Associations of different body fat components with cardiometabolic and cancer risks

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Για την οικογένεια μου, τη γιαγιά Σοφία και τον παππού Γιάννη

Abstract

Background: Excess total or central adiposity is associated with intermediate disease markers and increased risks of cardiometabolic disease (CMD) and cancer. However, there is limited evidence on the relevance of visceral and ectopic adiposity, which are more metabolically active and potentially oncogenic.

Methods: UK Biobank (UKB) recruited 502,359 participants during 2006-10, among whom 64,025 attended the imaging sub-study subsequently. The correlations between anthropometric and imaging (magnetic resonance imaging [MRI], dual x-ray absorptiometry [DXA]) derived adiposity traits were examined in published studies and UKB. The analyses then examined the associations in UKB of total, central, visceral and ectopic adiposity with levels of 14 disease markers, using linear regression, and with risks of CMD and cancer, using Cox regression. For the entire UKB, adiposity traits were estimated using “imputed category medians” (within BMI deciles at baseline) and analysed continuously to assess risks.

Results: Anthropometric measures correlated strongly with imaging-derived total, central and visceral adiposity, but weakly with ectopic adiposity. All adiposity traits per SD increase were associated with disease markers, except oestradiol, with MRI-derived visceral adiposity (i.e. VAT-MRI) exhibiting the greatest associations with most markers and with T2D risk (adjusted HR=2.50 [95% confidence intervals: 2.07-3.00]) compared with BMI (1.79 [1.57-2.04]), waist circumference (WC) (2.11 [1.80-2.48]) and liver adiposity (1.83 [1.58-2.12]). For ischemic heart disease, colorectal, and breast cancer in postmenopausal women, the HRs were modest but differed little across adiposity traits. In analyses of the entire UKB, liver adiposity showed a greater association with endometrial cancer risk (12.88 [10.05-16.51]) than BMI (1.90 [1.78-2.02]), WC (1.99 [1.85-2.14]) and VAT-MRI (2.32 [2.13-2.53]), with similar,

albeit less extreme, patterns of associations with risks of colorectal, oesophageal adenocarcinoma, liver, breast, and all cancers combined. Adiposity showed inverse associations with prostate cancer and oesophageal squamous cell carcinoma risks, with no differences between adiposity traits.

Conclusions: All body fat components were associated with risks of CMD and cancer and their associated markers, with visceral adiposity having greater associations with certain markers and T2D risk than other adiposity traits, and liver adiposity having the greatest association with most cancers.

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Statement of contribution to work

I was responsible for conceiving and developing the research questions addressed in this thesis. I conducted all aspects of the literature review and its analysis, performed the statistical analyses, produced the tables and figures, interpreted the findings, and completed all the writing presented in this thesis.

The author published the literature review and meta-analysis in Chapter 3 as a first-author publication (1).

Table of contents

List of tables

List of figures

List of abbreviations

Abbreviations	Full description
%BF	% Body fat
ASAT	Abdominal subcutaneous adipose tissue
ATAT	Abdominal total adipose tissue
ATATI	Abdominal total adipose tissue index
BMI	Body mass index
CI	Confidence interval
CKB	China Kadoorie Biobank
CMD	Cardiometabolic disease
CRP	C-reactive protein
CT	Computed Tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DXA	Dual X-ray absorptiometry
EPIC	European Prospective Investigation Into Cancer
FHS	Framingham Heart Study
HbA1c	Haemoglobin A1C
HDL-C	High-density lipoprotein Cholesterol
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-0	International Classification of Diseases of Oncology
ICD-10	International Classification of Diseases 10th Revision
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IHD	Ischaemic heart disease
LDL-C	Low-density lipoprotein Cholesterol
LPDFF	Liver proton density fat fraction
MASLD	Metabolic dysfunction-associated steatotic liver disease
MHT	Menopausal hormone therapy
MR	Mendelian Randomisation
MRI	Magnetic resonance imaging
MWS	Million Women Study
N/A	Not available
OR	Odds ratio
OSCC	Oesophageal Squamous Cell Carcinoma
PBP	Pulse blood pressure
Q	Quartile
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SD	Standard deviation
SHBG	Sex hormone binding globulin
SNP	Single-nucleotide polymorphism
T2D	Type 2 diabetes

TAT	Total adipose tissue
TC	Total cholesterol
TG	Triglycerides
TMFI	Thigh muscle fat infiltration
UK	United Kingdom
UKB	UK Biobank
VAT	Visceral adipose tissue
WC	Waist circumference
WCRF	World Cancer Research Fund
WHO	World Health Organisation
WHR	Waist to hip ratio

Chapter 1. Introduction

1.1 Background

1.1.1 Burdens of obesity

In 2015, a total of 603.7 million adults were recorded as obese, with the prevalence of obesity having doubled in more than 70 countries since 1980 (2). Worldwide, the number of overweight and obese individuals has risen from 857 million in 1980 to 2.1 billion in 2013 (3), with distinctive variations in sex, sociodemographic characteristics, and geographical regions. Obesity prevalence is higher in developed compared to developing countries (3). In developed countries, men have a greater prevalence of obesity, whereas in developing countries it is greater in women. Certain island nations in the Pacific, the Caribbean and countries in the Middle East and Central America already have some of the highest proportions of obesity globally (3).

These global trends are reflected in specific regions and countries, with the presented thesis focusing on the United Kingdom (UK). In 2015, the prevalence of overweight and obesity in the UK was 43.5% and 23.4% among men, and 32% and 24.9% among women, respectively (2).

The World Health Organisation (WHO) classifies individuals as overweight or obese using body mass index (BMI), calculated as weight over height squared. Overweight is defined as a BMI of 25-29 kg/m^2, and obesity is a BMI of 30 kg/m^2 or higher (4).

1.1.2 Physiology of adiposity

Body fat, stored in adipose tissue found throughout the body was historically seen as a static organ, primarily for energy storage. However, it is now recognised for its

multiple roles in major physiological functions. Besides energy storage, adipose tissue plays crucial roles in thermoregulation, organ protection through cushioning, inflammatory response, appetite regulation, and overall metabolic homeostasis, including insulin sensitivity and hormonal regulation (5, 6). These functions are subject to adaptive or maladaptive changes in response to weight fluctuations. For instance, adipose tissue regulates insulin secretion, and its insufficiency or dysfunction (as seen in obesity) may lead to excessive lipid deposition in other organs like the liver and muscle fat contributing to insulin resistance (7).

Adipose tissue may be classified as subcutaneous, visceral or ectopic based on its anatomical location. Subcutaneous adipose tissue (SAT) is located beneath the skin, and surrounding muscles in areas such as the upper arm, buttocks, abdomen, hips and thighs (8). Visceral adipose tissue (VAT) is found within the body cavity, specifically in the intrathoracic, intra-abdominal and intrapelvic regions (9, 10). Additionally, ectopic fat is excess adipose tissue in organs, which normally stores small amounts of adiposity (i.e., liver, heart, pancreas and skeletal muscle) (8, 11).

Lean and healthy individuals typically store around 80% of their fat in SAT and generally do not accumulate large amounts of visceral or ectopic adiposity (12). Conversely, individuals with excessive visceral and ectopic adiposity deposition may face subsequent metabolic health consequences, even if their BMI falls within the normal range (13).

SAT plays a physiological role in storing excess lipid storage but has a finite expansion capacity (14). Studies in humans and rodents have shown that when SAT is unable to expand, visceral and ectopic adipose tissue deposition occurs. Each individual has a personal fat threshold for which SAT may either store excess fat or

generate new adipocytes (15). When this threshold is reached excess fat is stored in visceral and ectopic adiposity. VAT is more metabolically active than SAT and it releases free fatty acids into the portal circulations (16).

The determinants of fat deposition in different body fat components include sex, age, ancestry, smoking, nutrition, genetics, and other environmental factors (11). For example, women tend to store more fat in their glutes, a pattern called gynoid fat, whereas men store more fat in the abdominal area, called android fat which is mainly composed of VAT (9, 17). Although individuals of Asian-Pacific ancestry often demonstrate overweight and obesity at lower levels of BMI than those of White ancestry (2), they have higher levels of VAT (18).

1.1.3 Adiposity measures

1.1.3.1 Anthropometry- and impedance-based measures

Conventional anthropometric measures of adiposity are easy and inexpensive to implement at a large scale. Some of these measurements assess total adiposity, while others assess central adiposity.

The most commonly used anthropometric measurement to assess total adiposity is BMI. It measures body weight while taking into account standing height, but it cannot distinguish lean from fat mass. BMI has been a valuable tool in epidemiological studies for assessing the risk of morbidity and mortality (2, 19). Another measurement of total adiposity is the percentage body fat (%BF), derived by bioelectrical impedance (20). During its assessment, a safe, low electrical current passes through the body. The speed at which the current passes determines the muscle mass, as muscle contains about 70% water, which conducts electricity unlike fat, which contains very little water (21).

While BMI and %BF measure total adiposity, waist circumference (WC) and waist to hip ratio (WHR) are considered proxy measurements of central adiposity. However, these central adiposity traits are susceptible to measurement errors due to the difficulty in detecting anatomical locations needed to measure them accurately. Also, they have been shown to have considerable inter-observer variability (22), and it is still unclear how well they capture different levels of body fat composition.

1.1.4 Magnetic Resonance Imaging and Dual X-ray absorptiometry measures

Advances in medical imaging have enabled the accurate measurement of human body fat composition. This thesis focuses on magnetic resonance imaging (MRI) and dual X-ray absorptiometry (DXA) as key methods for assessing adiposity. Although computed tomography (CT) is another method for measuring body fat, it is beyond the scope of this thesis.

MRI relies on the magnetic properties of different tissues to differentiate between fat, muscle and other structures. By utilising radio waves and magnetic fields, MRI produces detailed images that enable the measurement of both total and regional adipose tissue. Unlike DXA, MRI does not involve exposure to ionising radiation, making it a safe method of measuring body fat composition in longitudinal studies (23).

DXA is an X-ray imaging method primarily utilised for measuring bone density and is also employed for assessing body fat composition. However, unlike MRI, its use carries some risks as it exposes participants to low doses of X-ray radiation. While DXA reliably distinguishes between lean and fat tissue, providing accurate quantification of total and abdominal fat, it can only indirectly measure visceral fat by subtracting subcutaneous from total abdominal fat (23). Furthermore, DXA may

underestimate visceral fat in individuals with normal weight and overestimate it in those with severe obesity (24).

Compared with conventional anthropometric measures of adiposity, imaging-based techniques are difficult to implement at a large scale due to resource limitations and high costs.

To summarise, although conventional measurements of adiposity allow an inexpensive and easy measurement of adiposity they are not as accurate as the imaging-measured adiposity on measuring regional adiposity.

1.1.5 Adiposity and disease risk

Excess adiposity increases the risk of adverse health conditions, including cardiovascular diseases (CVD) (25), certain types of cancer (26), type 2 diabetes (T2D) (27), respiratory complications, osteoarthritis in both large or small joints (26-36), and mortality (19). In 2016, approximately one-third (15.2 million) of all deaths from non-communicable diseases occurred in those aged 30–69 years (37) Of these premature deaths, 0.7 million (4.5%) were due to diabetes, 6.2 million (40.8%) due to CVD, and 4.5 million (29.8%) due to cancer (37). Globally, the economic impact of overweight and obesity is estimated to reach $4.32 trillion annually by 2035, equivalent to 3% of the global gross domestic product (38).

This thesis focuses specifically on certain cardiometabolic diseases (CMD) and cancers. There is a plethora of evidence suggesting an association of excess adiposity with CMD and cancers with most studies using anthropometric measurements to assess total and central adiposity. While animal studies suggest that excess visceral and ectopic adiposity are associated with more adverse levels of

metabolic risk factors and are more oncogenic compared to other body fat components, the evidence is limited in epidemiological studies (11).

1.1.5.1 Type 2 diabetes

T2D is a condition characterised by chronic hyperglycaemia resulting from reduced insulin production and/or resistance to glucose-lowering, which can lead to damage in tissues mostly of the retina, kidneys, nerves and arteries (39).

A wealth of epidemiological evidence suggests that increased adiposity increases the risk of developing T2D throughout an individual's lifetime (40). A meta-analysis of 18 prospective cohort studies, of 590,251 participants involving 15,771 T2D cases found that obese individuals were at a 7-fold greater risk of developing T2D than normal-weight people, while overweight individuals were at a 2-fold greater risk (41).

The mechanisms linking excess adiposity to T2D are well established (12). Briefly, the primary mechanism involves insulin resistance originating from excess ectopic adiposity in the liver, and skeletal muscle, which subsequently leads to impaired insulin secretion by pancreatic beta-cells (42-44). Furthermore, excess adiposity and adipose tissue inflammation are associated with increased insulin resistance (45, 46). This cascade results in hyperglycaemia, glucose intolerance, and ultimately the onset of T2D (44).

Most epidemiological studies on adiposity and T2D have focused on total or central adiposity, measured primarily using anthropometric methods. A meta-analysis of 26 million individuals, involving 2.3 million individuals with T2D reported a positive association in T2D hazard ratio (HR) of 1.72 (95% Confidence intervals [CI]:1.65-1.81) per 5 kg/m^2 in BMI; 1.61 (1.52-1.70) per 10 cm in WC; and 1.53 (1.40-1.65) per 0.08 increase in WHR (47). The associations had a positive linear or monotonic

shape, with no significant differences across subgroups based on sex, age, geographical region, ethnicity, or health status. However, this meta-analysis had some key limitations with only half of the studies employing a prospective design, and just 18% adjusted for key confounders.

In contrast, a prospective study of 161,127 participants from the UK Biobank (UKB), involving 6,315 T2D cases found a greater association on a J-shaped pattern between adiposity markers and T2D risk, which was greater than the above meta-analysis (48). Specifically, they highlighted differences in the strength of the associations across different adiposity markers, with central adiposity showing a greater association with T2D than total, while the risk was greater in women than men (HR: 2.27 [2.19-2.35] per 0.07 increase in WHR vs. 1.96 [1.90-2.01]; 2.07 [2.01-2.15] per 5 kg/m^2 increase in BMI vs. 1.98 [1.92-2.04]).

Similarly, a large prospective study of 0.5 million Chinese from the China Kadoorie Biobank (CKB), involving 13,416 T2D cases reported a greater positive log-linear association between various adiposity traits and T2D risk compared to findings from the meta-analysis (49). In contrast to the study of UKB participants, the magnitude of the association was greater for total (HR: 2.66 [2.56-2.77] per 5 kg/m^2 of BMI in men vs. 2.23 [2.17-2.29] in women) than central adiposity (HR: 2.04 [1.99-2.10] per 10 cm of WC in men vs.1.73 [1.70-1.77] in women) and the associations were greater in men than women. This may be due to differences in the body fat composition of different ancestry groups and more epidemiological studies are needed to investigate these differences.

There is a notable lack of studies comparing the association of total and central adiposity vs. visceral and ectopic with T2D risk. Limited research on visceral

adiposity, often using CT, has shown strong positive associations with T2D, but there is little direct comparison with other adiposity traits. For example, the Framingham Heart Study (FHS) analysed 3,001 White participants involving 156 T2D cases and found an odds ratio (OR) for T2D per standard deviation (SD) increase in CT-derived visceral fat of 2.1 (1.6-2.6) in women and 1.6 (1.3-2.0) in men (50). Another study of 2,477 White participants involving 568 T2D cases found that an SD increase in visceral fat increased the OR of T2D by 1.82 (1.6-2.1) in women and 1.58 (1.40-1.80) in men (51). However, these studies had cross-sectional designs, and small sample sizes, and did not compare the magnitude of the associations between visceral adiposity and other body fat components with T2D risk.

Mendelian Randomisation (MR) studies aim to eliminate the bias of observational studies by exploiting the random distribution of individuals according to genotypic variation. A published MR study defined genetically predicted BMI and WHR adjusted for BMI (based on 97 and 49 single-nucleotide polymorphism (SNPs) respectively) and concluded they had a causal effect on T2D of a similar magnitude between an increase in total or central adiposity increase with T2D OR (1.92 [1.42-2.61] per 5 kg/m^2 of BMI and 1.98 [1.41-2.78] per 0.08 units of WHR adjusted for BMI) (52).

In summary, both total and central adiposity, measured by BMI, WC, and WHR, are well-established risk factors for T2D. However, there is a notable gap in research comparing the magnitude of these associations with those of other adiposity traits such as visceral and ectopic adiposity, which are likely to be better measures of specific body fat components than anthropometric measures. In addition, although those studies have reported strong associations between visceral adiposity and T2D they are limited by their cross-sectional design and small sample sizes. Future

studies, with comprehensive assessments of different body fat components, are needed to help clarify the relative impacts of different body fat components on T2D risk.

1.1.5.2 Ischaemic heart disease

Ischaemic heart disease (IHD) occurs when the heart muscle receives an inadequate blood supply, often due to blockages in the coronary arteries. IHD is a component of the broader category of CVD, which includes conditions affecting the heart and blood vessels. CVD includes disorders such as IHD, cerebrovascular disease, peripheral vascular disease, rheumatic and congenital heart disease, deep vein thrombosis, pulmonary embolism, heart failure, and stroke (53). Only in 2019 9.17 million global deaths were attributable to IHD (54).

Epidemiological studies consistently show a strong association between total and central adiposity, as measured by anthropometric methods, and IHD risk. A published umbrella review and meta-analysis of 501 cohort studies, with over 2.5 million participants found a strong positive association between BMI and IHD risk (HR: 1.15 [1.12-1.20] per 5 kg/m^2 of BMI) (55). Similarly, the Emerging Risk Factors Collaboration, which analysed 143,710 primarily White participants involving 5,259 IHD cases, reported that both total and central adiposity were positively associated with IHD risk of a comparable magnitude (i.e. HR: 1.32 [1.24-1.41] per 5 kg/m^2 BMI and 1.19 [1.14-1.25] per 10 cm WC) (56). Likewise, a study of 0.5 million Chinese adults from the CKB involving 50,698 IHD cases, concluded that each 5 kg/m^2 increase in BMI was associated with an IHD risk of 1.28 (1.26-1.29), suggesting a comparable strength in the association of BMI with IHD risk between White and Chinese populations (57). The CKB study above further performed an MR analysis, where genetically predicted BMI had a greater association with IHD risk (HR: 1.49

[1.38-1.61] per 5 kg/m^2) than the observational analyses. This suggested that a greater amount of total adiposity measured by BMI, with an increased risk of IHD, is more likely causal. Also, both of the above studies found a log-positive relationship between BMI and IHD risk (56, 57). Given the limited evidence directly linking central or visceral adiposity with IHD, the following section will instead focus on the association between central or ectopic adiposity and overall CVD risk.

There is some evidence on the association of visceral adiposity measured with imaging methods and CVD. A study including 3,001 participants from the FHS found that visceral adiposity measured with CT had a strong association with systolic (SBP) and diastolic blood pressure (DBP) (p-value≤0.0001 for men and women), both of which are risk factors of CVD (50). Another study of the same cohort, including 90 CVD cases found that an increase in CT-derived visceral adiposity was associated with CVD risk (HR: 1.44 [1.08-1.92] per 1cm^3) (58). In 1,267 participants from the FHT Offspring, no evidence was found between CT-derived visceral fat and CVD (OR: 1.23 [0.92-1.63] per 1cm^3) (59). However, these studies did not report risks of CVD in relation to other body fat components other than visceral. Overall, there is a lack of evidence on comparing the magnitude of the association of CVD with different body fat components measured in the same individuals simultaneously.

Certain mechanisms are considered to be involved in the adiposity-CVD relationship. Briefly, excess adipose tissue releases certain mediators, such as leptin, adiponectin, interleukin-6, and tumour necrosis factor, which affect body weight homeostasis and cause alteration in blood lipids, blood pressure, coagulation, fibrinolysis and inflammation. These changes lead to endothelial dysfunction and atherosclerosis (60), and a detailed review can be found at (61).

1.1.5.3 Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and potentially spread to other parts of the body (62).

The International Agency for Research on Cancer (IARC) after reviewing more than 1,000 epidemiological studies and performing a meta-analysis has established a list of cancer sites with sufficient evidence that excess adiposity increases the risk of cancer (63). IARC found a positive dose-response relationship between BMI and cancer risk for cancers of the colon, rectum, gastric cardia, liver, gallbladder, pancreas, kidney, oesophageal adenocarcinoma, breast cancer in postmenopausal women, corpus uteri, ovary, meningioma, thyroid, and multiple myeloma cancers. However, the evidence on the associations between excess adiposity with fatal prostate cancer, diffuse large B-cell lymphoma, and breast cancer in men is limited.

Large prospective studies have demonstrated a positive association between increased total and central adiposity, primarily measured by BMI and WC, and the risk of developing all cancers combined. For example, a study of 233,249 from the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort involving 32,549 cancer cases found a slight positive association between BMI and risk of all cancers combined (HR: 1.04 [1.02-1.06] per 5 kg/m^2) (64), with a similar risk reported in 344,094 participants from the UKB, involving 19,833 cancer cases (HR:1.05 [1.04-1.06] per 5 kg/m^2). Similarly, an analysis of 1.3 million women, involving 45,037 cancer cases in the UK reported a slight positive association between BMI and all cancers combined risk (HR: 1.05 [1.04-1.06] per 5 kg/m^2) (65). However, these studies did not report any association between body fat components other than total and cancer risk.

In contrast, a study of 0.5 million Chinese adults involving 21,474 cancer cases from the CKB found no significant association between high BMI and all cancers combined risk (HR: 0.97 [0.94-0.99] per 5 kg/m² increase), but a slight positive association between central adiposity, measured by WHR, and all cancers combined risk (HR: 1.03 [1.01-1.04] per 0.07 in WHR) (66). This may suggest that in Chinese individuals, central adiposity may have a greater magnitude of an association with all cancers combined risk than total adiposity.

Overall, the studies above reported a log-linear positive relationship between adiposity and cancer risk, implemented similar statistical analyses and adjusted for a similar set of variables.

This thesis focuses on the risks associated with specific cancer sites, including colorectal cancer, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma (OSCC), liver cancer, breast cancer and endometrial cancer in postmenopausal women and prostate cancer in men. These cancer subtypes were selected based on the availability of a sufficient number of cases to ensure adequate statistical power. A brief overview of the epidemiological evidence these cancer sites is given below.

Regarding colon cancer, a meta-analysis of 57 prospective studies with 894,576 participants involving 40,000 colon cancer cases found that increased BMI was associated with an elevated risk of colorectal cancer, with a greater association in men than women (HR: 1.24 [1.20-1.28] per 5 kg/m² vs. 1.09 [1.05-1.13]) (67). A study of 368,277 participants involving 984 colon cancer cases from the EPIC cohort reported that total adiposity measured with BMI was associated with colon cancer risk in men but not in women (HR: 1.05 [1.02-1.08] per 5 kg/m² vs. 1.02 [1.00-1.04]),

while central adiposity measured by WC (HR: 1.21 [1.11-2.43] per 10 cm in men vs. 1.14 [1.06-1.25] in women) and WHR (HR: 1.24 [1.05-1.46] in men vs. 1.24 [1.10-1.39] in women), was associated with increased colon cancer risk in both sexes (68).

An MR concluded that total adiposity, as measured by genetically predicted BMI (based on 312 SNPs) involving 58,221 colon cancer cases, was positively associated with an increased OR for colon cancer in men but not in women (OR: 1.27 [1.08-1.47] per 5kg/m^2 vs. 1.08 [0.97-1.21]) (69). However, central adiposity measured with genetically predicted WHR (based on 209 SNPs) was associated with colorectal cancer in women but not in men (OR: 1.25 [1.08-1.43] per 0.07 vs. 1.05 [0.81-1.36]) (69). This may suggest that sex may play a role in the magnitude of the association between excess adiposity and colorectal cancer risk.

A positive association between excess adiposity and risk of oesophageal adenocarcinoma is well-established (26, 31). A meta-analysis of 9 cohort studies, found that a 5 kg/m^2 increase in BMI was positively associated with an increased risk of oesophageal adenocarcinoma, with an HR of 1.47 (1.31-1.61) (70). Similarly, to observational studies, an MR study of White participants involving 999 oesophageal adenocarcinoma cases found that genetically predicted BMI (based on 29 SNPs) was positively associated with oesophageal adenocarcinoma, with an OR of 2.10 (1.05-4.16) per 5 kg/m^2 (71).

In contrast, a negative association has been found between excess adiposity and OSCC (70), with IARC characterising the strength of the evidence as limited (26). A meta-analysis conducted by the World Cancer Research Fund (WCRF), involving 9 cohort studies found that a 5 kg/m^2 increase in BMI was inversely associated with an increased risk of OSCC, with an HR of 0.64 (0.56-0.73) (70). There is a lack of

studies reporting MR studies investigating the causal association of excess adiposity and OSCC.

Regarding liver cancer, a positive association has been found with an increase in body fat (4, 31, 63). The WCRF conducted a meta-analysis of 12 prospective studies and found that a 5 kg/m² increase in BMI was associated with an increased HR of 1.30 (1.16-1.46) (31). Similarly, a meta-analysis of 3 MR studies reported an HR of 1.62 (1.19-2.21) for a 5 kg/m² increase in genetically predicted BMI (estimated based on SPS of 92 to 305 in total) (72).

In women, the breast cancer risk associated with increasing BMI varies with menopausal status. For premenopausal women, the risk decreases with increasing BMI, whereas for postmenopausal women (who have not received menopausal hormone therapy [MHT]), the risk increases with BMI (63).

A study of 1.3 million women in the UK, involving 5,629 breast cancer cases found a positive association between the breast cancer risk of postmenopausal women (restricted to never users of MHT) and increasing BMI (HR: 1.18 [1.14-1.22] per 5 kg/m^2) (65). Another study of 162,691 postmenopausal women in UKB involving 2,913 breast cancer cases concluded that total adiposity measured with BMI was strongly associated with breast cancer risk (HR: 1.21 [1.15-1.27] per SD [not reported]), while no association was found in relation to central adiposity (measured with WC or WHR) (73). Similarly, a study of approximately 300,137 Chinese postmenopausal women involving 1,202 breast cancer cases reported a positive association between BMI increase and postmenopausal breast cancer risk (HR: 1.29 [1.18-1.40] per 5 kg/m²), consistent with findings from studies in White populations (66).

In contrast to these observational findings, an MR study of 173,389 women in the UKB, which used genetically predicted increased adiposity (based on 82 BMI-associated SNPs) and included 8,320 breast cancer cases, reported an inverse association between genetically predicted adiposity and breast cancer risk (OR: 0.72 [0.61–0.83]) (74). This apparent inconsistency may be explained by the fact that genetically predicted adiposity is likely to better reflect the influence of adiposity during critical hormonal developmental stages, in contrast to measures of adult adiposity.

Previous epidemiological evidence suggests a positive association between excess adiposity and increased risk of endometrial cancer (31). A meta-analysis of 30 prospective studies, including over 6 million women involving 22,320 endometrial cancer cases, reported a positive association between BMI and WC with endometrial cancer HR of a similar magnitude (1.54 [1.47-1.61] per 5 kg/m^2 and 1.27 (1.17-1.39) per 10 cm respectively) (75).

Regarding prostate cancer, the association between increased adiposity and prostate cancer overall remains unclear, with limited evidence of association with fatal prostate cancer (26).

It is well-established that excess total or central adiposity is positively associated with certain cancers. However, limited evidence exists regarding the association of different body fat components with cancer risk, such as visceral or ectopic adiposity. For example, FHS analysed 3,086 participants involving 141 cancer cases and found that CT-derived visceral adiposity was positively associated with all cancers combined risk (58). Similarly, a cross-sectional study of 4,276 reported that increased CT-derived visceral adiposity was positively associated with colorectal

adenoma risk (VAT quartile [Q] 4 vs. Q1 OR: 3.09 [2.19-4.36]) (76). To date, no prospective studies have investigated the association between ectopic adiposity and the risk of any cancer, or site-specific cancers. Furthermore, these studies did not report cancer risk in relation to different body fat components, and it remains unclear whether certain fat types may be more oncogenic than others.

Mechanisms on the association of adiposity to cancer risk are thought to vary, with some cancers influenced by sex hormones and others by metabolic changes and inflammation. A comprehensive review of these mechanisms is provided by Louie et al. (77).

For specific women's reproductive cancers, the relationship between adiposity and cancer risk is believed to be mediated primarily via sex hormones. The Million Women Study (MWS), which included 1.3 million women in the UK, offered valuable insights into the association between adiposity and women's cancers, as well as potential mechanisms. One study from this cohort provided some evidence that increased BMI in premenopausal women, who never used MHT was associated with a slight inverse risk of breast cancer (HR: 0.92 [0.96-1.00] per 5 kg/m^2]), whereas a positive association was observed in postmenopausal women (HR: 1.18 [1.14-1.22] per 5 kg/m^2) (65). The transition from premenopause to postmenopause is accompanied by rising oestrogen levels, which are thought to mediate the relationship between body fat and breast cancer risk (78). Postmenopausal women also have twice the risk of developing endometrial cancer compared to premenopausal women when adiposity is elevated. In premenopausal women, the impact of excess adiposity on endometrial cancer is mediated by progesterone deficiency rather than excess oestrogens, whereas in postmenopausal women, it is mediated by increased levels of unopposed oestrogens (79).

Excess adipose tissue leads to increased levels of insulin and other growth factors, which stimulates cells to divide more rapidly. A review study found that insulin resistance is a risk factor for endometrial cancer (80). Furthermore, cancer patients with T2D have worse cancer prognosis compared to cancer patients without T2D (81, 82). Insulin-like growth factors 1 (IGF-1) and 2 (IGF-2) play a critical role in insulin signalling. The effect of obesity on elevated IGF levels is key in amplifying the proliferative effects of oncogenic signalling pathways that promote cancer growth. Elevated levels of IGF-1 and IGF-2 have been observed in various cancers, including glioblastomas, neuroblastomas, meningioma (83), medulloblastomas (84), breast cancer (85) and prostate cancer (86). In human epidermal growth factor receptor 2 positive breast cancer patients, those expressing IGF-1 receptor are more likely to be resistant to the preoperative chemotherapeutic drugs compared to matched patients without IGF-1 receptor expression (87).

Obesity induces low-grade and chronic inflammation (88). This pathway is involved in the development of lymphoma (89), pancreatic (90), and liver (91) cancers. It has been shown that aspirin may be effective in preventing colorectal cancer in those with high BMI, possibly by reducing circulating cytokines (92).

There is evidence suggesting that the association between body fat components and cancer risk may differ by sex and ancestry. A systematic review and meta-analysis found a strong association between BMI and premenopausal breast cancer in women of Asian-Pacific ancestry, while evidence for this relationship in individuals of White ancestry was insufficient (67). The study also highlighted sex differences in cancer risk, showing a greater association between elevated BMI and colon cancer in men compared to women. However, it remains unclear whether visceral or ectopic

adiposity may have a more pronounced effect on cancer risk across different ethnic groups or sexes, as current epidemiological studies lack sufficient evidence on this.

While there is substantial evidence supporting the association between total and central adiposity and cancer risk, the evidence for visceral or ectopic adiposity is less conclusive. Most of this data comes from studies that use anthropometric methods to measure adiposity. There is limited research examining the association between various body fat components, especially total, central, visceral, and ectopic with cancer incidence. To address this gap, large prospective studies incorporating both imaging and anthropometric measures, including measures of total, central, visceral and ectopic adiposity within the same individuals, are needed to allow comparison of associations of the different body fat components with CMD and cancer risk and their intermediate markers.

1.2 Thesis aims

The main objectives of this thesis are to:

1. Review and synthesise the existing evidence regarding the correlations between anthropometric and imaging-based measures of body fat.
2. Obtain novel evidence regarding the correlations between anthropometric and imaging-derived measures of body fat in the UKB.
3. Compare the size and shape of associations of total, central, visceral and ectopic adiposity measured with conventional anthropometric and imaging methods in a subset of participants in the imaging sub-study in the UKB, with selected disease markers and risk of CMD and cancers.

4. Compare the magnitude and functional form of associations of “imputed category medians” of total, central, visceral and ectopic adiposity with specific cancers in 0.5 million UKB participants.

Chapter 2. UK Biobank data source description

2.1 Study design and recruitment

Between 2006 and 2010, 9.2 million men and women aged 40-69 who were registered with the UK National Health Service and living within 25 km of one of the 22 assessment centres across England, Wales, and Scotland, were invited to participate in the UKB study. Overall, a total of 503,317 people (54.4% women, 45.6% men) attended the assessment, with an overall participation rate of 5.5% (93). The initial aim of the UKB was to investigate a large number of exposure-outcome relations, with a long-term aim of improving prevention, diagnosis and treatment of diseases in middle and older age. A detailed description of the study protocol, the data collected at baseline assessment, and the characteristics of the population has been published elsewhere (94, 95). UKB has received ethics approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank approval (96). All the participants provided written informed consent to participate in the study. For this research, the UKB application number is 67506.

At baseline assessment, participants gave consent for their health to be followed up through linkage to routinely collected health records, which included mortality, hospital admission, and cancer registration data. At the time of analysis, 639 participants had withdrew their consent, leaving 502,678 participants for inclusion in the present analyses.

2.2 Baseline assessment procedures

At the initial baseline visit, participants provided detailed information on sociodemographic and lifestyle factors, and health-related conditions by answering a

self-completed screen questionnaire and a computer-assisted personal interview (95). Sociodemographic and lifestyle factors considered in this thesis include: education level (college/university degree, A levels/AS levels or equivalent, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications, none of the above), deprivation (quintiles of Townsend deprivation index), smoking status (never, previous, current), alcohol intake (0, 1, 2, ≥3 drinks/week), and ancestry. Where relevant, number of live births, menopause status (yes, no, had a hysterectomy), years since menopause, and use of MHT (current, past, never). Self-reported health-related factors included the use of cholesterol-lowering medication, the use of hypertension medication, and the diagnosis of T2D or cancer by a doctor.

Assessment of various anthropometric measures, biochemical markers, and blood pressure were conducted as presented below.

2.2.1 Anthropometric measures of adiposity

Participants had measurements taken of their weight, standing height, BMI, WC, hip circumference and percentage body fat (%BF) (while clothed and without shoes) by a trained healthcare professional or nurse (97). The Tanita BC415MA body composition analyser (or bio-impedance) was used to provide measures of total weight and %BF (21). BMI was calculated as weight (in kg) over height (in metres) squared.

2.2.2 Blood pressure measures

Systolic (SBP), diastolic (DBP), and pulse (PBP) blood pressure were measured twice for each participant after allowing them to rest in a seated position for a

minimum of 5 minutes, using an Omron 705IT (Omron, Japan) (98). The mean of the two blood pressures was used for each participant.

2.2.3 Biochemical assays

A wide range of biomarkers were selected for assay for about 480,000 participants at the initial baseline visit (99). These biomarkers are known to be strongly associated with many common conditions. The biochemical assays which are subsequently considered in this thesis are (i) blood lipids: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and total cholesterol (TC); (ii) blood proteins: haemoglobin A1C(HbA1c), insulin-like growth factor 1 (IGF-1), and C-reactive protein (CRP); and iii) sex hormones: sex-hormone binding globulin (SHBG), (total) testosterone, and oestradiol. Analyses of oestradiol were restricted to premenopausal women because almost all postmenopausal women in UKB had a concentration below the minimum reportable value for the assay (175 pmol/L).

A description of the technical aspects of the various biomarker assays is described elsewhere in detail (100). Briefly, LDL-C was measured by enzymatic protective selection analysis, HDL-C by enzyme immunoinhibition analysis, TG by GPO-POD analysis, and CRP by immunoturbidimetric high sensitivity analysis, all using a Beckman Coulter AU5800. TC by Nightingale Health DataHbA1c was measured by HPLC analysis on a Bio-Rad VARIAN II Turbo. Testosterone was measured using a one-step competitive analysis, oestradiol by a two-step competitive analysis, and SHBG by a two-step sandwich immunoassay analysis, all on a Beckman Coulter Unicel Dxl 800. IGF-1 was measured by CLIA analysis on a DiaSorin Ltd LIASON XL.

2.3 Imaging sub-cohort assessment

In 2014, 100,000 participants were re-invited to undergo imaging assessment (on average 10 years after the baseline assessment) involving abdominal MRI and whole-body composition DXA imaging, along with the same anthropometric measurements and blood pressure metrics as in baseline visit to assess body fat composition (101). At the time of data request, 64,025 participants had attended the re-assessment visit between 2014 and 2022 at imaging centres in England, with at least one adiposity measure available. This represents the largest population-based study to date with data on body fat composition from both MRI and DXA.

Abdominal MRI (1.5 Tesla Siemens scanner, 10-minute sequence, AMRA Medical) and DXA imaging (GE-Lunar, 20-minute protocol) were performed to acquire the imaging-based measures of adiposity (101). MRI-derived adiposity traits of interest included: total adipose tissue (TAT), defined as total adipose tissue volume from the bottom of the thigh muscles to the top vertebrae T9; VAT, located within the abdominal cavity, excluding adipose tissue outside the abdominal skeletal muscles, and adipose tissue and lipids within the cavity and posterior of the spine and back muscles; abdominal subcutaneous adipose tissue (ASAT), found in the abdomen from the top of the femoral head to the top of the thoracic vertebrae T9; abdominal total adipose tissue (ATAT), calculated as the sum of VAT and ASAT; and ATAT index (ATATI), defined as ATAT divided by height square. Additional measures were liver proton density fat fraction (LPDFF), which measures the average proton density fat fraction between three to nine regions of interest in the liver; and thigh muscle fat infiltration (TMFI), defined as the mean fat infiltration in the anterior thigh muscles. TMFI represents the fat fraction within viable muscle tissue. DXA-derived adiposity

traits of interest included TAT, VAT, %BF, and android fat mass (AFM), found between the abdomen and the waist area.

2.4 Body fat components

Although UKB includes a wide range of imaging-derived adiposity variables, the measures selected for this analysis were those with the highest availability, while also being representative of the main components of body fat composition (total, central, visceral, and ectopic). This approach also enabled meaningful comparisons between anthropometric and imaging-derived measures.

The various adiposity traits were categorised as measures of either total, central, visceral, or ectopic adiposity, to facilitate comparison of the role of these different body fat components with disease. The four categories of body fat components were defined as follows: (i) total adiposity, including BMI, %BF bio-impedance-based and DXA-based (%BF-DXA), MRI and DXA measured TAT (TAT-MRI and TAT-DXA); (ii) central adiposity, measured using WC, WHR and MRI-derived measures such as ATAT (ATAT-MRI), ATAT index (ATATI-MRI), ASAT (ASAT-MRI), and DXA-derived AFM (AFM-DXA); (iii) visceral adiposity, measured by MRI- and DXA-derived VAT (VAT-MRI and VAT-DXA); and (iv) ectopic adiposity, assessed by MRI-derived TMFI (TMFI-MRI) and LPDFF (LPDFF-MRI).

2.5 Follow-up procedures

UKB obtains data on disease endpoints through coded information based on the International Classification of Diseases 10th revision (ICD-10) from hospital episode statistics and cancer registration data. The end of follow-up for the hospital episode statistics was 31 October 2022 for England, 31 August 2022 in Scotland and 31 May

2022 for Wales; and for the cancer registration data, it was 31 December 2020 for England, 30 November 2021 for Scotland, and 31 December 2016 for Wales.

2.6 Study populations for the thesis

This thesis investigates the cohort of 502,359 UKB participants at baseline and those 64,025 individuals who were part of the imaging sub-cohort. To assess the representativeness of this sub-cohort relative to the broader UKB baseline cohort, population characteristics were calculated for each group and compared. A total of 4,274 participants of those attending the imaging sub-cohort had complete adiposity data. To further explore the representativeness of the imaging sub-cohort population with all their adiposity traits of interest available, additional population characteristics were extracted and presented here.

2.6.1 Baseline visit

Among the 502,359 participants in the baseline visit, the mean age was 57 years (**Table 2.1**). Of these participants, 54% were females, 95% were White, and 72% of female participants were postmenopausal. More men than women reported a history of regular smoking (51% vs. 40%) and weekly alcohol consumption (77% vs. 62%).

There were some differences in anthropometric and bio-impedance-based measures of body fat at baseline between women and men. While BMI was similar between the sexes (mean BMI 27 kg/m^2), women had a higher total adiposity, as measured by %BF (37% vs. 25%). In contrast, men had greater central adiposity (i.e., WC: 97 cm vs. 85 cm; WHR: 0.9 vs 0.8).

There were also some notable differences in levels of key blood-based biomarkers between men and women. Women tended to have slightly higher levels of blood lipids than men (for example, mean HDL-C in mmol/L: 1.6 vs 1.3; TC in mmol/L: 4.8 vs. 4.4), while men tended to have a higher blood pressure than women (e.g. SBP in mmHg: 141 vs. 135), and higher levels of certain blood proteins (e.g. HbA1c, mmol/mol: 36.5 vs 35.8). Women had higher mean SHBG than men (62 nmol/L vs. 39.6 nmol/L), while men had higher mean testosterone levels (12.0 nmol/L vs. 1.1 nmol/L). In premenopausal females, the mean oestradiol value was 576 pmol/L.

2.6.2 Imaging visit

Anthropometric and bio-impedance measurements of adiposity were re-assessed while MRI- and DXA-derived adiposity was further acquired for the cohort of participants attending the imaging sub-cohort assessment.

At the time of data analysis, at least one of the adiposity traits of interest was available for 64,025 participants (**Table 2.2**). Of these participants, 52% were women and 97% were White. More men than women reported a history of regular smoking (i.e. 41% vs. 34%) and weekly alcohol consumption (i.e. 78% vs. 65%).

There were distinct differences in the body fat distribution between women and men. Although BMI, which does not differentiate between fat and lean mass, was similar in men and women (mean BMI 27 kg/m^2), women had greater levels of imaging-based measures of total adiposity. This was true for both proportional measures of total adiposity (i.e. mean %BF: 36% vs. 26% or %BF-DXA: 38% vs. 29.2%) and absolute measures of total adiposity (i.e. TAT-MRI: 22 L vs. 19.6 L; TAT-DXA: 27 kg vs. 25 kg). However, men had higher levels of central adiposity (i.e. WC: 95 cm vs. 834 cm), visceral fat (i.e. VAT-MRI: 5 L vs. 3 L; VAT-DXA: 2 L vs. 1 L) and ectopic liver

fat (i.e. LPDFF-MRI: 5% vs. 4%), while women had higher levels of subcutaneous fat (i.e. ASAT-MRI: 8 L vs. 6 L) and ectopic muscle fat (i.e. TMFI-MRI: 8 L vs. 7 L).

Mean lipid levels tended to be slightly higher in women than men (i.e. HDL-C 1.6 mmol/L vs. 1.3 mmol/L), while men had greater mean values of blood pressure (i.e. DBP 80.8 vs. 77.5 mm Hg), and blood proteins (i.e. IGF-1 22.4 nmol/L vs 21.7nmol/L). Women had a higher mean SHBG value (i.e. 64.5 nmol/L vs. 38.8 nmol/L), and much lower mean testosterone levels (i.e. 1.1 nmol/L vs. 12.2 nmol/L). In premenopausal women, the mean oestradiol value was 566 pmol/L.

Anthropometric measures, including BMI, WC, and WHR, were available for approximately 63,000 participants, while %BF was available for a slightly smaller number (n=54,973) (**Figure 2.1**). MRI-derived adiposity traits were processed for around 40,000 participants, except for LPDFF, which was available for a smaller subset of 9,780 participants. DXA-derived adiposity traits were processed for approximately 5,000 participants.

To assess potential selection bias, the characteristics of participants with complete adiposity traits at the imaging visit were further analysed (n=4,274) (**Table 2.3**). The mean age of those with complete adiposity traits at the imaging visit was slightly younger than the mean age of those at the wider imaging visit (i.e. 62 vs 65). Despite this difference, their sociodemographic characteristics and body fat distribution were largely comparable to those of the broader imaging population, suggesting an absence of selection bias. This suggests that the availability of complete adiposity traits is not related to individual characteristics but is likely random, determined by the order of processing MRI and DXA images.

2.6.3 Comparison of baseline with imaging

Table 2.4 compares baseline characteristics of the entire UKB cohort with subsets of participants from the imaging study, including those with at least one adiposity trait available and those with all adiposity traits. At the baseline visit, participants in the imaging subset (n=64,025), compared with the entire cohort, were slightly younger (i.e. mean age: 55 years vs. 57), had a lower proportion of postmenopausal females (i.e. 63% vs. 72%), were more likely to hold a college or university degree (i.e. 46% vs. 32%), more frequently reported weekly alcohol consumption (i.e. 76% vs. 69%), and had a slightly higher proportion of White participants (i.e. 97% vs. 95%). These differences suggest potential selection biases that may influence the generalisability of findings to the broader cohort.

In terms of body fat measurements, participants in the imaging subset had a slightly lower mean value of baseline adiposity than the entire cohort. Specifically, the mean BMI (i.e. 26.6 vs. 26.7 kg/m^2) and WC (i.e. 88.3 cm vs. 90.3 cm) in the imaging subset were slightly lower than those in the entire UKB cohort.

Participants with all adiposity traits within the imaging sub-cohort had similar demographic and lifestyle trends, and body fat metrics compared to the wider imaging subset. For instance, age, education level, alcohol consumption patterns and BMI were comparable to those observed in the larger imaging cohort, indicating that this subgroup remains representative of the wider imaging sub-set.

Differences between the baseline and imaging cohorts may reflect that those attending the imaging visit were generally in better health. Furthermore, as the imaging visit occurred approximately 10 years after baseline, some baseline

participants may had been in poor health or deceased by the time of the imaging assessment.

Table 2.1 Characteristics of UK Biobank participants attending the baseline visit by sex

Baseline characteristics	All (N=502,359)	Women (N=273,294)	Men (N=229,065)
Sociodemographic and lifestyle			
Age, Mean (SD), years	57 (8)	56 (8)	57 (8)
College or University degree, %	32	31	34
Ancestry White, %	95	95	95
Menopausal women, %	72	72	N/A
Ever regular smoker, %	45	40	51
Weekly alcohol drinking, %	69	62	77
Total adiposity, Mean (SD)			
BMI, kg/m²	27.4 (4.8)	27.1 (5.2)	27.8 (4.2)
%BF	31.5 (8.5)	36.6 (6.9)	25.3 (5.8)
Central adiposity, Mean (SD)			
WC, cm	90.3 (13.5)	84.7 (12.6)	97.0 (11.4)
WHR	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)
Lipid concentration, Mean (SD), mmol/L			
LDL-C	3.6 (0.9)	3.6 (0.9)	3.5 (0.9)
HDL-C	1.4 (0.4)	1.6 (0.4)	1.3 (0.3)
TG	1.7 (1.0)	1.6 (0.9)	2.0 (1.2)
TC	4.6 (0.9)	4.8 (0.9)	4.4 (0.9)
Blood pressure, Mean (SD), mm Hg			
Systolic	136.5 (18.0)	135.3 (19.2)	140.9 (17.5)
Diastolic	78.8 (10.0)	80.7 (10.0)	84.1 (10.0)
Pulse	57.6 (13.5)	54.6 (15.9)	56.8 (14.3)
Blood protein, Mean (SD)			
HbA1c, mmol/mol	36.1 (6.8)	35.8 (6.0)	36.5 (7.6)
IGF-1, nmol/L	21.4 (5.7)	21.0 (5.8)	21.9 (5.5)
CRP, mg/L	2.6 (4.4)	2.7 (4.4)	2.5 (4.4)
Sex hormone, Mean (SD)			
SHBG, nmol/L	52.9 (28.4)	62.0 (31.0)	39.6 (16.8)
Testosterone, nmol/L	N/A	1.1 (0.6)	12.0 (3.7)
Oestradiol in premenopausal women, pmol/L	575.8 (492.5)	575.8 (492.5)	N/A

N/A= Not available

Table 2.2 Characteristics of UK Biobank participants who participated in the imaging sub-cohort

Imaging characteristics	All (N=64,025)	Women (N=33,016)	Men (N=31,009)
Sociodemographic and lifestyle			
Age, Mean (SD), years	65 (8)	64 (8)	66 (8)
College or University degree, %	48	47	49
Ancestry White, %	97	97	97
Menopausal females, %	95	95	N/A
Ever regular smoker, %	38	34	41
Weekly alcohol drinking, %	71	65	78
Total adiposity, Mean (SD)			
BMI, kg/m²	26.6 (4.5)	26.2 (4.9)	27.1 (4.0)
%BF	31.2 (8.2)	36.4 (6.7)	25.8 (5.7)
%BF-DXA	33.8 (8.1)	38.0 (7.2)	29.2 (6.3)
TAT-MRI, L	20.9 (7.1)	22.0 (7.5)	19.6 (6.5)
TAT-DXA, kg	26 (9)	27 (10)	25 (9)
Central adiposity, Mean (SD)			
WC, cm	89.3 (12.9)	83.7 (12.2)	95.1 (11.0)
WHR	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)
ATAT-MRI, L	10.6 (4.5)	10.5 (4.6)	10.7 (4.4)
ATATI-MRI, L/m²	3.7 (1.6)	4.0 (1.8)	3.4 (1.4)
ASAT-MRI, L	6.9 (3.2)	7.9 (3.4)	5.8 (2.5)
AFM-DXA, g	2.5 (1.2)	2.2 (1.2)	2.7 (1.2)
Visceral adiposity, Mean (SD)			
VAT-MRI, L	3.7 (2.3)	2.6 (1.5)	4.9 (2.3)
VAT-DXA, L	1.3 (1.0)	0.8 (0.6)	1.8 (1.0)
Ectopic adiposity, Mean (SD)			
Liver PDFF, %	4.2 (4.6)	3.7 (4.5)	4.7 (4.7)
TMFI, L	7.3 (1.9)	7.8 (1.9)	6.8 (1.7)
Lipid concentration†, Mean (SD), mmol/L			
LDL-C	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)
HDL-C	1.5 (0.4)	1.6 (0.4)	1.3 (0.3)
TG	1.7 (1.0)	1.4 (0.8)	1.9 (1.1)
TC	4.7 (0.9)	4.8 (0.9)	4.5 (0.9)
Blood pressure, Mean (SD), mm Hg			
Systolic	140.6 (19.1)	138.0 (20.0)	143.2 (17.7)
Diastolic	79.1 (10.1)	77.5 (10.1)	80.8 (9.9)
Pulse	61.4 (15.2)	60.5 (15.9)	62.5 (14.3)
Blood protein†, Mean (SD)			
HbA1c, mmol/mol	35.0 (5.1)	34.8 (4.7)	35.2 (5.5)
IGF-1, nmol/L	22.0 (5.5)	21.7 (5.7)	22.4 (5.2)
CRP, mg/L	2.1 (3.6)	2.1 (3.7)	2.0 (3.4)
Sex hormone†, Mean (SD)			
SHBG, nmol/L	51.9 (27.9)	64.5 (31.2)	38.8 (15.6)
Testosterone, nmol/L			
Males	12.2 (3.6)	N/A	12.2 (3.6)
Females	1.1 (0.6)	1.1 (0.6)	N/A
Oestradiol in premenopausal females, pmol/L	565.7 (757.5)	565.7 (757.5)	N/A

† Biochemical measurements were measured at baseline visit only. N/A= Not available

Table 2.3 Characteristics of UK Biobank participants with complete information on all adiposity traits who participated in the imaging sub-cohort (measured at the imaging visit unless otherwise stated)

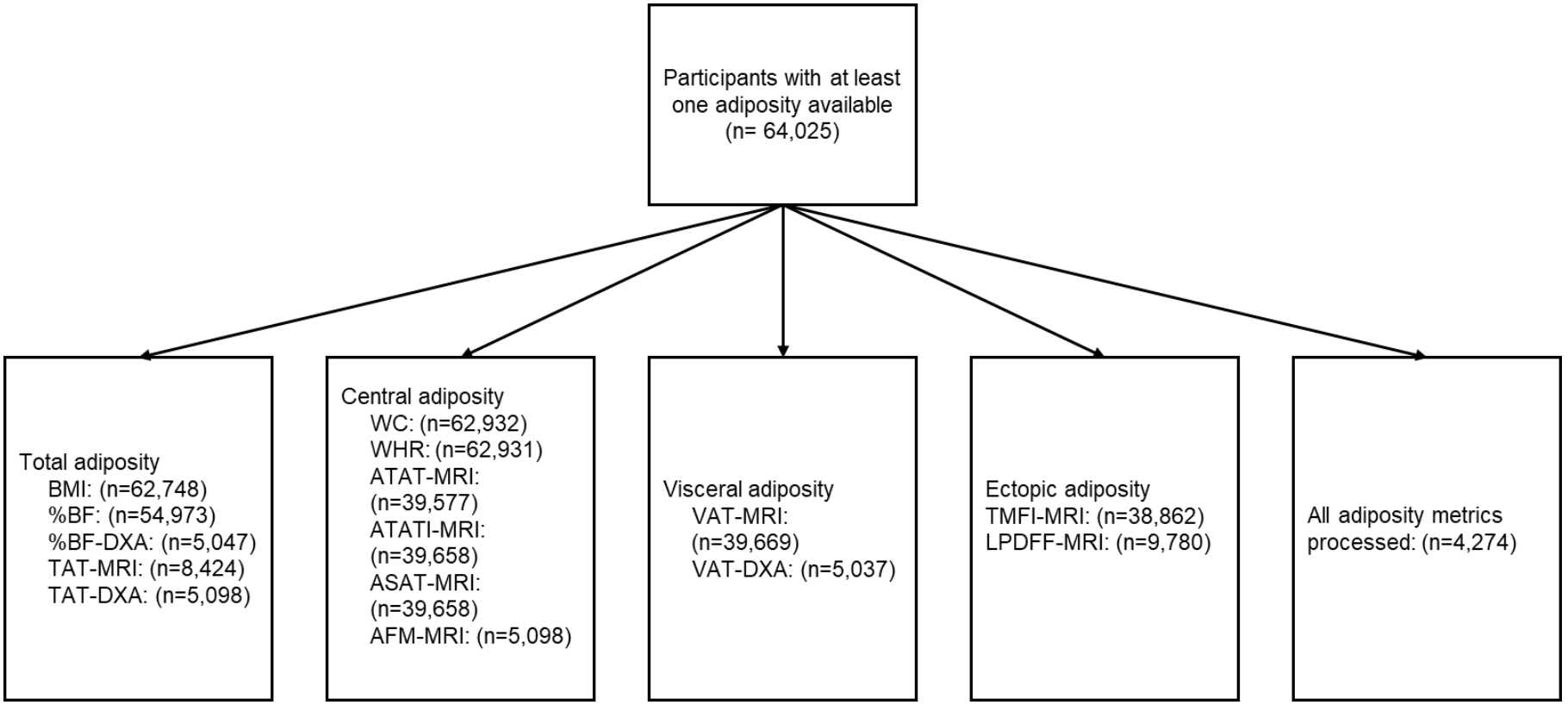
Imaging characteristics	All (N=4,274)	Women (N=2,295)	Men (N=1,979)
Sociodemographic and lifestyle			
Age, Mean (SD), years	62 (7)	61 (7)	63 (7)
College or University degree, %	45	42	48
Ancestry White, %	97	97	96
Menopausal females, %	89	89	N/A
Ever regular smoker, %	39	35	43
Weekly alcohol drinking, %	71	65	78
Anthropometric-derived adiposity, Mean (SD)			
BMI, kg/m²	26.6 (4.2)	26.2 (4.6)	27.0 (3.6)
Waist circumference, cm	87.1 (11.7)	81.9 (11.1)	93.0 (9.2)
WHR	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)
%BF	33.7 (8.0)	37.8 (7.1)	28.9 (6.1)
MRI-derived adiposity, Mean (SD)			
Total fat, L	20.8 (7.0)	21.7 (7.3)	19.7 (6.4)
Total abdominal fat, L	10.6 (4.4)	10.6 (4.5)	10.7 (4.2)
Total abdominal fat index, L/m2	3.7 (1.6)	4.0 (1.7)	3.5 (1.3)
Visceral fat, L	3.6 (2.2)	2.6 (1.5)	4.9 (2.2)
Abdominal subcutaneous fat, L	7.0 (3.1)	8.0 (3.3)	5.8 (2.3)
Liver PDFF, %	4.1 (4.5)	3.6 (4.4)	4.6 (4.6)
Muscle fat infiltration, L	7.4 (1.8)	7.9 (1.8)	6.9 (1.6)
DXA-derived adiposity, Mean (SD)			
Total fat, kg	25 (9)	27 (9)	24 (8)
Visceral fat, L	1.2 (0.9)	0.8 (0.6)	1.7 (1.0)
Lipid concentration†, Mean (SD), mmol/L			
LDL-C	3.6 (0.8)	3.6 (0.8)	3.5 (0.8)
HDL-C	1.5 (0.4)	1.6 (0.4)	1.3 (0.3)
TG	1.7 (1.0)	1.5 (0.8)	1.9 (1.1)
TC	4.7 (0.9)	4.9 (0.9)	4.5 (0.9)
Blood pressure, Mean (SD), mm Hg			
Systolic	136.5 (18.0)	133.3 (18.8)	140.1 (16.4)
Diastolic	78.8 (10.0)	77.4 (9.9)	80.5 (9.7)
Pulse	57.6 (13.5)	56.0 (13.9)	59.6 (12.7)
Blood protein†, Mean (SD)			
HbA1c, mmol/mol	35.1 (4.9)	34.9 (4.6)	35.3 (5.1)
IGF-1, nmol/L	21.9 (5.7)	21.5 (5.8)	22.4 (5.4)
CRP, mg/L	2.1 (3.7)	2.3 (3.7)	2.0 (3.7)
Sex hormone†, Mean (SD)			
SHBG, nmol/L	52.9 (28.4)	64.4 (31.6)	39.9 (16.5)
Testosterone, nmol/L			
Males	12.3 (3.6)	N/A	12.3 (3.6)
Females	1.1 (0.6)	1.1 (0.6)	N/A
Oestradiol in premenopausal females, pmol/L	567.2 (372.0)	567.2 (372.0)	N/A

Conventions as in Table 2.2.

Table 2.4 Comparison of participants' characteristics measured at baseline

Baseline characteristics	Baseline Entire cohort (N=502,359)	Imaging sub-cohort At least one adiposity metric available (N=64,025)	Imaging sub-cohort All adiposity metrics available (N=4,274)
Sociodemographic and lifestyle			
Age, Mean (SD), years	57 (8)	55 (8)	56 (8)
Women, %	54	52	54
College or University degree, %	32	46	43
Ancestry White, %	95	97	97
Menopausal females, %	72	63	66
Ever regular smoker, %	45	39	40
Weekly alcohol drinking, %	69	76	75
Total adiposity, Mean (SD)			
BMI, kg/m²	27.4 (4.8)	26.7 (4.3)	26.6 (4.1)
%BF	31.5 (8.5)	30.0 (8.2)	30.5 (8.2)
Central adiposity, Mean (SD)			
WC, cm	90.3 (13.5)	88.3 (12.7)	87.8 (12.2)
WHR	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, Mean (SD), mmHg			
Systolic	137.9 (18.7)	135.1 (17.7)	135.1 (17.5)
Diastolic	82.3 (10.1)	81.6 (9.9)	81.2 (9.7)
Pulse	55.6 (15.2)	53.5 (15.2)	53.9 (13.5)
Blood lipid, Mean (SD), mmol/L			
LDL-C	3.6 (0.9)	3.6 (0.8)	3.6 (0.8)
HDL-C	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)
TG	1.7 (1.0)	1.7 (1.0)	1.7 (1.0)
Total cholesterol	4.6 (0.9)	4.7 (0.9)	4.7 (0.9)
Blood protein, Mean (SD)			
HbA1c, mmol/mol	36.1 (6.8)	35.0 (5.1)	35.1 (4.9)
IGF-1, nmol/L	21.4 (5.7)	22.0 (5.5)	21.9 (5.7)
CRP, mg/L	2.6 (4.4)	2.1 (3.6)	2.1 (3.7)
Sex hormone, Mean (SD)			
SHBG, nmol/L	51.6 (27.8)	51.9 (27.9)	52.9 (28.4)
Testosterone, nmol/L			
Males	12.0 (3.7)	12.2 (3.6)	12.3 (3.6)
Females	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)
Oestradiol in premenopausal females, pmol/L	575.8 (492.5)	590.1 (561.5)	567.0 (407.0)

Figure 2.1 Availability of adiposity traits for different body fat components in participants of the UK Biobank imaging sub-cohort



Chapter 3. Correlation between anthropometric and imaging-derived measures of adiposity: a systematic review and a UK Biobank analysis

3.1 Background and aims

While BMI, WC, and WHR are commonly used adiposity traits, they do not reliably capture variations in different body fat components. On the other hand, imaging techniques such as MRI and DXA allow precise body fat quantification, but uncertainty remains in the published literature about how well conventional anthropometric measures of adiposity correlate with MRI- and DXA-derived methods of measuring adiposity.

The aims of this chapter are:

1) To perform a systematic literature review of published scientific papers since the year 2000 on the correlation between conventional anthropometric (i.e. BMI, WC and WHR) and imaging-based (i.e. MRI and DXA) adiposity traits.

2) To undertake meta-analyses of the published findings comparing conventional anthropometric with MRI- and DXA-based adiposity traits.

3) To assess whether these correlation coefficients differ by ancestry, sex, age, and study setting.

4) To assess the correlation of conventional anthropometric with MRI- and DXA-derived measures of adiposity in a cross-sectional analysis of UKB participants who underwent simultaneous body fat measurements (at the imaging sub-cohort), overall and by sex.

3.2 Methods

3.2.1 Systematic review and meta-analyses

The systematic literature review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist Eligibility criteria (102).

Studies were eligible for inclusion if they reported correlations between any of the conventional anthropometric measures and MRI- or DXA-derived adiposity measures of body fat composition in adolescent or adult participants. Explicit details on inclusion and exclusion criteria can be found in **Table 3.1**.

3.2.2 Search strategy

Two online biographic databases (Scopus and Web of Science) were searched covering a period from January 2000 to January 2023. Details of the search strategy are given in **Table 3.2**. Results were limited to publications in English.

For included studies, two reviewers (Sofia Mouchti and Josefina Oriacq) independently extracted pre-defined data on the study population, including participant demographic characteristics (e.g. sex, age, and ethnicity), the study setting (community or hospital), whether a trained examiner measured weight and height, and whether the study adjusted for confounders. Adiposity traits were grouped as follows: (i) conventional anthropometric measures: BMI, WC, and WHR; (ii) MRI-derived measures: ATAT, ASAT, VAT, and hepatic fat; and (iii) DXA-derived measures: ATAT, VAT, and %BF. The extracted information was recorded onto a spreadsheet and compared between the two reviewers. Any discrepancies were checked, reviewed and resolved upon further discussion.

3.2.3 Statistical analyses of the meta-analyses

All analyses were performed in the programming language R version 4.1.1. The "metacor" function from the "meta" package in R was used to calculate the weighted average correlations between anthropometric-based and imaging-based adiposity traits. In this method, study-specific correlations (r) were transformed to Fisher's Z values, with an estimated variance of 1/(n-3), where n is the number of participants included in the study. The overall weighted correlation for all studies was derived by applying study-specific weights proportional to the inverse of the variance of the study-specific Fisher's Z values (103).

Absolute correlations of magnitude <0.20 were characterised as very weak, 0.20-0.39 as weak, 0.40-0.59 as moderate, 0.60-0.79 as strong, and ≥0.80 as very strong. Heterogeneity in estimated correlations according to study, ethnicity, sex and age was assessed using the Cohran's Q-test (104). Statistical tests with a p-value less than or equal to 0.05 were considered significant.

The study by Perez et al. had a significantly larger population than the other included studies and therefore contributed substantially to the overall findings (105). To assess the potential impact of this study on the overall findings, two separate meta-analyses were performed: one with and one without the inclusion of this study.

Publication bias was assessed using Funnel plots and Egger's test (106).

3.2.4 Study population

Briefly, from the baseline cohort of 0.5 million participants in the UKB, 100,000 were re-invited to participate at the imaging sub-cohort, during which body fat was measured simultaneously using anthropometric, MRI and DXA methods. Of these,

64,025 individuals had at least one of their adiposity traits available. Details are given in Section 2.6 with population characteristics shown in **Table 2.2**

3.2.5 Statistical analyses of the cross-sectional analysis

Partial Pearson correlations, adjusting for sex, were calculated between anthropometric and MRI- and DXA-derived measures of adiposity in a cross-sectional analysis.

The Pearson correlation coefficient was further calculated as sex-specific. A two-sample Z-test for correlations was performed to assess the significance of the difference between the correlation coefficients of women and men, and the p-values were extracted.

A sensitivity analysis was also performed in the subset of participants with all available adiposity traits (n=4,274 participants) to evaluate potential selection bias in the study sample.

3.3 Results

3.3.1 Literature review

In total, the initial search identified 4,978 reports. After removing duplicate reports (n=2,102) and records with no reported correlations (n=2,814), 62 full-text articles were assessed for eligibility. Of these, 20 articles were further excluded for the following reasons: (i) correlations were not reported (n=12) (107-118); (ii) articles were not retrievable online (n=5) (119-123); and (iii) articles were in a language other than English (n=3) (124-126); Finally, 42 studies were included in the meta-analysis: 22 on MRI, 20 on DXA and 2 on both MRI and DXA (**Figure 3.1**). Overall, these 42 studies included a total of 42,556 participants, with 15,130 having MRI data (105,

127-147) and 27,426 having DXA data (105, 143, 148-165) (**Table 3.3**). Of the participants included, 98% were adults (i.e. 18+ years), 85% were men, 95% were White, and 95% were recruited from the general community. The mean BMI of study populations ranged from normal to obese class II according to the WHO criteria. Participant characteristics of the included articles in the meta-analyses of the MRI and DXA studies are presented in **Table 3.4** and **Table 3.5** respectively.

3.3.2 Meta-analysis

3.3.2.1 Anthropometric vs. MRI-derived body composition

Figure 3.2 presents the weighted average correlations between imaging-derived and anthropometric measures of body fat composition. Overall, BMI and WC showed very strong correlations with ATAT-MRI (BMI: r=0.88 [95%CI: 0.87, 0.88]; WC: 0.88, [0.88, 0.89]) and with ASAT-MRI (BMI: 0.85 [0.85, 0.86]; WC: 0.83 [0.82, 0.83]), and strong correlations with VAT-MRI (BMI: 0.76, [0.76, 0.77]; WC: 0.79 [0.79, 0.80]. Compared with BMI and WC, the correlations between WHR and derived measures of body fat composition were generally lower (ATAT: 0.60 [0.59, 0.61]; VAT: 0.67 [0.66, 0.68]; ASAT: 0.54 [0.52, 0.55]). All the anthropometric measures were at best only weakly to moderately correlated with hepatic fat (BMI: 0.43 [0.41, 0.44]; WC: 0.41 [0.40, 0.43]; WHR: 0.36 [0.34, 0.37]). Overall, the results of the meta-analysis with and without the UKB study of Perez et al. were comparable.

