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Causality between migraine and cardiovascular disease: a bidirectional Mendelian randomization study

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Abstract

Background While growing evidence suggests a relationship between migraine and cardiovascular disease, the genetic evidence for a causal relationship between migraine and cardiovascular disease is still scarce. Investigating the causal association between migraine and cardiovascular disease is vital.

Methods We carried out a bidirectional Mendelian randomization (MR) study including discovery samples and replication samples using publicly available genome-wide association study (GWAS) summary datasets and stringent screening instrumental variables. Four different MR techniques—Inverse variance weighted (IVW), MR –Egger, weighted median, and weighted mode—as well as various sensitivity analyses—Cochran's Q, IVW radial, leave-one-out (LOO), and MR-PRESSO—were utilized to investigate the causal relationship between cardiovascular disease and migraine.

Results The protective causal effects of genetically predicted migraine on coronary artery disease (OR, 0.881; 95% CI 0.790–0.982; $p=0.023$) and ischemic stroke (OR, 0.912; 95% CI 0.854–0.974; $p=0.006$) were detected in forward MR analysis but not in any other cardiovascular disease. Consistently, we also discovered protective causal effects of coronary atherosclerosis (OR, 0.865; 95% CI 0.797–0.940; $p=0.001$) and myocardial infarction (OR, 0.798; 95% CI 0.668–0.952; $p=0.012$) on migraine in reverse MR analysis.

Conclusion We found a potential protective effect of migraine on coronary artery disease and ischemic stroke and a potential protective effect of coronary atherosclerosis and myocardial infarction on migraine. We emphasised epidemiological and genetic differences and the need for long-term safety monitoring of migraine medications and future research to improve cardiovascular outcomes in migraine patients.

Keywords Migraine, Cardiovascular disease, GWAS, Causal association, Mendelian randomization

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Introduction

Migraine, a prevalent and long-term condition, is generally identified by repeated incapacitating bouts of headaches along with other associated symptoms, including aura [1]. The typical clinical features of this neurological disorder include unilateral, throbbing headache attacks accompanied by nausea, vomiting, photophobia, and phonophobia [2]. It affects at least 1 billion people globally, posing a significant socioeconomic burden [3].

Co-morbidity between migraine and cardiovascular disease (CVD) are becoming increasingly common. As the leading cause of death worldwide and the cause of the highest mortality and disability globally, CVD has been posing an increasingly health and social burden as the world's population aging [4]. The guidelines on preventing CVD issued by the European Society of Cardiology (ESC) in 2021 suggest that migraine with aura should be factored into the assessment of CVD risk [5].

Numerous cohort studies and meta-analyses have established correlations between migraine and various CVDs, including stroke, coronary artery disease (CAD), myocardial infarction (MI), atrial fibrillation (AF), and cardiovascular death [3, 6–8]. Although much progress has been made in preventing CVDs, the potential interactions with migraine remain unclear due to the complexity and diversity of factors contributing to CVDs. It might be implied by a positive causal association that the prevention of migraine could reduce CVD risk, and novel pathways and therapeutic targets for CVD risk reduction may be identified. In contrast, it might be inferred by an inverse causal association that CVD risk could be increased by therapeutics modifying migraine liability, such as anti-CGRP antibodies, CGRP (receptor) mAbs, and triptans [9–11]. Therefore, establishing causality between liability to migraine and CVD would have clinical significance. However, most of the previous studies were conducted at the individual level rather than at the summary level, which is susceptible to confounding factors.

Mendelian randomization (MR), a statistical method that uses exposure-related single nucleotide polymorphisms (SNPs) as instrumental variables, was utilized by neurologists and cardiologists to investigate the potential causal association between exposures and outcomes [12]. MR analysis, which is based on the principle of random assignment of alleles at meiosis, ensures that MR methods are independent of the external factors that confound observational epidemiological studies [13].

We utilized MR data from extensive genome-wide association studies (GWASs) of migraine [14–16] and CVD [17–23] to explore the potential causal association between migraine and CVD. Establishing the causal association between these factors and implementing preventive strategies may therefore emphasize the value of migraine patients being screened for CVD, which may offer fresh perspectives on cardiovascular disease treatment.

Methods

Study design

In this study, we conducted a bidirectional MR study to determine whether migraine and CVD are causally related. SNPs were utilized as instrumental variables (IVs) to estimate the causal effect of exposure on outcomes. In MR analysis, three key assumptions should be followed: 1). Exposure should strongly correlate with IVs; 2). There will be no correlation between IVs and any potentially confounding factors that may impact the outcome and exposure; and 3). IVs cannot affect outcomes through any means other than exposure but can only affect outcomes through exposure [24] (Fig. 1). Due to the ethical approval and informed consent that had already been obtained from each of the initial studies, any further ethical reviews were not needed.

Data sources

First, two meta-analyses focused on migraine, collectively analyzing data from 873,341 [15] and 554,569 [14] individuals, which we used as a discovery sample and replication sample for positive MR, respectively. Additionally, two large publicly accessible GWAS datasets, which include 484,598 and 463,010 participants of European ancestry, provide summary-level statistics on migraine in the reverse MR.

In the GWAS meta-analysis [15] of migraine, which was utilized in forward discovery MR, SNPs were also identified using a strict genome-wide significance threshold. A total of 123 SNPs were identified using a strict genome-wide significance threshold in the initial set, and 23 SNPs (rs10128028, rs11578492, rs56019088, rs6693567, rs7564469, rs950570, rs73138150, rs12653216, rs11957829, rs10866704, rs74434374, rs11248546, rs200314499, rs12295710, rs566673, rs4842676, rs75002882, rs28929474, rs34914463, rs1285294, rs111404218, rs1507220, and rs4403550) were excluded due to evidence of linkage disequilibrium. As a result, a total of 100 SNPs were retained for subsequent analytical evaluation.

