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Glucosamine supplementation contributes to reducing the risk of type 2 diabetes: Evidence from Mendelian randomization combined with a meta-analysis

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Abstract

Objective: Observational studies on glucosamine supplementation and type 2 diabetes risk have shown inconsistent results, necessitating the use of Mendelian randomization to clarify the true causal relationship.

Methods: The glucosamine supplementation–related genome-wide association study dataset was obtained from the MRC Integrative Epidemiology Unit consortium, whereas type 2 diabetes–related genome-wide association study datasets were obtained from the FinnGen consortium (discovery) and Xue et al.'s meta-analysis (validation). Two-sample Mendelian randomization analyses were performed separately in the discovery and validation datasets, followed by meta-analysis and multivariable Mendelian randomization analyses to verify the robustness of the results of two-sample Mendelian randomization. The estimation of the causal relationship was conducted through the inverse variance weighted method.

Results: Glucosamine supplementation exhibited a significant protective effect against type 2 diabetes, as identified by two-sample Mendelian randomization analysis in the FinnGen consortium (odds ratio: 0.13, 95% confidence interval: 0.02–0.89) and validated in Xue et al.'s meta-analysis (odds ratio: 0.06, 95%; confidence interval: 0.01–0.29). A combined meta-analysis (odds ratio: 0.08, 95%; confidence interval: 0.02–0.27) of the results of two-sample Mendelian randomization confirmed the robustness of these findings. Additionally, multivariable Mendelian

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randomization analysis (odds ratio: 0.12, 95%; confidence interval: 0.02–0.94), after adjusting for confounding factors, supported the results of two-sample Mendelian randomization. No evidence of heterogeneity or pleiotropy was observed.

Conclusion: Overall, our results revealed that genetically predicted glucosamine supplementation was inversely associated with the risk of type 2 diabetes, highlighting the potential importance of glucosamine supplementation in preventing type 2 diabetes.

Keywords

Type 2 diabetes, glucosamine, Mendelian randomization, causal relationship, genome-wide association study

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Introduction

As the global population ages, the incidence of type 2 diabetes (T2D) is rising, with the prevalence rate approaching 10% worldwide, imposing a substantial burden on medical systems and the society.[1,2] T2D, the most common type of diabetes, accounts for 90%–95% of all diabetes cases.[3,4] T2D is primarily caused by insulin resistance, which refers to the decreased metabolic responsiveness and sensitivity of cells to insulin.[5–7] Consequently, alleviating insulin resistance is crucial in preventing the onset of T2D. Previous studies have indicated an association between glucosamine supplementation and insulin resistance[8–10]; however, there is insufficient evidence regarding the causal relationship between glucosamine supplementation and T2D.

Glucosamine, a common over-the-counter dietary supplement, is widely recommended for the management of osteoarthritis and joint pain.[11,12] However, existing evidence linking glucosamine supplementation to T2D remains limited and controversial. According to Pham et al., at doses used for oral treatment of osteoarthritis in humans, glucosamine exacerbated insulin resistance among individuals with T2D.[13] In contrast, Simon et al. reported that glucosamine had no impact on insulin sensitivity in healthy participants, those with diabetes, or those with impaired glucose tolerance at any oral dose level.[14] Furthermore, a recent prospective study revealed that glucosamine use was associated with a lower risk of developing T2D.[15]

Given the widespread use of glucosamine as a dietary supplement and the prevalence of T2D within the population, it is crucial to clarify the true causal relationship between them. Mendelian randomization (MR) is an emerging method that utilizes genetic variants, usually single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to investigate a causal relationship. Genetic variants are randomly allocated at conception, analogous to the random assignment of treatment in randomized controlled trials, thereby reducing the influence of confounding factors.[16] Furthermore, as genetic variants are not affected by disease status, MR can avoid the interference of reverse causality.[17] Therefore, we conducted an MR study to evaluate the causal relationship between glucosamine supplementation and T2D by analyzing the summary-level genome-wide association study (GWAS) datasets of glucosamine supplementation and T2D.

