

Association between obesity and frailty: A two-sample Mendelian randomization

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ABSTRACT

Background: Although obesity and frailty interrelationship remains debated, it is biologically plausible that obesity accelerates frailty through chronic inflammation, insulin resistance, and oxidative stress; however, observational evidence is limited by confounding and reverse causality. Mendelian randomization leverages genetic variants as instrumental variables to strengthen causal inference and help clarify the directionality of the obesity–frailty relationship.

Objectives: This study aims to investigate the bidirectional causal relationship between obesity and frailty using a two-sample Mendelian randomization (MR) approach. Recognizing the potential interplay between these conditions, where obesity may contribute to frailty and vice versa, we seek to clarify the causality and magnitude of their association, addressing critical gaps in the current understanding of these interlinked health challenges.

Methods: We utilized genome-wide association study (GWAS) data from 638,236 individuals, with obesity and frailty data sourced from the UK Biobank (GWAS ID: Ukb-b-15541) and the European Bioinformatics Institute (GWAS ID: Ebi-a-GCST90020053), respectively. A total of 94 single-nucleotide polymorphisms were selected as instrumental variables for both traits following stringent statistical screening criteria. MR analyses were conducted using multiple approaches to ensure the robustness and consistency of causal estimates.

Results: The findings reveal a significant bidirectional causal relationship between obesity and frailty. Genetic liability to obesity was associated with an increased risk of frailty, while genetic predisposition to frailty was also linked to a higher likelihood of obesity. These results suggest a reinforcing feedback loop between the two conditions. Sensitivity analyses further supported these findings, demonstrating minimal evidence of heterogeneity or pleiotropy.

Conclusion: This study provides robust evidence for a bidirectional causal relationship between obesity and frailty, emphasizing the importance of integrated clinical and public health interventions addressing both conditions. The findings highlight the potential for targeted strategies to mitigate frailty risks by managing obesity and vice versa, offering valuable insights for promoting healthier aging.

Keywords: Bidirectional causal relationship, frailty, genome-wide association study, Mendelian randomization, obesity

INTRODUCTION

Obesity^[1] and frailty^[2] are two major public health concerns worldwide, and each independently contributes to increased morbidity and mortality across various populations. Obesity, characterized by an excess of body fat, is commonly

associated with a range of adverse health outcomes, including cardiovascular disease, diabetes, and certain cancers, which are well-documented in clinical research.^[1,3] Frailty, a

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multidimensional clinical syndrome marked by diminished strength, endurance, and reduced physiological function, poses a significant risk of adverse outcomes, particularly in older adults.^[2,4] As the global population ages, frailty has become increasingly prevalent, leading to a heavier burden on healthcare systems.^[2,4] Despite the individual effects of obesity and frailty, their potential interrelationship remains a topic of ongoing debate.^[5-7]

The association between obesity and frailty is biologically plausible, given that obesity can exacerbate inflammatory responses,^[8] insulin resistance,^[9] and oxidative stress,^[10] which are key contributors to physical and physiological decline. Observational studies have suggested that individuals with obesity are at increased risk of frailty, as excess body weight can accelerate physical decline and lead to greater vulnerability to health adversities.^[10-12] However, these studies are inherently limited by potential confounders and reverse causality, making it challenging to establish a causal relationship between obesity and frailty. Moreover, while weight loss interventions in older populations have shown promise in improving frailty outcomes, the directionality and strength of the obesity–frailty relationship remain uncertain.^[13]

To address these limitations, Mendelian randomization (MR) offers a promising approach for examining causal relationships between obesity and frailty by leveraging genetic variants as instrumental variables.^[14,15] MR allows researchers to overcome the common pitfalls of observational studies, particularly confounding and reverse causation, providing a more reliable framework to infer causality.^[14,15] Two-sample MR, an extension of traditional MR, allows for the assessment of exposure and outcome variables from separate samples, thereby enhancing the robustness and generalizability of findings.^[16,17] In this study, we utilized two large datasets, “ebi-a-GCST90020053” for frailty and “ukb-b-15541” for obesity, to perform a two-sample MR and test the hypothesis that obesity is causally associated with an increased risk of frailty.

