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Bidirectional Causal Relationship Between Sleep Duration, Insomnia, and Cerebral Infarction: A Two-Sample Mendelian Randomization Study

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Abstract: *Objective:* Observational studies suggest that abnormal sleep duration and insomnia are associated with stroke, but residual confounding factors, reverse causal bias, and the nonlinear characteristics of exposure-response relationships limit precise causal inference. This study employed a two-sample Mendelian randomization (MR) approach to systematically investigate the bidirectional causal relationship between sleep duration, insomnia, and cerebral infarction, clarifying their genetic causal effects. *Methods:* Genome-wide association study (GWAS) summary statistics were retrieved from the IEU OpenGWAS platform for sleep duration (ieu-a-1088; 128,266 participants of European descent), insomnia (ukb-b-3957; 462,341 participants of European descent), and cerebral infarction (ukb-d-I63; 361,194 participants of European descent). The inverse variance weighted (IVW) method was used as the core analytical approach, combined with the maximum likelihood method, MR-Egger regression, weighted median method, and weighted mode method for sensitivity analysis. Cochran's Q test quantified heterogeneity across genetic instruments, while the MR-Egger intercept test was applied to detect directional horizontal pleiotropy. *Results:* After data harmonization, 26, 38, 24, and 128 genetic variants were included in the analyses of sleep duration → cerebral infarction, insomnia → cerebral infarction, cerebral infarction → sleep duration, and cerebral infarction → insomnia, respectively. IVW analysis revealed no significant causal effect of genetically predicted sleep duration on cerebral infarction [OR=1.002, 95% confidence interval (CI): 0.998-1.006, *P*=0.252], nor did genetic susceptibility to insomnia significantly affect the risk of cerebral infarction (OR=0.994, 95% CI: 0.988-1.001, *P*=0.100). In reverse analyses, genetic susceptibility to cerebral infarction showed no significant causal relationship with sleep duration (β=0.394, 95% CI: -1.620-2.408, *P*=0.701) or the insomnia phenotype (β=0.057 SD, 95% CI: -0.245-0.360, *P*=0.711). The results of various supplementary analyses were consistent with the core IVW results, demonstrating stable conclusions. Neither the Cochran's Q test nor the MR-Egger intercept test detected significant heterogeneity or directional horizontal pleiotropy. *Conclusion:* This bidirectional MR study indicates that there is currently no reliable genetic evidence supporting a bidirectional causal relationship between sleep duration, insomnia, and cerebral infarction. Their clinical correlation may be largely mediated by non-genetic confounding factors.

Keywords: Sleep duration; Insomnia; Cerebral infarction; Mendelian randomization; Bidirectional analysis

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1. Introduction

Cerebral infarction is a major cause of death and long-term neurological deficits in the population, imposing a heavy burden on the public health system. Its complex genetic architecture and subtype heterogeneity have been confirmed by multiple cross-ancestry genetic studies [1–2]. Identifying modifiable risk factors is crucial for primary prevention of cerebral infarction, but traditional behavioral risk factors are often confounded by vascular pathology, psychological state, and socioeconomic factors, making it difficult to establish independent causal relationships accurately. Abnormal sleep duration and insomnia are prevalent and modifiable lifestyle risk factors in the population that can participate in the cerebrovascular pathology process through various pathways, including autonomic nervous system dysfunction, increased blood pressure, metabolic abnormalities, chronic inflammation, and endothelial damage. Existing observational studies and meta-analyses indicate that both short and long sleep durations are associated with an increased risk of stroke incidence and mortality, often exhibiting U-shaped or J-shaped nonlinear exposure-response relationships. Persistent insomnia has also been shown to increase the risk of stroke incidence [3–7]. However, current studies suffer from methodological heterogeneity, with inconsistent sleep assessment methods, study populations, and outcome definitions. Moreover, sleep disturbances are often accompanied by confounding factors such as hypertension, obesity, depression, and sleep-disordered breathing, leading to observational associations susceptible to residual confounding, reverse causality, and subclinical disease interference [8]. The true causal relationship between sleep and cerebral infarction remains to be further validated.

Mendelian randomization, by selecting germline genetic variants stably associated with exposure phenotypes as instrumental variables, can effectively circumvent confounding bias and reverse causality issues inherent in traditional observational studies, providing reliable genetic evidence for causal inference of diseases [9–10]. Nevertheless, issues such as sample overlap, weak instrument bias, horizontal pleiotropy, and non-standardized analytical reporting can still affect the accuracy and stability of MR study conclusions [11–12]. Existing MR studies have not found a stable linear causal relationship between sleep duration and overall stroke risk and suggest potential heterogeneity between different sleep characteristics and stroke phenotypes, with no unified conclusion on their causal relationship [13].

