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Causal Association between Body Mass Index and Adverse Blood Transfusion Reactions: A Mendelian Randomization Study

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Received: 9 July 2024; Accepted: 26 November 2024; Available online: 30 December 2024

ABSTRACT: The study aims to investigate the potential causative relationship between body mass index (BMI) and adverse blood transfusion reactions (ABTR). A two-sample Mendelian randomization (MR) study was conducted using inverse variance weighted (IVW), MR-Egger regression, weighted median method (WME), weighted model method (WM), simple model method, and simple median method. We utilized publicly available summary statistics from genome-wide association studies (GWAS) on BMI as the exposure (n = 126 003; GWAS ID: ebi-a-GCST90095042) and a GWAS for adverse blood transfusion reactions as the outcome variable (n = 199 451; GWAS ID: finn-b-ST19). We identified 42 single nucleotide polymorphisms of genome-wide significance in genome-wide association studies on BMI, which could serve as instrumental variables. The IVW technique showed that there is a causal relationship between BMI and negative blood transfusion outcomes (odds ratio (OR) = 0.29, 95% confidence interval (CI) = 0.10–0.85). Nonetheless, the effect value β of MR-Egger regression approach differed from that of IVW. A meta-analysis was conducted to determine the aggregated value of OR and 95% CI. The combined odds ratio (95% CI) was 0.43 (0.21–0.86), with a P-value of 0.017. Both the Cochran's Q test and the funnel plot indicated no signs of heterogeneity or asymmetry, indicating the absence of directional pleiotropy. The results suggest that there may be a direct connection between BMI and ABTR.

Keywords: BMI; Mendelian randomization; Adverse transfusion response

1. Introduction

Blood transfusion is a critical method for preserving patients' lives [1]. Adverse blood transfusion responses (ABTR) primarily denote a collection of symptoms and indications in blood recipients that cannot be attributed to the underlying condition during or after transfusion [2]. The prevalent categories of transfusion responses include allergy, non-hemolytic febrile reactions, hemolytic transfusion reactions, transfusion-related acute lung injury, and inefficient platelet transfusions [3]. ABTR may present either as an acute transfusion response or as a delayed transfusion reaction occurring several days to weeks after the transfusion, and severe adverse blood transfusion reactions posing a significant risk to patient safety [4]. In clinical practice, identifying and treating ABRT is crucial to maintain the safety of transfusion recipients.

Body Mass Index (BMI) (weight (kg)/height (m)^2) is a metric that can be measured and computed with relative simplicity and precision using weight and height, hence facilitating a more intuitive assessment of obesity *via* particular values. It is commonly used as a measure and diagnostic criteria for obesity [5]. BMI is extensively used in epidemiological research to evaluate the risk of disease associated with various weight categories. An observational research on coronary artery bypass grafting revealed that BMI serves as a predictor for blood transfusion, as

https://doi.org/10.70322/BG20240210007

individuals with lower BMI levels tend to experience higher blood loss and require more transfusions based on their body weight [6]. However, there have been few research conducted to establish a causal link between BMI and ABTR.

Mendelian randomization (MR) is a method that uses genetic variation as instrumental variables (IVs) to determine whether the observed correlations between risk factors and outcomes align with causal effects [7]. Two-sample MR can assess the causal impacts of exposure and outcome factors across various samples [8]. This study employed a two-sample MR analysis to examine the causal association between BMI and ABTR.

2. Materials and Methods

2.1. Sources of Data and Selection of Genetic Variants

Summary statistics for BMI and blood transfusion complications are available from the database of IEU Open GWAS project (https://gwas.mrcieu.ac.uk/ (accessed on 11 March 2022)), as shown in Table 1. The GWAS ID for BMI is ebi-a-GCST90095042, with a sample size of 126 003 and containing 2 343 330 single nucleotide polymorphisms (SNPs). The GWAS ID for transfusion complications is finn-b-ST19, including 199 451 samples and comprising 16 380 395 SNPs. The data for this study were sourced from a public database, therefore obviating the need for further ethical review.

Table 1. IVs correlated with BMI and ABTR.

