

## Cardiovascular Disease

# Independent relevance of adiposity measures to coronary heart disease risk among 0.5 million adults in UK Biobank

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## Abstract

**Background:** Evidence on body fat distribution shows opposing effects of waist circumference (WC) and hip circumference (HC) for coronary heart disease (CHD). We aimed to investigate the causality and the shape of such associations.

**Methods:** UK Biobank is a prospective cohort study of 0.5 million adults aged 40–69 years recruited between 2006 and 2010. Adjusted hazard ratios (HRs) for the associations of measured and genetically predicted body mass index (BMI), WC, HC and waist-to-hip ratio with incident CHD were obtained from Cox models. Mendelian randomization (MR) was used to assess causality. The analysis included 456 495 participants (26 225 first-ever CHD events) without prior CHD.

**Results:** All measures of adiposity demonstrated strong, positive and approximately log-linear associations with CHD risk over a median follow-up of 12.7 years. For HC, however, the association became inverse given the BMI and WC (HR per usual SD 0.95, 95% CI 0.93–0.97). Associations for BMI and WC remained independently positive after adjustment for other adiposity measures and were similar (1.14, 1.13–1.16 and 1.18, 1.15–1.20, respectively), with WC displaying stronger associations among women. Blood pressure, plasma lipids and dysglycaemia accounted for much of the observed excess risk. MR results were generally consistent with the observational, implying causality.

**Conclusions:** Body fat distribution measures displayed similar associations with CHD risk as BMI except for HC, which was inversely associated with CHD risk (given WC and BMI). These findings suggest that different measures of body fat distribution likely influence CHD risk through both overlapping and independent mechanisms.

**Keywords:** Obesity, epidemiology, genetics, coronary heart disease.

## Key Messages

- Measures of general adiposity and body fat distribution showed strong, positive and approximately log-linear associations with risk of coronary heart disease (CHD) independently of each other, apart from hip circumference, which was inversely associated.
- Blood pressure, plasma lipids and dysglycaemia (or correlates thereof) explained much of the observed association between adiposity and CHD risk.
- Mendelian randomization of adiposity on CHD showed overall consistent results with those from the observational analyses, implying potential causality.

## Introduction

Excess adiposity is a leading risk factor for coronary heart disease (CHD) globally.<sup>1</sup> The majority of evidence for adiposity-related CHD risk has been derived from epidemiological studies of body mass index (BMI) but additional

evidence from clinical trials further supports cardiovascular benefits of weight loss.<sup>2</sup> Although BMI reflects general adiposity, it does not indicate body fat distribution. There is growing evidence that distinct fat depots exert different effects on CHD risk compared with overall body fat such as the

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opposing effect of waist circumference (WC) and hip circumference (HC) on CHD risk beyond other indicators.<sup>3–5</sup> Therefore, it is possible that other measures of body fat distribution, such as WC, HC or waist-to-hip ratio (WHR), could complement or supersede BMI when estimating adiposity-related CHD risk.<sup>6,7</sup>

The exact mechanisms underlying the relationship between adiposity and CHD remain unclear but it is thought to be chiefly mediated by blood pressure, cholesterol and insulin resistance.<sup>8</sup> Prior evidence on the role of intermediate factors includes large-scale meta-analyses, but most included studies were unable to account for medication use.<sup>9,10</sup>

It has not been possible to assess the independent causal relevance of different adiposity measures to CHD risk using observational evidence alone due to reverse causality, confounding and the correlation between different adiposity measures. Mendelian randomization (MR) approaches can overcome some of these limitations by using genetic variants as proxies—or ‘instrumental variables’ (IVs)—for an exposure, which, given a number of assumptions, can provide unbiased causal estimates of exposure–outcome associations.<sup>11,12</sup>

The causal relevance of elevated adiposity to CHD risk has been studied previously using MR.<sup>13–19</sup> However, due to a lack of genetic information on large longitudinal cohorts, the majority of MR studies have used summary-level data for the primary analysis. Only a handful of studies have included a subset of individual-level participant data, which allows the investigation of the shape of associations, and most of them have focused on general adiposity rather than body fat distribution.

With full genetic data available in a very large and contemporary prospective cohort study with sufficient follow-up time, UK Biobank (UKB) allows a direct comparison of the relevance of different measures of general adiposity as well as body fat distribution to CHD risk using both observational and genetic data in the same study population more reliably and in greater detail than has previously been done (e.g. by examining the shape of the association and assessing potential mediators).

## Methods

### Study population characteristics and baseline procedures

UKB is a large observational study of 502 678 UK adults aged 40–69 years. Eligible adults were invited to one of 22 assessment centres around the UK from 2006 to 2010. The study has been described in detail previously.<sup>20,21</sup> Participants reported lifestyle exposures, medical history and medications before undergoing standardized assessments including body size and biomarker measurements. Anthropometric measurements included body weight (using a Tanita BC418MA body composition analyser or a standard scale if the participant did not undergo bioimpedance), standing height (Seca 240-cm height measure) and waist and HC (Seca 200-cm tape measure around the narrowest part of the trunk and the widest part of the hips, respectively).

### Baseline exclusions

Participants were excluded from the analysis if they: (i) were aged <40 or ≥70 years at baseline; (ii) had withdrawn at the time of analysis; or (iii) had missing or outlying values for selected anthropometric measures at baseline ([Supplementary](#)

[Figure S1](#), available as [Supplementary data](#) at *IJE* online). To limit reverse causation, individuals who self-reported or whose hospital records indicated previous cardiovascular disease (CVD) were also excluded. Participants who were genetically related ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online), of self-reported non-European ancestry, with discordance between the genetic sex and the self-reported biological sex, with sex chromosome aneuploidy or who lacked genetic information were excluded from genetic analyses ([Supplementary Figure S1](#), available as [Supplementary data](#) at *IJE* online).

