Exploring genetic association of insomnia with allergic disease and asthma: a bidirectional Mendelian randomization study

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Abstract

Background: Insomnia is highly prevalent among patients with allergic disease and asthma; however, few studies have investigated their causal relationship. We aim to explore the causal association between insomnia and allergic disease/asthma by performing bidirectional Mendelian randomization (MR) study.

Methods: Instrumental variables were constructed using single nucleotide polymorphisms (SNPs). Summary statistics for insomnia, allergic disease, and asthma were obtained from four large-scale genome-wide association studies (GWAS) of European ancestry. The pleiotropy analysis was applied by using the MR-Egger intercept test and the MR pleiotropy residual sum and outlier (MR-PRESSO) test. MR analyses were conducted by using inverse variance weighted (IVW), weighted median, and MR-Egger method.

Results: Based on the multiplicative random effects IVW method, the MR analysis showed that genetically predicted insomnia was causally associated with an increased risk of allergic disease (OR = 1.054, 95% CI = 1.031–1.078, P = 3.817 × 10⁻⁶), asthma (OR = 1.043, 95% CI = 1.010–1.077, P = 9.811 × 10⁻³), moderate-severe asthma (OR = 1.168, 95% CI = 1.069–1.277, P = 6.234 × 10⁻⁴), and adult-onset asthma (OR = 1.086, 95% CI = 1.037–1.138, P = 4.922 × 10⁻⁴). In bidirectional analyses, we did not find evidence supporting the reverse causality relations.

Conclusions: Our MR study suggested that genetically predicted insomnia was the risk factor for allergic disease and asthma. Improving sleep quality could be one of the cornerstones in the prevention of allergic disease and asthma.

Keywords: Mendelian randomization, Single nucleotide polymorphisms, Insomnia, Allergic disease, Asthma

Introduction

Insomnia is a widespread sleep disorder, with an annual incidence of approximately 35–50% in general population [1, 2]. It is characterized by difficulty in initiating or maintaining sleep, awakening in the morning, or feeling of non-resistant sleep [1]. Insomnia can cause significant daytime symptoms and negative health outcomes, including fatigue, daytime sleepiness, impairment in cognitive performance, and mood disturbances [1, 3]. The detrimental effects of insomnia cardiovascular and nervous function have been recognized by prospective epidemiology studies [4, 5]. However, available data on the role of insomnia in allergic disease such as asthma is limited.
In recent decades, the prevalence of allergic disease has been increasing, and allergic disease has become a momentous public health problem [6]. In 2016, the number of people suffering from asthma worldwide was close to 339 million [7]. Insomnia is highly prevalent among patients with allergic disease, and it is reported that 44% to 70% of asthma patients and 33% to 87% of atopic dermatitis people have symptoms of insomnia [8, 9]. And the converse is also true that poor sleep itself could cause or worsen allergic disease [8–12]. Two longitudinal observational studies have provided supportive evidence that insomnia carried an increased risk of newly-onset asthma [8, 11]. It seemed that there is a bidirectional causal relationship between insomnia and atopic dermatitis [9], and mutual causality seem to be plausible when explaining the association between insomnia and allergic disease. However, the majority of epidemiological data on insomnia and allergic disease was embedded in an observational design, though these studies attempted to increase their credibility by adjusting confounding factors, which is less likely to fully account for confounding and reverse causation bias. Therefore, the causal directionality between insomnia and allergic disease remains unclear, and it warrants further exploration.

Mendelian randomization (MR) overcomes the limitations of observation methods by using genetic variants (mainly single nucleotide polymorphisms, SNPs) as instrumental variables (IVs) to assess the potential causal impact of exposure on the results. Genetic variants are randomly assigned at conception, reflecting the randomization process in controlled trials and limiting the impact of confounding always. Genetic variants precede the onset of disease, eliminating adverse events to causality. Moreover, the selected IV is related to exposure, but neither related to any confounding factors in the exposure-result relationship, nor is it related to the result by means other than exposure [13]. Thus, MR is an ideal technique to explore the causal relationship between insomnia and allergic disease.

In this study, based on the summary statistics from large genome-wide association studies (GWAS) datasets, we performed a bidirectional MR study to determine the causal associations of genetically predicted insomnia with allergic disease, asthma, and its phenotypes.