SNPs	Chr	Position	EA	Beta	SE
rs1045241	5	118729286	T	−0.0299	0.0042
rs10919388	1	170372503	C	0.0338	0.0044
rs10991433	9	107726918	C	0.0391	0.0066
rs11048456	12	26463082	T	−0.0391	0.0041
rs11231693	11	63862612	A	0.0462	0.0075
rs1128249	2	165528624	T	−0.0502	0.004
rs12454712	18	60845884	C	−0.0296	0.0048
rs12679556	8	72514228	G	0.027	0.0042
rs1294410	6	6738752	C	0.0374	0.0039
rs13147949	4	123838107	C	0.0272	0.0048
rs13173241	5	55861359	A	0.0344	0.0048
rs13256367	8	128334900	C	−0.0272	0.0047
rs1358980	6	43764551	T	0.0559	0.0042
rs1443512	12	54342684	C	−0.0352	0.0044
rs1534696	7	26397239	A	−0.0281	0.0042
rs17819328	3	12489342	G	0.0341	0.0041
rs1936807	6	127448249	G	0.0465	0.0039
rs2371767	3	64718258	C	−0.0557	0.0043
rs2373078	2	218392555	T	0.0377	0.0068
rs2820443	1	219753509	C	−0.0577	0.0043
rs2925979	16	81534790	C	−0.0345	0.0043
rs351377	1	212425771	C	−0.0266	0.0045
rs3792603	4	56302058	G	0.034	0.0057
rs3902751	7	25861639	A	0.0318	0.0043
rs4512391	8	126516988	C	0.0222	0.004
rs4646404	17	17420199	A	−0.0301	0.0045
rs4765219	12	124440110	A	−0.0354	0.004
rs4823006	22	29451671	G	−0.0245	0.0039
rs6090583	20	45558831	G	−0.0235	0.0039
rs6795831	3	129341403	C	−0.0458	0.0055
rs7251505	19	33802542	A	−0.0424	0.0068
rs7492628	14	91547136	G	0.0263	0.0047
rs761711	6	100626148	G	0.0241	0.0043
rs7705502	5	173320815	A	0.0268	0.0044
rs7830933	8	23603324	G	−0.0285	0.0046
rs7917772	10	104487443	A	0.0251	0.0039
rs8030605	15	56504598	A	0.0333	0.0059
rs8066985	17	68453345	G	−0.0262	0.0039
rs905938	1	154991389	C	−0.0299	0.0047
rs9425301	1	172363815	C	−0.0273	0.0042
rs984225	1	119504284	A	0.0314	0.0039

rs9991328	4	89713121	T	0.0307	0.0039

IVs: instrumental variables; BMI: body mass index; ABTR: adverse blood transfusion reactions; SNPs: single-nucleotide polymorphisms; Chr: chromosome; EA: effect allele; SE: standard error.

2.2. Selection of Instrumental Variables

An MR study demonstrates that genetic variations are associated with an exposure, without being confounded by potential variables [9]. Initially, we identified SNP instrumental factors using a criterion of $P < 5 \times 10^{-8}$, a linkage disequilibrium coefficient of 0.001, and an area width of 10 000 kb. We selected SNPs from the BMI dataset as IVs that exhibited a substantial correlation with BMI and lacked gene pleiotropy. A dataset on transfusion complications was then included to examine the causal relationship between BMI and ABTR.

2.3. Statistical Analysis of Mendelian Randomization

This research primarily used the inverse variance weighted (IVW) method in MR Analysis to examine the relationship between BMI and unfavorable blood transfusion responses. IVW employed a meta-analytical method to combine the analytical effects derived from several SNPs *via* the Wald ratio, yielding a coherent assessment of the causal effects of exposure and outcomes, given that each genetic variation satisfied the IV hypothesis and reached statistical significance at $P < 0.05$ [10]. We included MR-Egger regression, weighted median estimator (WME), weighted mode (WM), simple mode, and simple median as extra methods. The consistency in β values among MR-Egger regression, WME, WM, simple mode, and simple median with the β values of IVW signified the stability and reliability of the IVW findings. In cases where the outcomes of the six approaches were incongruent, we turned to meta-analysis to obtain a result that approximates the actual situation. Cochran's Q test was utilized in this study to identify heterogeneity. When $P < 0.05$, heterogeneity was present, necessitating the employment of a random effects model. A fixed-effect model was used. The presence of pleiotropy was assessed using the MR-Egger technique with a significant level of $P < 0.05$. A "leave-one-out" analysis was performed to determine whether the causal connection was influenced by a single SNP. This research included scatter plots to illustrate how individual SNPs affect exposure and outcome, forest plots to depict the causal relationship between exposure variables and outcomes, and funnel plots to assess the existence of selection bias. All MR studies were conducted using R Studio (R4.3.1) along with the Two Sample MR and MR-PRESSO packages.

