• Clinical Research •

Association of sleep quality with myopia based on different genetic risk levels

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Abstract

● **AIM:** To analyse the association of sleep quality with myopia under different genetic risk (GR) levels.

● **METHODS:** A cross-sectional survey of students aged 9-14y in Wenzhou, China, was conducted. Refraction without cycloplegia and ocular parameters were measured. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI). Seventeen single nucleotide polymorphisms (SNPs) were replicated by association analysis and used to compute the GR score (GRS). Possible confounders were assessed by a questionnaire that collected information about the children and their parents. Generalized linear models were used to analyse the sleep quality, the GR, and their interaction effects on the risk of myopia.

● **RESULTS:** Out of 1354 children included in this study, 353 (26.07%) had sleep disturbances. The GRS ranged from 4.49 to 12.89 with a mean of 7.74±1.23, and the participants were divided into a low GR group, a moderate GR group and a high GR group according to the GRS quartile. In the generalized linear model, the children with sleep disturbances and high GR had a higher risk of myopia than those without sleep disturbances and with low GR (OR=1.59, 95%CI: 1.12-2.25; OR=1.88, 95%CI: 1.23-2.88, respectively). Compared to those with low GR and SDs, children with high GR with or without SDs had a higher risk of myopia (OR=4.88, 95%CI: 2.03-11.71; OR=1.70, 95%CI: 1.06-2.72, respectively).

● **CONCLUSION:** The prevalence of sleep disturbances in elementary school students in Wenzhou was 26.07%. There is a significant interaction between sleep disturbances and a high GR of myopia, suggesting that a high GR of myopia may increase children's sensitivity to sleep disturbances. This study indicates that children with a high GR of myopia need to achieve adequate sleep duration and excellent sleep quality.

● **KEYWORDS:** sleep quality; genetic risk score; myopia; children

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INTRODUCTION

In recent years, the prevalence of myopia has shown a continuous increase in younger individuals[1-3], and the prevalence of high myopia has also grown[4]. Patients with high myopia are prone to complications such as retinal detachment, glaucoma, cataracts, and myopic macular degeneration, which increase the risk of irreversible visual impairment and blindness later in life[5].

Although the pathogenesis of myopia is still unknown, a great deal of studies have suggested that myopia is a multigenic condition induced by a complex interplay between genes and the environment[6-7]. Hundreds of loci associated with refractive error and myopia in Europeans and Asians have been identified by several large-scale genome-wide association studies (GWASs)[8-9]. These loci provided the possibility to calculate the genetic risk score (GRS), which estimates the overall risk of genetic susceptibility to myopia[10]. Individuals with a GRS in the top 25% have been reported to have a 2.34- and 1.76-fold higher risk of high and moderate myopia than the remaining 75%, respectively[11]. In addition, GRS explains more phenotypic variance of spherical equivalent (SE) in adolescents than the number of parents with myopia, suggesting that GRS may be more effective as a proxy for genetic factors than parental myopia[11].

Sleep is a physiological process of human life activities, and adequate sleep duration and high-quality sleep are important guarantees for the healthy growth of children and adolescents.

However, the prevalence of sleep disturbances worldwide is 20%-40%, which indicates that sleep disturbances are very common in children and adolescents[12-14]. Sleep disturbances not only lead to anxiety and depression, daytime drowsiness, difficulty concentrating, and poor academic performance[15] but also may affect refractive development in children and adolescents[16-17]. Some studies have reported the association of sleep quality with myopia[18-21]; however, the results are not consistent. We speculated that the reason for the inconsistencies may be that the variation in individual genetic susceptibility to myopia leads to different sensitivities to sleep disturbances.

Thus, we analysed the association of sleep quality with myopia under different levels of genetic risk (GR) in this study. This study will offer a reference for the prevention and control of myopia in children.

SUBJECTS AND METHODS

Ethical Approval The Wenzhou Epidemiology of Refraction Error (WERE) study complied with the principles of the Declaration of Helsinki and was authorized by the Ethics Committee of the Eye Hospital of Wenzhou Medical University. All the parents signed an informed consent form after being informed of the study's purpose and details. This trial is registered as ChiCTR1900020584 at www.Chictr.org.cn.

Subjects A cross-sectional study was carried out. Three elementary schools in Wenzhou, Zhejiang Province, China, were selected with cluster sampling. Students in grades 3-6 were examined from April to June 2021. A total of 1410 children were enrolled in the study, and subjects with ocular inflammation or trauma or ill-matched subjects were excluded.

