Contents lists available at Lighthouse Scholar
EYE SCIENCE
journal homepage: journal.gzzoc. com

doi: 10.12419/es24083001
**View this article at:** https://dx.doi.org/10.12419/es24083001

· **Review Article** ·

# The Guangzhou Twin Eye Study: what we learn in the context of myopia control

Yanxian Chen (陈燕先)[1,2], Hui Li (李辉)[3], Xiaohu Ding (丁小虎)[3], Mingguang He (何明光)[1,2,3]

1. School of Optometry, The Hong Kong Polytechnic University, Hong Kong 999077, China
2. Research Centre for SHARP Vision (RCSV), The Hong Kong Polytechnic University, Hong Kong 999077, China
3. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangzhou 510060, China

## HIGHLIGHTS

- The Guangzhou Twin Eye Study (GTES) has significantly deepened our understanding of myopia by demonstrating the strong genetic influence on its development, with high heritability estimates for axial length and peripheral refraction. The study also revealed the important role of environmental factors, suggesting that increased educational exposure accelerates myopia onset and progression, and that lifestyle factors like near work and reduced outdoor time contribute to myopia even among genetically identical twins.
- The GTES employed a unique longitudinal twin study design over 15 years, providing comprehensive annual data collection of ocular parameters and environmental exposures. Additionally, the study developed predictive models and risk assessment tools for myopia onset and progression, enhancing early identification of at-risk children.
- The findings from The GTES support the implementation of educational reforms and lifestyle interventions, such as increasing outdoor activities, to decrease the rising incidence of myopia. Clinically, the predictive models can assist early interventions and personalized treatment plans for myopia control. Future research directions include investigating gene-environment interactions through DNA methylation studies and monitoring the long-term outcomes of acquired myopia.

**Received date:** 2024-08-30; **Revised date:** 2024-09-19; **Accepted date:** 2024-10-16; **Published online:** 2024-12-20
**Corresponding authors**: Xiaohu Ding, E-mail: xiaohuding@163.com; Mingguang He, E-mail: mingguang.he@polyu.edu.hk.

Full Text

**Abstract:** The Guangzhou Twin Eye Study (GTES) is a cohort of twins living in South China that has been longitudinally followed for more than 15 years. This study has extensively investigated the heritability of myopia and the influence of environmental factors, producing significant and far-reaching impacts. GTES has found a high heritability of axial length and peripheral refraction, the significant role of education in myopia progression, and established prediction model for myopia onset and progression. The study has also explore the impact of both genetic and environmental factors on myopia development. By reviewing the major findings on myopia from the GTES, we hope to better inform public health strategies and clinical practices aimed at mitigating the global myopia epidemic.

**Keywords:** Guangzhou Twin Eye Study (GTES); myopia; heritability

**Cite this article as:** Chen YX, Li H, Ding XH, He MG. The Guangzhou Twin Eye Study: what we learn in the context of myopia control. Eye Science, 2024, 1(4): 249-258. doi: 10.12419/es24083001.

## INTRODUCTION

Myopia has become a notable health challenge worldwide, especially in East Asia. It affects up to 80% of school-aged children living in East Asia.[1-4] In other part of the world, such as Europe and the United States, the prevalence among school-aged children has risen rapidly over the past few decades, reaching approximately 20%–40%.[5-6] The escalating onset and rapid progression of myopia will lead to a substantial rise in high myopia. Each diopter of the increase of myopia substantially increases the risk of vision-threatening complications, such as glaucoma, myopic maculopathy, and retinal detachment.[7] As a result, myopia remains a critical focus for clinical practice and research endeavors, posing a significant global challenge not only in recent times but also for the foreseeable future.

Multiple factors contribute to the development of myopia, including both genetic and environmental factors. Genetic factors play an important role, as revealed by the higher prevalence of myopia among children with myopic parents.[8-10] While environmental factors, especially those associated with modern lifestyles, such as increased near work activities (reading, screen time) and reduced time spent outdoors, have been implicated in the rising prevalence of myopia.[11-13] Understanding the interplay between genetic and environmental factors is crucial for developing effective prevention and control strategies.