**Methods**

**Study design**

To assess whether insomnia is associated with allergic disease, asthma, and three phenotypes of asthma (including moderate-severe asthma, adult-onset asthma, and childhood asthma) and to assess the direction of association, we performed a bidirectional MR study using the most up-to-date publicly available GWASs. The MR approach was based on 3 assumptions: (1) The genetic variants used as IVs are associated with exposure; (2) The genetic variants are not associated with any confounders; (3) There is no direct correlation between genetic variation and the outcome, or any way other than the exposure to correlate with the outcome [14].

**Genetic associations with insomnia**

Based on a large-scale GWAS, which includes 1,331,010 individuals of European ancestry (944,477 individuals from 23andMe, and 386,533 individuals from UK Biobank), 248 SNP associated with insomnia at the genome-wide significance level \( (P < 5 \times 10^{-8}) \) were extracted, which is capable of explaining 2.6% of the variance in insomnia [2]. Insomnia was a self-reported condition collected through an electronic questionnaire integrated into UK Biobank’s touchscreen devices and an online questionnaire from 23andMe. The questionnaire of the UK Biobank has higher sensitivity (98%) and specificity (96%) when comparing with the insomnia severity index or the Pittsburgh sleep quality index. The phenotypes in the UK Biobank and 23andMe have acceptable sensitivity and specificity (> 80%) compared to those identified by structured interviews [15]. The association tests were adjusted for age, sex, genotype array, and 10 genetic principal components in the UK Biobank, and age, sex, the top 5 principal components in 23andMe.

**Genetic associations with allergic disease**

Genetic association data for the allergic disease came from a publicly available GWAS (meta-analysis of results from the 13 studies) with the largest sample sizes hitherto [16], and they identified 136 independent risk variants \( (P < 3 \times 10^{-8}) \), including 73 not previously reported, which implicate 132 nearby genes in allergic disease pathophysiology. This study included 180,129 cases with self-reported suffering from asthma and/or hay fever and/or eczema, and 180,709 controls without suffering from any of these diseases/symptoms, all of European ancestry [16].

**Genetic associations with asthma, adult-onset asthma and childhood asthma**

Summary-level statistics for asthma, adult-onset asthma, and childhood asthma were derived from the UK Biobank, a cohort study involving approximately 500,000 adults aged 37–73 years enrolled between 2006 and 2010 [17]. Asthma cases in the UK Biobank were identified by participant questionnaires whether they had ever been diagnosed with asthma by doctor. The current study limited analysis to 394,283 subjects of European ancestry to minimize population stratification (46,802 asthma patients, and 347,481 controls) [18]. Adult-onset asthma
was defined as the age of onset 26 years (22,296 cases and 347,481 controls), childhood asthma was defined as the age of onset \( \leq \) 12 years (9676 cases and 347,481 controls) [18].

**Genetic associations with moderate-severe asthma**

We selected a large-scale GWAS dataset of 30,810 individuals who have European ancestry, including 5135 moderate-to-severe asthma cases and 25,675 controls [19]. These moderate-to-severe asthma cases came from the Genetics of Asthma Severity and Phenotype study (GASP, \( n = 1858 \)), the Unbiased Biomarker Prediction of respiratory diseases outcomes project (U-BIOPRED, \( n = 281 \)), and the UK Biobank (\( n = 2996 \)). The selected controls were from U-BIOPRED (\( n = 75 \)) and UK Biobank (\( n = 25,600 \)). Patients in GASP and U-BIOPRED were evaluated using clinical records according to the 2014 guidelines of the British Thoracic Society. In UK Biobank, cases of moderate to severe asthma are based on a physician’s diagnosis.

The summary statistics excluded the 23andMe sample, intending to protect the privacy of the 23andMe research participants. Detailed information on data sources was shown in Additional file 1: Table S1.

