Heliyon 10 (2024) e34560

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A mendelian randomization study investigating the causal relationships between 1400 serum metabolites and autoimmune diseases

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ARTICLE INFO

Keywords:
Mendelian randomization analysis
Serum metabolites
Single nucleotide polymorphism
Inverse variance weighted

ABSTRACT

Objective: This study aims to explore the causal relationships between 1400 serum metabolites (SMs) and five autoimmune diseases (Myasthenia gravis [MG], Multiple sclerosis [MS], Systemic lupus erythematosus [SLE], Type 1 diabetes mellitus [T1DM], and Ulcerative colitis [UC]) through Mendelian randomization analysis.

Method: Data on MG, MS, SLE, T1DM, and UC were obtained from the IEU OpenGWAS Project database, while information on 1400 SMs was extracted from GWAS summary statistics provided by Chen et al. Causal relationships were assessed using the inverse variance weighted (IVW), MR-Egger, Weighted Median (WME), and Simple median (SME) methods. The robustness of instrumental variables was verified through computation of the *F*-statistic. Heterogeneity was evaluated using Cochran's Q test and the leave-one-out (LOO) method. Horizontal pleiotropy was assessed using MR-Egger regression and MR-PRESSO.

Result: Following correction of the IVW *P* values using the False Discovery Rate (FDR) method, it was found that increased levels of 5-methyluridine (ribothymidine) (*OR* = 1.191, 95%*CI* 1.086–1.307, *FDR-P* = 0.000) and 2′-deoxyuridine (*OR* = 1.337, 95%*CI* 1.127–1.586, *FDR-P* = 0.001) were found to be correlated with a higher risk of MS. Conversely, the ratio of S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) (*OR* = 0.771, 95%*CI* 0.649–0.916, *FDR-P* = 0.007) was linked to a decreased risk of MS. Levels of 1,2-dilinoleoyl-GPE (18:2/18:2) (*OR* = 0.877, 95%*CI* 0.791–0.974, *FDR-P* = 0.003) appear to be a protective factor for T1DM. No notable correlations between SMs and MG, SLE, or UC. The study detected no heterogeneity or horizontal pleiotropy.

Conclusion: Levels of 5-methyluridine (ribothymidine), 2′-deoxyuridine, and the ratio of S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) can serve as predictors for MS. Similarly, 1,2-dilinoleoyl-GPE (18:2/18:2) levels can be used to predict T1DM. However, no significant causal relationships were found between SMs and MG, SLE, or UC. This observation holds significant clinical implications for crafting tailored preventive and therapeutic approaches for ADs.

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https://doi.org/10.1016/j.heliyon.2024.e34560
Received 19 December 2023; Received in revised form 10 July 2024; Accepted 11 July 2024
Available online 14 July 2024

1. Introduction

Autoimmune disease (AD) represents a category of chronic inflammatory conditions where the immune system becomes dysregulated and autoantigens react, resulting in tissue or system damage. The frequency and occurrence of ADs, such as MG, MS, SLE, T1DM, and UC, have been on the rise recently [1]. ADs encompass both organ-specific and systemic conditions. The organ-specific ADs target pathological damage or dysfunction in particular organs, such as T1DM. Systemic ADs like SLE, on the other hand, result in pathological damage across multiple organs and tissues throughout the body [2]. Currently, some treatment methods for ADs exhibit broad functionality and lack disease specificity, resulting in noticeable side effects [3]. The development of ADs is closely linked to immune system dysfunction and abnormal cytokine expression [4]. Clinical research has demonstrated that the mechanisms underlying ADs are associated with abnormal alterations in SMs. Patients with T1DM exhibited higher levels of serum hypoxanthine and uridine compared to healthy individuals [5], and lipid metabolism disorders were also observed in T1DM [6]. In MS, changes in SMs can trigger an immune response [7]. Ouyang et al. [8] discovered that serum amino acid levels were reduced in SLE patients. Blackmore et al. [9] observed that, compared to the control group, MG patients exhibited up-regulated ketone bodies and short-chain fatty acids, while bile acid metabolites were down-regulated. Additionally, the abundance of metabolites has been identified as a potential indicator for UC pathology [10]. Yet, observational researches frequently face challenges from unknown confounding variables and backward causation, which currently obscure the causal link between SMs and the five ADs (MG, MS, SLE, T1DM, and UC).

Mendelian randomization (MR) employs single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) under the assumption that genetic variations influencing risk factors are randomly allocated at conception, thereby minimizing the influence of reverse causality. This approach offers a more accurate estimation of disease risk [11].

MR can be viewed as a quasi-natural experiment akin to a randomized clinical trial (RCT). Compared to traditional RCT designs, the primary advantage of MR is that SNPs, used as risk factor tools, are randomly assigned, which helps to avoid the impact of potential confounding factors or reverse causality [12]. Additionally, the development of genetic variation is independent of social environment, lifestyle, and other traits, theoretically eliminating the impact of confounding factors [13].

This study utilized a genome-wide association study (GWAS) to collect data, employing MR analysis to explore causal relationships between SMs and five ADs (MG, MS, SLE, T1DM, and UC). This approach aims to provide genetic evidence supporting their association, offering a theoretical foundation and potential clinical value. The results may guide risk prediction and treatment development for these ADs. The study protocol is depicted in Fig. 1.