### Study outcome and follow-up procedures

Participants were followed up by linkage to electronic health databases including Hospital Episode Statistics, disease registries and Office for National Statistics cause-of-death data to obtain fatal and non-fatal incident CHD events. The main outcome in the present study was first incident CHD as recorded on a hospital admission (based on any reason for admission) ([Supplementary Table S1](#), available as [Supplementary data](#) at *IJE* online). The censoring date was defined as the date of the first non-fatal CHD event or the date of death due to CHD if no non-fatal CHD event had been recorded. Otherwise participants were followed up until the end of the study period or date of death.

### Selection and construction of genetic instruments

Details on the genotyping and quality control of the genetic data have been previously reported.<sup>20</sup> The causal relevance of the four adiposity measures on CHD risk was estimated by using individual-level data from UKB to create a genetic risk score (GRS) for each measure. After exclusions of single-nucleotide polymorphisms (SNPs) based on quality control checks ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online), we identified from Genome Wide Association Study (GWAS) of the Genetic Investigation of Anthropometric Traits (GIANT) consortium (not including UKB) 75 independent SNPs to derive the GRS for BMI, 45 SNPs for WHR and WHR adjusted for BMI (WHRadjBMI), 69 SNPs for WC and WC adjusted for BMI (WCadjBMI) and 89 SNPs for HC and HC adjusted for BMI (HCadjBMI), respectively, using the sex-specific external betas from GIANT as weights due to observed heterogeneity in the betas by sex for WHR and WC ([Supplementary Figure S2](#) and [Supplementary Tables S2–S5](#), available as [Supplementary data](#) at *IJE* online).<sup>22–24</sup> Each GRS was expressed per average allele effect ([Supplementary Methods](#), available as [Supplementary data](#) at *IJE* online).<sup>25</sup>

### Statistical analysis

#### Prospective associations between adiposity and CHD risk

Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for the association between adiposity and risk of incident CHD were calculated using Cox proportional-hazards regression models. Where appropriate, models were stratified by age at risk in 5-year groups, region and sex, and adjusted for education, Townsend Deprivation Index, ethnicity, smoking and alcohol consumption. In a secondary analysis, we also adjusted for physical activity and family history of CVD. [Supplementary Methods](#) (available as [Supplementary data](#) at *IJE* online) provide more information on the derivation of the covariates.

To correct for regression dilution bias,<sup>26</sup> the ‘usual SD’ of each adiposity measure was obtained by multiplying the baseline standard deviation (SD) by the square root of the regression dilution ratios calculated as partial correlation coefficients between baseline and resurvey measures.<sup>27</sup> Likewise, to describe the shapes of associations between ‘usual’ levels of adiposity and CHD risk, estimates were plotted against the mean value at resurvey within each baseline group. Group-specific variances were used to calculate 95% CIs for all groups, including the reference group.<sup>28</sup> Where associations were approximately log-linear, CHD risk was estimated per the usual SD higher adiposity level. The main analyses were performed separately for men and women.<sup>29</sup> Joint effects and independence between adiposity measures were investigated by comparing HRs with increasing BMI (per SD usual levels) before and after adjusting for measures of body fat distribution (WC, HC and WHR) and vice versa.

The potential mediating effects of systolic blood pressure (SBP), lipids [Apolipoprotein A (Apo A), Apolipoprotein B (Apo B), low-density lipoprotein, high-density lipoprotein, triglycerides], glycated haemoglobin (HbA1c), self-reported type II diabetes, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR) and liver enzymes [alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT)]<sup>30</sup> on adiposity-related CHD risk were investigated. Proportional reductions in the log-HR and Wald  $\chi^2$  following adjustment for potential mediators provided semi-quantitative estimates of mediation.

### Genetically predicted adiposity and CHD risk

An IV ratio estimate method was used to scale results to represent the effect size per SD higher adiposity measure.<sup>31</sup> Associations of each GRS with CHD risk were stratified by age at risk and UKB region, and adjusted for sex, baseline age, baseline age squared, the first 10 principal components, batch number and array type in Cox models. Non-linear associations of BMI with CVD have been previously reported in observational studies.<sup>10</sup> Therefore, in order to assess the shape and strength of associations, we employed a non-linear MR approach in addition to standard linear MR (Supplementary Methods, available as Supplementary data at IJE online).<sup>32,33</sup>

To assess the MR assumptions: (i) the strength of association between each GRS and respective adiposity measure was quantified by estimating the F-statistic ( $F > 10$  suggesting lower probability of weak instrument bias); (ii) the association of covariates with each GRS was assessed separately to investigate whether GRSs were independent of confounders; and (iii) MR-Egger regression using effect sizes on associations of SNPs with adiposity traits from GIANT (not including UKB) and effect sizes on associations of SNPs with CHD from UKB was performed to assess whether genetic variants are only associated with the exposure of interest and to provide an indication of directional pleiotropy.<sup>34</sup> The  $I^2GX$  statistic was used to assess the no measurement error assumption, which provides an assessment of the expected dilution of the MR-Egger estimate due to uncertainty in the SNP-exposure associations and has been suggested as a measure of instrument strength for the MR-Egger method.<sup>34</sup> The simulation extrapolation (SIMEX) method was used in combination with MR-Egger to get more robust estimates when the  $I^2GX$  statistic was lower.<sup>34</sup> Weighted median MR, which

assumes that at least half of the information comes from valid instruments, and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO), which detects and corrects for horizontal pleiotropy by removing outliers,<sup>35</sup> were also employed for additional sensitivity analyses. Multivariable MR was also performed using the GRSs that were not adjusted for BMI.