Notably, most existing studies have focused on the unidirectional effect of sleep phenotypes on stroke, neglecting their bidirectional interaction effects. Clinical studies have confirmed that patients with cerebral infarction often experience sleep disturbances such as abnormal sleep duration, insomnia, and decreased sleep quality after onset, and these abnormal sleep states are closely related to neurological recovery, cognitive prognosis, and the risk of recurrent cardiovascular and cerebrovascular events in patients [14–15]. However, no study has yet determined whether genetic susceptibility to cerebral infarction can reversely regulate sleep duration and insomnia phenotypes at the population level. Based on this, this study employed a bidirectional two-sample MR analysis to clarify:

(1) the causal effect of genetically predicted sleep duration and insomnia on the risk of cerebral infarction incidence;

(2) the reverse causal impact of genetic susceptibility to cerebral infarction on sleep duration and insomnia phenotypes, providing genetic evidence to clarify the causal relationship between sleep and cerebral infarction and refine precise prevention strategies for cerebral infarction.

2. Methods

2.1. Study design and fundamental assumptions

This study employed a bidirectional two-sample Mendelian Randomization (MR) design based on publicly available GWAS summary statistics. The analysis was conducted in accordance with three core assumptions regarding instrumental variables: the selected genetic variants are associated with the exposure; the genetic variants are independent of confounding factors in the exposure-outcome relationship; and the genetic variants affect the outcome solely through the exposure, without exhibiting unbalanced horizontal pleiotropy [11]. The study design, analysis, and result reporting adhered to the recommendations of the STROBE-MR statement and recent quality studies on MR reporting [12]. This study evaluated four directions: sleep duration → cerebral infarction, insomnia → cerebral infarction, cerebral infarction → sleep duration, and cerebral infarction → insomnia.

2.2. GWAS data sources

Summary statistics were obtained from the IEU OpenGWAS platform. All datasets primarily consisted of participants of European ancestry to minimize bias caused by significant population stratification. For sleep duration, the ieu-a-1088 dataset was used, derived from 128,266 UK Biobank participants; for insomnia, the ukb-b-3957 dataset was utilized, representing an ordinal categorical phenotype from the UK Biobank with 462,341 participants; and for cerebral infarction, the ukb-d-I63 dataset was employed, based on ICD-10 I63 diagnoses from 361,194 UK Biobank participants, including 2,353 cases and 358,841 controls. The main characteristics of each dataset are presented in **Table 1**.

Table 1. GWAS datasets used in the bidirectional Mendelian randomization study

Trait	OpenGWAS ID	Role	Population	Sample size	Phenotype/scale	Year
Sleep duration	ieu-a-1088	Exposure and outcome	European	128,266	Self-reported; continuous; SD	2016
Insomnia symptoms	ukb-b-3957	Exposure and outcome	European	462,341	Ordered categorical phenotype; SD	2018
Cerebral infarction	ukb-d-I63	Exposure and outcome	European	361,194	ICD-10 I63; binary; 2,353 cases	2018

Abbreviations: GWAS, genome-wide association study; ICD-10, International Classification of Diseases, 10th Revision; SD, standard deviation

2.3. Selection of instrumental variables and data harmonization

To ensure the reliability and statistical power of the bidirectional Mendelian Randomization (MR) analysis, this study rigorously screened eligible single nucleotide polymorphisms (SNPs) as genetic instrumental variables. Independent SNPs associated with each exposure were selected using a genome-wide significance threshold of $P < 5 \times 10^{-8}$. Linkage disequilibrium pruning was performed using a European reference population, with parameters set at $r^2 < 0.001$ and a window distance of 10,000 kb. To mitigate weak instrument bias, variants with an F-statistic ≤ 10 were excluded. The effect alleles in the exposure and outcome data were harmonized to ensure that the SNP effects corresponded to the same effect allele. Palindromic SNPs with intermediate allele frequencies and indeterminate directions were excluded. When an exposure SNP was missing in the outcome data, it was handled according to the proxy SNP and allele alignment rules specified in the analytical protocol. Due to differences in variant availability and allele

compatibility, the number of instrumental variables ultimately included varied across the different analytical directions.