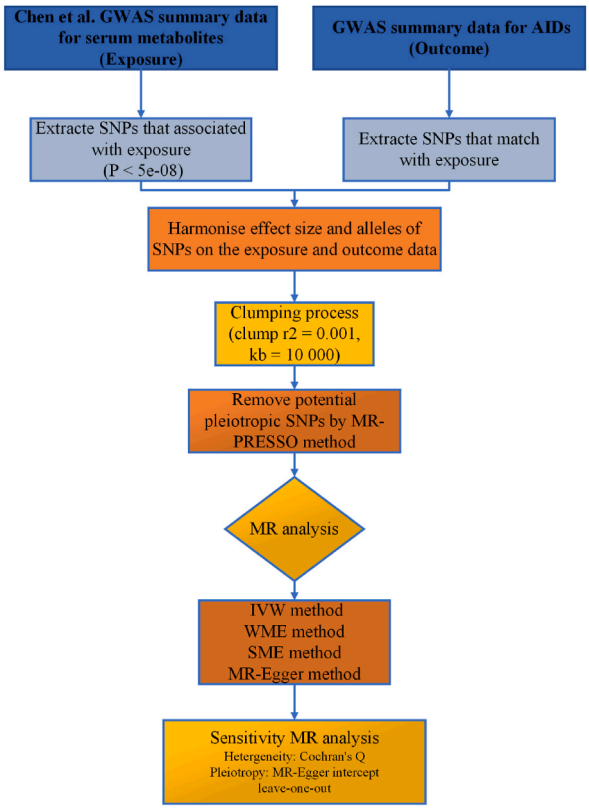

Fig. 1. Protocol of the study procedure.

2. Material and methods

2.1. Data sources

For estimating the effects of SNPs related with SMs, we utilized GWAS summary statistics from Chen et al. (GCST90199621-GCST902010202), encompassing a total of 1400 SMs [14]. Outcome data for the five ADs (MG, MS, SLE, T1DM, and UC) were sourced from the IEU OpenGWAS Project website (gwas.mrcieu.ac.uk). Since this study utilizes publicly accessible data, no further ethical approval or consent was required. The study population's genetic ancestry is of European descent to mitigate potential confounding factors related to race. Supplementary Table 1 provides a detailed overview of the GWAS data sources utilized in this research.

2.2. IV selection

IVs were selected following the hub hypothesis of MR (Fig. 2), with stringent controls as outlined below: Firstly, Genome-wide Significance: SNP loci linked with MG, MS, SLE, T1DM, and UC were screened using a significance threshold of $P < 5 \times 10^{-8}$ to test hypothesis (1). Secondly, Linkage Disequilibrium (LD) Adjustment: Parameters were tuned ($r^2 = 0.001$ and kb = 10,000) to minimize LD effects. SNPs exhibiting strong LD (LD parameter $r^2 \geq 0.001$) were excluded to fulfill hypothesis (2). Thirdly, Phenotypic and Confounding Factor Screening: Phenotypes related to IVs were manually screened using a phenotypic correlation database. SNPs associated with outcomes or confounding factors ($P < 5 \times 10^{-8}$) were omitted. Abnormal SNPs were identified and removed using the MR-PRESSO test to meet hypothesis (3). Fourthly, Alignment of Effect Alleles: Data extraction ensured that exposure and outcome effect values aligned with the same effect allele. Fifthly, *F*-statistics were calculated to assess the correlation hypothesis and determine the explanatory power of IVs for exposure variables. An *F*-statistics value > 10 indicates lower likelihood of violating the correlation hypothesis and introducing weak IV bias. This systematic approach aims to establish robust causal relationships between SMs and the five ADs using MR analysis, ensuring rigorous selection and validation of IVs.

2.3. Statistical analysis

2.3.1. MR analysis

In this study, MR analysis was implemented using the following methods: IVW method served as the primary method to estimate causal effects. Cochran's Q test assessed heterogeneity among IVs influencing the five ADs. In cases where $P < 0.05$, indicating significant heterogeneity, the IVW random-effects model was applied for causal inference. Conversely, if the absence of significant heterogeneity ($P \geq 0.05$), the IVW fixed-effects model was utilized [15]. MR-Egger Regression, WME, and SME methods: These supplementary MR methods were employed to further estimate causal effects [16]. A significance level of $P < 0.05$ was employed to establish a causal relationship between exposure (SMs) and outcomes (MG, MS, SLE, T1DM, and UC) [17]. This comprehensive approach ensures rigorous evaluation of these relationships, incorporating various MR techniques to enhance reliability and validity of findings.

2.3.2. Sensitivity analysis

MR-Egger regression and MR-PRESSO methods were employed to evaluate horizontal pleiotropy, which evaluates whether IVs affect outcomes through pathways other than the exposure of interest. A regression intercept *P* value > 0.05 indicates no evidence of such pleiotropy [18]. The LOO method was utilized to examine the impact of individual SNPs on the causal relationship. Each SNP was sequentially removed, and the combined effect estimate of the remaining SNPs was recalculated to assess the influence of each SNP on

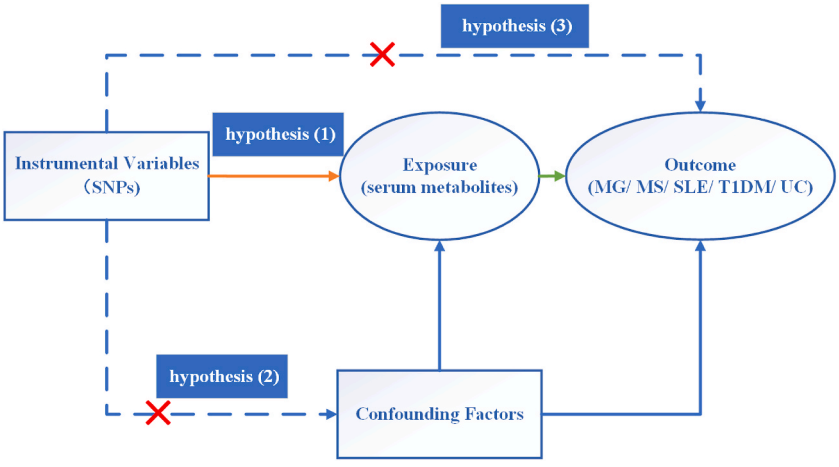

Fig. 2. Hypothesis of MR analysis.

the overall MR analysis results [19]. These sensitivity analyses aim to ensure the robustness of the MR findings by detecting and addressing potential biases such as horizontal pleiotropy and the influence of individual SNPs.

