Genetic Causal Association between Malnutrition, Overweight and Venous Thromboembolism: A Two-Sample Mendelian Randomization Study

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Running Title: Malnutrition, Overweight and VTE: MR Study

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Abstract

Despite previous observational studies suggesting that malnutrition could be involved in venous thromboembolism (VTE), definitive causality still lacks in high-quality research evidence. This study aims to explore the genetic causal association between malnutrition and VTE. The study was performed using summary statistics from genome-wide association studies (GWAS) for VTE (cases =23,367; controls =430,366). Single nucleotide polymorphism (SNP) associated with exposure was selected based on quality control steps. The primary analysis employed the Inverse-variance weighted (IVW) method, with additional support from MR-Egger, weighted median, and weighted mode approaches. MR-Egger, leave-one-SNP-out analysis and MR-PRESSO was used for sensitivity analysis. Cochran's Q test was used to assess heterogeneity between instrumental variables (IVs). IVW suggested that overweight have a positive genetic casual effect on VTE (OR=1.1344, 95% CI= 1.056-1.2186, p<0.001). No genetic casual effect of malnutrition (IVW: OR=0.9983, 95% CI= 0.9593-1.0388, p=0.9333) was found on VTE. Cochran's Q test suggests no possible heterogeneity in both related exposures. The results of the MR-Egger regression suggest that the analysis is not affected by horizontal pleiotropy. The results of the MR-PRESSO suggest that there are no outliers. The results revealed a statistical genetical association where overweight correlate with an increased risk of VTE. Meanwhile, no genetical causal link was observed between malnutrition and VTE. Further research is warranted to deepen our understanding of these associations.

Keywords: malnutrition; overweight; venous thromboembolism; Mendelian randomization; causal association; single nucleotide polymorphism

List of abbreviations: VTE: venous thromboembolism; GWAS: genome-wide association studies; SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted; IVs: instrumental variables; DVT: deep vein thrombosis; MR: Mendelian randomization; MAF: minimum allele frequency; LD: linkage disequilibrium; OR: odds ratio; CI: confidence intervals; MR-PRESSO: MR pleiotropy residual sum and outlier; PE: pulmonary embolism; WC: waist circumference; HC: hip circumference; UC: ulcerative colitis

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism, is a prevalent cardiovascular disorder with significant morbidity and mortality[1]. It presents with symptoms ranging from painful leg swelling to life-threatening pulmonary embolism and contributes to long-term complications such as recurrent VTE, post-pulmonary embolism syndrome, and chronic thromboembolic pulmonary hypertension[2]. VTE affects approximately 10 million individuals globally, ranking as the third leading vascular diagnosis[3]. The economic burden of VTE is substantial with annual healthcare costs estimated between €1.5 to €3.3 billion in Europe and between $7 to $10 billion in the United States[4, 5]. VTE is responsible for significant mortality rates differing markedly between genders and age groups in Europe[5]. Although the prevalence in Asia is lower than in Western countries, the incidence is increasing annually[6, 7].

The multifactorial nature of VTE risk encompasses acute triggers like surgery and sub-acute conditions such as inflammation, alongside demographic and behavioral factors such as obesity, highlighting the complexity of its epidemiology[8]. Recent prevention strategies have evolved to focus on not only hospital-associated risk factors but also broader, lifestyle-related risks[9]. Therefore, appropriate control of risk factors is important in the management of VTE.

Malnutrition, defined as any nutritional imbalance, is a critical yet often overlooked condition that impacts health outcomes[10]. While traditionally associated with undernutrition, malnutrition due to overnutrition also poses a significant risk particularly in the context of severe acute illness or major trauma[10]. Observational studies have shown that malnutrition is associated with increased risks of hospitalization, surgery, and VTE among patients with inflammatory conditions like inflammatory bowel disease[11]. Early screening for malnutrition and prompt nutrition intervention if indicated has been shown to prevent or mitigate many of these outlined risk factors[12]. However, despite the evidences in observational studies, definitive causal relationship still lacks in high-quality research evidence between malnutrition and VTE.

