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Refractive errors: Public health challenges and interventions

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Published in
Frontiers in Public Health
Frontiers in Medicine
Frontiers in Pediatrics

ISSN 1664-8714
ISBN 978-2-8325-3721-3
DOI 10.3389/978-2-8325-3721-3

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Refractive errors: Public health challenges and interventions

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Citation
Lanca, C., Grzybowski, A., Pang, C. P., eds. (2023). *Refractive errors: Public health challenges and interventions*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-3721-3

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Frontiers | Frontiers in Public Health

TYPE Editorial
PUBLISHED 02 October 2023
DOI 10.3389/fpubh.2023.1289173

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 05 September 2023
ACCEPTED 19 September 2023
PUBLISHED 02 October 2023

CITATION
Lanca C, Pang CP and Grzybowski A (2023) Editorial: Refractive errors: public health challenges and interventions.
Front. Public Health 11:1289173.
doi: 10.3389/fpubh.2023.1289173

Editorial: Refractive errors: public health challenges and interventions

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KEYWORDS

myopia, public health, refractive errors, prevention, health promotion

Editorial on the Research Topic
Refractive errors: public health challenges and interventions

Uncorrected refractive errors are a leading cause of visual impairment and blindness across many countries. Refractive errors that are not corrected during the critical period of visual system development may lead to serious conditions, such as amblyopia. The largest burden of refractive error is myopia which significantly increases the risk of blinding conditions such as myopic macular degeneration, glaucoma, and cataract. Previous studies show that vision impairment in children is associated with symptoms of depression and anxiety, and children with myopia revealed higher scores of depression compared with children having normal vision (1). Substantial impact in the economic health of individuals as well as decreased educational and employment opportunities have been associated with visual impairment and blindness in adults (2, 3). Decreased quality of life, increased risk of falls and increased risk of death have also been associated with visual impairment and blindness in older adults (4–7). Additionally, visual impairment may coexist with other health conditions, amplifying the impact of comorbidities, thereby increasing the disability risk (8). In the past few years, epidemiological research has shown that uncorrected refractive errors are a major public health issue in many parts of the world. However, more research is needed to determine the full extent of the threat posed by refractive errors, to establish effective interventions and to consolidate prevention efforts.

This Research Topic comprises 28 studies including original research articles and reviews on refractive errors, such as research trends and prevalence, risk factors, retinal biomarkers, treatment, and health promotion.

Research trends and prevalence

Yang et al. described the global trends of research on pathologic myopia using a bibliometric analysis, showing that countries such as China, USA, and Japan have the greatest influence. Several studies on the prevalence of refractive errors show the burden on urban Asia regions. For example, Wang Y. et al. concluded that urban settings are more affected by myopia and anisometropia compared to rural areas in Dalian, China. Many studies reported increases in myopia prevalence during the COVID-19 lockdowns and research is moving to identify if those trends persisted after the pandemic. In Xuzhou, China, Zhou et al. concluded that the prevalence of myopia increased during the COVID-19 epidemic. The trends of myopia development remained stable in the post-COVID-19 epidemic period in younger children but increased for older children. In Chengdu, China, Pan et al. found significant increases on myopia and axial length (AL) that remained 1 year after the lockdown. Interestingly, there are regional differences in the prevalence of refractive errors in China. Wang W. et al. reported that the prevalence of refractive errors in children and adolescents was lower in Tibet than in Chongqing during the COVID-19 pandemic, probably due to higher outdoor time and lower time of use of digital devices in Tibet. The prevalence of myopia also varies with age. You et al. found a lower prevalence of myopia in preschool children younger than 5 years old. Myopia slightly increased from 5 to 6 years of age, which may indicate an early sign of myopia in school-age children in the Changsha children eye study. Several risk factors have been associated with myopia, and educational pressure seems to be a consistent factor across studies, namely the number of years of education and possibly the type of educational activities. The study by Liu et al. confirmed that the prevalence of myopia increased in students aged between 15 and 18 years in China from standard high schools, remaining stable among students from vocational schools where there were less academic work and more physical activities in the curriculum.

Myopia diagnosis can be challenging, mainly due to inaccuracy of measures without cycloplegia. Can myopia be accurately measured without the side effects caused by cycloplegics? Big data acquisition and machine learning technique have been utilized for prediction of spherical equivalent (SE) in school-age children. Du B. et al. found that the difference before and after cycloplegia can be effectively predicted in school-age children, providing evidence for the usefulness of machine learning in epidemiological studies of myopia in large populations.

Another refractive error that needs attention is anisometropia particularly due to its association with amblyopia. Xu et al. found a prevalence of 13% in Chinese children aged 4–17 years, which was associated with several risk factors, namely indoor near work time and outdoor activity time. According to Wu Z. et al. the prevalence of total astigmatism (28%) increased with age and astigmatism correction was effective, improving visual quality. Correction of refractive errors is indeed of paramount relevance. Latif et al. observed a significant impact in the average academic scores of Pakistanis high school children in Lahore after refractive corrections.

Risk factors

For the past few years several research studies connected sleep with myopia. Nevertheless, significant gaps in knowledge still exist. Although Huang et al. found an association between sleep and myopia during the COVID-19 pandemic in Chinese children, the association was not significant after adjusting for other risks factors. Other environmental factors may also be associated with myopia. For example, Li et al. found that sedentary time was strongly related to the prevalence of poor vision among Chinese children and adolescents. On the other hand, Du W. et al. found associations between anthropometric parameters and refractive error in school-age children during the post-COVID-19 pandemic. These three studies show the need for further research on environmental factors to develop effective interventions to prevent myopia and to predict myopia risk and myopia progression at early stages.

Retinal biomarkers

The search for retinal biomarkers related to refractive errors is increasing. Hui et al. assessed choroidal vascularity and choriocapillaris blood perfusion in Chinese children with anisometropic hyperopic amblyopia. They found that subfoveal and peripapillary choroidal thickness was higher in amblyopic children and correlated with shorter AL and higher SE, affecting choroidal structure and vascular density. The authors concluded that choroidal blood flow may be decreased in amblyopic eyes. Similarly, Zhu et al. found higher subfoveal choroidal thickness in high hyperopic eyes that correlated with shorter AL and higher SE, indicating decreased choroidal blood flow in amblyopic eyes. Structural changes in the retina may lead to functional changes and proper diagnosis is necessary to avoid delaying care. Chan et al. described the role of myopic titled disc and its implications on patient's quality of life and cost of treatment. The authors concluded that strategies to overcome examination errors should also be thoroughly explored.

Treatment

New publications on the control of myopia progression continue to emerge each year. In the past few years such new information had profound effects on ophthalmology practice. Nowadays treating myopia progression is of paramount importance. Children that progress about half a dioptre per year until their teenage years are at great risk of developing high myopia and potential blinding conditions, such as macular myopic maculopathy. In a systematic review on the cost-effectiveness analysis of myopia management Agyekum et al. concluded that 0.01% atropine and corneal refractive surgery were cost-effective in the treatment of myopia. More importantly, the results of the study show that prevention of myopia progression is more cost-effective than treating pathologic myopia.

Machine learning (ML) is rapidly evolving, allowing for more accurate prediction of treatment effects. Fang et al. developed a ML-assisted model to assist eye care professionals in the management and prediction of the effect of orthokeratology.

The choice of atropine concentration has been the subject of intensive discussions over the past few years. Recent studies concluded that atropine 0.01% is not as effective as 0.05% in Asian children. According to Lanca et al. low-dose atropine 0.01% was not effective in reducing AL progression in two studies. However, treatment efficacy with low-dose atropine of 0.05% showed good efficacy. Nevertheless, studies published in this Research Topic, still find that atropine 0.01% is effective. For example, Yu et al.

found that children, aged 6–13 years from Shanghai, treated with 0.01% atropine had less myopia progression during the lockdown compared with children that discontinued the treatment. However, the authors also found that the effect of atropine can be strengthened with defocus incorporated multiple segments lenses (DIMS) lenses. Wang M. et al. concluded that 0.02% and 0.01% atropine are effective in the control of myopia progression, mainly by reducing AL elongation, with no clinical effects on corneal and lens power, ocular and corneal astigmatism, anterior chamber depth or intraocular pressure compared to the control group.

Myopes have a higher risk of developing cataracts and cataract management in highly myopic eyes can be challenging. The review by Du Y. et al. described those challenges advocating for a prudent choice of the formula to calculate the intraocular lens (IOL) power. Additionally, the authors called for consideration of the necessary clinical parameters for selection of the correct IOL to achieve the best possible surgery outcomes.

Sub-Tenon's bupivacaine injection is a widely used local anesthesia technique for strabismus surgery. However, published research regarding effectiveness is not consistent. Weijuan et al. found that sub-Tenon's bupivacaine injection relieved postoperative pain, reducing the incidence of oculocardiac reflex and vomiting. In addition, the injection reduced the use of supplementary drugs in the management of strabismus surgery.

Health promotion

Interventions to prevent myopia are essential to curb the myopia epidemic. Jiang et al. found that the combination of the health belief model and the theory of planned behavior improved parents' intentions to prevent myopia in preschool children. Wearing appropriate correction is essential for most refractive errors to avoid visual impairment. Wu L. et al. showed that providing free spectacles along with educational interventions can lead to higher compliance. According to Kodjebacheva et al. several issues remain in the promotion of the use of eyeglasses based on a study on Romani families in Bulgaria. Although the study subjects needed eyeglasses, they did not have any at pre-test of the intervention. Further interventions need to consider how to educate individuals on the importance of eye examinations. Thereby, increasing the adherence to eye examinations and use of eyeglasses may be advocated. Social media should also have an important role in health promotion educating adolescents regarding myopia. However, caution is necessary as Ming et al. found that content was of moderate-to-poor reliability and with variable quality on TikTok. Nevertheless, online videos may serve as an additional source of information if providers can ensure reliable content.

We hope that the scientific research findings in this Research Topic help scientists to find new hypotheses, thereby accelerating further innovation in refractive error's management. More importantly, the newly generated evidence combined with known evidence from reported studies may assist in the development of health and education policies to improve the health of patients with refractive errors.

Author contributions

CL: Writing—original draft. CP: Writing—review and editing. AG: Writing—review and editing.

Acknowledgments

The guest editors would like to acknowledge the contributions of all authors and reviewers that made the publication of this Research Topic possible.

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ORIGINAL RESEARCH
published: 06 May 2022
doi: 10.3389/fpubh.2022.869294

Impact of Refractive Errors on the Academic Performance of High School Children of Lahore

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Introduction: The process of learning begins in childhood and accurate vision can greatly affects a child's learning capacity. It is documented that visual impairment in children can have a significant impact on their performance at school as well as their social interaction and development.

Objective: This research aimed to study the impact of refractive corrections on the academic performance of high school children in Lahore.

Methodology: A total of 2,000 students with equal distribution of gender, public, private school, and locality were included in the study. All students were screened for defective vision. The academic performance before and after corrections was recorded on the prescribed proforma.

Results: The prevalence of refractive error was high among the public high schools 244 (59.2%) as compared to the private schools 168 (40.8%). The area-based prevalence was higher among the students in urban settings 255 (62%) while in rural it was 157 (38%). It was found that in the public sector, the average score of academic results before the intervention was 56.39 ± 13.24 which was increased to 60.27 ± 14.94 after the intervention while in the private sector, before the intervention, the average score was 63.53 ± 17.50 which was improved to 67.12 ± 18.48. It was found to be statistically significant at p-value < 0.05.

Conclusion: A significant impact was observed in the average academic scores of the results after refractive corrections.

Keywords: prevalence, refractive error, refractive corrections, school children, academic score

OPEN ACCESS

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Specialty section:
This article was submitted to Public Health Education and Promotion, a section of the journal Frontiers in Public Health

Received: *04 February 2022*
Accepted: *01 April 2022*
Published: *06 May 2022*

Citation:
Latif MZ, Hussain I, Afzal S, Naveed MA, Nizami R, Shakil M, Akhtar AM, Hussain S and Gilani SA (2022) Impact of Refractive Errors on the Academic Performance of High School Children of Lahore. Front. Public Health 10:869294. doi: 10.3389/fpubh.2022.869294

INTRODUCTION

Refractive errors are considered an important public health problem affecting people all over the world. These errors are classified into three types: myopia, hypermetropia, and astigmatism (1). Generally, the reports about the link between factors associated with education and refractive errors among the children of high school levels imposed major consequences on public health.

According to the estimates of the World Health Organization (WHO), 285 million people are visually impaired including 246 million having low vision and 39 million blind (2). Diverse community-based studies of uncorrected refractive errors (URE) in different countries conclude a prevalence of 22.3% in China, 17.3% in Singapore, 17.1% in Malaysia, 15.8% in Chile, 10.2% in Australia, 10.2% in Bangladesh, and 6% in the United States, respectively (3). However, in contrast to the above-mentioned prevalence, a school-based study among the students aged 5–16 years from Rawalpindi reported a prevalence of 3.35% (4). Research studies have also revealed that the most common reason for the visit to an ophthalmologist or eye care professional is related to refractive errors (5).

Refractive errors can have many issues including educational loss, economic issues, low productivity, and impaired quality of life (6). The available literature identifies that a significant number of Pakistani school children are suffering from refractive errors (7). A relevant study concluded that every 5th Pakistani high school student is having a visual disability in the form of refractive errors, which reflects a serious threat to the individual and societal academic achievements (8). A study conducted in Bengaluru, India, showed a prevalence of 10% whereas the prevalence found in different relevant studies from Pakistan was 19.8% in Lahore, 20.43% in Kohat, 17.24% in Southern Punjab, and 21.7% in Lahore, respectively (8–10). Another research among the students of a religious school (Madrassa) at Haripur showed a high prevalence of 41% in the refractive errors (11). Moreover, a significant impact of the visual acuity on the academic performance of school students has also been shown in a study from Nigeria (12). For instance, the occurrence of the refractive error in the educational system fluctuates according to the ethnicity and area. It is a serious matter to carry out an updated study on school-level Pakistani students to explore the association of the refractive errors with the academic performance.

Lahore is the second-largest city of Pakistan, provincial headquarter, and a historic cultural center of South Asia. The city is known as the educational capital of Pakistan and includes public and private education institutions of international standards. The public sector is governed by the provincial government with minor financial burdens on the learner while the private schools are led by organizations with variable fee structures. The reasonable socioeconomic status of the parents, availability of financial resources, and comparatively perceived better level of awareness regarding child health were the major reasons to include the private sector high school students along with the students of public sector high schools in this research.

This research aims to study the impact of refractive corrections on the academic performance of high school children in Lahore.

METHODS

Before the start of the study, ethical approval was granted by the Institutional Research Board of the University of Lahore vide letter reference number IRB-UOL-FAHS/00248A. The Helsinki Declaration (modified in 2013) was followed due to the inclusion of human subjects. Also, the permission of the district administration was obtained from the Education Department to recruit the children of the high schools. Written informed consent was obtained from each participant or guardian or teacher to execute the process.

Study Population

The study was carried out on 2,000 children in high schools in Lahore. The sample size was calculated by the Open Epi Tool kit (13). Multistage random sampling technique opted for the recruitment of the subjects. Out of the five tehsils (a local unit of administrative division) of Lahore, one tehsil was selected randomly followed by the random sampling of one union council (UC) from unban and one UC from the rural setting of the selected tehsil. Later, a list of the public and private boys' and girls' high schools was obtained and one school from each category was randomly selected as presented in **Figure 1**. Children of high school levels (from class 6th to class 10 th) with both genders (boys and girls), from the public, private sector, and rural, urban settings were included in the study. The children with ophthalmic infections, visual acuity <6/6, and coexisting organic defects were excluded from this study.

Data Collection Process

A structured questionnaire consisting of four sections was prepared for data collection. That was validated and pretested. The first component contained the basic information about the study subjects including the demographic profile, personal history, family history, and relevant medical history. The second part consisted of the questions regarding the educational status of the parents, learning activities of the participants after the school timing, and the academic performance of the study subjects. The third part of the questionnaire was developed to record the information about the ocular examination including visual acuity, pinhole examination, and refraction. The last part consisted of the final diagnosis and type of the refractive errors. The first two parts were filled by the trained research assistants whereas the third part was completed by the qualified optometrists and the last part of the questionnaire was filled by an ophthalmologist as shown in **Figure 2**.

Screening for Refractive Errors

After the collection of basic information and relevant history, visual acuity was measured by using the illuminated Snellen chart separately for each eye placed at a distance of 6 m from the study participant. The students having a visual acuity of <6/6 in either eye were examined again by putting the pinhole in front of each eye for any improvement on the Snellen chart. The improvement of visual acuity by pinhole represents the presence of refractive errors. The students having a visual acuity of <6/6 in either eye underwent the objective and subjective refraction using an auto refractometer, retinoscopy, and subjective refraction. The ophthalmologist had the final examination of the student with a handheld slit lamp to see any ocular disease for inclusion or exclusion of the study subject.

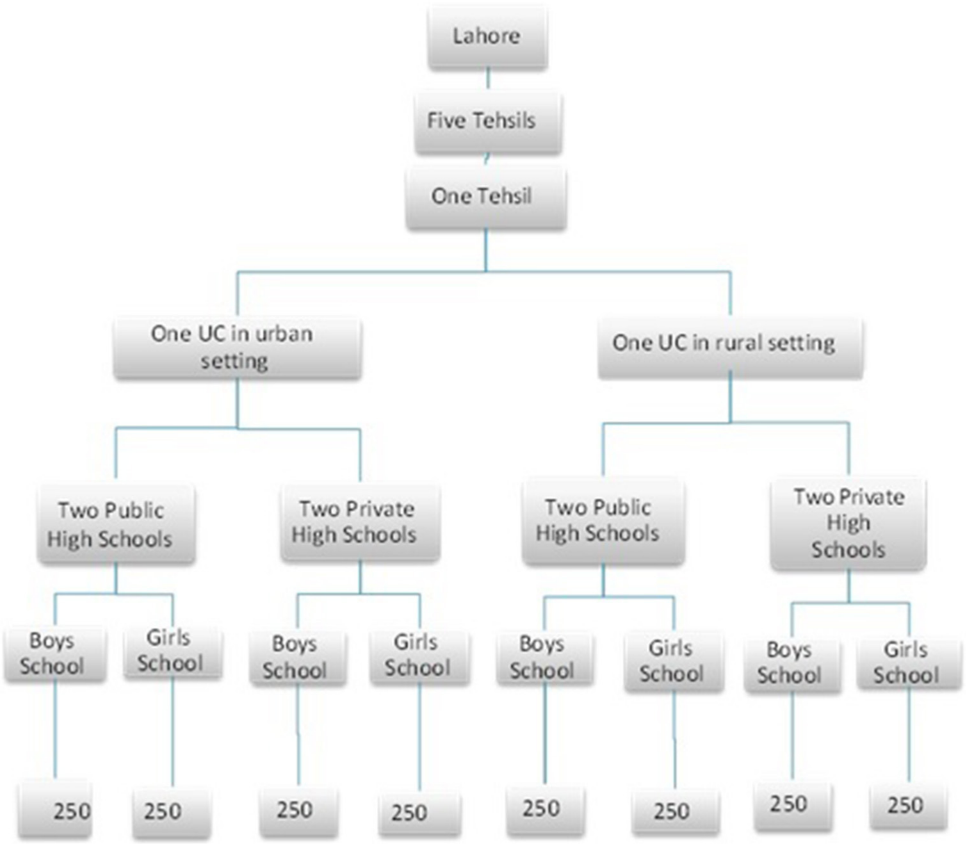

FIGURE 1 | Flow diagram showing the sampling of study subjects.

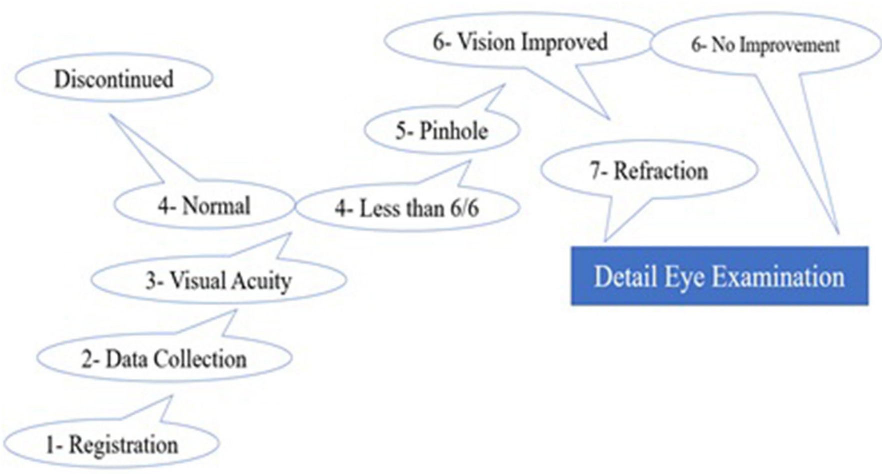

FIGURE 2 | Schematic diagram of the screening protocols for measurement of refractive errors at school.

Data Collection About Academic Performance

The data were recorded on the questionnaire along with the academic performance of the students. The academic scores after intervention were assessed based on the next upcoming annual exam. The examination system is based on subjective and objective patterns evaluated by external boards of examinations on an annual basis. The annual examination, percentage score was assessed as academic performance in this study.

Intervention

After 2–4 weeks, the researcher along with the professional team again visited the school and prepared spectacles of advised numbers that were distributed to the respective students. A training session for these students about the use of glasses was also conducted. The respective teachers were also trained to ensure the use of spectacles. Follow-up bi-monthly visits were also managed to ensure that students were wearing the spectacles.

Statistical Analysis

The data were entered into version 21 of SPSS (Statistical Package for Social Sciences) and analyzed using statistical tests. The means were calculated for numeric variables, that is, age, academic score, etc. Categorical variables, for example, gender, family history, ocular examination, and refraction type were presented in the form of frequency and percentages. The mean academic score was taken before and after the intervention. Relevant statistical tests including chi-square, independent samples test, and ANOVA were applied. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Out of the total 2,000 study participants, it was found that 412 (20.6%) were having refractive errors with 95% CI. The types of refractive errors were also investigated and myopia was found as the leading type 215 (52.2%) followed by astigmatism 136 (33%) and hypermetropia 61 (14.8%), respectively, among the 412 study participants having refractive errors. The prevalence was found higher among the public high schools 244 (59.2%) compared to private schools 168 (40.8%) while the area-based prevalence of refractive errors was found to be higher among the students of urban settings 255 (62%), while in rural, it was 157 (38%). These results were cross-tabulated and found statistically significant at a *p*-value < 0.01 regarding schools and localities and gender-based results.

With our methods, refractive errors were found prevalent among 412 (20.6%) out of the 2,000 study subjects. However, 159 (38.5%) of the participants having refractive errors were using corrected spectacles. They were excluded while 253 (61.5%) newly diagnosed candidates proceeded for intervention. The mean score of the results among the study participants before and after intervention were compared and are reported below.

Gender and area-based academic performance were compared and the results are presented in **Table 1**. There were no significant differences in the academic scores of urban vs. rural children, or between genders, before and after the intervention.

The public and private sector results were also compared and it was found that, among the public sector, the average score of results before intervention was 56.39 ± 13.24 which increased to 60.27 ± 14.94 after the intervention. The average score of public schools at different times of study was found statistically significant at *p*-value < 0.05. Among the private sector, the before intervention average score was 63.53 ± 17.50, while after the intervention, it was 67.12 ± 18.48. Differences between the average score of private schools at different times of the study were statistically significant (*p*-value < 0.05) as shown in **Table 1**.

TABLE 1 | Shows the gender, area, tuition, and refractive correction intervention effects on academics.

Gender-based comparison of the academic performance

	Gender	Mean	SD	*p*-value
Before intervention	Male (119)	57.54	16.48	0.220
	Female (134)	59.89	13.85	
After Intervention	Male (119)	63.88	15.98	0.204
	Female (134)	61.27	16.80	

Area-based comparison of academic performance

	Area	Mean	SD	*p*-value
Before Intervention	Rural	57.42	17.02	0.227
	Urban	59.76	13.66	
After Intervention	Rural	60.23	18.18	0.068
	Urban	64.04	15.00	

Comparison of results (Public and Private) before and after intervention

	Public	Private	*p*-value
Before Intervention	56.39 ± 13.24	63.53 ± 17.50	<0.001*
After Intervention	60.27 ± 14.94†‡	67.12 ± 18.48	<0.001*

Comparison of effect of tuition on academic performance

	Tuition	Public	Private
Before Intervention	Yes	57.05 ± 13.03	62.39 ± 16.28
	No	55.68 ± 13.45	65.82 ± 21.27
After Intervention	Yes	62.01 ± 14.17†	68.36 ± 17.06†
	No	58.90 ± 14.58†	66.44 ± 20.36†

***p-value significant at 0.05.*
†Difference from before intervention was statistically significant.
‡Statistically significant difference.

The mean score before the intervention was 57.05 ± 13.03 among the subjects of public schools with refractive errors who took tuition, while after the intervention, it was increased to 62.01 ± 14.17. Whereas, among students who did not take tuition, their mean score before the intervention was 55.68 ± 13.45 while after the intervention, it was improved to 58.90 ± 14.58. Among private school students, who took tuition, the mean score was 62.39 ± 16.28 before the intervention, while after the intervention, it was increased to 68.36 ± 17.06. Similarly, for students who did not take tuition, their mean score before intervention was 65.82 ± 21.27 which was increased to 66.44 ± 20.36, which was statistically significant as described in **Table 1**.

DISCUSSION

Refractive error has been discussed in the literature in detail. It is estimated that out of 2.3 billion people with refractive errors only 1.8 billion can have the access to affordable ophthalmic examination and their correction worldwide (14).

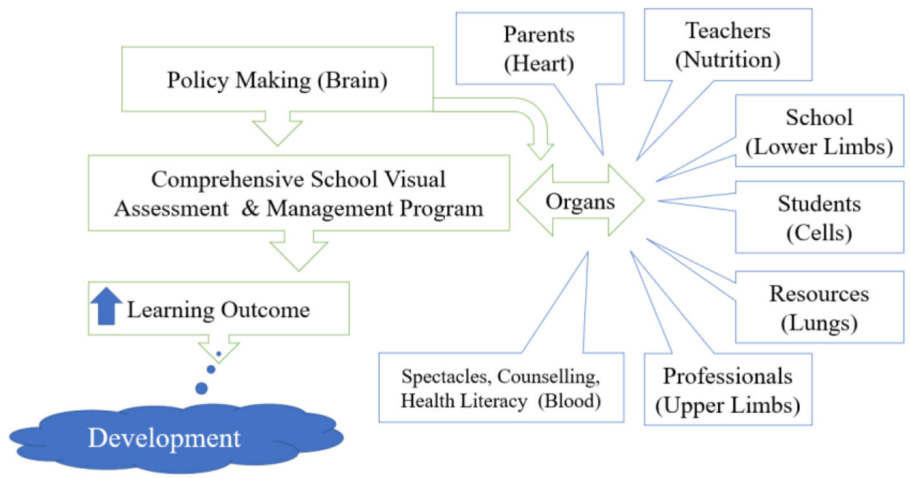

FIGURE 3 | Proposed model for the Comprehensive School Eye Care Program (CSECP).

So, accessibility and affordability are major problems but it is also worth mentioning that the management of these errors is considered among the most cost-effective interventions in health care (15).

The results of this study revealed that 20.6% of the study subjects were having refractive errors. Myopia was found as the leading type accounting for 52.2% of the refractive errors followed by astigmatism 33% and hypermetropia 14.8% among the 412 study participants having refractive errors. These findings are contradictory to the results of the previous studies in which the prevalence was 7% (16), 15.4% (17), 13.7% (18) 10.5% (19) 13.1% (20), and 11.6% (21), respectively. The results are similar regarding the type of refractive errors as myopia was the most common refractive error 61.9% (16) and 58.5% (19) in India. However, the findings of this study are comparable to a study of Muzaffarabad city in Azad Jammu and Kashmir concluding a prevalence of 19.6% (22) and 22% (23) in Saudi Arabia. However, the burden of the types of refractive errors revealed that the Libyan study is different from the findings of this study and conclude hyperopia 32.2% (23) and 53.2% (21) as the leading type. The prevalence of two similar studies in Ghana and Nepal concluded the 3.25 and 10.35% prevalence of refractive errors, respectively (21, 24). The low prevalence in the school of Ghana may be due to differences in methodology as this study's subjects were comparatively older children and cycloplegic refraction was not performed (21).

The findings of this study are similar to the results of some relevant research from Pakistan concluding a prevalence of 21.7 and 20.07% (9, 10). The results are against the findings of another similar study conducted among 1,644 schoolchildren of 5–15 years at Kohat, Pakistan, concluding the burden of refractive errors was 8.2%. However, this research was cross-sectional and a convenience-based sampling technique was opted (9).

The gender-based prevalence of refractive errors was analyzed among the present study subjects and it was found that the prevalence was high among the girls 238 (57.8%) as compared to boys 174 (42.2%). There was a statistically significant association between refractive error and the gender of the study participants (p-value < 0.001). These results are like the findings of another school-based research from Muzaffarabad which concluded a gender-based significant association ($p = 0.001$) and prevalence was higher among the female participants as compared to the male study subjects. However, this study reflects quite a high prevalence of 88.7% among the females and 11.3% prevalence among the male participants (22).

The results of the present research are in line with the findings of other similar studies concluding that the female students are having a higher prevalence of refractive errors as compared to the male students 7.86 (16), 15.3 (18), 52% (14), and 51.9% (14), respectively. The findings of the present study favor another study concluding a higher prevalence among the female participants (57.5%) as compared to the male subjects, 42.5% (19). However, these results were not statistically significant which contrasts with the findings of this study (19). The gender-based findings of the present study oppose the results of another cross-sectional Nigerian study conducted between the private and public schools among 1,197 subjects aged 8–15 years recruited through multistage random sampling. This research concluded that there was no statistically significant association between the prevalence of myopia among the male and female participants (25). These gender-based results are consistent with the findings of a relevant study reporting a high prevalence among the female study subjects (26). However, another study revealed a high magnitude among the male participants (27, 28).

The academic performance of the study participants was investigated and presented in the form of mean scores of the examination before and after the intervention. The cumulative groups mean score before intervention was found as 56.39 ± 13.24 and 63.53 ± 17.50 in public and private schools, while it was improved to 60.27 ± 14.94 and 67.12 ± 18.4 after the intervention, respectively; the subsequent, post-intervention examination results represented a clear improvement. The findings of after-intervention follow-ups are in clear contradiction to the findings of a study from Singapore which revealed that presenting visual acuity does not have a significant effect on the current or academic school performance after a year of the correction (29). The possible reason may be the differences in participant age between this and the Singapore study. However, the evidence of a randomized trial from rural China about the impact of spectacles on the academic performance of primary school children revealed an increased average score on the tests by the availability of glasses which corroborates the findings of this study (30). Similarly, another study also corresponds to the findings by concluding significant relations between the quality of academic performance and the presence of visual impairments (31). Another Chinese study about the effects of free glasses provision on the outcome of education concluded a statistically significant impact on academic performance which also favors the findings of this study (32).

CONCLUSION

A significant impact was found in the mean score of results after intervention considering the adjustment of tuition and extra coaching after the school timing. Despite the presence of multiple public, private, and free eye care services in Lahore, diagnosis and management of refractive errors are still serious issues that directly influence academic achievement. The findings also reflect the state of affairs in the remote and deprived areas demanding an immediate response by the policymakers not only for the visual health but rather for improving the academic performance of the schoolchildren as well.

Recommendations

A comprehensive School Visual Assessment & Management Program (SVA&MP) with the provision of required spectacles is the need of the hour. A schematic diagram of SVA&MP is presented in **Figure 3**.

Limitations

This study was conducted in Lahore having better educational and eye care facilities, which may limit the generalizability of the study. The study could reveal better results if a control group or prospective cohort design had opted. A multi-center study with an increased number of participants may result in a more precise and accurate outcome but the feasibility and resource management will be an uphill task.

Moreover, this research was conducted to study the impact of refractive errors on the academic performance of high school children in Lahore. Considering the sample size and issues regarding informed consent and cycloplegic effects, it was not feasible for us to make cycloplegic examinations in schools and this is a limitation of our study.

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

The studies involving human participants were reviewed and approved by Institutional Research Board of the University of Lahore vide letter reference number IRB-UOL-FAHS/00248A. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ML: conception or design of the work and final approval of the version to be published. ML, IH, and SA: data collection. ML, MN, and SH: data analysis and interpretation. ML, MS, AA, SH, and MN: drafting the article. ML and SG: critical revision of the article. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors are thankful to all individuals who participated on a voluntary basis and also wish to acknowledge the help and support of all team members of the Prevention of Blindness Trust (POB Trust) for their unconditional support. This article is a part of the Ph.D. in Public Health thesis at the University of Lahore.

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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.

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 29 August 2022
DOI 10.3389/fpubh.2022.917781

Rural-urban differences in prevalence of and risk factors for refractive errors among school children and adolescents aged 6–18 years in Dalian, China

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Purpose: To assess the prevalence of refractive errors (REs) in school children aged 6–18 years in urban and rural settings in Dalian, Northeast of China.

Methods: This is a school-based cross-sectional survey using multi-stage randomization technique. Six- to eighteen-year-old school children from elementary schools, junior and senior high schools from a rural area and an urban area in Dalian were included in December 2018. All subjects underwent a comprehensive questionnaire and eye examination.

Results: A total of 4,522 school children with 6–18 years of age were investigated. The age, gender-adjusted prevalence of myopia, and anisometropia were 82.71 and 7.27% among the urban students as compared to 71.76% and 5.41% among the rural ones (OR = 1.80, 95 % CI = 1.53 - 2.11, $P < 0.001$; OR = 1.29, 95 % CI = 1.00–1.67, $P = 0.049$), respectively. The hyperopia was less common in urban students than in rural ones (5.63 *vs*. 10.21%; OR = 0.54, 95 % CI: 0.43–0.67, $P < 0.001$). However, there was no significant difference in prevalence of astigmatism between urban (46.07%) and rural (44.69%) participants (OR = 0.96, 95 % CI: 0.84–1.10, $P = 0.559$). The differences on prevalence of REs were attributed to different social-demographic and physiologic factors.

Conclusions: The students from urban settings are more likely to have myopia and anisometropia but less likely to have hyperopia than their rural counterparts. Although considerable attention had been paid to controlling REs, it is necessary to further consider the urban-rural differences in REs.

KEYWORDS

prevalence, refractive errors, risk factors, schoolchildren, urban-rural disparity

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 11 April 2022
ACCEPTED 08 August 2022
PUBLISHED 29 August 2022

CITATION
Wang Y, Liu L, Lu Z, Qu Y, Ren X, Wang J, Lu Y, Liang W, Xin Y, Zhang N, Jin L, Wang L, Song J, Yu J, Zhao L, Ma X and Zhang L (2022) Rural-urban differences in prevalence of and risk factors for refractive errors among school children and adolescents aged 6–18 years in Dalian, China. *Front. Public Health* 10:917781. doi: 10.3389/fpubh.2022.917781

Introduction

The refractive errors (REs), especially myopia, have become the primary cause of vision impairment (VI) and preventable blindness in children. Myopia suggests a significant increase in prevalence globally in the past 50 years and become a significant public health problem across the globe, especially in East Asian countries like Singapore and China (1, 2). In Singapore, the incidence of myopia in children is about 62% (3), and Chinese having higher rates compared with Indians and Malays (4). In Guangzhou China, the prevalence of myopia among schoolchildren is 49.7%, much higher than the United States (20%) (5), Australia (11.9%) (6), and Nigeria (1.9%) (7). Among them, the increase in school children is particularly remarkable, 73.9–90% of high school students were myopia in urban areas of Aisa (8–10).

Various factors, including genetic and environmental factors play a role in the etiology of myopia. Genetically, the prevalence of myopia in children is greater if their parents are myopic (11, 12). Rapidly changing environmental factors are predominant in determining the current patterns of myopia (13). Near-work, time outdoors have shown to be associated with the occurrence and development of myopia (14, 15). Region of habitation, are also thought to influence presence of REs (16). In China, there were two population-based studies reported the rural-urban prevalence of REs among children and adolescents. According to Beijing Pediatric Eye Study, first, they found that prevalence of myopia was significantly associated with urban region (17). However, in further analysis on factors for myopia, prevalence of myopia was not significantly associated with urban region of habitation after adjusting for age, gender, school type, family income, and parental myopia (18). Although separate prevalence rates of REs in rural vs. urban children were reported in Shandong Children Eye Study (19), there remain some gaps in this study. Those prevalence rates were crude rates without adjusting age, gender and other potential confounders.

At present, the prevalence and risk factors of REs in urban and rural school children in Northeast China are still unclear. Whether there are differences in the associated factors of REs in different regions needs further research. In order to understand the prevalence of REs and the risk factors disparity among school children (6–18 years old) between urban and rural settings, we performed this school-based survey in the urban and rural areas of Dalian, Northeast China.

Methods

Participants

This school-based study was initially performed in December 2018. Multi-stage random cluster approach was conducted for sampling. In the first step, one district from each of the rural (Wafangdian County) and urban (Xigang District) regions of Dalian was randomly selected. In the second step, one primary school, one junior high school, and one senior high school were randomly selected from each of the two selected districts. In the third step, two classes of each grade were of randomly selected from each of the including schools. In the final step, all students of the selected classes with age of 6–18 years were sampled. The exclusion criteria were the followings: (1) Participants who reported eye conditions within the last month (e.g., optical correction with othokeratology, eye injuries, conjunctivitis, and corneal irritation); (2) Participants whose parents refused to sign the informed consents.

The study was approved by the respective ethics committees of The Third People's Hospital of Dalian and the Health commission of Dalian. This study followed the Declaration of Helsinki. Written consent was obtained from the parents of all children and teenagers.

Interview and data collection

In current study, all participants and their parents completed a detailed questionnaire form. The quality of the questionnaire was controlled by head teacher in each class. The questionnaires are conducted at home.

The questionnaire included two parts (participants' information section and parents' information section). Basic socio-demographic data, such as age, gender, ethnic origin, habitation in urban or rural areas, degree of class and grade, and medical history was included in the first part of the questionnaire. Moreover, this questionnaire section additionally included questions on near-work activities such as the amount of time spent on studying or watching television, mobile phone and on computer activities per day. The first part of the questionnaire also includes questions about outdoor activities such as how long the children spent in outdoor activities per day. The first part of the questionnaire was filled in by the children and assisted by their parents. For very young children who could not read or understand the questionnaire very well (e.g., the youngest children of 6 years old), help was sought from their parents.

In the second part, information of parents' education level, refractive error history (e.g., myopia, hyperopia, astigmatism) were obtained using questionnaire from participants' parents.

After the interview, comprehensive ophthalmological examinations were conducted on the school premises by two trained optometrists. Refractive error measurements, uncorrected visual acuity as well as best corrected visual acuity (BCVA) were tested using non-cycloplegic auto-refractometry (AR-1, NIDEK, Japan) by a senior experienced optometrist. Moreover, intraocular pressure (IOP) was measured by non-contact tonometry (NT-510, NIDEK, Japan). Axial length was

TABLE 1 Characteristics of all participants.

Variables	Overall	Urban	Rural	*P*
N (subjects, %)	4,522	2,429 (53.72)	2,093 (46.28)	
Gender				0.062
Male (%)	2,336 (51.66)	1,286 (52.94)	1,050 (50.17)	
Female (%)	2,186 (48.34)	1,143 (47.06)	1,043 (49.83)	
Age (year)				<0.001
6–10	1,708 (37.77)	856 (35.24)	852 (40.71)	
11–15	1,797 (39.74)	855 (35.20)	942 (45.00)	
16–18	1,017 (22.49)	714 (29.56)	299 (14.29)	
Height (cm)	151.28 ± 19.67	152.97 ± 19.95	149.26 ± 19.12	<0.001
Weight (cm)	45.82 ± 18.96	46.98 ± 19.48	44.44 ± 18.18	<0.001
BMI (kg/m^2)	19.18 ± 4.60	19.19 ± 4.64	19.15 ± 4.56	<0.001
Parental refractive error (%)				<0.001
Myopia	1,580 (34.94)	918 (37.79)	662 (31.63)	
No Myopia	2,942 (65.06)	1,511 (62.21)	1,431 (68.37)	
Parental education level (%)				<0.001
Junior high school	1,649 (36.47)	574 (23.63)	1,075 (51.36)	
Senior high school	1,286 (28.44)	668 (27.50)	618 (29.53)	
Bachelor	1,365 (30.19)	986 (40.59)	379 (18.11)	
Master	222 (4.90)	201 (8.28)	21 (1.00)	
Annual household income (yuan, %)				<0.001
>200,000	504 (11.15)	373 (15.36)	131 (6.26)	
≤200,000	4,018 (88.85)	2,056 (84.64)	1,962 (93.74)	
Daily hours of near-work (%)				0.981
<2 h	331 (7.32)	178 (7.33)	153 (7.31)	
≥2 h	4,191 (92.68)	2,251 (92.67)	1,940 (92.69)	
Daily hours of outdoor activities (%)				<0.001
>2 h	2,790 (61.70)	1,348 (55.50)	1,442 (68.90)	
≤2 h	1,732 (38.30)	1,081 (44.50)	651 (31.10)	
Spherical equivalence (D)	−2.18 ± 3.30	−2.53 ± 2.57	-1.76 ± 3.96	<0.001

tested by IOL Master (Carl Zeiss Meditec, Jena, Germany). The mean of three readings were taken.

Measured variables

The definitions of refractive error vary across the selected prevalence studies, we choose the definition that is common in clinical use (19, 20). The spherical equivalent (SE) of the refraction was calculated as the spherical refractive error plus half of the minus cylindrical refractive error. Myopia was defined as SE < -0.5 dioptres (D), and hyperopia was defined as SE $> +0.5$ D in one or both eyes. Myopia can be classified as low, moderate, or high myopia. Low myopia was defined as SE −0.75 D to −2.75 D, moderate myopia was defined as SE −3.00 D to −4.75 D, and high myopia was defined as SE ≤-5.0 D. Astigmatism was defined as ≥ +0.75 D of the cylinder in either eye. Anisometropia was defined as difference between right eye to left eye in refractive error (SE) of ≥1.0 D.

Statistics

The data were analyzed using a commercially available statistical program SAS 9.3 (SAS institute, Cary, NC, USA) and SPSS 20.0 (SPSS Inc., Chicago, IL). Only the data for eye with high severity of refraction is presented. Participants included in the final analysis were divided into three age groups (6–10, 11–15, and 16–18 years old, respectively) which were consistent with the distribution of education level for including participants. The age- and gender-specific prevalence rates of REs and subtypes were assessed. The difference of the variables (age groups, gender and region) with REs was assessed using the Student's *t*-test for the continuous variables and the Pearson's χ^2 test for the categorical variables. Logistic regression analysis

TABLE 2 Crude and age-adjusted prevalence of different refractive errors.

Items	*N*	Crude prevalence (95%CI)	Age, gender-adjusted prevalence (95%CI)	*P*
Myopia				<0.001
Urban	1,840	75.75% (74.01%, 77.42%)	82.71% (80.89%, 84.38%)	
Rural	1,297	61.97% (59.78%, 63.95%)	71.76% (69.24%, 74.15%)	
Over all	3,137	69.37% (68.01%, 70.70%)	–	
Low myopia				<0.001
Urban	930	61.22% (58.78%, 63.68%)	70.52% (67.76%, 73.13%)	
Rural	801	50.16% (47.61%, 52.52%)	58.54% (55.34%, 61.67%)	
Over all	1,731	55.55% (53.80%, 57.29%)	–	
Moderate myopia				<0.001
Urban	494	45.61% (42.68%, 48.62%)	50.88% (46.65%, 55.09%)	
Rural	296	27.11% (24.51%, 29.78%)	32.16% (28.25%, 36.34%)	
Over all	790	36.32% (34.33%, 38.37%)	,	
High myopia				<0.001
Urban	416	41.39% (38.31%, 44.41%)	38.68% (33.73%, 43.87%)	
Rural	200	20.08% (17.65%, 22.62%)	21.55% (17.78%, 25.87%)	
Over all	616	30.78% (28.80%, 32.84%)	–	
Hyperopia				<0.001
Urban	178	7.33% (6.40%, 8.50%)	5.63% (4.78%, 6.63%)	
Rural	286	13.66% (12.26%, 15.20%)	10.21% (8.85, 11.75%)	
Over all	464	10.26% (9.41%, 11.18%)	–	
Astigmatism				0.379
Urban	1,107	45.57% (43.53%, 47.50%)	46.07% (44.00%, 48.15%)	
Rural	847	40.47% (38.37%, 42.58%)	44.69% (42.37%, 47.02%)	
Over all	1,954	43.21% (41.77%, 44.66%)	–	
Anisometropia				0.013
Urban	196	8.07% (7.02%, 9.19%)	7.27% (6.27%, 8.42%)	
Rural	111	5.30% (4.44%, 6.37%)	5.41% (4.47%, 6.54%)	
Over all	307	6.79% (6.09%, 7.56%)	–	

CI, Confidence Interval.

was performed to determine risk factors using odds ratio (OR) estimates with 95% confidence intervals (CI). A multivariate regression analysis was performed with *P*-value <0.05 being required for entering the model. All *P*-values were 2-sided and considered statistically significant when <0.05.

Results

In our study, the seven schools had a total student of 4,583 individuals 6–18 years old, and all of participants were given offers to accept the body and eye examination. In total, 4,522 students (2,336 boys) participated in the all examination, corresponding to an overall response rate of 98.7% (98.9% for urban and 98.4% for rural, respectively). Socio-demographic characteristics were compared between urban students and rural students (Table 1). The rural students and the urban students group varied significantly in the level of age with a significantly higher frequency of 6–10 and 11–15 years old in the rural students, and complementarily, a significantly higher frequency of 16–18 years old in the urban students. The urban students were more likely to be with higher frequency of parental refractive error ($P < 0.001$), annual household income exceeds Renminbi (RMB) 200,000 Yuan ($ 28,982 USD) ($P < 0.001$), higher parental education level ($P < 0.001$), daily hours of outdoor activities ≤2 h ($P < 0.001$), and have higher level of height, weight as well as BMI ($P < 0.001$) but lower refractive status ($P < 0.001$) than those rural students. Further, there is no significant difference in gender ($P = 0.062$), and daily hours of near-work ($P = 0.981$) distribution between urban and rural students.

Crude and adjusted-prevalence of REs distributed by region is shown in Table 2. There were differences in the prevalence of different REs values between the urban and rural students. After adjusted for age and gender, the prevalence of overall myopia, low myopia, moderate myopia and high myopia among urban

TABLE 3 Bivariate regression results for both the urban and rural participants.

	Myopia		Hyperopia		Astigmatism		Anisometropia	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Region								
Rural	1		1		1		1	
Urban	1.97 (1.73, 2.24)	<0.001	0.50 (0.41, 0.61)	<0.001	1.24 (1.10, 1.40)	<0.001	1.61 (1.27, 2.04)	<0.001
Gender								
Male	1		1		1		1	
Female	1.10 (0.97, 1.25)	0.143	0.94 (0.78, 1.14)	0.550	0.79 (0.70, 0.89)	<0.001	0.97 (0.77, 1.22)	0.790
Age								
6–10	1		1		1		1	
11–15	7.07 (6.05, 8.27)	<0.001	0.20 (0.16, 0.26)	<0.001	1.81 (1.57, 2.08)	<0.001	2.88 (2.06, 4.03)	<0.001
16–18	18.86 (14.57, 24.43)	<0.001	0.19 (0.14, 0.26)	<0.001	3.92 (3.33, 4.62)	<0.001	4.67 (3.31, 6.59)	<0.001
Average parental refractive error								
Without	1		1		1		1	
With	1.24 (1.09, 1.42)	0.002	0.76 (0.62, 0.93)	0.009	1.34 (1.19, 1.51)	<0.001	1.10 (0.87, 1.39)	0.438
Annual household income (yuan)								
>200,000	1		1		1		1	
≤ 200,000	0.73 (0.59, 0.91)	0.006	1.79 (1.21, 2.64)	0.003	0.88 (0.72, 1.06)	0.170	0.68 (0.48, 0.94)	0.020
Daily hours of near-work								
<2 h	1		1		1		1	
≥2 h	4.76 (3.75, 6.04)	<0.001	0.28 (0.21, 0.37)	<0.001	1.86 (1.45, 2.37)	<0.001	1.55 (0.91, 2.64)	0.105
Daily hours of outdoor activities								
>2 h	1		1		1		1	
≤2 h	0.93 (0.81, 1.06)	0.249	0.90 (0.74, 1.10)	0.309	1.05 (0.93, 1.18)	0.455	1.10 (0.87, 1.39)	0.451
Parental education level								
Middle school	1		1		1		1	
High school	1.25 (1.06, 1.47)	0.007	1.09 (0.86, 1.39)	0.464	1.28 (1.10, 1.48)	0.001	1.17 (0.87, 1.57)	0.304
Bachelor	1.14 (0.98, 1.34)	0.097	0.93 (0.73, 1.19)	0.566	1.28 (1.11, 1.49)	0.001	1.25 (0.94, 1.67)	0.122
Master	0.95 (0.70, 1.29)	0.756	0.57 (0.32, 1.02)	0.057	0.95 (0.71, 1.27)	0.721	0.82 (0.43, 1.56)	0.544

OR, odds ratio; CI, Confidence Interval.

students was 82.71, 70.52, 50.88, and 38.68%, and it was higher than that among rural students (71.76, 58.54, 32.16, and 21.55%, respectively). Similar results were found in anisometropia, the age, gender-standardized prevalence of anisometropia was higher in the urban students than in the rural students (7.27 *vs.* 5.41%, $P = 0.013$). However, the age, gender-adjusted prevalence of hyperopia in the rural students was higher than that in the urban students (10.21 *vs.* 5.63%, $P < 0.001$). Additionally, no difference was found in astigmatism between the rural and urban students (44.69 *vs.* 46.07%, $P = 0.379$).

Bivariate analysis showed factors associated with REs among all subjects (Table 3). Currently, students' age, region of habitation, average parental refractive error, parental education level, annual household income and daily hours of near-work were associated with myopia (all $P < 0.05$). However, students' age, region of habitation, average parental refractive error, annual household income and daily hours of near-work were associated with hyperopia (all $P < 0.05$). Further, students' age, gender, region of habitation, average parental refractive error, parental education level and daily hours of near-work were associated with astigmatism (all $P < 0.05$). In addition, there was a significant correlation between age, region of habitation, annual household income and anisometropia (all $P < 0.05$).

Stepwise multiple logistic models were used to analyze the correlation between region and REs (Table 4). In model 1, after controlling for age and gender, the risk of students living in urban setting developing myopia, hyperopia, and anisometropia were 1.88 (95%CI: 1.62–2.18, $P < 0.001$), 0.53 (95%CI: 0.43–0.65, $P < 0.001$), 1.07 (95%CI: 0.94–1.21, $P = 0.300$), and 1.37 (95%CI: 1.07–1.76, $P = 0.013$), respectively. However, there is no significant difference on presence of astigmatism between students in rural and urban settings (OR: 1.07, 95%CI: 0.94–1.21, $P = 0.300$). In model 2 adjusting with age, gender and any variables analyzed significantly in the bivariate analysis (Table 3),

TABLE 4 Multivariate regression results for the differences on the risk for REs by region of habitation.

		Myopia		Hyperopia		Astigmatism		Anisometropia	
		OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR(95%CI)	*P*
Model 1	Rural	1		1		1		1	
	Urban	1.88 (1.62, 2.18)	<0.001	0.53 (0.43, 0.65)	<0.001	1.07 (0.94, 1.21)	0.300	1.37 (1.07, 1.76)	0.013
Model 2	Rural	1		1		1		1	
	Urban	1.80 (1.53, 2.11)	<0.001	0.54 (0.43, 0.67)	<0.001	0.96 (0.84, 1.10)	0.559	1.29 (1.00, 1.67)	0.049

Model 1: adjusted with age and gender.
Model 2: adjusted with age, gender and any the variables analyzed significantly in the bivariate analysis.
OR, odds ratio; CI, Confidence Interval.

students living in urban were 1.80 (95% CI: 1.53–2.11, $P < 0.001$) times more likely to be myopic, 1.29 (95% CI: 1.00, 1.67, $P = 0.049$) times more likely to be anisometropia, but 0.54 (95% CI: 0.43–0.67, $P < 0.001$) times less likely to be hyperopia. Further, there was no significant association between the student's area of residence and astigmatism (OR: 0.96, 95%CI: 0.84–1.10, $P = 0.559$).

Bivariate and multivariate analyses identified the risk factors for the presence of any REs in the urban (Supplementary Table S1) and rural (Supplementary Table S2) students. After multivariate analysis, increasing age and daily hours of near-work were found to be a risk factor for myopia in both the rural and urban groups but with parental refractive error was a risk factor for myopia only in the rural group (all $P < 0.001$). Increasing age, daily hours of near-work and lower annual household income were independent risk factors for hyperopia in the urban participants while increasing age, daily hours of near-work and average parental refractive error were independent risk factors for hyperopia in the rural participants (all $P < 0.05$). Female gender was found to be reduced risk for astigmatism in the urban population ($P < 0.001$). Further, increasing age ($P < 0.001$) and average parental refractive error ($P < 0.05$) were independent risk factors for astigmatism in the urban participants. However, increasing age, higher level of annual household income, parental education level and with average parental refractive error were independent risk factors for astigmatism in the rural participants (all $P < 0.001$).

For anisometropia, we found that only increasing age was a risk factor for urban students but both increasing age and higher level of annual household income were risk factor anisometropia in the rural students (all $P < 0.05$).

Discussion

Currently, our study provides the population-based cross-sectional data on the region-specific prevalence of REs and its associated risk factors among the urban and rural school children and adolescents across several gradients of age groups which have different socio-cultural factors in Northeast China. First, our findings revealed that the students living in urban setting have higher prevalence rates and risk for myopia and anisometropia than students living in rural, while the prevalence and risk of hyperopia in the urban students was lower than that in the rural students. Moreover, there is no difference on the prevalence and risk of astigmatism between the urban and rural students. Secondly, the prevalence disparities of REs may be due to the various factors between rural and urban areas. Thirdly, there appeared to be significant difference in factors of REs between study participants residing in urban and rural settings.

Consistent with our findings, a previous meta-analysis reported that children from urban environments have 2.6 times the odds of myopia compared with those from rural environments (16). Similarly, the prevalence of myopia in urban setting was higher compared with rural setting based in other region of China (Shandong and Guangzhou) (19, 21). In southern China, the prevalence of myopia in urban children was 73.1% (15 years old), while the prevalence of myopia in rural children was 36.8% (13 years old) and 53.9% (17 years old) (21, 22). However, this disparity was did not adjusted comprehensive variables. Furthermore, we found studies regarding the other prevalence of REs between urban and rural students in China are limited. Table 5 shows the comparison of prevalence of REs between rural and urban settings among school children and adolescents in mainland China. The crude prevalence of myopia, hyperopia, astigmatism, and anisometropia in urban ranges from 5 to 87.7%, 1 to 35.9%, 2.0 to 42.7%, and 7.9%, while in rural ranges from 13.75 to 60%, 1 to 49.2%, 3.75 to 32.1%, and 6.1%, respectively. Our prevalence astigmatism was higher than the surveys while prevalence of myopia, hyperopia and anisometropia data fall somewhere in between. Further, the prevalence disparity of astigmatism between rural and urban areas is still controversial. In Shandong children eye study, students with urban habitation had higher prevalence of astigmatism (40.7%) than those with rural habitation (32.1%) (19). In Dezful County of Iran, school children with urban habitation also had higher prevalence of astigmatism (21%) than those with rural habitation (14.8%) (38). The varying difference in the prevalence of REs between rural and urban habitation may be attributed to the different living environments and variability

10.3389/fpubh.2022.917781

TABLE 5 Comparison of the reported prevalence of refractive errors in selected population-based studies in school children and adolescents in mainland China.

References	Area	Sample size	Survey year	Age rage (years)	Study area	Definition for REs	Prevalence of myopia	Prevalence of hyperopia	Prevalence of astigmatism	Prevalence of Anisometropia
Wu et al. (23)	12 cities*	43,771	N.A	11.45 ± 2.65	R+U	Questionnaires	25.7% (R) *vs.* 38% (U)	N.A	N.A	N.A
He et al. (24)	Yangxi	2,400	2005	13–17	R	Myopia SE ≤-0.50 D; Hyperopia SE > +2.00 D; Astigmatism: cylinder of > or = 0.75 D (Cycloplegia)	33.0	1.0	25.3	N.A
Wu et al. (19)	Shandong#	6,026	2013	4–18	R+U	Myopia: SE ≤ −0.50 D; Mild Hyperopia +0.5D < SE ≤ +2.0 D; Medium to Marked Hyperopia SE > +2.0 D; Astigmatism: cylindrical RE ≥ 0.75 D; Anisometropia: difference between right eye to left eye in SE of ≥ 1.0 D (Cycloplegia)	30.7 (R) vs 43.5 (U)†	Mild: 49.2 (R) vs. 35.9 (U)†; Medium to Marked: 6.4 (R) vs. 5.2 (U)†	32.1 (R) vs. 40.7 (U)†	6.1 (R) vs. 7.9 (U)†
You et al. (17)	Beijing	15,066	N.A.	7–18	R+U	SE≤ −0.50 D (Cycloplegia)	64.9 (overall)	NA	NA	NA
Pan et al. (25)	Mojiang	4,778		7.7–13.8	R	SE < −0.5 D (Cycloplegia)	29.4% (7.7 y) 2.4% (13.8 y)	NA	NA	NA
Congdon et al. (26)	Xichang	1,892	2007	11.4–17.1	U	SE < −0.5 D (Cycloplegic)	62.3%	NA	NA	NA
Guo et al. (27)	Ejina	1,565	2012	6–21	R	SE ≤ −0.50 D (Cycloplegic)	60.0%	NA	NA	NA
He et al. (21)	Guanghzou	4,364	2002–2003	5–15	U	Myopia SE ≤ −0.50 D; Hyperopia SE > +2.00 D; Astigmatism: cylinder of > or = 0.75 D (autorefraction under cycloplegia)	78.4	1%	42.7%	NA
Li et al. (28)	Anyang	4,861	2011	5–16	U	Myopia SE ≤ −0.50 D; Hyperopia SE > +2.00 D; (Cycloplegia)	3.9% (5–6 y); 67.3% (15- 16 y)	23.3% (grade 1); 1.2% (grade 7)	NA	NA

(Continued)

TABLE 5 (Continued)

References	Area	Sample size	Survey year	Age rage (years)	Study area	Definition for REs	Prevalence of myopia	Prevalence of hyperopia	Prevalence of astigmatism	Prevalence of Anisometropia
Li et al. (29)	Heilongjiang	1,675	2008–2009	5–18	U	Myopia SE ≤ −0.50 D; Hyperopia SE > +0.50 D; Astigmatism: cylinder of > or = 0.75 D (Cycloplegia)	5.0%	1.6%	2.0%	N.A
Chen et al. (30)	Fenghua	43,858	2001–2015	17–18	U	Myopia SE ≤ −0.50 D; (Without Cycloplegia)	79.5% (2001); 87.7% (2015)	NA	NA	NA
Sun et al. (31)	Qingdao	3,753	2015–2016	10–15	U	Myopia SE < −0.50 D (Cycloplegia)	52.02%	NA	NA	NA
Guo et al. (32)	Beijing	35,745	2016	6–18	R+U	Myopia SE < −0.50 D (Without cycloplegia)	70.9%	NA	NA	NA
Ma et al. (33)	Shanghai	8,267	2013	10	U	Myopia SE ≤ −0.50 D; Hyperopia SE > +0.50 D; (Cycloplegia)	52.2%	2.6%	NA	NA
Guo et al. (34)	Guangzhou	3,055	2014	6–15	U	Myopia SE≤−0.50 D; (Cycloplegia)	47.3%	NA	NA	NA
Lyu et al. (35)	Beijing	4,249	2011	5–14	U	Myopia SE ≤ −0.50 D; (Cycloplegia)	36.7%	NA	NA	NA
Wu et al. (36)	Beijing	4,677	N.A.	16–18	U	Myopia SE ≤ −1.00 D; (Without cycloplegia)	80.7%	NA	NA	NA
Pi et al. (37)	Yongchuan	3,070	2006–2007	6–15	R	Myopia SE ≤ −0.50 D; Hyperopia SE ≥ +2.00 D; Astigmatism: cylinder of > or = 1.0 D (Cycloplegia)	13.75%	3.26%	3.75%	NA

[*] Beijing, Shaoxing, Shenzhen, Chongqing, Guizhou, Taiyuan, Ma'anshan, Shenyang, Urumqi, Changsha, Yinchuan and Zhengzhou.
[#] Weihai (urban), Guanxian (rural).
[†] Statistical significant, $P < 0.05$.
REs, refractive errors; U, urban; R, rural; SE, spherical equivalence; D, dioptres; NA, not applicable.

10.3389/fpubh.2022.917781

in the cut-off point adopted to define the presence of REs. In Shandong study, the generational REs shift was measured to by cycloplegia while in our study without cycloplegia (19).

To date, there are few studies investigating the different associated factors for REs between rural and urban participants. The current study performed in Dalian reports the effect and possible factors on REs in a wide age range among the Chinese urban and rural students. For both rural and urban students, we found that increasing age and longer daily hours of near-work were independently associated with myopia, which was consistent with previous reports in Beijing urban students (39, 40). However, in another rural study (Handan), there was no significant association between daily near work and presence of myopia even adjusted with potential confounders (22). Interestingly, significant association between parental refractive error and myopia was found in rural participants rather than urban individuals. Further, myopia was associated with senior high parental education among our rural participants which was consistent with Yangxi County eye study (24). In addition, increasing age and longer daily hours of near-work were protective factors for hyperopia in both rural and urban students. Moreover, the prevalence rates of hyperopia for urban students were higher with lower annual household income which was consistent with study outcomes among adults in Sumatra, Indonesia (41). In both rural and urban children and adolescents, risk factors that were related to astigmatism were age and parental refractive error. Interestingly, female gender has lower risk for astigmatism among urban students and lower annual household income level has lower risk for astigmatism among rural ones. In study in Singaporean children (7–9 years), girls had significantly greater progression of astigmatism than did boys (42) which was inconsistent with our findings. Increasing age was an independent risk factor for anisometropia in both rural and urban participants. Protective factor, only in the rural arm, was lower annual household income level. These socio-demographic and lifestyle factors disparities may contribute to the prevalence disparities of REs between rural and urban students in this study.

A noteworthy finding is that the prevalence of REs including myopia was not significant with daily hours of outdoor activities in both urban and rural children and adolescents. In contrast, outdoor activities are negatively associated with myopia after adjustment for potential factors in both urban regions such as Hubei (43) and Qingdao (31)and rural settings e.g., Handan (22). Three cross section studies [mainland China (44), Taiwan (45) and Singapore (46)] did not find any relationship between outdoor activities and presence of myopia.

The major strength of this study included a comprehensive population-based sample from a large city, urban and rural areas; reasonable response rates; and reliable demographic data. This data are extremely useful for healthcare providers to develop long-term strategies to combat avoidable visual impairments due to REs. It is heartening to see a declining prevalence of REs as compared to epidemiological studies done in past worldwide. The study also found socio-demographic and health-related factors for REs between rural and urban students. It is possible that modulating this variable may control the occurrence of RE, however, this warrants longitudinal studies. A limitation of the study is the inability to validate the causal relationship between the significant risk factors and presence of REs. Cohort studies are recommended for the future. In addition, we excluded those participants with optical correction using othokeratology which may lower-evaluating the prevalence of myopia.

Conclusions

Our study investigated the overall prevalence of REs including myopia, hyperopia, astigmatism and anisometropia in rural and urban areas in Dalian China in children and adolescents aged 6–18 years. The students with urban habitation had a higher prevalence of myopia and anisometropia but a lower risk of hyperopia than those with rural habitation. With multivariate logistic regression, the factors regarding REs between rural and urban participants were different. Herein, the implementation and findings from this screen will guide the efficient prevention strategy of refractive error and eye care services in urban and rural school children and adolescents.

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 Dalian Third People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LZhan, LL, XM, JW, and WL contributed to the conception of the study. YW, ZL, YQ, JW, YL, WL, YX, NZ, LJ, LW, JS, JY, and LZhao performed the experiment. YW, LL, XR, and LZhan contributed significantly to analysis and manuscript preparation. YW, LL, and XR performed the data analyses and wrote the manuscript. LZhan, LL, and XM helped perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Dalian Health Commission Department; Ministry of Education of Dalian. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.917781/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 04 October 2022
DOI 10.3389/fpubh.2022.970751

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SPECIALTY SECTION
This article was submitted to
Children and Health,
a section of the journal
Frontiers in Public Health

RECEIVED 16 June 2022
ACCEPTED 16 September 2022
PUBLISHED 04 October 2022

CITATION
Zhou W, Li Q, Chen H, Liao Y, Wang W,
Pei Y, Li S, Zhang W, Wang Q and
Wang X (2022) Trends of myopia
development among primary and
junior school students in the
post-COVID-19 epidemic period.
Front. Public Health 10:970751.
doi: 10.3389/fpubh.2022.970751

Trends of myopia development among primary and junior school students in the post-COVID-19 epidemic period

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Purpose: To investigate the trends of myopia among primary and junior school students in the post-COVID-19 epidemic period.

Method: A prospective of cross-sectional study using spot photoscreenings in 123,538 children among primary and junior school students from 2019 to 2021 was conducted to evaluate the development of myopia in Xuzhou, China in the post-COVID-19 epidemic period. Equivalent refraction and the prevalence of myopia were recorded.

Results: The spherical equivalent refraction of myopia decreased across all grades except grade 1 (0.23 ± 0.56 D in 2019, 0.24 ± 0.63 D in 2020) from 2019 to 2020. However, refraction exhibited a hyperopic shift in 2021 compared to 2020 for grades 1–5 (no significant decreased for grade 4). The prevalence of myopia in all grades increased in 2020 compared to 2019, and the most dramatic changes were observed from grades 2–5 and grades 7–8 ($P < 0.05$). The changes in myopia prevalence in grades 1–4 were mild, and the reduction in myopia for Grade 5 is significant from 2020 to 2021. Nevertheless, students in grades 6 and 9 exhibited the greatest growth in myopia prevalence ($P < 0.01$). All grades had higher myopia prevalence in 2021 compared with 2019, except grade 1 ($P = 0.25$). The prevalence of myopia in girls was higher compared with boys, and the urban myopia prevalence was higher than in rural areas over the 3 years except in 2019 ($P = 0.18$).

Conclusions: The prevalence of myopia increased during the COVID-19 epidemic. However, the spherical equivalent refraction of lower grade children drifted to hyperopia and the trends of myopia development remained stable in the post-COVID-19 epidemic period. We should be more concerned about the prevalence of myopia in graduating for the primary or junior grades in the future.

KEYWORDS

myopia development, post-COVID-19, spherical equivalent refraction, primary and junior students, epidemic

Introduction

Myopia is the most common type of refractive error, and its prevalence is increasing yearly. According to the current trends of progression, by 2050, ∼50% (5 billion) of the global population will be afflicted by myopia (1). The rapid development of myopia requires timely treatment and prevention because it causes inconvenience to daily life, and the degree of myopia may be exacerbated if not treated. In addition, high myopia is often accompanied by eye diseases, such as retinal detachment, glaucoma, cataracts, posterior scleral staphyloma, and other complications that can lead to permanent visual impairment or even blindness in severe cases (2). Less outdoor activity and more near-work study time are common risk factors for myopia development (3).

An outbreak of viral pneumonia called coronavirus disease (COVID-19) has swept the country since mid-December 2019. Various containment measures were implemented nationwide, and a widespread "shutdown" of activities, including outdoor activities and school closures (4), occurred during the pandemic, to protect the health of young people eliminate virus transmission, and ensure the successful completion of education and teaching, people were forced to stay home in isolation. In addition, outdoor activities were banned for at least 3 months (from February to April), and students were required to study online using digital screen devices for 4 months (from February to May) (5). As online classes continue, students' exposure to electronic devices has increased significantly, seriously affecting their vision (6). Several studies have demonstrated increased myopia development in children during the COVID-19 epidemic (7, 8). Nevertheless, after strenuous efforts, the current epidemic prevention and control situation has been positively effective in China, allowing the school to open normally in September 2020. The country has now entered the "post-COVID-19 epidemic period" (9). Despite the measures taken to respond to the epidemic, the highly variable and rapid spread of the new coronavirus has created a great deal of uncertainty in the development of myopia among students in the post-COVID-19 epidemic period. The long-term persistence of the epidemic in the post-COVID-19 epidemic period may have a more pronounced effect on changes in myopia development and study behavior in our children and adolescents than the occasional outbreaks of the epidemic in the short term. In this study, we aimed to investigate trends in the development of myopia among Chinese students in the post-COVID-19 epidemic period.

Methods

Study population

According to the requirements of the "Comprehensive Prevention and Control of Myopia in Children and Adolescent Implementation Plan" (10), medical and health institutions in Xuzhou City started to conduct a comprehensive vision health screening work for primary and secondary schools under the guidance of the Provincial Health and Health Commission from 2019 and students in all grades were screened in the first 4 months of the new school year, from September to December. Cluster sampling was performed from each of the five districts in 2019, including Tongshan District, Quanshan District, Yunlong District, Jiawang District, and Gulou District. Then, the same schools selected in 2019 were also assessed in 2020 and 2021. In total, 123,728 students were selected for the study, of which 190 students were excluded due to missing eye data. Thus, a total of 123,538 students were included in the final analysis. Thirty-five primary schools and 10 junior schools were chosen for final analysis. Including 20 schools in the urban and 25 schools in the rural. Grades 1–6 were assessed in primary school, and grades 7–9 were assessed in junior high school.

This prospective of cross-sectional study was approved by the Ethics Board of The First People's Hospital of Xuzhou (No.xyyll[2019]022). The purpose and process were explained to all children and their parents before the start of the study. No compensation or rewards were offered for participation. Finally, all study procedures adhered to the Declaration of Helsinki.

Measurements

The school was informed of the screening date 1 week in advance, and consent was obtained from the student and parents. Students who regularly wore contact lenses were instructed not to wear them at the time of the screening. Students undergoing corneal refractive therapy were also asked not to wear ortho-K lenses on the night before the screening and to wear their glasses on the screening date. Students were asked to remove their glasses for refractive testing.

The Spot photoscreener (Welch Allyn, VS100), a non-cycloplegic photorefrator, was used to measure the refractive status of students. Both eyes can be tested simultaneously through the visual stimulation of the screener and the sound played to attract the attention of the child. Testing was conducted by staff with extensive inspection experience. Due to the epidemic, staff and students wore masks during screening in 2020 and 2021, and the testing distance was approximately 1 m. A relative darkroom environment was chosen for screening, and different age patterns of Spot for students were selected according to their age. Then, the screener automatically generated the results. If severe refractive error, strabismus, or anisometropia was detected, the device would display a message advising the child to go to a specialized hospital for a complete eye examination.

Definitions

The examination range of the Spot photoscreener was within ±7 D. If the outcome was beyond the ±7.50 D range, the value was recorded as ±8 D for further analysis. The spherical equivalent refraction (SER) was defined as the sum of the spherical refraction and one-half of the cylindrical refraction. If either eye of a student was myopic, the student was defined as having myopia. The severity of myopia was classified according to the following criteria: mild myopia (-3.00 D $<$ SER≤ -0.50 D), moderate myopia (-6.00 D $<$ SER ≤ -3.00 D), high myopia (SER$\leq$ -6.00 D) (7). Cases not meeting these criteria were classified as no myopia.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBMSPSS, Armonk, NY, USA), Microsoft Excel 2010, and the figures were prepared using OriginPro 2021. One-way analysis of the variance of the means was used to compare categorical variables between groups. If $P < 0.05$, *post-hoc* LSD was used to compare the two groups. Both the chi-squared test and multiple comparisons were used to test for the prevalence of myopia in 2019, 2020, and 2021. Spearman's rank correlation coefficient was used to assess the correlation between the SER of the left and right eyes. Given that the SERs of both eyes were highly correlated (Spearman's rank correlation = 0.803, $P < 0.001$), we used the SER of the student's right eye as the basis for assessing myopia development and degree of myopia. $P < 0.05$ were considered statistically significant.

Result

A total of 42,918 students in 2019, 41,964 students in 2020, and 38,656 students in 2021 were included in this study, with grades ranging from 1st-6th grade in primary school to 7th-9th grade in junior school. More detailed information about the number of observations for different grades and the distribution of sex and region over the 3 years are provided in Table 1. There were 2 students with SER > -8.00 D. No students had SER > $+8.00$ D in at least 1 eye.

The mean SER from 2019 to 2021 is shown in Table 2. Except for grade 1 (0.24 ± 0.63 D in 2020, 0.23 ± 0.56 D in 2019), the SER for other grades decreased to varying degrees from 2019 to 2020. The greatest decrease in SER was observed in grades 3–5 and 7–9 ($P < 0.01$). However, almost all the mean SER for grades 1–5 exhibited hyperopic shifts in 2021 compared to 2020 (insignificant reduction of SER in grade 4). Grades 6 and 9 had the highest decrease in SER in 2021 compared to 2020 ($P < 0.05$). The mean SER decreased in 2021 compared to 2019 for all grades except grade 1. To demonstrate the distribution of SER from grades 1 to 9 over the 3 years, Gaussian fitting curves based on the frequency histogram are displayed in Figure 1.

TABLE 1 The distribution of populations with different demographic parameters.

		2019	2020	2021
Grade				
Primary school	1	5,149 (11.9)	4,527 (10.8)	4,041 (10.5)
	2	5,234 (12.2)	4,988 (11.9)	4,049 (10.5)
	3	5,084 (11.8)	5,164 (12.3)	4,500 (11.6)
	4	4,981 (11.6)	5,365 (12.8)	4,554 (11.8)
	5	5,293 (12.3)	5,418 (12.9)	4,143 (10.7)
	6	5149 (12.0)	5,403 (12.9)	4,673 (12.1)
Junior school	7	4,821 (11.2)	4,343 (10.3)	4680 (12.1)
	8	3,883 (9.0)	3,689 (8.8)	4,256 (11.0)
	9	3,369 (7.8)	3,067 (7.3)	3,760 (9.7)
Sex				
Male		23,797 (55.4)	23,114 (55.1)	21,267 (55.0)
Female		19,121 (44.6)	18,850 (44.9)	17,389(45.0)
Region				
Urban		23,916 (55.7)	25,159 (60.0)	20,893 (54.0)
Rural		19,002 (44.3)	16,805 (40.0)	17,763 (46.0)
Total		42,918	41,964	38,656

The prevalence of myopia from 2019 to 2021 in grades 1–9 is presented in Table 3. From 2019 to 2020, the prevalence of myopia for all grades increased, and the most dramatic change was observed from grades 2–5 and grades 7–8 ($P < 0.05$). Grade 5 had the largest increase in myopia prevalence (5.6%), followed by grades 8 (5.1%), 3 (4.6%), and 7 (4.3%), all of which had an >3.0% increase in prevalence. From 2020 to 2021, the changes in myopia in grades 1–4 were mild and not significantly different. Students in grade 5 had the greatest reduction in myopia ($P = 0.01$). Nevertheless, students in grades 6 and 9 had the greatest growth in myopia prevalence ($P < 0.01$). Prevalence of myopia were higher for all grades in 2021 except grade 1 ($P = 0.25$).

Further analysis showed that the mean SER in urban areas was greater than in rural areas over 3 years except in 2019 ($P = 0.18$), whereas the females were more myopic than males over the 3 years (Table 4). Chi-square tests for trend revealed that the amount of mild myopia increased as the grade level increased from grades 1–6, and gradually decreased with increasing grades from grades 7–9 over 3 years ($P < 0.001$) (Table 5). The prevalence of moderate myopia increased gradually from grades 1–9 over 3 years.The proportion of severe myopia remained stable from Grade 1 to grade 4 but gradually increased from grade 5 (Table 5, Figure 2).

TABLE 2 SER values from grades 1 to grade 9 over the 3 years.

Grade		SER, mean			*P*-value [a]	*P*-value [b]	*P*-value [c]
		2019	2020	2021			
Primary school	1	0.23 ± 0.56	0.24 ± 0.63	0.32 ± 0.71	0.52	<0.01*	<0.01*
	2	0.05 ± 0.758	0.03 ± 0.85	0.05 ± 0.93	0.30	0.92	0.39
	3	−0.21 ± 0.98	−0.28 ± 1.11	−0.25 ± 1.15	<0.01*	0.07	0.17
	4	−0.52 ± 1.25	−0.62 ± 1.33	−0.67 ± 1.40	<0.01*	<0.01*	0.06
	5	−0.93 ± 1.50	−1.04 ± 1.59	−1.01 ± 1.60	<0.01*	0.01*	0.39
	6	−1.35 ± 1.68	−1.41 ± 1.76	−1.49 ± 1.81	0.09	<0.01*	0.01*
Junior school	7	−1.54 ± 1.75	−1.72 ± 1.85	−1.77 ± 1.94	<0.01*	<0.01*	0.20
	8	−1.84 ± 1.88	−2.13 ± 1.94	−2.17 ± 2.03	<0.01*	<0.01*	0.31
	9	−2.28 ± 2.02	−2.35 ± 2.04	−2.57 ± 2.05	0.18	<0.01*	<0.01*

*Significance was set at 0.05.
One-way analysis of variance of the means was used to compare categorical variables between groups.
a, b and c represent P-values for using *Post-Hoc* Multilpe Comparisons between 2019 and 2020, 2019 and 2021, 2020 and 2021, respectively.

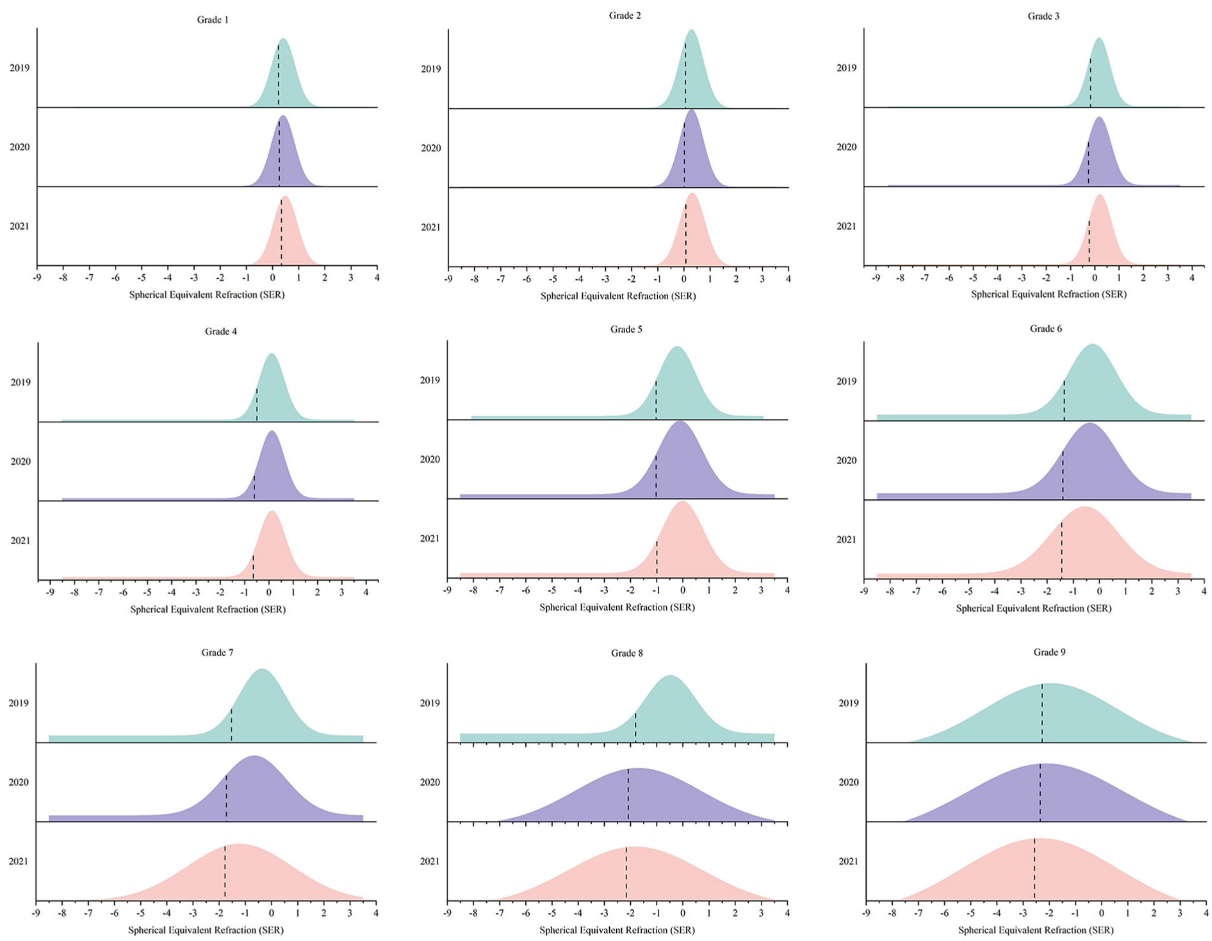

FIGURE 1
The distribution of Spherical Equivalent Refraction (SER) from grades 1 to grade 9 over the 3 years.

TABLE 3 Prevalence of myopia (SER ≤ −0.5D) from grades 1 to grade 9 over the 3 years.

Grades		Prevalence per year, %					
		2019	2020	2021	*P*-value[a]	*P*-value[b]	*P*-value[c]
Primary school	1	6.8	7.1	6.2	0.47	0.25	0.07
	2	16.0	18.3	19.1	0.01*	<0.01*	0.33
	3	29.4	34.0	33.0	<0.01*	<0.01*	0.29
	4	45.0	47.7	49.5	0.01*	<0.01*	0.07
	5	56.8	62.4	59.9	<0.01*	0.01*	0.01*
	6	68.1	69.7	72.5	0.08	<0.01*	0.01*
Junior school	7	72.1	76.4	77.1	<0.01*	<0.01*	0.44
	8	77.0	82.1	82.6	<0.01*	<0.01*	0.54
	9	82.7	83.3	88.0	0.52	<0.01*	<0.01*

*Significance was set at 0.05.
The Chi-square test was used to compare categorical variables between groups.
a, b and c represent P-values for Multiple Comparisons between 2019 and 2020, 2019 and 2021, 2020 and 2021, respectively.

TABLE 4 SER values stratified by gender and region over 3 years.

	SER, mean				
	2019	2020	2021	F	*P*[e]
Male	−0.79 ± 1.60	−0.87 ± 1.69	−0.98 ± 1.80	74.82	<0.001
Female	−0.92 ± 1.65	−1.02 ± 1.73	−1.16 ± 1.88	84.00	<0.001
t	8.27	8.93	9.21		
P[d]	<0.001	<0.001	<0.001		
Urban	−0.84 ± 1.63	−0.96 ± 1.72	−1.11 ± 1.87	139.70	<0.001
Rural	−0.86 ± 1.62	−0.89 ± 1.69	−1.00 ± 1.80	34.76	<0.001
t	1.35	−4.02	−5.84		
P[d]	0.18	<0.001	<0.001		

[d]Comparison underwent Independent Samples T Test.
[e]Comparison underwent One-way ANOVA, P-values of LSD were all <0.05.

Discussion

In this survey, we reported changes in the development of myopia among primary and junior school students before and after the COVID-19 epidemic in Xuzhou, China. The Spot photoscreener used in this investigation showed good diagnostic accuracy and consistency in children's refractive errors screening (11, 12). The SE values obtained by the screener showed good agreement before and after ciliary muscle paralysis in students aged 7–18 years, and the difference in SE values between the autorefractor and Spot screener was ∼ −0.3 D for both the mild and moderate myopia groups (13). Although Spot's accuracy was not as good as cycloplegic refraction, it is useful and effective for screening and monitoring myopia in large populations.

During the COVID-19 pandemic, primary and junior school students in Xuzhou were restricted to home and online education to ensure the successful completion of education and teaching. Our findings showed that the mean SER declined fastest in grades 3–5 and grades 7–8 in 2020 compared with 2019. In other grades, the change was not significant. This finding was slightly different from the results that also used the Spot photoscreener, which indicated the fastest change in SER was noted among children aged 6–8 years from 2019 to 2020 (7). Previous studies have confirmed accelerated myopic progression and more negative SER change during the COVID-19 pandemic (6, 7, 14–17), and we hypothesized that refraction may change in the post-COVID-19 epidemic period. Surprisingly, in this study, except for grades 6 and 9, the refraction of students in other grades remained almost the same in 2021 compared to 2020 and even drifted toward hyperopia in some cases. This finding may be explained by the high pressure experienced by the graduating classes for the primary and junior grades and the stress of offline teaching compared with online teaching.

The mean SER in grades 1 and 2 was higher than that in other reports (18, 19). Xuzhou city is located in the north of Jiangsu Province, which is an economically underdeveloped area with a relatively high proportion of rural areas. The pressure of schoolwork is not as high in this area compared with other developed areas, resulting in a lower myopia rate compared with other developed areas. In addition, the use of a Spot photoscreener in non-ciliary muscle paralysis optometry and examination at a farther distance leads to reduced accommodation stimulation. Thus, the refraction is more hyperopic compared with an autorefractor. In contrast, the stimulation of near-perceived accommodation of autorefractor is evident in non-myopic children. Therefore, the result trends toward myopia, but the effect of accommodation is not evident for myopes. Thus, this setup has minimal effect on the results of examinations in upper grades.

The development of myopia in students is closely related to lifestyle changes, and the prevalence of myopia is increasing

10.3389/fpubh.2022.970751

TABLE 5 The percentage of different degrees of myopia from grades 1 to grade 9 over the 3 years.

Grades	2019				2020				2021			
	No myopia	Mild myopia	Moderate myopia	Severe myopia	No myopia	Mild myopia	Moderate myopia	Severe myopia	No myopia	Mild myopia	Moderate myopia	Severe myopia
Grade 1	93.2%	6.3%	0.4%	0.1%	92.9%	6.7%	0.4%	0.0%	93.8%	5.6%	0.4%	0.1%
Grade 2	84.0%	14.6%	1.4%	0.0%	81.7%	16.6%	1.7%	0.0%	80.9%	17.1%	1.8%	0.1%
Grade 3	70.6%	26.2%	3.2%	0.1%	66.0%	29.4%	4.4%	0.2%	67.0%	28.3%	4.6%	0.1%
Grade 4	55.0%	37.6%	7.3%	0.1%	52.3%	38.6%	8.9%	0.2%	50.5%	38.9%	10.3%	0.4%
Grade 5	43.2%	42.5%	13.7%	0.6%	37.6%	45.8%	16.1%	0.6%	40.1%	43.3%	15.7%	0.8%
Grade 6	31.9%	45.1%	21.9%	1.1%	30.3%	45.3%	23.2%	1.3%	27.5%	46.2%	24.7%	1.6%
Grade 7	27.9%	45.8%	24.9%	1.4%	23.6%	45.7%	28.6%	2.1%	22.9%	44.8%	29.8%	2.5%
Grade 8	23.0%	43.9%	30.9%	2.2%	17.9%	43.2%	35.0%	3.9%	17.4%	42.3%	35.9%	4.3%
Grade 9	17.3%	41.1%	36.3%	5.2%	16.7%	39.0%	39.6%	4.8%	12.0%	39.4%	42.3%	6.4%
χ^2	13,326.301				13,163.838				13,343.917			
P*	<0.001				<0.001				<0.001			

*Significance was set at 0.05.

yearly, especially in China (20). Asian countries are under more academic pressure and have a higher incidence of student myopia than Western countries. A 5-year longitudinal follow-up study of 6–15 years old students in Chongqing showed an annual prevalence of myopia of 10.6% (21). However, the results of a German survey of children aged 0–17 years over the last decade years showed minimal change in the prevalence of myopia (22). In our study, the prevalence of myopia among primary and junior school students increased between 2019 and 2020, and the prevalence of myopia increased with grade level. The increase in myopia prevalence was greater in grades 3–5 and 7–8. Li et al. found that the prevalence of myopia was lower before grade 3 (23), which is consistent with our findings. In contrast, compared to 2020, myopia rates in grades 1–5 were minimally changed in 2021, and even myopia reversal was observed. Myopia drifted to hyperopia after lockdown, as reported by Chang et al. (24). We supposed that this may be explained by accommodation spasms. The refractive system of the human eye is mainly composed of corneal curvature, eye axis length, and eye accommodation. Corneal curvature develops steadily after 2 years of age (25), and Ma et al. (16). reported no significant difference in the change of eye axis during the COVID-19 epidemic. Due to COVID-19, students were restricted to online learning at home, increasing digital screen time, reducing outdoor activities, and leading to accommodation spasms and consequent progression of myopia. However, when offline learning resumes in 2021, the accommodation spasms reverse and cause the refractive state to drift toward hyperopia. Therefore, we believe that partial reversal of the accommodation spasm can change the refractive state. In this study, children in the lower grades were experiencing a highly plastic period of myopia development, and myopia prevention and control may be more effective during this period. This notion should be further evaluated in additional studies. In addition, to guide the prevention and control of myopia among children and adolescents during the COVID-19 epidemic, the National Health Commission of the People's Republic of China has developed myopia prevention guidelines (26). These guidelines included how to provide myopia prevention after online learning and resumption of classes and emphasized reducing time spent on electronics and increasing outdoor activities. This policy contributed to a lower increase in students' myopia rates in 2021 than in 2020.

In our study, the prevalence of myopia in grade 1 was not reduced from 2019 to 2021, and was not affected by the COVID-19 epidemic. Because our annual screenings were conducted in the first 2 months of the school year, students in grade 1 were not truly in the learning stage. Thus, the prevalence of myopia was lower than in other grades.

The prevalence of myopia from grades 7–8 also increased in 2021 but was not statistically significant. However, the change in myopia rates for grades 6 and 9 was higher in 2021 than in 2020. The increased intensity of education in the graduating grades led to more time spent performing near-work activities, less time spent outdoors, and less time sleeping compared to the non-graduating grade. Educational intensity (27), outdoor activity time (28), and sleep duration (29) are associated with myopia progression. Offline courses were resumed in April 2020 (30). To compensate for the knowledge not covered by online education, graduating grades faced more pressure to pursue further education with stronger supervision from schools and teachers, leading to a surge in their learning pressure and a sharp increase in myopia. We recommend that schools and parents pay more attention to graduating grades during the post-COVID-19 epidemic period.

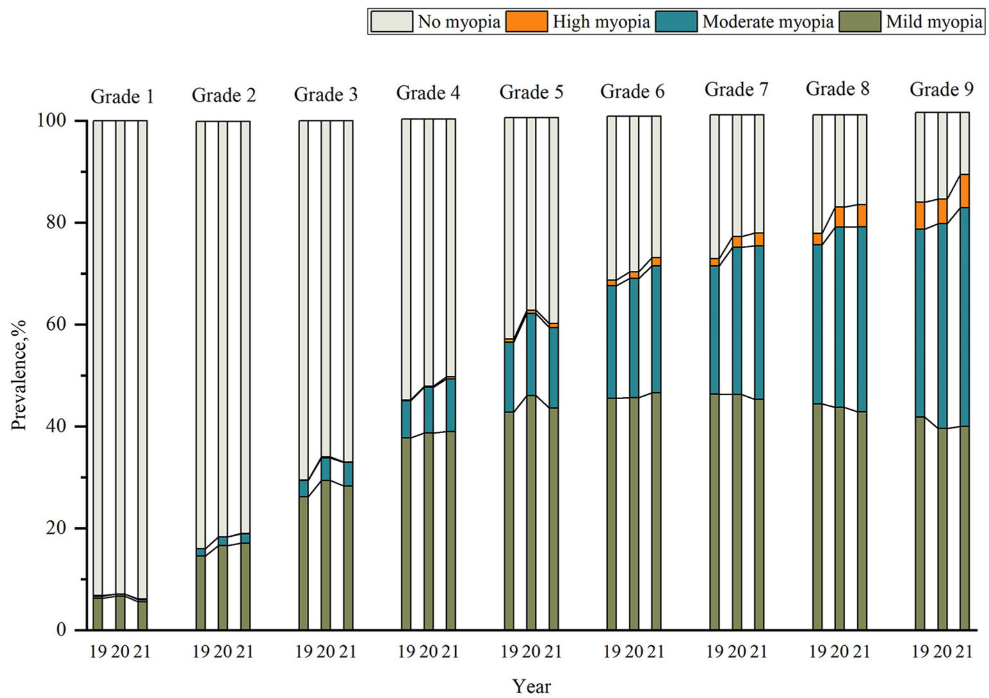

FIGURE 2
Changes in the degree of myopia in grades 1–9 over the 3 years.

As shown in other studies (7, 14, 15), in our three-year study, females had higher myopia rates than males. This finding may be explained by the notion that girls are quieter than boys and spend more time studying and less time participating in outdoor activities than boys. An epidemiological study reports female is a risk factor for myopia (31). An article monitoring refractive development in children found that girls have steeper corneas, shallower anterior chambers (32), and shorter eye axes than boys (33). The present study noted that gender differences occurred primarily after grade 3 (Figure 2). Some studies suggest that this founding is due to estrogenic changes that alter female vision during adolescence (34). In addition, this study also confirmed that urban students have higher myopia rates than rural students over the 3 years except in 2019. During the epidemic period, the urban students were required to be segregated at home, while the rural students may be in the yard or in a more open area for activites. This phenomenon persisted in the post-COVID-19 epidemic. This result is comparable to the results of previous studies (35, 36). This finding suggests that environmental factors may play a major role in the development of myopia in Chinese children (37). However, more urban students were analyzed in higher numbers than the rural students over 3 years which could have also contributed to the gross increase in the number in raw data rather than a "true" increase in incidence, and further investigation is needed in future studies.

This study had some limitations. First, the myopia assessment index selected in this study was collected using the Spot photoscreener. Although this technology is useful for screening, it is currently not a substitute for cycloplegic refraction. Second, studies have shown that myopia is caused by a variety of factors, including light and time spent performing outdoor activities and near-work activities (38). Third, we did not include preschoolers and could not understand changes in the development of myopia in younger children in the post-COVID-19 epidemic period. Fourth, our study only analyzed the development of myopia according to gender and region. Subsequent studies should be designed more specifically to assess the factors influencing myopia development.

Conclusion

Our research confirmed the prevalence of myopia increased during the COVID-19 epidemic. However, the spherical equivalent refraction of lower grades children drifted to hyperopia and the trends of myopia development remained stable in the post-COVID-19 epidemic period. We should be more concerned about the prevalence of myopia in graduating for the primary or junior grades in the future.

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

Study approval was obtained from the Ethics Board of The First People's Hospital of Xuzhou (No.xyyll[2019]022). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

WZho and XW: concept and design. WZho, QL, HC, and YL: acquisition, analysis, and interpretation of data. WZho, QL, and SL: drafting of the manuscript. YL and XW: critical revision of the manuscript for important intellectual content. WZho, HC, WW, and YP: statistical analysis. XW: obtained funding and supervision. WZha and QW: administrative, technical, and material support. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Xuzhou Medical Leading Talent Training Project (Grant No. XWRCHT20210022), Postgraduate Research and Practice Innovation Program of Jiangsu Province (Grant No. KYCX22_2978).

Acknowledgments

The manuscript has received English editing. We thank the children who participated in our study and the families that supported the Xuzhou Children's Eye Study. We also thank our colleagues and volunteers for all their hard work and dedication in collecting the data for this study.

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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 13 October 2022
DOI 10.3389/fpubh.2022.993728

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 14 July 2022
ACCEPTED 08 September 2022
PUBLISHED 13 October 2022

CITATION
Wang W, Xiang Y, Zhu L, Zheng S, Ji Y, Lv B, Xiong L, Li Z, Yi S, Huang H, Zhang L, Liu F, Zhang T, Wan W and Hu K (2022) Myopia progression and associated factors of refractive status in children and adolescents in Tibet and Chongqing during the COVID-19 pandemic.
Front. Public Health 10:993728.
doi: 10.3389/fpubh.2022.993728

Myopia progression and associated factors of refractive status in children and adolescents in Tibet and Chongqing during the COVID-19 pandemic

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Objectives: To investigate myopia progression and associated factors of refractive status among children and adolescents in Tibet and Chongqing in China during the COVID-19 pandemic.

Methods: A population-based cross-sectional study was conducted to compare rates of myopia and high myopia, axial length (AL), spherical equivalent (SE), outdoor activity time, digital device use, and frequency of visual examinations for children and adolescents affected by myopia in Chongqing and Tibet in 2021.

Results: A total of 2,303 students from Chongqing and 1,687 students from Tibet were examined. The overall prevalence of myopia and high myopia in these two groups were 53.80 and 7.04% vs. 43.86 and 1.30%, respectively in each case. The Chongqing students had a longer AL than the group from Tibet (23.95 vs. 23.40 mm, respectively; $p < 0.001$). The mean SE of the students with myopic parents in Tibet was lower than that of the students in Chongqing with myopic parents (-2.57 ± 2.38 diopters (D) vs. -2.30 ± 2.34 D, respectively) ($p < 0.001$). Conversely, the mean SE of the students from urban areas in Chongqing was lower than that of the students in Tibet (-2.26 ± 2.25 D vs. -1.75 ± 1.96 D, respectively; $p < 0.001$). The Chongqing students exhibited lower SE (-2.44 ± 2.22 D) than their Tibetan counterparts (mean SE: -1.78 ± 1.65 D ($p = 0.0001$) when spending more than 2.5 h outdoors. For example, 61.35% of the students in Tibet spent more than 2.5 h outdoors daily, compared with 43.04% of the students in Chongqing. Correspondingly, the proportion of students using digital devices in Tibet (64.43%) was lower than that in Chongqing (100%). For the latter, 38.62% of the students in Chongqing spent more than 2.5 h online using digital devices compared to 10.49% of the students in Tibet. Greater monitoring of visual status was observed for the Chongqing students (mean SE:

−1.90 ± 1.98 D) compared with students in Tibet (mean SE: −2.68 ± 1.85 D) (p = 0.0448), with the frequency of optimal examinations being every 6 months. Outdoor activity time was identified as a common risk factor for myopia in both of the populations examined, with odds ratios (ORs) of 1.84 (95% CI: 1.79–1.90) in Chongqing and 0.84 (95% CI: 0.73–0.96) in Tibet. Digital screen time was associated with myopia and high myopia in Chongqing, with ORs of 1.15 (95% CI: 1.08–1.22) and 1.06 (95% CI: 0.94–1.77), respectively. Digital screen time was also found to be a risk factor for high myopia in Tibet (OR: 1.21, 95% CI: 0.77–1.61). The type of digital devices used was also associated with myopia and high myopia in Tibet (OR: 1.33, 95% CI: 1.06–1.68 and OR: 1.49, 95% CI: 0.84–2.58, respectively). Finally, examination frequency was found to correlate with high myopia in the Tibet group (OR: 1.79, 95% CI: 0.66–2.71).

Conclusion: Based on our data, we observed that the prevalence of refractive errors in children and adolescents was significantly lower in Tibet than in Chongqing. These results are potentially due to prolonged outdoor activity time, and the type and time of use for digital devices that characterize the group of children and adolescents from Tibet. It is recommended that parents and children in Chongqing would benefit from increased awareness regarding myopia progression and its prevention.

KEYWORDS

plateau, outdoor activity time, digital screen time, digital devices, parental awareness, COVID-19

Introduction

Myopia has been widely recognized as a major cause of visual impairment. It is predicted by 2050 that nearly half of individuals worldwide will be affected by myopia, with one in five diagnosed with high myopia (1, 2). The countries currently reporting high prevalence of myopia are clustered in East and Southeast Asia. There is a socioeconomic burden associated with cases of myopia due to treatments and monitoring that are needed (3–5). In China, the world's most populous country, the rate of myopia among children and adolescents has continued to rise in recent years. Moreover, the age-adjusted prevalence of myopia in the Chinese population is approximately twice as high as the prevalence rates reported for Caucasian or African populations of children and adolescents (6). By 2050, the prevalence of myopia among children and adolescents aged 3–19 years in China is estimated to be approximately 84% (6). An increased incidence of myopic-related complications is also predicted, and these may involve myopic macular degeneration, retinal detachment, cataracts, and open-angle glaucoma. Furthermore, these conditions may represent important risk factors for irreversible vision loss in cases of high myopia (7).

Prior to the COVID-19 pandemic, at least 2.6 billion people worldwide were experiencing vision impairment. Moreover, a significant proportion of affected individuals were younger than 18 years of age, which is a crucial stage for sensory function growth and intensive eye use (8, 9). Studies have shown that myopia is caused by interactions between both genetic and environmental factors, with identified risk factors, including reduced time outdoors and increased near work (10). During the COVID-19 pandemic, a decrease in outdoor activities and increases in digital screen time due to online courses contributed to the onset and progression of myopia (11, 12). Long-term school closures and home-based study hall may also have impacted the visual status of students. In addition to the effects of visual impairment on reading speed, accuracy, and fluency (13), it can also negatively affect economic development (14). However, if refractive error is corrected, the annual monetary cost for rehabilitation and medical care can be lessened by up to 15% (15).

The Tibetan population in China is distinct from inland populations of China due to its geographical environment, socioeconomic level, and cultural characteristics. Accordingly, congenital heart disease, hypertension, and cataracts have a high incidence and regional characteristics unique to Tibet (16). Some studies have reported that the incidence of myopia among children and adolescents in Tibet is lower than that in the plain areas of China (17–19). However, possible reasons for the observed difference remain unclear. In addition, controlled studies of populations in plain and plateau areas have not been conducted. Qamdo is located in eastern Tibet and has an average altitude of over 3,500 m. It is also characterized by low atmospheric pressure and strong ultraviolet radiation. In contrast, the region of Chongqing is approximately 400 m above sea level and is a much more developed region. Therefore, in this study, we included children and adolescents from two representative regions in China, Qamdo in Tibet and Chongqing, to investigate progression of myopia in plateau vs. plain areas during the COVID-19 pandemic.

Methods

Study population

A total of 2,302 students from Chongqing and 1,687 students from Qamdo in Tibet were enrolled in this population-based study. The regions of Chongqing and Tibet represent distinct differences in elevation, at approximately 400 and 3,500 m above sea level, respectively. The rural districts that are encompassed by Tibet include the counties of Chagyab, Markam, and Dengqen. Exclusion criteria for this study were a diagnosis of strabismus or amblyopia. This study included students from first grade of primary school through the senior 2 level. Senior 3 students did not participate due to their preparation for College Entrance Exams. Students from primary schools through junior high schools and their parents/custodians were involved. Each class was randomly selected. If there were less than 25 students per class, students from adjacent classes of the same grade level were enrolled.

Study design and questionnaire

This population-based cross-sectional study was conducted between January 2021 and May 2021 by adopting stratified cluster sampling. Eligible students and their parents were invited to participate in field tests, questionnaires, and home visits in accordance with the National Student Physique and Health Survey. The questionnaires addressed basic information such as name, age (grade), birth date, gender, heredity, and region, and associated factors such as outdoor activity time, digital device type and time of use, and parental awareness. The Ethics Board of the First Affiliated Hospital of Chongqing Medical University approved this study, and it was conducted in accordance with the tenets of the Declaration of Helsinki. At least one parent or legal guardian of each enrollee was provided with information about the study, and informed consent was signed.

Visual acuity measurement

The inspection team designated professionals to refine and monitor visual acuity and refractive status for the enrolled students. The equipment used was approved and checked by relevant departments, and received metrological verification and calibration on a regular basis. The logarithmic visual acuity chart used conforms to the national standard (GB11533 standard logarithmic acuity chart). The autorefractometer used meets the requirements of standard criteria (ISO10342 Ophthalmic Instruments-Optometry). Axial length (AL) and mean spherical equivalent (SE) refraction were measured with an optometry unit (Supore, China). SE equals diopter of spherical power (DS) plus 1/2 diopter of cylindrical power (DC). Students exhibiting either of two conditions were judged to be myopic: (a) those wearing orthokeratology lenses or (b) those having a mean uncorrected visual acuity (UCVA) <5.0 and a mean SE < -0.50D (20). In addition, high myopia was defined as having an SE ≤ -6.00 D (21).

Statistical analysis

Data analysis was conducted by using GraphPad Prism 8 statistical software (GraphPad Software, Inc., San Diego, CA, USA). Reported mean ± standard deviation values represent data exhibiting normal distribution, whereas median (M) and interquartile range (P25 and P75) values represent data without normal distribution. Binary logistic regression was used to correct for influencing factors. The Kruskal–Wallis and Mann–Whitney tests were adopted to compare variables. Multivariate logistic regression was performed to screen risk factors associated with myopia and high myopia. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

Results

General information

Overall myopia rates for the adolescent populations examined in Chongqing and Tibet were 53.80 and 43.86%, respectively. The overall high myopia rates were 7.04 and 1.30%, respectively. Compared to Tibet, the myopic rate was higher among each grade of students from Chongqing (Table 1).

Gender, heredity, and regional factors

The students in Chongqing had a longer AL than their counterparts in Tibet (23.95 vs. 23.40 mm, respectively; $p < 0.001$). Mean SE with demographic factors is presented in Table 2. Female gender exhibited a greater predisposition for myopia than the male gender, and the mean SE for female in Chongqing (-2.23 ± 1.41 D) was lower than that of the female in Tibet (-1.40 ± 1.88 D) ($p < 0.001$). For students with myopic parents, the mean SE for the Tibet group (-2.57 ± 2.38 D) was

10.3389/fpubh.2022.993728

TABLE 1 Comparison of myopic rates according to grade for the students examined from Tibet and Chongqing.

Categories	Tibet(N)	Chongqing(N)
P1	20(13.42%)	58(26.61%)
P2	18(11.04%)	60(33.52%)
P3	35(21.88%)	61(34.68%)
P4	43(26.06%)	69(39.66%)
P5	64(36.36%)	92(54.76%)
P6	86(44.33%)	108(63.16%)
J1	87(48.04%)	211(68.73%)
J2	87(50.98%)	242(81.61%)
J3	108(63.53%)	237(77.19%)
H1	164(64.65%)	288(80.83%)
H2	167(74.44%)	294(88.74%)

Myopic rate of each grade in Tibet and Chongqing.
N%, myopia rate; P, primary school; J, junior school; H, high school; "1–6," grade.

lower than that of the Chongqing group (−2.30 ± 2.34 D) ($p < 0.001$). The numbers of students from rural and urban districts in Tibet and Chongqing were 1,176 and 511, and 1,505 and 797, respectively in each case. Accordingly, the mean SE for children and adolescents in the urban areas of Chongqing was lower than for the children and adolescents from Tibet (−2.26 ± 2.25 D and −1.75 ± 1.96 D, respectively; $p < 0.001$ in each case).

The data obtained for Tibet were based on children and adolescents enrolled from three rural districts. These districts include the counties of Chagyab ($N = 341$, mean SE = −0.94 ± 1.32, $p < 0.001$), Markam ($N = 401$, mean SE = −0.80 ± 1.39, $p < 0.001$), and Dengqen ($N = 434$, mean SE = −0.70 ± 1.40, $p < 0.001$). These regions have minimum altitudes of 3,170, 3,865, and 3,870 m above sea level, respectively. The myopia rates of these three districts were: 24.75, 30.48, and 33.24%, respectively.

Outdoor activity time

Outdoor activity time was defined as daily exposure to sunlight outdoors (22), with categories of <2.5 h and ≥2.5 h established for this study. The percentage of Tibetan students who spent more than 2.5 h outdoors each day (61.35%) was higher than that for the Chongqing students (43.04%). Moreover, extended outdoor activity time corresponded with better visual status in both the Chongqing and Tibet populations examined. For example, the students in Tibet and Chongqing who experienced ≥2.5 h outdoors each day had mean SE values of −1.78 ± 1.65 D and −2.44 ± 2.22 D, respectively ($p = 0.0001$).

Digital devices

The digital devices considered included: televisions, computers, cell phones, and tablet PCs. Digital screen time was defined as the average amount of time students spent on these devices each day (23). The overall proportion of students using digital devices in Tibet (64.43%) was lower than that (100%) in Chongqing. Cell phones were the most commonly used digital devices in both Tibet and Chongqing, with use by 366 (21.70%) and 949 (41.23%) students, respectively. In Tibet, this was followed by televisions (344, 20.39%), tablet PCs (189, 11.20%), and computers (188, 11.14%). In Chongqing, tablet PCs (838, 36.40%), computers (413, 17.94%), and televisions (102, 4.43%) followed. It was further observed that in Chongqing, cell phone users exhibited the lowest SE (−2.53 ± 2.32 D), whereas cell phone users in Tibet exhibited relatively better visual acuity (−1.88 ± 1.87 D) ($p < 0.001$). Computer users demonstrated the best visual acuity in Chongqing and Tibet, with the mean SE of the Chongqing group (−1.46 ± 1.38 D) being higher than that of the Tibet group (−1.52 ± 1.76 D) ($p < 0.0001$).

Classification of utility time on digital devices was consistent with that of outdoor activity time. For example, students in both Chongqing and Tibet exhibited the greatest visual status when they reported use of digital devices for less than 2.5 h/day. In contrast, 38.62% students in Chongqing used digital devices for more than 2.5 h/day, whereas this percentage was 10.49% for the students in Tibet. Similarly, the SEs for these two groups were −2.52 ± 2.09D and −2.48 ± 2.07 D, respectively ($p = 0.004$).

Parental awareness of myopia prevention

Parental awareness is one of the factors associated with myopia prevention. For our cohort, the frequency of visual examinations ranged from once per quarter, to twice a year, and to once a year. In Chongqing, the proportions of students for these three frequencies were 389 (16.90%), 1,086 (47.18%), and 827 (35.92%), respectively; meanwhile, the frequencies for Tibet were 169 (10.01%), 149 (8.83%), and 155 (9.19%), respectively. The students undergoing a visual examination twice a year exhibited the highest SE (which was the most appropriate recheck period), followed by the quarterly and yearly frequencies (Figure 1). The students in Chongqing who received a visual examination twice a year had a higher SE (−1.90 ± 1.98 D) than the students with the same examination frequency in Tibet (mean SE: −2.68 ± 1.85 D ($p = 0.0448$).

Multivariate logistic regression analysis

Multivariate logistic regression identified outdoor activity time as a common risk factor for myopia in both of the adolescent populations from Chongqing and Tibet [OR: 1.84

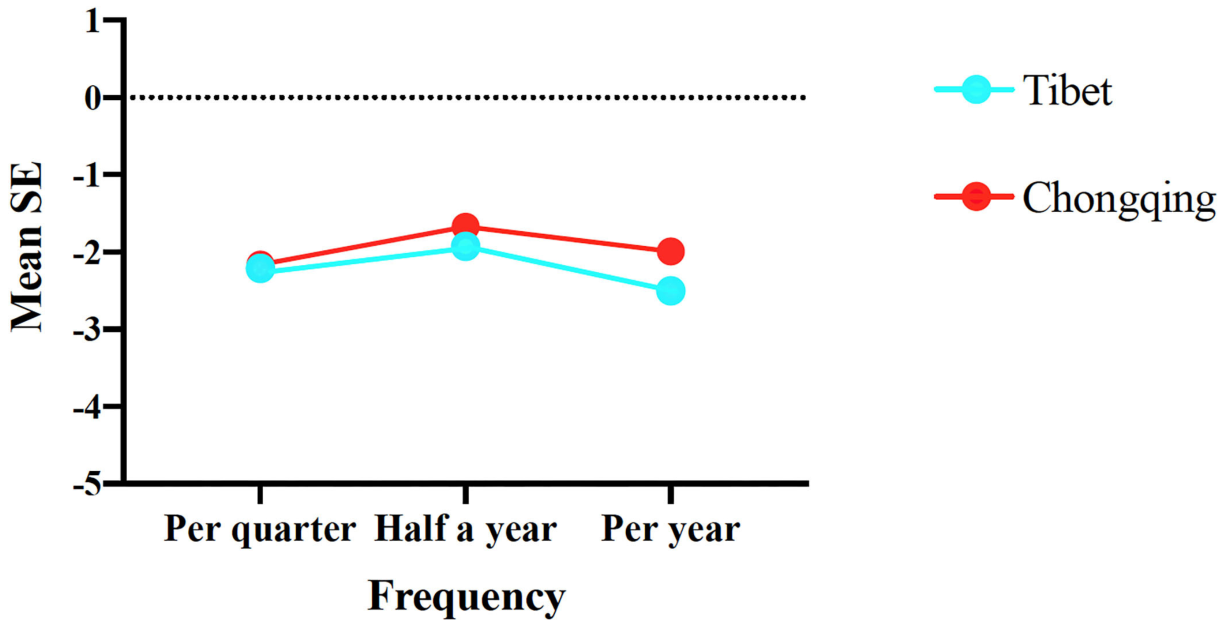

FIGURE 1
Mean SE according to parental awareness for the student groups from Chongqing and Tibet. The Kruskal–Wallis test was used to compare mean SE of examination frequency in Chongqing and Tibet.

TABLE 2 The mean uncorrected visual acuity and spherical equivalent refraction with demographic factors.

	Tibet		Chongqing		*P*
	Categories	**Mean SE(D) ± SD**	**Categories**	**Mean SE(D) ± SD**	
Gender	Male (N = 829)	−1.02 ± 1.56	Male (N = 1,142)	−2.19 ± 2.14	< 0.001
	Female (N = 858)	−1.40 ± 1.88	Female (N = 1,160)	−2.23 ± 1.41	< 0.001
Heredity	With myopic parents (N = 548)	−2.57 ± 2.38	With myopic parents (N = 789)	−2.30 ± 2.34	< 0.001
	With emmetropic parents (N = 1,139)	−2.02 ± 1.98	With emmetropic parents (N = 1,499)	−1.95 ± 1.94	< 0.001
Region	Rural (N = 1,176)	−0.92 ± 1.30	Rural (N = 797)	−1.37 ± 2.09	< 0.001
	Urban (N = 511)	−1.75 ± 1.96	Urban (N = 1,505)	−2.26 ± 2.25	< 0.001

The mean SE in Chongqing and Tibet were compared by the Mann–Whitney test.

(95% CI: 1.79–1.90) vs. 0.84 (95% CI: 0.73–0.96), respectively] (Tables 3, 4). Digital screen time was associated with myopia and high myopia in Chongqing, with ORs of 1.15 (95% CI: 1.08–1.22) and 1.06 (95% CI: 0.94–1.77), respectively (Table 3). However, digital screen time was only a risk factor for high myopia in Tibet (OR: 1.21, 95% CI: 0.77–1.61), whereas use of digital devices was associated with both myopia and high myopia in Tibet (OR: 1.33, 95% CI: 1.06–1.68; OR: 1.49, 95% CI: 0.84–2.58). Examination frequency was also identified as a risk factor for high myopia in Tibet (OR: 1.79, 95% CI: 0.66–2.71) (Table 4). Meanwhile, in Chongqing, outdoor activity time, digital screen time, digital device use, and examination frequency were identified as risk factors for AL. In Tibet, the only risk factors for AL were digital screen time and examination frequency (Tables 3, 4).

Discussion

In this population-based cross-sectional study of incidence of myopia among children and adolescents in Tibet and Chongqing, the total myopia rate of Tibetan children and adolescents (N = 1,687) living in a plateau region was higher than that of Han children and adolescents living in Chongqing (N = 2303) during the recent COVID-19 outbreak. The mean SE of children and adolescents in urban areas of Chongqing

TABLE 3 Multivariate logistic regression results for myopia and high myopia in Chongqing.

Variable (Chongqing)	Myopia ($N = 1,239$)			High myopia ($N = 162$)			Axial length(mm)		
	Odds ratio (95% CI)	P	β	Odds ratio (95% CI)	P	β	95% CI	P	β
Outdoor activity time	1.84 (1.79–1.90)	< 0.0001	0.17	0.84 (0.73–0.96)	< 0.0001	−0.17	−0.14 to 0.06	< 0.0001	0.02
Digital screen time	1.15 (1.08–1.22)	< 0.0001	0.19	1.0 6 (0.94–1.77)	< 0.0001	0.05	0.06 to 0.13	0.0011	0.02
Digital devices	0.85 (0.77–0.88)	< 0.0001	−0.16	0.63 (0.51–0.79)	< 0.0001	−0.44	−0.18 to 0.06	< 0.0001	0.03
Examination frequency	0.82 (0.76–0.88)	< 0.0001	−0.19	0.91 (0.80–1.05)	< 0.0001	−0.09	−0.13- to 0.05	< 0.0001	0.02

CI, confidence interval; OR, odds ratio.
Odds ratio (95% confidence interval) of myopia (SE < 0.50 D) and high myopia (SE ≤ −6.00 D), comparing the outdoor activity, digital screen time, digital devices and examination frequency. OR = 1, no correlation between exposure and outcome; OR > 1, exposure contributes to outcome; OR < 1, exposure prevents the outcome.

TABLE 4 Multivariate logistic regression results for myopia and high myopia in Tibet.

Variable(Tibet)	Myopia ($N = 740$)			High myopia ($N = 22$)			Axial length (mm)		
	Odds ratio (95% CI)	P	β	Odds ratio (95% CI)	P	β	(95% CI)	P	β
Outdoor activity time	1.04 (0.92–1.18)	= 0.0013	0.04	0.77 (0.44–1.23)	= 0.0021	−0.26	−0.16 to 0.01	0.0048	−0.07
Digital screen time	0.93 (0.81–1.09)	= 0.0001	−0.07	1.21 (0.77–1.61)	= 0.0024	0.11	0.05 to 0.20	0.0041	0.08
Digital devices	1.33 (1.06–1.68)	< 0.0001	0.03	1.49 (0.84–2.58)	= 0.0001	0.40	−0.12 to 0.02	0.0089	−0.05
Examination frequency	0.93 (0.65–1.31)	< 0.0004	−0.07	1.79 (0.66–2.71)	=0.0001	0.58	−0.15 to 0.25	0.0044	0.05

CI, confidence interval; OR, odds ratio.
Odds ratio (95% confidence interval) of myopia (SE < 0.50 D) and high myopia (SE ≤ −6.00 D), comparing the outdoor activity, digital screen time, digital devices and examination frequency. OR = 1, no correlation between exposure and outcome; OR > 1, exposure contributes to outcome; OR < 1, exposure prevents the outcome.

was also lower than that in Tibet (−2.26 ± 2.25 D vs. −1.75 ± 1.96 D, respectively) ($p < 0.001$). However, it was also observed that the mean SE of students with myopic parents in Tibet (−2.57 ± 2.38 D) was lower than that in Chongqing (−2.30 ± 2.34 D) ($p < 0.001$). Overall, the percentage of students in Tibet who spent more than 2.5 h outdoors each day was higher in Tibet than in Chongqing (61.35 vs. 43.04%, respectively). Conversely, the percentage of students who spent more than 2.5 h on digital devices was 3× higher among the students in Chongqing compared with those in Tibet (38.62 vs. 10.49%, respectively). Furthermore, greater monitoring of visual status among the Chongqing students was observed compared with the students of Tibet, with the optimal examination frequency being every 6 months.

Our observation showed that the myopia rate of children and adolescents living in plateau areas is lower than that of children and adolescents living in plain areas and is consistent with previously published results (24). There are multiple factors that may contribute to the observed differences in myopia rates. Accumulating evidence consistently demonstrates that time outdoors is a protective factor for myopia (25–27), with prolonged light exposure or increased light intensity promoting secretion of dopamine in the retina (28, 29). As a result, myopic progression is mitigated (30). Jin et al. (31) and He et al. (32) also revealed that an additional 20–40 min outside the classroom can help slow progression of myopia. For children with myopic parents, outdoor activity time with stronger sunlight intensity can protect these children from the onset of myopia (33). In Tibet, the average number of hours of sunshine and the light intensity are longer than in Chongqing. Moreover, we found that the percentage of Tibetan students who spent more than 2.5 h outdoors every day (61.35%) was higher than that in Chongqing (43.04%), which is consistent with the lower myopia rate observed among children and adolescents in our sample from Tibet.

Oculometric differences between different ethnic groups have been reported in a previous study (34). For example, Goh et al. (35) and Pan et al. (36) reported that Chinese populations have a higher prevalence of myopia than Indian and Malaysian populations in Singapore. Wang et al. (37) also found that myopia prevalence in the Han population (32.93%) is significantly higher than in the Tibetan population (21.64%) when they studied individuals over the age of 50 years living in Xining and surrounding areas. The same group also reported a higher age-adjusted prevalence of myopia in the Han population (31.8%) than in the Mongolian population (23.0%) in Inner Mongolia (38). Thus, ethnic differences appear to contribute to myopia incidence, and that was observed in the present study. However, most of the students included from Qamdo were Tibetan, so there were insufficient data to compare differences in myopia rates among different ethnic groups in the plateau regions. Previously, Wei et al. (39) reported that exposure to ambient air pollutants is associated with the pathogenesis of myopia. According to the official website of the Ministry of Ecology and Environment People's Republic of China (https://www.mee.gov.cn/), air pollution in Chongqing is consistently more serious than in Tibet. Thus, it is possible that environmental pollution may have further contributed to the difference in myopia rates observed in the present study.

Myopia appears to be strongly associated with near-work activities related to education and digital screen use (40). In the present study, students in Tibet had lower rates of digital device use, higher rates of choosing televisions and computers when using digital devices, and lower rates of using digital devices for more than 2.5 h compared with students in Chongqing. In a systematic review, a possible association between exposure to smart devices and an increased risk of myopia was observed (41). Ma et al. (42) also reported that time spent on digital screen devices was related to increases in myopia prevalence, whereas progression of myopia was slowed with use of projectors and televisions compared with use of mobile phones and tablets. Therefore, time spent using digital devices, and the type of digital devices used, contributed to the difference in myopia rates between plain and plateau areas. An association between myopia and years of education has also been reported in previous studies (43, 44). In China, children usually start primary school at an age of 6 or 7 years. However, the age of preschool education varies in different regions. In general, children in rural areas spend less time in preschool compared to urban areas, and less developed areas are characterized by shorter periods of preschool education than relatively developed areas. Similarly, there are also differences in educational pressure. Consistent with the results of previous studies (45, 46), we observed that the myopia rate of rural students in both plain and plateau areas was significantly higher than that of urban students. It is possible that earlier access to preschool education and greater educational pressure may have contributed to the higher rate of myopia among urban students than rural students, and it may represent an important reason for the higher rate of myopia observed in plain areas compared with plateau areas.

Interestingly, a recent study (47) showed that children ranging in age from 11 to 15 years exhibited a significantly enhanced risk of high myopia. These data indicate that younger children may represent a population that is more susceptible to myopia, and they suggest that myopic parents should pay greater attention to their children's eyesight in this age bracket. It has been observed that parents are generally nonchalant regarding health risks, incidence of myopia, and potential for a diagnosis of myopia (48, 49). Therefore, we propose that advocating frequent visual examinations may advance parents' awareness of myopia. In plateau areas, parents have been motivated to raise consciousness about myopic progression in children and the possibility of preventing myopia. However, this awareness and advocacy has not been matched with supporting measures (50). In the present study, the importance of parental awareness was demonstrated by investigating students' visual examination frequency. Other studies have revealed that parents worry about myopia in terms of time and financial burdens, in addition to concern regarding predisposition for high myopia (51). Economic and civilization standards are closely related to efforts to mitigate myopia progression. Parents also need to be directly engaged given their dominant role in determining the amount of indoor vs. outdoor activities that their children participate in Lee et al. (52). Therefore, parental behavior and impact with respect to children to mitiprogression is of particular concern and represents an acute area for awareness in societies.

Study limitations

There are limitations associated with the present study. First, missing data and uncooperative participants were inevitable despite our efforts to perform a thorough survey of children and adolescents in the Chongqing and Tibet regions. As a result, broad 95% CIs were observed. Second, data regarding visual acuity prior to the COVID-19 pandemic were not obtained. Consequently, differences in the degree of myopia between the two regions with and without pandemic conditions could not be confirmed. Third, the other ethnic populations living in Tibet and Chongqing were not included in our present investigation. It is anticipated that these considerations can be addressed in future studies.

Conclusion

The prevalence of myopia in Tibet was lower than that in Chongqing, accounting for gender, heredity, and regional factors. Outdoor activity time, selection of and time on digital devices, and parental awareness were factors associated with myopia progression. To identify and promote preventive strategies for myopia, risk factors for myopia and high myopia will continue to be examined. Moreover, this longitudinal epidemiological survey will continue to explore the prevalence of myopia in distinct altitudes.

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 Ethics Board of the First Affiliated Hospital of Chongqing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

WWang and YX analyzed the data. LZ, BL, YJ, SZ, ZL, SY, LX, and TZ provided constructive advice for conception and data analysis. WWang wrote the manuscript. KH and WWan designed the study and reviewed the manuscript. KH, HH, FL, and LZ supervised the study. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (General Program, Grant Nos. 81100657, 81570832, 81870650, and 81970832), the Project Foundation of Chongqing Science and Technology Commission of China (General Program, Grant Nos. cstc2018jcyjA0429 and Cstc2021jcyj-msxmX0967), Chongqing Education Commission Project Fund of China (CQGJ17062B), and the Project of Chongqing Health Commission combined with Science and Technology Commission of China (2018GDRC008 and 2018MSXM003).

Acknowledgments

We are indebted to KH and WWan from Chongqing Medical University, the First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, and Chongqing Eye Institute, Chongqing, China for their help in supervising this manuscript.

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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TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fped.2022.1056888

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 29 September 2022
ACCEPTED 24 October 2022
PUBLISHED 17 November 2022

CITATION
Hui W, Xiaofeng H, Hua X, Yihan D and Yong T (2022) Assessment of choroidal vascularity and choriocapillaris blood perfusion in Chinese preschool-age anisometropic hyperopic amblyopia children.
Front. Pediatr. 10:1056888.
doi: 10.3389/fped.2022.1056888

Assessment of choroidal vascularity and choriocapillaris blood perfusion in Chinese preschool-age anisometropic hyperopic amblyopia children

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Purpose: To determine the macular and peripapillary area choroid microstructure parameters of hyperopic anisometropic amblyopia eyes and compare to fellow and age-matched control eyes. To assess the correlation between the axial length (AL), choroidal thickness (CT) and choroid microstructure parameters.

Methods: This cross-sectional comparative, non-interventional study involved 52 hyperopic anisometropic amblyopia children and 48 age-matched heathy controls. 52 eyes with hyperopic anisometropic amblyopia and 48 age-matched control eyes were studied. The peripapillary and subfoveal CT were determined. The total choroidal area (TCA), luminal area (LA), and stromal area (SA) of the subfoveal and peripapillary choroid were measured. In addition, the correlation between the AL, CT and choroid microstructure parameters were calculated.

