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Keywords:	abnormal visual acuity, school myopia, prenatal and neonatal factors

Prenatal and neonatal factors for the development of childhood abnormal visual acuity in primary and middle school students

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Abstract

Objectives: In this cross-sectional survey, we sought to determine the prevalence and risk factors of abnormal visual acuity (VA) and the influence of prenatal and neonatal factors on childhood VA in a pediatric population from Guangzhou, China.

Setting: Health survey covered 11 administrative districts in Guangzhou, including 991 schools.

Participants: All primary and middle school students in Guangzhou were invited to complete a questionnaire online with the help of their parents. The results of physical examinations were reported by school medical departments. The results of the questionnaire were collected by the researchers. In total, 253,301 questionnaires were collected.

Primary outcome measures: Uncorrected visual acuity (UCVA) with three levels: light anomaly>=6/18 to <6/12, mild anomaly>=6/60 to <6/18 and severe anomaly<6/60.

Results: A total of 39,768 individuals (15.7%; 95% CI, 15.6-15.9) had abnormal VA, and the rates rapidly increased from Grade 1-6 students (6.71%; 95% CI, 6.58-6.85) to Grade 10-12 students (51.4%; 95% CI, 50.6-52.1). The results supported that older age, female gender, high birth weight, formula feeding, only child status, higher level of parents' education, parental myopia, and longer homework time significantly increase the risk of abnormal VA. Conversely, late or premature birth, participation in outdoor activities, and father current smoking decrease the risk of abnormal VA. Delivery mode was not associated with the risk of abnormal VA.

Conclusions: This study validates known major environmental factors and heredity for myopia, and reports potential prenatal and neonatal factors for abnormal VA development in school students. In conclusion, prenatal and neonatal factors can affect the onset of childhood abnormal VA, but parental myopia and certain environmental factors represent the leading factors.

Keywords: abnormal visual acuity; school myopia; prenatal and neonatal factors.

Strengths and limitations of this study:

- A retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China
- Collection and analysis of both prenatal factors and environmental factors associated with myopia.
- Reactionary bias unavoidable as a voluntary participation survey.

Introduction

Abnormal visual acuity (VA) is highly prevalent in school students, and myopia accounts for over 90% of the cases in China, although hyperopia, astigmatism, and other eye diseases can also lead to decreased VA [1]. Myopia is caused by an inconsistency of the eye's refractive power with the length of the eye axis and includes two clinical types. In refractive myopia, the axial length (AL) is normal, but the refractive power of the cornea or lens is too strong, while in axial myopia, the refractive power of the lens is normal, but the AL is too long [2]. Although myopia is not a life-threatening disease, the World Health Organization recognizes it as a major cause of further visual impairment if not fully corrected [3]. However, at present, the high prevalence of myopia has become a serious public health problem in East Asia. In China specifically, the prevalence of myopia in high school students ranges from 43.0% to 78.4% [4].

Myopia is etiologically heterogeneous and is believed to be driven by numerous environmental factors and genetic variations, with onset beginning in the preschool stage. Environmental factors such as outdoor activities are strongly associated with myopia inception and development. Increasing outdoor time thus represents an important environmental factor that can protect young children from myopia and which has been supported by numerous studies. The protective effects of outdoor activity may be due to the high light intensity outdoors, the chromaticity of daylight, or increased vitamin D levels [4-8]. Separately, a number of studies have shown that parental myopia is an important risk factor for myopia in children, due to carriers of myopia susceptibility genes or a shared myopia-driving environment [6, 7, 9-11].

According to the developmental origins of health and disease theory, the development of childhood diseases may be affected by factors in prenatal life [12]. There are several epidemiological studies that have shown that cesarean delivery and premature departure may lead to a higher prevalence of myopia in childhood [13-16]. For example, premature departure may affect ocular development or later emmetropization, and may have a more complicated mechanism that affects the development of refractive status [13, 17-21]. In addition, breastfeeding in early life may have a greater effect on eyeball development, as the docosahexaenoic acid and arachidonic acid in breast milk may affect retinal and neural development[22].

Here, we sought to study the effects of multiple prenatal and neonatal factors on the development of myopia in primary and middle school students in Guangzhou area of China. For this study, the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality released an annual online health survey of primary and secondary school students and we subsequently received relevant information from this institution. We used descriptive statistics, logistic analysis, and multiple logistic regression models to analyze the data and explore the relationships between various environmental, parental myopia, and prenatal and neonatal factors and myopia. Our results are expected to provide additional evidence for childhood myopia etiology in East Asia and help to confirm potential prenatal factors for long-term diseases.

Methods

Data source

This study was approved by the institutional review board of The Third Affiliated Hospital of Guangzhou Medical University [2017(No.128)], and studies involving human subjects were conducted in accordance with the Declaration of Helsinki guidelines. A cross-sectional survey design was used and a health survey was conducted by the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality, which is responsible for monitoring the health status of primary and secondary schools in Guangzhou. All primary and secondary school students in Guangzhou were invited by their school to participate in the survey in October 2017.

The health survey covered 11 administrative districts in Guangzhou, including 991 schools. In total, 253,301 questionnaires were collected (Figure 1). On the first page of the questionnaire, it was stated that the results of the health questionnaire would be used for health research. According to the Education Statistics Manual of Guangzhou in 2017, the number of primary and middle school students in 2017 was 1,514,122, so the response rate of this survey was 16.73%.

This health survey consisted of a questionnaire and a physical examination. The questionnaire was divided into four parts, including basic conditions, psychological behavior, exercise and sleep, and diet. Children and parents jointly filled out the questionnaire on the Internet according to their own situation and submitted the questionnaire directly online. This study used the first part of the data, including on aspects such as birth weight, sex, neonatal feeding, delivery, delivery date, maternal diseases in pregnancy, parents' education, parental myopia, parental smoking, and average household monthly income per person. The school and professional medical examination institutions were responsible for performing the physical examinations and collating data, including height, weight, blood pressure, visual acuity examination, cardiopulmonary examination, and blood routine examination.

Patient and Public Involvement

No patient involved.

Statistical methods

Characteristics of participants were described as mean (standard deviation, SD) for continuous variables and frequency (proportion) for categorical variables. Abnormal visual acuity was defined by uncorrected visual acuity (UCVA<6/12) with three levels: light anomaly>=6/18 to <6/12, mild anomaly>=6/60 to <6/18 and severe anomaly<6/60. Prevalence (95% confidence interval, CI) of abnormal VA was estimated by categorization of the participants' characteristics. The prevalence between categories was compared using logistic regression. Multiple logistic regression analysis was performed to detect the potential risk factors of abnormal VA. The participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorders during pregnancy were included in the regression analysis. Two binary outcomes of abnormal visual acuity defined by UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference). Variables with $P<0.05$ in simple regression analysis were included in the multiple regression model. All P values were based on 2-sided tests ($P<$ 0.05 was considered to be significant). Statistical analyses were performed using the SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of all participants were shown in Table 1. Students of primary school, junior high school, and high school ages were 74.6%, 17.8%, and 7.57% of the total study population, respectively, with 53.8% of them being male. The average birth weight was 2.99 kg (±0.40 kg). There were three ways of neonatal feeding: breastfeeding only, formula feeding only, and breastfeeding and formula feeding together, accounting for 38.8%, 26.7%, and 34.6%, respectively. Natural labor accounted for 63.5%, while cesarean section delivery was 36.5%. The proportion of maternal gestational diseases including hypertension, diabetes, intrahepatic cholestasis, hypothyroidism, hyperthyroidism, anemia, and viral hepatitis was 11.3%. Only child made up 45.0%. One or both parents' education was more than 12 years for 74.4%. Paternal and maternal smoking was 45.5% and 0.85%, respectively (Table 1).

Of the 253,301 children in the study, 15.7% children experienced abnormal VA (Table 2). Refractive error was divided into three levels: namely −3 d, −3 to −6 d, and less than −6 d. For these, the distributions of father's refractive error were 13.8%, 8.28%, and 1.37% and were 16.6%, 9.63%, and 1.66% for mother's refractive error (Table 1). Both parents having myopia and neither of them having myopia were 14.0% and 58.8%, while only the father or mother having myopia were 11.5% and 15.8%, respectively (Table 1). Less than 1 h, 1–2 h, 2–3 h, and more than 3 h for homework per day accounted for 29.8%, 36.0%, 23.8%, and 10.4%, respectively; in addition, less than 1 h, 1–2 h, 2–4 h, and more than 4 h for outdoor activities per day accounted for 45.2%, 40.1%, 10.8%, and 3.88%, respectively, in all participants (Table 1).

With an increase of grade and age (all P<0.001), the increasing prevalence (95% confidence interval, CI) of uncorrected visual acuity (UCVA)< 6/12 in grades 10–12 and older than 15 years students were 51.4% (50.6%, 52.1%) and 52.4% (51.5%, 53.3%, Table 2). Especially, the increased prevalence of severely abnormal VA was obvious (all P<0.001), which were 9.92% (95% CI: 44.89.47%, 10.4%) and 10.6% (95% CI: 10.0%, 11.1%). Prevalence of UCVA < 6/12 was difference (P<0.001) between female sex (17.8%, 95% CI: 17.5%, 18.0%) and male sex (13.9%, 95% CI: 13.7%, 14.1%).

The prevalence of all three levels of abnormal VA were close in different modes of neonatal feeding, but breastfeeding and formula feeding together showed significant differences comparing with breast feeding only (All P<0.01, Table 2). Caesarean contributed to higher prevalence of severely abnormal VA (P<0.001), however lower prevalence of light (P<0.001), mild (P<0.05) abnormal VA and overall anomaly. Unexpectedly, the prevalence of UCVA<6/12(14.7%, 95%CI: 14.4%, 14.9%) in the case of before duedate was less than with due date[16.7%, 95%CI: (16.4%, 17.0%), P<0.001] or overdue births[(16.2%, 95%CI: 15.9%, 16.6%), P<0.001]. Maternal pregnancy diseases were significantly negatively associated with abnormal VA, as shown in Table 2.

Only children had higher prevalence for all levels of abnormal VA than that of non-only children. The prevalence of UCVA<6/12 or worse than 6/18 among students with one or both parents' education > 12 years was higher than that of ≤12 years (Table 2). Students with father smoking currently had lower prevalence (All P<0.05). The more severe the refraction error of either the father or the mother was, the higher the prevalence of all levels of abnormal VA was in children. Additionally, a more average time for homework per day and a less average time for outdoor activities per day caused a higher prevalence of abnormal VA (all P<0.001).

Table 3 summarized the results of two multiple logistic regression models for detecting the potential risk factors of abnormal VA with 6/12 (>=6/12 as reference) and 6/18 (>=6/18 as reference) as cutoff points separately. Because low weight birth and maternal diseases were known factors affecting children eye development, here, we only studied the 155,556 participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorder during pregnancy. Age[odds ratio (OR): 1.52; 95% CI: 1.51–1.53, $P<0.001$] and only child [OR (95% CI), 1.09 (1.06, 1.13), $P<0.001$] were positively associated with the risk of UCVA<6/12.Samely Age [OR (95% CI): 1.56 (1.55–1.57), $P<0.001$] and only child [OR (95% CI), 1.18 (1.13, 1.23), $P<0.001$] were positively associated with the risk of UCVA<6/18. Male had less risk of either UCVA<6/12 [OR (95% CI): 0.77 (0.75, 0.80), $P<0.001$] or UCVA<6/18 [OR (95% CI): 0.78 (0.75, 0.81), $P<0.001$].

In Table 3, students' birth weight was only positively associated with UCVA<6/18 [OR (95% CI): 1.11 (1.05, 1.17), $P<0.001$]. Comparing with breast feeding only, formula feeding only contributed to a higher risk of UCVA<6/12 [OR (95% CI): 1.14 (1.09, 1.20), $P<0.001$], while breast and formula feeding together contributed to a lower risk [OR (95% CI): 0.96 (0.93, 1.00), $P=0.039$]. Delivery mode was not associated with both outcomes of abnormal VA. Students who was delivered overdue or before due date had a lower risk of UCVA<6/12 [OR (95% CI): 0.93 (0.89, 0.97), $P=0.002$, and 0.91 (0.87, 0.94), $P<0.001$ respectively], and UCVA<6/18 [OR (95% CI): 0.93 (0.88, 0.98), $P=0.005$, and 0.93 (0.89, 0.98), $P=0.003$ respectively] than those delivered on due date.

In addition, the students whose parents had higher level of education had a higher risk of UCVA<6/18 [OR (95% CI): 1.10 (1.04, 1.16), $P<0.001$] (Table 3). The students' father smoking currently had a lower risk of UCVA<6/18 comparing with those who never smoked [OR (95% CI): 0.94 (0.90, 0.99), $P=0.010$], while a marginally significant effect of current smoking on UCVA<6/12 [OR (95% CI): 0.97 (0.93, 1.00), $P=0.049$]. Parental myopia increased the risk of UCVA<6/12 or <6/18 (all $P<0.001$): only the father having myopia [OR (95% CI): 1.97 (1.87, 2.07), 1.98 (1.87, 2.11) respectively], only the mother having myopia [OR (95% CI): 1.80 (1.72, 1.89), 1.83 (1.73, 1.94) respectively], both parents having myopia [OR (95% CI): 2.96 (2.82, 3.10), 3.09 (2.92, 3.27) respectively]. As average time for homework per day was up to 2–3h or more than 3h, the higher risk of UCVA<6/18 the students could have [OR (95% CI): 1.07 (1.01, 1.13), 1.10 (1.03, 1.17) respectively] comparing with less than 1h. The effect of outdoor activities can decrease the risk of abnormal VA which was consistent with the previous findings with <1h as reference: 1–2 h [OR (95% CI): 0.95 (0.92, 0.99), $P=0.006$, and 0.92 (0.88, 0.96), $P<0.001$ respectively]; 2–4 h [OR (95% CI): 0.94 (0.89, 0.99), $P=0.017$, and 0.90 (0.84, 0.96), $P=0.002$ respectively]; and >4 h[OR (95% CI): 0.88 (0.81, 0.96), $P=0.003$, and 0.80 (0.72, 0.88), $P<0.001$

respectively].

Discussion

Myopia, the dominant disease for low VA in teenagers, has become a major health issue in East Asia because of its increasingly high prevalence in the past few decades [23]. It is commonly believed the high prevalence of myopia in East Asia is associated with increasing educational pressures, combined with lifestyle changes, which have reduced the time children spend outside [2]. Recent studies have suggested that the development of childhood diseases may also be affected by factors in prenatal and neonatal life, in that factors like delivery mode, feeding manner, and pregnancy diseases can alter the risks for childhood diseases such as asthma [24, 25]. However, the prenatal and neonatal factors for low VA especially myopia for children remains largely unclear. Therefore, a retrospective survey involving Guangzhou primary and middle school students was launched to evaluate the association between most important prenatal and neonatal factors, environmental factors, and heredity with myopia prevalence in 6-year-old to 17-year-old school students.

Based on 253,301 completed questionnaire and medical records, the present cross-sectional study revealed that total abnormal VA prevalence was 6.71%, 30.0%, and 51.4% and severe anomaly value was 0.16%, 2.25%, and 9.92%, in grades 1–6, grades 7–9, and grades 10–12 school children in Guangzhou, respectively (Table 2). The prevalence of myopia here is high as compared to in other countries and areas, but was close to the reported prevalence in Chinese urban area [26]. It is believed that myopia is etiologically heterogeneous, with a low level of myopia of genetic origins that appears without exposure to risk factors [5]. Although no clear evidence that there are independent critical factors exist at present, increasing educational pressures, near-vision work activities, time spent outdoors, and exposure to ambient lighting are considered critical for myopia; besides, the importance of individual prenatal and early-life influences, such as birth order, season of birth, and feeding manner, was also speculated for myopia development [5].

Parental myopia is a high-risk factor for childhood myopia, but no major genes for school myopia have been reported until now, although there are several genes known to be associated with high myopia [2]. A cohort study of 298 probands with early-onset high myopia using whole-exome sequencing showed that mutations in genes known to be responsible for retinal diseases were found in approximately one-fourth of the probands with early-onset high myopia [10]. In another study for myopia prevalence in a Chinese rural area, the grade 7 students had relatively lower prevalence of myopia (29.4%) and high myopia (0.4%) as compared with in Chinese urban cities, suggesting that Chinese people may not have a genetic predisposition to myopia and that environmental factors may play a major role in the development of school myopia in Chinese children [27]. In our study, the association between parental myopia and children myopia is strong (Table 3). In grades 10–12 students, the ORs was 2.06, 1.85, and 3.17 in paternal myopia only, maternal myopia only, and both parents having myopia, respectively. Although the idea of heredity for myopia was not excluded, families share environments as well as genes, and myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors, increasing the myopia risk of their children [17]. In a study on the gene–environmental interaction in myopia, the prevalence of children myopia was only 9.9% in farmer families without myopia, but the prevalence in those who entered colleges was similar between farmer families and other families with parental myopia, suggesting a leading role of environmental factors in the formation of myopia [9]. In another study on high myopia across three different generations in Korea, results supported that the environmental portion of the phenotypic variance increased and the additive genetic portion decreased as South Korea became more urbanized [28]. Therefore, how gene–environment interactions contribute to variations in school myopia within populations remains to be established [2].

It is well-known that environmental factors play critical roles in childhood myopia development. In an analysis combining the amount of outdoor activity and near-vision work activity spent, children with low outdoor time and high near-vision work were two to three times more likely to be myopic as compared with those performing low near-vision work and high outdoor activities [17]. In the Beijing area of China, greater axial elongation was associated with less time spent outdoors, more time spent indoors with studying [6]. In Finland, higher adulthood myopia was mainly related to parents' myopia and less time spent on sports and outdoor activities in childhood [7]. In the Netherlands, seven parameters were associated independently ($P< 0.05$) with faster AL elongation, as follows: parental myopia, books read per week, time spent reading, no participation in sports, non-European ethnicity, less time spent outdoors, and baseline AL to corneal refraction (CR) ratio [29]. In our study, the results clearly support that home work time is positively associated but outdoor activity was negatively associated with myopia and high myopia prevalence in students of all grades (Table 2 and 3). Therefore, environmental factors should be the leading consideration for school myopia development. As proof, in a recent clinical trial among 6-year-old children in Guangzhou, the researchers found that the addition of 40 min of outdoor activity at school versus usual activity resulted in a reduced incidence rate of myopia over the next 3 years [30]. Therefore, intervention in this manner could be the most promising way for decreasing myopia in Chinese cities.

Our results also supported that female gender, older age, high birth weight, and only child status would increase the risks for myopia in our data. Similarly, in a study including 2,760 7-year-old children and 2,198 12-year-old children, higher intraocular pressure (IOP) was associated with female gender, older age, and higher body mass index, while younger age at commencement of reading and being born with a caesarean section were also associated with higher IOP in adolescence[16]. However, these factors may be largely linked with environmental factors such as outdoor activity and near-vision work. For example, boys are more likely to have outdoor sports; as one ages, the educational pressure increases; only children are more likely to have indoor activities and near-vision work; and overweightness decreases the outdoor activity of children. Therefore, the observed linkage may be a causal association.

Smoking is a common environmental factor for health hazards. Numerous epidemiologic studies have reported a negative impact of environmental tobacco smoke or parental cigarette smoking on pediatric diseases such as asthma [31, 32]. In Guangzhou, the male smoking rate is high but female smoking is rare (48.4% vs. 0.08%). Therefore, while unlikely in other countries, maternal smoking in China may not be an important factor for consideration. Additionally, data showed that paternal smoking did not significantly increased the prevalence of myopia (Table 3), suggesting that indoor pollution might not provoke myopia development. In a study in Singapore, an inverse association was found between parental smoking and childhood myopia [33], and our data also indicated that father current smoking decreased the risk of abnormal VA (Table 3). Evidence also came from the fact that Guangzhou has markedly reduced its atmospheric pollution during the past 10 years, but there has been a further increase in the prevalence of myopia [5]. Therefore, we believed that parental smoking, as well as other types of indoor or outdoor environmental pollution, should not be major factors for school myopia.

Prenatal factors such as delivery manner, delivery mode, and pregnancy diseases on myopia are under investigation in this study. Pregnancy diseases in mothers include maternally related complications such as hyperemesis, hypertension, and preeclampsia and uterus-related complications such as antepartum hemorrhage, preterm contractions, insufficient placenta, and fetal grow restriction. All of these pregnancy diseases affect fetal growth in uterus and probably later long-term health. For instance, diabetes during pregnancy is associated with changes in retinal morphology in the offspring [34]. Our results found that pregnancy diseases decrease the prevalence of child myopia, though the linkage may be causal (Table 2). One possibility is that children suffered with maternal pregnancy diseases may have lower educational pressure than those without diseases in the family.

Premature birth and low birth weight affect the general growth of the fetus, including the eye development. An analysis determined that, in children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia is mainly attributable to short AL [17]. In a British birth cohort study, myopia was positively associated with low birth weight for gestational age [13], and in the Sydney Paediatric Eye Disease Study, vision impairment was independently associated with low birth weight [18]. In this study, students only self-reported duedate or not, and no further information on precise gestational age can be obtained. Regretfully, we cannot analysis the association between the premature birth and school myopia. Accordingly, we used multiple logistic regression models to analyze only the population who have normal birth weight without pregnancy complications.

Breastfeeding may influence the early life growth of a baby. In a study aimed to determine whether an association existed between breastfeeding and myopia, a cross-sectional study of 527 Chinese primary school students was evaluated. Breastfeeding was associated with a decreased risk of myopia among children aged 6–12 years, and breastfeeding during the first 6 months of infancy was associated with more hyperopic spherical equivalent refraction (SER). Furthermore, breastfeeding was associated with myopic refraction and was not related to AL, and this association could exist in childhood [22]. In another study in Singaporean preschoolers, results showed that breastfeeding was associated with more hyperopic spherical equivalent refraction in young Chinese children in Singapore [35]. Our results supported the idea that that breastfeeding decreases but formula feeding increases the risks for myopia (Table 3). The reasons for why remain unclear, but body development maybe is associated with eye development as well.

Recent research also suggested that environmental risk factors such as birth season and postnatal light levels have also been linked to myopia. A cross-sectional study of older British adults reported that subjects born during summer and autumn were more likely to be highly myopic versus those born in winter [8]. An analysis of a subset of the longitudinal, United Kingdom–based Twins Early Development Study found factors that were significantly associated with myopia included level of summer birth (OR: 1.93, 95% CI: 1.28–2.90) [14]. Our study did not find any association between birth season and myopia (data not shown), probably because Guangzhou is a tropical city with similar daylight times during the entire year.

In conclusion, in this retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China, results supported the female gender, high birth weight, formula feeding, only child status, parental myopia, and homework time led to a significantly increased myopia risk. Conversely, the factors of cesarean section, overdue or preterm birth, and outdoor activity decreased myopia risk. Parents' education and smoking were not associated with myopia. Therefore, this study has proven known major environmental factors and heredity for myopia and also reported several potential prenatal factors for school myopia. However, as a retrospective study, this study cannot reach the power of a prospectively designed cohort study. Although the school encouraged parents and children to fill out the questionnaire in various forms such as posters and text message notifications, reactionary bias exists because it is a voluntary participation survey. As a result, the response rate is low and we cannot rule out bias. In addition, the medical records of pregnancy conditions were self-reported, so selection bias was unavoidable. However, based on the current data, we concluded that prenatal and neonatal factors can affect childhood myopia but that environmental factors and parental myopia are the leading factors.

Author Contributions

Conceived and designed the research: Dunjun Chen. Collected the data: Nali Deng. Analyzed the data: Juanjuan Chen, Wen Sun, Jingsi Chen, and Lili Du. Wrote the paper: Bolan Yu and Lijuan Dai.

Competing interests

There are no competing interests for any author

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Data sharing statement

Deidentified participant data are available upon reasonable requisition.

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Figure Legend

Figure 1. Participant distribution in Guangzhou area.