Examinations The ophthalmic examinations were conducted by well-trained staff. Refractive error without cycloplegia was estimated by an autorefractor (RM-800, Topcon Corp., Tokyo, Japan). The average value was calculated after three repeated measurements in each eye. The SE was computed as the sphere power +1/2×cylinder power. Myopia was defined as SE of -0.5 diopter (D) or less in at least one eye[22-24]. Ocular biological structure parameters, such as the axial length (AL) and corneal curvature (CR), were estimated with the IOL Master (Carl Zeiss Meditec, Oberkochen, Germany) and a Lenstar 900 optical biometer (Haag Streit AG, Koeniz, Switzerland). The average value was taken after 5 measurements of AL. The CR was repeatedly measured three times, and the mean CR was defined as the average of the steepest and flattest meridians of the CR. The AL/CR ratio was defined as the ratio of the average AL to the average CR. Since SE was highly correlated in both eyes (Spearman correlation coefficient=0.835, P<0.001), only the SE, AL, and AL/CR data were provided for the right eye.

Questionnaires A detailed questionnaire was used to collect information about children's demographic characteristics (age, sex, grade), near-work time, outdoor time, parental myopia status and parental education level. Sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI) by asking about children's sleep habits in a typical recent month. The Chinese version of the PSQI has been effectively validated in a previous report[25] and covers seven factors, namely, subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, hypnotic medication, and daytime dysfunction. The higher the global PSQI score is, the worse the sleep quality. Sleep disturbances were defined as a score of 6 or more[19]. The Cronbach's α of the PSQI in this study was 0.617. All the questionnaires were administered by at least 2 subject group trained surveyors who were also well experienced in explaining these questions to facilitate the investigation of each investigated class.

Single Nucleotide Polymorphism Selection and Genotyping We retrieved a total of 108 single nucleotide polymorphisms (SNPs) associated with myopia by searching the SNPedia database, GWAS catalogue database, CREAM Consortium database, and published papers, with a cut-off date of September 2019[9,26]. A DNA extraction kit (Tiangen Biotechnology Co., Ltd., Beijing, China) was used to extract DNA from oral mucosa samples from the children, and genotyping was performed using a custom-designed 48-Plex SNP Scan™ kit (Cat#: G0104; Shanghai Tianhao Biotechnology Co., Ltd.). Genotyping of a random duplicated sample was performed as an internal control to guarantee the quality of the genotyping data, and there were no genotyping errors detected for any of the SNPs. The success rate of genotyping was greater than 99%, and the concordance rate was 100% for 3% of replicate samples. The genotyping data for this study were completed in April 2020. Since the individual genome remains unchanged throughout life, it does not affect the results of this data analysis.

Genetic Risk Score Using the gene polymorphism data, 17 SNPs associated with myopia were replicated by association analysis in this study and used to calculate the GRS. The 17 SNPs were rs13217285 (near LINC00240, HIST1H2BJ), rs524952 (near LINC02252, GJD2), rs2855530 (near BMP4), rs2181346 (near BMP4, CDKN3), rs2738265 (near BMP4), rs334354 (near TGFBR1), rs10760673 (near TGFBR1), rs1532278 (near CLU), rs745480 (near LRIT2), rs9416017 (near DNAJB12), rs1994840 (near C4orf22), rs10122788 (near MVB12B), rs837323 (near PCCA), rs7042950 (near RORB), rs11101263 (near FRMPD2), rs12898755 (near APH1B), and rs511217 near (KCNA4). Each locus of each study subject was assigned a 0 or ln odds ratio (OR) score according to whether the subject carried the risk allele. After scoring all the SNPs,

the scores were synthesized to obtain the GRS for each study subject[27]. GRS=$\sum_{i=1}^{k} \ln(OR_i)n_i$ (i=1,2...k; n_i=0,1,2). The higher the GRS is, the higher the genetic susceptibility to myopia. The study subjects were divided into a low GR group ($\leq P_{25}$), a moderate GR group (P_{25}-P_{75}) and a high GR group ($\geq P_{75}$) according to the GRS quartile[28].