3. Results

3.1. Instrumental Variables for Mendelian Randomization

We identified 42 distinct SNPs from the GWAS data on BMI as instrumental factors with a F value over 30, which were linked to ABTR, and these IVs may alone influence outcome events *via* the exposure factor BMI (Table 1). An F value of less than 10 was classified as a weak instrumental variable, rendering it unsuitable for use as an instrumental variable in MR research.

3.2. MR Analysis

The main analytical method, IVW analysis, demonstrated evidence supporting a causal connection between BMI and hazardous blood transfusion responses (OR = 0.29, 95% CI = 0.10–0.85, $P = 0.02$; Table 2, Figures 1 and 2). The effect value β of WME, WM, simple model, and simple median analysis techniques was consistent with that of IVW, whereas the effect value β of the MR-Egger analysis method was contrary to that of IVW (Table 2, Figures 1 and 2).

Table 2. MR estimates of the causal effect of BMI and ABTR.

MR methods	Beta	SE	*P*-value	OR
MR-Egger regression	1.71	2.05	0.41	5.53
Weighted median estimator	−0.44	0.79	0.58	0.64
Inverse variance weighted	−1.23	0.54	0.02 *	0.29
Weighted mode	−0.11	1.15	0.92	0.89
Simple mode	−0.51	1.65	0.76	0.60
Simple median	−0.94	0.81	0.25	0.39

MR: mendelian randomization; BMI: body mass index; ABTR: adverse blood transfusion reactions; SE: standard error; OR: odds ratio. * $P < 0.05$ indicated a statistically significant relationship between the exposure and outcome variables.