The correlations between anthropometric and specific MRI-derived measures of body fat varied to some extent by ancestry, sex, age and study setting. Notably, the correlations of BMI with VAT-MRI were significantly stronger in Whites than non-Whites (0.77 vs 0.66), as were those of BMI with ASAT-MRI (0.85 vs 0.71), WC with VAT-MRI (0.80 vs 0.58), WC with ASAT-MRI (0.83 vs 0.69); and WHR with VAT-MRI

(0.67 vs 0.36) (**Figure 3.3**). Women had stronger correlations than men of BMI with ATAT-MRI (0.92 vs 0.88), and with ASAT-MRI (0.91 vs 0.85), but weaker correlations of BMI with VAT-MRI (0.72 vs 0.78); and weaker correlations of WHR with ATAT-MRI (0.38 vs 0.60) and with VAT-MRI (0.55 vs 0.67) (**Figure 3.4**). There was also some evidence of differences by age, with the most notable being that individuals aged <18 had a somewhat lower correlation than those aged 18+ of BMI with ATAT-MRI (0.82 vs 0.88), and with VAT-MRI (0.65 vs 0.77); and of WC with VAT-MRI (0.70 vs 0.79); and WHR with VAT-MRI (0.54 vs 0.67). Conversely, those aged <18 had a greater correlation than those aged 18+ of WHR with ASAT-MRI (0.69 vs 0.54) **(Figure 3.5**). There was some evidence that correlation coefficients between anthropometric and MRI-derived measures were somewhat greater in studies conducted within the community as opposed to a hospital setting. In particular, correlations of BMI with VAT-MRI (0.78 vs 0.59), and with ASAT-MRI (0.86 vs 0.61); WC with ATAT-MRI (0.89 vs 0.81), with VAT-MRI (0.80 vs 0.70), and with ASAT (0.83 vs 0.61); and WHR with ATAT-MRI (0.60 vs 0.47), and with ASAT-MRI (0.54 vs 0.06), were greater in community-based studies compared to hospital-based studies (**Figure 3.6**). At least some of the between-study heterogeneity observed in certain pairwise comparisons (22 out of 36 heterogeneity tests were significant, **Figure 3.3**-**Figure 3.6**) may be due to differences in the study-specific study populations according to one or more of ancestry, sex, age and study setting.

3.3.2.2 Anthropometric vs. DXA-derived body composition

Figure 3.7 shows correlations of anthropometric measures with DXA-based measures of body fat. BMI was very strongly correlated with ATAT- DXA (0.86 [0.86, 0.87]) and with VAT- DXA (0.80 [0.79, 0.80]) and strongly correlated with %BF-DXA

(0.76 [0.76, 0.77]). Compared with BMI, the correlations between WC and DXA-derived measures of body fat were generally weaker for ATAT-DXA (0.50 [0.48, 0.52]), and almost the same with BMI, between WC with VAT-DXA (0.80 [0.79, 0.80]) and BF-DXA (0.76 [0.76, 0.77]). Compared with BMI and WC, WHR showed weaker correlations with ATAT-DXA (0.13 [-0.22, 0.45]), VAT-DXA (0.65 [0.64, 0.66]) and %BF-DXA (0.58 [0.57, 0.59]), albeit based on relatively few studies. Overall, the results of the meta-analysis with and without the UKB study were comparable. However, for the correlation of WC with VAT-DXA the addition of the UKB study by Perez et al. increased the correlation from moderate to strong (0.51 vs 0.80).

Women showed stronger correlations than men of BMI with VAT-DXA (0.81 vs 0.74), and with %BF-DXA (0.77 vs 0.66); and of WC with ATAT-DXA (0.61 vs 0.40) and VAT-DXA (0.84 vs 0.43) (**Figure 3.8**). Correlations were significantly weaker in those aged <18 than in those 18+ for BMI with VAT-DXA (0.59 vs 0.80) and with %BF-DXA (0.39 vs 0.77); and for WC with VAT-DXA (0.68 vs 0.80) and %BF-DXA (0.46 vs 0.76), but stronger in those 18+ than those aged <18 with ATAT-DXA (0.84 vs 0.48) (**Figure 3.9)**.

Some of the between-study heterogeneity observed for certain correlations (9 out of 10 shown in **Figure 3.8** and **Figure 3.9**) may be due to differences in the study-specific study populations according to one or more of sex and age. None of the studies included reported correlations of interest for different ancestry groups**,** while subgroup analyses by study setting were not feasible because fewer than 2% of the studies with information on DXA had been conducted within a hospital setting.

In general, correlations between anthropometric measures with imaging-derived ATAT and VAT were higher for MRI-derived measures of adiposity than DXA-

derived, with the only exception being for BMI and WC, which showed a slightly greater correlation with DXA-derived than MRI-derived VAT (**Figure 3.10**).

3.3.2.3 Assessment of publication bias

Although the number of included studies was relatively small, funnel plots showed some evidence of an asymmetric distribution for some pairwise comparisons, with the majority of the smaller studies clustering to the left of the mean Fisher's Z correlations, suggesting some degree of publication bias (**Figure 3.11** and **Figure 3.12**). Based on Egger tests there was some evidence that publication bias may have affected the findings for correlations of (a) BMI vs. both MRI- (p=value=0.006) and DXA-derived VAT (p-value=0.007), (b) WC vs. VAT-MRI (p-value=0.003), and (c) WHR vs. VAT-DXA (p-value=0.0029). This may be due to the different population characteristics between studies. For example, the MRI studies included a mixture of large and small studies, with sample sizes ranging from 34 (143) to 18,827 (105), recruited from both hospital and community settings, and at different ages such as adolescents (159) to elderly (160).

3.3.3 UK Biobank

3.3.3.1 Anthropometric vs MRI-derived body composition

Overall, BMI, WC and %BF showed very strong correlations with TAT-MRI, and abdominal fat components (ATAT-MRI, ASAT-MRI and ATATI-MRI), with correlation coefficients ranging from 0.89 to 0.92 for BMI, 0.83 to 0.88 for WC, and 0.84 to 0.88 for %BF. The correlation coefficients with VAT-MRI were slightly lower, but still strong (BMI: r=0.74; WC: 0.78; %BF 0.72) (**Table 3.6)**. Compared with BMI, WC and %BF, WHR had generally lower correlations with MRI-derived body fat measures:

0.47 with TAT, 0.56 with both ATAT-MRI and ATATI-MRI, 0.61 with VAT-MRI and 0.45 with ASAT-MRI. All the anthropometric metrics of adiposity had, at best, moderate correlations with LPDFF-MRI (BMI: 0.47; WC: 0.48; WHR: 0.39; %BF: 0.42) and TMFI-MRI (BMI: 0.49; WC: 0.50; WHR: 0.36; %BF: 0.54).

The correlations between anthropometric and MRI-derived measures of body fat varied to some extent by sex (**Table 3.7**). Notably, the correlations of BMI, and %BF with TAT-MRI (BMI: 0.93 vs. 0.88; %BF: 0.90 vs. 0.84), ASAT-MRI (BMI: 0.91 vs. 0.85; %BF: 0.88 vs. 0.78) and TMFI-MRI (BMI: 0.51 vs. 0.45) were somewhat stronger in women than men. Similarly, WC showed a greater correlation in women than men with ASAT-MRI (0.84 vs. 0.82) and ectopic adiposity (LPDFF-MRI: 0.51 vs. 0.44; TMFI-MRI: 0.51 vs. 0.48). In contrast, WHR showed stronger correlations in men than women with most MRI-derived adiposity traits (TAT-MRI: 0.60 vs. 0.39; VAT-MRI: 0.67 vs. 0.58).

3.3.3.2 Anthropometric vs DXA-derived body composition

Table 3.6 shows the correlations of anthropometric measures with DXA-based measures of body fat. BMI, WC %BF were very strongly correlated with DXA-derived TAT-DXA (BMI: 0.92; WC: 0.89; %BF: 0.88), %BF-DXA (BMI: 0.80; %BF: 0.91; WC: 0.78), and AFM-DXA (BMI: 0.89; WC: 0.89; %BF: 0.84), with the next largest correlation for VAT-DXA (BMI: 0.75; WC: 0.78; %BF: 0.70). Compared with BMI, WC and %BF, WHR had generally lower correlations with DXA-derived body fat measures: 0.50 with TAT-DXA, 0.61 with VAT-DXA, 0.50 with %BF-DXA, and 0.59 with AFM-DXA.

The correlations between anthropometric and DXA-derived adiposity differed to some extent by sex. Women showed stronger correlations than men for BMI and

%BF with DXA-derived metrics of TAT (BMI: 0.94 vs. 0.90; %BF: 0.90 vs. 0.84) and %BF (BMI: 0.82 vs. 0.77; %BF: 0.92 vs. 0.88) (**Table 3.7**). In contrast to BMI and %BF, WHR showed a greater correlation in men than women with DXA-derived TAT (0.61 vs. 0.42), %BF (0.63 vs. 0.42) and AFM (0.66 vs 0.54).

In a sensitivity analysis of 4,274 participants who had all the conventional and imaging-based adiposity traits available, the results were similar to the main analysis (**Table 3.8**).

3.3.4 Comparison of the meta-analysis with analysis in the UK Biobank

Table 3.9 presents a summary of the correlations reported in both the meta-analysis and the UKB. Overall, the correlations between the UKB cross-sectional analysis and those reported by the meta-analysis were generally similar. However, differences were observed for VAT-DXA, with the UKB analysis showing much stronger correlations compared to those reported by the meta-analysis (i.e. WC: 0.78 vs. 0.50; WHR: 0.61 vs.0.1).

3.4 Discussion

3.4.1 Summary of evidence

This systematic literature review and meta-analysis of 42 studies, provides a comprehensive summary of the evidence on the correlation of conventional anthropometric measurements with MRI- and DXA-based body fat composition. The meta-analysis showed that both BMI and WC were found to be very strongly correlated with MRI-derived total and subcutaneous fat in the abdominal area, and to a slightly lesser extent, with visceral fat. In contrast, WHR showed at best moderate correlations with all MRI-derived measures, which were somewhat stronger with

visceral fat than with subcutaneous or total abdominal fat. All the anthropometric measures considered were weakly to moderately correlated with MRI-derived ectopic liver adiposity. In general, correlations of anthropometric measurements with imaging-based abdominal total fat and visceral abdominal fat tended to be higher for MRI-derived than for DXA-derived metrics. For certain pairwise comparisons, there was evidence of heterogeneity across certain population subgroups. For example, correlations were somewhat stronger in Whites than non-Whites for BMI with VAT-MRI and ASAT-MRI; similarly, correlations were stronger in women than men for BMI with ATAT-MRI and ASAT-MRI, but weaker with VAT-MRI.

The analysis of the UKB participants who participated in the imaging sub-cohort showed similar results to the meta-analysis, while also providing novel insights into the anthropometric measurement of %BF and the MRI-derived measure of TMFI. This analysis showed that BMI, WC, and %BF were very strongly correlated with MRI- or DXA-derived measures of total and central adiposity, and to a lesser extent with visceral adiposity. Compared with BMI, WC and %BF, WHR had weak to moderate correlations with MRI- or DXA-derived adiposity traits, though its association with visceral adiposity was slightly stronger. In contrast, all anthropometric measures demonstrated weak to moderate correlations with MRI-derived ectopic adiposity of liver adiposity and muscle fat infiltration in the thigh.

A key finding from this chapter is that BMI, which is generally viewed as a measure of total adiposity, had similar if not higher correlations with imaging-based measures of visceral adiposity as did WC and WHR, which are commonly used as anthropometric markers of central adiposity. Although the correlation of BMI with VAT-MRI (i.e. meta-analysis: 0.76; UKB: 0.74) was slightly weaker than that for WC

(i.e. meta-analysis: 0.79; UKB: 0.78), it was slightly greater than that for WHR (i.e. meta-analysis: 0.67; UKB: 0.61). The more modest correlation of WHR with visceral adiposity compared to that of BMI or WC may reflect a greater degree of error in its measurement since, unlike BMI and WC, it is derived from two separate body measurements of waist and hip (22, 166, 167). Despite anthropometric measures of adiposity being strongly correlated with abdominal adiposity traits of total, visceral and subcutaneous fat, they were weakly to moderately correlated with MRI-measured hepatic fat.

3.4.2 Comparison of findings with published literature

Previous studies have suggested that both MRI and DXA provide an extremely accurate assessment of adipose tissue distribution (140, 168-173). Unfortunately, it was not possible to directly assess this because none of the studies included in the present meta-analyses simultaneously applied both imaging techniques to the same participants. Nevertheless, an indirect comparison of the meta-analysis data showed that the correlations of anthropometric with MRI-derived adiposity traits were consistently greater than those with DXA-derived measures. These differences may reflect variations in study population characteristics. For instance, 90% of participants in studies reporting MRI-derived adiposity were community-based, compared to 98% in studies reporting DXA-derived adiposity. Notably, significant differences in correlations were observed for MRI-derived measures between community-based and hospital-based participants, which supports this argument. However, studies reporting DXA-based measures were mostly community-based, so no substantial variation in correlations was expected for these measures. In contrast, the UKB analysis found that correlations between anthropometric measures and

MRI-derived adiposity were of a similar magnitude to those with DXA-derived adiposity.

As in the present study, previous studies have reported modest differences in the correlations between anthropometric and imaging measurements by sex, ancestry and age (127, 131, 135, 137-140, 142, 143, 149, 150, 154, 156, 161, 163, 174). There is evidence in the published literature that East and South Asians are more likely to accumulate visceral fat, compared to other ancestry populations (175). Although there was a lack of studies to allow the investigation of these correlations in specific ancestry groups, significant differences were found between Whites and non-Whites in the meta-analysis, albeit based on the small number of participants. For example, correlations of BMI, WC and WHR with MRI-derived visceral fat were somewhat stronger in Whites than non-Whites.

It is well established that body shape and fat distribution differ by sex, with men more likely to store fat around their abdomen, known as the android fat, and women more likely to store subcutaneous fat around their hips, buttocks and thighs producing a body profile known as the gynoid pattern (31). These differences in fat distribution by sex may have contributed to the higher correlations observed in women compared to men of BMI with MRI-derived abdominal total and subcutaneous fat.

Aging also affects body fat distribution, with visceral fat increasing and subcutaneous fat decreasing with age (176). Some evidence of age-related differences was found in the meta-analysis, particularly notable in the correlations between BMI and MRI-derived total abdominal and visceral fat. Those under 18 showed lower correlations compared to those above 18 in these specific pairwise comparisons.

The observed differences in the correlations for those <18 years old and 18+ may reflect key physiological transitions occurring around the age of 18 (177). Adolescence and early adulthood are characterised by rapid changes in body composition, hormonal profiles, and growth trajectories, which can influence fat distribution and the accuracy of anthropometric measures of adiposity (178, 179). Puberty leads to sex-specific shifts in fat storage: SAT tends to increase in women, while men are more likely to accumulate VAT, potentially weakening correlations between anthropometric measures and imaging-derived adiposity traits in younger individuals (178). In those aged 60 or 65 years and above, body composition changes include sarcopenia (loss of muscle mass) (180), redistribution of fat from subcutaneous to visceral area (176), all of which may affect the correlation between anthropometric traits and imaging-derived adiposity.

It is well-established that certain diseases, such as sarcopenia and cachexia, affect body fat distribution (181). Evidence from community-based studies indicates greater correlations between anthropometric with MRI-derived adiposity traits compared to hospital-based studies. This suggests that anthropometric indices may be less accurate in measuring specific body fat components in individuals with underlying health conditions. Previous studies have also reported that factors such as activity levels, medications, dietary habits, alcohol, and smoking consumption influence the body fat profile (182, 183). However, these factors could not be investigated in the present study due to the lack of available correlations in the published literature.

3.4.3 Strengths and limitations

This study has certain strengths. This is the first systematic literature review and meta-analysis investigating the correlation between anthropometric and imaging-

derived adiposity measurements, encompassing over 12,000 predominantly healthy participants. Comprehensive searches of the online bibliographic databases covered the period until 4 January 2023, with subsequent searches identifying three additional studies published by 26 June 2024. Wu et al. (184), analysed 2,989 adolescents, and Michel et al. (185), analysed 181 adults, both found correlations between anthropometric and imaging measures comparable to those observed here. Wang et al. (186) analysed 400 adults and reported a very weak correlation between BMI and MRI-derived hepatic fat (0.16), lower than the moderate weighted correlation reported here. However, Wang et al. included participants across a wide age range (22-83 years), potentially reflecting heterogeneity in body fat distribution across different ages. Moreover, to the author's knowledge, the UKB cross-sectional analysis is the largest population-based study that included simultaneous assessment of anthropometric and various imaging-based measures to investigate their correlations.

This study had several limitations. Firstly, the definitions of body fat components in the abdominal area varied significantly among the included studies in the meta-analyses. For example, while one study defined visceral fat as that between the L4 and L5 intervertebral disks (132), another study defined it as that between L1 and L5 (131). Moreover, while most studies focused on total and/or subcutaneous abdominal fat, two studies (131, 135) assessed fat distribution from head to toe, and one specifically examined gluteal subcutaneous fat (187). Additionally, discrepancies in imaging techniques and data extraction software, particularly for MRI in terms of scanner brand, field strength, and segmentation method, may have contributed to the observed heterogeneity among the studies.

Secondly, despite the inclusion of more than 40 individual studies, the majority excluding the UKB study (105) had relatively small sample sizes. Collectively, the total number of participants involved in these studies was limited and there was evidence of publication bias, which could potentially skew estimates and comparisons. Furthermore, the skewed distribution in funnel plots and significant Egger's tests may reflect heterogeneity due to diverse population characteristics across studies.

Thirdly, given the limited power, the subgroup findings related to ancestry, sex and age should be interpreted with caution. Larger studies involving diverse populations are necessary to validate these findings rigorously.

Fourth, other imaging-derived measures of ectopic adiposity such as pericardial and epicardial adiposity, muscle fat infiltration, and pancreatic adiposity, were not explored in the published literature, thereby limiting a comprehensive understanding of the adiposity distribution, especially about ectopic adiposity. Also, these adiposity traits were not available in the UKB participants who attended the imaging subset assessment.

Fifth, the weighted correlations included in the meta-analyses were mainly based on a mixture of direct and indirect comparisons of different participants. Future large-scale studies encompassing various adiposity traits within the same study populations are crucial to confirm or challenge the findings presented here.

Lastly, regarding the UKB cross-sectional analysis although the 64,025 individuals had at least one of their adiposity traits available, the number of individuals with MRI-derived measures of adiposity processed varied between 8,000 and 40,000,

whereas around 5,000 individuals had their DXA-derived measures of adiposity processed. However, a sensitivity analysis in participants with all available adiposity traits showed correlations were comparable with the wider imaging sub-cohort study.

3.5 Conclusion

This literature review and meta-analysis demonstrated that anthropometric measures of adiposity, particularly BMI and WC, strongly correlate with imaging-derived total abdominal, subcutaneous abdominal, and visceral abdominal fat. However, their correlation with imaging-derived hepatic fat was found to be weaker. A separate new analysis was reported here presenting the correlations between anthropometric and imaging-derived adiposity in the UKB participants who were part of the imaging sub-study assessment and the correlations aligned with the results of the meta-analysis. Future studies with simultaneous assessments of anthropometric and various imaging-based measures in large population-based studies of different ages and ancestry are needed. This will allow the assessment of the correlation between anthropometric measures and imaging-derived adiposity across populations of diverse age, sex and ancestry to allow comparison with the findings presented here.

Table 3.1 Inclusion and exclusion criteria used in the literature search

Criteria	Inclusion	Exclusion
Population	Adults and/or adolescents	1. Infants 2. Non-humans
Outcome	The correlation coefficient between any one of the specified anthropometric measures of adiposity (BMI, WC, WHR) and any one of the specified MRI-derived or DXA-derived adiposity traits (ATAT, VAT, ASAT, %BF)	MRI-derived adiposity corrected with magnetic resonance spectroscopy
Date	Between January 2000 and January 2023	Before January 2000 and after January 2023
Language	English	Manuscript unavailable online

Table 3.2 Search strategy used

Database	Search term
Scopus	TITLE-ABS-KEY (("D? XA" OR "Dual*energy X*ray absorptiometry" OR "MRI" OR "magnetic*resonance imaging") AND ("anthropometric*" OR "BMI" OR "body*mass*index" OR "weight*" OR "waist*circumference*") AND ("body composition" OR "fat distribution" OR "adipose tissue" OR "adipos?" OR "obesity")) AND PUBYEAR > 1999 AND (LIMIT-TO (LANGUAGE , "English"))
Web of Science (Editions: Science Citation Index Expanded; Social Sciences Citation Index; Arts & Humanities Citation Index; Conference Proceedings Citation Index- Science; Conference Proceedings Citation Index-Social Science & Humanities; Books Citation Index - Social Sciences & Humanities; Emerging Sources Citation Index; Current Chemical Reactions; Index Chemicus)	("D? XA" OR "Dual*energy X*ray absorptiometry" OR "MRI" OR "magnetic*resonance imaging") AND ("anthropometric*" OR "BMI" OR "body*mass*index" OR "weight*" OR "waist*circumference*") AND ("body composition" OR "fat distribution" OR "adipose tissue" OR "adipos?" OR "obesity") (All Fields) and English (Language)

Table 3.3 Summary of participant characteristics in the meta-analysis

Characteristics	Imaging method	
	MRI	DXA
No. of studies	23[a]	20
No. of participants	15,130	27,426
Age group, %		
<18 years	2.5	1.4
≥18 years	97.5	98.6
Male,%	89.8	83.1
BMI range[b], kg/m²	22.0-35.0	17.7-33.3
Ethnicity, %		
White	96.1	95.1
Non-White	3.9	4.9
Study setting, %		
Community	89.1	98.1
Hospital	8.5	1.5
Unspecified	2.4	0

a. The number of unique studies included was 22. Kulberg et al. was included as two studies with distinct age groups (mixed younger adults and elderly adults).

b. Mean or median depends on what was reported in the study

Table 3.4 Characteristics of selected MRI studies included in the meta-analysis

First author, publication year, country	Ethnicity, %	N	Males, %	Mean age[a], years	Mean BMI[a,] kg/m^2	Weight/height measured by trained examiner	Study settings	Adjustment for confounders
Perez-Cornago, 2022, UK	White 100	11501	100	57	29	Yes	Healthy community	No
JZ Yang, 2020, New Zeeland	White 51, Other 29, Asians 20	104	0	53	28.1	Yes	Healthy community	No
Ulbrich, 2018, Switzerland	White	80	0	21-62	17.5-26.2	Yes	Healthy community	No
V. Lee, 2018, USA	White	32	0	9.3-13.7	15.3-33.4	Yes	Healthy community	No
Eloi, 2017, Brazil	White	57	0	16-18	18-35	Yes	Healthy community	No

Setiawan, 2016, USA	White 19, Black 19, Native Hawaiian 21, Japanese American 22, Latino 19	256	0	68.4	28	Self-reported	Hepatocellular carcinoma	Age
Neeland, 2015, USA	White 80, Asian 18 Black 2	99	0	55.6	32.4	N/A	T2D	No
Lange, 2015, Germany	White	11	0	13	18-35	Yes	Healthy community	No
Neamat-Allah, 2014, Germany	White	119 2	0	47-81	17-40.5	Yes	Healthy community	Age, height

Mantatzis, 2014, Greece	White	76	0	38-72	31.5 T2DM, 30.1 healthy	Yes	50% T2D, 50%no metabolic syndrome	No
Dong, 2014, China	Asian	56	0	43-58	<25 n=24, >=25 n=18	Yes	n=42 healthy community, n=14 impaired glucose tolerance	No
Koren, 2013, USA	African-American 71 White 29	72	0	12-16	18-35	Yes	Healthy community	No
Maislin, 2012, Iceland	White	668	0	20.9-83.2	20-51.2	Yes	Obstructive sleep apnoea	No

Zhang, 2011, China	Asian	10	0	9-14	29	Yes	Community-based obese children	No
Browning, 2011, UK	White	120	0	18-79	27.5 men, 27.4 women	Yes	Healthy community	No
Ducluzeau, 2010, France	White	65	71	57	31	N/A	People with one or more CVD risk factor addressed by their general practitioner	No
Ludescher, 2009, Germany	White	68	0	42.3	24.4	N/A	n=39 healthy community, n=17 depressive	Age, sex

							syndrome, n=13 bulimia nervosa	
Illouz, 2008, France	White	34	74	59	33.2	N/A	Obese, T2D with metabolic syndrome	No
Kullberg, 2007, Sweeden	White	306	52	70	27 men, 26.5 women	Yes	N/A	No
Kullberg, 2007, Sweeden	White	50	54	14-66	26.8 men, 26.2 women	Yes	N/A	No
Ball, 2006, USA	Latino	196	58	8-13	>25	Yes	BMI more or equal to the 85th percentile,	No

							Latino background positive family history for T2D and absence of T2D	
Poll, 2004, Germany	White	37	87	48	27.9	Yes	Diabetes	No
Kamel et al, 2000, USA	White	40	0	26-57	30-39.9	Yes	Healthy community based	No

a. Or shown as range using "-", or median and (interquartile range), or otherwise stated.

Table 3.5 Characteristics of selected DXA studies included in the meta-analysis

First author, publication year, country	Ethnicity, %	N	Males, %	Mean age[a], years	Mean BMI[a], kg/m^2	Weight / height assessed by a trained examiner	Study settings	Adjustment for confounders
Perez-Cornago, 2022, UK	White 100	18,827	100	57	29	Yes	Healthy community	No
Correa, 2021, Brazil	White 67, Black 12, Other 21	81	100	18-35	24.7	Yes	Healthy community	No
Staynor, 2020, West Australia	White 82, Other 18	1,415	48	18-65	23.0 (21.1–25.6)	Yes	Healthy community	No
Redondo, 2020, USA	White 77, Hispanic 12, African-Americans 7, Other 4	122	32	12-19.5	>25	Yes	Type 1 diabetes	No
Martin, 2020, South Africa	Black	34	62	43.9	25.7	Yes	HIV positive undergoing haemodialysis	No

Grzegorczyk, 2019, Poland	White	50	0	51-85	28.5	N/A	Healthy community based post-menopausal	No
Guzman-Leon, 2019, Mexico	Other	61	52	20-37	24.7	Yes	Healthy community based	No
Pasha, 2017, USA	White 57, Asian 4 African-American 6, Hispanic 5, Other 8	126	45	49.1	28	Yes	Healthy community	No
Vasan, 2017, UK	White	4,950	44	29-55	25.2	Yes	Healthy community	fat mass index
Verduin, 2016, Netherlands	White	217	48	10-11	17.7	Yes	Healthy community	No
Saki, 2016, Iran	Other	477	51	89-19	17.7	Yes	Healthy community	No
Bhatia, 2015, USA	White	41	78	10-17	33.3	Yes	Healthy community obese/overweight children with habitual snoring	No
Grier, 2015, USA	White 74, Asian 3,	110	100	23	26.4	Yes	Army soldiers	No

	Black 9 Hispanic 9							
Smith, 2014, Australia	White	406	45	74-94	26.9	N/A	Healthy community based without psychotic symptoms, schizophrenia, bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy, and dementia	No
Direk, 2013, UK	White	54	0	49.3-72.8	25.1	Yes	Healthy community	No
Lam, 2013, China	Asians	105	52	21-65	28.1	Yes	Healthy community	No
Kaul, 2012, USA	White 92, Hispanic 4, Asian 4	109	44	18-90	26.7	Yes	Healthy community	No
Segatto, 2012, Brazil	White	67	58	44	26.7	Yes	HIV/AIDS	No

Oreopoulos, 2010, Canada	White 90 African American, Asian 6, Other 4	140	74	63	18-35	N/A	Systolic and/or diastolic heart failure	Age and sex
Illouz, 2008, France	White	34	74	59	33.2	N/A	Obese, T2D with metabolic syndrome	No

Conventions as in Table 3.4.

Table 3.6 Partial pairwise correlations of adiposity traits in the UK Biobank

Pearson partial correlations were adjusted for sex.

Anthropometric	MRI							DXA			
	TAT	ATAT	ATATI	VAT	ASAT	LPDFF	TMFI	TAT	VAT	%BF	AFM
BMI	0.91	0.90	0.92	0.74	0.89	0.47	0.49	0.92	0.75	0.80	0.89
WC	0.87	0.88	0.86	0.78	0.83	0.48	0.50	0.89	0.78	0.78	0.89
WHR	0.47	0.56	0.56	0.61	0.45	0.39	0.36	0.50	0.61	0.50	0.59
%BF	0.88	0.87	0.87	0.72	0.84	0.42	0.54	0.88	0.70	0.91	0.84

Table 3.7 Pairwise correlation coefficients of adiposity traits by sex

Pearson correlations were calculated. P-values represent the result of the two-sample Z-test for differences in the correlations between men and women.

		MRI							DXA			
		TAT	**ATAT**	**ATAT index**	**VAT**	**ASAT**	**LPDFF**	**TMFI**	**TAT**	**VAT**	**%BF**	**AFM**
Anthropometric												
BMI	Men	0.88	0.89	0.90	0.78	0.85	0.47	0.45	0.90	0.81	0.77	0.89
	Women	0.93	0.92	0.93	0.78	0.91	0.48	0.51	0.94	0.78	0.82	0.90
	p-value	<0.0001	<0.0001	<0.0001	1	<0.0001	1	<0.0001	<0.0001	0.4	<0.0001	1
WC	Men	0.89	0.88	0.86	0.80	0.82	0.44	0.48	0.90	0.81	0.78	0.89
	Women	0.86	0.88	0.86	0.81	0.84	0.51	0.51	0.88	0.83	0.77	0.91
	p-value	<0.0001	1	1	0.5	<0.0001	<0.0001	<0.01	<0.1	1	1	<0.1
WHR	Men	0.60	0.65	0.66	0.67	0.53	0.38	0.40	0.61	0.66	0.63	0.66
	Women	0.39	0.48	0.48	0.58	0.40	0.40	0.33	0.42	0.62	0.42	0.54
	p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1	<0.0001	<0.0001	1	<0.0001	<0.0001
%BF	Men	0.84	0.84	0.86	0.76	0.78	0.43	0.53	0.84	0.76	0.88	0.83
	Women	0.90	0.89	0.88	0.76	0.88	0.42	0.55	0.90	0.73	0.92	0.86
	p-value	<0.0001	<0.0001	<0.0001	1	<0.0001	1	0.7	<0.0001	1	<0.0001	<0.1

Table 3.8 Partial pairwise correlations of adiposity traits in those UK Biobank participants with all adiposity traits available

Conventions as in Table 3.6.

Anthropometric	MRI							DXA			
	TAT	ATAT	ATATI	VAT	ASAT	LPDFF	TMFI	TAT	VAT	%BF	AFM
BMI	0.90	0.89	0.92	0.72	0.88	0.45	0.46	0.92	0.74	0.80	0.88
WC	0.87	0.89	0.87	0.77	0.85	0.46	0.49	0.88	0.77	0.77	0.88
WHR	0.49	0.58	0.58	0.61	0.47	0.40	0.38	0.50	0.61	0.5	0.59
%BF	0.88	0.87	0.87	0.72	0.85	0.40	0.53	0.88	0.70	0.9	0.85

Table 3.9 Comparison of correlations between anthropometric measures and MRI/DXA-derived adiposity traits reported in both the meta-analysis and the UK Biobank (64,025 participants)

		MRI				DXA	
	Correlation coefficient	**ATAT**	**VAT**	**ASAT**	**LPDFF**	**VAT**	**%BF**
Anthropometric							
BMI	Meta-analysis	0.88	0.76	0.85	0.43	0.86	0.76
	UKB	0.90	0.74	0.89	0.47	0.75	0.80
WC	Meta-analysis	0.88	0.79	0.83	0.41	0.50	0.76
	UKB	0.88	0.78	0.83	0.48	0.78	0.78
WHR	Meta-analysis	0.60	0.67	0.54	0.36	0.13	0.58
	UKB	0.56	0.61	0.45	0.39	0.61	0.50

Figure 3.1 Flow diagram of selection procedures in the literature review.

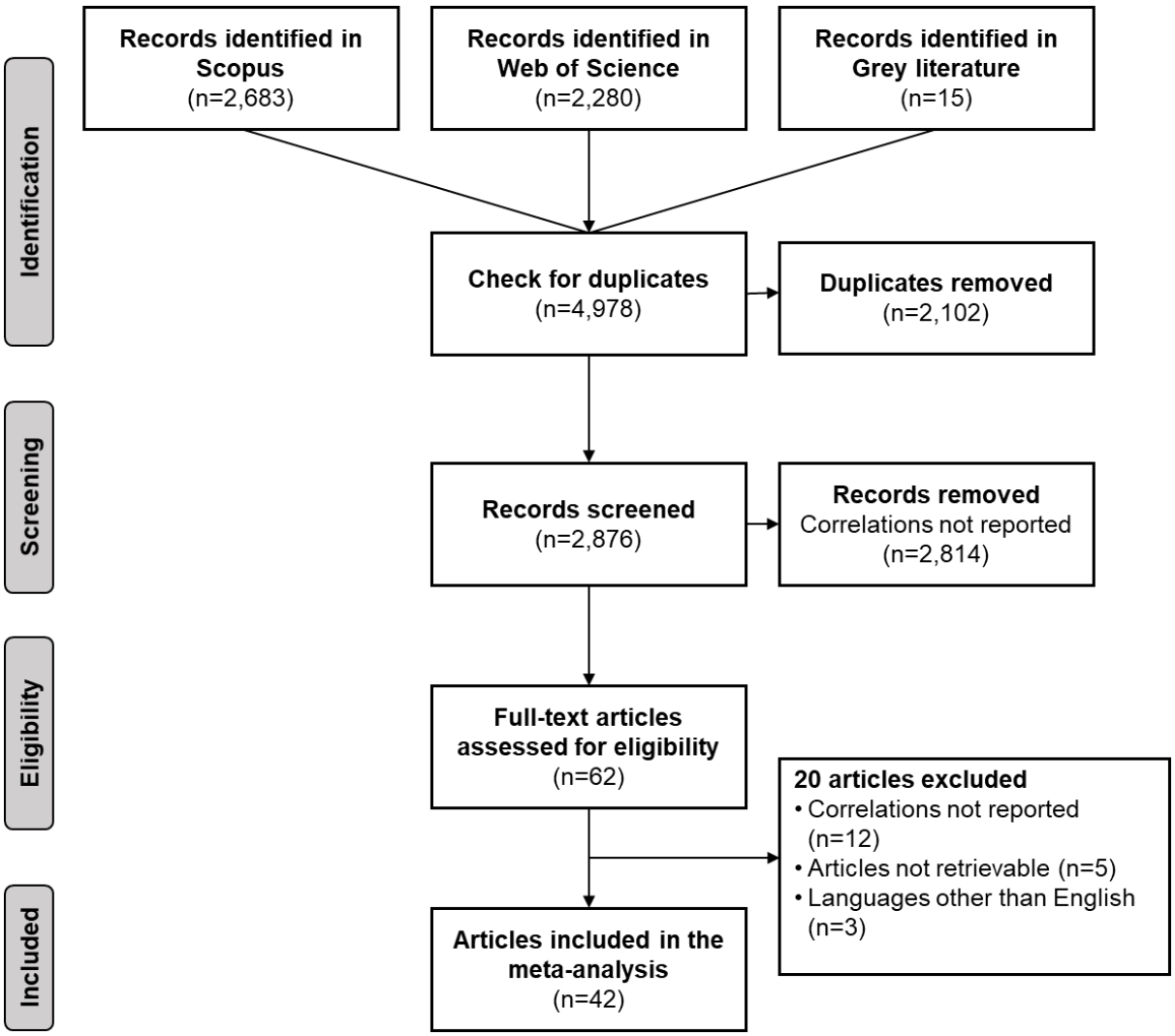


Figure 3.2 Correlations between MRI-derived adiposity and conventional anthropometric adiposity traits

The black box represents the correlation coefficient reported in each study with its size proportional to 1/(n -3), where n is the sample size of the study. Diamond is a meta-analysed overall correlation coefficient with the solid line indicating zero correlation. Heterogeneity is assessed with a Q-test.

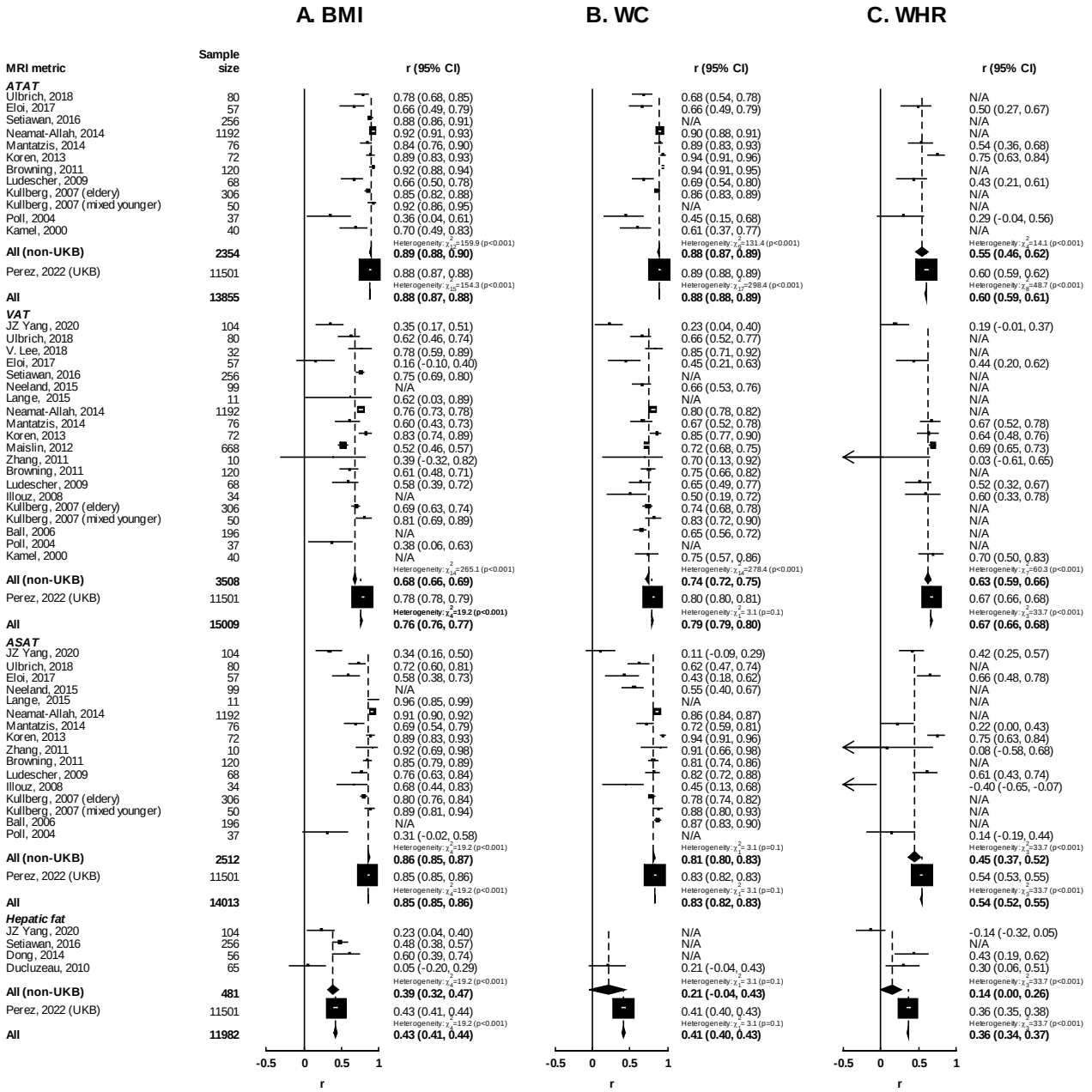


Figure 3.3 Correlations between MRI-derived and conventional anthropometric adiposity traits by ancestry.

Conventions as in Figure 3.2.

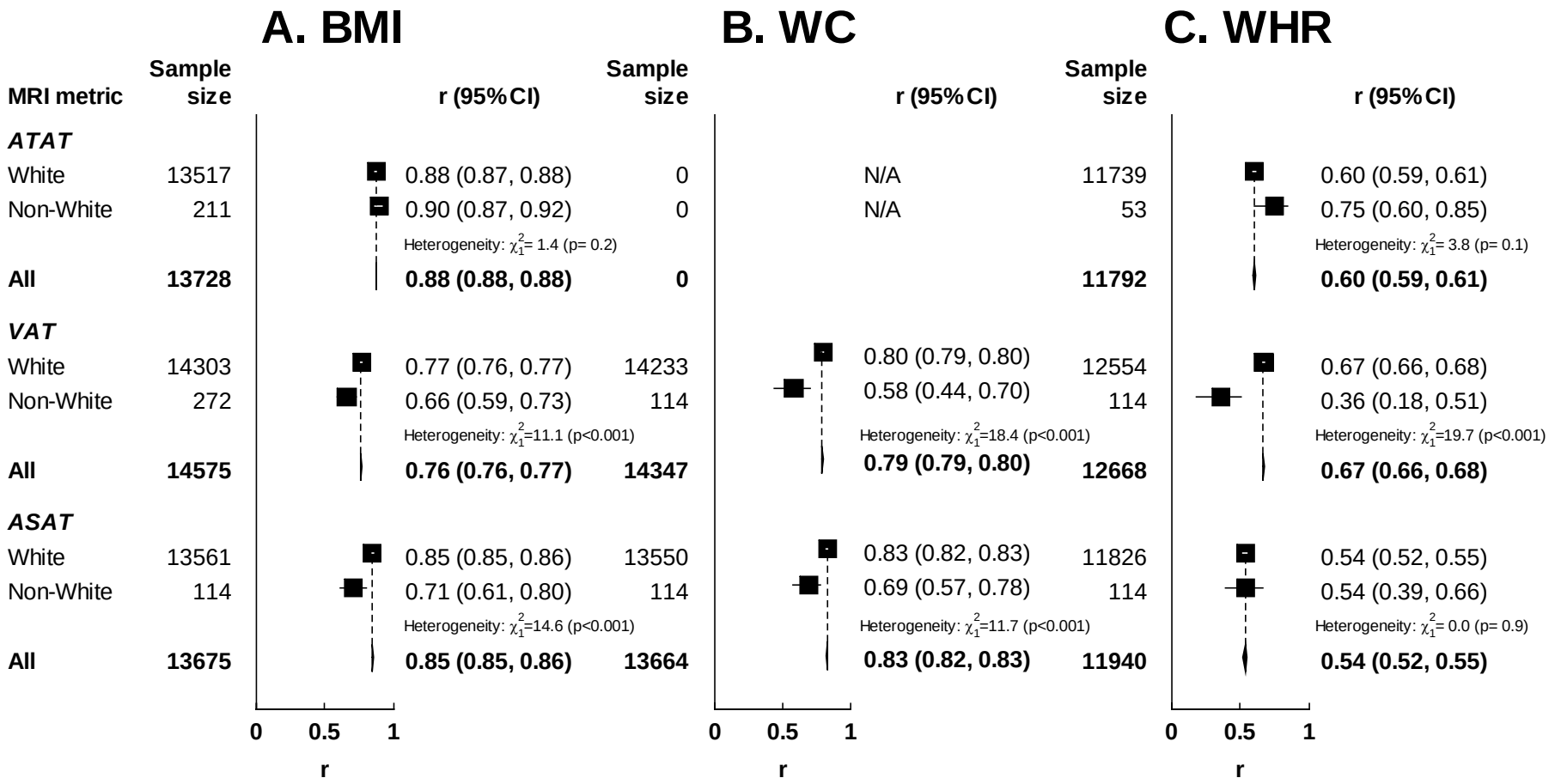


Figure 3.4 Correlations between MRI-derived and conventional anthropometric adiposity traits by sex.

Conventions as in Figure 3.2.

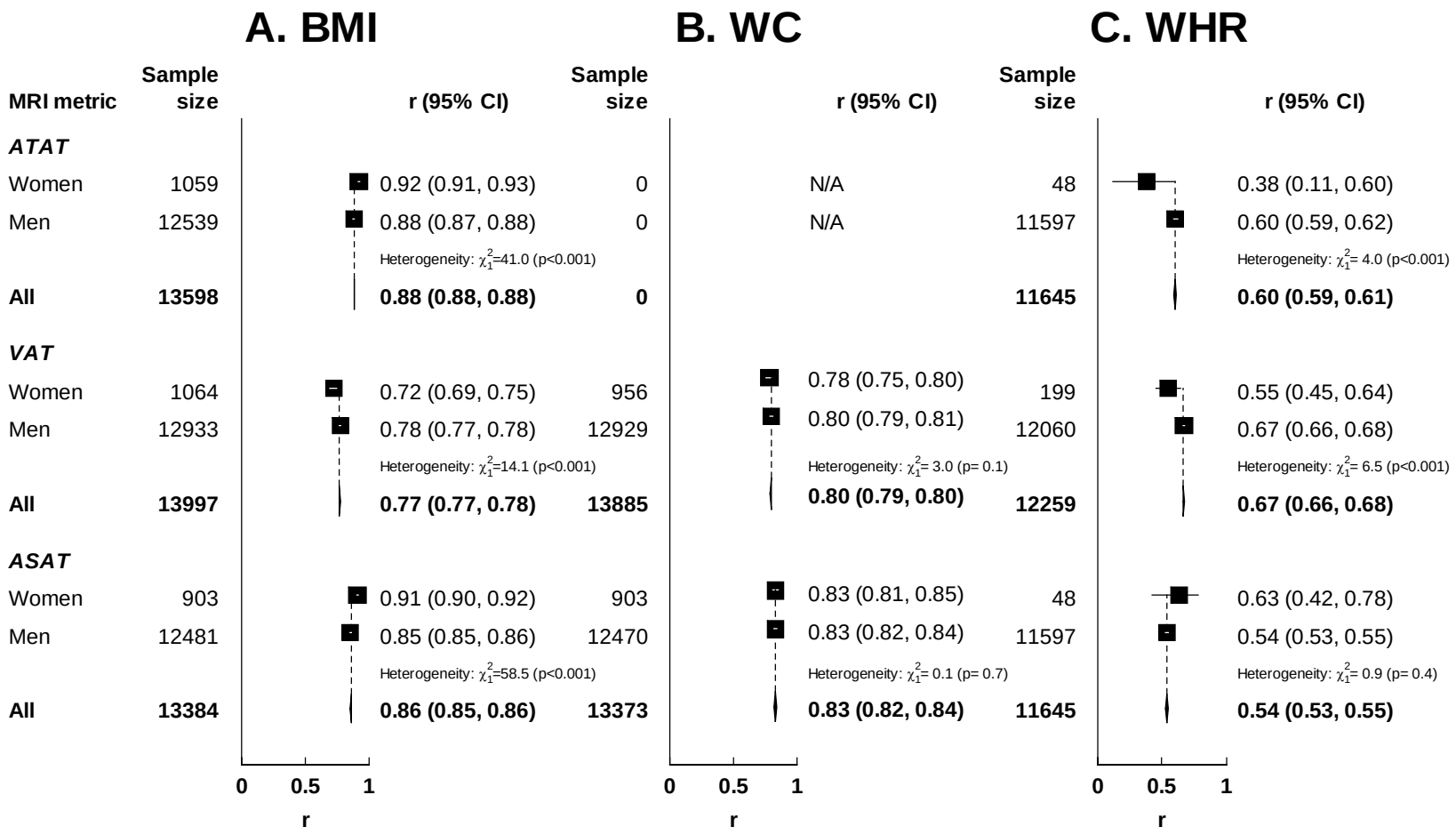


Figure 3.5 Correlations between MRI-derived and conventional anthropometric adiposity traits by age

Conventions as in Figure 3.2.

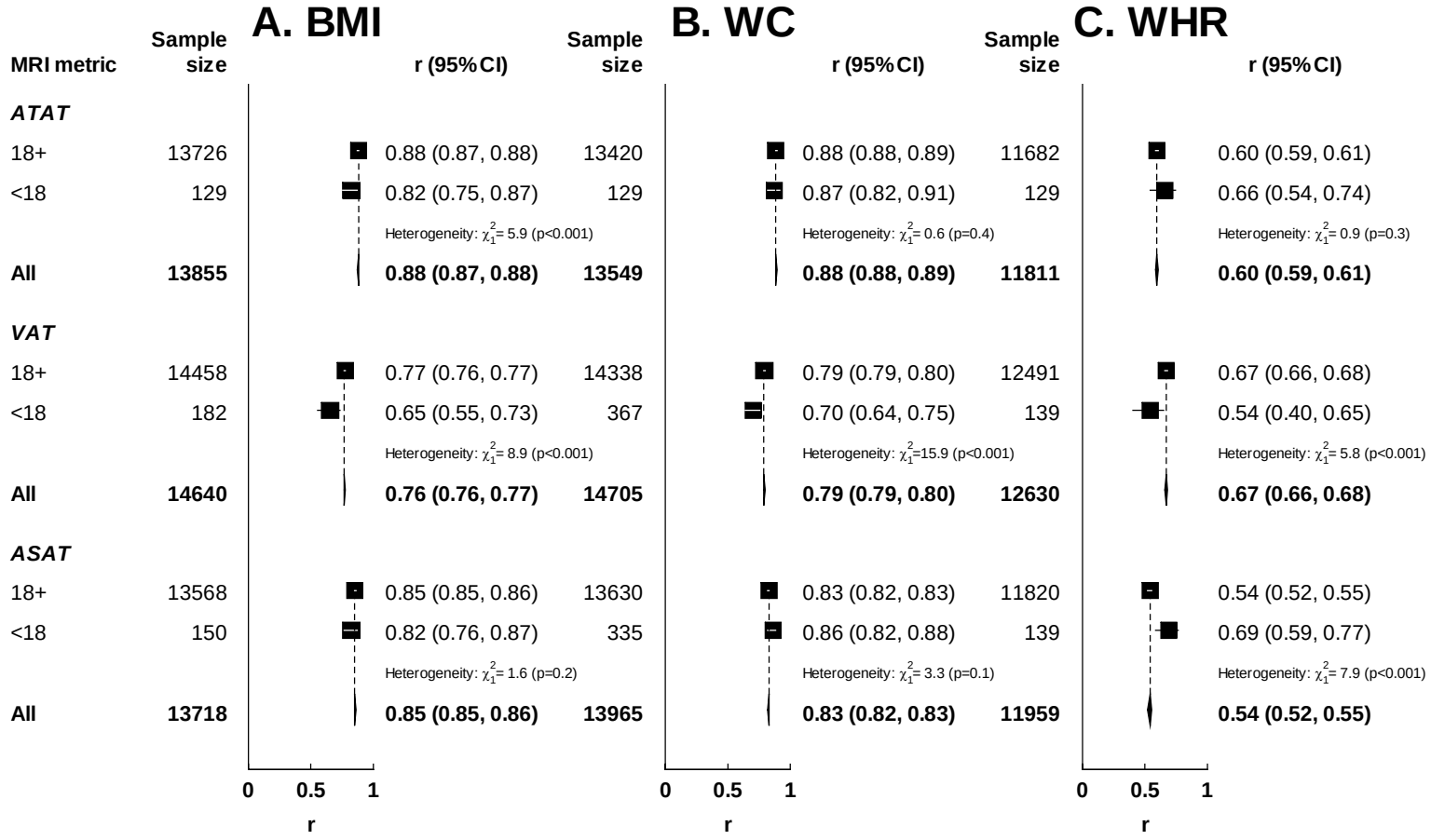


Figure 3.6 Correlations between MRI-derived and conventional anthropometric adiposity traits by study setting

Conventions as in Figure 3.2

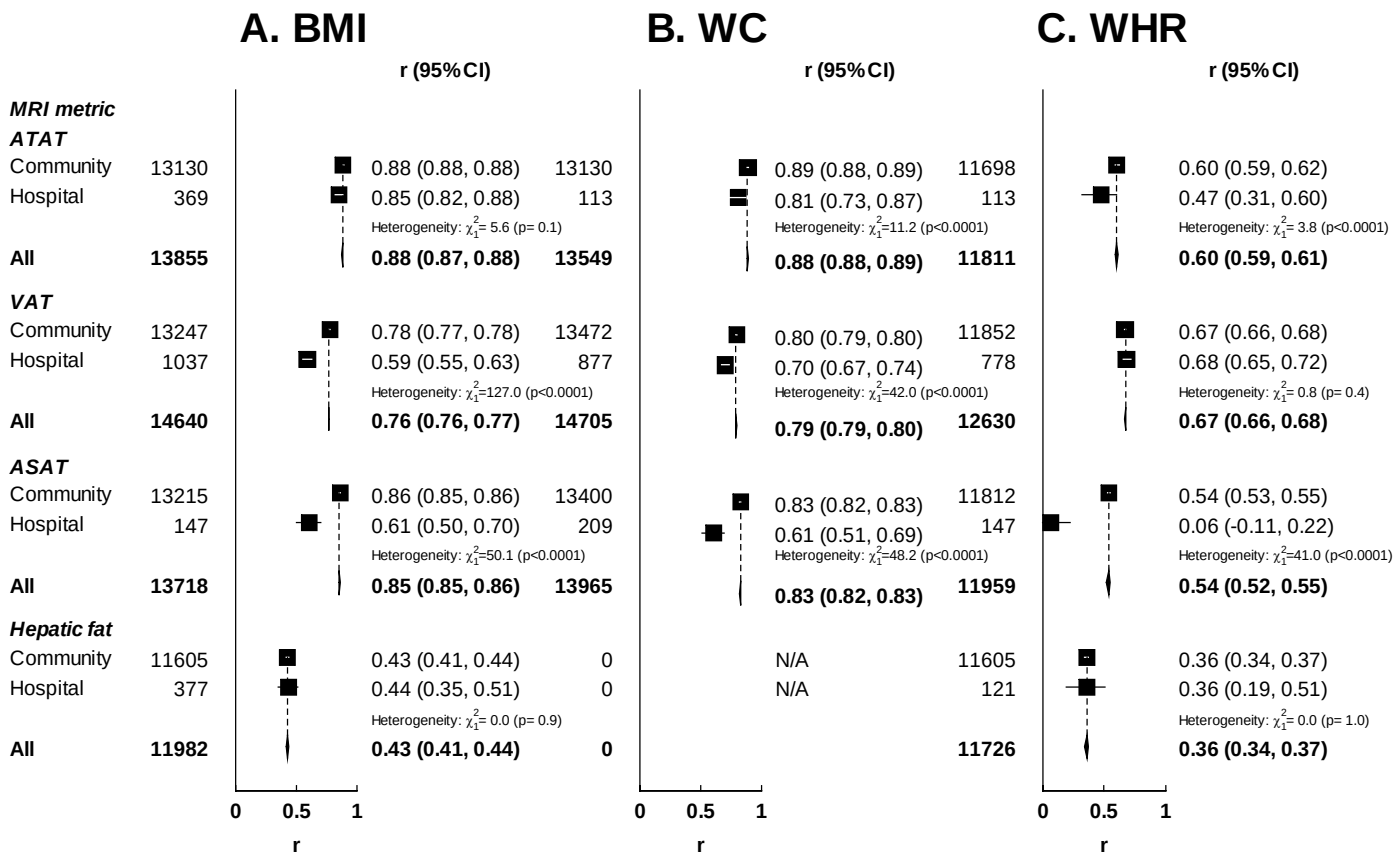


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Figure 3.7 Correlations between DXA-derived measures of adiposity and conventional anthropometric adiposity traits

Conventions as in Figure 3.2.

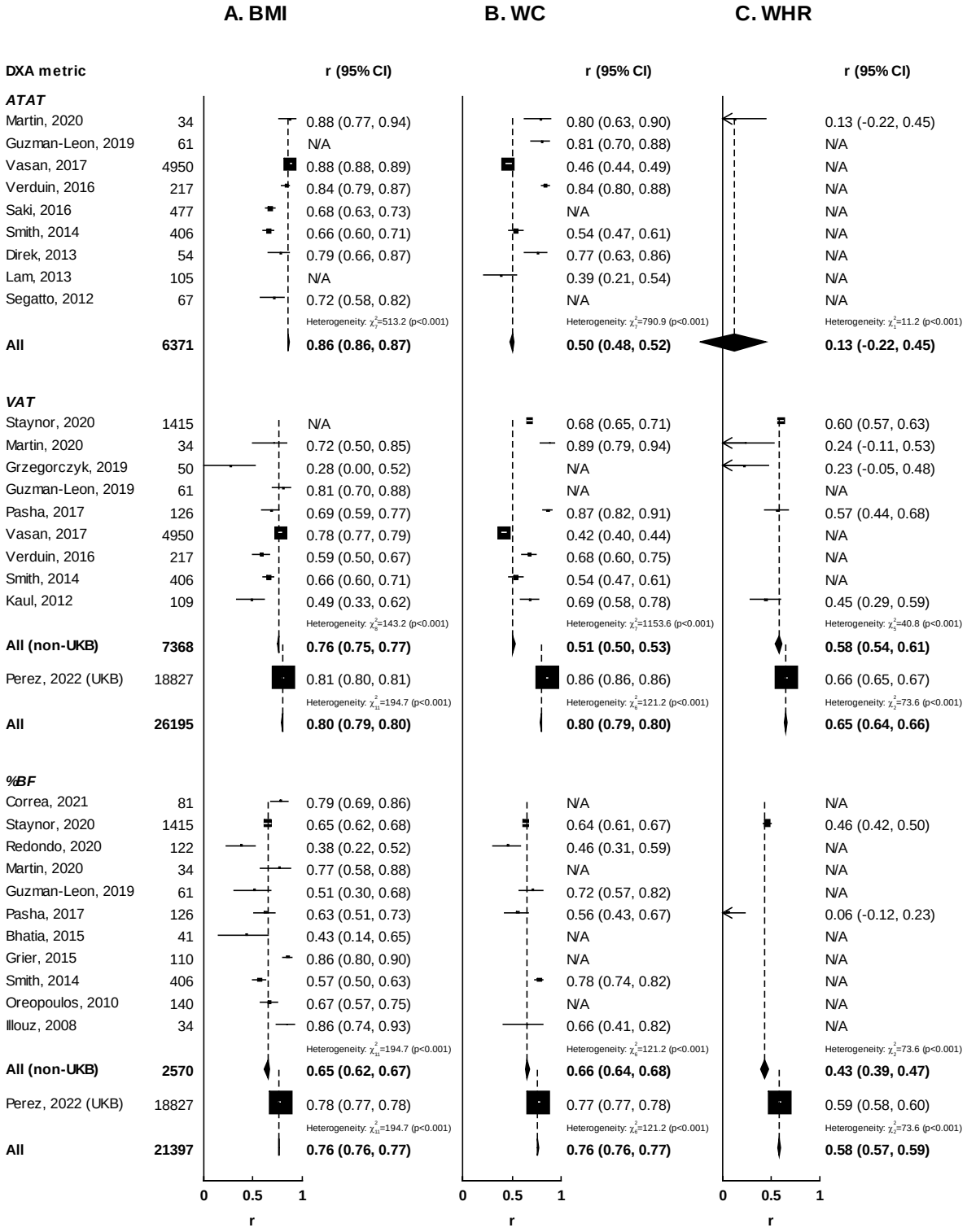


Figure 3.8 Correlations between DXA-derived and conventional anthropometric adiposity traits by sex

Conventions as in Figure 3.2.

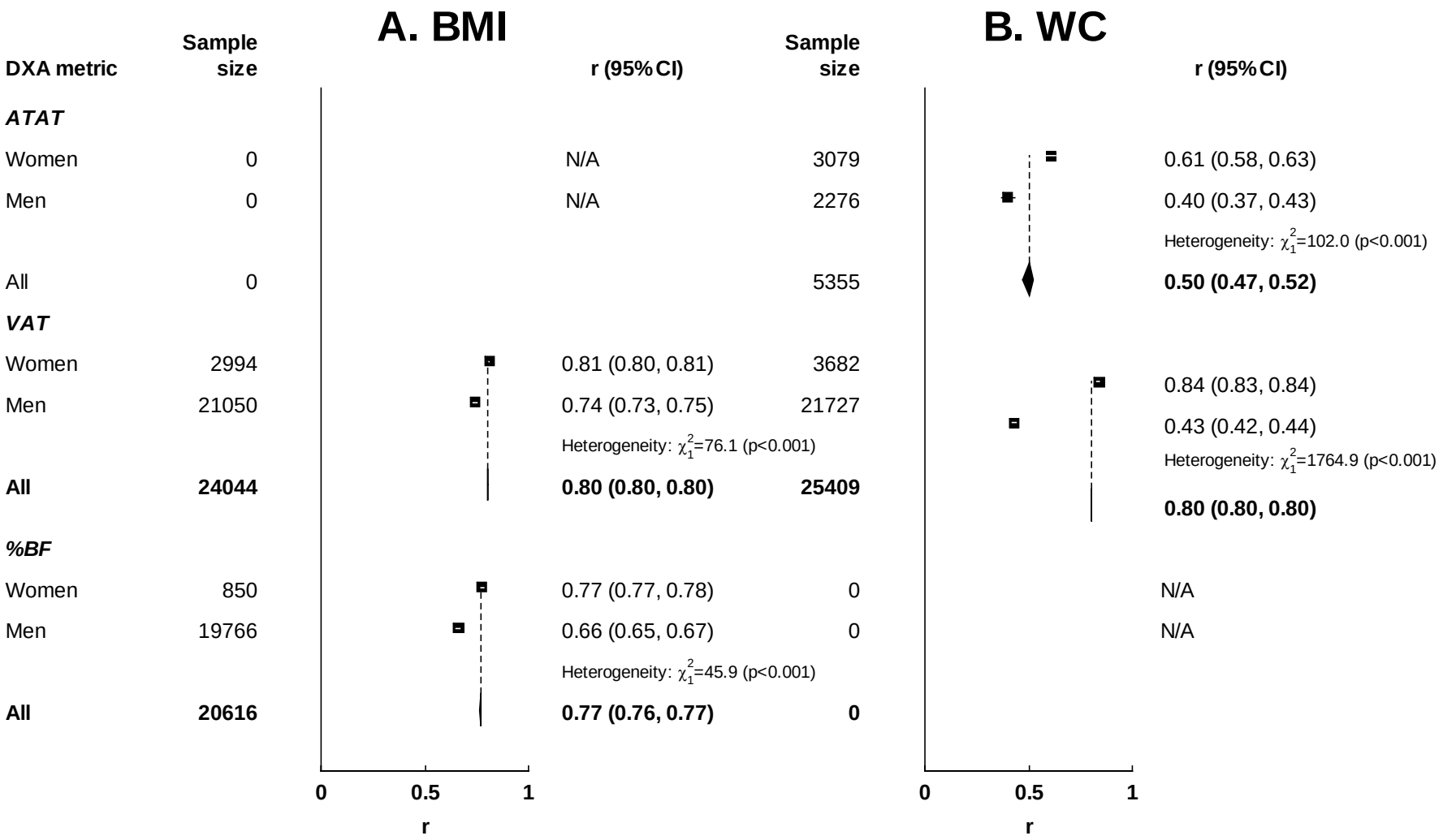


Figure 3.9 Correlations between DXA-derived and conventional anthropometric adiposity traits by age

Conventions as in Figure 3.2.