Statistical Analysis EpiData 3.1 software was used to input the data. Using gPlink1.07 software, multivariate logistic regression was used to analyse the relationship between the SNPs and myopia, and the GRS was calculated. The questionnaire data and examinations were assessed with SPSS (version 24.0; IBM Corporation, Chicago, IL, USA). The global scores of the PSQI and GRS are reported as the mean±standard deviation based on a normal distribution with comparisons between groups by independent-sample Student's *t*-test and analysis of variance. The SE, AL, and AL/CR ratio are reported as medians with interquartile ranges (IQRs) for nonnormal distributions with comparisons between groups using the Mann-Whitney *U* test and Kruskal-Wallis H test. The prevalence of myopia and sleep disturbances are reported as percentages with comparisons between groups by the Chi-square test. The influence of GRS, sleep disturbances, and their interaction on the risk of myopia was evaluated, and the ORs and 95% confidence intervals (95%CIs) were calculated by generalized linear models. A two-tailed P<0.05 was considered to be statistically significant.

RESULTS

A total of 1410 children, namely, 782 (55.46%) boys and 628 (44.54%) girls aged 9-14y (10.74±1.15y), who were subjected to the eye examinations were enrolled in this analysis. There was no significant difference in the prevalence of myopia between boys (63.62%) and girls (65.45%, P>0.05). The age of children with myopia (10.89±1.14y) was significantly higher than that of children without myopia (10.48±1.12y, P<0.001). The prevalence of myopia in grade 3 to grade 6 children was 49.03%, 62.02%, 70.04%, and 76.62%, respectively. The prevalence of myopia was significantly different between grades (P<0.001) and increased significantly with increasing grade (P for trend<0.001).

The global score of PSQI ranged from 0 to 14, with a mean of 4.09±2.48. The students in the myopia group exhibited poorer PSQI scores (4.22±2.52) than those in the nonmyopia group (3.84±2.40, P=0.006), while there were no significant differences in age, sex, parental education level, or the number of parents with myopia (Table 1). Subscale analyses of the PSQI results revealed worse subjective sleep scores (P=0.022), sleep efficacy scores (P=0.007) and daytime dysfunction scores (P=0.026) in the myopia group than in the nonmyopia group. However, there were no statistically significant differences in the other factors (P>0.05, Table 2). Of the 1354 students, 353 (26.07%) had sleep disturbances. The prevalence of myopia in children with sleep disturbances was significantly higher than that in children without sleep disturbances (69.69% *vs* 62.34%, P=0.013; Figure 1A). In addition, the children with sleep disturbances had more negative SEs (P=0.032) and higher AL/CR ratios (P=0.050) than those without sleep disturbances. However, there was no significant difference in the AL between children with sleep disturbances and those without sleep disturbances (P>0.05, Table 3).

Table 1 Sleep quality and the GRS in children mean±SD

Parameters	Sleep quality	*P*	GRS	*P*
Age (y)		0.142[a]		0.925[a]
9	3.89±2.46		7.76±1.12	
10	3.94±2.31		7.75±1.26	
11	4.09±2.47		7.69±1.29	
12	4.37±2.72		7.75±1.22	
13-14	4.37±2.63		7.80±1.15	
Sex		0.993[b]		0.232[b]
Boys	4.09±2.51		7.70±1.21	
Girls	4.09±2.45		7.79±1.26	
Paternal education level		0.139[b]		0.292[b]
Under college	4.24±2.56		7.70±1.26	
College and above	4.01±2.50		7.78±1.20	
Maternal education level		0.137[b]		0.993[b]
Under college	4.26±2.59		7.74±1.28	
College and above	4.02±2.49		7.74±1.19	
No. of myopic parents		0.659[a]		0.787[a]
0	4.14±2.55		7.71±1.27	
1	4.23±2.53		7.77±1.24	
2	4.01±2.53		7.71±1.17	
Refractive status		0.006[b]		<0.001[b]
Nonmyopia	3.84±2.40		7.57±1.20	
Myopia	4.22±2.52		7.84±1.23	

[a]Analysis of variance; [b]Independent-sample Student's *t*-test. GRS: Genetic risk score.

The GRS ranged from 4.49 to 12.89, with a mean of 7.74±1.23. The GRS in the myopia group (7.84±1.23) was significantly higher than that in the nonmyopia group (7.57±1.20, P<0.001). However, there were no significant differences in age, sex, parental education level or the number of parents with myopia (Table 1). The prevalence of myopia in children with high GR was significantly higher than those with moderate GR and low GR (71.01% *vs* 62.41% *vs* 58.60%, P=0.002) and increased significantly with increasing GR level (P for trend <0.001; Figure 1B). In addition, there were statistically significant differences in the SE, AL, and AL/CR ratio among the high GR group, moderate GR group, and low GR group (P=0.008, 0.010, 0.003, respectively). With increasing GR level, the SE decreased (P for trend=0.008), and the AL (P for trend=0.003) and AL/CR ratio (P for trend=0.001) increased (Table 3).

