MYOPIA: PUBLIC HEALTH CHALLENGES AND INTERVENTIONS

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MYOPIA: PUBLIC HEALTH CHALLENGES AND INTERVENTIONS

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Editorial: Myopia: Public health challenges and interventions

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Editorial on the Research Topic
Myopia: Public health challenges and interventions

Most school myopia results from an excessive axial length of the eye that develops in childhood. In the past three decades there were significant increases in the prevalence of childhood myopia. By 2050, half of the world population is expected to have myopia, a 2-fold increase compared to year 2000 (1). In the last years, the achievements made by scientists have been exceptional, leading to major advancements in the treatment of myopia progression. This Research Topic comprises 14 studies including original research articles and reviews covering several aspects related with myopia.

Myopia has become one of the fastest-growing eye health challenges of the twenty-first century, with a disproportionate burden on urban Asia regions (2). Shi et al. conducted a study on temporal and spatial characterization of myopia in China. The authors showed that there was an increase in the prevalence of myopia in children aged 7–18 years old from 1995 to 2014. The study results also showed a shift of myopia to the southeast, identifying the existence of high-risk areas. Those results are important for targeted myopia prevention.

Myopia is a leading cause of visual impairment and blindness across many countries (3). Many myopic adolescents with high myopia today may be legally blind due to myopic maculopathy in 30 years' time. Considering the significant burden of the disease and its complications, tackling myopia becomes imperative. Thus, it is important to understand risks factors for myopia, to develop appropriate prevention plans and treatment strategies. The evidence for the association between sleep and myopia or gender and myopia has been mixed. Li, Tan et al. showed that sleep quality, duration, timing, and the consistency of specific sleep factors were not associated with myopia among school-aged children. Xu et al. reported that puberty status among adolescents may be an independent risk factor for myopia in girls but not boys, suggesting that earlier puberty in girls explained a significant proportion of the sex disparity in myopia prevalence. However, detailing the public health implications of both study findings requires further longitudinal studies with more accurate measures of sleep and puberty status.

The pandemic lockdowns established by the authorities for curving COVID-19 pandemic led to detrimental effects on myopia development due to a significant decrease in outdoor time and increase in near work activities (4, 5). Limwattanayingyong et al. reviewed the evidence supporting the association between environmental and social factors and myopia resulting from the COVID-19 Pandemic. The authors found sufficient evidence to support the association between an increase in near work from home confinement or a reduction of outdoor activities and worsening of myopia during the COVID-19 lockdown. The findings from this review may help to better understand myopia development and progression, and lead to recommendations to prevent myopia and its progression. Efforts to reduce the prevalence, progression, and severity of myopia could have a profound impact on public health. Keel et al. propose a digital message program named "WHO-ITU MyopiaEd Programme" targeting education on myopia and its prevention. The program aims to strengthen countries' efforts to develop sustainable, cost-effective, and acceptable activities to support education on myopia and its prevention. Those programs may need to be implemented taking in consideration the diversity of eye care behaviors among adolescents. According to Li, Wang et al. there are differential profiles related with basic demographic characteristics and visual acuity development. Personalized group intervention for students in different latent classes behaviors may enhance the intervention results.

Myopia is a chronic condition where the evidence is changing at an accelerated pace and 1,000's of research studies about myopia have been published within the last 100 years. Shan et al. conducted a bibliometrics analysis to help researchers to comprehend the global trends of myopia research from 1900 to 2020. Research Topics were clustered into six groups, with "prevalence and risk factors of myopia" and "surgical control of myopia" being the largest groups with higher number of publications. With the increasing prevalence of myopia, interventions to control myopia progression are a potential research hotspot and pressing public health issue. Shinojima et al. conducted a mini review on the current evidence-based treatments for myopia progression, such as atropine eye drops, optical treatment with defocus and orthokeratology. New research with optical treatments also showed good efficacy in the control of myopia progression. However, there are other factors that need to be considered, such as the uptake by eye care practitioners that can be improved if more education is given. Yang et al. conducted a study on eye care practitioners and their influence in prescribing myopia control. The authors found that the cost of myopia control is of concern to eye care practitioners. Further research is also required to establish the minimum age, amount of myopia, and progression to start prescribing myopia control interventions.

Previous epidemiological research on myopia has been mainly focused on school-age children. However, it is essential to identify children at high risk of developing myopia to prevent myopia in an early stage, especially during the preschool period. The findings of a cross-sectional study by Matsumura et al. outline the importance of obtaining an accurate family history of myopia to identify at-risk children before they develop myopia and to raise awareness on lifestyle-based myopia prevention. You et al. analyzed longitudinal changes in refractive error among preschool children and found a myopic shift of 0.20 D on average per year. The most important change in spherical equivalent occurred in 3-years-olds prompting the need for more prospective studies to better explain the factors related to refractive status changes and to prevent myopia in preschool children.

Tao et al. suggest that during the growth of school-age children, a significant correlation exists between axial length and height, and between axial length growth and height growth, especially in children with newly developed myopia. This indicates that during the period of rapid height growth, the elongation of axial length also needs to be considered. On the other hand, Lee and Mackey reviewed the findings from the Raine study in young adults with myopia. The results support that myopia can progress in the third decade of life, with some individuals progressing at alarming rates. Thus, it is also critical that longitudinal birth cohort studies in other populations increase their focus on research in young adults. Lan et al. showed that about half of the interviewed adults patients believed laser refractive surgery could cure myopia and its complications. The results of this study show that patients with myopia need to receive more education on laser refractive surgery and rhegmatogenous retinal detachment to increase early detection and potentially prevent the disease complications.

To prevent myopia and its complications it is essential to unravel the causes that have produced the myopia epidemic in East and Southeast Asian urban environments. More research is necessary on the lack of outdoor exposure since an early age in childhood, and early high academic load of more than 10 h of schooling a day 6 days a week with short annual vacations, at which Asian children in many urban cities are exposed. The manuscripts published in this Research Topic show that the myopia epidemic has occurred along with urbanization and that myopia develops early since kindergarten years, continuing to progress in young adulthood. Recent changes in the tutorial classes education system by the government in China have been accepted by the society but myopia education programs are welcome to prevent myopia. One of the main concerns about myopia control is the cost effectiveness of the new available treatments. Thus, much has still to be learned and we hope the Research Topic of studies presented in this Research Topic of Frontiers in Public Health inspires, informs, and provides directions and guidance to governments and researchers in the field of myopia.

Author contributions

CL prepared the original draft. RI and AG critically reviewed and edited the manuscript. All authors have reviewed and approved the final manuscript.

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References

1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006

2. Holden BA, Wilson DA, Jong M, Sankaridurg P, Fricke TR, Smith EL, et al. Myopia: a growing global problem with sight-threatening complications. *Community Eye Heal.* (2015) 28:35.

3. Holden B, Sankaridurg P, Smith E, Aller T, Jong M, He M. Myopia, an underrated global challenge to vision: where the current data takes us on myopia control. *Eye.* (2014) 28:142–6. doi: 10.1038/eye.2013.256

4. Zhang X, Cheung SL, Chan HN, Zhang Y, Wang YM, Yip BH, et al. Myopia incidence and lifestyle changes among school children during the COVID-19 pandemic: a population-based prospective study. *Br J Ophthalmol.* (2021) 2021:bjophthalmol-2021-319307. doi: 10.1136/bjophthalmol-2021-319307

5. Mirhajianmoghadam H, Piña A, Ostrin LA. Objective and subjective behavioral measures in myopic and non-myopic children during the COVID-19 pandemic. *Transl Vis Sci Technol.* (2021) 10:4. doi: 10.1167/tvst.10.11.4

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ORIGINAL RESEARCH
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Correlation Between Increase of Axial Length and Height Growth in Chinese School-Age Children

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Purpose: To identify the relationship between the increase in axial length (AL) and height in school-age children and explore the influence of refractive status on such a relationship.

Methods: In this 5-year cohort study, 414 Chinese children (237 boys) aged 6–9 years (mean 7.12) underwent measurements annually. AL was measured using the Lenstar; height with the children standing, without shoes; and refraction using subjective refraction without cycloplegia. Participants were divided according to the refractive status: persistent emmetropia, persistent myopia, and newly developed myopia. The measurement time points of the persistent emmetropia and persistent myopia groups were marked as T_1, T_2, T_3, T_4, and T_5. The time of myopia onset in the newly developed myopia group was marked as t_0; the preceding time points were marked as t_{-1}, t_{-2}, and so on, and the succeeding as t_1, t_2, and so on. The association between increase in AL and height was analyzed using simple correlation analysis.

Results: The mean changes in AL, height, and refraction were 1.39 mm, 23.60 cm, and −1.69 D, respectively, over 5 years in all children. The increase in AL and height were positively correlated for $T_1{\sim}T_2$, $T_1{\sim}T_3$, $T_1{\sim}T_4$, and $T_1{\sim}T_5$ ($r = 0.262$, $P < 0.001$; $r = 0.108$, $P = 0.034$; $r = 0.165$, $P = 0.001$; $r = 0.174$, $P = 0.001$, respectively). The changes in AL and height in the newly developed myopia group were significantly correlated ($r = 0.289$, $P = 0.009$) after myopia onset ($t_0{\sim}t_2$).

Conclusion: The increase in AL and height were positively correlated, especially in the newly developed myopia group after myopia onset. Thus, when children grow quickly, AL elongation should be monitored.

Keywords: axial length (AL), height, myopia, correlation, school-age children

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INTRODUCTION

In recent decades, the prevalence of myopia has rapidly increased (1). It is predicted that nearly half of the world's population will suffer from myopia by 2050 (2). The rate may be greater for eastern Asia, including China, Japan, South Korea, and Singapore (3–5), where the incidence of myopia is higher than in other areas. School-age children are the main group of people diagnosed with myopia (6), whose elongation of axial length (AL) plays a major role in the incidence and progression of myopia (7–10). Therefore, changes in AL may reflect changes in refractive status to some extent.

The association between height and AL has been demonstrated in previous cross-sectional studies (11–14) and longitudinal cohort studies (15–17). In 2002, Saw et al. (11) proved that taller children have longer AL by analyzing the height and AL of 1,449 children aged 7–9 years. Later, in 2011, Wang et al. (15) demonstrated the correlation between them through a longitudinal cohort study. They analyzed follow-up data of 553 children aged between 7 and 15 from 2006 to 2008 and concluded that height and AL are positively correlated. In brief, all previous studies agree with the statement that height and AL are positively correlated.

However, few studies have discussed the relationship between growth in height and AL. A previous study reported that the association between height and AL is largely attributable to shared genes (18). Therefore, we predicted that an association may also be present between the speed of the growth in height and AL. Huang et al. (19) proved that average changes in height and AL were correlated in a three-year follow-up experiment. However, they did not show such association at the different stages during follow-up, and the sample size was relatively small ($N = 88$). Later, Kearney et al. (20) and Li et al. (21) also explored the correlation between the increases in AL and height, but obtained different results. Kearney et al. argued that the association existed in persistent emmetropic children, while Li et al. found no association in the entire participant cohort during the 3-year follow up. This discrepancy may be ascribed to the differences in sample size ($N = 140$ and 452, respectively) and age range (5–20 and 6–8 years old, respectively). As the elongation of AL in myopic children differs from that of emmetropic children (22–24), the AL growth of those who will become myopic accelerates before the onset of myopia and slows down after it, while the annual AL change of emmetropic children is relatively stable (22). Thus, to explore the relationship between changes in height and AL, the refractive status should be considered.

In the present study we aimed to explore the association between the changes in height and AL in children through a five-year follow-up of children aged 6 to 9 years, and to determine whether the growth in height can predict the increase in AL. Furthermore, we aimed to explore the correlation between changes in height and AL in myopic children before and after the onset of myopia.

METHODS

Participants

This was a five-year cohort study conducted from 2015 to 2020 in Jinhua, a city situated in eastern China. The subjects were students of 10 schools in the Wucheng District, Jindong District, and Jinhua Economic and Technological Development Zone. Children with systemic diseases that affect height growth or ocular health, strabismus, or amblyopia were excluded. Participants who received myopia control treatment such as orthokeratology lenses or low-concentration atropine, other than single vision lenses, were also excluded. In total, 456 children of grades 1–4 successfully completed the baseline ocular examinations, and 414 (90.8%) continuously attended their measurements in the following examinations. The age at baseline (date of first examination) of the participants ranged from 6 to 9 years.

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent was obtained from all participants or their parents.

Examinations

All participants underwent an examination at Jinhua Eye Hospital every 12 months since their first examination. The examination included height assessment and comprehensive eye examination. Height was evaluated without shoes: each child stood with the buttocks, shoulder blades, and back of the head against the wall. The doctor placed the headpiece firmly on the head and recorded the height (25). AL was measured using non-invasive, non-contact optical low-coherence reflectometry (Lenstar LS900; Haag-Streit AG, 3098 Koeniz, Switzerland) without pupil dilation. Three consecutive measurements were acquired, and the mean result was used (13). If the error of the three measurements was >0.1 mm, AL was remeasured. Refraction was measured using subjective refraction without cycloplegia by experienced optometrists. The child looked at the Standard Logarithmic Visual Acuity Chart 5 m away, while the optometrist presented a variety of lenses (including spherical lenses and cylinder lenses) and altered the power of lenses in the phoropter according to the child's subjective responses until the best-corrected visual acuity (BCVA) was achieved. The refraction was transformed into spherical equivalent (SE = sphere power + 0.5cylinder power). Refractive status was judged according to SE [myopia: SE ≤ -0.5D (26, 27); emmetropia: $-0.5\text{D} < \text{SE} < +1.0\text{D}$; hypertropia: SE ≥ 1.0D].

Data Analysis

SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.) was used to analyze the data. Because data from the two eyes were highly correlated (the Spearman's rank correlation coefficient of AL and SE was 0.976 and 0.907, respectively, and both *p*-values were lower than 0.01), the data from the right eye were analyzed. The participants were classified according to the refractive status of each examination. Those who maintained emmetropia/myopia were grouped into the persistent emmetropia/persistent myopia groups. The newly developed myopia group included participants who had emmetropia or hyperopia at the first examination, became myopic in the following four examinations, and later maintained myopia. The time of each examination was marked as T_1, T_2, T_3, T_4, and T_5 corresponding to the successive examinations for all participants/persistent emmetropia group/persistent myopia group. We then calculated the differences between the results of each examination and those at T_1. For the newly developed myopia group, the time of first discovery of myopia was marked as t_0. The previous time points were marked as $t_{-1}, t_{-2}, \ldots$, and the following time points as $t_1, t_2 \ldots$. The difference between the results of each examination and those of t_0 was calculated.

Data are presented as median (interquartile range). The correlation between the change in height and the change in AL was analyzed using simple correlation analysis. The bootstrap

TABLE 1 | Summary of baseline participants' demographic characteristics.

	Children included in analysis				Children not included in analysis	
	All (n = 414)	**Boys (n = 237)**	**Girls (n = 177)**	***P****	**All (n = 42)**	***P*†**
Age	7.00 (6.00 to 9.00)	7.00 (6.00 to 9.00)	7.00 (6.00 to 9.00)	0.523	7.00 (6.00 to 9.00)	0.297
H (cm)	125.00 (108.00 to 151.00)	126.00 (109.00 to 151.00)	125.00 (108.00 to 145.00)	**0.031**	128.00 (112.00 to 143.00)	0.201
AL (mm)	23.00 (20.28 to 25.17)	23.06 (20.65 to 25.17)	22.63 (20.28 to 24.92)	**<0.001**	23.00 (21.20 to 24.48)	0.382
SE (D)	0.00 (-4.13 to 9.50)	0.00 (-4.13 to 9.50)	0.00 (−3.75 to 6.25)	0.541	0.00 (−2.75 to 5.50)	**0.001**

H, height; AL, axial length; SE, spherical equivalent.
**Comparison between boys and girls.*
†Comparison between children included in analysis and those not included in analysis. Bold font indicates to point the P values <0.05.

TABLE 2 | Age distribution of the participants in the first examination.

Group	Age (years)				Total
	6	**7**	**8**	**9**	
PE	41	44	19	6	110
PM	3	13	18	16	50
NDM	72	86	49	19	226
PH	4	4	4	0	12
Other	5	7	4	0	16
All	125	154	94	41	414

PE, persistent emmetropia; PM, persistent myopia; NDM, newly developed myopia; PH, persistent hyperopia; Other, children who developed hypertropia into emmetropia but did not further develop into myopia during the research.

method was used to calculate the 95% confidence interval (95% CI) of the correlation coefficient (r-value). Age and sex were added as covariates in partial correlation analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Descriptive Data

In total, 456 children (260 boys and 196 girls) participated in this study at baseline. Forty-two children were lost to follow-up in the following four examinations and were excluded from the analysis. The remaining 414 children (57.2% boys, 42.8% girls) completed the 5-year examination cycle, including 110 in the persistent emmetropia group, 50 in the persistent myopia group, and 226 in the newly developed myopia group. Twenty-eight children had hyperopia or developed from hyperopia to emmetropia but did not develop myopia. These children were taken into account when considering the correlation in all children but not analyzed separately as a specific sub-group. There was no significant difference between participants who dropped out and the remaining participants in terms of age at baseline ($P = 0.297$), height at baseline ($P = 0.201$), AL at baseline ($P = 0.382$), or sex ($P = 0.757$). Demographic characteristics of the participants at baseline are summarized in **Table 1**, while the age distribution at the first examination is presented in **Table 2**. Height, AL, and refraction at each examination are presented in **Tables 3**, **4**.

During the five-year follow-up, on average, the children grew by 23.60 ± 4.65 cm in height, their AL increased by 1.39 ± 0.53 mm, and their SE change was −1.69 ± 1.29 D. The prevalence of myopia in each examination (from T_1 to T_5) was 12.1, 20.0, 32.9, 48.8, and 66.7%, respectively.

Correlation of Height With Axial Length and Refraction

In each examination of all children, height and AL were positively and significantly correlated. The correlation was still statistically significant after adjusting for age and sex (**Table 3**). Conversely, height and refraction were negatively correlated before and after controlling for age and sex (**Table 4**).

In the persistent emmetropia group, height and AL were positively correlated in each examination. The correlation was statistically significant with or without adjusting for sex and age (**Table 3**; **Figure 1**).

In the persistent myopia group, the correlation between height and AL only existed at T_1, and was no longer present after correcting for age and sex (**Table 3**).

In the newly developed myopia group, height and AL were positively correlated at t_{-2}, t_{-1}, and t_0 only before adjusting for confounding factors. From t_1 to t_3, height and AL were positively correlated both before and after controlling for sex and age (**Table 3**; **Figure 2**).

Correlation Between Changes in Height and Changes in Axial Length

Correlations between the changes in height and AL were statistically significant for $T_1 \sim T_2$, $T_1 \sim T_3$, $T_1 \sim T_4$, and $T_1 \sim T_5$ ($r = 0.262$, $P < 0.001$; $r = 0.108$, $P = 0.034$; $r = 0.165$, $P = 0.001$; $r = 0.174$, $P = 0.001$, respectively). Furthermore, the correlations were still statistically significant for $T_1 \sim T_2$, $T_1 \sim T_4$, and $T_1 \sim T_5$ after adjusting for age and sex ($r = 0.187$, $P < 0.001$; $r = 0.154$, $P = 0.003$; $r = 0.154$, $P = 0.002$; **Table 5**; **Figure 3**).

Significant correlations were found in the newly developed myopia group after the onset of myopia. Changes in height and AL were positively correlated both before and after correcting for age and sex for $t_0 \sim t_2$ ($r = 0.289$, $P = 0.009$; $r = 0.317$, $P = 0.004$), while no significant correlations were found before myopia onset (**Table 5**; **Figure 4**).

No significant correlation was observed between changes in AL and changes in height in the persistent emmetropia group.

TABLE 3 | Correlation between height and AL in different groups.

Time	*n*	*H* (cm)	AL (mm)	*R* (95% CI)	*P*	Adj. R*(95% CI)	*P*
All							
T_1	387	126.00 (108.00 to 151.00)	23.00 (20.28 to 25.17)	0.282 (0.180 to 0.373)	**<0.001**	0.162 (0.063 to 0.251)	**0.001**
T_2	363	130.00 (110.00 to 159.00)	23.15 (20.53 to 25.45)	0.325 (0.224 to 0.426)	**<0.001**	0.176 (0.072 to 0.271)	**0.001**
T_3	409	135.00 (120.00 to 168.00)	23.49 (20.87 to 25.99)	0.297 (0.202 to 0.383)	**<0.001**	0.172 (0.082 to 0.262)	**<0.001**
T_4	405	140.50 (120.00 to 175.00)	23.85 (20.95 to 26.39)	0.297 (0.206 to 0.382)	**<0.001**	0.211 (0.112 to 0.308)	**<0.001**
T_5	414	150.00 (120.00 to 180.00)	24.20 (21.04 to 26.62)	0.287 (0.189 to 0.378)	**<0.001**	0.245 (0.155 to 0.336)	**<0.001**
PE							
T_1	92	125.00 (108.00 to 150.00)	22.81 (21.42 to 24.51)	0.318 (0.125 to 0.499)	**0.002**	0.290 (0.070 to 0.479)	**0.006**
T_2	89	128.00 (117.00 to 153.00)	22.79 (21.00 to 24.23)	0.418 (0.225 to 0.575)	**<0.001**	0.381 (0.187 to 0.547)	**<0.001**
T_3	109	133.00 (120.00 to 162.00)	23.11 (21.45 to 24.53)	0.293 (0.106 to 0.458)	**0.002**	0.265 (0.078 to 0.446)	**0.006**
T_4	106	138.00 (120.00 to 168.00)	23.37 (21.81 to 24.76)	0.280 (0.082 to 0.458)	**0.004**	0.269 (0.088 to 0.448)	**0.006**
T_5	110	145.00 (120.00 to 178.00)	23.55 (22.01 to 25.16)	0.288 (0.100 to 0.447)	**0.002**	0.350 (0.163 to 0.504)	**<0.001**
PM							
T_1	49	130.00 (120.00 to 151.00)	23.63 (21.96 to 25.17)	0.311 (0.055 to 0.569)	**0.029**	0.102 (−0.205 to 0.358)	0.495
T_2	47	134.00 (124.50 to 159.00)	24.17 (22.27 to 25.45)	0.185 (−0.113 to 0.454)	0.213	0.095 (−0.214 to 0.371)	0.534
T_3	50	139.50 (127.50 to 168.00)	24.63 (22.44 to 25.99)	0.218 (−0.046 to 0.473)	0.129	0.170 (−0.139 to 0.427)	0.248
T_4	49	145.00 (131.00 to 175.00)	24.89 (22.56 to 26.39)	0.183 (−0.118 to 0.427)	0.208	0.132 (−0.133 to 0.374)	0.376
T_5	50	154.00 (138.00 to 180.00)	25.24 (22.70 to 26.62)	0.382 (−0.156 to 0.402)	0.126	0.170 (−0.106 to 0.447)	0.247
NDM							
t_{-4}	73	125.00 (111.00 to 140.00)	22.86 (20.98 to 24.35)	0.104 (−0.132 to 0.355)	0.383	−0.043 (−0.293 to 0.197)	0.720
t_{-3}	132	128.00 (110.00 to 147.00)	23.00 (21.01 to 24.64)	0.162 (−0.040 to 0.341)	0.064	0.015 (−0.159 to 0.178)	0.861
t_{-2}	178	130.00 (109.00 to 152.00)	23.19 (21.15 to 24.96)	0.205 (0.042 to 0.355)	**0.006**	0.019 (−0.137 to 0.168)	0.802
t_{-1}	215	135.00 (110.00 to 160.00)	23.46 (21.41 to 25.36)	0.230 (0.092 to 0.373)	**0.001**	0.034 (−0.102 to 0.172)	0.622
t_0	221	142.00 (120.00 to 171.00)	24.02 (21.67 to 25.88)	0.199 (0.048 to 0.342)	**0.003**	0.105 (−0.036 to 0.227)	0.123
t_1	150	144.00 (122.50 to 168.00)	24.42 (21.93 to 26.37)	0.214 (0.044 to 0.378)	**0.008**	0.223 (0.064 to 0.379)	**0.006**
t_2	86	148.00 (125.00 to 170.00)	24.82 (22.38 to 26.41)	0.343 (0.155 to 0.505)	**0.001**	0.327 (0.134 to 0.507)	**0.002**
t_3	33	151.00 (139.00 to 166.00)	24.95 (22.80 to 26.56)	0.419 (0.145 to 0.635)	**0.015**	0.468 (0.103 to 0.710)	**0.008**

*AL, axial length; H, height; PE, persistent emmetropia; PM, persistent myopia; NDM, newly developed myopia; *correlation coefficients adjusted for age and sex. Bold font indicates to point the P values <0.05.*

TABLE 4 | Correlation between height and refraction in all participants.

Time	*n*	*H* (cm)	SE (D)	*R* (95% CI)	*P*	Adj. R*(95% CI)	*P*
All							
T_1	413	125.00 (108.00 to 151.00)	0.00 (-4.13 to 9.50)	−0.162 (−0.256 to −0.062)	**0.001**	−0.120 (−0.214 to −0.025)	**0.015**
T_2	399	130.00 (110.00 to 159.00)	0.00 (-5.00 to 9.00)	−0.207 (−0.296 to −0.109)	**<0.001**	−0.108 (−0.207 to 0.003)	**0.031**
T_3	409	135.00 (120.00 to 168.00)	0.00 (-6.13 to 8.25)	−0.206 (−0.303 to −0.102)	**<0.001**	−0.098 (−0.190 to 0.001)	**0.048**
T_4	406	140.75 (120.00 to 175.00)	−0.38 (-7.25 to 7.63)	−0.155 (−0.259 to −0.056)	**<0.001**	−0.274 (−0.363 to −0.187)	**0.002**
T_5	414	150.00 (120.00 to 180.00)	−1.25 (-7.88 to 6.88)	−0.236 (−0.327 to −0.141)	**<0.001**	−0.144 (−0.251 to −0.040)	**0.003**

*H, height; SE, spherical equivalent; *correlation coefficients adjusted for age and sex. Bold font indicates to point the P values <0.05.*

Similarly, no significant associations were found in the persistent myopia group, except for $T_1 \sim T_2$ ($r = 0.388$, $P = 0.008$) before adjusting for the confounding factors (**Table 5**).

Correlation Between Changes in Height and Refraction

Table 6 shows the correlation between the changes in height and refraction. Changes in height and SE were negatively correlated for $T_1 \sim T_3$, $T_1 \sim T_4$, and $T_1 \sim T_5$ ($r = -0.097$, $P = 0.049$; $r = -0.186$, $P < 0.001$; $r = -0.167$, $P = 0.001$). The pattern of correlation in the sub-groups was similar to that of changes in AL and height, but with negative correlation coefficients.

DISCUSSION

This cohort study was conducted in Jinhua, a city located in eastern China, where the incidence of myopia is relatively high (28). In total, 414 children aged 6–9 participated in the study and completed a five-year series of follow-up examinations from 2015 to 2020, in which every child was examined every 12 months.

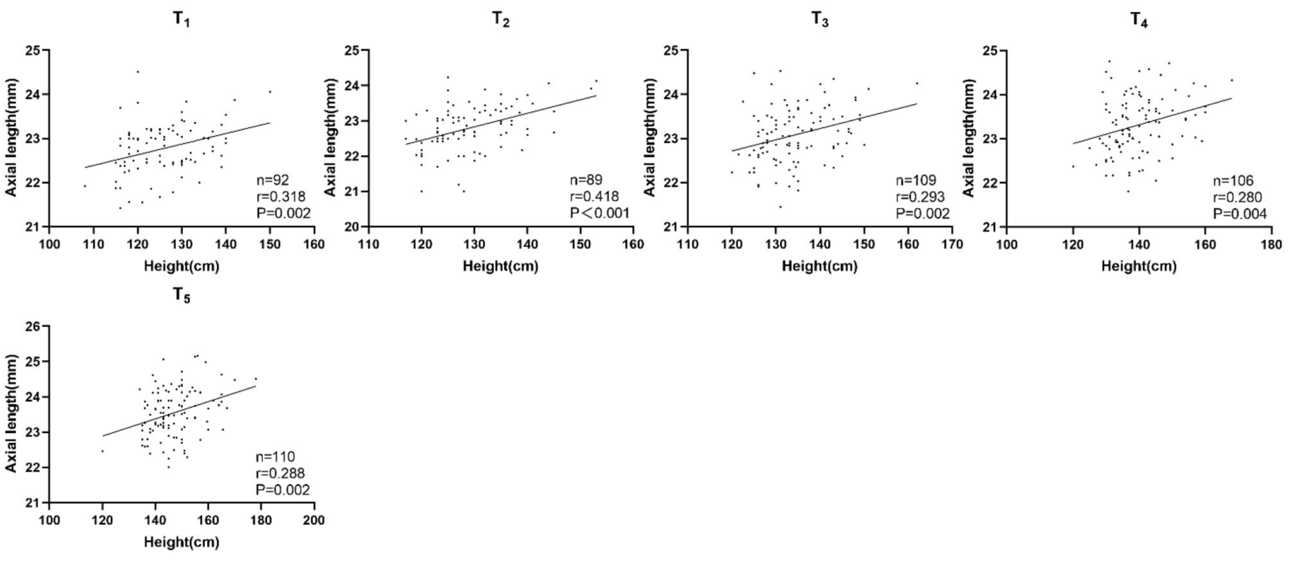

FIGURE 1 | Correlation between height and axial length in the persistent emmetropia group.

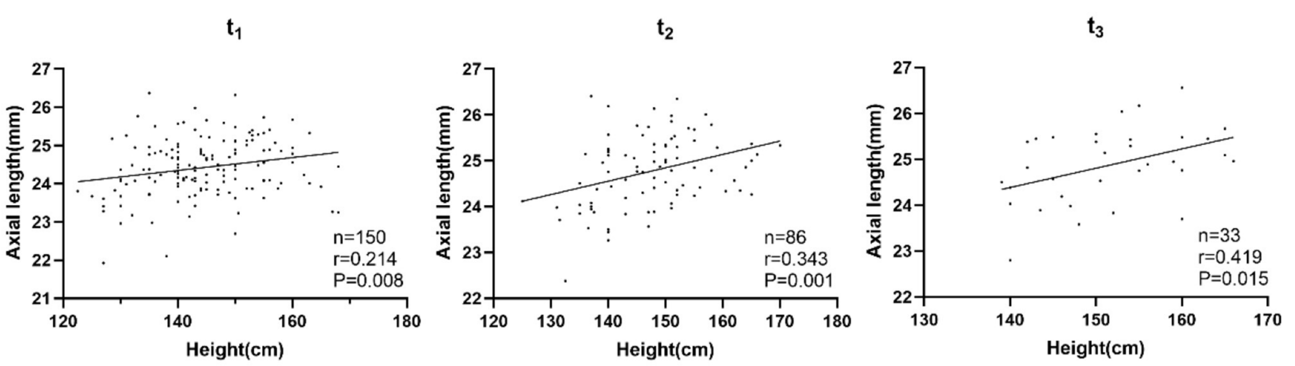

FIGURE 2 | Correlation between height and axial length in the newly developed myopia group.

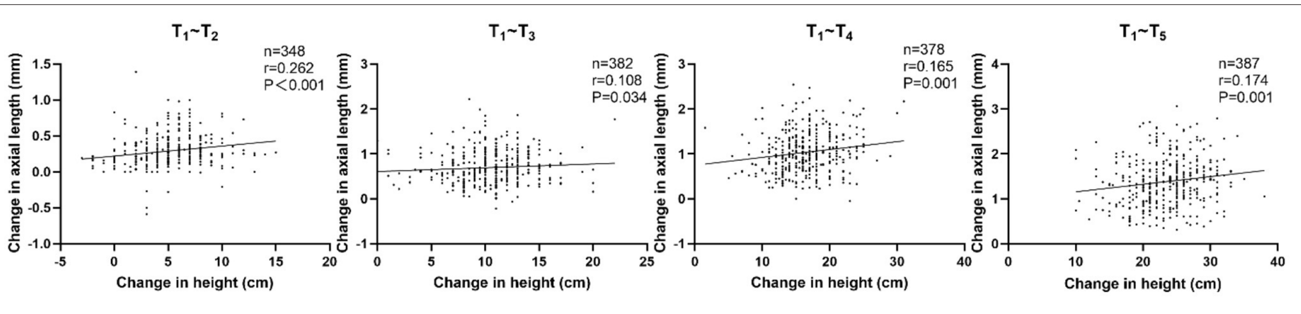

FIGURE 3 | Correlation between changes in height and changes in axial length in all participants.

A correlation was found between the growth in height and the increase in AL in children and adolescents, especially in the newly developed myopia group. Our results suggest that children may also experience increased AL growth when they present with rapid height growth.

We assessed the relationship between the changes in height and the increase in AL and found that they were positively correlated in children aged 6–9. This is essentially consistent with the results of Huang et al.'s study (19), which included 65 children aged 7–9 years old followed up every 6 months in a three-year period. They concluded that growth in height and AL during the research period were correlated. Compared with their study, the present one included more participants and had longer follow-up. Furthermore, we proved that the correlation existed not only in the whole period (T_1~T_5), but also at every follow-up time point (T_1~T_2, T_1~T_3, T_1~T_4, T_1~T_5).

However, the study by Li et al. did not find that the changes in height and AL were correlated (21). In their study, a total of 452 children aged 6–8 years accepted measurements every year during the 3-year follow-up period. They analyzed the relationship between the mean change in AL and the mean change in height through multivariate linear regression analysis, finding that they were not correlated at any point in the 3-year follow-up period (2015–2014, 2016–2014, or 2017–2014). This may be related to the lack of representativeness of the sample, composed of students of grades 1 and 2 from a single school. It may also be related with the shorter follow-up time (3 years) and the fact that refractive status was not considered. Kearney et al. (20) concluded that changes in height and AL were correlated in the persistent emmetropia group ($n = 55$), but not in the newly developed myopia group, in 105 subjects aged 5–20 years, with examination conducted every 2 years for 4 years. The disagreement between the results of the study by Kearney et al. and ours may result from the difference in the age of the participants and the follow-up time intervals.

We also found a positive correlation between changes in height and AL after myopia onset in the newly developed myopia group. That might be due to the fact that children have a peak incidence of myopia at the age of growth spurt at least in Chinese. A previous study reported that the onset of myopia and the peak of its progression may be associated with growth spurts (16). Moreover, AL elongation and growth in height may be partially mediated by the same genes (18). The changes in height are the result of both genetic and environmental factors (29, 30),

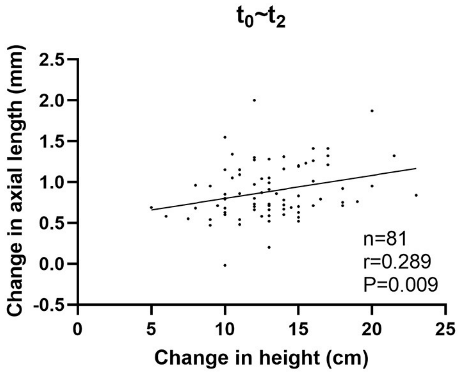

FIGURE 4 | Correlation between changes in height and changes in axial length in the newly developed myopia group after the onset of myopia.

TABLE 5 | Correlation between changes in height and changes in AL in different groups.

Time	*n*	Δ*H* (cm)	ΔAL (mm)	*R* (95% CI)	*P*	Adj. R*(95% CI)	*P*
All							
T_1~T_2	348	5.00 (−3.00 to 15.00)	0.25(−0.59 to 1.39)	0.262 (0.163 to 0.358)	**<0.001**	0.187 (0.086 to 0.288)	**<0.001**
T_1~T_3	382	10.00 (0.00 to 22.00)	0.62(−0.22 to 2.22)	0.108 (0.013 to 0.202)	**0.034**	0.068 (−0.035 to 0.170)	0.186
T_1~T_4	378	16.00(1.50 to 31.00)	1.00 (−0.05 to 2.54)	0.165 (0.065 to 0.263)	**0.001**	0.154 (0.047 to 0.258)	**0.003**
T_1-~T_5	387	24.00 (10.00 to 38.00)	1.37 (0.31 to 3.06)	0.174 (0.079 to 0.269)	**0.001**	0.154 (0.057 to 0.248)	**0.002**
PE							
T_1~T_2	79	4.00 (−2.00 to 13.00)	0.17 (−0.28 to 1.39)	0.198 (−0.220 to 0.407)	0.08	0.058 (−0.110 to 0.314)	0.615
T_1~T_3	91	9.50 (1.00 to 17.00)	0.41 (0.02 to 1.73)	−0.075 (−0.288 to 0.128)	0.477	−0.033 (−0.210 to 0.133)	0.757
T_1~T_4	88	14.50 (5.00 to 23.00)	0.64 (−0.05 to 2.08)	0.035 (−0.184 to 0.252)	0.748	−0.024 (−0.214 to 0.199)	0.827
T_1~T_5	92	22.50 (10.00 to 32.00)	0.88 (0.31 to 2.65)	0.120 (−0.103 to 0.334)	0.254	0.151 (−0.035 to 0.335)	0.156
PM							
T_1~T_2	46	5.00 (−1.00 to 10.00)	0.43 (0.00 to 0.82)	0.389 (0.094 to 0.623)	**0.008**	0.294 (−0.018 to 0.565)	0.053
T_1~T_3	49	11.00 (1.00 to 22.00)	0.85 (0.17 to 1.85)	0.234 (−0.092 to 0.520)	0.105	0.259 (−0.042 to 0.524)	0.079
T_1~T_4	48	18.00 (10.00 to 31.00)	1.17 (0.29 to 2.47)	0.113 (−0.232 to 0.444)	0.443	0.183 (−0.152 to 0.462)	0.223
T_1~T_5	49	25.00 (10.00 to 34.00)	1.56 (0.38 to 3.06)	−0.074 (−0.326 to 0.196)	0.612	0.036 (−0.243 to 0.317)	0.809
NDM							
t_{-4}~t_0	73	25.00 (15.00 to 32.00)	1.33 (0.42 to 2.61)	0.116 (−0.134 to 0.374)	0.328	0.054 (−0.199 to 0.363)	0.654
t_{-3}~t_0	132	17.50 (6.50 to 31.00)	1.14 (0.00 to 2.61)	−0.095 (−0.274 to 0.073)	0.277	−0.120 (−0.332 to 0.105)	0.173
t_{-2}~t_0	177	12.00 (1.00 to 24.00)	0.90 (0.00 to 1.99)	−0.038 (−0.182 to 0.107)	0.620	0.115 (−0.035 to 0.259)	0.130
t_{-1}~t_0	211	6.00 (−2.00 to 16.00)	0.50 (−1.58 to 1.47)	0.018 (−0.127 to 0.159)	0.795	0.037 (−0.073 to 0.167)	0.596
t_0~t_1	145	6.00 (−1.00 to 14.00)	0.43 (−0.35 to 2.41)	0.031 (−0.118 to 0.192)	0.712	0.054 (−0.060 to 0.186)	0.524
t_0~t_2	81	13.00 (5.00 to 23.00)	0.80 (−0.02 to 2.00)	0.289 (0.084 to 0.480)	**0.009**	0.317 (0.126 to 0.507)	**0.004**
t_0~t_3	29	19.00 (8.50 to 26.00)	1.13 (0.50 to 2.29)	0.362 (−0.056 to 0.642)	0.054	0.278 (−0.122 to 0.610)	0.161

*AL, axial length; H, height; PE, persistent emmetropia; PM, persistent myopia; NDM, newly developed myopia; *correlation coefficients adjusted for age and sex. Bold font indicates to point the P values <0.05.*

TABLE 6 | Correlation between changes in height and changes in refraction in different groups.

Time	*n*	Δ*H* (cm)	ΔSE (D)	*R* (95% CI)	*P*	Adj. R*(95% CI)	*P*
All							
$T_1 \sim T_2$	398	5.00 (−3.00 to 15.00)	−0.25 (−2.25 to 2.50)	−0.057 (−0.161 to 0.041)	0.26	−0.092 (−0.182 to 0.004)	0.067
$T_1 \sim T_3$	408	10.00 (0.00 to 22.00)	−0.50 (−3.50 to 2.00)	−0.097 (−0.188 to 0.000)	**0.049**	−0.082 (−0.173 to 0.020)	0.100
$T_1 \sim T_4$	405	16.00 (1.50 to 31.00)	−0.90 (-5.30 to 1.80)	−0.186 (−0.285 to −0.086)	**<0.001**	−0.154 (−0.258 to −0.057)	**0.002**
$T_1 \sim T_5$	413	24.00 (10.00 to 38.00)	−1.50 (-6.00 to 1.75)	−0.167 (−0.262 to −0.072)	**0.001**	−0.131 (−0.221 to −0.037)	**0.008**
PE							
$T_1 \sim T_2$	104	4.00 (−2.00 to 13.00)	0 (−0.75 to 0.75)	−0.021 (−0.211 to 0.164)	0.832	−0.037 (−0.229 to 0.146)	0.709
$T_1 \sim T_3$	110	9.00 (1.00 to 17.00)	0 (−0.75 to 0.75)	0.056 (−0.126 to 0.238)	0.563	0.052 (−0.114 to 0.231)	0.592
$T_1 \sim T_4$	106	15.00 (5.00 to 23.00)	0 (−0.88 to 0.75)	0.008 (−0.184 to 0.185)	0.936	−0.009 (−0.198 to 0.182)	0.925
$T_1 \sim T_5$	110	22.00(10.00 to 32.00)	−0.25 (−1.00 to 0.75)	−0.039 (−0.228 to 0.146)	0.683	−0.041 (−0.209 to 0.147)	0.676
PM							
$T_1 \sim T_2$	47	5.00 (−1.00 to 10.00)	−0.75 (−2.00 to 0.63)	−0.264 (−0.558 to 0.018)	0.073	−0.199 (−0.484 to 0.108)	0.191
$T_1 \sim T_3$	48	11.00 (1.00 to 22.00)	−1.75 (−3.50 to 0.13)	−0.196 (−0.459 to 0.094)	0.181	−0.150 (−0.401 to 0.105)	0.321
$T_1 \sim T_4$	48	18.00 (10.00 to 31.00)	−2.30 (-5.30 to 0.10)	−0.141 (−0.460 to 0.169)	0.338	−0.127 (−0.412 to 0.181)	0.401
$T_1 \sim T_5$	49	25.00 (10.00 to 34.00)	−3.00 (-6.00 to −0.13)	0.057 (−0.225 to 0.293)	0.695	0.036 (−0.266 to 0.331)	0.809
NDM							
$t_{-4} \sim t_0$	74	24.75 (15.00 to 32.00)	−1.25 (−3.63 to −0.25)	0.051 (−0.205 to 0.283)	0.666	0.014 (−0.174 to 0.237)	0.905
$t_{-3} \sim t_0$	138	18.00 (6.50 to 31.00)	−1.25 (−2.75 to −0.25)	0.019 (−0.149 to 0.186)	0.824	0.050 (−0.130 to 0.213)	0.564
$t_{-2} \sim t_0$	188	12.00 (1.00 to 24.00)	−1.00 (−2.75 to −0.25)	0.137 (−0.007 to 0.276)	0.061	0.073 (−0.075 to 0.213)	0.321
$t_{-1} \sim t_0$	221	6.00 (−2.00 to 16.00)	−0.75 (−2.38 to −0.13)	0.001 (−0.137 to 0.130)	0.991	−0.003 (−0.142 to 0.138)	0.969
$t_0 \sim t_1$	148	6.00 (−1.00 to 14.00)	−0.75 (−2.25 to 0.75)	−0.016 (−0.177 to 0.151)	0.850	−0.063 (−0.205 to 0.067)	0.451
$t_0 \sim t_2$	84	13.00 (5.00 to 23.00)	−1.50 (−3.25 to 0.75)	−0.221 (−0.391 to −0.037)	**0.044**	−0.219 (−0.391 to −0.055)	**0.048**
$t_0 \sim t_3$	32	19.00 (8.50 to 28.00)	−1.94 (-4.00 to 0.75)	−0.356 (−0.590 to −0.044)	**0.046**	−0.291 (−0.544 to 0.011)	0.119

*SE, spherical equivalent; H, height; PE, persistent emmetropia; PM, persistent myopia; NDM, newly developed myopia; *correlation coefficients adjusted for age and sex. Bold font indicates to point the P values <0.05.*

and the same applies to AL (31, 32). The experiment by He proved that the correlation between AL and height is largely (89%) attributable to shared genes (18). In addition to genes, hormones play an important role: many hormones involved in height growth, such as GH, IGF-1, and TH, have also been shown to accelerate the growth of eyes (33–36). Although there may be shared genes and hormones related to both growths, height is more susceptible to nutritional environmental factors and gastrointestinal infection, while AL growth is more susceptible of being modified by illumination and visual cues.

In the present study, we also explored the relationship between height and AL for different refractive status. Selovic et al. found that height and AL were positively correlated in persistent emmetropes by analyzing the data of 1,600 pupils (37). However, they neither investigated the correlation in newly developed or persistent myopes, nor conducted a follow-up study. Our further exploration also revealed that height and AL were positively correlated in every examination in the persistent emmetropia group as well as in the newly developed myopia group after the onset of myopia. However, the association did not exist in any examination in the newly developed myopia group before the onset of myopia or in the persistent myopia group. Whether the onset of myopia plays a role in the relationship between height and AL in children and adolescents, further researches are required.

Similar results were obtained for the correlation between height and refraction, because refraction is largely determined by the AL (38, 39). Though AL plays an important role in refraction, a longer AL doesn't necessarily mean more myopic. Emmetropia is a balance between AL, corneal power and lens power (40). That means longer eyes can be compensated by less lens power or flatter corneas to keep emmetropic (41–45). So future studies should take lens power and corneal radius of curvature into consideration to account for their possible compensation of greater axial growth.

The current research has proved that changes in height and AL are positively correlated in the transition from childhood to adolescence. Myopia gradually becomes prevalent from the age of 6–9 years old (6, 46–49), when height also grows relatively fast (50). Yip et al. (16) argued that children who experienced peak height velocity earlier may also become myopic earlier. Our study further found that when children grow fast in height, their AL may also elongate quickly, just at the time they may be more likely to become myopic in this environment. Thus, observing the growth rate of children can serve as an indicator to monitor the growth velocity of their AL. When a child is in a stage of rapid height growth, we may need to be aware that his/her AL is also in a period of easy elongation. The elongation of the AL is closely related to the occurrence and development of myopia. As to whether the strengthening of myopia prevention and control measures can slow the growth of AL in the period of rapid height growth, further research is warranted.

Based on prior studies, we further proved the correlation between changes in height and changes in AL. However, there are some limitations to our study. First, we did not produce genetic data or measure hormone levels. Therefore, we cannot directly prove whether the correlation between height and AL is mediated by genes or hormones. Second, we did not use a questionnaire to acquire information that may be associated with the onset of myopia, such as reading and writing distance, and time spent outdoors. Such information will help us better understand the development of myopia in our participants. Third, some of the subjects in our study may have grown into adolescence later in the follow-up period. Adolescents are likely to grow faster than children (51). However, we didn't have the exact puberty parameters such as age of maximum height velocity, age of menarche and voice changes. Although, in agreement with Yip et al. (16), we could observe a correlation between the time of rapid growth of AL and height, to adjust for antecedents of the pubertal peak, detailed information of puberty and a longer follow up time would be required. Finally, the follow up time is still too short to include the whole period of accelerated growth. We chose children aged 6–9 years old and followed up for 5 years which covers the time of rapid change of refraction based on our previous study (52). However, some subjects may be outside the peak of accelerated growth. A longer follow up period would be necessary to clarify the relationship between the peak of accelerated growth and the progression of myopia, and changes in AL and height after the onset of myopia in future studies.

Ulaganathan et al. (53) previously described that the mean amplitude of daily variations in AL is 0.029 ± 0.007 mm, thus, minor variations could be neglected when considering yearly AL changes. So, the AL was not measured at the same time each day in this study. The non-cycloplegic refraction may render an overestimation of myopia. However, it may have less effect in a longitudinal study such as our own, which monitored the progression of refraction in the same population (6).

In summary, we suggest that during the growth of school-age children, a significant correlation exists not only between AL and height, but also between AL growth and height growth, especially in children with newly developed myopia. This indicates that during the period of rapid height growth, the elongation of AL also needs to be considered. Whether the strengthening of outdoor activities or other myopia control measures can delay the elongation of AL during the rapid height growth period may be an urgent question that needs to be answered.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Jinhua Eye Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LT: research design and collect data. CW, YP, MX, and MW: technical assistance and guidance. XY: research and academic guidance. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Morgan IG, Ohno-Matsui K, Saw S-M. Myopia. *Lancet.* (2012) 379:1739–48. doi: 10.1016/S0140-6736(12)60272-4
2. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006
3. Morgan IG, French AN, Ashby RS, Guo X, Ding X, He M, et al. The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res.* (2018) 62:134–49. doi: 10.1016/j.preteyeres.2017.09.004
4. Xiang ZY, Zou HD. Recent epidemiology study data of myopia. *J Ophthalmol.* (2020) 2020:4395278. doi: 10.1155/2020/4395278
5. Ding B-Y, Shih Y-F, Lin LLK, Hsiao CK, Wang IJ. Myopia among schoolchildren in East Asia and Singapore. *Surv Ophthalmol.* (2017) 62:677–97. doi: 10.1016/j.survophthal.2017.03.006
6. Wang J, Li Y, Zhao Z, Wei N, Qi X, Ding G, et al. School-based epidemiology study of myopia in Tianjin, China. *Int Ophthalmol.* (2020) 40:2213–22. doi: 10.1007/978-981-13-7896-6
7. Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, et al. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol.* (2005) 123:977–87. doi: 10.1001/archopht.123.7.977
8. Jones LA, Mitchell GL, Mutti DO, Hayes JR, Moeschberger ML, Zadnik K. Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci.* (2005) 46:2317–27. doi: 10.1167/iovs.04-0945
9. Hou W, Norton TT, Hyman L, Gwiazda J, Group C. Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation trial. *Eye Contact Lens.* (2018) 44:248–59. doi: 10.1097/ICL.0000000000000505
10. Tideman JWL, Polling JR, Vingerling JR, Jaddoe VWV, Williams C, Guggenheim JA, et al. Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmol.* (2018) 96:301–9. doi: 10.1111/aos.13603
11. Saw S-M, Chua W-H, Hong C-Y, Wu H-M, Chia K-S, Stone RA, et al. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* (2002) 43:1408–13.

12. Ojaimi E, Morgan IG, Robaei D, Rose KA, Smith W, Rochtchina E, et al. Effect of stature and other anthropometric parameters on eye size and refraction in a population-based study of Australian children. *Invest Ophthalmol Vis Sci.* (2005) 46:4424–9. doi: 10.1167/iovs.05-0077
13. Ye S, Liu S, Li W, Wang Q, Xi W, Zhang X. Associations between anthropometric indicators and both refraction and ocular biometrics in a cross-sectional study of Chinese schoolchildren. *BMJ Open.* (2019) 9:e027212. doi: 10.1136/bmjopen-2018-027212
14. Goss DA, Cox VD, Herrin-Lawson GA, Nielsen ED, Dolton WA. Refractive error, axial length, and height as a function of age in young myopes. *Optom Vis Sci.* (1990) 67:332–8. doi: 10.1097/00006324-199005000-00006
15. Wang D, Ding X, Liu B, Zhang J, He M. Longitudinal changes of axial length and height are associated and concomitant in children. *Invest Ophthalmol Vis Sci.* (2011) 52:7949–53. doi: 10.1167/iovs.11-7684
16. Yip VC, Pan CW, Lin XY, Lee YS, Gazzard G, Wong TY, et al. The relationship between growth spurts and myopia in Singapore children. *Invest Ophthalmol Vis Sci.* (2012) 53:7961–6. doi: 10.1167/iovs.12-10402
17. Northstone K, Guggenheim JA, Howe LD, Tilling K, Paternoster L, Kemp JP, et al. Body stature growth trajectories during childhood and the development of myopia. *Ophthalmology*. (2013) 120:1064–73 e1. doi: 10.1016/j.ophtha.2012.11.004
18. Zhang J, Hur Y-M, Huang W, Ding X, Feng K, He M. Shared genetic determinants of axial length and height in children: the Guangzhou twin eye study. *Arch Ophthalmol.* (2011) 129:63–8. doi: 10.1001/archophthalmol.2010.323
19. Huang CY, Hou CH, Lin KK, Lee JS, Yang ML. Relationship of lifestyle and body stature growth with the development of myopia and axial length elongation in Taiwanese elementary school children. *Indian J Ophthalmol.* (2014) 62:865–9. doi: 10.4103/0301-4738.141047
20. Kearney S, Strang NC, Cagnolati B, Gray LS. Change in body height, axial length and refractive status over a four-year period in caucasian children and young adults. *J Optom.* (2020) 13:128–36. doi: 10.1016/j.optom.2019.12.008
21. Li T, Jiang B, Zhou X. Axial length elongation in primary school-age children: a 3-year cohort study in Shanghai. *BMJ Open.* (2019) 9:e029896. doi: 10.1136/bmjopen-2019-029896
22. Mutti DO, Hayes JR, Mitchell GL, Jones LA, Moeschberger ML, Cotter SA, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci.* (2007) 48:2510–9. doi: 10.1167/iovs.06-0562
23. Xiang F, He M, Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. *Ophthalmology.* (2012) 119:1478–84. doi: 10.1016/j.ophtha.2012.01.017
24. Rozema J, Dankert S, Iribarren R, Lanca C, Saw SM. Axial growth and lens power loss at myopia onset in singaporean children. *Invest Ophthalmol Vis Sci.* (2019) 60:3091–9. doi: 10.1167/iovs.18-26247
25. Louer AL, Simon DN, Switkowski KM, Rifas-Shiman SL, Gillman MW, Oken E. Assessment of Child Anthropometry in a Large Epidemiologic Study. *J Vis Exp*. (2017) 120:e54895. doi: 10.3791/54895
26. Wong YL, Yuan Y, Su B, Tufail S, Ding Y, Ye Y, et al. Prediction of myopia onset with refractive error measured using non-cycloplegic subjective refraction: the WEPrOM Study. *BMJ Open Ophthalmol.* (2021) 6:e000628. doi: 10.1136/bmjophth-2020-000628
27. Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, et al. IMI—Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci.* (2019) 60:M20–30. doi: 10.1167/iovs.18-25957
28. Wu GY, Huang TQ, Hospital JE. Correlation analysis of the development of children's myopia and the length of axial length in Jinhua. *Chin J Strabismus Pediatric Ophthalmol.* (2017).
29. Andrade AC, Jee YH. Nilsson O, New genetic diagnoses of short stature provide insights into local regulation of childhood growth. *Horm Res Paediatr.* (2017) 88:22–37. doi: 10.1159/000455850
30. Baron J, Sävendahl L, De Luca F, Dauber A, Phillip M, Wit JM, et al. Short and tall stature: a new paradigm emerges. *Nat Rev Endocrinol.* (2015) 11:735–46. doi: 10.1038/nrendo.2015.165
31. Pozarickij A, Williams C, Hysi PG, Guggenheim JA, Eye UKB, Vision C. Quantile regression analysis reveals widespread evidence for gene-environment or gene-gene interactions in myopia development. *Commun Biol.* (2019) 2:167. doi: 10.1038/s42003-019-0387-5
32. Harb EN, Wildsoet CF. Origins of refractive errors: environmental and genetic factors. *Annu Rev Vis Sci.* (2019) 5:47–72. doi: 10.1146/annurev-vision-091718-015027
33. Liu YX, Sun Y. MMP-2 participates in the sclera of guinea pig with form-deprivation myopia *via* IGF-1/STAT3 pathway. *Eur Rev Med Pharmacol Sci.* (2018) 22:2541–8.
34. Prashar A, Hocking PM, Erichsen JT, Fan Q, Saw SM, Guggenheim JA. Common determinants of body size and eye size in chickens from an advanced intercross line. *Exp Eye Res.* (2009) 89:42–8. doi: 10.1016/j.exer.2009.02.008
35. Rada JA, Wiechmann AF. Ocular expression of avian thymic hormone: changes during the recovery from induced myopia. *Mol Vis.* (2009) 15:778–92.
36. Seko Y, Tanaka Y, Tokoro T. Influence of bFGF as a potent growth stimulator and TGF-beta as a growth regulator on scleral chondrocytes and scleral fibroblasts in vitro. *Ophthalmic Res.* (1995) 27:144–52. doi: 10.1159/000267651
37. Selovic A, Juresa V, Ivankovic D, Malcic D, Selovic Bobonj G. Relationship between axial length of the emmetropic eye and the age, body height, and body weight of schoolchildren. *Am J Hum Biol.* (2005) 17:173–7. doi: 10.1002/ajhb.20107
38. van AG. On emmetropia and ametropia. *Opt Acta. (Lond).* (1961) 142:1–92. doi: 10.1159/000304181
39. Young TL, Metlapally R, Shay AE. Complex trait genetics of refractive error. *Arch Ophthalmol.* (2007) 125:38–48. doi: 10.1001/archopht.125.1.38
40. Ip JM, Huynh SC, Kifley A, Rose KA, Morgan IG, Varma R, et al. Variation of the contribution from axial length and other oculometric parameters to refraction by age and ethnicity. *Invest Ophthalmol Vis Sci.* (2007) 48:4846–53. doi: 10.1167/iovs.07-0101
41. Iribarren R, Morgan IG, Hashemi H, Khabazkhoob M, Emamian MH, Shariati M, et al. Lens power in a population-based cross-sectional sample of adults aged 40 to 64 years in the Shahroud Eye Study. *Invest Ophthalmol Vis Sci.* (2014) 55:1031–9. doi: 10.1167/iovs.13-13575
42. Iribarren R, Hashemi H, Khabazkhoob M, Morgan IG, Emamian MH, Shariati M, et al. Hyperopia and lens power in an adult population: the Shahroud eye study. *J Ophthalmic Vis Res.* (2015) 10:400–7. doi: 10.4103/2008-322X.158895
43. Iribarren R. Crystalline lens and refractive development. *Prog Retin Eye Res.* (2015) 47:86–106. doi: 10.1016/j.preteyeres.2015.02.002
44. He X, Sankaridurg P, Naduvilath T, Wang J, Xiong S, Weng R, et al. Normative data and percentile curves for axial length and axial length/corneal curvature in Chinese children and adolescents aged 4-18 years. *Br J Ophthalmol.* (2021). doi: 10.1136/bjophthalmol-2021-319431
45. Muralidharan G, Martínez-Enríquez E, Birkenfeld J, Velasco-Ocana M, Pérez-Merino P, Marcos S. Morphological changes of human crystalline lens in myopia. *Biomed Opt Express.* (2019) 10:6084–95. doi: 10.1364/BOE.10.006084
46. Wang SK, Guo Y, Liao C, Chen Y, Su G, Zhang G, et al. Incidence of and factors associated with myopia and high myopia in chinese children, based on refraction without cycloplegia. *JAMA Ophthalmol.* (2018) 136:1017–24. doi: 10.1001/jamaophthalmol.2018.2658
47. Tsai DC, Fang SY, Huang N, Hsu CC, Chen SY, Chiu AW, et al. Myopia development among young schoolchildren: the myopia investigation study in Taipei. *Invest Ophthalmol Vis Sci.* (2016) 57:6852–60. doi: 10.1167/iovs.16-20288
48. Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol.* (2016) 100:882–90. doi: 10.1136/bjophthalmol-2015-307724
49. Dong YH, Liu HB, Wang ZH, Yang ZP, Xu RB, Yang ZG, et al. Prevalence of myopia and increase trend in children and adolescents aged 7-18 years in Han ethnic group in China, 2005-2014. *Zhonghua Liu Xing Bing Xue Za Zhi.* (2017) 38:583–7. doi: 10.3760/cma.j.issn.0254-6450.2017.05.005
50. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child.* (1976) 51:170–9. doi: 10.1136/adc.51.3.170

51. Li H, Ji CY, Zong XN, Zhang YQ. Height and weight standardized growth charts for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi.* (2009) 47:487–92. doi: 10.3760/cma.j.issn.0578-1310.2009.07.003
52. Qin Z, Peng T, Zhang Z, Lou J, Wang C, Deng R, et al. Myopia progression and stabilization in school-aged children with single-vision lenses. *Acta Ophthalmol.* (2021). doi: 10.1111/aos.15038. [Epub ahead of print].
53. Ulaganathan S, Read SA, Collins MJ, Vincent SJ. Daily axial length and choroidal thickness variations in young adults: associations with light exposure and longitudinal axial length and choroid changes. *Exp Eye Res.* (2019) 189:107850. doi: 10.1016/j.exer.2019.107850

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Global Tendency and Frontiers of Research on Myopia From 1900 to 2020: A Bibliometrics Analysis

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Background: Myopia is one of the most common causes of vision impairment in children and adults and has become a public health priority with its growing prevalence worldwide. This study aims to identify and evaluate the global trends in myopia research of the past century and visualize the frontiers using bibliometric analysis.

Methods: The literature search was conducted on the Web of Science for myopia studies published between 1900 and 2020. Retrieved publications were analyzed in-depth by the annual publication number, prolific countries and institutions, core author and journal, and the number of citations through descriptive statistics. Collaboration networks and keywords burst were visualized by VOSviewer and CiteSpace. Myopia citation network was visualized using CitNetExplorer.

Results: In total, 11,172 publications on myopia were retrieved from 1900 to 2020, with most published by the United States. Saw SM, from the National University of Singapore, contributed the most publications and citations. *Investigative Ophthalmology & Visual Science* was the journal with highest number of citations. *Journal of Cataract and Refractive Surgery* with the maximum number of publications. The top 10 cited papers mainly focused on the epidemiology of myopia. Previous research emphasized myopia-associated experimental animal models, while recent keywords include "SMILE" and "myopia control" with the stronger burst, indicating a shift of concern from etiology to therapy and coincided with the global increment of incidence. Document citation network was clustered into six groups: "prevalence and risk factors of myopia," "surgical control of myopia," "pathogenesis of myopia," "optical interventions of myopia," "myopia and glaucoma," and "pathological myopia."

Conclusions: Bibliometrics analysis in this study could help scholars comprehend global trends of myopia research frontiers better. Hundred years of myopia research were clustered into six groups, among which "prevalence and risk factors of myopia" and "surgical control of myopia" were the largest groups. With the increasing prevalence of myopia, interventions of myopia control are a potential research hotspot and pressing public health issue.

Keywords: myopia, public health, bibliometric analysis, global trends, myopia control, refractive surgery, CitNetExplorer

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INTRODUCTION

Myopia, also known as short-sightedness or near-sightedness, is one of the most prevalent eye disorders worldwide that lead to vision impairment in young individuals (1). It is one of the five ocular conditions listed as an immediate priority by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness. A meta-analysis predicted that up to half of the world's population would have myopia by 2050, 10% of which would have high myopia (2). The recent findings around the world imply an increased myopia incidence and myopia progression during the COVID-19 pandemic. The increasing prevalence combined with the rising early onset of myopia, which naturally leads to an increased risk of high myopia (3). High myopia can generate irreversible blindness owing to the secondary changes in the choroid, retina, and sclera (4). Optical interventions, such as spectacles, contact lenses, and refractive surgeries can correct the refractive error; however, they may not prevent high myopia-related complications (5). The large number of patients suffering from myopia and its impact on public health, such as its economic burden and quality of life implications, makes a bibliometric analysis of research studies significant.

Since E.W. Hulme, a British library scientist, first put forward "Statistical Bibliography" in 1922, bibliometric analysis has continued for nearly a 100 years (6). The field started to attract widespread attention with the proliferation of easily accessible online databases and the development of analysis software. Bibliometric analysis is a method that gives a valuable overview of existing academic literature and predicts the development trends of research based on citation reports and content, using mathematical and statistical methods (7). To date, bibliometric analysis has been applied to explore the development and trends of a specific field (8–10).

The research on myopia is so extensive, the number of publications is enormous and the research directions are different which make it difficult to identify the research focus and frontiers in the field. Thus, the study aimed to manifest a general status of global myopia research based on Web of Science (WOS) data from the entire 20th century. The bibliometric method was applied to analyze the research focus, frontiers, and key publications of myopia combined with citation network, and explore the research trend by keywords burst, to provide a comprehensive and promising reference for interested researchers.

MATERIALS AND METHODS

Sources of the Data and Search Strategy

The search for papers to be included in this study was carried out in July 2021 through the Web of Science Core Collection (WOS) provided by Thomson Reuters (Philadelphia, PA, USA). There are many databases available for worldwide research assessment; however, the WOS database is one of the most comprehensive databases with papers dating back to the year 1900 (11). We used the advanced feature and selected the keywords "myopia," "nearsightedness," or "shortsightedness" in the title and/or abstracts. The search strategy was as follows: TI = "Myopia" OR AB = "Myopia" OR TI="nearsightedness" OR AB = "nearsightedness" OR TI = "shortsightedness" OR AB = "shortsightedness." Only articles and reviews were included as the document types. There were no language restrictions for literature collection. The search covered the period from 1900 to 2020. Data were downloaded from WOS in "plain text" format with "full record and cited references." The search strategy for the terms related to Myopia was restricted to Title/Abstract to achieve greater accuracy in the results because many reported publications were not related to Myopia if applied to other search fields such as keywords. The use of title/abstract search is recommended in the bibliometric studies in contrast to the title-abstract-keywords search query because it substantially increases the specificity with minimum loss of sensitivity.

Bibliometric Software

In bibliometric analysis, the annual number of publications, prolific countries and institutions, core author and journal, paper citations, keywords, and bibliometric indicators are presented through descriptive analysis. The built-in analysis tool of Web of Science can create the citation network, but it is limited to offering the connections that exist between the citations of specific groups of articles and the co-authorship between the specific items. We applied bibliometric software to this study due to this reason. CitNetExplorer software was used to evaluate the development of scientific research within a specific field, which enable the researcher to visualize the citation networks and the relationship among these articles (12). VOSviewer software offers text mining functionality that can be used to construct and visualize co-occurrence networks of important terms extracted from a body of scientific literature, represented as nodes and links (13). The nodes size represented the number, and the links between the nodes reflected the partnership between the items. The graphic display ability of CiteSpace is not as strong as that of the VOSviewer, but it has the unique burst analysis function of keywords, which can demonstrate the changes in the hot spots in this field (14).

Data Analysis

The data from the WOS database was imported to the bibliometric software to produce visualization results and quantitative analysis for researchers. For this analysis, the most common bibliometric indicators were used: the number of publications, the number of citations. Microsoft Excel was used to arrange and sort the data, and extract the top results. The publication citation network was calculated using CitNetExplorer software. The setting of the clustering parameters resolution was set at 1.20 and a minimum cluster size of 1,000 articles. The co-authorship networks of countries, authors, organizations were made by VOSviewer, respectively. We chose the optimized parameter, which is described in detail in each figure notes. The burst keywords were assessed using CiteSpace software with the following parameters: time slicing (1990–2020), years per slice (1), term source (title, abstract, author keyword, keyword plus), node type (keyword), selection criteria (top 30).

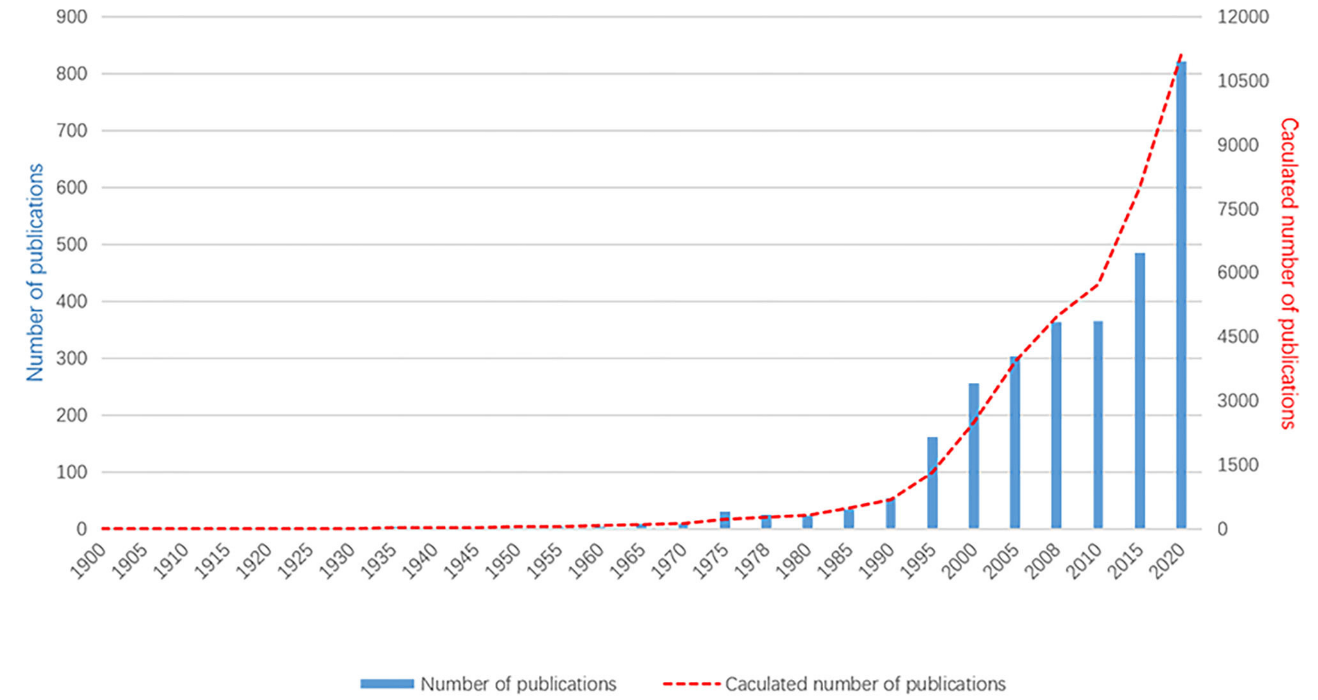

FIGURE 1 | The annual number of published myopia studies, 1900–2020. As the data in 2021 are still updated, they are not included in this figure.

RESULTS

Description of Publication

Growth Trends of Publications

Based on the WOS database analysis, 11 172 documents on myopia published between 1900 and 2020 were retrieved. The first article on myopia was published in 1907. Prior to 1990, this field of research had not received much attention. Since 1991, the number of articles published increased gradually from 100 publications to over 400 after 2011 (**Figure 1**). There were 822 articles published in 2020. In 2021, 429 articles have been published as of June, and the number is likely to increase.

Distribution of Countries

According to the retrieved articles, the articles on myopia originated from 127 countries. **Table 1** shows that the United States accounted for the most number of articles published (19.82%), followed by China and Australia. Studies from the United States were cited 105 738 times, ranking first among all countries, followed by Australia and China. The collaboration relationship was analyzed using VOSviewer. As shown in **Supplementary Figure 1**, the United States (USA), the largest node, is the most active country in this field. The cooperation map showed that the USA intensively collaborated with many countries in myopia fields, such as Germany, France, and Spain.

Distribution of Authors

According to the retrieved results, over 71,292 authors contributed to myopia research. **Table 2** lists the 10 most productive authors in the field of myopia research. Among all authors, Saw SM contributed the most publications (175), the most citations (10,448 times). As shown in **Supplementary Figure 2**, the cooperative relationships among the productive authors are close, except for the group marked in yellow. There are several co-authorship groups, such as the red group with Saw SM as the core, the green group with Smith EL as the core, and the blue group with Mutti DO as the core.

TABLE 1 | Top 10 most influential countries in myopia research.

Rank	Country	Number of citations	Number of publications
1	USA	105,738	2,786
2	Australia	35,433	913
3	China	34,961	2,088
4	England	26,674	764
5	Germany	22,381	839
6	Japan	20,944	664
7	Singapore	20,569	433
8	Spain	13,484	508
9	Italy	9,452	416
10	Canada	8,518	293

Distribution of Journals

Based on the retrieved results, the articles on myopia research were distributed among 164 journals. The top 10 journals that published articles on this topic are listed in **Table 3**. According

TABLE 2 | Top 10 most influential authors for myopia studies.

Rank	Author	Number of citations	Number of publications
1	Saw SM	10,448	175
2	Mitchell P	8,384	121
3	Wong TY	7,161	107
4	Ohno-Matsui K	5,779	140
5	Wallman J	4,834	27
6	Mutti DO	4,736	68
7	Zadnik k	4,665	58
8	Morgan IG	4,146	50
9	Jonas JB	4,033	108
10	Schaeffel F	3,849	104

TABLE 3 | Top 10 influential source journals for myopia studies.

Journal	Country	Number of citations	Number of publications
Investigative Ophthalmology & Visual Science	USA	37,443	708
Ophthalmology	USA	37,220	491
Journal of Cataract and Refractive Surgery	USA	23,368	834
American Journal of Ophthalmology	USA	17,993	414
Journal of Refractive Surgery	USA	16,539	701
Optometry and Vision Science	USA	12,554	437
British Journal of Ophthalmology	UK	10,886	313
Archives of Ophthalmology	USA	10,062	157
Vision Research	UK	8,180	155
Ophthalmic and Physiological Optics	USA	6,621	260

to the citations, *Investigative Ophthalmology & Visual Science* and *Ophthalmology* ranked first and second, respectively. The *Journal of Cataract and Refractive Surgery* published the largest number of myopia articles (834 papers), followed by *Investigative Ophthalmology & Visual Science*. Among the top 10 journals, eight were from the USA, one was from the United Kingdom, and one from Germany.

Distribution of Organizations

As shown in **Table 4**, the top 10 organizations published 2,161 articles. Citation analysis showed that the National University of Singapore had 14,968 citations and ranked first. According to the publications, National University of Singapore and Sun Yat-sen University ranked first with 285 publications. The University of Melbourne, with 264 articles, ranked third. In the knowledge domain map of collaboration among main research organizations, 45 countries, 6 clusters, and 874 links were displayed and selected. As shown in **Supplementary Figure 3**, the National University of Singapore has the highest number (35 links) and the strongest link strength (629).

Top Cited Publications

The top 10 cited references are summarized in **Table 5**. The top 10 papers were co-cited over 6,000 times in total, and the first was co-cited more than 800 times, while the 10th was cited 516 times. Additionally, the fifth paper was the only one published before the year 2000 cited 538 times. The top 10 cited references mainly focused on the prevalence and risk factors of myopia, which is consistent with the latest burst keyword.

Myopia Research Keywords and Tendency

Through co-occurrence analysis, the keywords were visualized by density network map (**Figure 2**). The keyword "*in-situ* keratomileusis," "prevalence," and "photorefractive keratectomy" turned out to be significant. These keywords were the core keywords in myopia research. The top 29 keywords with the strongest citation bursts were extracted via keyword burst analysis from 1990 to 2020 (**Figure 3**). "Chick," the first keyword detected, appeared in 1990 and lasted for 12 years. Among the 29 keywords, "photorefractive keratectomy" had the highest burst strength (114.58) in the steady development stage. The latest keywords in the rapid development stage were "myopia control" and "trend."

Myopia Research Citation Network

Figure 4 shows the main publication citation network of myopia. Based on the clustering function, each publication would be assigned to six research focuses. Each color marks a group. Each direction has its own citation network, which consists of publications that are strongly linked to each other.

The color green represents the prevalence and risk factors of myopia group, containing 2,711 publications, and almost 32% of the total citation score. The color blue represents the surgical control of myopia group with 3,059 publications, and the total citation score was 34,557. The color purple represents the pathogenesis of myopia group, where 1,456 articles were found within the network. The color yellow represents the optical interventions of myopia group. The color orange represents the myopia and glaucoma group. The color brown represents the pathological myopia group.

Supplementary Figures 4–9 show the citation network of each of the six research focuses.