Analyses were conducted using SAS (version 9.4) and R (version 3.6.2). R package ‘MendelianRandomization’ was used for MR-Egger. Plots were created using R package ‘Jasper’ (<https://github.com/arnhew99/Jasper>). Reporting of analyses and results followed the recommendations of the STROBE<sup>36</sup> and STROBE-MR<sup>37</sup> statements.

## Results

### Baseline characteristics

The adiposity measures were higher among men than women (except HC) and within each sex among those who developed CHD (Table 1). Men were also more likely than women to be smokers, daily drinkers, highly active, have diabetes and have higher SBP and liver enzyme levels and lower ApoA levels. Those who developed CHD were older, of lower educational level and higher deprivation index, and more likely to smoke and have diabetes. Further, those who developed CHD had higher baseline levels of SBP, HbA1c and GGT, but lower levels of ApoA than those who did not develop CHD. For each measure of adiposity, there was a strong correlation between baseline and resurvey values ( $r^2 > 0.8$  apart from WHR with  $\sim 0.65$ ; Supplementary Table S6, available as Supplementary data at IJE online). The adiposity measures were generally highly correlated with each other ( $r^2 = 0.61$ – $0.89$ ; Supplementary Table S7, available as Supplementary data at IJE online) with the exception of BMI and WHR among women ( $r^2 = 0.46$ ) and WHR and HC in both men ( $r^2 = 0.33$ ) and women ( $r^2 = 0.25$ ). The genetic analysis included 368 613 participants with similar characteristics at baseline compared with the main study population (Supplementary Table S8, available as Supplementary data at IJE online).

### Genetic risk scores

Most variants included in each GRS were positively associated with their respective adiposity measure in UKB, with no evidence of heterogeneity between the UKB and GIANT for BMI or WHRadjBMI and with a small underestimation of associations for WCadjBMI and HCadjBMI. (Supplementary Figure S3, available as Supplementary data at IJE online). The scores were robustly associated with each adiposity measure that they were derived for at baseline (Q5–Q1: BMI =  $1.8 \text{ kg/m}^2$ , WC =  $7.2 \text{ cm}$  and HC =  $1.9 \text{ cm}$ ) and, whereas the BMI GRS was positively associated with all adiposity measures, all other GRSs were weakly and inversely associated with BMI (Supplementary Tables S9 and S10, available as Supplementary data at IJE online). Potential confounders and mediators did not materially differ across quintiles of the GRSs, whereas more favourable markers were observed among those in the bottom quintiles of the measured adiposity markers. Together the GRSs explained 2.2%, 2.4%, 4.8% and 0.7% of variance for BMI, WHR, WC and HC, respectively, in UKB (corresponding F-statistics: 6883, 1544, 14 577 and 2367).

**Table 1.** Baseline characteristics by first-ever CHD event status over follow-up<sup>a</sup> and sex

	Men		Women	
	CHD ( <i>n</i> =17 010)	No CHD ( <i>n</i> =183 652)	CHD ( <i>n</i> =9215)	No CHD ( <i>n</i> =246 618)
Body mass index (kg/m <sup>2</sup> )	28.5 (4.3)	27.6 (4.0)	28.6 (5.5)	26.9 (5.0)
Hip circumference (cm)	104.0 (7.8)	103.2 (7.2)	105.5 (11.1)	103.0 (10.0)
Waist circumference (cm)	99.2 (11.5)	96.2 (10.9)	89.2 (13.1)	84.2 (12.2)
Waist-to-hip ratio	0.95 (0.06)	0.93 (0.06)	0.84 (0.07)	0.82 (0.07)
Socio-demographic and lifestyle factors				
Age (years)	59.7 (7.0)	55.8 (8.2)	60.6 (6.6)	55.9 (8.0)
Achieved higher education	9723 (57%)	119 727 (65%)	4319 (47%)	142 795 (58%)
Townsend deprivation index	-1.1 (3.2)	-1.3 (3.1)	-1.0 (3.2)	-1.4 (3.0)
Current smoker	2641 (16%)	22 144 (12%)	1286 (14%)	21 079 (9%)
Daily drinker	4306 (25%)	46 956 (26%)	1356 (15%)	40 339 (16%)
Very physically active (METs ≥50 h/week)	3311 (19%)	37 075 (20%)	1412 (15%)	38 843 (16%)
Family history of CVD	10 306 (61%)	94 118 (51%)	6469 (70%)	141 045 (57%)
Potential mediators				
Systolic blood pressure (mmHg)	145.8 (18.1)	140.6 (17.2)	142.8 (20.2)	134.7 (19.2)
Apolipoprotein A (g/L)	1.40 (0.23)	1.44 (0.23)	1.60 (0.27)	1.64 (0.27)
Apolipoprotein B (g/L)	1.07 (0.25)	1.04 (0.23)	1.09 (0.26)	1.04 (0.24)
Low-density lipoprotein cholesterol (mmol/L)	3.6 (0.9)	3.6 (0.8)	3.8 (1.0)	3.6 (0.9)
High-density lipoprotein cholesterol (mmol/L)	1.2 (0.3)	1.3 (0.3)	1.5 (0.4)	1.6 (0.4)
Triglycerides (mmol/L)	2.1 (1.2)	2.0 (1.1)	1.9 (1.0)	1.5 (0.8)
HbA1c (mmol/mol)	38.1 (9.1)	35.9 (6.8)	38.3 (8.8)	35.5 (5.5)
Diabetes	1895 (11%)	9436 (5%)	886 (10%)	7595 (3%)
C-reactive protein (mg/L)	3.0 (4.9)	2.3 (4.1)	3.7 (5.3)	2.6 (4.2)
Estimated glomerular filtration rate	92.3 (13.9)	95.7 (12.5)	90.9 (14.5)	95.1 (12.9)
Alkaline phosphatase (U/L)	84.7 (26.6)	81.5 (24.4)	92.5 (29.8)	84.1 (27.1)
Aspartate aminotransferase (U/L)	28.4 (12.0)	28.1 (11.3)	25.6 (11.0)	24.4 (9.5)
Alanine aminotransferase (U/L)	27.5 (16.1)	27.5 (15.3)	21.9 (13.2)	20.1 (12.1)
Gamma-glutamyl transferase (U/L)	48.8 (51.9)	44.6 (46.4)	36.7 (41.6)	29.5 (32.4)