Results: The peripapillary and subfoveal CT of the amblyopic eyes was significantly thicker than the fellow and control eyes (all $P < 0.05$). The subfoveal and peripapillary choroidal SA, LA and TCA of the amblyopic eyes were significantly increased than that of the fellow and control eyes (all $P < 0.05$). The choroidal vascularity index (CVI) values of the amblyopic eye were significantly different among the three groups ($P < 0.05$). There was a statistically significant negative correlation between AL and subfoveal CT (SFCT), LA and TCA levels ($P < 0.001$, $P = 0.039$, $P = 0.027$, respectively). Spherical equivalent (SE) was positive correlated with SFCT, LA and TCA levels ($P = 0.456$, 0.229 and 0.240, respectively; all $P < 0.05$). There was a statistically significant positive correlation between SFCT, SE, LA, SA, TCA and CVI levels (all $P < 0.05$).

Conclusion: The subfoveal and peripapillary CT of amblyopic children abnormally increased and correlated with shorter AL and higher SE. The choroidal structure of the amblyopic eyes was different from the fellow and control eyes, the hyperopic anisometropic amblyopic eyes had significantly thicker sub-foveal choroid, higher LA, SA, and TCA. AL and CT affect choroidal structure and vascular density. Choroidal blood flow may be increased in amblyopic eyes. The larger LA, SA, TCA, and lower CVI were characteristic of the amblyopic eye.

KEYWORDS
hyperopia, amblyopia, choroidal vascularity index, anisometropic, choriocapillaris blood perfusion choroidal thickness

Introduction

Amblyopia is a monocular or binocular visual dysfunction caused by form deprivation and abnormal binocular interaction during the critical period of the visual cortex. It is one of the most common causes of unilateral vision impairment in children and young adults, and the incidence is reported to range 1%–3.5% (1, 2). Amblyopia is thought to be related to dysfunction in the processing of visual information or a deficit in optotype acuity in the absence of ocular and neural pathological changes (3, 4). The risk factors of amblyopia include anisometropia, strabismus, form deprivation, and high bilateral refractive errors (5). Hyperopic anisometropia is the most frequent risk factor for amblyopia. Amblyopic eyes are structurally normal on clinical examinations.

In recent years, whether the microscopic retina and choroid are changed in the patients with amblyopia has aroused widespread attention. The choroid plays a role in the growth of sclera, hence regulating emmetropization (6). Choroid has been shown to be involved in the development of refractive state and axial elongation in animal models (7). Hung et al. (8) found changes in the monkey eye's effective refractive state produce rapid compensating changes in choroidal thickness (CT), and the choroidal changes may play an important role in the visual regulation of axial growth associated with emmetropization. In addition to animal experiments, many current studies have confirmed that the choroidal structures in anisometropic amblyopic eyes of children were significantly different from that of normal eyes. A meta-analysis of unilateral amblyopia reported that CT increased in amblyopic eyes (9). Although recent studies have shown that amblyopic eyes exhibit greater sub-foveal CT than that of their fellow eyes and age-matched control eyes (10–13), it is also quite controversial whether the choroidal microstructural changes are involved in the pathogenesis of amblyopia (11).

Since various variables can affect choroidal thickness in children, such as age, spherical equivalent, and axial length (AL), it is necessary to explore more reliable marker for the assessment of choroidal vascular structural characteristics. Agrawal et al. (14) proposed a new parameter-choroidal vascularity index (CVI) to quantitative assess choroidal vascular structure by calculating the ratio of vascular luminal area (LA) to total choroidal total choroidal area (TCA) through enhanced depth imaging optic coherence tomography (EDI-OCT) images. With growing evidence, CVI is emerging as a potentially more robust marker for choroidal vascularity in various ocular diseases (14–16). Nishi et al. (17) reported a higher choroidal luminal/stromal ratio in amblyopic eyes than in fellow and control eyes, implicating morphological differences in the choroid may be a factor in amblyopia. Baek et al. (18) found choroidal vascularity was higher in amblyopic eyes. Although previous studies have evaluated CT changes in amblyopia eyes, the relationship between amblyopia and choroidal blood perfusion has not yet been adequately studied, and there is no consensus about whether the amblyopic choroid vascularity is structurally abnormal in children. The aim of this study was to assess the choroidal microstructural and choroidal blood perfusion changes and assess the correlation between AL, CT, and choroid vascular microstructure parameters in preschool-age children with anisometropic hyperopic amblyopia.

Materials and methods

Subjects

This was a cross-sectional comparative, non-interventional study conducted at Beijing Chaoyang Hospital, Capital Medical University from January 2022 to July 2022. This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki and approved by the ethics committee of Beijing Chaoyang Hospital, Capital Medical University. The parents were also informed about the study and procedures, and written informed consent was obtained from all the patients and controls or their parents to perform the measurements and to review their medical records.

This study involved 52 hyperopic anisometropic amblyopia children and 48 age-matched heathy controls. The inclusion criteria were as follows: age between 3 and 10 years; IOP lower than 21 mmHg; normal anterior chamber angles; normal optic nerve head without glaucomatous changes, such as the neuroretinal rim narrowing, cup-disc ratio increasing; and no retinal nerve fiber layer abnormalities. Patients with a history of ocular or systemic diseases, including strabismus, organic eye diseases, history of intraocular surgery, cataract, neurologic disease, glaucoma, or any other retinal disorders; Spectralis OCT images with a quality score less than 20 or erroneous segmentation, illumination, or centration were excluded.

Ophthalmic examination

All the patients and controls had dilated funduscopic examinations. Best-corrected vision acuity (BCVA), slit-lamp biomicroscopy, AL (IOL Master; Carl Zeiss Meditec, Dublin, CA), spherical equivalent (SE) and intraocular pressure (IOP) were measured. The visual acuity was measured with a standard logarithmic visual acuity chart, and the decimal visual acuity was converted to logMAR units for the statistical analyses.

OCT imaging of the optic nerve head (ONH), the retinal nerve fiber layer (RNFL), and choroidal architectural parameters were obtained using the Spectralis OCT device (Heidelberg Engineering, Heidelberg, Germany) by experienced ophthalmologist. The peripapillary RNFL thickness (pRNFLT) was measured through the dilated pupil using OCT, scans were

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centered on the optic disc, and the 12° scan circle was positioned exactly in the middle of the optic nerve head. Utilizing the Fast RNFL program, the RNFLT was determined around a set diameter (3.5 mm) from the center of the optic disc. The global (G), nasal (N), nasal superior (NS), nasal inferior (NI), temporal (T), temporal superior (TS) and temporal inferior (TI) RNFLT measurements were recorded and analyzed.

The choroid was imaged using the EDI mode of OCT. The macular region was scanned using a 7 horizontal line scan centered on the fovea, with 100 frames averaged in each B-scan. For the macular CT measurement, 7 points were selected for manual measurement: the subfoveal CT (SFCT) point, the temporal and nasal points at a radius of 0.5-mm, 1.5-mm, and 3-mm (**Figure 1**). The comparison of macula choroidal structure in a patient with anisometropia amblyopia was shown in **Figure 2**. For peripapillary CT (pCT) measurement, a 3.5 mm diameter area centered on optic disc was selected for measurement. The pRNFLT data can be automatically calculated and displayed. For pCT measurement, we manually moved the automatically segmented internal limiting membrane line to the choroid sclera junction and moved RNFL line to the retina pigment epithelial line. Once we changed the automatically segmented line, the pCT data were automatically calculated and displayed (**Figure 3**). Three consecutive measurements were performed by one experienced ophthalmologist and the average of three measurements was used for statistical analyses. All analyses were corrected for the magnification effect. Littmann formula was used to calculate true image size, as described previously (19, 20).

OCT system uses fixed eye AL to scan. With the elongation of AL, the scanning area increases, resulting in optical amplification effect. Measurements performed with OCT have inherent errors when the scale of retinal image is not corrected for AL of each eye (20, 21). In order to correct the optical amplification effect of OCT measurement, Littmann formula was used to calculate true image size make the results more accurate. The measured OCT image diameter (D_m) and the true diameter (D_t) can be converted by Littmann formula: $D_t = p \times q \times D_m$, p is the magnification factor of the imaging system and q is a factor related to the eye [$q = 0.01306 \times (AL - 1.82)$], p is a constant 3.46 according to the previous study (22).

$$D_t = 3.46 \times 0.01306 \times (AL - 1.82) \times D_m$$

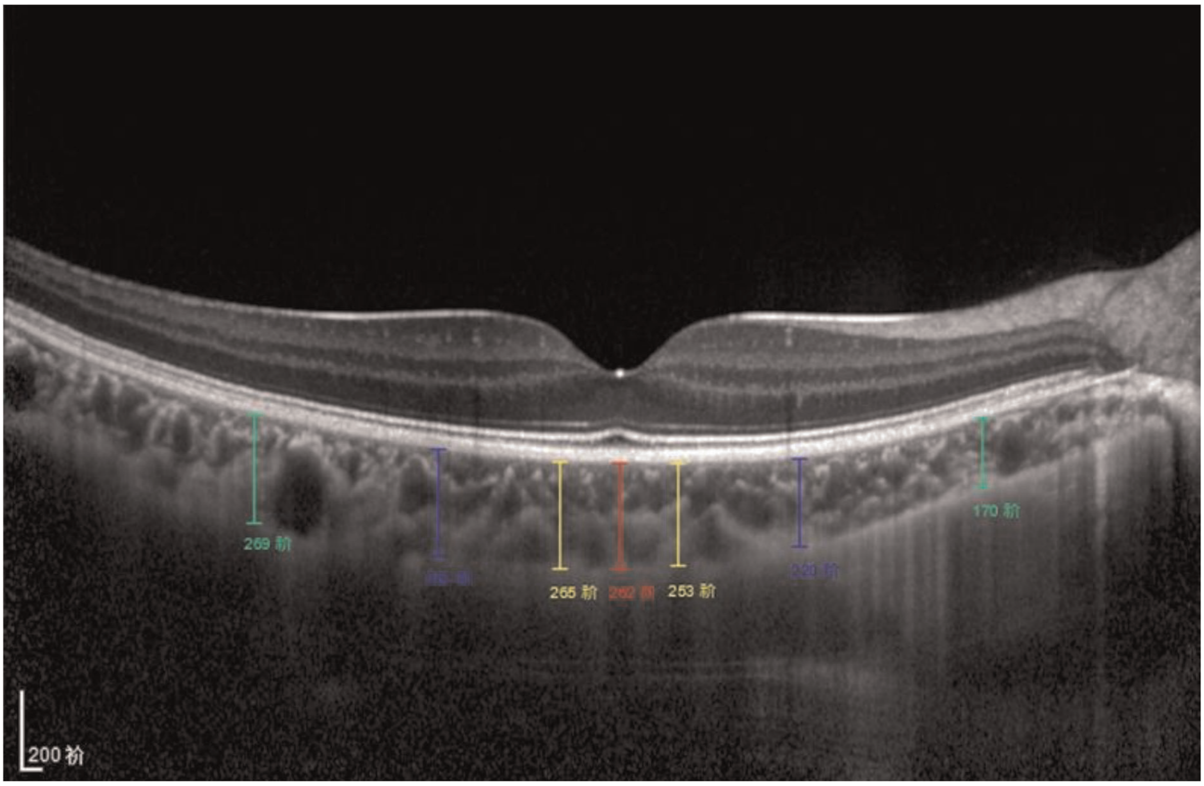

FIGURE 1
Subfoveal CT measurement. CT was measured at 7 points: directly beneath the fovea or the subfoveal area (SFCT) point, and 0.5/1.5/3 mm to the fovea nasally (N1/N2/N3), 0.5/1.5/3 mm to the fovea temporally (T1/T2/T3).

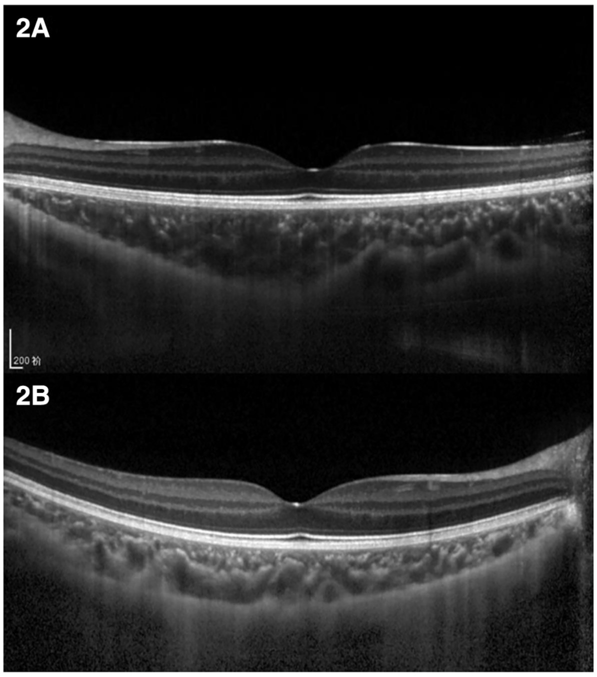

FIGURE 2
Comparison of choroidal structure of macula in a patient with anisometropia amblyopia. (A) Choroidal thickness of the hyperopic anisometropic amblyopia eye. (B) Choroidal thickness of the fellow eye.

Binarization of EDI OCT images

For the measurement of sub-fovea choroidal area, a 3,000-μm wide area was chosen. For the measurement of peripapillary choroidal area, the total circumferential choroid area with a diameter of 3.5 mm centered at the fovea was chosen to determine the binarization (**Figure 4**). The choroidal vascular structure parameters were measured by Niblack method using ImageJ software version 1.47 (National Institutes of Health, Bethesda, MD, United States) as described previously (23). In brief, Niblack's auto local threshold tool was applied to allow demarcation of LA, the stromal area (SA), and TCA. The proportion of LA to TCA was defined as CVI.

Statistical analysis

The Kolmogorov–Smirnov test was used to identify the normality of distribution. Descriptive statistics and optic characteristics were calculated as the mean and standard deviation for normally distributed variables. Age differences were performed with the Independent-samples T test. The categorical data were analyzed using the Fisher's exact test. One-way analysis of variance was used to compare the differences among the three groups, and the Bonferroni method was used for *post hoc* tests. The significance of the correlations between the ocular parameters and choroid microstructure parameters was determined by Pearson's correlation coefficient. All reported *P* values were two sided. A *P*-value < 0.05 was regarded as statistically significant. Statistical analysis was performed using the SPSS software version 26 (SPSS, Inc., IL, United States).

Results

Demographic data and clinical characteristics

The demographic and ocular characteristics were analyzed in the study (**Table 1**). The mean age of the subjects with amblyopia was 5.65 ± 1.22 years (range 3 to 9 years), and the mean age in the control group was 5.71 ± 0.80 years (range 4 to 9 years). No significant difference between the mean age of the groups was observed.

The mean BCVA was 0.46 ± 0.22 logMAR units in the amblyopic eyes, 0.10 ± 0.18 logMAR units in the fellow eyes, and −0.01 ± 0.07 logMAR units in the controls. The mean BCVA was significantly worse in the amblyopic eyes than the other two groups ($P < 0.001$). The mean SE of amblyopic eyes, fellow eyes and controls were 6.16 ± 1.54 D (range +3.00 to +10.00 D), 3.84 ± 1.99 D (range 0.50 to + 8.0 D) and 0.31 ± 0.43 D (range 0.38 to +1.25 D), respectively. The mean AL was significantly lower in the amblyopic eyes than in other groups.

Macular choroidal parameters in amblyopic eyes, fellow eyes, and controls

The mean SFCT was 323.39 ± 35.37 μm, 290.07 ± 48.04 μm, and 278.40 ± 24.10 μm in the amblyopic eyes, fellow eyes, and controls, respectively (**Table 2**). The subfoveal choroid of the amblyopic eyes was significantly thicker than that of the fellow eyes and control eyes ($P < 0.001$). The nasal choroidal sectors at 1.5 mm and 3.0 mm diameter of the amblyopic eyes were thicker than that of the fellow eyes and control eyes ($P < 0.001$). The choroidal thickness at 1.5 mm and 3.0 mm diameter was not significantly different among the three groups ($P > 0.05$).

For the choroidal vascular parameters, SA values were 915,837.31 ± 143,148.45 μm^2 in the amblyopic eyes, 790,779.50 ± 216,348.44 μm^2 in the fellow eyes, 758,347.15 ± 79,039.03 μm^2 in the control eyes; LA values were 1,555,572.28 ± 240,531.00 μm^2, 1,434,537.31 ± 317,146.02 μm^2, and 1,392,546.06 ± 183,442.60 μm^2 among the three groups, respectively. TCA values were 2,471,409.59 ± 318,427.55 μm^2 in the amblyopic eyes, 2,225,316.81 ± 343,679.17 μm^2 in the fellow eyes, 2,150,893.20 ± 225,859.85 μm^2 in the control eyes; SA, LA and TCA of the amblyopic eyes were significantly larger than that of the fellow and control eyes (all $P < 0.05$).

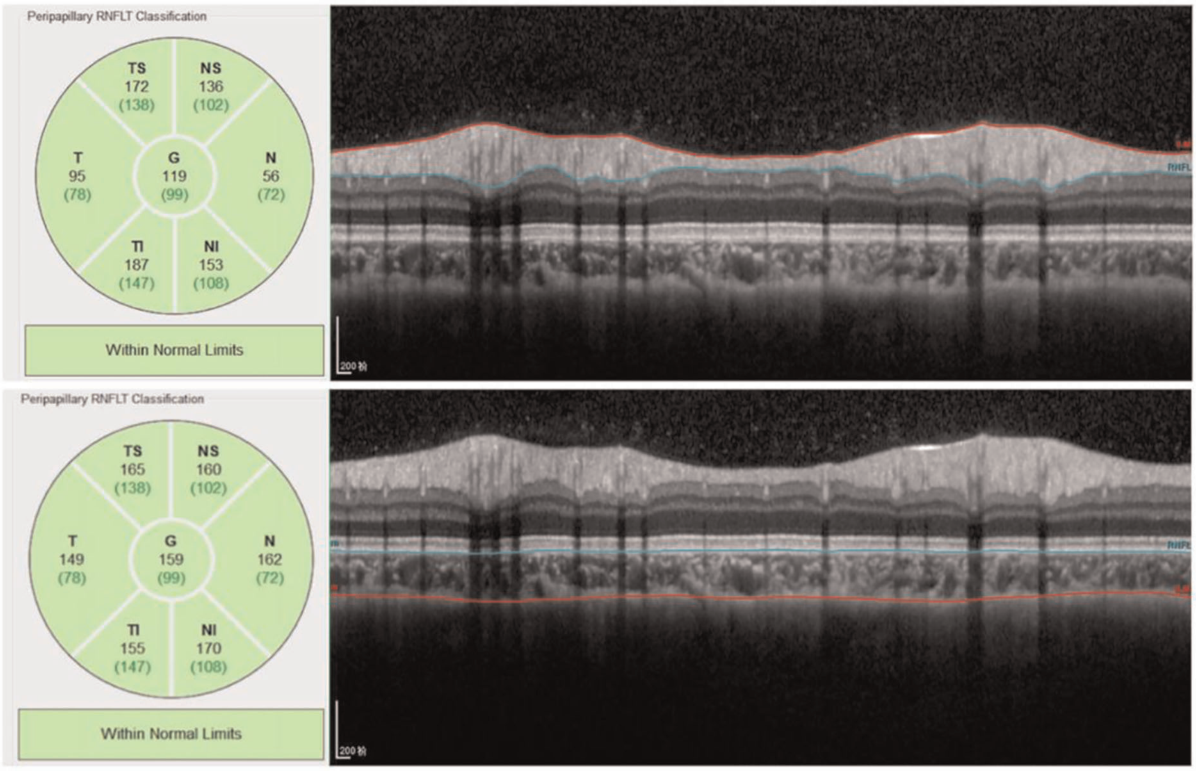

FIGURE 3
Peripapillary RNFL and choroidal thickness measurement. The RNFL thickness data can be automatically calculated and displayed. For peripapillary choroidal thickness measurement, we manually moved the automatically segmented internal limiting membrane line to the choroid sclera junction and moved RNFL line to the retina pigment epithelial line. Once we changed the automatically segmented line, the choroidal thickness data were automatically calculated and displayed.

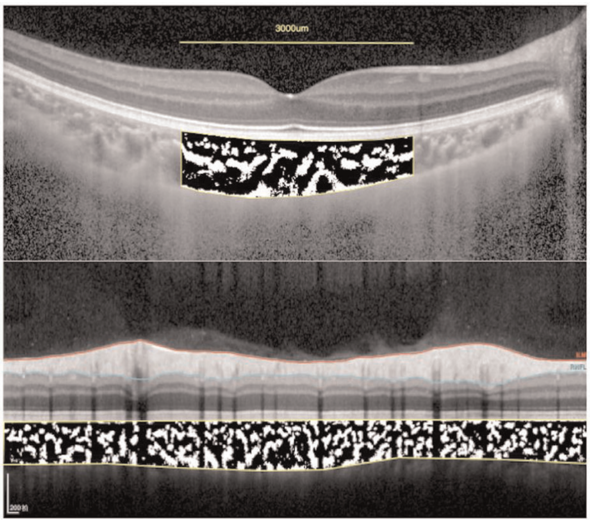

FIGURE 4
The subfoveal choroidal area and peripapillary choroidal area measurement. Using ImageJ software, the image was binarized with Niblack's method, and the ratio of vascular area (black pixels) to stromal area (white pixels) was quantified.

The CVI values of the amblyopic eyes was significantly different among the three groups ($P = 0.018$).

CT and choroidal vascular parameters among the three groups were shown in **Figure 5**.

Peripapillary RNFL thickness and choroidal parameters

The mean global and temporal superior RNFLT in the amblyopic eyes were significantly higher than those of normal control eyes (all $P < 0.05$; **Table 3**). The pCT in all directions of the amblyopic eyes was significantly thicker than the control eyes (all $P < 0.05$).

For the peripapillary choroidal vascular parameters, SA values were 2,897,700.89 ± 471,994.36 μm^2 in the amblyopic eyes, 2,483,938.16 ± 380,585.43 μm^2 in the fellow eyes, 2,459,067.96 ± 241,667.84 μm^2 in the control eyes; LA values were 5,011,039.04 ± 719,632.91 μm^2, 4,481,049.92 ± 737,795.37 μm^2, and 4,596,272.08 ± 548,053.75 μm^2 among the three groups, respectively. TCA values were 7,908,739.94 ± 962,558.03 μm^2 in the amblyopic eyes, 6,964,988.08 ±

TABLE 1 Demographic and ocular characteristics.

Parameters	Unilateral amblyopic children		Controls	P1	P2	P3
	Amblyopic eyes	Fellow eyes				
No. eyes (patients)	52		48	–	–	–
Age, years, mean ± SD	5.65 ± 1.22		5.71 ± 0.80	–	–	$P = 0.513$*
Male, *n* (%)	24 (46.15%)		22 (45.83%)	–	–	$P = 0.615$†
SE, D, mean ± SD	6.16 ± 1.54	3.84 ± 1.99	0.31 ± 0.43	**$P < 0.001$‡**	**$P < 0.001$**	**$P < 0.001$**
BCVA	0.46 ± 0.22	0.10 ± 0.18	−0.01 ± 0.07	**$P < 0.001$‡**	**$P < 0.001$**	**$P < 0.001$**
AL (mm)	21.02 ± 1.07	21.96 ± 1.29	23.24 ± 0.54	**$P < 0.001$‡**	**$P < 0.001$**	**$P < 0.001$**

AL, axial length; BCVA, best corrected visual acuity; SE, spherical equivalent; SD, standard deviation; D, diopter; logMAR, minimal angle of logarithm.
Data are expressed as the means ± standard deviations.
P1, Significant difference among amblyopic eyes, fellow eyes, and controls.
P2, Significant difference between amblyopic eyes and fellow eyes.
P3, Significant difference amblyopic eyes and controls.
*Independent-samples *T* test.
†Chi-square test.
‡One-way ANOVA test, all comparisons were corrected with *post hoc* test.

TABLE 2 Macular choroidal parameters in amblyopic eyes, fellow eyes, and controls.

Choroidal parameters	Unilateral amblyopic children		Controls	P1	P2	P3
	Amblyopic eyes	Fellow eyes				
CT, µm, mean ± SD						
SFCT	323.39 ± 35.37	290.07 ± 48.04	278.40 ± 24.10	**$P < 0.001$**	**$P < 0.001$**	**$P < 0.001$**
Nasal 1.5 mm	289.22 ± 30.49	254.77 ± 46.84	231.46 ± 38.66	**$P < 0.001$**	**$P < 0.001$**	**$P < 0.001$**
Nasal 3 mm	216.88 ± 39.96	204.65 ± 42.78	157.32 ± 27.29	**$P < 0.001$**	$P = 0.084$	**$P < 0.001$**
Temporal 1.5 mm	299.41 ± 38.95	290.79 ± 40.81	300.40 ± 31.36	$P = 0.301$	$P = 0.212$	$P = 0.848$
Temporal 3 mm	258.90 ± 41.32	260.75 ± 35.70	272.60 ± 40.60	$P = 0.157$	$P = 0.848$	$P = 0.078$
Choroidal Vascular Parameters						
LA, μm^2, mean ± SD	1,555,572.28 ± 240,531.00	1,434,537.31 ± 317,146.02	1,392,546.06 ± 183,442.60	**$P = 0.005$**	**$P = 0.017$**	**$P = 0.002$**
SA, μm^2, mean ± SD	915,837.31 ± 143,148.45	790,779.50 ± 216,348.44	758,347.15 ± 79,039.03	**$P < 0.001$**	**$P < 0.001$**	**$P < 0.001$**
TCA, μm^2, mean ± SD	2,471,409.59 ± 318,427.55	2,225,316.81 ± 343,679.17	2,150,893.20 ± 225,859.85	**$P < 0.001$**	**$P < 0.001$**	**$P < 0.001$**
CVI	0.63 ± 0.04	0.64 ± 0.09	0.65 ± 0.03	**$P = 0.018$**	$P = 0.244$	**$P = 0.041$**

CT, choroidal thickness; CVI, choroidal vascularity index; SFCT, subfoveal choroidal thickness; SA, stromal area; LA, luminal area; TCA, total choroidal area.
One-way ANOVA test, all comparisons were corrected with *post hoc* test.
P1, Significant difference among amblyopic eyes, fellow eyes, and controls.
P2, Significant difference between amblyopic eyes and fellow eyes.
P3, Significant difference amblyopic eyes and controls.

1,092,260.95 μm^2 in the fellow eyes, 7,055,340.04 ± 711,275.62 μm^2 in the control eyes; SA, LA and TCA of the amblyopic eyes were significantly larger than that of the fellow eyes and control eyes (all $P < 0.001$). There was significant statistical difference of the CVI values among the three groups ($P = 0.017$).

Correlation analyses between the parameters and choroid microstructure parameters

A correlation analysis between parameters and choroid microstructure parameters were shown in **Table 4**. There was a statistically significant negative correlation between AL and SFCT, LA and TCA levels ($r = -0.372$, -0.193 and -0.280, respectively; $P < 0.001$, $P = 0.039$, $P = 0.027$, respectively). There was a statistically significant positive correlation between SE, SFCT, LA and TCA levels ($r = 0.456$, 0.229 and 0.240, respectively; $P < 0.001$, $P = 0.019$, 0.014, respectively). SFCT was positive correlated with LA, SA, TCA and CVI levels (r = 0.557, 0.197, 0.561 and 0.231, respectively; all $P < 0.05$).

Discussion

In the present study, we determine the pRNFLT, SFCT, pCT, and choroid microstructure parameters in children with

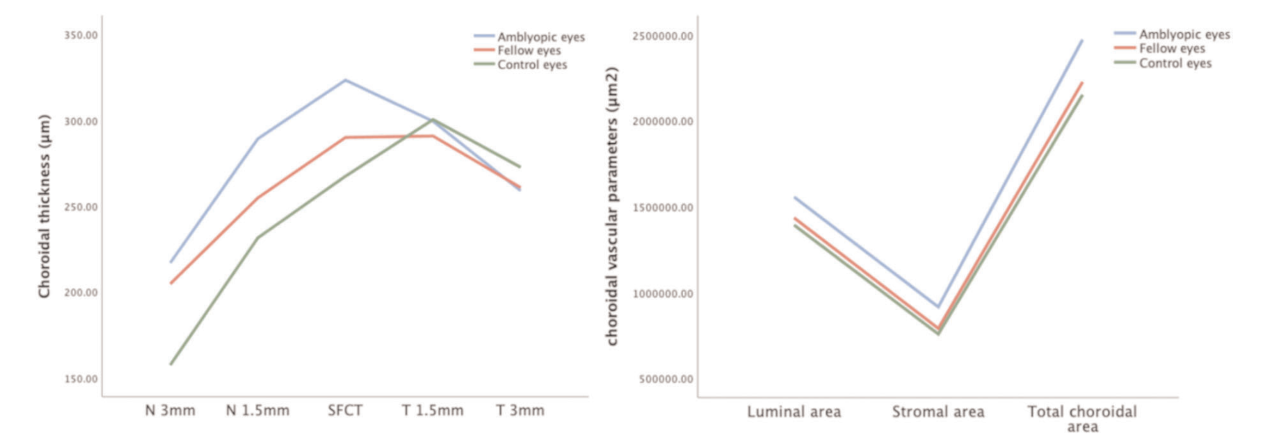

FIGURE 5
Choroidal thickness and vascular parameters among the three groups. The subfoveal choroidal thickness, temporal and nasal choroidal thickness, LA, SA, and TCA values of amblyopic eyes, fellow eyes, and controls.

hyperopic anisometropic amblyopia and compare that of fellow eyes and age-matched controls. We also analyze the correlation between the AL, CT, and choroid microstructure parameters.

The results of different studies on the changes of nerve fiber layer thickness in hyperopia patients are controversial. Most studies suggested that the pRNFL of children with high hyperopia was significantly thicker than low hyperopia or emmetropic children (24–26). While Qian et al. (27) found that the RNFL in the inferior and temporal quadrants in the 1 to 3 mm diameter of the macular fovea in moderate-to-high hyperopia children were thinner than those in emmetropic children. In the present study, the mean global and temporal pRNFLT were significantly higher than those of normal control eyes. To date, it is not clear why the RNFLT in hyperopia children is changed. This may be due to the influence of retinal development in children with hyperopia. There are also several studies explored the factors associated with RNFL in different types of ametropia patients. It is suggested that SE or AL was associated with RNFL thickness (28–30). Eslami et al. (31) found RNFLT in Iranian children aged below 18 years positively correlated with SE, but no significant association between RNFLT and age. In our study, we also found that highly hyperopic children with a shorter eye axis had thicker pRNFLT than the normal controls.

We also analyzed the macular and peripapillary choroid microstructure parameters in hyperopic anisometropic amblyopia eyes. The choroid plays a role in refractive error development and has been shown to be involved in the visual feedback pathway in humans (6). The question of whether the choroid is affected in human amblyopia is an important issue for ophthalmologists. Previous studies showed that the subfoveal choroid of hyperopic amblyopia eyes was significantly thicker than that of the fellow and the control eyes (9, 11, 12, 13, 32–36). These results suggesting that amblyopia might have a profound influence on CT (32). In the present study, we found SFCT and pCT in all directions of the amblyopic eye was significantly thicker than the fellow and control eyes. CT was influenced by age, sex, AL, or refraction (37–39). Recently different researchers had different hypotheses on the mechanisms of choroidal thickness increased in anisometropic hyperopic amblyopia eyes. Bidaut-Garnier et al. (40) and Nagasawa et al. (38) reported that CT was negatively correlated with AL in healthy people. Mori et al. (36) found a negative correlation between the CT and AL in preschool children with hyperopic anisometropic. However, the causal relationship between choroidal thickening and hyperopia remains controversial. Nishi and his colleagues described the possibility that the increased SFCT of amblyopic eyes is under the influence of the amblyopia (13). Kara et al. (41) thought that amblyopia affected the development process of the choroids. Troilo et al. (42) believe that the thickened choroid might hinder the growth of the eye during development, it provides a barrier to the diffusion of growth factors or acts as a mechanical buffer to limit the eye's elongation. Another idea is that the foveola was thicker in the amblyopic eyes, and a thicker retina may require additional blood for nourishment, then the CT increased to supply additional blood. At the same time, it is also believed that the thickening of choroid will affect the axis length elongation. It is reported that the choroid thickens during the normal development of primate eyes, which may slow down the growth of the eye during development (42).

Myopic or hyperopic defocus may also affect choroid thickness. The choroid becomes thicker with myopic defocus and thinner with hyperopic defocus, which in turn adjusts the position of the retina to maintain clear vision (9). Hung et al. (8), and Nishi et al. (13) suggested hyperopic defocus promotes choroidal thinning, myopic defocus promotes choroidal

TABLE 3 Peripapillary RNFL thickness and choroidal parameters in the three groups.

Parameters	Unilateral amblyopic children		Controls	*P1*	*P2*	*P3*
	Amblyopic eyes	Fellow eyes				
RNFL, μm, mean ± SD						
G	97.37 ± 9.56	94.51 ± 5.83	92.37 ± 6.98	***P* = 0.005**	*P* = 0.058	***P* = 0.001**
T	74.92 ± 7.13	72.21 ± 8.90	72.60 ± 6.36	*P* = 0.148	*P* = 0.070	*P* = 0.127
TS	132.28 ± 11.94	127.71 ± 13.95	123.80 ± 8.73	***P* = 0.002**	*P* = 0.050	***P* < 0.001**
TI	141.09 ± 12.97	139.83 ± 14.18	136.99 ± 22.16	*P* = 0.463	*P* = 0.702	*P* = 0.224
N	69.47 ± 15.60	68.47 ± 11.08	64.77 ± 10.22	*P* = 0.152	*P* = 0.687	*P* = 0.064
NS	116.06 ± 15.44	115.46 ± 16.73	114.79 ± 19.30	*P* = 0.934	*P* = 0.859	*P* = 0.712
NI	114.16 ± 13.74	112.38 ± 16.78	114.62 ± 19.87	*P* = 0.780	*P* = 0.592	*P* = 0.893
CT, μm, mean ± SD						
G	156.62 ± 20.21	150.74 ± 25.52	143.62 ± 12.57	***P* = 0.007**	*P* = 0.142	***P* = 0.002**
T	161.99 ± 26.72	148.31 ± 22.78	144.88 ± 11.14	***P* = 0.001**	***P* = 0.004**	***P* < 0.001**
TS	160.18 ± 21.20	157.32 ± 28.15	147.65 ± 9.75	***P* = 0.011**	*P* = 0.495	***P* = 0.004**
TI	151.00 ± 22.93	145.10 ± 28.50	138.52 ± 11.11	***P* = 0.022**	*P* = 0.179	***P* = 0.006**
N	151.35 ± 27.58	147.58 ± 31.97	137.58 ± 13.19	***P* = 0.025**	*P* = 0.458	***P* = 0.008**
NS	156.79 ± 27.39	155.22 ± 33.38	139.63 ± 12.68	***P* = 0.002**	*P* = 0.773	***P* = 0.004**
NI	151.45 ± 26.84	144.65 ± 16.55	135.37 ± 16.56	***P* = 0.011**	*P* = 0.191	***P* = 0.003**
Choroidal Vascular Parameters						
SA	2,897,700.89 ± 471,994.36	2,483,938.16 ± 380,585.43	2,459,067.96 ± 241,667.84	***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
LA	5,011,039.04 ± 719,632.91	4,481,049.92 ± 737,795.37	4,596,272.08 ± 548,053.75	***P* < 0.001**	***P* < 0.001**	***P* = 0.003**
TCA	7,908,739.94 ± 962,558.03	6,964,988.08 ± 1,092,260.95	7,055,340.04 ± 711,275.62	***P* < 0.001**	***P* < 0.001**	***P* < 0.001**
CVI	0.63 ± 0.04	0.64 ± 0.02	0.65 ± 0.02	***P* = 0.017**	*P* = 0.110	***P* = 0.005**

CT, choroidal thickness; G, global; N, nasal; NS, nasal superior; NI, nasal inferior; RNFL, retinal nerve fiber layer; T, temporal; TS, temporal superior; TI, temporal inferior; SA, stromal area; LA, luminal area; TCA, total choroidal area; CVI, choroidal vascularity index.
One-way ANOVA test, all comparisons were corrected with *post hoc* test.
P1, Significant difference among amblyopic eyes, fellow eyes, and controls.
P2, Significant difference between amblyopic eyes and fellow eyes.
P3, Significant difference amblyopic eyes and controls.

thickening. Nishi et al. (13) also hypothesized that the ocular compensation and choroidal accommodation for the hyperopic defocus was suppressed in amblyopic eyes, which resulted in an increased SFCT. These reports suggested that modulation of choroidal thickness is a response to optical defocus. Myopic defocus induces choroidal thickening and develops hyperopia, while hyperopic defocus induces choroidal thinning and leads to myopia. The ocular growth with emmetropization after birth is regulated by visual feedback from visual signals on the retina, effective visual stimuli and visual feedback mechanism may also affect choroid microstructure changes. Previous animal experiment reports raised the possibility that choroid is involved in the visual feedback (43, 44). Mori et al. (36) concluded that choroidal accommodation may be inhibited with the little visual

TABLE 4 Correlation analyses between the parameters and choroid microstructure parameters.

Parameters	SFCT		LA		SA		TCA		CVI	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age	0.019	0.847	−0.016	0.874	0.163	0.098	0.077	0.437	−0.146	0.139
AL	−0.372	**<0.001**	−0.193	**0.039**	−0.071	0.472	−0.280	**0.027**	−0.084	0.398
SE	0.456	**<0.001**	0.229	**0.019**	0.098	0.324	0.240	**0.014**	0.086	0.385
Choroid parameters										
SFCT	-	-	0.557	**<0.001**	0.197	**0.046**	0.561	**<0.001**	0.231	**0.018**
Nasal 3 mm	0.291	**0.003**	0.306	**0.002**	0.285	**0.003**	0.406	**<0.001**	−0.053	0.593
Temporal 3 mm	0.214	**0.029**	0.232	**0.018**	0.254	**0.009**	0.328	**0.001**	−0.070	0.479

AL, axial length; SFCT, subfoveal choroidal thickness; SE, Spherical equivalent; SA, stromal area; LA, luminal area; TCA, total choroidal area; CVI, choroidal vascularity index.

feedback in the amblyopic eye in hyperopic anisometropic amblyopia, and the anomalous subfoveal choroidal thicknesses may reflect a delay in emmetropization. Troilo et al. (42) found that the choroid thickens during postnatal eye growth, which may slow down the eye growth during development. However, it is not clear whether the lack of visual stimulation in patients with high hyperopia causes the thickening of the choroid, or the thickening of the choroid causes the restriction of axial elongation, which leads to the occurrence of hyperopia.

Most studies suggesting that the choroid is thicker in amblyopic eyes than in normal eyes, but CT can be affected by various variables. The choroid is composed of abundant blood vessels surrounded by stromal tissue, the role of choroid tissue in amblyopia may be related to the blood supply to the outer retina, choroidal thickness only cannot fully reflect the choroid structural changes and blood supply situation. Agrawal et al. (14) proposed CVI to assess choroidal vascular structure by calculating the LA to TCA ratio through EDI-OCT images. In recent years, these parameters had been used widely used in the field of refractive error research.

Ruiz-Medrano (45) reported that the average percentage of the vascularity was 60.56% in children. However, there are conflicting views on choroidal blood perfusion in the pediatric hyperopia research field. Baek et al. claimed that the choroidal CV was higher in both hyperopia and the fellow eyes compared to normal eyes, but no significant difference was found between amblyopic eyes and fellow eyes choroidal LA to TCA ratio (i.e., CVD) was higher in hyperopia eyes than the control eyes; Eraydın et al. reported that they did not find any difference in CVI in hyperopic amblyopic eyes compared with the control group (18, 46). Enrico Borrelli et al. (47) reported that amblyopic eyes were found to have increased choriocapillaris vessel density and speculated an increase in choriocapillaris vessel density might be a compensatory response that supplies more blood to a thickened outer retina in amblyopic eyes. But most studies concluded that the choroidal blood flow in patients with high hyperopia is lower than that in normal children. Huang et al. (48) found the choriocapillaris flow void (FV) in the amblyopic group was greater than that in the age- and sex-matched heathy control group and concluded that children with amblyopic eyes have attenuated macular and choriocapillaris perfusion. There are other studies reported that both the amblyopic and the fellow eyes also had lower CVI values than control eyes (49–51). The results in this study are consistent with most of the previous studies, the average CVI in the hyperopic amblyopic eyes was lower than the fellow eyes and the normal control eyes. When exploring the relationship between choroidal vascularity parameters and choroid thickness, different researchers have drawn opposite conclusions. Beak et al. (18) reported the choroidal vascularity was negatively correlated with CT may suggests insufficient blood supply to the outer retina and choroid in the affected eyes of patients with unilateral anisometropic hyperopic amblyopia. Fujiwara et al. (52) found SCT had a significant positive relationship with vascular density of the choroid in normal eyes. In our cohort, the average CVI of sub-fovea choroidal area was comparable at 0.63 ± 0.04 in the amblyopic eyes, 0.64 ± 0.09 in the fellow eyes and 0.65 ± 0.03 in the control eyes ($P = 0.002$), and SCT had a slight negative correlation with CVI, but the difference was not statistically significant. Studies on CVI changes in amblyopia patients have shown controversial results, which may be due to the following reasons. First, the age of the enrolled patients in different studies varies, which may affect the conclusion, because age may affect choroidal thickness and choroidal blood flow. The second possible reason is that current studies have shown that amblyopia treatment may affect the choroid structure changes. Nishi et al. (53) showed that the amblyopic eyes had a larger LA than control eyes at the baseline, but wearing the optical correction led a significant decrease in the LA and widened SA in the amblyopic eyes one year after the treatment. Thirdly, differences in results among these studies may thus be due to differences in the methods used for choroidal blood flow analysis. Some studies use binary OCT images to analyze the macular choroidal fault surface. However, other studies used OCTA scanning for automatic blood flow analysis. The choroid position and section selected by these two measurement methods are different, so there may be differences in research results.

At present, it is controversial whether the thickening of choroid in hyperopia is caused by the increase of stromal area or the vascular luminal area. Ruiz-Medrano et al. (45) reported that the LA and the percentage of vascular/total area decreased with increasing age in normal children, while SA remains stable. Alis et al. (54) found that TCA and SA were higher in hyperopia than in both emmetropic and myopic eyes, they also proposed that the reason for the decrease in the CVI in hyperopia is the excess of the SA. Nishi et al. hold different opinions that the LA was significantly larger, the SA was significantly smaller, and the luminal/stromal ratio was larger in amblyopic eyes than in control hyperopic eyes (17). Kaderli et al. (55) found both refractive error increase and axial length decrease have resulted in an increase in largest macular choroidal vascular lumen diameters and areas in hyperopic adults. Araki showed that choroidal blood flow with respect to total choroidal volume may be increased in amblyopic eyes than in fellow and normal control eyes (33). Terada et al. (56) found that the outer choroidal vascular area in both amblyopic and fellow eyes was markedly larger than in healthy eyes, and they also speculated that an outer choroidal vascular area >59% in fellow eyes with normal vision, may indicate a risk for amblyopia onset. This finding might be helpful in detecting amblyopia risk before onset in many young-age children (56). As to why the choroidal vascular area in anisometropic hyperopic amblyopia eyes increases, some researchers have also conducted research. Guo et al. (57) discovered that most amblyopic eyes displayed a dark atrophic patch, the choroidocapillary atrophy patch caused a wide range of compensatory dilatation of its surrounding capillaries, and dilatation of the choroidal vessels may lead to increased CT. This study showed that the SA, LA, and TCA in the amblyopic eyes was significantly larger than that of the fellow and the control eyes, the larger LA and SA at the baseline was characteristic of the amblyopic eye. The results indicate that choroidal blood flow with respect to total choroidal volume may be increased in amblyopic eyes than in fellow and normal control eyes.

Some studies further explored the choroid structure changes before and after amblyopia treatment. LA was characteristic of the amblyopic eye, and it was significantly reduced after the optical treatment. Nishi et al. (53) showed that the amblyopic eyes had a larger LA than control eyes at the baseline, but wearing the optical correction led a significant decrease in the LA and widened SA in the amblyopic eyes one year after the treatment. Toor et al. (58) suggested that the amblyopic eyes with widened SA had more nonvascular smooth muscle cells and had better accommodation, which induced the improvement of the visual acuity. Thus, the widened SA in the amblyopic eyes after treatment is probably a response to the optical correction of the refractive error. The amblyopic eyes with larger SA at the baseline had better improvements of the visual acuity.

The correlation between the AL, CT and choroid microstructure parameters were also evaluated in the present study, there was a statistically significant negative correlation between AL and SFCT, LA and TCA levels, and a positive correlation between SE, SFCT and LA levels. Kaderli et al. (55) found macular CT increased with increasing hyperopic refractive error and decreasing AL in all quadrants. Nishi et al. (17) showed that there was a significant negative correlation between the LA/SA ratio and AL in the control eyes, but no significant correlation was found in the amblyopic eyes. Baek et al. (18) found a negative correlation between subfoveal CT and choroidal vascularity in amblyopic eyes. Araki et al. (33) reported the SFCT was significantly positive associated with CVD. Ruiz-Medrano et al. (45) reported that the LA and the percentage of LA/TCA decreased with increasing age while the SA remained stable in normal children and adults.

The present study had some limitations. First, the sample size was small. A further study of a larger number of subjects will be necessary to confirm our findings. Secondly, we did not discuss the correlation between choroid structural and blood flow changes with age, gender, and other factors, so we will expand the sample size in the further research to explore this. Third, the measurement of CVI may be difficult, as it requires the acquisition of good quality EDI-OCT scans, the binarization of the image will be inaccurate if the fundus picture is not clear enough, poor-quality OCT images or eye movement further limit the detailed choroidal evaluation and CVI calculation. In addition, in the process of image grading, there is a step that requires doctors to judge the choroidal boundary, which requires high requirements for the operator.

Conclusions

In conclusion, the current study showed that the choroidal structure of the amblyopic eyes was different from the fellow and the normal control eyes, the hyperopic anisometropic amblyopic eyes had significantly thicker sub-foveal choroid, higher LA, SA, and TCA. The subfoveal and peripapillary choroidal thickness of amblyopic children abnormally increased and the thicker subfoveal choroid is mildly correlated with their shorter axial length. AL and CT affect choroidal structure and vascular density of the choroid. Choroidal blood flow may be decreased in amblyopic eyes. The larger LA, SA, TCA, and lower CVI were characteristic of the amblyopic eye.

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 Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (No. 2021-sci-714). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Involved in the design of the study (WH, TY); conduct of the study (HXF); collection, patients epidemiological survey and baseline data statistics (WH, XH); patient follow-up data collection (DYH); preparation of the manuscript (WH); and critical revision of the manuscript (WH, TY). All authors contributed to the article and approved the submitted version.

Funding

This work was supported in part by the National Natural Science Foundation of China to WH (grant number: 62006161). This funding had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This funding will not lead to any conflict of interests regarding the publication.

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.

Publisher's note

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TYPE Original Research
PUBLISHED 22 November 2022
DOI 10.3389/fpubh.2022.1019816

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Public Health Education and Promotion,
a section of the journal Frontiers in Public Health

RECEIVED 15 August 2022
ACCEPTED 31 October 2022
PUBLISHED 22 November 2022

CITATION
You Y, Fu J, Xu M, Song Y, Zhou H and Wei S (2022) Prevalence of refractive error among Chinese preschool children: The Changsha children eye study.
Front. Public Health 10:1019816.
doi: 10.3389/fpubh.2022.1019816

Prevalence of refractive error among Chinese preschool children: The Changsha children eye study

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Purpose: We aimed to investigate the refractive status and prevalence of refractive error, as well as its characteristics in Chinese preschool children aged 1–6 years old.

Methods: A population-based cross-sectional study—Changsha Children Eye Study (CCES) was conducted. The prevalence of refractive errors among children aged 1–6 years old from 18 community health service centers was surveyed. A handheld child vision screener, Suowei, was used for examination.

Results: A total of 43,105 preschool children were included. The mean spherical equivalent (SE) was 0.42 ± 1.05 D for the right eyes. The mean astigmatism (diopter of cylinder, DC) was −0.83 ± 1.02 D for the right eyes. The magnitude of refractive error was lower in older children, indicating the ongoing of the emmetropization during the 1–6-year-old children. The prevalence of myopia (SE ≤ −1.00 D), hyperopia (SE ≥ +2.00 D) and astigmatism (DC ≥1.50 D) was 2.94, 13.8 and 17.6%, respectively. The prevalence of myopia decreased with the increase of age between the six age groups ($P < 0.001$). The prevalence of hyperopia was lower in 5–6 years old, whereas, the prevalence of myopia was slightly higher at this period of time. With-the-rule (WTR) astigmatism (+ cylinder axis 90° ± 15°) was the most prevalent type of astigmatism than against-the-rule (ATR) astigmatism (+ cylinder axis 180° ± 15°) and oblique (OBL) astigmatism ($X^2 = 209.5$, $P < 0.001$). The binary logistic regression model showed that older age and suffering astigmatism were independently associated with the development of myopia. In addition, there was no significant gender difference in the prevalence of myopia, emmetropia, and hyperopia.

Conclusions: Our population-based cross-sectional study investigated the prevalence of myopia, hyperopia, and astigmatism in preschool children aged 1–6 years old. The distribution of the refractive error was disperse in the younger group and gradually turned more centralized in older group. Similar to hyperopia, with age increased, the prevalence of myopia was lower in preschool children younger than 5 years old and then slightly increased at 5–6 years, which may indicate an early sign of myopia in school-age children. Therefore, we emphasize that more attention should be given to the children at this age.

KEYWORDS

refractive error, preschool children, prevalence, myopia, myopia epidemiology

Introduction

Myopia has emerged as a significant health issue (1). The prevalence of myopia has increased rapidly over the past few decades worldwide (2, 3). It is reported that ∼60% of 12-year-old primary school students, 80% of 16-year-old high school students, and more than 90% of university students have myopia in China (4–6). Myopia mainly occurs in school-age children (7), and for children under 6 years old, the prevalence of myopia is relatively lower (8–11).

Many studies reported the refractive status of school-aged children in the world (12–14), however, only a few studies focused on the refractive status of preschool children, especially in China. The uncorrected refractive error among preschool children could raise the higher risk of amblyopia and strabismus. Furthermore, preschool children with amblyopia and or strabismus have a high risk of developing high myopia, leading to secondary irreversible blinding complications (15–18). It might become a huge economic burden for both family and society. As the visual system is not fully developed, the preschool myopia might share different risk factors (19–21) with school-age myopia (22–24). To better understand the refractive status among preschool children, we performed a cross-sectional study. We aimed to investigate the refractive status and prevalence of refractive error, as well as its characteristics in Chinese preschool children aged from 1 to 6 years old.

Methods

The Changsha Children Eye Study (CCES) is a population-based study to estimate the prevalence and risk factors for refractive error and ocular diseases (25). The study was approved by the ethics committee of Beijing Aier Intech Eye Hospital. The data were obtained through the Mulin telemedicine platform (Hunan Super Vision Technology Co., Ltd.).

This study was performed from April 2016 to July 2019 among children aged 1–6 years from 18 community health service centers in Changsha, China. The consent to participate in the study was obtained from children's parents or their legal guardians. Children with systemic diseases such as congenital heart diseases and ocular trauma or eye diseases such as glaucoma, cataracts, and strabismus were excluded.

The examination workflow of CCES was as follows: a handheld child vision screener Suowei (Tianjin Suowei Electronic Technology Co., Ltd.) was used to screen children's binocular refractive condition (26). The examination was routinely conducted by a general practitioner in a dark room. Before the study, all the general practitioners were trained by ophthalmologists in terms of conducting standard eye examinations and using the handheld child vision screener. The binocular sphere, astigmatism, pupil size, pupillary distance, and fixation direction were obtained, recorded, and uploaded to the Mulin telemedicine platform.

The children were categorized into 6 groups by their age at the first examination: 1-year-old group ($0 < \text{age} \leq 12$ months), 2-year-old group ($1 < \text{age} \leq 2$ years), 3-year-old group ($2 < \text{age} \leq 3$ years), 4-year-old group ($3 < \text{age} \leq 4$ years), 5-year-old group ($4 < \text{age} \leq 5$ years), 6-year-old group ($5 < \text{age} \leq 6$ years).

The refractive error was evaluated using the spherical equivalent (SE), calculated by adding the sum of the sphere power with half of the cylinder power. In previous studies, SE ≤ -0.50 D or SE ≤ -1.0 D after cycloplegia is defined as myopia, and SE $\geq +2.00$ D is defined as hyperopia. In our study, considering that none of the participants underwent cycloplegia, we used three thresholds (SE ≤ -50 D, SE ≤ -1.00 D and SE ≤ -2.00 D) to calculate the prevalence of myopia to reduce the false positive rate. The data of right eyes were taken to calculate the prevalence of myopia. The definition of hyperopia was SE $\geq +2.00$ D. The definition of astigmatism was the cylinder power ≥ 1.50 D and astigmatism was classified into three categories: with-the-rule (WTR) (+ cylinder axis $90^\circ \pm 15^\circ$), against-the-rule (ATR) (+ cylinder axis $180^\circ \pm 15^\circ$), and all the other orientations were considered oblique (OBL) (9).

The statistical analyses were performed with an open-source R-program (version 3.6.2) and SPSS software (IBM-SPSS, V 16.0). The mean value and standard deviation were used for the statistical description of continuous variables, and frequency and percentage were used for the statistical description of categorical variables. The univariate analysis was performed by the chi-square test or chi-square trend test. The multivariable analysis was performed by the bivariate logistics analysis. The odds ratio (OR) value of each variable with the corresponding 95% confidence interval (95% CI) was calculated. $P < 0.05$ was considered statistically significant.

TABLE 1 Refractive error of the 1-6 years old children in the Changsha Children Eye Study.

Age group (-year-old)	Number	Percentage (%)	SE (mean ± SD)	DC (mean ± SD)
1	15,451	35.85	0.61 ± 1.20	−1.02 ± 0.78
2	7,115	16.51	0.41 ± 1.03	−0.75 ± 0.67
3	6,073	14.09	0.35 ± 0.93	−0.77 ± 2.02
4	6,593	15.30	0.33 ± 0.95	−0.72 ± 0.68
5	5,163	11.98	0.25 ± 0.85	−0.67 ± 0.65
6	2,710	6.29	0.06 ± 0.68	−0.64 ± 0.64
Total	43,105	100	0.42 ± 1.05	−0.83 ± 1.02

n, number; SE, spherical equivalent; DC, astigmatism; SD, standard deviation.

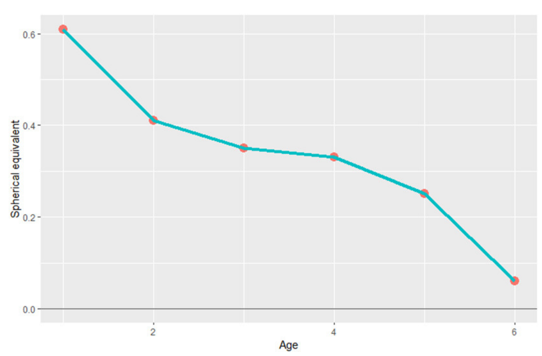

FIGURE 1
The mean SE among the different age groups. SE, spherical equivalent.

Results

Basic characteristics

A total of 43,105 children were enrolled in our study (Table 1). 35.8% of the children were in the 1-year-old group, 16.51% were in the 2-year-old group, 14.09% were in the 3-year-old group, 15.30% were in the 4-year-old group, 11.98% were in the 5-year-old group, and 6.29% were in the 6-year-old group. The number of boys and girls was roughly balanced among all age groups. The mean SE of preschool children was 0.42 ± 1.05 D for right eyes. The mean astigmatism (DC) was −0.83 ± 1.02 D for right eyes (Table 1). As shown in Figure 1, the mean SE is lower in older groups. This tendency indicated that the emmetropization is ongoing among children aged 1–6 years. Mean astigmatism is lower between the ages of 1 and 2 and stayed relatively stable between the age of 2 and 4. The mean value of astigmatism was higher in the group of 4-year-old and 6-year-old, reaching ∼-0.65 D at six years old (Table 2).

Prevalence of myopia

The prevalence of myopia was 8.39%, 2.94%, 0.34% with the definition of SE ≤ -0.50 D, SE ≤ -1.00 D, and SE ≤ -2.00 D, respectively (Table 3). In the group of SE ≤ -0.50 D and SE ≤ -1.00 D, the prevalence of myopia decreased as age increased (Figure 2). Whereas in the group of SE ≤ -2.00 D, the prevalence of myopia was relatively lower and stable among all age groups. Moreover, no significant difference was found in the prevalence of myopia between genders in all age groups ($p \geq 0.05$, Table 4). The binary logistic regression model showed that older age and suffering from astigmatism were independently associated with the development of myopia (Table 5).

Prevalence of hyperopia

As shown in Table 4, the prevalence of hyperopia (SE $\geq$ 2.00 D) was 13.8%. According to the outcome of the Chi-square trend test, the prevalence of hyperopia showed a descending tendency with the increase of age, which has statistical significance ($P < 0.001$). Instead, children with emmetropia have tapered, and there was no significant difference in the prevalence of hyperopia between different genders. The proportion of myopia, emmetropia and hyperopia was shown in Figure 3. In addition, there was no significant gender difference in the prevalence of myopia, emmetropia and hyperopia (Table 4).

Prevalence of astigmatism

The prevalence of astigmatism (DC $\geq$ 1.50 D) was 17.6%. Similarly, with the increase in age, the prevalence of astigmatism showed a descending tendency among all age groups, which has statistical significance ($P < 0.001$, Figure 4). With-the-rule (WTR) astigmatism (+ cylinder axis $90^\circ \pm 15^\circ$) was the most common type of astigmatism than against-the-rule (ATR) (+ cylinder axis $180^\circ \pm 15^\circ$) and oblique (OBL) ($X^2 = 209.5$, $P < 0.001$). According to the outcome of the chi-square test, the prevalence of WTR is significantly greater than that of ATR and Oblique ($X^2 = 209.5$, $P < 0.001$). The boy had a higher prevalence of astigmatism than the girl ($X^2 = 209.5$, $P < 0.001$, Table 2).

Discussion

Our study was based on the vision screening of 43,105 preschool children from 18 community health service centers in the urban area of Changsha. As the capital city of Hunan Province, Changsha is an economically important key city in China. The GDP per capita of Changsha in 2019 was 20,000 U.S. dollars, stably in the top-ranking of Hunan province,

TABLE 2 Prevalence of different astigmatism types of the 1-6 years old children in the Changsha Children Eye Study.

Age(-year-old)	WTR (n, %)			ATR (n, %)			Oblique (n, %)		
	Boy	Girl	All	Boy	Girl	All	Boy	Girl	All
1	1,403 (17.3)	1,435 (19.5)	2,838 (18.4)	116 (1.4)	91 (1.2)	207 (1.3)	604 (7.5)	522 (7.1)	1,126 (7.3)
2	289 (7.8)	297 (8.7)	586 (8.2)	47 (1.3)	47 (1.4)	94 (1.3)	154 (4.2)	127 (3.7)	281 (4.0)
3	573 (9.4)	304 (9.6)	269 (9.3)	21 (0.7)	13 (0.4)	34 (0.6)	93 (2.9)	85 (2.9)	178 (2.9)
4	325 (9.1)	287 (9.4)	612 (9.3)	10 (0.3)	12 (0.4)	22 (0.3)	90 (2.5)	80 (2.6)	170 (2.6)
5	255 (9.3)	230 (9.6)	485 (9.4)	9 (0.3)	6 (0.2)	15 (0.3)	51 (1.9)	43 (1.8)	94 (1.8)
6	117 (7.7)	96 (8.1)	213 (7.9)	3 (0.2)	3 (0.3)	6 (0.2)	20 (1.3)	25 (2.1)	45 (1.7)

n, numbers, WTR, with-the-rule; ATR, against-the-rule.
According to the outcome of the chi-square test, the prevalence of WTR is significantly greater than that of ATR and Oblique ($X^2 = 209.5$, $P < 0.001$). The boy had a higher prevalence of astigmatism than the girl ($X^2 = 209.5$, $P < 0.001$). Moreover, with the increase of age, the prevalence of astigmatism showed a descending tendency which has statistical significance ($P < 0.001$).

TABLE 3 The prevalence of myopia with different thresholds and astigmatism in 1–6 years old children.

Age	*n*	Myopia (*n*, %)			Astigmatism (*n*, %)
		≤-0.50 D	≤-1.00 D	≤-2.00 D	≥1.50 D
1	15,451	1,815 (11.75%)	686 (4.44%)	60 (0.39%)	4,171 (27.00%)
2	7,115	649 (9.12%)	198 (2.78%)	24 (0.34%)	961 (13.51%)
3	6,073	398 (6.55%)	125 (2.06%)	14 (0.23%)	784 (12.91%)
4	6,593	353 (5.35%)	123 (1.87%)	22 (0.33%)	804 (12.19%)
5	5,163	259 (5.02%)	83 (1.61%)	14 (0.27%)	594 (11.50%)
6	2,710	141 (5.20%)	51 (1.88%)	13 (0.48%)	264 (9.74%)
Total	43,105	3,615(8.39%)	1,266 (2.94%)	147(0.34%)	7,578 (17.58%)

n, number; D, diopter.

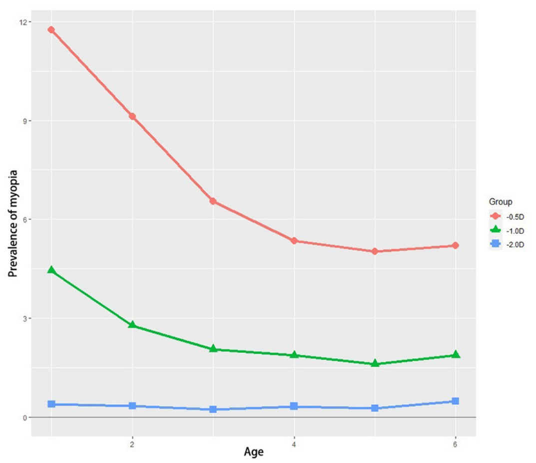

FIGURE 2
The prevalence of myopia that is defined by three thresholds among the six different age groups. D, diopter.

as well as in the leading position than majority of the cities in China.

In this study, we found that the prevalence of hyperopia and myopia was higher in younger groups of preschool children, and the refractive distribution of preschool children was gradually getting to the average level as the children grew up.

It is well accepted that most infants are hyperopes and the degree of hyperopia gradually declines with age until the completion of emmetropization, which is the similar process that happens in the myopic infants due to the rounder lenses (27, 28). Similarly, our study showed that the mean SE of children aged 1–6 years in CCES was positive and gradually decreased from 0.61 D at 1-year-old to 0.06 D at 6-year-old. The peak of the magnitude of refractive error stayed in positive.The distribution of the magnitude of the refractive error was more disperse in younger groups and more centralized in older groups. The values of refractive error gradually centralize to zero, which was most evident in the first year after birth, indicating significant emmetropization.

The average prevalence of myopia in preschool children in CCES was 8.39%, 2.94%, and 0.34%, with the threshold of SE ≤ -0.50 D, SE ≤ -1.00 D, and SE ≤ -2.00 D, respectively. If we defined SE ≤ -1.00 D as the criteria of myopia to reduce the false-positive rate, the average prevalence of myopia in preschool children in our study was 2.94%. Myopia prevalence in other previous studies around the world was variable (Table 6). Wen G et al. reported that the myopia prevalence was only 1.2% in non-Hispanic whites (aged 6–72 months) in the MEPEDS

TABLE 4 The proportion of myopia, emmetropia, and astigmatism with different thresholds in 1–6 years old children.

Age(-year-old)	*n*	Myopia (≤-1.0 D, *n*, %)			Emmetropia (≤2.0 D and ≥-1.0 D, *n*, %)			Hyperopia(≥2.0 D, *n*, %)		
		Boy	girl	All	Boy	girl	All	Boy	girl	All
1	15,451	368(2.4%)	318(2.1%)	686 (4.4%)	6,182(40.0%)	5,458(35.3%)	11,640 (75.4%)	1,650(10.7%)	1,474(9.5%)	3,124 (20.2%)
2	7,115	100(1.4%)	98(1.4%)	198 (2.8%)	3,223(45.3%)	2,781(39.1%)	6,004(84.4%)	483(6.8%)	428(6.0%)	911 (12.8%)
3	6,073	66(1.1%)	59(1.0%)	125 (2.1%)	2,779(45.8%)	2,533(41.7%)	5,312(87.5%)	325(5.4%)	309(5.1%)	634 (10.4%)
4	6,593	71(1.1%)	52(0.8%)	123 (1.9%)	3,095(46.9%)	2,617(39.7%)	5,712(86.6%)	386(5.9%)	362(5.5%)	748 (11.4%)
5	5,163	52(1.0%)	31(0.6%)	83 (1.6%)	2,457(47.6%)	2,161(41.9%)	4,618(89.4%)	245(4.7%)	215(4.2%)	460 (8.9%)
6	2,710	30(1.1%)	21(0.8%)	51 (1.9%)	1,457(53.8%)	1,148(42.4%)	2,605(96.1%)	34(1.3%)	20(0.7%)	54 (2.0%)
Total	43,105	687(1.6%)	579(1.3%)	1,266 (2.9%)	19,193(44.5%)	16,707(38.8%)	35,900(83.3%)	3,123(7.2%)	2,808(6.5%)	5,931 (13.8%)

According to the outcome of the Chi-square trend test, the prevalence of hyperopia showed a descending tendency with the increase of age, which has statistical significance ($P < 0.001$). Instead, children with emmetropia have tapered off. Moreover, the prevalence of myopia decreases with the increase of age, and the tendency has statistical significance ($P < 0.001$). In addition, there was no significant gender difference in the prevalence of myopia, emmetropia, and hyperopia.

TABLE 5 The prevalence of myopia and astigmatism with different thresholds in 1–6 years old children.

Characteristic	Subgroup	OR (95%CI)	*P*-value
Gender	Boy	1.00	
	Girl	0.92 (0.82,1.026)	0.131
Age	1-years old	1.00	< 0.001
	2-years old	0.82 (0.70,0.97)	0.021
	3-years old	0.61 (0.50,0.74)	< 0.001
	4-years old	0.56 (0.46,0.68)	< 0.001
	5-years old	0.49 (0.39,0.62)	< 0.001
	6-years old	0.61 (0.45,0.81)	0.001
Astigmatism	No	1.00	
	Yes	5.03 (4.48,5.65)	< 0.001

OR, Odds ratio; CI, Confidence interval.
The binary logistic regression model showed that older age and suffering from astigmatism were independently associated with the development of myopia. The results are shown in Table 4. As the Collinearity diagnostics showed, the VIF (variance inflation factor) was 2.63 < 10. Therefore, there was no multicollinearity among these factors.

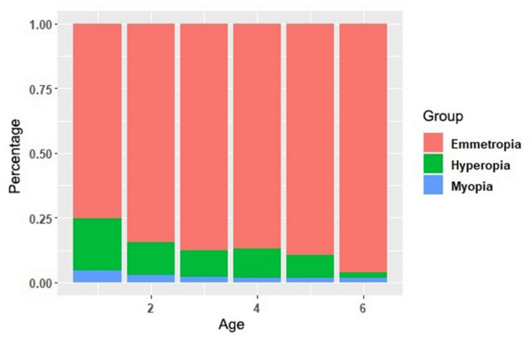

FIGURE 3
The proportion of emmetropia, hyperopia, and myopia.

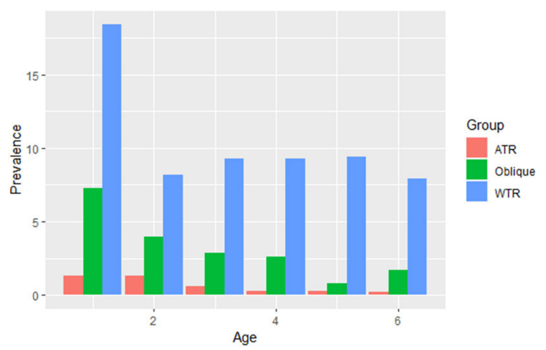

FIGURE 4
The prevalence of different types of astigmatism among the different age groups. WTR: with the rule (+ cylinder axis 90° ± 15°); ATR: against the rule (+ cylinder axis 180° ± 15°); all other orientations were considered oblique (OBL).

study (29). However, the STARS study showed that the average prevalence of myopia in Chinese children from 6 to 72 months in Singapore was as high as 11.0% (11), while the prevalence of myopia of 6-year-old children in Taiwan was 6% (30). When we compared our results with the studies in other regions of China, we found that, in this study, the average prevalence of myopia of children aged 1–6 years was 2.94% and was 1.61% for 5-year-old children, which was slightly lower than the children with corresponding age in Hong Kong (31), Taiwan (32) and Shanghai (33). Neverthelss, it is relatively higher than that in Chongqing (34). This might attribute to the different economic levels of these regions. In our study, only the children in urban areas were included, while the Chongqing study focused more on rural areas, and the Shandong study included children both from urban and rural areas.

Notably, we found that the prevalence of myopia in preschool children decreased with age, particularly evident from birth to 2 years, then it stayed relatively stable between 2 and 5 years, and followed by a slight increase at 5- to 6-year-old. This trend is similar to the MEPEDS study among African-American

TABLE 6 Studies about prevalence of myopia among preschool children (%).

Study	Ethnic	Numbers	Cycloplegia	Definition of Myopia	Prevalence (%)					
				(SE)	1Y	2Y	3Y	4Y	5Y	6Y
MEPEDS	African-American	2994	1% cyclopentolate or 0.5%	≤-1.00 D	13.7	9.1	6.4	5.5	4.2	4.1
	Hispanic	3030	cyclopentolate was used in children		6.4	7.2	4.0	1.5	1.8	2.4
	Non-Hispanic white	1501	≤12-month-old				1.20 (mean)			
	Asian-American	1507					3.98 (mean)			
BPEDS	African-American	1268	1% cyclopentolate or 0.5%	≤-1.00 D	9.6	7.5	10.5	5.9	6.2	6.6
	Non-Hispanic white	1303	cyclopentolate was used in children ≤		0.0	2.3	1.1	0.0	1.5	1.2
			12-month-old							
STARS	Singaporean Chinese	2639	Yes, detail is not described	≤-0.50 D	15.8	14.9	20.2	8.6	7.6	6.4
Japan	Japanese	17320	No	≤-0.50 D	-	-	-	-	-	3.0
Hong Kong	Chinese	108	1% cyclopentolate	≤-0.50 D	-	-	-	-	4.6	-
Taiwan	Chinese	618	1% tropicamide	≤-0.50 D	-	-	3.0	4.2	4.7	12.2
Shanghai	Chinese	5532	0.5% proparacaine/ 1% cyclopentolate	≤-0.50 D	-	-	1.8	2.3	3.5	5.2
Shandong	Chinese	6026	1% cyclopentolate	≤-0.50 D	-	-	-	1.7	0.8	4.1
Guangzhou	Chinese	495	1% cyclopentolate	≤-0.50 D	-	-	-	-	3.3	-
Guangzhou	Chinese	2480	1% cyclopentolate	≤-0.50 D	-	-	2.1	0.9	0.2	1.6
Chongqing	Chinese	3070	1% cyclopentolate	≤-0.50 D	-	-	-	-	-	0.4
CCES *	Chinese	43,105	No	≤-1.00 D	4.4	2.8	2.1	1.88	1.6	1.9

SE, spherical equivalent; Y, -year-old; MEPEDS, the Multi-Ethnic Pediatric Eye Disease Study; BPEDS, the Baltimore Pediatric Eye Disease Study; STARS, The Strabismus, Amblyopia and Refractive Error in Singaporean Children; NA, not available; CCES, The Changsha Children Eye Study; Asterisk indicates our study.

and Hispanic-American children (10) and the other two studies (27, 31). Unlike the prevalence of myopia among preschool children, the prevalence of myopia in school-age children increases steadily (5, 35). What is more, emmetropization in infancy is widely acknowledged to decline from farsightedness. However, our study indicated that the emmetropia process could be from nearsightedness to emmetropization too. The nearsightedness in infants and young children might be due to the convex lens shape in the early stage. Although the ocular axis is getting longer with the increase of age, the lens is becoming thinner. Therefore, the refractive status tends to shift from myopia to emmetropia. In addition, it is reported that emmetropization is most obvious within the age of two, and it usually completes before 4 years old (36, 37). Therefore, the slight increase in the prevalence of myopia between 5 and 6-year-olds might be an early sign of myopia in school-age children.

In our study, the prevalence of hyperopia in preschool children was 13.76% and it decreased with age. It is lower than that of the African descent children (20.8%) and Hispanic (26.9%) in the United States (10), but higher than the average prevalence of hyperopia in Chinese children in Singapore MEPEDS study (7.5%), and the 5-year-old children in Taiwan study (4.7%) (Table 6). Moreover, there were two periods of time when the hyperopia were significantly lower than other age group: the one is from 1-year-old (20.22%) to 2-year-old (12.80%), which might be due to emmetropization. The other one is 5-year-old (8.91%) to 6-year-old (1.99%). The reason might be that children at this age are usually ready for school, and more near-distant work is required in their daily life. Besides the physiological emmetropization, we strongly insist that more attention should be paid, both from parents and clinical doctors to myopia monitoring with children aged 5–6 years old.

The prevalence of astigmatism has been reported to vary from 3.8 to 50% in different studies (11). However, in our study, the prevalence of astigmatism among preschool children was 17.6%, and it was lower in older age group. It distinctly dropped from 27.0% at 1 year old to 13.51% at 2 years old, followed by a slow decrease to 9.74% at 6 years old. The prevalence of astigmatism in our study is much lower than that of the Shandong study (36.3%) (5), but higher than that of the Singapore STARS study (8.6%) (11). It is close to another study (19.2%, ages 7–9) in Singapore (17) and the MEPEDS and BPEDS studies (11.4%) for white children. WTR astigmatism was by far the most common form in all age groups, similar to the population-based MEPEDS, BPEDS and STARS studies.

In this study, we included 43,105 preschool children, and 28,639 of them were under three years. To our knowledge, it was an unprecedently enormous sample of the Chinese population with this period of age. However, there were several limitations in the study. Firstly, a cross-sectional study, which, to some extent, indicated the age-related trends, such as emmetropization, was not as reliable as cohort studies. Secondly, due to the difficulty in the practice of cycloplegia, we defined SE ≤ -1.00 D as myopia, which would reduce the false myopia rate, but bias still exists. Thirdly, the younger children group, especially the 1-year-old group, has poor cooperation, which could lead to deviations. Lastly, though many studies have confirmed that automated refraction and retinal retinoscopy are highly correlated, they are different and unavoidable deviations might exist when we use handheld child vision screeners for examination.

Overall, our population-based cross-sectional study investigated the prevalence of myopia, hyperopia, and astigmatism in preschool children aged 1–6 years. We observed that the distribution of the refractive error was disperse in the younger group and gradually turned more centralized in older group. Similar to hyperopia, with age increased, the prevalence of myopia decreased in preschool children younger than 5 years old and then slightly increased at 5–6 years, which may indicate an early sign of myopia in school-age children. According to our study, two periods of time require more attention. One is from 1 to 2 years old, which is a rather physiological change stage when the prevalence of myopia, hyperopia, and astigmatism decreases significantly, indicating that the refractive error within 1 year is likely to decrease at 2 years old. The other one is 5–6 years old, in which the prevalence of hyperopia was lower and the prevalence of myopia was higher, that alarms us to monitor and prevent potential early myopia at this time.

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 Beijing Aier Intech Eye Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YY: data curation, investigation, methodology, writing—original draft, and writing—review and editing. JF: data curation and writing—original draft. MX: data curation, methodology, and supervision. YS: data curation, investigation, and methodology. HZ: methodology, supervision, and writing—review and editing. SW: conceptualization, project administration, supervision, and writing—review and editing. 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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 24 November 2022
DOI 10.3389/fpubh.2022.1036929

Parents' intentions toward preschool children's myopia preventive behaviors: Combining the health belief model and the theory of planned behavior

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 05 September 2022
ACCEPTED 10 November 2022
PUBLISHED 24 November 2022

CITATION
Jiang N, Chen J, Cao H, Liu Y, Zhang Y, Wang Q, Wang T, Zhao H, Lu H, Yang L and Wang J (2022) Parents' intentions toward preschool children's myopia preventive behaviors: Combining the health belief model and the theory of planned behavior.
Front. Public Health 10:1036929.
doi: 10.3389/fpubh.2022.1036929

Objective: This study aimed to develop an integrated model based on the health belief model (HBM) and the theory of planned behavior (TPB) to explore the influencing factors of parents' intentions toward preschool children's myopia preventive behaviors.

Methods: This cross-sectional study was conducted in Minhang District, Shanghai, China in January 2022. One thousand six hundred and twenty-eight parents of preschool children from seven preschools were recruited in the study. A four-part questionnaire was used to collect data on socio-demographic characteristics, HBM variables, TPB variables and parental intentions. This study used exploratory factor analysis to analyze HBM and TPB items. Hierarchical multiple regression analysis was performed to explore the relationship between independent variables and parents' intentions toward preschool children's myopia preventive behaviors.

Results: The final integrative model showed that perceived severity, perceived barriers, attitudes, subjective norms, and perceived behavioral control were associated with parents' intentions toward preschool children's myopia preventive behaviors. In model 1, Child's age was entered as a control variable and explained 0.6% of the variance ($F = 7.241$, $p = 0.007$). When the HBM variables were entered in model 2, the proportion of variance increased to 25.4% ($F = 73.290$, $P < 0.001$). In model 3, TPB variables were entered and explained 63.2% of the variance ($F = 246.076$, $p < 0.001$).

Conclusion: The integrated model of HBM and TPB constructed in this study significantly improved the degree of explanation of parents' intentions toward preschool children's myopia preventive behaviors. Parents' perceived severity, perceived barriers, attitudes, subjective norms, and perceived behavioral control can be prioritized intervention targets for myopia preventive practices in preschool children.

KEYWORDS

health belief model, theory of planned behavior, myopia, preschool children, parental intention

Introduction

Myopia is a growing public health concern, especially in Asian countries due to its high prevalence (1). A recent study showed that the prevalence of myopia in 4-year-old, 5-year-old, and 6-year-old children in China was 5.7, 5.8, and 7.1%, respectively (2), higher than the finding from Australia (1.4%) (3) and Kosovo (3.4%) (4). Most importantly, previous studies have shown that the earlier the onset of myopia, the more likely it is to progress into more severe myopia and even lead to irreversible loss of vision (5, 6). For example, the increased risk of myopic complications such as myopic macular degeneration, retinal detachment, cataract, and open angle glaucoma, have become the leading cause of untreatable visual loss in East Asian countries (7, 8).

Although the cure for myopia has not yet been established, the risk of myopia progression is manageable. There is empirical evidence that both genetic and environmental factors contribute to the development of myopia (9, 10). As modifiable environmental risk factors, myopia preventive behaviors are receiving increasing attention. Myopia preventive behaviors were divided into two categories. The first is the risk behaviors for myopia, such as prolonged screen exposure, prolonged reading and writing, and prolonged near work (10). The second category is protective behaviors for myopia, such as plenty time for outdoor activities (11). Restricting individual risk behaviors and promoting protective behaviors will help prevent the development of myopia (1, 12). It has been well-documented that the period from birth to 3–5 years of age is critical for visual development (13, 14). However, because preschool children have poor self-control, they always tend to follow their parents' arrangements (15, 16). Thus, near work, screen and outdoors time among preschool children are significantly influenced by parental attitudes and intentions (16).

Complicated psychosocial factors influence parents' intentions toward preschool children's myopia preventive behaviors, such as self-efficacy, response efficacy, and susceptibility (17). Therefore, a single theoretical model has limitations in explaining behavioral intentions (18). Under this circumstance, many researchers begin to explore the possibilities of combining various theories to construct a more comprehensive theoretical system to explain behavior or behavioral intentions. For example, one study constructed an integrated model of the theory of planned behavior (TPB) and self-determination theory to explain myopia-preventive behaviors (19). In addition, some researchers have proposed the comprehensive application of TPB and health belief model (HBM) interpretation of parents' intentions to vaccinate their children (20).

TPB is one of the most widely used social cognitive models that attempts to predict behavioral intentions and health behaviors (21, 22), which is an extension of the theory of reasoned action (23). Specifically, TPB posits that intention is the immediate predictor of behavior, which is determined by attitude, subjective norm, and perceived behavioral control. This theory states that when individuals perceive a behavior as positive (attitude), know that important people want them to perform the behavior (subjective norms), and perceive that the behavior is under their own volitional control (perceived behavioral control), then the individual will perform the behavior (24). The TPB has been applied to many health behaviors including myopia preventive behavior and parents' intentions to vaccinate their children (19, 25).

The HBM is a theoretical guideline and general conceptual framework for health behaviors (26). HBM focuses on changes in health beliefs, which lead to changes in health behaviors (27). According to the HBM, individuals' involvement in health-related behaviors can be explained by perceived susceptibility, perceived severity, perceived benefits, perceived barriers, self-efficacy, and cues to action. The theory postulates that individuals are more likely to adopt healthy behaviors when they perceived risks and believe these behaviors can promote their health (28). HBM has been widely used in various health behaviors, including myopia preventive behavior intentions (29, 30).

HBM and TPB are two of the most common and accepted theories in the field of health behavior. Both of them are based on the expectancy value theory, but offer different perspectives on behavioral decision-making (28, 31). However, a number of studies have identified that existing single theories may have some shortcomings that potentially reduce their predictive power (19, 32). For example, TPB is considered not to identify the more global cognitive variables related to its constituent variables and the model does not account how general motivation serves as a source of information to guide social cognitive processes (32). One of the limitations of HBM is that

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it ignores the influence of external pressures such as subjective norms on one's acceptance of a healthy behavior (33). Therefore, the combination of the two models not only helps to improve the limitations of existing theories on health behavior and helps to explain health behaviors to a greater degree, but also provides more recommendations for healthy behavior management. For myopia preventive behaviors, applying an integrative model to design a health education program should not only take into account parents' confidence in helping children adopt healthy behaviors, the behaviors and expectations of their friends and family, but also consider that parents' low awareness and beliefs may also influence their decisions. The combination of HBM and TPB has many applications in explaining parents' intentions to vaccinate their children and parental beliefs related to children's behavioral problems (20, 34). However, there is still a lack of exploration of the combination of two theories in explaining parents' intentions toward preschool children's myopia preventive behaviors. Therefore, based on the integrated model of HBM and TPB, this study explores the influencing factors of parents' intentions toward preschool children's myopia preventive behaviors, with the goal of exploring effective intervention measures to improve myopia preventive behavior and reduce the occurrence of myopia in preschool children in China.

Materials and methods

Study design and population

This cross-sectional study recruited parents of preschool children from seven preschools in Minhang District, Shanghai in January 2022. According to the calculation method of the sample size of the cross-sectional study, the average score of behavioral intention is 3.47, and the standard deviation is 0.94 (35). The significance level is 0.05 and allowable error was taken as 0.015 mean score, the sample size was required to be at least 1,253. With a possible invalid rate of 20%, no fewer than 1,566 participants should be recruited. There are 189 preschools in Minhang District with about 71,000 students. This study adopted the method of cluster sampling and recruitment invitations were sent to 189 preschools. Seven preschools were recruited on a first-come, first-served basis. Finally, a total of 1,628 parents of preschool children from seven preschools were included. The inclusion criteria for this study including (1) parents are guardians of children; (2) parents of children aged 3–6; (3) be able to complete the questionnaire independently. Exclusion criteria include (1) parents who have participated in other myopia intervention programs in the past 12 months; (2) parents of children with severe eye or head trauma. Parents of each preschooler were invited to complete an online questionnaire, the content of the questionnaire and the purpose of the study were explained to all parents prior to the start of the survey. Before participating in this study, all participants had only received the simplest school-based education on myopia knowledge required by the government, and had not received special training in myopia intervention. Informed consent was obtained from the parents.

In order to ensure the quality of the questionnaires filled in by parents, we set up two quality control questions. A questionnaire was considered valid only if all two quality control questions were answered correctly. In addition, the questionnaire was set to be submitted only after all questions have been answered, and each account could only submit the questionnaire once. In the end, a total of 1,537 questionnaires were collected, with a response rate of 94.41%, of which 1,300 were valid questionnaires, with a valid rate of 84.58%. The study was approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University (The international registry nos. IRB00002408 and FWA00002399).

Measurement

The questionnaires used in this study were developed by the research team after referencing to the questionnaire framework in the relevant literature. We mainly made some modifications to the behavioral content in the questionnaire to make it more in line with our research purposes, the question frames in different dimensions were retained, and none of the existing items were used. The 24 items of the HBM variables referred to two studies on parental intentions of children (20, 36). For example, perceived benefits and perceived barriers were measured using items like "It is good for my child to [target behavior]," "It is difficult for me keep my child [target behavior]." The content of the questionnaire for TPB variables was mainly based on a study about parents' decisions for limiting their young child's screen time (37). For example, items like "Most people who are important to me think that I should ensure that [target behavior]" were used to measure subjective norms. All items in the HBM and TPB models use a 5-point Likert scale and response scale from 1 "strongly disagree" to 5 "strongly agree." Each dimension is expressed using the mean score, calculated by adding up the score for each item under each dimension and dividing by the corresponding number of items.

Socio-demographic characteristics

Data regarding child gender, child's age, preterm birth, single child, father's age, mother's age, father's educational level, mother's educational level, annual household income, father myopia and mother myopia were obtained from each participant.

HBM variables

The HBM variables include (Table 1): perceived susceptibility (2 items), perceived severity (6 items), perceived benefits (6 items), perceived barriers (5 items), and cues to action (5 items). For our study, Cronbach's alpha was 0.83, indicating acceptable internal consistency reliability.

TPB variables

The TPB variables include (Table 1): attitude (4 items), subjective norms (6 items), perceived behavioral control (4 items). For our study, Cronbach's alpha was 0.92, implying good internal consistency reliability.

Intention

Parents' intentions toward preschool children's myopia preventive behavior were measured by 4 items, including: "I intend to take measures to protect my child's vision in the next 12 months," "I intend to limit my child's screen time to no more than 1 a day in the next 12 months," "I intend to limit the time my child spends reading, writing, and drawing to no more than 1 h a day in the next 12 months," "I intend to keep my child's outdoor time at least 1 h a day in the next 12 months." Questions were scored on a 5-point rating scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores reflected higher levels of parents' intentions.

Statistical analysis

Numbers and percentages were used to describe qualitative variables, while quantitative variables were presented as mean and standard deviation. Cronbach's alpha was calculated to test the internal consistency of each dimension in the HBM and TPB models. Use *t*-test or ANOVA to analyze differences in parental intention, where appropriate. Exploratory factor analysis was used to examine the construct validity and factors were extracted by applying principal component analysis with a varimax rotation. Items with factor loadings <0.40 or loadings >0.40 on multiple factors were eliminated (38). To explore the relationship between independent variables and parents' intentions toward preschool children's myopia preventive behaviors, a hierarchical multiple regression was performed. Model 1 consisted of significant socio-demographic variables found in the univariate analysis. Model 2 entered perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and cues to action; these were HBM variables. Model 3 entered TPB variables, which were attitude, subjective norms and perceived behavioral control. The order of variables inclusion in the model was based on two prior hypotheses. First, HBM variables can explain additional variance after accounting for individual socio-demographic factors. Second, after accounting for the variance of individual factors and HBM variables, the increased variance may be explained by the TPB variables. All statistical analysis were performed using IBM SPSS Statistics 20 software (IBM Corp.). Statistical significance was set at 0.05.

Results

Exploratory factor analysis, descriptive analysis and reliability of the HBM and TPB variables

The Bartlett test of sphericity ($\chi^2 = 36208.14$, $p < 0.001$) and Kaiser–Meyer–Olkin measure (0.91) verified interpretability of the exploratory factor analysis. Eight factors with eigenvalues >1 were retained, explaining 69.24% of the total variance. Two questionnaire items were eliminated: "It is serious If my child develops myopia (or worsens myopia) that increases expenses" (perceived severity) and "The ophthalmologist once told me to protect my child's vision" (cues to action). Besides, the factor loadings for the remaining items ranged from 0.560 to 0.901, which is acceptable (Table 1). The Cronbach's alpha coefficient of perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, attitude, subjective norms and perceived behavioral control were 0.625, 0.914, 0.932, 0.861, 0.817, 0.822, 0.946, and 0.903, respectively, indicating good internal consistency reliability. The mean scores and standard deviation for the HBM and TPB variables are detailed in Table 1.

Differences among sample socio-demographic and parental intention

A total of 1,300 parents of preschool children aged 3–6 years were recruited for this study. Table 2 presents the socio-demographic characteristics of the children and parents. The average age of the fathers was 35.79 (SD = 4.40) years, and the average age of the mothers was 34.16 (SD = 4.01) years. About half are single-child families (53.0%). Most of the parents have a bachelor's degree or above. The self-reported prevalence of myopia was 49.9% for fathers and 54.5% for mothers. Among these socio-demographic variables, univariate analysis found there were significant differences in parental intention scores in child's age ($F = 2.75$, $p = 0.042$).

Hierarchical multiple regression

A hierarchical multiple regression analysis was conducted to investigate the association between child's age, HBM variables, TPB variables and the parents' intentions toward

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TABLE 1 Exploratory factor analysis, descriptive analysis and reliability of the HBM and TPB variables.

Study variables	Item	Mean	SD	Item loading	*a*
Perceived susceptibility		3.38	0.77		0.625
	My child is at risk of developing myopia (or worsening myopia)	3.08	0.93	0.837	
	My child will be at increased risk for myopia (or myopia progression) without proper myopia prevention measures	3.69	0.87	0.800	
Perceived severity		3.87	0.90		0.914
	It is serious If my child develops myopia (or worsens myopia) that affects his daily activities	3.66	1.09	0.821	
	It is serious if my child develops myopia (or worsens myopia) that affects his studies	3.86	1.09	0.888	
	It is serious if my child develops myopia (or worsens myopia) that affects his appearance	3.49	1.18	0.797	
	It is serious if my child develops myopia (or worsens myopia) that affects his mental health	3.92	1.12	0.830	
	It is serious if my child develops myopia (or worsens myopia) that lead to eye disease such as retinal detachment in the future	4.37	0.96	0.645	
	It is serious if my child develops myopia (or worsens myopia)	3.90	1.03	0.845	
Perceived benefits		4.36	0.63		0.932
	It is good for my child to protect his/her vision by accumulating <1 h of screen time every day	4.24	0.83	0.679	
	It is good for my child to take a break or look into the distance after watching a screen for a while to protect his/her vision	4.43	0.69	0.863	
	It is good for my child to protect his/her vision by accumulating <1 h of reading and writing every day	4.21	0.79	0.724	
	It is good for my child to take a break after reading, writing, drawing or looking into the distance to protect his/her vision	4.41	0.67	0.901	
	It is good for my child to protect his/her vision by keeping good eye habits (such as not watching TV for too long, keeping enough distance, maintaining a good reading posture, etc.)	4.44	0.67	0.898	
	It is good for my child to protect his/her vision by reaching 1 h of outdoor activities every day	4.42	0.67	0.884	
Perceived barriers		1.70	0.75		0.861
	It is difficult for me to limit my child's screen time to no more than 1 h a day	1.90	1.05	0.757	
	It is difficult for me to get my kids to maintain good eye habits (such as not watching TV for too long, keeping enough distance, maintaining a good reading posture, etc.)	1.64	0.92	0.862	
	It is difficult for me to limit my child's reading, writing and drawing to no more than 1 h a day	1.65	0.90	0.794	
	It is difficult for me to keep my child's eye habit when reading and writing (for example, when writing homework, the distance between the book and the eyes should be 30–40 cm, do not lie down to read, etc.)	1.68	0.85	0.829	
	It is difficult for me to keep my kids outdoors for at least 1 h a day	1.63	0.92	0.718	
Cues to action		2.67	0.69		0.817
	Educational courses or lectures on myopia prevention in preschool children would motivate me to protect my child's vision	2.16	0.92	0.704	
	Paper brochures, books, newspapers and magazines related to the prevention and treatment of myopia in preschool children would motivate me to protect my child's vision	2.50	0.91	0.848	

(Continued)

TABLE 1 (Continued)

Study variables	Item	Mean	SD	Item loading	a
	The popular science knowledge on the prevention and treatment of myopia in preschool children on the Internet would motivate me to protect my child's vision	2.72	0.84	0.835	
	Relatives, friends, colleagues, elders, etc. have told me about the prevention and treatment of myopia in preschool children, which would motivate me to protect my child's vision	2.56	0.93	0.795	
	The preschool has provided information on the prevention and treatment of myopia in preschool children (such as the issuance of relevant manuals on myopia prevention, or the teacher will regularly remind me to pay attention to the child's eye behavior at home, etc.), which would motivate me to protect my child's vision	3.41	0.92	0.560	
Attitudes		4.24	0.75		0.822
	My child should not accumulate more than 1 h of screen time per day	4.15	0.99	0.721	
	My child's cumulative reading, writing and drawing time should not exceed 1 h per day	3.94	1.01	0.720	
	My child should maintain good eye habits	4.46	0.84	0.737	
	My child should not spend <1 h outdoors per day	4.39	0.88	0.716	
Subjective norms		4.03	0.86		0.946
	Most people who are important to me or my child think I should be concerned about my child's vision health	4.05	0.94	0.792	
	Most of the people who are important to me or my child think I should take steps to protect my child's vision	4.07	0.96	0.855	
	Most people who are important to me or my children think I should limit my child's cumulative screen time to no more than 1 h per day	4.03	0.95	0.867	
	Most people who are important to me or my children think I should limit my child's cumulative reading, writing, and drawing time to no more than 1 h per day	3.82	1.07	0.780	
	Most people who are important to me or my child think I should keep my child's good eye habits	4.14	0.91	0.826	
	Most people who are important to me or my children think I should keep my children outdoors for at least 1 h a day	4.07	0.95	0.805	
Perceived behavioral control		3.50	1.04		0.903
	For the next year, I am confident to limit my child's cumulative screen time to no more than 1 h per day	3.41	1.21	0.805	
	For the next year, I am confident to limit my child's cumulative reading, writing, and drawing time to no more than 1 h per day	3.37	1.22	0.808	
	For the next year, I am confident to ensure that my child develops good eye habits (such as not watching TV for too long, keeping enough distance, maintaining a good reading posture, etc.)	3.58	1.12	0.842	
	For the next year, I am confident that my kids will be outdoors for at least 1 h a day	3.62	1.16	0.757	

[a]Cronbach's alpha; HBM a = 0.83; TPB a = 0.92; integrative model a = 0.91.
SD, standard deviation.

preschool children's myopia preventive behaviors (Table 3). Multicollinearity analysis was performed on all independent variables, and all variance inflation factor were <1.34. In model 1, Child's age was entered as a control variable and explained 0.6% of the variance ($F = 7.241$, $p = 0.007$). When the HBM variables were entered in model 2, the proportion of variance increased to 25.4% ($F = 73.290$, $P < 0.001$). In model 3, TPB variables were entered and explained 63.2% of the variance ($F = 246.076$, $p < 0.001$). It was found that perceived severity ($\beta = 0.049$, $p = 0.008$), perceived barrier ($\beta = -0.083$, $p < 0.001$), attitude ($\beta = 0.145$, $p < 0.001$), subjective norms ($\beta = 0.230$, $p < 0.001$) and perceived behavioral control ($\beta = 0.507$, $p < 0.001$) were significantly associated with parents' intentions toward preschool children's myopia preventive behaviors.

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TABLE 2 Relationships between the parents' intentions scores and socio-demographic characteristics for children and parents ($n = 1{,}300$).

Characteristics	*N* (%)	Parental intention score, mean ± SD	*t*/*F*	*P*
Child's gender			0.38	0.702
Male	676 (52.0%)	3.92 ± 0.82		
Female	624 (48.0%)	3.90 ± 0.81		
Child's age			2.75	0.042
3	226 (17.4%)	4.00 ± 0.75		
4	409 (31.5%)	3.94 ± 0.81		
5	497 (38.2%)	3.90 ± 0.84		
6	168 (12.9%)	3.77 ± 0.84		
Preterm birth (<37 weeks)			1.06	0.288
Yes	112 (8.6%)	3.92 ± 0.82		
No	1,188 (91.4%)	3.80 ± 0.82		
Single child			1.52	0.130
Yes	689 (53.0%)	3.95 ± 0.80		
No	611 (47.0%)	3.88 ± 0.83		
Father's age			1.16	0.315
24–30 years	135 (10.4%)	4.01 ± 0.83		
31–40 years	973 (74.8%)	3.91 ± 0.82		
41–49 years	192 (14.8%)	3.88 ± 0.80		
Mother's age			2.27	0.103
20–30 years	221 (17.0%)	4.02 ± 0.79		
31–40 years	1,000 (76.9%)	3.89 ± 0.82		
41–47 years	79 (6.1%)	3.87 ± 0.80		
Annual household income (CNY¥)			1.55	0.213
≤100,000	239 (18.4%)	3.86 ± 0.85		
100,001–300,000	552 (42.4%)	3.89 ± 0.80		
≥300,001	509 (39.2%)	3.96 ± 0.82		
Father's educational level			1.01	0.363
High school or below	268 (20.6%)	3.97 ± 0.82		
College or university	957 (73.6%)	3.91 ± 0.82		
Postgraduate	75 (5.8%)	3.83 ± 0.80		
Mother's educational level			0.45	0.636
High school or below	263 (20.2%)	3.94 ± 0.84		
College or university	965 (74.3%)	3.91 ± 0.82		
Postgraduate	72 (5.5%)	3.84 ± 0.74		
Father myopia			−0.15	0.881
Yes	649 (49.9%)	3.91 ± 0.81		
No	651 (50.1%)	3.92 ± 0.82		
Mother myopia			−0.62	0.535
Yes	708 (54.5%)	3.90 ± 0.80		
No	592 (45.5%)	3.93 ± 0.84		

Income is presented in Chinese yuan.
N, number; SD, standard deviation.

Discussion

This study comprehensively used HBM and TPB theories to explore the influencing factors of parents' intentions toward preschool children's myopia preventive behaviors. The final integrative model showed that perceived severity, perceived barriers, attitudes, subjective norms, and perceived behavioral control were associated with parents' intentions. The present study found that the combination of the two theories significantly improved the degree of explanation

TABLE 3 Hierarchical multiple regression analysis including age, HBM variables and TPB variables.

Variables	Model 1		Model 2		Model 3	
	B (SE)	Beta (β)	B (SE)	Beta (β)	B (SE)	Beta (β)
Intercept	4.207 (0.111)**		1.906 (0.195)**		0.616 (0.144)**	
Age	−0.066 (0.024)	−0.074**	−0.042 (0.021)	−0.047	0.003 (0.015)	0.003
Perceived susceptibility			0.032 (0.026)	0.030	0.033 (0.018)	0.031
Perceived severity			0.130 (0.024)	0.144***	0.045 (0.017)	0.049**
Perceived benefits			0.353 (0.035)	0.270***	0.036 (0.027)	0.028
Perceived barriers			−0.292 (0.027)	−0.267***	−0.090 (0.020)	−0.083***
cues to action			0.203 (0.029)	0.171***	0.019 (0.021)	0.016
Attitudes					0.158 (0.023)	0.145***
Subjective norms					0.219 (0.021)	0.230***
Perceived behavioral control					0.399 (0.017)	0.507***
R^2	0.006**		0.254***		0.632***	
F	7.241**		73.290***		246.076***	
ΔR^2	0.006**		0.248***		0.378***	
ΔF	7.241**		86.025***		441.752***	

**P < 0.01, ***P < 0.001; B, unstandardized regression coefficient; SE, standard error of unstandardized regression coefficient; β, standardized regression coefficient.

of parents' intentions toward preschool children's myopia preventive behaviors.

Child's age was the only significant sociodemographic variable in the univariate analysis. Increasing children's age was associated with a decline in parents' intentions toward preschool children's myopia preventive behaviors. An intervention study of preschool children have found that parents report increasing difficulty controlling their children's time spent outdoors and screen use as children get older (39). This decline in parental control as children age might contribute to the decrease in parents' intentions, suggesting that parents should supervise their children to form good myopia preventive behaviors in their early years.

Consistent with other research findings, there was a significant positive association between perceived severity and parents' intentions toward preschool children's myopia preventive behaviors (17). As such, the higher level of perceived severity of myopia, the greater intention parents would exhibit to help their children take myopia preventive behaviors. A previous study further supported this result, where parents with higher levels of severity perception were more likely to supervise children to reduce screen time (40). Besides, this study found perceived severity to be a less influential factor, possibly because the public tends to view myopia as a non-life-threatening condition, distinct from infectious and degenerative diseases such as measles and cancer (17). However, the importance of perceived severity cannot be overlooked, since the intention to act against the threat is not activated if parents perceive myopia as not a threat (26, 41).

Perceived barrier is another variable significantly correlated with parents' intentions toward preschool children's myopia preventive behaviors in HBM theory, which is consistent with other research findings (17). When parents realize there are barriers to helping their children maintain good myopia preventive behaviors, their intentions decrease. Importantly, time cost has been reported as a major barrier in other studies (39). Most families are dual-employed parents who are too busy with their jobs to supervise their children's screen viewing or spend time with their children in outdoor activities (39). However, the average level of parents' perceived barriers was not high in this study. This may indicate that for most preschool children, it is not difficult for parents to control them to adopt various types of myopia preventive behaviors. Nonetheless, perceived barrier shows a significant effect in the final integrative model, possibly due to the strong correlation between perceived barrier and health protective behaviors (42). Although the effect size of perceived barrier on parents' intentions may be weaker than other variables in the integrative model, it still suggests that intervention on parents' perceived barrier can play a role. Therefore, we still recommend that appropriate educational training should be conducted to improve parental intervention techniques and strategies for children, while advocating for parents to spend more time helping children adopt myopia preventive behaviors.

Our study demonstrated a significant positive relationship between parental intentions and attitudes toward preschool children's myopia preventive behaviors. Given the crucial influence of parents on children's lifestyles, parental attitudes are considered to be a key agent in controlling the development of children's myopia (43). Therefore, improving parents' awareness of myopia and changing their attitudes will help motivate parents to take active measures to prevent children's myopia.

The relationship between subjective norms and intentions was often considered to be weak (44). However, our findings suggested that subjective norms not only have a significant positive correlation with parents' intentions toward preschool children's myopia preventive behaviors, but also explain intentions in a large degree. This is consistent with a study finding that subjective norm is a strong predictor of parents' intentions to limit their child's screen time behavior (37). This may be explained by the fact that parents are perceived to have parenting responsibilities and are responsible for their children's healthy behaviors, thereby reinforcing parents' perceived social norms (45, 46). In practical terms, this study provides evidence that subjective norms play an important role in involving parents' intentions toward preschool children's myopia preventive behaviors. Based on the apparent influence of subjective norms, it can be hypothesized that directing social change in a positive direction will be effective, especially emphasizing the advocacy of myopia preventive behaviors by influential people (e.g., teachers). This suggested that it is necessary to provide teachers and parents with appropriate training in children's vision health. Similarly, emphasizing to parents that more and more people are paying attention to maintaining myopia preventive behaviors in their children can have a positive effect.

In this study, the perceived behavioral control component showed the strongest effect on parents' intentions toward preschool children's myopia preventive behaviors. This was supported by a previous study revealing that perceived behavioral control was the main predictor of behavioral intentions (31). The more resources individuals have and the fewer obstacles they anticipate, the greater control they perceived over their behaviors, and the stronger confidence they have to perform behaviors (22). Therefore, when parents have a more comprehensive understanding of children's vision health and myopia preventive behaviors, their confidence in controlling children's related behaviors will increase, and they will be more willing to take action. Accordingly, parents' perceived behavioral control should be strengthened through enhanced advocacy and practice.

Based on the survey results, most parents are aware of their children's possible risk of myopia and the benefits of myopia preventive behaviors, and feel a general level of health cues. But this did not increase their intentions to adopt myopia preventive behaviors for their children. Previous studies based either on TPB or HBM to explain parents' intentions to vaccinate their children found that not all TPB and HBM constructs had significant effects, with some variables showing significant effects in one study and others in another study showing a significant impact (20, 25, 47–49). Just as the findings of this study that perceived susceptibility, perceived benefits and cues to action were not significant variables are inconsistent with other findings on parents' intentions toward preschool children's myopia preventive behaviors (17, 30, 40). It is not surprising that these results are different from those of other populations. Given that few studies have explored factors related to parents' intentions toward preschool children's myopia preventive behaviors using TPB and HBM constructs simultaneously, interventions should be designed based on both models to further verify the effects of each construct. Overall, the integrated model of HBM and TPB can better explain the effects of variables on parents' intentions toward preschool children's myopia preventive behaviors compared to using each of the two behavior models separately.

There are several limitations for this study to consider. First, the participants were recruited from Minhang District, Shanghai, which is a city with a high level of economic and urbanization. This might limit the generalization of the findings to populations in other regions, particularly rural areas. Second, the data of this study were collected through an online survey, which means that there may be some situations that affect the quality of the data, such as comprehension bias in the content of the questionnaire and fill out the questionnaire without reading it. However, we avoid these problems by answering questions from participants in real time online, and setting quality control questions. In addition, to ensure the smooth conduct of research, the use of online surveys during a pandemic is reasonable. Third, this study did not collect data on the refractive errors/ prevalence of myopia of the children recruited as this may have influenced parental knowledge of myopia. Future research may consider incorporating these factors. Finally, although the integrated model of HBM and TPB used in this study can explain parents' intentions toward preschool children's myopia preventive behaviors well. However, other theoretical models of behavior change such as Self-Determination Theory and Integrated Behavioral Models were not included in the study. Future research can incorporate more theoretical models to explore.

Conclusions

The integrated model of HBM and TPB constructed in this study could be well used to explain parents' intentions toward preschool children's myopia preventive behaviors. Parents' perceived severity, perceived barriers, attitudes, subjective norms, and perceived behavioral control can be prioritized intervention targets for myopia preventive practices in preschool children. In particular, there should be more advocacy and practical training for the public and parents of preschool children. Not only to promote myopia preventive behaviors and expectations of the public, but also to improve parents' awareness and attitude, thereby increasing the parents' intentions.

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 Medical Research Ethics Committee of the School of Public Health, Fudan University (The international registry nos. IRB00002408 and FWA00002399). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

NJ, JC, and HC were responsible for the acquisition, analysis and interpretation of data, and the drafting of the manuscript. YL and YZ contributed to the acquisition, interpretation of data, and critically reviewed the manuscript for important intellectual content. QW, TW, HZ, and HL provided advice regarding study design and developed the questionnaire. JW and JC were the project coordinator and contributed to the review and revision of the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the Minhang District Natural Science Research Project of Shanghai (Grant No. 2021MHZ047), the Shanghai Eye Starlight Children and Adolescent Myopia Prevention and Control Personnel Training Program (Grant No. 2022HYXG-SQ01), and the Fudan-Minhang Health Consortium Cooperation Project (Grant No. 2021FM10).

Acknowledgments

We are very grateful to all preschools for their support of this research, and to every parent who willingly and generously granted us their time.

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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 05 December 2022
DOI 10.3389/fpubh.2022.1043977

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 16 September 2022
ACCEPTED 16 November 2022
PUBLISHED 05 December 2022

CITATION
Li L, Liao J, Fu H and Zong B (2022) The association between sedentary behavioral characteristics and poor vision among Chinese children and adolescents.
Front. Public Health 10:1043977.
doi: 10.3389/fpubh.2022.1043977

The association between sedentary behavioral characteristics and poor vision among Chinese children and adolescents

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Introduction: To understand the features of sedentary behavior of Chinese children and adolescents and its relationship with poor visual acuity, a self-administered "Questionnaire on Sedentary Behavior of Children and Adolescents" was used to survey 4,203 students in grades 4–12 in six administrative regions of China.

Results: (1) The average time spent in sedentary behaviors (SB) of Chinese children and adolescents was about 8.1 h per day, of which the academic sedentary time was the longest, accounting for 79.2% of total sedentary time. The total time spent on SB and the time spent on studying SB were more in the upper grades and less in screen SB and cultural leisure SB, respectively. There were significant sex differences in total SB time ($p < 0.05$) and weekend sedentary behaviors time (SB-WD) ($p < 0.01$) among Chinese children and adolescents, with girls being more likely to be higher than boys. There were also significant differences in sedentary time across different regions ($p < 0.05$), and the longest total sedentary time in East China. (2) Reduction parents' sedentary time and limitation of sedentary behaviors and the use of electronics among children and adolescents can effectively reduce sedentary time among Chinese children and adolescents. (3) Sedentary time was significantly higher in children and adolescents with poor vision than in those with normal vision ($p < 0.01$), and study SB and screen SB were important independent factors affecting vision. (4) Timing of breaks in SB can play a positive role in promoting vision health.

Conclusion: There were significant grade, sex, and regional differences in the SB of Chinese children and adolescents, and sedentary time was strongly related to the prevalence of poor vision detection rate.

KEYWORDS

sedentary behavior, sedentary time, sedentary type, children and adolescents, poor vision

Introduction

As societies become more modernized, people's lifestyles have gradually changed. Sedentary behaviors refer to behaviors that consume energy in the range of 1.0 to 1.5 metabolic equivalents when an individual is sitting or lying in a awake state (1). In recent years, the sedentary behavior of children and adolescents worldwide has become a common phenomenon, although there are slight differences in each country (2–6).

Studies have confirmed that sedentary behavior in children and adolescents is associated with physical activity (7) and other health-related outcomes, such as obesity (8) and cardiovascular disease (9). Notably, sedentary behavior may also be strongly associated with poor visual acuity (10). The longer the sedentary time, the higher the risk of poor vision (11). Studies have found that academic stress and excessive use of electronic devices contribute to vision loss in children and adolescents (12–14). In China, the average school time for children and adolescents is around 9 h and excessive school time leads to increased eye stress. Meanwhile, Chinese children have hand-held screen devices at an early age, and premature exposure to electronic screen devices may result in vision loss. To improve visual acuity of children and adolescents, most schools require students to do eye exercises more than once a day and organize a vision examination per school year. In addition, some parents also take their children to the eye hospital for vision examination and eye care. Recent studies have shown that sedentary school-age children's behaviors, including reading and writing homework, as well as excessive Internet use and television viewing, have been associated with vision loss (13, 15). However, contrary results were also reported. Mountjoy et al. (16) reported that sedentary behaviors like reading are not associated with visual acuity in children and adolescents. Wu et al. have shown that sedentary behaviors such as watching television are also not associated with visual acuity in children (17). Thus, there are few studies and inconsistent findings on the relationship between sedentary behaviors and poor visual acuity in children and adolescents, which makes the relationship difficult to clarify and needs to be further explored.

This study selected students from grades four to 12 in six administrative regions of China, including North China, East China, South Central China, Northeast China, Southwest China and Northwest China (except Hong Kong, Macao and Taiwan), to understand the current situation of sedentary behavior of Chinese children and adolescents and reveal the characteristics of sedentary behavior of Chinese children and adolescents by investigating indicators such as the total time of sedentary behavior, types of sedentary behavior and interval time of sedentary behavior. On this basis, we explore the relationship between sedentary behavior and poor vision of children and adolescents, identify the main factors affecting poor vision caused by sedentary behavior, and hope to open up new ideas for improving the sedentary lifestyle of children and adolescents and promoting eye health of children and adolescents.

Methods

Study design and participants

The participants were selected according to the six administrative regions (Northeast China, North China, East China, Northwest China, Southwest China and South Central China) of the country, covering 20 provinces (cities, districts) including Shanghai, Tianjin, Chongqing, Anhui, Fujian, Guangdong, Hebei, Henan, Heilongjiang, Jilin, Jiangsu, Liaoning, Shandong, Sichuan, Zhejiang, Yunnan, Shanxi, Inner Mongolia Autonomous Region, Xinjiang Uygur Autonomous Region, and Tibet Autonomous Region, according to each administrative division plans to distribute 900 students. Considering that the cognitive abilities of children and adolescents in grades one to three are still immature, they do not understand the content of the questionnaire, and have no ability to fill in the questionnaire independently, students in grades four to 12 with an age range of 11 to 17, were selected for the questionnaire. Five thousand four hundred online questionnaires were distributed, and 4,735 questionnaires were returned. The following participants were excluded: (1) the filling attitude was incorrect, which means participants filled in the questionnaire with incomplete content, such as missing questions, wrong lines, no personal information, the answer choices did not meet the filling requirement, such as ticking $\geq$2 answers for a single choice question, and it was obvious that the questionnaire was filled in randomly; (2) the questionnaire was repeatedly filled. Finally, 4,203 valid questionnaires were obtained, with a recovery rate of 77.8%, including 2,041 boys and 2,162 girls (Table 1). This study was reviewed and approved by the human subject protection committee of East China Normal University (approval No.: HR234-2019). Consents were obtained from all participants and their parents/guardians, and informed consent was signed.

Sedentary behavior measurement

With reference to the relevant items of the "Last 7-d Sedentary Time Questionnaire" (18) and "Adolescent Sedentary Activity Questionnaire" (ASAQ) (19), combined with the "Seven-day Activity Record Form for Children and Adolescents" in this study, the "Chinese Children and Adolescents Sedentary Behavior Questionnaire" was initially formulated. One hundred forty-two participants were invited to complete the repeated survey with an interval of seven days, and on the basis of combining the results of the

TABLE 1 Region, sex and grade distribution of children and adolescents.

Region	Northeast China		North China		East China		Northwest China		Southwest China		South Central China		Total
Grade	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	
4	0	0	43	43	35	32	65	61	90	62	79	74	584
5	0	0	54	47	21	25	47	44	57	73	34	45	447
6	0	0	73	92	14	12	42	39	41	49	44	41	447
7	19	8	104	86	57	56	8	10	2	1	76	57	484
8	7	14	54	56	32	26	4	6	26	27	31	25	308
9	35	44	47	55	59	67	9	17	25	33	11	8	410
10	43	70	49	47	65	71	63	99	30	23	23	52	635
11	25	35	26	37	109	84	64	87	22	41	26	25	581
12	14	27	6	6	14	23	22	26	13	15	82	59	307
Total	143	198	456	469	406	396	324	389	306	324	406	386	4203

pre survey and expert opinions, the questionnaire items were deleted and improved. After that, 181 participants were surveyed repeatedly at intervals of seven to 14 days. The reliability and validity of the revised questionnaire was good. The Spearman correlation coefficient of the two tests was between 0.51 and 0.85, and both were significant. The intra group correlation coefficient ICC (Intra class correlation coefficient) was 0.43 to 0.75, which met the expectations of the study. The validity of the questionnaire was tested using the criterion validity. The ASAQ questionnaire was used as the criterion. Spearman's correlation test showed that the correlation coefficient was 0.786, and the difference was statistically significant.

The revised questionnaire mainly investigates the basic information of the participants, the time they spent in regular cultural courses and different types of sedentary behaviors in a week (generally divided into study days and weekends). The questionnaire contains four dimensions and a total of 12 questions, including study sedentary behaviors (homework, reading, extracurricular tutoring classes, online courses), screen sedentary behaviors (watching TV, using mobile phones, computers), transportation sedentary behaviors (taking buses, taxis, etc.) and cultural leisure sedentary behaviors (painting, playing musical instruments, etc.). Since the sedentary behavior time of traffic accounts for a small proportion in daily life, it was not analyzed. This study used 8 h as the threshold, and divided the sedentary behavior time ≥8 h into the high sedentary behavior group. In addition, a survey on sedentary behavior interruption (i.e., how often children and adolescents walk when they are engaged in the above sedentary activities) has also been added. In previous studies, the sedentary behavior interruption interval was divided into 15 min (20), 20 min (21, 22), 30 min (23), 60 min (24), and 85 min (25). In this study, the median value of 30 min in previous studies was used as the sedentary behavior interruption interval.

Parental lifestyle measurement

The "Parents' Living Habits Questionnaire" was used to investigate parental occupations, education status, per capita monthly household income, weekly time spent by parents on various types of sedentary behaviors, parents' intervention on children's sedentary time, and restrictions on the use of electronic products.

Eye habits and vision measurement

Referring to the items of the relevant questionnaires, according to the eye habits of Chinese children and adolescents, the "Chinese Children and Adolescents' Eye Habit Questionnaire" was compiled. The contents of the questionnaire include the use of eyes in school (including the frequency of desks and chairs, the frequency of eye exercises, etc.), the use of eyes outside the school (including reading and writing posture, vision examination and correction, etc.), and the eyesight of students and their parents. Due to the epidemic, we were unable to go to the locality to measure the participants' visual acuity, it was obtained through the school visual acuity examination, using the "Standard Logarithmic Visual Acuity Scale" (GB11533-2011) in accordance with the requirements of GB/T26343-2010 "Technical Specification for Student Health Examination." In addition, according to the filled visual acuity, the visual acuity level is graded: if the unaided visual acuity of both the left and right eyes is 5.0, the visual acuity is normal; If the vision of any unaided eye in both eyes is <5.0, it is considered as poor vision; If the vision of left and right eyes is inconsistent, the one with lower vision shall prevail. The World Health Organization (WHO) recommends that children and adolescents spend no more than 2 h of screen time per day, therefore, spending more than 2 h a day on screen time is defined as excessive use.

Physical activity measurement

The Physical Activity Rating Scale compiled and revised by Chinese scholar Liang Deqing et al. and Japanese scholar Kimio Hashimoto was used to investigate the physical activity of individuals in the past week (26). Each dimension corresponds to five levels, of which the time dimension is scored from zero to four points, and the other two dimensions are scored from one to five points. The calculation method is: exercise volume = time * intensity * frequency, the minimum score is 0 points, and the maximum score is 100 points. The test-retest reliability of the scale was 0.82. The physical activity rating scale of this study is divided into two parts. The first part investigates the level of in-class physical activity of children and adolescents in the past week, and the second part investigates the level of extra-curricular physical activity of children and adolescents in the past week.

Statistical analyses

The data collected from the questionnaire were sorted and screened by Excel software, and the data were statistically analyzed by SPSS 25.0 software and LMS chart maker software. Descriptive statistics was used to analyze demographic variables, sedentary time and sedentary type distribution characteristics, high sedentary behavior detection rate and poor vision detection rate of children and adolescents; Non normal distribution data are expressed in the form of median ± interquartile range. The preliminary analysis of the data found that the time standard deviation of sedentary behavior of the total sample was large, reflecting the high degree of dispersion of the data. In this case, the representation of the mean was low. Therefore, the median was used as a substitute for the mean. Independent samples t-tests were used to analyze differences in various sedentary behaviors among children and adolescents of different genders, to test for differences in the types of sedentary time between children and adolescents with normal and poor vision as well as to analyze differences in physical activity levels between children and adolescents with normal and poor vision. One-way ANOVA was used to examine the differences in the types of sedentary behaviors among children and adolescents in different grades and the differences in the duration of sedentary time among children and adolescents in different regions. A χ^2 test was used to analyze the differences in the detection rate of poor vision among children and adolescents with different sexes, grades, and the habit of sedentary interruption. Through correlation analysis and stepwise regression analysis, on the premise of excluding the influence of parental occupation, education status and other factors, a model is gradually established to test the correlation between parents' sedentary time and children's and adolescents' sedentary time. Finally, logistic regression was used to analyze the relationship between the duration of sedentary, intermittent habits and the detection rate of poor vision. $P < 0.05$ indicates significant difference, $P < 0.01$ indicates very significant difference, and $P < 0.001$ indicates extremely significant difference.

Results

Sedentary behavior of Chinese children and adolescents

Times of sedentary behavior

The results of the survey showed the average total sedentary time of children and adolescents in grades four to 12 in China is about 8.1 h/day, 8.75 h/day on weekdays, and 7.2 h/day on weekends. The sedentary time on weekdays was significantly longer than that on weekends ($p < 0.001$). The total sedentary behavior time and weekend sedentary behavior time of students in grades 4–12 showed significant sex differences. The total sedentary behavior time ($p < 0.05$) and weekend sedentary behavior time ($p < 0.01$) of girls were significantly higher than those of boys. There was no significant sex difference in sedentary behavior time on weekdays (SB-WE) (Table 2).

Figures 1–3 shows the percentile distribution of sedentary time of Chinese students from Percentile 3 (P3) to Percentile 97 (P97) and Table 3 shows the specific values of percentile sedentary time of Chinese students from P3 to P97, which generally show that children and adolescents in the upper grades have higher sedentary time. The sedentary time on weekends is longer in the upper grades than in the lower grades. The sedentary time on weekdays generally shows a trend of gradually increasing with the increase of grade, and reaches the highest point in Grade 11.

According to one-way ANOVA, there was a significant difference in the total sedentary time of children and adolescents in different regions, East China > Northwest China > Northeast China > Southwest China > North China > Central and South China; The sedentary time on weekdays and weekends was also significantly different in different regions; Multiple comparisons showed that the sedentary time of children and adolescents in other regions on weekdays and weekends was significantly longer than that in central and southern regions ($p < 0.001$); The longest sitting time of weekdays was the highest in Northwest China ($p < 0.05$), and there was no difference between Northwest China and East China ($p > 0.05$); The sedentary time on weekends was the highest in East China, but there was no significant difference with southwest China (Table 4).

Types of sedentary behaviors

In this study, study sedentary behaviors time, screen sedentary behaviors time, cultural leisure sedentary behaviors

TABLE 2 Sedentary time of Chinese children and adolescents (min/d).

Grade	N	SB			SB-WE			SB-WD		
		M	F	Total	M	F	Total	M	F	Total
4	584	422.5 ± 177.6	414.3 ± 183.1	419.1 ± 177.8	429.5 ± 141.5	443.0 ± 133.5	438.0 ± 137.3	390.0 ± 266.3	387.5 ± 249.4	390.0 ± 254.4
5	447	445.8 ± 182.5	468.5 ± 177.9	453.0 ± 183.0	450.0 ± 146.5	455.5 ± 153.3	453.0 ± 150.0	390.0 ± 293.5	465.0 ± 257.5	435.0 ± 285.0
6	447	454.9 ± 174.6	447.5 ± 170.1	450.0 ± 175.7	455.9 ± 142.3	446.0 ± 138.3	452.0 ± 136.0	430.0 ± 245.0	420.0 ± 245.0	425.0 ± 250.0
7	484	498.5 ± 217.1	492.0 ± 211.3	495.4 ± 211.9	552.5 ± 155.5	550.8 ± 142.3	551.8 ± 147.8	437.5 ± 314.4	446.3 ± 338.1	442.5 ± 326.3
8	308	498.5 ± 217.4	525.4 ± 199.2	505.5 ± 206.7	523.7 ± 196.8	534.1 ± 189.0	531.5 ± 189.5	460.0 ± 332.5	492.5 ± 301.0	470.0 ± 315.0
9	410	500.0 ± 218.9	541.3 ± 207.1	526.8 ± 215.0	539.0 ± 161.8	569.3 ± 168.0	550.5 ± 177.8	480.0 ± 271.6	537.5 ± 310.0	493.8 ± 292.5
10	635	505.5 ± 200.5	498.5 ± 214.6	502.5 ± 207.0	571.0 ± 177.5	550.2 ± 155.5	555.6 ± 164.0	425.0 ± 304.8	420.0 ± 320.0	420.0 ± 310.0
11	581	521.8 ± 224.8	525.0 ± 223.3	524.3 ± 220.3	603.0 ± 163.6	585.0 ± 169.6	593.0 ± 166.0	450.0 ± 330.0	440.0 ± 326.0	440.0 ± 334.5
12	307	469.5 ± 186.5	506.7 ± 187.4	490.3 ± 195.0	558.0 ± 202.0	615.0 ± 179.3	586.6 ± 190.0	350.0 ± 300.0	402.3 ± 270.0	375.0 ± 270.0
Total	4,203	477.5 ± 207.4	489.8 ± 200.3	484.0 ± 204.1	521.0 ± 184.0	529.0 ± 186.4	525.0 ± 184.8	420.0 ± 285.0	435.0 ± 297.6	430.0 ± 300.0

(1) Interquartile ± interquartile range; (2) SB = total sedentary behavior time; (3) SB-WE = sedentary behavior time on weekdays; (4) SB-WD = sedentary behavior time on weekends (the same below).

TABLE 3 Percentile distribution of sedentary time among Chinese children and adolescents.

	Grade	L	M	S	P3	P10	P25	P50	P75	P90	P97
SB	4	0.24	415.16	0.32	216.11	269.16	332.39	415.16	512.65	614.36	729.04
	5	0.17	439.45	0.32	233.6	287.8	353.01	439.45	542.87	652.57	778.38
	6	0.12	464.47	0.32	250.58	306.51	374.14	464.47	573.57	690.53	826.17
	7	0.1	491.68	0.31	267.37	325.93	396.82	491.68	606.55	730.1	873.89
	8	0.1	508.8	0.31	277.4	337.96	411.13	508.8	626.77	753.29	900.15
	9	0.13	514.98	0.31	280.14	341.9	416.24	514.98	633.5	759.8	905.43
	10	0.16	515.89	0.31	278.36	341.15	416.43	515.89	634.5	759.99	903.59
	11	0.19	506.92	0.32	270.32	333.02	408.06	506.92	624.36	748.04	888.89
	12	0.2	477.9	0.32	251.69	311.62	383.38	477.9	590.09	708.1	842.26
SB-WE	4	−0.86	430.90	0.24	293.76	327.56	370.01	430.90	513.52	617.47	766.47
	5	−0.87	451.11	0.24	307.39	342.78	387.25	451.11	537.89	647.29	804.57
	6	−0.87	481.39	0.24	328.34	366.03	413.40	481.39	573.77	690.22	857.62
	7	−0.88	521.13	0.24	356.62	397.18	448.09	521.13	620.30	745.23	924.75
	8	−0.88	537.74	0.24	369.33	410.96	463.13	537.74	638.66	765.17	945.75
	9	−0.86	550.01	0.23	379.27	421.70	474.67	550.01	651.12	776.53	952.99
	10	−0.83	570.04	0.23	394.27	438.21	492.83	570.04	672.72	798.57	972.70
	11	−0.80	579.62	0.23	400.80	445.68	501.30	579.62	683.16	809.03	981.27
	12	−0.78	569.80	0.23	392.89	437.31	492.35	569.80	672.03	796.02	965.07
SB-WD	4	0.57	388.55	0.48	110.10	182.97	272.23	388.55	522.02	656.19	801.22
	5	0.52	413.54	0.48	123.04	197.66	290.44	413.54	557.45	704.59	866.07
	6	0.49	432.71	0.48	131.42	208.00	304.02	432.71	584.78	741.80	915.64
	7	0.48	446.84	0.48	134.57	213.72	313.21	446.84	605.04	768.63	949.99
	8	0.50	462.96	0.49	135.79	218.76	323.08	462.96	628.14	798.49	986.82
	9	0.51	465.99	0.50	130.45	215.54	322.63	465.99	634.75	808.17	999.21
	10	0.53	454.27	0.51	118.04	202.86	310.27	454.27	623.64	797.35	988.28
	11	0.54	429.48	0.53	101.17	183.16	288.10	429.48	596.04	766.87	954.50
	12	0.55	379.54	0.55	79.95	153.78	249.59	379.54	533.12	690.84	864.10

In LMS analysis, L is lambda, that is power; M is mu, that is median; S is Sigma, that is coefficient of variation; P is Percentile, that is percentile.