DISCUSSION

Bibliometric analysis is one of the most prominent methods for researchers to identify and predict new trends in potential topics. Moreover, it has been widely recognized as an alternative tool for evaluating academically detailed information in the library and information science. There has been some studies on myopia, but their coverages were limited in a single area of myopia research and did not include keywords bursts in its analysis (15, 16). In this study, we conducted a comprehensive bibliometric analysis of

TABLE 4 | Top 10 influential organizations for myopia studies.

Rank	Organization	Country	Number of citations	Number of publications
1	National University of Singapore	Singapore	14,968	285
2	University of Sydney	Australia	10,709	179
3	University of Melbourne	Germany	10,592	264
4	Singapore National Eye Center	Singapore	10,342	223
5	Singapore Eye Research Institute	Singapore	9,641	192
6	Sun Yat-sen University	China	6,381	285
7	Tokyo Medical & Dental University	Japan	6,201	160
8	Hong Kong Polytechnic University	China	4,311	158
9	Capital Medical University	China	2,980	176
10	Fudan University	China	2,836	239

TABLE 5 | Top 10 cited papers in myopia citation network.

Ranking	Title	Author	Year	Number of citations
1	Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050	Holden BA	2016	844
2	The multifunctional choroid	Nickla NL	2010	773
3	Myopia	Morgan IG	2012	728
4	Outdoor activity reduces the prevalence of myopia in children	Rose KA	2008	602
5	The relationship between glaucoma and myopia—the blue mountains eye study	Mitchell P	1999	538
6	Homeostasis of eye growth and the question of myopia	Wallman J	2004	586
7	Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes	Fujiwara T	2009	537
8	Prevalence and risk factors for refractive errors in adult Chinese in Singapore	Wong TY	2000	535
9	Myopia and associated pathological complications	Saw, SM	2005	533
10	Refractive error and visual impairment in urban children in southern China	He MG	2004	516

the literature available on myopia from 1900 to 2020; six groups were identified within the citation network, and keywords bursts detection was performed.

Global Contribution in Myopia Research

Trend variations in publication quantity can reflect changes in knowledge on a certain subject. The number of documents on myopia studies has been through three stages: the initial stage (before 1991), steady development stage (from 1991 to 2011), and rapid development stage (after 2011). In the initial stage, the total publications were about 700, the annual average amount was about 7 papers. The increase in the global pattern of published papers was particularly prominent after the 1990's, which may be associated with a shift in focus toward newly developed techniques for refractive surgery with better safety and effectiveness (17, 18).

International cooperation has become one of the main scientific research patterns among countries. In the current study, the United States was found to be the leading country in myopia research, accounting for 19.82% of total publications and the highest number of citations. According to the connection between various nodes, the United States attaches great importance to exchanges and cooperation in the academic community. This also explains why the United States has greater output to some extent. It can be speculated that adequate funding, advanced techniques, and equipment are essential factors. However, it is equally important that numerous authors from the United States produced high-quality research with good communication and collaboration with others. Smith EL of the University of Houston conducted animal experiments on myopia and explored the role of visual signals on refractive development. He stated that optical defocus can regulate eye growth and myopia progression by a small but statistically significant amount (19). In the initial stage, Curtin BJ was the most cited author, who was from the USA as well. The most cited article found that high myopia was associated with abnormal proteoglycans in sclera which changed the size and organization of collagen fibrils (20). In terms of the authors' analysis, Saw SM from Singapore was the most cited author in the steady development stage and the rapid development stage. In 2009, the article titled "Outdoor activity and myopia in Singapore teenage children" was published in the British Journal of Ophthalmology. This study suggested that outdoor activity may protect against the progression of myopia in children (21). Top source journals also came from the United States, with the *Journal of Cataract and Refractive Surgery* (JCRS) being the most prolific in publishing myopia research. Synthetically, *Investigative Ophthalmology & Visual Science* was the most influential journals, which ranked first of citations. As for the research institutions, among the top 10 institutions, eight institutions were located in Asia, which was in accordance with the increasing prevalence of myopia in East and Southeast Asia (22, 23).

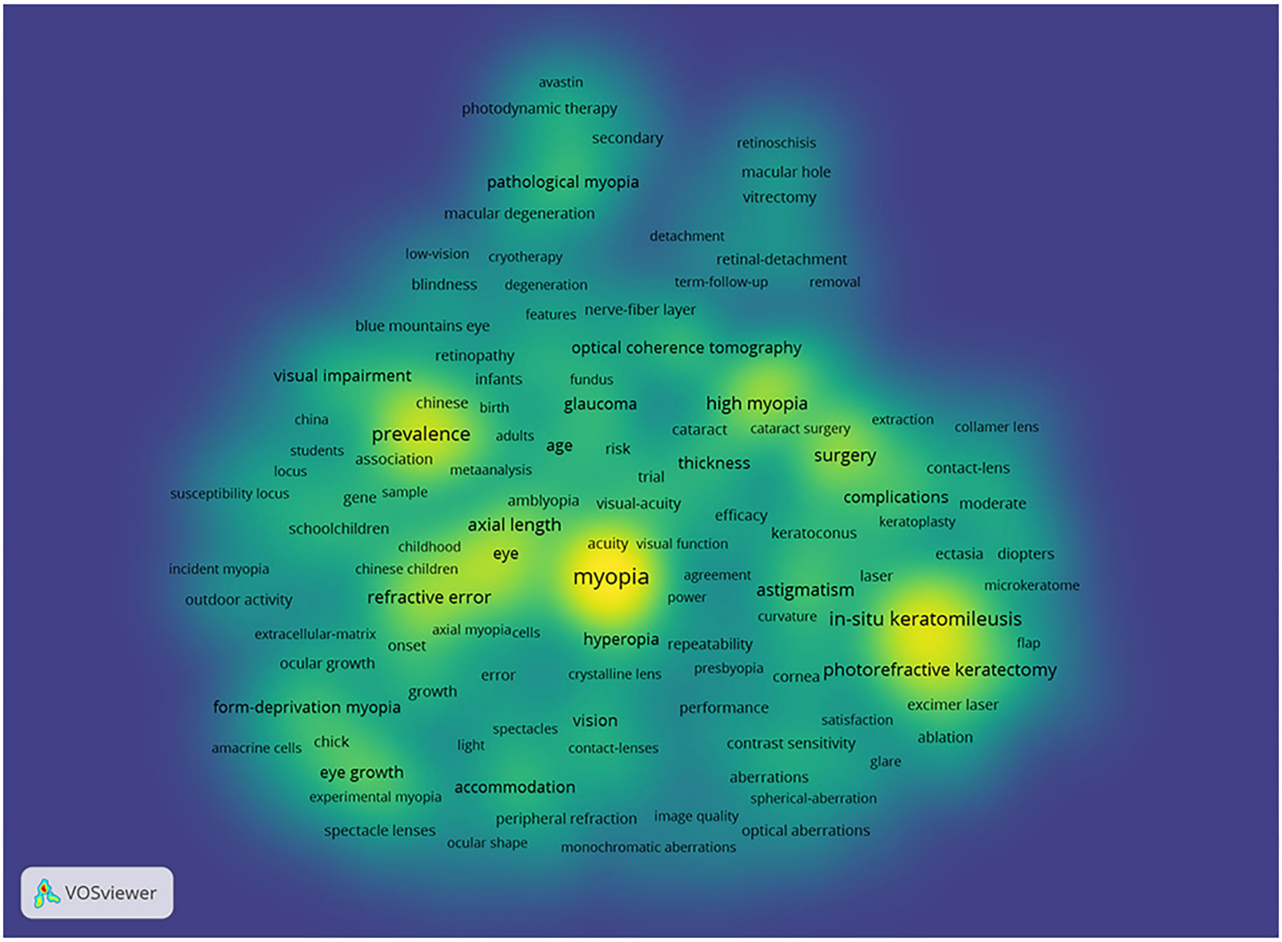

FIGURE 2 | Density visualization for keywords in co-occurrence network map. Each keyword in the density visualization has colors that indicates its appearing frequency. Keywords in yellow emerge more frequently, while green emerge blue less frequently.

Focus in Myopia Research

Research focus represents the combination of clinical subjects and basic research and indicates the increasing or emerging themes in the field of myopia. In bibliometrics, the cluster function showed that all publications can be separated into six groups, and each group was summarized to a specific theme. With reference to the characteristics and status of myopia research, the following six groups are discussed.

Prevalence and Risk Factors of Myopia

The sharp rise in the myopic population increased its socioeconomic burden and posed a public health problem worldwide. Thus, the prevalence of myopia and its risk factors have gained widespread attention (**Supplementary Figure 1**, Green). Carrying out scientific epidemiological research on myopia is a mainstay for exploring related influencing factors for myopia, which are critical for intervening on its onset and progression. Before 1980, little was known about the distribution of myopia in the worldwide population. East and Southeast Asia showed the highest prevalence, reaching 80–90% at 18 years of age, which was much higher than that of Central Europe and Central Asia (24, 25). A meta-analysis has suggested that by the year 2050, nearly 50% of the world's population will have myopia, and approximately 10% will be high myopic. This is the most cited paper in this myopia area published by Holden et al. in 2016 (2). The first prospective study of the risk factors for myopia, showed that earlier age of onset of myopia was a risk factor for the development of high myopia, which induced non-correctable visual impairment or blindness (3). The genetic pool has changed little over the past few decades, but the changes in the environmental factors may be responsible for the rapid increase in the prevalence of myopia (26). It seems that school myopia is multifactorial, strongly associated with intensive educational pressure and limited outdoor activities (27). In terms of educational level, there was a high prevalence of myopia in boys attending Orthodox schools in Israel compared with their peers attending secular schools (27). The mechanism involved is unclear; however, near-work requires more accommodation which may stimulate eye

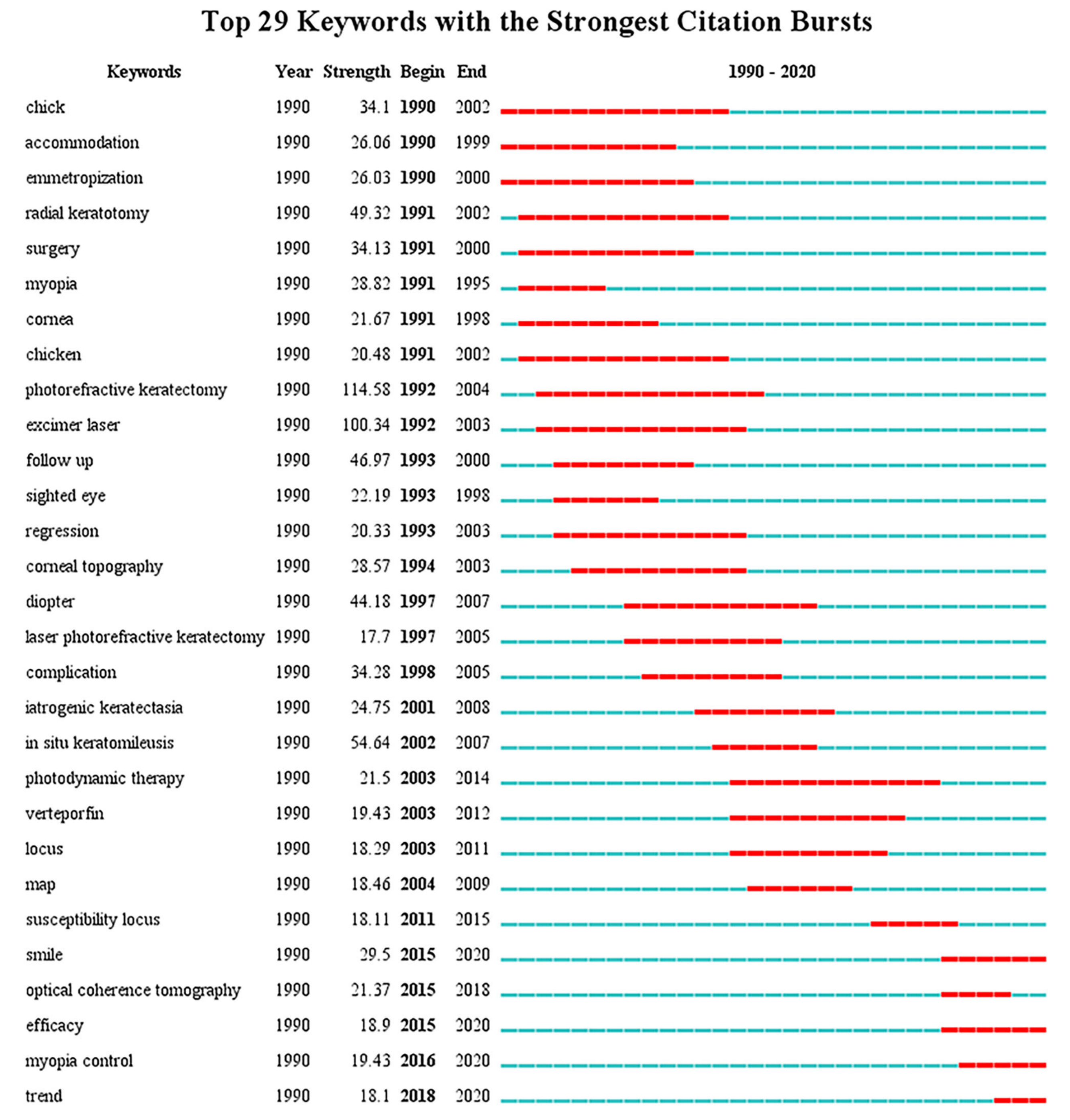

FIGURE 3 | The top 29 keywords with the strongest citation bursts in myopia research from 1990 to 2020. The blue lines represent the base timeline, while the red segments represent the burst duration of the keywords.

growth. According to the prevailing view, longer time spent outdoors can prevent myopia (28). The available data revealed that high-intensity outdoor light may act as a protective factor by adding retinal dopamine concentrations and thus preventing myopia (29).

Surgical Control of Myopia

With the development of laser technology in modern ophthalmic surgery, refractive surgery is an important research area to improve the refractive status (30) (**Supplementary Figure 5**, Blue). Refractive surgery, a safe and effective measure that

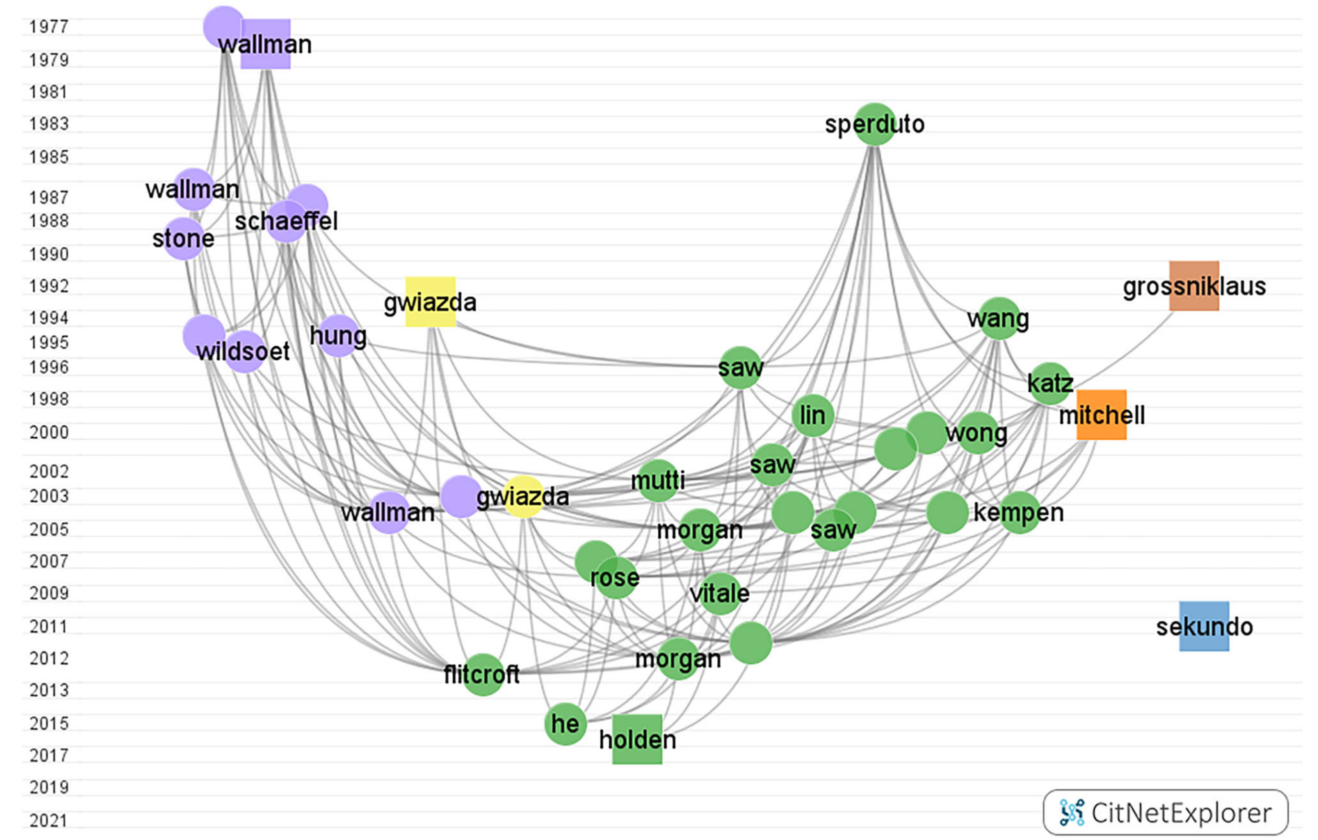

FIGURE 4 | Myopia citation network graph from CitNetExplorer from 1900 to 2000. The vertical axis coordinates indicate the publication year. Each dot/square indicates a publication which is labeled with the last name of the first author. Each color marks a group. Group 1 to group 6, in turn, were colored green, blue, purple, yellow, orange, and brown, respectively. The square represents the publication with the highest citation score in each group.

corrects refractive errors, is generally not recommended until refractive development has stabilized around the age of eighteen. The first case of radial keratotomy surgery was reported by Fyodorov in 1979; however, it has been replaced by cornea laser surgery owing to its lower security and poor efficiency (31). The keratorefractive surgery revolution began with surface ablation techniques. Surface ablation is potentially suitable for high myopia and thin corneas due to the relatively thicker residual stromal thickness (32). Nonetheless, corneal haze and myopic regression may be more common after surface ablation (33). Laser-assisted *in situ* keratomileusis (LASIK) is a new revolution, which has been the standard refractive surgery used for treating myopia since the 1990's (34). A review of LASIK outcomes was published in 2016 by Sandoval et al. (35). The authors reported that the spherical equivalent refraction (SE) and the uncorrected distance visual acuity of eyes both obtained pretty good correction effects and up to 98.8% of patients were satisfied with their outcome. However, complications associated with this procedure are not rare, such as free cap, buttonhole flap (36, 37). Presently, small-incision lenticule extraction (SMILE) has emerged as a novel surgery for myopia with the introduction of the femtosecond laser platform. The most frequently cited article in this cluster was published in 2011 and written by Sekundo et al. (38). The authors acknowledged that SMILE was a promising new minimally invasive procedure. SMILE has shown a reduced degree of dry eye symptoms and higher-order aberrations relative to LASIK (39, 40). These advantages may stem from small side cut and lower laser energy which retains corneal nerve and reduce inflammatory responses to a large extent (41, 42). Refractive surgery has already achieved excellent visual outcomes; however, the next challenge for clinicians is to choose the best refractive surgery method for each patient. Recently, with the addition of artificial intelligence in preoperative evaluation, data derived from corneal topography, biometry, and aberrometry can optimize customized refractive surgical strategies (43, 44). Based on the keywords, myopia correction remains centered on the corneal refractive operation. Intraocular surgery, which avoids the risk of corneal ectasia, is also developing rapidly (45).

Pathogenesis of Myopia

At present, one of the areas that require further studies is the pathogenesis of myopia (**Supplementary Figure 6**, Violet). The mechanisms underlying axial elongation may provide scientific clues for the prevention and control of this global epidemic. From birth to adolescence, the eye achieves a close match between the power of its optics and its axial length, with images that are focused on the retina without accommodative effort (emmetropia) (46). Interestingly, Rucker FJ discovered that the retina may be using contrast perception to decode the sign of defocus using contrast perception. The chromatic signals of longitudinal chromatic aberration may rely on cone modulation to provide a direction signal for accommodation and eye growth (47, 48). Within the past several decades, it has become clear that alterations in the visual experience can provoke myopia in animal models (19, 49). For instance, form deprivation causes axial myopia through reduced visual stimulation, which is different from defocused-myopia related to the central system (50). The most frequently cited publication is the paper written by Wallman et al.. The authors reported that reading for long periods may disturb the homeostasis in the posterior globe, resulting in scleral remolding (51). The advances in clinical and basic experiments are mainly in the posterior ocular segment (52–54). Recently, Zhou et al. proposed a hypothesis that scleral hypoxia is a target for myopia control in 2018 (54). They speculated that special visual stimulation regulates the choroidal blood, thus initiating scleral hypoxia, leading to the onset and progression of myopia and axial elongation. Therefore, choroidal blood perfusion might be a "rapid predictive index" for myopia management (55). However, despite the progress, the chain of events of choroidal signals and scleral targets are still largely unknown. These clues may direct researchers to improve the understanding of myopia through the expansion of omics and big data analysis. In addition, some studies showed that atropine was found to increase the release of dopamine, strengthen the sclera, and increase the choroidal blood (56, 57).

Optical Interventions of Myopia

As for group 4, the frequently cited articles were related to the optical interventions study (**Supplementary Figure 7**, Yellow). This group was led by the cross-sectional study by Millodot et al., published in 1981, in which the effect was measured between peripheral refraction and ametropia, where peripheral hyperopic defocus accelerated the onset of myopia (58). The first optical intervention was based on the reasoning that there was a relationship between myopia and excessive accommodation. The use of single-vision lenses (SVLs) was the mainstream method to correct myopia; however, SVLs poorly controlled myopia progression. It is not possible to clear the causality between peripheral retinal defocus and central myopia. However, it has been widely recognized that peripheral hyperopia can promote myopia progression (19, 59). Thus, peripheral defocus spectacle lenses (PDSL) and orthokeratology that were precisely designed to reduce peripheral retinal defocus, were effective (60, 61). The most cited publication was the article by Jane Gwiazda et al., which was published in 2003 in Investigative Ophthalmology & Visual Science (62). The authors reported that compared with SVLs, PALs limited the progression of myopia during the 1st year. The evaluation of visual quality in the human eye has always been an important issue in the field of ophthalmology and visual optics, which generally focus on the correlation analysis of visual acuity, wavefront aberrations, and contrast sensitivity (63–65). Previous research has indicated that visual quality was negatively related to the degree of myopia. It decreases gradually and concomitantly as the degree of myopia increases, while contrast sensitivity decreases and higher-order aberrations increase (66, 67).

Myopia and Glaucoma

The connection between myopia and glaucoma clinically has also been a significant research topic in recent years (**Supplementary Figure 8**, Orange). Glaucoma is the leading cause of irreversible blindness worldwide, and primary open-angle glaucoma (POAG) is the major type of glaucoma. Glaucoma is strongly linked with the onset and progression of myopia, with homogeneity in structural and functional changes (68). The most cited paper was published in 1999 in Ophthalmology by Mitchell et al. and was ranked fifth in the top 10 cited publications (69). The study revealed that myopia, an independent risk, increased the prevalence of glaucoma by 2 or 3-fold. A study from Korea found a positive trend between increased myopic refractive error and POAG prevalence (70). Recently, a meta-analysis by Ahnul Ha et al. corroborated this finding: every diopter in myopia increases the risk of glaucoma by ∼20% (71). Thus, high myopia is now regarded as a risk factor for glaucoma (72–74). With increased axial length, high myopia appears to have optic disc morphological changes and optic nerve fiber layer defects, accelerating visual field defects (72, 73). In this group, the newest, most cited citation centers on myopia-related optic disc changes. Saw SM et al. reported that tilted discs and peripapillary atrophy were common in Singaporean adolescent children, which were similar to the pathological changes in glaucoma (75). Retinal degeneration makes it difficult to detect glaucoma with severe myopia, which requires a myopic normative database for analysis (76). Taken together, there is a need for a multimodal approach combining structural images with functional assessments to overcome the clinical diagnostic dilemmas of myopic eyes with glaucoma (77).

Pathological Changes of Myopia

Pathological myopia has gained attention because of its sustained axial elongation and irreversible fundus degeneration that leads to severe vision loss (**Supplementary Figure 9**, Brown). This cluster focuses on myopic maculopathy, especially in myopic choroidal neovascularization (mCNV) (78). The reasons behind the development of myopic maculopathy are not clear, but evidence has shown that excessive axial elongation weakens the retina, choroid, and sclera, which is accompanied by vascular complications and degeneration (79, 80). Curtin and associates first proposed five fundus changes in myopia associated with axial elongation in 1970 (81). This classification did not cover all myopic maculopathy lesions. The development of fundus imaging technology facilitated a clearer visualization of myopic maculopathy. Grossniklaus et al. published an article in 1992 that described the pathological changes in pathological myopia and was the most cited paper in this group (82). A simplified classification system was proposed by Ohno-Matsui et al. (83). In this system, myopic maculopathy lesions were classified into five categories: no myopic retinal lesions (category 0), tessellated fundus only (category 1), diffuse chorioretinal atrophy (category

2), patchy chorioretinal atrophy (category 3), and macular atrophy (category 4), in combination with the three "plus signs" of lacquer crack, myopic choroidal neovascularization, and the Fuchs spot. Choroidal neovascularization may develop in 5–10% of individuals with pathological myopia (84), which is easily diagnosed using optical coherence tomography, optical coherence tomography angiography, and fundus fluorescein angiography. Photodynamic therapy with verteporfin (vPDT) was the first approved treatment for mCNV. Nevertheless, vPDT also resulted in chorioretinal atrophy and influenced the final visual outcome (85, 86). In recent years, intravitreal anti-endothelial growth factor (anti-VEGF) injection has become the first-line treatment for CNV secondary to pathological myopia (87). Anti-VEGF agents, such as ranibizumab and aflibercept, can control neovascularization and reduce macular edema, thereby improving visual acuity (88). However, patients do not acquire significant benefits in long-term vision with this treatment due to the development of mCNV-related macular atrophy (89).

Tendency in Myopia Research

The strongest citation burst keywords were considered the indicators of research trends in basic and clinical research. As a result of the fewer numbers of annual average publications, no distinct research trend was observed in the initial stage. Despite this, the most cited paper showed that lid fusion led to elongation of the eye globe and varying degrees of myopia in monkeys published in 1977 (90).

In the steady development stage and rapid development stage, we conducted the keywords burst to explore myopia tendency and frontiers. According to the keyword co-occurrence chronology, the most prominent keywords in steady development stage are "photorefractive keratectomy," "excimer laser," and "*in situ* keratomileusis," indicating that the study focus was refractive surgery. Experts such as Da Vinci proposed the first theories as to the source of refractive errors long ago. At the Aerospace Medical Association, an intervention reported excimer laser can be used to change the corneal shape, piqued experts' curiosity (91). McDonald and colleagues became the first to utilize an excimer laser in the human eye with myopia in 1988 (92). As the number of surgeries rose, the drawbacks of photorefractive keratectomy, started to emerge such as postoperative pain and corneal haze. In the 1990's, Pallikaris with colleagues proposed a novel surgical procedure (LASIK) that merged the microkeratome with the excimer laser, and it has now become a wildly used refractive technique (93). In addition to clinical studies, animal studies had a high profile within the steady development stage. Notably, the keyword chick appeared twice in the analysis. Several animal studies have demonstrated environmental factors can exert a significant effect on myopia. In this regard, we found that Wildsoet CF is the most cited author at the second period. Most attention was drawn to an article published in 1994 showing that hyperopic defocus induced with negative lens led to increased ocular length and choroidal chinning, whereas myopic defocus induced with positive lens led to decreased ocular elongation and choroidal thickening (94). According to recent studies by Wildsoet CF, the Bone Morphogenetic Proteins (BMP 2, 4, and 7) gene is down-regulated with form-deprivation and hyperopic defocus, and up-regulated with myopic defocus in chicks, which exhibited regional differences in retinal pigment epithelium. Consequently, it is tempting to speculate that BMPs played a crucial role in ocular growth signaling (95, 96).

During the rapid development stage, we have observed that a new chapter in refractive surgery was opened with the application of the femtosecond laser in ophthalmology. SMILE has been the most recent, strongest burst, which has been approved by the Food and Drug Administration for the treatment of myopia and astigmatism preventing iatrogenic dry eye and allowed better spherical aberration control (97, 98). Beyond 2020, refractive surgery might be guided by artificial intelligence to make precise decisions regarding surgery details and improve the quality of the retinal image (99, 100). In the third phase, the keywords "myopia control" and "trend" show that there is an urgent need for society to take interventions on myopia, which are the new research hotspots in this field. With the rapidly growing prevalence of myopia already at epidemic levels in some regions and imposing a heavy public health burden (5), the scientific interest in myopia control is growing with each passing day. The amount of scientific papers has increased excessively concerning myopia control. Myopia management strategies consist of two parts: the prevention of myopia onset and slowing the progression of myopia (99). The current control measures, including optical, pharmacological, behavioral, and surgical interventions. On the basis of a series of influential studies, increased time outdoors could preclude high engagement in near-work activities and exposure to ultraviolet radiation, which is more meaningful in preventing myopia (21). A recent review suggested that the changes in SE and axial length were better in the outdoor group than that in the control group (101). Studies using animal models reported that bright light may play an inhibitory role in response to imposed form-deprivation (102). When compared with other measures, wearing optical devices is a convenient method that reduces the peripheral hyperopic defocus to limit myopic progression. Substantial evidence from animal research indicates that hyperopic defocus induces axial elongation whereas myopic defocus inhibits the growth of axial elongation (103). For the present research outcomes, pharmacological treatment was insufficient to cluster into groups in the myopia field. Atropine is the most extensively studied medicine in slowing progression. Low-dose atropine (0.01%) seemed to be the most effective treatment and had a lower risk of rebound according to the Atropine for Treatment of Myopia (ATOM2) study (104). It was suggested that atropine may exert its function by altering choroidal thickness to reduce scleral proteoglycan synthesis (105, 106). As for surgical interventions for the control of myopia, scleral reinforcement to slow ocular elongation has a long history. The revitalized interest arose from collagen cross-linking scleral strengthening (CCL) controlling scleral biochemistry which has involved animals only (107). Recently, Bullimore et al. reported that the potential benefits of myopia control outweigh the risks (108). Moreover, applying artificial intelligence to ocular data may provide a better approach for reducing public burden focusing on myopia control. Generally, the preventive strategies aim to avoid younger age of myopia onset or lower the risk of high myopia; therefore, the sooner the intervention, the better is the outcome and the impact on public health. In short, the efforts of myopia controls could have a profound impact on public health.

Strengths and Limitations

The present study is the first bibliometric analysis of myopia performed using the literature from the entire 20th century. To acquire deep insight into myopia research, VOSviewer was used to identify the hotspots and major clusters in this field. However, despite these advantages, several limitations should be noted in our study. The data were only retrieved from the WOS database and did not include other medical databases such as PubMed and Scopus. As reported, the WOS database has more accuracy in document type assignment than Scopus (109). The WOS was preferred over PubMed due to a unique citation report function (11). Regardless, the WOS database is the most commonly used reference database for bibliometric analysis.

CONCLUSIONS

Based on the bibliometric analysis, myopia has been growing as a core research area. United States has the most significant academic impact on myopia studies. The most productive and cited institution was the National University of Singapore. Saw SM is one of the key researchers in this field. The priority themes involved the prevalence and risk factors of myopia and surgical control of myopia. With the increasing prevalence of myopia, the interventions of myopia control are the potential research hotspot and pressing issue. Taken together, these analysis results should help researchers realize the current state and provide promising directions for future research.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

MS and YD did this bibliometrics analysis and drafted manuscript. MS and JC organized the manuscript writing. QS searched strategy. YW reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.846601/full#supplementary-material

REFERENCES

1. Baird PN, Saw SM, Lanca C, Guggenheim JA, Smith EL, Zhou X, et al. Myopia. *Nat Rev Dis Primers.* (2020) 6:99. doi: 10.1038/s41572-020-00231-4
2. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006
3. Li J, Lanca C, Htoon HM, Wong YL, Nyunt SZ, Tan D, et al. High myopes in Singapore: 19-year progression from childhood to adulthood. *Ophthalmology.* (2020) 127:1768–70. doi: 10.1016/j.ophtha.2020.05.031
4. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt.* (2005) 25:381–91. doi: 10.1111/j.1475-1313.2005.00298.x
5. Modjtahedi BS, Ferris FL, 3rd, Hunter DG, Fong DS. Public Health Burden and Potential Interventions for Myopia. *Ophthalmology.* (2018) 125:628–30. doi: 10.1016/j.ophtha.2018.01.033
6. Edward WH. Statistical bibliography in relation to the growth of modern civilization. *Economica*. (1923) 112:585–6.
7. Agarwal A, Durairajanayagam D, Tatagari S, Esteves SC, Harlev A, Henkel R, et al. Bibliometrics: tracking research impact by selecting the appropriate metrics. *Asian J Androl.* (2016) 18:296–309. doi: 10.4103/1008-682X.171582
8. Fagundes MVC, Teles EO, Vieira de Melo SAB, Freires FGM. Decision-making models and support systems for supply chain risk: literature mapping and future research agenda. *Eur Res Manage Business Econ.* (2020) 26:63–70. doi: 10.1016/j.iedeen.2020.02.001
9. Peng X, Luo Z. A review of q-rung orthopair fuzzy information: bibliometrics and future directions. *Artifi Intellig Rev.* (2021) 54:3361–430. doi: 10.1007/s10462-020-09926-2
10. Lu K, Liao H, Kazimieras Zavadskas E. An overview of fuzzy techniques in supply chain management: bibliometrics, methodologies, applications and future directions. *Technol Econ Dev Economy.* (2021) 27:402–58. doi: 10.3846/tede.2021.14433
11. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. *FASEB J.* (2008) 22:338–42. doi: 10.1096/fj.07-9492LSF
12. Van Eck NJ, Waltman L. CitNetExplorer: A new software tool for analyzing and visualizing citation networks. *J Inform.* (2014) 8:802–23. doi: 10.1016/j.joi.2014.07.006
13. Van Eck NJ, Waltman L. Citation-based clustering of publications using CitNetExplorer and VOSviewer. *Scientometrics.* (2017) 111:1053–70. doi: 10.1007/s11192-017-2300-7
14. Hu S, Alimire A, Lai Y, Hu H, Chen Z, Li Y. Trends and frontiers of research on cancer gene therapy from 2016 to 2020: a bibliometric analysis. *Front Med (Lausanne).* (2021) 8:740710. doi: 10.3389/fmed.2021.740710
15. Efron N, Morgan PB, Jones LW, Nichols JJ. Topical review: bibliometric analysis of the emerging field of myopia management. *Optom Vis Sci.* (2021) 98:1039–44. doi: 10.1097/OPX.0000000000001766
16. Alvarez-Peregrina C, Martinez-Perez C, Villa-Collar C, Sanchez-Tena MA. A bibliometric and citation network analysis of myopia genetics. *Genes (Basel).* (2021) 12:447. doi: 10.3390/genes12030447

17. Pérez-Santonja JJ, Bellot J, Claramonte P, Ismail MM, Alio JL. Laser *in situ* keratomileusis to correct high myopia. *J Cataract Refractive Surg.* (1997) 23:372–85. doi: 10.1016/S0886-3350(97)80182-4
18. Pallikaris IG, Siganos DS. Excimer laser *in situ* keratomileusis and photorefractive keratectomy for correction of high myopia. *J Refract Corneal Surg.* (1994) 10:498–510. doi: 10.3928/1081-597X-19940901-07
19. Smith EL, 3rd, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. Peripheral vision can influence eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci.* (2005) 46:3965–72. doi: 10.1167/iovs.05-0445
20. Curtin BJ, Iwamoto T, Renaldo DP. Normal and staphylomatous sclera of high myopia. An electron microscopic study. *Arch Ophthalmol.* (1979) 97:912–5. doi: 10.1001/archopht.1979.01020010470017
21. Dirani M, Tong L, Gazzard G, Zhang X, Chia A, Young TL, et al. Outdoor activity and myopia in Singapore teenage children. *Br J Ophthalmol.* (2009) 93:997–1000. doi: 10.1136/bjo.2008.150979
22. Saw S-M, Carkeet A, Chia K-S, Stone RA, Tan DTH. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology.* (2002) 109:2065–71. doi: 10.1016/S0161-6420(02)01220-4
23. Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci.* (2004) 45:1071–5. doi: 10.1167/iovs.03-1151
24. Foster PJ, Jiang Y. Epidemiology of myopia. *Eye (Lond).* (2014) 28:202–8. doi: 10.1038/eye.2013.280
25. Morgan IG, French AN, Ashby RS, Guo X, Ding X, He M, et al. The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res.* (2018) 62:134–49. doi: 10.1016/j.preteyeres.2017.09.004
26. Morgan IG, Wu PC, Ostrin LA, Tideman JWL, Yam JC, Lan W, et al. IMI risk factors for myopia. *Invest Ophthalmol Vis Sci.* (2021) 62:3. doi: 10.1167/iovs.62.5.3
27. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. *J Pediatr Ophthalmol Strabismus.* (1993) 30:319–22. doi: 10.3928/0191-3913-19930901-12
28. Jonas JB, Xu L, Wei WB, Wang YX, Jiang WJ, Bi HS, et al. Myopia in China: a population-based cross-sectional, histological, and experimental study. *Lancet.* (2016) 388:20. doi: 10.1016/S0140-6736(16)31947-X
29. Landis EG, Chrenek MA, Chakraborty R, Strickland R, Bergen M, Yang V, et al. Increased endogenous dopamine prevents myopia in mice. *Exp Eye Res.* (2020) 193:107956. doi: 10.1016/j.exer.2020.107956
30. Kim T-i, Alió del Barrio JL, Wilkins M, Cochener B, Ang M. Refractive surgery. *Lancet.* (2019) 393:2085–98. doi: 10.1016/S0140-6736(18)33209-4
31. Fyodorov SN, Durnev VV. Operation of dosaged dissection of corneal circular ligament in cases of myopia of mild degree. *Ann Ophthalmol.* (1979) 11:1885–90.
32. Sanchez P, Moutsouris K, Pandolfi A. Biomechanical and optical behavior of human corneas before and after photorefractive keratectomy. *J Cataract Refract Surg.* (2014) 40:905–17. doi: 10.1016/j.jcrs.2014.03.020
33. Na KS, Chung SH, Kim JK, Jang EJ, Lee NR, Joo CK. Comparison of LASIK and surface ablation by using propensity score analysis: a multicenter study in Korea. *Invest Ophthalmol Vis Sci.* (2012) 53:7116–21. doi: 10.1167/iovs.12-9826
34. Sandoval HP, de Castro LE, Vroman DT, Solomon KD. Refractive surgery survey 2004. *J Cataract Refract Surg.* (2005) 31:221–33. doi: 10.1016/j.jcrs.2004.08.047
35. Sandoval HP, Donnenfeld ED, Kohnen T, Lindstrom RL, Potvin R, Tremblay DM, et al. Modern laser in situ keratomileusis outcomes. *J Cataract Refract Surg.* (2016) 42:1224–34. doi: 10.1016/j.jcrs.2016.07.012
36. Jain V, Mhatre K, Shome D. Flap buttonhole in thin-flap laser in situ keratomileusis: case series and review. *Cornea.* (2010) 29:655–8. doi: 10.1097/ICO.0b013e3181c377d5
37. Geggel HS. Treatment of lost flaps and slipped flaps. *Int Ophthalmol Clin.* (2008) 48:65–71. doi: 10.1097/IIO.0b013e31815eb96d
38. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. *Br J Ophthalmol.* (2011) 95:335–9. doi: 10.1136/bjo.2009.174284
39. Ganesh S, Gupta R. Comparison of visual and refractive outcomes following femtosecond laser- assisted lasik with smile in patients with myopia or myopic astigmatism. *J Refract Surg.* (2014) 30:590–6. doi: 10.3928/1081597X-20140814-02
40. Kobashi H, Kamiya K, Shimizu K. Dry eye after small incision lenticule extraction and femtosecond laser-assisted LASIK: meta-analysis. *Cornea.* (2017) 36:85–91. doi: 10.1097/ICO.0000000000000999
41. Aristeidou A, Taniguchi EV, Tsatsos M, Muller R, McAlinden C, Pineda R, et al. The evolution of corneal and refractive surgery with the femtosecond laser. *Eye Vis.* (2015) 2:12. doi: 10.1186/s40662-015-0022-6
42. Riau AK, Angunawela RI, Chaurasia SS, Lee WS, Tan DT, Mehta JS. Early corneal wound healing and inflammatory responses after refractive lenticule extraction (ReLEx). *Invest Ophthalmol Vis Sci.* (2011) 52:6213–21. doi: 10.1167/iovs.11-7439
43. Cui T, Wang Y, Ji S, Li Y, Hao W, Zou H, et al. Applying machine learning techniques in nomogram prediction and analysis for SMILE treatment. *Am J Ophthalmol.* (2020) 210:71–7. doi: 10.1016/j.ajo.2019.10.015
44. Redd TK, Campbell JP, Chiang MF. Artificial intelligence for refractive surgery screening: finding the balance between myopia and hype-ropia. *JAMA Ophthalmol.* (2020) 138:526–7. doi: 10.1001/jamaophthalmol.2020.0515
45. Guell JL, Morral M, Kook D, Kohnen T. Phakic intraocular lenses part 1: historical overview, current models, selection criteria, and surgical techniques. *J Cataract Refract Surg.* (2010) 36:1976–93. doi: 10.1016/j.jcrs.2010.08.014
46. Bradley DV, Fernandes A, Lynn M, Tigges M, Boothe RG. Emmetropization in the rhesus monkey (Macaca mulatta): birth to young adulthood. *Invest Ophthalmol Vis Sci.* (1999) 40:214–29.
47. Rucker FJ, Wallman J. Chick eyes compensate for chromatic simulations of hyperopic and myopic defocus: evidence that the eye uses longitudinal chromatic aberration to guide eye-growth. *Vision Res.* (2009) 49:1775–83. doi: 10.1016/j.visres.2009.04.014
48. Rucker FJ. The role of luminance and chromatic cues in emmetropisation. *Ophthalmic Physiol Opt.* (2013) 33:196–214. doi: 10.1111/opo.12050
49. Wallman J, Turkel J, Trachtman J. Extreme myopia produced by modest change in early visual experience. *Science.* (1978) 201:1249–51. doi: 10.1126/science.694514
50. Kee CS, Marzani D, Wallman J. Differences in time course and visual requirements of ocular responses to lenses and diffusers. *Invest Ophthalmol Vis Sci.* (2001) 42:575–83. Available online at: https://iovs.arvojournals.org/article.aspx?articleid=2123787
51. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron.* (2004) 43:447–68. doi: 10.1016/j.neuron.2004.08.008
52. McBrien N. Role of the sclera in the development and pathological complications of myopia. *Prog Retinal Eye Res.* (2003) 22:307–38. doi: 10.1016/S1350-9462(02)00063-0
53. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res.* (2010) 29:144–68. doi: 10.1016/j.preteyeres.2009.12.002
54. Wu H, Chen W, Zhao F, Zhou Q, Reinach PS, Deng L, et al. Scleral hypoxia is a target for myopia control. *Proc Natl Acad Sci USA.* (2018) 115:E7091–100. doi: 10.1073/pnas.1721443115
55. Zhou X, Ye C, Wang X, Zhou W, Reinach P, Qu J. Choroidal blood perfusion as a potential "rapid predictive index" for myopia development and progression. *Eye Vis (Lond).* (2021) 8:1. doi: 10.1186/s40662-020-00224-0
56. Upadhyay A, Beuerman RW. Biological mechanisms of atropine control of myopia. *Eye Contact Lens.* (2020) 46:129–35. doi: 10.1097/ICL.0000000000000677
57. Cristaldi M, Olivieri M, Pezzino S, Spampinato G, Lupo G, Anfuso CD, et al. Atropine differentially modulates ECM production by ocular fibroblasts, and its ocular surface toxicity is blunted by colostrum. *Biomedicines.* (2020) 8:78. doi: 10.3390/biomedicines8040078
58. Millodot M. Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt.* (1981) 58:691–5. doi: 10.1097/00006324-198109000-00001
59. Smith EL, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* (2009) 49:2386–92. doi: 10.1016/j.visres.2009.07.011
60. Sankaridurg P, Donovan L, Varnas S, Ho A, Chen X, Martinez A, et al. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci.* (2010) 87:631–41. doi: 10.1097/OPX.0b013e3181ea19c7

61. Swarbrick HA, Alharbi A, Watt K, Lum E, Kang P. Myopia control during orthokeratology lens wear in children using a novel study design. *Ophthalmology.* (2015) 122:620–30. doi: 10.1016/j.ophtha.2014.09.028
62. Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci.* (2003) 44:1492–500. doi: 10.1167/iovs.02-0816
63. Shamir RR, Friedman YG, Joskowicz L, Mimouni M, Blumenthal EZ. The influence of varying the number of characters per row on the accuracy and reproducibility of the ETDRS visual acuity chart. *Graefes Arch Clin Exp Ophthalmol.* (2016) 254:971–6. doi: 10.1007/s00417-015-3252-3
64. LN T. Wavefront data reporting and terminology. *J Refractive Surg.* (2001) 17:S578–83. doi: 10.3928/1081-597X-20010901-14
65. Pang Y, Allen M, Robinson J, Frantz KA. Contrast sensitivity of amblyopic eyes in children with myopic anisometropia. *Clin Exp Optom.* (2019) 102:57–62. doi: 10.1111/cxo.12817
66. Stoimenova BD. The effect of myopia on contrast thresholds. *Invest Ophthalmol Vis Sci.* (2007) 48:2371–4. doi: 10.1167/iovs.05-1377
67. Liou SW, Chiu CJ. Myopia and contrast sensitivity function. *Curr Eye Res.* (2001) 22:81–4. doi: 10.1076/ceyr.22.2.81.5530
68. Kim MJ, Park KH, Kim CY, Jeoung JW, Kim SH. The distribution of intraocular pressure and associated systemic factors in a Korean population: the Korea National Health and Nutrition Examination Survey. *Acta Ophthalmol.* (2014) 92:e507–13. doi: 10.1111/aos.12327
69. Mitchell P, Hourihan F, Sandbach J, Jin Wang J. The relationship between glaucoma and myopia. *Ophthalmology.* (1999) 106:2010–5. doi: 10.1016/S0161-6420(99)90416-5
70. Shim SH, Sung KR, Kim JM, Kim HT, Jeong J, Kim CY, et al. The prevalence of open-angle glaucoma by age in myopia: The Korea national health and nutrition examination survey. *Curr Eye Res.* (2017) 42:65–71. doi: 10.3109/02713683.2016.1151053
71. Ha A, Kim CY, Shim SR, Chang IB, Kim YK. Degree of myopia and glaucoma risk: a dose-response meta-analysis. *Am J Ophthalmol.* (2021) 236:107–19. doi: 10.1016/j.ajo.2021.10.007
72. Park HY, Lee K, Park CK. Optic disc torsion direction predicts the location of glaucomatous damage in normal-tension glaucoma patients with myopia. *Ophthalmology.* (2012) 119:1844–51. doi: 10.1016/j.ophtha.2012.03.006
73. Samarawickrama C, Mitchell P, Tong L, Gazzard G, Lim L, Wong TY, et al. Myopia-related optic disc and retinal changes in adolescent children from singapore. *Ophthalmology.* (2011) 118:2050–7. doi: 10.1016/j.ophtha.2011.02.040
74. Biswas S, Jhanji V, Leung CK. Prevalence of glaucoma in myopic corneal refractive surgery candidates in Hong Kong China. *J Refract Surg.* (2016) 2016:32298–304. doi: 10.3928/1081597X-20160229-01
75. Chang L, Pan CW, Ohno-Matsui K, Lin X, Cheung GC, Gazzard G, et al. Myopia-related fundus changes in Singapore adults with high myopia. *Am J Ophthalmol.* (2013) 155:991–9.e1. doi: 10.1016/j.ajo.2013.01.016
76. Biswas S, Lin C, Leung CK. Evaluation of a myopic normative database for analysis of retinal nerve fiber layer thickness. *JAMA Ophthalmol.* (2016) 134:1032–9. doi: 10.1001/jamaophthalmol.2016.2343
77. Tan NYQ, Sng CCA, Jonas JB, Wong TY, Jansonius NM, Ang M. Glaucoma in myopia: diagnostic dilemmas. *Br J Ophthalmol.* (2019) 103:1347–55. doi: 10.1136/bjophthalmol-2018-313530
78. Wong YL, Sabanayagam C, Ding Y, Wong CW, Yeo AC, Cheung YB, et al. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. *Invest Ophthalmol Vis Sci.* (2018) 59:4603–13. doi: 10.1167/iovs.18-24032
79. Ohno-Matsui K, Yoshida T, Futagami S, Yasuzumi K, Shimada N, Kojima A, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. *Br J Ophthalmol.* (2003) 87:570–3. doi: 10.1136/bjo.87.5.570
80. Yokoi T, Jonas JB, Shimada N, Nagaoka N, Moriyama M, Yoshida T, et al. Peripapillary diffuse chorioretinal atrophy in children as a sign of eventual pathologic myopia in adults. *Ophthalmology.* (2016) 123:1783–7. doi: 10.1016/j.ophtha.2016.04.029
81. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. *Am J Ophthalmol.* (1971) 71:42–53. doi: 10.1016/0002-9394(71)91092-0
82. Grossniklaus HE, Green WR. Pathologic findings in pathologic myopia. *Retina.* (1992) 12:127–33. doi: 10.1097/00006982-199212020-00009
83. Ohno-Matsui K, Kawasaki R, Jonas JB, Cheung CM, Saw SM, Verhoeven VJ, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol.* (2015) 159:877–83.e7. doi: 10.1016/j.ajo.2015.01.022
84. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol.* (2014) 157:9–25.e12. doi: 10.1016/j.ajo.2013.08.010
85. Hayashi K, Ohno-Matsui K, Teramukai S, Shimada N, Moriyama M, Hayashi W, et al. Comparison of visual outcome and regression pattern of myopic choroidal neovascularization after intravitreal bevacizumab or after photodynamic therapy. *Am J Ophthalmol.* (2009) 148:396–408. doi: 10.1016/j.ajo.2009.03.026
86. Parodi MB, Da Pozzo S, Ravalico G. Angiographic features after photodynamic therapy for choroidal neovascularisation in age related macular degeneration and pathological myopia. *Br J Ophthalmol.* (2003) 87:177–83. doi: 10.1136/bjo.87.2.177
87. Cohen SY. Anti-VEGF drugs as the 2009 first-line therapy for choroidal neovascularization in pathologic myopia. *Retina.* (2009) 29:1062–6. doi: 10.1097/IAE.0b013e3181b1bb1a
88. Ikuno Y, Ohno-Matsui K, Wong TY, Korobelnik JF, Vitti R, Li T, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: the MYRROR study. *Ophthalmology.* (2015) 122:1220–7. doi: 10.1016/j.ophtha.2015.01.025
89. Hamilton RD, Clemens A, Minnella AM, Lai TYY, Dai H, Sakamoto T, et al. Real-world effectiveness and safety of ranibizumab for the treatment of myopic choroidal neovascularization: Results from the LUMINOUS study. *PLoS ONE.* (2020) 15:e0227557. doi: 10.1371/journal.pone.0227557
90. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature.* (1977) 266:66–8. doi: 10.1038/266066a0
91. Taboada J, Archibald CJ. An extreme sensitivity in the corneal epithelium to far UV-ArF excimer laser pulses. In: *Proceedings of the Aerospace Medical Association, 52 Annual Meeting.* Washington, DC (1981).
92. McDonald MB, Kaufman HE, Frantz JM, Shofner S, Salmeron B, Klyce SD. Excimer laser ablation in a human eye. Case report. *Arch Ophthalmol.* (1989) 107:641–2. doi: 10.1001/archopht.1989.01070010659013
93. Pallikaris IG, Papatzanaki ME, Stathi EZ, Frenschock O, Georgiadis A. Laser *in situ* keratomileusis. *Lasers Surg Med.* (1990) 10:463–8. doi: 10.1002/lsm.1900100511
94. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res.* (1995) 35:1175–94. doi: 10.1016/0042-6989(94)00233-C
95. Zhang Y, Azmoun S, Hang A, Zeng J, Eng E, Wildsoet CF. Retinal defocus and form-deprivation induced regional differential gene expression of bone morphogenetic proteins in chick retinal pigment epithelium. *J Comp Neurol.* (2020) 528:2864–73. doi: 10.1002/cne.24957
96. Zhang Y, Phan E, Wildsoet CF. Retinal defocus and form-deprivation exposure duration affects RPE BMP gene expression. *Sci Rep.* (2019) 14:7332. doi: 10.1038/s41598-019-43574-z
97. Wu W, Wang Y. Corneal higher-order aberrations of the anterior surface, posterior surface, and total cornea after SMILE. FS-LASIK, and FLEx surgeries. *Eye Contact Lens.* (2016) 42:358–65. doi: 10.1097/ICL.0000000000000225
98. Zhao X, Zhang L, Ma J, Li M, Zhang J, Zhao X, et al. Comparison of wavefront-guided femtosecond LASIK and optimized SMILE for correction of moderate-to-high astigmatism. *J Refract Surg.* (2021) 37:166–73. doi: 10.3928/1081597X-20201230-01
99. Ang M, Gatinel D, Reinstein DZ, Mertens E, Alio Del Barrio JL, Alio JL. Refractive surgery beyond 2020. *Eye (Lond).* (2021) 35:362–82. doi: 10.1038/s41433-020-1096-5
100. Heradio R, Fernandez-Amoros D, Cerrada C, Cobo MJ. Group decision-making based on artificial intelligence: a bibliometric analysis. *Mathematics.* (2020) 8:1566. doi: 10.3390/math8091566
101. Cao K, Wan Y, Yusufu M, Wang N. Significance of outdoor time for myopia prevention: a systematic review and meta-analysis based on randomized controlled trials. *Ophthalmic Res.* (2020) 63:97–105. doi: 10.1159/000501937

102. Ashby R, Ohlendorf A, Schaeffel F. The effect of ambient illuminance on the development of deprivation myopia in chicks. *Invest Ophthalmol Vis Sci.* (2009) 50:5348–54. doi: 10.1167/iovs.09-3419
103. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res.* (1988) 28:639–57. doi: 10.1016/0042-6989(88)90113-7
104. Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops. *Ophthalmology.* (2016) 123:391–9. doi: 10.1016/j.ophtha.2015.07.004
105. Nickla DL, Zhu X, Wallman J. Effects of muscarinic agents on chick choroids in intact eyes and eyecups: evidence for a muscarinic mechanism in choroidal thinning. *Ophthalmic Physiol Opt.* (2013) 33:245–56. doi: 10.1111/opo.12054
106. Lind GJ, Chew SJ, Marzani D, Wallman J. Muscarinic acetylcholine receptor antagonists inhibit chick scleral chondrocytes. *Invest Ophthalmol Vis Sci.* (1998) 39:2217–31.
107. Dotan A, Kremer I, Gal-Or O, Livnat T, Zigler A, Bourla D, et al. Scleral cross-linking using riboflavin and ultraviolet-a radiation for prevention of axial myopia in a rabbit model. *J Vis Exp.* (2016) 3:e53201. doi: 10.3791/53201
108. Choi JA, Han K, Park YM, Park CK. Age-related association of refractive error with intraocular pressure in the Korea National Health and Nutrition Examination Survey. *PLoS ONE.* (2014) 9:e111879. doi: 10.1371/journal.pone.0111879
109. Yeung AWK. Comparison between Scopus, Web of Science, PubMed and publishers for mislabelled review papers. *Curr Sci.* (2019) 116:1909–14. doi: 10.18520/cs/v116/i11/1909-1914

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Longitudinal Changes in Refractive Error Among Preschool Children Aged 1–6 Years: The Changsha Children Eye Study

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Purpose: To investigate the longitudinal changes in refractive error of preschool children and explore the factors related to these changes and the timing of intervention.

Methods: The refractive data of preschool children aged 1–6 years were collected from 16 community Health Service Centers in Changsha during April 2016 to July 2019 for the retrospective cohort study. The refractive data of each participant was measured with a hand-held vision screener without cycloplegia. A follow-up for all the included participants was performed. The spherical equivalent change was calculated, subsequently, an analysis of risk factors related to the change was performed.

Results: Four thousand nine hundred twenty-one cases were included in the study with the follow-up for 1–2 years. The refractive status was found smoothly changed in 67.8% of children. The overall initial SE was 0.62 ± 1.13 D, and the average SE change was −0.20 ± 1.23 D per year. However, profound myopic shift was observed in 32.2% of children. The change of SE in 3-year-old group is most overt. The proportions of 1–6 years old who showed moderate and severe myopic shift (SE change ≥–1.00 D) were 21.6, 18.9, 28.2, 25.5, 13.4, and 10%, respectively. At the first visit, the younger children with greater hyperopic state exhibited more noticeable myopic shift, no significant difference was found in gender.

Conclusion: The shift from hyperopia to myopia in preschool children is smooth, with −0.20D change on average per year. We suggest that an optometry screening should start at 3-year-old to track children's refractive status. We recommend that preschool children whose SE changes more than −1.00 D per year go to the ophthalmology department for further examination. Our study also found that at the first visit, the younger the child is and the more positive initial SE is, the degree of shift of myopia is greater.

Keywords: refractive error, preschool myopia, myopia, risk factors, retrospective cohort studies

INTRODUCTION

Myopia is an underrated but profound public health problem, which brings enormous potential economic impact (1). In 2015, uncorrected refractive errors were estimated to be the leading cause of moderate or severe visual impairment, affecting over 116 million people (2), and the global economic burden associated with uncorrected myopia was estimated to be 244 billion U.S. dollars (3). Furthermore, it is estimated that nearly half of the worldwide population will be myopic, including 10% high myopia by 2050 (4).

Among some of young adults in Asia, the prevalence of high myopia is 38% (5). At present, the prevalence of myopia in China remains high, with 60% in 12-year-old primary school graduates, around 80% in 16-year-old high school students, and more than 90% in college students (6–8). Myopia has brought a substantial economic burden to China. Reference to the direct cost of myopia in Singapore children is US$148 per child per year (9).

Myopia mainly occurs in school-age children over 6 years old (10), and the prevalence of it under 6 years old, which is called preschool myopia, is relatively low (11–14). However, in preschool myopia, the risk of developing into high myopia and secondary related irreversible blinding complications are higher (15, 16). Since myopia is irreversible once it occurs, we should move the prevention of myopia ahead of time and pay attention to the refractive status and its' change of preschool children to better control the progress myopia.

Although the government and the general public are paying more attention to myopia, the ophthalmologists and optometry are too few to provide the professional ophthalmic care to all patients with myopia. Nowadays, community health service centers undertake most of primary eye care services, for instance vision screening for preschool children aged 1–6 years. To check the refraction status of children, the general practitioners in community health service centers usually use a hand-held vision screening equipment which is portable, convenient, easy to use, quick in inspection, and the results are intuitive and easy to interpret. For optical status inspection, many studies have also confirmed that the test results are highly consistent with the previous retinoscopy and computer refractor (17).

For vision screening, cycloplegia is not routinely applied, unless a child is known to have abnormal refractive error. Except for children with abnormal vision acuity, preschool children with what kind of refractive state should go to the ophthalmology department for further dilated refraction? There is no definite conclusion yet. Until now, there are few cohort studies on the refractive status of preschool children, especially the lack of extensive sample studies on the refractive status of children before 3 years old. Therefore, in cooperation with the community health center in Changsha, we conducted a retrospective cohort study about the changes in the refractive status of preschool children aged 1–6 years and explored the factors related to these changes and the timing of intervention.

SUBJECTS AND METHODS

Research Object

The Changsha Children Eye Study (CCES) is a population-based study of Chinese children to estimate the prevalence and risk factors for refractive errors and ocular diseases. This study was approved by the ethics committee of Beijing Aier Intech Eye Hospital and performed from April 2016 to July 2019 among children aged 1–6 years from 16 communities in Changsha, China. The data were obtained through the Mulin telemedicine platform (Hunan Super Vision Technology Co., Ltd.).

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Preschool children aged 1–6 years. According to the child's date of birth, children under 6 years old were included in this study on the examination day. Six groups were generated by age: 1-year-old group (child with age ≤1-year-old on the examination day), 2-year-old group (1 year < age on the examination day ≤2 years), 3-year-old group (2 years < age on the examination day ≤3 years), 4-year-old group (3 years < age on the examination day ≤4 years), 5-year-old group (4 years < age on the examination day ≤5 years), 6-year-old group (5 years < age on the examination day ≤6 years).

Exclusion criteria: (1) Children with systemic cardiovascular diseases, such as congenital heart disease. (2) Children with eye trauma or eye diseases, such as congenital glaucoma, congenital cataract, strabismus. (3) Children with incomplete electronic medical records.

Examination Method

All children who came to the community for child health checkups were invited to participate in vision screening. After the consent of participating the study were obtained from children's parents or their legal guardians. The community doctors who were trained in standardized procedures would ask about the history of childhood systemic diseases and eye diseases and exclude children with systemic diseases and congenital eye diseases such as glaucoma and cataracts. The cover-uncover test was performed to exclude children with strabismus.

A handheld child vision screener Suowei (Tianjin Suowei Electronic Technology Co., Ltd.), was used to screen children's binocular refractive condition. The vision screener was calibrated daily before the testing. Children underwent routinely examinations without cycloplegia in a dark room by a general practitioner. Before the study, all the general practitioners were trained by ophthalmologists in terms of conducting standard eye examination and using the handheld child vision screener. The binocular spherical, astigmatism, astigmatism axis, pupil size, pupilary distance, and fixation direction were obtained, recorded, and uploaded on the Mulin telemedicine platform.

Diagnostic Criteria

Spherical equivalent (SE) is calculated by the sphere plus half of astigmatism. The main result of this study is the change of SE, which is the difference between the final SE and the initial SE to represent the change in the refractive error of each child. It is defined that the change of SE(ΔSE) exceeds 0.50 D (Diopter, D) as the shift of myopia. In our study, four criteria (≤−0.5D,

≥0.50 D, ≥−1.00 D, ≥−2.00 D) was used to classify the degree of shift of myopia (no change, mild shift of myopia, moderate shift of myopia, and severe shift of myopia).

Statistical Analysis

Statistical analysis was performed using SPSS software (IBM-SPSS, V 20.0). In addition to general descriptive statistics, paired T-test, one-way ANOVA, and logistics regression were used to analyze data. $P < 0.05$ is considered statistically significant.

RESULTS

Characteristics of Data

This study included 4,921 preschool children aged 1–6 who completed 1–2 years of follow-up in 16 community health service centers in Changsha from April 9, 2016, to July 30, 2019, of which 2,571 (52.25%) were in 1-year-old group, 392 cases (7.97%) were in 2-year-old group, 756 cases (15.36%) were in 3-year-old group, 916 cases (18.61%) were in 4-year-old group, 276 (5.61%) cases were in 5-year-old group , and 10 cases (0.20%) were in 6-year-old.

Initial Refractive Error

The average SE of 1–6 years old preschool children is 0.62 ± 1.13 D for the right eye and 0.71 ± 1.18 D for the left eye; the average astigmatism of the right eye is −0.94 ± 0.75 D, and the left eye is −0.95 ± 0.75 D (**Table 1**). Among the groups, with the increasing of age, the SE decreased and slightly shifted to myopia (**Figure 1**); astigmatism decreased from 1 to 5 years old, among which astigmatism decreased significantly at 1–2 years old and then stayed relatively stable (**Figure 2**).

Follow-Up Refractive Error

After 1–2 years of follow-up, the average SE of preschool children aged 1–6 years is 0.43 ± 0.93 D for the right eye and 0.47 ± 0.96 D for the left eye; the average astigmatism of the right eye is −0.72 ± 0.62 D, and the left eye is −0.71 ± 0.63 D (**Table 2**). Similarly, with the increasing of age, the average SE decreased and shifted toward myopia among age groups (**Figure 1**). Whereas, astigmatism was approximately stable among all age groups (**Figure 2**).

Changes in Refractive Error

To calculate the changes of refractive errors, ΔSE and ΔDC was calculated by subtracting the initial SE and initial astigmatism by mean SE and mean astigmatism measured at the end-point of follow-up, respectively. The average ΔSE of preschool children aged 1–6 years are −0.20 ± 1.23 D (right eye) and −0.24 ± 1.26 D (left eye); the average ΔDC of preschool children aged 1–6 years are: 0.22 ± 0.73 D (right eye) and 0.23 ± 0.72 D (left eye) (**Table 3**). Compared with mean value of initial SE and astigmatism, both of mean SE and mean astigmatism measured at the end-point of follow-up decreased. with the most obvious decrease (−0.38 ± 1.22 for right eye, −0.37 ± 1.24 for left eye) found in 3-year-old group. Astigmatism changes more obviously in the 1-year-old group (0.35 ± 0.81 for right eye, 0.37 ± 0.80 for left eye), and changes slightly in other age groups (**Figures 1**, **2**).

There was no statistically significant difference in the change of binocular SE ($t = 2.454$, $P = 0.117$); the change of binocular astigmatism was not statistically significant ($t = 3.113$, $P = 0.078$).

For the degree of shift of myopia, generally 67.8% (3335/4921) of preschool children present SE change ≤ −0.5 D, 32.2% (1586/4921) of children exhibit variable degrees of myopic drift. Similar tendency was found in all age groups (**Figure 3**). Notably, in 3-year-old group, 18.4% children were found with sever shift of myopia, which is distinctly higher than others (**Table 4**).

Analysis of Factors Related to Changes in Refractive Error

Logistic regression was used to analyze the factors related to the change of SE. After the statistical test, $\chi^2 = 13.951$, $P = 0.003$, and the logistic regression model are significant.

The change of the SE exceeds −2.00 D, that is, the shift of myopia exceeds 2.00 D in 684 cases, which are related to age and the initial SE ($P = 0.000$; $P = 0.000$), not related to gender and initial astigmatism ($P = 0.508$; $P = 0.429$). The change of the SE exceeds −1.00 D in 1,114 cases, which are related to age and the initial SE ($P = 0.000$; $P = 0.000$) but are not related to gender and initial astigmatism ($P = 0.139$; $P = 0.775$). The change of the SE exceeded −0.50 D in 1,586 cases, which were related to gender, initial SE, and initial astigmatism ($P = 0.021$; $P = 0.000$; $P = 0.000$), Not related to age ($P = 0.094$) (**Table 5**).

TABLE 1 | The initial refractive error of preschool children aged from 1 to 6-year-old.

Age	Number	Right eye		Left eye	
(years)		SE	DC	SE	DC
1	2,571	0.65 ± 1.25	−1.13 ± 0.80	0.74 ± 1.27	−1.13 ± 0.80
2	392	0.60 ± 1.07	−0.81 ± 0.70	0.67 ± 1.14	−0.85 ± 0.70
3	756	0.70 ± 1.04	−0.73 ± 0.59	0.80 ± 1.10	−0.74 ± 0.58
4	916	0.59 ± 0.99	−0.74 ± 0.64	0.68 ± 1.06	−0.73 ± 0.63
5	276	0.26 ± 0.75	−0.59 ± 0.53	0.44 ± 0.98	−0.68 ± 0.57
6	10	−0.31 ± 0.34	−0.77 ± 0.73	−0.28 ± 0.34	−0.95 ± 0.48
Total	4,921	0.62 ± 1.13	−0.94 ± 0.75	0.71 ± 1.18	−0.95 ± 0.75

SE, spherical equivalent; DC, cylinder degree.

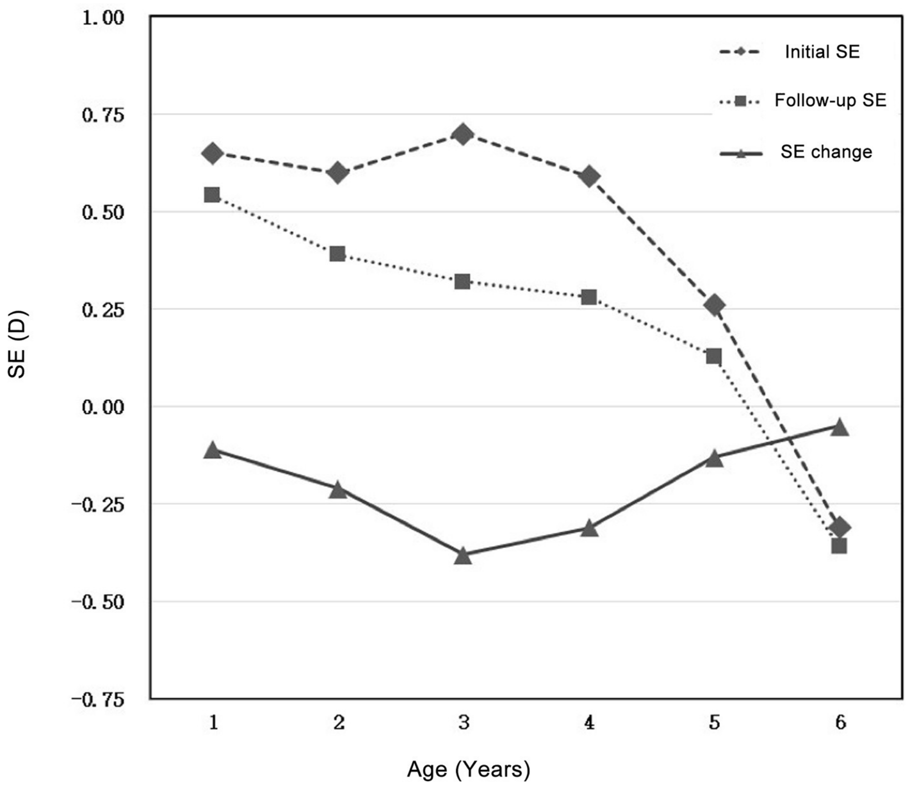

FIGURE 1 | Initial SE, follow-up SE, and SE change for preschool children aged 1–6 years.

DISCUSSION

Most infants are with hyperopia. As they grow up, the degree of hyperopia graudually declines until emmetropization completes or even develops into myopia (18–20). The refractive error of preschool children has been reported by different studies (21–24), but the sample numbers are relatively small, and most of them are cross-sectional studies. In this study, we carried out a retrospective cohort study about the longitudinal changes of 4,921 preschool children aged 1–6 years from the Changsha Community Health Service Center. All the participants were followed up for 1–2 years to analyze the changes of refractive status. Correlation of related factors which may contribute to the changes were analyzed.

The initial mean SE of all participants was 0.62 ± 1.13 D (right eye), after 1–2 years of follow-up, the value decreased by 0.20 ± 1.23 D (right eye), indicating a tendency of emmetropization. For majority of children in different age groups, the degree of change was slight ($\Delta SE \leq 0.5D$) with minor changes in astigmatism. The initial average astigmatism of right eye of all participants was −0.94 ± 0.75 D, after 1–2 years it dropped by 0.22 ± 0.73 D. In general, astigmatism shows a downward trend with the increasing age, and the 1-year-old group presents the most apparent decline.

Different cohort studies (21, 25, 26) reported that the degree of shift of myopia per year of school-age children was 0.39–0.68 D. In this study, preschool children's shift of myopia is 0.20 D in 1–2 years, which is lower than the research (5) (0.59 D) in Guangzhou. Most school-age children have myopia progression after myopia develops, while for preschool children, shift of myopia is the process of emmetropia. Our previous cross-sectional study found that the prevalence of myopia in preschool children decreases with age (unpublished). With age, the distribution of refractive status appears to be more concentrated toward the average. Therefore, when calculating the average change in SE of all preschool children, this offset from myopia to the emmetropia makes the average SE change smaller than the school-age myopia progression.

Many studies of school-age children (5, 27, 28) found that gender is a risk factor for myopia. The Beijing Children's Eye Disease Study (29) also showed that females and older age are high-risk factors for myopia. Shandong Children's Eye Disease Study (7), which includes mainly school-age children and some pre-school children, also found that females and older age are risk factors for myopia. Our study found that myopia drift is not related to gender. We presume that school-age girls spend more time studying and have fewer outdoor activities than boys, but the two behaviors are not significantly different at the preschool age.

However, some cohort studies (30, 31) showed that the younger the age at the first follow-up is, and the more negative

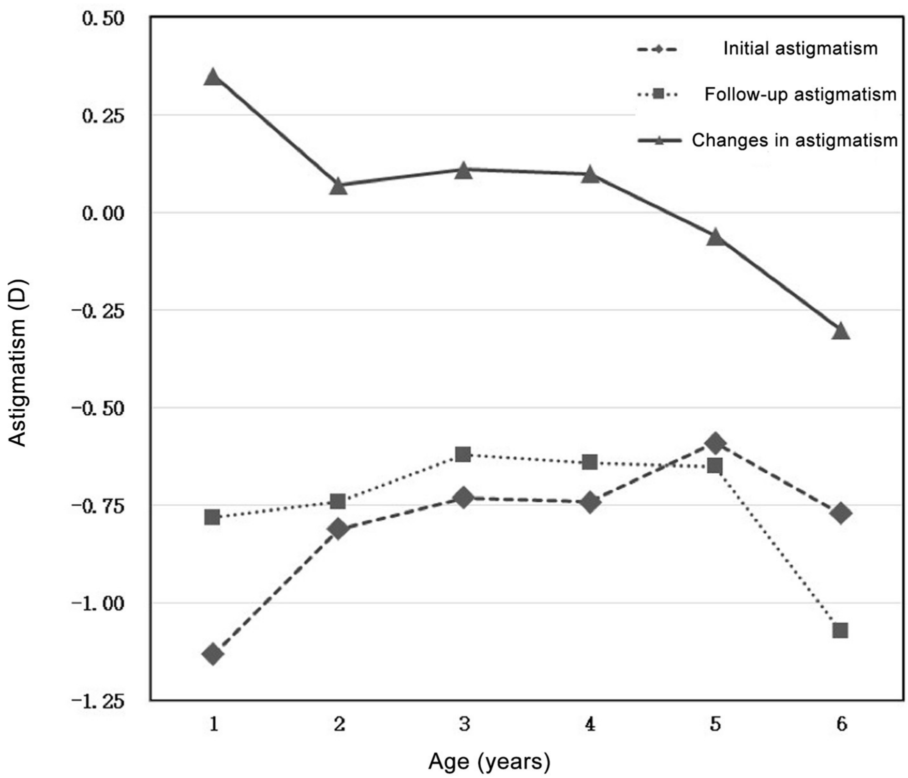

FIGURE 2 | Initial astigmatism, follow-up astigmatism, and changes in astigmatism in preschool children aged 1–6 years.

TABLE 2 | Follow-up refractive error of preschool children aged from 1 to 6-year-old.

Age (years)	Number	Right eye		Left eye	
		SE	DC	SE	DC
1	2,571	0.54 ± 1.01	−0.78 ± 0.63	0.58 ± 1.01	−0.76 ± 0.64
2	392	0.39 ± 0.88	−0.74 ± 0.67	0.36 ± 0.91	−0.73 ± 0.68
3	756	0.32 ± 0.83	−0.62 ± 0.56	0.42 ± 0.90	−0.62 ± 0.59
4	916	0.28 ± 0.83	−0.64 ± 0.61	0.34 ± 0.90	−0.63 ± 0.61
5	276	0.13 ± 0.53	−0.65 ± 0.61	0.22 ± 0.65	−0.74 ± 0.63
6	10	−0.36 ± 0.62	−1.07 ± 0.80	−0.39 ± 0.65	−1.05 ± 0.86
Total	4,921	0.43 ± 0.93	−0.72 ± 0.62	0.47 ± 0.96	−0.71 ± 0.63

SE, spherical equivalent; DC, cylinder degree.

the SE is, the faster myopia progresses. Our study found that at the first visit, the younger children with greater hyperopic state exhibited more noticeable myopic shift. Our findings are consistent with many reports (25, 32, 33), but the Guangzhou preschool myopia cohort study found that older preschool children and children with lower negative SE at the first visit showed higher myopia progression. It may be considered that the children they enrolled in the group were already myopic at the beginning, which is more similar to the progression of school-age myopia.