2.3.3. Statistical software

Statistical analyses utilized the "TwoSampleMR" and "MRPRESSO" software packages. FDR correction was applied to adjust the *P* values derived from the IVW method, addressing multiple testing concerns.

3. Results

3.1. IV selection

IVs in this study were selected based on stringent criteria. Specifically, the *F*-statistic corresponding to each SNP was required to be greater than 10, ensuring exclusion of weak IVs from the MR analysis. This criterion aimed to bolster the reliability and validity of the MR findings (Fig. 3A–E, Supplementary Table 2). This rigorous selection process aimed to ensure that only IVs with strong explanatory power for exposure variables were included in the analysis, thereby minimizing potential biases and strengthening the causal inference between SMs and ADs.

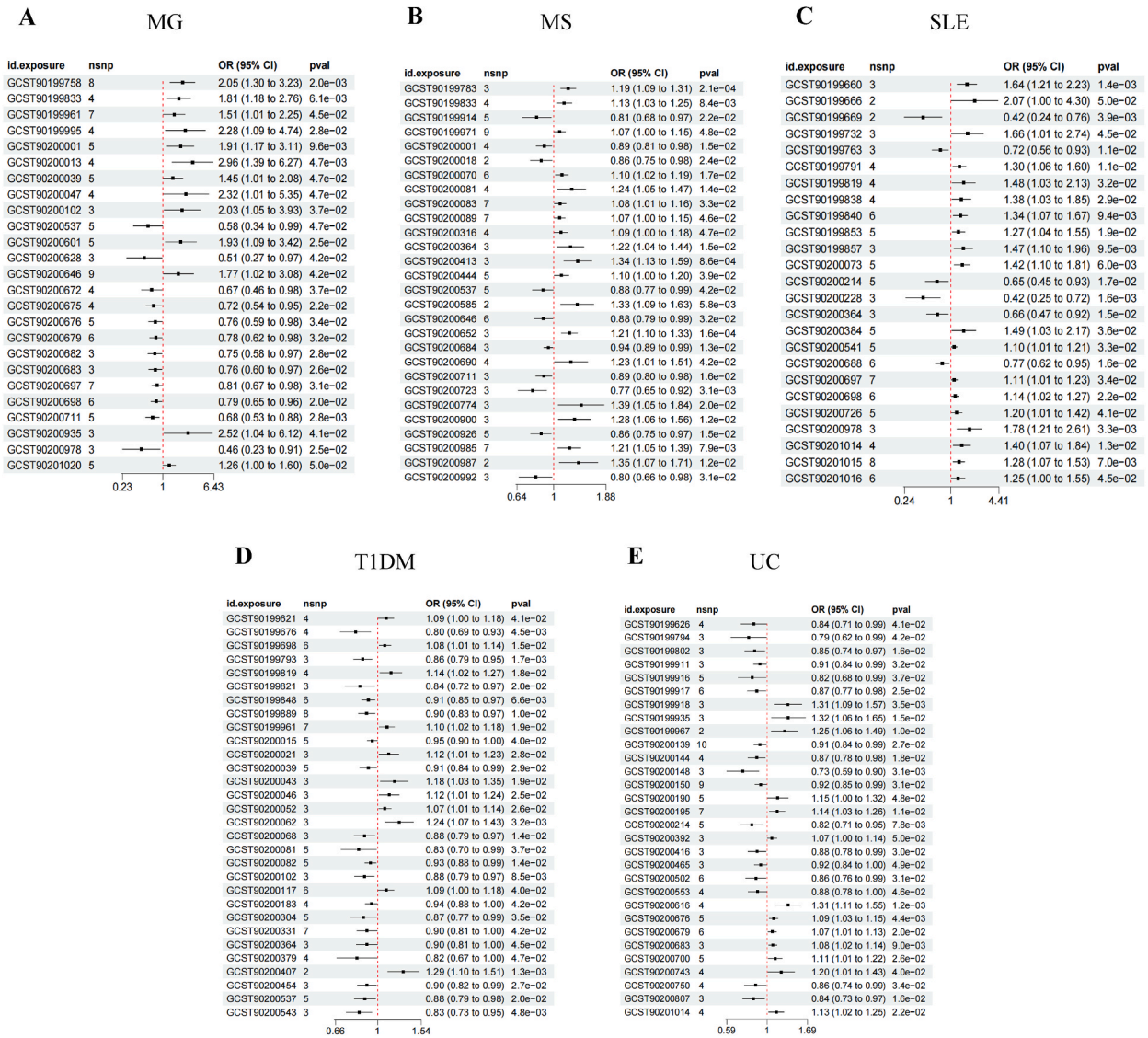

Fig. 3. Forest plot of the MR findings for the five ADs. (A) MG; (B) MS; (C) SLE; (D) T1DM; (E) UC.

3.2. MR analysis

In the four models examined, multiple SMs exhibited significant causal relationships with the five ADs. Specifically, 25 SMs were found to be significantly correlated with MG, 28 with MS, 25 with SLE, 30 with T1DM, and 30 with UC (Fig. 4A–E, Supplementary Table 3). The significant associations between these identified SMs and ADs are detailed in Supplementary Fig. 1. This analysis highlights the diverse metabolic factors potentially influencing ADs pathogenesis, providing valuable insights into their underlying mechanisms.