2.4. Mendelian randomization analysis

This study pre-specified the inverse variance weighted (IVW) method as the primary approach for estimating causal effects. This method combines the Wald ratios of each instrumental variable to estimate the overall effect size, providing precise and reliable causal effect estimates under the premise that all instrumental variables are valid or that sample-level pleiotropy cancels out. To verify the robustness of the results, multiple sensitivity analyses were conducted using the maximum likelihood method, MR-Egger regression, weighted median method, and weighted mode method [9–10].

2.5. Sensitivity analysis

Heterogeneity among SNP-specific estimates was assessed using the Cochran Q statistic from the IVW and MR-Egger models. Directional horizontal pleiotropy was examined using the MR-Egger intercept test. Statistical significance was set at $P < 0.05$. The analysis was performed using the TwoSampleMR framework in R software, and data sources, instrumental variable selection, primary analysis, and sensitivity analysis were transparently reported in accordance with STROBE-MR guidelines [16–17].

3. Results

3.1. Composition of instrumental variables

After data extraction and harmonization, 26 SNPs were retained for the sleep duration → cerebral infarction analysis, 38 SNPs for the insomnia → cerebral infarction analysis, 24 SNPs for the cerebral infarction → sleep duration analysis, and 128 SNPs for the cerebral infarction → insomnia analysis. The variation in the number of instrumental variables across different directions reflects the genetic architecture of each exposure GWAS and the number of variants that could be harmonized in the outcome dataset.

3.2. Effects of sleep duration and insomnia on cerebral infarction

The primary IVW analysis did not support a causal effect of genetically predicted sleep duration on cerebral infarction (OR = 1.002, 95% CI: 0.998-1.006, $P = 0.252$). Similar non-significant results were obtained using the maximum likelihood method, MR-Egger, weighted median method, and weighted mode method, with effect estimates closely clustered around the null value **(Table 2)**.

The IVW analysis also failed to detect an association between genetic susceptibility to insomnia and cerebral infarction (OR = 0.994, 95% CI: 0.988-1.001, $P = 0.100$). The maximum likelihood method yielded a similar estimate (OR = 0.994, 95% CI: 0.988-1.001, $P = 0.077$), and none of the other robust estimation methods reached statistical significance. Thus, the forward analysis provided no evidence to support that a linear increase in sleep duration or heightened genetic susceptibility to the insomnia phenotype leads to cerebral infarction.

Table 2. Bidirectional Mendelian randomization estimates

Direction	Method	SNPs	Effect scale	Estimate	95% CI	*P* value
Sleep duration → cerebral infarction	IVW	26	OR	1.002	0.998 to 1.006	0.252
	Maximum likelihood	26	OR	1.002	0.998 to 1.006	0.248
	MR-Egger	26	OR	1.005	0.992 to 1.019	0.419
	Weighted median	26	OR	1.001	0.996 to 1.006	0.666
	Weighted mode	26	OR	1.002	0.993 to 1.011	0.692
Insomnia symptoms → cerebral infarction	IVW	38	OR	0.994	0.988 to 1.001	0.100
	Maximum likelihood	38	OR	0.994	0.988 to 1.001	0.077
	MR-Egger	38	OR	0.991	0.969 to 1.012	0.397
	Weighted median	38	OR	0.997	0.987 to 1.006	0.487
	Weighted mode	38	OR	0.999	0.985 to 1.012	0.835
Cerebral infarction → sleep duration	IVW	24	β (SD)	0.394	−1.620 to 2.408	0.701
	Maximum likelihood	24	β (SD)	0.414	−1.474 to 2.303	0.667
	MR-Egger	24	β (SD)	1.389	−2.809 to 5.588	0.523
	Weighted median	24	β (SD)	1.045	−1.649 to 3.739	0.447
	Weighted mode	24	β (SD)	0.956	−3.600 to 5.512	0.685
Cerebral infarction → insomnia symptoms	IVW	128	β (SD)	0.057	−0.245 to 0.360	0.711
	Maximum likelihood	128	β (SD)	0.058	−0.253 to 0.368	0.715
	MR-Egger	128	β (SD)	−0.040	−0.662 to 0.582	0.901
	Weighted median	128	β (SD)	−0.007	−0.443 to 0.429	0.974
	Weighted mode	128	β (SD)	−0.014	−1.175 to 1.146	0.981

Note: Forward effects are expressed as odds ratios (ORs) for cerebral infarction per 1-SD increase in the genetically predicted sleep phenotype. Reverse effects are expressed as β coefficients in SD units for the standardized sleep phenotype per unit increase in genetic liability to cerebral infarction. Abbreviations: CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; SD, standard deviation; SNP, single-nucleotide polymorphism.