Table 1. Characteristics of participants

Characteristics	n	Mean (SD) / n (%)
Total	253,301	/
Grade, n (%)	253,301	
1-6		189,008 (74.6)
7-9		45,119 (17.8)
10-12		19,174 (7.57)
Age, Years	253,301	
6-10		156,992 (62.0)
11-15		82,092 (32.4)
>15		14,217 (5.61)
Mean (SD)		9.96 (2.99)
Sex, n (%)	253,301	
Male		136,200 (53.8)
Female		117,101 (46.2)
Birth weight, kg, Mean (SD)	249,610	2.99 (0.40)
Neonatal feeding, n (%)	253,292	
Breast feeding		98,164 (38.8)
Breast+ formula feeding		87,532 (34.6)
Formula feeding		67,596 (26.7)
Delivery, n (%)	253,292	
Natural labor		160,873 (63.5)
Caesarean		92,419 (36.5)
Delivery date, n (%)	253,291	
On the due date		91,409 (36.1)
Overdue		54,161 (21.4)
Before the due date		107,721 (42.5)
Diseases in pregnancy, n (%)		
Hypertension	252,013	3,722 (1.48)
Diabetes	252,068	5,237 (2.08)
Intrahepatic cholestasis	251,930	622 (0.25)
Hypothyroidism	251,878	764 (0.30)
Hyperthyroidism	248,301	978 (0.39)
Anemia	248,374	16,236 (6.54)
Viral hepatitis	248,311	2,330 (0.94)
Other	248,273	1,679 (0.68)
Any disease above	248,461	27,998 (11.3)

Only child, n (%)	253,286	
No		139,318 (55.0)
Yes		113,968 (45.0)
One or both parents' education, n (%)	253,288	
<=12 years		64,943 (25.6)
>12 years		188,345 (74.4)
Father smoking, n (%)	253,286	
Never smoked		138,077 (54.5)
Quit for >1 year		17,998 (7.11)
Quit for <1 year		5,362 (2.12)
Current smoking		91,849 (36.3)
Mother smoking, n (%)	253,286	
Never smoked		251,159 (99.2)
Quit for >1 year		900 (0.36)
Quit for <1 year		276 (0.11)
Current smoking		951 (0.38)
Father's refractive error, diopter, n (%)	238,888	
Normal		182,857 (76.6)
>-3		32,982 (13.8)
<= -3 to >= -6		19,770 (8.28)
<-6		3,279 (1.37)
Mother's refractive error, diopter, n (%)	240,291	
Normal		173,256 (72.1)
>-3		39,915 (16.6)
<= -3 to >= -6		23,135 (9.63)
<-6		3,985 (1.66)
Parental myopia, n (%)	242,006	
Two of them were normal		142,238 (58.8)
Only father having myopia		27,794 (11.5)
Only mother having myopia		38,172 (15.8)
Two of them having myopia		33,802 (14.0)
Average time for homework per day, hour, n (%)	251,925	
<=1		75,123 (29.8)
1-2		90,674 (36.0)
2-3		59,901 (23.8)
>3		26,227 (10.4)
Average time for outdoor activities per day, hour	253,280	

<1	114,471 (45.2)
1-2	101,658 (40.1)
2-4	27,332 (10.8)
>4	9,819 (3.88)

SD: Standard deviation;

Table 2. Prevalence of abnormal visual acuity by characteristics

	Total UCVA[#]<6/12	Light anomaly UCVA>=6/18 to <6/12	Mild anomaly UCVA>=6/60 to <6/18	Severe anomaly UCVA<6/60
All	15.7 (15.6, 15.9)	6.11 (6.00, 6.22)	8.12 (8.00, 8.24)	1.49 (1.44, 1.54)
Grade				
1-6	6.71 (6.58, 6.85)	3.70 (3.60, 3.80)	2.85 (2.76, 2.94)	0.16 (0.14, 0.18)
7-9	30.0 (29.6, 30.5)***	11.6 (11.3, 11.9)***	16.2 (15.8, 16.5)***	2.25 (2.10, 2.39)***
10-12	51.4 (50.6, 52.1)***	11.7 (11.2, 12.2) ***	29.7 (29.1, 30.4)***	9.92 (9.47, 10.4)***
Age, Years				
6-10	4.56 (4.43, 4.69)	2.66 (2.56, 2.76)	1.80 (1.72, 1.88)	0.10 (0.08, 0.12)
11-15	25.1 (24.8, 25.4)***	10.1 (9.85, 10.3)***	13.1 (12.9, 13.4)***	1.88 (1.79, 1.98)***
>15	52.4 (51.5, 53.3)***	11.3 (10.7, 11.8)***	30.6 (29.8, 31.4)***	10.6 (10.0, 11.1)***
Sex				
Female	17.8 (17.5, 18.0)	6.75 (6.58, 6.91)	9.33 (9.14, 9.52)	1.70 (1.62, 1.79)
Male	13.9 (13.7, 14.1)***	5.55 (5.41, 5.69)***	7.07 (6.91, 7.22)***	1.30 (1.24, 1.37)***
Neonatal feeding				
Breast feeding	16.1 (15.9, 16.4)	6.42 (6.24, 6.60)	8.22 (8.02, 8.42)	1.49 (1.40, 1.57)
Breast + formula feeding	15.2 (14.9, 15.5)***	5.71 (5.53, 5.89)***	7.80 (7.60, 8.01)**	1.67 (1.57, 1.76)**
Formula feeding	15.8 (15.5, 16.1)	6.16 (5.96, 6.37)	8.38 (8.14, 8.62)	1.27 (1.17, 1.36)**
Delivery				
Natural labor	15.9 (15.6, 16.1)	6.31 (6.17, 6.44)	8.22 (8.06, 8.37)	1.32 (1.26, 1.39)
Caesarean	15.5 (15.2, 15.8)*	5.77 (5.60, 5.94)***	7.95 (7.75, 8.15)*	1.77 (1.67, 1.87)***
Delivery date				
Due date	16.7 (16.4, 17.0)	6.56 (6.37, 6.74)	8.82 (8.60, 9.03)	1.31 (1.23, 1.40)
Overdue	16.2 (15.9, 16.6)*	6.20 (5.97, 6.43)*	8.29 (8.02, 8.55)**	1.73 (1.61, 1.86)***
Before due date	14.7 (14.4, 14.9)***	5.68 (5.52, 5.84)***	7.45 (7.27, 7.63)***	1.52 (1.43, 1.60)***
Diseases in pregnancy				
Hypertension				
No	15.7 (15.5, 15.9)	6.10 (5.99, 6.21)	8.12 (8.00, 8.25)	1.48 (1.43, 1.54)
Yes	17.5 (16.1, 18.9)**	7.22 (6.26, 8.18)*	8.18 (7.17, 9.19)	2.13 (1.60, 2.67)**
Diabetes				
No	15.8 (15.6, 16.0)	6.13 (6.02, 6.24)	8.17 (8.04, 8.29)	1.49 (1.43, 1.54)
Yes	12.7 (11.6, 13.8)***	5.31 (4.57, 6.05)*	5.82 (5.05, 6.59)***	1.60 (1.19, 2.01)
Intrahepatic cholestasis				
No	15.7 (15.6, 15.9)	6.12 (6.01, 6.23)	8.13 (8.01, 8.25)	1.49 (1.44, 1.55)
Yes	11.9 (8.84, 14.9)*	4.79 (2.79, 6.80)	5.71 (3.54, 7.88)	1.37 (0.28, 2.46)
Hypothyroidism				

No	15.7 (15.6, 15.9)	6.11 (6.01, 6.22)	8.13 (8.00, 8.25)	1.49 (1.44, 1.55)
Yes	14.0 (11.0, 17.0)	5.83 (3.80, 7.85)	6.99 (4.79, 9.19)	1.17 (0.24, 2.09)
Hyperthyroidism				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.50 (1.45, 1.56)
Yes	16.0 (13.3, 18.7)	6.93 (5.06, 8.80)	7.92 (5.93, 9.91)	1.13 (0.35, 1.91)
Anemia				
No	16.0 (15.8, 16.1)	6.15 (6.04, 6.27)	8.28 (8.16, 8.41)	1.53 (1.47, 1.59)
Yes	12.9 (12.3, 13.5)***	5.64 (5.22, 6.06)*	6.16 (5.73, 6.60)***	1.08 (0.89, 1.26)***
Viral hepatitis				
No	15.8 (15.6, 16.0)	6.12 (6.01, 6.23)	8.17 (8.05, 8.29)	1.51 (1.45, 1.56)
Yes	13.2 (11.6, 14.8)**	5.97 (4.85, 7.09)	6.32 (5.17, 7.47)**	0.93 (0.48, 1.38)
Other				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.51 (1.45, 1.56)
Yes	15.2 (13.2, 17.2)	6.47 (5.07, 7.86)	7.89 (6.36, 9.42)	0.84 (0.32, 1.36)
Any disease above				
No	16.0 (15.9, 16.2)	6.15 (6.04, 6.27)	8.36 (8.22, 8.49)	1.52 (1.46, 1.58)
Yes	13.6 (13.1, 14.1)***	5.82 (5.50, 6.15)	6.47 (6.13, 6.81)***	1.31 (1.15, 1.46)*
Only child				
No	13.4 (13.2, 13.6)	5.75 (5.61, 5.89)	6.84 (6.69, 7.00)	0.76 (0.71, 0.081)
Yes	18.5 (18.3, 18.8)***	6.53 (6.37, 6.70)***	9.65 (9.45, 9.85)***	2.36 (2.26, 2.46)***
One or both parents' education				
<=12 years	14.0 (13.7, 14.4)	6.12 (5.91, 6.33)	7.39 (7.15, 7.62)	0.53 (0.47, 0.60)
>12 years	16.3 (16.1, 16.5)***	6.10 (5.98, 6.23)	8.37 (8.22, 8.51)***	1.81 (1.74, 1.88)***
Father smoking				
Never smoked	16.1 (15.9, 16.3)	6.15 (6.01, 6.30)	8.38 (8.21, 8.55)	1.56 (1.48, 1.64)
Quit for >1 year	17.8 (17.2, 18.5)***	6.83 (6.41, 7.25)**	9.23 (8.74, 9.71)***	1.76 (1.54, 1.97)
Quit for <1 year	15.4 (14.3, 16.5)	6.41 (5.65, 7.18)	7.81 (6.97, 8.64)	1.19 (0.85, 1.53)
Current smoking	14.8 (14.5, 15.0)***	5.88 (5.70, 6.05)*	7.52 (7.33, 7.72)***	1.35 (1.26, 1.43)***
Father's refractive error, diopter				
Normal	13.9 (13.7, 14.1)	5.67 (5.55, 5.79)	7.17 (7.03, 7.30)	1.04 (0.99, 1.09)
>-3	20.4 (19.9, 20.9)***	7.31 (6.99, 7.64)***	10.5 (10.1, 10.9)***	2.66 (2.45, 2.86)***
<= -3 to >= -6	23.4 (22.8, 24.1)***	7.35 (6.92, 7.77)***	12.5 (12.0, 13.0)***	3.60 (3.30, 3.90)***
<-6	27.3 (25.5, 29.0)***	8.01 (6.93, 9.08)***	14.1 (12.7, 15.4)***	5.19 (4.31, 6.14)***
Mother's refractive error, in either eye, diopter				

Normal	14.1 (13.9, 14.3)	5.70 (5.57, 5.82)	7.31 (7.16, 7.45)	1.07 (1.02, 1.13)
>-3	18.9 (18.5, 19.3)***	6.82 (6.53, 7.11)***	9.79 (9.45, 10.1)***	2.29 (2.12, 2.46)***
<= -3 to >= -6	20.9 (20.3, 21.5)***	7.09 (6.70, 7.47)***	10.6 (10.2, 11.1)***	3.14 (2.88, 3.40)***
<-6	25.8 (24.2, 27.4)***	8.06 (7.07, 9.05)***	13.2 (12.0, 14.5)***	4.49 (3.74, 5.25)***
Parental myopia				
Two of them were normal	13.1 (12.9, 13.3)	5.44 (5.30, 5.57)	6.77 (6.62, 6.92)	0.86 (0.80, 0.91)
Only father having myopia	19.3 (18.8, 19.8)***	7.02 (6.67, 7.36)***	10.1 (9.69, 10.5)***	2.19 (1.99, 2.39)***
Only mother having myopia	16.8 (16.4, 17.2)***	6.46 (6.18, 6.75)***	8.58 (8.25, 8.90)***	1.75 (1.60, 1.90)***
Two of them having myopia	23.1 (22.6, 23.7)***	7.64 (7.31, 7.97)***	11.9 (11.5, 12.3)***	3.55 (3.32, 3.78)***
Average time for homework per day, hour				
<=1	15.1 (14.8, 15.4)	6.13 (5.92, 6.34)	7.93 (7.70, 8.17)	1.00 (0.91, 1.08)
1-2	12.4 (12.1, 12.6)***	5.42 (5.25, 5.59)***	6.16 (5.97, 6.34)***	0.81 (0.75, 0.88)***
2-3	17.0 (16.7, 17.3)***	6.38 (6.17, 6.60)	8.87 (8.62, 9.12)***	1.76 (1.64, 1.87)***
>3	24.1 (23.5, 24.6)***	7.49 (7.15, 7.83)***	12.6 (12.2, 13.1)***	3.96 (3.70, 4.21)***
Average time for outdoor activities per day, hour				
<1	16.5 (16.3, 16.8)	6.18 (6.02, 6.34)	8.62 (8.44, 8.81)	1.73 (1.65, 1.82)
1-2	15.0 (14.8, 15.3)***	5.99 (5.82, 6.16)	7.66 (7.47, 7.85)***	1.38 (1.30, 1.47)***
2-4	15.0 (14.5, 15.4)***	6.18 (5.85, 6.51)	7.74 (7.38, 8.10)***	1.04 (0.90, 1.17)***
>4	15.2 (14.4, 16.1)**	6.29 (5.74, 6.83)	7.94 (7.33, 8.54)*	1.02 (0.79, 1.24)***

#: Abnormal visual acuity was defined by uncorrected visual acuity in better-seeing eye (UCVA). Light anomaly: UCVA>=6/18 to <6/12, mild anomaly: UCVA>=6/60 to <6/18, severe anomaly: UCVA<6/60.

Logistic regression was used for comparisons between categories. CI: Confidence Interval. Prevalence (95% CI) was presented, * P<0.05, ** P<0.01, *** P<0.001 indicating the significance of the difference from the reference group.

Table 3. Multiple Logistic regression model for detecting the potential risk factors of abnormal visual acuity*

Variable	UCVA[#]<6/12(n=148,672)†		UCVA<6/18 (n=148,672)†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, Year	1.52 (1.51, 1.53)	<0.001	1.56 (1.55, 1.57)	<0.001
Male	0.77 (0.75, 0.80)	<0.001	0.78 (0.75, 0.81)	<0.001
Birth weight, kg	1.00 (0.96, 1.04)	0.974	1.11 (1.05, 1.17)	<0.001
Neonatal feeding				
Breast feeding	Reference		Reference	
Breast+ formula feeding	0.96 (0.93, 1.00)	0.039	/	/
Formula feeding	1.14 (1.09, 1.20)	<0.001	/	/
Delivery				
Natural labor	Reference		Reference	
Caesarean	/	/	/	/
Delivery date				
Due date	Reference		Reference	
Overdue	0.93 (0.89, 0.97)	0.002	0.93 (0.88, 0.98)	0.005
Before due date	0.91 (0.87, 0.94)	<0.001	0.93 (0.89, 0.98)	0.003
Only child	1.09 (1.06, 1.13)	<0.001	1.18 (1.13, 1.23)	<0.001
One or both Parents' education >12 years	1.03 (0.99, 1.07)	0.185	1.10 (1.04, 1.16)	<0.001
Father smoking				
Never smoked	Reference		Reference	
Quit for >1 year	1.00 (0.94, 1.07)	0.893	0.94 (0.88, 1.02)	0.117
Quit for <1 year	0.97 (0.87, 1.09)	0.644	0.93 (0.81, 1.07)	0.302
Current smoking	0.97 (0.93, 1.00)	0.049	0.94 (0.90, 0.99)	0.010
Parental myopia, n (%)				
Two of them were normal	Reference		Reference	
Only father having myopia	1.97 (1.87, 2.07)	<0.001	1.98 (1.87, 2.11)	<0.001
Only mother having myopia	1.80 (1.72, 1.89)	<0.001	1.83 (1.73, 1.94)	<0.001
Two of them having myopia	2.96 (2.82, 3.10)	<0.001	3.09 (2.92, 3.27)	<0.001
Average time for homework per day, hour				
<=1	Reference		Reference	
1-2	1.00 (0.95, 1.05)	0.891	0.97 (0.91, 1.03)	0.287
2-3	1.05 (1.00, 1.10)	0.059	1.07 (1.01, 1.13)	0.026

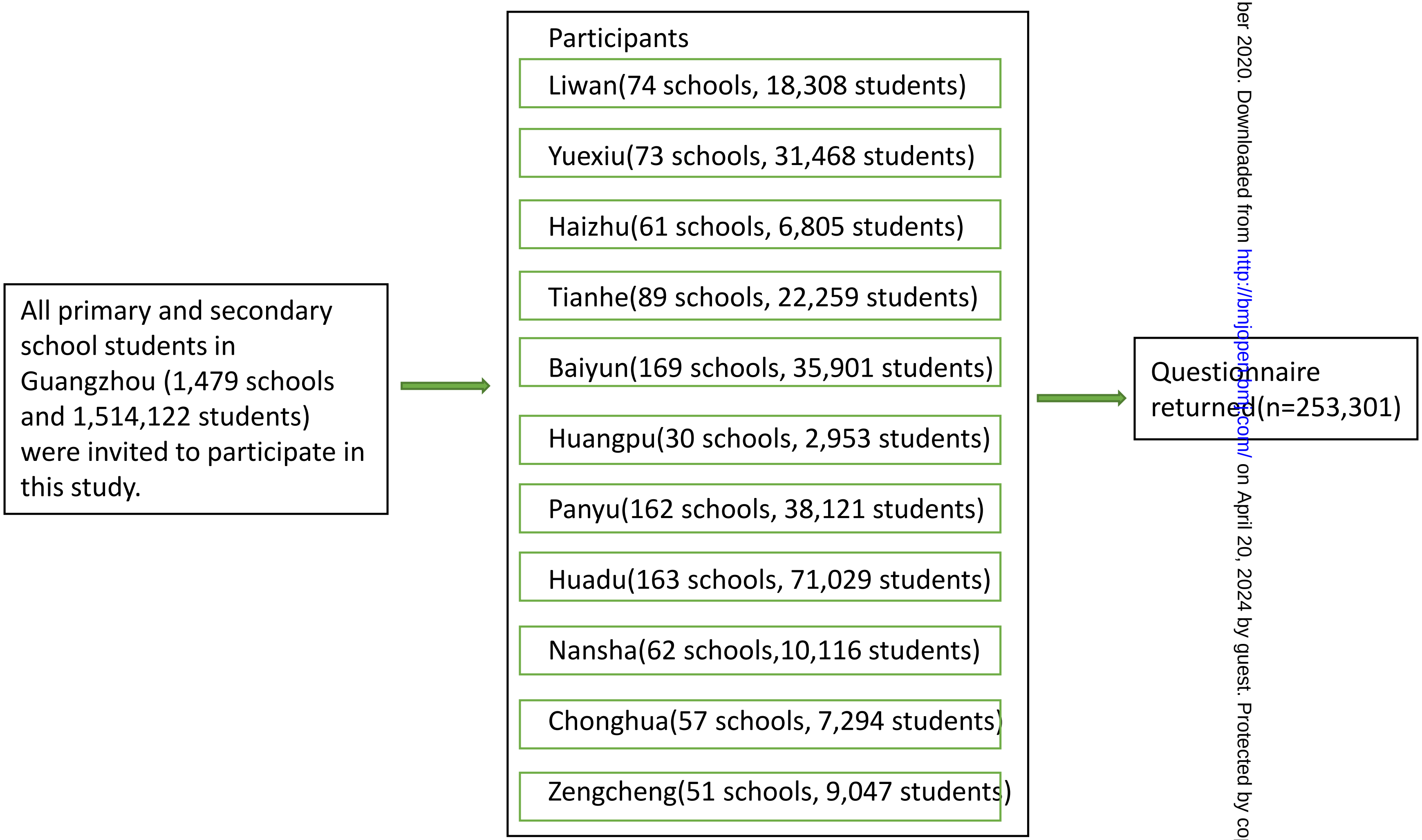
>3	1.05 (0.99, 1.11)	0.092	1.10 (1.03, 1.17)	0.004
Average time for outdoor activities per day, hour				
<1	Reference		Reference	
1-2	0.95 (0.92, 0.99)	0.006	0.92 (0.88, 0.96)	<0.001
2-4	0.94 (0.89, 0.99)	0.017	0.90 (0.84, 0.96)	0.002
>4	0.88 (0.81, 0.96)	0.003	0.80 (0.72, 0.88)	<0.001

*Variables with P<0.05 in simple regression analysis were included in the multiple regression model. The results of simple regression analysis were not listed in the table. OR: Odds Ratio, CI: Confidence Interval.

#: Abnormal visual acuity was defined by uncorrected visual acuity in better-seeing eye (UCVA). Analysis of UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference) among participants who were singletons with normal birth weight (2.5-4kg) and whose mother had no pregnancy disorder during pregnancy.

†There were 6,882 (4.42%) to 6,884 (4.43%) observations excluded due to missing values for the response or explanatory variables.

Figure 1


All primary and secondary school students in Guangzhou (1,479 schools and 1,514,122 students) were invited to participate in this study.
Participants
Liwan(74 schools, 18,308 students)
Yuexiu(73 schools, 31,468 students)
Haizhu(61 schools, 6,805 students)
Tianhe(89 schools, 22,259 students)
Baiyun(169 schools, 35,901 students)
Huangpu(30 schools, 2,953 students)
Panyu(162 schools, 38,121 students)
Huadu(163 schools, 71,029 students)
Nansha(62 schools,10,116 students)
Chonghua(57 schools, 7,294 students)
Zengcheng(51 schools, 9,047 students)
Questionnaire returned(n=253,301)

BMJ Open

Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Abstract

Objectives: In this cross-sectional survey, we sought to determine the prevalence and risk factors of visual impairment (VI) and the influence of prenatal and neonatal factors on childhood VI in a pediatric population from Guangzhou, China.

Setting: Health survey covered 11 administrative districts in Guangzhou, including 991 schools.

Participants: All primary and middle school students in Guangzhou were invited to complete a questionnaire online with the help of their parents. The results of physical examinations were reported by school medical departments. The results of the questionnaire were collected by the researchers. In total, 253,301 questionnaires were collected.

Primary outcome measures: The students' uncorrected visual acuity (UCVA) was examined by trained optometrists by standard logarithmic visual acuity charts. VI was defined by UCVA (better eye) (UCVA<6/12) with three levels: light VI (UCVA>=6/18 to <6/12), mild VI (UCVA>=6/60 to <6/18) and severe VI (UCVA<6/60).

Results: A total of 39,768 individuals (15.7%) had VI, and the rates rapidly increased from Grade 1-6 students (6.71%) to Grade 10-12 students (51.4%). The results supported that female gender, high birth weight, formula feeding, child without siblings, higher level of parents' education, parental myopia, high homework time, and low outdoor activity significantly increase the risk of VI. Delivery mode was not associated with the risk of VI.

Conclusions: This study validates known major prenatal/genetic, perinatal and postnatal factors for school VI. In conclusion, prenatal and perinatal factors can affect the onset of childhood VI, but parental myopia and postnatal factors represent the leading factors.

Keywords: abnormal visual acuity, school myopia, prenatal and neonatal factors

Strengths and limitations of this study:

- A retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China
- Collection and analysis of both prenatal factors and environmental factors associated with VI.
- Selection bias, recall bias and reporter bias unavoidable as a voluntary participation survey.

Introduction

Visual impairment (VI) is highly prevalent in school students, and myopia related VI accounts for over 90% of the cases in China, although hyperopia, astigmatism, and other eye diseases can also lead to decreased visual acuity [1]. Myopia is caused by an inconsistency of the eye's refractive power with the length of the eye axis and includes two clinical types. In refractive myopia, the axial length is normal, but the refractive power of the cornea or lens is too strong, while in axial myopia, the refractive power of the lens is normal, but the axial length is too long[2]. Although myopia is not a life-threatening disease, the World Health Organization recognizes it as a major cause of further visual impairment if not fully corrected [3]. However, at present, the high prevalence of myopia has become a serious public health problem in East Asia. In China specifically, the prevalence of myopia in high school students ranges from 43.0% to78.4% [4].

Myopia is etiologically heterogeneous and is believed to be driven by numerous environmental factors and genetic variations, with onset beginning in the preschool years. Environmental factors such as outdoor activities are associated with myopia inception and development[4]. Increasing outdoor time thus represents an important environmental factor that can protect young children from myopia and which has been supported by numerous studies [5-7]. The protective effects of outdoor activity may be due to the high light intensity outdoors, the chromaticity of daylight, or increased vitamin D levels [8, 9]. Separately, a number of studies have shown that parental myopia is an important risk factor for myopia in children, due to carriers of myopia susceptibility genes or a shared myopia-driving environment [10-12].

According to the developmental origins of health and disease theory, the development of childhood diseases may be affected by factors in prenatal life [13]. There are several epidemiological studies that have shown that cesarean delivery and preterm birth may lead to a higher prevalence of myopia in childhood [14-17]. For example, preterm birth may affect ocular development or later emmetropization, and may have a more complicated mechanism that affects the development of refractive status [14, 18-22]. In addition, breastfeeding in early life may be facilitative to ocular development, as the docosahexaenoic acid and arachidonic acid in breast milk may affect retinal and neural development, therefore associate with a decreased risk of myopia [23].

Here, we sought to study the effects of multiple prenatal/genetic, perinatal and postnatal factors on the development of myopia related VI in primary and middle school students in Guangzhou area of China. For this study, the Health Promotion

Centre for Primary and Secondary Schools of Guangzhou Municipality released an annual online health survey of primary and secondary school students and we subsequently received relevant information from this institution. We used descriptive statistics, logistic analysis, and multiple logistic regression models to analyze the data and explore the relationships between various environmental, parental myopia, and prenatal and neonatal factors and myopia. Our results are expected to provide additional evidence for childhood myopia etiology in East Asia and help to confirm potential prenatal factors for long-term diseases.

Methods

Data source

This study was approved by the institutional review board of The Third Affiliated Hospital of Guangzhou Medical University [2017(No.128)], and studies involving human subjects were conducted in accordance with the Declaration of Helsinki guidelines. A cross-sectional survey design was used and a health survey was conducted by the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality, which is responsible for monitoring the health status of primary and secondary schools in Guangzhou. All primary and secondary school students in Guangzhou were invited by their school to participate in the survey in October 2017. Consent was provided to all participants by school teachers and oral informed ones were obtained from the participants' parents.

The health survey covered 11 administrative districts in Guangzhou, including 991 schools. In total, 253,301 questionnaires were collected (Figure 1). On the first page of the questionnaire, it was stated that the results of the health questionnaire would be used for health research. According to the Education Statistics Manual of Guangzhou in 2017, the number of primary and middle school students in 2017 was 1,514,122, so the response rate of this survey was 16.73%.

This health survey consisted of a questionnaire and a physical examination. The questionnaire was divided into four parts, including basic conditions, psychological behavior, exercise and sleep, and diet. Children and parents jointly filled out the questionnaire on the Internet according to their own situation and submitted the questionnaire directly online. This study used the first part of the data, including aspects such as birth weight, sex, neonatal feeding, delivery, delivery date, maternal diseases in pregnancy, parents' education, parental myopia, parental smoking, and average household monthly income per person. The school and professional medical examination institutions were responsible for performing the physical examinations and collating data, including height, weight, blood pressure, visual acuity examination, cardiopulmonary examination, and blood routine examination.