In the GWAS meta-analysis [14] of migraine, which was utilized in forward replication MR, SNPs were identified using a strict genome-wide significance threshold. From the initial set of 73 SNPs, eight were excluded due to evidence of linkage disequilibrium. The excluded SNPs were rs4704232, rs12936464, rs75002882, rs7093087, rs1268083, rs6693567, rs4278348, and rs1026332. Consequently, a total of 65 SNPs were retained for subsequent analytical evaluation.

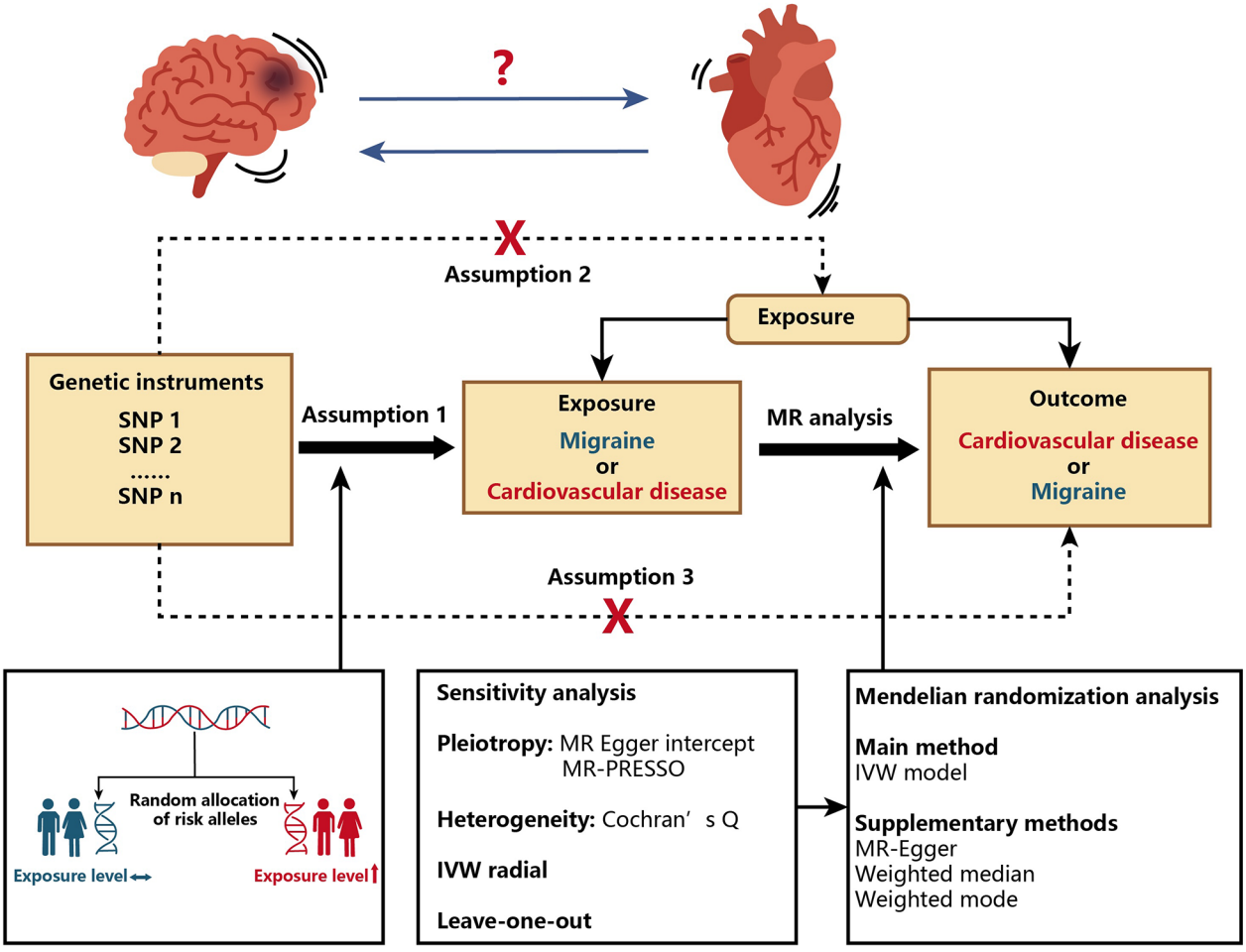

Fig. 1 Study design for the association between cardiovascular disease and migraine in our Mendelian randomization

Then, we utilized a number of summary-level statistics of CVD, including migraine [16, 22], atrial fibrillation (AF) [19], coronary atherosclerosis (CA) [22], coronary artery disease (CAD) [17], heart failure (HF) [18], hypertension [22], myocardial infarction (MI) [16], transient ischemic attack (TIA) [23], peripheral artery disease (PAD) [21], stroke and its subtype [20]. Except for two meta-analyses [14, 15], all GWAS data were obtained from the IEU GWAS database [25]. Table 1 provides an overview of all the summary-level statistics utilized in this study.