In this study, the most apparent change in SE occurred at the age of three, which may be related to the beginning of kindergarten. We recommend that regular optometry examinations should be started at this time. For a child with SE change more than 1.00 D per year, we recommend the child to go to the ophthalmology department for further examination and track the changes in axial length, and if necessary, to determine the refraction degree after cycloplegia.

The limitations of this study are (1) This is a retrospective cohort study, so other related factors such as parents' refractive status, outdoor activities and light intensity, and other lifestyle differences may not be well controlled. (2) Failure to use cycloplegia drugs may result in relative inaccurate refractive

TABLE 3 | Changes in refractive error of preschool children aged from 1 to 6-year-old.

Age (years)	Number	Right eye		Left eye	
		Δ SE	Δ DC	Δ SE	Δ DC
1	2,571	−0.11 ± 1.31	0.35 ± 0.81	−0.16 ± 1.32	0.37 ± 0.80
2	392	−0.21 ± 1.08	0.07 ± 0.70	−0.31 ± 1.10	0.11 ± 0.66
3	756	−0.38 ± 1.22	0.11 ± 0.57	−0.37 ± 1.24	0.12 ± 0.56
4	916	−0.31 ± 1.16	0.10 ± 0.57	−0.34 ± 1.22	0.10 ± 0.54
5	276	−0.13 ± 0.79	−0.06 ± 0.55	−0.22 ± 0.85	−0.05 ± 0.55
6	10	−0.05 ± 0.52	−0.30 ± 0.47	−0.11 ± 0.50	−0.10 ± 0.54
Total	4,921	−0.20 ± 1.23	0.22 ± 0.73	−0.24 ± 1.26	0.23 ± 0.72

Δ SE, the change of spherical equivalent; Δ DC, the change of cylinder degree.

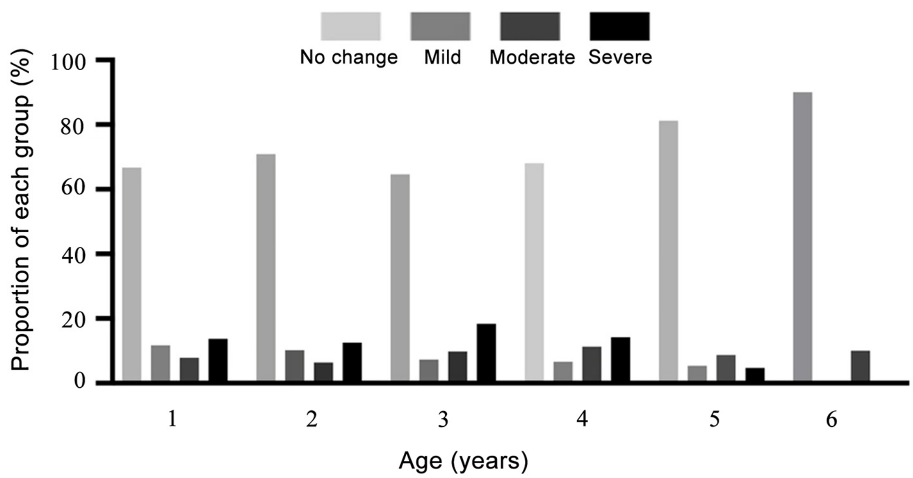

FIGURE 3 | The proportions of each group in myopia progression classification for preschool children aged 1–6 years.

TABLE 4 | Classification of the degree of shift of myopia in preschool children aged from 1 to 6-year-old.

Age (years)	Number	No change	Mild	Moderate	Severe
1	2,571	1,714 (66.7%)	302 (11.7%)	203 (7.9%)	352 (13.7%)
2	392	278 (70.9%)	40 (10.2%)	25 (6.4%)	49 (12.5%)
3	756	488 (64.6%)	55 (7.3%)	74 (9.8%)	139 (18.4%)
4	915	622 (68.0%)	60 (6.6%)	103 (11.3%)	130 (14.2%)
5	276	224 (81.2%)	15 (5.4%)	24 (8.7%)	13 (4.7%)
6	10	9 (90.0%)	0 (0%)	1 (10.0%)	0 (0%)

error. Although our main observation index is the change in SE, there may still be deviations. (3) Although many studies have reported that automated refraction and retinoscopy are highly correlated (34), there are still minor differences. Therefore, there may be a small deviation when we use children's vision screeners to obtain data. (4) The young age group, especially the infants in the 1-year-old group, had poor cooperation which might cause some deviations in corresponding data.

In general, our research studied the changes of refractive status of 4,921 preschool children aged 1–6 years old in 1–2 years, and found that there was a stable shift from hyperopia to myopia, with −0.20D change on average per year. Since the change of SE in 3-year-old group is most overt, we suggest that an optometry screening should start at this age to track children's refractive status. We recommend that preschool children whose SE changes more than −1.00 D per year go to the ophthalmology department for further examination. As age increases, astigmatism also shows

TABLE 5 | Correlation analysis for the risk factors and the change of SE.

Factors	Δ SE		
	> −0.50 D	> −1.00 D	> −2.00 D
Age	0.094	0.000	0.000
Gender	0.021	0.139	0.508
Initial SE	0.000	0.000	0.000
Initial DC	0.000	0.775	0.429

Δ SE, the change of SE.

a downward trend. Our study also found that at the first visit, the younger the child is and the more positive initial SE is, the degree of shift of myopia is greater. The change of SE is not related to gender. More prospective studies need to be carried out, such as changes in ocular biological parameters, to better explain the factors related to changes in preschool refractive status and to better prevent and control myopia in preschool children.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Aier Intech Eye Hospital's Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SW and YY designed the experiment. YY, YS, MX, and HZ performed the experiment. YY wrote the paper. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Modjtahedi BS, Ferris FL, Hunter DG, Fong DS. Public health burden and potential interventions for myopia. *Ophthalmology.* (2018) 125:628–30. doi: 10.1016/j.ophtha.2018.01.033
2. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. (2017) 5:e1221–34. doi: 10.1016/S2214-109X(17)30393-5
3. Naidoo KS, Fricke TR, Frick KD, Jong M, Naduvilath TJ, Resnikoff S, et al. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. *Ophthalmology.* (2019) 126:338–46. doi: 10.1016/j.ophtha.2018.10.029
4. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006
5. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern china. *Invest Ophthalmol Vis Sci.* (2004) 45:793–9. doi: 10.1167/iovs.03-1051
6. Li SM, Liu LR, Li SY, Ji YZ, Fu J, Wang Y, et al. Design, methodology and baseline data of a school-based cohort study in Central China: the anyang childhood eye study. *Ophthalmic Epidemiol.* (2013) 20:348–59. doi: 10.3109/09286586.2013.842596
7. Wu JF, Bi HS, Wang SM, Hu YY, Wu H, Sun W, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The shandong children eye study. *PLoS ONE.* (2013) 8:e82763. doi: 10.1371/journal.pone.0082763
8. Sun J, Zhou J, Zhao P, Lian J, Zhu H, Zhou Y, et al. High prevalence of myopia and high myopia in 5060 Chinese university students in Shanghai. *Invest Ophthalmol Vis Sci*. (2012) 53:7504–9. doi: 10.1167/iovs.11-8343
9. Lim MC, Gazzard G, Sim EL, Tong L, Saw SM. Direct costs of myopia in Singapore. *Eye (Lond).* (2009) 23:1086–9. doi: 10.1038/eye.2008.225
10. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet*. (2012) 379:1739–48. doi: 10.1016/S0140-6736(12)60272-4
11. Guo X, Fu M, Ding X, Morgan IG, Zeng Y, He M. Significant axial elongation with minimal change in refraction in 3- to 6-year-old chinese preschoolers: the shenzhen kindergarten eye study. *Ophthalmology.* (2017) 124:1826–38. doi: 10.1016/j.ophtha.2017.05.030
12. Giordano L, Friedman DS, Repka MX, Katz J, Ibironke J, Hawes P, et al. Prevalence of refractive error among preschool children in an urban population: the baltimore pediatric eye disease study. *Ophthalmology*. (2009) 116:739–46, 746.e1–4. doi: 10.1016/j.ophtha.2008.12.030
13. Multi-ethnic pediatric eye disease study group. Prevalence of myopia and hyperopia in 6- to 72-month-old African American and Hispanic children: the multi-ethnic pediatric eye disease study. *Ophthalmology.* (2010) 117:140–7.e3. doi: 10.1016/j.ophtha.2009.06.009
14. Dirani M, Chan YH, Gazzard G, Hornbeak DM, Leo SW, Selvaraj P, et al. Prevalence of refractive error in Singaporean Chinese children: the strabismus, amblyopia, and refractive error in young Singaporean Children (STARS) study. *Invest Ophthalmol Vis Sci.* (2010) 51:1348–55. doi: 10.1167/iovs.09-3587
15. Jones LA, Mitchell GL, Mutti DO, Hayes JR, Moeschberger ML, Zadnik K. Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci.* (2005) 46:2317–27. doi: 10.1167/iovs.04-0945
16. Cumberland PM, Peckham CS, Rahi JS. Inferring myopia over the lifecourse from uncorrected distance visual acuity in childhood. *Br J Ophthalmol.* (2007) 91:151–3. doi: 10.1136/bjo.2006.102277
17. Wesemann W, Dick B. Accuracy and accommodation capability of a handheld autorefractor. *J Cataract Refract Surg.* (2000) 26:62–70. doi: 10.1016/S0886-3350(99)00325-9
18. Ingram RM, Gill LE, Lambert TW. Emmetropisation in normal and strabismic children and the associated changes of anisometropia. *Strabismus.* (2003) 11:71–84. doi: 10.1076/stra.11.2.71.15104
19. Wood IC, Hodi S, Morgan L. Longitudinal change of refractive error in infants during the first year of life. *Eye*. (1995) 9:551–7. doi: 10.1038/eye.1995.138
20. Ehrlich DL, Braddick OJ, Atkinson J, Anker S, Weeks F, Hartley T, et al. Infant emmetropization: longitudinal changes in refraction components from nine to twenty months of age. *Optom Vis Sci.* (1997) 74:822–43. doi: 10.1097/00006324-199710000-00022
21. Baird PN, Schäche M, Dirani M. The GEnes in Myopia (GEM) study in understanding the aetiology of refractive errors. *Prog Retin Eye Res.* (2010) 29:520–42. doi: 10.1016/j.preteyeres.2010.05.004
22. Ip JM, Saw SM, Rose KA, Morgan IG, Kifley A, Wang JJ, et al. Role of near work in myopia: findings in a sample of Australian school children. *Invest Ophthalmol Vis Sci.* (2008) 49:2903–10. doi: 10.1167/iovs.07-0804
23. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA*. (2015) 314:1142–8. doi: 10.1001/jama.2015.10803
24. Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology.* (2008) 115:1279–85. doi: 10.1016/j.ophtha.2007.12.019

25. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. Factors related to the progression of myopia in Singaporean children. *Optom Vis Sci.* (2000) 77:549–54. doi: 10.1097/00006324-200010000-00009
26. Jones-Jordan LA, Sinnott LT, Cotter SA, Kleinstein RN, Manny RE, Mutti DO, et al. Time outdoors, visual activity, and myopia progression in juvenile-onset myopes. *Invest Ophthalmol Vis Sci.* (2012) 53:7169–75. doi: 10.1167/iovs.11-8336
27. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB. Refractive error study in children: results from Shunyi District, China. *Am J Ophthalmol.* (2000) 129:427–35. doi: 10.1016/S0002-9394(99)00452-3
28. Naidoo KS, Raghunandan A, Mashige KP, Govender P, Holden BA, Pokharel GP, et al. Refractive error and visual impairment in African children in South Africa. *Invest Ophthalmol Vis Sci.* (2003) 44:3764–70. doi: 10.1167/iovs.03-0283
29. You QS, Wu LJ, Duan JL, Luo YX, Liu LJ, Li X, et al. Prevalence of myopia in school children in greater Beijing: the Beijing childhood eye study. *Acta Ophthalmol.* (2014) 92:e398–406. doi: 10.1111/aos.12299
30. Tong L, Saw SM, Carkeet A, Chan WY, Wu HM, Tan D. Prevalence rates and epidemiological risk factors for astigmatism in Singapore school children. *Optom Vis Sci.* (2002) 79:606–13. doi: 10.1097/00006324-200209000-00012
31. Watanabe S, Yamashita T, Ohba N. A longitudinal study of cycloplegic refraction in a cohort of 350 Japanese schoolchildren. Cycloplegic refraction. *Ophthalmic Physiol Opt.* (1999) 19:22–9. doi: 10.1046/j.1475-1313.1999.00406.x
32. Goss DA. Variables related to the rate of childhood myopia progression. *Optom Vis Sci.* (1990) 67:631–6. doi: 10.1097/00006324-199008000-00014
33. Braun CI, Freidlin V, Sperduto RD, Milton RC, Strahlman ER. The progression of myopia in school age children: data from the Columbia medical plan. *Ophthalmic Epidemiol.* (1996) 3:13–21. doi: 10.3109/09286589609071597
34. Lai YH, Hsu HT, Wang HZ, Chang SJ, Wu WC. The visual status of children ages 3 to 6 years in the vision screening program in Taiwan. *J AAPOS.* (2009) 13:58–62. doi: 10.1016/j.jaapos.2008.07.006

Conflict of Interest: YS and MX were employed by the company Hunan Super Vision Technology Co., Ltd.

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Sleep Patterns and Myopia Among School-Aged Children in Singapore

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Purpose: To evaluate the associations of sleep factors with myopia, spherical equivalent (SE), and axial length (AL) in elementary school-aged children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort.

Methods: This cross-sectional study included multi-ethnic children who participated in the GUSTO prospective birth cohort and were delivered in two major tertiary hospitals in Singapore (2009–2010). Sleep factors and myopia outcomes were assessed at the 8- and 9-year study visits, respectively. Parent-reported sleep quality was assessed with the Children's Sleep Habits Questionnaire (CSHQ) total scores. Additionally, each child's sleep duration, timing (bedtime; waketime), and the consistency of sleep duration or timing (i.e., the difference between weekends and weekdays) were parent-reported. Outcomes included cycloplegic SE, myopia (SE ≤ -0.5 D) and AL. Eye measurements from both eyes were included in the analyses. Multivariable linear or logistic regression with Generalized Estimating Equations were used to account for the correlation between paired eyes and confounders in the associations of sleep factors at age 8 and myopia at age 9.

Results: A total of 572 multi-ethnic children (49.5% boys; 56.1% Chinese) aged 9 years were included in the analyses. Overall, 37.3% of eyes were myopic. Children reported a mean total CSHQ score of 46 [standard deviation (SD) = 6]. The mean duration of sleep was 9.2 (SD = 1.0) hours per day (h/day), with 59.9% of children reporting sufficient sleep ($\geq$9 h/day) based on guidelines recommended by the National Sleep Foundation, USA. The mean bedtime and wake time were 22:00 (SD = 00:53) and 07:08 (SD = 00:55), respectively. In multivariable regression models, total CSHQ scores, the duration of sleep, bedtime and wake time were not significantly associated with myopia, SE, or AL ($p \geq 0.05$ for all), adjusting for gender, ethnicity, time outdoors, near-work, parental myopia, maternal education levels (and additionally the child's height when the outcome was AL). Similarly, the consistency of both the duration and timing of sleep (across weekends and weekdays) were not significantly associated with myopia, SE, or AL ($p \geq 0.05$ for all).

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Conclusion: In this cross-sectional study, sleep quality, duration, timing, and the consistency of specific sleep factors were not independently associated with myopia, SE, or AL among elementary school-aged children in Singapore. Large longitudinal studies are warranted to corroborate these results.

Keywords: myopia, sleep, refractive error, axial length, children

INTRODUCTION

Myopia has reached epidemic levels in urban East Asia and Singapore, affecting up to 80–90% of young adults (1, 2). The onset of myopia in childhood increases the risks of high myopia (3), and consequently, myopic macular degeneration (4), cataracts and glaucoma (5) in adulthood. Genetic factors and environmental factors [notably increased education (6) and decreased time outdoors (7–10)] are associated with myopia onset, and myopic children are more likely to engage in near work (11). However, these factors only partially accounted for the risk of myopia (12, 13), and other environmental factors may be involved (14).

The sleep-wake cycle is closely related to the circadian system (15). A recent meta-analysis of genome-wide association studies has linked genetic factors regulating circadian rhythms to refractive error development (16). While sleep patterns in children are closely linked to lifestyle behavioral factors (17), sleep disruptions may also result from (18) or result in (19) perturbations to circadian rhythms. Thus, the evaluation of sleep factors may offer insights into potential circadian effects on myopia. Several cross-sectional and prospective studies have evaluated the association between sleep and myopia, but the findings are mixed. In cross-sectional studies, although a lower quality of sleep (20), shorter (21, 22) or longer (23) duration of sleep, and later bedtime (24) were associated with higher odds of myopia in some studies, null associations were reported in other studies with regards to the quality (25) or duration (20, 24, 26) of sleep and, bedtime (26). Importantly, only a few studies have been conducted with cycloplegic refraction data (20, 21, 25). Two prospective studies with cycloplegic data reported mixed findings between a limited set of sleep factors (duration of sleep or bedtime) and myopia (27, 28). In the study by Wei et al., neither duration of sleep nor bedtime was associated with 4-year incidence of myopia ($p \geq 0.05$ for all) among 1,887 Chinese children aged 5–9 years at baseline (27). Conversely, in another study by Liu et al., late bedtime, but not the duration of sleep ($p \geq 0.05$), was associated with 2-year myopia incidence {odds ratio (OR) = 1.45, 95% confidence interval (CI) [1.05, 2.00], $p = 0.02$} in 4,982 Chinese children aged 6–9 years (at baseline) participating in a school-based outdoor trial (28). Moreover, there is a lack of evidence on the effects of the quality (20, 25) or consistency of sleep [linked to sleep problems (29) or circadian phase shifts (30)] on myopia. Overall, given the scarcity of studies with cycloplegic refraction data and the limited range of sleep factors studied, associations between sleep factors and myopia remain poorly understood.

We aim to evaluate the associations of sleep factors (quality, duration, timing, and consistency) with myopia in school-aged children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort.

METHODS

Study Population

The Singapore GUSTO birth cohort recruited pregnant mothers and babies born to these mothers from two major public maternity hospitals in Singapore (National University Hospital and KK Women's and Children's Hospital) between 2009 and 2010 (31). The children in the GUSTO birth cohort were followed up prospectively to assess multiple childhood outcomes at various study visits. Data for this study was derived from children who attended both the 8-year study visit (point of sleep exposure assessments) and the 9-year study visit (point of ocular outcomes assessments as part of the GUSTO myopia study). Of the 1,176 children at birth, 716 (61%) returned at the 9-year GUSTO myopia study visit for ocular examinations. Of these 716 children, 709 who were not on myopia control treatment were eligible. Among those eligible, 572 children with both cycloplegic refraction outcomes and sleep exposure data were included in the final analyses [137 children without available cycloplegic refraction data ($n = 82$) or CSHQ questionnaires ($n = 55$) were excluded]. The majority of children in Singapore (over 90%) (32) attend compulsory education in government elementary schools, which have similar start times (around 7:30 a.m.) (33). Parents and children provided written consent and assent before participation. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (D/2009/021), the Singhealth Centralized Institutional Review Board (2018/2767) and both Review Boards (2018/2270; R1517/16/2018), respectively. The conduct of this study adhered to the tenets of the Declaration of Helsinki.

Sleep Factors (Exposures)

The Children's Sleep Habits Questionnaire (CSHQ) (parent-reported) was administered for the first time at the 8-year visit in the GUSTO birth cohort. The CSHQ has been widely used to assess sleep patterns and to screen for sleep problems in children aged 4–10 years across various ethnic groups (34–36). Validation studies for the CSHQ have been conducted in community samples across multiple countries [including the United States of America (34, 37), China (38), Portugal (39), Germany (40), and Italy (41)], with adequate full-scale internal consistency (given by Cronbach's alpha) ranging between 0.68 and 0.82. The quality of sleep was assessed by the total CSHQ score, calculated from the sum of 8 CSHQ subscales encompassing the major presenting sleep complaints in children (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness). A higher total CSHQ score indicates a lower quality of sleep (or more sleep problems).

In addition to the CSHQ questionnaire, parents also responded to additional questions on other sleep factors including the duration [duration of sleep, duration in bed (night only, naps only, or total combining the sum of night and naps)], timing (bedtime, wake time), and consistency of sleep. Parents reported the duration of sleep based on the following question: "In the past week or most recent typical week, what is the child's usual amount of sleep each day combining nighttime sleep and naps?". Duration in bed during the night (or during naps) was calculated as the interval between the child's bedtime and wake time in the morning (or between usual naptime and time of the day when the child wakes after the nap). All parents completed the electronic questionnaires in quiet and private settings. The daily duration of sleep, hours per day (h/day), or the duration spent in bed (h/day) across all days of the week were computed as follows: $5/7 \times$ daily hours on weekdays (h/day) $+ 2/7 \times$ daily hours on weekends (h/day). Similar calculations were performed in the computation of daily bedtime and wake time (clock hours) across all days of the week. The consistency of the duration and timing of each sleep factor was computed as the difference in reported values between weekends [Saturday and Sunday (WE)] and weekdays [Monday to Friday (WD)] for each child [i.e., WE-WD; (42)].

Ocular Examination (Outcomes)

Cycloplegic spherical equivalent (SE) and AL were assessed using autorefractors (Canon RK-5/RK-F2, Canon; Japan) and optical biometers (IOL Master 500, Carl Zeiss-Meditec; Germany), respectively, at the 9-year visit. Cycloplegia was induced using 3 drops of 1% cyclopentolate hydrochloride, instilled 5 minutes apart. Autorefraction was performed at least 30 min after the first drop, with pupil dilation of $\geq$6 mm. SE was calculated as the sphere power plus half of the cylinder power. The main refractive error outcomes were myopia, SE, and AL. In the current study, myopia was defined as SE ≤ -0.5 D. Emmetropia was defined as SE > -0.5 D to SE < 2.0 D, hyperopia was defined as SE ≥ 2.0 D, and astigmatism was defined as cylinder power >0.75 D.

Anthropometric and Questionnaire Measurements

Paper questionnaires were administered to parents to collect demographic information and information on other potential confounders (43). Parents reported on their child's gender, ethnicity (Chinese or non-Chinese comprising Malays, Indians, and others) and the daily duration (h/day) spent on time outdoors (including physical and leisure activities) or near-work activities (i.e., reading, writing, drawing, crafts, use of computers, or hand-held devices), on both WE and WD, in the past month, at the 9-year visit. Similarly, the daily duration of time outdoors or near-work activities across all days of the week (h/day) was computed as follows: $5/7 \times$ daily hours on WD (h/day) $+ 2/7 \times$ daily hours on WE (h/day). As standing height may be associated with axial length (44), each child's standing height [centimeters (cm)] was measured using stadiometers (Seca 213, Seca, Hamburg, Germany). Additionally, we collected parent-reported information on maternal education levels (secondary school and lower or GCE O levels and above) (45, 46) and the number of myopic parents of the child (none or at least one parent) (47, 48), as these factors have been associated with myopia. All parents completed the paper questionnaires in quiet and private settings.

Statistical Analysis

All sleep factors (exposures) were analyzed as both continuous and categorical variables. Children with a duration of sleep of $\geq$9 h/day were considered to have met the recommendations for sufficient sleep, based on guidelines for school-aged children aged 6–13 years (49). Given that recommended clinical cutoffs for other sleep factors are lacking (50), sleep quality, duration in bed and timings of sleep were assessed as tertile categories. The consistency of sleep factors was also assessed as binary categories, where differences between WE and WD that were within an hour [approximate median and referencing previously cited cut-offs (51)] corresponded to the group with higher consistency. Sensitivity analyses were conducted by assessing the consistency of sleep factors as the absolute difference between WE and WD. Myopia was analyzed as a binary variable whereas outcomes SE and AL were analyzed as continuous variables.

Two-sample *t*-tests and Fisher's exact tests were used to compare continuous and categorical characteristics of children included in and excluded from the analyses, respectively. Paired *t*-tests and McNemar's tests were used to compare continuous and binary variables across WE and WD. In the analyses of ocular measures and tests of associations between sleep factors and each outcome after 1 year, eye measurements from each child were analyzed. In the tests of associations, multivariable logistic (myopia) or linear (SE or AL) regression models with Generalized Estimating Equations (GEE) (52, 53) were used to account for the correlation between paired eyes and confounders. Confounders considered in an initial multivariable model were based on a priori knowledge from the literature and included gender (54, 55), ethnicity (56, 57), near-work (58, 59), time outdoors (7, 8), the number of myopic parents (47, 48), and maternal education level (45, 46) [additionally child's height in models with AL (44) as the outcome]. Final multivariable models were determined with backward manual stepwise selection, starting with the full model and identifying a single confounder with the least significant p-value (if $p > 0.05$) to exit the model at each step. Instead of an automated procedure, manual exclusion and inclusion of confounders were made as the decision for the final model accounted for both model fits (e.g., quasi-likelihood under the independence model criterion, QICu) and strong evidence from the literature. Wald tests were conducted to test for any association between the tertile categories and each outcome, while tests of linear trends were performed by modeling tertile categories of specific sleep factors as numeric variables (first to third tertiles were assigned numerical values 1–3). All statistical tests were two-sided with statistical significance set at $p < 0.05$.

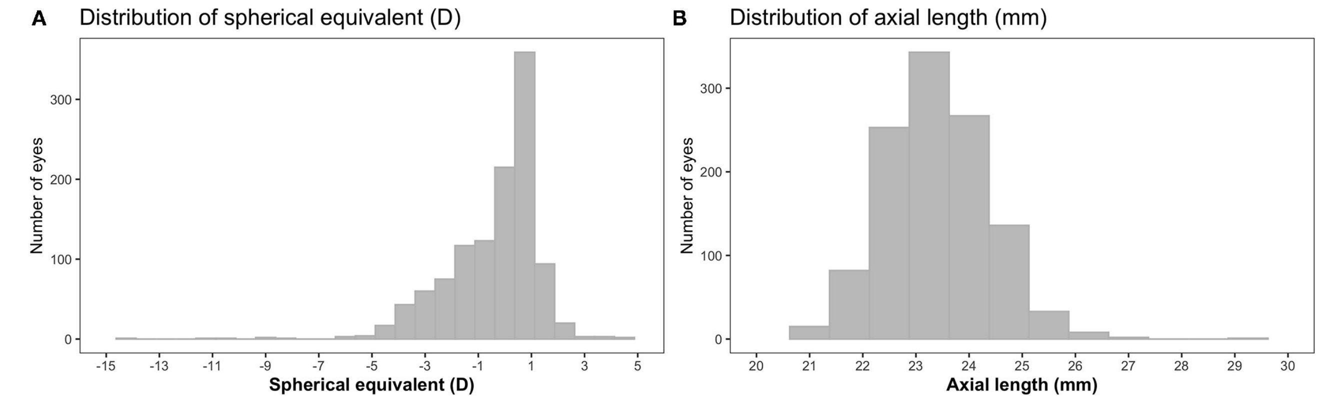

FIGURE 1 | Distributions of spherical equivalent (SE) **(A)** and axial length (AL) **(B)** in children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort ($n = 572$). D, diopters.

Estimated measures of association and their 95% confidence intervals (CI) were reported. Statistical analyses were performed using Stata v13 (StataCorp, USA).

RESULTS

A total of 572 children (1,144 eyes) were included in the analyses, of which 283 (49.5%) were boys and 321 (56.1%) were Chinese. The majority of the children had at least one myopic parent (76.7%) or mothers with higher education levels (67.3%). On average, children reported a mean duration of time outdoors of 1.7 [standard deviation (*SD*) = 1.6] h/day and near work duration of 5.5 (*SD* = 3.0) h/day. There were 427 myopic eyes (37.3%), 689 emmetropic eyes (60.3%) and 28 hyperopic eyes (2.4%) (there were no eyes with astigmatism). The mean of SE was −0.4 (*SD* = 1.7) D and the mean of AL was 23.4 (*SD* = 1.0) mm (**Figure 1**). The mean AL of eyes demonstrated an increasing trend with increasing severity of myopic SE (*p*-linear trend <0.001): 23.0 (*SD* = 0.7) mm [SE > −0.50 D], 23.9 (*SD* = 0.7) mm [SE ≤ −0.50 D to SE > −3.0 D], 24.7 (*SD* = 0.7) mm [SE ≤ −3.0 D to SE > −5.0 D], and 26.2 (*SD* = 1.1) mm [SE ≤ −5.0 D]. Being Chinese (compared to non-Chinese), spending less time outdoors or having at least one myopic parent (compared to no myopic parent) was associated with higher odds of myopia and more myopic SE ($p < 0.05$ for all). Similarly, being Chinese, female, taller, or having at least one myopic parent was associated with longer AL ($p < 0.05$ for all). Comparing eligible children included in ($n = 572$) and excluded ($n = 137$) from (due to the lack of cycloplegic refraction data or CSHQ) analyses, there were no differences in the proportion of myopic eyes, mean of SE and mean of AL ($p > 0.05$ for all). Additionally, children included for analyses had comparable proportions of boys or Chinese, and comparable proportions of children with at least one myopic parent or mothers having higher educational levels ($p > 0.05$ for all), compared to those excluded. Furthermore, children included (compared to excluded) for analyses did not differ in the mean of the duration of time outdoors or height ($p > 0.05$ for all), but had higher levels of near-work [5.5 (*SD* = 3.0) vs. 4.8 (*SD* = 2.6) h/day, $p = 0.010$].

Across all days, the mean duration of sleep was 9.2 (*SD* = 1.0) h/day (range: 4.3–13.1 h/day), with 59.9% of children meeting the recommendations for sleep sufficiency (**Table 1**). The mean of total CSHQ score was 45.8 (*SD* = 6.2), with mean of subscale scores of 9.7 (*SD* = 2.6) (bedtime resistance), 1.3 (*SD* = 0.5) (sleep onset delay), 4.0 (*SD* = 1.3) (sleep duration), 6.4 (*SD* = 2.1) (sleep anxiety), 3.6 (*SD* = 0.9) (night wakings), 8.1 (*SD* = 1.2) (parasomnias), 3.3 (*SD* = 0.6) (sleep-disordered breathing), and 13.1 (*SD* = 3.0) (daytime sleepiness). On weekends, children reported a significantly longer duration of sleep (with a higher proportion of children achieving sleep sufficiency), longer duration in bed at night, shorter duration in bed during naps, later bedtime and wake time, compared to weekdays ($p < 0.001$ for all).

In multivariable models, there were no significant associations between total CSHQ scores, duration of sleep, duration in bed (total, night only, or naps only) or timings of sleep (bedtime, wake time) and myopia, SE, or AL ($p \geq 0.05$ for all), adjusting for gender, ethnicity, near-work, time outdoors, parental myopia, and maternal education (additionally child's height when the outcome was AL) (**Table 2**). Comparing children meeting and below the recommendations for sufficient sleep, there were no significant differences in myopia, SE, or AL ($p \geq 0.05$ for all). Similarly, when sleep factors were analyzed as tertile categories, the Wald tests ($p \geq 0.05$ for all) and tests of linear trend (*p*-linear trend ≥ 0.05 for all) suggested no significant associations with myopia, SE, or AL.

In multivariable models, there were similarly no significant associations between the consistency of sleep factors (difference between WE and WD), in terms of duration of sleep, duration in bed (total, night, or nap only), bedtime or wake time and myopia, SE, or AL ($p \geq 0.05$ for all), adjusting for gender, ethnicity, near-work, time outdoors, parental myopia, and maternal education (additionally child's height when the outcome was AL) (**Table 3**). Children with lower, compared to higher consistency of sleep factors did not differ significantly in myopia, SE, or AL outcomes

TABLE 1 | Summary of sleep patterns and Children's Sleep Habits Questionnaire (CSHQ) scores in children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort ($n = 572$).

	Mean (*SD*) or *n* (%)[+]			
Sleep factors	**All days**[†]	**Weekends**	**Weekdays**	***p***[‡]
CSHQ total scores, mean (*SD*)	45.8 (6.2)			
Duration of sleep [hours/day, (h/day)], mean (*SD*)	9.2 (1.0)	9.8 (1.2)	8.9 (1.1)	<0.001
Sleep sufficiency[#], *n* (%)				<0.001
Meeting recommendations (≥9 h/day)	340 (59.9)	487 (85.7)	328 (57.4)	
Below recommendations (<9 h/day)	228 (40.1)	81 (14.3)	243 (42.6)	
Duration in bed (h/day), mean (*SD*)				
Total (night and naps) (h/day)	9.5 (1.0)	10.1 (1.2)	9.3 (1.1)	<0.001
Night only (h/day)	9.1 (0.9)	9.8 (1.0)	8.9 (1.0)	<0.001
Naps only (h/day)	0.4 (0.6)	0.3 (0.7)	0.4 (0.8)	<0.001
Bedtime (clock hours), mean (*SD*)	21:59 (00:53)	22:34 (1:00)	21:45 (00:54)	<0.001
Wake time (clock hours), mean (*SD*)	07:08 (00:55)	08:24 (01:14)	06:38 (1:01)	<0.001
Consistency of duration of sleep[§] (h), mean (*SD*)	0.9 (1.2)	–	–	
Consistency of duration in bed[§] (h), mean (*SD*)				
Total (night and naps) (h)	0.8 (1.3)	–	–	
Night only (h)	0.9 (1.2)	–	–	
Naps only (h)	−0.1 (0.8)	–	–	
Consistency of bedtime[§] (clock hours), mean (*SD*)	00:49 (00:40)	–	–	
Consistency of wake time[§] (clock hours), mean (*SD*)	01:46 (01:17)	–	–	

SD, standard deviation; %, percentage; CSHQ, Children's Sleep Habits Questionnaire.
[†]*Values presented for sleep duration and timing are mean daily values across all days of the week (h/day), aggregated using the following formula: [5/7* daily hours on weekdays (h/day) + 2/7* daily hours on weekends (h/day)].*
[‡]*p-values from two-sample paired t-tests (continuous variables) or McNemar's test (categorical variables) indicate if there are any significant differences comparing weekends and weekdays for each sleep factor.*
[§]*Consistency of each sleep factor was defined as the difference in values between weekends and weekdays (i.e., weekends-weekdays).*
[#]*Missing sleep sufficiency data for all days (n = 4), weekends (n = 4), and weekdays (n = 1).*
[+]*Continuous variables were presented as mean (SD) and categorical as n (%).*

($p \geq 0.05$ for all). In sensitivity analyses, there was similarly no significant associations between the consistency of sleep factors (absolute difference in reported values between WE and WD) and myopia, SE, or AL ($p \geq 0.05$ for all).

DISCUSSION

In this cross-sectional study, sleep quality, duration, timing, and the consistency of specific sleep factors were not independently associated with myopia, cycloplegic SE or AL among school-aged children in Singapore.

In this study, the mean total CSHQ score was comparable to other studies on children of a similar age living in China (44) (reference number 20) or Australia (AUS) (44–54) (reference number 60). Compared to the mean duration of sleep in this study (9.2 h/day), other studies have reported mean durations of 9.5 h/day (China) (28), 10 h/day (Australia) (60), and 10.2 h/day (United States of America, USA) (61). We reported relatively later mean bedtime (21:59), compared to Chinese (21:02) (61), Australian (21:00) (60), or American children (20:27) (61), but children in this study do not stand out in mean wake time (60–62). Differences in sleep factors across studies may reflect varied educational loads (higher in Asian countries) (63–65), sleep practices (61), social schedules, or other lifestyle behaviors (17).

The overall null associations between sleep factors and myopia, SE, or AL in this study concur with the lack of associations between specific sleep factors and myopia reported in other prospective studies (27, 28, 66). Our findings corroborate with the 4-year prospective study by Wei et al., where duration of sleep and bedtime were not significantly associated with myopia incidence, myopic progression, or AL elongation [$p \geq 0.05$ for all; (27)]. Similarly, in the 2-year prospective study by Liu et al., duration of sleep was not significantly associated with myopia incidence [$p \geq 0.05$; (28)]. Moreover, in a previous report from the same GUSTO prospective study, we reported no significant associations between the duration of sleep or number of night wakings at 12 months and myopia, SE, and AL in 376 children aged 3 years [$p \geq 0.05$ for all; (66)]. Additionally, in a cross-sectional study of 474 pairs of Chinese children aged 13–14 years, sleep problems (total CSHQ scores) were also not found to be significantly associated with myopia [$p \geq 0.05$; (25)].

Conversely, significant associations between sleep factors and myopia have been reported in the Liu et al. study and in two other cross-sectional studies (20, 21, 28). In the Liu et al. study, later bedtime (defined as ≥9:30 p.m. vs. <9 p.m.), but not the duration of sleep, was associated with higher 2-year myopia incidence (OR = 1.45, 95% CI [1.05, 2.00], $p = 0.02$), adjusting for age, gender, residency area (urban/suburban) and outdoor intervention group (28). Of note, children with later bedtime in Liu et al. also reported significantly less time outdoors, more near-work, and a higher likelihood of having more myopic and educated parents (28), all of which may be associated with more myopia (7, 43, 45, 48, 58). On the other hand, consistent with the 4-year prospective study by Wei et al., the current study found no significant associations ($p > 0.05$ for all), but there were suggestions of an inverse trend where those with a later bedtime had lower odds of myopia, less myopic SE and shorter AL. In a cross-sectional study of 15,316 Chinese students aged 6–18 years by Xu et al., shorter duration of sleep (<7 h/day vs. ≥9 h/day) was associated with higher odds of myopia [OR = 3.37, 95% CI [3.07–3.70], $p < 0.001$; (21)]. However, daily time outdoors, a key risk factor for myopia, was not accounted for in the Xu et al. study. Conversely, in the current study, both a higher duration of sleep and a higher duration spent in bed at night were not significantly associated with myopia outcomes ($p > 0.05$ for all), and there were suggestions of a positive trend between

TABLE 2 | Associations of sleep factors with myopia (SE ≤ −0.5 D), spherical equivalent (D) and axial length (mm) in children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort (n = 572).

		Myopia (SE ≤ −0.5 D)				SE (D)				AL (mm)			
		Univariable model		Multivariable model†		Univariable model		Multivariable model†		Univariable model		Multivariable model†	
Sleep factors	**Eyes#**	**OR [95% CI]**	**p‡**	**OR [95% CI]**	**p‡**	**Beta coefficient [95%CI]**	**p§**	**Beta coefficient [95%CI]**	**p§**	**Beta coefficient [95%CI]**	**p§**	**Beta coefficient [95%CI]**	**p§**
Total CSHQ score (per point increment)	1,006	0.99 [0.96, 1.01]	0.34	0.99 [0.96, 1.02]	0.38	−0.001 [−0.03, 0.02]	0.93	−0.0004 [−0.03, 0.03]	0.97	−0.003 [−0.02, 0.01]	0.64	−0.01 [−0.02, 0.01]	0.37
Duration of sleep+ [hours/day, (h/day)] (per hourly increment)	1,044	1.16 [0.99, 1.38]	0.071	1.15 [0.95, 1.39]	0.16	−0.06 [−0.20, 0.07]	0.37	−0.04 [−0.18, 0.10]	0.59	−0.003 [−0.08, 0.08]	0.95	0.02 [−0.06, 0.09]	0.64
Sleep sufficiency+													
≥9 h/day	623	(Ref)		(Ref)		(Ref)		(Ref)		(Ref)		(Ref)	
<9 h/day	421	0.87 [0.62, 1.21]	0.41	0.89 [0.62, 1.28]	0.53	0.01¶ [−0.28, 0.30]	0.96	−0.02¶ [−0.32, 0.28]	0.88	0.07¶ [−0.09, 0.24]	0.40	0.03¶ [−0.13, 0.18]	0.75
Duration in bed+ (h/day)													
Total (h/day) (per hourly increment)	1,020	1.01 [0.85, 1.20]	0.90	1.001 [0.82, 1.22]	0.99	0.04 [−0.10, 0.17]	0.62	0.02 [−0.12, 0.17]	0.75	−0.03 [−0.12, 0.05]	0.46	−0.001 [−0.08, 0.08]	0.97
Night only (h/day) (per hourly increment)	1,044	1.14 [0.95, 1.38]	0.16	1.11 [0.90, 1.37]	0.33	−0.07 [−0.22, 0.08]	0.34	−0.06 [−0.21, 0.10]	0.45	−0.003 [−0.10, 0.09]	0.96	0.02 [−0.07, 0.11]	0.68
Naps only (h/day) (per hourly increment)	1,022	0.78 [0.59, 1.02]	0.072	0.82 [0.61, 1.10]	0.18	0.21 [0.02, 0.41]	0.033	0.16 [−0.04, 0.37]	0.12	−0.06 [−0.18, 0.06]	0.30	−0.03 [−0.15, 0.08]	0.55
Bedtime+ (per clock hour increment)	1,044	0.92 [0.76, 1.12]	0.41	0.87 [0.71, 1.07]	0.19	0.11 [−0.04, 0.26]	0.14	0.14 [−0.01, 0.29]	0.074	−0.04 [−0.13, 0.05]	0.37	−0.03 [−0.12, 0.06]	0.49
Wake time+ (per clock hour increment)	1,046	1.05 [0.88, 1.26]	0.58	0.97 [0.78, 1.21]	0.78	0.04 [−0.11, 0.18]	0.61	0.08 [−0.09, 0.25]	0.36	−0.04 [−0.13, 0.05]	0.37	−0.01 [−0.10, 0.08]	0.80

SD, standard deviation; SE, spherical equivalent; D, diopters; AL, axial length; OR, odds ratio; CI, confidence interval; CSHQ, Children's Sleep Habits Questionnaire.
† *Multivariable models adjusted for gender, ethnicity, near-work, time outdoors, parental myopia and maternal education. When the outcome was AL, multivariable models further adjusted for the child's height.*
‡ *p-values from logistic regression with generalized estimating equations (GEE).*
§ *p-values from linear regression with GEE.*
\# *Number of eyes in multivariable models for outcome AL, representing the minimum number of eyes analyzed are presented. The number of eyes analyzed for all univariable (for outcomes myopia, SE, and AL) and multivariable models (for outcomes myopia and SE) are equal to or larger than the values presented.*
\+ *Values presented are mean daily values across all days of the week (h/day), aggregated using the following formula: [5/7* daily hours on weekdays (h/day) + 2/7* daily hours on weekends (h/day)].*
¶ *The mean difference was presented for sleep sufficiency.*

these factors and myopia, myopic SE or AL. These null results corroborate the null findings from three other prospective studies (27, 28, 66). In another cross-sectional study of 1902 Chinese children aged 6–12 years, by Zhou et al., higher total CSHQ scores (or lower quality of sleep) was associated with higher odds of myopia [OR = 1.01, 95% CI [1.00, 1.02], $p = 0.014$; (20)]. Similar to the small magnitude of estimates reported by Zhou et al., the estimates between CSHQ scores and myopia outcomes were close to null in the current study, with no significant associations or trends ($p > 0.05$ for all). Additionally, despite accounting for time outdoors, adjustments were not made for parental myopia in the Chinese study. Similar to previous studies (7, 9, 48, 67), the current study showed that higher time outdoors had an inverse association, while having myopic parents had a positive association with myopia. Thus, although significant associations may arise from differences in population characteristics, sample sizes or sleep assessment instruments, these findings have been inconsistent overall and require careful interpretation, given residual confounding by known risk factors of myopia could not be ruled out.

Overall, the results in this study suggest that sleep factors may not be independently associated with myopia. The inconsistent evidence overall, together with the null associations in this study, suggests that the evidence supporting specific sleep factors as independent risk factors for myopia remains weak. Increased education (possibly linked to increases in near-work) and decreased time outdoors have been identified as the two major environmental risk factors for myopia (6–8, 43, 68). Sleep factors may serve as surrogate markers of either near-work, time outdoors, or both of these major risk factors for myopia. The extent to which later bedtime, shorter sleep or poorer sleep simply reflect longer duration spent on near-work or screen

TABLE 3 | Associations of the consistency of sleep duration and timing with myopia (SE ≤ −0.5 D), spherical equivalent (D) and axial length (mm) in children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort (*n* = 572).

		Myopia (SE ≤ −0.5 D)				SE (D)				AL (mm)			
		Univariable model		Multivariable model†		Univariable model		Multivariable model†		Univariable model		Multivariable model†	
Sleep factors#	**Eyes+**	**OR [95% CI]**	***p*‡**	**OR [95% CI]**	***p*‡**	**Beta coefficient [95%CI]**	***p*§**	**Beta coefficient [95%CI]**	***p*§**	**Beta coefficient [95%CI]**	***p*§**	**Beta coefficient [95%CI]**	***p*§**
Consistency of duration of sleep [hours, (h)] (per hourly increment)	1,044	0.91 [0.80, 1.04]	0.17	0.91 [0.78, 1.05]	0.20	0.06 [−0.06, 0.17]	0.33	0.04 [−0.08, 0.15]	0.52	−0.03 [−0.09, 0.04]	0.46	0.003 [−0.06, 0.07]	0.93
Consistency of duration in bed (h)													
Total (night + nap) (h) (per hourly increment)	1,020	0.93 [0.82, 1.05]	0.24	0.90 [0.79, 1.03]	0.14	0.005 [−0.11, 0.12]	0.93	0.02 [−0.09, 0.14]	0.71	0.003 [−0.06, 0.07]	0.93	−0.003 [−0.06, 0.06]	0.93
Night only (h) (per hourly increment)	1,044	0.95 [0.83, 1.08]	0.43	0.95 [0.82, 1.10]	0.50	0.02 [−0.09, 0.14]	0.68	0.01 [−0.10, 0.13]	0.81	−0.03 [−0.10, 0.03]	0.32	−0.02 [−0.08, 0.04]	0.52
Naps only (h) (per hourly increment)	1,022	0.88 [0.73, 1.06]	0.18	0.83 [0.67, 1.03]	0.093	0.004 [−0.15, 0.15]	0.96	0.04 [−0.12, 0.19]	0.65	0.04 [−0.04, 0.13]	0.32	0.02 [−0.06, 0.10]	0.58
Consistency of bedtime (per clock hour increment)	1,044	0.86 [0.67, 1.10]	0.23	1.001 [0.76, 1.33]	1.00	0.07 [−0.12, 0.27]	0.47	−0.05 [−0.27, 0.17]	0.65	−0.07 [−0.20, 0.06]	0.28	0.02 [−0.10, 0.14]	0.75
Consistency of wake time (per clock hour increment)	1,046	0.92 [0.81, 1.04]	0.17	0.96 [0.84, 1.09]	0.53	0.04 [−0.05, 0.13]	0.39	−0.001 [−0.09, 0.09]	0.98	−0.05 [−0.11, 0.01]	0.11	−0.01 [−0.07, 0.04]	0.66

SD, standard deviation; SE, spherical equivalent; D, diopters; AL, axial length; OR, odds ratio; CI, confidence interval; CSHQ, Children's Sleep Habits Questionnaire.
† Multivariable models adjusted for gender, ethnicity, near-work, time outdoors, parental myopia and maternal education. When the outcome was AL, multivariable models further adjusted for the child's height.
‡ p-values from logistic regression with generalized estimating equations (GEE).
§ p-values from linear regression with GEE.
 # Consistency of sleep factors was defined as the difference between reported values for weekends and weekdays.
+ Number of eyes from multivariable models for outcome AL, representing the minimum number of eyes analyzed are presented. The number of eyes analyzed for all univariable (for outcomes myopia, SE, and AL) and multivariable models (for outcomes myopia and SE) are equal to or larger than the values presented.

time (17, 65, 69, 70), or near-work activity close to bedtime (27) needs to be clarified. Further large prospective studies are required to evaluate if sleep factors are independently associated with myopia, with careful adjustments for established risk factors for myopia.

The strengths of this study include the capture of multiple sleep factors and the use of cycloplegic refraction data. The findings from this study should be interpreted considering the following limitations. First, the GUSTO myopia study was nested in the main GUSTO study assessing multiple childhood outcomes. Due to limits on the number of tests that could be performed at each study visit, sleep factors and myopia assessments of the subset GUSTO myopia study were limited to ages 8 and 9, respectively. As sleep factors and myopia were not assessed in the same year, changes to sleep patterns between ages 8 to 9 could not be precluded, although the likelihood of large changes within 1 year was likely to be low. In a meta-analysis of 9 studies (29,663 children) conducted in Asian, European, and Middle Eastern countries, the mean duration of sleep in children aged 8 years (mean: 9.3 [range: 7.8–10.8] h/day) was similar to that in children aged 9 years (mean: 9.3 [range: 7.8–10.8] h/day) (71). Second, the cross-sectional assessments do not allow for the capture of temporal patterns in sleep factors and ocular parameters. Third, for associations of the duration of sleep with SE or AL, the current sample size was adequately powered (at 80%) to detect effect sizes of 0.118 and 0.122, respectively, but not smaller effect sizes. Fourth, given the constraints of administering "gold standard" polysomnography (72), which are more disruptive and resource-intensive on a broad scale, subjective assessment of sleep was performed using questionnaires, which may be prone to recall bias. Although we expect the recall bias to be minimal given the questionnaire elicited parents' responses on their child's habitual sleep patterns during the "most recent typical week," validated and objective measures of sleep should be considered where feasible to corroborate the subjective measurements. A recent study demonstrated that parental reports tend to over-estimate the duration of sleep (compared to polysomnography), however, the observed differences were small, with a substantial agreement between the two methods [intraclass correlation coefficient of 0.78, $p < 0.01$; (73)]. Validated objective measures (i.e., wrist-worn actigraphy) may provide information on unique sleep factors, over different timescales, and sampling resolution. However, as actigraphy may be limited in capturing certain aspects of sleep, such as wake after sleep onset (74), questionnaires may remain an indispensable instrument for assessing sleep disruptions or quality of sleep. Finally, although we reported null associations between specific sleep factors (which are closely regulated by the intrinsic circadian clock) and myopia, studies directly assessing circadian rhythms may be required to further elucidate potential circadian effects on myopia, independent of sleep factors.

In conclusion, our study results showed that sleep quality, duration, timing, and the consistency of specific sleep factors at age 8 were not independently associated with myopia, SE, or AL among school-aged children aged 9 years in Singapore. Although the current findings do not support associations of specific sleep factors with myopia, much larger longitudinal studies may be required to corroborate these results.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset can only be made available upon request and approval by the GUSTO Executive Committee. Requests to access the datasets should be directed to mijie@u.nus.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Healthcare Group Domain Specific Review Board (D/2009/021), Singhealth Centralized Institutional Review Board (2018/2767), and both the National Healthcare Group Domain Specific and Singhealth Centralized Institutional Review Boards (2018/2270; R1517/16/2018). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ML: drafting of manuscript. ML, C-ST, LX, L-LF, ET, SC, MA, S-MS, and CS: conceptualization, design, analysis, or interpretation of data. ML, FY, C-HS, ET, SC, and S-MS: acquisition of data. S-MS: acquisition of funding. All authors were involved in the critical revision, review, and approval of the manuscript.

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REFERENCES

1. Jung SK, Lee JH, Kakizaki H, Jee D. Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in seoul, South Korea. *Invest Ophthalmol Vis Sci.* (2012) 53:5579–83. doi: 10.1167/iovs.12-10106
2. Koh V, Yang A, Saw SM, Chan YH, Lin ST, Tan MM, et al. Differences in prevalence of refractive errors in young Asian males in Singapore

between 1996-1997 and 2009-2010. *Ophthalmic Epidemiol.* (2014) 21:247–55. doi: 10.3109/09286586.2014.928824

3. Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt.* (2016) 36:388–94. doi: 10.1111/opo.12305
4. Ohno-Matsui K. Pathologic myopia. *Ann Eye Sci.* (2018) 3:8–8. doi: 10.21037/aes.2018.01.03
5. Saw SM, Gazzard G, Chan SY, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt.* (2005) 25:381–91. doi: 10.1111/j.1475-1313.2005.00298.x
6. Mountjoy E, Davies NM, Plotnikov D, Smith GD, Rodriguez S, Williams CE, et al. Education and myopia: assessing the direction of causality by mendelian randomisation. *BMJ.* (2018) 361:k2022. doi: 10.1136/bmj.k2022
7. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA.* (2015) 314:1142–48. doi: 10.1001/jama.2015.10803
8. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology.* (2013) 120:1080–85. doi: 10.1016/j.ophtha.2012.11.009
9. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology.* (2013) 120:2100–08. doi: 10.1016/j.ophtha.2013.02.035
10. Zadnik K, Sinnott LT, Cotter SA, Jones-Jordan LA, Kleinstein RN, Manny RE, et al. Prediction of juvenile-onset myopia. *JAMA Ophthalmol.* (2015) 133:683–9. doi: 10.1001/jamaophthalmol.2015.0471
11. Huang HM, Chang DS, Wu PC. The association between near work activities and myopia in children-a systematic review and meta-analysis. *PLoS ONE.* (2015) 10:e0140419. doi: 10.1371/journal.pone.0140419
12. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Opthalmol.* (2008) 126:527–30. doi: 10.1001/archopht.126.4.527
13. Guggenheim JA, St Pourcain B, McMahon G, Timpson NJ, Evans DM, Williams C. Assumption-free estimation of the genetic contribution to refractive error across childhood. *Mol Vis.* (2015) 21:621–32.
14. Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol.* (2016) 100:882–90. doi: 10.1136/bjophthalmol-2015-307724
15. Tzischinsky O, Lavie P. Melatonin possesses time-dependent hypnotic effects. *Sleep.* (1994) 17:638–45. doi: 10.1093/sleep/17.7.638
16. Hysi PG, Choquet H, Khawaja AP, Wojciechowski R, Tedja MS, Yin J, 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) 52:401–7. doi: 10.1038/s41588-020-0599-0
17. Chaput JP, Katzmarzyk PT, LeBlanc AG, Tremblay MS, Barreira TV, Broyles ST, et al. Associations between sleep patterns and lifestyle behaviors in children: an international comparison. *Int J Obes Suppl.* (2015) 5:S59–65. doi: 10.1038/ijosup.2015.21
18. Potter GD, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. *Endocr Rev.* (2016) 37:584–608. doi: 10.1210/er.2016-1083
19. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep.* (2017) 9:151–61. doi: 10.2147/NSS.S134864
20. Zhou Z, Morgan IG, Chen Q, Jin L, He M, Congdon N. Disordered sleep and myopia risk among Chinese children. *PLoS ONE.* (2015) 10:e0121796. doi: 10.1371/journal.pone.0121796
21. Xu X, Wang D, Xiao G, Yu K, Gong Y. Sleep less, myopia more. *Theor Clin Pract Pediatr.* (2017) 1:11–17. doi: 10.25082/tcpp.2017.01.004
22. Jee D, Morgan IG, Kim EC. Inverse relationship between sleep duration and myopia. *Acta Ophthalmol.* (2016) 94:e204–10. doi: 10.1111/aos.12776
23. O'Leary DJ, Millodot M. Eyelid closure causes myopia in humans. *Experientia.* (1979) 35:1478–79. doi: 10.1007/bf01962795
24. Qu Y, Yu J, Xia W, Cai H. Correlation of myopia with physical exercise and sleep habits among suburban adolescents. *J Ophthalmol.* (2020) 2020:2670153. doi: 10.1155/2020/2670153
25. Pan CW, Liu J-H, Wu R-K, Zhong H, Li J. Disordered sleep and myopia among adolescents: a propensity score matching analysis. *Ophthalmic Epidemiol.* (2019) 26:155–60. doi: 10.1080/09286586.2018.1554159
26. Ostrin LA, Read SA, Vincent SJ, Collins MJ. Sleep in myopic and non-myopic children. *Transl Vis Sci Technol.* (2020) 9:22. doi: 10.1167/tvst.9.9.22
27. Wei SF, Li SM, Liu L, Li H, Kang MT, Sun YY, et al. Sleep duration, bedtime, and myopia progression in a 4-year follow-up of chinese children: the Anyang Childhood Eye Study. *Invest Ophthalmol Vis Sci.* (2020) 61:37. doi: 10.1167/iovs.61.3.37
28. Liu XN, Naduvilath TJ, Wang J, Xiong S, He X, Xu X, et al. Sleeping late is a risk factor for myopia development amongst school-aged children in China. *Sci Rep.* (2020) 10:17194. doi: 10.1038/s41598-020-74348-7
29. Bei B, Wiley JF, Trinder J, Manber R. Beyond the mean: a systematic review on the correlates of daily intraindividual variability of sleep/wake patterns. *Sleep Med Rev.* (2016) 28:108–24. doi: 10.1016/j.smrv.2015.06.003
30. Agostini A, Carskadon MA, Dorrian J, Coussens S, Short MA. An experimental study of adolescent sleep restriction during a simulated school week: changes in phase, sleep staging, performance and sleepiness. *J Sleep Res.* (2017) 26:227–35. doi: 10.1111/jsr.12473
31. Soh SE, Tint MT, Gluckman PD, Godfrey KM, Rifkin-Graboi A, Chan YH, et al. Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. *Int J Epidemiol.* (2014) 43:1401–9. doi: 10.1093/ije/dyt125
32. Ministry of Education Singapore. *Education Statistics Digest 2020: Ministry of Education Singapore.* (2020). Available online at: https://www.moe.gov.sg/-/media/files/about-us/education-statistics-digest-2021.pdf?la=en&hash=66F301F1705A29404802981D2B8D4E96F8AAE5CC (accessed January 18, 2022).
33. Ministry of Education Singapore. *School Start Time: Ministry of Education Singaopre.* (2021). Available online at: https://www.moe.gov.sg/news/parliamentary-replies/20210803-school-start-time (accessed January 18, 2022).
34. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep.* (2000) 23:1043–51.
35. Aishworiya R, Chan P, Kiing J, Chong SC, Laino AG, Tay S. Sleep behaviour in a sample of preschool children in Singapore. *Ann Acad Med Singap.* (2012) 41:99–104.
36. Shen S, Li X, Li R, Huang D, Zhao X, Zhang X, et al. Association of sleep disorders with subfoveal choroidal thickness in preschool children. *Eye.* (2021) doi: 10.1038/s41433-021-01489-y
37. Duraccio KM, Carbine KA, Barnett KA, Stevens KS, Jensen CD. The utility of the Children's Sleep Habits Questionnaire: associations between parental report and an objective measure of sleep behavior. *Children's Health Care.* (2018) 47:119–35. doi: 10.1080/02739615.2017.1316198
38. Li SH, Jin XM, Shen XM, Wu SH, Jiang F, Yan CH, et al. Development and psychometric properties of the Chinese version of Children's Sleep Habits Questionnaire. *Zhonghua Er Ke Za Zhi.* (2007) 45:176–80.
39. Loureiro H, Rebelo-Pinto T, Pinto J, Pinto HR, Paiva T. Validation of the Children Sleep Habits Questionnaire and the Sleep Self Report for portuguese children. *Sleep Sci.* (2013) 6:151–58.
40. Schlarb AA, Schwerdtle B, Hautzinger M. Validation and psychometric properties of the German version of the Children's Sleep Habits Questionnaire (CSHQ-DE). *Somnologie.* (2010) 14:260–66. doi: 10.1007/s11818-010-0495-4
41. Borrelli M, Scala I, Festa P, Bruzzese D, Michelotti A, Cantone E, et al. Linguistic adaptation and psychometric evaluation of Italian version of children's sleep habits questionnaire. *Ital J Pediatr.* (2021) 47:170. doi: 10.1186/s13052-021-01119-z
42. Zhang R, Tomasi D, Shokri-Kojori E, Wiers CE, Wang GJ, Volkow ND. Sleep inconsistency between weekends and weekdays is associated with changes in brain function during task and rest. *Sleep.* (2020) 43:zsaa076. doi: 10.1093/sleep/zsaa076
43. Morgan IG, Wu PC, Ostrin LA, Tideman JWL, Yam JC, Lan W, et al. IMI risk factors for myopia. *Invest Ophthalmol Vis Sci.* (2021) 62:3. doi: 10.1167/iovs.62.5.3
44. Northstone K, Guggenheim JA, Howe LD, Tilling K, Paternoster L, Kemp JP, et al. Body stature growth trajectories during childhood

and the development of myopia. *Ophthalmology.* (2013) 120:1064–73.e1. doi: 10.1016/j.ophtha.2012.11.004
45. Williams KM, Kraphol E, Yonova-Doing E, Hysi PG, Plomin R, Hammond CJ. Early life factors for myopia in the British Twins Early Development Study. *Br J Ophthalmol.* (2019) 103:1078–84. doi: 10.1136/bjophthalmol-2018-312439
46. Hsu CC, Huang N, Lin PY, Tsai DC, Tsai CY, Woung LC, et al. Prevalence and risk factors for myopia in second-grade primary school children in Taipei: a population-based study. *J Chin Med Assoc.* (2016) 79:625–32. doi: 10.1016/j.jcma.2016.02.011
47. Tang SM, Kam KW, French AN, Yu M, Chen LJ, Young AL, et al. Independent influence of parental myopia on childhood myopia in a dose-related manner in 2,055 trios: the Hong Kong Children Eye Study. *Am J Ophthalmol.* (2020) 218:199–207. doi: 10.1016/j.ajo.2020.05.026
48. Jiang X, Tarczy-Hornoch K, Cotter SA, Matsumura S, Mitchell P, Rose KA, et al. Association of parental myopia with higher risk of myopia among multiethnic children before school age. *JAMA Ophthalmol.* (2020) 138:501–9. doi: 10.1001/jamaophthalmol.2020.0412
49. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health.* (2015) 1:40–3. doi: 10.1016/j.sleh.2014.12.010
50. Chaput J-P, Dutil C, Featherstone R, Ross R, Giangregorio L, Saunders TJ, et al. Sleep timing, sleep consistency, and health in adults: a systematic review. *Appl Physiol Nutr Metab.* (2020) 45:S232–47. doi: 10.1139/apnm-2020-0032
51. Koopman ADM, Rauh SP, van Riet E, Groeneveld L, van der Heijden AA, Elders PJ, et al. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the New Hoorn Study. *J Biol Rhythms.* (2017) 32:359–68. doi: 10.1177/0748730417713572
52. Fan Q, Teo YY, Saw SM. Application of advanced statistics in ophthalmology. *Invest Ophthalmol Vis Sci.* (2011) 52:6059–65. doi: 10.1167/iovs.10-7108
53. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics.* (1988) 44:1049–60. doi: 10.2307/2531734
54. Czepita M, Czepita D, Safranow K. Role of gender in the prevalence of myopia among Polish schoolchildren. *J Ophthalmol.* (2019) 2019:9748576. doi: 10.1155/2019/9748576
55. Chen M, Wu A, Zhang L, Wang W, Chen X, Yu X, et al. 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) 18:159. doi: 10.1186/s12886-018-0829-8
56. Pan CW, Zheng YF, Anuar AR, Chew M, Gazzard G, Aung T, et al. Prevalence of refractive errors in a multiethnic Asian population: the Singapore epidemiology of eye disease study. *Invest Ophthalmol Vis Sci.* (2013) 54:2590–98. doi: 10.1167/iovs.13-11725
57. Luong TQ, Shu Y-H, Modjtahedi BS, Fong DS, Choudry N, Tanaka Y, et al. Racial and ethnic differences in myopia progression in a large, diverse cohort of pediatric patients. *Invest Ophthalmol Vis Sci.* (2020) 61:20. doi: 10.1167/iovs.61.13.20
58. Harrington SC, Stack J, O'Dwyer V. Risk factors associated with myopia in schoolchildren in Ireland. *Br J Ophthalmol.* (2019) 103:1803–09. doi: 10.1136/bjophthalmol-2018-313325
59. Saxena R, Vashist P, Tandon R, Pandey RM, Bhardawaj A, Gupta V, et al. Incidence and progression of myopia and associated factors in urban school children in Delhi: the North India Myopia Study (NIM Study). *PLoS ONE.* (2017) 12:e0189774. doi: 10.1371/journal.pone.0189774
60. Price AM, Brown JE, Bittman M, Wake M, Quach J, Hiscock H. Children's sleep patterns from 0 to 9 years: Australian population longitudinal study. *Arch Dis Child.* (2014) 99:119–25. doi: 10.1136/archdischild-2013-304150
61. Liu X, Liu L, Owens JA, Kaplan DL. Sleep patterns and sleep problems among schoolchildren in the United States and China. *Pediatrics.* (2005) 115:241–49. doi: 10.1542/peds.2004-0815F
62. Wang G, Xu G, Liu Z, Lu N, Ma R, Zhang E. Sleep patterns and sleep disturbances among Chinese school-aged children: prevalence and associated factors. *Sleep Med.* (2013) 14:45–52. doi: 10.1016/j.sleep.2012.09.022
63. Ang M, Flanagan JL, Wong CW, Muller A, Davis A, Keys D, et al. Review: myopia control strategies recommendations from the 2018 WHO/IAPB/BHVI meeting on myopia. *Br J Ophthalmol.* (2020) 104:1482–87. doi: 10.1136/bjophthalmol-2019-315575
64. Morgan IG, Ohno-Matsui K, Saw S-M. Myopia. *Lancet.* (2012) 379:1739–48. doi: 10.1016/s0140-6736(12)60272-4
65. Yeo SC, Tan J, Lo JC, Chee MWL, Gooley JJ. Associations of time spent on homework or studying with nocturnal sleep behavior and depression symptoms in adolescents from Singapore. *Sleep Health.* (2020) 6:758–66. doi: 10.1016/j.sleh.2020.04.011
66. Sensaki S, Sabanayagam C, Chua S, Htoon HM, Broekman BFP, Thiam DGY, et al. Sleep duration in infants was not associated with myopia at 3 years. *Asia Pac J Ophthalmol.* (2018) 7:102–08. doi: 10.22608/APO.2017390
67. Ghorbani Mojarrad N, Williams C, Guggenheim JA. A genetic risk score and number of myopic parents independently predict myopia. *Ophthalmic Physiol Opt.* (2018) 38:492–502. doi: 10.1111/opo.12579
68. Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw S-M. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol.* (2020) 20:27. doi: 10.1186/s12886-019-1220-0
69. Mindell JA, Sadeh A, Kwon R, Goh DY. Cross-cultural differences in the sleep of preschool children. *Sleep Med.* (2013) 14:1283–89. doi: 10.1016/j.sleep.2013.09.002
70. Nuutinen T, Ray C, Roos E. Do computer use, TV viewing, and the presence of the media in the bedroom predict school-aged children's sleep habits in a longitudinal study? *BMC Public Health.* (2013) 13:684. doi: 10.1186/1471-2458-13-684
71. Galland BC, Taylor BJ, Elder DE, Herbison P. Normal sleep patterns in infants and children: a systematic review of observational studies. *Sleep Med Rev.* (2012) 16:213–22. doi: 10.1016/j.smrv.2011.06.001
72. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography-a systematic review. *J Sleep Res.* (2011) 20:183–200. doi: 10.1111/j.1365-2869.2009.00814.x
73. Combs D, Goodwin JL, Quan SF, Morgan WJ, Hsu CH, Edgin JO, et al. Mother knows best? Comparing child report and parent report of sleep parameters with polysomnography. *J Clin Sleep Med.* (2019) 15:111–7. doi: 10.5664/jcsm.7582
74. Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev.* (2012) 16:463–75. doi: 10.1016/j.smrv.2011.10.002

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Eye Care Practitioners Are Key Influencer for the Use of Myopia Control Intervention

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Background: The study sought to investigate the self-reported practices of Singaporean eye care practitioners on myopia management and the interaction between eye care practitioners and parents.

Methods: Self-reported questionnaire (1) to eye care practitioners to understand their clinical practice behavior, their opinion in myopia management (2) to parents on their knowledge of myopia control products and interaction with eye care practitioners.

Results: 80.0% of eye care practitioners prescribe myopia control in their practice but only 33.1% of eye care practitioners prescribed myopia control interventions during the first visit, and only 41.4% of parents were recommended myopia control interventions by eye care practitioners, of which 75.6% followed the recommendations of eye care practitioners. Eye care practitioners (53.1%) prefer atropine the most and parents prefer controlling the amount of time doing near work (54.5%) and outdoor activities (52.5%). Eye care practitioners had the highest influence on the choice of vision correction with 78.8% of parents choosing to follow them. 66.9% of eye care practitioners did not prescribe myopia control interventions during the first visit as they lack myopia progression data from the patient. Eye care practitioners felt that more education on myopia control products (57.7%), hands-on workshops (47.7%) and management of children (44.6%) would encourage them to use myopia control interventions more frequently. 40.0% of the eye care practitioners were concerned about the cost of myopia control products.

Conclusions: Eye care practitioners strongly influence parents to uptake myopia control interventions. More education and hands-on workshops on myopia and children management can help encourage the use of myopia control interventions by eye care practitioners.

Keywords: myopia, myopia management, parental awareness, questionnaire, eye care practice, opinion of parents, opinion of eye care practitioners

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INTRODUCTION

Myopia prevalence is on the rise, and its trajectory is not slowing down worldwide (1, 2). Myopia is a global public health issue, and with the increase of myopia prevalence, the risk of sight-related pathologies and impairment will increase as well (3–5). Myopia has an impact on public healthcare and the economy (6, 7). Several studies showed that myopia control interventions effectively slowed down the progression of myopia, reducing the severity of myopia endpoint (8–13). Guidelines were even developed to help several of these interventions to be implemented within eye-care practice (14, 15).

Despite available evidence showing the efficacy of interventions for myopia control, the adoption of these interventions by parents and eye care practitioners has been slow. A global survey found that in 2015, 68% of eye care practitioners still prescribed single vision spectacle or contact lenses as the primary mode of correction for myopic patients (16). The main reason for not prescribing myopia control interventions was the high cost of these products, inadequate information on these products, and unpredictability of outcomes (16). A later study in 2019 showed that 52% still prescribe single vision lenses, an improvement from 2015 (17). Another study in Australia found that the absence of regulatory approval poses a concern about medico-legal aspects of prescribing interventions other than conventional glasses, with 50% of the respondents prescribing normal spectacles (single vision lenses) (18).

Singapore is one of the most myopic nations globally, with a myopia prevalence of 81.6% and high myopia prevalence of 13.1% in young adults (19). Though there were studies conducted globally, it is interesting to examine the trends of myopia management amongst eye care practitioners and their interaction with parents in Singapore. This study sought to investigate the self-reported practices of eye care practitioners on myopia management and the interaction between eye care practitioners and parents in Singapore.

MATERIALS AND METHODS

Questionnaire Design for Eye Care Practitioners

The questionnaire was developed to assess:

1. the self-reported clinical practice behavior and opinion of eye care practitioners in myopia management.
2. the perception of eye care practitioners in promoting myopia control interventions to understand the barriers.

A self-administered, internet-based cross-sectional survey in English was distributed using SurveyMonkey (Palo Alto, California, USA) through various professional bodies in Singapore to reach eye care practitioners (optometrist, dispensing opticians, ophthalmologists). The questionnaire comprised 10 questions relating to the self-reported clinical management behaviors of practitioners for myopia.

- What is your profession? (Optician, optometrist, ophthalmologist, student in the eye care course)
- Are you an optical shop/ clinic owner? (Yes, no)
- Do you prescribe Myopia Control interventions? (Yes, No)
- If you do prescribe, may I know what do you prescribe to your customers/ patients? (Multiple options could be selected)
    - Atropine
    - Myopia control spectacle lenses
    - Orthokeratology lenses
    - Multifocal soft contact lenses
    - Contact lenses [Soft/RGP]
- Do you prescribe Myopia Control the moment the child has myopia on the first visit? (yes, no)
- May I know the reason for prescribing or not on the first visit? (free text)
- What is preventing you from using Myopia Control on the first visit? (multiple options could be selected)
    - limited by parent's budget
    - lack of confidence/experience to prescribe
    - too much chair time/ too much time spent explaining Myopia control
    - not knowing enough about myopia control [lack of information]
    - lack of trust from parents
    - lack of products to recommend
    - lack of support from the lens company
    - the cost price is too high
    - lack of education to the parents
    - lack of confidence to manage children
    - due to unpredictable outcomes
    - safety of product
    - limited access to instrumentation [e.g., To prescribe orthokeratology lenses, a corneal topographer is needed]
- What would be your most preferred option to prescribe to your patient when it comes to Myopia Control? (Ranking: Atropine, Myopia control spectacles lenses, multifocal soft contact lenses, orthokeratology lens)
- What would encourage you to fit Myopia Control Interventions more often? (multiple options could be selected)
    - Education and confidence [product update, myopia management]
    - experience [having workshops to practice more often]
    - having safer products
    - more product choice
    - cheaper products, education to manage children
    - guideline from government
    - Please specify other reasons if not stated above (free text).

Questionnaire Design for Parents

Another questionnaire was designed to assess:

1. the knowledge of parents about myopia control products.
2. the interaction between parents and eye care practitioners.

The questionnaire was self-administered, internet-based cross-sectional survey in English was distributed using Google Forms (Google Inc., California, USA) through parents' networks in schools and social media to reach Singaporean parents with myopic children. The survey for parents comprises seven questions related to their opinion about myopia management and experience with practitioners.

- Do you have a child/children with myopia (shortsightedness)? (Yes, No)

- What is your child/children using to correct their vision? (Normal spectacles, orthokeratology lenses, myopia control spectacle lenses, atropine, multifocal soft contact lenses, normal soft contact lenses, RGP [hard lenses], NIL)
- Why are they using these methods to correct their vision? (free text)
- Did any eye care specialist recommend any Myopia Control options? (Yes, No, NA)
- May I know what have they recommended? (free text)
- What influenced you in choosing the types of vision correction for your child? (multiple options could be selected)

- recommended by friends/family
- recommended by social media
- recommended by your eye care specialists
- advertisements
- due to superstition/traditional reasons
- affordability in the long run
- family consent

- What do you think will work best for Myopia Control? (Ranking: Normal spectacles, orthokeratology lenses, myopia control lenses, atropine, multifocal soft contact lenses, normal soft contact lenses, RGP [hard lens], outdoor activities, control the amount of time doing near work, nutrition, Ayurveda, Tradition Chinese Medicine).

Participation was voluntary and anonymous in the survey. The explanation for the research was explained in the message that was sent out and before the beginning of the survey. The data was collected between April 2020 and May 2020.

Statistical Analysis

Statistical analysis was conducted with IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, New York, USA). Count and proportion were calculated for each question response, and comparison was done using the chi-square test with $p < 0.05$.

RESULTS

Responses

A total of 130 complete survey responses were received from the professional groups. Of the study participants, 32 (24.6%) were ophthalmologists, 91 (70.0%) were optometrists, 2 (1.5%) were opticians and 5 (3.8%) were optometrist students. For the survey on parents' opinion, a total of 138 parents responded to the survey, of which 99 (71.7%) of them had at least one myopic child.

Frequency of Prescribing Myopia Correction

Majority of the practitioners (80.0%), do prescribe myopia control intervention to myopic patients; $X^2(0) = 416$, $p < 0.001$. However, only 33.1% did so during the first visit; $X^2(0) = 21$, $p < 0.001$). Overall, most practitioners preferred myopia control spectacle lenses (30.0%) and atropine (53.1%) as myopia control interventions; $X^2(3) = 3{,}477$, $p < 0.001$. As such, most of them dispensed myopia control spectacle lenses (56.2%), followed atropine (43.8%) and orthokeratology (26.2%) in real life (see **Figure 1**).