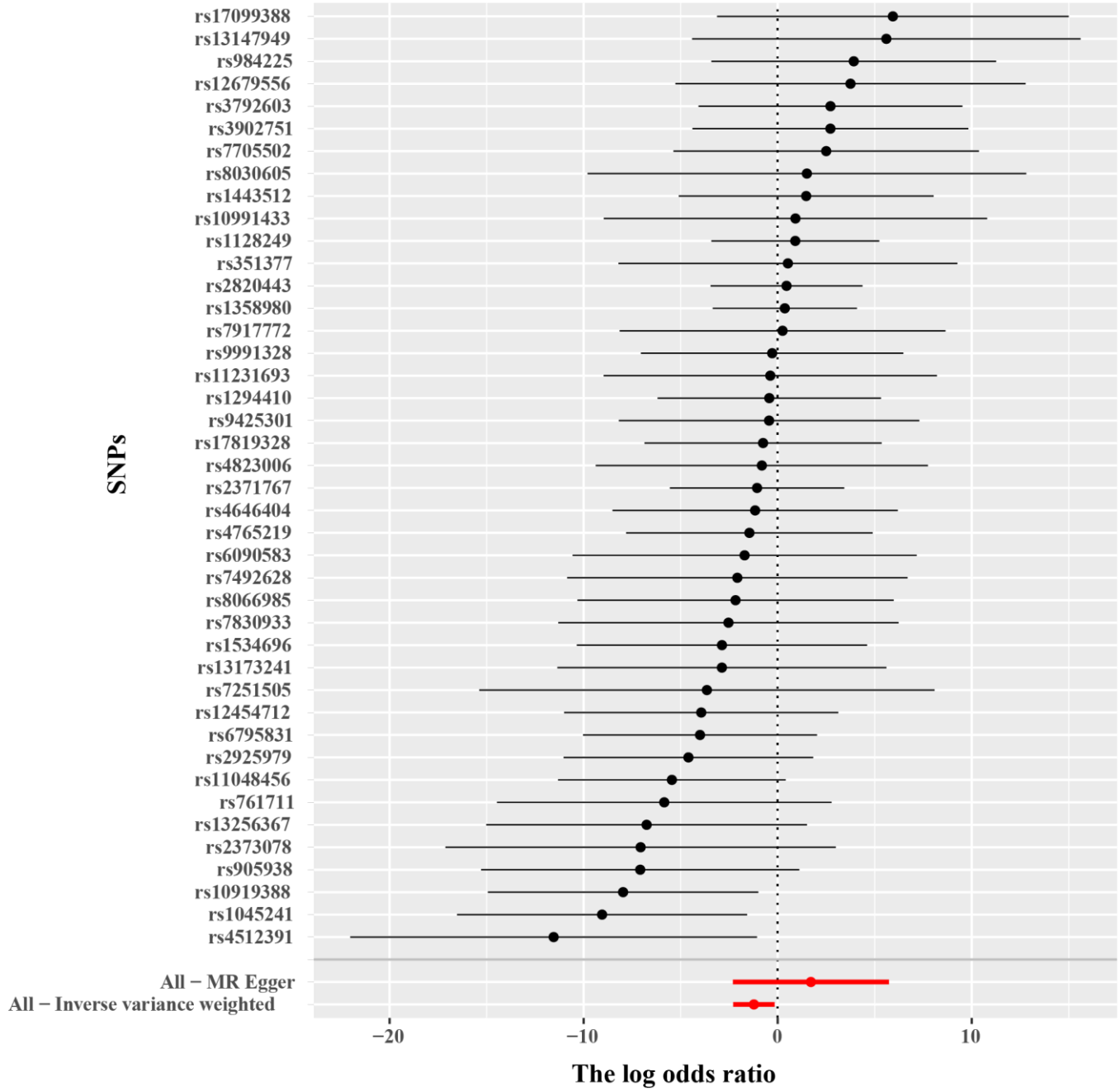

Figure 1. Forest plot illustrating the causative effects of single nucleotide polymorphisms correlated with BMI on ABTR. The importance of red lines pertained to the MR findings of MR-Egger test and IVW methodology. BMI: body mass index; ABTR: adverse blood transfusion reactions; MR: mendelian randomization; IVW: inverse variance weighted; SNPs: single nucleotide polymorphisms.

3.3. Validation of Causal Relationship

Given the inconsistency in the direction of β values across the six techniques, a meta-analysis was conducted to calculate the aggregated value of OR and 95% CI. The overall OR (95% CI) was 0.46 (0.23–0.91) with a *P*-value of 0.027, indicating a potential causative association between exposure variables and the outcome, as seen in Figure 3.