Twin studies provide a unique resource for myopia research. The Guangzhou Twin Eye Study (GTES) is a longitudinal population-based investigation of twins in Guangzhou, China. Commencing in 2006, eye examinations were conducted for twins aged 7-15 residing in select districts near the Zhongshan Ophthalmic Center, Guangzhou.[14] The study has grown to encompass 1,291 twin pairs, with a 15-year annual follow-up completed in 2023. Biological parents of these twins were also included in the baseline assessments. Key ocular parameters linked to myopia progression, such as cycloplegic refraction, axial length (AL), cornea curvature, height, and weight, were recorded each year. The GTES offers not only an excellent resource for the assessment of genetic and environmental contributions to myopia phenotypes, but also provides a comprehensive and ongoing dataset on myopia progression, leading the way for significant advancements in myopia research. This article aims to summarize the research achievements of the GTES in the field of myopia, shedding light on the lessons it provides for future research.

## KEY FINDINGS FROM THE GUANGZHOU TWIN EYE STUDY

### Genetic and environmental influences on myopia

*Heritability of myopia and peripheral refraction*

Numerous systemic traits that are genetically related often occur alongside ocular traits, indicating that these phenotypes or diseases may share common genetic pathways. By annually collecting a broad range of phenotypes, we have found that shared genetic factors accounted for 89% of the adjusted correlation between AL and height.[15] Additionally, the cross-time correlations between longitudinal changes in AL and height were statistically significant.[16] These findings indicate that the significant association between AL and height in children is primarily driven by genetic factors. Some other twin studies have reported the similar high heritability. For instance, Hammond et al. found that the heritability of refractive error was approximately 84% in adult twins in the United Kingdom.[17] Dirani et al.[18] reported heritability estimates of 90% for axial length in Australian twins, emphasizing the role of genetic predisposition in myopia development.

Peripheral defocus has been recognized as an important factor in the development of myopia.[19-20] We investigated the heritability of peripheral refraction through the classic twin study design of the GTES. Our findings revealed that genetic effects play a significant role in determining peripheral refraction, with heritability estimates ranging from 55% to 84%.[21] Additionally, our study on peripheral eye length (PEL) was the first to report that the estimated proportion of total variation explained by genetic effects ranged from 74.5% to 89.8%.[22] These findings suggest that the development of eye shape, as indicated by phenotypic variation in PEL and relative peripheral eye length (RPEL), is primarily influenced by genetic factors rather than environmental ones.The influence of peripheral refraction on myopia development has some essentialimplications. As peripheral hyperopic defocus is thought to stimulate axial elongation, it can lead to myopia progression.[23] Understanding that peripheral refraction is highly heritable underscores the potential for genetic factors to influence susceptibility to myopia through peripheral optical mechanisms.

Additionally, understanding the role of peripheral refraction in myopia development can inform the design of optical interventions. Our findings on the heritability of peripheral refraction suggest that individualized optical treatments that manipulate peripheral defocus may be beneficial in controlling myopia progression.[23] Studies have shown that lenses designed to reduce peripheral hyperopic defocus can slow myopia progression in children.[24] Incorporating these insights into clinical practice can enhance myopia control strategies.

*Impact of parental myopia on children*

Parental myopia has been reported to be strongly associated with the onset of myopia and the acceleration of myopic progression. However, our results showed that in children living in Guangzhou, 45.3% of those with high myopia had parents with no reported myopia.[25] Parental myopia may significantly affect children's refraction in early childhood. In our 12-year follow-up analysis, we found that children with highly myopic parents tended to have a longer axial length (AL) and a more myopic spherical equivalent (SE) at the age of 7. Additionally, the ratio of SE to AL was significantly higher in children with severely myopic parents, indicating that the influence of parental myopia takes effect at an early age and may accelerate myopic progression. However, the impact of parental myopia on SE progression diminished in adulthood.[26] These findings are consistent with other studies that have shown parental myopia to be a risk factor for early-onset myopia in children.[27-28] For example, Jones et al. reported that children with two myopic parents were six times more likely to develop myopia than those with no myopic parents.[27]