CHD, coronary heart disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; METs, metabolic equivalents of task.

<sup>a</sup> First-ever CHD event defined as documentation of a CHD event upon hospital admission in medical records over the study period among persons without CHD at baseline.

## Observed associations between adiposity measures and CHD risk

During a median of 12.7 years, 26 225 (17 010 in men, 9215 in women) first-ever CHD events occurred. After adjusting for potential confounders, all four adiposity measures demonstrated strong, positive and approximately log-linear associations with incident CHD in both men and women (Figures 1 and 2). Associations for WC and WHR were slightly stronger for women than for men [HR per SD increasing WC: 1.27 (1.25–1.29) vs 1.21 (1.19–1.23) and WHR: 1.25 (1.23–1.27) vs 1.22 (1.21–1.24) for women vs men: [Supplementary Figure S4](#), available as [Supplementary data](#) at *IJE* online,  $P_{\text{Het}} < 0.05$ ]. HC displayed weaker positive associations with CHD risk in both men (1.13, 1.12–1.15) and women (1.16, 1.14–1.17). Results did not materially differ when further adjusted for physical activity and family history of CVD ([Supplementary Figure S5](#), available as [Supplementary data](#) at *IJE* online).

For a given HC, the associations for both BMI and WC became stronger (Figure 2). However, after accounting for BMI and WC, HC displayed an inverse association with CHD risk. Associations with CHD risk for both BMI and WHR remained after mutual adjustment.

## Intermediate factors

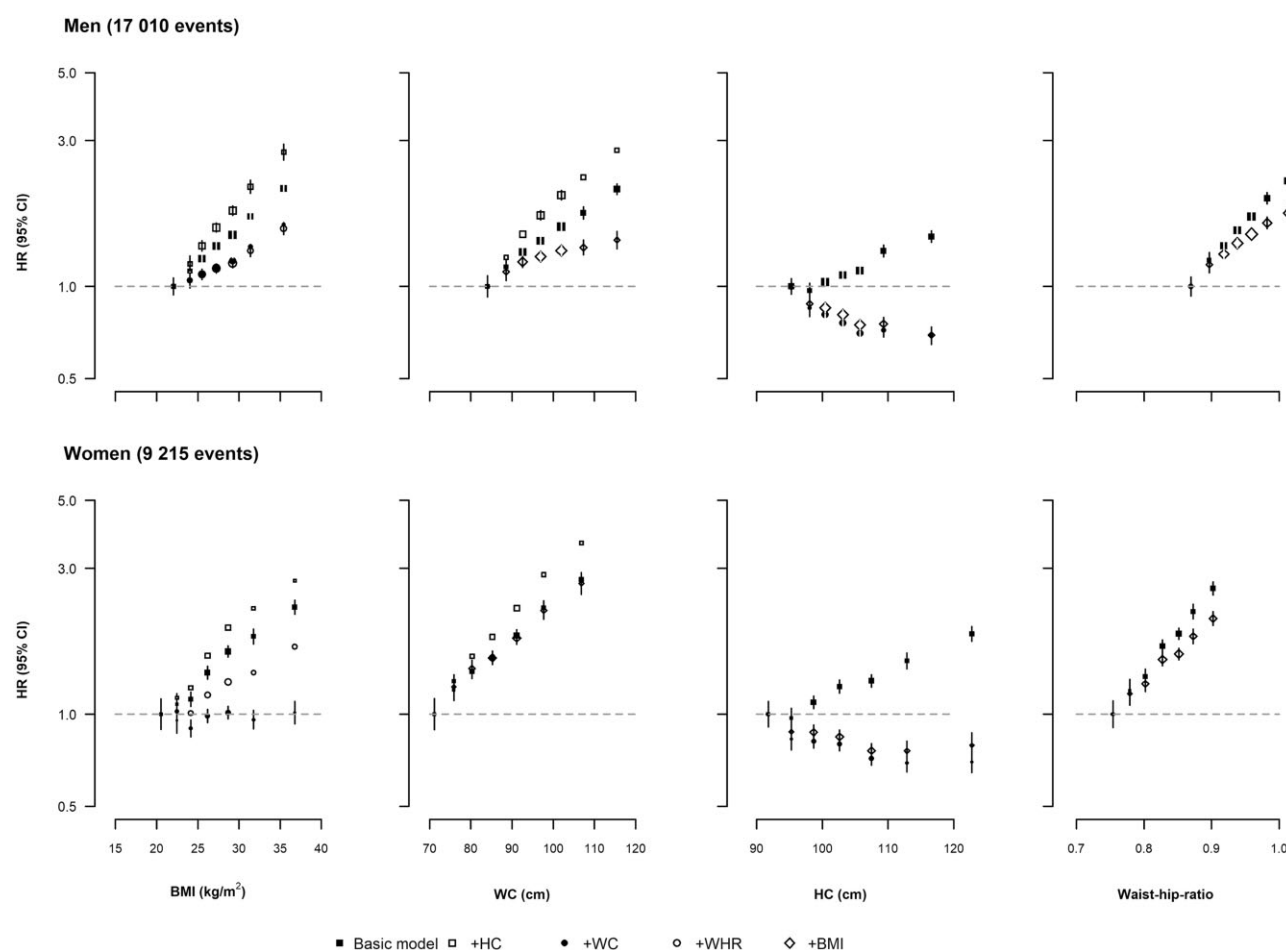
The associations of CHD risk with all four adiposity measures were largely accounted for by blood pressure, lipids, HbA1c levels and diabetes diagnosis (log-HR decrease by a range of 50% for WHR to 81% for HC among men and 55% for WC to 66% for BMI in women and the corresponding decreases