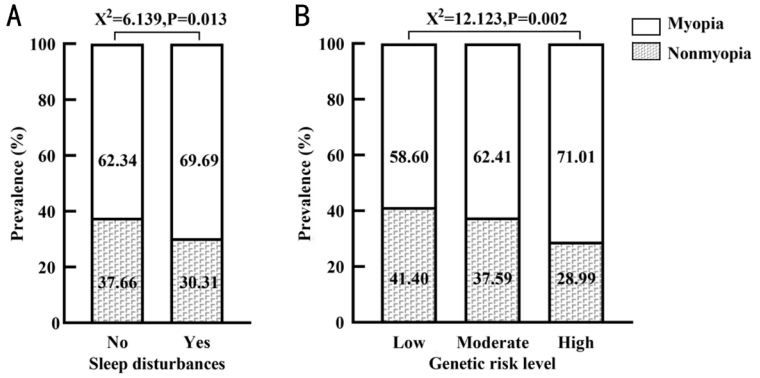

Figure 1 Prevalence of myopia in all children with or without sleep disturbances (A) and based on the genetic risk level (B).

Table 2 Scores of factors in the PSQI mean±SD

Parameters	All	Nonmyopia	Myopia	*t*	*P*
Subjective sleep	0.82±0.71	0.76±0.69	0.85±0.71	-2.288	0.022[a]
Sleep latency	0.95±0.97	0.90±0.96	0.99±0.97	-1.599	0.110
Sleep duration	0.07±0.31	0.05±0.29	0.07±0.32	-1.227	0.220
Sleep efficacy	0.11±0.41	0.08±0.33	0.13±0.45	-2.721	0.007[a]
Sleep difficulty	1.00±0.59	0.99±0.60	1.00±0.58	-0.311	0.756
Daytime dysfunction	1.13±0.93	1.06±0.92	1.17±0.93	-2.229	0.026[a]
PSQI global score	4.09±2.48	3.84±2.40	4.22±2.52	-2.746	0.006[a]

PSQI: Pittsburgh Sleep Quality Index. [a]*P*<0.05.

Table 3 Analysis of the differences in the SE, AL, and AL/CR ratio among different sleep quality and genetic risk levels

Parameters	SE[c]	*P*	AL[c]	*P*	AL/CR[c]	*P*
Sleep disturbances		0.032[a]		0.221[a]		0.050[a]
No	-0.63 (1.88)		23.96 (1.37)		3.05 (0.16)	
Yes	-0.88 (2.13)		24.09 (1.40)		3.07 (0.18)	
Genetic risk		0.008[b]		0.010[b]		0.003[b]
Low	-0.50 (1.63)		23.91 (1.38)		3.04 (0.16)	
Moderate	-0.63 (1.75)		23.94 (1.40)		3.04 (0.16)	
High	-0.88 (2.13)		24.16 (1.44)		3.07 (0.17)	

[a]Mann-Whitney *U* test; [b]Kruskal-Wallis *H* test; [c]Median (interquartile range). SE: Spherical equivalent; AL: Axial length; AL/CR: The ratio of the axial length to the corneal curvature.

Generalized linear model was used to assess factors associated with myopia after adjusting for confounders. In the generalized linear model, sleep disturbances and high GR were independent risk factors for myopia. The children with sleep disturbances and high GR had a higher risk of myopia than those without sleep disturbances and with low GR (OR=1.59, *P*=0.010; OR=1.88, *P*=0.003, respectively; Table 4). Compared to those with low GR and without sleep disturbances, children with high GR with or without sleep disturbances had a higher risk of having myopia (OR=4.88, 95%CI: 2.03-11.71, *P*<0.001; OR=1.70, 95%CI: 1.06-2.72, *P*=0.028; Figure 2).

DISCUSSION

In the WERE study consisting of 1410 children, we found that both sleep disturbances and high GR were significantly associated with an increased risk of myopia. Notably, we also found a significant interaction between sleep disturbances and high GR of myopia, as represented by 17 associated SNPs, suggesting that a high GR of myopia may increase children's sensitivity to sleep disturbances.