*Education and myopia*

The rise in myopia has been strongly linked to the demands of modern education systems, which are characterized by intense near work and limited outdoor time. Evidence suggests that increased educational exposure has contributed significantly to the myopia epidemic. Previous studies have confirmed that educational exposures, rather than age, accelerate the development of myopia.[29] However, for ethical reasons, no randomized intervention trials have been conducted to determine whether halting education would slow or prevent the onset and progression of myopia. The GTES cohort offers a natural experiment to examine the influence of education on the development of myopia after adolescence. We included a total of 880 first-born twins aged between 7 and 18 years, with participants from academic senior high schools (AHS), who experience extensive educational pressure, and vocational senior high schools (VHS), who face less pressure from the GaoKao. The study suggested that the onset and progression of myopia can continue even between the ages of 15 and 18, and that academic school education significantly increases myopic shifts in refraction in both non-myopes and myopes. Therefore, preventing the onset and progression of myopia during the later years of school, particularly in AHS, is an urgent and challenging task. (Hu Y et al., The onset and progression of myopia slows in Chinese 15-year-old adolescents following vocational rather than academic school pathways, accepted by *Investigative Ophthalmology Visual Science*). These findings align with other studies demonstrating the association between educational intensity and myopia development. A Mendelian randomization study by Mountjoy et al. provided evidence that increased years of education cause myopia.[30] Another study by Mirshahi et al.[31] showed that each additional year of education was associated with a more myopic refractive error, highlighting the impact of educational demands on myopia progression.

*Environmental impact on myopia*

Traditional epidemiological studies have grappled with disentangling the impact of genetic variations from environmental exposures. The discordance of characteristics among monozygotic (MZ) twin pairs presents a distinctive opportunity to delve into environmental effects, given the substantially more similar pairwise genetic backgrounds compared to randomly selected individuals. In our research, we employed cotwin methodology to investigate the influence of discordance in nearwork and variance in outdoor time on discordance in SE after accounting for genetic predispositions.[32] Through a mixed-effects model analysis, we identified age and nearwork as factors contributing to SE discordance. Notably, we observed an interaction effect between differences in outdoor time and age, indicating that the impact of outdoor time discrepancies on SE discordance was predominantly notable in older children, possibly due to behavioral differences emerging as twins and their cotwins mature.

Moreover, our comparison of refraction and ocular biometry data between twins and their parents revealed a significant shift towards myopia in the second generation. The increase in myopia prevalence was particularly pronounced in the range of −0.5 D to −9.0 D in twins compared to their parents (paper under review). Examination of intergenerational changes in biometry highlighted substantial increases in axial length across generations, with minimal changes in corneal dimensions. These findings underscore the prevalence of myopia during school-age years, disrupting traditional patterns of genetic distribution.Other studies have also shown the significant impact of environmental factors on myopia development. Our previous study reported that increased time spent outdoors reduced the incidence of myopia.[33] Ip et al.[34] found that children who engaged in more near work activities had a higher risk of developing myopia. These studies, along with our findings, emphasize the critical role of environmental exposures in the myopia epidemic.

*Collaborative GWAS findings on refractive error*

In recent years, we collaborated with the Consortium for Refractive Error and Myopia (CREAM) and contributed to several large-scale genome-wide association studies (GWAS) meta-analysis studies. These studies revealed gene-environment interactions during childhood and the age-dependent effects of genetic variants associated with refractive error and myopia, illustrating how genetic and environmental factors interplay over time to influence myopia development,[35] as well as the shared genetic influences on corneal curvature, axial length, and refractive error.[36] Most recently, a multiethnic genome-wide analysis by CREAM reported the identification of novel loci associated with axial length and revealed shared genetic influences with refractive error and myopia.[37] These findings have illustrated the genetic impact on myopia development at a genome-wide level, significantly increasing the understanding of the etiology of AL variation.

## Predictive models and risk factors

*Role of genome-wide significant SNPs in myopia prediction*

Although GWAS have uncovered an increasing number of common single nucleotide polymorphisms (SNPs) associated with refractive error and myopia, their predictive value for myopia development appears to be limited. In the GTES data, we found that genome-wide significant SNPs contributed minimally to predicting myopia progression and the development of high myopia by the age of 18.[38] This suggests that, compared to age-specific SE measures, SNPs offer little additional value in predicting myopia. The most accurate predictions were achieved using only age and its associated SE. Furthermore, we revealed that the optimal time for predicting the risk of developing high myopia by age 18 was during early adolescence (at ages 12 to 13). These findings have practical implications for the clinical screening and monitoring of children with myopia, especially in populations with a high prevalence of the condition. Similarly, a study by Verhoeven et al.[39] found that genetic risk scores had limited predictive value for individual myopia risk, explaining only a small fraction of the variance in refractive error.