According to the survey on 99 parents with myopic children, 41.4% were recommended to use myopia control interventions by their eye care practitioners; $X^2(1) = 82$, $p < 0.001$. Of which, 24.4% were recommended to use atropine, 39.0% of them were advised to use myopia control spectacle lenses and 9.8% were recommended orthokeratology. The rest were recommended other interventions like increasing outdoor time, reducing near work, looking at green pasture and blue-cut lenses, **Figure 2**, gray bars. Out of those that were recommended to use myopia control interventions, 75.6% were using myopia control interventions. Of which, 39.0% used myopia control spectacle lenses, 9.8% used orthokeratology, 24.4% used atropine and 2.4% used combination treatment (see **Figure 2**), gray bars. Despite the recommendation from eye care practitioners, even up to 24.4% of those given myopia control recommendations used single vision lenses (spectacle or soft contact lenses) for correction.

Factors Influencing Parents' Decision to use Myopia Control Options

78.8% of the parents would follow what the eye care practitioners recommended, with only 21.2% taking advice from their friends or family members. 18.2% needed to have affordability in the long run, and 7.1% would follow social media or get consent from their family (see **Figure 3**).

Perceived Effectiveness of Myopia Control Options by Parents

Parents perceived increasing outdoor time (52.5%) and controlling the amount of near work (54.5%) to be effective myopia control options. 38.4% perceived myopia control spectacle lenses and single vision lenses (36.4%) to be the best for myopia control. Followed by nutrition (27.3%), Atropine (17.2%) and orthokeratology (11.1%) (see **Figure 4**).

Factors Preventing the Prescription of a Myopia Control Intervention

64.4% wanted to monitor the rate of myopia progression first before prescribing myopia control intervention. 13.8% were worried that parents cannot afford it, 8.0% wanted to look at the age and 11.5% wanted to assess the risk of myopia first. Other 2.3% needed more evidence that the product would work. In comparison, the remaining 6.9% would advise behavioral change like less near work and more outdoor time, ensure good binocular vision and find it easier to give single vision lenses and 1.1% were concerned about the safety of the product (see **Figure 5**).

Factors That Will Help Eye Care Practitioners to Prescribe Myopia Control Interventions

Most (57.7%) felt that having more education on myopia management and product would encourage them to prescribe myopia control interventions. 47.7% also felt that a hands-on workshop to experience the fitting of myopia control interventions would give them more confidence. 44.6% also

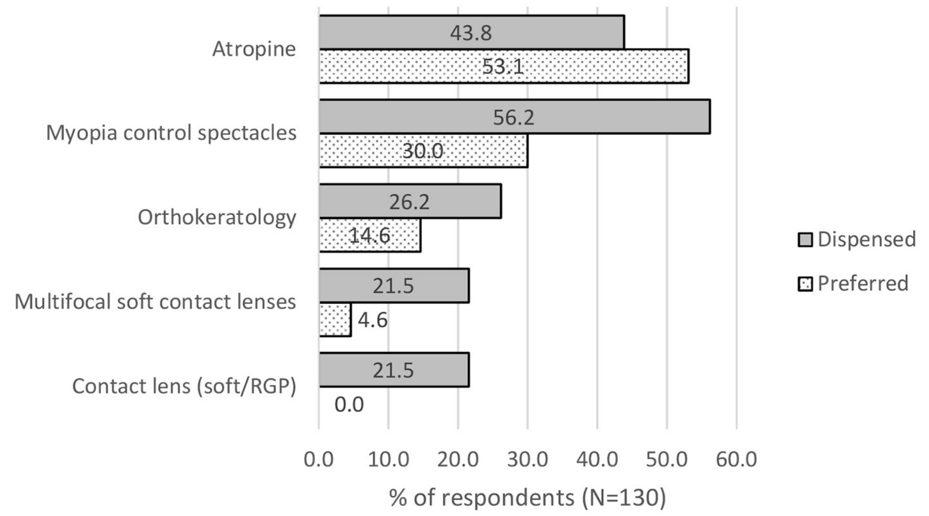

FIGURE 1 | Preference and actual dispensing of the type of myopia control products by eye care practitioners.

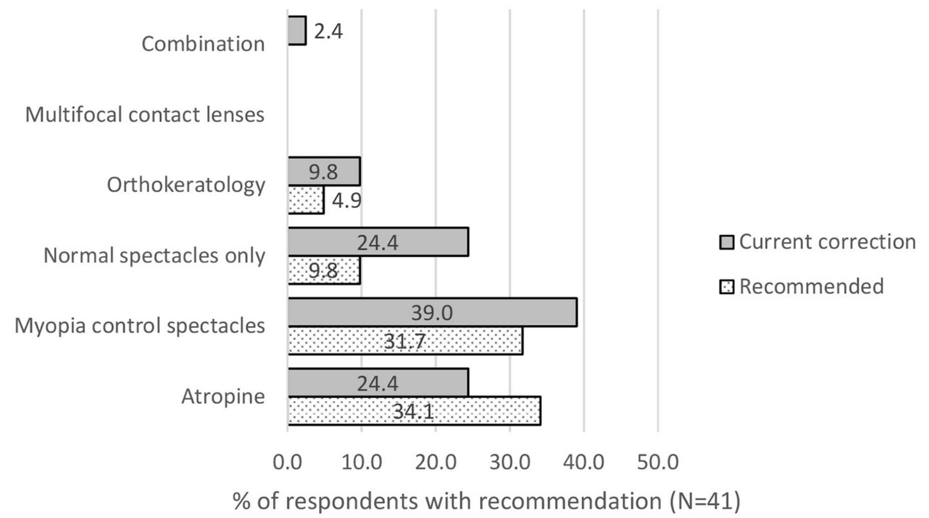

FIGURE 2 | Out of those parents recommended to use myopia control, which product was most recommended (grey bars) by eye care professionals and used (dotted bars) by respondents.

wanted more education on managing children as they lack experience in pediatric optometry/ophthalmology (see **Figure 6**).

DISCUSSION

This study examines the self-reported attitudes and practices of eye care practitioners and parents' opinions toward myopia control in Singapore. One hundred and thirty eye care practitioners responded out of about 2,000 registered opticians and optometrists and about 300 registered ophthalmologists in Singapore. That is about 7.4% of registered optometrists and 10.7% of registered ophthalmologists in Singapore. The exact response rate was unknown as we could not measure the number of eye care practitioners who had received the questionnaire. It may be presumed that questionnaires are completed by people interested in myopia control of myopia in general based on 80.0% of them prescribing myopia control intervention in their practice. The type of myopia control prescribed by each eye care practitioner was in line with the healthcare regulation in Singapore. The ophthalmologists would mainly prescribe atropine as it can only be done by ophthalmologists under the Singapore Medicine Act and Optician and Optometrist act (20, 21). Nevertheless, the regulation did not stop them from recommending interventions that they cannot prescribe as they could refer out to practitioners that prescribe them.

A study on pediatric ophthalmologists in Germany showed that 57% routinely treat to slow down myopia progression and 74.8% do so if the progression rate was 1 dioptre or more per

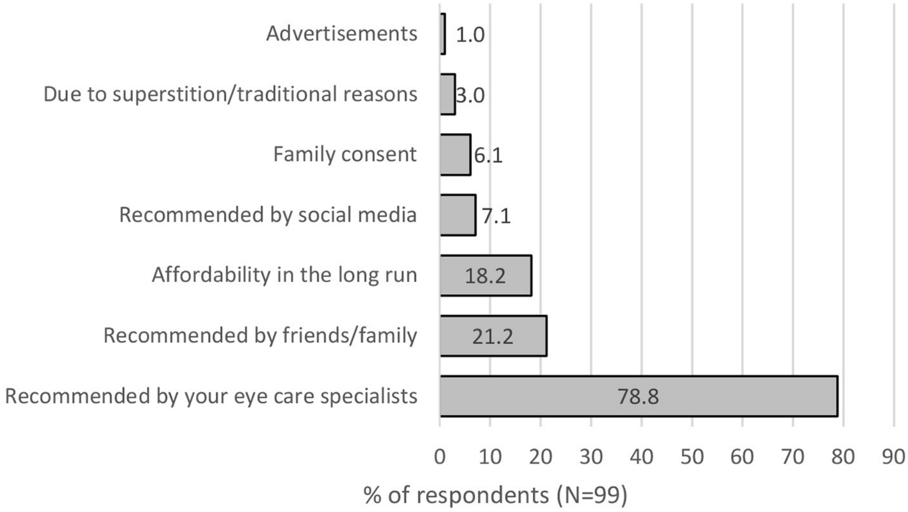

FIGURE 3 | The factors that will influence parents to use the type of vision correction.

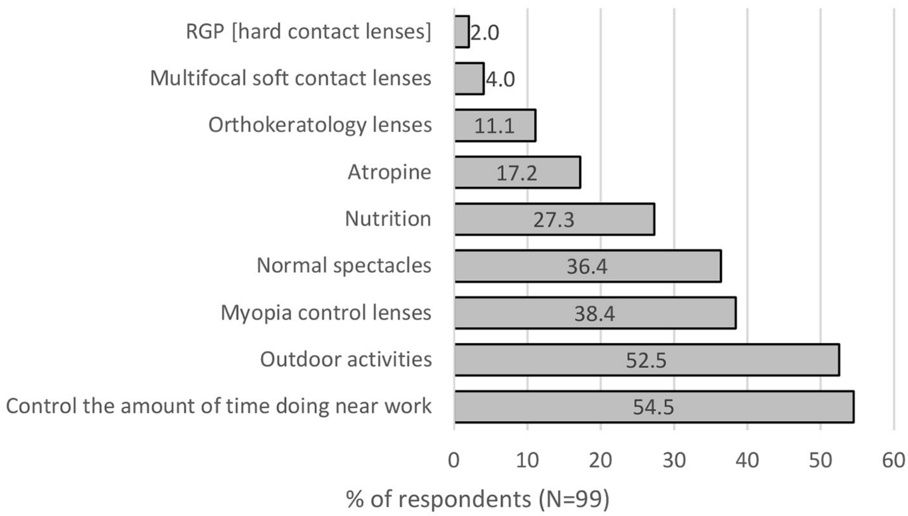

FIGURE 4 | Perceived effectiveness of myopia control interventions by parents.

year. The most common treatment used were atropine 0.01% (63.4%), followed by atropine 1% (10.9% and atropine 0.5% (8.9%). In addition, most of them also recommend more outdoor time (86%) and less screen time (60.2%) (22). This is similar to the outcome of this survey where 40.63% of ophthalmologists treated myopia at the first visit with 62.5% of them monitoring the rate of progression first. Though 100% of them prescribes atropine, 96.9% preferred atropine as the first choice, 78.13% preferred myopia control spectacles as the second choice and 56.3% selected multifocal contact lenses as the third choice.

Out of 138 parents, 99 have at least one myopic children responded to the questionnaire for their opinions about myopia control. Similar to the questionnaire for eye care practitioners, the exact response rate could not be adequately estimated. It was presumed that parents who responded to the questionnaire are interested in myopia and are assumed to be more aware of myopia control methods.

Though 80.0% of the eye care practitioners prescribe myopia control interventions, only 33.1% do so for patients who visited them for the first time. This outcome was also reflected in the parents' questionnaire, with only 41.4% given any recommendation. The main reason (56.6%) for not dispensing myopia control intervention during the first visit as 64.4% of them wanted to monitor the rate of myopia progression. However, there was a lack of myopia progression data from a first-time patient. This is especially true for first-time wearers of visual correction. If parents do not return to the same practice, they will always be first-time patients in another practice.

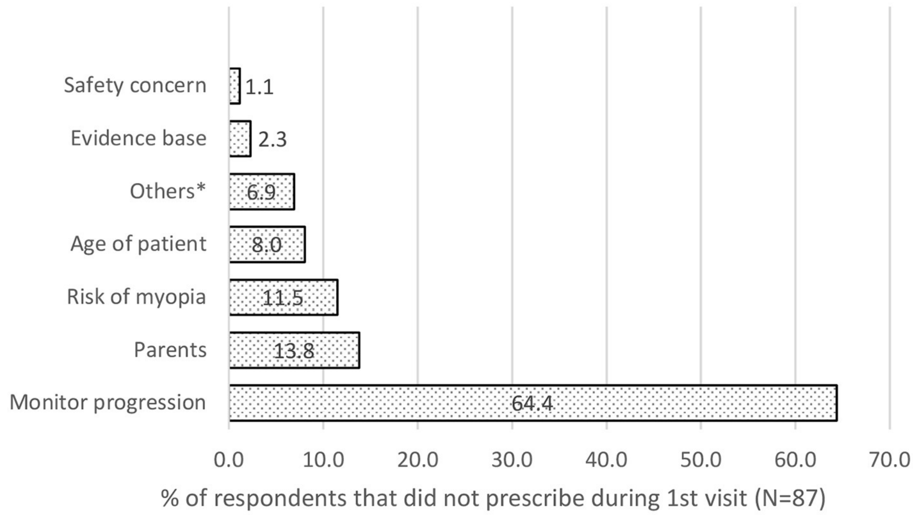

FIGURE 5 | Main factors preventing Eye care practitioners from prescribing myopia control intervention during the first visit.

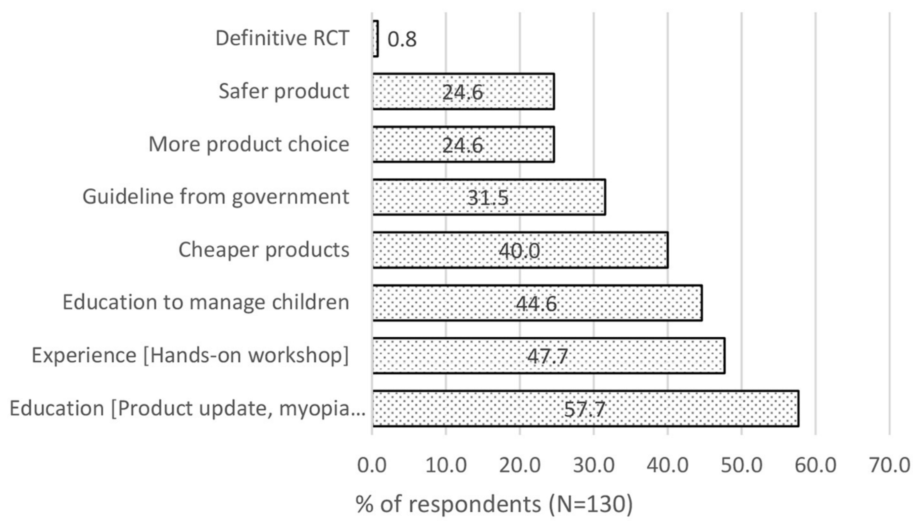

FIGURE 6 | Factors that will encourage Eye care practitioners to prescribe myopia control interventions.

Atropine was the preferred option in the opinion of 53.1% of eye care practitioners but 52.5% of parents preferred more outdoor time. From this study, if eye care practitioners gave parents advice, most of them (75.6%) took the advice and used myopia control interventions like myopia control spectacles, atropine and orthokeratology. However, all parents who were not given any advice had normal spectacle lenses or soft contact lenses (single vision lenses) prescribed for their children. Without any prior knowledge and proper advice from eye care practitioners, normal spectacle was the next preferred choice of most parents. Parents' responses to factors that influence their choice of vision correction further proved that eye care practitioners' recommendation is pivotal in parents' decision to use myopia control intervention for their children as 78.8% of parents were influenced by eye care practitioners' recommendation.

13.8% of eye care practitioners were worried that parents could not afford myopia control intervention, contrary to the findings that 78.8% of parents were influenced by eye care practitioners' recommendations and only 18.2% of parents were concerned about affordability in the long run. Concern about cost by eye care practitioners was similar to the global survey conducted by Wolffsohn et al. (16, 17), where the main reason for not prescribing myopia control intervention was due to cost (20.6%), followed by inadequate information about modalities (17.6%) and unpredictable outcomes (9.6%).

Finally, most eye care practitioners felt that continuous education on myopia management products and hands-on workshops would give them more confidence and experience to prescribe them in their practice. Ability to manage young patients was also crucial since myopia onset usually happens at a young age (23). Despite the vast volume of research evidence for myopia management (14), a lack of confidence in appraising studies (24) and insufficient time in clinical practice (25) are possible reasons for eye care practitioners to not read up scientific publications on myopia control. Moreover, eye care practitioners have the added benefit of accruing points from education programs to maintain their professional license instead of learning by themselves through reading scientific publications on myopia control. Similar to Australia, there is an absence of clinical guidelines for myopia control from regulatory bodies like the Optometrists and Opticians Board in Singapore. However, the lack of regulatory approved guidelines was not the main concern (31.5%) in Singapore, unlike the study in Australia by Douglass et al. (18). Though there are published guidelines that recommend that myopia onset at a younger age should be offered myopia control intervention (15), and the type of intervention could be based on the rate of myopia progression (14). There was no clear definition in the published guidelines on minimum age, degree of myopia and rate of myopia progression for eye care practitioners to recommend myopia control interventions and criteria for ceasing treatments. This is evident in the findings of different regions in response to the minimum age and amount of myopia to prescribe myopia control (17, 18, 20, 21). Hence, further studies are needed to have an improved guideline to provide more consistent and evidence-based care.

As this study was conducted within a short period, the sample size was small and may not be representative of the whole eye care community in Singapore. Due to the options designed in the questionnaire to focus more on myopia control interventions, outdoor time, screen time and near work was not included in the multiple choices. As such this study was not able to investigate the awareness of outdoor time, screen time and near work for myopia control in parents and eye care practitioners. Nevertheless, there was a previous study done to establish that 87.7% of parents in Singapore were aware of the protective role of outdoor activity in myopia development and progression (26). This was mostly attributed to the public education done by the National Myopia Prevention Program together with other representatives from the Ministry of Education, Singapore Armed Forces, Ministry of Social and Family Development, National University of Singapore, Singapore Eye Research Institute, Optometrists and Opticians Board, Ministry of Health, and Singapore optometric and professional groups (27). Whether awareness translates to actual practice will be interesting to investigate further.

CONCLUSIONS

This study where questionnaires were given to eye care practitioners and parents in Singapore identified that eye care practitioners are the critical influence for prescribing myopia control. Uptake of myopia control can improve if more education is given to eye care practitioners for more updates and experience with the products for and management of myopic children. The cost of myopia control is of concern to eye care practitioners. Hence health economic evaluation should be done to understand the cost-effectiveness of using myopia control interventions to prevent myopia related pathology. Despite the availability of published guidelines on myopia management, further research is required to establish the minimum age, amount of myopia, and progression to start prescribing myopia control intervention, age to cease treatment or give myopia control to all myopic patients at the first visit. Regulatory approval of myopia guidelines should be considered to support the change in behaviour in eye care practitioners on myopia management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AY: conceptualization, methodology, supervision, project administration, and writing—original draft preparation. AY and BD: validation. AY and BP: formal analysis. AY and PV: investigation. BD: resources. BD and BP: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

1. Resnikoff S, Jonas JB, Friedman D, He M, Jong M, Nichols JJ, et al. Myopia – a 21st century public health issue. *Investig Ophthalmol Vis Sci.* (2019) 60:Mi–ii. doi: 10.1167/iovs.18-25983
2. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006

3. Saw SM, Gazzard G, Shin-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt.* (2005) 25:381–91. doi: 10.1111/j.1475-1313.2005.00298.x
4. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell, P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol.* (2014) 157:9–25.e12. doi: 10.1016/j.ajo.2013.08.010
5. Wong YL, Sabanayagam C, Ding Y, Wong CW, Yeo ACH, Cheung YB, et al. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. *Investig Ophthalmol Vis Sci.* (2018) 59:4603–13. doi: 10.1167/iovs.18-24032
6. Chua SYL, Foster, P.J. The economic and societal impact of myopia and high myopia BT - updates on myopia: a clinical perspective. In: Ang M, Wong TY, editors. Singapore: Springer (2020). pp. 53–63. ISBN 978-981-13-8491-2
7. Naidoo KS, Fricke TR, Frick KD, Jong M, Naduvilath TJ, Resnikoff S, et al. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. *Ophthalmology.* (2019) 126:338–46. doi: 10.1016/j.ophtha.2018.10.029
8. Wildsoet CF, Chia A, Cho P, Guggenheim JA, Polling JR, Read S, et al. IMI – Interventions myopia institute: interventions for controlling myopia onset and progression report. *Investig Ophthalmol Vis Sci.* (2019) 60:M106–31. doi: 10.1167/iovs.18-25958
9. Bao J, Yang A, Huang Y, Li X, Pan Y, Ding C, et al. One-year myopia control efficacy of spectacle lenses with aspherical lenslets. *BMJ J.* (2021) 1–6. doi: 10.1136/bjophthalmol-2020-318367
10. Lam CSY, Tang WC, Tse DYY, Lee RPK, Chun RKM, Hasegawa K, et al.H. Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. *Br J Ophthalmol.* (2019) 104:363–8. doi: 10.1136/bjophthalmol-2018-313739
11. Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young, et al. A 3-year randomized clinical trial of misight lenses for myopia control. *Optom Vis Sci.* (2019) 96:556–67. doi: 10.1097/OPX.0000000000001410
12. Kang P, Swarbrick, H. New perspective on myopia control with orthokeratology. *Optom Vis Sci.* (2016) 93:497–503. doi: 10.1097/OPX.0000000000000826
13. Yam JC, Li FF, Zhang X, Tang SM, Yip BHK, Kam KW, et al. Two-year clinical trial of the Low-Concentration Atropine for Myopia Progression (LAMP) study: phase 2 report. *Ophthalmology.* (2020) 127:910–19. doi: 10.1016/j.ophtha.2019.12.011
14. Gifford KL, Richdale K, Kang P, Aller TA, Lam CS, Liu YM, et al. IMI – Clinical management guidelines report. *Investig Ophthalmol Vis Sci.* (2019) 60:M184–203. doi: 10.1167/iovs.18-25977
15. Németh J, Tapasztó B, Aclimandos WA, Kestelyn P, Jonas JB, De Faber, et al. Update and guidance on management of myopia. European Society of Ophthalmology in cooperation with International Myopia Institute. *Eur J Ophthalmol.* (2021) 31:853–83. doi: 10.1177/1120672121998960
16. Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Li M, et al. Global trends in myopia management attitudes and strategies in clinical practice. *Contact Lens Anterior Eye.* (2016) 39:106–16. doi: 10.1016/j.clae.2016.02.005
17. Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Jones D, et al. Global trends in myopia management attitudes and strategies in clinical practice – 2019 update. *Contact Lens Anterior Eye.* (2020) 43:9–17. doi: 10.1016/j.clae.2019.11.002
18. Douglass A, Keller PR, He M, Downie, L.E. Knowledge, perspectives and clinical practices of Australian optometrists in relation to childhood myopia. *Clin Exp Optom.* (2020) 103:155–66. doi: 10.1111/cxo.12936
19. Koh V, Yang A, Saw SM, Chan YH, Lin ST, Tan MMH, et al. Differences in prevalence of refractive errors in young asian males in Singapore between 1996-1997 and 2009-2010. *Ophthalmic Epidemiol.* (2014) 21:247–55. doi: 10.3109/09286586.2014.928824
20. The Statutes of the Republic of Singapore. *Medical Registration Act (Chapter 174) LAW Revis. Comm. UNDER Auth. Revis. Ed. LAWS ACT (CHAPTER 275)* (2014).
21. The Statutes of the Republic of Singapore. *Optometrists and Opticians Act (Chapter 213A) LAW Revis. Comm. UNDER Auth. Revis. Ed. LAWS ACT (CHAPTER 275)* (2008).
22. Gomez-de-Liaño R, Farzavandi SK, Zloto O, Sprunger DT, Wygnanski-Jaffe T, Mezer, et al. Correction to: current trends among pediatric ophthalmologists to decrease myopia progression—an international perspective. *Graefe's Arch Clin Exp Ophthalmol.* (2018) 256:2015–17. doi: 10.1007/s00417-018-4110-x
23. Chua SYL, Sabanayagam C, Cheung, Y.-B., Chia A, Valenzuela RK, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt.* (2016) 36:388–94. doi: 10.1111/opo.12305
24. Haynes B, Haines A. Barriers and bridges to evidence based clinical practice. *BMJ.* (1998) 317:273–6. doi: 10.1136/bmj.317.7153.273
25. Heiwe S, Kajermo KN, Tyni-Lenné R, Guidetti S, Samuelsson M, Andersson L, et al. Wengström, Y. Evidence-based practice: attitudes, knowledge and behaviour among allied health care professionals. *Int J Qual Heal Care.* (2011) 23:198–209. doi: 10.1093/intqhc/mzq083
26. Salim AT, Keel S, Foreman J, Dirani M. *Awareness of Myopia: A Survey Among Parents Residing in Singapore*. (2019) 1–13. doi: 10.21203/rs.2.10314/v1. Available online at: https://assets.researchsquare.com/files/rs-1337/v5/97c4db86-e2b7-4529-a6e9-aded1457f65c.pdf?c=1631827803
27. Karuppiah V, Wong L, Tay V, Ge X, Kang, L.L. School-based programme to address childhood myopia in Singapore. *Singapore Med J.* (2021) 62:63–8. doi: 10.11622/smedj.2019144

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Prevalence and Risk Factors of Myopia in Young Adults: Review of Findings From the Raine Study

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Myopia tends to develop and progress fastest during childhood, and the age of stabilization has been reported to be 15–16 years old. Thus, most studies on myopia have centered on children. Data on the refractive error profile in young adulthood — a time in life when myopia is thought to have stabilized and refractive error is unaffected by age-related pathology such as cataract — are limited. The Raine Study has been following a community-based cohort of young adults representative of the general Western Australia population since their prenatal periods in 1989–1991, with eye examinations performed when participants were 20 and 28 years old. At 20 years old, prevalence of myopia in the cohort was 25.8%. Using long-term trajectory of serum vitamin D levels and conjunctival ultraviolet autofluorescence (CUVAF) area to objectively quantify sun exposure, the Raine Study confirmed a negative relationship between time spent outdoors and myopia prevalence. However, prospective studies are required to determine the amount of CUVAF area or serum vitamin D levels associated with time duration. Combining data from the Raine Study and several other cohorts, Mendelian randomization studies have confirmed a link between myopia and a genetic predisposition toward higher education. Several novel potential associations of myopia or ocular biometry were investigated, including fetal growth trajectory, which was found to be significantly associated with corneal curvature at 20 years. By age 28, myopia prevalence had increased to 33.2%. Between 20 and 28 years old, myopia progressed and axial length elongated, on average, by −0.041D/year and 0.02 mm/year, respectively. Smaller CUVAF area at follow-up, female sex, and parental myopia were significant risk factors for myopia incidence and progression between 20 and 28 years. Given the limited research in young adults, further investigations are warranted to confirm the Raine Study findings, as well as identify novel genetic or environmental factors of myopia incidence and progression in this age group.

Keywords: axial length, the Raine Study, myopia, risk factors, young adults, education, sun exposure, time spent outdoors

INTRODUCTION

Eye conditions tend to arise during childhood or older adulthood, thus most studies of eye diseases and refractive error have involved children or older adults. Conversely, the eye health of young adults has received limited attention in the literature (1). Young adulthood tends to be a period when eye health and vision is expected to be at its peak, and when refractive error, especially myopia, has stabilized while unaffected by cataracts. Studying young adults, rather than measuring ocular parameters during childhood when eye development is still occurring, may inform on early life and childhood factors that may influence eye health. The eye examinations in the Raine Study aimed to address this gap in the literature. This article summarizes the myopia findings arising from the Raine Study, with a focus on the risk factors and progression of myopia during young adulthood.

THE RAINE STUDY

In 1989–1991, 2,900 pregnant women were recruited from obstetric clinics in Perth, Western Australia (2). The study explored the effect of frequent ultrasound scans during pregnancy on birth outcomes and formed a cohort for studying the effects of early life events on later health outcomes. The women were randomly assigned to an "intensive imaging" group (ultrasound and Doppler imaging performed at 18, 24, 28, 34, and 38 weeks' gestation) or the control group (standard single ultrasound scan at 18 weeks') (3). Children born to these women (n= 2,868) formed the original study cohort (Gen2) and have been undergoing a series of various health and medical examinations from birth. With the enrolment of their parents (Gen1), grandparents (Gen0), and children (Gen3), the Raine Study has become one of the longest running multigenerational cohort studies in the world.

A main strength of exploring associations with myopia or other refractive error in the Raine Study Gen2 cohort is that it is generally representative of the general Western Australia adult population of similar age (4). At birth, and at the 8-, 14-, 17-, 20-, and 22-year follow-ups, elements of participants' socioeconomic profile, such as employment and income levels, were all within 7% difference from that of the West Australian population. However, because Gen2 participants were recruited before birth, an inherent limitation of the Raine Study is that the majority are Caucasian (∼85.5%) and all were born in the state, as opposed to the rest of the state which has seen the number of overseas-born residents increase from 32.2% in 2001 to 39.7% in 2016. Additionally, a gradual loss to follow-up due to the longitudinal nature of the study has occurred, but participants and non-participants of the 20-year follow-up had similar birth and demographic characteristics (4). The representativeness of the Gen2 sample at the 28-year follow-up requires evaluation, although its profile is not expected to be markedly divergent from that of the general population.

Eye Examinations

The Gen2 20-year follow-up was conducted from March-2010 to February-2012, when 1,344 participants (46.9% of the original cohort of 2,868) had their first eye examination as part of the study. Data collected from this allowed us to document the prevalence of refractive error, pterygium, and keratoconus (5–7), and profile the normative optical coherence tomography-derived parameters (8–11), in community-based young adults.

The Gen2 28-year follow-up eye examination (12) was conducted from March-2018 to March-2020 and attended by 813 participants (28.3% of original cohort; it is worth noting that data collection for this follow-up ended early because of the COVID-19 pandemic). This follow-up documented the longitudinal change in eye measures in young adults, with a focus on the 8-year change in refraction and optic disc measures. Both follow-ups included ocular biometry and cycloplegic autorefraction using the same instrument models (IOLMaster V.5; Carl Zeiss Meditec AG and Nidek ARK-510A; NIDEK, respectively).

MYOPIA AT 20 YEARS OLD

Based on the International Myopia Institute definitions (13), 25.8% of the Raine Study participants had myopia at age 20 (spherical equivalent [SphE] ≤-0.50 D in either eye) (14), including 5.5% with SphE ≤-3.00 D and 1.5% with ≤-6.00 D (high myopia) (6, 14).

Confirmation of Risk Factors by the Raine Study

Time Spent Outdoors

Many studies quantified time spent outdoors using self- or parent-reported data, which is subject to recall bias, especially if the data were collected retrospectively (15). Light sensors such as actigraphs can quantify time spent outdoors objectively; however, participants are required to wear the device on a regular basis and this approach is typically only used for short-term data collection.

Our eye provides natural markers of sun exposure: the presence of pterygia and the amount of conjunctival ultraviolet autofluorescence (CUVAF). While pterygium is uncommon in young adults, areas of CUVAF are measurable in adults and children, although it is less common in younger children (16). Like pterygium, the formation of CUVAF is due to the Coroneo effect, where light rays enter at an oblique angle, through the cornea and crystalline lens, and focus at the limbal area. With more UV entering from the temporal aspects, the light rays are focused at the nasal bulbar conjunctiva. Thus, CUVAF and pterygium tend to be larger and more common at the nasal than the temporal bulbar conjunctiva (17). Just as actinic damage on the skin fluoresces under short wavelength light due to cellular changes from chronic sun exposure (18), actinic changes in the bulbar conjunctiva secondary to UV exposure cause affected areas to fluoresce under low-level UV light, which can be photographed and measured using specialized instruments.

Using CUVAF to quantify sun exposure, the Raine Study confirmed a significant relationship between sun exposure and myopia. Myopia rates in the participants in the lowest quartile of CUVAF area (indicating less sun exposure) were more than double those in the highest quartile (33 vs. 16%) (19). Total CUVAF area (right+left eyes) was also significantly smaller in those with myopia compared to non-myopes (median= 31.9 vs. 47.9 mm^2) (19). The authors pointed out that this difference in CUVAF area was unlikely to be related to the use of spectacles or contact lenses, as demonstrated by the similar CUVAF area in myopes who did and did not normally wear optical correction (31.9 vs. 31.6 mm^2) and hyperopes who did and did not wear optical correction (43.8 vs. 49.1 mm^2). When only the participants who wore optical correction were included, a significant difference in CUVAF area was still found between myopes and hyperopes (31.9 vs. 43.8 mm^2). Even though spectacles often now have UV-filters, these may not provide protection against UV rays entering the eyes at oblique angles, which are responsible for CUVAF formation.

Serum vitamin D is an objective measure of recent time spent outdoors. In concordance with previous observations of the link between less time spent outdoors and myopia, the Raine Study found an inverse relationship between serum vitamin D levels and myopia, after correcting for sex, ethnicity, parental myopia, and CUVAF area (20, 21), with an odds ratio (OR) of 0.88 for myopia for every 10 nmol/L increase in vitamin D levels at age 20. Statistical significance was found for vitamin D measured in recent years (17- and 20-year) but not during childhood (6-year) or adolescence (14-year) (21). This finding appears at odds with the notion that sun exposure during early childhood may be protective against myopia. The authors suggest that the lack of statistical significance could be because vitamin D may be a poorer indicator of sun exposure at younger ages, although it is not clear why this may be the case and this has yet to be verified (The limitations of using serum vitamin D as a marker for time outdoors are discussed in the next sub-section). The authors also suggested that insufficient study power, where there were fewer participants with vitamin D measurements at 6 and 14 years ($n =$ 618 and 988, respectively), could also explain why no relationship between these variables was found (21).

Strengths and Limitations of Objective Measures of Time Outdoors

Using CUVAF area and serum vitamin D levels to quantify sun exposure has significant advantages: the measures are objective and do not require participants to use any special device (e.g., actigraphs). CUVAF area is unaffected by dry eyes (22) and measures long-term sun exposure (23, 24), which may be more relevant for the study of myopia development and progression than short-term sun exposure measures. Vitamin D levels can provide information on short-term sun exposure.

However, both methods are more difficult to obtain compared to self-reported data. CUVAF photography requires specialized camera lenses and electronic filtered flash, then measurement of the CUVAF area manually or by an automated program (22, 24, 25). Even though manual measurement of CUVAF area is subjective, the intra- and interobserver reliability of CUVAF area measurements is high (correlation coefficients of both >0.9) (26). While CUVAF is generally a good representation of cumulative long-term sun exposure, shrinking of CUVAF area with age has been observed (24, 27), possibly because of use of sunglasses during adulthood and development of cataracts (thus allowing less UV to enter the eye) in older age. CUVAF may therefore become less accurate as a measure of sun exposure with older age. Serum vitamin D analysis requires collecting blood samples, which may be considered too invasive for some people, especially children. Another drawback of these markers is that a time duration is not quantified, i.e., how much time spent outdoors, as quantified using CUVAF, is associated with a unit decrease in myopia risk or progression. Prospective studies should be undertaken to explore this. The use of sunglasses (which tends to provide more coverage against UV light entering from oblique angles than conventional prescription glasses) or UV-blocking contact lenses, may influence the area of CUVAF (19, 24), while use of sunscreen can reduce synthesis of vitamin D. Actual time spent outdoors would then be underestimated using these approaches (24, 28).

Education

Several studies have confirmed that higher education is a risk factor for myopia (29, 30). Fan et al. (30) performed a meta-analysis of the gene–environment interaction effect, combining data from the Raine Study together with results from 33 other studies totaling over 50,000 participants. Participants who completed education beyond secondary school were, on average, 0.59D more myopic than those who had not, with a greater impact of education in Asians compared to Caucasians (difference of −1.09D and −0.49D, respectively).

While Mendelian randomization studies have shown that a genetic predisposition to higher education is linked with higher risks of myopia (31, 32), we should be cautious in concluding a causal link between education and myopia as this relationship is likely confounded by other risk factors such as less time spent outdoors and increased near work (30).

Novel Data: Effects of Taking a Gap Year Between High School and University

With increased push to pursue tertiary and higher education, more individuals are likely to enroll in university. As myopia can start to develop and continue progressing in early adulthood (14), this may further drive the myopia epidemic. However, it is not prudent to discourage higher education as it contributes to individual wellbeing, economic growth, and advancements in science and technology. Given that myopia progression slows with age, taking a break from formal education during the late teenage years between high school and university may help to reduce overall myopia progression or risk of myopia onset, relative to completing all formal education early in life, through the teenage years when myopia may still progress quickly. We tested this hypothesis by exploring the association between taking a gap year after high school and myopia.

Of the 1,344 participants who attended the Gen2 20-year eye examination, 816 had refraction data and information on any gap years taken after high school. We did not find a significant difference in myopia prevalence between those who took a gap year and those who did not (26.3 vs. 23.5%, $p = 0.70$ adjusted for sex, ethnicity, CUVAF area, and eventual attainment of undergraduate degree). Similarly, there was no difference in SphE or axial length (AL). While participants who spent their gap year working had slightly longer eyes than those who spent it traveling

(Estimate = 0.21 mm; 95% confidence interval [CI] = −0.01 to +0.43), this failed to reach statistical significance ($p = 0.06$).

Taking a gap year is a common experience among Australian high school graduates. The COVID-19 pandemic has reduced international travel and casual employment, resulting in many young people choosing to start their tertiary education immediately rather than taking a gap year (33). Our data suggest that skipping a gap year will not have a major impact on myopia progression or prevalence.

Birth Order

There has been some evidence that first-born children are at higher risk of myopia than later-born children. However, previous studies had defined myopia based on level of unaided vision (6/12 or worse) (34, 35). To address this, four cohorts were analyzed: Raine Study Gen2 ($n = 1{,}344$), Avon Longitudinal Study of Parents And Children (ALSPAC; $n = 4{,}401$), Singapore Cohort Study Of Risk factors of Myopia (SCORM; $n = 1{,}959$), and Israeli Defense Force Pre-recruitment Candidates (IDFP; $n = 88{,}277$) (36). The larger cohorts found significantly higher rates of myopia in first-born compared to later-born children (ALSPAC: OR = 1.31, 95%CI = 1.05–1.64; IDFP: OR = 1.04, 95%CI = 1.03–1.06). In the IDFP, the difference in myopia prevalence between first- and fourth-born children was larger than the difference between the first- and second- or third-born children. The associations between birth order and myopia rates were unlikely to be due to chance, given that the two smaller cohorts also found a trend, albeit without statistical significance (Raine: OR = 1.18, 95%CI = 0.90–1.55; SCORM: OR = 1.25, 95%CI = 0.89–1.77). This association was significant even after excluding "only children" (who are, by definition, first-born), suggesting that this link is not mediated by environmental risk factors after birth. Guggenheim et al. (37) further confirmed this association in the United Kingdom Biobank (first- vs. second-born children OR = 1.12; 95%CI = 1.08-1.16) and noted that this association was weakened when highest level of education was accounted for, suggesting that the link could be partly mediated by increased educational pressure on first-born children. However, given the small increase in odds of myopia in first-born children, the association between birth order and myopia is unlikely to be clinically significant.

Explorations for Novel Risk Factors

The myriad of health and medical data collected by the Raine Study allowed us to explore for other potential risk factors of myopia that may otherwise be overlooked. In particular, information on gestation and birth parameters, activity and eating habits during childhood and adolescence collected prospectively can be used to identify early life associations of myopia.

Fetal Growth

The human eye starts to develop in the first trimester of gestation (38). Thus, disruptions or alterations to this ocular developmental process may affect visual outcomes. Indeed, lower birth weight has been linked with steeper corneas and shorter AL (39, 40). Thus, myopia associated with low birth weight is pathophysiologically different from school-myopia, which tends to result from axial elongation.

Birth weight is frequently used as a measure of intrauterine growth, and neonates with low birth weight are often assumed to have intrauterine growth restriction. However, many neonates with low birth weight may be constitutionally small, e.g. because the mother has a small stature, and have no other evidence of fetal growth restriction or associated complications (41, 42). Using multiple ultrasound images taken during gestation is a better way to examine fetal growth. Approximately half of the original Raine Study cohort underwent an "intensive imaging" protocol during gestation (3), providing a unique opportunity to model longitudinal fetal growth for each participant.

Multiple ultrasound scans and refractive information were available for 498 Raine Study Gen2 participants. The ultrasound scans were used to model the fetal growth trajectory based on fetal anthropomorphic measures, including head circumference, abdominal circumference, femur length, and estimated fetal weight (43). Dyer et al. (43) found that participants with consistently short or consistently long femur length during gestation tended to have a higher prevalence of myopia (27–29%) at 20 years old compared to those who had moderate femur lengths during late gestation (i.e., those with medium, big, or accelerated growths; 14–22%, $p = 0.04$). This suggests that there may be some *in utero* factors at play in late gestation that disrupted the coordination between ocular biometric measures (43).

Additionally, steeper corneas were found in participants who had slower growth in head circumference, femur length, and estimated fetal weight. While shorter AL was noted in those with slower fetal growths, this association did not reach statistical significance, which could be related to the large environmental influences on AL by the time an individual reaches 20 years of age.

Non-significant Risk Factors

As critical as it is to find risk factors for myopia, it is equally important to rule out other causal links and report these non-significant risk factors. Findings from the Raine Study have suggested limited associations of myopia (and other ocular parameters) with *in utero* ultrasound exposure (44), anesthesia exposure during childhood (45), sleep quality trajectory from childhood to adolescence (46), and dietary vitamin A intake (47). These are discussed briefly in the **Supplementary Notes**.

MYOPIA DEVELOPMENT AND PROGRESSION DURING YOUNG ADULTHOOD

Reports have suggested that myopia tends to stabilize around 15–16 years old (48, 49). However, longitudinal studies in university students in their early 20's (50–54) have demonstrated that myopia can progress or even begin after adolescence. However, beyond these university (50–54) or myopia (48, 49) cohorts, there are limited data on myopia development and progression in young adults, especially in the general population. This gives the impression that myopia progression during young adulthood is related to the pursuit of higher education. With the rising proportion of the population in indoor-based occupations (55), even if no higher education is completed, myopia development and progression in young adults may not be confined to university students.

Findings From the Raine Study

Based on the data collected at the 20- (baseline) and 28-year Raine Study Gen2 follow-ups, the prevalence of myopia and high myopia increased from 25.8 to 33.2% and 1.4 to 1.5%, respectively, with incidence of 14% and 0.7% (35). While the majority (52.2%) of participants had a stable refraction in both eyes over the 8 years, about one-third ($n = 261$) of participants had a myopic shift (change in 0.50D over 8 years) in at least one eye, including 152 who progressed in both eyes. A novel case study is presented in **Figure 1**, demonstrating rapid myopia progression in one participant (~5D over 8 years).

Across all participants, SphE progression, axial elongation, and lens thickening were also observed over the 8 years, at average rates of −0.041D/year, 0.02 mm/year, and 0.220 mm/year, respectively (all $p < 0.001$), although corneal curvature did not change over time (14). Based on these findings, it appears that myopia progression in young adults has a similar mechanism to that in children, i.e., driven by axial elongation. This suggests that childhood risk factors of myopia, such as decreased time spent outdoors, may also have a myopigenic role during young adulthood. The sub-section below discusses these potential risk factors.

As shown in **Table 1**, the Raine Study cohort had lower annual myopia incidence and progression that those previously reported in young adults (50–54). This is most likely because previous studies included only university students, who may be spending less time outdoors due to their studies.

Risk Factors

In our study (14), we further tested the hypothesis that major risk factors of childhood myopia — parental myopia, less time spent outdoors, and higher education — are also associated with myopia progression in early adulthood. Indeed, for each parent with myopia, odds of incident myopia increased by 1.6 times, while SphE and AL progression rates were increased by 0.01D/year and 0.005 mm/year. Interestingly, level of education was not associated with myopia incidence or progression. While less time spent outdoors, as quantified by CUVAF area, was associated with incident myopia, it was not associated with myopia progression, as has been suggested in some studies, although findings on the latter observation have been conflicting (56–58).

We additionally found that women had higher odds of incident myopia (OR = 1.8) and double the progression rate compared to men (SphE and AL progression: women: −0.04D/year and 0.02 mm/year vs. men: −0.02D/year and 0.01 mm/year), after correcting for education and CUVAF area (14). Longitudinal studies in children have similarly noted that girls' myopia progressed faster than boys' (59–61), attributing this difference to pubertal growth spurts (62). However, this is unlikely to explain the sex difference seen in our cohort of young adults. Given that potential confounding factors of education and time spent outdoors have been accounted for in this study, this difference in myopia status between males and females could be influenced by other factors, such as ocular changes during pregnancy, which should be explored in future studies (63–65).

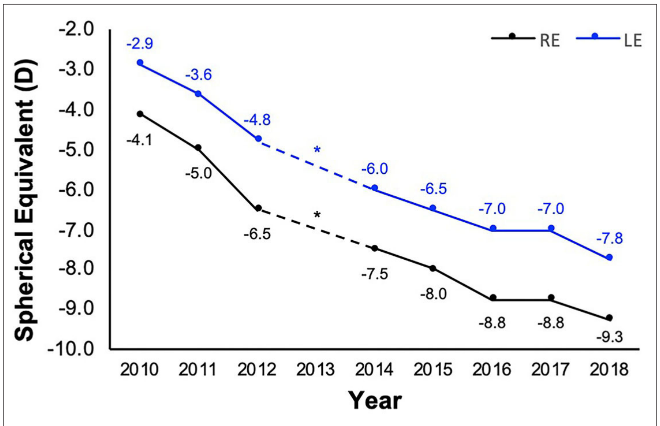

FIGURE 1 | Refraction of a participant with rapid myopia progression from 20 (year 2010) to 28 years old (year 2018). Refraction (spherical equivalent) history obtained from participant's optometrist *apart from 2013 when the participant did not visit the optometrist. The participant reported their occupation during the 8-year period to be computer-intensive (at or close to 100%), with the exception of the year 2013 and mid-2016 to 2017, when most of their time was spent on outdoor academic field work or traveling. While no refraction data was available at 2013 (*), from 2016 to 2017, no myopia progression was documented.

Novel Data: Sleep/Wake Time

Possible links exist between sleep parameters and myopia (66–70) (also see **Supplementary Notes**), although findings have been conflicting. Some cross-sectional studies (71, 72) have noted that myopes tend to go to sleep and rise later than non-myopes. In a 2-year longitudinal study of over 6,000 children, Liu et al. (73) similarly found a significant link between sleep/wake times and myopia. Children who went to sleep at 9:30 p.m. or later had a 1.45-OR for incident myopia and faster myopia progression by −0.16D, compared to those who went to sleep before 9 p.m. However, the 4-year longitudinal study by Wei et al. (74) failed to find such an association.

Here, we explored the relationship between sleep/wake time and myopia progression between 20- and 28-years in the Raine Study Gen2 cohort. At the 22-year follow-up (75), participants completed a questionnaire on their typical sleep and wake times on weekdays and weekends, and whether they considered themselves to be more of a "morning" or an "evening person." A total of 620 participants had sleep/wake time information at the 22-year follow-up and refractive data at both the 20- and 28-year follow-ups. Linear mixed-effect models were used to explore the effect of sleep measures

TABLE 1 | Myopia incidence and progression in young adults, as reported by previous studies.

References	Cohort	Follow-up duration	Myopia incidence	Myopia progression
The Raine Study (n = 701)	Community-based; baseline age = 20 years	8 years	1.75%/year	−0.041 D/year
Jacobsen et al. (52) (n = 143)	Medical students; baseline age = 23 years	2 years	4.8%/year	−0.12 D/year
Jorge et al. (50) (n = 118)	University students; baseline age = 21	3 years	6.5%/year	−0.10 D/year
Jiang et al. (53) (n = 64)	Optometry students; baseline age = 25 years	9 months during school term	-	−0.37 D/year
Loman et al. (54) (n = 117)	Law students; age = 27 years	3 years, retrospective[a]	6.3%/year[a]	-
Kinge and Midelfart, (51) (n = 224)	Engineering students; baseline age = 21 years	3 years	11%/year[b]	−0.17 D/year

[a]*Based on participant-reported information;* [b]*Kinge and Middelfart defines myopia as spherical equivalent ≤-0.25D.*

on longitudinal change in myopia measures, accounting for known confounders (CUVAF area, sex, ethnicity, and parental myopia) (14).

There was no obvious association between sleep time and SphE change. However, later times of falling asleep on weekends was associated with faster axial elongation by 0.003 mm/year for each hour delay in sleep time (95%CI = 0.000 to 0.004). A similar association was found for sleep time on weekdays but this was not significant (Estimate = 0.001 mm/year, 95%CI = −0.002 to 0.003).

Additionally, each hour delay in wake time on weekends was associated with increased rates of SphE and AL change by 0.006D/year (95%CI = 0.001 to 0.011) and 0.003 mm/year (95%CI = 0.001 to 0.005), respectively. A similar association was found for wake time during weekdays although this failed to reach statistical significance (SphE: Estimate = 0.001D/year, 95%CI = −0.003 to 0.005; AL: Estimate = 0.001 mm/year, 95%CI = −0.000 to 0.003). Sleep duration and self-report of "morning" or "evening" were not associated with myopia progression.

These findings along with those from other cross-sectional studies (71–73) suggest that falling asleep later was associated with a higher risk of myopia progression, even after accounting for sun exposure. While the effect of sleep and wake times found in the current analysis on young adults is small and unlikely to be clinically significant, it is possible that sleep/wake times may be more important in children when myopia progresses faster. The mechanism underlying this link is unclear, although Liu et al. (73) suggested that late-night near-work activities, such as reading, could confound this relationship. Future studies exploring sleep time or circadian rhythm and myopia should account for near work at night, for example, reading and using smart mobile devices in bed, to rule out any possible confounding effect of late-night near work. A disruption to the circadian rhythm with later time of falling asleep has also been suggested to be myopigenic, as the choroidal thickness and AL vary diurnally (76, 77). Genetic factors could also be at play, with Hysi et al. (78) recently reporting shared genes between refractive error and circadian rhythm.

CONCLUSION AND FUTURE DIRECTIONS

Findings from the Raine Study has confirmed many of the previously reported childhood risk factors of myopia and found fetal growth, and ruled out several other variables (*in utero* ultrasound exposure, childhood anesthesia exposure, sleep quality trajectory, dietary vitamin A), as a risk factor. Importantly, the Raine Study confirmed that myopia can begin or continue to progress in the third decade of life, and this change is not limited to those who studied at university. While refractive changes in young adulthood are generally smaller than those observed during childhood, we highlight that some individuals may still be susceptible to myopia progression at alarming rates. Further explorations are warranted to identify young adults who have rapid myopia progression. Given that myopia progression in young adults seems to have a similar mechanism and risk factors to those in children, it is worth investigating if myopia control intervention (e.g., pharmacological or optical interventions, or spending more time outdoors) may be beneficial in susceptible young adults. The differential rate of myopia progression between sexes also requires further investigation to understand the mechanism underlying this effect. Finally, it is critical that longitudinal birth cohort studies in other populations increase their focus on young adults given the historical lack of attention in this age group. The ALSPAC (79) and the Generation R cohort (80) are on track to accomplish this.

AUTHOR CONTRIBUTIONS

SL wrote the first draft of the manuscript and performed the statistical analysis. DM performed a supervisory role and acquired funded. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Forward H, Hewitt AW, Mackey DA. Missing X and Y: a review of participant ages in population-based eye studies. *Clin Exp Ophthalmol.* (2012) 40:305–19. doi: 10.1111/j.1442-9071.2011.02626.x
2. McKnight CM, Newnham JP, Stanley FJ, Mountain JA, Landau LI, Beilin LJ, et al. Birth of a cohort–the first 20 years of the Raine study. *Med J Aust.* (2012) 197:608–10. doi: 10.5694/mja12.10698
3. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet.* (1993) 342:887–91. doi: 10.1016/0140-6736(93)91944-H
4. Straker L, Mountain J, Jacques A, White S, Smith A, Landau L, et al. Cohort Profile: The Western Australian Pregnancy Cohort (Raine) Study–Generation 2. *Int J Epidemiol*. 2017:dyw308. doi: 10.1093/ije/dyw308
5. Chan E, Chong EW, Lingham G, Stevenson LJ, Sanfilippo PG, Hewitt AW, et al. Prevalence of Keratoconus Based on Scheimpflug Imaging: the Raine Study. *Ophthalmology.* (2020). doi: 10.1016/j.ophtha.2020.08.020
6. Yazar S, Forward H, McKnight CM, Tan A, Soloshenko A, Oates SK, et al. Raine eye health study: design, methodology and baseline prevalence of ophthalmic disease in a birth-cohort study of young adults. *Ophthalmic Genet.* (2013) 34:199–208. doi: 10.3109/13816810.2012.755632
7. McKnight CM, Sherwin JC, Yazar S, Forward H, Tan AX, Hewitt AW, et al. Pterygium and conjunctival ultraviolet autofluorescence in young Australian adults: the Raine study. *Clin Exp Ophthalmol.* (2015) 43:300–7. doi: 10.1111/ceo.12455
8. Sanfilippo PG, Huynh E, Yazar S, Hewitt AW, Mackey DA. Spectral-domain optical coherence tomography-derived characteristics of Bruch membrane pening in a young adult Australian population. *Am J Ophthalmol.* (2016) 165:154–63. doi: 10.1016/j.ajo.2016.03.008
9. Lingham G, Lee SSY, Charng J, Clark A, Chen FK, Yazar S, et al. Distribution and Classification of Peripapillary Retinal Nerve Fiber Layer Thickness in Healthy Young Adults. *Transl Vis Sci Technol.* (2021) 10:3. doi: 10.1167/tvst.10.9.3
10. Lee SSY, Lingham G, Alonso-Caneiro D, Charng J, Chen FK, Yazar S, et al. Macular Thickness Profile and Its Association With Best-Corrected Visual Acuity in Healthy Young Adults. *Transl Vis Sci Technol.* (2021) 10:8. doi: 10.1167/tvst.10.3.8
11. Lee SSY, Lingham G, Alonso-Caneiro D, Chen FK, Yazar S, Hewitt AW, et al. Choroidal Thickness in Young Adults and its Association with Visual Acuity. *Am J Ophthalmol.* (2020) 214:40–51. doi: 10.1016/j.ajo.2020.02.012
12. Lee SS, Lingham G, Yazar S, Sanfilippo PG, Charng J, Chen FK, et al. Rationale and protocol for the 7- and 8-year longitudinal assessments of eye health in a cohort of young adults in the Raine Study. *BMJ Open.* (2020) 10:e033440. doi: 10.1136/bmjopen-2019-033440
13. Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, et al. Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. *Invest Ophthalmol Vis Sci.* (2019) 60:M20–30. doi: 10.1167/iovs.18-25957
14. Lee SSY, Lingham G, Sanfilippo PG, Hammond CJ, Saw SM, Guggenheim JA, et al. Incidence and Progression of Myopia in Early Adulthood. *JAMA Ophthalmol.* (2022) 140:162–9. doi: 10.1001/jamaophthalmol.2021.5067
15. Lingham G, Yazar S, Lucas RM, Milne E, Hewitt AW, Hammond CJ, et al. Time spent outdoors in childhood is associated with reduced risk of myopia as an adult. *Sci Rep.* (2021) 11:6337. doi: 10.1038/s41598-021-85825-y
16. Sun C, Pezic A, Mackey DA, Carlin JB, Kemp A, Ellis JA, et al. Conjunctival Ultraviolet Autofluorescence as a Measure of Past Sun Exposure in Children. *Cancer Epidemiol Biomarkers Prev.* (2017) 26:1146–53. doi: 10.1158/1055-9965.EPI-16-0846
17. Coroneo MT, Muller-Stolzenburg NW, Ho A. Peripheral light focusing by the anterior eye and the ophthalmohelioses. *Ophthalmic Surg.* (1991) 22:705–11. doi: 10.3928/1542-8877-19911201-04
18. Asawanonda P, Taylor CR. Wood's light in dermatology. *Int J Dermatol.* (1999) 38:801–7. doi: 10.1046/j.1365-4362.1999.00794.x
19. McKnight CM, Sherwin JC, Yazar S, Forward H, Tan AX, Hewitt AW, et al. Myopia in young adults is inversely related to an objective marker of ocular sun exposure: the Western Australian Raine cohort study. *Am J Ophthalmol.* (2014) 158:1079–85. doi: 10.1016/j.ajo.2014.07.033
20. Yazar S, Hewitt AW, Black LJ, McKnight CM, Mountain JA, Sherwin JC, et al. Myopia is associated with lower vitamin D status in young adults. *Invest Ophthalmol Vis Sci.* (2014) 55:4552–9. doi: 10.1167/iovs.14-14589
21. Lingham G, Mackey DA, Zhu K, Lucas RM, Black LJ, Oddy WH, et al. Time spent outdoors through childhood and adolescence - assessed by 25-hydroxyvitamin D concentration - and risk of myopia at 20 years. *Acta ophthalmologica.* (2021) 99:679–87. doi: 10.1111/aos.14709
22. Kearney S, O'Donoghue L, Pourshahidi LK, Richardson PM, Saunders KJ. The use of conjunctival ultraviolet autofluorescence (CUVAF) as a biomarker of time spent outdoors. *Ophthalmic Physiol Opt.* (2016) 36:359–69. doi: 10.1111/opo.12309
23. Haworth KM, Chandler HL. Seasonal Effect on Ocular Sun Exposure and Conjunctival UV Autofluorescence. *Optom Vis Sci.* (2017) 94:219–28. doi: 10.1097/OPX.0000000000001014
24. Lingham G, Kugelman J, Charng J, Lee SS, Yazar S, McKnight CM, et al. Conjunctival ultraviolet autofluorescence area decreases with age and sunglasses use. *Br J Ophthalmol.* (2021). doi: 10.1136/bjophthalmol-2021-320284 [Epub ahead of print].
25. Huynh E, Bukowska DM, Yazar S, McKnight CM, Mian A, Mackey DA. Quantification of sun-related changes in the eye in conjunctival ultraviolet autofluorescence images. *J Med Imaging (Bellingham).* (2016) 3:034001. doi: 10.1117/1.JMI.3.3.034001
26. Sherwin JC, McKnight CM, Hewitt AW, Griffiths LR, Coroneo MT, Mackey DA. Reliability and validity of conjunctival ultraviolet autofluorescence measurement. *Br J Ophthalmol.* (2012) 96:801–5. doi: 10.1136/bjophthalmol-2011-301255
27. Sherwin JC, Hewitt AW, Kearns LS, Coroneo MT, Griffiths LR, Mackey DA. Distribution of conjunctival ultraviolet autofluorescence in a population-based study: the Norfolk Island Eye Study. *Eye.* (2011) 25:893–900. doi: 10.1038/eye.2011.83

28. Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? *Br J Dermatol.* (2009) 161:732–6. doi: 10.1111/j.1365-2133.2009.09332.x
29. Williams KM, Bertelsen G, Cumberland P, Wolfram C, Verhoeven VJ, Anastasopoulos E, et al. Increasing prevalence of myopia in Europe and the impact of education. *Ophthalmology.* (2015) 122:1489–97. doi: 10.1016/j.ophtha.2015.03.018
30. Fan Q, Verhoeven VJ, Wojciechowski R, Barathi VA, Hysi PG, Guggenheim JA, et al. Meta-analysis of gene-environment-wide association scans accounting for education level identifies additional loci for refractive error. *Nat Commun.* (2016) 7:11008. doi: 10.1038/ncomms11008
31. Mountjoy E, Davies NM, Plotnikov D, Smith GD, Rodriguez S, Williams CE, et al. Education and myopia: assessing the direction of causality by mendelian randomisation. *Bmj.* (2018) 361:k2022. doi: 10.1136/bmj.k2022
32. Cuellar-Partida G, Lu Y, Kho PF, Hewitt AW, Wichmann HE, Yazar S, et al. Assessing the genetic predisposition of education on myopia: a Mendelian randomization study. *Genet Epidemiol.* (2016) 40:66–72. doi: 10.1002/gepi.21936
33. Chrysanthos N. *'Treat Australia as Europe': The Domestic Gap Year Options Opening Up for Year 12.* Sydney: Sydney Morning Herald. (2021).
34. Rudnicka AR, Owen CG, Richards M, Wadsworth ME, Strachan DP. Effect of breastfeeding and sociodemographic factors on visual outcome in childhood and adolescence. *Am J Clin Nutr.* (2008) 87:1392–9. doi: 10.1093/ajcn/87.5.1392
35. Peckham CS, Gardiner PA, Goldstein H. Acquired myopia in 11-year-old children. *Br Med J.* (1977) 1:542–5. doi: 10.1136/bmj.1.6060.542
36. Guggenheim JA, McMahon G, Northstone K, Mandel Y, Kaiserman I, Stone RA, et al. Birth order and myopia. *Ophthalmic Epidemiol.* (2013) 20:375–84. doi: 10.3109/09286586.2013.848457
37. Guggenheim JA, Williams CU, K Biobank Eye Vision Consortium. Role of educational exposure in the association between myopia and birth order. *JAMA Ophthalmol.* (2015) 133:1408–14. doi: 10.1001/jamaophthalmol.2015.3556
38. Achiron R, Kreiser D, Achiron A. Axial growth of the fetal eye and evaluation of the hyaloid artery: in utero ultrasonographic study. *Prenat Diagn.* (2000) 20:894–9. doi: 10.1002/1097-0223(200011)20:11<894::aid-pd949>3.0.co;2-j
39. Fiess A, Schuster AK, Nickels S, Urschitz MS, Elflein HM, Schulz A, et al. Association of Low Birth Weight With Altered Corneal Geometry and Axial Length in Adulthood in the German Gutenberg Health Study. *JAMA Ophthalmol.* (2019) 137:507–14. doi: 10.1001/jamaophthalmol.2018.7121
40. Saw SM, Tong L, Chia KS, Koh D, Lee YS, Katz J, et al. The relation between birth size and the results of refractive error and biometry measurements in children. *Br J Ophthalmol.* (2004) 88:538–42. doi: 10.1136/bjo.2003.025411
41. Altman DG, Hytten FE. Intrauterine growth retardation: let's be clear about it. *Br J Obstet Gynaecol.* (1989) 96:1127–32. doi: 10.1111/j.1471-0528.1989.tb03185.x
42. Resnik R. One size does not fit all. *Am J Obstet Gynecol.* (2007) 197:221–2. doi: 10.1016/j.ajog.2007.07.019
43. Dyer KIC, Sanfilippo PG, White SW, Guggenheim JA, Hammond CJ, Newnham JP, et al. Associations Between Fetal Growth Trajectories and the Development of Myopia by 20 Years of Age. *Invest Ophthalmol Vis Sci.* (2020) 61:26. doi: 10.1167/iovs.61.14.26
44. Forward H, Yazar S, Hewitt AW, Khan J, Mountain JA, Pesudovs K, et al. Multiple prenatal ultrasound scans and ocular development: 20-year follow-up of a randomized controlled trial. *Ultrasound Obstet Gynecol.* (2014) 44:166–70. doi: 10.1002/uog.13399
45. Yazar S, Hewitt AW, Forward H, Jacques A, Ing C, von Ungern-Sternberg BS, et al. Early anesthesia exposure and the effect on visual acuity, refractive error, and retinal nerve fiber layer thickness of young adults. *J Pediatr.* (2016) 169:256–9. doi: 10.1016/j.jpeds.2015.10.048
46. McVeigh JA, Smith A, Howie EK, Stamatakis E, Ding D, Cistulli PA, et al. Developmental trajectories of sleep during childhood and adolescence are related to health in young adulthood. *Acta Paediatr.* (2021) 110:2435–44. doi: 10.1111/apa.15911
47. Ng FJ, Mackey DA, O'Sullivan TA, Oddy WH, Yazar S. Is Dietary Vitamin A Associated with Myopia from Adolescence to Young Adulthood? *Transl Vis Sci Technol.* (2020) 9:29. doi: 10.1167/tvst.9.6.29
48. COMET Group. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest Ophthalmol Vis Sci.* (2013) 54:7871–84. doi: 10.1167/iovs.13-12403
49. Polling JR, Klaver C, Tideman JW. Myopia progression from wearing first glasses to adult age: the DREAM Study. *Br J Ophthalmol.* (2021). doi: 10.1136/bjophthalmol-2020-316234 [Epub ahead of print].
50. Jorge J, Almeida JB, Parafita MA. Refractive, biometric and topographic changes among Portuguese university science students: a 3-year longitudinal study. *Ophthalmic Physiol Opt.* (2007) 27:287–94. doi: 10.1111/j.1475-1313.2007.00475.x
51. Kinge B, Midelfart A. Refractive changes among Norwegian university students–a three-year longitudinal study. *Acta Ophthalmol Scand.* (1999) 77:302–5. doi: 10.1034/j.1600-0420.1999.770311.x
52. Jacobsen N, Jensen H, Goldschmidt E. Does the level of physical activity in university students influence development and progression of myopia? –a 2-year prospective cohort study. *Invest Ophthalmol Vis Sci.* (2008) 49:1322–7. doi: 10.1167/iovs.07-1144
53. Jiang BC, Schatz S, Seger K. Myopic progression and dark focus variation in optometric students during the first academic year. *Clin Exp Optom.* (2005) 88:153–9. doi: 10.1111/j.1444-0938.2005.tb06688.x
54. Loman J, Quinn GE, Kamoun L, Ying GS, Maguire MG, Hudesman D, et al. Darkness and near work: myopia and its progression in third-year law students. *Ophthalmology.* (2002) 109:1032–8. doi: 10.1016/S0161-6420(02)01012-6
55. Wyatt ID. Occupational changes during the 20th century. *Monthly Lab Rev.* (2006) 129:35.
56. Jin JX, Hua WJ, Jiang X, Wu XY, Yang JW, Gao GP, et al. Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun Eye Care Study. *BMC Ophthalmol.* (2015) 15:73. doi: 10.1186/s12886-015-0052-9
57. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta ophthalmologica.* (2017) 95:551–66. doi: 10.1111/aos.13403
58. Wu PC, Chen CT, Lin KK, Sun CC, Kuo CN, Huang HM, et al. Myopia Prevention and Outdoor Light Intensity in a School-Based Cluster Randomized Trial. *Ophthalmology.* (2018) 125:1239–50. doi: 10.1016/j.ophtha.2017.12.011
59. Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci.* (2004) 45:1071–5. doi: 10.1167/iovs.03-1151
60. Saw SM, Tong L, Chua WH, Chia KS, Koh D, Tan DT, et al. Incidence and progression of myopia in Singaporean school children. *Invest Ophthalmol Vis Sci.* (2005) 46:51–7. doi: 10.1167/iovs.04-0565
61. Saxena R, Vashist P, Tandon R, Pandey RM, Bhardawaj A, Gupta V, et al. Incidence and progression of myopia and associated factors in urban school children in Delhi: The North India Myopia Study (NIM Study). *PLoS ONE.* (2017) 12:e0189774. doi: 10.1371/journal.pone.0189774
62. Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, et al. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol.* (2005) 123:977–87. doi: 10.1001/archopht.123.7.977
63. Fernandez-Montero A, Bes-Rastrollo M, Moreno-Montanes J, Moreno-Galarraga L, Martinez-Gonzalez MA. Effect of pregnancy in myopia progression: the SUN cohort. *Eye.* (2017) 31:1085–92. doi: 10.1038/eye.2017.24
64. Pizzarello LD. Refractive changes in pregnancy. *Graefes Arch Clin Exp Ophthalmol.* (2003) 241:484–8. doi: 10.1007/s00417-003-0674-0
65. Wu F, Schallhorn JM, Lowry EA. Refractive status during pregnancy in the United States: results from NHANES 2005-2008. *Graefes Arch Clin Exp Ophthalmol.* (2020) 258:663–7. doi: 10.1007/s00417-019-04552-3
66. Chakraborty R, Ostrin LA, Nickla DL, Iuvone PM, Pardue MT, Stone RA. Circadian rhythms, refractive development, and myopia. *Ophthalmic Physiol Opt.* (2018) 38:217–45. doi: 10.1111/opo.12453
67. Nickla DL. Ocular diurnal rhythms and eye growth regulation: where we are 50 years after Lauber. *Exp Eye Res.* (2013) 114:25–34. doi: 10.1016/j.exer.2012.12.013

68. Nickla DL, Wildsoet CF, Troilo D. Endogenous rhythms in axial length and choroidal thickness in chicks: implications for ocular growth regulation. *Invest Ophthalmol Vis Sci.* (2001) 42:584–8.
69. Cohen Y, Belkin M, Yehezkel O, Avni I, Polat U. Light intensity modulates corneal power and refraction in the chick eye exposed to continuous light. *Vision Res.* (2008) 48:2329–35. doi: 10.1016/j.visres.2008.07.010
70. Nickla DL, Totonelly K. Brief light exposure at night disrupts the circadian rhythms in eye growth and choroidal thickness in chicks. *Exp Eye Res.* (2016) 146:189–95. doi: 10.1016/j.exer.2016.03.003
71. Qu Y, Yu J, Xia W, Cai H. Correlation of Myopia with Physical Exercise and Sleep Habits among Suburban Adolescents. *J Ophthalmol.* (2020) 2020:2670153. doi: 10.1155/2020/2670153
72. Ayaki M, Torii H, Tsubota K, Negishi K. Decreased sleep quality in high myopia children. *Sci Rep.* (2016) 6:33902. doi: 10.1038/srep33902
73. Liu XN, Naduvilath TJ, Wang J, Xiong S, He X, Xu X, et al. Sleeping late is a risk factor for myopia development amongst school-aged children in China. *Sci Rep.* (2020) 10:17194. doi: 10.1038/s41598-020-74348-7
74. Wei SF, Li SM, Liu L, Li H, Kang MT, Sun YY, et al. Sleep Duration, Bedtime, and Myopia Progression in a 4-Year Follow-up of Chinese Children: The Anyang Childhood Eye Study. *Invest Ophthalmol Vis Sci.* (2020) 61:37. doi: 10.1167/iovs.61.3.37
75. McArdle N, Ward SV, Bucks RS, Maddison K, Smith A, Huang RC, et al. The prevalence of common sleep disorders in young adults: a descriptive population-based study. *Sleep.* (2020) 43:72. doi: 10.1093/sleep/zsaa072
76. 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. doi: 10.1016/j.exer.2013.01.001
77. Chakraborty R, Read SA, Collins MJ. Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. *Invest Ophthalmol Vis Sci.* (2011) 52:5121–9. doi: 10.1167/iovs.11-7364
78. Hysi PG, Choquet H, Khawaja AP, Wojciechowski R, Tedja MS, Yin J, 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) 52:401–7. doi: 10.1038/s41588-020-0599-0
79. Ghorbani Mojarrad N, Williams C, Guggenheim JA. A genetic risk score and number of myopic parents independently predict myopia. *Ophthalmic Physiol Opt.* (2018) 38:492–502. doi: 10.1111/opo.12579
80. Tideman JWL, Polling JR, Hofman A, Jaddoe VW, Mackenbach JP, Klaver CC. Environmental factors explain socioeconomic prevalence differences in myopia in 6-year-old children. *Br J Ophthalmol.* (2018) 102:243–7. doi: 10.1136/bjophthalmol-2017-310292

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Multiple Factors Causing Myopia and the Possible Treatments: A Mini Review

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The myopia epidemic has become a global public health problem. Although myopia is progressing worldwide, the recent coronavirus infections 2019 (COVID-19) outbreak has spurred myopia progression. The current evidence-based treatments for humans are atropine eye drops, optical treatment with defocus, use of orthokeratology, extending proximity working distance, pausing from near work every half hour and increased time outside the home. Studies on myopia using animal models have been conducted for more than 40 years. In recent years, new mechanisms of myopia suppression have been revealed from animal experiments such as inflammation control, intraocular pressure control, light control, and the activity of early growth response protein 1 control. This mini-review provides a summary of the scientific evidence currently available on the control of myopia, and the possible treatments mitigating myopia.

Keywords: myopia, anthropometrics, Asian, axial length (AL), treatments

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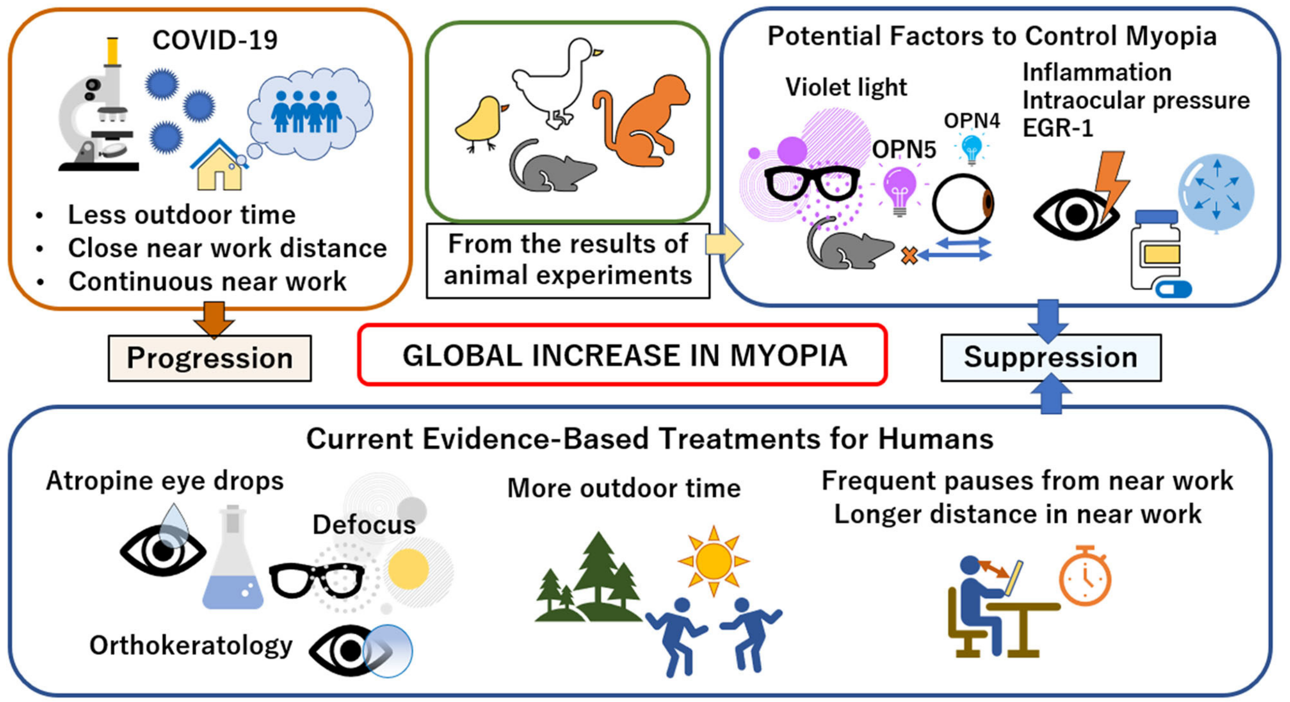
INTRODUCTION

The widespread prevalence of myopia is a global public health problem. East Asia is experiencing unprecedented myopia. In China, between 10 and 20% of the population was nearsighted 60 years ago. Nowadays, in the teenage and twenties, maximum 90% are myopic (1). The myopia rate for 19-year-old males in Seoul, Korea is 96.5% (1). Myopia is increasing rapidly in other countries such as Europe and the United States, where about half of the young population is found to be myopic (1). We have reported that ∼77% of schoolchildren between 6 and 11 and 95% of schoolchildren between 12 and 14 had myopia in two schools in Tokyo, Japan (2). Holden et al. projected that 50% of the global population will have myopia and the 10% will have high myopia by 2050, with the prevalence of myopia doubling (from 22% in 2000) and the prevalence of high myopia increasing 5-fold (from 2% in 2000) (3). Although myopia has been gradually increasing, studies on myopia using animal models have been conducted for more than 40 years. In 1977, Wiesel and Raviola became the first in the world to create an animal model of myopia after neonatal lid fusion in monkeys (4). Subsequently, from the fact that myopia did not progress in animals kept in the dark, they suggested that myopia is caused by changes in visual input and neurological mediation. Their experiments suggested that although the refractive state is largely genetically programmed, unusual visual experiences disturb the growth process of the eye after birth and trigger the development of axial myopia (5). Wallman et al. reported myopia models of chicks that are reared with white translucent eye occluders and are visually deprived of the nasal, temporal, or entire retina (6). As a result, myopia with a median of−15 diopters was limited to the portion of the retina that was deprived of vision (6). These studies have suggested that visual information can cause acquired



GRAPHICAL ABSTRACT | Factors in myopia control and progression.

myopia. It has been reported that near work can cause myopia even in humans (7). Huang et al. investigated 2-year refraction data every 6 months with a questionnaire; the protective behaviors of extending proximity working distance, pausing from near work every half hour and increased time outside the home from parents' self-reports on the prevalence and progression of myopia in 9–11 year olds in Taipei, Taiwan. The risk ratios were 0.71, 0.89, and 0.77 in each behavior. In a spherical equivalent analysis, each behavior also significantly reduced myopia progression from 6 to 24 months (7).