The findings of this study have critical public health implications. Establishing the causal nature of the obesity–frailty relationship could inform targeted interventions to reduce obesity, thereby mitigating frailty-related adverse health outcomes, particularly in aging populations.

By conducting this two-sample MR study, we aim to provide robust evidence of the causal relationship between obesity and frailty, advancing scientific understanding of these interconnected health challenges. Our findings seek to bridge critical knowledge gaps, offering insights into effective interventions for healthier aging.

MATERIALS AND METHODS

Study design

We used the publicly available genome-wide association study (GWAS) (<https://gwas.mrcieu.ac.uk/>) catalog from the University of Bristol, UK, to conduct an MR study. No additional ethical approval was required due to the re-analysis of previously summarized-level data. The MR analysis was done using R software version 4.4.2 (U.S., University of Auckland).

Data sources

The exposure and outcome data for this study were sourced from the University of Bristol [Table 1]. Drawing on established research concerning mitochondrial DNA and sex chromosome variability across populations, we assumed that the genetic patterns of the included cases were consistent with those observed in other European populations. The study comprised a total of 638,236 subjects, including 463,010 blood samples for obesity and 175,226 for frailty. We conducted a meta-analysis of 17,441,584 single-nucleotide polymorphism (SNP) loci using GWAS. SNP loci with $P < 5 \times 10^{-6}$ were selected as instrumental variables by applying restrictions on P values and linkage disequilibrium parameters ($P < 5 \times 10^{-6}$, $R^2 < 0.001$, kb = 10,000).^[18] These loci served as proxy indicators of frailty, representing clinical risk exposure factors. The association strength between the loci and exposure factors was evaluated based on the F-statistic ($F = [\beta/SE]^2$) for each SNP.^[19] In general, when $F > 10$, the SNP loci were considered free from instrumental variable bias, and loci with F values of 10 or less were excluded from the study.

Statistical analysis

To understand the interplay between obesity and frailty, we applied several MR methods to take into account the complexity and potential pleiotropy in the genetic instruments. The following describes the methods used and their application:

Inverse variance-weighted method

This method served as the primary analytical approach to estimate the causal effect of exercise intensity on frailty using a fixed-effects model. The inverse variance weighted (IVW) approach combines the Wald ratios (the ratio of the SNP-outcome effect to the SNP-exposure effect) for each SNP, with each ratio weighted by the inverse variance of the SNP-outcome effect.^[20]

Weighted median method

To achieve a robust estimate less influenced by outliers or invalid instruments, the weighted median (WMe) estimator was applied. This method provides a consistent estimate of the causal effect as long as at least 50% of the information weight comes from valid instruments.^[21]

Table 1: Sources of information

Year	Sample size	Sex	Number of SNPs	Population	GWAS ID
2018	463,010	Males and females	9,851,867	European	ukb-b-15541
2021	175,226	NA	7,589,717	European	ebi-a-GCST90020053

GWAS: Genome-wide association study, SNPs: Single-nucleotide polymorphisms, NA: Not applicable

Weighted mode method

This approach determines the mode of the causal effect distribution as the central estimate, providing a robust measure even when up to 50% of the instruments are invalid. This method helps mitigate bias from invalid instruments by relying on the most frequently observed estimate among the SNPs.^[22]

Simple mode method

Similar to the weighted mode method, the simple mode (SM) approach is unweighted, focusing on the most common causal effect estimate among the SNPs without applying inverse-variance weighting. This method provides an additional means of estimating the causal effect using the most frequent value in the distribution of causal estimates.^[23]

Mendelian randomization-egger method

This method was employed to detect and adjust for horizontal pleiotropy, which could introduce bias into causal estimates. The intercept from the MR-Egger regression indicates the presence of directional pleiotropy, allowing for an adjustment in cases where pleiotropy may otherwise distort the causal effect estimate.^[24]

The robustness of the primary findings from the IVW method was assessed through sensitivity analyses utilizing the aforementioned MR methods, each of which offers distinct assumptions and strengths for addressing potential biases from SNP pleiotropy. All analyses were performed using the TwoSample MR package in R, ensuring the reproducibility and reliability of results. Causal effect estimates were presented as odds ratios (OR) with 95% confidence intervals for frailty calculated from each MR approach. A Bonferroni-corrected *P* value threshold of <0.005 was applied to adjust for multiple testing, ensuring that statistical significance was rigorously maintained across all analyses.