Mendelian randomization (MR) offers a robust approach to infer causal relationships between modifiable exposures and health outcomes, employing genetic variants as instrumental variables (IVs)[13, 14]. This method helps overcome the limitations of traditional observational studies, such as confounding and reverse causation, and provide a more reliable estimation of the effects of long-term exposure[15].

Therefore, the primary objective of this study is to explore the causal relationship between

malnutrition, overweight, and VTE using a two-sample MR design. By employing genetic data to approximate a randomized control setting, this study aims to clarify whether nutritional status significantly influences the risk of developing VTE, addressing a gap in current medical understanding and potentially guiding future nutritional and preventive strategies.

Experimental methods

Study design

This study utilized a two-sample MR approach to investigate the causal relationship between malnutrition and VTE, as illustrated in **Figure S1**. The conceptual framework was anchored in three fundamental principles essential to MR methodology. First, the relevance criterion requires a strong and demonstrable association between the instrumental variables (IVs) and the exposure of interest. Second, the independence criterion demands that the IVs are not associated with any confounders that might simultaneously affect the exposure and the outcome. Third, the exclusion-restriction criterion mandates that the IVs influence the outcome exclusively through their impact on the exposure, precluding any alternative causal pathways [(16)].

This article is a mendelian randomization study. The data for this study were obtained from publicly available databases and published literature data and does not require ethical approval and written informed consent.

Data Sources

The exposures of this study included malnutrition and overweight. Malnutrition is defined as inadequate intake of protein and calories. Overweight is defined as body mass index (BMI) BMI ≥25 kg/m^2[(17)]. Following datasets were selected as outcome data: 1) malnutrition (IEU GWAS Catalog GCST90435738, https://www.ebi.ac.uk/gwas/studies/GCST90435738) with 1,057 British ancestry cases and 406,492 British ancestry controls; 2) overweight (IEU GWAS Catalog ieu-a-93) with 93,015 European ancestry cases and 65,840 controls[(17)]. For the examination of the association with VTE as an outcome, GWAS summary-level data pertinent to VTE were derived from the IEU's pooled datasets with 23,367 European ancestry cases and 430,366 controls. The outcome and exposure data were carefully selected to ensure the robustness and relevance of the genetic tools used in this study. **Table S1** systematically presents more details of the exposure factor and outcome datasets.

Instrumental variable selection

The selection of IVs for this study was guided by a systematic process: 1) Single nucleotide polymorphisms (SNPs) exhibiting significant associations with the entire genome of malnutrition or VTE were identified. A stringent significance threshold of $p < 5 \times 10^{-8}$ was applied for associations with overweight, and $p < 5 \times 10^{-6}$ for malnutrition, with a minimum allele frequency (MAF) criterion set at 0.01[18]; 2) To evaluate and reduce the potential for linkage disequilibrium (LD) among the chosen IVs, a clumping procedure was employed, setting a threshold of $R^2 < 0.001$ and a clumping distance of 10,000 kb[15, 19]; 3) In cases where an identified IV SNP was unavailable in the outcome summary data, substitute SNPs with high LD ($R^2 > 0.8$) were considered as substitutes[15, 19]; 4) To ensure the robustness of each SNP within the IV and to minimize the risk of weak instrument bias, the F statistic for each SNP was calculated using the formula: $F = R^2*(N-2)/(1-R^2)$. R^2 refers to the proportion of variance in exposure explained by the SNPs in IV, and the requirement for the F value is >10[20]. Detailed information regarding the selected IVs is provided in **Table S2**.

MR analysis

The primary analytical method employed in this study was the inverse variance weighted (IVW) approach, which computes a weighted average of the effect sizes and uses the inverse variances of each single nucleotide polymorphism (SNP) as weights [21]. The IVW analysis adopted the fixed effects estimation method. This approach allows to assess the causal relationship between exposure and risk of outcomes, producing estimates of the odds ratio (OR) and 95% confidence intervals (CI). To ensure the robustness of the results, additional analyses were conducted using the MR-Egger, weighted median, and weighted mode methods. The MR-Egger approach, accounting for the potential presence of pleiotropy through an intercept term, offers an unbiased estimate of causal effects even in its presence[22]. The weighted median method, predicated on the validity of at least half of the instrumental variables, was applied to examine the causal link between exposure and outcome[23]. To further ensure the robustness of our findings and address potential reverse causality, we applied the Steiger filtering method from the R package. This method helps to identify and exclude SNPs that may have a stronger association with the outcome than the exposure, thereby reducing the risk of reverse causality.

