12.4,E13.4, E14.4, E10.6, E11.6, E12.6, E13.6, E14.6, E10.7, E11.7, E12.7,E13.7, E14.7, E10.8, E11.8, E12.8,E13.8, E14.8, E10.9, E11.9, E12.9, E13.9, E14.9, E10-E14 (without any decimal)
Chronic kidney disease	N02-N03, N07, N11, N18

COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, ICH: intracerebral haemorrhage, IHD: ischaemic heart disease, IS: ischaemic stroke

Table 6.2. Baseline characteristics by BMI among individuals with and without diabetes at baseline

	No diabetes, BMI (kg/m^2)					Diabetes, BMI (kg/m^2)				
Characteristics[a]	**<18.5**	**18.5 to <25.0**	**25.0 to <30.0**	**≥30.0**	**All**	**<18.5**	**18.5 to <25.0**	**25.0 to <30.0**	**≥30.0**	**All**
No. of participants (%)	16,947 (4.0)	270,403 (63.9)	119,736 (28.3)	15,785 (3.7)	422,871	527 (2.2)	11,613 (48.7)	9,719 (40.8)	1,983 (8.3)	23,842
Age and socioeconomic factors										
Mean age (SD), years	53.0 (14.2)	50.2 (10.3)	50.8 (10.0)	50.6 (11.9)	50.6 (10.2)	58.2 (14.8)	57.4 (9.7)	56.6 (9.4)	55.2 (11.0)	57.0 (9.4)
Women, %	61.7	58.7	60.9	71.2	59.8	59.0	60.5	61.7	70.2	61.9
Urban, %	32.8	39.1	50.4	55.8	42.6	32.7	54.2	64.2	69.5	59.0
≥6 years of education, %	50.1	51.0	50.9	49.0	50.6	48.3	47.9	46.4	44.7	46.8
Lifestyle factors										
Men ever-regular smoker[b], %	79.4	75.3	70.7	71.0	74.2	79.6	72.2	69.6	72.6	71.4
Women ever-regular smoker[b], %	4.3	2.6	2.3	2.8	2.6	9.7	4.1	4.1	5.1	4.2
Men ever-regular alcohol drinker[c], %	32.1	37.3	37.2	35.9	37.2	38.6	37.9	37.1	39.8	37.6
Women ever-regular alcohol drinker[c], %	2.4	2.4	2.5	2.1	2.4	3.5	2.0	1.8	1.8	1.9
Mean physical activity (SD), MET-h/day	21.9 (15.8)	22.5 (11.9)	21.4 (12.4)	20.1 (15.1)	22.1 (11.9)	15.7 (11.2)	16.7 (10.4)	16.1 (10.3)	15.7 (11.6)	16.4 (10.1)
Adiposity measures, mean (SD)										
BMI, kg/m^2	17.6 (0.9)	22.1 (1.7)	26.8 (1.4)	31.7 (2.1)	23.6 (3.1)	17.5 (0.7)	22.6 (1.6)	27.0 (1.4)	32.0 (2.1)	25.0 (3.4)
Weight, kg	44.5 (4.9)	55.9 (5.8)	67.8 (6.0)	80.3 (9.0)	59.7 (9.0)	43.5 (3.8)	56.7 (5.9)	68.0 (5.8)	80.9 (8.0)	63.0 (9.7)
Standing height, cm	158.8 (7.7)	158.7 (5.5)	158.9 (5.7)	159.0 (7.1)	158.8 (5.4)	157.4 (6.4)	158.3 (5.7)	158.6 (5.5)	158.8 (5.9)	158.4 (5.4)
WC, cm	65.7 (6.4)	76.4 (6.3)	87.7 (6.2)	98.5 (8.7)	79.9 (8.9)	66.7 (5.4)	80.0 (6.4)	90.4 (6.0)	101.2 (7.5)	85.6 (9.3)
WHR	0.80 (0.08)	0.86 (0.06)	0.92 (0.06)	0.96 (0.07)	0.88 (0.06)	0.82 (0.07)	0.90 (0.06)	0.94 (0.06)	0.97 (0.07)	0.92 (0.07)
Body fat percentage	16.8 (3.6)	25.5 (4.4)	33.6 (4.6)	40.1 (7.0)	28.0 (6.4)	16.7 (3.1)	26.7 (4.5)	34.1 (4.5)	40.8 (6.6)	30.7 (6.7)
Fat body mass, kg	7.4 (2.0)	14.2 (3.5)	22.6 (4.1)	32.0 (7.3)	17.0 (6.1)	7.2 (1.6)	15.1 (3.6)	23.0 (4.0)	32.7 (6.7)	19.6 (6.8)
Lean body mass, kg	37.2 (4.2)	41.7 (3.8)	45.2 (4.5)	48.3 (7.2)	42.7 (4.5)	36.3 (3.2)	41.6 (3.9)	45.1 (4.4)	48.2 (6.6)	43.4 (4.8)
Blood pressure and glucose, mean (SD)										
SBP, mmHg	120.3 (24.9)	127.4 (18.6)	135.0 (20.1)	142.0 (26.4)	129.8 (19.0)	126.3 (23.1)	138.1 (21.8)	143.9 (21.3)	148.4 (23.5)	141.2 (21.5)
Heart rate, bpm	79.9 (15.8)	78.1 (11.4)	79.3 (12.2)	81.4 (16.1)	78.6 (11.4)	87.1 (14.9)	83.2 (12.7)	83.1 (12.7)	84.1 (15.5)	83.3 (12.4)
RPG[d], mmol/L	5.6 (1.5)	5.6 (1.1)	5.8 (1.2)	6.0 (1.7)	5.7 (1.1)	13.8 (7.1)	12.5 (6.0)	12.1 (5.2)	11.9 (6.2)	12.3 (5.5)
Medical history[e], %										
Hypertension	2.8	6.6	13.6	21.8	8.9	8.8	18.9	29.9	38.2	24.5
Chronic liver disease	1.4	1.2	1.1	1.1	1.2	1.1	1.4	1.1	1.2	1.3
Chronic kidney disease	1.3	1.3	1.5	1.6	1.3	1.2	1.6	1.8	2.2	1.7
Self-rated poor health	14.4	7.8	7.4	10.2	8.0	29.9	18.0	15.7	17.5	17.1

[a]Adjusted for age (5-year groups), sex, and study area (where appropriate). [b]Participants were classified as ever-regular smokers if they answered "on most days" or "daily or almost every day" to either "How often do you smoke tobacco now?" or "In the past, how frequently did you smoke?". [c]Participants were classified as ever-regular alcohol drinkers if they answered "usually at least once a week" to the question "During the past 12 months, how often did you drink alcohol?" or they answered yes to the question "In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?".
[d]Data available for 439,628 participants. [e]Self-reported doctor-diagnosed.
BMI: body mass index, MET-h/day: metabolic equivalent of task hours per day, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference, WHR: waist-to-hip ratio.

Table 6.3. Number of events by diabetes status at baseline

Events	No. of events (%)	
	No diabetes (n=422,871)	Diabetes (n=23,842)
Deaths from any cause	23,305 (5.5)	3509 (14.7)
Non-CVD deaths	14,928 (3.5)	2070 (8.7)
COPD	932 (0.2)	81 (0.3)
Cancer	9032 (2.1)	823 (3.5)
Diabetic ketoacidosis or coma	164 (0.04)	636 (2.7)
Chronic kidney disease	34 (0.01)	173 (0.7)
CVD deaths	8377 (2.0)	1439 (6.0)
IHD	2862 (0.7)	592 (2.5)
Stroke	3983 (0.9)	594 (2.5)
IS	828 (0.2)	188 (0.8)
ICH	2920 (0.7)	381 (1.6)
All CVD events	99,065 (23.4)	9940 (41.7)
Survived to the end of follow-up	86,800 (20.5)	7664 (32.1)
Fatal CVD (died within 28 days)	4839 (1.1)	718 (3.0)
All-cause mortality post non-fatal CVD event	6570 (1.6)	1424 (6.1)
CVD mortality	3601 (0.9)	760 (3.2)
Diabetes related non-CVD mortality	60 (0.01)	225 (0.9)
Non-diabetes related non-CVD mortality	2909 (0.7)	439 (1.8)

CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease, IS: ischaemic stroke, ICH: intracerebral haemorrhage.

Figure 6.1. Association of baseline BMI with CVD incidence, CVD mortality, non-CVD mortality and all-cause mortality among individuals with and without diabetes

The HRs for the outcomes by baseline BMI are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. Squares represent the HR with area inversely proportional to the variance. Vertical lines represent the corresponding 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the ±1S and ±2S represent 1 and 2 SD from the mean, respectively.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

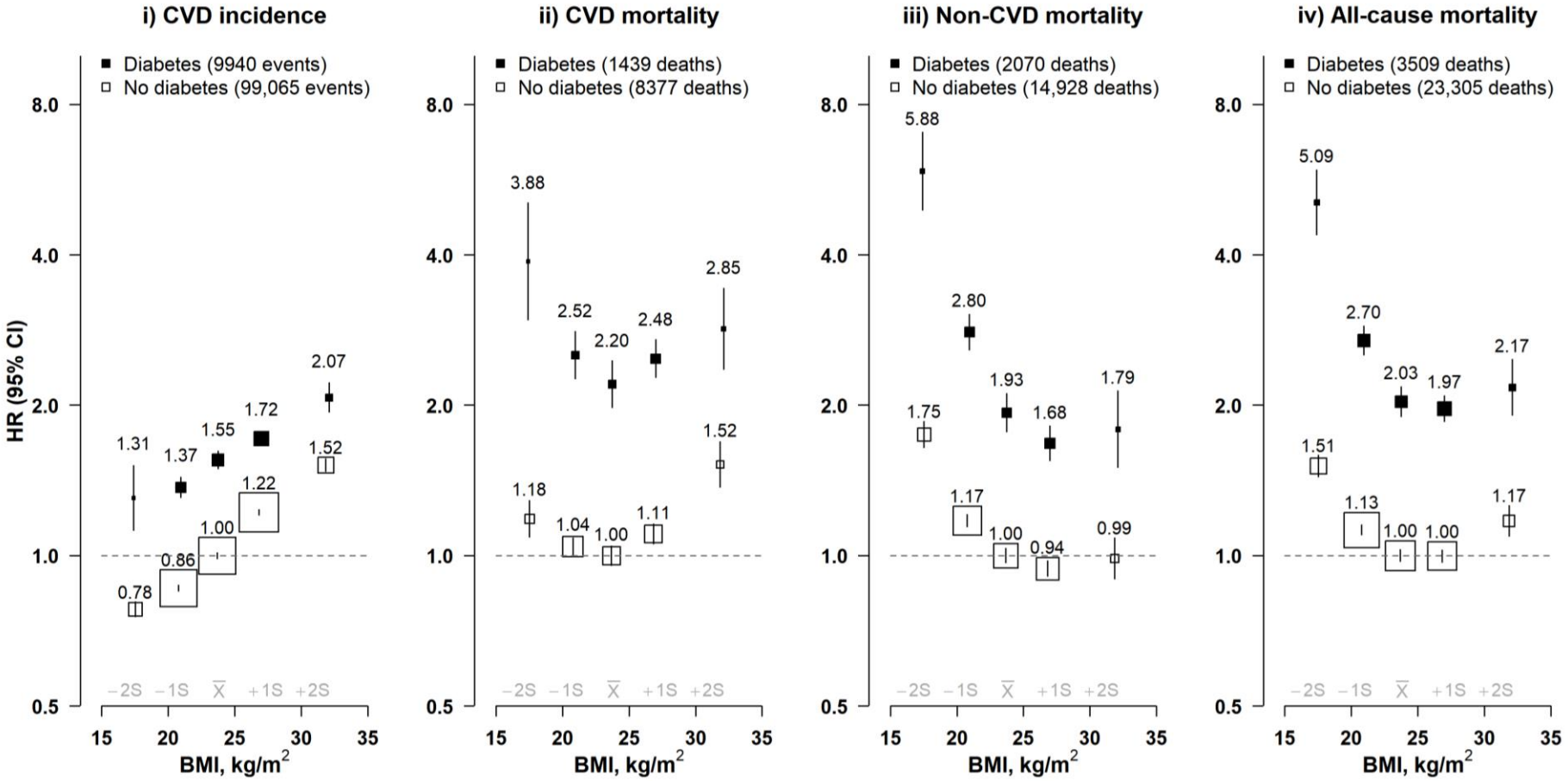


Figure 6.2. Association of baseline BMI with IHD and stroke mortality among individuals with and without diabetes

Conventions as Figure 6.1.
BMI: body mass index,HR: hazard ratio, ICH: intracerebral haemorrhage, IHD: ischaemic heart disease, IS: ischaemic stroke.

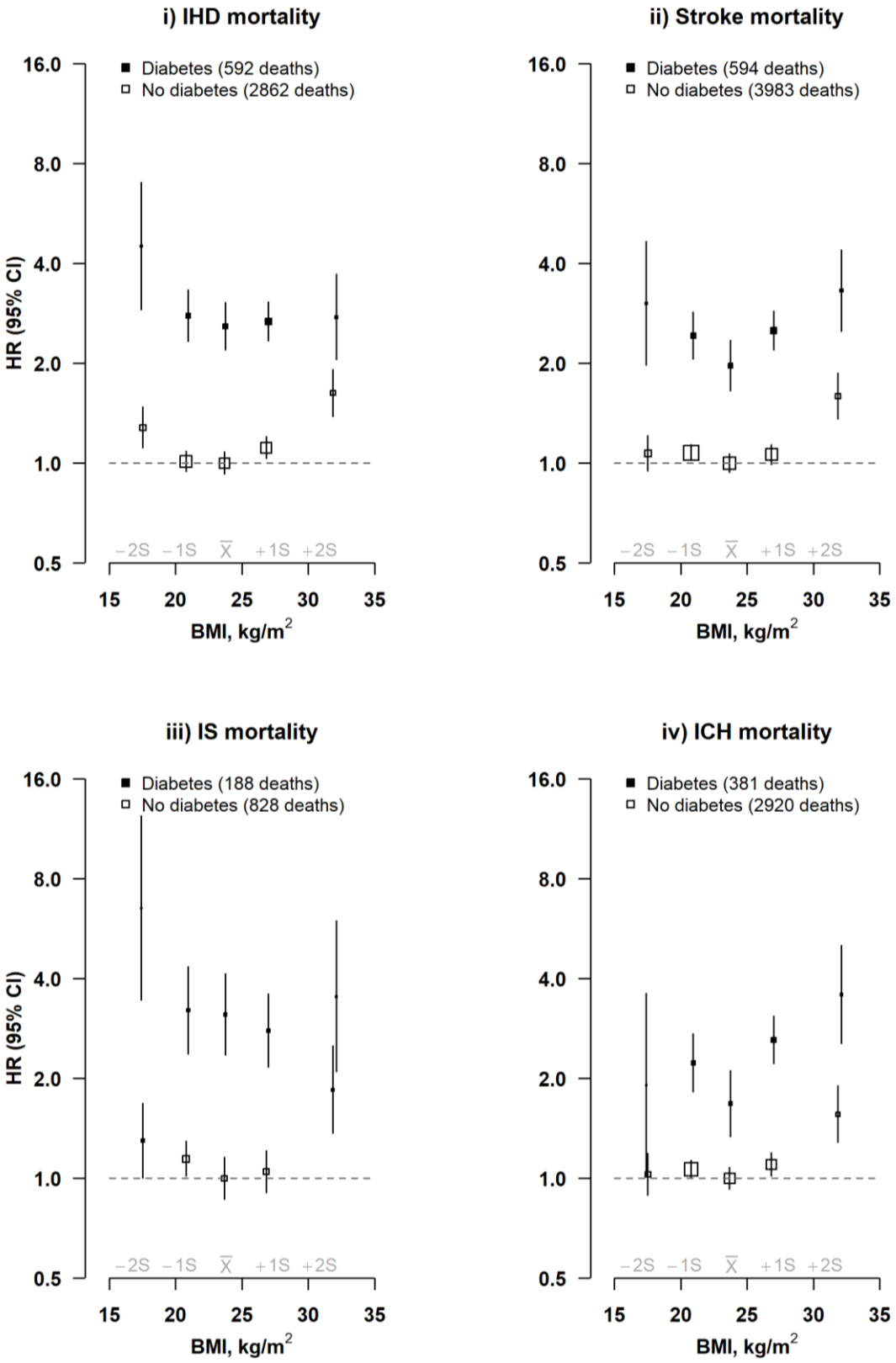


Figure 6.3. Association of baseline BMI with cause-specific non-CVD mortality among individuals with and without diabetes

Conventions as Figure 6.1.
BMI: body mass index, COPD: chronic obstructive pulmonary disease, HR: hazard ratio.

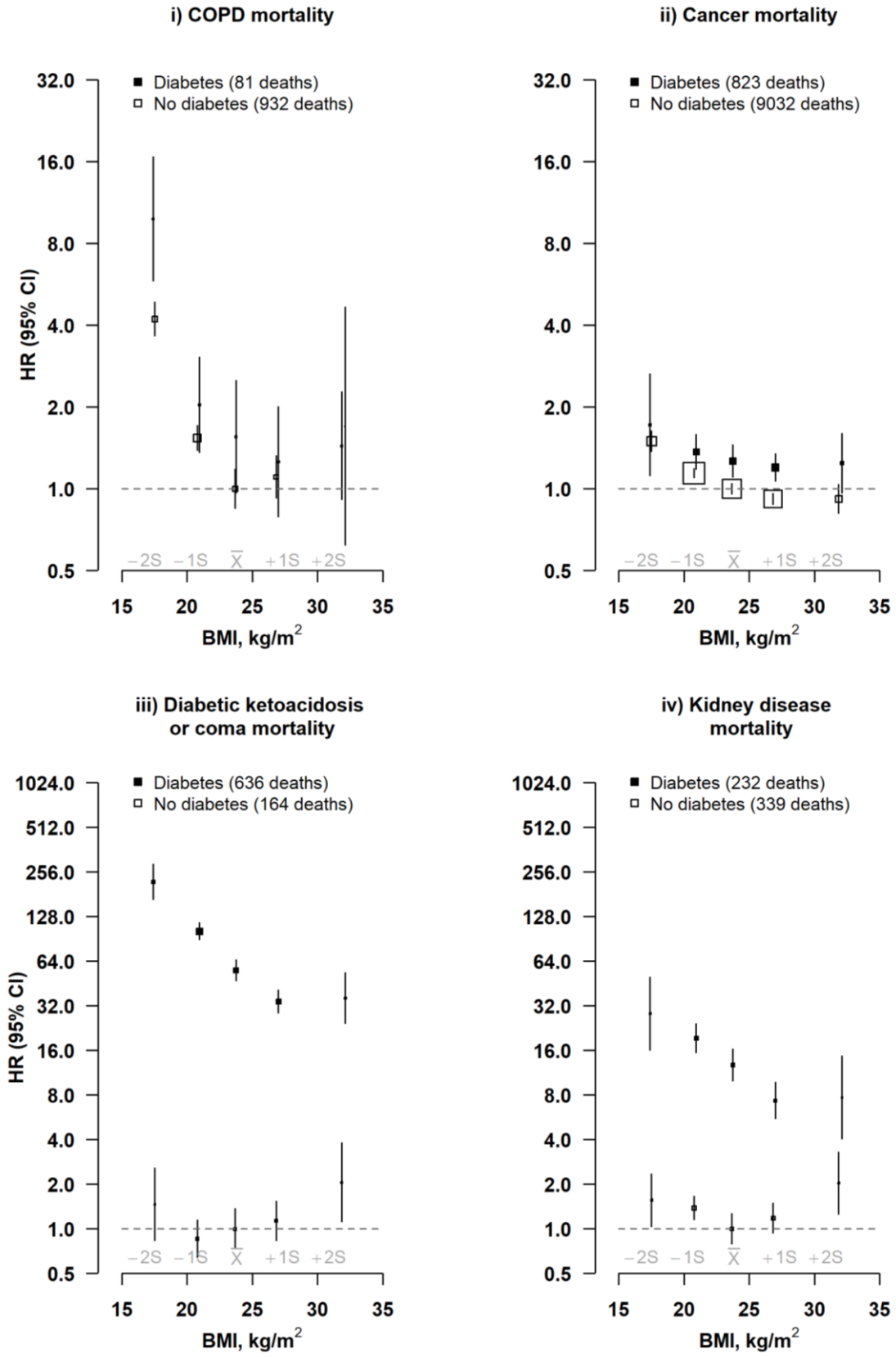


Figure 6.4. Association of baseline BMI with CVD, non-CVD and all-cause mortality among individuals with and without diabetes by age at baseline

Conventions as Figure 6.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

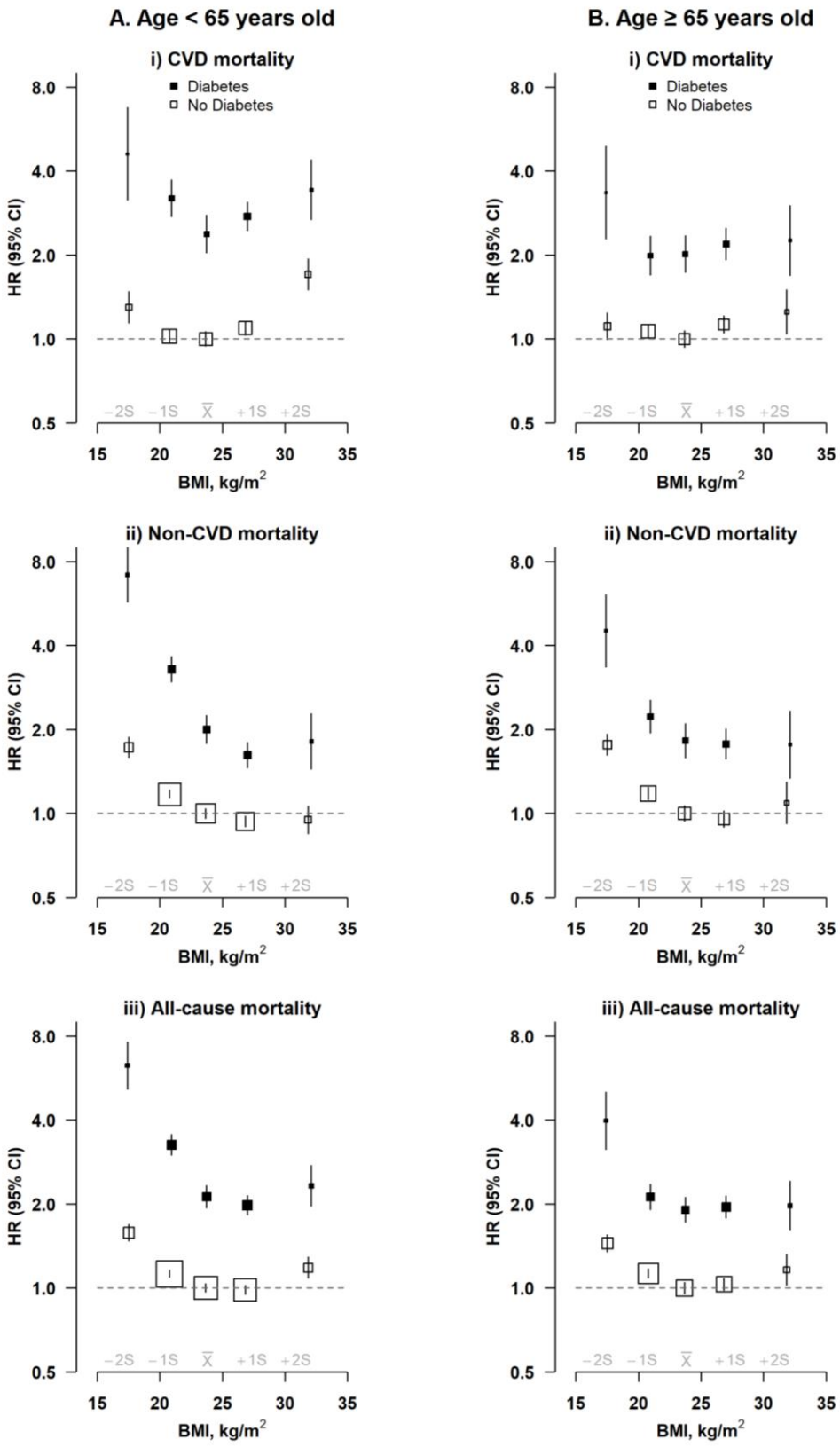


Figure 6.5. Association of baseline BMI with CVD and non-CVD mortality among individuals with and without diabetes among never-regular smokers, and after excluding the first 5 years of follow-up

Conventions as Figure 6.1.
Participants were classified as ever-regular smokers if they answered “on most days” or “daily or almost every day” to either “How often do you smoke tobacco now?” or “In the past, how frequently did you smoke?”.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

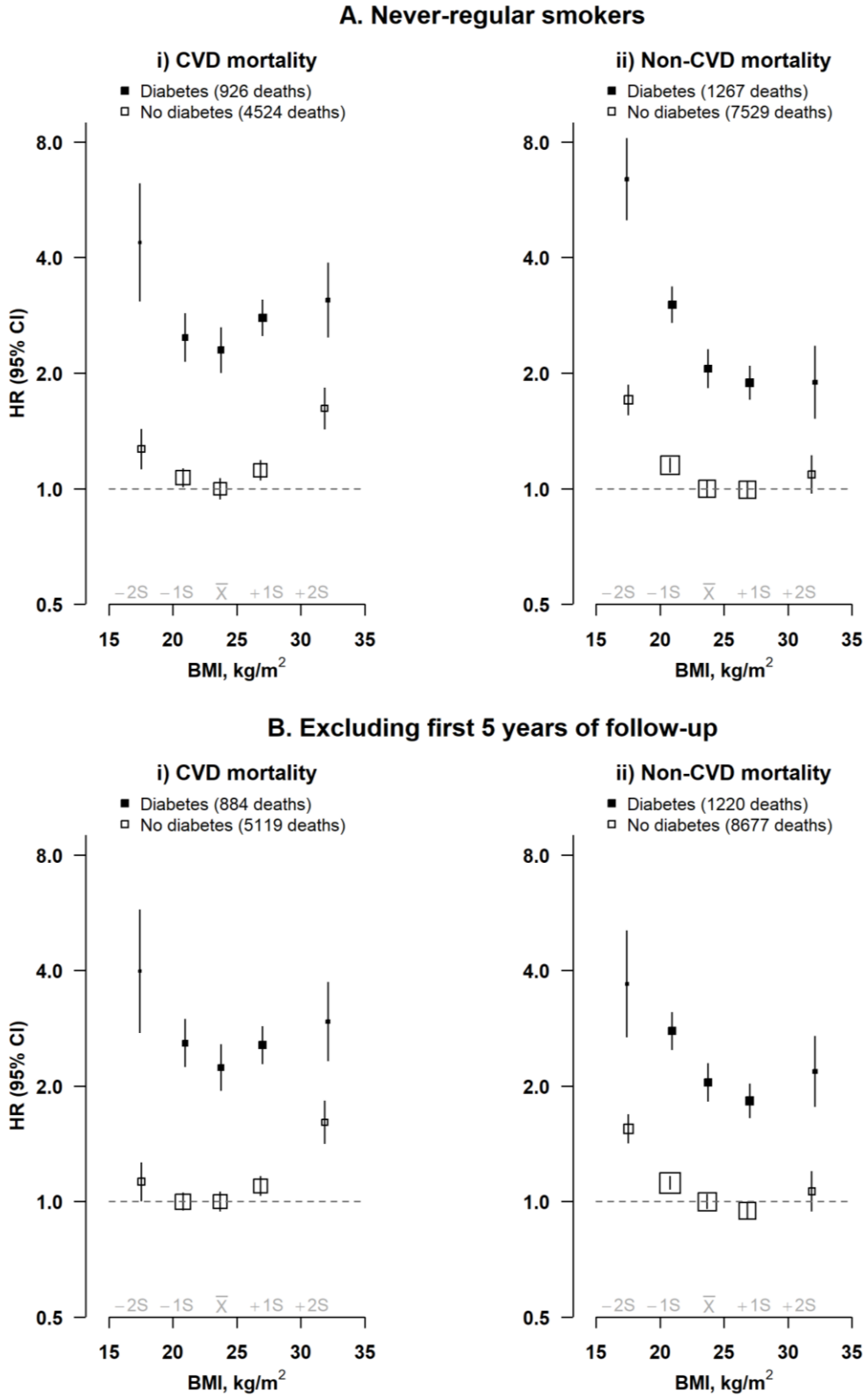


Figure 6.6. Association of baseline BMI with fatal CVD, CVD mortality post non-fatal CVD event, and all-cause mortality post non-fatal CVD event among individuals with and without diabetes

Conventions as Figure 6.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

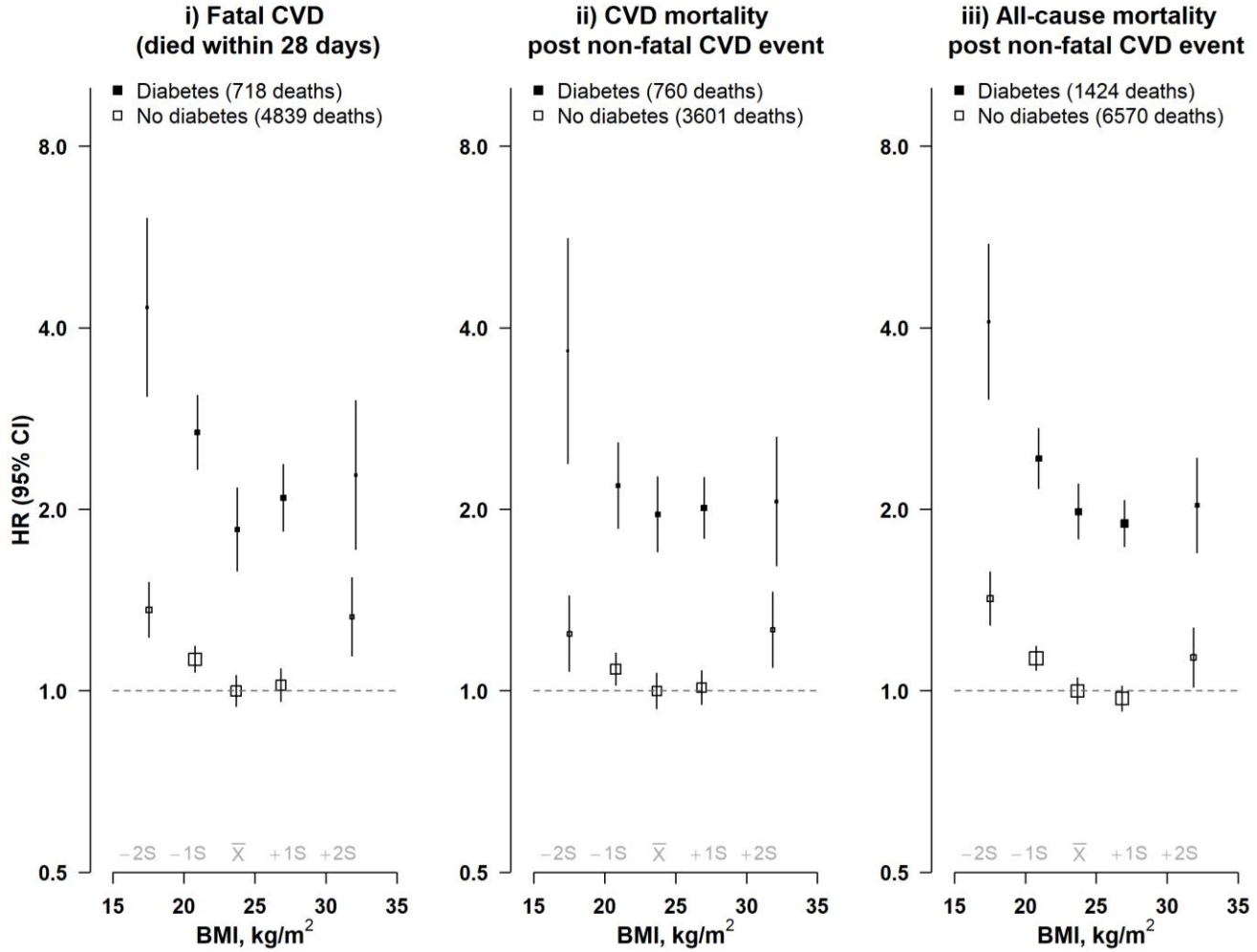


Figure 6.7. Association of baseline BMI with fatal CVD and all-cause mortality post non-fatal CVD event, among individuals with and without diabetes among never-regular smokers, and after excluding the first 5 years of follow-up

Conventions as Figure 6.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

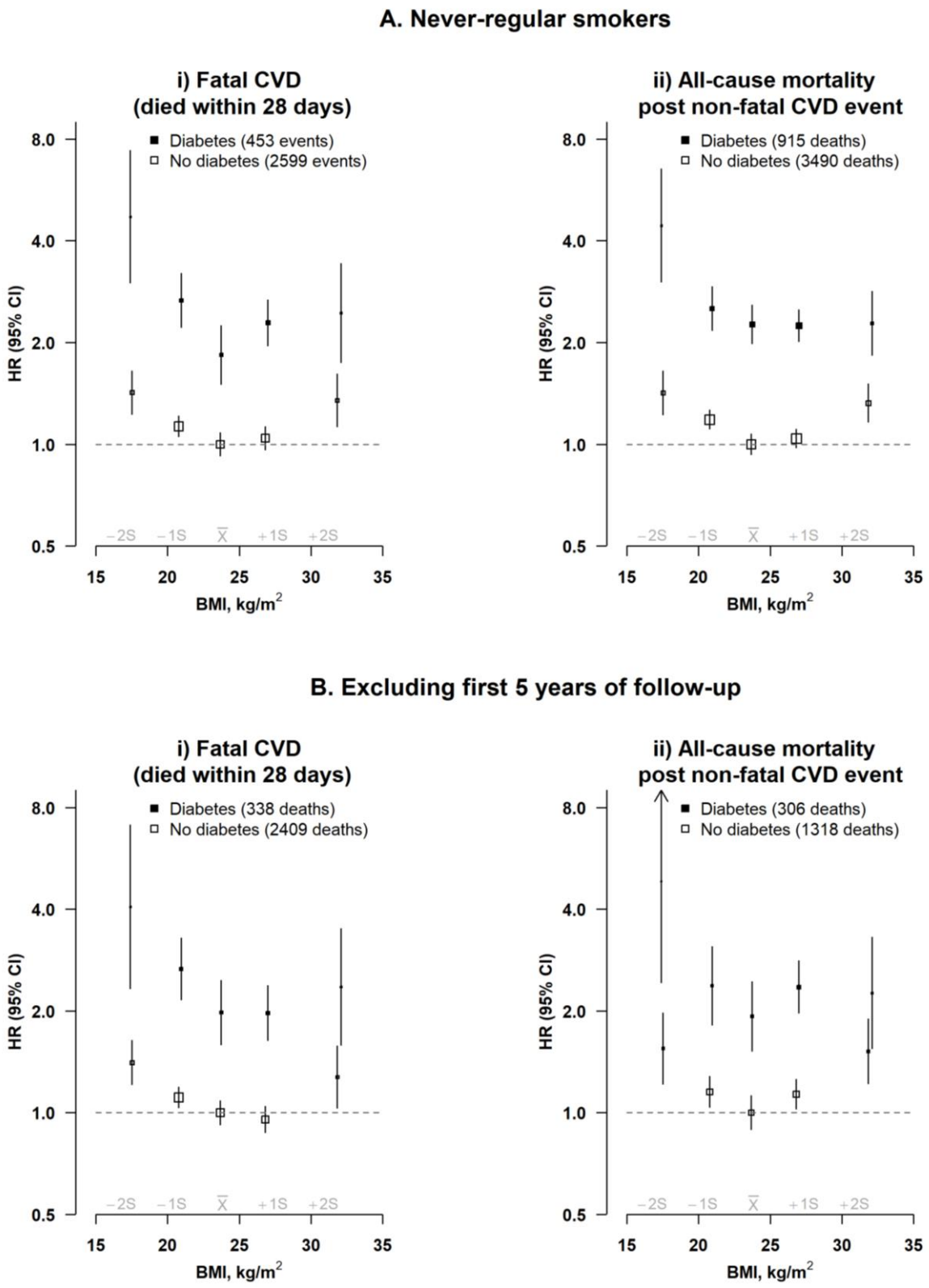


Figure 6.8. HRs per 1 kg/m^2 higher BMI at BMI <25 kg/m^2 for mortality following CVD events among individuals with and without diabetes, applying various exclusions

The HRs for stroke types per 1 kg/m^2 higher BMI are stratified by age-at-risk and sex, and adjusted for education, smoking, alcohol and physical activity. Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs.
BMI: body mass index, CKD: chronic kidney disease: COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, GI: gastrointestinal, HR: hazard ratio, TB: tuberculosis.

