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Review Article

Association of sleep traits with myopia in children and adolescents: A meta-analysis and Mendelian randomization study

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ABSTRACT

Purpose: The association between sleep and myopia in children and adolescents has been reported, yet it remains controversial and inconclusive. This study aimed to investigate the influence of different sleep traits on the risk of myopia using meta-analytical and Mendelian randomization (MR) techniques.

Methods: The literature search was performed in August 31, 2023 based on PubMed, Embase, Web of Science, and Cochrane library. The meta-analysis of observational studies reporting the relationship between sleep and myopia was conducted. MR analyses were carried out to assess the causal impact of genetic pre-disposition for sleep traits on myopia.

Results: The results of the meta-analysis indicated a significant association between the risk of myopia and both short sleep duration [odds ratio (OR) = 1.23, 95% confidence interval (CI) = 1.08–1.42, P = 0.003] and long sleep duration (OR = 0.75, 95% CI = 0.66–0.86, $P < 0.001$). MR analyses revealed no significant causal associations of genetically determined sleep traits with myopia, including chronotype, sleep duration, short sleep duration and long sleep duration (all $P > 0.05$).

Conclusions: No evidence was found to support a causal relationship between sleep traits and myopia. While sleep may not independently predict the risk of myopia, the potential impact of sleep on the occurrence and development of myopia cannot be disregarded.

1. Introduction

Myopia is a common condition in childhood and early adulthood resulting in blurred distance vision due to the focal point of parallel light rays falling in front of the retina. (Han et al., 2022; Baird et al., 2020) The prevalence of myopia has increased dramatically in recent decades, with 4.8 billion individuals projected to be affected by this condition by 2050. (Holden et al., 2016) As one of the leading causes of visual impairment and blindness, myopia poses significant economic loss and public health burden, especially in East and Southeast Asia. (Baird et al., 2020; Morgan et al., 2018) Considering the increasing prevalence and adverse consequences of myopia, feasible interventions are essential to achieve effective prevention and control.

Sleep disorders are highly prevalent among children and adolescents (57.8%) (Wheaton et al., 2018) and have been proven to be associated with a number of adverse health outcomes, including obesity (Chaput et al., 2023), depression (Roberts and Duong, 2014)and decreased immunity. (Haspel et al., 2020) The association between sleep and myopia in children and adolescents has been reported in previous studies (Liu et al., 2023), but the conclusions are inconsistent and require further

Abbreviations: MR, Mendelian randomization; OR, Odds ratio; CI, Confidence interval; IVs, Instrumental variables; SNP, Single nucleotide polymorphism; GWAS, Genome-wide association study; PRISMA, Preferred reporting items for systematic Revie; AHRQ, Agency for Healthcare Research and Quality; NOS, Newcastle-Ottawa scale; IVW, Inverse-variance-weighted; CS, Cross-sectional study; LS, Longitudinal study; M, Mean; SD, Standard deviation; SE, Spherical equivalent; h, Hours; PSQI, Pittsburgh sleep quality index; CSHQ, Children's sleep habits questionnaire; Ref., Reference; Trial sequential analysis, TSA.

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clarification. A recent study in China suggested that insufficient sleep and irregular sleep-wake schedules may be risk factors for myopia. (Xu et al., 2023) A cross-sectional study conducted among school-aged children showed no significant association between sleep patterns (sleep quality, sleep duration, bedtime and wake time) and myopia. (Li et al., 2022a) The evidence from a nationwide study suggested that long sleep duration (sleep duration >9 h) has a protective effect on myopia. (Jee et al., 2016)

Mendelian randomization (MR) is a novel and effective approach to causal inference by using genetic variants of exposure as instrumental variables (IVs). (Lu et al., 2020) MR overcomes the limitations of traditional epidemiological research in causal inference by reducing residual confounding and eliminating reverse causality bias. (Bowden et al., 2016; Sheehan et al., 2008) In recent years, the application of MR in the assessment of influencing factors for ocular disorders has gradually received increasing attention. For example, several MR studies have established causal relationships between education and myopia (Mountjoy et al., 2018), glucose and myopia (Li et al., 2023), and behavior and cataract. (Li et al., 2023)

Sleep is a multi-dimensional concept (Billings et al., 2020; Gardiner et al., 2023), and multiple aspects need to be taken into account when assessing the association of sleep with myopia. In the current study, we conducted a meta-analysis of observational studies to assess the association between different sleep traits and the risk of myopia. Subsequently, we employed MR analysis using genome-wide association study (GWAS) summary statistics to ascertain the causal effect of genetically determined sleep traits on myopia.

2. Methods

2.1. Meta-analysis

2.1.1. Search strategy

To ensure unbiased responses, a double-blind search strategy was implemented. A comprehensive literature search was conducted in PubMed, Web of Science, Embase, and Cochrane Library from the inception of each database until August 31, 2023. The search strategy used in PubMed was as follows: "(bedtime [All Fields] OR wake time [All Fields] OR sleep duration [Mesh] OR total sleep time OR sleep time OR sleep quantity OR sleep quantities OR sleep quality [Mesh] OR sleep qualities OR sleep [Mesh] OR sleeping habits OR sleep habits OR sleep habit OR sleeping habit)". For consistency, all keywords were adjusted according to the respective syntactic requirements in the Web of Science, Embase, and Cochrane Library. Complete search strategies for other databases are provided in the **Supplementary Table 1**. The reference lists of identified review articles were manually searched to retrieve any additional relevant publications. The reporting of this study was based on the Preferred Reporting Items for Systematic Review (PRISMA) reporting guidelines. (Zhang et al., 2022)

2.1.2. Inclusion and exclusion criteria

The eligible studies for inclusion in the analysis had to meet the following criteria: (a) cross-sectional study or cohort study; (b) English language; (c) studies demonstrating the association between sleep traits and myopia; (d) studies that reported or provided sufficient data to calculate odds ratio (*OR*) and 95% confidence interval (95% *CI*); and (e) studies with larger sample size were preferred when there were overlapping study populations reporting the same disease outcomes. (Zhou et al., 2023) The following criteria were used for exclusion: (a) systematic reviews, meta-analyses, editorials, case reports, comments, and letters; (b) summaries or abstracts from conferences or meetings; and (c) studies conducted on animals or in vitro.