Sensitivity analysis

Sensitivity analyses were conducted to explore potential heterogeneity and horizontal pleiotropy which could bias MR estimates. Heterogeneity among IVs was assessed using

Cochran's Q test, where a P-value greater than 0.05 indicates low heterogeneity. This suggests that any variation among the IVs is likely random and has minimal impact on the IVW results[24]. To evaluate the presence of horizontal pleiotropy, MR-Egger regression was employed. A non-significant intercept in this regression model suggests an absence of pleiotropy that could skew the MR estimates[25]. Additionally, the MR pleiotropy residual sum and outlier (MR-PRESSO) method was utilized to detect and adjust for outliers among the SNPs. SNPs with a P-value less than 0.05 were considered potential outliers and were excluded from the analysis to mitigate the effects of horizontal pleiotropy and enhance the accuracy of the causal estimates[26]. Leave-one-out analysis was applied to identify the influence of outliers by systematically excluding each genetic variant one at a time from the analysis, ensuring that the findings are not driven by a single genetic instrument[15].

Statistical Analysis

The analysis was conducted using R version 4.0.5, employing the "Two-sample MR" package designed specifically for MR studies. Graphical representations such as forest plots, scatter plots, and funnel plots were utilized to visually interpret the data.

Results

SNP selection

In this study, a total of 23 IVs relevant to malnutrition and overweight were selected. When MR analyses were conducted with VTE as the outcome, all IVs were aligned with corresponding information in the summary data sets. The detailed information of the included IVs is summarized in **Table S2**. All selected IVs exceeded the F-statistic threshold of 10.

MR analysis

The Inverse-Variance Weighted (IVW) analysis suggested a positive genetic influence of overweight on the risk of VTE, with an Odds Ratio (OR) of 1.1344, and a statistically significant 95% Confidence Interval (CI) ranging from 1.056 to 1.2186 ($p<0.001$). (**Table 1 and Figure 1,2**). However, the result of weighted median analysis, MR Egger and weighted mode analysis were not consistent with the IVW method ($p>0.05$). IVW showed no genetic casual effect of protein-calorie malnutrition (OR=0.9983, 95% CI= 0.9593-1.0388, p=0.9333) on VTE. The result of weighted median analysis, MR Egger and weighted mode analysis were consistent with the IVW method (**Table 1 and Figure 3**).

Sensitivity Analysis

Cochran's Q test for heterogeneity affirmed the consistency of MR analysis outcomes,

revealing no significant heterogeneity in the relationship between malnutrition, overweight and VTE (all p-values surpassed 0.05) (**Table 2**). Furthermore, the MR PRESSO analysis identified no outliers in the data (**Table 3**). The MR-Egger intercept test, designed to detect potential directional pleiotropy, also did not yield compelling evidence of substantial horizontal pleiotropy (all p-values exceeding 0.05), thereby supporting the robustness of our findings (**Table 2**). **Figure S2** depicted the funnel charts of sensitivity analysis between all p-values and the results were not significant. To further explore the potential impact of outlying genetic variants, a leave-one-out analysis was performed, systematically removing each instrumental variable and recalculating the causal estimate. This analysis did not demonstrate any significant changes in the overall causal estimates (**Figure S3**), indicating that the null findings were not influenced by any individual influential instrumental variable.

