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Sleep duration and the risk of major eye disorders: a systematic review and meta-analysis

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BACKGROUND: To assess the relationship between sleep duration and the risk of major eye disorders including myopia, glaucoma, cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR).
METHODS: Databases including PubMed, Embase, Web of Science, and Cochrane library were searched for eligible publications before July 2021. Studies assessing the relationship between sleep duration and any one of the major eye disorders were identified. Pooled odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were estimated using random-effects models.
RESULTS: We identified 21 relevant articles including 777348 participants, and 17 were cross-sectional, 3 were longitudinal, and 1 was case-control. Pooled results indicated that long sleep duration was significantly associated with the risk of DR (OR = 1.84, 95% CI 1.24, 2.73), and short sleep duration was significantly associated with the risk of cataract (OR = 1.20, 95% CI 1.05, 1.36). Besides, a significant relationship was observed between the risk of DR and long sleep duration per day (i.e., nighttime sleep plus daytime napping, OR = 1.74, 95% CI 1.23, 2.44) rather than per night (OR = 2.17, 95% CI 0.95, 4.99). The extreme of long sleep duration (i.e., >10 h per night) increased the risk of myopia (OR = 1.02, 95% CI 1.01, 1.04).
CONCLUSIONS: Inappropriate sleep duration might increase the risk of major eye disorders. The findings could contribute to the growing knowledge on the possible relationship between circadian rhythms and eye disorders.

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INTRODUCTION

Visual impairment and blindness is a global public health concern [1]. By 2050, the worldwide estimate of blind people would be 114.6 million, and another 587.6 million would be affected by moderate or severe visual impairment [1]. Major eye disorders including myopia and age-related eye disorders such as glaucoma, cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR) have been reported to be leading causes of visual impairment and blindness [2–5]. From a public health perspective, understanding modifiable risk factors for these major eye disorders is a critically important step to initiate preventive measures.

Inappropriate sleep duration has already been defined as a modifiable risk factor for several health outcomes at the population level, including diabetes, metabolic syndrome, and all-cause mortality [6–8]. Despite a growing body of evidence supporting the correlation between sleep duration and major eye disorders, the evidence remains inconsistent and the conclusion is debatable [9–12]. For example, different epidemiological studies may demonstrate inverse [9], positive [13], and even nonsignificant [10, 14] relevance of sleep duration to myopia. Furthermore, there is no systematic review or meta-analysis summarizing the association between sleep duration and any one of the major eye disorders.

We aimed to systematically review the published literature on the association between sleep duration and major eye disorders including myopia, glaucoma, cataract, AMD, and DR. The findings would provide valuable evidence on the potential to recognize sleep health as a novel component of eye-care strategies.

METHODS

In this systematic review and meta-analysis, we strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (Supplementary Table 1) [15]. Besides, we registered our study in International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42021278901).

Search strategy and study selection

The pertinent literature was sourced using PubMed, Embase, Web of Science, and Cochrane library before July 2021. The search keywords were presented as follows: “sleep” as exposure factors; and “myopia” or “glaucoma” or “cataract” or “age-related macular degeneration” or “diabetic retinopathy”, as outcome factors. Full search strategies used for PubMed were as follows: ((“myopia” [MeSH Terms] OR “glaucoma” [MeSH Terms] OR “cataract” [MeSH Terms] OR “diabetic retinopathy” [MeSH Terms] OR “macular degeneration” [MeSH Terms]) AND “sleep” [MeSH Terms]). Additionally, we also searched reference lists of identified studies to avoid omitting potentially relevant studies.

The process of identifying relevant articles followed the gold-standard two-step process. We first removed duplicate publications and screened studies for initial inclusion based on titles and abstracts simultaneously. Based on the full-text screening, two authors (MZ and JYK) independently

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retrieved and perused for further assessment. Any disagreement was settled through discussion with a third expert (CWP).

Eligibility criteria and data collection

In accordance with the PICOS selection criteria, studies were included if they: (1) were original studies; (2) regarded sleep duration as the exposure; (3) demonstrated the relationship between sleep duration and major eye disorders; (4) reported individuals without sleeping disorders; (5) provided sufficient data for the calculation of odds ratio (OR) and its 95% confidence interval (95% CI); (6) were published in the English language; (7) obtained written informed consent from participants and complied with the Declaration of Helsinki. Studies excluded were case reports, reviews, protocols, conference abstracts, or animal experiments. When multiple publications presented data from the same population, only the study with the largest sample size was preferentially included in the meta-analysis.