2.1.3. Data extraction and quality assessment

Two independent authors were responsible for extracting data from the eligible studies. The Agency for Healthcare Research and Quality (AHRQ) (Zeng et al., 2015) was utilized to assess the quality of the cross-sectional studies. Each cross-sectional study was classified as low quality (0–7 points) or high quality ($\geq$ 8 points) based on the overall score assigned by the AHRQ. For cohort studies, the Newcastle-Ottawa Scale (NOS) was applied to assess their quality. The NOS score ranged from 0 to 9, with a score of 7–9 indicating high quality. (Zhou et al., 2023)

2.2. Statistical analysis

The meta-analysis was conducted using the "*Meta*" Package in STATA 17.0 software. A forest plot was generated to illustrate the association between sleep traits and myopia by pooling effect estimates from the included studies. The heterogeneity of the literature included in the analysis was assessed using the I-squared (I^2) statistic. (Chen and Benedetti, 2017) A random effects model was employed if I^2 was greater than or equal to 50%, indicating substantial heterogeneity. If I^2 was <50%, a fixed effects model was used. (DerSimonian and Laird, 2015) To explore potential sources of heterogeneity, subgroup analysis and meta-regression were performed. The statistical significance level for heterogeneity was set at two-sided $P < 0.05$. Publication bias was assessed by examining the symmetry of the funnel plot, which can indicate the potential for bias in the included studies. (Zhou et al., 2021) Sensitivity analysis was performed to assess the impact of each study on the overall results by sequentially excluding each study. (Zhou et al., 2021) We used trial sequential analysis to estimate the sample size of the meta-analysis (Brok et al., 2009), aiming to improve the reliability of the results of the combined analysis.

2.3. Mendelian randomization

2.3.1. Study design and data sources

The MR analysis was performed using data based on publicly available GWAS (**Supplementary Table 2**). Summary statistics for chronotype were obtained from a GWAS among 403,195 European individuals in the UK Biobank and 23andMe. (Jones et al., 2019) Chronotype was determined by asking "Do you consider yourself to be?". Morningness was defined as definitely a "morning" person and more a "morning" than an "evening" person. Summary statistics for sleep duration, short sleep duration and long sleep duration were extracted from a large-scale GWAS including 446,118 individuals of European ancestry from the UK Biobank. (Dashti et al., 2019) Sleep duration (n = 305,742 controls), short sleep duration (n = 106,192 cases) and long sleep duration (n = 34,184 cases) were defined as 7 h $\leq$ sleep duration <9 h, sleep duration <7 h and sleep duration $\geq$9 h, respectively. Summary statistics for myopia were integrated by the MRC IEU with a sample size of 460,536. Myopia was defined as reason for glasses/contact lenses: for short-sightedness, i.e., only or mainly for distance viewing such as driving, cinema, etc.

2.4. Statistical analysis

MR analysis between the sleep traits (chronotype, sleep duration, short sleep duration and long sleep duration) and myopia was performed using the "*TwoSampleMR*" and "*MRlap*" package in R version 4.2.1. "*MRlap*" packge simultaneously accounts and corrects for bias of weak instruments and winner's curse using cross-trait LD-score regression (LDSC). Single-nucleotide polymorphisms (SNPs) used as IVs in the MR analysis are required to meet three assumptions: linkage disequilibrium, population stratification, and pleiotropy. (Larsson et al., 2017) Therefore, SNPs meeting the following criteria were included: (a) $P < 5 \times 10^{-8}$; (b) $r^2 < 0.001$, clumping distance = 10,000 kb; and (c) F statistic >10. The inverse-variance-weighted (IVW) method was the main method to evaluate the causal associations between sleep traits and myopia. Sensitivity analysis was conducted to test the robustness using the MR-Egger method, weighted median method and weighted mode method. Leave-one-out analysis was applied to measure the influence of each IV on the overall results. Heterogeneity was examined using Cochran's Q test. When significant heterogeneity was observed, random-effects models were utilized for the MR analysis; otherwise, fixed-effects models were employed. The MR-Egger regression method was utilized to detect the presence of directional pleiotropy by examining whether the intercept significantly deviated from zero. If the intercept term shows a significant difference from zero, it indicates the presence of horizontal pleiotropy. The MR analysis was performed using R version 4.2.1. Two-sided P values of <0.05 were considered to be statistically significant.

The protocol and data collection procedures were approved by the ethics committee of the original articles and genome-wide association studies, and and written informed consents were obtained from each participant before data collection.

3. Results

3.1. Meta-analysis of the association between sleep traits and myopia

The detailed literature screening process is shown in Fig. 1. Based on the inclusion and exclusion criteria, a total of 29 articles were included (Xu et al., 2023; Li et al., 2022a; Jee et al., 2016; Peng et al., 2022; Li et al., 2022b; Zhou et al., 2015; Wang et al., 2017; Zhou et al., 2017; Pan et al., 2019; Huang et al., 2019; Qi et al., 2019; Wei et al., 2020; Qu et al., 2020; Rayapoullé et al., 2021; Hu et al., 2021; Xu et al., 2017; Liu et al., 2020; Lu et al., 2021; Liu et al., 2021; Saara et al., 2022; Wang et al., 2022; He et al., 2022; Yang et al., 2022a; Zhuang et al., 2022; Shi et al., 2023; Mu et al., 2023; Lin et al., 2023; Cui et al., 2023; Huang et al., 2022), comprising 22 cross-sectional studies and 7 cohort studies (*Kappa* = 0.872), demonstrating good consistency. The protocol for this meta-analysis was registered in PROSPERO (CRD 42023470049). Table 1 shows the characteristics of the included studies. A total of 209,979 participants were recruited from 2015 to 2023. The quality scores of the 22 cross-sectional studies ranged from 6 to 10, with 13 of them (59%) scoring >8 points, indicating relatively high quality. The cohort studies received quality scores ranging from 7 to 9, and all of them were classified as high-quality studies. **Supplementary Tables 3–4** present the methodological quality assessment table for the included studies.