3.3. Effects of genetic susceptibility to cerebral infarction on sleep phenotypes

The reverse analysis revealed no significant association between genetic susceptibility to cerebral infarction and sleep duration (IVW β = 0.394, 95% CI: -1.620-2.408, P = 0.701). Estimates from other methods were also non-significant. The wide confidence intervals suggest limited precision in the estimates, and a potentially clinically meaningful effect of genetic susceptibility to cerebral infarction on sleep duration cannot be excluded.

Similarly, no significant association was found between genetic susceptibility to cerebral infarction and insomnia (IVW β = 0.057, 95% CI: -0.245-0.360, P = 0.711). Consistent negative results were obtained using the maximum likelihood method, MR-Egger, weighted median method, and weighted mode method. As with the sleep duration analysis, this result reflects genetic susceptibility to cerebral infarction and does not exclude sleep disturbances caused by neurological impairment, psychological changes, or treatment consequences following the actual occurrence of cerebral infarction. The effect estimates from various methods in the bidirectional MR analysis of sleep phenotypes and cerebral infarction are shown in **Figure 1**.

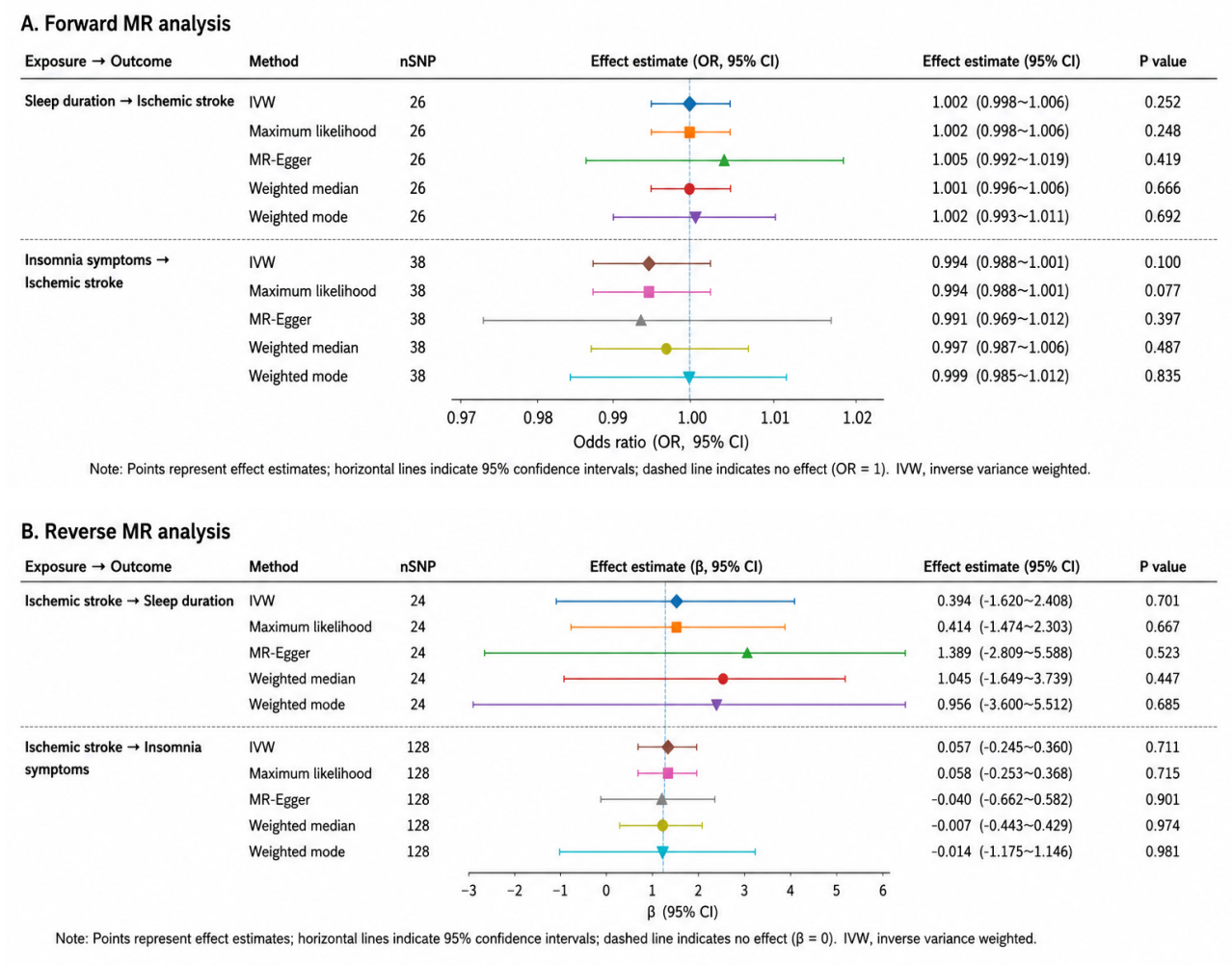

Figure 1. Forest plot of bidirectional Mendelian randomization (MR) analysis on sleep duration, insomnia, and cerebral infarction. (A) Forward MR analysis of the effects of sleep duration and insomnia on cerebral infarction, with effect sizes expressed as odds ratios (ORs) and 95% confidence intervals (CIs); (B) Reverse MR analysis of the effects of genetic predisposition to cerebral infarction on sleep duration and insomnia, with effect sizes expressed as β coefficients and 95% CIs. The dashed line represents the line of no effect, and the inverse-variance weighted (IVW) method was the primary analytical approach

3.4. Heterogeneity, pleiotropy, and directionality

No significant heterogeneity was indicated by the Cochran Q test in any of the analytical directions (**Table 3**). The *P*-values for the IVW Q test were as follows: sleep duration → cerebral infarction: 0.913, insomnia → cerebral infarction: 0.242, cerebral infarction → sleep duration: 0.223, cerebral infarction → insomnia: 0.665. The MR-Egger intercept test was also non-significant in all cases ($P = 0.600–0.727$), providing no statistical evidence of directional horizontal pleiotropy.

Table 3. Heterogeneity and directional pleiotropy analyses

Direction	Q-test method	Q statistic	df	Q-test P value	MR-Egger intercept	SE	Intercept *P* value
Sleep duration → cerebral infarction	IVW	16.055	25	0.913	−0.000084	0.000165	0.613
	MR-Egger	15.792	24	0.895			
Insomnia symptoms → cerebral infarction	IVW	42.613	37	0.242	0.000045	0.000126	0.721
	MR-Egger	42.460	36	0.213			