Discussion

This study provides a comprehensive analysis of the genetic underpinnings linking malnutrition to VTE. Our results suggest that being overweight has a positive genetic causal effect on the risk of developing VTE. However, this positive result needs to be interpreted with caution as the weighted median and weighted mode methods do not support the results of IVW method. Conversely, no significant genetic causal associations were observed for malnutrition in relation to VTE. This finding remains consistent across various analytical approaches. By employing a two-sample MR approach, the study minimizes potential confounding and provides a clearer causal inference between genetic predispositions to certain nutritional statuses and the risk of VTE. These insights highlight the potential for targeted interventions in populations at risk due to their genetic profile, thus paving the way for more personalized approaches in managing and preventing VTE.

The World Health Organization classifies overweight as a type of malnutrition, emphasizing imbalances in nutrient and energy intake[27]. Our MR study substantiates the possible positive genetic causal effect of being overweight on the risk of developing VTE, providing novel insights into how imbalance nutritional status influences VTE, particularly due to overweight. Several observational studies have demonstrated that obesity and components of metabolic syndrome are significant risk factors for VTE, with specific impacts on the recurrence and development of thrombotic events[28, 29]. Notably, the elevated risk associated with obesity is apparent across different age groups and is particularly pronounced in younger individuals[30, 31]. However, it has also been noted that no evidence of an association between obesity and

recurrent VTE has been observed in elder groups[32]. Inconsistency in observational studies reflects the need for further research. Our MR results align with most observational findings, which further elucidate the genetic basis of these observations and reinforce the role of overweight in VTE risk. Meanwhile, analyses by MR minimize the confounders and reverse causality, which are common limitations in observational studies. Notably, the effect of overweight on VTE appears to be extremely small in this study. Also, there is some heterogeneity among the different MR methods. While the effect may be detectable in a statistical sense due to the large sample size or the precision of measurement, its practical importance is minimal. We therefore believe that more careful consideration should be given to whether the effect of overweight on VTE is clinically significant.

Recent MR studies have demonstrated various aspects of body composition as significant contributors to VTE risk. Xiao et al. demonstrated that leptin is a risk factor for pulmonary embolism (PE), suggesting that targeting leptin levels in obese individuals could reduce PE risk[33]. Similarly, Wang et al. found significant causal relationships between both waist circumference (WC) and hip circumference (HC) and VTE, reinforcing the role of central obesity in VTE pathogenesis[34]. Furthermore, the study by Li et al. expanded on this by showing that height and BMI have causal effects on varicose veins and DVT, further underscoring the systemic impact of body size on venous thrombotic risks[35]. Martin et al. provided insight into the broader spectrum of diseases associated with higher adiposity, identifying conditions where metabolic effects of adiposity primarily exacerbate disease risks, including VTE[36]. Yuan et al. and a subsequent study emphasized the dose-response relationships between BMI, WC, and VTE, highlighting the significant population-attributable risks due to elevated body mass indices and reinforcing the causal role of abdominal obesity in VTE[37]. Our MR study further pointed out the possible positive genetic causal effect of overweight on the risk of VTE, suggesting that in addition to WC, HC, simple weight gain may also be involved in the development of VTE. These findings collectively suggest that interventions aimed at reducing obesity levels, particularly central adiposity, could possibly decrease the incidence of VTE. More research is still needed to further confirm this conclusion.

Our MR study indicates that malnutrition due to inadequate protein or calorie intake does not exhibit a genetic causal effect on the risk of developing VTE. This finding contrasts with observational studies that have suggested malnutrition associated with inflammatory conditions like inflammatory bowel disease may increase VTE risk. Fine et al. observed that

high malnutrition risk significantly correlates with increased occurrences of VTE in IBD patients[11]. Other studies have also shown that malnutrition is a risk factor for many complications in IBD, including VTE[12]. However, our MR findings do not support these associations strongly, indicating that while malnutrition correlates with VTE in clinical settings, its genetic basis in causing VTE may not be as pronounced.

Additionally, existing literature has shown that conditions like ulcerative colitis (UC), a type of IBD, are genetically linked to higher VTE risk.[38] Research into other nutrients such as vitamin D and its metabolic pathways suggests that while traditional deficiency symptoms are not causally linked to VTE, the genetic expressions involved in vitamin D metabolism might influence VTE risks[39]. These disparities highlight the complexity of nutritional impacts on VTE, suggesting that the relationship may be influenced by other factors or types of malnutrition. The MR approach encourages a nuanced examination of how different aspects of nutritional status may interact with genetic predispositions to influence VTE risk. Therefore, further studies are required to explore other forms of nutritional status and their potential causal relationships with VTE to fully understand the spectrum of nutritional impacts on venous thromboembolic diseases.