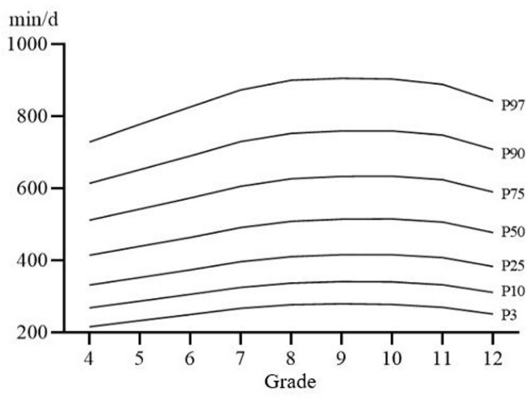

FIGURE 1
The percentile distribution curve of total sedentary time.

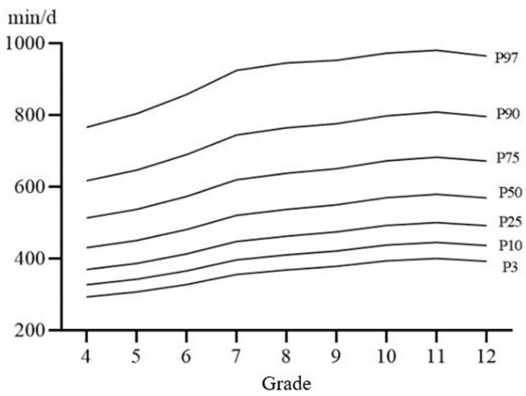

FIGURE 2
The percentile distribution curve of sedentary time in weekdays.

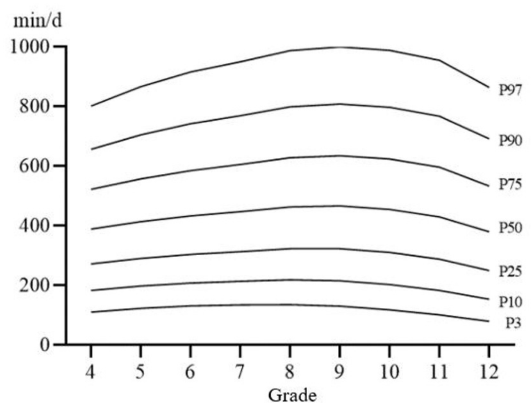

FIGURE 3
Distribution curve of percentile of sedentary time on weekends.

TABLE 4 Comparison of sedentary time among children and adolescents in different regions (min/d).

Region	N	SB	SB-WE	SB-WD
Northeast China	341	489.5 ± 192.0	527.0 ± 141.1	440.0 ± 315.0
North China	925	470.0 ± 220.1	510.0 ± 196.0	417.0 ± 305.0
East China	802	501.1 ± 203.1	553.1 ± 177.3	450.0 ± 298.1
Northwest China	713	501.0 ± 213.9	557.0 ± 209.4	435.0 ± 294.0
Southwest China	630	487.9 ± 187.6	507.5 ± 162.2	450.0 ± 274.3
South Central China	792	462.7 ± 195.4	487.0 ± 166.6	408.8 ± 300.0
Total	4,203	484.0 ± 204.1	525.0 ± 184.8	430.0 ± 300.0
F		10.596	21.655	3.055
P		0.001	0.001	0.006

time and transportation sedentary behaviors time accounted for 79, 10, 9, and 2% of the total sedentary time in children and adolescents, respectively. The results showed that the sedentary time of study ($p < 0.001$), screen ($p < 0.001$) and transportation ($p < 0.001$) was significantly different between sex. The sedentary time of girls in learning ($p < 0.001$) and transportation ($p < 0.05$) was significantly higher than that of boys, and the sedentary time of boys in video was significantly higher than that of girls ($p< 0.05$). There was no difference between boys and girls in the sedentary time of cultural leisure.

The results showed that there were significant differences in study [$F_{(8,4202)} = 270.674$, $p < 0.001$], screen [$F_{(8,4202)} = 7.458$, $p < 0.001$], culture and leisure [$F_{(8,4202)} = 18.070$, $p < 0.001$] and transportation sedentary time [$F_{(8,4202)} = 4.711$, $p < 0.001$] in grades. The study sedentary time increased with the increase of grade. The study sedentary time in grades 11 and 12 was significantly higher than that in other grades ($p < 0.001$); The screen sedentary time of grade four and grade 12 was significantly lower than that of other grades ($p < 0.001$); The sedentary time of cultural leisure decreased with the increase of grade, and the sedentary time of cultural leisure in grade 12 was the lowest (Table 5).

Children and adolescents in different regions also have significant differences in sedentary time in study, screen, cultural leisure and transportation. The study sedentary time in Northeast China was significantly higher than that in other regions ($p < 0.001$); The screen sedentary time in Northwest China was significantly higher than that in other regions ($p < 0.001$), and the screen sedentary time in Northeast China was the lowest ($p < 0.05$); The sedentary time of cultural leisure in Northwest and southwest regions was significantly higher than that in other regions ($p < 0.001$), and the sedentary time of cultural leisure in northeast region was significantly lower than that in other regions ($p < 0.001$); The sedentary time of traffic in Northeast China was significantly higher than that in other regions ($p < 0.001$) (Table 6).

TABLE 5 Sedentary behavior types of Chinese children and adolescents.

	N	Studying			Screen			Leisure			Transportation		
		Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
4	584	380.0 ± 107.9	375.7 ± 108.2	380.0 ± 110.7	26.4 ± 49.1	25.7 ± 49.9	25.7 ± 49.8	46.1 ± 48.9	55.7 ± 52.5	51.4 ± 51.7	4.3 ± 15.7	7.1 ± 17.1	7.1 ± 17.1
5	447	380.0 ± 97.9	397.1 ± 114.1	389.3 ± 104.3	40.0 ± 72.9	42.8 ± 61.2	41.7 ± 64.3	51.4 ± 62.1	54.3 ± 48.6	54.3 ± 54.7	6.4 ± 18.6	4.3 ± 15.5	5.7 ± 17.1
6	447	393.6 ± 102.1	381.4 ± 97.9	387.9 ± 101.4	43.2 ± 72.0	42.9 ± 53.6	42.9 ± 58.5	45.7 ± 56.9	51.4 ± 57.1	49.6 ± 57.1	5.7 ± 18.6	8.6 ± 18.9	7.1 ± 18.6
7	484	478.7 ± 119.3	497.1 ± 131.6	489.1 ± 119.7	42.9 ± 80.4	33.9 ± 62.9	39.6 ± 70.6	38.6 ± 48.8	37.1 ± 44.3	38.6 ± 45.7	10.0 ± 21.4	10.7 ± 21.4	10.7 ± 21.4
8	308	483.9 ± 129.2	491.4 ± 137.1	486.1 ± 130.9	54.3 ± 83.4	40.0 ± 71.9	44.3 ± 76.8	33.9 ± 49.5	39.3 ± 48.6	36.1 ± 49.6	7.9 ± 20.4	8.6 ± 21.4	8.6 ± 21.4
9	410	491.4 ± 141.8	538.6 ± 138.9	522.1 ± 141.4	40.0 ± 71.8	38.6 ± 65.4	38.9 ± 68.6	24.6 ± 46.1	32.1 ± 46.1	30.0 ± 47.3	8.7 ± 20.4	10.7 ± 21.4	10.0 ± 21.4
10	635	504.0 ± 122.7	519.4 ± 115.4	512.1 ± 117.1	51.4 ± 78.6	35.7 ± 63.5	42.9 ± 70.7	30.7 ± 53.6	31.8 ± 43.2	31.4 ± 48.6	8.6 ± 21.4	9.4 ± 21.4	9.3 ± 21.4
11	581	521.4 ± 112.5	529.2 ± 122.9	525.0 ± 117.5	51.4 ± 92.7	40.0 ± 77.1	47.1 ± 82.1	35.0 ± 55.7	34.3 ± 47.9	34.3 ± 51.4	7.1 ± 17.1	10.7 ± 22.9	8.6 ± 20.0
12	307	499.3 ± 128.6	542.1 ± 143.9	528.6 ± 141.4	26.9 ± 60.0	30.7 ± 56.2	30.0 ± 56.3	21.5 ± 38.6	30.7 ± 36.8	28.6 ± 38.6	2.9 ± 17.1	10.0 ± 25.7	8.6 ± 21.3
Total	4,203	460.7 ± 141.2	477.3 ± 153.6	469.3 ± 148.6	40.7 ± 73.6	36.1 ± 59.2	38.6 ± 66.4	37.1 ± 53.8	40.0 ± 51.4	38.6 ± 53.1	7.1 ± 18.6	8.6 ± 21.4	8.6 ± 20.0

Detection rate of high sedentary behavior

This study used 8 h as the threshold, and divided the sedentary behavior time ≥8 h into the high sedentary behavior group. Table 7 shows the distribution of the detection rate of high sedentary behavior in children and adolescents. The detection rate of high sedentary behavior in total sedentary time is 51.2%, the detection rate of high sedentary behavior on weekdays was 64.0%, and the detection rate of high sedentary behavior on weekends was 42.6%. The detection rate of high sedentary behavior on weekdays was significantly higher than that on weekends ($p < 0.001$).

There are significant differences in the detection rate of high and long sitting behavior among children and adolescents of different sex. The detection rate of high and long sitting behavior among girls was significantly higher than that of boys, both in the total sitting time and on weekdays ($p < 0.01$), and there was no significant sex difference in the detection rate of high sitting behavior on weekends ($p > 0.05$).

The detection rate of sedentary behavior in different grades was in the total sedentary time ($p < 0.001$), weekdays ($p < 0.001$) and sedentary time on weekends ($p < 0.001$), showing a trend of gradually increasing with the increase of grade. The detection rate of high sedentary behavior surged in Grade seven, but decreased significantly in grade 12 on weekends (Table 8).

The detection rate of high sedentary behavior in different regions was shown in Table 9, and there are significant differences among different regions ($p < 0.001$). The detection rate of high sedentary behavior among students in East China was the highest (58.0%), followed by Northwest China (55.5%), and the lowest in South Central China (44.1%). There were also significant differences among various regions on school day ($p < 0.001$) and weekends ($p < 0.01$). The detection rate of high sitting behavior on school days was the highest in Northwest China (73.9%), and the lowest in South Central China (53.7%). The detection rate of high sedentary behavior on weekends was the highest in East China (47.0%), and the lowest in South Central China (38.1%).

According to this standard, this study found that the compliance rates of Chinese children and adolescents in total screen-based sedentary time, screen-based sedentary time during weekdays, and screen-based sedentary time on weekends were 85.2, 85.8, and 63.3%, respectively (Figure 4).

Parental influence on children and adolescent's sedentary behaviors

The results in Table 10 show that the sedentary time of parents was significantly and positively correlated with the sedentary time of children and adolescents and various types of sedentary behavior. The intervention of sedentary behavior and the restriction of electronic products are significantly negatively correlated with the sedentary time of children and adolescents and the types of sedentary behavior.

TABLE 6 Comparison of sedentary types of children and adolescents in different regions.

	N	Studying	Screen	Leisure	Transportation
Northeast China	341	519.4 ± 112.1	17.1 ± 45.0	21.4 ± 28.2	17.1 ± 22.4
North China	925	442.9 ± 169.3	51.4 ± 78.6	42.9 ± 54.6	5.0 ± 17.1
East China	802	502.9 ± 169.3	34.3 ± 60.0	31.4 ± 41.6	8.6 ± 20.0
Northwest China	713	460.7 ± 143.9	64.3 ± 95.2	58.6 ± 63.6	7.4 ± 21.2
Southwest China	630	446.6 ± 140.9	33.6 ± 51.5	49.4 ± 60.0	10.7 ± 21.4
South Central China	792	460.0 ± 132.4	25.7 ± 48.6	34.3 ± 42.9	7.1 ± 17.1
F		51.708	75.646	47.129	22.688
P		0.001	0.001	0.001	0.001

TABLE 7 Detection rate of high sedentary behavior in children and adolescents of different sex [*N* (%)].

	N	SB		SB-WE		SB-WD	
		<8 h	≥8 h	<8 h	≥8 h	<8 h	≥8 h
Boys	2,041	1,037 (50.8)	1,004 (49.2)	780 (38.2)	1,261 (61.8)	1,187 (58.2)	854 (41.8)
Girls	2,162	1,015 (46.9)	1147 (53.1)	732 (33.9)	1,430 (66.1)	1,224 (56.6)	938 (43.4)
Total	4,203	2,052 (48.8)	2,151 (51.2)	1,512 (36.0)	2,691 (64.0)	2,411 (57.4)	1,792 (42.6)

TABLE 8 Detection rate of high sedentary behavior in children and adolescents of different grades [N (%)].

	N	SB		SB-WE		SB-WD	
		<8 h	≥8 h	<8 h	≥8 h	<8 h	≥8 h
4	584	392 (67.1)	192 (32.9)	385 (65.9)	199 (34.1)	385 (65.9)	199 (34.1)
5	447	258 (57.7)	189 (42.3)	263 (58.8)	184 (41.2)	256 (57.3)	191 (42.7)
6	447	271 (60.6)	176 (39.4)	263 (58.8)	184 (41.2)	274 (61.3)	173 (38.7)
7	484	219 (45.2)	265 (54.8)	118 (24.4)	366 (75.6)	266 (55.0)	218 (45.0)
8	308	123 (39.9)	185 (60.1)	104 (33.8)	204 (66.2)	158 (51.3)	150 (48.7)
9	410	151 (36.8)	259 (63.2)	110 (26.8)	300 (73.2)	189 (46.1)	221 (53.9)
10	635	278 (43.8)	357 (56.2)	117 (18.6)	518 (81.6)	357 (56.2)	278 (43.8)
11	581	219 (37.7)	362 (63.2)	87 (15.6)	494 (85.0)	318 (54.7)	263 (45.3)
12	307	141 (45.9)	141 (54.1)	65 (21.2)	242 (78.8)	208 (67.8)	99 (32.2)
Total	4,203	2,052 (48.8)	2,151 (51.2)	1,512 (36.0)	2,691 (64.0)	2,411 (57.4)	1,792 (42.6)

TABLE 9 Detection rate of high sedentary behavior in children and adolescents in different regions [N (%)].

	N	SB		SB-WE		SB-WD	
		<8 h	≥8 h	<8 h	≥8 h	<8 h	≥8 h
Northeast China	341	163 (47.8)	178 (52.2)	90 (26.4)	251 (73.6)	187 (54.8)	154 (45.2)
North China	925	486 (52.5)	439 (47.5)	392 (42.4)	533 (57.6)	554 (59.9)	371 (40.1)
East China	802	317 (42.0)	4 65 (58.0)	226 (28.2)	576 (71.8)	425 (53.0)	377 (47.0)
Northwest China	713	317 (44.5)	396 (55.5)	186 (26.1)	527 (73.9)	415 (58.2)	298 (41.8)
Southwest China	630	306 (48.6)	324 (51.4)	251 (39.8)	379 (60.2)	340 (53.9)	290 (46.1)
South Central China	792	443 (55.9)	349 (44.1)	367 (46.3)	425 (53.7)	490 (61.9)	302 (38.1)
Total	4,203	2,052 (48.8)	2,151 (51.2)	1,512 (36.0)	2,691 (64.0)	2,411 (57.4)	1,792 (42.6)

Taking different types of sedentary time as dependent variables and the remaining three variables as independent variables, they were included in the multiple linear regression analysis. The regression results showed that the sedentary time of parents, the restrictions on the use of electronic products and the interventions for sedentary behavior significantly and differentially affected the sedentary time of children and adolescents (Table 11).

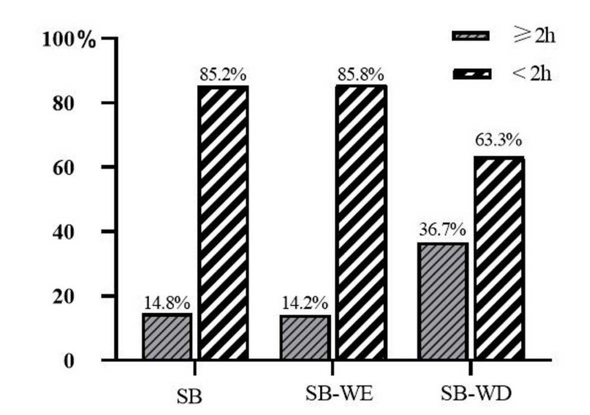

FIGURE 4
Detection rate of high sedentary behaviors in the screen category (%).

Vision status and influencing factors of Chinese children and adolescents

Detection rate of poor vision in children and adolescents

It can be seen from Table 12 that the detection rate of poor vision of Chinese children and adolescents is 62.3%, and there are significant differences among different grades and sex. The detection rate of poor vision of girls is significantly higher than that of boys ($p < 0.001$). Higher detection rates of poor vision in upper grades, and the detection rate of poor vision is the highest in Grade 11 ($p < 0.001$).

In addition, there were also significant differences in the detection rate of poor vision between different regions ($p < 0.001$), with the highest in East China (79.7%) and the lowest in Northwest China (48.2%) (Figure 5).

Influencing factors of poor vision in children and adolescents

A questionnaire survey was conducted on the habit of using eyes, and it was found that habits including "Is your chest more than 6 cm from your desk?" ($p < 0.001$), "Are your eyes more than 33 cm from the books?" ($p < 0.001$), "Are your fingers 3 cm from the tip of the pen when you hold it?" ($p < 0.001$), "Whether the eyes are more than 66 cm away from the computer screen when using the computer?" ($p < 0.001$), "How many times a week do you do ocular gymnastics?" ($p < 0.001$), "Do you turn on a desk lamp or a roof lamp when you read or write at home

TABLE 10 Correlation analysis of sedentary behavior in children and adolescents.

Independent variable	Dependent variable	Correlation coefficient	*p*
Total sedentary time	Parents' sedentary time	0.274	0.001
	Restrictions on the use of electronic products	−0.135	0.001
	Interventions for sedentary behavior	−0.083	0.001
Weekdays sedentary time	Parents' sedentary time	0.209	0.001
	Restrictions on the use of electronic products	−0.172	0.001
	Interventions for sedentary behavior	−0.100	0.001
Weekend sedentary time	Parents' sedentary time	0.230	0.001
	Restrictions on the use of electronic products	−0.069	0.001
	Interventions for sedentary behavior	−0.067	0.001
Study sedentary time	Parents' sedentary time	−0.157	0.001
	Restrictions on the use of electronic products	−0.110	0.001
	Interventions for sedentary behavior	0.055	0.001
Screen sedentary time	Parents' sedentary time	0.210	0.001
	Restrictions on the use of electronic products	−0.210	0.001
	Interventions for sedentary behavior	−0.026	0.046
Cultural leisure sedentary time	Parents' sedentary time	0.252	0.001
	Restrictions on the use of electronic products	−0.061	0.001
	Interventions for sedentary behavior	−0.054	0.001

TABLE 11 Regression analysis of sedentary behavior in children and adolescents.

Dependent variable	Independent variable	β	Standard error	Standardized β	t	*p*	ΔR^2
Total sedentary time	Parents' sedentary time	0.341	0.015	0.374	23.04	0.001	0.151
	Restrictions on the use of electronic products	−0.105	0.019	−0.088	−5.388	0.001	0.009
	Interventions for sedentary behavior	−0.226	0.069	−0.053	−3.272	0.001	0.003
weekdays sedentary time	Parents' sedentary time	0.249	0.015	0.278	16.434	0.001	0.087
	Restrictions on the use of electronic products	−0.139	0.02	−0.121	−7.126	0.001	0.017
	Interventions for sedentary behavior	−0.244	0.069	−0.059	−3.514	0.001	0.003
Weekend sedentary time	Parents' sedentary time	0.385	0.021	0.304	17.942	0.001	0.099
	Interventions for sedentary behavior	−0.476	0.053	−0.156	−8.99	0.001	0.031
	Restrictions on the use of electronic products	−0.07	0.027	−0.043	−2.543	0.011	0.002
Study sedentary time	Interventions for sedentary behavior	−0.476	0.053	−0.156	−8.99	0.001	0.031
	Parents' sedentary time	0.34	0.057	0.103	5.963	0.001	0.011
	Restrictions on the use of electronic products	−0.078	0.015	−0.091	−5.273	0.001	0.008
Screen sedentary time	Parents' sedentary time	0.133	0.009	0.26	15.391	0.001	0.072
	Restrictions on the use of electronic products	−0.06	0.007	−0.143	−8.399	0.001	0.092
	Interventions for sedentary behavior	−0.054	0.025	−0.036	−2.156	0.031	0.106
Cultural leisure sedentary time	Parents' sedentary time	0.331	0.016	0.352	21.282	0.001	0.124
	Interventions for sedentary behavior	−0.103	0.022	−0.076	−4.562	0.001	0.131
	Restrictions on the use of electronic products	−0.014	0.006	−0.038	−2.246	0.025	0.125

TABLE 12 Detection rate of poor vision in children and adolescents.

Grade	N	Boys	Girls	Detection rate
4	584	140 (44.9)	120 (44.1)	260 (44.5)
5	447	100 (46.9)	128 (54.7)	228 (51.0)
6	447	110 (51.4)	139 (59.7)	249 (55.7)
7	484	151 (56.8)	138 (63.3)	289 (59.7)
8	308	96 (62.3)	98 (63.6)	194 (63.0)
9	410	121 (65.1)	160 (71.4)	281 (68.5)
10	635	188 (68.9)	268 (74.0)	456 (71.8)
11	581	196 (72.1)	241 (78.0)	437 (75.2)
12	307	107 (70.9)	119 (76.3)	226 (73.6)
Total	4,203	1,209 (59.2)	1,411 (65.3)	2,620 (62.3)

after dark? Or do you use both?" ($p < 0.001$), and "During the past week, did you turn on the lights in the classroom? Or just turn on the lights when the weather was bad considering the lack of light?" ($p < 0.001$) are all important factors affecting the visual acuity of children and adolescents.

Genetics is also an important factor affecting poor vision. This study found that children and adolescents with both myopic parents had significantly higher rates of poor vision than children and adolescents whose parents had normal vision ($p < 0.05$).

The results show that the level of physical activity in class ($p < 0.001$) and the level of physical activity after class ($p < 0.05$) of children and adolescents with poor vision are significantly lower than those with good vision. Therefore, it can be seen that the level of physical activity will also affect the vision of children and adolescents.

The relationship between sedentary behavior and poor vision in children and adolescents

The relationship between sedentary time and poor vision in children and adolescents

Table 13 presents the sedentary time of students with normal vision and those with poor vision. After normal transformation of the data and independent sample *t*-test, the results show that there is a significant difference between children and

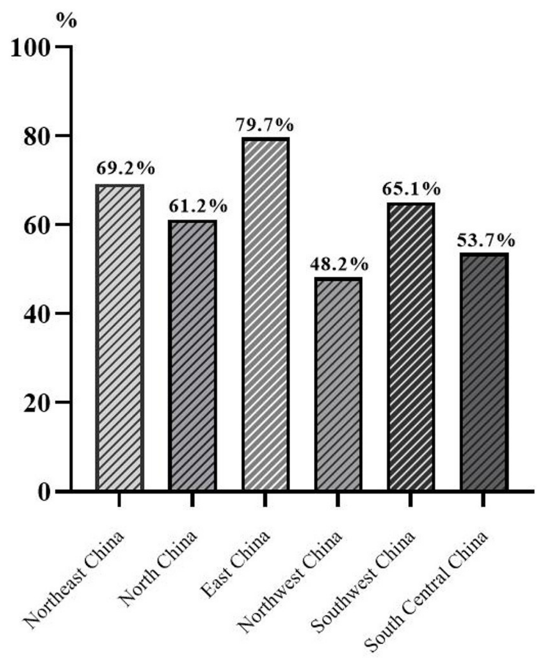

FIGURE 5
The detection rate of poor vision in children and adolescents by region.

TABLE 13 Differences in sedentary time of children and adolescents with different vision conditions (min/d).

	SB	SB-WE	SB-WD
Normal vision	560.0 ± 198.6	506.0 ± 181.0	417.5 ± 300
Poor vision	591.4 ± 189.3	534.1 ± 185.5	440 ± 292.1

adolescents with normal vision and those with poor vision in sedentary time. Students with poor vision have significantly higher total sedentary time, school day sedentary time and weekend sedentary time than students with normal vision.

The relationship between sedentary types and poor vision in children and adolescents

The results showed that the sedentary time of students with poor vision was significantly higher than that of students with normal vision in study, screen, and cultural leisure, but there was no significant difference in sedentary time in transportation (Table 14).

Taking writing posture, eye habits, parents' myopia, eye environment, physical activity level and other variables as covariates, the covariance method was used for analysis. indicating that excluding other influencing factors, study sedentary and screen sedentary still significantly affect the vision of children and adolescents, children and adolescents with poor vision have more sedentary time than normal vision in study and screen sedentary of children and adolescents. It can be seen in the binary logistic regression model that included poor vision as the dependent variable (Table 15), each unit of time spent in sedentary behavior in study and screen-based sedentary behaviors increased the risk of children and adolescents suffering from poor vision by 1.002 times.

TABLE 14 Comparison of sedentary time differences among students with different vision conditions.

	Study	Screen	Transportation	Cultural leisure
Normal vision	445.0 ± 145.0	36.4 ± 65.7	8.9 ± 21.4	35.7 ± 52.1
Poor vision	482.1 ± 146.4	42.9 ± 68.6	7.1 ± 17.8	41.4 ± 52.9

The relationship between sedentary behavior types and visual acuity was explored in different grades (Table 16). The results showed that in the primary school period, the screen sedentary time of students with poor vision was significantly higher than that of students with normal vision ($p < 0.01$); the sedentary time of students with poor vision in junior ($p < 0.01$) and senior high schools $p < 0.001$) was significantly higher than that of students with normal vision. Controlling for the influence of writing posture, eye habits, physical activity level and other variables, further covariance analysis found that screen sedentary still had a significant effect on primary school students' vision ($p < 0.05$), while in junior high school and senior high school, study sedentary was the main sedentary type affecting students' vision ($p < 0.05$).

The relationship between the detection rate of high sedentary behavior and the detection rate of poor vision in children and adolescents

In this study, the total sedentary time of children and adolescents was ≥8 h per day as high sedentary behavior. Table 17 shows the result of the difference in the detection rate of poor visual acuity. The analysis shows that the detection rate of poor vision of students with a total sedentary time of more than 8 h (65.7%) was significantly higher than that of students with a total sedentary time of <8 h (58.8%); The detection rate of poor vision of students who sat for more than 8 h on weekdays (65.5%) was significantly higher than that of students who sat for <8 h (56.7%); The detection rate of poor vision (64.8%) of students who sat more than 8 h on weekends was significantly higher than that of students who sat <8 h on weekends (60.5%).

Effects of sedentary behavior interruption on vision in children and adolescents

In this study, the median value of 30 min in previous studies was used as the sedentary behavior interruption interval. From

TABLE 15 Binary logistic regression results of the effects of various sedentary time on visual acuity.

	β	S.E.	Walds	df	Sig.	Exp (B)
Study	0.002	0.001	20.485	1	0.000	1.002
Screen	0.002	0.001	14.218	1	0.000	1.002
Cultural leisure	0.001	0.001	1.437	1	0.231	1.001
Transportation	0.001	0.002	0.187	1	0.666	1.001

TABLE 16 Comparison of sedentary types of students with different visual acuity conditions in different grades.

	Primary school		Junior high school		Senior high school	
	Normal vision	Poor vision	Normal vision	Poor vision	Normal vision	Poor vision
Study	380.0 ± 110.4	387.1 ± 102.5	485.0 ± 134.6	502.9 ± 131.25	503.8 ± 105.6	527.1 ± 127.9
Screen	30.0 ± 53.6	42.9 ± 60.0	40.0 ± 71.4	42.9 ± 40.0	39.3 ± 72.9	41.4 ± 79.4

Table 17, it can be seen that there are significant differences in the detection rate of poor vision in the combination of different sedentary time and interrupted habits ($p < 0.001$). Among them, the students whose sedentary time was more than 8 h without interrupting habits or interrupted once more than 30 min (BPS_1) have poor vision detection (28.8%). Students whose sedentary time did not break once within 8 h and 30 min (BPS_4) had the lowest detection rate of poor vision (21.1%), indicating that sedentary time and sedentary intermittent habits are important factors that significantly affect students' vision (Table 18).

TABLE 17 Differences in the detection rate of high sedentary behavior among children and adolescents with different vision conditions [*n* (%)].

	Normal vision	Poor vision	Total	x^2
SB				
<8 h	845 (41.2)	1,207 (58.8)	2,052 (48.8)	21.109***
≥8 h	738 (34.3)	1,413 (65.7)	2,151 (51.2)	
SB-WE				
<8 h	655 (43.3)	857 (56.7)	1,512 (35.9)	32.184***
≥8 h	928 (34.5)	1,763 (65.5)	2,691 (64.1)	
SB-WD				
<8 h	952 (39.5)	1,459 (60.5)	2,411 (57.4)	7.997***
≥8 h	631 (35.2)	1,161 (64.8)	1,792 (42.6)	
Total	1,583 (37.7)	2,620 (62.3)	4,203 (100)	

Discussion

Characteristics of sedentary behavior among Chinese children and adolescents

Significant differences in sedentary behavior among children and adolescents in different grades, sex and regions

From a global perspective, the sedentary time of children and adolescents in various countries has become a common problem. However, there are difference on sedentary time in children and adolescents among different countries. For instance, the average sedentary time of 13–17 years old adolescents in Spain is about 7.5 h per day (27), the average sedentary time of 12–17 years old adolescents in South Korea is about 9.5 h per day (27), and the average sedentary time of 9–10 years old children in European is about 9.6 h per day (3), the average sedentary time of 12-19 years old adolescents in the United States is about 6.9 h per day (2).

The results of this study show that the average total sedentary time of Chinese students in grades four to 12 is about 8.1±3.4 h/day. Studying sedentary behaviors such as class, homework, and reading are the main sedentary behaviors of Chinese children and adolescents, accounting for 79.2% of the total sedentary time. At present, the research on the sedentary behavior of Chinese children and adolescents is more consistent with the result that studying sedentary accounts for the largest proportion of total sedentary time. The participants of this study covered students from grades four to 12 in six administrative regions across the country. The survey results reflect the basic characteristics and changing laws of sedentary behaviors of Chinese children and adolescents to a certain extent.

Our study shows that Chinese children and adolescents in the upper grades have longer total sedentary behavior time and study sedentary behavior time, while screen sedentary behavior time and cultural leisure sedentary behavior time are shorter. This result is consistent with other studies (5). The reason for this result may be that as the grade increases, the academic workload increases, which leads to the students spending more time in and out of school for studying, doing homework and tutoring. This study found that although the change trend of

TABLE 18 Differences in the detection rate of poor vision in children and adolescents with different sedentary habits.

	BPS_1	BPS_2	BPS_3	BPS_4	Total	x^2	p
Normal vision	372 (23.5)	366 (23.1)	433 (27.4)	412 (26.0)	1,583 (37.7)	24.700	0.001
Poor vision	755 (28.8)	658 (25.1)	655 (25.0)	552 (21.1)	2,620 (62.3)		
Total	1,127 (26.8)	1,024 (24.4)	1,088 (25.9)	964 (22.9)	4,203 (100)		

Breaking up prolonged sitting (BPS); BPS1 = sedentary time more than 8 h without interruption or more than 30 min without interruption; BPS2 = sedentary time exceeds 8 h and breaks once within 30 min; BPS 3 = sedentary time not more than 8 h without interruption or more than 30 min without interruption; BPS 4 = sedentary time not more than 8 h, interrupted once within 30 min.

sedentary time of male and female students was the same on the whole, the sedentary time of female students on weekends was significantly higher than that of male students. This may be due to the fact that students on weekends were far away from school constraints and had increased freedom in scheduling, which made the sedentary lifestyle of female students manifest. A study by Pereira et al. (28) also showed that boys spend slightly less sedentary time than girls. However, a systematic review of sedentary behavior tracking from childhood to adolescence abroad found that there was no significant sex difference in sedentary time between males and females (29). On the one hand, the retrospective process is pre-adolescence, and the difference between men and women has not been fully revealed, so the results are different from this study. The study also found that girls spend significantly more time studying on weekends than boys, and boys spend significantly more screen time than girls. The study by Guo et al. (6) also found that the sedentary time of screen sedentary in boys was slightly higher than that of girls, but they did not find a difference in total sedentary time.

Influence of family factors on sedentary behavior of children and adolescents

The family is an important place for children and adolescents to live and learn, and there is a close relationship between parents' living habits and children's sedentary behavior (30). This study found that the factors of influence were ranked according to standardized regression coefficients, with the order of importance being parents' sedentary time > restrictions on the use of electronic products > interventions for sedentary behavior. This shows that parental sedentary time has the greatest impact on the sedentary time of children and adolescents, and there is a significant positive correlation. Studies have pointed out that parents' intervention on children and adolescents' sedentary time also plays a very important role in shaping their healthy behaviors (31). Velazquez-Romero et al. (32) also believe that in today's increasingly popular models such as computers and smartphones, it is very important to set time limits on the use of electronic products. The results of this study are consistent with previous studies, that is, parents restricting children and adolescents' sedentary behavior and electronic product use time can effectively reduce children's and adolescents' sedentary time.

The relationship between sedentary behavior and poor vision in Chinese children and adolescents

Sedentary time in children and adolescents is closely related to the detection rate of poor vision

In the World Health Organization's 2020 Guidelines on Physical Activity and Sedentary Behavior, it is pointed out that the longer the sedentary time is, the greater the harm to human health (33), and the same is undoubtedly true for the eyes and vision health of children and adolescents. This study found that both weekdays and weekends, children and adolescents with vision impairment were significantly more sedentary than children and adolescents with normal vision. A cohort study by Guggenheim et al. (34) also pointed out that the increased sedentary time has a hazard ratio of 1.17 for poor vision, that is, the longer the sedentary time, the higher the risk of developing poor vision. In addition, this study also found that the sedentary time and the detection rate of poor vision in Chinese children and adolescents have the same developmental characteristics, that is, both show that the higher the grade, the longer the sedentary time. This may be due to the increased schoolwork burden as the grade increases, resulting in increased sedentary time and longer eye-use time, resulting in decreased visual acuity in children and adolescents (35). Therefore, in order to protect the visual health of children and adolescents, it is necessary to reduce the academic burden of students, so as to fundamentally change the situation of sedentary time and improve students' eye habits.

In this survey, it was found that the detection rate of poor vision in children and adolescents with an average sedentary time of more than 8 h per day was significantly higher than that of children and adolescents with <8 h of sedentary time, and showed the same characteristics on weekdays and weekends. It can be seen that the daily sedentary time of more than 8 h will significantly affect the visual health of children and adolescents. At present, there are few studies on children and adolescents with high sedentary behavior, and there is a lack of specific countermeasures. Therefore, it is necessary to increase research on children and adolescents with high sedentary behavior in the later stage, and introduce corresponding preventive and intervention measures.

Study and screen sedentary are the main types of sedentary behaviors that affect poor vision in Chinese children and adolescents

This study shows that study and screen sedentary are the two main types of sedentary behaviors among children and adolescents in China, and for each additional unit of sedentary behavior in these two types of sedentary behavior, the risk of children and adolescents suffering from poor vision increases by 1.002 times. After excluding other factors that affect visual acuity, such as writing posture, eye habits, eye environment, parental myopia, and physical activity level, this study found that study and screen sedentary are still significant factors affecting children's and adolescents' vision.

Asian students have very heavy academic pressure, they are in a competitive learning environment from an early age and spend a lot of time on their studies, resulting in excessive eye use from an early age. A recent study in Japan found that the rate of poor eyesight among primary school students reached 75.6 and 95.9% among junior high school students (36). In China, a common occurrence in schools is that as students' homework time increases, children and adolescents' physical activity time and sleep time are significantly reduced, and the detection rate of poor vision increases significantly. However, poor vision may lead to poor academic performance (37). It is possible to yield twice the result with half the effort by adopting a scientific and reasonable study schedule and maintaining healthy and effective study and living habits.

Screen sedentary behavior is also an important factor affecting the eyesight health of children and adolescents. Studies have shown that the increased use of electronic devices by children and adolescents increases the risk of visual impairment (35). The results of a study in Taiwan also pointed out that children's addiction to screen entertainment has a negative impact on eye health (38). The WHO recommends that children and adolescents spend no more than 2 h of screen time per day (33). A study of the visual health of Danish adolescents also noted that adolescents who used screen devices for <2 h per day had better vision (39). According to this standard, 85.2% of children and adolescents in China in this study reached the standard. In Western countries, including the United States (40), Australia (41), Brazil (42) and other countries (43), only one third of children met the daily screen time recommendation of <2 h in the past decade. In the background of the widespread use of mobile electronic devices such as cell phones and computers has become the main way of learning, communicating or playing for children and adolescents (43). Health education programmes should emphasize the importance of limiting children's screen time, which will benefit children's eye health. Not only China, but also research reports from Europe (44), North America (45), and the Czech Republic (46). In view of the independent effects of screen sedentary on children and adolescents with poor vision, schools should reduce the use of electronic products in the teaching environment, and parents should limit the time children use electronic products.

This study further found that the poor vision of students in various stages was affected by different types of sedentary behavior. In primary school, the eyesight condition of students was largely affected by sedentary behavior of screen, and in junior high school and senior high school, study sedentary behavior had a greater impact on the eyesight level of students. Therefore, in order to protect the visual health of children and adolescents, parents, schools, society and the government should join hands to jointly monitor the sedentary time of children and adolescents in study and screen, and jointly protect the visual health of children and adolescents in China.

Interruption of sedentary behavior positively affects vision health

Continued sedentary time can adversely affect the body. Therefore, people should try to avoid prolonged sedentary behaviors in their lives and reduce the accumulation of sedentary time. This study found that children and adolescents whose sedentary time was interrupted once within 30 min and whose total sedentary time did not exceed 8 h a day had a significantly lower detection rate of poor vision than those who had accumulated sedentary time of more than 8 h without interruption or continuous sedentary Children and adolescents with an interruption after a time >30 min. Jenny (47) also pointed out that children who read continuously for more than 30 minu are more likely to have poor vision than children who read <30 min. Therefore, it is speculated that an interruption after 30 min of sedentary time is beneficial to reduce the rate of poor vision in children and adolescents. Studies have also shown that after a long period of sitting for a long time, intermittently every 30 min, standing for 2–3 min or short-term outdoor activities in the middle, can improve human metabolism (48), reduce self-fatigue (49), and reduce the risk of cardiovascular disease (20). In addition, staying indoors for too long is also detrimental to the visual development of children and adolescents (50). Therefore, going outdoors during sedentary breaks is a good way to rest, and this method has been proven to have a positive effect on children and adolescents' vision (51). Chastin (48) and Wennberg (49) both noted that breaking prolonged periods of sedentary activity every 30 min, coupled with 2–3 min of standing or low-intensity physical activity can alleviate feelings of fatigue and improve metabolic status. Considering with the current sedentary behavior of children and adolescents, 2–3 min of low-intensity walking as a sedentary break is more achievable and beneficial.

Conclusion

(1) The average sedentary time of children and adolescents in grades four to 12 in China is about 8.1 h a day, of which study sedentary accounts for the highest proportion; With the increase of grade, the total sedentary time and study sedentary time gradually increased, and the sedentary time of screen and cultural leisure gradually decreased; There are significant sex differences in the total sedentary behaviors time and weekend sedentary behaviors time of Chinese children and adolescents, and girls are higher than boys; There are also significant differences in sedentary behaviors time among different regions, and the total sedentary behaviors time in East China is the highest.

(2) Reducing the sedentary time of parents and limiting the sedentary behavior of children and adolescents and the use of electronic products can effectively reduce the sedentary behavior of Chinese children and adolescents.

(3) The sedentary time of Chinese children and adolescents is closely related to the detection rate of poor vision; study and screen sedentary time are independent factors affecting the visual health of Chinese children and adolescents; The detection rate of poor vision in primary school is mainly affected by screen sedentary behavior, while the detection rate of poor vision in junior high school is mainly affected by study sedentary behavior.

(4) The interruption of sedentary behavior plays a positive role in visual health. Children and adolescents who have been sedentary for no more than 8 h a day and have interrupted behavior once after 30 min of sedentary behavior have a significantly lower risk of poor vision than children and adolescents who have been sedentary for more than 8 h a day and have been sedentary for more than 30 min.

Strengths and key limitations

This study has a few limitations and strengths. There are several strengths over previous studies that need to be emphasized. On the one hand, the collection of participants in previous studies on sedentary behavior and poor vision in Chinese children and adolescents was limited to certein province and city, or even to a school. The study sample was not representative enough to reflect the current situation of sedentary behavior and visual health of Chinese children and adolescents. The participants in this study included children and adolescents in grades four to 12 in six major administrative regions of China. The study sample covers a wide range of regions and all administrative regions in China, and the age range includes children and adolescents who have the ability to fill in the questionnaire. On the other hand, compared with previous studies, this study not only investigated the relationship between the duration of sedentary behavior, type of sedentary behavior and poor vision of children and adolescents, but also explored the effect of interruption of sedentary behavior on poor vision of children and adolescents, and determined that sedentary behavior interruption is an indicator that cannot be ignored in the study of children and adolescents' visual health.

Several limitations of this study warrant noting. First, the visual acuity data collection was based on the report of the school visual acuity examination and completed by the participants through filing in the questionnaire without precise visual acuity assessment; Second, the study did not distinguish between urban and rural areas of residence of the participants, which may also be a variable affecting the relationship.

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 East China Normal University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LL and HF conceived the study and its design. JL and HF performed data analysis and drafted the initial manuscript. LL, JL, and BZ modified the manuscript. LL contributed to manuscript preparation, 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.

Funding

This study was supported by the Ministry of Education Humanities and Social Sciences Research General Program (19YJA890014). The funding bodies did not have a role in the design of the study, collection, analysis, data interpretation, and writing of this manuscript.

Acknowledgments

The authors appreciate the students who participated in the surveys for their cooperation and contribution.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1043977/full#supplementary-material

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TYPE Original Research
PUBLISHED 06 December 2022
DOI 10.3389/fpubh.2022.1047787

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SPECIALTY SECTION
This article was submitted to Public Health Education and Promotion, a section of the journal Frontiers in Public Health

RECEIVED 18 September 2022
ACCEPTED 10 November 2022
PUBLISHED 06 December 2022

CITATION
Yang J, Wu S, Zhang C, Yu W, Dai R and Chen Y (2022) Global trends and frontiers of research on pathologic myopia since the millennium: A bibliometric analysis.
Front. Public Health 10:1047787.
doi: 10.3389/fpubh.2022.1047787

Global trends and frontiers of research on pathologic myopia since the millennium: A bibliometric analysis

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Background and purpose: Pathologic myopia (PM) is an international public health issue. This study aimed to analyze PM research trends by reporting on publication trends since 2000 and identifying influential journals, countries, authors, and keywords involved in PM.

Methods: A bibliometric analysis was performed to evaluate global production and development trends in PM since 2000 and the keywords associated with PM.

Results: A total of 1,435 publications were retrieved. PM has become a fascinating topic (with relative research interest ranging from 0.0018% in 2000 to 0.0044% in 2021) and a global public health issue. The top three countries with the highest number of publications were China, the USA, and Japan. The journals, authors, and institutions that published the most relevant literature came from these three countries. China exhibited the most rapid increase in the number of publications (from 0 in 2000 to 69 in 2021). *Retina* published the most papers on PM. Kyoko Ohno-Matsui and Tokyo Medical and Dental University contributed the most publications among authors and institutions, respectively. Based on keyword analysis, previous research emphasized myopic choroidal neovascularization and treatment, while recent hotspots include PM changes based on multimodal imaging, treatment, and pathogenesis. Keyword analysis also revealed that deep learning was the latest hotspot and has been used for the detection of PM.

Conclusion: Our results can help researchers understand the current status and future trends of PM. China, the USA, and Japan have the greatest influence, based on the number of publications, top journals, authors, and institutions. Current research on PM highlights the pathogenesis and application of novel technologies, including multimodal imaging and artificial intelligence.

KEYWORDS

pathologic myopia, bibliometric analysis, maculopathy, myopic degeneration, myopia control

Introduction

Myopia is a leading cause of vision loss worldwide, with an increasing trend; it can be divided into simple myopia and pathologic myopia (PM). There is no standardized definition for PM. However, most researchers and clinicians agree that PM is a subtype of myopia that accompanies characteristic myopic fundus changes that usually occur in eyes with high myopia, including myopic maculopathy equal to or more serious than diffuse choroidal atrophy or the presence of posterior staphyloma (1). The prevalence of myopic retinopathy in PM was reported to range from 1.2 to 3.7% in the population (2–6). Moreover, the visual prognosis for eyes with myopic maculopathy is much worse than that for those without maculopathy (7–9). A bibliometric analysis of publications is important due to the growing number of pathologic myopic eyes and their influence on public health, which has prompted researchers to analyze the development trend and research hotspots of PM.

Bibliometric analyses were first proposed in 1922 by Hulme; however (10), these analyses are not equal to reviews. Bibliometric analyses provide an overview of publications using mathematical and statistical methods and predict possible development trends based on citation reports and academic outputs. Bibliometric analysis, which has a century-long history, has been applied in medicine to investigate its development and trends.

Research on PM has received increasing attention in recent years, which makes it difficult for many researchers and clinicians to determine the research focus and frontiers of PM from the growing number of publications. However, to our knowledge, no bibliometric analysis has specifically focused on PM. Therefore, the current study aimed to investigate frontier research and PM trends across the international scientific literature based on the Web of Science (WOS) Core Collection over the past two decades. We also aimed to predict trends for the next few years, noting that the increase in the number of publications on PM is expected to lead to a valuable reference for clinicians and researchers.

Abbreviations: FA, fluorescein angiography; FP, fundus photograph; HDI: human development index; mCNV, myopic choroidal neovascularization; MRI, magnetic resonance imaging; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PM, pathologic myopia; RRI, relative research interest; VEGF, vascular endothelial growth factor; WOS, web of science.

Methods

Search strategy

The WOS Core Collection is the most suitable database for bibliometric analysis, particularly because of the high quality of the included publications. The search for papers to be included in the current study was carried out on 7 August 2022, and all the included publications were published from 1 January 2000, to 1 August 2022. The search strategy was "TS = pathologic myopia OR TS = myopic degeneration OR TS = myopic maculopathy." One thousand and thirty-seven pieces of literature were identified. Two published poems and news items were excluded according to the document type. One thousand and thirty-five publications were finally included.

Data collection

All the data were extracted and downloaded from the WOS Core Collection databases, including metrics of publication numbers, countries and regions, authors, citations, self-citations, and H-indexes. We also investigated the relationship between the global productivity of PM and the human development index (HDI), which measures the level of human development based on knowledge, life expectancy, and income per capita indicators rather than economic growth alone. The United Nations Development Programme published the Human Development Report 2020, in which countries and areas were divided into four categories based on HDI: very high human development, high human development, medium human development, and low human development (11). Countries and regions were classified according to the default classification in the WOS and the HDI. Prism 9, R (R. app. GUI 1.79) and its tools Biblioshiny, VOSviewer 1.6.18, and SPSS 26 were used to input and analyze the data.

Bibliometric analysis

Descriptive indices were extracted from the WOS Core Collection and calculated using SPSS. The co-occurrence network was constructed using the VOSviewer software. Keywords were extracted from the titles and abstracts of the included publications. R and its tool Biblioshiny were used to generate word-cloud maps. To provide a better classification of keyword clusters and a better summarization of research trends, frequencies over 30 were the criteria for the inclusion of these analyses. H-indices were collected from the WOS database and can partially reflect the impact of researchers. Relative research interest (RRI) was measured as the number of publications in a specific field divided by the number of all publications in all fields. The value of this metric reflects the global attention

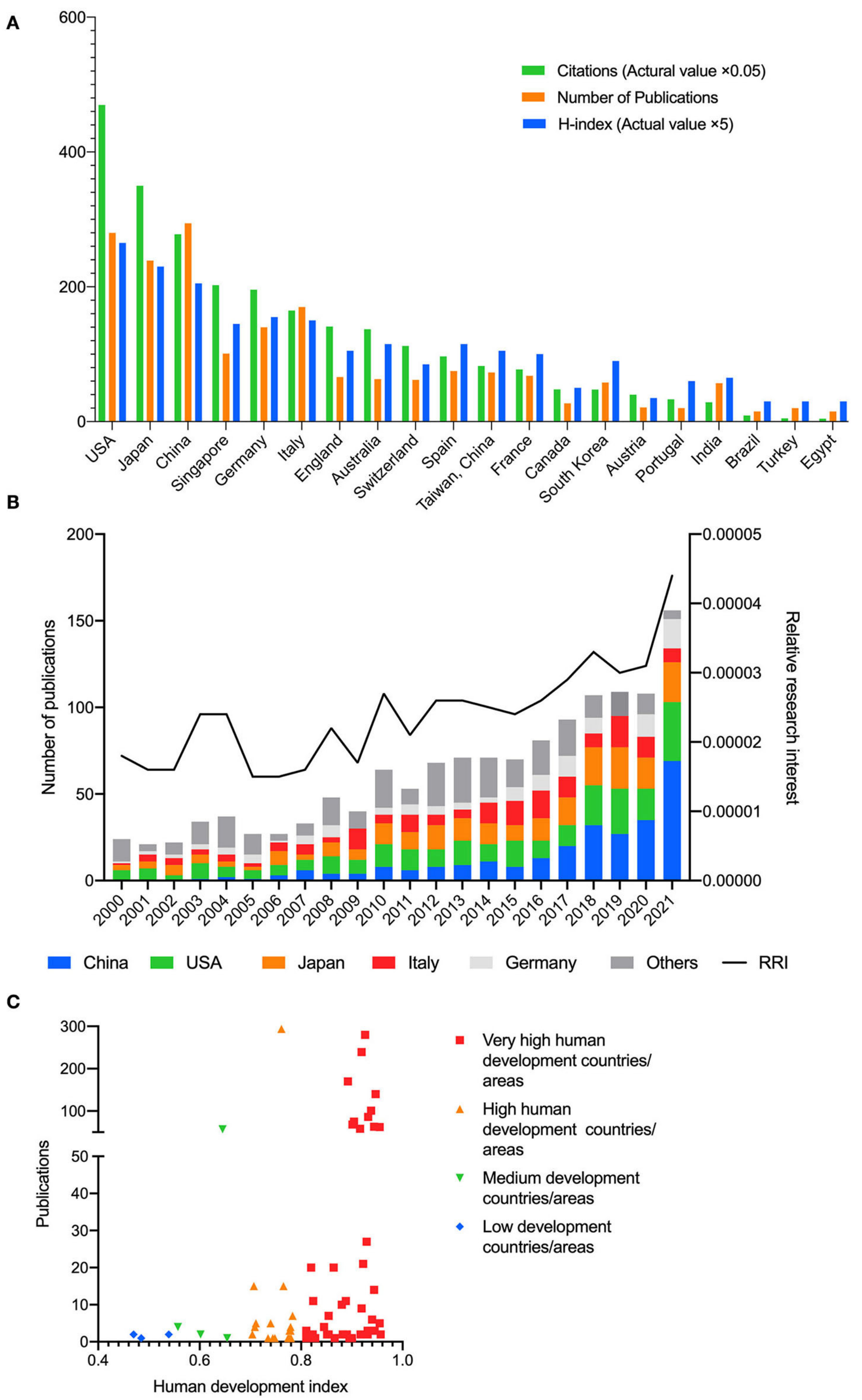

FIGURE 1
(A) Top 20 countries/regions in the publications on pathologic myopia. The green bar shows the number of citations (actual value multiply by 0.05), the orange bar shows the number of publications, and the blue bar shows the H-index (actual value multiply by 5). **(B)** The proportion of publications of China Mainland, USA, Japan, Italy, Germany, and other countries/regions and relative research interest (RRI) in each year on the field of pathologic myopia. **(C)** The number of publications on pathologic myopia in countries or areas of various levels of human development. Very high human development countries or areas contributed to most publications.

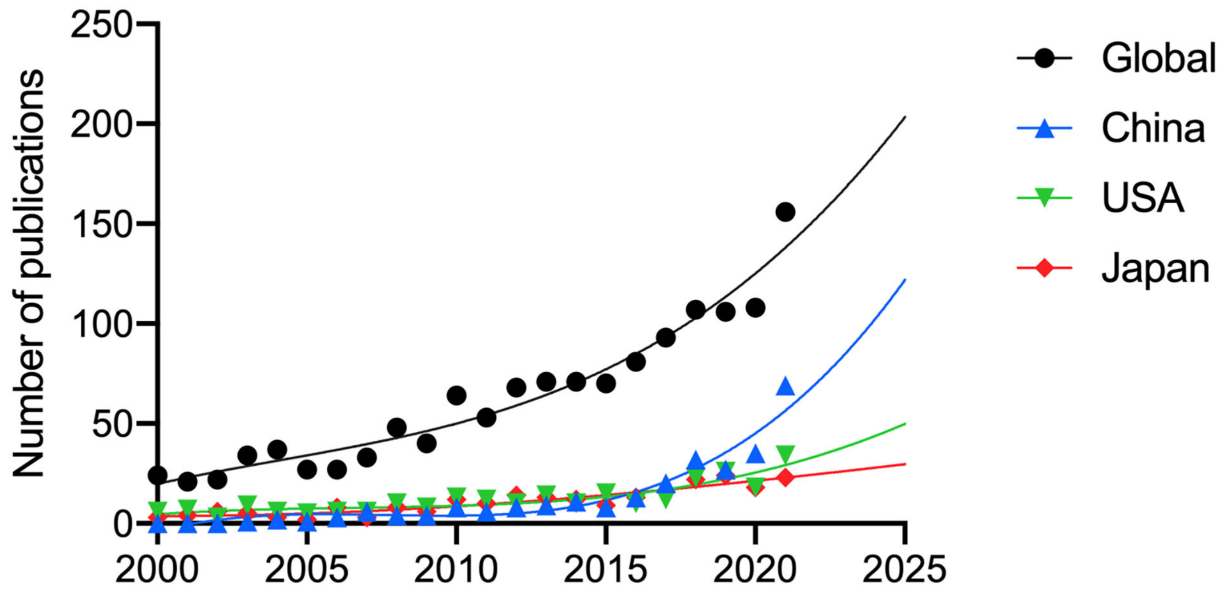

FIGURE 2
The publication trends and prediction curve of global and countries which had the most publications of pathologic myopia since 2000. **(A)** Global. **(B)** China Mainland. **(C)** USA. **(D)** Japan.

and interest in a specific field. Higher RRI values represent more research interest and hotspots in this field. A third-order polynomial method was used in the prediction model using the Prism software. The average year of appearance was used to assess the novelty of the keywords.

Results

Contributions of various countries and regions to global publications

A total of 1,435 publications were analyzed. Since 2000, Mainland China has contributed to the majority of publications (294, 20.5%), followed by the USA (280, 19.5%) and Japan (239, 16.7%) (Figure 1A). The remaining countries had published fewer than 200 publications. The USA, Japan, China, Germany, Italy, and Singapore were the top five countries with the highest number of publications and H-index. The total number of publications on PM has grown over the past 22 years, especially in recent years (Figure 1B). Additionally, the RRI of PM has increased from 0.0018% in 2000 to 0.0044% in 2021, indicating that research interest in PM has continued to increase worldwide over the past two decades. In the first 8 months of 2022, the RRI of PM reaches 0.0046%. According to the HDI category, we noticed that most publications were from very high HDI countries or regions, and the numbers of publications on PM were consistent with the HDI classification (Figure 1C).

We analyzed the co-occurrence of 34 countries and regions (Supplementary Figure 1). The analysis suggests six clusters: (1) Mainland China, Australia, and Iran; (2) USA, Switzerland, France, South Korea, Canada, Austria, Brazil, Turkey, Greece, and Venezuela; (3) Japan, Singapore, Spain, and Portugal; (4) Germany, England, the Netherlands, Russia, Scotland, Northern Ireland, Poland, Wales, Ireland, and Egypt; (5) Italy, India, Tunisia, and Israel; and (6) Taiwan, Denmark, and Saudi Arabia.

The publication rate of papers on PM has been increasing in the past two decades, and predictions for the coming years reflect this increase (Figure 2). China exhibited the most rapid increase in the number of publications in the last 5 years. China is also projected to maintain its leading position and show steady growth in the number of publications.

Citations and H-index

WOS citation reports revealed a total of 21,432 citations without self-citations of the 30,234 relevant citations since 2000 (details for top countries and regions in Supplementary Table 1). Each paper cited an average of 21.07 times. The USA contributed the most citations (9,395 citations, 9,062 without self-citations) and the highest H-index (53) (Figure 1A) from 2000. Japan ranked second in terms of both citations (6,999 citations, 6,026 without self-citations) and H-index (46), and Mainland China ranked third in both citations (5,559 citations, 4,895 without self-citations) and H-index (41). The most-cited publication was cited 618 times. We divided the publications into three groups according to citation frequency: high frequency (more than 100 citations), medium frequency (>50 and <100 citations), and low frequency (<50 citations). Most publications were in a low-frequency group. One hundred and ten publications were cited with a medium frequency, and 46 were cited with a high frequency.

To investigate the distribution of citation numbers each year, we drew heat maps of each group of citation frequency (Supplementary Figures 2B–D). Every row in the heatmap represents a publication, the x-axis represents the year, and the color represents the citation number. The timespan of citations with high and medium frequency is similar and longer than most publications with low citation frequency. Moreover, most publications with high and medium citation frequencies have been published in the last 10 years (Supplementary Figure 2A).

The leading institutions, journals, and authors

We investigated the top institutions in this field; the Tokyo Medical and Dental University in Japan (136, 9.5%), Singapore National Eye Center in Singapore (93, 6.5%), Ruprecht-Karls-Universität Heidelberg in Germany (78, 5.4%), and Sun Yat-Sen University (55, 3.8%) and Capital Medical University (54, 3.8%) in China published the most publications (Figure 3A).

Approximately half (726, 50.6%) of the papers on PM were published in 10 journals, including *Retina*, which published the maximum number of relevant publications (160). *Investigative Ophthalmology and Visual Science* and the *American Journal of Ophthalmology* published the second and third-most publications, with 129 and 93, respectively (Figure 3B).

The 10 papers with the most citations are listed in Table 1. The most cited paper was published in *Ophthalmic and Physiological Optics*, an ophthalmic periodical that has ceased publication, and was called *Myopia and Associated Pathological Complications*. The corresponding author was Seang Mei Saw. Most publications on PM were published in ophthalmology journals (Table 2).

The top 10 authors in this field are listed in Table 3 according to the number of publications. The works of Kyoko Ohno-Matsui from Tokyo Medical and Dental University have been published the most since 2000, with 139 papers and 4,710 citations (4,033 without self-citations). The H-indexes of both the author and the institution were 39. Jost B. Jonas, from Ruprecht-Karls-Universität Heidelberg, ranked second, with 77 publications and 2,224 citations (2,025 without self-citations). Tien Y Wong ranked third with 44 publications and 2,135 citations (2,045 without self-citations) (Table 3).

We also analyzed the cooperation between investigators (Supplementary Figure 3). The node size within a collaboration network indicates the strength of the connections between each author. Several authors, including Kyoko Ohno-Matsui, Takeshi Yoshida, Muka Moriyama, Jost B. Jonas, and Noriaki Shimada, closely cooperated with other researchers and teams.

Research hotspots in PM

Keyword analysis identified the most frequently used words and their linkages within the field of PM research. We analyzed keywords that appeared more than 30 times across the included publications. Merging repeated words, excluding meaningless ones, resulted in 70 keywords that could be divided into three primary clusters by co-occurrence frequency, including an epidemiology-related cluster (in red), a treatment-related cluster (in green), and a lesion-related cluster (in blue) (Figure 4A). Keywords with high link strength were assigned to the same cluster.

We also color-coded the keywords by the average time of appearance and found that most of the keywords appeared in recent years (Figure 4B). Figure 4B shows the temporal evolution of these keywords. The *classification* and *progression* keywords were the latest keywords with high occurrence.

To attain an intuitive impression of the most frequent keywords, we listed the most used keywords in 2000–2010 and 2011–2022 in word-cloud images, respectively (Figure 4C for keywords from 2000 to 2010 and Figure 4D for keywords from 2011 to August 2022). Besides the keywords of myopia and high myopia, keywords related to pathologic lesions and treatments, such as myopic maculopathy, myopic choroidal neovascularization (mCNV), and ranibizumab, were the most frequent words. We extracted the most frequent keywords to explore changes in hotspots and keywords in the field (Supplementary Figure 4). A changing trend was noticed from treatment for choroidal neovascularization to myopic lesions and complications and to deep learning.

Discussion

This study involved a bibliometric analysis focusing on PM over the last two decades. We identified an increasing trend in publications on PM since 2000 (from 24 publications in 2000 to 156 publications in 2021). Although China and the USA had the most publications (294 and 280, respectively), authors from Japan, Singapore, and Germany had the greatest influence (4, 4, and 1 of the top 10 authors, respectively). To our knowledge, this is the first bibliometric analysis to focus on PM.

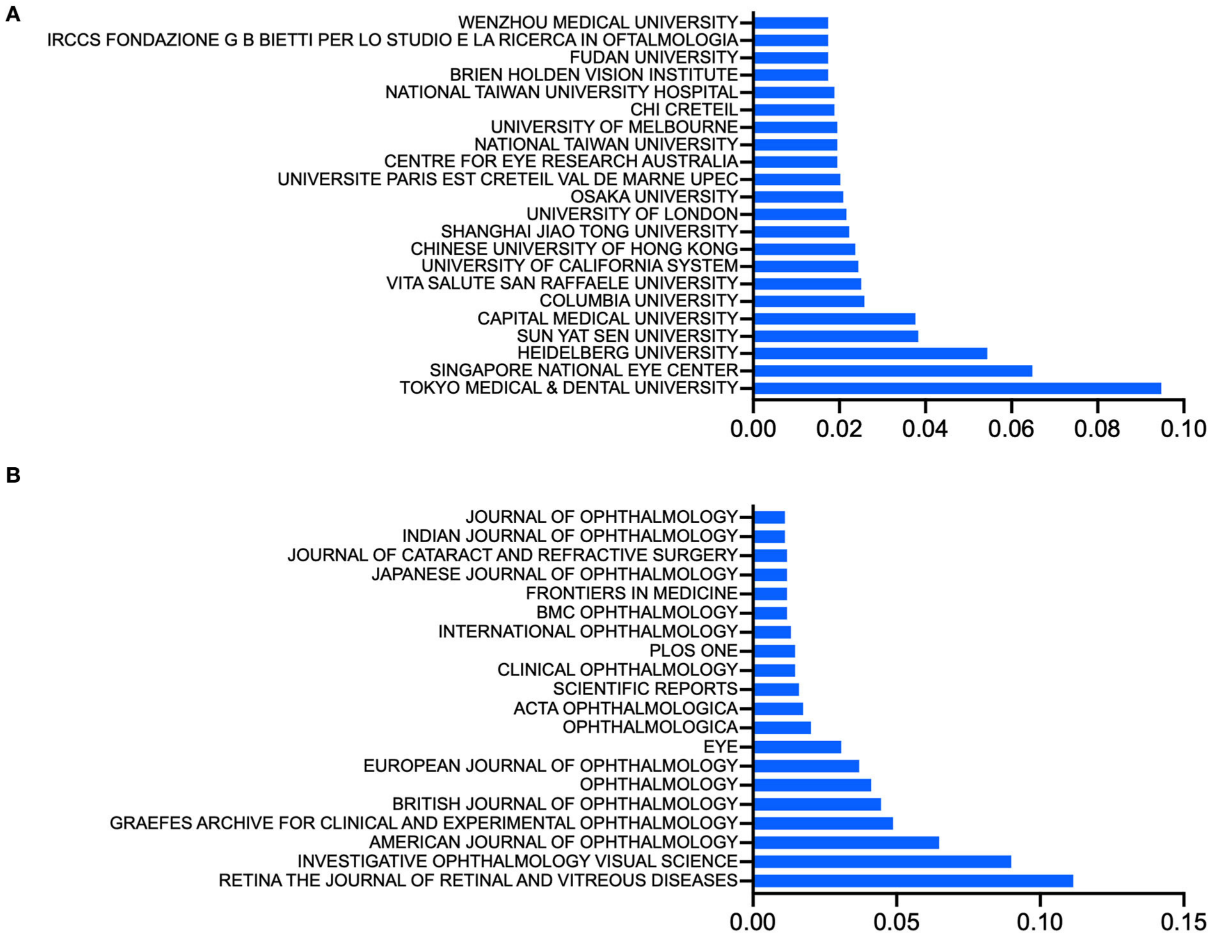

FIGURE 3
(A) Top institutions, ranked by the ratio of the number of publications from an institution to the total number of included publications about pathologic myopia. **(B)** Top journals, ranked by the ratio of the number of publications from a journal to the total number of included publications about pathologic myopia.

Country- or region-based contributions to PM research

The prevalence of PM in a country or region did not completely parallel its number of publications (Table 4). For example, although the USA contributed a large number of PM publications, only Asian and Pacific Islanders in the USA had a greater prevalence (ethnicity OR 1.64) (12). Conversely, Asian countries, especially some countries in East Asia, including Japan and China (1.7% and 3.7%, respectively), had a relatively higher prevalence of myopic retinopathy than some Western countries, such as Australia (1.2%) (2–6). Therefore, the factors influencing the number of publications on PM are not solely the prevalence of the disease.

The number of publications by country or region is usually associated with the interest in and knowledge of a certain field. The global number of publications related to PM has continued to increase since the millennium, with the greatest growth occurring in 2021 (increased by 48 publications compared to 2020), in which China contributed 70.8% of the global growth (34 publications). This increasing trend might have benefited from the state policy of prevention and control of myopia in China, which has been set in recent years (13). Therefore, not only research interest but also administrative encouragement was an important motivation for PM research. State policy can create an encouraging environment for researchers with adequate funding, advanced techniques, and equipment, which are essential for conducting relevant studies.

As PM is a global healthcare challenge, international collaboration has become a mainstream research pattern. In the present study, the USA had the most international collaboration (total link strength of 306 in VOSviewer), followed by China (total link strength of 236), Germany (total link strength of 227), Singapore (total link strength of 213), and

TABLE 1 Top 10 papers with the most citations relevant to pathologic myopia.

Title	Corresponding authors	Journal	Publication year	Total citations
Myopia and associated pathological complications	Saw, SM	OPHTHALMIC AND PHYSIOLOGICAL OPTICS	2005	618
Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes	Spaide, Richard F	AMERICAN JOURNAL OF OPHTHALMOLOGY	2009	572
Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin-—1-year results of a randomized clinical trial—VIP report no. 1	Bressler, NM	OPHTHALMOLOGY	2001	377
The complex interactions of retinal, optical, and environmental factors in myopia etiology	Flitcroft, D. I	PROGRESS IN RETINAL AND EYE RESEARCH	2012	361
Prevalence and causes of low vision and blindness in a Japanese adult population—The Tajimi Study	Araie, Makoto	OPHTHALMOLOGY	2006	349
Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review	Wong, Tien Y	AMERICAN JOURNAL OF OPHTHALMOLOGY	2014	334
International photographic classification and grading system for myopic maculopathy	Ohno-Matsui, Kyoko	AMERICAN JOURNAL OF OPHTHALMOLOGY	2015	327
Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis	Hafezi, Farhad	JOURNAL OF CATARACT AND REFRACTIVE SURGERY	2007	316
Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs	He, Mingguang	OPHTHALMOLOGY	2018	292
Long-term pattern of progression of myopic maculopathy: a natural history study	Ohno-Matsui, Kyoko	OPHTHALMOLOGY	2010	292

TABLE 2 Top 10 Web of Science categories of journals on pathologic myopia research.

Web of science categories	No. of publications (%)
Ophthalmology	1,189 (82.86)
Medicine general internal	76 (5.3)
Surgery	53 (3.69)
Multidisciplinary sciences	47 (3.28)
Pharmacology pharmacy	33 (2.3)
Medicine research experimental	29 (2.02)
Genetics heredity	15 (1.05)
Optics	14 (0.98)
Biochemistry molecular biology	13 (0.91)
Engineering biomedical	12 (0.84)

Japan (total link strength of 206) (Supplementary Figure 1). The USA is also the second-most productive country, in which authors published ~51% of studies from at least two countries or regions. It can be speculated that the USA was the most productive country. Collaboration and exchange are important in the academic community, and the USA performs well in international research. Although none of the top 10 authors hailed from the USA, the country had the most citations (9,395 total citations) and the highest H-index (53), indicating that the USA's research had a relatively high quality with good international collaboration and communication.

Therefore, not only is the burden of PM on patients, local economics, and public health a significant determinant of promoting PM research, but state policy and international collaboration are also essential factors contributing to global PM research.

We used the metric of the H-index, which has been widely used, to evaluate a country/area's productivity and citation impact of publications. However, this metric has some limitations (14). We did not evaluate the number of authors in an article or a specific author's position in an article (15), which could result in the distribution of citations from an article to all authors equally. Similar to the distribution of authors, the H-index of a country or region does not consider that the contributions from each country or region in the research were usually heterogeneous, and the equal distribution of citations of a publication to all countries and regions might be unjustified. Moreover, this metric does not differentiate between different cited sections of a publication (e.g., results or discussion, etc.) or between different types of publications (e.g., a review or original research). Additionally, this metric counts self-citations, and some intentional citations might have influenced it; for example, citing the publications of potential reviewers or editors (16, 17).

We also investigated the associations between HDI and publications; all of the top 10 authors came from countries with very high HDI. In addition to China, countries with very high HDI contributed the most publications. Patients from medium- and low-HDI countries and regions also suffer from PM; however, the number and influence of publications from these countries and regions

TABLE 3 Top 10 authors who published most in the field of pathologic myopia.

Author	Country	Latest affiliation	No. of publications	No. of citations
Kyoko Ohno-Matsui	Japan	Tokyo Medical and Dental University	139	4,710
Jost B Jonas	Germany	Ruprecht-Karls-Universität Heidelberg	77	2,224
Tien Y Wong	Singapore	National University of Singapore	44	2,135
Seang Mei Saw	Singapore	Singapore National Eye Center	42	2,088
Muka Moriyama	Japan	Tokyo Medical and Dental University	41	1,931
Noriaki Shimada	Japan	Kurashiki Central Hospital	35	1,588
Takeshi Yoshida	Japan	Kyoto University	35	1,290
Francesco Bandello	Italy	Università Vita-Salute San Raffaele	34	903
Quan V.Hoang	Singapore	National University of Singapore	34	229
Chee Wai Wong	Singapore	National University of Singapore	33	228

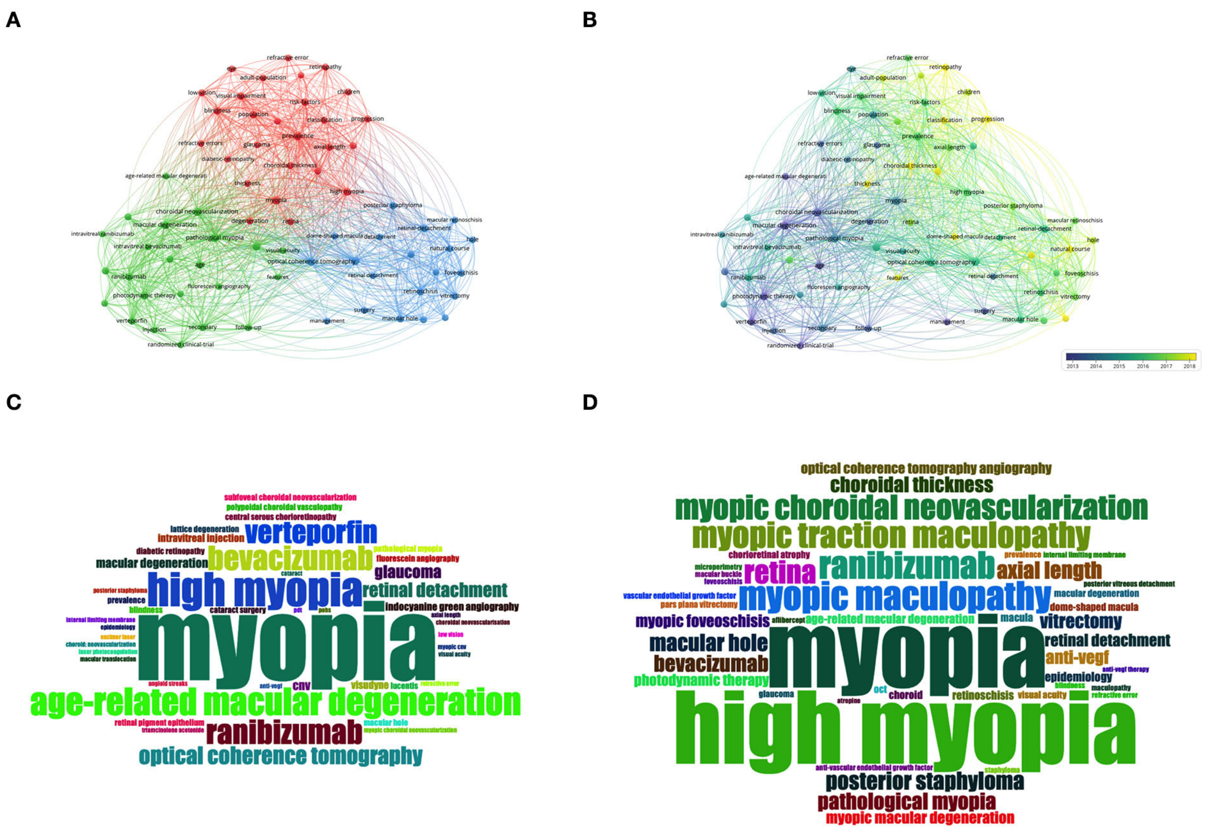

FIGURE 4
Keywords analysis by VOSviewer and R. **(A)** Co-occurrence map of keywords in titles and abstracts. Keywords were classified into 3 clusters by co-occurrence frequency, including an epidemiology-related cluster (in red), a treatment-related cluster (in green), and a lesion-related cluster (in blue). **(B)** Color-coded map of keywords by the average time of appearance. Blue keywords appeared earlier, while yellow keywords appeared more recently. **(C)** The word-cloud map of the most frequent keywords from 2000 to 2010. **(D)** The word-cloud map of the most frequent keywords from 2011 to August 2022.

need to be improved due to financial-, technical-, and equipment-related restrictions. The application of advanced technology, such as artificial intelligence, telemedicine, and advanced communication technology, might enhance the diagnosis, screening, and regular examinations in these underdeveloped areas.

Publication tendency in PM research

We analyzed the top papers with the most citations; 80% of the publications were published in clinical ophthalmology journals, indicating that PM research mainly focuses on clinical medicine rather than basic medical research. Similarly, most publications belong to the WOS category of ophthalmology (82.86%). The analysis revealed that this research field involves more clinicians than scientists and also explained the phenomenon that many PM-related manifestations were noticed by applying multimodal imaging methods, but their pathogenesis was not fully understood, such as dome-shaped maculopathy. In the future, greater efforts should be made to investigate the pathogenesis of PM using animal models.

In PM research, the RRI metric has maintained growth from 0.0018% in 2001 to 0.0044% in 2021, and the number of publications has also increased from 24 in 2000 to 156 in 2021. These results indicate a great interest in PM raised in the medical community, which also conforms with the increasing worldwide prevalence of PM (Figure 1B).

The study trends based on keywords can be considered indicators of basic and clinical research directions. Based on the analysis of keywords in the current study, most studies on PM correlate with epidemiology and risk factors, treatments, lesions, and abnormalities. The color-coded average time of appearance map of co-occurrence keywords showed that the research hotspots transformed from treatment for mCNV to epidemiologic and public health studies and then to more manifestations of PM and their treatments. In more detail

(Supplementary Figure 4), we noticed that besides the keywords "myopic, high myopic, and pathologic myopia," the keywords of "photodynamic therapy, ranibizumab, (myopic) choroidal neovascularization" (year of the median from 2006 to 2014), and "optical coherence tomography, myopic maculopathy, myopic traction maculopathy" (year of the median from 2013 to 2017) had a frequency no <50, which indicates that the main interest of researches focused on treatment for mCNV, followed by PM-related maculopathy and its imaging findings. The latest hotspot keyword was "deep learning," revealing a novel research direction. Automated diagnosis, screening, and regular examinations with artificial intelligence and advanced communication technology might enhance teleophthalmology and improve practice patterns in these underdeveloped areas.

The changes in keywords (Figures 3A, 4B) in various periods indicate increasing and emerging research themes in the PM field. Based on the bibliometric analysis, especially the keyword and research hotspots analysis, the following themes have reported the latest outcomes.

TABLE 4 The population-based prevalence of myopic retinopathy and the number of publications since 2020.

Country/ region	Study (*n*)	Age	Prevalence of myopic retinopathy*	Number of publications
China	Beijing eye study (4,139)	≥40	3.7%	294
Japan	Hisayama study (1,892)	≥40	1.7%	239
Taiwan	Shihpai eye study (1,058)	≥65	3.0%	73
Australia	Blue mountains eye study (3,653)	≥49	1.2%	63

*The definition of myopic retinopathy in various studies is not totally the same.

Multimodal imaging and pathologic manifestations

Since the millennium, optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), magnetic resonance imaging (MRI), and other imaging methods have been applied in clinical practice, enabling researchers to evaluate pathologic myopic alterations and detect myopic complications (18). For example, current ultrawide-field imaging can show peripheral retinal abnormalities, and swept-source OCT can exhibit vitreous and retinal changes, such as the formation of posterior vitreous detachment, paravascular cystic lesions, and paravascular lamellar holes (19, 20).

Posterior staphyloma

Posterior staphyloma is defined as an outpouching of the eye wall with a radius of curvature less than the surrounding curvature of the eye wall (21). However, its formation is not yet fully understood. Currently, ultrawide-field OCT, ultrawide-field photography and MRI can visualize and evaluate the structure of staphyloma and its complications (21–23). Relevant complications include tractional maculopathy (such as retinoschisis), lacquer cracks, mCNV, and chorioretinal atrophy. Traditionally, posterior staphyloma was divided into 10 subtypes by Curtin (24). Recently, five types of posterior staphylomas have been proposed using MRI by Ohno-Matsui (21). Compared with MRI, ultrawide-field OCT provides visualization of retinal tissues simultaneously with scleral changes (usually when the choroid is not too thick, based on our experience).

Myopic choroidal neovascularization

Based on the analysis of keywords, we can observe that mCNV has always been the focus of PM research. Approximately 5.2–11.3% of eyes with PM develop mCNV (25). Ninety percent of eyes with PM progress to legal blindness in 10 years without treatment (26). Ischemia and breaks in Bruch's membrane may contribute to the development of mCNV (27, 28). In addition to fluorescein angiography (FA) and OCT, which can determine the activity of mCNV, non-invasive OCTA can demonstrate neovascularization volumetrically and can be performed repeatedly during follow-up. Anti-vascular endothelial growth factor (VEGF) agents are the first-line therapy (29–31).

Myopic maculopathy

According to several population-based studies, the frequency of myopic maculopathy varies from 1.2 to 3.8% (32–35). The classification of myopic maculopathy in PM was established using fundus photography (FP) and OCT images (Supplementary Table 2) (36–40). Myopic traction maculopathy can be evaluated using OCT for macular status, as well as surgical indications (41). However, these classification systems do not include some manifestations, such as the dome-shaped macula.

Dome-shaped maculopathy

Dome-shaped maculopathy refers to an inward convex protrusion of the macula within the posterior concavity of the eye that is mainly visualized using OCT and MRI (42, 43). The alteration can be detected only in horizontal scanning images, only in vertical images, or in both horizontal and vertical images because of the morphologic pattern of the round dome (43, 44). However, domes in children only appear in vertical OCT scanning images (45). Dome-shaped maculopathy can be identified quantitatively as a macular inward bulge height of more than 50 μm in the most convex image (46). Serous retinal detachment was detected in 2–67% of eyes with dome-shaped maculopathy (42, 46–49), and CNV was observed in 41.2% of the affected eyes (46). A bulge height of more than 400 μm is purportedly associated with decreased visual acuity, serous detachment, and greater retinal pigment epithelial atrophy (50). However, the mechanism of dome formation remains unclear.

Myopic glaucoma-like optic neuropathy

In PM, expansion, tilting, torsion, and effacement of the optic nerve head had been noticed, which resembled glaucoma-like neuropathy with loss of the neuroretinal rim (51). However, the irregularity of the optic nerve head shape and macula makes it challenging to determine the neuroretinal rim and to evaluate the thickness of the retinal nerve fiber layers and ganglion cell layers using OCT (52, 53). Fortunately, OCTA might be helpful in the future to differentiate myopia from glaucoma by exploring vascular changes under various conditions (54).

Impact on public health and management

The global prevalence of PM-related visual impairment is estimated to rise from 0.1% in 2020 to 0.6% in 2050 (55); therefore, the public health burden and impact on the quality of life will likely increase. PM affects patients' reading, mobility, and emotional wellbeing (56). For PM patients who suffer from visual loss or low vision, care and rehabilitation with adaptive technologies are recommended (57, 58).

Patients with myopia are usually unaware that the development of pathological complications might result in irreversible vision impairment (59). Public education campaigns on the increased risk of PM and regular eye examinations are urgently needed, particularly for high-risk individuals. Myopia control and prevention programs, national-level policies, and healthcare providers should be available to PM patients to provide timely medical care (60–63). Moreover, more research was performed on adult subjects (808 publications involving adults vs. 56 publications involving juveniles), and more research on juvenile patients is expected.

Increasing outdoor time (at least 3 h per day) and decreasing near-work activities are beneficial to the prevention and control of myopia (61, 64–66), which also implicitly controls the progression of simple myopia on PM. Optical aids with myopia control properties, including orthokeratology and soft multifocal lenses, can be used in children with myopia (67–69). Atropine and pirenzepine are alternative interventions for myopic control (70–74). Regular measurement of refraction and axial length helps monitor the progression of PM.

Pathogenesis mechanism

Both environmental and genetic factors contribute to the pathogenesis of PM, and the sclera has profound effects on the development of PM. Environmental factors include educational stress, economic level, outdoor time, and near-work time and intensity. Regarding genetic factors, *CCDC102B* is a susceptibility gene for myopic maculopathy in the Japanese population (75). However, other studies have not found an association between candidate genes and PM.

Animal models with PM features have mainly been established using mice, chicks, and monkeys (76–79). However, no animal models precisely matched the characteristic patterns of PM in human eyes. Therefore, extrapolation from animal models to human beings needs to be done cautiously, and mimicking the formation of PM in human eyes in developing animal models is not promising.

Scleral remolding plays an important role in the pathogenesis of PM (80). Pathologic visual stimulation influences choroidal blood and initiates scleral hypoxia, resulting in the development of myopia and axial elongation (81–83). However, its pathogenesis at the molecular level remains largely unknown.

The sclera has been a treatment target for PM, and several surgical approaches have been reported (84–96). However, no sclera-targeted treatment regimens have been proven safe and effective for the long-term management of PM.

Artificial intelligence and future direction

Deep learning, as the main component of artificial intelligence, has a great ability to manipulate multiple-dimensional data and perform complex tasks on medical data. Several studies have investigated the diagnostic performance of deep-learning models for identifying PM based on fundus photos or OCT images and have achieved an AUC of more than 0.95 (97–100). Other studies have used deep-learning methods to automatically detect PM-related lesions, such as myopic maculopathy (101–104). However, the performance of these models in real-world clinical practice and population-based screening remains unclear and requires further validation.

Moreover, three directions require further research. First, a deep-learning approach based on multimodal imaging for diagnosing PM and detecting lesions has not yet been studied. The latest ATN classification system comprehensively evaluates myopic maculopathy based on fundus photographs and OCT images (105, 106). Deep-learning methods based on bimodal or multimodal imaging can provide a more precise evaluation of PM. Second, PM is a disease requiring timely diagnosis and regular checks and examinations, which consume large amounts of medical resources unavailable in many underdeveloped countries and regions. Therefore, teleophthalmology systems with embedded automated deep-learning models for PM diagnosis and follow-up could help solve this dilemma in the real world. Third, deep learning in PM may serve additional tasks, including designing treatment regimens and predicting the prognosis of PM.

Strengths and limitations

The current study was the first bibliometric analysis of PM based on publications since 2000, reflecting the latest updates in this field. Data were extracted from the authoritative WOS Core Collection, and VOSviewer and Biblioshiny were used for bibliometric analysis. However, this study has several limitations. The nature of selection bias existed in the methods; only papers published in authoritative and influential journals that were listed in the WOS Core Collection were included in our analysis, and publications from other databases such as Medline and Scopus were not included. Medline and Scopus did not provide complete records of citations as the WOS Core Collection did. WOS provides better accuracy in document type assignment than Scopus and more comprehensive citation data than Medline (107, 108). Therefore, the WOS database is the most commonly used reference database for bibliometric analysis.

Moreover, no perfect and comprehensive metrics exist for analyzing and predicting future trends in PM research, and the drawbacks of the H-index have been explained. The metric of impact factor is also not perfect. It is only calculated for journals by Clarivate, and this metric is not available for authors or institutions. A comprehensive and consistent metric to evaluate academic influence for authors, institutions, journals, and countries is always needed and under investigation. Furthermore, although we evaluated the number of publications each author participated in, we did not identify the author's positions in individual publications. However, the author's position in an article does not necessarily correlate with their specific contribution to PM research.

Conclusion

This study comprehensively analyzed published research on PM since the millennium and presents the current status of mainstream studies on PM. PM is a topic of interest for both scientific and clinical research. China, the USA, and Japan contributed the greatest number of publications; the journals, authors, and institutions that published the most relevant literature also came from these three countries. More pathologic changes in the macula have been observed using multimodal imaging methods, and their pathogenesis is under investigation. With the increasing prevalence of PM, interventions for PM have become a public health issue and a research hotspot. Combined with the latest technology, including artificial intelligence, automated diagnosis, and screening of PM is a novel field. Taken together, our results should help researchers understand the current status and provide future directions.

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.

Author contributions

JY: design, definition of intellectual content, data acquisition, data analysis, manuscript preparation, and manuscript editing. SW: design, definition of intellectual content, data acquisition, data analysis, funding, manuscript preparation, and manuscript editing. CZ: data analysis and manuscript review. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by National High Level Hospital Clinical Research Funding (BJ-2021-208) and National Natural Science Foundation of China (82200730).

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.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1047787/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The co-occurrence map of 34 countries and regions, which showed the international collaboration among countries/regions.

SUPPLEMENTARY FIGURE 2
The distribution of publication year for publications of various citation frequency **(A)**. High frequency: more than 100 citations; medium frequency: more than 50 citations and <100 citations; low frequency <50 citations. The heatmaps of high citation frequency (more than 100 citations) group **(B)**, medium frequency (more than 50 citations and <100 citations) group **(C)**, and low frequency (<50 citations) group **(D)** in each year, respectively. Every row in the heatmap represents a publication. The color represents the total citation number in each year (x axis).

SUPPLEMENTARY FIGURE 3
The co-occurrence map of scholars who published papers of pathologic myopia, which showed the cooperation among researchers.

SUPPLEMENTARY FIGURE 4
The top keywords with strongest burst in pathologic myopia research since 2,000 based on the authors' keywords lists. On the base timeline, the location of the circles represents the median year of the duration when keywords were used frequently, and the size of the circles represents the frequency. The blue segments represent the first quartile time point to the third quartile time point of the duration when keywords were used frequently.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 15 December 2022
DOI 10.3389/fpubh.2022.992784

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 13 July 2022
ACCEPTED 22 November 2022
PUBLISHED 15 December 2022

CITATION
Pan W, Lin J, Zheng L, Lan W, Ying GS, Yang Z and Li X (2022) Myopia and axial length in school-aged children before, during, and after the COVID-19 lockdown–A population-based study. *Front. Public Health* 10:992784. doi: 10.3389/fpubh.2022.992784

Myopia and axial length in school-aged children before, during, and after the COVID-19 lockdown–A population-based study

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Background: Myopic shift had been observed during the COVID-19 lockdown in young school children. It remains unknown whether myopic shift is accompanied with increase in axial length. We aimed to evaluate the impact of the COVID-19 lockdown on myopia and axial length of school children in China by comparing them before, during and after the lockdown.

Methods: In this population-based cross-sectional study, school-based myopia screenings were conducted in the Fall of 2019, 2020, and 2021 (representing before, during and after COVID-19 lockdown respectively) in Chengdu, China. Myopia screenings were performed on 83,132 students aged 6 to 12 years. Non-cycloplegic refractive error was examined using NIDEK auto-refractor (ARK-510A; NIDEK Corp., Tokyo, Japan) and axial length was measured using AL-Scan (NIDEK Corp., Tokyo, Japan). Spherical equivalent (SER, calculated as sphere+ 0.5*cylinder), prevalence of myopia (SER $\leq$-0.50 D), and axial length were compared across 3 years stratified by age.

Results: Myopia prevalence rate was 45.0% (95% CI: 44.6–45.5%) in 2019, 48.7% (95% CI: 48.3–49.1%) in 2020, and 47.5% (95% CI: 47.1–47.9%) in 2021 ($p < 0.001$). The mean non-cycloplegic SER (SD) was −0.70 (1.39) D, −0.78 (1.44) D, and −0.78 (1.47) D respectively ($p < 0.001$). The mean (SD) axial length was 23.41 (1.01) mm, 23.45 (1.03) mm, and 23.46 (1.03) mm across 3 years respectively ($p < 0.001$). From the multivariable models, the risk ratio (RR) of myopia was 1.07 (95% CI: 1.06–1.08) times, the SER was 0.05 D (95% CI: 0.04 D to 0.06 D) more myopic and the mean axial length increased by 0.01 mm (95% CI: 0.01 mm to 0.02 mm) in 2020 compared to 2019. In 2021, the risk ratio (RR) of myopia was 1.05 (95% CI: 1.04–1.06), the mean SER was 0.06 D (95% CI: 0.05 D to 0.07 D) more myopic, and the mean axial length increased by 0.03 mm (95% CI: 0.02 mm to 0.04 mm) compared to 2019.

Conclusions: The COVID-19 lockdown had significant impact on myopia development and axial length, and these impacts remained 1 year after the lockdown. Further longitudinal studies following-up with these students are needed to help understand the long-term effects of COVID-19 lockdown on myopia.

KEYWORDS

myopia, COVID-19, prevalence, axial length (AL), Chinese young students

Key messages

- COVID-19 postpone great burden on children's myopia development.
- Myopia risks brought by the COVID-19 lockdown is accompanied with axial length elongation.
- Even as social restriction policies loosen in 2021, the effect of COVID-19 lockdown on myopia still remained.

Introduction

Myopia, a major cause of irreversible blindness, is a major public health concern worldwide (1). According to the World Health Organization's projection made in 2016, about 50% of all population will be myopic by the year 2050 (2). The nationwide school closure from the outbreak of coronavirus disease 2019 (COVID-19) in December 2019 in China bestowed a great burden upon children's myopia development and progression. Multiple studies have found myopia prevalence was significantly increased among school-aged children during the home quarantine period (3–8), likely due to behavioral changes induced by home quarantine, including decrease of outdoor activities and increased use of electronic devices (9–20).

The year 2020 is the year of "Quarantine Myopia" (21). Since the outbreak of COVID-19, the virus quickly spread around the world and became a global pandemic. To suppress the virus spreading in the early stage, stringent measures like home quarantine were implemented. During this time, schools in more than 190 countries/territories were partially or fully closed, affecting more than 1.5 billion school-age children (22). In China, students were confined at home taking virtual class from Jan 2020 to Apr 2020. Remote learning, increased use of electronic devices, decreased outdoor time, and lack of organized sports activities were the dominant lifestyle of students during the COVID-19 pandemic (10). In May 2020, schools in China were reopened, and students attended in-person classes the same way as in the pre-COVID period.

In the year 2021, while Delta and Omicron variants deepened the COVID-19 pandemic globally, China had contained the COVID cases to a relatively small number domestically. Schooling and social lives were uninterrupted in general for the whole year of 2021. As a result, China became a natural experiment that provided us a unique opportunity to assess how students' refractive error and axial length progressed at different control phases of the COVID-19 pandemic, and to identify the age at which refractive error was most sensitive to the lifestyle changes that myopia prevention and control should be focusing on.

While the impact of lifestyle changes from the COVID-19 pandemic on the incidence and progression of myopia based on non-cycloplegic refractive error (known to over-estimate the myopia prevalence and severity) in school students were reported in several studies (3, 4, 8). the myopic change after the lift of lockdown remains unknown. More importantly, the previous studies have not evaluated the effect of the COVID-19 pandemic on the axial length, an objective measurement that can be accurately measured in children, and is not affected by the cycloplegia (23). We are interested in investigating whether the effect of COVID-19 lockdown on students' myopia persisted as students returned to school, and whether myopia change was accompanied by the increase in axial length. Herein, we conducted a population-based prospective cross-sectional study with three myopia screenings across three years covering before (2019), during (2020), and after (2021) the COVID-19 lockdown as demonstrated in Figure 1. This study aims to evaluate the impact of the COVID-19 lockdown on myopia and axial length of school children in China by comparing them before, during, and after the lockdown.

Methods

This study is a prospective cross-sectional study started in the Fall of 2019 under the Chinese government's initiative on "National Screening and Intervention of Common Diseases and Health Risk Factors in Students 2019." The study included three school-based myopia screenings conducted in the Fall of 2019, 2020, and 2021 respectively. Students between the ages of 6 and 12 years old at the date of screening were invited to participate. All data collection and eye examinations followed the tenets of the Declaration of Helsinki. The nature of the study was

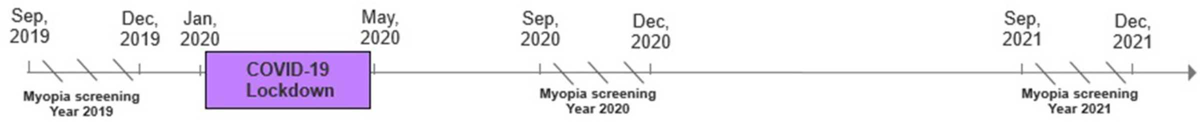

FIGURE 1
Timeline of COVID-19 lockdown and myopia screenings.

explained to the participating children and their parents through the school, and verbal informed consent was obtained from parents before the commencement of the study.

Study subjects

Students from all classes and grades of 88 schools in Qingyang District, Chengdu were invited to participate. Chengdu is the capital city of Sichuan Province in Southwestern China. It is one of the most important economic, financial, commercial, cultural, transportation, and communication cities in China. Chengdu consists of 12 municipal districts with a total population of approximately 20.9 million. Qingyang District is one of 12 districts in Chengdu, located in downtown Chengdu with a population of about 0.96 million. The residents at Qingyang District are mostly of Han ethnicity with a wide spectrum of socioeconomic status. Thus, participants in the study are representative of students in the Southwestern metropolitan area of China. The exclusion criteria were the following: (1) history of ocular surgeries (2) ocular diseases, such as strabismus, amblyopia et al. (3) wore Orthokeratology lenses 4) incomplete measurements or information. Detailed flow chart was shown Supplementary Figure S1.

Myopia screenings

Three population-based cross-sectional myopia screenings were performed in the Fall (from September to December) of 2019, 2020 and 2021, representing before, during, and after the COVID-19 lockdown in China. A screening team consisting of one certified ophthalmologist, two certified optometrists, and seven certified nurses performed the myopia screening in both eyes, including non-cycloplegic refractive error using NIDEK auto-refractor (ARK-510A; NIDEK Corp., Tokyo, Japan) and axial length using AL-Scan (NIDEK Corp., Tokyo, Japan) following the standard study protocol. As part of the standard screening procedure, the certified ophthalmologist performed slit lamp examination and referred students of any suspicious ocular diseases to eye specialists on-site.

Statistical analysis

Non-cycloplegic spherical equivalent (SER) in diopters (D) was calculated as sphere plus half of cylinder. Myopia is defined as non-cycloplegic SER$\leq$-0.50 D. Continuous measures (e.g., SER, axial length) were summarized by mean $\pm$ standard deviation (SD), categorical measures were summarized by count and percentage. For SER and axial length, the average from two eyes was used due to the high inter-eye correlation in SER and axial length (Pearson correlation coefficient = 0.85 and 0.95 respectively).

As age is strongly associated with myopia development and progression (24), we performed age-specific comparison in three different cohorts from 2019 (before COVID-19 lockdown), 2020 (during COVID-19 lockdown) and 2021 (after COVID-19 lockdown). For example, the 6-year-old students in 2019 were compared to 6-year-old students in 2020 (who were 5-year-old in 2019), and compared to 6-year-old students in 2021 (who were 4-year-old in 2019, 5-year-old in 2020). To evaluate the effect of COVID-19 lockdown for each age group of students, we compared the mean SER and mean axial length across three years using analysis of variance (ANOVA), and using chi-square test for comparison of myopia prevalence rate across 3 years (e.g., before, during, and after COVID-19 lockdown). If the overall difference across 3 years is statistically significant ($p <$ 0.05), post-hoc pairwise comparisons were made for each pair of years. To assess the overall effect of COVID-19 lockdown on the refractive error and axial length, we performed Poisson regression models for myopia prevalence and generalized linear models for refractive error and axial length. These analyses were adjusted for age and gender, and generalized estimating equations were applied to account for the repeated measures correlation for subjects in more than one myopia screenings. All analyses were conducted using SAS 9.4 (SAS Inst., Cary, NC), and two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 83,132 students aged 6 to 12 years old were included in the analysis, including 52,748 students in year 2019, 59,002 in year 2020, and 64,368 in year 2021. The mean (SD) age of the students at myopia screening was 8.5 (1.9) years and 52.1% (95% CI: 51.8–52.3%) of the students were male.

The distributions of age and gender for each year are shown in Supplementary Table S1.

The myopia prevalence rate was 45.0% (95% CI: 44.6–45.5%) in 2019, 48.7% (95% CI: 48.3–49.1%) in 2020, and 47.5% (95% CI: 47.1–47.9%) in 2021 (Table 1). The overall myopia prevalence rate was significantly higher in 2020 than 2019, and remained higher in 2021 than 2019 (all $p < 0.001$ for comparison with 2019). In analyses stratified by age of students, the greatest increase in myopia prevalence during the COVID-19 lockdown was observed in students 7 years of age, with myopia prevalence of 28.2% in 2019, increased to 33.8% in 2020, and decreased to 31.2% in 2021(all $p < 0.001$ for comparison with 2019). Increase in myopia prevalence after the lift of the COVID-19 lockdown compared to during lockdown was observed in 6-year-old students (from 19.1 to 20.6%, $p = 0.005$). Decrease in myopia prevalence after the lift of the COVID-19 lockdown compared to during lockdown was observed in 9-year-old students (from 55.8 to 54.2%, $p = 0.03$) and 12-year-old students (from 81.0 to 77.7%, $p < 0.001$). Histogram of myopia prevalence across 3 years stratified by age are shown in Supplementary Figure S2.

The overall mean (SD) of SER was −0.70 (1.39) D in 2019, and became more myopic with mean (SD) of −0.78 (1.44) D in 2020, and −0.78 (1.47) D in 2021 (all $p < 0.001$ for comparison with 2019) (Table 2). As age increased, the difference in SER across the 3 years decreased, and was not significant in 11 and 12-year-old students. The distributions of SER across 3 years stratified by age are shown in Supplementary Figure S3.

The overall mean (SD) of axial length was 23.41 (1.01) mm in 2019, 23.45 (1.03) mm in 2020 and 23.46 (1.03) mm in 2021 as shown in Table 3 (all $p < 0.001$ for comparison with 2019). The change of axial length across 3 years followed a similar trend as myopia prevalence and SER. Among the 7-year-old students, mean axial length increased from 23.01 mm in 2019 to 23.05 mm in 2020 ($p < 0.001$), and slightly decreased to 23.04 mm in 2021 ($p = 0.006$ for comparison with 2019). Among 8-year-old students, mean axial length was 23.34 mm in 2019, 23.33 mm in 2020 ($p = 0.60$) and increased to 23.39 mm in 2021 ($p < 0.001$ for comparison to 2019). The distributions of axial length across 3 years stratified by age are shown in Supplementary Figure S4.

In the multivariable analysis of all students adjusted for age and gender, the risk ratio (RR) of myopia was 1.07 (95% CI: 1.06–1.08) in 2020, and 1.05 (95% CI: 1.04–1.06) in 2021 when compared to 2019 (Table 4). Older age (RR = 1.63 to 4.12 for students aged 7–12 compared to 6-year-old, $p < 0.001$), and female gender (RR = 1.10, $p < 0.001$) were significantly associated higher prevalence of myopia. The mean SER was 0.05 D (95% CI: 0.04 D to 0.06 D) more myopic in 2020, and 0.06 D (95% CI: 0.05 D to 0.07 D) more myopic in 2021 when compared to 2019. The mean axial length increased by 0.01 mm (95% CI: 0.01 mm to 0.02 mm) in 2020 and increased by 0.03 mm (95% CI: 0.02 to 0.04 mm) in 2021 when compared to 2019.

Discussion

In this large prospective population-based cross-sectional study of 83,132 Chinese school students aged 6 to 12 years old, we evaluated the impact of COVID-19 lockdown on development of refractive error and axial length. We found that the COVID-19 lockdown is associated with higher myopia prevalence and longer axial length, and these effects remained 1 year after the lift of lockdown. Significant myopic shift among students during the COVID-19 lockdown was observed, which was consistent with previous studies (3–8). The comparison of results from different studies related to impact of COVID-19 lockdown on myopia is shown in Supplementary Table S2. In our study, the myopia prevalence rate increased by 3.7%, and SER became more myopic by 0.08 D. Unique in our study, we evaluated the impact of COVID-19 lockdown on axial length and found that mean axial length increased by 0.04 mm, supporting the increase in myopic refractive error. Another highlight of our study is that we evaluated the change of refractive error and axial length 1 year after the lockdown was lifted, and found that the impact of the COVID-19 lockdown remained with SER staying the same, and axial length increasing by an additional 0.01 mm in 2021 compared to 2020, despite no home quarantine taking place in Chengdu in 2021.

During the outbreak of COVID-19, many environmental changes occurred including the decrease in outdoor activities and increase in screen time, which may contribute to the increase of myopia shift and elongation of axial length during the home quarantine. Both increasing screen time and reduced time outdoors are strong risk factors for the development of myopia (24). Xu et al. reported Chinese students screen time increased 2.07–3.14 times and outdoor activities time decreased by 1.14–1.71 times during COVID-19 lockdown based on a large-scale survey using questionnaire (8).

After the COVID-19 lockdown was lifted and students returned to in-person school, we expected students to be less myopic compared to during the lockdown; however, we observed the refractive error and axial length remained progressing in 2021 when there was no COVID-19 lockdown in the whole year in China. What are the reasons for the myopic shift after the lift of lockdown? Certain myopia-prone behaviors may persist after the lift of lockdown, but they may not seem be the main reason for the persistent effect. In a recent study from Israel, Shneor et al. showed once students returned to in-person school, the time spent outdoor and amount of physical activities returned to pre-pandemic levels using objective behavior measurements (15). As students returned to school, near work activities were no more than that during the lockdown. Rather, the persistent effect may be the consequence of myopic shift made during the lockdown. Hu et al. studied longitudinal myopia development of students from grade 2 to grade 3 during the COVID-19 lockdown, and found among

TABLE 1 Comparisons of myopia prevalence rate across 3 years overall and stratified by age at myopia screening.

	Myopia (%)			*p*-value*			
Age at myopia screening	Year 2019	Year 2020	Year 2021	Overall	2020 vs. 2019	2021 vs. 2020	2021 vs. 2019
6	1,873 (18.7%)	2,036 (19.1%)	2,531 (20.6%)	<0.001	0.44	0.005	<0.001
7	2,916 (28.2%)	3,482 (33.8%)	3,435 (31.2%)	<0.001	<0.001	<0.001	<0.001
8	3,640 (41.6%)	4,589 (44.4%)	4,643 (45.1%)	<0.001	<0.001	0.35	<0.001
9	4,077 (52.9%)	4,738 (55.8%)	5,489 (54.2%)	<0.001	<0.001	0.03	0.07
10	4,310 (63.3%)	4,872 (65.8%)	5,357 (64.3%)	0.007	0.002	0.051	0.20
11	3,141 (73.0%)	4,768 (72.9%)	5,162 (71.9%)	0.30			
12	3,792 (79.2%)	4,263 (81.0%)	3,983 (77.7%)	<0.001	0.03	<0.001	0.06
All	23,749 (45.0%)	28,748 (48.7%)	30,600 (47.5%)	<0.001	<0.001	<0.001	<0.001

*From Chi-square test. When overall p-value across 3 years is significant, pairwise comparisons between years were made.

TABLE 2 Comparison of spherical equivalent across 3 years overall and stratified by age at myopia screening.

	Mean (SD)			*P*–value*			
Age at myopia screening	Year 2019	Year 2020	Year 2021	Overall	2020 vs. 2019	2021 vs. 2020	2021 vs. 2019
6	0.01 (0.82)	0.02 (0.87)	−0.02 (0.96)	<0.001	0.40	<0.001	0.002
7	−0.19 (0.94)	−0.30 (1.00)	−0.26 (1.03)	<0.001	<0.001	0.005	<0.001
8	−0.49 (1.11)	−0.56 (1.14)	−0.60 (1.18)	<0.001	<0.001	0.03	<0.001
9	−0.81 (1.28)	−0.86 (1.30)	−0.88 (1.35)	<0.001	0.005	0.44	<0.001
10	−1.19 (1.48)	−1.24 (1.50)	−1.25 (1.52)	0.03	0.04	0.77	0.02
11	−1.59 (1.67)	−1.58 (1.66)	−1.61 (1.70)	0.57			
12	−1.97 (1.78)	−2.01 (1.83)	−1.98 (1.89)	0.41			
All	−0.70 (1.39)	−0.78 (1.44)	−0.78 (1.47)	<0.001	<0.001	0.93	<0.001

*From analysis of variance. When overall p-value across 3 years is significant, pairwise comparisons between years were made.

students who were not myopic before lockdown, the proportion of students with SER between −0.50 to +0.50 D increased from 30 to 50% comparing to 2019 (7). Because students with SER below "age-normal hyperopia" (i.e., below +0.50 D for ages 7 to 8 years, below +0.25D at ages 9 to 10 years and emmetropia at age 11 years) were at significant risk of developing myopia (25), the COVID-19 lockdown might have substantially increased the proportion of students that had SER drop below such borderline. Therefore, both myopia and axial length could still increase even after the lift of COVID-19 lockdown, when students returned to in-person school.

In our study, the effect of COVID-19 lockdown on myopia was observed in all age groups, but not to the same magnitude. The 7-year-old students showed the greatest changes of myopia from the COVID-19 lockdown, with myopia prevalence rate of 28.2, 33.8, and 31.2% respectively before, during and after lockdown. Students in other age groups were less affected. Wang et al. similarly reported that home quarantine has most substantial impact on the myopia risk for students of age 6–8 years old (3). However, the magnitude of myopic shift during COVID-19 lockdown in our study was much smaller comparing to Wang et al.'s results (13.6 in 2019 and 26.2% in 2020 for 7-year-old students) (3). We speculate the reasons may be the following: 1) the time of myopia screening in 2020 took place during September to December 2020 in our study, whereas the photoscreening in Wang et al.'s study was in June 2020 (3). In Chang et al.'s study, the author found a "hyperopic progression" from May to October 2020 which may be explained by short-term accommodative spasm (4). The myopia screening immediately after the COVID-19 lockdown may overestimate the actual myopic shift among students. (2) The difference may be due to myopia screening methods. Our study used NIDEK autorefractor, while Wang et al. used Photoscreening. These devices have different sensitivity and specificity for detecting myopia. (3) The myopia prevalence rate before the COVID-19 outbreak was much higher in our study than the rate in Wang et al.'s study. This difference may due to cohort difference. Wang et al. included students from Feicheng, a county-level city in Northern China and our cohort was from Chengdu, a capital city in which students were more likely exposed to electronic devices early in life and less per capita outdoor area compared to Feicheng. Notably a large cohort from Wenzhou city in Xu et al.'s study, the results were closer to our study (overall myopia prevalence among primary school students from 34.4 to

TABLE 3 Comparison of axial length across 3 years overall and stratified by age at myopia screening.

Age at myopia screening	Mean (SD)			*P*-value*			
	Year 2019	Year 2020	Year 2021	Overall	2020 vs. 2019	2021 vs. 2020	2021 vs. 2019
6	22.71 (0.72)	22.67 (0.72)	22.70 (0.73)	0.002	<0.001	0.02	0.19
7	23.01 (0.77)	23.05 (0.78)	23.04 (0.78)	<0.001	<0.001	0.17	0.006
8	23.34 (0.85)	23.33 (0.84)	23.39 (0.84)	<0.001	0.60	<0.001	<0.001
9	23.61 (0.92)	23.62 (0.91)	23.64 (0.90)	0.02	0.19	0.12	0.004
10	23.88 (0.96)	23.89 (0.97)	23.92 (0.97)	0.02	0.89	0.02	0.02
11	24.09 (1.01)	24.11 (1.00)	24.14 (1.03)	0.03	0.51	0.051	0.02
12	24.26 (1.07)	24.32 (1.07)	24.31 (1.05)	0.01	0.004	0.56	0.02
All	23.41 (1.01)	23.45 (1.03)	23.46 (1.03)	<0.001	<0.001	<0.001	<0.001

*From analysis of variance. When overall p-value across 3 years is significant, pairwise comparisons between years were made.

TABLE 4 Multivariable analysis for effect of COVID−19 lockdown on myopia, spherical equivalent and axial length adjusted by age and gender.

Factors	Myopia		Spherical equivalent		Axial length	
	Adjusted relative risk (95%CI)	*P*-value	Adjusted Spherical equivalent (95%CI) in diopters	*P*-value	Adjusted Axial length (95%CI) in mm	*P*-value
Age at myopia screening		<0.001		<0.001		<0.001
6	Ref		Ref		Ref	
7	1.63 (1.59, 1.67)		−0.26 (−0.27, −0.25)		0.34 (0.33, 0.35)	
8	2.31 (2.26, 2.37)		−0.56 (−0.57, −0.54)		0.66 (0.65, 0.67)	
9	2.90 (2.83, 2.97)		−0.86 (−0.88, −0.84)		0.93 (0.92, 0.94)	
10	3.43 (3.35, 3.51)		−1.23 (−1.26, −1.21)		1.20 (1.19, 1.21)	
11	3.82 (3.73, 3.91)		−1.59 (−1.62, −1.57)		1.42 (1.40, 1.43)	
12	4.12 (4.03, 4.22)		−1.99 (−2.02, −1.96)		1.60 (1.58, 1.62)	
Gender		<0.001		<0.001		<0.001
Male	Ref		Ref		Ref	
Female	1.10 (1.09, 1.11)		−0.09 (−0.11, −0.08)		−0.52 (−0.53, −0.50)	
Time		<0.001		<0.001		<0.001
Year 2019	Ref		Ref		Ref	
Year 2020	1.07 (1.06, 1.08)		−0.05 (−0.06, −0.04)		0.01 (0.00, 0.01)	
Year 2021	1.05 (1.04, 1.06)		−0.06 (−0.07, −0.05)		0.03 (0.02, 0.04)	

42.8%, comparing to our study from 45.0 to 48.7% in myopia rate before and during COVID-19 lockdown) (8). (4) The smaller degree of myopic shift in our study during COVID-19 lockdown than other studies may partially be explained by well-implemented school-based eye health education in Qingyang district of Chengdu. A 2-year randomized clinical trial by Li et al. showed school-based family health education was effective in myopia prevention and control (26). Since 2019, large amount of work for promoting myopia-control education has been consistently implemented in Qingyang district. In each school semester, seminars on myopia prevention and control were presented by experts to students, their parents and teachers in Qingyang district. Educational videos, comics, live streaming of famous ophthalmologists/optometrists and other educational materials for promoting myopia prevention and control were also used through social medias (eg., WeChat).

Our study showed the effect of COVID-19 lockdown on students' myopic shift was accompanied with elongation of axial length. We were concerned with the high myopia prevalence in these young students, because early onset of myopia was associated with a higher risk of subsequently developing high myopia (27). Given that children typically progress from hyperopia to emmetropia in ages 5–12 (28), reducing near-work time and increasing time on outdoor activities should be encouraged, especially among lower grade students. A study in Taiwan for promoting outdoor activities among preschoolers showed outdoor activities effectively reduced myopia prevalence from 15.5 in 2014 to 10.3% in 2020 (29). Implementing a myopia prevention program among preschoolers, especially in areas with a high prevalence of myopia early at age 6, should be encouraged.

Limitations

To our knowledge, this study represents one of the largest samples of Chinese students aged 6–12 years with axial length data and provides the first population-based evidence of students' myopia status and progression after the lift of the COVID-19 lockdown. However, this study has limitations. First, our study did not collect any lifestyle data, including near-work and outdoor activities, which limit our interpretation of observed changes in refractive error and axial length. Second, similar to other previous large studies of myopia during the COVID-19 pandemic (3, 4, 8), our refractive error was measured without administration of cyclopegia, which were reported to overestimate myopia prevalence (30). However, this limitation is remedied by the axial length measurement, which was not impacted by the cycloplegia (23). Third, our study was limited to school students aged from 6 to 12 years old, however the age range are most sensitive to the impact from intervention or environmental factors.

Conclusions

In conclusion, this large population-based cross-sectional study across 3 years of before, during, and after COVID-19 lockdown found the COVID-19 outbreak had significant impact on the development of refractive error and axial length of- Southwestern Chinese school students, and its impact remained even 1 year after the COVID-19 lockdown was lifted. Longitudinal studies for following-up with these students impacted by COVID-19 outbreak will help us further understand its long-term effect on refractive error and vision.

Data availability statement

The datasets are not available to the public because confidentiality agreement with the Education Bureau. The study is collaborating with the Qingyang Education Bureau under the Chinese government's initiative on "National Screening and Intervention of Common Diseases and Health Risk Factors in Students 2019". For any potential collaboration, please sent request to the corresponding author Dr. XL (lixiaoning@aierchina.com).

Ethics statement

The studies involving human participants were reviewed and approved by Committee of Research Ethics of the Aier Eye Hospital Group Ethical Committee, Hunan, China (ID:AIER2019IRB05). The nature of the study was explained to the participating children and their parents through the school, and verbal informed consent was obtained from parents before the commencement of the study.

Author contributions

ZY, WL, and XL designed the study. WL, JL, and LZ directed the study's implementation. WP and GY designed the analytical strategy and helped to interpret the findings. WP prepared the draft. All authors helped to review the manuscript.

Funding

This study was funded by The Science and Technology innovation Program of Hunan Province (2019SK2051), Science Research Foundation of Aier Eye Hospital Group (AF2003D7), and Hunan Provincial Natural Science Foundation of China (2019JJ20034).

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.992784/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 22 December 2022
DOI 10.3389/fpubh.2022.1072574

Prevalence of anisometropia and associated factors in Shandong school-aged children

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 17 October 2022
ACCEPTED 30 November 2022
PUBLISHED 22 December 2022

CITATION
Xu Z, Wu Z, Wen Y, Ding M, Sun W, Wang Y, Shao Z, Liu Y, Yu M, Liu G, Hu Y and Bi H (2022) Prevalence of anisometropia and associated factors in Shandong school-aged children. *Front. Public Health* 10:1072574. doi: 10.3389/fpubh.2022.1072574

Objective: To investigate anisometropia's prevalence and associated factors in school-aged children.

Methods: A cross-sectional school-based study was conducted in Shandong Province, China, including children aged 4 to 17 from 9 schools. Anisometropia was defined as the differences between the two eyes in spherical equivalent (SE) or cylinder degree of 1.00 diopter (D) or more [SE or cylindrical (CYL) difference $\geq$ 1.00 D] after cycloplegic autorefraction. The Generalized Linear Model (GLM) was used to analyze the effects of ocular parameters [the differences between eyes in axial length (AL), habitual visual acuity (HVA), and corneal astigmatism (CA)] and lifestyle parameters (time spent indoor near work and outdoor activities) on anisometropia.

Results: Total 4,198 (93.4%) of the 4,494 children were included in the statistical analysis. The mean difference in inter-eye SE was 0.42 $\pm$ 0.61 D. The prevalence of anisometropia was 13.2% (95%CI: 12.1 to 14.2%) (SE anisometropia's prevalence:10.3%; CYL anisometropia's prevalence: 4.1%), increased with older age (OR = 1.10, $P = 0.002$), the worse myopic eye (myopia vs. premyopia, OR = 1.87, $P = 0.002$), the worse hyperopic eye (hyperopia vs. premyopia, OR = 1.77, $P = 0.013$), larger difference in inter-eye AL (0.1–0.3 vs. $\leq$ 0.1, OR = 1.67, $P = 0.008$; >0.3 vs. $\leq$ 0.1, OR = 28.61, $P < 0.001$), HVA (>0.2 vs. $\leq$ 0.2, OR = 3.01, $P < 0.001$), CA (OR = 6.24, $P < 0.001$), the worse stereoacuity (>100 vs. $\leq$ 100, OR = 1.59, $P = 0.001$), longer indoor near work time per day on weekends (4–8 vs. <4, OR = 1.41, $P = 0.038$; $\geq$8 vs. <4, OR = 1.40, $P = 0.131$), and shorter outdoor activity time per day on weekdays ($\geq$1 vs. <1, OR = 0.75, $P = 0.046$) in multivariable analysis. In the SE anisometropia group, the difference in inter-eye AL (>0.3 vs. $\leq$ 0.1, β: 0.556, 95%CI: 0.050 to 1.063), HVA (>0.2 vs. $\leq$ 0.2, β: 0.511, 95%CI: 0.312 to 0.710), and CA (β: 0.488, 95%CI: 0.289 to 0.688), stereoacuity (>100 vs. $\leq$ 100, β: 0.299, 95%CI: 0.110 to 0.488) had a positive impact on the difference in inter-eye SE.

Conclusions: Ocular parameters and lifestyle parameters are associated with the occurrence of anisometropia in children aged 4 to 17 years, including the difference in inter-eye AL, HVA, CA, stereoacuity, indoor near work time, and outdoor activity time. Preventing myopia and early treating anisometropic amblyopia may be effective ways to reduce the prevalence of anisometropia.

KEYWORDS

anisometropia, school-based study, associated factors, myopia, children

Introduction

Anisometropia, a difference in the refractive error between two eyes, is a common cause of poor binocular vision and amblyopia, which is widely popular among all ages. A patient with anisometropia may also have symptoms of diplopia, aniseikonia, and decreased stereoacuity, which might severely affect binocular dysfunction. Anisometropia may cause visual fatigue, difficulty in binocular image fusion, monocular macular central fovea depression, or decreased stereoacuity, which should be paid more attention (1–3).

Both eyes of the individual have the same genetic background and are influenced by the same environment, but they may develop different refractive status due to asymmetric growth. Studies have confirmed that both ocular parameters and lifestyle parameters are closely related to the occurrence of anisometropia (4). However, the etiology and pathogenesis of anisometropia have not been well-studied. The key to reducing its harm remains early detection and control of its further progression (5). Thus in the current study, we aimed to investigate the prevalence of anisometropia in children and assess the impact of potential factors based on a cross-sectional school-based study.

Materials and methods

Study participants

In September 2020, we conducted a cross-sectional study based on a multistage stratified cluster random sampling in Huantai City, Shandong Province, China. Total of 4,494 children from 9 schools (2 kindergartens, 4 primary schools, 2 middle schools, and 1 high school) participated in the survey. Children with eye diseases, such as nystagmus, fundus diseases, and any history of eye surgery, were excluded.

Study examinations

All children underwent examinations at school, including an interview with a standardized questionnaire similar to the one used in the RESC (Refractive Error Study in Children) studies. The questionnaire included basic demographic data such as age, gender, parental refractive status, and lifestyle parameters such as indoor near work time and outdoor activity time.

Firstly, two ophthalmologists performed slit-lamp examinations and fundus examinations for all children before the study, to exclude children with eye diseases that affected this study. All other examinations were performed by professional optometrists, including habitual visual acuity (HVA) at a standard testing distance of 3 meters (#600722, Good-Lite Co., Elgin, IL, USA), non-contact tonometers (Topcon CT80; Topcon Corp., Tokyo, Japan), non-cycloplegic and cycloplegic autorefraction (Nidek ARK-1, CO., LTD, Japan) and Stereoacuity test (Titmus test, described below). Axial length (AL) was acquired using laser interferometry (IOL-Master 500, Carl Zeiss Meditec AG, Jena, Germany), measured 3 times, and the average of readings was calculated. The cycloplegic eye drops used in this study were 1% cyclopentolate hydrochloride Ophthalmic Solution (Alcon, Fort Worth, TX, USA), instilled once every 5 min for a total of 3 times. Then the subjects closed their eyes and rested for 30 min before observing pupil light response and diameter. If the pupillary light reflex disappeared or the pupil diameter was > 6 mm, an autorefractor was performed. If the pupil diameter is < 6 mm, another eye drop was put in. The cycloplegic refraction was acquired 10 min later.

Stereoacuity was assessed by using the Titmus test (Stereo Optical Co., Inc., Chicago, IL, USA). Titmus test ranged from 800 to 40 sec of arc. Wearing polarized glasses, the subjects viewed the fly at a distance of 40 cm and were asked to "pinch" the tip of a wing between the thumb and forefinger. If successful, they were asked to point to the circle that appeared ahead of the plane and seemed to come closer to them. If the subject made one mistake, the previous target was reassessed. If the subject made an accurate judgment on the previous one, we recorded the level of stereopsis. Other detailed examinations have been reported in previous studies (6).

Definition

Spherical equivalent (SE) was defined as the sum of the spherical refractive error plus half of the cylindrical (CYL) refractive error (measured as minus values). SE and CYL anisometropia was defined as the difference in cycloplegic inter-eye SE or cylinder degree≥1.00 D, respectively. The differences in inter-eye SE and CYL were presented in the form of absolute values. According to the International Myopia Institute (IMI) (7), myopia was defined as SE ≤ −0.50 D after cycloplegia. Premyopia was defined as −0.50 D<SE ≤ 0.75 D after cycloplegia, and hyperopia was defined as SE > 0.75 D after cycloplegia. Myopic anisometropia was defined as an unequal amount of myopia in both eyes, and hyperopic anisometropia was defined as an unequal amount of hyperopia in both eyes. The worse eye refers to refractive error of the eye with the highest absolute refractive error. If both eyes had the same SE, the right eye was defined as the worse eye. According to the average of cycloplegic SE [(SE of the right eye + SE of the left eye)/2], the refractive status was divided into five groups, including moderate to high hyperopia (SE>2.00 D), low hyperopia (0.75 D <SE ≤ 2.00 D), premyopia, low myopia (−3.00 D<SE ≤ −0.50 D), and moderate to high myopia (SE ≤ −3.00 D).

Statistical analysis

All data were analyzed using the SPSS 25.0 software (Inc Chicago, IL). Measurement data were given as mean ± standard deviation (M ± SD) and median. Enumeration data were expressed as cases/percentage [N (%)] and 95% confidence interval (CI). Independent-Samples *t*-test was used to compare the differences between groups. Categorical data were analyzed using the Chi-square test for variance and trend test (P_{trend}). Continuous data were tested using polynomial linear correlation in one-way ANOVA for differences between multivariate groups and trend test (P_{trend}). The influencing factor analysis uses Variance Inflation Factor (VIF) diagnostics to diagnose the multicollinearity of independent variables. The Generalized Linear Model (GLM) was used for multivariate analysis of all ocular parameters and lifestyle parameters with statistically significant differences ($P < 0.050$) in univariate analysis and VIF<4. The effect size of the covariates was based on GLM coefficients (β) with a 95% CI. Under a logistic model, odds ratio (OR) and 95% CI were computed to assess associated factors for the prevalence of anisometropia. All *P*-values were 2-sided and were considered statistically significant when the values were < 0.05.

Results

Among 4,494 eligible children who were recruited in the cross-sectional study, 4,198 children [93.4%, 2,123 (50.6%) boys] were finally included in the statistical analysis, and 285 were excluded (283 with non-cycloplegia, 13 with incomplete refraction data). Among them, total of 432 [10.3%, 198 (48.5%) boys] and 172 [4.1%, 98 (56.4%) boys] children were diagnosed with SE and CYL anisometropia, including 51 children (1.2%) were diagnosed with both SE and CYL anisometropia, and 3,645 children (86.8%) were included in the non-anisometropia group. Table 1 shows the distribution of basic demographic and ocular parameters.

The mean difference in inter-eye SE and CYL was 0.42 ± 0.61D (median: 0.25D; range: 0–7.25D) and 0.27 ± 0.32D (median: 0.25D; range: 0–4.75D) among all children. With increasing age, the anisometropia's prevalence gradually increased, and the difference in inter-eye SE gradually widened ($P_{trend} < 0.001$). No significantly different occurrence of anisometropia was found according to gender ($\chi^2 = 1.336$, P>0.050). The results are shown in Figure 1, Table 2. The multivariable logistic regression analysis showed the prevalence increased with older age (OR = 1.10, *P* = 0.002), the worse myopic eye (myopia vs. premyopia, OR = 1.87, *P* = 0.002), the worse hyperopic eye (hyperopia vs. premyopia, OR = 1.77, *P* = 0.013), larger difference in inter-eye AL (0.1–0.3 vs. ≤ 0.1, OR = 1.67, *P* = 0.008; >0.3 vs. ≤ 0.1, OR = 28.61, *P* < 0.001), HVA (>0.2 vs. ≤ 0.2, OR = 3.01, *P* < 0.001), CA (OR = 6.24, *P* < 0.001), the worse stereoacuity (>100 vs. ≤ 100, OR = 1.59, *P* = 0.001), longer indoor near work time per day on weekends (4–8 vs. <4, OR = 1.41, *P* = 0.038; ≥8 vs. <4, OR = 1.40, *P* = 0.131), and shorter outdoor activity time per day on weekdays (≥1 vs. <1, OR = 0.75, *P* = 0.046) (shown in Table 3).

When comparing the difference in inter-eye SE in different refractive statuses among all children, it was found that the difference in inter-eye SE showed a U-shape curve. The difference was greater when in the stage of moderate to high hyperopia and moderate to high myopia. The difference decreased significantly from moderate to high hyperopia until low hyperopia and then showed a continuous upward trend at the premyopia and low myopia. Finally, at the stage of moderate to high myopia, the difference decreased slightly but stabilized ($P_{trend} < 0.001$) (shown in Figure 2).