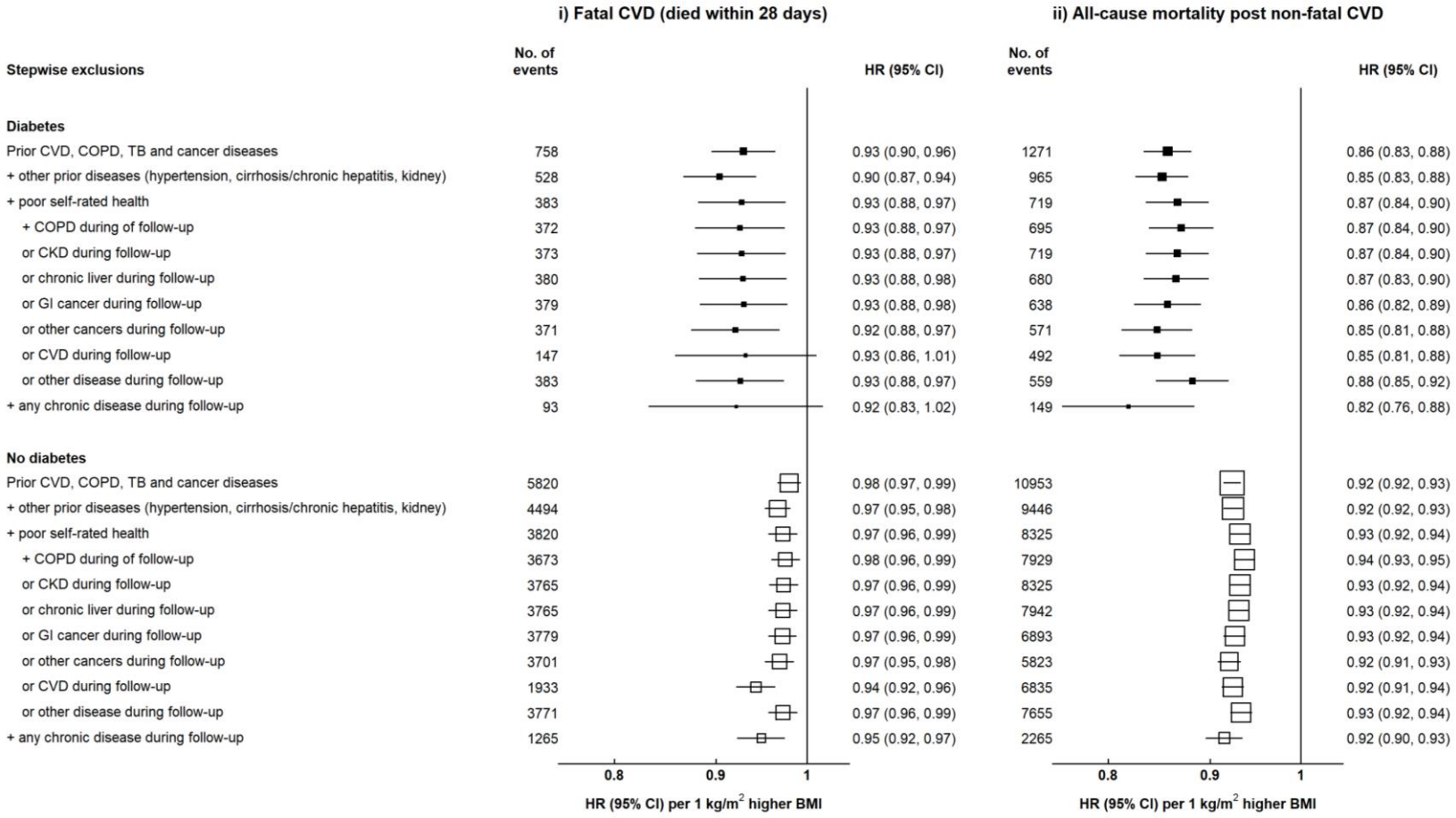


Figure 6.9. Association of baseline BMI with CVD mortality, non-CVD mortality, and all-cause mortality among individuals with and without diabetes, excluding individuals who developed diabetes during follow-up

Conventions as Figure 6.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

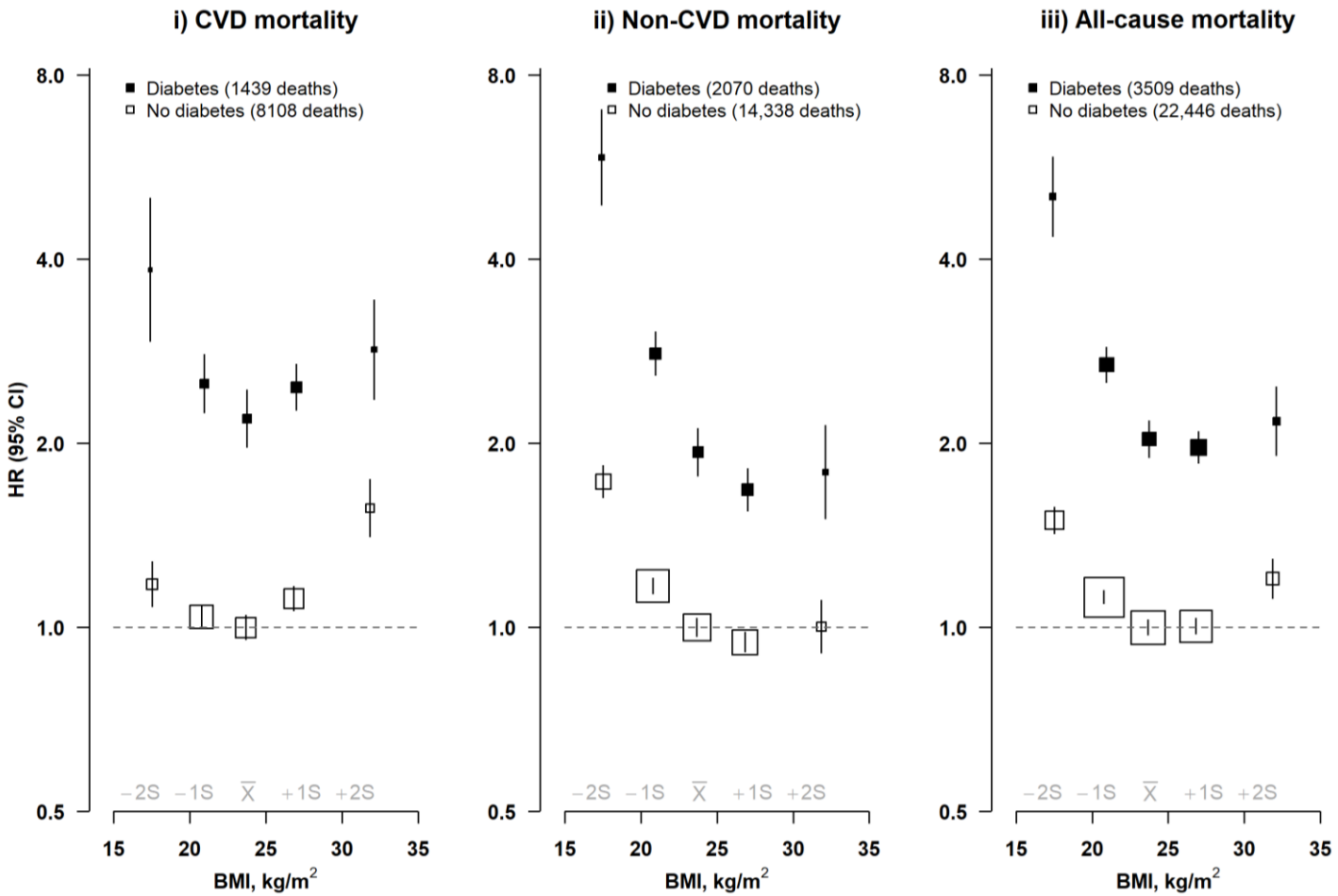


Figure 6.10. Association of baseline BMI with CVD mortality, non-CVD mortality, and all-cause mortality among individuals with self-reported and screen-detected diabetes at baseline

Conventions as Figure 6.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

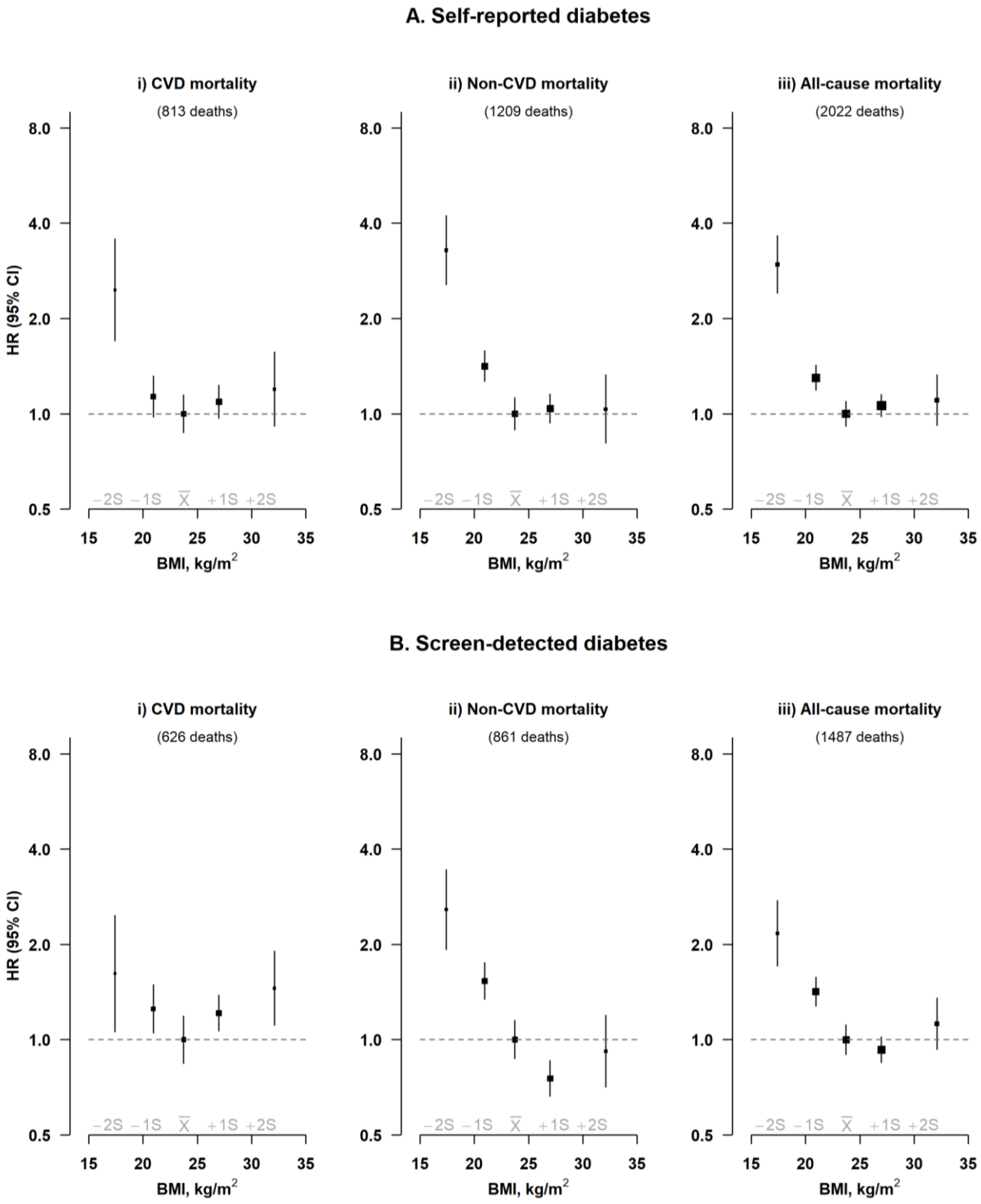


Figure 6.11. Association of baseline waist circumference and waist-to-hip ratio with CVD incidence, fatal CVD, and all-cause mortality post non-fatal CVD event among individuals with and without diabetes at baseline

The HRs for the outcomes by baseline sex-specific quintiles of WC and WHR, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. Conventions as Figure 6.1.
CVD: cardiovascular disease, HR: hazard ratio, WC: waist circumference, WHR: waist-to-hip ratio.

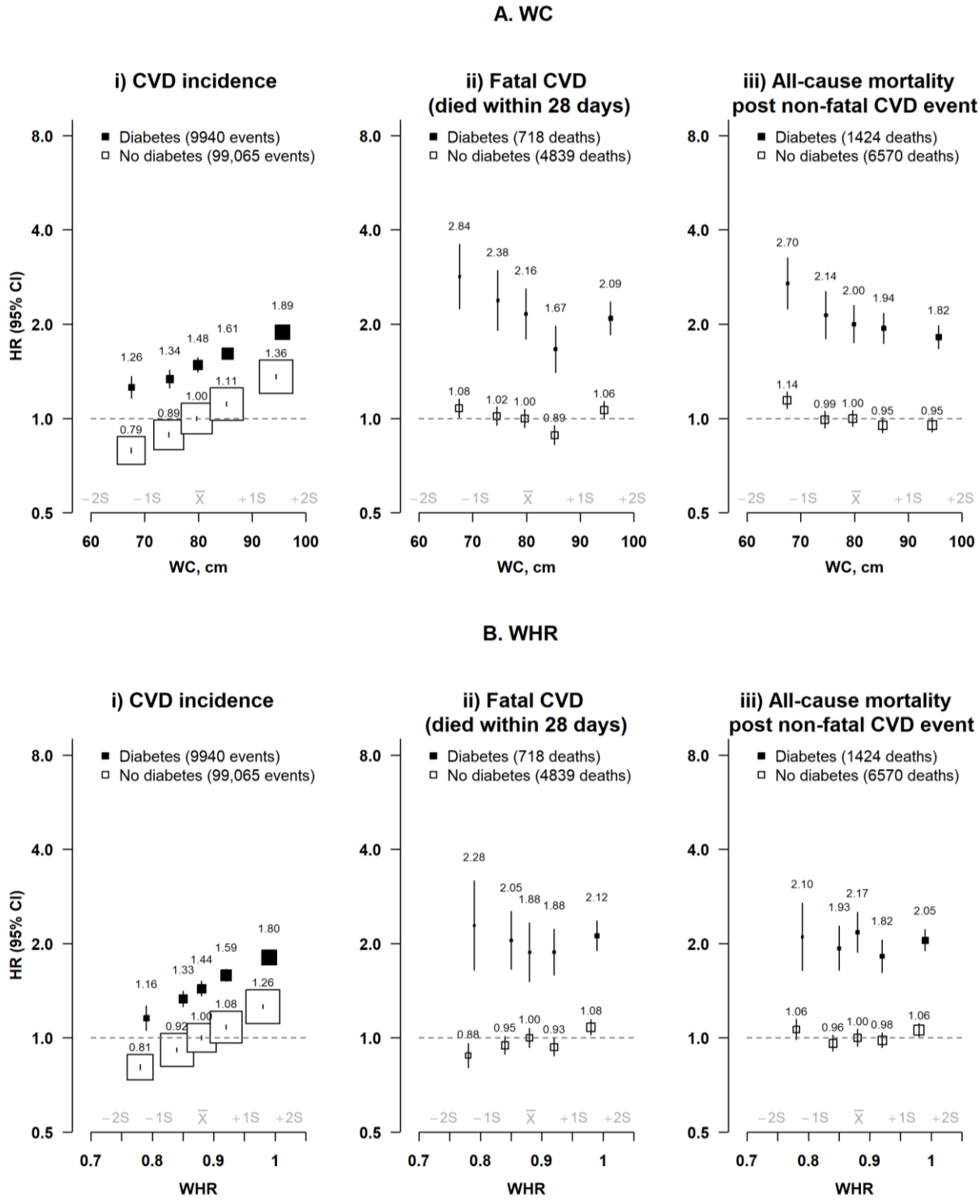
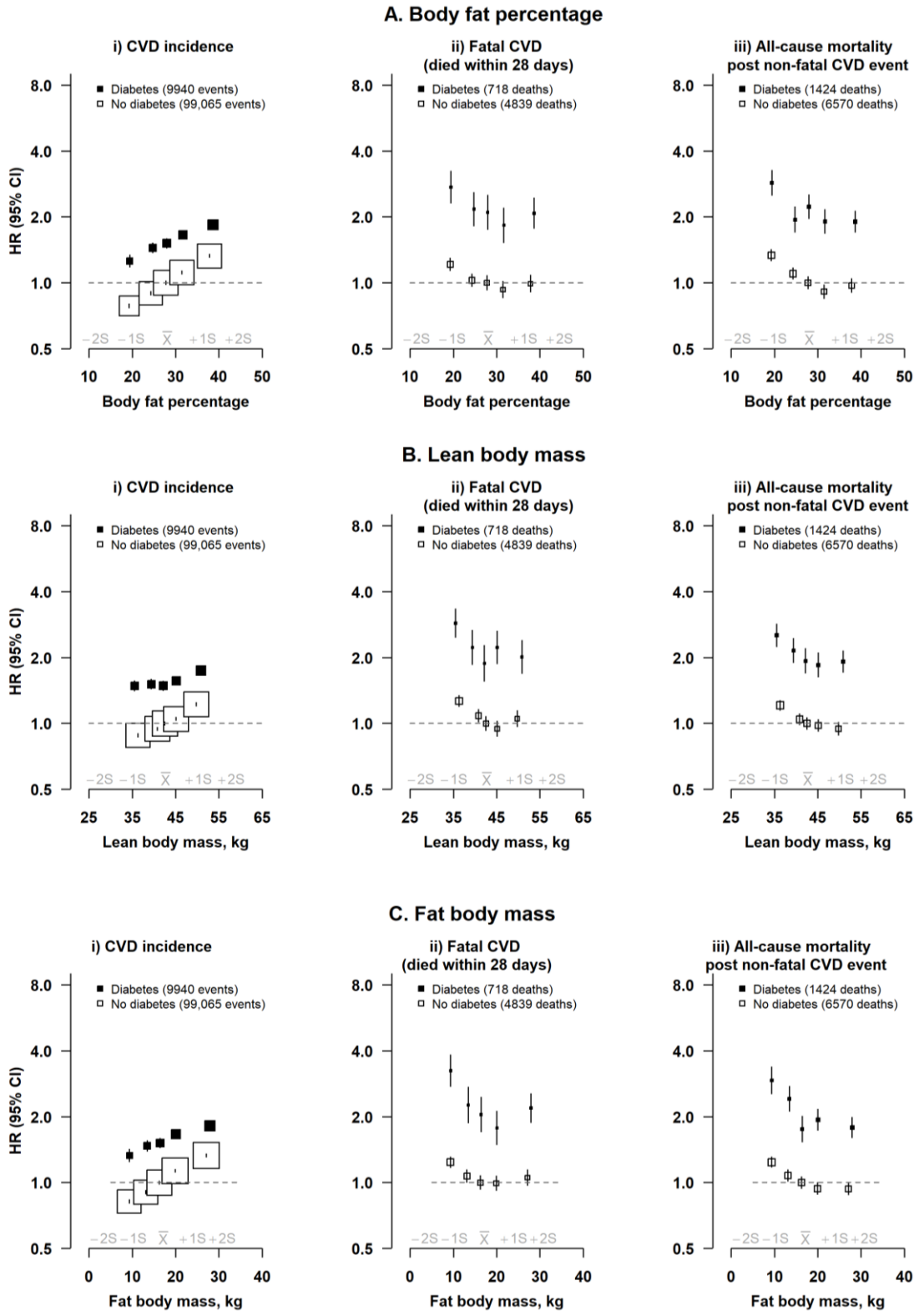


Figure 6.12. Association of baseline body fat percentage, lean body mass and fat body mass with CVD incidence, fatal CVD, and all-cause mortality post non-fatal CVD event, among individuals with and without diabetes

The HRs for the outcomes by baseline sex-specific quintiles of adiposity measures, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. Conventions as Figure 6.1.
CVD: cardiovascular disease, HR: hazard ratio.



Chapter 7. General discussion

The burden of obesity has nearly tripled globally over the last four decades, including in LMICs such as China.[4] Indeed, China is now estimated to account for approximately 10% (60 million) of the world's obese individuals.[7] Previous prospective studies suggested that excess adiposity was associated with various diseases, including major CVD, such as IHD[80,82,83,86] and stroke,[80,81] and MR studies have suggested that these associations are causal.[68,84,85] CVD is the major cause of premature death globally, accounting for approximately 30% of annual deaths.[71] One fifth of the global annual deaths occur in China (~4 million deaths), of which about half are due to stroke.

Despite the well-established associations of adiposity with incident IHD and total stroke,[68,80-86] uncertainty remains regarding the association (both shape and strength) of adiposity with different stroke types (e.g., IS and ICH) and their main subtypes (e.g., lacunar and non-lacunar IS; lobar and non-lobar ICH).[80,86-95] Furthermore, while the roles of blood pressure and lipids in mediating the association of adiposity with IHD and total stroke are now accepted,[80,81,217] their mediating roles in the association of adiposity with stroke types are not fully investigated or understood.[80,86,90,92,94,95] In addition, for stroke subtypes, and particularly for ICH subtypes, the evidence is even more limited, and current evidence is derived only from one small study including limited ICH events.[97] Furthermore, evidence is limited in LMICs such as China.[80,90,92,94,95] where the mean levels of adiposity are lower than in Western populations, the rates of stroke are higher and the proportion of stroke events that are HS is greater. Therefore, a better understanding of the potential mediating effects of established and

emerging factors (e.g., inflammatory biomarkers) on the association of adiposity with incident stroke will help improve our understanding of mechanisms underlying those associations and possibly inform future strategies for disease prevention.

An additional area of uncertainty regarding the disease associations of adiposity is its relevance for CVD and all-cause mortality risk among certain specific population subgroups, especially those with type 2 diabetes.[109,111,112,114,224-226] Many previous studies have reported that among individuals with diabetes, those with elevated BMI (e.g., >25.0 kg/m^2) appear to have lower subsequent mortality risk, compared with those with BMI within the "normal" range. This has led to the notion of a so-called "obesity paradox".[109,111,112,114-116] Previous studies also reported that individuals with low BMI (e.g., <18.5 kg/m^2) experience the highest risk of mortality.[109-112,115,118] Although, some studies have previously attempted to clarify these associations, it remains unclear whether the obesity paradox phenomenon, and the excess risk at low BMI merely reflect uncontrolled biases (e.g., reverse causality), or could possibly reflect a true survival benefit of overweight/obesity following development of type 2 diabetes.[108,110-116] Reliable assessment of the relationship is important for informing weight management among patients with type 2 diabetes.

With data from the CKB cohort study of 0.5 million Chinese adults, this thesis has provided important and robust new evidence on both of these continuing areas of uncertainty regarding the disease risks associated with adiposity.

7.1 Summary of main findings in the context of previous literature

7.1.1 Adiposity and the risk of incident stroke types and subtypes

In CKB, there was a positive log-linear association of BMI with incident IS and its main subtypes (e.g., lacunar and non-lacunar IS) throughout the range of BMI examined (18.0 to 30.0 kg/m^2). Every 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI was associated with 19% (HR 1.19 [95% CI 1.18-1.20]) higher risk of IS, and, among the adjudicated IS events, it was associated with 21% (1.21 [1.19-1.23]) higher risk of lacunar IS and 24% (1.24 [1.22-1.28]) higher risk of non-lacunar IS. The association of BMI with IS incidence in CKB is consistent with previous prospective studies of Western and East Asian populations.[80,86,90-95] In line with CKB findings, a few previous prospective studies found that the association of central adiposity with incident IS[80,92,93] was largely similar to the association of BMI. A few MR studies have shown that the observed association between adiposity and IS is probably causal,[68,84] whereas a number of MR studies reported that it is unlikely to be causal[85,126] (Table 7.1). For IS subtypes, no previous large studies have provided robust evidence about their associations with adiposity.[97-100]

In this thesis, given the strong positive association of BMI with SBP and the positive log-linear associations of SBP with IS and IS subtypes, baseline SBP explained almost half of the observed associations of BMI with IS and IS subtypes. Given baseline SBP, RPG only had a small additional effect on the associations of BMI with stroke types and their subtypes. In the CKB biochemistry cohort, additional adjustments for selected plasma biomarkers (LDL- and HDL-cholesterol, albumin, AST and uric acid) completely attenuated the association of BMI with IS.

Previous studies did not examine the individual effect of blood pressure as a mediator on the association of BMI with IS incidence, but they investigated the mediating roles of multiple variables (e.g., blood pressure, diabetes and lipids) simultaneously, and reported attenuation of the initial association, similar to that in CKB analyses involving multiple mediating factors.[90,94,95] The present study is the first to additionally account for intra-individual variation or measurement error in SBP and showed a weak positive association of BMI with IS (HR 1.02 [95% CI 0.98-1.05]) after adjustment for usual SBP (in addition to baseline RPG and selected plasma biomarkers).

For ICH incidence, this thesis showed that the risk did not start to rise with increasing adiposity until BMI of ~25.0 kg/m^2. In contrast, previous studies, mainly focused on incident HS rather than ICH, reported either positive[87,88,94,95] or inverse[91] approximately log-linear associations. The higher fatality rate of ICH, as compared to IS, in CKB (~45% vs. ~2.5%) suggested that the ICH findings were driven more by fatal events, whereas for IS they were driven mainly by non-fatal events. Therefore, the CKB findings on the relationship of adiposity with ICH incidence may reflect biases from reverse causality, particularly at lower BMI levels. In the presented analyses, it was possible to examine the associations of BMI with fatal and non-fatal ICH separately. For fatal ICH, there was no clear association, while for non-fatal ICH there was a positive approximately log-linear association throughout the BMI range examined. Moreover, among the adjudicated ICH cases in CKB (~83% of which were non-fatal events), there was a positive log-linear association of adiposity with non-lobar ICH, but unclear association with lobar ICH due to the relatively small number of events. There is lack of robust evidence on the association of adiposity with ICH subtypes from

previous large studies.[101] The present study is the first East Asian study to investigate the association of other adiposity measures with ICH and the first ever with ICH subtypes. Findings from this thesis showed that the associations of other adiposity measures (WC and body fat percentage) with ICH and ICH subtypes were similar to the association with BMI.

In analyses included in this thesis there were also strong positive log-linear associations of SBP with incident ICH and ICH subtypes. Adjustments for baseline SBP reversed the initial associations of BMI with ICH and ICH subtypes, throughout the BMI range examined. In the CKB biochemistry sub-cohort, given baseline SBP and RPG, further adjustments for selected plasma biomarkers (mainly LDL-related biomarkers and albumin which were positively associated with BMI and inversely approximately log-linearly associated with ICH) slightly attenuated the HR of the association of BMI with ICH incidence towards the null (from HR 0.91 [95% CI 0.88-0.94] to 0.95 [0.92-0.99]). The inverse association between BMI and non-fatal ICH, given baseline SBP and RPG was completely attenuated after adjustments for LDL-related biomarkers (from HR 0.94 [95% CI 0.89-0.98] to 0.97 [0.93-1.02]). However, the inverse association of BMI with fatal ICH given baseline SBP and RPG was only slightly attenuated after adjustments for LDL-related biomarkers (from HR 0.88 [95% CI 0.83-0.92] to 0.93 [0.88-0.98]). After accounting for usual SBP (i.e., SBP adjusted for intra-individual variation and measurement error) and selected baseline plasma biomarkers the associations of BMI with both fatal and non-fatal ICH became inverse (more marked for fatal ICH). In the present analyses, adjustments for usual values of plasma biomarkers were not performed and therefore it is unclear whether usual values of plasma biomarkers account for the remaining association of BMI with ICH. Moreover, the

CKB findings suggested that biases from reverse causality may persist (particularly for the relationship of BMI with fatal ICH). A few previous prospective studies that have examined the effects of blood pressure, diabetes and lipids in the association of BMI with HS, suggested that those variables completely attenuated the initial association of BMI with HS, consistent with CKB findings.[90,94,95] It is possible that high adiposity may itself confer protective effect on ICH risk, which can be further explored using MR approach. A few MR studies reported no association between BMI and ICH (possibly due to limited number of ICH events) (Table 7.1).[68,85] However, the complete attenuation of the relationship of inverse BMI with non-fatal ICH after adjustments for LDL-related biomarkers (given baseline SBP and RPG) observed in CKB is plausible given MR evidence suggesting that there is an inverse causal association between LDL-cholesterol and ICH (Table 7.3).[182]

7.1.2 Adiposity and the risk of vascular and non-vascular mortality among individuals with and without diabetes

In this large study of relatively lean Chinese adults, diabetes was associated with a two-fold higher risk of overall mortality. There were U- and *reverse* J-shaped associations of BMI with CVD and non-CVD mortality, respectively, with these associations generally shallower among those without diabetes than those with diabetes. The associations persisted after extensive attempts to control for reverse causality and confounding. There were, however, contrasting relationships of BMI with incident CVD events (log-linear) compared with fatal CVD and mortality post non-fatal CVD events (*reverse* J-shaped associations with a strong log-linear inverse association at BMI <25 kg/m^2). Taken together, they suggested an

adverse survival effect associated with low BMI, especially among people with diabetes.

