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Original Article

Limb Fatness Increases the Risk of Heart Failure: A Mendelian Randomization Study

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Abstract:

Background. Numerous observational studies have indicated an association between obesity and heart failure (HF) risk. However, no consistent conclusions have been reached regarding the relationship between regional body fat and HF, and the causal relationship remains unclear. Our study aimed to evaluate the relationship between regional body fat and HF.

Methods. We conducted a two-sample Mendelian randomization (MR) to ascertain the causal association between regional body fat and HF. Single-nucleotide polymorphisms (SNPs) correlated with regional body fat were extracted from several genome-wide association studies (GWAS) with more than 400,000 individuals. Summary statistics for HF were obtained from the FinnGen consortium, which comprised 3,903 cases and 114,735 controls. The analysis utilized the inverse variance-weighted (IVW), MR-Egger, and weighted median (WME) methods. Sensitivity tests were also performed, including the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO), MR-Egger intercept tests, and leave-one-out analysis.

Result. Genetically predicted per one standard deviation (SD) increased regional body fat, including the left leg, right leg, left arm, and right arm fat mass, increased the HF risk with ORs of 1.96, 2.02, 1.63, and 1.64, respectively. The sensitivity assessments confirmed that our results were reliable and stable.

Conclusions. Our study demonstrated a causal association between regional body fat and an increased risk of HF. These findings may contribute to the development of HF prevention strategies.

Keywords. Heart failure, Regional fat mass, Obesity, Mendelian randomization

1. Introduction

Heart failure (HF), which affects more than 60 million individuals globally, is associated with substantial morbidity.[1] Despite improvements in the prognosis of HF over time, the mortality rate remains high. Data from the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) revealed that between 2011 and 2013, the 1-year mortality rate for acute HF was 23.6% and for chronic HF was 6.4% in 21 European countries.[2] Furthermore, hospitalizations and readmissions of HF patients are high.[1,3] HF places a significant financial burden on healthcare systems and economies around the world,[4] with the projected total cost for HF estimated to reach $30.7 billion in the USA by 2030.[1] Similarly, the prevalence of obesity is escalating, with the Global Burden of Disease Obesity Collaborators estimating that 603.7 million adults are obese.[5] Obesity independently contributes to the risk of cardiovascular disease.[6] Cardiovascular disease (CVD) accounts for over two-thirds of deaths attributable to high body mass index (BMI) [5]. A meta-analysis incorporating observational studies and a MR study showed an augmented risk of HF with an increased BMI [7]. In fact, the adverse cardiovascular effects of obesity may stem from the distribution of adipose tissue in the body.[8–10]

Obesity should be considered not merely as weight gain but rather as an excess accumulation of fat mass.[11] The limitation of employing BMI as a sole indicator of obesity lies in its inability to distinguish between fat and lean mass and its disregard for variations in fat distribution.[12,13]

A large prospective cohort study demonstrated that elevated trunk and decreased leg fat were associated with an increased risk of cardiovascular disease.[9] Conversely, the Health ABC study yielded contrasting findings, linking higher ectopic skeletal muscle fat markers with an elevated risk of heart failure.[14] Even after adjusting for heart failure risk factors, a higher intramuscular fat infiltration within the thigh muscle remained significantly associated with an increased risk of heart failure.[14] A recent cross-sectional study echoed these results, with higher thigh intermuscular fat in patients with heart failure with preserved ejection fraction than in controls, and this association persisted even after adjusting for age, sex, and body surface area.[15] The results from related studies were inconsistent, and traditional observational studies can suffer from confounding biases, leading to discrepant results. Consequently, the causal relationship between regional body fat and heart failure remains unclear.

MR is a robust methodology that employs genetic variants to assess potential causal relationships between exposures and outcomes.[16] Through the random assignment of single nucleotide polymorphisms (SNPs) during conception, MR can help minimize residual confounding. In addition, avoiding reverse causality is a notable advantage, as genotypes remain unaffected by disease status. Thus, MR offers a valuable avenue for gaining deeper insights into the underlying etiology of HF, laying a foundation for informed preventive strategies.