Data extracted from each study included: first author, publication year, geographic location, sex ratio and mean age of the study population, sample size, study design, source of subjects, the number of positive cases, sleep duration measurement and category, definitions of eye disorders (myopia, DR, glaucoma, AMD, and cataract), covariates used in adjustment, diabetes duration, the hemoglobin A1c (HbA1C) concentration, and data on major eye disorders.

Definition of sleep duration

Short, long and normal sleep durations were defined according to the source articles, due to racial/ethnic differences in sleep duration [16, 17]. For articles reporting multiple categories of short and long sleep, long and short sleep durations were defined as the longest and shortest categories reported in the original article, respectively. In those studies where both subjective (e.g., self-reported questionnaires) and objective (via actigraphy or polysomnography) sleep duration were reported, only the latter was applied in this paper because subjective measures may not capture the actual amount of sleep compared with actigraphy [18] or polysomnography [19]. When both sleep per day (including daytime napping) and per night were presented separately, we chose the latter only.

Risk of bias assessment

The quality of the eligible cross-sectional studies was evaluated by the Agency for Healthcare Research and Quality (AHRQ) [20], which consists of 11 items with a yes/no/unclear response option: "Yes" was scored as "1", while "No" or "unclear" was scored as "0" for each item. Based on the whole score, each cross-sectional study was classified as having a higher bias risk (score 0–3), a moderate bias risk (score 4–7), or a lower bias risk (score ≥8). The quality assessment of each included case-control and cohort study was conducted using the Newcastle-Ottawa Scale (NOS), which consists of 3 major items: selection of studies, comparability, and exposure [21]. The total score assessed by the NOS ranges from 0 to 9, with a NOS score of 7–9 indicating high quality. Two investigators rated each study based on the relevant quality criteria independently, and any disagreement was discussed and resolved by consensus.

Statistical analysis

The adjusted ORs and 95% CIs within each included study assessing the associations between sleep duration and major eye disorders were coded and fully combined to obtain pooled ORs and their corresponding 95% CI using random-effects models. When multiple models were used to adjust the OR value, the model with the most covariates included would be employed [22]. For studies where the longest or shortest sleep category was used as the reference category, we changed the reference group to the medium group, and the statistical methodology given by Bucher et al. was applied for indirect comparisons [23]. For studies that only reported stratum specific ORs (e.g., OR for men and women), we combined the ORs across stratum and used pooled ORs in the subsequent meta-analysis. For example, for the study which reported results for sleep duration in semester and holidays separately [24], we have calculated pooled ORs based on the published data and subsequently included the pooled OR in the meta-analysis.

The extent of heterogeneity between studies was quantified by the I^2 statistical test [25]. An I^2 value greater than 50% denoted moderate-to-high heterogeneity. Evidence of publication bias was assessed using Egger's test (a *p*-value of less than 0.05 was considered statistically significant) [26]. Subgroup analyses were also conducted based on stratification by mean age, gender, sleep duration measurement and category, degree of disorders, and methodological quality for studies on relationships with statistically significance in the primary analysis and with at least 3 articles included. To explore possible mediator effects of the sleep duration definition, we performed additional subgroup analyses to cluster studies according to the definition of sleep duration for each eye disorder (short sleep duration: <5 h, <6 h; normal sleep duration: 7–8 h; long sleep duration: >9 h, >10 h). The above analyses were performed using Stata 12.0.

RESULTS

As shown in Fig. 1, 1615 potentially relevant articles were retrieved from the four databases up to July 2021 after duplicates were removed, of which 131 were related to our scientific topic according to their titles and abstracts. After reviewing the full texts of the remaining papers, a total of 21 observational articles were considered eligible for our meta-analysis.

Characteristics of studies

The demographic characteristics of the participants from eligible studies are shown in Table 1. Overall, the 21 included studies published from 2002 to 2020 recruited 777,348 participants and provided sufficient data. The number of positive cases of each study ranged from 46 [27] to 88,464 [28]. The eligible studies evaluated the effect of sleep duration in relation to major eye disorders such as myopia ($n = 9$) [9, 10, 14, 24, 29–33], DR ($n = 6$) [11, 34–38], glaucoma ($n = 2$) [39, 40], AMD ($n = 2$) [41, 42], and cataract ($n = 2$) [28, 43]. Of them, 20 studies investigated long sleep duration, and 19 studies investigated short sleep duration. The majority of the included studies ($n = 8$) were conducted in China, with 4 studies in Korea, 3 in U.S.A., 2 in Singapore, and 1 each in Spain, South Africa, India and Indonesia. Examination of the study design revealed varied approaches: 17 were cross-sectional, 3 were longitudinal, and 1 was case-control. Among these 3 longitudinal studies for myopia, the follow-up duration was four years in 1 study [10], whereas the follow-up durations in the other 2 studies were less than four years [14, 33]. Among all studies, 3 were hospital-based and 18 were population-based. Sleep duration was measured based on self-report in 17 papers, parent-report in three, and objective methods in one. Definitions of major eye disorders and adjusted covariates used in each study are displayed in Supplementary Table 2. Four studies provided the respective diabetes duration in participants with and without DR, and in all these four studies the diabetes duration was significantly longer in DR patients than in the participants without DR ($p < 0.05$) (Supplementary Table 3). Three studies compared the HbA1C concentration of DR and non-DR participants, with no significant differences between DR and non-DR participants in the remaining two studies, except for one that showed higher levels in DR patients ($p < 0.05$) (Supplementary Table 3).