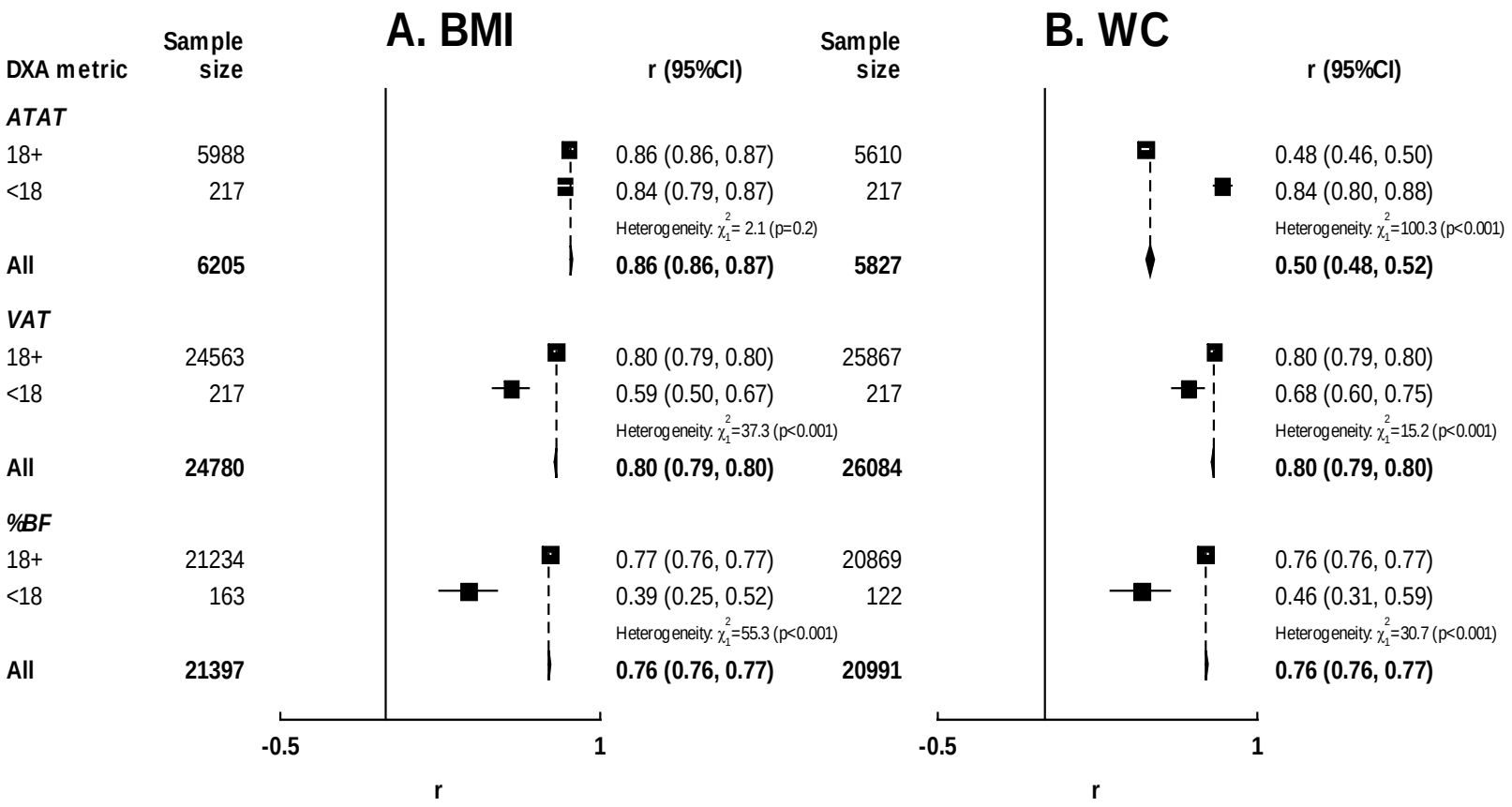


Figure 3.10 Weighted average correlations between MRI-derived (black), DXA-derived (grey) and conventional anthropometric adiposity traits

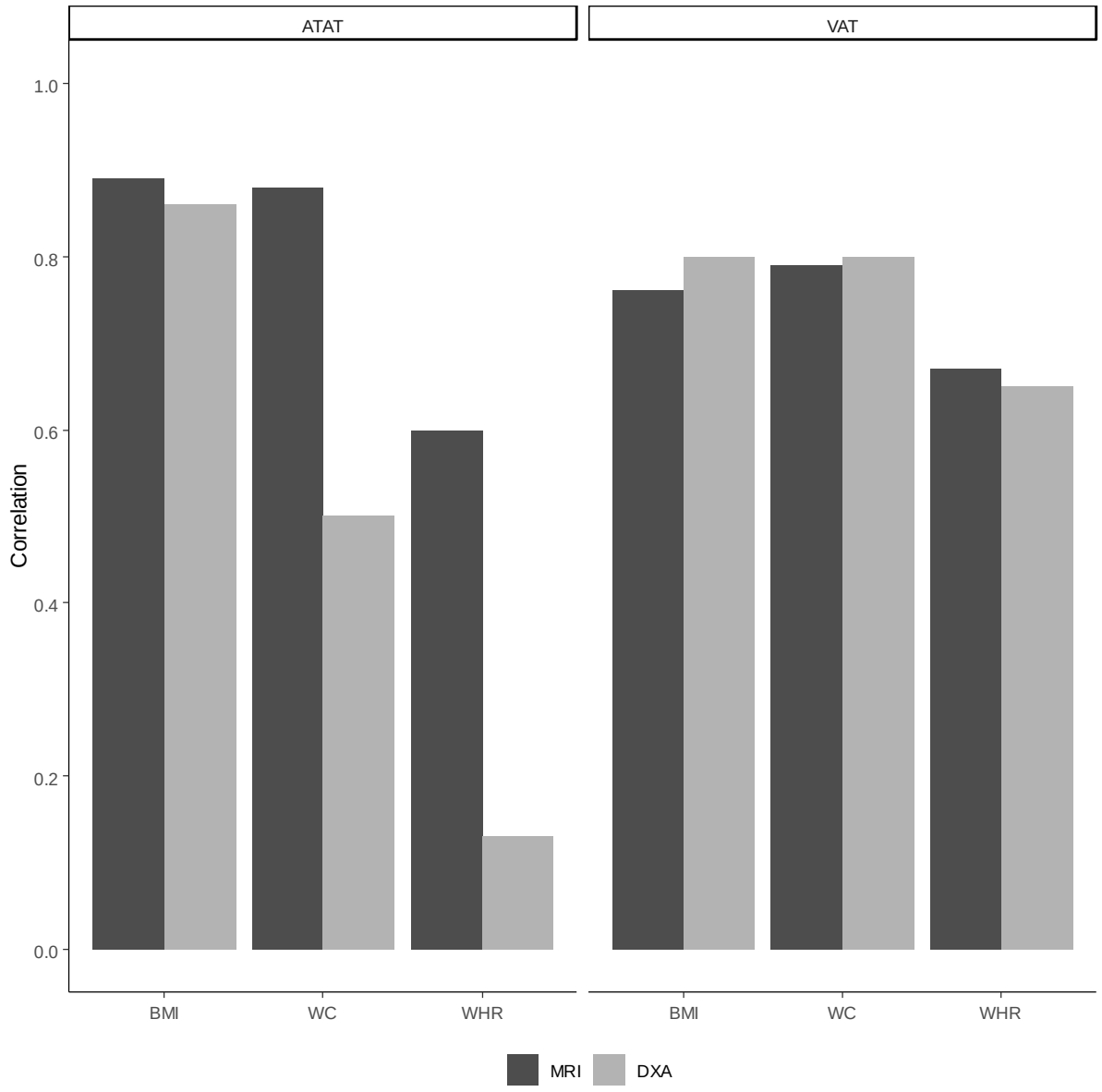


Figure 3.11 Funnel plots of study-specific correlations between correlations of MRI-derived and conventional anthropometric adiposity traits

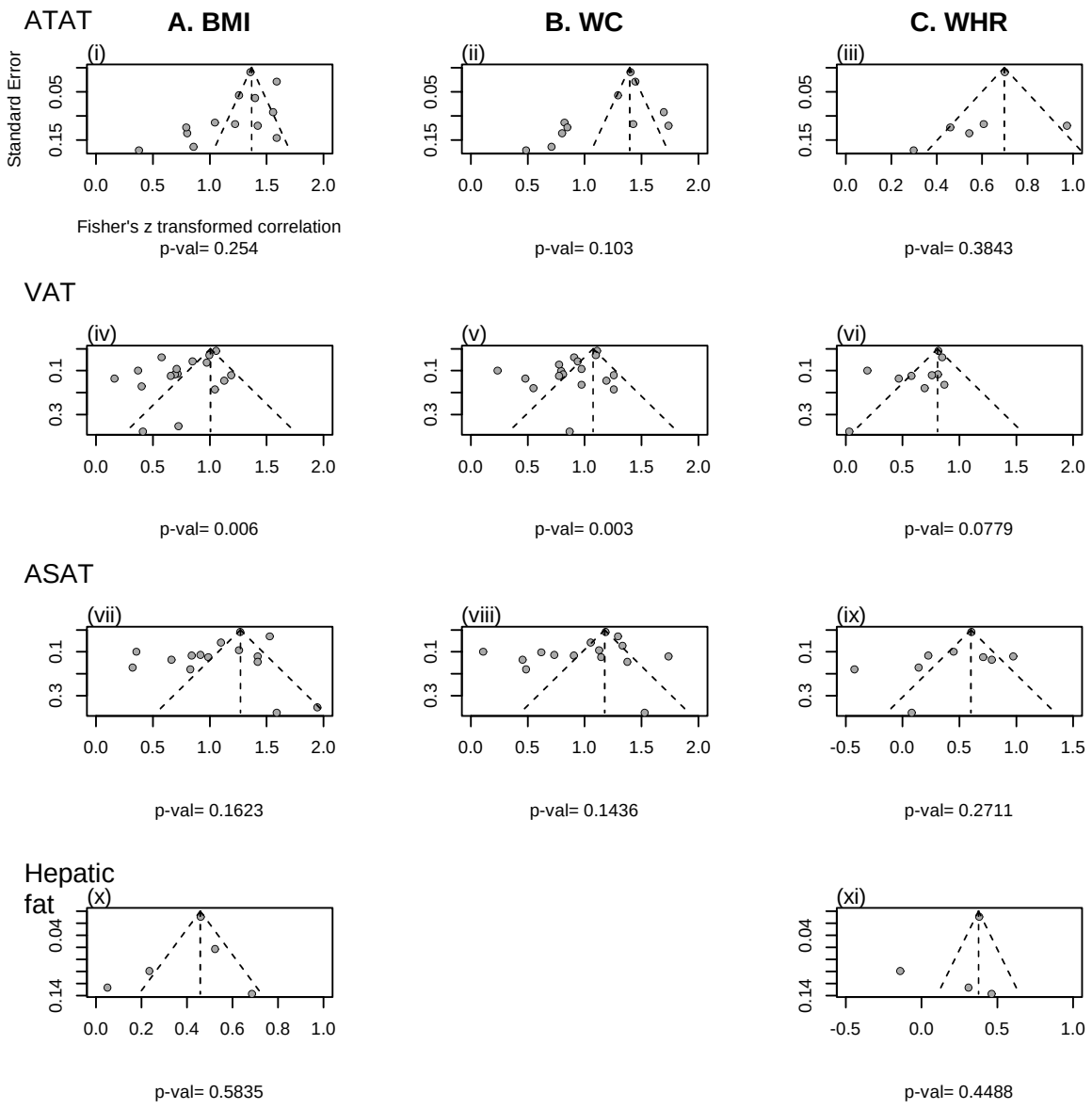
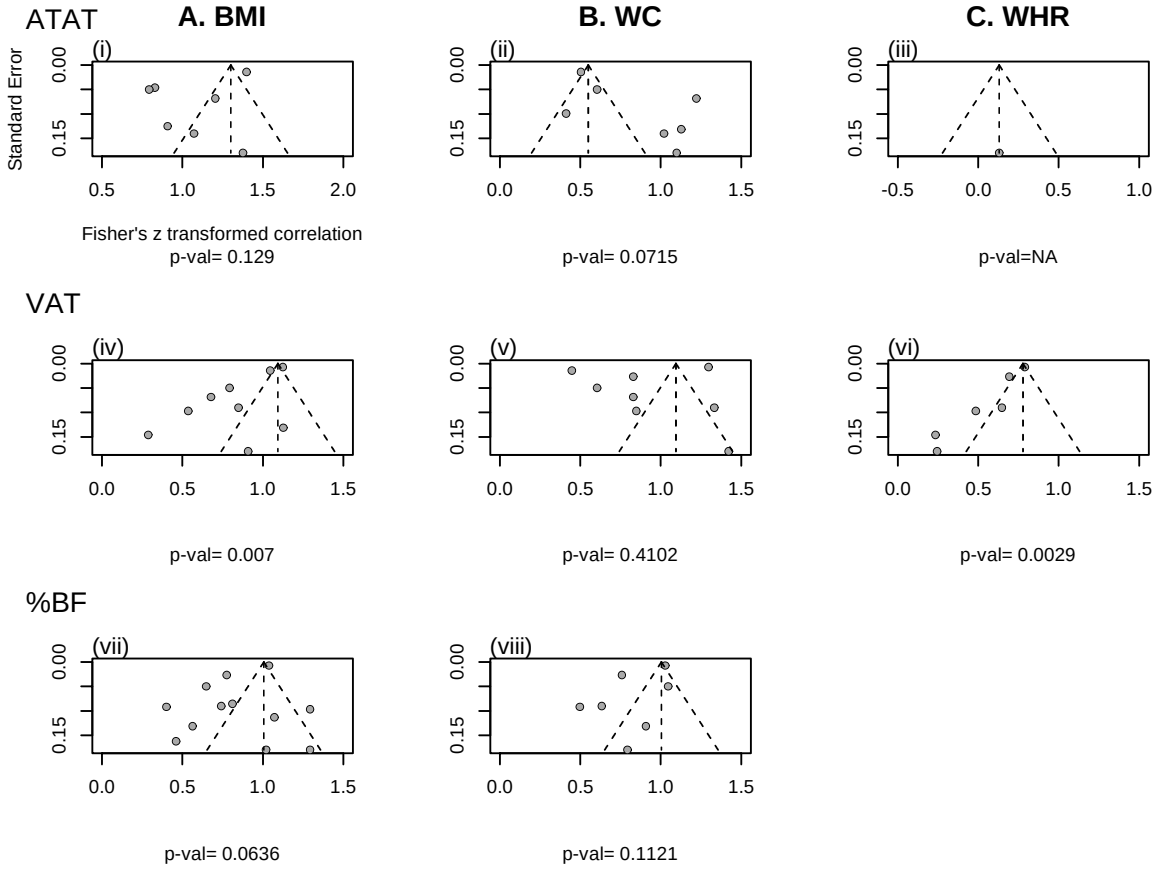


Figure 3.12 Funnel plots of study-specific correlations between DXA-derived and conventional anthropometric adiposity traits



Chapter 4. Associations of different body fat components with intermediate markers of disease

4.1 Background and aims

Different types of adipose tissue, defined by their anatomical locations have certain physiological roles and health implications. Research in humans and rodents has shown that excess visceral adiposity is more metabolically active than subcutaneous adiposity, contributing to hypertension, dyslipidaemia, hyperinsulinemia, systematic inflammation and atherosclerosis (188, 189), as well as CVD and certain cancers, even among individuals with a normal BMI range (58). Furthermore, excess ectopic adiposity, stored in organs such as the liver, pancreas, and skeletal muscle, disrupts normal insulin signalling, promoting insulin resistance and increasing the risk of T2D (42, 43). These findings suggest that specific body fat components are more metabolically active and oncogenic than others.

In epidemiological studies, elevated levels of adiposity are associated with a range of intermediate markers of disease. For example, blood pressure and blood lipids are markers of IHD, (190), while HbA1c is a key biomarker for diabetes (191). Furthermore, proteins such as SHBG, CRP, and IGF, and certain sex hormones such as oestradiol, and testosterone themselves, are key intermediate markers of certain cancers (192-198).

In the epidemiological literature, these associations have primarily been studied in relation to total or central adiposity mostly measured by anthropometric methods with intermediate markers of disease. However, there is a lack of studies investigating the association of visceral or ectopic adiposity with intermediate markers of disease.

This chapter aims to provide a comprehensive assessment of the associations of different measures of body fat components with a range of intermediate disease markers among >60,000 individuals who participated in the UKB imaging sub-cohort.

4.2 Methods

4.2.1 UK Biobank study population

The 64,025 UKB participants who participated in the imaging sub-cohort were analysed here. Each participant had at least one measure of adiposity assessed during the imaging visit, derived from anthropometric, MRI, or DXA methods. The primary aim was to examine associations between adiposity traits and intermediate markers of disease measured at the imaging visit. For instances where intermediate disease markers were not assessed at the imaging visit, corresponding measurements from the baseline visit were utilised.

4.2.2 Intermediate markers

Blood pressure measures (SBP, DBP, and PBP) were obtained at the imaging visit, while blood-based markers were measured at the baseline visit.

A range of intermediate disease markers were included in the analyses, including (i) blood lipids: LDL-C and HDL-C, TG, TC; (ii) sex hormones: SHBG, testosterone, and oestradiol; (iii) blood proteins: HbA1c, IGF-1, and CRP; and (iv) blood pressure: SBP, DBP, and PBP.

4.2.3 Exclusions

Participants were excluded if, at the time of the imaging visit, they were: on cholesterol-lowering medication (for blood lipids analysis); on MHT (for sex

hormones analysis in women); on hypertension medication (for blood pressure analysis); or if they had been diagnosed with diabetes or had prevalent T2D (for HbA1c analysis). Analyses of oestradiol were restricted to premenopausal women as most postmenopausal had concentrations below the assay's minimum reportable value (175 pmol/L) (see **Table 4.1** for exclusion numbers).

4.2.4 Statistical analyses

Linear regression models were used to calculate the mean values of specific markers by deciles of each adiposity measure, overall and by sex. Since the associations were approximately linear, the estimated difference in each marker per SD of each adiposity trait was further quantified (SDs are shown in **Table 2.2**). All analyses were adjusted for factors measured at imaging visits including age (5-year groups), sex, smoking status (never, previous, current), alcohol intake (0, 1, 2, ≥3 drinks/week), and education level (college/university degree, A levels/AS levels or equivalent, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications, none of the above), deprivation (quintiles of Townsend deprivation index), and, where relevant, number of live births, menopause status (yes, no, had hysterectomy), years since menopause, and use of MHT (current, past, never). A complete case analysis was applied for each model, meaning that only participants with complete data for all relevant variables were included.

4.3 Results

4.3.1 Associations of different body fat components with intermediate markers

Adiposity traits were generally linearly associated with intermediate disease markers, except for LPDFF-MRI (for which associations appear to be approximately

logarithmic) and IGF-1 (for which associations were non-linear, especially for BMI, with the highest IGF-1 in the BMI range of 25-29 kg/m^2) (**Figure 4.1** and **Figure 4.2**).

There were differences in the magnitude of the associations, with measures of visceral adiposity having stronger associations with certain markers (TG, DBP, and HbA1c) than measures of adiposity representing total, central or ectopic adiposity. In contrast, associations of TMFI-MRI with many markers (LDL-C, HDL-C, TG, SHBG, SBP, and DBP) tended to be less marked than those of other adiposity traits.

These differences were most notable for certain blood lipids (**Figure 4.3**). For example, the mean difference in TG per SD higher VAT-MRI was 0.36 (95% confidence intervals [CI]: 0.34, 0.37), greater than the corresponding difference associated with BMI, WC, and LPDFF-MRI of 0.21 (0.20, 0.22), 0.25 (0.24, 0.26), and 0.25 (0.23, 0.27) respectively. Similarly, the mean difference in LDL-C per SD increase in VAT-MRI was 0.15 (0.14, 0.16), greater than the corresponding difference associated with BMI, WC, and LPFF-MRI: 0.09 (0.08, 0.10), 0.10 (0.09, 0.11), and 0.08 (0.06, 0.09) respectively. For HDL-C, the mean differences per SD higher VAT-MRI was -0.13 (-0.13, -0.12), which was greater than the corresponding differences for BMI, WC and LPFF-MRI of -0.09 (-0.10, -0.09), -0.11 (-0.11, -0.11) and -0.08 (-0.09, -0.07) respectively.

Visceral adiposity also had a greater association with blood pressure markers especially DBP, than other adiposity traits (**Figure 4.4**). The mean difference in DBP per SD higher VAT-MRI was 3.40 (3.25, 3.55), which was greater than the corresponding difference associated with BMI, WC and LPFF-MRI of 2.89 (2.80, 2.99), 2.93 (2.82, 3.04), and 2.14 (1.91, 2.38) respectively. For HbA1c, the mean differences per SD higher VAT-MRI 0.42 (0.37, 0.46) and LPFF-MRI 0.44 (0.36,

0.51) were substantially greater than the corresponding differences for BMI 0.29 (0.26, 0.32) and WC 0.29 (0.26, 0.33).

4.3.2 Sex differences

For certain markers, there were sex differences in their associations with body fat components (**Figure 4.5** and **Figure 4.6**). For HDL-C, SHBG, IGF-1, and TG, most adiposity traits showed greater associations in men. The only exception to this was the association of visceral adiposity with TG which was more marked in women than in men. The converse was true for LDL-C, SBP, DBP, HbA1c and CRP in that associations with most adiposity indices, particularly those measuring visceral adiposity, were greater in women than men. Similarly, greater associations in women than men were also evident for testosterone.

Although the analysis combining women and men for SHBG showed no obvious differences in the magnitude of the associations of different adiposity traits, in women the mean difference per SD higher VAT-MRI was greater than the corresponding differences for BMI, WC, and LPDFF-MRI of -10.27 (-10.60,-9.95), -11.91 (-12.28,-11.54) and -9.40 (-10.35-8.44) respectively (**Figure 4.5**).

4.4 Discussion

In this large-scale imaging study, the association of various adiposity traits was quantified and compared, according to body fat component, with a range of intermediate disease markers. While most adiposity traits showed clear associations with almost all of the intermediate markers considered here, those relating to visceral adiposity tended to have the largest, and TMFI-MRI the smallest, associations with certain disease markers. This pattern was most notable for LDL-C, HDL-C, TG, SBP, DBP, and HbA1c. There were important differences in associations of adiposity traits

with many intermediate markers of disease by sex, but the nature of these differences varied by marker and body fat component.

Substantial association of adiposity with elevated blood pressure, LDL-C, TG, and reduced HDL-C were confirmed. Moreover, imaging-based visceral adiposity was found to have a greater association with these markers compared with other body fat components which is a novel finding. In line with these findings, a study of approximately 5,000 White adults in the UK from the Oxford Biobank found that visceral adiposity had a stronger association with the prevalence of hypertension and hypertriglyceridemia compared to central and other regional fat components (such as arm and gynoid fat and ASAT) (154). However, in contrast to the findings here, no differences in the associations by sex were found in the above study, possibly due to reduced power in sex subgroup analysis. Similar to the findings here, a study of 25,296 Chinese from the Malaysian Cohort and 413,737 Whites from the UKB found broadly comparable associations of both BMI and WC with SBP, LDL-C, and TG, with greater associations in Chinese than in White European adults (199). However, the latter ethic-specific analysis could not be investigated here as the UKB cohort consists predominantly of White Europeans. In contrast to the findings here, a study of 10,260 White adults from the UKB (5,033 participants) and Oxford Biobank (5,227 participants) reported no major differences in the magnitude of associations between total, central and visceral adiposity increase with SBP (200). This discrepancy may be due to the smaller sample size of the above study, as well as the lack of adjustments for smoking status or alcohol intake, which were accounted for in the current analysis.

Observational studies are inherently limited in their ability to assess the causal effects of adiposity on disease markers and risk by the potential for confounding. MR aims to address this by using genetic variants as proxies for the exposure of interest, allowing for unbiased causal estimates under certain assumptions (201, 202). Consistent with the results here, an MR study of UKB participants found that genetically predicted central adiposity traits by WHR (based on 208 SNPs) had a greater association with TG and HDL-C than genetically predicted total adiposity measured by BMI (based on 312 SNPs), while each of total or central adiposity had a similar magnitude of association with LDL-C (203). However, in contrast to findings here for blood pressure, an MR study of Swedish participants concluded that there were no differences in the associations between each of the genetically predicted total, central and visceral adiposity (based on 565, 324, and 208 SNPs to measure BMI, WHR and VAT respectively) with SBP and DBP (204). This discrepancy may be due to differences between the UK and Swedish cohorts, including the greater prevalence of obesity in UKB and hypertension in the Swedish study, as well as their greater proportion of women.

No obvious differences in the magnitude of associations of different adiposity traits with sex hormones were observed, except for SHBG in women, where visceral adiposity had a greater association compared to other body fat components. While numerous observational and MR studies have shown associations between one measure of adiposity, usually BMI, WC or WHR, with markers of SHBG (205-207), testosterone (208, 209), and oestradiol (210) there is little evidence on relative associations of different body fat components with sex hormones with which to compare findings in the current chapter.

In these data, visceral and ectopic liver adiposity had a greater association with HbA1c compared with other body fat components, while there was no clear difference in the magnitude of different adiposity traits with CRP and IGF-1. Consistent with these findings, a study of 66,882 participants from the Malaysian Cohort and 413,737 participants from the UKB found the total and central adiposity measured with BMI and WC respectively were associated with HbA1c of a similar magnitude (199). Moreover, in line with these findings, a study of 0.5 million UKB participants reported positive associations of total (BMI) and central adiposity (WC, WHR) with CRP of a comparable magnitude and a higher association in women than men for central adiposity (211). However, the majority of observational (199, 212, 213) and MR studies (74) have examined the association of total adiposity (BMI) with CRP, and do not allow the comparison of different adiposity traits with CRP. In line with findings in this chapter, a previous study of 2,139 White women found a similar trend between total or central adiposity increase (measured with BMI or WC respectively) with IGF-1 (214). Overall, the majority of evidence comes from studies assessing the association of anthropometric measures of total or central adiposity with blood proteins, with no studies on visceral or ectopic adiposity available for comparison with the results presented here.

4.4.1 Strengths and limitations

The main strength of this study is that, to the best of the author's knowledge, it is the largest study comparing associations between various body fat components measured with both anthropometric and imaging-based methods and intermediate markers of disease. However, this study has certain limitations.

Most of the investigated markers of disease (except blood pressure) were measured at baseline, on average 10 years before the adiposity measurements at the imaging assessment were assessed, potentially introducing some degree of bias. Nonetheless, the findings were consistent with UKB studies using concurrent measurements of adiposity and intermediate markers of disease (199, 200, 203, 210, 215). Additionally, participants were primarily White and middle-aged, and the results may not be generalisable to individuals of other ancestry and age groups.

4.4.2 Conclusion

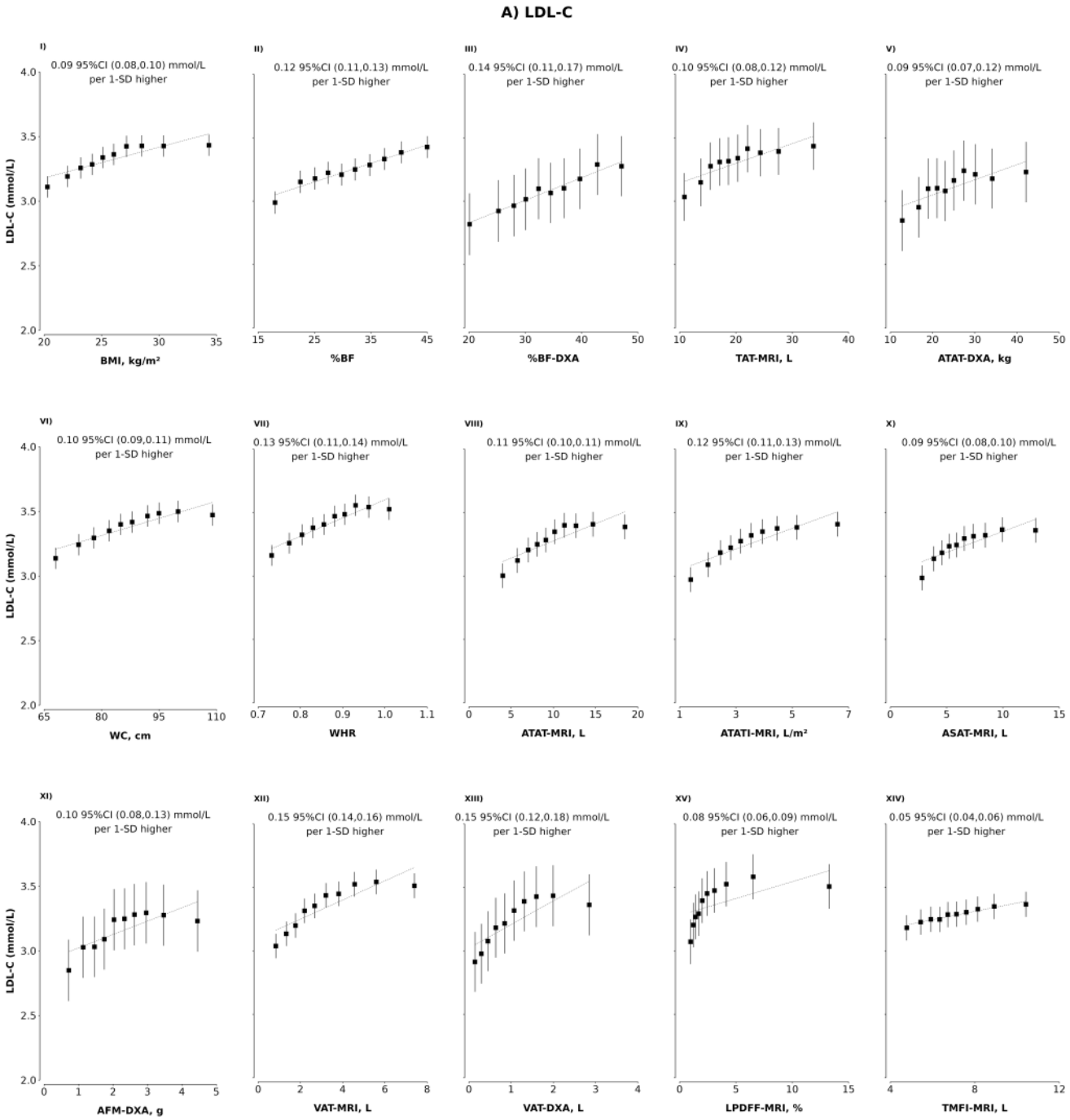
In conclusion, this large-scale study of UK individuals revealed significant associations of various body fat components with certain intermediate markers of disease. Visceral adiposity, and to some extent ectopic adiposity, demonstrated a greater magnitude of association with TG, LDL-C, DBP and HbA1c than total or central adiposity. Excess adiposity associations were greater in men with HDL-C, SHBG, IGF-1 and TG, while mostly visceral adiposity increase had a greater association with blood pressure, LDL-C, HbA1c, CRP, testosterone and SHBG in women. Future studies with a larger number of individuals with their body fat measured simultaneously with anthropometric and imaging methods are needed to investigate whether certain body fat components like visceral and ectopic adiposity may have a greater association with intermediate markers of disease than total or central adiposity. Furthermore, future studies are needed to compare the magnitude of the association of different body fat components with obesity-related diseases. This will be further investigated in Chapter 5.

Table 4.1 Numbers of participants included in analyses after relevant exclusions

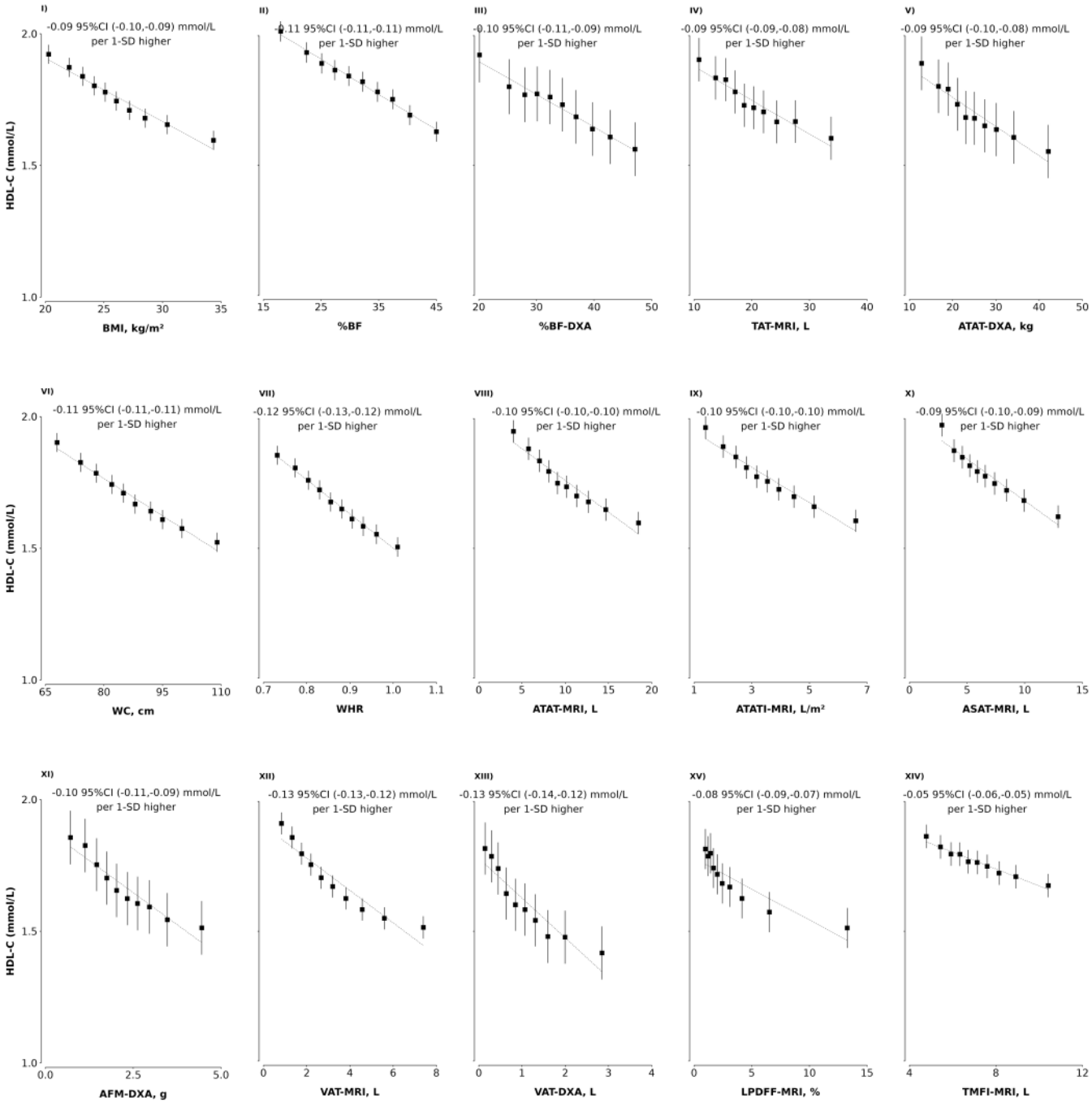
Outcome	Exclusions	Analysed participants
Blood lipids		
HDL-C, LDL-C, TG, TC	● Cholesterol-lowering medication (n=16,337)	47,688
Sex hormones		
SHBG, testosterone	● Women on menopausal hormonal therapy (n=2,670)	61,355
Oestradiol	● Men (n=31,009) ● Postmenopausal women (n=25,384) ● Women on menopausal hormonal therapy (n=2,670) ● Women with unknown menopausal hormonal therapy status (n=4,962)	1,332
Blood pressure		
SBP, DPB, PBP	● On hypertension medication (n=16,197)	47,828
Blood proteins		
HbA1c	● Prevalent T2D detected from hospital inpatient data (n=3,601) ● Self-reported diabetes (n=3,143)	57,281
IGF-1 and CRP	None	64,025

Figure 4.1 Associations of adiposity traits with selected lipids and sex hormones

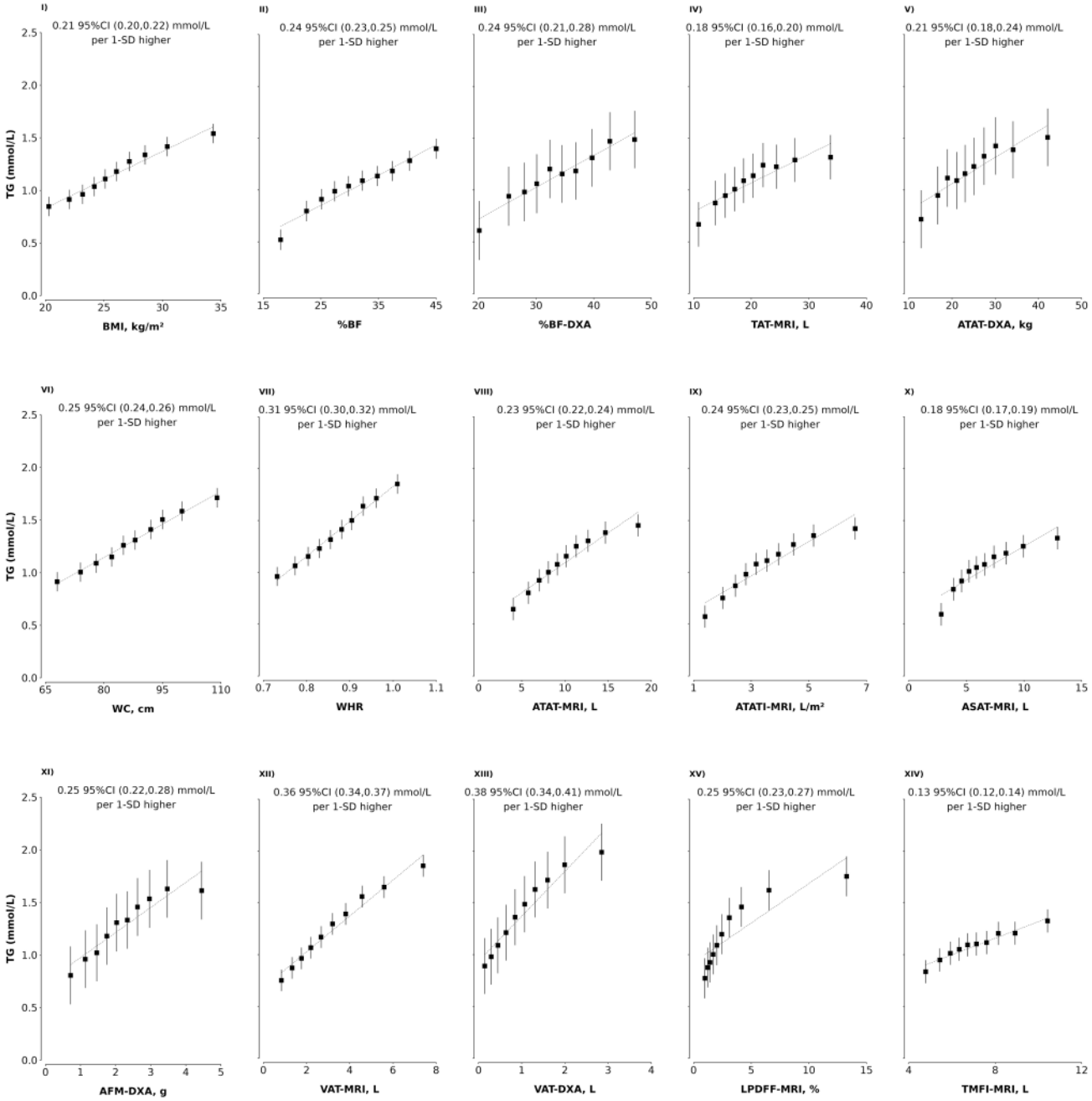
Associations were adjusted for factors measured at imaging visits including age, sex, smoking status, alcohol consumption, education level, Townsend Deprivation index score, and among women number of live births, menopause status, years since menopause, and use of MHT. The plotted square denotes the adjusted mean of the disease marker within each decile of the adiposity trait (y-axis), plotted against the mean value of the adiposity trait within that decile. The size of the square is proportional to the inverse of the variance of the estimated mean value. The dashed line represents the estimated linear trend. The text above each plot refers to the estimated difference in the disease marker per SD increase in the adiposity trait on a continuous scale.

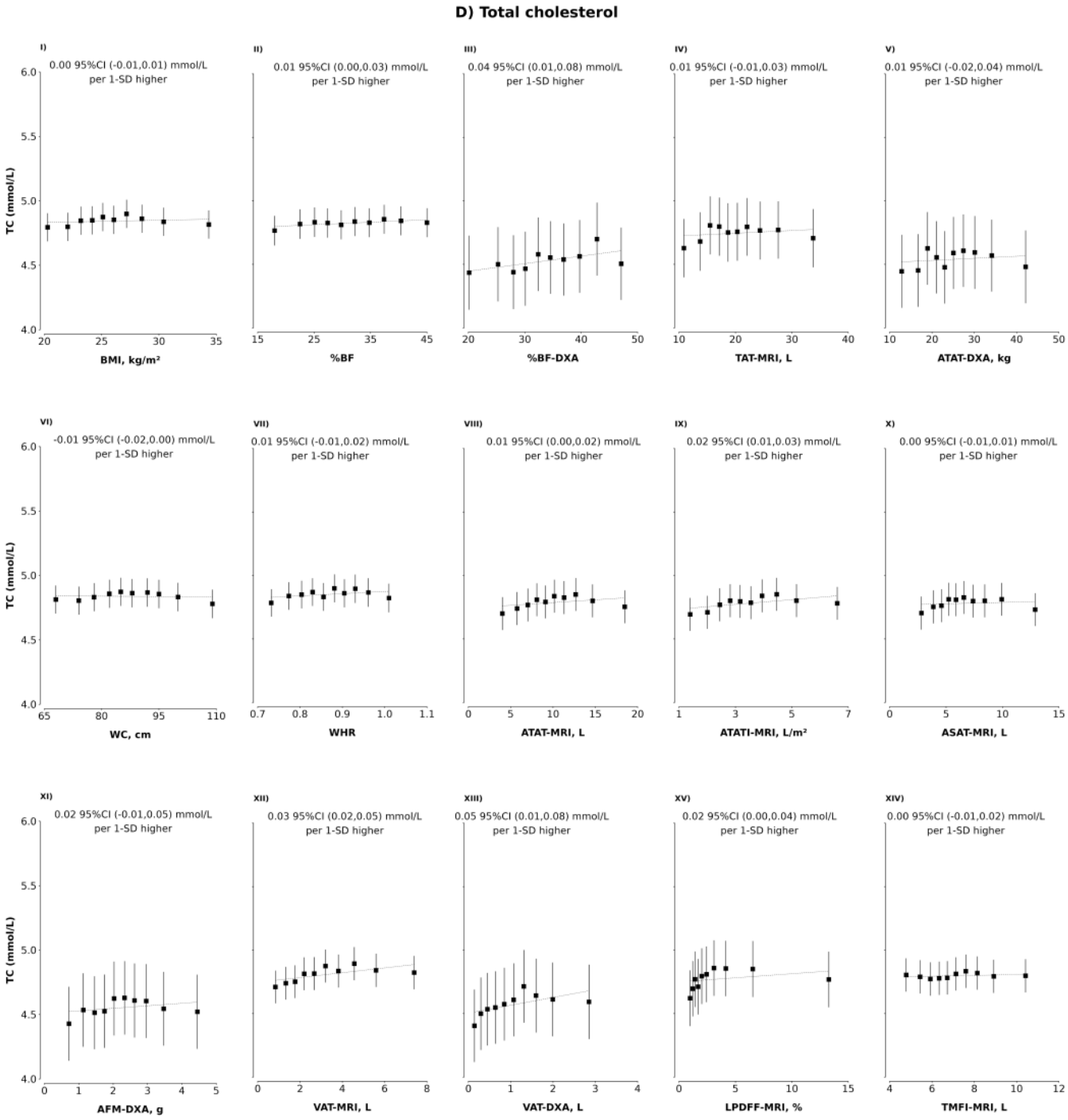


B) HDL-C

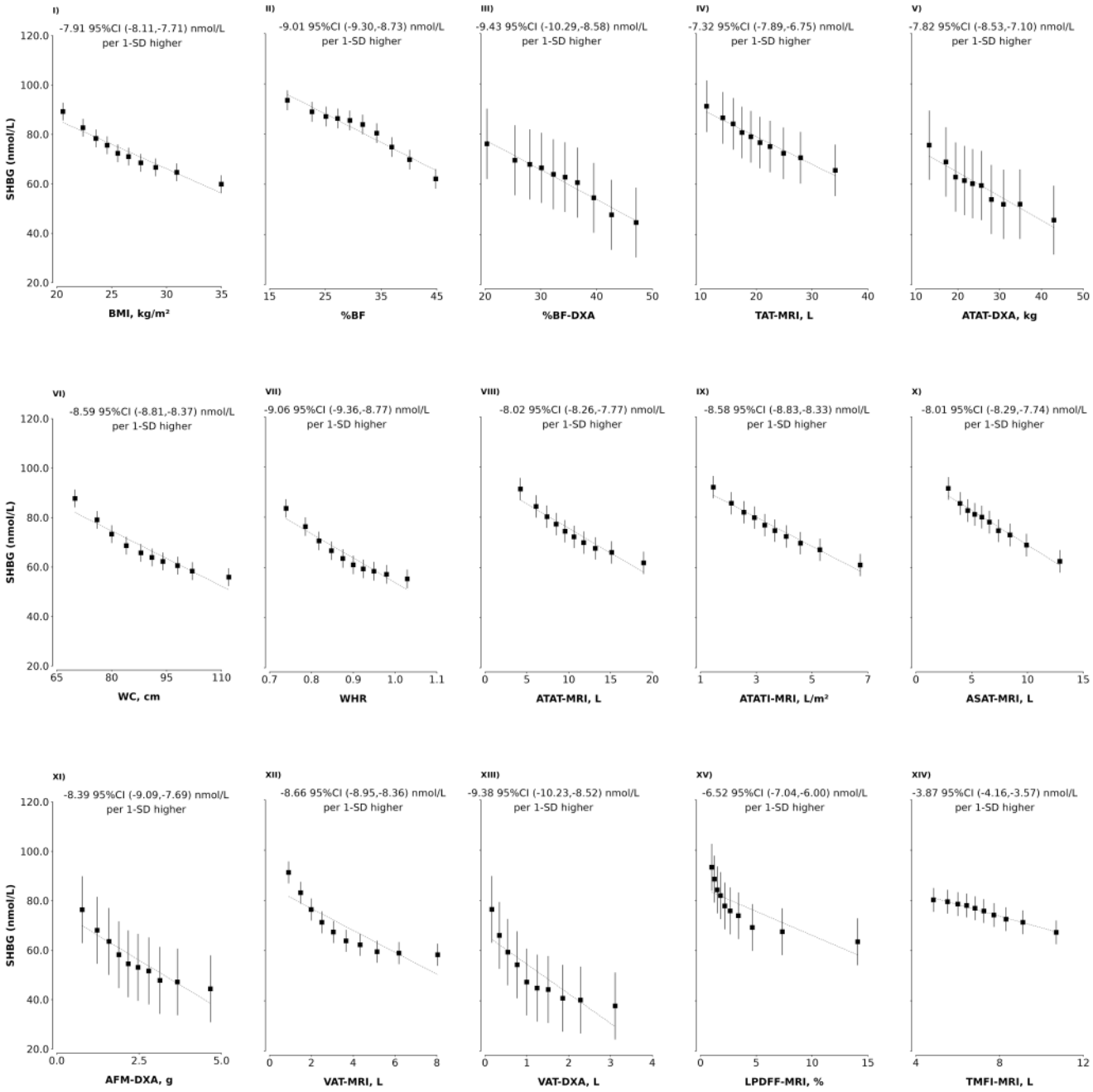

I)
-0.09 95%CI (-0.10,-0.09) mmol/L
per 1-SD higher
BMI, kg/m²
II)
-0.11 95%CI (-0.11,-0.11) mmol/L
per 1-SD higher
%BF
III)
-0.10 95%CI (-0.11,-0.09) mmol/L
per 1-SD higher
%BF-DXA
IV)
-0.09 95%CI (-0.09,-0.08) mmol/L
per 1-SD higher
TAT-MRI, L
V)
-0.09 95%CI (-0.10,-0.08) mmol/L
per 1-SD higher
ATAT-DXA, kg
VI)
-0.11 95%CI (-0.11,-0.11) mmol/L
per 1-SD higher
WC, cm
VII)
-0.12 95%CI (-0.13,-0.12) mmol/L
per 1-SD higher
WHR
VIII)
-0.10 95%CI (-0.10,-0.10) mmol/L
per 1-SD higher
ATAT-MRI, L
IX)
-0.10 95%CI (-0.10,-0.10) mmol/L
per 1-SD higher
ATATI-MRI, L/m²
X)
-0.09 95%CI (-0.10,-0.09) mmol/L
per 1-SD higher
ASAT-MRI, L
XI)
-0.10 95%CI (-0.11,-0.09) mmol/L
per 1-SD higher
AFM-DXA, g
XII)
-0.13 95%CI (-0.13,-0.12) mmol/L
per 1-SD higher
VAT-MRI, L
XIII)
-0.13 95%CI (-0.14,-0.12) mmol/L
per 1-SD higher
VAT-DXA, L
XV)
-0.08 95%CI (-0.09,-0.07) mmol/L
per 1-SD higher
LPDFF-MRI, %
XIV)
-0.05 95%CI (-0.06,-0.05) mmol/L
per 1-SD higher
TMFI-MRI, L
HDL-C (mmol/L)

C) Triglycerides

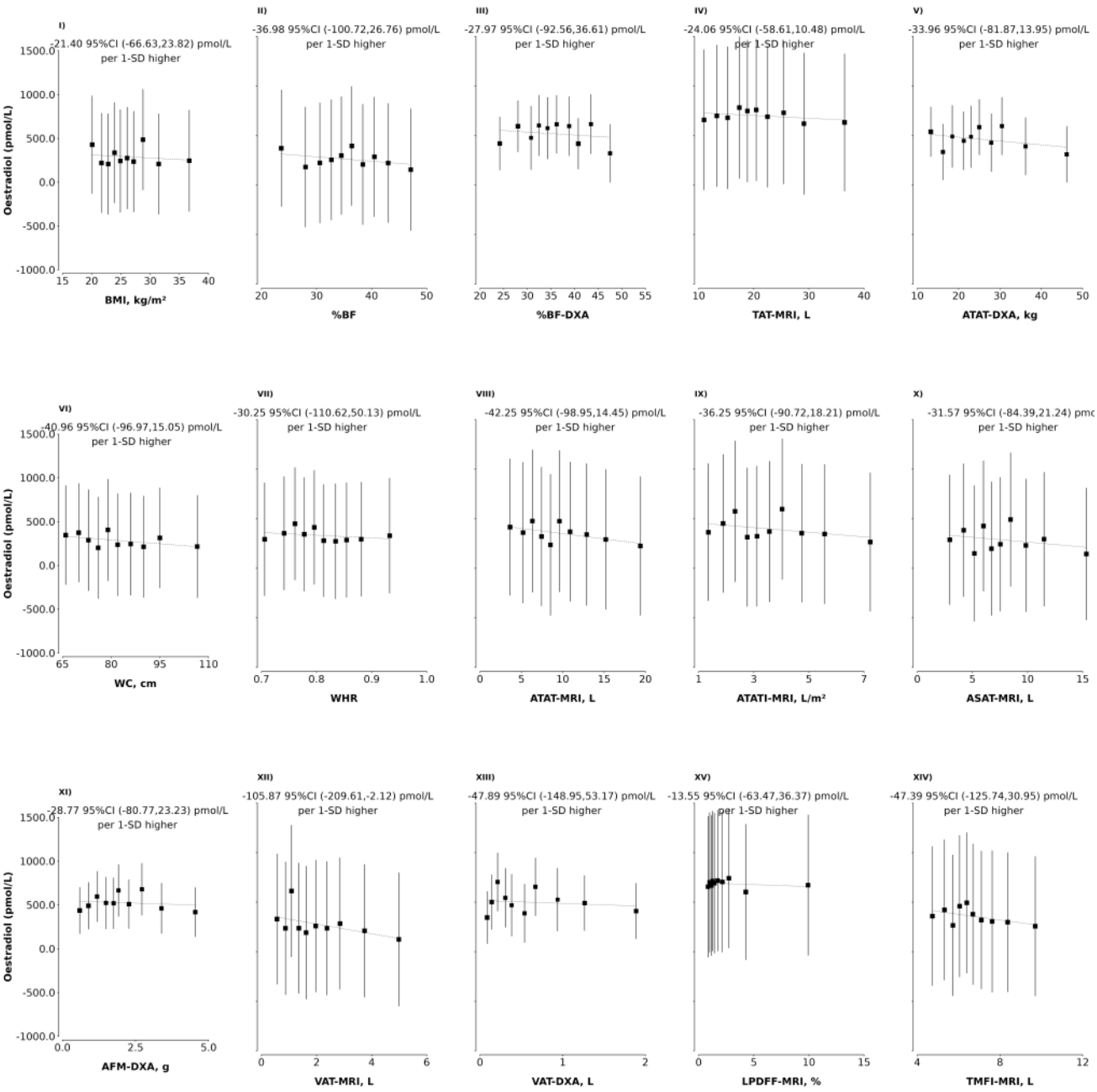



D) Total cholesterol
I)
0.00 95%CI (-0.01,0.01) mmol/L
per 1-SD higher
BMI, kg/m²
II)
0.01 95%CI (0.00,0.03) mmol/L
per 1-SD higher
%BF
III)
0.04 95%CI (0.01,0.08) mmol/L
per 1-SD higher
%BF-DXA
IV)
0.01 95%CI (-0.01,0.03) mmol/L
per 1-SD higher
TAT-MRI, L
V)
0.01 95%CI (-0.02,0.04) mmol/L
per 1-SD higher
ATAT-DXA, kg
VI)
-0.01 95%CI (-0.02,0.00) mmol/L
per 1-SD higher
WC, cm
VII)
0.01 95%CI (-0.01,0.02) mmol/L
per 1-SD higher
WHR
VIII)
0.01 95%CI (0.00,0.02) mmol/L
per 1-SD higher
ATAT-MRI, L
IX)
0.02 95%CI (0.01,0.03) mmol/L
per 1-SD higher
ATATI-MRI, L/m²
X)
0.00 95%CI (-0.01,0.01) mmol/L
per 1-SD higher
ASAT-MRI, L
XI)
0.02 95%CI (-0.01,0.05) mmol/L
per 1-SD higher
AFM-DXA, g
XII)
0.03 95%CI (0.02,0.05) mmol/L
per 1-SD higher
VAT-MRI, L
XIII)
0.05 95%CI (0.01,0.08) mmol/L
per 1-SD higher
VAT-DXA, L
XV)
0.02 95%CI (0.00,0.04) mmol/L
per 1-SD higher
LPDFF-MRI, %
XIV)
0.00 95%CI (-0.01,0.02) mmol/L
per 1-SD higher
TMFI-MRI, L
TC (mmol/L)

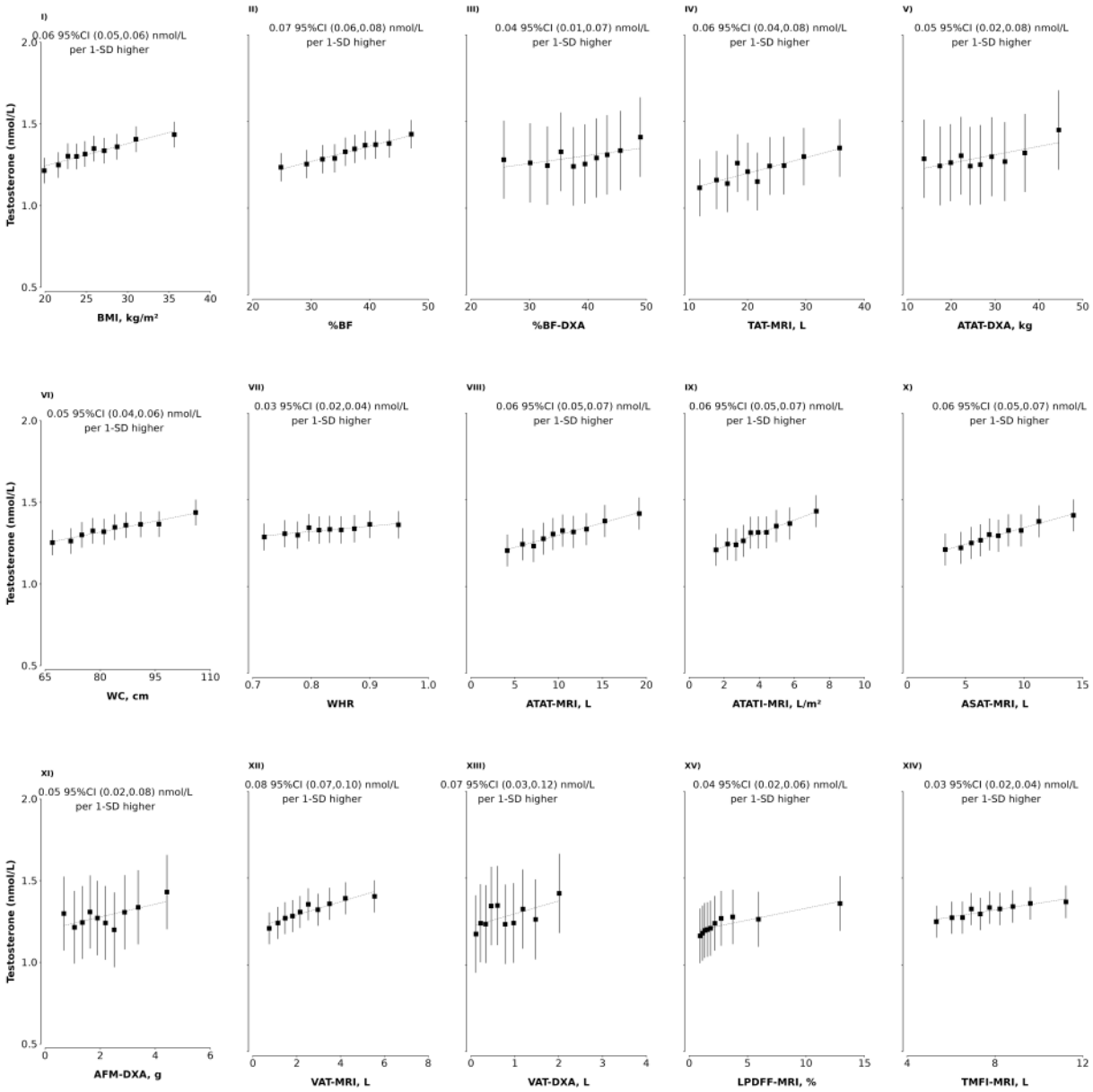
E) SHBG


I)
-7.91 95%CI (-8.11,-7.71) nmol/L
per 1-SD higher
BMI, kg/m²
II)
-9.01 95%CI (-9.30,-8.73) nmol/L
per 1-SD higher
%BF
III)
-9.43 95%CI (-10.29,-8.58) nmol/L
per 1-SD higher
%BF-DXA
IV)
-7.32 95%CI (-7.89,-6.75) nmol/L
per 1-SD higher
TAT-MRI, L
V)
-7.82 95%CI (-8.53,-7.10) nmol/L
per 1-SD higher
ATAT-DXA, kg
VI)
-8.59 95%CI (-8.81,-8.37) nmol/L
per 1-SD higher
WC, cm
VII)
-9.06 95%CI (-9.36,-8.77) nmol/L
per 1-SD higher
WHR
VIII)
-8.02 95%CI (-8.26,-7.77) nmol/L
per 1-SD higher
ATAT-MRI, L
IX)
-8.58 95%CI (-8.83,-8.33) nmol/L
per 1-SD higher
ATATI-MRI, L/m²
X)
-8.01 95%CI (-8.29,-7.74) nmol/L
per 1-SD higher
ASAT-MRI, L
XI)
-8.39 95%CI (-9.09,-7.69) nmol/L
per 1-SD higher
AFM-DXA, g
XII)
-8.66 95%CI (-8.95,-8.36) nmol/L
per 1-SD higher
VAT-MRI, L
XIII)
-9.38 95%CI (-10.23,-8.52) nmol/L
per 1-SD higher
VAT-DXA, L
XV)
-6.52 95%CI (-7.04,-6.00) nmol/L
per 1-SD higher
LPDFF-MRI, %
XIV)
-3.87 95%CI (-4.16,-3.57) nmol/L
per 1-SD higher
TMFI-MRI, L
SHBG (nmol/L)

F) Oestradiol



G) Testosterone (Women)



H) Testosterone (Men)

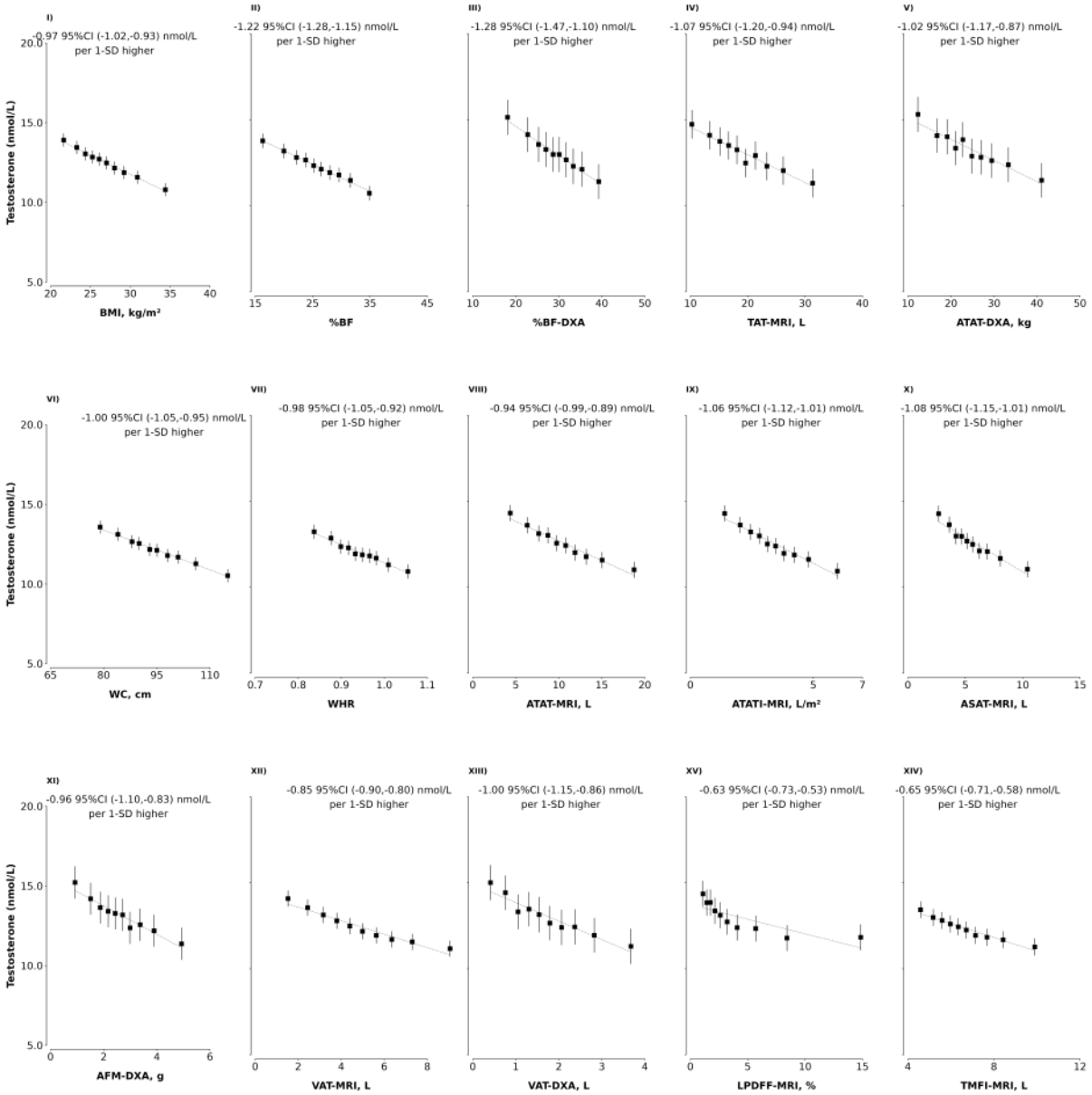
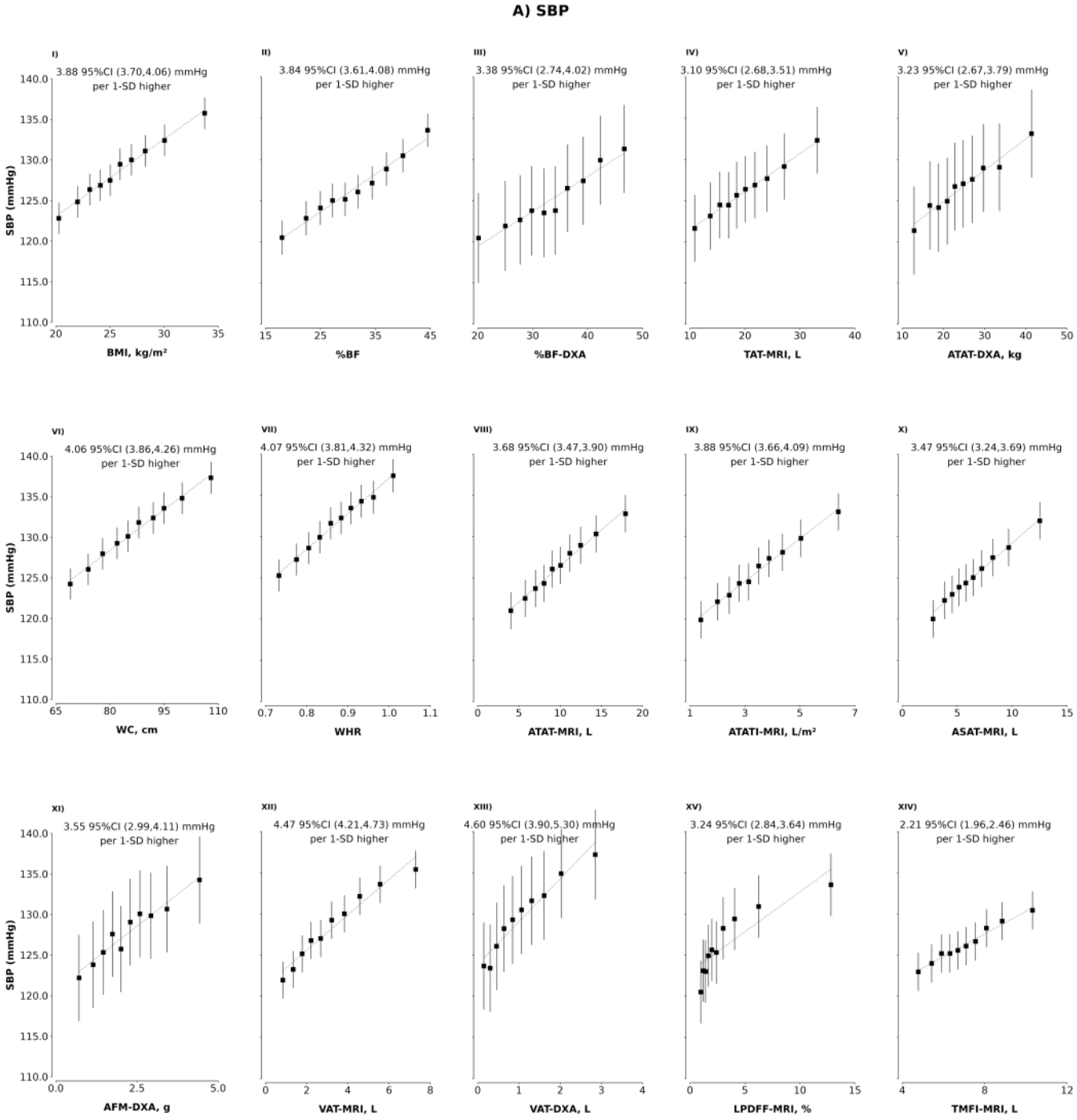
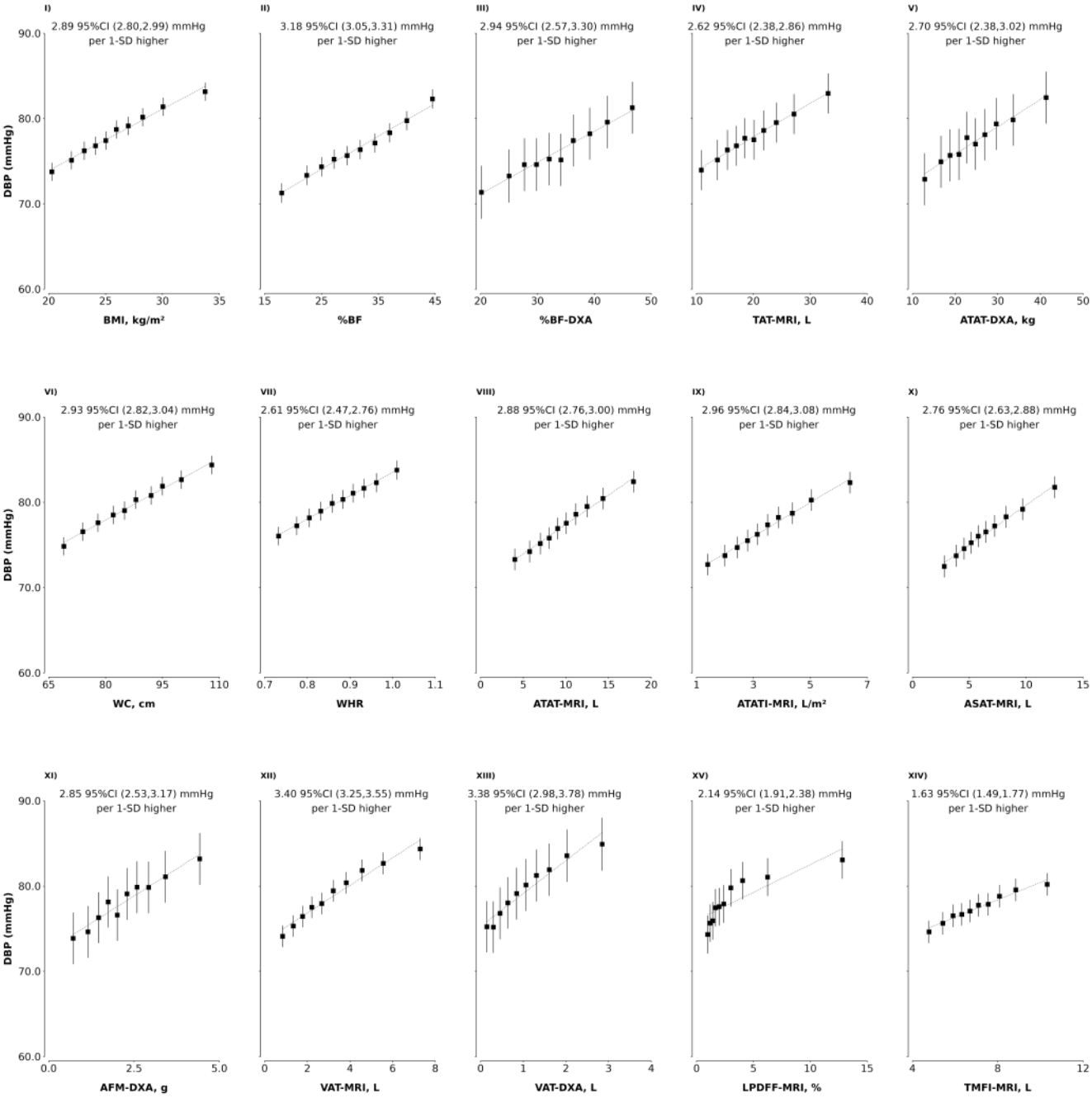


Figure 4.2 Associations of adiposity traits with blood pressure and blood proteins

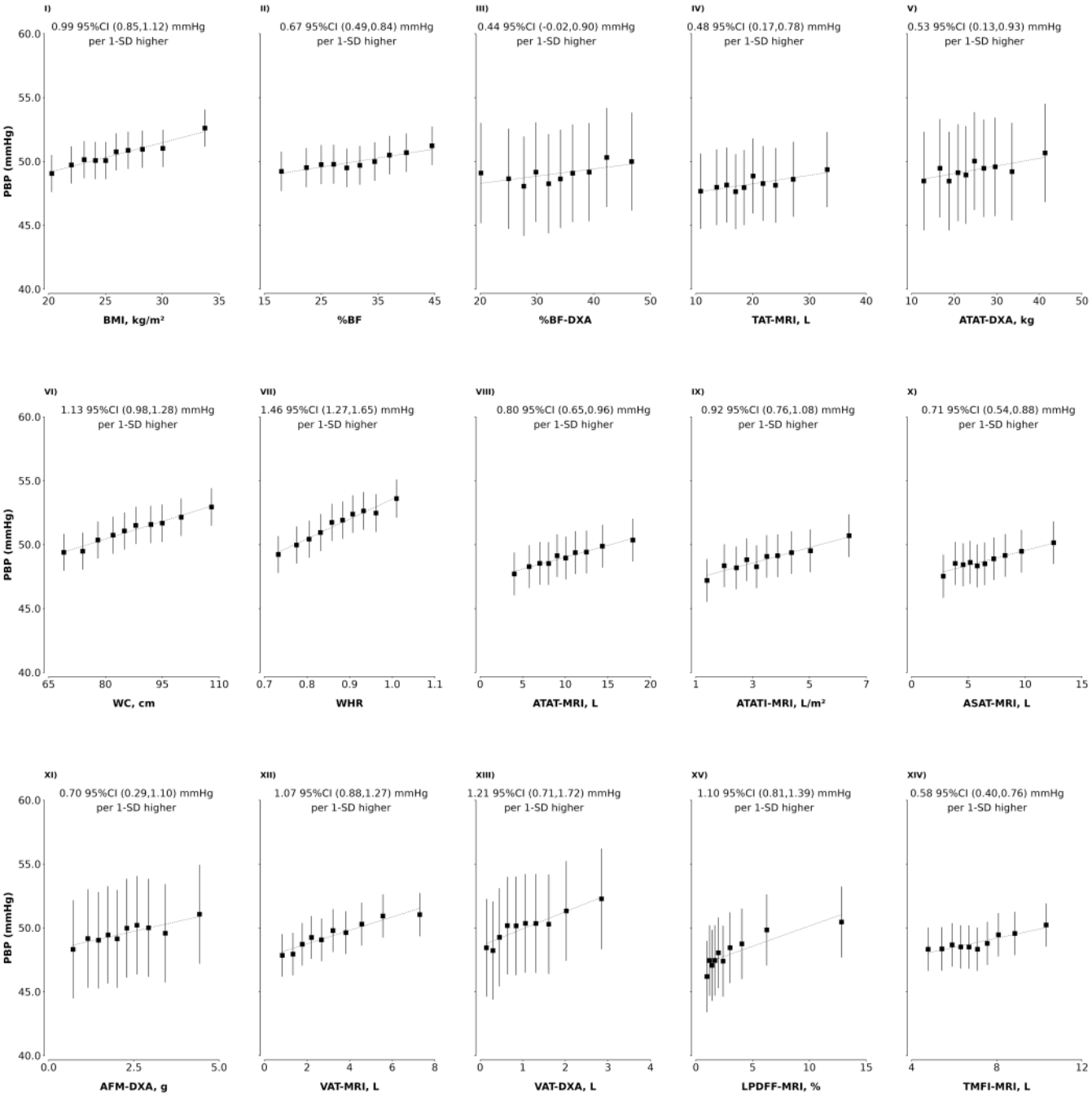
Conventions as in Figure 4.1.