In this thesis the U- and *reverse* J-shaped associations of adiposity with CVD and all-cause mortality among individuals without diabetes were similar to findings from previous Western and East Asian general population studies.[82,102-107] In the present study, the lowest risk of CVD and all-cause mortality was at BMI levels 22.5 to <25.0 kg/m^2 and 25.0 to <30.0 kg/m^2, respectively, but in previous studies the BMI level associated with the lowest risk varied greatly, from levels within the "normal" range to levels in the obese BMI range.[82,102-107] A few of those studies showed that after attempts to control for reverse causality, the BMI levels associated with the lowest mortality risk appeared to shift downwards, from the obese or overweight BMI ranges to the "normal" BMI range.[105,106]

The *reverse* J-shaped association of BMI with all-cause mortality (mainly driven by the association of BMI with non-CVD mortality) among CKB participants with diabetes was largely consistent with previous large studies.[108-112,114,115,118,119] In addition, evidence on the relationship of adiposity with CVD mortality among individuals with diabetes provided by the present study, showing a U-shaped association, is the most robust evidence to date derived from an East Asian population study (given the small number of deaths included in previous East Asian population studies).[112,113,117,118] Moreover, it is consistent with previous large Western population studies.[111,114,119] In CKB, the lowest risks of all-cause and CVD mortality were at BMI levels 22.5 to <30.0 kg/m^2 and 22.5 to <25.0 kg/m^2, respectively. Previous large East Asian population studies also reported the lowest risk of all-cause mortality at BMI levels within the overweight range,[112,115,118] in

contrast to Western population studies that reported lowest all-cause[108-111,114,117,119] and CVD[111,114,119] mortality risks at slightly higher BMI levels, within the obese and overweight ranges, respectively. Moreover, this study is the only one to also investigate the association of adiposity with CVD mortality at different time points (e.g., fatal CVD and CVD mortality post non-fatal CVD events), and showed *reverse* J-shaped associations. In CKB and most previous studies, individuals with low BMI (<20 kg/m^2) experience the highest risk of mortality.[109-112,115,118,119] Other adiposity measures showed similar associations with mortality outcomes to those with BMI.

Among CKB participants with diabetes, the associations of adiposity with all-cause and CVD mortality persisted after extensive attempts to control for reverse causality and confounding. These included excluding the first five years of follow-up, restricting the analyses to never smokers, and excluding individuals who developed major diseases during follow-up. Previous studies that excluded the first few years of follow-up similarly reported that the findings for all-cause mortality remain unchanged.[108,111,113,115,116] In addition, a few studies have reported little difference in the association of BMI with all-cause mortality by smoking status,[110,112,115] similar to CKB findings. However, other studies have shown a less pronounced “obesity paradox” phenomenon among never smokers,[111] or that the lowest risk of mortality was at lower BMI levels among never smokers as compared to ever smokers,[108] or, indeed, a null association among never smokers.[114] Attempts to control for reverse causality on the association of adiposity with CVD mortality from previous studies were extremely limited.[111]

7.2 Causality

Observational epidemiological studies are limited in their ability to assess cause and effect associations, since they are prone to biases, residual confounding and reverse causality. Recent evidence from genetic studies, using an MR approach, has suggested that the associations between BMI and IS[68,84] and CVD-mortality are largely causal, but there is no clear evidence for the association of BMI with ICH. Bradford Hill proposed nine criteria that could be considered in order to contribute to understanding the likely causality of an observational exposure-outcome association. The nine criteria are, *strength*, *biological gradient*, *consistency*, *plausibility*, *coherence*, *temporality*, *experiment*, *specificity* and *analogy*. The findings included in this thesis are discussed in the context of those criteria. There was a relatively strong association between BMI and IS incidence (19% higher risk per 1 SD higher BMI), a weaker association with ICH incidence (8% higher risk per 1 SD higher BMI; Chapter 5) and a higher mortality risk among individuals with either low (<18.5 kg/m^2) or high (25.0 kg/m^2) BMI (Chapter 6). These findings persisted after attempts to control for residual confounding and reverse causality, and after adjustments for other potential confounders suggesting that the criterion of *strength* is fulfilled for IS incidence. The dose-response relationship of BMI with IS throughout the BMI range also provides evidence that the criterion of *biological gradient* is fulfilled. In contrast, for incident ICH and mortality (CVD and all-cause) there were flat or inverse associations of BMI at low BMI levels (approximately <25.0 kg/m^2), respectively, but positive log-linear associations at higher BMI levels. These findings suggest that the criterion of *biological gradient* is not fulfilled for the adiposity-ICH incidence or adiposity-mortality relationships.

The CKB findings were consistent internally across 10 study areas and across most subgroups examined (e.g., sex, and for mortality by diabetes at baseline and self-reported and screen-detected diabetes). The CKB findings for IS were largely consistent with previous large prospective studies.[80,86,90-95] However, a number of MR studies reported conflicting findings on whether the observed positive adiposity-IS relationship is unlikely to be causal,[85,126] or is probably causal[68,84] (Table 7.1). The findings for HS incidence are inconsistent between previous studies (positive, approximately log-linear associations among East Asian population studies[87,88,94,95] but an inverse log-linear association in the Million Women Study[91] which was the only Western large population study that examined the association of BMI with HS). The inconsistency on the shape of the association of BMI with HS between the Million Women study and East Asian population studies it is not fully understood. However, the authors of the Million Women Study speculated that the inverse association with HS (or ICH) might reflect the inverse association of LDL-related lipids with HS (or ICH), although they were not able to investigate the effect of lipids on the association.[91] In addition, in the present analysis there was a flat association between BMI and all ICH incidence at BMI <25.0 kg/m^2 and higher BMI levels were associated with higher risk, but for non-fatal ICH there was a positive nearly log-linear association throughout the BMI range. Moreover, CKB results for mortality (among individuals with[108-112,114,115,118,119] and without[82,102-107] diabetes) were consistent with previous large prospective studies, and an MR study that suggested that the association between BMI and CVD-mortality is likely to causal. The *consistency* of CKB findings (within the study and with other prospective population studies), particularly for CVD mortality and IS incidence, fulfil this criterion.

The mediation analysis presented in this thesis can fulfil the criterion of *plausibility*. The association between BMI and IS incidence is mainly explained through SBP particularly after accounting for measurement error and intra-individual variation in SBP. This is consistent with a few MR studies that suggested that the positive association between adiposity and blood pressure is probably causal[68,238,239] (Table 7.2) and an MR study that suggested that the associations of SBP with total stroke and IHD are probably causal. For non-fatal ICH, the initial positive, approximately log-linear association was reversed after adjustment for SBP. This suggests that other risk factors, such as major plasma biomarkers, might offset the beneficial effect of low SBP at low BMI. Indeed, further adjustments for LDL-related biomarkers attenuated towards the null the inverse association of BMI with non-fatal ICH. This is somewhat consistent with evidence derived from MR studies suggesting that the observed positive associations of adiposity with LDL-cholesterol,[68] and ApoB with IHD,[184] and the inverse association of LDL-cholesterol with ICH,[182] are probably causal (Tables 7.2 and 7.3). In addition, the observed associations did not contradict current biological knowledge, which fulfilled the criterion of *coherence*.

The criterion of *temporality* is fulfilled by the prospective design of CKB in addition to exclusions of individuals with prior CVD diseases (and the initial years of follow-up as a sensitivity analysis). To my knowledge, the effect of weight loss on stroke types and CVD mortality has not been study in the general population, therefore the criterion of *experiment* cannot be fully assessed. However, studies have examined the effect of weight loss as a result of bariatric surgery on CVD incidence and all-cause mortality.[240-242] For instance, the Swedish Obese Subjects non-randomised matched prospective controlled study found that, after more than

10 years' follow-up, weight loss following bariatric surgery reduced the risk of all-cause mortality and total stroke.[240] The same study also reported reduced blood pressure, and lower incidence of hypertension, diabetes and hypertriglyceridemia[243] following bariatric surgery-related weight loss. In addition, the risk of mortality and CVD incidence was also reduced among individuals with type 2 diabetes that underwent bariatric surgery.[241,242] There is a lack of evidence on the effect of weight loss on mortality and CVD incidence from randomised clinical trials. MR studies, which can be considered analogies of randomised clinical trials, have shown conflicting findings on whether the observed associations of BMI with incident IS are likely to be causal.[68,84,85,126]

The criterion of *specificity* cannot be fully assessed in this thesis, due to the focus of the thesis on the association of adiposity with a relatively narrow range of outcomes (e.g., stroke types, CVD mortality). For adiposity, given its wide range of biological effects and associations with many different types of cardio-metabolic conditions, *specificity* may be less relevant in this context. Likewise, the significance of the *analogy* criterion (the observational exposure-outcome association is more likely to be causal if similar exposure-outcome associations are considered causal) may also be questionable, mainly due to the lack of clear-cut analogies, which highlights its subjective nature.[244]

Although fulfilment of Bradford Hill's criteria cannot prove causality,[245] the observed association of adiposity with IS incidence included in this thesis is likely to be causal. However, for CVD mortality and incident ICH it is unclear whether the nature of the entire association with adiposity is likely to be causal. For non-fatal ICH, the association is likely to be causal.

7.3 Strengths and limitations of the study

The strengths and limitations of the study have been discussed in detail in previous chapters. In brief, the major strengths of CKB included the extremely large sample size, diverse population, high quality exposure data and near complete follow-up for stroke incidence and CVD mortality. In addition, the well-characterised information on stroke types and their main subtypes using brain imaging allowed robust classification of those events. The number of IS events included in CKB is among the largest as compared to previous studies. In addition, to date CKB includes the largest number of ICH events, IS and ICH subtypes events, as compared to previous studies, which enabled uniquely robust estimates. The relatively lean CKB study population, compared with Western studies, enabled robust investigation of relationships over a wider adiposity range and particularly at the lower end of adiposity spectrum. Moreover, CKB included multiple adiposity measures, enabling separate assessment of general (BMI and body fat percentage) and central (WC and WHR) adiposity, with disease outcomes. This is particularly important for East Asian populations, given their characteristic patterns of adiposity, including higher levels body fat[13] and central adiposity[246] at a given BMI level, when compared with Caucasian populations, and the limited evidence and conflicting findings from previous studies on the relevance of central adiposity for risk of CVD.[79,83]

The present study is the only study to date that has simultaneously investigated the mediating effect of SBP and major plasma biomarkers on the association of adiposity with stroke types and subtypes, with appropriate correction for measurement error and intra-individual variability using resurvey measurements

for SBP. The CKB findings presented suggested that previous studies may have underestimated the true effect of SBP on those associations. Also, this study further investigated the possible mediating effects of a wider range of biomarkers among a subset of individuals, while most previous studies have focused only on the effects of glucose and lipids.

The present study also attempted to rigorously control for reverse causality and residual confounding. This included excluding individuals with self-reported prior history of major diseases, and the first few years of follow-up and restricting analyses to never smokers. However, those attempts had little effect on the findings, and confounding may persist.

The present study also has limitations. The relatively low participation rate (~30%) may limit the generalisability of results to the general population in China. However, non-participation in the study is unlikely to be related to both exposure (adiposity measures) and to possible confounders (e.g., smoking, alcohol) in the investigated associations, so this is unlikely to have significantly biased the study findings. Furthermore, in estimating exposure-disease associations, the diversity of the study population in terms of the exposure, and low loss to follow-up, as achieved in CKB, are more important than the representativeness of the study population.[247] The findings presented in this thesis, as in many prospective studies, may have been affected by the “healthy volunteer effect”, which may have led to underestimation of the CVD and mortality risk. This is because of the nature of recruitment to CKB, since individuals with severe chronic disease may have been unable to participate into the study.

Although, this study included much larger numbers of stroke cases, particularly for ICH, than previous studies, the relatively small number of ICH cases with subtyping data currently available through the detailed adjudication process limited the ability to draw robust conclusions about the associations of adiposity with ICH subtypes. Likewise, the existing data available from the adjudication process did not differentiate non-lacunar IS into large artery and cardioembolic IS, precluding investigation of these IS subtypes. However, the ongoing adjudication process will provide more detailed data on IS subtypes in the near future. In addition, this thesis did not assess whether the observed associations are causal, for example using an MR approach. This will be particularly important for the association of adiposity with ICH, where the observed associations between prospective studies are conflicting, and there is no available evidence on the nature of this association.

In addition, the plasma biomarker measurements were available only among a subset of the CKB cohort, which precluded investigation of the mediating effects of plasma biomarkers in the association of adiposity with stroke subtypes, or of the effect of those plasma biomarkers on the association of adiposity with mortality, particularly among individuals with diabetes. Repeated measurements of plasma biomarkers were available among a small subset of participants. However, these were not used for adjustment for intra-individual variation in the mediation analyses for various reasons. These included the availability of only limited data on repeated plasma biomarker measurements, preventing reliable estimates, the complexity of the methods required to adjust for measurement error in multiple covariates (e.g., correlation matrix) and difficulties in testing the underlying assumptions of the method.[210,211] Furthermore, despite the extensive attempts to control for reverse causality, residual confounding from measured and

unmeasured factors may still persist. In addition, selection bias (e.g., collider bias) may affect the findings on the association of adiposity with mortality among individuals with diabetes through several pathways, as discussed in detail in Chapter 6.

7.4 Clinical and public health implications

Over the last four decades, levels of adiposity have been increasing worldwide[3] and the proportion of individuals classified as overweight or obese has nearly tripled.[4] As a consequence, in 2015 approximately 4 million adult deaths worldwide were attributed directly or indirectly to excess adiposity, mainly through hypertension, diabetes and CVDs.[5] As demonstrated in this thesis elevated levels of adiposity were associated with higher risk of incident IS and its subtypes, non-fatal ICH, and CVD and all-cause mortality, with those association likely to be causal (Section 7.2). This implies that if current adiposity rates continue, then the future health burden, including CVD incidence and mortality, will be substantial.

Strategies to reduce the burden of adiposity, including diets low in calories, are therefore of great importance because of their potential health benefits.[218] Lifestyle-based weight management interventions are frequently unsustainable among overweight or obese adults.[219,220] However, evidence based on observations following bariatric surgery suggest that health benefits may be achieved by long-term weight loss.[240-242] In contrast, interventions to control elevated levels of blood pressure,[221,222] the main mediator of the association between adiposity and stroke types, are arguably more feasible and easily sustained. However, the often progressive nature of dysglycaemia[248] and elevated

blood pressure[249] pose challenges, frequently requiring escalating treatment regimens which may nor achieve normalisation of these cardiovascular risk factors. Therefore, although interventions to control blood pressure and major plasma biomarkers (e.g., glucose and lipids) might contribute to lessen the adverse cardiovascular effects of excess adiposity, they do not diminish the importance of interventions for maintaining healthy weight. In addition, this would depend on the effectiveness of treatments to control these mediators. This is particularly relevant in China where diagnosis and management of hypertensio[250] and diabetes[251] are frequently suboptimal.

The relatively lean population included in CKB enabled robust investigation of disease risks at the lower end of the BMI range, in contrast to most other, predominantly Western population, studies. Although low BMI levels are not associated with high risk of CVD incidence, they are associated with the highest risk of CVD mortality, even in the absence of any known chronic disease (e.g., diabetes), possibly reflecting biases from reverse causality. This highlights the importance of maintaining a healthy weight, which is an important indicator of health among people both with and without diabetes.

7.5 Future research

Although CKB has already captured more incident CVD events and CVD deaths than most previous studies, longer follow-up would further improve the study power and the precision of the risk estimates. Also, it would allow exclusion of longer initial follow-up in an attempt to control for reverse causality. Once completed, the more detailed stroke phenotyping currently underway in CKB will

provide not only more subtyped ICH events, increasing the reliability of current risk estimates, but also more detailed IS subtyping data, enabling investigation of the associations of adiposity with additional IS subtypes, such as large artery and cardioembolic IS. In addition, investigation of the mediating effects of metabolomic markers (e.g., LDL particles) in the adiposity-stroke types and subtypes association will provide a deeper understanding of the underlying mechanisms. Genome-wide genotyping data are available for approximately 100,000 CKB participants, including 17,000 IS and ~7,000 ICH events. Use of these data in MR analyses will be of importance in improving our understanding of the likely causal nature of the associations of adiposity with stroke types and subtypes, particularly for ICH, where the evidence from previous prospective analyses is conflicting. In addition, it will be valuable to investigate the independent associations of general and central adiposity with incident stroke types and CVD mortality.

In this thesis the cross-sectional association of adiposity with plasma biomarkers was investigated in both CKB and UKB study populations. This provided opportunity to examine possible ethnic differences in these associations. Given the known differences in the adiposity range and stroke rates between East Asian and Western populations, future analyses on the association of adiposity with stroke types, and on the mediating roles of blood pressure and plasma biomarkers on those associations, using data from UKB, would enable comparison with CKB findings and a better understanding of possible ethnic differences. However, that would require a longer follow-up in UKB, given the currently relatively limited number of incident IS and ICH events.[252]

Moreover, uncertainty remains on the relevance of adiposity on mortality among other specific disease populations, such as individuals with heart failure.[253-255] Future research investigating those associations will provide a better understating of the relevance of adiposity on mortality in the presence of diseases to inform future policies for disease management.

7.6 Conclusion

These presented analyses, have shown a positive log-linear association between adiposity and the incidence of IS and IS subtypes. About three-quarters of the excess risk of IS and IS subtypes associated with adiposity could be explained by usual SBP. There was no association between BMI and ICH at BMI levels <25.0 kg/m^2, but higher BMI levels were associated high higher risk of ICH. However, there was a positive, approximately log-linear association of BMI with non-fatal ICH. Given usual SBP, there was a strong inverse association of adiposity with non-fatal ICH, which was fully attenuated towards the null after adjustments for selected plasma biomarkers, including LDL-related biomarkers. Findings from this thesis suggest that weight management, along with management of hypertension, glycemia and dyslipidaemia, will diminish the adverse effect of high adiposity on stroke risk among individuals with BMI levels in the overweight or obese ranges. Future research is needed to investigate the prospective associations between adiposity and stroke types and subtypes using data from populations of different ethnicity, and MR studies are required to confirm whether the observed associations are causal, particularly for ICH.

Finally, the contrasting associations of adiposity with CVD incidence and mortality at different time points indicated poor survival following disease onset at the lower end of the BMI spectrum, among both individuals with and without diabetes. In addition, elevated levels of adiposity were associated with higher risk of both CVD incidence and mortality, regardless of diabetes status. Therefore, optimal bodyweight in individuals with and without chronic disease is associated with the lowest risk of mortality. Although CKB's follow-up is longer than that of most previous studies, longer follow-up will enable more precise estimates and allow exclusion of a longer period of initial follow-up in an attempt to control for reverse causality. In addition, further research on the mediating effects of plasma biomarkers on the adiposity-mortality association among individuals with diabetes will provide insight into the underlying mechanisms.

Table 7.1. Findings from MR studies on the association of instrumental variables for adiposity with cardiovascular diseases and mortality

Outcome	First author's name (year published)	No. of events	HR (95% CI)
IS incidence	Larsson[126] (2017)	18,476	Per 1 SD higher BMI: 1.11 (0.98-1.27)
	Dale[68] (2017)	12,389	Per 1 SD (4.6 kg/m^2) higher BMI: 1.09 (0.93-1.28) Per 1 SD (0.13) higher WHRadjBMI: 1.32 (1.03-1.70)
	Larsson[85] (2020)	3554	Per 1 kg/m^2 higher BMI: 1.03 (0.99-1.07)
	Hagg[84] (2015)	1500	Per 1 SD higher BMI: 1.83 (1.05-3.20)
HS incidence	Dale[68] (2017)	N/S	Per 1 SD (4.6 kg/m^2) higher BMI: 1.51 (0.73-3.13) Per 1 SD (0.13) higher WHRadjBMI: 1.89 (0.69-5.18)
	Larsson[85] (2020)	1655	Per 1 kg/m^2 higher BMI: 1.03 (0.97-1.07)
Total stroke mortality	Wade[256] (2018)	346	Per 1 kg/m^2 higher BMI: 0.98 (0.80-1.20)
CVD mortality	Wade[256] (2018)	1967	Per 1 kg/m^2 higher BMI: 1.10 (1.01-1.25)
All-cause mortality	Wade[256] (2018)	9579	Per 1 kg/m^2 higher BMI: 1.03 (0.99-1.07)

BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio, HS: haemorrhagic stroke, IS: ischaemic stroke, MR: Mendelian randomization, N/S: not stated, WHRadjBMI: waist-to-hip ratio adjusted for body mass index.

Table 7.2. Findings from MR studies on the association of instrumental variables for adiposity with blood pressure and cardiometabolic traits

Cardiometabolic traits	First author's name (year published)	No. of individuals	Mean difference of each continuous trait per SD increase of IV of adiposity	P-value
Blood pressure				
SBP	Dale[68] (2017)	37,524	BMI: 0.07 (0.00 to 0.14)[a]	0.049
		32,850	WHRadjBMI: 0.15 (0.05 to 0.25)[a]	0.002
	Lyall[239] (2017)	111,637	BMI: 1.65 (0.78 to 2.52) mmHg	<0.001
DBP	Lyall[239] (2017)	111,638	BMI: 1.37 (0.88 to 1.85) mmHg	<0.001
Hypertension	Hypponen[238] (2019)	269,580	BMI: OR 1.55 (95% CI 1.373-1.76)	N/S
Diabetes related				
Glucose	Dale[68] (2017)	23,955	BMI: 0.13 (0.06 to 0.21)[a]	0. 001
			WHRadjBMI: -0.01 (-0.16 to 0.14)[a]	0.856
Log insulin	Dale[68] (2017)	18,363	BMI: 0.39 (0.29 to 0.49)[a]	<0.001
			WHRadjBMI: 0.33 (0.15 to 0.51)[a]	<0.001
Lipids				
LDL-cholesterol	Dale[68] (2017)	194,045	BMI: -0.05 (-0.17 to 0.06)[a]	0.368
		194,047	WHRadjBMI: 0.14 (0.05 to 0.22)[a]	0.002
HDL-cholesterol	Dale[68] (2017)	213,556	BMI: -0.22 (-0.29 to -0.14)[a]	<0.001
			WHRadjBMI: -0.38 (-0.49 to -0.28)[a]	<0.001
Log triglycerides	Dale[68] (2017)	32,082	BMI: 0.19 (0.12 to 0.26)[a]	<0.001
		32,083	WHRadjBMI: 0.45 (0.28 to 0.62)[a]	<0.001
Inflammation				
Albumin	Dale[68] (2017)	16,335	BMI: -0.19 (-0.33 to -0.05)[a]	0.009
			WHRadjBMI: 0.17 (-0.04 to 0.39)	0.116
CRP	Welsh[69] (2010)	5804	BMI: 1.24 mg/L difference between extremes	0.002
Renal function				
Log creatinine	Dale[68] (2017)	17,070	BMI: -0.02 (-0.11 to 0.08)[a]	0.703
			WHRadjBMI: -0.01 (-0.16 to 0.14)[a]	0.890
eGFR	Dale[68] (2017)	10,090	BMI: -0.03 (-0.17 to 0.11)[a]	0.649
			WHRadjBMI: 0.08 (-0.10 to 0.25)[a]	0.399

[a]Dale et al. study for comparability across cardiometabolic traits, measurements were z-score standardized.
BMI: body mass index, CRP: C-reactive protein, IV: instrumental variable, MR: Mendelian randomization, N/S: not stated, WHRadjBM: waist-to-hip ratio adjusted for body mass index

Table 7.3. Findings from MR studies on the association of instrumental variables for cardiometabolic traits with stroke types

Outcomes	Cardiometabolic traits	First author's name (year published)	No. of events	HR (95% CI)
IS	**Diabetes related**			
	Fasting glucose	Larsson[126] (2017)	18,476	Per 1 SD higher: 1.12 (0.98-1.28)
	Fasting insulin	Larsson[126] (2017)	18,476	Per 1 SD higher: 1.03 (0.78-1.37)
	Type 2 diabetes	Larsson[126] (2017)	18,476	Per 1-unit higher log-odds: 1.12 (1.07-1.17)
		Gan[257] (2019)	17,097	Per 1-unit higher log-odds: 1.91 (1.22-2.98)
	Lipids			
	LDL-cholesterol	Hindy[258] (2019)	16,851	Per 1 mmol/l higher: 1.12 (1.01-1.24)
		Valdez-Marques[259] (2018)	12,389	Per 1 mmol/l higher: 1.12 (0.96-1.30)
		Sun[182] (2019)	5,567	Per 1 mmol/l lower: 0.75 (0.20-0.95)
	HDL-cholesterol	Hindy[258] (2019)	16,851	Per 1 mmol/l higher: 0.91 (0.83-1.01)
	Triglycerides	Hindy[258] (2019)	16,851	Per 1 mmol/l higher: 0.98 (0.89-1.08)
	Inflammation			
	CRP	Prins[188] (2016)	9,520	Per 1 mg/l higher in lnCRP: 1.06 (0.87-1.29)
		Zhang[189] (2020)	378	Per 10% higher CRP: 1.00 (0.88-1.13)
	Renal function			
	Cystatin C	Van der Laan[260] (2016)	16,782	Per doubling of cystatin C: 0.82 (0.57-1.18)
ICH	**Diabetes related**			
	Type 2 diabetes	Gan[257] (2019)	6973	Per 1-unit higher log-odds: 1.14 (0.51-2.54)
	Lipids			
	LDL-cholesterol	Sun[182] (2019)	4,911	Per 1 mmol/l lower: 1.13 (0.91-1.40)
IHD	**Lipids**			
	LDL-cholesterol	Ference[184] (2019)	91,129	Per 10 mg/dL lower: 0.85 (0.83-0.86)
	ApoB	Ference[184] (2019)	91,129	Per 10 mg/dL lower: 0.77 (0.76-0.78)
	Triglycerides	Ference[184] (2019)	91,129	Per 50 mg/dL lower: 0.82 (0.80-0.85)
	Inflammation			
	Fibrinogen	Ward-Caviness[261] (2019)	4629	Per 1 g/L higher: 0.98 (0.70-1.39)
	Renal function			
	Cystatin C	Van der Laan[260] (2016)	43.068	Per doubling of cystatin C: 1.09 (0.85-1.39)

ApoB: apolipoprotein B, CRP, C-reactive protein, HDL-cholesterol: high-density lipoprotein cholesterol, ICH: intracerebral haemorrhage, IHD: ischaemic heart disease, IS: ischaemic stroke, LDL-cholesterol: low-density lipoprotein cholesterol.

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Appendix A. Additional China Kadoorie Biobank methods and study design

Appendix Note A.1. Outcome adjudication

Stroke cases were identified using linked electronic health insurance records. The events were then confirmed and classified into stroke types and subtypes through the adjudication process. A local research assistant visited the hospitals where stroke events had been reported and retrieved relevant medical records that matched reported stroke events. The medical records were photographed, including information regarding primary and secondary diagnoses of stroke at discharge (including stroke pathological types if available), vital status, other events occurring during hospitalisation, diagnostic tests (e.g., brain imaging reports, which were available for over 92% of retrieved stroke events) and their results, and all prescribed medication. The medical records were verified and recorded electronically using a standardised data entry form and uploaded onto a secure internet website for subsequent adjudication by a panel of trained neurologists in China, using the World Health Organization criteria for stroke. The neurologists classified strokes into the pathological types (IS, ICH or SAH) using radiological reports on brain imaging and other relevant medical records. The confirmed IS and ICH events were then further classified into pathological subtypes (lacunar and non-lacunar IS, and lobar and non-lobar ICH).

Appendix B. Additional methods and results: Associations of plasma biomarkers with adiposity and stroke types

Appendix Note B.1. UK Biobank

Study population

The study design of UKB is similar to that of CKB, and has been described in detail elsewhere.[149] In summary, between 2006 and 2010 approximately nine million individuals, aged between 40-69 years, who were registered with the National Health Service were invited to attend to one of 22 study assessment centres. In total, 503,325 individuals were recruited (5.5% response rate). During their visit to the assessment centre, participants completed a questionnaire related to their socioeconomic status, lifestyle habits and medical history. In addition, physical measurements (e.g., weight, height, and blood pressure) were performed and non-fasting blood samples were collected.

Exclusions

For consistency, the exclusions applied in analyses based on UKB data were similar to exclusions applied in the design of the CKB nested-case control study of CVD. Individuals with pre-existing diseases (e.g., MI, stroke and cancer; n=56,463), using statins (n=62,258), with incomplete biochemical data (n=75,015) or with missing values for adiposity measures (n=1193) were excluded from the analyses. Following these exclusions, 308,396 participants remained for inclusion in these analyses.

Adiposity measures

The associations of BMI and two central (WC, WHR) adiposity measures were examined.

Plasma biomarkers

For these analyses, 17 plasma biomarkers were considered as fibrinogen was not measured in UKB.

