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Genetic causal association between malnutrition, overweight and venous thromboembolism: a two-sample Mendelian randomisation study

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Research Article

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Abbreviations:
IV, instrumental variables; IVW, inverse variance weighted; MR, Mendelian randomisation; MR-PRESSO, MR pleiotropy residual sum and outlier; PE, pulmonary embolism; VTE, venous thromboembolism

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Abstract

Despite previous observational studies suggesting that malnutrition could be involved in venous thromboembolism (VTE), definitive causality still lacks 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 for VTE (cases = 23 367; controls = 430 366). 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 Mendelian randomisation (MR)-Egger, weighted median and weighted mode approaches. MR-Egger, leave-one-SNP-out analysis and MR pleiotropy residual sum and outlier (MR-PRESSO) were used for sensitivity analysis. Cochran's Q test was used to assess heterogeneity between instrumental variables (IV). IVW suggested that overweight has a positive genetic causal effect on VTE (OR = 1·1344, 95 % CI = 1·056, 1·2186, $P < 0·001$). No genetic causal 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 genetic association where overweight correlates with an increased risk of VTE. Meanwhile, no genetic causal link was observed between malnutrition and VTE. Further research is warranted to deepen our understanding of these associations.

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism (PE), is a prevalent cardiovascular disorder with significant morbidity and mortality[1]. It presents with symptoms ranging from painful leg swelling to life-threatening PE and contributes to long-term complications such as recurrent VTE, post-PE 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 and €3·3 billion in Europe and between $7 and $10 billion in the USA[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 behavioural factors such as obesity, highlighting the complexity of its epidemiology[8]. Recent prevention strategies have evolved to focus not only on hospital-associated risk factors but also on 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 hospitalisation, 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, a definitive causal relationship still lacks in high-quality research evidence between malnutrition and VTE.

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

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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 randomised 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 utilised a two-sample MR approach to investigate the causal relationship between malnutrition and VTE, as illustrated in online Supplementary 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 IV and the exposure of interest. Second, the independence criterion demands that the IV are not associated with any confounders that might simultaneously affect the exposure and the outcome. Third, the exclusion–restriction criterion mandates that the IV influence the outcome exclusively through their impact on the exposure, precluding any alternative causal pathways[16].

This article is an MR study. The data for this study were obtained from publicly available databases and published literature data and do 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 energies. Overweight is defined as BMI ≥ 25 kg/m^2[17]. The following datasets were selected as outcome data: (1) malnutrition (IEU GWAS Catalog GCST90435738, https://www.ebi.ac.UK/gwas/studies/GCST90435738) with 1057 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. Online Supplementary Table S1 systematically presents more details of the exposure factor and outcome datasets.

Instrumental variable selection

The selection of IV for this study was guided by a systematic process: (1) SNP 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 criterion set at 0·01[18]; (2) To evaluate and reduce the potential for linkage disequilibrium among the chosen IV, a clumping procedure was employed, setting a threshold of $R^2 < 0{\cdot}001$ 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 SNP with high linkage disequilibrium ($R^2 > 0{\cdot}8$) were considered as substitutes[15,19]; (4) To ensure the robustness of each SNP within the IV and minimise the risk of weak instrument bias, the F statistic for each SNP was calculated using the formula: $F = R^2 \times (N - 2)/(1 - R^2)$. R^2 refers to the proportion of variance in exposure explained by the SNP in IV, and the requirement for the F value is > 10[20]. Detailed information regarding the selected IV is provided in online Supplementary Table S2.

Mendelian randomisation 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 SNP as weights[21]. The IVW analysis adopted the fixed effects estimation method. This approach allows us to assess the causal relationship between exposure and risk of outcomes, producing estimates of the OR and 95 % 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 IV, 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 SNP 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 IV 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 IV 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 utilised to detect and adjust for outliers among the SNP. SNP 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 utilised to visually interpret the data.

Results

SNP selection

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

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Table 1. Genetic prediction of causal association between body weight and risk of VTE using IVW, MR-Egger, weighted mode and weighted median analysis (OR and 95 % CI)

Exposure	Outcome	SNP	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

MR, Mendelian randomization; IVW, inverse variance weighted; VTE, venous thromboembolism.