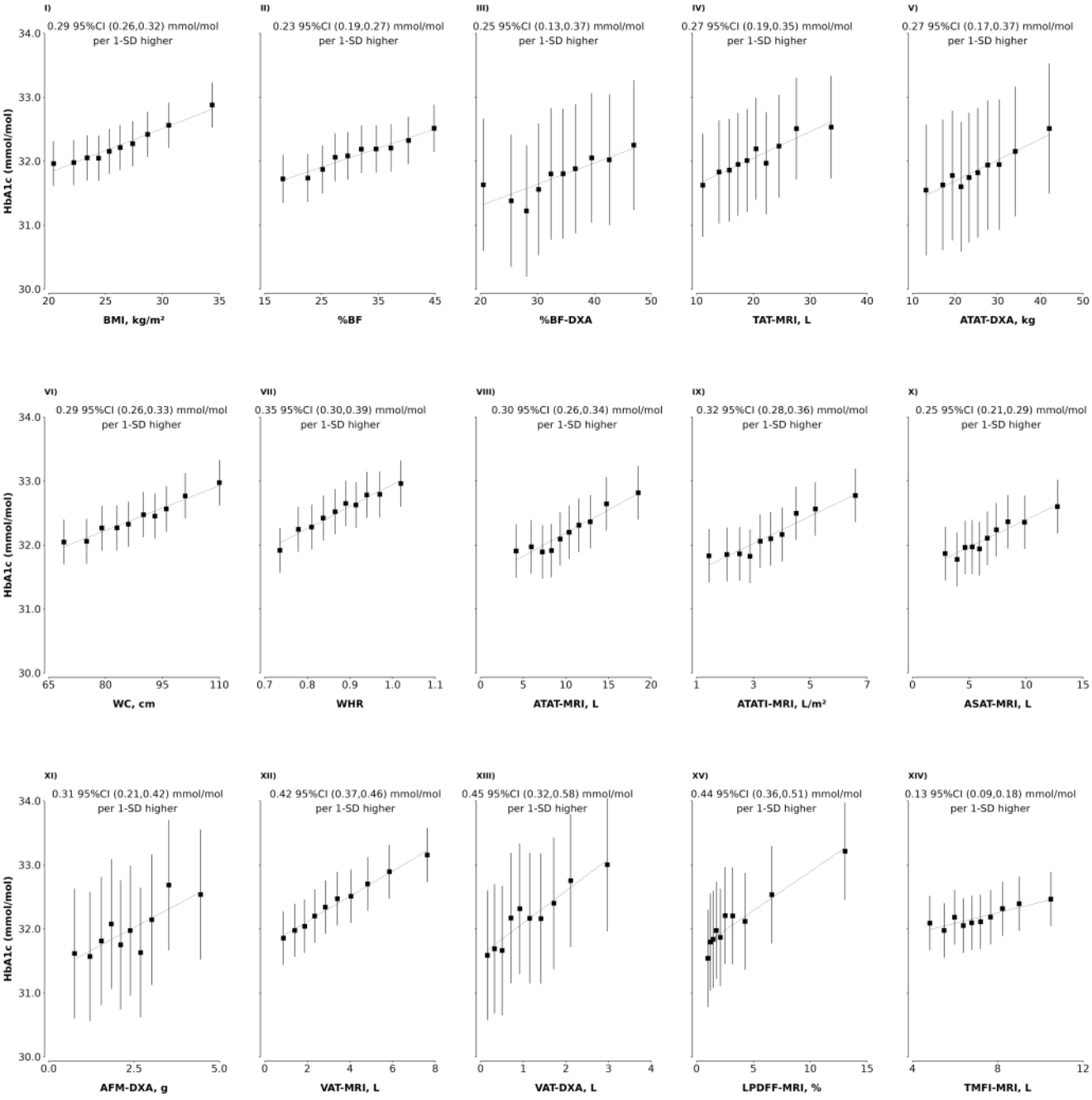
B) DBP


I)
2.89 95%CI (2.80,2.99) mmHg
per 1-SD higher
BMI, kg/m²
II)
3.18 95%CI (3.05,3.31) mmHg
per 1-SD higher
%BF
III)
2.94 95%CI (2.57,3.30) mmHg
per 1-SD higher
%BF-DXA
IV)
2.62 95%CI (2.38,2.86) mmHg
per 1-SD higher
TAT-MRI, L
V)
2.70 95%CI (2.38,3.02) mmHg
per 1-SD higher
ATAT-DXA, kg
VI)
2.93 95%CI (2.82,3.04) mmHg
per 1-SD higher
WC, cm
VII)
2.61 95%CI (2.47,2.76) mmHg
per 1-SD higher
WHR
VIII)
2.88 95%CI (2.76,3.00) mmHg
per 1-SD higher
ATAT-MRI, L
IX)
2.96 95%CI (2.84,3.08) mmHg
per 1-SD higher
ATATI-MRI, L/m²
X)
2.76 95%CI (2.63,2.88) mmHg
per 1-SD higher
ASAT-MRI, L
XI)
2.85 95%CI (2.53,3.17) mmHg
per 1-SD higher
AFM-DXA, g
XII)
3.40 95%CI (3.25,3.55) mmHg
per 1-SD higher
VAT-MRI, L
XIII)
3.38 95%CI (2.98,3.78) mmHg
per 1-SD higher
VAT-DXA, L
XV)
2.14 95%CI (1.91,2.38) mmHg
per 1-SD higher
LPDFF-MRI, %
XIV)
1.63 95%CI (1.49,1.77) mmHg
per 1-SD higher
TMFI-MRI, L
DBP (mmHg)

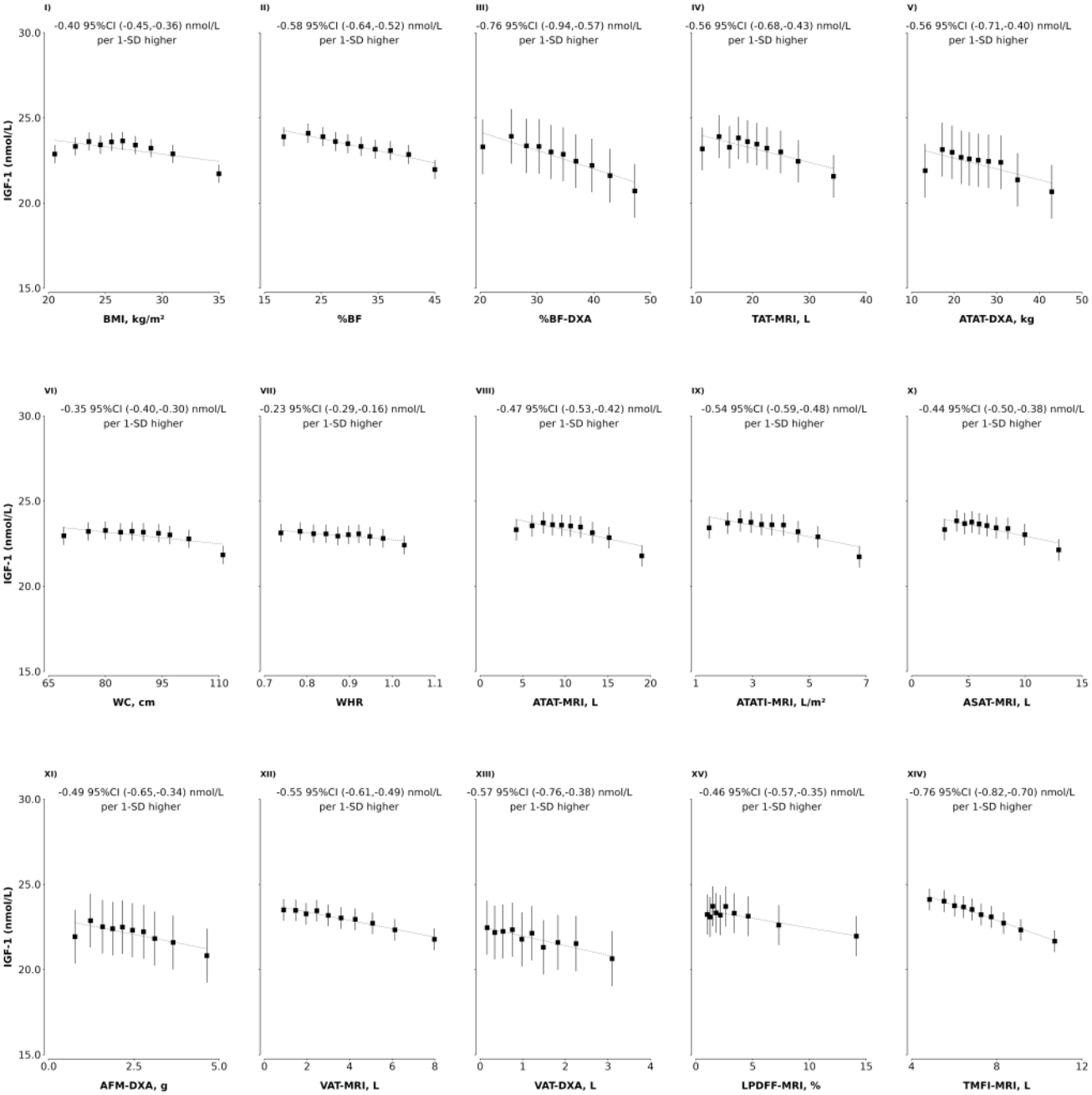
C) PBP


I)
0.99 95%CI (0.85,1.12) mmHg
per 1-SD higher
BMI, kg/m²
II)
0.67 95%CI (0.49,0.84) mmHg
per 1-SD higher
%BF
III)
0.44 95%CI (-0.02,0.90) mmHg
per 1-SD higher
%BF-DXA
IV)
0.48 95%CI (0.17,0.78) mmHg
per 1-SD higher
TAT-MRI, L
V)
0.53 95%CI (0.13,0.93) mmHg
per 1-SD higher
ATAT-DXA, kg
VI)
1.13 95%CI (0.98,1.28) mmHg
per 1-SD higher
WC, cm
VII)
1.46 95%CI (1.27,1.65) mmHg
per 1-SD higher
WHR
VIII)
0.80 95%CI (0.65,0.96) mmHg
per 1-SD higher
ATAT-MRI, L
IX)
0.92 95%CI (0.76,1.08) mmHg
per 1-SD higher
ATATI-MRI, L/m²
X)
0.71 95%CI (0.54,0.88) mmHg
per 1-SD higher
ASAT-MRI, L
XI)
0.70 95%CI (0.29,1.10) mmHg
per 1-SD higher
AFM-DXA, g
XII)
1.07 95%CI (0.88,1.27) mmHg
per 1-SD higher
VAT-MRI, L
XIII)
1.21 95%CI (0.71,1.72) mmHg
per 1-SD higher
VAT-DXA, L
XV)
1.10 95%CI (0.81,1.39) mmHg
per 1-SD higher
LPDFF-MRI, %
XIV)
0.58 95%CI (0.40,0.76) mmHg
per 1-SD higher
TMFI-MRI, L
PBP (mmHg)

D) HBa1c


I)
0.29 95%CI (0.26,0.32) mmol/mol
per 1-SD higher
HbA1c (mmol/mol)
BMI, kg/m²
II)
0.23 95%CI (0.19,0.27) mmol/mol
per 1-SD higher
%BF
III)
0.25 95%CI (0.13,0.37) mmol/mol
per 1-SD higher
%BF-DXA
IV)
0.27 95%CI (0.19,0.35) mmol/mol
per 1-SD higher
TAT-MRI, L
V)
0.27 95%CI (0.17,0.37) mmol/mol
per 1-SD higher
ATAT-DXA, kg
VI)
0.29 95%CI (0.26,0.33) mmol/mol
per 1-SD higher
WC, cm
VII)
0.35 95%CI (0.30,0.39) mmol/mol
per 1-SD higher
WHR
VIII)
0.30 95%CI (0.26,0.34) mmol/mol
per 1-SD higher
ATAT-MRI, L
IX)
0.32 95%CI (0.28,0.36) mmol/mol
per 1-SD higher
ATATI-MRI, L/m²
X)
0.25 95%CI (0.21,0.29) mmol/mol
per 1-SD higher
ASAT-MRI, L
XI)
0.31 95%CI (0.21,0.42) mmol/mol
per 1-SD higher
AFM-DXA, g
XII)
0.42 95%CI (0.37,0.46) mmol/mol
per 1-SD higher
VAT-MRI, L
XIII)
0.45 95%CI (0.32,0.58) mmol/mol
per 1-SD higher
VAT-DXA, L
XV)
0.44 95%CI (0.36,0.51) mmol/mol
per 1-SD higher
LPDFF-MRI, %
XIV)
0.13 95%CI (0.09,0.18) mmol/mol
per 1-SD higher
TMFI-MRI, L

E) IGF-1


I)
-0.40 95%CI (-0.45,-0.36) nmol/L
per 1-SD higher
BMI, kg/m²
II)
-0.58 95%CI (-0.64,-0.52) nmol/L
per 1-SD higher
%BF
III)
-0.76 95%CI (-0.94,-0.57) nmol/L
per 1-SD higher
%BF-DXA
IV)
-0.56 95%CI (-0.68,-0.43) nmol/L
per 1-SD higher
TAT-MRI, L
V)
-0.56 95%CI (-0.71,-0.40) nmol/L
per 1-SD higher
ATAT-DXA, kg
VI)
-0.35 95%CI (-0.40,-0.30) nmol/L
per 1-SD higher
WC, cm
VII)
-0.23 95%CI (-0.29,-0.16) nmol/L
per 1-SD higher
WHR
VIII)
-0.47 95%CI (-0.53,-0.42) nmol/L
per 1-SD higher
ATAT-MRI, L
IX)
-0.54 95%CI (-0.59,-0.48) nmol/L
per 1-SD higher
ATATI-MRI, L/m²
X)
-0.44 95%CI (-0.50,-0.38) nmol/L
per 1-SD higher
ASAT-MRI, L
XI)
-0.49 95%CI (-0.65,-0.34) nmol/L
per 1-SD higher
AFM-DXA, g
XII)
-0.55 95%CI (-0.61,-0.49) nmol/L
per 1-SD higher
VAT-MRI, L
XIII)
-0.57 95%CI (-0.76,-0.38) nmol/L
per 1-SD higher
VAT-DXA, L
XV)
-0.46 95%CI (-0.57,-0.35) nmol/L
per 1-SD higher
LPDFF-MRI, %
XIV)
-0.76 95%CI (-0.82,-0.70) nmol/L
per 1-SD higher
TMFI-MRI, L
IGF-1 (nmol/L)

F) CRP

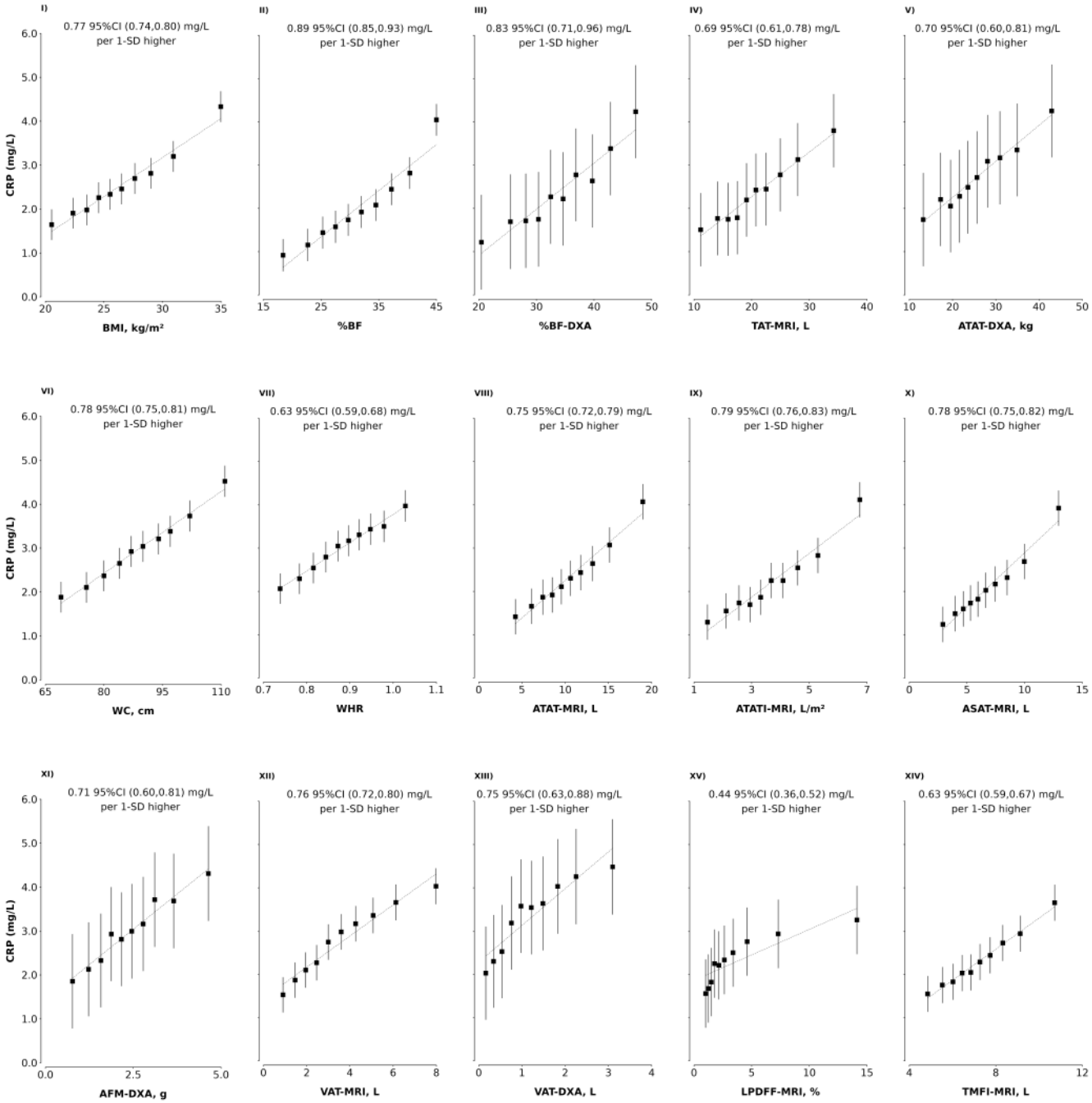

I)
0.77 95%CI (0.74,0.80) mg/L
per 1-SD higher
CRP (mg/L)
BMI, kg/m²
II)
0.89 95%CI (0.85,0.93) mg/L
per 1-SD higher
%BF
III)
0.83 95%CI (0.71,0.96) mg/L
per 1-SD higher
%BF-DXA
IV)
0.69 95%CI (0.61,0.78) mg/L
per 1-SD higher
TAT-MRI, L
V)
0.70 95%CI (0.60,0.81) mg/L
per 1-SD higher
ATAT-DXA, kg
VI)
0.78 95%CI (0.75,0.81) mg/L
per 1-SD higher
CRP (mg/L)
WC, cm
VII)
0.63 95%CI (0.59,0.68) mg/L
per 1-SD higher
WHR
VIII)
0.75 95%CI (0.72,0.79) mg/L
per 1-SD higher
ATAT-MRI, L
IX)
0.79 95%CI (0.76,0.83) mg/L
per 1-SD higher
ATATI-MRI, L/m²
X)
0.78 95%CI (0.75,0.82) mg/L
per 1-SD higher
ASAT-MRI, L
XI)
0.71 95%CI (0.60,0.81) mg/L
per 1-SD higher
CRP (mg/L)
AFM-DXA, g
XII)
0.76 95%CI (0.72,0.80) mg/L
per 1-SD higher
VAT-MRI, L
XIII)
0.75 95%CI (0.63,0.88) mg/L
per 1-SD higher
VAT-DXA, L
XV)
0.44 95%CI (0.36,0.52) mg/L
per 1-SD higher
LPDFF-MRI, %
XIV)
0.63 95%CI (0.59,0.67) mg/L
per 1-SD higher
TMFI-MRI, L

Figure 4.3 Differences in blood lipids and sex hormones per SD increase in adiposity traits

Linear regression models were used to calculate the mean values of specific markers per SD increase of each adiposity trait on a continuous scale. Associations were adjusted for factors measured at imaging visits including age, sex, smoking status, alcohol consumption, education level, Townsend Deprivation index score, and in women the number of live births, menopause status, years since menopause, and use of MHT. The sizes of the boxes are inversely proportional to the variance of the estimated differences in disease markers. The dashed line denotes the increase in disease marker for an SD increase in BMI. The standard deviations for each adiposity trait are shown in Table 2.2.

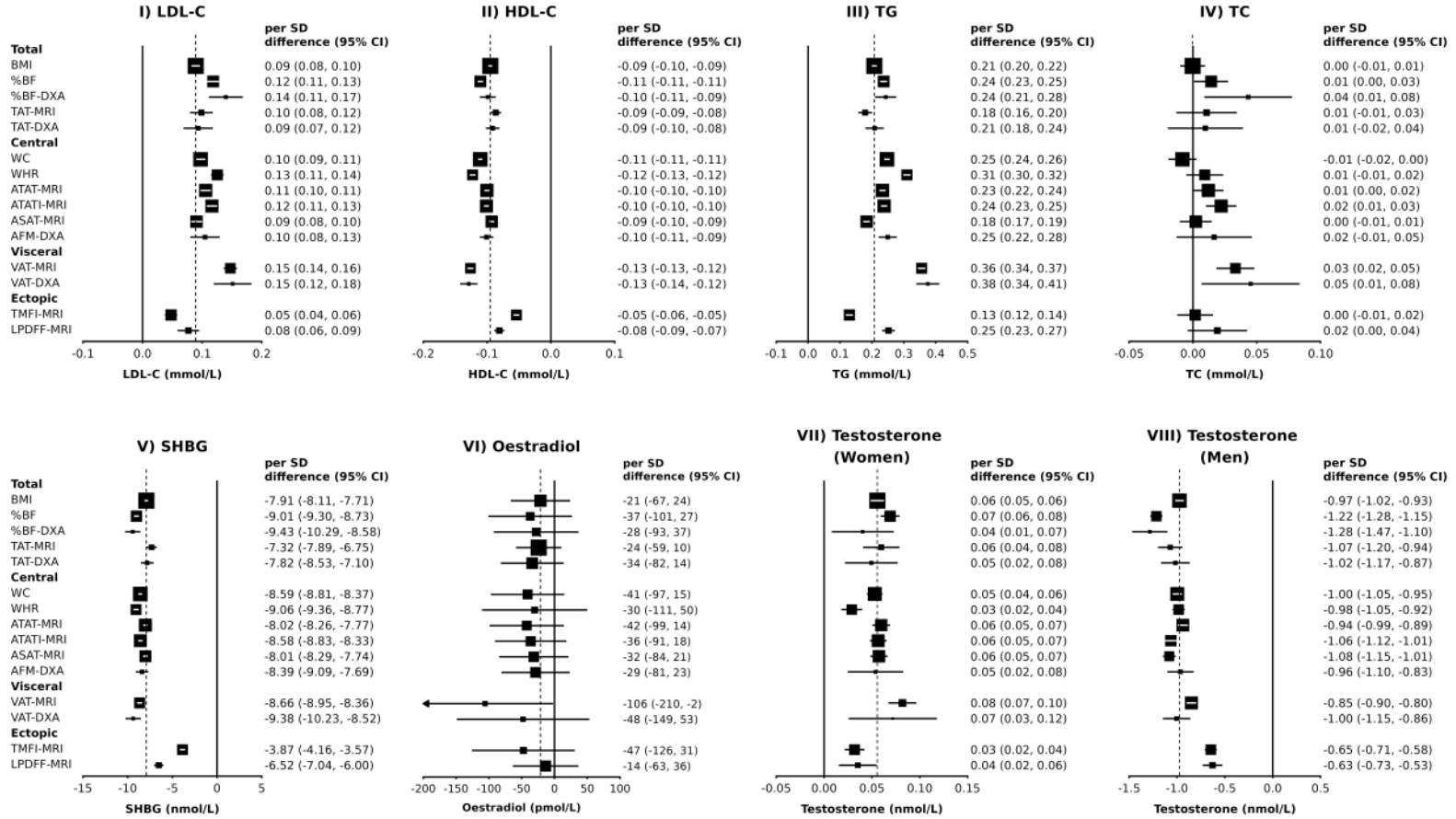


Figure 4.4 Differences in blood pressure and blood proteins per SD increase of adiposity traits

Conventions as in Figure 4.3.

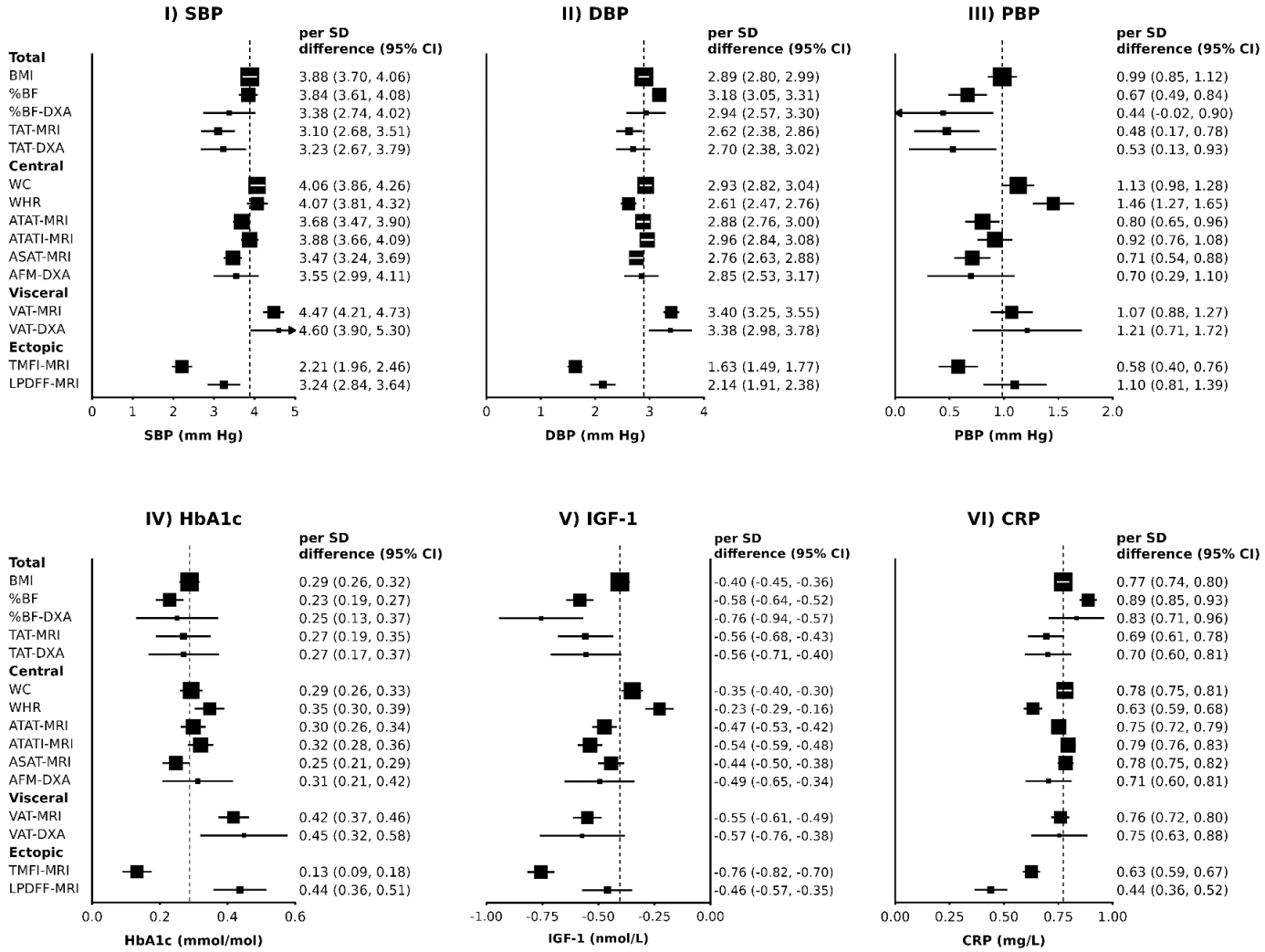
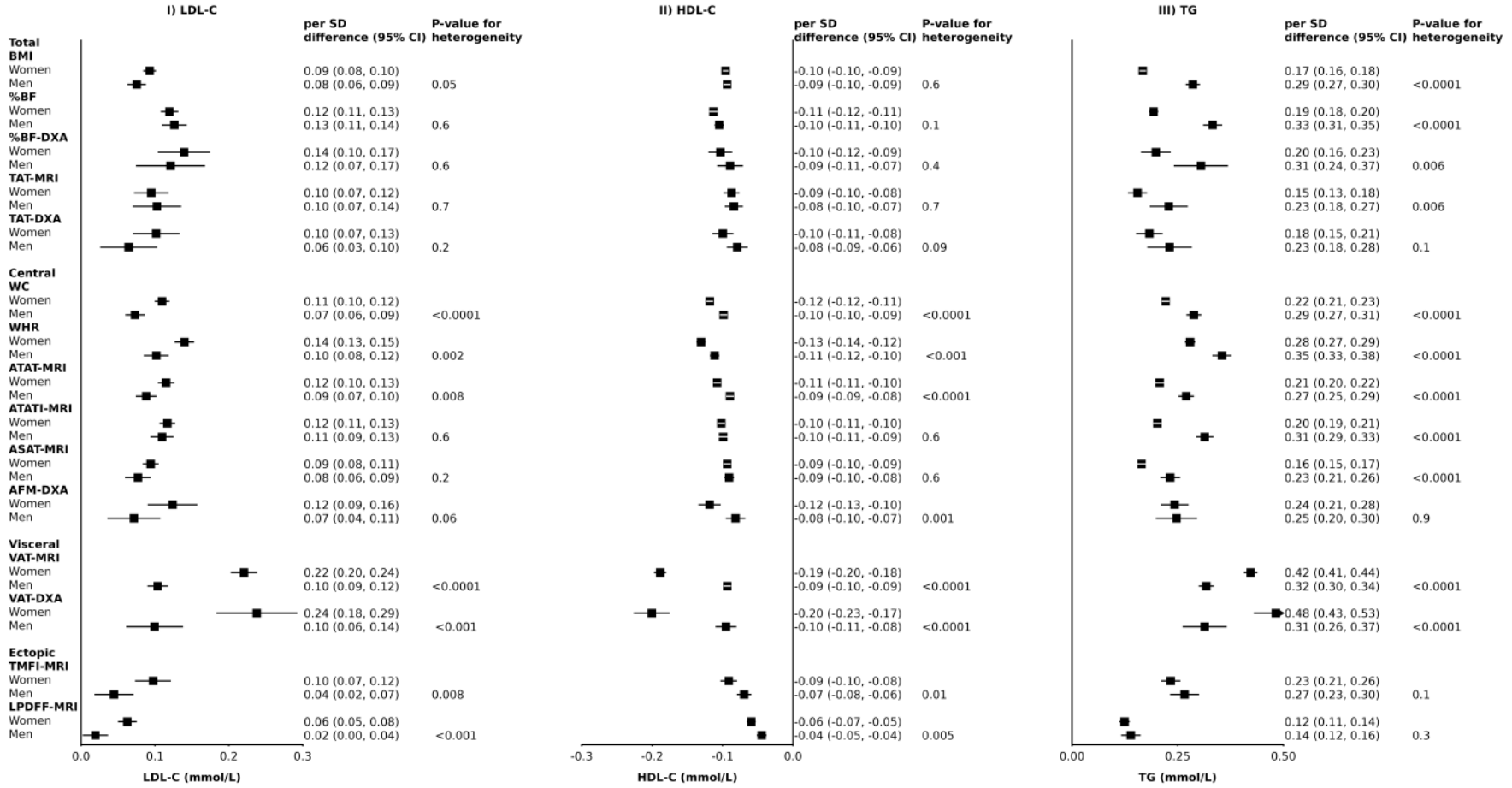


Figure 4.5 Sex-specific differences in blood lipids and sex hormones per SD increase in adiposity traits

Conventions as in Figure 4.3. The standard deviations for each adiposity measure were sex-specific as shown in Table 2.2. The p-values were corrected with false discovery rate correction to account for multiple comparisons across adiposity traits.



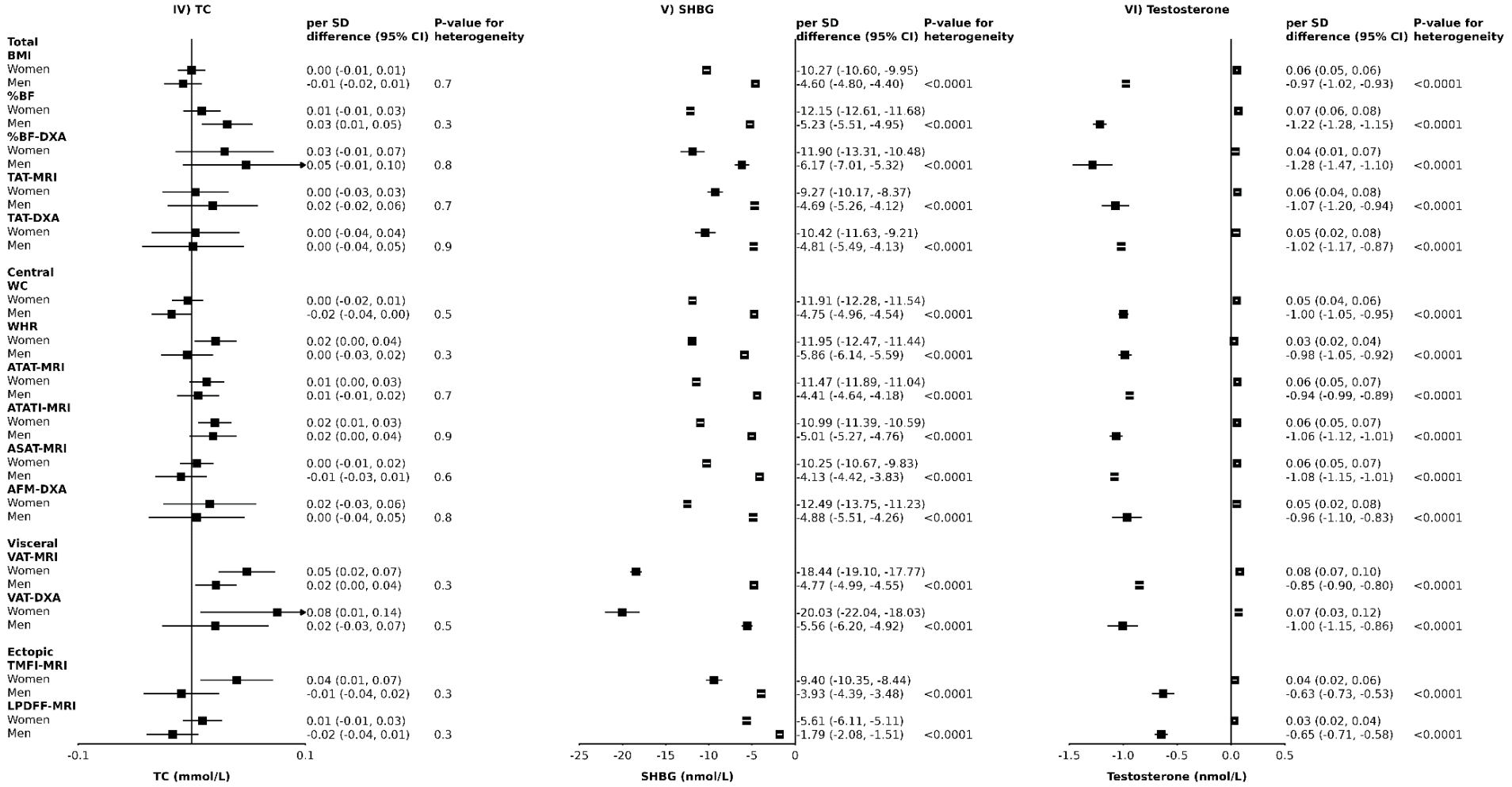
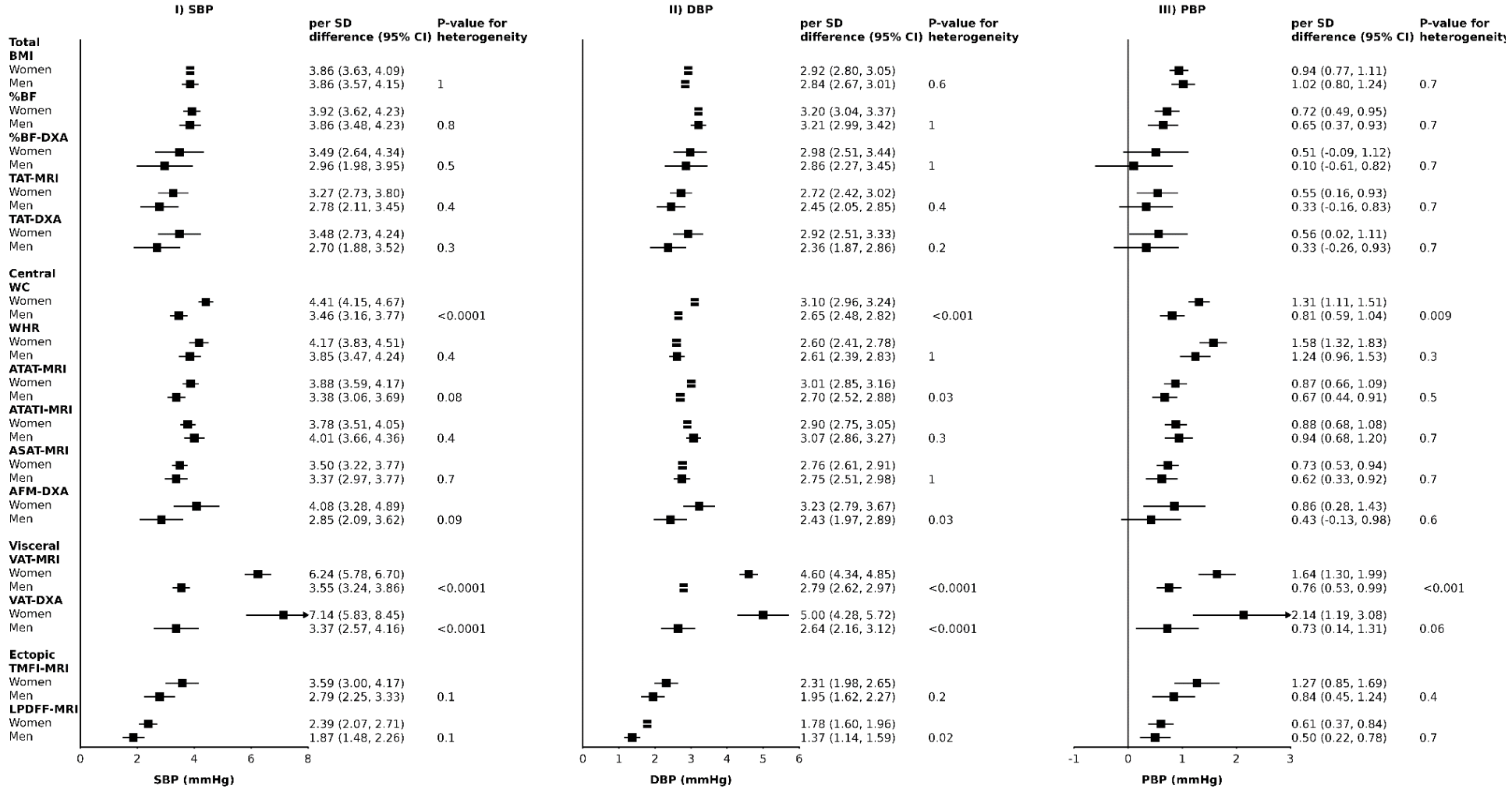
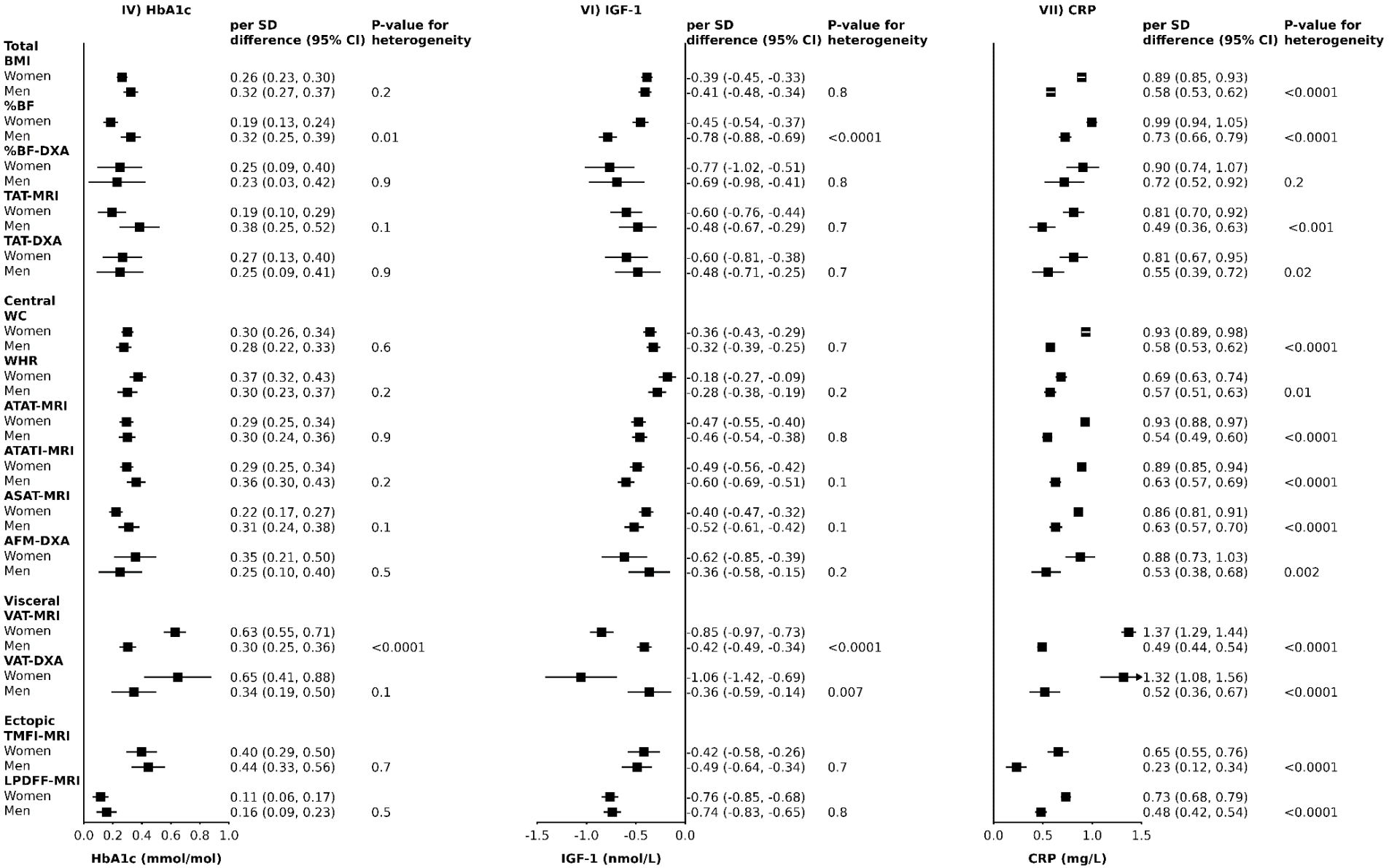

IV) TC
per SD difference (95% CI)
P-value for heterogeneity
Total
BMI
Women 0.00 (-0.01, 0.01)
Men -0.01 (-0.02, 0.01) 0.7
%BF
Women 0.01 (-0.01, 0.03)
Men 0.03 (0.01, 0.05) 0.3
%BF-DXA
Women 0.03 (-0.01, 0.07)
Men 0.05 (-0.01, 0.10) 0.8
TAT-MRI
Women 0.00 (-0.03, 0.03)
Men 0.02 (-0.02, 0.06) 0.7
TAT-DXA
Women 0.00 (-0.04, 0.04)
Men 0.00 (-0.04, 0.05) 0.9
Central
WC
Women 0.00 (-0.02, 0.01)
Men -0.02 (-0.04, 0.00) 0.5
WHR
Women 0.02 (0.00, 0.04)
Men 0.00 (-0.03, 0.02) 0.3
ATAT-MRI
Women 0.01 (0.00, 0.03)
Men 0.01 (-0.01, 0.02) 0.7
ATATI-MRI
Women 0.02 (0.01, 0.03)
Men 0.02 (0.00, 0.04) 0.9
ASAT-MRI
Women 0.00 (-0.01, 0.02)
Men -0.01 (-0.03, 0.01) 0.6
AFM-DXA
Women 0.02 (-0.03, 0.06)
Men 0.00 (-0.04, 0.05) 0.8
Visceral
VAT-MRI
Women 0.05 (0.02, 0.07)
Men 0.02 (0.00, 0.04) 0.3
VAT-DXA
Women 0.08 (0.01, 0.14)
Men 0.02 (-0.03, 0.07) 0.5
Ectopic
TMFI-MRI
Women 0.04 (0.01, 0.07)
Men -0.01 (-0.04, 0.02) 0.3
LPDFF-MRI
Women 0.01 (-0.01, 0.03)
Men -0.02 (-0.04, 0.01) 0.3
-0.1
0.1
TC (mmol/L)
V) SHBG
per SD difference (95% CI)
P-value for heterogeneity
-10.27 (-10.60, -9.95)
-4.60 (-4.80, -4.40) <0.0001
-12.15 (-12.61, -11.68)
-5.23 (-5.51, -4.95) <0.0001
-11.90 (-13.31, -10.48)
-6.17 (-7.01, -5.32) <0.0001
-9.27 (-10.17, -8.37)
-4.69 (-5.26, -4.12) <0.0001
-10.42 (-11.63, -9.21)
-4.81 (-5.49, -4.13) <0.0001
-11.91 (-12.28, -11.54)
-4.75 (-4.96, -4.54) <0.0001
-11.95 (-12.47, -11.44)
-5.86 (-6.14, -5.59) <0.0001
-11.47 (-11.89, -11.04)
-4.41 (-4.64, -4.18) <0.0001
-10.99 (-11.39, -10.59)
-5.01 (-5.27, -4.76) <0.0001
-10.25 (-10.67, -9.83)
-4.13 (-4.42, -3.83) <0.0001
-12.49 (-13.75, -11.23)
-4.88 (-5.51, -4.26) <0.0001
-18.44 (-19.10, -17.77)
-4.77 (-4.99, -4.55) <0.0001
-20.03 (-22.04, -18.03)
-5.56 (-6.20, -4.92) <0.0001
-9.40 (-10.35, -8.44)
-3.93 (-4.39, -3.48) <0.0001
-5.61 (-6.11, -5.11)
-1.79 (-2.08, -1.51) <0.0001
-25
-20
-15
-10
-5
0
SHBG (nmol/L)
VI) Testosterone
per SD difference (95% CI)
P-value for heterogeneity
0.06 (0.05, 0.06)
-0.97 (-1.02, -0.93) <0.0001
0.07 (0.06, 0.08)
-1.22 (-1.28, -1.15) <0.0001
0.04 (0.01, 0.07)
-1.28 (-1.47, -1.10) <0.0001
0.06 (0.04, 0.08)
-1.07 (-1.20, -0.94) <0.0001
0.05 (0.02, 0.08)
-1.02 (-1.17, -0.87) <0.0001
0.05 (0.04, 0.06)
-1.00 (-1.05, -0.95) <0.0001
0.03 (0.02, 0.04)
-0.98 (-1.05, -0.92) <0.0001
0.06 (0.05, 0.07)
-0.94 (-0.99, -0.89) <0.0001
0.06 (0.05, 0.07)
-1.06 (-1.12, -1.01) <0.0001
0.06 (0.05, 0.07)
-1.08 (-1.15, -1.01) <0.0001
0.05 (0.02, 0.08)
-0.96 (-1.10, -0.83) <0.0001
0.08 (0.07, 0.10)
-0.85 (-0.90, -0.80) <0.0001
0.07 (0.03, 0.12)
-1.00 (-1.15, -0.86) <0.0001
0.04 (0.02, 0.06)
-0.63 (-0.73, -0.53) <0.0001
0.03 (0.02, 0.04)
-0.65 (-0.71, -0.58) <0.0001
-1.5
-1.0
-0.5
0.0
0.5
Testosterone (nmol/L)

Figure 4.6 Sex-specific differences in blood pressure and blood proteins per SD increase in adiposity traits

Conventions as in Figure 4.3. The standard deviations for each adiposity measure were sex-specific as shown in Table 2.2.




IV) HbA1c
per SD difference (95% CI)
P-value for heterogeneity
Total
BMI
Women 0.26 (0.23, 0.30)
Men 0.32 (0.27, 0.37) 0.2
%BF
Women 0.19 (0.13, 0.24)
Men 0.32 (0.25, 0.39) 0.01
%BF-DXA
Women 0.25 (0.09, 0.40)
Men 0.23 (0.03, 0.42) 0.9
TAT-MRI
Women 0.19 (0.10, 0.29)
Men 0.38 (0.25, 0.52) 0.1
TAT-DXA
Women 0.27 (0.13, 0.40)
Men 0.25 (0.09, 0.41) 0.9
Central
WC
Women 0.30 (0.26, 0.34)
Men 0.28 (0.22, 0.33) 0.6
WHR
Women 0.37 (0.32, 0.43)
Men 0.30 (0.23, 0.37) 0.2
ATAT-MRI
Women 0.29 (0.25, 0.34)
Men 0.30 (0.24, 0.36) 0.9
ATATI-MRI
Women 0.29 (0.25, 0.34)
Men 0.36 (0.30, 0.43) 0.2
ASAT-MRI
Women 0.22 (0.17, 0.27)
Men 0.31 (0.24, 0.38) 0.1
AFM-DXA
Women 0.35 (0.21, 0.50)
Men 0.25 (0.10, 0.40) 0.5
Visceral
VAT-MRI
Women 0.63 (0.55, 0.71)
Men 0.30 (0.25, 0.36) <0.0001
VAT-DXA
Women 0.65 (0.41, 0.88)
Men 0.34 (0.19, 0.50) 0.1
Ectopic
TMFI-MRI
Women 0.40 (0.29, 0.50)
Men 0.44 (0.33, 0.56) 0.7
LPDFF-MRI
Women 0.11 (0.06, 0.17)
Men 0.16 (0.09, 0.23) 0.5
0.0 0.2 0.4 0.6 0.8 1.0
HbA1c (mmol/mol)
VI) IGF-1
per SD difference (95% CI)
P-value for heterogeneity
Women -0.39 (-0.45, -0.33)
Men -0.41 (-0.48, -0.34) 0.8
Women -0.45 (-0.54, -0.37)
Men -0.78 (-0.88, -0.69) <0.0001
Women -0.77 (-1.02, -0.51)
Men -0.69 (-0.98, -0.41) 0.8
Women -0.60 (-0.76, -0.44)
Men -0.48 (-0.67, -0.29) 0.7
Women -0.60 (-0.81, -0.38)
Men -0.48 (-0.71, -0.25) 0.7
Women -0.36 (-0.43, -0.29)
Men -0.32 (-0.39, -0.25) 0.7
Women -0.18 (-0.27, -0.09)
Men -0.28 (-0.38, -0.19) 0.2
Women -0.47 (-0.55, -0.40)
Men -0.46 (-0.54, -0.38) 0.8
Women -0.49 (-0.56, -0.42)
Men -0.60 (-0.69, -0.51) 0.1
Women -0.40 (-0.47, -0.32)
Men -0.52 (-0.61, -0.42) 0.1
Women -0.62 (-0.85, -0.39)
Men -0.36 (-0.58, -0.15) 0.2
Women -0.85 (-0.97, -0.73)
Men -0.42 (-0.49, -0.34) <0.0001
Women -1.06 (-1.42, -0.69)
Men -0.36 (-0.59, -0.14) 0.007
Women -0.42 (-0.58, -0.26)
Men -0.49 (-0.64, -0.34) 0.7
Women -0.76 (-0.85, -0.68)
Men -0.74 (-0.83, -0.65) 0.8
-1.5 -1.0 -0.5 0.0
IGF-1 (nmol/L)
VII) CRP
per SD difference (95% CI)
P-value for heterogeneity
Women 0.89 (0.85, 0.93)
Men 0.58 (0.53, 0.62) <0.0001
Women 0.99 (0.94, 1.05)
Men 0.73 (0.66, 0.79) <0.0001
Women 0.90 (0.74, 1.07)
Men 0.72 (0.52, 0.92) 0.2
Women 0.81 (0.70, 0.92)
Men 0.49 (0.36, 0.63) <0.001
Women 0.81 (0.67, 0.95)
Men 0.55 (0.39, 0.72) 0.02
Women 0.93 (0.89, 0.98)
Men 0.58 (0.53, 0.62) <0.0001
Women 0.69 (0.63, 0.74)
Men 0.57 (0.51, 0.63) 0.01
Women 0.93 (0.88, 0.97)
Men 0.54 (0.49, 0.60) <0.0001
Women 0.89 (0.85, 0.94)
Men 0.63 (0.57, 0.69) <0.0001
Women 0.86 (0.81, 0.91)
Men 0.63 (0.57, 0.70) <0.0001
Women 0.88 (0.73, 1.03)
Men 0.53 (0.38, 0.68) 0.002
Women 1.37 (1.29, 1.44)
Men 0.49 (0.44, 0.54) <0.0001
Women 1.32 (1.08, 1.56)
Men 0.52 (0.36, 0.67) <0.0001
Women 0.65 (0.55, 0.76)
Men 0.23 (0.12, 0.34) <0.0001
Women 0.73 (0.68, 0.79)
Men 0.48 (0.42, 0.54) <0.0001
0.0 0.5 1.0 1.5
CRP (mg/L)

Chapter 5. Associations of different body fat components with cardio-metabolic disease, and cancer risks: findings from the UK Biobank imaging-sub-cohort

5.1 Background and aims

Excess adiposity is positively associated with an increased risk of certain cancers (26). While this association is well-established, the majority of evidence comes from studies measuring total or central adiposity, primarily using anthropometric methods. In contrast, there is a lack of studies that assess adiposity using other measures, particularly visceral or ectopic adiposity quantified accurately through imaging methods, in relation to cancer risk. Some animal studies concluded that visceral adiposity may have a greater oncogenic and pro-atherogenic effect compared to other body fat components (11). Furthermore, findings presented in Chapter 4 suggested that visceral adiposity had a greater magnitude of association with certain intermediate markers of disease than total, central, or ectopic adiposity.

This chapter investigates the association of different adiposity traits with certain cancers. The choice to examine colorectal, breast, and prostate cancer is based on their high clinical significance and prevalence, as well as the availability of sufficient cases in the UKB, which allows robust statistical power. Most of these cancers are well-documented to be associated with adiposity (26, 31), with colorectal cancer consistently positively associated with excess adiposity, and breast cancer showing a positive association in postmenopausal women and a negative association in premenopausal women (65). In contrast, evidence for the association with prostate cancer remains limited. Given that the majority of women in the UKB are postmenopausal, the focus of this chapter is on this group for breast cancer.

This chapter aims to quantify and compare the magnitude of associations between different body fat components including total, central, visceral, and ectopic adiposity, and the risk of selected cancers. Also, considering the association between excess adiposity and CMD, such as IHD and T2D, is well-documented (25, 27), these associations will also be investigated as part of a control analysis.

5.2 Methods

5.2.1 Disease endpoints

The endpoints of interest considered here were selected CMD outcomes (ICD-10 of IHD: I20-I25; T2D: E10-E14), all cancers (C00-C26, C30-C41, C43, C45-C97), and site-specific cancers (colorectal cancer: C18-C20; breast cancer [in postmenopausal women] C50; prostate cancer: C61), which occurred after the imaging visit. These endpoints of interest were selected to ensure a minimum of 20 incident cases per adiposity trait investigated, thereby allowing robust statistical inference. In addition, endpoints were chosen based on their well-established or biologically plausible associations with obesity-related diseases, including CVD and cancer, although the association between obesity and prostate cancer remains limited and less consistent in the published literature. These disease outcome data were obtained through electronic linkages with hospital inpatient data for CMD and national health registries for cancers. Death was obtained through linkage to the UK national death registries. Menopause status for breast cancer analysis was assessed during the imaging assessment.

Participants with a relevant prevalent disease of interest (except for non-melanoma skin cancer ICD-10 C44 in analyses of cancer endpoints) at the time of attending the imaging assessment were excluded from the main analyses. For IHD, participants

diagnosed before baseline with any CMD other than IHD, such as conduction disorders, cerebrovascular diseases, and transient cerebral ischemic attacks and related syndromes (ICD-10: I45, I60-I69, and G45), were further excluded. In cases where participants were hospitalised with a relevant IHD diagnosis and subsequently died during the same hospitalisation, the event was classified as a single incident case of IHD. The date of hospital admission (or episode start) was used as the time of onset. For IHD, 3,286 participants with prevalent disease were excluded, including 1,046 with a prior myocardial infarction and 2,240 with other chronic IHD (i.e., angina, conduction disorders and cerebrovascular disease). This approach focuses the analysis on first-ever (acute) IHD events rather than chronic disease progression or recurrent MI. Deaths occurring during hospitalisation for the same condition were not treated as separate endpoints, thereby avoiding double-counting and ensuring consistency in time-to-event calculations. For breast cancer, men and premenopausal women were excluded. For prostate cancer, women were excluded.

The exposure person-years were calculated from the date of attending the imaging assessment until death, loss to follow-up, end of follow-up, or first occurrence of relevant disease outcome, whichever came first. The end of follow-up for the selected endpoints of T2D and IHD was 31 October 2022 for England, 31 August 2022 in Scotland and 31 May 2022 for Wales; and for the cancers, it was 31 December 2020 for England, 30 November 2021 for Scotland, and 31 December 2016 for Wales. In addition, for IHD incidence, participants diagnosed with any CMD other than IHD, and for cancer incidence with any cancer other than the cancer of interest (except non-melanoma skin cancer), during the follow-up period were censored at the date of diagnosis of the relevant disease.

5.2.2 Statistical analyses

Cox proportional hazard models were used to estimate hazard ratios (HR) of the selected diseases by quintiles of each adiposity measure, with variances and 95% CIs for the group-specific log risks estimated using the floating absolute risk method (216), with the HRs for specific diseases associated with SD higher levels of each adiposity measure further estimated overall and by sex. All analyses were adjusted for factors measured at imaging visits including age (5-year groups), sex, smoking status (never, previous, current), alcohol intake (0, 1, 2, ≥3 drinks/week), education level (college/university degree, A levels/AS levels or equivalent, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications, none of the above), and deprivation (quintiles of Townsend deprivation index), and among women, where relevant, adjustments were also made for the number of live births, menopause status (yes, no, had hysterectomy), years since menopause, and use of MHT (current, past, never). A complete case analysis was applied for each model, meaning that only participants with complete data for all relevant variables were included.

As part of the sensitivity analysis, the analyses were repeated after excluding the first 3 years of follow-up to minimise the potential for reverse causation, as preclinical symptoms of the disease may lead to weight loss (19).

5.3 Results

Among participants who attended the imaging sub-study, there were 140 T2D cases, 1,027 IHD cases, 1,257 all cancers combined cases, 141 colorectal cancer cases, 149 breast cancer cases among postmenopausal women, and 349 prostate cancer cases, during a mean follow-up of 3 years.

A log-linear trend was observed in the association between adiposity traits and disease outcomes (**Figure 5.1** and **Figure 5.2**).

All adiposity traits showed a marked positive association with the risk of T2D. The adjusted HRs of T2D per SD increase in visceral (VAT-MRI: 2.50 95%CI: [2.07-3.00]) and central (WC: 2.11 [1.80-2.48]; WHR: 2.66 [2.10-3.37]) adiposity were somewhat greater than those in total (BMI: 1.79 [1.57-2.04]) or ectopic adiposity (LPDFF-MRI: 1.83 [1.58-2.12]) (**Figure 5.3**).

For IHD, the associations with body fat components were less pronounced, with no obvious differences across different adiposity traits. Specifically, there was a 23% (1.23 [1.15-1.32]) increase in IHD risk per SD increase in VAT-MRI, similar to the HRs per SD increase in total (BMI: 1.15 [1.08-1.22]), central (WC: 1.15 [1.08-1.23]) or ectopic adiposity (LPDFF-MRI: 1.18 [1.08-1.29]).

For cancer-specific sites, including colorectal cancer, breast cancer and all cancers combined, weak positive associations with adiposity were reported, with no major differences in magnitude across various body fat components (**Figure 5.4**). Overall, the HRs per SD increase in different indices of adiposity ranged from 0.97 to 1.38 for colorectal cancer, from 1.13 to 137 for breast cancer and from 1.08 to 1.17 for all cancers combined. There was no evidence of an association of adiposity with the risk of prostate cancer incidence regardless of how it was measured.

No sex differences were found in associations of adiposity traits and the risk of T2D, IHD, colorectal cancer and all cancers combined (**Figure 5.5** and **Figure 5.6**).

Further exclusion of the first 3 years of follow-up did not materially alter the results (**Figure 5.7** and **Figure 5.8**).

5.4 Discussion

In this large-scale imaging study, the association of various adiposity traits, categorised according to body fat component, was quantified and compared with risks of certain CMDs and cancers. Greater adiposity was generally associated with a greater risk of T2D, IHD, breast cancer, colorectal cancer and all cancers combined, but no evidence of association was found with prostate cancer risk. There were, however, no clear differences in the magnitude of the associations of different adiposity traits with any of these disease endpoints, except for T2D, for which visceral and central adiposity showed greater associations compared with total and ectopic adiposity.

It is well-established in epidemiological literature that both total and central adiposity, measured mostly with anthropometric methods, are positively associated with the risk of CVD (25), T2D (27), and certain cancers (26). Biological studies further suggest that certain body fat components, particularly visceral and ectopic adiposity, are more metabolically active and oncogenic than others (11). Visceral adiposity, being highly metabolically active, contributes to systemic inflammation by releasing pro-inflammatory cytokines and adipokines, leading to endothelial dysfunction, insulin resistance, and metabolic disturbances (60, 217). In CVD and consequently, IHD, excess visceral adiposity promotes atherosclerosis and plaque rupture (217), while in T2D, it disrupts glucose metabolism and insulin signalling (17). Ectopic adiposity, especially in organs such as the liver and muscle, exacerbates insulin resistance and metabolic dysfunction (42-44). Moreover, visceral and ectopic adiposity influence hormone production, including increased oestrogen and IGF, which can drive tumour development and progression (83, 85, 86), thereby linking

excess adiposity to cancer risk. However, in epidemiological literature, the evidence of the association of adiposity with risk of T2D, IHD and cancers is limited to studies measuring total or central adiposity with anthropometric methods.

T2D events were defined using hospitalisation records because, at the time of the imaging visit, less than half of participants had linked primary care data available until 2016, making it infeasible to use these records. As most diabetes diagnoses occur in primary care and only a subset are hospitalised for complications, this definition captures primarily severe or complicated cases. Consequently, the recorded date of T2D case may be substantially later than the true date of diagnosis. This delay could lead to underestimation of early risk and overestimation of later risk in time-to-event models. The findings here reflect associations with clinically recognised or severe diabetes rather than all incident cases.

Here, increased visceral or central adiposity had a somewhat greater risk of T2D compared with total or ectopic adiposity. Consistent with the findings here, a meta-analysis of 26 million individuals from 216 studies involving 2.3 million T2D cases found significant associations of both total (BMI: 1.54 [1.49-1.60] per 5 kg/m^2) and central adiposity (WC: 1.61 [1.52-1.70] per 10 cm) with T2D incidence, with a comparable magnitude of relative risks (47).

Although no studies have quantified and compared the associations of total and central vs. visceral and ectopic adiposity in relation to T2D risk, indirect comparisons can be made from their associations with HbA1c (shown in Chapter 4) which is considered a diabetes biomarker (218). Consistent with the findings here, visceral adiposity had a greater association with HbA1c than total adiposity. However, liver and visceral adiposity demonstrated a similar magnitude of association with HbA1c.

