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CARDIOVASCULAR DISEASE

Genetically predicted body composition in relation to cardiometabolic traits: a Mendelian randomization study

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Abstract

Fat mass and fat-free mass are found to be associated with different health outcomes in observational studies, but the underlying causality remains unclear. We aimed to investigate the causal relationships between body composition and cardiometabolic traits using a two-sample Mendelian randomization (MR) approach. Independent genetic variants associated with body fat mass, fat-free mass, and fat percentage in UK Biobank population were used as genetic instrumental variables, and their causal effects on circulatory diseases, type 2 diabetes, glycemic traits, and lipid fractions were estimated from large-scale genome-wide association studies (GWAS) in European populations. Univariable, multivariable, and bidirectional MR analyses were performed. Genetically predicted high fat mass and fat percentage significantly increased risks of most cardiometabolic diseases, and high fat-free mass had protective effects on most cardiometabolic diseases after accounting for fat mass. Fat mass, fat-free mass, and fat percentage were all positively associated with higher risks of atrial fibrillation and flutter, varicose veins, and deep vein thrombosis and pulmonary embolism. High fat mass increased fasting glucose, homeostasis model assessment-insulin resistance (HOMA-IR), triglycerides, decreased high-density lipoprotein cholesterol, and high fat-free mass reduced HOMA-IR, triglycerides, and low-density lipoprotein cholesterol. Genetically predicted fat-free mass was bidirectionally negatively associated with 2-h glucose and total cholesterol. The findings may be helpful in risk stratification and tailoring management of body composition in patients with different cardiometabolic statuses.

Keywords Body composition · Cardiovascular disease · Glucose metabolism · Lipids · Mendelian randomization

Introduction

Numerous epidemiological studies have established an association between higher body mass index (BMI) and the increased risks of diseases. However, BMI is not an ideal measure to represent anthropometric characteristics, as it does not distinguish between fat mass and fat-free mass. Assessing body composition is important because fat tissue has different physiological properties from non-fat tissues, and they may pose distinct influences on health. Several observational studies have documented detrimental impacts of fat accumulation and beneficial impacts of higher lean mass on glucose metabolism [1, 2] and cardiovascular health [3, 4], but some others found no protective role of lean mass on major adverse cardiovascular events [5] and that lean mass is the predominant anthropometric risk factor for atrial fibrillation [6, 7].

Mendelian randomization (MR) uses genetic variants associated with an exposure of interest as instrumental variables to assess its causal effect on an outcome of interest

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[8]. It can be thought of as analogous to a randomized controlled trial (RCT) wherein individuals are naturally assigned at birth to inherit genetic variants that affect a risk factor, and therefore, are randomly allocated to variation in levels of the exposure, rather than randomized allocation to an intervention (e.g., a drug or a treatment) [8]. It is less vulnerable to biases from confounding and reverse causation since the random allocation of the genetic variants occurs at conception and is typically unassociated with confounders. It has been widely used to test causal relationships between BMI and health outcomes [9–11]. However, there is scarce research on the causal effects of body fat mass, fat-free mass or their proportion (i.e., fat percentage) on cardiometabolic traits. The few MR studies reported that fat mass index was associated with most cardiovascular traits [12], higher fat-free mass causally increased risk of atrial fibrillation [13], higher lean mass causally protected against type 2 diabetes and diabetes reduced lean mass [14], and both genetically predicted fat mass and fat-free mass were associated with varicose veins [15].

In the present study, we hypothesize that body fat mass and fat-free mass have distinct causal relationships with cardiometabolic traits. We carried out MR analyses investigating the causal effects of fat mass, fat-free mass and fat percentage on 8 cardiometabolic diseases, 4 glycemic traits, and 4 lipid fractions using well-powered genetic instruments from UK Biobank and summary data from large-scale genome-wide association studies (GWAS) in European populations.

Methods

Genetic instruments for body composition

The primary exposure phenotype of interest was body composition, and the GWAS summary data of body fat mass (n = 454,137), fat-free mass (n = 454,850), and fat percentage (n = 454,633) in UK Biobank population from the MRC integrative Epidemiology Unit (MRC-IEU) OpenGWAS database [16] were used to identify genetic instruments for our MR analyses. Body composition of UK Biobank participants was assessed using the Tanita BC418MA body composition analyzer. The details of the GWAS pipeline for the full UK Biobank (version 3, March 2018) genetic data can be accessed on https://data.bris.ac.uk/data/dataset/pnoat8cxo0u52p6ynfaekeigi. GWAS was conducted using linear mixed model (LMM) association method as implemented in BOLT-LMM (v2.3), adjusting for sex and genotyping array. The analyses were restricted to autosomal variants and the population had been restricted to individuals of European ancestry after standard exclusion. Genetic instrumental variables were extracted using the "extract_instruments" function of the R package TwoSampleMR on the MR-Base platform [17] with default parameters ($p < 5e\text{-}8$, linkage disequilibrium (LD) $r2 < 0.001, > 10{,}000$ kb), and 435, 556, and 395 instrumental variables for fat mass, fat-free mass, and fat percentage respectively were obtained (Supplementary Table 1). There were 24 overlapping instrumental variables between fat mass and fat-free mass, 151 overlapping instrumental variables between fat mass and fat-percentage, and 9 overlapping instrumental variables between fat-free mass and fat percentage (Supplementary Fig. 1). We used MR Steiger directionality test to calculate R2 values (variance of exposure explained by the instrumental variables), and *F* statistics were used to assess the strength of relationships between instrumental variables and phenotypes [18].

GWAS summary data of cardiometabolic traits

GWAS summary data of cardiometabolic traits consisting the most homogeneous populations of European ancestry while minimizing sample overlap with UK Biobank population, having the largest sample sizes and covering the majority of instrumental SNPs of the exposure phenotype (i.e., body composition) were selected. Data sources and related information are presented in Supplementary Table 2. The FinnGen study is a public–private partnership project combining genotype data from Finnish biobanks and digital health record data from Finnish health registries. Detailed methods (e.g., participating biobanks/cohorts, data collection, endpoints, genotyping and data analysis) are presented on its webpage (https://finngen.gitbook.io/documentation/). The mixed model logistic regression package SAIGE [19] was used for GWAS, with sex, age, 10 principal components (PCs) and genotyping batch included as covariates. Values of homeostasis model assessment-insulin resistance (HOMA-IR) and fasting insulin were log-transformed, values of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were inverse normal transformed prior to GWAS.

Mendelian randomization methods

One of the main assumptions of MR states that the genetic instruments should only be related to the outcome of interest through the instrumented exposure—that is, an absence of horizontal pleiotropy[8]. Horizontal pleiotropy is common and may occur when a variant affects the exposure and the outcome through separate mechanisms (uncorrelated pleiotropy) or through a shared heritable process or pathway (correlated pleiotropy) [20]. The complementary methods of two-sample MR adopted in the present study make different assumptions about horizontal pleiotropy.

In general, apart from the conventional inverse variance weighted (IVW) method [8], weighted median [21] allows

some horizontal pleiotropy of any kind; MR-Egger [22] and MR-PRESSO [23] (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) allow for directional uncorrelated pleiotropy; CAUSE [20] (Causal Analysis Using Summary Effect estimates) accounts for uncorrelated and correlated pleiotropy simultaneously; multivariable MR (MVMR) [24] addresses "measured" pleiotropic effects by accounting for a specific exposure.