The multivariate GLM analysis showed ocular parameters and lifestyle parameters with a significant effect on the difference in inter-eye SE among all children (Table 4). The difference in inter-eye AL (0.1–0.3 vs. ≤ 0.1, β: 0.073, 95%CI: 0.004 to 0.106; >0.3 vs. ≤ 0.1, β: 0.931, 95%CI: 0.881 to 0.980), HVA (>0.2 vs. ≤ 0.2, β: 0.465, 95%CI: 0.404 to 0.526), CA (β: 0.155, 95%CI: 0.109 to 0.200), age (β: 0.011, 95%CI: 0.006 to 0.017), stereoacuity (>100 vs. ≤ 100, β: 0.088, 95%CI: 0.056 to 0.121), indoor near work time per day on weekends (≥8 vs. <4, β: 0.056, 95%CI: 0.004 to 0.107) may contribute to a larger difference in inter-eye SE. Additionally, outdoor activity time per day on weekdays (≥1 vs. <1, β: −0.040, 95%CI: −0.072 to −0.008) negatively impacts on it.

In the SE and CYL anisometropia group, the mean difference in inter-eye SE and CYL were 1.82 ± 1.01 D (median: 1.44 D;

TABLE 1 Distribution of characteristics among all children.

Associated factors	Total ($n = 4198$)	SE anisometropia group ($n = 432$)	CYL anisometropia group ($n = 172$)	Non-anisometropia group ($n = 3766$)	P-value[a]	P-value [b]
Age (years)	9.24 ± 3.15	11.98 ± 2.84	10.56 ± 3.52	8.93 ± 3.04	0.000	0.000
Difference in inter-eye SE (D)	0.42 ± 0.61	1.82 ± 1.01	0.99 ± 1.29	0.26 ± 0.22	0.000	0.000
Difference in inter-eye CYL (D)	0.27 ± 0.32	0.44 ± 0.47	1.31 ± 0.54	0.22 ± 0.20	0.000	0.000
Difference in inter-eye CA (D)	0.32 ± 0.33	0.20 ± 0.62	0.94 ± 0.64	0.06 ± 0.42	0.000	0.000
Gender						
Boy	2,123 (50.6%)	198 (45.8%)	97 (56.4%)	1,925 (51.1%)	0.038	0.119
Girl	2,075 (49.4%)	234 (54.2%)	75 (43.6%)	1,841 (48.9%)		
Worse eye refractive status						
Premyopia	1,369 (32.6%)	42 (9.7%)	39 (22.7%)	1,327 (35.2%)	0.000	0.000
Hyperopia	1,285 (30.6%)	57 (13.2%)	33 (19.2%)	1,228 (32.6%)		
Myopia	1,544 (36.8%)	333 (77.1%)	100 (58.1%)	1,211 (32.2%)		
Difference in inter-eye AL (mm)						
≤0.1	2,031 (48.4%)	15 (3.5%)	47 (27.3%)	1,972 (54.1%)	0.000	0.000
0.1–0.3	1,537 (36.6%)	49 (11.3%)	63 (36.6%)	1,433 (39.3%)		
>0.3	626 (14.9%)	367 (85.0%)	62 (36.0%)	237 (6.5%)		
Difference in inter-eye HVA (LogMAR)						
≤0.2	3,885 (92.5%)	281 (65.0%)	138 (80.2%)	3,604 (95.7%)	0.000	0.000
>0.2	313 (7.5%)	151 (35.0%)	34 (19.8%)	162 (4.3%)		
Stereoacuity (arc-s)						
≤100	2,904 (69.2%)	217 (50.2%)	97 (56.4%)	2,687 (71.4%)	0.000	0.000
>100	1,281 (30.5%)	212 (49.2%)	75 (43.6%)	1,069 (28.4%)		

[a]For comparison between SE anisometropia group vs. non-anisometropia group.
[b]For comparison between CYL anisometropia group vs. non-anisometropia group.
SE, Spherical equivalent; CYL, Cylinder; CA, Corneal astigmatism; AL, Axial length; HVA, Habitual visual acuity; D, Diopter; mm, Millimeter.
Due to the lack of cooperation in test, missing data occurred in 4 (0.1%) children for interocular difference in AL, and 13 (0.3%) children in stereoacuity.

range: 1.00–7.25 D) and 1.31 ± 0.54 D (median: 1.00 D; range: 1.00–4.75 D). The distribution is shown in Figure 3. In the SE anisometropia group, using multivariate analysis, the difference in inter-eye AL (>0.3 vs. ≤ 0.1, β: 0.556, 95%CI: 0.050 to 1.063), HVA (>0.2 vs. ≤ 0.2, β: 0.511, 95%CI: 0.312 to 0.710), and CA (β: 0.488, 95%CI: 0.289 to 0.688), stereoacuity (>100 vs. ≤100, β: 0.299, 95%CI: 0.110 to 0.488) had a positive impact on the outcome (shown in Table 5). Mean difference in inter-eye SE was 1.67 ± 0.85 D (median: 1.38 D; range: 1.00–7.25 D) and 1.86 ± 1.09 D (median: 1.38 D; range: 1.00–5.88 D) with a prevalence of 6.8% (286/4198, 95% CI: 6.1 to 7.6%) and 2.3% (98/4198, 95%CI: 1.9 to 2.8%) in myopic and hyperopic anisometropia group. Compared to hyperopic anisometropia (18.4%, 98/553), myopic anisometropia was the most prevalent (51.7%, 286/553).

Discussion

Anisometropia is a type of refractive error and is a common cause of amblyopia that affects binocular vision. However, the etiology and pathogenesis have not been fully clarified. Improving the detection rate of anisometropia and early intervention and treatment are still the key points to reducing its harm. We investigated the prevalence of anisometropia and associated factors in school-aged children. The results showed that ocular parameters and lifestyle parameters were associated to anisometropia. Ocular parameters such as the refractive state of the worse eyes, the difference in inter-eye AL, HVA, CA, and lifestyle parameters such as indoor near work time per day on weekends and outdoor activity time

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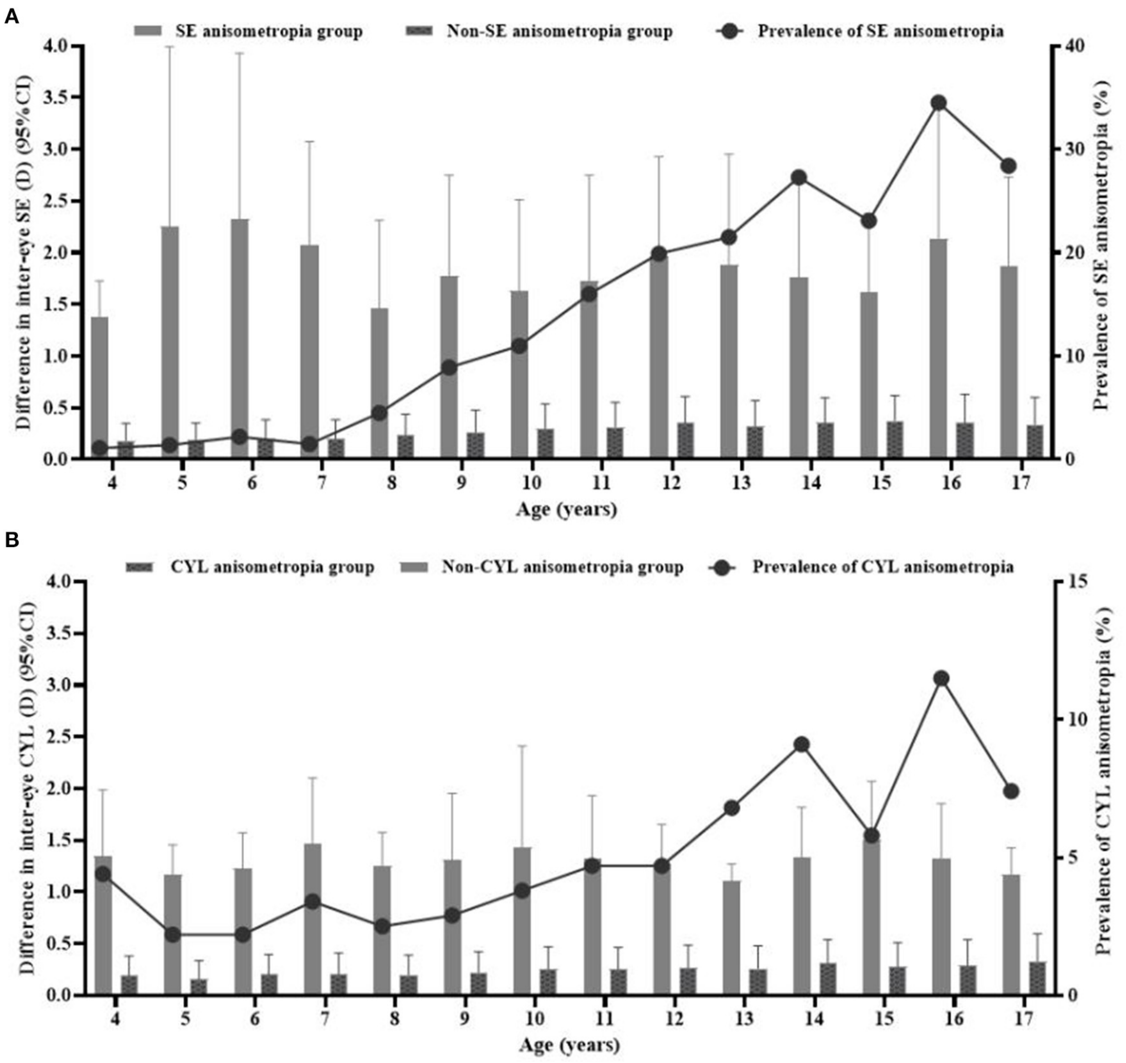

FIGURE 1
Distribution of the difference in inter-eye spherical equivalent (SE) and cylinder (CYL) and prevalence of SE **(A)** and CYL **(B)** anisometropia at different ages. The grey bars represented the difference in inter-eye SE and CYL in the anisometropia and Non-anisometropia groups (corresponding to the left y-axis). The black line represented the prevalence of SE and CYL anisometropia (corresponding to the right y-axis).

per day on weekdays were associated with the occurrence of anisometropia.

The prevalence of anisometropia (difference in inter-eye SE or CYL $\geq$ 1.00 D) was 13.2%, and myopic anisometropia was the most prevalent (51.7%), which was in good agreement with research results in China (4). Since there was no national multi-center large sample study in China, the high prevalence of anisometropia might be related to the high prevalence of myopia, as well as the race, age, and different diagnostic criteria of anisometropia (1). The results showed that the prevalence and severity of anisometropia increased with age. We think it may be caused by the increased burden on children's eyes (8, 9).

Associated factors of anisometropia

We found that anisometropia was more common in hyperopic and myopic children, and more myopic and hyperopic refractive errors in one eye were associated with the occurrence of anisometropia, which has also been validated in other studies (10, 11). The greater difference in the speed of emmetropia and myopia, the greater the possibility of anisometropia, which may be due to the failure of the regulation of the inter-eye homeostatic mechanism (12). It was suggested that preventing myopia and early treating anisometropic amblyopia could be an effective way to reduce the prevalence of anisometropia.

TABLE 2 The prevalence of anisometropia at different age.

Age	Number of children (%)	Number of SE anisometropia children (%)	Difference of inter-eye SE in SE anisometropia group (D)	Cycloplegic SE of the worse eye in SE anisometropia group (D)	Number of CYL anisometropia children (%)	Difference of inter-eye CYL in CYL anisometropia group (D)
4	180 (4.3)	2 (0.5)	0.20 ± 0.21	1.31 ± 0.77	8 (4.4)	0.24 ± 0.33
5	139 (3.3)	2 (0.5)	0.22 ± 0.33	1.13 ± 0.74	3 (2.2)	0.18 ± 0.23
6	556 (13.2)	12 (2.8)	0.25 ± 0.42	1.03 ± 0.72	12 (2.2)	0.22 ± 0.25
7	596 (14.2)	9 (2.1)	0.23 ± 0.31	0.63 ± 1.07	20 (3.4)	0.25 ± 0.33
8	555 (13.2)	25 (5.8)	0.29 ± 0.37	0.17 ± 1.19	14 (2.5)	0.22 ± 0.26
9	450 (10.7)	40 (9.3)	0.40 ± 0.56	−0.02 ± 1.51	13 (2.9)	0.25 ± 0.29
10	372 (8.9)	41 (9.5)	0.45 ± 0.56	−0.73 ± 1.69	14 (3.8)	0.30 ± 0.36
11	319 (7.6)	51 (11.8)	0.54 ± 0.69	−1.06 ± 1.79	15 (4.7)	0.30 ± 0.33
12	301 (7.2)	60 (13.9)	0.68 ± 0.81	−1.61 ± 1.86	14 (4.7)	0.31 ± 0.31
13	205 (4.9)	44 (10.2)	0.66 ± 0.84	−2.24 ± 2.28	14 (6.8)	0.32 ± 0.30
14	253 (6.0)	69 (16.0)	0.74 ± 0.84	−2.90 ± 2.38	23 (9.1)	0.41 ± 0.39
15	104 (2.5)	24 (5.6)	0.66 ± 0.67	−3.45 ± 2.16	6 (5.8)	0.35 ± 0.39
16	87 (2.1)	30 (6.9)	0.97 ± 1.14	−3.72 ± 2.23	10 (11.5)	0.41 ± 0.44
17	81 (1.9)	23 (5.3)	0.78 ± 0.86	−3.92 ± 2.37	6 (7.4)	0.39 ± 0.34
Total	4,198 (100.0)	432 (100.0)	0.42 ± 0.61	−2.02 ± 2.53	172 (100.0)	0.27 ± 0.32
χ^2 (F)		363.457*	(38.491)	(281.513)	31.728*	(10.945)
P-value		0.000*	0.000	0.000	0.000*	0.000

*Results of Chi-square test for trend test (P_{trend}).
SE, Spherical equivalent; CYL, Cylinder; D, Diopter.

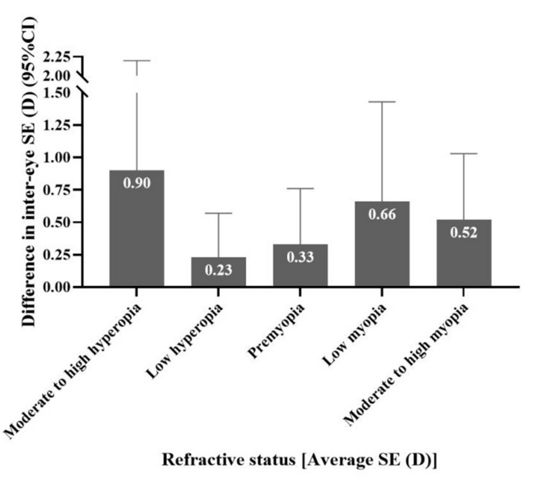

FIGURE 2
The distribution of the difference in inter-eye spherical equivalent (SE) in different refractive states among all children.

The difference in inter-eye AL was associated with the occurrence of anisometropia in our study, which confirmed that the unbalanced development of two eyes was the main reason for anisometropia in the previous study (13). A cross-sectional study (13) found that differences in the growth rate of the AL were the main factors in the development of anisometropia, which validated our conclusion. Astigmatism in children is mainly from corneal astigmatism (CA). The difference in inter-eye CA may be attributed to increased AL and changes in posterior scleral structure affecting the cornea at the limbus (14). The difference in inter-eye CA would lead to the occurrence of anisometropia and the further development of the difference in inter-eye SE. The results showed that the larger difference in inter-eye CA was associated with anisometropia in our study. In other words, if children with differences in inter-eye AL and CA were found, special attention should be paid to the possibility of anisometropia in clinical diagnosis.

In our study, after adjusting the refractive error and difference in inter-eye AL, the difference in inter-eye HVA was strongly associated with anisometropia. HVA was more conducive to visual performance in everyday conditions (either with or without optical correction) (15). The difference in inter-eye HVA≥0.2 logMAR indicated a higher risk of anisometropia. Previous studies also have shown that the severity of anisometropia was positively correlated with visual impairment (16, 17). Retinal image blur and unequal images

TABLE 3 Logistic regression analysis assessing associated factors for the prevalence of anisometropia.

Associated Factors	Number of children	Number of SE anisometropia children (%)	Univariate analysis		Multivariate analysis	
			OR (95%CI)	*P*-value	OR (95%CI)	*P*–value
Age (years)	4,198	553 (13.2%)	1.29 (1.25 to 1.34)	0.000	1.10 (1.03 to 1.16)	0.002
Refractive status of the worse eye						
Premyopia	1,369	78 (5.7%)	Ref.		Ref.	
Hyperopia	1,285	83 (6.5%)	1.28 (0.90 to 1.82)	0.173	1.77 (1.13 to 2.77)	0.013
Myopia	1,544	392 (25.4%)	5.83 (4.38 to 7.76)	0.000	1.87 (1.26 to 2.76)	0.002
Difference in inter-eye AL (mm)						
≤0.1	2,031	59 (2.9%)	Ref.		Ref.	
0.1-0.3	1,537	104 (6.8%)	2.17 (1.52 to 3.10)	0.000	1.67 (1.14 to 2.45)	0.008
>0.3	626	390 (62.3%)	52.40 (37.71 to 72.81)	0.000	28.61 (19.85 to 41.25)	0.000
Difference in inter-eye HVA (LogMAR)						
≤0.2	3,885	387 (10.0%)	Ref.		Ref.	
>0.2	313	166 (53.0%)	10.41 (7.95 to 13.63)	0.000	3.01 (2.08 to 4.35)	0.000
Difference in inter-eye CA (D)	4,198	553 (13.2%)	6.28 (4.78 to 8.25)	0.000	6.24 (4.37 to 8.93)	0.000
Stereoacuity (arc-s)						
≤100	2,904	297 (10.2%)	Ref.		Ref.	
>100	1,281	256 (20.0%)	2.12 (1.73 to 2.58)	0.000	1.59 (1.21 to 2.10)	0.001
Indoor near work time per day on weekends (hours)						
<4	1,856	165 (8.9%)	Ref.		Ref.	
4-8	1,565	228 (14.6%)	1.92 (1.52 to 2.42)	0.000	1.41 (1.02 to 1.94)	0.038
≥8	777	160 (20.6%)	3.27 (2.52 to 4.25)	0.000	1.40 (0.91 to 2.17)	0.131
Outdoor activity time per day on weekdays (hours)						
<1	1,946	302 (15.5%)	Ref.		Ref.	
≥1	2,252	251 (11.1%)	2.09 (1.71 to 2.57)	0.000	0.75 (0.56 to 0.99)	0.046

Multivariable from logistic regression model were adjusted for gender, indoor near work time per day on weekdays (hours) and outdoor activity time per day on weekends (hours).
AL, Axial length; HVA, Habitual visual acuity; CA, Corneal astigmatism; OR, Odds ratio; CI, Confidence interval; D, Diopter; mm, Millimeter; Ref, Reference.
Due to the lack of cooperation in test, missing data occurred in 4 (0.1%) children for interocular difference in AL, and 13 (0.3%) children in stereoacuity.

caused by anisometropia were the main reasons affecting stereoscopic vision (17). Therefore, when these symptoms are found, it is recommended that ophthalmologists and optometrists take measures to intervene in advances, such as eliminating the form deprivation and abnormal interaction between the eyes (eliminating the inhibition of non-amblyopic eyes on amblyopic eyes).

Early intervention in the lifestyle of anisometropia

Goldschmitt (18) speculated that environmental factors might affect the symmetry of binocular refraction. Some etiological studies (9, 19) also found that long time spent in near work was a risk factor for anisometropia. In our study, after adjusting for factors such as age and AL, the larger anisometropia was associated with indoor near work time per day on weekends and outdoor activity time per day on weekdays, which was consistent with our previous findings (4).

When children engaged in near work, such as daily reading and writing, the eyes with more myopic refraction were better to work at a near distance [20]. The difference between inter-eye accommodation demands may provide stimulation for the asymmetric growth of the eyes, which could accelerate the process of myopia in the worse eye, resulting in a larger difference in inter-eye SE and the occurrence of anisometropia. For example, when the working distance was close and

TABLE 4 Multivariate analysis of generalized linear models to estimate the relationship between the difference in inter-eye SE and associated factors among all children ($n = 4,198$).

Associated Factors	Difference in inter-eye SE (D)	Univariate analysis			Multivariate analysis		
		β	95%CI	*P*-value	β	95%CI	*P*-value
Difference in inter-eye AL (mm)							
≤0.1	0.21 ± 0.19	0[a]			0[a]		
0.1–0.3	0.32 ± 0.30	1.119	1.081 to 1.158	0.000	0.073	0.004 to 0.106	0.000
>0.3	1.35 ± 1.06	3.128	2.988 to 3.276	0.000	0.931	0.881 to 0.980	0.000
Difference in inter-eye HVA (LogMAR)							
≤0.2	0.35 ± 0.46	0[a]			0[a]		
>0.2	1.28 ± 1.24	2.585	2.407 to 2.776	0.000	0.465	0.404 to 0.526	0.000
Age (years)	0.42 ± 0.61	1.062	1.056 to 1.069	0.000	0.012	0.005 to 0.019	0.001
Difference in inter-eye CA (D)	0.42 ± 0.61	1.439	1.355 to 1.529	0.000	0.155	0.109 to 0.200	0.000
Stereoacuity (arc-s)							
≤100	0.36 ± 0.47	0[a]			0[a]		
>100	0.56 ± 0.83	1.217	1.165 to 1.271	0.000	0.088	0.056 to 0.121	0.000
Indoor near work time per day on weekends (hours)							
<4	0.35 ± 0.51	0[a]			0[a]		
4–8	0.43 ± 0.60	1.094	1.046 to 1.143	0.000	−0.006	−0.040 to 0.028	0.733
≥8	0.63 ± 0.83	1.337	1.261 to 1.417	0.000	0.056	0.004 to 0.107	0.035
Outdoor activity time per day on weekdays (hours)							
<1	0.48 ± 0.70	0[a]			0[a]		
≥1	0.37 ± 0.53	0.893	0.857 to 0.930	0.000	−0.040	−0.072 to −0.008	0.014

Multivariable from generalized linear models were adjusted for gender, refractive status of the worse eye, indoor near work time per day on weekdays (hours) and outdoor activity time per day on weekends (hours). SE, Spherical equivalent; AL, Axial length; HVA, Habitual visual acuity; CA, Corneal astigmatism; D, Diopter; mm, Millimeter; CI, Confidence interval; 0[a], Reference group.

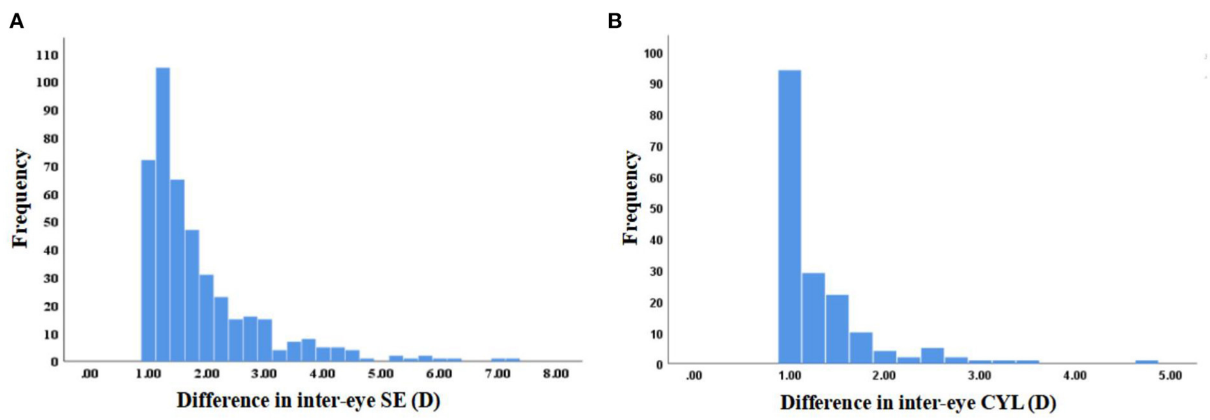

FIGURE 3
Distribution of difference in inter-eye spherical equivalent (SE) and cylinder (CYL) in the SE **(A)** and CYL **(B)** anisometropia group.

the head was tilted, it was assumed that the eyes with lower binocular accommodation requirements had a consistent adaptive response. It might lead to hyperopic defocus in eyes with lower accommodation demand (9). The state of the object image focused on the retina was different. The differences can result in different image quality, which could provide

TABLE 5 Multivariate analysis of generalized linear models to estimate the relationship between the difference in inter-eye SE and ocular or lifestyle parameters among in the SE anisometropia group ($n = 432$).

Associated Factors	Difference in inter-eye SE (D)	Univariate analysis			Multivariate analysis		
		β	95%CI	*P*-value	β	95%CI	*P*-value
Difference in inter-eye AL (mm)							
≤0.1	1.19 ± 0.38	0[a]			0[a]		
0.1–0.3	1.23 ± 0.65	0.013	−0.611 to 0.636	0.968	0.034	−0.538 to 0.606	0.907
>0.3	1.92 ± 1.03	0.689	0.138 to 1.240	0.014	0.556	0.050 to 1.063	0.031
Difference in inter-eye HVA (LogMAR)							
≤0.2	1.61 ± 0.83	0[a]			0[a]		
>0.2	2.21 ± 1.19	0.623	0.414 to 0.833	0.000	0.511	0.312 to 0.710	0.000
Difference in inter-eye CA (D)	1.82 ± 1.01	0.551	0.335 to 0.766	0.000	0.488	0.289 to 0.688	0.000
Stereoacuity (arc-s)							
≤100	1.59 ± 0.82	0[a]			0[a]		
>100	2.05 ± 1.13	0.428	0.224 to 0.632	0.000	0.299	0.110 to 0.488	0.002

Multivariable from generalized linear models were adjusted for the outdoor activity time per day on weekends (hours). AL, Axial length; HVA, Habitual visual acuity; CA, Corneal astigmatism; mm, Millimeter; D, Diopter; CI, Confidence interval; 0[a], Reference group.

stimulation for the occurrence of anisometropia. Thus, indoor near work time and outdoor activity time may be associated with the occurrence of anisometropia. Children's lifestyles are difficult to accurately record, and the evidence related to lifestyle research is not yet clear. Our study is not strong enough to address this issue. The association can be studied in future research.

Strengths of this study included a school-based design which had a relatively large sample size and the availability of multivariate confounding factors adjusted in the model. The subgroup analyses further supported the robustness of the study findings. HVA more accurately reflects children's daily visual state and was included in the discussion of associated factors. In our study, SE and CYL anisometropia were considered, which the latter being disregarded in several studies. Several limitations should also be noted. Firstly, constrained by cross-sectional studies, no causal relationship between associated factors and anisometropia has been demonstrated. Lastly, the collection of outdoor activity time and near work time by self-reported questionnaires inevitably leads to recall bias.

In summary, we found that anisometropia in children aged 4 to 17 was likely the result of a combination of genetic and environmental factors. Preventing the occurrence of myopia and early treating anisometropic amblyopia might help to control the further development of anisometropia. Ophthalmologists and optometrists should pay attention to the changes of difference in inter-eye SE, AL, CA, and HVA, stereoacuity, to identify the current situation of anisometropia and the effect of the intervention. Indoor near work time and outdoor activity time may be associated with the occurrence of anisometropia.

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 the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HB and YH led the overall study, contributed to the research design, and participated in writing the manuscript. ZX, ZW, and YWe contributed to the data collection, data analysis, and manuscript edits. MD, WS, YWa, ZS, and YL collected the epidemiological and clinical data. MY and GL processed statistical data. All authors read, contributed to the research design, and approved the final manuscript.

Funding

This research was supported by the National Key Research and Development Program (2019YFC1710202 and 2019YFC1710203), the Key Research and Development Program of Shandong Province (2019GSF108252), the Project for Specific Diseases Prevention and Control (Integration of Chinese and Western Medicine) of Shandong Province (YXH2019ZXY001), and Health Science and Technology Development Program of Shandong Province (202007020915).

Acknowledgments

We thank the participants of this study, as well as the staff of the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine who made the survey possible.

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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 04 January 2023
DOI 10.3389/fpubh.2022.1068582

TikTok and adolescent vision health: Content and information quality assessment of the top short videos related to myopia

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SPECIALTY SECTION
This article was submitted to Digital Public Health, a section of the journal Frontiers in Public Health

RECEIVED 13 October 2022
ACCEPTED 08 December 2022
PUBLISHED 04 January 2023

CITATION
Ming S, Han J, Li M, Liu Y, Xie K and Lei B (2023) TikTok and adolescent vision health: Content and information quality assessment of the top short videos related to myopia. *Front. Public Health* 10:1068582. doi: 10.3389/fpubh.2022.1068582

Background: Despite the increasing recognition of the public health value of social media platforms, TikTok short videos focusing on adolescent vision health have not received much attention. We aimed to evaluate the content, sources, and information quality of myopia-related videos on TikTok.

Methods: The top 200 most-liked myopia-related videos on the Chinese version of TikTok were queried and screened on March 12, 2022. The descriptive characteristics, contents, and sources of the selected 168 videos were obtained, and their overall quality, reliability, understandability, and actionability were assessed using the validated scoring instruments DISCERN and PEMAT-A/V.

Results: Medical professionals were the main source (45.8%, 77/168) of videos. Misinformation (10.1%, 17/168) was mainly attributable to for-profit organizations (20%, 3/15) and individual non-medical users (31.3%, 10/32). However, their videos enjoyed the highest numbers of "likes," "comments," and "shares" ($P < 0.05$). The mean reliability and overall quality regarding treatment choice were (2.5 ± 0.5) and (3.1 ± 0.9), respectively. Videos on TikTok showed relatively high understandability (84.7%) and moderate actionability (74.9%). Video producers tended to partly or fully provide information regarding management (81.5%, 137/168) and outcome (82.1%, 138/168), and to ignore or only slightly mention content related to definition (86.9%, 146/169) and signs (82.1%, 138/168). The five video sources showed significant differences in the prevalence of misleading information ($P < 0.001$), publication reliability ($P < 0.001$), overall quality ($P = 0.039$), content score ($P = 0.019$), and understandability ($P = 0.024$).

Conclusion: Considering the moderate-to-poor reliability and variable quality across video sources, the substantial myopia-related content on TikTok should be treated with caution. Nevertheless, TikTok videos may serve as a surrogate or supplement for information dissemination if providers can ensure more comprehensive and accurate content.

KEYWORDS

myopia, social media, information quality, misinformation, public health, TikTok

Introduction

Myopia has been commonly recognized as an important adolescent public health issue causing significant disease burden of vision loss (1, 2). The rapid increase in the prevalence of myopia in adolescents and young adults represents a major vision health challenge in East and Southeast Asia (3). The prevalence of myopia in Chinese children and adolescents has increased steadily from 25.7% to 46.1% between 2000 to 2015 (4). Moreover, a recent large-scale study reported that the city-level total prevalence of myopia increased to 73.4% among school-aged children and adolescents (5). Thus, prevention and management of adolescent myopia should be included in the healthcare agenda in severely afflicted counties.

Family management and care play vital roles in myopia prevention and management among children and adolescents (6, 7). Education on myopia and appropriate management of children have been reported to encourage the execution of myopia control interventions by eye care practitioners and parents (8). Recognizing the important role of education in myopia management, the World Health Organization conducted myopia education programs worldwide to facilitate the dissemination of high-quality myopia education and information regarding prevention across countries (9). Nevertheless, a social media platform with high acceptance is urgently required to deliver evidence-based information to the public, especially to adolescents.

TikTok, a short video social media platform, has continued to gain popularity among adolescents and young adults and offers significant potential benefits for public health and medical education (10). TikTok was recently described as a new plausible platform to disseminate public health information in the coronavirus disease 2019 pandemic (11, 12). Despite its promising potential, other studies began to call for attention toward a series of research agenda, such as video content quality and dis/misinformation spread (11). Studies on TikTok video quality related to different diseases have shown inconsistent results (13–15). However, the current status of misinformation prevalence related to the topics of coronavirus disease 2019 (16), prostate cancer (17), and mental health disorders (18) does not indicate an optimistic outlook.

To our knowledge, the quality of online eye-related disease videos has not yet been sufficiently investigated, especially myopia, which is a high-profile topic on TikTok. Thus, to fill this gap in the literature, this study aimed to evaluate the content and quality of myopia-related medical information provided on the TikTok platform.

Abbreviations: PEMAT A/V, Patient Education Materials Assessment Tool for Audiovisual Materials.

Methods

Search strategy and data extraction

On March 12, 2022, the keyword "近 视," which means "myopia," was used to run a search in the search box located on the top of the opening interface of the TikTok App (Chinese version of 20.2.0). Three sort buttons, namely, "overall rank," "most recent," and "most likes" were provided in the search function. We assumed that users would tend to view videos with more likes; therefore, the "most likes" ranking algorithm was chosen to sort the retrieved 423 videos. Among these, videos ranked beyond 200 were less likely to be originated by the publisher and less likely to be viewed by users. Thus, only the top 200 most-liked videos were included for further eligibility evaluation. After removing unrelated, duplicated videos and those with no audio or text, we finally obtained 168 videos for data extraction and analysis (Figure 1).

Primary baseline characteristics were extracted for each video and saved in Excel format. Information included the rank on the initial TikTok search, uniform resource locator, introduction of the uploader, posted dates, length and description of each video, and the number of saves/likes/shares/comments received.

Video source coding

Based on the authors' verification and the information provided in the video introduction, the videos were categorized into those generated by individual users and organizational users. The individual users were further categorized as medical and non-medical users. Medical users included health professionals who were verified as hospital physicians by TikTok or described themselves as health workers. Non-medical individual users were mainly general users or individual science communicators who disseminated their opinions on myopia. Organizational users included non-profit users (e.g., academic institutions, governmental accounts), for-profit users (e.g., optical shops or private sector organizations), and news agencies (19).

Evaluation methodology

The DISCERN tool (20) and the Patient Education Materials Assessment Tool for Audiovisual Materials (PEMAT-A/V) (21) were applied for assessing video quality. The DISCERN contains 16 question items covering three aspects—reliability (8 items), the information quality about treatment choice (7 items), and the overall rating (1 items)—of the video, which are rated according to the question items. Each question is scored from 1 to 5 (question being not at all, or partially or completely

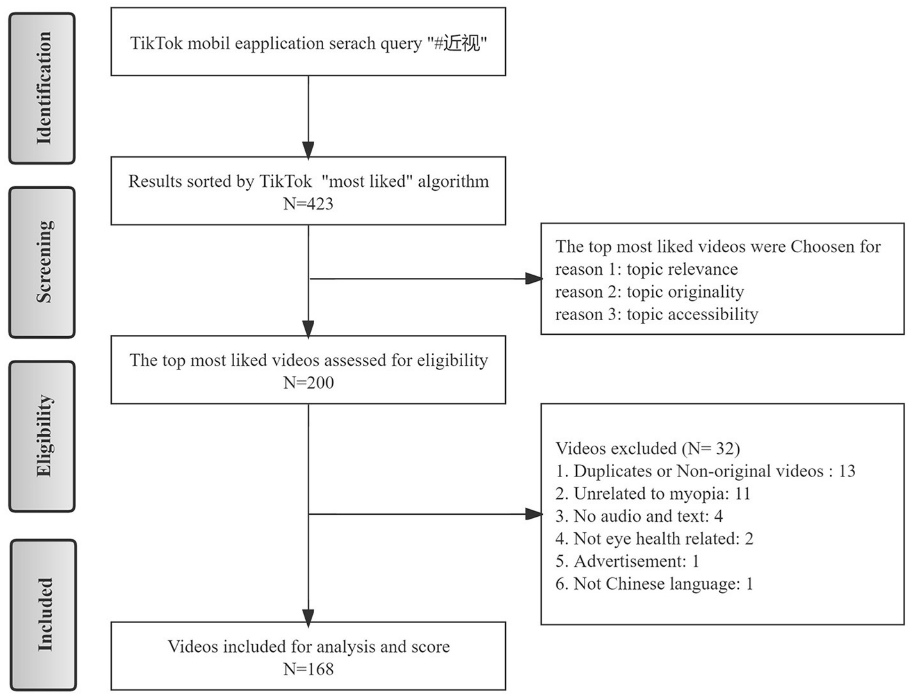

FIGURE 1
The flow chart of the inclusion method of the retrived tiktok videos.

answered in the video). PEMAT-A/V is a validated instrument to assess the understandability (13 items) and actionability (4 items) of audiovisual patient education. Questions are scored on a 0–1 scale that reflects disagree and agree, respectively. The final score (%) is equal to "Total points/Total possible points × 100%."

According to the instructions, self-care is considered a form of treatment throughout the DISCERN "treatment choice" section. Therefore, we judged myopia prevention measures (more outdoor activities or less short-distance eye use, etc.) as treatment choices to avoid underestimation of the score.

We also assessed video content quality focusing on misleading information and information coverage about myopia. Content was evaluated using a predefined scoring system based on works published by the International Myopia Institute in 2019 or 2021 (22–25), which were also the standards for characterizing misleading information. Myopia video content was classified into six aspects, namely, definition, symptoms, risk factors, evaluation, management, and outcomes of myopia (see Supplementary Table 1) (19). The updated International Myopia Institute 2021 yearly digest was the main reference that represented the newest views of peer reviews (22). Diagnostic and risk content was compared with the 2019 IMI definition report and the 2021 risk factors guideline (23, 24), and management was compared with the 2019 IMI white paper on myopia clinical management guideline (25). Each aspect was scored based on a three-item scale, with a score of 0 indicating "not even addressed," 1 indicating "partially addressed," and 2 indicating "sufficiently addressed." Considering some aspects involved several criteria, we defined "sufficient" when ≥3 criteria were addressed in the video.

The evaluations were performed by one ophthalmologist and one eye public health physician independently (XK and MS), based on the official handbooks. Two raters came to a consensus in understanding these constructions from beginning. The raters were only allowed to see the videos during the evaluation process. Video authors' information and classification were concealed to avoid selection bias. The intraclass correlation coefficient of the total DISCERN score between the two raters was 0.957 (0.931–0.972, $P < 0.001$). Discrepancies, if any, were resolved by discussion.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 19.0 software. Data were described as frequency (percentage, %), mean (standard deviation, SD), or median (inter-quartile range, IQR), as appropriate. The kappa statistic and intraclass correlation coefficient were calculated to appraise inter-rater reliability for the source video classification and the total DISCERN score. Score differences among video source categories were tested using one-way analysis of variance coupled with the LSD-t test for the *post-hoc* test, or the Kruskal–Wallis H test followed by Bonferroni's correction on the basis of the variables' characteristics. Misleading prevalence differences related to two or more groups were tested with Chi-square test or Fisher's exact test. Pearson or Spearman rank correlation were used to explore the association of variables of content with DISCERN scores. A $P < 0.05$ was considered significant.

Results

Basic video characteristics

In this study, the included 168 myopia videos gathered 2,246,062 likes, 101,582 comments, and 352,365 shares after being posted for a median of 230 (164–307) days on TikTok. The videos were mainly posted by individual users (109/168, 64.9%), especially by medical professionals (77/168, 45.8%). The agreement between the raters on the source classification was 93.5%, with a kappa of 0.906 ($P < 0.001$). The median video length was 60 s, of which videos uploaded by medical professions was shortest, only 49 s. Video posted by for-profit organizations and non-medical users had higher user interactions of likes, comments, and shares ($P < 0.05$). The detail characteristics by the different sources were described in Table 1.

Prevalence of misinformation

A total of 19 descriptions were determined as misinformation in 17 videos. The total crude prevalence was 10.1% (17/168), and the prevalence of misinformation differed significantly among the five subgroups ($P < 0.001$). For-profit organizations (20%, 3/15) and individual non-medical users (31.3%, 10/32) were the main sources of misinformation. They tended to deliver some absolute descriptions or use terminology that was not sufficiently rigorous in their videos (see Table 2).

Information quality

The full descriptive characteristics of different sources and *post-hoc* analysis are shown in Tables 3, 4. Publication reliability was evaluated by DISCERN items 1–8. The total and mean reliability score were (19.8 ± 4.4) and (2.5 ± 0.5), respectively. Organizational users showed higher reliability than individual users ($P = 0.001$). Non-profit organizations and news agencies published videos with higher reliability than for-profit organizations and non-medical and medical individuals. The information quality of treatment choices was assessed by DISCERN items 9–15. A total of 107 (63.7%) videos provided

TABLE 1 Basic characteristics by the source of videos.

Source of videos	Subgroup	*N* (%)	Length (Sec)* Median (IQR)	Days posted* Median (IQR)	*N* of likes* Median (IQR)	*N* of comments* Median (IQR)	*N* of shares Median (IQR)	*N* of saves* Median (IQR)
Organizational user	Non-profit	32 (19.1)	50 (33–89)	228 (176–276)	1,049 (553–4,621)	18 (6–70)	243 (98–616)	52 (26–115)
	For-profit	15 (8.9)	104 (73–182)	259 (160–427)	3,659 (2,204–23,537)	223 (38–943)	647 (69–5,317)	274 (23–3,966)
	News agencies	12 (7.1)	83 (46–149)	314 (223–494)	549 (271–29,114)	25 (3–1,042)	659 (13–4,276)	98 (11–717)
Individual user	Non-medical	32 (19.1)	59 (42–143)	239 (189–441)	9,715 (1,469–30,397)	107 (60–1,533)	433 (120–4,086)	228 (31–980)
	Medical	77 (45.8)	49 (34–75)	213 (106–260)	864 (373–2,371)	65 (23–177)	172 (74–547)	67 (25–141)
Overall		168 (100)	60 (35–90)	230 (164–307)	1,554 (530–5,096)	69 (20–230)	243 (91–903)	73 (27–239)

*Characteristics were significantly different in the five source subgroups. IQR, interquartile range.

TABLE 2 Misinformation categorized by video numbers.

Video series number	*N*	Descriptions that were not accurate or sufficiently rigorous
14, 17	2	Too absolute: artificial light, other than asthenopia, causes myopia
22	1	All refractive surgeries cause thinning of the cornea
25, 160, 172	3	Myopia can cause hearing loss
28, 32	2	Myopia other than asthenopia can be alleviated
32	1	Too absolute: no eyedrops (without excluding atropine) are helpful for myopia
44	1	Myopia is recoverable
55, 57, 95	3	Sweet food or sodas cause myopia as being introduced in the whole video
72	1	The axial lengths, other than the diopter, that determines the definition of high myopia
96	1	The author refused to believe the fact of myopia irreversibility
104	1	Median myopia (−3.00 to −6.00 D) can recover to emmetropia with preventive methods.
105	1	The reason for myopia is an excessively thick crystalline lens
141	2	(1) Incorrect figures. (2) Correct vision care habit is the only preventive method for myopia

treatment choice information. The total and mean treatment choice score were 17.2 ± 4.1 and 2.5 ± 0.6, respectively. Although non-profit organization users received the highest score, the five subgroups showed no significant differences ($P = 0.073$). Item 16 of the DISCERN tool provided an overall quality score to each video that involved treatment choice. Overall, the score showed a moderate quality score of 3.1 ± 0.9. The mean DISCERN score for each item is shown in Figure 2. Non-profit organization users and medical individual users published higher-quality videos than non-medical individual users ($P = 0.010$ and 0.018).

This sample showed relatively high understandability (84.7%) and moderate actionability (74.9%) as assessed by the PEMAT-A/V tool. Moreover, the understandability of videos produced by non-profit organizations (89.3%) was higher than that produced by for-profit organizations (89.3% vs. 81.2%, $P = 0.025$) and non-medical individuals (89.3% vs. 80.8%, $P = 0.003$).

Video content

Figure 3 shows the degree to which each video addresses six predefined content areas (0 = no, 1 = partly, 2 = fully). More than 80% of the videos partly or fully addressed information regarding "management" (81.5%, 137/168) and "outcomes" (82.1%, 138/168) of myopia. Moreover, 60.1% (101/168) of the videos fully addressed the "management" area. However, for the "definition" area, the proportion of "not even addressed" was high (76.8%, 129/168) (see Figure 3). Overall, more than half (54.8%, 92/168) of the videos addressed 3–4 contents, and only 12.5% (21/168) of the videos addressed 5–6 contents (see Table 3).

The total myopia video content scores were different both between the two main groups ($P = 0.001$) and in the five subgroups ($P = 0.019$). Medical individual users received the lowest (4.5 ± 1.6) content score and had lower scores than non-profit ($P = 0.005$) and profit organizational users ($P = 0.013$) (see Table 4). The total content score was positively associated with DISCERN quality variables of reliability ($r = 0.490$, $P < 0.001$), treatment choice ($r = 0.455$, $P < 0.001$), overall quality ($r = 0.406$, $P < 0.001$), and the DISCERN total score ($r = 0.537$, $P < 0.001$) (see Figure 4).

Discussion

Considering the existing barriers to promoting child and adolescent vision health in families (6), popular social media apps like TikTok can be easily accessed by parents and young people to receive myopia information. Some previous studies have evaluated adolescent health issues related to TikTok, such as social media addiction (26), vaping content (27), mental health/disorder among adolescents (28, 29), and pediatric urology (30). However, TikTok videos on adolescent vision health have been seldom evaluated. Our study is the first to describe the content and assessed information quality of short, easy-to-view myopia videos available on TikTok.

TikTok as a source of health information

The fact that these videos amassed ∼ 2.25 million likes and 102,000 comments in <1 year highlighted the potential of TikTok as a source of vision health information for adolescent and their parents. However, in comparison with non-medical individuals and for-profit organizations,

TABLE 3 Videos content and quality scores by source.

Variable	Overall (n = 168)	Organization users			Individual users		P_1 value	P_2 value
		Non-profit (n = 32)	For-profit (n = 15)	News agencies (n = 12)	Non-medical (n = 32)	Medical (n = 77)		
Misinformation, n (%)	17 (10.1)	1 (3.1)	3 (20.0)	0 (0)	10 (31.3)	3 (3.9)	0.423	<0.001
DISCERN total scores (/80), mean (SD)	38.2 (7.6)	41.4 (6.6)	36.7 (11.0)	40.3 (5.9)	35.1 (8.5)	37.8 (7.0)	0.051	0.094
Publication reliability (n = 168), mean (SD)	19.8 (4.4)	22.1 (3.4)	18.9 (5.9)	22.3 (3.0)	17.6 (4.6)	19.5 (3.9)	0.001	<0.001
Treatment choice (n = 107), mean (SD)	17.2 (4.1)	19.0 (3.8)	15.9 (5.1)	16.6 (4.2)	15.5 (4.8)	17.4 (3.5)	0.303	0.073
Overall quality score (n = 107), mean (SD)	3.1 (0.9)	3.4 (0.7)	2.7 (1.1)	3.0 (1.1)	2.7 (1.0)	3.3 (0.9)	0.786	0.039
Low, n (%)	27 (25.2)	3 (13.6)	4 (44.4)	2 (25.0)	8 (47.1)	10 (19.6)	0.490	0.046
Moderate, n (%)	41 (38.3)	7 (31.8)	4 (44.4)	3 (37.5)	5 (29.4)	22 (43.1)		
High, n (%)	39 (36.4)	12 (54.5)	1 (11.1)	3 (37.5)	4 (23.5)	19 (37.3)		
PEMAT-A/V understandability, mean (SD)	84.7% (11.7%)	89.3% (10.9%)	81.2% (13.7%)	88.4% (12.4%)	80.8% (12.5%)	84.4% (10.6%)	0.050	0.024
PEMAT-A/V actionability, mean (SD)	74.9% (38.0%)	86.7% (26.4%)	73.3% (40.2%)	69.4% (43.7%)	63.8% (41.8%)	75.8% (38.5%)	0.220	0.189
Total content (/30), Mean (SD)	4.9 (2.0)	5.6 (2.2)	5.8 (2.3)	5.1 (1.7)	4.7 (2.2)	4.5 (1.6)	0.001	0.019
Reported 1–2 contents, n (%)	55 (32.7)	8 (14.5)	3 (5.5)	2 (3.6)	11 (20.0)	31 (56.4)	0.007	0.050
Reported 3–4 contents, n (%)	92 (54.8)	17 (18.5)	8 (8.7)	9 (9.8)	15 (16.3)	43 (46.7)		
Reported 5–6 contents, n (%)	21 (12.5)	7 (33.3)	4 (19.0)	1 (4.8)	6 (28.6)	3 (14.3)		

P_1 represented the significance of the difference between organization users and individual users. P_2 represented the overall significance of the difference in five subgroups. SD, standard deviation.

10.3389/fpubh.2022.1068582

TABLE 4 The *post-hoc* analysis for exploring the underlying differences between video sources.

	Sources	Non-profit	Profit	News agencies	Non-medical	Medical
Overall quality and publication reliability	Non-profit	—	**0.040**	0.274	**0.010**	0.504
	For-Profit	**0.012**	—	0.448	0.958	**0.074**
	News agencies	0.881	**0.031**	—	0.363	0.459
	Non-medical	**<0.001**	0.312	**0.001**	—	**0.018**
	Medical	**0.003**	0.574	**0.029**	**0.025**	—
Understandability and total content score	Non-profit	—	**0.025**	0.825	**0.003**	**0.044**
	For-profit	0.730	—	0.105	0.912	0.323
	News agencies	0.429	0.332	—	0.051	0.259
	Non-medical	0.068	0.071	0.572	—	0.137
	Medical	**0.005**	**0.013**	0.289	0.510	—

Overall quality and understandability were light gray highlighted; Publication Reliability and Total content score were dark gray highlighted. Bold values means the significant differences were found between each pairs of subgroups ($P < 0.05$).

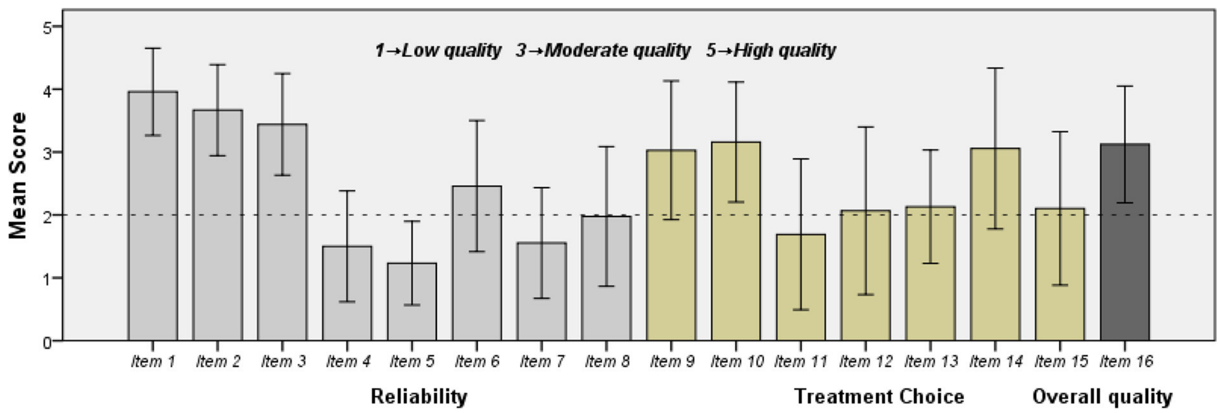

FIGURE 2
The mean DISCERN score for each item. Error bars: +/− 1 SD (standard devision). Item 1. Clear aims. Item 2. Achieves aims. Item 3. Relevant. Item 4. Clear sources of information. Item 5. Clear date of publication. Item 6. Unbiased. Item 7. Provides additional sources. Item 8. Describes areas of uncertainty. Item 9. Describes mechanism of action for treatment. Item 10. Describes benefites of treatment. Item 11. Describers risks of treatment. Item 12. Describes what would happen without treatment. Item 13. Describes how treatment would affect life quality. Item 14. Deacribes alternative treatment. Item 15. Supports shared decision making. Item 16. Overall quality regarding treatment choices.

credible medical professionals who contributed to most of the myopia videos (45.8%) received the fewest likes, comments, shares, and saves. One possible explanation might be the poorly designed forms of expression in these videos (15). Most ophthalmologists uploaded videos in a lecture-like narrative form or even videos of casual dialogue during medical activities. This form of expression, which was less vivid and lacked design, was less likely to gain popularity. As the main source of myopia-related videos, health professionals should aim to create attractive educational videos, for example, by adding trending hashtags and background sounds (31), using rich supplementary visuals (lively images or realistic figures) (32), and enhancing well-organized communication skills to increase the interaction with viewers.

Misinformation

A few previous studies have reported the prevalence of misinformation in TikTok videos, with the prevalence largely varying from 10.6% to 77.8% for various health conditions, including genitourinary cancers (36.1%, $n = 61$) prostate cancer (41.2%, $n = 17$) (17), attention-deficit/hyperactivity disorder (52%, $n = 100$) (18), mask use during the coronavirus disease-19 pandemic (10.6%, $n = 75$), (16) and pediatric urological disease (77.8%, $n = 27$) (33). The low prevalence of 10.1% identified in the present study could be attributed to the following reasons. First, most of the myopia videos (65%) were sourced from board-certified optometrists or ophthalmologists or non-profit organizations, which had the least possibility of spreading misleading information (18). Second, based on the inclusion

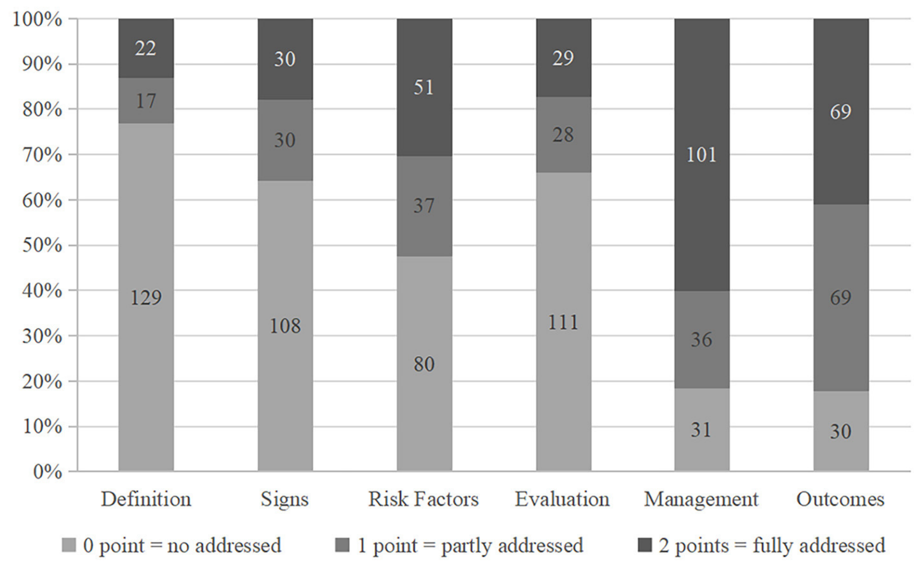

FIGURE 3
The proportion of videos addressing each content of myopia.

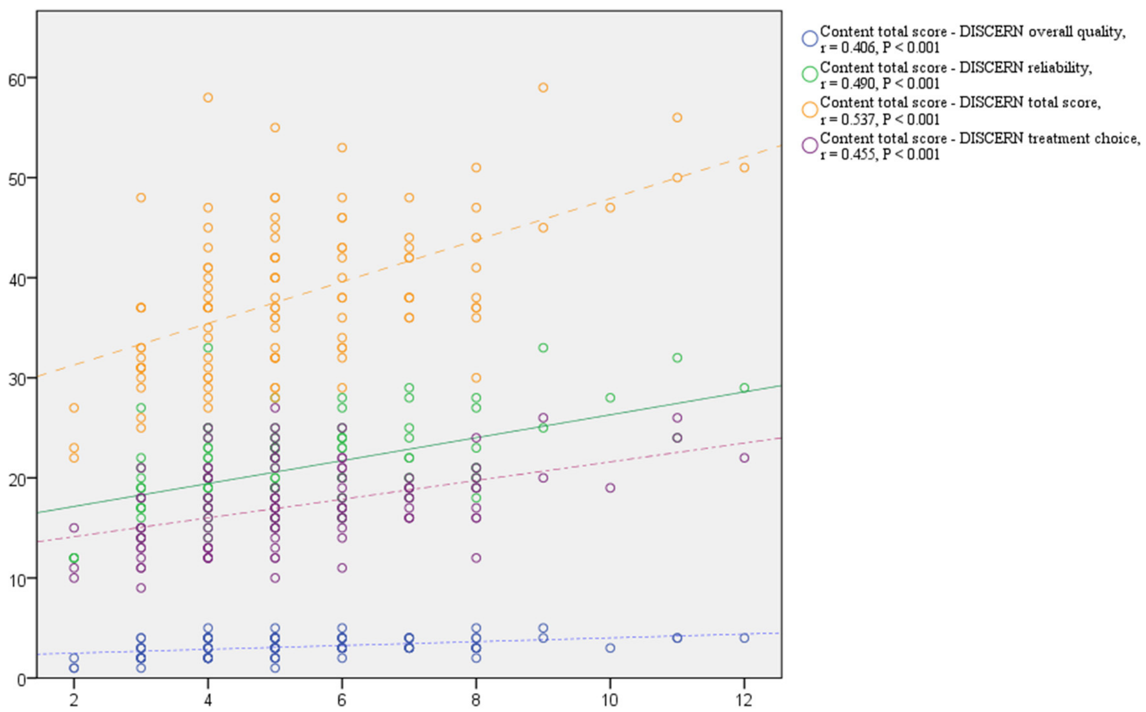

FIGURE 4
Scatter plot of DISCERN scores and content score. r, coefficient of pearson product-moment correlation.

criteria, we chose scientific educational videos that tended to contain less misinformation with high quality (34, 35). Third, information that slightly deviated from IMI standards, such as that related to eye exercises or myopia classification, was not determined to be misinformation in line with people's habits.

Although the misinformation identified in myopia-related TikTok videos was not too much and not dangerous, efforts are still needed to stop misinformation spread by for-profit organizations and individual non-medical users, since these sources published videos with higher levels of user interaction in the form of likes, comments, and shares and unfortunately contained more misinformation as well. Therefore, we strongly suggest video producers to update their knowledge according to the latest guidelines or consensus published by trusted authorities. Myopia yearly digests being published every 2 years by IMI, could be good references.

Content of myopia-related TikTok videos

More than two-thirds of the videos referred to at least three of the six contents. The majority (>80%) of myopia videos partly or fully addressed the "management" and "outcomes" content. In comparison, "definition" and "sign" content was ignored or only slightly discussed in most videos (>80%). This imbalance has been reported in diabetes and genitourinary cancer-related disease (13, 15). The results also highlighted the challenge in providing full-content information in a 60-s TikTok video. Among the videos prepared by medical professionals, 56.4% only reported 1–2 contents. Information providers were more likely to advise viewers on preventing and controlling myopia instead of emphasizing the definition of myopia and its symptoms. Since the "sign" content (especially for high myopia) is far more complex than the general public knowledge level, videos with more comprehensive educational content are still urgently needed. Thus, medical professionals should aim to refine their video content by highlighting the complexity of myopia and the importance of early regular evaluations by an optometrist or ophthalmologist.

Quality of myopia-related TikTok videos

Similar to the findings for most other topics, (15, 17, 32, 34–36) myopia-related TikTok videos had moderate-to-low quality in our study. The low reliability and poor treatment choice score might be explained by the poor DISCERN scores for items 4, 5, 7, and 11 (as shown in Figure 2), which implied that information providers rarely reported references to the sources used as evidence. Without clear sources and publication dates of the information, it was difficult to guarantee good reliability, even if the educational aims were clear and highly achieved. The risks or side effects were also largely ignored when treatment choices were suggested to the public. Video producers should aim to fill these gaps to ensure dissemination of evidence-based information to parents and adolescents.

Moreover, information quality varied across video sources. Non-profit organization published videos with the highest reliability and overall quality. In comparison, videos from non-medical individuals scored the lowest. Medical individuals have a natural advantage in propagating accurate educational information. However, their videos were unreliable without reporting the information sources. These results provided important insights for utilizing TikTok as a platform for vision health communication among adolescents and young people. Medical practitioners should strengthen their cooperation with non-profit organization and news agencies to better deliver educational information with high quality. Nevertheless, adolescents and parents should exercise caution while viewing videos uploaded by non-medical individuals or for-profit organizations.

The PEMAT-A/V score of 85% for understandability was relatively high. This suggested that most of the video content was presented in an understandable manner. A score of 75% for actionability was also higher than those for mental disorder (18) and prostate cancer videos (17). This might be explained by the high proportion (>80%) of "management" content addressed in myopia-related videos. These videos were likely to provide suggestions to parents and adolescents about actions for myopia prevention.

Limitations

First, we chose the top "liked" videos with high popularity as the analysis sample, since videos with higher "likes" implicitly attract more attention. However, this was based on the assumption that viewers sorted the TikTok algorithm-recommended videos by the "most liked" label before watching the content, which might be not completely representative. The public still might directly browse the default TikTok searching list without performing other operations. Therefore, we will apply this sample-selection strategy in future studies. Second, based on the nature of cross-sectional studies, the current results only represented the condition at the time point when we captured the sample, but these results will vary over time on a dynamic platform like TikTok. Thirdly, although the DISCERN tool has been previously applied for analysis of the quality of Youtube (19), Twitter, and TikTok videos, this tool was mainly developed for written material. In our final analysis, the strong positive associations with content measures ascertained its reasonable use for TikTok videos. Finally, all videos in the Chinese version of TikTok were presented in Mandarin, precluding analysis of videos in English and other languages, which could undermine the external validity of this study. Despite these limitations, as the first quality assessment of TikTok myopia-related videos, our study still provides first-hand information on this topic.

Conclusion

Myopia-related TikTok videos with high interactivity and a low prevalence of misinformation could be a surrogate or supplement for medical information outreach. However, the most popular videos on the platform were not sourced from mainstream medical professionals. Considering the moderate-to-low reliability and variable quality across video sources, parents and adolescents should exercise caution while reviewing the large body of myopia-related information on TikTok. Video providers, especially medical professionals, are responsible for creating more comprehensive and accurate content to satisfy public information requirements.

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 authors.

Author contributions

SM designed the study and drafted the manuscript. SM, JH, and KX collected all relevant data and assisted in results interpretation. SM and ML carried out data analysis. BL conceived the study. YL, KX, and BL participated in the design and coordination. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by (1) Henan Province Key Research and Development and Promotion Special Project (212102311013) and (2) Medical Science and Technology Tackling Plan of Henan Province (LHGJ20210078).

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1068582/full#supplementary-material

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frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 06 January 2023
DOI 10.3389/fped.2022.1057863

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 30 September 2022
ACCEPTED 14 December 2022
PUBLISHED 06 January 2023

CITATION
Fang J, Zheng Y, Mou H, Shi M, Yu W and Du C (2023) Machine learning for predicting the treatment effect of orthokeratology in children. Front. Pediatr. 10:1057863.
doi: 10.3389/fped.2022.1057863

Machine learning for predicting the treatment effect of orthokeratology in children

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Purpose: Myopia treatment using orthokeratology (ortho-k) slows myopia progression. However, it is not equally effective in all patients. We aimed to predict the treatment effect of ortho-k using a machine-learning-assisted (ML) prediction model.
Methods: Of the 119 patients who started ortho-k treatment between January 1, 2019, and January 1, 2022, 91 met the inclusion criteria and were included in the model. Ocular parameters and clinical characteristics were collected. A logistic regression model with least absolute shrinkage and selection operator regression was used to select factors associated with the treatment effect.
Results: Age, baseline axial length, pupil diameter, lens wearing time, time spent outdoors, time spent on near work, white-to-white distance, anterior corneal flat keratometry, and posterior corneal astigmatism were selected in the model (aera under curve: 0.949). The decision curve analysis showed beneficial effects. The C-statistic of the predictive model was 0.821 (95% CI: 0.815, 0.827).
Conclusion: Ocular parameters and clinical characteristics were used to predict the treatment effect of ortho-k. This ML-assisted model may assist ophthalmologists in making clinical decisions for patients, improving myopia control, and predicting the clinical effect of ortho-k treatment *via* a retrospective non-intervention trial.

KEYWORDS

myopia, myopia control, orthokeratology, logistic regression model, nomogram, machine learning, artificial intelligence

Introduction

Myopia has emerged as a major public health issue worldwide (1), with a higher prevalence in East Asia than in Europe and America. The condition may underlie several vision-threatening diseases such as cataract, glaucoma, retinal detachment, chorioretinal atrophy, and maculopathy, especially in high and pathological myopia (2, 3). Consequently, both optical and pharmacological treatments are vital for inhibiting axial elongation, thus decreasing potential complications. Orthokeratology (ortho-k) is popular in China due to its efficiency in controlling myopia in children, which is only second to muscarinic antagonists (4). However, the effect of ortho-k varies from child to child due to factors such as age, sex, axial length (AL), refractive error, ocular components, pupil diameters, and lens wearing time, among others (5).

Although a few studies have reported the predictive quality of these baseline factors (5, 6), it is still unclear which factors are more accountable in estimating the long-term outcome of ortho-k treatments in children. A previous study has tried to predict the specific AL increase after wearing ortho-k, but there is no specific model to predict the efficacy of ortho-k (7).

This study, therefore, aimed to identify the characteristics and ocular components available to clinicians before the initiation of ortho-k. This information was used to construct a machine-learning (ML) -assisted (a subset of artificial intelligence) prediction model for the effects of ortho-k treatment.

Methods

Study design

This was a retrospective clinical trial conducted in The First Affiliated Hospital of the Medical College of Zhejiang University, based on patient records. Logistic regression prediction modeling, decision curve analysis, and receiver operating characteristic (ROC) were used to provide guidance for the evaluation of clinical treatment effects.

The study was conducted in conformance with the Declaration of Helsinki, and the study protocol was approved before initiation by the institutional review board of The First Affiliated Hospital of Medical College of Zhejiang University (IIT20220037B-R2).

Participants

We collected the data of minor patients ($n = 119$) who received ortho-k treatment between January 1, 2019, and January 1, 2022, according to the study protocol. The exclusion criteria were: previous use of myopia treatments other than ortho-k; having a chronic disease, tumor, or injury after the treatment with ortho-k; and parents unwilling to take a telephone survey.

Of the study population, five patients used other treatments, four patients discontinued ortho-k treatment, 10 patients were excluded due to follow-ups shorter than 3 months, and nine patients did not adhere to the follow-up (**Figure 1**). The minimum follow-up period among the remaining 91 patients who met the inclusion criteria was 3 months. Optometry and lens fitting were performed by the same doctor.

Clinical data measurement

All clinical data were obtained with the high-resolution rotating Scheimpflug camera system for anterior segment analysis (Pentacam® HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). Calibration frequency is every 2 years of use or every 25,000 times of uses, whichever is earlier. This analysis was conducted by the same physician in a dark room. The measurement was performed three times for each patient, and the average value was retrieved for analysis. AL measurements were performed by OA2000 (Tomey, Nagoya, Japan). Cycloplegia was then induced with 1–2 drops of Compound tropicamide (0.5% tropicamide plus 0.5% phenylephrine hydrochloride; Tianjin Kingyork Group Hebei Univision Pharmaceutical Co., Ltd., Hebei, China) instilled every 5 min over a 20-min period. Cycloplegic refraction was performed 45 min later by autorefraction (Nidek ARK-1, Nidek Co., Ltd., Aichi, Japan).

Lenses

Three ortho-k brands were used in this study: Paragon corneal refractive therapy (CRT) (Paragon CRT, Paragon, Gilbert, AZ, United States); Dream Vision IV-DF (Dream Vision, Ovctek, Zhejiang, Anhui, China); and Alpha ORTHO-K (Alpha Orthokeratology, Alpha Corporation, Nagoya, Japan). CRT is made of paflufocon D (DK 100×10^{-11} [cm^2/s]/[ml O_2/ml × mmHg]) (ISO). Dream Vision is made of Boston XOP material with oxygen permeability of 100×10^{-11} (cm^2/s)/(ml O_2/ml × mmHg). Alpha ORTHO-K is made of Boston EM material with oxygen permeability of 104×10^{-11} (cm^2/s)/(ml O_2/ml × mmHg) (ISO). Lens fitting was performed according to the manufacturer's protocols based on corneal topography, cycloplegic refraction, and manifest refraction. Every patient wore trial lenses. They were observed under a slit lamp to ensure that the correct centration and refractive outcomes were achieved. The ordered lenses were dispensed to patients after 2–3 weeks, and patients were asked to return for follow up visits on the first day, first week, second week, first month, second month, and every 2–3 months thereafter. Every patient had corresponding complimentary lenses, solutions, and accessories to facilitate replacement in case of damage.

Variables, outcome measures, information source

The myopia control effect of ortho-k was defined as the change in AL from the start of treatment. We defined a 1-year AL elongation ≤0.19 mm as the desired outcome, while an elongation >0.19 mm was defined as an unwanted outcome (1-year $AL_{elongation} = AL_{elongation}/months \times 12$) (8). The data of right eyes were included in our experiment. Ocular parameters, including spherical equivalent refraction (SER), baseline AL, white-to-white distance (WTW), pupil diameter,

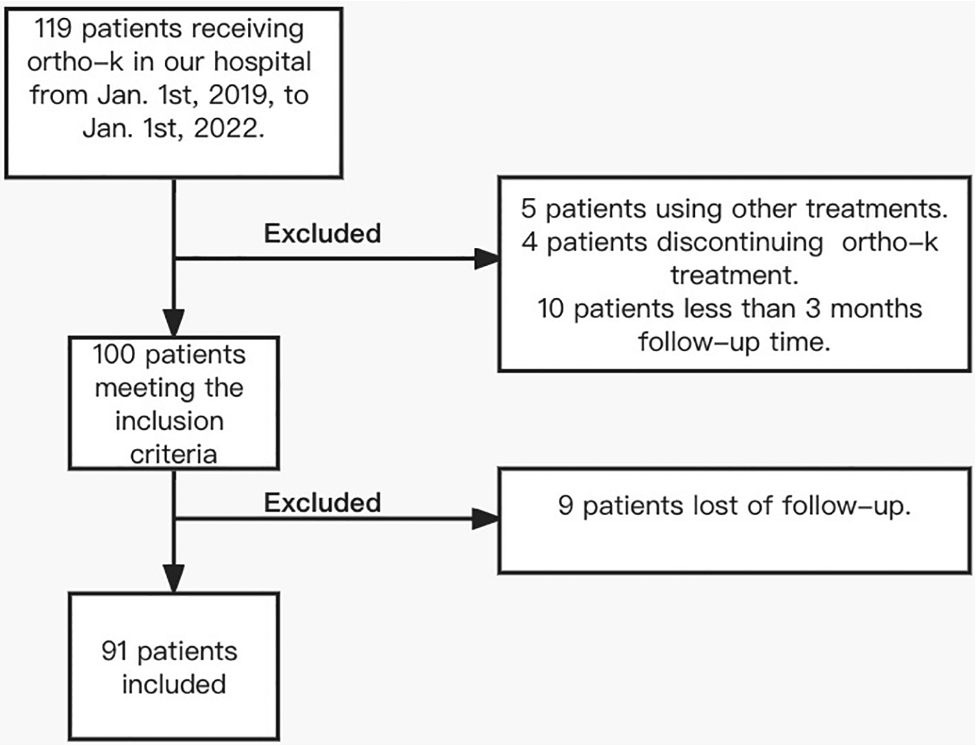

FIGURE 1
Flowchart of study.

anterior chamber depth, anterior and posterior corneal steep and flat keratometry (flat K), anterior and posterior corneal astigmatism, anterior and posterior corneal high order aberrations (aberrations above 3rd order in Zernike polynomials) and central corneal thickness, were measured and used for our model. In addition, clinical characteristics, including age, sex, parental myopia history, time spent outdoors and near work every day, ortho-k brands, and lens-wearing time every night, were collected from patient medical records and telephonic surveys.

Statistical analyses

Logistic least absolute shrinkage and selection operator (LASSO) regression was used to select factors related to the treatment effect. LASSO performs a continuous shrinking operation to minimize the regression coefficient and, consequently, the possibility of overfitting. By shrinking the sum of the absolute value of regression coefficients and compressing the coefficients to 0, this technique selects and retains the most relevant variables in the model (9). In our study, LASSO regression was performed for 100 cycles for all variables collected, and the variables retained more than 60 times were selected to determine the factors related to the treatment effect. The R package glmnet() function was utilized to fit the logistic LASSO regression.

The data were randomly divided in a training set-to-test set ratio of 7:3, thus establishing the logistic regression model. Secondly, the variables selected by LASSO were included in the nomogram. The discriminative ability was evaluated by the concordance index (C-index), which ranges from 0.5 (random chance) to 1.0 (perfect fit) (10). A calibration plot was used to evaluate calibrating ability: the prediction probability of the result is overestimated if the correction intercept is less than 0. On the contrary, if the correction intercept is positive, the algorithm is underestimated (11, 12). In addition, a decision curve analysis calculated the clinical net benefit for a given prediction model, comparing the default strategies for treating all or no patients (13). The "thin black line (none)" showed the expected net benefit where the intervention was not made, and the "thick black line (all)" showed the expected net benefit for all patients where the intervention was made (10). A heat map can intuitively display the relationship between variables and treatment effects.

K-fold cross-validation was carried out to evaluate the prediction ability of the model performances. To obtain the best estimate of model performance, a variant of the k-fold cross-validation technique was applied to the model, which would reduce the risk of overfitting. One-fold was used for

TABLE 1 Demographic, ocular components, and follow-up clinical characteristics of included participants ($n = 91$).

Continuous variables	Median (interquartile range)	Categorical variables	Proportion
Age (years)	11 (9–13)	Sex (male: female)	46:45
Follow-up time (months)	12 (8–15)	Father's myopia history (high: moderate: low: no myopia)	19:25:29:18
SER at baseline (D)	−2.50 (−1.75 to −3.41)	Mother myopia history: (high: moderate: low: no myopia)	21:19:32:19
AL at baseline (mm)	24.66 (24.17–25.22)	Brands of Ortho-k (CRT: Alpha: Dream Vision)	46:35:10
Pupil diameter (mm)	3.50 (3.01–3.89)		
White-to-white (mm)	11.80 (11.50–12.00)		
ACD (mm)	3.25 (3.12–3.43)		
Time spent outdoors (hours)	1.3 (1.0–2.0)		
Lens wearing time (hours)	8.5 (8.0–9.0)		
Time spent on near work (hours)	8.5 (8.0–9.0)		
Anterior corneal steep K (D)	43.70 (42.80–44.50)		
Anterior corneal flat K (D)	42.40 (41.70–43.30)		
Anterior corneal astigmatism (D)	1.20 (0.90–1.50)		
Posterior corneal steep K (D)	−6.40 (−6.30 to −6.60)		
Posterior corneal flat K (D)	−6.10 (−6.00 to −6.30)		
Posterior corneal astigmatism (D)	0.30 (0.20–0.40)		
CCT (μm)	557 (533–577)		
Anterior corneal HOA (μ)	0.39 (0.33–0.46)		
Posterior corneal HOA (μ)	0.19 (0.18–0.21)		

SER, spherical equivalent refraction; AL, axial length; ACD, anterior chamber depth; K, keratometry; CCT, central corneal thickness; HOA, high order aberrations.

validation, while the other k-1 folds were used to train the model and subsequently predict the target variables in the test data. Due to this process repeating k times ($k = 10$), the performance of each model in predicting the hold-out set was tracked using performance metrics such as accuracy, false-positive rate, and false-negative rate. The trainControl() function and train() function in the R package caret were used.

The ROC curve and confusion matrix were used to evaluate the performance of the model. SPSS software ver. 26.0 (IBM Corp., Armonk, NY, United States) and R software ver. 4.0.3 (The R Foundation Inc., Vienna, Austria) were used for the statistical analyses, curve drawing, and model building.

Results

Demographics

Table 1 shows the (median) demographic, ocular components, and clinical characteristics for all participants who met the study's final inclusion criteria ($n = 91$). The median post-treatment time was 12 months [interquartile range (IQR) 8–15 months].

LASSO regression for treatment effect

According to the result of feature selection by LASSO method, initial 22 features were reduced to 9 predictors, which retained more than 60 times. Therefore, the age, baseline AL, pupil diameter, lens wearing time, time spent outdoors, time spent on near work, WTW, anterior corneal flat K, and posterior corneal astigmatism were selected through LASSO. The coefficients of the variables filtered by LASSO showed its importance (**Table 2**).

Two-year logistic regression prediction model

$$p = \frac{1}{1 + \exp(-A)}$$

The equation was derived from logistic regression, where $A = [(-5.257\ +1.577\ \text{age}) - (0.419\ \text{baseline AL}) + (1.557\ \text{pupil diameter}) + (3.145\ \text{lens wearing time}) + (1.542\ \text{time spent}$

outdoors) − (2.928 time spent on near work) + (1.562 WTW) − (0.722 anterior corneal flat K) + (3.794 posterior corneal astigmatism)] (Table 3).

In the equation, $p = \frac{1}{1 + \exp(-A)}$, p is the probability of cumulative effect. A cut-off value greater than 0.5 was effective. The estimates of each variable in logistic regression modeling prediction are shown in Table 4, showing the excellent predictive ability of the predictive model for good treatment effect (1). The heat map shows the correlation coefficients after the logistic regression model (Figure 2). Figure 3 shows the ROC, Figure 4 shows the decision curve analysis, and Figure 5 shows the calibration plot. Figure 6 presents the prediction of the cumulative effect. The 50% possibility of a cumulative effect was approximately 12 months. According to our model, we divided the patients in the validation set into two groups: risk ≤50% and risk >50%. The risk ≤50% group was more likely to obtain a better effect than the other group ($p < 0.001$). Figure 7 shows the nomogram for the possibility of the 2-year cumulative effect of ortho-k treatment.

TABLE 2 The LASSO regression selection for ortho-k treatment effect.

Variables	Coefficient
Age (years)	0.254
Baseline AL (mm)	0.068
Pupil diameter (mm)	0.146
Lens wearing time (hours)	0.834
Time spent on near work (hours)	−0.287

LASSO, least absolute shrinkage and selection operator; AL, axial length. Only the coefficients of variables that occur 100 times in 100 cycles are presented here. Other variables are omitted.

TABLE 3 Prediction model results using logistic regression.

Variables	Parameter			
	Estimate	Standard error	Z value	Pr (>|z|)
Age	1.577	0.534	2.952	0.003
Baseline AL	−0.419	0.901	−0.465	0.642
Pupil diameter	1.557	1.498	1.039	0.299
Wearing lens time	3.145	1.371	2.294	0.022
Time spent outdoors	1.542	1.437	1.072	0.284
Time spent on near work	−2.928	1.480	−1.979	0.048
WTW	1.562	2.343	0.667	0.505
Anterior corneal flat K	−0.722	0.672	−1.074	0.283
Posterior corneal astigmatism	3.794	4.819	0.787	0.431

AL, axial length; WTW, white-to-white distance; K, keratometry. The Pr(>|z|) value there corresponds to the z-statistic. The smaller the Pr(>|z|) value, the more significant the estimate.

TABLE 4 Logistic regression modeling prediction results.

	Prediction group		Correctly classified
Reference group	0	1	
0	13	2	86.7%
1	0	13	100%
Overall correct classified rate			93.4%

Accuracy: 0. 9286 (95% CI: 0.7650, 0.9912); Kappa: 0.8579; sensitivity: 0.8667; specificity: 1.0000. "0", bad treatment effect, "1", good treatment effect.

Discussion

Background and rationale

Although the mechanism underlying the myopia control effect is still unclear, peripheral myopia defocuses (14, 15) and the retardation effect of ortho-k has been widely recognized (15–17). Several possible factors have been previously associated with the effect of ortho-k (6), however, prediction models to estimate who will benefit from a better myopic retardation effect are lacking. Our prediction model quantified the myopia control effect classified by age, AL, pupil diameter, lens wearing time, time spent outdoors, time spent on near work, WTW, anterior corneal flat K, and posterior corneal astigmatism.

Risk factors for cumulative effect

The variables, including clinical characteristics and ocular components, were screened as detailed in previous studies (5, 6). Kong et al. (6) reported that a smaller diopter and corneal eccentricity value were significantly associated with the treatment effect. Meanwhile, Santodomingo et al. (5) reported that, among other variables, earlier onset of myopia, female gender, lower initial myopia, a more prolate corneal shape, and larger pupil diameters constitute predictive factors for axial elongation in children wearing ortho-k. However, their conclusion was drawn by comparing the ortho-k group with a group wearing spectacles.

Interestingly, posterior corneal astigmatism was also associated with the ortho-k effect and ranked first in the model. Traditionally, ocular astigmatism, including posterior corneal astigmatism, has been considered for corneal

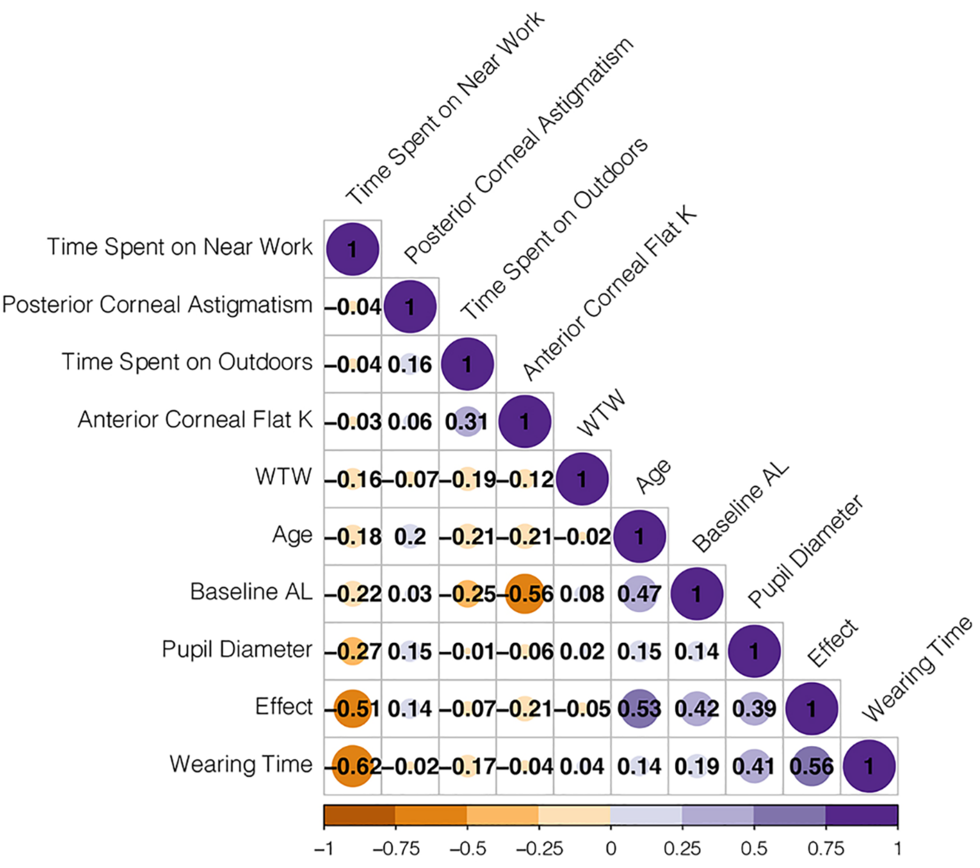

FIGURE 2
Heat map of correlation coefficient after logistic regression model. K, keratometry; WTW, white-to-white distance; AL, axial length. The figures are Pearson coefficients. The larger the absolute value of the figure, the stronger the relationship. The minus sign represents a negative relationship; the plus sign represents a positive relationship. For example, −0.51 represents a negative relationship between time on near work and effect.

refractive and cataract surgery due to its effect on postoperative visual function (18). Changes in posterior corneal astigmatism are associated with fluctuating changes in SER after corneal refractive surgery, but the effect is negligible for ortho-k treatments with minimal changes in corneal thickness and biomechanics. Of course, the long-term effects need to be further investigated.

Lens-wearing time ranked second in our model. The retardation of myopia progression improved when children's lens-wearing time increased, possibly because wearing ortho-k for longer leads to a more stable peripheral myopia defocus, resulting in a better myopia control effect.

Several studies had investigated the impact of environment and behavior management on myopia progression (19–22). Time spent on near work had the third greatest impact on the effect of ortho-k, and controlling it may significantly improve the treatment effect. The gradual extension of time spent on near work is a direct manifestation of the overloaded academic burden. In fact, people with higher education have a higher risk of myopia (23, 24). Time spent on near work was negatively associated with the cumulative effect of ortho-k. A meta-analysis by Lanca et al. (25) and Huang et al. (26) reports that time spent on near work and higher odds of myopia are positively correlated (odds ratio = 1.05 and 1.14), emphasizing the importance of managing this factor.

The impact of age on the effect of ortho-k ranked fourth in our prediction model. The nomogram (**Figure 7**) in our present study showed that the older the child, the better the effect. We speculated that as children age, the rate of myopia progression slows and generally stops at the age of 18. Consequently, the AL increase becomes smaller than at a younger age (27). This, however, does not mean that older children who begin wearing ortho-k will get better results than younger children. This result still suggests that the benefits of the ortho-k treatment increase if eligible children are subjected to it as early as possible.

The visible iris diameter often used in initial lens selection (28) was also associated with the ortho-k effect. Santodomingo et al. also confirmed that patients with larger iris diameters have better treatment effect with ortho-k (5). It

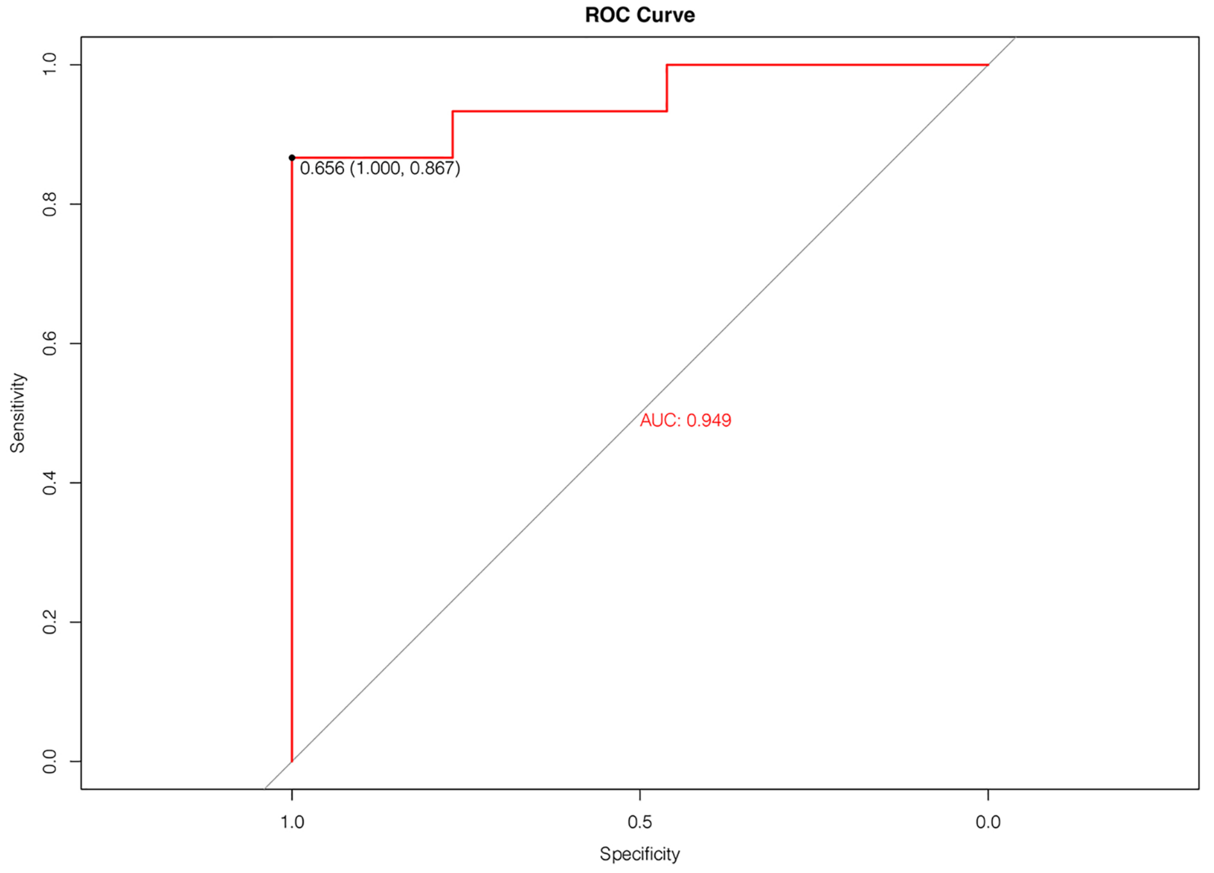

FIGURE 3
ROC curve of the prediction model we constructed.

is speculated that a larger iris diameter will prompt the prescription of a larger lens, which will form a larger defocus area, thus reducing more hyperopia defocus as described above. However, the specific mechanism still needs to be further studied in the future.

Pupil diameter has been positively associated with the cumulative effect of ortho-k (5, 29). Our results demonstrated that a larger pupil diameter with more significant redistribution of corneal epithelium from the corneal center to the peripheral cornea results in a larger reduction in peripheral hyperopic defocus (30, 31). Additionally, more defocused light tends to focus in front of the peripheral retina thus reducing axial elongation (14).

Increased time spent outdoors has been shown to protect against myopia onset and progression (19, 32, 33). The constantly increasing academic burden leaves school-aged children with less time for outdoor activities, sometimes limited to one physical education class (approximately 45 min). Our results indicated that the longer time invested in outdoor activities, the better the myopia control effect. Although there was little difference in the time spent outdoors of each child, it did have an impact on the therapeutic effect of ortho-k. This is similar to the result from a 3-year randomized controlled trial in Guangzhou, China, which suggested that more than 40 min of outdoor activities a day can reduce the incidence of myopia by 20% (19).

In clinical ortho-k practice, the corneal curvature, height, visible iris diameter, anterior corneal astigmatism, and eccentricity data retrieved from the corneal topography guide the first lens selection (28). In our nomogram, the smaller the anterior corneal flat *K* of the children, the better the effect. This result seems to contradict previous studies (5, 6). Santodomingo et al. (5) took the *p*-value (cornea shape factor) from the central 7 mm range of the cornea, and the larger corneal area taken into consideration may have led to a more significant relationship between *p*-value and myopia control effects. As for Kong et al.'s paper, they took the flat meridian of the whole eyeball and the corneal eccentricity value as the variables different from ours to identify factors influencing the therapeutic outcome of ortho-k (6). Therefore, these two values also affect the consistency of the results. In the future, we should try to expand the corneal range, as well as develop models including more predictive variables to predict the treatment effect more fully.

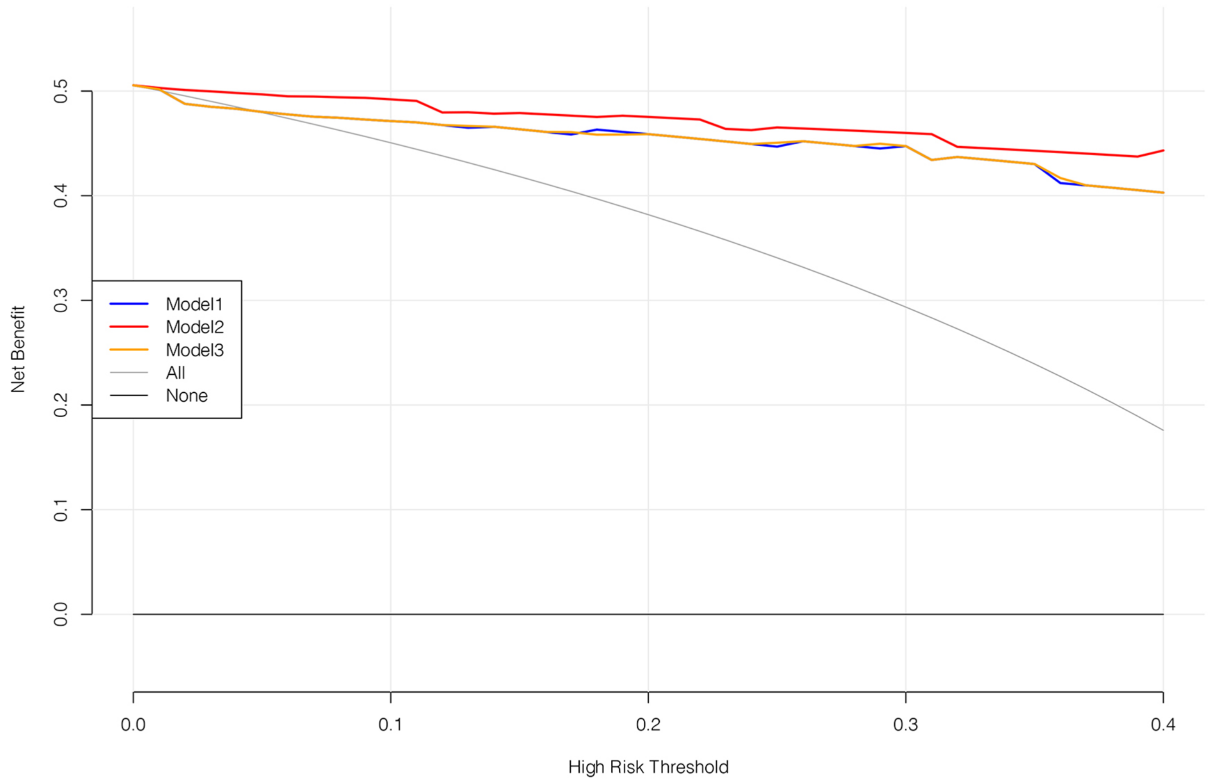

FIGURE 4
Decision curve analysis. Model 1 includes the age, baseline AL, pupil diameter, time spent outdoors, time spent on near work, and ortho-k brands. Model 2 is the model we constructed. Model 3 includes the age, baseline AL, pupil diameter, time spent outdoors, and time spent on near work. Among the three models, model 2 works best.

AL and SER are two major indicators reflecting the refractive state. An AL increase can serve as a good indicator of myopia progression because SER cannot be independently measured when wearing ortho-k (34). In most cases, the AL increase is in correlation with the SER (35). In the nomogram, the closer a child's AL is to 23 mm, the better the treatment effect. Considering the correlation between AL and SER, our results are consistent with the findings published by Santodomingo et al. (5).

In our study, different brands of ortho-k (mainly different designs, CRT and VST) had no significant effect on efficacy. In the future, the impact of different designs on the efficacy of ortho-k still needs to be determined by further randomized clinical studies with larger sample size.

A 2-year logistic regression prediction model

Nomograms have been widely used in other medical specialties to predict the survival rate of patients and disease recurrence (36, 37). To construct the prediction model for treatment effect, we selected patients whose follow-up time was longer than 3 months ($n = 91$). The variables selected from LASSO regression were chosen to maximize the predictive power and used as a basis for the nomogram. LASSO regression can be used to predict the benefits of ortho-k treatment and recommend optimal myopia treatments or management for different children.

In this model, if the prediction model predicts "1", ortho-k will be the most optimal treatment. If "0" is predicted, other myopia treatments instead of ortho-k will be recommended for the children. The optimism-corrected C-statistic of the prediction model was 0.821 (95% CI: 0.815, 0.827). The decision analysis curve showed that our model was good enough to guide lens fitting work in clinics (**Figure 4**). The calibration plots showed excellent overall agreement between the prediction, while observation of 2-year outcomes presented a good correlation between prediction and actual observation (**Figure 5**).

Limitations

Our study has a few limitations. First, the sample size was relatively small, and because this was the first model to predict

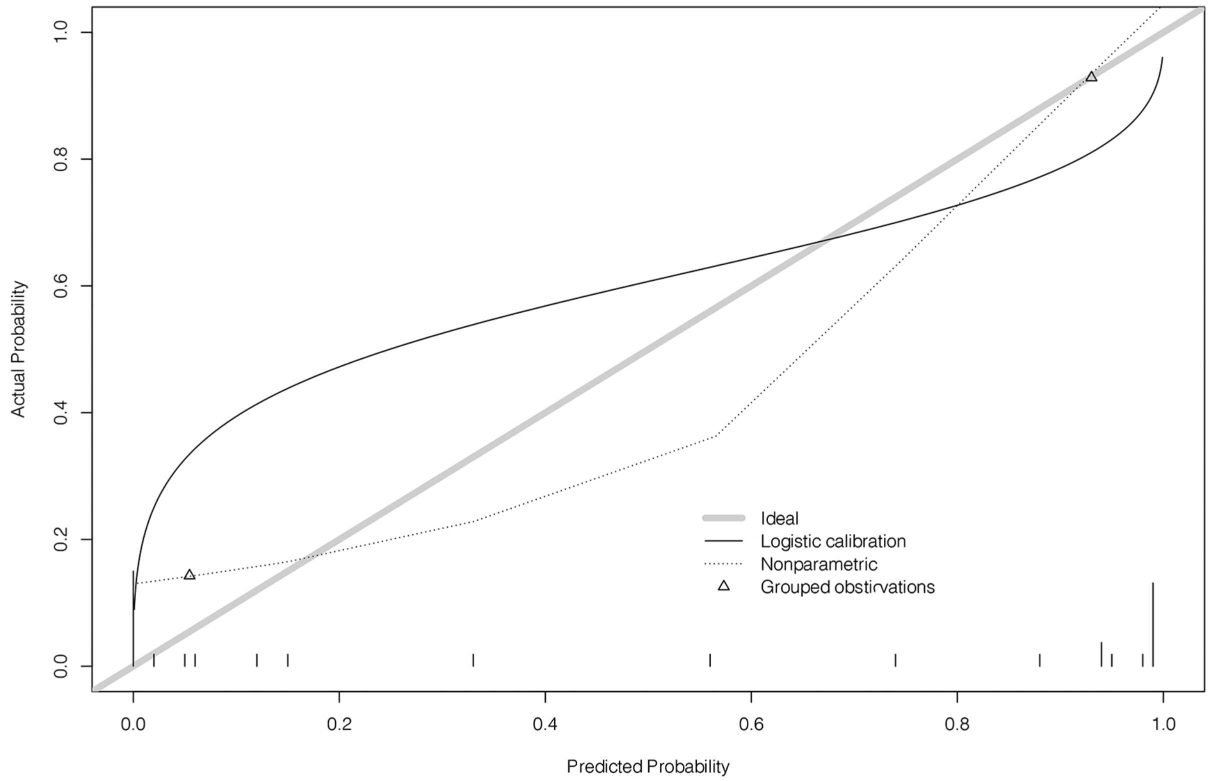

FIGURE 5
Prediction of cumulative effect. AL, axial length; WTW, white-to-white; K, keratometry.

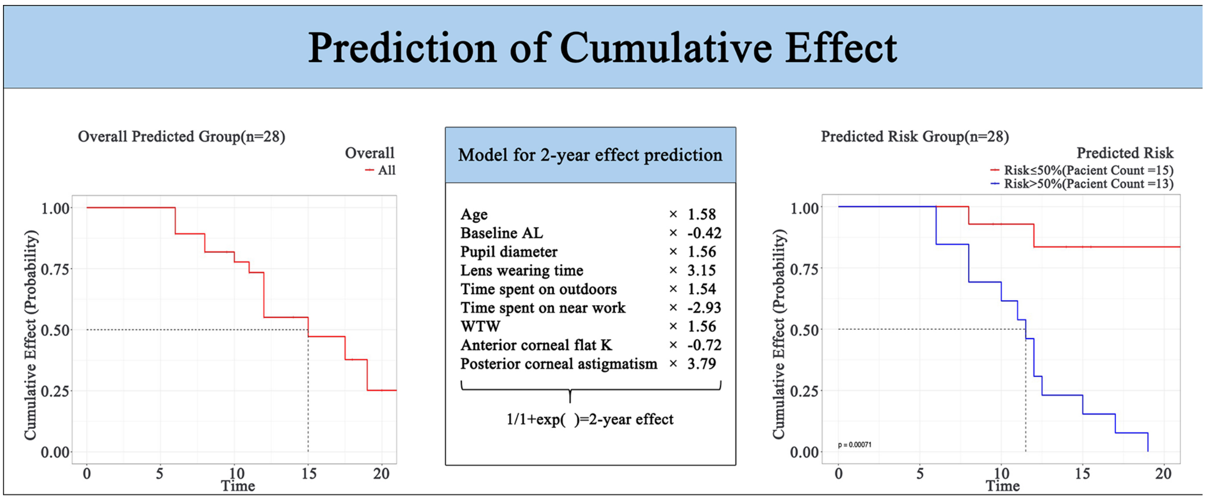

FIGURE 6
Nomogram of the 2-year possibility of the cumulative effect of ortho-k. K, keratometry; WTW, white-white distance; AL, axial length.

the cumulative effect of ortho-k, data for external validation was lacking. Second, our study only showed a potential association between pre-treatment variables and the cumulative effect. We did not explore the specific mechanism behind the correlation coefficient of each variable, which requires a larger sample to accomplish. Third, our study did not consider the corneal eccentricity value or the corneal shape factor p value within 7 mm of the central cornea; these need to be investigated in more depth in future studies.

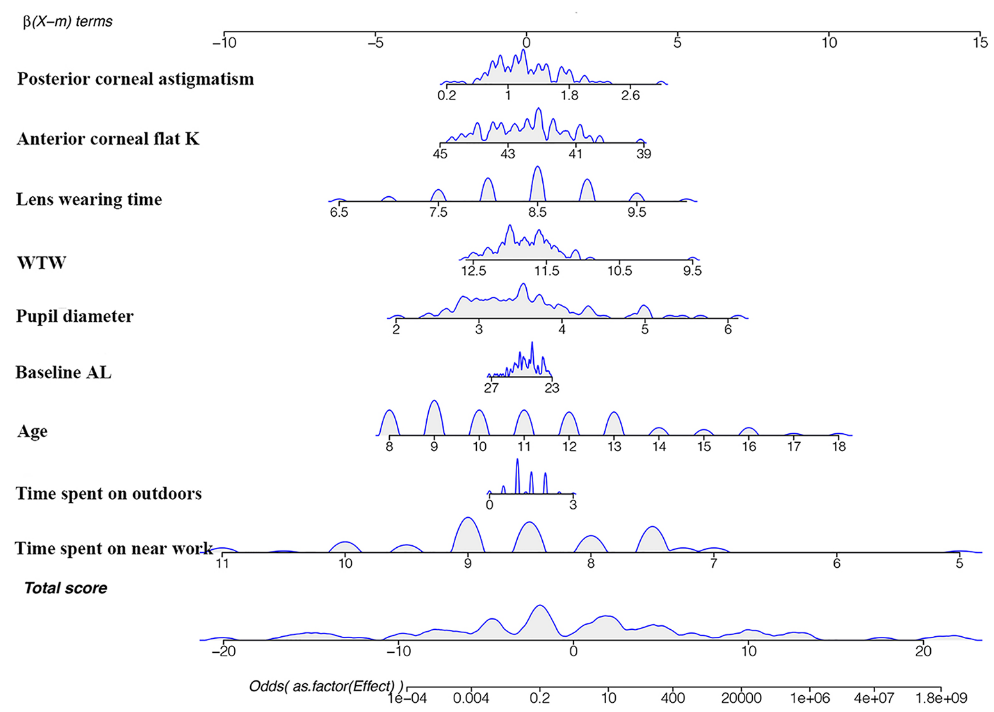

FIGURE 7
Calibration plot.

Conclusion

In conclusion, ML was applicable to predict the effect of ortho-k. We were able to predict a 2-year possible cumulative effect of ortho-k through age, baseline AL, pupil diameter, lens wearing time, time spent outdoors, time spent on near work, WTW, anterior corneal flat *K*, and posterior corneal astigmatism. This ML-assisted prediction model may instruct doctors' clinical decision-making for patients to achieve the best treatment effect.

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 Institutional review board of The First Affiliated Hospital of Medical College of Zhejiang University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CD: conceptualized, organized, and edited the manuscript. JF: conceptualized, conducted, drafted the manuscript, and ran the software. HM: performed a literature search and made one of the figures. YZ: organized and reviewed the manuscript. MS: made some of the figures and reviewed the manuscript. WY: reviewed the manuscript. 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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fpubh.2022.1015138

Association between sleep duration and myopia among Chinese children during the COVID-19 pandemic: A cross-sectional study

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 09 August 2022
ACCEPTED 19 December 2022
PUBLISHED 09 January 2023

CITATION
Huang L, Chen X, Lin J, Fan X, Chen T, Yu Y, Chen J and Hu J (2023) Association between sleep duration and myopia among Chinese children during the COVID-19 pandemic: A cross-sectional study. *Front. Public Health* 10:1015138. doi: 10.3389/fpubh.2022.1015138

Background: The studies on the association between sleep duration and myopia are limited, and the evidence is inconsistent. This study aimed to evaluate the association between sleep duration and myopia, cycloplegic spherical equivalent (SE) and axial length (AL) among Chinese children during the Corona Virus Disease 2019 (COVID-19) pandemic.

Methods: The study was a cross-sectional study on Chinese children aged 6–18 years. The comprehensive ophthalmic examinations for children included cycloplegic SE, AL, and standardized questionnaires. The questionnaire included sleep duration, parental myopia, outdoor time, and continuous near work duration without breaks. Myopia was defined as SE ≤-0.50 diopters (D).

Results: A total of 1,140 children were included in the analyses, with 84.7% of myopic children and 74.4% of children's daily sleep duration being more than 8 h/d. In univariate regression analysis, compared with sleep duration < 8 h/d, children with sleep duration of 8–9 and >9 h/d were less myopia ($p < 0.01$ for all), and had less myopic SE ($p < 0.01$ for all), and shorter AL ($p < 0.01$ for all). After adjusting for age, gender, parental myopia, outdoor time, and continuous near work duration without breaks, sleep duration was not associated with myopia, cycloplegic SE, and AL ($p > 0.05$ for all).

Conclusions: This study showed sleep duration was related to myopia, cycloplegic SE, and AL among Chinese children during the COVID-19 pandemic-related lifestyles, but no independent association.

KEYWORDS

sleep, myopia, axial length, children, COVID-19

1. Introduction

Myopia, as a global public health problem, affects the vision health of children and adolescents (1). The prevalence of myopia among children in China is increasing, and the myopia rate among college students has been more than 85% (2). High myopia increases the risk of ocular diseases such as cataracts (3), glaucoma (4), myopic maculopathy (5) and retinal detachment (5). The increase in myopia has brought a substantial economic burden to society (6).

Large-scale population-based epidemiological studies have extensively investigated the risk factors for myopia. Genetic and environmental factors have been evidenced to be associated with myopia. In particular, changes in lifestyle and environment, such as short sleep duration, less outdoor activities and spending more time near work and electronic devices, are critical factors in myopia development (7–9). From the perspective of public health, changing lifestyle habits is an effective means of disease prevention, such as increasing outdoor activities can effectively reduce the incidence of myopia (10). Recently, studies have concentrated on sleep, one of the modifiable lifestyle habits. Epidemiological studies have provided preliminary evidence that sleep disorders or shorter sleep duration may influence the incidence or progression of myopia (11, 12). Jee et al. found that refractive error increased by 0.1 D for each per-hour increase in sleep duration in Korean adolescents aged 12–19 years (11). The study on Japanese children aged 10–19 indicated that children with high myopia had the poorest sleep quality and shortest sleep duration than children with emmetropia (12). In contrast, sleep duration was unrelated to myopia in studies of Chinese and Singaporean children (13–15). These inconsistent results complicate the relationship between sleep and myopia. Besides, due to the global pandemic of COVID-19, many countries have implemented social restrictions, including citywide lockdowns, home isolation, and school closures (16). These restrictions result in lifestyle changes dramatically, such as more screen time (17), less outdoor activities (18), and more sleep duration (19) among children. Compared with pre-COVID, the prevalence of myopia in children increased significantly (20). Given these, our study aimed to assess the association between sleep duration and myopia, cycloplegic spherical equivalent (SE), and axial length (AL) among Chinese children during the COVID-19 pandemic.

2. Methods

2.1. Study population

From February to December 2021, children aged 6–18 years in Fujian Province, southeastern China, were recruited to participate in this study, and the study's purpose and procedures were explained to the children and guardians. Verbal consent was obtained from each child, and written permission from the parents or guardians. The study received ethical approval from the Ethics Committee of The Second Hospital of Fujian Medical University (No. 2022244) and followed the principles of the Declaration of Helsinki. The children and their parents or guardians both agreed to the premise of using cycloplegic eye drops for dilated ophthalmic examination. Children with vision-threatening severe eye diseases, such as congenital cataracts, ocular trauma, strabismus, and amblyopia, were excluded from the study.

2.2. Ophthalmic examination and questionnaire

Trained ophthalmologists and optometrists conducted ophthalmic examinations of the child. Cycloplegia was induced using 3 drops of 0.5% tropicamide phenylephrine (Santen, Osaka, Japan), administered to both eyes at 5-min intervals. Pupil dilation and pupil light reflex were examined 15 min later to determine whether complete cycloplegia was achieved (pupil dilation $\geq$6 mm and loss of pupil light reflex). If the pupil light reflex or pupil dilation $<$ 6 mm was still present, drops of 0.5% tropicamide phenylephrine were administered again to both eyes. Refraction was measured using autorefraction (KR-8900, Topcon, Tokyo, Japan); Axial length (AL) was measured using AL-Scan (Nidek, Gamagori, Japan). All measurements were performed 3 times, and the mean value was calculated for each eye. If the difference between any two readings in one eye was $\geq$0.5 D, the refraction of that eye was remeasured. Spherical equivalent (SE) was calculated as the refraction of the sphere power plus half the cylinder power. Myopia was defined as SE $\leq$-0.50 D.

The online questionnaire was completed by the child or guardian (the child who could not complete the questionnaire independently) and asked to describe the behavior in the past month. The questionnaire included demographic information, parental myopia, the daily duration of sleep, the daily duration spent on outdoor activities, and continuous near work duration without breaks. The questions were designed according to the Chinese National Health Commission recommendation (21): sleep duration $<$8 h/d, 8–9 h/d, $>$ 9 h/d. Outdoor activities time options were categorized as $<$2 h/d and $\geq$2 h/d. How long was the duration of a single continuous near work without breaks, options were categorized as $<$ 30 min and $\geq$ 30 min.

2.3. Statistical analysis

Because of highly correlated data of cycloplegic SE and AL for the right and left eyes (Pearson correlation coefficient (r) =0.84 for SE and 0.92 for AL), only the right eye data was included in the analyses. Continuous non-parametric data were expressed as median and interquartile range and analyzed using

TABLE 1 Characteristics of children stratified by myopia status.

Variable	Total	Non-myopia	Myopia	p
Age (years), $n = 1,140$	12 (9, 14)	9 (7, 11)	12 (9,14)	<0.01†
SE (D), $n = 1,140$	−1.88 (−3.13, −0.88)	0.13 (−0.25, 0.50)	−2.19 (−3.50, −1.25)	<0.01†
AL (mm), $n = 957$	24.0 (23.69, 25.06)	23.0 (22.68, 23.69)	25.0 (23.97, 25.25)	<0.01†
Gender				0.09*
Boys	552 (48.4%)	74 (42.5%)	478 (49.5%)	
Girls	588 (51.6%)	100 (57.5%)	488 (50.5%)	
Sleep duration, h/d				<0.01*
<8	292 (25.6%)	28 (16.1%)	264 (27.3%)	
8–9	548 (48.1%)	93 (53.4%)	455 (47.1%)	
>9	300 (26.3%)	53(30.5%)	247 (25.6%)	
Parental myopia				0.27*
None	439 (38.5%)	70 (40.2%)	369 (38.2%)	
One	410 (36.0%)	68 (39.1%)	342 (35.4%)	
Both	291 (25.5%)	36 (20.7%)	255 (26.4%)	
Time outdoor, h/d				0.26*
<2 h/d	123 (10.8%)	23 (13.2%)	100 (10.4%)	
≥2 h/d	1,017 (89.2%)	151 (86.8%)	866 (89.6%)	
Continuous near work duration without breaks, min				0.49*
<30	133 (11.7%)	23 (13.2%)	110 (11.4%)	
≥30	1,007 (88.3%)	151 (86.8%)	856 (88.6%)	

† Analyzed using Mann-Whitney U-test.
* Analyzed using Chi-square test.
Data are presented as medians and quartiles (p25, p75) or as n (%).
SE, spherical equivalent; D, diopters; AL, axial length.

the Mann-Whitney U test or Kruskal-Wallis test; categorical variables were analyzed using the Chi-square or Fisher exact test. Myopia, cycloplegic SE, and AL were used as dependent variables (outcomes), and sleep duration categorical variables were used as independent variables (exposures) to assess the association using univariate logistic or linear regression models; multivariate logistic or linear regression models were conducted to adjust for confounders such as age, gender, parental myopia, outdoor time, and continuous near work duration without breaks. Statistical software SPSS 24.0 (Statistical Product Service Solutions, version 24, Chicago, IL, USA) was used for analysis. Statistical significance was assumed at $p < 0.05$ with two-sided.

3. Results

A total of 1,206 participants were enrolled in the study. Excluding the subjects with missing data and those who did not meet the inclusion criteria, 1,140 children were available for statistical analysis (Table 1). Sleep duration was significantly associated with myopia ($p < 0.01$). Parental myopia, outdoor time, and continuous near work duration without breaks were not associated with myopia ($p > 0.05$ for all).

Table 2 shows the SE and AL stratified by sleep duration and gender. Myopia was associated with sleep duration ($p < 0.01$). Myopic SE and AL significantly decreased with increasing sleep duration for all children and girls ($p < 0.01$ for all). Myopia was not associated with sleep duration among boys ($p = 0.57$).

In univariate logistic regression model analysis, compared with sleep duration <8 h/d, children with sleep duration of 8–9 and >9 h/d had less myopia ($p < 0.01$ for all) in all children (Table 3). In univariate linear regression model analysis, compared with sleep duration < 8h/d, children with sleep duration of 8–9 and >9 h/d had less myopic SE ($p < 0.01$ for all) and shorter AL ($p < 0.01$ for all) in all children. However, after adjusting for potential confounders such as gender, age, parental myopia, outdoor time, and continuous near work duration without breaks, sleep duration was not significantly associated with myopia, cycloplegic SE, and AL ($p > 0.05$ for all).

TABLE 2 The spherical equivalent and axial length stratified by sleep duration and gender.

Variable	n	Myopia	p^*	n	SE, D	$p^\dagger$	n	AL, mm	$p^\dagger$
Total	1,140			1,140			957		
Sleep duration, h/d			<0.01			<0.01			<0.01
<8	292	264 (90.4%)			−2.50 (−4.13, −13.80)			24.71 (24.04, 25.55)	
8–9	548	455 (83.0%)			−1.63 (−2.88, −0.75)			24.30 (23.58, 24.95)	
>9	300	247 (82.3%)			−1.69 (−2.88, −0.75)			24.25 (23.65, 24.87)	
Boys	552			552			460		
Sleep duration, h/d			0.57			<0.01			<0.01
<8	130	116 (89.2%)		130	−2.56 (−4.13, −1.38)		114	25.14 (24.57, 25.84)	
8–9	268	229 (85.4%)		268	−1.75 (−3.13, −0.88)		229	24.61 (24.04, 25.37)	
>9	154	133 (86.4%)		154	−1.88 (−3.00, −0.88)		117	24.64 (24.00, 25.12)	
Girls	588			588			497		
Sleep duration, h/d			<0.01			<0.01			<0.01
<8	162	148 (91.4%)		162	−2.38 (−4.00, −1.38)		142	24.44 (23.77, 25.04)	
8–9	280	226 (80.7%)		280	−1.50 (−2.75, −0.63)		237	23.87 (23.28, 24.59)	
>9	146	114 (78.1%)		146	−1.44 (−2.75, −0.50)		118	23.85 (23.31, 24.50)	

*Analyzed using Fisher exact test.
†Analyzed using Kruskal-Wallis test.
Data are presented as medians and quartiles (p25, p75) or as n (%).
SE, spherical equivalent; D, diopters; AL, axial length.

10.3389/fpubh.2022.1015138

TABLE 3 Univariable and multivariable analysis of sleep duration in participants.

Variable	Myopia				SE, D				AL, mm			
	Univariable model		Multivariable model		Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR [95%CI]	$p^{\dagger}$	OR [95%CI]	$p^{\dagger}$	Coefficient β [95%CI]	p^{*}	Coefficient β [95%CI]	p^{*}	Coefficient β [95%CI]	p^{*}	Coefficient β [95%CI]	p^{*}
Total												
Sleep duration, h/d												
<8	Ref		Ref		Ref		Ref		Ref		Ref	
8–9	0.52 [0.33, 0.81]	<0.01	1.29 [0.78, 2.16]	0.34	0.78 [0.52, 1.04]	<0.01	−0.01 [−0.28, 0.25]	0.92	−0.44 [−0.61, −0.28]	<0.01	0.06 [−0.10, 0.21]	0.47
>9	0.50 [0.30, 0.81]	<0.01	1.57 [0.88, 2.79]	0.13	0.79 [0.50, 1.08]	<0.01	−0.23 [−0.54, 0.08]	0.15	−0.49 [−0.68, −0.30]	<0.01	0.13 [−0.05, 0.31]	0.16
Boys												
Sleep duration, h/d												
<8	Ref		Ref		Ref		Ref		Ref		Ref	
8–9	0.71 [0.37, 1.36]	0.30	1.76 [0.83, 3.74]	0.14	0.67 [0.27, 1.07]	<0.01	−0.16 [−0.55, 0.23]	0.42	−0.42 [−0.65, −0.18]	<0.01	0.11 [−0.11, 0.33]	0.34
>9	0.77 [0.37, 1.57]	0.47	2.60 [1.10, 6.13]	0.03	0.73 [0.29, 1.17]	<0.01	−0.39 [−0.84, 0.06]	0.09	−0.50 [−0.77, −0.24]	<0.01	0.16 [−0.10, 0.42]	0.23
Girls												
Sleep duration, h/d												
<8	Ref		Ref		Ref		Ref		Ref		Ref	
8–9	0.40 [0.21, 0.74]	<0.01	0.96 [0.47, 1.97]	0.91	0.90 [0.56, 1.24]	<0.01	0.15 [−0.21, 0.5]	0.43	−0.53 [−0.73, −0.32]	<0.01	0.11 [−0.21, 0.22]	0.96
>9	0.34 [0.17, 0.66]	<0.01	1.02 [0.46, 2.26]	0.96	0.87 [0.48, 1.27]	<0.01	−0.08 [−0.51, 0.34]	0.69	−0.54 [−0.78, −0.30]	<0.01	0.13 [−0.15, 0.36]	0.41

Ref indicates reference.
† Analyzed using logistic regression analysis.
* Analyzed using linear regression analysis.
Multivariable model adjusted for age, gender, parental myopia, outdoor time and continuous near work duration without breaks.
SE, spherical equivalent; D, diopters; AL, axial length; OR, odds ratio; CI, confidence interval.

10.3389/fpubh.2022.1015138

4. Discussion

The present study showed sleep duration was related to myopia, cycloplegic SE, and AL among Chinese children during the COVID-19 pandemic-related lifestyles, but no independent association.

In this study, boys had a more myopic SE ($Z = -2.18$, $p = 0.029$) and longer AL ($Z = -10.24$, $p < 0.01$) than girls, both of which were statistically different. The data was similar to that of Shanghai and Wuhan children in China (22, 23). Studies assessing the association between sleep duration and myopia have not been widely conducted, and findings vary. Our results show that sleep duration was no independent relation to myopia, cycloplegic SE, and AL among Chinese children. Similar to Singapore (GUSTO) study showed no association between sleep duration and myopia, SE, or AL among 376 3-year-old children (24). Recently, Li et al. also found no independent correlation between sleep duration and myopia, SE, or AL in the same GUSTO study in 572 9-year-old Singaporean children (15). Moreover, the study by Liu et al. of 4,982 Chinese children aged 6–9 years revealed that late bedtime but not sleep duration related to 2-year myopia onset (25). Additionally, the 4-year follow-up study of 1,187 children aged 5–9 years indicated that sleep duration and bedtime were not significantly associated with myopia progression and axial elongation after adjusting for potential confounders (13). In contrast, a study of 3,625 Korean adolescents aged 12–19 years showed that sleep duration was negatively associated with myopia and showed a dose-response pattern (11). Similarly, Ayaki et al. (12) found in 278 Japanese children aged 10–19 years that children with high myopia had the shortest sleep duration compared to other groups ($p < 0.01$). In a study of Chinese children aged 6–18 years, Gong et al. (26) found a progressively lower risk of myopia in children who slept about 8 and 7 h/d or less compared to those who slept 9 h/d or more (OR,2.12; 95%CI, 1.94∼2.31; OR, 3.37; 95%CI, 3.07∼3.70, respectively). We speculate that this may be due to non-cycloplegic refraction and different ages leading to inconsistent results. Non-cycloplegic refraction may overestimate the prevalence of myopia in children (27), leading to refractive category errors. In our study, the extensive age range is also an important confounding factor that cannot be ignored. The prevalence of myopia increases with age, and sleep duration decreases gradually, which is related to the vast educational pressure on children. Additionally, our study was conducted during COVID-19 pandemic and children's activities were limited. Their lifestyles changed dramatically (28, 29), such as increased screen time (17) and decreased time outdoors (18), and their sleep would also be affected (19). People's lifestyle is also different from usual in a specific living environment, and children's myopic shifts are changed. Several studies reported higher myopia incidence (by around 2.0–2.6 fold) among Chinese children compared to pre-COVID in the period during COVID-19 (20, 30–32). The narrow sleep duration classification (74.4% children more than 8 h/d) and higher myopic prevalence (84.7% myopic children) may partially explain the inconsistent results of our study.

At present, the mechanism between sleep and myopia is not precise. A potential mechanism explanation was that the disorder of circadian rhythm might be related to the onset and development of myopia. When the eyes develop to high myopia, the pathological changes of intrinsically photosensitive retinal ganglion cells (ipRGCs) may be caused by the tissue changes of the retina due to axial elongation. Animal model studies have demonstrated that myopia progression may increase the risk of retinal stretch and damage, damaging the ipRGCs in the inner retina (33, 34). And ipRGCs are closely related to light reception and circadian rhythm. In patients with blindness and cataracts, reduced transmittance and photoreception in the eyes lead to disturbances in circadian rhythm and sleep disorders (35). There is a distinct circadian rhythm in children's eyes, with intraocular pressure, AL, choroidal thickness, and retinal thickness all showing particular rhythmic changes (36). Dopamine expression levels have significant circadian rhythmicity and are regulated by the rhythm clock and melatonin, which have an essential role in myopia development (37). Stone et al. suggested that retinal rhythm and clock genes may underlie refractive control (38). Bmal1 is an important molecule that regulates rhythm, and it has been reported that retina-specific Bmal1 knockout mice of different ages exhibit a myopic compared to wild-type mice. The phenotype suggests that rhythm abnormalities may be associated with myopia (39). Chakraborty et al. found that myopia was associated with delayed melatonin circadian rhythm phasing in young adults and lower melatonin output (40).

The strengths of this study included the large sample size and the use of cycloplegic SE and AL, thus minimizing errors in estimating SE and myopia categories. The online questionnaire provided a convenient way to address the questionnaire, minimizing the entry errors of paper questionnaires during the transfer to digital data. Additionally, we provided data on children's sleep duration and myopia in specific lifestyles during the COVID-19 pandemic. However, there were several limitations should be mentioned. First, sleep duration was collected from questionnaires, and the results may be subject to recall bias resulting in reduced accuracy. Although the differences in sleep duration obtained using the questionnaire and polysomnography were minimal (41). Questionnaires to collect sleep data may be a suitable method in studies with large samples. Second, sleep data did not include bedtime, wake time, and sleep quality. However, prior studies could not provide sufficient evidence to support the association of sleep quality and bedtime with myopia (15, 42, 43). Third, the study did not include screen time in children. More screen time might lead to decrease sleep duration. Finally, the present study was cross-sectional and could not clarify the causal relationship between sleep duration and myopia. And Our study conducted during the COVID-19 pandemic with specific lifestyles might not be representative to clarify these associations, and more studies on unspecific lifestyles are needed to confirm.

5. Conclusions

In conclusion, this study showed no independent association between sleep duration and myopia, cycloplegic SE and AL among Chinese children during the COVID-19 pandemic-related lifestyles. Cohort studies with precise sleep data to confirm the relationship between sleep and myopia should be conducted in unspecific lifestyles.

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 study obtained ethical approval from the Ethics Committee of The Second Hospital of Fujian Medical University (No. 2022244) and followed the principles of the Declaration of Helsinki. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LH and JL designed the study. LH, XC, and JL drafted the initial manuscript. JL and XC collected the data. LH, JL, and TC analyzed the data. LH, XC, JL, XF, TC, YY, JC, and JH reviewed and edited the manuscript. JH acts as a guarantor of the study. All authors reviewed and approved the final version of the manuscript.

Funding

This study was supported by the Special Task of the Ministry of Education of the People's Republic of China (087280), Fujian Medical University High-level Talents Scientific Research Launch Fund (XRCZX2021011), and Sanming Project of Medicine in Shenzhen (SZSM201812090).

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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frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 17 January 2023
DOI 10.3389/fped.2023.1095495

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 11 November 2022
ACCEPTED 02 January 2023
PUBLISHED 17 January 2023

CITATION
Wang M, Cui C, Yu S-A, Liang L-l, Ma J-X and Fu A-C (2023) Effect of 0.02% and 0.01% atropine on ocular biometrics: A two-year clinical trial.
Front. Pediatr. 11:1095495.
doi: 10.3389/fped.2023.1095495

Effect of 0.02% and 0.01% atropine on ocular biometrics: A two-year clinical trial

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Background: Several studies have shown that various concentrations of low-concentration atropine can reduce myopia progression and control axial elongation safely and efficiently in children. The aim of this study was to evaluate the effects of 0.02% and 0.01% atropine on ocular biometrics.
Methods: Cohort study. 138 and 142 children were randomized to use either 0.02% or 0.01% atropine eye drops, respectively. They wore single-vision (SV) spectacles, with one drop of atropine applied to both eyes nightly. Controls ($N = 120$) wore only SV spectacles. Ocular and corneal astigmatism were calculated using Thibos vector analysis and split into J0 and J45.
Results: The changes in cycloplegic spherical equivalent refraction (SER) and axial length (AL) were -0.81 ± 0.52D, -0.94 ± 0.59D, and -1.33 ± 0.72D; and 0.62 ± 0.29 mm, 0.72 ± 0.31 mm, and 0.89 ± 0.35 mm in the 0.02% and 0.01% atropine and control groups, respectively (all $P < 0.05$). Both anterior chamber depth (ACD) and ocular astigmatism (including J0) increased, and lens power decreased in the three groups (all $P < 0.05$). However, there were no differences in the changes in ACD, ocular astigmatism, and lens power among the three groups (all $P > 0.05$). Intraocular pressure (IOP), corneal curvature, ocular astigmatism J45, and corneal astigmatism (including J0 and J45) remained stable over time in the three groups (all $P > 0.05$). The contributions to SER progression from the changes in AL, lens and corneal power of the three groups were similar ($P > 0.05$). The contribution of AL change alone to the change in SER was 56.3%, 63.4% and 78.2% in the above corresponding three groups.
Conclusions: After 2 years, 0.02% and 0.01% atropine had no clinical effects on corneal and lens power, ocular and corneal astigmatism, ACD or IOP compared to the control group. 0.02% and 0.01% atropine helped to control myopia progression mainly by reducing AL elongation.