Visual acuity assessment

The students' uncorrected visual acuity (UCVA) in all schools were examined by trained optometrists by same standard logarithmic visual acuity charts on light box with illumination 300-500 lux according to regular procedure. During the test, students sat a 5 m distance away from the chart with covering one eye first and read out the letters students saw with the uncovered eye. This process was repeated with the other eye. Students pointed in the direction the letter "E" is facing: up, down, left, or right. The test started at the 6/6 line. If students can't see clearly, then they go up one line at a time, otherwise go down one line at a time. The identification time of each "E" must not exceed five seconds. It is stipulated that there was no misidentification in 6/60-6/20 lines on each line, and less than two errors on each line of 6/15-6/6 lines and less than three errors on each line of 6/5-6/3. If the top line could not be read at 5 m, the student was tested at 2.5 m or 1 m and the measured visual acuity was subtracted by 0.3 or 0.7 respectively and then recorded as the student's visual acuity.

Patient and Public Involvement

No patient involved.

Statistical methods

Characteristics of participants were described as mean (standard deviation, SD) for continuous variables and frequency (proportion) for categorical variables. Visual impairment (VI) was defined by UCVA (better eye) (UCVA<6/12) with three levels: light VI (UCVA>=6/18 to <6/12), mild VI (UCVA>=6/60 to <6/18) and severe VI (UCVA<6/60) referring to the previous studies [24] and definitions of impaired vision by the World Health Organization (WHO). Prevalence (95% confidence interval, CI) of VI was estimated by categorization of the participants' characteristics. The prevalence between categories was compared using logistic regression. Multiple logistic regression analysis was performed to detect the potential risk factors for VI. The participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorders during pregnancy were included in the regression analysis. Two binary outcomes of VI defined by UCVA (better eye) <6/12 (>=6/12 as reference) and UCVA (better eye) <6/18 (>=6/18 as reference).Variables with $P<0.05$ in simple regression analysis were included in the multiple regression model. All P values were based on 2-sided tests ($P< 0.05$ was significant). Statistical analyses were performed using the SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of participants

Characteristics of all participants were shown in Table 1. All factors can be grouping into (i) prenatal/genetic factors, including father's refractive error, mother's refractive error, parental myopia, one or both parents' education; (ii) perinatal factors, including birth weight, neonatal feeding, delivery, delivery date, and diseases in pregnancy; (iii) postnatal factors, including grade, age, sex, only child status, parent smoking, average time for homework per day, and average time for outdoor activities per day.

In brief, refractive error was divided into three levels: namely −3.00D, −3.00 D to −6.00D, and less than −6.00D. Results showed that the distributions of father's refractive error were 13.8%, 8.28%, and 1.37% and were 16.6%, 9.63%, and 1.66% for mother's refractive error (Table 1). Both parents having myopia and neither of them having myopia were 14.0% and 58.8%, while only the father or mother having myopia were 11.5% and 15.8%, respectively. One or both parents' education was more than 12 years for 74.4% (Table 1).

There were three ways of neonatal feeding: breastfeeding only, formula feeding only, and breastfeeding and formula feeding together, accounting for 38.8%, 26.7%, and 34.6%, respectively. Vaginal delivery accounted for 63.5%, while cesarean section delivery was 36.5%. The proportion of maternal gestational diseases including hypertension, diabetes, intrahepatic cholestasis, hypothyroidism, hyperthyroidism, anemia, and viral hepatitis was 11.3%. The average birth weight was 2.99 kg (±0.40 kg). (Table 1).

In addition, students of primary school, junior high school, and high school ages were 74.6%, 17.8%, and 7.57% of the total study population, respectively, with 53.8% of them being male. Less than 1 h, 1–2 h, 2–3 h, and more than 3 h for homework per day accounted for 29.8%, 36.0%, 23.8%, and 10.4%, respectively; less than 1 h, 1–2 h, 2–4 h, and more than 4 h for outdoor activities per day accounted for 45.2%, 40.1%, 10.8%, and 3.88%, respectively, in all participants. Children without siblings made up 45.0%. Paternal and maternal smoking was 45.5% and 0.85%, respectively (Table 1).

Prevalence of VI by characteristics

Of the 253,301 children in the study, 15.7% children experienced VI (Table 2). The more severe the refraction error of either the father or the mother was, the higher the prevalence of all levels of VI was in children. Additionally, a higher average time for homework per day and a lower average time for outdoor activities per day caused a higher prevalence of VI (all $P<0.001$).

The prevalence of all three levels of VI were close in different modes of neonatal feeding, but breastfeeding and formula feeding together showed significant differences comparing with breast feeding only (All $P<0.01$, Table 2). Caesarean contributed to higher prevalence of severely VI ($P<0.001$), however lower prevalence of light ($P<0.001$), mild ($P<0.05$) VI and overall VI. Unexpectedly, the prevalence of UCVA<6/12 in the case of before due date was less than with due date (16.7%, $P<0.001$) or overdue births (16.2%, $P<0.001$). Maternal pregnancy diseases were significantly negatively associated with VI, as shown in Table 2.

With an increase of grade and age (all $P<0.001$), the increasing prevalence of UCVA < 6/12 in grades 10–12 and older than 15 years students were 51.4% and 52.4% (Table 2). Especially, the increased prevalence of severely VI was obvious (all $P<0.001$), which were 9.92% and 10.6%. Prevalence of UCVA < 6/12 was different ($P<0.001$) between female sex (17.8%) and male sex (13.9%). Children without siblings had higher prevalence for all levels of VI than that of children with siblings. The prevalence of UCVA (better eye) <6/12 or worse than 6/18 among students with one or both parents' education > 12 years was higher than that of ≤12 years (Table 2). Students with father smoking currently had lower prevalence (All $P<0.05$).

Multiple Logistic regression model for detecting the potential risk factors for VI

Table 3 summarized the results of two multiple logistic regression models for detecting the potential risk factors for VI with 6/12 (>=6/12 as reference) and 6/18 (>=6/18 as reference) as cutoff points separately. Because low weight birth and maternal diseases were known factors affecting children's eye development, here, we only studied the 155,556 participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorder during pregnancy.

Results indicated that the students whose parents had higher level of education had a higher risk of UCVA <6/18 [OR (95% confidence interval, CI): 1.10 (1.04, 1.16), $P<0.001$] (Table 3). Parental myopia increased the risk of UCVA <6/12 or <6/18 (all $P<0.001$): only the father having myopia [OR (95% CI): 1.97 (1.87, 2.07), 1.98 (1.87, 2.11) respectively], only the mother having myopia[OR (95% CI): 1.80 (1.72, 1.89), 1.83 (1.73, 1.94) respectively], both parents having myopia [OR (95% CI): 2.96 (2.82, 3.10), 3.09 (2.92, 3.27) respectively].

In addition, students' birth weight was only positively associated with UCVA<6/18

[OR (95% CI): 1.11 (1.05, 1.17), *P*<0.001]. Comparing with breast feeding only, formula feeding only contributed to a higher risk of UCVA <6/12 [OR (95% CI): 1.14 (1.09, 1.20), *P*<0.001], while breast and formula feeding together contributed to a lower risk [OR (95% CI): 0.96 (0.93, 1.00), *P*=0.039]. Delivery mode was not associated with both outcomes of VI. Students who were delivered overdue or before due date had a lower risk of UCVA <6/12 [OR (95% CI): 0.93 (0.89, 0.97), *P*=0.002, and 0.91 (0.87, 0.94), *P*<0.001 respectively], and UCVA <6/18 [OR (95% CI): 0.93 (0.88, 0.98), *P*=0.005, and 0.93 (0.89, 0.98), *P*=0.003 respectively] than those delivered on due date.

Age [odds ratio (OR): 1.52; 95% CI: 1.51–1.53, P<0.001] and children without siblings [OR (95% CI), 1.09 (1.06, 1.13), P<0.001] were positively associated with the risk of UCVA<6/12. Similarly, age [OR (95% CI): 1.56 (1.55–1.57), P<0.001] and children without siblings [OR (95% CI), 1.18 (1.13, 1.23), P<0.001] were positively associated with the risk of UCVA<6/18. Male had less risk of either UCVA <6/12 [OR (95% CI): 0.77 (0.75, 0.80), P<0.001] or UCVA<6/18 [OR (95% CI): 0.78 (0.75, 0.81), P<0.001]. Average time for homework per day of 2–3h or more than 3h significantly increased the risk of mild VI [OR (95% CI): 1.07 (1.01, 1.13), 1.10 (1.03, 1.17) respectively], comparing with less than 1h.

The effect of outdoor activities can decrease the risk of VI which was consistent with the previous findings with <1h as reference: 1–2 h [OR (95% CI): 0.95 (0.92, 0.99), P=0.006, and 0.92 (0.88, 0.96), P<0.001 respectively]; 2–4 h [OR (95% CI): 0.94 (0.89, 0.99), P=0.017, and 0.90 (0.84, 0.96), P=0.002 respectively]; and >4 h[OR (95% CI): 0.88 (0.81, 0.96), P=0.003, and 0.80 (0.72, 0.88), P<0.001 respectively]. The students' father smoking currently had a lower risk of UCVA <6/18 comparing with those who never smoked [OR (95% CI): 0.94 (0.90, 0.99), P=0.010], while a marginally significant effect of current smoking on UCVA <6/12 [OR (95% CI): 0.97 (0.93, 1.00), P=0.049].

Discussion

Myopia, the dominant disease for visual impairment (VI) in teenagers, has become a major health issue in East Asia because of its increasingly high prevalence in the past few decades[25]. It is commonly believed the high prevalence of myopia in East Asia is associated with increasing educational pressures, combined with lifestyle changes, which have reduced the time children spend outside[2]. Recent studies have suggested that the development of childhood diseases may also be affected by factors in prenatal and neonatal life, in that factors like delivery mode, feeding manner, and pregnancy diseases can alter the risks for childhood diseases such as asthma[26, 27]. However, the prenatal and neonatal factors for VI especially myopia for child remains largely unclear. Therefore, a retrospective survey involving Guangzhou primary and middle school students was launched to evaluate the association between most important prenatal, perinatal and postnatal factors with VI prevalence in 6-year-old to 17-year-old school students.

Based on 253,301 completed questionnaire and medical records, the present cross-sectional study revealed that total VI prevalence was 6.71%, 30.0%, and 51.4% and severe VI value was 0.16%, 2.25%, and 9.92%, in grades 1–6, grades 7–9, and grades 10–12 school children in Guangzhou, respectively (Table 2). The prevalence of VI here is high as compared to in other countries and areas, but was close to the reported prevalence in Chinese urban area[28].

It is believed that VI is etiologically heterogeneous, with a low level of VI of prenatal and genetic origins that appears without exposure to risk factors [5]. Parental myopia is a high-risk factor for childhood VI, but no major genes for school myopia have been reported until now, although there are several genes known to be associated with high myopia[2]. A cohort study of 298 probands with early-onset high myopia using whole-exome sequencing showed that mutations in genes known to be responsible for retinal diseases were found in approximately one-fourth of the probands with early-onset high myopia [11]. In another study for myopia prevalence in a Chinese rural area, the grade 7 students had relatively lower prevalence of myopia (29.4%) and high myopia (0.4%) as compared with in Chinese urban cities, suggesting that Chinese people may not have a genetic predisposition to myopia and that environmental factors may play a major role in the development of school myopia in Chinese children [29].

In our study, the association between parental myopia and child VI is strong (Table 3). In grades 10–12 students, the ORs was 2.06, 1.85, and 3.17 in paternal myopia only, maternal myopia only, and both parents having myopia, respectively. Although the idea of heredity for VI was not excluded, families share environments as well as genes, and myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors, increasing the myopia risk of their children[18]. In a study on the gene–environmental interaction in myopia, the prevalence of children myopia was only 9.9% in farmer families without myopia, but the prevalence in those who entered colleges was similar between farmer families and other families with parental myopia, suggesting a leading role of environmental factors in the formation of myopia[10]. In another study on high myopia across three different generations in Korea, results supported that the environmental portion of the phenotypic variance increased and the additive genetic portion decreased as South Korea became more urbanized[30]. Therefore, how gene–environment interactions contribute to variations in school myopia within populations remains to be established[2].

Perinatal factors such as delivery manner, delivery mode, and pregnancy diseases on myopia are under investigation in this study. Pregnancy diseases such as hyperemesis, hypertension, and preeclampsia and uterus-related complications, may affect fetal growth in uterus and probably later long-term health. For instance, diabetes during pregnancy is associated with changes in retinal morphology in the offspring [31]. Our results found that pregnancy diseases decrease the prevalence of child's VI, though the linkage may be causal (Table 2). One possibility is that children who suffered with maternal pregnancy diseases may have lower educational pressure than those without diseases in the family.

Premature birth and low birth weight affect the general growth of the fetus, including the eye development. An analysis determined that, in children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia is mainly attributable to short axial length [18]. In a British birth cohort study, myopia was positively associated with low birth weight for gestational age [14], and in the Sydney Paediatric Eye Disease Study, vision impairment was independently associated with low birth weight[19].In this study, the parents only self-reported due date or not, and no further information on precise gestational age can be obtained. Regretfully, we cannot analyze the association between the premature birth and school VI. Accordingly, we used multiple logistic regression models to analyze only the population who have normal birth weight without pregnancy complications.

Breastfeeding may influence the early life growth of a baby. In a cross-sectional study of 527 Chinese primary school students, breastfeeding was reported to be associated with a decreased risk of myopia among children aged 6–12 years, and breastfeeding during the first 6 months of infancy was associated with more hyperopic spherical equivalent refraction[23]. Furthermore, breastfeeding was associated with myopic refraction and was not related to axial length, and this association could exist in childhood[23]. In another study in Singaporean preschoolers, results showed that breastfeeding was associated with more hyperopic spherical equivalent refraction in young Chinese children in Singapore[32]. Our results supported the idea that breastfeeding decreases but formula feeding increases the risks for VI (Table 3). The reasons for why remain unclear, but body development maybe is associated with eye development as well.

Postnatal factors including environmental factors play critical roles in childhood myopia development [4]. In an analysis combining the amount of outdoor activity and near-vision work activity spent, children with low outdoor time and high near-vision work were two to three times more likely to be myopic as compared with those performing low near-vision work and high outdoor activities [18]. In the Beijing area of China, greater axial elongation was associated with less time spent outdoors, more time spent indoors with studying[6]. In Finland, higher adulthood myopia was mainly related to parents' myopia and less time spent on sports and outdoor activities in childhood[8]. In the Netherlands, seven parameters associated independently with faster axial length elongation included books read per week, time spent reading, no participation in sports, and less time spent outdoors [33].

In our study, the results clearly support that home work time is positively associated but outdoor activity was negatively associated with myopia and high VI prevalence in students of all grades (Table 2 and 3). Therefore, environmental factors should be the leading consideration for school myopia development. As proof, in a recent clinical trial among 6-year-old children in Guangzhou, the researchers found that the addition of 40 min of outdoor activity at school versus usual activity resulted in a reduced incidence rate of myopia over the next 3 years [7]. Therefore, intervention in this manner could be the most promising way for decreasing VI in Chinese cities.

Our results also supported that female gender, older age, and child without siblings would increase the risks for myopia in our data. Similarly, in a study including 2,760 7-year-old children and 2,198 12-year-old children, higher intraocular pressure was associated with female gender, older age, and higher body mass index, while younger age at commencement of reading and being born with a caesarean section were also associated with higher intraocular pressure in adolescence[17]. However, these factors may be largely linked with environmental factors such as outdoor activity and near-vision work. For example, boys are more likely to have outdoor sports; as one ages, the educational pressure increases; children without siblings are more likely to have indoor activities and near-vision work; and overweightness decreases the outdoor activity of children. Therefore, the observed linkage may be a causal association.

Additionally, data showed that paternal smoking did not significantly increase the prevalence of VI (Table 3), suggesting that indoor pollution might not provoke myopia development. In a study in Singapore, an inverse association was found between parental smoking and childhood myopia[34], and our data also indicated that father current smoking decreased the risk of VI (Table 3). Evidence also came from the fact that Guangzhou has markedly reduced its atmospheric pollution during the past 10 years, but there has been a further increase in the prevalence of myopia[5].Therefore, we believe that parental smoking, as well as other types of indoor or outdoor environmental pollution, should not be major factors for school myopia.

In conclusion, in this retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China, results supported factors, such as the female gender, high birth weight, formula feeding, child without siblings, higher level of parents' education, parental myopia, high homework time, low outdoor activity, led to a significantly increased VI risk. Conversely, the factors of overdue or before due date, and outdoor activity decreased VI risk. Therefore, this study has proven known major prenatal/genetic, perinatal and postnatal factors for school VI. Although selection bias, recall bias, and reporter bias were unavoidable as this is a retrospective, self-reported survey, based on the current data, we concluded that prenatal and perinatal factors can affect the onset of childhood VI, but parental myopia and postnatal factors represent the leading factors. Therefore, children whose parents have myopia should be considered as high-risk population for school VI, and intervention of environment factors such as outdoor activities should be conducted for effective prevention.

Competing interests

None declared

Author Contributions

Conceived and designed the research: Dunjun Chen. Collected the data: Nali Deng. Analyzed the data: Juanjuan Chen, Wen Sun, Jingsi Chen, and Lili Du. Wrote the paper: Bolan Yu and Lijuan Dai.

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Data sharing statement

Deidentified participant data are available upon reasonable requisition.

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Figure Legend

Figure 1. Participant distribution in Guangzhou area.

Table 1. Characteristics of participants

Characteristics	n	Mean (SD) / n (%)
Total	253,301	/
Grade, n (%)	253,301	
1-6		189,008 (74.6)
7-9		45,119 (17.8)
10-12		19,174 (7.57)
Age, Years#	253,301	
6-10		156,992 (62.0)
11-15		82,092 (32.4)
>15		14,217 (5.61)
Mean (SD)		9.96 (2.99)
Sex, n (%)	253,301	
Male		136,200 (53.8)
Female		117,101 (46.2)
Birth weight, kg, Mean (SD)	249,610	2.99 (0.40)
Neonatal feeding, n (%)	253,292	
Breast feeding		98,164 (38.8)
Breast+ formula feeding		87,532 (34.6)
Formula feeding		67,596 (26.7)
Delivery, n (%)	253,292	
Vaginal delivery		160,873 (63.5)
Caesarean		92,419 (36.5)
Delivery date, n (%)	253,291	
On the due date		91,409 (36.1)
Overdue		54,161 (21.4)
Before the due date		107,721 (42.5)
Diseases in pregnancy, n (%)		
Hypertension	252,013	3,722 (1.48)
Diabetes	252,068	5,237 (2.08)
Intrahepatic cholestasis	251,930	622 (0.25)
Hypothyroidism	251,878	764 (0.30)
Hyperthyroidism	248,301	978 (0.39)
Anemia	248,374	16,236 (6.54)
Viral hepatitis	248,311	2,330 (0.94)
Other	248,273	1,679 (0.68)
Any disease above	248,461	27,998 (11.3)

Children without siblings, n (%)	253,286	
No		139,318 (55.0)
Yes		113,968 (45.0)
One or both parents' education, n (%)	253,288	
<=12 years		64,943 (25.6)
>12 years		188,345 (74.4)
Father smoking, n (%)	253,286	
Never smoked		138,077 (54.5)
Quit for >1 year		17,998 (7.11)
Quit for <1 year		5,362 (2.12)
Current smoking		91,849 (36.3)
Mother smoking, n (%)	253,286	
Never smoked		251,159 (99.2)
Quit for >1 year		900 (0.36)
Quit for <1 year		276 (0.11)
Current smoking		951 (0.38)
Father's refractive error, diopter, n (%)	238,888	
Normal		182,857 (76.6)
>-3.00 D		32,982 (13.8)
<= -3.00 D to >= -6.00 D		19,770 (8.28)
<-6.00 D		3,279 (1.37)
Mother's refractive error, diopter, n (%)	240,291	
Normal		173,256 (72.1)
>-3.00 D		39,915 (16.6)
<= -3.00 D to >= -6.00 D		23,135 (9.63)
<-6.00 D		3,985 (1.66)
Parental myopia, n (%)	242,006	
Two of them were normal		142,238 (58.8)
Only father having myopia		27,794 (11.5)
Only mother having myopia		38,172 (15.8)
Two of them having myopia		33,802 (14.0)
Average time for homework per day, hour, n (%)	251,925	
<=1		75,123 (29.8)
1-2		90,674 (36.0)
2-3		59,901 (23.8)
>3		26,227 (10.4)
Average time for outdoor activities per day, hour	253,280	

<1	114,471 (45.2)
1-2	101,658 (40.1)
2-4	27,332 (10.8)
>4	9,819 (3.88)

SD: Standard deviation;

#: The mean age of school grade 1 is 6 years old.

Table 2. Prevalence of visual impairment (VI)by characteristics

	Total UCVA#<6/12	Light VI UCVA>=6/18 to <6/12	MildVI UCVA>=6/60 to <6/18	Severe VI UCVA<6/60
All	15.7 (15.6, 15.9)	6.11 (6.00, 6.22)	8.12 (8.00, 8.24)	1.49 (1.44, 1.54)
Grade				
1-6	6.71 (6.58, 6.85)	3.70 (3.60, 3.80)	2.85 (2.76, 2.94)	0.16 (0.14, 0.18)
7-9	30.0 (29.6, 30.5)***	11.6 (11.3, 11.9)***	16.2 (15.8, 16.5)***	2.25 (2.10, 2.39)***
10-12	51.4 (50.6, 52.1)***	11.7 (11.2, 12.2) ***	29.7 (29.1, 30.4)***	9.92 (9.47, 10.4)***
Age, Years				
6-10	4.56 (4.43, 4.69)	2.66 (2.56, 2.76)	1.80 (1.72, 1.88)	0.10 (0.08, 0.12)
11-15	25.1 (24.8, 25.4)***	10.1 (9.85, 10.3)***	13.1 (12.9, 13.4)***	1.88 (1.79, 1.98)***
>15	52.4 (51.5, 53.3)***	11.3 (10.7, 11.8)***	30.6 (29.8, 31.4)***	10.6 (10.0, 11.1)***
Sex				
Female	17.8 (17.5, 18.0)	6.75 (6.58, 6.91)	9.33 (9.14, 9.52)	1.70 (1.62, 1.79)
Male	13.9 (13.7, 14.1)***	5.55 (5.41, 5.69)***	7.07 (6.91, 7.22)***	1.30 (1.24, 1.37)***
Neonatal feeding				
Breast feeding	16.1 (15.9, 16.4)	6.42 (6.24, 6.60)	8.22 (8.02, 8.42)	1.49 (1.40, 1.57)
Breast + formula feeding	15.2 (14.9, 15.5)***	5.71 (5.53, 5.89)***	7.80 (7.60, 8.01)**	1.67 (1.57, 1.76)**
Formula feeding	15.8 (15.5, 16.1)	6.16 (5.96, 6.37)	8.38 (8.14, 8.62)	1.27 (1.17, 1.36)**
Delivery				
Vaginal delivery	15.9 (15.6, 16.1)	6.31 (6.17, 6.44)	8.22 (8.06, 8.37)	1.32 (1.26, 1.39)
Caesarean	15.5 (15.2, 15.8)*	5.77 (5.60, 5.94)***	7.95 (7.75, 8.15)*	1.77 (1.67, 1.87)***
Delivery date				
Due date	16.7 (16.4, 17.0)	6.56 (6.37, 6.74)	8.82 (8.60, 9.03)	1.31 (1.23, 1.40)
Overdue	16.2 (15.9, 16.6)*	6.20 (5.97, 6.43)*	8.29 (8.02, 8.55)**	1.73 (1.61, 1.86)***
Before due date	14.7 (14.4, 14.9)***	5.68 (5.52, 5.84)***	7.45 (7.27, 7.63)***	1.52 (1.43, 1.60)***
Diseases in pregnancy				
Hypertension				
No	15.7 (15.5, 15.9)	6.10 (5.99, 6.21)	8.12 (8.00, 8.25)	1.48 (1.43, 1.54)
Yes	17.5 (16.1, 18.9)**	7.22 (6.26, 8.18)*	8.18 (7.17, 9.19)	2.13 (1.60, 2.67)**
Diabetes				
No	15.8 (15.6, 16.0)	6.13 (6.02, 6.24)	8.17 (8.04, 8.29)	1.49 (1.43, 1.54)
Yes	12.7 (11.6, 13.8)***	5.31 (4.57, 6.05)*	5.82 (5.05, 6.59)***	1.60 (1.19, 2.01)
Intrahepatic cholestasis				
No	15.7 (15.6, 15.9)	6.12 (6.01, 6.23)	8.13 (8.01, 8.25)	1.49 (1.44, 1.55)
Yes	11.9 (8.84, 14.9)*	4.79 (2.79, 6.80)	5.71 (3.54, 7.88)	1.37 (0.28, 2.46)
Hypothyroidism				