In the present analyses, IVW, MR-Egger, weighted median, and MVMR as well as tests for directional horizontal pleiotropy by Egger-intercept were conducted using the MR-Base [17] R package TwoSampleMR version 0.5.5 with default parameters (LD r2 ≥ 0.8 for proxy SNPs if available and minor allele frequency ≤ 0.3 for strand aligning for palindromic SNPs when necessary). MR-PRESSO was conducted using the MRPRESSO R package version 1.0 (https://github.com/rondolab/MR-PRESSO). The number of distributions was set to 10,000 and the threshold was set to 0.05. We present results from MR-PRESSO raw tests unless *p* value for MR-PRESSO global test was lower than 0.05 and the result from outlier-corrected test was given. We performed CAUSE using the R package cause version 1.2.0 (https://github.com/jean997/cause). Briefly, GWAS summary data of the exposure and the outcome were merged and formatted, followed by nuisance parameters estimation with a sample of 1000,000 unique variants. LD pruning was conducted for SNPs with *p* values lower than 1e-3 (default) for both the exposure and the outcome, with LD estimates in the 1000 Genomes CEU population (https://zenodo.org/record/1464357#.X5ozQFMzbAJ) as the reference panel. We applied MVMR to identify the independent causal effects of fat mass, fat-free mass, and fat percentage, accounting for the potential pleiotropic influence of each other, on cardiometabolic traits. In MVMR1, fat mass and fat-free mass were included as exposures; In MVMR2, fat mass and fat percentage were included as exposures; In MVMR3, fat-free mass and fat percentage were included as exposures.

Bidirectional Mendelian randomization

We conducted bidirectional MR analyses to test whether there was any evidence for causal effects of cardiometabolic traits on body composition. For each trait, SNPs with $p < 5e\text{-}8$, LD r2 < 0.001 (clumping window 10,000 kb) were extracted (Supplementary Table 3). Similarly, IVW, MR-Egger, weighted median, MR-PRESSO and CAUSE were applied. GWAS of HOMA-IR had no significant ($p < 5e\text{-}8$) SNPs, bidirectional MR using other methods could not be performed, and CAUSE was regarded as the primary analysis. GWAS of 2-h glucose had only one instrumental SNP; therefore, only Wald ratio test and CAUSE were applied.

Statistical analyses

The MR methods were applied to investigate causal effects of genetically predicted fat mass, fat-free mass and fat percentage respectively on each outcome in turn and vice versa for bidirectional MR. Each effect represents the estimated causal odds ratio (OR) of cardiometabolic diseases, or change of fasting glucose, 2-h glucose, log-transformed fasting insulin or HOMA-IR, or inverse normal transformed total cholesterol, triglycerides, HDL cholesterol, or LDL cholesterol in response to per standard deviation (SD) increase of fat mass, fat-free mass, or fat percentage, respectively.

A consistent effect estimation across the MR methods is not likely to be a false positive. The conventional IVW method was used as the primary univariable analysis, and MR-Egger, weighted median, MR-PRESSO, and CAUSE were used as sensitivity analyses. We considered the relationships significant if the directions of the estimates by the 5 methods were consistent, the IVW method passed the Bonferroni-corrected significance level (0.05/16 = 3.13e-3), no significant pleiotropy was detected by MR-Egger (i.e., *p* value of Egger-intercept term was ≥ 0.05) or *p* value of MR-Egger regression was < 0.05, and *p* values of weighted median, MR-PRESSO and CAUSE were lower than 0.05. For MVMR, *p* values < 3.13e-3 were considered significant and *p* values between 3.13e-3 and 0.05 were considered suggestive evidence of causal associations. All statistical tests were two-tailed, and analyses were conducted with R version 3.6.2.

Results

In MR analyses assessing causal effects of body composition on cardiometabolic traits, numbers of instrumental variables used in the final analyses ranged between 281 and 409 for fat mass, between 315 and 523 for fat-free mass, and between 255 and 370 for fat percentage (Supplementary Table 4). *F* statistics ranged between 65 and 109, which were much higher than 10 and indicated small possibility of weak instrument bias (Supplementary Table 4).

Causal effects of body composition on cardiometabolic diseases

In univariable MR, genetically predicted high fat mass was causally associated with higher risks of 7 cardiometabolic diseases, including and with decreasing magnitude of association: type 2 diabetes, atrial fibrillation and flutter, varicose veins, deep vein thrombosis (DVT) and pulmonary embolism (PE), hypertension, ischemic heart diseases, and major coronary heart disease (CHD) event. Causal ORs estimated using IVW method ranged between 1.16 (95% CI: 1.05 to

1.28) and 1.91 (1.68 to 2.18) per SD increase of fat mass with p values < 3.13e-3 (Fig. 1 and Supplementary Table 5). IVW causal OR of stroke was 1.19 (95% CI: 1.10 to 1.29) with $p = 2.71e-5$, but beta estimate from weighted median MR was insignificant ($p = 0.055$). Genetically predicted high fat-free mass showed causal effects on higher risks of atrial fibrillation and flutter, varicose veins, and DVT and PE, but was not associated with risks of other cardiometabolic diseases investigated (Fig. 1 and Supplementary Table 5). Genetically predicted high fat percentage was significantly associated with higher risks of type 2 diabetes, atrial fibrillation and flutter, DVT and PE, hypertension, varicose veins, and ischemic heart diseases. MR-Egger regression of major CHD event on fat percentage indicated pleiotropy (Egger intercept $p = 0.031$) and p value was higher than 0.05 ($p = 0.253$). Besides, causal effect of fat percentage on stroke estimated by CAUSE was insignificant ($p = 0.110$) (Fig. 1 and Supplementary Table 5).

In MVMR1, fat mass showed greater causal effects than those estimated by univariable MR on higher risks of ischemic heart diseases, major CHD event, hypertension, stroke, and type 2 diabetes; whereas fat-free mass showed protective effects on them. And causal effects of fat mass and fat-free mass on atrial fibrillation and flutter, varicose veins, and DVT and PE were all attenuated in MVMR1 than those in univariable MR (Fig. 1 and Supplementary Table 5). In MVMR2, both fat mass and fat percentage had little independent causal associations with ischemic heart diseases, major CHD event, or stroke. Intriguingly, fat mass had greater causal associations with higher risks of atrial fibrillation and flutter, varicose veins, DVT and PE, hypertension, and type 2 diabetes in MVMR2 compared with univariable MR estimates, and fat percentage turned out insignificantly or negatively associated with them after accounting for fat mass. These results indicated that the effects of fat mass might outweigh those of fat percentage on these cardiometabolic diseases. MVMR3 including fat-free mass and fat percentage as exposures suggested that fat percentage but not fat-free mass was associated with higher risks of the cardiometabolic diseases except for atrial fibrillation and flutter, varicose veins, and DVT and PE.

Causal effects of body composition on glycemic traits

Univariable MR revealed that per SD increase of fat mass, fat-free mass and fat percentage were associated with 0.05 (95% CI: 0.03 to 0.08) mmol/L, 0.06 (95% CI: 0.03 to 0.09) mmol/L, and 0.08 (95% CI: 0.05 to 0.11) mmol/L increase of fasting glucose, respectively. After accounting for fat mass in MVMR1, fat-free mass had no significant causal effect on fasting glucose ($p = 0.475$) (Fig. 2 and Supplementary Table 6). None of fat mass, fat-free mass, or fat percentage was significantly associated with 2-h glucose in univariable MR, but high fat-free mass significantly reduced 2-h glucose level after accounting for fat mass or fat percentage (MVMR causal effects: −0.051 mmol/L and −0.38 mmol/L per SD increase of fat-free mass, respectively).