Materials & Methods

Study design

We performed MR, which was performed by using genetic variants strongly associated with regional body fat as instrumental variables (IVs) to assess the causal relationship between regional body fat and HF. The study design was based on three critical assumptions: (1) genetic instruments exhibited a significant association with exposure; (2) genetic instruments remained unaffected by confounding factors influencing both exposure and outcome; and (3) genetic instruments affect the outcome only via exposure.[17] (Fig. 1).

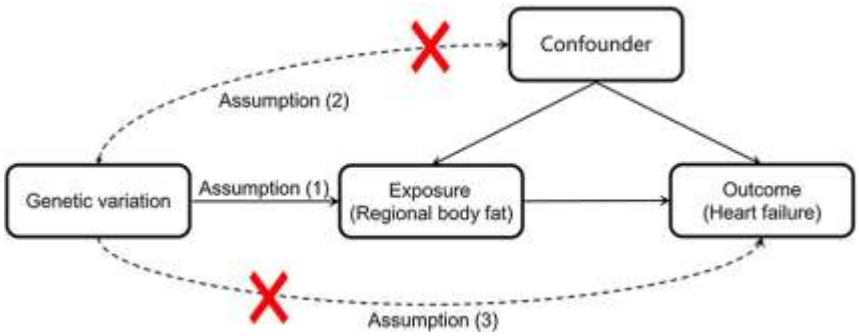

Fig.1 Study design of Mendelian randomization

Data resource

The summary-level genetic data correlated with regional body fat, output from the GWAS pipeline using Phesant-derived variables from the UK Biobank were obtained from the UK Medical Research Council Integrative Epidemiology Unit's (instrumental variable) at MR-base database (https://gwas.mrcieu.ac.uk/).[18] All the fat mass was measured via bioelectrical impedance analysis and originated from European ancestry.

The regional body fat mass was leg fat mass (right) with 454,846 individuals, leg fat mass (left) with 454,823 individuals, arm fat mass (right) with 454,757 participants, arm fat mass (left) with 454,684 participants, and trunk fat mass with 454,588 populations.

To mitigate potential bias from population stratification, we specifically selected outcome data derived exclusively from individuals of European descent. GWAS summary statistics for HF (n = 26,872 cases and 349,361 controls) were obtained from the FinnGen consortium R9 release data.[19] The FinnGen study is a nationwide research project collecting genetic and electronic health record data. The study used genome-wide association analyses conducted with adjustments for pertinent variables, including sex, age, genetic components, and genotyping batch. The ICD-10, ICD-9, and ICD-8 codes ascertained HF.

SNP selection for MR analysis

We selected optimal SNPs in four steps. Initially, we included SNPs at a threshold of genome-wide significance ($p < 5\times10^{-8}$) to ensure that selected SNPs were strongly correlated. Subsequently, we excluded SNPs with linkage disequilibrium ($r2 > 0.001$ and clumping window of 10,000 kb) to confirm the independence of selected SNPs. In the third step, F-statistics, calculated as (beta/se),[2,20] represent the strength of the association between the instruments and the risk of exposure, considering the strength sufficient if the F value was >10. Finally, preceding the MR analysis, we harmonized the effect of each SNP on both exposure and outcome, ensuring that they referred to the same allele. Any duplicate SNPs were meticulously removed to enhance the accuracy of analysis.