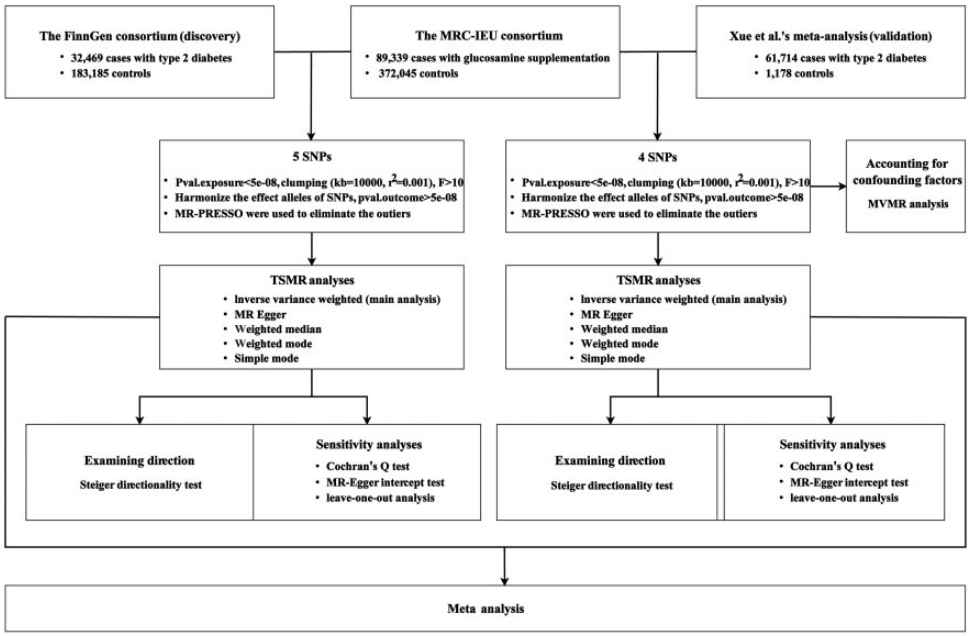

Figure 1. The MR study design. MR: Mendelian randomization; TSMR: two-sample Mendelian randomization; MVMR: multivariable Mendelian randomization; MRC-IEU: MRC Integrative Epidemiology Unit; SNPs: single nucleotide polymorphisms.

Materials and methods

Study design

The overall study design is illustrated in Figure 1. We conducted two-sample MR (TSMR) to assess the causal relationship between glucosamine supplementation and T2D in two independent population-scale T2D GWAS datasets. For valid causal inference, the MR study relied on three main assumptions about IVs: (a) relevance assumption (the IVs should be strongly associated with the exposure); (b) independence assumption (the IVs should not be associated with any confounding factors of the exposure–outcome relationship); and (c) exclusion restriction assumption (the IVs should affect the risk of the outcome only through exposure, not via alternative pathways). We utilized the T2D GWAS dataset from the FinnGen consortium, featuring a large sample size, as the discovery dataset, and the T2D GWAS dataset of Xue et al.'s meta-analysis as the validation dataset. Subsequently, meta-analysis was conducted on the TSMR estimates from the discovery and validation phases under a fixed-effects model. Furthermore, multivariable MR (MVMR) was performed using the summary-level GWAS datasets in the validation phase to test the independence of the causal relationship between glucosamine supplementation and T2D after accounting for potential confounding factors. The study was reported based on recommendations by the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) as well as Reports and Guidelines for Mendelian Randomization Analysis (Supplement Tables S1 and S2).[18,19]

Data sources

The summary-level GWAS dataset of glucosamine supplementation (ukb-b-11535) was obtained from the MRC Integrative Epidemiology Unit (MRC-IEU) consortium, which consisted of 89,339 cases and 372,045 controls. The summary-level GWAS dataset of T2D utilized in the discovery phase originated from the FinnGen consortium, which comprised 32,469 cases and 183,185 controls (finn-b-E4_DM2), whereas that utilized in the validation phase originated from Xue et al.'s meta-analysis, comprising 61,714 cases and 1178 controls (ebi-a-GCST006867).[20]