Following FDR correction for significant causality results, it was determined that SMs were not associated with the onset of MS, SLE, and UC. However, specific findings indicated significant causal relationships for certain SMs: Higher levels of 5-methyluridine (ribothymidine) (*OR* = 1.191, 95 % *CI* 1.086–1.307, *FDR-P* = 0.000) and 2′-deoxyuridine (*OR* = 1.337, 95%*CI* 1.127–1.586, *FDR-*

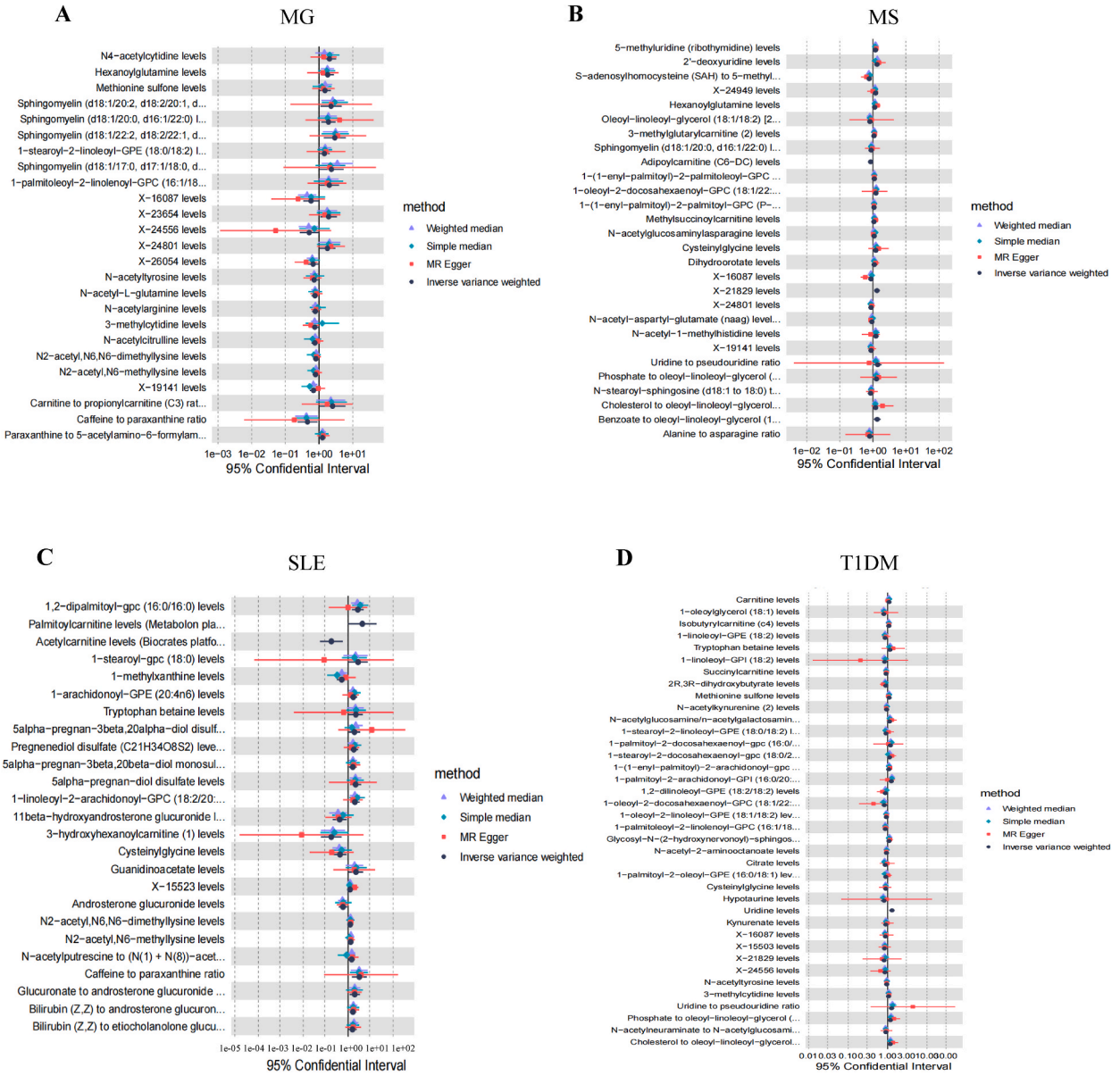

Fig. 4. Forest plot of MR estimates of the causal impacts of serum metabolites on the five ADs
(A) MG;
(B) MS;
(C) SLE;
(D) T1DM;
(E) UC.