Statistical analyses

As the primary analysis to evaluate the causal relationship between fat mass and cardiovascular disease, we employed the inverse-variance weighted (IVW) method, which assumes the validity of all genetic instruments.[21] A P below 8.33E−03 (0.05/6) was considered statistically compelling evidence after the Bonferroni correction.[22] Associations with P ranging from 8.33E−03 to 0.05 were deemed suggestive and necessitated further validation. Then, the MR-Egger regression and the Weighted median method were used as complementary sensitivity analysis. MR Egger allows directional pleiotropic effects where some SNPs could be acting on the outcome through another pathway than the exposure of interest, albeit at a potential cost to statistical power [23]; Weighted Median can provide valid estimates if at least 50% of the information in the analysis comes from SNPs as valid instrumental variables.[24] We performed the MR-Egger intercept test and the MR-PRESSO, considering the potential influence of horizontal pleiotropy. The P for its intercept ≤0.05 from the MR-Egger intercept test suggests the presence of horizontal pleiotropy.[25] The MR-PRESSO method detects horizontal pleiotropy and performs outlier testing for each SNP. In cases where significant outliers were detected, we removed the outlier variants (with a P less than the threshold in the MR-PRESSO outlier test) and re-conduct the MR analysis.[26,27] The presence of heterogeneity necessitates careful consideration of the results of the IVW method. To assess heterogeneity, we calculated Cochran's Q statistic. In addition to sensitivity analysis, we used forest and scatter plots. Additionally, we performed the MR Steiger directionality test to ascertain whether our results supported our hypothesis.[28] At the end of the analysis, we conducted a leave-one-out analysis to estimate whether any single variant drove the causal association between exposure and outcome.[28] All calculations were done through the "TwoSampleMR" and "MR-PRESSO" packages in R software (Vision 4.2.2).

Results

Following meticulous screening, 26 SNPs were

causally associated with HF in leg fat mass (right). As for leg fat mass (left), we found 25 SNPs causally related to HF. In parallel, 27 SNPs in arm fat mass (right) and 25 SNPs in arm fat mass (left) were used to calculate the effect size of genetically predicted arm fat mass on the risk of HF. In Trunk fat mass, 27 SNPs were used for the MR analyses. Notably, the F-statistics for all selected SNPs exceeded 10, underpinning the robustness of the instruments. (See Table S1, Supplemental Digital Content, which demonstrates the selected SNPs of regional fat mass associated with heart failure and their F-statistic)

MR analyses results

As illustrated in Figure 2, the IVW method demonstrated that genetically predicted leg fat mass (right) was a risk factor for HF (OR = 1.96; 95% CI 1.41–2.72; P = 6.77E-05). The ORs obtained from the MR-Egger regression and WME methods remained congruent with those obtained using the IVW method, albeit with a slightly lower precision (Fig. 2). As for leg fat mass (left), IVW suggested a heightened risk of HF (OR = 2.02; 95% CI 1.53–2.66; P = 6.03E-07). The MR-Egger and WME methods showed similar ORs with IVW, though the OR from the MR-Egger analysis did not achieve statistical significance (Fig. 2). The IVW method showed evidence of an adverse causal effect of arm fat mass (right) on HF (OR = 1.64; 95% CI 1.29–2.10; P = 5.81E-05). Similar patterns emerged from the MR-Egger and WME analyses, although with lower statistical power (Fig. 2). For arm fat mass (left), we found evidence that HF risk was associated with genetically predicted arm fat mass (left) as revealed by the IVW method (OR = 1.63; 95% CI 1.28–2.07; P = 6.67E-05). These associations were consistent primarily across the MR-Egger and WME methods. (Fig. 2). However, there was no significant evidence of a causal relationship between trunk fat mass and HF by IVW analysis (OR = 1.63; 95% CI 1.28–2.07; P = .011). The results obtained from the MR-Egger and WME methods were in alignment with those obtained from the IVW method, which showed directional consistency (Fig. 2).