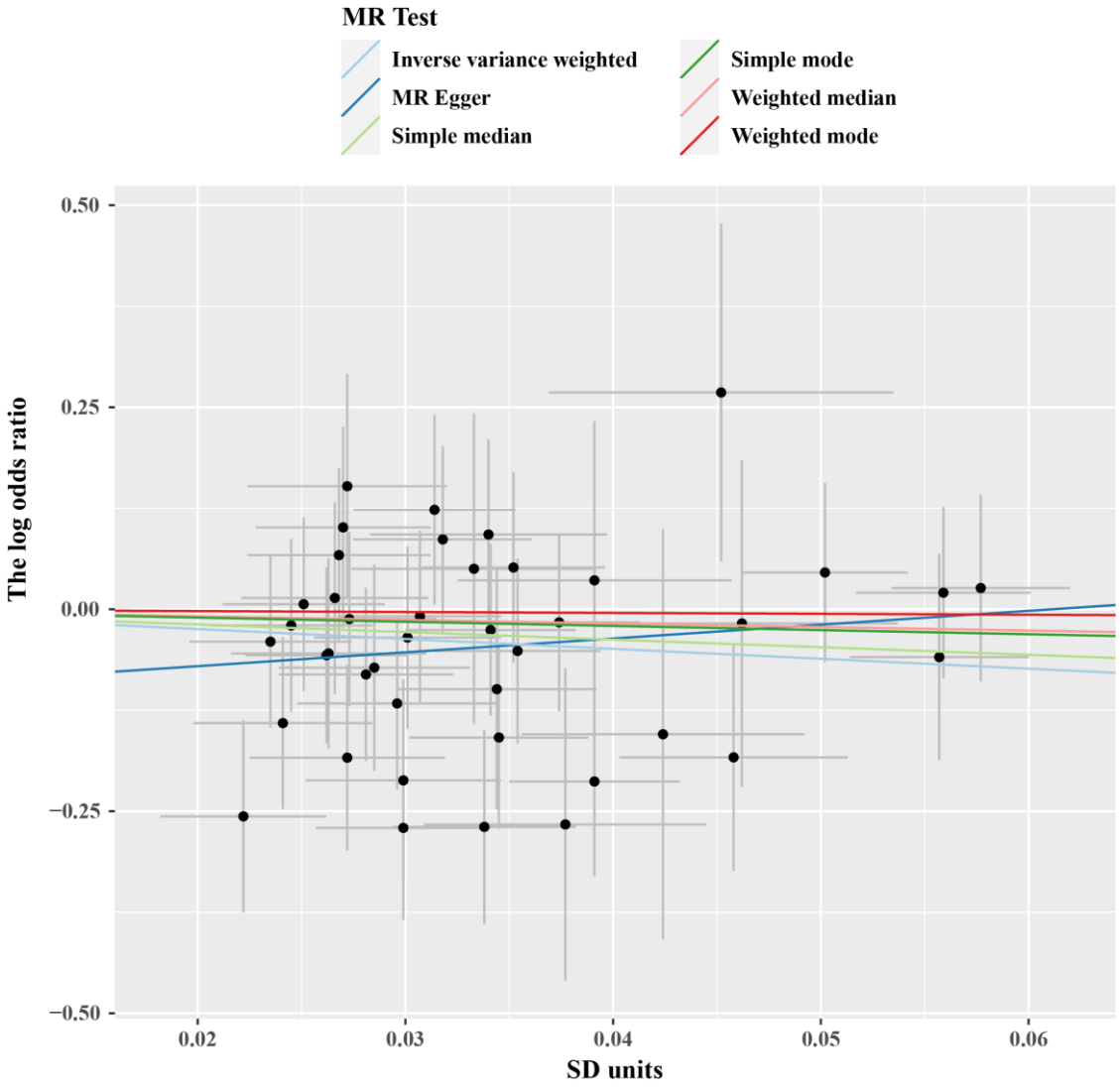

Figure 2. Scatter plots depicting genetic relationships with BMI in relation to genetic associations with ABTR. The slopes of each line indicated an association for each method. BMI: body mass index; ABTR: adverse blood transfusion reactions; MR: mendelian randomization.

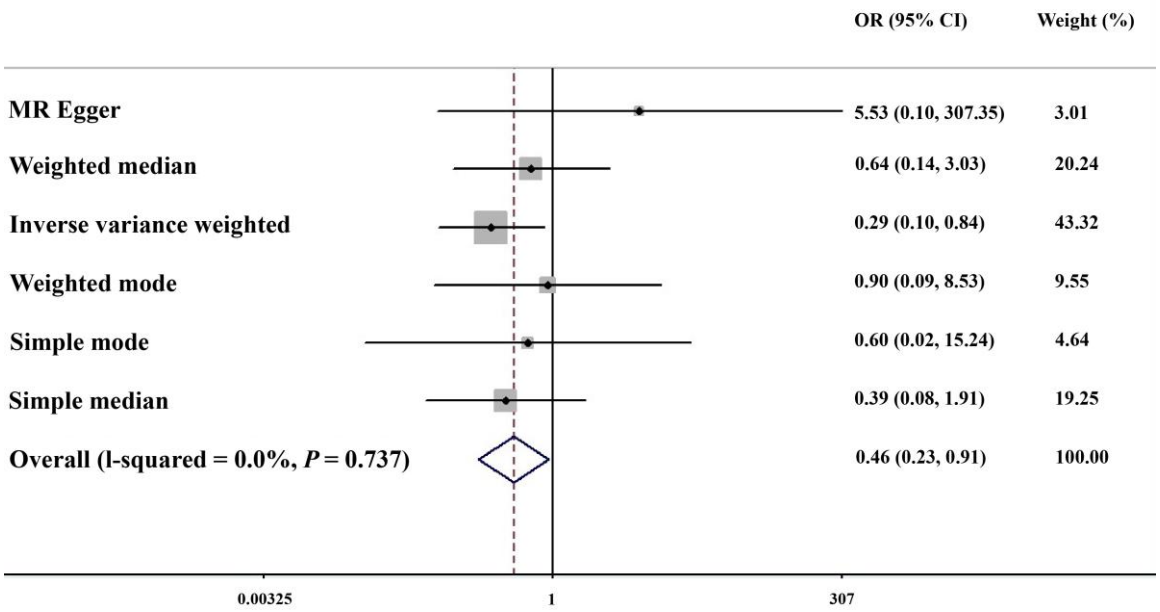

Figure 3. Forest plot showing MR results. MR: mendelian randomization; OR: odds ratio; CI: confidence interval.

3.4. Analysis of Heterogeneity and Pleiotropy

Heterogeneity was assessed using two methodologies. The IVW analysis indicated that Cochran's Q = 37.25, I^2 = 10.01%, P = 0.638. The MR Egger analysis revealed Cochran's Q = 35.04, I^2 = 14.15%, P = 0.693. Both methodologies demonstrated that there was very little variability in instrumental factors due to individual variation. Less heterogeneity indicates more reliable MR results, as it reflects the variability of each SNP causal estimate. The pleiotropy analysis indicated an Egger intercept of −0.1 with a P-value of 0.145, suggesting no horizontal pleiotropy and demonstrating relative robustness of the results. The funnel plot findings showed that the estimated causal impact of the included SNP was mostly symmetrical, suggesting stability and the absence of publication bias, as illustrated in Figure 4.