Association Between Sleep Quality and Myopia Our study showed that sleep quality was significantly related to myopia in children. The PSQI global scores in the children with myopia were higher than those in the children without myopia, and the subscales of the PSQI scores revealed that the myopia group had worse scores for subjective sleep, sleep efficacy and daytime dysfunction than the nonmyopia group, which is consistent with the research conclusions of Ayaki *et al*[19], Lin *et al*[21] and Wang *et al*[29]. The sleep disturbances prevalence of 26.07% in this study is consistent with that reported in previous national[30] and international studies[12-13]. In recent years, with the popularization and expansion of electronic products, the massive use of artificial light sources, the increase in

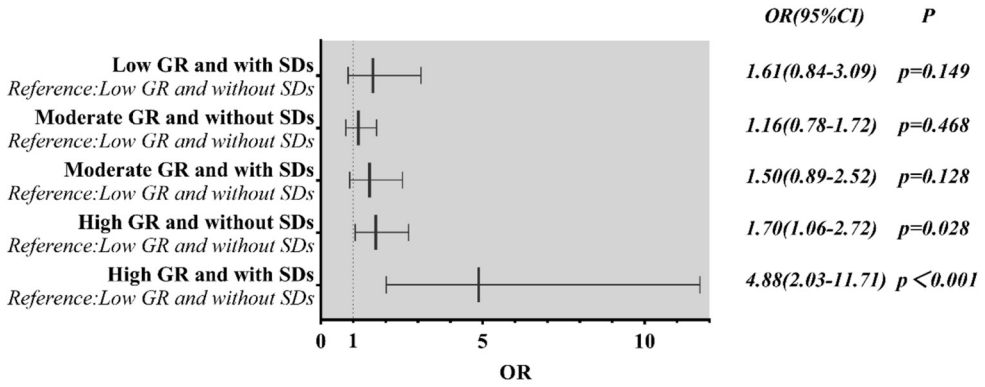

Figure 2 Risk of myopia based on sleep disturbances and the GR Multivariable-adjusted OR (adjusted for children's age, sex, maternal and paternal education level, number of myopic parents, near-work time, outdoor time) for myopia versus the GR level and SDs. The GR was divided into low, moderate, and high GR levels. OR: Odds ratio; GR: Genetic risk.

Table 4 Generalized linear model analysis of the association of sleep quality and the genetic risk level with children's myopia

Parameters	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Sleep disturbances						
No	1		1		1	
Yes	1.31 (1.00-1.72)	0.049	1.51 (1.09-2.10)	0.012	1.59 (1.12-2.25)	0.010
Genetic risk						
Low	1		1		1	
Moderate	1.23 (0.94-1.63)	0.136	1.10 (0.79-1.53)	0.581	1.10 (0.78-1.55)	0.601
High	1.81 (1.30-2.52)	<0.001	1.84 (1.24-2.74)	0.003	1.88 (1.23-2.88)	0.003

Model 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, number of myopic parents, paternal education levels, and maternal education levels; Model 3: Adjusted for age, sex, number of myopic parents, paternal education levels, maternal education levels, average daily outdoor activities time, and average daily near-work time. OR: Odds ratio.

educational pressure and other factors, normal sleep times have been affected, leading to late sleep, insufficient sleep time and sleep disturbances[31-35].

We found that sleep disturbances are an independent risk factor for myopia. Children with sleep disturbances have a 1.59 times higher risk of myopia and have more negative SEs and higher AL/CR ratios than those without sleep disturbances. A finding by Lin *et al*[21] showed that poor sleep quality was a risk factor for myopia. This finding is also consistent with another study by Ayaki *et al*[19], suggesting that sleep quality in children was significantly correlated with myopic error, with the high myopia group being the worst affected. In this study, we also found that the prevalence of sleep disturbances was higher in students with more near-work time, which indicated that the correlation between sleep disturbances and myopia may be confounded by accommodative dysfunction caused by nearwork. Therefore, to reduce the interference of confounding factors, we used generalized linear model to control for relevant confounders such as near-work time, and the results showed that sleep disturbances remained associated with myopia. Although the specific mechanism is still unclear, most scholars believe that sleep may affect refractive development. Sleep disturbances with late sleep and insufficient sleep time cause circadian rhythm disturbances, in turn affecting retinal circadian rhythms[16]. The retinal circadian rhythm is the centre of the signalling mechanism, and the retinal neurotransmitter response controls the daily rhythm of eyeball growth and eyeball size after interacting with the retinal circadian clock, thereby regulating the refractive development of the eyeball[17]. However, there are also studies indicating insufficient evidence that sleep disturbances are associated with myopia[18,20]. This may be due to variations in the genetic susceptibility of myopia resulting in different sensitivities to sleep disturbances.