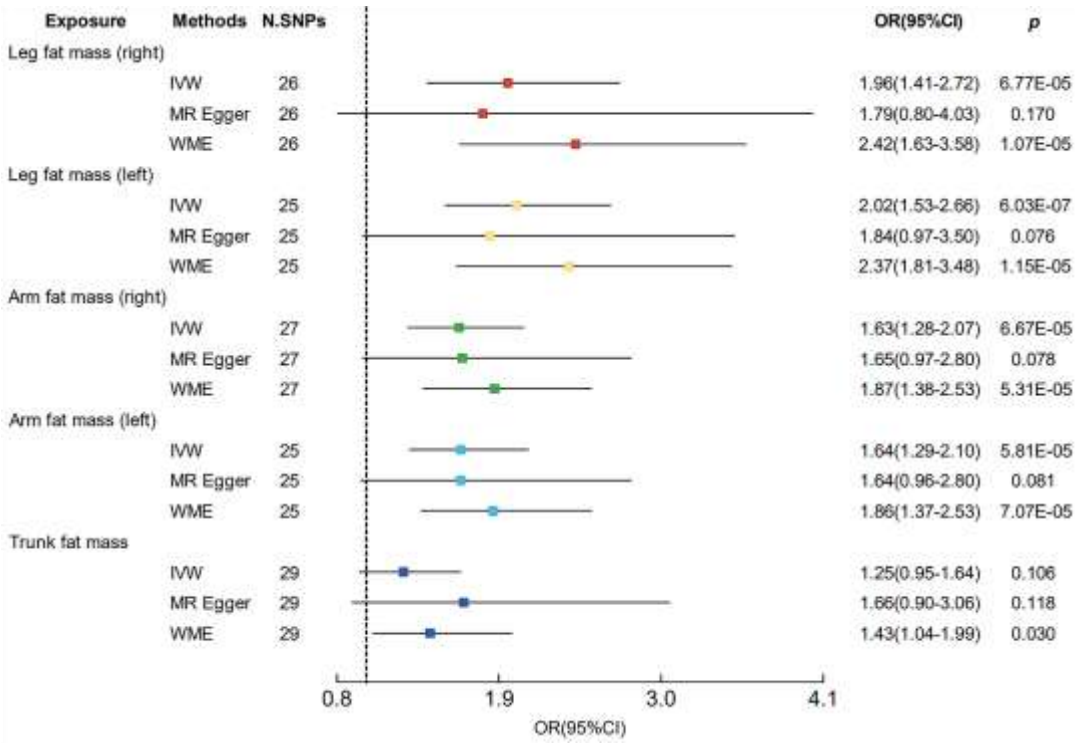

Fig.2 Associations of regional body fat with heart failure. SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted; WME, Weighted median.

Horizontal pleiotropy and heterogeneity analysis

MR-PRESSO suggested no horizontal pleiotropy or the presence of outliers in the selected SNPs of regional body fat to HF. Likewise, the MR-egger intercept test found that the intercept did not significantly deviate from zero (all P > .32), which showed the same result as MR-PRESSO. Apart from this, evidence of heterogeneity for the selected IVs was not observed by Cochran's Q test derived from IVW estimation (See Table S2, Supplemental Digital Content, which illustrates the horizontal pleiotropy and heterogeneity of instrument effects).

Sensitivity analysis

The leave-one-out sensitity analyses have been presented in Figure 3, revealing that estimates of all region fat mass on HF were unaffected by any SNP. Furthermore, the funnel plots' impact on causation between regional body fat and HF is roughly symmetrical (Fig. 4). The forest plot and scatter plot can be seen in Fig 5 and 6, respectively. Finally, the MR Steiger analysis shows the congruence of our study with the intended causal direction, effectively discounting the possibility of reverse causation (Table S3, Supplemental Digital Content, which illustrates the MR Steiger directionality test of instrument effects).