Statistical analysis

UKB data were analysed using the same methods as described in section 4.1.2.5. However, the analyses were adjusted for assessment centre instead of study area. Figures 4.1.15-4.1.17 show the associations of BMI and WC with plasma biomarkers in UKB. The length of x-axes are in SD units of the adiposity measures. The length of y-axes represent the same absolute levels of plasma biomarkers as those in the CKB figures (Figure 4.1.2, 4.1.6 and 4.1.10) for all plasma biomarkers, with the exception of HDL-related biomarkers, cystatin C and uric acid where they are double those of the corresponding CKB figures (due to differing plasma biomarker ranges in UKB)

Table B.1. Correlation coefficients between adiposity, blood pressure and plasma biomarkers, in UKB

		WC	SBP	DBP	LDL-cholesterol	HDL-cholesterol	Triglycerides	Total cholesterol	ApoA1	ApoB	Log hs-CRP	Albumin	Creatinine	Cystatin C	eGFR	ALT	AST	GGT	RPG	Uric acid	Vitamin D
BMI	**Men:**	0.88	0.19	0.28	0.09	-0.32	0.28	0.04	-0.25	0.15	0.35	-0.08	0.07	0.22	-0.08	0.29	0.11	0.14	0.12	0.34	-0.12
	Women:	0.88	0.21	0.32	0.15	-0.36	0.31	0.05	-0.28	0.19	0.51	-0.22	0.08	0.33	-0.08	0.20	0.05	0.15	0.12	0.43	-0.20
	All:	0.88	0.20	0.30	0.13	-0.34	0.28	0.05	-0.27	0.17	0.45	-0.16	0.08	0.28	-0.08	0.23	0.08	0.14	0.12	0.38	-0.17
WC	**Men:**	0.17	0.26	0.09	-0.33	0.29	0.04	-0.25	0.15	0.37	-0.09	0.04	0.24	-0.04	0.28	0.10	0.16	0.12	0.32	-0.15	
	Women:	0.19	0.31	0.17	-0.39	0.37	0.07	-0.29	0.22	0.50	-0.20	0.06	0.32	-0.05	0.21	0.06	0.17	0.13	0.42	-0.21	
	All:	0.18	0.29	0.14	-0.36	0.32	0.06	-0.28	0.19	0.44	-0.15	0.05	0.28	-0.05	0.24	0.08	0.16	0.12	0.38	-0.19	
SBP	**Men:**	0.74	0.10	0.03	0.11	0.12	0.07	0.11	0.11	0.13	-0.02	0.01	0.02	0.13	0.09	0.12	0.11	0.12	-0.07		
	Women:	0.74	0.11	-0.01	0.11	0.11	0.04	0.11	0.15	0.10	-0.02	0.05	0.02	0.09	0.05	0.09	0.10	0.13	-0.08		
	All:	0.74	0.10	0.00	0.11	0.12	0.05	0.11	0.13	0.12	-0.02	0.03	0.02	0.11	0.07	0.10	0.11	0.12	-0.07		
DBP	**Men:**	0.14	-0.04	0.14	0.14	0.02	0.16	0.14	0.12	0.00	0.06	-0.01	0.18	0.09	0.14	0.07	0.16	-0.08			
	Women:	0.14	-0.07	0.15	0.13	-0.01	0.15	0.20	0.06	0.00	0.10	-0.01	0.11	0.05	0.10	0.07	0.18	-0.10			
	All:	0.14	-0.06	0.14	0.13	0.00	0.15	0.18	0.08	0.00	0.08	-0.01	0.14	0.07	0.12	0.07	0.17	-0.09			
LDL-cholesterol	**Men:**	0.01	0.24	0.95	0.02	0.95	0.06	0.18	0.00	0.00	-0.02	0.11	0.02	0.08	-0.02	0.12	-0.10				
	Women:	-0.10	0.32	0.93	-0.06	0.95	0.09	0.14	-0.01	0.08	0.00	0.09	0.03	0.08	0.02	0.13	-0.12				
	All:	-0.05	0.28	0.94	-0.03	0.95	0.08	0.16	0.00	0.04	-0.01	0.10	0.02	0.08	0.00	0.13	-0.11				
HDL-cholesterol	**Men:**	-0.43	0.23	0.92	-0.12	-0.22	0.12	-0.06	-0.22	0.09	-0.13	0.03	0.04	-0.04	-0.13	0.10					
	Women:	-0.44	0.23	0.90	-0.22	-0.28	0.20	-0.02	-0.23	0.01	-0.10	0.01	-0.04	-0.06	-0.20	0.10					
	All:	-0.42	0.23	0.91	-0.18	-0.25	0.17	-0.04	-0.22	0.03	-0.11	0.02	0.00	-0.05	-0.17	0.10					
Triglicerides	**Men:**	0.30	-0.27	0.30	0.16	0.05	0.02	0.14	-0.01	0.23	0.09	0.17	0.08	0.23	-0.19						
	Women:	0.28	-0.24	0.36	0.28	-0.03	0.00	0.20	0.01	0.18	0.07	0.16	0.12	0.28	-0.17						
	All:	0.29	-0.25	0.33	0.21	0.01	0.01	0.16	0.00	0.21	0.08	0.17	0.10	0.25	-0.18						
Total cholesterol	**Men:**	0.25	0.88	0.02	0.20	-0.02	-0.03	0.00	0.10	0.04	0.12	-0.02	0.12	-0.10							
	Women:	0.27	0.84	0.02	0.20	-0.02	0.02	0.01	0.07	0.04	0.08	0.01	0.09	-0.10							
	All:	0.26	0.86	0.02	0.20	-0.02	-0.01	0.01	0.09	0.04	0.10	-0.01	0.10	-0.10							
ApoA1	**Men:**	-0.11	-0.20	0.16	-0.06	-0.18	0.06	-0.09	0.04	0.09	-0.02	-0.07	0.07								
	Women:	-0.17	-0.19	0.21	-0.03	-0.17	0.02	-0.07	0.02	0.00	-0.03	-0.12	0.08								
	All:	-0.14	-0.19	0.19	-0.04	-0.17	0.04	-0.08	0.03	0.04	-0.03	-0.10	0.07								
ApoB	**Men:**	0.11	0.15	0.00	0.04	-0.02	0.15	0.03	0.10	0.01	0.17	-0.11									
	Women:	0.15	0.10	-0.01	0.10	0.01	0.11	0.03	0.09	0.03	0.18	-0.12									
	All:	0.13	0.12	-0.01	0.07	0.00	0.13	0.03	0.09	0.02	0.17	-0.11									
Log hs-CRP	**Men:**	-0.17	0.02	0.24	0.00	0.16	0.09	0.18	0.08	0.20	-0.08										
	Women:	-0.23	0.04	0.27	-0.03	0.17	0.08	0.20	0.09	0.33	-0.10										
	All:	-0.21	0.03	0.26	-0.02	0.17	0.09	0.19	0.08	0.27	-0.09										
Albumin	**Men:**	0.00	-0.09	-0.01	0.08	0.04	0.01	0.00	0.06	0.02											
	Women:	-0.04	-0.12	0.02	0.04	0.05	0.02	0.00	-0.03	0.07											
	All:	-0.02	-0.11	0.01	0.06	0.05	0.02	0.00	0.01	0.05											
Creatinine	**Men:**	0.57	-0.84	-0.01	-0.02	-0.04	-0.04	0.25	0.06												
	Women:	0.53	-0.88	-0.01	0.01	-0.01	-0.01	0.28	0.05												
	All:	0.55	-0.85	-0.01	-0.01	-0.03	-0.03	0.26	0.06												
Cystatin C	**Men:**	-0.41	0.08	0.04	0.06	-0.03	0.26	-0.05													
	Women:	-0.42	0.11	0.07	0.10	0.00	0.39	-0.07													
	All:	-0.42	0.09	0.06	0.08	-0.01	0.33	-0.06													
eGFR	**Men:**	0.02	0.03	0.07	0.06	-0.28	-0.09														
	Women:	0.02	0.00	0.03	0.03	-0.29	-0.07														
	All:	0.02	0.01	0.05	0.05	-0.28	-0.08														
ALT	**Men:**	0.73	0.42	0.12	0.20	-0.10															
	Women:	0.78	0.50	0.08	0.19	-0.05															
	All:	0.75	0.45	0.10	0.20	-0.07															
AST	**Men:**	0.43	0.05	0.13	-0.03																
	Women:	0.43	0.03	0.11	0.00																
	All:	0.43	0.05	0.12	-0.01																
GGT	**Men:**	0.10	0.15	-0.08																	
	Women:	0.07	0.17	-0.05																	
	All:	0.08	0.16	-0.06																	
RPG	**Men:**	0.01	-0.06																		
	Women:	0.08	-0.05																		
	All:	0.04	-0.06																		
Uric acid	**Men:**	-0.02																			
	Women:	-0.06																			
	All:	-0.04																			

Pearson correlation coefficients, adjusted for sex, age (5-years group) and assessment centre (except where it is the variable of interest).
ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, BMI: body mass index, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein, RPG: random plasma glucose, SBP: systolic blood pressure, WC: waist circumference

Table B.2. Plasma biomarker increments per 1 SD higher BMI by sex, in UKB

Plasma biomarkers	Men		Women	
	Mean[a] (SD)	Estimate[a] (SE) per 1 SD higher BMI	Mean[a] (SD)	Estimate[a] (SE) per 1 SD higher BMI
Lipids and lipoproteins				
LDL-cholesterol, mmol/L	3.65 (0.71)	0.06 (0.002)	3.61 (0.73)	0.10 (0.001)
HDL-cholesterol, mmol/L	1.30 (0.31)	-0.10 (0.001)	1.60 (0.37)	-0.13 (0.001)
Triglycerides, mmol/L	1.91 (1.06)	0.30 (0.002)	1.50 (0.77)	0.24 (0.001)
Total cholesterol, mmol/L	5.68 (0.92)	0.04 (0.002)	5.84 (0.93)	0.04 (0.002)
ApoA1, mg/dL	1.43 (0.23)	-0.06 (0.001)	1.63 (0.27)	-0.07 (0.001)
ApoB, mg/dL	1.06 (0.21)	0.03 (0.001)	1.03 (0.21)	0.04 (0.001)
Inflammatory				
Log hs-CRP, log mg/L	0.27 (1.03)	0.36 (0.003)	0.31 (1.11)	0.56 (0.002)
Albumin, g/L	45.53 (2.56)	-0.21 (0.01)	44.89 (2.55)	-0.56 (0.01)
Renal function				
Creatinine, umol/L	80.84 (14.70)	1.09 (0.04)	63.85 (11.40)	0.93 (0.03)
Cystatin C, mg/L	0.92 (0.15)	0.03 (0.001)	0.86 (0.14)	0.04 (0.001)
eGFR, ml/min/1.73m^2	94.35 (16.73)	-1.35 (0.04)	92.09 (16.89)	-1.33 (0.04)
Liver function				
ALT, u/L	26.85 (15.34)	4.37 (0.04)	19.45 (12.21)	2.40 (0.03)
AST, u/L	27.82 (11.47)	1.28 (0.03)	23.98 (9.65)	0.46 (0.02)
GGT, u/L	42.89 (45.01)	6.42 (0.12)	28.38 (31.21)	4.79 (0.07)
Other				
RPG, mmol/L	5.03 (1.04)	0.13 (0.003)	4.97 (0.85)	0.10 (0.002)
Uric acid, umol/L	351.12 (68.98)	23.13 (0.18)	264.59 (62.65)	26.42 (0.13)
Vitamin D, mg/ml	48.16 (21.17)	-2.41 (0.06)	48.50 (21.03)	-4.22 (0.05)

[a]Adjusted for age (5-year groups) and assessment centre. The estimates of plasma biomarkers per 1 SD higher adiposity measures were estimated using sex-specific SDs. SD of BMI 4.06 kg/m^2 for men and 5.05 kg/m^2 for women.

ALT: alanine aminotransferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate aminotransferase, BMI: body mass index, eGFR: estimated glomerular filtration rate, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein, RPG: random plasma glucose.

Figure B.1. Distribution of lipids and lipoproteins, in CKB

ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol

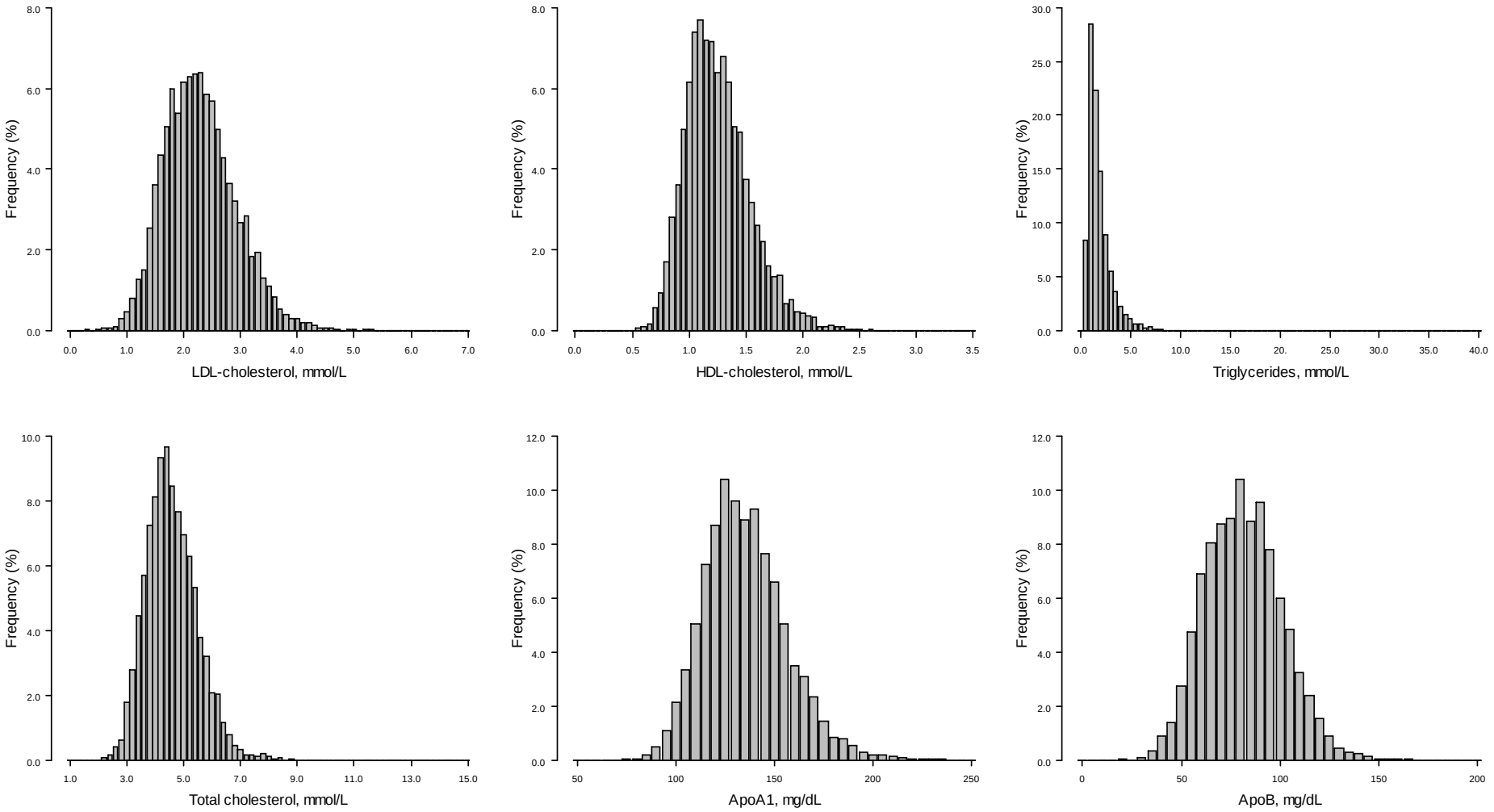


Figure B.2. Distribution of inflammatory and renal function biomarkers, in CKB

eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

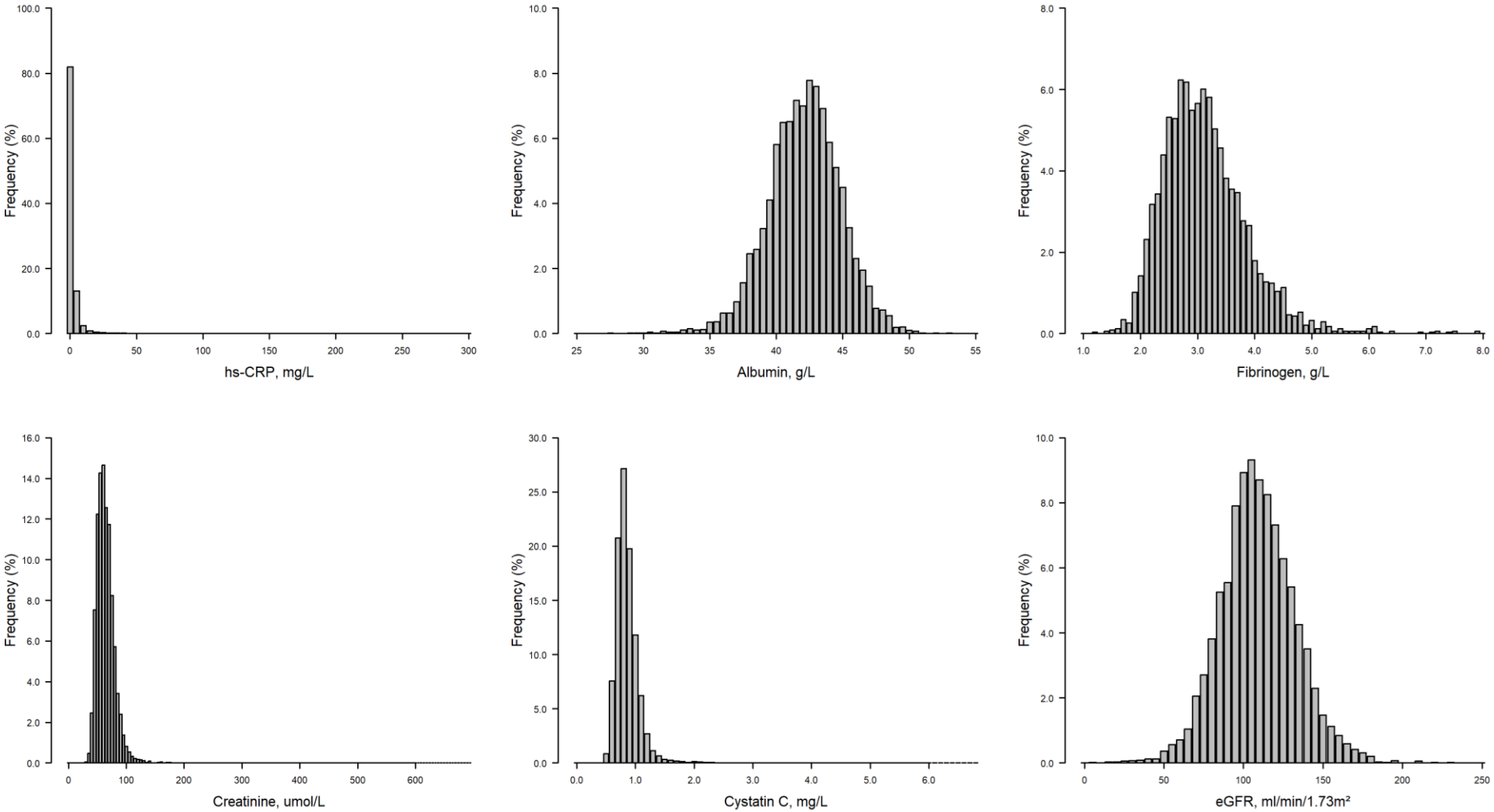


Figure B.3. Distribution of liver function and other plasma biomarkers, in CKB

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

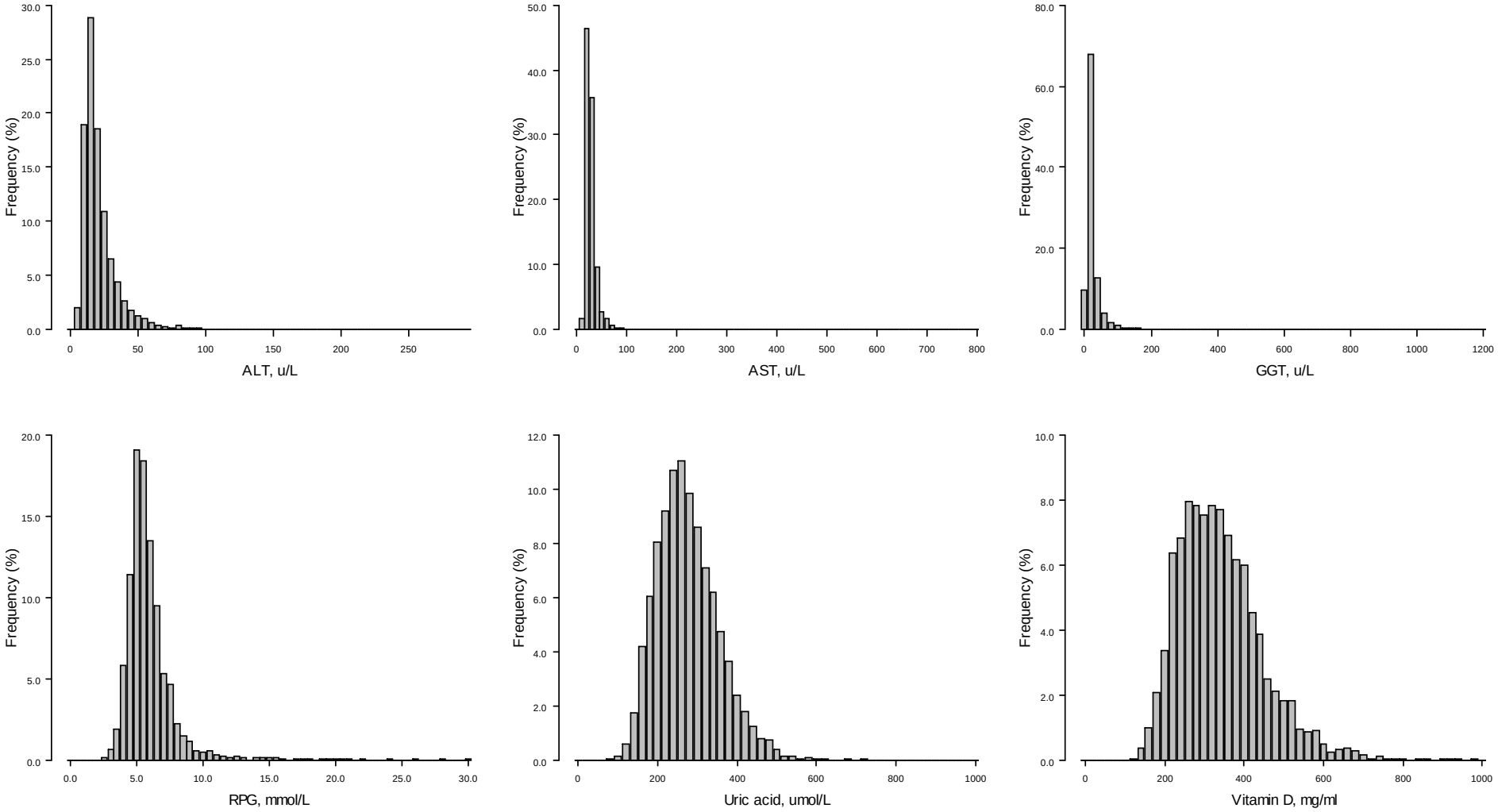


Figure B.4. Association of waist-to-hip ratio with lipids and lipoproteins by sex, in CKB

Mean values adjusted for age (5-year groups) and study area, by sex. Each closed square represents the mean value. The $\bar{x}$ above the x-axis represents the mean value of adiposity measure and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The vertical lines indicate 95% Cis. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.

ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol, WHR: waist-to-hip ratio.

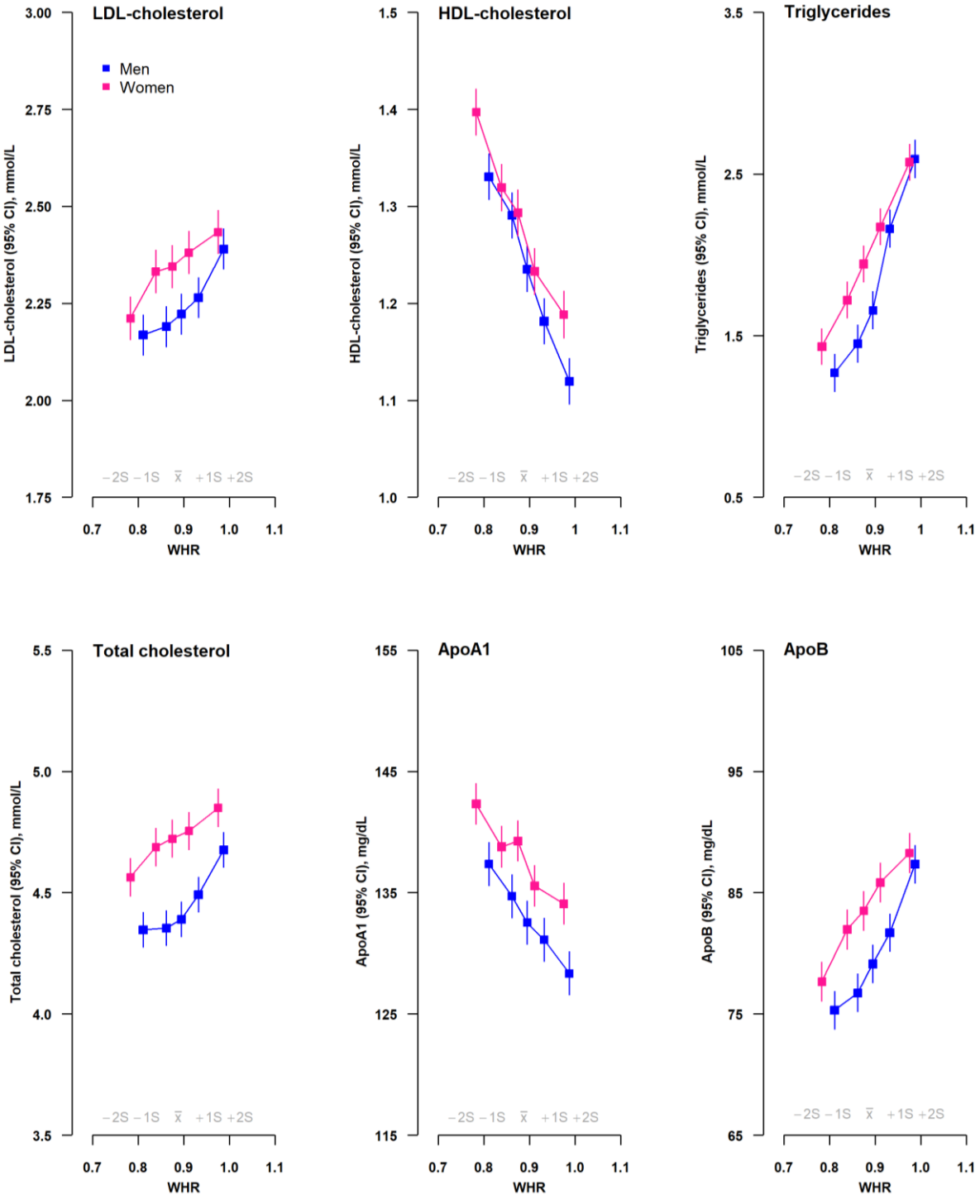


Figure B.5. Association of body fat percentage with lipids and lipoproteins by sex, in CKB

Conventions as Figure B.4.
Mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol.

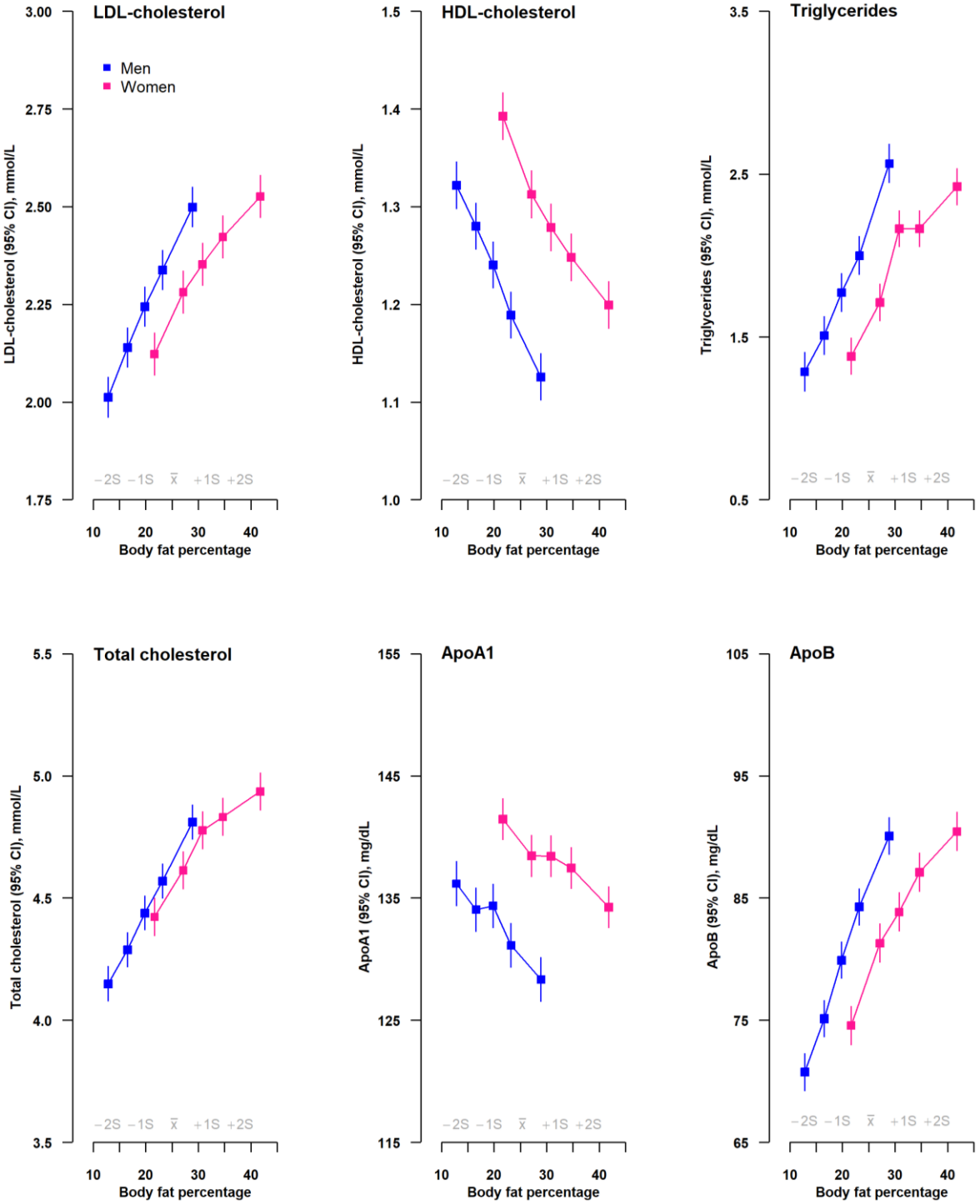


Figure B.6. Association of BMI with lipids and lipoproteins by diabetes status at baseline, in CKB

Mean values adjusted for age (5-year groups) and study area, by alcohol status in men. Participants were classified as having diabetes if they answered yes to the question “Has a doctor ever told you that you had diabetes?” or if they had random plasma glucose level ≥7.0 mmol/L if time since last food ≥8 hours, or ≥11.1 mmol/L if time since last food <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L. ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol.

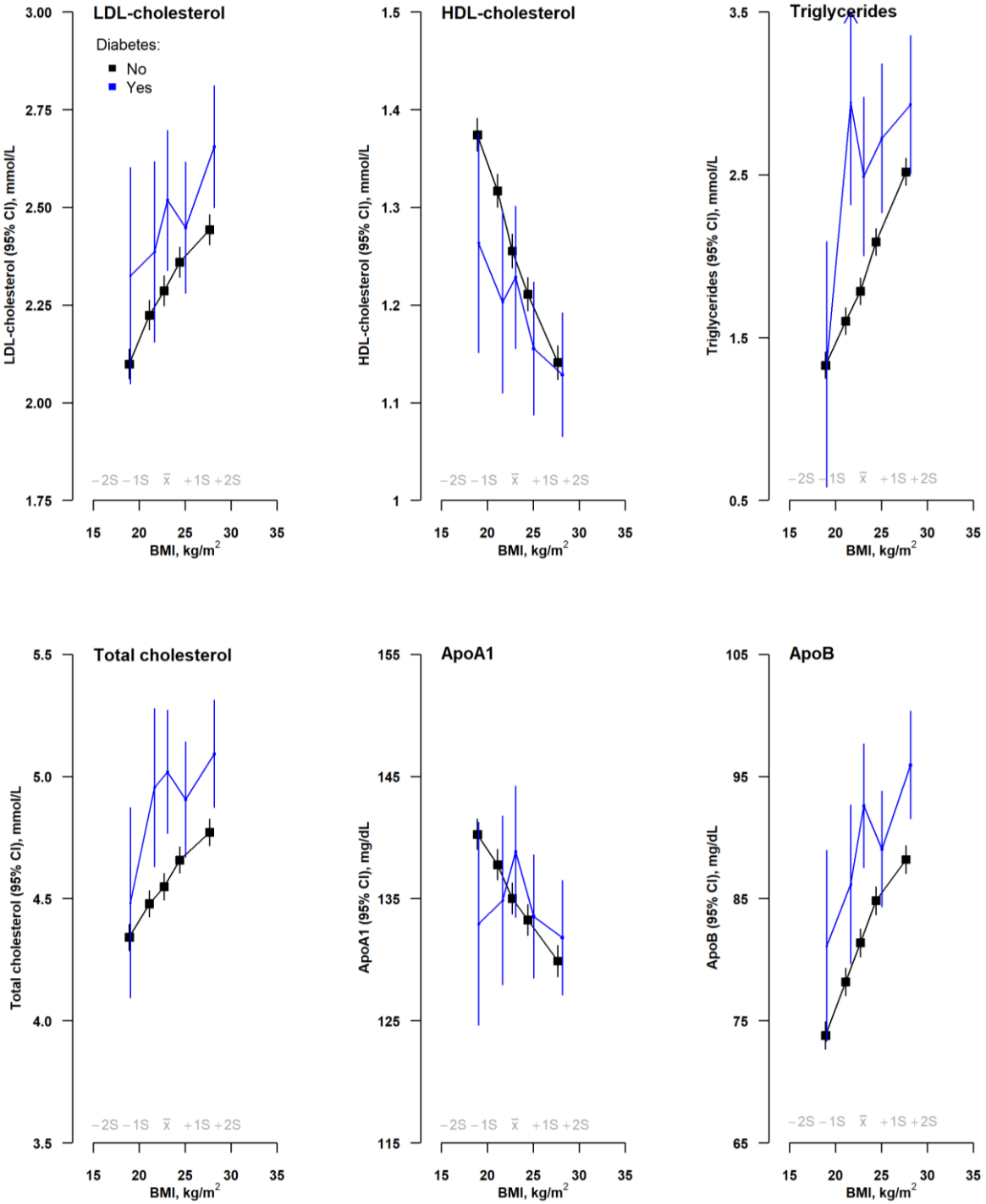


Figure B.7. Association of BMI with lipids and lipoproteins by hypertension status at baseline, in CKB

Mean values adjusted for age (5-year groups) and study area, by alcohol status in men. Participants were classified as having hypertension if they answered yes to the question “Has a doctor ever told you that you had hypertension?”. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol.