No	15.7 (15.6, 15.9)	6.11 (6.01, 6.22)	8.13 (8.00, 8.25)	1.49 (1.44, 1.55)
Yes	14.0 (11.0, 17.0)	5.83 (3.80, 7.85)	6.99 (4.79, 9.19)	1.17 (0.24, 2.09)
Hyperthyroidism				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.50 (1.45, 1.56)
Yes	16.0 (13.3, 18.7)	6.93 (5.06, 8.80)	7.92 (5.93, 9.91)	1.13 (0.35, 1.91)
Anemia				
No	16.0 (15.8, 16.1)	6.15 (6.04, 6.27)	8.28 (8.16, 8.41)	1.53 (1.47, 1.59)
Yes	12.9 (12.3, 13.5)***	5.64 (5.22, 6.06)*	6.16 (5.73, 6.60)***	1.08 (0.89, 1.26)***
Viral hepatitis				
No	15.8 (15.6, 16.0)	6.12 (6.01, 6.23)	8.17 (8.05, 8.29)	1.51 (1.45, 1.56)
Yes	13.2 (11.6, 14.8)**	5.97 (4.85, 7.09)	6.32 (5.17, 7.47)**	0.93 (0.48, 1.38)
Other				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.51 (1.45, 1.56)
Yes	15.2 (13.2, 17.2)	6.47 (5.07, 7.86)	7.89 (6.36, 9.42)	0.84 (0.32, 1.36)
Any disease above				
No	16.0 (15.9, 16.2)	6.15 (6.04, 6.27)	8.36 (8.22, 8.49)	1.52 (1.46, 1.58)
Yes	13.6 (13.1, 14.1)***	5.82 (5.50, 6.15)	6.47 (6.13, 6.81)***	1.31 (1.15, 1.46)*
Children without siblings				
No	13.4 (13.2, 13.6)	5.75 (5.61, 5.89)	6.84 (6.69, 7.00)	0.76 (0.71, 0.081)
Yes	18.5 (18.3, 18.8)***	6.53 (6.37, 6.70)***	9.65 (9.45, 9.85)***	2.36 (2.26, 2.46)***
One or both parents' education				
<=12 years	14.0 (13.7, 14.4)	6.12 (5.91, 6.33)	7.39 (7.15, 7.62)	0.53 (0.47, 0.60)
>12 years	16.3 (16.1, 16.5)***	6.10 (5.98, 6.23)	8.37 (8.22, 8.51)***	1.81 (1.74, 1.88)***
Father smoking				
Never smoked	16.1 (15.9, 16.3)	6.15 (6.01, 6.30)	8.38 (8.21, 8.55)	1.56 (1.48, 1.64)
Quit for >1 year	17.8 (17.2, 18.5)***	6.83 (6.41, 7.25)**	9.23 (8.74, 9.71)***	1.76 (1.54, 1.97)
Quit for <1 year	15.4 (14.3, 16.5)	6.41 (5.65, 7.18)	7.81 (6.97, 8.64)	1.19 (0.85, 1.53)
Current smoking	14.8 (14.5, 15.0)***	5.88 (5.70, 6.05)*	7.52 (7.33, 7.72)***	1.35 (1.26, 1.43)***
Father's refractive error, diopter				
Normal	13.9 (13.7, 14.1)	5.67 (5.55, 5.79)	7.17 (7.03, 7.30)	1.04 (0.99, 1.09)
>-3.00 D	20.4 (19.9, 20.9)***	7.31 (6.99, 7.64)***	10.5 (10.1, 10.9)***	2.66 (2.45, 2.86)***
<= -3.00 D to >= -6.00 D	23.4 (22.8, 24.1)***	7.35 (6.92, 7.77)***	12.5 (12.0, 13.0)***	3.60 (3.30, 3.90)***
<-6.00 D	27.3 (25.5, 29.0)***	8.01 (6.93, 9.08)***	14.1 (12.7, 15.4)***	5.19 (4.31, 6.14)***
Mother's refractive error, in either eye, diopter				

Normal	14.1 (13.9, 14.3)	5.70 (5.57, 5.82)	7.31 (7.16, 7.45)	1.07 (1.02, 1.13)
>-3.00 D	18.9 (18.5, 19.3)***	6.82 (6.53, 7.11)***	9.79 (9.45, 10.1)***	2.29 (2.12, 2.46)***
<= -3.00 D to >= -6.00 D	20.9 (20.3, 21.5)***	7.09 (6.70, 7.47)***	10.6 (10.2, 11.1)***	3.14 (2.88, 3.40)***
<-6.00 D	25.8 (24.2, 27.4)***	8.06 (7.07, 9.05)***	13.2 (12.0, 14.5)***	4.49 (3.74, 5.25)***
Parental myopia				
Two of them were normal	13.1 (12.9, 13.3)	5.44 (5.30, 5.57)	6.77 (6.62, 6.92)	0.86 (0.80, 0.91)
Only father having myopia	19.3 (18.8, 19.8)***	7.02 (6.67, 7.36)***	10.1 (9.69, 10.5)***	2.19 (1.99, 2.39)***
Only mother having myopia	16.8 (16.4, 17.2)***	6.46 (6.18, 6.75)***	8.58 (8.25, 8.90)***	1.75 (1.60, 1.90)***
Two of them having myopia	23.1 (22.6, 23.7)***	7.64 (7.31, 7.97)***	11.9 (11.5, 12.3)***	3.55 (3.32, 3.78)***
Average time for homework per day, hour				
<=1	15.1 (14.8, 15.4)	6.13 (5.92, 6.34)	7.93 (7.70, 8.17)	1.00 (0.91, 1.08)
1-2	12.4 (12.1, 12.6)***	5.42 (5.25, 5.59)***	6.16 (5.97, 6.34)***	0.81 (0.75, 0.88)***
2-3	17.0 (16.7, 17.3)***	6.38 (6.17, 6.60)	8.87 (8.62, 9.12)***	1.76 (1.64, 1.87)***
>3	24.1 (23.5, 24.6)***	7.49 (7.15, 7.83)***	12.6 (12.2, 13.1)***	3.96 (3.70, 4.21)***
Average time for outdoor activities per day, hour				
<1	16.5 (16.3, 16.8)	6.18 (6.02, 6.34)	8.62 (8.44, 8.81)	1.73 (1.65, 1.82)
1-2	15.0 (14.8, 15.3)***	5.99 (5.82, 6.16)	7.66 (7.47, 7.85)***	1.38 (1.30, 1.47)***
2-4	15.0 (14.5, 15.4)***	6.18 (5.85, 6.51)	7.74 (7.38, 8.10)***	1.04 (0.90, 1.17)***
>4	15.2 (14.4, 16.1)**	6.29 (5.74, 6.83)	7.94 (7.33, 8.54)*	1.02 (0.79, 1.24)***

#: Visual impairment (VI)was defined by uncorrected visual acuity in better-seeing eye (UCVA).Light VI: UCVA>=6/18 to <6/12, mildVI: UCVA>=6/60 to <6/18, severe VI: UCVA<6/60.

Logistic regression was used for comparisons between categories. CI: Confidence Interval. Prevalence (95% CI) was presented, * P<0.05, ** P<0.01, *** P<0.001 indicating the significance of the difference from the reference group.

Table 3. Multiple Logistic regression model for detecting the potential risk factors forVI*

Variable	UCVA#<6/12(n=148,672)†		UCVA<6/18 (n=148,672)†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, Year	1.52 (1.51, 1.53)	<0.001	1.56 (1.55, 1.57)	<0.001
Male	0.77 (0.75, 0.80)	<0.001	0.78 (0.75, 0.81)	<0.001
Birth weight, kg	1.00 (0.96, 1.04)	0.974	1.11 (1.05, 1.17)	<0.001
Neonatal feeding				
Breast feeding	Reference		Reference	
Breast+ formula feeding	0.96 (0.93, 1.00)	0.039	/	/
Formula feeding	1.14 (1.09, 1.20)	<0.001	/	/
Delivery				
Vaginal delivery	Reference		Reference	
Caesarean	/	/	/	/
Delivery date				
Due date	Reference		Reference	
Overdue	0.93 (0.89, 0.97)	0.002	0.93 (0.88, 0.98)	0.005
Before due date	0.91 (0.87, 0.94)	<0.001	0.93 (0.89, 0.98)	0.003
Child without siblings	1.09 (1.06, 1.13)	<0.001	1.18 (1.13, 1.23)	<0.001
One or both Parents' education >12 years	1.03 (0.99, 1.07)	0.185	1.10 (1.04, 1.16)	<0.001
Father smoking				
Never smoked	Reference		Reference	
Quit for >1 year	1.00 (0.94, 1.07)	0.893	0.94 (0.88, 1.02)	0.117
Quit for <1 year	0.97 (0.87, 1.09)	0.644	0.93 (0.81, 1.07)	0.302
Current smoking	0.97 (0.93, 1.00)	0.049	0.94 (0.90, 0.99)	0.010
Parental myopia, n (%)				
Two of them were normal	Reference		Reference	
Only father having myopia	1.97 (1.87, 2.07)	<0.001	1.98 (1.87, 2.11)	<0.001
Only mother having myopia	1.80 (1.72, 1.89)	<0.001	1.83 (1.73, 1.94)	<0.001
Two of them having myopia	2.96 (2.82, 3.10)	<0.001	3.09 (2.92, 3.27)	<0.001
Average time for homework per day, hour				
<=1	Reference		Reference	
1-2	1.00 (0.95, 1.05)	0.891	0.97 (0.91, 1.03)	0.287
2-3	1.05 (1.00, 1.10)	0.059	1.07 (1.01, 1.13)	0.026

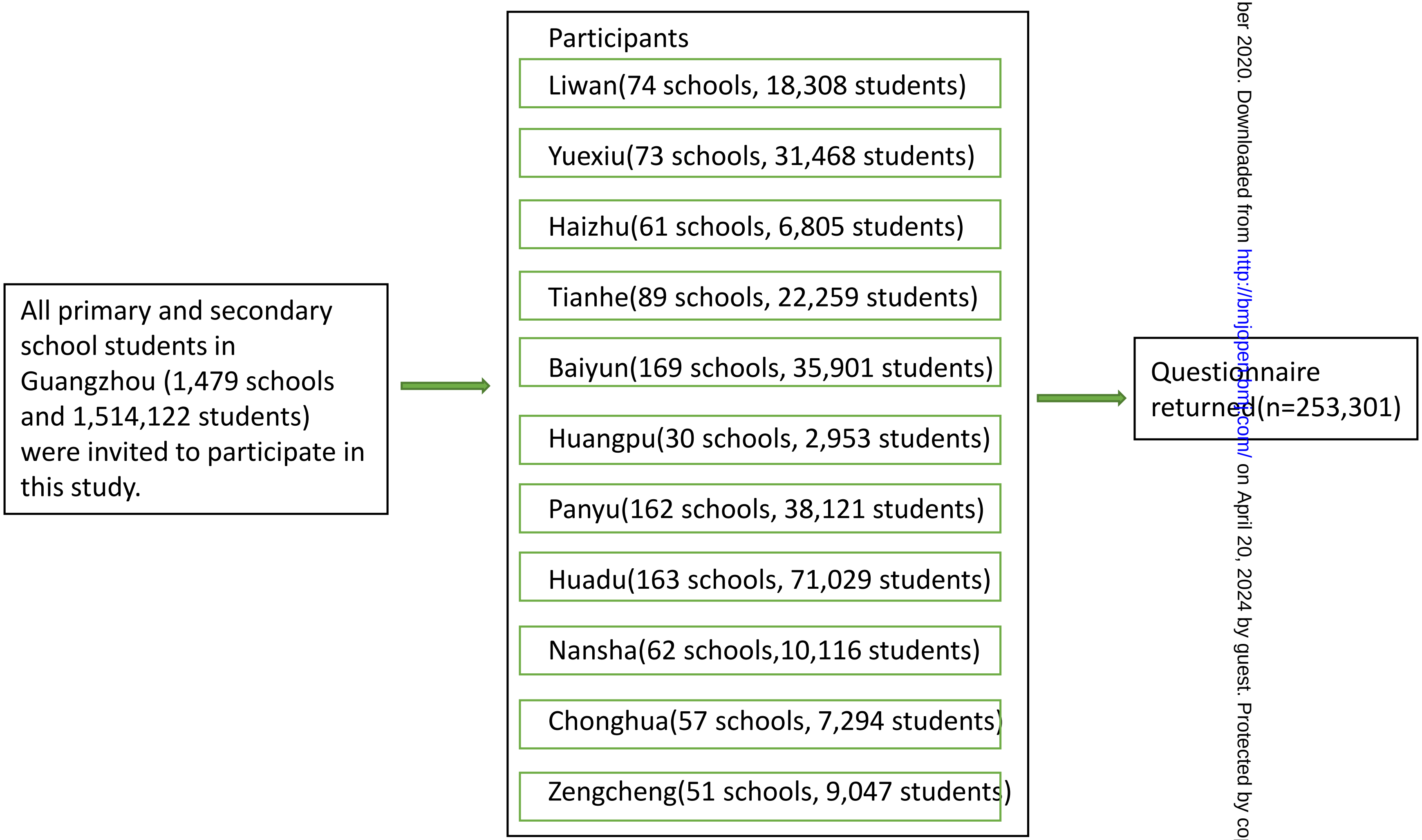
>3	1.05 (0.99, 1.11)	0.092	1.10 (1.03, 1.17)	0.004
Average time for outdoor activities per day, hour				
<1	Reference		Reference	
1-2	0.95 (0.92, 0.99)	0.006	0.92 (0.88, 0.96)	<0.001
2-4	0.94 (0.89, 0.99)	0.017	0.90 (0.84, 0.96)	0.002
>4	0.88 (0.81, 0.96)	0.003	0.80 (0.72, 0.88)	<0.001

*Variables with P<0.05 in simple regression analysis were included in the multiple regression model. The results of simple regression analysis were not listed in the table. OR: Odds Ratio, CI: Confidence Interval.

#: VI was defined by uncorrected visual acuity in better-seeing eye (UCVA). Analysis of UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference) among participants who were singletons with normal birth weight (2.5-4kg) and whose mother had no pregnancy disorder during pregnancy.

†There were 6,882 (4.42%) to 6,884 (4.43%) observations excluded due to missing values for the response or explanatory variables.

Figure 1


All primary and secondary school students in Guangzhou (1,479 schools and 1,514,122 students) were invited to participate in this study.
Participants
Liwan(74 schools, 18,308 students)
Yuexiu(73 schools, 31,468 students)
Haizhu(61 schools, 6,805 students)
Tianhe(89 schools, 22,259 students)
Baiyun(169 schools, 35,901 students)
Huangpu(30 schools, 2,953 students)
Panyu(162 schools, 38,121 students)
Huadu(163 schools, 71,029 students)
Nansha(62 schools,10,116 students)
Chonghua(57 schools, 7,294 students)
Zengcheng(51 schools, 9,047 students)
Questionnaire returned(n=253,301)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, Line 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, Line 1-26**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3, Line 1-32**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3, Line 34-36**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, Line 27-36**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4, Line 11-26**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 4, Line 14-20**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, Line 27-36**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 5, Line 2-16**
Bias	9	Describe any efforts to address potential sources of bias **Page 12, Line 12-14**
Study size	10	Explain how the study size was arrived at **Page 4, Line 21-26**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5, Line 19-35**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5, Line 19-35**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5, Line 19-35**
		(*c*) Explain how missing data were addressed **Page 4, Line 21-26**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **N/A**
		(*e*) Describe any sensitivity analyses **N/A**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 4, Line 21-26**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4, Line 21-26**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1, Column 2**
Outcome data	15	Report numbers of outcome events or summary measures **Page 6-8, Results Section**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 6-8, Results Section**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 8-12, Discussion Section**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 12, Line 12-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 8-12, Discussion Section**
Generalisability	21	Discuss the generalisability (external validity) of the study results **N/A**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12, Line 26-31**

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Abstract

Objectives: In this cross-sectional survey, we sought to determine the prevalence of and the influence of prenatal and neonatal factors on childhood visual impairment (VI) in a pediatric population from Guangzhou, China.

Setting: The health survey covered 11 administrative districts in Guangzhou, including 991 schools.

Participants: All of the primary and middle school students in Guangzhou were invited to complete an online questionnaire with the help of their parents. The results of physical examinations were reported by school medical departments. The results of the questionnaire were collected by the researchers. In total, 253,301 questionnaires were collected.

Primary outcome measures: The students' uncorrected visual acuity (UCVA) was examined by trained optometrists by standard logarithmic visual acuity charts. VI was defined by UCVA (of the better eye) (UCVA<6/12) with three levels: light VI (UCVA≥6/18 to <6/12), mild VI (UCVA≥6/60 to <6/18), and severe VI (UCVA<6/60).

Results: A total of 39,768 individuals (15.7%) had VI, and the rate was much higher among grade 10–12 students (51.4%) than among grade 1–6 students (6.71%). The following factors were significantly associated with an increased risk of VI: female gender, high birth weight, formula feeding, not having siblings, higher level of parents' education, parental myopia, much homework time, and little outdoor activity. Delivery mode was not associated with the risk of VI.

Conclusions: This study validates known major prenatal/genetic, perinatal, and postnatal factors for childhood VI. In conclusion, prenatal and perinatal factors can affect the onset of childhood VI, but parental myopia and postnatal factors are the main factors.

Keywords: abnormal visual acuity, childhood myopia, prenatal and neonatal factors

Strengths and limitations of this study:

- A retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China
- Collection and analysis of both prenatal and environmental factors associated with VI.
- Selection bias, recall bias, and reporter bias are unavoidable as the survey was based on voluntary participation.

Introduction

Visual impairment (VI) is highly prevalent in school students, and myopia-related VI accounts for over 90% of the cases in China. Other causes of decreased visual acuity include hyperopia, astigmatism, and other eye diseases [1]. Myopia is caused by an inconsistency between the eye's refractive power and the length of the eye axis. Two clinical types exist. In refractive myopia, the axial length is normal, but the refractive power of the cornea or lens is too strong, while in axial myopia, the refractive power of the lens is normal, but the axial length is too long [2]. Although myopia is not a life-threatening disease, the World Health Organization (WHO) recognizes it as a major cause of further VI if not fully corrected [3]. At present, the high prevalence of myopia has become a serious public health problem in East Asia. In China specifically, the prevalence of myopia in high school students ranges from 43.0% to 78.4% [4].

Myopia is etiologically heterogeneous and is believed to be driven by numerous environmental factors and genetic variations, with onset beginning in the preschool years. Environmental factors such as outdoor activity are associated with myopia inception and development [4]. Increasing outdoor time thus represents an important environmental factor that can protect young children from myopia, as supported by numerous studies [5-7]. The protective effects of outdoor activity may be due to the high light intensity outdoors, the chromaticity of daylight, or increased vitamin D levels [8-9]. A number of studies have separately shown that parental myopia is an important risk factor for myopia in children, due to the inheritance of myopia susceptibility genes or a shared myopia-driving environment [10-12].

According to the developmental origins of health and disease theory, the development of childhood diseases may be affected by factors in prenatal life [13]. Several epidemiological studies have shown that cesarean delivery and preterm birth increase the risk of childhood myopia [14-17]. For example, preterm birth may affect ocular development or later emmetropization, and it may affect the development of the refractive status through a more complicated mechanism[14] [18-22]. In addition, breastfeeding in early life may stimulate ocular development, as the docosahexaenoic acid and arachidonic acid in breast milk may affect retinal and neural development, therefore decreasing the risk of myopia [23].

Here, we sought to study the effects of multiple prenatal/genetic, perinatal, and postnatal factors on the development of myopia-related VI in primary and middle school students in the Guangzhou area of China. For this study, the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality released an annual online health survey of primary and secondary school students, and we subsequently received relevant information from this institution. We used descriptive statistics, logistic analysis, and multiple logistic regression models to analyze the data and explore the relationships between various environmental factors, parental myopia, prenatal and neonatal factors, and myopia. Our results improve our understanding of the etiology of childhood myopia in East Asia and confirm known potential prenatal factors for long-term diseases.

Methods

Data source

This study was approved by the institutional review board of The Third Affiliated Hospital of Guangzhou Medical University [2017(No.128)], and studies involving human subjects were conducted in accordance with the Declaration of Helsinki guidelines. A cross-sectional survey design was used, and a health survey was conducted by the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality, which is responsible for monitoring the health status of primary and middle schools in Guangzhou. All of the primary and middle school students in Guangzhou were invited by their school to participate in the survey in October 2017. Consent was provided to all of the participants by school teachers, and oral informed consent was obtained from the participants' parents. All of the parents of school students were informed about this study at the parent-teacher conference, using posters and a short messaging service. Only verbal consent was obtained as this study was a health survey.

The health survey covered 11 administrative districts in Guangzhou, including 991 schools. In total, 253,301 questionnaires were collected. On the first page of the questionnaire, it was stated that the results of the health questionnaire would be used for health research. According to the Education Statistics Manual of Guangzhou in 2017, the number of primary and middle school students in 2017 was 1,514,122, so the response rate of this survey was 16.73%.

This health survey consisted of a questionnaire and a physical examination. The questionnaire was divided into four parts, including basic conditions, psychological behavior, exercise and sleep, and diet. Only the part of basic conditions was used in this study. Children and parents jointly filled out the questionnaire on the Internet according to their own situation and submitted the questionnaire directly online. This study used the first part of the data, including aspects such as birth weight, sex, neonatal feeding, delivery mode, delivery date, maternal diseases in pregnancy, parents' education, parental myopia, parental smoking, and average monthly household income per person.

Visual acuity assessment

The students' uncorrected visual acuity (UCVA) was examined in all schools by trained optometrists by the same standard logarithmic visual acuity charts on a light box with 300–500 lux illumination, following regular procedures. During the test, students sat at a 5 m distance from the chart with one eye covered and read out the direction of the letter "E." Students pointed in the direction the letter "E" was facing: up, down, left, or right. The test started at the 6/6 line. If students cannot see clearly, they go up one line at a time; otherwise, they go down one line at a time. The identification time of each "E" must not exceed 5 s. This process was repeated with the other eye. It is stipulated that there was no misidentification in 6/60–6/20 lines on each line, and less than two errors on each line of 6/15–6/6 lines and less than three errors on each line of 6/5–6/3. If the top line could not be read at 5 m, the student was tested at 2.5 m or 1 m, and the measured visual acuity was subtracted by 0.3 or 0.7, respectively, and then recorded as the student's visual acuity.

Patient and public involvement

No patients were involved.

Statistical methods

Characteristics of participants are presented as mean (standard deviation, SD) for continuous variables and as frequency (proportion) for categorical variables. VI was defined according to UCVA (better eye) (UCVA<6/12) with three levels: light VI (UCVA≥6/18 to <6/12), mild VI (UCVA≥6/60 to <6/18), and severe VI (UCVA<6/60), referring to the previous studies [24] and definitions of impaired vision by the WHO. The prevalence (95% confidence interval, CI) of VI was estimated by categorization of the participants' characteristics. The prevalence between categories was compared using logistic regression. Multiple logistic regression analysis was performed to detect the potential risk factors for VI. The participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorders during pregnancy were included in the regression analysis. Two binary outcomes of VI were defined by UCVA (better eye) <6/12 (≥6/12 as reference) and UCVA (better eye) <6/18 (≥6/18 as reference). Observations with missing values for the response or explanatory variables were excluded in the logistic regression analysis. Variables with *P*<0.05 in the simple regression analysis were included in the multiple regression model. All of the *P* values were based on two-sided tests, where *P*<0.05 was considered as statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of participants

Characteristics of all of the participants are presented in Table 1. All of the factors can be grouped into (i) prenatal/genetic factors, including the father's refractive error, the mother's refractive error, parental myopia, and one or both parents' education; (ii) perinatal factors, including birth weight, neonatal feeding, delivery mode, delivery date, and diseases in pregnancy; and (iii) postnatal factors, including grade, age, sex, only child status, parents' smoking, average time spent on homework per day, and average time spent on outdoor activities per day.

In brief, the refractive error was divided into three levels: namely −3.00 D, −3.00 D to −6.00 D, and less than −6.00 D. The results showed that the distributions of the father's refractive error were 13.8%, 8.28%, and 1.37%, and those of the mother's refractive error were 16.6%, 9.63%, and 1.66% (Table 1). Both parents had myopia, and neither of them had myopia in 14.0% and 58.8% of the cases, while only the father or the mother had myopia in 11.5% and 15.8% of the cases, respectively. One or both parents' education was more than 12 years in 74.4% of the cases (Table 1).

There were three ways of neonatal feeding: breastfeeding only, formula feeding only, and breastfeeding and formula feeding together, accounting for 38.8%, 26.7%, and 34.6%, respectively. Vaginal delivery accounted for 63.5%, while the cesarean section delivery rate was 36.5%. The proportion of maternal gestational diseases, including hypertension, diabetes, intrahepatic cholestasis, hypothyroidism, hyperthyroidism, anemia, and viral hepatitis, was 11.3%. The average birth weight was 2.99 kg ± 0.40 kg (Table 1).

In addition, students of primary school (grade 1–6), junior middle school (grade 7–9), and high middle school (grade 10–12) represented 74.6%, 17.8%, and 7.57% of the total study population, respectively, with 53.8% being male. Less than 1h, 1–2h, 2–3h, and more than 3h spent on homework per day were reported in 29.8%, 36.0%, 23.8%, and 10.4% of the cases, respectively; less than 1h, 1–2h, 2–4h, and more than 4h spent on outdoor activities per day were reported in 45.2%, 40.1%, 10.8%, and 3.88% of the cases, respectively. Children without siblings made up 45.0%. Paternal and maternal smoking rates were 45.5% and 0.85%, respectively (Table 1).

Prevalence of VI by characteristics

Of the 253,301 children included in the present study, 15.7% children experienced VI

(Table 2). The larger the refraction error of either the father or the mother, the higher the prevalence of all levels of VI in children. Additionally, more time spent on homework per day and less time spent on outdoor activities per day was associated with a higher risk of VI (all $P<0.001$).

The prevalence of all three levels of VI was similar in the subgroups with different modes of neonatal feeding, but breastfeeding and formula feeding together showed statistically significant differences compared with breast feeding only (all $P<0.01$, Table 2). Cesarean section was associated with a higher prevalence of severe VI ($P<0.001$) but with a lower prevalence of light VI ($P<0.001$), mild VI ($P<0.05$), and overall VI ($P<0.05$). Unexpectedly, the prevalence of UCVA<6/12 in participants born before their due date was lower than in participants born on their due date (16.7%, $P<0.001$) or who were overdue (16.2%, $P<0.001$). Maternal pregnancy diseases were significantly associated with an increased risk of VI (Table 2).

With increasing grade and age, the prevalence of UCVA<6/12 also increased (all $P<0.001$); the prevalence among students in grades 10–12 and students older than 15 years was 51.4% and 52.4%, respectively (Table 2). The increase in the prevalence of severe VI, which was 9.92% and 10.6%, respectively, was most significant (all $P<0.001$).The prevalence of UCVA<6/12 was different ($P<0.001$) in female (17.8%) and male (13.9%) participants. The prevalence of all levels of VI was higher among children without siblings than among children with siblings. The prevalence of UCVA (better eye) <6/12 or worse than 6/18 was higher among students with one or both parents' education >12 years than among students with both parents' education ≤12 years (Table 2). Students with a father currently smoking had a lower risk of VI (all $P<0.05$).

Multiple logistic regression model for detecting the potential risk factors for VI

The results of two multiple logistic regression models for detecting the potential risk factors for VI are presented in Table 3, with 6/12 (≥6/12 as reference) and 6/18 (≥6/18 as reference) as cutoff points. Because low birth weight and maternal diseases are known factors affecting children's eye development, here, we only studied the 155,556 participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no disease during pregnancy.