in  $\chi^2$  statistic were 79% and 96% for men and 86% and 90% for women, respectively) (Figure 3). Any remaining associations were further attenuated by additional adjustment for liver enzymes, glomerular filtration rate and inflammatory markers ([Supplementary Figure S6](#), available as [Supplementary data](#) at *IJE* online).

## Associations between genetically predicted adiposity and CHD risk

Non-linear MR estimates from piecewise linear plots, as well as the doubly ranked method, showed linear trends similar to the observational associations ([Supplementary Figures S7 and S8](#), available as [Supplementary data](#) at *IJE* online). Although less precise and weaker, estimated CHD risk per SD genetically predicted elevated adiposity from linear MR showed similar trends to the observed risk of CHD across all measures, but less for HC (Figure 4). Multivariable MR showed similar results. No heterogeneity by sex was observed ([Supplementary Figure S4](#), available as [Supplementary data](#) at *IJE* online). With the exception of HC, each GRS was associated with at least one socio-economic or lifestyle confounder implicating potential pleiotropic effects ([Supplementary Table S10](#), available as [Supplementary data](#) at *IJE* online). MR-Egger regression revealed that there was little evidence for directional pleiotropy for BMI among both men and women, WCadjBMI among women ([Supplementary Tables S11A and B](#), available as [Supplementary data](#) at *IJE* online). After accounting for some evidence of pleiotropy for BMI, BMI was not associated with CHD risk whereas WC displayed strong





**Figure 1.** Sex-specific hazard ratios for coronary heart disease with increasing levels of adiposity among men and women before and after mutual adjustment. Hazard ratios (HRs) were stratified by age at risk and UK region, and adjusted for education, deprivation index, ethnicity, smoking and alcohol consumption among (a) men and (b) women. HRs were calculated for tenths defined by the overall baseline adiposity measurements, with the middle six tenths combined in pairs, thus plotting seven groups corresponding to the top and bottom two tenths and the middle three fifths of each distribution. The area of each box is proportional to the amount of statistical information (i.e. it is inversely proportional to the variance of the log-HR). Error bars indicate the 95% CI. Closed squares represent HRs not adjusted for other adiposity measures.  $n=456\,495$  after exclusion of participants as described in [Supplementary Figure S1](#) (available as [Supplementary data](#) at *IJE* online). BMI, body mass index; HC, hip circumference; WHR, waist-to-hip ratio; WC, waist circumference