Methodological quality of studies

The quality of the included cross-sectional studies was evaluated by the AHRQ, whereas the quality assessment of each included case-control and cohort study was conducted using the NOS. As shown in Table 1, the overall quality of the eligible studies ranged from moderate to high (AHRQ: 4-8 and NOS: 4-7).

Long sleep duration and major eye disorders

Compared with normal sleep duration, long sleep duration was significantly linked to the risk of DR (OR = 1.84, 95% CI 1.24, 2.73), but not associated with the risk of myopia (OR = 0.84, 95% CI 0.58, 1.21), glaucoma (OR = 1.80, 95% CI 0.66, 4,95), AMD (OR = 1.29, 95% CI 0.71, 2.33), or cataract (OR = 0.91, 95% CI 0.77, 1.08) (Fig. 2). No significant publication bias was detected for any outcome by Egger's test (all *p*-values for Egger's test >0.05).

The subgroup meta-analysis results among studies examining the correlation between long sleep and DR are listed in

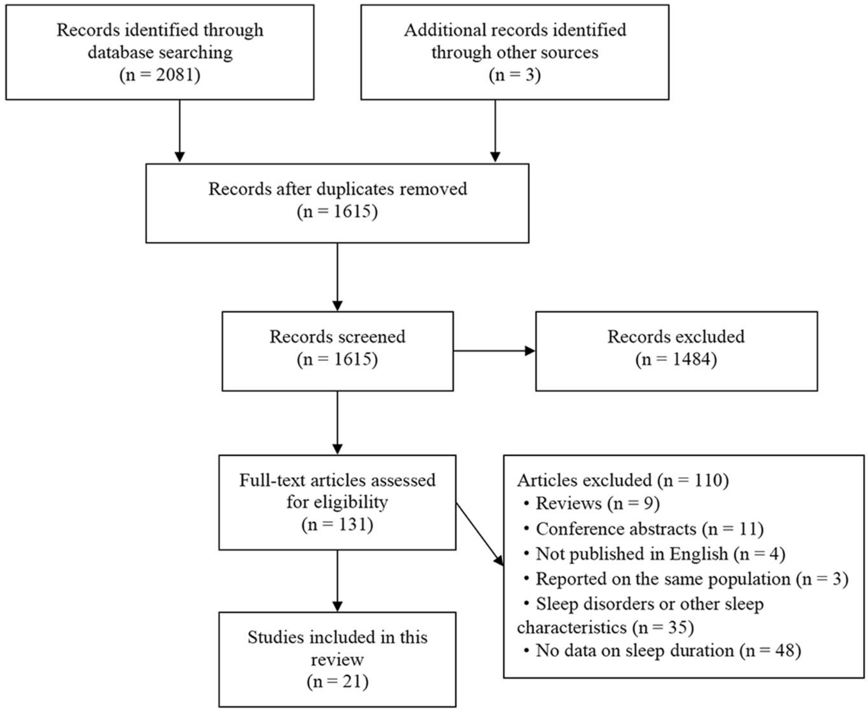

Fig. 1 Selection process of articles in the review ($n = 21$).

Supplementary Table 4. These five studies included seven populations with sample sizes ranging from 1116 to 1670, all of which were conducted in Asia with cross-sectional designs and self-reported measurements. Long sleep was consistently associated with DR during subgroup analysis of sleep duration categories, methodological quality, and the severity of DR. According to mean age, a significant association was observed among long sleepers aged >59 years (OR = 2.07, 95% CI 1.47, 2.92), rather than among those aged ≤59 years (OR = 1.97, 95% CI 0.62, 6.26). In the subgroup meta-analyses of sex, long sleep duration was not associated with the odds of DR in either males (OR = 1.77, 95% CI 0.90, 3.49) or females (OR = 1.48, 95% CI 0.74, 2.96). Moreover, DR was significantly associated with long sleep duration per 24 h (OR = 1.74, 95% CI 1.23, 2.44) rather than per night (OR = 2.17, 95% CI 0.95, 4.99).