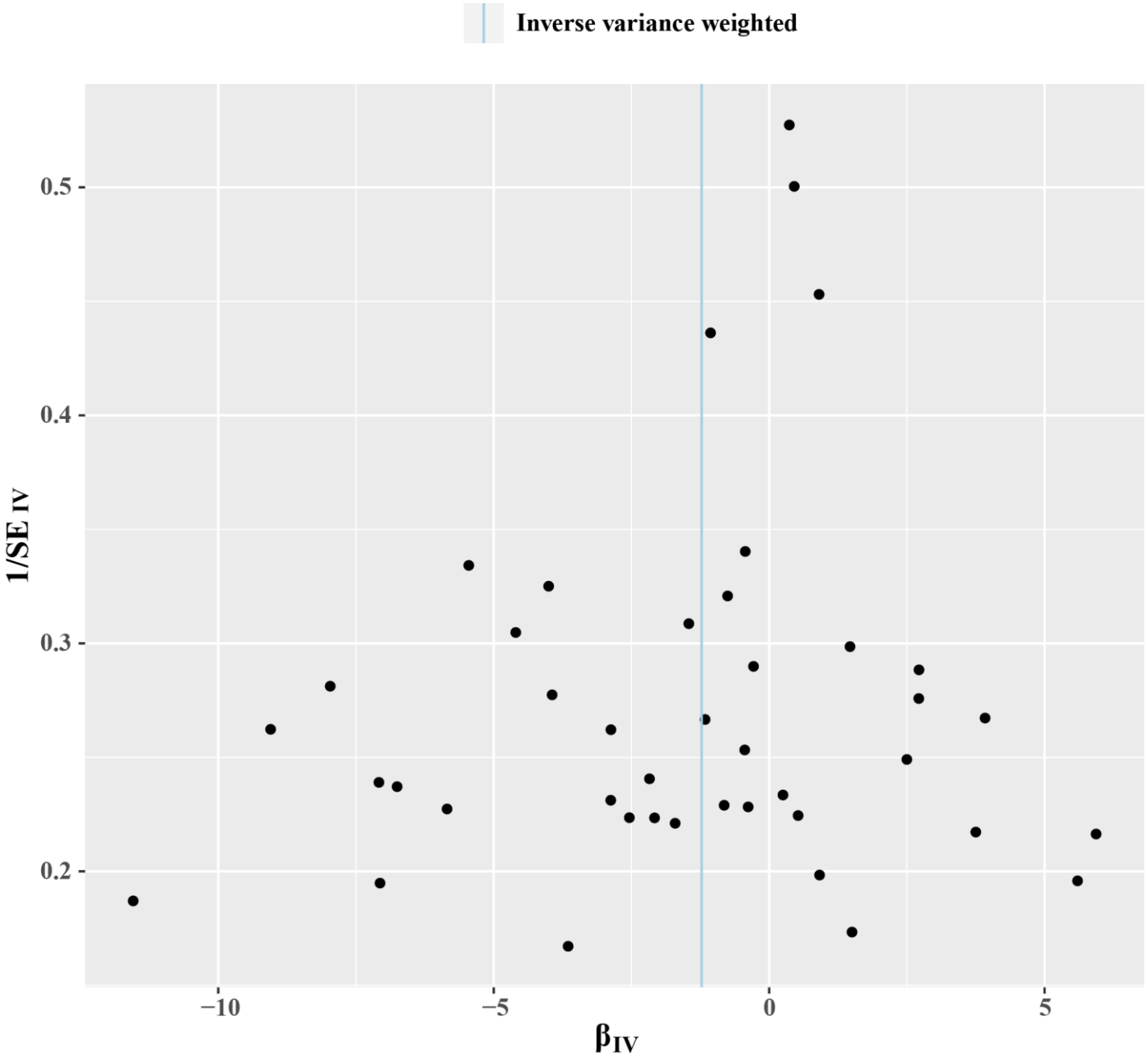

Figure 4. Funnel plot of evaluating heterogeneity. MR: mendelian randomization; SE: standard error.