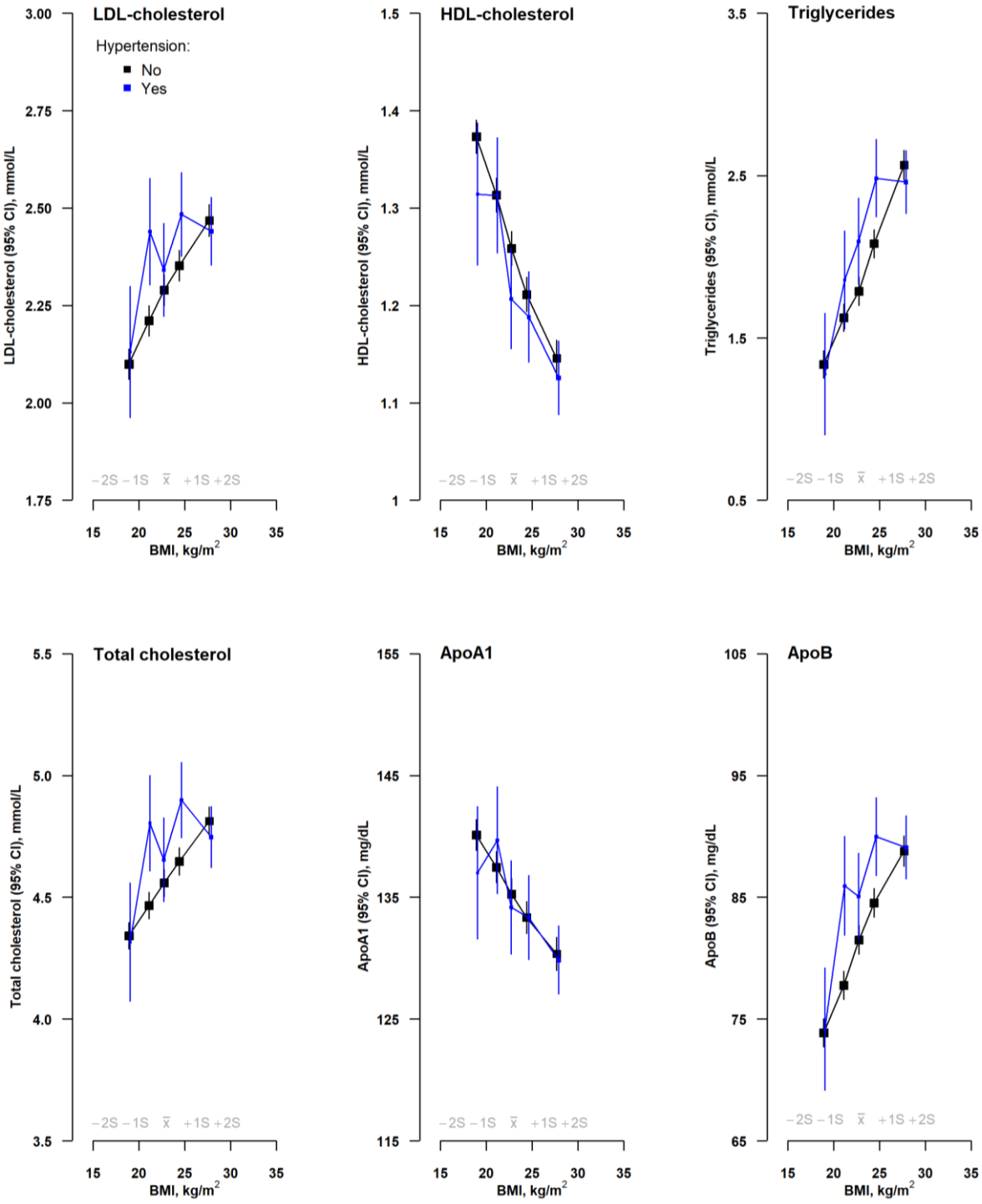


Figure B.8. The association of BMI with lipids and lipoproteins by smoking status among CKB men

Mean values adjusted for age (5-year groups) and study area, by smoking status in men. Participants were classified as ever-regular smokers if they answered “on most days” or “daily or almost every day” to either “How often do you smoke tobacco now?” or “In the past, how frequently did you smoke?”. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L.
ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol.

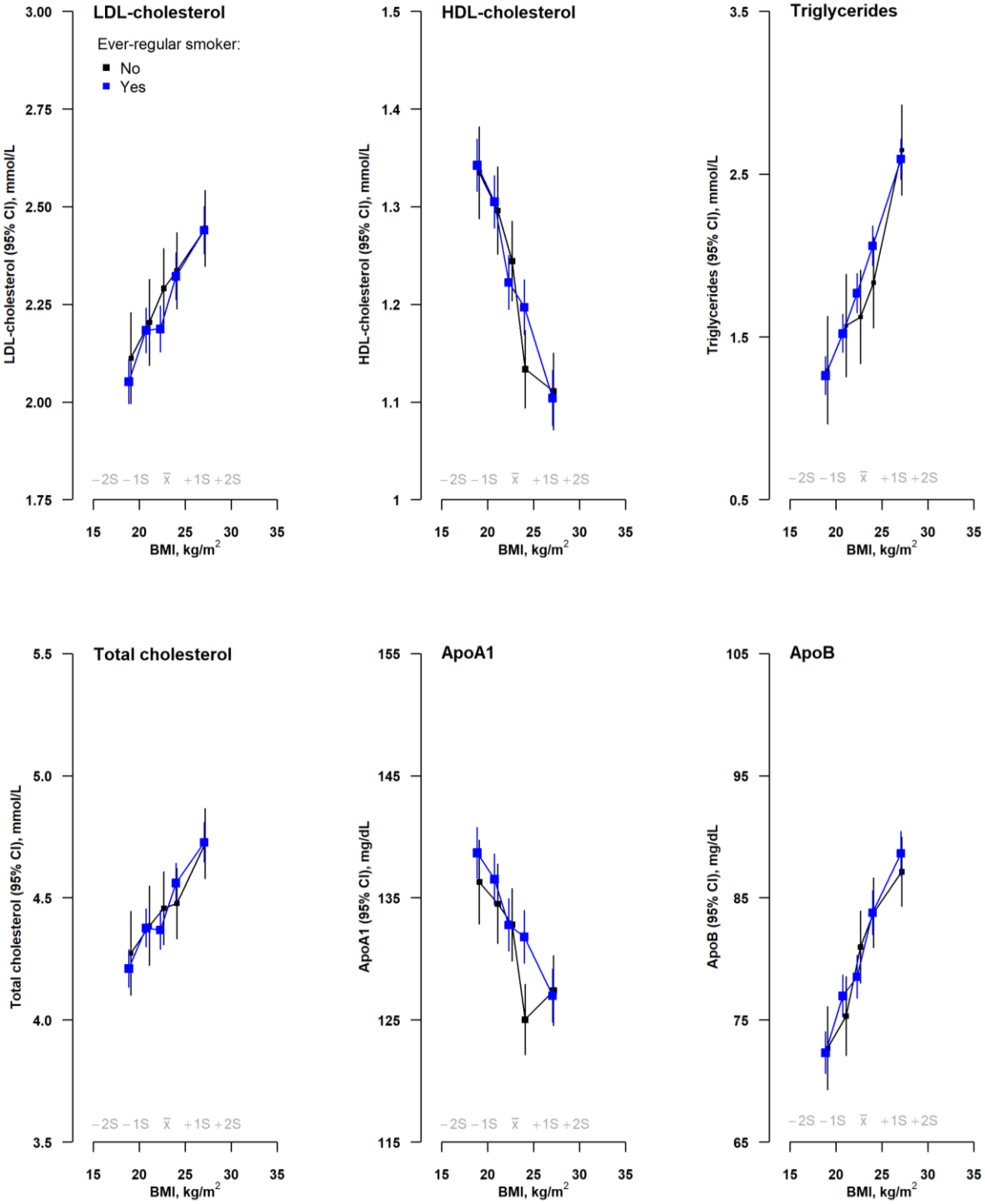


Figure B.9. Association of BMI with lipids and lipoproteins by alcohol consumption among CKB men

Mean values adjusted for age (5-year groups) and study area, by alcohol status in men. Participants were classified as ever-regular alcohol drinkers if they answered “usually at least once a week” to the question “During the past 12 months, how often did you drink alcohol?” or they answered yes to the question “In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?”. Each closed square represents the mean value. The vertical lines indicate 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively. The length of y-axis represents approximately ± 1 SD from the mean of the corresponding plasma biomarker, mean (SD): ApoA1: 135.3 (20.2) mg/dL, ApoB: 81.7 (18.4) mg/dL, HDL-cholesterol: 1.3 (0.3) mmol/L, LDL-cholesterol: 2.3 (0.6) mmol/L, total cholesterol: 4.6 (0.9) mmol/L, triglycerides: 1.9 (1.4) mmol/L. ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, BMI: body mass index, HDL-cholesterol: high-density lipoprotein cholesterol, LDL-cholesterol: low-density lipoprotein cholesterol.

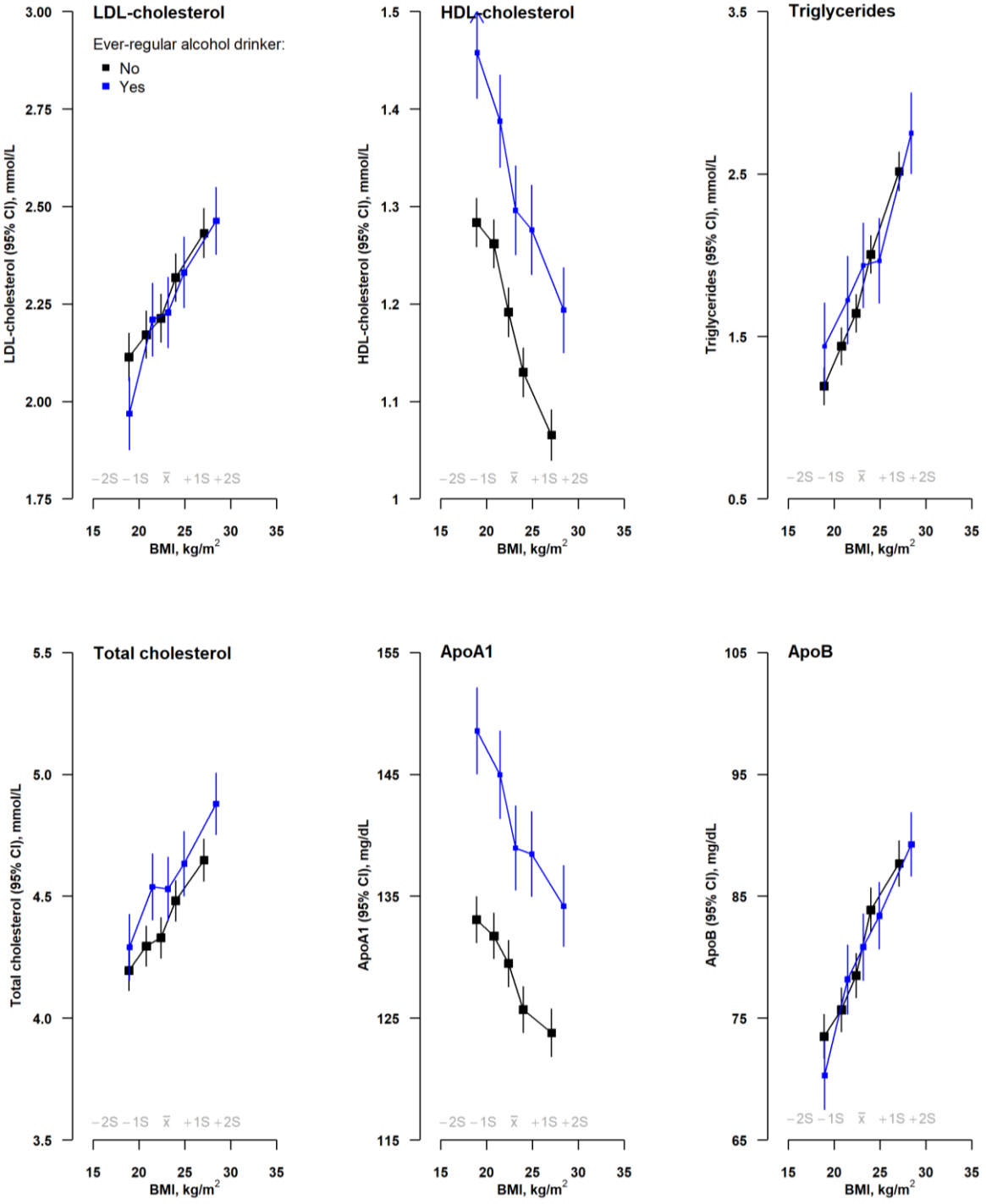


Figure B.10. Association of BMI with inflammatory and renal function plasma biomarkers by smoking status in CKB men

Conventions as Figure B.6.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were available for 2877 men.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

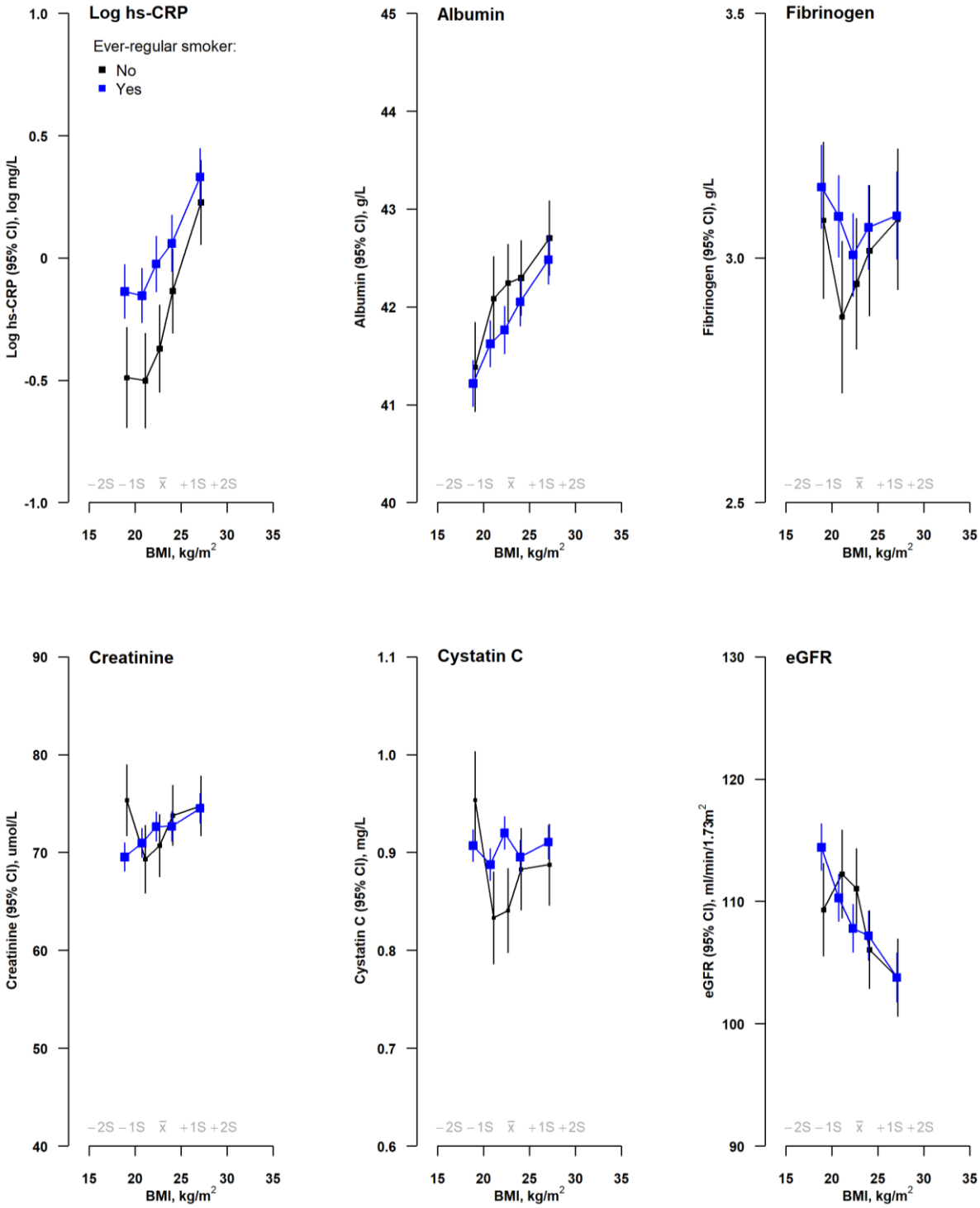


Figure B.11. Association of BMI with inflammatory and renal function plasma biomarkers by alcohol consumption in CKB men

Conventions as Figure B.7.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were available for 2877 men.
BMI: body mass index, eGFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

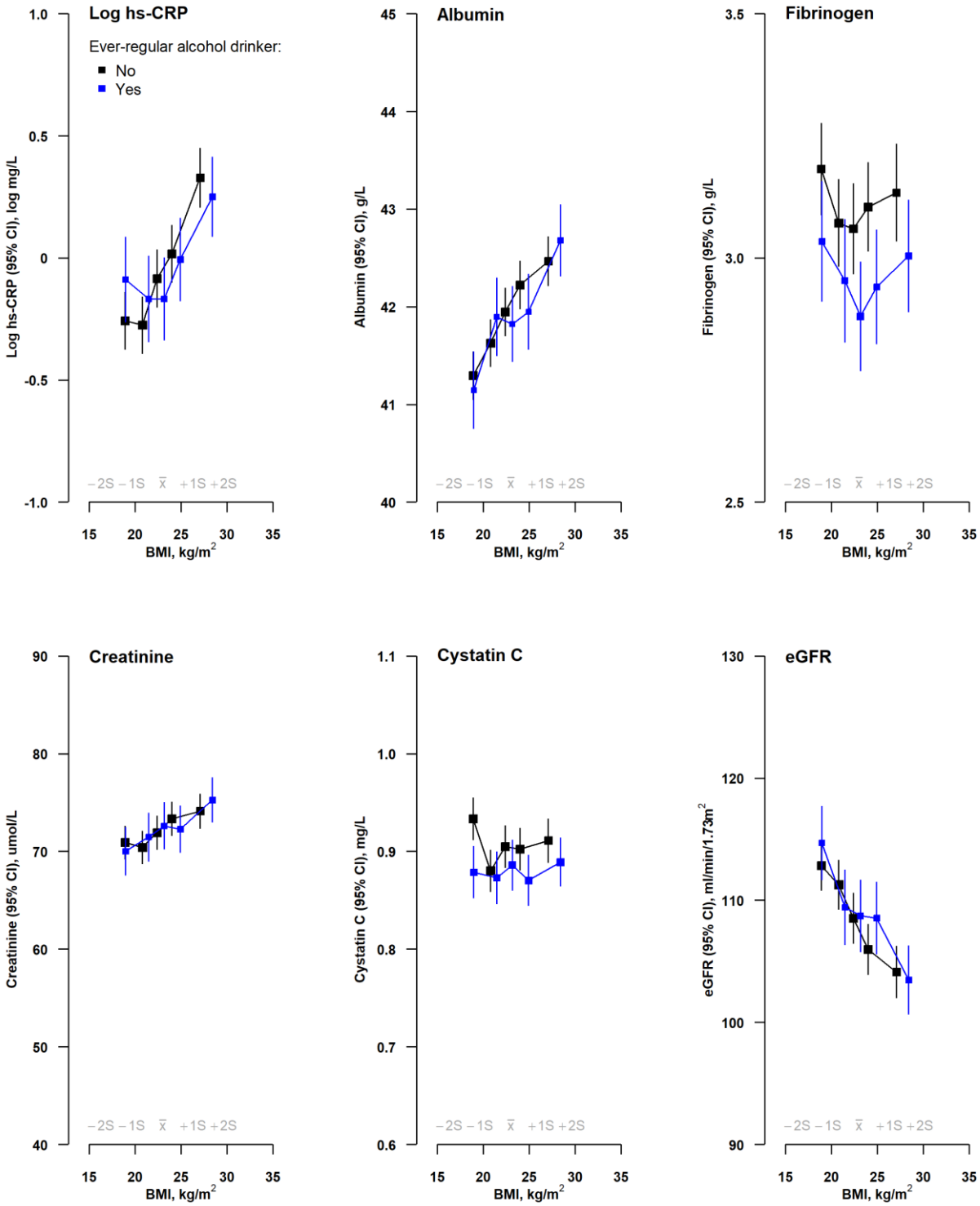


Figure B.12. Association of BMI with inflammatory and renal function plasma biomarkers by diabetes status at baseline, in CKB

Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were data were available for 3460 participants.

BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

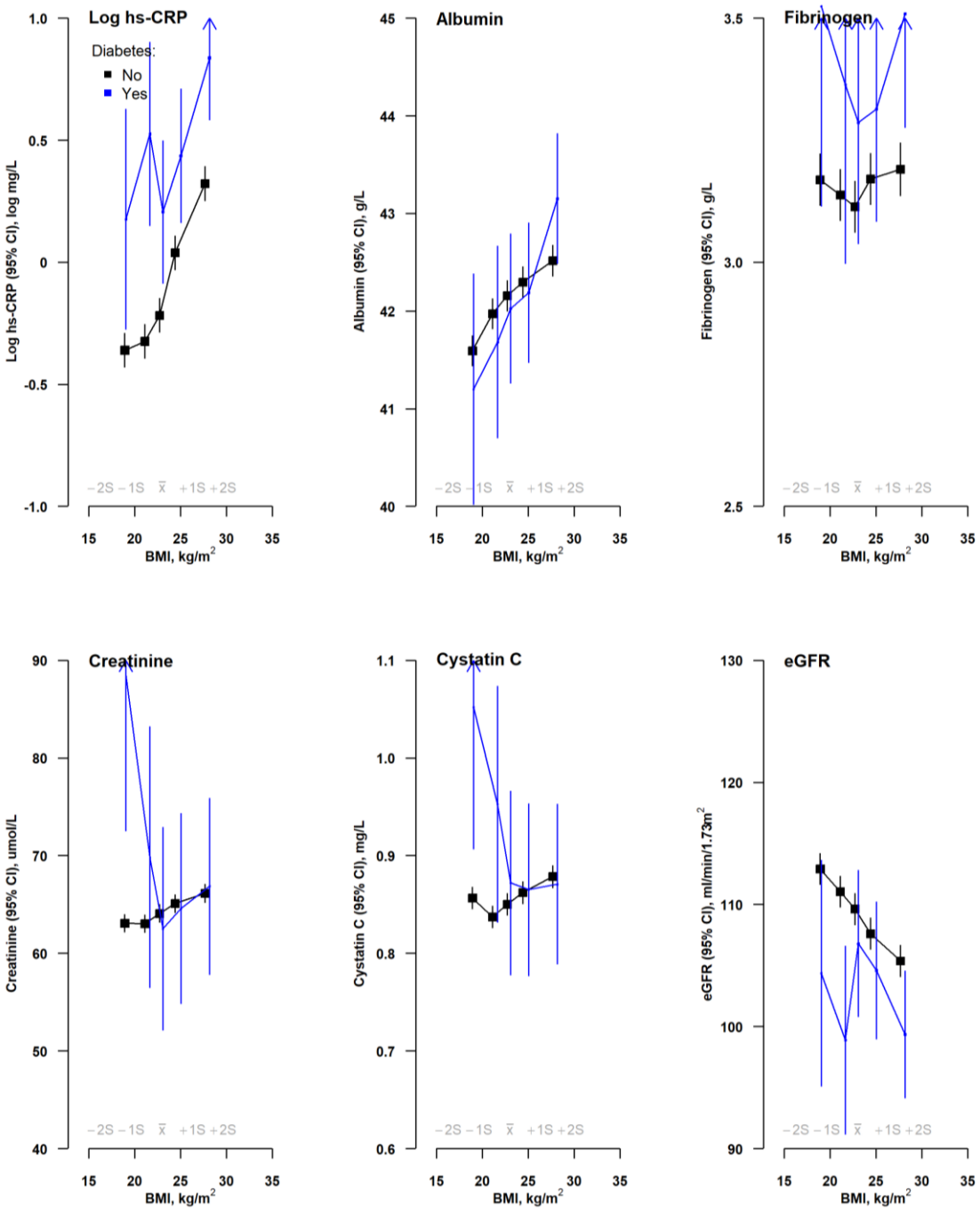


Figure B.13. Association of BMI with inflammatory and renal function plasma biomarkers by hypertension status at baseline, in CKB

Conventions as Figure B.9.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were available for 3460 participants.
BMI: body mass index, eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

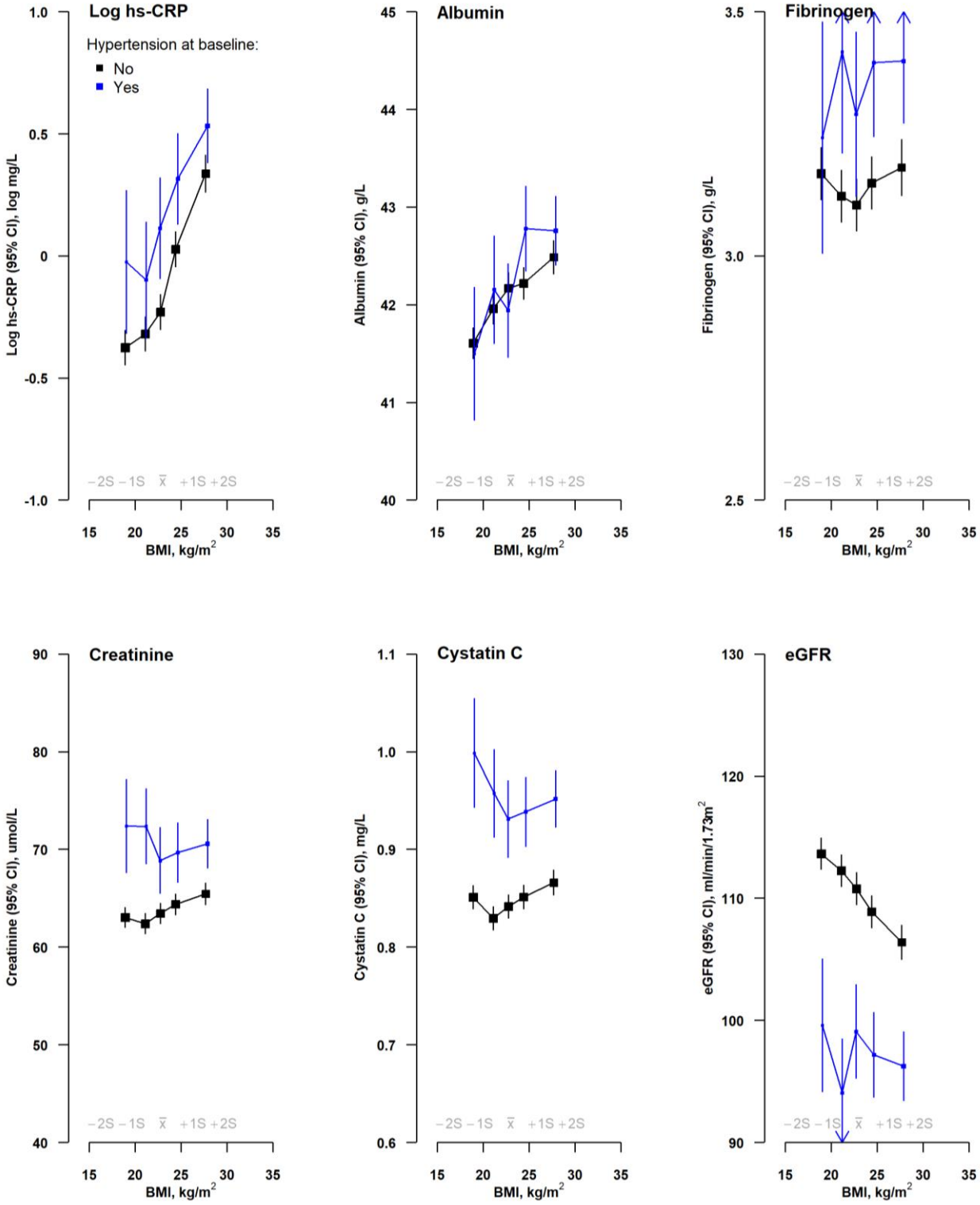


Figure B.14. Association of waist-to-hip ratio with inflammatory and renal function plasma biomarkers by sex, in CKB

Conventions as Figure B.4.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were available for 3460 participants.
eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, WHR: waist-to-hip ratio.

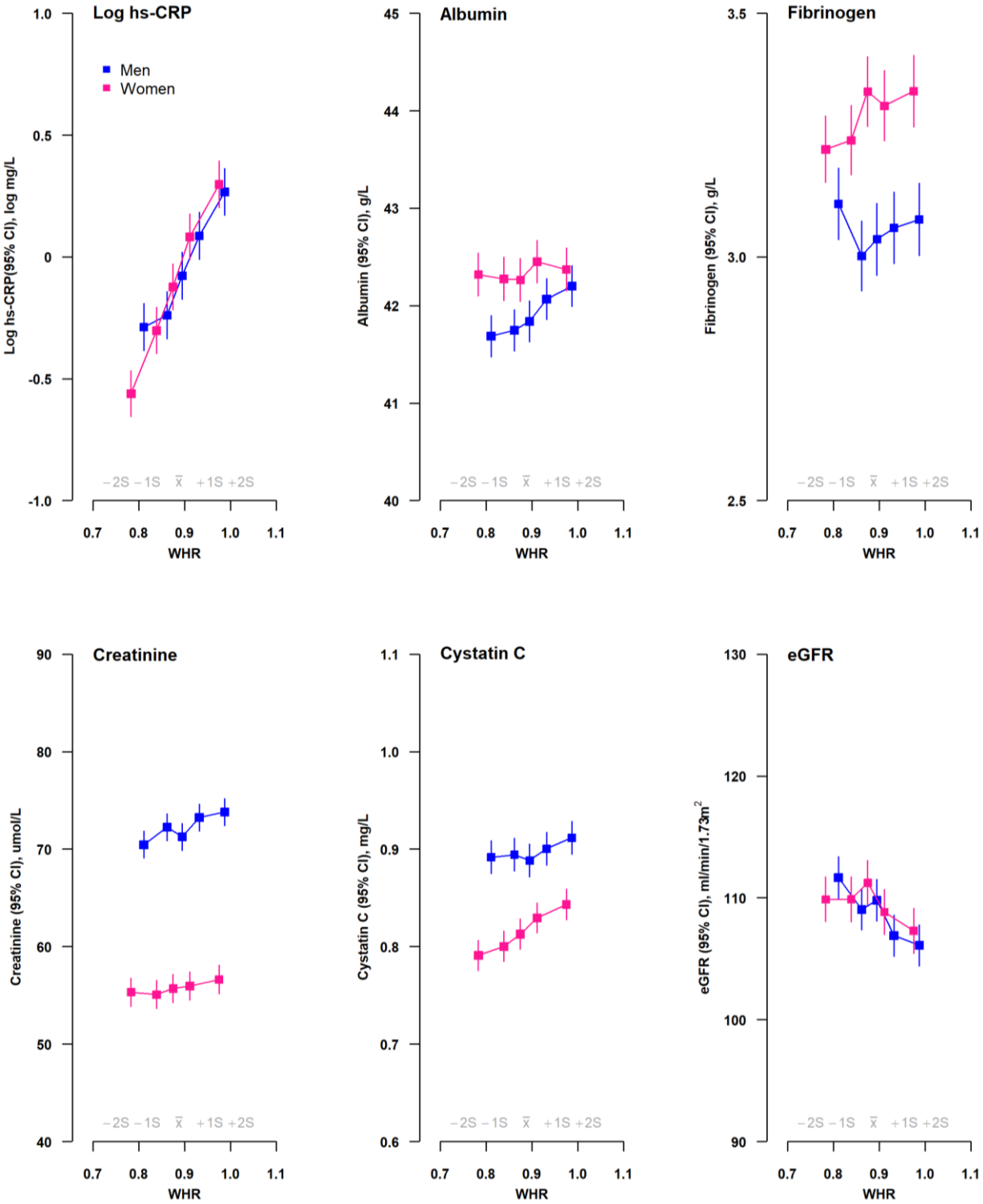


Figure B.15. Association of body fat percentage with inflammatory and renal function plasma biomarkers by sex, in CKB

Conventions as Figure B.4.
Mean (SD): albumin: 42.1 (2.5) g/L, creatinine: 64.4 (16.1) umol/L, cystatin C: 0.9 (0.2) mg/L, eGFR: 109.1 (20.2) ml/min/1.73m^2, fibrinogen: 3.1 (0.7) g/L, log hs-CRP: -0.01 (1.1) log mg/L. Fibrinogen data were available for 3460 participants.
eGFR: estimate glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein.