Instrumental variable selection

To identify genetic IVs that met these three MR assumptions, a series of quality control procedures were performed [12]. For SNPs that showed a strong association with exposure, a genome-wide significance threshold of $P<5\times10^{-8}$ was applied for initial screening. If SNPs did not satisfy the threshold, the P value requirement was loosened to $<5\times10^{-6}$ following protocols from prior MR studies. Due to the limited number of SNPs, the significance thresholds for large artery atherosclerosis ischemic stroke, small vessel ischemic stroke, and transient ischemic attack were relaxed to 5×10^{-5} in the reverse replication MR. Additionally, to address the effects of linkage disequilibrium among the SNPs, a clumping process was conducted using an $R^2<0.001$ and a clumping distance of greater than 10,000 kb. Furthermore, traits related to SNPs were examined after the clumping process. Palindromic SNPs possessing intermediate allele frequencies were removed by harmonizing the exposure and outcome datasets to ensure that SNPs matched on the identical effect allele for both. None of the single SNPs demonstrated any correlation with the relevant confounding factors. The F-statistic of the selected SNPs was calculated using the formula $F=\beta2/se^2$ to avoid weak IV bias ($F<10$) for our MR analysis study [26]. After the filtering protocol described above, these stringently screened SNPs served as the final IVs for subsequent MR analysis.

Table 1 The GWAS data source details in our study

Phenotype	Consortium	Ancestry	PMID	Sample size	MRC-IEU ID
Datasets for CVDs utilized in the Mendelian randomization					
Atrial fibrillation	NA	European	30,061,737	1,030,836	ebi-a-GCST006414
Coronary atherosclerosis	Neale lab	European	NA	361,194	ukb-d-I9_CORATHER
Heart failure	NA	European	31,919,418	977,323	ebi-a-GCST009541
Hypertension	Neale lab	European	NA	337,159	ukb-a-61
Myocardial infarction	NA	European	33,959,723	484,598	ebi-a-GCST90038610
Any Stroke	NA	European	29,531,354	446,696	ebi-a-GCST005838
Any Ischemic stroke	NA	European	34,594,039	484,121	ebi-a-GCST90018864
Cardioembolic Ischemic stroke	NA	European	29,531,354	211,763	ebi-a-GCST005842
Small vessel Ischemic stroke	NA	European	29,531,354	198,048	ebi-a-GCST005841
Large artery atherosclerosis Ischemic stroke	NA	European	29,531,354	150,765	ebi-a-GCST006907
Transient ischemic attack	FinnGen	European	NA	214,634	finn-b-G6_TIA
Vascular/heart problems diagnosed by doctor: Stroke	MRC-IEU	European	NA	461,880	ukb-b-8714
Peripheral artery disease	NA	European	34,594,039	483,078	ebi-a-GCST90018890
Datasets for migraine utilized in the discovery samples					
Migraine	NA	European	35,115,687	873,341	NA
Migraine	NA	European	33,959,723	484,598	ebi-a-GCST90038646
Datasets for migraine utilized in the replication samples					
Migraine	NA	European	34,294,844	554,569	NA
Migraine	MRC-IEU	European	NA	463,010	ukb-b-13,190

Mendelian randomization analysis

The causal association between migraine and CVD was evaluated using four MR analysis methods. The inverse variance-weighted (IVW) method was used to determine the causal relationship between exposure and outcome due to having the highest statistical validity, while the MR–Egger, weighted median, and weighted mode methods were utilized as additional MR methods [12]. The MR–Egger regression intercept can be utilized to measure horizontal pleiotropy, which provides a conservative estimate of causality but with decreased statistical accuracy [27]. The weighted median method can be utilized to offer an unbiased estimation when up to 50% of the IVs are invalid [28]. The weighted mode method can be applied to evaluate the robustness of MR results [29].

In addition, a series of sensitivity analyses were performed to assess heterogeneity and pleiotropy. Cochran's Q test was utilized to quantify the heterogeneity associated with IVW and MR–Egger regression [29]. $P>0.05$ indicated no significant heterogeneity among the IVs. The IVW radial method was then used to examine instrumental variables with significant heterogeneity contributions [30]. The MR-Pleiotropy Residual Sum and Outlier (PRESSO) global test was utilized to detect potential horizontal pleiotropy [27]. If necessary, the results were recalculated after the exclusion of outliers. $P>0.05$ suggested an absence of pleiotropy in IVs, thus fulfilling a key assumption.

All these analyses were performed using R software (version 4.3.2) with the R packages TwoSample MR (version 0.5.8), MR-PRESSO (version 1.0), and RadialMR (version 1.1).

Results

Effects of migraine on CVD

The MR results of migraine patients on CVD are listed in Fig. 2. In the discovery MR study, the IVW method revealed that genetically determined migraine was associated with CAD (OR=0.881, 95% CI: 0.790–0.982, $p=0.023$) (Figure S1)and ischemic stroke (OR=0.912, 95% CI: 0.854–0.974, $p=0.006$) (Figure S2). However, we did not find a significant correlation between migraine and AF, CA, MI, HF, hypertension, any stroke, cardioembolic ischemic stroke, small vessel ischemic stroke, large artery atherosclerotic ischemic stroke, TIA or PAD. Similar results to those of the IVW method were obtained using MR–Egger analyses, the weighted median, and the weighted mode. Additionally, we obtained similar results in the replication MR study, demonstrating the reliability of the results (Fig. 3).