Forest plots showed a significant association of short sleep duration (OR = 1.23, 95% CI = 1.08–1.42, P = 0.003) and long sleep duration (OR = 0.75, 95% CI = 0.66–0.86, P < 0.001) with the risk of myopia (Fig. 2). Sleep duration (continuous) (OR = 1.04, 95% CI = 0.90–1.19, P = 0.60), bedtime (OR = 1.17, 95% CI = 0.95–1.43, P = 0.14), wake time (OR = 0.99, 95% CI = 0.75–1.31, P = 0.94) and sleep quality (OR = 1.59, 95% CI = 0.98–2.56, P = 0.06) were not significantly associated with myopia (Fig. 2). A statistically significant association between sleep quality and myopia risk was shown in studies in China (OR = 1.94, 95% CI: 1.18–3.19, P = 0.009) (Table 2). Table 2 showd that short sleep duration (OR = 1.23, 95% CI: 1.05–1.44, P = 0.01) and long sleep duration (OR = 0.74, 95% CI: 0.65–0.85, P < 0.001) were associated with myopia in the cross-sectional study. However, short sleep duration (OR = 1.28, 95% CI: 0.92–1.77, P = 0.14) and long sleep duration (OR = 0.81, 95% CI: 0.54–1.21, P = 0.29) were not associated with myopia in cohort studies. Subgroup analysis results showed that study design was not a source of heterogeneity. The funnel plot exhibited basic symmetry, and no publication bias was observed within the included studies (**Supplementary Fig. 1**). The sensitivity analysis chart of the meta-analysis regarding bedtime, wake time, sleep duration, and myopia risk demonstrated stable and reliable combined results (**Supplementary Fig. 2**). Sample-size estimates were performed for eligible studies. The sample size in our study was higher than the TSA estimate of 125,715. (See Table 2.)

3.2. MR analyses of associations between sleep traits and myopia

We selected 122, 65, 24, and 6 SNPs as IVs based on their relevance, independence, and statistical strength in relation to chronotype, sleep duration, short sleep duration, and long sleep duration, respectively.

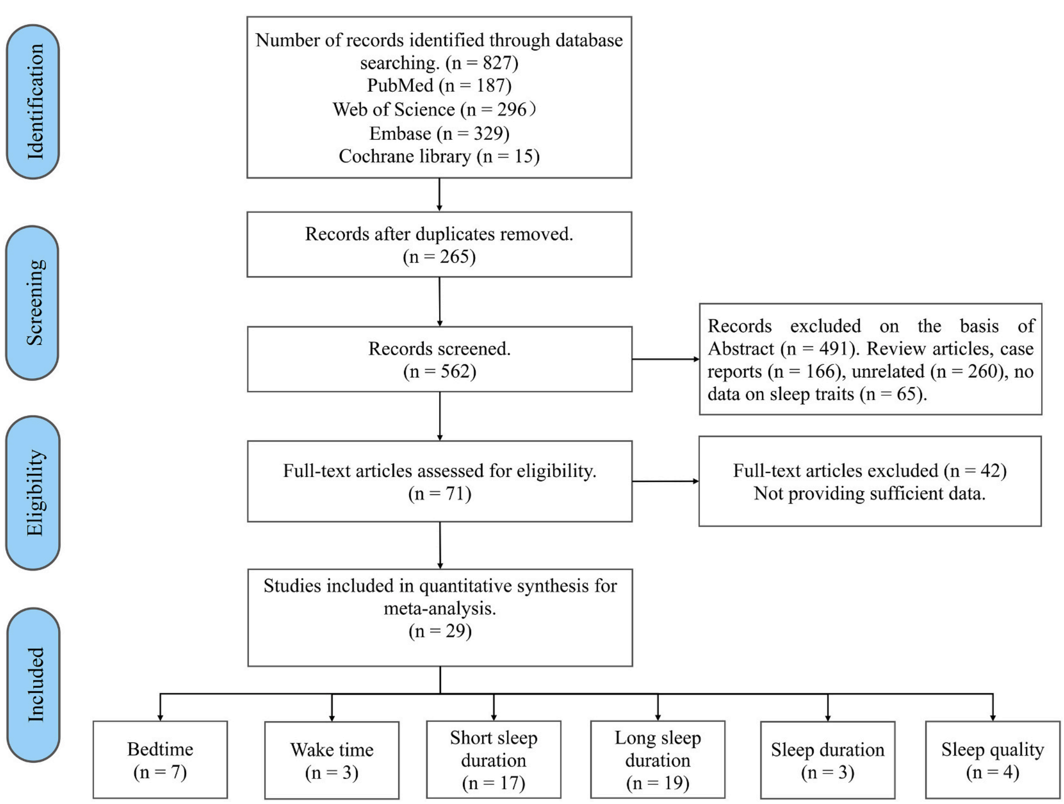

Fig. 1. Flowchart for identification of relevant articles for the meta-analysis.

Table 1
Characteristics of the included studies on the association between sleep traits and myopia.

Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	OR (95% CI)
Peng, et al. 2022	China	Asia	CS	6154	53.4%	13–16	Sleep duration \bedtime	Self-designed questionnaire	Visual acuity <20/20 a & SER < −0.50 D	Sleep duration: City: 1.09 (0.73,1.65) rural: 0.99 (0.67,1.48) bedtime: City: 0.56 (0.32,0.93) rural: 0.50 (0.28,0.90)
Saara, et al. 2022	India	Asia	CS	3850	16.1%	15.08 (1.23)	Sleep duration	Self-designed questionnaire	SE < −0.5D	> 7 h: Ref. < 7 h: 2.77 (2.03,3.79)
Lu, et al. 2021	China	Asia	CS	556	55.2%	9–12	Sleep duration	Self-designed questionnaire	Visual acuity <20/20 a & SER ≤ −0.50 D	≥ 8 h: Ref. < 8 h: 0.45 (0.17, 1.18)
Wang, et al. 2022	China	Asia	LS	24,318	51.2%	6–18	Sleep duration	Self-designed questionnaire	Visual acuity <20/20 a & SER ≤ −0.50 D	> 9 h: Ref. 8 - 9 h: 1.50 (1.36,1.65) 7–8 h: 3.39 (3.02,3.79) ≤ 7 h: 4.16 (3.45,5.02)
Jee, et al. 2016	Korea	Asia	CS	3625	52.9%	12–19	Sleep duration	Interview	SE ≤ − 0.5 D in both eyes	<5: Ref 6 h: 0.77 (0.49,1.19) 7 h: 0.85 (0.55,1.30) 8 h: 0.57 (0.37,0.89) >8 h: 0.59 (0.38,0.93)
Xu, et al. 2017	China	Asia	CS	15,316	48.5%	6–18	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	> 9 h: Ref. 8 h: 2.12 (1.94,2.31) < 7 h: 3.37 (3.07,3.70)
Wei, et al. 2020	China	Asia	LS	2328	57.9%	7.09 (0.41)	Sleep duration \bedtime	Self-designed questionnaire	SE ≤ −0.5 D	Sleep duration: ≤ − 9.56 h: Ref. 9.57–10 h: 1.01 (0.77,1.33) ≥ 10.01 h: 0.94 (0.71,1.25) bedtime: Early level: Ref. middle level: 1.02 (0.84, 1.25) late level: 0.88 (0.63, 1.24)
Liu, et al. 2020	China	Asia	LS	6295	53.2%	7.2 (0.7)	Sleep duration \bedtime	Self-designed questionnaire	SE ≤ − 0.5 D in both eyes	Sleep duration: < 9.5 h: Ref. 9.5–10 h: 1.02 (0.88,1.20) > 10 h: 1.04 (0.82,1.32) bedtime: < 9 p.m.: Ref. 9 - 9: 29 p.m.: 1.21 (0.91,1.61) > 9: 30 p.m.: 1.45 (1.05,2.00)
Li, et al. 2022	Singapore	Asia	CS	572	49.5%	8–9	Sleep duration\ bedtime\sleep quality\ wake time	CSHQ questionnaire	SE ≤ − 0.5 D	Sleep quality: 0.99 (0.96,1.02) sleep duration: 0.87(0.72,1.05) Bedtime: 0.87