Other GWAS datasets utilized in our study included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides with 187,167, 173,082, 187,365, and 177,861 participants, respectively, from the Global Lipids Genetics Consortium (GLGC; HDL-C: ieu-a-299, LDL-C: ieu-a-300, total cholesterol: ieu-a-301, triglycerides: ieu-a-302)[21]; coronary artery disease with 141,217 participants (42,096 cases and 361 controls) from Nikpay et al.'s meta-analysis (ebi-a-GCST003116)[22]; body mass index with 681,275 participants from the Genetic Investigation of Anthropometric Traits (GIANT) consortium (ieu-b-40)[23]; smoking initiation with 607,291 participants (311,629 cases and 321,173 controls) from the GWAS and Sequencing Consortium of Alcohol and Nicotine Use (GSCAN) consortium (ieu-b-4877)[24]; and alcohol consumption with 112,117 participants from the UK Biobank consortium (ieu-a-1283).[25]

All abovementioned GWAS datasets were of European ancestry or mainly comprised data from European ancestry, and they were available from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). Our study exclusively utilized publicly available summary-level GWAS datasets, thereby obviating the need for ethical approval and informed consent.

IVs selection

SNPs significantly associated ($P < 5 \times 10^{-8}$) with glucosamine supplementation were selected as IVs from the relevant GWAS dataset. First, we filtered the IVs for linkage disequilibrium (the linkage disequilibrium correlation coefficient $[r^2] > 0.001$) and discarded variants located within a 10,000 kb distance from other IVs exhibiting a stronger association. If $r^2 = 1$, it denotes that the two loci are in complete linkage disequilibrium, indicating a nonrandom association between them. Conversely, if $r^2 = 0$, it suggests that the two loci are in complete linkage disequilibrium and coinherited. Subsequently, we excluded IVs that were significantly associated ($P < 5 \times 10^{-8}$) with T2D. F statistics were calculated for each single nucleotide polymorphism (SNP) to assess the strength of the IVs. An F-statistic less than 10 indicated evidence of weak instrument bias,[26] which compromised the estimation of causal effects.[27,28] Therefore, SNPs with an F-statistic below 10 were excluded. Additionally, we employed Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) ($P < 0.05$) to detect outliers.[29]

MR analysis

The investigation of the causal relationship was conducted through the inverse variance weighted (IVW) method under a fixed-effects model,[30–32] supplemented with four MR analyses, including MR Egger, weighted median, weighted mode, and simple mode. After TSMR analyses, sensitivity analyses were conducted to assess the validity and robustness of the results, incorporating heterogeneity test (Cochran's Q test),

pleiotropy test (MR Egger intercept test), and leave-one-out analysis.

The IVW method was employed under a fixed-effects model if no significant heterogeneity was detected (P of Cochran's Q test ≥ 0.05); otherwise, a random-effects model was utilized.[33,34] A significantly nonzero intercept in the MR Egger method implies the existence of pleiotropic effects (P of MR Egger intercept < 0.05).[35] Leave-one-out analysis, which recalibrates the results by removing SNPs one by one, was performed to identify outliers with significant influence on the causal effect. In addition, we used the Steiger directionality test to investigate the direction of the causal relationship between glucosamine supplementation and T2D. Moreover, the meta-analysis of IVW results was employed to combine the TSMR estimates from the discovery and validation phases ($I^2 < 50\%$: fixed-effects model; $I^2 \geq 50\%$: random-effects model).

We considered the results as significant when they fulfilled the following criteria: (a) the directions of the estimates obtained by all five MR methods (IVW, MR Egger, weighted median, weighted mode, and simple mode) were consistent; (b) the P-value for the IVW method was less than 0.05; and (c) there was no significant pleiotropy or heterogeneity detected.

Although a range of statistical methods have been employed in the sensitivity analyses, we performed confounding analyses via LDlink (https://ldlink.nih.gov/) to explore the traits significantly related to the selected SNPs. To assess the robustness of our results, MVMR analyses were performed with adjustments for potential confounding factors identified by confounding analyses.