**Selection of genetic instrument**

Based on European ancestry, we used cluster functions implemented in the TwoSampleMR package to assess linkage disequilibrium between loci (LD), 207 genome-wide significance level (\( P < 5 \times 10^{-8} \)) and independent SNPs were proposed as IVs for insomnia, 98 SNPs for allergic disease, 86 SNPs for asthma, and 12 SNPs for moderate-severe asthma (\( r^2 < 0.01 \) and clump window > 10,000 kb) (Additional file 2: Table S2). Bidirectional analysis for the adult-onset asthma and childhood asthma could not be conducted due to insufficient independent SNPs as IVs (0 and 1 SNP, respectively). To evaluate the strength of IV, we use the following formula to calculate the F statistic for each SNP. F statistic = \( R^2 \times (N - 2)/(1 - R^2) \), where \( R^2 \) is the phenotypic variance explained by each genetic variation in the exposure, and N is the sample size [20]. IVs with F-statistic <10 were considered weak instruments [21]. Subsequently, these SNPs were harmonized in summary data of outcomes GWAS in the TwoSampleMR package (Additional file 2: Table S3).

**Statistical analysis**

To evaluate the causal directionality between insomnia and allergic disease, asthma and it’s three phenotypes, we performed a bidirectional MR study using three models, including: (1) the inverse variance weighted (IVW) model; (2) the weighted median model; and (3) the MR-Egger regression model. The IVW model took a meta-analysis approach to combine Wald estimates for each SNP to get the overall estimates of the effect. If there is no horizontal pleiotropy and heterogeneity, an unbiased causal estimate could be obtained by IVW linear regression, and fixed and multiplicative random effects IVW approaches are available [22]. Due to the heterogeneity of causal estimates of different variants, the multiplicative random effects model would be more appropriate than the fixed effects model, so we used the former as the main analysis method [23]. The weighted median model can provide a consistent estimate of causality when at least 50% of genetic IVs are effective [24]. The advantage of the MR-Egger regression model is that it evaluates the null causal hypothesis under the assumption of Instrument Strength Independent of Direct Effect. Even if all SNPs included in the selection are invalid, MR-Egger can still provide a robust unbiased estimate [25, 26].

An important prerequisite for the MR approach is that exposure-related SNPs affect allergic disease, asthma, and its phenotypes, only through insomnia itself [25]. To assess whether IVs affect the level of pleiotropic effects of outcomes through more than one biological pathway, we used MR-Egger regression and MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) to test for evidence of pleiotropy [25]. MR-Egger regression intercept that deviates from the origin may provide evidence for potential multiple pleiotropic effects in genetic IVs [26]. MR-PRESSO is a method that allows for the evaluation of horizontal pleiotropy in multi-instrument Mendelian Randomization utilizing genome-wide summary association statistics, and the MR-PRESSO global test is used to detect the horizontal pleiotropy [27]. The IVW and MR-Egger regression were used to detect potential heterogeneity among causal effects of different variants, the heterogeneities were quantified by the Cochran Q statistic, and \( I^2 \) statistic [28]. The leave-one-out sensitivity method was performed to compute whether random estimates were affected by an individual genetic locus. For further interpretation, scatterplots, forest plots, and funnel plots were also produced.

Bonferroni method was performed to correct for multiple testing. The association with two-sided \( P \)-values < 0.01 (0.05/5, insomnia as outcome) and \( P \)-values < 0.01 (0.05/3, allergic disease, asthma, moderate-severe asthma as outcome) were deemed statistically significant, \( P \)-values between 0.05 and 0.01 were regarded as suggestive evidence of association. Besides, other statistical tests were two-sided and the statistical significance was set at the level of \( P < 0.05 \). MR analysis
was performed using TwoSampleMR packages (version 0.5.6) in R (version 4.1.1).

**Results**

**Genetically predicted insomnia on the risk of allergic disease, asthma and its phenotypes**

Based on the multiplicative random effects IVW method, the MR analysis showed that genetically predicted insomnia increased the risk of allergic disease (odds ratio \( \text{OR} = 1.054 \); 95% confidence interval \( [\text{CI}] = 1.031–1.078 \), \( P = 3.817 \times 10^{-06} \)), and the similar results were also obtained in the weighted median model (Fig. 1, and Additional file 1: Table S4). Moreover, we observed causal effects of genetically predicted insomnia on the risk of asthma, with odds ratios of 1.043 (95% CI 1.010–1.077, \( P = 9.811 \times 10^{-03} \)). As for asthma phenotypes, there were evidences to support causal associations between genetically predicted insomnia and both moderate-severe asthma \( \text{OR} = 1.168 \), 95% CI = 1.069–1.277, \( P = 6.234 \times 10^{-04} \) and adult-onset asthma \( \text{OR} = 1.086 \), 95% CI = 1.037–1.138, \( P = 4.922 \times 10^{-04} \), which was similarly observed in the weighted median model, but MR-Egger regression estimate was only statistically significant in moderate-severe asthma. By contrast, there was no significant causal relationship between genetically predicted insomnia and childhood asthma \( \text{OR} = 0.982 \), 95% CI = 0.915–1.053, \( P = 0.602 \). The estimated effect sizes for SNPs of insomnia on allergic disease, asthma, and its phenotypes were displayed in scatter plot (Fig. 2).