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Table 1 (*continued*)

Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
										(0.71,1.07) wake time: 0.97 (0.78,1.21)
Zhou, et al. 2015	China	Asia	CS	1902	53.1%	9.80 (0.4)	Sleep duration	CSHQ questionnaire	SE ≤ − 0.5 D in both eyes	1.02 (1.01,1.04)

Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
Pan, et al. 2019	China	Asia	CS	948	55.7%	13–14	Sleep quality	CSHQ questionnaire	SE ≤ − 0.5 D	1.54 (0.90, 2.57)
Li, et al. 2022	China	Asia	CS	10,142	53.2%	7–12	Sleep duration \bedtime\wake time	CSHQ questionnaire	Self-report	Sleep duration: < 9 h: Ref. 9 - 10 h: 0.66 (0.58,0.73) 10 h: 0.46 (0.39,0.54) bedtime: < 9 p.m.: Ref. 9 p.m. - 9: 30 p.m.: 1.46 (1.16,183) 9: 30 p.m. - 10 p.m.: 1.51 (1.18,1.93) > 10 p.m.: 2.08 (1.57,2.77) wake time: < 6: 30 a.m.: Ref. 6: 30–7 a.m.: 1.15 (0.99,1.32) > 7 a.m.: 1.36 (1.16,1.60)
He, et al. 2022	China	Asia	CS	1410	55.5%	9–14	Sleep quality	PSQI、questionnaire	SE ≤ − 0.5 D	1.59 (1.12,2.25)
Shi, et al. 2023	China	Asia	CS	876	51.9%	7–16	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	1.21(1.07,1.36)

Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
Qi, et al. 2019	China	Asia	LS	522	100.0%	14–16	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	≤ 7 h: Ref. > 7 h: 0.97 (0.60,1.56)
Yang, et al. 2022	China	Asia	CS	14,051	52.2%	7–18	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	7–9 age: 0.78 (0.62–0.95) 10–12 age: 0.75 (0.66–0.85) 13–15 age: 0.83 (0.70–0.97) 16–18 age: 0.73 (0.56–0.96)
Liu, et al. 2021	China	Asia	CS	13,642	50.1%	9–18	Sleep duration	Self-designed questionnaire	Monocular visual acuity <6/6	≥ 9 h: Ref. 7 - 8 h: 1.2 (1.06,1.42) < 7 h: 1.3 (1.12,1.49)
Qu, et al. 2020	China	Asia	CS	1831	53.7%	11–18	Sleep duration \bedtime\wake time	Self-designed questionnaire	Self-report	Sleep duration: < 6 h: Ref. 6 - 8 h: 1.37 (0.93,2.03) ≥ 8 h: 1.18 (0.71,1.98) bedtime: < 10 p.m.: Ref. 10 pm - 11 p.m.: 0.90 (0.65,1.25) > 11 p.m.: 0.97 (0.63,1.49)

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Table 1 (*continued*)

Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
Mu, et al. 2023	China	Asia	LS	7597	54.3%	8–10	Sleep duration	Self-designed questionnaire	Visual acuity <20/20 a & SER < −0.50 D	wake time: < 6 a.m.: Ref. > 6 a.m.: 0.76 (0.58,1.00) < 8 h: Ref. 8 - 9 h: 0.51 (0.34,0.68) > 9 h: 0.45 (0.26,0.64)
Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
Zhuang, et al. 2022	China	Asia	CS	35,614	51.9%	12.38(1.78)	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	< 8 h: Ref. 8 - 10 h: 0.75 (0.7,0.8) > 10 h: 0.50 (0.46,0.55)
Rayapoullé, et al. 2021	France	Europe	LS	1130	52.6%	0–1\2\5	Sleep duration	Self-designed questionnaire	Self-report	< 10.75 h: 1.29 (0.47,3.53) 10.75–11.5 h: Ref > 11.5 h: 0.75 (0.20,2.85)
Xu, et al. 2023	China	Asia	CS	30,188	56.0%	11–18	Sleep duration	Self-designed questionnaire	Self-report	> 7 h: Ref. < 7 h: 1.27 (1.17,1.38)
Lin, et al. 2023	China	Asia	CS	9327	51.1%	13.6(2.6)	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	< 8 h: Ref. 8 - 9 h: 1.02 (0.88,1.19) 9–10 h: 1.06 (0.90,1.26) ≥ 10 h: 0.98 (0.80,1.20)
Cui, et al. 2023	China	Asia	LS	1496	48.3%	8–12 \13–14 \16–17	Sleep quality	Self-designed questionnaire	SE < −0.5D	4.51 (1.87,10.92)
Zhou, et al. 2017	China	Asia	CS	894	50.1%	11.37(2.83)	Sleep duration	Self-designed questionnaire	SE < −0.5D	0.45 (0.24,0.85)
Hu, et al. 2021	China	Asia	CS	2149	46.3%	16–18	Sleep duration	Self-designed questionnaire	Monocular visual acuity <5.0	< 7 h: Ref. 7 - 9 h: 1.13 (0.88,1.45) ≥ 9 h: 1.51 (1.09,2.10)
Huang, et al. 2023	China	Asia	CS	1140	48.4%	6–18	Sleep duration	Self-designed questionnaire	SE ≤ − 0.5 D	< 8 h: Ref. 8 - 9 h: 0.52 (0.33, 0.81) > 9 h: 0.50 (0.30, 0.81)
Study	Country	Ethnicity	Study design	Sample size (*n*)	Gender (male, %)	Age range [(years, *M* (*SD*)]	Sleep traits	Measurements (sleep related)	Definition of myopia	*OR* (95% *CI*)
Huang, et al. 2019	China	Asia	CS	968	66.1%	19.6 (0.9)	Sleep duration	Self-designed questionnaire	Self-report	≤ 7 h: Ref. > 7 h: 0.71 (0.49,1.04)
Wang, et al. 2017	China	Asia	CS	11,138	27.3%	21.08 (1.57)	Bedtime	Self-designed questionnaire	Self-report	< 10 p.m.: Ref. 10 p.m. - 12 p.m.: 0.84 (0.59,1.19) > 12 p.m.: 1.16 (0.96,1.41)