Both high fat mass and high fat percentage were significantly and causally associated with high levels of fasting insulin and HOMA-IR in univariable MR and after accounting for fat-free mass. IVW causal effects were 0.14 (95% CI: 0.11 to 0.17) pmol/L and 0.18 (95% CI: 0.14 to 0.23) pmol/L increase of log- fasting insulin, and 0.13 (95% CI: 0.10 to 0.17) unit and 0.18 (95% CI: 0.12 to 0.23) unit increase of log- HOMA-IR per SD increase of fat mass and fat percentage, respectively. MVMR anslyses showed that high fat mass was the predominant causal factor of higher fasting insulin and HOMA-IR, while fat-free mass was negatively associated with them after accounting for fat mass (MVMR causal effects: -0.12 pmol/L of log- fasting insulin and -0.08 unit of log- HOMA-IR per SD increase of fat-free mass, respectively).

Causal effects of body composition on lipid fractions

As shown in Fig. 3 and Supplementary Table 7, per SD increase of fat mass and fat percentage were associated with 0.13 (95% CI: 0.07 to 0.18) and 0.14 (95% CI: 0.06 to 0.23) SD increase of triglycerides, respectively. The effect of fat mass became greater after accounting for fat-free mass or fat percentage (MVMR causal effects: 0.32 and 0.44 SD, respectively). Per SD increase of fat-free mass was associated with 0.21 SD decrease of total cholesterol in IVW MR analysis, and high fat-free mass causally reduced levels of triglycerides, total cholesterol and LDL cholesterol after accounting for fat mass or fat percentage (Fig. 3 and Supplementary Table 7). We observed no significant causal effect of fat mass or fat percentage on total cholesterol or LDL cholesterol. Univariable MR analyses showed that genetically predicted fat mass, fat-free mass and fat percentage were all negatively associated with HDL cholesterol, and MVMR analyses suggested that fat mass was the predominant causal factor that reduced HDL cholesterol level (MVMR causal effects: −0.30 and −0.82 SD per SD increase of fat mass in MVMR1 and MVMR2, respectively).

Causal effects of cardiometabolic traits on body composition

In bidirectional MR assessing causal effects of cardiometabolic traits on body composition, numbers of instrumental variables used in the final analyses ranged between 1 and 86 except for HOMA-IR, and F statistics ranged between 37 and 573 (Supplementary Table 8).

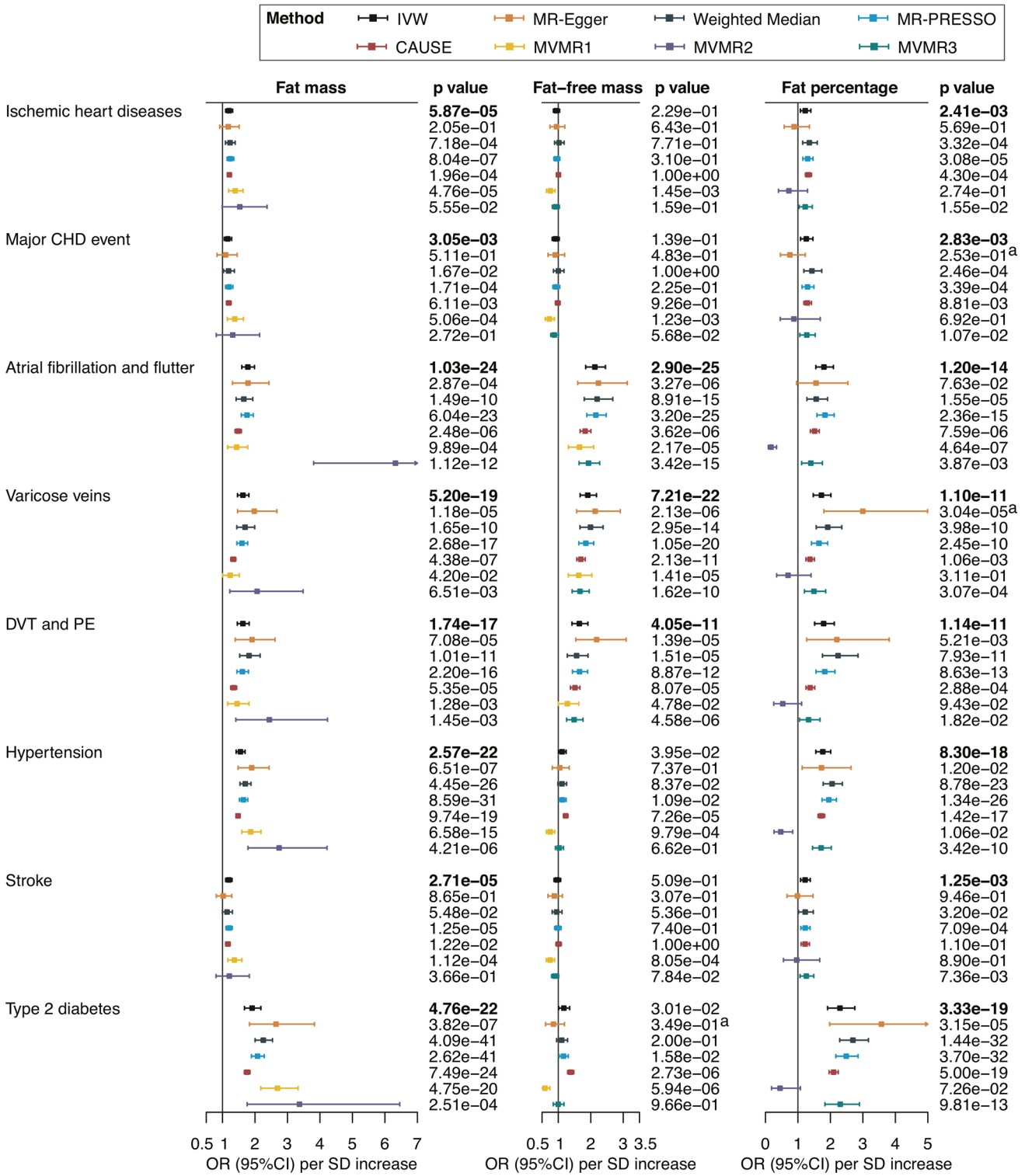

Fig. 1 Forest plots illustrating causal effects of genetically predicted body composition on cardiometabolic diseases. In MVMR1, fat mass and fat-free mass were included as exposures; In MVMR2, fat mass and fat percentage were included as exposures; In MVMR3, fat-free mass and fat percentage were included as exposures. For IVW method, p values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 5. [a]MR-Egger intercept p value < 0.05