The reason why liver adiposity demonstrated a greater association with HbA1c but not with T2D remains unclear. One possible explanation is that liver adiposity drives hyperglycaemia and insulin resistance without reaching the HbA1c threshold necessary to diagnose T2D. Furthermore, this may be due to the limited statistical power to investigate T2D in the imaging sub-cohort.

For IHD, a positive association was found between different body fat components with no major differences in the magnitudes of the associations. In line with the findings here, the Emerging Risk Factors Collaboration analysed around 89,413 primarily White participants involving 2,582 IHD cases and found that a 5 kg/m^2 increase in BMI was associated with an HR of 1.32 (1.24-1.41) for IHD, while measures of central adiposity (WC, WHR) showed similar magnitude of associations (56). Another study compared the evidence from an MR analysis of 369,225 UKB participants (HR: 1.34 [1.19-1.50] per 5 kg/m^2 genetically predicted BMI based on 75 SNPs; 1.24 [1.22-1.25] per 10 cm genetically predicted WC based on 69 SNPs) with that from an observational study of 456,495 UKB participants including 26,225 IHD cases (HR: 1.27 [1.26-1.28] per 5 kg/m^2 BMI; 1.23 [1.21-1.24] per 10 cm WC) and found that each of total and central adiposity had a positive association with IHD risk of a similar magnitude (219). Indirect comparisons can be made with blood pressure and blood lipids presented in Chapter 4.

Blood lipids and blood pressure are considered intermediate markers of IHD (190). Chapter 4 found that elevated visceral adiposity had a somewhat greater magnitude of association with certain blood lipids (LDL-C, TG, HDL-C) and blood pressure (SBP, DBP), compared with total, central or ectopic adiposity. However, in contrast to these findings, here no major differences were observed across different body fat

components in relation to IHD risk. The reason for this inconsistency is unclear, but it may be due to blood lipids and blood pressure serving as early biomarkers of CVD.

A positive association was found across different body fat components with no major difference in the magnitude of the associations with risks of each of colorectal cancer, breast cancer and all cancers combined. It is well established that an increase in total or central adiposity measured with anthropometric measures is associated with an increased risk of colorectal cancers, and breast cancers in postmenopausal women (26, 31). Chapter 4 provided evidence of the association of different adiposity components with intermediate markers of cancer.

Firstly, the literature suggests that high IGF-1 levels are associated with an increase in the risk of colorectal cancer and breast cancer among other cancer sites (198). Consistent with the findings here, Chapter 4 found no major differences in the magnitude of associations between different body fat components and IGF-1 levels.

Secondly, previous studies have found that increased CRP is associated with the risk of colorectal cancer, breast cancer and all cancers combined (195-197). Similarly to the findings here, no major differences were found in the association of different body fat components with CRP.

Thirdly, SHBG is inversely associated with breast cancer risk in post-menopausal women (194). In Chapter 4, visceral adiposity had a greater magnitude of association with SHBG than total, central, or ectopic adiposity in predominantly postmenopausal women. However, here no major differences were found in the magnitude of different body fat components and breast cancer risk in postmenopausal women. This inconsistency in the magnitude of associations across

different body fat components may be due to the limited statistical power in the prospective analysis of breast cancer.

Oestradiol is associated with increased breast cancer (193). However, no evidence of an association between different body fat components and oestradiol was found in Chapter 4. This may be due to the limited sample size for oestradiol analysis, as the investigation was restricted to premenopausal women. Furthermore, a direct comparison between oestradiol and breast cancer risk regarding the magnitude of associations is not possible, as the breast cancer analysis was limited to postmenopausal women.

Increased testosterone levels are associated with prostate cancer in men (192), and breast cancer in women (220). Although findings in Chapter 4 showed an inverse association between different adiposity traits of a similar magnitude with testosterone in men, here there was no evidence of an association with prostate cancer. However, the findings here regarding adiposity and prostate cancer are consistent with what is found in the literature (26, 31).

On the other hand, increased adiposity had a positive association with testosterone in women of a similar magnitude. Consistent with the findings here, different body fat components had a positive association with breast cancer of a similar magnitude.

This study's main strength lies in it being the largest to compare the associations of various body fat components, based on both anthropometric and imaging-based adiposity traits, with markers of disease (in Chapter 4) and disease incidence. It does, however, have some limitations. Firstly, the relatively small number of disease cases in the prospective analysis limits statistical power, and a longer follow-up is required for a robust investigation of reverse causation and to capture more cases.

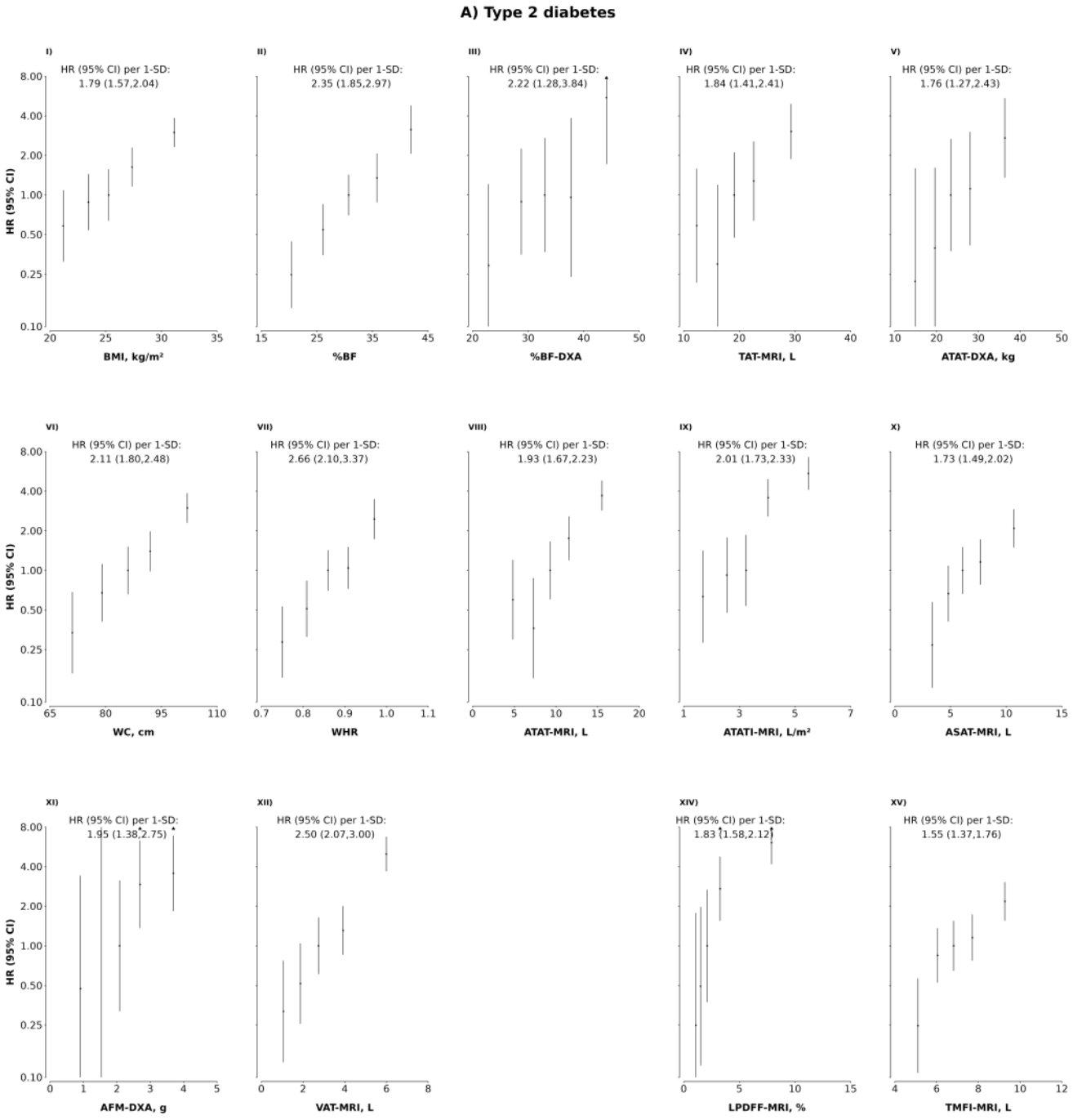
Secondly, the relatively small number of participants with imaging-based adiposity traits constrains generalisability. Thirdly, the classification of hospital deaths as single incident events may obscure distinctions between fatal and non-fatal IHD presentations. However, this approach was chosen to maintain consistency in endpoint definitions and avoid double-counting. Last but not least, while the present analysis was designed to ensure adequate statistical power by selecting endpoints with a minimum of 20 incident cases per adiposity trait, the overall sample size and stratification limits may have constrained the detection of more nuanced or subgroup-specific associations, for example, among individuals younger than 45 years or those of non-White ancestry. It is possible that a larger dataset, combined with correction for multiple testing, could reveal associations between adiposity traits and disease risks and their markers of a different magnitude than those observed in the present analysis. Future studies with broader representation and increased sample size may help uncover such relationships, particularly in underrepresented age or ancestry groups. Future analyses should be conducted once imaging-derived adiposity data are processed for the full cohort of 100,000 participants expected to be included in the imaging sub-study.

In conclusion, this large-scale study of UK individuals revealed significant associations between various body fat components with risks of T2D, IHD and certain cancers. Greater adiposity was also generally associated with a greater risk of T2D, IHD, colorectal cancer, breast cancer and all cancers, but no evidence of association was found with prostate cancer risk. There was, however, no major difference in the magnitude of the association of adiposity with any of these disease endpoints according to body fat component except for T2D, for which visceral and central adiposity showed greater associations compared with total and ectopic

adiposity. Future studies with a larger number of cases are needed to investigate whether certain body fat components like visceral and ectopic adiposity may have a greater magnitude of association with disease risk than total or central adiposity.

Figure 5.1 Adjusted HRs for T2D and IHD by quintiles of adiposity traits

Associations were adjusted for factors measured at imaging visits including age, sex, smoking status, alcohol consumption, education level, Townsend Deprivation index score, and among women number of live births, menopause status, years since menopause, and use of MHT. The relationship between each adiposity trait and HR was plotted in the form of a log-linear trend in HR per quintiles of adiposity trait. The position of the square indicates the value of HRs with its corresponding floated confidence intervals, and its area is inversely proportional to the variance of the logarithm of the HR, indicating the amount of statistical information available for the particular estimate. Results in the text refer to the HR per SD increase of each of the adiposity traits on a continuous scale in the form of conventional HR and their corresponding CI to allow comparisons across adiposity traits. In plot (A) the association of VAT-DXA with T2D was not illustrated due to the large CIs.



B) Ischaemic heart disease

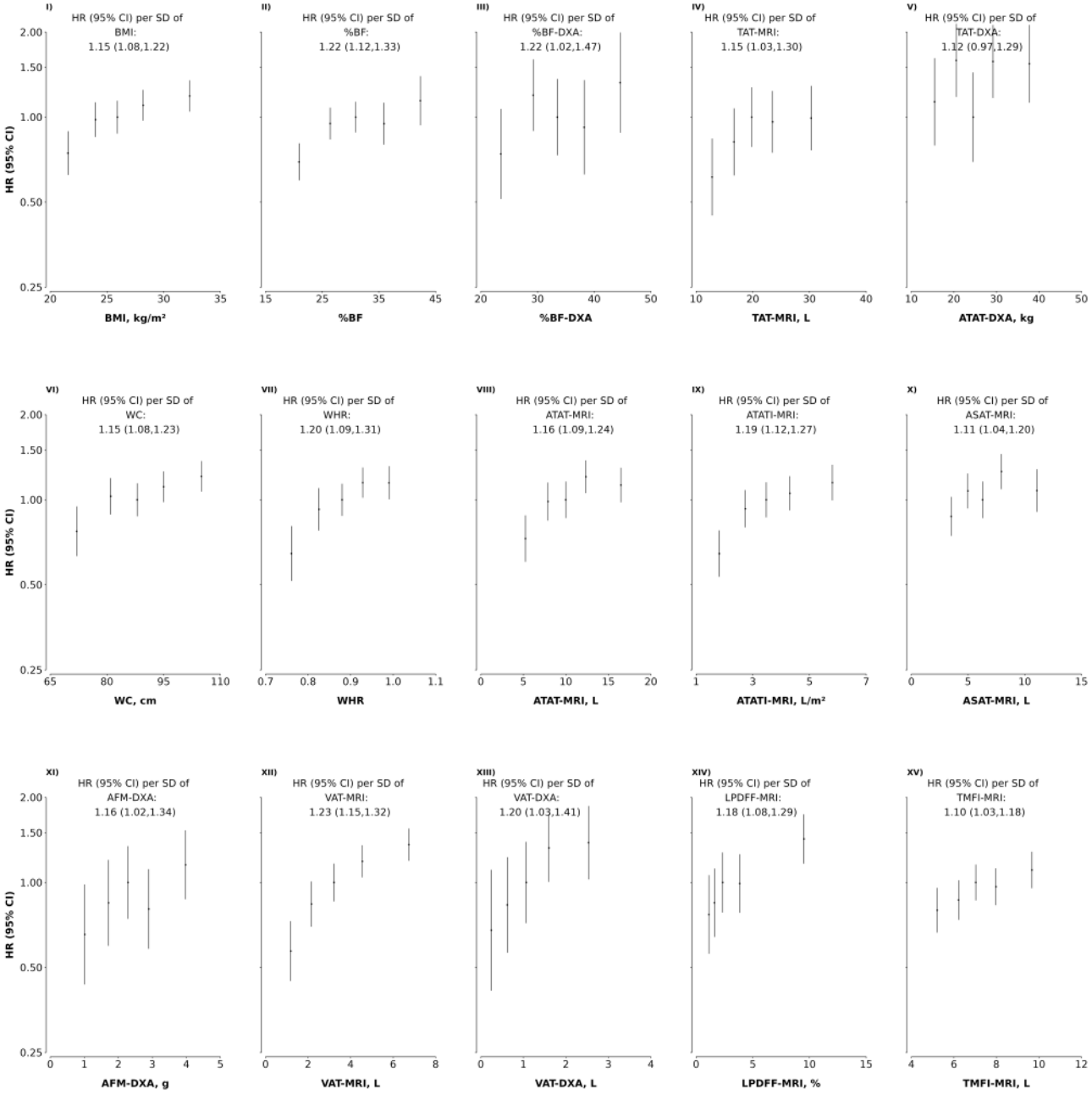
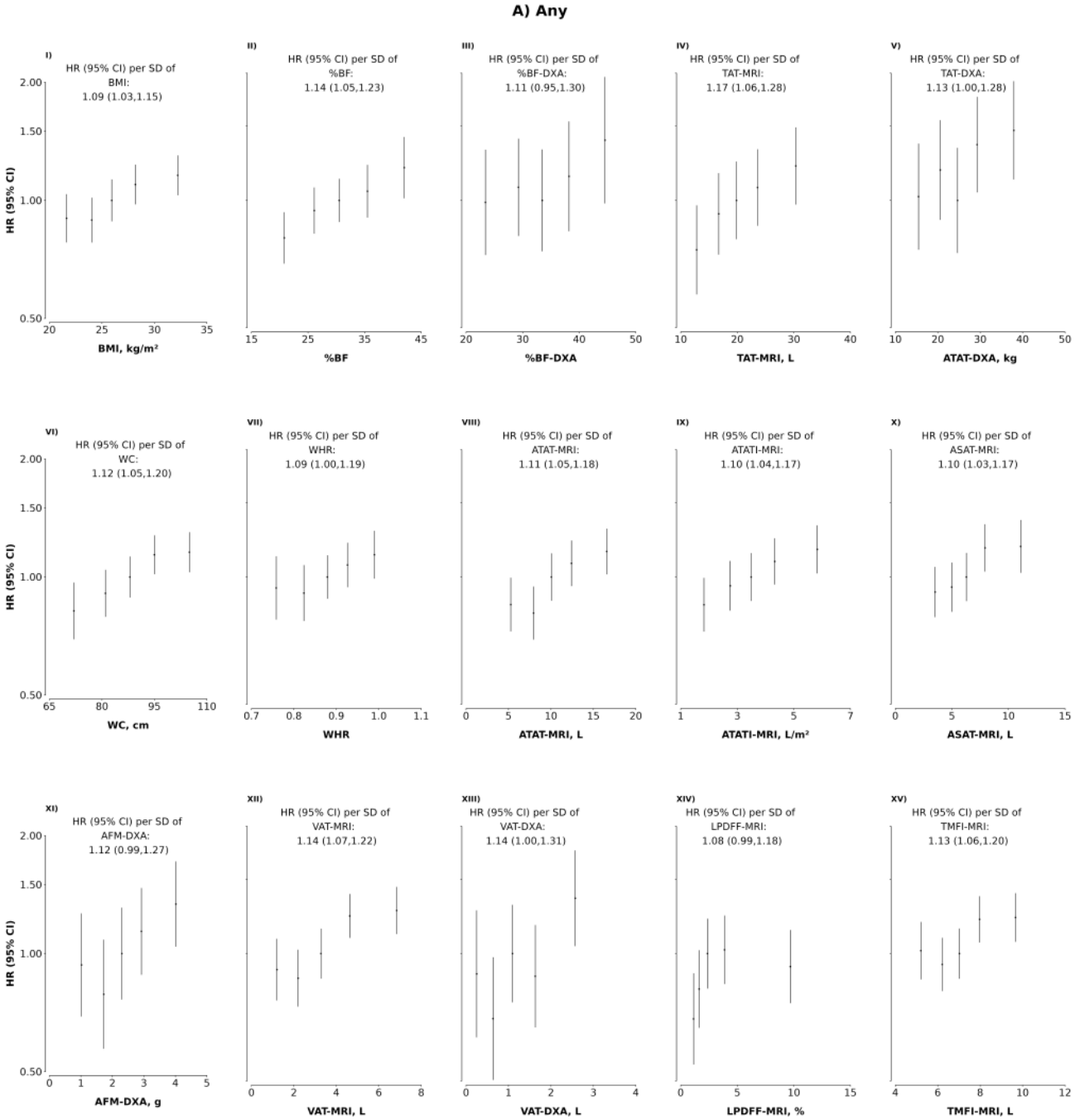
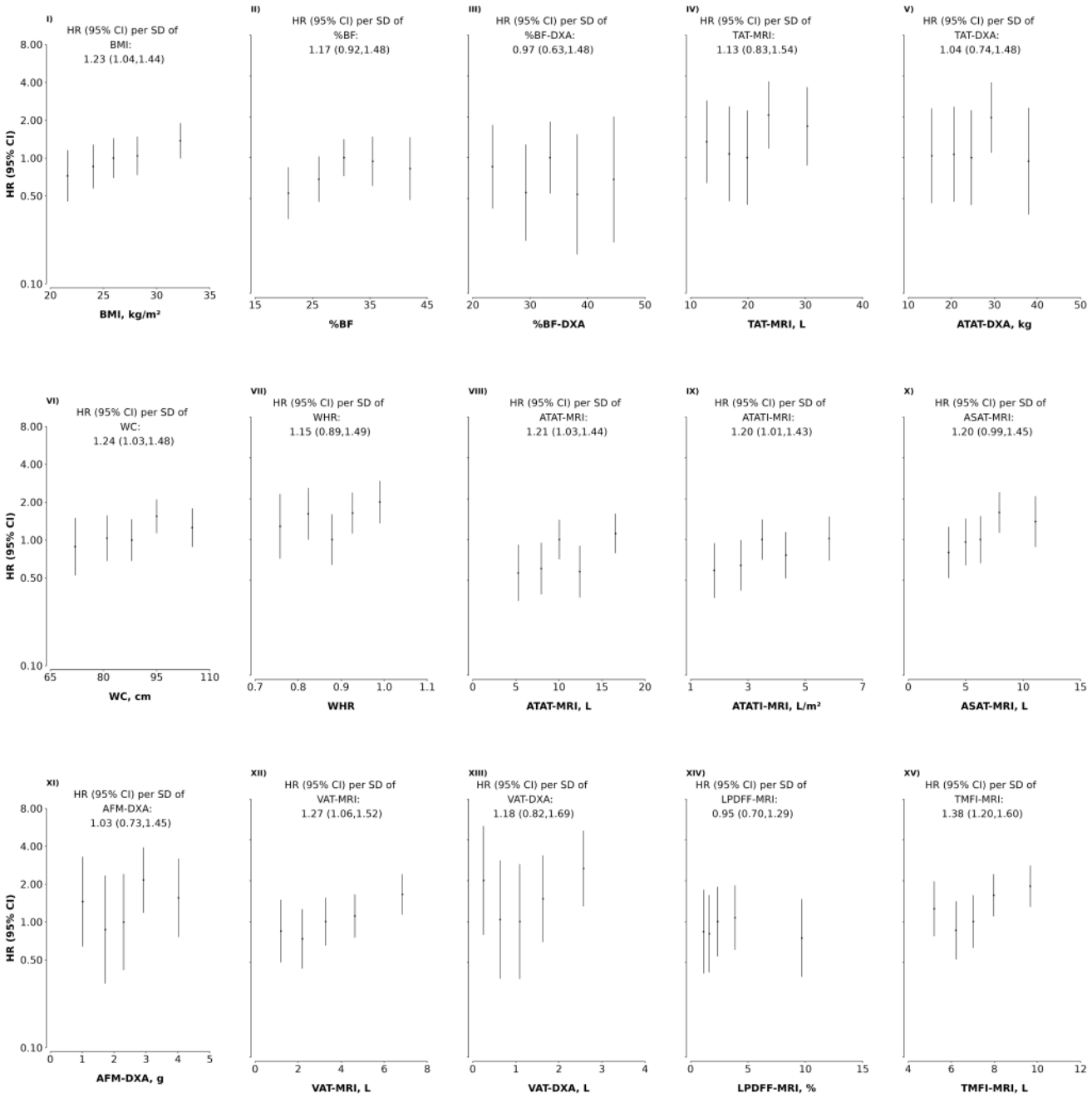


Figure 5.2 Adjusted HRs for total and selected site-specific cancers by quintiles of adiposity traits

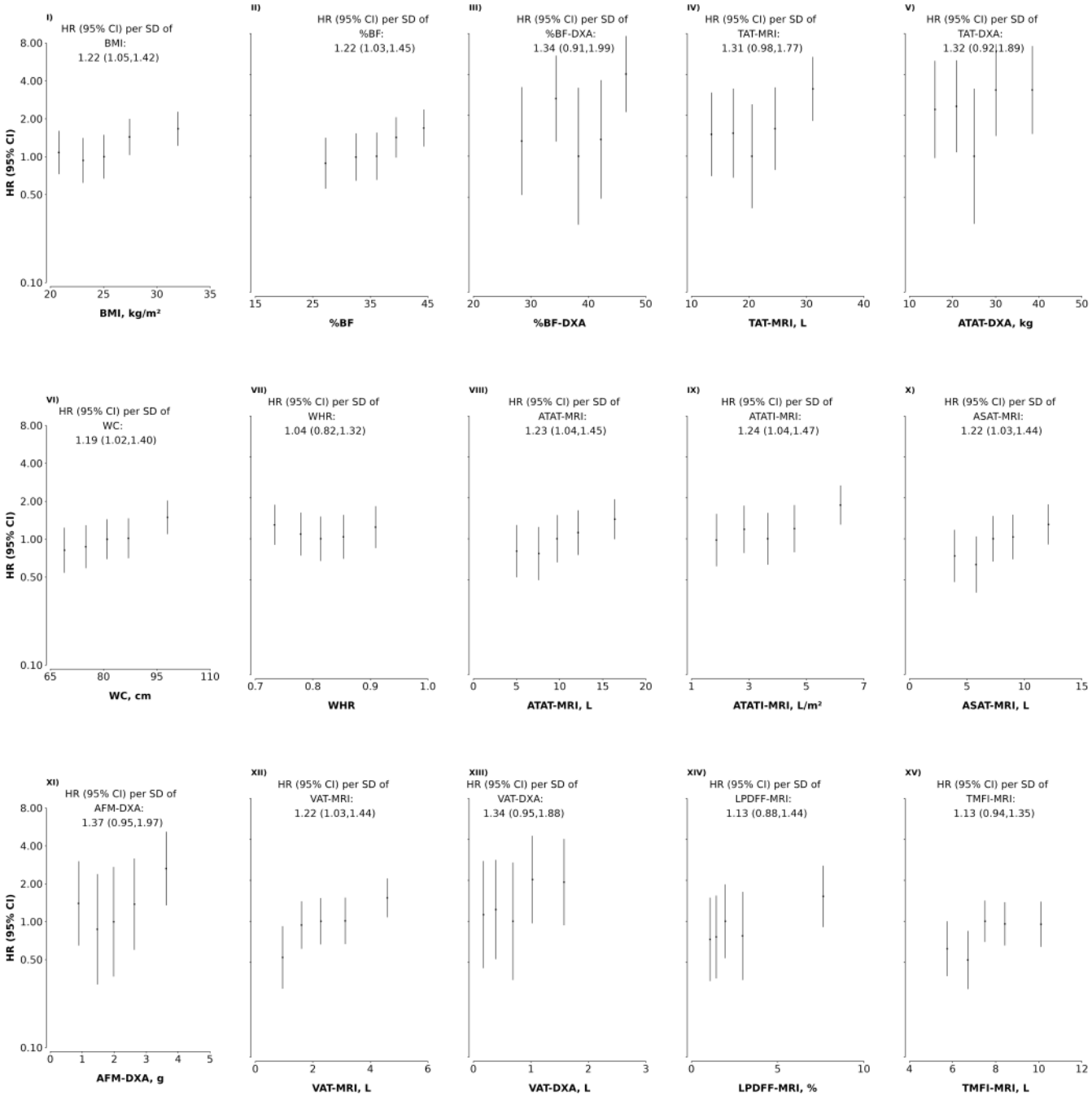
Conventions as in Figure 5.1.



B) Colon


I)
HR (95% CI) per SD of
BMI:
1.23 (1.04,1.44)
HR (95% CI)
BMI, kg/m²
II)
HR (95% CI) per SD of
%BF:
1.17 (0.92,1.48)
%BF
III)
HR (95% CI) per SD of
%BF-DXA:
0.97 (0.63,1.48)
%BF-DXA
IV)
HR (95% CI) per SD of
TAT-MRI:
1.13 (0.83,1.54)
TAT-MRI, L
V)
HR (95% CI) per SD of
TAT-DXA:
1.04 (0.74,1.48)
ATAT-DXA, kg
VI)
HR (95% CI) per SD of
WC:
1.24 (1.03,1.48)
WC, cm
VII)
HR (95% CI) per SD of
WHR:
1.15 (0.89,1.49)
WHR
VIII)
HR (95% CI) per SD of
ATAT-MRI:
1.21 (1.03,1.44)
ATAT-MRI, L
IX)
HR (95% CI) per SD of
ATATI-MRI:
1.20 (1.01,1.43)
ATATI-MRI, L/m²
X)
HR (95% CI) per SD of
ASAT-MRI:
1.20 (0.99,1.45)
ASAT-MRI, L
XI)
HR (95% CI) per SD of
AFM-DXA:
1.03 (0.73,1.45)
AFM-DXA, g
XII)
HR (95% CI) per SD of
VAT-MRI:
1.27 (1.06,1.52)
VAT-MRI, L
XIII)
HR (95% CI) per SD of
VAT-DXA:
1.18 (0.82,1.69)
VAT-DXA, L
XIV)
HR (95% CI) per SD of
LPDFF-MRI:
0.95 (0.70,1.29)
LPDFF-MRI, %
XV)
HR (95% CI) per SD of
TMFI-MRI:
1.38 (1.20,1.60)
TMFI-MRI, L

C) Breast


I)
HR (95% CI) per SD of BMI: 1.22 (1.05,1.42)
HR (95% CI)
BMI, kg/m²
II)
HR (95% CI) per SD of %BF: 1.22 (1.03,1.45)
%BF
III)
HR (95% CI) per SD of %BF-DXA: 1.34 (0.91,1.99)
%BF-DXA
IV)
HR (95% CI) per SD of TAT-MRI: 1.31 (0.98,1.77)
TAT-MRI, L
V)
HR (95% CI) per SD of TAT-DXA: 1.32 (0.92,1.89)
ATAT-DXA, kg
VI)
HR (95% CI) per SD of WC: 1.19 (1.02,1.40)
HR (95% CI)
WC, cm
VII)
HR (95% CI) per SD of WHR: 1.04 (0.82,1.32)
WHR
VIII)
HR (95% CI) per SD of ATAT-MRI: 1.23 (1.04,1.45)
ATAT-MRI, L
IX)
HR (95% CI) per SD of ATATI-MRI: 1.24 (1.04,1.47)
ATATI-MRI, L/m²
X)
HR (95% CI) per SD of ASAT-MRI: 1.22 (1.03,1.44)
ASAT-MRI, L
XI)
HR (95% CI) per SD of AFM-DXA: 1.37 (0.95,1.97)
HR (95% CI)
AFM-DXA, g
XII)
HR (95% CI) per SD of VAT-MRI: 1.22 (1.03,1.44)
VAT-MRI, L
XIII)
HR (95% CI) per SD of VAT-DXA: 1.34 (0.95,1.88)
VAT-DXA, L
XIV)
HR (95% CI) per SD of LPDFF-MRI: 1.13 (0.88,1.44)
LPDFF-MRI, %
XV)
HR (95% CI) per SD of TMFI-MRI: 1.13 (0.94,1.35)
TMFI-MRI, L

D) Prostate

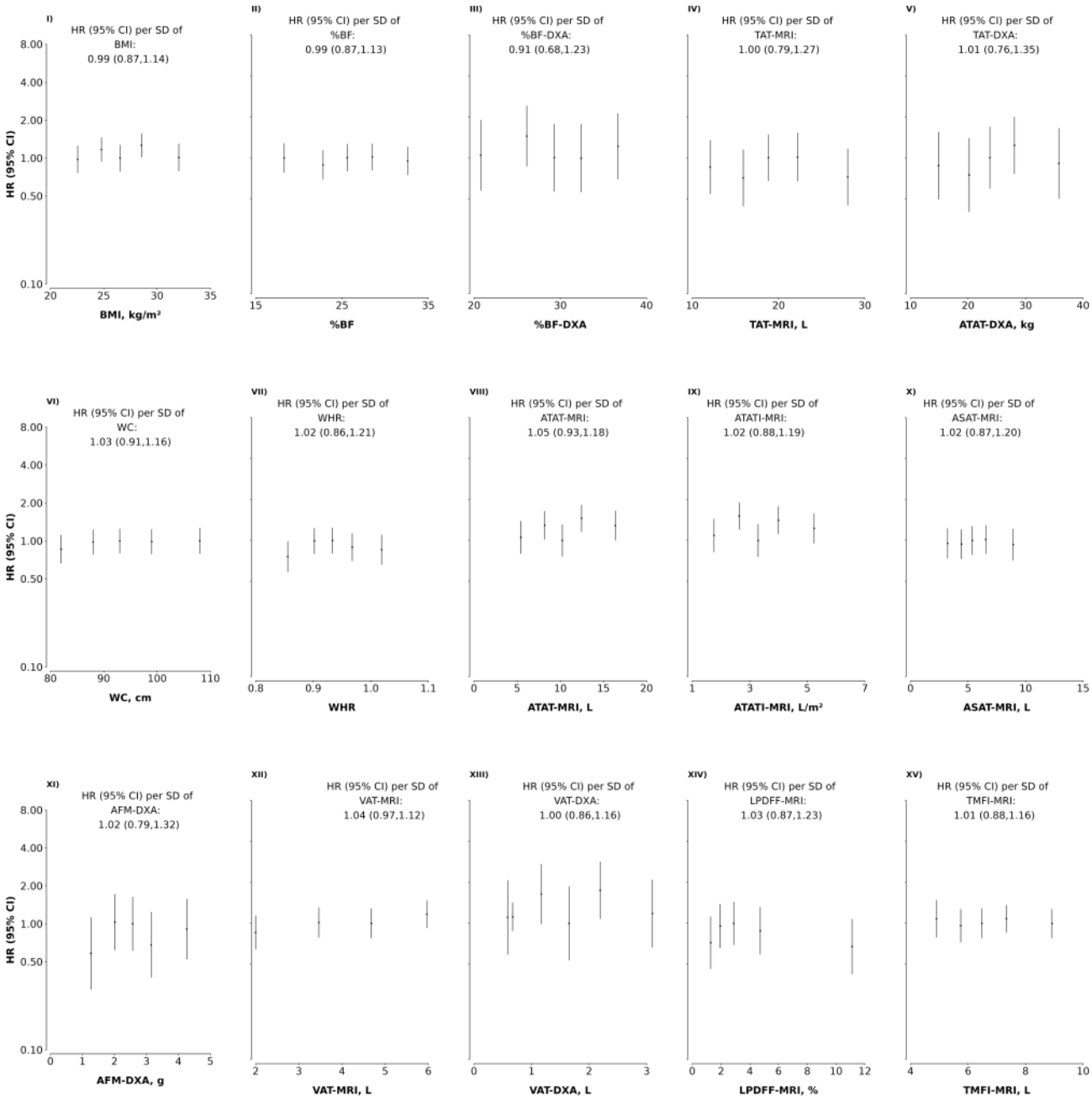

I)
HR (95% CI) per SD of
BMI:
0.99 (0.87,1.14)
HR (95% CI)
BMI, kg/m²
II)
HR (95% CI) per SD of
%BF:
0.99 (0.87,1.13)
%BF
III)
HR (95% CI) per SD of
%BF-DXA:
0.91 (0.68,1.23)
%BF-DXA
IV)
HR (95% CI) per SD of
TAT-MRI:
1.00 (0.79,1.27)
TAT-MRI, L
V)
HR (95% CI) per SD of
TAT-DXA:
1.01 (0.76,1.35)
ATAT-DXA, kg
VI)
HR (95% CI) per SD of
WC:
1.03 (0.91,1.16)
WC, cm
VII)
HR (95% CI) per SD of
WHR:
1.02 (0.86,1.21)
WHR
VIII)
HR (95% CI) per SD of
ATAT-MRI:
1.05 (0.93,1.18)
ATAT-MRI, L
IX)
HR (95% CI) per SD of
ATATI-MRI:
1.02 (0.88,1.19)
ATATI-MRI, L/m²
X)
HR (95% CI) per SD of
ASAT-MRI:
1.02 (0.87,1.20)
ASAT-MRI, L
XI)
HR (95% CI) per SD of
AFM-DXA:
1.02 (0.79,1.32)
AFM-DXA, g
XII)
HR (95% CI) per SD of
VAT-MRI:
1.04 (0.97,1.12)
VAT-MRI, L
XIII)
HR (95% CI) per SD of
VAT-DXA:
1.00 (0.86,1.16)
VAT-DXA, L
XIV)
HR (95% CI) per SD of
LPDFF-MRI:
1.03 (0.87,1.23)
LPDFF-MRI, %
XV)
HR (95% CI) per SD of
TMFI-MRI:
1.01 (0.88,1.16)
TMFI-MRI, L

Figure 5.3 Adjusted HRs for incidence of T2D and IHD per SD increase of adiposity traits

The plotted square denotes the estimated HR per SD of each of the adiposity traits from a multivariable Cox Hazards model adjusted for age, sex, smoking status, alcohol intake in drinks per week, education, fifths of Townsend Deprivation index score, and for women only the number of live births, menopause status, years since menopause, and use of MHT. The vertical line denotes the HR of 1. The size of the box is proportional to the inverse variance of the relevant log hazard ratio. The standard deviations for each adiposity measure are shown in Table 2.2.

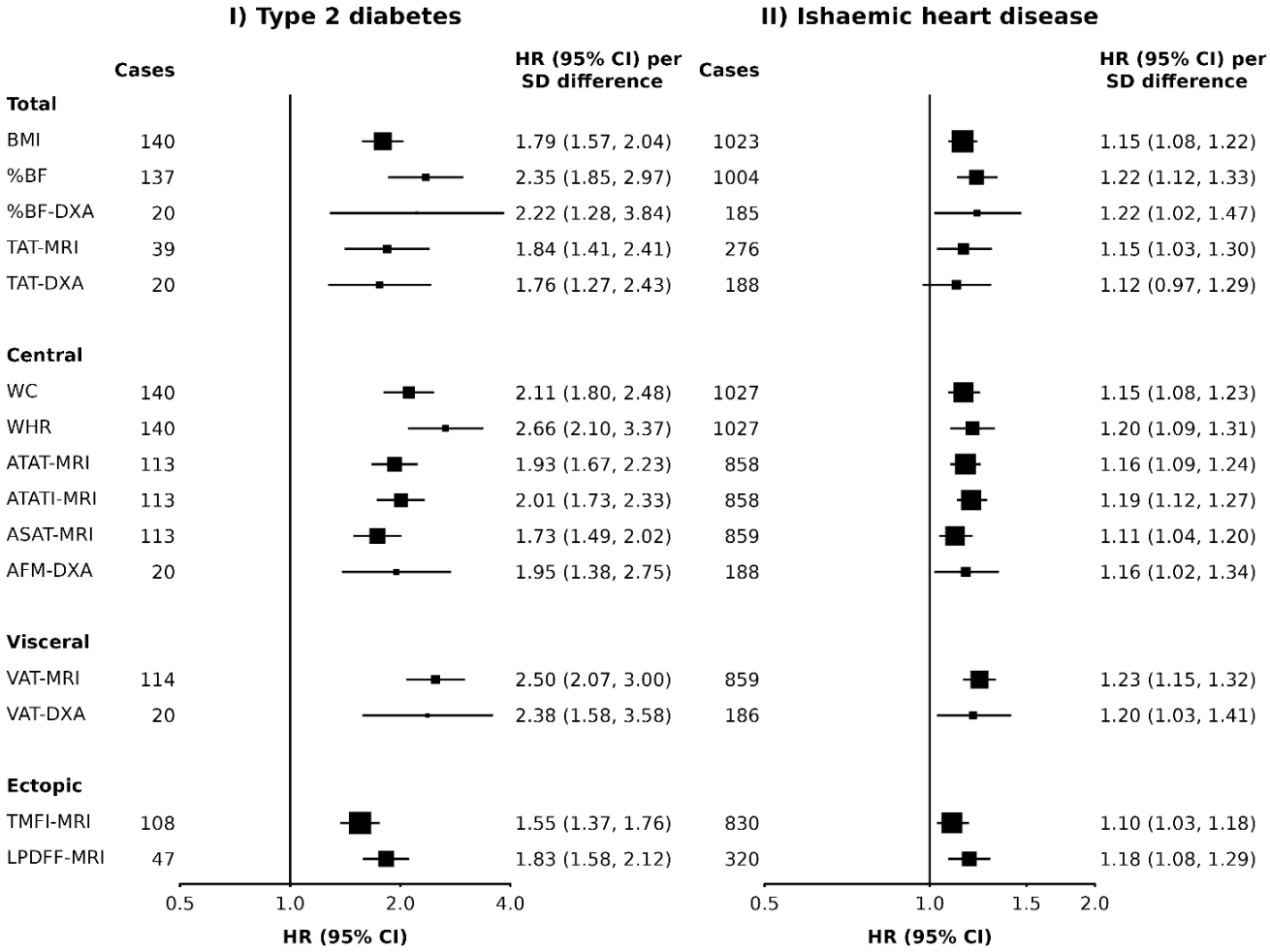


Figure 5.4 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits

Conventions as in Figure 5.3.

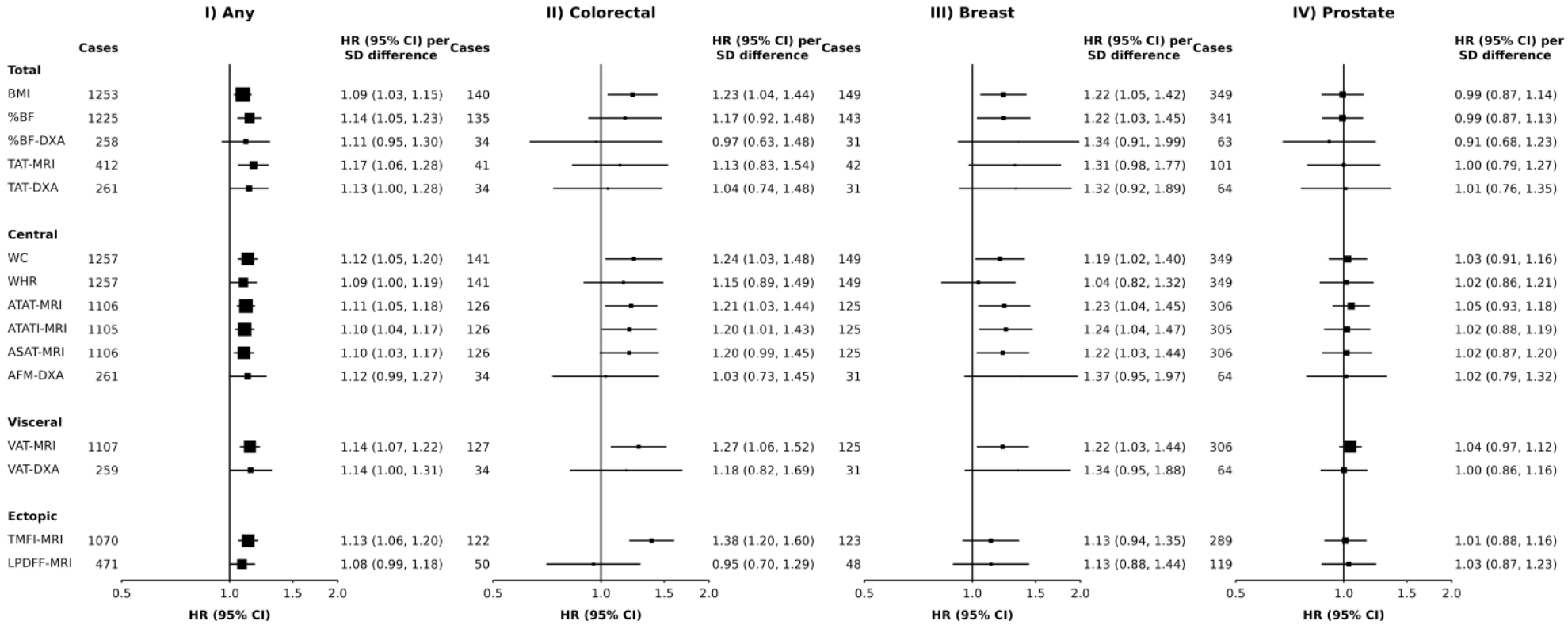
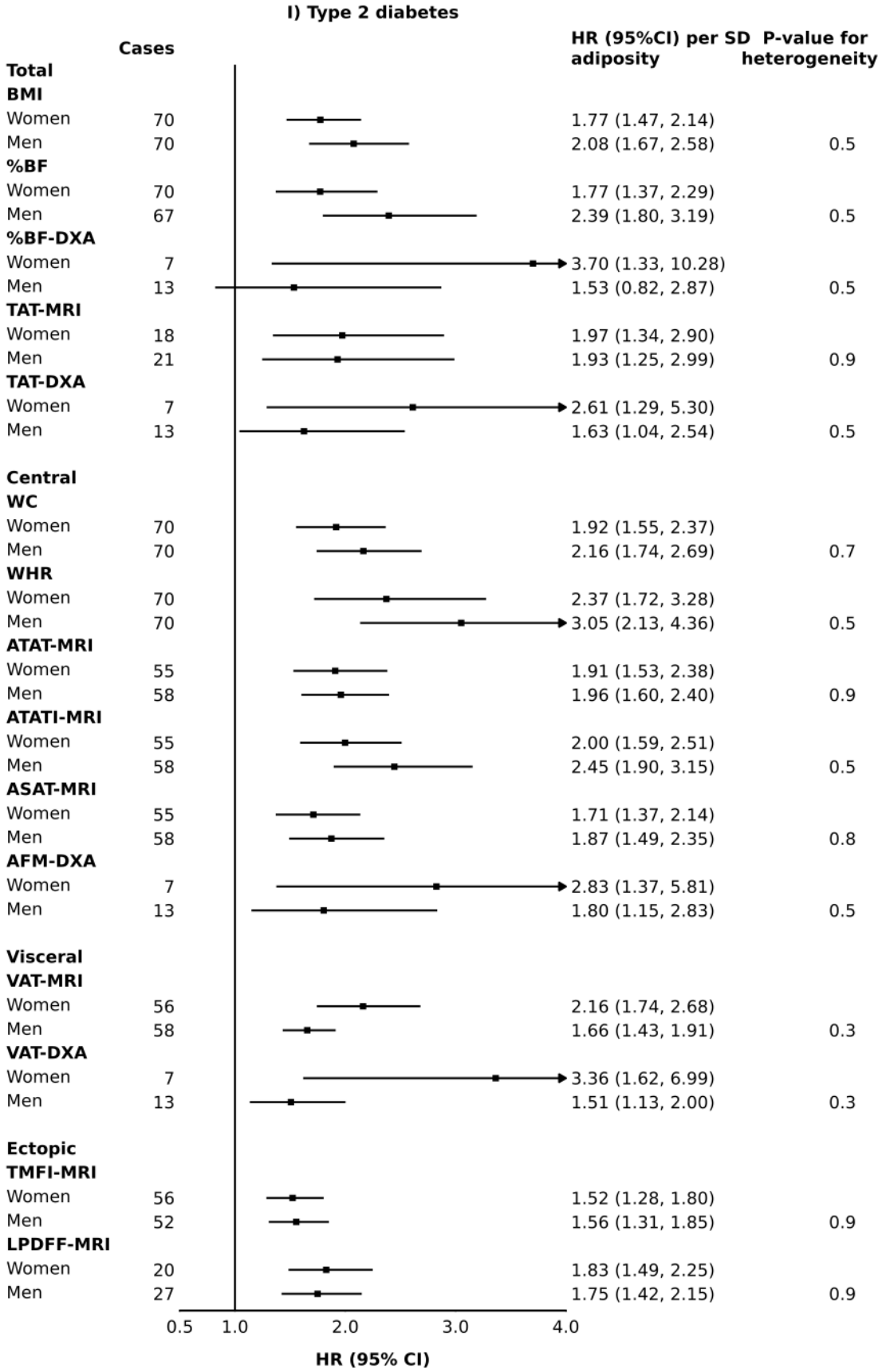


Figure 5.5 Sex-specific adjusted HRs for T2D and IHD per SD increase of adiposity traits

Conventions as in Figure 5.3. The standard deviations for each adiposity measure were sex-specific as shown in Table 2.2.



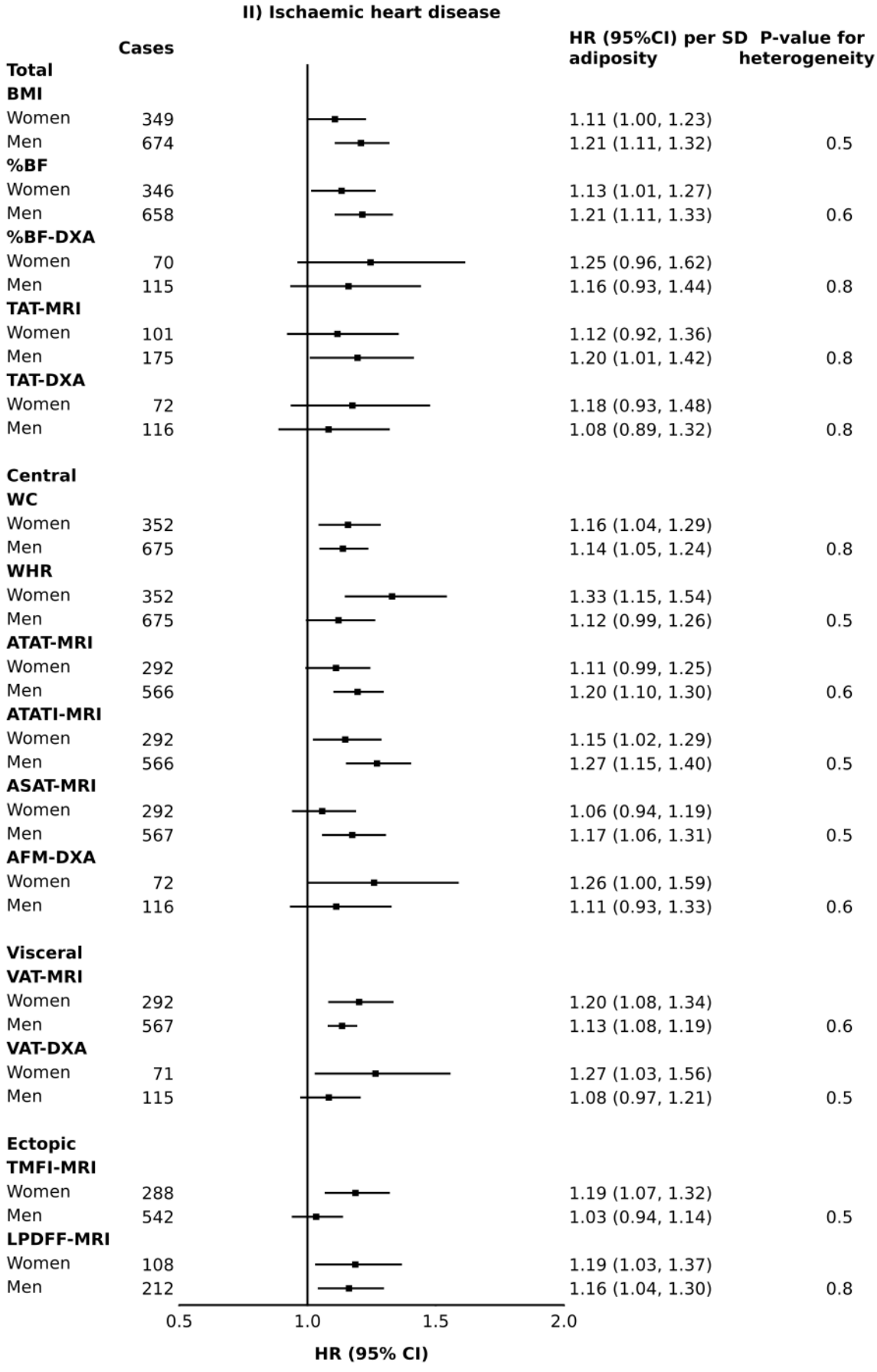
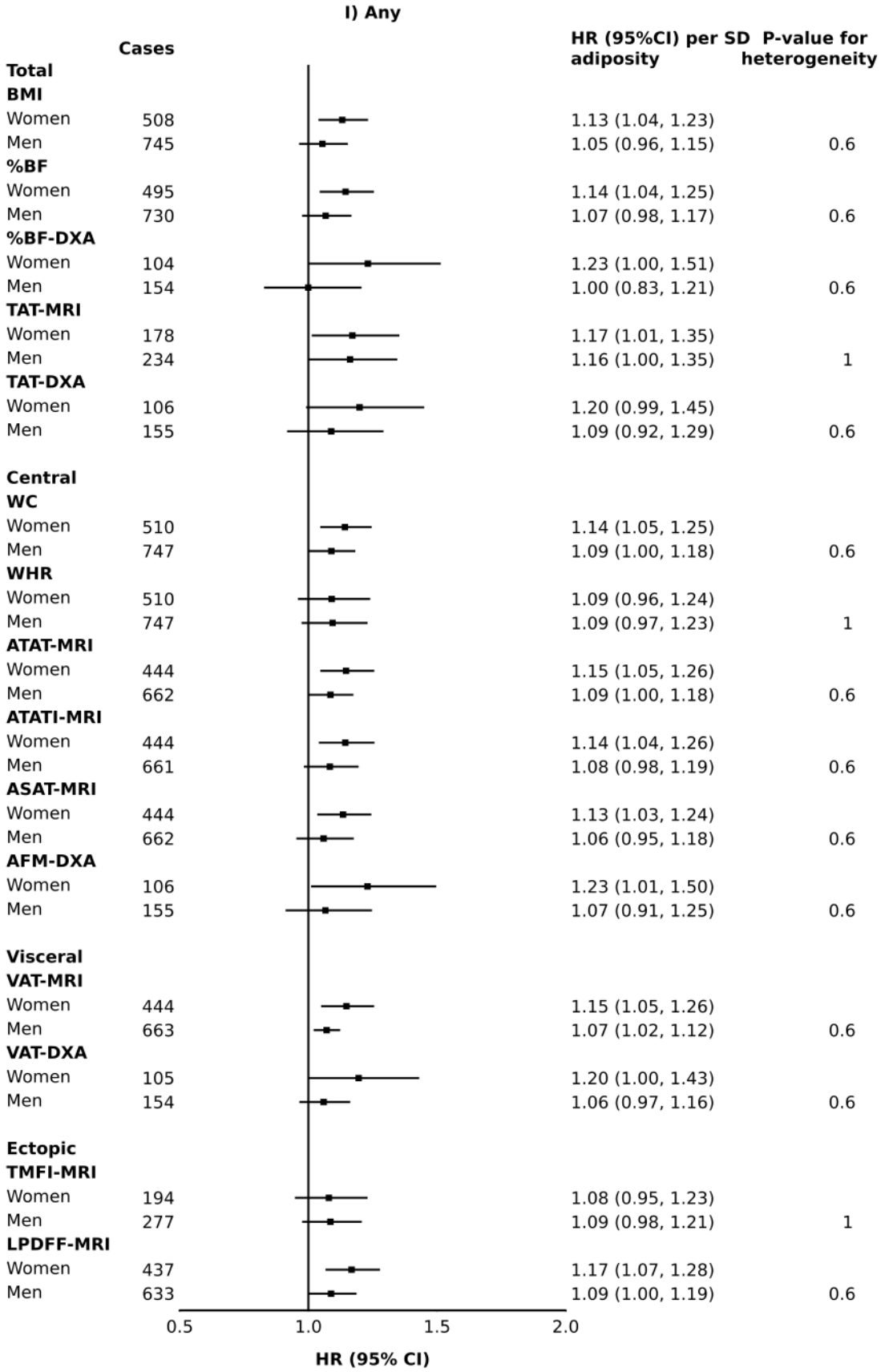

II) Ischaemic heart disease
Cases
HR (95%CI) per SD adiposity
P-value for heterogeneity
Total
BMI
Women 349 1.11 (1.00, 1.23)
Men 674 1.21 (1.11, 1.32) 0.5
%BF
Women 346 1.13 (1.01, 1.27)
Men 658 1.21 (1.11, 1.33) 0.6
%BF-DXA
Women 70 1.25 (0.96, 1.62)
Men 115 1.16 (0.93, 1.44) 0.8
TAT-MRI
Women 101 1.12 (0.92, 1.36)
Men 175 1.20 (1.01, 1.42) 0.8
TAT-DXA
Women 72 1.18 (0.93, 1.48)
Men 116 1.08 (0.89, 1.32) 0.8
Central
WC
Women 352 1.16 (1.04, 1.29)
Men 675 1.14 (1.05, 1.24) 0.8
WHR
Women 352 1.33 (1.15, 1.54)
Men 675 1.12 (0.99, 1.26) 0.5
ATAT-MRI
Women 292 1.11 (0.99, 1.25)
Men 566 1.20 (1.10, 1.30) 0.6
ATATI-MRI
Women 292 1.15 (1.02, 1.29)
Men 566 1.27 (1.15, 1.40) 0.5
ASAT-MRI
Women 292 1.06 (0.94, 1.19)
Men 567 1.17 (1.06, 1.31) 0.5
AFM-DXA
Women 72 1.26 (1.00, 1.59)
Men 116 1.11 (0.93, 1.33) 0.6
Visceral
VAT-MRI
Women 292 1.20 (1.08, 1.34)
Men 567 1.13 (1.08, 1.19) 0.6
VAT-DXA
Women 71 1.27 (1.03, 1.56)
Men 115 1.08 (0.97, 1.21) 0.5
Ectopic
TMFI-MRI
Women 288 1.19 (1.07, 1.32)
Men 542 1.03 (0.94, 1.14) 0.5
LPDFF-MRI
Women 108 1.19 (1.03, 1.37)
Men 212 1.16 (1.04, 1.30) 0.8
0.5
1.0
1.5
2.0
HR (95% CI)

Figure 5.6 Sex-specific adjusted HRs for incidence of total and colorectal cancer per SD increase of adiposity traits

Conventions as in Figure 5.3.



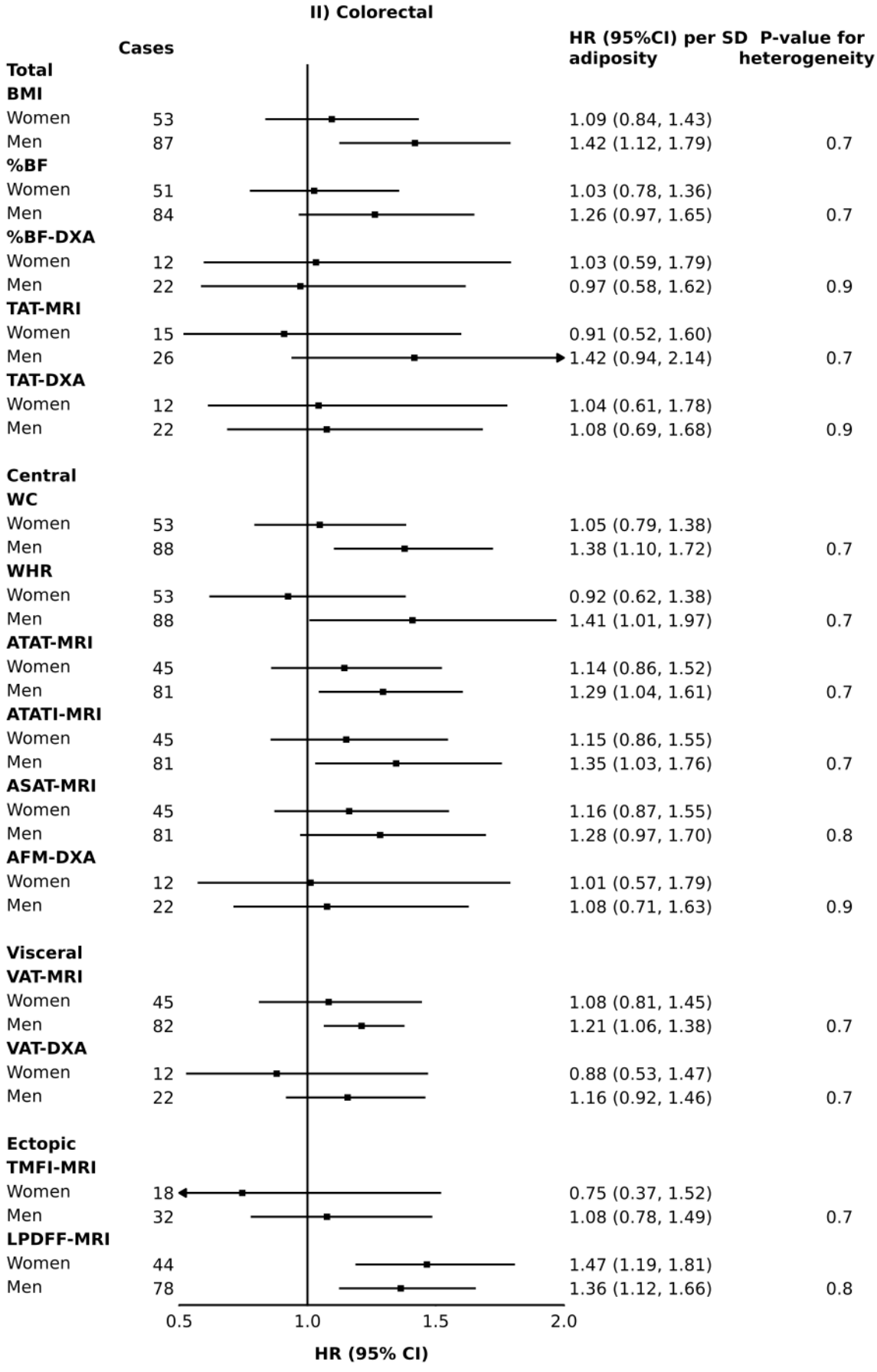

II) Colorectal
Cases
HR (95%CI) per SD adiposity
P-value for heterogeneity
Total
BMI
Women 53 1.09 (0.84, 1.43)
Men 87 1.42 (1.12, 1.79) 0.7
%BF
Women 51 1.03 (0.78, 1.36)
Men 84 1.26 (0.97, 1.65) 0.7
%BF-DXA
Women 12 1.03 (0.59, 1.79)
Men 22 0.97 (0.58, 1.62) 0.9
TAT-MRI
Women 15 0.91 (0.52, 1.60)
Men 26 1.42 (0.94, 2.14) 0.7
TAT-DXA
Women 12 1.04 (0.61, 1.78)
Men 22 1.08 (0.69, 1.68) 0.9
Central
WC
Women 53 1.05 (0.79, 1.38)
Men 88 1.38 (1.10, 1.72) 0.7
WHR
Women 53 0.92 (0.62, 1.38)
Men 88 1.41 (1.01, 1.97) 0.7
ATAT-MRI
Women 45 1.14 (0.86, 1.52)
Men 81 1.29 (1.04, 1.61) 0.7
ATATI-MRI
Women 45 1.15 (0.86, 1.55)
Men 81 1.35 (1.03, 1.76) 0.7
ASAT-MRI
Women 45 1.16 (0.87, 1.55)
Men 81 1.28 (0.97, 1.70) 0.8
AFM-DXA
Women 12 1.01 (0.57, 1.79)
Men 22 1.08 (0.71, 1.63) 0.9
Visceral
VAT-MRI
Women 45 1.08 (0.81, 1.45)
Men 82 1.21 (1.06, 1.38) 0.7
VAT-DXA
Women 12 0.88 (0.53, 1.47)
Men 22 1.16 (0.92, 1.46) 0.7
Ectopic
TMFI-MRI
Women 18 0.75 (0.37, 1.52)
Men 32 1.08 (0.78, 1.49) 0.7
LPDFF-MRI
Women 44 1.47 (1.19, 1.81)
Men 78 1.36 (1.12, 1.66) 0.8
0.5
1.0
1.5
2.0
HR (95% CI)

Figure 5.7 Adjusted HRs for incidence of T2D and IHD per SD increase of adiposity traits after excluding those participants with less than 3 years of follow-up

Conventions as in Figure 5.3.

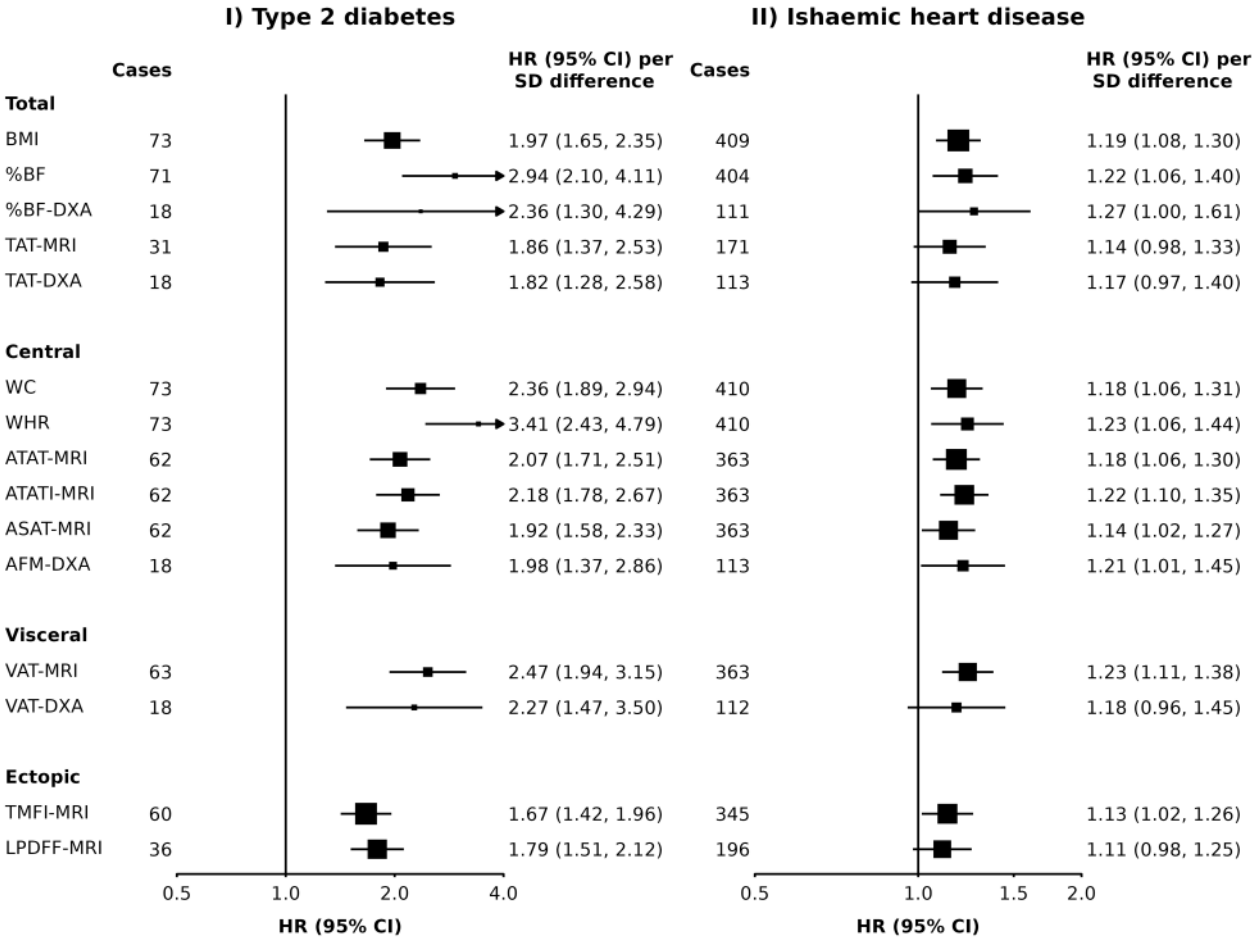
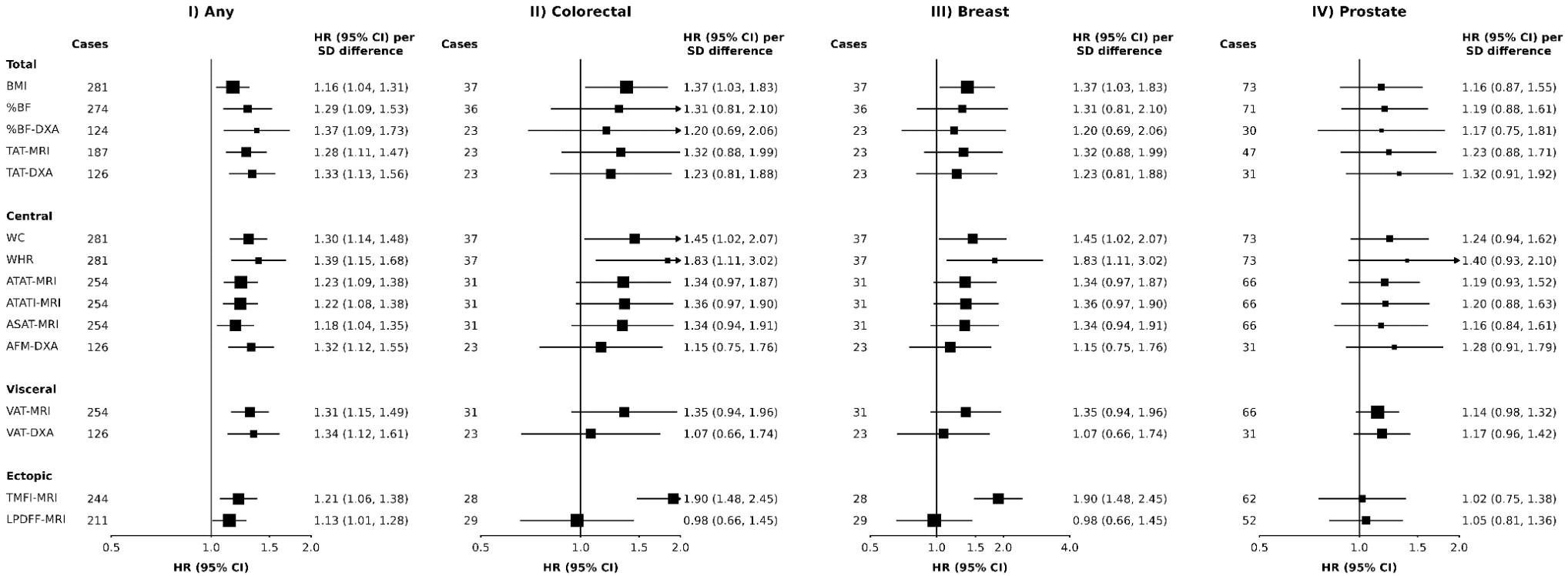


Figure 5.8 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits after excluding those participants with less than 3 years of follow-up

Conventions as in Figure 5.3.