KEYWORDS
myopia, children, efficacy, ocular biometrics, low-concentration atropine

Introduction

Myopia, also known as short-sightedness, continues to worsen over time because of changes in lifestyle and behavior, leading to high myopia. Prominently, high myopia, also called pathologic myopia, is relevant to excessive axial length (AL) growth, which can exponentially increase a person's risk of developing sight-threatening eye diseases such as macular hemorrhage, retinal detachment, glaucoma and cataracts (1–3). Therefore, effective treatment controlling myopia progression is critically important to preserve eye health and quality of life.

Several studies have shown that various concentrations of low-concentration atropine can reduce myopia progression and control axial elongation safely and efficiently in children (4–12). To date, five studies (5, 6, 11, 13, 14) on the efficiency of low-concentration atropine in managing myopia progression have been conducted over two years. However, there were different results regarding whether the effects of low-concentration atropine were similar in the second and first years; two 2-year studies (6, 11) found that the second-year efficacies of low-concentration atropine were similar to the first year, and another 2-year study (13) found that low-concentration atropine was more effective in the second year than in the first year.

Currently, only one 1-year study (15) found that low-concentration atropine had no effects on corneal and lens power, and antimyopic impact of low-concentration atropine acted mainly to reduce AL elongation. However, how ocular biometrics change and which ocular biometrics are associated with the antimyopic effects of low-concentration atropine for a longer time are unknown. In this prospective two-year cohort trial, the changes in ocular biometrics [including ocular and corneal astigmatism after vector analysis, corneal and lens power, intraocular pressure, and anterior chamber depth (ACD)] and their respective contributions to spherical equivalent refraction (SER) (i.e., spherical power plus 1/2 cylindrical power) progression were evaluated in children using 0.02% and 0.01% atropine compared with a control group.

Material and methods

Data source

The research approach has been published previously and is briefly described here (6, 7). Four hundred Chinese children with myopia (Han nationality, right eyes) who attended the First Affiliated Hospital of Zhengzhou University were enrolled on this cohort study between July 2016 and June 2018. The inclusion criteria were as follows: (1) 6–14 years of ages; (2) SER from −1.25 to 6.00 D; (3) astigmatism of <2.0 D; (4) anisometropia of <1.0 D; (5) monocular best-corrected visual acuity of 16/20 or better; (6) intraocular pressures (IOP) between 10 and 21 mmHg. There were no other eye diseases or past surgery. The exclusion criteria were previous use of atropine, pirenzepine, rigid gas-permeable, and orthokeratology lenses to reduce the progression of myopia and failure to adhere to the study's follow-up schedule.

Eligible children had the option of atropine or no atropine, and then the atropine groups were subsequently divided into either 0.01% or 0.02% in a double-blinded and randomized manner. This study conforms to the ethical norms and standards in the Declaration of Helsinki. The possible risks were thoroughly explained before the commencement of the treatment.

One clinician examined all subjects, who was unaware of the experimental groups of each participant. The children in the control group wore the full-correction single-vision (SV) spectacles with the least negative power, consistent with the best visual acuity of long-term wearing. Both experimental groups were prescribed SV spectacles according to the same protocol as the control group. The children in the experimental groups were given one drop of atropine eye drops in both eyes every night at bedtime.

After instilling one drop of compound tropicamide in both drops (0.5% tropicamide and 0.5% neo-synephrine) (Santen, Japan) 4 times at 10-minute intervals. Cycloplegic autorefraction was performed 10 min after the last administration of the eyedrop. Taking three autorefraction measurements (Topcon RM 8000A, CA, United States), the mean was obtained. The degree of myopia was expressed as the SER. Using Thibos vector analysis (16–18) calculated ocular and corneal astigmatism(minimum-maximum keratometry), which were split into its power vector components, J0 (with-the-rule astigmatism) and J45 (oblique).The ocular and corneal astigmatic components are denoted as OJ0, OJ45 and CJ0, CJ45, respectively. A non-contact partial coherence interferometer (IOLMaster-500, Carl Zeiss, Germany) was used for biometric measurements (AL, ACD, and corneal curvature) after cycloplegia. Five successive measurements were taken on each occasion, and their mean was used as the representative value. The machine IOLMaster-500 had corrected by the model eye every month. The signal-to-noise ratio for AL readings is greater than 2.0 according to the manufacturer's recommendations. IOP was measured using non-contact tonometry (TX-10, Canon, Japan). Using the Bennett-Rabbetts formula (19) calculated the lens power.

$$P_{L,\mathrm{BR}} = \frac{L(S_{\mathrm{CV}} + K) - 1000n}{(L - \mathrm{ACD} - c_{\mathrm{BR}})\left(\frac{\mathrm{ACD} + c_{\mathrm{BR}}}{1000n}(S_{\mathrm{CV}} + K) - 1\right)}$$

Here: $P_{L,\mathrm{BR}}$-lens power using Bennett–Rabbetts method; L-axial length, S_{cv}-spherical equivalent refraction at the corneal vertex [$S_{cv} = S/(1 - 0.014S)$, S-spherical refraction at spectacle back vertex plane]; K-corneal power, $n = 1.336$ (the refractive index of aqueous and vitreous humors); ACD-anterior chamber depth; $c_{\mathrm{BR}} = 2.564$ mm (distance between thin lens position and anterior lens surface).

Statistical analysis

Only data from the right eye was used for analysis. Continuous baseline variables were expressed as the mean ± SD and evaluated using an analysis of variance. The chi-squared test was used to compare the number of male and female. A generalized additive mixed model was used to estimate the longitudinal trend with time (at baseline, 12, and 24 months) for dependent variables such as SER, corneal curvature, ocular astigmatism (OJ0 and OJ45), and corneal astigmatism (CJ0 and CJ45), and differences in the rate of change among the three groups. The change represents the slope for each treatment group of dependent variables over time, and the change difference represents the difference in the slope of dependent variables over time between the groups. Multivariate linear regression analysis was used to detect the relationship between the dependent variable (change in SER) and independent variables (sex, baseline age and changes in AL, lens power, corneal curvature, ACD, IOP). The adjusted R^2 value was used to represent the proportion of the variance of the dependent variable predicted by the independent variable in the regression model. Statistical analysis was performed using the Empower software (www.empowerstats.com); X & Y Solutions, Boston, MA, United States) and SPSS 25.0 (IBM SPSS, Chicago, United States). Statistical significance was set at $P < 0.05$.

Results

In total, there were 138, 142, and 120 children in the 0.02% atropine, 0.01% atropine, and control groups, respectively (Figure 1). There were no differences in any of the baseline parameters between the three groups (Table 1).

Changes in SER and AL over the two-year period

Over the two-year period, the changes in SER were −0.81 ± 0.52 D, −0.94 ± 0.59 D and −1.33 ± 0.72 D and changes in AL were 0.62 ± 0.29 mm, 0.72 ± 0.31 mm, and 0.89 ± 0.35 mm in the 0.02% and 0.01% atropine, and control groups, respectively. There were significant differences in the changes in SER and AL among the three groups (all $P < 0.05$) (Table 2 and Figure 2). In the 0.02% and 0.01% atropine and control groups, the changes in SER were −0.39 ± 0.35 D, −0.48 ± 0.45 D, and −0.70 ± 0.60 D, respectively, during the first year of treatment and −0.42 ± 0.32 D, −0.46 ± 0.45 D, and−0.63 ± 0.59 D, respectively, during the second year of treatment. The changes in AL were 0.30 ± 0.21 mm, 0.37 ± 0.22 mm, and 0.47 ± 0.35 mm during the first year of treatment and 0.32 ± 0.21 mm, 0.35 ± 0.22 mm, and 0.42 ± 0.34 mm during the second year in the three groups, respectively. The changes in SER during the first year in the three groups (all $P > 0.05$), and AL showed a tendency similar to that of SER every year.

Changes in other ocular biometric parameters over the two-year period

The changes in ACD, IOP, corneal curvature, astigmatism, and lens power in the 0.02% and 0.01% atropine and control groups are summarized in Table 2 and Figures 3–5. The IOP, flattest, and steepest corneal curvature remained stable over time before and after treatment, and there were no significant differences in the changes in IOP, flattest, and steepest corneal curvatures (Figures 3, 4) among the three groups (all $P > 0.05$). The ACD increased over time in all three groups, but the degree of change was similar (Figure 3). Lens power decreased over time in each group, but the differences were identical (Figure 3).

The ocular astigmatism changes were −0.38 ± 0.29 D, −0.47 ± 0.38 D, −0.41 ± 0.35 D and ocular astigmatism J0 changes were 0.19 ± 0.28 D, 0.22 ± 0.36 D, 0.18 ± 0.31 D in the 0.02%, 0.01% atropine and control groups, respectively. There was a small but significant increase in ocular astigmatism (including J0) (all $P < 0.05$) but no change in J45 (all $P > 0.05$; Figure 5) in the three groups. However, there were no significant differences in the changes in ocular astigmatism (including J0) among the three groups. The corresponding changes in corneal astigmatism were −0.20 ± 0.34 D, −0.28 ± 0.35 D, and −0.26 ± 0.26 D in the three groups. There was no significant increase or difference in the change in corneal astigmatism (including J0 and J45) among the three groups (all $P > 0.05$).

The contributions of ocular biometric changes (sex, baseline age and changes in AL, lens power, corneal curvature, ACD, IOP) to SER progression were summarized in Table 3. Myopia progression was mainly caused by AL elongation, which contributed 56.3%,63.4% and 78.2% of the myopia progression in the 0.02%, 0.01% atropine and control groups, followed by corneal and lens power. The relationship between the changes in AL (independent variable) and SER (dependent variable) was −1.71, −1.65 and −2.09 in the above corresponding three groups (all $P < 0.001$). Considering the ocular biometric changes (changes in AL, lens power, corneal curvature, ACD, IOP), sex, and age, the multiple linear regression model explained 80.6%, 77.1%, 84.7% of the SER change in the three groups (Model 4).

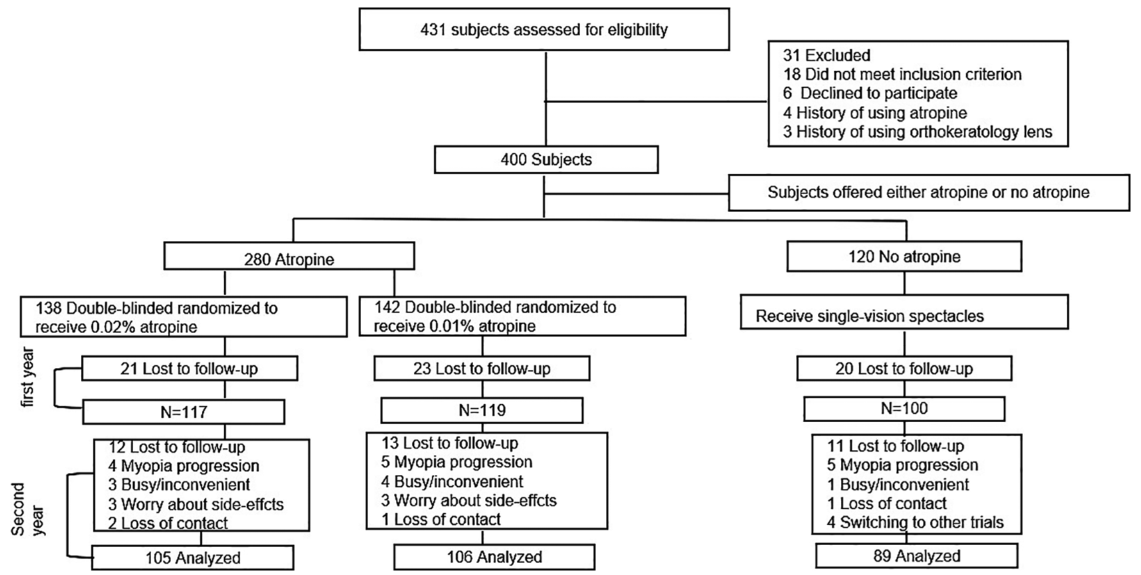

FIGURE 1
Subject recruitment and randomization flowchart.

TABLE 1 Baseline characteristics of study participants who completed 2 years vs. those who have not completed 2 years.

Variables	Completed 2 years ($N = 300$)				Not completed 2 years ($N = 100$)			
	0.02% atropine ($N = 105$)	0.01% atropine ($N = 106$)	control group ($N = 89$)	*P* Value	0.02% atropine ($N = 33$)	0.01% atropine ($N = 36$)	control group ($N = 31$)	*P* Value
Age (year)	9.6 ± 1.8	9.4 ± 1.7	9.3 ± 1.4	0.56	9.3 ± 2.1	9.2 ± 2.5	9.6 ± 2.3	0.66
Sex (male, *n* and %)	55 (52.4%)	55 (51.9%)	47 (52.8%)	0.99	18 (54.5%)	20 (55.6%)	15 (48.4%)	0.82
Spherical equivalent refractive errors (D)	−2.81 ± 1.47	−2.76 ± 1.56	−2.66 ± 1.39	0.62	−2.70 ± 1.79	−2.65 ± 1.88	−2.72 ± 1.75	0.58
Axial length (mm)	24.61 ± 0.69	24.60 ± 0.72	24.54 ± 0.69	0.80	24.58 ± 0.76	24.56 ± 0.79	24.56 ± 0.80	0.58
Anterior chamber depth (mm)	3.69 ± 0.20	3.70 ± 0.20	3.66 ± 0.21	0.92	3.62 ± 0.26	3.74 ± 0.27	3.69 ± 0.31	0.88
Intraocular pressure (mmHg)	15.9 ± 3.1	16.9 ± 2.8	17.0 ± 3.0	0.38	15.9 ± 3.1	16.9 ± 2.8	17.0 ± 3.0	0.42
Lens power (D)	22.75 ± 1.54	22.73 ± 1.41	22.78 ± 1.49	0.80	22.76 ± 1.52	22.75 ± 1.43	22.77 ± 1.51	0.80
Flattest *K* (D)	42.79 ± 1.50	42.81 ± 1.33	42.90 ± 1.09	0.76	42.81 ± 1.56	42.83 ± 1.44	42.94 ± 1.32	0.81
Steepest *K* (D)	43.98 ± 1.61	43.98 ± 1.45	44.02 ± 1.21	0.64	43.94 ± 1.65	43.99 ± 1.58	44.08 ± 1.46	0.40
Ocular astigmatism (D)								
Total	−0.43 ± 0.49	−0.42 ± 0.54	−0.34 ± 0.47	0.42	−0.41 ± 0.45	−0.41 ± 0.51	−0.36 ± 0.46	0.07
J0	0.16 ± 0.25	0.19 ± 0.27	0.17 ± 0.23	0.54	0.18 ± 0.25	0.17 ± 0.25	0.20 ± 0.24	0.07
J45	0.00 ± 0.15	−0.01 ± 0.09	0.00 ± 0.06	0.71	−0.01 ± 0.12	−0.02 ± 0.09	−0.01 ± 0.08	0.99
Corneal astigmatism (D)								
Total	−1.15 ± 0.53	−1.22 ± 0.61	−1.12 ± 0.40	0.32	−1.18 ± 0.55	−1.20 ± 0.60	−1.13 ± 0.40	0.55
J0	−0.53 ± 0.26	−0.58 ± 0.30	−0.54 ± 0.21	0.07	−0.60 ± 0.28	−0.62 ± 0.33	−0.59 ± 0.19	0.07
J45	0.04 ± 0.21	0.06 ± 0.18	0.02 ± 0.13	0.31	0.04 ± 0.20	0.05 ± 0.16	0.04 ± 0.15	0.49

Discussion

This two-year cohort clinical trial showed that 0.02% atropine had a better effect on controlling myopia progression and axial elongation than 0.01% atropine. Additionally, no significant differences in the changes in corneal and lens power, ocular and corneal astigmatism, ACD, and IOP between the 0.02% atropine, 0.01% atropine, and control groups. Contributions to SER progression from AL, corneal and lens power in the three groups were similar, axial elongation contributed to most of the SER progression, and 0.02% and 0.01% atropine helped to control myopia progression mainly by reducing axial elongation.

Several studies (5, 11, 20, 21), have found that the efficacy of low-dose atropine for myopia control is concentration-dependent. The higher the concentration of low-dose atropine, the better the myopia progression control, and the less the axial elongation. Also, low-dose atropine synchronously controlled SER progression and AL elongation, as described in Hong Kong (11), Korea (21), and mainland China studies (6, 7). Although 0.02% and 0.01% atropine controlled the myopia progression and AL elongation synchronously, the control rate of AL elongation was less than that of myopia progression. This was consistent with other studies that explored the significantly higher control rate of SER progression than AL elongation in myopic children using low-dose atropine and whose baseline profiles were similar to those of the current study (7, 11, 15, 22, 23). There are two potential explanations for this finding. First, changes in AL were not the only factors causing changes in SER. LAMP study (15) found that AL alone contributed to an SER variance ranging from 72% to 81%. The remaining SER variance was accounted for by lens and corneal factors in myopic children using low-dose atropine. In the current study, we found no significant effect on corneal and lens power of 0.02% and 0.01% atropine compared with the control group and similar contributions to SER progression from AL, corneal and lens power between two atropine and control groups. The contribution of change in AL alone to the change in SER was 56.3% and 63.4% in 0.02% and 0.01% atropine groups, axial elongation contributed to most of the SER progression, and the remaining change in SER was accounted for by corneal and lens power, and other factors that have not yet been discovered. Second, children's AL elongation includes small average age-related growth and SER progression-associated growth (24, 25). This may partly explain why the effect of low atropine on total axial elongation is less than that of SER progression. Overall, the myopia control effects of 0.02% and 0.01% atropine in myopia children were mainly achieved by inhibiting axial elongation, and lens power, corneal curvature, and age were rarely involved.

Furthermore, 0.02% and 0.01% atropine did not affect corneal and ocular astigmatism (after vector decomposition) and ACD compared to with the control group in the current two-year study.

TABLE 2 Change and change difference of ocular biometrics in three groups over 2-year[a], mean (95% CI).

Variables	0.02% atropine		0.01% atropine		Control group		Change difference between-group			
	Baseline	24 months change	Baseline	24 months change	Baseline	24 months change	0.02% vs. 0.01% atropine	*P*-value	0.01% atropine vs. control group	*P*-value
Spherical equivalent refractive error (SER)	−2.81 (−2.90 to −2.72)	−0.12* (−0.19 to −0.05)	−2.76 (−2.81 to −2.71)	−0.17* (−0.25 to −0.09)	−2.66 (−2.70 to −2.62)	−0.24* (−0.28 to −0.17)	0.05 (0.01 to 0.07)	0.02	0.07 (0.04 to 0.10)	0.04
Axial length (AL)	24.61 (24.48 to 24.74)	0.10* (0.02 to 0.18)	24.60 (24.48 to 24.72)	0.15* (0.05 to 0.25)	24.54 (24.41 to 24.67)	0.26* (0.11 to 0.41)	0.05 (0.01 to 0.09)	0.04	0.11 (0.04 to 0.18)	0.002
Anterior chamber depth	3.69 (3.22 to 4.16)	0.08* (0.03 to 0.13)	3.70 (3.32 to 4.08)	0.06* (0.02 to 0.10)	3.66 (3.29 to 4.03)	0.06* (0.03 to 0.09)	0.01 (−0.01 to 0.02)	0.58	−0.04 (−0.09 to 0.02)	0.83
Intraocular pressure	15.9 (15.1 to 16.7)	−0.09 (−0.17 to 0.01)	16.9 (16.2 to 17.6)	−0.16 (−0.35 to 0.03)	17.0 (16.2 to 17.8)	−0.12 (−0.25 to 0.02)	−0.07 (−0.16 to 0.02)	0.12	0.04 (−0.01 to 0.08)	0.23
Lens power	22.75 (22.5 to 23.0)	−0.04* (−0.07 to −0.01)	22.73 (22.33 to 23.13)	−0.04* (−0.08 to −0.01)	22.78 (22.53 to 23.03)	−0.04* (−0.07 to −0.02)	0.005 (−0.003 to 0.012)	0.56	−0.002 (−0.006 to 0.002)	0.66
Flattest K	42.79 (42.44 to 43.14)	−0.05 (−0.10 to 0.01)	42.81 (42.46 to 43.16)	−0.06 (−0.14 to 0.02)	42.90 (42.51 to 43.29)	−0.10 (−0.26 to 0.04)	−0.01 (−0.04 to 0.02)	0.45	−0.04 (−0.08 to 0.01)	0.19
Steepest K	43.98 (43.58 to 44.38)	0.08 (−0.03 to 0.19)	43.98 (43.52 to 44.44)	0.09 (−0.03 to 0.21)	44.02 (43.72 to 44.32)	0.06 (−0.02 to 0.14)	0.01 (−0.03 to 0.05)	0.51	−0.02 (−0.05 to 0.01)	0.33
Total ocular astigmatism	0.16 (0.10 to 0.22)	−0.19* (−0.26 to −0.12)	0.19 (0.12 to 0.26)	−0.23* (−0.35 to −0.11)	0.17 (0.11 to 0.23)	−0.20* (−0.30 to −0.10)	−0.03 (−0.06 to 0.01)	0.26	0.03 (−0.02 to 0.08)	0.58
Ocular astigmatism (J0)	0.16 (0.13 to 0.19)	0.09* (0.06 to 0.12)	0.19 (0.14 to 0.24)	0.11* (0.05 to 0.17)	0.17 (0.08 to 0.26)	0.08* (0.02 to 0.14)	0.02 (−0.01 to 0.05)	0.35	−0.03 (−0.06 to 0.01)	0.47
Ocular astigmatism (J45)	0.00 (−0.01 to 0.00)	−0.01 (−0.03 to 0.01)	−0.01 (−0.04 to 0.02)	−0.01 (−0.03 to 0.01)	0.00 (−0.03 to 0.03)	−0.01 (−0.03 to 0.01)	−0.01 (−0.04 to 0.02)	0.10	0.01 (−0.01 to 0.03)	0.24
Total corneal astigmatism	−1.15 (−1.45 to −0.85)	−0.10 (−0.25 to 0.05)	−1.22 (−1.32 to −1.12)	−0.14 (−0.31 to 0.03)	−1.12 (−0.82 to −1.42)	−0.13 (−0.33 to 0.07)	−0.04 (−0.08 to 0.01)	0.37	0.01 (−0.02 to 0.04)	0.95
Corneal astigmatism (J0)	−0.53 (−0.45 to −0.61)	0.02 (−0.01 to 0.04)	−0.58 (−0.41 to −0.75)	−0.04 (−0.10 to 0.02)	−0.54 (−0.24 to −0.84)	−0.03 (−0.07 to 0.01)	−0.06 (−0.13 to 0.01)	0.28	0.02 (−0.01 to 0.05)	0.75
Corneal astigmatism (J45)	0.04 (0.01 to 0.07)	0.003 (−0.001 to 0.007)	0.06 (0.02 to 0.10)	−0.005 (−0.01 to 0.01)	0.02 (0 to 0.04)	0.005 (−0.001 to 0.010)	0.01 (−0.01 to 0.03)	0.78	−0.02 (−0.05 to 0.01)	0.48

Note: CI, confidence interval. Change: represents the slope of SER, AL, and other ocular biometrics over time for three groups. Change difference: represents the difference in SER, AL, and other ocular biometrics over time between each two groups.

[a]A generalized additive mixed model was used to estimate the longitudinal trend from baseline to 24 months.

*Represents: changes were significantly different.

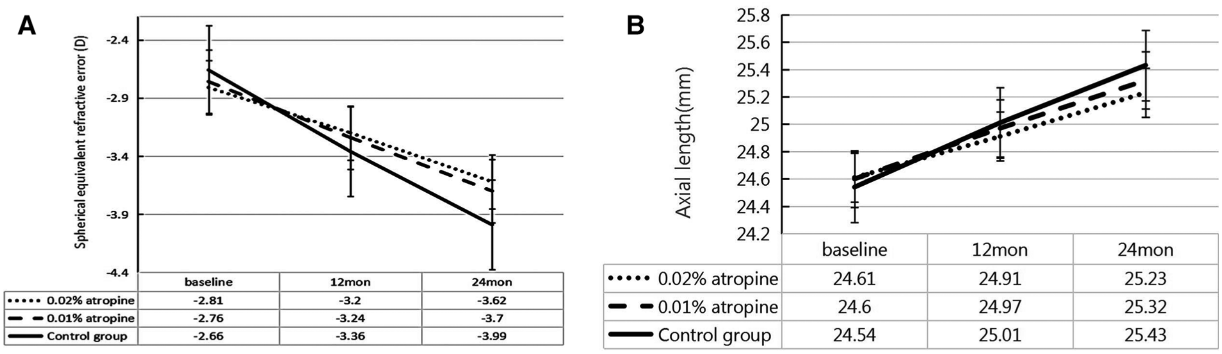

FIGURE 2
Measurement of spherical equivalent refractive error (A) and axial length (B) over time.

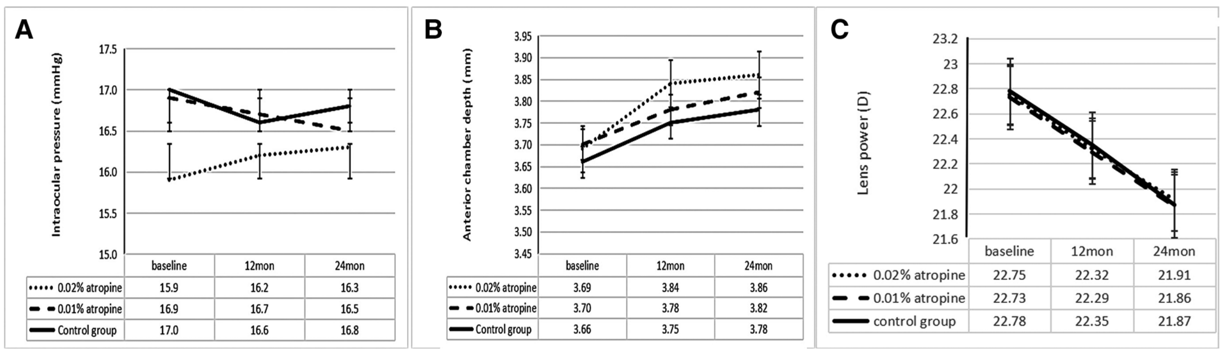

FIGURE 3
Measurement of intraocular pressure (A) and anterior chamber depth (B) and lens power (C) over time.

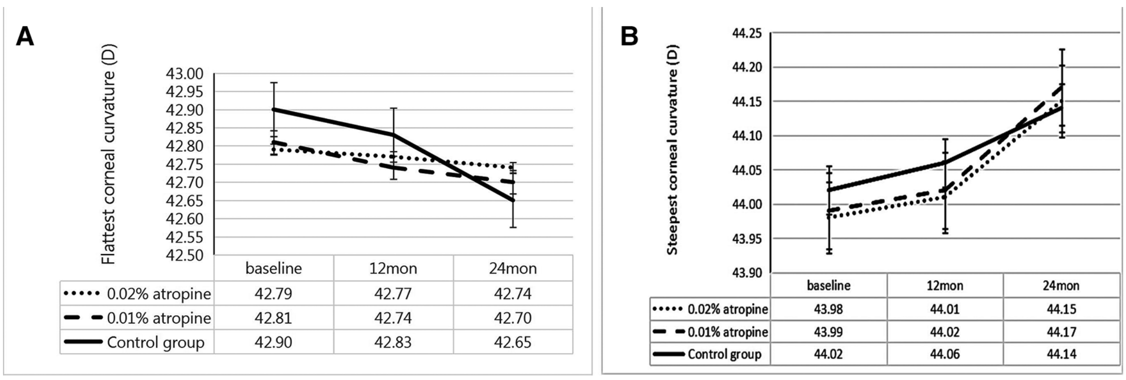

FIGURE 4
Measurement of flattest corneal curvature (A) and steepest corneal curvature (B) over time.

LAMP study (15) also found that 0.05%, 0.025%, and 0.01% atropine had no significant effects on corneal astigmatism in the first year of treatment. However, the changes in ocular and corneal astigmatism are not vectorized.) Studies (26, 27) have found that the change in astigmatism was presumably because of the flattening and motorial of the lens during cycloplegia, which results from the axis tilt around the horizontal axis. When the atropine concentration was below 0.05%, it may have been too low to change the lens thickness and power and not increase astigmatism further. In addition, 0.02% and 0.01% atropine did not affect IOP in the current study, although pupillary dilation caused by low-dose atropine is a predisposing factor for high IOP. Other reports have also found that using different concentrations of atropine (e.g., 1%, 0.5%, 0.25%, 0.125%, and 0.1%) has no effect on IOP in myopic

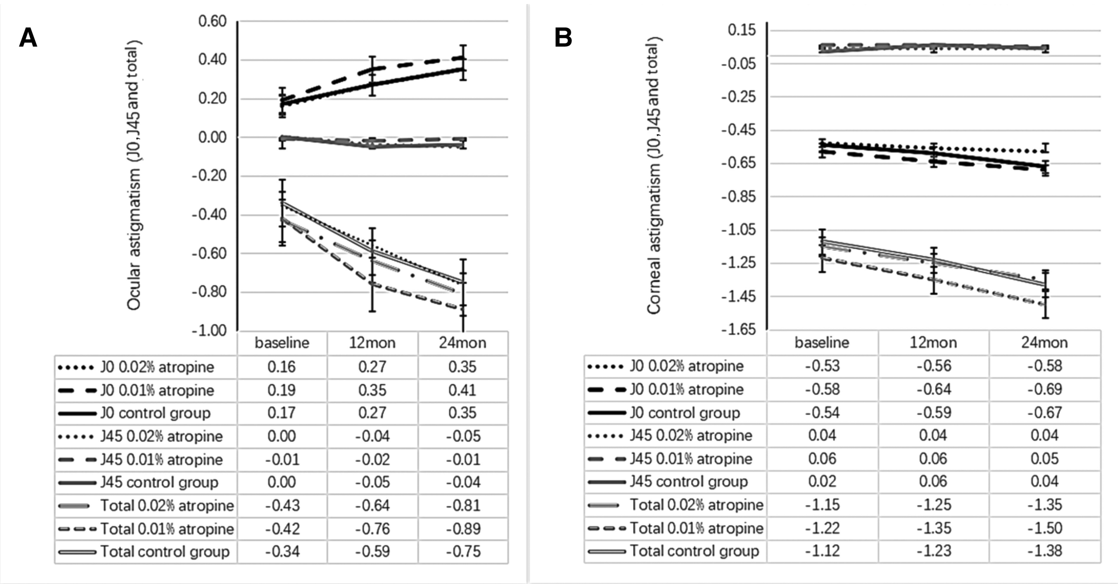

FIGURE 5
Measurement of ocular astigmatism (J0, J45 and total) (A) and corneal astigmatism (J0, J45 and total) (B) over time.

TABLE 3 Multivariate linear regression analyses of change in spherical equivalent refractive error and ocular biometrics.

Variables	0.02% atropine			0.01% atropine			Control group		
	β	Standard error	*P* value	*β*	Standard error	*P* value	*β*	Standard error	*P* value
M1									
ΔAL (mm)	−1.71	0.24	<0.001	−1.65	0.20	<0.001	−2.09	0.11	<0.001
Adjusted R^2 (%)	56.3			63.4			78.2		
M2									
ΔAL (mm)	−2.23	0.21	<0.001	−1.80	0.19	<0.001	−2.20	0.10	<0.001
ΔLens power (D)	−0.30	0.06	0.001	−0.16	0.06	0.007	−0.29	0.06	<0.001
Adjusted R^2 (%)	74.7			69.2			82.9		
M3									
ΔAL (mm)	−2.41	0.20	<0.001	−1.84	0.18	<0.001	−2.40	0.12	<0.001
ΔLens power (D)	−0.39	0.06	<0.001	−0.24	0.07	0.001	−0.36	0.06	<0.001
ΔCorneal power (D)	−0.60	0.22	0.009	−0.47	0.23	<0.001	−0.68	0.23	0.003
Adjusted R^2 (%)	78.5			71.6			84.2		
M4									
ΔAL (mm)	−2.51	0.21	<0.001	−2.04	0.17	<0.001	−2.41	0.12	<0.001
ΔLens power (D)	−0.38	0.06	<0.001	−0.31	0.07	<0.001	−0.36	0.06	<0.001
ΔCorneal power (D)	−0.78	0.23	0.002	−0.51	0.16	0.002	−0.70	0.23	0.003
ΔACD (mm)	0.33	0.13	0.60	0.30	0.14	0.06	0.37	0.24	0.12
ΔIOP (mmHg)	0.03	0.01	0.02	−0.02	0.18	0.21	−0.002	0.004	0.71
Sex	0.16	0.07	0.81	−0.05	0.06	0.45	−0.005	0.02	0.85
Age	−0.03	0.02	0.25	−0.04	0.02	0.09	−0.02	0.007	0.03
Adjusted R^2 (%)	80.6			77.1			84.7		

Note: Δ, change over 2 years; AL, axial length; ACD, anterior chamber depth; IOP, intraocular pressure.

children (28–30). Overall, considering the ocular biometrics such as corneal curvature, lens power, corneal and ocular astigmatism, ACD, and IOP, 0.02% and 0.01% atropine all appear to be safe for children with myopia.

The strength of this study was to include a control group. The human ethics committee advised that subjects were to be offered either atropine or no atropine, and double-blinded randomization is carried out only for the two active arms of the study. The control and test groups had similar demographic and clinical parameters. The subjects were recruited using identical inclusion criteria contemporaneously and from the same population. A limitation of the current study is that a changing trend in ocular biological parameters after atropine withdrawal was not observed. This topic is currently under further investigation.

Conclusion

Use of 0.02% and 0.01% atropine had no clinically significant effect on corneal curvature, corneal and ocular astigmatism, lens power, ACD, or IOP. 0.02% and 0.01% atropine mainly help control myopia by reducing axial elongation over the two-year follow-up period.

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 he Ethics Board of the First Affiliated Hospital of Zhengzhou University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Participated in study design: MW, CC, SAY, LLL, JXM and ACF. Conduct of the study: MW, CC, SAY, LLL, JXM and ACF. Performed data analysis: MW, CC, SAY, LLL, JXM and ACF. Wrote or contributed to the writing of the manuscript: MW, CC, SAY, LLL, JXM and ACF. All authors contributed to the article and approved the submitted version.

Funding

Key R&D and Promotion Project of Henan Science and Technology Department (201801591); Key Scientific Research Project of Universities of Henan Education Department (19A320066).

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.

Publisher's note

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TYPE Original Research
PUBLISHED 18 January 2023
DOI 10.3389/fpubh.2022.1059465

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 01 October 2022
ACCEPTED 20 December 2022
PUBLISHED 18 January 2023

CITATION
Du W, Ding G, Guo X, Abudukeyimu K, Wang Y, Wang L, Qi X, Ning Y, Hua N, Song L, Li X, Li J, Zhang Y, Wei N and Qian X (2023) Associations between anthropometric indicators and refraction in school-age children during the post-COVID-19 era. *Front. Public Health* 10:1059465. doi: 10.3389/fpubh.2022.1059465

Associations between anthropometric indicators and refraction in school-age children during the post-COVID-19 era

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Purpose: To explore the associations between anthropometric indicators and refraction in school-aged children in the post-COVID-19 era.

Methods: Data were collected from 25,644 children aged 7 to 12 years in 48 elementary schools in Tianjin. The comprehensive examination included height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), refraction, and calculation of BMI, with a follow-up visit after 6 months. Myopia was defined as spherical equivalent refraction (SER) $\leq$-0.50 diopter (D). Bivariate correlation coefficients and multiple linear regression models were used to explore the cross-sectional and longitudinal associations between anthropometric indicators (height, weight, BMI, SBP, and DBP) and refraction.

Results: The mean changes in height, weight, BMI, SBP, DBP, and SER of the participants were 4.03 ± 2.18 cm, 3.10 ± 2.39 kg, 0.45 ± 1.16 kg/m^2, 2.26 ± 14.74 mmHg, 2.18 ± 11.79 mmHg and −0.17 ± 0.51 D, respectively. Overall, height, weight, BMI, SBP, and DBP were all correlated with SER ($r = -0.324$, $r = -0.234$, $r = -0.121$, $r = -0.112$, $r = -0.066$, both $p < 0.001$), and changes in height and weight were correlated with changes in SER ($r = -0.034$, -0.031, both $p < 0.001$). Furthermore, multiple linear regression analysis revealed that the association of BMI, SBP, and DBP with SER was significant in myopic children but not in non-myopic children. The association between changes in weight and changes in SER was only present in non-myopic children but not in myopic children.

Conclusion: Height and weight were negatively correlated with SER in both cross-sectional analysis and longitudinal changes, indicating that children's height, weight and growth rate may be used as a reference indicator for myopia risk prediction and myopia progression monitoring.

KEYWORDS

myopia, refraction, anthropometric indicators, associations, school-age children

Introduction

In recent decades, the prevalence of myopia has rapidly increased (1). According to projections, nearly half of the world's population will suffer from myopia by 2050 (2). Among children and adolescents, myopia is also showing a high prevalence. Within East and Southeast Asia, including China, Korea, and Singapore, myopia rates among school-age children are significantly higher than in other parts of the world (3). Myopia's high prevalence severely impacts people's physical and mental health (4). The etiology of myopia has not yet been fully understood, so there is an urgent need to discover the key factors affecting the formation of early myopia through the study of refractive development patterns and then discover effective prevention methods and intervention measures.

As we considered the etiology of myopia, we noted that anthropometric indicators, such as height, were thought to be related to refraction. Previous studies consistently show that height positively correlates with eye axis length (AL) (5, 6). Nevertheless, there is no consensus on the relationship between height and refraction. In addition, some studies report that people with higher body mass index (BMI) are more likely to be myopic (7), but some studies did not find this association (8). In brief, previous studies on the correlation between anthropometric indicators and refraction have not reached consistent conclusions.

The outbreak of a new coronavirus disease (COVID-19) in December 2019 has affected many aspects of people's lives. The Chinese government started closing schools and providing distance education for children nationwide in late January 2020 as an emergency measure to prevent the spreading of the infection. As China entered the post-COVID-19 era, most schools were gradually reopened from August to September 2020. Despite the effectiveness of the overall epidemic prevention efforts, there are still sporadic and recurring outbreaks in some places, which has promoted appropriate adjustments to campus epidemic prevention measures. Usually, campuses act relatively loosely against the epidemic; conversely, campuses will immediately be on alert if the pandemic has signs of resurgence and take anti-epidemic actions such as closing schools.

The COVID-19 pandemic has profoundly affected children's daily life, including insufficient physical activity, excessive sedentary behavior, and unbalanced diets (9, 10). School closures associated with COVID-19 may affect children's physical growth and weight changes (11, 12), and may also accelerate the change of their refraction toward myopia (13, 14). Nearly all previous studies on the relationship between anthropometric indicators and refraction were conducted prior to the COVID-19 outbreak, and they were all cross-sectional in design. A longitudinal set of data is needed to understand the relationship between them during the post-COVID-19 era. Myopia commonly occurs in children during their early school years and increases in magnitude as they age (15). Therefore, it is most appropriate to study the effect of physical growth on the refractive development of growing students. In this study, we explored the associations between anthropometric indicators, including height, weight, BMI and blood pressure and refraction in children aged 7–12 years in the post-COVID-19 era in China.

Methods

Study design and population

This school-based study was approved by the Ethics Board of Tianjin Medical University Eye Hospital. Informed written consent was obtained prior to the start of the study from the parents of all participants according to the Declaration of Helsinki. Anthropometric indicators, including height, weight, BMI and blood pressure, and refraction screening were performed on two consecutive occasions from April to June 2021 and from October to December 2021 in 48 elementary schools in Beichen District, Tianjin, China. All students aged 7–12 were invited, but participation in this study was voluntary. Students without parental consent and those with amblyopia, heterotropia or any ocular or systemic pathologies were excluded. In total, 31,068 children were recruited, and 25,644 (82.5%) children successfully completed two examinations.

Refraction screening

Non-cycloplegic refractive error was tested using the Spot™ vision screener (Welch Allyn, Skaneateles Falls, NY). Testing was conducted by trained staff who obtained results from each child in three trials. During the test, the examiner asks the subject to look at the device binocularly from a one-meter distance. Red reflex images are acquired from the subject, and

TABLE 1 Summary of the characteristics of the participants.

	Total	Myopic	Non-myopic	P* value
Age (years)	9.35 ± 1.50	10.04 ± 1.36	8.97 ± 1.45	<0.001
SER (D)				
Baseline	−0.53 ± 1.44	−1.98 ± 1.44	0.26 ± 0.56	<0.001
After 6 months	−0.69 ± 1.57	−2.28 ± 1.54	0.17 ± 0.63	<0.001
Δ SER	−0.17 ± 0.51	−0.30 ± 0.65	−0.10 ± 0.40	<0.001
Height (cm)				
Baseline	139.16 ± 11.12	143.92 ± 10.57	136.58 ± 10.54	<0.001
After 6 months	143.19 ± 11.39	148.04 ± 10.80	140.56 ± 10.82	<0.001
Δ Height	4.03 ± 2.18	4.12 ± 2.22	3.98 ± 2.16	<0.001
Weight (kg)				
Baseline	36.87 ± 12.46	40.56 ± 12.97	34.87 ± 11.69	<0.001
After 6 months	39.97 ± 13.35	43.93 ± 13.79	37.81 ± 12.59	<0.001
Δ Weight	3.10 ± 2.39	3.37 ± 2.51	2.95 ± 2.31	<0.001
BMI (kg/m^2)				
Baseline	18.60 ± 4.07	19.20 ± 4.23	18.27 ± 3.94	<0.001
After 6 months	19.05 ± 4.14	19.67 ± 4.27	18.71 ± 4.02	<0.001
Δ BMI	0.45 ± 1.16	0.47 ± 1.16	0.44 ± 1.16	0.057
SBP (mmHg)				
Baseline	105.52 ± 12.89	107.18 ± 12.86	104.62 ± 12.82	<0.001
After 6 months	107.78 ± 13.70	110.12 ± 13.82	106.51 ± 13.47	<0.001
Δ SBP	2.26 ± 14.74	2.94 ± 14.68	1.89 ± 14.76	<0.001
DBP (mmHg)				
Baseline	67.13 ± 9.41	67.91 ± 9.36	66.70 ± 9.41	<0.001
After 6 months	69.31 ± 9.99	70.17 ± 9.95	68.85 ± 9.99	<0.001
Δ DBP	2.18 ± 11.79	2.25 ± 11.70	2.14 ± 11.84	0.484

Data are presented as the means with SD. SER, spherical equivalent refraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Determined using independent-samples t-test.

non-cycloplegic refractive status, pupil size and gaze deviation are automatically recorded. The device will flag a referral for a complete eye examination if significant refractive error, anisometropia or strabismus are detected. All screened subjects from this study were successfully tested. The measurement range of the Spot screener was limited to ± 7.50 D. If the refraction was out of range, ± 8.00 D was recorded for further analysis. The child's spherical equivalent refraction (SER) is recorded automatically for both eyes. Myopia was defined as an SER of −0.50 D or less.

Anthropometric measurements

Height and weight were measured by removing heavy clothing and standing barefoot on a calibrated electronic height and weight meter, with the medical staff holding the measuring scale firmly over the subject's head and recording the readings in centimeters (cm) and kilograms (kg), respectively after they had stabilized. BMI was calculated as weight/height and recorded in kilograms per square meter (kg/m^2). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were using an automated device (OMRON HEM-7136). The measurement was taken in the seated position with the right arm supported at heart level after at least 2 min rest and recorded in millimeters of mercury (mmHg).

Statistical analysis

All statistical analyses were performed with the SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and p <0.05 were considered statistically significant. As the biometric data for the right and left eye were highly correlated, analyses were performed using data for the right eye only. Participants were classified into myopic and non-myopic groups based on their refractive status at baseline examination. The difference between the second

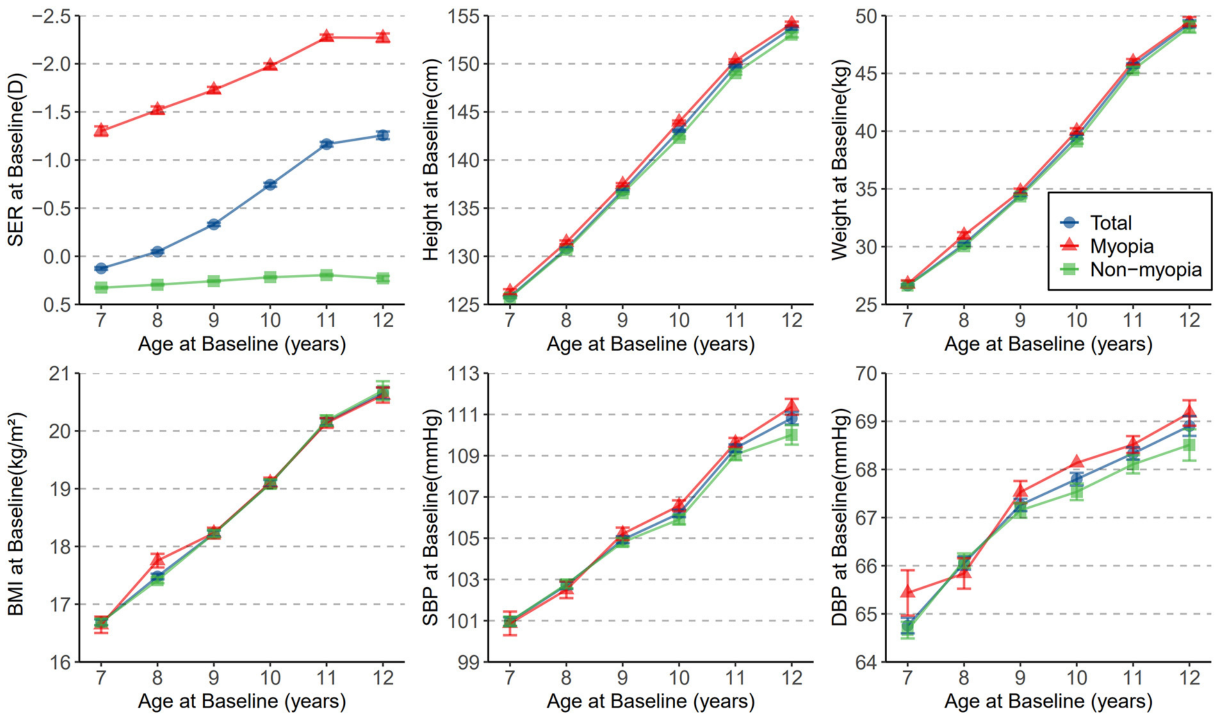

FIGURE 1
The distribution of mean SER, height, weight, BMI, SBP, and DBP with age at baseline. Dots represents means and whiskers indicate SEM. SER, spherical equivalent refraction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

and baseline examinations is defined as changes. Descriptive statistics of changes in SER and anthropometric indicators were calculated. *T*-tests were performed for quantitative variables, and Chi-square tests were performed for categorical variables to analyse the differences in basic characteristics between the two examinations and between the two groups of participants.

Bivariate correlations between SER and anthropometric indicators were calculated. Linear regression models were constructed to assess the effects of anthropometric indicators (as independent variables) on refraction (as dependent variables). Tests for linear trends were performed by entering the median value of each category of the anthropometric indicator based on quartiles as a continuous variable into the models. Multiple linear regression models were fitted separately to participants with and without myopia to assess the effect of anthropometric indicators on refraction for different refractive states. The relationship between anthropometric indicators changes and refraction changes were then analyzed according to the method described above.

Results

A total of 31,068 children were recruited for this study. Five hundred twenty-four children were not examined because they had ocular or systemic diseases or were not cooperative for personal reasons. Four thousand nine hundred children did not complete follow-up examinations due to graduation, school changes, or other reasons. The remaining 25,644 (82.5%) children aged 7–12 (mean = 9.35 ± 1.51) years completed two examinations, consisting of 13,308 (51.9%) males and 12,336 (48.1%) females. At the final examination, there were significant differences in the SER, height, weight, BMI, SBP, and DBP compared to the first examination (paired *t*-test, both $p < 0.001$). The overall prevalence of myopia increased from 35.17% (9,020 of 25,644) to 39.78% (10,200 of 25,644), with significant differences (Chi-square test, $p < 0.001$). Table 1 presents the demographic characteristics of the analysis cohort by myopic or non-myopic at baseline. Myopic participants were taller, heavier, had a larger BMI, and had higher SBP and DBP. These individuals grew faster in height, gained more weight, and had more remarkable changes in SBP. Moreover, myopic children had more negative refraction and had greater myopic shifts than non-myopic children (both $p < 0.001$).

Figure 1 shows the distribution of mean SERs and mean anthropometric indicators with age at baseline. Some similar trends in participants' negative refraction with each anthropometric indicator. Overall, negative SER and all anthropometric indicators increased with age. Moreover, myopic children showed a significant trend in SER with

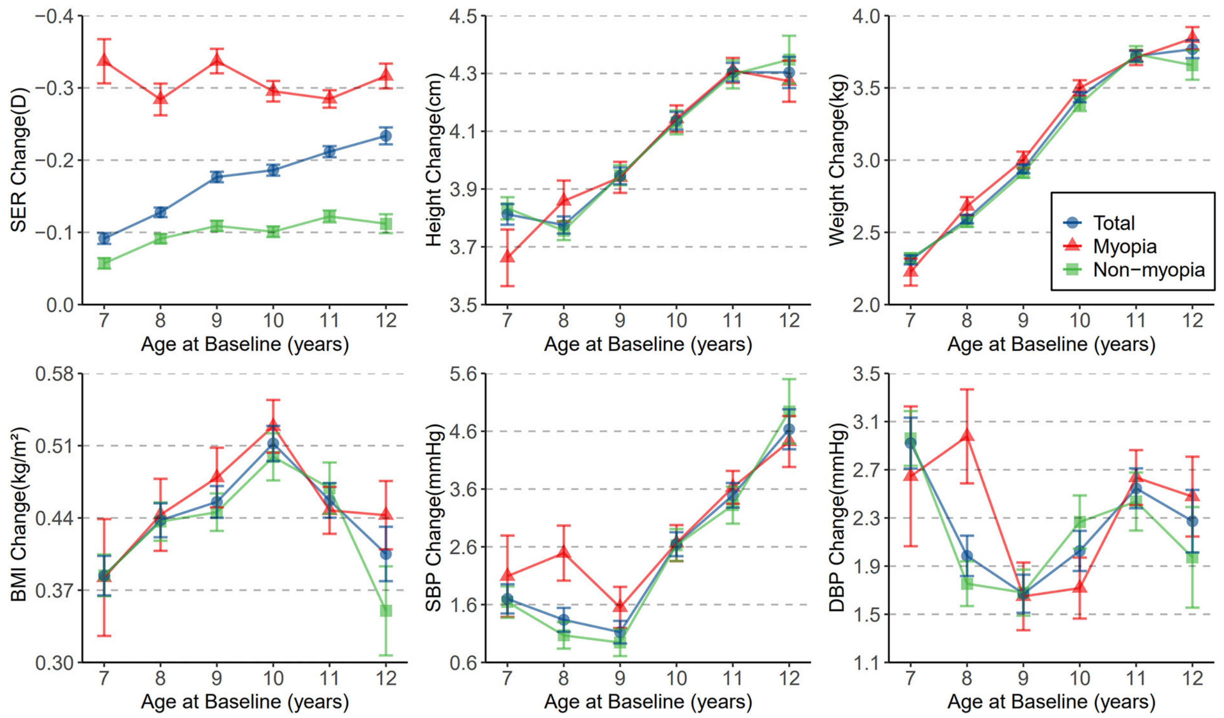

FIGURE 2
The distribution of mean change in SER, height, weight, BMI, SBP, and DBP with age at baseline. Dots represents means and whiskers indicate SEM.

age than non-myopic children. While myopic children had higher height than non-myopic children at all ages, other anthropometric measures differed significantly at only a few ages (Supplementary Table 1). Figure 2 describes the 6-month mean changes of SER and anthropometric indicators with age. Regarding general trends, the trends in subjects' height and weight and in negative SER were somewhat similar, all increasing with age. Among myopic and non-myopic children, the only significant difference in anthropometric indicators changes was in SBP and DBP at age 8 (Supplementary Table 2).

Bivariate correlations of SER with height, weight, BMI, SBP, and DBP at baseline are shown in Table 2, which was of low to moderate strength. Height, weight, BMI, SBP, and DBP were negatively correlated with SER ($r = -0.324$, $r = -0.234$, $r = -0.121$, $r = -0.112$, $r = -0.066$, both $p < 0.001$). The mean SER by quartiles of height, weight, BMI, SBP, and DBP are shown in Table 3. The taller, heavier, fatter (students with higher BMIs), and higher blood pressure (students with higher SBPs or DBPs) individuals were found to have lower SER and their refractive status tended to be more myopic ($p < 0.001$ for each linear trend test). These results are consistent with the findings for the bivariate correlation of anthropometric indicators with SER. Stratifying the population by refractive status at baseline revealed refractive

TABLE 2 Bivariate correlations of SER with height, weight, BMI, SBP, and DBP.

	SER (D)			
	Baseline		Changes	
	R	***P*-value**	***R***	***P*-value**
Height (cm)	−0.324	<0.001	−0.034	<0.001
Weight (kg)	−0.234	<0.001	−0.031	<0.001
BMI (kg/m^2)	−0.121	<0.001	0.000	0.974
SBP (mmHg)	−0.112	<0.001	−0.004	0.509
DBP (mmHg)	−0.066	<0.001	0.007	0.248

Data are the Pearson correlation coefficients.

status based differences between refraction and anthropometric indicators (Table 4). In multiple linear regression models, height, weight, BMI, SBP, and DBP were all correlated with refraction in myopic children. Nonetheless, refraction in non-myopic children is only correlated with height, not weight, BMI, SBP, and DBP.

Bivariate correlation analysis showed that SER changes were negatively correlated with height changes ($r = -0.034$, $p < 0.001$) and weight changes ($r = -0.031$, $p < 0.001$), the two correlation coefficients were low but statistically significant. And

TABLE 3 Mean values of SER by quartiles of height, weight, BMI, SBP, and DBP.

	Range	*n*	SER (D)
Height (cm)			
1st quartile	97∼131	7,054	0.01 ± 0.98
2nd quartile	132∼138	5,914	−0.31 ± 1.19
3rd quartile	139∼147	6,481	−0.68 ± 1.48
4th quartile	148∼180	6,195	−1.19 ± 1.75
P for trend*			<0.001
Weight (kg)			
1st quartile	15∼27	6,438	−0.07 ± 1.05
2nd quartile	28∼34	6,767	−0.39 ± 1.31
3rd quartile	35∼43	6,032	−0.67 ± 1.48
4th quartile	44∼129	6,407	−0.98 ± 1.70
P for trend			<0.001
BMI (kg/m^2)			
1st quartile	10.56∼15.56	6,411	−0.31 ± 1.27
2nd quartile	15.58∼17.51	6,428	−0.43 ± 1.34
3rd quartile	17.53∼20.85	6,414	−0.60 ± 1.47
4th quartile	20.89∼44.37	6,391	−0.76 ± 1.63
P for trend			<0.001
SBP (mmHg)			
1st quartile	53∼96	6,549	−0.35 ± 1.30
2nd quartile	97∼105	6,661	−0.45 ± 1.37
3rd quartile	106∼114	6,247	−0.57 ± 0.02
4th quartile	115∼180	6,187	−0.74 ± 0.02
P for trend			<0.001
DBP (mmHg)			
1st quartile	20∼61	7,238	−0.39 ± 1.35
2nd quartile	62∼66	5,652	−0.50 ± 1.42
3rd quartile	67∼73	6,787	−0.60 ± 1.46
4th quartile	74∼128	5,967	−0.63 ± 1.55
P for trend			<0.001

Data are presented as the means with SD. *Tests for linear trend is performed by entering the median value of each category of the anthropometric indicator as a continuous variable in the models.

there was no linear correlation between SER changes and BMI changes ($r = 0.000$, $p = 0.974$), SBP changes ($r = -0.004$, $p = 0.509$) and DBP changes ($r = 0.007$, $p = 0.248$) (Table 2). Table 5 shows that the trend of changes in SER and height, SER and weight were generally consistent, indicating that there is also a significant longitudinal correlation between SER and both height and weight ($p < 0.001$ for each linear trend test). In model 2 of Table 6, growth in height was associated with changes in SER in both groups of children. For every increase in height of 10 cm, SER decreased by 0.12 D ($p < 0.001$) for myopic children and 0.03 D ($p = 0.035$) for non-myopic children. Weight gain in non-myopic but not myopic children is associated with a decrease in SER. Changes in BMI, SBP, and DBP were not correlated with changes in SER in our multiple linear regression model.

Discussion

Although the peak period of the epidemic has passed, in the post-epidemic era, repeated small-intensity epidemics and the continuous mutation of the virus are still a realistic situation that the public cannot escape (16). Children need to be ready to learn at home for the next wave of the epidemic. We conducted this work because there are few studies on the effects of anthropometric indicators on refraction in children in the post-COVID-19 era. This study found that SER was negatively correlated with height and weight in both cross-sectional and longitudinal analyses. SER was negatively correlated with BMI and blood pressure cross-sectionally but not longitudinally. In addition, refractive status differences were found between the various anthropometric indicators with refraction. The anthropometric and refractive cross-sectional correlations are more robust in myopic children than in non-myopic children, and myopia progresses more rapidly in myopic children than in non-myopic children when they grow to the same height.

AL is an essential indicator of eye growth and is highly correlated with changes in refraction. Many studies have

TABLE 4 Multiple linear regression models of SER by height, weight, BMI, SBP, and DBP for myopic and non-myopic children separately.

	SER (D)							
	Myopic				Non-myopic			
	Model 1		Model 2		Model 1		Model 2	
	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
Height (10 cm)	−0.30	<0.001	−0.20	<0.001	−0.04	<0.001	−0.02	0.003
Weight (10 kg)	−0.19	<0.001	−0.11	<0.001	−0.02	<0.001	0.01	0.217
BMI (10 kg/m^2)	−0.36	<0.001	−0.20	<0.001	−0.01	0.611		
SBP (10 mmHg)	−0.12	<0.001	−0.07	<0.001	−0.01	0.019	0.00	0.809
DBP (10 mmHg)	−0.09	<0.001	−0.06	0.001	0.00	0.718		

Model 1 constructs based on crude data. In model 2 we adjusted for age and gender.

confirmed a significant correlation between height and AL (17, 18). Given that AL is a critical factor in myopia, then there should also be a more significant correlation between refraction and height, but differently, studies on the correlation between height and refraction have not achieved consistent conclusions. A study conducted in Britain on the relationship between height growth trajectory and myopia development found that for each standard deviation increase in height among children aged 2.5–10 years, their SER decreased by 0.075 D and 0.081 D by age 11 and 15 years (19). Another study in Tianjin, China, yielded similar results to us, with the higher the height of the child, the more the refraction tended to be myopic (20). However, Ojami et al. indicated that height is strongly associated with the AL but not with refraction (21).

The AL plays a vital role in refraction, but a long AL does not necessarily mean more severe myopia. Emmetropia is a balance between AL, corneal power and lens power (22). In patients with emmetropes or low myopia, the function of the cornea seems to compensate for the possible myopic effects of slight increases in AL. When increases in AL are excessive, this effect on the cornea tends to disappear (23). In addition, previous studies have proved that the crystalline lens thins during the period of coordinated ocular growth in children, which may also compensate for some of myopia associated with AL growth (24). For these reasons, the relationship between height and refraction may become blurred. Although there is no consensus on the relationship between height and refraction, our study will provide clues for further exploration of the complicated association between the two. In our findings, height and refraction had significant cross-sectional and longitudinal associations under the influence of COVID-19 prevention policies. Therefore, we presume that there may be some common biological regulatory pathways for height and refraction. Several hormones that regulate longitudinal bone growth during childhood have been experimentally demonstrated to play a role in experimental myopia, such as thymic hormones, IGFs, and thyroid hormones (25–27). Additionally, a signaling molecule associated with bone growth, Hedgehog homologs, has also been found to be associated with eye development (28, 29). There is also the view that height and refraction might not be directly related and that they are both independent consequences of increasing socioeconomic status (30, 31). Yet our current study does not include this method of adjusting socioeconomic status.

In a 4-year study, Kearney et al. found that the relationship between height and axial elongation varied by refractive state (5). But the refraction was not included in their analysis. For our analysis, the negative correlation between height and SER was found to be more pronounced in the myopic group. For every 10 cm increase in height, SER shifts 0.3 D toward myopia in myopic children and decreases 0.04 D in non-myopic children. Also, the longitudinal correlation between height and SER was more pronounced in myopic children. How the onset of myopia plays a role in the relationship between height and SER in school-aged children and whether this association is related to the current COVID-19 prevention policy requires further research in the future.

While the impact of obesity on physical health and its association with many systemic diseases is well recognized, little is known about the ocular manifestations of obesity, particularly its impact on refractive development. Weight and BMI correlation with refraction has not been as widely studied as height, and there is no consensus on these correlations. A Burmese-based study shows that heavier individuals tended to be slightly hyperopic (32). In contrast, a study conducted

TABLE 5 Mean values of SER changes by quartiles of change in height, weight, BMI, SBP, and DBP.

	Range	*n*	ΔSER (D)
ΔHeight (cm)			
1st quartile	−4∼3	10,415	−0.156 ± 0.49
2nd quartile	4	4,893	−0.157 ± 0.55
3rd quartile	5	4,326	−0.171 ± 0.45
4th quartile	6∼12	6,010	−0.198 ± 0.55
P for trend*			*P* < 0.001
ΔWeight (kg)			
1st quartile	−20∼2	1,0957	−0.149 ± 0.47
2nd quartile	3	5,112	−0.155 ± 0.50
3rd quartile	4	3,746	−0.188 ± 0.53
4th quartile	5∼20	5,829	−0.205 ± 0.57
P for trend			*P* < 0.001
ΔBMI (kg/m^2)			
1st quartile	−12.88∼−0.17	6,427	−0.171 ± 0.50
2nd quartile	−0.16∼0.43	6,481	−0.167 ± 0.51
3rd quartile	0.44∼1.07	6,353	−0.163 ± 0.48
4th quartile	1.08∼9.84	6,383	−0.174 ± 0.55
P for trend			*P* = 0.825
ΔSBP (mmHg)			
1st quartile	−70∼−7	6,469	−0.170 ± 0.49
2nd quartile	−6∼2	6,531	−0.181 ± 0.50
3rd quartile	3∼11	6,479	−0.149 ± 0.54
4th quartile	12∼110	6,165	−0.175 ± 0.52
P for trend			*P* = 0.574
ΔDBP (mmHg)			
1st quartile	−62∼−5	6,419	−0.180 ± 0.52
2nd quartile	−4∼2	6,849	−0.164 ± 0.52
3rd quartile	3∼9	6,457	−0.171 ± 0.50
4th quartile	10∼106	5,919	−0.160 ± 0.51
P for trend			*P* = 0.082

Data are presented as the means with SD. *Tests for linear trend is performed by entering the median value of each category of the anthropometric indicator as a continuous variable in the models.

TABLE 6 Multiple linear regression models of SER changes by change in height, weight, BMI, SBP, and DBP for myopic and non-myopic children separately.

	ΔSER (D)							
	Myopic				Non-myopic			
	Model 1		Model 2		Model 1		Model 2	
	B	*P*-value	B	*P*-value	B	*P*-value	B	*P*-value
ΔHeight (10 cm)	−0.11	<0.001	−0.12	<0.001	−0.04	0.010	−0.03	0.035
ΔWeight (10 kg)	0.01	0.809			−0.06	<0.001	−0.04	0.002
ΔBMI (10 kg/m^2)	0.10	0.087			−0.04	0.136		
ΔSBP (10 mmHg)	0.00	0.347			0.00	0.625		
ΔDBP (10 mmHg)	0.01	0.091			0.00	0.954		

Model 1 constructs based on crude data. In model 2 we adjusted for age and gender.

in Korea on young adults claimed no association between weight and refraction (33). In this study, heavier children tended to be myopic in their refraction, and the more they gained weight, the more they reduced their SER. Due to the fact that growth in height usually accompanies an increase in weight, height is essentially positively correlated with weight, which may explain why weight is also negatively correlated with refraction. BMI is independent of height and is a considerably better indicator of obesity than weight. Similar to the results of some cross-sectional studies (34, 35), we found a negative cross-sectional correlation between BMI and refraction but no significant longitudinal correlation. The reason for this is speculated that obese children spend more time in front of TV and computer screens, and they spend less time than recommended on outdoor activities (36). With the mediation effect of outdoor activity time, myopia gradually progresses. Few studies have been conducted on the correlation between blood pressure and myopia. In our study, SBP and DBP were negatively correlated with refraction cross-sectionally but with low correlation coefficients and no correlation longitudinally.

There are some limitations to our study. First, this is a non-cycloplegic photoscreening study. Although spot provides reliable measurements in screening (37, 38), it is not currently considered a substitute for cycloplegic refraction. In China, performing cycloplegic refraction in an extensive sample screening program is a great challenge. Second, part of our subjects with undetected ocular diseases may not have been appropriately excluded from this study due to insufficient information. Given the large sample size of this study, the impact of this limitation on the conclusions should be minimal. Third, the follow-up time is so short that the changes in anthropometric indicators and SER are small among some participants. A longer follow-up period would be necessary to validate our conclusions in further research. Fourth, we did not provide ocular biometrics. Given the strong relationship between refraction and ocular biometrics (39), the association between anthropometric indicators and ocular biometrics should also be considered in further research to explore the complex relationship and mechanisms between anthropometric indicators and refraction.

In conclusion, during the growth of school-age children in the post-COVID-19 era, a significant correlation exists not only between height, weight, BMI, SBP, DBP and refraction but also between height and weight gain and refractive changes. These associations vary by refractive status. It indicates that children's height, weight, and growth rate may be used as reference indicators for myopia risk prediction and progression monitoring. In addition, refractive monitoring of school-aged children should focus on those significantly taller and heavier than their peers.

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 Board of Tianjin Medical University Eye Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XQian, WD, and GD designed the study. XG, WD, GD, KA, YW, LW, XL, JL, XQi, YN, LS, and YZ collected participants' data. WD and JL performed the data analysis and participated in manuscript preparation. XQian, NH, and NW revised the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by Tianjin Key Clinical Discipline (Specialty) Construction Project (TJLCZDXKT001) and Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-037A).

Acknowledgments

The authors would like to thank all families who participated in our study, Tianjin Beichen Traditional Chinese Medicine Hospital for their help in the comprehensive examination and all team members of the Strabismus and Pediatric Ophthalmology Department of Tianjin Medical University Eye Hospital.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1059465/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Brief Research Report
PUBLISHED 24 January 2023
DOI 10.3389/fpubh.2023.1096322

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Public Health Education and Promotion, a section of the journal Frontiers in Public Health

RECEIVED 12 November 2022
ACCEPTED 06 January 2023
PUBLISHED 24 January 2023

CITATION
Kodjebacheva GD, Hristova SG and Savov V (2023) Development and evaluation of an intervention to promote the use of eyeglasses among Romani families in Bulgaria. *Front. Public Health* 11:1096322.
doi: 10.3389/fpubh.2023.1096322

Development and evaluation of an intervention to promote the use of eyeglasses among Romani families in Bulgaria

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Objective: Uncorrected refractive error (i.e., lack of eyeglasses for the treatment of refractive error) is one of the leading causes of visual impairment in Eastern Europe. Limited information is available on how to promote the use of eyeglasses among Romani families in Bulgaria. In step 1, the objective was to obtain suggestions by Romani mothers on how to promote the use of eyeglasses among children. In step 2, the objective was to evaluate an intervention to promote the use of eyeglasses based on suggestions received during step 1.

Methods: During step 1, 5 focus groups with Romani mothers took place in one neighborhood in Bulgaria. During step 2, the intervention used a one-group pre-test, post-test design. Families received eye examinations. Those who needed eyeglasses chose attractive eyeglasses. Parents received education on how to encourage their children to wear eyeglasses.

Results: During step 1, 54 mothers participated. Mothers suggested that the whole family should receive eye examinations and eyeglasses. During step 2, of 33 family members, 14 did not have refractive errors and 19 did. Of the 19 family members with refractive error, none had eyeglasses at pre-test. Approximately 6 months following the end of the intervention, 11 of the 19 family members (57.9%) wore eyeglasses and the remaining 8 (42.1%) did not.

Conclusion: Romani family members needed eyeglasses but did not have any at pre-test of the intervention. Future interventions that offer education on the importance of eye examinations may increase receipt of eye examinations and adherence to wearing eyeglasses.

KEYWORDS

eyeglasses, refractive errors, children, families, Roma, Bulgaria

1. Introduction

In Europe, "Roma" and "Romani" are terms to describe people who self-identify as Roma, Gypsy, Sinti, Travelers, Ashkali, Manush, Dom, and Lom (1). The Roma represent one of the largest and most vulnerable minority groups in Europe (2, 3). The number of Roma is difficult to quantify (3). According to estimates, 10–12 million Roma reside in Europe (4). Six million Roma out of these 10–12 million reside in the European Union (4). Countries with largest populations of Roma in the European Union include Bulgaria, Romania, Slovakia, Hungary, Greece, Czechia, and Spain (4). According to estimates, approximately 784,041 Romani people revised in Bulgaria in 2020 representing 11.7% of the Bulgarian population (5).

The Roma have suffered racism, discrimination, and social exclusion (1). The Roma were the victims of horrific treatment that included slavery and genocide. According to estimates, 5 million Roma were murdered during the Holocaust (1). The Roma were once nomadic; today, the Roma have varied residences within nomadic, semi-nomadic, and settled groups (6). Lags in education among the Roma and existence of discrimination contributed to high unemployment and access to primarily low skilled jobs among the Roma (7).

The overall health of the Romani population is worse than that of the general population due to factors such as extreme poverty, high unemployment, domestic violence, alcoholism, and malnutrition (8–10). Infant mortality and decreased socio-economic status contribute to the lower life expectancy of the Romani population when compared to the general European population (3). Researchers emphasized that the wide gap in income that exists between Roma and non-Roma across Europe should be reduced as a priority, through targeted interventions (3, 10, 11).

Romani children suffer from worse health outcomes compared to other children in Europe. Roma infants have increased odds of having low birthweight and birth defects (12–15). The low access to safe sex education and reproductive health services results in teenage and unwanted pregnancies (16, 17). Roma children have higher rates of communicable diseases than other children (18). A combination of social isolation, lack of education, domestic violence, and absence of community health programs leaves Romani families including children severely disadvantaged (8, 10, 11).

While studies on the general health of Romani children have been conducted (12–15, 19, 20), research on eye health and care is very limited. Uncorrected refractive error is defined as the lack of eyeglasses for the treatment of myopia, hyperopia, and astigmatism (21–24). The lack of eyeglasses among children with vision problems may result in decreased academic achievement (25, 26). Even in schools with higher socio-economic status in the United States, over 95% of first-graders who needed eyeglasses did not have eyeglasses and/or did not wear them (21). In adults, uncorrected refractive error was associated with reduced vision-related quality of life (27). Research identified uncorrected refractive error as one of the leading causes of correctable visual impairment in Eastern Europe (28–30). Limited information is available on the eye care of Roma children in Eastern Europe. A study of adults in Hungary published in 2022 found that in groups with visual acuity below 0.5 in both eyes, the percentage of people wearing eyeglasses was significantly lower in Roma compared to non-Roma (14.3 vs. 77.1%, $p < 0.001$) (31).

Given the gaps in the research, the current study consisted of 2 steps. During step 1, the study focused on understanding the eye care needs of Romani children by conducting focus groups with mothers. Step 1 sought to receive suggestions for strategies that promoted the use of eyeglasses among Romani children by Romani mothers from one poor Romani neighborhood in Bulgaria.

During step 2, the study implemented an intervention to increase the use of eyeglasses among Romani families in the same poor Romani neighborhood in Bulgaria by using suggestions provided by mothers during step 1. During step 2, the study tested the feasibility of an intervention that offered complimentary eye examinations and attractive eyeglasses to family members and provided education to parents on how to encourage children to wear eyeglasses. During step 2, the study tested the effectiveness of the intervention in promoting the use of eyeglasses by using 2 methods: (1) randomly visiting the neighborhood to observe if family members wore their eyeglasses and (2) conducting focus groups with parents to receive feedback on the use of eyeglasses. Step 2 allowed to investigate what proportion of those who needed eyeglasses based on the optometrist examination had eyeglasses at pre-test.

2. Methods

2.1. Steps, ethical approval, and setting

The study consisted of 2 steps (Supplementary Figure 1). We received Institutional Review Board (IRB) approval from the University of Michigan—Flint for both steps. The IRB categorized step 1 as exempt due to the limited risk for the focus group participants. The IRB categorized step 2 as a "no more than minimal risk study" since the use of eyeglasses was accepted and common in society.

Suggestions that participants provided during the focus groups during step 1 were used to develop the intervention during step 2. Recruitment for step 2 began ∼13 months after the end of the last focus group during step 1. The 13 months were needed to analyze the focus group information during step 1, develop the intervention for step 2, receive IRB approval for step 2, and partner with a local optometrist for step 2. Recruitment for steps 1 and 2, therefore, was completed independently. Verbal informed consent for participation was required for step 1 of the study. Written informed consent for participation was required for steps 2 of the study. The consent forms were verbally described and/or read as needed. It was emphasized that participation was voluntary.

Both steps 1 and 2 were conducted in Bulgarian in Bulgaria meaning that the consent forms were provided to participants in Bulgarian and all focus groups and activities were conducted in Bulgarian. All study materials such as consent forms and focus group guides were submitted to and approved by the IRB in English with translations in Bulgarian.

The setting for both steps 1 and 2 was a neighborhood located in the outskirts of the city following an unpaved, steep, and curvy road. No public bus traveled to the neighborhood. The study team visited the neighborhood by car while driving slowly due to the road condition. Neighborhood residents could be seen walking on foot going to and from the neighborhood. No stores, pharmacies, or other businesses were located in the neighborhood. Farm animals could be seen outside in front of the houses. Children playing and adults interacting could be observed in the neighborhood.

2.2. Step 1: Focus groups among mothers

Five focus groups with Romani mothers in one neighborhood where Romani people concentrated in one industrialized city in Bulgaria were conducted in Bulgarian to (1) understand mothers' experiences with any prior vision screening among children, issues surrounding wearing eyeglasses among children (such as factors preventing children from wearing eyeglasses, mother's perceptions toward children wearing eyeglasses, mothers' perceptions on what types of eyeglasses looked better than others, and peer bullying among children due to wearing eyeglasses), cultural perceptions toward wearing eyeglasses, knowledge on the benefits of eyeglasses and eye conditions in general, and perceptions on the importance of eyesight and (2) recommend strategies for the increased receipt and use of eyeglasses among Romani children. Focus groups are established research techniques to explore attitudes, opinions and perceptions through the use of open-ended questions (32).

2.2.1. Inclusion criteria

The inclusion criteria were: Each mother had to understand and speak Bulgarian and have the responsibility for taking care of at least one child (aged 5–17 years) to be eligible. Biological mothers, stepmothers, and guardians (referred to as "mothers" in this study) were eligible to participate. The numbers of mothers for each focus group were: 11 mothers in focus group 1, 9 in focus group 2, 12 in focus group 3, 10 in focus group 4, and 12 mothers in focus group 5.

2.2.2. Recruitment of mothers

In the Romani neighborhood, people spend much of their time outside. When outside visitors arrive in the Romani neighborhood, Roma gather outside of their homes to greet the visitors. The five focus groups took place during five visits to the neighborhood. As Roma people gathered outside of their homes, they were invited to participate in the focus groups if they met the inclusion criteria. As residents were approached, residents stated they would bring additional mothers who may want to join. The focus groups took place shortly after mothers expressing interest gathered and after the consent forms were described and provided to mothers, any questions were answered, and verbal consent was received. It was emphasized that participation was voluntary. The focus groups took place outside, in front of houses in the neighborhood where places for seating were available. Refreshments were provided for both mothers and accompanying children.

A focus group guide (Table 1) was developed by the author (GK) who had previous experience in conducting focus groups among parents on the need and use of eyeglasses in the United States (33). While mothers had to have at least 1 child aged 5–17 to participate, mothers were asked regarding issues surround eye care for any of their children aged 5–17 years. Each focus group took between 1 and 1.5 h to conduct. The focus group discussions were categorized under common topics/themes using grounded theory techniques (32).

TABLE 1 Focus group guide questions* asked during step 1 of the study.

Topic/question
Vision screening in the office of the pediatrician
When do you recall that the eyes of your child were screened for the first time ever, if ever? Where? How?
Describe your experience with children's vision screening at the office of the pediatrician?
How does the pediatrician screen the eyes of the child?
What happened after the vision screening at the pediatrician's office?
How would you (did you) feel if the pediatrician told you your child might need eyeglasses?
Issues surrounding wearing eyeglasses
Do your children wear eyeglasses? For what conditions?
How do you feel (would you feel) about your child (if your child wore) wearing eyeglasses?
How do you think children feel about wearing eyeglasses?
What prevents children from wearing their eyeglasses?
Do some eyeglasses look better than others? Please explain.
What would you do if your child does not want to wear his/her eyeglasses?
Have you heard of negative experiences in children when children wear eyeglasses?
Cultural perceptions
What is the general attitude toward wearing eyeglasses among people around you?
What do your relatives and you think about others who wear eyeglasses?
Are there any names relatives use for people wearing eyeglasses?
Knowledge on the benefits of eyeglasses and on eye conditions in general
Do you think eyeglasses help children? How?
Do you think eyeglasses hurt children? How?
Is not wearing eyeglasses a serious problem in the development of the child? How?
What are the consequences of not wearing eyeglasses in children?
What eye conditions have you heard of?
Perceptions on the importance of eyesight
How important are people's eyes to their health and wellbeing?
Strategies for the increased receipt and use of eyeglasses among Romani children
What do you suggest be done so that we improve children's eye care?
What do you suggest be done to evaluate/examine the eyes of the children?
What do you suggest be done so that children have eyeglasses in they need eyeglasses?
What do you suggest be done to help children wear their eyeglasses if they need eyeglasses?

*While mothers had to have at least 1 child aged 5–17, mothers could discuss issues related to any of their children aged 5–17 when answering questions.

2.3. Step 2: Intervention to promote the use of eyeglasses among family members

2.3.1. Inclusion criteria

Children aged 5–17 years residing in the Romani neighborhood where the focus groups in step 1 were conducted were the most important part of the target population. All children within these ages from the same family were eligible.

During the focus groups in step 1, mothers stated that the family (i.e., mothers and fathers along with children) should have the opportunity to visit the optometrist. Mothers stated that if they and fathers wore eyeglasses, their children would be encouraged to wear them as well. We realized that because Roma people were part of an impoverished community, all family members (i.e., mothers, stepmothers, or female guardians and biological fathers, stepfathers, or male guardians along with children aged 5–17) should be given the opportunity to visit the optometrist and receive free eyeglasses. Children's parents were thus also eligible to participate in step 2.

The inclusion criteria for inclusion in the intervention thus were children aged 5–17 years and their parents such as biological mothers, stepmothers, or female guardians and/or biological fathers, stepfathers, or male guardians. A family was defined as the children aged 5–17 years and the parents who could be biological mothers, stepmothers, or female guardians and/or biological fathers, stepfathers, or male guardians. Grandparents were not eligible to participate unless they were guardians. From this point on, mothers, stepmothers, and female guardians are called mothers. Biological fathers, stepfathers, and male guardians are called fathers. Parents were not required to have eye examinations; they could choose to either have eye examinations only for their children and/or for both them and their children. Parents could not choose to have eye examinations only for themselves.

2.3.2. Recruitment of adults (i.e., mothers and fathers) and children

The intervention was advertised by approaching residents in the same neighborhood as in step 1. As Roma people gathered outside of their homes, the intervention was verbally described.

The consent form was developed in English and translated into Bulgarian. Some adult participants were illiterate. The consent form was both read/explained and provided to the adults. Participants were asked if they had questions. It was emphasized that participation was voluntary. Adults asked their children to participate. The following was stated in the form: "Please ask your child or the child you care for aged 5–17 years if he/she would like to participate in this research. If the child does not wish to participate, you do not need to come to the office of the optometrist. The child is free to refuse participation in the study. If you have or care for more than 1 child within these ages, you can ask each child to participate."

2.3.3. Intervention design

A one group pre-test post-test intervention was conducted (Supplementary Figure 1).

2.3.4. Intervention strategies

The intervention strategies were:

- Complimentary eye examinations by an optometrist in the office of the optometrist for children and their mothers and/or fathers. Free transportation to the office of the optometrist was not provided. Participants went to the office of the optometrist on their own. The optometrist office was located close to the main hospital in the city. The office was open Monday–Friday 8 a.m.—7 p.m. and Saturday 8 a.m.—1 p.m. The optometrist was available to offer eye examinations only on Mondays and Wednesdays 9 am – 6 pm.
- Provision of complimentary eyeglasses that participants selected at the office of the optometrist. Provision of eyeglasses was based on the clinical decision of the optometrist according to the refractive error status of the patient. The office of the optometrist was reimbursed for the eye examinations and eyeglasses by the study grant.
- Eye care education for mothers and fathers on how to encourage children to wear eyeglasses. The education was provided by the optometrist during the visit using strategies discussed between the study team and the optometrist. To encourage children to wear eyeglasses, parents were advised to allow children to participate in choosing frames, take slow steps while children become used to their eyeglasses without forcing children to wear the eyeglasses, practice taking eyeglasses on and off, and return to the office of the optometrist if eyeglasses needed adjustments.

TABLE 2 Characteristics of mothers participating in the five focus groups during step 1, $n = 54$.

	Number	%
Role		
Biological mother	41	75.9%
Stepmother	7	13.0%
Guardian	6	11.1%
Age		
18–29	6	11.1%
30–39	16	29.6%
40–49	21	38.9%
50–67	11	20.4%
Education		
No formal education	12	22.2
First-grade education	15	27.8
Third-grade education	18	33.3
Fourth-grade education	9	16.7
Employment		
Unemployed	9	16.7
Employed part-time	45	83.3
Number of children younger than 18		
2	6	11.1
3	13	24.1
4	22	40.7
5	13	24.1

2.3.5. Quantitative outcome evaluation with the outcome measure use of eyeglasses at pre- and post-test

To assess if the intervention was effective, the optometrist asked participants if they had eyeglasses during the eye examination at the start of the intervention; the numbers of participants who needed eyeglasses and who already had eyeglasses were recorded at pre-test. The neighborhood was then randomly visited a total of 3 times to count the number of people wearing their eyeglasses to understand if the intervention was effective ∼6 months after the provision of the eyeglasses at post-test. The neighborhood was visited 3 times in case some of the participants were not in the neighborhood at the time of the visit. Use of eyeglasses was measured only at the first visit when the participant was encountered. If participants had to wear their eyeglasses only for close work according to the optometrist notes, participants were asked if they wore their eyeglasses while doing close work and were asked to bring their eyeglasses; if participants brought their eyeglasses, they were marked as wearing their eyeglasses. If participants had to wear their eyeglasses all the time according to the notes of the optometrist and if participants did not wear the eyeglasses at the time of the visit, the participants were marked as not wearing their eyeglasses.

2.3.6. Qualitative outcome and process evaluations: Focus groups at post-test only

During the 3 random visits to check if participants wore their eyeglasses ~6 months after the receipt of eyeglasses, we sought to conduct focus groups with the mothers and fathers who received eyeglasses either for themselves and/or their children to obtain information on how wearing eyeglasses may have affected participants and suggestions for improving the intervention. Children were excluded from the focus groups. All adults who received eyeglasses for themselves and/or their children regardless of whether they and/or their children adhered to wearing them were invited to participate in the focus groups during step 2.

The focus groups during step 2 served as both outcome and process evaluations. The outcome evaluation focused on how the intervention may have improved family members' vision and lives. The process evaluation focused on suggestions adults had to improve the intervention. During the first random visit, participants stated they were not available for a focus group due to lack of time. During the second random visit, one focus group was conducted and during the third random visit, a second focus group was conducted. A focus group guide was used. Questions asked during the step 2 focus groups included:

Outcome evaluation to assess adherence to wearing eyeglasses and influence of using eyeglasses on life:

- How frequently did you/your child(ren) wear the eyeglasses?
  - Why did you wear them frequently/less frequently?
  - Where did you/your child(ren) wear them more frequently (at home, in school, or outside)?
- How did your life (the life of your child or children) change after receiving the eyeglasses?

Process evaluation to receive suggestions for improving the intervention:

- What was your overall experience with the program?
- What was your overall experience at the office of the optometrist?
- Please share any problems you had during this program.
- What suggestions do you have to improve the program in the future?

TABLE 3 Age and gender of the 33 participants whose eyes were examined by the optometrist during step 2 of the study.

Characteristic	Number	%
Age		
5–9	4	12.1%
10–14	9	27.3%
15–17	10	30.3%
18–29	2	6.1%
30–39	1	3.0%
40–49	1	3.0%
50–67	6	18.2%
Gender		
Male	8	24.2
Female	25	75.8

TABLE 4 Children with and without eyeglasses at the beginning of the intervention (i.e., during the appointment with the optometrist) and ~6 months after the provision of eyeglasses among the 19 participants who needed eyeglasses during step 2 of the study.

Use of eyeglasses	Yes		No	
	Number	%	Number	%
Wore eyeglasses at the beginning of the intervention	0	0	19	100
Wore eyeglasses ~6 months after receiving them	11	57.9	8	42.1

3. Results

3.1. Step 1: Focus groups among mothers

3.1.1. Mother's characteristics

The 54 mothers were either unemployed or had part-time employment (Table 2). All mothers had either completed no education or completed one to four grades. Seventy-five point nine percent of mothers (41) had 4 children younger than 18.

3.1.2. Vision screening for children

The mothers stated that their children aged 5–17 had received vision screening by the pediatrician. The parents described the vision screening. The pediatrician used an eye chart. The pediatrician then referred the child to the optometrist if visual impairment was suspected. The parents felt respected by the pediatrician. The pediatrician answered parents' questions. No mother stated to have been to the optometrist.

3.1.3. Eyeglasses

Mothers reported that no child or adult in the neighborhood wore eyeglasses. Some mothers stated that their children needed eyeglasses but did not have any. Most mothers stated that their children had no complaints about their eyes and did not need eyeglasses. Mothers stated that they could not afford to purchase eyeglasses for their children. Some of the mothers stated that they needed eyeglasses for themselves but could not afford them. Some mothers asked if the moderators could purchase eyeglasses for them. The mothers stated that they found some frames for eyeglasses more attractive than others; they preferred thinner frames.

3.1.4. Mother's perceptions and knowledge related to eyesight and vision

The mothers stated that they understood the importance of wearing eyeglasses. One mother stated: "Eyes carry the future." Mothers stated that eyes along with the head and legs were the most important body parts. They stated that if one had a problem with his/her eyes, the problem would be serious because eyes were a part of the head. When asked what the benefits of eyeglasses were, the mothers stated that eyeglasses helped children see well and do better in school. Mothers believed that if children had a problem with their eyes, they would be able to communicate the problem with the parents. Mothers stated that they had no objections to children wearing eyeglasses. If their children needed and received eyeglasses, the mothers would encourage and even require the children to wear eyeglasses. The mothers stated that they were unaware of cases of bullying among the children due to wearing eyeglasses. Mothers had heard of farsightedness and nearsightedness. They could not appropriately define the conditions. Mothers had heard of cataracts; several parents stated their relatives were diagnosed with and treated for cataracts.

3.1.5. Suggestions on promoting the use of eyeglasses

Mothers stated that the whole family (mothers, fathers, and children) should visit the optometrist. The whole family should receive complimentary eye examinations and eyeglasses if needed. The mothers would like to receive education on how to encourage their children to wear eyeglasses.

3.2. Step 2: Intervention to promote the use of eyeglasses among family members

3.2.1. Characteristics of intervention participants

A total of 33 family members visited the office of the optometrist. Among the 33 participants, 75.8% (or 25) were female and 69.7% (23) were aged 5–17 years (Table 3). The 33 participants represented a total of 14 families.

3.2.2. Feasibility of the intervention

One of the authors (SGH) was present in the waiting room at the office of the optometrist for all scheduled eye examinations. Romani people seemed enthusiastic to receive eyeglasses. Roma selected eyeglasses that they stated they liked.

3.2.3. Quantitative outcome evaluation with the outcome measure use of eyeglasses at pre- and post-test

Out of the 33 family members, 14 did not have refractive errors and 19 had refractive errors according to the results of the examination by the optometrist. Of the 19 family members with refractive error, none previously had eyeglasses at pre-test (Table 4). Approximately 6 months following the end of the intervention at post-test, 11 of the 19 family members (57.9%) wore eyeglasses and the remaining 8 (42.1%) did not. The following are the age groups of the 19 participants with refractive error who received eyeglasses by adherence to the use of eyeglasses at post-test. Among the 11 who adhered to wearing eyeglasses at post-test, 2 were aged 10–14, 4 were aged 15–17, 1 was aged 18–29, 1 was aged 40–49, and 3 were aged 50–67. Among the eight who did not adhere to wearing eyeglasses at post-test, 2 were aged 5–9, 2 were aged 10–14, 1 was aged 15–17, 1 was aged 18–29, and 2 were aged 50–67. At post-test, out of the eight people who did not have/wear their eyeglasses, two broke the eyeglasses, four expressed that the eyeglasses were not comfortable, and two expressed that there was no need for eyeglasses due to good vision.

3.2.4. Qualitative outcome and process evaluations: Focus groups at post-test only

Out of the 19 parents who received eyeglasses, six agreed to participate in the focus groups. Out of the six parents who agreed to participate in the focus groups, five adhered to wearing eyeglasses (either for themselves and/or their children) and one did not adhere due to accidentally breaking the eyeglasses. These six parents represented six families. All six parents who participated in the focus groups were mothers. Mothers expressed they were very thankful for the services offered and did not express problems. As part of the outcome evaluation to understand how wearing eyeglasses affected people's lives, mothers stated that they and/or their children could see better as a result of receiving eyeglasses. Some participants stated that they preferred to only wear their eyeglasses at home and did not like to be seen with them outside. Mothers stated they would continue to wear their eyeglasses especially at home. One mother expressed gratitude for the program with tears in her eyes stating that she could not do close work such as knitting prior to receiving eyeglasses. As part of the process evaluation to receive suggestions on improving the intervention, we asked follow-up questions so that mothers would freely express any problems and satisfaction with the intervention, but they continued affirming that they experienced no problems and had no recommendations. One mother who not adherent to wearing her eyeglasses stated she broke the eyeglasses and requested to receive new eyeglasses.

4. Discussion

4.1. Summary

4.1.1. Step 1

No child was reported to wear eyeglasses in the poor Roma neighborhood. Some mothers stated that they needed eyeglasses or had problems with their eyesight. Mothers could not afford to purchase eyeglasses for themselves or their children. Mothers recognized the positive influence of eyeglasses for the development of children.

Valuable lessons were learned regarding the feasibility of conducting focus groups in the poor Roma neighborhood based on step 1. All focus groups took place in front of the homes of Roma people as requested by the Roma. There were distractions from people passing and by children playing. In the future, it will be useful to locate quieter places for focus groups in close proximity to the Romani neighborhood. Recruitment was a smooth process. Roma were very friendly and wished to participate.

4.1.2. Step 2

The results indicated that Roma in the neighborhood in this study needed eyeglasses but did not have any at pre-test. The intervention increased the use of eyeglasses even months after providing the eye care. A relatively large percentage of all participants who visited the office of the optometrist received eyeglasses (19 out of 33 or 57.6%); the large percentage may be because people who experienced problems with their eyesight were motivated to visit the optometrist.

Lessons were learned regarding the feasibility of conducting the intervention. Initial recruitment was a smooth process. Roma were friendly and wished to participate in the intervention in the beginning. However, initial agreement to participate did not mean that Roma would attend the office of the optometrist. On several occasions, the author (SGH) waited for participants at the office of the optometrist at the arranged time, but none arrived. Lack of time and transportation barriers may have been reasons why participants who initially agreed did not attend the office of the optometrist. Lack of education on the need for eye examinations prior to the visits to the office of the optometrist may have contributed to Roma not wishing to visit the optometrist. Another plausible explanation is that the people who did not attend the office of the optometrist may have not perceived they had vision problems. Males were especially less likely to participate than females. Past research found that males were more likely to ignore vision symptoms and less likely to seek early care compared to females (34). A hypothesis why males have a decreased likelihood to seek preventative health services is related to masculine gender norms where seeking help is considered a sign of weakness among males (35, 36). Another hypothesis for the decreased likelihood to seek preventative health is alcohol and substance abuse among some males (35). Other issues during the intervention included insistent requests by Roma to be paid for their participation and receive payment to cover their monthly utility bills. Roma were informed that the goals of the intervention were to offer eye examinations and eyeglasses.

4.2. Limitations

4.2.1. Step 1

The total number of mothers in the neighborhood was not ascertained; therefore, the percent of mothers in the neighborhood who participated was not known. The sample size of participants was small. Romani participants were not invited to a separate location where the focus groups could take place. Instead, focus groups took place outside in the neighborhood. At the same time, given transportation and time barriers, conducting the focus groups where participants were may have contributed to the larger sample size for each focus group.

Mothers stated during the focus groups that the pediatrician had referred the child to the optometrist if visual impairment was suspected. No mother, however, stated to have been to the optometrist. This study did not elaborate on the reasons why mothers did not visit the optometrist despite having referrals. Yet another limitation is that the findings of the focus groups may not be generalized to all Roma mothers/children in Bulgaria. The opinions of fathers were not taken into account since fathers did not participate in the focus groups in step 1. It is not known how many children of mothers participating in the focus groups may have needed eyeglasses.

4.2.2. Step 2

The number of participants who were invited while visiting the neighborhood was not ascertained. Another limitation of the intervention is that the sample size of participants was small. Another limitation is that the percentage of male participants was low. Yet another limitation is that the findings may not be generalized to all Romani parents/children in Bulgaria. Transportation was not offered to the office of the optometrist. Both children and parents participated. Parent could choose to have eye examinations only for the children. Another limitation is that the study did not investigate the prevalence of refractive error and type of refractive error. Provision of eyeglasses was based on the assessment of the optometrist. It is likely that individuals with worse refractive error were more likely to wear their eyeglasses due to poor vision.

Another limitation is that it is uncertain whether participants wore their eyeglasses regularly. On random visits 6 months after the end of the intervention, some participants may have put on their eyeglasses only because they heard that the authors were visiting the neighborhood. Therefore, the random visits were supplemented with the use of focus groups. A study limitation is that the participants who initially agreed to participate in the intervention and visit the optometrists were not interviewed to understand their reasons for lack of participation. Five out of the six participants in the focus groups in step 2 adhered to wearing eyeglasses (either for themselves and/or their children). Having additional participants who lacked adherence to wearing eyeglasses either for themselves and/or their children in the focus groups could have resulted in more recommendations on how to improve the intervention.

4.3. Implications

In the literature, up to 30% of children aged 2-17 overall may need eyeglasses (22, 23). In 2019, in the United States while there were still very high rates of uncorrected refractive error, according to the CDC, among boys, 3.0% wore eyeglasses among those aged 2–5 years, 20.0% among those aged 6–11 years, and 35.3% among those aged 12–17 years (37). Among girls, the respective percentages were 3.1, 26.4, and 48.2% (37). The Romani mothers stated during the step 1 focus groups that no one in the neighborhood wore eyeglasses which may be due to financial and other barriers. During step 2, none of the individuals who needed eyeglasses had them at pre-test. An intervention is needed to offer eye examinations by optometrists in the Romani neighborhood to understand what percentage of Romani children need eyeglasses. Future interventions should offer eye care education to parents prior to visiting the optometrist to increase the likelihood that parents understand the importance of eye care visits.

The current intervention in step 2 needs to be enhanced to increase the use of eyeglasses. Initial and follow-up visits by optometrists in the neighborhood to provide, adjust, and/or replace eyeglasses will be valuable. Future focus groups or interviews may ask parents what strategies they recommend to encourage the use of eyeglasses in school. Partnering with schools to assist children in wearing their eyeglasses may be especially effective. Teachers should be informed when children need eyeglasses. Children can receive a second pair of eyeglasses to wear in school such as a in a previous intervention among non-Romani children (24). Teachers can remind children to wear their eyeglasses in school (24). Such a program that involves a partnership with schools may promote the academic development of children should be developed with the suggestions by Romani parents and even children.

5. Conclusion

Based on the suggestions by mothers during the step 1 focus groups, future interventions may include: complimentary eye examinations by an optometrist for children and parents in the neighborhood; provision of complimentary eyeglasses; and eye care education for parents on the importance of eye examinations and how to encourage children to wear eyeglasses both prior to and during/after eye examination visits. Future studies may assess whether such interventions promote the academic and healthy development of Romani children.

Nineteen Romani family members who agreed to participate in our study in one neighborhood in this study needed eyeglasses but did not have any at pre-test. The intervention increased the use of eyeglasses even months after providing the eye care. Roma seemed enthusiastic to receive eyeglasses. Roma were able to select eyeglasses that they stated they liked. There were problems with bringing Roma to the office of the optometrist possibly due to transportation and time barriers as well as perceptions for not needing eye examinations. Future interventions that bring the optometrist repeatedly to the neighborhood where Roma reside may result in higher participation rates and increased use of eyeglasses. They may offer eye care education on the importance of eye examinations to parents prior to optometrist visits so that parents will agree to have eye examinations for themselves and their children. The lessons learned can be used in future efforts to implement interventions in Romani communities and help promote the health of underserved populations.

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 University of Michigan Institutional Review Board. Verbal informed consent for participation was required for step 1 of the study. Written informed consent for participation was required for steps 2 of the study.

Author contributions

GDK, SGH, and VS: conceived and designed the study, collected the data, and reviewed final paper. GDK and SGH: designed data collection tools. GDK: performed analysis. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by internal grants from the University of Michigan—Ann Arbor International Institute and University of Michigan—Flint Office of Research.

Acknowledgments

We are extremely thankful to Vasil Tiganev, Registered Nurse, for outstanding and tireless support in the management of the study.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1096322/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 26 January 2023
DOI 10.3389/fpubh.2023.1074272

Effect of atropine 0.01% on myopia control in children aged 6–13 years during the 2022 lockdown in Shanghai

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 19 October 2022
ACCEPTED 10 January 2023
PUBLISHED 26 January 2023

CITATION
Yu M, Jiang L and Chen M (2023) Effect of atropine 0.01% on myopia control in children aged 6–13 years during the 2022 lockdown in Shanghai. *Front. Public Health* 11:1074272. doi: 10.3389/fpubh.2023.1074272

Purpose: To compare the myopic progression in children treated with 0. 01% atropine and those who discontinued atropine during the 2022-home quarantine in Shanghai.

Methods: In this retrospective study, children aged 6–13 years with follow-up visits before (between January 2022 and February 2022) and after the lockdown (between July 2022 and August 2022) were included. Cycloplegic refraction and axial length (AL) were measured at both visits. The atropine group had continuous medication during the lockdown while the control group discontinued. The 0.01% atropine eyedrops were administered daily before bedtime. The types of spectacle lens were recorded: single vision (SV) spectacles or defocus incorporated multiple segments lenses (DIMS).

Results: In total, 41 children (81 eyes) in the atropine group and 32 children (64 eyes) in the control group were enrolled. No significant difference was found in the demographic characteristics, spherical diopter, spherical equivalent (SE), AL, and follow-up time between the two groups before the lockdown in 2022 (all $p > 0.1$). After the home confinement, a greater myopia progression was observed in the control group (-0.46 ± 0.42 D) compared to atropine group (-0.26 ± 0.37 D; $p = 0.0023$). Axial elongation was also longer in the control group than that in children sustained with atropine (0.21 ± 0.17 vs. 0.13 ± 0.15 mm, $p = 0.0035$). Moreover, there was no significant change of spherical diopter and SE during lockdown in the atropine + DIMS combined subgroup (0.03 ± 0.033 D for spherical diopter, $p = 0.7261$ and 0.08 ± 0.27 D for SE, $p = 0.2042$, respectively). However, significant myopic shift was observed in the atropine + SV subgroup during the quarantine time (-0.31 ± 0.39 D for SE and 0.15 ± 0.16 mm for AL, both $p < 0.001$).

Conclusion: Children treated with 0.01% atropine had slower myopia progression during the lockdown period in Shanghai compared with children discontinued. Moreover, the effect of atropine on myopic prevention can be strengthened with DIMS lenses.

KEYWORDS

myopia control, atropine, COVID-19, Shanghai, myopia progression, quarantine, children, defocus incorporated multiple segments (DIMS)

Introduction

The widespread prevalence of myopia makes it a major public health concern. By 2050, close to 50% of the world's population are expected to have myopia and with as much as 10% highly myopic (1). Meanwhile, the increasingly high prevalence of myopia and high myopia have been already witnessed in the past few decades (2). Moreover, early-onset myopia among preschoolers has become more prevalent in recent years in China (3), indicating longer duration of myopia progression and more likely to have high myopia in the future (4, 5). Consequently, the Chinese Ministry of Education issued the Comprehensive Plan to Prevent Nearsightedness among Children and Teenagers (CPPNCT) in aim to reduce the incidence of myopia and control myopic progression in China in 2018 (6). Though numerous items are included in the CPPNCT, increasing time outdoors and reducing near-work time are the key content (6). For example, mandatory outdoor time has already been implemented as part of myopia prevention programs in cities of mainland China.

However, the pandemic of coronavirus disease (COVID-19) in December 2019 has caused huge behavioral changes. Home confinement was imposed and children were forced to study *via* online platforms. As a result, significant progression in myopia has been evidenced in numerous reports during the lockdown (7–11). Considerable evidences are provided to support the association between the progression of myopia and an increase in near work or a reduction of outdoor activities during the COVID-19 home confinement (7, 8, 10). To make matters worse, in late February, 2022, another wave of COVID-19 infection rapidly appeared in Shanghai, China (12). Strict home confinement was applied again and the "home education" was implemented once more until the end of June.

Nowadays, low-concentration atropine eye drops is recommended and widely used to slow myopic progression (13–16). Though 0.05% atropine has been proved to be the optimal concentration for myopia control (15, 16), it is not commercially available in our country compared with 0.01% atropine which is clinically easy to prescribe in Shanghai. Only two clinical-based studies have observed that myopia could still progress during COVID-19 quarantine even in children treated with 0.01% atropine (17, 18). But neither study had a control group, indicating the same group of the children were analyzed and compared only in a temporal relation (17, 18). Thus it remains unknown if beneficial effect of 0.01% atropine could be achieved in comparison to the cessation of atropine treatment during the lockdown.

In this study, we analyzed the myopic progression among primary students treated with 0.01% atropine eye drops compared to those who discontinued during the 2022-home quarantine in Shanghai, aiming to explore the effect of 0.01% atropine in the prevention of myopia during the COVID-19 pandemic.

Patients and methods

In this retrospective study, the medical records of children aged from 6 to 13 years old (Shanghai primary students from grades 1 to 7) who visited our refractive department clinic before (between January 2022 and February 2022) and after the lockdown (between July 2022 and August 2022) were reviewed. These students took online courses at home from March 13th until the end of the semester, they received comprehensive ophthalmic examinations within 2 weeks after 2 months lockdown. In total, the continuous subjects of 41 children (81 eyes) in the atropine group and 32 children (64 eyes) in the control group were included. All children were prescribed 0.01% atropine eye drops before 2022 according to the protocol which was when calculated myopic progression rate exceeded −0.75 diopter (D)/year (y). The atropine group had continuous medication during the lockdown, while the control group discontinued since the epidemic began in February 2022 due to the home quarantine and inconvenience to get the eyedrops. The 0.01% atropine drops were administered daily before bedtime. Parents were instructed to use the eye drops during clinic and would be asked whether their children used every day. The 0.01% atropine eyedrops were produced by adding 1 ml of 0.05% Kg/L atropine sulfate (atropine sulfate injection, Hubei Xinghua Pharmaceutical Co., Ltd., China) to 4 ml of polyethylene glycol eye drops (Systane ULTRA, Alcon Laboratories, Inc., USA) by the Pharmaceutical Department of Eye & ENT Hospital (19). To further analyze the data, we classified children in the atropine group into single vision (SV) spectacle lenses subgroup and defocus incorporated multiple segments (DIMS, MiYOSMART, manufactured by HOYA Corporation, Japan) lenses subgroup. Children were asked to wear the spectacles in full-time mode, for no less than 12 hours per day. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University. Parents or guardians of patients aged <18 years provided written informed consent.

All children received comprehensive ophthalmic examinations. The best-corrected visual acuity in both eyes of all children was not less than 0.0 Log MAR. Subjects with any other eye diseases, injury and history of orthokeratology or concentric contact lenses were excluded from the study.

Cycloplegic refraction was measured at both visits. Each subject was administered five drops of compound tropicamide eyedrops (0.5% tropicamide and 0.5% phenylephrine eyedrops; Univision, China) with a 5-min interval. Three readings of spherocylindrical auto-refraction (KR-8800, Topcon Corporation, Tokyo, Japan) were taken and averaged 30 min after the last eyedrop. Subjective refraction was then performed by an experienced optometrist. IOL Master (Carl Zeiss Meditec AG, Jena, Germany) was used to measure axial length (AL). Five repeated measurements were taken and averaged before cycloplegia.

Statistical analysis

All statistical analyses were performed using the Stata 14.0 (Stata Corp., College Station, TX, USA). Both eyes were included in the analysis. The spherical equivalent (SE) was calculated as spherical power plus half-negative cylinder power. A paired *t*-test or matched-pairs signed-rank test was used to analyze the time course difference in both groups. Between-group differences were checked with the *t*-test or Wilcoxon rank-sum test. Numeration data were compared between the two groups using χ^2 tests. The statistical significance threshold was set at $p = 0.05$.

Results

There was no significant difference in terms of gender and age distribution between the two groups, ranging from 6 to 13 years (Table 1). Before the lockdown, the mean spherical diopter was −1.53

TABLE 1 Baseline general characteristics of all participants.

	Atropine group ($n = 41$, 81 eyes)	Control group ($n = 32$, 64 eyes)	p-Values
Age (year)	9.39 ± 1.58	9.41 ± 1.93	0.9690
Female, no. (%)	41.46%	31.25%	0.370
DIMS lenses, no. (%)	21.95%	12.50%	0.295
Follow-ups (month)	5.13 ± 0.10	5.20 ± 0.10	0.6280
Spherical diopter (D)	−1.53 ± 1.30	−1.26 ± 1.29	0.2106
Spherical equivalent (D)	−1.75 ± 1.36	−1.45 ± 1.36	0.1890
AL (mm)	24.47 ± 0.93	24.24 ± 0.83	0.1198

DIMS, defocus incorporated multiple segments; D, diopter; AL, axial length.

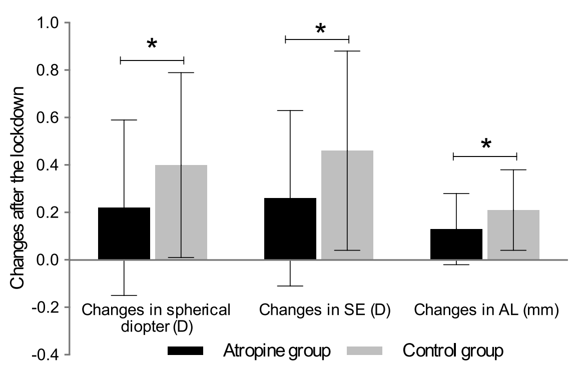

FIGURE 1
Changes of spherical diopter, SE and AL in atropine and control group after the 2022-lockdown in Shanghai. *Significant difference between the two groups. SE, spherical equivalent; AL, axial length.

± 1.30 and −1.26 ± 1.29 D in the atropine group and control group, respectively ($p = 0.2106$). SE and AL were also comparable between the two groups. There were nine subjects wearing DIMS lenses in the atropine group compared to four subjects in the control group ($p = 0.295$).

Myopic shift was found in both groups after the lockdown (all $p < 0.001$). During the lockdown, the change in SE in the control group was significantly greater than that in the atropine group ($p = 0.0023$), with an average myopic shift of −0.46 ± 0.42 and −0.26 ± 0.37 D in the control group and atropine group, respectively. Similar results were observed in spherical diopters ($p = 0.0053$; Figure 1). A marked increase in AL was seen in both groups with 0.13 ± 0.15 mm in the atropine group and 0.21 ± 0.17 mm in the control group during the lockdown (both $p < 0.05$). Greater changes in AL were seen in children who discontinued medication during the 2022 pandemic ($p = 0.0035$).

Additive effect of DIMS lenses

The additive effect of DIMS spectacle lenses on myopia control was also studied. Children sustained with atropine in the current study were classified into two subgroups according to whether wearing DIMS lenses or SV spectacles. Though age and gender distribution were comparable between the two populations, children wearing DIMS lenses had more myopia as well as AL (Table 2). After home confinement, a myopic progression of −0.27 ± 0.36 D was found in SV + atropine subgroup ($p < 0.001$), while no significant myopia shift was observed in DIMS + atropine group (Figure 2; 0.03 ± 0.033 D for spherical diopter, $p = 0.7261$ and 0.08 ± 0.27 D for SE, $p = 0.2042$, respectively). The mean change of AL was 0.15 ± 0.16 mm in the SV + atropine monotherapy group during the home quarantine, which was 0.09 ± 0.09 mm in the DIMS + atropine combined therapy subjects.

Discussion

Nowadays, as the pandemic of COVID-19 continues and the Chinese government enacts strict stay-at-home quarantine policies, studying at home during the pandemic is inevitable, accompanied by more digital screen time and less outdoor activities. It is urgent to find effective and generalizable methods to prevent and control myopia in children. In the current study, during the 2022-home-quarantine period in Shanghai, less myopia progression was found in 6-to 13-year-old students who received 0.01% atropine compared to children who discontinued. Moreover, the combination of 0.01% atropine and DIMS lenses offered benefit in controlling myopia during the pandemic.

Numerous studies demonstrated myopia progression during the study-at-home period was higher than the highest myopia progression during the period before COVID-19 (7–11). Most studies focused on the progression rate from 2019 to 2020, when this pandemic first broke out. However, all the children in Shanghai experienced quarantine again in 2022. One research in Shanghai reported that myopic progression in children aged 7–12 years was −0.98 ± 0.52 D during the 5.4 months of the first pandemic (7), which was nearly twice greater than that in current study of −0.46 ± 0.42 D in the control group during the 2022 pandemic of 5.2 months. Another study in Wenzhou found an average −0.343D myopia progression at 6-month for all schoolchildren after the first COVID-19 quarantine (20), consistent with the data identified in Chongqing, China (21). We speculate that this difference could be due to a number of factors. First of all, differences in optometric methods, inclusion criteria and educational environment may account for part of the discrepancy. Secondly, myopia development in Chinese children during study-at-home attracted much attention since the pandemic in 2019. Public awareness and educational campaigns

TABLE 2 Demographic characteristics and ocular parameters based on the types of spectacle lenses wearing.

	SV + atropine (*n* = 32, 63 eyes)	DIMS + atropine (*n* = 9, 18 eyes)	*p*-Values
Female, no. (%)	40.63%	44.44%	0.8370
Age (year)	9.44 ± 1.63	9.22 ± 1.48	0.7228
Follow-ups (month)	5.16 ± 0.12	5.06 ± 0.15	0.6720
Spherical diopter (D)	−1.32 ± 1.26	−2.26 ± 1.19	0.0060
Spherical equivalent (D)	−1.54 ± 1.33	−2.49 ± 1.25	0.0078
AL (mm)	24.30 ± 0.93	25.07 ± 0.66	0.0017

SV, single vision spectacle lenses; DIMS, defocus incorporated multiple segments lenses; D, diopter; AL, axial length.

focusing on preventive strategies of myopia have been gradually promoted, including avoiding prolonged near work activities, room lighting, writing posture, interval break after 20 min of screen time and preferred larger screen (22). Therefore, it is reasonable that these forced behavioral changes due to the 2022 pandemic may have an impact on children's refractive status.

Against the rapid and widespread development of myopia, a series of interventions for myopia control in children have reached high-level evidence, among which low concentration atropine is an effective one (13–16). This study compared the myopic progression in children treated with 0.01% atropine or not during the 2022 quarantine, and found the myopic progression decelerated in children with continuous medication since the outbreak of the pandemic in February 2022, though two previous studies showed that 0.01% atropine had little effect on myopic progression during the lockdown (17, 18). For one thing, the refractive data was collected in the same group at different ages in previous studies (Longitudinal cohort), indicating that the data was analyzed and compared in a time course (17, 18). In another word, neither previous studies included an age-matched control group, which was complementarily designed in the present study. It is well-acknowledged that there is a natural progression of axial elongation among children. The design of this study eliminated the confounding effect of natural myopia progression with increasing age and therefore might reflect the true effect of atropine on myopia progression during the lockdown. For another, younger age of children in Yum et al. (18) study located in South Korean and relatively small sample size (14 children) in Erdinest et al. (17) study located in Israel may also interpret their insignificant results. Besides, children in the current control group were also applied with 0.01% atropine before the pandemic in 2022. Recently, a cross-over trial suggested that there is no rebound effect after cessation of 0.01% atropine eyedrops in preventing myopia progression (23). Thus in the present study, children in control group experienced natural development of myopia and had more myopic shift and axial elongation in contrast with the atropine group.

Though interventions for controlling myopia progression were widely applied, neither of them could achieved a 100% success (24). Subsequently, several studies have investigated the effect of combination therapy, and revealed that the addition of orthokeratology and low-dose atropine was better than orthokeratology alone in myopia control (19, 24–26). To our knowledge, this is the first study showing adjunctive effect of DIMS lenses and 0.01% atropine in controlling myopic progression in 6-to 13-year-old students during the home quarantine period in 2022. The specially designed DIMS lenses has been proved

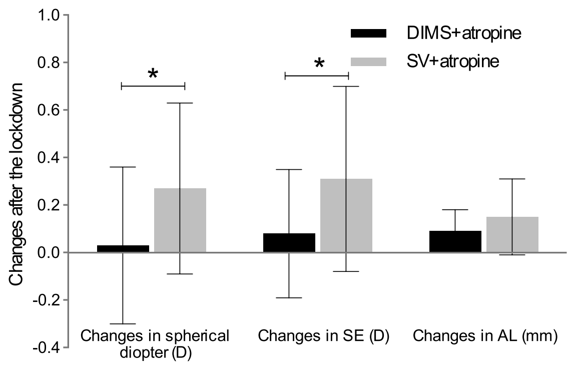

FIGURE 2
Changes of spherical diopter, SE and AL in DIMS + atropine and SV + atropine group after the 2022-lockdown in Shanghai. *Significant difference between the two groups. SE, spherical equivalent; AL, axial length; DIMS, defocus incorporated multiple segments lenses; SV, single vision spectacle lenses.

to have greater effect in myopia control compared to SV lenses through incorporating myopic defocus (27). Furthermore, the effect of DIMS spectacles was also proved to significantly prevent myopia progression compared with SV lenses treatment during the lockdown period (28). Consistent with the previous study, negligible increments of 0.08 ± 0.27 D in SE and 0.09 ± 0.09 mm in AL were evidenced in DIMS and atropine combined therapy compared with significant myopic progression in children treated with atropine alone in the present study. As a kind of frame glasses, DIMS lenses are convenient for children, making it easy to be promoted and applied. The complementary effect of DIMS lenses and atropine observed here enlightens the synergistic treatments in myopia control in the future. Though DIMS lenses were also used in control group here, the small sample size (four children) prevented us from analyzing its effect any further.

However, this study has several limitations. Firstly, the sample size was relatively small, so both eyes were included in the analysis which could have created potential bias. Secondly, data about time spent each day on learning, on different types of digital screen devices (including mobile phone, tablet, television, and projector) as well as outdoor activities were not collected. Multiple studies have concluded that development of myopia accelerated during pandemic due to the excessive time spent on digital screen devices for online learning and less time spent on outdoor activities (8, 29). Without data of those behavioral changes during the lockdown, the associated factors influencing the myopic progression could not be interpreted. Thirdly, this study did not collect data on rate of myopic progression before the 2022-pandemic, which made the investigation less comprehensive and convincing.

In summary, pharmaceutical treatment with 0.01% atropine was significantly associated with slower myopia progression compared to children who experienced cessation of therapy during 2022 lockdown in Shanghai. In addition, better performance was observed in synergistic efforts of DIMS spectacles and 0.01% atropine in myopic prevention. The findings from our data may help better to adjust the behaviors to prevent myopia and the progression in the future, especially during the quarantine period of COVID-19. This study could pave wave for better understanding regarding the efficacy of current myopia control measures by helping to design a larger and multicenter study.

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 Institutional Review Board of the Eye and ENT Hospital of Fudan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MY was responsible for collecting and analyzing data, interpreting results, and writing the abstract and the paper. LJ contributed to reviewing of the data, interpreting results, and writing the paper, tables, and figures. MC contributed to the design of the study, review, and feedback on the paper. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (82101175). All sources of funding received for the research being submitted.

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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 06 February 2023
DOI 10.3389/fpubh.2023.1119654

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 09 December 2022
ACCEPTED 16 January 2023
PUBLISHED 06 February 2023

CITATION
Wu Z, Hu Y, Xu Z, Sun W, Wang Y, Shao Z, Liu Y, Yu M, Si P, Huo H, Wang X and Bi H (2023) Characteristics of full compensation and its association with total astigmatism: A cross-sectional study. *Front. Public Health* 11:1119654. doi: 10.3389/fpubh.2023.1119654

Characteristics of full compensation and its association with total astigmatism: A cross-sectional study

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Objective: To evaluate the characteristics of full compensation and its association with the prevalence of total astigmatism (TA), and to analyze the effects of TA on uncorrected distance visual acuity (UDVA).

Methods: With random cluster sampling based on a school-based cross-sectional design, children aged 4 to 18 years were recruited in September 2020, Shandong Province, China. TA, anterior corneal astigmatism (ACA), and ocular residual astigmatism (ORA) were converted to vectorial components (*J0*, *J45*), followed by an assessment of the compensatory effect of ACA by ORA. Astigmatism was defined as a cylinder that was better than or equal to 0.75 diopters (D). Logistic regression analysis was used to assess the related factors for children with full compensation, and the generalized linear model was used to assess the influence of TA on UDVA.

Results: Out of 4,494 eligible children, data of 4,145 children (92.3%, 9.23 ± 3.15 years, 50.4% boys) were included in the statistical analysis. The prevalence of TA (27.9%) increased significantly with age ($P_{trend} < 0.001$). The distribution of full compensation in *J0* and *J45* components were similar (22.1% and 25.6%, respectively), which decreased with age ($P_{trend} < 0.001$). The closer the refractive status was to emmetropization, the higher the proportion of full compensation and the lower the prevalence of TA were. Shorter axial length (*J0*: Odds Ratio (OR) = 0.76, 95% confidence interval (CI): 0.61 to 0.94, $P = 0.010$), better UDVA (*J0*: OR = 0.37, 95% CI: 0.21 to 0.65, $P < 0.001$; *J45*: OR = 0.34, 95% CI: 0.20 to 0.59, $P < 0.001$), and longer average corneal curvature radius (*J0*: OR = 3.72, 95% CI: 2.18 to 6.34, $P < 0.001$; *J45*: OR = 2.82, 95% CI: 1.67 to 4.76, $P < 0.001$) were associated with full compensation. Higher TA was associated with a worse UDVA ($\beta = 0.03$, 95% CI: 0.02 to 0.04, $P < 0.001$).

Conclusions: The prevalence of TA gradually increased with age, and showed a U-shaped distribution with increased refraction. Full compensation was associated with smaller TA and better UDVA. This indicated that considering the compensatory effect of ORA is vital for astigmatism correction in clinical work, which may improve the visual quality.

KEYWORDS

full compensation, total astigmatism, related factors, uncorrected distance visual acuity, cross-sectional study

Introduction

Astigmatism is a significant and common clinical and public health problem. Uncorrected astigmatism may increase the risk of developing amblyopia and various ocular symptoms (such as glare, monocular diplopia, visual fatigue, and distortion) (1, 2). Total astigmatism (TA) is the result of the combined effect of corneal astigmatism (CA) and ocular residual astigmatism (ORA). CA theoretically consists of anterior corneal astigmatism (ACA) and posterior corneal astigmatism (PCA). However, CA usually refers to ACA. ORA was defined as an astigmatism of posterior corneal surface, plus the crystalline lens astigmatism, and astigmatism caused by aqueous humor.

Previous studies have shown that the cornea was not spherically perfect, and a compensating mechanism between ORA and CA existed (3, 4). In those studies, ACA often exceeded TA, but a balance between internal and corneal optics helped to minimize TA. ORA, however, could not be calculated simply by subtracting ACA from TA unless the astigmatic axis of total and corneal coincide. Instead, Thibos et al. proposed the calculation formula of *J0* and *J45* components (5, 6). Both the magnitude and directional of astigmatism were took into consideration.

The compensatory role of ORA has been already proved to exist. Based on Park and Muftuoglu (3, 7), the ACA of the same magnitude as ORA but in the opposite axial direction was defined as full compensation. However, few studies have assessed the impact on TA by integrating the compensatory effect between ACA and ORA and there is shortage evidence of the related factors about full compensation. In addition, the magnitude of astigmatism might also result in the reduction of uncorrected distance visual acuity (UDVA) and the visual impairment (8). Therefore, our study aimed to analyze the characteristics of compensatory role of ORA, and the associated factors of full compensation in school-aged children, evaluating its influence on the prevalence of TA and UDVA. We hope that these could help understand the general framework of astigmatism occurrence and progression.

Materials and methods

Study population

This was a school-based cross-sectional study conducted in Huantai, Shandong, China, in September 2020, which used a multi-stage stratified cluster sampling to recruit children from nine schools (two kindergartens, four primary schools, two middle schools, and one high school). First of all, the local authorities of education provided a list of all schools in Huantai area. Nine schools were then chosen by using convenience sampling. Next, according to the enumeration of grades within the schools, the sampling frame was defined, and ensuring that students aged from 4 to 18 years were included. Finally, classes for each grade level were chosen by simple random sampling. All students in the chosen classes were invited to take part in the research. Children with fundus diseases, cataracts and lens dislocations, or any history of eye surgery, were excluded. Additionally, some individuals with deficient astigmatism data were also excluded from the statistical analysis.

The study was approved by the Ethics committee of the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine (HEC-KS-2020016KY). Written consent was obtained from parents and children, and verbal permission was obtained from all participants before the examination.

Examinations

After supplying questionnaires similar to that used in the previous Refractive Error Study in Children studies to obtain information on parental maternal refractive status, a series of comprehensive ophthalmic examination were carried out by two experienced ophthalmologists. Slit-lamp was the first step to assess anterior and posterior ocular segments, followed by testing UDVA at a distance of 3 meter using the "E" chart (#600722, Good-Lite Co., Elgin, IL, USA). The non-cycloplegic and cycloplegic auto-refractive status of participants were measured by an autorefractor (Nidek ARK-1, CO., LTD, Japan) with consistent parameters (the vertex distance: 12 mm; the measurement step size: 0.25 D). The difference between the maximum and minimum values of spherical and cylindrical degree should be <0.5 D; otherwise, remeasurement was conducted. The cycloplegia was done as follows: one drop of 1% cyclopentolate (Alcon, Fort Worth, TX, USA) was applied to each eye every 5 min for a total of three times. The pupil≥6 mm in diameter was considered as adequate cycloplegia, otherwise, one more drop of cyclopentolate was added and refraction was measured after 10 min. We used IOL-Master 500 (Carl Zeiss Meditec AG, Jena, Germany) to measure Axial length. If the signal-to-noise ratio was <2.1, additional measures were performed until reliable readings were obtained.

Other ophthalmic examination steps have been described in detail in previous researches (9).

Definition

Astigmatism correction needed in daily life is in the status of natural pupil size (9). Thus, TA and ACA were represented by non-cycloplegic values in the study. Astigmatism is defined as a cylindrical refractive error $\geq$ 0.75 diopters (D). ACA was obtained by autorefractometry in the range of 3-millimeter corneal diameter and calculated as the difference between the flattest and steepest corneal medians of the anterior corneal surface. The cylindrical axis is equal to the flattest meridian. The sum of the spherical refractive error and half of the cylindrical refractive error was defined as the Spherical Equivalent (SE, expressed as negative values). After cycloplegia, Myopia, pre-myopia, and hyperopia were defined as SE $\leq$ −0.50 D, −0.50 D $<$ SE $\leq$ 0.75 D, and SE $>$ 0.75 D, respectively (10). In addition, we classified myopia as mild myopia (−3.00 D $<$ SE $\leq$ −0.50 D), moderate myopia (−6.00 D $<$ SE $\leq$ −3.00 D), and high myopia (SE $\leq$ −6.00 D). We classified hyperopia as mild hyperopia (0.75 D $<$ SE $\leq$ 2.00 D), moderate hyperopia (2.00 D $<$ SE $\leq$ 5.00 D), and high hyperopia (SE $>$ 5.00D).

According to Equations 1–2, the cylinder (C), and axis (α) may be converted to power vector (*J0* and *J45* components) (5, 6). C represents negative-cylinder power, and α represents the radians

TABLE 1 Age and refractive status related changes in TA and ACA.