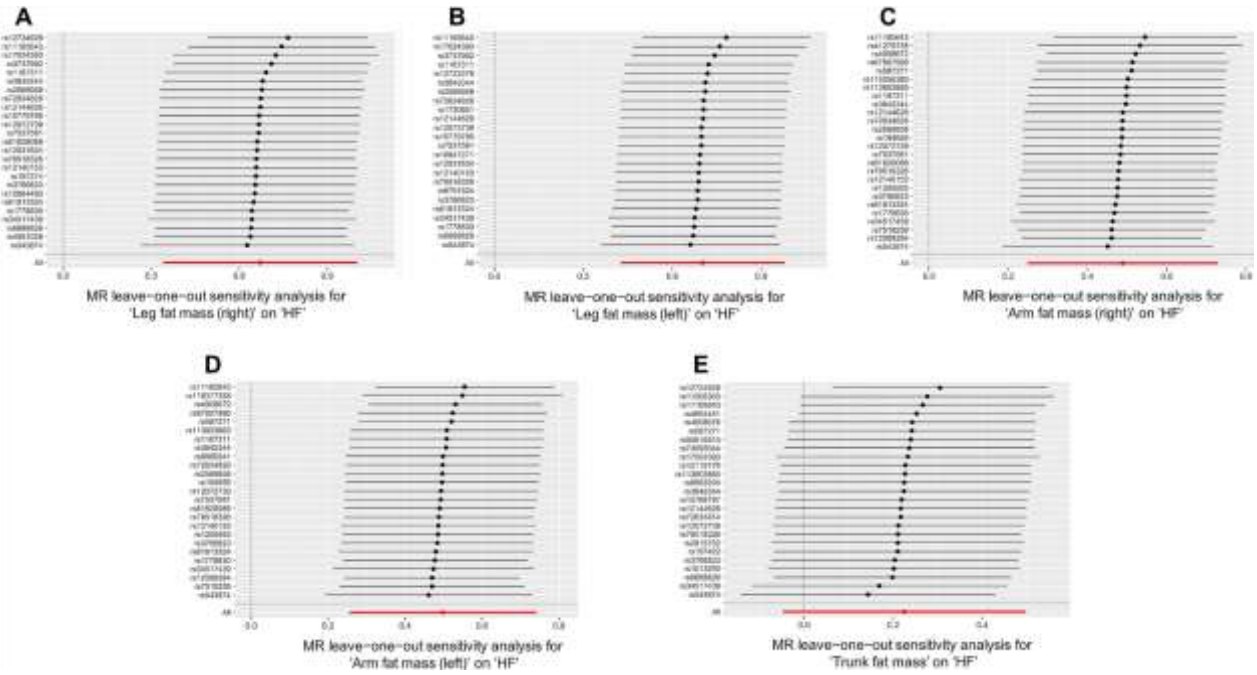

Fig. 3 Leave-one-out plot to visualize the causal effect of regional body fat on the risk of heart failure when leaving one SNP out. (A) Leg fat mass (right) on HF risk; (B) Leg fat mass (left) on HF risk; (C) Arm fat mass (right) on HF risk; (D) Arm fat mass (left) on HF risk; (E) Trunk fat mass on HF risk. MR, Mendelian randomization; HF, heart failure.