The results indicated that the students whose parents had a higher level of education had a higher risk of UCVA<6/18 (OR [95% CI], 1.10 [1.04, 1.16]; $P<0.001$) (Table 3). Parental myopia increased the risk of UCVA<6/12 or <6/18 (all $P<0.001$) when only the father had myopia (OR [95% CI], 1.97 [1.87, 2.07] and 1.98 [1.87, 2.11]), when only the mother had myopia (OR [95% CI], 1.80 [1.72, 1.89] and 1.83 [1.73, 1.94]), and when both parents had myopia (OR [95% CI], 2.96 [2.82, 3.10] and 3.09 [2.92, 3.27]).

In addition, birth weight was only positively associated with UCVA<6/18 (OR [95% CI], 1.11 [1.05, 1.17]; *P*<0.001). Compared with breast feeding only, formula feeding only contributed to a higher risk of UCVA<6/12 (OR [95% CI], 1.14 [1.09, 1.20]; *P*<0.001), while breast and formula feeding together was associated with a lower risk (OR [95% CI], 0.96 [0.93, 1.00]; *P*=0.039). Delivery mode was not associated with both outcomes of VI. Students who were delivered overdue or before due date had a lower risk of UCVA<6/12 (OR [95% CI], 0.93 [0.89, 0.97]; *P*=0.002 and 0.91 [0.87, 0.94]; *P*<0.001, respectively) and UCVA<6/18 (OR [95% CI], 0.93 [0.88, 0.98]; *P*=0.005 and 0.93 [0.89, 0.98]; *P*=0.003, respectively) than those delivered on their due date.

Age (OR [95% CI], 1.52 [1.51, 1.53]; *P*<0.001) and not having siblings (OR [95% CI], 1.09 [1.06, 1.13]; *P*<0.001) were positively associated with the risk of UCVA<6/12. Similarly, age (OR [95% CI], 1.56 [1.55, 1.57]; *P*<0.001) and not having siblings (OR [95% CI], 1.18 [1.13, 1.23]; *P*<0.001) were positively associated with the risk of UCVA<6/18. Male students had a lower risk of either UCVA<6/12 (OR [95% CI], 0.77 [0.75, 0.80]; *P*<0.001) or UCVA<6/18 (OR [95% CI], 0.78 [0.75, 0.81]; *P*<0.001]. An average time spent on homework per day of 2–3h (OR [95% CI], 1.07 [1.01, 1.13]) or more than 3h (OR [95% CI], 1.10 [1.03, 1.17]) was significantly associated with a higher risk of mild VI compared with the group spending less than 1 h.

In agreement with previous findings, among participants who spent ≥1h on outdoor activities, the prevalence of VI was lower, i.e., for 1–2h (OR [95% CI], 0.95 [0.92, 0.99]; *P*=0.006 and 0.92 [0.88, 0.96]; *P*<0.001), for 2–4h (OR [95% CI], 0.94 [0.89, 0.99]; *P*=0.017 and 0.90 [0.84, 0.96]; *P*=0.002), and for >4h (OR [95% CI], 0.88 [0.81, 0.96]; *P*=0.003 and 0.80 [0.72, 0.88]; *P*<0.001), compared with participants who spent <1h on outdoor activities. The current smoking status of the father was associated with a lower risk of UCVA<6/18 compared with participants with a father who never smoked (OR [95% CI], 0.94 [0.90, 0.99]; *P*=0.010], and also a marginally significant association between current smoking status of the father and the prevalence of UCVA<6/12 was observed (OR [95% CI], 0.97 [0.93, 1.00]; *P*=0.049).

Discussion

Myopia, the dominant cause of VI in teenagers, has increased in prevalence in East Asia in the past few decades and has therefore become a major health issue [25]. It is commonly believed that the high prevalence of myopia in East Asia is associated with increased educational pressure, combined with lifestyle changes, which have reduced the time children spend outside [2]. Recent studies have suggested that the development of childhood diseases may also be affected by factors in prenatal and neonatal life, in that factors like delivery mode, feeding manner, and pregnancy diseases can alter the risks for childhood diseases such as asthma [26 27]. However, the prenatal and neonatal factors for VI, especially childhood myopia, remain largely unclear. Therefore, a retrospective survey involving primary and middle school students in Guangzhou was launched to evaluate the association between most important prenatal, perinatal, and postnatal factors and the prevalence of VI in 6-year-old to 17-year-old school students.

The present cross-sectional study, which included 253,301 completed questionnaires and medical records, revealed that among children in grades 1–6, grades 7–9, and grades 10–12 in Guangzhou, the total prevalence of VI was 6.71%, 30.0%, and 51.4% and that of severe VI was 0.16%, 2.25%, and 9.92%, respectively (Table 2). The prevalence of VI presented here is high compared with other countries and areas but was close to the reported prevalence in Chinese urban areas [28].

It is believed that VI is etiologically heterogeneous. A small part of VI cases is caused by prenatal and genetic factors and appears without exposure to additional risk factors [5]. Parental myopia is a high-risk factor for childhood VI, but although several genes have been shown to be associated with high myopia, no major genes affecting childhood myopia have been reported until now[2]. A cohort study of 298 probands with early-onset high myopia using whole-exome sequencing showed that mutations in genes known to be responsible for retinal diseases were found in approximately one-fourth of the probands with early-onset high myopia [11]. In another study of myopia prevalence, grade 7 students in a Chinese rural area showed a lower prevalence of myopia (29.4%) and high myopia (0.4%) than those in Chinese urban cities, suggesting that Chinese people may not have a genetic predisposition to myopia and that environmental factors may play a major role in the development of childhood myopia in Chinese children [29].

In the present study, the association between parental myopia and childhood VI was strong (Table 3). In grade 10–12 students, the ORs were 2.06, 1.85, and 3.17 for paternal myopia only, maternal myopia only, and both parents having myopia, respectively. Although the possibility of heredity for VI was not excluded, families also share environments, and myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors, increasing the myopia risk of their children [18]. In a study on the gene–environment interaction in myopia, the prevalence of child myopia was only 9.9% in farmer families without parental myopia, but the prevalence among college students was similar between farmer families and other families, suggesting a leading role of environmental factors in the formation of myopia [10]. In another study on high myopia across three different generations in Korea, results showed that the environmental portion of the phenotypic variance increased and the additive genetic portion decreased as South Korea became more urbanized [30]. Therefore, it remains to be established how gene–environment interactions contribute to myopia within various populations [2].

In the present study, we analyzed the effects of perinatal factors, such as delivery manner, delivery mode, and pregnancy diseases, on the prevalence of myopia. Pregnancy diseases, such as hyperemesis, hypertension, preeclampsia, and uterus-related complications may affect fetal growth in the uterus and probably later long-term health. For instance, diabetes during pregnancy is associated with changes in retinal morphology in the offspring [31]. We found that pregnancy diseases decrease the prevalence of childhood VI, and this relationship may be causal (Table 2). Children whose mothers suffered from pregnancy diseases may have lower educational pressure than those without diseases in the family.

Premature birth and low birth weight affect the general growth of the fetus, including eye development. A previous analysis determined that in children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia was mainly attributed to short axial length [18]. In a British birth cohort study, myopia was positively associated with low birth weight for gestational age [14], and in the Sydney Paediatric Eye Disease Study, VI was independently associated with low birth weight [19]. In the present study, the parents only reported whether the participants were born before, on, or after their due date, and no further information on precise gestational age was obtained. Regretfully, we cannot analyze the association between premature birth and childhood VI. Accordingly, we used multiple logistic regression models to analyze only the population with normal birth weight and without pregnancy complications.

Breastfeeding may influence the early growth of a baby. In a cross-sectional study of 527 Chinese primary school students aged 6–12 years, breastfeeding was reported to be associated with a decreased risk of myopia, and breastfeeding during the first 6 months of infancy was associated with higher hyperopic spherical equivalent refraction [23]. Furthermore, breastfeeding was associated with myopic refraction and was not related to axial length, and this association could exist in childhood [23]. In a study of Singaporean preschoolers, results showed that breastfeeding was associated with higher hyperopic spherical equivalent refraction[32]. Our results support the idea that breastfeeding decreases and formula feeding increases the risks for VI (Table 3). The underlying mechanisms remain unclear, but physical development may be associated with eye development as well.

Postnatal factors, including environmental factors, play critical roles in the development of childhood myopia [4]. In an analysis of time spent on outdoor activity and on near-vision work, children with little outdoor time and much near-vision work were two to three times more likely to be myopic compared with those performing little near-vision work and spending much time outdoors [18]. In the area of Beijing, China, greater axial elongation was associated with less time spent outdoors and with more time spent indoors [6]. In Finland, a higher risk of myopia was mainly related to parents having myopia and less time spent on sports and outdoor activities in childhood [8]. In the Netherlands, seven parameters were associated independently with faster axial length elongation, including the number of books read per week, time spent reading, no participation in sports, and less time spent outdoors [33].

Our present results clearly support the idea that homework time is positively associated and outdoor activity is negatively associated with the prevalence of myopia and VI in students of all grades (Tables 2 and 3). Therefore, environmental factors should be the leading consideration to reduce the incidence of childhood myopia. Indeed, in a recent clinical trial among 6-year-old children in Guangzhou, the incidence of myopia significantly reduced over the 3 years after the addition of 40 min of outdoor activity to the daily curriculum, replacing usual activity [7]. Therefore, such interventions could be the most effective strategy to decrease the prevalence of VI in Chinese cities.

Our results also show that female gender, older age, and not having siblings are associated with an increased risk for myopia. Similarly, in a study including 2,760 7-year-old children and 2,198 12-year-old children, higher intraocular pressure was associated with female gender, older age, and higher body mass index, while younger age at the commencement of reading and being born with a cesarean section were also associated with higher intraocular pressure in adolescence [17]. However, these factors may be largely linked with environmental factors, such as outdoor activity and near-vision work. For example, boys are more likely to do outdoor sports; as one ages, the educational pressure increases; children without siblings are more likely to have indoor activities and near-vision work; and overweight decreases the outdoor activity of children. Therefore, the observed correlation may be causal.

Additionally, our data showed that paternal smoking did not significantly increase the prevalence of VI (Table 3), suggesting that indoor pollution might not provoke the development of myopia. In a study in Singapore, an inverse association was found between parental smoking and childhood myopia [34], and our data also indicated that a current smoking status of the father decreased the risk of VI (Table 3). Moreover, Guangzhou has markedly reduced its atmospheric pollution during the past 10 years, but the prevalence of myopia has further increased [5]. Therefore, environmental pollution does not seem to be a major risk factor for childhood myopia. It is notable that female smoking is rare in China, to such an extent that in this study 99.2% of the mothers never smoked. Therefore, maternal smoking may not be a significant factor for consideration.

In conclusion, the results of the present retrospective study, conducted using 253,301 completed surveys in the Guangzhou area of Southern China, indicated that factors such as the female gender, high birth weight, formula feeding, not having siblings, higher levels of parents' education, parental myopia, much homework time, and little outdoor activity are significantly associated with a higher risk of VI. Conversely, being born before the due date, being overdue, and outdoor activity were associated with a decreased risk of VI. Therefore, we here confirm known major prenatal/genetic, perinatal, and postnatal factors for childhood VI. Although selection bias, recall bias, and reporter bias were unavoidable, as this is a retrospective, self-reported survey, based on the current data, we conclude that prenatal and perinatal factors can affect the onset of childhood VI, but parental myopia and postnatal factors are the main factors. Therefore, children whose parents have myopia should be considered as a high-risk population for childhood VI, and intervention by changing environmental factors such as outdoor activities should be conducted for effective prevention of VI.

Competing interests

None declared

Author Contributions

Conceived and designed the research: DunjunChen. Collected the data: NaliDeng. Analyzed the data: JuanjuanChen, Wen Sun, JingsiChen, and LiliDu. Wrote the paper: Bolan Yu and LijuanDai.

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Hospital.

Data sharing statement

Deidentified participant data are available upon reasonable requisition.

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Table 1. Characteristics of participants

Characteristics	n	n (%)
Total	253,301	/
Grade	253,301	
1-6		189,008 (74.6)
7-9		45,119 (17.8)
10-12		19,174 (7.57)
Age[#]	253,301	
6-10		156,992 (62.0)
11-15		82,092 (32.4)
>15		14,217 (5.61)
Sex	253,301	
Male		136,200 (53.8)
Female		117,101 (46.2)
Birth weight, kg	249,610	2.99 (0.40)[†]
Neonatal feeding	253,292	
Breast feeding		98,164 (38.8)
Breast+ formula feeding		87,532 (34.6)
Formula feeding		67,596 (26.7)
Delivery	253,292	
Vaginal delivery		160,873 (63.5)
Caesarean		92,419 (36.5)
Delivery date	253,291	
On the due date		91,409 (36.1)
Overdue		54,161 (21.4)
Before the due date		107,721 (42.5)
Diseases in pregnancy		
Hypertension	252,013	3,722 (1.48)
Diabetes	252,068	5,237 (2.08)
Intrahepatic cholestasis	251,930	622 (0.25)
Hypothyroidism	251,878	764 (0.30)
Hyperthyroidism	248,301	978 (0.39)
Anemia	248,374	16,236 (6.54)
Viral hepatitis	248,311	2,330 (0.94)
Other	248,273	1,679 (0.68)
Any disease above	248,461	27,998 (11.3)
Children without siblings	253,286	

No		139,318 (55.0)
Yes		113,968 (45.0)
One or both parents' education	253,288	
<=12 years		64,943 (25.6)
>12 years		188,345 (74.4)
Father smoking	253,286	
Never smoked		138,077 (54.5)
Quit for >1 year		17,998 (7.11)
Quit for <1 year		5,362 (2.12)
Current smoking		91,849 (36.3)
Mother smoking	253,286	
Never smoked		251,159 (99.2)
Quit for >1 year		900 (0.36)
Quit for <1 year		276 (0.11)
Current smoking		951 (0.38)
Father's refractive error, diopter	238,888	
Normal		182,857 (76.6)
>-3.00 D		32,982 (13.8)
<= -3.00 D to >= -6.00 D		19,770 (8.28)
<-6.00 D		3,279 (1.37)
Mother's refractive error, diopter	240,291	
Normal		173,256 (72.1)
>-3.00 D		39,915 (16.6)
<= -3.00 D to >= -6.00 D		23,135 (9.63)
<-6.00 D		3,985 (1.66)
Parental myopia	242,006	
Two of them were normal		142,238 (58.8)
Only father having myopia		27,794 (11.5)
Only mother having myopia		38,172 (15.8)
Two of them having myopia		33,802 (14.0)
Average time for homework per day, hour	251,925	
<=1		75,123 (29.8)
1-2		90,674 (36.0)
2-3		59,901 (23.8)
>3		26,227 (10.4)
Average time for outdoor activities per day, hour	253,280	
<1		114,471 (45.2)
1-2		101,658 (40.1)

2-4	27,332 (10.8)
>4	9,819 (3.88)

#: The mean age of school grade1 is 6 years old.

†: Data is represented as Mean (Standard deviation).

Table 2. Prevalence of VI by characteristics

Variable	Total UCVA<6/12	Light VI UCVA>=6/18 to <6/12	Mild VI UCVA>=6/60 to <6/18	Severe VI UCVA<6/60
	% (95% CI) †	% (95% CI) †	% (95% CI) †	% (95% CI) †
All	15.7 (15.6, 15.9)	6.11 (6.00, 6.22)	8.12 (8.00, 8.24)	1.49 (1.44, 1.54)
Grade				
1-6	6.71 (6.58, 6.85)	3.70 (3.60, 3.80)	2.85 (2.76, 2.94)	0.16 (0.14, 0.18)
7-9	30.0 (29.6, 30.5)***	11.6 (11.3, 11.9)***	16.2 (15.8, 16.5)***	2.25 (2.10, 2.39)***
10-12	51.4 (50.6, 52.1)***	11.7 (11.2, 12.2) ***	29.7 (29.1, 30.4)***	9.92 (9.47, 10.4)***
Age, Years				
6-10	4.56 (4.43, 4.69)	2.66 (2.56, 2.76)	1.80 (1.72, 1.88)	0.10 (0.08, 0.12)
11-15	25.1 (24.8, 25.4)***	10.1 (9.85, 10.3)***	13.1 (12.9, 13.4)***	1.88 (1.79, 1.98)***
>15	52.4 (51.5, 53.3)***	11.3 (10.7, 11.8)***	30.6 (29.8, 31.4)***	10.6 (10.0, 11.1)***
Sex				
Female	17.8 (17.5, 18.0)	6.75 (6.58, 6.91)	9.33 (9.14, 9.52)	1.70 (1.62, 1.79)
Male	13.9 (13.7, 14.1)***	5.55 (5.41, 5.69)***	7.07 (6.91, 7.22)***	1.30 (1.24, 1.37)***
Neonatal feeding				
Breast feeding	16.1 (15.9, 16.4)	6.42 (6.24, 6.60)	8.22 (8.02, 8.42)	1.49 (1.40, 1.57)
Breast + formula feeding	15.2 (14.9, 15.5)***	5.71 (5.53, 5.89)***	7.80 (7.60, 8.01)**	1.67 (1.57, 1.76)**
Formula feeding	15.8 (15.5, 16.1)	6.16 (5.96, 6.37)	8.38 (8.14, 8.62)	1.27 (1.17, 1.36)**
Delivery				
Vaginal delivery	15.9 (15.6, 16.1)	6.31 (6.17, 6.44)	8.22 (8.06, 8.37)	1.32 (1.26, 1.39)
Caesarean	15.5 (15.2, 15.8)*	5.77 (5.60, 5.94)***	7.95 (7.75, 8.15)*	1.77 (1.67, 1.87)***
Delivery date				
Due date	16.7 (16.4, 17.0)	6.56 (6.37, 6.74)	8.82 (8.60, 9.03)	1.31 (1.23, 1.40)
Overdue	16.2 (15.9, 16.6)*	6.20 (5.97, 6.43)*	8.29 (8.02, 8.55)**	1.73 (1.61, 1.86)***
Before due date	14.7 (14.4, 14.9)***	5.68 (5.52, 5.84)***	7.45 (7.27, 7.63)***	1.52 (1.43, 1.60)***
Diseases in pregnancy				
Hypertension				
No	15.7 (15.5, 15.9)	6.10 (5.99, 6.21)	8.12 (8.00, 8.25)	1.48 (1.43, 1.54)
Yes	17.5 (16.1, 18.9)**	7.22 (6.26, 8.18)*	8.18 (7.17, 9.19)	2.13 (1.60, 2.67)**
Diabetes				
No	15.8 (15.6, 16.0)	6.13 (6.02, 6.24)	8.17 (8.04, 8.29)	1.49 (1.43, 1.54)
Yes	12.7 (11.6, 13.8)***	5.31 (4.57, 6.05)*	5.82 (5.05, 6.59)***	1.60 (1.19, 2.01)
Intrahepatic cholestasis				
No	15.7 (15.6, 15.9)	6.12 (6.01, 6.23)	8.13 (8.01, 8.25)	1.49 (1.44, 1.55)
Yes	11.9 (8.84, 14.9)*	4.79 (2.79, 6.80)	5.71 (3.54, 7.88)	1.37 (0.28, 2.46)

Hypothyroidism				
No	15.7 (15.6, 15.9)	6.11 (6.01, 6.22)	8.13 (8.00, 8.25)	1.49 (1.44, 1.55)
Yes	14.0 (11.0, 17.0)	5.83 (3.80, 7.85)	6.99 (4.79, 9.19)	1.17 (0.24, 2.09)
Hyperthyroidism				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.50 (1.45, 1.56)
Yes	16.0 (13.3, 18.7)	6.93 (5.06, 8.80)	7.92 (5.93, 9.91)	1.13 (0.35, 1.91)
Anemia				
No	16.0 (15.8, 16.1)	6.15 (6.04, 6.27)	8.28 (8.16, 8.41)	1.53 (1.47, 1.59)
Yes	12.9 (12.3, 13.5)***	5.64 (5.22, 6.06)*	6.16 (5.73, 6.60)***	1.08 (0.89, 1.26)***
Viral hepatitis				
No	15.8 (15.6, 16.0)	6.12 (6.01, 6.23)	8.17 (8.05, 8.29)	1.51 (1.45, 1.56)
Yes	13.2 (11.6, 14.8)**	5.97 (4.85, 7.09)	6.32 (5.17, 7.47)**	0.93 (0.48, 1.38)
Other				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.51 (1.45, 1.56)
Yes	15.2 (13.2, 17.2)	6.47 (5.07, 7.86)	7.89 (6.36, 9.42)	0.84 (0.32, 1.36)
Any disease above				
No	16.0 (15.9, 16.2)	6.15 (6.04, 6.27)	8.36 (8.22, 8.49)	1.52 (1.46, 1.58)
Yes	13.6 (13.1, 14.1)***	5.82 (5.50, 6.15)	6.47 (6.13, 6.81)***	1.31 (1.15, 1.46)*
Children without siblings				
No	13.4 (13.2, 13.6)	5.75 (5.61, 5.89)	6.84 (6.69, 7.00)	0.76 (0.71, 0.081)
Yes	18.5 (18.3, 18.8)***	6.53 (6.37, 6.70)***	9.65 (9.45, 9.85)***	2.36 (2.26, 2.46)***
One or both parents' education				
<=12 years	14.0 (13.7, 14.4)	6.12 (5.91, 6.33)	7.39 (7.15, 7.62)	0.53 (0.47, 0.60)
>12 years	16.3 (16.1, 16.5)***	6.10 (5.98, 6.23)	8.37 (8.22, 8.51)***	1.81 (1.74, 1.88)***
Father smoking				
Never smoked	16.1 (15.9, 16.3)	6.15 (6.01, 6.30)	8.38 (8.21, 8.55)	1.56 (1.48, 1.64)
Quit for >1 year	17.8 (17.2, 18.5)***	6.83 (6.41, 7.25)**	9.23 (8.74, 9.71)***	1.76 (1.54, 1.97)
Quit for <1 year	15.4 (14.3, 16.5)	6.41 (5.65, 7.18)	7.81 (6.97, 8.64)	1.19 (0.85, 1.53)
Current smoking	14.8 (14.5, 15.0)***	5.88 (5.70, 6.05)*	7.52 (7.33, 7.72)***	1.35 (1.26, 1.43)***
Father's refractive error, diopter				
Normal	13.9 (13.7, 14.1)	5.67 (5.55, 5.79)	7.17 (7.03, 7.30)	1.04 (0.99, 1.09)
>-3.00 D	20.4 (19.9, 20.9)***	7.31 (6.99, 7.64)***	10.5 (10.1, 10.9)***	2.66 (2.45, 2.86)***
<= -3.00 D to >= -6.00 D	23.4 (22.8, 24.1)***	7.35 (6.92, 7.77)***	12.5 (12.0, 13.0)***	3.60 (3.30, 3.90)***
<-6.00 D	27.3 (25.5, 29.0)***	8.01 (6.93, 9.08)***	14.1 (12.7, 15.4)***	5.19 (4.31, 6.14)***
Mother's refractive error, in either eye,				

diopter				
Normal	14.1 (13.9, 14.3)	5.70 (5.57, 5.82)	7.31 (7.16, 7.45)	1.07 (1.02, 1.13)
>-3.00 D	18.9 (18.5, 19.3)***	6.82 (6.53, 7.11)***	9.79 (9.45, 10.1)***	2.29 (2.12, 2.46)***
<= -3.00 D to >= -6.00 D	20.9 (20.3, 21.5)***	7.09 (6.70, 7.47)***	10.6 (10.2, 11.1)***	3.14 (2.88, 3.40)***
<-6.00 D	25.8 (24.2, 27.4)***	8.06 (7.07, 9.05)***	13.2 (12.0, 14.5)***	4.49 (3.74, 5.25)***
Parental myopia				
Two of them were normal	13.1 (12.9, 13.3)	5.44 (5.30, 5.57)	6.77 (6.62, 6.92)	0.86 (0.80, 0.91)
Only father having myopia	19.3 (18.8, 19.8)***	7.02 (6.67, 7.36)***	10.1 (9.69, 10.5)***	2.19 (1.99, 2.39)***
Only mother having myopia	16.8 (16.4, 17.2)***	6.46 (6.18, 6.75)***	8.58 (8.25, 8.90)***	1.75 (1.60, 1.90)***
Two of them having myopia	23.1 (22.6, 23.7)***	7.64 (7.31, 7.97)***	11.9 (11.5, 12.3)***	3.55 (3.32, 3.78)***
Average time for homework per day, hour				
<=1	15.1 (14.8, 15.4)	6.13 (5.92, 6.34)	7.93 (7.70, 8.17)	1.00 (0.91, 1.08)
1-2	12.4 (12.1, 12.6)***	5.42 (5.25, 5.59)***	6.16 (5.97, 6.34)***	0.81 (0.75, 0.88)***
2-3	17.0 (16.7, 17.3)***	6.38 (6.17, 6.60)	8.87 (8.62, 9.12)***	1.76 (1.64, 1.87)***
>3	24.1 (23.5, 24.6)***	7.49 (7.15, 7.83)***	12.6 (12.2, 13.1)***	3.96 (3.70, 4.21)***
Average time for outdoor activities per day, hour				
<1	16.5 (16.3, 16.8)	6.18 (6.02, 6.34)	8.62 (8.44, 8.81)	1.73 (1.65, 1.82)
1-2	15.0 (14.8, 15.3)***	5.99 (5.82, 6.16)	7.66 (7.47, 7.85)***	1.38 (1.30, 1.47)***
2-4	15.0 (14.5, 15.4)***	6.18 (5.85, 6.51)	7.74 (7.38, 8.10)***	1.04 (0.90, 1.17)***
>4	15.2 (14.4, 16.1)**	6.29 (5.74, 6.83)	7.94 (7.33, 8.54)*	1.02 (0.79, 1.24)***

#: VI was defined by uncorrected visual acuity in better-seeing eye (UCVA). Light VI: UCVA>=6/18 to <6/12, mild VI: UCVA>=6/60 to <6/18, severe VI: UCVA<6/60.