Abbreviations: CS, cross-sectional study; LS, longitudinal study; *M*, mean; *SD*, standard deviation; *OR*, odds ratio; *CI*, confidence interval; *SE*, spherical equivalent; h, hours; PSQI, Pittsburgh sleep quality index; CSHQ, Children's sleep habits questionnaire, Ref., Reference.

The F statistics for all IVs was above 10. The detailed list of SNPs used as proxies for genetically determined sleep traits included in this study are shown in **Supplementary Tables 5–8**.

The causal relationship between sleep traits and myopia is presented in Fig. 3. We found that genetically predicted sleep traits were not causally associated with the risk of myopia, including chronotype (IVW: *OR* = 1.00, 95% *CI* = 0.99–1.01, *P* = 0.71), sleep duration (IVW: *OR* = 1.00, 95% *CI* = 0.99–1.01, *P* = 0.91), long sleep duration (IVW: *OR* = 0.95, 95% *CI* = 0.87–1.04, *P* = 0.27) and short sleep duration (*OR* = 0.96, 95% *CI* = 0.90–1.02 *P* = 0.16). Consistent effect estimates for each sleep trait were observed using the MR-Egger method (chronotype: *OR* = 1.01, 95% *CI* = 0.99–1.02, *P* = 0.12; sleep duration: *OR* = 1.01, 95% *CI* = 0.95–1.06, *P* = 0.85; long sleep duration: *OR* = 0.91, 95% *CI* = 0.68–1.23, *P* = 0.58; short sleep duration: *OR* = 0.77, 95% *CI* =

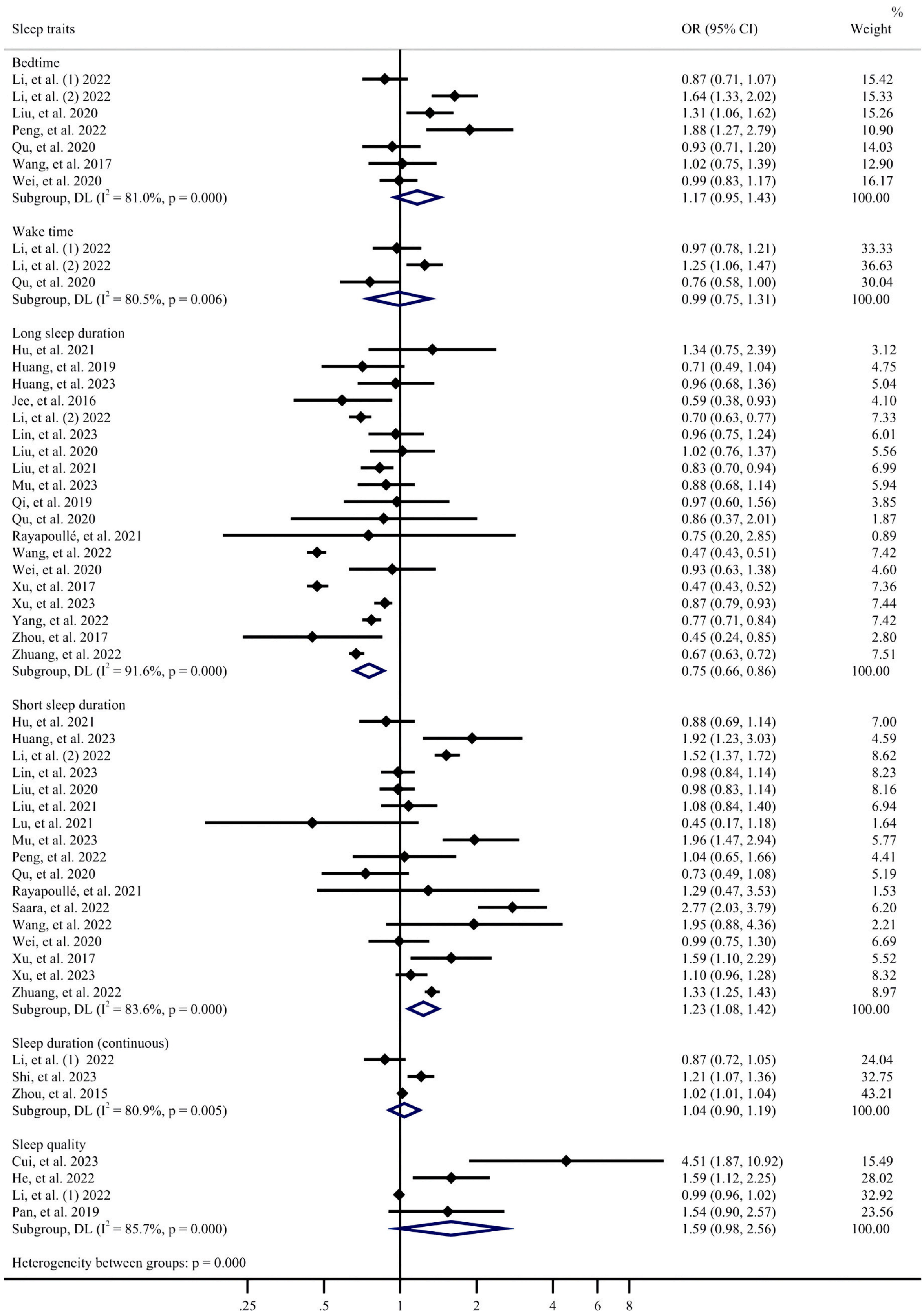

Fig. 2. Meta-analysis results for the association between sleep traits and myopia.
Abbreviations: *OR*, odds ratio; *CI*, confidence interval.