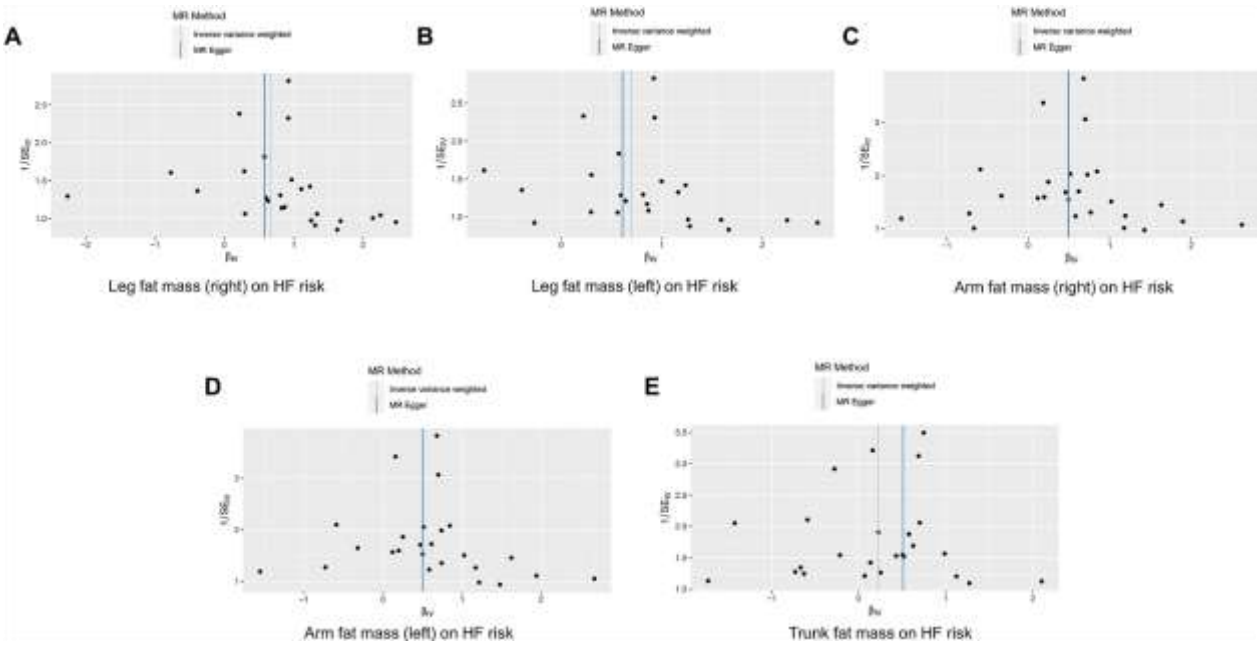

Fig.4 Funnel plots to visualize the overall heterogeneity of MR estimates for the effect of regional body fat on heart failure. (A) Leg fat mass (right) on HF risk; (B) Leg fat mass (left) on HF risk; (C) Arm fat mass (right) on HF risk; (D) Arm fat mass (left) on HF risk; (E) Trunk fat mass on HF risk. MR, Mendelian randomization; HF, heart failure.

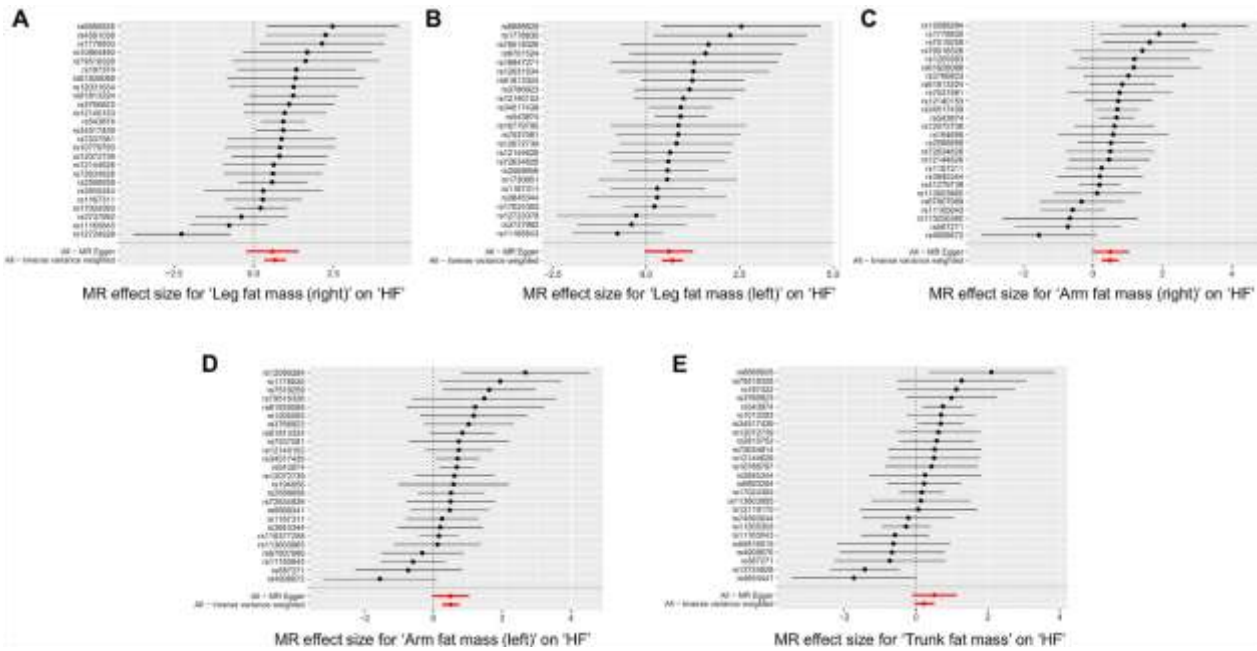

Fig.5 Forest plot to visualize the causality of every single SNP on heart failure risk. (A) Leg fat mass (right) on HF risk; (B) Leg fat mass (left) on HF risk; (C) Arm fat mass (right) on HF risk; (D) Arm fat mass (left) on HF risk; (E) Trunk fat mass on HF risk. MR, Mendelian randomization; HF, heart failure.