RESULTS

Selection of instrumental variables

We analyzed the instrumental variables using 94 SNPs as (IVs) according to the IV selection criteria. No weak instrumental bias was observed as the F-statistic of each SNP exceeded 10. Finally, we used 12 and 82 SNPs as IVs for frailty and obesity, respectively. This approach was taken to explore the potential causal relationship between obesity and frailty, separately.

Causal effect between obesity and frailty

We present the association between obesity and frailty across two datasets: “ukb-b-15541,” and “ebi-a-GCST90020053.” Multiple MR methods, including IVW, WMe, WMm, SM, and MR-Egger, were used to estimate the causal effects between physical activity and frailty, separately. Cochran’s *Q*-test and MR-PRESSO technique^[25] were applied to ensure there was no significant heterogeneity or pleiotropy among the instrumental variables, supporting the robustness of these results [Table 2].

Association between obesity and frailty using Mendelian randomization

The results indicate a positive association between obesity and

Table 2: Causal effect between obesity and frailty in Mendelian randomization methods

Exposure	MR method	SNP	OR (OR_95)	SE	P
Obesity population: ukb-b-15541	IVW	12	1.01 (1.007–1.013)	2.811	0.021
	WMe		1.01 (1.005–1.013)	1.21	0.017
	WMO		1.01 (1.001–1.013)	1.58	0.090
	SM		1.01 (1.001–1.022)	2.12	0.129
	MR-Egger		1.01 (0.992–1.023)	5.57	0.519
Frailty population: ebi-a-GCST90020053	IVW	82	1.01 (1.007–1.013)	0.001	3.082613e-11
	WMe		1.01 (1.005–1.013)	0.002	1.286905e-05
	WMO		1.01 (1.001–1.017)	0.004	0.023
	SM		1.01 (1.001–1.022)	0.005	0.034
	MR-Egger		1.01 (0.992–1.023)	0.008	0.319

MR: Mendelian randomization, SNP: Single-nucleotide polymorphism, IVW: Inverse variance weighted, SM: Simple mode, WMO: Weighted mode, WMe: Weighted median, SE: Standard error, OR: Odds ratio

frailty across multiple MR methods. For instance, the IVW method reports an OR of 1.01 with a *P* = 0.021, suggesting that increased obesity is likely associated with an increased risk of frailty. Similarly, consistent associations with ORs of 1.01 (IVW) and 1.01 (WMe) both support the hypothesis that obesity contributes to higher frailty [Figure 1].

Association between frailty and obesity using Mendelian randomization

The results indicate a positive association between genetic predisposition to frailty and frailty across multiple MR methods. For instance, the IVW method reports an OR of 1.01 with a *P* = 3.08e-11, suggesting that increased obesity is likely associated with higher frailty. Similarly, consistent associations are observed with ORs of 1.01 (IVW) and 1.01 (WMe), both supporting the hypothesis that obesity susceptibility to frailty contributes to higher frailty [Figure 2].

DISCUSSION

This study investigated the bidirectional causal relationship between obesity and frailty, elucidating their reciprocal effects and underlying biological mechanisms. Employing a two-sample MR approach, we sought to address the limitations of observational studies, including confounding and reverse causation, and to provide robust evidence for the causality between these conditions. Our findings underscore a significant bidirectional association, suggesting that obesity causally contributes to frailty risk, while a genetic predisposition to frailty increases the likelihood of obesity. These results have critical public health and clinical implications, highlighting the importance of integrated interventions to address both conditions concurrently, particularly in aging populations.