While this study provides valuable insights into the genetic association between malnutrition, overweight and VTE, several limitations must be acknowledged. The lack of statistical significance in the MR-Egger, weighted median and weight mode estimates for being overweight warrants careful interpretation of the results. The intercept term of the MR-Egger regression was close to zero in our analysis, indicating minimal horizontal pleiotropy and reinforcing the validity of the IVW results [22, 25, 40]. Therefore, we assume that the result of IVW method was valuable to some extent, but other replicated studies are needed to further argue for this result. Also, if these variants influence VTE risk through pathways unrelated to nutritional status, it could lead to biased estimates, thereby complicating the causal interpretation. Lastly, the generalizability of our findings may be constrained by the demographic characteristics of the study population, which primarily included individuals of broadly defined European ancestry. While two-sample Mendelian Randomization assumes that the exposure and outcome datasets are ancestrally homogeneous and that the same causal processes operate in both datasets, subtle differences within European populations may still exist. Variations in genetic architecture, environmental exposures, and lifestyle factors across subpopulations could influence the observed associations. These limitations highlight the need for caution when generalizing these findings to more diverse populations or subgroups

within European ancestry. Therefore, it is essential to replicate this study in diverse populations to verify the validity and applicability of the findings and to ensure a broader understanding of the genetic relationships between weight status and VTE. In addition, trauma and surgery are recognized as major risk factors for VTE as noted before, which highlights the importance of understanding how these factors interact with other potential influences. Therefore, an interesting and potentially impactful direction for future research could be to examine whether overweight (or obesity) acts as an effect modifier in the relationship between trauma or surgery and VTE risk, which could potentially lead to more tailored prevention strategies for those at the highest risk of VTE.

Analysis using two-sample MR revealed a statistically significant genetical association where overweight correlate with an increased risk of VTE. No causal relationships were established between malnutrition and VTE, which could provide new insights into the etiology of VTE.