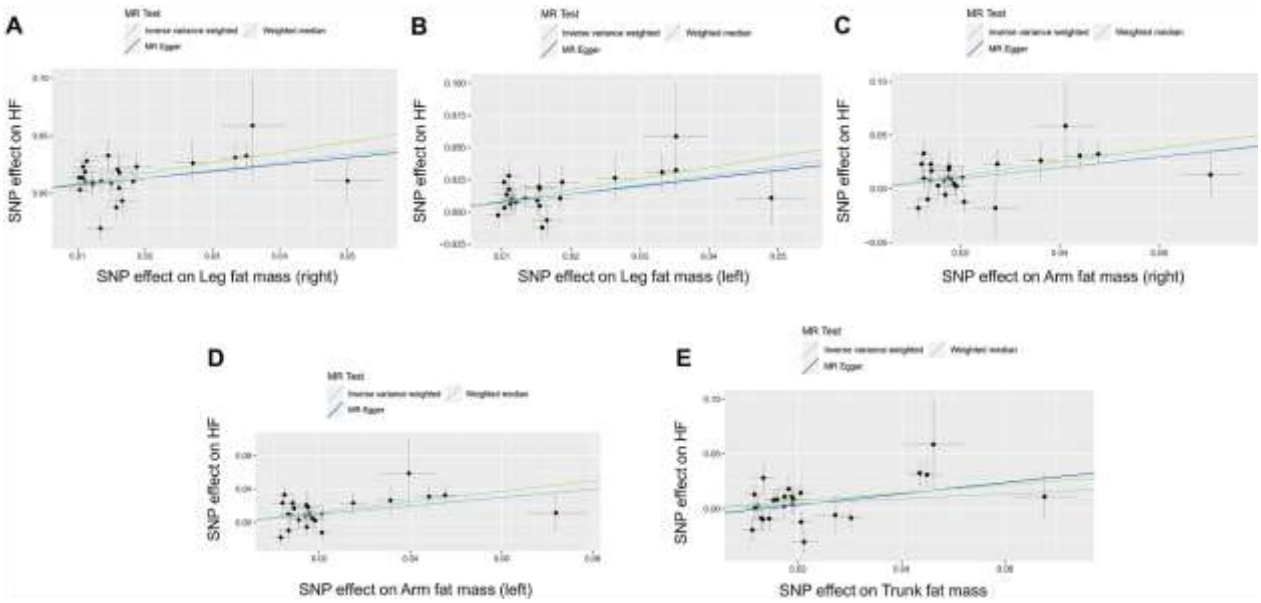

Fig. 6 Scatter plots illustrate the causal relationship between regional body fat and heart failure. The slope of the straight line represents the magnitude of the causal relationship. (A) Leg fat mass (right) on HF risk; (B) Leg fat mass (left) on HF risk; (C) Arm fat mass (right) on HF risk; (D) Arm fat mass (left) on HF risk; (E) Trunk fat mass on HF risk. MR, Mendelian randomization; SNP, single-nucleotide polymorphism; HF, heart failure

Discussion

To the best our knowledge, this is the first study to investigate the causal association between body fat mass and the risk of heart failure within the two-sample MR paradigm. Our results revealed that fat mass in the extremities constitutes an exacerbating factor for HF risk. Conversely, no significant causal relationship was found between trunk fat mass and HF. It is well known that obesity is an established risk factor for the development of heart failure, and previous MR analyses support this conclusion.[29,30] There are no consistent results for the relationship between regional body fat and heart failure. Previous investigations of the relationship between extremity fat mass and heart failure have focused on leg fat mass, with fewer studies on arm fat mass. In addition, relevant observational studies have yet to yield consistent conclusions. Our MR results are consistent with a longitudinal community-based cohort of older adults, including 3075 subjects, in that thigh fat was associated with a higher risk of heart failure.[14] After adjusting for confounders, including visceral adiposity, the correlation between higher intramuscular fat in the thighs and the risk of heart failure was still significant.[14] Haykowsky et al. showed that intermuscular fat was significantly increased in the thighs of patients with heart failure compared with those without heart failure[31], and another cross-sectional study showed similar results.[32] A prospective cohort study on fat distribution yielded conflicting results. Leg fat mass was found to protect against heart failure, while there was no evident correlation between heart failure and arm and trunk fat mass.[33] When normal adipose tissue reaches its maximum expansion capacity, excessive free fatty acids in the body can lead to fat spillage, culminating in the emergence of ectopic adipose tissue.[34] Intramuscular fat, constituting ectopic adipose tissue, is an essential adverse factor in heart failure. On the one hand, inflammation has been linked to the risk and severity of HF.[35,36] Intramuscular fat deposition instigates an enhanced secretion of large amounts of cytokines and myokines, such as IL-6 and IL-8,