†: Logistic regression was used for comparisons between categories. CI: Confidence Interval. Prevalence (95% CI) was presented, * *P*<0.05, ** *P*<0.01, *** *P*<0.001 indicating the significance of the difference from the reference group.

Table 3. Multiple Logistic regression model for detecting the potential risk factors for VI*

Variable	UCVA#<6/12(n=148,672)†		UCVA<6/18 (n=148,672)†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, Year	1.52 (1.51, 1.53)	<0.001	1.56 (1.55, 1.57)	<0.001
Male	0.77 (0.75, 0.80)	<0.001	0.78 (0.75, 0.81)	<0.001
Birth weight, kg	1.00 (0.96, 1.04)	0.974	1.11 (1.05, 1.17)	<0.001
Neonatal feeding				
Breast feeding	Reference		Reference	
Breast+ formula feeding	0.96 (0.93, 1.00)	0.039	/	/
Formula feeding	1.14 (1.09, 1.20)	<0.001	/	/
Delivery date				
Due date	Reference		Reference	
Overdue	0.93 (0.89, 0.97)	0.002	0.93 (0.88, 0.98)	0.005
Before due date	0.91 (0.87, 0.94)	<0.001	0.93 (0.89, 0.98)	0.003
Child without siblings	1.09 (1.06, 1.13)	<0.001	1.18 (1.13, 1.23)	<0.001
One or both Parents' education >12 years	1.03 (0.99, 1.07)	0.185	1.10 (1.04, 1.16)	<0.001
Father smoking				
Never smoked	Reference		Reference	
Quit for >1 year	1.00 (0.94, 1.07)	0.893	0.94 (0.88, 1.02)	0.117
Quit for <1 year	0.97 (0.87, 1.09)	0.644	0.93 (0.81, 1.07)	0.302
Current smoking	0.97 (0.93, 1.00)	0.049	0.94 (0.90, 0.99)	0.010
Parental myopia, n (%)				
Two of them were normal	Reference		Reference	
Only father having myopia	1.97 (1.87, 2.07)	<0.001	1.98 (1.87, 2.11)	<0.001
Only mother having myopia	1.80 (1.72, 1.89)	<0.001	1.83 (1.73, 1.94)	<0.001
Two of them having myopia	2.96 (2.82, 3.10)	<0.001	3.09 (2.92, 3.27)	<0.001
Average time for homework per day, hour				
<=1	Reference		Reference	
1-2	1.00 (0.95, 1.05)	0.891	0.97 (0.91, 1.03)	0.287
2-3	1.05 (1.00, 1.10)	0.059	1.07 (1.01, 1.13)	0.026
>3	1.05 (0.99, 1.11)	0.092	1.10 (1.03, 1.17)	0.004
Average time for outdoor activities per day, hour				
<1	Reference		Reference	

1-2	0.95 (0.92, 0.99)	0.006	0.92 (0.88, 0.96)	<0.001
2-4	0.94 (0.89, 0.99)	0.017	0.90 (0.84, 0.96)	0.002
>4	0.88 (0.81, 0.96)	0.003	0.80 (0.72, 0.88)	<0.001

*: Variables with $P<0.05$ in simple regression analysis were included in the multiple regression model. The results of simple regression analysis were not listed in the table. OR: Odds Ratio, CI: Confidence Interval.

#: VI was defined by uncorrected visual acuity in better-seeing eye (UCVA). Analysis of UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference) among participants who were singletons with normal birth weight (2.5-4kg) and whose mother had no pregnancy disorder during pregnancy.

†: There were 6,882 (4.42%) to 6,884 (4.43%) observations excluded due to missing values for the response or explanatory variables.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, Line 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, Line 1-26**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3, Line 1-32**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3, Line 34-36**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, Line 27-36**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4, Line 11-26**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 4, Line 14-20**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, Line 27-36**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 5, Line 2-16**
Bias	9	Describe any efforts to address potential sources of bias **Page 12, Line 12-14**
Study size	10	Explain how the study size was arrived at **Page 4, Line 21-26**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5, Line 19-35**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5, Line 19-35**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5, Line 19-35**
		(*c*) Explain how missing data were addressed **Page 4, Line 21-26**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **N/A**
		(*e*) Describe any sensitivity analyses **N/A**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 4, Line 21-26**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4, Line 21-26**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1, Column 2**
Outcome data	15	Report numbers of outcome events or summary measures **Page 6-8, Results Section**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 6-8, Results Section**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 8-12, Discussion Section**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 12, Line 12-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 8-12, Discussion Section**
Generalisability	21	Discuss the generalisability (external validity) of the study results **N/A**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12, Line 26-31**

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Keywords:	abnormal visual acuity, prenatal and neonatal factors, Paediatric ophthalmology < OPHTHALMOLOGY

Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Abstract

Objectives: In this cross-sectional survey, we sought to determine the prevalence of and the influence of prenatal and neonatal factors on childhood visual impairment without correction (VIUC) in a pediatric population from Guangzhou, China.

Setting: The health survey covered 11 administrative districts in Guangzhou, including 991 schools.

Participants: All of the primary and middle school students in Guangzhou were invited to complete an online questionnaire with the help of their parents. The results of physical examinations were reported by school medical departments. The results of the questionnaire were collected by the researchers. In total, 253,301 questionnaires were collected.

Primary outcome measures: The students' uncorrected visual acuity (UCVA) was examined by trained optometrists by standard logarithmic visual acuity charts. VIUC was defined by UCVA (of the better eye) (UCVA<6/12) with three levels: light VIUC (UCVA≥6/18 to <6/12), mild VIUC (UCVA≥6/60 to <6/18), and severe VIUC (UCVA<6/60).

Results: A total of 39,768 individuals (15.7%) had VIUC, and the rate was much higher among grade 10–12 students (51.4%) than among grade 1–6 students (6.71%). The following factors were significantly associated with an increased risk of VIUC: female gender, high birth weight, formula feeding, not having siblings, higher level of parents' education, parental myopia, much homework time, and little outdoor activity. Delivery mode was not associated with the risk of VIUC.

Conclusions: This study validates known major prenatal/genetic, perinatal, and postnatal factors for childhood VIUC. In conclusion, prenatal and perinatal factors can affect the onset of childhood VIUC, but parental myopia and postnatal factors are the main factors.

Keywords: abnormal visual acuity, childhood myopia, prenatal and neonatal factors

Strengths and limitations of this study:

- A retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China
- Collection and analysis of both prenatal and environmental factors associated with vision impairment without correction.
- Selection bias, recall bias, and reporter bias are unavoidable as the survey was based on voluntary participation.

Introduction

Visual impairment is highly prevalent in school students, and myopia-related visual impairment without correction (VIUC) accounts for over 90% of the cases in China.[1] Myopia is caused by an inconsistency between the eye's refractive power and the length of the eye axis. Two clinical types exist. In refractive myopia, the axial length is normal, but the refractive power of the cornea or lens is too strong, while in axial myopia, the refractive power of the lens is normal, but the axial length is too long.[2] Although myopia is not a life-threatening disease, the World Health Organization (WHO) recognizes it as a major cause of further visual impairment if not fully corrected.[3] At present, the high prevalence of myopia has become a serious public health problem in East Asia. In China specifically, the prevalence of myopia in high school students ranges from 43.0% to 78.4% .[4]

Myopia is etiologically heterogeneous and is believed to be driven by numerous environmental factors and genetic variations, with onset beginning in the preschool years. Environmental factors such as outdoor activity are associated with myopia inception and development.[4] Increasing outdoor time thus represents an important environmental factor that can protect young children from myopia, as supported by numerous studies.[5-7] The protective effects of outdoor activity may be due to the high light intensity outdoors, the chromaticity of daylight, or increased vitamin D levels.[8 9] A number of studies have separately shown that parental myopia is an important risk factor for myopia in children, due to the inheritance of myopia susceptibility genes or a shared myopia-driving environment.[10-12]

According to the developmental origins of health and disease theory, the development of childhood diseases may be affected by factors in prenatal life.[13] Several epidemiological studies have shown that cesarean delivery and preterm birth increase the risk of childhood myopia.[14-17] For example, preterm birth may affect ocular development or later emmetropization, and it may affect the development of the refractive status through a more complicated mechanism.[18-22] In addition, breastfeeding in early life may stimulate ocular development, as the docosahexaenoic acid and arachidonic acid in breast milk may affect retinal and neural development, therefore decreasing the risk of myopia.[23]

Here, we sought to study the effects of multiple prenatal/genetic, perinatal, and postnatal factors on the development of myopia-related VIUC in primary and middle school students in the Guangzhou area of China. For this study, the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality released an annual online health survey of primary and secondary school students, and we subsequently received relevant information from this institution. We used descriptive statistics, logistic analysis, and multiple logistic regression models to analyze the data and explore the relationships between various environmental factors, parental myopia, prenatal and neonatal factors, and myopia. Our results improve our understanding of the etiology of childhood myopia in East Asia and confirm known potential prenatal factors for long-term diseases.

Methods

Data source

This study was approved by the institutional review board of The Third Affiliated Hospital of Guangzhou Medical University [2017(No.128)], and studies involving human subjects were conducted in accordance with the Declaration of Helsinki guidelines. A cross-sectional survey design was used, and a health survey was conducted by the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality, which is responsible for monitoring the health status of primary and middle schools in Guangzhou. All of the primary and middle school students in Guangzhou were invited by their school to participate in the survey in October 2017. Consent was provided to all of the participants by school teachers, and oral informed consent was obtained from the participants' parents. All of the parents of school students were informed about this study at the parent-teacher conference, using posters and a short messaging service. Only verbal consent was obtained as this study was a health survey.

The health survey covered 11 administrative districts in Guangzhou, including 991 schools. In total, 253,301 questionnaires were collected. On the first page of the questionnaire, it was stated that the results of the health questionnaire would be used for health research. According to the Education Statistics Manual of Guangzhou in 2017, the number of primary and middle school students in 2017 was 1,514,122, so the response rate of this survey was 16.73%.

This health survey consisted of a questionnaire and a physical examination. The questionnaire was divided into four parts, including basic conditions, psychological behavior, exercise and sleep, and diet. Only the part of basic conditions was used in this study. Children and parents jointly filled out the questionnaire on the Internet according to their own situation and submitted the questionnaire directly online. This study used the first part of the data, including aspects such as birth weight, sex, neonatal feeding, delivery mode, delivery date, maternal diseases in pregnancy, parents' education, parental myopia, parental smoking, and average monthly household income per person.

Visual acuity assessment

The students' uncorrected visual acuity (UCVA) was examined in all schools by trained optometrists by the same standard logarithmic visual acuity charts (Chinese standard for logarithmic visual acuity charts, GB11533-2011) on a light box with 300–500 lux illumination, following regular procedures.[24] During the test, students sat at a 5 m distance from the chart with one eye covered and read out the direction of the letter "E." Students pointed in the direction the letter "E" was facing: up, down, left, or right. The test started at the 6/6 line. If students cannot see clearly, they go up one line at a time; otherwise, they go down one line at a time. The identification time of each "E" must not exceed 5 s. This process was repeated with the other eye. It is stipulated that there was no misidentification in 6/60–6/20 lines on each line, and less than two errors on each line of 6/15–6/6 lines and less than three errors on each line of 6/5–6/3. If the top line could not be read at 5 m, the student was tested at 2.5 m or 1 m, and the measured visual acuity was subtracted by 0.3 or 0.7, respectively, and then recorded as the student's visual acuity.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical methods

Characteristics of participants are presented as mean (standard deviation, SD) for continuous variables and as frequency (proportion) for categorical variables. VIUC was defined according to UCVA (better eye) (UCVA<6/12) with three levels: light VI (UCVA≥6/18 to <6/12), mild VI (UCVA≥6/60 to <6/18), and severe VI (UCVA<6/60), referring to the previous studies and definitions of impaired vision by the WHO.[25] The prevalence (95% confidence interval, CI) of VIUC was estimated by categorization of the participants' characteristics. The prevalence between categories was compared using logistic regression. Multiple logistic regression analysis was performed to detect the potential risk factors for VIUC. The participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorders during pregnancy were included in the regression analysis. Two binary outcomes of VIUC were defined by UCVA (better eye) <6/12 (≥6/12 as reference) and UCVA (better eye) <6/18 (≥6/18 as reference). Observations with missing values for the response or explanatory variables were excluded in the logistic regression analysis. Variables with $P<0.05$ in the simple regression analysis were included in the multiple regression model. All of the P values were based on two-sided tests, where $P<0.05$ was considered as statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of participants

Characteristics of all of the participants are presented in Table 1. The mean age of school grade one in China is 6 years old. All of the factors can be grouped into (i) prenatal/genetic factors, including the father's refractive error, the mother's refractive error, parental myopia, and one or both parents' education; (ii) perinatal factors, including birth weight, neonatal feeding, delivery mode, delivery date, and diseases in pregnancy; and (iii) postnatal factors, including grade, age, sex, only child status, parents' smoking, average time spent on homework per day, and average time spent on outdoor activities per day.

In brief, the parental refractive error was divided into three levels: namely −3.00D, −3.00D to −6.00D, and less than −6.00D.The results showed that the distributions of the father's refractive error were 13.8%, 8.28%, and 1.37%, and those of the mother's refractive error were 16.6%, 9.63%, and 1.66% (Table 1). Both parents had myopia, and neither of them had myopia in 14.0% and 58.8% of the cases, while only the father or the mother had myopia in 11.5% and 15.8% of the cases, respectively. One or both parents' education was more than 12 years in 74.4% of the cases (Table 1).

There were three ways of neonatal feeding: breastfeeding only, formula feeding only, and breastfeeding and formula feeding together, accounting for 38.8%, 26.7%, and 34.6%, respectively. Vaginal delivery accounted for 63.5%, while the cesarean section delivery rate was 36.5%. The proportion of maternal gestational diseases, including hypertension, diabetes, intrahepatic cholestasis, hypothyroidism, hyperthyroidism, anemia, and viral hepatitis, was 11.3%. The average birth weight was 2.99 kg ± 0.40 kg (Table 1).

In addition, students of primary school (grade 1–6), junior middle school (grade 7–9), and high middle school (grade 10–12) represented 74.6%, 17.8%, and 7.57% of the total study population, respectively, with 53.8% being male. Less than 1h, 1–2h, 2–3h, and more than 3h spent on homework per day were reported in 29.8%, 36.0%, 23.8%, and 10.4% of the cases, respectively; less than 1h, 1–2h, 2–4h, and more than 4h spent on outdoor activities per day were reported in 45.2%, 40.1%, 10.8%, and 3.88% of the cases, respectively. Children without siblings made up 45.0%. Paternal and maternal smoking rates were 45.5% and 0.85%, respectively (Table 1). The smoking rates and the number of siblings in this study were comparable to the norm of China according to recent reports.[26 27]

Prevalence of VIUC by characteristics

Of the 253,301 children included in the present study, 15.7% children experienced VIUC (Table 2). The larger the refraction error of either the father or the mother, the higher the prevalence of all levels of VIUC in children. Additionally, more time spent on homework per day and less time spent on outdoor activities per day was associated with a higher risk of VIUC (all $P<0.001$).

The prevalence of all three levels of VIUC was similar in the subgroups with different modes of neonatal feeding, but breastfeeding and formula feeding together showed statistically significant differences compared with breast feeding only (all $P<0.01$, Table 2). Cesarean section was associated with a higher prevalence of severe VIUC ($P<0.001$) but with a lower prevalence of light VIUC ($P<0.001$), mild VIUC ($P<0.05$), and overall VIUC ($P<0.05$). Unexpectedly, the prevalence of UCVA<6/12 in participants born before their due date was lower than in participants born on their due date (16.7%, $P<0.001$) or who were overdue (16.2%, $P<0.001$). Maternal pregnancy diseases were significantly associated with an increased risk of VIUC (Table 2).

With increasing grade and age, the prevalence of UCVA<6/12 also increased (all $P<0.001$); the prevalence among students in grades 10–12 and students older than 15 years was 51.4% and 52.4%, respectively (Table 2). The increase in the prevalence of severe VIUC, which was 9.92% and 10.6%, respectively, was most significant (all $P<0.001$).The prevalence of UCVA<6/12 was different ($P<0.001$) in female (17.8%) and male (13.9%) participants. The prevalence of all levels of VIUC was higher among children without siblings than among children with siblings. The prevalence of UCVA (better eye) <6/12 or worse than 6/18 was higher among students with one or both parents' education >12 years than among students with both parents' education ≤12 years (Table 2). Students with a father currently smoking had a lower risk of VIUC (all $P<0.05$).

Multiple logistic regression model for detecting the potential risk factors for VIUC

The results of two multiple logistic regression models for detecting the potential risk factors for VIUC are presented in Table 3, with 6/12 (≥6/12 as reference) and 6/18 (≥6/18 as reference) as cutoff points. Because low birth weight and maternal diseases are known factors affecting children's eye development, here, we only studied the 155,556 participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no disease during pregnancy.

The results indicated that the students whose parents had a higher level of education had a higher risk of UCVA<6/18 (OR [95% CI], 1.10 [1.04, 1.16]; *P*<0.001) (Table 3). Parental myopia increased the risk of UCVA<6/12 or <6/18 (all *P*<0.001) when only the father had myopia (OR [95% CI], 1.97 [1.87, 2.07] and 1.98 [1.87, 2.11]), when only the mother had myopia (OR [95% CI], 1.80 [1.72, 1.89] and 1.83 [1.73, 1.94]), and when both parents had myopia (OR [95% CI], 2.96 [2.82, 3.10] and 3.09 [2.92, 3.27]).

In addition, birth weight was only positively associated with UCVA<6/18 (OR [95% CI], 1.11 [1.05, 1.17]; *P*<0.001). Compared with breast feeding only, formula feeding only contributed to a higher risk of UCVA<6/12 (OR [95% CI], 1.14 [1.09, 1.20]; *P*<0.001), while breast and formula feeding together was associated with a lower risk (OR [95% CI], 0.96 [0.93, 1.00]; *P*=0.039). Delivery mode was not associated with both outcomes of VIUC. Students who were delivered overdue or before due date had a lower risk of UCVA<6/12 (OR [95% CI], 0.93 [0.89, 0.97]; *P*=0.002 and 0.91 [0.87, 0.94]; *P*<0.001, respectively) and UCVA<6/18 (OR [95% CI], 0.93 [0.88, 0.98]; *P*=0.005 and 0.93 [0.89, 0.98]; *P*=0.003, respectively) than those delivered on their due date.

Age (OR [95% CI], 1.52 [1.51, 1.53]; *P*<0.001) and not having siblings (OR [95% CI], 1.09 [1.06, 1.13]; *P*<0.001) were positively associated with the risk of UCVA<6/12. Similarly, age (OR [95% CI], 1.56 [1.55, 1.57]; *P*<0.001) and not having siblings (OR [95% CI], 1.18 [1.13, 1.23]; *P*<0.001) were positively associated with the risk of UCVA<6/18. Male students had a lower risk of either UCVA<6/12 (OR [95% CI], 0.77 [0.75, 0.80]; *P*<0.001) or UCVA<6/18 (OR [95% CI], 0.78 [0.75, 0.81]; *P*<0.001]. An average time spent on homework per day of 2–3h (OR [95% CI], 1.07 [1.01, 1.13]) or more than 3h (OR [95% CI], 1.10 [1.03, 1.17]) was significantly associated with a higher risk of mild VI compared with the group spending less than 1 h.

In agreement with previous findings, among participants who spent ≥1h on outdoor activities, the prevalence of VIUC was lower, i.e., for 1–2h (OR [95% CI], 0.95 [0.92, 0.99]; *P*=0.006 and 0.92 [0.88, 0.96]; *P*<0.001), for 2–4h (OR [95% CI], 0.94 [0.89, 0.99]; *P*=0.017 and 0.90 [0.84, 0.96]; *P*=0.002), and for>4h (OR [95% CI], 0.88 [0.81, 0.96]; *P*=0.003 and 0.80 [0.72, 0.88]; *P*<0.001), compared with participants who spent <1h on outdoor activities. The current smoking status of the father was associated with a lower risk of UCVA<6/18 compared with participants with a father who never smoked (OR [95% CI], 0.94 [0.90, 0.99]; *P*=0.010], and also a marginally significant association between current smoking status of the father and the prevalence of UCVA<6/12 was observed (OR [95% CI], 0.97 [0.93, 1.00]; *P*=0.049).

Discussion

Myopia, the dominant cause of VIUC in teenagers, has increased in prevalence in East Asia in the past few decades and has therefore become a major health issue.[28] It is commonly believed that the high prevalence of myopia in East Asia is associated with increased educational pressure, combined with lifestyle changes, which have reduced the time children spend outside.[2] Recent studies have suggested that the development of childhood diseases may also be affected by factors in prenatal and neonatal life, in that factors like delivery mode, feeding manner, and pregnancy diseases can alter the risks for childhood diseases such as asthma.[29 30] However, the prenatal and neonatal factors for VIUC, especially childhood myopia, remain largely unclear. Therefore, a retrospective survey involving primary and middle school students in Guangzhou was launched to evaluate the association between most important prenatal, perinatal, and postnatal factors and the prevalence of VIUC in 6-year-old to 17-year-old school students.

The present cross-sectional study, which included 253,301 completed questionnaires and medical records, revealed that among children in grades 1–6, grades 7–9, and grades 10–12 in Guangzhou, the total prevalence of VIUC was 6.71%, 30.0%, and 51.4% and that of severe VIUC was 0.16%, 2.25%, and 9.92%, respectively (Table 2). The prevalence of VIUC presented here is high compared with other countries and areas but was close to the reported prevalence in Chinese urban areas.[31]

It is believed that VIUC is etiologically heterogeneous. A small part of VIUC cases is caused by prenatal and genetic factors and appears without exposure to additional risk factors.[5] Parental myopia is a high-risk factor for childhood VIUC, but although several genes have been shown to be associated with high myopia, no major genes affecting childhood myopia have been reported until now.[2] A cohort study of 298 probands with early-onset high myopia using whole-exome sequencing showed that mutations in genes known to be responsible for retinal diseases were found in approximately one-fourth of the probands with early-onset high myopia.[11] In another study of myopia prevalence, grade 7 students in a Chinese rural area showed a lower prevalence of myopia (29.4%) and high myopia (0.4%) than those in Chinese urban cities, suggesting that Chinese people may not have a genetic predisposition to myopia and that environmental factors may play a major role in the development of childhood myopia in Chinese children.[32]

In the present study, the association between parental myopia and childhood VIUC was strong (Table 3). In grade 10–12 students, the ORs were 2.06, 1.85, and 3.17 for paternal myopia only, maternal myopia only, and both parents having myopia, respectively. Although the possibility of heredity for VIUC was not excluded, families also share environments, and myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors, increasing the myopia risk of their children.[18] In a study on the gene–environment interaction in myopia, the prevalence of child myopia was only 9.9% in farmer families without parental myopia, but the prevalence among college students was similar between farmer families and other families, suggesting a leading role of environmental factors in the formation of myopia.[10] In another study on high myopia across three different generations in Korea, results showed that the environmental portion of the phenotypic variance increased and the additive genetic portion decreased as South Korea became more urbanized.[33] Therefore, it remains to be established how gene–environment interactions contribute to myopia within various populations.[2]

In the present study, we analyzed the effects of perinatal factors, such as delivery manner, delivery mode, and pregnancy diseases, on the prevalence of myopia. Pregnancy diseases, such as hyperemesis, hypertension, preeclampsia, and uterus-related complications may affect fetal growth in the uterus and probably later long-term health. For instance, diabetes during pregnancy is associated with changes in retinal morphology in the offspring.[34] We found that pregnancy diseases decrease the prevalence of childhood VIUC, and this relationship may be causal (Table 2). Children whose mothers suffered from pregnancy diseases may have lower educational pressure than those without diseases in the family.

Premature birth and low birth weight affect the general growth of the fetus, including eye development. A previous analysis determined that in children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia was mainly attributed to short axial length.[18] In a British birth cohort study, myopia was positively associated with low birth weight for gestational age,[14] and in the Sydney Paediatric Eye Disease Study, vision impairment was independently associated with low birth weight.[19] In the present study, the parents only reported whether the participants were born before, on, or after their due date, and no further information on precise gestational age was obtained. Regretfully, we cannot analyze the association between premature birth and childhood vision impairment. Accordingly, we used multiple logistic regression models to analyze only the population with normal birth weight and without pregnancy complications.

Breastfeeding may influence the early growth of a baby. In a cross-sectional study of 527 Chinese primary school students aged 6–12 years, breastfeeding was reported to be associated with a decreased risk of myopia, and breastfeeding during the first 6 months of infancy was associated with higher hyperopic spherical equivalent refraction.[23] Furthermore, breastfeeding was associated with myopic refraction and was not related to axial length, and this association could exist in childhood.[23] In a study of Singaporean preschoolers, results showed that breastfeeding was associated with higher hyperopic spherical equivalent refraction.[35] Our results support the idea that breastfeeding decreases and formula feeding increases the risks for VIUC (Table 3). The underlying mechanisms remain unclear, but physical development may be associated with eye development as well.

Postnatal factors, including environmental factors, play critical roles in the development of childhood myopia.[4] In an analysis of time spent on outdoor activity and on near-vision work, children with little outdoor time and much near-vision work were two to three times more likely to be myopic compared with those performing little near-vision work and spending much time outdoors.[18] In the area of Beijing, China, greater axial elongation was associated with less time spent outdoors and with more time spent indoors.[6] In Finland, a higher risk of myopia was mainly related to parents having myopia and less time spent on sports and outdoor activities in childhood.[8] In the Netherlands, seven parameters were associated independently with faster axial length elongation, including the number of books read per week, time spent reading, no participation in sports, and less time spent outdoors.[36]

Our present results clearly support the idea that homework time is positively associated and outdoor activity is negatively associated with the prevalence of myopia and VIUC in students of all grades (Tables 2 and 3). Therefore, environmental factors should be the leading consideration to reduce the incidence of childhood myopia. Indeed, in a recent clinical trial among 6-year-old children in Guangzhou, the incidence of myopia significantly reduced over the 3 years after the addition of 40 min of outdoor activity to the daily curriculum, replacing usual activity.[7] Therefore, such interventions could be the most effective strategy to decrease the prevalence of VIUC in Chinese cities.