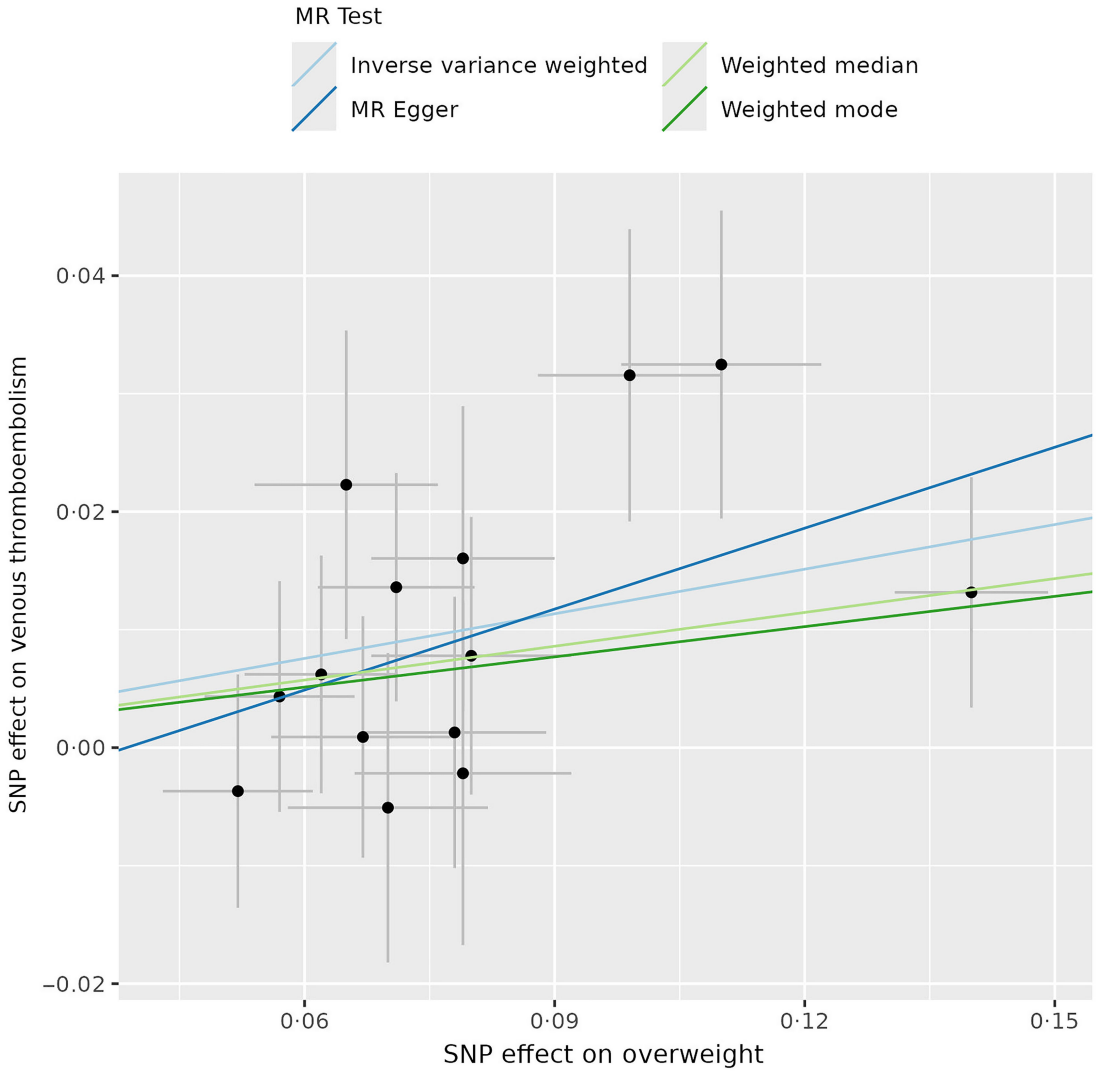


Figure 1. Scatter plots visualise the causal effects of overweight on venous thromboembolism (VTE).

Mendelian randomisation analysis

The inverse variance weighted (IVW) analysis suggested a positive genetic influence of being overweight on the risk of VTE, with an OR of 1·1344 and a statistically significant 95 % CI ranging from 1·056 to 1·2186 ($P < 0·001$). (Table 1 and Figures 1 and 2). However, the results of weighted median analysis, MR Egger and weighted mode analysis were not consistent with the IVW method ($P > 0·05$). IVW showed no genetic causal effect of protein–energy malnutrition (OR = 0·9983, 95 % CI = 0·9593, 1·0388, $P = 0·9333$) on VTE. The results of weighted median analysis, MR Egger and