by skeletal muscle cells.[37,38] Additionally, heightened immune cell infiltration, particularly encompassing macrophages and T-lymphocytes predominantly clustered within intramuscular fat depots, contributes to inflammation within skeletal muscle. These cells tend to polarize toward a pro-inflammatory phenotype, intensifying inflammation in adipose and skeletal muscle tissues.[38] This further exacerbates inflammation in adipose tissue and skeletal muscle. On the other hand, intramuscular fat assumes a pivotal role in promoting insulin resistance,[39] which is a significant contributor to the risk of HF.[40,41] Indeed, increased intramuscular fat is thought to be an indication of significant skeletal muscle loss.[42,43] Reduced skeletal muscle mass and function are risk factors for HF and adversely impact prognosis.[44,45] Furthermore, thigh intramuscular fat has been shown to affect skeletal muscle mitochondrial function, which may further contribute to the development of heart failure.[31]

Our MR analysis showed that genetically predicted trunk fat mass was not causally associated with HF. However, it would be imprudent to deny their relationship. It is almost a given that abdominal fat causes an increased incidence of heart failure.[31,46] Nevertheless, it is crucial to acknowledge that trunk fat mass encompasses both abdominal fat and chest and hip fat mass. Trunk fat mass may have an adverse or neutral effect on the development of HF,[9,33] although only a few studies have been performed. This underscores the need for further research to delve deeper into elucidating this relationship.

The chief strength of our study lies in applying a two-sample MR design. By selecting genetic variants associated with regional body fat and HF as instrumental variables, confounding biases and reverse causality are minimized and circumvent the challenges posed by conventional epidemiological study frameworks. Moreover, by avoiding sample overlap, we consequently mitigate the impact of the Winner's Curse on the MR estimates. Additionally, all the participants are of European descent. This emphasis on European populations helps mitigate bias resulting from population stratification. However, it also leads to the need for our findings to be generalized cautiously to other people. It represents a limitation of our study. Beyond this, we acknowledge several additional limitations. Firstly, it was difficult to exclude potential directional pleiotropy, so we performed MR-PRESSO and MR-Egger intercept test, and no evidence of horizontal pleiotropy was observed in the sensitive analysis. Secondly, our study refrained from a detailed classification of heart failure, therefore, we could not determine the causal association of regional body fat on heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. This limitation curtailed the depth of analytical exploration.

Conclusion

In conclusion, this study provided evidence that genetically predicted extremity fat mass is related to an increased risk of HF. The implications of our findings hold significance in the context of heart failure prevention.

Acknowledgments

We want to acknowledge the participants and investigators of the FinnGen study. We also acknowledge other participants and investigators who provided the GWAS data.

Declarations

Acknowledgments

We want to acknowledge the participants and investigators of the FinnGen study. We also acknowledge other participants and investigators who provided the GWAS data.

Authors' contributions

WJC and WX designed the study. WX wrote the manuscript. WJC and WX collected, analyzed,

and interpreted the data. YCQ and WJC critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets analyzed during the current study are available in the IEU Open GWAS, https://gwas.mrcieu.ac.uk/ and FinnGen consortium, https://r9.finngen.fi/pheno/I9_HEARTFAIL_ALL CAUSE.

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Not applicable.

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