Our results also show that female gender, older age, and not having siblings are associated with an increased risk for myopia. Similarly, in a study including 2,760 7-year-old children and 2,198 12-year-old children, higher intraocular pressure was associated with female gender, older age, and higher body mass index, while younger age at the commencement of reading and being born with a cesarean section were also associated with higher intraocular pressure in adolescence.[17] However, these factors may be largely linked with environmental factors, such as outdoor activity and near-vision work. For example, boys are more likely to do outdoor sports; as one ages, the educational pressure increases; children without siblings are more likely to have indoor activities and near-vision work; and overweight decreases the outdoor activity of children. Therefore, the observed correlation may be causal.

Additionally, our data showed that paternal smoking did not significantly increase the prevalence of VIUC (Table 3), suggesting that indoor pollution might not provoke the development of myopia. In a study in Singapore, an inverse association was found between parental smoking and childhood myopia,[37] and our data also indicated that a current smoking status of the father decreased the risk of VIUC (Table 3). Moreover, Guangzhou has markedly reduced its atmospheric pollution during the past 10 years, but the prevalence of myopia has further increased.[5] Therefore, environmental pollution does not seem to be a major risk factor for childhood myopia. It is notable that female smoking is rare in China, to such an extent that in this study 99.2% of the mothers never smoked. Therefore, maternal smoking may not be a significant factor for consideration.

In conclusion, the results of the present retrospective study, conducted using 253,301 completed surveys in the Guangzhou area of Southern China, indicated that factors such as the female gender, high birth weight, formula feeding, not having siblings, higher levels of parents' education, parental myopia, much homework time, and little outdoor activity are significantly associated with a higher risk of vision impairment. Conversely, being born before the due date, being overdue, and outdoor activity were associated with a decreased risk of vision impairment. Therefore, we here confirm known major prenatal/genetic, perinatal, and postnatal factors for childhood VIUC. Although selection bias, recall bias, and reporter bias were unavoidable, as this is a retrospective, self-reported survey, based on the current data, we conclude that prenatal and perinatal factors can affect the onset of childhood VIUC, but parental myopia and postnatal factors are the main factors. Therefore, children whose parents have myopia should be considered as a high-risk population for childhood VIUC, and intervention by changing environmental factors such as outdoor activities should be conducted for effective prevention of VIUC.

Competing interests

None declared

Author Contributions

Conceived and designed the research: Dunjun Chen. Collected the data: Nali Deng. Analyzed the data: Juanjuan Chen, Wen Sun, Jingsi Chen, and Lili Du. Wrote the

paper: Bolan Yu and Lijuan Dai.

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Data sharing statement

Deidentified participant data are available upon reasonable requisition.

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Table 1. Characteristics of participants

Characteristics	n	n (%)
Total	253,301	/
Grade	253,301	
1-6		189,008 (74.6)
7-9		45,119 (17.8)
10-12		19,174 (7.57)
Age[#]	253,301	
6-10		156,992 (62.0)
11-15		82,092 (32.4)
>15		14,217 (5.61)
Sex	253,301	
Male		136,200 (53.8)
Female		117,101 (46.2)
Birth weight, kg	249,610	2.99 (0.40)[†]
Neonatal feeding	253,292	
Breast feeding		98,164 (38.8)
Breast+ formula feeding		87,532 (34.6)
Formula feeding		67,596 (26.7)
Delivery	253,292	
Vaginal delivery		160,873 (63.5)
Caesarean		92,419 (36.5)
Delivery date	253,291	
On the due date		91,409 (36.1)
Overdue		54,161 (21.4)
Before the due date		107,721 (42.5)
Diseases in pregnancy		
Hypertension	252,013	3,722 (1.48)
Diabetes	252,068	5,237 (2.08)
Intrahepatic cholestasis	251,930	622 (0.25)
Hypothyroidism	251,878	764 (0.30)
Hyperthyroidism	248,301	978 (0.39)
Anemia	248,374	16,236 (6.54)
Viral hepatitis	248,311	2,330 (0.94)
Other	248,273	1,679 (0.68)
Any disease above	248,461	27,998 (11.3)
Children without siblings	253,286	

No		139,318 (55.0)
Yes		113,968 (45.0)
One or both parents' education	253,288	
<=12 years		64,943 (25.6)
>12 years		188,345 (74.4)
Father smoking	253,286	
Never smoked		138,077 (54.5)
Quit for >1 year		17,998 (7.11)
Quit for <1 year		5,362 (2.12)
Current smoking		91,849 (36.3)
Mother smoking	253,286	
Never smoked		251,159 (99.2)
Quit for >1 year		900 (0.36)
Quit for <1 year		276 (0.11)
Current smoking		951 (0.38)
Father's refractive error, diopter	238,888	
Normal		182,857 (76.6)
>-3.00 D		32,982 (13.8)
<= -3.00 D to >= -6.00 D		19,770 (8.28)
<-6.00 D		3,279 (1.37)
Mother's refractive error, diopter	240,291	
Normal		173,256 (72.1)
>-3.00 D		39,915 (16.6)
<= -3.00 D to >= -6.00 D		23,135 (9.63)
<-6.00 D		3,985 (1.66)
Parental myopia	242,006	
Two of them were normal		142,238 (58.8)
Only father having myopia		27,794 (11.5)
Only mother having myopia		38,172 (15.8)
Two of them having myopia		33,802 (14.0)
Average time for homework per day, hour	251,925	
<=1		75,123 (29.8)
1-2		90,674 (36.0)
2-3		59,901 (23.8)
>3		26,227 (10.4)
Average time for outdoor activities per day, hour	253,280	
<1		114,471 (45.2)
1-2		101,658 (40.1)

2-4	27,332 (10.8)
>4	9,819 (3.88)

#: The mean age of school grade1 is 6 years old.

†: Data is represented as Mean (Standard deviation).

Table 2. Prevalence of VIUC by characteristics

Variable	Total UCVA<6/12	Light VIUC UCVA>=6/18 to <6/12	Mild VIUC UCVA>=6/60 to <6/18	Severe VIUC UCVA<6/60
	% (95% CI)†	% (95% CI)†	% (95% CI)†	% (95% CI)†
All	15.7 (15.6, 15.9)	6.11 (6.00, 6.22)	8.12 (8.00, 8.24)	1.49 (1.44, 1.54)
Grade				
1-6	6.71 (6.58, 6.85)	3.70 (3.60, 3.80)	2.85 (2.76, 2.94)	0.16 (0.14, 0.18)
7-9	30.0 (29.6, 30.5)***	11.6 (11.3, 11.9)***	16.2 (15.8, 16.5)***	2.25 (2.10, 2.39)***
10-12	51.4 (50.6, 52.1)***	11.7 (11.2, 12.2) ***	29.7 (29.1, 30.4)***	9.92 (9.47, 10.4)***
Age, Years				
6-10	4.56 (4.43, 4.69)	2.66 (2.56, 2.76)	1.80 (1.72, 1.88)	0.10 (0.08, 0.12)
11-15	25.1 (24.8, 25.4)***	10.1 (9.85, 10.3)***	13.1 (12.9, 13.4)***	1.88 (1.79, 1.98)***
>15	52.4 (51.5, 53.3)***	11.3 (10.7, 11.8)***	30.6 (29.8, 31.4)***	10.6 (10.0, 11.1)***
Sex				
Female	17.8 (17.5, 18.0)	6.75 (6.58, 6.91)	9.33 (9.14, 9.52)	1.70 (1.62, 1.79)
Male	13.9 (13.7, 14.1)***	5.55 (5.41, 5.69)***	7.07 (6.91, 7.22)***	1.30 (1.24, 1.37)***
Neonatal feeding				
Breast feeding	16.1 (15.9, 16.4)	6.42 (6.24, 6.60)	8.22 (8.02, 8.42)	1.49 (1.40, 1.57)
Breast + formula feeding	15.2 (14.9, 15.5)***	5.71 (5.53, 5.89)***	7.80 (7.60, 8.01)**	1.67 (1.57, 1.76)**
Formula feeding	15.8 (15.5, 16.1)	6.16 (5.96, 6.37)	8.38 (8.14, 8.62)	1.27 (1.17, 1.36)**
Delivery				
Vaginal delivery	15.9 (15.6, 16.1)	6.31 (6.17, 6.44)	8.22 (8.06, 8.37)	1.32 (1.26, 1.39)
Caesarean	15.5 (15.2, 15.8)*	5.77 (5.60, 5.94)***	7.95 (7.75, 8.15)*	1.77 (1.67, 1.87)***
Delivery date				
Due date	16.7 (16.4, 17.0)	6.56 (6.37, 6.74)	8.82 (8.60, 9.03)	1.31 (1.23, 1.40)
Overdue	16.2 (15.9, 16.6)*	6.20 (5.97, 6.43)*	8.29 (8.02, 8.55)**	1.73 (1.61, 1.86)***
Before due date	14.7 (14.4, 14.9)***	5.68 (5.52, 5.84)***	7.45 (7.27, 7.63)***	1.52 (1.43, 1.60)***
Diseases in pregnancy				
Hypertension				
No	15.7 (15.5, 15.9)	6.10 (5.99, 6.21)	8.12 (8.00, 8.25)	1.48 (1.43, 1.54)
Yes	17.5 (16.1, 18.9)**	7.22 (6.26, 8.18)*	8.18 (7.17, 9.19)	2.13 (1.60, 2.67)**
Diabetes				
No	15.8 (15.6, 16.0)	6.13 (6.02, 6.24)	8.17 (8.04, 8.29)	1.49 (1.43, 1.54)
Yes	12.7 (11.6, 13.8)***	5.31 (4.57, 6.05)*	5.82 (5.05, 6.59)***	1.60 (1.19, 2.01)
Intrahepatic cholestasis				
No	15.7 (15.6, 15.9)	6.12 (6.01, 6.23)	8.13 (8.01, 8.25)	1.49 (1.44, 1.55)
Yes	11.9 (8.84, 14.9)*	4.79 (2.79, 6.80)	5.71 (3.54, 7.88)	1.37 (0.28, 2.46)

Hypothyroidism				
No	15.7 (15.6, 15.9)	6.11 (6.01, 6.22)	8.13 (8.00, 8.25)	1.49 (1.44, 1.55)
Yes	14.0 (11.0, 17.0)	5.83 (3.80, 7.85)	6.99 (4.79, 9.19)	1.17 (0.24, 2.09)
Hyperthyroidism				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.50 (1.45, 1.56)
Yes	16.0 (13.3, 18.7)	6.93 (5.06, 8.80)	7.92 (5.93, 9.91)	1.13 (0.35, 1.91)
Anemia				
No	16.0 (15.8, 16.1)	6.15 (6.04, 6.27)	8.28 (8.16, 8.41)	1.53 (1.47, 1.59)
Yes	12.9 (12.3, 13.5)***	5.64 (5.22, 6.06)*	6.16 (5.73, 6.60)***	1.08 (0.89, 1.26)***
Viral hepatitis				
No	15.8 (15.6, 16.0)	6.12 (6.01, 6.23)	8.17 (8.05, 8.29)	1.51 (1.45, 1.56)
Yes	13.2 (11.6, 14.8)**	5.97 (4.85, 7.09)	6.32 (5.17, 7.47)**	0.93 (0.48, 1.38)
Other				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.51 (1.45, 1.56)
Yes	15.2 (13.2, 17.2)	6.47 (5.07, 7.86)	7.89 (6.36, 9.42)	0.84 (0.32, 1.36)
Any disease above				
No	16.0 (15.9, 16.2)	6.15 (6.04, 6.27)	8.36 (8.22, 8.49)	1.52 (1.46, 1.58)
Yes	13.6 (13.1, 14.1)***	5.82 (5.50, 6.15)	6.47 (6.13, 6.81)***	1.31 (1.15, 1.46)*
Children without siblings				
No	13.4 (13.2, 13.6)	5.75 (5.61, 5.89)	6.84 (6.69, 7.00)	0.76 (0.71, 0.081)
Yes	18.5 (18.3, 18.8)***	6.53 (6.37, 6.70)***	9.65 (9.45, 9.85)***	2.36 (2.26, 2.46)***
One or both parents' education				
<=12 years	14.0 (13.7, 14.4)	6.12 (5.91, 6.33)	7.39 (7.15, 7.62)	0.53 (0.47, 0.60)
>12 years	16.3 (16.1, 16.5)***	6.10 (5.98, 6.23)	8.37 (8.22, 8.51)***	1.81 (1.74, 1.88)***
Father smoking				
Never smoked	16.1 (15.9, 16.3)	6.15 (6.01, 6.30)	8.38 (8.21, 8.55)	1.56 (1.48, 1.64)
Quit for >1 year	17.8 (17.2, 18.5)***	6.83 (6.41, 7.25)**	9.23 (8.74, 9.71)***	1.76 (1.54, 1.97)
Quit for <1 year	15.4 (14.3, 16.5)	6.41 (5.65, 7.18)	7.81 (6.97, 8.64)	1.19 (0.85, 1.53)
Current smoking	14.8 (14.5, 15.0)***	5.88 (5.70, 6.05)*	7.52 (7.33, 7.72)***	1.35 (1.26, 1.43)***
Father's refractive error, diopter				
Normal	13.9 (13.7, 14.1)	5.67 (5.55, 5.79)	7.17 (7.03, 7.30)	1.04 (0.99, 1.09)
>-3.00 D	20.4 (19.9, 20.9)***	7.31 (6.99, 7.64)***	10.5 (10.1, 10.9)***	2.66 (2.45, 2.86)***
<= -3.00 D to >= -6.00 D	23.4 (22.8, 24.1)***	7.35 (6.92, 7.77)***	12.5 (12.0, 13.0)***	3.60 (3.30, 3.90)***
<-6.00 D	27.3 (25.5, 29.0)***	8.01 (6.93, 9.08)***	14.1 (12.7, 15.4)***	5.19 (4.31, 6.14)***
Mother's refractive error, in either eye,				

diopter				
Normal	14.1 (13.9, 14.3)	5.70 (5.57, 5.82)	7.31 (7.16, 7.45)	1.07 (1.02, 1.13)
>-3.00 D	18.9 (18.5, 19.3)***	6.82 (6.53, 7.11)***	9.79 (9.45, 10.1)***	2.29 (2.12, 2.46)***
<= -3.00 D to >= -6.00 D	20.9 (20.3, 21.5)***	7.09 (6.70, 7.47)***	10.6 (10.2, 11.1)***	3.14 (2.88, 3.40)***
<-6.00 D	25.8 (24.2, 27.4)***	8.06 (7.07, 9.05)***	13.2 (12.0, 14.5)***	4.49 (3.74, 5.25)***
Parental myopia				
Two of them were normal	13.1 (12.9, 13.3)	5.44 (5.30, 5.57)	6.77 (6.62, 6.92)	0.86 (0.80, 0.91)
Only father having myopia	19.3 (18.8, 19.8)***	7.02 (6.67, 7.36)***	10.1 (9.69, 10.5)***	2.19 (1.99, 2.39)***
Only mother having myopia	16.8 (16.4, 17.2)***	6.46 (6.18, 6.75)***	8.58 (8.25, 8.90)***	1.75 (1.60, 1.90)***
Two of them having myopia	23.1 (22.6, 23.7)***	7.64 (7.31, 7.97)***	11.9 (11.5, 12.3)***	3.55 (3.32, 3.78)***
Average time for homework per day, hour				
<=1	15.1 (14.8, 15.4)	6.13 (5.92, 6.34)	7.93 (7.70, 8.17)	1.00 (0.91, 1.08)
1-2	12.4 (12.1, 12.6)***	5.42 (5.25, 5.59)***	6.16 (5.97, 6.34)***	0.81 (0.75, 0.88)***
2-3	17.0 (16.7, 17.3)***	6.38 (6.17, 6.60)	8.87 (8.62, 9.12)***	1.76 (1.64, 1.87)***
>3	24.1 (23.5, 24.6)***	7.49 (7.15, 7.83)***	12.6 (12.2, 13.1)***	3.96 (3.70, 4.21)***
Average time for outdoor activities per day, hour				
<1	16.5 (16.3, 16.8)	6.18 (6.02, 6.34)	8.62 (8.44, 8.81)	1.73 (1.65, 1.82)
1-2	15.0 (14.8, 15.3)***	5.99 (5.82, 6.16)	7.66 (7.47, 7.85)***	1.38 (1.30, 1.47)***
2-4	15.0 (14.5, 15.4)***	6.18 (5.85, 6.51)	7.74 (7.38, 8.10)***	1.04 (0.90, 1.17)***
>4	15.2 (14.4, 16.1)**	6.29 (5.74, 6.83)	7.94 (7.33, 8.54)*	1.02 (0.79, 1.24)***

#: VIUC was defined by uncorrected visual acuity in better-seeing eye (UCVA).Light VIUC: UCVA>=6/18 to <6/12, mild VIUC: UCVA>=6/60 to <6/18, severe VIUC: UCVA<6/60.

†: Logistic regression was used for comparisons between categories. CI: Confidence Interval. Prevalence (95% CI) was presented, * P<0.05, ** P<0.01, *** P<0.001 indicating the significance of the difference from the reference group.

Table 3. Multiple Logistic regression model for detecting the potential risk factors for VIUC*

Variable	UCVA#<6/12(n=148,672)†		UCVA<6/18 (n=148,672)†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, Year	1.52 (1.51, 1.53)	<0.001	1.56 (1.55, 1.57)	<0.001
Male	0.77 (0.75, 0.80)	<0.001	0.78 (0.75, 0.81)	<0.001
Birth weight, kg	1.00 (0.96, 1.04)	0.974	1.11 (1.05, 1.17)	<0.001
Neonatal feeding				
Breast feeding	Reference		Reference	
Breast+ formula feeding	0.96 (0.93, 1.00)	0.039	/	/
Formula feeding	1.14 (1.09, 1.20)	<0.001	/	/
Delivery date				
Due date	Reference		Reference	
Overdue	0.93 (0.89, 0.97)	0.002	0.93 (0.88, 0.98)	0.005
Before due date	0.91 (0.87, 0.94)	<0.001	0.93 (0.89, 0.98)	0.003
Child without siblings	1.09 (1.06, 1.13)	<0.001	1.18 (1.13, 1.23)	<0.001
One or both Parents' education >12 years	1.03 (0.99, 1.07)	0.185	1.10 (1.04, 1.16)	<0.001
Father smoking				
Never smoked	Reference		Reference	
Quit for >1 year	1.00 (0.94, 1.07)	0.893	0.94 (0.88, 1.02)	0.117
Quit for <1 year	0.97 (0.87, 1.09)	0.644	0.93 (0.81, 1.07)	0.302
Current smoking	0.97 (0.93, 1.00)	0.049	0.94 (0.90, 0.99)	0.010
Parental myopia, n (%)				
Two of them were normal	Reference		Reference	
Only father having myopia	1.97 (1.87, 2.07)	<0.001	1.98 (1.87, 2.11)	<0.001
Only mother having myopia	1.80 (1.72, 1.89)	<0.001	1.83 (1.73, 1.94)	<0.001
Two of them having myopia	2.96 (2.82, 3.10)	<0.001	3.09 (2.92, 3.27)	<0.001
Average time for homework per day, hour				
<=1	Reference		Reference	
1-2	1.00 (0.95, 1.05)	0.891	0.97 (0.91, 1.03)	0.287
2-3	1.05 (1.00, 1.10)	0.059	1.07 (1.01, 1.13)	0.026
>3	1.05 (0.99, 1.11)	0.092	1.10 (1.03, 1.17)	0.004
Average time for outdoor activities per day, hour				
<1	Reference		Reference	

1-2	0.95 (0.92, 0.99)	0.006	0.92 (0.88, 0.96)	<0.001
2-4	0.94 (0.89, 0.99)	0.017	0.90 (0.84, 0.96)	0.002
>4	0.88 (0.81, 0.96)	0.003	0.80 (0.72, 0.88)	<0.001

*: Variables with $P<0.05$ in simple regression analysis were included in the multiple regression model. The results of simple regression analysis were not listed in the table. OR: Odds Ratio, CI: Confidence Interval.

#: VIUC was defined by uncorrected visual acuity in better-seeing eye (UCVA). Analysis of UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference) among participants who were singletons with normal birth weight (2.5-4kg) and whose mother had no pregnancy disorder during pregnancy.

†: There were 6,882 (4.42%) to 6,884 (4.43%) observations excluded due to missing values for the response or explanatory variables.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, Line 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, Line 1-26**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3, Line 1-32**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3, Line 34-36**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, Line 27-36**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4, Line 11-26**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 4, Line 14-20**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, Line 27-36**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 5, Line 2-16**
Bias	9	Describe any efforts to address potential sources of bias **Page 12, Line 12-14**
Study size	10	Explain how the study size was arrived at **Page 4, Line 21-26**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5, Line 19-35**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5, Line 19-35**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5, Line 19-35**
		(*c*) Explain how missing data were addressed **Page 4, Line 21-26**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **N/A**
		(*e*) Describe any sensitivity analyses **N/A**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 4, Line 21-26**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4, Line 21-26**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1, Column 2**
Outcome data	15	Report numbers of outcome events or summary measures **Page 6-8, Results Section**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 6-8, Results Section**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 8-12, Discussion Section**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 12, Line 12-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 8-12, Discussion Section**
Generalisability	21	Discuss the generalisability (external validity) of the study results **N/A**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12, Line 26-31**

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Prenatal and neonatal factors for the development of childhood visual impairment in primary and middle school students: a cross-sectional survey in Guangzhou, China

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Abstract

Objectives: In this cross-sectional survey, we sought to determine the prevalence of and the influence of prenatal and neonatal factors on childhood visual impairment without correction (VIUC) in a pediatric population from Guangzhou, China.

Setting: The health survey covered 11 administrative districts in Guangzhou, including 991 schools.

Participants: All of the primary and middle school students in Guangzhou were invited to complete an online questionnaire with the help of their parents. The results of physical examinations were reported by school medical departments. The results of the questionnaire were collected by the researchers. In total, 253,301 questionnaires were collected.

Primary outcome measures: The students' uncorrected visual acuity (UCVA) was examined by trained optometrists by standard logarithmic visual acuity charts. VIUC was defined by UCVA (of the better eye) (UCVA<6/12) with three levels: light VIUC (UCVA≥6/18 to <6/12), mild VIUC (UCVA≥6/60 to <6/18), and severe VIUC (UCVA<6/60).

Results: A total of 39,768 individuals (15.7%) had VIUC, and the rate was much higher among grade 10–12 students (51.4%) than among grade 1–6 students (6.71%). The following factors were significantly associated with an increased risk of VIUC: female gender, high birth weight, formula feeding, not having siblings, higher level of parents' education, parental myopia, much homework time, and little outdoor activity. Delivery mode was not associated with the risk of VIUC.

Conclusions: This study validates known major prenatal/genetic, perinatal, and postnatal factors for childhood VIUC. In conclusion, prenatal and perinatal factors can affect the onset of childhood VIUC, but parental myopia and postnatal factors are the main factors.

Keywords: abnormal visual acuity,childhoodmyopia,prenatal and neonatal factors

Strengths and limitations of this study:

- A retrospective study conducted using 253,301 completed surveys in the Guangzhou area of Southern China
- Collection and analysis of both prenatal and environmental factors associated with vision impairment without correction.
- Selection bias, recall bias, and reporter bias are unavoidable as the survey was based on voluntary participation.

Introduction

Visual impairment is highly prevalent in school students, and myopia-related visual impairment without correction (VIUC) accounts for over 90% of the cases in China.[1] Myopia is caused by an inconsistency between the eye's refractive power and the length of the eye axis. Two clinical types exist. In refractive myopia, the axial length is normal, but the refractive power of the cornea or lens is too strong, while in axial myopia, the refractive power of the lens is normal, but the axial length is too long.[2] Although myopia is not a life-threatening disease, the World Health Organization (WHO) recognizes it as a major cause of further visual impairment if not fully corrected.[3] At present, the high prevalence of myopia has become a serious public health problem in East Asia. In China specifically, the prevalence of myopia in high school students ranges from 43.0% to 78.4% .[4]

Myopia is etiologically heterogeneous and is believed to be driven by numerous environmental factors and genetic variations, with onset beginning in the preschool years. Environmental factors such as outdoor activity are associated with myopia inception and development.[4] Increasing outdoor time thus represents an important environmental factor that can protect young children from myopia, as supported by numerous studies.[5-7] The protective effects of outdoor activity may be due to the high light intensity outdoors, the chromaticity of daylight, or increased vitamin D levels.[8 9] A number of studies have separately shown that parental myopia is an important risk factor for myopia in children, due to the inheritance of myopia susceptibility genes or a shared myopia-driving environment.[10-12]

According to the developmental origins of health and disease theory, the development of childhood diseases may be affected by factors in prenatal life.[13] Several epidemiological studies have shown that cesarean delivery and preterm birth increase the risk of childhood myopia.[14-17] For example, preterm birth may affect ocular development or later emmetropization, and it may affect the development of the refractive status through a more complicated mechanism.[18-22] In addition, breastfeeding in early life may stimulate ocular development, as the docosahexaenoic acid and arachidonic acid in breast milk may affect retinal and neural development, therefore decreasing the risk of myopia.[23]

Here, we sought to study the effects of multiple prenatal/genetic, perinatal, and postnatal factors on the development of myopia-related VIUC in primary and middle school students in the Guangzhou area of China. For this study, the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality released an annual online health survey of primary and secondary school students, and we subsequently received relevant information from this institution. We used descriptive statistics, logistic analysis, and multiple logistic regression models to analyze the data and explore the relationships between various environmental factors, parental myopia, prenatal and neonatal factors, and myopia. Our results improve our understanding of the etiology of childhood myopia in East Asia and confirm known potential prenatal factors for long-term diseases.