Short sleep duration and major eye disorders

In comparison with normal sleep, short sleep was significantly related to the risk of cataract (OR = 1.20, 95% CI 1.05, 1.36), but not associated with the risk of myopia (OR = 1.06, 95% CI 0.88, 1.26), DR (OR = 1.00, 95% CI 0.78, 1.28), glaucoma (OR = 1.11, 95% CI 0.84, 1.46), or AMD (OR = 1.49, 95% CI 0.40, 5.59) (Fig. 3). No significant publication bias was detected for any outcome by Egger's test (all p-values for Egger's test >0.05).

Subgroup analyses for specific definitions of short-and-long sleep duration

When extremes of sleep duration were evaluated as compared with normal sleep duration (7–8 h), long sleep defined as >10 h was significantly related to increased risks of myopia (OR = 1.02, 95% CI 1.01, 1.04) and glaucoma (OR = 3.30, 95% CI 1.29, 8.44), whereas short sleep defined as the duration <6 h was significantly associated with increased odds of cataract (OR = 1.18, 95% CI 1.02, 1.38) and AMD (OR = 3.09, 95% CI 1.20, 7.97) (Fig. 4). In addition, long sleep defined as >9 h was significantly associated with an increased risk of DR (OR = 2.09, 95% CI 1.27, 3.45), but a decreased risk of myopia (OR = 0.51, 95% CI 0.31, 0.83).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis summarizing the association between sleep duration and major eye disorders based on a comprehensive literature search. The present review compiled available evidence and revealed that long sleep duration could significantly increase the risk of DR, while short sleep duration was correlated with significantly elevated odds for cataract. Besides, long sleep duration per day including nighttime sleep and daytime napping, rather than per night was significantly associated with an increased risk of DR. Overall, our results suggest that sleep duration may be an important modifiable risk factor for major eye disorders.

As a public health epidemic, insufficient sleep has recently surfaced as a modifiable contributing factor for many health outcomes including diabetes, hypertension, and all-cause mortality [44], but its impacts on eye disorders remain controversial. Interestingly, our findings indicated that short sleep duration was significantly associated with cataract. This increased risk of cataract in short sleepers may be a result of lower resilience toward oxidative stress [45], longer exposure to ultraviolet light [28], and greater chances of hypertension and diabetes [44], all of which are well-known risk factors for cataract. However, given the limited studies evaluating the relationship of short sleep with cataract, the conclusion remains far from definitive. Specifically, a single cross-sectional study contributed to the majority of the total participant numbers [28].

The cross-sectional data suggested that long sleep duration was correlated with a two-fold increase in odds of DR, which is consistent with recent research [38]. Nevertheless, the exact mechanisms remain unclear [36, 38]. One plausible explanation is the disruption of circadian rhythms in long sleepers, which subsequently interfere with retinal metabolism including the lipid/glucose dysregulation, hence leading to the onset and deterioration of DR [36, 46]. An alternative explanation concerning the relevance of long sleeping to DR may be the confounding factors and underlying comorbidities. Self-reported long sleepers may not actually be long sleepers, but may be poor sleepers [47],

Table 1. Characteristics of the included studies on the association between sleep duration and major eye disorders.