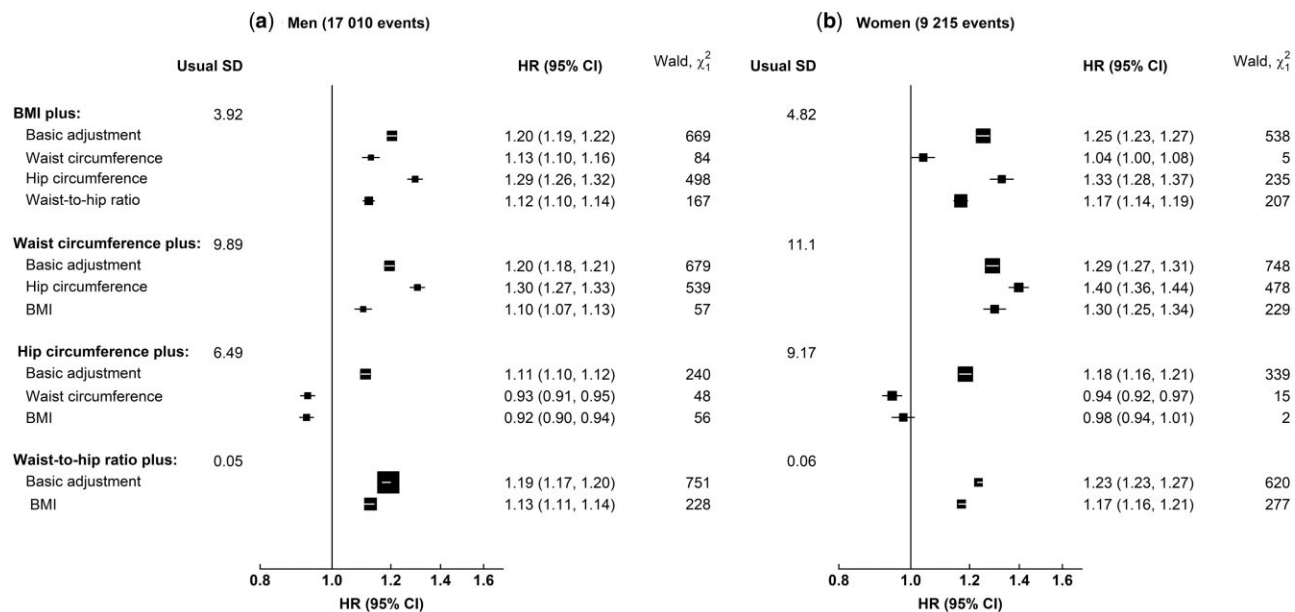
positive associations with CHD among women [MR-Egger OR (95% CI): 2.89 (1.71, 4.90)]. However, MR-Egger has been shown to only work well when  $I^2_{GX}$  is large ( $>90\%$ )<sup>34</sup> and, whilst the  $I^2_{GX}$  statistic was relatively large for BMI, WC and WHR (women only) ( $>80\%$ ), it was lower for WHRadjBMI among men (63.0%) and HCadjBMI ( $\sim 62\%$ ) ([Supplementary Tables S11A and B](#), available as [Supplementary data](#) at *IJE* online). In these cases, SIMEX did not show any evidence of regression dilution bias or any substantial associations. Results from weighted median MR only showed an association for WHRadjBMI among women [weighted median MR OR (95% CI): 1.32 (1.02, 1.70)] and results from MR-PRESSO did not show any evidence of a causal association between adiposity measures and CHD risk, apart from BMI and WHR among women, which were positively associated after removal of one outlier, which was considered to cause horizontal pleiotropy.

## Discussion

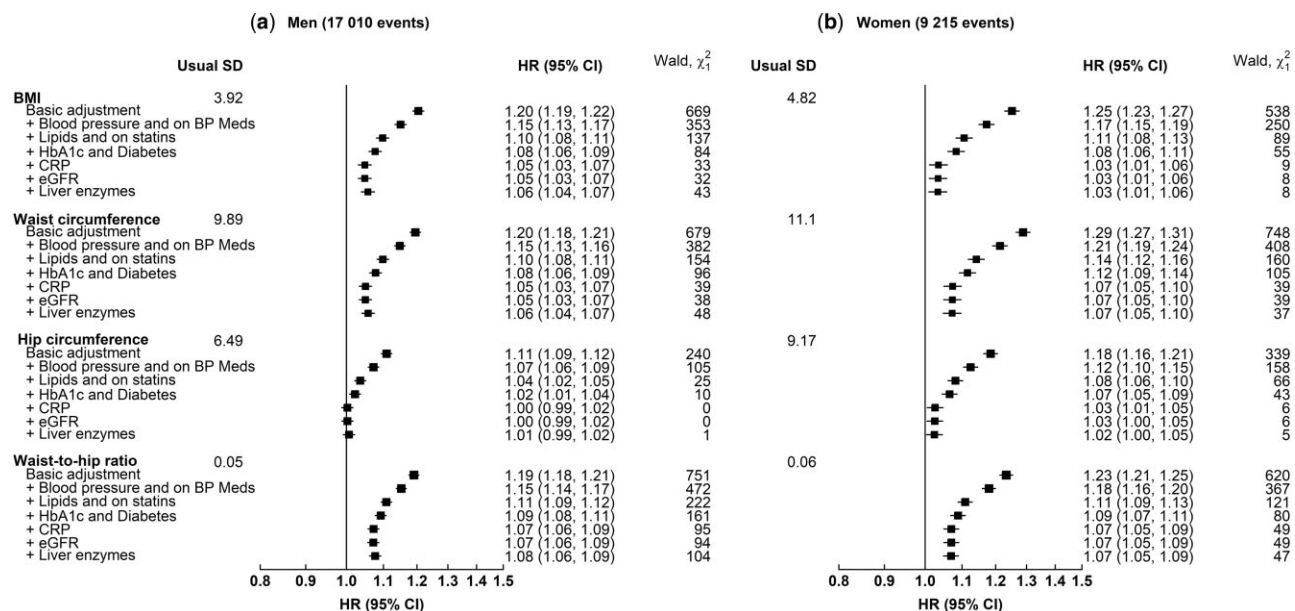
This study demonstrates the independent relevance of body fat distribution and general adiposity to CHD risk in a large contemporary UK adult population. Apart from HC,

adiposity measures remained independently associated with CHD over and above their associations with established risk factors, which together explained much of the associations with adiposity measures. Importantly, we found an independent inverse association between HC and CHD risk. This is the largest single study to investigate the observational and genetic associations of four commonly used adiposity measures with CHD risk in the same population. The standardized exposure measurements, together with the availability of repeat measurements, biomarkers and genetic data have allowed the assessment of adiposity-related CHD risk with greater detail and precision than has been possible previously.