**Genetically predicted allergic disease, asthma and moderate-severe asthma on the risk of insomnia**

In bidirectional analyses, based on the multiplicative random effects IVW method, there was no evidence for potential causal effects of genetically predicted allergic disease, asthma and moderate-severe asthma on insomnia, with odds ratios of 0.989 (95% CI 0.963–1.017, \( P = 0.448 \)), 1.008 (95% CI 0.986–1.032, \( P = 0.470 \)), 1.001 (95% CI 0.981–1.021, \( P = 0.930 \)), respectively (Fig. 3, and Additional file 1: Table S5). Similar results were obtained for the weighted median model and MR-Egger...
regression estimate. The estimated effect sizes for SNPs of allergic disease, asthma and moderate-severe asthma on insomnia were displayed in scatter plot (Fig. 4).

Results for sensitivity analyses
Using the MR-Egger regression intercept test and MR-PRESSO global test, there was no evidence of horizontal pleiotropy for SNPs of insomnia as exposure with allergic disease, asthma and its phenotypes as outcomes (all $P > 0.05$) (Table 1). Cochran $Q$ statistic and $I^2$ statistic indicated low heterogeneity and more reliability of these SNPs (all $P > 0.05$). The funnel plots showed general symmetry, suggesting little evidence of heterogeneity (Additional file 1: Fig. S1). We performed the leave-one-out sensitivity analysis using conventional IVW methods, and the results were similar after removing single SNPs in the leave-one-out analysis, suggesting that no single SNP has an exorbitant influence on the overall estimates (Additional file 1: Figs. S2–S6). The forest plots were shown in Additional file 1: Figs. S7–S11.

In bidirectional analyses, the MR-Egger regression intercept and MR-PRESSO global test also suggested that no evidence of horizontal pleiotropy for SNPs of allergic disease, asthma and moderate-severe asthma as exposures with insomnia as outcome (all $P > 0.05$) (Table 2). Likewise, no heterogeneity was found in the Cochran $Q$ statistic, $I^2$ statistic, and funnel plots (all $P > 0.05$). (Table 2, and Additional file 1: Figure S12) The leave-one-out analysis also suggested that no single SNP has an exorbitant influence on the overall estimates (Additional file 1: Figs. S13–S15). The forest plots were shown in Additional file 1: Fig. S16–S18.

Discussion
To the best of our knowledge, this is the first bidirectional MR analysis to explore the potential causal relationship of insomnia with allergic disease, asthma, and its phenotypes. Our MR analyses demonstrated that genetically predicted insomnia was causally associated with increased risks of allergic disease, asthma and its phenotypes.
phenotypes, moderate-severe asthma and adult-onset asthma but not childhood asthma. By contrast, the bidirectional analyses did not find evidence supporting genetically predicted allergic disease or asthma was causally associated with the risk of insomnia. Our findings, based on model of population genetic variation, pointed out the prophetic function of sleep disorder in individual’s susceptibility to allergic disease and asthma, but the opposition is not necessarily the case.

Although the previous observational studies were limited, the majority of them identified that insomnia was associated with the increased risks of allergic disease and asthma in both Western and Eastern populations, which was supported by the present MR study. A 5-year prospective cohort of 2316 middle-aged adults reported that patients with insomnia at baseline had a higher incidence of asthma and allergic rhinitis than those without insomnia [29]. Two cohort data from China and Norway also revealed insomnia was a risk factor for new-onset asthma [8, 11]. In addition, several studies have focused on other sleep traits, and the findings consistently demonstrated that poor sleep behavior has an impact on the development of allergic disease [30–34]. A study carried out in Britain explored the potential explanation why night shift