Implications of findings: Bidirectional association between obesity and frailty

The study’s findings reveal a significant positive association between obesity and frailty, supported by multiple MR methods, such as IVW, WMe, and MR-Egger. These consistent

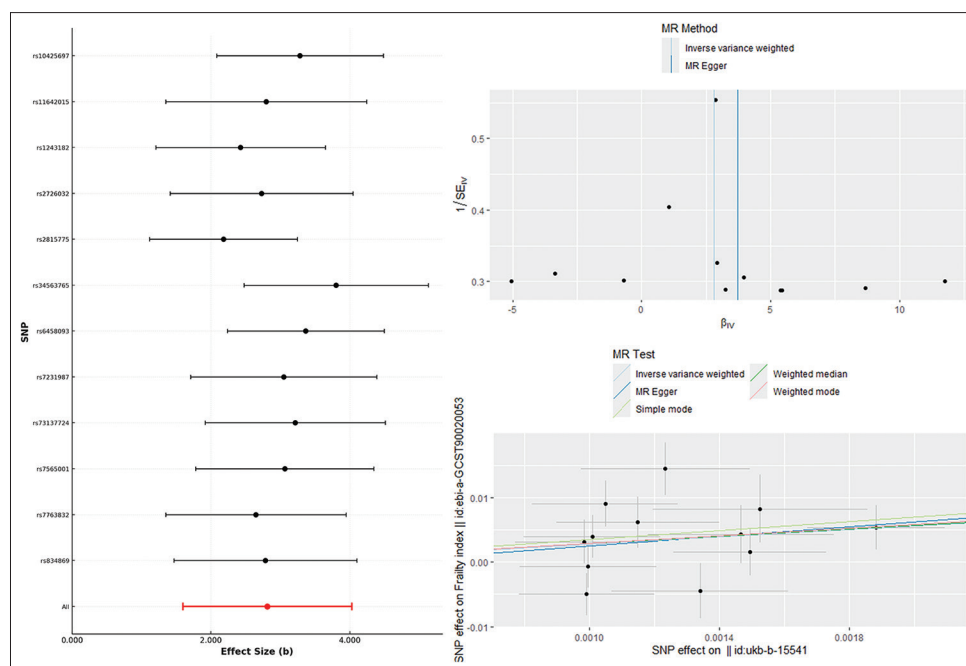


Figure 1: Mendelian randomization analysis of obesity on frailty. MR: Mendelian randomization, SNP: Single-nucleotide polymorphism

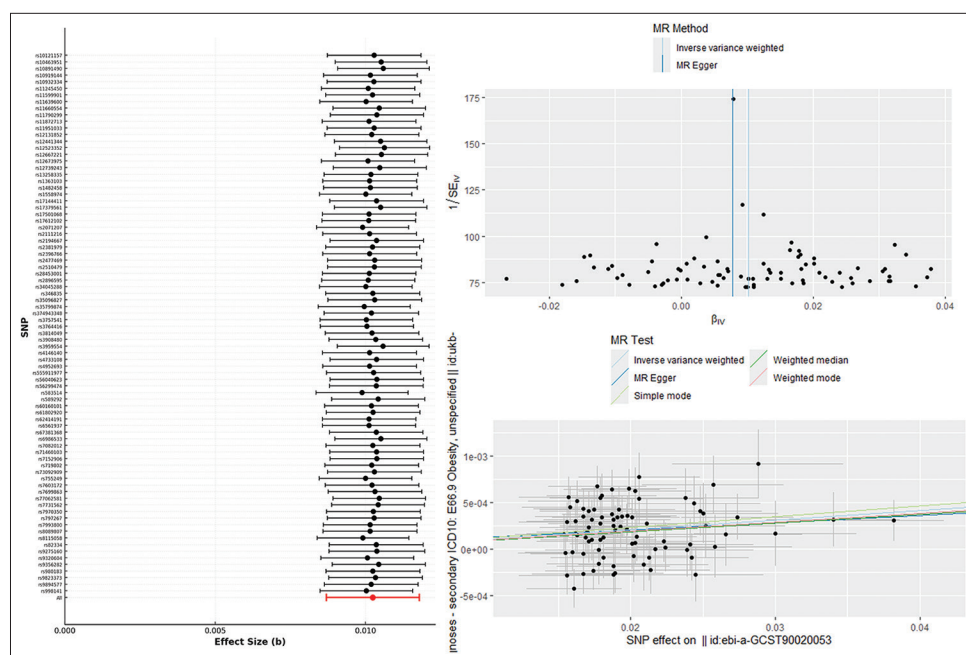


Figure 2: Mendelian randomization analysis of frailty on obesity. MR: Mendelian randomization, SNP: Single-nucleotide polymorphism