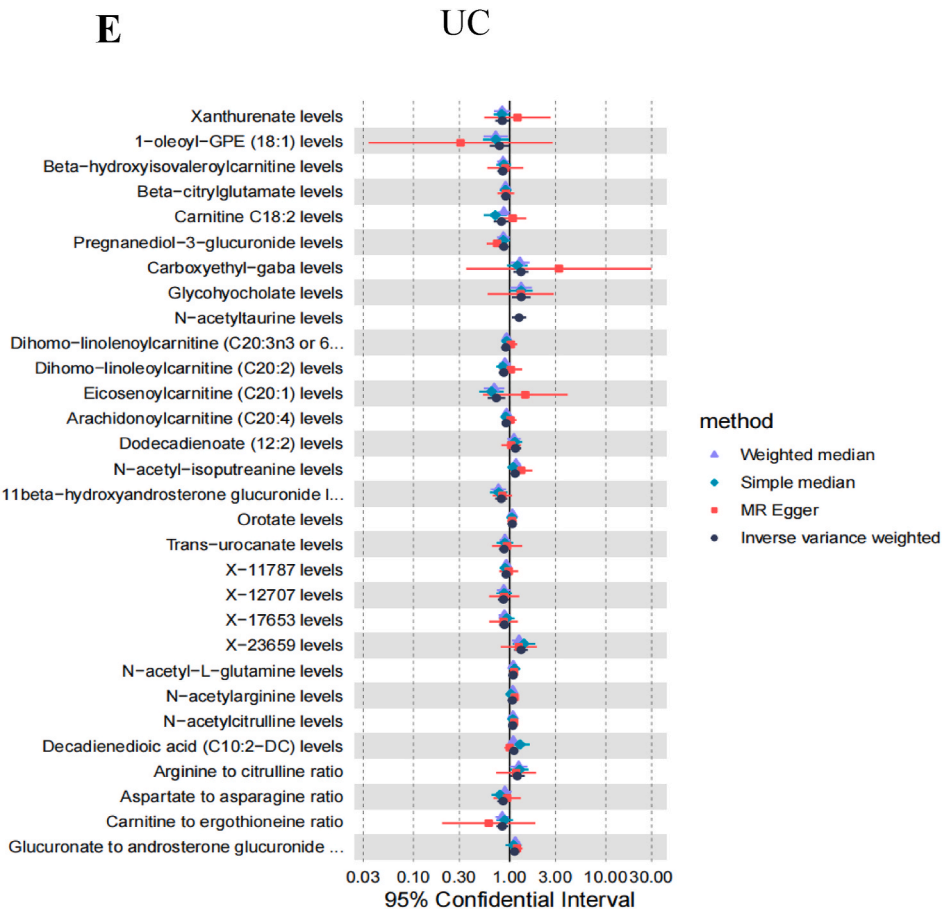

Fig. 4. (*continued*).

$P = 0.001$) were correlated with elevated MS susceptibility, while a higher ratio of S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) (*OR* = 0.771, 95 % *CI* 0.649–0.916, *FDR-P* = 0.005) was related with decreased MS risk. Elevated levels of 1,2-dilinoleoyl-GPE (18:2/18:2) (*OR* = 0.877, 95 % *CI* 0.791–0.974, *FDR-P* = 0.003) were connected to reduced T1DM risk (Fig. 5A–D, Supplementary Table 3). Scatter plots illustrated consistent directions across all four models (Fig. 6A–D). These findings underscore the connections between specific SMs and ADs, highlighting their potential roles in disease pathogenesis.

3.3. Sensitivity analysis

The findings of Cochran's Q test and MR-Egger intercept indicated *P* values above 0.05, suggesting no evidence of potential horizontal pleiotropy or heterogeneity across the analyses. Similarly, MR-PRESSO yielded consistent findings (Supplementary Table 4). Funnel plots indicated minimal likelihood of influential factors affecting causality (Fig. 7A–D). Additionally, LOO analysis demonstrated that the overall findings were not motivated by any single SNP, as no individual SNP had a substantial impact on the outcomes (Fig. 8A–D). These sensitivity analyses affirm the strength of the MR findings, reinforcing the validity of the observed causal links between SMs and ADs.

4. Discussion

ADs arise from an intricate interaction of genetic, epigenetic, immune, and environmental factors, with genetic susceptibility playing a pivotal role. This study identified that levels of 5-methyluridine (ribothymidine), 2′-deoxyuridine, and the S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio can serve as predictors for MS. Additionally, levels of 1,2-dilinoleoyl-GPE (18:2/18:2) were identified as predictors for T1DM. However, no significant causal relationships between SMs and MG, SLE, and UC were observed. Uridine, to which 5-methyluridine (ribothymidine) and 2′-deoxyuridine belong, plays a critical role in biosynthesis, glycogen deposition, protein and lipid glycosylation, as well as in maintaining body temperature and circadian rhythm, and is closely associated with various metabolic diseases [20]. Uridine exerts influences on blood glucose homeostasis, islet cell function, and fat metabolism through various indirect mechanisms. For instance, postprandial bile release triggered by eating can facilitate uridine