Effects of CVD on migraine

To further explore the causal association between migraine and CVD, a reverse MR study was performed with CVD as the exposure and migraine as the outcome (Fig. 4). Specifically, in the reverse discovery MR study, the IVW method showed that genetic CA (OR=0.865, 95% CI: 0.797–0.940 $p=0.001$) (Figure S3) and MI (OR=0.798, 95% CI: 0.668–0.952, $p=0.012$) (Figure S4) had a protective causal effect on migraine. However, we did not find a causal relationship between CVDs and

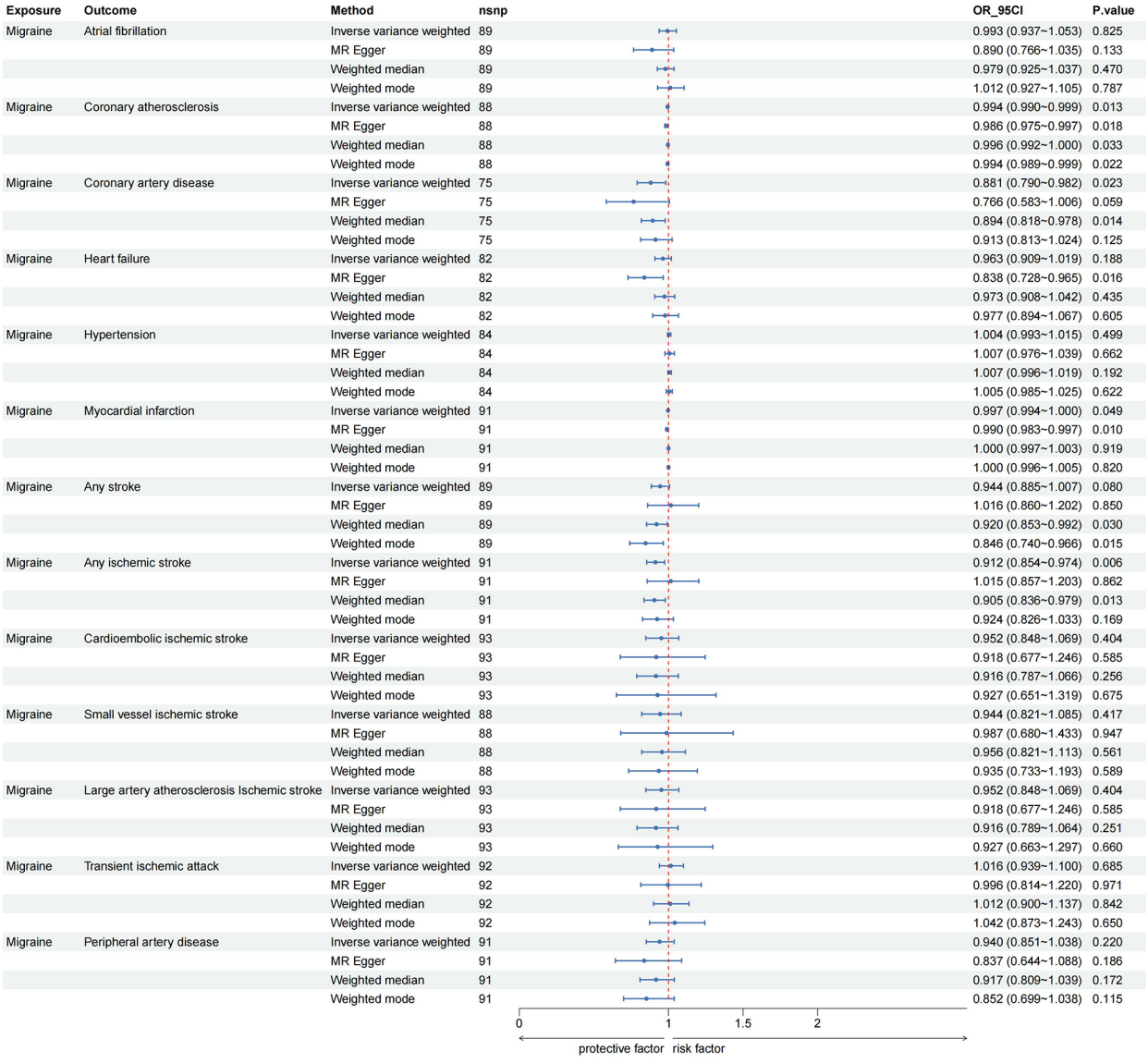

Fig. 2 Mendelian randomization for the association of migraine with CVD in the discovery samples. Estimated causal effects of CVD on migraine and its subtypes using different MR methods. The scale of the x-axis is logarithmic. nSNPs, number of SNPs used in MR; OR, odds ratio; CI, confidence interval

migraine in the replication samples (Fig. 5). This could be a consequence of the limited number of IVs, which leads to insufficient statistical validity.

Discussion

Migraine and cardiovascular disease (CVD) are prominent public health problems worldwide [31]. Many studies have reported the epidemiological overlap between migraine and CVD [32, 33]. Although, previous epidemiological studies have found an increased risk of CVD in patients with migraine, the evidence for a causal relationship between migraine and CVD is scarce. In our Mendelian randomization (MR) study, a potentially protective effect of migraine on the risk of coronary artery disease (CAD) and ischemic stroke was identified. According to the reverse MR analysis, coronary atherosclerosis (CA) and myocardial infarction (MI) potentially led to a decreased risk of migraine. This is the most comprehensive MR article currently available to evaluate the causal association between migraine and CVD. However, the potentially protective effects of migraine and CVD on each other are unexpected given the existing epidemiologic research, but are consistent with previous studies from a genetic perspective.