Cerebral infarction → sleep duration	IVW	27.803	23	0.223	−0.001708	0.003210	0.600
	MR-Egger	27.450	22	0.195			
Cerebral infarction → insomnia symptoms	IVW	119.679	127	0.665	0.000173	0.000494	0.727
	MR-Egger	119.556	126	0.645			

Note: The MR-Egger intercept is shown once for each analytical direction. A nonsignificant intercept test does not prove the absence of pleiotropy but indicates no statistical evidence of unbalanced directional horizontal pleiotropy. Abbreviations: df, degrees of freedom; IVW, inverse-variance weighted; SE, standard error.

4. Discussion

This bidirectional two-sample MR study found no clear evidence to support a causal effect of genetically predicted sleep duration or genetic predisposition to insomnia on cerebral infarction, nor did it find evidence that genetic predisposition to cerebral infarction alters sleep duration or insomnia. Consistent results across the IVW, maximum likelihood, MR-Egger, weighted median, and weighted mode methods reinforced the internal consistency of the negative findings. The Cochran Q test revealed no heterogeneity, and the MR-Egger intercept did not suggest directional pleiotropy.

Several observational studies and meta-analyses have indicated a U-shaped or J-shaped nonlinear relationship between sleep duration and stroke risk, with both insufficient and excessive sleep, as well as persistent insomnia, identified as potential risk factors for cardiovascular and cerebrovascular diseases [6, 18–21]. This genetic causal analysis found no linear causal association between sleep duration, insomnia, and cerebral infarction, consistent with recent studies combining observational cohorts with MR approaches, suggesting that observational correlations do not equate to genetic causal effects [22]. The discrepancies primarily stem from inherent limitations of observational research methods: observational studies are susceptible to confounding factors, reverse causation, and subclinical disease interference, revealing only association trends; in contrast, Mendelian randomization effectively circumvents postnatal confounding biases through germline genetic variations, making it more suitable for causal inference. Furthermore, previous studies have primarily focused on the stroke risk associated with extreme sleep durations and long-term insomnia trajectories, whereas conventional two-sample MR can only evaluate overall average linear effects and cannot capture nonlinear risk characteristics at both ends, which may be a significant reason for the absence of positive linear associations in this study. Additionally, the ukb-b-3957 insomnia phenotype used in this study is a self-reported genetic proxy phenotype in the population, differing phenotypically from clinically confirmed chronic insomnia, and does not differentiate stroke subtypes, potentially overlooking potential subtype-specific associations between the two.