Association Between Genetic Risk and Myopia It is well known that genetic factors are a very important aetiology of myopia that cannot be ignored. The GRS is a condensed indicator of genetic susceptibility to disease. In this study, we found that the risk of myopia in children with a high GR was 1.88 times higher than that in children with a low GR, indicating that children with a high GR have a higher genetic susceptibility to myopia. Many studies have shown that the higher the GR score is, the greater the risk of myopia. For example, a study by Lanca *et al*[11] in Chinese children aged 6 to 11y in Singapore showed that the risk of high and moderate myopia was increased by 2.34- and 1.76-fold in children with GRSs above 75%, respectively, compared with those

with GRSs below 75%. Additionally, a study by Ghorbani Mojarrad *et al*[10] reached the same conclusion. At present, the GRS has been used to predict myopia in a number of studies. A study by Ghorbani Mojarrad *et al*[10] reported that the GRS had a receiver operating characteristic curve value of 0.67 for myopia, 0.75 for moderate myopia, and 0.73 for high myopia. Moreover, we found that the SE decreased, while the AL and AL/CR ratio increased with increasing GR level in this study. Previous studies by Lanca *et al*[11] and Tideman *et al*[36] reached the same conclusion that the GRS had a negative correlation with the SE and a positive correlation with the AL and AL/CR ratio.

Interaction Between Sleep Quality and Genetic Risk In this study, we found that the interaction between sleep quality and GR significantly increases the risk of myopia in children. Children with a high GR but without sleep disturbances or those with a high GR with sleep disturbances had a 70% and 388% (OR 1.70, 95%CI: 1.06-2.72; OR=4.88, 95%CI: 2.03-11.71) increased risk of myopia, respectively, compared to those with a low GR and no sleep disturbances. Recently, an increasing number of scholars have investigated the influence of the interaction between genes and the environment (including near work, outdoor activities and education) on myopia and found that the interaction between genes and the environment is related to a greater risk of myopia than that due to the existence of the two independently[37-38]. For example, a study by Enthoven *et al*[39] reported a significant interaction between the GRS and lifestyle (near work and outdoor), showing that their combination has the strongest influence. Another study by Verhoeven *et al*[38] reported that subjects with a high GR and high levels of education had a far higher risk of myopia than subjects with only one of the two factors, providing proof of a gene–environment interaction. The school-age period is a sensitive or critical period, and school-aged children are more vulnerable to environmental factors. Additionally, children vary in their sensitivity to their surroundings, and this variation is affected by the interaction among developmental timing, genetic factors and environments[40]. The interaction of sleep quality and GR indicated that children vary in their sensitivity to sleep disturbances due to differences in genetic susceptibility to myopia. Thus, the GR of myopia was not taken into consideration, which may be the reason why the relationship between sleep disturbances and myopia remains controversial. The children with sleep disturbances and a high GR had a higher risk of myopia in this study. This finding suggested that to reduce the risk of myopia, children with high GR need to improve their sleep quality since an individual's GR remains essentially fixed throughout their lifetime. However, this strategy needs to be further investigated by cohort studies or randomized controlled trials.

The strength of our study is that the GRS is a genetic index that is measured objectively without subjective bias and it can estimate the overall risk of individual genetic susceptibility to myopia. To the best of our knowledge, we are the first to find that the interaction between sleep disturbances and GR is associated with myopia. On the other hand, there were some potential limitations to this study. First, there may be some errors in the measurement of refractive without cycloplegia. Although refractive without cycloplegia is less exact than cycloplegic refraction, it is more feasible for screening and monitoring myopia in a large-scale cohort. Moreover, the AL and AL/CR measurements used here are unlikely to be influenced by cycloplegia. Additionally, since sleep quality and environmental factors were estimated by questionnaires, there is a potential for recall bias. Therefore, objective measurement tools such as actiwatches and cloud clamps will be used to collect data in the future.