The R packages 'ieugwasr' (version 1.0.1, available at https://mrcieu.github.io/ieugwasr/) and 'TwosampleMR' (version 0.6.6, available at https://github.com/MRCIEU/TwoSampleMR) were used for univariate and multivariate MR analyses. The R package 'MR-PRESSO' (version 1.0, available at https://github.com/rondolab/MR-PRESSO) was used for sensitivity analysis. The R package 'Meta' (version 6.5-0, available at https://cran.r-project.org/web/packages/meta/index.html) was utilized for meta-analysis. Additionally, the R packages 'grid' (a base package included in the R distribution) and 'forestploter' (version 1.1.0, available at https://cran.r-project.org/web/packages/forestploter/index.html) were used for plotting. All these R packages were executed in R version 4.2.3 software. The threshold of significance was $P = 0.05$.

Results

Identification and validation of the causal effect of glucosamine supplementation on T2D

Based on the criteria for selecting IVs, five and four independent SNPs were ultimately selected as IVs for glucosamine supplementation in the discovery and validation phases, respectively (Supplement Table S3). The F-statistic for each SNP was greater than 10, indicating no evidence of weak instrument bias.

As shown in Figure 2, TSMR analyses identified a significant causal relationship between genetically predicted glucosamine supplementation and a reduced risk of T2D in the discovery phase using the FinnGen consortium (odds ratio (OR): 0.13, 95% confidence interval (CI): 0.02–0.89, $P = 0.0380$; IVW), which was subsequently validated in the validation phase using Xue et al.'s meta-analysis (OR: 0.06, 95% CI: 0.01–0.29, $P = 0.0005$; IVW).

Sensitivity analysis in the discovery and validation phases revealed no evidence of heterogeneity or pleiotropy, and the

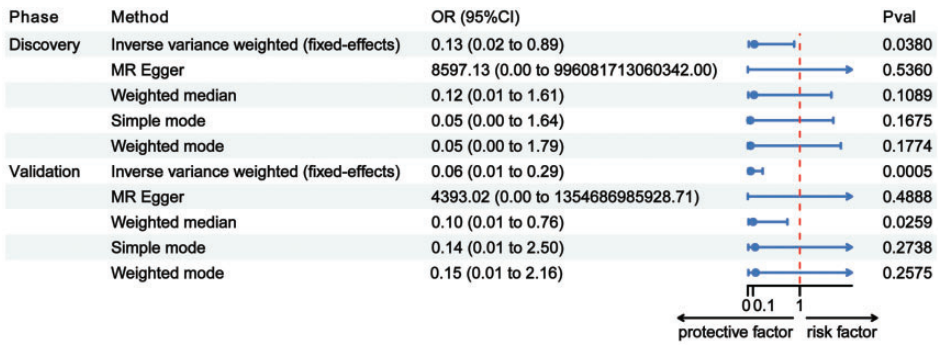

Figure 2. TSMR analyses of the causal relationship between glucosamine supplementation and T2D in the discovery and validation phases. TSMR: two-sample Mendelian randomization; T2D: type 2 diabetes.

Table 1. Results of heterogeneity, horizontal pleiotropy, and direction tests in the TSMR analyses.

	Heterogeneity		Horizontal pleiotropy			Directionality
Phase	Cochran's Q	*P*	MR Egger intercept	SE	*P*	*P* of the Steiger directionality test
Discovery	2.329	0.676	−0.060	0.070	0.453	7.936e-06
Validation	3.435	0.329	−0.060	0.053	0.375	0.042

MR: Mendelian randomization; SE: standard error; TSMR: two-sample Mendelian randomization.

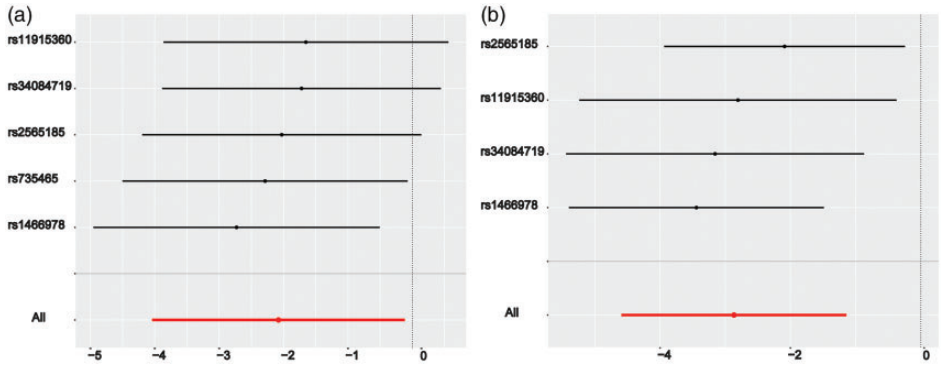

Figure 3. Results of "leave-one-out" sensitivity analysis in the discovery and validation phases. (a) The FinnGen consortium and (b) Xue et al.'s meta-analysis.