	N	TA (D)				ACA (D)			
		Total	Boys	Girls	P*	Total	Boys	Girls	P*
All	4,145	0.25 (0.25, 0.75)	0.50 (0.25, 0.75)	0.25, (0.25, 0.75)	<0.001	1.25 (0.75, 1.50)	1.25 (0.75, 1.50)	1.25 (0.75, 1.50)	0.165
Age (years)									
4–7	1,430	0.25 (0.25, 0.50)	0.25 (0.25, 0.50)	0.25 (0.00, 0.50)	0.001	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	0.629
8–12	1,975	0.50 (0.25, 0.75)	0.50 (0.25, 0.75)	0.25(0.25, 0.75)	<0.001	1.25 (0.75, 1.50)	1.25 (0.75, 1.50)	1.25 (1.00, 1.50)	0.022
13–15	549	0.50 (0.25, 1.00)	0.50 (0.25, 1.25)	0.50 (0.25, 0.75)	<0.001	1.25 (0.75, 1.50)	1.25 (0.75, 1.75)	1.25 (0.75, 1.50)	0.294
16–18	191	0.50 (0.25, 1.00)	0.50 (0.25, 1.25)	0.50 (0.25, 1.00)	0.317	1.25 (1.00, 1.75)	1.13 (0.81, 1.75)	1.25 (1.00, 1.75)	0.956
Refractive status									
High hyperopia	10	1.00 (0.50, 2.19)	1.25 (0.44, 2.19)	1.00 (0.63, 2.31)	0.830	1.63 (0.94, 2.81)	2.00 (1.38, 2.94)	0.88 (0.56, 2.50)	0.165
Moderate hyperopia	158	0.50 (0.25, 0.75)	0.50 (0.25, 0.75)	0.50 (0.25, 0.75)	0.297	1.25 (1.00, 1.75)	1.50 (1.00, 2.00)	1.25 (0.75, 1.75)	0.131
Low hyperopia	1,237	0.25 (0.25, 0.50)	0.25(0.25, 0.50)	0.25 (0.06, 0.50)	0.008	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	1.25 (0.75, 1.50)	0.231
Pre-myopia	1,339	0.25 (0.25, 0.50)	0.25 (0.25, 0.50)	0.25 (0.25, 0.50)	<0.001	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	0.102
Low myopia	909	0.50 (0.25, 0.75)	0.50 (0.25, 0.75)	0.25 (0.25, 0.75)	<0.001	1.25 (0.75, 1.50)	1.25 (0.75, 1.50)	1.25 (0.75, 1.50)	0.878
Moderate myopia	418	0.75 (0.25, 1.00)	0.75 (0.50, 1.25)	0.75 (0.25, 1.00)	0.002	1.25 (1.00, 1.75)	1.25 (1.00, 1.75)	1.25 (1.00, 1.75)	0.730
High myopia	74	1.25 (0.75, 1.75)	1.50 (1.00, 2.00)	1.00 (0.50, 1.56)	0.008	1.50 (1.00, 2.00)	1.63 (1.25, 2.25)	1.50 (1.00, 2.00)	0.096

TA, Total Astigmatism; ACA, Anterior Corneal Astigmatism; D, Diopter. *, Mann Whitney Wilcoxon Test.

of axis:

$$J0 = (-C/2)\cos(2\alpha) \quad (1)$$

$$J45 = (-C/2)\sin(2\alpha) \quad (2)$$

The compensation factor (CF), was calculated as following formulas (Eqs 3–4). ORA*J0*, TA*J0*, and ACA*J0* are the *J0* components of ORA, TA, and ACA, respectively. ORA*J45*, TA*J45*, and ACA*J45* are the *J45* components of ORA, TA, and ACA, respectively.

$$CF0 = (ACAJ0 - TAJ0)/ACAJ0 \quad (3)$$

$$CF45 = (ACAJ45 - TAJ45)/ACAJ45 \quad (4)$$

Based on the compensation mechanism of Park and Muftuoglu, CFs were classified as follows: (1) Same axis augmentation: CF< −0.1; (2) No compensation: CF = −0.1 to 0.1; (3) Under compensation: CF = 0.1 to 0.9; (4) Full compensation: CF = 0.9 to 1.1; (5) Over compensation: CF = 1.1 to 2; and (6) Opposite axis augmentation: CF>2 (3, 7).

Statistical analysis

Statistical analysis was performed by SPSS (SPSS for Windows, version 25.0, Chicago, IL). Only data from the right eyes were chosen for analysis. The Kolmogorov-Smirnov method was used to check the normality of quantitative data. Variables with normal distributions were expressed as mean ± standard deviation (M±SD), unless the median was applied instead. Variables were tested for normality using parametric test, unless non-parametric test was used. Chi-square analysis and P_{trend} values from the Linear-by-Linear Association (LLA) were used to investigate trends in the prevalence of TA and the proportion of full compensation. TA and Full compensation were considered as the dependent variable. Collinearity diagnostics were performed on the independent variables, and those parameters with variance inflation factor (VIF) < 5 were included in the generalized linear model (GLM). Coefficients (β) with 95% confidence intervals (CI) were calculated. All *P*-values were <0.050 were considered statistically significant.

Result

Participants

A total of 4,494 children aged 4–18 years were recruited in the cross-sectional study, of whom 349 were excluded (283 with non-cycloplegic refraction, 45 with amblyopia, and 21 with incomplete astigmatism data). The research ultimately included 4,145 (92.3%, 9.23 ± 3.15 years, 50.4% boys) children. As presented in Table 1, boys tended to show a higher magnitude of TA than girls, despite not all age groups reaching a statistically significant level.

The prevalence was 27.9% (1157/4145) for TA and 86.7% (3594/4145) for ACA, respectively ($\chi^2 = 139.50$, $P < 0.001$). Spearman correlation analysis in Figure 1 showed positive correlations between TA*J0* and ACA*J0* ($r = 0.710$, $P < 0.001$), TA*J0* and ORA*J0* ($r = 0.140$, $P < 0.001$), TA*J45* and ACA*J45* ($r = 0.541$, $P < 0.001$), and TA*J45* and ORA *J45* ($r = 0.129$, $P < 0.001$). However, there was a negative correlation between ACA and ORA for both *J0* ($r = -0.512$, $P < 0.001$) and *J45* ($r = -0.697$, $P < 0.001$) components, suggesting the existence of a compensatory mechanism for ACA by ORA.

Compensation factor

In $n = 29$ for *J0* and $n = 233$ for *J45* of ACA, CF was not determined as the denominator was zero. CF percentages of all

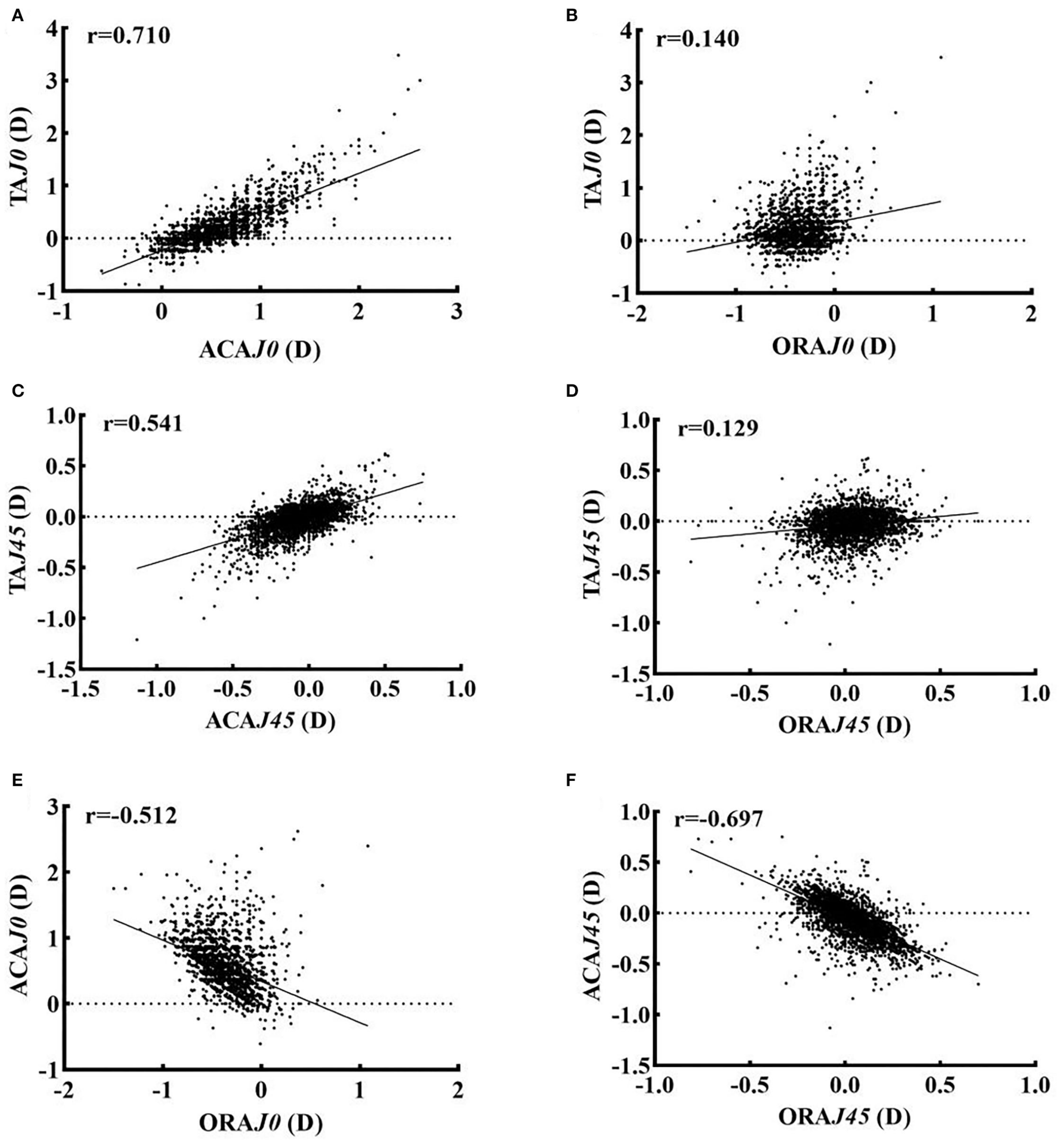

FIGURE 1
Spearman correlation analysis were used to analyze the correlation of TA, ACA, and ORA in *J0*, and *J45* components. **(A)** ACA *J0* vs. TA *J0*. **(B)** ORA *J0* vs. TA *J0*. **(C)** ACA *J45* vs. TA *J45*. **(D)** ORA *J45* vs. TA *J45*. **(E)** ACA *J0* vs. ORA *J0*. **(F)**. ACA *J45* vs. ORA *J45*. *J0* and *J45* components represent the orthogonal (power of Jackson cross cylinder at 90° and 180°) and oblique (power of the Jackson cross cylinder at 45° and 135°), respectively. TA, Total Astigmatism; ACA, Anterior Corneal Astigmatism; ORA, Ocular residual astigmatism; D, diopter.

children were summarized in Figure 2. Most of the compensation types were under compensation and full compensation (*J0*: 85.9%; *J45*: 61.6%), indicating TA fell below ACA, but the astigmatism axis remained the same. The percentages of full compensation in the *J0* and *J45* components (22.1 and 25.6%, respectively) were similar.

Correlations between the proportion of full compensation and the prevalence of TA with age and refractive status

Figure 3 suggests that boys tend to show a higher prevalence of TA than girls. For *J0* and *J45* components, Figure 3A presents that

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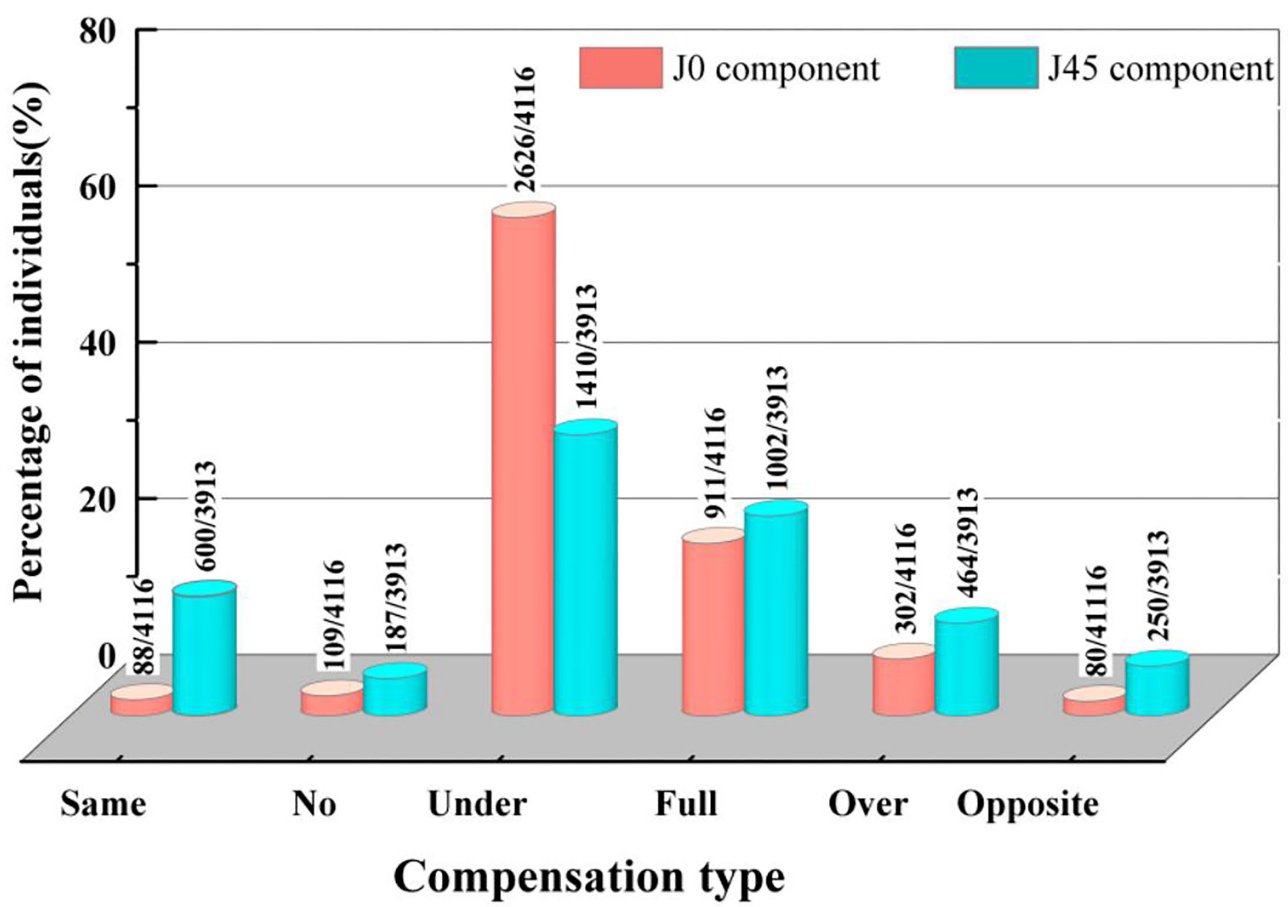

FIGURE 2
Distribution of compensation factor types in *J0* and *J45* components. *J0* and *J45* components represent the orthogonal (power of Jackson cross cylinder at 90° and 180°) and oblique (power of the Jackson cross cylinder at 45° and 135°), respectively. The percentage of compensation types in *J0*, *J45* components are shown on the y-axis. The groups of compensation types are shown on the x-axis. (1) Same: same axis augmentation; (2) No: no compensation; (3) Under; under compensation; (4) Full: full compensation; (5) Over: over compensation; (6) Opposite: opposite axis augmentation.

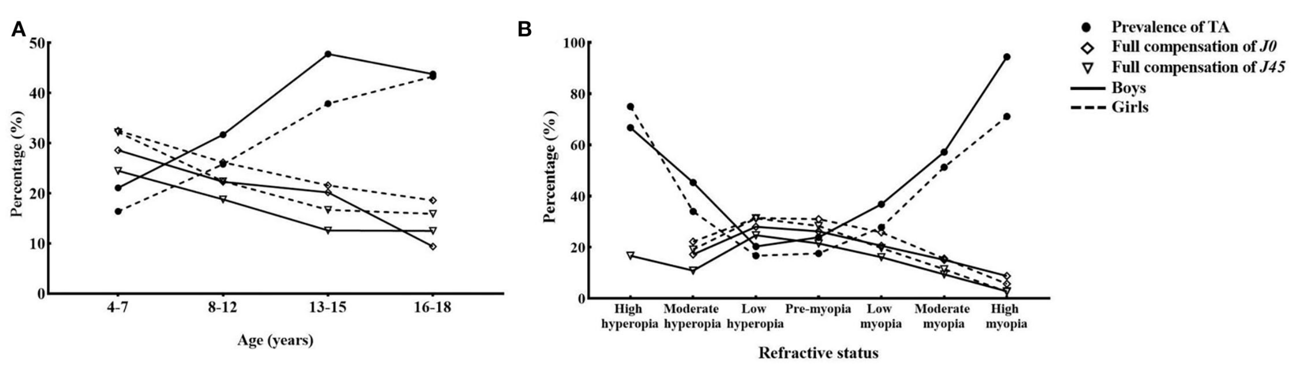

FIGURE 3
Age **(A)** and refractive status **(B)** related changes in full compensation and total astigmatism. *J0* and *J45* components represented the orthogonal (power of Jackson cross cylinder at 90° and 180°) and oblique (power of the Jackson cross cylinder at 45° and 135°), respectively. The percentage of TA and full compensation in *J0*, *J45* components are shown on the y-axis. The groups of age and refractive status are shown on the x-axis. After cycloplegia, pre-myopia was defined as–0.50 D < SE ≤ 0.75 D. We classified myopia as mild myopia (–3.00 D < SE ≤ –0.5 D), moderate myopia (–6.00 D) < SE ≤ 3.00 D, and high myopia (SE ≤ –6.00 D) after cycloplegia. We classified hyperopia as mild myopia (–0.75 D < SE ≤ 2.00 D), moderate myopia (2.00 D < SE ≤ 5.00 D), and high hyperopia (SE > 5.00 D). TA, Total Astigmatism; D, Diopter.

TABLE 2 Comparison of eye parameters for whether full compensation.

	J0 component (Whether full compensation)			*J45* component (Whether full compensation)		
	No	Yes	*P*-value	No	Yes	*P*-value
Gender						
Boys	1,659 (80.1%)	411 (19.9%)	<0.001	1,483 (76.0%)	468 (24.0%)	0.021
Girls	1,546 (75.6%)	500 (24.4%)		1,428 (72.8%)	534 (27.2%)	
Age (years)	9.00 (7.00, 12.00)	8.00 (6.00, 10.00)	<0.001	9.00 (7.00, 12.00)	8.00 (7.00, 10.00)	<0.001
Cycloplegic SE (D)	0.25 (−1.50, 1.00)	0.62 (−3.78, 1.13)	<0.001	0.25 (−1.38, 1.00)	0.63 (−0.50, 1.13)	<0.001
Axial length (mm)	23.38 (22.66, 24.34)	23.13 (22.55, 23.80)	<0.001	23.36 (22.63, 24.29)	23.24 (22.59, 23.95)	<0.001
Average anterior corneal curvature radius (mm)	7.78 (7.63, 7.96)	7.82 (7.64, 7.99)	<0.001	7.78 (7.61, 7.96)	7.83 (7.67, 7.99)	<0.001
Intraocular pressure (mmHg)	16.00 (15.00, 18.00)	16.00 (14.00, 18.00)	0.339	16.00 (15.00, 18.00)	16.00 (14.00, 18.00)	0.193
UDVA (log MAR)	0.00 (0.00, 0.40)	0.00 (0.00, 0.10)	<0.001	0.00 (0.00, 0.40)	0.00 (0.00, 0.10)	<0.001
Total astigmatism (D)	0.50 (0.25, 0.75)	0.00 (0.00, 0.00)	<0.001	0.50 (0.25, 0.75)	0.00 (0.00, 0.25)	<0.001
Anterior corneal astigmatism (D)	1.25 (1.00, 1.75)	1.00 (0.75, 1.25)	<0.001	1.25 (1.00, 1.75)	1.00 (0.75, 1.25)	<0.001

D, Diopter; mm, Millimeter; mmHg, Millimeter of mercury; UDVA, Uncorrected Distance Visual Acuity.

the proportion of full compensation decreases significantly with age (P_{trend} < 0.001), and the prevalence of TA increased significantly with age (P_{trend} < 0.001). The prevalence of TA in children varied with refractive status in a U-shaped distribution (Figure 3B). The closer the refractive status was to emmetropization, the higher the proportion of full compensation and the lower the prevalence of TA were.

Related factors of full compensation

For *J0* and *J45* components, comparisons for related factors about full compensation were shown in Table 2. Children with full compensation were more likely to be younger and associated with larger cycloplegic SE, shorter axial length, longer average anterior corneal curvature radius, better UDVA, and smaller TA and ACA ($P < 0.001$).

As shown in Table 3, multiple logistic regression was used to assess the related factors of full compensation (the univariate logistic regression shown in Supplementary Table 1). Better UDVA (*J0*: OR = 0.37, 95% CI: 0.21 to 0.65; $P = 0.001$; *J45*: OR = 0.34, 95% CI: 0.20 to 0.59, $P < 0.001$), shorter axial length (*J0*: OR = 0.76, 95% CI: 0.61 to 0.94, $P < 0.01$), and longer average anterior corneal radius (*J0*: OR = 3.72, 95% CI: 2.18 to 6.34, $P < 0.001$; *J45*: OR = 2.82, 95% CI: 1.67 to 4.76, $P < 0.001$) were associated with full compensation.

Correlations between full compensation, TA, and UDVA

As shown in Table 4, TA was determined as the dependent variable in model 1, and UDVA was determined as the dependent variable in models 2 and 3. The univariate GLM could be seen in Supplementary Table 2. After adjusting for age, gender, cycloplegic SE, and other factors. Multivariate GLM showed that children with full compensation may contribute to a smaller TA in model 1 (*J0*: $\beta = -0.42$, 95% CI: −0.47 to −0.37, $P < 0.001$; *J45*: $\beta = -0.18$, 95% CI: −0.23 to −0.14, $P < 0.001$) and better UDVA in model 2 (*J45*: $\beta = -0.02$, 95% CI: −0.04 to −0.00, $P = 0.015$). Moreover, larger TA was associated with worse UDVA in model 3 ($\beta = 0.03$, 95% CI: 0.02 to 0.04, $P < 0.001$).

Discussion

Using cross-sectional data in Shandong, China, we firstly explored the related factors of full compensation and found the effects of astigmatism on visual acuity. The results showed that children with full compensation had smaller TA. Yet, higher TA was associated with worse UDVA in children after adjusting for age, gender, spherical powers, and parental refractive status. Our study also provided new information on astigmatism distribution in children aged 4–18: the proportions of full compensation in the *J0* and *J45* components were 22.1 and 25.6%, and the prevalence of TA was 27.9%, respectively. However, Park et al. investigated 178 adults (aged 19–46 years) and examined the compensation of ORA. They found that for the *J0* component, 4% was full compensation, and for the *J45* component, 12% was full compensation (3). Their percentages were lower than those in our research in both the *J0* and *J45* components. This difference might be attributable to the age effect. We found that the efficiency of full compensation decreased with age in children aged 4–18 years. The phenomenon may be related to ocular development and myopic progression. The cornea is not perfectly spherical. ACA, PCA, the crystalline lens, the asymmetry of each refractive error component of the eye, the tear film conditions, and intrinsic variation of the refractive index, etc., are the complex factors that contribute to astigmatism (11). A disruption of any factor could affect the compensation mechanism.

CA theoretically is the combination of ACA and PCA. However, because of the difficulties in measuring PCA and the relatively small influence on TA, CA generally only refers to ACA. PCA was considered ORA in most cases. In addition, other components such as aqueous humor, crystalline lens, and vitreous body contribute to ORA (12), which may help neutralize or offset a portion of the ACA to diminish TA or superimpose with ACA to increase TA. Identifying the compensatory mechanism of ORA can help us understand the

TABLE 3 Multivariate Logistic regression analysis assessing related factors for children with full compensation.

	J0 component		*J45* component	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Gender _ Boys	0.69 (0.58,0.82)	<0.001	0.72 (0.61,0.85)	<0.001
Age (years)	0.94 (0.91,0.98)	0.003	0.96 (0.93,1.00)	0.047
Cycloplegic SE (D)	0.88 (0.79,0.99)	0.039	0.93 (0.83,1.04)	0.198
Axial length (mm)	0.76 (0.61,0.94)	0.010	0.90 (0.73,1.11)	0.322
Average anterior corneal curvature radius (mm)	3.72 (2.18,6.34)	<0.001	2.82 (1.67,4.76)	<0.001
UDVA (Log MAR)	0.37 (0.21,0.65)	<0.001	0.34 (0.20,0.59)	<0.001

D, Diopter; mm, millimeter; UDVA, uncorrected distance visual acuity.

TABLE 4 Effect of full compensation on total astigmatism and uncorrected distance visual acuity based on multivariate Generalized Linear Model.

	Model 1		Model 2		Model 3	
	β (95%CI)	P^*-value	β (95%CI)	P^*-value	β (95%CI)	P^*-value
Full compensation of *J0* component	−0.42 (−0.47, −0.37)	<0.001	−0.01 (−0.03, 0.01)	0.039	–	
Full compensation of *J45* component	−0.18 (−0.23, −0.14)	<0.001	−0.02 (−0.04, −0.00)	0.015	–	
Total astigmatism (D)	–		–		0.03 (0.02, 0.04)	<0.001
Gender _ Boys	0.08 (0.05, 0.11)	<0.001	−0.03 (−0.04, −0.02)	<0.001	−0.03 (−0.04, −0.02)	<0.001
Age (years)	0.00 (0.00, 0.01)	0.268	0.01 (0.01, 0.01)	<0.001	0.01 (0.01, 0.01)	<0.001
Cycloplegic SE (D)	−0.05 (−0.06, −0.04)	<0.001	−0.01 (−0.01, −0.09)	<0.001	−0.09 (−0.10, −0.09)	<0.001

Model 1: Total astigmatism was the dependent variable; Model 2 and Model 3: Uncorrected distance visual acuity (LogMAR acuity) was the dependent variable.
P^*-Values were calculated with a multivariate Generalized Linear Model adjusted for age, gender, cycloplegic spherical equivalence, maternal and parental refractive status.
D, Diopter; SE, spherical equivalence.

distribution of astigmatism and screen children who need early intervention. It also assists clinicians in designing post-operative RA, reducing unnecessary ORA after corneal remodeling. For example, when ORA exhibits an offsetting effect on ACA, leaving the ACA of the same magnitude as ORA but in the opposite axial direction should be considered in kerato-refractive laser surgery, which may improve post-operative vision.

Children with full compensation had better UDVA in the *J45* component (Shown in Table 4), and the larger TA was associated with worse UDVA (model 3, shown in Table 4). Similar findings also suggested a positive association between visual acuity and astigmatism (LogMAR acuity = 0.068 + 0.055 astigmatism) (13). Moreover, a case-control study revealed that low-level ORA induced by IOL implantation in patients also reduced their visual acuity (14). The reason is that astigmatism could prevent the human eye from focusing complex visual information on the retina, leading to blurred vision. Continuing to find or eliminate the reasons for ORA remains a goal and a challenge for clinical physicians in precision medicine. The balance between the optics in the eye and the cornea helps minimize ORA. ORA is often unpredictable and affects visual quality. Even excellent ortho-K lens fitting may lead to irregular ORA. This can even result in severe visual discomforts such as double vision, glare, metamorphopsia, and decreased visual quality (15). The accuracy of refractive data measurement and calculation needs to be continuously improved. Therefore, highlighting the need for astigmatism correction, based on the compensation mechanism, is important in clinical work and research.

Our study found that the magnitude and prevalence of TA showed a U-shaped distribution with refractive status. A similar study showed that children with myopia and hyperopia tended to develop astigmatism (16). In other words, children with refractive errors are more likely to have astigmatism than those without refractive errors. This phenomenon may be related to many factors. When children are young, they have a higher hyperopia reserve and present higher astigmatism. When children grow up, myopia progresses. The increase in axial length (a combined parameter about the chamber depth, and lens thickness, with vitreous chamber depth) may lead to changes in ORA (e.g., lens tilt). This could disrupt the attenuation of TA and thus cause an increase in TA. Correcting astigmatism may be an effective way to prevent and control refractive errors in children.

Astigmatism is associated with a significant social and financial burden all over the world. Though the precise cost of astigmatism treatment was unavailable, it was reported that the direct cost of myopia for each subject was $221.68 for Singapore school children (17). To reduce the effect of astigmatism, the accuracy of refractive data correction needs to be continuously improved in clinical work. Therefore, optometrists or ophthalmologists pay attention to the balance between the eye's optics and cornea to minimize TA.

The strengths of this study were that we use Fourier analysis to transform refractive clinical data into vector notation, which considered both the magnitude and axis of astigmatism. Then, we identified the risk factors for children with full compensation, and identified the relationship between TA and UDVA. Unfortunately, we did not measure the contribution of the internal structure of the ORA (such as the anterior chamber depth, and thickness of the crystal, or lens tilt) to the TA. We were also unable to assess the contribution of PCA on TA due to the difficulty of measuring PCA. At last, the compensatory effect of ORA and ACA on visual acuity was also significantly correlated with other factors (such as higher-order aberrations, pupil size, accommodation, and cortical modulation of astigmatism). These factors could not be further investigated due to the limitations of epidemiological investigations. Long-term longitudinal data are needed to provide more convincing evidence due to the limitations of cross-sectional studies.

In conclusion, we found the related risk factors of full compensation. Children with full compensation had better UDVA and smaller TA. In order to reduce the impact of TA, an emphasis on astigmatism vector analysis or compensatory efficiency is required, especially in corneal altering procedures (such as refractive surgeries and orthokeratology lens fitting) or IOL lens implantation.

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 the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine (HEC-KS-2020016KY). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

HB and XW had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis and conceptualized this study. HB supervised the study. ZW, YH, ZX, WS, YW, ZS, YL, MY, PS, and HH collected data for this study. ZW performed the statistical analyses. ZW, YH, and ZX drafted the manuscript. All authors contributed to the critical revision of the manuscript and approved the final manuscript.

Funding

This research was supported by the National Key Research and Development Program (2019YFC1710202 and 2019YFC1710203), and the Key Research and Development Program of Shandong Province (2019GSF108252).

Acknowledgments

We wish to thank the participants of this study, as well as the staff of the Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine who made the survey possible. A special acknowledgment to the schools and teachers for their support and cooperation.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1119654/full#supplementary-material

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TYPE Original Research
PUBLISHED 06 February 2023
DOI 10.3389/fped.2023.1092153

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 07 November 2022
ACCEPTED 13 January 2023
PUBLISHED 06 February 2023

CITATION
Zhu D, Wang H, Li R, Wen J, Li R and Zhao J (2023) Choroidal thickness and vascular microstructure parameters in Chinese school-age children with high **hyperopia** using optical coherence tomography.
Front. Pediatr. 11:1092153.
doi: 10.3389/fped.2023.1092153

Choroidal thickness and vascular microstructure parameters in Chinese school-age children with high hyperopia using optical coherence tomography

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Background: The current study was to evaluate the choroidal thickness (CT) and vascular microstructure parameters in Chinese children with high hyperopia through enhanced depth imaging optical coherence tomography (EDI-OCT).
Methods: Cross-sectional study. A total of 23 children with high hyperopia and 29 children with normal refractive status were retrospectively enrolled in the study. The measurement of the macular CT, 7 points: the sub-foveal area point, the temporal and nasal points at a radius of 0.5-mm, 1.5-mm, and 3-mm were measured. After binarization of the OCT images, the total choroidal area (TCA), stromal area (SA) as well as the luminal area (LA) were identified and measured. The choroidal vascularity index (CVI) was defined as the ratio of LA to TCA. The independent *t*-test for normal distributions and Kruskal-Wallis tests for non-normal distributions were used to compare other parameters between groups. The Tamhane's T2 test was performed to adjust for multiple comparisons between groups within each analysis.
Results: The subfoveal CT (SFCT) in the high hypermetropic group was significantly thicker than that in normal controls (309.22 ± 53.14 µm vs. 291.27 ± 38.27 µm; P = 0.019). At 0.5 mm, 1.5 mm, and 3.0 mm in diameter, the nasal choroidal sectors of the high hyperopia eyes were significantly thicker than that of the control ($P < 0.05$). There was significant difference in the choroidal vascular parameters. TCA and LA in the high hyperopia eyes was significantly larger than that of the normal control eyes (3078129.54 ± 448271.18 µm^2 vs. 2765218.17 ± 317827.19 µm^2, 1926819.54 ± 229817.56 µm^2 vs. 1748817.18 ± 191827.98 µm^2; P = 0.009, P = 0.011; Table 2). SA values were 1086287.55 ± 212712.11 um^2 in the high hyperopia eyes and 999712.71 ± 209838.12 µm^2 in the control eyes. The CVI and LA/SA ratio values were differed significantly in the two groups (P = 0.019, P = 0.030, respectively). AL was significantly correlated with SFCT (r = −0.325, P = 0.047), but not significantly correlated with other parameters. Spherical equivalent (SE) was significantly correlated with AL and SFCT (r = −0.711, r = 0.311; P = 0.001, P = 0.016), whereas no significant association between sphere and other parameters.

Abbreviations
AL, axial length; BCVA, best-corrected visual acuity; IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; CT, choroidal thickness; TCA, total choroidal area; S.A., stromal area; L.A., the luminal area; CVI, the choroidal vascularity index; EDI-OCT, enhance depth imaging-optical coherence tomography.

Conclusion: The choroidal structure of the high hyperopia eyes was different from the normal control eyes. The thicker SFCT, higher LA, and TCA were characteristic of high hyperopia eyes. Choroidal blood flow may be decreased in amblyopic eyes. SFCT of high hyperopia children abnormally increased and correlated with shorter AL and higher SE. AL and SE affect choroidal structure and vascular density.

KEYWORDS

choroidal thickness, choroidal vascularity index, EDI-OCT choroidal thickness, EDI-OCT, high hyperopia

1. Background

1.1. Clinical significance: we need an accurate method to evaluate the severity of hyperopia

By birth, human beings are predominantly hyperopic, and as the age progresses, hyperopic eyeballs grow to become emmetropic or even myopic (1–4). For children with refractive errors, the most common type is hyperopia worldly. If left untreated, the hyperopia, especially moderate-to-high hyperopia, may develop a series of sequelae, such as amblyopia and strabismus (5–8). Therefore, early diagnosis and severity stratification of hyperopia is vital for physicians to select appropriate management strategies, thus minimizing relevant sequelae.

1.2. Current status: current parameters and limitations

The choroid comprises blood vessels, melanocytes, fibroblasts, resident immunocompetent cells, and supporting collagenous and elastic connective tissue. It plays a vital role in ocular physiology by oxygenating and nourishing avascular outer retinal layers, particularly photoreceptors and the optic nerve pre-laminar section of the optic nerve (9). It is reported that the choroid may play an essential role in the visually guided regulation of eye growth and the development of myopia and hyperopia (1–4), so several choroid-related parameters have been investigated to evaluate the severity degree of hyperopia. Choroidal thickness (CT) is widely used in the evaluation of choroid status, and its value is associated with a range of factors, including age, gender, and refractive errors (10–15). However, CT provides limited information related to the choroid's subtle structural changes.

1.3. Problems: C.T. could not measure the subtle changes of hyperopia, but choroidal vascularity index might be

As we know, in the pathological changes of myopia, the choroidal thinning associated with myopic axial elongation is primarily the result of reduced thickness of the stromal rather than the vascular component of the choroid (16). In contrast, hyperopia eyes have shorter axis and a thicker choroid, but it is still not clear whether the choroid thickens due to stromal or vascular component. So, we need the parameters to provide more subtle structural changes, which are not available in CT.

1.4. The rationale of CVI: OCT presents the subtle vascular structures which are related to hyperopia

With the development of optical coherence tomography (OCT), the measurement of subtle choroid structures becomes possible. Recently, a new quantitative index, choroidal vascularity index (CVI), defined as the ratio of blood vessels' luminal area (LA) to the total choroidal area (TCA), has been developed to evaluate the vascular structure of the choroid (17). As CVI, which mainly measures choroidal vascularity, may play a more important role in evaluating hyperopia severity. Most of the previous studies focused on using the CVI to assess the subtle choroid structural changes related to myopia or high myopia. Still, its applications in children with high hyperopia have not been fully documented, especially in the Chinese pediatric population.

1.5. Aim of the study

In this study, we used the enhanced depth imaging OCT (EDI-OCT) to measure CT and CVI metrics in Chinese children with high hyperopia and normal controls. We aimed to determine the value of CVI as a characteristic parameter to evaluate the severity of hyperopia.

2. Methods

2.1. Study population

The Institutional Review Board of our hospital approved this observational cross-sectional study, and written informed consent were obtained from all participants.

The participants were consecutively recruited in the Department of Pediatric Ophthalmology of our hospital from June 2021 to September 2021. The inclusion criteria were (1) age between 4 and 14 years, (2) best-corrected visual acuity (BCVA) ≥ 0.8, (3) intraocular pressure (IOP) < 21 mmHg, (4) normal anterior chamber angles, (5) normal optic nerve head (ONH) without glaucomatous changes, such as the neuro-retinal rim narrowing, cup-disc ratio increasing, and no retinal nerve ber layer abnormalities. The participants with the following criteria were excluded, (1) history of ocular or systemic diseases, including congenital cataract and glaucoma, hypertension, and diabetes, (2) previous intraocular or refractive surgery, (3) neurologic disease, or (4) other evidence of retinal pathology. The demographic data of all enrolled patients were collected for analysis.

2.2. Ophthalmologic examinations

All participants underwent comprehensive ophthalmic examinations to collect the following data, which were BCVA, spherical equivalent (SE), slit-lamp biomicroscopy, axial length (IOL Master; Carl Zeiss Meditec, Dublin, CA), corneal curvature and IOP. Retinoscopy measurements were performed under the cycloplegia. The visual acuity was measured with a standard logarithmic visual acuity chart, and the decimal visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR) units.

2.3. EDI-OCT examinations of retinal and choroidal thickness

The choroidal area was obtained by the EDI-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) by one ophthalmologist with ten years of experience in OCT exam throughout the study to measure CT and choroid vascular parameters.

The macular CT was measured from the outer portion of the hyper-refractive line corresponding to the retinal pigment epithelium (RPE) to the inner surface of the sclera. The CT measurements were obtained at seven spots in a single horizontal scan centered on the fovea, including directly beneath the sub-foveal area CT (SFCT) point, the temporal and nasal points at a radius of 0.5- mm, 1.5-mm, and 3-mm (**Figure 1**). The elongation of AL may result in optical amplification effect. Littmann formula was used to calculate true image size to correct the optical amplification effect of OCT measurement.

2.4. Image binarization and choroidal vascularity index

Choroid vascular parameters were measured using the Niblack auto local threshold tool in the Image J platform (version 1.47, National Institutes of Health, Bethesda, MD, USA; http://imagej.nih.gov/ij/). Each segmented B-scan through the fovea on OCT was binarized with dark and light pixels to signify the L.A. and S.A. of the choroid, respectively (**Figure 2**). The TCA was calculated by multiplying the standard width of 3000 μm (1500 μm on the nasal and temporal side of the fovea) by the center choroidal thickness. Finally, TCA, LA, and SA were measured, followed by the CVI, defined as the ratio of LA to TCA.

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to analyze the normality of distribution. Descriptive statistics were calculated as the mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. The independent *t*-test for normal distributions and Kruskal-Wallis tests for non-normal distributions were used to compare other parameters between groups. The categorical data were described as frequencies and percentages and compared between groups using Fisher's exact test as appropriate. The Tamhane's T2 test was performed to adjust for multiple comparisons between groups within each analysis. A two-sided *P* value less than 0.05 was

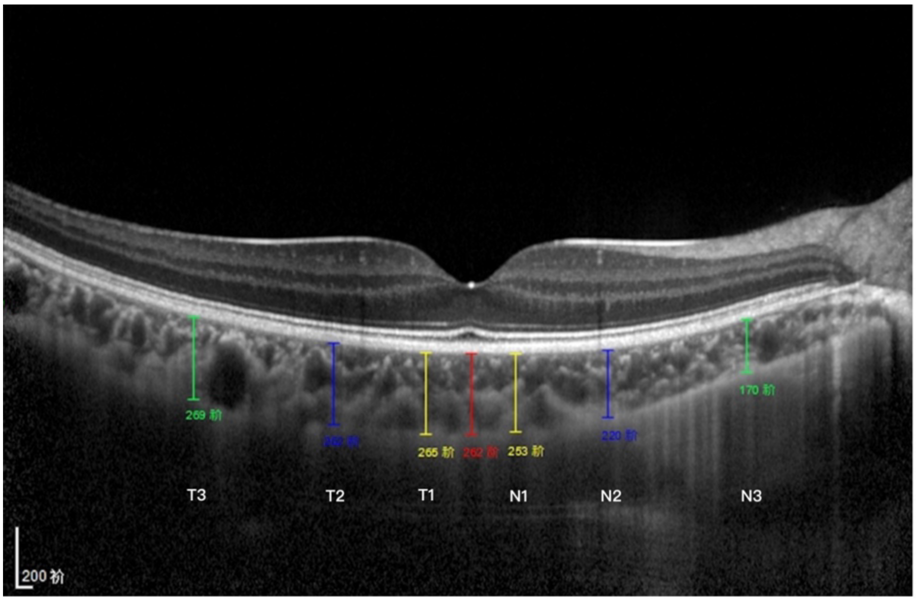

FIGURE 1
Subfoveal CT measurement. CT was measured at 7 points: directly beneath the fovea or the subfoveal area (SFCT) point, and 0.5/1.5/3 mm to the fovea nasally (N1/N2/N3), 0.5/1.5/3 mm to the fovea temporally (T1/T2/T3).

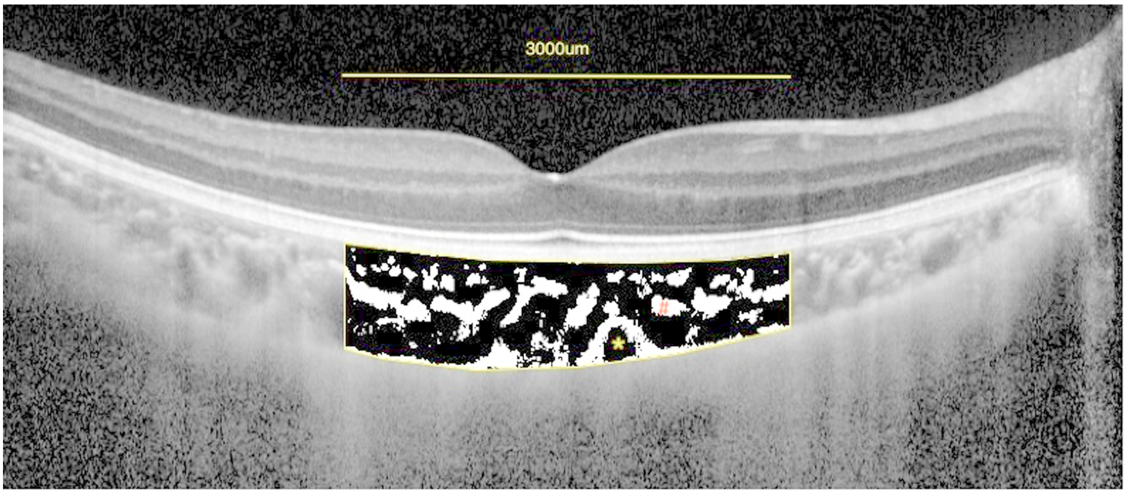

FIGURE 2
Enhanced depth imaging (EDI)-OCT image and converted binary image of a normal eye. An EDI-OCT image of a healthy eye (A) was converted to a binary image (B) using the ImageJ software. The luminal area (dark area, asterisk) and the interstitial area (cross) are seen. The rectangle surrounded by a red line was excised, and the dark areas were traced by the Niblack method.

considered statistically significant. Statistical analysis was performed using the SPSS software version 21 (SPSS, Inc., IL, USA).

Measures of central tendency in continuous data were described as median (or mean) and range, and categorical data were described as frequencies and percentages. The propensity score matching method was used to match the control cases with patients with complications. The continuous variables were compared using a *t*-test, and the ordinal variables were compared using conditional logistic regression. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Image binarization and choroidal vascularity index

3.1.1. Patients and baseline data

In the study interval, a total of **52** children were enrolled, including 23 with high hyperopia (female/male = 13/10, age 6.13 ± 2.24 years) and 29 normal controls (female/male = 15/14, age 7.00 ± 2.00 years) (**Table 1**). The patients were classified according to spherical equivalent (SE), which were high hyperopia with SE of + 5.00D or more, and normal controls with S.E. of −0.50D ∼ + 1.00D. The mean BCVA was 0.06 ± 0.11 logMAR units in the high hyperopia eyes and −0.01 ± 0.06 logMAR units in the control eyes.

The demographic and ocular characteristics were listed in the study (**Table 1**). Significant differences were observed on spherical equivalent (+5.84 ± 1.97D vs. 0.24 ± 0.07D, $P < 0.001$) and AL (20.55 ± 0.91 mm vs. 23.16 ± 0.45 mm, $P < 0.001$) between the two groups, while no differences were found on other parameters.

3.1.2. Choroidal parameters measured by OCT

The SFCT was significantly thicker in the high hyperopia eyes than that in normal controls (309.22 ± 53.14 µm vs. 291.27 ± 38.27 µm, $P = 0.017$) (**Table 2**). At 0.5 mm, 1.5 mm, and 3.0 mm in diameter, the nasal choroidal sectors of the high hyperopia eyes were significantly thicker than that of the normal control eyes ($P < 0.05$). The temporal CT at 0.5 mm, 1.5 mm, and 3.0 mm were not significant different in high hyperopia eyes than that in normal control eyes (all $P > 0.05$) (**Figure 3**).

There was significant difference in the choroidal vascular parameters. TCA and LA in the high hyperopia eyes was significantly larger than that of the normal control eyes (3078129.54 ± 448271.18 µm^2 vs. 2765218.17 ± 317827.19 µm^2, 1926819.54 ± 229817.56 µm^2 vs. 1748817.18 ± 191827.98 µm^2; $P = 0.009$, $P = 0.011$; **Table 2**). SA values were 1086287.55 ± 212712.11 µm^2 in the high hyperopia eyes and 999712.71 ± 209838.12 µm^2 in the control eyes. The CVI and LA/SA ratio values were differed significantly in the two groups ($P = 0.019$, $P = 0.030$, respectively).

3.1.3. Relationship between choroidal parameters and their potential impact factors

Correlation analyses were performed between the choroidal parameters and age, AL, and SE (**Table 3**). Our results showed that

TABLE 1 Demographic and clinical characteristics of enrolled participants ($n = 52$).

	High **hyperopia** group	Normal control group	*P* value
Number of eyes (*n*)	23	29	–
Age (year)	6.13 ± 2.24	7.00 ± 2.00	$P = 0.152$
Gender (male/female)	13/10	15/14	$P = 0.801$
SE (D)	+5.84 ± 1.97	0.24 ± 0.07	**$P < 0.001$**
BCVA	0.06 ± 0.11	−0.01 ± 0.06	$P = 0.504$
IOP (mmHg)	16.85 ± 0.34	15.19 ± 0.61	$P = 0.574$
Axial length (mm)	20.55 ± 0.91	23.16 ± 0.45	**$P < 0.001$**
Corneal curvature (mm)	8.02 ± 1.91	7.92 ± 1.69	$P = 0.174$

BCVA, best corrected visual acuity; D, diopter; SD, standard deviation; SE, spherical equivalent; logMAR, minimal angle of logarithm.
Factors with statistical significance are shown in bold.

TABLE 2 Comparison of CT and choroidal vascular characteristics (n = 52).

	High **hyperopia** group (n = 23)	Normal control group (n = 29)	P value
CT (um), mean ± SD			
Sub-foveal	309.22 ± 53.14	291.27 ± 38.27	**P = 0.017**
Nasal 0.5	303.21 ± 53.25	286.12 ± 41.81	**P = 0.044**
Nasal 1.5	282.97 ± 40.82	239.75 ± 50.47	**P < 0.001**
Nasal 3.0	204.98 ± 41.98	157.33 ± 35.40	**P < 0.001**
Temporal 0.5	305.21 ± 43.22	307.01 ± 48.02	P = 0.145
Temporal 1.5	287.20 ± 41.28	288.80 ± 36.31	P = 0.471
Temporal 3.0	270.94 ± 35.91	275.55 ± 39.17	P = 0.386
Choroid vascular parameters			
TCA in mm^2, mean ± SD	3078129.54 ± 448271.18	2765218.17 ± 317827.19	**P = 0.009**
LA in mm^2, mean ± SD	1926819.54 ± 229817.56	1748817.18 ± 191827.98	**P = 0.011**
SA in mm^2, mean ± SD	1086287.55 ± 212712.11	999712.71 ± 209838.12	P = 0.311
CVI (LA/TCA)	0.63 ± 0.06	0.64 ± 0.03	**P = 0.019**
Luminal/stromal ratio	1.78 ± 0.26	1.74 ± 0.24	**P = 0.030**

CT, choroidal thickness; CVI, choroidal vascularity index; CT, choroidal thickness; SA, stromal area; LA, luminal area; TCA, total choroidal area.
Factors with statistical significance are shown in bold.

AL was significantly correlated with SFCT and LA (r = −0.325, r = −0.417, P = 0.007), but not significantly correlated with other parameters. SE was found to be significantly correlated with AL and SFCT (r = −0.711, r = 0.311; P = 0.001, P = 0.016), whereas no significant association between sphere and other parameters.

4. Discussion

This study has provided a comprehensive assessment of the topographical variations in choroidal microstructure parameters in Chinese children with high hyperopia. CT is different between the two groups and the significantly higher in the high hyperopia group. A significant difference was found in the following spots, including sub-foveal, Nasal 0.5, Nasal 1.5, and Nasal 3.0. Our analyses also showed that TCA, LA, and the LA/SA ratio of high hyperopia eyes were significantly larger, CVI was significantly smaller than that of the normal control eyes.

CT is the main parameter used to obtain information about the choroidal layer and has been examined in children and adolescents in many studies (18–21). In healthy pediatric populations, the mean sub-foveal from these studies ranged from 245 to 361 µm (18, 20, 21). Read et al. (22) reported that the mean of the sub-foveal CT was 330 ± 65 µm in Australian children (4–12 years) with spherical equivalent refractive errors (SER) (+1.25−−0.50 D). Takafumi Mori and Yukinori Sugano also found a similar result in preschool Japanese children (23). Additionally, Zha Yi et al. (24) reported that the SFCT was of 328.12 ± 65.93 µm in 4–12 years old Chinese children with SER was between −1.75D to +0.63D. Our study in normal children had very close values for age-matched normal children. The value of CT in evaluating the degree of refractive errors or amblyopia had also been depicted in some studies (19, 23–25). The results are roughly the same in different cohorts: the myopic eyes had thinner sub-foveal choroidal thickness, and the hyperopic eyes and hyperopic amblyopic eyes had thicker CT than emmetropic eyes and myopic eyes. However, few studies focused on the structural characteristic of the choroid in high hyperopia subjects. In the current study, both the subfoveal CT and topographical variation in high hyperopic children were described. Consistent with the existing conclusions, we found that the SFCT

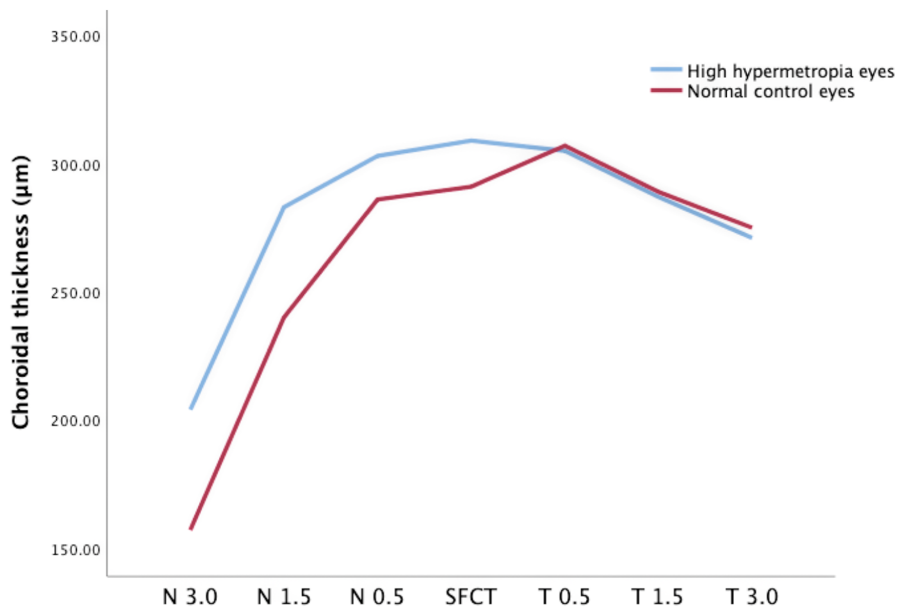

FIGURE 3
CT at different locations of high **hyperopia** and normal eyes.

TABLE 3 Correlation between choroid microstructure parameters and other baseline parameters in high hyperopia patients .

Parameters	AL		SFCT		LA		SA		TCA		CVI	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Age	0.128	0.465	−0.220	0.204	−0.159	0.363	−0.198	0.255	−0.163	0.349	0.005	0.975
AL	–	–	−0.325	**0.047**	−0.417	**0.007**	−0.218	0.208	−0.254	0.141	0.071	0.687
SE	−0.711	**0.001**	0.311	**0.016**	−0.079	0.651	−0.156	0.372	−0.098	0.576	0.076	0.666

AL, axial length; SFCT, sub-foveal choroidal thickness; S.A., stromal area; SE, spherical equivalent; L.A., luminal area; TCA, total choroidal area; CVI, choroidal vascularity index. Factors with statistical significance are shown in bold.

in high hyperopia children was significantly thicker than that in the normal control group. The average CT in the hyperopia group in our study was similar to the results of previous studies, but they seemed to be lower than those in the hyperopic amblyopia children with lower SER, which might verify the previous speculation that hyperopia was associated with subfoveal ChT, whereas amblyopia had no significant independent effect on subfoveal ChT in our study population (24). The pathophysiologic mechanisms involved need further verification. Additionally, the topographic features of the choroid in the hyperopia group in this study were almost the same as those in controls: the choroid was the thickest in the sub-foveal region and the thinnest in nasal regions which approach the optic nerve. These findings were also consistent with previous results of children either with different refractive status or with amblyopia, indicating the relatively stable choroid contour in pediatric populations (19, 24).

In normal eyes, CT in children can be affected by various factors, such as age, gender, diopter, and axial length. Previous studies reported a significant association between the AL and CT (26–28). Nagasawa et al. and Bidaut-Garnier reported that CT was negatively correlated with AL (29, 30). Li et al. reported that a thinner subfoveal CT correlated with a longer AL but no other factors, such as age, sex, and SER in myopic children (31). Read et al. found that CT increased in children with normal axial elongation, whereas children undergoing faster AL elongation tended to exhibit less thickening and a thinning of the choroid in some cases (32). In the current study, a thinner SFCT was also found to be negatively correlated with longer A.L. However, the causal relationship between choroidal thickening and hyperopia remains controversial.

OCT system uses fixed eye AL to scan. With the elongation of AL, the scanning area increases, resulting in optical amplification effect. Even if the Littmann formula is used to correct the optical amplification effect, there will be some errors in the results. CT could be also affected by sorts of variables and could not represent the choroid's subtle structural changes; we cannot assess the choroid structural changes and blood supply only by CT. measurement. Recently, Agrawal et al. (17) assessed the LA, SA, and TCA through EDI-OCT images and proposed a new parameter-CVI to assess the choroidal vascular structure. In their study, they found that CVI was less affected than the sub-foveal CT and suggested CVI be a more robust marker of choroidal diseases. Subsequently, other studies have also demonstrated less variability of CVI.

However, there are conflicting views on choroidal blood flow in the study of choroidal hyperopic patients. Baek et al. (33) claimed that hyperopia eyes were found to have increased choroidal CV compared to normal eyes. But most studies concluded that the choroidal blood flow in patients with high hyperopia eyes is lower than that in normal children (34–36). The results in this study are consistent with most of the previous studies, the average CVI in the hyperopic amblyopic eyes was lower than the normal control eyes. In our study, we found that the AL was significantly correlated with SFCT but not the CVI, which was consistent with the previous results, further indicating that CVI might be an alternative metric for the evaluation of choroidal disorders.

On the other hand, a shorter AL tended to be associated with bigger LA, SA, and TCA. Li et al. reported that changes in luminal areas might directly influence choroidal thickness, as blood vessels represent the main component of the choroid (31). Alis et al. (37) found that TCA and SA were higher in hyperopia than in both emmetropic and myopic eyes. Nishi et al. found that the LA was significantly larger, the SA was significantly smaller, and the luminal/stromal ratio was larger in amblyopic eyes than that of normal children (38). Meryem et al. (37) found that TCA and SA were higher in hyperopia than in both emmetropic and myopic eyes. In the present study, LA, and TCA values of the high hyperopia eyes were significantly larger than that of the normal control eyes suggesting an increase in blood flow and blood vessel area in eyes with shorter AL. It is still unknown whether the thickening of the choroid in hyperopia is caused by the increase of stromal area or the enlargement of the vascular luminal area. Multicenter studies with large sample sizes are needed for further validation.

Age is also an important factor affecting choroid structure. Previous studies found that the CT tended to decrease with increasing age in adults (27, 28), Fujiwara et al. found that choroidal vascular density had a negative association with age in healthy adults (39). In the present study, SFCT had a significant negative relationship with AL and positive relationship with SE. Ruiz-Medrano et al. (40) found that the choroidal stromal area was not affected by age in a healthy population that included normal children. In our study, there were no significant association among AL, SA, LA, and TCA.

Our study has several limitations. First, the sample size is relatively small, and the high hyperopes are all Chinese children. Second, the OCT measurement of each subject in our study was performed at a randomized time at their convenience, and the CT measurements only occurred in a single horizontal scan centered on the fovea. Further studies with a large population and unified examination time are needed for more positive and robust results.

5. Conclusions

In summary, to our knowledge, the current study provides the first description of the structural features of the choroid and the factors influencing them in Chinese children with high hyperopia.

The choroidal structure of the high hyperopia eyes was different from the normal control eyes. The thicker SFCT, higher LA, and TCA were characteristic of high hyperopia eyes. Choroidal blood flow may be decreased in amblyopic eyes. SFCT of high hyperopia children abnormally increased and correlated with shorter AL and higher SE. AL and SE affect choroidal structure and vascular density. We suggest that choroidal topographic features, are biomarker of high hyperopia, but CVI is another more robust indicator.

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 Institutional Review Board of Peking University First Hospital. 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 individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

DHZ and HW: were responsible for the study design. RSL, JW, RYL and JJZ: examined all subjects. HW: collected the data. HW and RSL: contributed to the data analysis. DHZ: made major contributions to writing the manuscript. DHZ: revised and edited the manuscript. 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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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 09 February 2023
DOI 10.3389/fmed.2023.1094937

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

RECEIVED 10 November 2022
ACCEPTED 23 January 2023
PUBLISHED 09 February 2023

CITATION
Chan PP, Zhang Y and Pang CP (2023) Myopic tilted disc: Mechanism, clinical significance, and public health implication. *Front. Med.* 10:1094937. doi: 10.3389/fmed.2023.1094937

Myopic tilted disc: Mechanism, clinical significance, and public health implication

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Myopic tilted disc is a common structural change of myopic eyes. With advancing ocular imaging technology, the associated structural changes of the eye, particularly the optic nerve head, have been extensively studied. These structural changes may increase patients' susceptibility to axonal damage and the risk of developing serious optic neuropathies including glaucoma. They also lead to diagnostic difficulties of disease suspects and treatment dilemmas of patients, which implicate clinical practice and subsequently the health care system. In the context of the mounting prevalence of myopia worldwide and its implications to irreversible visual impairment and blindness, it is essential to gain a thorough understanding of the structural changes of myopia. Myopic tilted disc has been extensively investigated by different study groups. However, generalizing the knowledge could be difficult because of the variable definitions of myopic tilted disc utilized in these studies and the complexities of the changes. The current review aimed to clarify the concepts and discuss various aspects of myopic tilted disc, including the definitions, association with other myopia-related changes, mechanism of tilted disc development, structural and functional changes, and clinical implications.

KEYWORDS

myopia, myopic tilted disc, optic disc tilting, optic disc torsion, myopic glaucoma

1. Introduction

Myopia is thriving as an epidemic in many parts of the world especially in the developed countries of East and Southeast Asia, mounting a prevalence of 80–90%, with a 10–20% prevalence of high myopia among young adults (1, 2). By 2050, approximately 4,758 million, or almost half of the global population, could become myopic, with as much as 10% highly myopic (3). High myopia–usually defined as refractive error of < -6.00 diopters (D) and axial length of $\geq$26.5 mm–is associated with various structural changes, including optic nerve head (ONH) deformity, retinal stretching, and posterior scleral expansion. The ONH is where retinal ganglion cell axons exit, accompanied by retinal blood vessels. It is one of the most affected structures by myopia progression (or myopization).

Myopic tilted disc is one of the most common morphological changes found in myopic eyes. It appears as oval-shaped and obliquely rotated ONH, often separately described as optic disc tilt and optic disc torsion, respectively, according to different definitions (4). Myopic tilted disc could lead to alteration of the retinal nerve fiber layer (RNFL) peak locations, changes of the macular ganglion cell inner-plexiform layer (GCIPL) distribution (5–9). It can also cause structural changes of the sclera (10), choroid thickness (11–13), and microvasculature (14–16). It is also a mediator between the presence of peripapillary hyperreflective ovoid mass-like structure (PHOMS) and myopic shifting in children (17, 18). Furthermore, myopic tilted disc is associated with an increased risk of developing RNFL defect (19–24). These structural changes could render myopic eyes more susceptible to axonal loss. They may ultimately lead to the development of glaucomatous damage and subsequently irreversible visual impairment and even blindness (25, 26). Furthermore, the changes of RNFL, GCIPL, and optic disc morphology also cause difficulties in diagnosing glaucoma and disease monitoring (27, 28). This is one of the most encountered diagnostic dilemmas in ophthalmology practice.

The prevalence of myopic tilted disc has been reported in different populations. Generally, the prevalence ranged from 0.4 to 57.4% for tilted disc and 39.2 to 64.7% for disc torsion (29–33). The variable figures reported by different studies could be related to their diverse definition of the terms (Tables 1–3). The Blue Mountains Eye Study reported the presence of tilted disc in 0.4% of eyes with <1.0 D of astigmatism and 17.9% with ≥5.0 D of astigmatism (29). The Tanjong Pagar study showed that 3.5% of healthy young individuals had tilted optic discs and 64.7% had torsional discs; myopia was present in 88.5% of eyes with tilted disc (30). They also revealed that decreased spherical refraction, decreased cylindrical refraction, and increased axial length were significant risk factors for the presence of tilted optic disc. For children, the rate of detecting tilted disc among a cohort of Chinese children with a mean age of 6.3 ± 0.5 years was 6.6% (32). For adolescents, Samarawickrama et al. (33) found that 37% of adolescents aged 12–16 years had tilted discs in a Singapore cohort. For adult, Chang et al. (31) showed that tilted disc was present in 57.4% of high myopic eyes aged 40–80 years. Marsh-Tootle et al. (34) found that the level of disc tilt varied between different ethnicities; Asian had the highest unadjusted mean value of disc tilt (10.47°), followed by White (5.64°), Hispanic (5.25°), and African American (5.13°).

Myopic tilted disc is the second most common ONH structural change after peripapillary atrophy (PPA); the latter has already been extensively reviewed (35–37). Myopic tilted disc is commonly considered as a single entity with different definitions. However, titled disc and disc torsion might impact structural and functional changes differently (Figure 1). There is a need to clarify the concept as myopic tilted disc is becoming a public health concern worldwide. The present review of myopic tilted disc aimed to comprehensively summarize the definitions, association with myopia, developmental mechanisms, structural and functional changes, and clinical implications. Table 4 summarizes the outline of this review.

2. Definitions and measurements of myopic tilted disc

Myopic tilted disc can be observed on fundi examination. It appears as an oval-shaped optic disc with an elevated disc rim on one side which is associated with a white half-moon or C-shaped halo around the disc (Figure 2A). Optical coherence tomography (OCT) has revealed a sloping of the lamina cribrosa (LC) of the ONH, with a protruding nasal edge of the Bruch's membrane (BM) and choroid (38) (Figure 2B). Myopic tilted disc may be described as two different but mutually inclusive ONH structural changes–optic disc tilt and optic disc torsion (Figure 1)–depending on the definitions and measurement methods that quantify the level of deformity in different studies. They may have different clinical implications.

The optic disc usually tilts toward the temporal direction, followed by superotemporal tilting (33). The ovality index is commonly used to quantify optic disc tilt in fundus photography. It estimates the amount of optic disc ovality by the ratio between the longest and shortest diameter of the optic disc in a 2-dimensional manner (i.e., the x- and y-axis) (Figure 3A) (25). OCT provides cross-sectional imaging of the ONH, allowing quantitative measurement of disc tilt along the z-axis (5, 14, 17, 20, 24, 39–41). It was found that horizontal disc tilting measured by OCT correlated better with spherical equivalent and axial length than the ovality index (42), showing the usefulness of OCT in assessing the deformity of the globe.

TABLE 1 A list of the associations between myopic tilted disc (disc tilt and disc torsion) and myopic-related structural changes.

RNFL
• Defect within papillomacular bundle (19) • Location of RNFL defect in myopic NTG and POAG eyes (20) (23). • Risk of developing RNFL defect (21)
RNFL and GCIPL distribution
• Location of the superior and inferior RNFL peaks. (5) • Thickness of different regions of the peripapillary RNFL • Thickness of different regions of macular GCIPL (associated with disc torsion only and more likely to occur in high myopic eyes) (6, 7, 9, 68)
Disc rim and peripapillary area
• The size of disc, rim area, cup area, cup-to-disc area ratio, cup volumes or cup depth, and measurement of rim volume (33, 68, 70) • Presence of PPA, width of parapapillary gamma-zone, and location of beta-zone PPA (73) • Presence of peripapillary hyperreflective ovoid mass-like structure (PHOMS)
Lamina cribrosa (LC)
• Lamina cribrosa defect in POAG eyes (smaller ovality index and larger vertical and horizontal tilt angle) (75) • Different regions of lamina cribrosa surface depth of optic disc (40) • Direction of lamina cribrosa tilt (76)
Sclera
• Difference in thickness between superior and inferior sclera in (in myopic glaucoma eyes) (41)
Choroid
• Average and peripapillary choroidal thickness (11–13)
Microvasculature
• Peripapillary vessel density (14) • Area of superficial Foveal avascular zone (14) • Vessel density in the deeper retinal plexus of the macula (nasal and temporal sectors) (15) • Vessel density of the peripapillary area
Macular
• Intrapapillary hemorrhage (77, 78) • Retinal pigment epithelial change • Choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV) (80–82) • Lamellar macular hole, foveoschisis, and retinoschisis. (21, 82, 86)

NTG, normal tension glaucoma; POAG, primary open angle glaucoma; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell inner-plexiform layer; PPA, peripapillary atrophy.

Optic disc torsion usually refers to the rotation of the optic disc along the sagittal axis. It was commonly measured with the deviation angle between the longest axis of the optic disc and a vertical line perpendicular to the line connecting the center of the optic disc and the fovea (**Figure 3A**). The optic disc is regarded as torted disc when the deviation angle is larger than 15 degrees. Our review adapted this definition of optic disc torsion for easy illustration, although different definitions have been described by other studies (4). The detailed definitions for each study are summarized in **Tables 2**, **3**.

3. Relationship between myopic tilted disc and myopic parameters

Studies have identified the relationship between myopic tilted disc and other myopic changes, including refractive error, axial length, and peripapillary structures. For refractive error, eyes with myopic tilted disc had a larger magnitude of refractive error (43). Hyung et al. (44) found a correlation between a larger vertical/horizontal disc diameter ratio and higher refractive error ($r = -0.298$, $P < 0.01$). In another study more negative spherical equivalent was associated with a smaller disc tilt ratio (calculated by the minimum disc diameter divided by the maximum disc diameter) (25). In addition to a cross-sectional relationship between disc tilt and the magnitude of refractive error, disc tilt was associated with a greater magnitude of myopia progression (45). Similar results had been reported in other studies (33, 46, 47).

Several studies investigated the relationship between axial length and myopic disc tilt with controversial results. Eyes with myopic tilted disc had longer axial lengths (43). Using Pearson's correlation analysis, Han et al. (20) demonstrated a positive correlation between longer axial length and larger optic nerve head tilt angle. Using multivariate linear regression analysis, Sung et al. (9) also demonstrated an association between axial length and optic disc rotation. However, other studies did not find an association between myopic tilted disc and axial length (48, 49) and the result was supported by a longitudinal study (50). During a follow-up period of 1 year, the progression of diopter, rather than the progression of axial length, was correlated with the progression of disc ovality index in 1,008 eyes from children aged 10.20 ± 0.48 years old (50).

4. Development of myopic tilted disc

The formation of disc tilt and torsion probably begins in childhood. Maximal progression of myopia occurs between the age of 6–10 years (51), while changes in the ONH and PPA predominantly occurs between 7–9 years old (52). Several mechanisms of myopic tilted disc development have been proposed. One proposal suggested that with axial elongation during myopization, the BM in the posterior pole grows and pushes the papillary BMO backward, leaving the optic nerve head of the scleral opening relatively behind and presenting with overhanging of BM on the nasal side of the optic disc (53). Based on their observation of myopic children, Kim et al. (54) proposed that during myopization, the ONH and the peripapillary region change more dramatically while the BMO distance remains relatively stable (**Figure 4**). The distance between the fovea and the BMO margin did not change with axial elongation, while the straight-line distance between BMO and the scleral end (known as the border length, BL) and the angle between the BM reference line and the border tissue (known as the border tissue angle, BTA) were associated with increased axial length. They hypothesized that the temporal border tissue was initially converted from an internal oblique to an external oblique configuration. During axial elongation, the BL increased, and the BTA decreased significantly, accompanied by optic disc tilt and flattening of temporal border tissue (**Figure 4**).

Jonas et al. (55) supported this observation; they reported no correlation between the axial length and the fovea-to-BMO margin distance. They also noted that the BM thickness and the choriocapillaris did not differ between the staphyloma region and other regions of the eyes (56), unless the staphyloma causes a BM defect. The theory of a more dramatic shifting of ONH tissue with relatively unchanged BMO during myopization was also supported by a 2-year longitudinal study involving children with an average age of 9.6 years (57). The angle between the two temporal retinal arteries (superior and inferior) measured from the vascular trunk decreased during axial elongation, reflecting a dragging predominantly toward the nasal side of the optic disc. Hence, the LC was also shifted nasally (57). Since the LC is connected to the sclera, the LC shifting can be due to disproportional growth between the inner structures and expansion of the outer supporting structures during axial elongation. The deformation of the supporting structures (including LC and peripapillary sclera) leads to the rotation of border tissue through the BMO window (58). With a buffering effect of the redundant inner retinal structures, the optic disc appears as an elevated disc margin at the shifting direction of LC, while the opposite side experiences the greatest stretch followed by the deformation of LC defect, rendering the site more susceptible to axonal damage in myopic tilted eyes. Results of other studies also support this hypothesis (39, 40).

Apart from the LC shifting, the position of the deepest point of eyeball (DPE, the most protruded point in a posterior staphyloma) was also associated with the formation of myopic titled disc. Eyes with DPE located in the inferior hemisphere had the largest disc torsion and vertical tilt angles (58). Primate studies suggested that the development of myopia is associated with scleral deformation. An animal experiment on tree shrews showed that the eyes had scleral tissue loss and scleral thinning after a short-term (12 days) treatment with monocular deprivation. The collagen fibril diameter was also reduced after long-term monocular deprivation (3–20 months) (59). Other studies showed alteration in scleral thickness in myopic animal models, especially the posterior pole (60–63). Such scleral thickness alteration was associated with a rapid reduction in scleral glycosaminoglycan synthesis and cell proliferation (64, 65), rendering the weakened area more susceptible to progressive ocular enlargement and leading to posterior staphyloma formation. In human eyes, increased temporal torsion of the optic disc was also associated with a more inferiorly positioned DPE and an increase in fovea-disc depth, which is the depth between the interface of the fovea and the interface of the temporal border of the optic disc on the OCT horizontal scan (66). Moreover, a longer disc-DPE distance was significantly associated with longer axial length (58).

Interestingly, adduction of the globe may also influence the optic disc tilt development. During extreme adduction, the increased axial length could strengthen the pulling force of the optic nerve dura mater on the sclera because the optic nerve was too short to perform full adduction in an elongated globe. Given that the optic nerve

TABLE 2A Change of retinal nerve fiber layer and ganglion cell inner-plexiform layer in related to myopic tilted disc in myopic eyes.

References	Study subjects	Mean age (mean ± SD) (years)	Images	Definitions of disc tilt, tilt angle, and disc torsion	Main outcomes
RNFL defect					
Kimura et al. (19)	61 Highly myopic and 55 non-highly myopic eyes with early VF defect.	High myopia: 44.7 ± 11.3, Non-high myopia: 55.5 ± 12.8	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest.	Tilted disc was significantly associated with the nearest RNFL defect within papillomacular bundle. (OR: 2.73, 95% CI: 1.13–6.61).
RNFL and GCIPL distribution					
Hwang et al. (5)	93 Myopic eyes	21.04 ± 1.40	Fundus photograph, OCT	Tilt angle: The degree of optic disc tile was defined as the angle between the lines connecting the BMO and the imaginary horizontal line. Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with tilted disc had thicker temporal RNFL and more temporally positioned superior/inferior peak locations than eyes without tilted disc. Eyes with disc rotation (torsion) had thicker temporal RNFL and a more temporally positioned superior peak location than eyes without disc rotation (torsion).
Ilhan et al. (6)	185 Myopic eyes and 122 healthy controls	48.8 ± 16.3	OCT	Disc tilt: The OCT images were evaluated to determine the presence of a tilted optic disc according to the presence of oblique orientation of the vertical axis, the elevation of the superotemporal neuroretinal rim, and inferonasal crescent.	For eyes with high myopia, the superior quadrant of the peripapillary RNFL was significantly thinner in eyes with disc tilt than eyes without disc tilt.
Fan et al. (7)	3,037 Eyes from healthy individuals	64.6 ± 9.8	OCT	Disc torsion: Vertical optic disc rotation: angle between BM line and the OCT image line on OCT scans running horizontally through the optic disc. Horizontal optic disc rotation: angle between BM line and the OCT image line on OCT scans running vertically through the optic disc.	Larger horizontal optic disc rotation was associated with thinner superior nasal RNFL thickness and thicker inferior nasal RNFL thickness.
Lee et al. (8)	94 Eyes with optic disc torsion and 114 eyes without optic disc torsion	Optic disc torsion: 48.29 ± 13.64, Without optic disc torsion: 50.59 ± 13.02	Fundus photograph	Disc tilt: Ratio of disc diameter = shortest/longest. Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with inferotemporal optic disc torsion have significantly thicker temporal RNFL and had more temporally positioned superior peak of RNFL than eyes with superonasal optic disc torsion or eyes without disc torsion. The GCIPL thickness at all segments was unaffected by disc torsion direction.
Sung et al. (9)	220 Myopic eyes	27.94 ± 6.67	Fundus photograph	Disc tilt: Ratio of disc diameter = longest/shortest Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with inferior rotation (torsion) of optic disc showed thinner pRNFL and mGCIPL thickness in general compared with eyes with superior rotation (torsion).

VF, visual field; RNLF, retinal nerve fiber layer; NTG, normal tension glaucoma; OCT, optical coherence tomography; BMO, Bruch's membrane opening; ONH, optic nerve head; IOP, intraocular pressure; CDR, cup disc ratio; OR, odd ratio; OAG, open angle glaucoma; POAG, primary open angle glaucoma; BM, Bruch's membrane; GCIPL, ganglion cell inner-plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; mGCIPL, macular ganglion cell inner-plexiform layer.

originates from the nasal aspect of the eyeball, the backward puling will be more prominent on the temporal border of the optic disc. Repeated pulling may lead to optic disc rotation along the vertical axis and the temporal border may be drawn downward (35, 56, 67).

5. Structural changes related to myopic tilted disc

Various studies have investigated the impact of myopic tilted disc on structural change of RNFL defect, RNFL and GCIPL distribution, ONH, LC, sclera, choroid, and microvasculature of the globe. Although disc tilt and torsion are often described as myopic tilted disc, some studies had stratified the impact of the two changes. The association between myopic tilted disc and myopic-related structural changes are listed in Table 1. The studies are summarized in Tables 2A, B.

5.1. Retinal nerve fiber layer defect

The development of RNFL defect is possibly related to myopic tilted disc. Optic disc tilt was associated with the nearest RNFL defect within the papillomacular bundle (19). The ONH tilt angle was also

TABLE 2B Change of optic nerve head, lamina cribrosa, sclera, choroid, and microvasculature in related to myopic tilted disc in myopic eyes.

References	Study subjects	Mean age (mean ± SD) (years)	Image	Definitions of disc tilt and disc torsion	Main outcomes
Disc rim and peripapillary area					
Tong et al. (70)	316 Eyes from children	11.97 ± 0.60	Stereo fundus photograph	Disc tilt: the presence of tilt or otherwise in the optic discs was assessed from stereo retinal photographs independently by two ophthalmologists.	The eyes with optic disc tilt had smaller disc, rim and cup area, smaller cup-to-disc area ratios, smaller cup volumes and cup depths, larger measured rim volume, larger rim-to-disc area ratios, larger height variation of the contour, and thicker mean RNFL.
Samarawickrama et al. (33)	1,227 Eyes from adolescents	Tilted disc: 13.8 ± 1.2, Non-tilted disc: 13.6 ± 1.2	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The main directions of disc tilt were temporal tilt, followed by superotemporal tilt. After adjustment of age, gender ethnicity and axial length, tilted optic discs have smaller vertical cup diameter, vertical CDR, horizontal disc diameter, horizontal cup diameter, horizontal CDR.
Jonas et al. (71)	2,068 Eyes from healthy individuals	63.0 ± 9.0	OCT	Disc torsion: rotation around vertical axis: angle between the line connecting the ends of BM and the horizontal line; rotation around the horizontal axis: angle between the line connecting the ends of BM and the vertical line.	Larger width of parapapillary gamma zone was associated with larger vertical (β, 0.16, $P < 0.001$) optic disc rotation.
Sung et al. (9)	220 Myopic eyes	27.94 ± 6.67	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The area of β-zone PPA was significant related to the degree of optic disc rotation (torsion) ($R^2 = 0.07$, $P < 0.001$).
Chiang et al. (72)	215 Eyes from adult individuals	55.7 ± 15.1	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The RNFL herniation appeared as a dome-shaped hyperreflective RNFL bulge protruding into the neurosensory retina at the optic disc margins. The RNFL herniation was correlated with congenital disc tilt (disc torsion >45° and the tilt occurred inferonasally).
Lyu et al. (17)	132 Eyes with PHOMS and 92 eyes without PHOMS	PHOMS: 11.7 ± 2.6, Control: 11.4 ± 3.1	OCT	Tilt angle: the angle between the two lines drawn between the BM termination point and disc border.	Increased ONH tilt angle (OR = 1.29; $P = 0.001$) was associated with presence of PHOMS.
Behrens et al. (18)	1,407 Eyes from children	PHOMS: 11.64 ± 0.38, Non-PHOMS: 11.67 ± 0.40	Fundus photograph, OCT	Disc tilt: the presence of ONH tilt was identified by a white half-moon or C-shaped halo on the color fundus photograph being present together with a corresponding cross-sectional EDI-OCT revealing a corresponding extension of the border tissue of Elschnig.	The presence of ONH tilt (OR = 5.96, $p < 0.001$) and increased angle of ONH tilt (OR = 1.38, $p = 0.002$) were associated with increased risk of having PHOMS.
Asai et al. (48)	114 Myopic eyes	54.7 ± 16.7	Fundus photograph, OCT	Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	The peripapillary tilting showed correlation with disc torsion, especially in the superotemporal-inferonasal sectors and superior-interior sectors.
Choroid					
Yamashita et al. (11)	119 Healthy eyes	25.8 ± 3.9	OCT	Tilt angle: the "x" and "y" coordinates of each marked RPE were determined automatically. The "x" and "y" coordinates of each pixel were converted to a new set of "x" and "y" coordinates with zero at the center of the wave. Finally, the converted data were fit to a sine wave equation [y = a × sin (b × x-c)] with the curve fitting program of ImageJ. The amplitude of the sine wave, "a," was considered to represent the degree of the optic disc tilt relative to the optical axis.	The temporal and inferotemporal peripapillary choroidal thickness were negatively associated with the optic disc tilt (R = −0.31, −0.20, $P < 0.05$).

(Continued)

TABLE 2B (Continued)

References	Study subjects	Mean age (mean ± SD) (years)	Image	Definitions of disc tilt and disc torsion	Main outcomes
Chen et al. (12)	821 Eyes from healthy individuals	19.83 ± 2.61	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest.	Increased peripapillary choroid thickness (OR = 1.11; $P < 0.01$), and a decreased macular choroid thickness (OR = 0.93; $P < 0.01$) were associated with the presence of tilted optic disc. Every 0.1 increase in tilt ratio correlated with a 5.38 μm increase in average macular choroid thickness and a 6.21 decrease in average peripapillary choroid thickness.
Brito et al. (13)	27 Eyes with tilted optic discs and 20 eyes of age-matched control	47.1 ± 16.2	Slit-lamp examination	Disc tilt: elevation of a disc rim sector was present and observed at slit-lamp examination with a 90 D lens.	On the tilted group, peripapillary choroidal thickness was significantly thicker adjacent to the elevated rim.
Microvasculature					
Sung et al. (14)	71 Highly myopic and 26 emmetropic eyes	Control eyes: 23.11 ± 4.31, High myopic eyes: 23.63 ± 4.01	Fundus photograph, OCT-A	Disc tilt: ratio of disc diameter = shortest/longest. Tilt angle: the angle between the two lines drawn between the BM termination point and the disc border.	Large horizontal tilt angle was associated with a lower average peripapillary vessel density. Smaller ovality index ($r = -0.252$, $P = 0.036$) and horizontal tilt angle ($r = -0.330$, $P = 0.004$) was independently associated with a larger superficial FAZ area.
Sun et al. (15)	130 Eyes with non-pathological high myopia	35.24 ± 8.45	Fundus photograph, OCT-A	Parameters including optic disc tilt ratio were measured by ImageJ software without specifying the definitions.	The optic tilt ratio (R = -2.291; $P = 0.025$) was negatively correlated with the vessel density in the deep retinal plexus of the macular region at the nasal and temporal sectors.

RNFL, retinal nerve fiber layer; ONH, optic nerve head; CDR, cup disc ratio; OCT, optical coherence tomography; PPA, peripapillary atrophy; PHOMS, peripapillary hyperreflective ovoid mass-like structures; BM, Bruch's membrane; EDI-OCT, Enhanced depth imaging optical coherence tomography; OR, odd ratio; POAG, primary open angle glaucoma; LC, lamina cribrosa; OAG, open angle glaucoma; BMO, Bruch's membrane opening; OCT-A, optical coherence tomography angiography; FAZ, foveal avascular zone; NTG, normal tension glaucoma.

consistent with the location of RNFL defect in myopic eyes with normal tension glaucoma (NTG) (20). This indicates that the LC of a tilted disc may be shifted nasally, generating a tensile stretch on the temporal side of the LC and the axons in the papillomacular bundle. A longitudinal study that observed children with a mean age of 5.4 years for an average of 16.1 years of follow-up found that eyes with a greater change of spherical equivalent [odd ratio (OR) = 1.737, $P = 0.016$] and a greater increase in tilt ratio (OR = 2.364, $P = 0.002$) were associated with higher risk of developing RNFL defect (21). The higher OR of increase in tilt ratio than the OR of spherical equivalent change may indicate that the magnitude of optic disc deformation was more related to the RNFL defect development than the change of refractive error.

The direction of disc tilt was also correlated with the location of the RNFL defect. Lee et al. (22) demonstrated that temporally tilted optic disc were accompanied by superotemporal and inferotemporal RNFL loss, while inferiorly tilted disc showed more prominent RNFL thinning in the inferior sectors. Furthermore, for eyes with vertical disc tilt (disc torsion of less than 20°), the depth of LC at the superior location tends to be larger. They speculated that this causes an LC tilting. The LC depth leads to a larger tensile stress on the temporal aspect of the LC and the posterior sclera, causing damage to the axons that pass through the LC. Similarly, an inferiorly tilted disc may stretch on the RNFL inferior sector, which could be further strained by intraocular pressure (IOP) elevation. However, the direction of disc tilt and scleral expansion caused by axial elongation can differ when the disc tilts inferiorly. Hence, the deformation of LC could be less severe than temporal disc tilting (22).

The association between disc torsion and the location of RNFL defect has also been investigated. Lan et al. (23) demonstrated that the direction of disc torsion corresponded to the site of RNFL defect in eyes with primary open angle glaucoma (POAG); while disc tilt was associated with lower wedge-shaped RNFL defects in NTG. Interestingly, more disc tilt was found in myopic NTG than non-myopic NTG (but not in POAG eyes). This is consistent with the reported higher prevalence of superior disc tilt or torsion in NTG eyes than axial-length matched POAG eyes. (24). The observation could be related to the thinner and weaker posterior scleral structures (including posterior sclera and LC) in NTG eyes. It is possible that, in POAG eyes, RNFL defect can develop with less disc deformation because it is under the simultaneous stress of raised IOP and the mechanical stress of axial elongation and disc deformation. Whereas in NTG eyes with a relatively lower IOP, the direction of disc torsion and disc tilt need to be synchronized to achieve sufficient mechanical stress for RNFL defect to occur. Hence, more disc deformation could be observed in myopic NTG eyes than myopic POAG eyes. Nevertheless, further study is required to validate this hypothesis.

5.2. RNFL and GCIPL distribution

The distribution of RNFL in eyes with tilted disc differs from those without tilted disc. Eyes with tilted disc have more temporally located superior and inferior RNFL peaks (5). The superior quadrant of the peripapillary RNFL was significantly thinner than eyes with non-titled disc (6, 7); whereas GCIPL thickness was not affected

TABLE 2C Structural change associated with myopic tilted disc in myopic eyes with glaucoma.

References	Study subjects	Mean age (mean ± SD) (years)	Images	Definitions of disc tilt, tilt angle, and disc torsion	Main outcomes
RNFL defect					
Han et al. (20)	74 Myopic NTG eyes and 67 myopic control eyes	46.1 ± 13.5	OCT	Tilt angle: angle between BMO plane and optic canal plane.	ONH tilt angle was associated with the presence of myopic NTG (after adjustment of axial length and IOP).
Ha et al. (21)	65 Normotensive eyes from children with vertical CDR ≥0.5 but no other signs of glaucoma	5.4 ± 1.3	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. The direction of optic disc tilt: deviation of the long axis of the optic disc from the perpendicular meridian.	A greater increase in tilt ratio (OR = 2.364, *P* = 0.002) was associated with a higher risk of RNFL defect development.
Lee et al. (22)	66 Glaucomatous eyes and 48 healthy eyes	Healthy eyes with Vertical tilt: 47.6 ± 14.8, Horizontal tile: 48.8 ± 12.1 OAG eyes with Vertical tilt: 46.3 ± 15.3 Horizontal tile: 53.7 ± 11.8	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest. Tilt angle: the angular deviation of the long axis of the optic disc from the line perpendicular to the foveal–BMO axis. Optic discs with an angle of less than or equal to 20° were categorized as having a vertical tilt (included in the vertical tilt).	In the vertical tilt group, the RNFL thinning was prominent at the superotemporal and inferotemporal sectors. In the horizontal tilt group, the RNFL thinning was predominated at the inferotemporal sector.
Lan et al. (23)	53 Eyes with POAG and 82 eyes with NTG	46.00 ± 14.00	Fundus photograph	Disc tilt: Ratio of disc diameter = shortest/longest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	NTG: Eyes with lower wedge-shaped RNFL defect had significantly lower tilt ratio and more disc tilt than eyes with upper defects. Torsion degree was associated with the location of RNFL defect. POAG: Eyes with lower wedge-shaped RNFL defects had inferior disc torsion; eyes with upper defects had superior disc torsion. Disc tilt ratio was associated with the location of RNFL defect.
Park et al. (24)	78 Eyes with NTG and 78 eyes with POAG (matched axial length and age).	POAG: 56.16 ± 13.98, NTG: 54.96 ± 14.54	OCT	ONH vertical tilt: the ONH vertical tilt was measured from a B-scan passing through the 6 and 12 o'clock positions. The ONH horizontal tilt was measured from a B-scan passing through the 3 and 9 o'clock positions. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Direction of optic disc torsion was related to the location of the VF defect in myopic NTG. The presence of ONH torsion was significant related to the diagnosis of NTG.
RNFL and GCIPL distribution					
Shin et al. (68)	82 Eyes with glaucoma and 41 refraction-matched normal eyes	Glaucoma: 44.28 ± 12.11, without glaucoma: 47.94 ± 10.37	Fundus photograph	Disc tilt: Ratio of disc diameter = shortest/longest.	In glaucoma eyes, no significant difference in GCIPL thickness was found between eye with tilted disc or eyes without tilted disc. The diagnostic capability of GCIPL thickness in the tilted group is not inferior to that of non-tilted group.
Disc rim and peripapillary area					
Shin et al. (68)	82 Eyes with glaucoma and 41 refraction-matched normal eyes	Glaucoma: 44.28 ± 12.11, without glaucoma: 47.94 ± 10.37	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest.	The ONH parameters in the eyes with tilted disc (apart from rim area) were significantly smaller than eyes without tilted disc.
Chiang et al. (72)	215 Eyes from adult individuals	55.7 ± 15.1	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The RNFL herniation appeared as a dome-shaped hyperreflective RNFL bulge protruding into the neurosensory retina at the optic disc margins. The RNFL herniation was correlated with congenital disc tilt (disc torsion >45° and the tilt occurred inferonasally).
Lee et al. (73)	110 Myopic eyes with glaucoma	Disc torsion superiorly: 42.32 ± 7.83 Disc torsion inferiorly: 37.60 ± 7.65	Fundus photograph	Disc tilt: Ratio of disc diameter = longest/shortest. Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	The direction of disc torsion was associated with the location of PPA (superior/inferior). For eyes with disc torsion inferiorly, 97% of them showed inferiorly located β-zone PPA.

(Continued)

TABLE 2C (Continued)

References	Study subjects	Mean age (mean ± SD) (years)	Images	Definitions of disc tilt, tilt angle, and disc torsion	Main outcomes
Hasegawa et al. (74)	101 Eyes with suspected POAG	53.5 ± 14.0	Fundus photograph	Disc tilt: Ratio of disc diameter = shortest/longest. Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	Smaller ovality index was associated with larger width of PPA on temporal (β = −0.691, $P < 0.0001$) and nasal (β = −0.420, $P < 0.0001$) side.
Lamina cribrosa					
Kimura et al. (39)	129 POAG eyes and 55 age-matched control eyes with high myopia	POAG with LC defects: 49.0 ± 13.9, without LC defects: 50.2 ± 12.7, control: 49.4 ± 8.9	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = shortest/longest. Tilt angle: angle between the two lines drawn between the BM termination point and disc border. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	POAG eyes with LC defects showed a smaller ovality index (disc diameter ratio). Vertical tilt angle significantly correlated with the presence of LC defects.
Lee et al. (75)	66 Glaucomatous eyes and 48 healthy eyes	Healthy eyes with vertical tilt: 47.6 ± 14.8, healthy eyes with horizontal tilt: 48.8 ± 12.1, OAG eyes with vertical tilt: 46.3 ± 15.3, OAG eyes with horizontal tilt: 53.7 ± 11.8	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: the optic disc tilt axis was defined as the angular deviation of the longest axis of the optic disc from the line perpendicular to the foveal–BMO axis. Optic discs with an angle ≤20° were categorized in the "vertical-tilt group," while those with an angle >20° were categorized in the "horizontal-tilt group."	The vertical-tilt group had a larger LC surface depth at superior locations than the inferior locations, while the horizontal-tilt group had its the opposite direction. The RNFL thinning in glaucomatous eyes was most prominent at both the superotemporal and inferotemporal sectors in the vertical-tilt group, while it was most predominated at the inferotemporal sector in the horizontal-tilt group.
Park et al. (40)	139 OAG eyes	-Eyes with far-peripheral LC defects: 49.57 ± 13.41, -Eyes with mid-peripheral LC defects: 60.78 ± 9.38 -Eyes without focal LC defects: 54.39 ± 12.08	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest. Tilt direction: temporal disc tilt: degree between a horizontal line and a line drawn manually to connect the two points where the height profile and disc margin met; vertical disc tilt: angle between the vertical line and the line connecting the two points where the height profile and disc margin met. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with focal LC defects located at the temporal region of the disc had a greater temporal disc tilt degree, compared with myopic eyes with LC defects at other clock-hour locations and were myopic eyes.
Lee et al. (76)	55 Myopic eyes with glaucoma and 47 myopic eyes without glaucoma	Glaucoma: 47.90 ± 9.26, Without glaucoma: 47.19 ± 9.67	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. Tilt angle: the anterior LC tilt angle was defined as the angle between BMO reference plane and the representative anterior LC surface line. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The ovality index did not correlate with the LC tilt angle. Some severely tilted discs (with high ovality index and torsion degree) revealed minimal anterior LC tilt without RNFL or visual field defect.
Sclera					
Park et al. (41)	180 Normal eyes and 180 glaucomatous eyes	Control: 41.3 ± 13.5, Glaucomatous: 43.5 ± 11.8	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest. Tilt angle: the angle between the two lines drawn between the BM termination point and disc border. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	In glaucomatous eyes with high myopia, large disc tilt and torsion had a greater difference of the superior and inferior sclera thickness than glaucomatous eye without myopia.

RNFL, retinal nerve fiber layer; ONH, optic nerve head; CDR, cup disc ratio; OCT, optical coherence tomography; PPA, peripapillary atrophy; PHOMS, peripapillary hyperreflective ovoid mass-like structures; BM, Bruch's membrane; OR, odd ratio; POAG, primary open angle glaucoma; LC, lamina cribrosa; OAG, open angle glaucoma; BMO, Bruch's membrane opening; OCT-A, optical coherence tomography angiography; NTG, normal tension glaucoma.

TABLE 3A Functional change related to disc tilt.

References	Sample size	Mean age (mean ± SD) (years)	Follow-up	Image	Definitions of disc tilt and disc torsion	Main findings
Cross-sectional						
Tay et al. (25)	137 Myopic eyes	21.2 ± 1.1	–	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest.	Greater optic disc tilt was associated with higher myopia and reduced sensitivity of VF test (trial lenses) ($r = 4.25$, $P < 0.01$).
Hong et al. (16)	236 NTG eyes with myopia	53.14 ± 13.78	–	Fundus photograph, OCT-A	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Disc torsion degree and disc tilt ratio were negatively correlated with BCVA. Disc tilt ratio was also correlated with peripapillary area deep vessel density fluctuation. Worse mean retinal sensitivity of the central 12 points of SITA 24-2 VF test showed significant correlation with greater disc tilt ratio.
Sawada et al. (87)	118 Eyes with OAG	54.5 ± 13.6	–	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with worse VFs had significantly greater tilt ratio. The difference in the tilt ratio between paired eyes correlated with the difference of the MD.
Shoeibi et al. (88)	58 Highly myopic eyes	Tilted disc: 28.95 ± 7.2, Non-tilted disc: 27.87 ± 6.08	–	Fundus photograph	Disc tilt: ratio of disc diameter = shortest/longest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	No differences in the VF indices in highly myopic patients with or without tilted discs.
Choi et al. (90)	136 Glaucoma patients with isolated superior or inferior hemifield loss, 99 normal controls	Glaucoma: 54.3 ± 13.8 Normal control 52.9 ± 5.5	–	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest Tilt angle: Temporal disc tilt: the tilt degree between a horizontal line and a line that was manually drawn to connect the two points where the height profile and the disc margin met. Vertical disc tilt: the angle between the vertical line and the line connecting the two points where the height profile and the disc margin met. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Vertical disc tilt was an independent factor related to the initial location of a VF defect (superior vs. inferior) after controlling for age, MD, axial length, disc ovality index, torsion degree, disc size, and temporal disc tilt.
Choi et al. (91)	136 Patients with early-stage POAG	Single-hemispheric: 54.0 ± 13.9, Bi-hemispheric: 54.2 ± 14.1	–	Fundus photograph, OCT,	Disc tilt: ratio of disc diameter = longest/shortest Tilt angle: line connecting RPE border/BMO. An additional line connected 2 points that are located at an arbitrarily chosen distance of 80 pixels from the RPE/BMO on each side. The angle of tilt was the angle between these two lines.	The asymmetry in RNFL thickness decreased with increase disc ovality, without association with spherical equivalent, axial length, or the angle between the temporal retinal veins. Disc ovality was an independent risk factor for bi-hemispheric RNFL defects (after controlling for VF MD, age, axial length, and disc area).
Park et al. (92)	40 Myopic eyes without RNFL defects and 64 myopic eyes with RNFL defects in the superonasal region of the optic disc	Myopic control: 42.54 ± 13.74, Myopic eyes without VF defects: 39.04 ± 13.41, myopic eyes with VF defects: 36.42 ± 13.51	–	OCT, Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian. Tilt angle: Horizontal disc tilt: angle between a horizontal line and a line drawn manually to connect the two points where the height profile and disc margin met. Vertical disc tilt: angle between a vertical line and the line connecting the two points where the height profile and disc margin met.	86–97% of the myopic eye with superonasal RNFL or inferotemporal VF defects had border tissue overhang at 1, 2, 11, and 12 o'clock positions.

(Continued)

TABLE 3A (Continued)

References	Sample size	Mean age (mean ± SD) (years)	Follow-up	Image	Definitions of disc tilt and disc torsion	Main findings
Choi et al. (93)	112 bilateral myopic NTG patients	49.8 ± 11.3	–	OCT	Tilt angle: angle between ONH plane and BMO plane.	There was a correlation between horizontal ONH tilt angle and angular location of maximal ONH tilt. Both of them were associated with more advanced VF defect in eyes with myopic NTG. The location of VF defect was associated with the horizontal ONH tilt direction and angular location of maximal ONH tilt.
Longitudinal						
Kim et al. (102)	56 Myopic eyes with NTG	Stable group: 46.75 ± 11.24, Progression group: 47.00 ± 10.83	72.63 ± 20.46 months	Fundus photograph	Tilt angle: angle between the disc margin plane and BMO plane. Temporal tilt: positive degree of horizontal tilt, Nasal tilt: negative degree of horizontal tilt. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The vertical tilt angle (HR = 0.835, *P* = 0.026) and the DPE positioned temporal to fovea (HR = 4.314, *P* = 0.001) were associated with VF progression.
Seol et al. (104)	56 Myopic eyes with POAG	50.1 ± 11.7	90.8 ± 38.1 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest	Patients with non-tilted disc had a greater cumulative probability of progression than those with disc tilt. Lower disc tilt ratio was significantly associated with disease progression.
Lee et al. (22)	85 Eyes of 85 myopic glaucoma patients	48.3 ± 13.1	4.1 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with VF progression showed smaller mean tilt ratio than eyes with stable VF. Eyes with disc tilt had lower cumulative probability of progression than eyes without disc tile (24.7% vs. 68.7%). The tilt ratio (HR = 0.110; *P* = 0.046) were association with the VF progression.
Kwon et al. (103)	146 Myopic eyes with POAG	50.1 ± 12.7	4.6 ± 1.3 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes without optic disc tilt has faster VF progression than eyes with tilted disc. Less disc tilt was associated with superior and inferior VF progression (OR = 0.561; *P* = 0.018).
Sung et al. (107)	92 Myopic eyes with NTG	37.83 ± 10.89	55.78 ± 30.12 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Among the eyes with correspondence in direction optic disc torsion and location of VF defect, greater tilt ratio (HR, 73.412; *P* = 0.003) was independent predictive factors for VF progression.
Kwun et al. (98)	66 Myopic eyes with NTG	No focal LC defects: 47.65 ± 9.61 Focal LC defects: 45.53 ± 9.57	93.74 months	Fundus	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The greater optic disc tilt and torsion in myopic eyes with NTG were not associated with VF progression.
Baek et al. (99)	98 Eyes with pre-perimetric OAG	Non-progressor: 30.1 ± 6.4 Progressor: 31.3 ± 5.7	5.8 ± 1.7 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest	The tilt ratio was not associated with VF progression of OAG.
Seol et al. (101)	109 Myopic eyes with NTG	53.54 ± 9.17	7.55 ± 1.79 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest	The tilt ratio was not associated with VF progression of NTG.
Sawada et al. (105)	144 Eyes with OAG	56.2 ± 13.3	8.9 ± 4.4 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Tilt ratio was significantly greater in the eyes with faster VF progression than those with slower progression. This factor was significantly associated with faster VF progression, while SE and axial length were not associated with it.

(Continued)

TABLE 3A (Continued)

References	Sample size	Mean age (mean ± SD) (years)	Follow-up	Image	Definitions of disc tilt and disc torsion	Main findings
Lee et al. (94)	182 Myopic eyes with OAG and progressive VF deterioration	Horizontal disc tilt 48.6 ± 10.8, Vertical disc tilt 55.9 ± 7.8	7.43 years	Fundus photograph	Disc tilt: disc diameter ratio = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian. Vertical disc tilt group (temporal/nasal tilting): the largest dimension of the β-zone PPA from disc margin were located in the temporal or nasal quadrant of the optic disc. Horizontal disc tilt group (superior/inferior tilting): the largest dimension of the β-zone PPA from disc margin were located in the superior or inferior quadrant of the optic disc.	The vertical disc tilt group showed significantly faster VF progression at the inferior regional zones than the horizontal disc tilt group. Based on a multivariate linear mixed model, vertical disc tilt was associated with faster bi-hemifield VF progression, whereas horizontal disc tilt was associated with faster single-hemifield VF progression.
Han et al. (100)	97 Myopic eyes with NTG	53.8 ± 13.7	71.1 ± 29.7 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	In NTG with myopia, those aged ≤50 years had higher cumulative probability of progression than those aged >50 years.
LC defect						
Sawada et al. (110)	159 Myopic glaucomatous eyes with VF defect	Progression group: 46.3 ± 11.9 Non-progression group: 45.5 ± 10.5	7 years	Fundus photograph, OCT	Tilt angle: optic disc tilt angle was measured with the OCT B-scans; defined as the angle between the line connecting the BMO and the optic disc canal plane. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Presence of LC defect was associated with non-progressive VF defect (OR = 3.96; *P* = 0.002). The LC defect location and VF defect corresponded with each other. Non-progressive eyes with LC defect had greater myopic optic disc deformity, lower baseline IOP, and smaller% of IOP change than eyes without LC defect. Eyes with LC defect and higher baseline IOP exhibited progressive VF defect.
Kwun et al. (98)	66 Eyes with NTG	No focal LC defects: 47.65 ± 9.61 Focal LC defects: 45.53 ± 9.57	93.74 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with focal LC defect were associated with greater torsion degree and tilt ratio. They also have deeper VF MD slopes and faster localized VF progression than eyes without LC defect. VF progression was associated with the presence of focal LC defects.
Sawada et al. (111)	133 eyes with OAG and 83 eyes without OAG, axial length ≥24 mm	Myopic eyes with OAG: 52.5 ± 13.4, Myopic eyes without glaucoma: 49.4 ± 16.1	–	Fundus photograph, OCT	Tilt angle: angle between the reference plane (connects the inner edge of the nasal and temporal BMO) and the optic disc canal plane (connects the inner edge of the nasal BM and temporal margin of the optic disc canal, defined as the end of externally oblique border tissue). Disc torsion: Deviation of the longest axis of the optic disc from the perpendicular meridian.	The number of temporal LC defects and tilt angle were associated with the presence of paracentral scotoma, whereas the number of inferior and superior LC defects and torsion direction were associated with presence of superior and inferior VF defects.
DPE						
Jeon et al. (113)	97 Eyes of NTG with myopia	Central dominant VF defect group: 51.43 ± 11.47, Peripheral dominant VF defect: 48.87 ± 10.02	–	Fundus photograph, OCT(3D)	Disc tilt: ratio of disc diameter = longest/shortest. Tilt angle: angle between the BMO plane and the line connecting the nasal BMO and innermost margin of the externally oblique border issue. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian	The eyes with worse central VF defect had larger disc torsion and larger ONH tilt angle. Larger ONH tilt angle and smaller disc-DPE depth were related to the presence of central VF defect.

VF, visual field; OCT-A, optical coherence tomography angiography; BCVA, best-corrected visual acuity; MD, mean deviation; OCT, optical coherence tomography; POAG, primary open angle glaucoma; RPE, retinal pigmentary epithelium; BMO, Bruch's membrane opening; NTG, normal tension glaucoma; ONH, optic nerve head; HR, hazard ratio; DPE, deepest point of eyeball; OR, odd ratio; PPA, peripapillary atrophy; IOP, intraocular pressure; LC, laminar cribrosa.

TABLE 3B Functional change in related to disc torsion.

References	Sample size	Mean age (mean ± SD) (years)	Follow-up	Image	Definitions of disc tilt and disc torsion	Main findings
Cross-sectional						
Hung et al. (95)	100 Myopic eyes of 50 patients with POAG	50.1 ± 10.0	–	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	For the same patient, eyes with VF defect has greater degree of optic disc rotation than the fellow eyes without VF defect. Greater degree of optic disc rotation was significantly associated with the presence of VF defects (multivariate logistic regression analysis).
Kim et al. (96)	105 Myopic eyes with OAG	52.81 ± 11.69	–	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The artificial neural networks identified PPA area, peripapillary RNFL thickness, disc-foveal angle, and disc torsion degree as significant variables in OAG with myopia
Park et al. (97)	225 NTG eyes with or without myopia	Myopic NTG: 42.85 ± 11.81 Non-myopic NTG: 60.73 ± 11.43	–	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Torsion degree was the only factor related to VF defect location.
Choi et al. (90)	136 Glaucomatous patients and 99 normal controls	Glaucoma: 54.3 ± 13.8 Control: 52.9 ± 5.5	–	Fundus photograph, OCT	Disc tilt: ratio of disc diameter = longest/shortest. Tilt direction: Temporal disc tilt: angle between a horizontal line and the line connecting the disc margin. Vertical disc tilt: angle between the vertical line and the line connecting the disc margin. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Eyes with superior hemifield defects exhibited higher degree of disc torsion and higher proportion of inferiorly torsional disc than eyes with inferior hemifield defects.
Park et al. (10)	134 Myopic eyes with NTG	Without staphyloma: 49.78 ± 8.68 With staphyloma: 50.16 ± 12.06	–	OCT, Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Ten eyes (71.4%) from the inferior staphyloma group had superior VF defects, and five eyes (71.4%) from the superior staphyloma group had inferior VF defects. When the posterior staphyloma involved the optic disc, extensive disc enlargement with less disc torsion appeared.
Park et al. (24)	78 NTG and 78 POAG patients (matched axial length and age)	POAG 56.16 ± 13.98 NTG 54.96 ± 14.54	–	OCT	Tilt angle: ONH vertical and horizontal tilt were measured from a B-scan passing through the 6 to 12 o'clock and 3 to 9 o'clock position, respectively. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Myopic NTG eyes showed greater torsion degree than non-myopic NTG eyes (the POAG eyes did not show this finding). NTG eyes showed a significant difference in the degree of maximum tilt and torsion and the direction of vertical tilt and torsion by the location of visual field defect.
Longitudinal						
Han et al. (100)	97 Myopic eyes with NTG	53.8 ± 13.7	71.1 ± 29.7 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Myopic NTG eyes with disc tilt direction <45° had higher cumulative probability of progression than eyes with tilt direction ≥45°.
Baek et al. (106)	108 POAG eyes (single- hemifield defect at initial VF examination)	Progression sparing of opposite hemifield: 55.7 ± 10.7 Progression involvement of opposite hemifield: 61.0 ± 10.5	7.9 ± 3.0 years	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian. The presence of vertical tilt: angle of vertical tilt was < -15° or > + 15°.	Absence of optic disc vertical tilt (HR = 1.430; $P = 0.017$) were risk factors for the involvement of the opposite hemifield. Younger age and presence of optic disc vertical tilt showed greater cumulative probability of sparing the opposite hemifield.

(Continued)

TABLE 3B (Continued)

References	Sample size	Mean age (mean ± SD) (years)	Follow-up	Image	Definitions of disc tilt and disc torsion	Main findings
Sung et al. (107)	92 Myopic eyes with NTG	37.83 ± 10.89	55.78 ± 30.12 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Optic disc rotation and VF defect correspondence (HR, 0.441; *P* = 0.016) were associated with VF progression in myopic NTG eyes.
Kim et al. (102)	56 Myopic eyes with NTG	Stable group: 46.75 ± 11.24 Progression group: 47.00 ± 10.83	72.63 ± 20.46 months	Fundus photograph	Tilt angle: angle between the disc margin plane and BMO plane. Temporal tilt: positive degree of horizontal tilt. Nasal tilt: negative degree of horizontal tilt. Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The vertical tilt angle (HR = 0.835, *P* = 0.026) and the DPE positioned temporal to the fovea (HR = 4.314, *P* = 0.001) were associated with VF progression.
Kwun et al. (98)	66 Myopic eyes with NTG	46.62	93.74 months	Fundus	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	The greater optic disc tilt and torsion in myopic eyes with NTG were not associated with VF progression.
Na et al. (108)	102 Myopic eyes with POAG	57.17 ± 10.43	73.21 ± 12.81 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian	Eyes with VF defect corresponded to the disc torsion direction has faster VF progression than eyes without disc torsion or with disc torsion direction not corresponded to VF defect.
Han et al. (109)	82 OAG eyes without myopia and 150 OAG eyes with myopia	Non-myopic OAG: 46.0 ± 11.4 Myopic OAG: 45.6 ± 12.0.	Non-myopic OAG: 10.0 ± 2.4 years Myopic OAG: 9.8 ± 2.7 years	Fundus photograph	Disc tilt: disc diameter ratio = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian. Inferiorly tilted disc: torsional angle >15°. Temporally tilted disc: torsional angle ≤15°.	The cumulative probability of progression was faster for myopic OAG with inferiorly tilted disc compared with temporally tilted disc and non-myopic OAG. Inferiorly tilted disc was predictive of progression (HR = 2.378; *P* < 0.001). In the analysis of myopic OAG with inferiorly tilted disc, the progression group had younger age and earlier-stage VF defect at baseline compared with the stationary group.
Park et al. (26)	100 Myopic eyes with POAG	50.1 ± 10.0	Progression to NTG: 71.83 ± 9.81 months Non-progression to NTG: 67.18 ± 6.13 months	Fundus photograph	Disc tilt: ratio of disc diameter = longest/shortest Disc torsion: deviation of the longest axis of the optic disc from the perpendicular meridian.	Greater disc torsion was one of the risk factors for NTG suspects to convert to NTG. In subgroup analysis, greater disc torsion was a significant risk factor only for myopic NTG suspects.

POAG, primary open angle glaucoma; VF, visual field; OAG, open angle glaucoma; PPA, peripapillary atrophy; NTG, normal tension glaucoma; OCT, optical coherence tomography; ONH, optic nerve head; HR, hazard ratio; BMO, Bruch's membrane opening; DPE, deepest point of eyeball; OAG, open angle glaucoma.

by tilted disc (68). On the other hand, disc torsion affected both RNFL and GCIPL distribution. Eyes with torted disc exhibited thicker temporal RNFL and more temporally positioned superior peak of RNFL (7). Eyes with inferotemporally torted disc had more temporally located superior peaks of RNFL than non-torsion and superonasally torted disc (8). Sung et al. (9) found that eyes with superior optic disc torsion generally had thicker peripapillary RNFL than eyes with inferior disc torsion (9), in line with the results of other studies (13, 68, 69).

While investigation involving eyes with spherical equivalent of > −6.00 D suggested that disc torsion did not affect GCIPL thickness (8), evaluation of healthy myopic eyes with a wider range of refractive error (spherical equivalent of −9.00 D to −0.5D) found that eyes with inferior optic disc rotation had thinner macular GCIPL in the inferonasal sector, after controlling for spherical equivalent and axial length. The polemical findings of GCIPL distribution may be related to the range of refractive errors included in the studies (8, 9, 68). Highly myopic eyes are likely to have a greater extent of posterior scleral deformity, as reflected by the degree of optic disc tilt and torsion, that causes mechanical stress on the axonal fibers. The change of choroidal circulation due to posterior sclera deformation may also render the inferior macular GCIPL to be more vulnerable to damage. However, further studies are required to validate the results and possible mechanisms.

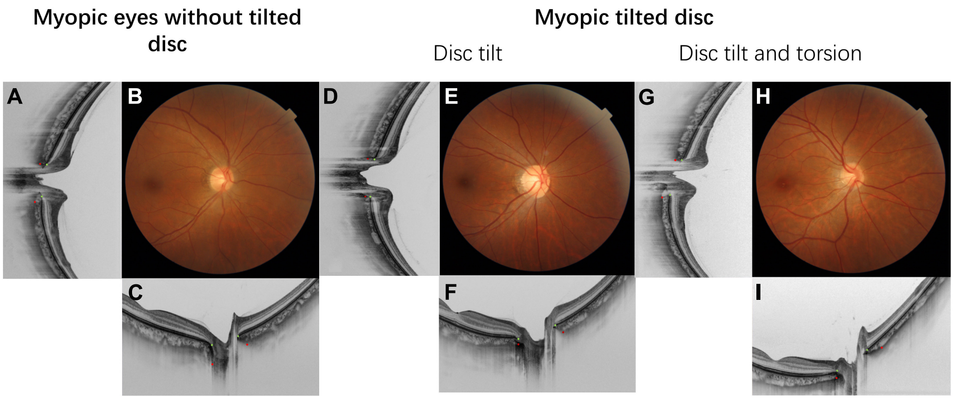

FIGURE 1
This figure demonstrated the fundus photograph and its corresponding horizontal and vertical cross-sectional optical coherence tomography (OCT) scan. The Bruch's membrane openings are marked with green dots and the anterior scleral openings are marked with red dots. Details of the ovality index and disc torsion angle measurement are provided in **Figure 3**. **(A–C)** Fundus photograph and OCT scan of myopic eyes without tilted disc. **(D–F)** Myopic tilted disc with ovality index = 1.34 with disc torsion angle = 0. **(G–I)** Myopic tilted disc with ovality index = 1.34 and disc torsion angle = 21.1°.

5.3. Disc rim and peripapillary area

Disc tilt was associated with a smaller disc, smaller rim area, cup area, cup-to-disc area ratio, cup volumes or cup depth, and larger measurement of rim volume (33, 68, 70). Greater disc tilt and torsion were also associated with a larger width of parapapillary gamma zone (8, 9, 71). During the myopic shift, the tilting and rotation of optic disc may be accompanied by nasal bulging and kinking of retinal nerve fibers. It was found that increased disc tilt was associated with the presence of PHOMSs (17). A study of 1,407 children found that PHOMS were present in 8.9% of the children (18) and most of the PHOMS were located in the superonasal sector of the optic disc. Eyes with increased disc tilt detected by OCT had a higher risk of having PHOMS (OR = 1.38, $P = 0.002$) (18). They suggested that PHOMS occurs because optic disc tilting leads to distention of the axons that herniate into the peripapillary retina. Similarly, Chiang et al. (72) demonstrated that congenital disc tilt (disc torsion greater than 45° and the tilting occurred inferonasally) correlated with a dome-shaped hyperreflective RNFL bulge that protrudes into the retina at the optic disc margin, which could be due to the convergence of a normal number of axons into a small sclera foramen, followed by loss of cupping. The margins become indistinctive due to the compression and bending of the converged axons at an oblique angle.

It is possible that optic disc tilting may be due to local protrusion of the posterior sclera rather than uniform global enlargement (see "Development of myopic tilted disc"). Indeed, other studies indicated that the optic disc tilt could reflect the tilting of the peripapillary sclera and the presence of PPA. Disc torsion was correlated with peripapillary tilting index on OCT at the superotemporal-inferonasal sectors and superior-inferior sectors (peripapillary tilting index is calculated by the height of retinal pigment epithelium) (48). The direction of optic disc torsion was associated with the location of β-zone PPA (73). For the association between disc tilt and the presence of PPA, Hasegawa et al. (74) pointed out that a larger distance between Bruch's membrane opening (BMO) and scleral canal opening detected by OCT–which corresponded to the β-zone PPA–was associated with great disc tilt.

5.4. Lamina cribrosa

Several changes in the LC were associated with myopic tilted disc. Lee et al. (75) found that POAG eyes with LC defect showed a smaller ovality index and larger vertical and horizontal tilt angles (**Figures 3C, D**). Optic disc with a smaller disc torsional angle has a deeper LC surface depth at the superior aspect of optic disc, whereas optic disc with larger angle of disc torsion has a deeper LC surface at the inferior aspect of the optic disc. They regarded optic disc torsion as another form of optic disc tilt along the oblique axis rather than a result of optic disc rotation (75). Park et al. (40) revealed that eyes with focal LC defect located at the temporal region had a greater degree of temporal disc tilt on OCT scan; while eyes with focal LC defect located at the inferotemporal region had more inferiorly positioned fovea in relation to the optic disc. Their results suggested that the temporal LC defect could be caused by temporal stretching of the optic disc. Of note, the depth of LC tilt and superficial ovality index are sometimes different. Lee et al. (76) found that some tilted discs with large ovality index only showed minimal anterior LC tilt in both directions. They speculated that only myopic eyes with a tilted position against the scleral opening would be prominent to glaucomatous axonal damage. However, more solid evidence is required to support this suggestion.

5.5. Sclera

The tilting of optic disc was related to the sclera thickness. Park et al. (41) revealed that larger disc tilt and torsion are associated with a larger difference in thickness between the superior and inferior sclera in glaucomatous eyes with high myopia.

5.6. Choroid

The thickness of the peripapillary choroid is associated with optic disc tilt. Yamashita et al. (11) discovered that larger optic disc tilt correlated with thinner temporal and inferotemporal peripapillary choroid. However, eyes with shorter foveo-papillary distance had thicker peripapillary choroid. This is consistent with Chen et al. (12) who demonstrated that every 5.38 μm increase in average macular choroidal thickness and 6.21 μm decrease in average peripapillary choroidal thickness were associated with an increase of 0.1 ovality index. Eyes with tilted discs had thicker peripapillary choroid at the region near the elevated rim (13). The tilting of optic disc and the change of choroidal thickness at different regions indicated asymmetrical enlargement or stretching of the posterior retina.

5.7. Microvasculature

The change of deep microvasculature in relation to disc tilt has been reported. Sung et al. (14) discovered that a large horizontal disc tilt angle was associated with a lower peripapillary vessel density; a smaller horizontal disc tilt angle was associated with a larger superficial foveal avascular zone (FAZ) area. Similarly, the optic tilt ratio negatively was correlated with vessel density in the deep retinal plexus of the macular region at the nasal and temporal sectors (15). Furthermore, the deep vessel density of the peripapillary area was correlated with the disc tilt ratio and not the disc torsion (16). The reduced vessel density could be related to the reduced blood supply around the optic disc and the FAZ, primarily due to mechanical stretching of the corresponding regions. Alternatively, it could be a consequence of reduced metabolic demand. However, these were cross-sectional studies and the theory requires further investigation.

5.8. Macula

Apart from the ONH, macular changes were also found in eyes with myopic titled disc. Case reports discovered intrapapillary hemorrhages in eyes with myopic titled disc without affecting the vision after the hemorrhages resolved (77, 78). It was believed that the tilting of the optic disc surface might predispose the hemorrhages (77). With axial length elongation and formation of posterior staphyloma in eyes with myopic tilted disc, the associated structural changes of the macular would also occur. A retrospective case series of six eyes with myopic tilted disc exhibited retinal pigment epithelial (RPE) change located along the superior margin of staphyloma and radially to it, reassembling a "T-shaped band" of RPE change (79). Choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV) were also found at the edge of inferior staphyloma in eyes with tilted disc (80–82). It is possible that the difference of curvature across the staphyloma leads to microrupture of the BM and disturbance of blood flow, causing RPE changes and the development of CNV and PCV (83). Indeed, macular serous retinal detachments were present in 17.3 to 29.5% of eyes with myopic tilted discs associated with CNV and PCV (82, 84); most of the cases happened in eyes with inferior staphyloma (85). Cohen et al. (82) also found that 3.2% of eyes with tilted disc had lamellar macular hole and 5.4% of eyes had foveoschisis; the latter was observed at the inferior staphyloma (21). In another study, they reported that 16.6% of eyes with tilted disc had retinoschisis, commonly located outside the bending area of the macula (86). These were likely due to "container-content" imbalance (83). During the elongation process of the eyeball, progressive growth of the staphyloma can induce tractional force on the BM-RPE-outer retinal layers while the inner retina remains attached to the internal limiting membrane and retinal vessels (83). Hence, separating the retinal layers.

TABLE 4 Summary of contents.

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6. Functional changes related to myopic tilted disc

Apart from the relationship between myopization and different structural changes, myopic tilted disc could also lead to functional changes and visual field loss, as demonstrated by multiple cross-sectional and longitudinal studies summarized in **Tables 3A, B**.

6.1. Cross-sectional studies

Generally, a larger degree of disc tilt is associated with a lower visual function according to visual field assessment (16, 25). Indeed, eyes with a larger disc tilt ratio had worse visual field mean deviation than the fellow eye of the same patient with lower disc tilt ratio (87). Interestingly, another study that included younger, highly myopic participants (mean age of 28.95 ± 7.2 for the tilted disc group and 27.87 ± 6.08 for the non-titled disc group) found no difference in the mean deviation, pattern standard deviation, and fovea threshold sensitivity of visual field between eyes with and without tilted disc (88). A meta-analysis showed that the pooled hazard ratio (HR) for optic disc tilt ratio and glaucoma progression was 0.988 (95% CI, 0.921–1.059) per 0.1-unit increase,

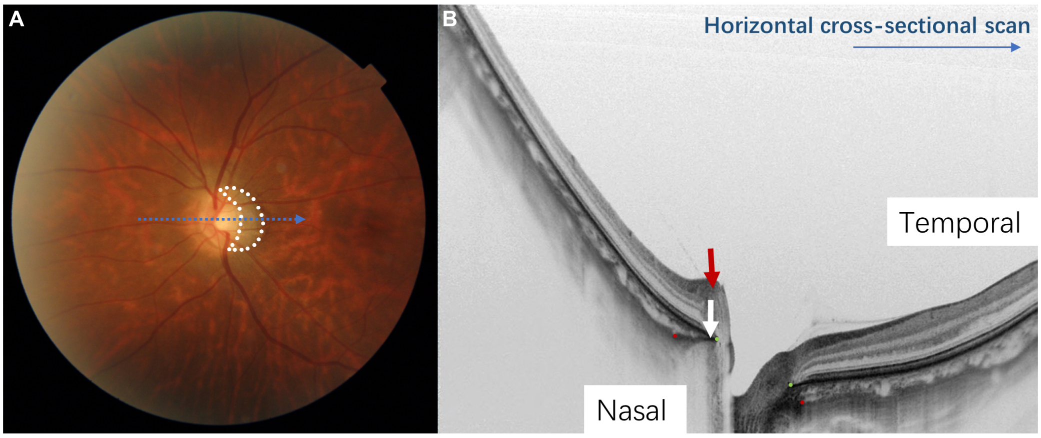

FIGURE 2
The appearance of a myopic tilted disc on fundus photography and optical coherence tomography (OCT). Panel **(A)** shows a half-moon or C-shaped crescent (circled in white dots) around the optic disc. Panel **(B)** shows the tilted disc on a horizontal cross-sectional OCT scan (corresponds to the blue arrow in Figure 1A). The Bruch's membrane opening is shown by the green dots and the red dots indicate the anterior scleral opening. The nasal border of the optic disc is elevated, and the Bruch's membrane-choroid complex (indicated by the white arrow) protrudes toward the optic disc, indicating temporal tilting of the optic disc. The nerve fiber layer on the nasal side of the optic disc is elevated (indicated by the red arrow), which also indicates that the optic disc is tilting toward the temporal direction.

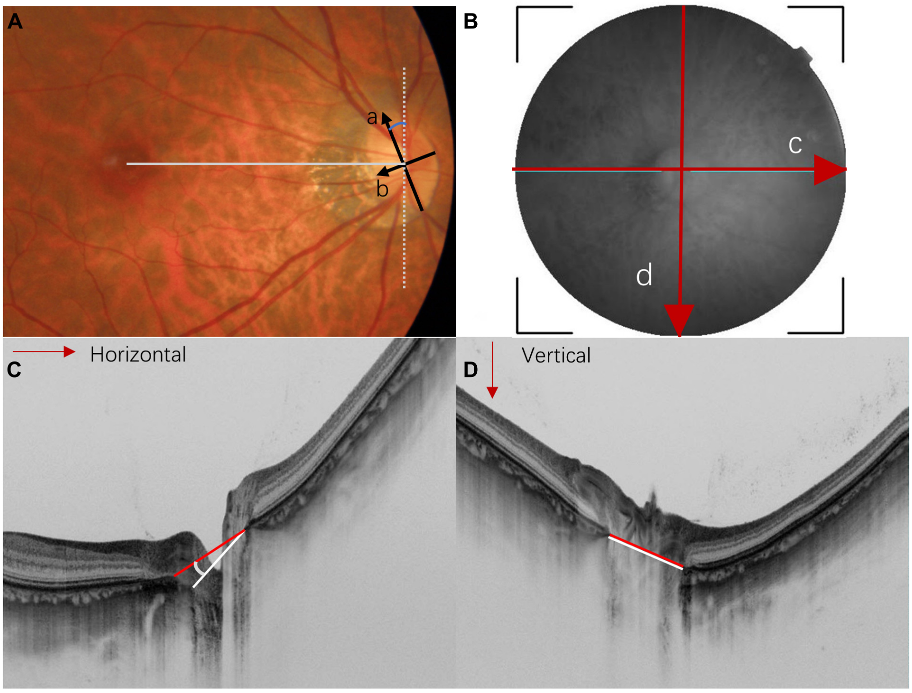

FIGURE 3
Methods for measuring optic disc torsion, ovality index, and optical coherence tomography (OCT)-measured tilt angle. **(A)** In the fundus photography, the optic disc ovality index is determined by the ratio (a/b) of the longest diameter (arrow a) and the shortest diameter (arrow b). An ovality index larger than 1.3 is usually considered as optic disc tilt. The optic disc torsion angle is defined as the deviation of the longest axis (arrow a) from the vertical meridian (white dot line). The vertical meridian is defined as a vertical line perpendicular to a horizontal line that connects the center of the optic disc and the center of the fovea (straight gray line). **(B)** The en face SS-OCT image of the optic nerve head is measured by horizontal scan (red arrow c) and vertical scan (red arrow d). **(C,D)** Represent the horizontal and vertical cross-sectional scans of the optic disc, respectively. Myopic tilted discs are usually measured by the angle between Bruch's membrane opening plane (also known as the reference plane) and the plane of the disc border. The red lines indicate the line connecting the Bruch's membrane opening; the white lines indicate the line connecting the clinical boundary of the optic disc. The horizontal tilt angle **(C)** and vertical tilt angle **(D)** are measured between the red and white lines.

and the risk reduced as the patients' mean age increased (89). The myopic deformation of the peripapillary sclera possibly increases the susceptibility to axonal damage and accelerates the axonal and visual field loss. It is likely that the progression of visual field defect occurs during myopization (i.e., when the patients are younger), and no progression could be detected at an older age because the stress on the myopic ONH reduces when the axial elongation ceases (89).