Chapter 6. Associations of different body fat components with cancer risks: findings from the entire UK Biobank

6.1 Background

In Chapter 5 all body fat components were found to be positively associated with the risks of colorectal cancer, breast cancer and all cancers combined but not with prostate cancer. However, as the analyses were limited to the 64,025 participants of the UKB imaging sub-cohort, there was a relatively small number of cancer cases and a short follow-up period, limiting the power to detect any modest associations reliably and most importantly to detect differences in the size of associations by body fat component.

To address these limitations, Chapter 6 expands the analysis to the entire UKB baseline cohort of 0.5 million participants, to investigate whether specific imaging-based body fat components, such as visceral or ectopic adiposity, are more strongly associated with cancer risk than total or central adiposity. Specifically, Chapter 6 will use information collected in the imaging sub-cohort to “impute” the median adiposity traits derived from anthropometric and imaging methods within baseline BMI and WC deciles across the entire cohort. Moreover, the range of site-specific cancers examined will be further expanded.

6.2 Methods

The UKB study population and data collection are described in detail in Section 2.1. Baseline BMI and WC were measured by a trained professional (see section 2.2.1). BMI and WC were selected as the anthropometric variables of interest here because

Chapters 4 and 5 showed that %BF and WHR had similar magnitudes of association with BMI and WC.

6.2.1 Disease endpoints

The endpoints of interest here were all cancer (ICD-10: C00-C26, C30-C41, C43, C45-C97), and selected site-specific cancers, including colorectal cancer (C18-C20); oesophageal adenocarcinoma (C15 and International Classification of Diseases of Oncology [ICD-O]: 8140, 8144, 8145, 8480, 8481, 8490); OSCC (C15 and ICD-O: 8070, 8071, 8072, 8073); liver cancer (C22); prostate cancer (C61); breast cancer (C50); and endometrial cancer (C54). These outcome data were obtained through electronic linkages with national cancer registries. These cancer endpoints were chosen based on prior evidence of associations with adiposity and/or the availability of a large number of cases (at least 300 cases), enhancing the statistical power and robustness of the analyses. Death was obtained through linkage to the UK national death registries.

Participants contributed person-years from baseline until death, loss to follow-up, end of follow-up, or first occurrence of relevant cancer outcome (excluding non-melanoma skin cancer, ICD-10: C44), whichever came first. In the present analyses, the end of follow-up for all the cancer outcomes was 31 December 2020 for England, 30 November 2021 for Scotland, and 31 December 2016 for Wales.

Participants with a relevant prior cancer diagnosis at baseline for each site-specific cancer (excluding non-melanoma skin cancer, ICD-10: C44) were excluded. For breast cancer, the analyses were restricted to postmenopausal women, and never MHT users. For endometrial cancer, the analysis was restricted to women who never had a hysterectomy and were never MHT users.

6.2.2 Estimation of adiposity traits

MRI-derived adiposity traits were only available for participants in the imaging sub-cohort. To estimate adiposity traits at baseline, a method analogous to a calibration study was applied. The following steps were taken:

1. All UKB participants were categorised into deciles according to BMI measured at baseline.
2. Within each BMI decile, the median value of each adiposity trait of interest (BMI and MRI-derived) was calculated per SD among participants who attended the imaging visit
3. The median values in (2) were assigned to each decile and treated as a continuous variable in order to estimate the trend in disease risk in relation to each adiposity trait of interest

Furthermore, steps 1-3 were repeated with participants categorised according to WC deciles measured at baseline. This approach will be referred to as the “imputed category median” method.

MRI-derived adiposity traits were included in this study and not the DXA-derived, as the latter had fewer processed traits available at the imaging visit compared to MRI (**Figure 2.1**).

Section 2.6.3 examined whether participants in the imaging sub-cohort differed from the entire baseline UKB cohort with respect to characteristics measured at baseline. It was concluded that, overall, individuals in the imaging sub-cohort were slightly younger, more educated, more likely to consume alcohol, and were less likely to be postmenopausal compared to the entire cohort, suggesting potential selection bias.

Additionally, participants in the imaging sub-cohort exhibited slightly lower mean values of adiposity traits, indicating that those selected for imaging may represent a somewhat healthier subgroup in terms of body fat distribution. However, characteristics by BMI classification (according to the WHO definition of obesity) for the entire and the imaging sub-cohort showed the distribution of anthropometric adiposity traits was comparable between the entire and the imaging sub-cohort (**Table 6.1** and **Table 6.2** overall; **Table A.1** - **Table A.4** sex-specific). Further analyses predicting BMI and WC, adjusted for age, sex, ancestry, and education level, confirmed that their distributions remained comparable across cohorts.

As the imaging visit occurred on average 10 years after recruitment, it was essential to assess whether the measures of adiposity may change over time during follow-up. For example, given that BMI may change throughout the follow-up the approach used here incorporated the median adiposity value from approximately two-thirds through follow-up, thereby accounting for potential real changes in adiposity.

The number of participants with adiposity traits available at imaging visits within BMI and WC deciles measured at baseline were tabulated**.**

6.2.3 Statistical analyses

Cox proportional hazard models were fitted to estimate HRs of the selected cancer outcomes by the imputed category median of adiposity trait (estimated as described in 6.2.2) treated as a categorical variable, with variances and 95% CI estimated using the floating absolute risk method (216). Since the associations were approximately linear (with the only exception of liver cancer which had a J-shape), the HRs were further estimated for specific cancers associated with a 1-SD increase in each imputed category median of adiposity trait treated on a continuous scale,

overall and by sex. The SDs were derived from the imaging sub-cohort, as shown in **Table 2.2**, with sex-specific SDs applied for sex-specific analyses. A heterogeneity test was used to compare women and men, with false discovery rate correction applied to account for multiple comparisons for each cancer outcome. A complete case analysis was applied for each model, meaning that only participants with complete data for all relevant variables were included.

All Cox models were adjusted for baseline age (in 5-year groups), sex, smoking status (never, previous, current), alcohol intake (0, 1, 2, ≥3 drinks/week), education level (college/university degree, A levels/AS levels or equivalent, O levels/GCSEs, CSEs, NVQ/HND/HNC, other professional qualifications, none of the above), deprivation (quintiles of the Townsend deprivation index), and, where relevant, reproductive factors such as number of live births, menopause status (yes, no, hysterectomy), years since menopause, and use of MHT (current, past, never). Forest plots were used to summarise the HRs with the corresponding CI, with the corresponding boxes representing the sample of participants available for each Cox model across each cancer outcome.

Further analysis was done on the association of adiposity traits directly measured at baseline with cancer risks. At baseline only anthropometric adiposity was available and here analyses included BMI and WC. Cox models were fitted to estimate HRs for the selected site-specific cancers per 1-SD increase in the median adiposity trait within each BMI and WC decile at baseline, treating the adiposity trait as a continuous variable.

To address potential biases, various sensitivity analyses were conducted. Firstly, the analysis was repeated after excluding the first 5 years of follow-up to investigate the

presence of reverse causation, as preclinical disease symptoms may lead to weight loss (19). Secondly, the analysis was performed in the cohort of participants who participated in the imaging sub-cohort to investigate potential biases related to the method used to assign MRI-derived adiposity traits. Thirdly, as only BMI and WC were available at the baseline visit, the analysis was performed using these measures to enable comparison with the estimates obtained when BMI and WC were imputed.

6.3 Results

Overall, there was a sufficient number of adiposity traits at the imaging sub-cohort within deciles of BMI and WC at baseline. This allowed adequate statistical power to estimate the imputed category medians of adiposity traits (**Table A.5** to **Table A.10**).

6.3.1 Association of body fat components with cancer risk

After applying exclusions, during an average of 12 years of follow-up, the main analysis included a total of 49,579 cancer cases, 5,921 colorectal cancers, 712 oesophageal adenocarcinomas, 306 OSCC, 649 liver cancers, 11,264 prostate cancers, 2,787 breast cancers, and 958 endometrial cancers.

Overall, all body fat components had a strong positive association of a log-linear shape with risks of colorectal cancer, oesophageal adenocarcinoma, breast cancer, endometrial cancer and all cancers combined, while the association had a positive J-shape with liver cancer (**Figure A.1** and **Figure A.2**). Also, there were differences in the strength of the associations with measures of liver adiposity having the greatest magnitude of associations with cancer risk, compared to metrics representing total, central or visceral adiposity, especially for liver and endometrial cancer. In contrast,

the association was strongly negative with OSCC and slightly negative with prostate cancer (**Figure 6.1**).

For endometrial cancer the adjusted HRs per SD of liver adiposity (i.e. LPDFF-MRI) were 12.88 (95%CI: 10.05-16.51) of a greater magnitude, compared to those for thigh muscle fat (TMFI-MRI: 3.43 [3.03-3.88]), visceral (VAT-MRI: 2.32 [2.13-2.53]), central (ATAT-MRI 1.98 [1.85-2.12]) and total adiposity (BMI: 1.90 [1.78-2.02]).

Similarly, for liver cancer, the adjusted HRs associated per SD of liver adiposity (LPDFF-MRI: 3.07 [2.35-4.00]) were of a greater magnitude than for measures of total (BMI: 1.41 [1.29-1.53]), central (ATAT-MRI: 1.44 [1.32-1.58]) and visceral (VAT-MRI: 1.58 [1.38-1.81]) adiposity.

For oesophageal adenocarcinoma, the adjusted HRs associated per SD of liver adiposity (LPDFF-MRI: 3.11 [2.41-4.02]) were greater than total (BMI: 1.45 [1.34-1.58]), central (ATAT-MRI: 1.50 [1.37-1.64]), and visceral adiposity (VAT-MRI: 1.82 [1.59-2.09]). In contrast, OSCC showed a strong negative association with increased adiposity, with consistent HRs per SD increase across different adiposity traits (e.g. BMI: 0.71 [0.61-0.81]; ATAT-MRI: 0.69 [0.59-0.80]; VAT-MRI: 0.61 [0.51-0.74]; LPDFF-MRI: 0.35 [0.22-0.56])

Furthermore, there was a 37% (LPDFF-MRI: 1.37 [1.24-1.50]) increase in colorectal cancer risk per SD higher liver adiposity, greater than the HRs associated with total (BMI: 1.11 [1.07-1.14]), central (ATAT-MRI: 1.11 [1.08-1.15]) or visceral adiposity (VAT-MRI: 1.16 [1.11-1.21]). Similarly, for breast cancer, the adjusted HRs associated per SD increase of liver adiposity (LPDFF-MRI: 1.77 [1.57-1.99]) were also greater than those for markers of total (BMI: 1.17 [1.13-1.20]), central (ATAT-MRI: 1.18 [1.14-1.22]) and visceral adiposity (VAT-MRI: 1.21 [1.17-1.26]).

In contrast, for prostate cancer, the association was weakly negative and showed little variation across body fat components. For example, the adjusted HRs per SD increase in liver adiposity (LPDFF-MRI: 0.86 [0.81,0.91]) were slightly more inverse compared to those markers of total (BMI: 0.95 [0.93-0.97]), central (ATAT-MRI: 0.95 [0.92-0.97]) and visceral adiposity (VAT-MRI: 0.95 [0.92-0.97]).

Finally, for all cancers combined there was a 25% increase in HRs associated with SD increase in liver adiposity (LPDFF-MRI: 1.25 [1.21-1.29]), which was comparable to thigh muscle fat (TMFI-MRI: 1.16 [1.13-1.18]), and greater than the HRs associated with total (BMI: 1.07 [1.06-1.08]), central (ATAT-MRI: 1.08 [1.07-1.09]) or visceral (VAT-MRI: 1.10 [1.09-1.12]) adiposity.

The analyses of the associations of BMI, as measured directly at baseline vs. the imputed category median method (**Figure 6.9**), showed that the magnitude of the associations was of similar strength. However, for endometrial cancer, the associations were somewhat of a weaker magnitude when measured with BMI directly at baseline (i.e. 1.66 [1.59-1.73] vs. 1.90 [1.78-2.02]).

6.3.2 Sex-specific analyses

For certain cancers, sex differences were observed in their associations with body fat components, as demonstrated by heterogeneity p-values less than 0.05 as shown in **Figure 6.2**.

For colorectal cancer and liver cancer, the HRs of most adiposity traits per SD increase were greater in men than in women (i.e. VAT-MRI: 1.20 [1.15-1.26] vs.1.05 [1.00-1.11] for colorectal cancer; and 1.75 [1.53-2.00] vs. 1.20 [0.99-1.45] for liver cancer). Similarly, a greater reduction in the risk of OSCC risk was found in men

than in women per SD increase of adiposity (i.e. LPDFF-MRI: 0.11 [0.05-0.27] vs. 0.84 [0.49-1.44]).

However, the opposite trend was observed for all cancers combined and oesophageal adenocarcinoma. For example, women had a greater association than men for each SD increase in VAT-MRI with the risk of all cancers combined risk of 1.14 (1.12-1.16) vs. 1.05 (1.03-1.07).

For oesophageal adenocarcinoma, no evidence of a difference between women and men in the disease risk with different adiposity traits was found.

Trends in risks per SD increase in adiposity traits, assigned based on WC deciles were comparable to those based on BMI (**Figure 6.3, Figure 6.4** and **Figure 6.9)**.

6.3.3 Sensitivity analyses

Firstly, excluding the first 5 years of follow-up resulted in the following number of cases for each cancer type: 30,3331 of all cancers combined, 3,485 of colorectal cancer, 472 oesophageal adenocarcinomas, 214 OSCC, 656 of liver cancer, 6,987 of prostate cancer, 1,574 of breast cancer and 565 of endometrial cancer. The exclusion of the first 5 years of follow-up showed associations of similar magnitude as found in the main analysis (**Figure 6.5** and **Figure 6.6**). For example, for endometrial cancer the adjusted HRs per SD of liver adiposity (LPDFF-MRI) were 16.00 (11.60-22.07) of a greater magnitude, compared to those for thigh muscle fat (TMFI-MRI: 3.81 [3.24-4.47]), visceral (VAT-MRI: 2.50 [2.24-2.80]), central (ATAT-MRI 2.10 [1.92-2.30]) and total adiposity (BMI: 2.00 [1.85-2.18]).

Secondly, the secondary analysis of those participants who participated in the imaging sub-cohort resulted in the following number of cases: 4,103 for all cancers combined, 234 for colorectal cancer, 21 for oesophageal adenocarcinomas, 11 for OSCC, 17 for liver cancer, 1,410 for prostate cancer, 253 for breast cancer and 93 for endometrial cancer. The analysis of those participants in the imaging sub-cohort showed associations of similar magnitude as found in the main analysis (**Figure 6.7** and **Figure 6.8**). For example, for endometrial the adjusted HRs per SD of liver adiposity (LPDFF-MRI) were 9.64 (4.26-21.84) of a greater magnitude, compared to those for thigh muscle fat (TMFI-MRI: 2.82 [1.89-4.18]), visceral (VAT-MRI: 2.01 [1.53-2.64]), central (ATAT-MRI 1.78 [1.43-2.21]) and total adiposity (BMI: 1.73 [1.41-2.13]).

6.4 Discussion

In this large-scale analysis of the entire cohort of 0.5 million UKB participants, greater adiposity was positively associated with an increased risk of most cancers, with ectopic liver adiposity showing the greatest magnitude of association, particularly for endometrial cancer and liver cancer. While all adiposity traits showed a clear positive association with most cancers, the association with OSCC was strongly negative, and with prostate cancer, it was slightly negative, with no clear differences between adiposity traits. Additionally, sex-specific differences were observed in the associations between adiposity traits and the risks of all cancers combined colorectal cancer and oesophageal cancer.

6.4.1 Digestive system cancers

The positive association between excess adiposity and colorectal cancer is well-established (26, 31), with the majority of the evidence coming from studies

measuring total or central adiposity with anthropometric methods. No studies have examined the association of different body fat components with colorectal cancer risk within the same cohort, not allowing direct comparisons with the present findings.

In line with the findings here a large meta-analysis of 5 million individuals from 30 studies, involving 44,777 colorectal cancer cases, found that an increase in BMI and WC had a similar magnitude of association with colorectal cancer risk (221). The HRs were 1.30 (1.25-1.35) per 5 kg/m^2 BMI in men and 1.12 (1.07-1.35) in women; and 1.33 (1.19-1.49) per 10 cm WC in men and 1.16 (1.09-1.23) in women (221). Although the HRs above were overall consistent with the results found here, the HR for BMI increase in men was slightly lower in the analysis presented here of 1.17 (1.12-1.22) per 5 kg/m^2. Consistent with the findings here a study of 0.5 million Chinese involving 3,024 cases of colorectal cancer found that increases in BMI and WC had a positive association with colorectal cancer risk of a similar magnitude (HR: 1.20 [1.10-1.28] per 5 kg/m^2 and 1.18 [1.07-1.18] per 10 cm respectively) (222).

Evidence from MR studies suggests that this positive association is likely causal. An MR study of 58,221 colorectal cancer cases found that a 5 kg/m^2 increase in genetically predicted BMI (based on 312 SNPs) was associated with increased odds of colorectal cancer in men and of a similar magnitude in women (OR: 1.27 95% CI: [1.09-1.47] per 5 kg/m^2 in men vs. 1.08 [0.97-1.21] in women) (69).

Regarding liver cancer, there is sufficient evidence in the epidemiological literature to suggest a positive association between excess adiposity measured with anthropometric methods and liver cancer risk (26, 31). However, no studies have been found measuring the association of different body fat components in the same

cohort of participants with liver cancer risk to allow comparisons with the findings here.

In line with results here, a study of 1.57 million White participants involving 2,162 liver cancer cases reported that increases in both BMI (HR: 1.38 [1.30–1.46] per 5 kg/m² in men and 1.25 [1.17–1.35] in women) and WC (HR: 1.16 [1.08–1.28] per 10 cm in both sexes) were associated with a similar magnitude of an association with risk of liver cancer (223). Furthermore, consistent with the findings here the association between BMI and liver cancer risk in the above study had a J-shape.

By contrast, a study of 0.5 million Chinese participants, involving 2,847 liver cancer cases, observed weaker associations to findings here, reporting an HR of 1.04 (0.95–1.15) per 5 kg/m² BMI and 1.09 (1.01–1.18) per 10 cm WC (224). The greater risk of liver cancer in Western populations compared to Chinese may be explained by different aetiology of liver cancer. Particularly, in Western populations metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol consumption are the main risk factors for liver cancer, while in East Asia and particularly China, the main risk factor is hepatitis B virus (225). This may suggest that the relative increase due to adiposity is smaller in the Chinese compared with the Western populations. Furthermore, the greater risk of liver cancer in the Western population may be due to a greater prevalence of physical inactivity which may change the association of central adiposity with liver cancer risk (226). However, here this was not possible to investigate due to a lack of Chinese individuals to analyse.

Evidence from MR studies suggests that the association between excess adiposity and liver cancer is most likely causal. An MR study of 400,000 UKB participants reported that an SD (was not reported) increase in each of the genetically predicted

BMI and WC (based on 458 and 374 SNPs respectively) was associated with similar OR for liver cancer of 1.67 (1.18-2.37) and 1.78 (1.18-2.37) respectively (227).

6.4.2 Hormone-related cancers

There is sufficient evidence in the epidemiological literature to suggest a positive association between increased adiposity and endometrial cancer (26, 31) with the evidence coming from studies assessing adiposity with anthropometric methods. There is a lack of studies measuring different body fat components with a combination of anthropometric and imaging methods in the same cohort of participants to allow comparison with the findings here.

In agreement with the findings presented here, a study of 135,110 women from the UKB involving 706 endometrial cancer cases found associations of both BMI and WC (HR: 1.70 [1.60-1.81] per 5 kg/m^2 and 1.80 [1.67-1.94] per 10 cm respectively) with endometrial cancer risk, of a similar magnitude (228). Similarly to the findings here, a large meta-analysis of 30 prospective studies, including over 6 million women (22,320 endometrial cancer cases), reported a positive association between BMI and WC with the risk of endometrial cancer increase of a similar magnitude (75). The association of a 10 cm increase in WC had an HR of 1.27 (1.17-1.39) of a similar magnitude to what found here (HR: 1.48 [1.36-1.61] per 10 cm), but a 5 kg/m^2 increase in BMI had an HR of 1.54 (1.47-1.61) of a slightly weaker magnitude to findings here (HR:1.90 [1.78-2.02]). Further analysis conducted here which used the direct measure of BMI at baseline had an association with endometrial cancer of a similar magnitude to the meta-analysis reported above (HR: 1.66 [1.59-1.73] per 5 kg/m^2). This may suggest that the imputed category median adiposity traits used in this chapter to assess the HRs may somewhat overestimate the actual endometrial

cancer risk. However, the same cannot be concluded for other cancer-specific site risks as the CI of the associations overlapped between the direct measures of BMI and WC at baseline vs. the imputed category medians.

Evidence from MR studies suggests that the association between excess adiposity and endometrial cancer is more likely causal. For example, a meta-analysis of 3 MR studies, involving 13,959 endometrial cancer cases found a strong association between genetically predicted BMI (based on 74 to 312 SNPs) and endometrial cancer risk, with HR of 1.49 (1.38-1.61) per 5 kg/m^2 (72), which aligns with findings here regarding the direct measurement of BMI.

There is a clear positive association in the published literature between excess adiposity and breast cancer in postmenopausal women (26, 31). However, existing evidence is largely based on studies using anthropometric measures of adiposity, with no studies identified that have examined the associations of different body fat components with breast cancer risk, limiting direct comparisons with the present findings. Consistent with the findings here a study of 1.2 million women in the UK, involving 5,629 breast cancer cases found that breast cancer incidence in postmenopausal women had an HR of 1.18 (1.14-1.22) per 5 kg/m^2 (65). Similarly to here, a UKB study of 126,691 postmenopausal women, involving 2,913 breast cancer cases found a positive increase in each of total and central adiposity with an HR of 1.21 (1.15-1.27) per 5 kg/m^2 BMI and 1.10 (1.08-1.19) per 10 cm WC respectively (73).

The evidence on the association between excess adiposity and prostate cancer is considered limited (26, 31). However, there is some evidence of studies investigating the association of excess adiposity with advanced prostate cancer or prostate cancer

mortality (26, 105). These studies have used anthropometric methods to assess adiposity and no studies were found comparing the associations of different body fat components with advanced prostate cancer or prostate cancer mortality. Consistent with the findings here, a published study of 218,237 men from the UKB, involving 661deaths due to prostate cancer cases reported that a 5 kg/m^2 increase in BMI had an HR of 1.00 (0.94 -1.08), and a 10 cm increase in WC with HR of 1.06 (0.99-1.14) for prostate cancer mortality (105). In contrast to the findings here, a meta-analysis of 19 cohort studies, involving 19,633 prostate cancer deaths for BMI and 3,181 for WC found an HR of prostate cancer death of 1.10 (1.07-1.12) per 5 kg/m^2 increase in BMI, and no evidence of an association with WC (i.e. HR: 1.06 [0.99-1.14] per 10 cm) (105). Although the findings here contrast with some of the studies mentioned above, it is important to note that the analyses in this chapter focused on prostate cancer risk rather than advanced prostate cancer or prostate cancer mortality. Moreover, the population in this study was predominantly middle-aged men, a group more likely to undergo prostate cancer screening, meaning that the prevalence of prostate cancer in this cohort may not accurately reflect that in the general population. Potential ascertainment bias in the association between adiposity and prostate cancer cannot be ruled out.

Some evidence from MR studies suggests a likely inverse causal relationship between increased BMI and prostate cancer, which aligns with the direction and the magnitude of the association observed here. For example, a meta-analysis of 4 MR studies, involving 97,541 prostate cancer cases found an inverse association between genetically predicted BMI (based on 5 to 300 SNPs) and prostate cancer with an HR of 0.90 (0.84-0.96) per 5 kg/m^2 (72).

6.4.3 Oesophageal adenocarcinoma and oesophageal squamous cell carcinoma

The positive association between excess adiposity and oesophageal adenocarcinoma is well established (26). However, most studies have relied on anthropometric measures of adiposity to estimate this association, with limited research examining different body fat components such as total, central, visceral and ectopic adiposity. The lack of studies directly comparing the magnitude of these associations within the same cohort restricts the ability to draw comparisons with the findings presented here.

Consistent with the findings here, a study of 218,854 Whites involving 253 oesophageal adenocarcinoma cases, found that increased BMI (≥35 kg/m^2 vs 18.5-25 HR: 2.11 [1.09-4.09]) and WC (Q4 vs Q1 HR: 2.01 [1.35-.00]) were associated with increased HR of oesophageal adenocarcinoma of a similar magnitude on a positive log-linear trend (229).

MR studies show some evidence that the association between excess adiposity and oesophageal adenocarcinoma is more likely causal. For example, an MR study of White participants involving 999 oesophageal adenocarcinoma cases found that a genetically predicted BMI (based on 29 SNPs) had a positive association with oesophageal adenocarcinoma OR of 2.10 (1.05-4.16) per 5 kg/m^2 (71).

The association between adiposity and oesophageal adenocarcinoma risk is thought to be primarily mediated by the presence of gastro-oesophageal reflux, with abdominal adiposity having a greater magnitude of association than total adiposity (230, 231). Furthermore, limited evidence suggests that adiposity may also elevate the risk of adenocarcinoma through mechanisms such as increased inflammation and IGF-1 (232, 233).

The epidemiological literature considers the evidence on the association between excess adiposity and OSCC risk as inconclusive (26, 31). Similar to the other cancer-specific sites mentioned above, published studies investigated the association of adiposity measured based on anthropometric methods with the risk of OSCC, and there is a lack of studies comparing the associations of different body fat components with OSCC risk in the same group of individuals to allow comparisons with the findings here.

Consistent with the findings here, the latest WCRF meta-analysed 8 prospective studies, involving 4,348 OSCC cases and concluded an HR of 0.64 (0.56-0.73) per 5 kg/m^2 increase in BMI (31). Similarly to the findings here, a study of 0.5 Chinese participants from the CKB cohort involving 726 cases concluded that BMI was inversely associated with the risk of OSCC with HRs of 0.80 (0.69-0.90) per 5 kg/m^2 (234). However, no association was observed between increased WC (HR: 0.96 [0.87-1.05] per 10 cm) and OSCC risk. Furthermore, consistent with the findings here, a study of 1.2 million women in the UK from the MWS involving 1,799 OSCC cases found that BMI had a strong inverse association with an HR of OSCC of 0.32 (0.22-0.46) per 5 kg/m^2 (235).

The reasons why increased adiposity is protective against OSCC risk remain unclear. Some studies have suggested that higher levels of BMI may be associated with inverse risk of OSCC due to lower levels of lean mass tissue due to malnutrition and/or nutrient deficiency which are risk factors of OSCC (236-238). However, the Chinese study discussed above found an inverse association between fat-free mass and oesophageal cancer risk, with the association being null when the analysis was further restricted to squamous cell carcinoma type (234).

The inverse association may be a result of reverse causation due to recent weight loss in those with preclinical disease. However, here the reverse associations remained after excluding the first 5 years of follow-up. These results are consistent with previous studies that excluded the first 5, 10 and 15 years of follow-up (234, 235), so it is unlikely this was due to reverse causation.

Another hypothesis is that the inverse association of adiposity and OSCC risk may be attributed to residual confounding, such as smoking or alcohol intake. The CKB, MWS and the WCRF meta-analysis all found consistently inverse associations of BMI and OSSC in either never, never-regular or non-smokers, suggesting that it is unlikely to be due to residual confounding by smoking (31, 234, 235). The CKB study found that the inverse association between BMI and oesophageal cancer risk remained in never-drinkers and regular drinkers, suggesting no evidence of residual confounding due to alcohol.

6.4.4 Liver adiposity and cancer risk

A key finding of this chapter is that liver adiposity showed the greatest magnitude of association with cancer risk compared to other body fat components. While there is a lack of epidemiological studies measuring liver adiposity and its association with cancer risk, there is some indirect evidence from conditions involving fatty liver. MASLD is a term used to characterise fatty liver disease characterised with at least one of the following: overweight/obesity, T2D diagnosis, or evidence of metabolic dysregulation (239). In a study of 352,911 UKB participants, MASLD was significantly associated with increased risk of several cancers compared to non-MASLD individuals, including endometrial cancer (HR: 2.36 [1.99-2.80]), liver cancer (1.81 [1.43-2.28]), oesophagus cancer (1.48 [1.25-1.76]), breast cancer in

postmenopausal (HR: 1.19 [1.11–1.27]), and colorectal and anus cancer (1.14 [1.06-1.23]) (240).

No studies were found investigating the association between TMFI and cancer risk.

6.4.5 Sex differences

Although some sex-specific differences were observed in the association between excess adiposity and the risks of specific cancer sites, the potential influence of confounding factors, such as smoking or alcohol consumption, cannot be ruled out.

The sex-specific findings regarding the association of excess adiposity with colorectal cancer risk were generally consistent with those in previous studies. A meta-analysis of 56 prospective cohort studies of 7 million participants (93,812 colorectal cases) reported that a 5 kg/m^2 increase in BMI had a greater HR of colorectal cancer in men than women (HR: 1.25 [1.20-1.30] vs. 1.12 [1.06-1.16]) (241).

A potential explanation as to why men than women have a greater risk of colorectal cancer risk with excess adiposity remains unclear. However, the role of sex hormones may explain it. Adiposity's association with testosterone differs by sex as shown in Chapter 4, being inversely related to testosterone in men and positively associated in women. It has been shown that testosterone therapy given in men reduces adiposity and improves insulin sensitivity (242), while androgen deprivation therapy increases insulin sensitivity (243, 244). High testosterone lowers T2D risk in men but raises it in women, which may explain why increased levels of adiposity are more associated with colorectal cancer risk in men than women (245). In women, the adiposity-cancer association may be influenced by menopause status as a previous

study has shown an increased risk of colorectal cancer in premenopausal women but not among postmenopausal women (65).

The sex-specific findings here about liver cancer were consistent with previous evidence. A large meta-analysis of 1.57 million individuals (2,162 liver cancer cases), found that an increase in BMI was associated with a greater risk of liver cancer in men than in women (HR: 1.38 [1.30–1.46] per 5 kg/m² BMI vs. 1.25 [1.17–1.35]) (223). This may be explained by men's greater accumulation of visceral adiposity, which is associated with increased insulin resistance, T2D and chronic low-grade inflammation, factors that contribute to a higher liver cancer risk in men (246). For instance, a previous analysis estimated that excess body weight accounted for 30,200 liver cancer cases per year in women and 54,600 cases per year in men (247). Sex hormone of androgens is considered to play an important role in the biological mechanism of liver cancer, by increasing susceptibility to hepatocellular carcinoma and affecting its aggressiveness (248). Sex hormones also modulate the impact of other liver damage factors, such as chronic hepatitis B virus and obesity.

Limited previous evidence was found on sex-specific associations between excess adiposity and risk of OSCC. In contrast to the findings presented here, a CKB study of 0.5 million Chinese participants (726 oesophageal cancer cases) found no evidence of sex-specific difference in the magnitude of the association between total or central adiposity with oesophageal cancer risk (234). Particularly it was found that a 5 kg/m^2 increase in BMI was associated with an HR of 0.83 (0.68-0.86) in women and 0.69 (0.62-0.76) in men, while a 10 cm increase in WC had an HR of 0.89 (0.82-0.99) in women and 0.84 (0.79-0.90) in men. This inconsistency may be due to differences in the definition of the outcome between this analysis and the CKB study. The latter used broader oesophageal cancer categories (dominated by squamous

cell carcinoma) in the definition of the outcome and used the regression dilution correction method to estimate “usual” adiposity. This method accounts for potential changes in adiposity after baseline, potentially providing a more accurate measure. Nevertheless, the CI of the HRs reported here for men and women overlapped with those of the CKB study.

Consistent with previous evidence the risk of any cancer was greater in men than women. A study of 4.1 million Swedish adults found that a 5 kg/m^2 increase in BMI in men have a greater risk of potential obesity-related cancers (HR: 1.17 [1.15-1.20] vs. 1.13 [1.11-1.15]; involving 51,690 cases) and for established obesity-related cancers (1.24 [1.22-1.26] vs. 1.12 [1.11-1.13]; involving 84,384 cases) (249).

6.4.6 A comparison of cancer risks between the imaging sub-cohort and the entire baseline cohort

This chapter provided further evidence supporting the conclusions of Chapter 5 regarding the imaging sub-cohort analysis. Overall, the association of excess adiposity with the risks of colorectal, breast, prostate, and all cancers combined were of a comparable magnitude between the two cohorts. However, a key difference is that while the risk of colorectal, breast, prostate, and all cancers combined were comparable across different adiposity traits in the imaging sub-cohort, liver adiposity showed a greater magnitude of association with most cancers in the entire baseline cohort. Similarly, for prostate cancer, the imaging sub-cohort analysis showed no association with excess adiposity traits, whereas in the baseline cohort analysis, the association was inverse. This difference between Chapters 5 and 6 is likely due to the greater statistical power of the entire baseline cohort, as shown by the overlapping CI but increased nominal significance in the larger sample.

Another key issue that needs to be discussed is how reliable are the imputed category medians of adiposity traits compared with the direct measures. Further analysis in Chapter 6 showed that the associations of the direct measurements of BMI and WC were somewhat of a weaker magnitude for endometrial cancer in comparison with the imputed category medians. However, no differences were found regarding the other cancer outcomes.

6.4.7 Strengths and limitations

The analysis in this chapter has certain strengths. Firstly, this is the largest prospective study up to date using the entire UKB cohort of approximately 0.5 million participants comparing the magnitude of the association across different MRI-derived and anthropometric measures of adiposity with cancer risk. This cohort allowed for an extended follow-up period (mean of 12 years) and a substantial number of cancer cases, enabling robust evaluations of these associations. However, this study also had several limitations.

For many cancers, weight loss often precedes clinical diagnosis by several years, and estimated body fat at the time of diagnosis may not accurately represent an individual's usual adiposity. This potential bias, termed reverse causation, can result in increased cancer risk for low adiposity. Although excluding the first 5 years of follow-up in sensitivity analyses did not alter the findings, the relatively short follow-up period precludes the exclusion of longer intervals. Given that reverse causation may exert an influence for up to 10 years post-recruitment, this remains a limitation of the study. For example, the J-shape trend between log-HR for liver cancer and adiposity traits remained even after exclusions in the first 5 years of follow-up, suggesting that the presence of reverse causation cannot be eliminated.

Furthermore, the MRI-derived measures of adiposity were not available at baseline and instead were estimated based on median values of these metrics within deciles defined by BMI and WC at baseline. These estimates were derived from participants in the imaging survey. The validity of this approach relies on the assumption that the imaging cohort is broadly representative of the wider cohort. While there was some evidence that the imaging sub-cohort was generally healthier in terms of their body fat than the entire cohort, the distribution of anthropometric traits at baseline remained comparable within BMI categories (as defined by WHO for overweight/obesity). Moreover, a comparison of the HRs of BMI and WC directly measured at baseline vs. imputed category medians showed associations of a similar magnitude with the only exception of endometrial cancer for which the direct measures had a somewhat weaker association.

6.4.8 Conclusion

In this analysis of 0.5 million UKB participants, increased adiposity was positively associated with an increased risk of most cancers including colorectal, oesophageal adenocarcinoma, breast, and all cancers combined. Liver adiposity tended to show a greater magnitude of association with cancer risk than other body fat components, particularly for endometrial cancer and liver cancer. On the other hand, adiposity was negatively associated with OSCC, and slightly negatively associated with prostate cancer, with no major differences between the magnitude of the associations with different adiposity traits for these cancer sites. Sex-specific differences were also observed in the associations with colorectal cancer, oesophageal cancer and all cancers combined. Future studies are needed in diverse populations with

simultaneous measurements of different body fat components, extended follow-up periods, and a large number of cancer cases to validate these findings.

Table 6.1 Baseline characteristics of the entire UK Biobank participants by BMI classification

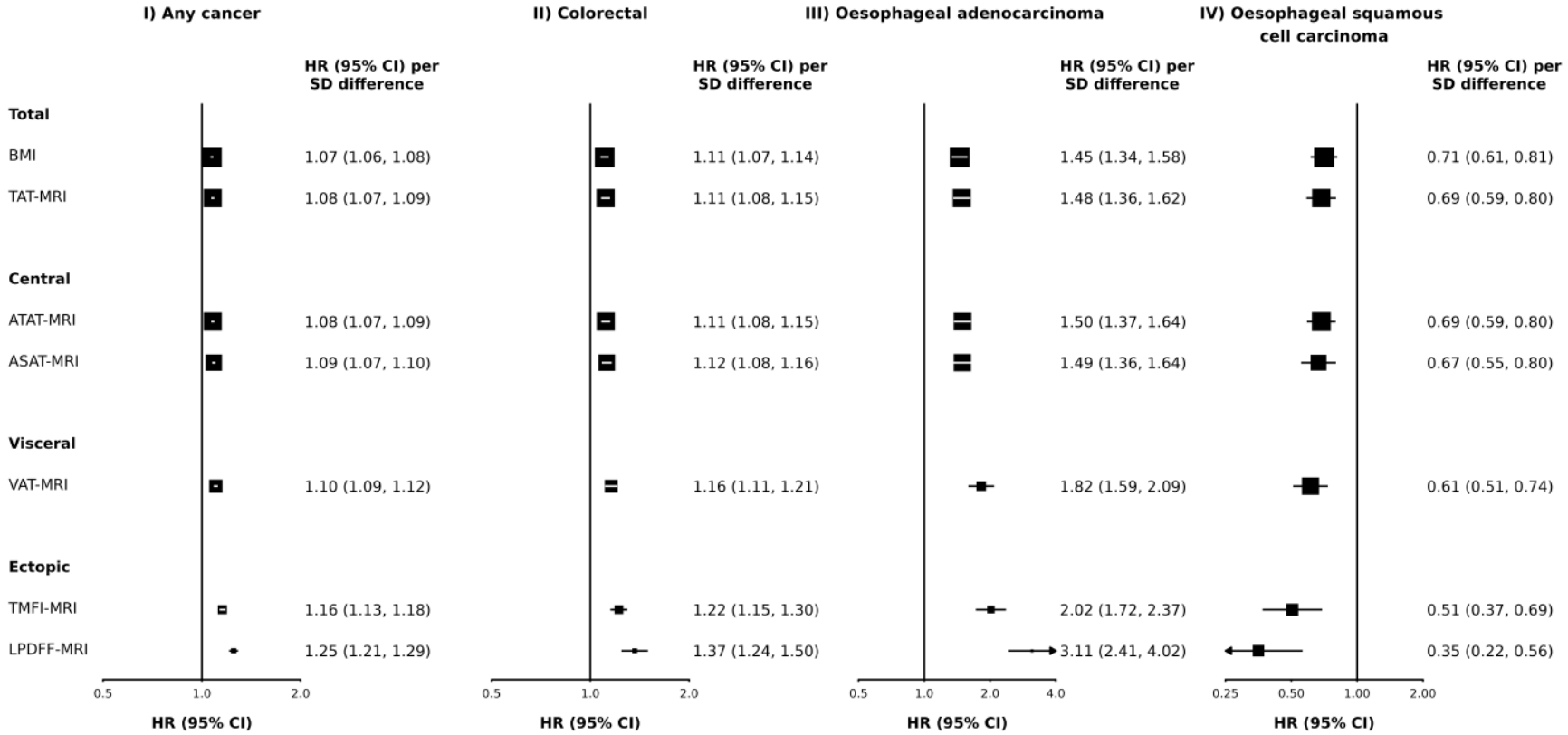
Baseline Characteristics	BMI classification, kg/m^2					
	<18 (N=2,626)	**18-25 (N=162,349)**	**25-30 (N=212,057)**	**30-35 (N=87,532)**	**35-40 (N=24,989)**	**>40 (N=9,699)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	56 (8)	56 (8)	57 (8)	57 (8)	57 (8)	55 (8)
College or University degree, %	38	40	31	25	23	22
Ancestry White, %	94	95	95	94	94	93
Menopausal females, %	73	68	75	76	74	70
Ever regular smoker, %	46	41	46	49	48	47
Weekly alcohol drinking, %	58	72	72	64	54	42
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.2 (0.8)	22.8 (1.6)	27.3 (1.4)	32.0 (1.4)	37.0 (1.4)	43.8 (3.8)
%BF	17.7 (5.4)	26.8 (7.1)	31.2 (7.4)	36.4 (7.2)	41.7 (6.7)	46.7 (6.1)
Central adiposity, Mean (SD)						
WC, cm	66.0 (5.9)	78.6 (8.2)	91.0 (8.4)	101.6 (8.7)	110.7 (9.7)	121.7 (12.2)
WHR	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	127.0 (20.0)	132.9 (18.8)	139.4 (18.2)	141.8 (17.8)	142.0 (17.8)	142.9 (17.8)
Diastolic	75.5 (10.8)	78.7 (9.7)	83.0 (9.7)	85.4 (9.7)	86.5 (9.9)	87.8 (10.2)
Pulse	51.5 (16.8)	54.2 (15.1)	56.4 (15.1)	56.4 (15.3)	55.5 (15.1)	55.1 (14.9)
Blood lipid, Mean (SD), mmol/L						
LDL-C	3.3 (0.8)	3.5 (0.8)	3.6 (0.9)	3.6 (0.9)	3.5 (0.9)	3.3 (0.9)
HDL-C	1.8 (0.5)	1.6 (0.4)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
TG	1.1 (0.6)	1.4 (0.7)	1.8 (1.0)	2.1 (1.2)	2.2 (1.2)	2.1 (1.1)
Total cholesterol	4.7 (0.9)	4.7 (0.9)	4.7 (1.0)	4.5 (1.0)	4.4 (1.0)	4.3 (0.9)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	35.2 (4.7)	34.7 (5.0)	35.8 (6.1)	37.8 (8.1)	39.8 (10.0)	41.9 (11.4)
IGF-1, nmol/L	19.3 (5.4)	21.8 (5.6)	21.8 (5.6)	20.6 (5.8)	19.2 (5.8)	17.9 (5.8)
CRP, mg/L	1.7 (4.8)	1.7 (3.8)	2.4 (4.0)	3.5 (4.6)	5.0 (5.4)	7.4 (6.8)
Sex hormone, Mean (SD)						
SHBG, nmol/L	90.5 (34.5)	65.1 (30.6)	47.8 (24.4)	40.7 (21.0)	38.3 (20.1)	36.5 (19.6)
Testosterone, nmol/L						
Males	14.6 (5.1)	13.4 (3.8)	12.0 (3.5)	10.8 (3.4)	9.9 (3.3)	8.9 (3.4)
Females	1.0 (0.6)	1.1 (0.6)	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)	1.3 (0.7)
Oestradiol in premenopausal females, pmol/L	545.5 (399.4)	599.1 (510.6)	569.8 (480.8)	539.5 (494.1)	503.1 (353.9)	510.9 (397.0)

Table 6.2 Baseline characteristics of the UK Biobank participants who participated in the imaging sub-cohort by BMI classification

Baseline Characteristics	BMI classification, kg/m^2					
	<18 (N=287)	**18-25 (N=24,471)**	**25-30 (N=27,302)**	**30-35 (N=9,107)**	**35-40 (N=2,108)**	**>40 (N=646)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	53 (8)	54 (8)	55 (8)	55 (7)	54 (7)	53 (7)
College or University degree, %	56	52	43	39	37	34
Ancestry White, %	95	97	97	97	97	96
Menopausal females, %	62	60	66	65	62	56
Ever regular smoker, %	32	35	41	45	44	42
Weekly alcohol drinking, %	67	78	78	73	62	51
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.2 (0.8)	22.8 (1.5)	27.2 (1.4)	31.9 (1.4)	36.9 (1.4)	43.2 (3.1)
%BF	17.5 (4.7)	26.3 (7.0)	30.2 (7.3)	35.5 (7.3)	41.4 (6.8)	46.0 (6.1)
Central adiposity, Mean (SD)						
WC, cm	65.2 (5.5)	78.3 (8.1)	90.7 (8.2)	101.0 (8.6)	109.9 (9.6)	120.4 (11.7)
WHR	0.8 (0.0)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	120.9 (16.0)	130.4 (17.6)	137.2 (17.1)	139.9 (16.9)	140.5 (16.3)	141.0 (17.1)
Diastolic	73.6 (8.7)	78.1 (9.4)	82.8 (9.5)	85.6 (9.3)	87.2 (9.2)	88.5 (9.5)
Pulse	47.3 (16.5)	52.3 (15.1)	54.4 (15.1)	54.3 (15.2)	53.3 (15.1)	52.4 (15.0)
Blood lipid, Mean (SD), mmol/L						
LDL-C	3.3 (0.8)	3.5 (0.8)	3.7 (0.8)	3.6 (0.9)	3.6 (0.8)	3.4 (0.8)
HDL-C	1.9 (0.5)	1.6 (0.4)	1.4 (0.3)	1.3 (0.3)	1.2 (0.3)	1.2 (0.3)
TG	1.0 (0.5)	1.3 (0.7)	1.8 (1.0)	2.1 (1.2)	2.2 (1.1)	2.1 (1.1)
Total cholesterol	4.9 (0.9)	4.7 (0.9)	4.7 (0.9)	4.6 (0.9)	4.5 (0.9)	4.3 (0.9)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	34.4 (3.5)	34.1 (4.0)	35.0 (4.8)	36.3 (6.3)	38.2 (8.4)	40.2 (9.7)
IGF-1, nmol/L	20.2 (5.3)	22.3 (5.4)	22.4 (5.5)	21.2 (5.4)	19.6 (5.6)	18.1 (5.4)
CRP, mg/L	0.6 (0.9)	1.4 (3.2)	2.0 (3.4)	3.0 (3.8)	4.5 (4.3)	6.8 (5.9)
Sex hormone, Mean (SD)						
SHBG, nmol/L	90.6 (34.2)	64.4 (30.4)	46.3 (23.7)	39.5 (20.4)	36.0 (17.6)	35.1 (18.5)
Testosterone, nmol/L						
Males	14.2 (3.7)	13.4 (3.6)	12.1 (3.5)	10.9 (3.1)	9.8 (3.1)	9.3 (3.5)
Females	1.2 (0.8)	1.1 (0.6)	1.1 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)
Oestradiol in premenopausal females, pmol/L	591.1 (382.9)	600.1 (552.3)	595.8 (620.8)	559.3 (446.5)	501.7 (315.8)	455.5 (292.6)

Figure 6.1 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within BMI deciles

Adiposity traits for the entire cohort were imputed as medians within deciles of BMI at baseline. Each adiposity trait was treated on a continuous scale to assess risk trends per SD. The plotted square presents the coefficient of each of the standardised adiposity traits from the multivariable Cox Hazards model that adjusted for sex, age, smoking status, alcohol intake in drinks per week, education, fifths of Townsend Deprivation index score, and where appropriate number of live births, menopausal status, years since menopause, and use of menopause hormone therapy. The vertical line marks HR=1 and box sizes are proportional to the inverse variance of the log HR. Standard deviations are in Table 2.2.



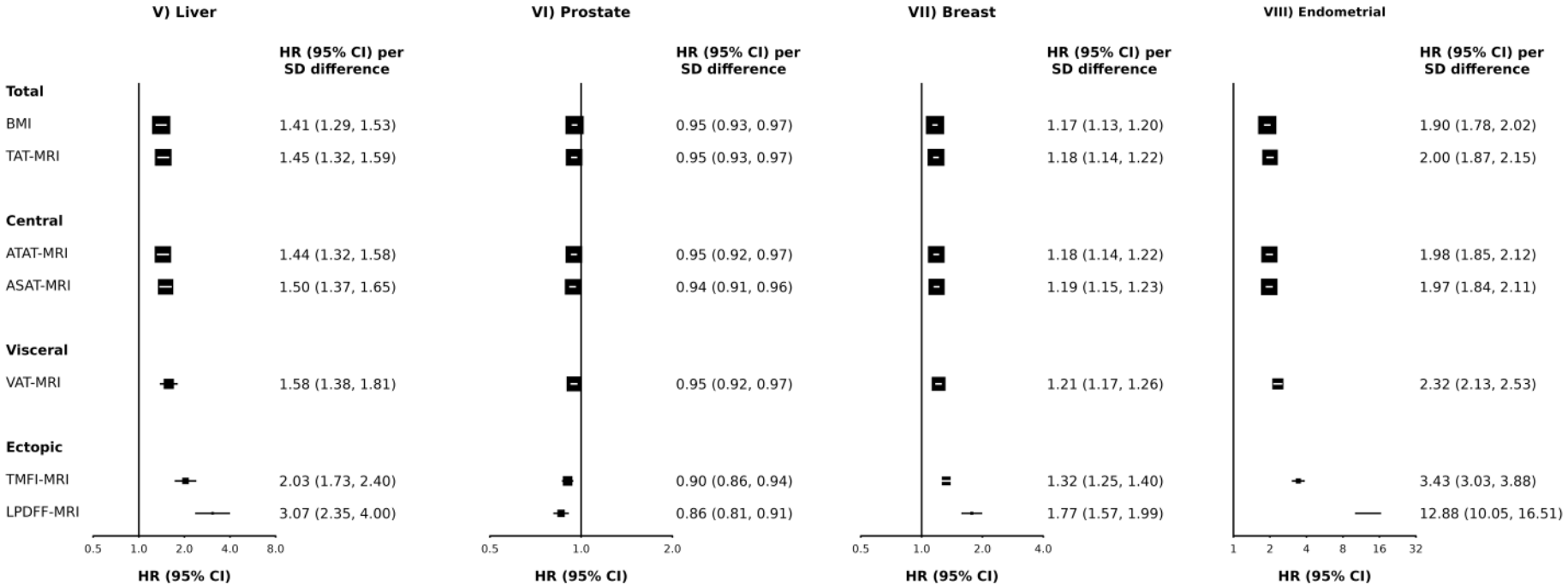
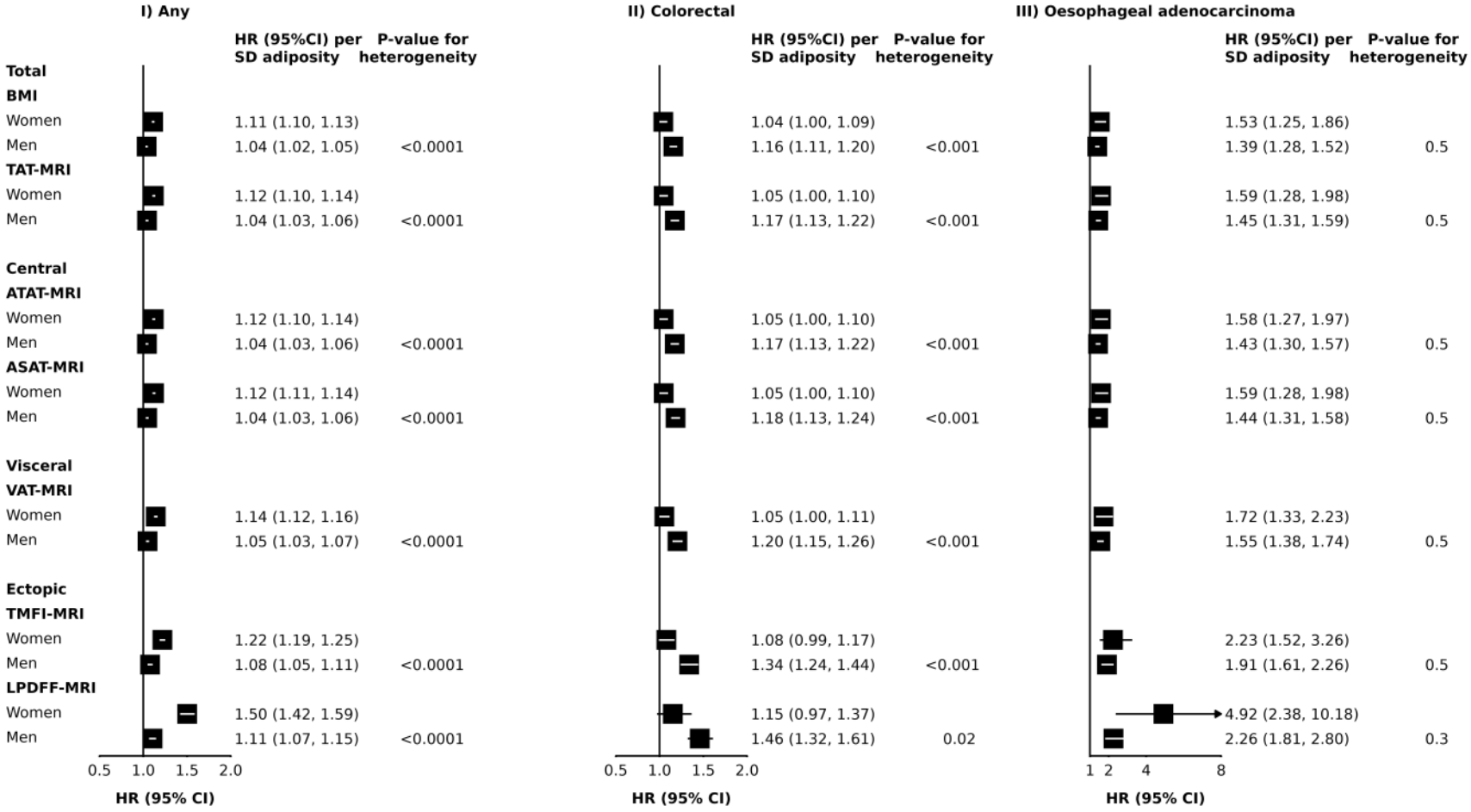

V) Liver
HR (95% CI) per SD difference
Total
BMI
1.41 (1.29, 1.53)
TAT-MRI
1.45 (1.32, 1.59)
Central
ATAT-MRI
1.44 (1.32, 1.58)
ASAT-MRI
1.50 (1.37, 1.65)
Visceral
VAT-MRI
1.58 (1.38, 1.81)
Ectopic
TMFI-MRI
2.03 (1.73, 2.40)
LPDFF-MRI
3.07 (2.35, 4.00)
0.5
1.0
2.0
4.0
8.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
0.95 (0.93, 0.97)
0.95 (0.93, 0.97)
0.95 (0.92, 0.97)
0.94 (0.91, 0.96)
0.95 (0.92, 0.97)
0.90 (0.86, 0.94)
0.86 (0.81, 0.91)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.17 (1.13, 1.20)
1.18 (1.14, 1.22)
1.18 (1.14, 1.22)
1.19 (1.15, 1.23)
1.21 (1.17, 1.26)
1.32 (1.25, 1.40)
1.77 (1.57, 1.99)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
1.90 (1.78, 2.02)
2.00 (1.87, 2.15)
1.98 (1.85, 2.12)
1.97 (1.84, 2.11)
2.32 (2.13, 2.53)
3.43 (3.03, 3.88)
12.88 (10.05, 16.51)
1
2
4
8
16
32
HR (95% CI)

Figure 6.2 Sex-specific adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within BMI deciles

Conventions as in Figure 6.1. Sex-specific SDs are shown in Table 2.2.



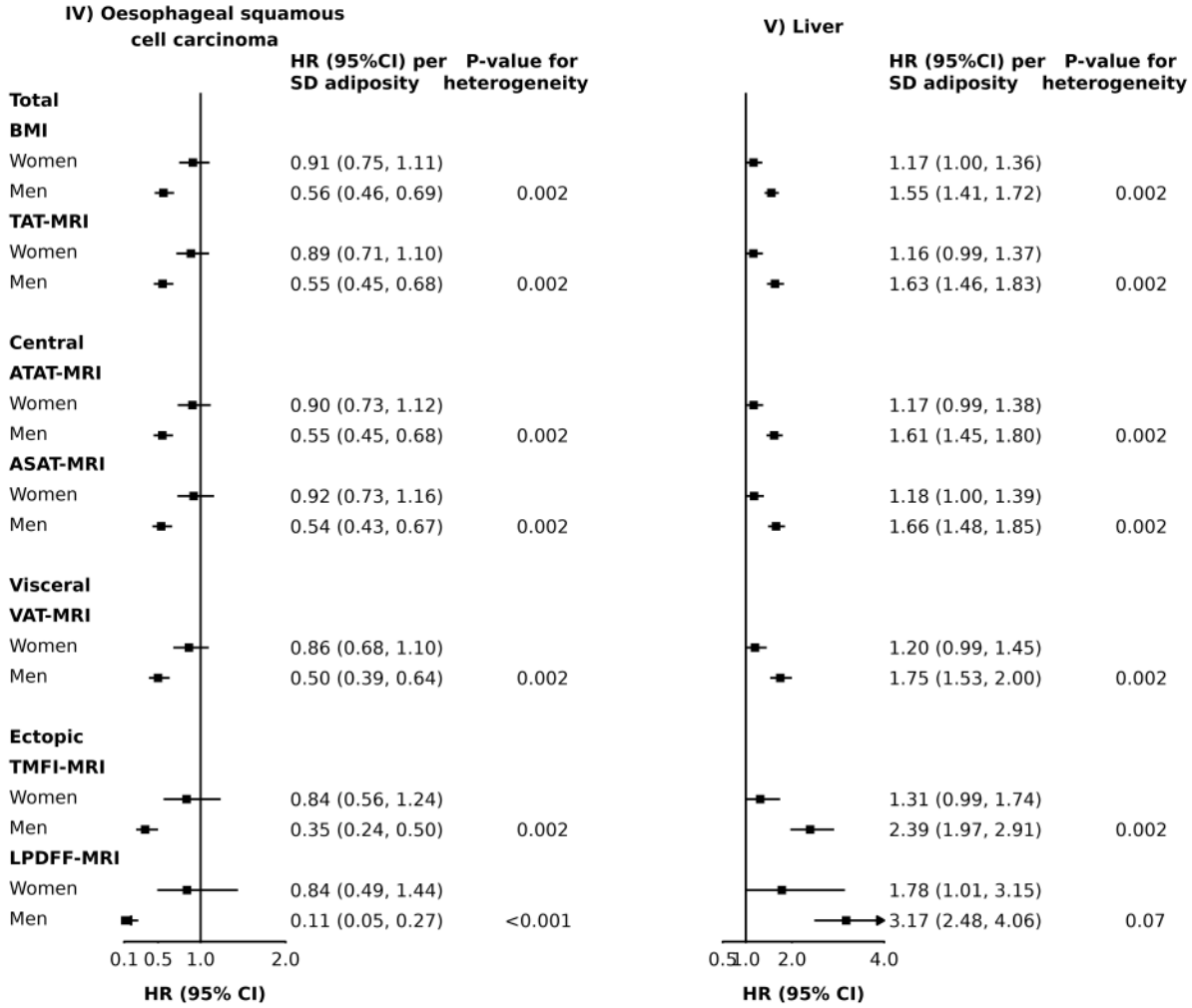
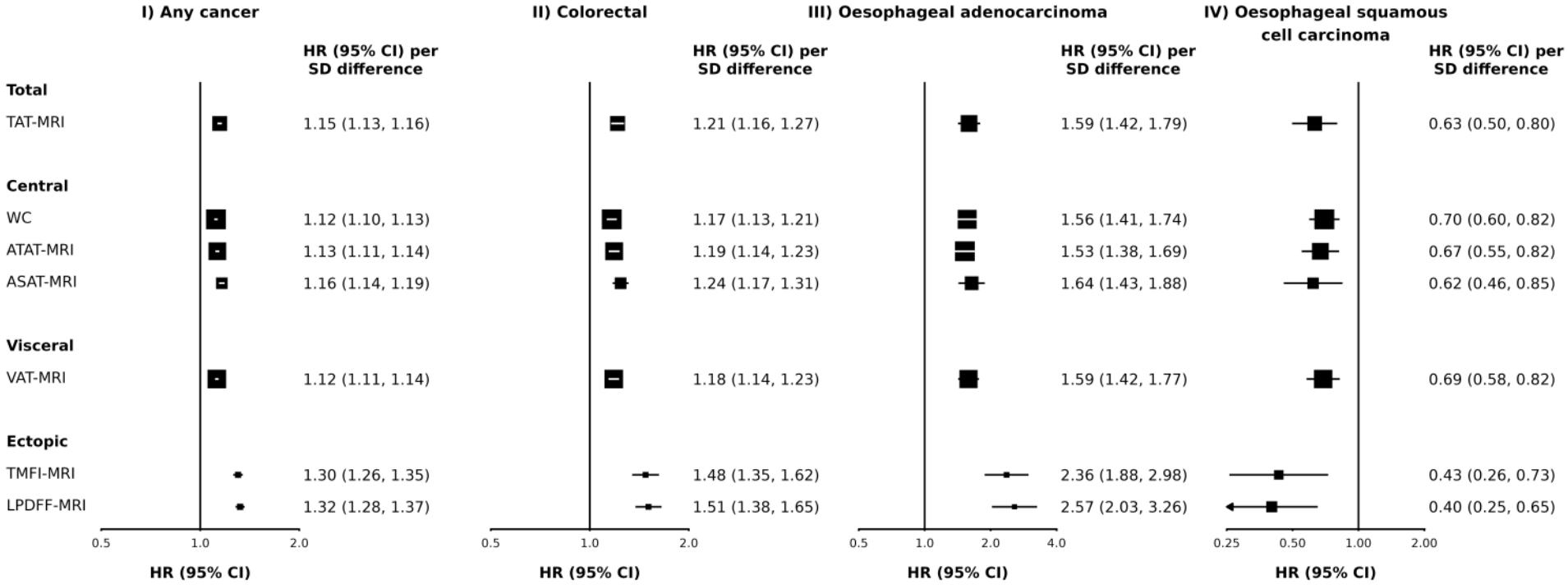

IV) Oesophageal squamous cell carcinoma
HR (95%CI) per SD adiposity
P-value for heterogeneity
Total
BMI
Women 0.91 (0.75, 1.11)
Men 0.56 (0.46, 0.69) 0.002
TAT-MRI
Women 0.89 (0.71, 1.10)
Men 0.55 (0.45, 0.68) 0.002
Central
ATAT-MRI
Women 0.90 (0.73, 1.12)
Men 0.55 (0.45, 0.68) 0.002
ASAT-MRI
Women 0.92 (0.73, 1.16)
Men 0.54 (0.43, 0.67) 0.002
Visceral
VAT-MRI
Women 0.86 (0.68, 1.10)
Men 0.50 (0.39, 0.64) 0.002
Ectopic
TMFI-MRI
Women 0.84 (0.56, 1.24)
Men 0.35 (0.24, 0.50) 0.002
LPDFF-MRI
Women 0.84 (0.49, 1.44)
Men 0.11 (0.05, 0.27) <0.001
0.1 0.5 1.0 2.0
HR (95% CI)
V) Liver
HR (95%CI) per SD adiposity
P-value for heterogeneity
Women 1.17 (1.00, 1.36)
Men 1.55 (1.41, 1.72) 0.002
Women 1.16 (0.99, 1.37)
Men 1.63 (1.46, 1.83) 0.002
Women 1.17 (0.99, 1.38)
Men 1.61 (1.45, 1.80) 0.002
Women 1.18 (1.00, 1.39)
Men 1.66 (1.48, 1.85) 0.002
Women 1.20 (0.99, 1.45)
Men 1.75 (1.53, 2.00) 0.002
Women 1.31 (0.99, 1.74)
Men 2.39 (1.97, 2.91) 0.002
Women 1.78 (1.01, 3.15)
Men 3.17 (2.48, 4.06) 0.07
0.5 1.0 2.0 4.0
HR (95% CI)

Figure 6.3 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within WC deciles

Adiposity traits for the entire cohort were imputed as medians within deciles of WC at baseline. Each adiposity trait was treated on a continuous scale to assess risk trends per SD. The plotted square presents the coefficient of each of the standardised adiposity traits from the multivariable Cox Hazards model that adjusted for sex, age, smoking status, alcohol intake in drinks per week, education, fifths of Townsend Deprivation index score, and where appropriate number of live births, menopausal status, years since menopause, and use of menopause hormone therapy. The vertical line marks HR=1 and box sizes are proportional to the inverse variance of the log HR. Standard deviations are in Table 2.2.