Outcome	First author, year	Region	Study design	Source of subjects	Age range (years)	Sample size (*n*)	Positive cases (*n*)	Sex (Male %)	Sleep duration measurement	Sleep duration categories (h)			Risk of bias score
										Short	Ref	Long	
Myopia	Loman, 2002	U.S.A.	CS	PB	23-44	177	116	58.2	Self-reported	≤7.30	7.31–8.40	≥8.41	6
	Gong, 2014	China	CS	PB	6-18	15316	8178	48.5	Self-reported	≤7	8	≥9	5
	Zhou, 2015	China	CS	PB	9.80 ± 0.44	1902	588	53.1	Parent-reported		7	>10	7
	Jee, 2016	Korea	CS	PB	12-19	3625	2895	52.9	Self-reported	<5	7	>9	8
	Huang, 2019	China	CS	PB	19.6 ± 0.9	968	840	66.1	Self-reported		≤7	>7	5
	Qi, 2019	China	LS	PB	14-16	522	141	100.0	Self-reported		≤7	>7	3*
	Liu, 2020	China	LS	PB	7.2 ± 0.7	5305	1177	53.2	Parent-reported	<9.5	9.5-10	≥10	5*
	Qu, 2020	China	CS	PB	11-18	1831	1246	53.7	Self-reported	<6	6-8	≥10	8
	Wei, 2020	China	LS	PB	5.67-9.27	2328	827	57.9	Parent-reported	≤9.56	9.57–10.00	≥10.01	7*
DR	Raman, 2012	India	CS	PB	40+	1414	209	53.0	Self-reported	<5	6-8	>9	5
	Meng, 2016	China	CS	PB	DR present: 57.78 ± 10.41, DR absent: 55.75 ± 11.72	1220	402	54.5	Self-reported	<6	7–8	>9	5
	Jee, 2017	Korea	CS	PB	40+	1670	261	50.6	Self-reported	≤5	6–8	≥9	6
	Dharmastuti, 2018	Indonesia	CS	PB	30+	1116	467	31.3	Self-reported	<6	7-8.5	>8.5	7
	Tan, 2018	Singapore	CS	PB	64.4 ± 9.0	1231	206	49.6	Self-reported	<6	6–8	≥8	8
	Chew, 2020	Singapore	CS	HB	57.6 ± 8.3	92	46	67.4	Polysomnography measured	<5	≥5		6
Glaucoma	Lee, 2016	Korea	CS	PB	40+	9410	368	Not-reported	Self-reported	<7	7–8	≥9	6
	Qiu, 2019	U.S.A.	CS	PB	56.3-57.9	6784	175	47.2	Self-reported	≤3	7	≥10	5
AMD	Khurana, 2016	U.S.A.	CS	HB	14-99	1003	503	41.9	Self-reported	<7	7–8	>8	4
	Pérez-Canales, 2016	Spain	CC	HB	65-92	165	57	35.2	Self-reported	<6	7–8	>8	7*
Cataract	Rim, 2015	Korea	CS	PB	40+	715554	88464	45.7	Self-reported	<6	7–9	>9	5
	Peltzer, 2018	South Africa	CS	PB	61.5 ± 13.0	4725	610	46.8	Self-reported	<7	7–8	≥9	6

DR diabetic retinopathy, *AMD* age-related macular degeneration, *CS* cross-sectional study, *LS* longitudinal study, *CC* case-control study, *PB* population-based, *HB* hospital-based.
*The quality assessment was conducted using the Newcastle-Ottawa Scale.