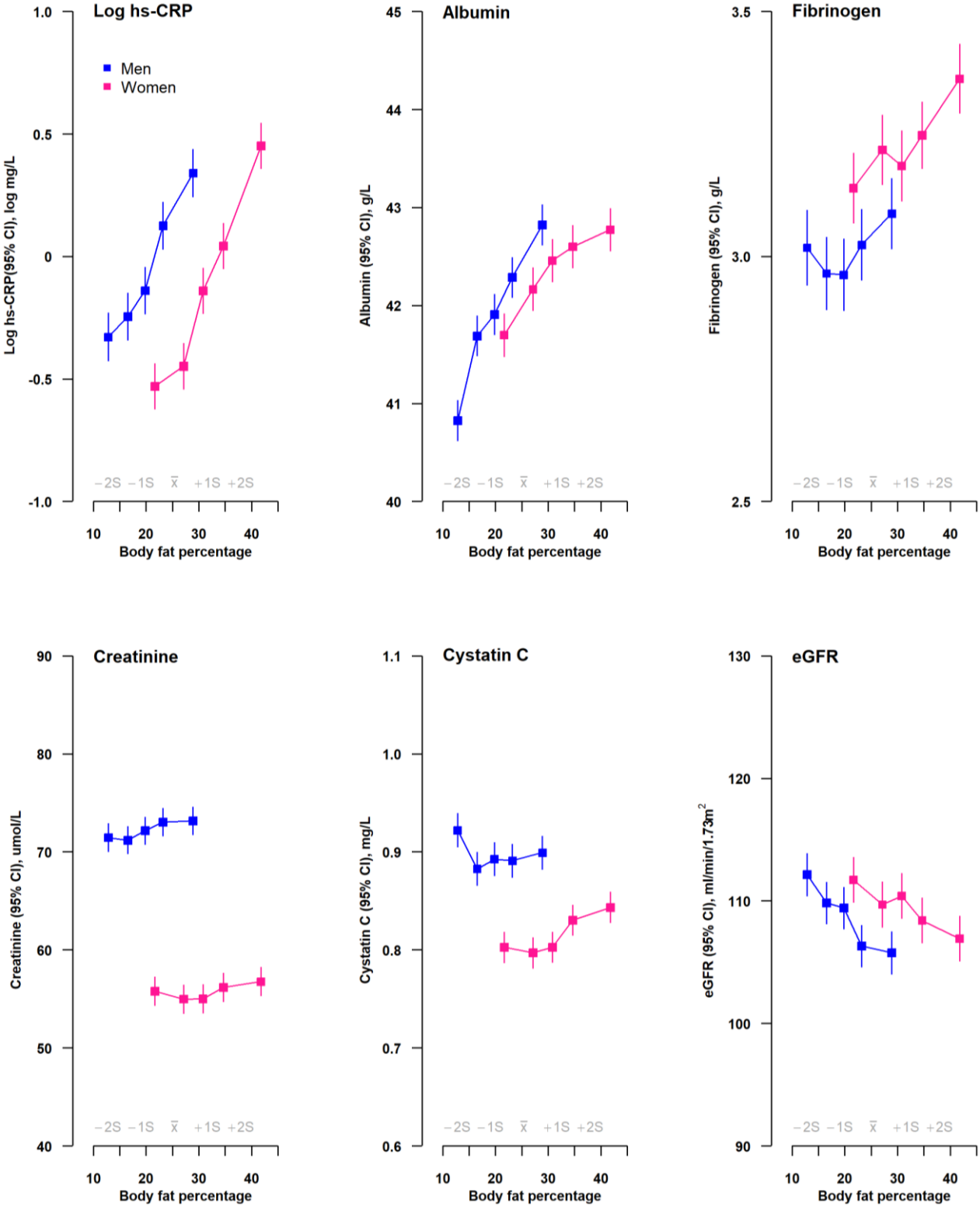


Figure B.16. Association of BMI with liver function and other plasma biomarkers by alcohol consumption among CKB men

Conventions as Figure B.7.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 2877 men.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

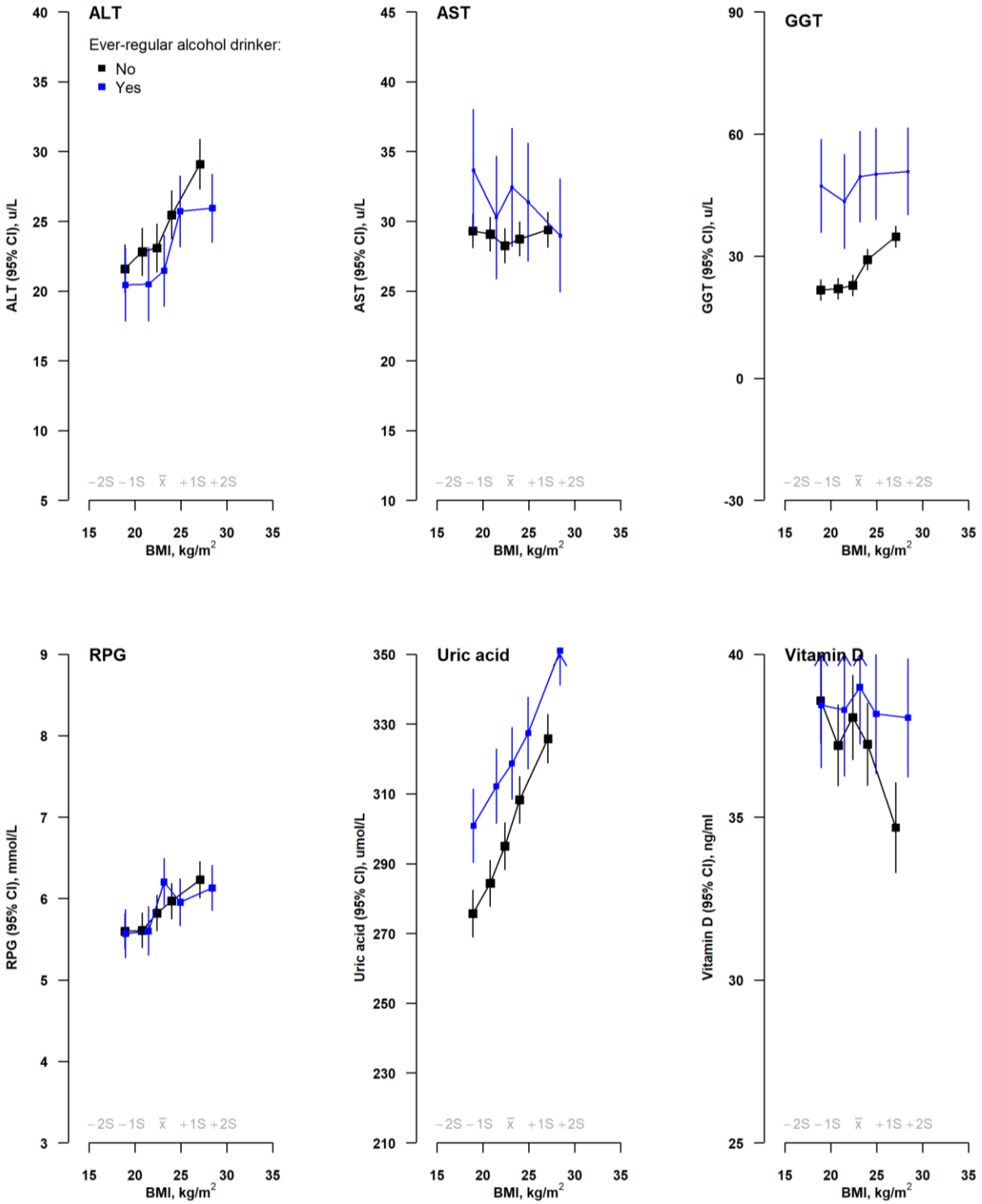


Figure B.17. Association of BMI with liver function and other plasma biomarkers by smoking status among CKB men

Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 2877 men.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

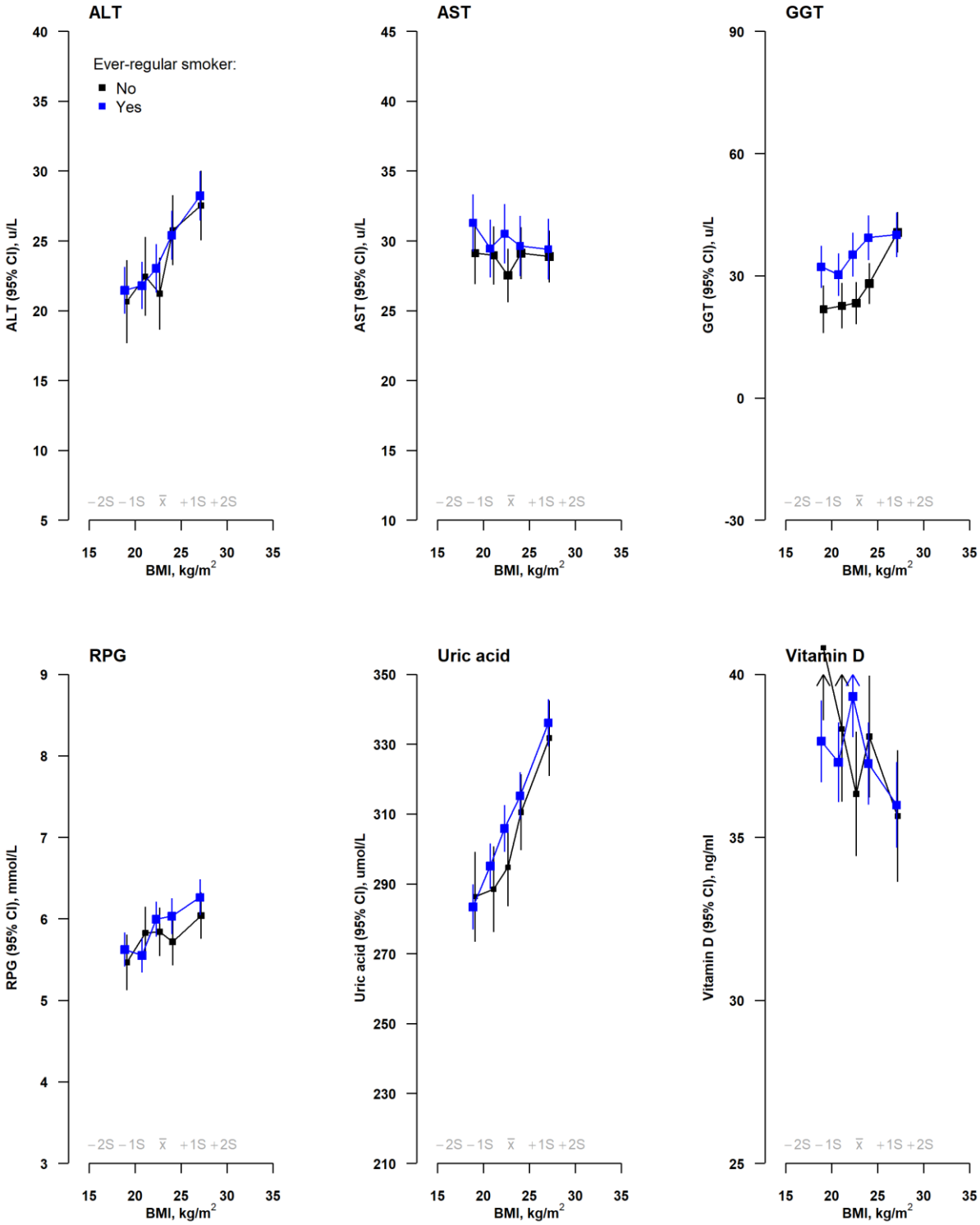


Figure B.18. Association of BMI with liver function and other plasma biomarkers by diabetes status at baseline, in CKB

Conventions as Figure B.8.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 3346 men.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

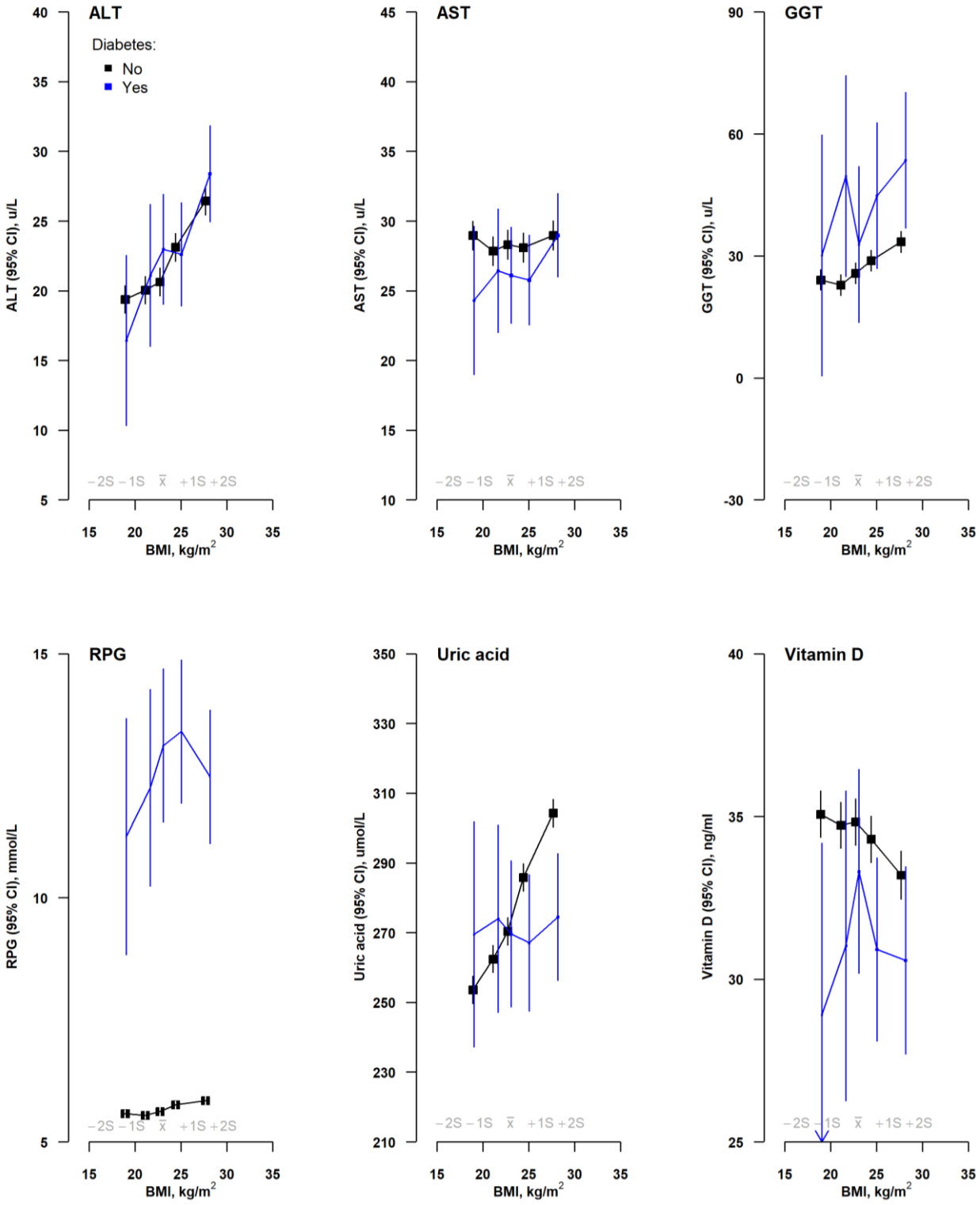


Figure B.19. The association of BMI with liver function and other plasma biomarkers by hypertension status at baseline, in CKB

Conventions as Figure B.9.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

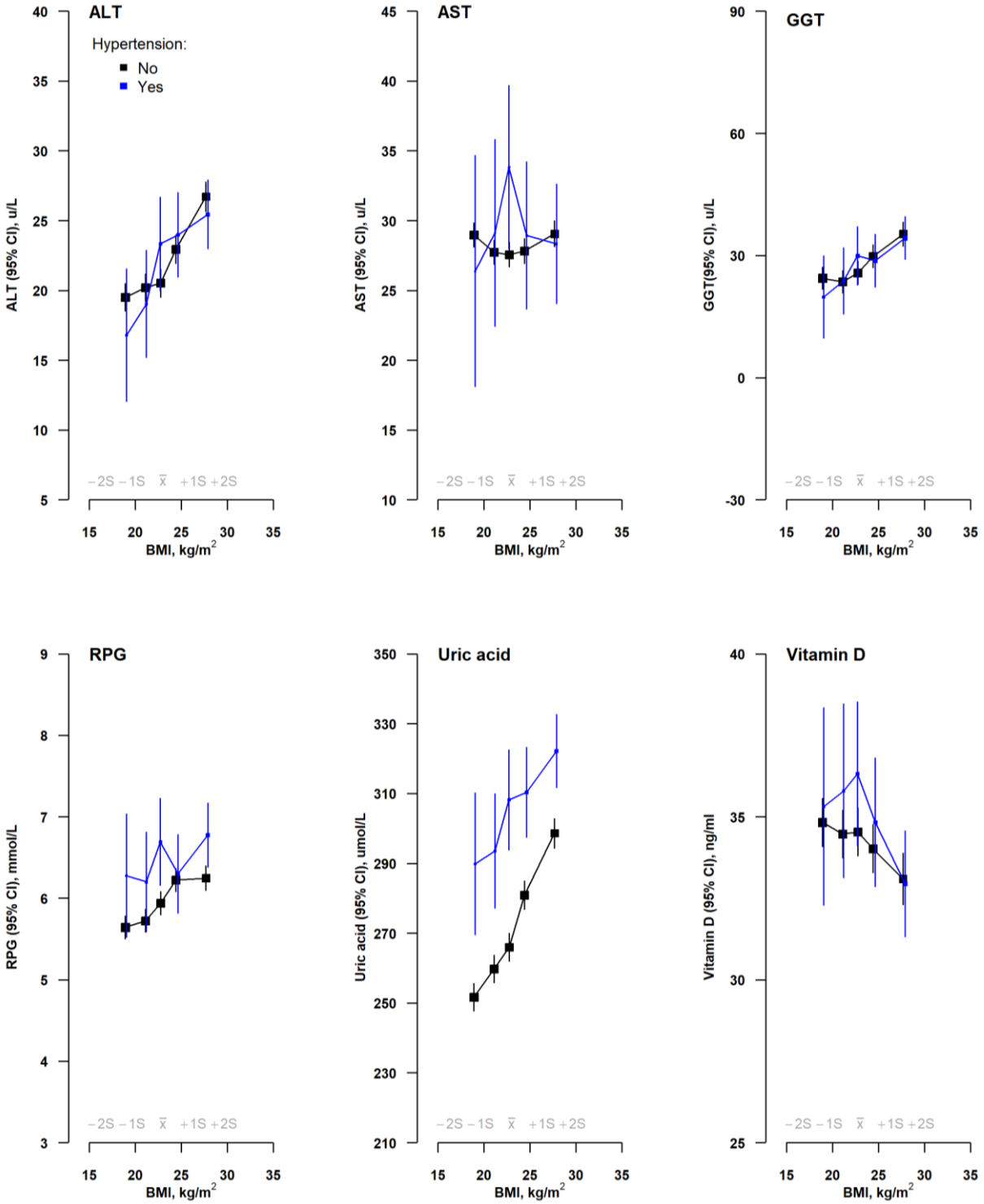


Figure B.20. Association of waist-to-hip ratio with liver function and other plasma biomarkers by sex, in CKB

Conventions as Figure B.4.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyl transferase, RPG: random plasma glucose, WHR: waist-to-hip ratio.

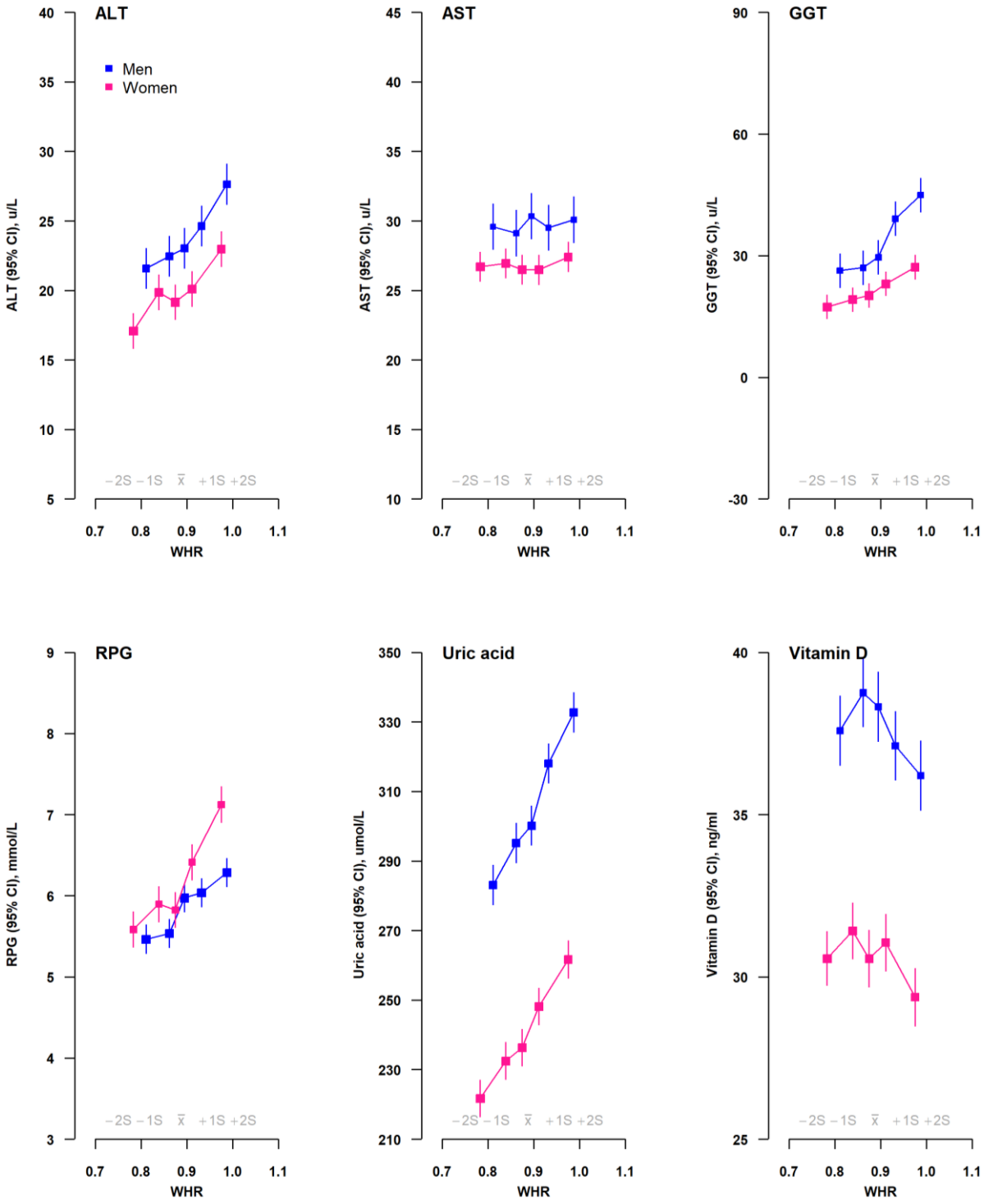


Figure B.21. Association of body fat percentage with liver function and other plasma biomarkers by sex, in CKB

Conventions as Figure B.4.
Mean (SD): ALT: 22.0 (15.6) u/L, AST: 28.4 (16.1) u/L, GGT: 27.8 (42.0) u/L, RPG: 6.0 (2.3) mmol/L, uric acid: 274.8 (64.9) umol/L, vitamin D: 34.1 (8.7) ng/ml. Vitamin D data were available for 3346 participants.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyl transferase, RPG: random plasma glucose.

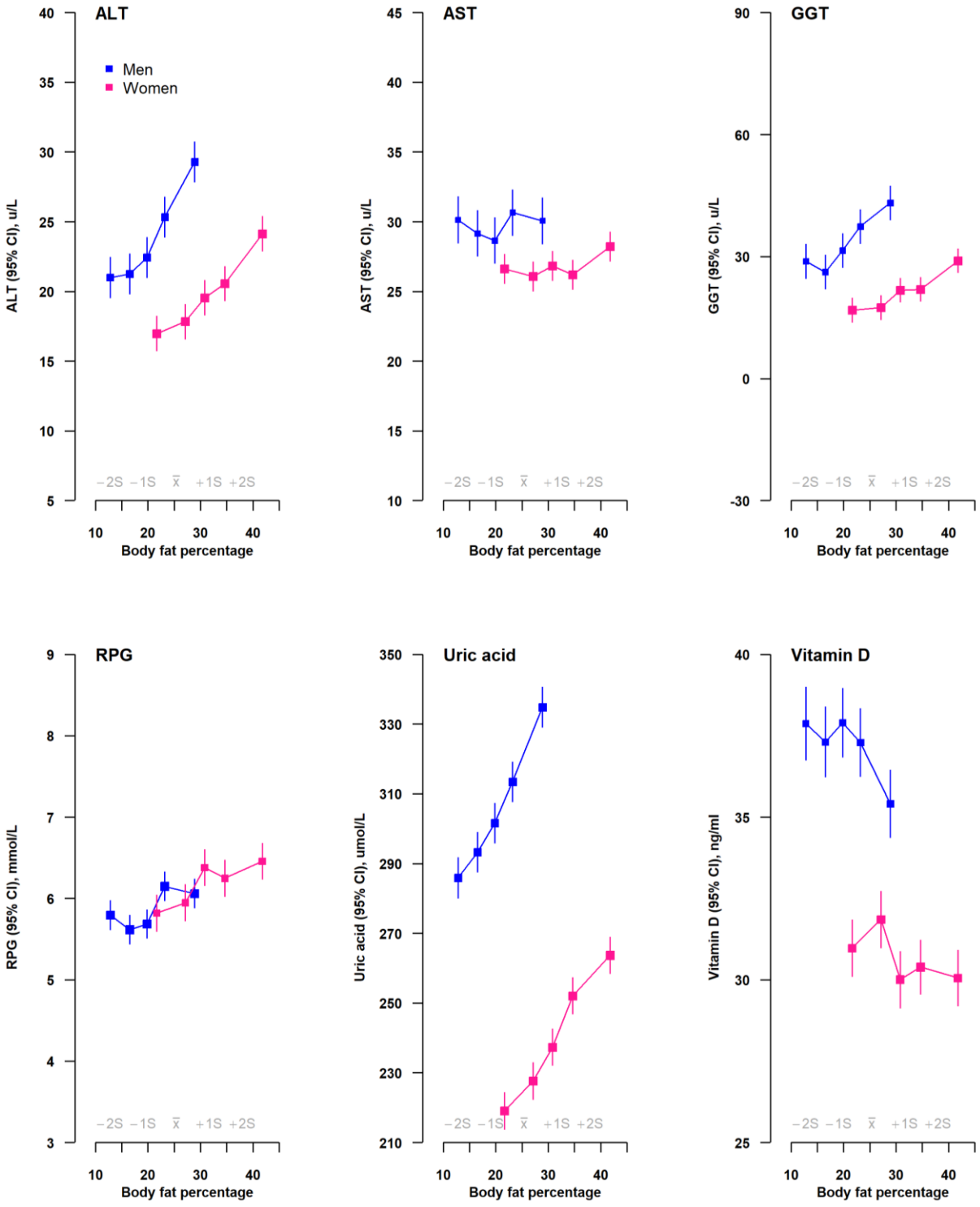


Figure B.22. Associations per SD higher of apolipoprotein B with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types per 1 SD (21.2 mgl/dL) higher of ApoB, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity (except where it is the variable of interest). Participants were classified as ever-regular smokers if they answered “on most days” or “daily or almost every day” to either “How often do you smoke tobacco now?” or “In the past, how frequently did you smoke?”. Participants were classified as ever-regular alcohol drinkers if they answered “usually at least once a week” to the question “During the past 12 months, how often did you drink alcohol?” or they answered yes to the question “In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?”. Participants were classified as having diabetes if they answered yes to the question “Has a doctor ever told you that you had diabetes?” or if they had random plasma glucose level ≥7.0 mmol/L if time since last food ≥8 hours, or ≥11.1 mmol/L if time since last food <8 hours, or a fasting plasma glucose level ≥7.0 mmol/L on subsequent testing. Squares represent the HR with area inversely proportional to the variance. Horizontal lines represent the corresponding 95% CIs. The diamond represents the overall HR and its 95% CI.
ApoB: apolipoprotein B, BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

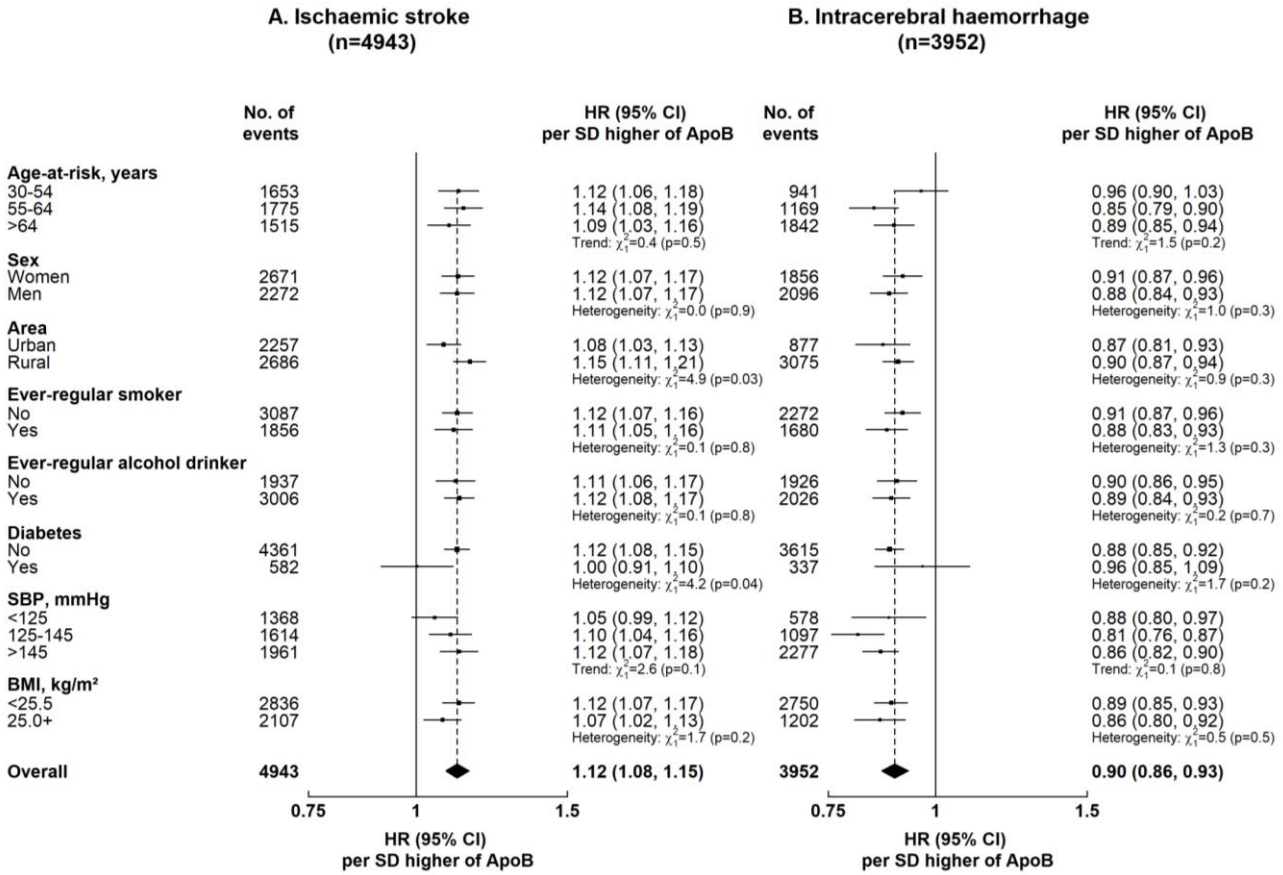


Figure B.23. Associations per SD higher of apolipoprotein A1 with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types per 1 SD (22.1 mgl/dL) higher of ApoA1. Conventions as Figure B.22.
ApoA1: apolipoprotein A1, BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.