Table 2
Subgroup analysis stratified by potentially related factors on the association between sleep traits and myopia.

Subgroup	No. of studies	*OR*(95% *CI*)	*P*-value	*P* for heterogeneity	I^2 (%)	*P* in meta-regression
Bedtime						
Overall	7	1.17 (0.95,1.43)	0.14	< 0.001	81.0%	
Study design						
Cross-sectional study	5	1.19 (0.88,1.62)	0.27	< 0.001	85.3%	0.87
Cohort study	2	1.13 (0.86,1.49)	0.38	0.044	75.3%	
Country						
China	6	1.23 (0.99,1.53)	0.06	< 0.001	79.0%	0.29
Singapore	1	0.87 (0.71,1.07)	0.18	/	/	
Measurements						
Refractive measures	5	1.13 (0.91,1.50)	0.27	0.003	75.3%	0.34
Self-report	2	1.24 (0.71,2.17)	0.44	0.001	90.9%	
Methodological quality						
High	3	1.29 (0.94,1.77)	0.11	0.006	80.6%	0.47
Low	4	1.08 (0.79,1.49)	0.62	< 0.001	85.6%	
Wake time						
Overall	3	0.99 (0.75,1.31)	0.94	0.006	80.6%	
Country						
China	2	0.99 (0.61,1.60)	0.96	0.002	89.4%	0.98
Singapore	1	0.97 (0.78,1.21)	0.79	/	/	
Measurements						
Refractive measures	1	0.97 (0.78,1.21)	0.96	/	/	0.98
Self-report	2	0.99 (0.61,1.60)	0.79	0.002	89.4%	
Short sleep duration						
Overall	17	1.23 (1.08,1.42)	0.003	< 0.001	83.6%	
Study design						
Cross-sectional study	12	1.23 (1.05,1.44)	0.01	< 0.001	85.8%	0.79
Cohort study	5	1.28 (0.92,1.77)	0.14	0.004	73.9%	
Country						
China	15	1.17 (1.03,1.33)	0.02	< 0.001	80.7%	0.36
India	1	2.77 (2.03,3.78)	<0.001	/	/	
France	1	1.29 (0.47,3.54)	0.62	/	/	
Measurements						
Refractive test	14	1.25 (1.07,1.45)	0.004	< 0.001	83.4%	0.70
Self-report	3	1.12 (0.63,2.01)	0.70	0.002	83.7%	
Methodological quality						
High	12	1.21 (1.04,1.40)	0.02	< 0.001	74.5%	0.83
Low	5	1.27 (0.91,1.78)	0.16	< 0.001	92.5%	
Long sleep duration						
Overall	19	0.75 (0.66,0.86)	< 0.001	< 0.001	91.6%	
Study design						
Cross-sectional study	13	0.74 (0.65,0.85)	< 0.001	< 0.001	90.2%	0.74
Cohort study	6	0.81 (0.54,1.21)	0.29	< 0.001	90.9%	

0.58–1.02, $P = 0.08$), weighted median method (chronotype: $OR = 1.00$, 95% CI = 0.99–1.01, $P = 0.96$; sleep duration: $OR = 0.99$, 95% CI = 0.98–1.02, $P = 0.95$; long sleep duration: $OR = 0.99$, 95% CI = 0.87–1.12, $P = 0.85$; short sleep duration: $OR = 0.98$, 95% CI = 0.92–1.04, $P = 0.43$), and weighted mode method (chronotype: OR = 1.01, 95% CI = 0.99–1.01, $P = 0.94$; sleep duration: $OR = 0.99$, 95% CI = 0.97–1.03, $P = 0.94$; long sleep duration: $OR = 1.01$, 95% CI = 0.85–1.21, $P = 0.90$; short sleep duration: $OR = 0.98$, 95% CI = 0.89–1.08, $P = 0.71$). Given the comparability of the meta-analysis and MR analyses, we extracted the same sleep duration defined in the meta-analysis and MR analyses, that is, short sleep duration was <7 h and long sleep duration was >9 h. According to **Supplementary Fig. 7**, short sleep duration ($OR = 1.29$, 95% CI = 0.95–1.79, $P = 0.10$), long sleep duration ($OR = 0.69$, 95% CI = 0.45–1.05, $P = 0.08$) and sleep duration ($OR = 1.04$, 95% CI = 0.90–1.19, $P = 0.60$) were not significantly associated with myopia, which was consistent with the results of MR analyses.

Significant heterogeneity among the SNPs for IVs was observed in chronotype (IVW: $Q = 170.764$, $P = 0.001$; MR-Egger: $Q = 167.418$, $P = 0.001$), sleep duration (IVW: $Q = 130.284$, $P < 0.001$; MR-Egger: $Q = 130.230$, $P < 0.001$), and short sleep duration (IVW: $Q = 58.650$, $P < 0.001$; MR-Egger: $Q = 52.973$, $P < 0.001$). The intercept from MR-Egger regression indicated no significant evidence of directional pleiotropy (chronotype: $P = 0.13$; sleep duration: $P = 0.87$; long sleep duration: $P = 0.68$; short sleep duration: $P = 0.14$). Forest plots, scatter plots, leave-one-out analyses and funnel plots of each sleep trait are shown in **Supplementary Figs. 3–6**. The results of the MR analysis were robust, and a single SNP had no influence on the causal association of sleep traits with myopia.

4. Discussion

The current study explored the association and causality between different sleep traits and myopia in children and adolescents through a combination of meta-analysis and MR analysis. The meta-analysis showed that short sleep duration served as a risk factor for myopia, whereas long sleep duration acted as a protective factor against the condition. No significant causal relationship was found between sleep traits and myopia in the MR analysis.