Declarations

Ethics approval and consent to participate

This article is a mendelian randomization study. The data for this study were obtained from publicly available databases and published literature data and does not require ethical approval and written informed consent.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this article and supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yan Wang and Jian Shi carried out the studies, participated in collecting data, and drafted the manuscript. Yan Wang and Jian Shi performed the statistical analysis and participated in its design. Yan Wang and Jian Shi participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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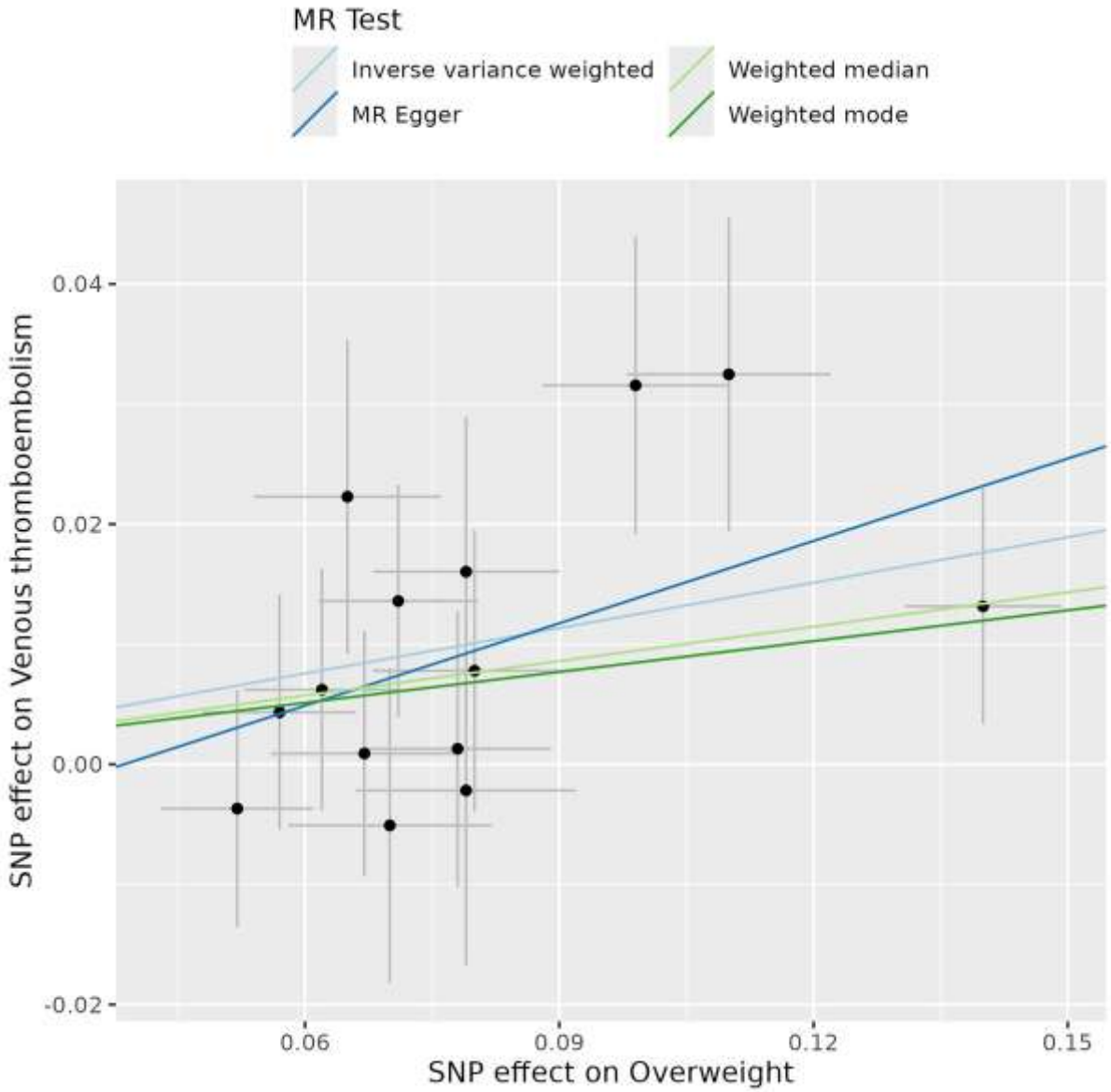

Figure 1. Scatter plots visualize the causal effects of overweight on venous thromboembolism (VTE).