Many epidemiological studies report an increased risk of CVD in migraineurs [6, 32, 34–38]. Large meta-analysis of case-control studies and observational cohort studies also reports increased risk of CVD in migraineurs [8,

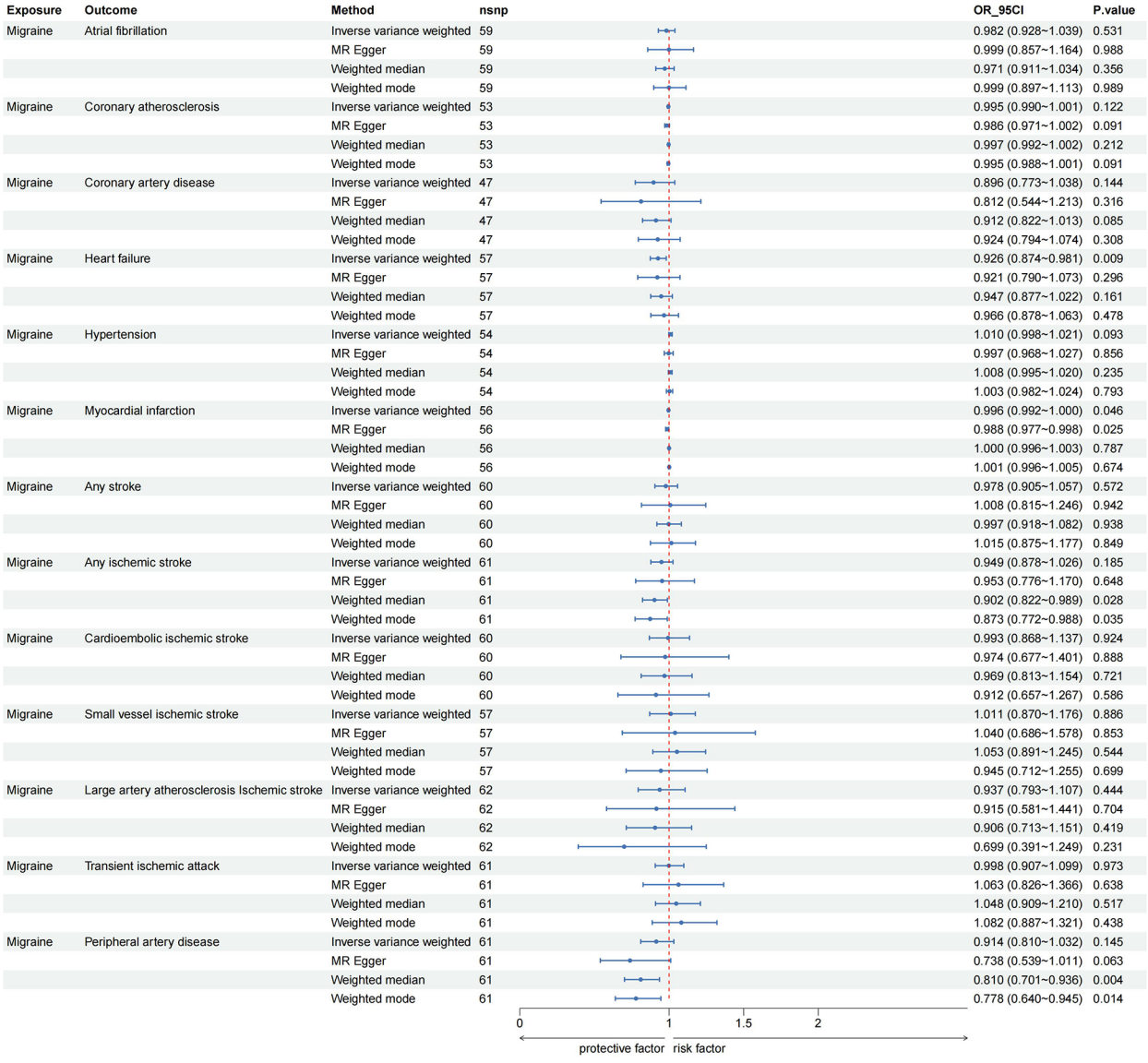

Fig. 3 Mendelian randomization for the association of migraine with CVD in the replication samples

39]. However, epidemiological studies of migraine-associated CVD risk have some inherent limitations. First, many observational studies about migraine and CVD are based on case–control and cross-sectional designs, which are ambiguous in terms of chronology, preventing the inference of transparent causal associations. Second, a variety of confounding factors, such as the drugs utilized for acute and prophylactic treatment of migraine and CGRP receptor antagonists, will be susceptible in the observational studies by affecting CVD. Third, the difference of diagnostic criteria utilized in some observational studies may reduce the reliability of the results. In addition, our MR study is a mechanism-only study, targeting the signaling pathways and genetics of migraine and CVD, without incorporating confounding factors such as the external environment.

It is currently unclear to which extent the genetic roots of migraine and CVD overlap and contribute to the coincidence of CVD. There is debate about how migraine and CVD interact to each other in genetic level. The GWAS data for migraine used in our discovery study identified 123 risk loci [15], including 86 previously unknown ones, with the new loci encompassing genes encoding recent migraine-specific drug targets such as Calcitonin gene-related peptide (CALCA/CALCB) and serotonin 1 F receptor (HTR1F). However, in their analysis, the migraine risk alleles neither consistently increased nor consistently decreased the risk of CAD, but migraine