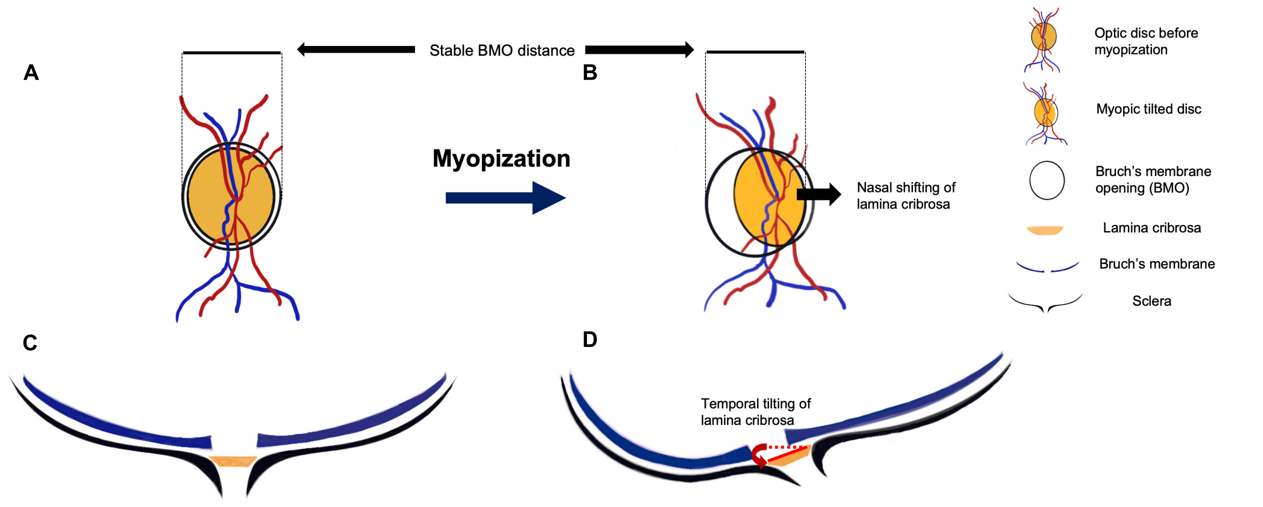

FIGURE 4
The anatomic change during myopic tilted disc development. Panels **(A,C)** show the initial optic disc on fundus photograph and optical coherence tomography (OCT) horizontal scan, respectively. The black circle outside the optic disc indicates the Bruch's membrane opening (BMO) windows **(A,C)**. The blue lines in Panels **(C,D)** indicate Bruch's membrane (BM) layer, the black lines indicate the sclera of the eyeball, and the orange planes in between them represent the lamina cribrosa (LC). Panels **(B,D)** show the anatomic change after myopic progression. After the posterior scleral deformation, the tensile strength of the sclera is conducted to the LC. The LC is dragged nasally under the BMO window, along with the blood vessels that pass through the LC **(B)**. This nasal shifting and tilting of LC lead to misalignment of BM and formation of peripapillary atrophy. During the optic disc tilting, the distance between BMO remains relatively unchanged **(B,D)**. In the cross-sectional view **(D)**, the posterior protrusion of the sclera stretches the LC toward the deepest point of eyeball, resulting in a more oval disc and disc torsion appearance on the fundus photograph **(B)**.

Correlation between the direction of disc tilt and the location of visual field defect has been reported. Choi et al. (90) found that eyes with superior hemifield defects had a larger degree of vertical disc tilt (superior or inferior direction). After adjustment of age, mean deviation, axial length, and other disc characteristics, the degree of vertical disc tilt was an independent factor defining the initial location of visual field defects (superior or inferior) (90). They suggested that the vertical disc tilt reflected an underlying asymmetric postnasal expansion of the posterior sclera around the peripapillary region (90). A larger vertical tilt may indicate an exaggerated inferior or superior scleral expansion, which may further strain the RNFL at the corresponding location (90). The hypothesis is supported by the association between increased disc ovality and increased asymmetry of RNFL thickness (91). Optic disc tilt or torsion may also lead to the formation of PPA, which could affect the visual field. Park et al. (92) showed in their cohort that 86–97% of the myopic eyes with superonasal RNFL defect or inferotemporal visual field defect had border tissue overhang at 1, 2, 11, and 12 o'clock position, representing the presence of PPA that could lead to preferential axonal damage at the location. The structural alteration also causes an asymmetrical burden of mechanical stress on different parts of the RNFL, which speeds up the progression of certain parts of the RNFL whilst sparing the staining on the opposite side. The finding was consistent with the correlation between a higher degree of horizontal disc tilt and more advanced visual field defect in myopic NTG eyes (93). Horizontal optic disc tilt might lead to a larger degree of tensile stress at the inferior or superior peripapillary scleral region, causing more prominent damage and advanced visual field defect in the superior or inferior hemifield (94).

The association between disc torsion and visual field defect has also been identified. By comparing eyes with similar optic disc tilt ratio but different disc torsional degrees in paired eyes, a greater degree of optic disc torsion was significantly associated with the presence of visual field defects (95, 96). The location of the visual field defect was also correlated with the degree of disc torsion. Park et al. (97) revealed that patients with superior visual field defect had an average inferotemporal disc torsion of 18.45°; whereas patients with inferior visual field defect had an average superonasal disc torsion of 3.81°. Thus, the direction of optic disc torsion may cause damage to the corresponding location of the nerve fiber bundle (e.g., superior torsion causes superior nerve fiber bundle damage). This is consistent with the higher proportion of eyes with superior optic disc torsion among those with inferior hemifield defect (90, 91).

Park et al. (41) also found that the torsion degree in eyes with staphyloma was significantly larger than in eyes without staphyloma. When the staphylomas involved the region of the optic disc, eyes showed longer axial length and smaller disc torsion than eyes with staphylomas involving the temporal side of optic disc (41). The location of staphyloma is consistent with the direction of disc torsion. For instance, 92.9% of eyes with inferior staphylomas had inferior disc torsion (41). Besides, 71.4% of eyes with inferior staphylomas showed superior visual field defect, while 71.4% of eyes with superior staphylomas showed inferior visual field defect (41). These results indicated that during the asymmetrical elongation of the globe, the superior or inferior expansion of the posterior sclera temporal to the optic disc might drive the optic disc torsions in different directions that lead to nerve fiber damage.

Disc tilt and torsion may play different roles in the visual field defect of NTG and POAG. Comparison of the ONH morphology of NTG eyes with axial-length-matched POAG eyes by Park et al. (24) did not show a significant difference between their degree of vertical and horizontal optic disc tilt, although NTG eyes showed a higher prevalence of superior disc tilt and torsion than POAG eyes. Moreover, while myopic NTG eyes showed a greater degree of disc torsion than non-myopic NTG eyes, there was no significant difference in the degree of disc torsion between myopic POAG and non-myopic POAG (24). In the study, the diagnosis of NTG was one of the factors associated with the degree of optic disc torsion. The authors explained that NTG eyes had a higher prevalence of change in optic disc morphology than POAG eyes because NTG eyes have thinner posterior sclera and LC than POAG eyes, rendering the former more suspectable to the changes.

6.2. Longitudinal studies

The relationship between disc tilt or torsion and visual field defect progression is controversial. Some studies did not find any significant association (98–101). Other studies suggested that the presence of disc tilt and a larger vertical disc tilt angle are protective factors against visual field progression (102, 103). Seol et al. (104) showed that patients at a mean age of 50.1 ± 11.7 years without tilted disc had a higher cumulative probability of visual field progression than patients with tilted disc. Eyes with a lower disc tilt ratio were associated with disease progression. In a group of myopic glaucoma patients at 48.3 ± 13.1 years for an average of 4.1 years, patients with visual field progression had a lesser degree of disc tilt and a higher prevalence of disc hemorrhage than patients with stable visual field (22). Besides, eyes with tilted optic disc showed a lower probability of progression than eyes without optic disc tilt (24.7 vs. 68.7%) (22).

On the contrary, an increase in disc tilt ratio was associated with visual field progression among a group of myopic glaucoma patients with a mean age of 56.2 ± 13.3 years (105). Lee et al. (75, 94) found that the presence of horizontal optic disc tilt (tilting toward the superior or inferior direction, mean age: 48.6 ± 10.8) was associated with a higher progression rate in the superior hemifield, while the presence of vertical disc tilt (tilting toward the temporal or nasal direction, age 55.9 ± 7.8 years) was associated with higher progression rate in both hemifields. Eyes with horizontal disc tilt were more likely to have peripheral visual field loss than eyes with vertical disc tilt (75, 94). Other studies suggested that visual field progression related to disc tilt could be age-dependent. Han et al. (100) showed that patients who were ≤50 years old had a higher cumulative probability of visual field progression than those >50 years old. A meta-analysis suggested that the pooled HR per 0.1 unit increase of tilt ratio and glaucoma progression was 0.988 (95% CI, 0.921–1.059). The risk decreased as the patients' mean age increased (HR for average age in 30 s, 40 s and 50 s were 1.116, 0.984, and 0.855, respectively) (89).

Despite the known correlation between optic disc torsion and the location of visual field defect, the association between disc torsion and visual field progression remains controversial. Different studies suggested that disc torsion was associated with lower risk (100, 106, 107) or higher risk (26, 108, 109) of visual field progression, although others did not find any relationship between the two (98, 102). For instance, Sung et al. (107) found that the presence of optic disc torsion with a visual field defect at the corresponding region was a protective factor against visual field progression (HR = 0.441, P = 0.016). On the contrary, Na et al. (108) found that eyes with visual field defect that corresponded to the direction of disc torsional had a faster visual field progression rate than eyes with no disc torsion or had visual field defect that did not correspond to the direction of disc torsion. They pointed out that their participants were older than those in the Sung et al.'s (107) study (57.17 ± 10.43 years vs. 37.83 ± 10.89 years), with their nerve fibers likely to be more vulnerable to damage. It was also possible that the functional loss due to RNFL defect might only reveal at an older age (108). In a Korean study myopic eyes with disc torsion greater than 15 degrees from the vertical meridian showed a faster progression rate than other myopic eyes (109), with the visual field defect limited to a single hemisphere even after 10 years of follow-up (109). Regarding the risk factor of conversion to NTG in myopic eyes, another Korean study found that a greater degree of disc torsion, rather than axial length, was significantly associated with NTG development (26). Their results indicated that the deformation of the posterior sclera is more critical than eyeball elongation for determining the development of NTG in myopic eyes. The meta-analysis of Ha et al. (89) defined "optic disc torsion" differently from the current review and their results have been previously discussed.

The "protective effect" of disc tilt could be related to the deformation of LC. The posterior peripapillary sclera and the LC are load-bearing tissues for the mechanical stress of IOP. The optic disc tilting displaces the LC and peripapillary sclera to a skewed position, such that the skewed peripapillary sclera could share some of the mechanical stress instead of being entirely taken up by the LC. Hence, the LC experiences less stress than before. The LC may also become separated from the adjacent sclera when the mechanical strain reaches a particular threshold under the combined effect of optic disc tilt and torsion, causing an LC defect. Sawada et al. (110) suggested that the greater diameter of LC defect in myopic glaucoma eye might be a protective factor against visual field progression, based on the association between LC defect and non-progression of visual field defect observed in their 7-year follow study (OR, 3.96; P = 0.002) when IOP was maintained below mid-teens. However, other studies suggested an opposite relationship (98), particularly if the IOP is elevated (111). In POAG eyes, the number of temporal LC defects was associated with the presence of paracentral scotoma, whereas the number of inferior and superior LC defects were related to visual field defects at the corresponding regions (111). The LC defect may affect the regional ganglion cells directly *via* mechanical stress by compression, extension, shearing, or impartment of nutrient delivery. The damage can be indirectly *via* damaging the supportive astrocytes and capillaries located inside the laminar beams, which are responsible for providing structural and nutritional support to the ganglion cells (98, 111). Hence, the structural damage was subsequently reflected as visual field progression.

One possible reason for the conflicting observation is that the myopization-related mechanical stress caused by the LC defect (and the consequential axonal injury) halted when myopia progression stopped in adolescence. Hence, the corresponding visual field defect may also stabilize. The axons in the LC defect are theoretically more prone to mechanical stress, axonal loss and progression of visual field defect will occur if IOP elevates up to a certain threshold value, i.e., worsen visual field defect in POAG eyes with disc torsion (111). The disease progression is less obvious when IOP is lower, i.e., a protective effect in myopia eyes with disc torsion and lower IOP (110). The characteristics of LC defects in myopic eyes may also play a role. Complete loss of the LC beam in myopic eye may mitigate IOP-induced injury (112) because the strain on the axons becomes more uniform regardless of the stretch direction. Whereas in eyes with partial loss of LC beam, the unsheathed neural tissues are strained by a stiffer beam, resulting in more localized and prominent damage of the local axonal fibers. Nonetheless, more longitudinal studies are needed to verify the hypotheses.

Several studies have also discovered the relationship between the position of DPE and the location of visual field defects. Jeon et al. (113) found that eyes with central dominant visual field defects tend to have DPE positioned more closely distributed around the optic disc. In multivariate analysis, larger disc tilt angle and smaller disc-DPE depth were related to central dominant visual field defect. The results support a previously mentioned hypothesis that the posterior scleral deformation around the optic disc may lead to its morphologic change, followed by axonal loss in myopic glaucoma eyes.

7. The implication of myopic tilted disc

Several studies have established the association between myopia and glaucoma. The Blue Mountain Study showed that the OR for high myopia and POAG association was 3.3; the OR for low myopia and POAG association was 2.3 (114). The Beaver Dam eye study also showed an increased risk of 60% for myopic eyes to have glaucoma (115). In Asian population, the Singapore Malay eye study showed that moderate to high myopia was associated with POAG (OR = 2.87) (116). In addition, longer axial length (>26 mm) was considered the most important risk factor for glaucoma development in myopic eyes (117). Myopic titled disc is the second most common morphological change of myopic eyes (31) and is present in 39% of myopic glaucoma eyes (47). Given the increasing prevalence of myopia worldwide, the accuracy of diagnosis and efficacy of treatment for glaucoma will be a significant global health concern.

7.1. The effect of myopic tilted disc on diagnosis

Apart from the pathogenic role of structural and functional deterioration, myopia tilted disc also create diagnostic challenges for ophthalmologists. Myopia is a risk factor for POAG and NTG. Early diagnosis and treatment of glaucoma can prevent disease progression and the risk of blindness. However, diagnosing glaucoma in myopic eyes is challenging especially in eyes with optic disc tilt or torsion. First, in the situation where a visual field defect is detected, it will be difficult to differentiate whether it is related to glaucoma or other structural changes of myopia (118), including myopic tilted disc, myopic maculopathy (119), and under-correction of refractive error (120). Second, it is also challenging to determine the real cup disc ratio of a tilted optic disc. Third, the distribution of RNFL and GCIPL also changes due to myopic tilted disc, leading to an increase in false positives of OCT reports. Indeed, the diagnostic capabilities of temporal RNFL thickness and vertical cup disc area measured by OCT were reduced in eyes with tilted disc compared with eyes without optic disc tilting (68). Forth, the optic disc margin of a myopic tilted disc is difficult to determine and would interfere with OCT measurements (121–123). Fifth, as myopic eyes with tilted disc are more susceptible to defocus error due to eye movements, long-term reproducibility of OCT-angiography (OCT-A) measurement of peripapillary vessel density was lower in eyes with tilted disc when compared with eyes without tilted disc (124), although the role of OCT-A currently remains as an investigative tool for research study rather than for routine examination.

There were attempts were to reduce the intersubject variability and false-positive error of OCT imaging for myopic eyes with myopic tilted disc. Chung et al. (27) discovered that for OCT imaging, the number of clock hours and the proportion of myopic eyes with thin RNFL (below 5% level) could be reduced if the scanning circle was centered based on the contour of the neural canal opening (i.e., optic disc and PPA) instead of centering the scanning circle based on optic disc. They speculated that the temporal displacement of the scanning circle could correct the nasal displacement of the scan and widen the superior and inferior peaks, thus reducing the false positive error. Resch et al. (28) rotated the RNFL measurements according to the Disc-Fovea angle but failed to reduce the intersubject variability of RNFL thickness because the positive and negative effects of compensation were balanced. Indeed, further investigations are required to overcome the problems that influence the accuracy of OCT measurement in eyes with myopic tilted disc.

Even though the deformation of the optic disc in myopic eyes has become a challenge in diagnosing glaucoma, it could have practical value. Kim et al. (125) compared the diagnostic power of the posterior scleral configuration and misaligned angle (displaced direction of ONH from the sclera). They revealed that the absolute misaligned angle and horizontal disc tilt had better performance than other parameters, with the area under the receiver operating characteristic curves of 0.696 and 0.682, respectively. They also compared the diagnostic ability of the crescent moon (CM) sign with the inferior-superior-nasal-temporal (ISNT) rule (126)–the latter described how a normal ONH should look like with inferior rim as the thickest, followed by superior, nasal, and thinners for the temporal rim. They found that the CM sign showed higher specificities (82.9–83.3%) and sensitivities (90.0–91.4%) than the ISNT rule in myopic eyes with tilted disc.

Other investigators also attempted to establish normative database for myopic eyes. Biswas et al. (127) built a Cirrus HD-OCT normative database with 180 healthy high myopic eyes' data and achieved superior specificity of detecting glaucomatous RNFL defect (63–100%) than the OCT built-in normative database (8.7–87.0%) without compromising the sensitivity. By changing the RNFL and GCIPL color code of spectral domain-OCT according to a 154 healthy myopic eyes' normative database, Seol et al. (128) significantly improved the diagnostic ability for myopic glaucoma. Application of the myopic database in NIDEK RS-3000 also achieved a higher specificity of detecting glaucoma in high myopic eyes (129). However, despite the heterogeneous morphological changes of myopic eyes, existing OCT RNFL and GCIPL myopic normative dataset label myopia as a homogenous entity without considering the heterogeneous range of axial length and disc morphology that affect the measurements.

7.2. The implication of myopic tilted disc on treatment

The diagnostic difficulties of glaucoma in eyes with myopic tilted disc also extends to the dilemma in clinical practice of whether or not to treat a glaucoma suspect with medication. This is especially true in myopic eyes with tilted disc and normal IOP, where the decision of treatment is based on the identification of glaucomatous change on a myopic tilted disc with or without visual field defect and the presence of glaucoma progression. In the presence of tilted disc, the diagnosis of myopic NTG could be equivocal in the first few clinical visits, because similar structural and functional defect could also be due to myopic tilted disc *per se*. Detecting disease progression is also challenging because of the slow progression of myopic NTG. Han et al. (100) showed that untreated myopic NTG had a slower progression rate (−0.13 dB/year) and a lower incidence of progression cases (24.8% at 60 months) than the untreated NTG patients in the Collaborative Normal Tension Glaucoma Study (progression rate of −0.39 dB/year and a 35% glaucoma progression at 60 months among the untreated NTG) (130). Indeed, longer follow-up period will be required to diagnose or observe disease progression in myopic NTG, as shown by Han et al. (100) that it took an average of 4.6 years to confirm a visual field progression. In this context, the chance of undesirably initiating treatment for patients without frank glaucoma is almost unavoidable. This unwanted overtreatment is an opportunistic cost to the health care system. It would also expose the patients to unnecessary glaucoma medication side effects (e.g., ocular surface disease and prostaglandin-associated periorbitopathy) that may negatively impact patients' quality of life without providing extra benefits.

Given the known treatment efficacy and cost-effectiveness of NTG (131, 132), initiating IOP-lowering therapy is probably justified despite the known relatively slow progression rate of NTG [progression rate of −0.36 to −0.39 dB/year for untreated NTG (130, 133, 134)]. However, the benefit of universal treatment for myopic NTG patients could be debatable. First, the progression rate is slow (−0.13 dB/year) with a low incidence of progression (24.8% at 60 months) (100); the minimal beneficial gain by treating patient with slow disease progression may not justified the potential reduction of quality of life due to medication side effects. Second, some studies have suggested that myopia does not contribute to glaucoma progression and may even act as a protective factor (100, 135–137). The "glaucomatous change" may be coincidental with myopic developmental changes at the young age (e.g., optic disc tilt and axial lengthening), which are stabilized after adolescence (89). If this debatable school of thought is true, IOP-lowering eye drops may not benefit the patients. Although there is no comment consensus of treatment, clinician should thoroughly discuss the advantage and disadvantage of treatment with the patients before making a treatment decision. It is also important to note that patients with fast disease progression is still possible among the overall slow progressor of myopic NTG patients. Therefore, careful monitoring of the condition is essential and prompt initial of treatment may be required if the condition deteriorate.

Age may influence the disease progression in glaucoma patients with myopic titled disc. Myopic NTG eyes with age $\leq$50 showed a faster progression than those with age >50 (100). Even though Bak et al. (99) indicated that older age at presentation (HR = 1.081, P = 0.004) was significantly related to glaucoma progression, their cohort consisted of young patients at a mean age of 31.3 ± 5.7 years in their progressing group. The study results suggested that younger patients could be more prone to visual field progression. Interestingly, Park et al. (138) showed that NTG and POAG patients >80 years old had faster disease progression than other age groups in myopic NTG, while the progression rates in the groups aged 40–60 and 60–80 were similar. Combining these results, patients between 30–50 years old and patients who are >80 years old may be more susceptible to visual field progression than other age groups; they should be monitored more attentively. However, other studies showed that age was unrelated to visual field progression in NTG and POAG (137, 139). Whether age should a factor to consider during management decision remains undetermined.

Since myopic tilted disc can lead to different structural changes and jeopardize the visual field, it is reasonable to avoid structural change at a younger age. Application of low-dose atropine eye drops is an effective means to prevent myopic progression and one may expect its effectiveness in preventing deformation in optic disc (140–142). However, a more extended period of longitudinal study is needed to observe the impact of early myopia treatment on the structural changes of the eyes.

8. Conclusion

Myopic tilted disc is one of the most common structural changes of myopia. It could lead to various structural and functional changes in the eye, which increases the susceptibility to axonal injury and the risk of developing serious optic neuropathy including glaucoma. Optic disc tilt and torsion tend to cause structural and functional changes differently and should be considered separately. Myopic titled disc also causes diagnostic and treatment dilemmas that could impact patients' quality of life and cost of treatment, which will be significant to the health care system due to the current surge of myopia prevalence. To date, longitudinal studies on young myopic patients with visual field defects or RNFL defects are scarce. The influence of myopic tilted disc on diagnostic parameters and the strategies for overcoming investigation errors should also be thoroughly investigated.

Author contributions

PC: conceptualization, supervision, writing, reviewing, and editing. YZ: conceptualization, literature search, draft preparation, and figures preparation. CP: supervision, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was supported in part by the General Research Fund, Research Grants Council, Hong Kong (Grant number 24107020 to PC).

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.

Publisher's note

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frontiers | Frontiers in Pediatrics

TYPE Systematic Review
PUBLISHED 16 February 2023
DOI 10.3389/fped.2023.1105186

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Pediatrics

RECEIVED 22 November 2022
ACCEPTED 17 January 2023
PUBLISHED 16 February 2023

CITATION
Weijuan Z, Zonghuan L, Qian W, Xizhi D, Bin J and Min K (2023) Sub-Tenon's bupivacaine injection is superior to placebo for pediatric strabismus surgery: A meta-analysis.
Front. Pediatr. 11:1105186.
doi: 10.3389/fped.2023.1105186

Sub-Tenon's bupivacaine injection is superior to placebo for pediatric strabismus surgery: A meta-analysis

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Background: The effect of post-operation sub-Tenon's bupivacaine injection for pediatric strabismus surgery is controversial. The objective of this meta-analysis is to compare the outcome of sub-Tenon injection of bupivacaine and placebo duringstrabismus surgery.
Methods: We searched the databases (Pubmed, Cochrane library and EMBASE) and reference lists systematically. Randomized controlled trials (RCTs) comparing sub-Tenon's bupivacaine and placebo injection for pediatric strabismus surgery were included. The methodological quality was evaluated by the Cochrane risk of bias (ROB) tool. Outcome measurements were pain score, oculocardiac reflex (OCR), additional drug consumption and related complications. RevMan 5.4 was used for the statistical analysis and graph preparation. For the outcomes that are not suitable for statistical analysis, descriptive analysis was performed.
Results: A total of 5 RCTs with 217 patients were finally identified and analyzed. Sub-Tenon's bupivacaine injection showed pain relief within 30 min after operation. But with the extension of time, the analgesic effect gradually disappeared at 1 h. It can reduce the incidence of OCR, vomiting and supplementary drug requirements. However, in terms of nausea, there is no difference between the two groups.
Conclusion: Sub-Tenon's bupivacaine injection can relieve short-term postoperative pain, reduce the incidence of OCR and vomiting, and reduce the use of supplementary drugs in strabismus surgery.

KEYWORDS
sub-Tenon's injection, bupivacaine, strabismus surgery, meta-analysis, pain

Introduction

Strabismus surgery is one of the most common ophthalmic operations in children. The cumulative incidence of strabismus at age 7 years was 2.5% in Denmark (1). During the perioperative period, strabismus surgery has an incidence of complications including oculocardiac reflex (OCR), pain and postoperative nausea and vomiting (PNAV).

The OCR is generally defined as a 20% decrease of heart rate or a new arrhythmia during ocular operation. The incidence of OCR during ophthalmic surgery ranges from 32% to 90%, and it is also frequent during strabismus surgery (2). Moreover, the OCR is often accompanied by PNAV, with an incidence of 46%–85% (3, 4). Because opioids and NSAIDs should be used with caution in children, ocular local anesthesia is often adopted as an auxiliary means of postoperative analgesia in pediatric ophthalmic surgery under general anesthesia.

In recent years, sub-Tenon's block is a widely used local anesthesia technique for ocular operations (5). Local anesthetic is injected between the Tenon capsule and sclera to anesthetize the short and long ciliary nerves (6). Children with sub-Tenon's block during retinal and cataract surgeries experience reduced postoperative pain and lower analgesic requirements. It is also reported that this technique can reduce perioperative pain and undesirable side effects during pediatric strabismus surgery (7).

In recent years, several RCTs have compared sub-Tenon's bupivacaine injection with placebo injection for strabismus surgery, but the results are not consistent. Therefore, we conducted this study to evaluate the effect of sub-Tenon's injection of bupivacaine in strabismus surgery.

Methods

The meta-analysis was conducted in accordance with PRISMA guidelines. The completed PRISMA checklist was uploaded as supplementary files (**Supplementary Table S1**).

Including and excluding criteria

The including and excluding criteria was based on PICOS principle (patient, intervention, comparison, outcome and study design). Including criteria: (i) P: pediatric patients diagnosed with strabismus; (ii) I and C: the patients were treated by surgery and sub-Tenon's bupivacaine/placebo injection were performed; (iii) O: at least one outcome (pain score, oculocardiac reflex, additional drug consumption and related complications) was (were) reported; (iv) S: only RCTs were included. No restriction of publication language was set.

The excluding criteria were as the follows: (i): the number of cases less than 10; (ii): the study included both children and adults patients simultaneously and the exact data of pediatric group could not be retrieved.

Search strategy

Databases including Pubmed, Cochrane library and Embase were systematically searched. RCTs comparing sub-Tenon's bupivacaine injection and placebo injection for pediatric strabismus surgery were included. Medical Subject Headings together with the free words/terms ("sub-Tenon's", "subtenon's", "bupivacaine", "squint" and "strabismus") were used. The reference lists were also screened and checked for additional studies. The time range of literature retrieval is from the establishment of the database to March 1, 2022.

Data extraction

The titles and abstracts were screened successively. The unrelated papers were deleted according to the including criteria. The full text of the remaining studies was obtained and checked rigorously. The two authors independently screened the literatures according to the inclusion and exclusion criteria. When there was divergence, the supervisor evaluated and made the decision.

Data were extracted from the included studies, including general information, such as first author, year of publication, country, sample size, age range of included patients, gender ratio, intervention and control measures, study design, etc. At the same time, the outcomes of the literature results were included. If the relevant outcome did not provide specific values, we calculated it from other provided relevant data. Otherwise, only descriptive analysis was made.

Methodological assessment

The two authors evaluated the quality of the included studies independently, and negotiated or consulted with the superior director to evaluate the divergence. The methodological assessment of included studies was carried out through the risk of bias (ROB) tool provided by the Cochrane Collaboration. The tool consists of seven items including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item can be judged as high risk, low risk and unclear risk according to the specific description in the included literature. If there are too many high-risk items or unclear items in the included studies, they will be regarded as low-quality studies and will be excluded or sensitivity analysis will be conducted.

Statistical analysis

RevMan 5.4 software was used for statistical analysis (8). RR and SMD were respectively used for statistical analysis of dichotomous data and continuous variable, both with 95% confidence interval (CI). The heterogeneity among the included studies was evaluated by I^2. When $I^2 > 50\%$, the heterogeneity was considered to be obvious and the random effect model was selected for analysis. Otherwise, the fixed effect model was adopted. $P < 0.05$ was considered statistically significant.

Results

Identification of relevant literature

The PRISMA flow chart was showed in **Figure 1**. A total of 25 studies were retrieved from database search and reference list check. Thirteen studies remained after the exclusion of 12 reduplicative studies. Seven studies were excluded after reviewing the title, abstract and full-text. Finally, a total of five RCTs (4, 7, 9–11) with 217 patients were included in this study.

The general information of all included studies was showed in **Table 1**. The included studies were published between 2005 and 2017. All the studies came from different countries and regions, followed by Iran, Turkey, Egypt, the United States and France. The number of included cases was 33–56, all of which were more than 10. All the cases in the study were minors under the age of 17, including 100 males and 117 females. All pediatric patients received general anesthesia. Sub-Tenon's bupivacaine injection was performed in all the study groups, and placebo or no treatment was used in the control group. Surgery was started 5 min after the

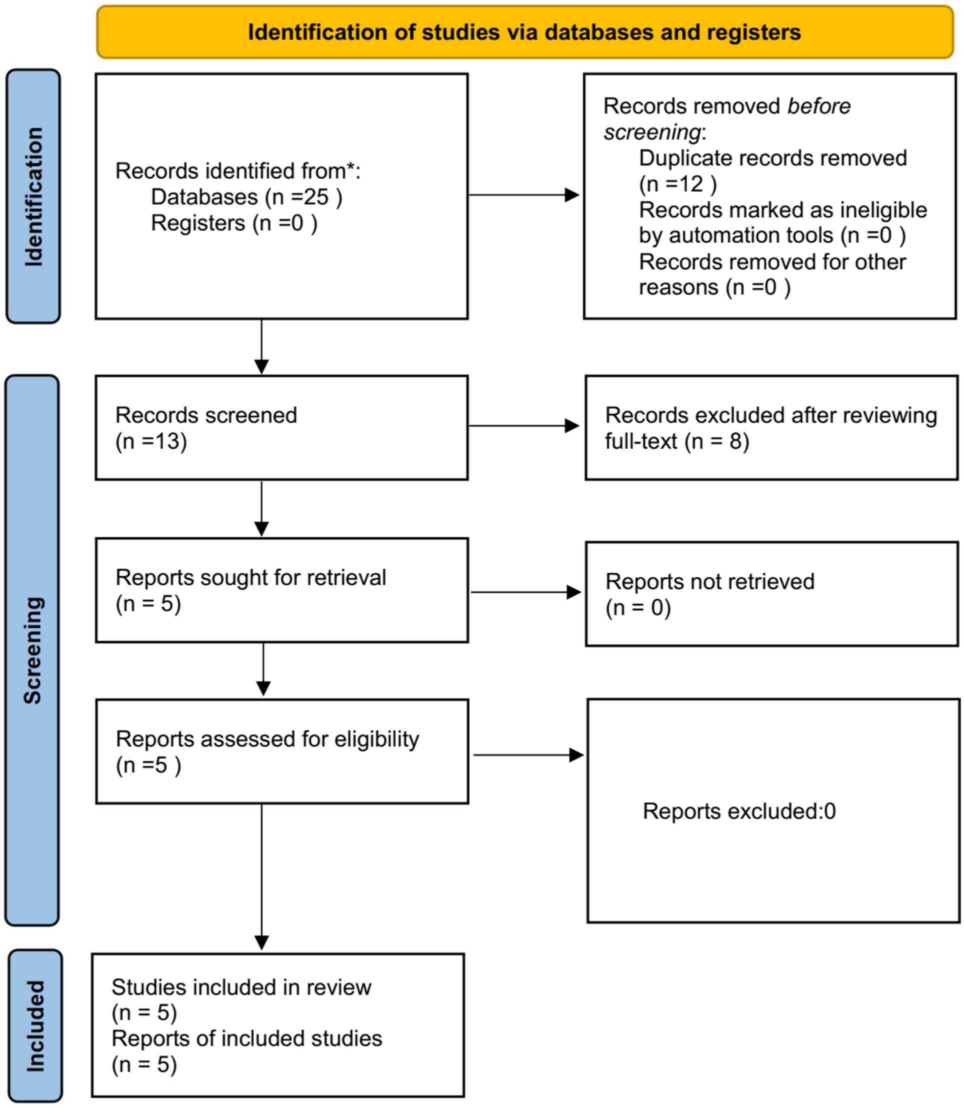

FIGURE 1
PRISMA flow chart.

TABLE 1 General characteristics of included studies.

Included study	Location	Cases	Age (years)	Sex (M/F)	Intervention	Comparison	Study design	Outcomes
Talebnejad 2017	Iran	50	12 (8–17)	24/26	Sub-Tenon's bupivacaine injection (0.1 ml, 0.5%)	Normal saline injection (0.1 ml)	RCT[†]	OCR[‡], VAS[§]
Tuzcu 2015	Turkey	40	10 (5–16)	18/22	Sub-Tenon's bupivacaine injection (0.08 ml/kg, 5%)	No treatment	RCT	OCR, Postoperative verbal rating scale, vomiting, nausea
BakR 2015	Egypt	56	3.3 (2–6)	23/33	Sub-Tenon's bupivacaine injection (0.5%, less than 2.5 mg/kg)	Placebo saline injection	RCT	OCR, pain score, nausea, vomiting
Enyedi 2017	USA	33	4.8 (1–7)	19/14	Sub-Tenon's bupivacaine (0.5 ml, 0.75%)	Balanced salt solution (0.5 ml)	RCT	CHEOPS[¶]
Steib 2005	France	38	4.4 (2.5–6)	16/22	Sub-Tenon's bupivacaine injection	Placebo saline injection	RCT	CHEOPS, OCR, PONV

[†]RCT, randomized controlled trial.
[‡]OCR, oculocardiac reflex.
[§]VAS, Visual Analog Scale.
[¶]CHEOPS, Children's Hospital of Eastern Ontario Pain Score.

sub-Tenon's injection in four studies (4, 7, 9, 10), while sub-Tenon's anesthetic was performed at the end of surgery in one (11). All included studies were RCTs.

Methodological assessment

The methodological quality of included studies was assessed by the ROB tool. As showed in Figure 2, the selection bias, including randomized sequence generation and allocation concealment, was reported and was of low risk in three studies. The blind method for the participants and staff was reported in all studies. Incomplete outcome data and selective reporting were of low risk. The rest items were unclear.

Outcome measurements

Pain evaluation was reported in five studies. Tuzcu (4) used postoperative verbal rating scale for pain assessment, and no specific value was given. Thus, data from other four studies were extracted and analyzed. The results showed that, compared with placebo, sub-Tenon's bupivacaine injection showed improvement of pain symptom immediately (Figure 3A), half an hour (Figure 3B) after the operation. However, there was no significant difference in pain score between the two groups 60 min after the operation (Figure 3C).

OCR occurrence was recorded in four studies (4, 7, 9, 10) with a total of 211 patients. The incidence of OCR in bupivacaine group was much lower than that in the placebo group (Figure 4).

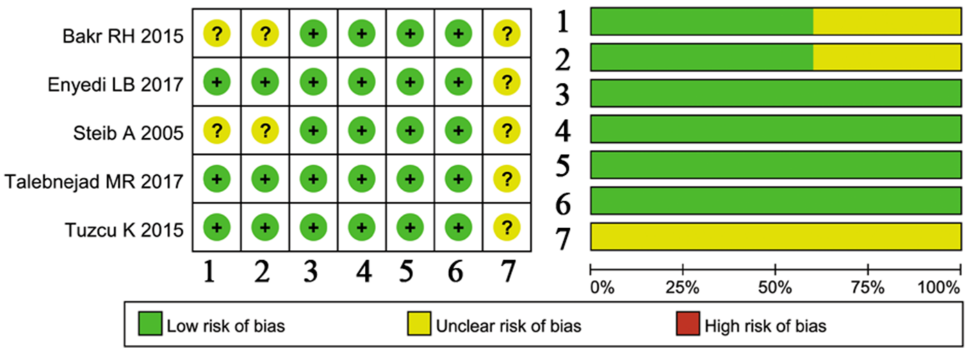

FIGURE 2
Methodological assessment of included studies by the ROB tool. 1, Random sequence generation; 2, allocation concealment; 3, blinding of participants and personnel; 4, blinding of outcome assessment; 5, incomplete outcome data; 6, selective reporting; 7, other bias.

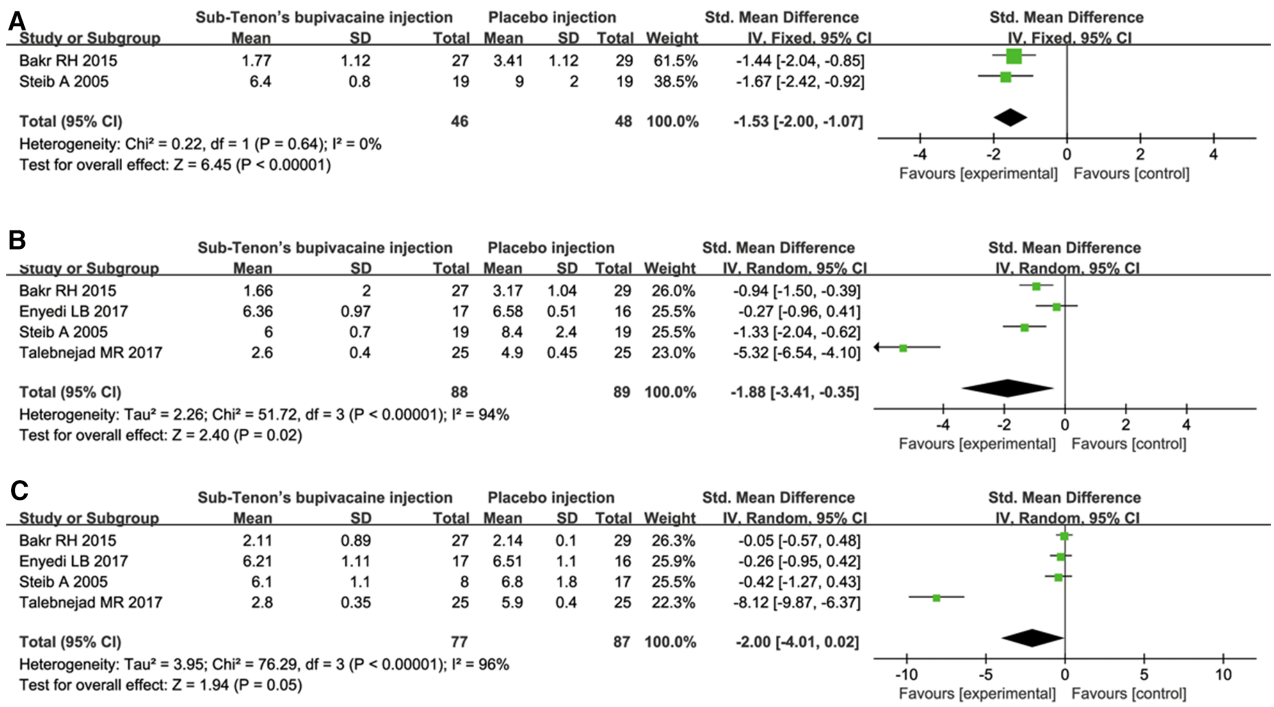

FIGURE 3
Pain evaluation comparison immediately (A), 30 min (B) and 60 min (C) after the operation.

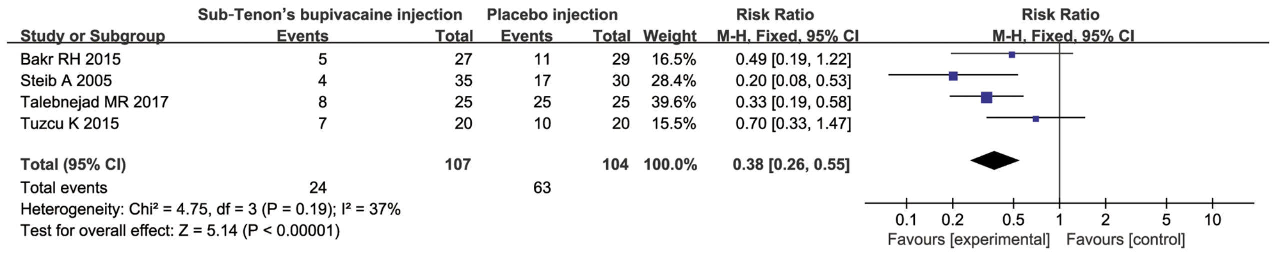

FIGURE 4
OCR occurrence comparison.

PONV was reported in four studies (4, 7, 9, 10). However, one study (11) did not report nausea and vomiting separately. Therefore, we conducted a pooled analysis of PONV, and then excluded the study and analyzed nausea and vomiting separately. The results showed a tendency of lower incidence of PONV in bupivacaine group ($P = 0.06$, Figure 5A). When analyzed separately, the incidence of vomiting was higher in the placebo group ($P = 0.007$, Figure 5B). There was no significant difference in the incidence of nausea between the two groups ($P = 0.20$, Figure 5C).

Two studies (4, 9) reported additional drug requirement. The number of patients who needed additional drugs in the bupivacaine group was significantly less than that in the placebo group ($P = 0.0005$, Figure 6).

Length stay recovery room was reported in two studies, but the timing of the reports was different. The average stay time in the recovery room of s bupivacaine group and placebo group was 95 and 145 min respectively (7). In the sub-Tenon's bupivacaine injection group, 8 of 19 cases were in the recovery room 1 h after operation, and only 3 cases at 1.5 h. In the placebo group, 15 of 19 patients were still in the recovery room for 1.5 h (7). The study by Bakr (9) reported similar results. Two hours after operation, 22 out of 29 children in the placebo group were still in the recovery room, while only 4 of the 27 children in the bupivacaine group.

Other outcomes, including chemosis (7) and heart rate deceleration (10), were reported in one study respectively. Although meta-analysis could not be carried out, the results are more favorable to the bupivacaine group.

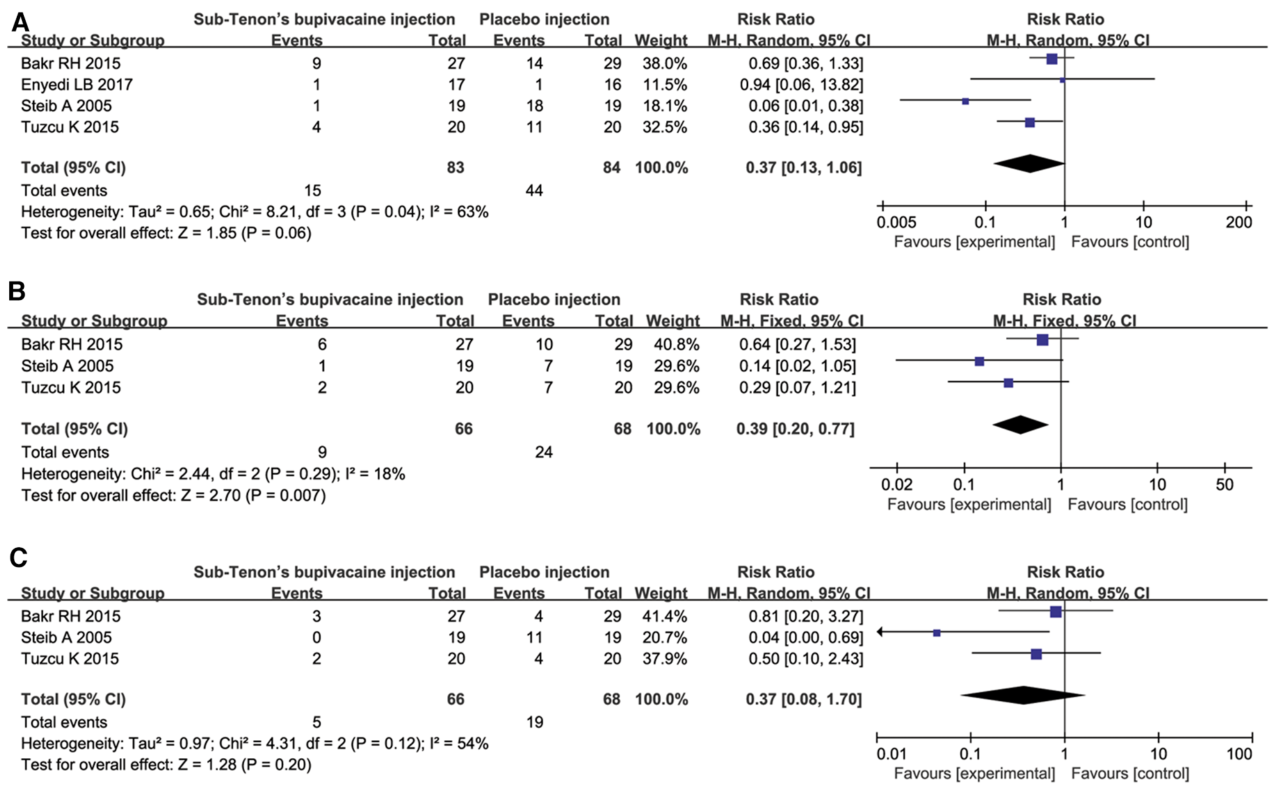

FIGURE 5
Incidence of PONV (A), vomiting (B) and nausea (C) respectively.

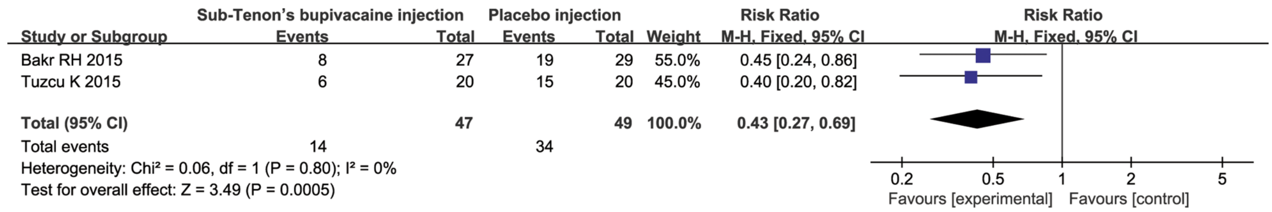

FIGURE 6
Additional drug requirement.

Discussion

Adjuvant local anesthesia has been proved to reduce postoperative pain and the incidence of OCR in pediatric ophthalmic surgery (12). The role of sub-Tenon's bupivacaine injection in cataract surgery has been confirmed (13), but its role in children strabismus surgery is still controversial. Therefore, a total of 5 RCTs and 217 patients were included and analyzed. The results showed that sub-Tenon's bupivacaine injection could reduce the short-term postoperative pain, and the analgesic effect gradually weakened with the extension of time. Meanwhile, it could reduce the incidence of OCR and vomiting, and it also had a certain effect on additional drug requirement and rapid recovery.

In this meta-analysis, all included studies were double-blind RCTs. This kind of rigorous and prospective study design can reduce the bias caused by subjective judgment and other factors, reduce the heterogeneity, and improve the credibility of the conclusion. All the studies were from different countries and regions, which minimized the bias caused by different ethnic and medical conditions.

Regional anesthesia has been proved to reduce postoperative pain and the use of postoperative analgesics. Sub-Tenon's bupivacaine injection under direct visualization is a relatively safe method of local anesthesia (4, 14), As a long-acting local anesthetic, bupivacaine can provide relatively long-term (3–3.5 h) analgesic effect (12). However, in this study, the analgesic effect was only maintained until 30 min after operation, and there was no significant difference in pain score between the two groups at 1 h after operation. On the one hand, the conclusion is more conservative because of the heterogeneity between studies, and on the other hand, it may be related to the time and dose of administration.

OCR refers to a 20% decrease in heart rate or new arrhythmia during eye muscle traction, which occurs in 90% of strabismus surgery (12). Several methods have been proposed to minimized the incidence of OCR. However, the effect of all these methods was limited. Sub-Tenon's bupivacaine injection was confirmed to be effective in reducing the incidence of OCR and PONV (7, 9, 10). However, another study by Tuzcu et al. (4) found that the incidence of OCR and PONV were less commonly for patients with sub-Tenon's bupivacaine injection, but the difference was not statistically significant. In this study, the incidence of OCR and PONV was lower in the experimental group, but there was no significant difference in PONV. When analyzing the data, we found that there was non-negligible heterogeneity of the data in the literature. Some studies only counted OCR, and some mentioned nausea/vomiting. Therefore, in order to make the study more objective and not omit important complications, we conducted statistical analysis on OCR and nausea/vomiting respectively. Interestingly, when the incidence of nausea and vomiting were analyzed separately, the incidence of vomiting in the bupivacaine group was lower, and the difference was statistically significant. Therefore, we speculate that the reason for no significant difference in PONV may be the high heterogeneity ($I^2 = 63\%$) among the included studies.

Two articles (4, 9) reported the data of additional systemic analgesia requirements, however, both articles did not report which specific drugs were used. In order to minimize the possible bias of PONV caused by opioids use, we excluded both articles in the analysis of PONV. The data of PONV in the remaining two articles (7, 11) were highly heterogeneous, and there was no significant difference using the random effect model. This suggests that the additional use of anesthetic drug may affect PONV, but it does not change the trend of this outcome. The concentration and volume of bupivacaine used in included studies were various. 0.5% bupivacaine is the most commonly used, and the volume varies from 0.1 to 3 ml. This difference is related to the different habits of deach surgeon. It needs further study to determine which concentration and volume are more appropriate.

The concentration and volume of bupivacaine used in included studies were various. 0.5% bupivacaine was the most commonly used, and the volume varied from 0.1 to 3 ml. This difference is related to the different habits of different surgeons. Which concentration and volume are more appropriate needs further study.

The sub-Tenon's bupivacaine injection has few major adverse reactions when applied to children's strabismus surgery. But there have been some sporadic reports of extraocular muscle injury, hemorrhage and globe perforation (15, 16). For children, other minor complications such as conjunctival hemorrhage, petechiae and chemosis may be more common. However, among all 217 patients included in this study, only one patient with chemosis was reported and no major complication was reported. It indicated that the technique is safe for strabismus surgery in children.

This is a secondary analysis based on published data. There are some shortcomings that should not be ignored. Firstly, Although the studies included are well-designed RCTs, there are still some heterogeneities between the studies, such as the age difference of the included patients, the choice of different pain scales and the different dosage of bupivacaine injection, which may have certain impacts on the final results. For strabismus surgery, the degree of pain and the incidence of OCR may be different with different surgical methods. However, several included literatures did not report the details of surgery, and the methodology focused on the description of anesthesia. Therefore, the clinical heterogeneity among the included studies should not be ignored. Caution is required in clinical practice of the conclusion. Secondly, the included studies focused on the pain, OCR and drug requirement in the operating room, but did not involve the operation technique, postoperative visual rehabilitation and follow-up, which need further supplement in future research. Finally, the number of cases included in this study is 217, which is not a large sample size. When the sample size is further expanded, it is not known whether the conclusion of this paper will change.

Meta analysis will exaggerate the positive research results by excluding the gray literature, leading to decision-making errors. In order to ensure that the results of meta-analysis are more comprehensive and objective, and to overcome publication bias, it is recommended to include gray literature in meta-analysis. In this study, only published studies were included, so we re-searched several commonly used gray literature websites (GreyNet International: http://www.greynet.org/, Grey Literature Report: http://www.greylit.org/, Open Grey: https://opengrey.eu/), but no literature that meets the inclusion criteria of this paper was found. Therefore, the publication bias of this article is acceptable.

Conclusion

Sub-Tenon's bupivacaine injection can relieve short-term postoperative pain, reduce the incidence of OCR and vomiting, and reduce the use of drugs in strabismus surgery.

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.

Author contributions

KM was responsible for designing the study. ZW and LZ was responsible for literature search, data extraction. WQ, DX and JB performed methodological assessment and statistical analysis. ZW draft the manuscript. KM and LZ contributed prepared the manuscript. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1105186/full#supplementary-material.

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frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 27 February 2023
DOI 10.3389/fpubh.2023.1093836

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 09 November 2022
ACCEPTED 10 February 2023
PUBLISHED 27 February 2023

CITATION
Agyekum S, Chan PP, Zhang Y, Huo Z, Yip BHK, Ip P, Tham CC, Chen LJ, Zhang XJ, Pang CP and Yam JC (2023) Cost-effectiveness analysis of myopia management: A systematic review. *Front. Public Health* 11:1093836.
doi: 10.3389/fpubh.2023.1093836

Cost-effectiveness analysis of myopia management: A systematic review

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The rising prevalence of myopia is a major global public health concern. Economic evaluation of myopia interventions is critical for maximizing the benefits of treatment and the healthcare system. This systematic review aimed to evaluate the cost-effectiveness of interventions for treating myopia. Five databases were searched – Embase, Emcare, PubMed, Web of Science, and ProQuest – from inception to July 2022 and a total of 2,099 articles were identified. After careful assessments, 6 studies met the eligibility criteria. The primary outcomes of this systematic review were costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). The secondary outcomes included utility values and net monetary benefits (NMB). One study determined the cost-effectiveness of photorefractive screening plus treatment with 0.01% atropine, 2 studies examined cost-effectiveness of corneal refractive surgery, and 3 studies evaluated cost-effectiveness of commonly used therapies for pathologic myopia. Corneal refractive surgeries included laser *in situ* keratomileusis (LASIK), femtosecond laser-assisted *in situ* keratomileusis (FS-LASIK), photorefractive keratectomy (PRK), and small-incision lenticule extraction (SMILE). Interventions for pathologic myopia included ranibizumab, conbercept, and photodynamic therapy (PDT). At an incremental cost of NZ$ 18 (95% CI 15, 20) (US$ 11) per person, photorefractive screening plus 0.01% atropine resulted in an ICER of NZ$ 1,590/QALY (US$ 1,001/QALY) (95% CI NZ$ 1,390, 1,791) for an incremental QALY of 0.0129 (95% CI 0.0127, 0.0131). The cost of refractive surgery in Europe ranged from €3,075 to €3,123 ([US$4,046 to $4,109 - adjusted to 2021 inflation). QALYs associated with these procedures were 23 (FS-LASIK) and 24 (SMILE and PRK) with utility values of 0.8 and ICERs ranging from approximately €14 (US$17)/QALY to €19 (US$23)/QALY. The ICER of LASIK was US$683/diopter gained (inflation-adjusted). The ICER of ranibizumab and PDT were £8,778 (US$12,032)/QALY and US$322,460/QALY respectively, with conbercept yielding a saving of 541,974 RMB (US$80,163)/QALY, respectively. The use of 0.01% atropine and corneal refractive surgery were cost-effective for treating myopia.

Treating pathologic myopia with ranibizumab and conbercept were more cost-effective than PDT. Prevention of myopia progression is more cost-effective than treating pathologic myopia.

KEYWORDS

myopia, cost-effectiveness analysis, cost, refractive surgery, pathological myopia

1. Introduction

Myopia is the most common ocular condition worldwide. It affected 2,620 million people (34% of the global population) in the year 2020 and is expected to affect 4,758 million people in the year 2050, or approximately half of the world's population by then (1). This is a serious health concern from a personal and societal perspective because myopia, especially high myopia, is associated with impaired vision and potentially blinding pathologies, including myopic macular degeneration (MMD), glaucoma, and retinal detachment (2). For instance, the odds ratio of developing MMD in high myopia was as high as 845 (3). Although individuals with myopia could achieve 20/20 vision with adequate refractive correction, visual impairment due to myopia reduces an individual's quality of life, limits their vocational choices (4, 5), and increases their risk of falls (6). The high prevalence of myopia also leads to profound consequences in terms of social benefits, risks, and costs (7). A recent estimate suggests that the cost of treating and preventing myopia in China is about US$10 billion annually (8).

In 2015, the global potential productivity loss due to uncorrected myopia and MMD were US$ 244 billion and US$ 6 billion, respectively (9). In Singapore, the annual direct cost of treating myopia was US$ 25 million (10) for teenagers and US$ 755 million for adults (11). These expenditures included costs of performing refractive surgery, purchasing spectacles, contact lenses, contact lens solutions, and treating myopic complications. Myopia can be corrected through optical or surgical means. Optical correction includes the use of spectacles or contact lenses. Surgical correction includes photorefractive keratectomy (PRK), transepithelial photorefractive keratectomy (T-PRK), laser epithelial keratomileusis (LASEK), epipolis laser *in situ* keratomileusis (Epi-LASIK), laser *in situ* keratomileusis (LASIK) with the flap created with either a mechanical microkeratome or femtosecond-based microkeratome (FS-LASIK), femtosecond lenticule extraction (FLEx) and small-incision lenticule extraction (SMILE). Over the years, several interventions for controlling myopia progression have been studied. These include the use of low concentration eye drops, orthokeratology, defocus modifying lenses, bifocal lenses, multifocal lenses, and increased outdoor times. Amongst these interventions, atropine was found to be the most efficacious (12).

An economic assessment of health-care interventions offers useful information for evidence-based advocacy, policy-making, and patient-care decisions (13). Given the burden on health care resources and the high prevalence of myopia, objective economic evaluation of myopia treatment is essential to maximize beneficial outcomes. The economic benefits of interventions for myopia have not yet been systematically examined. Widespread adoption of myopia interventions may be hindered by the lack of evidence on economic evaluations. This systematic review aimed to examine the cost-effectiveness of interventions for myopia and its complications. The present review examines interventions that represent the lifetime spectrum of myopia, including prevention of myopia progression, correction of refractive error, and treatment of pathologic myopia. Correction of myopia and controlling progression in children is crucial to preventing visual impairment from pathologic myopia in adulthood.

2. Methods

We conducted this systematic review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Appendix Table 1) and is registered with PROSPERO (CRD42022309196).

2.1. Eligibility criteria

The inclusion of studies was limited to full original economic evaluations (i.e., cost-effectiveness, cost-utility) of myopia interventions and were published in English. We included all economic evaluations regarding myopia with no restriction to age. We excluded publications that only evaluated costs, were reviews, reports, comments, letters, editorials, abstracts only or did not report the outcome of interest. Costs, quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) were the primary outcomes, while secondary outcomes were utility values and net monetary benefits (NMB). QALY is a summary measure used to assess the effectiveness of an intervention. QALYs are calculated using utility values, which are assessments of health-related quality of life evaluated on a scale where perfect health is valued as 1 and death as 0. The ICER is a summary measure that represents the economic value of an intervention, compared with an alternative. The NMB represents the monetary value of an intervention when a willingness to pay threshold is known (14).

2.2. Search methods

We searched five databases, including the Ovid platform (Embase and Emcare), PubMed, Web of Science, and ProQuest, from inception to July 2022. Search keywords included "cost" or "cost-effectiveness" or "economic evaluation" and "myopia" or "nearsightedness" or "shortsightedness". Additional information about the search method is provided in the Appendix 3. We modified the search terms and conducted an additional search with specific myopia progression interventions such as outdoor activity, orthokeratology lenses, contact lenses, and spectacle lenses (Appendix 3.6).

2.3. Study selection and data collection

The titles, abstracts, and full-text articles were reviewed for inclusion using data extraction forms created in Covidence. Data extracted comprised of first author, year of publication, location of study, interventions, start age, model used, time-horizon, perspective, discount rate, and outcomes. Data extracted from the included studies were analyzed using narrative synthesis.

2.4. Risk of bias assessment

The methodological quality of the included studies was assessed by the critical appraisal tool developed by Drummond et al. (15) for assessing economic evaluations. This appraisal tool consists of 10 appraisal questions covering the description of interventions, the measure of costs and outcomes, clinical effectiveness, and uncertainty (sensitivity analysis and generalizability). Study questions and objectives were clearly stated in all studies, along with comprehensive description of alternatives for which cost-effectiveness was determined. Evidence used to derive effectiveness estimates had to be clearly reported in all studies, each of which addressed uncertainties by conducting sensitivity analysis to determine the impact of varying study inputs on the results. Methodological quality of each study is summarized in Appendix 1.

3. Results

Figure 1 shows a flow chart of the study retrieval and selection procedure. In total, 2,099 articles were identified from the search strategy. Covidence was used to manage the retrieved studies and for duplicate removal. 1,856 articles remained after the removal of duplicates. After abstracts and titles screening, 1,827 articles failed to meet the inclusion criteria. Finally, a full-text review of 29 articles was conducted, and 23 were excluded because they did not measure relevant outcomes ($n = 10$), had abstracts only ($n = 6$), did not evaluate relevant interventions ($n = 3$), were not in English ($n = 2$), was a commentary ($n = 1$) or a review ($n = 1$). Overall, 6 studies met the criteria for inclusion.

The studies were conducted between the years 2002 and 2022 in Spain, the United Kingdom (UK), the United States of America (USA), China, Germany, and New Zealand (Table 1). All studies used local currencies to report their analyses. In reporting our study results, all currencies were converted into US dollars (USD) at official conversion rates as of 1st August 2022 and older costs were adjusted to 2021 inflation. Additional details of conversion rates can be found in the Appendix 4. Two studies evaluated the cost-effectiveness of refractive surgeries (17, 18), one study evaluated the use of 0.01% atropine to treat children who screened positive for myopia (16), and three studies evaluated the cost-effectiveness of treating pathological myopia (19–21). The studies reported varying

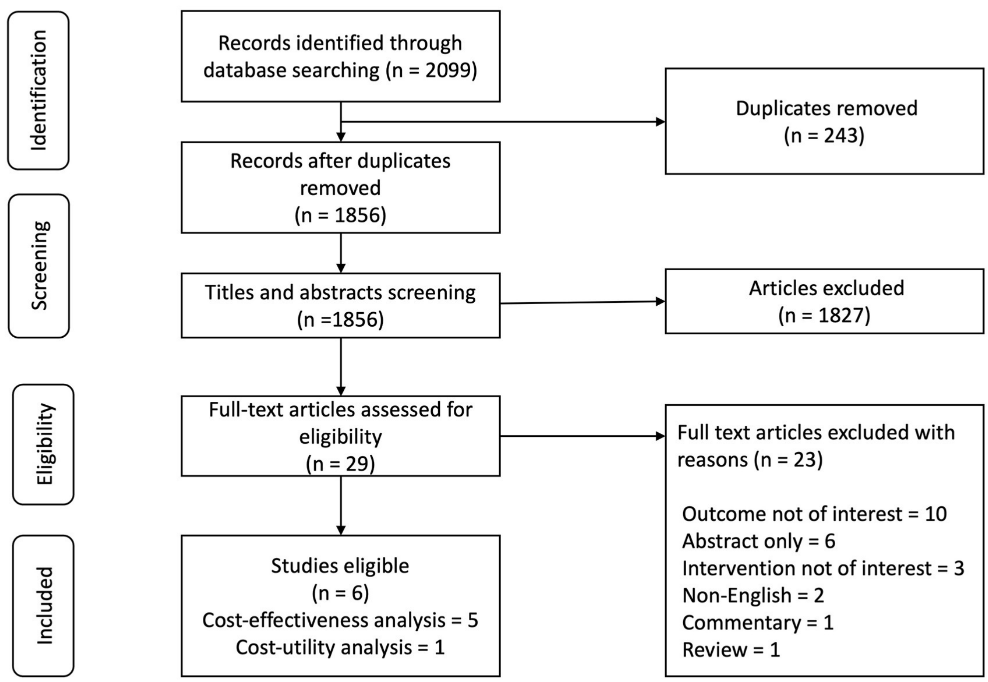

FIGURE 1
Flow chart of study retrieval and selection.

TABLE 1 Summary of included studies.

	Economic assessment	Perspective, year of costs	Country	Interventions	Start age (years)	Time-horizon (years)	Discount rate	Model	Outcomes	Study conclusions
Childhood myopia control										
Hong et al. (16)	CEA	Societal, 2021	New Zealand	Photorefractive screening plus atropine 0.01% vs. corrective lenses	11	Lifetime (80) years	3%	Markov model	Costs, Utility values, QALY, ICER	Photorefractive screening plus atropine 0.01% for 2 years is cost-effective compared to giving corrective lenses only
Myopia correction										
Balgos et al. (17)	CEA	Payer and healthcare, 2020	Spain	SMILE, vs. FS-LASIK vs. PRK	30	30	3%	Decision tree model	Costs, Utility values, QALY, ICER	SMILE, FS-LASIK and PRK are cost-effective when performed between the ages of 20 and 60 years
Lamparter et al. (18)	CEA	Healthcare and patient, NS	Germany	LASIK vs. no treatment	NS	NS	NS	NS	Costs, Utility values, QALY, ICER	LASIK is cost-effective for myopia correction
Pathologic Myopia										
Cui et al. (19)	CEA	Payer, NS	China	Conbercept vs. ranibizumab	NS	10	3.5%	Markov chain model	Costs, Utility values, QALY, ICER	Conbercept is more cost-effective than ranibizumab for pathologic myopia, from the Chinese payer's perspective
Claxton et al. (20)	CEA	Healthcare, 2011	United Kingdom (UK)	Ranibizumab vs. PDT vs. observation	55	Lifetime	3.5%	Markov model	Costs, Utility values, QALY, ICER, NMB	Ranibizumab is dominant over PDT for pathologic myopia in the UK healthcare setting and cost effective compared with observation only
Sharma and Bakal (21)	CUA	Insurer and patient, NS	USA	PDT	50	1	3%	Decision analysis model	Costs, Utility values, QALY, ICER	PDT was not cost-effective when time horizon was 1 year but cost-effective when time-horizon increased to 10 years

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; NS, not specified; LASIK, Laser *in situ* keratomileusis; FS-LASIK, femtosecond laser-assisted *in situ* keratomileusis; PRK, photorefractive keratectomy; PDT, photodynamic therapy; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

10.3389/fpubh.2023.1093836

time horizons ranging from 1 year to a lifetime. Five studies were cost-effectiveness analysis (CEA) and one study was a cost-utility analysis (CUA) (21). Study perspectives were specified as societal, healthcare, payer, patient, and insurer. One study used the societal perspective (16). The payer perspective was used in four of the studies, except one that used the healthcare perspective (20). One study each took both "healthcare and payer" (17), "healthcare and patient" (18), and "patient and insurer" (21) perspectives. Three studies used Markov model (19, 20), two studies used a decision tree model (17, 21), and one did not specify the model used (18). Outcomes reported in these studies were costs, utility values, QALYs, and ICERs, with one study also reporting the net monetary benefit (NMB) (20). The most common outcome of the cost-effectiveness summary was cost per QALY, except for one study whose outcome was cost per refractive gain unit (18). One study by Javit and Chiang (22) that examined the socioeconomic aspects of laser surgery met the inclusion criteria but was excluded because the outcome of effectiveness used was unclear (22).

3.1. Childhood myopia control and preventing myopia progression

Prevention of myopia progression is essential in children because it leads to visual impairment later in life, especially for children at high risk. Several myopia progression interventions have been studied over the years, including the use of pharmacological agents, special contact lenses, and spectacle lenses (12). To date, only one study evaluated the cost-effectiveness of childhood myopia control (16).

Hong et al. (16) determined the cost-effectiveness of a hypothetical photorefractive myopic screening program plus offering low-dose atropine (0.01%) in the New Zealand (NZ) setting (16). Based on a lifetime horizon (80 years) at a 3% discount rate and a Markov model simulation, the impact of screening plus the use of atropine compared to usual care (corrective lenses) in 11-year-old children was assessed. Costs included costs of consultation, optometry visits, corrective lenses, screening, monitoring, drugs, and low vision costs. The cost of myopia was directly related to its severity. For instance, the cost of myopia increased from NZ$ 264 (US$ 166) to NZ$ 1,923 (US$ 1,210) in pathologic myopia per year. A further progression to blindness resulted in an estimated cost of NZ$ 3,846 (US$ 2,420) per year. Utility values were specified as disability weights. A disability weight is a weight factor that reflects the relative severity of a health state, quantified on a scale from 0 (perfect health) to 1 (death). Myopia was associated with a disability weight of 0.003. At an incremental cost of NZ$ 18 (95% CI 15, 20) (US$ 11) per person, photorefractive screening plus 0.01% atropine resulted in an ICER of NZ$ 1,590/QALY (US$ 1,001/QALY) (95% CI NZ$ 1,390, 1,791) for an incremental QALY of 0.0129 (95% CI 0.0127, 0.0131). At a willingness-to-pay (WTP) threshold of NZ$ 58,000 (US$ 36,497), 0.01% atropine was cost-effective in New Zealand. According to this study, 816 cases of high myopia, 462 cases of pathological myopia, and 7 cases of blindness (for every 100,000 screened) could be prevented with the use of 0.01% atropine if all patients, who were at risk of myopia progression, accepted the treatment. To prevent 1 case of blindness, 14,286 children needed to be screened. In sensitivity analysis, it was more cost-effective to screen and treat children at an earlier age, i.e., at 5 years old rather than at 11 years old. Additionally, the intervention became more cost-effective when life expectancy increased from 80 to 95 years.

3.2. Myopia correction

Corneal refractive (keratorefractive) surgeries correct myopia by reshaping the cornea to reduce its refractive power and are alternatives to spectacles or contact lenses for optical correction of refractive errors (23). In general, these procedures can be classified into three types: corneal surface ablation surgery, corneal stromal ablation surgery, and refractive corneal lenticule extraction. Several surface ablation procedures available include photorefractive keratectomy (PRK), transepithelial photorefractive keratectomy (T-PRK), laser epithelial keratomileusis (LASEK), and epipolis laser *in situ* keratomileusis (Epi-LASIK) (24). Corneal stromal ablation surgeries (including laser *in situ* keratomileusis [LASIK] and femtosecond laser-assisted *in situ* keratomileusis [FS-LASIK]) involve the creation of corneal flap (25). Whereas, refractive corneal lenticule extraction procedures [including femtosecond lenticule extraction (FLEx) and small-incision lenticule extraction (SMILE)] do not require flap creation (26).

Two studies evaluated the cost-effectiveness of refractive surgeries. Balgos et al. (17) compared the cost-effectiveness of three corneal refractive procedures (PRK, FS-LASIK, and SMILE) for treating myopia and myopic astigmatism (17). With an annual discount rate of 3%, a decision tree model was used to project costs and outcomes associated with these procedures over a period of 30 years from the perspective of the payer (patient) and healthcare system (the eye center). From the payer's perspective, only costs directly incurred by patients were included. On the contrary, from the healthcare perspective, both direct and indirect costs incurred by the eye center were included. Direct costs included costs of consultation, screening for refractive surgery, postoperative medications, managing complications, medical equipment, and personnel. Costs associated with the procedures were high, with FS-LASIK being the most expensive. The annual costs of SMILE, PRK, and FS-LASIK were estimated at € 9,979 (US$ 10,212), € 6,868 (US$ 7,028), and € 10,314 (US$ 10,555), respectively. Over a period of 30 years, these costs were expected to increase to € 25,854 (US$ 26,456), € 22,444 (US$ 22,967), and € 25,889 (US$ 26,493), respectively. The annual cost of maintaining the operating facilities for corneal refractive surgery was € 403,000 (US$ 412,390) for SMILE, € 353,000 (US$ 361,225) for PRK, and € 403,000 (US$ 412,390) for FS-LASIK. Corneal refractive procedures improved utility values. The utility is a measure of patient-perceived quality of life associated with a health state, quantified on a scale from 0.00 (death) to 1.00 (perfect health). With a baseline average utility of 0.61 for myopic patients before undergoing refractive surgery, the weighted average utility values improved to 0.80 for patients who underwent SMILE or PRK and 0.77 for patients who underwent FS-LASIK. These utilities produced corresponded to QALYs of 24 for SMILE and PRK, and 23.1 for FS-LASIK. Hence, the ICER for SMILE, PRK, and FS-LASIK were approximately € 14 (US$ 14)/QALY, € 18 (US$ 18)/QALY, and € 15 (US$ 15)/QALY, respectively. In sensitivity analysis, the ICERs ranged from € 8 to € 19 (US$ 8–19)/QALY for SMILE, € 11 to € 31 (US$ 11 to 31)/QALY for PRK, and € 9 to € 25 (US $9 to 26)/QALY for FS-LASIK. These estimates were below the WTP thresholds specified, and the study concluded that these corneal refractive surgeries are cost-effective.

The cost-effectiveness of LASIK compared with no treatment in moderate myopia was examined by Lamparter et al. (18) from a health care service provider perspective (18). Accordingly, only direct costs were included. The discount rate, time horizon, and WTP threshold in this study were not reported. The study determined cost-effectiveness with a model that was not specified. Costs included the direct cost of LASIK treatment and treatment of surgical complications. The direct cost of primary LASIK procedure was estimated at € 2,426 (US$ 3,192) per eye. Complications associated with LASIK resulted in an additional cost of € 648 (US$ 853), increasing the total direct cost to € 3,075 (US$ 4,046). The outcome of effectiveness was refractive gain due to conventional LASIK procedures. With the aid of a meta-analysis, LASIK was reported to produce a clinical benefit of 5.93 dioptres (D) and an ICER of € 519 (US$ 683/gained refractive benefit unit. A deterministic sensitivity analysis varying costs by ± 10% and meta effects of refractive gain within 95% confidence intervals resulted in an ICER ranging from € 445 (US$ 585) per gained diopter to € 600 (US$ 789) per gained dioptre. The study concluded that LASIK was a cost-effective procedure for myopia treatment.

3.3. Treatment of myopia complications

Myopia progression can result in pathologic myopia that is characterized by extreme, continuous axial elongation and leads to degenerative alterations in the posterior segment of the eye (27). Pathologic myopia is one of the most common causes of blindness worldwide, affecting up to 3% of the world's population (28). Three studies evaluated the cost-effectiveness of treating pathologic myopia with intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) (e.g., ranibizumab, conbercept), and photodynamic therapy (PDT) (Tables 1, 2). In all three studies, pathologic myopia referred to choroidal neovascularization secondary to high myopia. The cost-effectiveness of interventions for myopia-related macular degeneration, retinal detachment, cataracts, and glaucoma were not studied despite their association with myopia (3).

Sharma and Bakal (21) investigated the cost-effectiveness of PDT for treating pathologic myopia from the patient and insurer perspectives. This cost-utility analysis was based on the case of a 50-year-old monocular patient with pathologic myopia who received PDT for subfoveal choroidal neovascular membrane over a year. At an annual discount rate of 3%, the incremental cost of PDT was estimated at US$ 1,998 (inflation-adjusted = US$ 3009), considering the cost of physician reimbursement, the cost of fluorescein angiography, and the cost of dye. Utility values based on visual acuity were used to determine QALYs. PDT yielded a QALY of 0.037 when compared to no treatment. ICER of PDT increased with an increasing number of treatments required (i.e., as the number of treatments required increased, PDT became less cost-effective). For instance, an ICER of $ 54,000 ($ 81,336)/QALY was obtained when only one treatment was required. This ICER increased to $ 214,085 ($ 322,460)/QALY for an average of 3.4 treatments of PDT and $ 246,486 ($ 371,263)/QALY when a patient required 4 treatments over the same period. These values exceeded the WTP threshold, indicating that PDT was not cost-effective. However, in sensitivity analysis, PDT became cost-effective when the time horizon was extended to 10 years, yielding an ICER of $ 20,000 ($ 30,124)/QALY.

The cost-effectiveness of ranibizumab and PDT compared with observation alone for treating myopic choroidal neovascularization (CNV) was assessed by Claxton et al. (20). Adapting a UK healthcare perspective, analysis was performed with a Markov model over a lifetime time horizon at an annual discount rate of 3.5%. Costs included costs of treatment, monitoring, management of adverse events, ophthalmologist consultations, cost of optical coherence tomography (OCT), injecting ranibizumab or performing PDT by ophthalmologist, and long-term cost of blindness. The lifetime costs of managing myopic CNV by ranibizumab [£ 12,866 (US$ 17,636)] was slightly lower than PDT [£ 14,421(US$ 19,767)] but higher than observation only [£ 8,163 (US$ 11,189)]. Health utility values were determined based on whether patients were treated in their better or worse seeing eyes. In the absence of visual impairment, this value was the same (0.85), irrespective of which eye received treatment. Utility values associated with treating the worse seeing eye were higher than treating the better seeing eye. Patients who read <25 letters had a utility of 0.353 and 0.750 when treated in their better and worse seeing eyes, respectively. Ranibizumab gained more QALYs (12.99) than PDT (12.60) and observation alone (12.45), resulting in an ICER of £ 8,778 (US$ 12,032)/QALY. Only this study reported the net monetary benefit (NMB). Ranibizumab gained a NMB of £ 9,289 (US$ 12,733) at a WTP threshold of £ 20,000 (US$ 27,414)/QALY. From a UK healthcare perspective, ranibizumab dominated PDT when compared with observation only. Hence, treating myopic CNV with ranibizumab was more cost-effective.

Cui et al. (19) adapted a real-world scenario and a randomized controlled trial (RCT) scenario to examine the cost-effectiveness of conbercept and ranibizumab for treating pathologic myopia from a payer's perspective in China. A Markov model was used for this study over a time horizon of 10 years, with a discount rate of 3.5% per year. Only direct medical costs of drugs, inspection, surgery, nursing, and treatment were included. Single conbercept and ranibizumab injections were estimated at 5,550 RMB (US$ 821) and 5,700 RMB (US$ 843), respectively. The number of injections in a year was approximately 2 times in the real-world scenario and 4 times in the RCT scenario. Over a 10-year period, the total cost of ranibizumab was 117,198 RMB (US$ 17,335) and conbercept was 106,587 RMB (US$ 15,765) in the real-world scenario. Whereas, in the RCT scenario over a 10-year period, the total cost of ranibizumab and conbercept were 238,059 RMB (US$ 35,211) and 222,648 RMB (US$ 32,932), respectively. QALYs were determined by utility values associated with best corrected visual acuities (BCVA) at different health states of pathologic myopia. Health utility values decreased from 0.7562 for patients with no visual impairment to 0.3254 for patients with blindness. Ranibizumab and

TABLE 2 Summary of outcome values from included studies.

Study	Time-horizon	Interventions	Costs	Incremental costs	Effectiveness*	Incremental effectiveness	Incremental cost-effectiveness ratios (ICERs)	Utilities	Net monetary benefits (NMB)
Childhood myopia control									
Hong et al. (16)	Lifetime (80) years	Photorefractive screening plus atropine 0.01% vs. corrective lenses	NA	NZ$ 18	NA	0.0129	1,590/QALY	NA	NA
Myopia correction									
Balgos et al. (17)	30 years	SMILE	€ 25,854	NA	24	NA	14/QALY	0.8	NA
		FS-LASIK	€ 25,889	NA	23.1	NA	15/QALY	0.77	NA
		PRK	€ 22,444	NA	24	NA	18/QALY	0.8	NA
Lamparter et al. (18)	NS	LASIK	€ 3,075	-	5.930D	-	519/dioptre gained	NA	NA
Pathologic myopia									
Cui et al. (19)	10 years	Conbercept	RMB 222,648	RMB −15,411	7.528	0.029	−541,974/QALY	+	NA
		Ranibizumab	RMB 238,059	-	7.499	NA	NA	+	NA
Claxton et al. (20)	Lifetime	Ranibizumab	£12,866	NA	12.99	NA	NA	+	NA
		PDT	£14,421	NA	12.6	NA	NA	+	NA
		Observation	£8,163	NA	12.45	NA	NA	+	NA
		Ranibizumab vs. PDT	-	£-1,555	-	0.39	Dominant	NA	£ 9,289
		Ranibizumab vs. observation	-	£4,703	-	0.54	8,778/QALY	NA	£ 6,013
Sharma and Bakal (21)	1 year	PDT (4 treatments)	-	$9,120	-	0.037	246,486/QALY	+	NA

NS, not specified; NA, not applicable; D, dioptre. *Effectiveness is measured in quality-adjusted life years (QALYs), unless specified. [+]Utility values reported were based on best corrected visual acuity.

conbercept gained 7.499 and 7.528 QALYs, respectively, in both a real world and an RCT scenario. Conbercept was found to be more cost-effective than ranibizumab for treating pathologic myopia in China. Compared with ranibizumab, the ICER of conbercept was−373,185 RMB (US-55,198)/QALY and−541,974 RMB (US-80,162)/QALY in real life and an RCT scenario, respectively.

4. Determinants for cost-effectiveness

All studies included in this systematic review conducted deterministic sensitivity analyses, which comprised of one and/or two-way sensitivity analyses. Two studies conducted only deterministic analysis (17, 18) and 4 conducted both deterministic and probabilistic sensitivity analyses (19–21).

Different scenarios that had an impact on cost-effectiveness were cost, utility gain, time-horizon, efficacy of 0.01% atropine, and the number of treatments required. 0.01% atropine became less cost-effective when its efficacy was reduced, and more cost-effective with extended time-horizon (16). Refractive surgery became more cost-effective over a longer period (i.e., when surgery was performed earlier) (17). Concerning treatments of myopic CNV (20), cost-effectiveness was greatly influenced by utility gain for the worse seeing eye, number of anti-VEGF injections, and follow-up visits. For maximum utility gain in the worse seeing eye, ranibizumab became more cost-effective than the base-case estimate compared to PDT or observation only. An increase in the number of treatments in year 2 had a more substantial impact on cost-effectiveness of ranibizumab when compared to PDT. The number of ranibizumab treatments given in year 1 was approximately 3.5 compared to 3.4 for PDT. Ranibizumab remained cost-effective when the number of treatments was assumed to be 12 compared with an average of 3.4 treatments of PDT but ceased to be cost-effective when 11 or more injections were given in year 2. Sharma and Bakal (21) demonstrated that PDT was not cost-effective regardless of the number of treatments required over a time horizon of 1 year but became cost-effective when the time horizon was increased to 10 years.

5. Discussion

In this systematic review, we analyzed the cost-effectiveness of various interventions for myopia, including prevention of myopia progression, refractive correction of myopia, and treatment of myopia complications (i.e., pathologic myopia in highly myopic patients). Myopia progression is associated with potentially blinding complications related to high myopia (2). Various interventions to control myopia progression have been studied over the years. These include the use of pharmacological agents (atropine, pirenzepine, timolol, and cyclopentolate), contact lenses (orthokeratology, soft contact lenses, rigid gas-permeable contact lenses, and peripheral defocus modifying contact lenses), spectacle lenses (single vision spectacle lenses, progressive addition spectacle lenses, prismatic bifocal spectacle lenses, peripheral defocus modifying spectacle lenses), and lifestyle modification (e.g., spending more time outdoors) (29–33). Among these options, atropine eye drops was shown to be the most efficacious treatment modality (12), and 0.05% atropine was suggested to be the optimal concentration (34).

Despite the availability of effective interventions to retard myopia progression in children, the cost-effectiveness is unknown. Pathologic myopia and blindness are associated with a high cost. For instance, Germany spent an estimated € 49.6 billion annually on blindness and moderate-to-severe visual impairment (35). The annual direct treatment cost of patients with myopic CNV was about four times higher than that of high myopia subjects without CNV (36). Identifying and treating myopic children should theoretically reduce disease severity and the risk of blinding complications. Hence, reduce the cost of treating myopic-related conditions in their adulthood. For example, screening 100,000 children and providing treatment to retard myopic progression could avoid 816 cases of high myopia, 462 cases of pathologic myopia, and 7 cases of blindness (16). Pathologic myopia incurred huge additional treatment costs; the cost increment was over 100% if myopia progressed to the pathologic state (US$ 166 to US$ 1,210) and a further 100% increment when pathologic myopia progressed to blindness (US$ 1,210 to US$ 2,420). Understanding the cost-effectiveness of preventing myopic progression and identifying a cost-effective intervention is crucial for health care policy-making and patients' quality of life.

We only identified one study [Hong et al. (16)] that demonstrated the cost-effectiveness of retarding myopia progression; by treating 11-year-old children with 0.01% atropine if they were screened positive for myopia. The approach was sensitive to the age of initiating treatment, life expectancy, and the efficacy of 0.01% atropine in reducing progression to high myopia. The intervention would be more cost-effective if treatment were started earlier, with more effective treatment, and a life expectancy increase from 80 to 95 years old. Furthermore, maximal myopia progression occurs between the age of 6 to 10 years (37); their approach of screening myopic children at the age of 11 years for intervention may not identify the highest risk group. Given the lack of CEA in the field, more CEA with different health care settings is warranted. For instance, our recent studies demonstrated that 0.05% atropine was more efficacious than 0.01% atropine (38, 39); the cost-effectiveness of the two treatments has not been compared. According to the sensitivity analysis of Hong et al. (16), we expect myopia screening and prompt initiation of a more efficacious concentration of atropine at an earlier age in high prevalence regions (e.g., using 0.05% atropine at 4 to 5 years old in East Asian countries) (29, 38, 39) will be an even more cost-effective approach. This is especially true for Asian countries known for their high and rising prevalence of myopia in children, which vaticinates the growing burden of myopia-related problems in their health care systems. For instance, the reported prevalence of myopia in Hong Kong was 25% among 6 to 8 years old children and 72.2% among adults (40). Standing as a region with one of the longest life expectancies worldwide, such a CEA based on level I evidence data will be pivotal for health care policy and formulation of treatment guidelines.

Corneal refractive surgeries (PRK, LASIK, FS-LASIK, and SMILE) were cost-effective based on the models included in this systematic review. This is consistent with the economic evaluations that showed PRK was more cost-effective than corrective lenses if the surgery was performed at an earlier age (17) and the cost of surgery and treatment failure were reduced (22). Although these procedures are cost-saving (41) with a low rate of complications (17, 42), they could lead to irreversible damage and much higher treatment costs if complications occur. The complications include infections, inflammation, light sensitivity, central islands, over or under correction, haze, dry eyes, and retinal detachment. The cost of LASIK could increase by € 648 (US$ 853) or 27% from € 2,426 (US$ US$ 3,192) with uneventful surgery to € 3,075 (US$ 4,046) if any complication occurs (18, 43). Refractive surgery is an elective procedure (44) (given the high cost and potential sight-threatening complications) and myopia is usually corrected by spectacles or contact lenses. The average cost of spectacles, soft contact lenses, and rigid lenses were € 204 (US$ 286), € 184 (US$ 258), and € 160 (US$ 224), respectively (45), compared with € 2,426 (US$ 3,192) of LASIK (18, 43). Furthermore, spectacle or contact lenses may require cleaning, replacement, or repair, which could incur additional fees. It was estimated that over a period of 30 years, the costs (direct and indirect) of LASIK, eyeglasses, and contact lenses would be € 3,792 (US$ 5,319), € 2,197 (US$ 3,082), and € 11,697(US$ 16,409), respectively (45). The drawback of correcting myopia with spectacle, contact lenses, or refractive surgery is that they do not retard myopia progression and the related complications.

Three studies (19–21) analyzed the cost-effectiveness of treating pathologic myopia with intravitreal injection of anti-VEGF (ranibizumab and conbercept) and PDT in different countries. In the UK, ranibizumab was more cost-effective than PDT when compared to observation alone (20). Ranibizumab is dominant over PDT for treating pathologic myopia because the former was more successful in visual improvement (46) and was less expensive [£ 12,866 (US$ 17,636) for ranibizumab vs. £ 14,421 (US$ 19,767) for PDT] (20). In China, ranibizumab was less cost-effective than conbercept for treating pathologic myopia from a payer's perspective. Conbercept showed significant cost-effectiveness even when the costs and the number of injections varied. Ranibizumab was about 49.6% likely to be cost-effective in China, according to the sensitivity analysis (19). The variation of economic settings and clinical practice is known to influence the results of CEA. The differences in cost-effectiveness of ranibizumab in the UK and China may be due to the differences in the economic settings of these countries. Ranibizumab, for example, costs more in the UK (US$ 17,636) than in China (US$ 17,335) (19, 20). No other study assessed the cost-effectiveness of conbercept in regions other than China because it was only approved for use in China at the time of this study. The three studies (19–21) differed in their settings and the type of comparators used, making it difficult to compare their cost-effectiveness. Nevertheless, ranibizumab and conbercept seem to be better options than PDT (19, 20), given that PDT was less cost-effective than observation alone (16, 18) and may lead to long term chorioretinal atrophy and visual loss in some patients (47, 48). Another potential anti-VEGF that has been shown to be safe and efficacious for treating pathologic myopia is aflibercept (49). However, aflibercept is reported to be the most expensive among the clinically available anti-VEGF drugs. Conbercept on the other hand is safe, efficacious, and cost-effective for treating pathologic myopia in China. No study that compared the cost-effectiveness of aflibercept with conbercept for treating pathologic myopia was identified. Further study is necessary to compare their cost-effectiveness.

Our review is the first systematic review that summarizes the cost-effectiveness of treating myopia. These studies were region-specific and not generalizable on their own. Therefore, we intended to draw them together and provide a broader view of the cost-effectiveness of treating various aspects of myopia. Notably, even though treating pathologic myopia is more expensive, preventing myopia progression and the associated complications also requires screening and treating a large number of children with atropine for an extended period of time. Having the heterogeneous studies presented side-by-side, we showed that preventing myopia progression at an early age is likely to be more cost-effective than treating pathologic myopia in adulthood. The use of 0.01% atropine for myopia progression produced an ICER of $ 1001/QALY versus between $ 12,852/QALY to $ 246,486/QALY for treating pathologic myopia (16, 20, 21). More costs are incurred as myopia progresses to pathological states and even blindness. Using 0.01% atropine to prevent myopia progression may reduce the undesirable eventualities associated with substantial additional costs (16). Furthermore, despite the lower cost-effectiveness estimation related to refractive surgery ($ 14/QALY to $ 18/QALY), 0.01% atropine appeared to be superior to refractive surgery with the lower treatment costs and the additional benefit of preventing myopia complication and blindness. Nonetheless, formal evaluation is necessary to confirm the cost-effectiveness of early myopia prevention

The systemic review has some limitations. First, there were a limited number of studies, with two (15, 16) reporting data from approximately 20 years ago. The lack of studies included in our review according to our selection criteria, coupled with the changing value of money and the health care environment, highlight the need for more CEA to evaluate myopia control. Second, the results of the studies in this review were heterogeneous. However, the interventions and the targeted patients' group represent the lifetime spectrum of the "myopia continuum"; drawing a relationship between these results provides insight into the future research direction and management approach in the field of myopia. Third, the data presented in our study were region-specific and not generalizable. These studies were conducted in different regions with varying economic environments and had different comparators, making it difficult to compare their results. In addition, since most studies were conducted in developed countries, the applicability of the result in low-income countries requires further investigation. Lastly, although corneal refractive surgeries are cost-effective, the most cost-effective approach still remains unknown. The only study that compared SMILE, PRK, and FS-LASIK could not perform a statistical analysis between the cost-effectiveness values, hence no conclusion on the better surgical approach could be made. Although LASIK is cost-effective, it remains unclear, however, the WTP threshold and the time period over which the analysis was conducted.

6. Conclusion

In conclusion, low concentration atropine (0.01%) and corneal refractive surgery are cost-effective options for treating myopia.

Ranibizumab and conbercept are cost-effective for treating pathologic myopia. 0.05% atropine can effectively slow or halt myopia progression in children with acceptable side effects and potentially reduce the cost of treating myopia complications in adulthood. Currently, there is a limited number of economic evaluations for the treatment of myopia; the cost-effectiveness of early interventions to prevent myopia progression in children is unknown. With the rising prevalence of children with myopia, a comprehensive cost-effectiveness analysis for the topic is necessary.

Author contributions

SA: conception of the study, study screening, drafting of the manuscript, and final approval. PC: conception of the study, study screening, co-supervised the work, drafting of the manuscript, and final approval. YZ, ZH, BY, PI, CT, and LC: critical review of manuscript and final approval. XZ: critical review of manuscript, co-supervised the work, and final approval. CP: conception of the study, critical review of manuscript, drafting of the manuscript, and final approval. JY: conception of the study, critical review of manuscript, supervised the work, and final approval. All authors contributed to the article and approved the submitted version.

Funding

Supported in part by the General Research Fund, Research Grants Council, Hong Kong (14111515 [JY]), the Direct Grants of the Chinese University of Hong Kong (4054197 [CP], 4054193 [LC], and 4054121 and 4054199 [JY]), the UBS Optimus Foundation Grant 8984 (JY), National Natural Science Foundation of China 82171089 (JY), and the CUHK Jockey Club Children Eye Care Programme.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1093836/full#supplementary-material

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TYPE Systematic Review
PUBLISHED 10 March 2023
DOI 10.3389/fpubh.2023.1053206

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 25 September 2022
ACCEPTED 16 February 2023
PUBLISHED 10 March 2023

CITATION
Wu L, Feng J and Zhang M (2023) Implementing interventions to promote spectacle wearing among children with refractive errors: A systematic review and meta-analysis. *Front. Public Health* 11:1053206. doi: 10.3389/fpubh.2023.1053206

Implementing interventions to promote spectacle wearing among children with refractive errors: A systematic review and meta-analysis

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Purpose: To investigate the level of compliance of children with refractive errors who are provided free spectacles, and to identify the reasons for non-compliance.

Methods: We systematically searched the PubMed, EMBASE, CINAHL, Web of Science, and Cochrane Library databases from the time these databases were established to April 2022, including studies published in English. The search terms were "randomized controlled trial" [Publication Type] OR "randomized" [Title/Abstract], OR "placebo" [Title/Abstract]) AND (("Refractive Errors"[MeSH Terms] OR ("error refractive" [Title/Abstract] OR "errors refractive" [Title/Abstract] OR "refractive error" [Title/Abstract] OR "refractive disorders" [Title/Abstract] OR "disorder refractive" [Title/Abstract] OR "disorders refractive" [Title/Abstract] OR "refractive disorder" [Title/Abstract] OR "Ametropia" [Title/Abstract] OR "Ametropias" [Title/Abstract])) AND ("Eyeglasses" [MeSH Terms] OR ("Spectacles" [Title/Abstract] OR "Glasses"[Title/Abstract]) AND ("Adolescent" [MeSH Terms] OR ("Adolescents" [Title/Abstract] OR "Adolescence"[Title/Abstract]) OR "Child"[MeSH Terms] OR "Children"[Title/Abstract])). We only selected studies that were randomized controlled trials. Two researchers independently searched the databases, and 64 articles were retrieved after the initial screening. Two reviewers independently assessed the quality of the collected data.

Results: Fourteen articles were eligible for inclusion, and 11 studies were included in the meta-analysis. The overall compliance with spectacle use was 53.11%. There was a statistically significant effect of free spectacles on compliance among children (OR = 2.45; 95% CI = 1.39–4.30). In the subgroup analysis, longer follow-up time was associated with significantly lower reported ORs (6–12 vs. <6 months, OR = 2.30 vs. 3.18). Most studies concluded that sociomorphic factors, RE severity, and other factors contributed to children not wearing glasses at the end of the follow-up.

Conclusion: The combination of providing free spectacles along with educational interventions can lead to high levels of compliance among the study participants. Based on this study's findings, we recommend implementing policies that integrate the provision of free spectacles with educational interventions and other measures. In addition, a combination of additional health promotion strategies may be needed to improve the acceptability of refractive services and to encourage the consistent use of eyewear.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=338507, identifier: CRD42022338507.

KEYWORDS

spectacle, refractive error, compliance, children, meta-analysis

1. Introduction

In 2020, 157 million people worldwide were affected by uncorrected refractive errors, which have become the primary cause of moderate or severe vision impairment on a global scale (1). In particular, the prevalence of myopia and high myopia is predicted to affect five and one billion people, respectively, by 2025 (2). Refractive error is increasingly regarded as a serious global public health problem. Although it can be safely and affordably corrected using precise spectacles, a high proportion of children exhibited low compliance with spectacle wear. Therefore, it is imperative to implement interventions to increase the rate of compliance with spectacle wear among affected children.

A meta-analysis of the economic costs of the global burden of myopia showed that the potential loss of productivity due to uncorrected myopia is substantially greater than the cost of correcting myopia (3). Providing spectacles to all individuals with a significant refractive error has been recommended by the World Health Organization's VISION 2020 targets to control blindness in children (4). One study reported that the number of individuals wearing spectacles was two-fold higher in the group that received spectacles free of charge than in the group that did not receive free spectacles (5). However, recent studies found that receiving free spectacles did not effectively improve compliance among the study participants (6–10). Although cross-sectional studies were conducted to analyze the effect of free spectacles on children's compliance with spectacle wear and the overall compliance of spectacle use in a recent meta-analysis of data from 20 studies was considerably low at 40.14% (11) in 2018, to date, no RCT studies on the effect of providing free spectacles on children's compliance with spectacle use have been conducted. Given the stronger causal association of RCT studies, to better address the inconsistencies in the literature as well as to assess the effect of the provision of free spectacles on improving children's compliance, we conducted this systematic review and meta-analysis based on recently published randomized controlled trials. In addition, some of the reasons why children with refractive errors do not wear spectacles require further research owing to our observation that spectacle ownership among migrant children requiring eyeglasses in cities in eastern China may be lower than that of local children (12), and we conducted a more comprehensive analysis of the reasons.

2. Method

The study protocol was registered in PROSPERO, ID: CRD42022338507.

2.1. Search methods

Two authors searched PubMed, CINAHL, Cochrane Library, EMBASE, and Web of Science databases (from inception to 9 April 2022) using the MeSH search strategy, including subject headings and free text terms relevant to refraction error, spectacles, and children (or adolescents). The search terms were "randomized controlled trial" [Publication Type] OR "randomized" [Title/Abstract], OR "placebo" [Title/Abstract]) AND (("Refractive Errors" [MeSH Terms] OR ("error refractive" [Title/Abstract] OR "errors refractive" [Title/Abstract] OR "refractive error" [Title/Abstract] OR "refractive disorders" [Title/Abstract] OR "disorder refractive" [Title/Abstract] OR "disorders refractive" [Title/Abstract] OR "refractive disorder" [Title/Abstract] OR "Ametropia" [Title/Abstract] OR "Ametropias" [Title/Abstract])) AND ("Eyeglasses" [MeSH Terms] OR ("Spectacles" Title/Abstract] OR "Glasses" [Title/Abstract]) AND ("Adolescent" [MeSH Terms] OR ("Adolescents" [Title/Abstract] OR "Adolescence" [Title/Abstract]) OR "Child"[MeSH Terms] OR "Children"[Title/Abstract])). We included studies that were published in English. We also performed forward citation tracking and reference list screening for eligible studies. The titles and abstracts of articles were screened by two authors based on the inclusion and exclusion criteria. Subsequently, we screened the full text and extracted data. Any disagreement was resolved by discussion until a consensus was reached or, if necessary, a third author was consulted.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) randomized controlled trials designed for children with refractive errors including myopia, hypermetropia and astigmatism; (b) interventions to provide free spectacles; (c) age limit being children (i.e., individuals <18 years old); and (d) outcome of self-reported or observed spectacle wearing.

The exclusion criteria were as follows: (a) review or meta-analysis, abstract, letter, comment, conference or case report; (b) republished literature; (c) research published in other language than English. (d) studies that had missing raw data or errors; and (e) studies that involved other interventions beyond free spectacles (such as the provision of custom glasses, contact lenses, and keratoplasty lenses).

2.3. Data extraction and analysis

Two authors extracted the following data: the first author's name, year of publication, country or area where the study was conducted, inclusion and exclusion criteria, sample size, age of the participants, intervention and control details, duration of follow-up outcomes assessed, and the number and percentage of the compliant and non-compliant participants. After the extraction process, all related data were entered into Microsoft Excel for compilation. Two reviewers conducted quality assessments independently. We assessed publication bias using Egger's test and asymmetric funnel plots and then used Trim-and-Fill analysis to adjust the OR (95% CI) to determine if publication bias existed. Sensitivity analyses were also performed to calculate pooled estimates for the remaining studies by removing one study at a time to determine whether the result depended on a particular study. Heterogeneity tests and statistical analyses were performed using Revman 5.3. A forest plot was used to generate a pooled compliance estimate for children's spectacle use. A subgroup analysis was conducted, which distinguished between studies

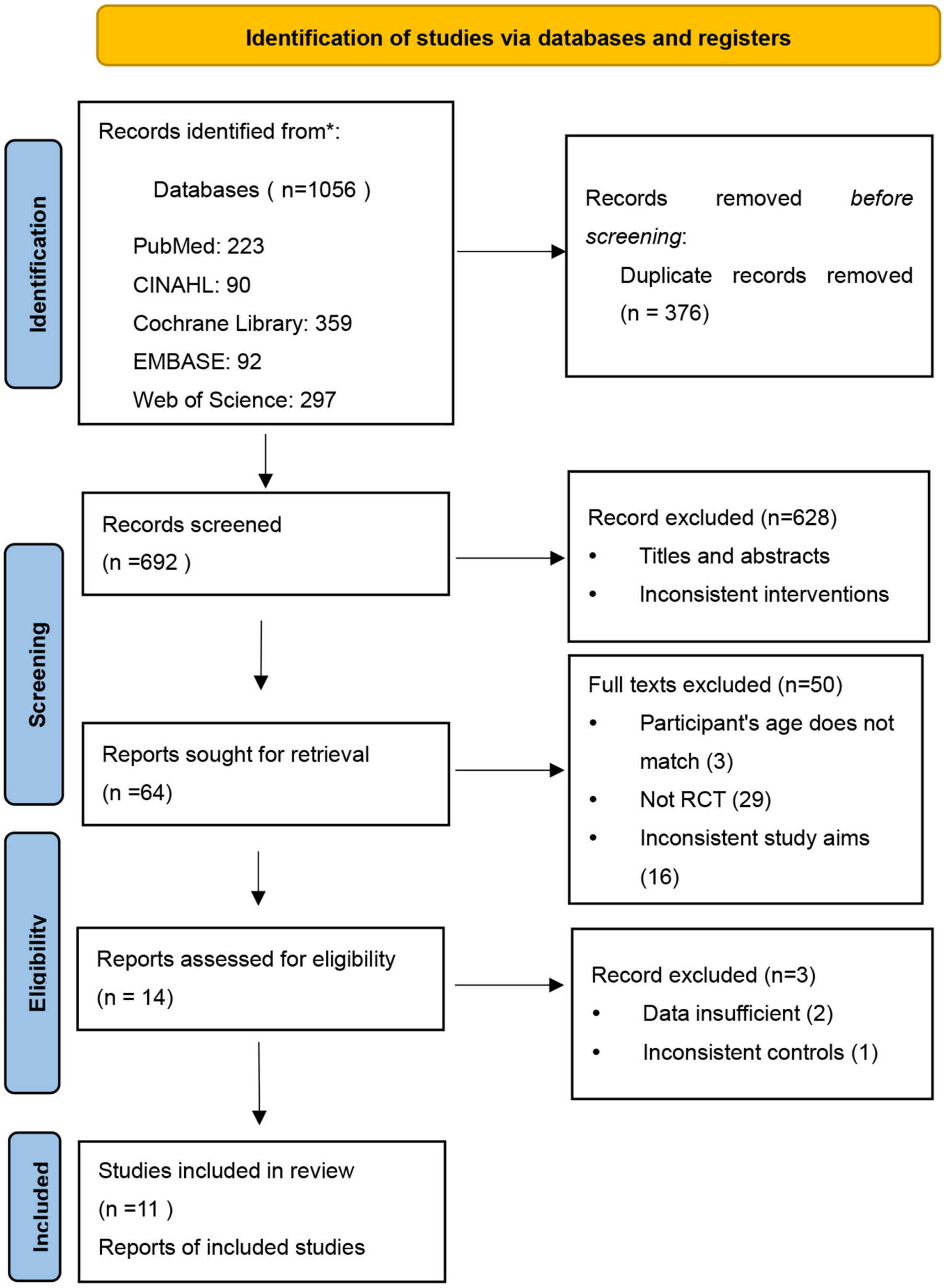

FIGURE 1
A flow diagram of the studies included in the review.

based on the duration of the follow-up and the mean age of the participants.

2.4. Synthesis

We conducted a meta-analysis for outcomes where more than one study assessed the same outcome for a similar intervention and narrative syntheses of other outcomes and studies.

3. Results

3.1. Study characteristics

A total of 1,056 articles were retrieved, of which 64 met the study criteria for inclusion (Figure 1). After constructing the full text, we finally included 14 studies for the review (Table 1). Nevertheless, three studies did not have enough data to pool the estimates of children's compliance with spectacle use, but descriptive data from these studies were still included in the review.

TABLE 1 Characteristics of selected studies included in the systematic review ($N = 14$).

NO.	Study	Country	Age (years)	Intervention	Control	Definition of compliance	Compliance measure	Follow-up years	Sample size	No. compliant (%)
1	Ethan et al. (24)	America	None	Free spectacle and teacher incentive	Spectacles only at the end of the study	Wearing	Direct observation in the classroom	None	Treatment group: 121 Control group: 127	41 (33.88%)
2	Du et al. (19)	China	10.46 ± 1.08	Free spectacle	Spectacle voucher	Wearing	Unannounced visits	7	Treatment group: 1,055 Control group: 771	439 (41.6%)
3	Thapa et al. (16)	Nepal	13 ± 4	Free spectacle	Eye screening only	Wearing	Unannounced visits	6	Treatment group: 109 Control group: 145	62 (57%)
4	Holguin et al. (6)	Mexico	10.4 ± 2.6	Free spectacle	None	Wearing	Direct inspection	18	Treatment group: 493 Control group: None	66 (13.9%)
5	Yi et al. (17)	China	10.9	Free spectacle, education on their use, and teacher incentive	Spectacle prescriptions only	Wearing	Unannounced visits and children self-reported	6	Treatment group: 341 Control group: 352	233 (68.3%)
6	Guan et al. (20)	China	10.53	A voucher that can be redeemed for free spectacles	Spectacle prescriptions only	Wearing	unannounced visits	7	Treatment group: 971 Control group: 1,018	825 (85%)
7	Nie et al. (22)	China	13.56 ± 1.14	Free spectacles	Spectacles only at the end of the study	Wearing	Children self-reported	3	Treatment group: 476 Control group: 434	343 (72%)
8	Keay et al. (13)	China	14.1 ± 0.9	Free spectacles	None	Wearing	Unannounced visit	1	Treatment group: 415 Control group: NONE	193 (46.5%)
9	Wedner et al. (15)	Tanzania	14.4	Free spectacles	Spectacle prescriptions only	Wearing	Unannounced visit	3	Treatment group: 58 Control group: 50	27 (46.55%)
10	Wang et al. (18)	China	10.6 ± 1.0	A: Free spectacles	Spectacle prescriptions only	Spectacle purchase and wearing	Unannounced visits and children self-reported	6	Treatment group: 252	80 (31.75%)

(Continued)

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TABLE 1 (Continued)

NO.	Study	Country	Age (years)	Intervention	Control	Definition of compliance	Compliance measure	Follow-up years	Sample size	No. compliant (%)
				B: Free spectacles + offer of $15 Upgrade spectacles C: Free spectacles + offer of $30 Upgrade spectacles					Control group: 250	
11	Ma et al. (5)	China	10.5 ± 1.1	Vouchers for free spectacles at a local facility, or free spectacles provided in class	Spectacle prescriptions only	Wearing	Unannounced direct examinations	8	Treatment group: 1,104 Control group: 1,033	453 (41.03%)
12	Ma et al. (21)	China	13.56	Free spectacles	Spectacle prescriptions only	Wearing	Unannounced visit	9	Treatment group: 476 Control group: 434	209 (43.91%)
13	Ma et al. (23)	China	10–12	Early referral to the vision center for refraction and free spectacles	Late referral for the identical intervention	Wearing	Children self-reported	6	Treatment group: 1,461 Control group: 1,252	806 (55.17%)
14	Ma et al. (14)	China	None	Free vision care and glasses	Spectacles only at the end of the study	Eyeglasses ownership and wearing	Children self-reported	3	Treatment group: 433 Control group: 516	347 (80.14%)

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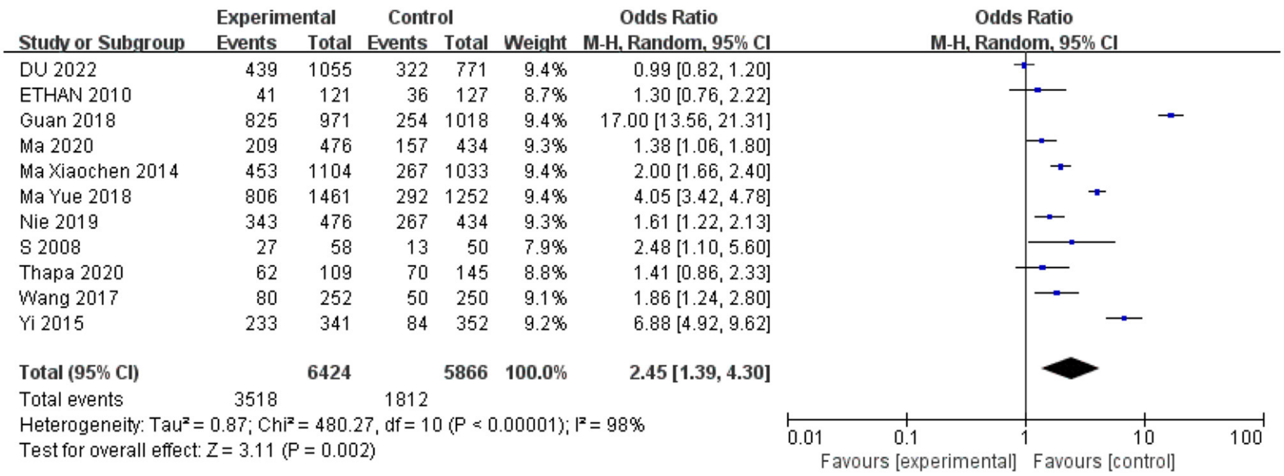

FIGURE 2
Random-effect meta-analyses of the spectacle-wear compliance ($N = 11$).

All of the studies included in this review were RCTs. All the data analyzed were based on previously published studies that received ethical approval and patient consent. Two studies were excluded from the meta-analysis because the data were insufficient (6, 13), and one study was excluded because the measures of the control group were inconsistent (14).

The 14 selected articles were conducted in five countries, and 67% were conducted in China. Sample sizes ranged from 108 to 2,713 (total $N = 14{,}147$ participants who were randomized, and $N = 12{,}290$ who contributed data to the synthesis). The overall compliance with spectacle use was 53.11% ($n = 4{,}124/7{,}765$). The age inclusion criteria ranged from 5 to 18 years (grades ranged from 1 to 8). The duration of follow-up visits ranged from 1 to 18 months. The differences in age and duration of follow-up may have contributed to the greater heterogeneity of the studies.

Children in the intervention group received free spectacles, and these children were considered compliant if they continued wearing spectacles at the end of the follow-up. Compliance was measured by experimenter observation or children's self-report. Of the included studies, nine assessed unannounced observed spectacle wear as their primary outcome (5, 13, 15–21), while three studies were conducted to collect children's self-reported wearing data as their primary outcome (14, 22, 23).

3.2. Spectacle compliance

A total of 11 studies reported the number of children compliant with spectacle wear and were included in the meta-analysis. Since the heterogeneity was significant ($I^2 > 50\%$, $P < 0.5$), the random effects model was used for the analysis. The two methods of providing only a prescription (5, 10, 15, 22) or a prescription and a letter to the parents (5, 17, 18, 20, 21, 25) had lower compliance than the measure of providing free eyeglasses. There was statistical significance in the effect of the receipt of free spectacles on children's compliance with wearing spectacles (odds ratio = 2.45; 95%CI = 1.39–4.30; Figure 2).

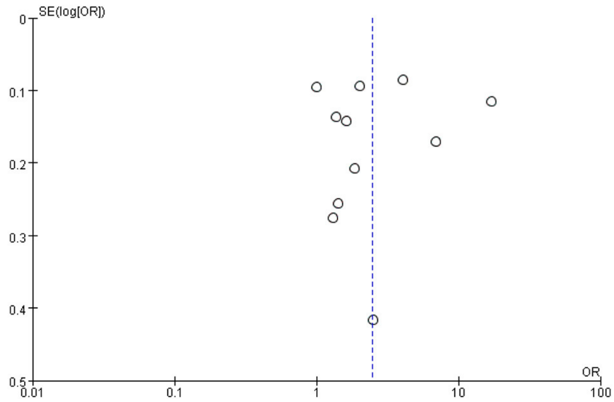

FIGURE 3
A funnel plot for the sensitivity analysis.

3.3. Sensitivity analysis

The results of the sensitivity analyses are presented in Figure 3. The odds ratio (OR) values were similar while excluding any study, and the P-values were all <0.05. There was no significant difference in the I^2 values while excluding any individual study. The Galbraith plot (Supplementary Figure 1) showed that there was significant heterogeneity among the studies. The heterogeneity could be attributed to the large age difference in the included samples and the different follow-up times.

3.4. Risk of bias

The risk of bias in the studies was assessed by one author using the Cochrane Risk of Bias Tool. Of the 11 articles, most (90%) reported a moderate to low risk of bias in Figure 4.

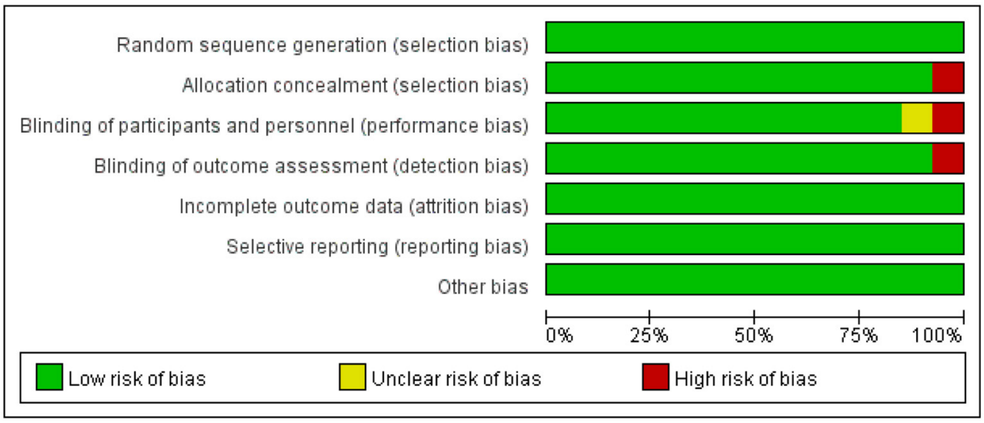

FIGURE 4
Risk of bias graph for included studies.

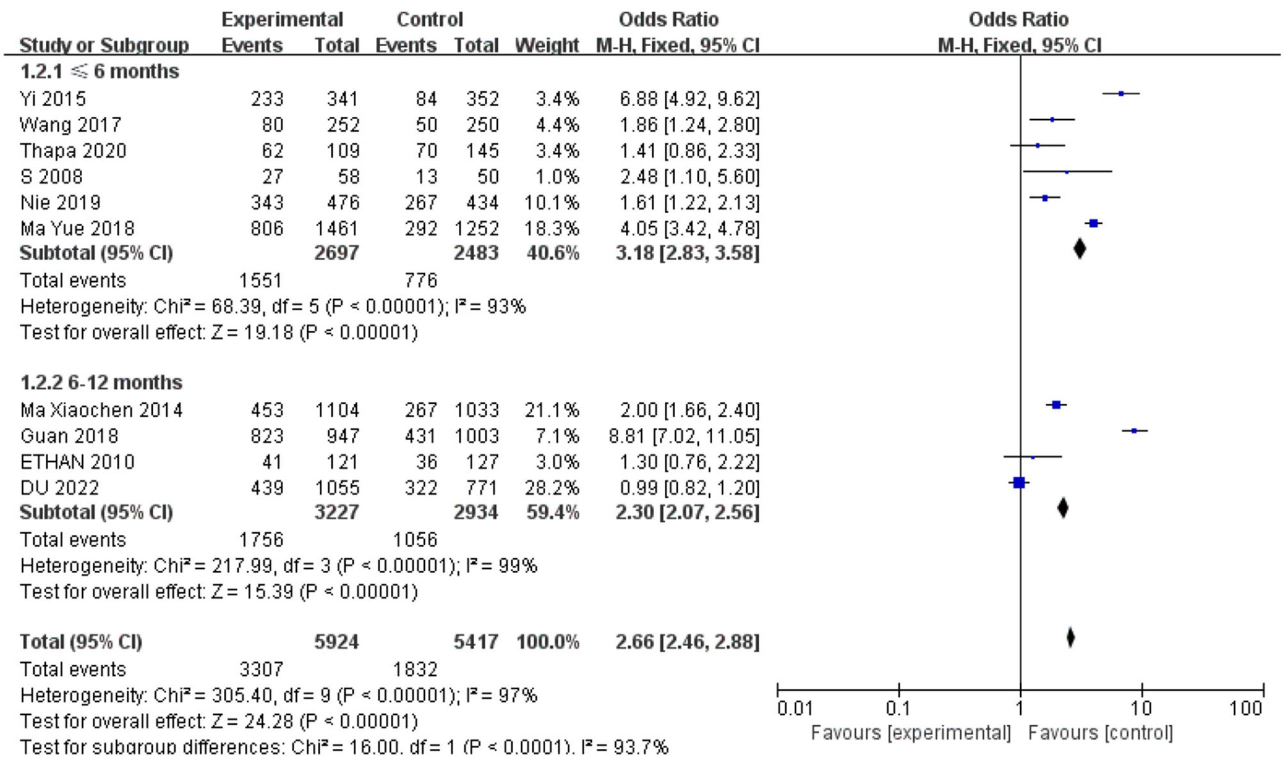

FIGURE 5
A subgroup analysis of included studies for follow-up time.

3.5. Subgroup analysis

In the subgroup analysis, 6–12 months of follow-up time was associated with a significantly smaller OR value (OR = 2.30, 95% CI: 2.07–2.56) compared to <6 months of follow-up time for studies (OR = 3.18, 95%CI: 2.83–3.58) evaluating associations between receipt of free spectacles and affected children's compliance with spectacle use in Figure 5.

In the subgroup analysis of participants' age, we found a smaller OR value (OR = 0.10, 95% CI: 0.06–0.14) in the Figure 6 in which the mean age of participants was over 12 years old compared with the subgroup in which their mean age was ≤12 years old (RR: 0.27, 95% CI: 0.08–0.46).

3.6. Factors associated with spectacle wear

Seven studies identified the factors contributing to children's use of spectacles at the end of follow-up after receiving free spectacles (6, 13, 17–20, 22). These included sociodemographic

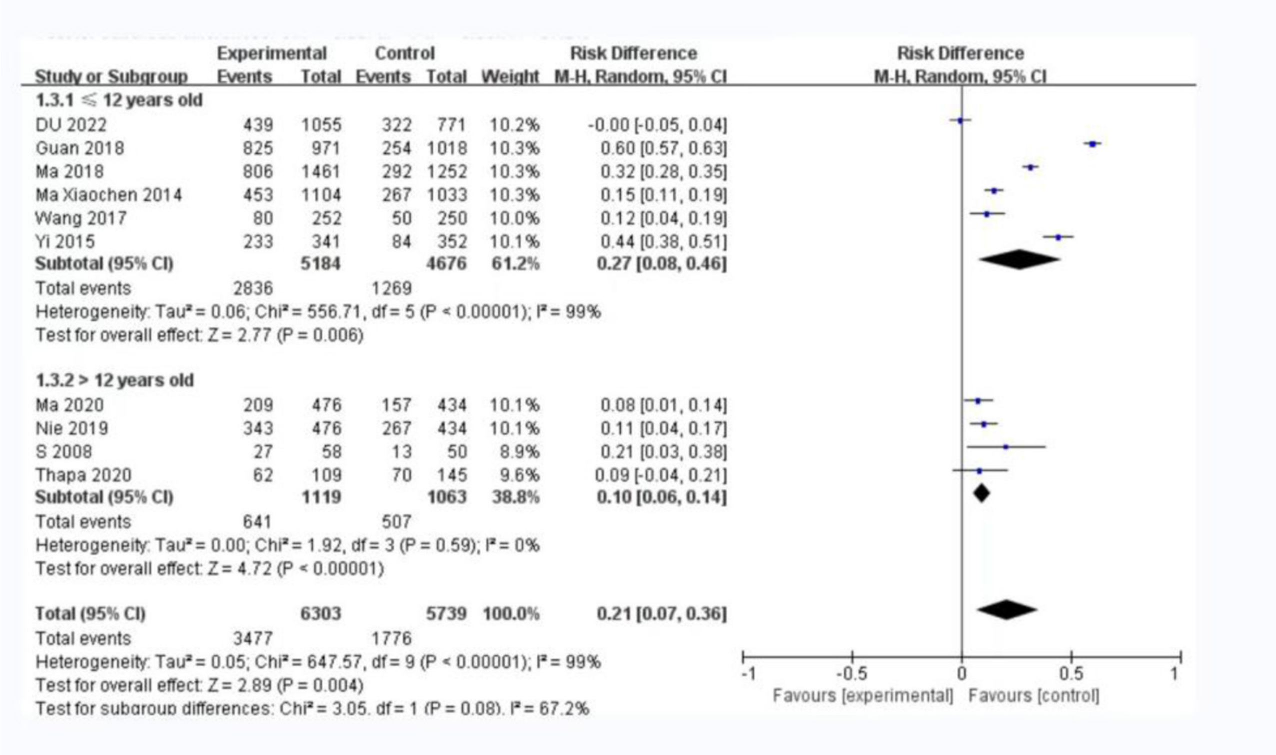

FIGURE 6
A subgroup analysis of the mean age of the participants.

factors, the severity of the refractive error, and other factors in Table 2.

Sociodemographic factors include children's age (or grade), sex, family income, urban vs. rural residence, and whether they were left behind, but this was not consistent with the findings of the studies. Holguin et al. (6) reported that older and urban-dwelling children were more likely not to wear spectacles, while Du et al. (19) concluded that older children were more compliant with free spectacles. Keay et al. reported that children from low-income families were more likely to wear spectacles. In the study by Guan et al. (20), left-behind children were more likely to wear spectacles than children who were not left behind.

Other factors that influenced compliance were whether children were in their seats to see the blackboard clearly and the attitude of their parents. Children who could not see the blackboard had higher compliance (19). In two studies including a teacher motivation incentive in addition to free spectacles in the treatment group (17, 23), the reported rate of wearing spectacles was 55.2 and 68.3%. Children's baseline spectacle wear largely determined whether they wore them during follow-up (17, 18). Children with higher levels of refractive error were more likely to wear spectacles than children with lower refractive errors (6, 17–19). Children might be concerned about their appearance and being teased by their classmates (26). The appearance of spectacles was a factor in the acceptance of spectacles by children (13). However, in studies where children were allowed to choose their own frames, fewer than half of the children were found to wear spectacles (13, 24).

4. Discussion

This systematic review included 14 RCTs that evaluated interventions that demonstrated that providing free spectacles can increase the use of children's spectacles. Some of these RCTs reported that fewer than half of the children wore their spectacles at the follow-up time, even when they were provided for free. However, it was more effective to provide free spectacles than to provide only a prescription or a prescription and a letter to the parents.

A combination of interventions may have increased children's compliance. The reasons reported by Yi et al. (17) for the increase in compliance were receipt of free spectacles combined with education on their use and a teacher incentive. A similar study on strengthening health education intervention in India showed that, in this experiment, education intervention alone did not improve the compliance of glasses wearers (27). In the study by Ma et al. (23), teachers were trained in VA screening and screened the children during the intervention in the treatment group, which may have encouraged children to wear spectacles. The provision of free spectacles may have brought additional benefits to children. Existing evidence shows that free spectacles can improve academic performance (5, 14, 22). The results of the subgroup analysis showed lower ORs at the longer follow-up of 6–12 months. Our study's results may provide important insights for refractive services in children. For example, the results suggest that incorporating education

TABLE 2 Reasons for compliance with spectacle use.

Study	Factors associated with spectacle wear
Holguin et al. (6)	Older (OR: 1.19 per year of age; 95% CI: 1.05–1.33), rural (OR: 10.6; 95% CI: 5.35–21.0) children, and those with myopia (OR: 3.97; 95% CI: 1.98–7.94) and hyperopia (OR: 3.63; 95% CI: 1.02–12.9)
Du et al. (19)	Older (RR: 1.56, 95%CI: 1.12–2.19), severity of RE < -2.00 (RR: 3.68; 95% CI: 2.23–6.07), wearing spectacles before baseline (RR: 3.91; 95% CI: 2.53–6.04), friends wear spectacles (RR: 1.87; 95% CI: 1.32–2.63)
Keay et al. (13)	Female (OR: 1.72; 95% CI: 1.10–2.68), low income (OR: 1.78; 95% CI: 1.32–2.39), less trouble with appearance (OR: 2.04; 95% CI: 1.25–3.36)
Guan et al. (20)	Left-behind children
Wang et al. (18)	Baseline wearing (RR: 3.01, 95% CI: 2.32–3.89), uncorrected visual acuity (children with better visual acuity were less likely to wear spectacles: RR: 0.24; 95% CI: 0.11–0.50, $P < 0.001$)
Yi et al. (17)	Membership in the treatment group (OR: 11.5, 95% CI: 5.91–22.5), baseline wearing (OR: 12.2; 95% CI: 5.63–26.4), VA <6/18 both eyes (OR: 1.70; 95% CI: 1.14–2.53), and at least one parent wears spectacles (OR: 1.90; 95% CI: 1.14–3.18)
Ma et al. (23)	Membership in the treatment group (OR: 11.89, 95% CI: 6.77–20.89), baseline ownership (OR: 31.82; 95% CI: 10.24–98.91), baseline mathematics score (OR: 1.19; 95% CI: 1.08–1.31)
Thapa et al. (16)	Lack of awareness of the need for distance glasses by the children's carers

and teacher incentives into long-term follow-up programs could encourage consistent spectacle use among children. At short-term follow-up, children may stop wearing spectacles because of the associated discomfort. Wearing spectacles during long-term follow-up may help children develop habits that allow them to benefit from refractive correction.

As the number and proportion of children with refractive errors are increasing worldwide, concerns have been raised about the increasing cost of eye care programs (8–10). Considering the fact that spectacle wear compliance was low among school children in some screening programs, it is necessary to adjust the strategies to improve compliance. A randomized clinical trial conducted in India found that using readymade spectacles can be a viable option for delivering refractive services in settings with a high level of need, limited resources, and low access to refractive services (28). The results of the study indicated that the cost of spectacles may be a barrier for children in low- and middle-income areas to access. Moreover, the reasons for non-compliance may include poor literacy, misconceptions, and lack of eye health knowledge among parents (29). Because economic considerations are important in low- and middle-income countries, the provision of low-cost or free spectacles can improve access (30).