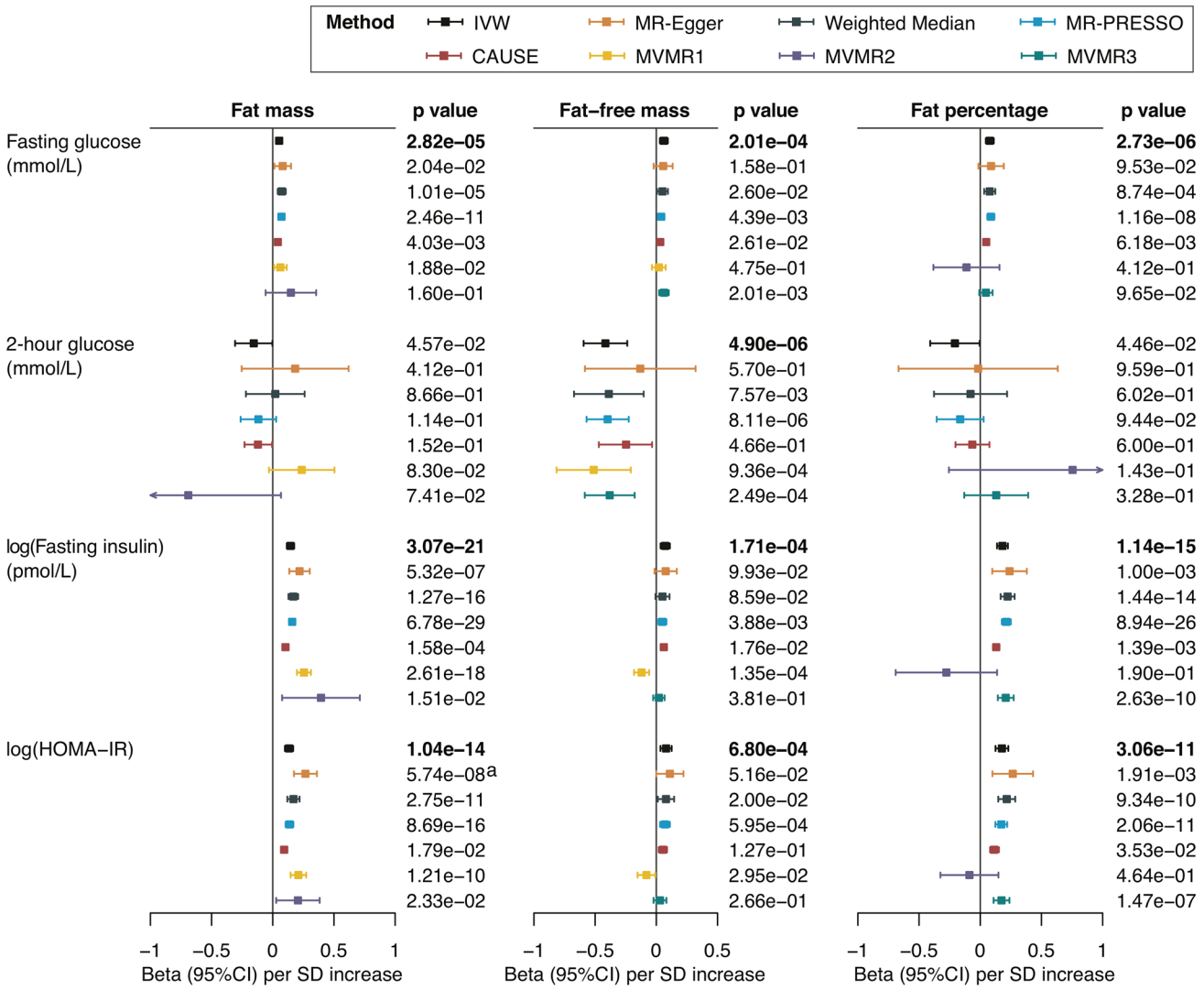

Fig. 2 Forest plots illustrating causal effects of genetically predicted body composition on glycemic traits. In MVMR1, fat mass and fat-free mass were included as exposures; In MVMR2, fat mass and fat percentage were included as exposures; In MVMR3, fat-free mass and fat percentage were included as exposures. For IVW method, p values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 6. [a]MR-Egger intercept p value < 0.05

Cardiometabolic diseases had little causal effect on body composition (Fig. 4 and Supplementary Table 9). Per mmol/L increase of 2-h glucose was associated with 0.05 SD decrease of fat-free mass (Fig. 5 and Supplementary Table 10). Per SD increase of total cholesterol causally reduced 0.05 SD of fat mass and 0.04 SD of fat-free mass (Fig. 6 and Supplementary Table 11). Per SD increase of LDL cholesterol was associated with 0.04 SD decrease of fat mass ($p = 1.89\text{e-}3$) and 0.02 SD decrease of fat-free mass ($p = 3.30\text{e}{-3}$). There was little evidence to support other cardiometabolic traits causally influencing body composition.

Discussion

In the present study, we performed bidirectional MR analyses to investigate causal relationships between body composition and 8 cardiometabolic diseases, 4 glycemic traits, and 4 lipid fractions. Value-added findings are: (1) high fat mass and fat percentage causally increased risks of most cardiometabolic diseases, and high fat-free mass had protective effects on cardiometabolic diseases only after accounting for fat mass. All of them were positively associated with higher risks of atrial fibrillation and flutter, varicose veins, and DVT and PE. (2) High fat mass