| Exposures                           | Cases       | Controls  | SNPs | P        | OR (95% CI)     |
|-------------------------------------|-------------|-----------|------|----------|----------------|
| Allergic disease                    | 180,129     | 180,709   | 98   |          |                |
| IVW (Multiplicative random effect)  | 0.448       |           |      | 0.989 (0.963 to 1.017) |
| IVW (Fixed effect)                  | 0.405       |           |      | 0.989 (0.965 to 1.014) |
| Weighted median                     | 0.508       |           |      | 0.987 (0.951 to 1.025) |
| MR Egger                            | 0.896       |           |      | 1.005 (0.929 to 1.088) |
| Asthma                              | 46,802      | 347,481   | 86   |          |                |
| IVW (Multiplicative random effect)  | 0.47        |           |      | 1.008 (0.986 to 1.032) |
| IVW (Fixed effect)                  | 0.43        |           |      | 1.008 (0.988 to 1.030) |
| Weighted median                     | 0.873       |           |      | 1.003 (0.971 to 1.036) |
| MR Egger                            | 0.875       |           |      | 1.005 (0.949 to 1.064) |
| Moderate-severe asthma              | 5,135       | 25,675    | 12   |          |                |
| IVW (Multiplicative random effect)  | 0.93        |           |      | 1.001 (0.981 to 1.021) |
| IVW (Fixed effect)                  | 0.928       |           |      | 1.001 (0.982 to 1.020) |
| Weighted median                     | 0.422       |           |      | 0.989 (0.963 to 1.016) |
| MR Egger                            | 0.668       |           |      | 1.028 (0.909 to 1.163) |

Fig. 3 Odds ratios for the associations between genetically predicted allergic disease, asthma, moderate-severe asthma and risk of insomnia. SNPs: the number of SNPs used as instrumental variables; P: P-value of the causal estimate; OR: odds ratio; CI: confidence interval

Fig. 4 Scatterplots of potential effects of SNPs on allergic disease, asthma, moderate-severe asthma versus insomnia. A: Allergic disease; B: asthma; C: moderate–severe asthma. Analyses were conducted using the fixed and multiplicative random effects IVW, MR-Egger, Weighted median methods. The slope of each line corresponding to the estimated MR effect per method.
work was associated with an increased risk of asthma, and it was proposed that circadian misalignment should be the main cause [30]. In terms of sleep duration, a clinical trial indicated that sleep restriction in asthmatics resulted in lower morning peak flow and forced expiratory volume in one second (FEV1) measurements [31]. Previous cross-sectional study has indicated that sleep duration < 7.8 h per night was associated with the higher odds of food and aeroallergens sensitization in rural Chinese adolescents [32]. In this study, we did not observe significant causal association between insomnia and childhood asthma. However, one retrospective cohort study demonstrated that frequent nocturnal awakening in early life is associated with subsequent asthma [34]. Given insomnia was not the pronounced sleep problem among children [35], evidence is quite limited to get clear knowledge; more studies are needed to focus on children population.

In individuals with allergic disease, insomnia usually appear to be frequent [8, 9]. Unfortunately, we could not find evidence that genetically predicted allergic disease, asthma, or moderate-to-severe asthma was causally linked with the increased risk of insomnia. The similar finding was observed by another MR analysis [12]. It seems that not all epidemiological link can be confirmed by MR study. A case in point is that most epidemiological data believed that there is a bidirectional causal relationship between insomnia and migraine, only a one-way link has been established by MR study, namely that genetically predicted insomnia is the risk for migraine [36]. In future studies, the causal associations between allergic disease, asthma, and insomnia need to be further explored by MR studies with larger GWAS samples.

Although the detailed pathophysiological bases remain to be resolved, several hypotheses have been set up to explain the link between insomnia and allergic disease. Insomnia or sleep loss could lead to a dysregulation of the immune system, which in turn reduces the number and the activity of natural killer cells and T cells in the body, which could increase individual's susceptibility to allergens [37–39]. Insomnia is involved in the regulation of hypothalamus–pituitary–adrenal axis and the sympathetic nervous system, both of which together with tilting the basal gene expression profile toward increased pro-inflammatory [40, 41], activating β-adrenergic signaling, and inducing the increases in NF-κB, inflammatory gene expression, proinflammatory cytokines production, and systemic inflammation markers [41]. Meanwhile, insomnia could disturb the functional rhythm of regulatory T cells [39, 42], shifting the T helper 1 cell (TH1)/TH2 balance toward TH2 dominance [43], and TH2 response contributes to allergic inflammatory disorders, including asthma, allergic rhinitis, atopic dermatitis, and anaphylaxis [44, 45]. Melatonin, a circadian regulating endocrine hormone, plays function in body's immunomodulatory, antioxidant, and cytoprotective