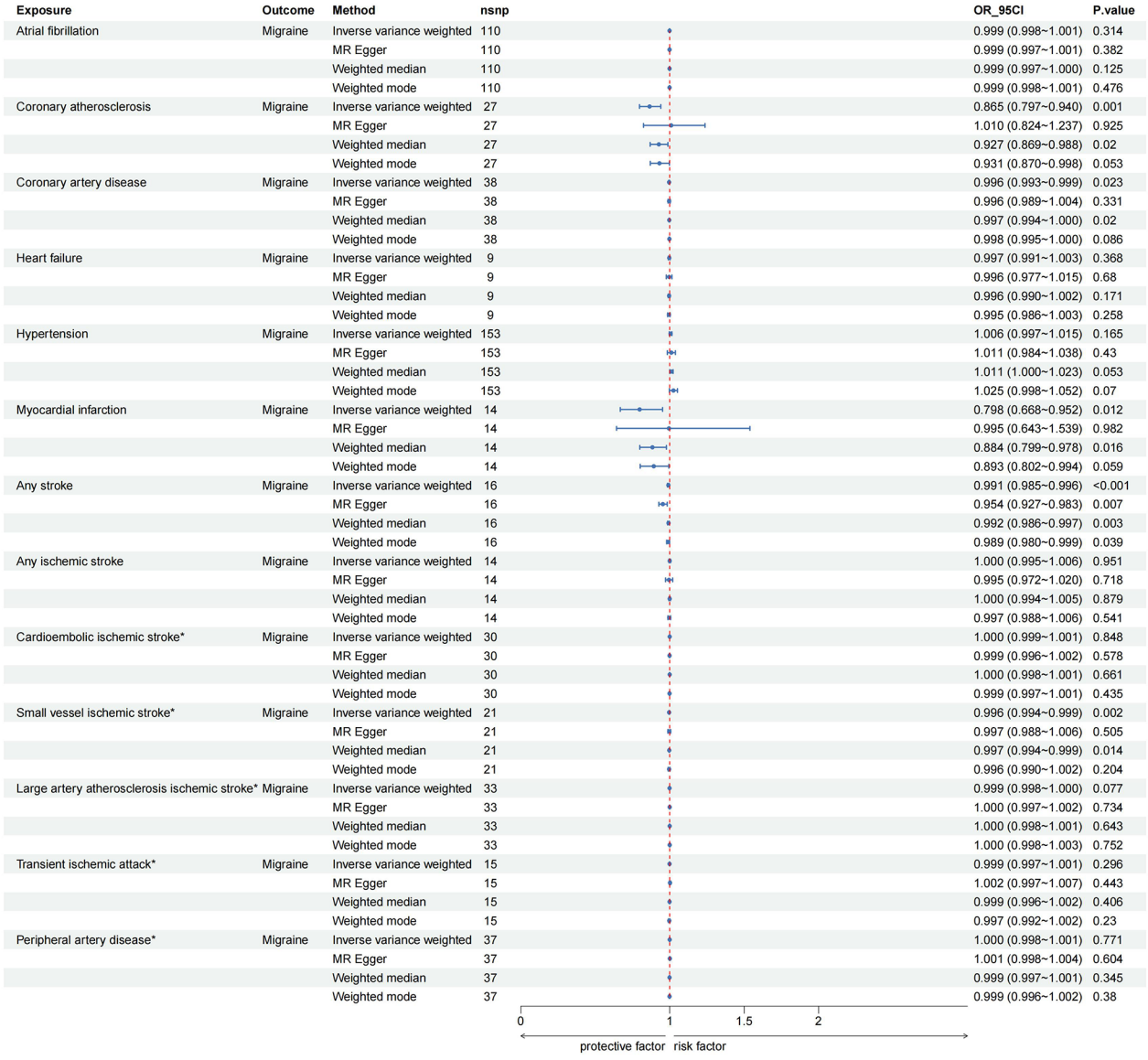

Fig. 4 Mendelian randomization for the association of CVD with migraine in the discovery samples. * SNPs did not satisfy the threshold, and the *P* value requirement was loosened to $< 5 \times 10^{-6}$

dominant variants in the CAD GWAS, at a *p*-value of less than 1e-5, there were eight variants, one with the same direction of effect and seven with the opposite direction of effect, with a *p*-value of 0.07. This could mean overall that the opposite direction effect is greater than the same direction effect for migraine and CAD. Besides, the paper by Bendik et al. [40] in 2017 identified the shared genetic risk between migraine and CAD that the index SNPs at two (in KCNK5and AS3MT) of the three loci (PHACTR1, KCNK5and AS3MT) had opposite effect directions in migraine and CAD. A genetic risk score study for coronary disease based on the UK Biobank revealed that an increased genetic predisposition to CAD was inversely associated with migraine headaches [41]. At the same time, this study suggests that, in addition to the LRP1, PHACTR1, and FHL5 loci, there might be a rather extensive opposing genetic component between CAD and migraine. This further suggests that the mechanisms involved influence critical and delicate homeostatic features of vascular biology in opposite ways. A genetic study analyses using summary statistics from GWAS studies identified that known migraine loci also revealed novel associations with opposite risk alleles [42]. Specifically, these associations were found for all stroke, ischemic stroke, and small vessel stroke at rs55928386 (HTRA1); for large artery stroke at rs11172113 (LRP1);