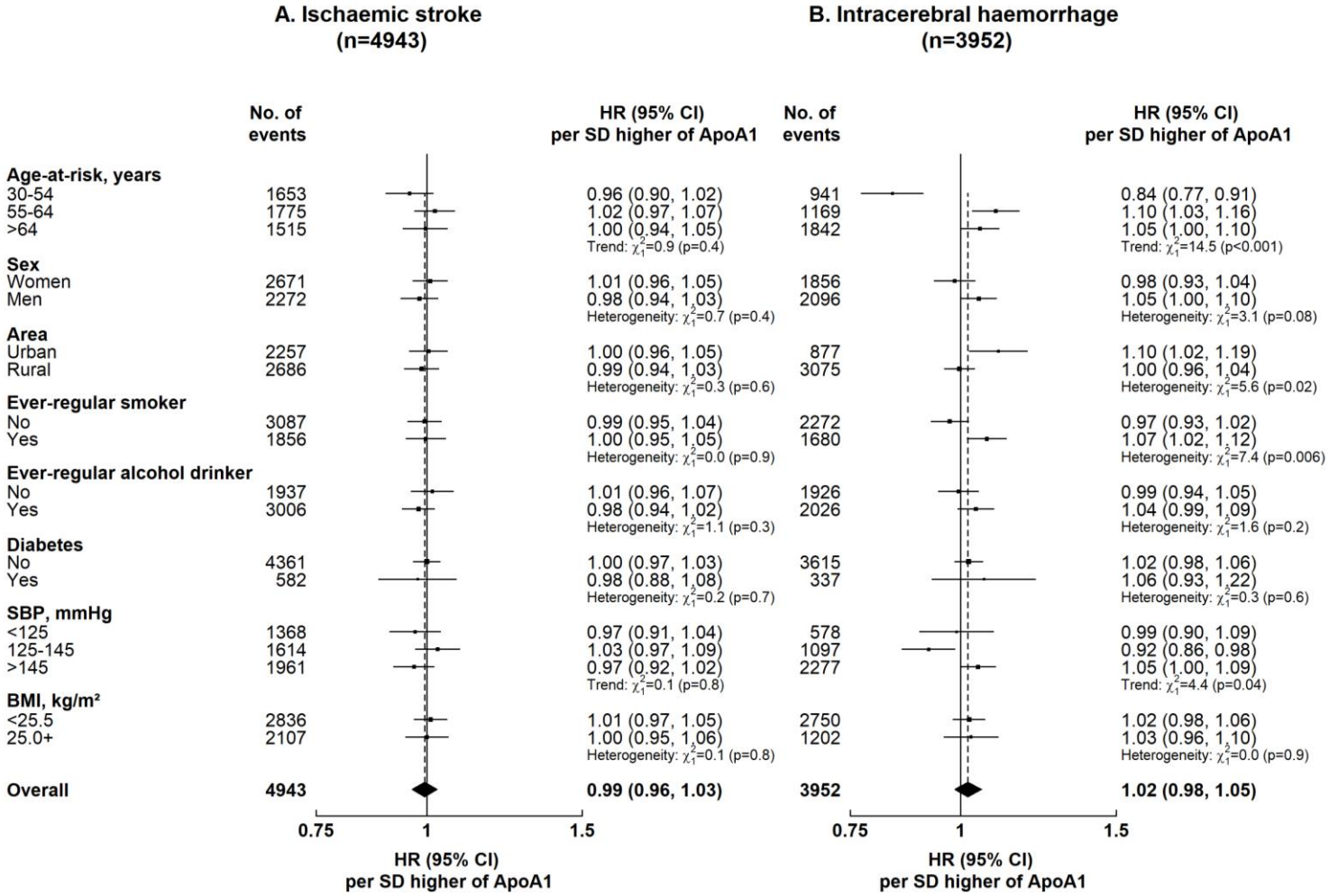


Figure B.24. Associations per SD higher of liver function biomarkers with intracerebral haemorrhage

HRs for stroke types per 1 SD higher of liver function biomarkers. SDs of liver function biomarkers ALT: 17.4 u/L, AST: 18.2 u/L, GGT: 71.6 u/L. Conventions as Figure B.22.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: Gamma glutamyl transferase, HR: hazard ratio, SBP: systolic blood pressure.

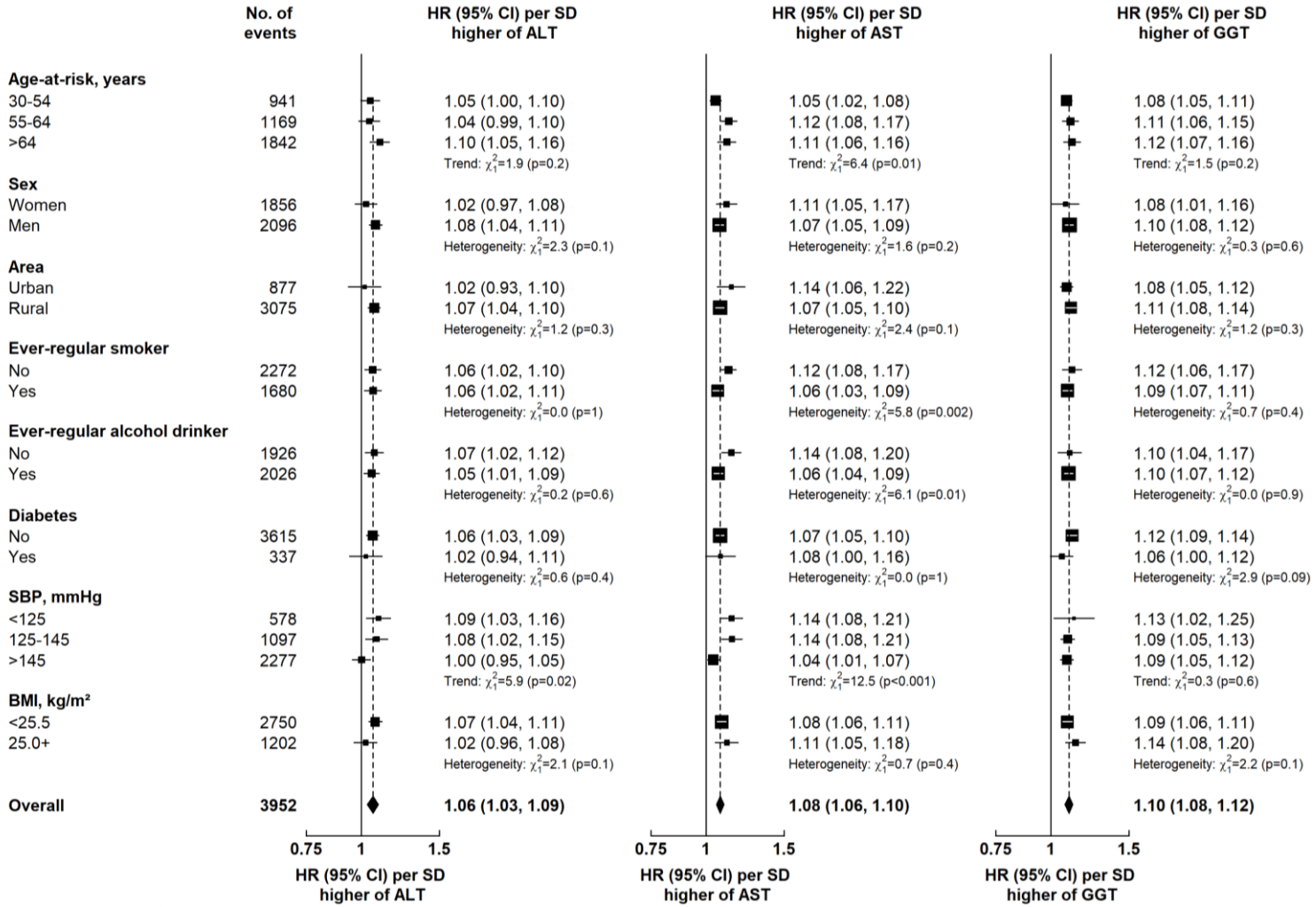


Figure B.25. Associations per SD higher of RPG with ischaemic stroke and intracerebral haemorrhage

The HRs for stroke types per 1 SD (3.0 mmol/L) higher of RPG. Conventions as Figure B.22.
BMI: body mass index, HR: hazard ratio, RPG: random plasma glucose, SBP: systolic blood pressure.

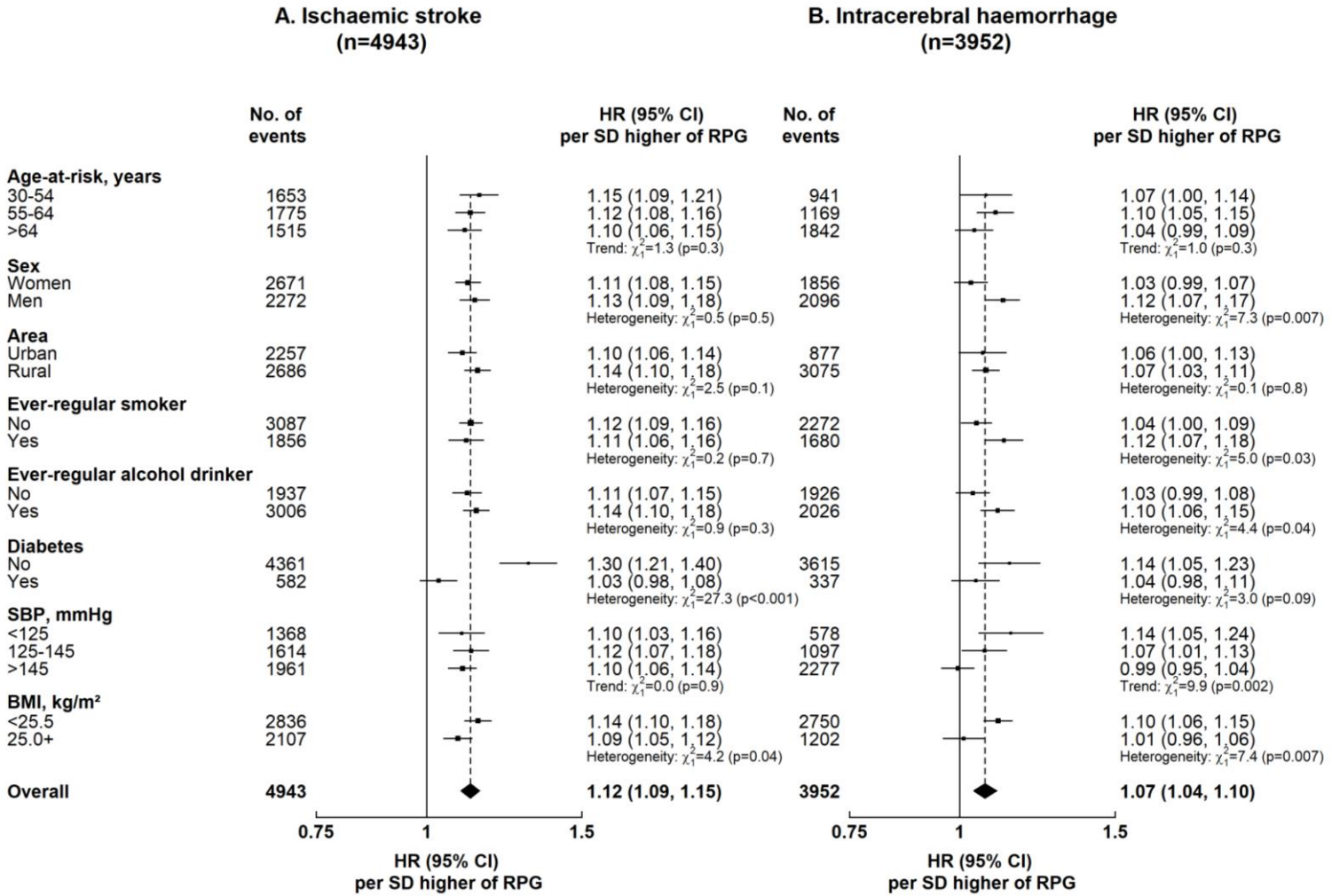
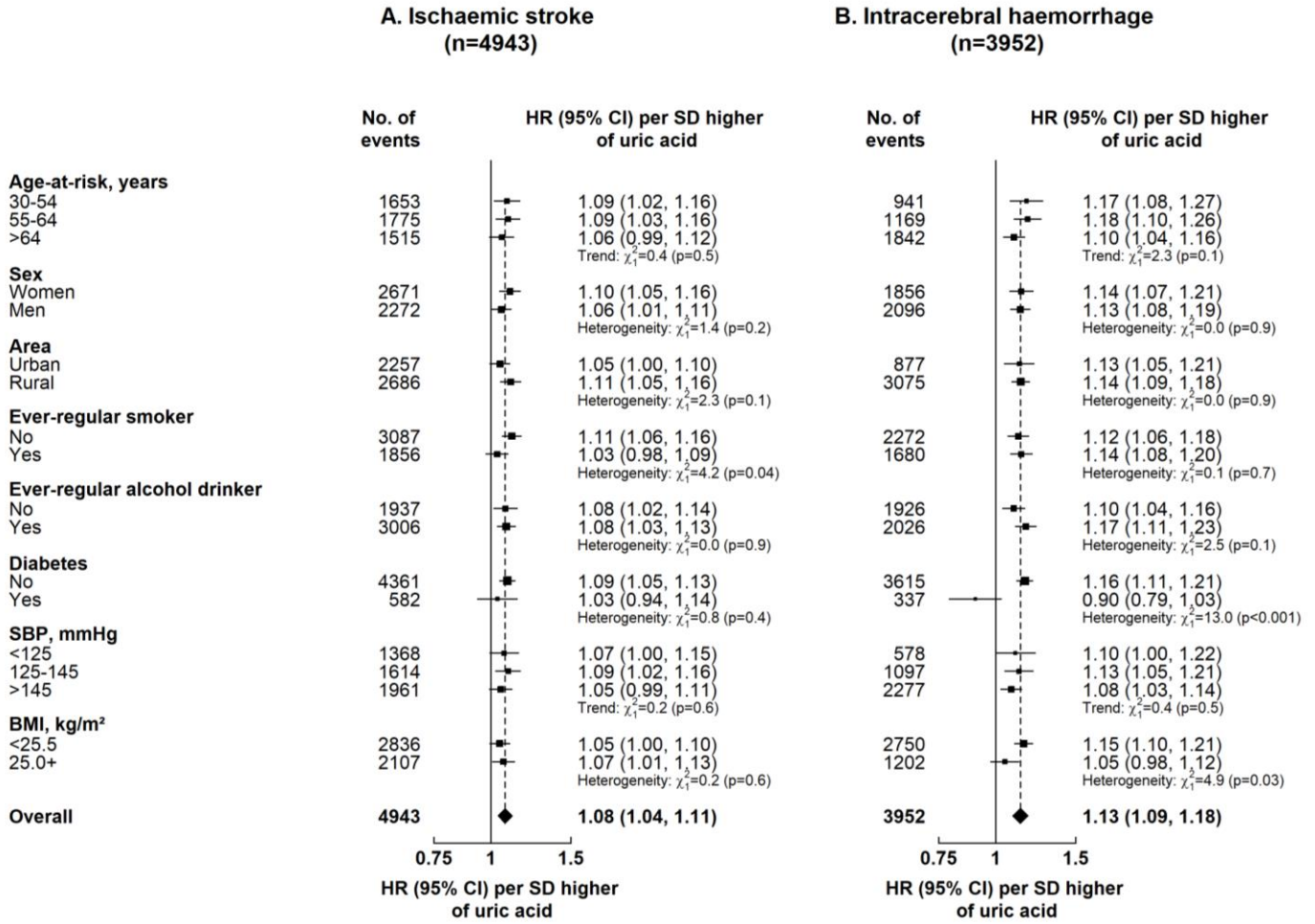


Figure B.26. Associations per SD higher of uric acid with ischaemic stroke and intracerebral haemorrhage

HRs for stroke types per 1 SD (82.8 umol/L) higher of uric acid. Conventions as Figure B.22.
BMI: body mass index, HR: hazard ratio, SBP: systolic blood pressure.



Appendix C. Additional results: Adiposity and the risk of stroke types and subtypes

Table C.1. Correlation of LDL-related terms with LDL-cholesterol and apolipoprotein B

LDL-related term of each stroke type	LDL-cholesterol	ApoB	Effect of LDL-related terms
Ischaemic stroke	0.87	0.60	**+**
Intracerebral haemorrhage	-0.44	-0.75	**-**
Fatal	-0.35	-0.70	**-**
Non-fatal	-0.51	-0.80	**-**

ApoB: apolipoprotein B, LDL: low-density lipoprotein.
LDL-related term= b_1*LDL-C + b_2*ApoB
The b_1 and b_2 are the parameter estimates of LDL-cholesterol and apolipoprotein B, respectively, from the final model from the stepwise regression in Figure 5.17 and 5.18.
The LDL-related terms were estimated separately for each outcome, as follow:
LDL-related term for ischaemic stroke = 0.4165*LDL-cholesterol - 0.0086*ApoB
LDL-related term for intracerebral haemorrhage = 0.3347*LDL-cholesterol - 0.0154*ApoB
LDL-related term for fatal intracerebral haemorrhage = 0.3123*LDL-cholesterol - 0.0137*ApoB
LDL-related term for non-fatal intracerebral haemorrhage = 0.3501*LDL-cholesterol - 0.0168*ApoB

Figure C.1. Association of baseline BMI with stroke types adjusted for different selected potential mediators and sex-interactions (n=14,529)

HRs for stroke types per 1 SD (3.1 kg/m^2 for men and 3.3 kg/m^2 for women) higher BMI. Basic adjustments were stratified by age-at-risk and sex, and adjusted for education, smoking, alcohol and physical activity. The Chi-squares are from the likelihood ratio test that compares the models with and without adjustments of the additional term (for measured values). Squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 95% CIs.
ALT: alanine transferase, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, AST: aspartate transferase, BMI, body mass index, eGFR: estimated glomerular filtration rate, GGT: gamma glutamyl transferase, HDL-cholesterol: high-density lipoprotein cholesterol, HR: hazard ratio, hs-CRP: high-sensitivity C-reactive protein, LDL-cholesterol: low-density lipoprotein cholesterol, RPG: random plasma glucose, SBP: systolic blood pressure.

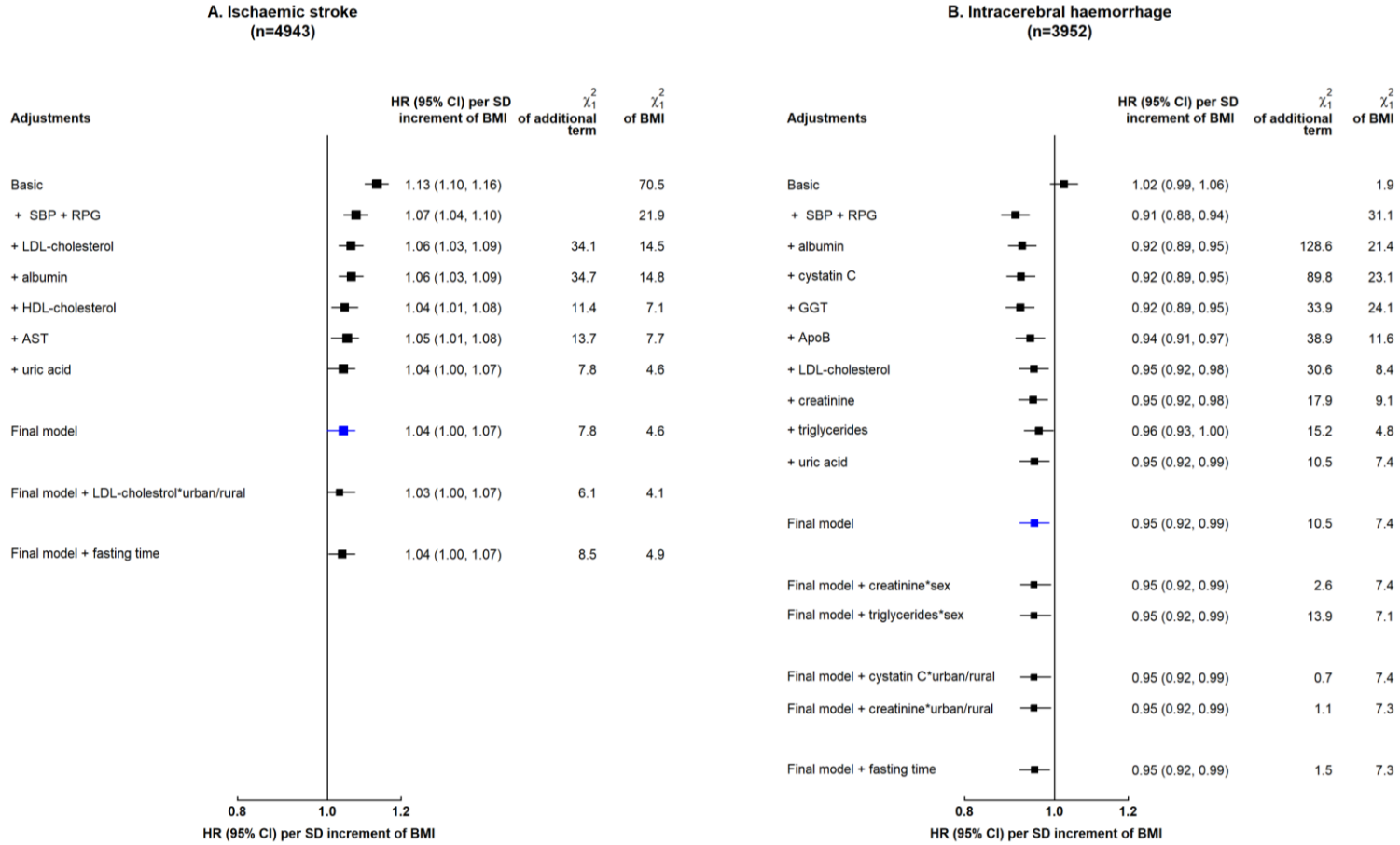


Figure C.2. Association of baseline BMI with stroke types and subtypes, stratified by age-at-risk, excluding the first 5 years of follow-up

The HRs for stroke types and subtypes by baseline BMI (sex-specific quintiles), are stratified by age-at-risk after excluding the first five years of follow-up. The HRs are stratified by sex and study area and adjusted for education, smoking, alcohol and physical activity. HRs are plotted on a floating absolute scale and against mean baseline BMI in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The $\bar{x}$ above the x-axis represents BMI mean value and the +1S and +2S represent the 1 and 2 SD from the mean, respectively.
BMI: body mass index, HR: hazard ratio.

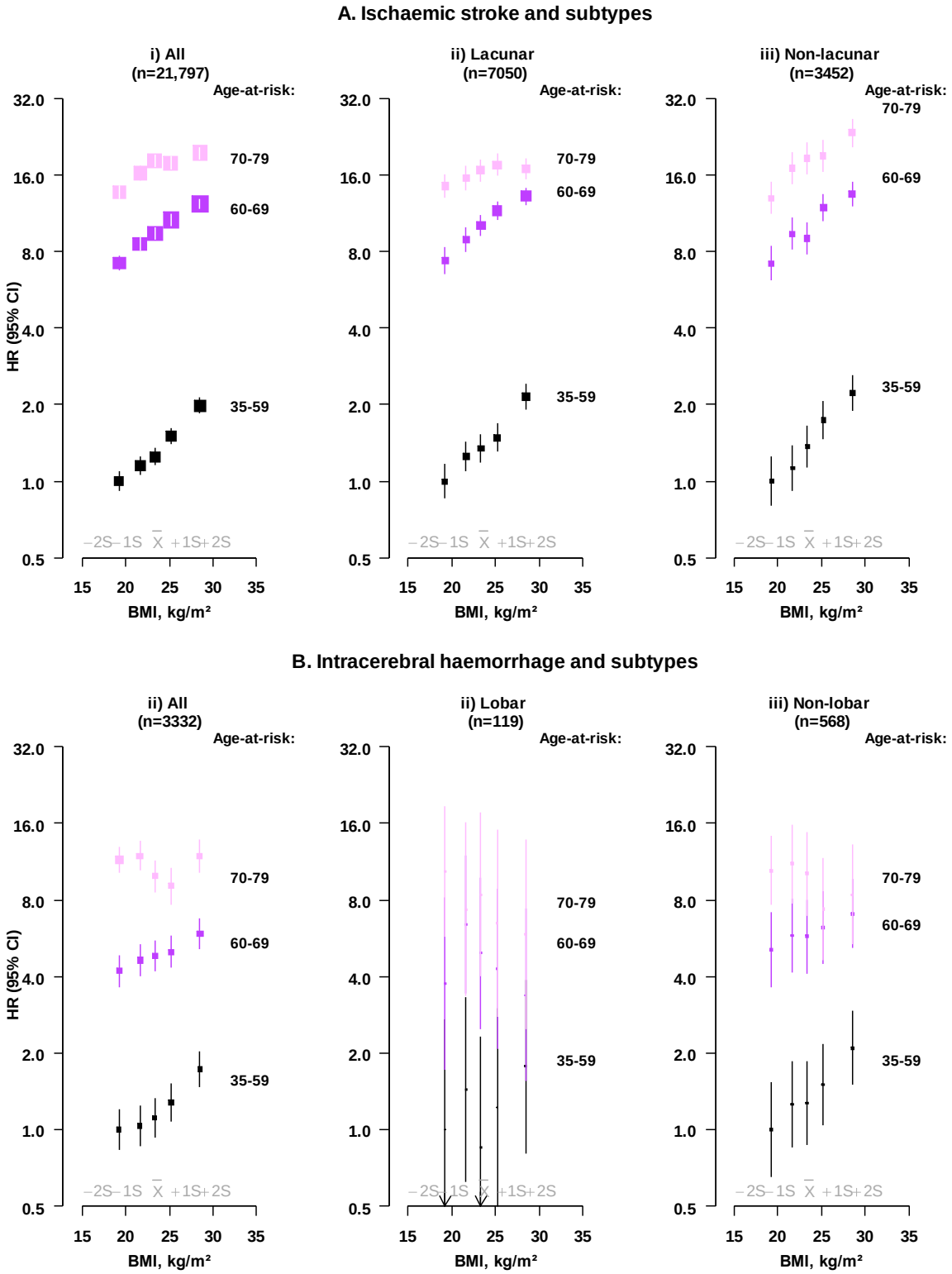


Figure C.3. Association of baseline BMI with stroke types and subtypes, stratified by age-at-risk, among never-regular smokers

The HRs for stroke types and subtypes by baseline BMI (sex-specific quintiles), are stratified by age-at-risk after restricting the analysis to never-regular smokers. Participants were classified as ever-regular smokers if they answered “on most days” or “daily or almost every day” to either “How often do you smoke tobacco now?” or “In the past, how frequently did you smoke?”. Conventions as Figure C.2.

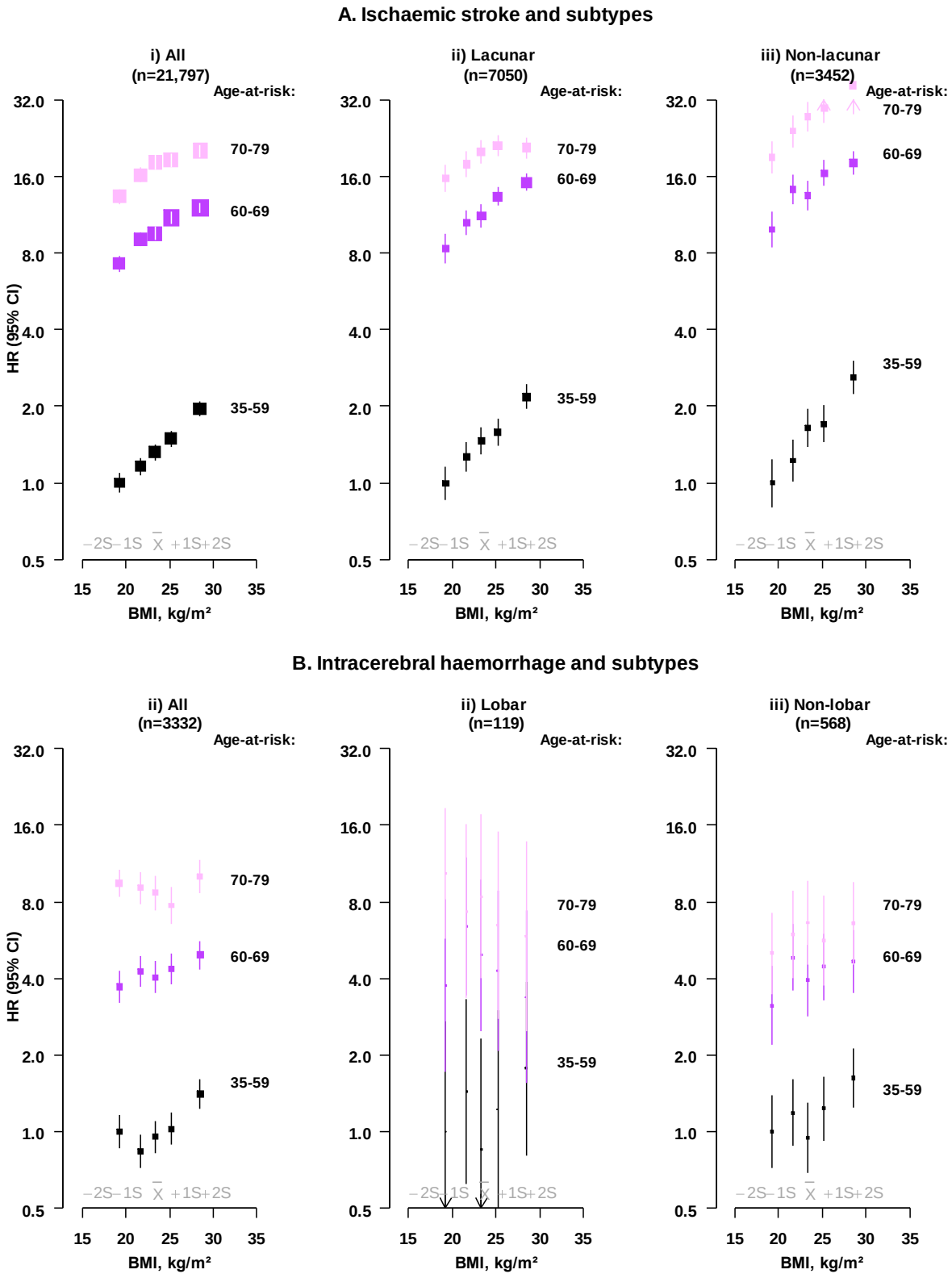
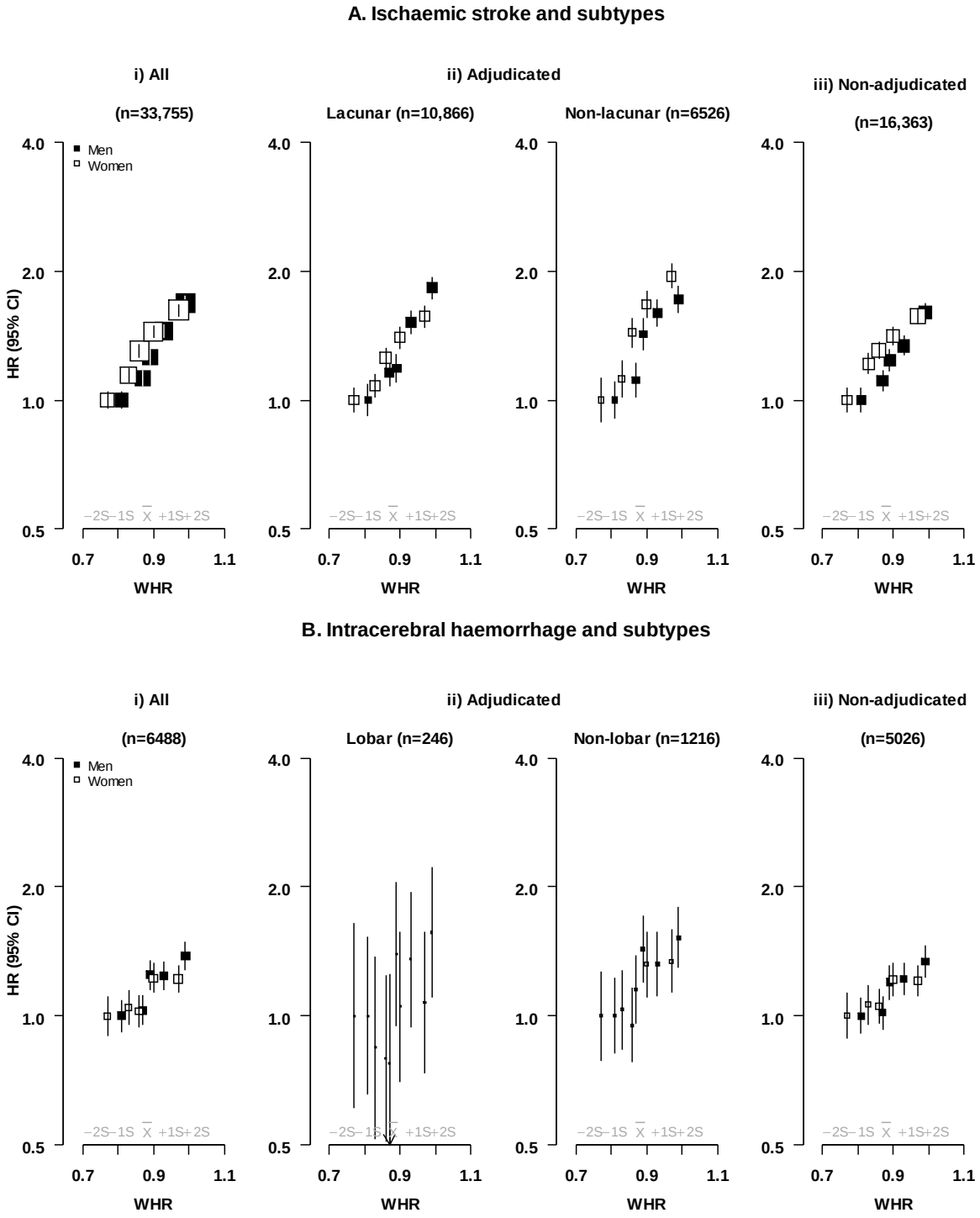


Figure C.4. Association of baseline waist-to-hip ratio with stroke types and subtypes by sex

The HRs for stroke types and subtypes by baseline waist-to-hip ratio, are stratified by age-at-risk study area and adjusted for education, smoking, alcohol and physical activity, by sex. HRs are plotted against mean baseline waist-to-hip ratio in each quintile. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. The $\bar{x}$ above the x-axis represents RPG mean value and the +1S and +2S represent the 1 and 2 SD from the mean, respectively.
HR: hazard ratio, WHR: waist-to-hip ratio.