The novel coronavirus infections 2019 (COVID-19) has been affecting the world for 2 years as of March 2022. Natural experiments provided empirical evidence that Chinese schoolchildren who were studying at home during the COVID-19 epidemic were at higher risk of myopia progression (8).

It is not true that myopia progresses only when we are young and does not progress when we become adults. Lee et al. reported that in a cohort study of the general young population, they observed significant increases in myopia and axial length of 0.04 diopters and 0.02 mm per year, respectively, over the 8-year study duration. Among the 526 individuals who were free of myopia at baseline, the incidence of myopia between the ages of 20 and 28 years was 14% (9). In addition, females have a risk factor of high myopia (10, 11), and there may be gender differences in the development of myopia (12).

In this mini-review article, we searched the topic of myopia suppression treatment and experimental topics in the electronic databases PubMed from the inception until February 2022. The following keywords were used: "Myopia" alone or in combination with "choroid," "hypoxia," "genetics," "inflammation," and "light." Relevant articles were also reviewed in this mini-review. This mini-review will provide a brief overview of the current scientific evidence on the control of myopia, and potential treatments to mitigate myopia.

CHOROIDAL THICKNESS AND MYOPIA

Others, as well as our team, have reported that myopia is associated with subfoveal choroidal thickness which is significantly related to refractive error (13–15) and axial length (13, 16). Choroidal thickness is also reported to fluctuate in response to diurnal variation and changes in visual input (17–19).

The average subfoveal choroidal thickness in healthy humans ranges from 200 to 300 μm from age twenties to eighties (20). In chickens, the choroidal thickness of the central region is about 250 μm under normal visual conditions (17, 21). The choroid in chickens, increases in thickness by as much as 1 mm (over 17 diopters) to accommodate myopic defocus (a focused image in front of the retina). It compensates for many refractive errors by pushing the retina toward the image plane (21). There is the diurnal modulation of choroidal thickness in addition to the modulation of choroidal thickness due to refractive state, with a maximum thickness around midnight and a minimum thickness at noon, with a maximum width of 40 μm (17, 18). This diurnal rhythm in chickens is free-running under constant darkness, suggesting that it is driven by a circadian oscillator (22).

Significant diurnal changes are known to occur even in healthy humans, and similar to the rhythm seen in chicken, the choroid has been found to be thicker at night and thinner during the day (19).

Pendrak et al. examined sources of chick choroidal extravascular fluid under conditions of two visually controlled ocular growths: goggle-induced myopia with an enhancement of ocular growth and delayed ocular growth in myopia recovery after goggle removal, and evaluated the evidence for changes in choroidal thickness. Fluorescein-dextran was injected intravenously as a tracer into 2-week-old chicks in each group of control, myopia and myopia recovery. As a result, suprachoroidal fluid protein concentration in myopic eyes at 1 h after intravenous injection fell significantly to 1.5% of plasma levels. On the other hand, recovery from myopia significantly increased the protein concentration of the suprachoroidal fluid to 30% of that of the plasma. They also reported that neither procedure affected the protein of suprachoroidal fluid in their contralateral eyes as controls (23). The altered levels of protein and marker dye in both myopic and recovering eyes suggest that choroidal circulation dynamics and capillary permeability are markedly altered (24).

HYPOXIA-INDUCIBLE FACTOR AND MYOPIA

Thinning of the sclera has been observed in myopic animal models (25–27) and humans (28). Myopia has been thought to result from inadequate ocular axial extension and associated remodeling of the extracellular matrix resulting in reduced scleral strength and thickness.

Wu et al. reported that hypoxic exposure of 5% oxygen promotes myofibroblast transdifferentiation with down-regulation of type I collagen in human scleral fibroblasts and hypoxia-inducible factor-1α (HIF-1α) signaling promotes myopia *via* myofibroblast transdifferentiation. They also reported that 45 of the 145 myopia risk genes, about one-third, interact with genes involved in the HIF-1α signaling pathway (29).

Zhao et al. reported novel genome-wide association study (GWAS) gene set analysis revealed that the HIF-1α signaling pathway is significantly enriched in extremely myopic individuals with refractive error <-10 D. In addition, they clarified that downregulation of HIF-1α in the sclera caused hyperopia and upregulation caused myopia in mice. They speculated that myopia risk factor such as near work, may cause hypoxia of the sclera by severely reducing blood circulation in the choroid in humans (30). We will discuss this again in the Discussion section.

INFLAMMATION AND MYOPIA

Inflammation in the etiology of myopia has not yet been fully assessed. However, there have been several reports on inflammation and myopia. Epidemiological observations have shown that allergic conjunctivitis children are at high risk in myopia (31). In an animal model, Wei et al. showed that ocular surface inflammation caused by mast cell degranulation alters corneal tight junctions, initiating the secretion of inflammatory cytokines in the cornea, which subsequently leads to retinal inflammation and promotes myopia progression (31). Lin et al. found from data on children in the National Health Insurance Surveillance Database under age 18 that the incidence of myopia was significantly higher in patients with type 1 diabetes and inflammatory diseases such as uveitis and systemic lupus erythematosus than in patients without inflammation (32).

Lin et al. also found that atropine downregulated inflammation in the Syrian hamster with an experimental myopia model, the monocular form-deprivation eye. They found that the expression of c-Fos, interleukin (IL)-6, nuclear factor κB (NFκB), and tumor necrosis factor (TNF)-α was increased in myopic eyes and decreased with atropine administration. They also found that the progression of myopia was slowed by cyclosporin A, but accelerated by lipopolysaccharide and peptidoglycan (32). Takahashi et al. reported that in Vogt-Koyanagi-Harada (VKH) disease, progression of myopia occurs with increasing axial length. In addition, the sunset glow fundus was more frequently observed in VKH patients with myopia progression than in patients without myopia progression, and the subfoveal choroidal thickness was found to be thinner (33). We investigated the inhibitory effect of lactoferrin on myopia onset and progression using a mouse model of lens-induced myopia. We found that oral administration of lactoferrin prevented the onset of lens-induced myopia in mice by modulating extracellular matrix remodeling through the IL-6-MMP-2 axis (34). Thus, these studies suggest that the suppression of inflammation may lead to the treatment of myopia.

LIGHT-RESPONSE AND MYOPIA

Recently, melanopsin-expressing RGCs (mRGCs: melanopsin-expressing retinal ganglion cell) have been found to be widely involved in light-induced control of a variety of physiological functions in mammals, changing the way we analyze the non-image-forming effects of light.

Melanopsin (OPN4) is primarily expressed in mammalian retinal ganglion cells, which are essentially light-sensitive cells (ipRGCs) with sensitivity to the blue spectrum (35). Currently, six subtypes of murine mRGCs have been characterized based on light-response properties, dendritic arborizations, morphologies, and brain projections (36). To date, OPN4 has been thought to account for the majority of non-image-forming photoreception in the retina, but the discovery of OPN5, which is sensitive to UVA light at wavelengths from 315 to 400 nm, is adding complexity to the known ocular and non-ocular photoreceptor system (37).

Dysfunction in retinal melanopsin signaling alters refractive development in mice. Retinal dopamine signaling is reduced in form-deprived mice lacking melanopsin. Systemic L-3,4-dihydroxyphenylalanine (L-DOPA) treatment attenuates Form-deprivation myopia in melanopsin knockout mice. Melanopsin is vital for refractive development and slowing myopia progression (38). Thakur et al. reported that irradiating the human eye with red and green light causes axial elongation, while irradiating with blue light suppresses axial elongation (39).

We have shown that violet light (360–400 nm wavelength) suppresses axial elongation in an experimental chicken myopia model, and by expression microarray analysis, we found that the expression of the myopia suppressor gene early growth response protein 1 (*Egr-1*) is upregulated by violet irradiation. We also reported violet light can prevent experimentally induced myopia in mice. In addition, the effect depended on exposure time of day, and evening exposure was sufficient to prevent experimental myopia (40). Not only violet light, but blue light was also reported to suppress the effects of lens-induced hyperopic defocus, resulting in a significant decrease in axial length, while red and green light exposure resulted in a significant increase in axial length and thinning of the choroid, with or without defocusing (39).

In a retrospective clinical study, comparing two types of contact lenses (partial violet light-blocking and violet light-transmissive), the violet light-transmissive contact lenses reduced myopia progression at ages <20 (41). In addition, the violet light-transmissive phakic intraocular lens reduced myopia progression and axial length elongation compared with the non-violet light-transmissive type (42). We conducted a clinical study in children aged 6–12 years and found that the axial elongation supression rate in the violet light transmissive glasses group was ∼20% over 2 years (43). Thus, these studies suggest the OPN5 pathway as a possible target for myopia treatment.

DISCUSSION

The increase in myopia worldwide is an important public health consideration. The mechanisms by which myopia occurs are not yet fully understood, and effective treatment options are limited. We discuss the possibilities and evidence for the treatment of myopia below.

The use of atropine in the treatment of myopia appears to vary from country to country (32). Lin et al. showed evidence that an inflammatory response is involved in myopia and their animal studies indicated that atropine and treatment with anti-inflammatory agents effectively inhibited the development of myopia (32). Atropine eye drops alone cannot completely suppress myopia, but they are clinically easy to prescribe. Therefore, it will be one of the treatment options.

Huang et al. reported the protective behaviors of extending proximity working distance, pausing from near work every half hour and increased time outside the home from parents' self-reports were found to have protective effects in diminishing myopia progression around 10 years-old children in Taipei (7). Therefore, home isolation and home study during COVID-19 may exacerbate worldwide burden of myopia (8). Indeed, Choi et al. reported that myopia progressed more rapidly in schoolchildren during periods of high lockdown procedures associated with COVID-19. Although, optical treatment with multiple segment-incorporated defocusing was significantly associated with slower myopia progression compared to monofocal lens treatment during locked-down periods (44). Nakamura et al. investigated the myopia suppression effect of orthokeratology in schoolchildren and found that orthokeratology treatment inhibited myopia progression by an average of 0.85 D over 2 years, regardless of orthokeratology lens design (45). In addition to medication, preventive lifestyle behaviors will help reduce the progression of myopia, and myopia suppression using devices such as optical treatment with defocus and orthokeratology will also be options for treatment.

Wu et al. suggested that HIF-1α signaling promoted myopia through myofibroblast transdifferentiation (29). This raises the question of whether oxygen administration can be a treatment option for hypoxic responses. Although different from the eye, there are many examples of oxygen administration in myocardial infarction. The clinical efficacy of routinely administered oxygen therapy in patients with suspected acute myocardial infarction without hypoxemia at baseline was previously uncertain. Hoffman et al. studied the DETO2X-AMI (the Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction) trial, a routine oxygen replenishment therapy, in the treatment of patients with suspected myocardial infarction without baseline hypoxemia, and compared it to ambient air. The DETO2X-AMI verified that routine oxygen supplementation in patients with suspected myocardial infarction without hypoxemia did not reduce all-cause mortality at 1 year. In other words, in this report, systemic oxygenation did not make a decisive difference to room air, even though local hypoxia was suspected (46). From this report, it makes questionable whether simple administration of oxygen would be effective for sclera with suspected ischemia. Whereas, Kloner et al. studied the localized delivery of supersaturated oxygen therapy to myocardial infarctions. In their clinical trials, patients with anterior ST-segment elevation myocardial infarction, localized delivery of supersaturated oxygen therapy was shown to be safe and effective in reducing infarct size, improving cardiac function, and inhibiting adverse remodeling of the left ventricle (47).

Using swept-source optical coherence tomography angiography, a gradual decrease in choroidal vascularity with myopia severity has been reported (48). Decreased choriocapillaris blood flow was associated with thinner choroid and increasing myopia severity (48). This suggests that the oxygen supply to the sclera may possibly be reduced. From the evidence of localized oxygenation for myocardial infarction, localized oxygenation for the eye may possibly be a treatment option in the future.

The therapeutic approach for myopia suppression by controlling intraocular pressure has not yet been established. However, Liu et al. suggested that lowering intraocular pressure can inhibit scleral fibroblast activation, suppress scleral remodeling, and reduce scleral dilatation force, which slows down balloon-like eye dilation. They also suggested that intraocular pressure reduction would increase blood perfusion in the choroid, alleviate scleral hypoxia, and slow scleral remodeling (49). The hypothesis of myopia treatment using violet light is now beginning to yield results through animal and clinical experiments (40–42). We investigated natural agents that inhibit myopia based on *Egr-1* activity and found that crocetin, a dietary factor, may have protective effects against myopia progression

(50). It has also been reported that in humans, reading black text on a white background makes the choroid 16 μm thinner in just 1 h, and reading white text on a black background makes the choroid about 10 μm thicker, suggesting that reading white text from a black screen or tablet may suppress myopia (51). Thus, research for myopia suppression, such as intraocular pressure control, violet light irradiation, crocetin intake, and contrast control, is becoming increasingly popular.

In conclusion, there may not be a single treatment solution from many research results. Further research and treatment to control myopia is expected.

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The topic was devised by AS under the conceptualization and supervision of TK. AS used PubMed for literature review. All authors have read and agreed to the published final version.

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REFERENCES

1. Dolgin E. The myopia boom. *Nature.* (2015) 519:276–8. doi: 10.1038/519276a
2. Yotsukura E, Torii H, Inokuchi M, Tokumura M, Uchino M, Nakamura K, et al. Current prevalence of myopia and association with environmental factors among schoolchildren in Japan. *J Am Med Assoc Ophthalmol.* (2019) 137:1233–9. doi: 10.1001/jamaophthalmol.2019.3103
3. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology.* (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006
4. Wiesel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature.* (1977) 266:66–8. doi: 10.1038/266066a0
5. Raviola E, Wiesel TN. An animal model of myopia. *N Engl J Med.* (1985) 312:1609–15. doi: 10.1056/NEJM198506203122505
6. Wallman J, Gottlieb MD, Rajaram V, Fugate-Wentzek LA. Local retinal regions control local eye growth and myopia. *Science.* (1987) 237:73–7. doi: 10.1126/science.3603011
7. Huang PC, Hsiao YC, Tsai CY, Tsai DC, Chen CW, Hsu CC, et al. Protective behaviours of near work and time outdoors in myopia prevalence and progression in myopic children: a 2-year prospective population study. *Br J Ophthalmol.* (2020) 104:956–61. doi: 10.1136/bjophthalmol-2019-314101
8. Ma D, Wei S, Li SM, Yang X, Cao K, Hu J, et al. The impact of study-at-home during the COVID-19 pandemic on myopia progression in Chinese children. *Front Public Health.* (2022) 9:720514. doi: 10.3389/fpubh.2021.720514
9. Lee SS, Lingham G, Sanfilippo PG, Hammond CJ, Saw SM, Guggenheim JA, et al. Incidence and progression of myopia in early adulthood. *J Am Med Assoc Ophthalmol.* (2022) 2022:e215067. doi: 10.1001/jamaophthalmol.2021.5067
10. Mo Y, Wang MF, Zhou LL. Risk factor analysis of 167 patients with high myopia. *Int J Ophthalmol.* (2010) 3:80–2. doi: 10.3980/j.issn.2222-3959.2010.01.19
11. Matamoros E, Ingrand P, Pelen F, Bentaleb Y, Weber M, Korobelnik JF, et al. Prevalence of myopia in France: a cross-sectional analysis. *Medicine.* (2015) 94:e1976. doi: 10.1097/MD.0000000000001976
12. Shinojima A, Kurihara T, Mori K, Iwai Y, Hanyuda A, Negishi K, et al. Association between ocular axial length and anthropometrics of Asian adults. *BMC Res Notes.* (2021) 14:328. doi: 10.1186/s13104-021-05745-y
13. Shinojima A, Mori R, Nakashizuka H, Shimada H. Characteristics of hyperautofluorescent choroidal vessels using fundus camera type short-wavelength autofluorescence. *Ophthalmologica.* (2016) 236:175–80. doi: 10.1159/000449262
14. Fujiwara T, Imamura Y, Margolis R, Slakter JS, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. *Am J Ophthalmol.* (2009) 148:445–50. doi: 10.1016/j.ajo.2009.04.029
15. Ikuno Y, Tano Y. Retinal and choroidal biometry in highly myopic eyes with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci.* (2009) 50:3876–80. doi: 10.1167/iovs.08-3325
16. Flores-Moreno I, Lugo F, Duker JS, Ruiz-Moreno JM. The relationship between axial length and choroidal thickness in eyes with high myopia. *Am J Ophthalmol*. (2013) 155:314–9.e1. doi: 10.1016/j.ajo.2012.07.015
17. Nickla DL, Wildsoet C, Wallman J. Visual influences on diurnal rhythms in ocular length and choroidal thickness in chick eyes. *Exp Eye Res.* (1998) 66:163–81. doi: 10.1006/exer.1997.0420
18. Papastergiou GI, Schmid GF, Riva CE, Mendel MJ, Stone RA, Laties AM. Ocular axial length and choroidal thickness in newly hatched chicks and one-year-old chickens fluctuate in a diurnal pattern that is influenced by visual experience and intraocular pressure changes. *Exp Eye Res.* (1998) 66:195–205. doi: 10.1006/exer.1997.0421
19. Usui S, Ikuno Y, Akiba M, Maruko I, Sekiryu T, Nishida K, et al. Circadian changes in subfoveal choroidal thickness and the relationship with circulatory factors in healthy subjects. *Invest Ophthalmol Vis Sci.* (2012) 53:2300–7. doi: 10.1167/iovs.11-8383
20. Wakatsuki Y, Shinojima A, Kawamura A, Yuzawa M. Correlation of aging and segmental choroidal thickness measurement using swept source optical coherence tomography in healthy eyes. *PLoS ONE.* (2015) 10:e0144156. doi: 10.1371/journal.pone.0144156
21. Wallman J, Wildsoet C, Xu A, Gottlieb MD, Nickla DL, Marran L, et al. Moving the retina: choroidal modulation of refractive state. *Vision Res.* (1995) 35:37–50. doi: 10.1016/0042-6989(94)E0049-Q
22. Nickla DL. The phase relationships between the diurnal rhythms in axial length and choroidal thickness and the association with ocular growth rate in chicks. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol.* (2006) 192:399–407. doi: 10.1007/s00359-005-0077-2
23. Pendrak K, Papastergiou GI, Lin T, Laties AM, Stone RA. Choroidal vascular permeability in visually regulated eye growth. *Exp Eye Res.* (2000) 70:629–37. doi: 10.1006/exer.2000.0825
24. Liu X, Lin Z, Wang F, Peng X, He W, Chen D, et al. Choroidal thickness and choriocapillaris vascular density in myopic anisometropia. *Eye Vis.* (2021) 8:48. doi: 10.1186/s40662-021-00269-9
25. Gottlieb MD, Joshi HB, Nickla DL. Scleral changes in chicks with form-deprivation myopia. *Curr Eye Res.* (1990) 9:1157–65. doi: 10.3109/02713689009003472
26. Kusakari T, Sato T, Tokoro T. Regional scleral changes in form-deprivation myopia in chicks. *Exp Eye Res.* (1997) 64:465–76. doi: 10.1006/exer.1996.0242
27. McBrien NA, Cornell LM, Gentle A. Structural and ultrastructural changes to the sclera in a mammalian model of high myopia. *Invest Ophthalmol Vis Sci.* (2001) 42:2179–87. Available online at: https://iovs.arvojournals.org/article.aspx?articleid=2200045
28. Avetisov ES, Savitskaya NF, Vinetskaya MI, Iomdina EN. A study of biochemical and biomechanical qualities of normal and myopic eye sclera in humans of different age groups. *Metab Pediatr Syst Ophthalmol.* (1983) 7:183–8.
29. Wu H, Chen W, Zhao F, Zhou Q, Reinach PS, Deng L, et al. Scleral hypoxia is a target for myopia control. *Proc Natl Acad Sci USA.* (2018) 115:E7091–100. doi: 10.1073/pnas.1721443115
30. Zhao F, Zhang D, Zhou Q, Zhao F, He M, Yang Z, et al. Scleral HIF-1alpha is a prominent regulatory candidate for genetic and environmental interactions in human myopia pathogenesis. *EBioMedicine.* (2020) 57:102878. doi: 10.1016/j.ebiom.2020.102878

31. Wei CC, Kung YJ, Chen CS, Chang CY, Lin CJ, Tien PT, et al. Allergic conjunctivitis-induced retinal inflammation promotes myopia progression. *EBioMedicine.* (2018) 28:274–86. doi: 10.1016/j.ebiom.2018.01.024
32. Lin HJ, Wei CC, Chang CY, Chen TH, Hsu YA, Hsieh YC, et al. Role of chronic inflammation in myopia progression: clinical evidence and experimental validation. *EBioMedicine.* (2016) 10:269–81. doi: 10.1016/j.ebiom.2016.07.021
33. Takahashi H, Takase H, Terada Y, Mochizuki M, Ohno-Matsui K. Acquired myopia in Vogt-Koyanagi-Harada disease. *Int Ophthalmol.* (2019) 39:521–31. doi: 10.1007/s10792-018-0841-2
34. Ikeda SI, Kurihara T, Toda M, Jiang X, Torii H, Tsubota K. Oral bovine milk lactoferrin administration suppressed myopia development through matrix metalloproteinase 2 in a mouse model. *Nutrients.* (2020) 12:3744. doi: 10.3390/nu12123744
35. Jones KA, Hatori M, Mure LS, Bramley JR, Artymyshyn R, Hong SP, et al. Small-molecule antagonists of melanopsin-mediated phototransduction. *Nat Chem Biol.* (2013) 9:630–5. doi: 10.1038/nchembio.1333
36. Aranda ML, Schmidt TM. Diversity of intrinsically photosensitive retinal ganglion cells: circuits and functions. *Cell Mol Life Sci.* (2021) 78:889–907. doi: 10.1007/s00018-020-03641-5
37. Calligaro H, Dkhissi-Benyahya O, Panda S. Ocular and extraocular roles of neuropsin in vertebrates. *Trends Neurosci.* (2021) 21:S0166-2236(21)00237-X. doi: 10.1016/j.tins.2021.11.008
38. Chakraborty R, Landis EG, Mazade R, Yang V, Strickland R, Hattar S, et al. Melanopsin modulates refractive development and myopia. *Exp Eye Res.* (2022) 214:108866. doi: 10.1016/j.exer.2021.108866
39. Thakur S, Dhakal R, Verkicharla PK. Short-term exposure to blue light shows an inhibitory effect on axial elongation in human eyes independent of defocus. *Invest Ophthalmol Vis Sci.* (2021) 62:22. doi: 10.1167/iovs.62.15.22
40. Jiang X, Pardue MT, Mori K, Ikeda SI, Torii H, D'Souza S, et al. Violet light suppresses lens-induced myopia via neuropsin (OPN5) in mice. *Proc Natl Acad Sci USA.* (2021) 118:e2018840118. doi: 10.1073/pnas.2018840118
41. Torii H, Kurihara T, Seko Y, Negishi K, Ohnuma K, Inaba T, et al. Violet light exposure can be a preventive strategy against myopia progression. *EBioMedicine.* (2017) 15:210–9. doi: 10.1016/j.ebiom.2016.12.007
42. Torii H, Ohnuma K, Kurihara T, Tsubota K, Negishi K. Violet light transmission is related to myopia progression in adult high myopia. *Sci Rep.* (2017) 7:14523. doi: 10.1038/s41598-017-09388-7
43. Mori K, Torii H, Hara Y, Hara M, Yotsukura E, Hanyuda A, et al. Effect of violet light-transmitting eyeglasses on axial elongation in myopic children: a randomized controlled trial. *J Clin Med.* (2021) 10:5462. doi: 10.3390/jcm10225462
44. Choi KY, Chun RKM, Tang WC, To CH, Lam CS, Chan HH. Evaluation of an optical defocus treatment for myopia progression among schoolchildren during the COVID-19 pandemic. *J Am Med Assoc Netw Open.* (2022) 5:e2143781. doi: 10.1001/jamanetworkopen.2021.43781
45. Nakamura Y, Hieda O, Yokota I, Teramukai S, Sotozono C, Kinoshita S. Comparison of myopia progression between children wearing three types of orthokeratology lenses and children wearing single-vision spectacles. *Jpn J Ophthalmol.* (2021) 65:632–43. doi: 10.1007/s10384-021-00854-4
46. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med.* (2017) 377:1240–9. doi: 10.1056/NEJMoa1706222
47. Kloner RA, Creech JL, Stone GW, O'Neill WW, Burkhoff D, Spears JR. Update on cardioprotective strategies for STEMI: focus on supersaturated oxygen delivery. *JACC Basic Transl Sci.* (2021) 6:1021–33. doi: 10.1016/j.jacbts.2021.07.011
48. Xu A, Sun G, Duan C, Chen Z, Chen C. Quantitative assessment of three-dimensional choroidal vascularity and choriocapillaris flow signal voids in myopic patients using SS-OCTA. *Diagnostics.* (2021) 11:1948. doi: 10.3390/diagnostics11111948
49. Wang P, Chen S, Liu Y, Lin F, Song Y, Li T, et al. Lowering intraocular pressure: a potential approach for controlling high myopia progression. *Invest Ophthalmol Vis Sci.* (2021) 62:17. doi: 10.1167/iovs.62.14.17
50. Mori K, Kurihara T, Miyauchi M, Ishida A, Jiang X, Ikeda SI, et al. Oral crocetin administration suppressed refractive shift and axial elongation in a murine model of lens-induced myopia. *Sci Rep.* (2019) 9:295. doi: 10.1038/s41598-018-36576-w
51. Aleman AC, Wang M, Schaeffel F. Reading and myopia: contrast polarity matters. *Sci Rep.* (2018) 8:10840. doi: 10.1038/s41598-018-28904-x

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The WHO-ITU MyopiaEd Programme: A Digital Message Programme Targeting Education on Myopia and Its Prevention

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The objective of this paper is to provide an overview of the World Health Organization - International Telecommunication Union MyopiaEd programme - a digital message programme targeting education on myopia and its prevention. The development of the MyopiaEd programme included 4 key steps: (1) Conceptualization and consultation with experts in the field of myopia, mHealth and health behavior change; (2) Creation of SMS message libraries and programme algorithm; (3) Review of the message libraries to ensure relevance to the target audience; and (4) Pre-testing amongst end-user groups to ensure that the design of the programme and the message content were understandable. After reviewing the available evidence and considering input of the experts, the aims, end users and key themes of the programme were finalized. Separate SMS-adapted message libraries were developed, reviewed and pre-tested for four target end-user groups; (1) general population involved in the care of children (2) parents or caregivers of children with myopia; (3) adolescents with myopia; and (4) adults with myopia. The message libraries are part of a comprehensive toolkit, developed through a consultative process with experts in digital health, to support implementation within countries. The development of the MyopiaEd programme aims to provide a basis for Member States and other stakeholders to develop, implement and monitor large-scale mHealth programmes. It is aimed at raising awareness of good eye care behaviors and addressing common reasons for non-compliance to spectacle wear. The next steps will involve adapting and evaluating the MyopiaEd programme in selected settings.

Keywords: myopia, mHealth, public health, digital health, behavior change

INTRODUCTION

Uncorrected myopia is a leading cause of vision impairment and poses a considerable financial burden on countries, with an estimated annual global productivity loss of US$ 244 billion (1). To further confound this problem, the prevalence of myopia is projected to increase substantially in the coming decade, with 3.36 billion people estimated to be impacted by 2030. (2) During the same period, the number of people with high myopia, an emerging cause of irreversible blindness, is projected to impact over 500 million. Although refractive correction provides an effective means of correcting myopia, compliance with spectacle-wear among children and adolescents is often suboptimal, commonly attributable to misconceptions and stigma (3). In addition, awareness of the risk factors and symptoms of myopia are low and may prevent or delay children from receiving a formal eye examination.

Growing evidence among child populations strongly implicates lifestyle risk factors, including intensive near vision activity (as a risk factor) and longer time spent outdoors (as a protective factor), in the onset and progression of myopia during childhood (4). Interventions targeting these lifestyle factors offer the possibility of reducing the risk of developing high myopia and its related potentially blinding complications later in life. To this end, large-scale programmes and policies have been established within countries with a high prevalence of myopia, aimed at myopia prevention through increased time spent outdoors among children (5, 6).

In October 2019, WHO launched the World Report on Vision which highlights the importance of preventive strategies for eye conditions (2). A key recommendation of the report was to raise general awareness and engage and empower people and communities (2). In line with this recommendation, WHO recognizes the vital role education campaigns play in the management of myopia and its associated complications, while also improving education of good eye care behaviors (e.g., the importance of regular eye examinations) and addressing common reasons for non-compliance to spectacle wear. However, research shows that in many countries, awareness of myopia is low (7, 8). Cognisance is also given to the possible deleterious effect of COVID-19 lockdown measures on myopia amongst children, with research indicating an increase in myopia incidence and progression attributed to less time spent outdoors due to home confinement and a substantial increase in near work activities such as online learning (9–11).

To facilitate countries in enhancing their domestic services for myopia education and prevention, WHO and ITU have developed the "Be He@lthy, Be Mobile" (BHBM) programme for myopia. The BHBM programme uses mobile technology for health (mHealth) to address a range of non-communicable diseases and health issues such as diabetes, dementia, aging, and tobacco consumption. In this case, building on already acquired experience in mHealth, and in collaboration with an international group of experts in the field of myopia and behavioral science, an mHealth programme for myopia – MyopiaEd – has been developed. The objective of this paper is to provide an overview of the MyopiaEd programme, including the development process, and outline the next steps.

METHODS

Development and Design of the MyopiaEd Programme

The development of the MyopiaEd programme was aligned with published development frameworks (12, 13) with a focus on implementation, use of behavioral change theory, and involvement of the target population. The development process followed a stepwise process with the involvement of different stakeholders (**Figure 1**).

Step 1. Conceptualization and Consultation

The WHO was responsible for the overall coordination of the project as well as technical and developmental work.

An Informal Expert Group (IEG), comprising experts in myopia and health behavior change, purposively recruited from all six WHO regions, was established at the project outset to provide technical input throughout the development of the MyopiaEd Programme. Initial technical consultations were held (22–23 October 2020) with WHO offices, including those from the Vision and Eye Care Programme and Digital Health Department, and the IEG with the principal objective being to agree on the scope of the MyopiaEd programme, including the context, purpose, end users and key topic themes to be covered.

In preparation for the IEG consultations, WHO offices identified existing evidence (e.g., systematic reviews, randomized control trials, white papers) (14–23) on a range of topics (e.g., spectacle compliance, time spent outdoors and near work-related parameters), as the basis for identifying key topic themes to be covered in the MyopiaEd programme. This evidence and proposed themes were summarized during the consultation, where IEG members provided technical input to WHO on the nature of the related message content within each theme, with consensus being the endpoint in all cases (14–23).

Step 2. Creation of the Message Libraries and Programme Algorithm

Following the initial consultation period with the IEG to finalize the key themes and end-users, an expert in health behavior change (RD), who previously led the development of message libraries for other Be He@lthy Be Mobile programmes, (24, 25) drafted separate MyopiaEd message libraries for each end user group (26). Message content was written with a global perspective and with the understanding that the messages may need to be adapted for use by specific countries. Behavior change techniques were used to underpin each of the messages. Each message was categorized into one of 4 domains: Motivation, Support, Information, or Reminders. Messages were designed to be clear and direct, offering practical and relevant advice, in simple language. Messages were designed to be positively (gain/benefit) framed, with a focus and emphasis on the benefits of action.

Suggested algorithms for the programme were also developed to guide the delivery of the messages. Based on the experience of WHO mHealth programmes, expert review and end user

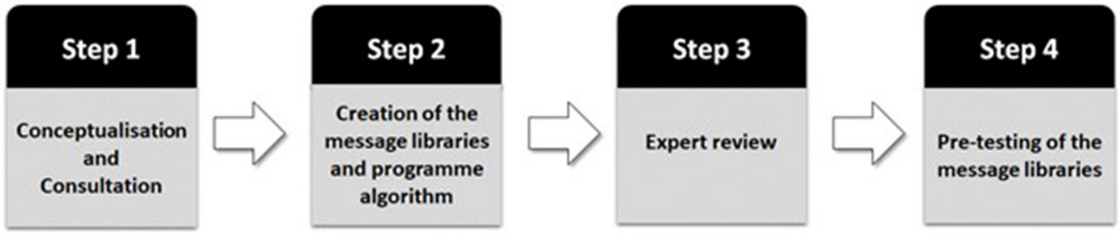

FIGURE 1 | Stages of development of the MyopiaEd programme.

feedback, suggestions regarding the format, the timing of the programme, and frequency of messages to be delivered were made.

The expert in health behavior change had access to the following reviews and information to assist in informing the initial draft of the MyopiaEd message libraries and algorithms:

(i) A scoping review commissioned by WHO to collate and synthesize the evidence on the use of mHealth interventions in eye care, where they provide information to raise awareness about services, provide condition-specific information or encourage individuals to adhere to a treatment or to attend an appointment.

(ii) A review of existing social media campaigns on myopia and collation of existing messages used in myopia-related awareness or health promotion campaigns. The search was conducted on News, blogs, websites (governmental or non-governmental organizations) and publications, together with a focused social media search using the Sprinklr® platform which listens to mentions across more than 20 social channels.

(iii) The results of unpublished end user qualitative and quantitative research conducted by the Global Myopia Awareness Coalition (GMAC). This research explored various strategies and campaigns on myopia education for key stakeholders including parents, children and healthcare providers in the United States (27).

Step 3. Expert Review

The initial message libraries and associated algorithm underwent two rounds of expert review. This included (i) review by experts in the field of myopia to ensure that the messages were clinically correct and evidence-based; and (ii) review by experts in behavior change from the WHO Behavioral Insights team (Geneva) and WHO Regional Office digital health advisors to ensure that the messages were relevant to the target audience. Following each stage of expert review, the message libraries were progressively updated to incorporate experts' feedback.

Step 4. Pre-testing of the Message Libraries

The purpose of pre-testing the message libraries was to ensure that both the design of the programme and the draft message content were understandable and acceptable to an English-speaking target audience.

Convenience targeted sampling was used to recruit participants for the pre-testing to ensure representation from all potential types of end users. During the pre-testing, the proposed programme was described, and a range of messages was shown. Participants were asked to provide feedback on aspects of the proposed programme (e.g., programme duration, target users, frequency of messaging), as well as on the individual messages (e.g., clarity, tone, content). Thirteen sessions of pre-testing were carried out by a trained interviewer in-person or over videoconferencing, according to the participant's preference. Feedback from participants were summarized by the interviewer and common themes were identified using a simple, general inductive thematic approach. Based on the feedback received during pre-testing, additional changes were made to the message libraries.

RESULTS

Key Outcomes of the Informal Expert Group Consultation

The key outcomes and discussion points from the IEG consultation (October 2020) for each of the proposed themes of the MyopiaEd programme are summarized in **Table 1**.

Scope of the MyopiaEd Programme

After reviewing the available evidence and considering the feedback of IEG members, and individuals from related WHO departments, the aims, end users, key themes and algorithm (i.e., format, frequency and duration) of the MyopiaEd programme were finalized (**Table 2**).

Message Libraries and Toolkit to Support Implementation

Key changes made to the message libraries following this peer review process, coupled with an overview of the feedback received during pre-testing of the message libraries, have been summarized in **Supplementary File 1**.

The resultant message libraries for the four target end-user groups, and an accompanying BHBM toolkit containing operational guidance and resources to support the implementation, can be found at the WHO webpage (26).

TABLE 1 | A summary of the key outcomes of the WHO consultation on the proposed themes of the MyopiaEd Programme.

Theme of messages	Key outcomes and discussion points
General myopia education and misconceptions	• It was agreed that the messages on general myopia education would cover the key areas of (i) what is myopia?; (ii) prevalence; (iii) causes; and (iv) warning signs and potential long term consequences of myopia. • It was acknowledged that some myopia misconceptions are very culturally specific. Given the MyopiaEd toolkit is aimed at a global audience, these misconceptions should be incorporated into the message libraries during the adoption phase that will happen at an individual country level. • It was agreed that the messages on global myopia misconceptions would focus on the key areas of: (i) wearing spectacles makes your child's myopia worse; (ii) there is nothing you can do to prevent myopia or vision loss from myopia; (iii) myopia only affects children; and (iv) myopia is just a spectacle/vision issue and not an eye health issue
Regular comprehensive eye exams	• It was agreed that messages promoting eye examinations amongst all population end-users are important. • While it was not considered feasible to make a recommendation on age and frequency of examinations at a global level, it was recommended that the toolkit should aim to be specific and instructional, to provide the end-user with actionable items for change. Therefore, the message libraries should promote inclusion of age and frequency when message content is adapted at a country level to be aligned with other eye health programme guidance within the specific country.
Time spent outdoors	• There was general agreement that the evidence is sufficient to promote time spent outdoors as a key theme in the MyopiaEd programme. • It was noted that the evidence is stronger for primary prevention (i.e., reducing the incidence) than secondary prevention (i.e., slowing progression to reduce the risk of high myopia). Therefore, messages promoting increased time spent outdoors are used most frequently in the MyopiaEd message library targeting the general population involved in the care of children without myopia. However, given the safety of the intervention, and the potential broader benefits for physical and mental health, it was agreed that messages promoting time spent outdoors should also be included in the message libraries targeting young people with myopia, albeit in a reduced frequency. • While it was acknowledged that further research is required in order to be able to provide precise recommendations on the amount of time per day, the IEG felt strongly that an amount of time per day should be specified in order to provide the end-user with actionable items for change. To this end, it was suggested that the evidence is sufficient to at the least include recommendations for a minimum daily time spent in outdoor leisure activities and, based on the evidence, 90 min was proposed (28–30). It was acknowledged that the message content should be adapted as further evidence becomes available. • Other key considerations for messages promoting increased time outdoors included: (1) the need to consider sun-protection in some latitudes; and (2) cultural commitment to educational success and weather as potential barriers. To this end, the messages aim to avoid people misinterpreting them as "anti-education"; rather the focus should be on encouraging more time outdoors during leisure time. Messages also aim to avoid exposing children to weather-related health risks.
Education, near work-related parameters, screen time	• There was general agreement that the evidence is sufficient to include time spent on near-work related activities as a theme in the MyopiaEd Programme. This was based on the findings of recent systematic reviews of cross-sectional studies that have concluded that more time spent on near work activities was associated with higher odds of having myopia. However, the paucity of evidence from RCTs on this topic, as well as the difficulty to conduct such research, was acknowledged. • It was agreed that the evidence on the relationship between personal digital devices use and myopia onset or progression is mixed and not yet comprehensive. However, many members of the IEG felt strongly that to *not* include messages on this theme would be a missed opportunity, particularly given that evidence strongly implicates device use and (i) other eye-related conditions, e.g., dry eye-related complications; and (ii) other health issues, e.g., mental health. Therefore, it was suggested that digital devices could be included within the message content as an example of a near-work activity. • As with outdoor activity, it was suggested that negative messaging on reading and education should be avoided. Rather the focus should be on encouraging changes in behavior during leisure time.

DISCUSSION

The WHO-ITU MyopiaEd programme provides a basis to support countries and other stakeholders to develop, implement and monitor large scale mHealth programmes aimed at (i) improving awareness of the importance of regular eye examinations and spectacle compliance, and (ii) supporting behavior change that may delay the age of onset, and slow the progression of myopia.

Traditionally, interventions aimed at health promotion and prevention in the field of eye care have received less attention and investment than those for treatment. However, the growing evidence implicating lifestyle risk factors in the onset and progression of myopia, coupled with the known impact of uncorrected myopia on academic performance and the need to address common reasons for non-compliance with spectacle wear, provide a strong rationale for educational campaigns targeting both those at risk of developing myopia and those who already have myopia. A text message-based programme, such as that described in this paper, offers a solution to reaching large audiences at low cost. While not extensive, literature on the use of mHealth messaging in eye care shows promising results for improving adherence to treatment of chronic eye conditions, (35, 36) increasing rates of attendance at eye care facilities (37–39) and, more recently, behavior modification for the prevention of myopia (40).

Similar to the other WHO BHBM programmes (41) the MyopiaEd programme is intended for implementation by government officials, academics, and other in-country partners (e.g., non-government organizations) who are involved

TABLE 2 | Overview of key aspects of the MyopiaEd programme (31).

Aim	1. To support behavior change that contributes to delaying the onset, and slowing the progression, of myopia 2. To improve awareness and health literacy of the importance of regular eye examinations and spectacle compliance among children and adults with myopia
End users	1. General population involved in the care of children, including general health workers and educators 2. Parents or caregivers of children with myopia 3. Adolescents with myopia 4. Adults with myopia
Themes of the messages*	1. General education on myopia: the causes, warning signs and misconceptions 2. Lifestyle behavior changes, including time spent outdoors and near-work related parameters, that can reduce the risk of high myopia and its complications 3. Importance of regular comprehensive eye examinations 4. Importance of compliance with refractive correction
Message format	Messages have been designed for one-way SMS (text message) delivery, but are appropriate for delivery via other modalities, including app messaging and social media.
Message frequency	The programme starts at a higher frequency and decreases over time (32). Repetition of key messages is important to ensure that they are understood, behavior change is supported and then maintained. Where repetition of key messages occurs, these are spaced to reduce the likelihood of user boredom.
Duration of the programme	The suggested algorithm for the message library aimed at the general population is 12 months in duration. For the remaining message libraries developed for end-user groups who already have myopia, the suggested algorithms are approximately 6 months in duration. This duration was chosen based on evidence showing that complex change in health behavior takes 6 months to be habitually incorporated into a person's lifestyle (33, 34).

**While messages on general myopia education (such as prevalence, and potential long-term consequences) apply to all population target end users, the themes of other messages vary according to the profile of the individual.*

in mHealth, or other health promotion, programmes. As mentioned, the message libraries (26) are accompanied by a comprehensive BHBM toolkit (31) to support the implementation of the programme within individual countries. Specifically included are introductions and considerations specific to the development of a workplan for an MyopiaEd programme, the role of different stakeholders, guidance for adapting the messages to the local context, selection and implementation of the best technology to deliver the programme, strategies for promotion and retention, and guidance and resources to support monitoring and evaluation (31). Of note, effective promotion will be essential to recruit users to the MyopiaEd programme and enabling them to subscribe in a convenient manner. To this end, it is recommended that multiple engagement channels are used (e.g., social media, SMS, community and civil society meetings, and various other gatherings). On enrolment to the programme, a pre-screening questionnaire will be used to select the most relevant message library for each user based on their characteristics.

A number of key actions are required prior to large scale implementation of the MyopiaEd programme (31, 41, 42). Firstly, the current MyopiaEd message libraries (26) have been written from a global perspective, and, although pre-tested in a high-income English-speaking target audience, it is acknowledged that many of the social environments in which these messages may be deployed will have difference characteristics. Therefore, prior to implementation, the message libraries will need to be translated, adapted, and/or additional content developed, based on the social or cultural context in each country or setting. For example, references to contact lenses and other treatment options could be added where available and accessible (the current message library refers to spectacles as the main form of correction), references to sun protection should be added where applicable in messages encouraging time spent outdoors, and the specific details of the recommended age of first eye examination, and frequency of eye examinations based on country-level guidelines should be added (taking into account national health service provision and current screening programmes). Adapted content will enable users to relate to and implement the strategies for behavioral change and may lead to higher retention of users. Local experts and target users should guide the adaptation process, with any new information being strictly evidence-based. Secondly, the next stage of the project will involve evaluating the MyopiaEd programme in selected settings to determine the impact of the programme, facilitate course correction, and make the case for expansion. Evaluation will focus on key outcome indicators, including changes in knowledge or behaviors that have occurred as a result of the programme. Lastly, acknowledging that evidence in the field of myopia is subject to change, future work will involve periodically reviewing, updating and refining the MyopiaEd message libraries.

The short-term objectives of the MyopiaEd programme are to (i) improve population awareness and health literacy on myopia; (ii) contribute to eliciting modifications in behavior of the population (i.e., care seeking, reduced time spent on near work activities during leisure time and increased time spent outdoors in children); and (iii) address misconceptions and stigma to positively impact on the willingness to wear and/or time spent wearing spectacles among children and adolescents. It is important to emphasize that the MyopiaEd is not intended to be conducted in isolation, but rather it should be complementary to existing and emerging screening and clinical interventions, policies and awareness related to general health (e.g., obesity control through physical activity), myopia and eye health in countries. If successful in the long-term, these interventions along the continuum of care have potential to reduce the incidence of (i) childhood myopia, (ii) high myopia and (iii) irreversible vision impairment due to myopia. As key underpinnings of an effective programme, robust monitoring and evaluation strategies are planned to assess the programme activities, outputs, and outcomes and thereby its overall performance (43).

In conclusion, it is the intention that the MyopiaEd programme will provide a basis to strengthen countries' efforts to develop sustainable, cost-effective, and acceptable activities to support education on myopia and its prevention. Of importance, it is recommended that the programme be implemented as part of an existing national or regional digital health or mHealth programme (where available) to ensure optimization of available resources. The next phase of this project will focus on country adaptation for implementation, and evaluation in selected settings.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SK, AC, and AM conceived the project. RD conducted the user-testing. SK prepared the first and subsequent drafts of this manuscript, following co-author review. All authors reviewed and approved the submission of the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.881889/full#supplementary-material

REFERENCES

1. Naidoo KS, Frick KD, Fricke TR, Jong M, Naduvilath TJ, Resnikoff S, et al. Estimated lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modelling. *Ophthalmology*. (2019) 196:338–46. doi: 10.1016/j.ophtha.2018.10.029
2. World Health Organization. *World Report on Vision*. (2019). Available online at: https://www.who.int/publications-detail/world-report-on-vision (accessed November 16, 2019).
3. Dhirar N, Dudeja S, Duggal M, Gupta PC, Jaiswal N, Singh M, et al. Compliance to spectacle use in children with refractive errors-a systematic review and meta-analysis. *BMC Ophthalmology*. (2020) 20:71. doi: 10.1186/s12886-020-01345-9
4. Morgan IG, Wu PC, Ostrin LA, Tideman JWL, Yam JC, Lan W, et al. IMI risk factors for myopia. *Invest Ophthalmol Vis Sci.* (2021). doi: 10.1167/iovs.62.5.3
5. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet.* (2012) 379:1739–48. doi: 10.1016/S0140-6736(12)60272-4
6. Jin J-X, Hua W-J, Jiang X, Wu XY, Yang JW, Gao GP, et al. Effect of outdoor 0activity on myopia onset and progression in school-aged children in northeast china: the sujiatun eye care study. *BMC Ophthalmology.* (2015) 15:73. doi: 10.1186/s12886-015-0052-9
7. Li L, Lam J, Lu Y, Ye Y, Lam DSC, Gao Y, et al. Attitudes of students, parents, and teachers toward glasses use in rural China. *Arch Ophthalmol.* (2010) 128:759–65. doi: 10.1001/archophthalmol.2010.73
8. McCrann S, Flitcroft I, Lalor K, Butler J, Bush A, Loughman J. Parental attitudes to myopia: a key agent of change for myopia control? *Ophthalmic Physiol Opt*. (2018) 38:298–302. doi: 10.1111/opo.12455
9. Picotti C, Sanchez V, Irigaray L, Morgan IG, Iribarren R. Myopia progression in children during COVID-19 home confinement in Argentina. *Oftalmol Clin Exp.* (2021) 14:156–61. doi: 10.2139/ssrn.3781660
10. Wang J, Li Y, Musch DC, Wei N, Qi X, Ding G, et al. Progression of myopia in school-aged children after COVID-19 home confinement. *JAMA Ophthalmol.* (2021) 139:293–300. doi: 10.1001/jamaophthalmol.2020.6239
11. Kuehn BM. Increase in myopia reported among children during COVID-19 lockdown. *JAMA*. (2021) 326:999–999. doi: 10.1001/jama.2021.14475
12. Abroms L, Whittaker R, Free C, Van Alstyne JM, Schindler-Ruwisch JM. Developing and pretesting a text messaging program for health behavior change: recommended steps. *JMIR Mhealth Uhealth.* (2015) 3:e107. doi: 10.2196/mhealth.4917
13. Whittaker R, Merry S, Dorey E, Maddison R. A development and evaluation process for mHealth interventions: examples from New Zealand. *J Health Commun*. (2012) Suppl. 1:11–21. doi: 10.1080/10810730.2011.649103
14. Wolffsohn JS, Kollbaum PS, Berntsen DA, Atchison DA, Benavente A, Bradley A, et al. IMI – Clinical myopia control trials and instrumentation report. *Invest Ophthalmol Vis Sci.* (2019) 60:M132–60. doi: 10.1167/iovs.18-25955
15. Wolffsohn JS, Flitcroft DI, Gifford KL, Jong M, Jones L, Klaver CCW, et al. IMI – Myopia control reports overview and introduction. *Investig Ophthalmol Vis Sci.* (2019) 60:M1–19. doi: 10.1167/iovs.18-25980
16. Wildsoet CF, Chia A, Cho P, Guggenheim JA, Polling JR, Read S, et al. IMI – Interventions myopia institute: interventions for controlling myopia onset and progression report. *Investig Ophthalmol Vis Sci.* (2019) 60:M106–31. doi: 10.1167/iovs.18-25958
17. Troilo D, Smith EL, Nickla DL, Ashby R, Tkatchenko AV, Ostrin LA, et al. Imi – Report on experimental models of emmetropization and myopia. *Investig Ophthalmol Vis Sci.* (2019) 60:M31–88. doi: 10.1167/iovs.18-25967
18. Tedja MS, Haarman AEG, Meester-Smoor MA, Kaprio J, Mackey DA, Guggenheim JA, et al. IMI – Myopia genetics report. *Investig Ophthalmol Vis Sci.* (2019) 60:M89–105. doi: 10.1167/iovs.18-25965
19. Jones L, Drobe B, González-Méijome JM, Gray L, Kratzer T, Newman S, et al. IMI – Industry guidelines and ethical considerations for

Myopia control report. *Investig Ophthalmol Vis Sci.* (2019) 60:M161–83. doi: 10.1167/iovs.18-25963
20. Gifford KL, Richdale K, Kang P, Aller TA, Lam CS, Liu YM, et al. IMI – Clinical management guidelines report. *Investig Ophthalmol Vis Sci.* (2019) 60:M184–203. doi: 10.1167/iovs.18-25977
21. Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, et al. IMI – Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Investig Ophthalmol Vis Sci.* (2019) 60:M20–30. doi: 10.1167/iovs.18-25957
22. Zhu Z, Chen Y, Tan Z, Xiong R, McGuinness MB, Muller A. Interventions recommended for myopia prevention and control among children and adolescents in China: a systematic review. *Br J Ophthalmol.* (2021). doi: 10.1136/bjophthalmol-2021-319306. [Epub ahead of print].
23. Huang HM, Chang DST, Wu PC. The association between near work activities and myopia in children-a systematic review and meta-analysis. *PloS ONE.* (2015) 10:e0140419. doi: 10.1371/journal.pone.0140419
24. World Health Organisation. *A Handbook on How to Implement mDementia*. Available online at: http://apps.who.int/bookorders (accessed February 13, 2022).
25. World Health Organisation. *Mobile Technologies for Oral Health: An Implementation Guide*. Available online at: https://www.who.int/publications/i/item/9789240035225 (accessed February 13, 2022).
26. World Health Organization, International Telecommunication Union. *Be he@lthy, be Mobile: a Toolkit on How to Implement MyopiaEd. Web Annex: MyopiaEd message libraries*. (2022). Available online at: https://www.who.int/publications/i/item/9789240044814 (accessed March 22, 2022).
27. Review of Myopia Management. *GMAC's Latest Campaign Shows Parents Respond Well to Myopia Education - Review of Myopia Management*. Available online at: https://reviewofmm.com/gmacs-latest-campaign-shows-parents-respond-well-to-myopia-education/ (accessed February 13, 2022).
28. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol.* (2017) 95:551–66. doi: 10.1111/aos.13403
29. Read S, Collins M, Vincent S. Light exposure and eye growth in childhood. *Investig Ophthalmol Vis Sci.* (2015) 56:6779–87. doi: 10.1167/iovs.14-15978
30. Wu P, Chen C, Chang L, Niu YZ, Chen ML, Liao LL, et al. Increased time outdoors is followed by reversal of the long-term trend to reduced visual acuity in taiwan primary school students. *Ophthalmology.* (2020) 127:1462–9. doi: 10.1016/j.ophtha.2020.01.054
31. World Health Organisation, International Telecommunication Union. *Be he@lthy, be Mobile: a Toolkit on How to Implement MyopiaEd Geneva*. (2022). Available online at: https://www.who.int/publications/i/item/9789240044814 (accessed March 22, 2022).
32. Head KJ, Noar SM, Iannarino NT, Harrington NG. Efficacy of text messaging-based interventions for health promotion: a meta-analysis. *Soc Sci Med.* (2013) 97:41–8. doi: 10.1016/j.socscimed.2013.08.003
33. Buchholz SW, Wilbur J, Ingram D, Fogg L. Physical activity text messaging interventions in adults: a systematic review. *Worldviews Evid Based Nurs.* (2013) 10:163–73. doi: 10.1111/wvn.12002
34. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet.* (2011) 378:49–55. doi: 10.1016/S0140-6736(11)60701-0
35. Lai Y, Wu Y, Chai C, Yen CC, Ho Y, Eng TC, et al. The effect of patient education and telemedicine reminders on adherence to eye drops for glaucoma. *Ophthalmol Glaucoma.* (2020) 3:369–76. doi: 10.1016/j.ogla.2020.05.005
36. Zhao YY, Dang FP, Zhai TT Li HJ, Wang RJ, Ren JJ. The effect of text message reminders on medication adherence among patients with coronary heart disease: a systematic review and meta-analysis. *Medicine.* (2019) 98:e18353. doi: 10.1097/MD.0000000000018353
37. Yang K, Jin L, Li L, Zeng S, Wei R, Li G, et al. Interventions to promote follow-up after trabeculectomy surgery in rural southern China: a randomized clinical trial. *JAMA Ophthalmol.* (2016) 134:1135–41. doi: 10.1001/jamaophthalmol.2016.2819
38. Chen T, Zhu W, Tang B, Jin L, Fu H, Chen Y, et al. A mobile phone informational reminder to improve eye care adherence among diabetic patients in rural china: a randomized controlled trial. *Am J Ophthalmol.* (2018) 194:54–62. doi: 10.1016/j.ajo.2018.07.006
39. Koshy E, Car J, Majeed A. Effectiveness of mobile-phone short message service (SMS) reminders for ophthalmology outpatient appointments: observational study. *BMC Ophthalmology.* (2008). doi: 10.1186/1471-2415-8-9
40. Li Q, Guo L, Zhang J, Zhao F, Hu Y, Guo Y, et al. Effect of school-based family health education via social media on children's myopia and parents' awareness: a randomized clinical trial. *JAMA Ophthalmol.* (2021) 139:1165–72. doi: 10.1001/jamaophthalmol.2021.3695
41. World Health Organisation. *Be Healthy Be Mobile*. Available online at: https://www.who.int/initiatives/behealthy (accessed February 4, 2022).
42. World Health Organisation. *Be Healthy Be Mobile*. Available online at: https://www.who.int/publications/i/item/9789240019966 (accessed December 23, 2021).
43. International Labour Organization. *Basic Principles of Monitoring and Evaluation*. Geneva (2015). Available online at: http://ilo.org/wcmsp5/groups/public/---ed_emp/documents/publication/wcms_546505.pdf (accessed March 22, 2022).

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Sex Disparity in Myopia Explained by Puberty Among Chinese Adolescents From 1995 to 2014: A Nationwide Cross-Sectional Study

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Importance: Girls in East Asia have a higher myopia prevalence than boys. Less research has been done on whether girls' earlier puberty could explain this sex difference.

Objective: The purpose of this study was to evaluate the association between myopia and puberty and the role of puberty in explaining the sex disparity in adolescent myopia prevalence.

Design, Setting, and Participants: In this nationwide cross-sectional study, data came from five consecutive national surveys from 1995 to 2014 in China. We included 338,896 boys aged 11–18 and 439,481 girls aged 9–18.

Main Outcomes and Measures: Myopia was defined according to unaided distance visual acuity and subjective refraction; puberty status was defined dichotomously as menarche or spermarche status. The association between myopia and puberty was evaluated by robust Poisson GEE regression. Mediation analyses were used to quantify how much of the sex disparity in myopia could be explained by puberty.

Results: Post-menarche girls and post-spermarche boys showed 29–41% and 8–19% higher risk of myopia than pre-menarche girls and pre-spermarche boys, respectively. The association remained significant in girls [prevalence ratio (PR) = 1.07, 95%CI:1.04–1.10] but disappeared in boys ($p > 0.05$) after adjusting for potential confounders. Girls had a 12–23% higher risk of myopia than boys. A total of 16.7% of the sex disparity in myopia could be explained by girls' earlier puberty, whereas 11.1% could be explained by behavioral factors.

Conclusion and Relevance: Puberty status is independently associated with myopia in girls but not in boys. A significant proportion of the sex disparity in adolescent myopia could be explained by girls' earlier puberty, suggesting the need to consider sex-differentiated strategies for myopia prevention and treatment.

Keywords: puberty, myopia, sex disparity, adolescents, Chinese, menarche, spermarche

INTRODUCTION

Myopia (near-sighted vision) has emerged as a major global public health concern (1) with its rapidly increasing prevalence (2) and heavy economic burden (3). The higher prevalence of myopia in girls is a consistent phenomenon in most ethnicities, but this trend has few satisfactory explanations (2). East Asians, including the Chinese (4), have the highest prevalence of myopia worldwide, reaching 80% at the age of 18 years. We previously found that the earlier a girl enters puberty, the higher their risk of myopia (5). Given that girls usually enter puberty 1–2 years earlier than boys (6, 7), earlier puberty may partly explain the higher prevalence of myopia in girls.

A cohort study found that nearly 80% of new myopia cases occurred in individuals aged 9–13 years (8), suggesting that myopia mostly develops during early and mid-puberty (1). Thus, we hypothesize that puberty development might be associated with myopia onset. This hypothesis is further supported by the finding that boys and girls with earlier growth spurts also experienced earlier axial growth and myopia onset (9). A total of two other cohort studies showed that growth in height before age 10 contributed was not associated with myopia development, indicating that puberty development after age 10 may play a bigger role (10, 11).

Evidence using puberty indicators other than growth is controversial and limited. A number of two cross-sectional studies investigating adults in India and South Korea found that women with an earlier menarche age had a higher prevalence of myopia. These results, however, may be compromised by recall bias because the age of menarche- and myopia-related covariates was collected in adulthood (12, 13). In contrast, another study found no association between the age of menarche and the age of axial growth or myopia onset, but this negative finding may result from selection bias and low statistical power because it only included 1,779 children from 3 schools in Singapore (9). Furthermore, studies have not been able to establish an association between myopia and spermarche, the male-specific puberty indicator. More studies with a large sample size and good measures of puberty status during adolescence are needed to clarify the role of puberty in myopia development. Such studies may be especially critical for China, the country with the largest myopic population (4).

Based on previous studies, we hypothesize that adolescent myopia is positively associated with the onset of puberty, as represented by menarche or spermarche status, and this association may help explain girls' higher myopia prevalence in China. The Chinese National Survey on Students' Constitute and Health (CNSSCH), a national survey of school-aged children, provided us with data to approach these questions. Testing these hypotheses could lead to more targeted or sex-specific strategies to prevent myopia.

METHODS

Study Design and Participants

Data were extracted from the 1995, 2000, 2005, 2010, and 2014 cycles of the CNSSCH, a series of cross-sectional national surveys among school-aged children in China that used identical stratified random cluster sampling procedures in each cycle. In total, the surveys reached 1,081,956 Han ethnicity students (the dominant ethnic group in China) aged 7–18, of which 1,080,030 (99.8%) had data on myopia. The CNSSCH covered 30 of the 31 mainland provinces (4 municipalities were also treated as provincial units), excluding Tibet where the Han people are a minority. Children from recognized non-Han ethnicity minority groups were not included (these groups constitute 8.9% of the population of the 30 included provinces). In each province, three cities or regions at different levels of economic development or regional socioeconomic status (SES) ("upper," "moderate," and "low") were chosen. Children aged 7–18 clustered by classroom were randomly chosen from these schools, ensuring that each sex × age combination in each city/region included at least 100 children (6). The project was approved by the Medical Research Ethics Committee of Peking University Health Science Center (IRB00001052-18002).

Visual Acuity and Refraction Status Measurements

Myopia was defined based on the vision chart assessment of unaided distance visual acuity (VA) (4) in the worse eye combined with simple subjective refraction. Unaided distance VA for each eye was measured by certified optometrists using a retro illuminated logarithm of the minimum angle of resolution (logMAR) chart with tumbling-E optotypes (Precision Vision, Denver Colorado) (8). Reduced VA was defined as distance VA worse than 6/6.

For eyes with reduced VA, subjective refraction was used to detect the refractive status with a positive/ negative diopter spherical lens of +/-0.75D. Compared with the unaided distance VA, if the distance VA wearing the positive lens reduced ≥1 line on the chart, and the distance VA wearing the negative lens improved ≥1 line, then the examined eye was defined as having "myopia"; if the result was reversed, then the examined eye was defined as having "hyperopia." Any other situations were defined as "other reduced VA." If one of the two eyes was defined as myopia, then the participant was defined as having myopia. According to a validation trial performed by our collaborators in 2012 (refer to **Supplementary Material**), our definition of myopia achieved a sensitivity of 91.9% and a specificity of 83.6%, compared with the most commonly used definition (3) (spherical equivalent refractive error measured by cycloplegic refraction ≤-0.50 D).

Puberty Status Measurements

In each CNSSCH, individual puberty status was defined by the menarche or spermarche status responses given to sex-matched interviewers (6). Girls aged ≥9 years were asked whether menarche had occurred by a school nurse or female physician (6). Similarly, boys ≥11 years were asked whether they had experienced a first ejaculation by male physicians or health professionals (5). As detailed in our previous publications, when needed we used several scripted statements from our well-trained interviewers to ensure that students understood the question and answered the question in a relaxed way (5, 6).

Other Measurements

Participants in the 2014 CNSSCH were asked to complete a self-administered questionnaire in their classrooms and under the guidance of trained investigators. The questionnaire was designed by a panel of experts. Pilot studies were carried out to test whether the questionnaire could be understood and answered accurately by the students. Prior to filling in the questionnaire, students were informed that their answers would be kept confidential and would have no effect on their grades. The questionnaire covered different behaviors, such as sleep duration, physical activity, homework time, near screen time, weekend outdoor activity, and weekend study activity. For individual students, weekend outdoor activity and weekend study activity were classified as "in top 3" and "not in top 3," meaning that the outdoor (or study) activity is one of the top three choices that the participants do on weekends. Age in years and age in days (exact age, presented in hundreds) were both calculated according to participants' date of birth and date of physical examination in the survey. Provincial Gross Domestic Product (GDP) per capita at 2014 prices in different survey years was sourced from the China Statistical Yearbook to provide a measure of regional socioeconomic status (SES). For each participant, VA, puberty status, and all other measures were performed in 1 day.

Statistical Analyses

First, we used the full sample to evaluate the association between myopia and puberty status. We compared the age-standardized prevalence of myopia between pre-menarche/spermarche and post-menarche/spermarche girls and boys across different ages and survey years using chi-square tests. A total of 338,896 boys aged 11–18 and 439,481 girls aged 9–18 with complete data on myopia and puberty status were included in this analysis. We used robust Poisson regression models based on a generalized estimated equation (Poisson GEE) to detect the association between myopia and puberty status (14, 15). This family of models adjusts for the cluster effect of school and estimates prevalence ratios (PRs), which are unbiased estimators of relative risk in cross-sectional studies (14, 15). PRs avoid the problem of odds ratios, which overestimate the relative risk when the prevalence is higher than 10% (14, 15).

Second, we used matched samples to evaluate the association between myopia and puberty status. To make the pre- and post-menarche girls or pre- and post-spermarche boys as comparable as possible, we extracted 5,641 pairs of boys and 6,151 pairs of girls from the 2014 CNSSCH. In each pair, one was pre-menarche or pre-spermarche whereas the other was post-menarche or post-spermarche, and they were the same age and from the same school. This pairing procedure helped to control the effect of age and other confounders at the school level or above and avoids the multi-collinearity of adding age to the regression model.

Finally, mediation analyses with two steps of regression were used to estimate the proportion of sex disparity in myopia explained by puberty and myopia-related behaviors, quantified as the percentage of excess risk mediated (PERM) (refer to **Supplementary Material**) (16). The median age at menarche or spermarche and their 95% CI were estimated by probit analyses (5, 6). The PRs and their 95% CI were estimated for each model. A two-sided $p < 0.05$ was considered statistically significant. We used SPSS (version 20.0, IBM, Chicago, Illinois, USA) to perform the probit analyses. All other analyses were performed in R (version 3.3.2, Boston, Massachusetts), and the *geepack* package (version 1.2-1) in R was used to perform the regression analyses.

RESULTS

The Myopia Prevalence Among Pre- and Post- Menarche/Spermarche Girls and Boys

From 1995 to 2014, the age-standardized prevalence of myopia was 8.7–12.8% points greater in post-menarche girls than pre-menarche girls aged 9–18 (all $p < 0.001$).

A similar pattern was seen in boys, but the disparity between pre- and post-puberty boys was smaller than that of girls. From 1995 to 2014, the age-standardized prevalence of myopia was only 2.5–5.8% points greater in post-spermarche boys than pre-spermarche boys aged 11–18 (all $p < 0.001$) (**Table 1**).

The Association Between Myopia and Puberty Status

As shown in **Figure 1**, post-menarche girls aged 9–17 had 29–41% (PRs ranged from 1.29 to 1.41, all $p < 0.05$) higher risk of being myopic than the pre-menarche girls at the same age. After adjusting for demographic and socioeconomic factors, the PRs consistently reduced to 1.13–1.32 in girls aged 9–17, but all remained statistically significant ($p < 0.05$). The result in 18-year-olds was slightly different, mainly due to the small sample of pre-menarche girls at 18 years of age, as shown in **Table 1**.

Similarly, unadjusted regression results in boys showed that post-spermarche boys aged 11 to 18 had an 8–19% (PRs ranged from 1.08 to 1.19) higher risk of being myopic than pre-spermarche boys at the same age. All PRs were statistically significant (higher than 1, $p < 0.05$) except in 18-year-olds, where the pre-spermarche sample is small. When further adjusted for demographic and socioeconomic factors, PRs reduced to 1.01–1.11 in the 8 age groups, and only the results of 13–15 and 17-year-olds remained statistically significant ($p < 0.05$).

Table 2 shows the basic characteristics of boys and girls from the paired sample. The median age of post-spermarche boys was only 3 days older than pre-spermarche boys, and the post-menarche girls were only 24 days older than pre-menarche girls (**Table 2**). Meanwhile, the distribution of pre- and post-spermarche/menarche exact ages was largely overlapping (**Supplementary Figure 1**), and thus, the residual confounding effect of age in paired sample analyses tended to be minimal.

In the paired sample, post-menarche girls had significantly higher myopia prevalence (66.2 vs. 62.0%), less weekend outdoor activity, more near screen time, and shorter sleep duration than pre-menarche girls ($p < 0.05$). No significant differences were seen between the two groups in weekend study activity, daily physical activity time, daily homework time, and self-reported study pressure ($p > 0.05$). Post-spermarche boys had significantly longer near screen time than pre-spermarche boys ($p < 0.05$), but

TABLE 1 | Comparison of myopia prevalence between pre- and post-menarche/spermarche subjects by sex and age, 1995–2014 [sample size (%)].

	1995			2000			2005			2010			2014		
Age (years)	**Pre**	**Post**	***p*-Value**	**Pre**	**Post**	***p*-Value**	**Pre**	**Post**	***p*-Value**	**Pre**	**Post**	***P*-Value**	**Pre**	**Post**	***P*-Value**
Girls															
9	8,179 (18.6)	15 (33.3)	0.14	8,912 (17.8)	87 (32.2)	<0.001	8,954 (28.3)	43 (41.9)	0.05	7,448 (38.3)	53 (45.3)	0.30	7,487 (39.9)	84 (44.0)	0.45
10	8,679 (22.7)	80 (27.5)	0.31	8,942 (22.7)	1,78 (27.5)	0.13	8,945 (35.2)	272 (41.2)	0.04	7,849 (46.3)	235 (58.7)	<0.001	7,546 (47.7)	536 (54.1)	0.01
11	7,988 (28.7)	676 (40.2)	<0.001	8,088 (27.3)	874 (38.0)	<0.001	8,017 (40.4)	1,286 (50.0)	<0.001	7,005 (52.4)	1,490 (62.8)	<0.001	6,211 (54.1)	2,233 (63.5)	<0.001
12	5,924 (34.0)	2,675 (43.7)	<0.001	5,848 (29.4)	3,170 (43.4)	<0.001	5,824 (43.1)	3,311 (54.6)	<0.001	4,238 (54.7)	4,423 (60.7)	<0.001	3,514 (56.2)	5,178 (64.7)	<0.001
13	2,458 (40.6)	6,096 (52.3)	<0.001	2,583 (34.4)	6,377 (46.5)	<0.001	2,360 (46.9)	6,976 (57.5)	<0.001	1,613 (56.1)	7,123 (68.8)	<0.001	1,139 (62.0)	7,688 (70.3)	<0.001
14	808 (42.3)	7,767 (56.2)	<0.001	897 (42.3)	8,071 (53.9)	<0.001	688 (47.4)	8,586 (63.6)	<0.001	374 (60.7)	8,350 (71.7)	<0.001	266 (63.5)	8,607 (75.1)	<0.001
15	307 (42.3)	8,277 (61.6)	<0.001	279 (49.5)	8,641 (64.3)	<0.001	203 (63.5)	9,262 (70.0)	0.05	96 (74.0)	8,690 (74.9)	0.76	48 (66.7)	8,878 (76.9)	0.12
16	177 (54.8)	8,340 (68.2)	<0.001	101 (64.4)	8,867 (72.1)	0.08	31 (51.6)	9,354 (75.3)	0.002	45 (71.1)	8,778 (80.3)	0.09	12 (58.3)	8,919 (79.3)	0.06
17	144 (54.9)	8,386 (72.4)	<0.001	152 (66.4)	8,809 (77.3)	0.002	77 (63.6)	9,267 (78.8)	0.001	17 (64.7)	8,849 (82.4)	0.05	11 (81.8)	8,945 (80.0)	0.94
18	114 (62.3)	8,343 (74.0)	0.01	115 (72.2)	8,885 (78.5)	0.10	69 (85.5)	9,304 (79.8)	0.24	18 (66.7)	8,822 (81.6)	0.09	7 (71.4)	8,518 (81.3)	0.46
Total	34,778 (27.4)	50,655 (63.3)	<0.001	35,917 (25.6)	53,959 (64.6)	<0.001	35,168 (37.3)	57,661 (69.9)	<0.001	28,703 (47.9)	56,813 (75.2)	<0.001	26,241 (49.0)	59,586 (75.4)	<0.001
Standardized* total	34,778 (40.1)	50,655 (52.9)	<0.001	35,917 (42.6)	53,959 (53.4)	<0.001	35,168 (50.6)	57,661 (61.3)	<0.001	28,703 (58.5)	56,813 (68.7)	<0.001	26,241 (60.2)	59,586 (68.9)	<0.001
Boys															
11	8,605 (22.9)	145 (27.6)	0.22	8,612 (20.8)	275 (14.5)	0.02	8,103 (31.9)	362 (37.3)	0.04	6,872 (45.1)	230 (50.0)	0.16	6,695 (49.2)	360 (50.8)	0.59
12	8,306 (28.5)	434 (29.7)	0.62	8,358 (25.6)	621 (27.7)	0.26	7,248 (35.4)	859 (40.6)	0.003	6,369 (49.6)	801 (47.8)	0.31	6,249 (53.5)	1,133 (55.3)	0.37
13	6,712 (38.5)	2,029 (42.1)	0.004	6,551 (32.2)	2,339 (39.5)	<0.001	5,412 (42.8)	2,592 (47.0)	<0.001	4,935 (55.2)	2,465 (59.0)	0.002	4,506 (57.7)	3,199 (62.1)	<0.001
14	4,330 (41.4)	4,419 (48.3)	<0.001	3,977 (37.5)	5,007 (46.2)	<0.001	2,978 (44.6)	5,373 (52.0)	<0.001	2,596 (58.9)	5,105 (63.7)	<0.001	2,316 (61.4)	5,630 (63.4)	0.19
15	2,238 (45.6)	6,508 (52.7)	<0.001	1,648 (42.1)	7,362 (54.1)	<0.001	1,422 (54.1)	7,679 (59.7)	<0.001	1,181 (62.1)	6,862 (66.9)	<0.001	889 (66.0)	7,393 (70.0)	0.02
16	901 (51.6)	7,781 (61.0)	<0.001	615 (56.6)	8,379 (62.1)	0.01	686 (68.1)	8,630 (67.1)	0.61	382 (74.3)	8,163 (72.4)	0.49	307 (74.3)	8,302 (72.5)	0.77
17	364 (57.1)	8,365 (64.4)	0.01	407 (54.1)	8,487 (68.6)	<0.001	533 (67.7)	8,805 (71.3)	0.09	193 (73.1)	8,480 (74.7)	0.61	174 (74.1)	8,539 (73.8)	0.99
18	286 (63.3)	8,369 (64.6)	0.70	194 (67.0)	8,736 (69.6)	0.49	397 (63.5)	9,051 (71.1)	0.001	183 (71.0)	8,518 (75.2)	0.22	125 (71.2)	8,254 (74.2)	0.40
Total	31,742 (33.4)	38,050 (58.1)	<0.001	30,362 (29.4)	41,206 (59.5)	<0.001	26,779 (39.7)	43,351 (63.6)	<0.001	22,711 (52.0)	40,624 (70.0)	<0.001	21,261 (55.0)	42,810 (70.1)	<0.001
Standardized* total	31,742 (43.6)	38,050 (48.8)	<0.001	30,362 (42.0)	41,206 (47.8)	<0.001	26,779 (51.0)	43,351 (55.7)	<0.001	22,711 (61.2)	40,624 (63.7)	<0.001	21,261 (63.4)	42,810 (65.3)	<0.001

**Standardized by age, with this aggregate based on each age having the same weight . p-Values for standardized total were obtained from logistic regression models, which tested statistical significance of the effect of puberty status (independent variable) on myopia (dependent variable) after adjusting for age. All other p-values came from a Chi-square test.*

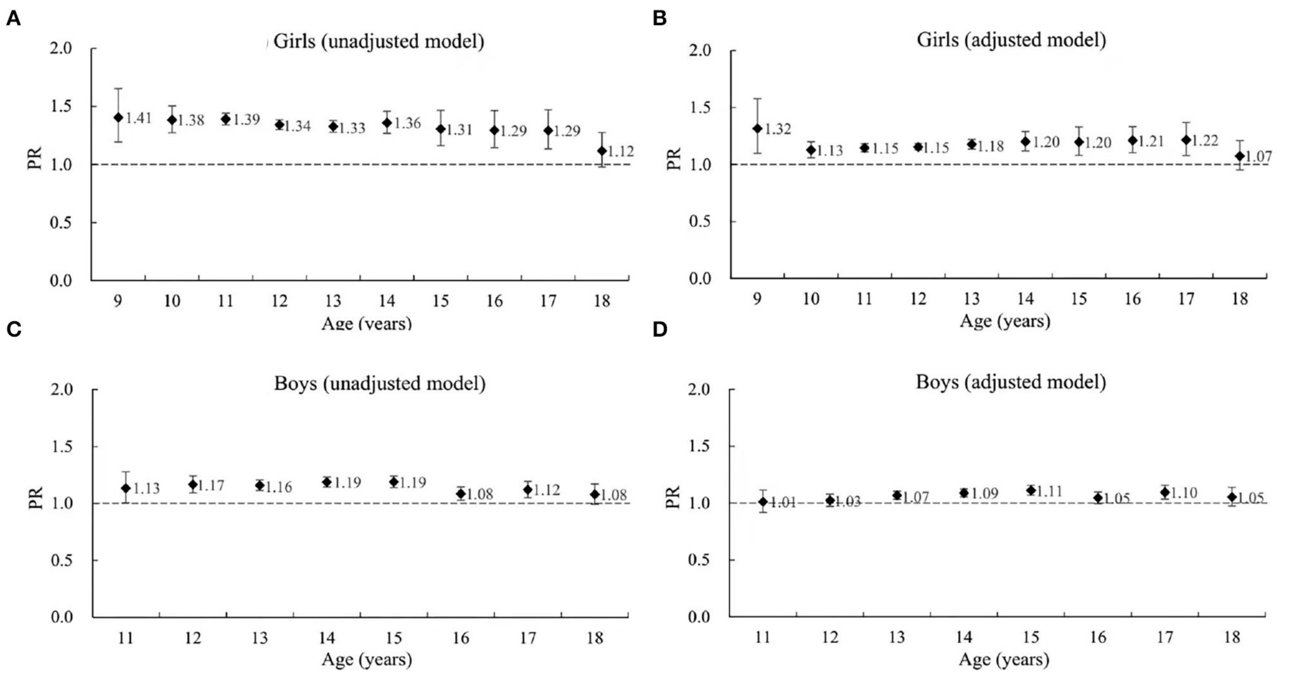

FIGURE 1 | The association between myopia and puberty (menarche for girls and spermarche for boys) status by age in the 1995, 2000, 2005, 2010, and 2014 CNSSCH. **(A)** Girls (unadjusted model). **(B)** Girls (adjusted model). **(C)** Boys (unadjusted model). **(D)** Boys (adjusted model). PR, prevalence ratio, represents the relative risk of myopia for post-menarche girls (or post-spermarche boys) compared to pre-menarche girls (or pre-spermarche boys). CNSSCH, Chinese National Survey on Students' Constitute and Health. The total sample sizes for girls and boys were 429,814 and 332,161, respectively. The unadjusted model only adjusted for the cluster effect of school. The adjusted model additionally adjusted for survey year, urban–rural location, regional socioeconomic status (SES) within province and provincial GDP per capita. The error bars represent 95% confidence intervals (CI).

there were no significant differences in myopia prevalence (66.4 vs. 65.4%) or in the six other measured behaviors (**Table 2**).