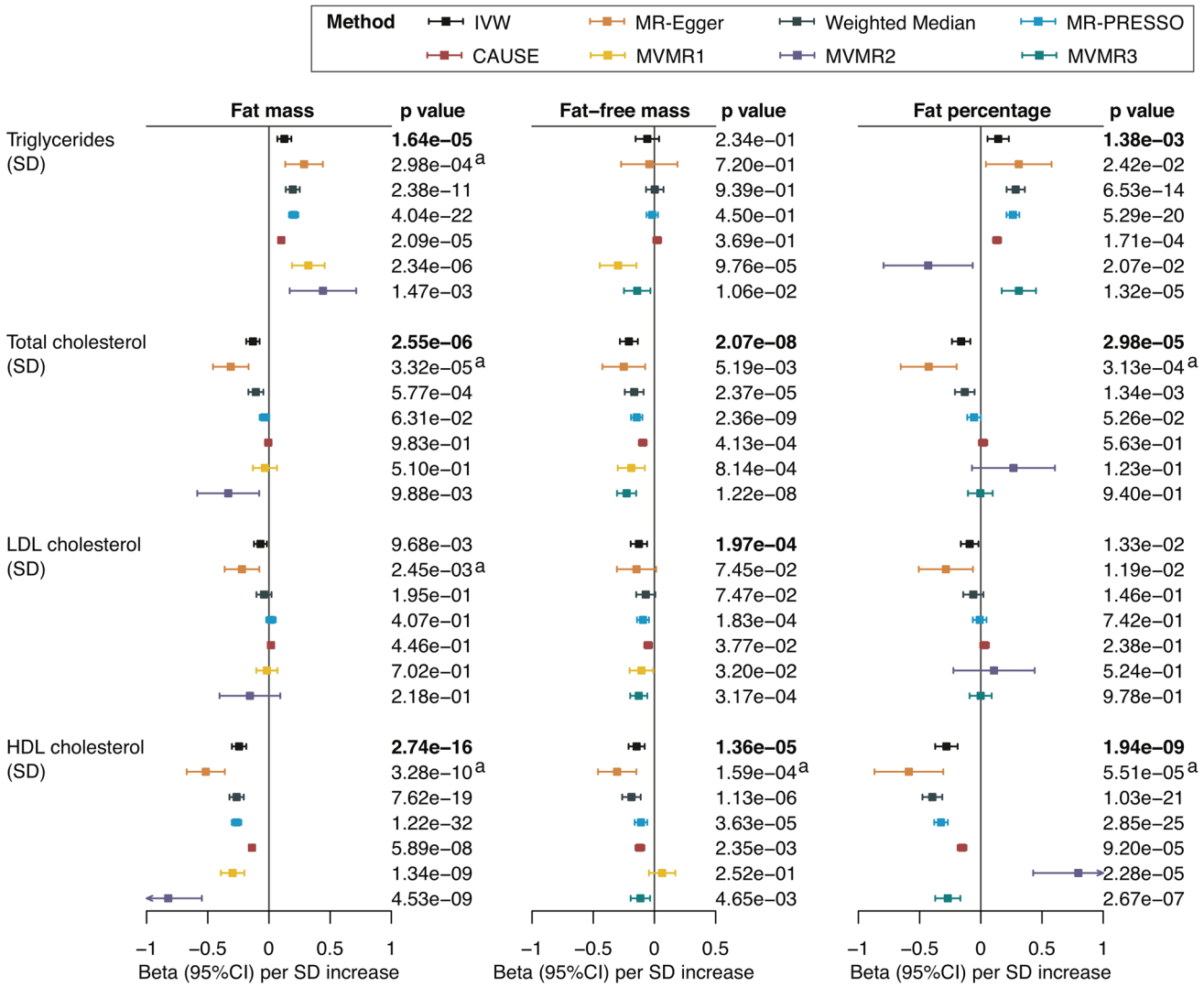

Fig. 3 Forest plots illustrating causal effects of genetically predicted body composition on lipid fractions. In MVMR1, fat mass and fat-free mass were included as exposures; In MVMR2, fat mass and fat percentage were included as exposures; In MVMR3, fat-free mass and fat percentage were included as exposures. For IVW method, *p* values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 7. [a]MR-Egger intercept *p* value < 0.05

causally increased fasting glucose, fasting insulin, HOMA-IR, triglycerides, decreased HDL cholesterol, and high fat-free mass causally reduced 2-h glucose, fasting insulin, HOMA-IR, triglycerides, total cholesterol, and LDL cholesterol. (3) High levels of 2-h glucose and total cholesterol causally reduced fat-free mass.

Another two-sample MR study investigated the causal relationships between fat mass index, fat-free mass index and 14 cardiovascular conditions [12]. However, effects were estimated with MVMR and all the exposures and the 14 outcomes were from UK Biobank, which were possibly biased by overfitting and brought the results close to phenotypic associations. Besides, the study had low power due to low proportions of cases. Their updated two-sample MR analysis using GWAS summary data from the DIAGRAM consortium and the Coronary ARtery DIsease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics (CARDIoGRAMplusC4D) consortium found that genetically predicted fat mass index was positively associated with type 2 diabetes and coronary artery disease [25]. In the present study, we used GWAS summary data of cardiometabolic diseases from the FinnGen study, which had no sample overlap with UK Biobank. Our results confirmed that high fat mass was associated with ischemic heart disease, major CHD event, hypertension, type 2 diabetes, and stroke (after accounting for fat-free mass). We also found that the effect of high absolute fat mass might outweigh that of fat percentage

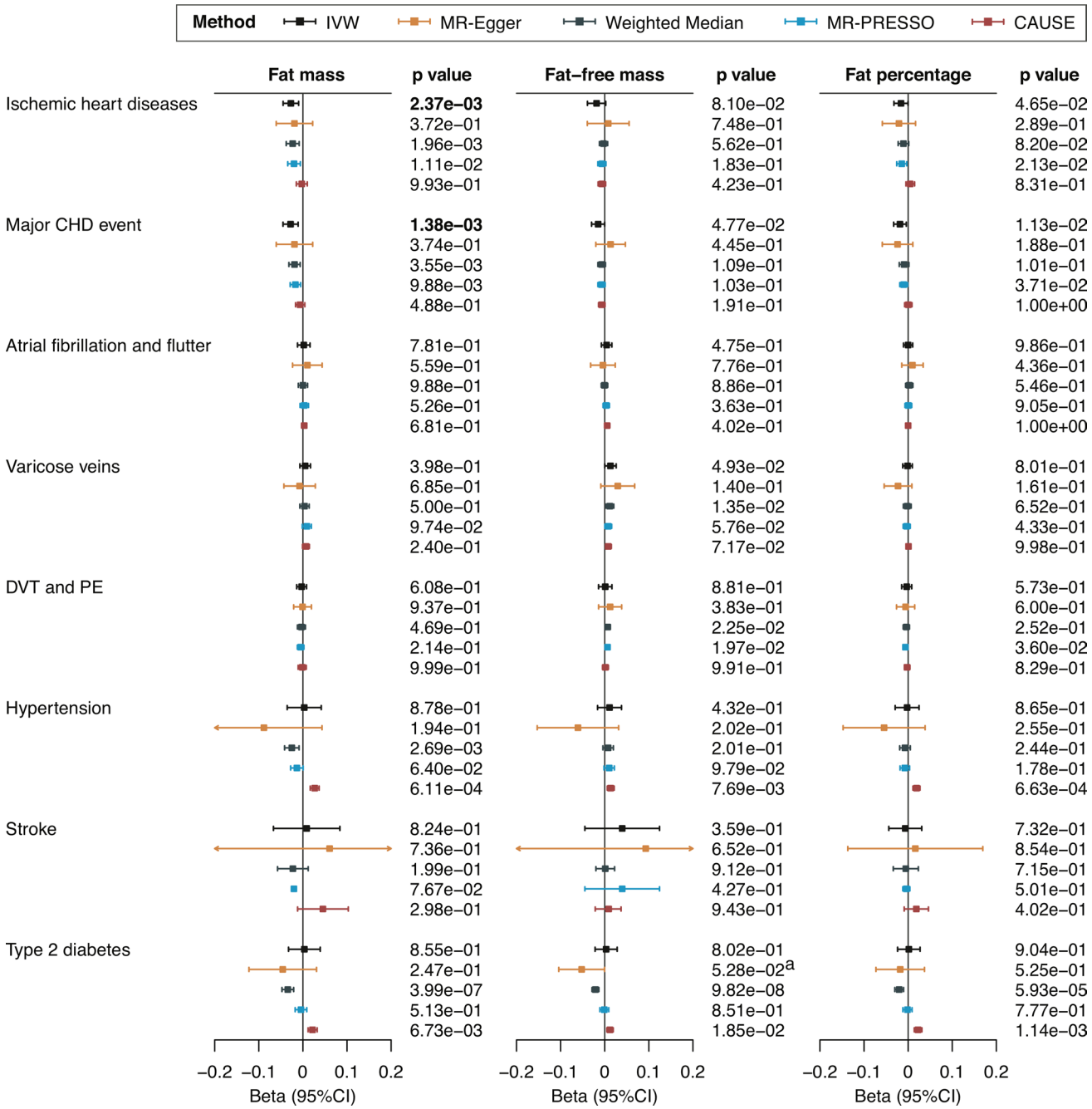

Fig. 4 Forest plots illustrating causal effects of cardiometabolic diseases on body composition. For IVW method, p values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 9. [a]MR-Egger intercept p value < 0.05

on cardiometabolic traits, which should be noted in body-building to keep fit. Previous observational studies reported that skeletal muscle mass was inversely associated with ten-year cardiovascular disease incidence [26], and loss of skeletal muscle mass might contribute to metabolic diseases [27, 28]. By applying MVMR approach, we provided additional evidence that higher fat-free mass was causally associated with lower risks of type 2 diabetes, hypertension, stroke, ischemic heart diseases, and major CHD event only after adjusting for fat mass.