directionality of the causal relationship between glucosamine supplementation and T2D was further confirmed by the Steiger directionality test, as shown in Table 1. Moreover, the leave-one-out analysis indicated that the causal relationship was effective and robust (Figure 3).

Meta-analysis combining the results of TSMR in the discovery and validation phases

To ensure the statistical power and reliability of our findings, we conducted a meta-analysis based on the IVW results obtained from the

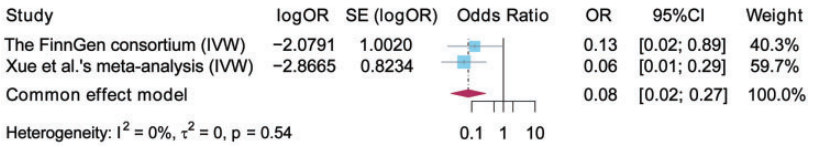

Figure 4. Meta-analysis under a fixed-effects model to verify the robustness of the causal relationship between glucosamine supplementation and T2D. T2D: type 2 diabetes.

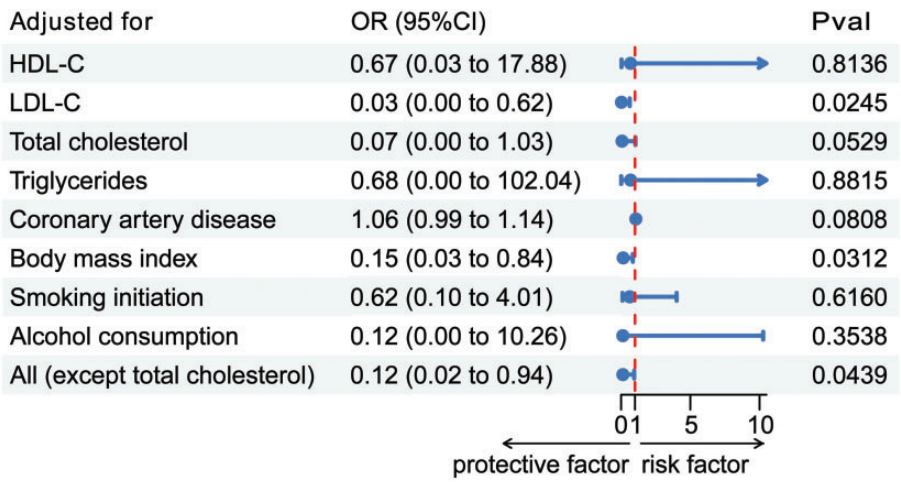

Figure 5. MVMR analyses of the effects of glucosamine supplementation on T2D (validation phase). MVMR: multivariable Mendelian randomization; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

discovery and validation phases, employing a fixed-effects model (Figure 4). The meta-analysis provided credible evidence that glucosamine supplementation was associated with a reduced risk of T2D (OR: 0.08, 95% CI: 0.02–0.27, $P < 0.0001$).

Confounding and MVMR analyses during the validation phase

After summarizing and analyzing the relevant information about the selected SNPs via LDlink (Supplement Table S4), we identified several potential confounding factors, mainly including HDL-C, LDL-C, total cholesterol, triglycerides, coronary artery disease, body mass index, smoking initiation, and alcohol consumption.

To further assess the causal relationship between glucosamine supplementation and T2D, we performed MVMR analyses of the T2D GWAS datasets obtained from Xue et al.'s meta-analysis (Figure 5). In MVMR analyses, the causal effect of glucosamine supplementation on T2D remained consistent with the TSMR results after adjusting for LDL-C (OR: 0.03, 95% CI: 0.00–0.62, $P = 0.0245$) or body mass index (OR: 0.15, 95% CI: 0.03–0.84, $P = 0.0312$). Notably, after adjusting for all confounding factors, except for total cholesterol, the causal relationship between glucosamine supplementation and T2D remained significant (OR: 0.12, 95% CI: 0.02–0.94, $P = 0.0439$).