Based on the paired sample, post-menarche girls have a 7% (PR = 1.07, 95% CI:1.04–1.10) higher risk of being myopic than pre-menarche girls. This association changed very less when stratified by or adjusted for the seven behaviors (**Table 3**). However, the association between myopia and spermarche in boys' paired samples was non-significant (unadjusted PR = 1.02, 95% CI:0.99–1.04) and remained non-significant after being stratified by or adjusted for the seven measured behaviors (**Table 4**).

The Sex Disparity in Myopia

The prevalence of myopia was consistently higher in girls than in boys regardless of age and survey year. Interestingly, in all survey years, the sex differences in myopia prevalence first went up after 9 years of age and then went down after reaching the highest values at 13–15-year-olds. These changes seemed to be in line with the changing pattern of sex disparity in puberty status (**Supplementary Table 2**).

The sex disparity in myopia was influenced by puberty status. Among post-spermarche/menarche adolescents, girls were 7.8–17.5%points higher in myopia prevalence than boys aged 11–18-year-olds ($p < 0.05$). However, among pre-spermarche/menarche adolescents, the sex differences ranged from −2.7–6.9% points, only reaching significance in 11–13-year-olds (**Figure 2**).

Figure 3 shows that girls had a 12–23% (PRs ranged from 1.12 to 1.23, all $p < 0.05$) higher risk of myopia than boys at the same age, from 7 to 18 years in both the unadjusted and adjusted models. The post-menarche girls had 11–49% (PRs ranged from 1.11 to 1.49, all $p < 0.05$) higher risk of myopia than post-spermarche boys. However, for pre-spermarche/menarche adolescents aged 11–18 years, girls only had a 1–22% higher risk of myopia than boys.

The Role of Puberty in Explaining the Sex Disparity in Myopia

As shown in **Supplementary Table 2**, the biggest difference between sex was puberty status. The median age at menarche was 12.2 years (95%CI: 12.0–12.4), which is 1.6 years earlier than the median age at spermarche (13.8, 95%CI:13.5–14.0). Girls showed less weekend outdoor activity, more weekend study activity, shorter daily physical activity time, shorter sleep duration, and longer homework time; boys were engaged in longer near screen time and reported heavier study pressure (all $p < 0.001$) (**Supplementary Table 3**).

According to the *basic model 1*, after adjusting for puberty status, the PR for sex disparity decreased from 1.122 to 1.102, indicating that 16.71% [PEMR = (1.122–1.102)/(1.122–1)] of the sex disparity in myopia could be explained by puberty status. In comparison, the seven measured behaviors

TABLE 2 | The basic characteristics of included pre- and post- menarche/spermarche subjects matched by sex, age, and school from the 2014 CNSSCH, *n* (%).

	Boys			Girls		
	Pre-	**Post-**	***p*-value**	**Pre-**	**Post-**	***p*-value**
Sample size	5,641 (100.0)	5,641 (100.0)		6,151 (100.0)	6,151 (100.0)	
Myopia			0.26			<0.001
Non-myopia	1,953 (34.6)	1,895 (33.6)		2,336 (38.0)	2,077 (33.8)	
Myopia	3,688 (65.4)	3,746 (66.4)		3,815 (62.0)	4,074 (66.2)	
Age group			1.00			1.00
9–10y	0 (0.0)	0 (0.0)		433(7.0)	433(7.0)	
11–12y	1,007 (17.9)	1,007 (17.9)		4,376(71.1)	4,376(71.1)	
13–15y	4,126 (73.1)	4,126 (73.1)		1,312(21.3)	1,312(21.3)	
16–18y	508 (9.0)	508 (9.0)		30(0.5)	30(0.5)	
Age in days (× 100), median(P25, P75)	51.2 (48.2, 54.2)	51.2 (48.6, 54.4)	0.00	44.5 (42.3, 46.9)	44.8 (42.7, 47.1)	<0.001
Urban–rural location			1.00			1.00
Urban	2,884 (51.1)	2,884 (51.1)		3,208 (52.2)	3,208 (52.2)	
Rural	2,757 (48.9)	2,757 (48.9)		2,943 (47.8)	2,943 (47.8)	
Regional SES within province			1.00			1.00
Upper	2,026 (35.9)	2,026 (35.9)		2,112 (34.3)	2,112 (34.3)	
Moderate	1,801 (31.9)	1,801 (31.9)		1,998(32.5)	1,998 (32.5)	
Low	1,814 (32.2)	1,814 (32.2)		2,041 (33.2)	2,041 (33.2)	
Weekend outdoor activity			0.16			<0.001
Not in top 3	1,562 (27.7)	1,510 (26.8)		1,610 (26.2)	1,832 (29.8)	
In top 3	4,079 (72.3)	4,131 (73.2)		4,541 (73.8)	4,319 (70.2)	
Weekend study activity			0.05			0.44
Not in top 3	698 (12.4)	709 (12.6)		445 (7.2)	468 (7.6)	
In top 3	4,943 (87.6)	4,932 (87.4)		5,706 (92.8)	5,683 (92.4)	
Physical activity time per day			0.14			0.31
<30 min	1,211 (21.5)	1,161 (20.6)		1,053 (17.1)	1,104 (17.9)	
30–60 min	2,910 (51.6)	2,870 (50.9)		3,340 (54.3)	3,262 (53.0)	
≥60 min	1,520 (26.9)	1,610 (28.5)		1,758 (28.6)	1,785 (29.0)	
Homework time per day			0.40			0.06
<1 h	1,767 (31.3)	1,714 (30.4)		2,719 (44.2)	2,749 (44.7)	
1–2 h	2,218 (39.3)	2,212 (39.2)		2,351 (38.2)	2,241 (36.4)	
≥2 h	1,656 (29.4)	1,715 (30.4)		1,081 (17.6)	1,161 (18.9)	
Self-report study pressure			0.14			0.3
Heavy or very heavy	1,996 (35.4)	2,073 (36.7)		1,045 (17.0)	1,001 (16.3)	
So-so or not heavy	3,645 (64.6)	3,568 (63.3)		5,106 (83.0)	5,150 (83.7)	
Near screen time per day			0.05			<0.001
0–0.5 h	2,597 (46.0)	2,504 (44.4)		3,711 (60.3)	3,343 (54.3)	
0.5–1 h	1,342 (23.8)	1,314 (23.3)		1,400 (22.8)	1,506 (24.5)	
≥1 h	1,702 (30.2)	1,823 (32.3)		1,040 (16.9)	1,302 (21.2)	
Sleep duration per day			0.07			<0.001
<7 h	1,694 (30.0)	1,807 (32.0)		786(12.8)	998(16.2)	
7–8 h	1,951 (34.6)	1,913 (33.9)		1,656 (26.9)	1,861 (30.3)	
≥8 h	1,996 (35.4)	1,921 (34.1)		3,709 (60.3)	3,292 (53.5)	

*CNSSCH, Chinese National Survey on Students' Constitute and Health. Near screen time refers to time spent using a computer, cellphone, tablet, playing video games or reading e-books. All p-values were obtained from chi-square tests except when testing the difference in age in days x 100 (in which a rank sum test was used). "in top 3" and "not in top 3" refers to whether the outdoor (or study) activity is a top 3 choice that the participant usually does on weekends. Because the samples displayed in this table were selected matched samples, rather than the original survey sample, it is inappropriate to use this table to compare the characteristics between boys and girls. To compare boys and girls, please refer to **Supplementary Table 3**.*

only explained 0.19–4.78% of the sex disparity in myopia, altogether equaling 11.14%. When fully adjusting for the seven behaviors (*basic model 2*), puberty explained 16.75% of the sex disparity in myopia (**Table 5**). Using adolescents aged 11–18 years in the 1995, 2000, 2005, and 2010 CNSSCH to repeat the mediation analyses provided consistent results: across years,

TABLE 3 | The association between menarche status and myopia in girls from the paired sample in the 2014 CNSSCH, stratified by behavioral factors.

	Sample size	No. with myopia	Prevalence ratio (95% CI)	*P* for difference*
Weekend outdoor activity				
Not in top 3	3,442	2,178	1.09 (1.04, 1.15)	Ref
In top 3	8,860	5,711	1.06 (1.03, 1.09)	0.267
Weekend study activity				
Not in top 3	913	514	1.03 (0.91, 1.16)	Ref
In top 3	11,389	7,375	1.07 (1.04, 1.10)	0.499
Physical activity time per day				
<30 min	2,157	1,379	1.09 (1.03, 1.17)	Ref
30–60 min	6,602	4,140	1.06 (1.02, 1.10)	0.754
≥60 min	3,543	2,370	1.07 (1.02, 1.11)	0.497
Homework time per day				
<1 h	5,468	3,334	1.08 (1.03, 1.13)	Ref
1–2 h	4,592	3,009	1.06 (1.01, 1.10)	0.498
≥2 h	2,242	1,546	1.07 (1.01, 1.13)	0.798
Self-reported study pressure				
Heavy or very heavy	2,046	1,272	1.08 (1.01, 1.15)	Ref
So-so or not heavy	10,256	6,617	1.07 (1.04, 1.10)	0.771
Near screen time per day				
0–0.5 h	7,054	4,592	1.06 (1.02, 1.09)	Ref
0.5–1 h	2,906	1,873	1.12 (1.06, 1.18)	0.089
≥1 h	2,342	1,424	1.05 (0.98, 1.13)	0.836
Sleep duration per day				
<7 h	1,784	1,147	1.11 (1.03, 1.19)	Ref
7–8 h	3,517	2,360	1.08 (1.03, 1.13)	0.538
≥8 h	7,001	4,382	1.05 (1.01, 1.08)	0.174
Overall (unadjusted model)	12,302	7,889	1.07 (1.04, 1.10)	—
Overall (adjusted model)	12,302	7,889	1.07 (1.04, 1.10)	—

CNSSCH, Chinese National Survey on Students' Constitute and Health. Near screen time refers to time spent using a computer, cellphone, tablet, playing video games or reading e-books. In stratified analyses by behavioral factors, an unadjusted model was used to estimate prevalence ratios and their 95% CI. The unadjusted model only controlled the cluster effect of school, while the adjusted model further controlled all behavioral factors in this table. "in top 3" and "not in top 3" refers to whether the outdoor (or study) activity is a top 3 choice that the participant usually does on weekends.

TABLE 4 | The association between myopia and spermarche status in boys from the paired sample in the 2014 CNSSCH, stratified by behavioral factors.

	Sample size	No. with myopia	Prevalence ratio (95% CI)	*P* for difference*
Weekend outdoor activity				
Not in top 3	3,072	2,021	1.00 (0.95, 1.05)	Ref
In top3	8,210	5,413	1.02 (0.99, 1.05)	0.496
Weekend study activity				
Not in top 3	1,407	780	1.06 (0.96, 1.16)	Ref
In top 3	9,875	6,654	1.03 (0.93, 1.13)	0.379
Physical activity time per day				
<30 min	2,372	1,539	1.04 (0.98, 1.11)	Ref
30–60 min	5,780	3,818	1.01 (0.97, 1.04)	0.221
≥60 min	3130	2,077	1.01 (0.97, 1.06)	0.256
Homework time per day				
<1 h	3,481	2,007	1.02 (0.97, 1.08)	Ref
1–2 h	4,430,	2,967	1.01 (0.98, 1.05)	0.789
≥2 h	3371	2,460	1.00 (0.97, 1.04)	0.560
Self-report study pressure				
Heavy or very heavy	4,069	2,653	1.02 (0.97, 1.07)	Ref
So-so or not heavy	7,213	4,781	1.02 (0.98, 1.05)	0.945
Near screen time per day				
0–0.5 h	5,101	3,493	1.05 (1.01, 1.09)	Ref
0.5–1 h	2,656	1,745	0.99 (0.94, 1.05)	0.119
≥1 h	3,525	2,196	0.99 (0.95, 1.04)	0.087
Sleep duration per day				
<7 h	3,501	2,407	1.03 (0.99, 1.08)	Ref
7–8 h	3,864	2,561	1.01 (0.96, 1.05)	0.652
≥8 h	3,917	2,466	1.00 (0.96, 1.05)	0.738
Overall (unadjusted model)	11,282	7,434	1.02 (0.99, 1.04)	—
Overall (adjusted model)	11,282	7,434	1.01 (0.99, 1.04)	—

*CNSSCH, Chinese National Survey on Students' Constitute and Health. Near screen time refers to time spent using a computer, cellphone, tablet, playing video games or reading e-books. In stratified analyses by behavioral factors, an unadjusted model was used to estimate the prevalence ratios and their 95% CI. The unadjusted model only controlled for the cluster effect of school, while the adjusted model further controlled all behavioral factors in this table. * estimated by adding an interaction term to the model. "in top 3" and "not in top 3" refers to whether the outdoor (or study) activity is a top 3 choice that the participant usually does on weekends.*

puberty explained 15.86–21.97% of the sex disparity in myopia after controlling for demographic and socioeconomic factors (**Supplementary Table 4**).

DISCUSSION

Menarche is a major milestone of female puberty (17), just as spermarche is for boys. We found that menarche was associated with a 7% higher risk of myopia among girls, but the association between spermarche and myopia in boys was smaller and non-significant. The sex disparity in myopia was consistent across 7–18-year-olds in all 5 surveyed years. Interestingly, the sex disparity in myopia was stronger and significant in post-menarche/spermarche adolescents, but smaller or non-significant in pre-menarche/spermarche adolescents. Over 16% of the sex disparity in myopia could be explained by girls' earlier puberty, compared to ∼11% explained by several other behavioral factors together.

The mechanism underlying the association between myopia and puberty is unclear. It is plausible that when the body grows rapidly during puberty, the axial length of the eyes also grows faster, so puberty could create a risk for myopia onset due to axial growth. The mechanisms that link puberty development and axial growth are unknown, but Lyu believes that increased estrogen after menarche could explain the association (12). Although two case–control studies found that serum estrogen was not higher in myopic girls compared with non-myopic girls, the two studies had several major flaws, including a small sample size and not controlling for critical confounders (e.g., age, outdoor time) (18, 19). Insulin-like growth factor-1 (IGF-1)

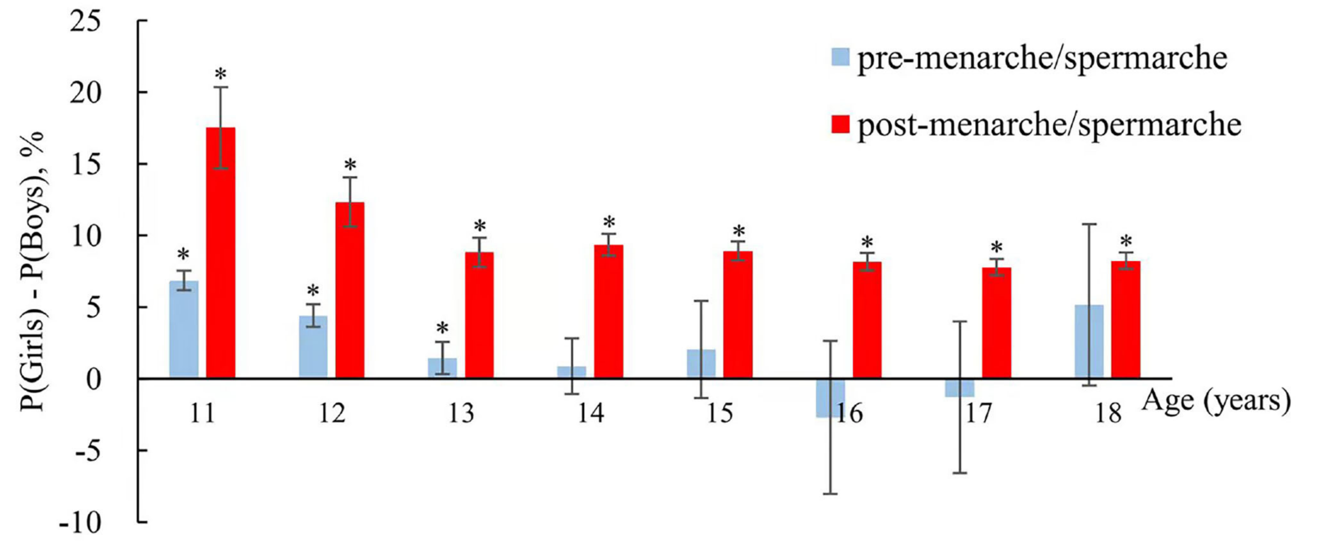

FIGURE 2 | Sex disparity of myopia prevalence among boys and girls aged 11–18 years in the 1995, 2000, 2005, 2010, and 2014 CNSSCH, stratified by age and menarche/spermarche status. P (Girls) and P (Boys) represent the prevalence of myopia in boys and girls, respectively. * represents the statistical significance of sex differences in myopia prevalence.

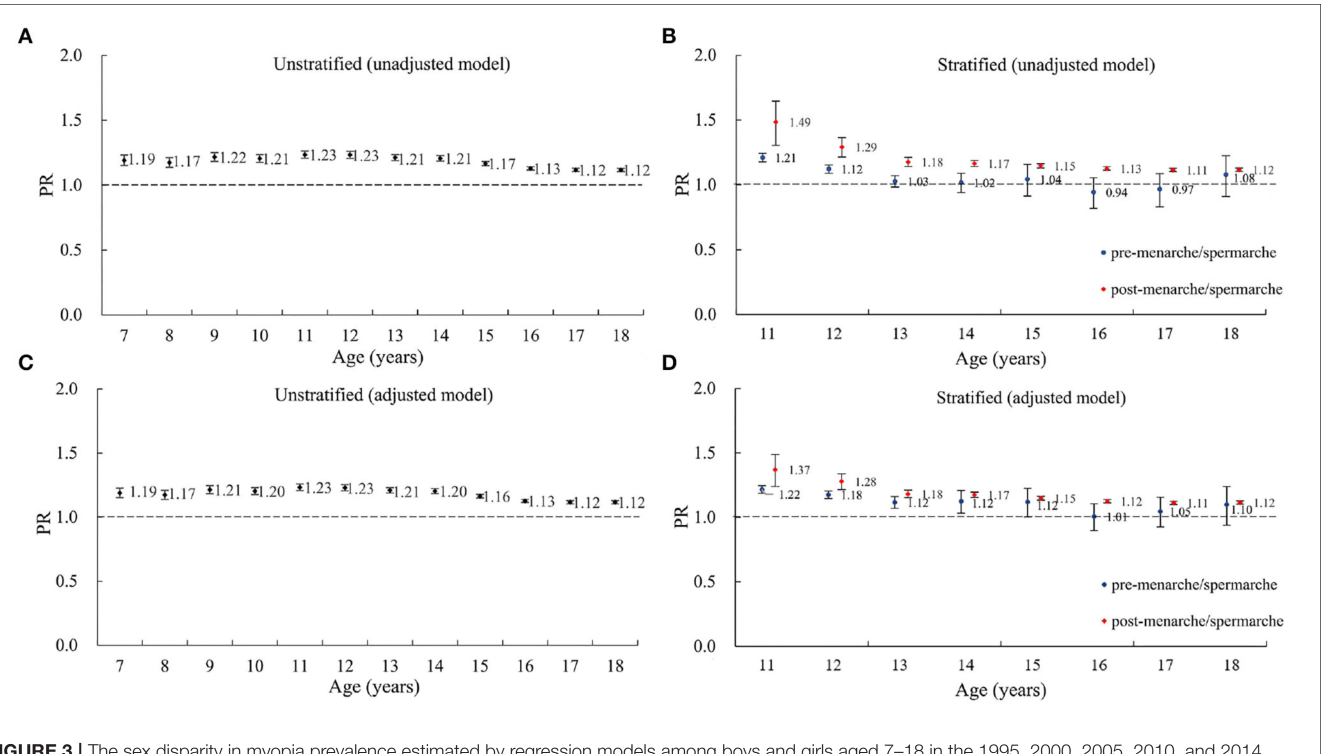

FIGURE 3 | The sex disparity in myopia prevalence estimated by regression models among boys and girls aged 7–18 in the 1995, 2000, 2005, 2010, and 2014 CNSSCH, stratified or unstratified by puberty status. **(A)** Unstratified (unadjusted model). **(B)** Stratified (unadjusted model). **(C)** Unstratified (adjusted model), **(D)** Stratified (adjusted model). PR, prevalence ratio, represents the relative risk of myopia for girls compared to boys. CNSSCH, Chinese National Survey on Students' Constitute and Health. The unadjusted model only adjusted for the cluster effect of school. The adjusted model additionally adjusted for survey year, urban–rural location, regional socioeconomic status (SES) within province, and provincial GDP per capita. The error bars represent 95% confidence intervals (CI).

is another, perhaps more convincing mediator. Serum IGF-1 level grows rapidly after menarche/spermarche (20, 21), and it could accelerate axial elongation in eyes (22) according to experimental studies in chicks (23, 24) and genetic studies (25). More human-based evidence is needed to test whether IGF-1 is an underlying mechanism driving axial growth during puberty.

TABLE 5 | The proportion of sex disparity in myopia explained by puberty and behavioral factors, in boys and girls 11 to 18 years of age in the 2014 CNSSCH. sample size = 125,466).

	Sex (girls vs. boys)			PERM
	β	PR (95%CI)	P	
Unadjusted model	0.11	1.118 (1.105, 1.132)	<0.001	NA
Basic model 1	0.12	1.122 (1.110, 1.135)	<0.001	NA
Additionally adjusted models Puberty	0.10	1.102 (1.090, 1.114)	<0.001	16.71%
Weekend outdoor activity	0.12	1.122 (1.109, 1.134)	<0.001	0.61%
Weekend study activity	0.11	1.116 (1.105, 1.129)	<0.001	4.78%
Physical activity time per day	0.11	1.121 (1.109, 1.134)	<0.001	0.94%
Homework time per day	0.11	1.117 (1.105, 1.129)	<0.001	4.30%
Self-report study pressure	0.12	1.122 (1.110, 1.135)	<0.001	0.19%
Near screen time per day	0.11	1.120 (1.108, 1.133)	<0.001	1.68%
Sleep duration per day	0.11	1.121 (1.108, 1.133)	<0.001	1.41%
All seven behavioral factors (Basic model 2)	0.10	1.109 (1.097, 1.120)	<0.001	11.14%
Basic model 2 + puberty	0.09	1.090 (1.079, 1.102)	<0.001	16.75%

PR, prevalence ratio. PERM, percentage of excess risk mediated. NA, not applicable. In the basic model, we adjusted for exact age, urban–rural location, regional SES within province, fixed effect of province, and the cluster effect of school.

The sex difference in the association between myopia and puberty may be explained by the differences in physiological and behavioral changes during puberty. Physiological changes could include hormone changes during puberty (e.g., androgen in boys vs. estrogen in girls), although the role played by hormones in myopia onset remains unknown (18, 19, 26). As for behavioral changes, menarche and spermarche, the milestones of sexual maturity (27), may make adolescents more concerned about appearance. In the perspective of Asian countries, white skin is a key component of attractiveness in girls. Thus, post-menarche girls may reduce outdoor activity to avoid being tanned and sweating from activities. This was supported by our finding that post-menarche girls were less active in weekend outdoor activities than pre-menarche girls, whereas no such difference was found between pre- and post-spermarche boys.

Sex disparity in myopia is a widespread phenomenon, especially in eastern Asia (2). Our results further support this conclusion. Traditional Chinese culture typically requires women to be quiet and men to be active (28), so previous studies have suggested that the sex disparity in myopia may be due to behavioral differences in outdoor activity and near work (activities requiring near focus). Also, the interest Chinese girls have in paler skin may make them avoid outdoor activities that are known to protect against myopia (29, 30). Girls generally study harder than boys and have longer homework time (29), predisposing them to myopia. However, the seven measured behaviors in our mediation analyses could each only explain 0.19–4.78% of the sex disparity in myopia (cumulatively explaining 11.14%). In contrast, puberty could explain more than 16% of the sex disparity. The mediation effect of puberty had two foundations. One was the association between myopia and puberty, as we discussed above. The other was the difference in puberty timing, where boys generally start puberty 1–2 years later than girls (5, 6). Compared to the behavioral factors described above, puberty is a better explanation of the sex disparity in adolescent myopia in other countries where the sex difference in those behaviors (e.g., outdoor activity, white skin preference, and homework time) may not exist or be reversed. Admittedly, puberty cannot explain the sex disparity in 7–9-year-olds, and there is still a large proportion of the sex disparity to be explained by other factors, such as opsin genetics. The human retina contains three types of cone photoreceptors, which are sensitive to long (L), middle (M), or short (S) wavelengths of light. Recent studies indicate that the L:M cone ratio, combined with L and/or M opsin exon 3 haplotypes at chromosome location Xq28, cause minor splicing defects that could increase myopia susceptibility. Because girls have two X-chromosomes, they are two times as likely to carry a cone opsin polymorphism, potentially making them more likely to develop myopia (31, 32).

This study has two public health implications. First, girls' earlier puberty contributes significantly to their higher prevalence of myopia than boys. This will put them at a higher risk of developing larger-grade myopia at an earlier age and therefore increase their risk of developing secondary ocular pathology (33–35). For these reasons, early interventions for preventing myopia onset might be more important in girls. Because our study did not analyze refraction and axial length data, it remains unclear whether earlier puberty could lead to a higher degree of myopia in girls. Until the evidence becomes clear, it is suggested to use early prevention and intervention methods against myopia irrespective of sex. The second public health implication is that menarche status seems to be an independent risk factor of myopia in girls. Thus, the early phases of puberty may be a sensitive period to control myopia in girls, and preventive strategies such as vision screening and increasing outdoor activity should be targeted to girls during this period.

The results of our study are consistent with findings from India (12) and South Korea (13), but our study uniquely minimizes recall bias because menarche statuses and covariates were gathered in participants' adolescence rather than in their adulthood. Although our findings differ from an analysis from Singapore (8), our study benefited from large, nationwide samples, minimizing selection bias and the risk of false-negative results due to low statistical power. Moreover, our study detected a small association between myopia and spermarche that was not observed in the previous studies.

Our study had several limitations that should be acknowledged. First, although our definition of myopia is not widely used, it is useful in the context of Chinese schools, where nearly 90% of vision impairment is due to uncorrected myopia. The increased statistical power of the large, uniformly-collected dataset justifies our use of unaided visual acuity as a surrogate for myopia (36). The convenience and accuracy of using unaided visual acuity assessment combined with simple subjective refraction has led the Chinese government to advocate its use for myopia screening in school children (37). Also, our validation trial has shown this method achieved high accuracy (refer to **Supplementary Material**) despite some misclassifications. The misclassifications tended to be non-differential (i.e., not related to sex and puberty) because the VA measurement followed a standard procedure independent of the participant's sex and puberty status. Additionally, the VA procedure had been used for over 30 years in CNSSCH and was implemented by well-trained examiners. If anything, non-differential misclassifications would likely attenuate the effects of puberty status and sex on myopia. Second, our study was not a cohort study, so the causal relationship between outcome and exposure cannot be established with certainty. While prospective studies could help to establish causality, it is unlikely that myopia causes early puberty. Third, CNSSCH questionnaires did not gather longitudinal information before or at puberty onset for each child, so important factors such as hormonal changes in puberty and social development were not considered. Plus, the questionnaires could not precisely measure behavioral factors such as near work, physical activity, and outdoor time, which could lead to residual confounding. For example, daily outdoor time was estimated by weekend outdoor activity frequency and daily physical activity time (given that most school gyms in China are outdoors). Despite this limitation and the lack of hormone biomarkers of sexual development, our findings provide a solid platform that can inform health and educational policies. Also, we did not measure actual refraction and axial length, and thus, our study can only provide implications on the impacts of puberty and sex on the prevalence of myopia, but not on the degree of myopia. The Chinese government is planning to include these measures in the future national monitoring system (37). Further, future iterations of the CNSSCH may be useful for assessing the regional and national impacts of evolving policies. Finally, while puberty and age are closely related and associated with the development of myopia, our matched sample analysis allowed us to precisely separate these two highly correlated factors.

Previous evidence suggests that physical activity might affect the timing of puberty onset in girls (33), potentially confounding menarche–myopia associations. Inaccurate physical activity measurements could also cause residual confounding. Fortunately, the overall confounding effect of the behaviors analyzed in this study was minimal. Additionally, although the timing of puberty onset in girls can also be affected by the age of parental puberty, body weight, high animal protein intake, and family stressors (38), these factors had a weak link with myopia (39) and are unlikely to confound or bias menarche–myopia associations.

In conclusion, puberty status among Chinese adolescents might be an independent risk factor for myopia in girls but not boys, suggesting early and mid-puberty may be a sensitive period for girls' myopia prevention. Earlier puberty in girls explained a significant proportion of the sex disparity in myopia prevalence, but detailing the public health implications of this finding requires further longitudinal studies with more accurate measures of myopia and puberty status.

DATA AVAILABILITY STATEMENT

All individual (de-identified) participant data collected in the surveys are accessible upon request. Researchers who are interested in using the data should contact Prof. Jun Ma (majunt@bjmu.edu.cn) and Prof. Yi Song (songyi@bjmu.edu.cn) with a study protocol and statistical analysis plan. There will be an assessment proposed by an independent review committee. Once approved by the committee, the researcher can access the data. An agreement on the use of the data may also needed.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Research Ethics Committee of Peking University Health Science Center (IRB00001052-18002) following the Declaration of Helsinki. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RX and YS conceived the study and its design. RX and PZ performed data analysis, and drafted the initial manuscript. RS, CJ, XX, DL, and YS modified the manuscript. RS, CJ, JM, and YS refined the data analysis plans and interpretation of the findings. JM, YS, YD, DL, and XX contributed to data collection. YS contributed to manuscript preparation and had full access to all aspects of the research and writing process as well as primary responsibility for the final content. All authors contributed to the article and approved the submitted version.

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and collection, analysis, data interpretation, or writing of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.833960/full#supplementary-material

REFERENCES

1. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet*. (2012) 379:1739–48. doi: 10.1016/S0140-6736(12)60272-4
2. Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol*. (2016) 100:882–90. doi: 10.1136/bjophthalmol-2015-307724
3. Fricke TR, Holden BA, Wilson DA, Schlenther G, Naidoo KS, Resnikoff S, et al. Global cost of correcting vision impairment from uncorrected refractive error. *Bull World Health Organ*. (2012) 90:728–38. doi: 10.2471/BLT.12.104034
4. Sun HP, Li A, Xu Y, Pan CW. Secular trends of reduced visual acuity from 1985 to 2010 and disease burden projection for 2020 and 2030 among primary and secondary school students in China. *JAMA Ophthalmol*. (2015) 133:262–8. doi: 10.1001/jamaophthalmol.2014.4899
5. Xu RB, Jan C, Song Y, Dong YH, Hu PJ, Ma J, et al. The association between menarche and myopia and its interaction with related risk behaviors among Chinese school-aged girls: a nationwide cross-sectional study. *J Dev Orig Hlth Dis*. (2020) 11:573–9. doi: 10.1017/S204017442000077X
6. Song Y, Ma J, Wang HJ, Wang Z, Lau PWC, Agardh A. Age at spermarche: 15-year trend and its association with body mass index in Chinese school-aged boys. *Pediatr Obes*. (2016) 11:369–74. doi: 10.1111/ijpo.12073
7. Song Y, Ma J, Wang HJ, Wang ZQ, Hu PJ, Zhang B, et al. Trends of age at menarche and association with body mass index in chinese school-aged girls, 1985-2010. *J Pediatr-Us*. (2014) 165:1172. doi: 10.1016/j.jpeds.2014.08.013
8. Kleinstein RN, Sinnott LT, Jones-Jordan LA, Sims J, Zadnik K, Longitudinal C. New cases of myopia in children. *Arch Ophthalmol-Chic*. (2012) 130:1274–9. doi: 10.1001/archophthalmol.2012.1449
9. Yip VCH, Pan CW, Lin XY, Lee YS, Gazzard G, Wong TY, et al. The Relationship between growth spurts and myopia in Singapore children. *Invest Ophth Vis Sci*. (2012) 53:7961–6. doi: 10.1167/iovs.12-10402
10. Huang CY, Hou CH, Lin KK, Lee JS, Yang ML. Relationship of lifestyle and body stature growth with the development of myopia and axial length elongation in Taiwanese elementary school children. *Indian J Ophthalmol*. (2014) 62:865–9. doi: 10.4103/0301-4738.141047
11. Northstone K, Guggenheim JA, Howe LD, Tilling K, Paternoster L, Kemp JP, et al. Body stature growth trajectories during childhood and the development of myopia. *Ophthalmology*. (2013) 120:1064. doi: 10.1016/j.ophtha.2012.11.004
12. Nirmalan PK, Katz J, Robin AL, Ramakrishnan R, Krishnadas R, Thulasiraj RD, et al. Female reproductive factors and eye disease in a rural south Indian population: the aravind comprehensive eye survey. *Invest Ophth Vis Sci*. (2004) 45:4273–6. doi: 10.1167/iovs.04-0285
13. Lyu IJ, Kim MH, Baek SY, Kim J, Park KA, Oh SY. The association between menarche and myopia: findings from the korean national health and nutrition examination, 2008-2012. *Invest Ophth Vis Sci*. (2015) 56:4712–8. doi: 10.1167/iovs.14-16262
14. Zhou S, Gao Y. A comparison between two-level and GEE based on robust poisson regression models in the estimation of relative risk or prevalence ratio. *Chin J Health Stat*. (2013) 30:683–6.
15. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol*. (2003) 3:21. doi: 10.1186/1471-2288-3-21
16. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England compared with Sweden: a birth cohort study. *Lancet*. (2018) 391:2008–18. doi: 10.1016/S0140-6736(18)30670-6
17. Gasser T, Molinari L, Largo R. A comparison of pubertal maturity and growth. *Ann Hum Biol*. (2013) 40:341–7. doi: 10.3109/03014460.2013.801510
18. Chen ZTY, Wang IJ, Liao YT, Shih YF, Lin LLK. Polymorphisms in steroidogenesis genes, sex steroid levels, and high myopia in the Taiwanese population. *Mol Vis*. (2011) 17:2297–310.
19. Xie H, Mao X, Yang H, Xie Z, Pan Y, Gao Y. [Analysis on the relationship between adolescent myopia and serum sex hormone]. *Zhonghua Yi Xue Za Zhi*. (2014) 94:1294–7. doi: 10.3760/cma.j.issn.0376-2491.2014.17.004
20. Ryan J, Mantle T, Costigan DC. A normal population study of human salivary insulin-like growth factor-I (Igf-1) concentrations from birth through puberty. *J Clin Endocr Metab*. (1992) 74:774–8. doi: 10.1210/jcem.74.4.1548339
21. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm Igf Res*. (2003) 13:113–70. doi: 10.1016/S1096-6374(03)00038-8
22. Galvis V, Lopez-Jaramillo P, Tello A, Castellanos-Castellanos YA, Camacho PA, Cohen DD, et al. Is myopia another clinical manifestation of insulin resistance? *Med Hypotheses*. (2016) 90:32–40. doi: 10.1016/j.mehy.2016.02.006
23. Penha AM, Schaeffel F, Feldkaemper M. Insulin, insulin-like growth factor-1, insulin receptor, and insulin-like growth factor-1 receptor expression in the chick eye and their regulation with imposed myopic or hyperopic defocus. *Mol Vis*. (2011) 17:1436–48.
24. Feldkaemper MP, Neacsu I, Schaeffel F. Insulin acts as a powerful stimulator of axial myopia in chicks. *Invest Ophth Vis Sci*. (2009) 50:13–23. doi: 10.1167/iovs.08-1702
25. Metlapally R, Ki CS Li YJ, Tran-Viet KN, Abbott D, Malecaze F, et al. Genetic association of insulin-like growth factor-1 polymorphisms with high-grade myopia in an international family cohort. *Invest Ophth Vis Sci*. (2010) 51:4476–9. doi: 10.1167/iovs.09-4912
26. Gong JF, Xie HL, Mao XJ, Zhu XB, Xie ZK, Yang HH, et al. Relevant factors of estrogen changes of myopia in adolescent females. *Chinese Med J-Peking*. (2015) 128:666–70. doi: 10.4103/0366-6999.151669
27. Christie D, Viner R. Adolescent development. *BMJ*. (2005) 330:301–4. doi: 10.1136/bmj.330.7486.301
28. Zhang YX, Zhou JY, Zhao JS, Chu ZH. The role of 1-h physical activity every day in preventing obesity in adolescents in Shandong, China. *Eur J Pediatr*. (2013) 172:325–30. doi: 10.1007/s00431-012-1882-6
29. Lu B, Congdon N, Liu XJ, Choi K, Lam DSC, Zhang MZ, et al. Associations between near work, outdoor activity, and myopia among adolescent students in rural China the xichang pediatric refractive error study report No. *2 Arch Ophthalmol-Chic*. (2009) 127:769–75. doi: 10.1001/archophthalmol.2009.105
30. Jang H, Koo FK, Ke L, Clemson L, Cant R, Fraser DR, et al. Culture and sun exposure in immigrant East Asian women living in Australia. *Women Health*. (2013) 53:504–18. doi: 10.1080/03630242.2013.806386
31. Gan J, Li SM, Atchison DA, Kang MT, Wei S, He X, et al. Association between color vision deficiency and myopia in Chinese children over a five-year period. *Invest Ophthalmol Vis Sci*. (2022) 63:2. doi: 10.1167/iovs.63.2.2
32. Hagen LA, Arnegard S, Kuchenbecker JA, Gilson SJ, Neitz M, Neitz J, et al. The association between L:M cone ratio, cone opsin genes and myopia susceptibility. *Vision Res*. (2019) 162:20–8. doi: 10.1016/j.visres.2019.06.006
33. Willis JR, Vitale S, Morse L, Parke DW 2nd, Rich WL, Lum F, et al. The prevalence of myopic choroidal neovascularization in the United States:

analysis of the IRIS((R)) data registry and NHANES. *Ophthalmology*. (2016) 123:1771–82. doi: 10.1016/j.ophtha.2016.04.021

34. Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol*. (2014) 157:9–25.e12. doi: 10.1016/j.ajo.2013.08.010
35. Asakuma T, Yasuda M, Ninomiya T, Noda Y, Arakawa S, Hashimoto S, et al. Prevalence and risk factors for myopic retinopathy in a Japanese population: the hisayama study. *Ophthalmology*. (2012) 119:1760–5. doi: 10.1016/j.ophtha.2012.02.034
36. Lin LLK, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singap*. (2004) 33:27–33.
37. National Health Commission of the People's Republic of China. *The Appropriate Technical Guidelines for Prevention and Control of Myopia in Children and Adolescents*. (2021). Available online at: http://www.nhc.gov.cn/jkj/s7934td/202110/0fc8a001d42345d9ac9b38842b295fe7.shtml (accessed february 13, 2022).
38. Yermachenko A, Dvornyk V. Nongenetic determinants of age at menarche: a systematic review. *Biomed Res Int*. (2014) 2014:371583. doi: 10.1155/2014/371583
39. Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol*. (2020): 20:27. doi: 10.1186/s12886-019-1220-0

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A Latent Class Analysis of Student Eye Care Behavior: Evidence From a Sample of 6–17 Years Old in China

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Purpose: To understand the latent classes and distribution of an adolescent eye care behavior, and to provide a basis for the formulation of appropriate adolescent vision health management interventions.

Methods: Information on eye behavior and eye health of primary and secondary school students in Wuhan was collected by multistage stratified cluster sampling. The latent class analysis (LCA) method was used to analyze the students' eye care behavior, and the latent class model (LCM) was built.

Results: A total of 6,130 students were enrolled in this study, of which 53.56% were males, aged from 6 to 17 years old, with an average age of 10.33 ± 2.60. The latent class results classified the adolescents' eye care behaviors into bad behaviors, moderate behaviors, and healthy behaviors. The model fitting results were as follows: Akaike Information Criterion (AIC) was 36,698.216, Bayesian Information Criterion (BIC) was 36,906.565, Adjusted Bayesian Information Criterion (aBIC) was 36,808.056, and entropy was 0.838.Compared with the healthy behaviors class, the bad behaviors class was more prevalent in high schools ($p = 0.003$), non-demonstration schools ($p = 0.001$), and most of this group had astigmatism ($p = 0.002$). The moderate behaviors class predominately consisted of females ($p = 0.001$), 15–17 years old ($p = 0.005$, 6∼8 years old as the reference), from non-demonstration schools ($p < 0.001$), and most had myopia ($p = 0.009$).

Conclusion: There were differences in basic demographic characteristics, visual acuity development level, and family visual environment among different classes. In the management and intervention of an adolescent vision health, we should continue to promote the visual health management of adolescents based on visual monitoring and realize the early intervention and guidance of individuals in bad behaviors class.

Keywords: adolescent, latent class analysis, visual health management, myopia, eye care

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INTRODUCTION

Visual health refers to normal visual physiology and visual psychology and good visual social adaptation on the premise of not suffering from eye diseases and abnormal symptoms such as visual fatigue. An analysis of studies suggests that by 2050, nearly half of the world's population may be myopic, with up to 10% being highly myopic (1).The World Health Organization (WHO) lists myopia as one of the 5 eye diseases requiring priority elimination and improvement (2). At the same time, there are racial and ethnic differences in the levels and prevalence of myopia, both of which are higher in Asia than in other parts of the world (3).At present, the prevalence of myopia among adolescents in China is characterized by a high prevalence (4, 5), fast growth rate (6, 7), and early age onset (8). China has the most teenage myopia patients in the world (9). Some researchers predict that if no intervention measures are taken, the myopia rate of Chinese adolescents will reach 61.8% in 2030 (10).

Comprehensive eye care (CEC) aims to ensure that people have access to the ophthalmic health services that meet the needs of each stage of their lives, which includes visual loss prevention, due to poor eye care habits and behavior (11, 12). Although a small percentage of myopia is inherited, much more is simply caused by poor eye care habits and behavior (13–16). A large number of studies have shown that near work, incorrect reading, and writing posture, and prolonged use of electronic devices can lead to visual fatigue, altered refractive state, and myopia (17–20). In terms of daily life, sleep deprivation is a risk factor for the development of myopia in teenagers (21). A diet high in sugar and cholesterol can also contribute to myopia (22, 23). There is a wealth of epidemiological evidence about the amount of time spent outdoors, indicating that adequate time spent outdoors is one of the most important factors in protecting visual health (24–26), which may be due to vitamin D and dopamine (27–29). Given the close relationship between behavior and visual health (30), it is necessary to effectively identify the accumulation of vision-related risks in adolescents by exploring and studying heterogeneous subsets of related behaviors.

Although most studies have shown that visual health development is significantly correlated with behavior, most of these studies have grouped adolescents according to gender, age, and other conditions for analysis, and it is impossible to judge whether subgroups can be defined only by significant variables. To explore the visual health and behavioral development of adolescents, Wuhan city has carried out visual health management and monitoring for primary and secondary school students. In this study, a latent class model was established to determine the class attributes of adolescents' eye health behaviors and analyze their distribution characteristics, providing a scientific basis for understanding the relationship between adolescents' eye care changes and visual health development.

METHODS

Study Population

Data were collected from the vision prevention and treatment project for adolescents in Wuhan, which was reviewed and approved by the Ethics Committee of the School of Public Health, Wuhan University. This study was conducted in 2019 and used a multistage stratified cluster sampling approach to recruit participants. According to the basic information released by the Wuhan Education Bureau in 2017, there are 735,799 students in Wuhan. The sample size of the sample survey is calculated as follows:

$$n \geq \frac{N}{\left(\frac{\alpha}{k}\right)^2 \frac{N-1}{P(P-1)} + 1} \tag{1}$$

N is the total sample number, and P is denoted as 0.50. If the sample population is large, the sampling size formula can be written as:

$$n \geq \left(\frac{k}{\alpha}\right)^2 P(1-P) \tag{2}$$

In general, α is denoted as 0.05 and K as 1.96. According to the statistical formula, it was estimated that 385 participants in each group were required. Considering grade differences, the sample size of this study is $n \geq 12$(grade)*385≈4,620, which means that the sample size needs to be >4,620 people.

Schools are divided by the Wuhan Education Bureau into vision health management demonstration schools and non-demonstration schools, and the classification standards are as follows: (1) Whether to carry out regular visual health management; (2) Whether to successfully apply for a municipal demonstration school; if both standards are met, the school will be regarded as a demonstration school of visual health. In consideration of geographical location (urban/rural region), whether it is a demonstration school or not, and the key age of myopia prevention and control, 140 schools in 14 districts (such as primary school, junior high school, and senior high school) were selected for this study, and a total of 6,130 students were enrolled.

This study adopted a self-made questionnaire as a survey tool, which development took reference from the Questionnaire of Vision Care Related Behavior for Students (AQVCRBS) (31). The results were filled in by students through the "Internet +" vision monitoring management application platform. The survey content included general demographic characteristics (sex, age, residence, education stage, school type);and eye care behaviors (near work, reading posture, time of electronics use, duration of sleep, eating habits, supplementation of vitamin A, outdoor exercise, eye exercises, non-sports training courses, eye muscle exercises). Each respondent completed a self-report questionnaire independently, and both the respondent and guardian signed informed consent forms.

Inclusion and Exclusion Criteria

The inclusion criteria for participants were as follows: (1) Students aged 6–17 years. (2) The legal guardian signed the informed consent. (3) Students without congenital eye diseases, such as congenital brain damage and visual impairment. (4)No neurological disorders, such as severe cognitive impairment.

The exclusion criteria for participants were as follows: (1) The legal guardian did not consent to participate in the vision test or related investigation. (2) Students with an incomplete investigation.

Examination Method

The results of vision monitoring will be reported by each school through the "Internet +" vision monitoring management platform and sent to the Wuhan Visual Prevention and Control Center. Visual acuity assessment uses the flat vision examination instrument, which has passed the approval and detection of relevant departments. Refractive inspection was performed according to the recommended desktop automatic computer optometry, and optometry equipment by the standard (ISO10342ophthalmic instrument-optometry) provisions. All physicians or investigators will be trained to independently perform standard ophthalmic examinations.

Diagnostic Criteria

In this study, the spherical equivalent (SE) was calculated as the dioptric powers of the sphere and half of the cylinder (sphere+0.5 cylinders). Myopia was defined as SE of <0.5 diopter (D) and visual acuity <5.0. Astigmatism is the diopter difference between 2 main diameters of the same eye (absolute diopter value of the column mirror) above 0.50D.

Data Analysis

In this study, each item of students' eye care behaviors in 2019 was parameterized by latent class analysis (LCA), and the latent class model (LCM) was constructed, which is a statistical analysis that addresses the relationship between types of latent variables. The optimal model is determined by the following criteria: Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted Bayesian information criterion (aBIC), Bootstrap likelihood ratio test (*BLRT*), and adjusted Lo-Mendell-Rubin likelihood ratio test (*aLMR*). After identifying the latent classes, the regression mixture modeling (RMM) was used to analyze the sociodemographic characteristics and visual health levels of different behavioral groups. SPSS 25.0 and Mplus 7.4 statistical software were used to analyze the data, and $p< 0.05$ was taken as the criterion of significance.

TABLE 1 | Distribution of basic demographic characteristics of participants.

Variables	Number	%
Sex		
Male	3,283	53.56
Female	2,847	46.44
Age(year)		
6–8	2,307	37.63
9–11	1,360	22.19
12–14	1,805	29.45
15–17	658	10.73
Education stage		
Primary school	3,464	56.51
Junior high school	1,859	30.33
High school	807	13.16
Type of school		
Demonstration school	3,667	59.82
Non-demonstration school	2,463	40.18
Urban/rural region		
Central urban area	3,396	55.40
Rural-urban area	2,734	44.60
Myopia		
Yes	3,067	50.03
No	3,063	49.96
Astigmatism		
Yes	3,173	51.76
No	2,957	48.24
Wear glasses		
Yes	1,465	23.90
No	4,665	76.10

RESULTS

Demographic Characteristics

A total of 7,840 primary and secondary school students were recruited for this study, among which 1.710 were excluded (21.81%) due to transfer to other schools, incomplete questionnaires, and other reasons. **Table 1** contains basic demographic characteristics. Among the participants, 6,130 were included in the final analysis, of which 3,283 (53.56%) were men and 2,847 (46.44%) were women. The sample population was 6–17 years old, with an average age of 10.33±2.60.Respondents aged 6–8 years accounted for the highest proportion (37.63%), and those aged 15–17 years accounted for the lowest proportion (10.73%). In terms of education, primary school students accounted for the highest proportion (56.51%), and the proportion of high school students was the lowest at 13.16%. The number of myopic students in the sample population was 3,067, accounting for 50.03%. The prevalence of myopia increased as age increased (**Figure 1**). There were statistically significant differences in the prevalence rate of myopia among students with different behaviors (**Table 2**).

Latent Class Analysis of Eye Care Behavior

Table 3 shows that the information criteria indices AIC, BIC, and aBIC decreased with the increase in the number of latent classes,

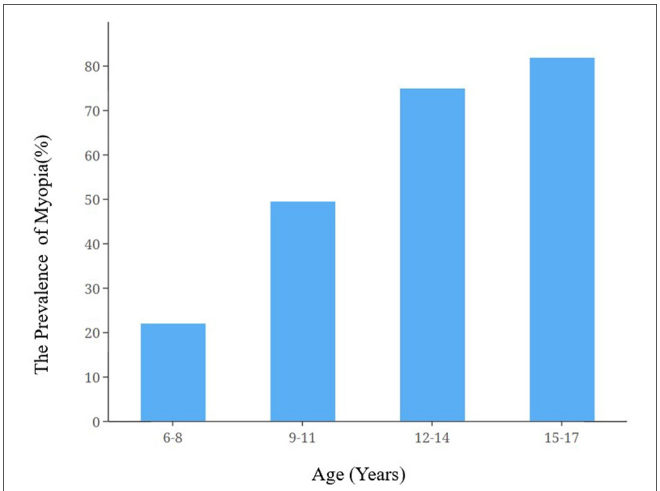

FIGURE 1 | Bar chart of the prevalence of myopia among adolescents of different ages.

and reached the maximum value in model 5. From the likelihood ratio test statistics, the entropy value reached 0.838 in model 3, indicating that the model was the most accurate for sample classification when there were 3 latent classes. Based on the model fitting evaluation results and conditional probability distribution of the latent class, the latent class of adolescent visual behavior was finally divided into 3 classes: class 1, class 2, and class 3.

Table 4 and **Figure 2** show the conditional probability of the latent class of adolescent eye care behavior. In class 1, the item probability of frequent use of the eyes for more than 40 min (78.2%) was the highest, and the item probability of holding a pen, reading, and writing correctly (1.2%) was the lowest. In class

TABLE 2 | Distribution of myopia rate in different eye hygiene behaviors (N = 6,130).

Variables	Number	%	χ^2	*p* value
Q1 Constant close eye contact for more than 40 min				
Yes	2,030	53.86	57.35	<0.001
No	1,037	43.92		
Q2 Hold a pen, read and write correctly				
Yes	1,255	40.34	237.34	<0.001
No	1,812	60.02		
Q3 Regularly use electronic devices for more than 30 min				
Yes	1,715	65.56	439.99	<0.001
No	1,352	38.47		
Q4 Get enough sleep each day				
Yes	1,398	35.21	991.51	<0.001
No	1,669	77.30		
Q5 Poor eating habits				
Yes	1,834	65.92	514.52	<0.001
No	1,233	36.83		
Q6 Pay attention to supplement foods rich in vitamin A				
Yes	1,342	44.25	80.39	<0.001
No	1,725	55.70		
Q7 Outdoor exercise time up to 2 h a day				
Yes	1,158	38.13	341.11	<0.001
No	1,909	61.72		
Q8 Do eye exercises every day				
Yes	1,379	41.19	230.80	<0.001
No	1,688	60.68		
Q9 Attend non-sports training courses regularly				
Yes	1,657	55.29	64.80	<0.001
No	1,410	45.00		
Q10 Exercise or train eye muscles regularly				
Yes	912	42.24	80.92	<0.001
No	2,155	52.26		

TABLE 4 | The conditional probability of the latent class of adolescent eye care behavior.

Variables	Class 1	Class 2	Class 3
Q1. Frequent close eye contact for more than 40 min	0.782	0.639	0.705
Q2. Hold a pen, read and write correctly	0.012	0.587	0.735
Q3. Regularly use electronics for more than 30 min	0.513	0.358	0.158
Q4. Get enough sleep each day	0.436	0.671	0.732
Q5. Poor eating habits	0.629	0.298	0.122
Q6. Pay attention to supplement foods rich in vitamin A	0.101	0.236	0.697
Q7. Outdoor exercise time up to 2 h a day	0.300	0.896	0.938
Q8. Do eye exercises every day	0.515	0.549	0.930
Q9. Attend non-sports training courses regularly	0.696	0.399	0.599
Q10. Exercise or train eye muscles regularly	0.271	0.354	0.892

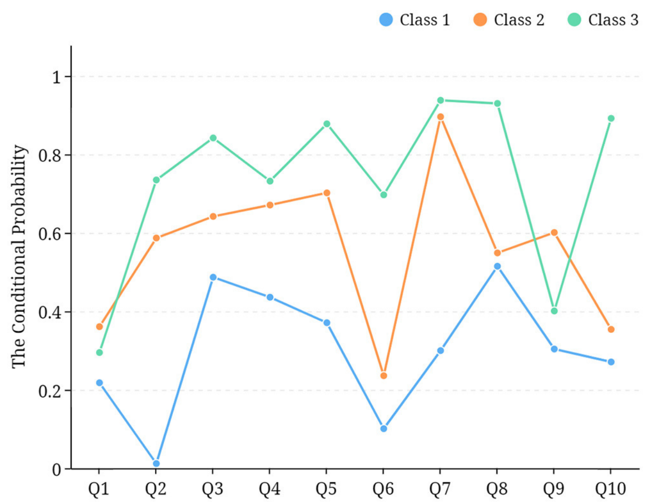

FIGURE 2 | Line chart of latent classes of adolescent eye care behavior. *Q1: Frequent close eye contact for more than 40 min; Q2: Hold a pen, read, and write correctly; Q3: Regularly use electronic devices for more than 30 min; Q4: Get enough sleep each day; Q5: Poor eating habits; Q6: Pay attention to supplement foods rich in vitamin A; Q7: Outdoor exercise time up to 2 h a day; Q8: Do eye exercises every day; Q9: Attend non-sports training courses regularly; Q10: Exercise or train eye muscles regularly. Q1, Q3, Q5 and Q9 were reverse scored.

TABLE 3 | Results of Latent Class Model (LCM) fitting information.

Model	AIC	BIC	aBIC	*Entropy*	*BLRT* *p* value	*aLMRp* value
1	37,630.335	37,677.381	37,655.137	1.000	-	-
2	36,827.359	36,981.941	36,908.854	0.761	<0.001	<0.001
3	36,698.216	36,906.565	36,808.056	0.838	<0.001	<0.001
4	36,609.493	36,871.610	36,747.679	0.764	0.001	0.014
5	36,525.758	36,841.642	36,692.289	0.735	0.002	0.036

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, Adjusted Bayesian Information Criterion; BLRT, Bootstrap Likelihood Ratio Test; aLMR, Adjusted Lo-Mendell-Rubin Likelihood Ratio Test.

3, the item probability of regularly using electronic devices for more than 30 min (15.8%) was the lowest, but outdoor exercise time reached up to 2 h a day (93.8%), and eye exercises were performed every day (93.0%). Compared with the other 2 classes, the conditional probability of class 2 tends to be in the middle. Therefore, class 1 was named the "bad behaviors class," class 2 was the "moderate behaviors class," and class 3 was the "healthy behaviors class."

Results of Univariate Analysis

Table 5 shows the influence of basic demographic characteristics and visual development on the distribution of latent classes of adolescent eye care behaviors.

Of the sociodemographic characteristics, the distribution of gender ($p = 0.016$), age ($p < 0.001$), education stage ($p < 0.001$), type of school ($p < 0.001$), and urban/rural region ($p = 0.030$) differed among the classes of students. In addition, the distributions of myopia ($p = 0.009$) and wearing glasses ($p < 0.001$) were also significantly different among the 3 classes of students.

Results of the Regression Mixed Model

The results of multicollinearity diagnosis showed that the tolerance between the respective variables was >0.1, and the variance inflation factor (VIF) was <10 (**Table 6**).The results of the parallel line test showed that $X^2 = 210.070$, $p < 0.05$. These results showed that polynomial logistic regression can be used.

In the bad behaviors class (reference: health behavior class), in terms of visual acuity development status, those with astigmatism was 1.26 ($p = 0.002$) times more likely to be found in the bad behaviors class than in the healthy behaviors class, and those with glasses were 1.90 times more likely to be found in the bad behaviors class than the healthy behaviors class ($p < 0.001$). In addition, the probability of

TABLE 6 | Multicollinearity diagnosis of influencing factors of adolescent eye care behavior.

Variables	Collinearity statistics	
	Tolerance	VIF
Gender	0.10	1.01
Age	0.17	5.81
Education stage	0.15	6.55
Type of school	0.83	1.21
Urban/rural region	0.98	1.02
Myopia	0.74	1.36
Astigmatism	0.97	1.03
Wear glasses	0.72	1.39

TABLE 5 | Influence of latent class distribution on adolescent eye care behavior.

Variables	Bad behaviors class (%)	Moderate behaviors class (%)	Health behaviors class(%)	χ^2	*p*-value
Gender					
Male	603 (18.37)	257 (7.83)	2,423 (73.80)	8.25	0.016
Female	476 (16.72)	275 (9.66)	2,096 (73.62)		
Age (year)					
6–8	388 (16.82)	203 (8.80)	1,716 (74.38)	67.43	<0.001
9–11	229 (16.84)	92 (6.76)	1,039 (76.40)		
12–14	286 (16.01)	153 (8.48)	1,363 (75.51)		
15–17	173 (26.29)	84 (12.77)	401 (60.94)		
Education stage					
Primary school	561 (16.20)	289 (8.34)	2,614 (75.46)	54.40	<0.001
Junior high school	313 (16.84)	151 (8.12)	1,395 (75.04)		
High school	205 (25.40)	92 (11.40)	510 (63.20)		
Type of school					
Demonstration school	608 (16.58)	225 (6.14)	2,834 (77.28)	89.14	<0.001
Non-model school	471 (19.12)	307 (12.46)	1,685 (68.41)		
Urban/rural region					
Central urban area	559 (16.46)	294 (8.66)	2,543 (74.88)	7.04	0.030
Rural-urban area	520 (19.02)	238 (8.71)	1,976 (72.28)		
Myopia					
Yes	534 (17.41)	300 (9.78)	2,233 (72.81)	9.42	0.009
No	545 (17.79)	232 (7.57)	2,286 (74.63)		
Astigmatism					
Yes	582 (18.34)	261 (8.23)	2,330 (73.43)	3.68	0.159
No	497 (16.81)	271 (9.16)	2,189 (74.03)		
Wearing glasses					
Yes	379 (25.87)	137 (9.35)	949 (64.78)	96.65	<0.001
No	700 (15.01)	395 (8.47)	3,570 (76.25)		

TABLE 7 | Results of a regressive mixed analysis of adolescent eye care behavior.

Variables	Bad behaviors classes (Refer to the health behaviors class)		Moderate behaviors classes (Refer to the health behaviors class)	
	OR	***p value***	**OR**	***p value***
Gender (reference:Female)				
Male	1.11 (0.96, 1.28)	0.153	0.74 (0.61, 0.89)	0.001
Age (reference: 15–17 years)				
6–8 years	1.80 (0.98, 3.30)	0.059	0.19 (0.06, 0.61)	0.005
9–11years	1.44 (0.81, 2.56)	0.209	0.17 (0.05, 0.53)	0.002
12–14years	0.64 (0.41, 0.10)	0.050	0.35 (0.16, 0.75)	0.007
Education stage (reference: Senior high school)				
Primary school	0.41 (0.23, 0.74)	0.003	2.52 (0.78, 3.19)	0.124
Junior high school	0.89 (0.58, 1.38)	0.608	1.51 (0.70, 3.23)	0.294
Type of school (reference: Non- demonstration School)				
Demonstration School	0.79 (0.68, 0.91)	0.001	0.48 (0.38, 0.58)	<0.001
Urban/rural region (reference: Rural-urban area)				
Central urban area	1.04 (0.89, 1.21)	0.657	1.16 (0.94, 1.43)	0.166
Myopia (reference: No)				
Yes	0.89 (0.76, 1.06)	0.185	1. 83 (1.33, 2.54)	0.009
Astigmatism (reference: No)				
Yes	1.26 (1.09, 1.46)	0.002	0.87 (0.71, 1.06)	0.156
Wear glasses (reference: No)				
Yes	1.90 (1.57, 2.27)	<0.001	1.22 (0.93, 1.60)	0.157

the high school group being distributed in the bad behaviors class was 2.44 (1/0.41, $p = 0.003$) times that of the primary school group, and the probability of a non-demonstration school population in the bad behaviors class was 1.27 times higher than that in the healthy behaviors class (1/0.79, $p = 0.001$).

In the moderate behaviors class (reference: health behavior class), those with myopia were 1.83 times more likely to be found in the moderate behaviors class than in the non-myopic group ($p = 0.009$).In terms of gender, females were 1.35 times more likely to be in the moderate behaviors class than males (1/0.74, $p = 0.001$).Compared with those aged 6–8 years old, those aged 15–17 years old were 5.26 (1/0.19, $p = 0.005$) times more likely to be found in the moderate behaviors class than the healthy behaviors class. Regarding the type of school, people from non-demonstration schools were 2.08 (1/0.48, $p<0.001$) times more likely to be found in the moderate behaviors class than those from demonstration schools. These results are shown in **Table 7**.

DISCUSSION

First, there were 3 subgroups among adolescent eye care behaviors, such as the bad behaviors class, moderate behaviors class, and health behaviors class. Second, the results of regression mixed analysis showed that those from the lower grade group, the demonstration school, and those with good vision were more likely to be distributed in the healthy behavior group.

The latent classes of adolescent behavior vary according to the findings of different researchers. As a survey on adolescent health risks in China in 2020, the Health Risk Behavior Assessment Questionnaire (HRBAQ) was used to analyze the latent class of 22,628 middle school students in China, and found 4 latent classes, such as low-risk classes (64.0%), medium risk class 1 (4.5%), medium risk class 2 (28.8%), and high-risk class (2.7%) (32).Our results were similar. According to the results of the Australian student health behavior survey in 2019, 1,965 students in Australia were divided into 3 latent classes, namely unhealthy class (11.2%), moderate class (40.2%), and healthy class (48.6%), based on their diet, exercise, and sleep habits. This study explored the latent categories of adolescents from the perspective of eye care behavior, which enriches the existing literature on adolescent behavior (33).

In the 3 latent classes of adolescents in Wuhan, class 1 had the highest conditional probability in the items of "Frequent near work" and "Regularly use electronic devices." Multiple studies have reported that near work and prolonged use of electronic devices significantly increase the risk of myopia (34–36). Therefore, class 1 was named the bad behaviors class because of its weak visual health management ability and high probability of bad behavior. Class 3 was named the healthy behaviors class because it had a higher conditional probability of the positive items. However, the healthy behaviors class was slightly higher than the moderate behaviors class in terms of the measurement items of "Regularly participating in non-sports excellent training courses," which may indicate that on the one hand, adolescents in the healthy behaviors class attach more importance to the cultivation of healthy behavior and can consciously manage vision health. On the other hand, it also indicates that adolescents are still under great pressure from extracurricular tutoring. Although the adolescents in this class consciously carried out self-vision management, they still had some negative eye care behaviors due to academic pressure.

There were significant differences in basic demographic characteristics among the different classes. Compared with the healthy behaviors class, the bad behaviors class was more distributed in high school and non-demonstration schools, while the moderate behavior group was more distributed in female, 15–17 years old, and non-demonstration schools. These findings suggested that with the increase in age and academic pressure, adolescents in high school may have to reduce the time for outdoor exercise and sleep and increase the time for near work, resulting in the heterogeneity of eye care behavior. Moreover, the results also suggested that there were significant differences in visual acuity development between the classes, with the prevalence of myopia and the number of people wearing glasses being higher in the bad and moderate behaviors class than in the healthy behaviors class. This finding is consistent with previous research. In 2014, the survey results showed that the ametropia of students in Beijing was significantly related to lower level activities (37). In 2021, Dutch researchers surveyed 525 teenagers' smartphone use, which also showed that refractive errors were significantly correlated with behaviors (38). Orlansky's findings suggest that poor vision affects a wide range of areas, such as reading, writing, posture, and movement, which may increase the likelihood of bad behavior in adolescents with poor vision (39). By identifying the characteristics of different latent behavior classes, students can be guided in a targeted way to protect their visual health.

CONCLUSION

In summary, the results of the present study offer support for the notion that there is a diversity of eye care behaviors among adolescents. These subgroups also illustrate differential profiles in basic demographic characteristics and visual acuity development. In the future, a short and valid instrument may be developed accordingly to quickly screen and classify these subgroups. Eventually, we could expect an efficient and precise group intervention for students in different latent classes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was reviewed and approved by the Ethics Committee of the School of Public Health, Wuhan University. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ML and BZ are responsible for manuscript writing and WW is responsible for data analysis. XT reviewed the manuscript. All the authors made substantial contributions to the completion of this manuscript, final approval of the version to be published, and agreed to be accountable for all aspects of the work.

REFERENCES

1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global Prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. (2016) 123:1036–42. doi: 10.1016/j.ophtha.2016.01.006
2. Bourne RRA. Vision 2020: where are we? *Curr Opin Ophthalmol.* (2020) 31:81–4. doi: 10.1097/ICU.0000000000000647
3. Walline JJ, Lindsley KB, Vedula SS, Cotter SA, Mutti DO, Ng SM, et al. Interventions to slow the progression of myopia in children. *Cochrane Database Syst Rev.* (2020) 1:CD004916. doi: 10.1002/14651858.CD004916.pub4
4. Jin JX, Hua WJ, Jiang X, Wu XY, Yang J, et al. Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun Eye Care Study. *BMC Ophthalmol.* (2015) 15:73. doi: 10.1186/s12886-015-0052-9
5. Wang J, Ying GS, Fu X, Zhang R, Meng J, Gu F, et al. Prevalence of myopia and vision impairment in school students in Eastern China. *BMC ophthalmology*. (2020) 20:2. doi: 10.1186/s12886-019-1281-0
6. Xiong F, Mao T, Liao H, Hu X, Shang L, Yu L, et al. Orthokeratology and low-intensity laser therapy for slowing the progression of myopia in children. *BioMed Res Int*. (2021) 2021:8915867. doi: 10.1155/2021/8915867
7. Liang Y, Kee CS. Risk Factors for Myopia in 2 Hong Kong School Systems: a pilot study. *Asia-Pac J Ophthalmol.* (2022) 11:19–26. doi: 10.1097/APO.0000000000000486
8. Dong L, Kang YK, Li Y, Wei WB, Jonas JB. Prevalence and Time Trends of Myopia in Children and Adolescents in China: A Systemic Review and

Meta-Analysis. *Retina*. (2020) 40:399–411. doi: 10.1097/IAE.0000000000002590
9. Jan C, Li L, Keay L, Stafford RS, Congdon N, Morgan I. Prevention of myopia, China. *Bull World Health Organ.* (2020) 98:435–7. doi: 10.2471/BLT.19.240903
10. Chen J, He X, Wang J, Xie H, Du L, Yang J, et al. Forcasting the prevalence of myopia among students aged 6-18 years in China from 2021 to 2030. *Zhonghua yan ke za Zhi.* (2021) 57:261–7. doi: 10.3760/cma.j.cn112142-20201228-000851
11. Cicinelli MV, Marmamula S, Khanna RC. Comprehensive eye care-Issues, challenges, and way forward. *Indian J Ophthalmol.* (2019) 68:316–23. doi: 10.4103/ijo.IJO_17_19
12. Rao G, Athota SM, Rani PK, Khanna R, Rajshekar V. Integrated model of primary and secondary eye care for underserved rural areas: The L V Prasad Eye Institute experience. *Indian J Ophthalmol.* (2012) 60:396–400. doi: 10.4103/0301-4738.100533
13. Baird PN, Saw SM, Lanca C, Guggenheim JA, Smith III EL, Zhou X, et al. Myopia. *Nat Rev Dis Primers.* (2020) 6:1–20. doi: 10.1038/s41572-020-00231-4
14. Tedja MS, Haarman AE, Meester-Smoor MA, Kaprio J, Mackey DA, Guggenheim JA, et al. IMI–myopia genetics report. *Invest Ophthalmol Vis Sci.* (2019) 60:M89–M105. doi: 10.1167/iovs.18-25965
15. Cooper J, Tkatchenko AV. A review of current concepts of the etiology and treatment of myopia. *Eye Contact Lens.* (2018) 44:231. doi: 10.1097/ICL.0000000000000499
16. Fabian ID, Abdallah E, Abdullahi SU, Abdulqader RA, Boubacar SA, Ademola-Popoola DS, et al. Global retinoblastoma presentation and analysis by national income level. *JAMA Oncol.* (2020) 6:685–95. doi: 10.1001/jamaoncol.2019.6716
17. Williams R, Bakshi S, Ostrin EJ, Ostrin LA. Continuous objective assessment of near work. *Sci Rep.* (2019) 9:1–10. doi: 10.1038/s41598-019-43408-y
18. Bhandari KR, Ostrin LA. Validation of the Clouclip and utility in measuring viewing distance in adults. *Ophthalmic Physiol Opt.* (2020) 40:801–14. doi: 10.1111/opo.12735
19. Dirani M, Crowston JG, Wong TY. From reading books to increased smart device screen time. *Br J Ophthalmol.* (2019) 103:1–2. doi: 10.1136/bjophthalmol-2018-313295
20. Tsai TH, Liu YL, Ma IH, Su CC, Lin CW, Lin LLK, et al. Evolution of the prevalence of myopia among Taiwanese schoolchildren: a review of survey data from 1983 through 2017. *Ophthalmology.* (2021) 128:290–301. doi: 10.1016/j.ophtha.2020.07.017
21. Liu XN, Naduvilath TJ, Wang J, Xiong S, He X, Xu X, et al. Sleeping late is a risk factor for myopia development amongst school-aged children in China. *Sci Rep.* (2020) 10:1–11. doi: 10.1038/s41598-020-74348-7
22. Berticat C, Mamouni S, Ciais A, Villain M, Raymond M, Daien V. Probability of myopia in children with high refined carbohydrates consumption in France. *BMC Ophthalmol.* (2020) 20:1–8. doi: 10.1186/s12886-020-01602-x
23. Lim LS, Gazzard G, Low YL, Choo R, Tan DT, Tong L, et al. Dietary factors, myopia, and axial dimensions in children. *Ophthalmology*. (2010) 117:993–7.e4. doi: 10.1016/j.ophtha.2009.10.003
24. Jonas JB, Ang M, Cho P, Guggenheim JA, He MG, Jong M, et al. IMI prevention of myopia and its progression. *Invest Ophthalmol Vis Sci*. (2021) 62:6. doi: 10.1167/iovs.62.5.6
25. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta ophthalmol.* (2017) 95:551–66. doi: 10.1111/aos.13403
26. Lingham G, Lucas RM, Milne E, Hewitt AW, Hammond CJ, MacGregor S, et al. Time spent outdoors in childhood is associated with reduced risk of myopia as an adult. *Sci Rep.* (2021) 11:1–11. doi: 10.1038/s41598-021-85825-y
27. Smith EL, Hung L-F, Arumugam B, Huang J. Negative lens–induced myopia in infant monkeys: effects of high ambient lighting. *Invest Ophthalmol Vis Sci.* (2013) 54:2959–69. doi: 10.1167/iovs.13-11713
28. Zhang LM, Lu Y, Gong L. Pterygium is related to short axial length. *Cornea.* (2020) 39:140. doi: 10.1097/ICO.0000000000002200
29. Sun HP, Lin Y, Pan CW. Iris color and associated pathological ocular complications: a review of epidemiologic studies. *Int J Ophthalmol.* (2014) 7:872. doi: 10.3980/j.issn.2222-3959.2014.05.25
30. Leo SW. Current approaches to myopia control. *Curr Opin Ophthalmol.* (2017) 28:267–75. doi: 10.1097/ICU.0000000000000367
31. Gao GP, Tan H, Zhang XJ. Development of the Assessment Questionnaire of Vision Care Related Behavior for Students(AQVCRBS) and its evaluation on reliability and validity. *Chin J Scl Health.* (2013) 34:1456–9. doi: 10.16835/j.cnki.1000-9817.2013.11.007
32. Song B, Hu W, Hu W, Yang R, Li D, Guo C, et al. Physical disorders are associated with health risk behaviors in chinese adolescents: a latent class analysis. *Int J Environ Res Public Health.* (2020) 17:2139. doi: 10.3390/ijerph17062139
33. Straker L, Smith A, Hands B, Olds T, Abbott R. Screen-based media use clusters are related to other activity behaviours and health indicators in adolescents. *BMC Public Health.* (2013) 13:1–12. doi: 10.1186/1471-2458-13-1174
34. Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol.* (2020) 20:1–11. doi: 10.1186/s12886-019-1220-0
35. Lin Z, Vasudevan B, Mao GY, Ciuffreda KJ, Jhanji V, Li XX, et al. The influence of near work on myopic refractive change in urban students in Beijing: a three-year follow-up report. *Graefe Arch Clin Exp Ophthalmol.* (2016) 254:2247–55. doi: 10.1007/s00417-016-3440-9
36. Huang PC, Hsiao YC, Tsai CY, Tsai DC, Chen CW, Hsu CC, et al. Protective behaviours of near work and time outdoors in myopia prevalence and progression in myopic children: a 2-year prospective population study. *Br J Ophthalmol.* (2020) 104:956–61. doi: 10.1136/bjophthalmol-2019-314101
37. Lin Z, Vasudevan B, Jhanji V, Mao GY, Gao TY, Wang FH, et al. Near work, outdoor activity, and their association with refractive error. *Optom Vis Sci.* (2014) 91:376–82. doi: 10.1097/OPX.0000000000000219
38. Enthoven CA, Polling JR, Verzijden T, Tideman JWL, Al-Jaffar N, Jansen PW, et al. Smartphone use associated with refractive error in teenagers: the myopia app study. *Ophthalmology.* (2021) 128:1681–8. doi: 10.1016/j.ophtha.2021.06.016
39. Orlansky G, Wilmer J, Taub MB, Rutner D, Ciner E, Gryczynski J. Astigmatism and early academic readiness in preschool children. *Optom Vis Sci.* (2015) 92:279–85. doi: 10.1097/OPX.0000000000000485

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Prevalence of Myopia and Its Associated Factors Among Japanese Preschool Children

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Purpose: To investigate the prevalence of myopia and factors associated with spherical equivalent (SE), axial length (AL), and axial length to corneal radius of curvature (AL/CR) ratio among Japanese preschool children.