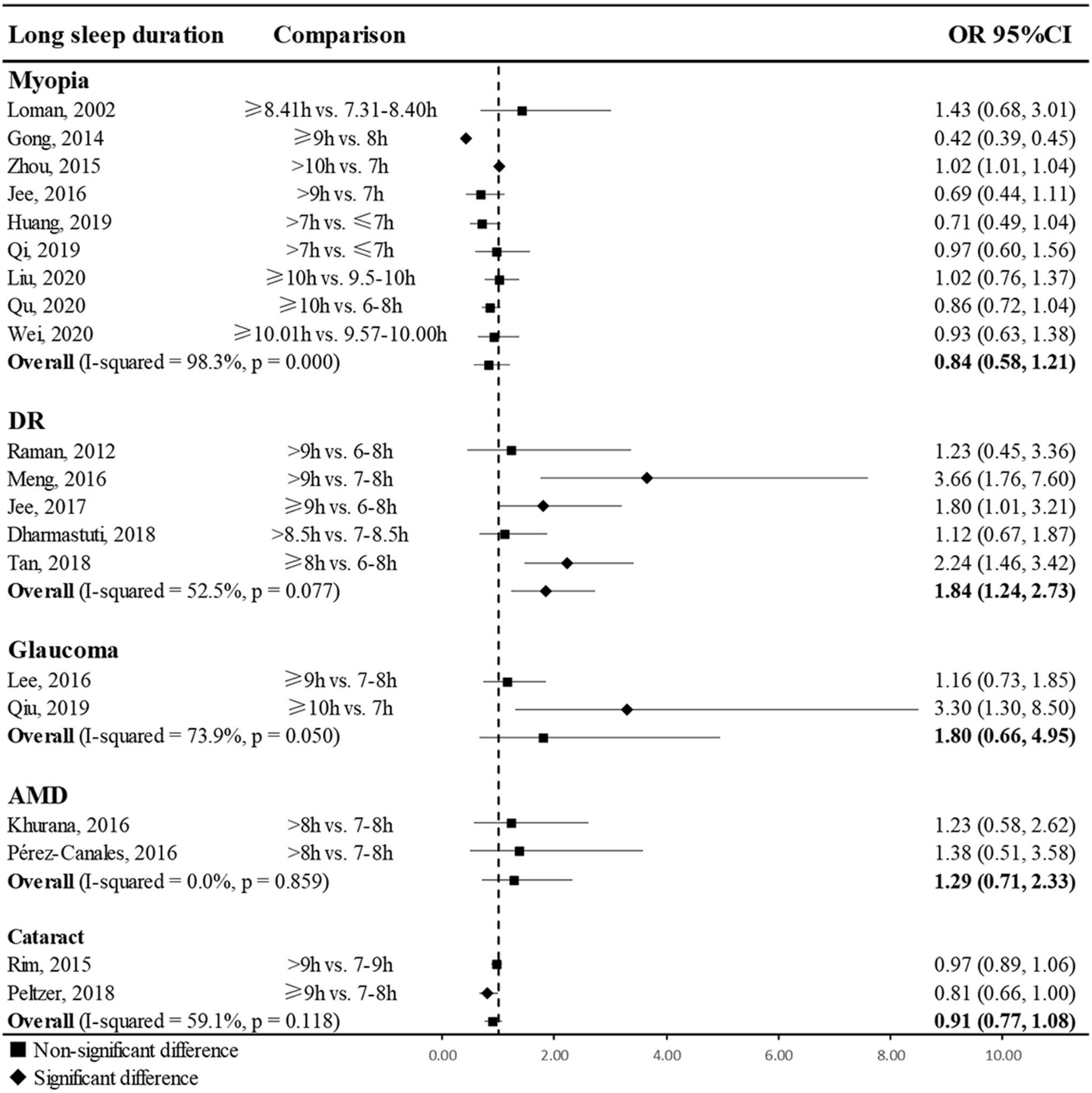

Fig. 2 Forest plot showing the association between long sleep duration and major eye disorders. DR diabetic retinopathy, AMD age-related macular degeneration, OR odds ratio, 95% CI 95% confidence interval.

who engage in more compensatory behaviors to increase sleep than do others [48]. Moreover, underlying co-morbidities could also produce an effect via long sleep duration on DR, such as obstructive sleep apnea (OSA) and heart diseases [48]. Other possible explanations involve the pro-inflammatory state [49] and retinal hypoxia [50] induced by long sleep duration. Specifically, a previous meta-analysis found that elevated levels of C-reactive protein and interleukin-6 might be caused by excessively long sleeping [49]. However, it is also possible that long sleep might be a consequence of the sleep-inducing effects of inflammation [51]. Furthermore, the subgroup analyses indicated that the significant association between long sleep duration and DR was only valid in those older than 59 years rather than those younger than 59 years. Given that diabetes duration is an important parameter for either sleeping duration or eye disease [36], possible reasons might be that older people could have longer diabetes duration. Interestingly, further analysis revealed that DR was significantly related to long sleep duration per day rather than per night, which indicated that DR seems to be associated with prolonged daytime napping, but not nighttime sleeping. Additional studies are required to determine the causality and mechanisms of this relationship.

In our analysis, we found that long sleep defined as >10 h per night was significantly related to the risk of myopia, consistent with the sleep duration recommendations for teenagers (8–10 h) updated by the National Sleep Foundation [52]. Besides, our findings also suggest relationships of extremes of sleep duration with AMD and glaucoma. However, we cannot conclude whether the associations existed were due to insufficient evidence included in these two eye disorders.