The meta-analysis uncovered a noteworthy correlation between both short and long sleep duration and myopia. However, the meta-regression indicates that there is no significant longitudinal association between any of the short, long sleep durations or continuous sleep duration and myopia. In addition, The MR analysis did not provide evidence for causal relationships of sleep duration, short sleep duration and long sleep duration on myopia. Excessive near work, such as excessive homework load, has been demonstrated to be a risk factor for the development and progression of myopia, which may contribute to short sleep duration. (Owens and Weiss, 2017) In addition, screen time (i.e., television, computers, video games, and mobile devices), a major risk factor for myopia, has been proven to contribute to short sleep duration in children and adolescents. (Hale and Guan, 2015) The impact

Table 2
Subgroup analysis stratified by potentially related factors on the association between sleep traits and myopia. (continued).

Subgroup	No. of studies	*OR*(95% *CI*)	*P*-value	*P* for heterogeneity	I^2 (%)	*P* in meta-regression
Country						
China	17	0.76 (0.66,0.87)	< 0.001	< 0.001	92.6%	0.53
Korea	1	0.59 (0.38,0.92)	0.02	/	/	
France	1	0.75 (0.20,2.83)	0.67	/	/	
Measurements						
Refractive measures	15	0.76 (0.65,0.89)	0.001	< 0.001	93.5%	0.81
Self-report	4	0.70 (0.64,0.77)	< 0.001	0.971	0.0%	
Methodological quality						
High	14	0.74 (0.63,0.88)	< 0.001	< 0.001	93.4%	0.62
Low	5	0.79 (0.69,0.90)	< 0.001	< 0.001	46.4%	
Sleep duration (continuous)						
Overall	3	1.04 (0.90,1.19)	0.60	0.005	80.9%	
Country						
China	2	1.10 (0.93,1.30)	0.27	0.006	87.0%	0.40
Singapore	1	0.87 (0.72,1.05)	0.15	/	/	
Methodological quality						
High	2	1.10 (0.93,1.30)	0.27	0.006	87.0%	0.40
Low	1	0.87 (0.72,1.05)	0.15	/	/	
Sleep quality						
Overall	4	1.59 (0.98,2.56)	0.06	< 0.001	85.7%	
Study design						
Cross-sectional study	3	1.28 (0.88,1.87)	0.20	0.008	79.4%	0.15
Cohort study	1	4.51 (1.87,10.90)	0.001	/	/	
Country						
China	3	1.94 (1.18,3.19)	0.009	0.085	59.5%	0.32
Singapore	1	0.99 (0.96,1.02)	0.52	/	/	
Methodological quality						
High	2	2.48 (0.87,7.06)	0.089	0.04	76.2%	0.36
Low	2	1.21 (0.77,1.92)	0.41	0.008	85.8%	

Abbreviations: *OR*, odds ratio; *CI*, confidence interval.

of outdoor activity on the development and progression of myopia has been extensively documented, although the underlying mechanism remains unclear. (Luo et al., 2020) A study conducted among Chinese school-aged children demonstrated that engaging in outdoor activities was associated with an increase in sleep duration. (Luo et al., 2020) Based on our research findings, we propose that the relationship between short and long sleep duration and myopia could be influenced or caused by other factors, such as near work, screen time and outdoor activity. Sleep duration might not independently contribute to the development and progression of myopia in children and adolescents.

According to the subgroup analysis and meta-regression results, no sources of heterogeneity were identified. Of note, subgroup analysis showed that short sleep duration was associated with myopia in Asian countries but not in European countries, and this phenomenon also existed in the association between long sleep and myopia. This may be influenced by factors such as cultural practices, educational systems and lifestyle patterns. (Billings et al., 2020; Musić Milanović et al., 2021) School schedules significantly affect the sleep patterns of children and adolescents. (Agostini and Centofanti, 2021) Given China's characteristic compulsory education model (Yang et al., 2022b), which involves long hours of study and extracurricular activities, students may have limited access to adequate sleep, potentially affecting their eye health and increasing the risk of myopia. (Chen et al., 2021) It is crucial to consider these country-specific factors in the investigation of the relationship between sleep duration and myopia. By conducting a meticulous analysis and investigation, considering factors such as cultural nuances, social environments, and economic conditions across diverse countries, a more profound comprehension of the potential correlation between sleep duration and myopia can be achieved.

The results of the meta-analysis revealed no significant association between wake time and bedtime with myopia. Sleep timing (e.g., bedtime and wake time) is driven by interactions of circadian and homeostatic oscillations and reflects individual preferences for sleep. (Dijk and von Schantz, 2005) In response to changes in modern educational patterns, children and adolescents usually adhere to a relatively fixed waking and sleeping routine based on school schedules. (Whiting et al., 2021) This standardized sleep pattern minimizes individual differences, which may not be enough to influence the occurrence and prevalence of myopia. Since there is a lack of GWAS for sleep timing, a similar concept called chronotype was utilized in the MR analysis. However, the results of some studies were inconsistent (Peng et al., 2022; Li et al., 2022b), possibly in part due to the large sample size or the presence of confounding factors. Therefore, sleep timing may not independently predict myopia risk.

The meta-analysis did not yield a significant association between sleep quality and myopia. However, previous studies have suggested that optimal sleep quality plays a role in the repair and regeneration of ocular tissue, while poor sleep quality can lead to problems such as eye fatigue, visual discomfort, and increased intraocular pressure, thereby increasing the risk of myopia. (Wang et al., 2023) Despite these associations, the precise mechanism underlying the relationship between sleep quality and myopia remains unclear and requires further investigation. Since there are no available GWAS specifically focused on sleep quality, we were unable to perform the MR analysis. Nevertheless, considering the relatively consistent and regular sleep patterns observed in children and adolescents (Brown et al., 2018), the results obtained from this meta-analysis appear reliable and convincing. In summary, although sleep quality may not be directly responsible for myopia, factors related to sleep quality may play an important role in the development and progression of myopia.