Study Design: Prospective observational study.

Methods: This cross-sectional study evaluated subjects aged 4–6 years from a preschool. Non-cycloplegic autorefraction was measured using the Spot Vision Screener, while AL and corneal radius (CR) were measured using the Myopia Master. Parental myopia and environmental factors were investigated using the myopia-related factor questionnaire. The worse eye with higher myopic SE was chosen for analysis, and multiple linear regression models was performed using AL, SE, and AL/CR ratio as dependent variables.

Results: A total of 457 out of 514 participants (239 males, 52.3%) aged 4–6 years (mean 4.77 ± 0.65 years) were included. The mean SE was 0.13 ± 0.63 D, AL was 22.35 ± 0.67 mm, CR was 7.76 ± 0.25 mm, and AL/CR ratio was 2.88 ± 0.72. The overall prevalence of myopia and high myopia were 2.9 and 0.2%, respectively. Multiple regression analysis showed that myopic SE was significantly associated with male sex ($\beta = -0.14$, $p = 0.02$) and parental myopia ($\beta = -0.15$, $p = 0.04$). Meanwhile, longer AL was significantly associated with older age ($\beta = 0.13$, $p = 0.02$), male sex ($\beta = 0.44$, $p < 0.001$), parental myopia ($\beta = 0.24$, $p = 0.01$), and screen time (including smartphones, tablets, and computers) (>1 h, $\beta = 0.14$, $p = 0.04$). A higher AL/CR was significantly associated with older age ($\beta = 0.02$, $p < 0.001$), male sex ($\beta = 0.03$, $p < 0.001$), ratio and parental myopia ($\beta = 0.03$, $p = 0.02$).

Conclusion: The prevalence of myopia and high myopia were 2.9 and 0.2%, respectively, among Japanese preschool children in 2021. Longer AL was associated with older age, male sex, parental myopia, and screen time in children aged 4–6 years. Children with a high risk of myopia can be identified early based on parental myopia information for early prevention.

Keywords: spherical equivalent, axial length, axial length to corneal radius of curvature ratio, myopia, parental myopia, screen time

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INTRODUCTION

Myopia has become a critical public health problem worldwide, with a marked increase in its prevalence in developed East Asian countries (1). In Japan, the prevalence of myopia has also increased, from 10% in 6-year-olds and 60% in 12-year-olds in 1999–63% in 6-year-olds and 95% in 12-year-olds in 2017 (2, 3). There have been changes in the rate of myopia not only in school-age children, but also preschool children. Similarly, myopia has increased from 2.3 to 6.3% among preschool children in Hong Kong over 10 years (4). Early onset of myopia has been reported to lead to more myopic refractive error or high myopia later in life (5). Risk factors for the development and progression of school myopia include near work, decreased outdoor time, parental myopia, and education; however, there are few reports of risk factors for preschool myopia. Chua et al. (6) reported that early-onset myopia in 572 preschool children was strongly associated with parental history of myopia [odds ratio (OR) = 4.8; 95% 95 confidence interval (CI): 1.4, 16.6] but not with other environmental factors (near time, outdoor time). An association between increased screen time and myopia has also been recently reported, but this remains controversial (7, 8).

Although a meta-analysis (7) concluded that there is no proven association between digital screen time and myopia, screen exposure in early life could influence preschool myopia. Yang et al. reported that compared to preschoolers without screen exposure, children with younger age at first contact with screens had a significantly higher risk of preschool myopia (9). In addition, the lockdown caused by COVID-19 altered children's life behaviors and increased the progression of myopia. In a report from China, screen time increased 3.14-fold while outdoor time decreased by 1.14-fold in the COVID era compared with the pre-COVID in grade stage 1 (grades 1–6) children, with a correspondingly marked increase in myopia progression over a 6-month period (10).

Amid these major changes in the living environment, it is important to identify children who are at high risk for early onset of myopia and to provide lifestyle guidance and myopia control therapy to slow the progression of myopia. Cycloplegic refraction testing is the gold standard to identify early onset myopia. However, it is difficult to perform due to its longer testing time required and side effects for screening. Given that ocular refractive error is interrelated with both Axial length (AL) and the refractive components of the eye (e.g., cornea and lens), the Axial length to corneal radius of curvature (AL/CR) ratio has been suggested as a proxy for refractive error in the absence of cycloplegic refraction (11). A previous study revealed that the correlation between Spherical equivalent (SE) and AL/CR ratio is stronger than that between AL or corneal radius (CR) alone, which suggests that AL/CR ratio can be a useful marker of the onset of myopia (12). Knowledge of modifiable risk factors associated with myopia may be useful in developing cost-effective strategies to prevent the progression of myopia in Japan. However, studies reporting the prevalence of myopia and its associated risk factors among preschool children in Japan are limited. Thus, this study aimed to investigate the prevalence of early onset myopia as well as the factors associated with longer AL, myopic SE, and longer AL/CR ratio among Japanese preschool children.

Abbreviations: AL, axial length; CR, corneal radius of curvature; AL/CR, axial length to corneal radius of curvature; OR, odds ratio; SE, spherical equivalent.

METHODS

Study Design and Subjects

This cross-sectional study evaluated subjects aged 4–6 years from a single preschool located in Kanagawa, Japan. Kanagawa Prefecture is located next to Tokyo and has the second largest population in Japan, 9 million. The kindergarten is located in the urban area of Kawasaki City, the second largest city in Kanagawa Prefecture. Data for all participants were collected from June 10th to June 28th, 2021. Children with chronic eye diseases, such as congenital cataracts, undergoing myopia control therapy, chronic medical disorders, and Down syndrome were excluded. The research protocol was approved by the Ethics Committee of Eiwakai (No. 2021-02) and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed written consent was obtained from all parents.

Eye Measurements

Refractive status was measured in a non-cycloplegic state for each child using the Spot Vision Screener (SVS) (Welch Allyn, Skaneateles Falls, NY). SVS is a device that measures refraction at 1 m and therefore shows agreement with cycloplegic retinoscope refraction (13, 14). Refractive data from SVS were used in this study because it reduces the effects of accommodations compared to stationary auto-refractometers. Habitual visual acuity was measured using an international standard visual acuity chart in a well-lit room during the day at a 5-m distance by two experienced senior optometrists. Children with prescription glasses had their visual acuity measured on their own glasses. AL and CR were measured using non-contact partial coherence interferometry (Oculus, Myopia Master, Germany).

Questionnaire on Environmental Factors and Parental Myopia

Parents completed a questionnaire about their children's demographic characteristics; ocular and medical history; and environmental factors, such as time spent on outdoor activities, near work, screen time, and sleeping. Near work activities included homework and pleasure reading. Screens included smartphones, computers, and tablets. Time spent outdoors was defined as the sum of outdoor leisure time and outdoor sports activities time. The average number of outdoor activities per day was calculated using the following formula: (hours spent on weekdays) x 5/7 ± (hours spent on weekends) x 2/7 (15). Parental myopia was defined as the use of glasses or contact lenses for distant viewing by biological parents. All questionnaires were entered twice to ensure their integrity and precision.

Variable Definition

SE was defined as the spherical power plus half negative cylinder power. Myopia was defined as an SE of −0.50 D or greater, and high myopia was defined as an SE of −6.00 D or greater. Because non-cycloplegic refraction led to overestimation of myopia prevalence, alternative methods have been reported to improve accuracy (16). Thorn et al. suggested that combining non-cycloplegic refraction with visual acuity makes the judgment of myopia more accurate than non-cycloplegic refraction alone (17). Additionally, the criteria for younger children aged 3–6 years should be determined carefully for each age group because the average visual acuity varies with age (16). Hence, following the previous method, myopia was defined as SE $\leq$ − 0.50 D + uncorrected visual acuity > 0.3 logMAR for children aged 3 years, > 0.2 logMAR for children aged 4–5 years, and > 0 logMAR for children aged 6 years (18). Analysis was performed on the worse eye only in view of the correlation in parental myopia, outdoor time and near work between right and left eyes (2, 18, 19). The worse eye with higher myopic SE was chosen for analysis. If both eyes had the same SE refractive error, the right eye was used in the analysis. The onset of myopia in mothers and fathers was defined by the criteria of the British Birth Cohort Study, with early onset defined as onset at <16 years of age and late onset defined as onset at 16 years of age or older (20).

Statistical Analysis

One-way analysis of variance was used to compare the mean values of continuous outcomes between the different categories of parental myopic status (none, one, and both). We examined the association of myopic risk factors with SE, AL, and AL/CR ratio using multiple linear regression analysis. Specifically, multiple linear regression models were constructed to evaluate how each myopic risk factor contributes to myopic SE, longer AL, and high AL/CR ratio. All statistical analyses were performed using a commercially available statistical software program (SPSS version 20.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

RESULT

A total of 457 out of 514 participants (participation rate = 88.9%; 239 males, 52.3%) aged 4–6 years (mean 4.77 ± 0.65 years) were included. The mean SE was 0.13 ± 0.63 D; AL, 22.35 ± 0.67 mm; CR, 7.76 ± 0.25 mm; and AL/CR ratio, 2.88 ± 0.72. The clinicodemographic characteristics of the subjects are shown in **Table 1**. The overall prevalence rates of myopia and high myopia were 2.9 and 0.2%, respectively. The prevalence rates of myopia in subjects aged 4, 5, and 6 years were 1.3% (2/152), 3.8% (9/237), and 3.6% (2/56), respectively. Compared with children without parental myopia, children in whom both parents had myopia had significantly greater myopic SE ($p < 0.05$) and longer AL ($p < 0.001$). Further, AL/CR ratio was higher in children with both myopia parents than in children with one myopia parent ($p < 0.05$) and without parental myopia ($p < 0.01$). Paternal myopia was associated with longer AL ($\beta = 0.23$; 95% CI: 0.09, 0.37; $p = 0.002$) and higher AL/CR ratio ($\beta = 0.02$; 95% CI: 0.002, 0.03; $p = 0.02$). Maternal myopia was associated with longer AL [$\beta = 0.15$; 95% CI: 0.02, 0.29; $p = 0.04$] and higher AL/CR ratio ($\beta = 0.02$; 95% CI: 0.006, 0.04; $p = 0.008$) (**Table 2**). Multiple regression analysis showed that myopic SE was significantly associated with male sex ($\beta = -0.14$; 95% CI: −0.25, −0.02; $p = 0.02$) and parental myopia ($\beta = -0.15$; 95% CI: −0.31, −0.01; $p = 0.04$) (**Table 3**). Longer AL was significantly associated with older age ($\beta = 0.13$; 95% CI: 0.02, 0.23; $p = 0.02$), male sex ($\beta = 0.44$, 95% CI: 0.31, 0.58; $p < 0.001$), parental myopia ($\beta = 0.24$; 95% CI: 0.05, 0.42; $p = 0.01$), and screen time >1 h, including smartphones, tablets, and computers ($\beta = 0.14$; 95% CI: 0.01, 0.28; $p = 0.04$) (**Table 4**). AL/CR ratio was significantly associated with age ($\beta = 0.02$; 95% CI: 0.01, 0.03; $p < 0.001$), male sex ($\beta = 0.03$; 95% CI: 0.01, 0.04; $p < 0.001$), and parental myopia ($\beta = 0.03$; 95% CI: 0.01, 0.05; $p = 0.02$) (**Table 5**).

TABLE 1 | Demographics and parental characteristics of Japanese preschool children.

Characteristics	Baseline *N* (%), Mean (SD)
Age (years)	4.77 ± 0.65
4	160 (35.0)
5	240 (52.5)
6	57 (12.5)
Sex	
Male	239 (52.3)
Female	218 (47.7)
Parental myopia	
None	74 (16.3)
One	192 (42.2)
Both	189 (41.5)
Paternal myopia	
No	172 (37.8)
Yes	283 (62.2)
Maternal myopia	
No	172 (37.8)
Yes	283 (62.2)
Outdoor time	
<1 h	57 (13.5)
1–2 h	222 (52.6)
2 h ≤	143 (33.9)
Near work[#]	
<1 h	397 (90.6)
1 h ≤	41 (9.4)
Screen time*	
<1 h	268 (61.4)
1 h ≤	167 (38.6)

*N, number; D, diopter; w, week; h, hours. [#]Including reading and studying. *Including smartphones, computers, and tablets.*

DISCUSSION

The prevalence of myopia and its associated risk factors among preschool children in Japan are unclear. In this study, myopia and high myopia were prevalent in 2.9 and 0.2% of children aged 4–6 years, respectively. Multivariate analysis revealed that a longer AL was significantly associated with older age, male sex, parental myopia, and screen time. Myopic SE was

TABLE 2 | Association of parental myopia with SE, AL and AL/CR ratio among Japanese preschool children.

	SE (Diopter)				AL (mm)				AL/CR ratio			
Characteristics	**N**	**Mean (SD)**	**β (95% CI)***	***P*-value**	**N**	**Mean (SD)**	**β (95% CI)***	***P*-value**	**N**	**Mean (SD)**	**β (95% CI)***	***P*-value**
No. of parents with myopia												
0	72	0.26 (1.14)	ref		60	22.14 (0.66)	ref		60	2.86 (0.08)	ref	
1	185	0.12 (0.48)	−0.14 (−0.34, −0.06)	0.12	143	22.32 (0.59)	0.18 (0.00, 0.37)	0.05	143	2.87 (0.07)	0.01 (−0.01, 0.03)	0.37
2	186	0.09 (0.63)	−0.08 (−0.18, 0.01)	0.05	152	22.47 (0.71)	0.17 (0.06, 0.27)	0.002	152	2.90 (0.06)	0.02 (0.01, 0.03)	0.003
Paternal myopia												
No	165	0.17 (0.81)	ref		130	22.21 (0.60)	ref		130	2.87 (0.08)	ref	
Yes	278	0.28 (0.50)	−0.06 (−0.18, 0.06)	0.33	225	22.44 (0.69)	0.23 (0.09, 0.37)	0.002	225	2.89 (0.07)	0.02 (0.002, 0.03)	0.02
Age of onset of paternal myopia (Y)												
≥16	85	0.06 (0.44)	ref		71	22.36 (0.69)	ref		71	2.89 (0.06)	ref	
<16	115	0.17 (0.48)	0.11 (−0.02, 0.24)	0.10	87	22.46 (0.69)	0.10 (−0.12, 0.32)	0.37	87	2.89 (0.07)	0.002 (−0.02, 0.02)	0.87
Maternal myopia												
No	164	0.20 (0.86)	ref		133	22.27 (0.66)	ref		132	2.87 (0.08)	ref	
Yes	279	0.09 (0.44)	−0.10 (−0.22, 0.02)	0.09	222	22.41 (0.67)	0.15 (0.02, 0.29)	0.04	222	2.89 (0.07)	0.02 (0.006, 0.04)	0.008
Age of onset of maternal myopia (Y)												
≥16	68	0.09 (0.50)	ref		56	22.31 (0.71)	ref		56	2.88 (0.08)	ref	
<16	208	0.09 (0.36)	−0.01 (0.11, 0.11)	0.99	163	22.38 (0.67)	0.07 (−0.14, 0.28)	0.52	163	2.89 (0.07)	0.01 (−0.01, 0.03)	0.51

N, number; Y, years; D, diopter; SE, spherical equivalent; SD, standard deviation; CI, confidence interval; AL, axial length; CR, corneal radius.
**Multivariate model includes adjustment for age, sex.*

TABLE 3 | Univariate and multivariate analyses of factors associated with SE among Japanese preschool children.

	SE (Diopter)				
Characteristics	**N**	**Unadjusted-β (95% CI)**	***P*-value**	**Adjusted-β (95% CI)**	***P*-value**
Age (years)	445	0.02 (−0.07, 0.11)	0.62	0.02(−0.07, 0.11)[a]	0.62
Sex					
Male	234	−0.14 (−0.25, −0.02)	0.02	−0.14 (−0.25, – 0.02)[a]	0.02
Female	211	ref		ref	
Parental myopia					
No	72	ref		ref	
Yes	371	−0.16 (−0.31, −0.01)	0.04	−0.15 (−0.31, −0.01)[a]	0.04
Near work					
<1 h	386	ref			
≥1 h	40	−0.01 (−0.21, 0.20)	0.96		
Outdoor time					
<1 h	55	ref			
1 h ≤ Outdoor time <2 h	213	0.08 (−0.10, 0.26)	0.36		
≥ 2 h	142	0.09 (−0.03, 0.21)	0.16		
Screen time*					
<1 h	263	ref			
≥1 h	161	0.08 (−0.05, 0.20)	0.24		

N, number; D, diopter; SE, spherical equivalent; SD, standard deviation; CI, confidence interval; AL, axial length.
[a]Multivariate model includes adjustment for age, sex, and parental myopia.
**Screen time including smartphone, computer, and tablet.*

TABLE 4 | Univariate and multivariate analyses of factors associated with AL among Japanese preschool children.

		AL (mm)			
Characteristics	***N***	**Unadjusted β (95% CI)**	***P*-value**	**Adjusted β (95% CI)**	***P*-value**
Age (years)	355	0.13 (0.02, 0.24)	0.02	0.13 (0.02, 0.23)[a]	0.02
Sex					
Male	184	0.44 (0.31, 0.57)	<0.001	0.44 (0.31, 0.58)[a]	<0.001
Female	171	ref		ref	
Parental myopia					
No	60	ref		ref	
Yes	295	0.26 (0.08, 0.44)	0.006	0.24 (0.05, 0.42)[a]	0.01
Near work					
<1 h	305	ref			
≥1 h	36	0.14 (−0.09, 0.37)	0.24		
Outdoor time					
<1 h	40	ref			
1 h ≤ Outdoor time < 2 h	170	0.02 (−0.21, 0.24)	0.89		
≥ 2 h	120	−0.03 (−0.27, 0.21)	0.80		
Screen time*					
< 1 h	206	ref		ref	
≥ 1 h	132	0.18 (0.03, 0.33)	0.02	0.14 (0.01, 0.28)[a]	0.04

N, number; D, diopter; SE, spherical equivalent; SD, standard deviation; CI, confidence interval; AL, axial length.
[a]Multivariate model includes for age, sex, parental myopia, screen time and outdoor time.
**Screen time including smartphone, computer, and tablet.*

TABLE 5 | Univariate and multivariate analysis of factors associated with AL/CR ratio among Japanese preschool children.

		AL/CR ratio			
Characteristics	***N***	**Unadjusted β (95% CI)**	***P*-value**	**Adjusted β (95% CI)**	***P*-value**
Age (years)	334	0.03 (0.01, 0.04)	<0.001	0.02 (0.01, 0.03)[a]	<0.001
Sex					
Male	183	0.03 (0.02, 0.05)	<0.001	0.03 (0.01, 0.04)[a]	<0.001
Female	171	ref		ref	
Parental myopia					
No	59	ref		ref	
Yes	295	0.02 (0.00, 0.04)	0.03	0.03 (0.01, 0.05)[a]	0.02
Near work					
<1 h	304	ref			
≥ 1 h	36	−0.01 (−0.03, 0.02)	0.80		
Outdoor time					
<1 h	39	ref			
1 h ≤ Outdoor time <2 h	170	−0.01 (−0.03, 0.02)	0.47		
≥2 h	120	0.00 (−0.03, 0.02)	0.74		
Screen time*					
<1 h	209	Reference			
≥1 h	129	0.01 (−0.01, 0.03)	0.09		

N, number; D, diopter; SE, spherical equivalent; SD, standard deviation; CI, confidence interval; AL, axial length.
[a]Multivariate model includes adjustment for age, sex, and parental myopia.
**Screen time includes for smartphone, computer, and tablet.*

significantly associated with male sex and parental myopia, and AL/CR ratio was significantly associated with age, male sex, and parental myopia.

Myopia is a disease influenced by environmental factors, and information on the prevalence of myopia is crucial for health policy planning. Our study revealed that, in the absence of cycloplegia, the overall prevalence of myopia was 2.9% among 4–6-year-old Japanese preschool children in urban areas. The prevalence of myopia differs between urban and rural areas, and these differences have been suggested to be possibly related to near-work time, education, outdoor activity level, and economic status. Although there are no reports for the preschool population in Japan, previous reports in China showed myopia was prevalent in 4.1, 1.6, 3.7, and 17.0% of 6-year-old children in Shandong, Guangzhou, Shenzhen, and Hong Kong, respectively (21–23). In comparison of prevalence rates among different studies, the differences in definition of refractive error and urbanity of the area and refractive error measurement techniques should be noted. Zhang et.al reported that the prevalence of myopia (SE ≤ -0.75D) with non-cycloplegic autorefraction was 3.5% in 3–6-year -old children in Hebei Province, China (24). Meanwhile, Li et al. reported that the prevalence of myopia (SE ≤ -1.00 D) with non-cycloplegic autorefraction was 5.9% in 4–6-year-old children in Shanghai (25). However, measurement of refractive error without cycloplegia could overestimate the prevalence of myopia in children.

In the current study, preschool children were examined using a binocular vision system in a non-mydriatic state. The SVS is widely used for refractive examinations in young children and is gradually gaining recognition in both clinical practice and research because of its rapidity, maneuverability, accuracy, and reproducibility (26–28). To reduce the effect of strong accommodation, myopia was additionally assessed by both non-cycloplegic autorefraction and visual acuity in our study. In the report by Wang et al., which assessed myopia in a similar manner, myopia was prevalent in 2.6% and 1.7% of children aged 4 and 5 years, respectively (18). Relatively close values were obtained in the current study. However, the prevalence of myopia at age 6 years was significantly higher at 8.6% in their report than in ours at 3.6%. They also concluded that the prevalence of myopia remained stable before the age of 6 years, but increased with age thereafter. The increase of myopia prevalence after age 6 can be understood by the fact that the bulk of emmetropization occurs in early childhood and is largely complete by age 6 (29). Another reason for this difference can be that their report included data for 6-year-olds in primary school, suggesting that environmental factors in different education systems may have an effect.

Our results revealed that the association of parental myopia, especially in both parents, with myopic SE, longer AL, and higher AL/CR ratio were independent of other environmental risk factors. These results support that children with parental myopia are at high risk of developing myopia. In addition, there was a dose-response relationship between AL and parental myopia. This is consistent with the results of pooled data from children in three population-based studies (19). Parental myopia is associated with a higher ratio of AL/CR ratio and greater myopic refractive error in a cohort study of cycloplegic refraction data from 9,793 children aged 6–72 months (19). Claire et al. revealed that parental myopia represents both a genetic and environmental risk factor. The predictive value for parental myopia (0.67) was as good as that of the genetic risk score (0.67) or environmental risk score (0.69) (30). Normally, genetic testing of young children is not feasible in a clinical setting or at the population level. Meanwhile, it is easy to confirm parental myopia and can be useful in detecting children at risk of myopia before it develops. In the current study, both paternal and maternal myopia were associated with longer AL, and higher AL/CR ratio. Previous studies have shown that parental myopia is associated with various environmental factors. It is possible that parents with higher education tend to provide an environment for children with more reading and studying.

Additionally, an association between myopic SE and other environmental factors, such as outdoor time and near work, was not observed in our study. This may be due to the recall bias of the questionnaires. Overall, as per the present study, genetic susceptibility probably plays a more important role in myopia than do other behavioral factors before school age.

The association between screen time and myopia remains controversial (7–9). A systematic review did not find a significant association between digital screen time and the prevalence of myopia. A recent meta-analysis revealed that smart device screen time alone (OR 1.26) or in combination with computer use (OR 1.77) was significantly associated with myopia in children and young adults (aged 3 months to 33 years). Huang et al. reported the possibility that impact of screen exposure during early childhood on preschool myopia could be diminished by outdoor time for children whose parents have myopia (31). We therefore adjusted for age, gender, parental myopia, and screen time as well as outdoor time in our multivariate analysis. Interestingly, our data showed that screen time was associated with a longer AL after adjusting for age, sex, parental myopia, and outdoor time. The underlying mechanism of the association between screen exposure and myopia has not yet been identified. Some researchers have described screen time as a substitute for near work. Very young children from birth to age 3 may be more sensitive to screen exposure, as very early childhood is an important period for visual development (9). Huang et.al. reported that exposure to fixed screen devices [adjusted odds ratio (AOR) = 2.66] and mobile screen devices (AOR = 2.66) during the early life years (1–3 years) was associated with preschool myopia (31). The World Health Organization recommends <1 h of screen time per day for preschoolers, but our results showed that 38.6% of children were exposed to more than 1 h of screen time. Our results were taken after COVID-19 became a pandemic and may have been affected by the COVID-19 lockdown. From February to the end of May 2020, Japan declared a state of emergency, ordering temporary school closing and voluntary curfews. Subsequently, a quasi-emergency state was declared each time there was a recurring outbreak, and people had to refrain from going out or moving around except when necessary. This has led to behavioral changes in children, such as a decrease in outdoor time and an increase in screen time (32). Our results show that increased screen time is associated with longer AL, which could be augmented by this COVID19-related situations. A report from China showed a 3.14-fold decrease in screen time and a 1.14-fold decrease in outdoor time and faster progression of myopia in elementary school children in the COVID-19 era compared with the pre-COVID-19 era (10). Our results suggest that screen exposure for more than 1 h may pose a risk for myopia in preschoolers.

In the present study, male sex was associated with myopic SE, longer AL, and higher AL/CR ratio among children aged 4–6 years, consistent with previous studies (24, 33). The AL and AL/CR ratio of boys were 0.43 mm and 0.03 higher than that of girls, respectively. These differences may be due to the harmony between eye growth and the body (34). Saw et al. analyzed the height and AL of 1,449 children aged 7–9 years and showed that taller children have a longer AL (35). Ye al. found that in Chinese schoolchildren, personal anthropometric measurements, such as height and weight, maintained an independent relationship with refraction (36). While the difference in height between males and females is considered small compared to school-age children, according to the Japanese Health Statistics Survey, males tend to be taller than females at age 5 (37). Further investigation including physical parameters are needed. Also, age was not associated with SE, but AL and AL/CR ratio in our study. These results may be due to underestimation of SE by non-cycloplegic refraction.

This study has some limitations. First, the possibility of observation and inclusion biases could not be rules out due to the retrospective study design and small sample size. In addition, the data were obtained from only one kindergarten in Kanagawa Prefecture, which is an urbanized and densely populated city. This might limit the generalizability of the findings to other populations in Japan. Second, refraction was determined by non-cycloplegic autorefraction, which may result in misclassification of refractive error with an overestimation of myopia. However, myopia was assessed by combining refractive correction and visual acuity to reduce this effect. Third, the data on environmental and genetic factors were provided by parents and collected with a self-administered questionnaire, which might introduce recall bias. However, the findings of this study are based on previous use of these questionnaires and are consistent with the findings of previous studies.

CONCLUSION

The prevalence of myopia and high myopia were 2.9 and 0.2%, respectively, among Japanese preschool children in 2021. Longer AL was associated with older age, male sex, parental myopia, and screen time in Japanese children aged 4–6 years. Parental myopia, especially in both parents, is associated with a greater risk of myopic SE, longer AL, and higher AL/CR ratio in preschool-aged children. Our study underlines the importance of obtaining an accurate family history of myopia to identify at-risk children before they develop myopia and to raise awareness on lifestyle-based myopia prevention from an early stage. These risk factors should be considered when developing screening and intervention guidelines for preschool children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author on reasonable request without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Eiwakai. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SM and KD: study concept and design. SM, KD, KU, AK, and AT: data collection. SM and MK: analysis and interpretation of data and statistical analysis. SM and YH: drafting of the manuscript. YH: critical revision of the manuscript for important intellectual content. All authors have reviewed the manuscript.

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REFERENCES

1. Matsumura S, Chen CY, Saw SM. *Global Epidemiology of Myopia*. Singapore: Springer (2020).
2. Yotsukura E, Torii H, Inokuchi M, Tokumura M, Uchino M, Nakamura K, et al. Current prevalence of myopia and association of myopia with environmental factors among schoolchildren in Japan. *JAMA Ophthalmol.* (2019) 137:1233. doi: 10.1001/jamaophthalmol.2019.3103
3. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. *Surv Ophthalmol.* (1999) 44(Suppl. 1):S109–15. doi: 10.1016/S0039-6257(99)00094-6
4. Fan DS, Lai C, Lau HH, Cheung EY, Lam DS. Change in vision disorders among Hong Kong preschoolers in 10 years. *Clin Experiment Ophthalmol.* (2011) 39:398–403. doi: 10.1111/j.1442-9071.2010.02470.x
5. Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt*. (2016) 36:388–94. doi: 10.1111/opo.12305
6. Chua SY, Ikram MK, Tan CS, Lee YS Ni Y, Shirong C, et al. Relative contribution of risk factors for early-onset myopia in young Asian children. *Invest Ophthalmol Vis Sci.* (2015) 56:8101–7. doi: 10.1167/iovs.15-16577
7. Lanca C, Saw SM. The association between digital screen time and myopia: a systematic review. *Ophthalmic Physiol Opt*. (2020) 40:216–29. doi: 10.1111/opo.12657
8. Foreman J, Salim AT, Praveen A, Fonseka D, Ting DSW, Guang He M, et al. Association between digital smart device use and myopia: a systematic review and meta-analysis. *Lancet Digital health.* (2021) 3:e806–18. doi: 10.1016/S2589-7500(21)00135-7

9. Yang GY, Huang LH, Schmid KL, Li CG, Chen JY, He GH, et al. Associations between screen exposure in early life and myopia amongst chinese preschoolers. *Int J Environ Res Public Health*. (2020) 17:1056. doi: 10.3390/ijerph17031056
10. Xu L, Ma Y, Yuan J, Zhang Y, Wang H, Zhang G, et al. COVID-19 Quarantine reveals that behavioral changes have an effect on myopia progression. *Ophthalmology.* (2021) 128:1652–4. doi: 10.1016/j.ophtha.2021.04.001
11. He X, Zou H, Lu L, Zhao R, Zhao H, Li Q, et al. Axial length/corneal radius ratio: association with refractive state and role on myopia detection combined with visual acuity in Chinese schoolchildren. *PLoS ONE.* (2015) 10:e0111766. doi: 10.1371/journal.pone.0111766
12. Foo VH, Verkicharla PK, Ikram MK, Chua SY, Cai S, Tan CS, et al. Axial length/corneal radius of curvature ratio and myopia in 3-year-old children. *Transl Vis Sci Technol.* (2016) 5:5. doi: 10.1167/tvst.5.1.5
13. Qian X, Li Y, Ding G, Li J, Lv H, Hua N, et al. Compared performance of spot and SW800 photoscreeners on Chinese children. *Br J Ophthalmol.* (2019) 103:517–22. doi: 10.1136/bjophthalmol-2018-311885
14. Mu Y, Bi H, Ekure E, Ding G, Wei N, Hua N, et al. Performance of spot photoscreener in detecting amblyopia risk factors in Chinese pre-school and school age children attending an eye clinic. *PLoS ONE.* (2016) 11:e0149561. doi: 10.1371/journal.pone.0149561
15. Tang SM, Kam KW, French AN Yu M, Chen LJ, Young AL, et al. Independent influence of parental myopia on childhood myopia in a dose-related manner in 2,055 trios: the Hong Kong children eye study. *Am J Ophthalmol.* (2020) 218:199–207. doi: 10.1016/j.ajo.2020.05.026
16. Wang J, Xie H, Morgan I, Chen J, Yao C, Zhu J, et al. How to conduct school myopia screening: comparison among myopia screening tests and determination of associated cutoffs. *Asia-Pacific J Ophthalmol.* (2022) 11:12–8. doi: 10.1097/APO.0000000000000487
17. Thorn F, Chen J, Li C, Jiang D, Chen W, Lin Y, et al. Refractive status and prevalence of myopia among Chinese primary school students. *Clin Exp Optom.* (2020) 103:177–83. doi: 10.1111/cxo.12980
18. Wang J, Liu J, Ma W, Zhang Q, Li R, He X, et al. Prevalence of myopia in 3-14-year-old Chinese children: a school-based cross-sectional study in Chengdu. *BMC Ophthalmol.* (2021) 21:318. doi: 10.1186/s12886-021-02071-6
19. Jiang X, Tarczy-Hornoch K, Cotter SA, Matsumura S, Mitchell P, Rose KA, et al. Association of parental myopia with higher risk of myopia among multiethnic children before school age. *JAMA Ophthalmol.* (2020) 138:501. doi: 10.1001/jamaophthalmol.2020.0412
20. Rahi JS, Cumberland PM, Peckham CS. Myopia over the lifecourse: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology.* (2011) 118:797–804. doi: 10.1016/j.ophtha.2010.09.025
21. Guo X, Fu M, Ding X, Morgan IG, Zeng Y, He M. Significant axial elongation with minimal change in refraction in 3- to 6-year-old chinese preschoolers: the shenzhen kindergarten eye study. *Ophthalmology.* (2017) 124:1826–38. doi: 10.1016/j.ophtha.2017.05.030
22. Fan DS, Rao SK, Cheung EY, Islam M, Chew S, Lam DS. Astigmatism in Chinese preschool children: prevalence, change, and effect on refractive development. *Br J Ophthalmol.* (2004) 88:938–41. doi: 10.1136/bjo.2003.030338
23. Lan W, Zhao F, Lin L, Li Z, Zeng J, Yang Z, et al. Refractive errors in 3-6 year-old Chinese children: a very low prevalence of myopia? *PLoS ONE.* (2013) 8:e78003. doi: 10.1371/journal.pone.0078003
24. Zhang Y, Su M, Liu H, Song Y, Liu J, Sun H, et al. Development of refractive parameters in 3- to 6-year-old children and its application in myopia prediction and intervention guidance. *Comput Math Methods Med.* (2021) 2021:3656831. doi: 10.1155/2021/3656831
25. Li T, Zhou X, Chen X, Qi H, Gao Q. Refractive error in chinese preschool children: the shanghai study. *Eye Contact Lens.* (2019) 45:182–7. doi: 10.1097/ICL.0000000000000555
26. Peterseim MMW, Trivedi RH, Feldman S, Husain M, Walker M, Wilson ME, et al. Evaluation of the spot vision screener in school-aged children. *J Pediatr Ophthalmol Strabismus.* (2020) 57:146–53. doi: 10.3928/01913913-20200331-02
27. Yakar K. Clinical performance of the spot vision photo screener before and after induction of cycloplegia in children. *J Ophthalmol.* (2019) 2019:5329121. doi: 10.1155/2019/5329121
28. Peterseim MM, Papa CE, Wilson ME, Davidson JD, Shtessel M, Husain M, et al. The effectiveness of the Spot Vision Screener in detecting amblyopia risk factors. *J AAPOS.* (2014) 18:539–42. doi: 10.1016/j.jaapos.2014.07.176
29. Flitcroft DI. Emmetropisation and the aetiology of refractive errors. *Eye.* (2014) 28:169–79. doi: 10.1038/eye.2013.276
30. Enthoven CA, Tideman JWL, Polling JR, Tedja MS, Raat H, Iglesias AI, et al. Interaction between lifestyle and genetic susceptibility in myopia: the generation R study. *Eur J Epidemiol.* (2019) 34:777–84. doi: 10.1007/s10654-019-00512-7
31. Huang L, Schmid KL, Yin XN, Zhang J, Wu J, Yang G, et al. Combination effect of outdoor activity and screen exposure on risk of preschool myopia: findings from longhua child cohort study. *Front. Public Health.* (2021) 9:607911. doi: 10.3389/fpubh.2021.607911
32. *Covid19 x Children Questionnaire 1st Survey Report Japan: National Center for Child Health and Development*. Available online at: https://www.ncchd.go.jp/center/activity/covid19_kodomo/report/ (accessed June 2, 2022).
33. Li T, Wan T, Yao X, Qi H, Chen X, She M, et al. Time trend of axial length and associated factors in 4- and 5-year-old children in Shanghai from 2013 to 2019. *Int. ophthalmol.* (2021) 41:835–43. doi: 10.1007/s10792-020-01637-5
34. Tao L, Wang C, Peng Y, Xu M, Wan M, Lou J, et al. Correlation between increase of axial length and height growth in chinese school-age children. *Front. Public Health.* (2021) 9:817882. doi: 10.3389/fpubh.2021.817882
35. Saw SM, Chua WH, Hong CY, Wu HM, Chia KS, Stone RA, et al. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* (2002) 43:1408–13.
36. Ye S, Liu S, Li W, Wang Q, Xi W, Zhang X. Associations between anthropometric indicators and both refraction and ocular biometrics in a cross-sectional study of Chinese schoolchildren. *BMJ Open.* (2019) 9:e027212. doi: 10.1136/bmjopen-2018-027212
37. *Growth reference 5-19 years [Homepage on the Internet]*. Japan: Ministry of Education, Culture, Sports, Science and Technology (MEXT). Available online at: https://www.mext.go.jp/b_menu/toukei/chousa05/hoken/kekka/k_detail/1411711_00004.htm (accessed June 2, 2022).

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REVIEW
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The Association Between Environmental and Social Factors and Myopia: A Review of Evidence From COVID-19 Pandemic

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Purpose: To review the association between children's behavioral changes during the restriction due to the pandemic of Coronavirus disease (COVID-19) and the development and progression of myopia.

Design: A literature review.

Method: We looked for relevant studies related to 1) children's behavioral changes from COVID-19 restriction and 2) children's myopia progression during COVID-19 restriction by using the following keywords. They were "Behavior," "Activity," "COVID-19," "Lockdown," "Restriction," and "Children" for the former; "Myopia," "COVID-19," "Lockdown," "Restriction" for the latter. Titles, abstracts and full texts from the retrieved studies were screened and all relevant data were summarized, analyzed, and discussed.

Results: Children were less active and more sedentary during COVID-19 restriction. According to five studies from China and six studies, each from Hong Kong, Spain, Israel, South Korea, Turkey and Taiwan included in our review, all countries without myopia preventive intervention supported the association between the lockdown and myopia progression by means of negative SER change ranging from 0.05–0.6 D, more negative SER change (compared post- to pre-lockdown) ranging from 0.71–0.98 D and more negative rate of SER changes (compared post- to pre-lockdown) ranging from 0.05–0.1 D/month. The reported factor that accelerated myopia is an increase in total near work, while increased outdoor activity is a protective factor against myopia progression.

Conclusion: The pandemic of COVID-19 provided an unwanted opportunity to assess the effect of the behavioral changes and myopia in the real world. There is sufficient evidence to support the association between an increase in near work from home confinement or a reduction of outdoor activities and worsening of myopia during the COVID-19 lockdown. The findings from this review of data from the real world may help better understanding of myopia development and progression, which may lead to adjustment of behaviors to prevent myopia and its progression in the future.

Keywords: myopia, COVID−19, lockdown, behavior, environment, social, association

INTRODUCTION

Myopia or nearsightedness is a refractive error of spherical equivalent refraction (SER) ≤ −0.5 D (diopter), commonly developed in young children to early adolescence (1). It is a significant public and economic visual health problem worldwide. Deterioration of myopia can lead to many ocular complications and irreversible blindness (2, 3) The prevalence of myopia and high myopia (SER ≤ −5.00 D) (1) tend to increase year by year. By 2050, 4,758 million people (49.8% of the world population) and 938 million people (9.8% of the world population) are expected to have myopia and high myopia respectively (1).

Considering the factors influencing myopia development, three tiers of factors have been proposed by Seet B et al. (4) First, proximal or genetic factors, this hypothesis is supported by the evidence of higher number of myopic children in myopic parents than non-myopic parents (5, 6) and lower variations of SER and axial length (AL) in monozygotic twin than dizygotic twin.(7, 8) Second, intermediate or behavioral and environmental factors, there are evidences supporting that outdoor activity was an effective protective factor to control myopia prevalence, incidence, and also the prevention of myopia progression by slowing down the change of SER and minimizing AL elongation (9–11). On the other hand, the duration of near work was found to be significant higher in prevalent and incident myopes, compared to those with emmetropes of the same age (12, 13). Time spent on reading and other near work in childhood was also related to myopic progression in adulthood (14) although some studies did not find an evidence to support that near work was in correlation with myopia (15, 16). Third, distal or societal factors, there was evidence showed that students who ranked in the top quartile on educational performance in high myopia prevalence countries (Shanghai-China, Hong Kong-China, Taiwan, Singapore, Japan and South Korea) had higher engagement in after-school tutorial classes or cram schools than those with similar educational performance in low myopia prevalence countries (Australia, Canada, Finland). This trend of competitive and stressful education with cram schools in the East Asian countries might contribute to the higher prevalence of myopia (3, 17). Moreover, proportion of myopia tends to rise from outer suburban to inner urban areas and confine spaced residences, such as apartments, were also significantly associated with myopia (18).

The pandemic of coronavirus disease (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which originated in December 2019 in Wuhan, China, has caused a huge impact on health care of the entire world population. To mitigate the widespread of the disease, governments worldwide implemented the lockdown policy, including home confinement and temporary closure of public recreational and academic spaces (19). Children were forced to adapt to this circumstance by working and studying via online platforms instead of going to regular schools and doing any outdoor activities.

It is therefore plausible that these forced behavioral changes to the children due to the pandemic may have an impact on their refractive states, such as worsening of existing myopia or causing more new cases of myopia, during the lockdown period. This period provides an unwanted but relevant opportunity to find evidence of changes of myopia due to behavioral changes in the real world. The objective of this study is to review the evidence of the changes of myopia in children during the lockdown period due to the pandemic of COVID-19 in the literature.

METHOD

We used electronic databases of PubMed, Medline and Google Scholar with the search terms or its combination of the following: "Behavior," "Activity," "COVID-19," "Lockdown," "Restriction," "Children" to find 1) the evidences of children's behavioral changes, and the search terms or its combination of the following: "Myopia," "COVID-19," "Lockdown," "Restriction" for 2) the evidences of changes of children's myopia condition during the COVID-19 lockdown. Associated references of these searched studies were included. Exclusion criteria for both topics were studies with irrelevant title or abstract and studies without their own original data.

For 1) the evidences of children's behavioral changes, we reviewed the abstracts of 1,924 studies. One thousand nine hundred and ten studies were excluded. The full articles of the remaining 14 studies were read. Studies were included if there were available full text in English and if they focused about general physical activities changes during the COVID-19 lockdown in general children or adolescents (not a specific group, for example medical students). Finally, nine studies were included in our review.

For 2) the evidences of changes of children's myopia condition during the COVID-19 lockdown, we reviewed the abstracts of 139 studies. We excluded the studies which measured myopia in subjective manner such as difficulty in seeing distant objects or eye strain. One hundred and twenty-three studies were excluded. The full article of the remaining 16 studies were read. Studies were included if there were available full text in English and if they reported an objective measurement of myopia prevalence and/or myopia incidence and/or myopia progression in general children or adolescents (not a specific group, for example medical students). Finally, eleven studies were included for review.

RESULTS

Children's behavioral changes during the COVID-19 lockdown (**Figure 1**).

We reviewed nine studies from ten countries (Canada, USA, Spain, Brazil, Slovenia, the Netherlands, the United Kingdom [UK], India, China and Israel). All cross-sectional and longitudinal questionnaire-based studies consistently reported similar results: there is a reduction in time spent outdoor, such as for sports and physical activities, and an increase in sedentary time and digital screen time including social media uses during the COVID-19 lockdown (Outdoor time: decrease in outdoor time ranging from 5.4–7.25 h/week (20–22) or 5-point Likert type scale of 2.12/5 (1 = a lot less, 5 = a lot more) (23) or

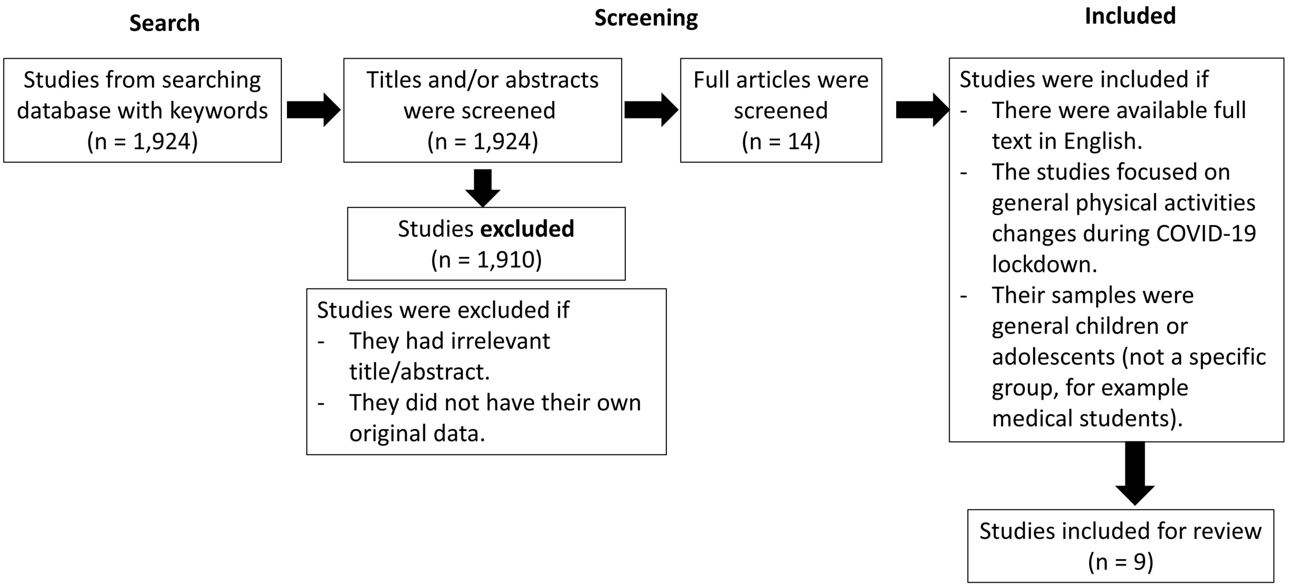

FIGURE 1 | Search and selection strategies of children's behavioral changes during the COVID-19 lockdown.

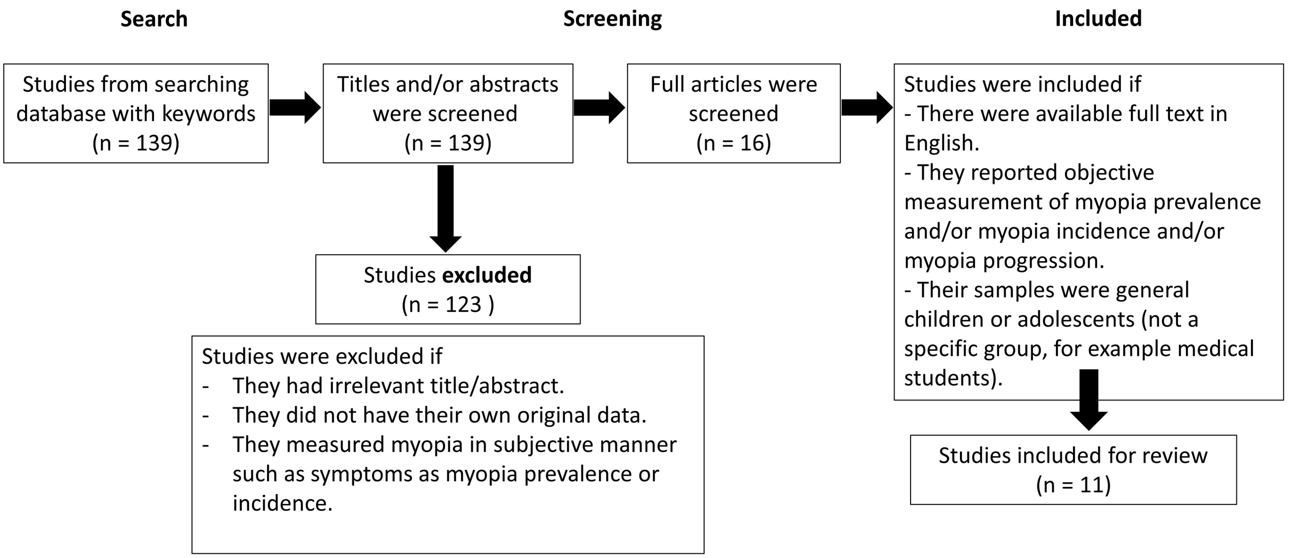

FIGURE 2 | Search and selection strategies of the changes in myopia during the COVID-19 lockdown.

19–47.5% of parents reported less physical activities of their children (24), Sedentary behavior: 28–47% of parents reported more sedentary behavior of their children (24), Screen time: increase in screen time ranging from 13.6–28.8 h/week (20, 22) or 5-point Likert type scale of 4.15/5 (1 = a lot less, 5 = a lot more)(23)). Two studies conducted in UK, Spain and Brazil also reported a significant decline in the number of children whose physical activities meet the World Health Organization (WHO) 24-h movement guidelines during the COVID-19 lockdown, compared to the period before the COVID-19 pandemic (decrease from 69.4% to 28.7% (25), from 3% to 0.3% and 11.7% to 7.5% in Spanish and Brazilian respectively (26)). In addition, researchers from Israel and the Netherlands also reported a reduction in physical and outdoor activities using an objective measuring method of accelerometry in pre and during COVID-19 lockdown (decrease physical activities from 1236 CPM to 1003 CPM, $p < 0.019$ (27), from 595 CPM to 429 CPM, $p = 0.001$(28) and decrease outdoor time from 1.8 h/day to 0.7 h/day, $p = 0.01$ (28)). These results were comparable with those results based on subjective questionnaire-based method described previously.The changes in myopia during the COVID-19 lockdown (**Figure 2**).

TABLE 1 | The selected studies without myopia preventive interventions, their characteristics and measurement outcomes.

				Measurement outcomes			
Setting	**Myopic status assessment**	**Study [country, participant (N)]**	**Study design**	**Prevalence (%) (Age, Pre vs. Post lockdown)**	**Incidence (%) (Age, Pre vs. Post lockdown)**	**SER (Diopter)**	**AL elongation (mm)**
School–based setting	Non–cycloplegic photorefraction	Wang J et al. (29) (China, 123,535)	Longitudinal cohort	6, 5.7 vs. 21.5 7, 16.2 vs. 26.2 8, 27.7 vs. 37.2 9–13, minimal change	NA	6, −0.32 7, −0.28 8, −0.29 9, −0.12 10, −0.11 11, −0.06 12, −0.05 13, −0.05*	NA
	Non–cycloplegic autorefraction	Chang P et al. (30) (China, 44,187)	Longitudinal cohort	NA, 53.2 vs. 73.7	NA	−0.030, −0.074, 0.016 ø	NA
	Cycloplegic autorefraction	Hu Y et al. (31) (China, 2,114)	Cross–sectional cohorts	Grade3, 13.3 vs. 20.8	Grade3, 7.5 vs.15.3	Grade3, −0.36* ($p < 0.01$)	Grade3, 0.08‡ ($p < 0.01$)
		Zhang X et al. (32) (Hong Kong, 1,793)	Cross–sectional cohorts	NA	Cannot compare †	6, −0.54 7, −0.53 8, −0.44 6–8, −0.5* ($p < 0.001$)	6, 0.3 7, 0.31 8, 0.26 6–8, 0.29‡ ($p < 0.001$)
Clinical–based setting	Non–cycloplegic autorefraction	Peregrina C et al. (33) (Spain, 1,600)	Longitudinal cohort	NA	NA	5, −0.21 ($p = 0.005$) 6, −0.05 ($p = 0.078$) 7, −0.26 ($p = 0.008$) 5–7, −0.18* ($p \leq 0.001$)	NA
	Cycloplegic autorefraction	Ma D et al. (34) (China, 291)	Cross–sectional cohorts	NA	NA	8–10, −0.60D** ($p < 0.001$)	8–10, 0.01‡ ($p = 0.37$)
		Ma M et al. (35) (China, 201)	Cross–sectional cohorts	NA	NA	7–12, −0.39 vs. −0.98¶ ($p < 0.001$)	NA
		Erdinest N et al. (36) (Israel, 14)	Longitudinal cohort	NA	NA	9–15, −0.33 vs.−0.74¶¶ ($p < 0.001$)	9–15, 0.29 vs. 0.47‡‡
		Yum H et al. (37) (South Korea, 103)	Longitudinal cohort	NA	NA	5–7, −0.066 vs. −0.103 ($p = 0.028$) 8–10, −0.044 vs. −0.064 ($p = 0.002$) 11–15, −0.038 vs. −0.049 $\phi\phi$ ($p = 0.065$)	5–7, 0.036 vs. 0.05 ($p = 0.022$) 8–10, 0.024 vs. 0.03 ($p = 0.005$) 11–15, 0.017 vs. 0.017‡‡‡ ($p = 0.792$)
		Aslan F et al. (38) (Turkey, 115)	Longitudinal cohort	NA	NA	8–17, −0.54 vs. −0.71 ¶¶ ($p = 0.003$)	NA

Longitudinal cohort means samples were the same group of children but different ages. Cross–sectional cohorts mean samples were in the different groups of children but the same age.
† Cannot compare because not equal follow–up time in each sub study (3 years in pre–covid cohort vs. 8 months in covid cohort).
** Age, mean diopter change from pre to post lockdown.*
*** Age, mean diopter change from pre to during lockdown.*
¶Age, mean diopter change pre vs. during lockdown.
¶¶Age, mean diopter change pre vs. post lockdown.
øRate of diopter change per month in pre, during, post– lockdown.
ø øAge, rate of diopter change per month in pre vs. post lockdown.
‡Age, mean AL change from pre to during lockdown.
‡‡Age, mean AL change in pre vs. post lockdown.
‡‡‡Age, mean AL change per month in pre vs. post lockdown.

TABLE 2 | The selected study with myopia preventive interventions, its characteristics and measurement outcomes.

				Measurement outcomes			
Study approach	**Myopic status assessment**	**Study [country, participant (*N*)]**	**Study design**	**Prevalence (%) (Age, Range between pre & post lockdown)**	**Incidence (%) (Age, Pre vs. Post lockdown)**	**SER (Diopter)**	**AL elongation (mm)**
Population–based approach	Cycloplegic autorefraction	Yang Y et al. (39) (Taiwan, 23,930)	Longitudinal cohort	5–6, 8.5% – 10.3%	NA	NA	NA

Longitudinal cohort means samples were the same group of children but different ages.

We included eleven studies (five studies from China and six studies, each from Hong Kong, Taiwan, South Korea, Israel, Turkey and Spain). The studies were conducted in either of the two settings: school-based setting or clinical-based setting. Cycloplegia was used in some studies to assess children's myopia status. The study from Taiwan is the only study conducted in the situation where myopia preventive intervention was implemented.

The characteristic and measurement outcomes of the selected studies without myopia preventive intervention are demonstrated in **Table 1** and the characteristic and measurement outcomes of the selected studies with myopia preventive intervention are demonstrated in **Table 2**.

We classified the selected studies into two types in this review. A total of seven studies were conducted in cohorts of the same group of children at different ages (Longitudinal cohort), the other four studies were conducted in cohorts of the different groups of children at the same age (Cross-sectional cohorts). All studies without myopia preventive intervention found at least one of the following outcomes: increased myopia prevalence (ranging from 7.5–20.5% with a trend of more rising of prevalence in younger age groups (29)), increased myopia incidence (from 7.5% to 15.3%), greater myopia progression (negative SER change ranging from 0.05–0.98 D (29, 31–36, 38) or negative rate of SER changes ranging from 0.05-0.1 D/month (30, 37)) during the COVID-19 lockdown. With preventive interventions, a study in Taiwan reported stable myopia prevalence throughout the COVID-19 lockdown (39).

A total of five studies monitored the changes in axial length (AL) during the COVID-19 lockdown. (31, 32, 34, 36, 37) Two of these studies reported an increase in AL during the lockdown (ranging from 0.08–0.31 mm) (31, 32). Another two studies found faster AL elongation during the lockdown (0.47 mm/year compared to 0.29 mm/year (36), the rate of AL increase ranging from 0.03–0.05 mm/month (37)). Whereas the only study from China (34) reported no difference of AL before and after that lockdown period (0.01 mm, $p = 0.37$).

Behavioral changes during the lockdown were evaluated by a questionnaire in seven studies. (32–35, 37–39) Increase in time spending on total near work, including reading, homework, online learning and digital screen time (2.4–4.63 h/day) (32, 34, 35, 37) and a reduction in total outdoor activities (0.1–0.86 h/day) (32, 34, 35, 37) were reported.

Among these studies, four studies reported the direct association of specific behavioral changes and worsening of myopia. Two studies from China (34, 35) found that an increase of digital screen time was associated with a greater SER change (odds ratio 2.658, 95% CI 1.587 to 4.450, $p < 0.005$(34) and 0.211, 95%CI 0.280 to 0.142, $p < 0.001$(35) respectively). Moreover, online education was also found to be associated with a greater SER change in Chinese children (odds ratio 3.717, 95% CI 1.587 to 8.665, $p = 0.02$) (34). Hongkong specified that increase in reading time was associated with myopic shift in term of a greater change of SER (odds ratio −0.04, 95% CI −0.07 to −0.01, $p = 0.02$) and an AL elongation (odds ratio 0.03, 95% CI 0.01 to 0.05, $p = 0.01$) (32). And 2-year exposure to myopia preventive intervention was found to be a protective factor against myopia progression among Taiwanese children (odds ratio, 0.56, 95% CI, 0.50 to 0.63, $p < 0.001$) (39).

DISCUSSION

We found indirect evidence showing the association between children's forced decrease in outdoor activities and increase in near work and worsening of myopia during the lockdown due to COVID-19. This finding is relevant in both settings we found in the literature. For the school-based settings, most studies were conducted in the high myopic prevalence countries where the eye examination and refraction are annually screened in each school. The advantages of the school-based approach are a large sample size and a completeness of the refractive data of the targeted population of children. On the contrary, for the clinical-based setting, most studies were conducted in the lower myopic prevalence region. The refractive data of the children in this setting are from those who regularly visit eye clinics in each year and may not represent the real-world population.

To obtain children's refractive status, both non-cycloplegic and cycloplegic refraction were used in the reviewed studies. Non-cycloplegic auto/photorefraction are easier and faster to conduct but their results are known to be exaggerated (40). This method is useful in the school-based screening where the cycloplegia may not properly be conducted. On the other hand, cycloplegic autorefraction, which requires more steps to instill a drop of cycloplegic medication into the children's eyes, is more reliable and commonly used in the clinical setting. Despite these different refractive methods, the study results on changes in myopia during the lockdown were similar.

For the studies on the cohorts of children in the same group at the different ages (Longitudinal cohort), the refractive data was collected in a group of samples at least three different time points: before the pandemic, at the beginning of the pandemic (before the lockdown) and after the pandemic (after the lockdown). This means that the refractive data of the same group of the children was analyzed and compared in a temporal relation. It is well documented that there is a progression of myopia among children in their natural history (per year). However, the progression of myopia reported in these studies were higher in terms of diopter changes and faster compared with the natural history.

For the studies on the cohorts of different groups of children at the same age (Cross-sectional cohorts), the refractive data between these two groups of the children, a group before the pandemic and another group during the pandemic, were compared. This study design eliminated the confounding effect of normal myopia progression with increasing age and might reflect the true effect of the social restriction on myopia progression. China is a country where there has been a high concern about the high prevalence of myopia. Half of the studies in this review were conducted in China, three of them were school-based (29–31) whereas the other two were clinical setting studies (34, 35). The detailed analysis in some of these studies indicated that specific types of near work might have an influence on myopic progression. Children who used mobile phones had the fastest myopia progression, followed by those who used tablets. Projectors and televisions might be better choices for online learning since both of them associated with significantly less myopic shift, compared to the other devices (35).

Apart from China, the school-based refraction screening was also conducted with related databases existing in Hong Kong and Taiwan. Taiwan (39) is the only country with myopia preventive intervention in this review. Interestingly, the study in Taiwan was the only study that showed no significant changes in myopic prevalence during the lockdown. It is possible that the reason behind this success was the Yilan Myopia Prevention and Vision Improvement Program (YMVIP), the initiative launched by the Taiwan government to promote children's outdoor activities. This policy was successfully implemented in 2014 and the prevalence of myopia continuously decreased in an L-shaped pattern since then. During the lockdown, Taiwanese were encouraged but not enforced to absolute stay at home, therefore, the promoting intervention may not be disrupted and children could continue to spend their time outdoors.

There were two clinical-based studies that observed that myopia could still progress during the lockdown even in children with myopia who were treated with atropine. This was from the review of medical records of 103 children in South Korean (37) and 14 children in Israel (36)). Even under the effect of atropine treatment, a greater SER progression (from 0.33D/year to 0.74 D/year, $p < 0.001$) and a greater AL elongation (from 0.21 mm/year to 0.47 mm/year, $p < 0.001$) between pre- and post-COVID-19 were found significantly in all Israeli children in the study. The faster rate of SER progression (from 0.047 D/month to 0.067 D/month, $p < 0.001$) and AL elongation (from 0.024 mm/month to 0.030 mm/month, $p = 0.001$) between pre- and post-COVID-19 were also found in South Korean children aged 5 to 7 and 8 to 10 years who were still under the treatment with atropine, but no statistically significant changes were observed in older children aged 11 to 15 years.

The age effect was also observed in some studies (29) in which a greater shift of myopic was observed in children aged 6–8 years than those who were older than 8 years old.

The worsening of myopia found during the COVID-19 lockdown suggested that even temporary increase in near work or decrease in outdoor activities for about 3 months can induce this condition. There are two main theories that may be used for the explanation. First, a defocusing theory (41). Defocusing means blurring of perceived images due to an accommodative lag. In response to the blurred vision, there is a release of chemicals causing AL elongation as a compensation for defocusing. This structural change of eye balls can be permanent. The second theory is about accommodative spasm or near work induced transient myopia (NITM). NITM is caused by the remaining accommodative effect after an abrupt change from a long duration of near work to distant vision. Hence, it can be reversed after a period of time (42).

From our review, there were five studies (31, 32, 34, 36, 37) evaluating AL before and after the pandemic of COVID-19. Four out of five studies (31, 32, 36, 37) found that AL elongation was faster during the lockdown. These findings might support the defocusing theory. Another study (34), meanwhile, did not find a statistical difference in AL between pre and post home studying. These two mechanisms of myopia might also be found in combination, since partial reversible of myopia progression was found after the lockdown was over in a study (30). A temporary accommodative spasm might be accounted for in the reversed part of myopia while the remaining was from permanent AL elongation.

The main strength of our review is the inclusion of studies from many countries in which the settings were both school-based and clinical-based. Therefore, the populations that we reviewed may represent a large number of children from many ethnicities. Limitations include difficulty to compare results from various studies. For example, refractive data from studies using non-cycloplegic measurement might overestimate the SER than those with cycloplegic measurements. Moreover, the refractive data after termination of the lockdown may be required to assess the permanent effect of myopic shift.

CONCLUSION

The pandemic of COVID-19 provided an unwanted opportunity to assess the effect of the behavioral changes and myopia in the real world. There is sufficient evidence to support the association between an increase in near work from home confinement or a reduction of outdoor activities and worsening of myopia during the COVID-19 lockdown. This worsening was found even in children who were under treatment with atropine. On the other hand, an initiative to increase outdoor activities, such as the Yilan Myopia Prevention and Vision Improvement Program in Taiwan, may be able to stabilize myopia progression during the lockdown period. The findings from this review of data from the real world may help better understanding of myopia development and progression, which may lead to adjustment of behaviors to prevent myopia and its progression in the future.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work: JL, AA, MC, AG, and PR. Drafting the work or revising it critically for important intellectual content: JL, AA, MC, and PR. Final approval of the version to be published: JL, AG, and PR. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology*. (2016) 123:1036-42. doi: 10.1016/j.ophtha.2016.01.006
2. Saw SM. How blinding is pathological myopia? *Br J Ophthalmol.* (2006) 90:525–6. doi: 10.1136/bjo.2005.087999
3. Haarman AEG, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJM, Klaver CCW. The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci.* (2020) 61:49. doi: 10.1167/iovs.61.4.49
4. Seet B, Wong TY, Tan DT, Saw SM, Balakrishnan V, Lee LK, et al. Myopia in Singapore: taking a public health approach. *Br J Ophthalmol.* (2001) 85:521–6. doi: 10.1136/bjo.85.5.521
5. Zhang X, Qu X, Zhou X. Association between parental myopia and the risk of myopia in a child. *Exp Ther Med.* (2015) 9:2420–8. doi: 10.3892/etm.2015.2415
6. Jiang D, Lin H, Li C, Liu L, Xiao H, Lin Y, et al. Longitudinal association between myopia and parental myopia and outdoor time among students in Wenzhou: a 2. 5-year longitudinal cohort study. *BMC Ophthalmol.* (2021) 21:11. doi: 10.1186/s12886-020-01763-9
7. Teikari JM, O'Donnell J, Kaprio J, Koskenvuo M. Impact of heredity in myopia. *Hum Hered.* (1991) 41:151–6. doi: 10.1159/000153994
8. Dirani M, Chamberlain M, Shekar SN, Islam AF, Garoufalis P, Chen CY, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. *Invest Ophthalmol Vis Sci.* (2006) 47:4756–61. doi: 10.1167/iovs.06-0270
9. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. *Ophthalmology.* (2012) 119:2141–51. doi: 10.1016/j.ophtha.2012.04.020
10. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol.* (2017) 95:551–66. doi: 10.1111/aos.13403
11. Cao K, Wan Y, Yusufu M, Wang N. Significance of outdoor time for myopia prevention: a systematic review and meta-analysis based on randomized controlled trials. *Ophthalmic Res.* (2020) 63:97–105. doi: 10.1159/000501937
12. Huang HM, Chang DS, Wu PC. The Association between near work activities and myopia in children-a systematic review and meta-analysis. *PLoS ONE.* (2015) 10:e0140419. doi: 10.1371/journal.pone.0140419
13. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology.* (2013) 120:2100–8. doi: 10.1016/j.ophtha.2013.02.035
14. Pärssinen O, Kauppinen M, Viljanen A. The progression of myopia from its onset at age 8-12 to adulthood and the influence of heredity and external factors on myopic progression a 23-year follow-up study. *Acta Ophthalmol.* (2014) 92:730–9. doi: 10.1111/aos.12387
15. Huang L, Kawasaki H, Liu Y, Wang Z. The prevalence of myopia and the factors associated with it among university students in Nanjing: a cross-sectional study. *Medicine (Baltimore).* (2019) 98:e14777. doi: 10.1097/MD.0000000000014777
16. Lu B, Congdon N, Liu X, Choi K, Lam DS, Zhang M, et al. Associations between near work, outdoor activity, and myopia among adolescent students in rural China: the Xichang Pediatric Refractive Error Study report no 2. *Arch Ophthalmol.* (2009) 127:769–75. doi: 10.1001/archophthalmol.2009.105
17. Morgan IG, Rose KA. Myopia and international educational performance. *Ophthalmic Physiol Opt.* (2013) 33:329–38. doi: 10.1111/opo.12040
18. Ip JM, Rose KA, Morgan IG, Burlutsky G, Mitchell P. Myopia and the urban environment: findings in a sample of 12-year-old Australian school children. *Invest Ophthalmol Vis Sci.* (2008) 49:3858–63. doi: 10.1167/iovs.07-1451
19. Fund IM. Policy Responses to COVID-19 2021. Available online at: https://www.imf.org/en/Topics/imf-and-covid19/Policy-Responses-to-COVID-19#C (accessed February 11, 2022).
20. Saxena R, Gupta V, Rakheja V, Dhiman R, Bhardawaj A, Vashist P. Lifestyle modification in school-going children before and after COVID-19 lockdown. *Indian J Ophthalmol.* (2021) 69:3623–9. doi: 10.4103/ijo.IJO_2096_21
21. Morrison SA, Meh K, Sember V, Starc G, Jurak G. The effect of pandemic movement restriction policies on children's physical fitness, activity, screen time, and sleep. *Front Public Health.* (2021) 9:785679. doi: 10.3389/fpubh.2021.785679
22. Xiang M, Zhang Z, Kuwahara K. Impact of COVID-19 pandemic on children and adolescents' lifestyle behavior larger than expected. *Prog Cardiovasc Dis.* (2020) 63:531–2. doi: 10.1016/j.pcad.2020.04.013
23. Moore SA, Faulkner G, Rhodes RE, Brussoni M, Chulak-Bozzer T, Ferguson LJ, et al. Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: a national survey. *Int J Behav Nutr Phys Act.* (2020) 17:85. doi: 10.1186/s12966-020-00987-8
24. Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U. *S BMC Public Health.* (2020) 20:1351. doi: 10.1186/s12889-020-09429-3
25. Bingham DD, Daly-Smith A, Hall J, Seims A, Dogra SA, Fairclough SJ, et al. Covid-19 lockdown: Ethnic differences in children's self-reported physical activity and the importance of leaving the home environment; a longitudinal and cross-sectional study from the Born in Bradford birth cohort study. *Int J Behav Nutr Phys Act.* (2021) 18:117. doi: 10.1186/s12966-021-01183-y
26. López-Gil JF, Tremblay MS, Brazo-Sayavera J. Changes in healthy behaviors and meeting 24-h movement guidelines in spanish and brazilian preschoolers, children and adolescents during the COVID-19 lockdown. *Children (Basel).* (2021) 8:83. doi: 10.3390/children8020083
27. Ten Velde G, Lubrecht J, Arayess L, van Loo C, Hesselink M, Reijnders D, et al. Physical activity behaviour and screen time in Dutch children during the COVID-19 pandemic: Pre-, during- and post-school closures. *Pediatr Obes.* (2021) 16:e12779. doi: 10.1111/ijpo.12779
28. Shneor E, Doron R, Levine J, Zimmerman DR, Benoit JS, Ostrin LA, et al. Objective Behavioral Measures in Children before, during, and after the COVID-19 Lockdown in Israel. *Int J Environ Res Public Health.* (2021) 18:8732. doi: 10.3390/ijerph18168732

29. Wang J, Li Y, Musch DC, Wei N, Qi X, Ding G, et al. Progression of Myopia in school-aged children after COVID-19 home confinement. *JAMA Ophthalmol.* (2021) 139:293–300. doi: 10.1001/jamaophthalmol.2020.6239
30. Chang P, Zhang B, Lin L, Chen R, Chen S, Zhao Y, et al. Comparison of Myopic Progression before, during, and after COVID-19 Lockdown. *Ophthalmology*. (2021) 128:1655–7. doi: 10.1016/j.ophtha.2021.03.029
31. Hu Y, Zhao F, Ding X, Zhang S, Li Z, Guo Y, et al. Rates of Myopia Development in Young Chinese Schoolchildren During the Outbreak of COVID-19. *JAMA Ophthalmol.* (2021) 139:1115–21. doi: 10.1001/jamaophthalmol.2021.3563
32. Zhang X, Cheung SSL, Chan HN, Zhang Y, Wang YM, Yip BH, et al. Myopia incidence and lifestyle changes among school children during the COVID-19 pandemic: a population-based prospective study. *Br J Ophthalmol.* (2021). doi: 10.1136/bjophthalmol-2021-319307
33. Alvarez-Peregrina C, Martinez-Perez C, Villa-Collar C, Andreu-Vázquez C, Ruiz-Pomeda A, Sánchez-Tena M. Impact of COVID-19 home confinement in children's refractive errors. *Int J Environ Res Public Health*. (2021) 18:5347. doi: 10.3390/ijerph18105347
34. Ma D, Wei S, Li SM, Yang X, Cao K, Hu J, et al. Progression of myopia in a natural cohort of Chinese children during COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol.* (2021) 259:2813–20. doi: 10.1007/s00417-021-05305-x
35. Ma M, Xiong S, Zhao S, Zheng Z, Sun T, Li C. COVID-19 Home Quarantine Accelerated the Progression of Myopia in Children Aged 7 to 12 Years in China. *Invest Ophthalmol Vis Sci.* (2021) 62:37. doi: 10.1167/iovs.62.10.37
36. Erdinest N, London N, Levinger N, Lavy I, Pras E, Morad Y. Decreased effectiveness of 0.01% atropine treatment for myopia control during prolonged COVID-19 lockdowns. *Cont Lens Anterior Eye*. (2021):101475. doi: 10.1016/j.clae.2021.101475
37. Yum HR, Park SH, Shin SY. Influence of coronavirus disease 2019 on myopic progression in children treated with low-concentration atropine. *PLoS ONE.* (2021) 16:e0257480. doi: 10.1371/journal.pone.0257480
38. Aslan F, Sahinoglu-Keskek N. The effect of home education on myopia progression in children during the COVID-19 pandemic. *Eye* (Lond). (2021):1-6. doi: 10.1038/s41433-021-01655-2 . [Epub ahead of print].
39. Yang YC, Hsu NW, Wang CY, Shyong MP, Tsai DC. Prevalence trend of Myopia after promoting eye care in preschoolers: a serial survey in Taiwan before and during the Coronavirus Disease 2019 pandemic. *Ophthalmology*. (2022) 129:181–90. doi: 10.1016/j.ophtha.2021.08.013
40. Sankaridurg P, He X, Naduvilath T, Lv M, Ho A, Smith E. 3rd, et al. Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. *Acta Ophthalmol.* (2017) 95:e633–e40. doi: 10.1111/aos.13569
41. Day M DL. Myopia and defocus: the current understanding. *Scandinavian J Optom Vis Sc***i**. (2011) 4:1–14. doi: 10.5384/sjovs.vol1i4p1-14
42. Vasudevan B, Ciuffreda KJ, Gilmartin B. Sympathetic inhibition of accommodation after sustained nearwork in subjects with myopia and emmetropia. *Invest Ophthalmol Vis Sci.* (2009) 50:114–20. doi: 10.1167/iovs.08-1762

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Outcomes and eye care knowledge in rhegmatogenous retinal detachment patients with a history of laser refractive surgery for myopia

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Purpose: To investigate the surgical outcomes and eye care knowledge of patients with rhegmatogenous retinal detachment (RRD) who had previously undergone laser refractive surgery (LRS) for myopia in a myopia epidemic area.