Prospective studies reported that higher lean body mass was predominantly and independently associated with increased risk of atrial fibrillation [6, 7]. A subsequent observational and MR study revealed that genetically programmed increases in fat mass and fat-free mass had independent causal effects on atrial fibrillation risk [13], which

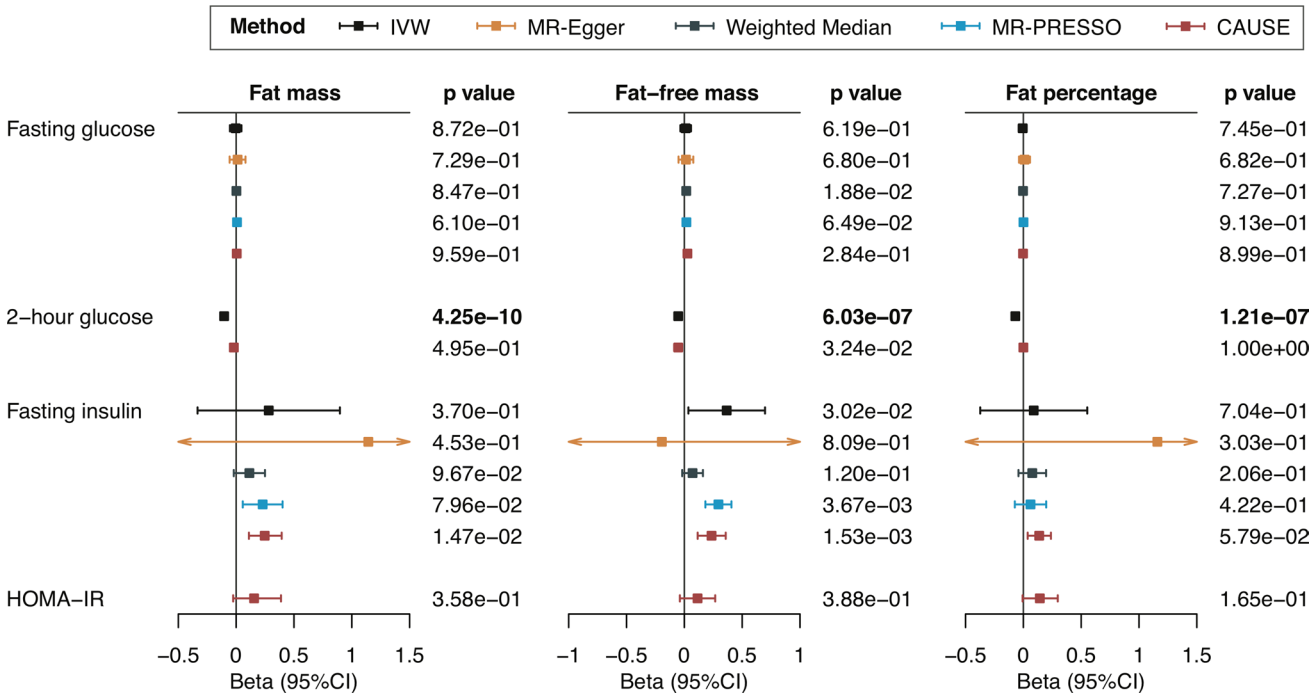

Fig. 5 Forest plots illustrating causal effects of glycemic traits on body composition. For IVW method, *p* values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 10

was in agreement with the present findings using the GWAS data of atrial fibrillation and flutter in Finnish population as the outcome. And roles of height, left atrial size, left ventricular mass, and myokines secreted by lean tissue on atrial fibrillation risk merit further exploration [29]. Genetically predicted high fat mass and fat-free mass also causally increased varicose veins and DVT and PE risk. A previous study in UK Biobank participants found greater body height as an independent risk factor for varicose vein disease after the adjustment for traditional risk factors in Cox regression, and MR analysis further supported the causal association [30]. Body height had also been reported to be an independent predictor and risk factor of venous thromboembolism in epidemiological [31] and MR studies [32]. One potential explanation is that the effects of fat mass and fat-free mass were mediated through body height, as taller individuals tend to have higher fat mass and fat-free mass.

Intriguingly, fat mass was positively associated with both fasting insulin and fasting glucose level, but had no significant effect on 2-h glucose; while higher fat-free mass causally reduced 2-h glucose, but showed little effect on fasting glucose, and higher 2-h glucose was related with reduced fat-free mass. Another MR study reported that lean mass was inversely associated with risk of type 2 diabetes and vice versa, but lean mass showed no association with fasting insulin or fasting glucose [14]. These results reflected different pathophysiological mechanisms of fasting and postprandial glucose metabolism. Elevated endogenous glucose production and insulin resistance is common in individuals with adiposity, which leads to higher fasting glucose, fasting insulin and HOMA-IR. Skeletal muscle is the major organ where insulin-mediated glucose uptake by glucose transporter 4 (GLUT4) takes place, thus higher muscle mass may reduce postprandial glucose as a sink for glucose disposal. Clinical trials and other studies have also shown that exercise lowered postprandial glucose but not fasting glucose in type 2 diabetes [33]. Hyperglycemia or insulin resistance result in decreased protein synthesis, which may accelerate muscle loss [34]. Taken together, these results suggested that tailored interventions to rebuild body composition could be considered in individuals with fasting or postprandial hyperglycemia, and patients with high postprandial glucose might break out of the vicious cycle by increasing muscle mass.

Genetically predicted fat mass and fat-free mass also showed disparities in causal relationships with lipid fractions. High fat mass increased triglycerides and reduced HDL cholesterol, and high fat-free mass mainly reduced total and LDL cholesterol. Previous MR studies examining the associations of BMI and cardiovascular risk factors showed causal effects of adiposity on higher triglycerides and lower HDL cholesterol, but no association between BMI and LDL cholesterol [35] or observed the negative causal association [36]. RCT of bariatric surgery also reported that intensive weight loss reduced plasma triglycerides and increased HDL cholesterol levels, but did not lower LDL cholesterol [37]. We were not aware of any other MR studies