*Development and validation of myopia prediction models*

Evaluating the risk of developing high myopia in adulthood is critical for the clinical decision-making process in myopia control. We presented reference centile curves for the distribution of refraction in children, derived from cross-sectional data of the Guangzhou Refractive Error Study in Children (RESC), and validated these curves by assessing their accuracy in estimating the severity of myopia and predicting the onset of high myopia using longitudinal data from the GTES.[40] These curves, with good sensitivity and specificity, can serve as valuable tools for assessing refractive error severity at different ages and identifying children at increased risk of developing high myopia later in life.

For children who have not yet developed myopia, we developed prediction models and a risk score system to assess the risk of myopia onset in the following year.[41] The model incorporated cycloplegic spherical equivalent (SE), axial length (AL), corneal curvature radius (CR), and the number of myopic parents. The study showed that either cycloplegic refraction or ocular biometry can predict the 1-year risk of myopia, and premyopia can be successfully defined through risk assessments based on these parameters.

Other studies have also developed predictive models for myopia progression which support the approach taken in the GTES to include multiple factors for better risk assessment. For example, Zadnik et al.[10] created a model using baseline refractive error and parental myopia to predict future myopia in children. Sankaridurg et al. [42] emphasized the importance of incorporating biometric measurements for accurate prediction.

## Longitudinal changes and progression

Understanding how refractive errors and ocular biometrics change over time is crucial for early detection and prevention. Monitoring and understanding these patterns can also help in predicting the progression of refractive errors and developing targeted interventions. Our early findings from the GTES revealed that the annual changes in AL and SE differ before and after the onset of myopia. The rates of progression of AL and SE were significantly higher before the onset of myopia, likely due to increased study intensity and decreased outdoor time. However, once myopic refraction was established, myopic progression could be reduced by imposed myopic defocus.[43] In addition to AL and SE, data from the GTES indicated that factors such as anterior chamber depth and corneal radius of curvature also correlate with myopia progression. These results underscore the importance of biometric measurements in understanding and predicting refractive errors and provide insights into the genetic and environmental factors influencing these relationships.[44] Moreover, our cluster and principal component analysis suggested that younger age with more severe baseline myopia, parental myopia, and extended periods of near work are linked to faster myopia progression, while increased time spent outdoors is associated with a delayed onset of refractive changes.[45] Our additional analysis further emphasized that the age of myopia onset is strongly associated with the risk of developing high myopia. Specifically, most children who developed myopia at ages 7 or 8 were likely to develop high myopia in adulthood.[46] These findings provide valuable insights into how refractive errors progress over time and the factors influencing these changes.

Other longitudinal studies have reported similar findings. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study also found that younger age at myopia onset predicted greater myopia progression.[47] These studies highlight the importance of early intervention to prevent high myopia.

## IMPLICATIONS FOR MYOPIA CONTROL

### Educational and lifestyle interventions

The rise in myopia is closely linked to the demands of modern education systems, which are characterized by extensive near work and limited outdoor time. Our aforementioned research has provided evidence that education, particularly academic education, significantly contributes to the prevalence of myopia. In countries with high rates of myopia, educational systems often emphasize early competition for entry into academic programs. This is accompanied by heavy homework burdens and widespread use of private tutoring. School schedules are tight and lengthy, leaving little time for outdoor activities. Therefore, reforming the education system is a fundamental measure to alter the prevalence of myopia in East Asia.

In the 1990s, Japan reduced classroom hours under the "Yutori Education" reform. A recent paper showed that the continuous increase in myopia and high myopia was curbed among medical students at Asahikawa Medical University who were educated under the new system. China has also issued a document titled "Notice of the Ministry of Education and Other Nine Departments on Printing and Distributing the Implementation Plan for Comprehensive Prevention and Control of Myopia in Children and Adolescents." This plan stipulates that, starting from the baseline prevalence in 2018, the annual prevalence of myopia should be reduced by at least 0.5% by 2023. In provinces with high prevalence rates, the target is to reduce it by at least 1% annually. By 2030, the prevalence of myopia should be controlled to within 3% for children aged 6, within 38% for primary school students, within 60% for middle school students, and within 70% for high school students. Increasing outdoor activity time is also part of this plan.