3.5. Sensitivity Analysis

The "leave-one-out" analysis assessed the impact of each SNP on the outcomes of the MR analysis, revealing no sensitive SNP, as seen in Figure 5.

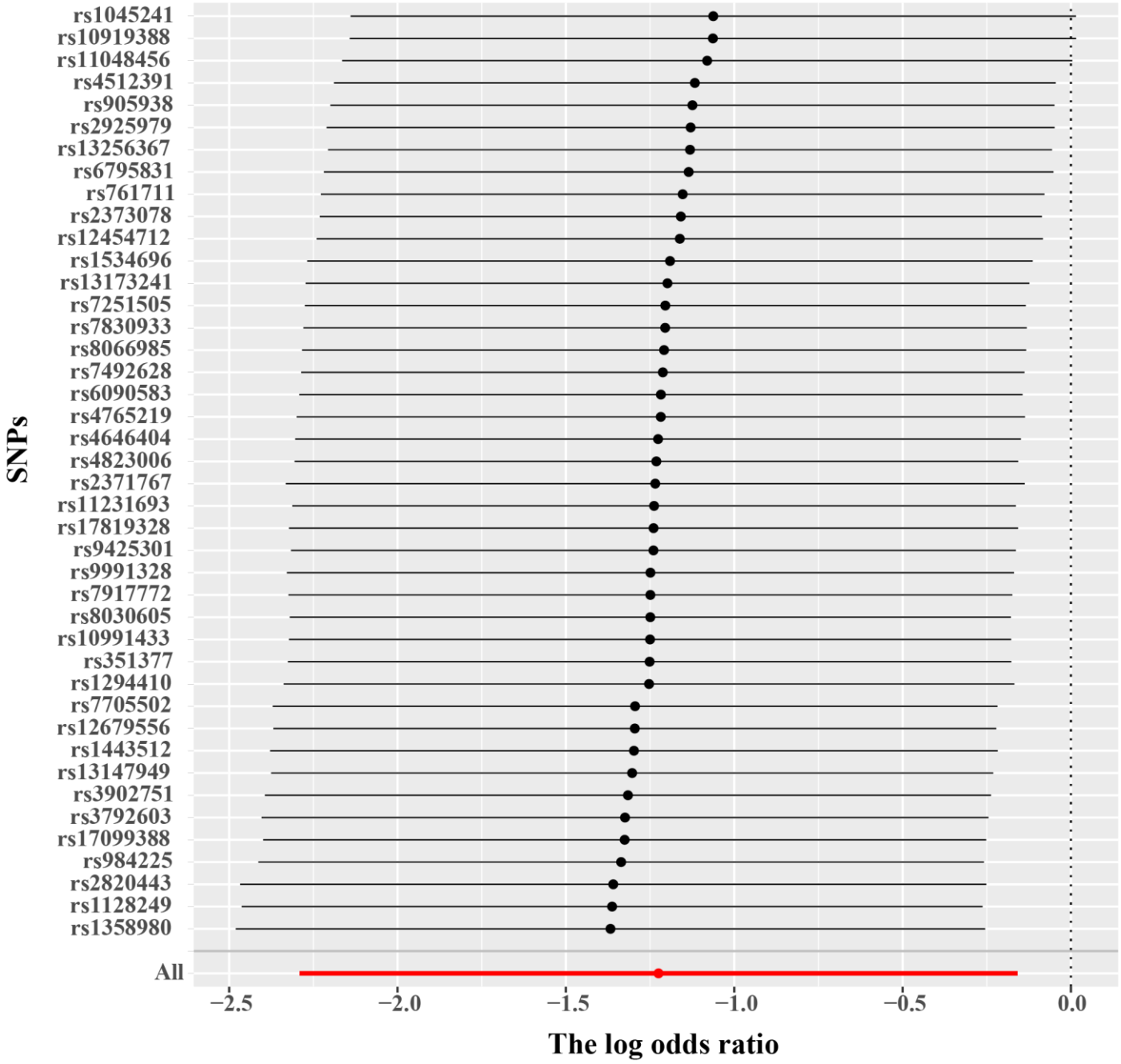

Figure 5. Sensitivity analysis. SNPs: single-nucleotide polymorphisms. The red line represents the weighted combined effect of all SNPs.