### Table 1 Pleiotropy and heterogeneity test of insomnia on allergic disease, asthma and its phenotypes

| Outcomes                        | MR‑Egger Test       | Cochrane Q Test | MR‑PRESSO Global Test |
|---------------------------------|---------------------|-----------------|-----------------------|
|                                 | Intercept SE P‑value| MR‑Egger Q Q_df | MR‑PRESSO Q Q_df I²  |
| Allergic disease                | 0.002 0.002 0.360   | 218.5 194 0.112 | 219.0 195 0.110 0.110 |
| Asthma                          | 0.004 0.003 0.135   | 130.7 111 0.151 | 133.3 112 0.160 0.083 |
| Moderate-severe asthma          | −0.018 0.009 0.038  | 182.6 174 0.047 | 187.2 175 0.065 0.250 |
| Adult-onset asthma              | 0.007 0.004 0.062   | 140.9 118 0.163 | 145.1 119 0.180 0.052 |
| Childhood asthma                | 0.002 0.006 0.747   | 129.9 114 0.123 | 130.0 115 0.116 0.160 |

**SE standard error, df degree of freedom**

### Table 2 Pleiotropy and heterogeneity test of allergic disease, asthma and its phenotype on insomnia

| Exposures                        | MR‑Egger test       | Cochrane Q test | MR‑PRESSO global test |
|----------------------------------|---------------------|-----------------|-----------------------|
|                                 | Intercept SE P‑value| MR‑Egger Q Q_df | MR‑PRESSO Q Q_df I²  |
| Allergic disease                 | −0.001 0.002 0.675  | 116.3 96 0.175  | 116.6 97 0.168 0.086 |
| Asthma                           | 0.0002 0.002 0.887  | 101.4 84 0.172  | 101.4 85 0.162 0.108 |
| Moderate-severe asthma           | −0.004 0.010 0.674  | 11.4 10 0.140   | 11.6 11 0.055 0.391 |

**SE standard error, df degree of freedom**
Insomnia suppresses melatonin production, thereby exacerbates immune disorders and activate the inflammatory pathway [47]. The present study includes the following pronounced strengths. First, the samples used were gathered across populations with the same European ancestries, which minimized stratification bias. Second, we used the publicly available GWAS datasets with the largest sample sizes hitherto for both the exposure and outcome datasets, and F-statistics were also large enough to control weak instrumental bias. Third, a range of pleiotropy assessment and sensitivity analyses relaxed the IV assumptions and supported the robustness of our MR findings. However, we must pay attention to several limitations. Firstly, there may have been some participant overlap in exposure and outcomes, which would reduce the data quality. Secondly, the diagnoses of some cases were based on self-reported condition collected through questionnaires, which is possible to lead to misclassification. Lastly, only populations of European ancestry were incorporated into our MR analysis, the findings need to be verified in populations with other ancestries.

Conclusion
Using a bidirectional MR approach, our results provided suggestive evidence that genetically predicted insomnia was associated with an increased risk of allergic disease, asthma, moderate-severe asthma, and adult-onset asthma. Improving sleep quality may be one of the cornerstones in the prevention of allergic disease and asthma. Conversely, no evidence supported that genetically predicted allergic disease, asthma, or moderate-severe asthma was associated with the risk of insomnia. In future, replication of these findings using even larger GWAS are required.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12931-022-02009-6.

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Author contributions
RL and YC designed the study, contributed to the data analysis, and wrote the manuscript. LH, AZ, ZL, and WK contributed to the data analysis and data interpretation. SL, ST, YG, and YY contributed to manuscript writing and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data used in the present study were obtained from genome-wide association study summary statistics which were publicly released by genetic consortia. Data can be obtained by a reasonable request to the corresponding author. All datasets generated for this study are included in the article/Additional files.

Declarations
Ethics approval and consent to participate
There were no patients directly involved in the overall process of our study. Our study was based on publicly available data only. All human studies included in this analysis were conducted according to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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