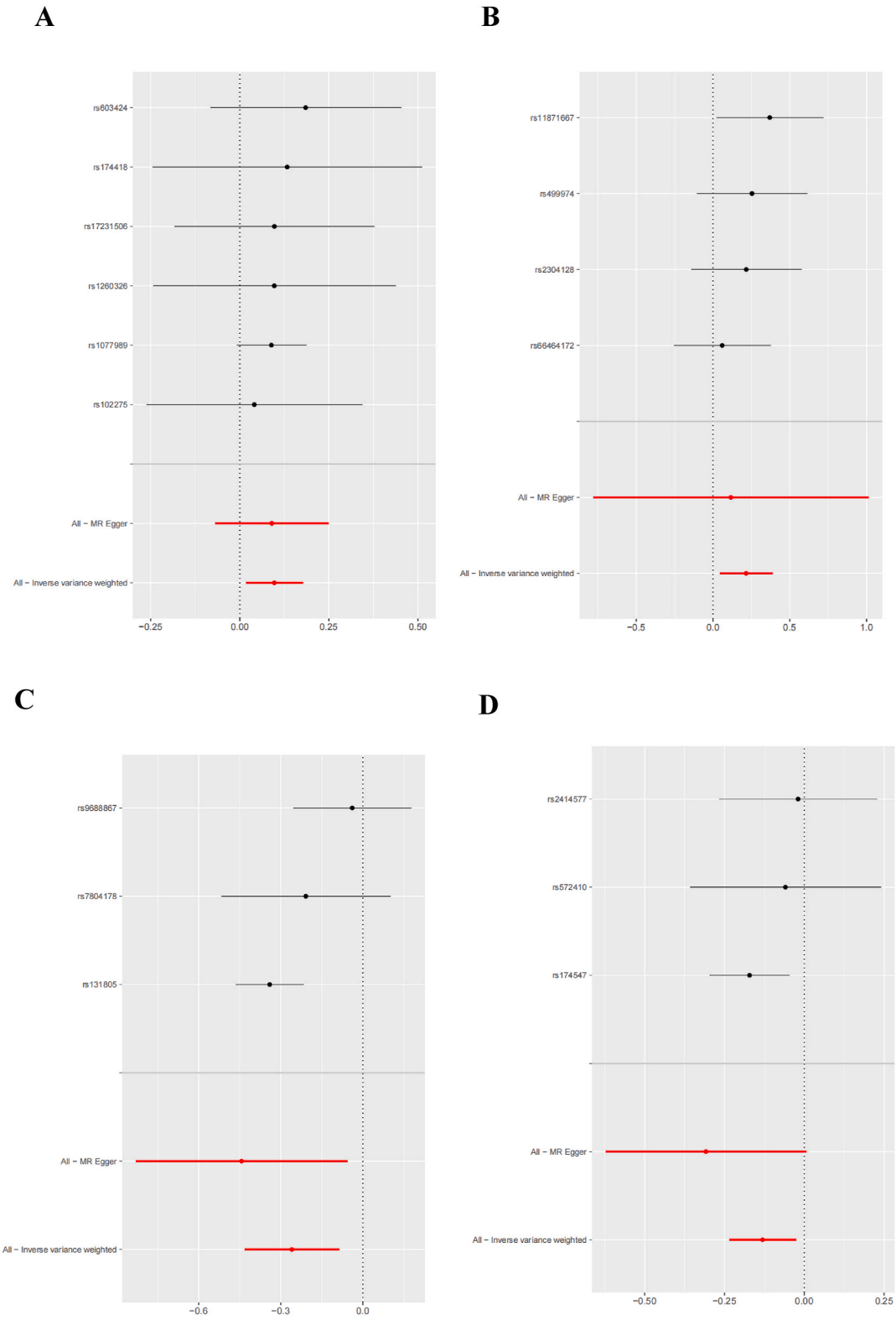

Fig. 5. Forest plot of the results of single SNP MR analysis
(A) 5-methyluridine (ribothymidine) levels;
(B) 2′-deoxyuridine levels;
(C) S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio;

(D) 1,2-dilinoleoyl-GPE (18:2/18:2) levels;
The black dot indicates ADs associated with elevated standard deviations (SD) in serum metabolites. The red dot represents the causal estimation of all combinations of SNPs using various MR methods. The horizontal line segment denotes the 95 % confidence interval (CI). Visualizations include the influence of the IVW causal estimate and the disproportionate impact on the overall estimate (red horizontal line) due to the exclusion of a single variant (black horizontal line).

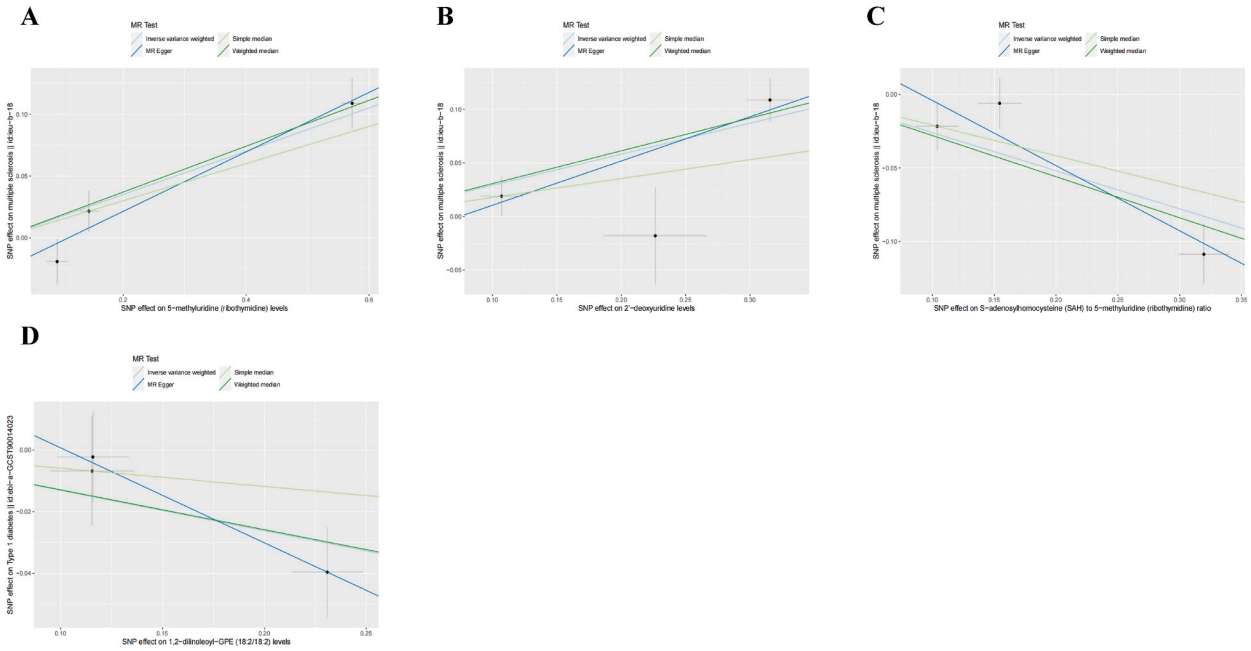

Fig. 6. Scatter plots of the analysis of SNPs
(A) 5-methyluridine (ribothymidine) levels;
(B) 2′-deoxyuridine levels;
(C) S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio;
(D) 1,2-dilinoleoyl-GPE (18:2/18:2) levels;
The light blue line represents the IVW approach, while the blue line denotes the MR-Egger method. The green line corresponds to the WME method, and the light green line represents the SME method.

excretion, thereby reducing plasma uridine levels and enhancing insulin sensitivity [21]. Additionally, studies by Faizan Ahmad et al. have highlighted the anti-angiogenic properties of 2′-deoxyuridine [22]. S-adenosylhomocysteine (SAH) serves as a metabolic intermediate in the synthesis of cysteine and adenosine. The relationship between increased cysteine levels and the pathogenesis of MS remains incompletely understood. Cysteine may contribute to MS through direct or indirect mechanisms, including structural and functional damage to vascular endothelial cells and genotoxic effects. It enhances lipid peroxidation, stimulates proliferation and migration of vascular smooth muscle cells (VSMCs), alters platelet function, affects the coagulation system, and facilitates vascular calcification. Recent research suggests that cysteine may also act as an inflammatory stimulus, triggering inflammatory responses [23]. Cysteine plays a significant role in activating the immunological system and inducing the expression of inflammatory factors. It induces the expression of chemokines and chemokine receptors in human vascular cells and monocytes, such as IL-10β, IL-6, IL-8, IL-12, IL-18, IL-1 receptor antagonist, C-reactive protein, adhesion molecules, and matrix metalloproteinases (MMPs) [24]. Chronic inflammation mediated by cellular immunity is critically involved in the development and progression of MS and its complications [25]. However, the specific relationship between levels of 5-methyluridine (ribothymidine) and 2′-deoxyuridine and MS remains unexplored. Interestingly, 1,2-dilinoleoyl-GPE (18:2/18:2) has been linked to an increased risk of Crohn's disease [10]. While there has been no prior report associating 1,2-dilinoleoyl-GPE (18:2/18:2) with T1DM, its potential role in this context could represent a novel and suggestive discovery.