4. Discussion

Adverse reactions from blood transfusion can occur due to a variety of factors, including immune system and inflammatory responses [11]. Numerous investigations have showed a correlation between BMI and various allergy responses, identifying BMI as a risk factor for their onset and progression [12,13]. Nonetheless, it remains ambiguous if there is a cause-and-effect relationship between BMI and ABTR. Therefore, we used MR to investigate the potential causal relationship between BMI and the incidence of ABTR. Each MR approach for effect measurement had distinct circumstances, benefits, and drawbacks, resulting in varying proven causal relationships [14]. The inverse variance weighting approach of random effects was frequently regarded as superior to other MR techniques for validating causal associations [15]. The intercept term in the inverse variance weighting method for random effects was constrained to zero, and a weighted linear regression was employed to explore the relationship between genotype and outcome variables, as well as between genotype and exposure factors, thereby summarizing the causal effects of multiple genetic variants [16,17]. Six distinct assessment approaches was utilized in this study for MR analysis, including MR-Egger regression, the weighted median method, inverse variance weighting method, WM method, SM,

and simple median method. The primary approach, IVW analysis, provided evidence corroborating the causal link between BMI and ABTR (OR = 0.29, 95% CI = 0.10–0.85, $P = 0.02$). The effect value β of the WME, WM, SM, and SM analysis techniques aligned with that of IVW. However, the effect value β of the MR-Egger analysis method was contrary to that of IVW. Subsequently, we further validated the causal association between BMI and ABTR through meta-analysis to calculate the combined value of OR and 95% CI. The overall OR (95% CI) was 0.46 (0.23–0.91), indicating a causal connection between exposure components and the outcome. As BMI decreases, the incidence of ABTR rises.

While MR reduced the likelihood of intrinsic bias in observational research, it was vulnerable to pleiotropy [18]. Genetic variation may correlate with several phenotypes, known as pleiotropy, leading to discrepancies in the causal estimates of MR results [19]. The pleiotropy analysis results indicated an absence of horizontal pleiotropy, and the findings were comparatively strong. Heterogeneity analysis evaluates the variability of each SNP and the degree of concordance among the causal estimates of all SNPs. Decreased heterogeneity signifies enhanced dependability of MR results. This study utilized two approaches to evaluate heterogeneity, and both methods indicated that the heterogeneity among instrumental factors based on individual variation was minimal. The funnel plot primarily serves to visually assess the presence of publication bias with more asymmetry suggesting a higher degree of bias. The estimated SNP causal impact shown in this study was almost symmetrical, suggesting stability in the findings and the absence of publication bias. MR research necessitates sensitivity analysis to evaluate the validity of the findings derived from MR studies. We employed the "leave-one-out" method to evaluate the influence of each SNP on the outcomes of MR study. No sensitive SNPs were identified, hence confirming the findings of this study.

This study provided several advantages over epidemiological research. Firstly, the causal link between BMI and ABTR was examined by two-sample MR, utilizing randomly assigned genotypes as IVs to mitigate the impact of confounding factors. Secondly, several MR analytic techniques was used for testing to ensure the reliability and stability of the findings. This study also presented some limitations, which also offered potential directions for future research. Firstly, there may be a issue of overidentification in two-sample MR studies, which could potentially result in an overestimation of the correlation between SNPs and exposure. Secondly, this study solely focused on the correlation between BMI and transfusion adverse responses from a genetic perspective. Nevertheless, no significant connection has been identified in clinical practice, highlighting the need for further research for validation in the future.

5. Conclusions

This study suggests a potential causal relationship between lower BMI and a higher risk of ABTR. Our findings emphasized that BMI could impact transfusion outcomes, indicating that individuals with lower BMI may be more at a risk for ABTR. These insights may aid in enhancing the management and prevention of transfusion-related complications. Additional research is required to confirm these findings and explore the mechanisms involved.

Acknowledgments

The authors are grateful to the study participants and research workers for their participation.

Author Contributions

Conceptualization, Y.Y.; Methodology, S.L.; Software, Y.L.; Validation, S.L., Y.Y.; Formal Analysis, Y.Y.; Investigation, S.L.; Resources, Y.L.; Data Curation, Y.Y.; Writing—Original Draft Preparation, Y.L.; Writing—Review & Editing, Y.Y.; Visualization, Y.L.; Supervision, S.L.; Project Administration, Y.Y.; Funding Acquisition, Y.Y.

Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the First Affiliated of Xi'an Medical University (STUDY20230130) on 26 March 2023.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Funding

The work was financed by the First Affiliated Hospital of Xi'an Medical University (XYFYPT-2023-03).

Declaration of Competing Interest

The authors declared no conflict of interests.

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