### Clinical applications

Early detection and monitoring of myopia are crucial for effective management and control. Our population-based centile curves can serve as a simple and effective screening tool to assess the likelihood of future high myopia in children with myopia, or to evaluate children who are not yet myopic using a premyopia prediction model. Tools like these, when applied in clinical settings, can help identify early signs of myopia, enabling early intervention and reducing the risk of developing high myopia and its associated complications.

Our research also provides evidence for personalized treatment. Clinicians can propose more aggressive treatment plans based on the age of onset of myopia in children, including timely use of orthokeratology lenses or pharmacological interventions such as atropine eye drops. Our data on annual changes in myopia can assist clinicians in regular monitoring and adjustment based on the progression of myopia, ensuring that each patient receives the most effective care.

## FUTURE DIRECTIONS AND RESEARCH GAPS

### The impact of gene-environment interactions on myopia

The high heritability of refractive errors observed in twin studies[48-49] suggests a genetic component to myopia. However, the rapid increase in myopia prevalence within just one or two generations[50] does not support the notion that genetic factors are the primary drivers. Environmental factors, particularly differences in educational environments, are believed to be the main contributors to the rapid rise in myopia prevalence. However, it remains unclear whether environmental factors influence myopia through gene-environment interactions. If environmental factors merely shift the mean refractive error without altering the shape of the refractive error distribution, this would imply that genetic factors still play a crucial role in refractive changes. The unique parental myopia data in the GTES can provide answers to this question. By comparing the refractive error distributions of parents and twins, as well as the lifestyle differences between generations, we can explore this issue further.

### Incidence of pathological myopia in acquired myopia

Pathological myopia is one of the top three causes of blindness worldwide,[51-53] but most of these data come from older populations from the last century, who predominantly had hereditary pathological myopia. In the recent myopia epidemic, most cases are acquired myopia, or school myopia, and it remains unknown whether these individuals will develop irreversible visual impairment similar to hereditary pathological myopia. The long-term follow-up of the GTES will enable us to answer this question. As these twins grow and enter adulthood, we can observe the occurrence and progression of pathological changes in high myopia patients and compare them with hereditary high myopia, exploring the differences and mechanisms of blindness between congenital and acquired myopia. Furthermore, the GTES will continue its data collection efforts, expanding its focus beyond myopia to encompass high myopia and its associated complications, as well as systemic diseases.

### Investigation of gene-environment interactions through DNA methylation in myopia onset

In recent years, genomic methylation has emerged as a focal point in myopia research, with numerous studies uncovering a close association between genomic methylation and myopia.[54-56] This discovery may potentially shed light on the genetic-environment interactions underlying myopia. Within the GTES cohort, we have identified five pairs of monozygotic twins exhibiting significant phenotypic variations. Through the analysis of DNA samples collected before and after the onset of myopia in these twins, utilizing the latest methylation sequencing technologies, we aim to investigate the impact of environmentally induced genomic methylation changes on myopia development. Research into gene methylation in naturally matched monozygotic twins holds promise in providing compelling evidence towards unraveling the mechanisms behind myopia formation.

## CONCLUSIONS

The findings from the Guangzhou Twin Eye Study have underscored the critical role of genetic factors in the development and progression of myopia. Twin studies like GTES provide a unique and powerful approach to disentangle the complex interplay between genetic and environmental factors. The high heritability estimates for traits such as axial length, peripheral refraction, and eye shape highlight the importance of genetic predisposition in myopia, especially in young children. The investigation of environmental exposures in GTES emphasized the need for comprehensive myopia control strategies that address both genetic predispositions and modifiable environmental factors, such as educational practices and outdoor activities. By continuing to explore the genetic and environmental determinants of myopia, we can better inform public health strategies and clinical practices aimed at mitigating the global myopia epidemic.

### Correction notice
None

### Acknowledgement
None

### Author Contributions
(I) Conception and design: Yanxian Chen, Xiaohu Ding, Mingguang He
(II) Administrative support: Mingguang He
(III) Provision of study materials or patients: Yanxian Chen, Hui Li
(IV) Collection and assembly of data: Yanxian Chen, Hui Li
(V) Data analysis and interpretation: Yanxian Chen, Hui Li, Xiaohu Ding
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

### Funding
None

### Conflict of Interests
None of the authors has any conflicts of interest to disclose.All authors have declared in the completed the ICMJE uniform disclosure form.

### Patient consent for publication
None

### Ethical Statement
None

### Provenance and Peer Review
This article was a standard submission to our journal. The article has undergone peer review with our anonymous review system.