To our knowledge, this systematic review is the first to focus on the provision of free spectacles to promote spectacle-wearing compliance in children. However, this study has several main limitations. First, there was a high degree of heterogeneity between the studies, reflecting methodological differences. The included studies differed considerably in the definition and measurement of compliance. Most studies on spectacle wear compliance used observed wear or relied on self-report. Observed wear is influenced by the degree of refractive error but cannot be fully explained (7). Self-reported spectacle wear may have resulted in overestimating the results of the study. Second, the majority of the studies were from the Asia region, which may reduce the representativeness of the results. Third, not all of the included studies were specifically designed to investigate children's compliance with free spectacles.

5. Conclusions

In conclusion, our systematic review and meta-analysis showed that providing free spectacles with educational interventions significantly improves children's compliance with spectacle wear. These findings highlight the importance of incorporating educational interventions and other health promotion strategies in policies aimed at increasing spectacle compliance. However, further research is needed to better understand the reasons for low compliance and to develop more effective measures for improving the acceptance of refractive services and eyewear use.

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.

Author contributions

LW: software, formal analysis, data curation, and writing—original draft. JF: data visualization and writing—original draft. MZ: conception and design of study. All authors contributed to the article and approved the submitted version.

Funding

This study was partly supported by the internal funding of JSIEC (No. 20-007).

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1053206/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 20 March 2023
DOI 10.3389/fpubh.2023.1100437

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 16 November 2022
ACCEPTED 03 March 2023
PUBLISHED 20 March 2023

CITATION
Liu Y, Meng D, Wang Y, Wang X, Xue C, Hao R and Zhang W (2023) Ocular biological parameters and prevalence of myopia in vocational high school and general high school in China.
Front. Public Health 11:1100437.
doi: 10.3389/fpubh.2023.1100437

Ocular biological parameters and prevalence of myopia in vocational high school and general high school in China

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Significance: Higher prevalence of myopia is possibly associated with more extended schooling schedules. Therefore, adjustments to high school curricula may aid in reducing the prevalence of myopia among adolescents.

Purpose: To investigate the prevalence of myopia among 15- to 18-year-old adolescents in Tianjin, China, and to evaluate the impact of different educational schedules on the prevalence of myopia among high school students.

Methods: This is a school-based epidemiological study with a cross-sectional design. Ocular biological parameters and noncycloplegic photorefraction were examined using optical biometry devices and photoscreener devices. Each student's spherical equivalent (SE) and ocular biometry were recorded, and the prevalence of myopia was calculated.

Results: A total of 2,867 participants (1,519 males and 1,348 females) were tested for non-cycloplegic refraction, axial length (AL), central corneal thickness (CCT), anterior chamber depth (ACD) and lens thickness (LT). In this research, the overall prevalence of myopia was 81.6%, with high myopia accounting for 11.8%. Myopia prevalence was substantially higher in general high schools than in vocational high schools, with 86.1 and 70.1%, respectively. There were no significant differences in the prevalence of myopia (p=0.744) or high myopia (p=0.851) across the three vocational school years. In the general high school, however, there was an increase of 4.6% (p<0.05) in myopia prevalence between year 10 and year12.

Conclusion: Comparing vocational and standard high school students, there are considerable disparities in prevalence of myopia, spherical equivalent, and ocular biological parameters. The prevalence of myopia and high myopia increased among standard high school students, but remained relatively consistent among students in vocational schools.

KEYWORDS

prevalence, ocular biometry, myopia, high school students, educational schedule

Introduction

Myopia is a multifactorial condition that has substantial medical and economic consequences for those affected, as well as for society as a whole. Because of the ocular comorbidities associated with severe myopia, such as rhegmatogenous retinal detachment, myopic macular degeneration, premature cataract, and glaucoma, severe myopia is a leading cause of visual impairment globally (1). In 2050, it is anticipated that 4,758 million individuals will have myopia, and 938 million will have severe myopia, representing approximately 50 and 10% of the global population, respectively (2). Both inherited and environmental variables have been implicated in the etiology of myopia. Near-work and outdoor activities throughout childhood, education, and residency (urban vs. rural) have all been related to the varied incidence and severity of myopia (3). Near work has long been thought to be a potential mediator for the connection between high myopia prevalence and increased educational intensity due to high accommodating demand (4). However, the precise reasons and mechanisms remain unclear. Prior studies on high school education have been limited to general high school students, with no vocational high school students of the same age included (5, 6). According to data issued by the National Bureau of Statistics of China in 2018, vocational education is a significant destination for junior high school graduates, with 15.925 million students, or 40.10% of high school students enrolled (7). In addition, the target group for myopia prevention and control is typically kindergarten through elementary school pupils. But adolescents aged 15 to 18 who attend high school are still in a crucial stage of myopia development. To contribute more effectively to the control and prevention of myopia in teenagers, it is required to research the prevalence of myopia and ocular biological parameters among high school students, as well as the association between myopia and educational patterns.

Materials and methods

Study settings and participants

We conducted a cross-sectional study based on a multistage stratified cluster random sampling in a suburban district of Tianjin, from October to December 2019. A total of 2,956 children from 5 schools (2 vocational high schools and 3 general high schools) participated in the survey. This school-based cross-sectional study was approved by the ethics board of Tianjin Eye Hospital, Tianjin, China. Written informed consent was obtained before the start of the study from the parents of all participants.

Prior to data collection, participants were screened to determine their eligibility for the experiment. Children with a history of ocular or systemic disease, current use of systemic or ocular medications that may modify refractive status, history of previous ophthalmic surgery, or substantial binocular vision, accommodative abnormalities, or ocular movement disorders were excluded from the study. At least 1 month in advance, schools were informed of the screening date. For screening, all individuals were instructed to remove their prescription refractive spectacles. Students who regularly wore rigid contact lenses or received corneal refractive therapy (Ortho-K) were instructed to cease using them 4 weeks prior to the day of the examination. Students who wore soft contact lenses were urged to stop wearing them 3 days before the assessment.

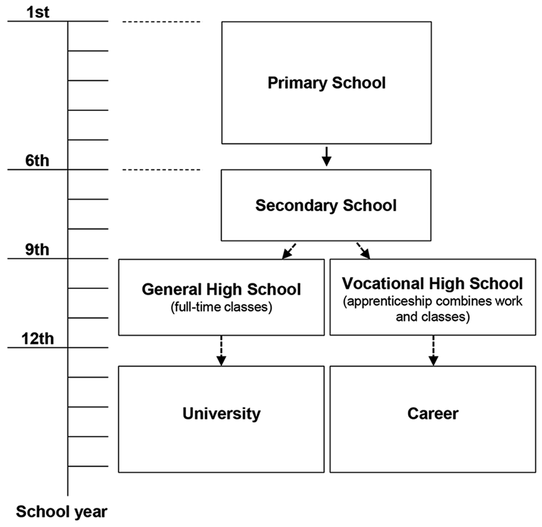

FIGURE 1
Demonstration of Chinese school system prior university.

Chinese high schools and training system

The Chinese educational system is comprised of 6 years of elementary school, 3 years of both lower and upper secondary high school, and 4 years of the standard university curriculum (Figure 1). After completing lower secondary school, adolescents can select between two educational tracks (general high school or vocational high school) based on their scores on high school entrance exams. Students with better academic performance have a greater chance of being admitted to general high schools. Typically, students in general high schools continue their academically-focused education to obtain a regular high school diploma, allowing them to apply to traditional universities. In vocational high schools, however, major efforts are undertaken to provide technical education to students in order to obtain employment following graduation. Due to the difference in teaching purposes, the curriculum of vocational high schools will place less emphasis on academic learning and more attention on skill development.

Refraction and ocular examinations

The ophthalmological examinations began at 09:00 a.m. for all participants to minimize daily fluctuations of the ocular biometrics by the biorhythm. All of the data was collected in a non-cycloplegic state by well-trained examiners. An optical biometry (SW9000, SUOER, China) was used to measure axial length, central corneal thickness, anterior chamber depth and lens thickness. The noncycloplegic refractive error was tested using the SW800 vision screener (SUOER, China), which is a recently developed photoscreener designed specifically for the Chinese population. The measurements of Spot and SW800 photoscreeners showed a strong agreement with cycloplegic

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TABLE 1 Prevalence of myopia and high myopia for students from vocational high school and general high school.

	Overall (*n*=2,867)	Vocational high school (*n*=814)	General high school (*n*=2053)	*P* value
Males, no. (%)	1,519 (53.0)	520 (63.9)	999 (48.7)	<0.001[a]
Age, median (IQR), year	16 (2)	17 (1)	16 (2)	<0.001[b]
SE, median (IQR), D	−3.38 (3.75)	−2.50 (3.25)	−3.88 (3.38)	<0.001[b]
Year 10	−3.25 (4.00)	−2.38 (4.19)	−3.63(3.63)	<0.001[b]
Year 11	−3.50 (3.63)	−2.44 (4.38)	−3.88(3.38)	<0.001[b]
Year 12	−3.38 (3.75)	−2.50 (4.38)	−4.00(3.25)	<0.001[b]
Myopia, no. (%)	2,339 (81.6)	571 (70.1)	1768 (86.1)	<0.001[a]
Year 10	747 (80.2)	185 (69.8)	562 (84.3)	<0.001[a]
Year 11	736 (82.1)	153 (72.2)	583 (85.1)	<0.001[a]
Year 12	856 (82.5)	233 (69.1)	623 (88.9)	<0.001[a]
High myopia, no. (%)	337 (11.8)	55 (6.8)	282 (13.7)	<0.001[a]
Year 10	86 (9.2)	16 (6.0)	70 (10.5)	0.034[a]
Year 11	105 (11.7)	15 (7.1)	90 (13.1)	0.016[a]
Year 12	146 (14.1)	24 (7.1)	122 (17.4)	<0.001[a]

[a]*p* value refers to difference between vocational high school and general high school by Chi-square test. [b]*p* value refers to difference between vocational high school and general high school by Mann–Whitney test.

retinoscopy refraction tests (8). The testing was undertaken by trained personnel, all measurements were repeated three times, and the average value of each parameter was calculated. In brief, the examiner held the photoscreener at a distance of 1 M from the child in a dark environment. The spherical equivalent refraction of the child was recorded automatically for both eyes. The screener's measuring range was restricted to −7.5–+7.5 diopters (D) in 0.25 D increments. The software algorithm of the photoscreener would flag a referral for a complete eye examination and record data if significant refractive error (the refraction was out of range), anisometropia, or strabismus were detected. And then, the non-cycloplegic retinoscopy (REF 18240, Welch Allyn, United States) was performed by a senior optometrist. Spherical equivalent (sphere power + cylinder power/2) was used to calculate refraction. When spherical equivalent (SE) ≤ −0.50D, a subject was classified as myopic; myopic patients were further classified as mild (−3.00D < SE ≤ −0.50D), moderate (−6.00D < SE ≤ −3.00 D), and high (SE ≤ −6.00 D) myopic (9). Anterior chamber depth was defined as the distance between the corneal endothelium and the lens. The axial length was defined as the distance from the anterior corneal pole to an interference peak corresponding to the posterior retinal pole. Lens position is defined as the sum of the aqueous depth and half of the lens thickness.

Statistical analysis

As the correlation coefficients of spherical equivalent ($R = 0.92$, $p < 0.001$) and axial length ($R = 0.95$, $p < 0.001$) were high in both left and right eyes, only data from the right eyes was used in the analysis. For the analysis, the statistical package R software for Windows and SPSS version 25.0 software (SPSS Inc., Chicago, IL, United States) were used for the statistical package. A normality test (Kolmogorov–Smirnov test) was performed. Logistic regression was carried out to investigate the effect of years, gender and two educational systems on the prevalence of myopia. A two-sided $p < 0.05$ was considered statistically significant at the 95% confidence interval (CI, a range of values defined such that there is a specified probability that the value of a parameter occurs inside it) level. The odds ratio (OR) quantifies the relationship between an exposure and an outcome.

Results

A total of 2,867 students were enrolled in this research, with a mean age of 16.33 ± 1.0 (range 14–19 years). Among the subjects, 814 were from vocational high schools (mean age 16.48 ± 1.06, range 14–19 years) and 2053 (mean age 16.27 ± 0.97, range 14–19 years) from general high schools. The proportion of males was 53% (1,519 subjects). Among the subjects, 5 (0.6%) of vocational high school students and 27 (1.3%) of general high school students were out of the measurement range. Eighty-nine students were eliminated from the study regarding systemic or visual abnormalities such as amblyopia, strabismus, or other disorders that might alter the results.

Sample size, age, sex distribution, SE, prevalence rate of myopia and high myopia are shown in Table 1. In this school-based screening, the prevalence of myopia was 81.6% overall, and the prevalence of high myopia was 11.8%. In the general high schools, the prevalence of myopia was higher than that in the vocational high schools, at 86.1% versus 70.1%, respectively. Similarly, the prevalence of high myopia was higher in general high schools (13.7%) than in vocational schools (6.8%). Both disparities between the two schools were statistically significant ($p < 0.001$). In addition, the SE in general high schools was lower than in vocational high schools ($p < 0.001$): −2.50 D (IQR = 3.25), compared −3.88 D (IQR = 3.38). In all three school years, there were substantial differences in the SE and the prevalence of myopia of the two

10.3389/fpubh.2023.1100437

TABLE 2 Logistic regression results for the students from vocational high school and general high school.

	Myopia			High myopia		
	OR	95%CI	*p* value	OR	95%CI	*p* value
Overall						
Age	1.04	0.94–1.14	0.471	1.09	0.97–1.23	0.132
Gender (girls vs. boys)	1.37	1.12–1.67	0.002	1.18	0.94–1.43	0.169
School (GHS vs. VHS)	2.55	2.09–3.11	<0.001	2.19	1.61–3.00	<0.001
Year 10						
Age	0.90	0.65–1.26	0.547	0.72	0.40–1.22	0.251
Gender (girls vs. boys)	1.46	1.04–2.05	0.029	1.10	0.70–1.73	0.674
School (GHS vs. VHS)	2.17	1.54–3.05	<0.001	1.65	1.02–2.77	0.048
Year 11						
Age	1.07	0.78–1.47	0.673	0.71	0.47–1.06	0.102
Gender (girls vs. boys)	1.63	1.13–2.35	0.009	0.97	0.65–1.50	0.950
School (GHS vs. VHS)	2.03	1.40–2.96	<0.001	1.93	1.08–3.43	0.026
Year 12						
Age	0.72	0.52–0.98	0.039	0.65	0.46–0.93	0.018
Gender (girls vs. boys)	1.08	0.78–1.52	0.634	1.31	0.94–1.84	0.111
School (GHS vs. VHS)	3.39	2.42–4.73	<0.001	2.53	1.59–4.02	<0.001

OR, odds ratio; CI, confidence interval; GHS, general high school; VHS, vocational high school.

schools ($p < 0.05$). After adjusting for differences in age and gender using logistic regression, the overall prevalence of myopia among high school pupils remained elevated (OR = 2.55, 95% CI: 2.09–3.11; $p < 0.001$), and the year 10 (OR = 2.17, 95% CI: 1.54–3.05; $p < 0.001$), year 11 (OR = 2.03, 95% CI: 1.40–2.96; $p < 0.001$), and year 12 (OR = 3.39, 95% CI: 2.42–4.73; $p < 0.001$) were higher, respectively (Table 2). The overall amount of high myopic students was likewise greater (OR = 2.19, 95% CI: 1.61–3.00; $p < 0.001$), and the year 10 (OR = 1.65, 95% CI: 1.02–2.77; $p = 0.048$), the year 11 (OR = 1.93, 95% CI: 1.08–3.43; $p = 0.026$) and year 12 (OR = 2.53, 95% CI: 1.59–4.02; $p < 0.001$) were higher, respectively (Table 2).

Besides, the prevalence of myopia and high myopia significant increased with school year in general high school ($p < 0.05$), reaching 84.3% for year 10, 85.1% for year 11, and 87.9% for year 12. The overall prevalence of high myopia, which is 10.5% in year 10, 13.1% in year 11, and 17.4% in year 12, followed the same pattern (Table 3). But there were no significant differences in the prevalence of myopia and high myopia among the three grades in the vocational high school ($p > 0.05$).

Distribution of students' ocular biometric characteristics are shown in Table 3. There were significant differences in the Axial length (AL), Anterior chamber Depth (ACD), Lens Thickness (LT), Lens Position (LP) and Vitreous Chamber Depth (VCD). The general high school students had significantly longer AL ($p < 0.001$), deeper ACD ($p < 0.001$), thinner LT ($p < 0.001$), larger LP ($p = 0.014$) and deeper VCD ($p < 0.001$; Table 4).

Discussion

Despite extensive evidence that hereditary factors play a role in the development of myopia (10–13), scientists have seen a major change in the incidence of myopia in various regions of the world throughout the twentieth century, notably in East Asia (3, 14, 15). Intensive near work has long been proposed as a possible mechanism for axial elongation and myopia development (16), with longitudinal studies supporting correlations between near employment and increasing myopia prevalence (17, 18). However, this relationship has been challenged (19, 20). Some research indicated that near-work had a non-significant influence on myopia status (21), myopia incidence (22), or myopia advancement (23). In addition, the direction of causation and the mechanisms involved have been questioned; schooling is a surrogate for near-work activities, but it is difficult to distinguish between reading, writing, and watching electronic screens. (24). Since accommodation occurs during close work in children, ocular changes may establish a reasonable relationship between the

TABLE 3 Differences in the prevalence of myopia and high myopia between two educational systems during the school years.

	Overall	*p*-value[a]	Vocational high school	*p*-value[a]	General high school	*p*-value[a]
Myopia, no. (%)						
Year 10	747 (80.2)	0.378	185 (69.8)	0.744	562 (84.3)	0.031
Year 11	736 (82.1)		153 (72.2)		583 (85.1)	
Year 12	856 (82.5)		233 (69.1)		623 (88.9)[b]	
High myopia, no. (%)						
Year 10	86 (9.2)	0.004	16 (6.0)	0.851	70 (10.5)	0.001
Year 11	105 (11.7)		15 (7.1)		90 (13.1)	
Year 12	146 (14.1)[b]		24 (7.1)		122 (17.4)[b]	

[a]*p* value refers to difference among 3 years by Chi-square test. [b]Significant to the level of $p < 0.017$, compared with year 10th by Chi-square test (Bonferroni correction).

TABLE 4 Distribution of students' ocular biometric characteristics and differences between two educational systems.

	Overall	Vocational high school	General high school	*p*-value
Axial lengths, mean (SD), mm	25.10 (1.24)	24.78 (1.28)	25.22 (1.21)	<0.001
Central corneal thickness, mean (SD), μm	551 (35)	552 (36)	551 (35)	0.576
Anterior chamber depth, mean (SD), mm	3.27 (0.28)	3.24 (0.30)	3.28 (0.27)	<0.001
Lens thickness, mean (SD), mm	3.52 (0.24)	3.55 (0.25)	3.51 (0.23)	<0.001
Lens position, mean (SD), mm	5.03 (0.25)	5.01 (0.26)	5.04 (0.24)	0.014
Vitreous chamber depth, mean (SD), mm	17.75 (1.20)	17.44 (1.22)	17.88 (1.17)	<0.001

p value refers to difference in mean between vocational high school and general high school by Student's *t*-test.

development and progression of myopia and close employment (25, 26). Certain near work habits, such as reading continuously for 30 min or more (17, 27, 28) and working at a distance of less than 30 cm (27, 28), have been attributed to myopia in youngsters. Furthermore, Wang et al. (29) discovered that Chinese children had reduced reading distances of 16–28 cm and a larger degree of head tilt when writing than other groups. As a result, the intensity of close work appears to be more significantly linked to myopia prevalence and longer axial length than near work in general.

In addition to behavioral findings, a number of studies have investigated the physiological changes that occur in the eye during close proximity activity. Studies examining modifications in ocular biometry during accommodation over a restricted range of demands have revealed comparable tendencies of decreased anterior chamber depth, vitreous chamber depth, increased lens thickness, and increased axial length in adults. Yet, due to the axial length inaccuracy generated by the increase in crystalline lens thickness, a number of the adult investigations likely overestimated the increase of axial length during accommodation (30). Hughes et al. (31) reported modest axial length increases that occurred during accommodation in toddlers, with a magnitude of change comparable to previous research on adults up to a 6 D demand when lens thickness errors are considered. Moreover, it was discovered that the variations in axial length were closely related to the accommodation-induced changes in lens thickness and anterior chamber depth. Similar patterns were also detected in our data.

In previous studies, myopia appears to be highly associated with educational attainment or intensity (1, 32), better academic achievement (21, 33, 34), and even level of intelligence in prior studies (35, 36). Due to the bidirectional relationship between refractive error and visual acuity on the one hand and academic accomplishment on the other, it is difficult to draw definitive cause-and-effect conclusions from studies (37). For instance, a high prevalence of myopia has been observed in communities that receive intense training at a young age, such as Jewish boys in Israel who underwent Orthodox or traditional Orthodox education (38). In contrast, the prevalence of myopia is mild and equivalent to the majority of western nations among East Asians with less education (39). In recent years, the increasing prevalence of myopia in East and Southeast Asia has prevented the implementation of mass rigorous schooling (40). Mirshahi et al. analyzed the myopia prevalence and severity in relation to years spent in school and level of post-secondary professional education (32). Their findings suggested that more myopic refraction was related to higher degrees of school and post-school professional education. This school-based analysis indicates, to the best of our knowledge, a plausible correlation between myopia prevalence, general secondary school education, and postsecondary professional training. After controlling for age and gender, the association remained strong.

For the first time in our study, we evaluated the effects of two distinct academic expectations and learning styles on the topic of teenage myopia. Initially, we assumed that this was the result of a cumulative effect; however, our investigation proved otherwise. According to the results of three school years in regular high schools, the prevalence of myopia (mild, moderate, and severe) grew dramatically from one school year to the following. However, the prevalence of myopia and high myopia among vocational high school students remained largely consistent as the school year advanced.

Comparing the curricular patterns of the two educational systems reveals substantial differences between general and vocational high schools. To begin with, the general high school teaching model requires pupils to devote the majority of their time to focused close work (except in physical education classes). During a normal day in general high school, Chinese students participate in teaching tasks for an average of 360 min (about two-thirds of the time spent at school) and continuous close tasks for an average of 30 min per task. Recent research on youngsters in Australia and China found that near working distances ranging from 25 cm to less than 10 cm (27, 41). In contrast to traditional high schools, vocational high schools emphasize technological subjects, covering welding technology applications, automotive applications and maintenance, electromechanical technology applications, numerical control technology applications, and so on. This modification could result in less time spent working in close proximity and more time spent engaging in outdoor activities. Secondly, traditional high schools have stricter academic requirements, and students spend more time outside of school completing assignments, whereas vocational high schools are more laid-back. Thirdly, the final year of general high schools typically include more study time preparing for university entrance examination. Comparatively, vocational high schools will have a greater emphasis on internships, and the compulsory academic time will be 4 lectures (approximately 4 h in total) less per school day than that of normal high schools. Therefore, we speculate that, compared to heritable characteristics, recurrent close tasks in schooling may be a more significant factor in the progression of myopia in adolescents aged 15 to 18 years (in school years 10–12).

It is important to note that this research has several limitations. In our investigation, the photoscreener only delivered findings for noncycloplegic refraction. It is beneficial for population-based screening and myopia monitoring due to its high efficiency, but it is not currently regarded as a substitute for cycloplegic refraction. In addition, our study focused on demonstrating the association between myopia and time spent in school among 15 to 18-year-olds, but did not adequately account for time spent after school. With the exception of studying, leisure activities at other times require more investigation. Additional information, including family history, parental myopia, and education level, should be included to the study. The next phase of this study will entail recruiting additional participants and refining the questionnaire in order to compare the behaviors of diverse pupils in greater detail. A longitudinal study of educationally relevant topics will be pursued next.

Conclusion

Between vocational high school students and general high school students, there are substantial differences in myopia prevalence, spherical equivalent, and other ocular biological parameters. Myopia and high myopia prevalence in general high school students increased significantly with school year, whereas the prevalence among vocational high school students are generally consistent. These findings might provide guidance in the prevention and care of myopia in high school students. Finally, the data reported in this study supplements real-world data from 15- to 18-year-old students, contributing in the standardization of optical modeling of the eyes of this age group.

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 Medical Ethics Committee of Tianjin Eye Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YL, DM, RH, and WZ contributed to the conception of the study and performed the data analyses and wrote the manuscript. YL, YW, XW, and CX collected the data. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Tianjin Key Research and Development Plan of Science and Technology (19YFZCSY00990), Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-016A), Tianjin Eye Hospital Science and Technology Fund Youth Cultivation Project (YKPY2201) and Open Fund of Nankai University Eye Institute Grant (NKYKD202202).

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.

Publisher's note

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TYPE Review
PUBLISHED 23 March 2023
DOI 10.3389/fpubh.2023.1125000

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Effectiveness of myopia control interventions: A systematic review of 12 randomized control trials published between 2019 and 2021

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SPECIALTY SECTION
This article was submitted to
Public Health Education and Promotion,
a section of the journal
Frontiers in Public Health

RECEIVED 15 December 2022
ACCEPTED 07 March 2023
PUBLISHED 23 March 2023

CITATION
Lanca C, Pang CP and Grzybowski A (2023) Effectiveness of myopia control interventions: A systematic review of 12 randomized control trials published between 2019 and 2021. *Front. Public Health* 11:1125000.
doi: 10.3389/fpubh.2023.1125000

Purpose: This study aims to investigate the effectiveness of interventions to control myopia progression. In this systematic review, the primary outcomes were mean differences (MD) between treatment and control groups in myopia progression (D) and axial length (AL) elongation (mm).

Results: The following interventions were found to be effective (p<0.001): highly aspherical lenslets (HAL, 0.80 D, 95% CI, 0.77–0.83; −0.35mm, 95% CI −0.36 to −0.34), MiSight contact lenses (0.66 D, 95% CI, 0.63–0.69; −0.28mm, 95% CI −0.29 to −0.27), low dose atropine 0.05% (0.54 D, 95% CI, 0.38–0.70; −0.21mm, 95% CI-0.28 to −0.14), Biofinity +2.50 D (0.45 D, 95% CI, 0.29, 0.61; −0.24mm, 95% CI −0.33 to −0.15), defocus incorporated multiple segments [DIMS] (0.44 D, 95% CI, 0.42–0.46; −0.34mm, 95% CI −0.35 to −0.33) and ortho-k lenses (−0.24mm, 95% CI −0.33 to −01.5).

Conclusion: Low-dose atropine 0.01% was not effective in reducing AL progression in two studies. Treatment efficacy with low-dose atropine of 0.05% showed good efficacy. Spectacles (HAL and DIMS) and contact lenses (MiSight and Biofinity) may confer a comparable treatment benefit compared to atropine, to slow myopia progression.

KEYWORDS
myopia, progression, axial length, elongation, treatment, efficacy, systematic review

1. Introduction

Myopia prevalence has increased worldwide and although myopia is more prevalent in East Asia, epidemiological studies show an increasing rate in European populations (1). The variations in myopia prevalence have been attributed to both genetic and environmental factors although the interactive causative effects are still to be established. Increasing intensity and duration of education are risk factors linked to higher myopia prevalence (2, 3). Increased risk of myopia has been found in children who perform more near work, spend less time outdoors and have myopic parents (4). Controlling myopia progression to avoid future high myopia and visual impairment is becoming more common in routine ophthalmology practice in some regions of the world where the prevalence is high, such as East Asian countries. The risk of developing myopic maculopathy (58%), retinal detachment (30%), posterior subcapsular cataract (21%) and open-angle glaucoma (20%) increases with each additional 1 D of myopia (5). Children with myopia are also at higher risk of developing depression compared to normally sighted children (6).

In recent years, various manuscripts (both original studies and narrative or systemic reviews) on myopia epidemiology, prevention, risk factors and myopia control, have been published. According to data from PubMed there were over 1,000 manuscripts published per year in 2019 ($n = 1{,}401$), 2020 ($n = 1{,}686$) and 2021 ($n = 1994$; www.pubmed.ncbi.nlm.nih.gov). Thus, following the knowledge developments in this field is becoming more difficult. Several treatment options for myopia control have emerged in recent years. A few meta-analyses on myopia treatment efficacy were published in 2022 (5–7). Those publications have analyzed the efficacy of individual therapies on myopia control, such as atropine (7), multifocal lens (8) or atropine and orthokeratology (9). However, those studies did not compare the overall treatment effects. Additionally, 2-year data on highly aspherical lenslets (HAL) have been published (8–10). The present study updates the published evidence by comparing the efficacy of known treatments with HAL. This information may be useful to facilitate decision-making in clinical practice, especially to assist eye care providers in the choice of treatment for myopia control.

This review aims to investigate the effectiveness of interventions to control myopia progression. We present an overview of the manuscripts published between 2019 and 2021, as well as recent and relevant contributions to this important area of ophthalmology. Additionally, this study compares the efficacy in myopia control among different myopia control therapies.

2. Materials and methods

In this review, randomized control trials (RCT) were included if they compared interventions for slowing myopia progression in children with a treatment duration of at least 1 year. The primary outcomes of this study were the mean differences between treatment and control groups in myopia progression (D) and axial length elongation (mm) for the longer follow-up time reported in the RCT. The inclusion criteria were as follows: (1) RCT; (2) studies on treatment for myopia control published between 2019 and 2021; (3) children with myopia aged <18 years; (4) follow-up period of 1 year or more; (5) studies written in English language. Studies were excluded if (1) they had a retrospective component, were review papers or protocols, (2) they lacked the required outcome measures of this study, (3) refraction was measured without cycloplegia or not obtained using automated refraction, or (4) children were older than 16 years at baseline.

A previous Cochrane systematic review reviewed studies published up to 2018 (11). Thus, in this review we searched Pubmed, Embase and Cochrane Library publications from January 2019 to August 2021. The following search terms were selected: "Myopia AND Disease Progression NOT Keratomileusis, Laser *in Situ* NOT surgery AND humans AND Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial OR English Abstract OR Journal Article AND infant OR child OR adolescent." We reviewed the references of all retrieved articles to identify articles not captured by the initial electronic search. Data was extracted and documented by one of the authors (CL) and verified by the other (AG). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist was used. We extracted the following information from each trial: type of intervention, follow-up duration, sample size and age, mean change in refraction and axial length.

The methodological quality of RCTs was evaluated using the Cochrane Collaboration's Risk of Bias Assessment tool (RoB v.2.0) (12). The methodology examined the following aspects of each trial: bias arising from randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. We graded each of the item domains as "low" and "high" risk of bias or "some concerns."

Missing standard deviations were derived from other statistics, such as *p*-values or confidence intervals (CI), if needed (13).

A random effects analysis was performed to obtain conservative pooled estimates that took in consideration heterogeneity and sampling error. We also assessed heterogeneity with the I^2 statistics. The statistical heterogeneity was considered significant when the I^2 statistic was greater than or equal to 50%. Data analysis was started with a fixed-effect model and then switched to a random-effects model upon realizing the significant test of heterogeneity. The results of the different studies and the overall effect (under the random effects model) with 95% CI were illustrated with forest plots graphs. For the outcome myopia progression, a positive mean difference [MD] indicates that the intervention was better compared with the control group (less myopia progression). For the outcome axial length, a negative MD indicates that the intervention was better compared with the control group (less axial elongation). As there was variation in sample sizes across the studies and more than 10 studies were included, we assessed publication bias using the funnel plot. A p-value of <0.05 was accepted as statistically significant. RevMan v. 5.4 software was used for the statistical analysis.

3. Results

The electronic search identified a total of 3638 studies. Figure 1 presents a PRISMA flow diagram showing the process of obtaining eligible studies. A total of 3436 non-RCTs were excluded, and 202 studies were screened. After screening, 12 studies met the inclusion criteria and were included in this review (Figure 1). Among the 12 RCTs four main types of interventions to control myopia progression were found, including topical low-dose atropine eye drops (5 studies), multifocal spectacles (2 studies), multifocal contact lenses with aspheric or discrete dual-focus designs (4 studies), and overnight orthokeratology (ortho-k lenses, 1 study). The characteristics of the 12 included studies are presented in Table 1.

Eleven studies reported both refraction and axial length outcomes, and 1 study only reported axial length.

Table 2 shows the quality assessment results. Overall, the RCTs included in this analysis seem to have a low to moderate risk of bias, with most of the RCTs reporting adequate random sequence generation, allocation concealment, and blinding of outcome

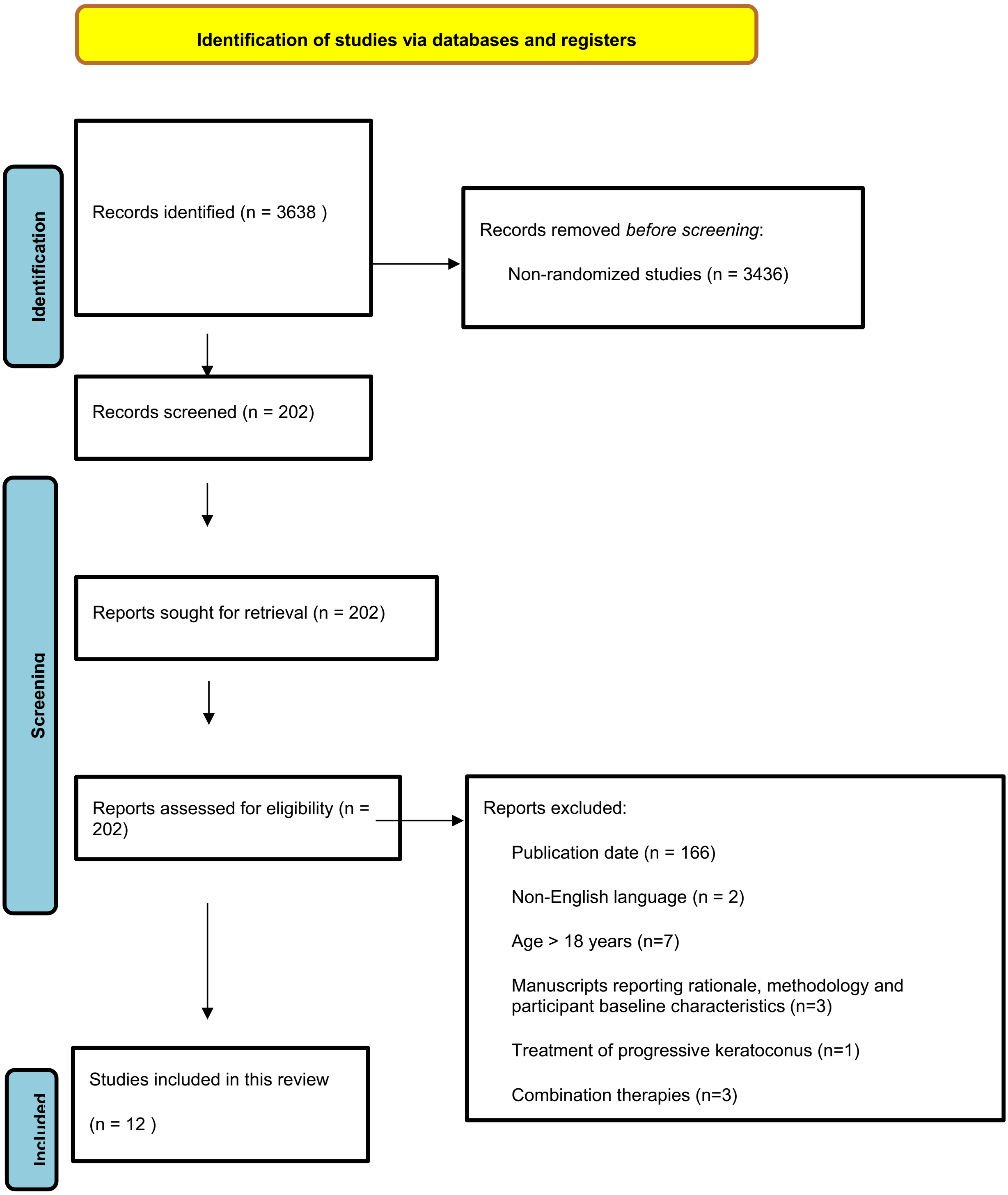

FIGURE 1
PRISMA flow diagram.

assessment. Two studies were classified as having "some concerns" arising from the randomization process and 5 were classified as having "some concerns" ($n = 2$) or "high risk of bias" ($n = 3$) due to loss of follow-up or missing data. However, in some studies the treatment may not be completely masked due to the type of lenses or its effects, such as pupil dilation.

There are some issues that should be noted, mainly related with the need to use data from intervention groups and the comparison with placebo groups: The Low-Concentration Atropine for Myopia Progression (LAMP) study was a RCT over 26 months, and we only used data from the first follow-up with 1-year treatment effects (11–13). The MiSight contact lenses study was a RCT over 6 years, and we only used data from the 36 months (14, 15). The defocus incorporated multiple segments [DIMS] spectacle lenses study was a RCT over 36 months, and we only selected data from the 2-year treatment effects (16, 21).

TABLE 1 Characteristics of RCTs included in the review (*n*=12).

Study	Location	Study group	Control group	Follow-up (months)	Age (years)	Myopia range (D)	Side effects
Atropine							
LAMP (Yam et al.) (14–16)	China	0.05, 0.025, and 0.01%	Placebo	12[a]	4–12	<−1.00	Severe adverse events (*n* = 20), were not related to atropine therapy
I-ATOM (Saxena et al.) (17)	India	0.01%	Placebo	12	6–14	−0.50 to −6.00	No side effects were reported
ATOM-J (Hieda et al.) (18)	Japan	0.01%	Placebo	24	6–12	−1.00 to −6.00	Mild allergic conjunctivitis side effects (*n* = 2)
Fu et al. (19)	China	0.02 and 0.01%	Single-vision spectacles	12	6–14	−1.25 to −6.00	Allergy (0.01%: *n* = 1) and photophobia in bright sunlight (0.02: *n* = 32); (0.01%: *n* = 33)
Wei et al. (20)	China	0.01%	Placebo	12	6–12	−1.00 to −6.00	No serious adverse events were reported
Soft contact lenses for myopia control							
MiSight contact lenses (Chamberlain et al.) (21, 22)	Portugal, United Kingdom, Singapore, and Canada.	Dual-focus optical design	Single vision contact lenses	36[c]	8 to <13	−0.75 to −4.00	No serious adverse events were reported
Bifocal Lenses Biofinity +2.50 D (Walline et al.) (23)	United States of America	Multifocal contact lenses with high add power (+2.50 D)	Single vision contact lenses	36	7–11	−0.75 to −5.00	No serious adverse events were reported
Extended depth of focus contact lenses (Sankaridurg et al.) (24)	China	Lenses I and II: power in the periphery increased up to +2.50D and +1.50D; Lenses III and IV: extended depth of focus up to +1.75D and +1.25D	Single vision contact lenses	24	8–13	−0.75 to −3.50	A large number of children discontinued the treatment (25.4%)
Esencia lens (Garcia-del valle et al.) (25)	Spain	Progressive multifocal and reverse geometry	Single vision contact lenses	12	7–15	−0.50 to −8.75	No serious adverse events were reported
Spectacle lenses for myopia control							
DIMS spectacle lenses (Lam et al.) (26, 27)	Hong Kong	Hexagonal central zone of distance refractive correction surrounded by an annular zone with dense microlens segments of 3.50 D addition	Single vision spectacle lenses	24[b]	8–13	−1.00 to −5.00	–

(Continued)

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TABLE 1 (Continued)

Study	Location	Study group	Control group	Follow-up (months)	Age (years)	Myopia range (D)	Side effects
Highly aspherical lenslets (Bao et al.) (10, 28, 29)	China	Volume of myopic defocus in front of the retina with 11 concentric rings of contiguous lenslets	Single vision spectacle lenses	24	8–13	−0.75 to −4.75	No serious adverse events were reported
Orthokeratology lenses							
Jakobsen and Møller (30)	Denmark	Dreamlite®: four-zone reverse geometry lens with a 6 mm optic zone diameter and 0.75 D compression factor	Single vision spectacle lenses	18	6–12	−0.5 to −4.75	No serious adverse events were reported (30% dropped out)

LAMP, Low-Concentration Atropine for Myopia Progression; I-ATOM, Atropine for treatment of childhood myopia in India; ATOM-J atropine in the treatment of myopia in Japan; DIMS, defocus incorporated multiple segments. [a]The 24-follow-up data was not included in the meta-analysis as children in the placebo group switched to the atropine 0.05%. At 36 months study children in continued treatment group were compared with a washout subgroup.
[b]The 36 months follow-up data was not included in the meta-analysis as children from the control group switched to DIMS lenses in the third year.
[c]The 6-year follow-up data was not included in the meta-analysis.

Most of the intervention methods slowed myopia progression compared to single vision spectacle lenses, single vision contact lenses or placebo. However, there were differences in treatment efficacy. The myopia progression MD for atropine was 0.29 D (95% CI 0.22, 0.36; $p = 0.03$), for soft contact lenses was 0.39 D (95% CI 0.21, 0.56; $p < 0.001$) and for spectacle lenses was 0.62 D (95% CI 0.27, 0.97; $p < 0.001$; Figure 2). The lowest heterogeneity was found in the atropine treatment subgroup (I^2 = 54%) and the highest in the spectacle lenses subgroup (I^2 = 100%). The axial length elongation MD for atropine was −0.12 mm (95% CI −0.15, −0.08; $p = 0.04$), for soft contact lenses was −0.18 mm (95% CI −0.26, 0.11; $p < 0.001$), for spectacle lenses was −0.34 mm (95% CI −0.35, −0.33; $p < 0.001$) and ortho-k lenses was −0.24 mm (95% CI −0.33 to −0.15; Figure 3). The lowest heterogeneity was found in the spectacle lenses treatment subgroup (I^2 = 41%) and the highest in the soft contact lenses subgroup (I^2 = 88%).

The following interventions were found to be effective in the reduction of myopia progression with statistical significance ($p < 0.001$): highly aspherical lenslets (HAL, refraction MD: 0.80, 95% CI 0.77–0.83; axial length: −0.35 mm, 95% CI -0.36 to −0.34), MiSight contact lenses (refraction MD: 0.66 D, 95% CI 0.63–0.69; axial length MD: −0.28 mm, 95% CI -0.29 to −0.27), low dose atropine 0.05% (refraction MD: 0.54 D, 95% CI 0.38–0.70; axial length MD: −0.21 mm, 95% CI-0.28 to −0.14), Biofinity +2.50 D (refraction MD: 0.45, 95% CI 0.29, 0.61; axial length: −0.24 mm, 95% CI -0.33 to −0.15), DIMS (refraction MD: 0.44, 95% CI 0.42–0.46; axial length: −0.34, 95% CI −0.35 to −0.33) and ortho-k lenses (axial length: −0.24 mm, 95% CI −0.33 to −0.15; Figures 2, 3).

Other interventions were also found to be effective but with lower effect sizes, such as extended depth of focus contact lenses, low dose atropine 0.025% or the esencia contact lens. The overall treatment effect was 0.37 D (95% 0.27–0.47) and −0.18 mm (95% −0.22 to −0.14). Low-dose atropine of 0.01% seemed to be the least effective method in controlling progression of myopia and axial length. Low-dose atropine 0.01% was not effective in reducing AL progression in 2 of the included studies (13, 22). There was high heterogeneity among treatment comparisons ($I^2 > 90\%$).

For topical low dose atropine, control effects reported as percentage reduction in progression ranged from 27% (0.01%) to 67% (0.05%) for myopia progression and from 12% (0.01%) to 51% (0.05%) for axial length elongation. Spectacle lenses such as DIMS and aspherical lenslets were effective in slowing myopia progression (percentage reduction of 87 and 67%, respectively) and axial elongation (percentage reduction of 61 and 64%, respectively) in children compared with controls. MiSight contact lenses (59% reduction in myopia progression and 52% reduction of axial elongation) and the Bifocal Lenses Biofinity +2.50 D also showed a significant slowing of myopia progression (reduction of 43%) and axial length elongation (reduction of 36%).

Funnel plots for myopia progression and axial elongation shown in Figures 4A,B, respectively, found no publication biases.

4. Discussion

This study investigated the effectiveness of interventions to control myopia progression. In addition, previous reviews such as the IMI-white papers (31) were updated by providing a meta-analysis of

TABLE 2 Quality of studies included in the review (*n*=12).

Study	Bias arising from randomization process	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
LAMP (Yam et al.) (14–16)	Low risk	Low risk	Low risk	Low risk	Low risk
I-ATOM (Saxena et al.) (17)	Low risk	Low risk	Low risk	Low risk	Low risk
ATOM-J (Hieda et al.) (18)	Low risk	Low risk	Low risk	Low risk	Low risk
Fu et al. (19)	Some concerns	Low risk	High risk	Low risk	Low risk
Wei et al. (20)	Some concerns	Low risk	Low risk	Low risk	Low risk
MiSight contact lenses (Chamberlain et al.) (21, 22)	Low risk	Low risk	Some concerns	Low risk	Low risk
Bifocal Lenses Biofinity +2.50 D (Walline et al.) (23)	Low risk	Low risk	Low risk	Low risk	Low risk
Extended depth of focus contact lenses (Sankaridurg et al.) (24)	Low risk	Low risk	Some concerns	Low risk	Low risk
Esencia lens (Garcia-del valle et al.) (25)	Low risk	Low risk	High risk	Low risk	Low risk
DIMS spectacle lenses (Lam et al.) (26, 27)	Low risk	Low risk	Low risk	Low risk	Low risk
Highly aspherical lenslets (Bao et al.) (10, 28, 29)	Low risk	Low risk	Low risk	Low risk	Low risk
Jakobsen and Møller (30)	Low risk	Low risk	High risk	Low risk	Low risk

Green: Low risk; Orange: Some concerns; Red: High risk.

treatment effect sizes. The following interventions were found to be effective in the reduction of myopia progression: HAL, MiSight contact lenses, low dose atropine 0.05%, Biofinity +2.50 D, DIMS and ortho-k lenses. Other interventions were also found to be effective but with lower effect sizes, such as extended depth of focus contact lenses and low dose atropine 0.025%. Low-dose atropine of 0.01% seemed to be the least effective method in the control of myopia progression and axial length elongation. Low-dose atropine 0.01% was not effective in the reduction of axial length elongation in two of the included studies.

Previous reviews concluded that there is high-level evidence to support the use of atropine to prevent myopia progression (7, 9, 11, 32). Those conclusions are consistent with our observations in this systematic review. The LAMP study (1-year) showed that topical atropine, even at low doses, remained one of the most effective treatments in slowing myopia progression in children aged 4–12 years (14). Although, concentrations of 1% are effective, there are associated side effects such as photophobia, as well as increases in myopia progression and axial length elongation following the cessation of treatment (rebound effect) (7). The results of our review showed that 0.01% seems to have less influence on axial elongation in Asian populations compared to 0.05% atropine that showed good efficacy and tolerability. Nevertheless, it is important to note that around 10% of children are non-responders and still have myopia progression even on high-dose atropine (33). In the 2-year follow-up of the LAMP study, 0.05% atropine remained the most effective concentration in the control of myopia progression (15). During the third year follow-up, children on continued treatment showed better myopia control results compared with children on the washout regimen (16). Nevertheless, the rebound phenomenon was small across the three atropine concentrations (0.05, 0.025, and 0.01%). Based on the 3-year trial results it seems that treatment should be ceased at an older age and that lower concentrations have smaller rebound effect. In fact, previous systematic-reviews and meta-analysis have found that low-dose atropine 0.01% showed good efficacy in controlling myopia progression (7, 17). Although low dosage atropine of 0.025 and 0.01% showed less effect in controlling myopia in some reported studies, the LAMP study also reported that myopia progression was effectively prevented by low dosage atropine 0.05, 0.025, and 0.01% among children with older age. Younger children required the highest 0.05% concentration to achieve similar reduction in myopic progression as older children receiving lower concentrations (34). Therefore, although more evidence and data are still needed, among the tested

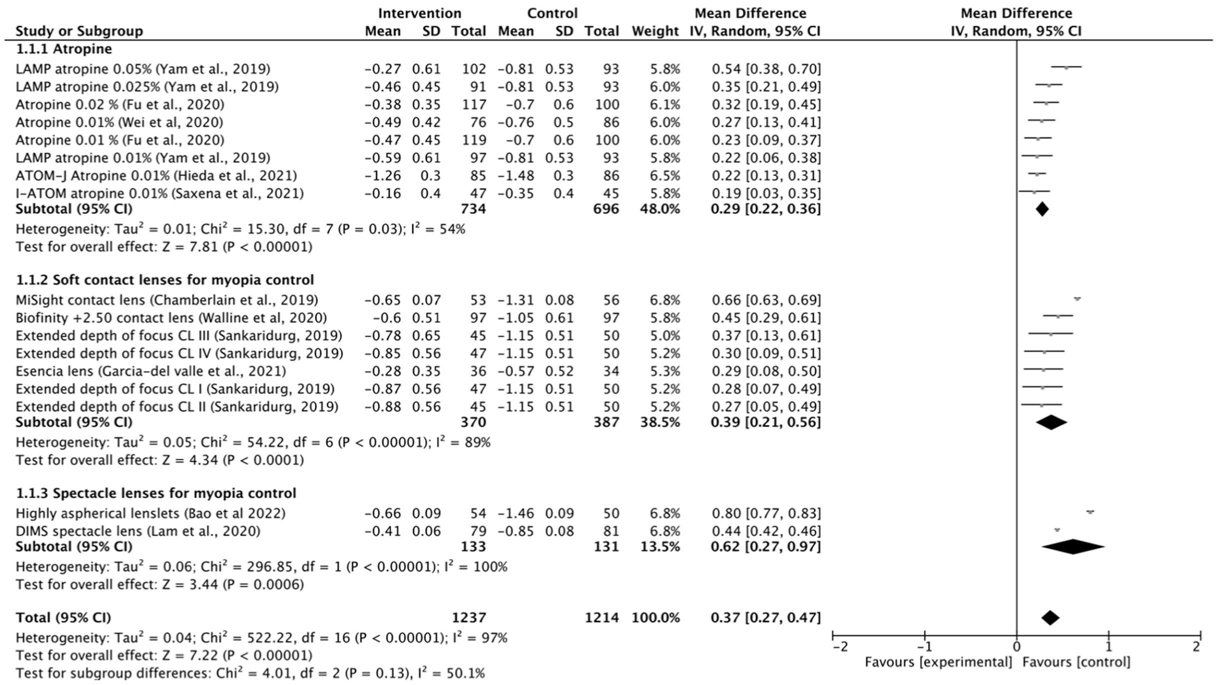

FIGURE 2
Forest plot of myopia progression (D) showing mean differences between treatment and control groups. The point estimate for the mean difference for each study is shown in gray color. The weight assigned to each study is represented by the size of each gray point estimate. The horizontal line through each gray point estimate shows the 95% confidence interval for the mean difference for each treatment. CL, contact lenses; CI, confidence interval; SD, standard deviation; K, keratology.

concentrations, 0.05% atropine may be optimal for children with older age.

However, the authors of those studies highlighted some limitations, such as the low sample size in some of the included studies, the reduced number of studies that evaluated the efficacy of 0.05% atropine and that most studies were conducted in Asia. Thus, findings may not be generalized to other ethnicities. Although, low-dose atropine is widely used in some East Asian countries for treating children with myopia, it has not been tested in European populations. Atropine is not commercially available in any of the European countries since clinical trials are still ongoing. There are 3 ongoing randomized trials in Europe, 2 in France and 1 in the United Kingdom, registered at the clinicaltrials.gov website. Differences between Asian and European populations are likely, given the well-known effects of iris pigmentation in relation to cycloplegic agents, such as atropine. A report on the efficacy of atropine arising from racial differences showed that atropine is less effective in populations of European than East Asian origin (35). New data also suggest that topical atropine treatment may be affected by environmental factors, such as extended time indoors. In a recent study from Israel children aged 9–15 years, under 0.01% atropine treatment ($n = 14$) had an increase in myopia progression and axial length during the COVID-19 lockdown year compared with the pre-lockdown year where the treatment was more effective (36).

The evidence regarding multifocal spectacles is evolving with time and the availability of new designs to slow myopia progression. Although a previous Cochrane systematic review concluded that there was no clinical meaningful slowing of eye growing (28), a more recent systematic review confirmed that multifocal lens have positive effects in slowing myopia progression both at 6 and 12 months with sustained effects until 36 months (8). Recent RCTs showed that multifocal lenses, either spectacles (HAL 2-year and DIMS 3-year including children aged 8–13 years) or contact lenses (MiSight 3-year and extended depth of focus 2-year including children aged 8–13 years), may confer a similar treatment benefit compared to atropine, with evidence of efficacy to slow both axial length and myopia progression in both Asian and European populations (9, 10, 14, 21, 26, 34, 35). HAL lenses (2-year) study were able to slow myopia progression by 0.80 D and axial length progression by 0.35 mm compared with children wearing single vision spectacle lenses (29). The myopia control efficacy was higher in children who wore their lenses full-time (≥12 h/day). Those results provide further proof of principle that devices such as HAL (based on the principle of imposing simultaneously a corrected image and a myopically blurred vision) slow the rate of myopia progression. This approach is further supported by the results obtained with the MiSight contact lenses (59% reduction in myopia progression and 52% reduction of axial elongation), which operate under the same principle (21). Children on the MiSight contact lenses trial were invited to continue the study for 3 additional years (MiSight 6-year). The results showed that MiSight contact lenses slowed the progression of myopia over a period of 6 years with a total reduction of 71% over the subsequent 3-year treatment period (22). The Bifocal Lenses Biofinity +2.50 D including children aged 7 to 11 years also showed a significant slowing of myopia progression (reduction of 43%) and axial length elongation (reduction of 36%) in a 3-year randomized trial (23). It should be noted that the MiSight lenses were approved by the US

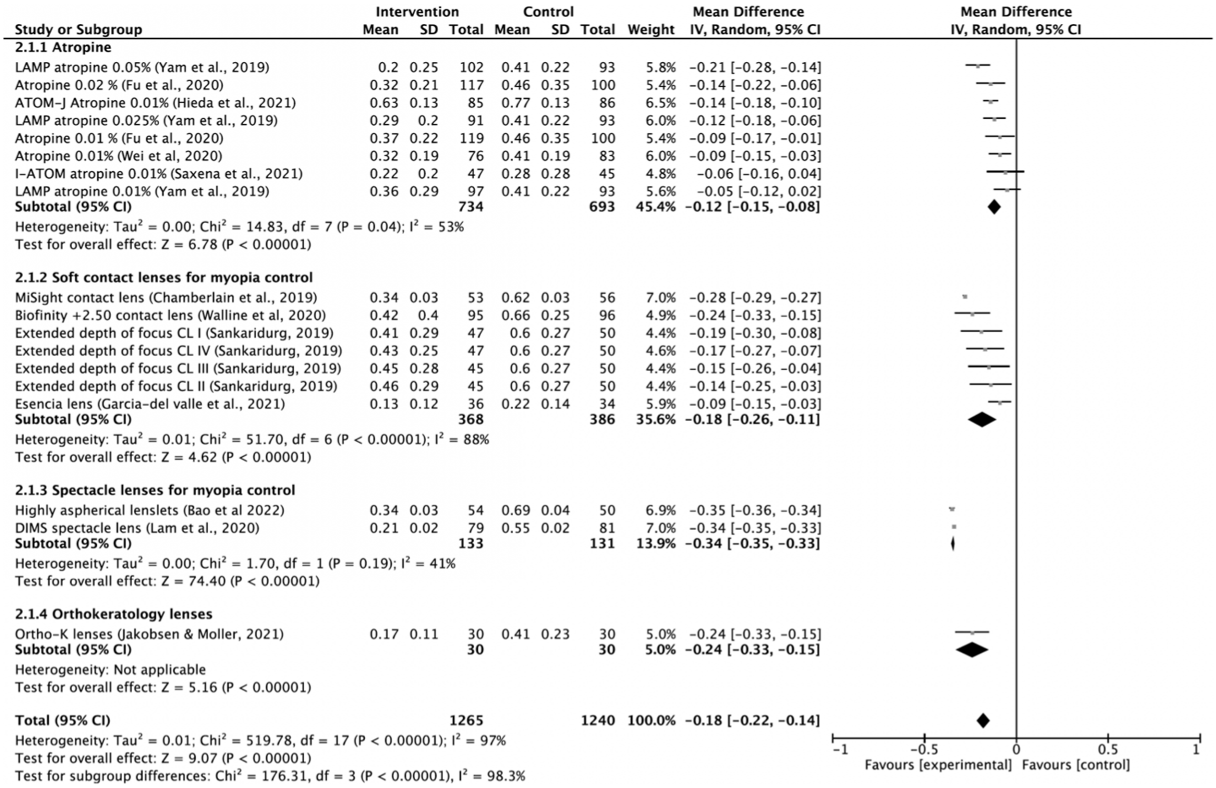

FIGURE 3

Forest plot of axial length elongation (mm) showing mean differences between treatment and control groups. The point estimate for the mean difference for each study is shown in gray color. The weight assigned to each study is represented by the size of each gray point estimate. The horizontal line through each gray point estimate shows the 95% confidence interval for the mean difference for each treatment. CL, contact lenses; CI, confidence interval; SD, standard deviation; K, keratology.

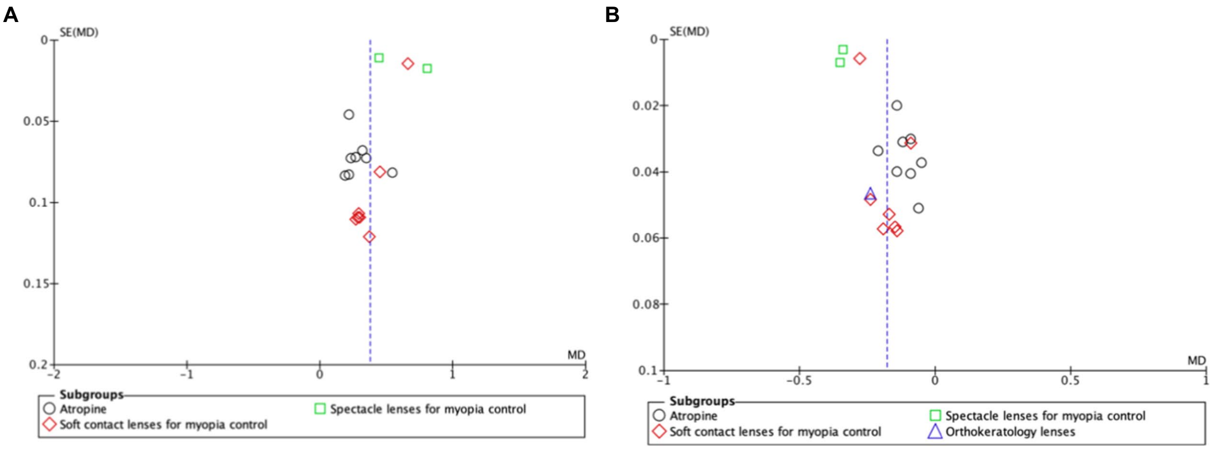

FIGURE 4

Funnel plot of comparison for myopia progression **(A)** and axial length elongation **(B)**. The funnel plot is a scatter plot that shows the effect estimates on the x-axis and measures of study precision (or study size) on the y-axis. The blue dotted vertical line represents the estimated common effect. SE, standard error; MD, mean difference.

FDA for myopia control in children, and the Stellest lenses (HAL) were granted breakthrough status in 2021, which facilitates clinical use.

The results of our review showed that HAL-2 year, DIMS 3-year and MiSight 3-year seem to be more effective than orthokeratology contact lenses (18 months) in slowing axial elongation. In

Scandinavian children aged 6–12 years orthokeratology lenses reduced AL elongation by 0.24 mm after 18-months follow-up without vision-threatening adverse events (30). However, most contact lenses and orthokeratology lenses (except for Menicon Bloom) are not approved for myopia control in Europe (off-label). Extended depth of focus soft lens are now available in some markets from Mark'ennovy (MYLO lens) and are CE marked for myopia management (37). Prescribing contact lenses in children is associated with risk of microbial keratitis. However, the risk is less (1 in 66 likelihood) than the risk of developing visual impairment due to complications of high myopia (1 in 5 likelihood), making contact lenses a worthy option for myopia control (38).

A study suggested that as a general goal, myopia control interventions should aim to provide a cumulative treatment effect of 1 D reduction to keep myopia below 6 D and axial length below 26 mm (40% less lifetime risk of developing myopic maculopathy) (39). Nevertheless, if a child progresses from −0.50 D in the early years of primary school, she or he will be highly myopic of −8.0 to −9.0 D by the end of schooling and 1 D reduction will not avoid the development of high myopia. With the new optical methods giving above 50% reduction in both spherical equivalent and axial length change over at least 3 years, eye care providers can aim for higher myopia reductions by incorporating myopic control into the first correcting spectacles to a child.

There are studies using combination of therapies for myopia control. Using topical 0.01% atropine with orthokeratology lenses has led to decreases in axial length elongation with most improvement during the first 6 months–1 year of treatment (40, 41). In another study, combining atropine 0.01% with orthokeratology was effective in children with baseline myopia of 1 to 3D, but no treatment benefit was found for children with higher baseline myopia (42). Nevertheless, the efficacy of this combined therapy was confirmed by two meta-analysis (43, 44). The interpretation of the results of those meta-analyses should take into consideration that the number of included studies was small and some studies were classified as having a high risk of bias. Thus, further research with well-designed RCT studies is important to understand if the treatment effect can be sustained over a longer follow-up period.

Although most of the treatment protocols seem to control progression of myopia, a few factors should be considered when analyzing the results. Most studies that tested treatment efficacy, recruited a small number of children and some children were lost-to-follow-up. For example, in the 3-year RCT of MiSight Lenses only 75.5% of the children concluded the study (53 MiSight children and 56 controls), in the ortho-k study 30% of the subjects dropped out before the treatment was well established and in the extended depth of focus study 25% of children discontinued the treatment soon after lens dispensing and prior to the 1-month visit (14, 35, 36). It is also important to note that refraction differences between the controls and experimental groups seem to diminish with time. Another limitation is the number of years of follow-up. One interesting point for discussion is the subgroup analysis and the covariate distribution such as the number of trials and participants contributing to each subgroup. Plausibility of interaction or lack of interaction, and possibility of confounding are important issues. Thus, further research is necessary.

Research on myopia control has increased over time with the number of publications increasing 4 times more from 1999 (almost 500 publications) to 2022 (about 2000 publications; www.pubmed.ncbi.nlm.nih.gov). Nevertheless, there is still no valid scientific criteria to decide when to initiate treatment based on progression and further research is necessary. Most pediatric ophthalmologists will treat children based on the rate of myopia progression (45). However, the ability to predict future myopia progression solely based on the rate of progression was found to be modest (46). The decision to treat should also be based on other factors, such as age of onset, ethnicity, parental myopia, axial length, and refraction at a given age. Different myopia progression risk calculators have been developed. Some will soon be available with new diagnostic devices designed to address the needs of myopia monitoring, usually based on autorefraction combined with biometry, and sometimes corneal topography (47).

When evaluating myopic progression and axial length elongation in treated children, it is important to analyze, for example, dose in the case of topical atropine, or when to discontinue treatment. For example, in children with myopia progression on low-dose atropine, the dose could be increased (0.01% twice a day; or 0.05, 0.1, 0.5%, or 1%). The decision must take into consideration that eye growth varies by season throughout the year, and it may be influenced by environmental factors (48, 49). Consequently there is the need to take at least a full year observation to keep track of environmental variables, such as outdoor time and near work (26, 33). Based on the 3-year trial results of the LAMP study (16) it seems that treatment can be continued until teenage years and later discontinued while monitoring the child for at least 12 months to avoid a rebound effect.

Our study has several limitations that should be highlighted. We only included 12 studies from 2019 to 2021. Although most studies were conducted in Asia, the target population varied. Both placebo, single vision spectacle lenses and single vision contact lenses were used as controls. These factors may have potential influence in our results. Thus, risk of bias cannot be excluded. There was high heterogeneity among each treatment regimen ($I^2 > 50\%$). Age was similar between studies and there was not sufficient data to explore how treatment varies with age.

The present study provides recent estimates of the efficacy of several therapies available to treat myopia progression by using data from 12 studies published over the last 3 years. This study also provides data on treatment comparisons that allows eye care providers to access the results and decide the best treatment options based on their efficacy and availability.

Further studies should focus on the effects of prolonged therapy taking in consideration the rebound phenomenon that is still present for some of the therapies. It is also important to determine the role of ethnicity in myopia treatment efficacy. Myopic macular degeneration has emerged as one of the leading causes of blindness and it is unclear how childhood myopia progresses into pathologic myopia in adulthood. Based on many ongoing experimental studies to control myopia progression, we can expect many new therapies to appear in the near future, and possibly some would stop myopia progression by 100%. The effective prevention of myopia onset is also awaited.

5. Conclusion

There is increasing evidence of myopia control by treatment protocols with proven efficacy. Based on evidence from the available RCTs reported in this analysis, the following evidence-based guidelines may be proposed: (1) HAL, MiSight contact lenses, low dose atropine 0.05%, Biofinity +2.50 D lenses, DIMS and ortho-k lenses were effective in the control of myopia progression; (2) Low dose atropine 0.025% and extended depth of focus contact lenses have also been found to be effective, but with lower effect sizes; (3) Low-dose atropine 0.01% was not as effective in reducing axial length progression according to some Asian studies. The recent data on new optical treatments, including soft contact lenses, DIMS and HAL, leads to optimism as these methods have shown considerable efficacy. Since they are much less invasive than alternatives such as orthokeratology and atropine, they are in principle likely to be preferable options. However, these results need to be confirmed in future as current knowledge is limited in the length of study periods and number of populations studied.

Author contributions

AG was responsible for the concept and design of the study. CL performed the data acquisition and analysis, as well as interpreting the results and drafting the manuscript. CP participated in interpretation of results and revision of the manuscript. 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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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 11 April 2023
DOI 10.3389/fpubh.2023.1096330

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Children and Health, a section of the journal Frontiers in Public Health

RECEIVED 12 November 2022
ACCEPTED 17 March 2023
PUBLISHED 11 April 2023

CITATION
Du B, Wang Q, Luo Y, Jin N, Rong H, Wang X, Nian H, Guo L, Liang M and Wei R (2023) Prediction of spherical equivalent difference before and after cycloplegia in school-age children with machine learning algorithms. *Front. Public Health* 11:1096330.
doi: 10.3389/fpubh.2023.1096330

Prediction of spherical equivalent difference before and after cycloplegia in school-age children with machine learning algorithms

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Purpose: To predict the need for cycloplegic assessment, as well as refractive state under cycloplegia, based on non-cycloplegic ocular parameters in school-age children.

Design: Random cluster sampling.

Methods: The cross-sectional study was conducted from December 2018 to January 2019. Random cluster sampling was used to select 2,467 students aged 6–18years. All participants were from primary school, middle school and high school. Visual acuity, optical biometry, intraocular pressure, accommodation lag, gaze deviation in primary position, non-cycloplegic and cycloplegic autorefraction were conducted. A binary classification model and a three-way classification model were established to predict the necessity of cycloplegia and the refractive status, respectively. A regression model was also developed to predict the refractive error using machine learning algorithms.

Results: The accuracy of the model recognizing requirement of cycloplegia was 68.5–77.0% and the AUC was 0.762–0.833. The model for prediction of SE had performances of R^2 0.889–0.927, MSE 0.250–0.380, MAE 0.372–0.436 and r 0.943–0.963. As the prediction of refractive error status, the accuracy and F1 score was 80.3–81.7% and 0.757–0.775, respectively. There was no statistical difference between the distribution of refractive status predicted by the machine learning models and the one obtained under cycloplegic conditions in school-age students.

Conclusion: Based on big data acquisition and machine learning techniques, the difference before and after cycloplegia can be effectively predicted in school-age children. This study provides a theoretical basis and supporting evidence for the epidemiological study of myopia and the accurate analysis of vision screening data and optometry services.

KEYWORDS
cycloplegia, children, machine learning, refractive error, refractive state

Introduction

Several studies have suggested that cycloplegic refraction should be considered the gold standard for epidemiological studies on refraction in school-aged children (1–3). Non-cycloplegic refractions are prone to significant errors, largely due to an active accommodation response (4–8). However, cycloplegia is challenging to perform for vision screening and epidemiological studies, resulting in a biased classification of ametropia; in fact, accommodation response cause a more negative value in SE, overestimating the presence and severity of myopia, and underestimating that of hyperopia (9, 10). Due to these biases, the research on myopia risk factors is likely to be significantly misguided, and inter-study comparisons will be affected (11–13). Therefore, an accurate prediction of SE after cycloplegia based on non-cycloplegic data could be an effective way to improve the accuracy of data in large-scale screening and epidemiological studies and would also be suitable for children for whom cycloplegia is contraindicated or refused.

Previous studies have examined the correlation between the difference in refraction before and after cycloplegia and patient characteristics. Significant correlations were found between age, non-cycloplegic spherical equivalent (SE), cylindrical power, intraocular pressure, whether wearing glasses and Lag of accommodation, axial length (14–16). A number of studies have tried to establish a prediction model based on the above-mentioned characteristics to predict the need for cycloplegia in children and adolescents. However, there are some problems in the research, such as the lack of independent validation set, insufficient number of features, simple mode, and the efficiency of prediction model is not ideal (13, 15, 16).

In the present study, detailed demographic and other relevant personal information, as well as vision screening data, of 2,467 school-age children were collected to explore the key influencing SE changes before and after cycloplegia. Our study could provide a convenient and helpful cycloplegic SE prediction model for clinical and epidemiological research.

Materials and methods

Ophthalmic examination and data set establishment

Data from 4,934 eyes of 2,467 school-age students was collected by Tianjin Medical University Eye Hospital in China during December 2018 to January 2019. None of the participants had a history of ocular disease or surgery. Written informed consent was obtained from parents or guardians, and verbal consent from all participants. This study was approved by the Institutional Ethics Committee of Tianjin Medical University Eye Hospital and followed the tenets of the Declaration of Helsinki for human research.

All subjects underwent general ocular examinations including visual acuity, non-cycloplegic autorefraction, optical biometry measurement, non-contact tonometry, lag of accommodation and gaze deviation in the primary position, which are basically routine examinations for school-age children and the digital results can be obtained directly to facilitate data processing. Subjects were excluded if their intraocular pressure was >25 mmHg. Cycloplegia was induced by instilling three drops of 1% cyclopentolate at 5 min intervals in each eye. One more drop of 1% cyclopentolate was administered if pupillary light reflex was still present or the pupil size was less than 6.0 mm at 30 min after the last drop. Cycloplegic refraction of both eyes was measured using the same autorefractor.

Visual acuity (uncorrected or with habitual correction, if any) was determined using a mounted and illuminated E chart at 5 m with ambient room lighting. Non-cycloplegic and cycloplegic refraction were measured with an autorefractor (KR.800, Topcon, Tokyo, Japan). Three repeated measurements were taken and averaged. The differences between the three readings had to be within 0.50D in both the spherical and cylinder components. Optical biometry parameters were measured using LENSTAR LS 900 system (HAAG-STREIT, Mason, Switzerland), including axial length, central corneal thickness (CCT), anterior chamber depth, lens thickness, and flat and steep keratometry. An average of the three measurements was considered in further analysis. If any two measurements of axial length differed by ≥0.02 mm, the readings were discarded and the eye remeasured. Intraocular pressure (IOP) was assessed using non-contact tonometer (CT.1 computerized tonometer, Topcon, Tokyo, Japan). Lag of accommodation (LOA) was measured by the open-field binocular autorefractor/keratometer (WR-5100 K; Grand Seiko Co., Ltd., Hiroshima, Japan). The subjects were instructed to view 20/100 Snellen letter at a distance of 33 cm, wearing the trial frame, with one eye occluded. Three repeated examinations were conducted, and the average SE was recorded as the accommodative response when the difference between the maximum and minimum was <0.25 D. LOA was calculated by subtracting accommodative response from accommodative stimulus (3.00 D). Gaze deviation in the primary position was measured using a Spot Vision Screener. Basic information including age, gender, and whether wearing glasses was collected by questionnaire.

A total of 33 parameters were included in the model, including 3 combined features (Figure 1). For the three combined features, one was the difference in SE between the sample-eye and the contralateral-eye (sample eye SE-contalateral eye SE), in order to avoid the effects of continuous adjustment fluctuations caused by binocular diopter disparity (17); the other two combined parameters were sample IOP/CCT and contralateral IOP/CCT, because the corneal thickness may affect the measurement of intraocular pressure (18).

Some values (4.6%) were missing in the non-cycloplegic ocular data due to technical problems, and we used a multivariate imputation method performed in an iterative round-robin fashion (19). More specifically, Bayesian ridge regression model was used to establish a mapping between each feature with missing values and other features to make predictions of missing data for each feature one by one, starting from the features with the least missing value (20). The final imputed data were obtained after iterating this imputation process for many rounds. In the present study, this imputation procedure was carried out using the Iterative Imputer algorithm implemented in the scikit-learn library and the iteration number was set to 100 (21).

We established prediction models at three outcome levels (online Supplementary Figure S1), each for a different clinical or epidemiological need in real practices. First, a binary classification model was trained to predict whether the subject had significant differences between cycloplegia and non-cycloplegia refractive measurement. Second, a three-way classification model was trained to

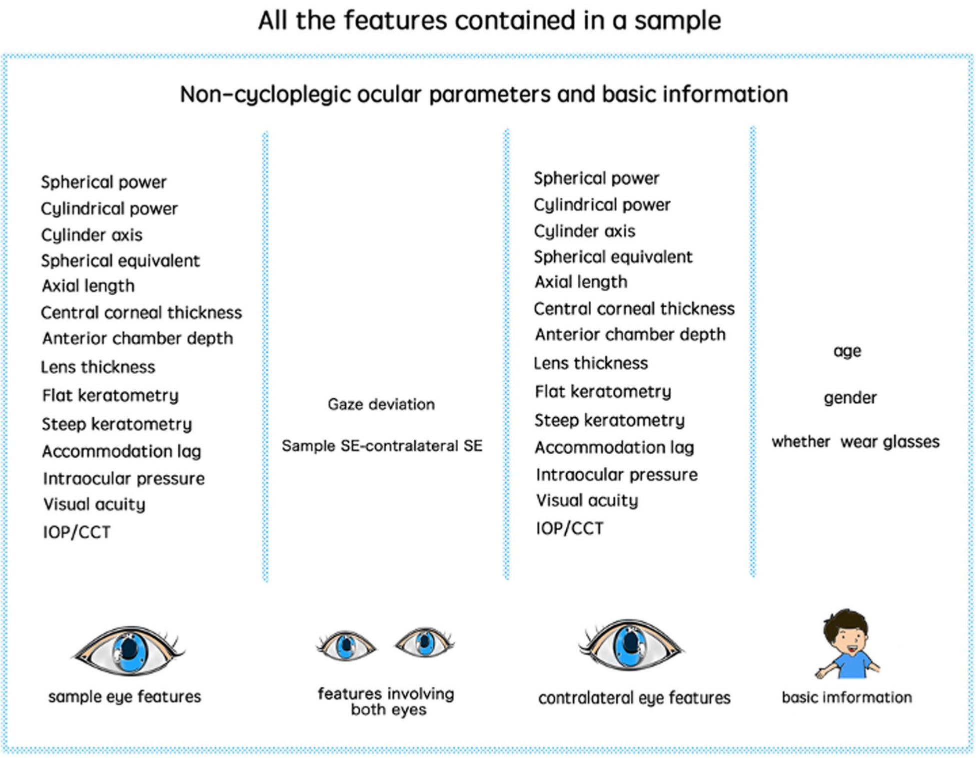

FIGURE 1
All the features contained in a sample.

predict cycloplegic refractive status. Third, a regression model was trained to predict cycloplegic refractive error.

Predicting the need for cycloplegia

In order to predict whether a child needs cycloplegia to obtain accurate refraction data, we performed a classification analysis to distinguish the eye samples with large differences in refractive error before and after cycloplegia (i.e., those who need cycloplegic) and those with small differences (i.e., those who do not need cycloplegic).

We tested three different thresholds to define large vs. small differences in refractive error (calculated as the value of cycloplegic SE minus non-cycloplegic SE), each corresponding to different needs of clinical and research tasks: 0.25, 0.50, and 0.75 D.

Binary classification models were trained and tested for each of the three thresholds using the following procedure: (1) 10% of all participations were randomly selected with both their eyes as the independent test dataset (i.e., 492 eyes) and the remaining 90% (i.e., 4,442 eyes) as the training dataset, (2) For the training set, the raw values of each feature was normalized to Z scores (i.e., mean of 0 and standard deviation of 1) using the following equation: $z_i = \left(x_i - \overline{x}_i\right) / s_i$, where x_i is the i-th feature vector, and $\overline{x}_i$ and s_i are the mean and standard deviation of $\overline{x}_i$, respectively. For the test set, each feature's mean and standard deviation values of the training dataset (i.e., the above $\overline{x}_i$ and s_i) were used to normalize the corresponding features of the test set, (3) During model training, 10-fold cross-validation within the training set was used for optimizing hyperparameters with the Hyperopt package (22, 23). Hyperopt is a Bayesian optimization method using a continuously updated probabilistic model based on hyperparameters and validation losses, which allows the search process to focus more on the hyperparameters that are likely to be optimal by reasoning from past validation losses, (4) Once the optimal hyperparameters were determined, the final model was trained using the full training set and evaluated using the test set, and (5) The performance of the final model was assessed using the receiver operating characteristic curve (ROC), classification accuracy, area under the ROC curve (AUC), sensitivity, and specificity.

Using the above machine learning procedure, we tested four machine learning algorithms: support vector machine (SVM) (24, 25), Random forest (RF) (26), Deep Neural Network (DNN) (27, 28), and Easy Ensemble Classifier (EEC) (29). Note that, at each threshold for defining the class labels of the eye samples (i.e., samples with large vs. small refractive error differences) in the present study, the number of samples of the two classes were unbalanced, which would lead to biased classification results. Therefore, we also adopted some balancing strategies for each machine learning algorithm to tackle this problem during model training, as follows:

1. SVM aims to find a decision hyperplane with a maximal margin separating the samples of two classes. To deal with the problem of unbalanced samples, we corrected the decision hyperplane by adjusting the parameter C_i for Class i with a weight: $C_i = class\ weight_i \times C$, where $class\ weight_i = \left(\sum_i n_i\right) / \left(2 \times n_i\right)$ and n_i is the sample size of Class i in the training dataset.

2. RF builds many decision tree models as the base learner, randomly samples a subset of features and a subset of training samples to train each decision tree, and then ensembles the results of all decision trees to form the final classification result based on the strategy of Bagging (30, 31).To deal with the problem of unbalanced samples, impurity calculations and prediction voting were adjusted using the same class weight as used in SVM.
3. DNN uses multiple fully connected layers and a non-linear activation function after each hidden layer to learn the feature representation of the nature of the original data, thereby facilitating the classification. To deal with the problem of unbalanced samples, different weights were assigned to the losses calculated for different classes during the training process so that the feedback given by the two classes were comparable when the error was back-propagated.
4. EEC is a classifier ensemble algorithm, specifically designed for learning with unbalanced samples. It draws a subset of samples from the majority class by bootstrapping to form balanced subsets of samples between the two classes for training an AdaBoost classification model (32). By repeating this procedure many times, multiple AdaBoost models were trained, and the classification results of all models were aggregated to form the final classification result.

Predicting the cycloplegic refractive state

To predict the cycloplegic refractive status using non-cycloplegic ocular parameters, each eye sample was categorized into three groups according to the cycloplegic SE – myopia (SE ≤ -0.50D), emmetropia (-0.50D < SE < 0.50D) and hyperopia (SE ≥ 0.50D). The same machine learning algorithms and classification procedures as described above were used here, except that a multi-class classification rather than a binary classification problem was to be solved. The confusion matrix, accuracy (ACC), precision, recall and F1 score were used to assess the classification performance. As a control condition, all eye samples were also categorized into the three refractive states mentioned above based on the non-cycloplegic SE. By comparing the refractive state predicted by the machine learning models with those defined directly using non-cycloplegic SE, we could assess how much the machine-learning-derived results could improve the accuracy of the non-cycloplegic-SE-defined refractive status.

Predicting the cycloplegic refractive error

As the cycloplegic refractive error has continuous values, predicting the actual values of cycloplegic refractive error corresponds to solving a regression problem, rather than a classification problem. Here, we tested four machine-learning algorithms for regression: Support Vector Regression (SVR), Random Forest Regression (RFR), AdaBoost Regression (ABR), and DNN. The training and test datasets were created in the same way as described in the above classification task, and the hyperparameters were optimized using the same 10-fold cross-validation procedure during training. The performance of the prediction model was assessed using r^2, r, mean absolute error (MAE), mean squared error (MSE), as well as the proportion of the samples with small prediction errors (< 0.50 D). The predicted SE and the true cycloplegic SE were also statistically compared using matched T-test to test whether there was a significant difference between them. To test whether the predicted SEs were significantly closer, than the non-cycloplegic SE, to the true cycloplegic SEs, the r^2, r, MAE, MSE, as well as the proportion of the samples with small prediction errors were calculated to assess the fitting degree between the cycloplegic SE and the non-cycloplegic SE. The *T*-test was also used to test whether there was a significant difference between them.

Results

Basic refractive results

A total of 4,934 eye samples of 2,467 children were included in this study and the mean age was 8.92 ± 2.21 years (ranging from 6 to18 years) and 1,292 participants (52.4%) were males. Before cycloplegia, the mean value of SE was −1.13 ± 1.58D and the prevalence was 60.3, 30.8 and 8.9% for myopia, emmetropia and hyperopia, respectively. After cycloplegia, the mean value of SE was −0.51 ± 1.81D, with a mean difference of 0.63 ± 0.69D compared with the non-cycloplegic SE, and the prevalence changed to 43.2, 21.7, and 35.1% for myopia, emmetropia and hyperopia, respectively.

Prediction of the need for cycloplegia

When the threshold for defining large and small refractive SE changes was set to 0.25 D, the positive (i.e., the samples with large SE changes) in the training set and test set accounted for 66.1 and 67.3%, respectively. With the threshold was set to of 0.50D, the proportions of the positive samples in the training and test sets were 47.0 and 44.5%, respectively. When the threshold was set to 0.75D, the proportions of the positive samples in the training and test sets were 30.6 and 31.1%, respectively.

The performances of the "large vs. small SE changes" classification obtained using the four machine learning algorithms for each class defining threshold were summarized in online Supplementary Table S1 and Figure 2. For contrast, the results obtained without sample balancing strategies are shown in online Supplementary Table S2 and online Supplementary Figure S2. The results confirmed that the machine learning algorithms performed much better when the sample balancing strategies were adopted: At the class defining threshold of 0.25D, very low specificities (49.7–54.0%) were obtained when the sample balancing strategies were not adopted as there were more positive samples than negative samples, and they were much improved (65.2–77.7%) when the sample balancing strategies were adopted; at the threshold of 0.75 D, very low sensitivities (47.1–60.1%) were obtained when the sample balancing strategies were not adopted as there were fewer positive samples than negative samples, and they were much improved (68.0–73.9%) when the sample balancing strategies were adopted.

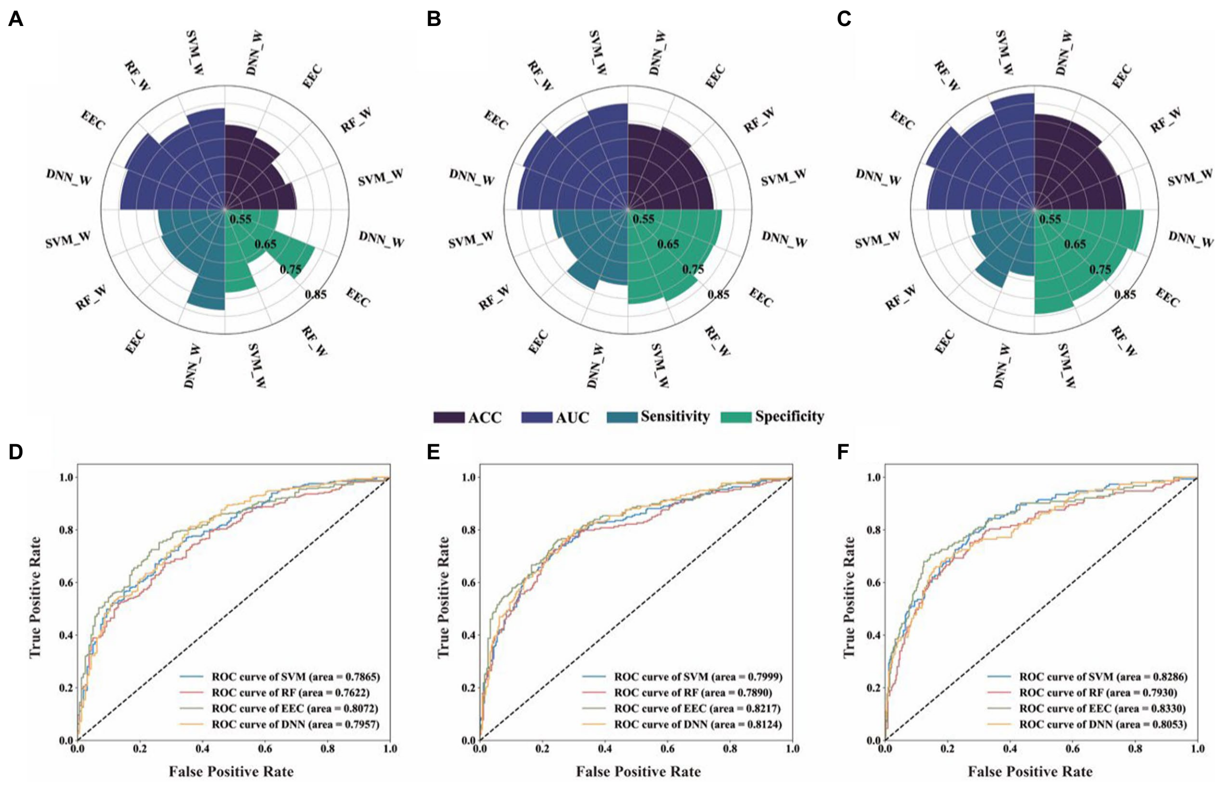

FIGURE 2
Performance of four machine learning models for binary classification of each class defining threshold. **(A,D)**, Threshold 0.25D, diagnostic values and ROC analysis of the four different predictive model; **(B,E)**, Threshold 0.5D, diagnostic values and ROC analysis of the four different predictive model; **(C,F)**, Threshold 0.75D, diagnostic values and ROC analysis of the four different predictive model. SVC_W, SVC algorithm with balancing strategies; RF_W, RF algorithm with balancing strategies; DNN_W, DNN algorithm with balancing strategies. (SVM_W, Support Vector Machine with balance method; RF_W, Random Forest with balance method; DNN_W, Deep Neural Network with balance method; EEC, Easy Ensemble Classifier; ROC curve, receiver operating characteristic curve; ACC, accuracy; AUC, area under the ROC curve).

Regarding the results obtained with sample balancing strategies adopted, we found that, for each threshold, samples with large vs. small SE changes could be successfully distinguished based on the non-cycloplegic data using all four machine learning models. The performances of different algorithms were generally similar, with the EEC model performed slightly better. When comparing the results across different thresholds, we found that the AUC increased gradually with the increase of threshold: AUC were about 0.762–0.807 when threshold value was 0.25D, 0.789–0.822 when threshold value was 0.50D, and 0.793–0.833 when threshold value was 0.75D.

Prediction of cycloplegic refractive state

The proportion of the three refractive states defined using cycloplegic SE were 42.58, 21.98 and 35.44% for myopia, emmetropia, and hyperopia, respectively, in the training set, and 48.37, 23.57 and 28.06%, respectively, in the test sets. The performances of the three-way classifications obtained using four machine learning algorithms with sample balancing strategies, together with the performances obtained directly using non-cycloplegic SE (the control condition) were summarized in online Supplementary Table S3 and Figure 3. The performances of machine learning algorithms without sample balancing strategies are shown in online Supplementary Table S4 and online Supplementary Figure S3 for contrast. The results showed that the classification performances of the four machine learning algorithms were similar (ACC ranging from 80.3 to 81.7%, precision ranging from 75.5 to 77.4%, recall rates ranging from 76.1 to 78.4%, F1 scores ranging from 0.757 to 0.775) and were much higher than those obtained directly from non-cycloplegic SE (ACC 66.8%, precision 69.4%, recall rates 59.0%, F1 scores 0.573).

Their corresponding confusion matrices with and without the sample balancing strategies are shown in online Supplementary Figures S4, S5, respectively. All confusion matrices obtained from the four machine learning models showed a clear diagonal structure (i.e., higher values on the diagonal), indicating successful classifications for each of the three classes, except the confusion matrix obtained directly from non-cycloplegic SE which showed a clear prediction bias toward myopia. Sensitivity and specificities for identifying myopia, emmetropia and hyperopia alone was shown in online Supplementary Table S5.

The proportions of the three refractive states defined using cycloplegic SE, non-cycloplegic SE, and obtained from the four machine learning algorithms predictions are shown in online Supplementary Figure S6 (the corresponding results obtained without the sample balancing strategies are shown in online Supplementary Figure S7). It clearly shows that non-cycloplegic SE strongly overestimated myopia and underestimated hyperopia,

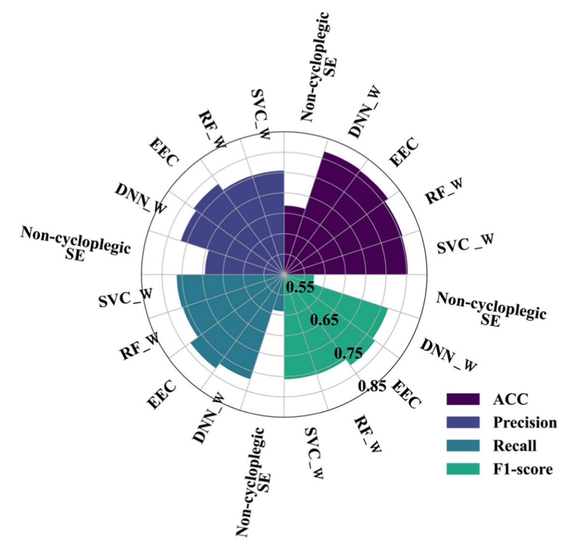

FIGURE 3
Performances of four machine learning algorithms and directly using non-cycloplegic SE for three- class classification. (SVC_W, Support Vector Machine with balance method; RF_W, Random Forest with balance method; DNN_W, Deep Neural Network with balance method; EEC, Easy Ensemble Classifier; ACC, accuracy; F1-score: balanced F Score).

whereas the proportions predicted by the machine learning models were much closer to the cycloplegic proportions.

Prediction of cycloplegic refractive error

The results of the machine learning algorithms in predicting the cycloplegic refractive error are summarized in online Supplementary Table S6. The prediction performances of the four machine learning models were similar (r^2 ranging from 0.899 to 0.927, MSE ranging from 0.250 to 0.380, MAE ranging from 0.372 to 0.436, r ranging from 0.943 to 0.963) and much better than the non-cycloplegic SE estimates ($r^2 = 0.723$, MSE = 0.942, MAE = 0.702, $r = 0.922$). Among the four models, AdaBoost regression model exhibited the best overall prediction performance, with $r^2 = 0.927$, MSE = 0.250, MAE = 0.372, $r = 0.963$.

The scatter plot for the relationship between predicted refractive error by Adaboost regression model and actual cycloplegic SE values is shown in Figure 4A, and the scatter plot for the relationship between non-cycloplegic SE and actual cycloplegic SE is shown in Figure 4B.

To assess the clinical value of the machine-learning-model predictions of the refractive error, we defined clinically significantly inaccurate prediction as a bias greater than or equal to 0.50D compared with cycloplegic refractive error. We found that the percentage of the clinically inaccurate samples predicted by Adaboost regression model (24.8%) was much smaller than that by non-cycloplegic SE estimates (54.3%) (Figures 4C,D). matched samples t-test showed that there was no significant difference between the mean predicted SE by machine learning models and the mean cycloplegic SE ($p = 0.169$ for SVR, $p = 0.153$ for RFR, $p = 0.533$ for ABR, for DNN $p = 0.227$), whereas the difference between the mean non-cycloplegic SE and the mean cycloplegic SE was highly significant ($p < 0.001$).

Weight analysis

To further interpret machine learning models, we explored the importance of each feature in different prediction tasks, as shown in Figure 5. As the tree-based models (i.e., EEC and ABR) performed the best overall in all three prediction tasks, we used the tree-based models to measure the importance of a feature using the importance score that is calculated as the impurity decrease when using a feature in split of a tree node.

It was found that in the task of predicting the need for cycloplegia, different features had relatively similar weights under each threshold for defining large vs. small differences in SE before and after cycloplegia, but the ranking order of features varied across different thresholds.

In the refractive status and refractive error prediction tasks, the SE, Spherical power and AL were among the top three features with the greatest importance, which is consistent with the fact that non-cycloplegic SE is often used to predict refractive status and refractive error in clinical work. Especially in the cycloplegic refractive error prediction model, these three features (SE, Spherical power and AL) were able to reduce the impurity by about 90%.

Discussion

To resolve the conflict between the necessity of cycloplegic refractive examination and the difficulty of performing cycloplegia in children and adolescents in practice, we applied a variety of commonly used machine learning algorithms to predict cycloplegic data based on non-cycloplegic data from a large dataset of Chinese school-age children. The predictions of the cycloplegic data were made at three different levels to meet the needs in different scenarios: prediction of the need for cycloplegia, prediction of the refractive status, and prediction of the refractive error. Our results showed successful predictions at all three levels, demonstrating the promising potential and practical value of predicting cycloplegic data using machine learning techniques based on non-cycloplegic data in clinical applications and epidemiological studies.

Identify patients with the need for cycloplegia

Several studies have shown that in children and adolescents, the fluctuation in refractive diopter is affected by many factors under non-cycloplegia condition (1, 2, 7, 11, 14–16), and the degree of such fluctuation varies greatly across individuals (33, 34). Clinically, recognizing when it is appropriate to forgo cycloplegia and when it is necessary to conduct cycloplegia for accurate refractive measurement is very useful for avoiding unnecessary cycloplegia. Simply thresholding in age and the state of ametropia cannot accurately identify the target patients with the need for cycloplegia (35, 36).

We obtained 30 parameters through clinical optometry routine examination under non-cycloplegia combined with machine learning analyses to predict the need for cycloplegia for the first level prediction. Identifying "significant SE change" is an important basis for cycloplegia in clinical decision. In this study, three thresholds were set for predicting SE changes before and after cycloplegia, which were

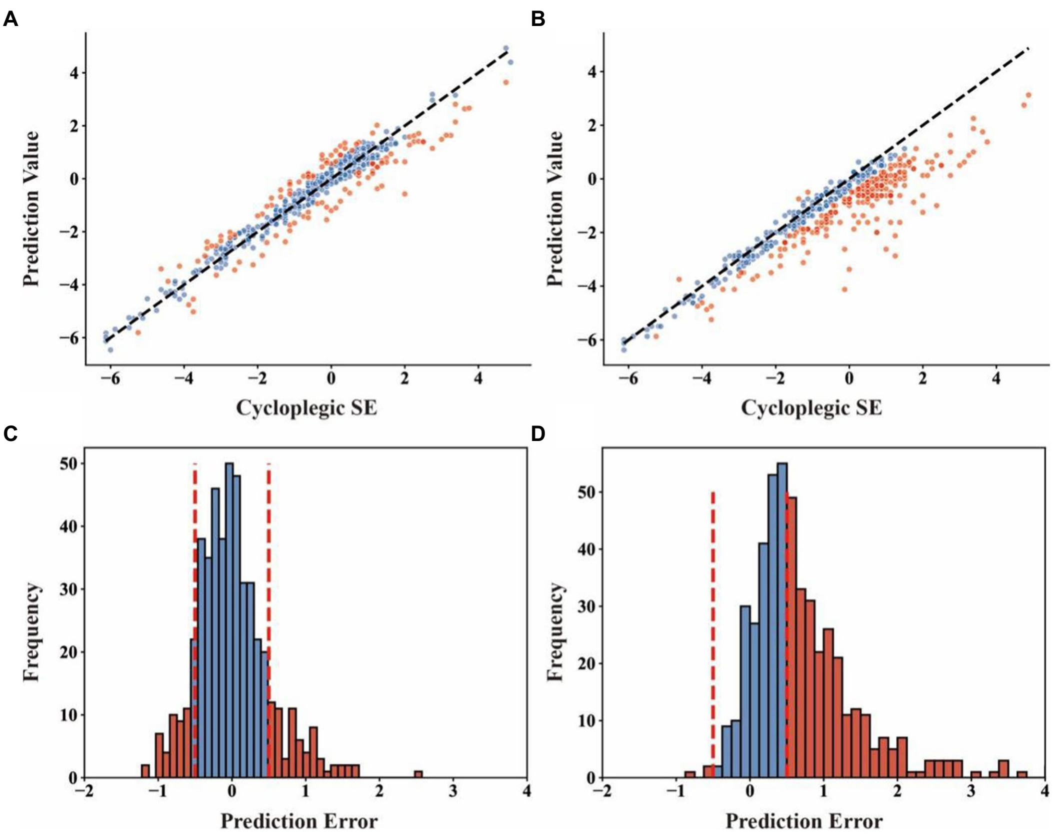

FIGURE 4
The scatter plot and distribution of prediction error of Adaboost regression model and directly using non-cycloplegic SE for the prediction of cycloplegic SE. **(A)**, the scatter plot with cycloplegic SE as the x-coordinate and predicted values from Adaboost regression model as the y-coordinate; **(B)**, the scatter plot with cycloplegic SE as the x-coordinates and predicted values directly using non-cycloplegic SE as the y-coordinates; **(C)**, the distribution of prediction errors by Adaboost regression model; **(D)**, the distribution of prediction errors by directly using non-cycloplegic SE. The red dots in **(A)** and **(B)** indicate the samples with prediction errors greater than 0.50D, and the vertical dashed lines in **(C)** and **(D)** indicate the boundary of the prediction error at 0.05D.

>0.25D, >0.50D and >0.75D. For predicting the target persons of SE change >0.50D, the performance of EEC model can reach an AUC of 0.822, with a specificity of 76.2% and a sensitivity of 74.4%. If the threshold of >0.75D was used to define the target persons, our EEC model can reach an AUC of 0.833, with a specificity of 78.5% and a sensitivity of 73.9%. We also tested the efficiency of the model at the threshold of >0.25D, which might not be of great clinical significance for a difference in SE between before and after cycloplegia, the EEC model still can reach an AUC of 0.807, with a specificity of 77.6% and a sensitivity of 69.5%. In the actual application of model prediction, we will adjust the model to keep the model high sensitivity, which ensures that patients who need cycloplegia are not missed. According to ROC curve, in the EEC model 0.50D threshold, when the sensitivity is set to 0.90, the specificity is 0.57, which means that more than half of the patients who do not need cycloplegic can be excluded from unnecessary cycloplegic operations when the patients who need cycloplegic are basically identified.

In addition, the weight analyses showed relatively similar importance scores for different features under each threshold for defining large vs. small differences in SE before and after cycloplegia, and with different ranking orders across different thresholds, suggesting that most features contributed to this binary prediction task.

Our results showed that the developed machine learning models could successfully identify the target patients and thus help avoid unnecessary cycloplegias, which may be valuable in clinical practice to reduce cycloplegia workload, or helpful to the optometrists in optical shops.

Improve the accuracy of refractive state assessment and refractive error measurement

It is known that assessing the refractive state using non-cycloplegic refractive data directly will lead to a myopic shift in the mean refractive error in school-age children (9, 10). Consistent with previous studies, such bias was also clearly observed in our study: 1301 (75.1%) eyes of hyperopia were wrongly assessed as emmetropic or even myopia and 535 (49.9%) eyes of emmetropic were wrongly assessed as myopia, thus an overestimation of myopia and emmetropia, and underestimation of hyperopia. Similarly, the mean refractive error changed from -0.51 ± 1.81 D to -1.13 ± 1.58 D under the non-cycloplegia condition with a mean difference of 0.63 ± 0.69 D toward myopia.

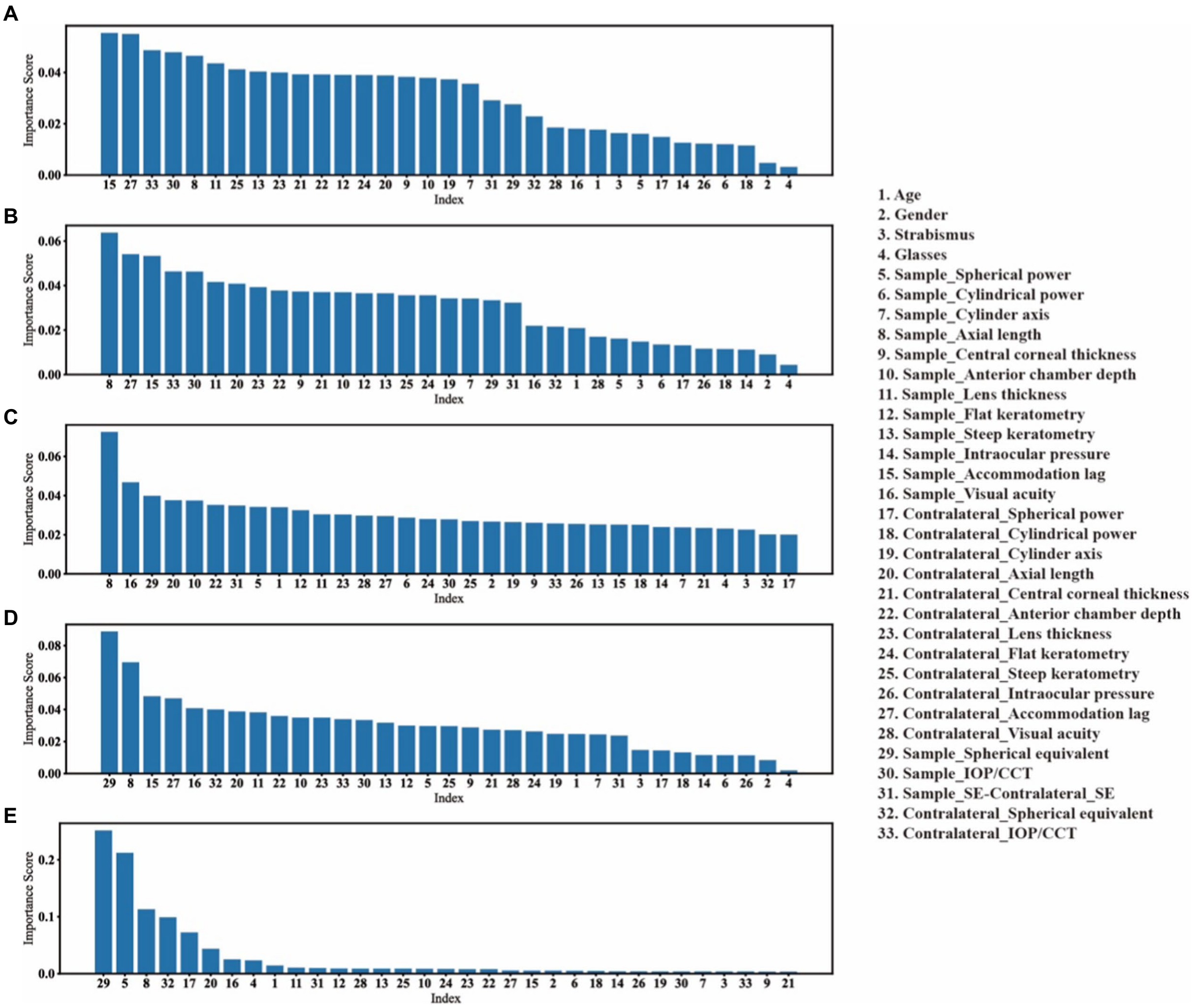

FIGURE 5
The features' importance in each prediction task. We take the reduction in impurity as the importance of that feature. **(A–C)**, the features importance of EEC model in predicting the need for cycloplegia with threshold is 0.25D, 0.5D and 0.75D, respectively. **(D)**, the features importance of EEC model in predicting the cycloplegic refractive states. **(E)**, the features importance of ABR model in predicting the values of cycloplegic SE.

Sankaridurg et al. established a linear regression model for children and adolescents aged 4–15 years, and predicted cycloplegic SE by age, uncorrected vision acuity, and non-cycloplegic SE. The prediction model R2 was 0.91, and 77% of participants were correctly predicted in refractive state, but the independent validation set was not used to test the effectiveness of the model (13).

In our study, the machine learning models predicted the distribution of refractive status with an accuracy of 81.7%, and for the Adaboost model of cycloplegic refractive error prediction, 75.2% of the predicted SE had a prediction error less than 0.50D. Such predictive power was much higher than direct non-cycloplegic SE estimates. At the same time, a t-test showed no significant difference in the means between the predicted SE of the model and the real SE. In addition, three easy-to-obtain parameters SE, Spherical Power and Axial Length were found to play an important role in the prediction. These results are reasonable, because these features indicate the pre-cycloplegia refractive result of the patient directly and the outcomes of pre-cycloplegic refraction are highly correlated with post-cycloplegic outcomes (2, 7). We speculate that the model also starts with the pre-cycloplegia refractive results, and adjust the results by some features related to ciliary muscle tension to obtain the final estimation.

The results of our present study suggest that, in school-based vision screening and epidemiological studies where cycloplegia may be considered impractical, predicting cycloplegic refractive error and refractive status by machine learning models based on noncycloplegic data at individual level may be an effective way. Especially, such improvement of the refractive state assessment and refractive error measurement provides an accurate estimation of the distributions of refractive status and refractive diopter at the population level, and thus has great value for epidemiological studies.

Limitations

There were several limitations in the present study. First, although missing data was a common problem in studies with large dataset and data imputation was adopted to remedy this problem in the present study, the missing data in our dataset may still have an impact on the performance of our machine learning models. Second, some ocular parameter used to build the machine learning models might not be easily available in practice, which would limit the applicability of the developed models in the present study. For example, the accommodation lag data in this study were obtained by open field autorefraction. In future studies, this measure may be replaced by dynamic retinoscopy that is a more convenient and widely available technique. Finally, although the sample size and features set in the present study was large compared to most previous studies (In this study, in order to expand the sample size, both eyes of a person are included in the data set, and there is a correlation between the eyes, which may have a certain impact on the robustness of the model), more data may be needed for developing machine learning models with higher prediction accuracies.

Conclusion

The machine learning algorithm can be used to estimate the demand for cycloplegia, the cycloplegia refractive error and the refractive status using the non-cycloplegia parameters. It is of application value in clinical work and epidemiological research.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by the human ethics committees at the Tianjin Medical University Eye Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BD, QW, and YL: collection and assembly of data, data analysis and interpretation, and manuscript writing. NJ and HR: collection of data. XW and HN: provision of study material. LG, ML, and RW: conception and design, financial support, manuscript writing, and final approval. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Social Science Major Project of Tianjin Municipal Education Commission (2020JWZD20 and 2022JWZD23), National Natural Science Foundation of China, Grant/Award number: 82070929, Tianjin Clinical Key Discipline Project (TJLCZDXKQ012) and (TJLCZDXKM007), and Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-037A). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1096330/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 19 September 2023
DOI 10.3389/fmed.2023.1128818

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RECEIVED 21 December 2022
ACCEPTED 04 September 2023
PUBLISHED 19 September 2023

CITATION
Du Y, Meng J, He W, Lu Y and Zhu X (2023) Challenges of refractive cataract surgery in the era of myopia epidemic: a mini-review. *Front. Med.* 10:1128818.
doi: 10.3389/fmed.2023.1128818

Challenges of refractive cataract surgery in the era of myopia epidemic: a mini-review

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Myopia is the leading cause of visual impairment in the world. With ever-increasing prevalence in these years, it creates an alarming global epidemic. In addition to the difficulty in seeing distant objects, myopia also increases the risk of cataract and advances its onset, greatly affecting the productivity of myopes of working age. Cataract management in myopic eyes, especially highly myopic eyes is originally more complicated than that in normal eyes, whereas the growing population of cataract with myopia, increasing popularity of corneal and lens based refractive surgery, and rising demand for spectacle independence after cataract surgery all further pose unprecedented challenges to ophthalmologists. Previous history of corneal refractive surgery and existence of implantable collamer lens will both affect the accuracy of biometry including measurement of corneal curvature and axial length before cataract surgery, which may result in larger intraocular lens (IOL) power prediction errors and a compromise in the surgical outcome especially in a refractive cataract surgery. A prudent choice of formula for cataract patients with different characteristics is essential in improving this condition. Besides, the characteristics of myopic eyes might affect the long-term stability of IOL, which is important for the maintenance of visual outcomes especially after the implantation of premium IOLs, thus a proper selection of IOL accordingly is crucial. In this mini-review, we provide an overview of the impact of myopia epidemic on treatment for cataract and to discuss new challenges that surgeons may encounter in the foreseeable future when planning refractive cataract surgery for myopic patients.

KEYWORDS
myopia epidemic, refractive surgery, cataract, biometry, IOL power calculation, complications

Introduction

The myopia epidemic is a major public health concern worldwide, and is particularly notable in East Asia. Over 80% of teenagers in East Asian countries and one-third in Europe and the United States of America (USA) are myopic (1). This prevalence is expected to increase over time due to modern lifestyles and increasing near-work activities, and the COVID-19 pandemic exacerbated the onset and progression of myopia (2–4). Myopia is not just a simple benign condition, and the socioeconomic consequences of myopia extend beyond the cost of its prevention and optical correction. With aging, myopic patients, especially those with high myopia, suffer various ocular comorbidities such as cataract and maculopathy, which can lead to severe visual impairment (5). Although cataract is a reversible cause of blindness, it can be challenging to manage in myopic patients (6–8).

Along with the surging myopic population, the number of patients with cataract and myopia, particularly high myopia (severe myopia with an axial length [AL] ≥ 26 mm), being seen in the clinic is increasing. Previously, when cataract surgery was only performed to restore vision, the difficulty of managing patients with high myopia was mainly related to intraoperative risk factors (e.g., posterior capsular rupture) and postoperative complications (e.g., retinal detachment). In recent decades, the advent of premium intraocular lenses (IOLs) and switching from traditional cataract surgery to refractive cataract surgery have escalated the challenges encountered by cataract surgeons. Patients are becoming more demanding about their desired postoperative vision. Furthermore, the increased demand for surgical correction of refractive errors, including corneal-and lens-based refractive surgery, has greatly shifted the clinical features of cataract patients with myopia, presenting unprecedented challenges for ophthalmologists.

The purpose of this mini-review is to describe the impact of myopia on cataract patients against the background of the myopia epidemic, and to discuss new challenges that surgeons may encounter when planning refractive cataract surgery for myopic patients with cataract.

Increasing prevalence of myopia

East and Southeast Asian countries, such as China and Japan, are myopia hotspots. The overall myopia rate in China was approximately 60% among schoolchildren, and exceeded 80% among high-school students (9–11). In Tokyo, 94.9% of teenagers were myopic according to a cross-sectional study conducted in 2017 (12). Although the current prevalence of myopia is lower in Europe and USA, the prevalence has doubled over the last decade (13–15). A landmark study by Professor Brien Holden predicted that, by 2050, almost half of the global population would be myopic and one in ten individuals would be highly myopic (1).

The COVID-19 pandemic affected countless aspects of people's lives. Many governments implemented strict home quarantine policies to limit the spread of COVID-19. Although COVID-19 itself did not directly affect myopia, the associated lockdown, online schooling, and reduced outdoor activity advanced the onset and accelerated the progression of myopia (16). According to Ma et al., the mean myopia progression of children aged 8–10 years during the COVID-19 pandemic was significantly higher than that before the pandemic in 2018 (−0.93 vs. −0.33 diopters [D], $p < 0.001$) in China (17).

Relationship between myopia and cataract

Myopia, in addition to the trouble seeing distant objects, may increase the risk of developing cataract. Population-based studies of different ethnicities have shown that myopia is associated with incident formation of nuclear cataract and posterior subcapsular cataract, with odds ratios ranging from 1.57 to 4.99 and from 1.34 to 1.93, respectively (18–23). Progression of mild myopia to high myopia is also associated with increased risk of cataract (20). Zhu et al. reported a significant correlation between high myopia and dark nuclear cataract, and suggested that the mechanism involved epigenetic downregulation of antioxidant genes in the lens in response to the increased oxygen tension caused by early vitreous liquefaction in highly myopic eyes (7, 8).

Changing characteristics of the cataract population in the myopia epidemic era

Modern lifestyles have led to ever-increasing worldwide prevalence of myopia and high myopia, leading to changes in the characteristics of cataract patients. In China, nearly one-third of cataract patients presenting at tertiary hospitals have high myopia (8). Patients with high myopia often develop cataract much earlier than those without refractive errors, affecting many people in their forties.

Cataract surgery in working-age adults differs from that in older adults. Working-age adults have greater expectations of postoperative visual acuity, visual quality, quality of life, and even spectacle independence. Cataract surgery becomes more challenging when complicated with high myopia because surgery carries higher risk in highly myopic eyes (24). Young patients, regardless of whether implantation of a monofocal IOL or premium IOL is planned, should be informed of their higher risk of developing maculopathy or open-angle glaucoma to manage their expectations of cataract surgery outcomes.

Another important change in patient characteristics is that an increasing number of patients have a history of corneal refractive surgery (CRS). Since the pioneering experimental work on the surgical procedure for changing the corneal curvature by Father Waclaw Szuniewicz in 1948, CRS has evolved hugely, from radial keratotomy (RK) in 1970 to the introduction of the VisuMax femtosecond laser in 2007, which led to small incision lenticule extraction (SMILE). SMILE is a minimally invasive and accurate method for refractive correction, and its popularity has increased; over 7 million procedures have now been performed globally (25). Over 40 million eyes have undergone CRS (26), and many are likely to develop cataract in the following decades.

Implantable collamer lenses (ICLs) may be an alternative to CRS for myopic patients with an extremely high degree of myopia or thin cornea. The earlier ICL models were associated with development of lens opacities. A prospective clinical trial revealed that 47.4% of eyes developed anterior subcapsular opacities and 26.3% of eyes developed clinically significant cataract within a mean follow-up of 3 years after implantation of an ICL V2/V3/V4 in highly myopic patients aged >45 years (27). The latest model, V4c, has a central port allowing sufficient aqueous flow between the posterior and the anterior chamber to maintain the normal physiology of the anterior segment, and had a lower rate of lens opacity at a 5 years follow up (28). Longer-term follow-up is warranted.

Emerging challenges and a paradigm shift in the management of cataract

The myopia epidemic has led to an unprecedented rise in the number of myopic and highly myopic patients. With aging, this population will be at very high risk of developing cataract. The popularity of subtractive and additive refractive surgery has caused many changes in these patients, and has led to greater demands on cataract surgeons, especially when planning refractive cataract surgery. Thus, new challenges are arising.

Management of refractive surprises

To accomplish a perfect refractive cataract surgery, hitting the refractive target is of paramount importance. The first step is to acquire accurate ocular biometrics. Ocular parameters, including the anterior chamber depth, the AL, and the corneal curvature, often change after refractive surgery (29, 30). Thereinto, precise measurement of the corneal refractive power is the greatest challenge when managing myopic post-CRS eyes. Pitfalls lie in the variations of the anterior curvature in the central area and the altered relationship between the front and back surfaces of the cornea after CRS. The former makes it difficult to perform standard keratometry or corneal topography to measure the anterior corneal curvature accurately. The latter means the well-acknowledged standardized refraction index of a virgin cornea (1.3375) is unsuitable for predicting the total corneal power from the anterior curvature. Wang et al. reported that the ratio was 0.82 in normal eyes and 0.76 after photorefractive keratectomy/laser-assisted *in situ* keratomileusis (LASIK) (31). These pitfalls often lead to overestimation of the cornea refractive power and underestimation of the IOL power. To overcome these errors, new devices, such as Scheimpflug cameras, and optical coherence tomography (OCT) allow accurate measurement of the anterior and posterior curvatures.

Kyuyeon et al. reported high predictability of IOL power calculation following myopic laser refractive surgery using a Scheimpflug true net power of 4 mm (Haigis) or a Scheimpflug total corneal refractive power of 4 mm (Haigis); the latter had a mean arithmetic predicted error of 0.00 ± 1.09 D (32). The average values of the central 4 mm zone are more reliable than the readings obtained by standard keratometry (33). Furthermore, a recent study compared the accuracy of the Barrett True-K, Holladay 1 (D-K), and Haigis formulas for calculating IOL power, and the Barrett True-K formula was the most accurate in Chinese cataract patients with prior RK. However, even using the Barrett True-K formula, only 46.8% of eyes had an absolute error within 0.5 D (34). Thus, newer and more accurate IOL formulas are desired.

Errors in AL measurement previously contributed to unwanted refractive surprises in highly myopic eyes due to eccentric measurement to the depth of a posterior staphyloma, rather than to the fovea. Partial coherence interferometry or swept-source OCT have greatly improved the AL measurement error (35). However, cataract itself may also subtly contribute to AL measurement error, and a slight but significant reduction in the AL measurement after cataract surgery was reported (36). One hypothesis explaining the preoperative measurement error is that the real refractive index of the implanted lens is known, whereas the refractive index of the human lens could change according to the cataract grade (37). Considering that cataract is more frequent in myopic patients, lens opacity might assume another decisive role in AL accuracy. However, the refractive index of the human lens could be unreliable, and De Bernardo et al. proposed a linear regression formula to correct the preoperative AL to eliminate systematic error derived from this biometric (36). Additionally, the ICL itself may introduce a source of measurement error. Zhang et al. compared the biometrics before and after ICL V4c implantation and reported a slight but significant increase in AL measured using a Pentacam-AXL (OCULUS) and IOLMaster 500 (ZEISS) (38). They concluded that this change in AL did not affect the IOL power calculation using the Barrett Universal II formula. However, given that current IOLs are mostly designed with a 0.5 D interval, future comparative studies using an IOLMaster 700 (ZEISS) and other formulas are necessary to improve the measurement accuracy, especially if IOLs with a smaller diopter interval or individualized IOLs are developed.

After acquiring accurate biometrics, another challenge is precise prediction of the effective lens position (ELP) in post-CRS eyes, which largely depends on the appropriate selection of the IOL formula. Considering the altered corneal refractive power and anterior chamber depth after CRS, the classic IOL formulas may lead to inaccurate prediction of the ELP. For example, a flattened cornea causes a falsely shallow ELP, resulting in an insufficient IOL power and a hyperopic shift after surgery. This error might be avoided by using formulas that do not use the corneal power to infer the ELP, such as the Haigis-L and Shammas formulas (39, 40). Rosa et al. proposed a further advanced lens measurement approach that combines the R factor and $AL \times K$ ($AL \times$ mean keratometry) methods for post-CRS IOL power calculation with unknown preoperative parameters, and 79.41% of eyes had a refractive error of <1 D (41–43).

The available formulas can be categorized into two groups depending on whether they use historical data before CRS. Cataract surgeons now mostly prefer formulas that do not rely on historical data because most patients cannot provide this information, and even when these data are provided, they are not useful because the biometrics may change after CRS (36). Recently, Cione et al. proposed a multi-formula approach that is independent of historical data, and could be applied to different ranges of the corneal curvature and AL to improve the IOL power calculation after CRS (44). Their approach could improve the refractive outcomes of post-CRS eyes. Newer formulas based on big data and artificial intelligence (AI), such as the Hill-RBF and Kane formulas, have improved the accuracy of the IOL power calculation (45). However, it is unclear how these formulas work in post-CRS patients because no studies have been published. Thus, AI-based formulas designed for patients with history of CRS are required.

Appropriate IOL selection

Implantation of a multifocal/extended-depth-of-focus (EDOF) IOL is a core aspect of refractive cataract surgery. Many studies have reported satisfactory visual outcomes for using different premium IOLs in myopic and highly myopic eyes and in eyes with a history of CRS. However, considering the increasing number of myopic patients and the popularity of CRS, every detail of cataract surgery needs to be ameliorated as much as possible.

The visual quality in terms of contrast sensitivity was reported to decrease in cataract patients after multifocal IOL implantation, possibly due to the distribution of light to different focal points (46). However, Bucci et al. reported that EDOF IOLs did not significantly decrease contrast sensitivity in cataract patients after LASIK compared with monofocal IOLs (47).

Despite concerns about visual quality, for highly myopic eyes with special anatomical features, ophthalmologists should select the appropriate IOL carefully, offering long-term stability. For example, Zhu et al. reported that IOL decentration was positively correlated with AL (48), which was probably due to incompatibility between the IOL size and the capsular bag size (6). For these eyes, a plate-haptic IOL might be more suitable than a C-loop haptic IOL because a plate-haptic IOL provides more friction as the main source of support. Due to the apparent inevitability of compromised IOL stability in highly myopic eyes, more knowledge of the tolerance to instability of different premium IOLs is necessary (49). Using the quick contrast-sensitivity function method, Guo et al. compared a trifocal IOL and an EDOF IOL, and suggested that the EDOF IOL showed better tolerance to IOL tilt (50).

Prior CRS might also cause irregular astigmatism and eccentric ablation is possible, which may contraindicate the implantation of multifocal/EDOF IOLs. However, myopic patients with a history of CRS usually express the greatest demand for achieving or continuing spectacle independence after cataract surgery. In this situation, careful planning of monovision cataract surgery and the use of a monofocal IOL might help (51), and crossed pseudophakic monovision could be planned in patients with refractive surprise after initial eye surgery to achieve spectacle independence if contraindications are to be avoided. Light-adjustable lens technology, offering postoperative refractive adjustments of IOL power, are theoretically appealing to patients with a history of CRS, whose preoperative IOL power calculation is relatively imprecise. However, as reported by Moshirfar et al., the precision of this technology is still compromised in patients with a history of CRS, emphasizing the need for further advancements in the technology of light adjustable lenses (52).

Requirements for the surgical approach

Decreased corneal integrity caused by structurally weakening RK incisions poses a challenge to cataract surgeons. Zhang et al. analyzed the outcomes of phacoemulsification using different sizes of clear corneal incision in post-RK eyes and found that dehiscence of the RK incisions could be closed successfully by injecting an air bubble into the anterior chamber at the end of surgery (53). Alternatively, Wang et al. reported a smaller clear corneal incision or scleral tunnel incision might be safer (54).

It has been over 20 years since the first ICL implantation and gradually more patients with high myopia and an ICL are presenting at clinics for cataract surgery. Although several studies have shown that replacing the ICL and cataract with an IOL is safe (55, 56), the potential risk of corneal endothelium abrasion and the prolonged surgery time add to the difficulty of cataract surgery (57).

Increasing frequency of complications after cataract surgery

As the number of myopic patients with cataract increase, surgeons are becoming more likely to encounter complications such as posterior capsular opacification (PCO) and retinal detachment.

PCO is the most common complication after cataract surgery and can be treated by Nd:YAG capsulotomy. In a study of 15,375 eyes, Lindholm et al. evaluated the 5 years cumulative probability of Nd:YAG capsulotomy after cataract surgery and found that low-diopter IOLs (5–16.5 D) implanted in myopic patients with cataract were associated with significantly greater risk (58). Another retrospective study of 500,872 operations confirmed that the risk of developing PCO was higher in eyes with an AL of >26 mm (59).

Retinal detachment is a severe complication of cataract surgery and can lead to irreversible visual impairment. Thylefors et al. and Lin et al. reported a strong correlation between pseudophakic rhegmatogenous retinal detachment and myopia (60, 61). The cumulative risk of retinal detachment development in highly myopic eyes after small incision coaxial phacoemulsification was 0.47, 0.71, 1.71, 2.59, and 3.28% at 3, 6, 15, 48, and 63–105 months, respectively (62). Thus, in myopic patients with cataract, especially those with high myopia, comprehensive preoperative fundus examination and regular follow-up are vitally important for protecting their vision.

What is in store for the future?

SMILE has evolved into an established CRS for the correction of myopia. In the foreseeable future, the number of patients requiring cataract surgery after SMILE is expected to increase. Although recent literature suggests that SMILE technologies, unlike excimer-based procedures, achieved more favorable keratometric and aberrometric profiles, there are limited data for IOL power calculations after SMILE and a standard protocol has not been established. Only two comparative studies have examined the predictability of different IOL formulas after SMILE, and both suggested that ray tracing was superior to conventional formulas (63, 64). However, 20% of eyes had an absolute prediction error of >0.50 D, which may significantly compromise visual function. With accumulation of patient numbers and clinical data, it is worth investigating the accuracy of the newer generation of IOL formulas incorporating AI.

Summary

The myopia epidemic is leading to an unprecedented increase in the global prevalence of myopia. Cataract surgery in myopic eyes, especially highly myopic eyes, is challenging, and the refractive surgery era has placed increasing demands on cataract surgeons, requiring highly accurate IOL power prediction to satisfy patients' greater expectations. Knowledge of the characteristics of different IOLs may facilitate appropriate IOL selection for optimal long-term stability. Careful perioperative management of patients is also essential to reduce the risk of complications and to minimize related visual impairment.

Author contributions

XZ and YL: conception or design of the work and critical revision of the manuscript. YD, JM, and WH: drafting the article.

All authors contributed to the article and approved the submitted version.

Funding

This work was supported by National Natural Science Foundation of China (82122017, 82271069, 82201161, 81870642, 81970780, 81670835), Science and Technology Innovation Action Plan of Shanghai Science and Technology Commission (19441900700, 21S31904900), Clinical Science and Technology Innovation Project of Shanghai Shenkang Hospital Development Center (SHDC12019X08, SHDC2020CR4078), Double-E Plan of Eye & ENT Hospital (SYA202006), Shanghai Municipal Key Clinical Specialty Program (shslczdzk01901).

Conflict of interest

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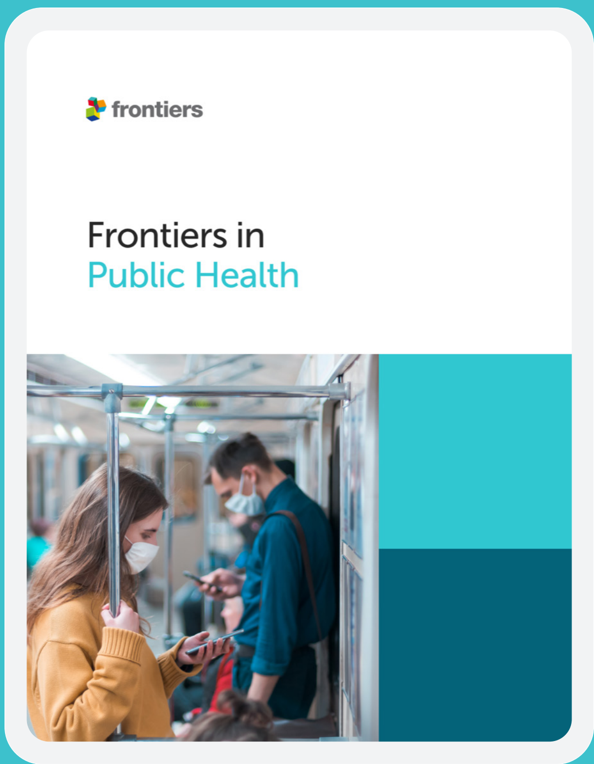

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