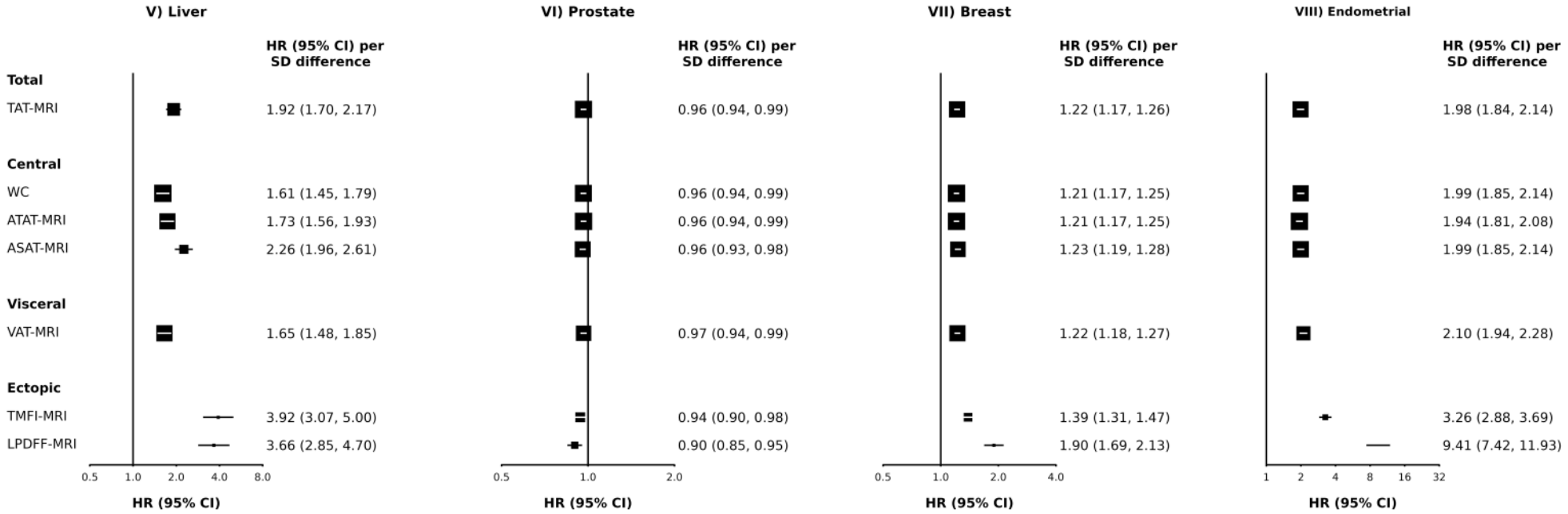
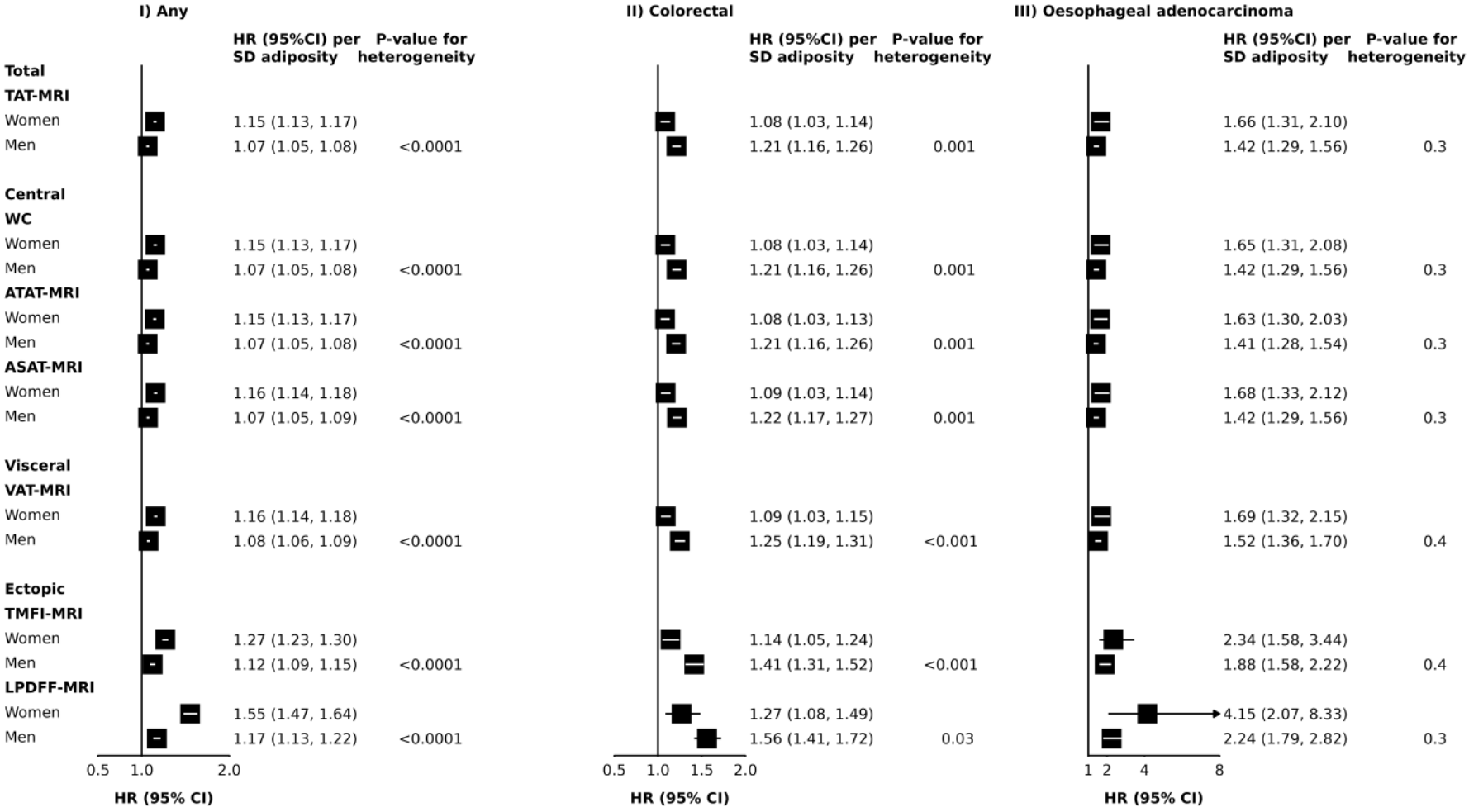

V) Liver
HR (95% CI) per SD difference
Total
TAT-MRI
1.92 (1.70, 2.17)
Central
WC
1.61 (1.45, 1.79)
ATAT-MRI
1.73 (1.56, 1.93)
ASAT-MRI
2.26 (1.96, 2.61)
Visceral
VAT-MRI
1.65 (1.48, 1.85)
Ectopic
TMFI-MRI
3.92 (3.07, 5.00)
LPDFF-MRI
3.66 (2.85, 4.70)
0.5
1.0
2.0
4.0
8.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
0.96 (0.94, 0.99)
0.96 (0.94, 0.99)
0.96 (0.93, 0.98)
0.97 (0.94, 0.99)
0.94 (0.90, 0.98)
0.90 (0.85, 0.95)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.22 (1.17, 1.26)
1.21 (1.17, 1.25)
1.21 (1.17, 1.25)
1.23 (1.19, 1.28)
1.22 (1.18, 1.27)
1.39 (1.31, 1.47)
1.90 (1.69, 2.13)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
1.98 (1.84, 2.14)
1.99 (1.85, 2.14)
1.94 (1.81, 2.08)
1.99 (1.85, 2.14)
2.10 (1.94, 2.28)
3.26 (2.88, 3.69)
9.41 (7.42, 11.93)
1
2
4
8
16
32
HR (95% CI)

Figure 6.4 Sex-specific adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within WC deciles

Conventions as in Figure 6.3. Sex-specific SDs are shown in Table 2.2.



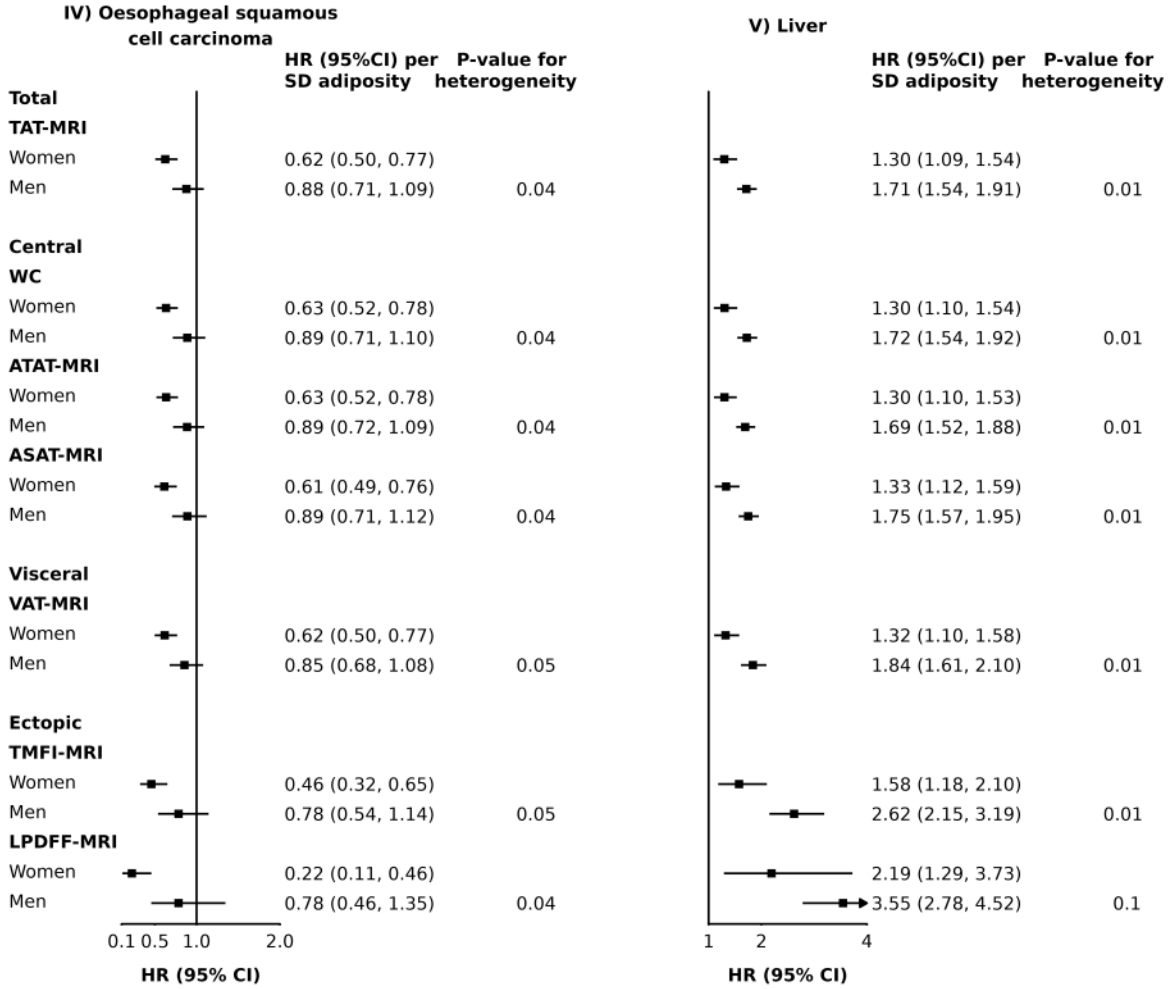
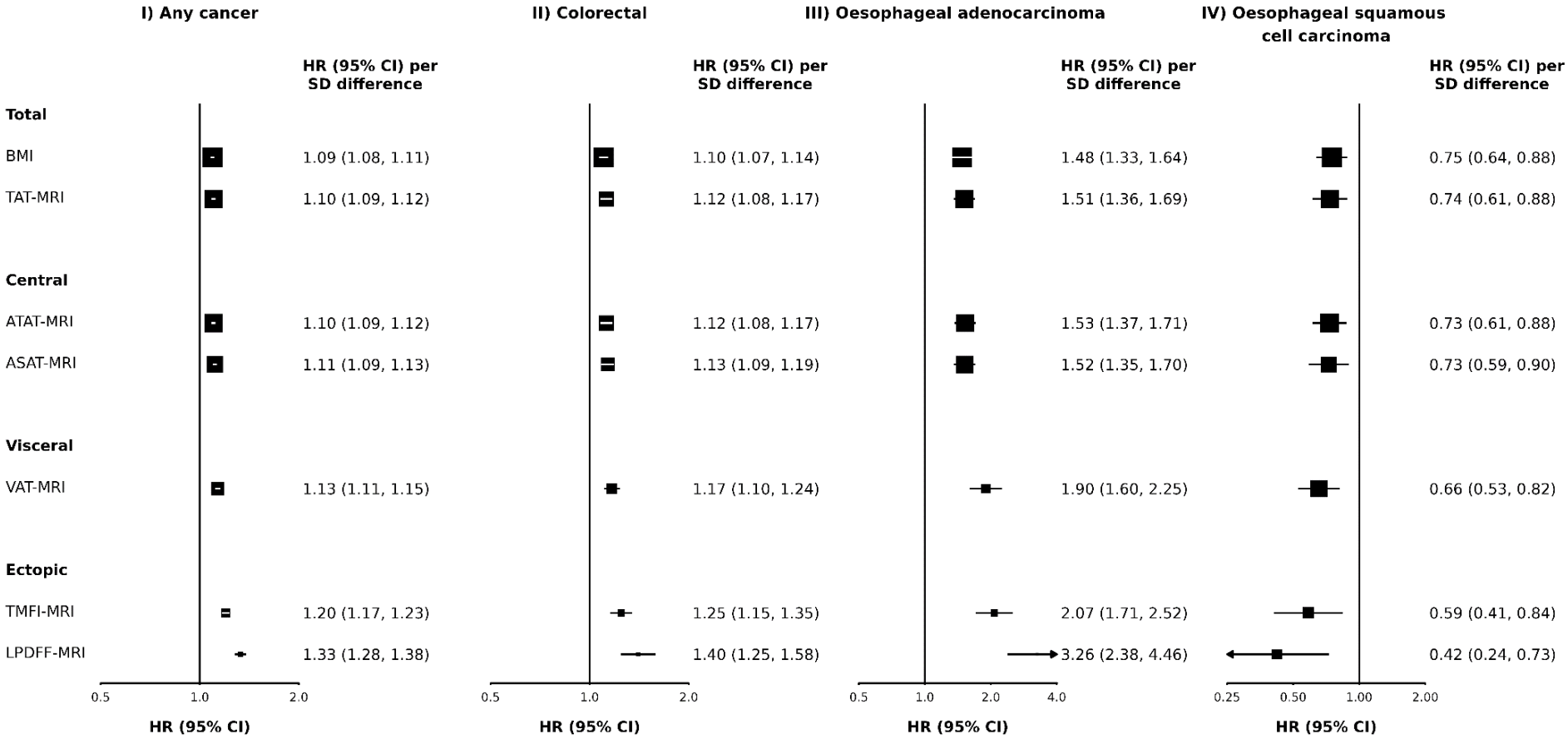

IV) Oesophageal squamous cell carcinoma
HR (95%CI) per SD adiposity
P-value for heterogeneity
Total
TAT-MRI
Women 0.62 (0.50, 0.77)
Men 0.88 (0.71, 1.09) 0.04
Central
WC
Women 0.63 (0.52, 0.78)
Men 0.89 (0.71, 1.10) 0.04
ATAT-MRI
Women 0.63 (0.52, 0.78)
Men 0.89 (0.72, 1.09) 0.04
ASAT-MRI
Women 0.61 (0.49, 0.76)
Men 0.89 (0.71, 1.12) 0.04
Visceral
VAT-MRI
Women 0.62 (0.50, 0.77)
Men 0.85 (0.68, 1.08) 0.05
Ectopic
TMFI-MRI
Women 0.46 (0.32, 0.65)
Men 0.78 (0.54, 1.14) 0.05
LPDFF-MRI
Women 0.22 (0.11, 0.46)
Men 0.78 (0.46, 1.35) 0.04
0.1 0.5 1.0 2.0
HR (95% CI)
V) Liver
HR (95%CI) per SD adiposity
P-value for heterogeneity
Women 1.30 (1.09, 1.54)
Men 1.71 (1.54, 1.91) 0.01
Women 1.30 (1.10, 1.54)
Men 1.72 (1.54, 1.92) 0.01
Women 1.30 (1.10, 1.53)
Men 1.69 (1.52, 1.88) 0.01
Women 1.33 (1.12, 1.59)
Men 1.75 (1.57, 1.95) 0.01
Women 1.32 (1.10, 1.58)
Men 1.84 (1.61, 2.10) 0.01
Women 1.58 (1.18, 2.10)
Men 2.62 (2.15, 3.19) 0.01
Women 2.19 (1.29, 3.73)
Men 3.55 (2.78, 4.52) 0.1
1 2 4
HR (95% CI)

Figure 6.5 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within BMI deciles, after excluding those with less than 5 years of follow-up

Conventions as Figure 6.1.



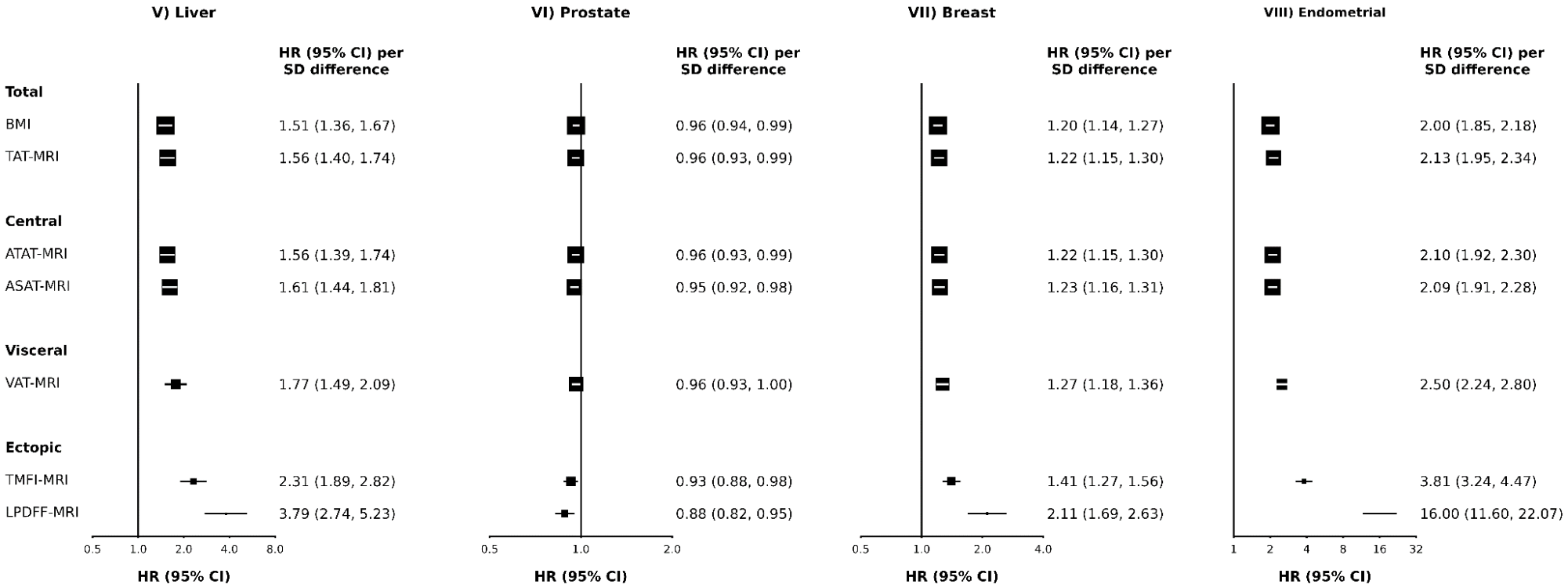
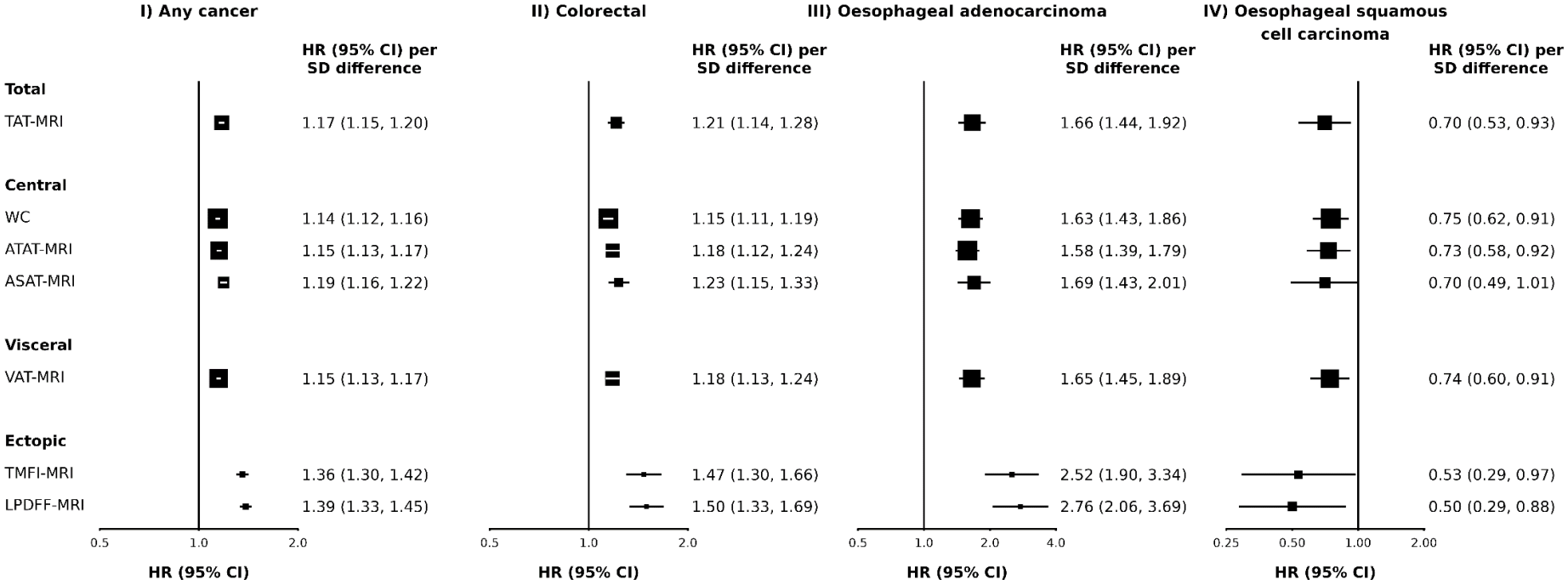

V) Liver
HR (95% CI) per SD difference
Total
BMI
1.51 (1.36, 1.67)
TAT-MRI
1.56 (1.40, 1.74)
Central
ATAT-MRI
1.56 (1.39, 1.74)
ASAT-MRI
1.61 (1.44, 1.81)
Visceral
VAT-MRI
1.77 (1.49, 2.09)
Ectopic
TMFI-MRI
2.31 (1.89, 2.82)
LPDFF-MRI
3.79 (2.74, 5.23)
0.5
1.0
2.0
4.0
8.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
0.96 (0.94, 0.99)
0.96 (0.93, 0.99)
0.96 (0.93, 0.99)
0.95 (0.92, 0.98)
0.96 (0.93, 1.00)
0.93 (0.88, 0.98)
0.88 (0.82, 0.95)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.20 (1.14, 1.27)
1.22 (1.15, 1.30)
1.22 (1.15, 1.30)
1.23 (1.16, 1.31)
1.27 (1.18, 1.36)
1.41 (1.27, 1.56)
2.11 (1.69, 2.63)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
2.00 (1.85, 2.18)
2.13 (1.95, 2.34)
2.10 (1.92, 2.30)
2.09 (1.91, 2.28)
2.50 (2.24, 2.80)
3.81 (3.24, 4.47)
16.00 (11.60, 22.07)
1
2
4
8
16
32
HR (95% CI)

Figure 6.6 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within WC deciles, after excluding those with less than 5 years of follow-up

Conventions as in Figure 6.3.



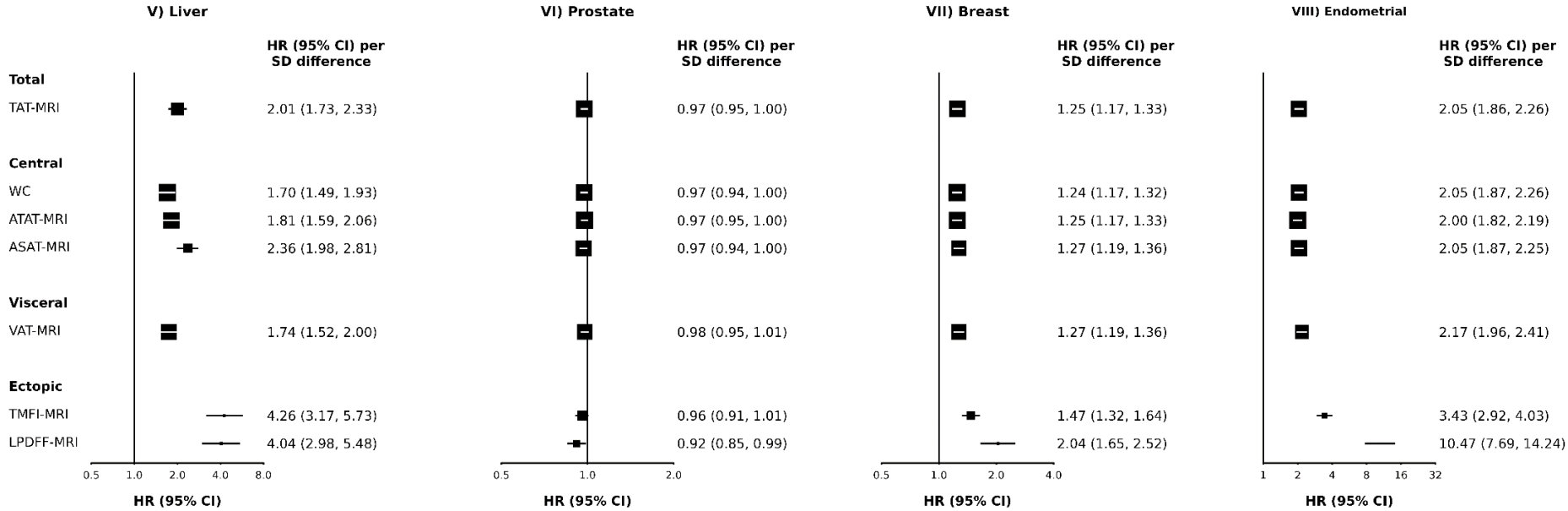
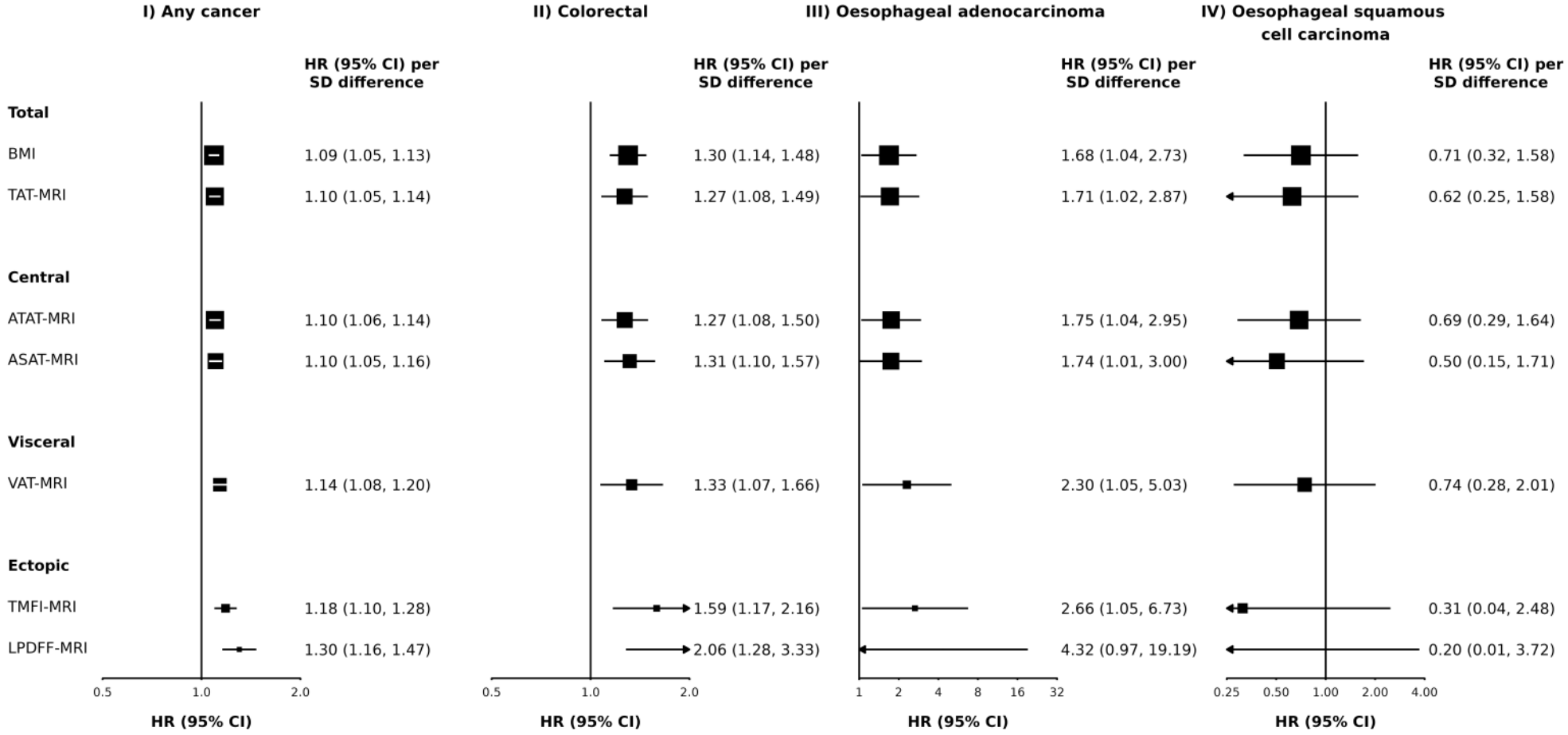

V) Liver
HR (95% CI) per SD difference
Total
TAT-MRI
2.01 (1.73, 2.33)
Central
WC
1.70 (1.49, 1.93)
ATAT-MRI
1.81 (1.59, 2.06)
ASAT-MRI
2.36 (1.98, 2.81)
Visceral
VAT-MRI
1.74 (1.52, 2.00)
Ectopic
TMFI-MRI
4.26 (3.17, 5.73)
LPDFF-MRI
4.04 (2.98, 5.48)
0.5
1.0
2.0
4.0
8.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
0.97 (0.95, 1.00)
0.97 (0.94, 1.00)
0.97 (0.95, 1.00)
0.97 (0.94, 1.00)
0.98 (0.95, 1.01)
0.96 (0.91, 1.01)
0.92 (0.85, 0.99)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.25 (1.17, 1.33)
1.24 (1.17, 1.32)
1.25 (1.17, 1.33)
1.27 (1.19, 1.36)
1.27 (1.19, 1.36)
1.47 (1.32, 1.64)
2.04 (1.65, 2.52)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
2.05 (1.86, 2.26)
2.05 (1.87, 2.26)
2.00 (1.82, 2.19)
2.05 (1.87, 2.25)
2.17 (1.96, 2.41)
3.43 (2.92, 4.03)
10.47 (7.69, 14.24)
1
2
4
8
16
32
HR (95% CI)

Figure 6.7 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within BMI deciles in those who were part of the imaging sub-cohort

Conventions as in Figure 6.1.



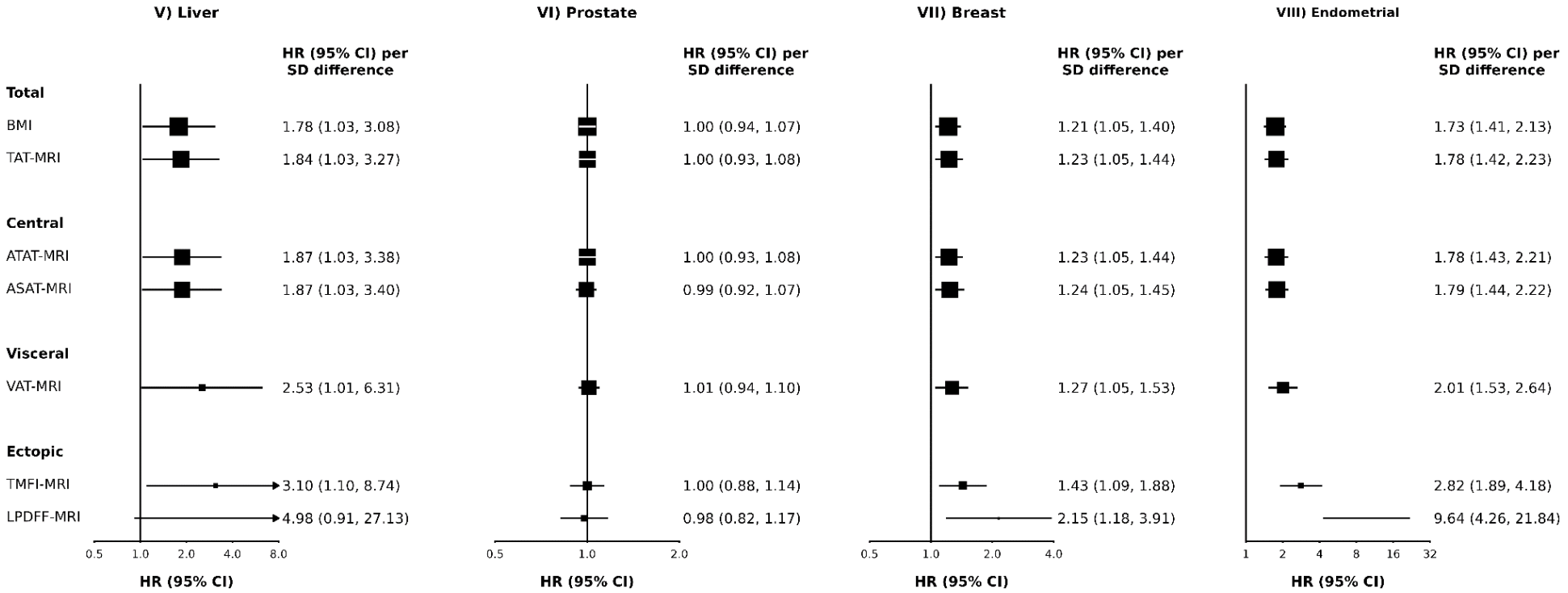
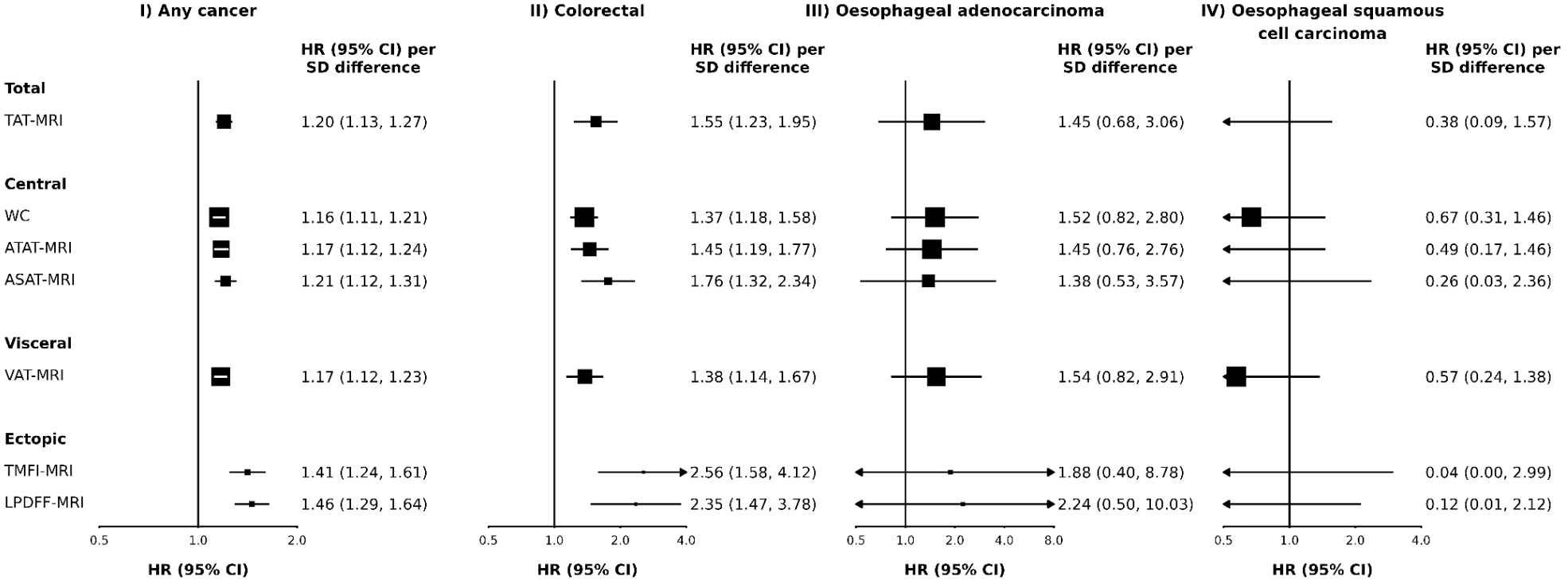

V) Liver
HR (95% CI) per SD difference
Total
BMI
1.78 (1.03, 3.08)
TAT-MRI
1.84 (1.03, 3.27)
Central
ATAT-MRI
1.87 (1.03, 3.38)
ASAT-MRI
1.87 (1.03, 3.40)
Visceral
VAT-MRI
2.53 (1.01, 6.31)
Ectopic
TMFI-MRI
3.10 (1.10, 8.74)
LPDFF-MRI
4.98 (0.91, 27.13)
0.5
1.0
2.0
4.0
8.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
1.00 (0.94, 1.07)
1.00 (0.93, 1.08)
1.00 (0.93, 1.08)
0.99 (0.92, 1.07)
1.01 (0.94, 1.10)
1.00 (0.88, 1.14)
0.98 (0.82, 1.17)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.21 (1.05, 1.40)
1.23 (1.05, 1.44)
1.23 (1.05, 1.44)
1.24 (1.05, 1.45)
1.27 (1.05, 1.53)
1.43 (1.09, 1.88)
2.15 (1.18, 3.91)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
1.73 (1.41, 2.13)
1.78 (1.42, 2.23)
1.78 (1.43, 2.21)
1.79 (1.44, 2.22)
2.01 (1.53, 2.64)
2.82 (1.89, 4.18)
9.64 (4.26, 21.84)
1
2
4
8
16
32
HR (95% CI)

Figure 6.8 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of adiposity traits based on imputed category medians within WC deciles in those who were part of the imaging sub-cohort

Conventions as in Figure 6.3.



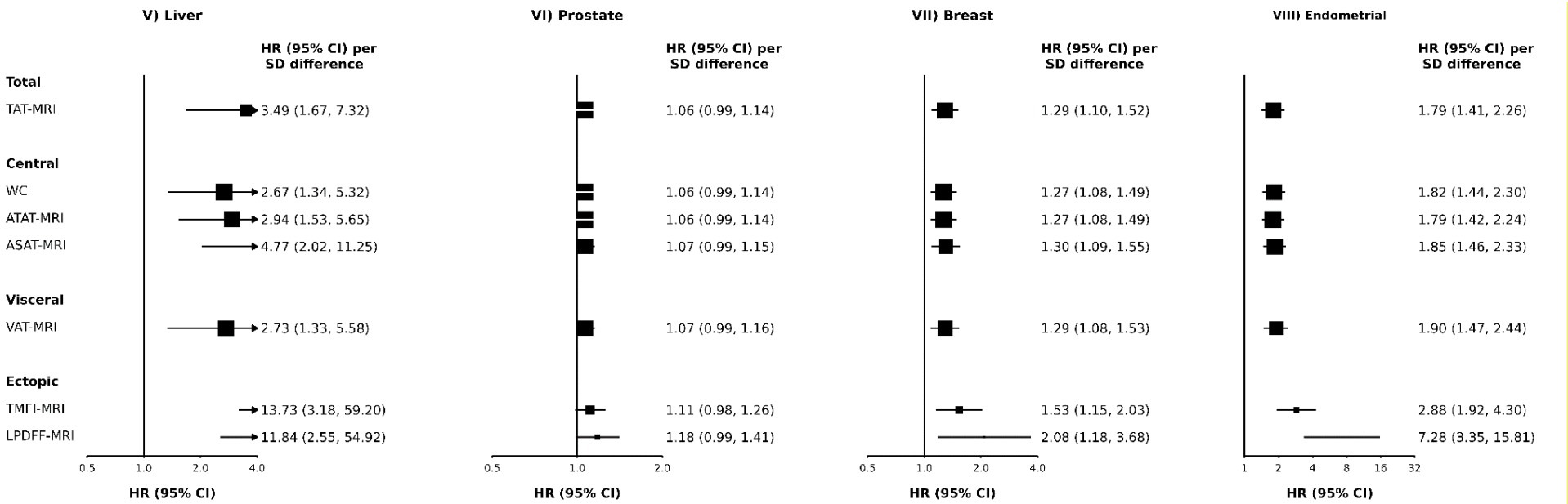
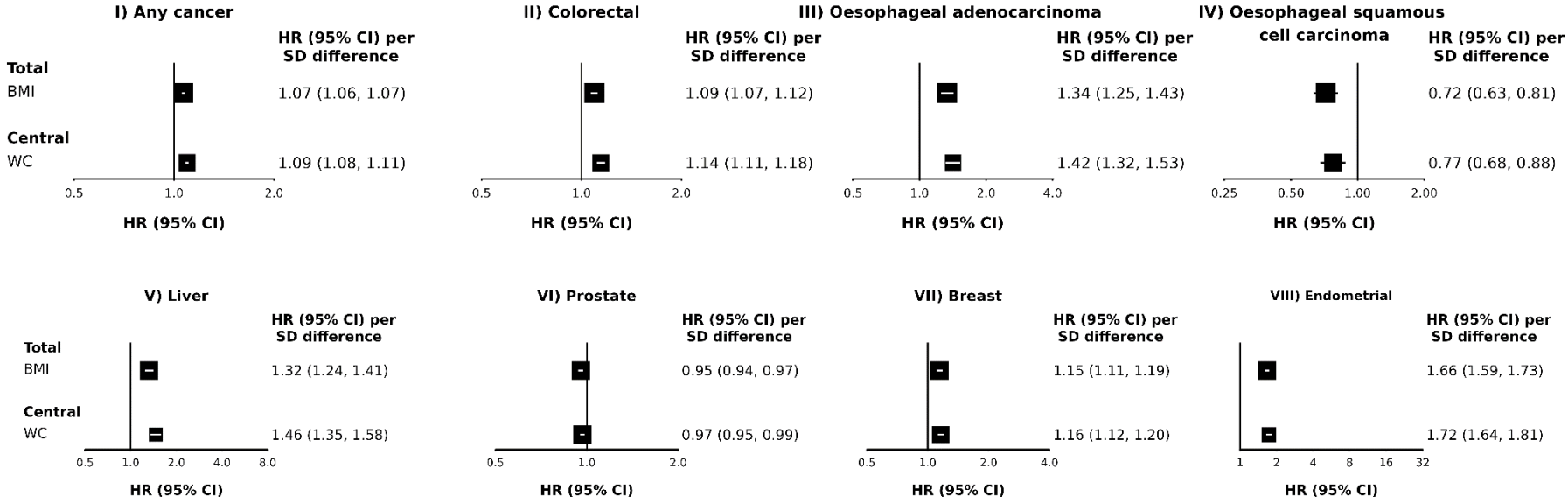

V) Liver
HR (95% CI) per SD difference
Total
TAT-MRI
3.49 (1.67, 7.32)
Central
WC
2.67 (1.34, 5.32)
ATAT-MRI
2.94 (1.53, 5.65)
ASAT-MRI
4.77 (2.02, 11.25)
Visceral
VAT-MRI
2.73 (1.33, 5.58)
Ectopic
TMFI-MRI
13.73 (3.18, 59.20)
LPDFF-MRI
11.84 (2.55, 54.92)
0.5
1.0
2.0
4.0
HR (95% CI)
VI) Prostate
HR (95% CI) per SD difference
1.06 (0.99, 1.14)
1.06 (0.99, 1.14)
1.06 (0.99, 1.14)
1.07 (0.99, 1.15)
1.07 (0.99, 1.16)
1.11 (0.98, 1.26)
1.18 (0.99, 1.41)
0.5
1.0
2.0
HR (95% CI)
VII) Breast
HR (95% CI) per SD difference
1.29 (1.10, 1.52)
1.27 (1.08, 1.49)
1.27 (1.08, 1.49)
1.30 (1.09, 1.55)
1.29 (1.08, 1.53)
1.53 (1.15, 2.03)
2.08 (1.18, 3.68)
0.5
1.0
2.0
4.0
HR (95% CI)
VIII) Endometrial
HR (95% CI) per SD difference
1.79 (1.41, 2.26)
1.82 (1.44, 2.30)
1.79 (1.42, 2.24)
1.85 (1.46, 2.33)
1.90 (1.47, 2.44)
2.88 (1.92, 4.30)
7.28 (3.35, 15.81)
1
2
4
8
16
32
HR (95% CI)

Figure 6.9 Adjusted HRs for incidence of total and selected site-specific cancers per SD increase of BMI and WC measured at baseline

The entire UKB cohort was stratified into BMI deciles measured at baseline. The imputed category median BMI was estimated as the median BMI at imaging within each decile of BMI at baseline. This adiposity trait was treated continuously to assess the risk trends per SD. The same method was repeated for WC. The plotted square presents the coefficient of each of the standardised adiposity traits from the multivariable Cox Hazards model that adjusted for sex, age, smoking status, alcohol intake in drinks per week, education, fifths of Townsend Deprivation index score, and where appropriate number of live births, menopausal status, years since menopause, and use of menopause hormone therapy. The vertical line marks HR=1 and box sizes are proportional to the inverse variance of the log HR. Standard deviations are in Table 2.2.



Chapter 7. General discussion

7.1 Summary of key findings

Anthropometric measures such as BMI and WC are widely used in epidemiological studies to assess adiposity. However, these metrics neither differentiate between lean and fat mass nor provide detailed information about body fat composition and their associations with specific diseases and associated traits. Advanced imaging techniques like MRI and DXA enable precise evaluations of specific body fat components, offering an accurate assessment of adiposity and its relevance for the aetiology of multiple diseases in prospective cohort studies.

7.1.1 Correlations between anthropometric and imaging-derived adiposity

Chapter 3 investigated the correlations between anthropometric and MRI- or DXA-based measures of adiposity through a systematic review and meta-analysis of 42 studies, alongside a cross-sectional analysis of UKB participants who underwent concurrent body fat assessments using anthropometric measures, MRI, and DXA imaging.

The findings from the literature review and meta-analysis, as well as the UKB analysis, were consistent and revealed several key insights. While BMI, WC, and %BF showed strong correlations with imaging-derived measures of total and central adiposity, particularly within the total and subcutaneous adiposity, they were weakly correlated with visceral adiposity. On the other hand, while WHR generally exhibited weaker correlations with imaging-derived adiposity overall, it showed a somewhat stronger correlation with visceral adiposity. This suggested that, at a population level, BMI, WC, and %BF are more reliable indicators of total and central adiposity, and

somewhat less so of visceral adiposity. WHR is a less reliable indicator of total and central adiposity, perhaps due to the presence of measurement error in both WC and hip circumference required for its calculation, but it appeared to better capture visceral adiposity compared with other adiposity traits.

Weaker correlations were observed between anthropometric measures and ectopic adiposity, such as liver adiposity and TMFI, suggesting that anthropometric measures of adiposity may not accurately capture certain types of body fat which are considered to be more oncogenic and more metabolically active than others (31).

Sex differences in correlations were also identified. Women exhibited stronger correlations between BMI, WC and %BF with most measures of total and central adiposity, which aligns with their typically gynoid fat distribution pattern (31). In contrast, men demonstrated greater correlations between WHR and most markers of total, central and visceral adiposity, consistent with their tendency toward a greater android fat distribution pattern (31). These findings emphasise the importance of accounting for sex-specific differences when interpreting associations between adiposity and disease outcomes.

In summary, Chapter 3 highlighted that while anthropometric measures of adiposity are strongly correlated with imaging-derived measures of total abdominal, subcutaneous abdominal, and to a slightly lesser extent with visceral adiposity, their correlations are weaker with imaging-derived ectopic adiposity such as liver adiposity and TMFI. This suggested the need to investigate further and compare the magnitude of the associations of anthropometric and imaging-derived measures of adiposity, particularly visceral and ectopic fat, with risks of specific diseases and their intermediate markers in large population-based studies.

7.1.2 Comparison of associations of different adiposity traits with intermediate markers of disease

Chapter 4 provided a detailed cross-sectional analysis of the associations between different body fat components and intermediate markers of disease in the UKB, which is, to the author's knowledge, the first study of this kind.

These findings showed that visceral, and to some extent liver adiposity, measured by MRI were more strongly associated with key disease markers such as blood lipids, blood pressure, and blood proteins (e.g. TG, DBP and HbA1c respectively) compared with measures of total or central adiposity. This highlighted the critical role of visceral and liver adiposity in influencing metabolic health.

Findings here suggest that while associations of commonly used anthropometric measures, such as BMI and WC with intermediate markers of disease were similar to those for most imaging-based measures, they were of a weaker magnitude than those from visceral adiposity, and to some extent, liver adiposity. Despite the limitations of anthropometric methods in accurately capturing body fat composition, they remain valuable tools for capturing associations with intermediate disease markers in population-based studies. However, imaging techniques provide greater precision, particularly in assessing visceral and liver adiposity, and may offer enhanced insights into disease mechanisms, risk prediction and potentially more targeted management.

7.1.3 Comparison of associations of different adiposity traits with disease risks

Chapter 5 presented detailed analyses of associations of different body fat components with CMD and cancer risks. The study was done in the imaging sub-

cohort that had their body fat measured with anthropometric and/or imaging methods.

Firstly, considering that CMD is well-established to be associated with increased BMI and WC, the risks of IHD and T2D in relation to different body fat components were assessed. Positive associations were observed between various adiposity traits and risks of IHD and T2D, with central and visceral adiposity having a somewhat stronger association with T2D compared to total or ectopic adiposity.

For cancer, there were positive associations between adiposity traits and risks of colorectal cancer, breast cancer, and all cancers, with similar magnitude of associations across different body fat components. In contrast, no evidence of an association was observed between the risk of prostate cancer and adiposity based on a more limited number of cases, which should be interpreted with caution.

To improve the study power of cancer outcomes, Chapter 6 analysed prospective associations of different adiposity traits with risks of cancer in the entire UKB cohort. Since imaging-derived adiposity traits were not available at baseline, they were estimated as imputed category medians within BMI and WC deciles. Across the entire cohort, all body fat components showed strong positive associations with risks of colorectal cancer, oesophageal adenocarcinoma, liver cancer, breast cancer, endometrial cancer, and total cancer. In contrast, a strongly negative association was identified with OSCC and a slightly significant negative association with prostate cancer. Importantly, the strength of these associations varied by the body fat component (except for prostate cancer), with measures of liver adiposity showing the strongest association with cancer risk, surpassing those of total, central, or visceral adiposity.

The greater association of liver adiposity with endometrial cancer in particular, was striking compared to other body fat components. However, this finding should be interpreted with caution, as it may partly reflect methodological artefact. While additional analyses found no evidence of reverse causation, there was some evidence that adiposity traits estimated using the imputed category medians may have led to an overestimation of risks. Specifically, associations between actual baseline BMI and WC with endometrial cancer were somewhat of a weaker magnitude than those observed for BMI and WC using the imputed category medians. However, this difference was of small magnitude, supporting the overall reliability of the imputed category medians method of estimating the adiposity traits.

These findings underscore the potential importance of liver adiposity in cancer risk and highlight the need for future research to consider specific adiposity traits when evaluating cancer risks.

In contrast to findings in the imaging sub-cohort, which showed directionally consistent findings across different body fat components, the analysis of the entire baseline cohort with greater statistical power detected differences in the magnitude and direction of the associations with certain cancers across adiposity traits. Further studies are needed to confirm (or refute) these findings.

7.2 Strengths and limitations

The primary strength of this study is its large sample size, with participants having their body fat measured simultaneously using both anthropometric and imaging methods. This is the first time that such a large sample size was available to allow for (i) a direct comparison of the correlations between anthropometric and imaging-derived adiposity within the same population and (ii) an assessment of the

associations between various body fat components measured through both anthropometric and imaging methods with disease risks and their intermediate markers.

However, this study also has certain limitations. Firstly, there was a relatively small number of disease cases in the imaging sub-cohort, which reduced statistical power and limited the site-specific cancers that could be investigated. A longer follow-up period is needed to robustly investigate reverse causation and capture a greater number of cases.

Secondly, for the analysis of the entire UKB at baseline, the imaging-derived adiposity was not available. Instead, a calibration study approach was used. Specifically, adiposity traits were estimated as the imputed category medians within BMI and WC deciles at baseline. This approach brings two issues that need to be discussed.

The first issue is selection bias. Participants in the imaging sub-cohort were slightly younger, better educated, more likely to consume alcohol, had a lower prevalence of postmenopausal women, and exhibited lower mean adiposity values. Consequently, they may have been healthier in terms of body fat distribution. Despite this, comparisons of BMI and WC within BMI categories (based on WHO overweight/obesity definitions) between those in the entire cohort and those in the imaging sub-cohort indicated they had similar body fat distribution, reducing concerns about representativeness in this regard.

The second issue is the uncertainty regarding how representative the adiposity traits taken, on average, 10 years after baseline were for the entire UKB cohort. As a result, adiposity traits were incorporated at approximately two-thirds of the way

through the follow-up period, rather than at the midpoint, which would have been more ideal. Nonetheless, while these measures were taken later, they still captured adiposity trends during a substantial portion of the follow-up period.

Thirdly, while the study demonstrated associations between different body fat components and various intermediate markers of disease and disease risks, it did not establish causal relationships, for example, by employing MR. Previous MR studies have mainly focused on anthropometric measures of adiposity such as BMI in relation to cancer risk, with a lack of studies measuring specific body fat components.

Fourthly, although efforts were made to assess the presence of reverse causation by excluding individuals with a follow-up period of less than 3 years in the imaging sub-cohort and 5 years for the entire baseline cohort, this approach had limitations. In some cases, preclinical symptoms may emerge up to 10 years before disease diagnosis, potentially influencing the association between adiposity and disease risk (250).

Fifthly, the cohort was predominantly White and middle-aged, which may limit the generalisability of the findings. This is particularly relevant as central and visceral adiposity tend to increase with age, while lean muscle mass declines (176). Moreover, there was also evidence of differences in body shape across different ethnic populations, with for example East Asians more likely to have central obesity for a given BMI (251). As a result, the comparative associations observed in this study may not apply to older and other ancestry populations. Furthermore, previous studies suggest that individuals of Asian-Pacific ancestry, although they might have a lower prevalence of overweight and obesity compared to White populations, have

increased CVD risks associated with excess adiposity at lower BMI levels (252, 253). However, due to the limited representation of Asian participants in the UKB cohort, this thesis did not investigate associations between different adiposity traits, intermediate markers, and disease risk in this population.

Finally, the study did not compare cancer incidence with cancer mortality risks, which could have provided more insight into whether certain body fat components are more indicative of death from incidence.

7.3 Clinical and public health implications

Firstly, imaging-based measures of adiposity, such as MRI and DXA, provide a more accurate assessment of body fat distribution, distinguishing between total, central, visceral and ectopic adiposity. This level of precision is crucial not only for understanding the pathophysiology of obesity-related diseases but also for identifying individuals who might benefit most from emerging obesity treatments, such as pharmacological interventions. In particular, individuals with normal or overweight BMI but elevated visceral and/or ectopic liver fat may benefit the most from such approaches. For instance, individuals with high levels of visceral and/or liver adiposity, which are strongly associated with metabolic dysfunction cardiovascular and cancer risk (11), could be prime candidates for obesity drugs that target fat reduction or metabolic improvement. By using imaging to identify these high-risk individuals, clinicians can better target their therapeutic strategies, ensuring that obesity drugs are prescribed to those who stand to gain the most from them. This approach not only enhances the efficacy of treatment but also supports more personalised, effective disease prevention and management.

Secondly, the robust cross-sectional analysis not only expands our understanding of adiposity's role in disease, but also lays the foundation for future longitudinal studies that investigate how changes in body fat components over time influence disease development.

Thirdly, although imaging-derived adiposity offers accurate measurements of specific body fat components, its cost remains high. A key finding of this thesis is that anthropometric measures, such as BMI and WC, demonstrated associations with cancer risks of a similar magnitude to certain imaging-derived measures of total, visceral, or central adiposity. This suggests that at a population level, conventional anthropometric measures are reliable estimates of cancer risk. This is in line with the recommendations from a recent report in the Lancet Diabetes and Endocrinology Commission particularly for BMI (254). However, it was also found that for certain cancers, such as endometrial cancer, excess liver adiposity had a greater magnitude of an association with cancer risk than other body fat components, underscoring the importance of considering ectopic adiposity in cancer risk assessments. These results, being the first of their kind, should be interpreted with caution, especially given the lack of detailed evidence on underlying mechanisms.

7.4 Future research

This thesis suggests several avenues for future research in this field.

Firstly, once the body fat components for all 100,000 UKB participants in the imaging sub-cohort are fully processed, analyses should be repeated to further validate the study findings with greater power. Additionally, the prospective analysis should be revisited once a follow-up period of at least 10 years has been reached to allow sufficient numbers of cancer cases.

Secondly, the imaging-derived adiposity was not available for the entire UKB cohort. Future research could explore alternative methods, such as imputation techniques, to estimate MRI- or DXA-derived adiposity more accurately.

Thirdly, to address reverse causation, future studies should be conducted with a follow-up period longer than ten years. This would help account for the possibility that preclinical cancer symptoms, which may lead to adiposity loss before diagnosis, could influence the observed associations.

Fourthly, to eliminate residual confounding from smoking and alcohol consumption, analyses should be repeated among non-smokers and non-drinkers. This would provide a clearer understanding of the associations between adiposity and disease markers and cancer risks, independent of smoking- or alcohol-related effects.

Fifthly, further investigation into the burden of excess adiposity on cancer risk should also include cancer mortality rates. This will help to more comprehensively assess the effectiveness of cancer prevention and treatment programmes aimed at reducing adiposity.

Sixthly, an intriguing question that arises from this thesis is whether the associations between total, central, visceral, and ectopic adiposity with cancer risk are independent of one another. Future research should aim to determine the extent to which these types of adiposities contribute independently to cancer risk, which, while requiring much bigger datasets, could have important implications for public health strategies.

Seventhly, future studies should consider more diverse cohorts to assess whether these associations are consistent across different populations. Examining potential interactions between adiposity, genetic factors, and environmental influences would

provide a more comprehensive understanding of how adiposity impacts disease risk and would help refine strategies for targeted disease prevention and management.

Eighthly, future research in this area could benefit from a multi-omics approach to better understand the complex relationships between adiposity and disease outcomes. Integrating multi-omics could reveal how genetic variations, epigenetic modifications, gene expression patterns, protein profiles, metabolic shifts, and gut microbiome composition influence the development of excess adiposity with cardio-metabolic diseases and cancer. Specifically, investigating how genetic predispositions and epigenetic changes contribute to different body fat distributions, such as visceral versus subcutaneous fat, could uncover novel biomarkers and therapeutic targets. Additionally, exploring the interaction between proteins, metabolites, and microbial communities in individuals with varying adiposity may offer insights into disease mechanisms and identify potential intervention points. By combining these omics layers, it is possible to create a more comprehensive model of disease risk, improving prediction, prevention, and personalised treatment strategies for CMD and cancer.

Finally, genetic studies such as MR should be employed to provide further evidence for potential causal relationships. Particularly, future studies are needed to generate genetic instruments that estimate more precise measures of body fat distribution, including visceral and ectopic adiposity, within an MR framework. This would enable researchers to explore whether certain body fat components are more oncogenic than others, thereby informing more effective strategies for the prevention and management of adiposity-related diseases.

7.5 Conclusion

This thesis systematically investigated the correlations between anthropometric and imaging-derived adiposity traits, their associations with intermediate disease markers, and with CMD and cancer risk. It was found that BMI, WC, and %BF strongly correlated with total and subcutaneous adiposity, but to a lesser extent with visceral adiposity. WHR showed weaker correlations but had a relatively greater correlation with visceral fat. Correlations of anthropometric measures with ectopic adiposity (e.g. liver and muscle fat infiltration) were weaker.

Analyses of the intermediate markers showed that visceral and liver adiposity, measured by MRI, showed greater associations with key disease markers of blood lipids, blood pressure, and blood proteins (e.g. TG, DBP, HbA1c) compared to total or central adiposity.

The prospective analysis in the UKB imaging sub-cohort confirmed established associations between greater adiposity and a greater risk of T2D and IHD. Expanding this analysis to cancer risk revealed positive associations between increased adiposity with colorectal cancer, breast cancer, and all cancers combined, but no association with prostate cancer. However, no differences in the strength of the associations with any of these disease risks across different adiposity traits were observed, except for T2D, for which visceral and central adiposity showed a greater association compared to total or ectopic adiposity.

Due to limited statistical power in the imaging sub-cohort, a subsequent prospective analysis using the entire UKB baseline cohort was conducted. This revealed positive associations between different body fat components with colorectal cancer, liver cancer, breast cancer, endometrial cancer, and all cancers combined, and a

negative association with OSCC risk and prostate cancer risk. Liver adiposity had a greater magnitude of association with most cancer risks, particularly endometrial cancer. Overall, this work highlights the relevance of detailed adiposity assessments in understanding the association between body fat distribution and cancer risk.