Regarding sleep duration, multiple dose-response meta-analyses have confirmed a U-shaped nonlinear association with cardiovascular and cerebrovascular risk, with both short and long sleep durations exerting adverse vascular effects, although the risk intensities of these two extreme phenotypes differ [6, 23–31]. Conventional linear MR can only estimate overall average effects, with opposing risk effects at both extremes canceling each other out, resulting in an overall effect approaching null. Therefore, this negative result does not negate the cerebrovascular damage caused by extreme abnormal sleep. The negative result for insomnia is primarily attributed to phenotypic heterogeneity: the insomnia phenotype in this study is based on a population self-reported sleep disturbance scale, not clinically confirmed pathological insomnia, and its genetic predisposition may overlap with confounding genetic traits such as mood and neuroticism, representing only the population's sleep-related genetic load and not directly generalizable to clinical insomnia subtypes. The negative results of the reverse analysis do not contradict clinical post-stroke sleep disorders: sleep abnormalities after clinical cerebral infarction are mostly secondary to brain injury, neurological deficits, mood changes, and clinical interventions, whereas this MR analysis focuses on the impact of congenital genetic predisposition on basic sleep phenotypes, with different research dimensions. Additionally, the confidence interval for the effect of cerebral infarction on sleep duration is wide, and a weak potential clinical effect cannot be completely ruled out.

This study's methodological design offers significant advantages. First, the bidirectional MR design comprehensively validated the bidirectional causal hypotheses between sleep and cerebral infarction, addressing the limitations of previous unidirectional studies that could not distinguish causal sequences or ignore bidirectional interactions. Second, the study, based on large-sample public GWAS data from individuals of European ancestry, effectively controlled for population stratification bias, and the high consistency of results across multiple MR methods with different statistical assumptions ensured the robustness of the conclusions. Third, the study strictly differentiated between the OR effects of binary cerebral infarction outcomes and the β effects of continuous sleep phenotypes, providing differentiated interpretations of bidirectional outcomes and avoiding bias caused by mismatched effect dimensions. Finally, systematic quality control of instrumental variables, along with heterogeneity and pleiotropy tests, minimized common biases in MR analysis, ensuring the accuracy of causal inference.

However, this study also has several methodological limitations. First, the study data were mostly sourced from the UK Biobank cohort, with potential sample overlap, which could introduce slight estimation bias under conditions of weak instrumental variables. Second, although weak instrumental variables with $F \leq 10$ were excluded, the use of conventional genome-wide significance thresholds for instrumental variable selection could not completely eliminate weak instrumental variable interference. Third, sleep duration and insomnia were self-reported phenotypes, subject to subjective bias and not fully reflective of objective sleep structure or clinical sleep disorders. Fourth, the study, based on overall cerebral infarction outcomes (ICD-10 I63), did not differentiate ischemic stroke subtypes, making it impossible to rule out the possibility of specific causal associations between different subtypes and sleep phenotypes. Fifth, the linear MR model could not test for nonlinear and threshold effects between sleep and cerebral infarction, making it difficult to identify special risks associated with extreme sleep durations. Sixth, the study included only individuals of European ancestry, requiring caution when generalizing the conclusions to other ethnic groups.

5. Conclusion

In summary, this bidirectional two-sample Mendelian randomization study suggests that, at the level of genetic linear effects, there is no clear bidirectional causal association between sleep duration, genetic predisposition to insomnia, and cerebral infarction. The correlations between sleep abnormalities and cerebral infarction reported in previous observational studies are not attributable to congenital genetic linear causal effects but are more likely mediated by postnatal confounding factors, nonlinear dose effects, and secondary sleep disorders after cerebral infarction. Future research could leverage individual clinical data to conduct nonlinear MR analyses, further exploring the specific associations between extreme sleep durations, clinically confirmed insomnia subtypes, and different ischemic stroke subtypes, elucidating the causal mechanisms between sleep disorders and cerebral infarction, and providing a more comprehensive genetic basis for the precise prevention and control of sleep-related risk factors for cerebral infarction.

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Disclosure statement

The authors declare no conflict of interest.

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