This is the first study to combine meta-analysis and MR analysis to examine the association between sleep traits and myopia, improving causal inference and ensuring reliable findings. However, several limitations should be acknowledged. First, some variables related to myopia and sleep were self-reported in both the meta-analysis and MR analysis, which may introduce recall bias. Of note, cyclorefraction is important for accurately measuring myopia in children as it does not rely on their ability and willingness to provide subjective feedback, thereby potentially yielding more reliable refractive error measurements compared to conventional subjective techniques. (Hashemi et al., 2016) Furthermore, the statistical model used in this meta-analysis and MR analysis did not account for this environmental factor, such as near work and outdoor

Exposures	SNPs	OR(95% CI)	P
Chronotype (morningness)	122		
Inverse variance weighted−random effects		1.00(1.00 to 1.00)	0.706
Inverse variance weighted−fixed effects		1.00(1.00 to 1.00)	0.706
MR Egger		1.01(1.00 to 1.02)	0.120
Weighted median		1.00(0.99 to 1.00)	0.960
Weighted mode		1.00(0.99 to 1.01)	0.942
MRlap		1.03(0.99 to 1.07)	0.121
Sleep duration (continuous)	65		
Inverse variance weighted−random effects		1.00(0.99 to 1.01)	0.911
Inverse variance weighted−fixed effects		1.00(0.99 to 1.01)	0.911
MR Egger		1.00(0.95 to 1.06)	0.854
Weighted median		1.00(0.98 to 1.01)	0.948
Weighted mode		1.00(0.97 to 1.02)	0.940
MRlap		1.02(0.95 to 1.09)	0.644
Long sleep duration	6		
Inverse variance weighted−random effects		0.95(0.87 to 1.04)	0.271
Inverse variance weighted−fixed effects		0.95(0.86 to 1.05)	0.322
MR Egger		0.91(0.68 to 1.23)	0.579
Weighted median		0.99(0.87 to 1.12)	0.846
Weighted mode		1.01(0.85 to 1.21)	0.904
MRlap		1.06(0.78 to 1.45)	0.692
Short sleep duration	24		
Inverse variance weighted−random effects		0.96(0.90 to 1.02)	0.155
Inverse variance weighted−fixed effects		0.96(0.90 to 1.02)	0.155
MR Egger		0.77(0.58 to 1.02)	0.083
Weighted median		0.98(0.92 to 1.04)	0.432
Weighted mode		0.98(0.89 to 1.08)	0.712
MRlap		0.90(0.79 to 1.04)	0.148

P < 0.05 was considered statistically significant.

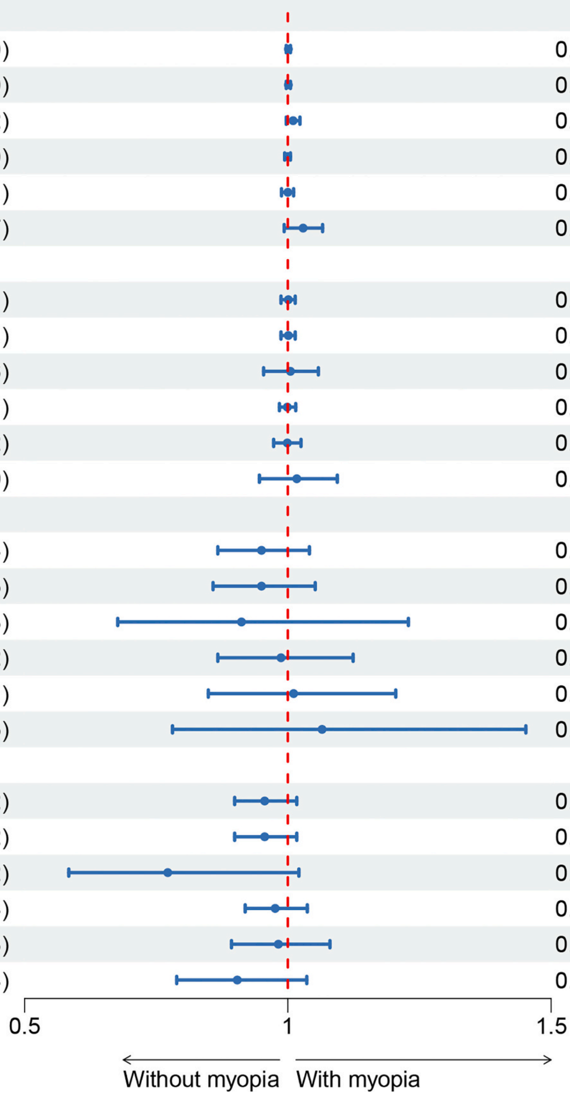

Fig. 3. Mendelian randomization estimations inferring causality of sleep traits on myopia.
Abbreviations: SNP, single nucleotide polymorphism; *OR*, odds ratio; *CI*, confidence interval; MR, Mendelian randomization.

time, and the validity of the results requires further verification. Second, most observational studies included in the meta-analysis were cross-sectional, limiting the ability to establish causal relationships. However, the application of MR analysis with SNPs as IVs helps overcome this limitation. Third, the populations included in the meta-analysis were predominantly Asian, while the MR analysis utilized European populations due to the lack of GWAS summary statistics for other populations. Future GWAS in different races are necessary to further elucidate the relationships between sleep traits and myopia. Although previous review and meta-analysis on the relationship between sleep and myopia have been published (Liu et al., 2023; Wang et al., 2023), they have limitations in establishing causality, updating data, and providing comprehensive research evidence. The combination of the meta-analysis and MR analysis used in the current study enhanced the causal inference regarding the associations between sleep traits and the risk of myopia, which provided a comprehensive perspective.

5. Conclusions

The combined findings from the meta-analysis and MR analysis did not reveal any valid evidence supporting an association between sleep and myopia. Sleep may not act as an independent influencing factor of myopia. However, it is noteworthy that sleep-related behaviors might influence the onset and progression of myopia, indicating a potential indirect association between sleep and myopia. Future studies with adequately powered designs are warranted to provide evidence of this association.

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CRediT authorship contribution statement

Xing-Xuan Dong: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Jia-Yu Xie:** Writing – review & editing, Writing – original draft, Formal analysis. **Dan-Lin Li:** Writing – review & editing, Formal analysis. **Yi Dong:** Visualization, Conceptualization. **Xiao-Feng Zhang:** Validation, Formal analysis. **Carla Lanca:** Writing – original draft. **Andrzej Grzybowski:** Writing – review & editing. **Chen-Wei Pan:** Writing – review & editing, Visualization, Validation, Funding acquisition.

Declaration of competing interest

None declared.

Data availability

I haved shared my data in the supplementary file.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2024.107893.

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