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Appendix A. Additional analyses in the entire UK Biobank cohort

Table A.1 Baseline characteristics of women in the entire UK Biobank by BMI classification

Baseline Characteristics in Women	BMI classification, kg/m^2					
	<18 (N=2,079)	**18-25 (N=105,623)**	**25-30 (N=99,840)**	**30-35 (N=42,710)**	**35-40 (N=14,941)**	**>40 (N=6,642)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	56 (8)	55 (8)	57 (8)	57 (8)	57 (8)	55 (8)
College or University degree, %	42	38	29	25	23	22
Ancestry White, %	94	96	95	93	93	92
Menopausal females, %	73	68	75	76	74	70
Ever regular smoker, %	41	39	41	41	42	42
Weekly alcohol drinking, %	56	69	63	53	44	34
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.2 (0.8)	22.7 (1.6)	27.2 (1.4)	32.1 (1.4)	37.0 (1.4)	43.9 (3.9)
%BF	19.3 (4.5)	30.8 (4.7)	37.9 (3.5)	43.0 (3.1)	46.6 (2.9)	50.1 (3.3)
Central adiposity, Mean (SD)						
WC, cm	64.3 (4.7)	74.8 (6.2)	85.4 (6.9)	96.1 (7.3)	105.6 (7.7)	116.9 (10.1)
WHR	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	126.2 (19.7)	131.1 (19.1)	137.0 (19.0)	139.6 (18.3)	140.6 (18.0)	142.1 (18.0)
Diastolic	74.8 (10.5)	77.7 (9.6)	81.4 (9.5)	84.1 (9.4)	85.9 (9.6)	87.9 (10.0)
Pulse	51.4 (17.4)	53.4 (15.6)	55.6 (16.1)	55.5 (16.4)	54.7 (15.6)	54.2 (15.1)
Blood lipid, Mean (SD), mmol/L						
LDL-C	3.3 (0.8)	3.5 (0.8)	3.7 (0.9)	3.7 (0.9)	3.6 (0.9)	3.5 (0.9)
HDL-C	1.9 (0.5)	1.7 (0.4)	1.6 (0.4)	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)
TG	1.1 (0.5)	1.3 (0.6)	1.6 (0.9)	1.9 (1.0)	2.0 (1.0)	2.0 (1.0)
Total cholesterol	4.8 (0.9)	4.9 (0.9)	4.9 (0.9)	4.8 (1.0)	4.6 (0.9)	4.4 (0.9)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	35.1 (3.9)	34.6 (4.3)	35.7 (5.5)	37.3 (7.2)	38.9 (8.7)	40.9 (10.5)
IGF-1, nmol/L	19.7 (5.3)	21.7 (5.7)	21.2 (5.7)	20.0 (5.7)	18.8 (5.7)	17.5 (5.5)
CRP, mg/L	1.2 (3.3)	1.6 (3.6)	2.5 (3.9)	4.0 (4.7)	5.6 (5.6)	8.2 (7.0)
Sex hormone, Mean (SD)						
SHBG, nmol/L	96.3 (34.5)	74.8 (31.3)	58.5 (28.3)	47.4 (24.6)	42.1 (22.2)	38.7 (21.1)
Testosterone, nmol/L	1.0 (0.6)	1.1 (0.6)	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)	1.3 (0.7)
Oestradiol in premenopausal females, pmol/L	545.5 (399.4)	599.2 (511.1)	569.8 (480.8)	539.5 (494.1)	503.1 (353.9)	510.9 (397.0)

Table A.2 Baseline characteristics of men in the entire UK Biobank by BMI classification

Baseline Characteristics in Men	BMI classification, kg/m^2					
	<18 (N=547)	**18-25 (N=56,726)**	**25-30 (N=112,217)**	**30-35 (N=44,822)**	**35-40 (N=10,048)**	**>40 (N=3,057)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	56 (8)	56 (8)	57 (8)	57 (8)	57 (8)	56 (8)
College or University degree, %	26	43	34	26	23	21
Ancestry White, %	92	94	95	95	96	96
Ever regular smoker, %	63	45	51	56	58	56
Weekly alcohol drinking, %	65	78	79	75	69	58
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.1 (0.8)	23.2 (1.4)	27.4 (1.4)	31.9 (1.4)	36.9 (1.4)	43.6 (3.6)
%BF	11.7 (4.2)	19.5 (4.4)	25.2 (3.8)	30.1 (3.3)	34.4 (3.0)	39.1 (3.4)
Central adiposity, Mean (SD)						
WC, cm	72.0 (5.8)	85.8 (6.2)	95.9 (6.2)	106.8 (6.6)	118.1 (7.1)	131.9 (9.9)
WHR	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	129.6 (21.0)	136.6 (17.6)	141.6 (17.1)	143.9 (17.2)	144.1 (17.1)	144.6 (17.4)
Diastolic	77.8 (11.4)	80.7 (9.7)	84.4 (9.7)	86.7 (9.9)	87.4 (10.2)	87.6 (10.6)
Pulse	51.9 (11.5)	55.9 (14.2)	57.2 (14.3)	57.3 (14.2)	56.7 (14.4)	57.0 (14.6)
Blood lipid, Mean (SD), mmol/L						
LDL-C	2.9 (0.8)	3.4 (0.8)	3.5 (0.9)	3.4 (0.9)	3.3 (0.9)	3.1 (0.9)
HDL-C	1.6 (0.4)	1.4 (0.3)	1.3 (0.3)	1.2 (0.3)	1.1 (0.2)	1.1 (0.2)
TG	1.1 (0.9)	1.5 (0.9)	2.0 (1.1)	2.4 (1.3)	2.5 (1.3)	2.4 (1.3)
Total cholesterol	4.1 (0.9)	4.5 (0.9)	4.4 (0.9)	4.3 (0.9)	4.1 (0.9)	3.9 (0.9)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	35.5 (6.7)	35.0 (6.1)	36.0 (6.6)	38.2 (8.8)	41.2 (11.5)	44.1 (12.9)
IGF-1, nmol/L	18.0 (5.9)	22.1 (5.3)	22.3 (5.4)	21.2 (5.7)	19.7 (5.8)	18.8 (6.2)
CRP, mg/L	3.2 (7.8)	1.9 (4.2)	2.3 (4.2)	3.0 (4.4)	4.0 (4.9)	5.6 (5.8)
Sex hormone, Mean (SD)						
SHBG, nmol/L	70.9 (26.6)	47.1 (18.4)	38.5 (15.4)	34.6 (14.6)	32.9 (15.0)	31.9 (15.2)
Testosterone, nmol/L	14.6 (5.1)	13.4 (3.8)	12.0 (3.5)	10.8 (3.4)	9.9 (3.3)	8.9 (3.4)

Table A.3 Baseline characteristics of women who participated in the imaging sub-cohort by BMI classification

Baseline Characteristics in Women	BMI classification, kg/m^2					
	<18 (N=247)	**18-25 (N=15,499)**	**25-30 (N=11,506)**	**30-35 (N=4,067)**	**35-40 (N=1,221)**	**>40 (N=423)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	53 (7)	54 (7)	55 (7)	55 (7)	54 (7)	53 (7)
College or University degree, %	55	49	40	38	37	34
Ancestry White, %	96	97	97	97	96	95
Menopausal females, %	62	60	66	65	62	56
Ever regular smoker, %	32	34	37	38	39	38
Weekly alcohol drinking, %	67	75	70	62	53	43
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.2 (0.8)	22.6 (1.6)	27.1 (1.4)	32.0 (1.4)	37.0 (1.4)	43.3 (3.2)
%BF	18.7 (3.7)	30.5 (4.6)	37.6 (3.5)	42.9 (3.0)	46.6 (3.0)	49.8 (2.9)
Central adiposity, Mean (SD)						
WC, cm	64.0 (4.5)	74.3 (6.0)	84.5 (6.7)	95.0 (7.2)	104.5 (7.6)	115.2 (9.4)
WHR	0.7 (0.0)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.9 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	120.0 (15.5)	128.0 (17.7)	133.5 (17.8)	136.8 (17.4)	138.8 (16.5)	140.3 (17.4)
Diastolic	73.2 (8.7)	76.9 (9.3)	80.7 (9.3)	84.0 (9.1)	86.3 (8.8)	88.7 (9.3)
Pulse	46.8 (17.2)	51.0 (15.5)	52.7 (16.1)	52.9 (16.4)	52.6 (15.6)	51.7 (15.2)
Blood lipid, Mean (SD), mmol/L						
LDL-C	3.4 (0.8)	3.5 (0.8)	3.7 (0.8)	3.7 (0.8)	3.7 (0.8)	3.6 (0.8)
HDL-C	1.9 (0.5)	1.7 (0.4)	1.6 (0.3)	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)
TG	1.0 (0.5)	1.2 (0.6)	1.5 (0.8)	1.8 (0.9)	2.0 (1.0)	2.0 (1.0)
Total cholesterol	5.0 (0.9)	4.8 (0.9)	4.9 (0.9)	4.8 (0.9)	4.7 (0.9)	4.5 (0.8)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	34.3 (3.5)	34.1 (3.9)	34.8 (4.3)	36.0 (5.4)	37.7 (8.2)	39.6 (9.0)
IGF-1, nmol/L	20.6 (5.3)	22.1 (5.6)	21.8 (5.7)	20.7 (5.6)	19.3 (5.5)	17.6 (5.2)
CRP, mg/L	0.6 (0.9)	1.4 (3.1)	2.2 (3.6)	3.5 (4.2)	5.1 (4.4)	7.6 (6.4)
Sex hormone, Mean (SD)						
SHBG, nmol/L	96.7 (32.8)	75.4 (31.2)	58.8 (28.3)	47.6 (24.3)	39.7 (19.9)	37.0 (19.7)
Testosterone, nmol/L	1.2 (0.8)	1.1 (0.6)	1.1 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)
Oestradiol in premenopausal females, pmol/L	591.1 (382.9)	600.6 (553.3)	595.8 (620.8)	559.3 (446.5)	501.7 (315.8)	455.5 (292.6)

Table A.4 Baseline characteristics of men who participated in the imaging sub-cohort by BMI classification

Baseline Characteristics in Men	BMI classification, kg/m^2					
	<18 (N=40)	**18-25 (N=8,972)**	**25-30 (N=15,796)**	**30-35 (N=5,040)**	**35-40 (N=887)**	**>40 (N=223)**
Sociodemographic and lifestyle						
Age, Mean (SD), years	53 (8)	55 (8)	56 (8)	55 (7)	55 (7)	54 (7)
College or University degree, %	63	57	45	39	37	35
Ancestry White, %	89	96	97	97	98	98
Ever regular smoker, %	37	36	44	51	50	50
Weekly alcohol drinking, %	68	83	84	81	76	66
Total adiposity, Mean (SD)						
BMI, kg/m^2	17.2 (0.8)	23.2 (1.4)	27.3 (1.4)	31.8 (1.3)	36.8 (1.3)	43.0 (2.8)
%BF	10.2 (3.6)	19.3 (4.2)	24.8 (3.6)	29.6 (3.2)	34.2 (2.9)	38.7 (3.0)
Central adiposity, Mean (SD)						
WC, cm	72.4 (4.9)	85.4 (6.0)	95.2 (6.1)	105.8 (6.2)	117.4 (6.7)	130.1 (9.1)
WHR	0.8 (0.0)	0.9 (0.1)	0.9 (0.0)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Blood pressure, Mean (SD), mmHg						
Systolic	126.5 (17.9)	134.8 (16.4)	140.0 (16.1)	142.3 (16.0)	142.7 (15.8)	142.2 (16.7)
Diastolic	75.9 (8.6)	80.3 (9.4)	84.3 (9.3)	86.9 (9.4)	88.5 (9.7)	88.3 (9.8)
Pulse	50.6 (11.5)	54.5 (14.2)	55.7 (14.3)	55.4 (14.2)	54.3 (14.4)	53.9 (14.7)
Blood lipid, Mean (SD), mmol/L						
LDL-C	2.8 (0.8)	3.5 (0.8)	3.6 (0.8)	3.6 (0.9)	3.5 (0.9)	3.2 (0.8)
HDL-C	1.7 (0.4)	1.4 (0.3)	1.3 (0.3)	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)
TG	0.8 (0.4)	1.5 (0.8)	2.0 (1.1)	2.4 (1.3)	2.5 (1.3)	2.3 (1.1)
Total cholesterol	4.4 (0.9)	4.5 (0.8)	4.5 (0.9)	4.4 (0.9)	4.3 (0.9)	4.0 (0.8)
Blood protein, Mean (SD)						
HbA1c, mmol/mol	35.0 (3.2)	34.3 (4.1)	35.1 (5.2)	36.6 (6.9)	39.0 (8.7)	41.3 (10.8)
IGF-1, nmol/L	18.4 (5.0)	22.5 (5.0)	22.8 (5.2)	21.7 (5.3)	20.0 (5.6)	18.8 (5.5)
CRP, mg/L	0.5 (0.5)	1.5 (3.5)	1.9 (3.2)	2.6 (3.5)	3.7 (3.9)	5.1 (4.5)
Sex hormone, Mean (SD)						
SHBG, nmol/L	57.5 (20.1)	45.3 (16.4)	37.5 (14.5)	33.1 (13.6)	30.9 (12.4)	31.9 (15.6)
Testosterone, nmol/L	14.2 (3.7)	13.4 (3.6)	12.1 (3.5)	10.9 (3.1)	9.8 (3.1)	9.3 (3.5)

Table A.5 Number of available adiposity traits measured at imaging visit by BMI deciles at baseline

BMI at baseline decile	Measured at the imaging visit						
	BMI	TAT-MRI	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	7,277	958	4,571	4,587	4,152	1,088	4,527
2	7,678	1,117	5,027	5,034	4,498	1,245	4,973
3	7,414	979	4,732	4,739	4,241	1,100	4,686
4	6,964	944	4,381	4,386	3,945	1,088	4,313
5	6,643	910	4,219	4,230	3,808	1,061	4,135
6	6,395	862	4,092	4,101	3,624	991	4,018
7	6,079	793	3,811	3,818	3,437	937	3,731
8	5,750	791	3,574	3,582	3,228	928	3,493
9	5,068	657	3,121	3,131	2,774	788	3,029
10	4,162	498	2,495	2,497	2,247	651	2,390

Table A.6 Number of available adiposity traits measured at imaging visit by BMI deciles at baseline in women

Women BMI at baseline decile	Measured at the imaging visit						
	BMI	TAT-MRI	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	3,978	2,266	2,490	516	2,501	585	2,478
2	4,114	2,335	2,618	562	2,623	620	2,606
3	3,920	2,287	2,582	589	2,584	640	2,572
4	3,708	2,110	2,364	511	2,369	570	2,348
5	3,362	1,943	2,141	475	2,147	529	2,124
6	3,166	1,782	2,012	454	2,014	495	1,999
7	2,937	1,655	1,851	431	1,854	474	1,839
8	2,844	1,629	1,810	419	1,812	468	1,797
9	2,536	1,358	1,561	379	1,566	425	1,541
10	2,162	1,169	1,319	281	1,320	331	1,299

Table A.7 Number of available adiposity traits measured at imaging visit by BMI deciles at baseline in men

Men	Measured at the imaging visit						
BMI at baseline decile	BMI	TAT-MRI	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	3,487	2,050	2,256	483	2,261	556	2,206
2	3,631	2,069	2,291	449	2,295	522	2,252
3	3,457	1,976	2,186	465	2,186	552	2,133
4	3,414	1,949	2,158	448	2,162	535	2,107
5	3,256	1,868	2,077	434	2,084	519	2,018
6	3,148	1,779	1,985	378	1,989	459	1,930
7	2,952	1,677	1,864	390	1,869	480	1,805
8	2,816	1,560	1,720	348	1,726	432	1,659
9	2,451	1,360	1,504	271	1,506	347	1,443
10	2,091	1,132	1,234	226	1,237	338	1,139

Table A.8 Number of available adiposity traits measured at imaging visit by WC deciles at baseline

	Measured at the imaging visit						
WC at baseline decile	TAT-MRI	WC	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	1,080	7,728	4,965	4,975	4,517	1,209	4,933
2	1,034	7,359	4,646	4,660	4,170	1,142	4,614
3	978	6,906	4,420	4,428	3,959	1,085	4,372
4	909	6,797	4,308	4,314	3,878	1,013	4,264
5	877	6,506	4,100	4,109	3,682	1,003	4,048
6	906	6,650	4,169	4,177	3,755	1,063	4,080
7	811	6,273	3,964	3,968	3,544	960	3,888
8	767	5,942	3,706	3,714	3,297	915	3,608
9	641	5,270	3,245	3,255	2,924	814	3,122
10	512	4,234	2,525	2,530	2,253	679	2,390

Table A.9 Number of available adiposity traits measured at imaging visit by WC deciles at baseline in women

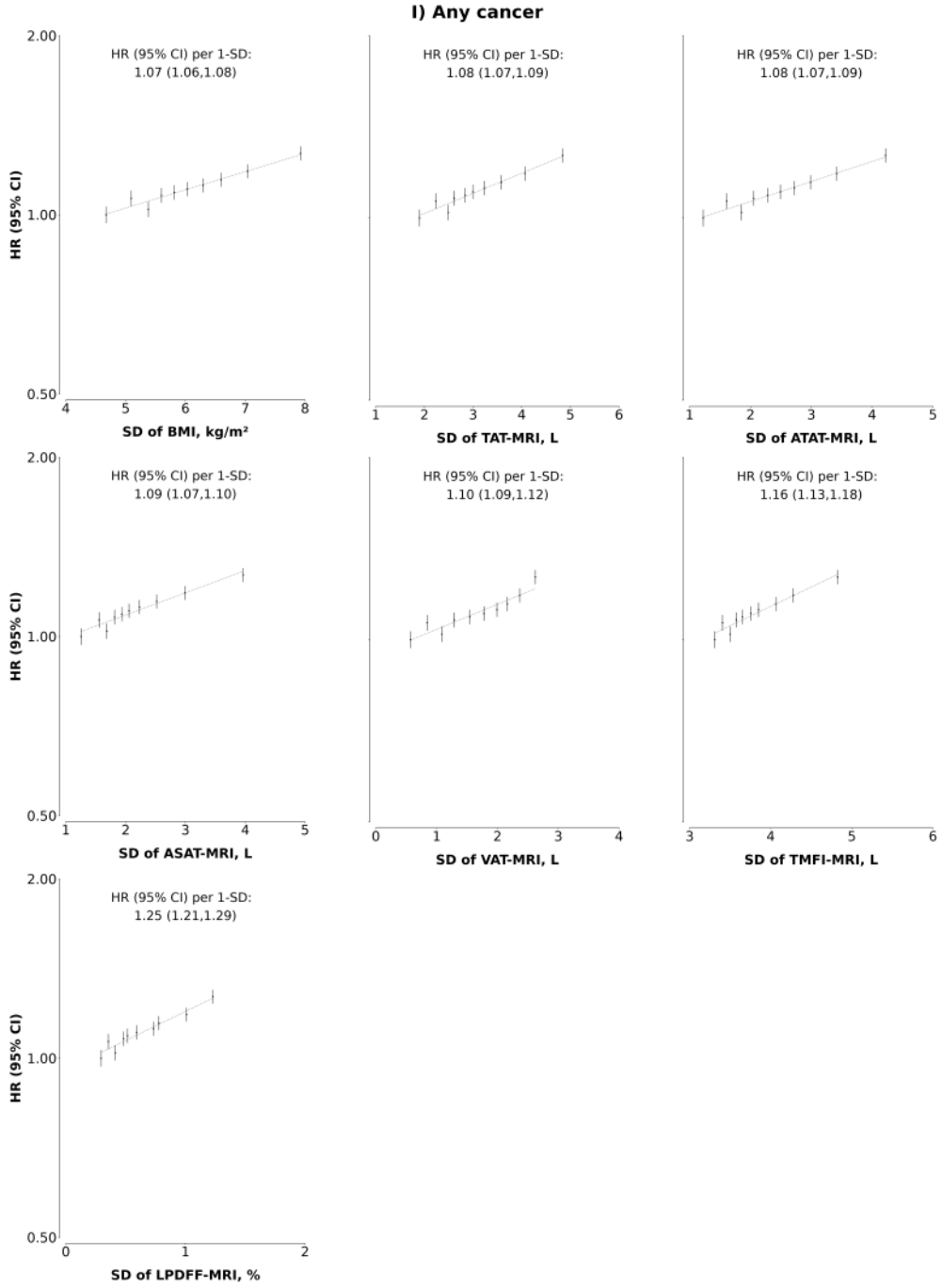
Women	Measured at the imaging visit						
WC at baseline decile	TAT-MRI	WC	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	536	4,189	2,672	2,679	2,438	611	2,658
2	639	4,253	2,734	2,737	2,469	705	2,717
3	531	3,975	2,510	2,521	2,238	581	2,496
4	547	3,695	2,354	2,359	2,113	604	2,337
5	479	3,440	2,202	2,207	1,955	515	2,190
6	445	3,231	2,034	2,035	1,812	485	2,025
7	414	2,863	1,791	1,793	1,578	464	1,782
8	416	2,788	1,755	1,759	1,557	476	1,740
9	351	2,457	1,531	1,532	1,347	385	1,515
10	264	1,964	1,177	1,180	1,040	316	1,154

Table A.10 Number of available adiposity traits measured at imaging visit by WC deciles at baseline in men

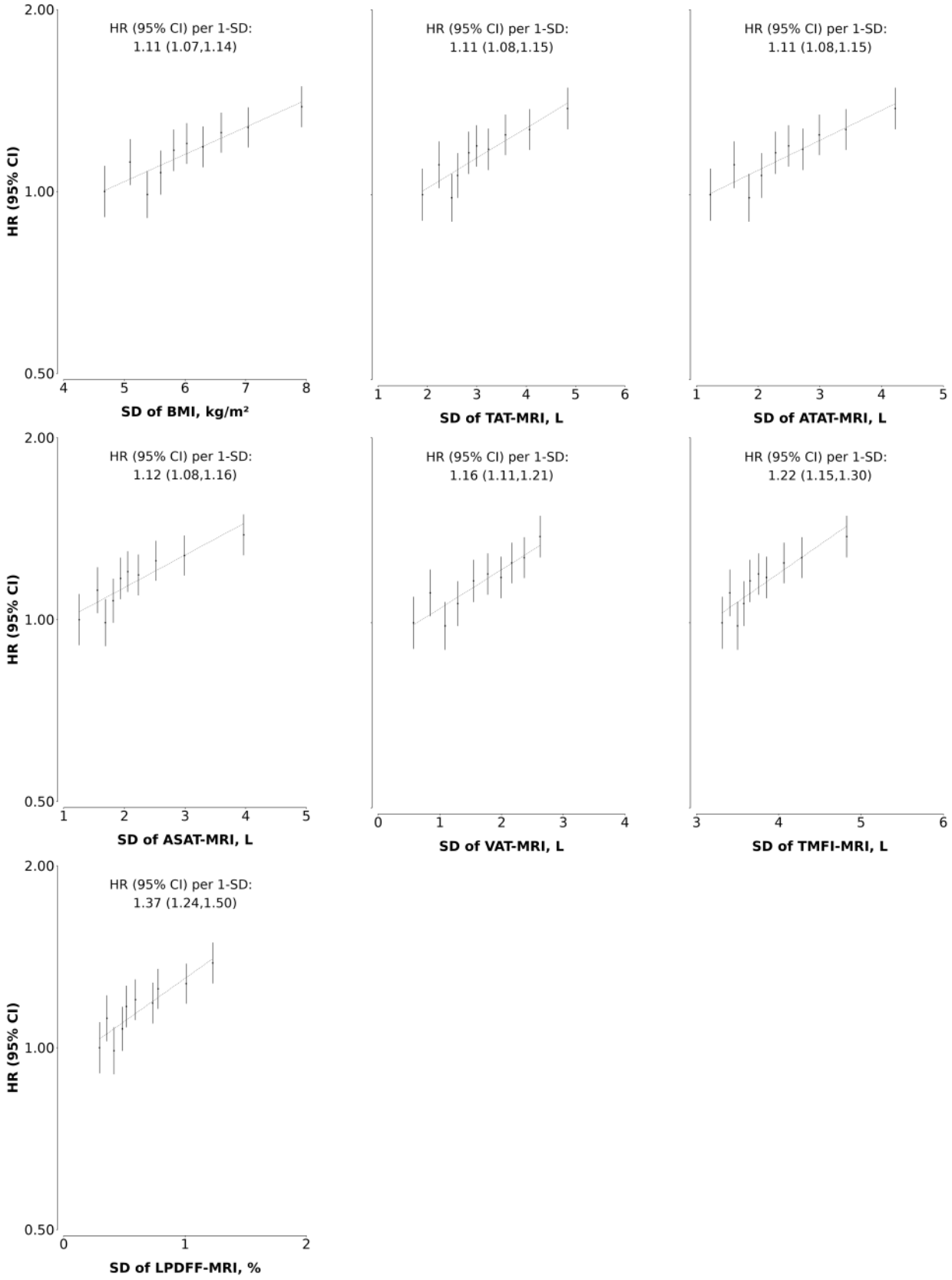
Men	Measured at the imaging visit						
WC at baseline decile	TAT-MRI	WC	ATAT-MRI	ASAT-MRI	VAT-MRI	LPDFF-MRI	TMFI-MRI
1	528	3,724	2,360	2,364	2,160	611	2,316
2	491	3,715	2,399	2,404	2,175	566	2,354
3	439	3,556	2,206	2,211	2,009	517	2,158
4	440	3,460	2,166	2,170	1,960	525	2,110
5	407	3,207	2,061	2,063	1,851	492	2,010
6	396	3,093	1,957	1,960	1,748	478	1,903
7	364	3,002	1,850	1,857	1,664	453	1,791
8	311	2,619	1,600	1,604	1,442	395	1,537
9	308	2,496	1,547	1,553	1,389	391	1,470
10	209	1,938	1,142	1,142	1,034	313	1,056

Figure A.1 Adjusted HRs for incidence of total and selected site-specific cancers by deciles of adiposity traits based on imputed category medians within BMI deciles

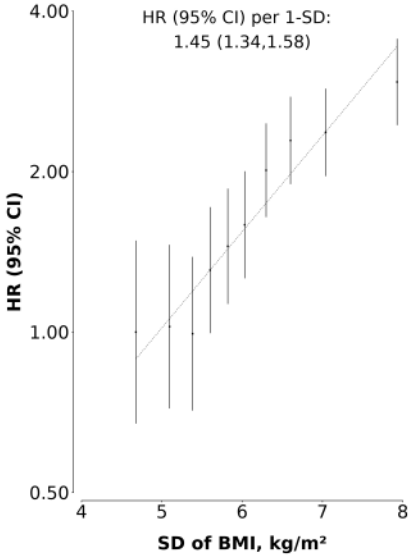
Adiposity traits for the entire cohort were imputed as medians within deciles of BMI at baseline. The relationship between each imputed category median of adiposity trait and HR was plotted in the form of a log-linear trend in HR per deciles of adiposity trait. The position of the square indicates the value of HRs with its corresponding floated confidence intervals, and its area is inversely proportional to the variance of the logarithm of the HR, indicating the amount of statistical information available for the particular estimate. Results in the text refer to the HR per SD increase of each of the imputed category median adiposity traits on a continuous scale in the form of conventional HR and their corresponding CI to allow comparisons across adiposity traits.

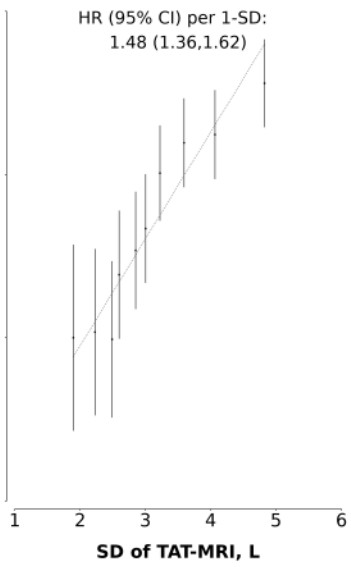


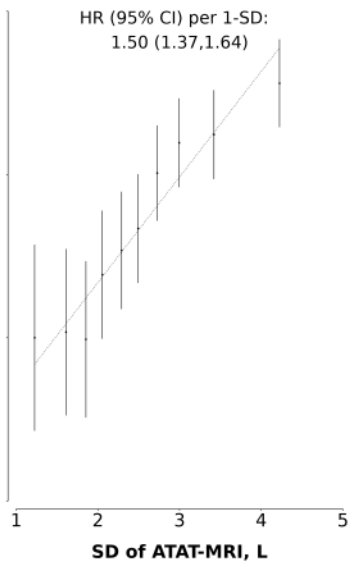
II) Colorectal cancer

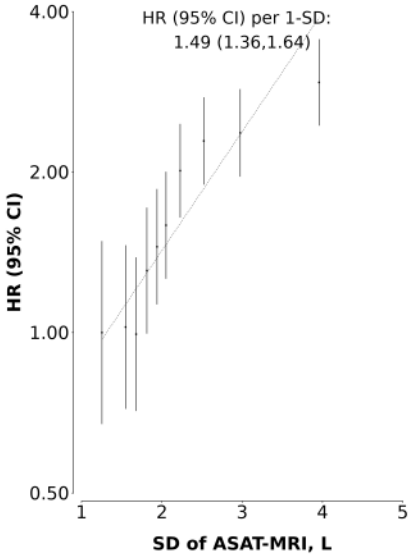


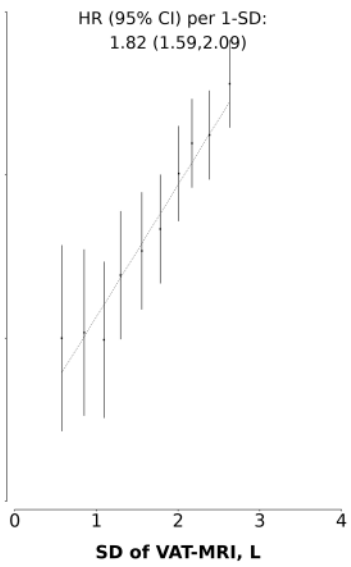
III) Oesophageal adenocarcinoma

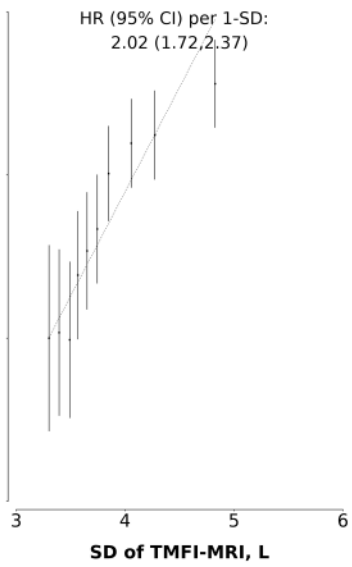


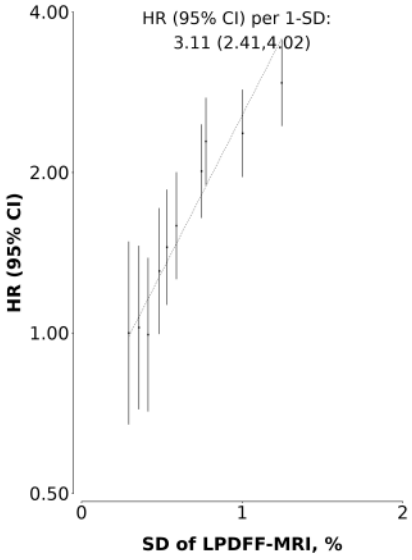




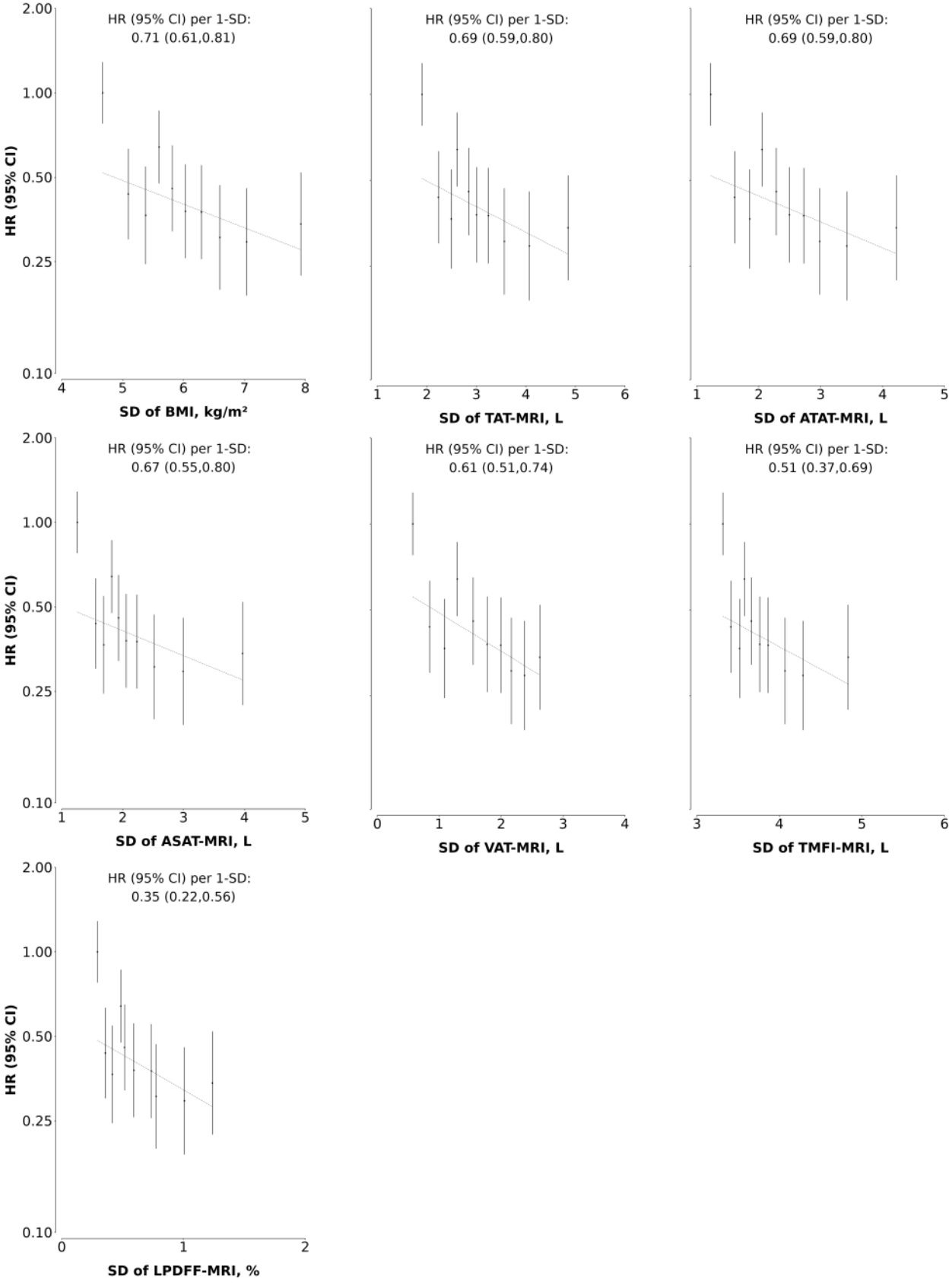




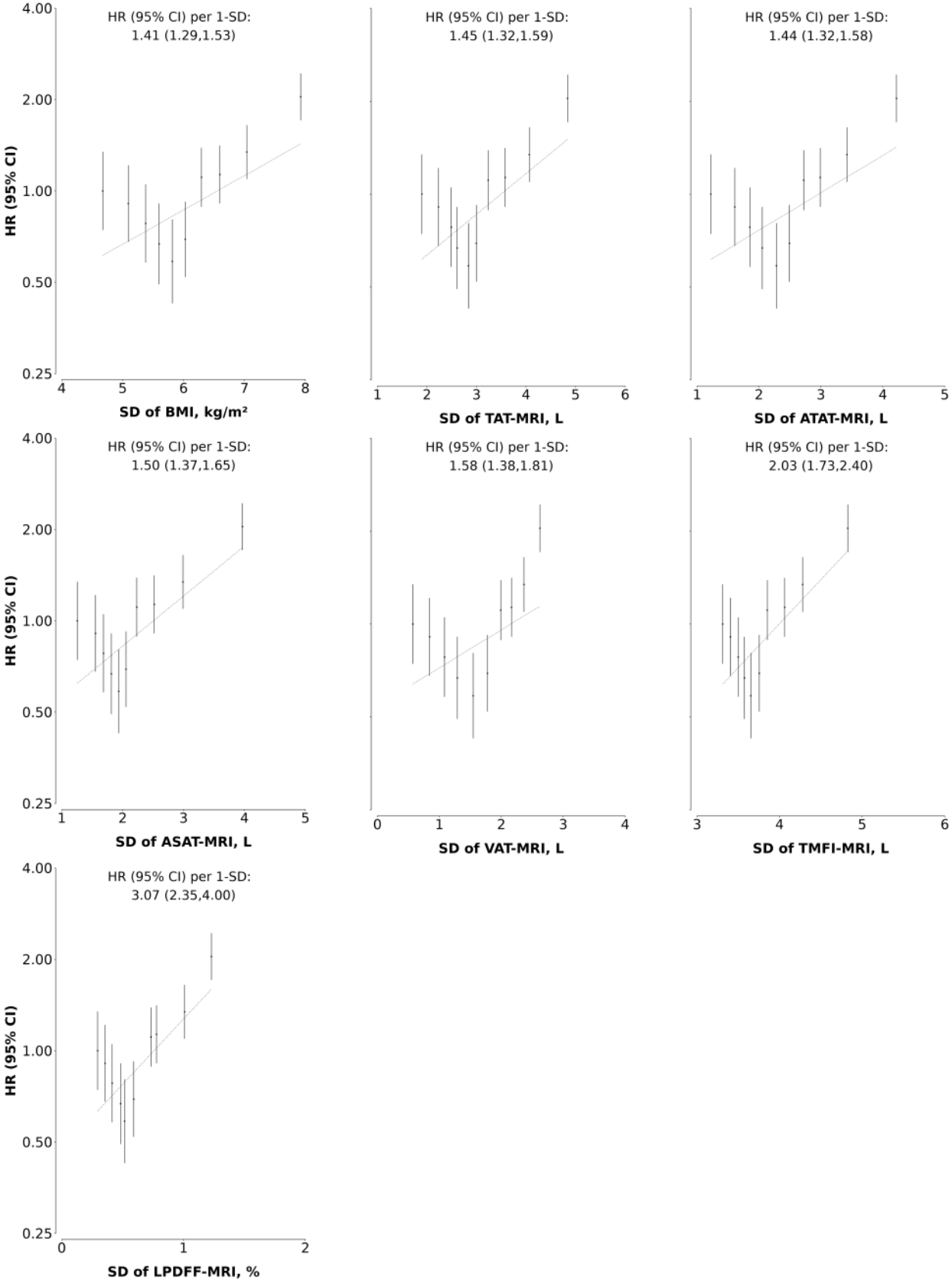




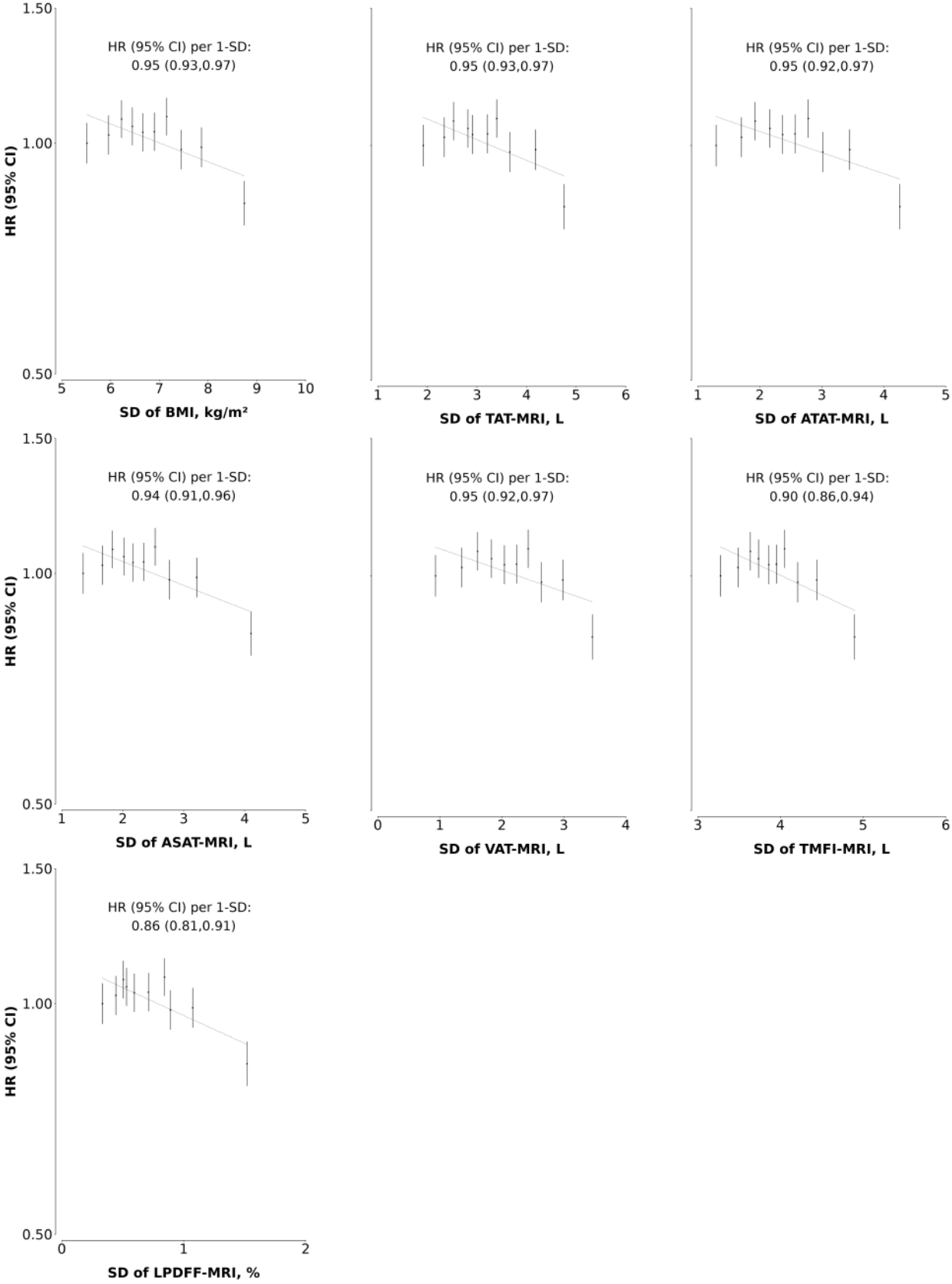
IV) Oesophageal squamous cell carcinoma



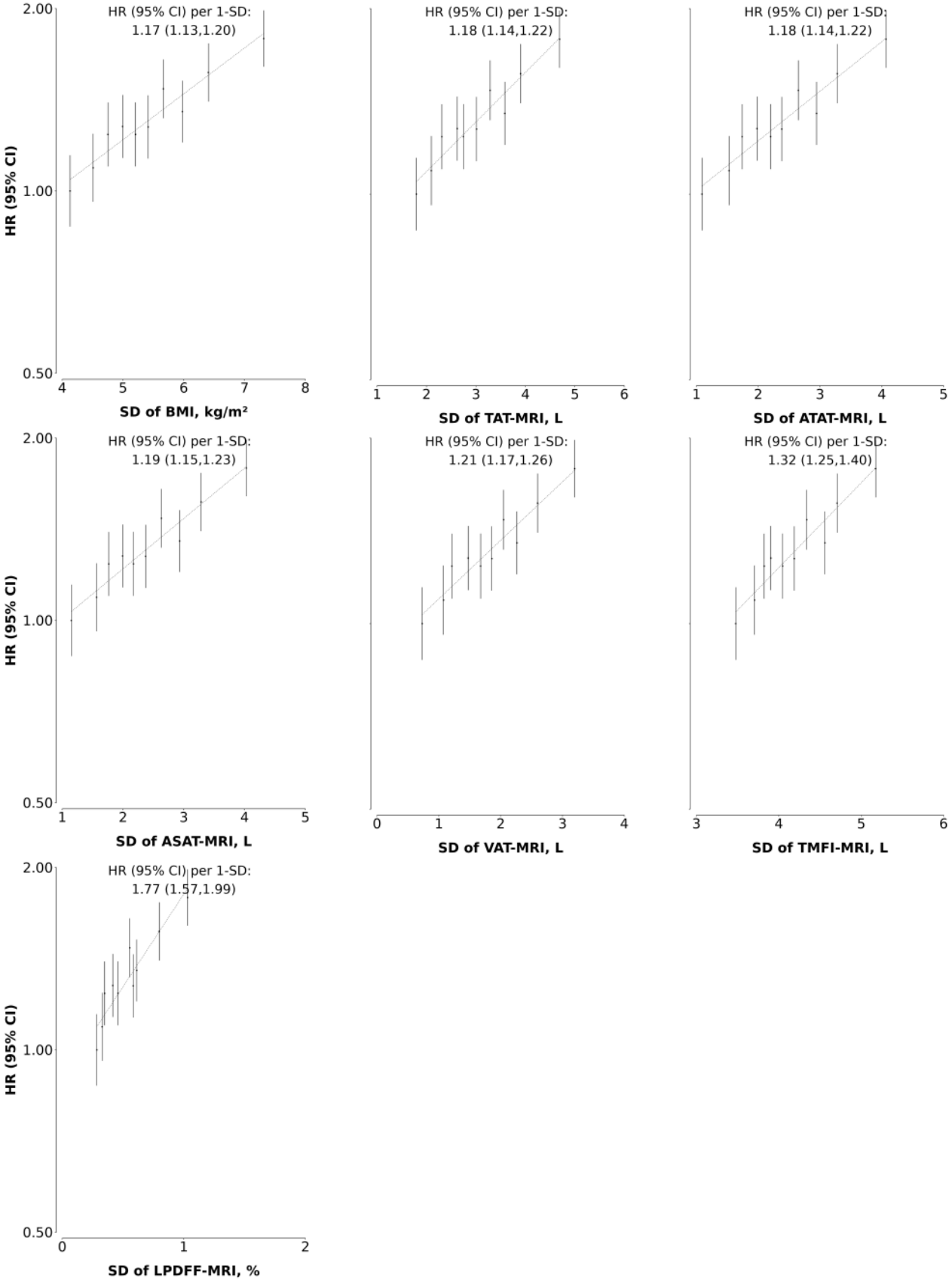
V) Liver cancer



VI) Prostate cancer



VII) Breast cancer



VIII) Endometrial cancer

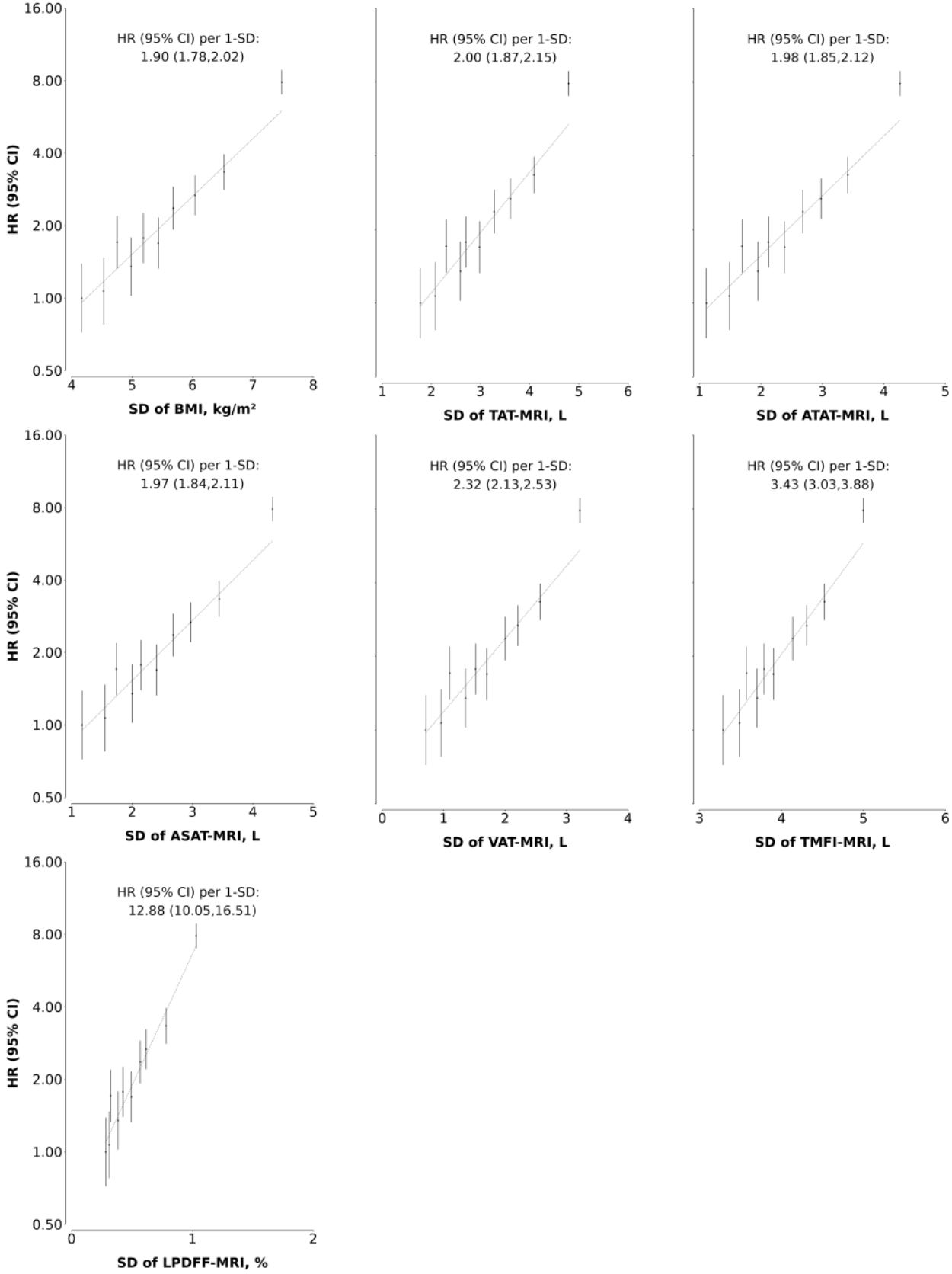
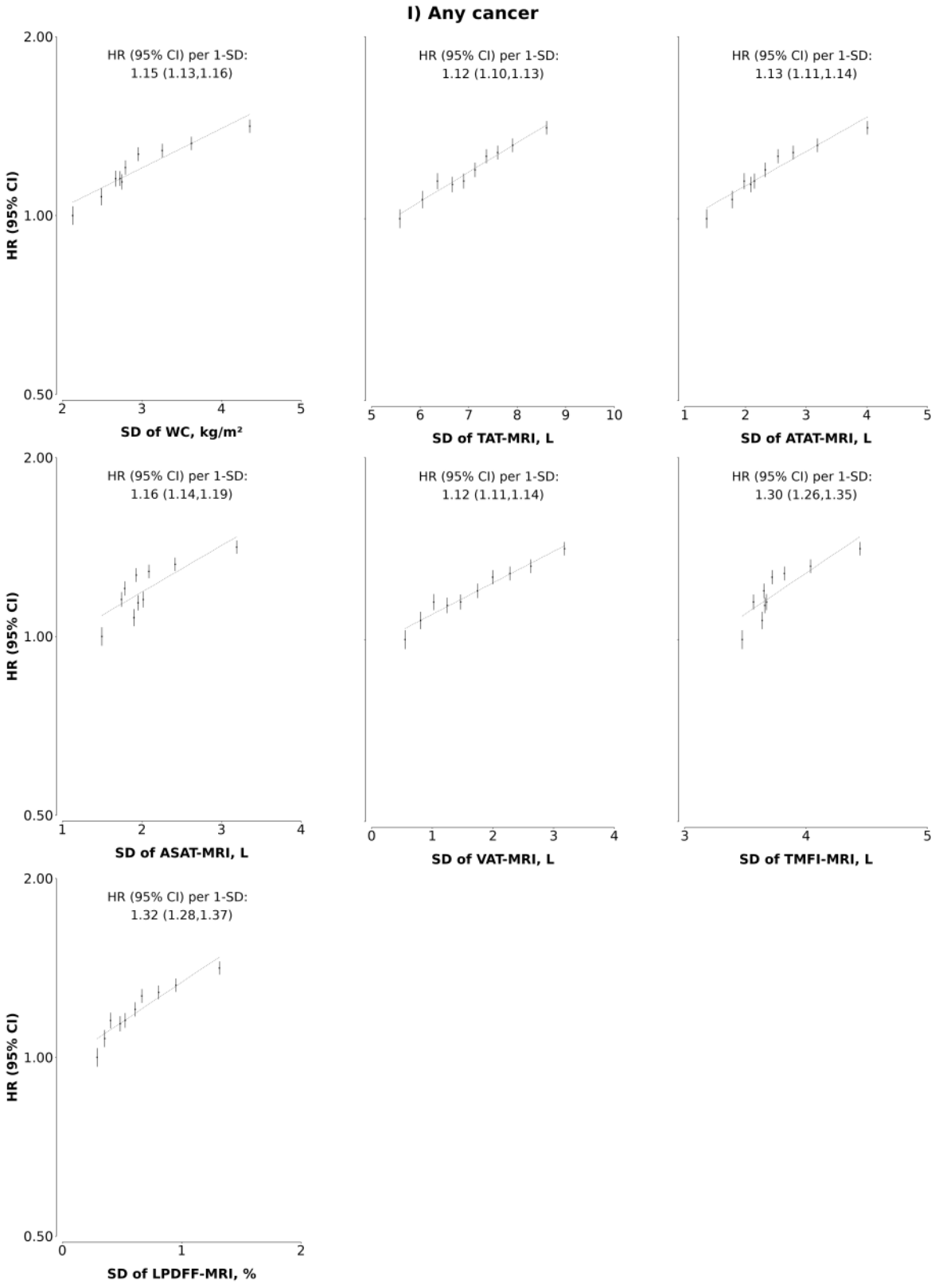
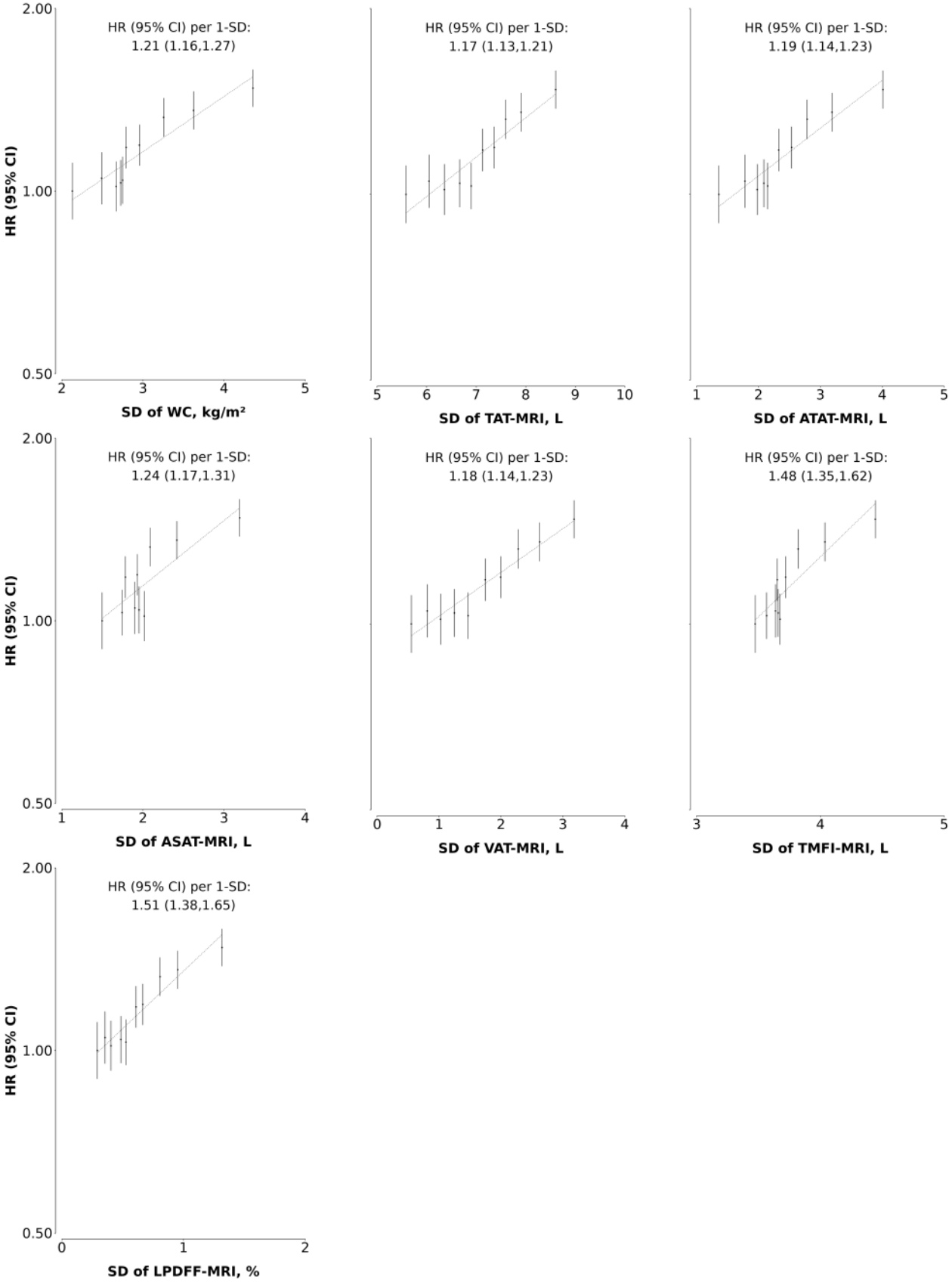


Figure A.2 Adjusted HRs for incidence of total and selected site-specific cancers by deciles of adiposity traits based on imputed category medians within WC deciles

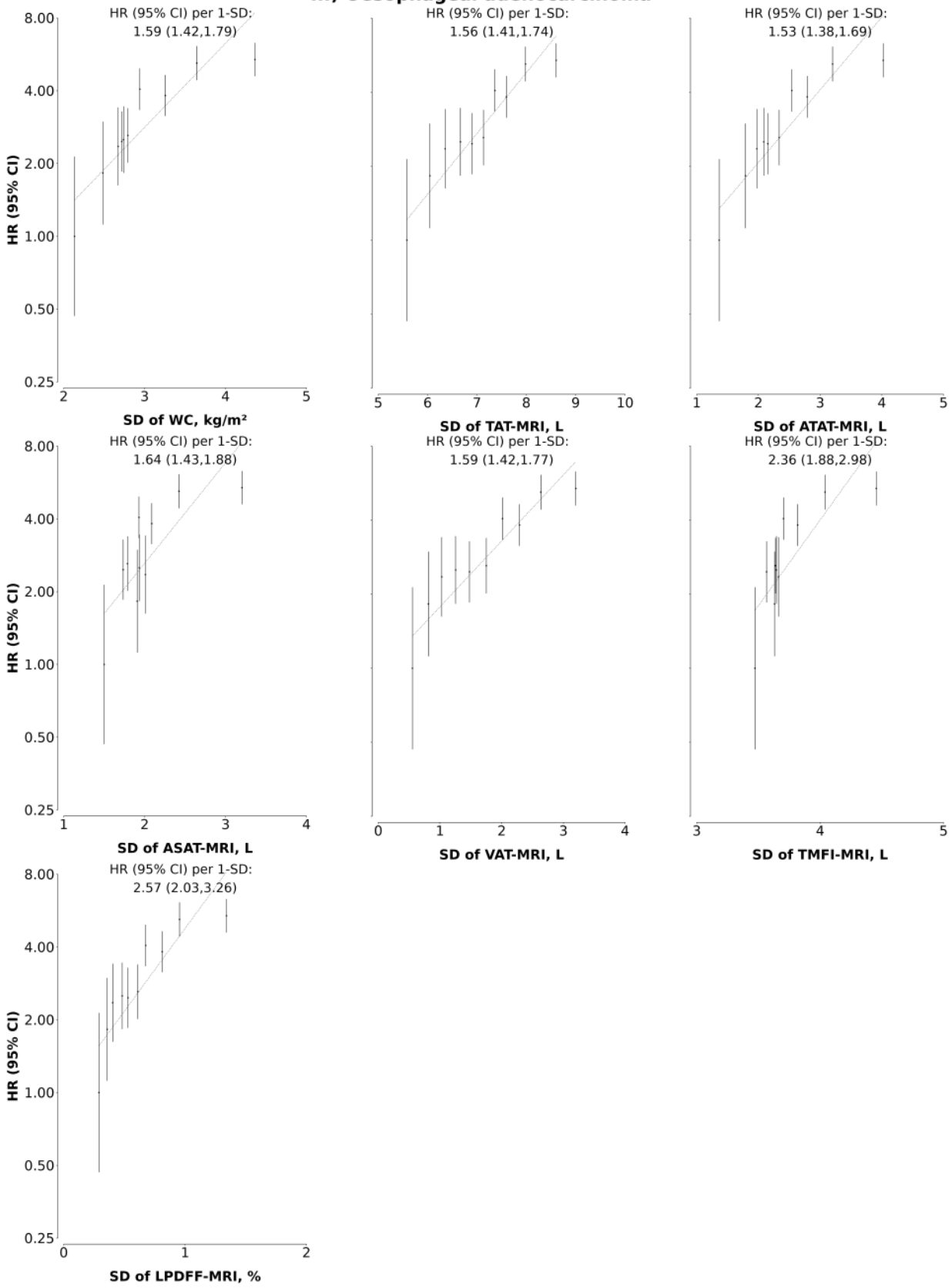
Trends in risk were estimated by stratifying participants into deciles based on baseline WC. Conventions as in Figure A.1.

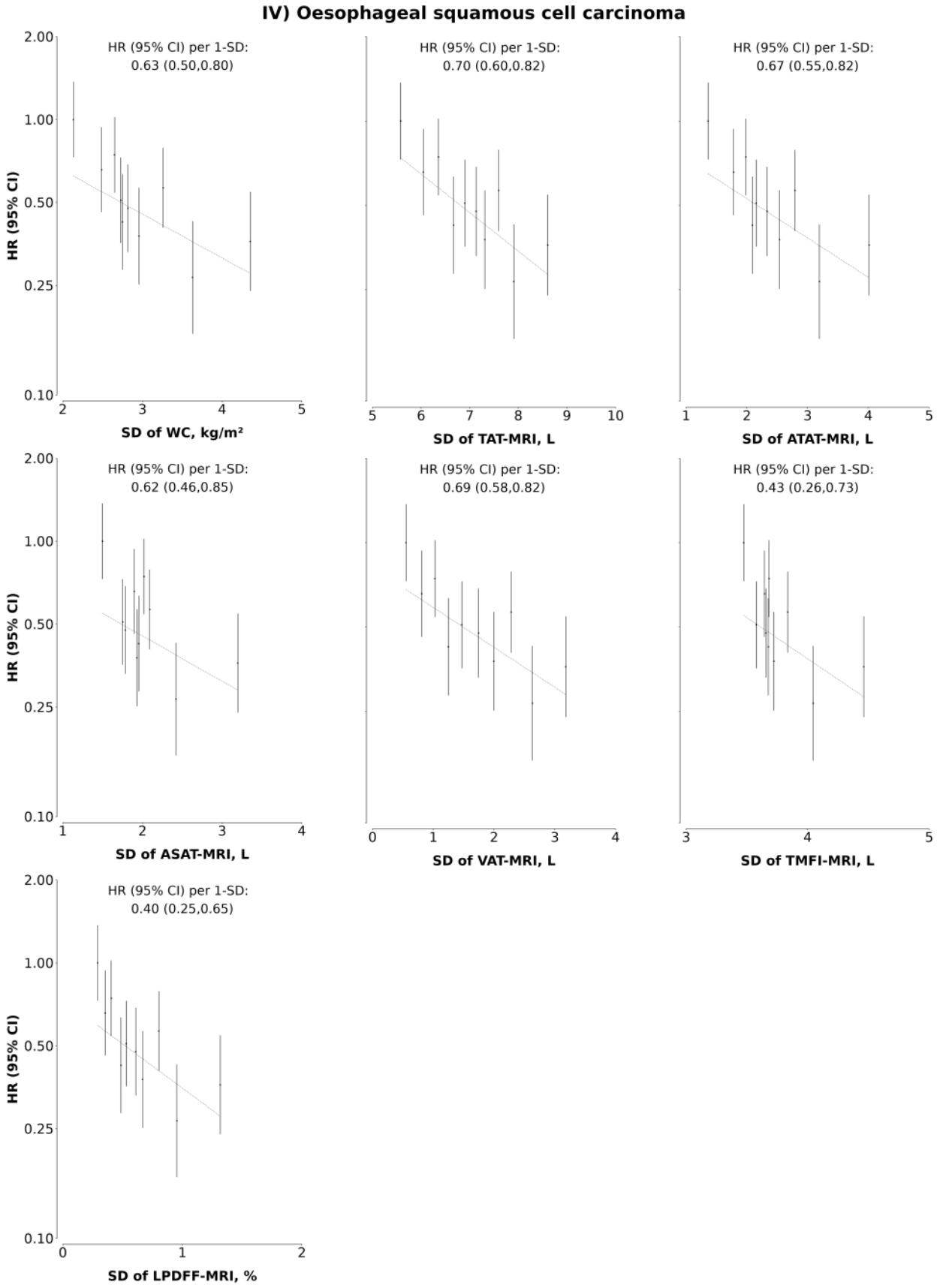


II) Colorectal cancer

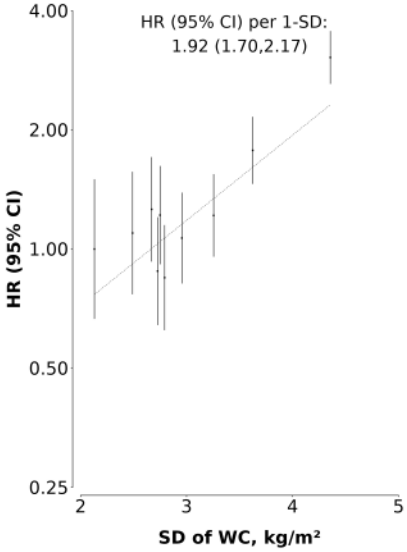


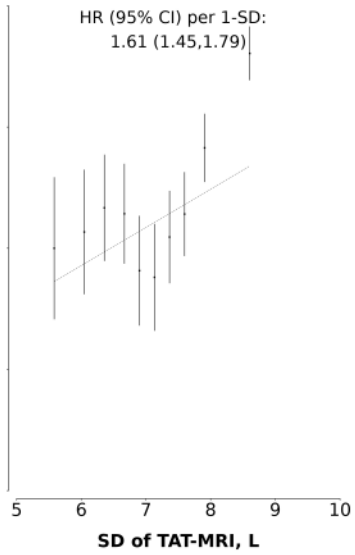
III) Oesophageal adenocarcinoma

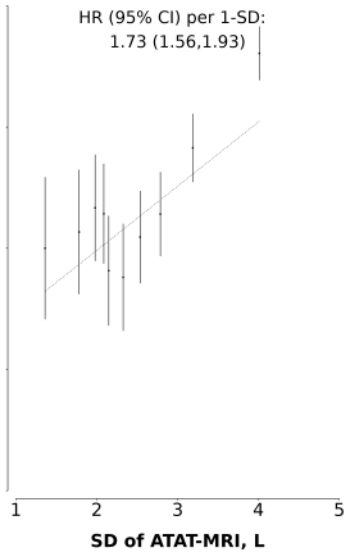


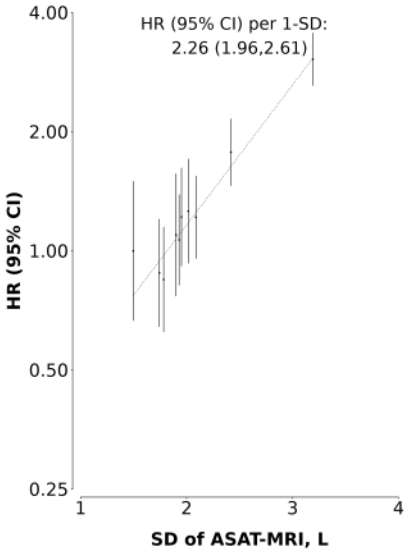

IV) Oesophageal squamous cell carcinoma
HR (95% CI) per 1-SD:
0.63 (0.50,0.80)
HR (95% CI)
SD of WC, kg/m²
HR (95% CI) per 1-SD:
0.70 (0.60,0.82)
SD of TAT-MRI, L
HR (95% CI) per 1-SD:
0.67 (0.55,0.82)
SD of ATAT-MRI, L
HR (95% CI) per 1-SD:
0.62 (0.46,0.85)
SD of ASAT-MRI, L
HR (95% CI) per 1-SD:
0.69 (0.58,0.82)
SD of VAT-MRI, L
HR (95% CI) per 1-SD:
0.43 (0.26,0.73)
SD of TMFI-MRI, L
HR (95% CI) per 1-SD:
0.40 (0.25,0.65)
SD of LPDFF-MRI, %

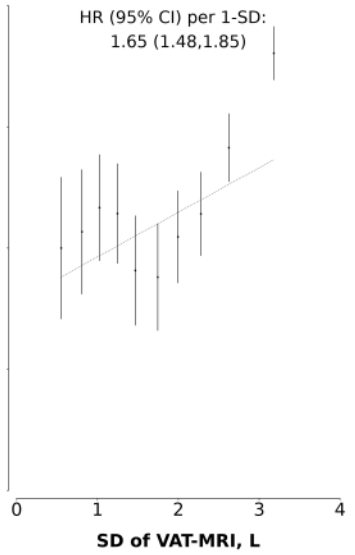
V) Liver cancer

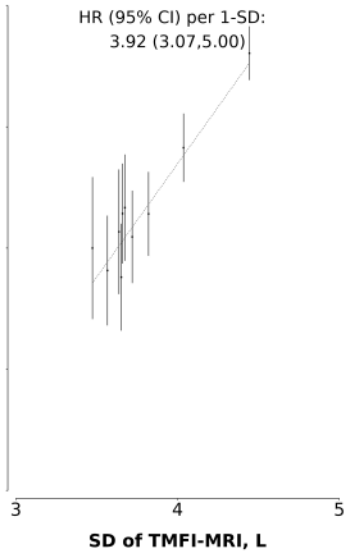


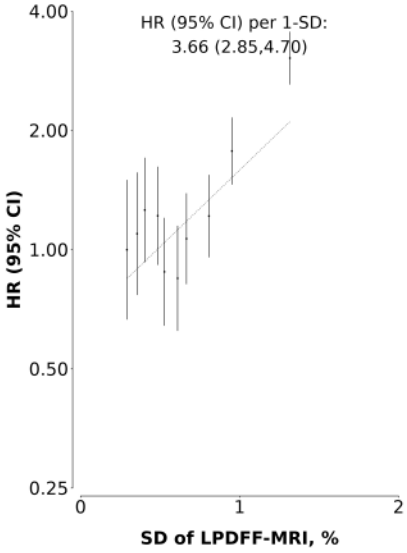




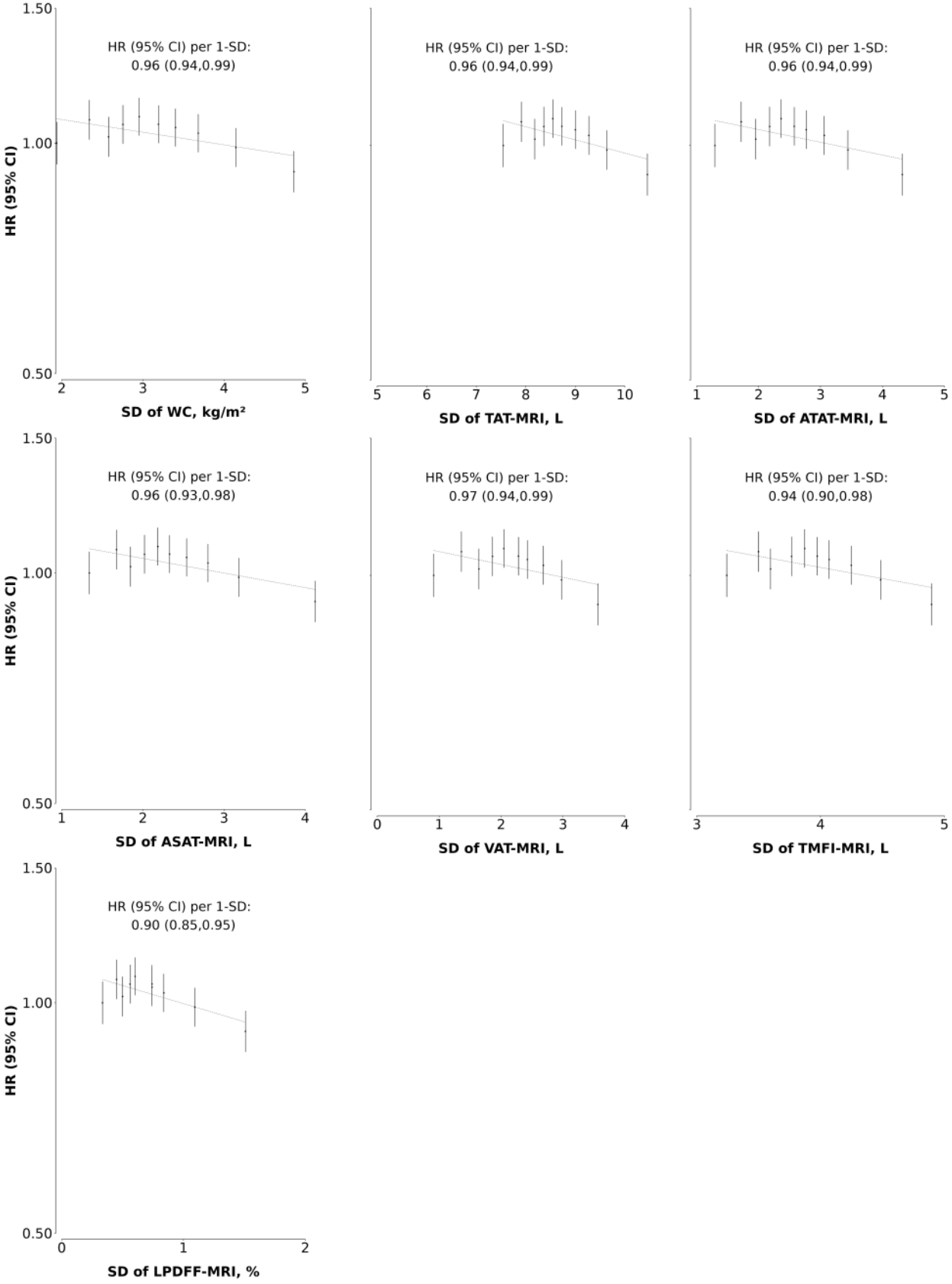








VI) Prostate cancer



VIII) Endometrial cancer