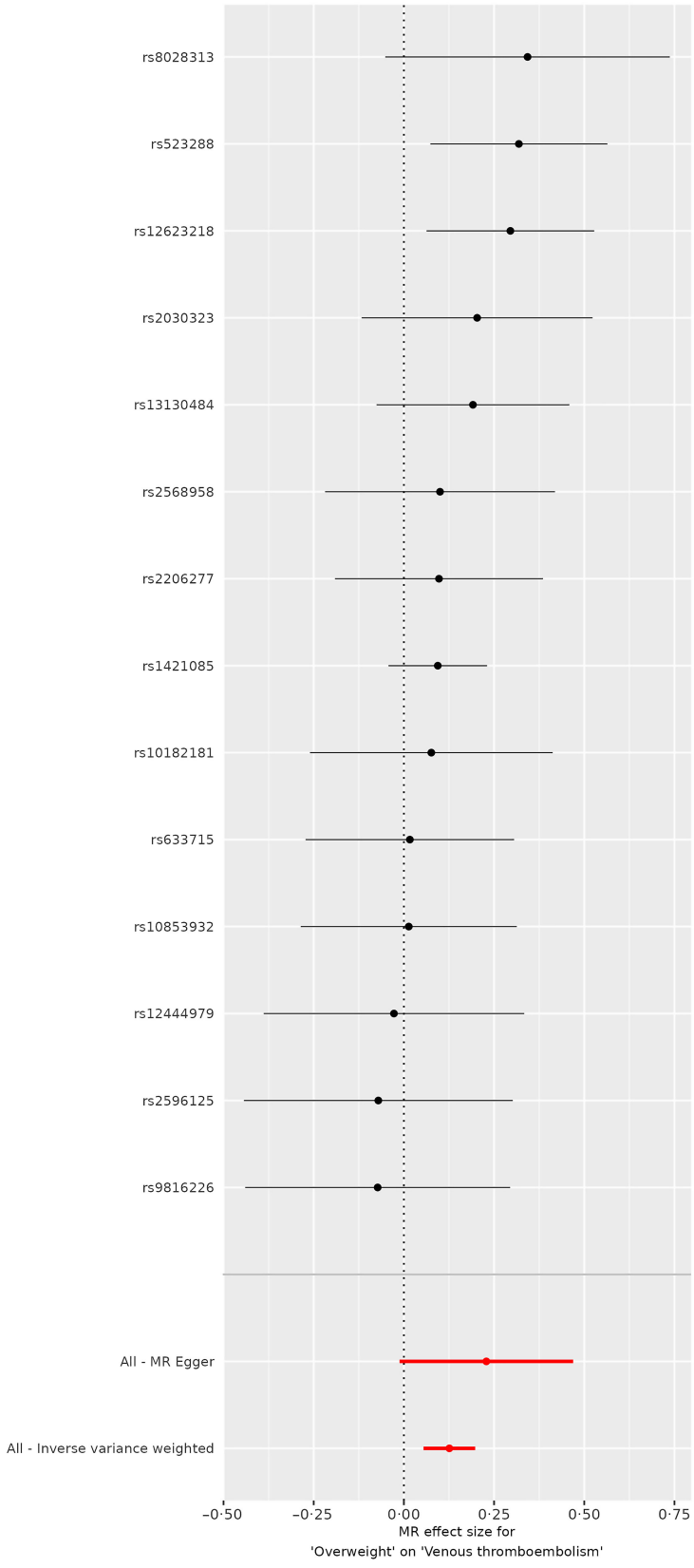


Figure 2. Forest plots visualise the causal effects of overweight on VTE.