### Data Sharing Statement
None

## References

1. Ding BY, Shih YF, Lin LLK, et al. Myopia among schoolchildren in East Asia and Singapore. Surv Ophthalmol 2017;62:677-697.DOI: 10.1016/j.survophthal.2017.03.006
2. Kim EC, Morgan IG, Kakizaki H, et al. Prevalence and risk factors for refractive errors: Korean National Health and Nutrition Examination Survey 2008-2011. PLoS One 2013;8:e80361.DOI: 10.1371/journal.pone.0080361
3. Wang SK, Guo Y, Liao C, et al. Incidence of and factors associated with myopia and high myopia in Chinese children, based on refraction without cycloplegia. JAMA Ophthalmol 2018;136:1017-1024. DOI: 10.1001/jamaophthalmol.2018.2658.
4. Resnikoff S, Pascolini D, Mariotti SP, et al. Global magnitude of visual impairment caused by uncorrected refractive errors in 2004. Bull World Health Organ. 2008, 86(1): 63-70. DOI: 10.2471/blt.07.041210.
5. Liang J, Pu Y, Chen J, et al. Global prevalence, trend and projection of myopia in children and adolescents from 1990 to 2050: a comprehensive systematic review and meta-analysis. Br J Ophthalmol.2024:bjo-2024-325427. DOI: 10.1136/bjo-2024-325427.
6. Grzybowski A, Kanclerz P, Tsubota K, et al. A review on the epidemiology of myopia in school children worldwide. BMC Ophthalmol. 2020, 20(1): 27. DOI: 10.1186/s12886-019-1220-0.
7. Bullimore MA, Brennan NA. Myopia control: why each diopter matters. Optom Vis Sci. 2019, 96(6): 463-465. DOI: 10.1097/OPX.0000000000001367.
8. Guggenheim JA, Northstone K, McMahon G, et al. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. Invest Ophthalmol Vis Sci. 2012, 53(6): 2856-2865. DOI: 10.1167/iovs.11-9091.
9. Jones-Jordan LA, Sinnott LT, Manny RE, et al. Early childhood refractive error and parental history of myopia as predictors of myopia. Invest Ophthalmol Vis Sci. 2010, 51(1): 115-121. DOI: 10.1167/iovs.08-3210.
10. Zadnik K, Sinnott LT, Cotter SA, et al. Prediction of juvenile-onset myopia. JAMA Ophthalmol. 2015, 133(6): 683-689. DOI: 10.1001/jamaophthalmol.2015.0471.
11. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. Ophthalmology. 2008, 115(8): 1279-1285. DOI: 10.1016/j.ophtha.2007.12.019.
12. Wu PC, Tsai CL, Wu HL, et al. Outdoor activity during class recess reduces myopia onset and progression in school children. Ophthalmology. 2013, 120(5): 1080-1085. DOI: 10.1016/j.ophtha.2012.11.009.
13. Huang HM, Chang DST, Wu PC. The association between near work activities and myopia in children: a systematic review and meta-analysis. PLoS One. 2015, 10(10): e0140419. DOI: 10.1371/journal.pone.0140419.
14. He M, Ge J, Zheng Y, et al. The Guangzhou Twin Project. Twin Res Hum Genet. 2006, 9(6): 753-757. DOI: 10.1375/183242706779462561.
15. Zhang J, Hur YM, Huang W, et al. Shared genetic determinants of axial length and height in children: the Guangzhou Twin Eye Study. Arch Ophthalmol. 2011, 129(1): 63-68. DOI: 10.1001/archophthalmol.2010.323.
16. Wang D, Ding X, Liu B, et al. Longitudinal changes of axial length and height are associated and concomitant in children. Invest Ophthalmol Vis Sci. 2011, 52(11): 7949-7953. DOI: 10.1167/iovs.11-7684.
17. Hammond CJ, Snieder H, Gilbert CE, et al. Genes and environment in refractive error: the twin eye study. Invest Ophthalmol Vis Sci. 2001, 42(6): 1232-1236.
18. Dirani M, Chamberlain M, Garoufalis P, et al. Refractive errors in twin studies. Twin Res Hum Genet, 2006, 9(4): 566-572. DOI: 10.1375/183242706778024955.
19. Smith EL 3rd, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. Vision Res. 2009, 49(19): 2386-2392. DOI: 10.1016/j.visres.2009.07.011.
20. Charman WN, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. Ophthalmic

Physiol Opt. 2010, 30(4): 321-338. DOI: 10.1111/j.1475-1313.2010.00746.x.