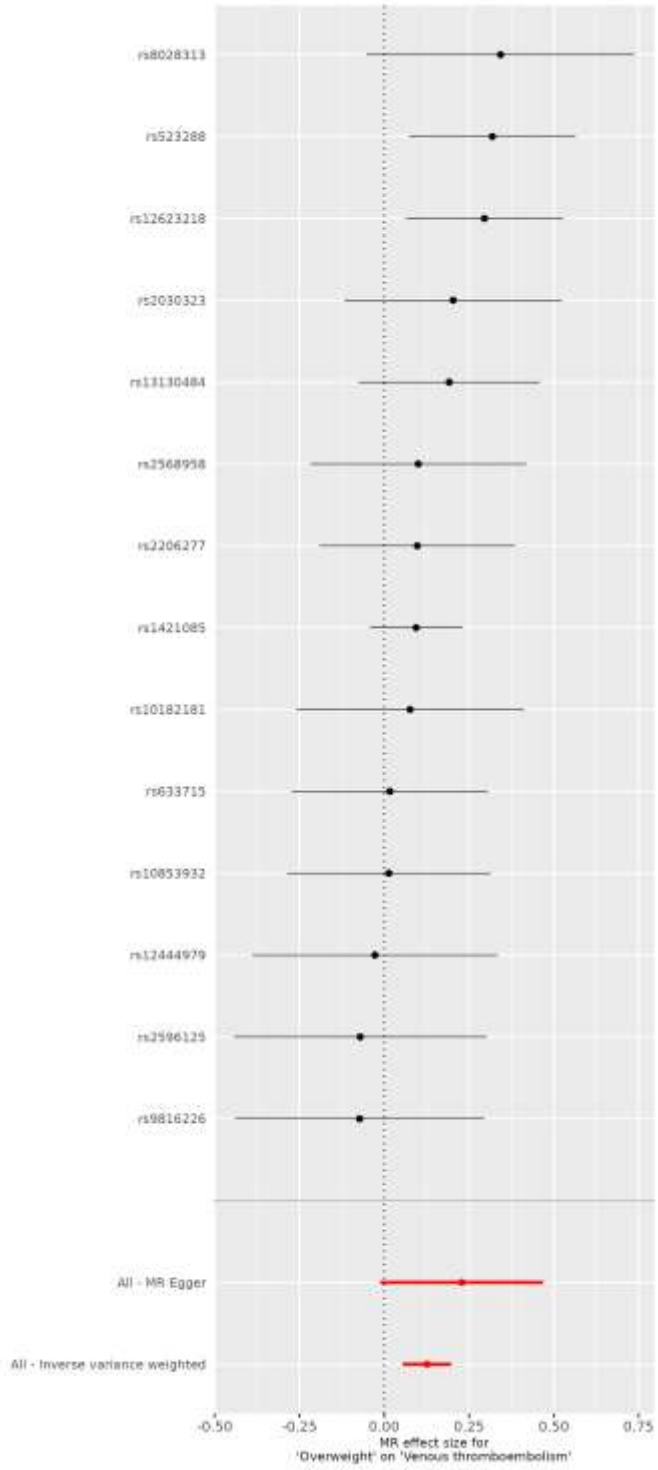

Figure 2. Forest plots visualize the causal effects of overweight on VTE.