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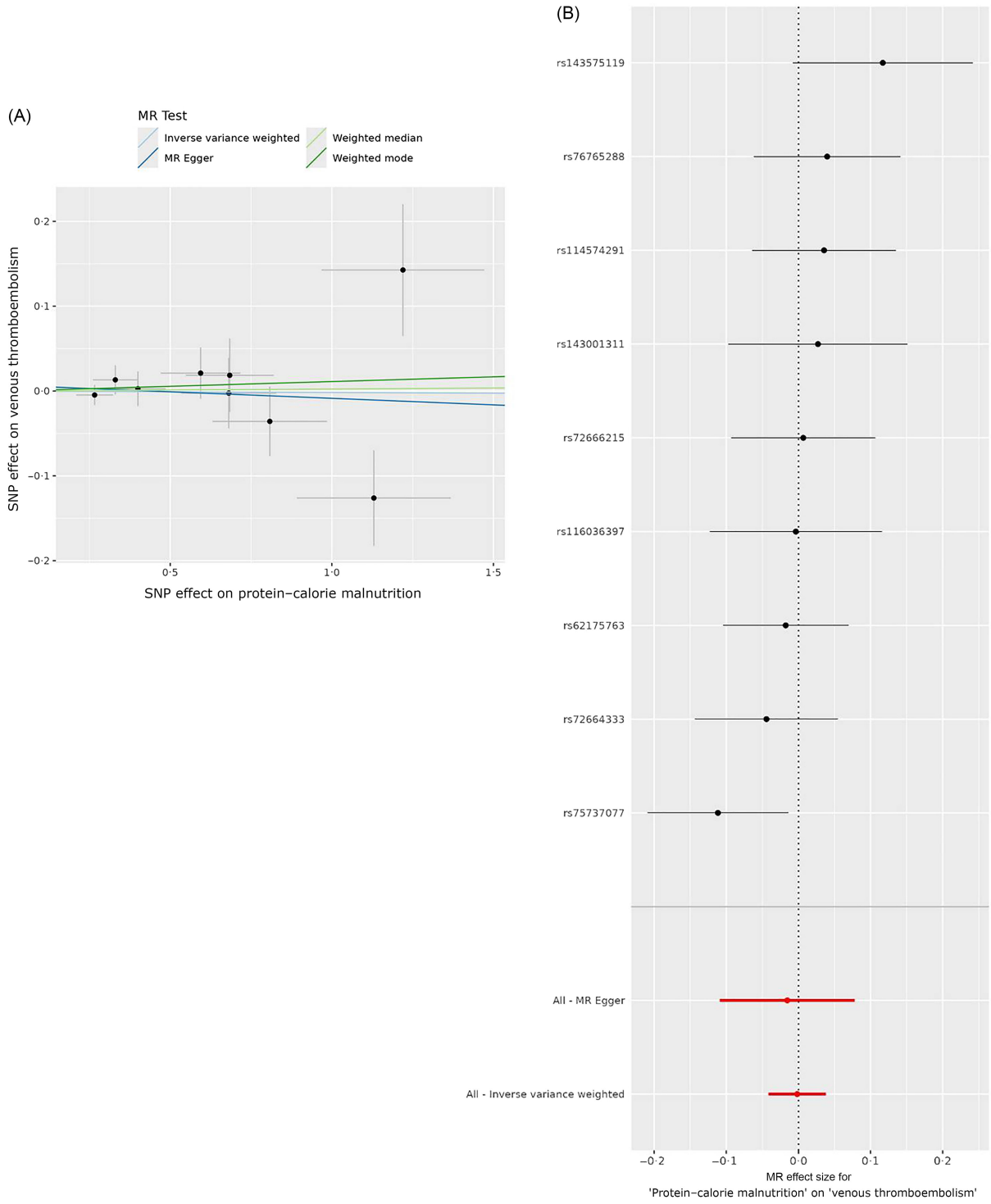


Figure 3. Scatter plot and forest plot visualise the causal effects of malnutrition on VTE.

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). Online Supplementary 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

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

		Heterogeneity			Pleiotropy	
Exposure	Outcome	Q statistic (IVW)	Degrees of freedom (df)	*P* value	MR-Egger Intercept	*P* value
Overweight	VTE	10·36 843	13	0·663 565	−0·00883	0·398 773
Malnutrition	VTE	10·58 706	8	0·226 212	0·006831	0·756 665

IVW, inverse variance weighted; MR, Mendelian randomization; VTE, venous thromboembolism.

Table 3. Genetic prediction of causal association between body weight status and risk of VTE after removing outliners using MR-PRESSO analysis (OR and 95 % CI)

		Raw			Outlier corrected				
Exposure	Outcome	OR	CI%	*P*	OR (CI%)	*P*	Global P	Number of outliers	Distortion P
Overweight	VTE	1·1344	1·0641, 1·2093	0·0 019 554	/	/	0·693333333	/	/
Malnutrition	VTE	0·9983	0·9593, 1·0388	0·9 353 964	/	/	0·250333333	/	/

MR-PRESSO, MR pleiotropy residual sum and outlier;VTE, venous thromboembolism.

IV and recalculating the causal estimate. This analysis did not demonstrate any significant changes in the overall causal estimates (online Supplementary Figure S3), indicating that the null findings were not influenced by any individual influential IV.

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 the 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 minimises 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 personalised approaches in managing and preventing VTE.

The WHO classifies overweight as a type of malnutrition, emphasising 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 an 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 elderly 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 minimise 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 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 and hip circumference 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 deep vein thrombosis, 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 emphasised the dose–response relationships between BMI, waist circumference and VTE, highlighting the significant population-attributable risks due to elevated BMI 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 waist circumference and hip circumference, 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 energy 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

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Inflammatory Bowel Disease (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, 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 the 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 generalisability 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 MR 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 generalising 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 ensure a broader understanding of the genetic relationships between weight status and VTE. In addition, trauma and surgery are recognised 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 genetic association where overweight correlates with an increased risk of VTE. No causal relationships were established between malnutrition and VTE, which could provide new insights into the aetiology of VTE.

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The authors declare that they have no competing interests.

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

Consent for publication: not applicable

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

Supplementary material. For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114525000704

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