Discussion

To the best of our knowledge, this is the first MR study to investigate the causal relationship between glucosamine supplementation and T2D. Herein, we provided robust evidence regarding a potentially causal relationship between glucosamine supplementation and a reduced risk of T2D. Furthermore, we confirmed the consistency of the causal effect of glucosamine supplementation on T2D with TSMR results, after adjusting for HDL-C, LDL-C, triglycerides, coronary artery disease, body mass index, smoking initiation, and alcohol consumption in MVMR analyses.

Previous studies have suggested an association between glucosamine supplementation and susceptibility to T2D.[10,36] Glucosamine exerted a slight glucose-lowering effect in participants who had undergone a 3-year intervention in a long-term controlled trial that involved 212 participants with arthritis.[37] Ma et al.[15] and Anderson et al.[38] reported that habitual glucosamine use was associated with a lower risk of T2D, which is consistent with our results. Previous studies have demonstrated that glucosamine possesses anti-inflammatory properties.[39,40] Moreover, glucosamine has the potential to modulate inflammation by regulating the activation of the nuclear factor kappa B (NF-κB) pathway. Specifically, it may attenuate the process of NF-κB nuclear translocation,[41] thereby reducing the expression of various proinflammatory mediators, including cytokines (e.g. interleukin-6, interleukin-1β, and tumor necrosis factor-alpha), chemokines, and cellular adhesion molecules.[42,43] This, in turn, leads to a significant reduction in the levels of C-reactive protein, a marker of systemic inflammation.[44,45] By mitigating these detrimental inflammatory responses, glucosamine may help alleviate systemic inflammation and improve insulin resistance. In addition, glucosamine may influence glucose metabolism through its effects on the hexosamine biosynthesis pathway, which has been implicated in insulin signaling and glucose homeostasis.[46]

Several animal studies have shown inconsistent findings. Baron et al.[8] and Patti et al.[10] revealed that high-dose intravenous administration of glucosamine induces insulin resistance in animals. The contradictory results may be partly due to the considerably higher dosages of glucosamine used in animal studies compared with humans' oral dosage as well as the significantly higher blood concentration achieved through intravenous administration than through oral administration. Furthermore, a recent animal study demonstrated that the oral administration of glucosamine in rats fed with a high-fat diet attenuated insulin resistance.[47]

Herein, we revealed a significant causal relationship between glucosamine supplementation and a reduced risk of T2D, which remained significant after accounting for all confounding factors, except for total cholesterol (HDL-C, LDL-C, triglycerides, coronary artery disease, body mass index, smoking initiation, and alcohol consumption). Our findings suggested that glucosamine supplementation is a vital measure for preventing T2D, offering a new perspective on T2D prevention.

There are certain limitations in our study. First, the GWAS datasets used in this study were primarily or entirely of European ancestry. Although this may reduce population stratification bias, the findings may not be generalizable to other populations. Second, although our evidence supports a causal relationship between glucosamine supplementation and T2D, the mechanisms underlying how glucosamine supplementation reduces the risk of T2D as well as the clinical benefits of such supplementation in humans remain unclear and require further investigation. Finally, it is necessary to determine the most suitable amounts of

glucosamine supplementation for the prevention of T2D in future research.

Conclusion

This study revealed that genetically predicted glucosamine supplementation is inversely associated with the risk of T2D, highlighting the potential importance of glucosamine supplementation in preventing T2D.

Acknowledgments

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Authors' contributions

Shuai Zhou collected the data and wrote the manuscript. Shuai Zhou, Peiwen Zhou, and Wenyan An performed MR analyses and analyzed the data. Junzhuo Si, Tianshi Yang, and Yanfang Jiang conceived the study, supervised the research, and edited the manuscript. All authors contributed to the article and approved the submitted version.

Data availability statement

All data used in this study are available in the public repository (IEU OpenGWAS project: https://gwas.mrcieu.ac.uk/). The detailed statistical code is included in the supplementary material.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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Supplementary material

Supplemental material for this article is available online.

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