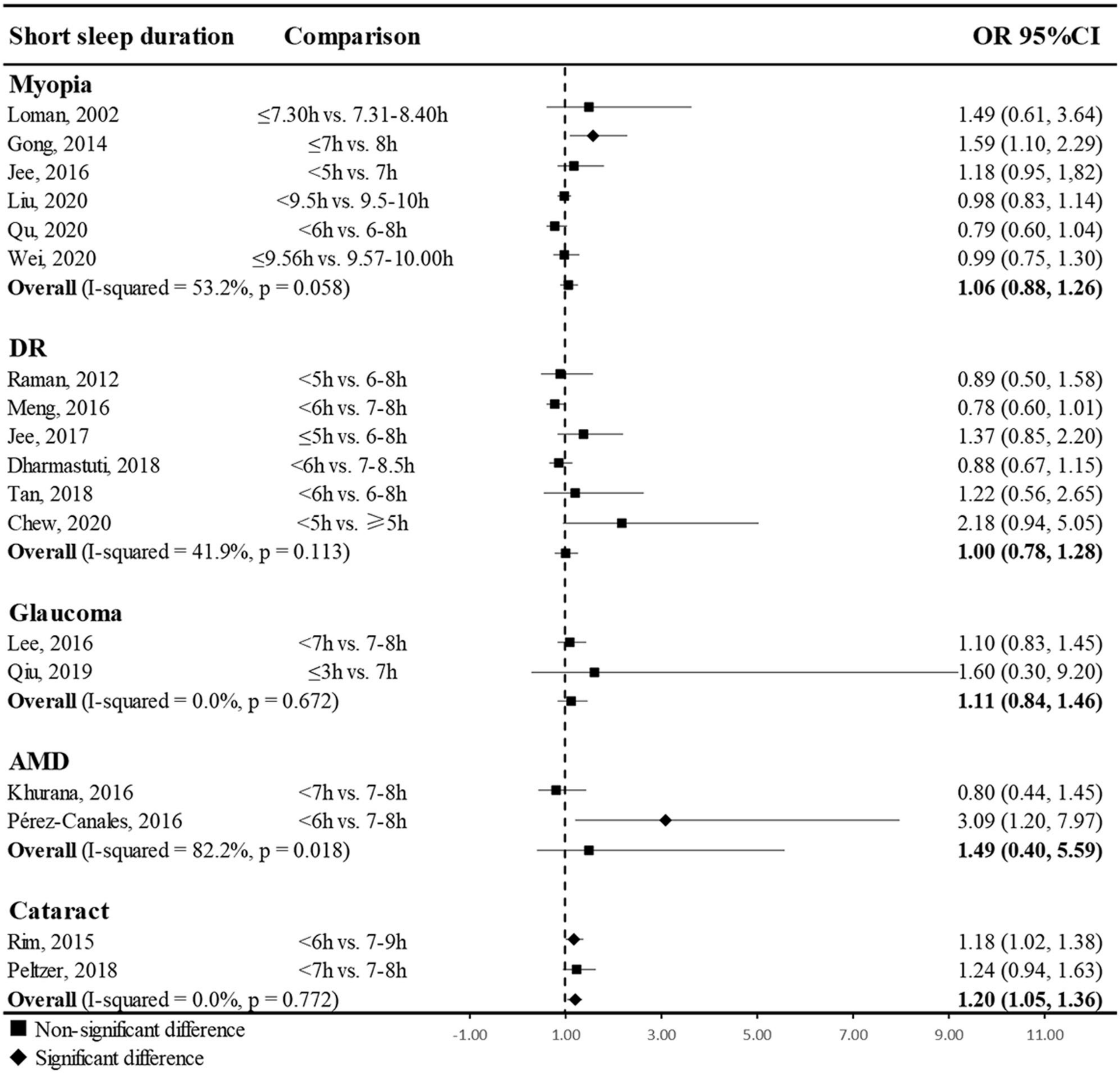

Fig. 3 Forest plot showing the association between short sleep duration and major eye disorders. DR diabetic retinopathy, AMD age-related macular degeneration, OR odds ratio, 95% CI 95% confidence interval.

The findings of significant correlations between short sleep as well as long sleep and major eye disorders are of both public health and clinical implications. From a public health perspective, fortunately, sleep duration is an inherently modifiable risk factor, which provides a new perspective for prevention programs specifically targeting eye disorders. However, caution should be exercised when considering the generality of our results. On the one hand, most of the included studies were cross-sectional which makes it difficult to ascertain the causal relationship. On the other hand, rigorous evidence is sorely lacking to prove whether normalizing sleep duration could modify health risks [53]. In this case, we do not intend to recommend provide sleeping medications, but low-intensity interventions, including psychoeducation, psychotherapy, and psychosocial interventions on sleep duration for major eye disorders [54, 55]. Clinically, in addition to classic risk factors for eye disorders, understanding the influence of sleep duration may help doctors better treat these disorders in a more holistic approach. For example, given the significant association between DR and long sleep per day rather than per night, mild daytime sleep restriction for long sleepers may reduce the DR risk in diabetic patients. Besides, the associations between inappropriate sleep duration and eye disorders also provide a simple approach to assist non-ophthalmologists in identifying high-risk patients in need of eye screening through sleep duration.

The evidence for a link between sleep duration and major eye disorders is accumulating, whereas the available literature has not yet been systematically reviewed. The main strength of this meta-analysis is that, to our knowledge, it is the first review to examine the relationship between sleep patterns and major eye disorders based on a comprehensive literature review and strict study inclusion criteria. However, the review has several limitations. First, the analysis was performed mainly based on cross-sectional data, which is unable to infer the direction of the causality. Besides, the number of eligible articles was limited in clarifying the actual