results strengthen the causal inference and align with prior observational studies,^[2,4,7] which identified an elevated risk of frailty among individuals with obesity. Notably, the results support the hypothesis that obesity not only correlates with but actively drives the progression of frailty through mechanisms such as chronic inflammation, insulin resistance, and oxidative stress.^[5,26]

Furthermore, this study highlights a reverse causal pathway, wherein a predisposition to frailty increases the risk of obesity. Frailty, characterized by reduced physiological reserves

and physical function, can exacerbate sedentary behavior, metabolic dysregulation, and appetite changes, contributing to weight gain or difficulty managing weight. This cyclical relationship underscores the complexity of these conditions and the need for integrated prevention and management strategies.

The bidirectional nature of the obesity–frailty association emphasizes obesity as a modifiable risk factor for frailty. Targeted weight management interventions could mitigate frailty risk, particularly in aging populations where both conditions are prevalent. Conversely, addressing frailty in

its early stages may reduce the likelihood of obesity, thereby preventing the compounding of health risks.

Limitations and future research directions

While the two-sample MR design mitigates biases from confounding and reverse causality, several limitations should be acknowledged. First, the study's reliance on GWAS data from populations of primarily European ancestry limits the generalizability of the findings to other ethnic groups.^[27] Obesity and frailty prevalence and their biological interactions may differ across populations due to genetic, environmental, and lifestyle factors. Future studies should incorporate diverse cohorts to explore these relationships in different demographic contexts.

Second, the stringent selection of SNPs as instrumental variables may exclude genetic variants with weaker associations, potentially underestimating the causal effect size. Despite employing MR-Egger to account for horizontal pleiotropy, residual pleiotropy cannot be entirely ruled out. Advances in multi-trait MR methods could refine causal estimates by analyzing multiple phenotypic traits simultaneously.

Finally, sex- and age-specific analyses were not performed in this study. Given the hormonal and physiological differences that may influence how obesity affects frailty in men and women, future research should explore these variations to inform tailored intervention strategies.

Public health and clinical implications

The bidirectional causal association between obesity and frailty carries significant implications for public health and clinical practice. With the global rise in obesity and an aging population, healthcare systems face increasing challenges related to these intertwined conditions. Early intervention strategies that promote healthy weight management could play a pivotal role in reducing frailty incidence, particularly among older adults.^[28]

For clinicians, these findings advocate for integrating frailty risk assessment into routine obesity management. Interventions such as resistance exercise programs, anti-inflammatory treatments, and dietary modifications can help address both conditions simultaneously. Understanding the shared biological pathways, such as inflammation and insulin resistance, could guide therapeutic approaches that target these mechanisms to improve outcomes.

From a policy perspective, these results emphasize the importance of multidimensional prevention strategies. Public health initiatives promoting healthy body weight through education, accessible nutrition, and physical activity programs could alleviate the burden of obesity and frailty. Policies targeting obesity reduction in midlife may delay or prevent the onset of frailty in later years, reducing healthcare costs and improving the quality of life for aging populations.

CONCLUSION

This study provides robust evidence of a bidirectional causal link between obesity and frailty, shedding light on their

reciprocal influence and shared biological mechanisms. These findings highlight the necessity for integrated approaches addressing both conditions simultaneously, particularly in aging populations. By advancing the understanding of the obesity–frailty relationship, this study lays the foundation for targeted interventions and prevention strategies aimed at healthier aging. Future research incorporating diverse populations, multi-trait MR methodologies, and sex-specific analyses will further enhance our ability to address the intertwined challenges of obesity and frailty, ultimately contributing to reduced healthcare burdens and improved public health outcomes globally.

Data availability statement

The original contributions presented in the study are included in the article material, further inquiries can be directed to the corresponding author.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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