Appendix D. Additional results: Adiposity and the risk of vascular and non-vascular mortality among individuals with and without diabetes

Table D.1. Association of baseline BMI with CVD mortality, applying various exclusions

Exclusions	Baseline BMI (kg/m^2)				
	<18.5	18.5 to <22.5	22.5 to <25.0	25.0 to <30.0	≥30.0
Among individuals with diabetes					
None					
No. of deaths	83	503	565	889	194
HR (95% CI)	1.62 (1.30-2.02)	1.19 (1.08-1.30)	1.00 (0.92-1.09)	1.10 (1.03-1.18)	1.21 (1.05-1.39)
Participants with known diseases[a] at baseline					
No. of deaths	56	346	356	563	118
HR (95% CI)	1.87 (1.43-2.45)	1.20 (1.08-1.34)	1.00 (0.90-1.11)	1.14 (1.04-1.24)	1.28 (1.07-1.54)
+ first 5 years of follow-up					
No. of deaths	30	205	220	354	75
HR (95% CI)	1.89 (1.31-2.72)	1.22 (1.06-1.40)	1.00 (0.88-1.14)	1.16 (1.04-1.29)	1.32 (1.04-1.66)
+ ever-regular smokers					
No. of deaths	19	120	147	241	55
HR (95% CI)	1.89 (1.20-2.99)	1.08 (0.90-1.30)	1.00 (0.85-1.18)	1.22 (1.08-1.39)	1.38 (1.05-1.81)
+ participants with poor self-rated health					
No. of deaths	12	86	107	188	40
HR (95% CI)	1.62 (0.91-2.89)	1.08 (0.87-1.34)	1.00 (0.83-1.21)	1.30 (1.13-1.51)	1.49 (1.08-2.05)
Among individuals with no diabetes					
None					
No. of deaths	1085	4646	3004	3216	573
HR (95% CI)	1.31 (1.23-1.39)	1.07 (1.04-1.10)	1.00 (0.97-1.04)	1.11 (1.07-1.15)	1.47 (1.35-1.60)
Participants with known diseases[a] at baseline					
No. of deaths	608	3136	2076	2170	387
HR (95% CI)	1.17 (1.08-1.27)	1.04 (1.00-1.08)	1.00 (0.96-1.04)	1.11 (1.06-1.16)	1.53 (1.38-1.70)
+ first 5 years of follow-up					
No. of deaths	337	1852	1302	1367	261
HR (95% CI)	1.11 (1.00-1.24)	0.99 (0.95-1.04)	1.00 (0.95-1.06)	1.10 (1.04-1.16)	1.62 (1.43-1.84)
+ ever-regular smokers					
No. of deaths	166	896	734	818	186
HR (95% CI)	1.13 (0.97-1.32)	0.99 (0.92-1.05)	1.00 (0.93-1.07)	1.09 (1.01-1.17)	1.63 (1.41-1.89)
+ participants with poor self-rated health					
No. of deaths	134	747	629	686	145
HR (95% CI)	1.12 (0.94-1.33)	0.96 (0.89-1.04)	1.00 (0.93-1.08)	1.09 (1.00-1.17)	1.59 (1.35-1.88)

The HRs for CVD mortality by baseline BMI sex-specific quintiles, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. [a]Self-reported doctor-diagnosed cardiovascular disease, respiratory disease or cancer. BMI: body mass index, HR: Hazard ratio.

Table D.2. Association of baseline BMI with non-CVD mortality, applying various exclusions

Exclusions	Baseline BMI (kg/m^2)				
	<18.5	18.5 to <22.5	22.5 to <25.0	25.0 to <30.0	≥30.0
Among individuals with diabetes					
None					
No. of deaths	204	5857	746	976	203
HR (95% CI)	2.90 (2.51-3.34)	1.46 (1.36-1.56)	1.00 (0.93-1.07)	0.90 (0.85-0.96)	0.95 (0.83-1.10)
Participants with known diseases[a] at baseline					
No. of deaths	127	618	526	666	133
HR (95% CI)	2.93 (2.44-3.51)	1.45 (1.34-1.58)	1.00 (0.92-1.09)	0.88 (0.82-0.95)	0.94 (0.79-1.12)
+ first 5 years of follow-up					
No. of deaths	40	341	324	421	94
HR (95% CI)	1.73 (1.26-2.37)	1.37 (1.23-1.53)	1.00 (0.90-1.12)	0.91 (0.82-1.00)	1.09 (0.88-1.34)
+ ever-regular smokers					
No. of deaths	24	205	207	268	64
HR (95% CI)	1.94 (1.29-2.92)	1.33 (1.15-1.53)	1.00 (0.87-1.15)	0.92 (0.82-1.04)	1.07 (0.83-1.38)
+ participants with poor self-rated health					
No. of deaths	15	153	163	204	43
HR (95% CI)	1.69 (1.01-2.84)	1.29 (1.09-1.52)	1.00 (0.86-1.17)	0.87 (0.76-1.00)	0.93 (0.69-1.27)
Among individuals with no diabetes					
None					
No. of deaths	2309	8367	4967	4557	633
HR (95% CI)	2.17 (2.08-2.27)	1.25 (1.22-1.28)	1.00 (0.97-1.03)	0.93 (0.90-0.96)	0.98 (0.90-1.06)
Participants with known diseases[a] at baseline					
No. of deaths	1210	5929	3814	3507	468
HR (95% CI)	1.75 (1.65-1.86)	1.18 (1.15-1.21)	1.00 (0.97-1.03)	0.94 (0.91-0.97)	0.98 (0.90-1.08)
+ first 5 years of follow-up					
No. of deaths	610	3346	2292	2126	303
HR (95% CI)	1.55 (1.43-1.69)	1.12 (1.08-1.16)	1.00 (0.96-1.04)	0.94 (0.90-0.99)	1.06 (0.94-1.18)
+ ever-regular smokers					
No. of deaths	257	1531	1201	1270	220
HR (95% CI)	1.38 (1.22-1.56)	1.12 (1.06-1.17)	1.00 (0.95-1.06)	1.00 (0.95-1.06)	1.15 (1.01-1.32)
+ participants with poor self-rated health					
No. of deaths	201	1330	1069	1111	182
HR (95% CI)	1.30 (1.13-1.50)	1.11 (1.05-1.17)	1.00 (0.94-1.06)	0.99 (0.93-1.05)	1.11 (0.95-1.28)

The HRs for CVD mortality by baseline hand grip strength sex-specific quintiles, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. [a]Self-reported doctor-diagnosed cardiovascular disease, respiratory disease or cancer. BMI: body mass index, HR: Hazard ratio.

Table D.3. Adjusted HRs for all-cause and CVD mortality by hand grip strength, among ~25,000 individuals included in the CKB second resurvey

Hand grip strength quintiles (mean, kg)	All-cause mortality		CVD mortality	
	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Male				
Q1 (20.79)	97	2.62 (2.01-3.41)	36	1.68 (1.08-2.61)
Q2 (28.38)	42	1.41 (1.05-1.89)	15	1.08 (0.66-1.77)
Q3 (32.66)	24	1.00 (0.67-1.50)	9	1.00 (0.51-1.95)
Q4 (37.10)	22	1.02 (0.66-1.5)	8	1.00 (0.47-2.10)
Q5 (11.52)	20	0.93 (0.55-1.57)	6	0.69 (0.26-1.83)
Female				
Q1 (12.40)	74	1.61 (1.20-2.51)	35	2.54 (1.66-3.89)
Q2 (17.23)	33	1.06 (0.75-1.49)	8	0.86 (0.43-1.72)
Q3 (20.18)	33	1.00 (0.71-1.41)	10	1.00 (0.53-1.87)
Q4 (23.39)	17	0.69 (0.42-1.12)	3	0.44 (0.14-1.39)
Q5 (28.62)	23	1.22 (0.76-1.93)	3	0.67 (0.20-2.22)

The HRs for the outcomes by baseline hand grip strength sex-specific quintiles are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity.
CVD: cardiovascular disease, HR: Hazard ratio.

Figure D.1. Association of BMI with CVD and non-CVD mortality among individuals with and without diabetes, by sex

The HRs for the outcomes by baseline BMI, are stratified by age-at-risk, sex and study area and adjusted for education, smoking, alcohol and physical activity. The HRs are plotted on floating absolute scale against mean baseline BMI category. Squares represent the HR with area inversely proportional to the variance. Vertical lines represent the corresponding 95% CIs. The $\bar{x}$ above the x-axis represents the mean value of BMI and the $\pm$1S and $\pm$2S represent 1 and 2 SD from the mean, respectively.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

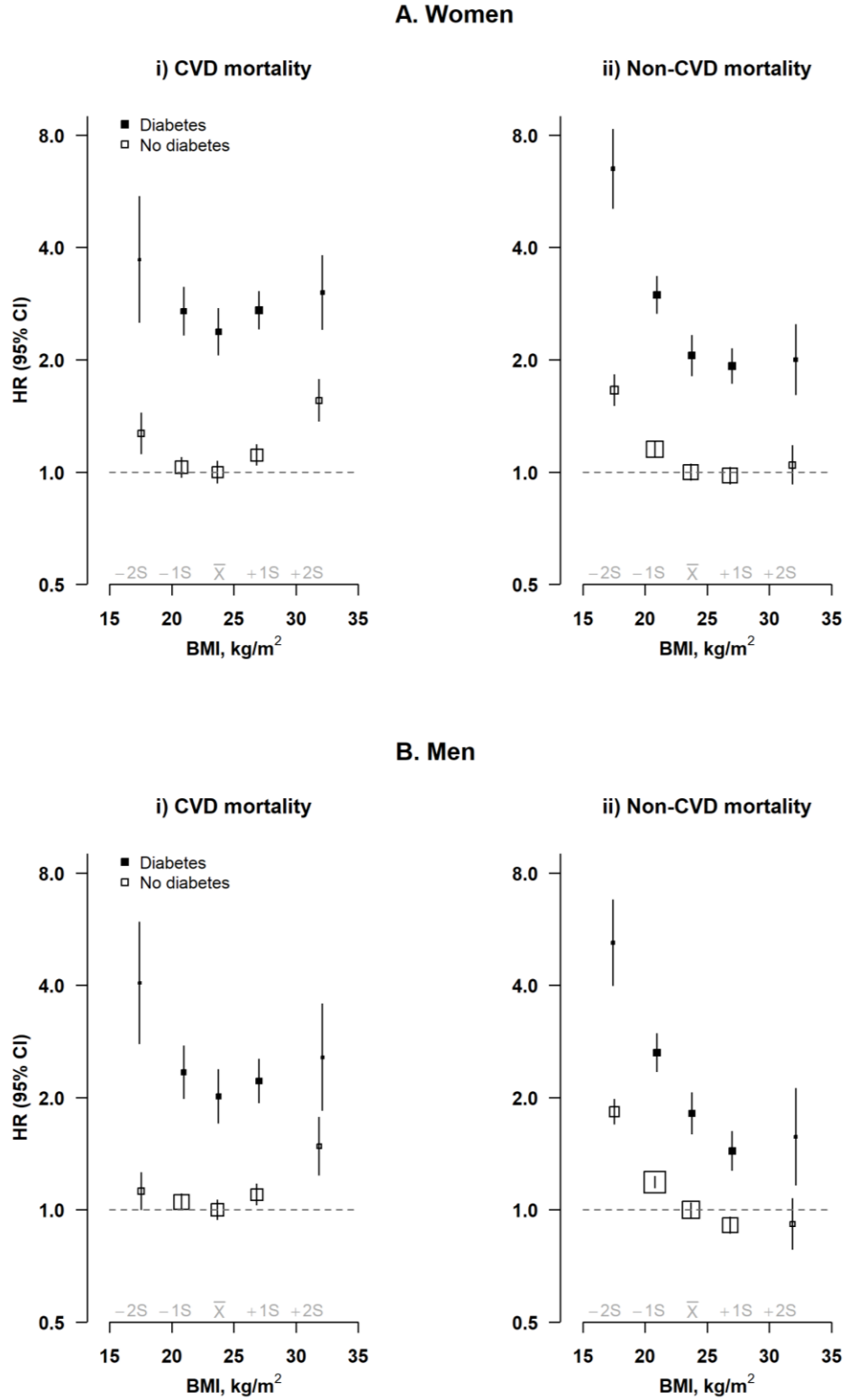
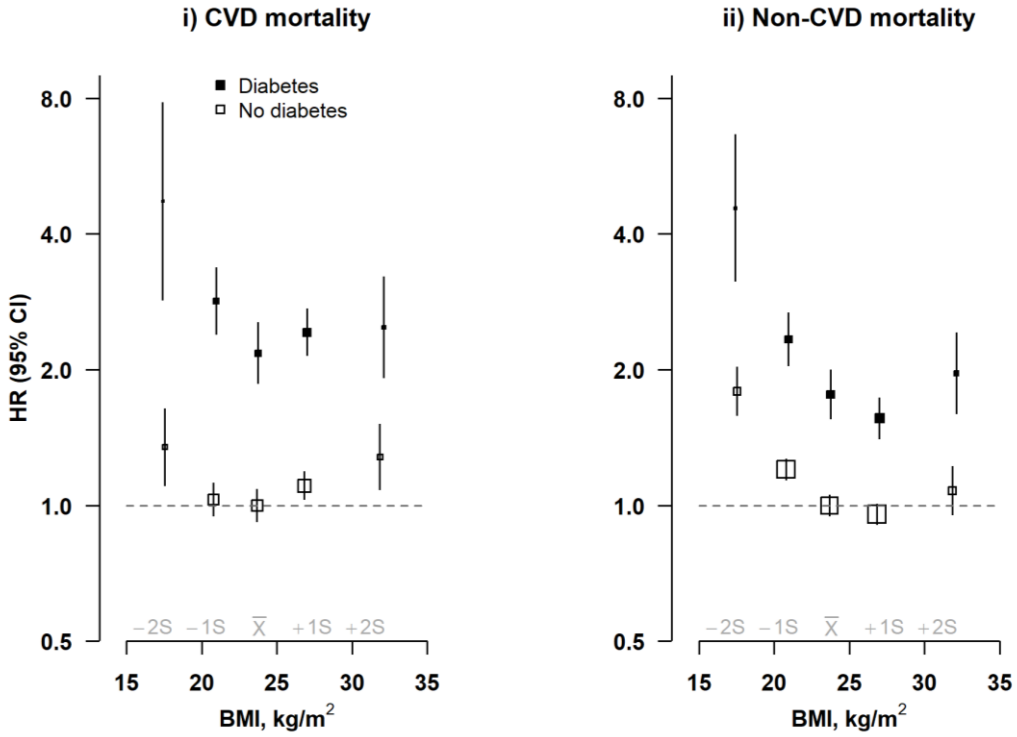


Figure D.2. Association of BMI with CVD and non-CVD mortality among individuals with and without diabetes in urban and rural areas

Conventions as Figure D.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.



B. Rural

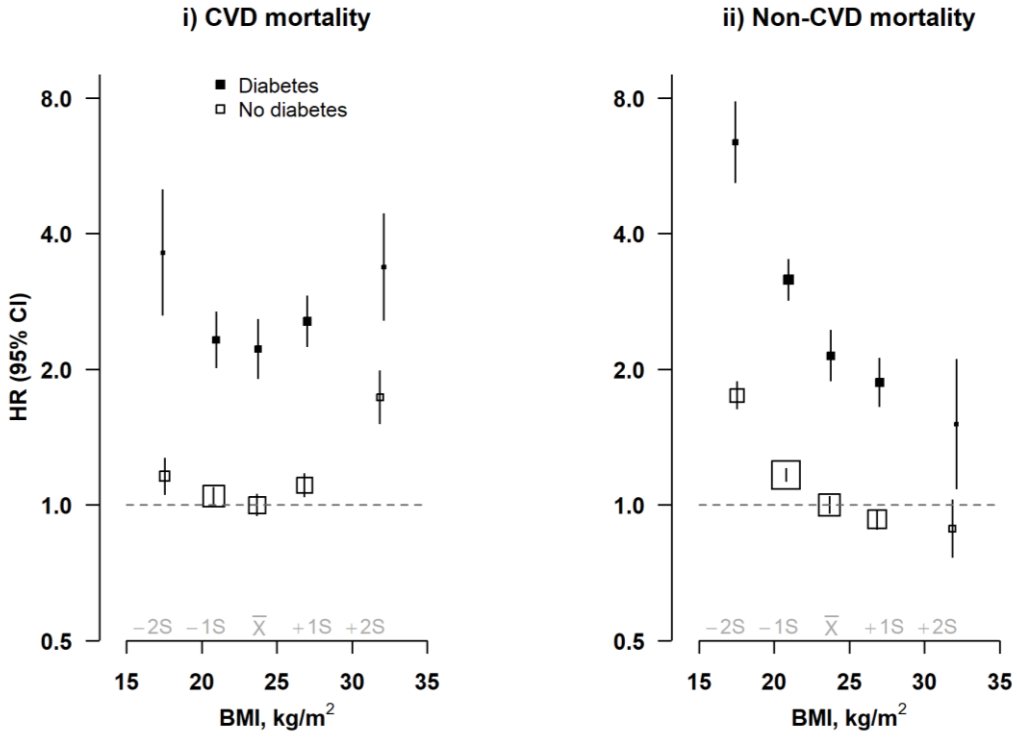


Figure D.3. Association of baseline BMI with CVD mortality, non-CVD mortality, and all-cause mortality among individuals with and without diabetes, additionally adjusted for baseline SBP

Conventions as Figure D.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

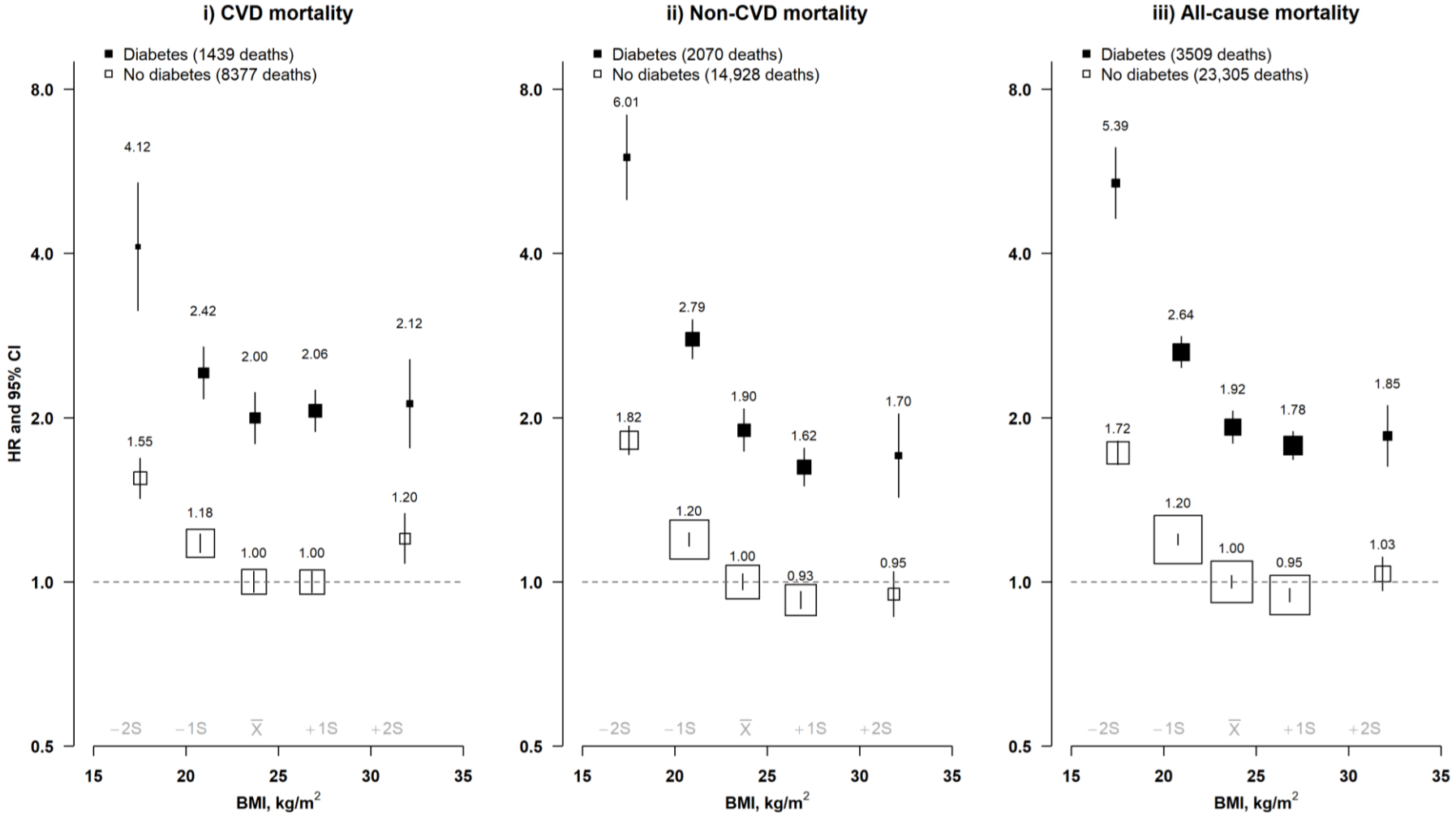


Figure D.4. Association of baseline BMI with CVD mortality, non-CVD mortality, and all-cause mortality among individuals with and without diabetes, additionally adjusted for baseline RPG

Conventions as Figure D.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

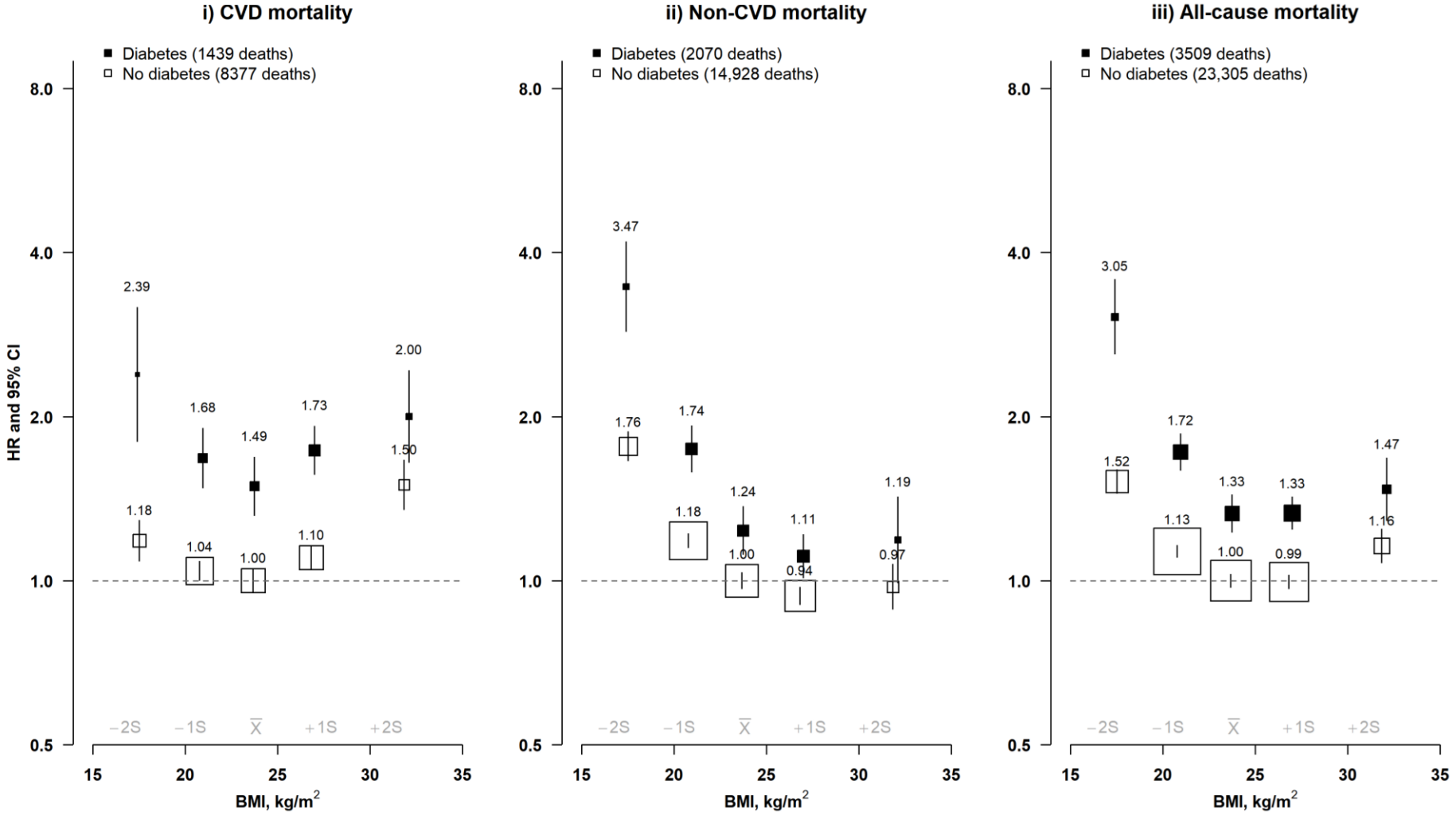


Figure D.5. Association of baseline BMI with CVD and non-CVD mortality among individuals with self-reported diabetes by diabetes medication at baseline

Conventions as Figure D.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.

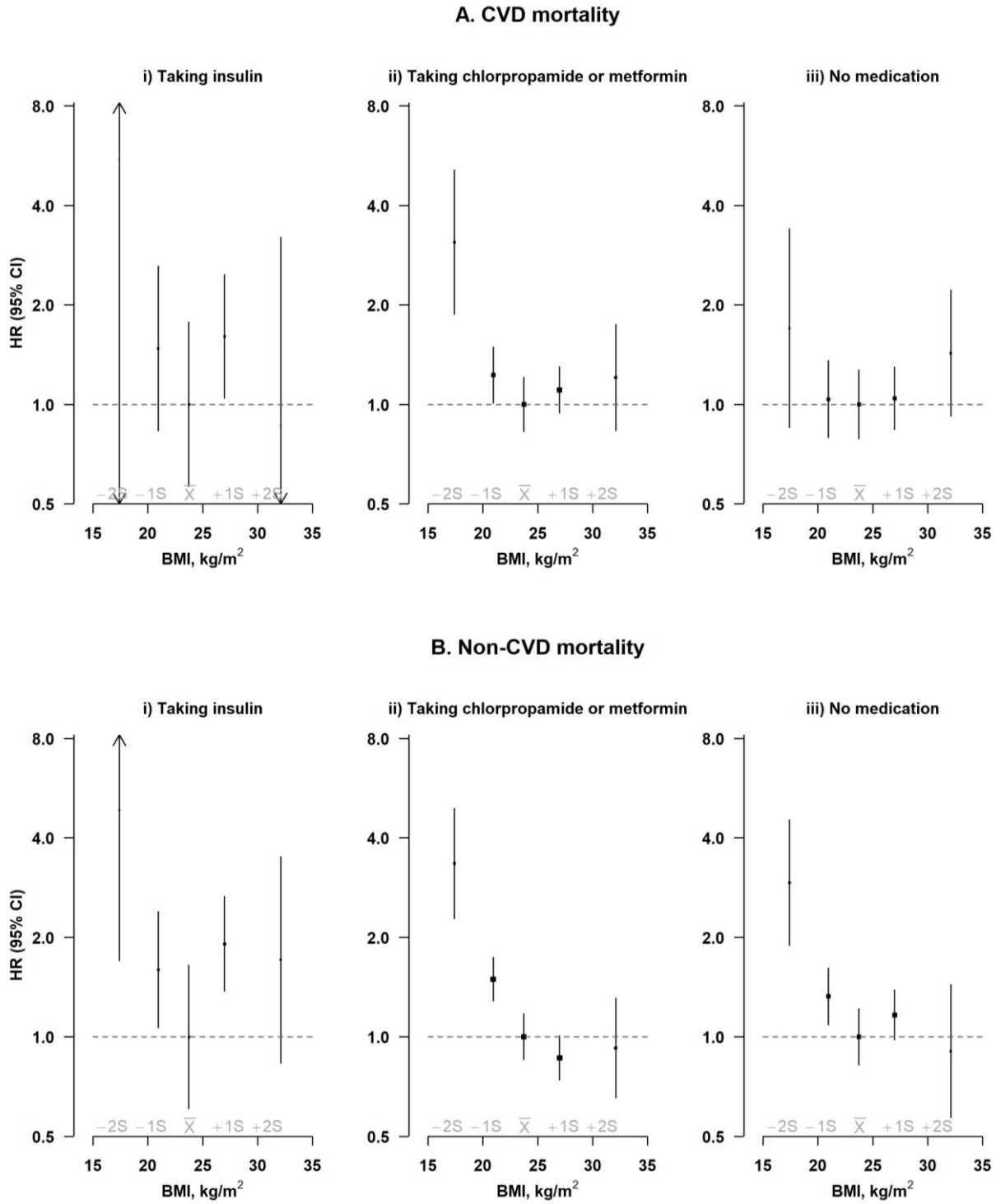


Figure D.6. Association of baseline BMI with CVD mortality, non-CVD mortality, and all-cause mortality among individuals with self-reported diabetes, by diabetes duration at baseline

Conventions as Figure D.1.
BMI: body mass index, CVD: cardiovascular disease, HR: hazard ratio.