In summary, the study suggests that elevated levels of 5-methyluridine (ribothymidine) and 2′-deoxyuridine may contribute to the development of MS, while the ratio of S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) could potentially mitigate MS progression. These findings propose these metabolites as potential auxiliary diagnostic markers for MS and as tools to assess prognosis. Similarly, levels of 1,2-dilinoleoyl-GPE (18:2/18:2) may alleviate the onset, progression, and prognosis of T1DM. This suggests promising avenues for utilizing these metabolites in clinical settings to better understand and manage MS and T1DM.

This study boasts multiple advantages. Firstly, it leverages a substantial sample size, thereby minimizing the influence of extraneous variables on the findings. Secondly, by employing MR analysis, the study circumvents potential biases inherent in observational

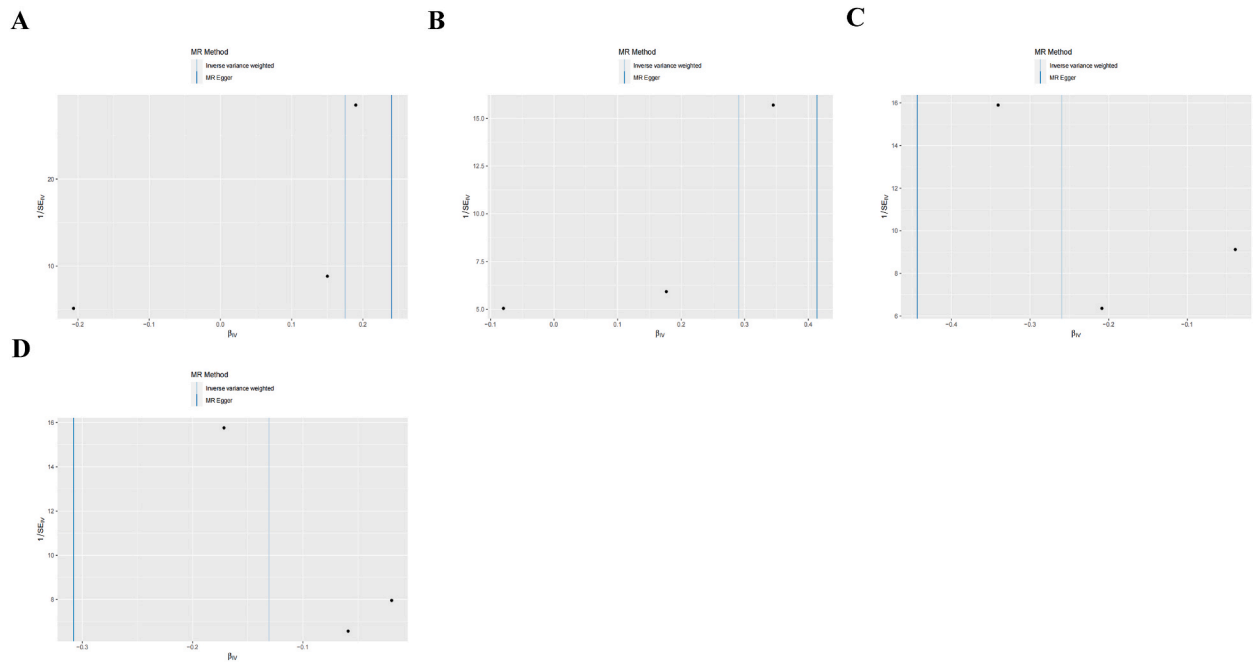

Fig. 7. Funnel plots of sensitivity analysis
(A) 5-methyluridine (ribothymidine) levels;
(B) 2′-deoxyuridine levels;
(C) S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio;
(D) 1,2-dilinoleoyl-GPE (18:2/18:2) levels;
The WME method is depicted by the purple triangle, the SME method by the green diamond, the MR-Egger method by the red square, and the IVW method by the grey circle.

research, ensuring high scientific rigor and reliability. Thirdly, it represents the first comprehensive exploration of the genetic-level relationships between 1400 SMs and five ADs. While previous research by Yu et al. [26] explored similar relationships, our study significantly expands upon this work by applying a stringent significance threshold (5e-08), thereby enhancing result robustness. Furthermore, sensitivity analyses were conducted to mitigate biases, allowing for unique insights and mechanisms distinct from prior research. Fourthly, unlike previous MR analyses focusing on single exposure factors, our study examines the complex landscape of SMs, presenting substantial analytical challenges and workload.

Despite its strengths, this study also faces several limitations. Firstly, the study cohort comprises individuals exclusively from Europe, potentially restricting the applicability of findings to other geographical and ethnic groups. Secondly, utilizing data from the IEU OpenGWAS Project restricts the ability to investigate potential nonlinear relationships or stratification effects related to age, health status, or gender. Thirdly, some SMs showing causal relationships with the five ADs lack known functional structures, hindering further detailed analysis and research. Fourthly, despite leveraging the largest available GWAS dataset on SMs, future research should consider expanding the sample size further to achieve a more precise assessment of the genetic impact of SMs. These limitations highlight areas where future studies could focus to enhance the applicability and depth of understanding regarding the role of SMs in ADs.