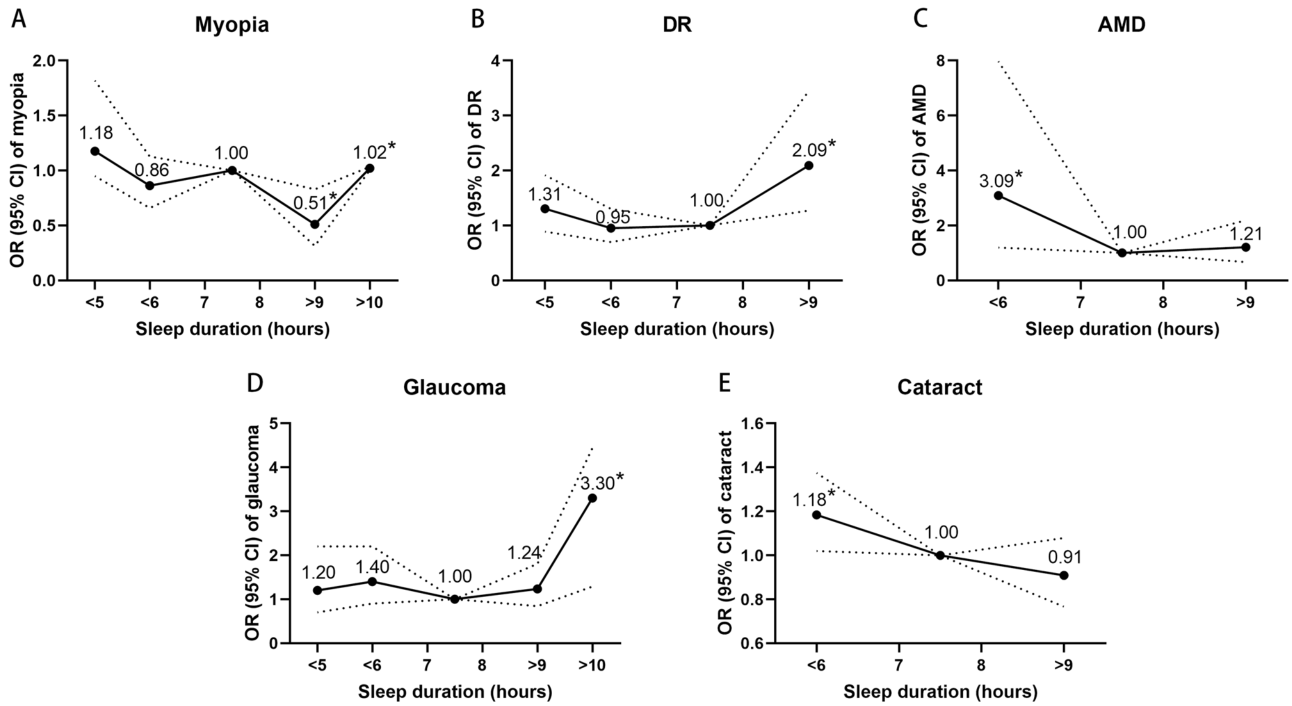

Fig. 4 Subgroup analyses for specific definitions of short-and-long sleep duration. **A**, myopia; **B**, DR; **C**, AMD; **D**, glaucoma; **E**, cataract. **P*-value < 0.05. DR diabetic retinopathy, AMD age-related macular degeneration, OR odds ratio, 95% CI 95% confidence interval.

connection. In addition, discrimination existed within the range of publications distinguished by geographical location. The majority of the included publications were conducted in Asia, hampering the identification of impact estimates in alternative areas. Furthermore, the included studies varied in sample size, and the majority of the participants actually came from a single cataract study with moderate bias risk [28]. Moreover, the majority of relevant literature assessed sleep length merely on the basis of self-report which may be subject to recall bias. Finally, the sleep duration category within each study and the criteria for defining major eye disorders varied across studies, which restricts the power to judge the impact of sleep duration on major eye disorders.

In summary, differential associations between sleep duration and the risk of various eye disorders were observed in the review. For cataract, long sleep duration might be a clinically negligible risk factor. For DR, long sleep duration, namely nighttime sleep plus daytime sleep, might be a clinically important risk factor. For myopia, extreme long sleep duration might be a clinically negligible risk factor. Future studies are needed to shed light on the causal directions and biological mechanisms behind the relationships between sleep behaviours and major eye disorders. Whether interventions to normalize sleep duration could improve vision health remains an open question.

SUMMARY

What was known before

- Major eye disorders including myopia and age-related eye disorders such as glaucoma, cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR) are leading causes of visual impairment and blindness. Inappropriate sleep duration has already been defined as a modifiable risk factor for several health outcomes at the population level, but the associations between sleep duration and major eye disorders remain controversial.

What this study adds

- Differential associations between sleep duration and the risk of various eye disorders were observed in this study. For cataract, long sleep duration might be clinically a negligible risk factor. For DR, long sleep duration, namely nighttime sleep plus daytime sleep, might be a clinically important risk factor. For myopia, extreme long sleep duration might be clinically a negligible risk factor.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

CWP and MZ contributed to the conception and design of the study. MZ, DLL and JYK performed the literature search and data collection. MZ drafted the manuscript and carried out the statistical analysis. CWP and XFZ critically revised the work. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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