For all the adiposity measures, we observed strong, positive log-linear associations with CHD risk throughout the range studied with no evidence of thresholds above or below which higher levels of adiposity were no longer associated with risk. In contrast, most previous studies have observed a J-shaped association, despite similarly strong, positive associations above a threshold.<sup>9,10,29,38,39</sup> However, most large prior observational studies have investigated fatal CHD events only, primarily in relation to BMI and WHR. Although the greater relevance of body fat distribution measures to CHD and CVD risk compared with general adiposity has also been observed



**Figure 2.** Adjusted hazard ratios (95% confidence intervals) for coronary heart disease per standard deviation higher adiposity measure before and after mutual adjustments in (a) men and (b) women. Hazard ratios (HRs) were stratified by age at risk and UK region, and adjusted for education, deprivation index, ethnicity, smoking and alcohol consumption. The area of each box is proportional to the amount of statistical information (i.e. it is inversely proportional to the variance of the log-HR). Error bars indicate the 95% CIs. BMI, body mass index

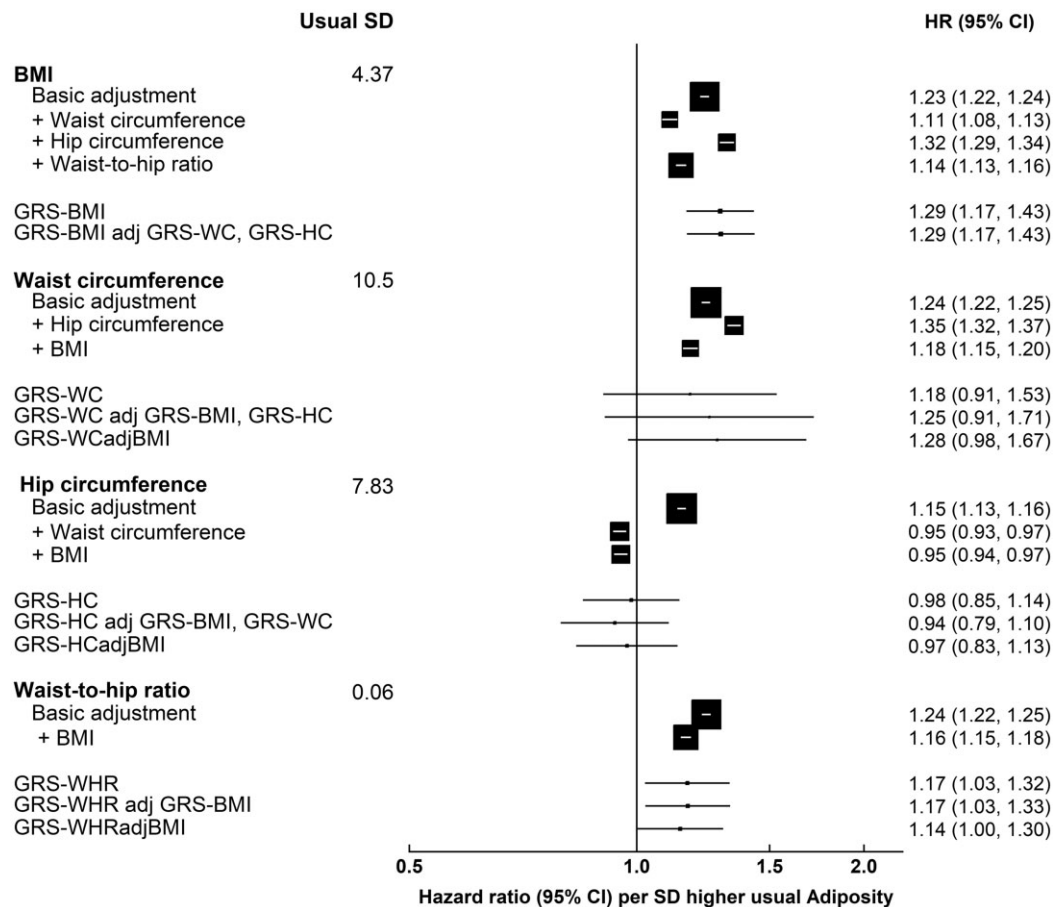


**Figure 3.** Hazard ratios (95% confidence intervals) for coronary heart disease risk per standard deviation higher adiposity measures with progressive adjustment for baseline risk factors. Hazard ratios (HRs) were stratified by age at risk and UK region, and adjusted for education, Townsend deprivation index, ethnicity, smoking and alcohol consumption. The area of each box is proportional to the amount of statistical information (i.e. it is inversely proportional to the variance of the log-HR). Error bars indicate the 95% CIs. Participants were excluded as shown in [Supplementary Figure S1](#) (available as [Supplementary data](#) at *IJE* online). BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin

previously,<sup>40–42</sup> large-scale data on HC are limited.<sup>5</sup> Consistently with the findings presented in the current study, a number of previous MR studies have identified positive associations with genetically elevated adiposity and CHD risk.<sup>13–19,43</sup> However, of the previous MR studies assessing the genetic associations of body fat distribution (as measured via WHRadjBMI or WC or HCadjBMI) with CHD risk,<sup>13–15,19</sup> the majority used summary-level statistics from the CARDIoGRAMplusC4D Consortium,<sup>13,15,19</sup> limiting the ability to investigate the shape of associations.

The biological mechanisms through which excess adiposity contributes to CHD risk are not fully understood, although elevated blood pressure, dysglycaemia and dyslipidaemia are thought to play key roles.<sup>8,9,17</sup> The results from the current study support this hypothesis, as evidenced by the observed attenuation of adiposity-related CHD risk after adjusting observational associations for multiple potential intermediate factors, although CHD risk remained for WHR that was unexplained by these risk factors.