5. Conclusion

This study represents the initial identification of genetic-level associations between 1400 SMs and five ADs. Genetically predicted SMs showed associations with MS and T1DM. Specifically, elevated levels of 5-methyluridine (ribothymidine) and 2′-deoxyuridine, as well as the ratio of S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine), were identified as potential predictors of MS risk. Conversely, 1,2-dilinoleoyl-GPE (18:2/18:2) levels were identified as a potential predictor of T1DM risk. However, no significant correlations were found between SMs and MG, SLE, or UC.

Ethics approval and consent to participate

Not applicable.

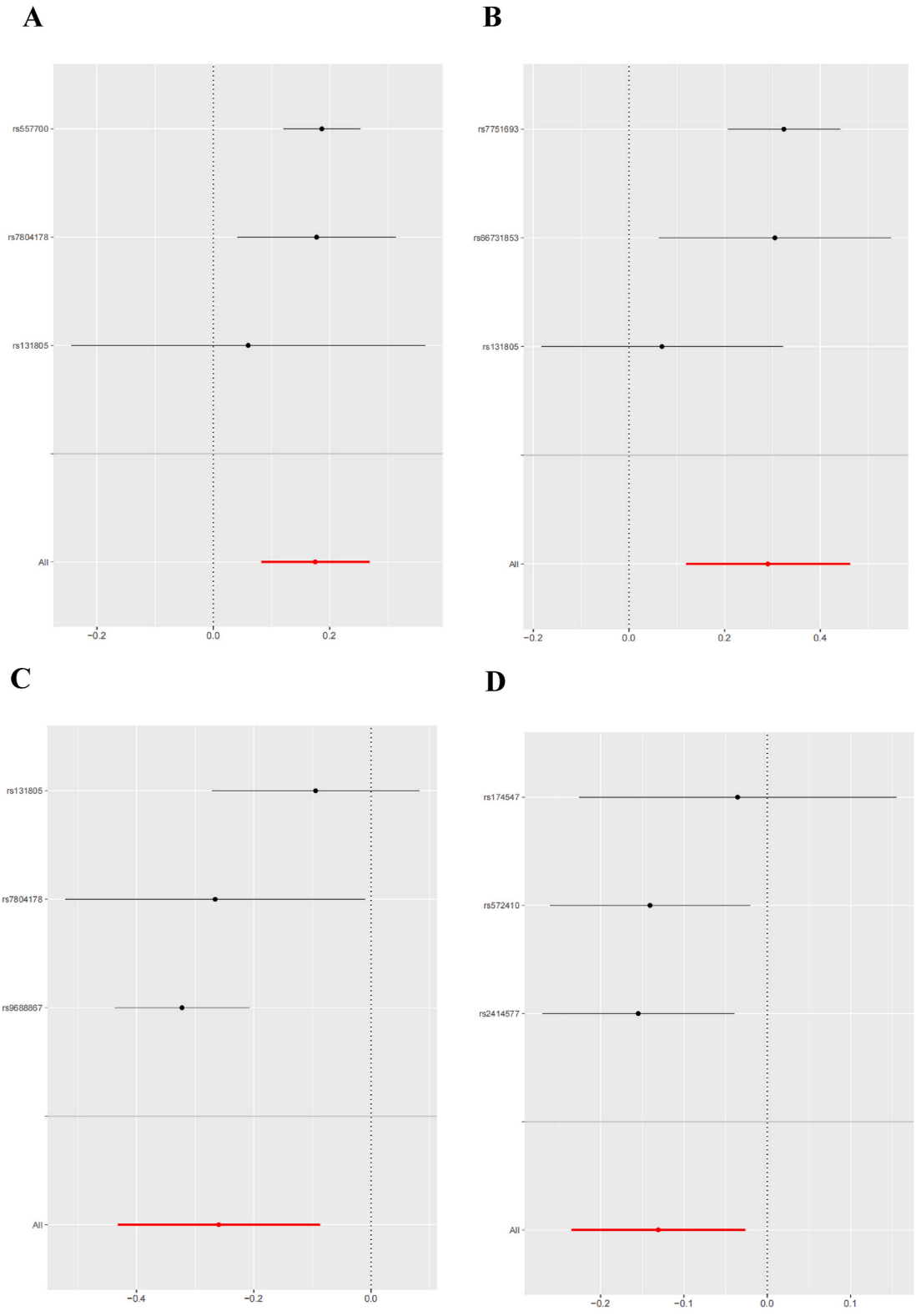

Fig. 8. Forest plots depicting LOO sensitivity analysis
(A) 5-methyluridine (ribothymidine) levels;
(B) 2′-deoxyuridine levels;
(C) S-adenosylhomocysteine (SAH) to 5-methyluridine (ribothymidine) ratio;

(D) 1,2-dilinoleoyl-GPE (18:2/18:2) levels;
The black dot represents the ADs with increased standard deviation (SD) in the serum metabolites. The red dot represents the causal estimation of all SNP combinations by different MR methods. The horizontal line segment represents 95%*CI*. The IVW causal estimate and how the overall estimate (red horizontal line) was disproportionately driven, which is influenced by the removal of a single variant (black horizontal line), were visualized.

Consent for publication

Not applicable.

Funding

Funding for this study was provided by the National Natural Science Foundation of China (82174293).

Data availability statement

The novel contributions presented in the study are incorporated in the article/supplementary material.

CRediT authorship contribution statement

Siyuan Song: Data curation, Conceptualization. **Qiling Zhang:** Formal analysis, Data curation. **Jiangyi Yu:** Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors wish to acknowledge the IEU OpenGWAS Project for their support of this study.

Abbreviations

ADs	Autoimmune diseases
CI	confidence interval
FDR	False discovery rate
MG	Myasthenia gravis
MMPs	matrix metalloproteinases
MR	Mendelian randomization
SME	Simple median
SMs	Serum metabolites
T1DM	Type 1 diabetes mellitus
UC	Ulcerative colitis
VSMCs	vascular smooth muscle cells
WM	Weighted median

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34560.

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