Methods: This retrospective study included patients with primary RRD who underwent surgery and had a history of LRS for myopia at a tertiary medical center. Data were reviewed from medical charts to analyse the surgical outcomes. Questions about eye care knowledge and attitude toward myopia and LRS were obtained.

Results: A total of 774 patients underwent RRD surgery, among whom 341 (44%) had myopia > -3 dioptres, 66% of whom had high myopia. Thirty eyes of 26 patients had a history of LRS for myopia. The mean age of patients with a history of LRS was significantly lower than that of those without a history of LRS (45.7 ± 2.9 years vs. 53.8 ± 1.0, $p < 0.001$). The mean pre-LRS spherical equivalent was -8.66 ± 0.92 (range: -3.00–-12.00) dioptres. In more than half the patients ($n = 15$, 57.7%), the interval between LRS and RRD was more than 10 years. The primary retinal reattachment rate was only 60%, whereas the final retinal reattachment rate was 93%. The mean final visual acuity (VA) improved from a 20/286 to 20/105 ($p = 0.006$). Linear mixed model analysis showed factors of male sex and macular detachment were significant with poor visual outcome ($p = 0.046$ and 0.008) Eye care knowledge obtained from the 19 RRD patients with history of LRS, 47% of patients (9/19) mistakenly thought that LRS could cure myopia and its complications, and 63% of patients were less willing to visit an ophthalmologist because uncorrected VA improvement after LRS. Eighty-four percent thought that proper knowledge and more education about LRS and myopia for the public are important.

Conclusion: In the RRD patients with a history of LRS for myopia, their age was relative younger. Male sex and macular detachment were associated with poor visual outcome. More education with proper knowledge of LRS, myopia and RRD is recommended for the patients to prevent or early detect the occurrence of RRD.

KEYWORDS

myopia, retinal detachment, laser refractive surgery, eye care knowledge, scleral buckle, vitrectomy

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Introduction

Myopia prevails globally, and an epidemic of myopia in East and Southeast Asia has been indicated by Morgan et al., reporting the prevalence of 80–90% for myopia in young adults and 10–20% for high myopia (1). This is concomitant with the prevalence of low vision and blindness arising from complications of myopia, such as g cataract formation, retinal detachment from peripheral retinal tears, myopic foveoschisis, macular hole with or without retinal detachment, peripapillary deformation, dome-shaped macula, choroidal/scleral thinning, myopic choroidal neovascularization, and glaucoma (2).

Laser refractive surgery (LRS) is a common surgical procedure which shows a favorable outcome of rapid improvement in uncorrected visual acuity (VA), with minimal postoperative pain and infrequent complications. These advantages further improve the quality of life of myopic patients. However, although LRS can correct refractive errors, it cannot reverse the elongation of the eyeball, as seen in myopia (3–5). Therefore, the risk of complications of an elongated eyeball still exists which may even increase after LRS.

Although the efficacy and predictability of laser-assisted *in situ* keratomileusis (LASIK) reportedly reduce low to high myopia, LRS may lead to various posterior segment complications (6, 7). Arevalo et al. reported the possibility of vitreoretinal complications after LRS, although serious complications occurring shortly after LRS are infrequent (7). An association between RD and LRS has been suspected, which emphasizes the importance of dilated fundus examination before LASIK. Furthermore, patients with a decrease in VA which is less than expected after LRS should be promptly referred to a vitreoretinal specialist.

Previously, a large telephone survey of 4,026 adults investigating their knowledge of myopia was conducted by the Health Promotion Administration in Taiwan. Seventy percent mistakenly thought that LRS for myopia could prevent the complications of myopia, while 64% did not know that high myopia entailed a high risk of RD and macular degeneration (8). Therefore, proper public health education for myopia, LRS, and RD is important and an emerging issue.

This study aimed to investigate the surgical outcomes and eye care knowledge of patients with rhegmatogenous retinal detachment (RRD) and a history of LRS for myopia.

Methods

This retrospective cohort study enrolled 774 patients who had undergone vitreoretinal surgery between April 2014 and December 2017 to manage RRD at Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan. This study was approved by the Institutional Ethics Review Board and adhered to the tenets of the Declaration of Helsinki. Among the total patients, 26 (30 eyes) had a history of LRS for myopia. Data reviewed from charts, included age, sex, myopia status before LRS, VA at the time of RRD detection, VA after surgical intervention, and follow-up duration after surgery for RRD. Surgical procedures included scleral buckling (SB), and pars plana vitrectomy (PPV) with or without lensectomy, endolaser photocoagulation, internal tamponade, a combination of both techniques, or pneumatic retinopexy with long-duration gases, such as C_3F_8 or SF_6. Success of the initial surgical procedure was defined based on the history of reintervention and the outcome of retinal reattachment. The non- to low-myopia, moderate myopia and high myopia were defined as spherical equivalent refractions lower than −3D, −3D or greater but lower than −6D, and −6D or greater, respectively. Primary success was defined as the retinal reattachment in one operation. Questions about eye care knowledge and attitudes toward myopia and the LRS were answered by the patients. The questions included the following: 1. Do you think the LRS cures myopia and the eyeball becomes normal? 2. Do you regularly follow up after LRS? If yes, was the ocular examination performed with or without pupil dilation? 3. Do you think that it is necessary to provide the public with proper knowledge and more education on myopia, LRS, and RRD?

Statistical analysis

Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analyses. VAs of "counting fingers," "hand motions," "light perception," and "no light perception" were assigned logMAR values of 2.3, 2.6, 3.0, and 4.0, respectively (9). We analyzed the demographic and clinical factors of patients with RRD using Student's *t*-test. using linear mixed model with compound symmetry model for analyses involving both eyes, multivariate analysis for the final logMAR VA of these 30 eyes was conducted for variables including age, sex (male = 1, female = 0), laterality of eye (right = 0, left = 1), myopic dioptre (spherical equivalent refraction), previous LRS duration (>10 year = 1, <10 year = 0), initial logMAR VA, macular on/off status (on = 0, off = 1), multiple break status (>2 breaks = 1, 1 break = 0), first surgical type (SB = 1, other = 0). The answer to the questionnaire was yes or no for each question and the result of the proportion was demonstrated for each question. For the questionnaire, the content validity index in each item was 1.0, 1.0 and 0.8, respectively. SPSS Base11.0 software (version 11.0; SPSS, Inc., Chicago, IL, USA) was used. Statistical significance was set at $P < 0.05$.

Results

During the study period, 774 patients underwent RRD surgery at our hospital. Among them, 341 (44%) patients had myopia > −3 dioptres, 66% had high myopia (-6 dioptres or

TABLE 1 Characteristics and surgical outcomes of rhegmatogenous retinal detachment patients with previous laser refractive surgery for myopia.

No.	Sex, Age	Eye	Myopia (Diopter)	Interval LRS-RRD(yrs)	Initial BCVA while RRD (logMAR)	Final BCVA (logMAR)	Macular involved	Multiple breaks (≥2)	Initial surgery type	Surgery again	Retina outcome	Follow up duration (months)
1	M, 35	OD	−10	>10	1	1.2	(-)	(-)	SB	(-)	Attach	5
2	M, 44	OS	−8	>10	2.6	1.3	(-)	(+)	SB	(-)	Attach	13
3	M, 35	OD	−8	5–10	2	0.5	(-)	(-)	SB	(-)	Attach	53
4	M, 36	OD	−8	>10	0.5	0	(-)	(-)	SB	(+)	Attach	46
5	F, 38	OS	−10	>10	0.7	0.3	(-)	(+)	SB	(+)	Attach	2
6	F, 55	OS	−10	>10	0.5	0.5	(-)	(-)	SB	(+)	Attach	48
7	F, 50	OD	−11	5–10	1	0.1	(-)	(-)	SB	(-)	Attach	46
8	M, 48	OD	−10	<1	2.6	1.5	(+)	(-)	C3F8	(+)	Attach	47
9	M, 52	OU	−10/−10	>10	0.3/0.7 (OD/OS)	0.2/0.1	(-)/(-)	(-)/(-)	TPPV/SB	(-)/(-)	Attach/Attach	45
10	F, 51	OS	−6.5	>10	1.7	0.2	(+)	(-)	SB	(-)	Attach	24
11	F, 46	OD	−10	>10	2.3	0.5	(+)	(-)	SB+TPPV	(-)	Attach	37
12	F, 41	OS	−6	>10	2.6	0	(+)	(+)	SB+TPPV	(-)	Attach	43
13	M, 51	OD	−9	>10	0.3	0.7	(+)	(-)	SB	(+)	Attach	42
14	F, 45	OD	−5	>10	2	0.4	(-)	(-)	SB	(-)	Attach	27
15	M, 48	OD	−8	5–10	0.7	0.7	(-)	(-)	TPPV	(+)	Attach	29
16	M, 45	OD	−7	>10	1.4	2.3	(+)	(+)	TPPV	(-)	Attach	30
17	F, 33	OD	−8	>10	0	0.1	(-)	(-)	SB	(-)	Attach	24
18	M, 47	OU	−10/−10	>10	0.7/1.7 (OD/OS)	0/2.3	(-)/(+)	(+)/(-)	TPPV/SB+TPPV	(-)/(+)	Attach/Attach	30
19	M, 51	OD	−4.5	>10	1.3	0.4	(-)	(-)	SB	(-)	Attach	38
20	M, 47	OD	−7	>10	1.5	1.7	(+)	(-)	TPPV	(-)	Attach	16
21	F, 61	OU	−12	>10	2/1 (OD/OS)	1.7/1.3	(+)/(+)	(-)	TPPV+SB/TPPV	(+)/(+)	Detach/Attach	24
22	F, 38	OD	−8	>10	1.5	0.3	(-)	(-)	SB	(-)	Attach	6
23	M, 57	OD	−6	>10	1.1	1	(-)	(-)	SB	(+)	Attach	18
24	F, 38	OD	−3	5–10	0.5	0	(+)	(+)	SB	(-)	Attach	10
25	M, 47	OU	−13/−13	>10	0.3/0 (OD/OS)	0.2/0	(-)/(-)	(-)/(-)	SF6/C3F8	(+)/(+)	Attach/Attach	13
26	F, 49	OS	−10	>10	0.2	2	(+)	(-)	SB	(+)	Detach	3

LRS: laser refractive surgery; RRD, rhegmatogenous retinal detachment; BCVA, best corrected visual acuity; SB, scleral buckling; TPPV, trans pars plana vitrectomy; C3F8, perfluoropropane; SF6, sulfur hexafluoride.

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greater). Thirty eyes of 26 patients had a history of LRS for myopia; 15 (57.7%) were men and 11 (42.3%) were women (Table 1). The mean age of patients with a history of LRS was significantly lower than that of those without a history of LRS [45.7 ± 2.9 years (range: 33–61 years, $n = 26$) vs. 53.8 ± 1.0 years (range: 15–85 years, $n = 748$), $p < 0.001$], and there was no significant difference in sex (57.7 vs. 64.2%, $p = 0.507$).

RRD with previous LRS

Among the 30 eyes of RRD with previous LRS, the mean pre-LRS spherical equivalent was −8.66 ± 0.92 (range: −3.00–−12.00) dioptres. In more than half of the patients ($n = 15$, 57.7 %), the interval between LRS and RRD was more than 10 years. In only one patient (3.8%), it was within a year.

The primary retinal reattachment rate was 60%, whereas the final retinal reattachment rate was 93.3%. Six eyes (20%) underwent PPV, 50% of which ($n = 3$) underwent surgery again. Seventeen eyes (56.7%) underwent SB, 35.3% ($n = 6$) of which underwent surgery again. Four (13.3%) eyes were operated with combined PPV and SB, 50% ($n = 2$) of which underwent surgery again. Three eyes (10%) underwent pneumatic retinopexy, all of which underwent surgery again.

Among the eyes of RRD with previous LRS, the macula was involved in 12 eyes (40%). Of these, four, four, three, and one eye underwent trans PPV (TPPV) + SB, SB, TPPV, and pneumatic retinopexy, respectively. Multiple breaks (>2 breaks) were observed in six eyes, one of which underwent surgery following the initial SB. Vision improved in 21 (70%) eyes. The final Snellen VA significantly improved from 20/286 to 20/105, with the logMAR value changing from 1.16 ± 0.28 to 0.71 ± 0.26 ($p = 0.006$).

For the analysis of final logMAR VA, multivariate analysis showed no statistically significance with age, laterality of eye, myopic dioptre, previous LRS duration, initial logMAR VA, multiple breaks status, and first surgical type. Two factors, sex and macular status, were statistically significant ($P = 0.046$ and 0.008, respectively Table 2). Male sex and macula-off status were associated with poor visual outcomes.

Questionnaire

Eye-care knowledge data were available for 19 patients (Figure 1), 47% of whom thought that their myopia was cured by LRS and that they had healthy eyeballs as normal people. While 64% did not undergo regular follow-up, 36% had regular follow-up within 2 years after LRS, but 71% had no pupil dilation during the retina survey. Furthermore, 63% patients reported that they only went back to the doctor once after LRS, and no further follow-up was requested. Sixteen patients (84.2%) thought necessary to provide the public with proper knowledge and education regarding myopia, LRS, and RRD.

Discussion

Our study demonstrated that nearly half of the primary RRD patients in this myopia epidemic area of Taiwan were myopic. It also revealed that patients with a history of LRS for myopia developed RRD at a relatively younger age. Furthermore, this is the first report regarding eye care knowledge in RRD patients with a history of LRS for myopia. The outcomes and knowledge were unfavorable in these patients, suggesting the key emerging need for proper public health education regarding myopia and LRS.

In Taiwan, the prevalence of myopia in the older population is much lower than that in the young to middle-aged population, although a substantial population of RRD patients are elderly. A recent study in Taiwan reported that the average age of the

TABLE 2 Linear mixed model analysis for factors associated with final logMAR visual acuity in the RRD patients with a history of LRS for myopia.

		Final logMAR VA			
$N = 26$ patients (30 eyes)	**coefficient (β)**	**95% CI**			***P***
Age	0.006	−0.035	∼	0.047	0.761
Sex(male = 1, female = 0)	0.581	0.012	∼	1.149	0.046*
Eye(right = 0, left = 1)	0.014	−0.670	∼	0.697	0.962
SER(myopic dioptre, D)	−0.064	−0.205	∼	0.077	0.358
LRS period(>10 yr = 1, ≤10 yr = 0)	0.200	−0.502	∼	0.902	0.558
Initial logMAR VA	0.205	−0.142	∼	0.552	0.232
Macula off(on = 0, off = 1)	0.913	0.271	∼	1.554	0.008*
Retinal break(≥2 breaks = 1, 1 break = 0)	−0.136	−0.862	∼	0.590	0.691
First surgery type(SB = 1, other = 0)	0.234	−0.476	∼	0.945	0.498

95% CI: confidence interval. * represents statistically significant. RRD = rhegmatogenous retinal detachment; LRS = laser refractive surgery; VA=visual acuity; VA=visual acuity; SER=spherical equivalent refraction; D: diopter.

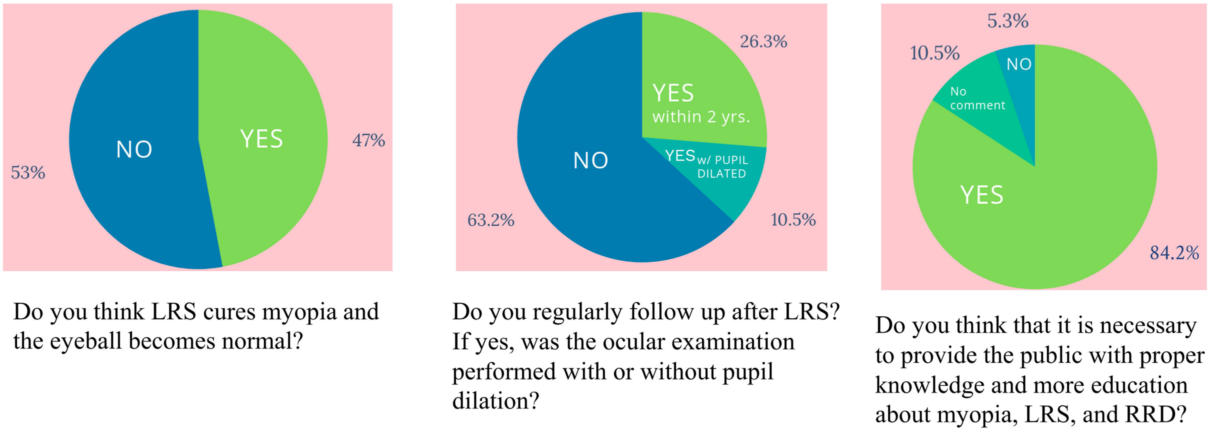

FIGURE 1
The result of the questionnaire about eye care knowledge and attitude toward myopia and laser refractive surgery.

incidence of RD was 47.76 ± 0.67 years, with an obvious peak at 50–69 years in both sexes and a secondary peak at 20–29 years in women (10). A study in China reported that the median age of patients with RRD was 51 years, with two peaks of incidence at 60–69 and 20–29 years of age. In our study, 26 patients with a history of LRS had an average age of 45.7 ± 2.9 years while patients with RRD were relatively young. Another study reported a bi-peak pattern in the age distribution of primary RRD that occurred in the third and sixth decades of life (11). In addition, the mean age of the patients with RRD differs according to ethnicity. Chandra et al. reported that South Asians have a younger age of onset and a higher myopic refraction than in Europeans. In this study, the mean age of onset was 58.3 years in European Caucasians and 54.5 years in South Asians, which was consistent with our findings (53.8 ± 1.0 years, $n = 748$) (12).

A pneumatic suction ring is used during the LRS to fix the eyeball, as the vacuum chamber seals against the globe. Intraocular pressure (IOP) may exceed 65 mmHg during resection, and it is both uniform and regular on the cornea of an appropriate diameter. The rapid change in IOP during suction or release of the microkeratome suction ring may mechanically stretch the vitreous base, leading to a higher incidence of posterior vitreous detachment or precipitation of RRD in the eyes (13). In Alrevalo's study, the frequency of RRD after LASIK for myopia was 0.06%, which was much lower than the incidence of RD in myopic eyes in general (0.7–6.0%). They stated that this is probably explained by the fact that most refractive surgery patients undergo preoperative examinations, including dilated indirect fundoscopy with or without scleral depression, and treatment of any retinal lesion predisposing them to the development of RRD before LASIK (14). However, the current study did not present data to support this theory. Only one patient developed RRD within 1 year of LRS. Most patients develop RRD after several years. Other studies have also indicated no direct association between the LRS and RD, as the incidence was mostly low (13–15).

The primary surgical success rate was 60%, which was much lower than the general anatomical success rate reported in other studies (16–19). However, the small sample size ($n = 30$ eyes) in our study should be noted. We therefore performed a power analysis to compare the results of these studies. A Japanese study showed the primary surgical success rate within 6 months was 90.8(2,519/2,775) (18). A German study showed the primary success rate after one operation was 90% (3,420/3,786) (19). An UK study showed the primary success rate with a single procedure was 86.8% (302/348) (16). Another large UK study showed 86.9% (2,958/3,403) (17). To compare with our study, the power was 0.98, 0.98, 0.90, and 0.93, respectively. This means that our RRD patients with a history of LRS had a lower primary success rate. The final reattachment rate of our study was 93.3%. Two other smaller studies showed 100% final reattachment rate for RRD with previous LRS (13, 15). Our study compared to the UK study (97.4%, 339/348) (16), where the power upon analysis was 0.17. This suggests no obvious difference between these two studies in terms of the final reattachment rate.

In the multivariate regression analysis, the poor final visual outcome of RRD patients with previous LRS was associated with male sex and macular detachment. A previous study showed male sex to be a risk factor for pseudophakic RRD (20). The reason remains unknown. Men reportedly have lower utilization of medical care service utilization than women (21, 22). The reason might be speculated to be the severity of RRD due to the delay in seeking medical care. The other factor associated with poor visual outcomes was macular detachment in this study. Previous studies have shown that macula-off RRD negatively affects postoperative BCVA (23, 24). The course of RRD mostly initially develops from a retinal break initially without retinal and macular detachment. Some patients experienced symptoms of floaters or flash sensations at that time. Subsequently, retinal detachment and macular detachment develop accompanied by visual field defects. Early detection and intervention in RRD are important for visual outcomes.

According to the popularity of the LRS for myopia, proper knowledge and education should be spread. Highly myopic eyes are more likely to develop lattice degeneration, retinal breaks, and RRD compared to normal eyes. The average pre-LRS spherical equivalent of our patients was as high as −8.66 ± 0.92 dioptres. Complications of high myopia, including retinal detachment, are characterized by axial length elongation (2). LRS is performed in the cornea to change the refraction but it cannot reverse the elongated axial length. Although their refractive status became relatively low after LRS for myopia, the risk of RRD remained as high as before. Almost half of the patients mistakenly thought that LRS cured myopia, and over half of them did not undergo regular complete fundus examination. As RRD is a vision-threatening disease and myopic RRD patients are relatively young and at a productive age, the better strategy is to prevent regular fundus examination with detect of the associated retinal lesions early-on. In this study, 83% of the patients thought that public awareness of LRS is necessary to encourage regular follow-up. Therefore, proper education including signs of RRD and shared decision making (SDM) for each patient before and after LRS is needed.

Regular dilated retinal examination might be recommended for high myopia even with or without LRS, especially when patients have floater or flash symptoms. It has been reported that evaluation and management of incident acute posterior vitreous detachment (PVD) offer a low cost and favorable cost-utility to minimize the cost and morbidity associated with the development of RRD (25). Furthermore, treatment and prevention of RRD are extremely cost-effective when compared with other treatment for other retinal diseases regardless of treatment modality (26).

The limitations of this study include its retrospective design, small sample size, failure to obtain the pre-LRS fundus status, axial length data, and the type of LRS including PRK and LASIK. Axial myopia is more common and results from an elongated eyeball (27). We obtain the information on the type of previous LRS, although LASIK is much more popular than PRK in Taiwan. The current questionnaire study which n=19 compared with the previous survey $n > 4,000$ is much lower. This small survey was only conducted for RRD patients with a previous LRS history. Seven of them could not be available due to loss of contact. This questionnaire has been designed by retinal specialist, it was not analysis using reliability and validity test. The questionnaire was answered after the RRD surgery and the last question might lead the patient to respond positively. Although showing the sign of the need for education, a large sample study with a questionnaire in patients with LRS is warranted. Another limitation is the mean ± SE in the non-LRS group was unavailable. Only categorical data of non to low-myopia, moderate myopia and high myopia were available in the non-LRS group. In addition, some of the patients were old and had pseudophakia without previous refraction data. Further prospective, longitudinal, and large-scale studies are necessary to determine the cause and effect relationship between RD and LRS.

In the ideal world, all high myopes should preferably have regular ocular and in particular dilated fundus examination; however, this would be difficult in practical reality. We recommend improved public education with regard to 1. LRS only changing refractive error. 2. LRS not altering the risk of complications of high myopia, namely, retinal tears and detachments. 3. Patients with high myopes and LRS should be monitored for acute onset of floaters and flashes, as well as partial loss of visual field or curtain sensation.

In conclusion, a high prevalence of myopia was observed in patients with primary RRD in the area of the myopia epidemic. Patients who developed RD after LRS for myopia were relatively young, and almost half of them mistakenly thought that LRS cured myopia. Therefore, patients should be informed that although LRS corrects the refractive status of myopia, elongated eyeballs still carry a high risk of myopic complications, including RD. More education with proper knowledge of LRS, myopia and RRD is recommended for myopic patients to prevent or detect RRD early.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Chang Gung Medical Foundation Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Design the study: P-CW. Data collection and statistics: Y-HC, Y-JC, J-JL, and H-KK. Writing manuscript: CL and P-CW. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Morgan IG, French AN, Ashby RS, Guo X, Ding X, He M, et al. The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res.* (2018) 62:134–49. doi: 10.1016/j.preteyeres.2017.09.004

2. Ikuno Y. Overview of the complications of high myopia. *Retina.* (2017) 37:2347–51. doi: 10.1097/IAE.0000000000001489

3. Winkler von Mohrenfels C, Gabler B, Lohmann CP. Optical biometry before and after excimer laser epithelial keratomileusis (LASEK) for myopia. *Eur J Ophthalmol.* (2003) 13:257–9. doi: 10.1177/112067210301300303

4. Tay E, Bajpai R. Small incision lenticule extraction (SMILE) lenticule thickness readout compared to change in axial length measurements with the IOLMaster. *Graefes Arch Clin Exp Ophthalmol.* (2020) 258:917–24. doi: 10.1007/s00417-019-04529-2

5. Hashemian SJ, Es'haghi A, Abdolalizadeh P, Ghiasian L, Aghaei H, Jafari ME, et al. Long-term visual and refractive stability and ocular biometric changes after laser-assisted subepithelial keratomileusis for correction of myopia: an 8-year follow-up. *J Curr Ophthalmol.* (2021) 33:417–21. doi: 10.4103/joco.joco_29_21

6. Arevalo JF, Freeman WR, Gomez L. Retina and vitreous pathology after laser-assisted in situ keratomileusis: is there a cause–effect relationship? *Ophthalmology.* (2001) 108:839–40. doi: 10.1016/S0161-6420(00)00471-1

7. Arevalo JF. Retinal complications after laser-assisted in situ keratomileusis (LASIK). *Curr Opin Ophthalmol.* (2004) 15:184–91. doi: 10.1097/01.icu.0000120674.27548.9c

8. *Health Promotion Administration, Ministry of Health and Welfare, Taiwan.* Behavior Risk Factor Surveillance System (2007). Available online at: https://www.mohw.gov.tw/fp-16-28550-1.html

9. Scott IU, Schein OD, West S, Bandeen-Roche K, Enger C, Folstein MF. Functional status and quality of life measurement among ophthalmic patients. *Arch Ophthalmol.* (1994) 112:329–35. doi: 10.1001/archopht.1994.01090150059023

10. Chen S-N, Lian I-B, Wei Y-J. Epidemiology and clinical characteristics of rhegmatogenous retinal detachment in Taiwan. *Br J Ophthalmol.* (2016) 100:1216–20. doi: 10.1136/bjophthalmol-2015-307481

11. Chou S, Yang C, Lee C, Yang C, Ho T, Huang J, et al. Characteristics of primary rhegmatogenous retinal detachment in Taiwan. *Eye.* (2007) 21:1056. doi: 10.1038/sj.eye.6702397

12. Chandra A, Banerjee P, Davis D, Charteris D. Ethnic variation in rhegmatogenous retinal detachments. *Eye.* (2015) 29:803. doi: 10.1038/eye.2015.43

13. Qin B, Huang L, Zeng J, Hu J. Retinal detachment after laser in situ keratomileusis in myopic eyes. *Am J Ophthalmol.* (2007) 144:921–3. doi: 10.1016/j.ajo.2007.07.032

14. Arevalo JF, Ramirez E, Suarez E, et al. Rhegmatogenous retinal detachment in myopic eyes after laser in situ keratomileusis: frequency, characteristics, and mechanism. *J Cataract Refract Surg.* (2001) 27:674–80. doi: 10.1016/S0886-3350(01)00821-5

15. Al-Rashaed S, Al-Halafi AM. Retinal detachment after laser in situ keratomileusis. *Middle East Afr J Ophthalmol.* (2011) 18:224–7. doi: 10.4103/0974-9233.84052

16. Comer MB, Newman DK, George ND, Martin KR, Tom BD, Moore AT. Who should manage primary retinal detachments? *Eye.* (2000) 14:572–8. doi: 10.1038/eye.2000.145

17. Jackson TL, Donachie PH, Sallam A, Sparrow JM, Johnston RL. United Kingdom national ophthalmology database study of vitreoretinal surgery: report 3, retinal detachment. *Ophthalmology.* (2014) 121:643–8. doi: 10.1016/j.ophtha.2013.07.015

18. Koto T, Kawasaki R, Yamakiri K, et al. Six months primary success rate for retinal detachment between vitrectomy and scleral buckling. *Retina.* (2021) 41:1164–73. doi: 10.1097/IAE.0000000000002994

19. Radeck V, Helbig H, Barth T, Gamulescu MA, Maerker D, Prahs P. The learning curve of retinal detachment surgery. *Graefes Arch Clin Exp Ophthalmol.* (2021) 259:2167–73. doi: 10.1007/s00417-021-05096-1

20. Sheu SJ, Ger LP, Chen JF. Male sex as a risk factor for pseudophakic retinal detachment after cataract extraction in Taiwanese adults. *Ophthalmology.* (2007) 114:1898–903. doi: 10.1016/j.ophtha.2007.02.030

21. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. *J Fam Pract.* (2000) 49:147–52. doi: 10.1093/fampra/17.suppl_1.S21

22. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. *BMC Public Health.* (2006) 6:155. doi: 10.1186/1471-2458-6-155

23. Kontos A, Williamson TH. Rate and risk factors for the conversion of fovea-on to fovea-off rhegmatogenous retinal detachment while awaiting surgery. *Br J Ophthalmol.* (2017) 101:1011–5. doi: 10.1136/bjophthalmol-2016-309178

24. Pastor JC, Fernandez I, Rodriguez de la Rua E, et al. Surgical outcomes for primary rhegmatogenous retinal detachments in phakic and pseudophakic patients: the Retina 1 Project–report 2. *Br J Ophthalmol.* (2008) 92:378–82. doi: 10.1136/bjo.2007.129437

25. Yannuzzi NA, Chang JS, Brown GC, Smiddy WE. Cost-utility of evaluation for posterior vitreous detachment and prophylaxis of retinal detachment. *Ophthalmology.* (2018) 125:43–50. doi: 10.1016/j.ophtha.2017.06.019

26. Chang JS, Smiddy WE. Cost-effectiveness of retinal detachment repair. *Ophthalmology.* (2014) 121:946–51. doi: 10.1016/j.ophtha.2013.11.003

27. Flitcroft DI, He M, 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:M20–30. doi: 10.1167/iovs.18-25957

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Temporal and spatial characterization of myopia in China

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Purpose: The aim of this study was to characterize the temporal and spatial distribution of myopia among students aged 7–18 years, by analyzing the aggregation area and providing the basis for the prevention and control of myopia in China.

Methods: A database for the spatial analysis of myopia in China during 1995–2014 was established using ArcGIS10.0 software as a platform for data management and presentation. A spatial autocorrelation analysis of myopia was undertaken, and a temporal and spatial scan analysis was performed using SaTScan9.5 software.

Results: Our data demonstrated that the prevalence of myopia in China in 1995, 2000, 2005, 2010, and 2014 was 35.9, 41.5, 48.7, 57.3, and 57.1%, respectively, thus indicating a gradual upward trend. The prevalence of myopia was analyzed in various provinces (municipalities and autonomous regions), and the highest was found in Jiangsu Province, with an average Moran's I index of 0.244295 in China ($P \leq 0.05$). According to the local Moran's I autocorrelation analysis, there was a spatial aggregation of myopia prevalence among students in the entire country, with Shandong, Jiangsu, Anhui, and Shanghai being classified as high–high aggregation areas, while Hainan and Guangxi were classified as low–low aggregation areas. In addition, the Getis-Ord General G results of the global hotspot analysis showed a countrywide myopia prevalence index of 0.035020 and a Z score of 1.7959 ($P = 0.07251$). Because the myopia prevalence correlation difference was not statistically significant, there were no "positive hotspots" or "negative hotspots." The local hotspot analysis shows that Shandong and Jiangsu belong to high-value aggregation areas, while Hainan and Guizhou belong to low-value aggregation areas. Further analysis using time-space scanning showed 15 aggregation regions in five stages, with four aggregation regions having statistically significant differences ($P \leq 0.05$). However, the aggregation range has changed over time. Overall, from 1995 to 2014, the aggregation areas for the myopia prevalence in Chinese students have shifted from the northwest, north, and northeast regions to the southeast regions.

Conclusion: Our data demonstrate that, from 1995 to 2014, the prevalence of myopia increased in students aged 7–18 years in China. In addition, the prevalence of myopia is randomly distributed in various provinces (municipalities and autonomous regions) and exhibits spatial aggregation. Also, the gathering area is gradually shifting to the southeast, with the existence of high-risk areas. It is, therefore, necessary to focus on this area and undertake targeted prevention and control measures.

KEYWORDS

myopia, geographic information system, spatial autocorrelation analysis, spatiotemporal analysis, China

Introduction

Myopia, a worldwide eye disease, affects 28% of the world's population and is associated with visual impairment (1). China is one of the countries with the highest incidence of myopia (2, 3). At present, there is a high prevalence of myopia among adolescents in China, as well as a significant disease progression. According to statistics, the prevalence of myopia among Chinese children and adolescents nationwide was 52.7% in 2020, and China's Ministry of Education issued an online survey to 14,532 students in nine provinces, which indicated that myopia prevalence increased by 11.7% in 2020 as compared with the end of 2019 (4, 5). Myopia not only endangers the eyesight of teenagers but also affects the mental health, lifestyle, and quality of life of families and society (6, 7). Myopia has become a global public health concern, and the World Health Organization (WHO) has incorporated myopia prevention and control measures into its global blindness prevention plan (8). In addition, the WHO has listed myopia as one of the five types of eye diseases that aims to improve and eliminate (9). It is, therefore, imperative to enhance educational reforms and develop effective and comprehensive prevention and control programs, as well as encourage the whole society to take action against visual impairment in children.

One important measure to enable the effective prevention of myopia is understanding the modifiable risk factors from a public perspective (10). Numerous studies have shown that many factors seem to contribute to the pathogenesis of myopia. However, considering the high prevalence of myopia, there is an increasing need to explore other environmental factors that may affect its prevalence. A previous study (11) showed that the incidence of myopia is associated with geography, population dynamics, and the economy. It is, therefore, important to characterize the spatial distribution and epidemic trend regarding myopia so as to inform the development of effective prevention and control measures (1–3).

A geographic information system (GIS) is a technical system based on a geospatial database and is supported by computer hardware and software systems that can collect, store, manage, compute, analyze, display, and describe the relevant geographical distribution of data in space (12). The use of GIS enables the convenient description and analysis of the spatial and temporal distribution patterns of population diseases, health, and health events (13). In addition, GIS enables the exploration of factors affecting the health status of specific populations, which helps in disease prevention and control, health promotion, and health services (14, 15).

In this study, we used GIS to analyze the spatial distribution and gather situations regarding myopia prevalence among students aged 7–18 years at the provincial level in China from 1995 to 2014. Our study offers critical insights and provides the basis for further research on myopia prevention and control strategies.

Materials and methods

Sources of materials

The prevalence of myopia from 1995 to 2014 was retrieved from the Report on Chinese Students' Physique and Health (1995, 2000, 2005, 2010, and 2014). The research object was students aged 7–18 years from various provinces and cities in mainland China. The stratified random cluster sampling method was used to select the survey samples. First, the province was divided into three areas (i.e., good, medium, and poor) according to the gross domestic product and other factors; second, the students were divided into 12 groups according to their age (7–18 years); finally, ≥50 students were randomly sampled in each area and from each age group. According to four categories (i.e., urban, rural, male, and female), the sample size for each province should be $\geq 50^*4^*12^*3 = 7{,}200$ students. After excluding students with abnormal or missing values, the final test sample in each province is about 7,000 students. The detailed sample size for each province has been described in the Report on Chinese Students' Physique and Health and presented in Table 1 (16–20). The five surveys were all inspected by professionally trained inspectors and completed between September and October of the year in question. In accordance with the unified requirements of the National Student Physique

TABLE 1 The number of participants in each province in the survey from 1995 to 2014.

Ranking	Province (district, municipality)	1995	2000	2005	2010	2014
1	Beijing	7,473	7,297	7,577	7,198	7,000
2	Tianjin	7,201	4,320	7,490	7,198	7,183
3	Hebei	7,200	6,621	7,904	6,921	7,187
4	Shanxi	7,210	7,189	7,091	7,192	7,200
5	Inner Mongolia	5,760	6,906	7,707	7,180	7,058
6	Liaoning	8,156	12,581	7,218	7,179	7,190
7	Jilin	7,209	7,342	8,587	7,168	7,114
8	Heilongjiang	7,683	7,188	7,124	7,173	7,175
9	Shanghai	7,919	7,362	6,404	7,200	7,143
10	Jiangsu	7,676	7,529	9,237	6,335	6,949
11	Zhejiang	8,416	7,195	7,211	7,192	6,825
12	Anhui	7,200	7,199	7,184	7,198	7,196
13	Fujian	5,733	7,121	7,690	7,179	7,200
14	Jiangxi	7,172	7,113	7,441	7,142	7,174
15	Shandong	7,198	8,487	8,570	7,135	7,178
16	Henan	8,639	7,192	8,620	7,200	7,200
17	Hubei	7,198	7,194	4,684	7,098	7,067
18	Hunan	8,314	7,191	7,381	7,165	7,196
19	Guangdong	7,200	7,194	7,194	7,199	7,189
20	Guangxi	8,662	7,204	7,189	7,088	6,905
21	Hainan	7,134	6,548	9,681	7,079	7,200
22	Sichuan	8,640	8,136	8,978	7,138	7,198
23	Guizhou	7,200	7,192	7,179	7,182	7,197
24	Yunnan	6,673	4,991	7,841	7,195	7,200
25	Chongqing	/	7,183	9,199	7,183	7,200
26	Shanxi	7,679	7,199	7,193	7,189	7,181
27	Gansu	8,545	8,025	8,472	7,199	7,196
28	Qinghai	/	2,401	7,379	7,165	7,197
29	Ningxia	7,199	7,200	7,430	6,975	6,879
30	Xinjiang	7,198	2,400	10,253	7,189	5,966
The whole nation		**209,487**	**208,700**	**235,505**	**216,474**	**215,160**

and Health Survey Work Manual, the on-site quality control was carried out by supervisors.

The 5M Standard Logarithmic Visual Chart was used to test the students' uncorrected visual acuity (21). A vision score of 5.0 is normal, and 4.9 indicates poor vision. The vision of subjects with a visual acuity below 4.9 was corrected with lenses so as to reach 5.0 visual acuity. If the applied lenses had a negative lens power, those students were chosen as myopic, and the accommodative accuracy was further ensured using retinoscopy. Students with $\leq$-0.5D were included in the myopia group in this study.

The Report on Chinese Students' Physique and Health was compiled by the Chinese Students' Physique and Health Research Group and has been reviewed by the Ministry of Education, the National Health Commission of the People's Republic of China, and other departments. The report was open to the public.

The national myopia data exploited the national provincial vector map (1:1.6 million) and established serial numbers for each province (municipality and autonomous region) from the attribute database. The sorted prevalence of myopia was associated and matched with the serial number on the basic map so as to establish a complete spatial analysis database.

Methods

Spatial autocorrelation analysis

The global and local Moran's I indexes were used to explore the spatial autocorrelation of the prevalence of myopia.

The spatial weight matrix was generated using the spatial conceptualization method based on inverse distance. We then used ArcGIS 10.2 software to calculate the global and local Moran's *I* indexes on the basis of the defined weight matrix. In the Moran's *I* matrix, the larger the *I*-value, the greater the correlation of spatial distribution and, thus, the more obvious the phenomenon of spatial aggregation distribution. On the contrary, as the *I*-value approaches 0, the spatial distribution is random (22). In addition, we used a test statistic *Z*-value of approximately normal distribution under random conditions. A *P*-value of <0.05 was taken to indicate statistical significance. We used the global spatial autocorrelation to analyze whether the study indicated aggregated distribution in general and the local spatial autocorrelation to describe the correlation between the prevalence of myopia in each province (municipality and autonomous region) and its neighboring provinces (municipality and autonomous region). We then defined the specific aggregation areas and aggregation mode (23).

Hotspot analysis (Getis-Ord G)

We used the global *G* statistics to evaluate the presence of "positive hotspots" or "negative hotspots" in the prevalence of myopia. Briefly, a *G* of more than 0 implies high-value aggregation regions, and *vice versa*, with a *P* of <0.05 in the research range (24). On the contrary, we used the local *G* statistics to evaluate the high- or low-value aggregation areas in all provinces (municipalities and autonomous regions) and neighboring provinces (municipalities and autonomous regions). A *Z*-value of more than 1.96 suggested a high-value aggregation area in and around the spatial unit i, while a *Z*-value of <-1.96 suggested the opposite (25).

Spatio-temporal scanning analysis

To ensure an accurate description of the distribution of temporal and spatial aggregation of the prevalence of myopia, we divided five surveys of the Chinese student system into five stages based on the spatial autocorrelation analysis (26). SaTScan9.5 software was used for the aggregation analysis, while ArcGIS10.2 software was used for the visualization of the results (27). The data on the prevalence of myopia in 31 provinces (municipalities and autonomous regions) from 1995 to 2014 were analyzed by visualizing the spatial distribution in ArcMap. The SaTScan 9.6 software detected the spatial aggregation of the disease in the research area through a series of scanning circles. Because the size and position of the window were dynamic, the statistical inference was made by calculating the log likelihood ratio (LLR) values of different spatial unit attributes within and outside the dynamic window regions. A large LLR value implied that the area under the window was likely to have aggregation (28). The spatial-temporal scanning analysis of this study adopted the space-time permutation model in the SaTScan 9.5 software. We adopted high-value clustering, the number of Monte Carlo simulation tests at 999, and the clustering of time interval at 5 years.

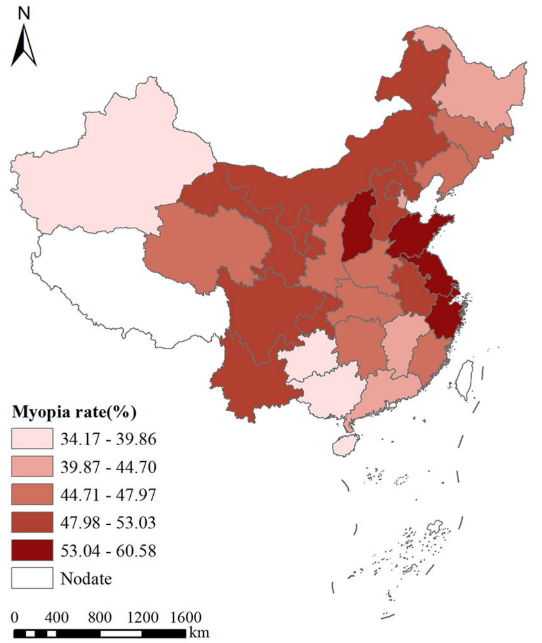

FIGURE 1
Spatial distribution of the prevalence of myopia in China from 1995 to 2014.

Results

Spatial distribution of the prevalence of myopia

The prevalence of myopia was 35.9, 41.5, 48.7, 57.3, and 57.1% in 1995, 2000, 2005, 2010, and 2014, respectively. Jiangsu and Hainan Provinces had the highest and lowest prevalence of myopia, respectively, among the provinces (municipalities and autonomous regions). The average prevalence of myopia from 1995 to 2014 was divided into five grades according to the natural breakpoint classification method. Hainan, Guizhou, Xinjiang, and Guangxi had the lowest myopia prevalence and are assigned to the first grade, while Jiangsu, Shandong, Shanghai, Zhejiang, and Shanxi had the highest myopia prevalence, thus ranking fifth, as shown in Figure 1 and Table 2.

Spatial autocorrelation analysis

Global spatial autocorrelation analysis

Our data demonstrated that the Moran's *I* indexes for the students' prevalence of myopia were 0.101352, 0.255234, 0.140538, 0.169005, and 0.087811 in 1995, 2000, 2005, 2010,

TABLE 2 The prevalence of myopia among children and adolescents in all provinces of China from 1995 to 2014.

Ranking	Province (district, municipality)	1995	2000	2005	2010	2014
1	Beijing	33.77%	40.63%	51.78%	60.20%	66.40%
2	Tianjin	24.42%	32.64%	43.68%	42.33%	66.30%
3	Hebei	41.72%	47.82%	51.71%	62.70%	41.70%
4	Shanxi	49.29%	46.46%	58.07%	68.48%	57.60%
5	Inner Mongolia	33.26%	35.35%	48.59%	68.38%	64.20%
6	Liaoning	33.46%	35.91%	54.62%	58.64%	56.90%
7	Jilin	34.24%	37.44%	46.40%	56.31%	58.20%
8	Heilongjiang	23.82%	31.00%	46.91%	54.36%	55.00%
9	Shanghai	45.84%	49.38%	59.96%	69.00%	71.80%
10	Jiangsu	43.55%	51.56%	66.02%	69.75%	72.00%
11	Zhejiang	52.57%	56.00%	63.09%	72.97%	47.90%
12	Anhui	34.93%	48.84%	45.80%	57.47%	63.00%
13	Fujian	41.82%	47.40%	31.04%	60.57%	57.10%
14	Jiangxi	34.80%	40.11%	41.03%	51.91%	52.20%
15	Shandong	46.75%	50.74%	63.56%	69.43%	66.90%
16	Henan	35.15%	39.77%	43.73%	55.85%	57.90%
17	Hubei	37.81%	41.52%	45.64%	55.13%	52.00%
18	Hunan	33.22%	39.05%	50.11%	52.85%	57.80%
19	Guangdong	29.92%	34.62%	45.28%	55.10%	58.60%
20	Guangxi	28.15%	33.56%	43.72%	51.65%	42.20%
21	Hainan	26.15%	27.92%	36.18%	39.38%	41.25%
22	Sichuan	39.14%	48.21%	57.33%	57.28%	63.20%
23	Guizhou	25.53%	29.10%	32.58%	50.30%	45.90%
24	Yunnan	36.72%	44.76%	49.78%	55.75%	64.30%
25	Chongqing	None	39.02%	52.29%	53.38%	56.00%
26	Shanxi	33.60%	41.48%	50.33%	56.02%	58.40%
27	Gansu	38.87%	42.90%	57.06%	57.28%	65.60%
28	Qinghai	None	42.61%	38.65%	54.97%	48.20%
29	Ningxia	39.76%	37.69%	55.16%	54.77%	61.60%
30	Xinjiang	26.50%	43.79%	39.37%	47.90%	39.80%
The whole nation		**35.93%**	**41.54%**	**48.71%**	**57.35%**	**57.09%**

and 2014, respectively, with all indexes having a $P < 0.05$. The average Moran's I index was 0.244295. Because the difference in autocorrelation within the regional range was statistically significant, there was a positive spatial correlation regarding the prevalence of myopia in China (Table 3).

TABLE 3 Global spatial autocorrelation analysis results for myopia prevalence in China from 1995 to 2014.

Year	Moran's *I* index	*Z* score	*P*-value
1995	0.101352	1.685217	0.091947
2000	0.255234	3.375541	0.000737
2005	0.140538	2.044891	0.040866
2010	0.169005	2.401253	0.016339
2014	0.087811	1.424233	0.154379
Average	0.244295	3.276747	0.001050

Local spatial autocorrelation analysis

The local Moran's I autocorrelation analysis shows that there was a spatial aggregation regarding the prevalence of myopia among students nationwide (Figure 2). Shandong, Jiangsu, Anhui, and Shanghai were classified as high–high aggregation areas, while Hainan and Guangxi were classified as low–low aggregation areas.

Global and local hotspot analysis

Our Getis-Ord General G results for the global hotspot analysis showed that the general G index for the prevalence of

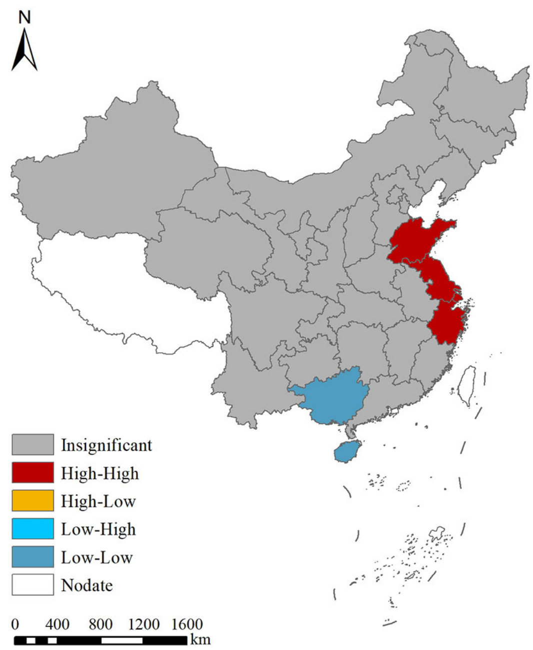

FIGURE 2
Local spatial autocorrelation analysis for the prevalence of myopia in China from 1995 to 2014.

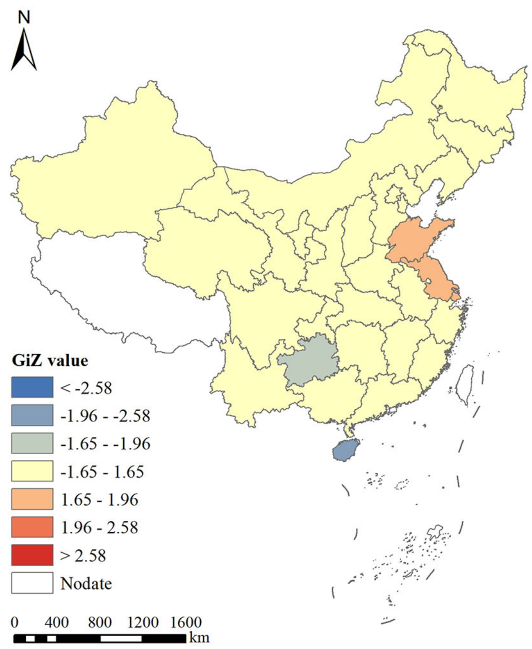

FIGURE 3
Hotspot analysis of average annual myopia prevalence in China from 1995 to 2014.

myopia was 0.035020, while the Z and P-values were 1.795897 and 0.072511, respectively. These data demonstrated a lack of statistical significance in the correlation of the prevalence of myopia within the region, as well as a lack of either "positive" or "negative" hot spots. In addition, the local hotspot analysis showed that Shandong and Jiangsu belong to a high-value aggregation area, while Hainan and Guizhou belong to a low-value aggregation area (Figure 3).

Spatio-temporal scanning analysis

Following the temporal and spatial scanning analysis of myopia prevalence, we realized a total of 15 aggregation areas in five stages, with obvious changes in the aggregation areas. From 1995 to 2000, the first-level gathering area was largest in 2000 and involved only Qinghai, while the second-level aggregation area was in Chongqing. The third aggregation area was mainly distributed in North and Northeast China. From 2000 to 2005, Fujian or Xinjiang and Qinghai became the first and the second aggregation areas, respectively. From 2005 to 2010, the aggregation area was mainly concentrated in Fujian. From 2010 to 2014, the first and the second aggregation areas were Tianjin and Zhejiang, while the third aggregation area included Shanxi and Hebei. On the contrary, from 1995 to 2014, the aggregation areas saw an overall shift from the northern regions to the southeast regions (Figure 4 and Table 4).

Discussion

The eye health of adolescents is an important aspect of national health. Adolescent myopia not only creates inconvenience in terms of one's personal life and studies but also increases the burden on society and one's family. Therefore, myopia is a major public health and social issue affecting people's livelihoods (29–34). The age between 7 and 18 years is critical for eye development; thus, it represents an important phase in which to protect and prevent the development of poor eyesight. Whereas myopia is a serious public health problem all over the world, the geographical vastness of China increases the complexity of myopic students in China (35–38).

An accurate characterization of the spatial distribution defines the myopia distribution dynamics and influencing factors and thus might inform effective prevention and control measures (27, 28). In this study, we used the spatial analysis technology of GIS to interrogate the spatial and temporal distribution of the prevalence of myopia among students in various provinces, as well as explore the hotspot regions. In the process of myopia prevention and control in

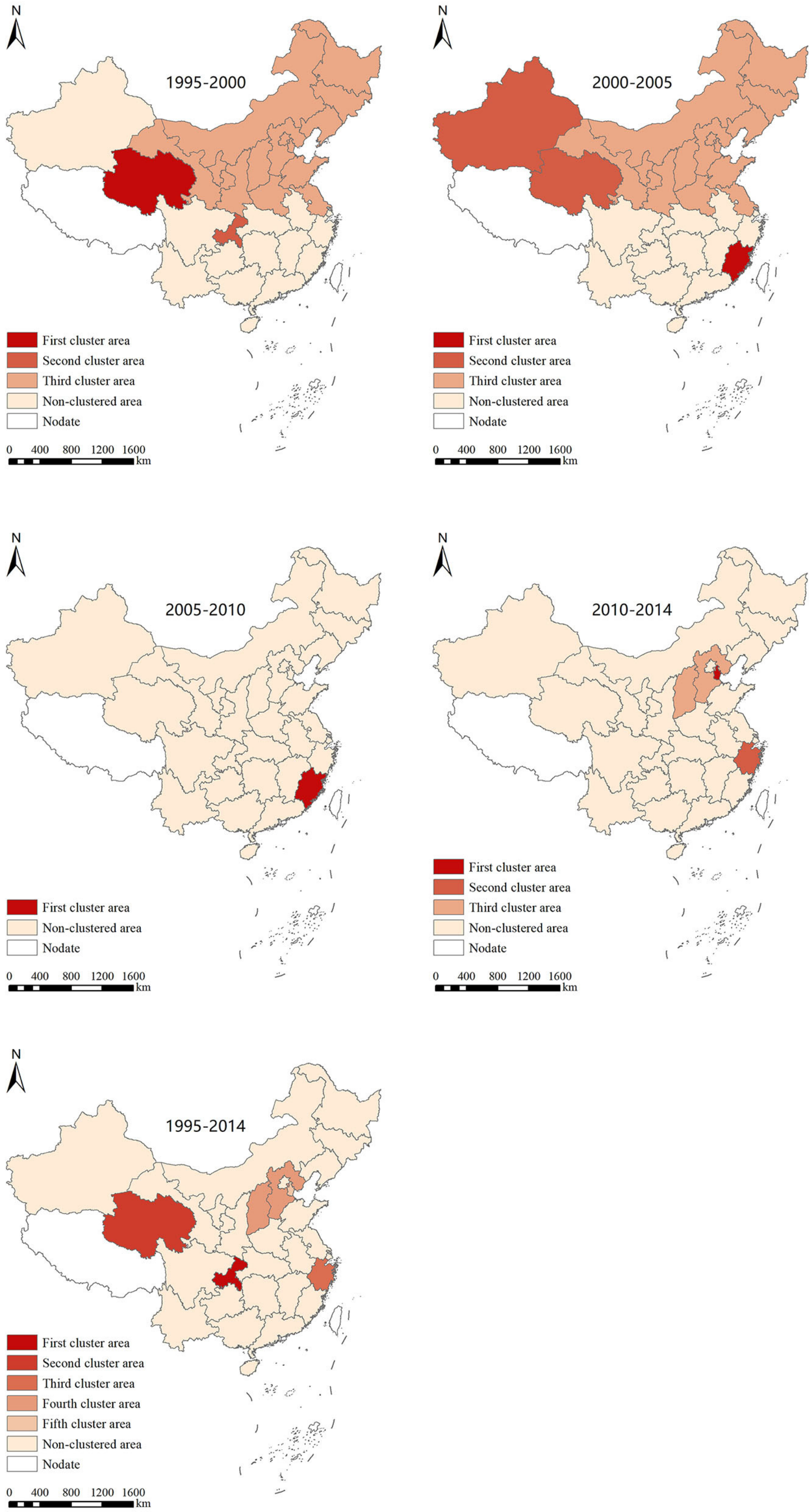

FIGURE 4
Spatial and temporal scanning aggregation area for the prevalence of myopia in Chinese students from 1995 to 2014.

TABLE 4 Temporal and spatial scanning aggregation analysis of myopia prevalence in China from 1995 to 2014.

Time phase	Aggregation area	Province and municipality	Aggregation time	RR value	LLR value	*P*-value
1995–2000	1	Qinghai	2000	1.81	6.38	0.000
	2	Chongqing	2000	1.81	5.78	0.000
	3	Heilongjiang, Inner Mongolia, Jilin, Gansu, Beijing, Shanxi, Shanxi, Ningxia, Henan, Hebei, Liaoning, Shandong, Tianjin, Jiangsu	1995	1.05	0.88	0.934
2000–2005	1	Fujian	2000	1.32	1.66	0.382
	2	Xinjiang, Qinghai	2000	1.15	0.87	0.916
	3	Heilongjiang, Inner Mongolia, Jilin, Gansu	2005	1.04	0.71	0.977
2005–2010	1	Fujian	2010	1.23	1.25	0.794
2010–2014	1	Tianjin	2014	1.23	1.29	0.725
	2	Zhejiang	2010	1.20	1.20	0.783
	3	Shanxi, Hebei	2010	1.13	1.00	0.913
1995–2014	1	Chongqing	2014	1.59	5.26	0.001
	2	Qinghai	2014	1.59	4.49	0.004
	3	Zhejiang	2010	1.42	2.91	0.059
	4	Shanxi, Hebei	2010	1.29	2.72	0.080
	5	Tianjin	2014	1.17	0.75	0.980

our country, time, space, and social factors are all crucial. Therefore, the distribution of the students' prevalence of myopia shows a certain degree of spatial heterogeneity in different areas (39–41). This study analyzed the temporal and spatial characteristics of the prevalence of myopia among students in China from 1995 to 2014 at the provincial level. The spatial distribution analysis showed that the prevalence of myopia among Chinese students was gradually increasing. The average prevalence of myopia from 1995 to 2014 was divided into five grades. Hainan, Guizhou, Xinjiang, and Guangxi had the lowest myopia prevalence, while Jiangsu, Shandong, Shanghai, Zhejiang, and Shanxi had the highest myopia prevalence. One potential explanation is that, given that Shandong and Jiangsu are located in the economically developed areas in eastern China, the rapid economic development and continuous improvement of education levels in the eastern coastal areas have led to high academic pressure on students, less time outdoors, and longer close-work hours (42, 43). A study (44) conducted in Anyang, China, by Wei et al. found that more time outdoors, close-work time, and time spent sleeping were associated with myopia in children.

However, our study used data only on visual acuity, and non-cycloplegic refractive errors have been shown to be problematic in epidemiological studies of myopia (45). Therefore, the results of this study may be biased. In addition, visual acuity was not adjusted for confounding factors, and we should improve on this aspect of the work in the next step.

From 1995 to 2014, there was no spatial positive correlation for the prevalence of myopia in students aged between 7 and 18 years. The local Moran's *I* autocorrelation analysis showed that there was a spatial aggregation of the students' myopia prevalence, with Shandong, Jiangsu, Anhui, and Shanghai being high–high aggregation areas and Hainan and Guangxi being low–low aggregation areas. On the contrary, the global hotspot analysis showed that there was no correlation difference regarding the students' myopia prevalence, with no "positive" or "negative" hotspot regions. The local hotspot analysis showed that Shandong and Jiangsu belonged to the high-value aggregation area, while Hainan and Guizhou belonged to the low-value aggregation area. This was related to the pressure of entering high school, heavy academic burden, and long reading times in Shandong and Jiangsu, while Hainan's low-value aggregation was related to its good living environment, broad vision on the part of students, backward local culture and economy, limited television watching time, small schoolwork burden, and sufficient extracurricular activities (46–48).

Because the spatial autocorrelation analysis could not determine the size and scope of aggregation, we employed the spatial-temporal scanning analysis. A total of 15 aggregation areas were found in the five stages. However, there was a shift in the aggregation area from the northwest, north, and northeast to the southeast. The unpublished data from our research group showed that the prevalence of myopia in children and adolescents in the eastern coastal areas showed a double-high trend, that is, a high prevalence of myopia and a high prevalence of high myopia. One potential explanation is that, as compared with the northwest region, the economic development speed of the southeast coastal area is fast, and the educational level is constantly improving, which leads to increased academic pressure on students. The gap between the southeast coastal region and the northwest region is increasing year by year, which leads to the gathering area gradually shifting to the southeast. In addition, as compared with the northwest region, the southeast coastal areas, with their developed economy and suitable environment, may attract more highly educated talents, and the prevalence of myopia in the next generation may be higher, which will also lead to a shift in the gathering area to the southeast coast (49, 50). It is suggested that we should focus on the occurrence and development of myopia in children and adolescents in the southeast coast and undertake timely intervention measures to protect children's and adolescents' eye health.

The occurrence and development of myopia are diverse and complex, with changes across time and space, as well as across age groups and learning stages. At present, the research on the prevention and control of myopia mainly focuses on two aspects. One aspect is the basic and clinical research; specifically, the effectiveness of atropine in the prevention and control of myopia has been preliminarily recognized (51). In addition, the orthokeratology lens has also been proven to be a safe, effective, and reversible intervention measure to halt myopia progress (52). Another aspect is myopia Big data research. The mechanism behind myopia remains unclear, and it is very important to clarify the process of children's refractive development and thus prevent and control myopia. The hyperopic reserve is considered an important indicator of the occurrence and development of myopia (53). However, the lack of data on the hyperopic reserve is a limitation of this study, and we will explore this issue in the next step.

Although there are many studies on the prevention and control of myopia, the current prevention effect is not significant. The most important issue for public health policies is the decrease in the academic load that has been established with the limitation of tutorial classes and a potential increase in time spent outdoors, which is very limited in those environments studied in this work (54). Therefore, it is urgent to build a diversified and interconnected myopia prevention and control network and thus create a mass myopia prevention and control mechanism for student-family-school-medical institutions. The whole society should work together to maintain the eye health of its children and adolescents.

Limitations

However, this study also has several limitations. First, our data come from a research report on Chinese students' physique and health, but due to national policies, the report was only updated until 2014, and the eye health data for primary and secondary school students from 2015 to 2019 could not be obtained, which means our research results include a certain amount of lag. Second, although we identified established physical fitness screening systems for primary and secondary school students in China, most provinces did not publish their data collection procedures. As a result of this, the accuracy of the data obtained from these cannot be verified. Finally, there may be other factors that influenced the findings that were not taken into account.

Conclusion

In conclusion, from 1995 to 2014, the prevalence of myopia in China shows an increasing trend over the years. The average annual myopia prevalence of each province (autonomous regions and municipality) is randomly distributed and has a certain spatial aggregation. The aggregation areas, based on phased spatio-temporal scanning, are increasing gradually and shifting from the northwest, north, and northeast to the southeast, where high-risk areas regarding myopia continue to exist. It is, therefore, necessary to focus on these areas and undertake targeted prevention and control measures.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

XS and ZGa carried out the procedure including the literature search, data extraction, statistical analysis, and manuscript writing. LL conceived the study and revised the manuscript. ZGu participated in the method development and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Hopf S, Pfeiffe N. Epidemiology of myopia. *Ophthalmologe.* (2017) 114:20–3. doi: 10.1007/s00347-016-0361-2

2. Repka MX. Prevention of myopia in children. *JAMA.* (2015) 314:1137–9. doi: 10.1001/jama.2015.10723

3. Schuster AK, Elflein HM, Pokora R, Urschitz MS. Prevalence and risk factors of myopia inchildren and adolescents in Germany Results of the KiGGS Survey. *Klin Padiatr*. (2017) 229:234–40. doi: 10.1055/s-0043-102938

4. Chen S. *The Overall Myopia Rate of Children and Adolescents in China is 52.7% in 2020*. Beijing: China Women's Daily (2021).

5. Liang J, Chen Y, Zhao Y, Kakaer A, Jiang N, Huang S, et al. Prevalence of visual impairment among students before and during the COVID-19 pandemic, findings from 1,057,061 individuals in Guangzhou, Southern China. *Front Pediatr*. (2021) 9:813856. doi: 10.3389/fped.2021.813856

6. Chu M, Zhao Y, Wu Z, Ni H, Yu Y. Current situation of orthokeratology in myopia control. *Chin J Optom Ophthalmol Vis Sci.* (2021) 23:791–5. doi: 10.3760/cma.j.cn115909-20210214-00059

7. Smith TST, Frick KD, Holden BA, Fricke TR, Naidoo KS. Potential lost productivity resulting from the global burden of uncorrected refractive error. *Bull World Health Organ.* (2009) 87:431–7. doi: 10.2471/BLT.08.055673

8. World Health Organization. "*Meeting on Developing Myopia Control Strategies, Singapore, 13-14 November 2018: meeting report*." Geneva: WHO (2018).

9. He M, Mathenge W, Lewallen S, Courtright P. Global efforts to generate evidence for Vision 2020. *Ophthalmic Epidemiol.* (2015) 22:237–8. doi: 10.3109/09286586.2015.1058958

10. Morgan IG, French AN, Ashby RS, Guo X, Ding X, He M. et al. The epidemics of myopia: aetiology and prevention. *Prog Retin Eye Res.* (2018) 62:134–49. doi: 10.1016/j.preteyeres.2017.09.004

11. Leng L, Zhang J, Xie S, Ding W, Ji R, Tian Y, et al. Effect of sunshine duration on myopia in primary school students from Northern and Southern China. *Int J Gen Med.* (2021) 14:4913. doi: 10.2147/IJGM.S328281

12. Hasker E, Assoumani Y, Mzembaba A, Zakir AM, Ortuno-Gutierrez N, Jong BC. Using a geographic information system as a management tool for tuberculosis control. *Int J Tuberc Lung Dis.* (2020) 24:354–6. doi: 10.5588/ijtld.19.0704

13. Fletcher-Lartey SM, Caprarelli G. Application of GIS technology in public health: successes and challenges. *Parasitology.* (2016) 143:401–15. doi: 10.1017/S0031182015001869

14. Qianqian M, Zhang J, Yang T. Application of GIS in modern medicine. *Pract Preven Med.* (2017) 24:892–6.

15. Su X, Chen X. Applications and perspectives of GIS in public health and military guard. *Southwestern Def Med.* (2019) 29:506–7.

16. The Chinese Students' Physique and Health Research Group. *The Research Report on Chinese Students' Physique and Health in 1995*. Peking: Higher Education Press (1997).

17. The Chinese Students' Physique and Health Research Group. *The Research Report on Chinese Students' Physique and Health in 2000*. Peking: Higher Education Press (2002).

18. The Chinese Students' Physique and Health Research Group. *The Research Report on Chinese Students' Physique and Health in 2005*. Peking: Higher Education Press (2007).

19. The Chinese Students' Physique and Health Research Group. *The Research Report on Chinese Students' Physique and Health in 2010*. Peking: Higher Education Press (2012).

20. The Chinese Students' Physique and Health Research Group. *The Research Report on Chinese Students' Physique and Health in 2014*. Peking: Higher Education Press (2018).

21. Wang T, Huang PJ, Chen C, Liu DW Yi JL, A. comparison of visual acuity measured by ETDRS chart and Standard Logarithmic Visual Acuity chart among outpatients. *Int J Ophthalmol.* (2021) 14:536–40. doi: 10.18240/ijo.2021.04.09

22. Pfeiffer DU, Robinson TP, Stevenson M, Stevens KB, Rogers DJ, Clements AC. *Spatial analysis in Epidemiology*. Oxford: Oxford University Press (2008), p. 35–7. doi: 10.1093/acprof:oso/9780198509882.001.0001

23. Chen WM, Wang XM, Chen B, Chen S, Zhou L, Wang S, et al. Analysis on spatial distribution characteristics of multidrug-resistant tuberculosis patients in Zhejiang Province from 2010 to 2012. *Chin J Epidemiol.* (2016) 37:831–5. doi: 10.3760/cma.j.issn.0254-6450.2016.06.018

24. Sokal RR, Thomson BA. Population structure inferred by local spatial autocorrelation: an example from an Amerindian tribal population. *Am J Phys Anthropol.* (2006) 129:121–31. doi: 10.1002/ajpa.20250

25. Ord JK, Getis A. Testing for local spatial autocorrelation in the presence of global autocorrelation. *J Reg Sci.* (2001) 41:411–32. doi: 10.1111/0022-4146.00224

26. Zhang ZJ, Peng WX, Zhou YB, Chen GX, Jiang QW. Research on quantitative indicators of disease distribution based on spatial point pattern analysis. *Chin J Prev Med.* (2008) 42:422–6. doi: 10.3321/j.issn:0253-9624.2008.06.012

27. Liu K, Li XL, Shao ZJ. Spatial epidemiology plays an important role in disease prevention and control. *Chin J Epidemiol.* (2018) 39:1143–5. doi: 10.3760/cma.j.issn.0254-6450.2018.09.001

28. Banu S, Hu WB, Hurst C, Guo YM, Islam MZ, Tong SL. Space-time clusters of dengue fever in Bangladesh. *Trop Med Int Health.* (2012) 17:1086–91. doi: 10.1111/j.1365-3156.2012.03038.x

29. Tang SM, Kam KW, French AN, Yu M, Chen LJ, Young AL, et al. Independent influence of parental myopia on childhood myopia in a dose-related

manner in 2055 trios: the Hong Kong Children Eye Study. *Am J Ophthalmol.* (2020) 218:199–207. doi: 10.1016/j.ajo.2020.05.026

30. Shah RL, Huang Y, Guggenheim JA, Williams C. Time outdoors at specific ages during early childhood and the risk of incident myopia. *Invest Ophthalmol Vis Sci.* (2017) 58:1158–66. doi: 10.1167/iovs.16-20894

31. Chang L, Pan CW, Ohno-Matsui K, Lin XY, Cheung GC, Gazzard G, et al. Myopia-related fundus changes in Singapore adults with high myopia. *Am J Ophthalmol*. (2013) 155:991–9.e1. doi: 10.1016/j.ajo.2013.01.016

32. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt*. (2005) 25:381–91. doi: 10.1111/j.1475-1313.2005.00298.x

33. Cho BJ, Shin JY Yu HG. Complications of pathologic myopia. *Eye Contact Lens.* (2016) 42:9–15. doi: 10.1097/ICL.0000000000000223

34. Saw SM, Chua WH, Hong CY, Wu HM, Tan D. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* (2002) 43:1408–13.

35. Lopes MC, Andrew T, Carbonaro F, Spector TD, Hammond CJ. Estimating heritability and shared environmental effects for refractive error in twin and family studies. *Invest Ophthalmol Vis Sci.* (2009) 50:126–31. doi: 10.1167/iovs.08-2385

36. Park DJ, Congdon NG. Evidence for an "epidemic" of myopia. *Ann Acad Med Singapore.* (2004) 33:21–6.

37. Chong TD, Fang SY, Huang N, Chih-Chien H, Chen SY, Wen-Hsiang CA, et al. Myopia development among young school children: the Myopia Investigation Study in Taipei. *Invest Ophthalmol Vis Sci.* (2016) 57:6852–60. doi: 10.1167/iovs.16-20288

38. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA*. (2015) 314:1142–8. doi: 10.1001/jama.2015.10803

39. Czepita M, Kuprjanowicz L, Safranow K, Mojsa A, Majdanik E, Ustianowska M, et al. Dose the month of birth influence the prevalence of refractive errors? *Pomeranian J Life Sci.* (2015) 61:143–5. doi: 10.21164/pomjlifesci.68

40. Mandel Y, Grotto I, EI-Yaniv R, Belkin M, Israeli E, Polat U, et al. Season of birth, natural light, and myopia. *Ophthalmology.* (2008) 115:686–92. doi: 10.1016/j.ophtha.2007.05.040

41. Mcmahon G, Zayats T, Chen YP, Prashar A, Williams C, Guggenheim JA. Season of birth, daylight hours of birth, and high myopia. *Ophthalmology.* (2009) 116:468–73. doi: 10.1016/j.ophtha.2008.10.004

42. Xu L, Zhuang Y, Zhang G, Ma Y, Yuan J, Tu C, et al. Design, methodology, and baseline of whole city-million scale children and adolescents myopia survey (CAMS) in Wenzhou, China. *Eye Vis.* (2021) 8:1–14. doi: 10.1186/s40662-021-00255-1

43. Wu JF Bi HS, Wang SM, Hu YY, Wu H, Sun W, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. *PLoS ONE.* (2013) 8:e82763. doi: 10.1371/journal.pone.0082763

44. Wei SF, Li SM, Liu L, Li H, Kang MT, Sun YY, et al. Sleep duration, bedtime, and myopia progression in a 4-year follow-up of Chinese children: the Anyang Childhood Eye Study. *Investig Ophthalmol Vis Sci*. (2020) 61.3:37. doi: 10.1167/iovs.61.3.37

45. Ilechie AA, Addo NA, Abraham CH, Owusu-Ansah A. Annan-Prah Alex. Accuracy of noncycloplegic refraction for detecting refractive errors in school-aged African children. *Optom Vis Sci.* (2021) 98:920–8. doi: 10.1097/OPX.0000000000001742

46. Fujimoto M, Hangai M, Suda K, Yoshimura N. Features associated with foveal retinal detachment in myopic macular retinoschisis. *Am J Ophthalmol.* (2010) 150:863–70. doi: 10.1016/j.ajo.2010.06.023

47. Morris TT, Guggenheim JA, Northstone K, Williams C. Geographical variation in likely myopia and environmental risk factors: a multilevel cross classified analysis of a UK cohort. *Ophthalmic Epidemiol.* (2020) 27:5–7. doi: 10.1080/09286586.2019.1659979

48. Deng L, Gwiazda J, Thorn F. Children' refractions and visual activities in the school year and summer. *Optom Vis Sci*. (2010) 87:406–13. doi: 10.1097/OPX.0b013e3181da8a85

49. Dong YH, Liu HB, Wang ZM, Xu RB, Yang ZH, Ma J. Epidemiological status and change trend of myopia among children and adolescents aged 7-18 in China from 2005 to 2014. *Chin J Prev Med.* (2017) 51:285–9. doi: 10.3760/cma.j.issn.0253-9624.2017.04.002

50. Schneider J, Leeder SR, Gopinath B, Wang JJ, Mitchell P. Frequency, course, and impact of correctable visual impairment (uncorrected refractive error). *Surv Ophthalmol.* (2010) 55:539–60. doi: 10.1016/j.survophthal.2010.02.004

51. Polling JR, Kok RG, Tideman JW, Meskat B, Klaver CC. Effectiveness study of atropine for progressive myopia in Europeans. *Eye.* (2016) 30:998–1004. doi: 10.1038/eye.2016.78

52. Na M, Yoo A. The effect of orthokeratology on axial length elongation in children with myopia: contralateral comparison study. *Jpn J Ophthalmol*. (2018) 62:327–34. doi: 10.1007/s10384-018-0573-x

53. Li SM, Kang MT, Li L, Wei SF, He X, Liu LR, et al. Cohort study on the association between hyperopia reserve and myopia incidence in primary school students: The anyang childhood eye study. *Chin J Ophthalmol.* (2022) 58:1–2. doi: 10.3760/cma.j.cn112142-20211028-00509

54. Morgan IG, Jan CL. China turns to school reform to control the myopia epidemic: a narrative review. *Asia Pac J Ophthalmol.* (2022) 11:27–35. doi: 10.1097/APO.0000000000000489

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