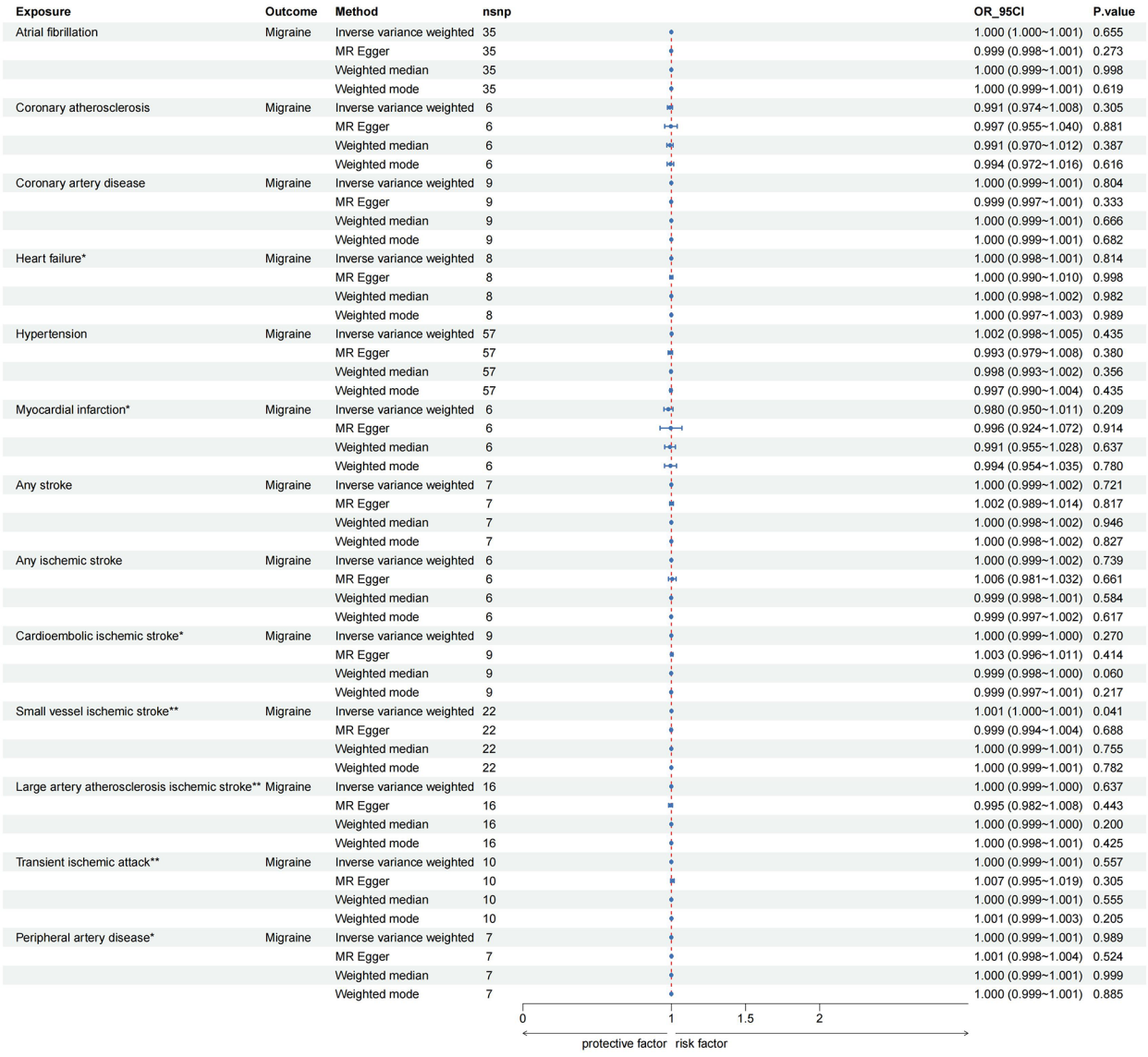

Fig. 5 Mendelian randomization for the association of CVD with migraine in the replication samples. * SNPs did not satisfy the threshold, and the *P* value requirement was loosened to $<5\times10^{-6}$. ** Due to the limited number of SNPs, the *P* value requirement was loosened to $<5\times10^{-5}$

and for all stroke and ischemic stroke at rs1535791 and rs4942561 (both LRCH1). The focus of these studies has been on prioritizing the identification of shared gene loci and the quantification of genetic correlations, but we are explicitly concerned with the identification of causality, in which case we aim to minimize the effects of pleiotropy. Although we cannot conclude that future larger-scale GWAS will never find some specific loci for migraine with aura, we can assume that the opposite effect between migraine and CAD and ischemic stroke in our research.

The opposite epidemiological and genetic effects of migraine and CAD might indicate that there are mediating factors which reverse the direction of the effect estimates. We hypothesized that migraine may influence CVD through mediating factors. Diabetes might be a potential mediator, as migraine reduces the risk of developing type 2 diabetes in women with migraine [43]. Since diabetes is a known risk factor for CA and CAD, migraine reduces the risk factors for CA and CAD. Alcohol consumption could also be a potential mediator, as an MR study showed that the genetic liability to migraine is inversely associated with alcohol consumption [44], which is a causal risk factor for CVD. Genotypes of APOB or PCSK9 related to higher LDL-C levels which is the risk factor for CVD have shown an inverse association with migraine according to GWAS summary data [45]. However, the combination of confounding and

overcontrol of protective mediators could influence not only the disease but also the medication taken by participants in the observational study, which could reverse the direction of the effect estimates [46].

Based on our MR results, we hypothesize that CGRP might be the potential biological mechanism that points to migraine as a protective factor for CAD. Migraine onset involves the release of large amounts of Calcitonin gene-related peptide (CGRP). CGRP receptors are located not only in the central and peripheral nervous system, but also in the cardiovascular system [47]. Simultaneously, CGRP is a potent vasodilator that functions through receptors on the endothelium to stimulate the production of nitric oxide (NO). This helps regulate blood flow and prevent ischemic damage, thereby providing a protective effect on the cardiovascular system. CGRP promotes coronary vasodilation and is involved in the formation of new blood vessels in response to ischemic insults [48]. This might explain the reason why migraine as a protective factor for CAD in our MR results. Some studies have also suggested that the protective effect of CGRP against ischemia [49], particularly in the context of brain ischemia, might reduce the extent of the infarct zone and protect against cerebral vasospasm [50]. The studies are consistent with our MR results and might be a potential pathway for migraine as an ischemic stroke. The effect of MI to reduce the risk of migraine is difficult to explain the potential mechanism. Because of the age-specific variability in the migraine and MI populations and the fact that epidemiologically migraine usually precedes MI, it is difficult to find additional paper that would support the effect of MI to reduce the risk of migraine occurrence. We speculate that this result may be due to the small number of SNPs included in the GWAS used for exposure and outcome, which may have contributed to the lack of robustness of the results. In the future, larger GWAS databases could give a more detailed explanation of MI and migraine.