21. Ding X, Lin Z, Huang Q, et al. Heritability of peripheral refraction in Chinese children and adolescents: the Guangzhou Twin Eye study. Invest Ophthalmol Vis Sci, 2012, 53(1): 107-111. DOI: 10.1167/iovs.11-8716.
22. Ding X, Wang D, Huang Q, et al. Distribution and heritability of peripheral eye length in Chinese children and adolescents: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2013, 54(2): 1048-1053. DOI: 10.1167/iovs.12-10066.
23. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron. 2004, 43(4): 447-468. DOI: 10.1016/j.neuron.2004.08.008.
24. Sankaridurg P, Holden B, Smith E 3rd, et al. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. Invest Ophthalmol Vis Sci. 2011, 52(13): 9362-9367. DOI: 10.1167/iovs.11-7260.
25. Xiang F, He M, Morgan IG. The impact of severity of parental myopia on myopia in Chinese children. Optom Vis Sci. 2012, 89(6): 884-891. DOI: 10.1097/OPX.0b013e318255dc33.
26. Liao C, Ding X, Han X, et al. Role of parental refractive status in myopia progression: 12-year annual observation from the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2019, 60(10): 3499-3506. DOI: 10.1167/iovs.19-27164.
27. Jones LA, Sinnott LT, Mutti DO, et al. Parental history of myopia, sports and outdoor activities, and future myopia. Invest Ophthalmol Vis Sci. 2007, 48(8): 3524-3532. DOI: 10.1167/iovs.06-1118.
28. Jiang X, Tarczy-Hornoch K, Cotter SA, et al. Association of parental myopia with higher risk of myopia among multiethnic children before school age. JAMA Ophthalmol. 2020, 138(5): 501-509. DOI: 10.1001/jamaophthalmol.2020.0412.
29. Ding X, Morgan IG, Hu Y, et al. The causal effect of education on myopia: evidence that more exposure to schooling, rather than increased age, causes the onset of myopia. Invest Ophthalmol Vis Sci. 2023, 64(4): 25. DOI: 10.1167/iovs.64.4.25.
30. Mountjoy E, Davies NM, Plotnikov D, et al. Education and myopia: assessing the direction of causality by Mendelian randomisation. BMJ. 2018, 361: k2022. DOI: 10.1136/bmj.k2022.
31. Mirshahi A, Ponto KA, Hoehn R, et al. Myopia and level of education: results from the Gutenberg Health Study. Ophthalmology. 2014, 121(10): 2047-2052. DOI: 10.1016/j.ophtha.2014.04.017.
32. Ding X, Hu Y, Guo X, et al. Possible causes of discordance in refraction in monozygotic twins: nearwork, time outdoors and stochastic variation. Invest Ophthalmol Vis Sci. 2018, 59(13): 5349-5354. DOI: 10.1167/iovs.18-24526.
33. He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. JAMA. 2015, 314(11): 1142-1148. DOI: 10.1001/jama.2015.10803.
34. Ip JM, Saw SM, Rose KA, et al. Role of near work in myopia: findings in a sample of Australian school children. Invest Ophthalmol Vis Sci. 2008, 49(7): 2903-2910. DOI: 10.1167/iovs.07-0804.
35. Fan Q, Guo X, et al. Childhood gene-environment interactions and age-dependent effects of genetic variants associated with refractive error and myopia: the CREAM Consortium. Sci Rep. 2016, 6: 25853. DOI: 10.1038/srep25853.
36. Fan Q, Pozarickij A, Tan NYQ, et al. Genome-wide association meta-analysis of corneal curvature identifies novel loci and shared genetic influences across axial length and refractive error. Commun Biol. 2020, 3(1): 133. DOI: 10.1038/s42003-020-0802-y.
37. Jiang C, Melles RB, Yin J, et al. A multiethnic genome-wide analysis of 19, 420 individuals identifies novel loci associated with axial length and shared genetic influences with refractive error and myopia. Front Genet. 2023, 14: 1113058. DOI: 10.3389/fgene.2023.1113058.
38. Chen Y, Han X, Guo X, et al. Contribution of genome-wide significant single nucleotide polymorphisms in myopia prediction: findings from a 10-year cohort of Chinese twin children. Ophthalmology, 2019, 126(12): 1607-1614. DOI: 10.1016/j.ophtha.2019.06.026.
39. Verhoeven VJM, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. Nat Genet. 2013, 45(3): 314-318. DOI: 10.1038/ng.2554.
40. Chen Y, Zhang J, Morgan IG, et al. Identifying children at risk of high myopia using population centile curves

of refraction. PLoS One. 2016, 11(12): e0167642. DOI: 10.1371/journal.pone.0167642.