The opposing associations with CHD risk observed between HC and central adiposity (WC and WHR) support the



**Figure 4.** Observed and genetic coronary heart disease risk (95% confidence intervals) per usual standard deviation higher adiposity measure among men and women combined. Observational analyses were restricted to 456 495 participants without outlying/missing adiposity variables or a history of cardiovascular disease at baseline. Genetic analyses were restricted to unrelated 369 225 participants of European ancestry, with complete genetic information, and without outlying/missing adiposity variables or a history of cardiovascular disease at baseline. Observational estimates were adjusted for age at baseline, ethnicity, education, region, smoking and alcohol. Genetic risk scores were composed of single-nucleotide polymorphisms (SNPs) discovered in European populations by using the GIANT consortia at genome-wide significance ( $P=5\times 10^{-8}$ ). All SNPs were weighted by the effect size as estimated in the GIANT consortia. Genetic analyses include also multivariable Mendelian randomization and were stratified by age at risk and region, and adjusted for age at baseline (5-year groups), age,<sup>2</sup> sex, the first 10 genetic principle components, batch number and array type. The area of each box is proportional to the amount of statistical information (i.e. it is inversely proportional to the variance of the log-HR). GRS, genetic risk score; GRS-BMI, genetic risk score for body mass index; GRS-HC, genetic risk score for hip circumference; GRS-WHR, genetic risk score for waist-to-hip ratio; GRS-WC, genetic risk score for waist circumference; HR, hazard ratio

theory that upper- and lower-body fat depots exert fundamental functional differences, although this has not been fully elucidated.<sup>44</sup> Comparing the adipose tissue function between lower- and upper-body fat, in particular visceral fat, the gluteofemoral tissue may exert protective cardiometabolic effects by acting as a metabolic ‘sink’, thereby reducing ectopic fat storage. Several potential underlying differences in mechanisms of action between adipose tissues include lower triglyceride turnover and resistance to stress hormone-induced lipolysis<sup>45</sup> or upregulated leptin or palmitoleic acid pathways in the lower-body adipose tissue.<sup>44</sup> Importantly, the findings from the current study have important implications for population health. Principally, by demonstrating an independent relevance of body fat distribution on CHD risk, our findings suggest that HC, WC and WHR could provide additional information beyond BMI for improved CHD risk prediction at the population level.<sup>40,41</sup> Many risk tools have been developed, most of which estimate an individual’s 10-year absolute risk of CHD or CVD from measures of varying applicability to general practice settings.<sup>46</sup> Pragmatic

risk scores that utilize simple measures such as body size instead of lipid levels may be of greater value in low-resource settings. This is of particular importance given the rising incidence of CVD in developing countries relative to developed countries.<sup>47</sup> Despite several population studies describing independent effects of WHR and WC on CVD outcomes beyond BMI,<sup>40,41</sup> there is a lack of evidence for the contribution of these measures to CVD risk tools. The current study has potential limitations. First, participants were primarily White and middle-aged, potentially limiting the generalizability of these findings. In contemporary Western populations exposed to ‘obesogenic’ environments for decades, the distribution of adiposity has shifted towards higher levels. Therefore, the current study lacks statistical power to investigate CHD risk at low levels of adiposity commonly seen in lower-income settings. Second, WC and HC measures are prone to measurement error. However, this was somewhat counteracted by the availability of repeat measures, which allowed us to calculate ‘usual’ levels.<sup>26</sup> Fifth, the GRSs were associated with a number of socio-economic and lifestyle

factors as noted previously in UKB<sup>48</sup> but GRSs did not display evidence of directional pleiotropy using MR–Egger, apart from WCadjBMI. After accounting for this, there was evidence of a causal association, supporting the primary results. Finally, the GRSs for WC and HC explained only a small proportion of variance of the corresponding adiposity measures, resulting in weak instrument bias. Future discovery efforts in diverse populations will be important to address this limitation.

## Conclusions

In summary, BMI, WC and WHR adiposity measures demonstrated strong, positive and approximately log-linear associations with CHD risk, with no evidence of threshold effects within the ranges studied. Blood pressure, lipids and dysglycaemia largely accounted for the observational prospective associations. In contrast, HC demonstrated an independent protective effect against CHD risk. Genetically predicted elevated adiposity measures were directionally concordant with observational estimates. Therefore, body fat distribution and general adiposity should be considered separately when estimating CHD risk and investigating the aetiology of CHD.

## Ethics approval

Ethics approval for UKB was granted by the North West Multi-Centre Research Ethics Committee in May 2006. All participants provided informed written consent.

## Data availability

The data underlying this article were provided by UKB under application number 31461. Data can be accessed under the UKB data access process (<https://www.ukbiobank.ac.uk/en/able-your-research>).

## Supplementary data

Supplementary data are available at *IJE* online.

## Author contributions

E.T. performed the analysis and completed the first draft of the manuscript. D.M. designed the project, acquired the data, performed part of the analysis and started the first draft of the manuscript. D.J. processed the outcome variable. H.T., N.W. and P.S. performed part of the analysis. F.D. processed and provided the genetic data. J.H. supervised the processing of the genetic data. B.L., J.E., D.B. and S.L. supervised the project and contributed to the project design. All the authors revised the manuscript and gave critical input.

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## Conflict of interest

The Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) receives research grants from industry that are governed by University of Oxford contracts that protect its independence and has a staff policy of not taking personal payments from industry; further details can be found at <https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf>. The authors declare no other conflict of interest.

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