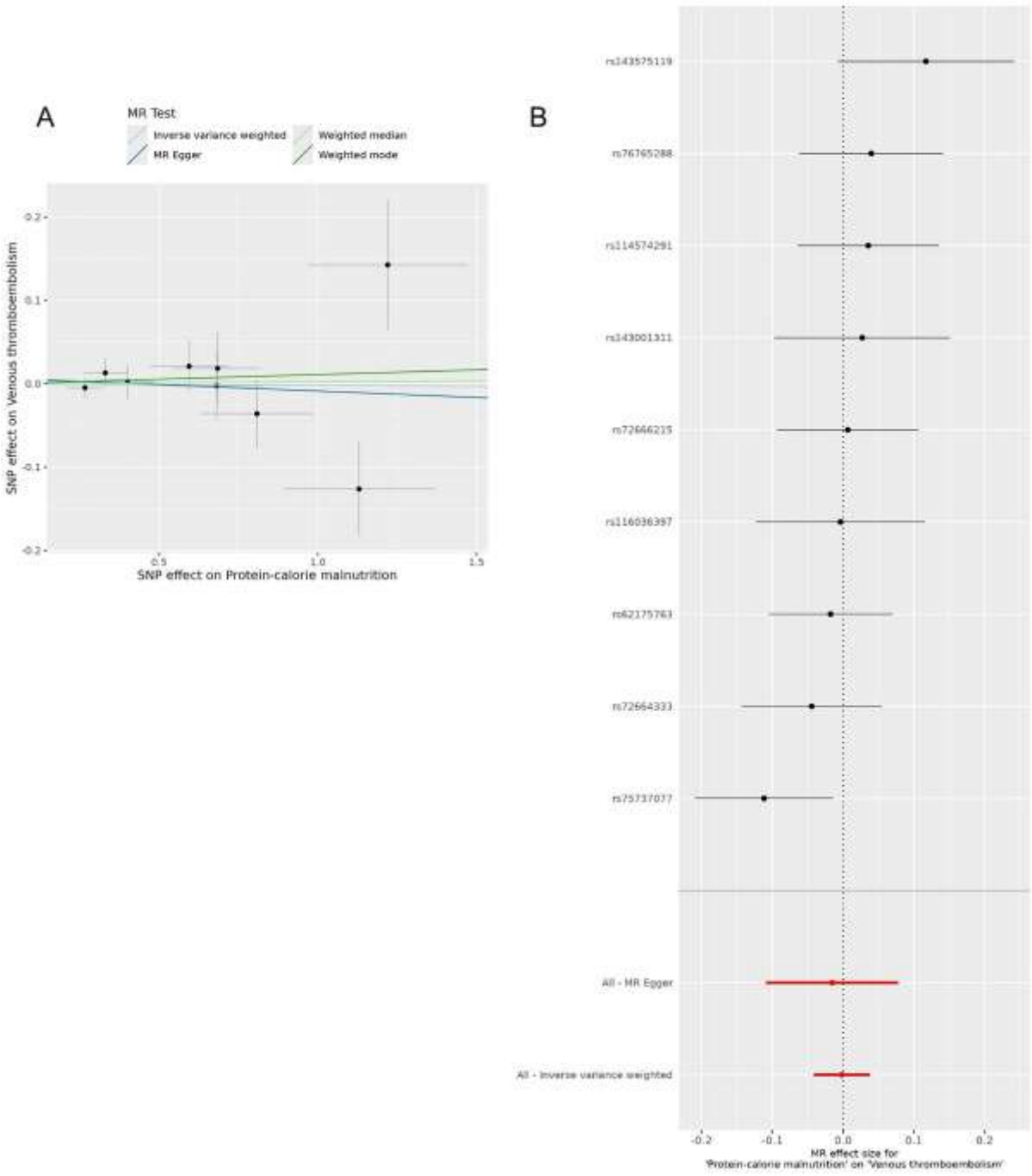

Figure 3. Scatter plot and forest plot visualize the causal effects of malnutrition on VTE.

Table 1. Genetic prediction of causal association between body weight and risk of VTE using IVW, MR-Egger, weighted mode and weighted median analysis

Exposure	Outcome	N.SNPs	Methods	OR (95% CI)	P
Overweight	VTE	14	Inverse variance weighted	1.1344 (1.056 - 1.2186)	6.00E-04
		14	MR Egger	1.2569 (0.988 - 1.5988)	0.0873
		14	Weighted median	1.1002 (0.9928 - 1.2193)	0.0685
		14	Weighted mode	1.0893 (0.9496 - 1.2494)	0.2435
Malnutrition	VTE	9	Inverse variance weighted	0.9983 (0.9593 - 1.0388)	0.9333
		9	MR Egger	0.9847 (0.8968 - 1.0813)	0.756
		9	Weighted median	1.0024 (0.956 - 1.051)	0.9217
		9	Weighted mode	1.0112 (0.9456 - 1.0814)	0.753

VTE, venous thromboembolism

Table 2. Heterogeneity tests and multiple validity tests for instrumental variables

Exposure	Outcome	Heterogeneity			Pleiotropy	
		Q statistic (IVW)	Degrees of freedom (df)	*P* value	MR-Egger Intercept	*P* value
Overweight	VTE	10.36843	13	0.663565	-0.00883	0.398773
Malnutrition	VTE	10.58706	8	0.226212	0.006831	0.756665

Table 3. Genetic prediction of causal association between body weight status and risk of VTE after removing outliners using MR-PRESSO analysis.

Exposure	Outcome	Raw		Outlier corrected		Global P	Number of outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
Overweight	VTE	1.1344 (1.0641 - 1.2093)	0.0019554	/	/	0.693333333	/	/
Malnutrition	VTE	0.9983 (0.9593 - 1.0388)	0.9353964	/	/	0.250333333	/	/

Supplementary materials

Table S1. Summary GWAS information of outcomes and exposure factors.

Table S2. Summary information of instrumental variables selection for outcomes and exposure factors

Figure S1. Flow chart of the study design

Figure S2. Funnel charts of sensitivity analysis for body weight on VTE: (A) malnutrition; (B) overweight.

Figure S3. MR results of leave-one-out sensitivity analysis for body weight on VTE: (A) malnutrition; (B) overweight.