41. Chen Y, Tan C, Foo LL, et al. Development and validation of a model to predict who will develop myopia in the following year as a criterion to define premyopia. Asia Pac J Ophthalmol. 2023, 12(1): 38-43. DOI: 10.1097/APO.0000000000000591.
42. Gifford KL, Richdale K, Kang P, et al. IMI - clinical management guidelines report. Invest Ophthalmol Vis Sci. 2019, 60(3): M184-M203. DOI: 10.1167/iovs.18-25977.
43. Xiang F, He M, Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. Ophthalmology. 2012, 119(7): 1478-1484. DOI: 10.1016/j.ophtha.2012.01.017.
44. Wang D, Liu B, Huang S, et al. Relationship between refractive error and ocular biometrics in twin children: the Guangzhou Twin Eye Study. Eye Sci. 2014, 29(3): 129-133.
45. Chen Y, Chang BHW, Ding X, et al. Patterns in longitudinal growth of refraction in Southern Chinese children: cluster and principal component analysis. Sci Rep. 2016, 6: 37636. DOI: 10.1038/srep37636.
46. Hu Y, Ding X, Guo X, et al. Association of age at myopia onset with risk of high myopia in adulthood in a 12-year follow-up of a Chinese cohort. JAMA Ophthalmol. 2020, 138(11): 1129-1134. DOI: 10.1001/jamaophthalmol.2020.3451.
47. Jones-Jordan LA, Mitchell GL, Cotter SA, et al. Visual activity before and after the onset of juvenile myopia. Invest Ophthalmol Vis Sci. 2011, 52(3): 1841-1850. DOI: 10.1167/iovs.09-4997.
48. Lopes MC, Andrew T, Carbonaro F, et al. Estimating heritability and shared environmental effects for refractive error in twin and family studies. Invest Ophthalmol Vis Sci. 2009, 50(1): 126-131. DOI: 10.1167/iovs.08-2385.
49. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci. 2006, 47(11): 4756-4761. DOI: 10.1167/iovs.06-0270.
50. Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: Aetiology and prevention. Prog Retin Eye Res. 2018, 62: 134-149. DOI: 10.1016/j.preteyeres.2017.09.004.
51. Iwase A, Araie M, Tomidokoro A, et al. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. Ophthalmology. 2006, 113(8): 1354-1362. DOI: 10.1016/j.ophtha.2006.04.022.
52. Guo Y, Liu LJ, Xu L, et al. Visual impairment and spectacle use in schoolchildren in rural and urban regions in Beijing. Eur J Ophthalmol. 2014, 24(2): 258-264. DOI: 10.5301/ejo.5000348.
53. Tang Y, Wang X, Wang J, et al. Prevalence and causes of visual impairment in a Chinese adult population: the Taizhou eye study. Ophthalmology. 2015, 122(7): 1480-1488. DOI: 10.1016/j.ophtha.2015.03.022.
54. Jiang D, Lin S, Gong Q, et al. PAX6 gene promoter methylation is correlated with myopia in Chinese adolescents: a pilot sutdy. Ophthalmic Genet. 2024, 45(3): 219-225. DOI: 10.1080/13816810.2024.2315152.
55. Swierkowska J, Vishweswaraiah S, Mrugacz M, et al. Differential methylation of microRNA encoding genes may contribute to high myopia. Front Genet. 2023, 13: 1089784. DOI: 10.3389/fgene.2022.1089784.
56. Swierkowska J, Karolak JA, Vishweswaraiah S, et al. Decreased levels of DNA methylation in the PCDHA gene cluster as a risk factor for early-onset high myopia in young children. Invest Ophthalmol Vis Sci. 2022, 63(9): 31. DOI: 10.1167/iovs.63.9.31.