In summary, the prevalence of sleep disturbances was 26.07% for elementary school students in Wenzhou. There was a significant interaction between sleep disturbances and a high GR of myopia, suggesting that a high GR of myopia may increase children's sensitivity to sleep disturbances. This study indicates that children with a high GR of myopia need to obtain adequate sleep duration and excellent sleep quality. However, longitudinal cohort studies and animal experiments are required to further validate our results.

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REFERENCES

1 Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol* 2020;20(1):27.

2 Xiang ST, Zhao S, Li X, Li LP, Xie LH, Kang RT, Zhong Y. The prevalence of reduced visual acuity in children from an urban district in China from 2002 to 2018. *Eye* (*Lond*) 2021;35(9):2550-2555.

3 Wang JY, Ying GS, Fu XJ, Zhang RH, Meng J, Gu F, Li JJ. Prevalence of myopia and vision impairment in school students in Eastern China. *BMC Ophthalmol* 2020;20(1):2.

4 Chen M, Wu AM, Zhang LN, Wang W, Chen XY, Yu XN, Wang KJ.

The increasing prevalence of myopia and high myopia among high school students in Fenghua City, Eastern China: a 15-year population-based survey. *BMC Ophthalmol* 2018;18(1):159.

5 Ikuno Y. Overview of the complications of high myopia. *Retina* 2017; 37(12):2347-2351.

6 Miraldi Utz V. Nature versus nurture: a systematic approach to elucidate gene-environment interactions in the development of myopic refractive errors. *Ophthalmic Genet* 2017;38(2):117-121.

7 Zhang XY, Wang Y, Pan CW, Yang WY, Xiang Y, Yang J, Zhang FY. Effect of genetic-environmental interaction on Chinese childhood myopia. *J Ophthalmol* 2020;2020:6308289.

8 Hysi PG, Choquet H, Khawaja AP, *et al*. Meta-analysis of 542, 934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat Genet* 2020;52(4):401-407.

9 Tedja MS, Wojciechowski R, Hysi PG, *et al*. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet* 2018;50(6):834-848.

10 Ghorbani Mojarrad N, Plotnikov D, Williams C, Guggenheim JA; UK Biobank Eye and Vision Consortium. Association between polygenic risk score and risk of myopia. *JAMA Ophthalmol* 2020;138(1):7-13.

11 Lanca C, Kassam I, Patasova K, Foo LL, Li J, Ang M, Hoang QV, Teo YY, Hysi PG, Saw SM. New polygenic risk score to predict high myopia in Singapore Chinese children. *Transl Vis Sci Technol* 2021;10(8):26.

12 Lewien C, Genuneit J, Meigen C, Kiess W, Poulain T. Sleep-related difficulties in healthy children and adolescents. *BMC Pediatr* 2021; 21(1):82.

13 de Almeida GMF, Nunes ML. Sleep characteristics in Brazilian children and adolescents: a population-based study. *Sleep Med X* 2019;1:100007.

14 Chen XR, Ke ZL, Chen YH, Lin XX. The prevalence of sleep problems among children in mainland China: a meta-analysis and systemic-analysis. *Sleep Med* 2021;83:248-255.

15 O'Brien LM. The neurocognitive effects of sleep disruption in children and adolescents. *Sleep Med Clin* 2011;6(1):109-116.

16 Logan RW, Hasler BP, Forbes EE, Franzen PL, Torregrossa MM, Huang YH, Buysse DJ, Clark DB, McClung CA. Impact of sleep and circadian rhythms on addiction vulnerability in adolescents. *Biol Psychiatry* 2018;83(12):987-996.

17 Stone RA, Pardue MT, Iuvone PM, Khurana TS. Pharmacology of myopia and potential role for intrinsic retinal circadian rhythms. *Exp Eye Res* 2013;114:35-47.

18 Zhou ZQ, Morgan IG, Chen QY, Jin L, He MG, Congdon N. Disordered sleep and myopia risk among Chinese children. *PLoS One* 2015;10(3):e0121796.

19 Ayaki M, Torii H, Tsubota K, Negishi K. Decreased sleep quality in high myopia children. *Sci Rep* 2016;6:33902.

20 Pan CW, Liu JH, Wu RK, Zhong H, Li J. Disordered sleep and myopia among adolescents: a propensity score matching analysis. *Ophthalmic Epidemiol* 2019;26(3):155-160.

21 Lin L, Man FT, Hu NB, Liu HX, Jia GZ, Wang YP. Risk factors of myopia in adolescents. *Chin J Child Heal Care* 2013;21(02):206-209.