Migraine and CVD are both genetically and environmentally regulated disorders. It has been suggested that 40–60% of the clinical presentation of migraine is determined by genetic factors, with the remainder being determined by non-genetic endogenous and exogenous risk modifiers and triggers [2]. This could mean that the influence of the external environment may be greater than that brought about by genes.

Indeed, differences in migraine between genders, which as the non-genetic endogenous, have been reported in the literature, such as higher CGRP plasma levels in women than in men [51], the cardiovascular benefits of CGRP, that may be strongly influenced by female sex hormones [52], and the possible interaction between CGRP and female sex hormones [53]. In addition, differences in gene expression occur in populations of different ages. For example, certain genes associated with migraine may have different expression levels in younger people, whereas their expression may be reduced or increased in older people [54]. Furthermore, not only does non-genetic endogenous influence the relationship between migraine and CVD, but also non-genetic exogenous. There are always dilemmas in the treatment of migraine and CVD in that medications such as NSAIDs, anti-CGRP antibodies, CGRP (receptor) monoclonal antibodies (mAbs), and triptans for migraine treatment or preventative medication can increase the risk of CVD as a side effect. NSAIDs combined with caffeine are often utilized as a first-line acute treatment for migraine [55]. However, chronic use or overuse of NSAIDs has been associated with a higher risk of venous thromboembolism and AF and may promote the conversion of episodic to chronic migraine [56, 57]. Calcitonin gene-related peptide receptor (CGRP receptor), a neuropeptide released by the trigeminal nerve, plays a crucial role in migraine pathophysiology [2]. In addition, while small-molecule antagonists of the CGRP receptor have been proven to be effective treatment options for migraine patients [58–60], blocking the vasodilatory effects of CGRP during ongoing (silent or transient) cerebral and cardiac ischemia could potentially lead to larger infarcts [10]. The subcutaneous administration of CGRP (receptor) mAbs, a relatively new preventative treatment for migraine, has been reported to increase the development of hypertension and worsen preexisting hypertension in the postmarketing setting [11]. Moreover, triptans are safe for most migraine patients but should be avoided in those with atherosclerotic diseases, such as coronary artery disease (CAD), stroke, and PAD, due to the risk of coronary artery vasoconstriction [61]. Therefore, our results highlight the importance of long-term clinical safety monitoring of migraine medications at the genetic level and the need for future research to focus on improving cardiovascular prognosis in migraine patients.

This study utilized large-exposure and outcome GWASs to conduct MR analysis to infer a causal association between migraine and CVDs. The major advantage of this study is the application of a robust MR design that minimizes reverse causality and confounding factors associated with traditional observational research. However, this study has several limitations. First, no subgroup analysis of migraine was performed, as summary statistics rather than raw data were utilized in the meta-analysis. Second, the GWAS cases in this study were all of European ancestry, so further studies are needed to determine whether the results of this study can be generalized to other human populations. Third, the sample sizes of some datasets were not large enough, resulting in insufficient statistical power in the replication MR. Therefore, a GWAS database with a larger sample

size may be needed in the future for additional validation. Fourth, the study populations of migraine and cardiovascular disease may differ significantly in age and gender composition. However, sex and age information was not included in the GWAS database we used, which made it challenging to conduct more detailed analyses. In addition, a potential limitation is the overlap of participants in both the exposure and outcome datasets, as well as between the GWAS for migraine and CVDs, which could introduce sample overlap bias and lead MR estimates towards observational estimates, although the true proportion of overlap is likely very small and difficult to quantify. Finally, we found a potential protective effect of migraine on CAD and ischemic stroke, and we also found that CA and MI reduce the risk of migraine. We particularly emphasize the importance of long-term clinical safety monitoring of migraine medications at the genetic level and the need for future studies to focus on improving cardiovascular prognosis in migraine patients.

Conclusion

In conclusion, we found a potential protective effect of migraine on coronary artery disease and ischemic stroke, and we also found that coronary atherosclerosis and myocardial infarction reduce the risk of migraine. We also emphasize epidemiological and genetic differences and the importance of long-term clinical safety monitoring of migraine medications at the genetic level and the need for future studies to focus on improving cardiovascular prognosis in migraine patients. In addition, it must be emphasized that further research is required to confirm the final result.

Abbreviations

MR	Mendelian randomization
GWAS	Genome-wide association study
IVW	Inverse variance weighted
LOO	Leave-one-out
ESC	European Society of Cardiology
CVD	Cardiovascular disease
CAD	Coronary artery disease
MI	Myocardial infarction
AF	Atrial fibrillation
CA	Coronary atherosclerosis
HF	Heart failure
TIA	Transient ischemic attack
PAD	Peripheral artery disease
SNP	Single nucleotide polymorphisms
IV	Instrumental variable
PRESSO	MR-Pleiotropy Residual Sum and Outliers
NHANES	National Health and Nutrition Examination Survey
CGRP	Calcitonin gene-related peptide receptor

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions

XR D, CD L and TF K created the concept and design of this study. XL D designed and painted the figures in this study. M Z provided knowledge about cardiovascular disease and migraine. GR Z, XY Z, N T, GC L and B L were responsible for the statistical analysis. XR D and CD L drafted, revised, and edited the manuscript. All the authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The data used in this MR analysis were entirely from previously reported summary data. Therefore, neither patient consent nor ethical approval was necessary for the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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