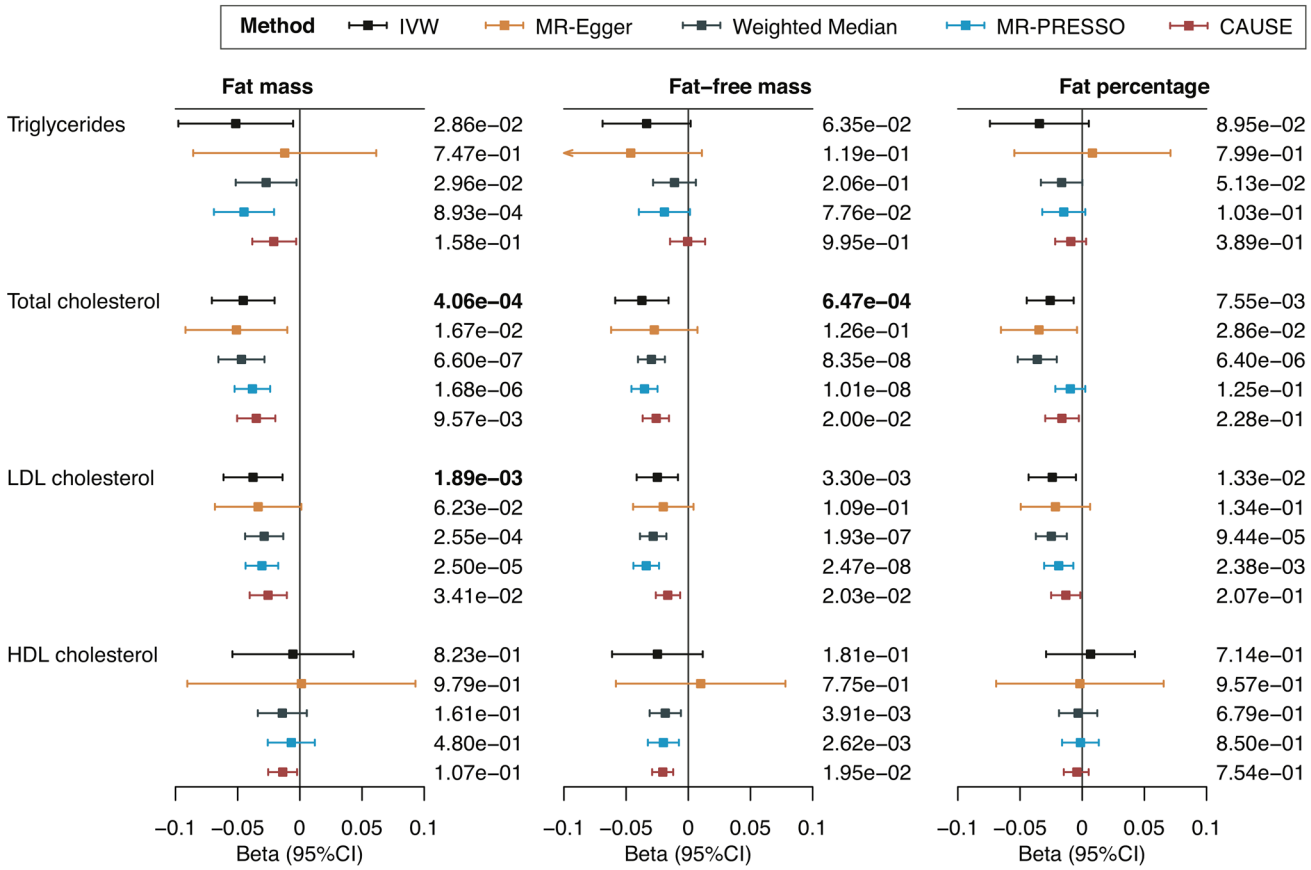

Fig. 6 Forest plots illustrating causal effects of lipid fractions on body composition. For IVW method, p values < 3.13e-3 are marked bold. Tabular statistics are presented in Supplementary Table 11

investigating causal relationships between body composition and lipids. Our findings indicated that losing fat mass and increasing muscle mass simultaneously could be recommended to obtain a favorable lipid profile. Furthermore, total cholesterol and LDL cholesterol were both negatively associated with fat mass and fat-free mass. This may partially explain why cholesterol-lowering medications such as statins have been reported to increase body weight and raise diabetes risk [38].

Some limitations warrant mention. First, there might be some sample overlap between UK Biobank and the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) or the Global Lipids Genetics Consortium (GLGC). We assumed the proportion of overlapping samples between UK-based cohorts and UK Biobank was about 5%, and sample overlaps between MAGIC and UK Biobank or GLGC and UK Biobank were estimated to be less than 1% [39–42]. Second, our results could have been biased by other potential pitfalls of MR studies. For example, the low response in UK Biobank (5.5%) and that UK Biobank participants were less likely to be obese, to smoke, to drink alcohol, and were "healthier" compared with the general population [43] could have resulted in selection bias [44]. Unobserved environmental confounds might exist due to differences in diets and lifestyles between participants in UK and those in Finland [45]. Within family GWAS data might be useful in avoiding this bias. However, such data was not available at this stage. Third, the causal relationships were assessed in European populations, large-scale GWAS data of body composition in other ethnicities was unavailable and represents a future endeavor. Lastly, time-varying relationships and sex differences need further investigation.

In summary, fat mass exerted detrimental effects on most cardiometabolic traits, fat-free mass had beneficial effects on most cardiometabolic traits after accounting for fat mass, and they had distinct causal associations with glycemic traits and lipid fractions. The findings may be of importance shedding light on risk stratification and tailoring management of body composition in different groups of patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-021-00779-9.

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Author contributions HZ conceived the study, performed the main analyses and drafted the original version of the manuscript. XG, YZ, and SW contributed to the study design, XG and SW provided the analysis platform, YZ and CL critically revised the manuscript. All authors were involved in the interpretation of results, helped refine the manuscript, and approved the final version.

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Availability of data and material Genetic instrumental variables and data sources are presented in Supplementary Tables.

Code availability Code used to undertake mendelian randomization analyses can be found in the R packages "TwoSampleMR", "MRPRESSO", and "cause".

Declarations

Conflicts of interest The authors declare they have no conflicts of interest.

Ethical approval The present research used publicly available summary data and did not contact with participants, where no extra ethical approval is required.

References

1. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. Eur J Epidemiol. 2018;33(11):1113–23. https://doi.org/10.1007/s10654-018-0433-5.
2. Son JW, Lee SS, Kim SR, Yoo SJ, Cha BY, Son HY, et al. Low muscle mass and risk of type 2 diabetes in middle-aged and older adults: findings from the KoGES. Diabetologia. 2017;60(5):865–72. https://doi.org/10.1007/s00125-016-4196-9.
3. Byambasukh O, Eisenga MF, Gansevoort RT, Bakker SJ, Corpeleijn E. Body fat estimates from bioelectrical impedance equations in cardiovascular risk assessment: the PREVEND cohort study. Eur J Prev Cardiol. 2019;26(9):905–16. https://doi.org/10.1177/2047487319833283.
4. Medina-Inojosa JR, Somers VK, Thomas RJ, Jean N, Jenkins SM, Gomez-Ibarra MA, et al. Association between adiposity and lean mass with long-term cardiovascular events in patients with coronary artery disease: no paradox. J Am Heart Assoc. 2018;7(10):e007505. https://doi.org/10.1161/jaha.117.007505.
5. Xing Z, Tang L, Chen J, Pei J, Chen P, Fang Z, et al. Association of predicted lean body mass and fat mass with cardiovascular events in patients with type 2 diabetes mellitus. CMAJ. 2019;191(38):E1042–8. https://doi.org/10.1503/cmaj.190124.
6. Fenger-Grøn M, Overvad K, Tjønneland A, Frost L. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. J Am Coll Cardiol. 2017;69(20):2488–97. https://doi.org/10.1016/j.jacc.2017.03.558.
7. Azarbal F, Stefanick ML, Assimes TL, Manson JE, Bea JW, Li W, et al. Lean body mass and risk of incident atrial fibrillation in post-menopausal women. Eur Heart J. 2016;37(20):1606–13. https://doi.org/10.1093/eurheartj/ehv423.
8. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey SG. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27(8):1133–63. https://doi.org/10.1002/sim.3034.
9. Lyall DM, Celis-Morales C, Ward J, Iliodromiti S, Anderson JJ, Gill JMR, et al. Association of body mass index with cardiometabolic disease in the uk biobank: a mendelian randomization study. JAMA Cardiol. 2017;2(8):882–9. https://doi.org/10.1001/jamacardio.2016.5804.
10. Richardson TG, Sanderson E, Elsworth B, Tilling K, Davey SG. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: mendelian randomisation study. BMJ. 2020;369: m1203. https://doi.org/10.1136/bmj.m1203.
11. Wang N, Cheng J, Ning Z, Chen Y, Han B, Li Q, et al. Type 2 diabetes and adiposity induce different lipid profile disorders: a mendelian randomization analysis. J Clin Endocrinol Metab. 2018;103(5):2016–25. https://doi.org/10.1210/jc.2017-02789.
12. Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. Eur Heart J. 2020;41(2):221–6. https://doi.org/10.1093/eurheartj/ehz388.
13. Tikkanen E, Gustafsson S, Knowles JW, Perez M, Burgess S, Ingelsson E. Body composition and atrial fibrillation: a Mendelian randomization study. Eur Heart J. 2019;40(16):1277–82. https://doi.org/10.1093/eurheartj/ehz003.
14. Yeung CHC, Au Yeung SL, Fong SSM, Schooling CM. Lean mass, grip strength and risk of type 2 diabetes: a bi-directional Mendelian randomisation study. Diabetologia. 2019;62(5):789–99. https://doi.org/10.1007/s00125-019-4826-0.
15. Shadrina AS, Sharapov SZ, Shashkova TI, Tsepilov YA. Varicose veins of lower extremities: Insights from the first large-scale genetic study. PLoS Genet. 2019;15(4): e1008110. https://doi.org/10.1371/journal.pgen.1008110.
16. Elsworth B, Lyon M, Alexander T, Liu Y, Matthews P, Hallett J, et al. The MRC IEU OpenGWAS data infrastructure. bioRxiv. 2020:2020.08.10.244293. https://doi.org/10.1101/2020.08.10.244293.
17. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018;7: e34408. https://doi.org/10.7554/eLife.34408.
18. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40(3):740–52. https://doi.org/10.1093/ije/dyq151.
19. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet. 2018;50(9):1335–41. https://doi.org/10.1038/s41588-018-0184-y.
20. Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. Nat Genet. 2020;52(7):740–7. https://doi.org/10.1038/s41588-020-0631-4.
21. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14. https://doi.org/10.1002/gepi.21965.

22. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25. https://doi.org/10.1093/ije/dyv080.
23. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8. https://doi.org/10.1038/s41588-018-0099-7.
24. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181(4):251–60. https://doi.org/10.1093/aje/kwu283.
25. Larsson SC, Burgess S. Fat mass and fat-free mass in relation to cardiometabolic diseases: a two-sample Mendelian randomization study. J Intern Med. 2020;288(2):260–2. https://doi.org/10.1111/joim.13078.
26. Tyrovolas S, Panagiotakos D, Georgousopoulou E, Chrysohoou C, Tousoulis D, Haro JM, et al. Skeletal muscle mass in relation to 10 year cardiovascular disease incidence among middle aged and older adults: the ATTICA study. J Epidemiol Commun Health. 2020;74(1):26–31. https://doi.org/10.1136/jech-2019-212268.
27. Zhang H, Lin S, Gao T, Zhong F, Cai J, Sun Y, et al. Association between sarcopenia and metabolic syndrome in middle-aged and older non-obese adults: a systematic review and meta-analysis. Nutrients. 2018;10(3):364. https://doi.org/10.3390/nu10030364.
28. Kim G, Lee SE, Jun JE, Lee YB, Ahn J, Bae JC, et al. Increase in relative skeletal muscle mass over time and its inverse association with metabolic syndrome development: a 7-year retrospective cohort study. Cardiovasc Diabetol. 2018;17(1):23. https://doi.org/10.1186/s12933-018-0659-2.
29. Fenger-Grøn M, Vinter N, Frost L. Body mass and atrial fibrillation risk: status of the epidemiology concerning the influence of fat versus lean body mass. Trends Cardiovasc Med. 2020;30(4):205–11. https://doi.org/10.1016/j.tcm.2019.05.009.
30. Fukaya E, Flores AM, Lindholm D, Gustafsson S, Zanetti D, Ingelsson E, et al. Clinical and genetic determinants of varicose veins. Circulation. 2018;138(25):2869–80. https://doi.org/10.1161/circulationaha.118.035584.
31. Zöller B, Ji J, Sundquist J, Sundquist K. Body height and incident risk of venous thromboembolism: a cosibling design. Circ Cardiovasc Genet. 2017;10(5): e001651. https://doi.org/10.1161/circgenetics.116.001651.
32. Roetker NS, Armasu SM, Pankow JS, Lutsey PL, Tang W, Rosenberg MA, et al. Taller height as a risk factor for venous thromboembolism: a Mendelian randomization meta-analysis. J Thromb Haemost. 2017;15(7):1334–43. https://doi.org/10.1111/jth.13719.
33. MacLeod SF, Terada T, Chahal BS, Boulé NG. Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using continuous glucose monitoring. Diabetes Metab Res Rev. 2013;29(8):593–603. https://doi.org/10.1002/dmrr.2461.
34. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014;2(10):819–29. https://doi.org/10.1016/s2213-8587(14)70034-8.
35. Xu L, Borges MC, Hemani G, Lawlor DA. The role of glycaemic and lipid risk factors in mediating the effect of BMI on coronary heart disease: a two-step, two-sample Mendelian randomisation study. Diabetologia. 2017;60(11):2210–20. https://doi.org/10.1007/s00125-017-4396-y.
36. Holmes MV, Lange LA, Palmer T, Lanktree MB, North KE, Almoguera B, et al. Causal effects of body mass index on cardiometabolic traits and events: a mendelian randomization analysis. Am J Hum Genet. 2014;94(2):198–208. https://doi.org/10.1016/j.ajhg.2013.12.014.
37. Martins C, Strømmen M, Stavne OA, Nossum R, Mårvik R, Kulseng B. Bariatric surgery versus lifestyle interventions for morbid obesity–changes in body weight, risk factors and comorbidities at 1 year. Obes Surg. 2011;21(7):841–9. https://doi.org/10.1007/s11695-010-0131-1.
38. Robinson JG. Statins and diabetes risk: how real is it and what are the mechanisms? Curr Opin Lipidol. 2015;26(3):228–35. https://doi.org/10.1097/mol.0000000000000172.
39. Lagou V, Mägi R, Hottenga JJ, Grallert H, Perry JRB, Bouatia-Naji N, et al. Sex-dimorphic genetic effects and novel loci for fasting glucose and insulin variability. Nat Commun. 2021;12(1):24. https://doi.org/10.1038/s41467-020-19366-9.
40. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45(11):1274–83. https://doi.org/10.1038/ng.2797.
41. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet. 2010;42(2):105–16. https://doi.org/10.1038/ng.520.
42. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nat Genet. 2010;42(2):142–8. https://doi.org/10.1038/ng.521.
43. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol. 2017;186(9):1026–34. https://doi.org/10.1093/aje/kwx246.
44. Taylor AE, Jones HJ, Sallis H, Euesden J, Stergiakouli E, Davies NM, et al. Exploring the association of genetic factors with participation in the avon longitudinal study of parents and children. Int J Epidemiol. 2018;47(4):1207–16. https://doi.org/10.1093/ije/dyy060.
45. Koellinger PD, de Vlaming R. Mendelian randomization: the challenge of unobserved environmental confounds. Int J Epidemiol. 2019;48(3):665–71. https://doi.org/10.1093/ije/dyz138.