22 Chang PJ, Zhang B, Lin L, Chen RR, Chen SP, Zhao YE, Qu J. Comparison of myopic progression before, during, and after COVID-19 lockdown. *Ophthalmology* 2021;128(11):1655-1657.

23 Wang JX, Li Y, Musch DC, Wei N, Qi XL, Ding G, Li X, Li J, Song LL, Zhang Y, Ning YX, Zeng XY, Hua N, Li S, Qian XH. Progression of myopia in school-aged children after COVID-19 home confinement. *JAMA Ophthalmol* 2021;139(3):293-300.

24 Flitcroft DI, He MG, Jonas JB, *et al*. IMI—defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci* 2019;60(3):M20-M30.

25 Ağargün YM, Kara H, Anlar O. The reliability and validity of Pittsburgh sleep quality ındex. *Turkish J Psychiatry* 1996;7:107-111.

26 Lin HJ, Wan L, Tsai Y, Liu SC, Chen WC, Tsai SW, Tsai FJ. Sclera-related gene polymorphisms in high myopia. *Mol Vis* 2009;15:1655-1663.

27 Wang C, Dai JC, Sun YM, Xie L, Pan LB, Hu ZB, Shen HB. Genetic risk score: principle, methods and application. *Zhonghua Liu Xing Bing Xue Za Zhi* 2015;36(10):1062-1064.

28 Liu SX, Zhi XY, Xi W, Shi R, Xiong WJ, Zhang X. The association between myopic refraction and near work among children and adolescents based on genetic risk score. *Zhonghua Yu Fang Yi Xue Za Zhi* 2021;55(4):446-452.

29 Wang Y, Zheng KJ, Xie H, Yi M, Pan CW, He XG. Impact of different myopia degree on sleep quality among adolescents in Baoshan District. *Chin J Sch Health* 2021;42(2):190-194.

30 Zhang JJ, Lu ZJ, Gui X, Yan WJ, Gao XY. Investigation on the prevalence of myopia in middle school students and its relationship with sleep disturbances. *Chin Gen Prac* 2013;16(07):665-667.

31 Lin QF, Hang RN, Chen JY, Yang JW. Academic pressure and sleep quality among secondary school students in Guangzhou. *Chin J Sch Health* 2018;39(6):903-905, 909.

32 Zhu M, Zhang AH, Cao Z, Li YX, Tao FB, Hao JH. Investigation on the exposure status of electronic screen in preschool children and the influencing factors. *Maternal & Child Health Care of China* 2017;32(04):833-836.

33 Yu ZY, Liu W. A meta-analysis of relation of smartphone use to anxiety, depression and sleep quality. *Chin Ment Health J* 2019; 33(12):938-943.

34 Fadzil A. Factors affecting the quality of sleep in children. *Children* (*Basel*) 2021;8(2):122.

35 Rafique N, Al-Asoom LI, Alsunni AA, Saudagar FN, Almulhim L, Alkaltham G. Effects of mobile use on subjective sleep quality. *Nat Sci Sleep* 2020;12:357-364.

36 Tideman JWL, Fan Q, Polling JR, *et al,* CREAM Consortium. When do myopia genes have their effect? Comparison of genetic risks between children and adults. *Genet Epidemiol* 2016;40(8):756-766.

37 Shi HN, Fu J, Liu XJ, *et al*. Influence of the interaction between parental myopia and poor eye habits when reading and writing and poor reading posture on prevalence of myopia in school students in

Urumqi, China. *BMC Ophthalmol* 2021;21(1):299.

38 Verhoeven VJM, Buitendijk GHS, Consortium for Refractive Error and Myopia (CREAM), Rivadeneira F, Uitterlinden AG, Vingerling JR, Hofman A, Klaver CCW. Education influences the role of genetics in myopia. *Eur J Epidemiol* 2013;28(12):973-980.

39 Enthoven CA, Tideman JWL, Polling JR, Tedja MS, Raat H, Iglesias AI, Verhoeven VJM, Klaver CCW. Interaction between lifestyle and genetic susceptibility in myopia: the Generation R study. *Eur J Epidemiol* 2019;34(8):777-784.

40 Boyce WT, Levitt P, Martinez FD, McEwen BS, Shonkoff JP. Genes, environments, and time: the biology of adversity and resilience. *Pediatrics* 2021;147(2):e20201651.