Methods

Data source

This study was approved by the institutional review board of The Third Affiliated Hospital of Guangzhou Medical University [2017(No.128)], and studies involving human subjects were conducted in accordance with the Declaration of Helsinki guidelines. A cross-sectional survey design was used, and a health survey was conducted by the Health Promotion Centre for Primary and Secondary Schools of Guangzhou Municipality, which is responsible for monitoring the health status of primary and middle schools in Guangzhou. All of the primary and middle school students in Guangzhou were invited by their school to participate in the survey in October 2017. Consent was provided to all of the participants by school teachers, and oral informed consent was obtained from the participants' parents. All of the parents of school students were informed about this study at the parent-teacher conference, using posters and a short messaging service. Only verbal consent was obtained as this study was a health survey.

The health survey covered 11 administrative districts in Guangzhou, including 991 schools. In total, 253,301 questionnaires were collected. On the first page of the questionnaire, it was stated that the results of the health questionnaire would be used for health research. According to the Education Statistics Manual of Guangzhou in 2017, the number of primary and middle school students in 2017 was 1,514,122, so the response rate of this survey was 16.73%.

This health survey consisted of a questionnaire and a physical examination. The questionnaire was divided into four parts, including basic conditions, psychological behavior, exercise and sleep, and diet. Only the part of basic conditions was used in this study. Children and parents jointly filled out the questionnaire on the Internet according to their own situation and submitted the questionnaire directly online. This study used the first part of the data, including aspects such as birth weight, sex, neonatal feeding, delivery mode, delivery date, maternal diseases in pregnancy, parents' education, parental myopia, parental smoking, and average monthly household income per person.

Visual acuity assessment

The students' uncorrected visual acuity (UCVA) was examined in all schools by trained optometrists by the same standard logarithmic visual acuity charts(Chinese standard for logarithmic visual acuity charts, GB11533-2011)on a light box with 300–500 lux illumination, following regular procedures.[24] During the test, students sat at a 5 m distance from the chart with one eye covered and read out the direction of the letter "E." Students pointed in the direction the letter "E" was facing: up, down, left, or right. The test started at the 6/6 line. If students cannot see clearly, they go up one line at a time; otherwise, they go down one line at a time. The identification time of each "E" must not exceed 5 s. This process was repeated with the other eye. It is stipulated that there was no misidentification in 6/60–6/20 lines on each line, and less than two errors on each line of 6/15–6/6 lines and less than three errors on each line of 6/5–6/3. If the top line could not be read at 5 m, the student was tested at 2.5 m or 1 m, and the measured visual acuity was subtracted by 0.3 or 0.7, respectively, and then recorded as the student's visual acuity.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical methods

Characteristics of participants are presented as mean (standard deviation, SD) for continuous variables and as frequency (proportion) for categorical variables. VIUC was defined according to UCVA (better eye) (UCVA<6/12) with three levels: light VI (UCVA≥6/18 to <6/12), mild VI (UCVA≥6/60 to <6/18), and severe VI (UCVA<6/60), referring to the previous studies and definitions of impaired vision by the WHO.[25] The prevalence (95% confidence interval, CI) of VIUC was estimated by categorization of the participants' characteristics. The prevalence between categories was compared using logistic regression. Multiple logistic regression analysis was performed to detect the potential risk factors for VIUC. The participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no pregnancy disorders during pregnancy were included in the regression analysis. Two binary outcomes of VIUC were defined by UCVA (better eye) <6/12 (≥6/12 as reference) and UCVA (better eye) <6/18 (≥6/18 as reference). Observations with missing values for the response or explanatory variables were excluded in the logistic regression analysis. Variables with $P<0.05$ in the simple regression analysis were included in the multiple regression model. All of the P values were based on two-sided tests, where $P<0.05$ was considered as statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of participants

Characteristics of all of the participants are presented in Table 1.The mean age of school grade one in China is 6 years old. All of the factors can be grouped into (i) prenatal/genetic factors, including the father's refractive error, the mother's refractive error, parental myopia, and one or both parents' education; (ii) perinatal factors, including birth weight, neonatal feeding, delivery mode, delivery date, and diseases in pregnancy; and (iii) postnatal factors, including grade, age, sex, only child status, parents' smoking, average time spent on homework per day, and average time spent on outdoor activities per day.

In brief, the parental refractive error was divided into three levels: namely −3.00D, −3.00D to −6.00D, and less than −6.00D.The results showed that the distributions of the father's refractive error were 13.8%, 8.28%, and 1.37%, and those of the mother's refractive error were 16.6%, 9.63%, and 1.66% (Table 1). Both parents had myopia, and neither of them had myopia in 14.0% and 58.8% of the cases, while only the father or the mother had myopia in 11.5% and 15.8% of the cases, respectively. One or both parents' education was more than 12 years in 74.4% of the cases (Table 1).

There were three ways of neonatal feeding: breastfeeding only, formula feeding only, and breastfeeding and formula feeding together, accounting for 38.8%, 26.7%, and 34.6%, respectively. Vaginal delivery accounted for 63.5%, while the cesarean section delivery rate was 36.5%. The proportion of maternal gestational diseases, including hypertension, diabetes, intrahepatic cholestasis, hypothyroidism, hyperthyroidism, anemia, and viral hepatitis, was 11.3%. The average birth weight was 2.99 kg ± 0.40 kg (Table 1).

In addition, students of primary school (grade 1–6), junior middle school (grade 7–9), and high middle school (grade 10–12) represented 74.6%, 17.8%, and 7.57% of the total study population, respectively, with 53.8% being male. Less than 1h, 1–2h, 2–3h, and more than 3h spent on homework per day were reported in 29.8%, 36.0%, 23.8%, and 10.4% of the cases, respectively; less than 1h, 1–2h, 2–4h, and more than 4h spent on outdoor activities per day were reported in 45.2%, 40.1%, 10.8%, and 3.88% of the cases, respectively. Children without siblings made up 45.0%. Paternal and maternal smoking rates were 45.5% and 0.85%, respectively (Table 1). The smoking rates and the number of siblings in this study were comparable to the norm of China according to recent reports.[26 27]

Prevalence of VIUC by characteristics

Of the 253,301 children included in the present study, 15.7% children experienced VIUC (Table 2). The larger the refraction error of either the father or the mother, the higher the prevalence of all levels of VIUC in children. Additionally, more time spent on homework per day and less time spent on outdoor activities per day was associated with a higher risk of VIUC (all $P<0.001$).

The prevalence of all three levels of VIUC was similar in the subgroups with different modes of neonatal feeding, but breastfeeding and formula feeding together showed statistically significant differences compared with breast feeding only (all $P<0.01$, Table 2). Cesarean section was associated with a higher prevalence of severe VIUC ($P<0.001$) but with a lower prevalence of light VIUC ($P<0.001$), mild VIUC ($P<0.05$), and overall VIUC ($P<0.05$). Unexpectedly, the prevalence of UCVA<6/12 in participants born before their due date was lower than in participants born on their due date (16.7%, $P<0.001$) or who were overdue (16.2%, $P<0.001$). Maternal pregnancy diseases were significantly associated with an increased risk of VIUC (Table 2).

With increasing grade and age, the prevalence of UCVA<6/12 also increased (all $P<0.001$); the prevalence among students in grades 10–12 and students older than 15 years was 51.4% and 52.4%, respectively (Table 2). The increase in the prevalence of severe VIUC, which was 9.92% and 10.6%, respectively, was most significant (all $P<0.001$).The prevalence of UCVA<6/12 was different ($P<0.001$) in female (17.8%) and male (13.9%) participants. The prevalence of all levels of VIUC was higher among children without siblings than among children with siblings. The prevalence of UCVA (better eye) <6/12 or worse than 6/18 was higher among students with one or both parents' education >12 years than among students with both parents' education ≤12 years (Table 2). Students with a father currently smoking had a lower risk of VIUC (all $P<0.05$).

Multiple logistic regression model for detecting the potential risk factors for VIUC

The results of two multiple logistic regression models for detecting the potential risk factors for VIUC are presented in Table 3, with 6/12 (≥6/12 as reference) and 6/18 (≥6/18 as reference) as cutoff points. Because low birth weight and maternal diseases are known factors affecting children's eye development, here, we only studied the 155,556 participants who were singletons with normal birth weights (2.5–4 kg) and whose mothers had no disease during pregnancy.

The results indicated that the students whose parents had a higher level of education had a higher risk of UCVA<6/18 (OR [95% CI], 1.10 [1.04, 1.16]; $P<0.001$) (Table 3).

Parental myopia increased the risk of UCVA<6/12 or <6/18 (all *P*<0.001) when only the father had myopia (OR [95% CI], 1.97 [1.87, 2.07] and 1.98 [1.87, 2.11]), when only the mother had myopia (OR [95% CI], 1.80 [1.72, 1.89] and 1.83 [1.73, 1.94]), and when both parents had myopia (OR [95% CI], 2.96 [2.82, 3.10] and 3.09 [2.92, 3.27]).

In addition, birth weight was only positively associated with UCVA<6/18 (OR [95% CI], 1.11 [1.05, 1.17]; *P*<0.001). Compared with breast feeding only, formula feeding only contributed to a higher risk of UCVA<6/12 (OR [95% CI], 1.14 [1.09, 1.20]; *P*<0.001), while breast and formula feeding together was associated with a lower risk (OR [95% CI], 0.96 [0.93, 1.00]; *P*=0.039). Delivery mode was not associated with both outcomes of VIUC. Students who were delivered overdue or before due date had a lower risk of UCVA<6/12 (OR [95% CI], 0.93 [0.89, 0.97]; *P*=0.002 and 0.91 [0.87, 0.94]; *P*<0.001, respectively) and UCVA<6/18 (OR [95% CI], 0.93 [0.88, 0.98]; *P*=0.005 and 0.93 [0.89, 0.98]; *P*=0.003, respectively) than those delivered on their due date.

Age (OR [95% CI], 1.52 [1.51, 1.53]; *P*<0.001) and not having siblings (OR [95% CI], 1.09 [1.06, 1.13]; *P*<0.001) were positively associated with the risk of UCVA<6/12. Similarly, age (OR [95% CI], 1.56 [1.55, 1.57]; *P*<0.001) and not having siblings (OR [95% CI], 1.18 [1.13, 1.23]; *P*<0.001) were positively associated with the risk of UCVA<6/18. Male students had a lower risk of either UCVA<6/12 (OR [95% CI], 0.77 [0.75, 0.80]; *P*<0.001) or UCVA<6/18 (OR [95% CI], 0.78 [0.75, 0.81]; *P*<0.001]. An average time spent on homework per day of 2–3h (OR [95% CI], 1.07 [1.01, 1.13]) or more than 3h (OR [95% CI], 1.10 [1.03, 1.17]) was significantly associated with a higher risk of mild VI compared with the group spending less than 1 h.

In agreement with previous findings, among participants who spent ≥1h on outdoor activities, the prevalence of VIUC was lower, i.e., for 1–2h (OR [95% CI], 0.95 [0.92, 0.99]; *P*=0.006 and 0.92 [0.88, 0.96]; *P*<0.001), for 2–4h (OR [95% CI], 0.94 [0.89, 0.99]; *P*=0.017 and 0.90 [0.84, 0.96]; *P*=0.002), and for>4h (OR [95% CI], 0.88 [0.81, 0.96]; *P*=0.003 and 0.80 [0.72, 0.88]; *P*<0.001), compared with participants who spent <1h on outdoor activities. The current smoking status of the father was associated with a lower risk of UCVA<6/18 compared with participants with a father who never smoked (OR [95% CI], 0.94 [0.90, 0.99]; *P*=0.010], and also a marginally significant association between current smoking status of the father and the prevalence of UCVA<6/12 was observed (OR [95% CI], 0.97 [0.93, 1.00]; *P*=0.049).

Discussion

Myopia, the dominant cause of VIUC in teenagers, has increased in prevalence in East Asia in the past few decades and has therefore become a major health issue.[28] It is commonly believed that the high prevalence of myopia in East Asia is associated with increased educational pressure, combined with lifestyle changes, which have reduced the time children spend outside.[2] Recent studies have suggested that the development of childhood diseases may also be affected by factors in prenatal and neonatal life, in that factors like delivery mode, feeding manner, and pregnancy diseases can alter the risks for childhood diseases such as asthma.[29 30] However, the prenatal and neonatal factors for VIUC, especially childhood myopia, remain largely unclear. Therefore, a retrospective survey involving primary and middle school students in Guangzhou was launched to evaluate the association between most important prenatal, perinatal, and postnatal factors and the prevalence of VIUC in 6-year-old to 17-year-old school students.

The present cross-sectional study, which included 253,301 completed questionnaires and medical records, revealed that among children in grades 1–6, grades 7–9, and grades 10–12 in Guangzhou, the total prevalence of VIUC was 6.71%, 30.0%, and 51.4% and that of severe VIUC was 0.16%, 2.25%, and 9.92%, respectively (Table 2). The prevalence of VIUC presented here is high compared with other countries and areas but was close to the reported prevalence in Chinese urban areas.[31] However, as the clustered nature of the data has not been accounted for in the analysis, the width of the confidence intervals may be underestimated.

It is believed that VIUC is etiologically heterogeneous. A small part of VIUC cases is caused by prenatal and genetic factors and appears without exposure to additional risk factors.[5] Parental myopia is a high-risk factor for childhood VIUC, but although several genes have been shown to be associated with high myopia, no major genes affecting childhood myopia have been reported until now.[2] A cohort study of 298 probands with early-onset high myopia using whole-exome sequencing showed that mutations in genes known to be responsible for retinal diseases were found in approximately one-fourth of the probands with early-onset high myopia.[11] In another study of myopia prevalence, grade 7 students in a Chinese rural area showed a lower prevalence of myopia (29.4%) and high myopia (0.4%) than those in Chinese urban cities, suggesting that Chinese people may not have a genetic predisposition to myopia and that environmental factors may play a major role in the development of childhood myopia in Chinese children.[32]

In the present study, the association between parental myopia and childhood VIUC was strong (Table 3). In grade 10–12 students, the ORs were 2.06, 1.85, and 3.17 for paternal myopia only, maternal myopia only, and both parents having myopia, respectively. Although the possibility of heredity for VIUC was not excluded, families also share environments, and myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors, increasing the myopia risk of their children.[18] In a study on the gene–environment interaction in myopia, the prevalence of child myopia was only 9.9% in farmer families without parental myopia, but the prevalence among college students was similar between farmer families and other families, suggesting a leading role of environmental factors in the formation of myopia.[10] In another study on high myopia across three different generations in Korea, results showed that the environmental portion of the phenotypic variance increased and the additive genetic portion decreased as South Korea became more urbanized.[33] Therefore, it remains to be established how gene–environment interactions contribute to myopia within various populations.[2]

In the present study, we analyzed the effects of perinatal factors, such as delivery manner, delivery mode, and pregnancy diseases, on the prevalence of myopia. Pregnancy diseases, such as hyperemesis, hypertension, preeclampsia, and uterus-related complications may affect fetal growth in the uterus and probably later long-term health. For instance, diabetes during pregnancy is associated with changes in retinal morphology in the offspring.[34] We found that pregnancy diseases decrease the prevalence of childhood VIUC, and this relationship may be causal (Table 2). Children whose mothers suffered from pregnancy diseases may have lower educational pressure than those without diseases in the family.

Premature birth and low birth weight affect the general growth of the fetus, including eye development. A previous analysis determined that in children born prematurely, the development of myopia is mainly influenced by anterior segment components, whereas hyperopia was mainly attributed to short axial length.[18] In a British birth cohort study, myopia was positively associated with low birth weight for gestational age,[14] and in the Sydney Paediatric Eye Disease Study, vision impairment was independently associated with low birth weight.[19] In the present study, the parents only reported whether the participants were born before, on, or after their due date, and no further information on precise gestational age was obtained. Regretfully, we cannot analyze the association between premature birth and childhood vision impairment. Accordingly, we used multiple logistic regression models to analyze only the population with normal birth weight and without pregnancy complications.

Breastfeeding may influence the early growth of a baby. In a cross-sectional study of

527 Chinese primary school students aged 6–12 years, breastfeeding was reported to be associated with a decreased risk of myopia, and breastfeeding during the first 6 months of infancy was associated with higher hyperopic spherical equivalent refraction.[23] Furthermore, breastfeeding was associated with myopic refraction and was not related to axial length, and this association could exist in childhood.[23] In a study of Singaporean preschoolers, results showed that breastfeeding was associated with higher hyperopic spherical equivalent refraction.[35] Our results support the idea that breastfeeding decreases and formula feeding increases the risks for VIUC (Table 3). The underlying mechanisms remain unclear, but physical development may be associated with eye development as well.

Postnatal factors, including environmental factors, play critical roles in the development of childhood myopia.[4] In an analysis of time spent on outdoor activity and on near-vision work, children with little outdoor time and much near-vision work were two to three times more likely to be myopic compared with those performing little near-vision work and spending much time outdoors.[18] In the area of Beijing, China, greater axial elongation was associated with less time spent outdoors and with more time spent indoors.[6] In Finland, a higher risk of myopia was mainly related to parents having myopia and less time spent on sports and outdoor activities in childhood.[8] In the Netherlands, seven parameters were associated independently with faster axial length elongation, including the number of books read per week, time spent reading, no participation in sports, and less time spent outdoors.[36]

Our present results clearly support the idea that homework time is positively associated and outdoor activity is negatively associated with the prevalence of myopia and VIUC in students of all grades (Tables 2 and 3). Therefore, environmental factors should be the leading consideration to reduce the incidence of childhood myopia. Indeed, in a recent clinical trial among 6-year-old children in Guangzhou, the incidence of myopia significantly reduced over the 3 years after the addition of 40 min of outdoor activity to the daily curriculum, replacing usual activity.[7] Therefore, such interventions could be the most effective strategy to decrease the prevalence of VIUC in Chinese cities.

Our results also show that female gender, older age, and not having siblings are associated with an increased risk for myopia. Similarly, in a study including 2,760 7-year-old children and 2,198 12-year-old children, higher intraocular pressure was associated with female gender, older age, and higher body mass index, while younger age at the commencement of reading and being born with a cesarean section were also associated with higher intraocular pressure in adolescence.[17] However, these factors may be largely linked with environmental factors, such as outdoor activity and near-vision work. For example, boys are more likely to do outdoor sports; as one ages, the educational pressure increases; children without siblings are more likely to have indoor activities and near-vision work; and overweight decreases the outdoor activity of children. Therefore, the observed correlation may be causal.

Additionally, our data showed that paternal smoking did not significantly increase the prevalence of VIUC (Table 3), suggesting that indoor pollution might not provoke the development of myopia. In a study in Singapore, an inverse association was found between parental smoking and childhood myopia,[37] and our data also indicated that a current smoking status of the father decreased the risk of VIUC (Table 3). Moreover, Guangzhou has markedly reduced its atmospheric pollution during the past 10 years, but the prevalence of myopia has further increased.[5] Therefore, environmental pollution does not seem to be a major risk factor for childhood myopia. It is notable that female smoking is rare in China, to such an extent that in this study 99.2% of the mothers never smoked. Therefore, maternal smoking may not be a significant factor for consideration.

In conclusion, the results of the present retrospective study, conducted using 253,301 completed surveys in the Guangzhou area of Southern China, indicated that factors such as the female gender, high birth weight, formula feeding, not having siblings, higher levels of parents' education, parental myopia, much homework time, and little outdoor activity are significantly associated with a higher risk of vision impairment. Conversely, being born before the due date, being overdue, and outdoor activity were associated with a decreased risk of vision impairment. Therefore, we here confirm known major prenatal/genetic, perinatal, and postnatal factors for childhood VIUC. Although selection bias, recall bias, and reporter bias were unavoidable, as this is a retrospective, self-reported survey, based on the current data, we conclude that prenatal and perinatal factors can affect the onset of childhood VIUC, but parental myopia and postnatal factors are the main factors. Therefore, children whose parents have myopia should be considered as a high-risk population for childhood VIUC, and intervention by changing environmental factors such as outdoor activities should be conducted for effective prevention of VIUC.

Competing interests

None declared

Author Contributions

Conceived and designed the research: DunjunChen. Collected the data: NaliDeng.

Analyzed the data: JuanjuanChen, Wen Sun, JingsiChen, and LiliDu. Wrote the paper: Bolan Yu and LijuanDai.

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Data sharing statement

Deidentified participant data are available upon reasonable requisition.

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Table 1. Characteristics of participants

Characteristics	n	n (%)
Total	253,301	/
Grade	253,301	
1-6		189,008 (74.6)
7-9		45,119 (17.8)
10-12		19,174 (7.57)
Age[#]	253,301	
6-10		156,992 (62.0)
11-15		82,092 (32.4)
>15		14,217 (5.61)
Sex	253,301	
Male		136,200 (53.8)
Female		117,101 (46.2)
Birth weight, kg	249,610	2.99 (0.40)[†]
Neonatal feeding	253,292	
Breast feeding		98,164 (38.8)
Breast+ formula feeding		87,532 (34.6)
Formula feeding		67,596 (26.7)
Delivery	253,292	
Vaginal delivery		160,873 (63.5)
Caesarean		92,419 (36.5)
Delivery date	253,291	
On the due date		91,409 (36.1)
Overdue		54,161 (21.4)
Before the due date		107,721 (42.5)
Diseases in pregnancy		
Hypertension	252,013	3,722 (1.48)
Diabetes	252,068	5,237 (2.08)
Intrahepatic cholestasis	251,930	622 (0.25)
Hypothyroidism	251,878	764 (0.30)
Hyperthyroidism	248,301	978 (0.39)
Anemia	248,374	16,236 (6.54)
Viral hepatitis	248,311	2,330 (0.94)
Other	248,273	1,679 (0.68)
Any disease above	248,461	27,998 (11.3)
Children without siblings	253,286	

No		139,318 (55.0)
Yes		113,968 (45.0)
One or both parents' education	253,288	
<=12 years		64,943 (25.6)
>12 years		188,345 (74.4)
Father smoking	253,286	
Never smoked		138,077 (54.5)
Quit for >1 year		17,998 (7.11)
Quit for <1 year		5,362 (2.12)
Current smoking		91,849 (36.3)
Mother smoking	253,286	
Never smoked		251,159 (99.2)
Quit for >1 year		900 (0.36)
Quit for <1 year		276 (0.11)
Current smoking		951 (0.38)
Father's refractive error, diopter	238,888	
Normal		182,857 (76.6)
>-3.00 D		32,982 (13.8)
<= -3.00 D to >= -6.00 D		19,770 (8.28)
<-6.00 D		3,279 (1.37)
Mother's refractive error, diopter	240,291	
Normal		173,256 (72.1)
>-3.00 D		39,915 (16.6)
<= -3.00 D to >= -6.00 D		23,135 (9.63)
<-6.00 D		3,985 (1.66)
Parental myopia	242,006	
Two of them were normal		142,238 (58.8)
Only father having myopia		27,794 (11.5)
Only mother having myopia		38,172 (15.8)
Two of them having myopia		33,802 (14.0)
Average time for homework per day, hour	251,925	
<=1		75,123 (29.8)
1-2		90,674 (36.0)
2-3		59,901 (23.8)
>3		26,227 (10.4)
Average time for outdoor activities per day, hour	253,280	
<1		114,471 (45.2)
1-2		101,658 (40.1)

2-4	27,332 (10.8)
>4	9,819 (3.88)

#: The mean age of school grade1 is6 years old.

†: Data is represented as Mean (Standard deviation).

Table 2. Prevalence ofVIUCby characteristics

Variable	Total UCVA<6/12	Light VIUC UCVA>=6/18 to <6/12	Mild VIUC UCVA>=6/60 to <6/18	Severe VIUC UCVA<6/60
	% (95% CI)†	% (95% CI)†	% (95% CI)†	% (95% CI)†
All	15.7 (15.6, 15.9)	6.11 (6.00, 6.22)	8.12 (8.00, 8.24)	1.49 (1.44, 1.54)
Grade				
1-6	6.71 (6.58, 6.85)	3.70 (3.60, 3.80)	2.85 (2.76, 2.94)	0.16 (0.14, 0.18)
7-9	30.0 (29.6, 30.5)***	11.6 (11.3, 11.9)***	16.2 (15.8, 16.5)***	2.25 (2.10, 2.39)***
10-12	51.4 (50.6, 52.1)***	11.7 (11.2, 12.2) ***	29.7 (29.1, 30.4)***	9.92 (9.47, 10.4)***
Age, Years				
6-10	4.56 (4.43, 4.69)	2.66 (2.56, 2.76)	1.80 (1.72, 1.88)	0.10 (0.08, 0.12)
11-15	25.1 (24.8, 25.4)***	10.1 (9.85, 10.3)***	13.1 (12.9, 13.4)***	1.88 (1.79, 1.98)***
>15	52.4 (51.5, 53.3)***	11.3 (10.7, 11.8)***	30.6 (29.8, 31.4)***	10.6 (10.0, 11.1)***
Sex				
Female	17.8 (17.5, 18.0)	6.75 (6.58, 6.91)	9.33 (9.14, 9.52)	1.70 (1.62, 1.79)
Male	13.9 (13.7, 14.1)***	5.55 (5.41, 5.69)***	7.07 (6.91, 7.22)***	1.30 (1.24, 1.37)***
Neonatal feeding				
Breast feeding	16.1 (15.9, 16.4)	6.42 (6.24, 6.60)	8.22 (8.02, 8.42)	1.49 (1.40, 1.57)
Breast + formula feeding	15.2 (14.9, 15.5)***	5.71 (5.53, 5.89)***	7.80 (7.60, 8.01)**	1.67 (1.57, 1.76)**
Formula feeding	15.8 (15.5, 16.1)	6.16 (5.96, 6.37)	8.38 (8.14, 8.62)	1.27 (1.17, 1.36)**
Delivery				
Vaginal delivery	15.9 (15.6, 16.1)	6.31 (6.17, 6.44)	8.22 (8.06, 8.37)	1.32 (1.26, 1.39)
Caesarean	15.5 (15.2, 15.8)*	5.77 (5.60, 5.94)***	7.95 (7.75, 8.15)*	1.77 (1.67, 1.87)***
Delivery date				
Due date	16.7 (16.4, 17.0)	6.56 (6.37, 6.74)	8.82 (8.60, 9.03)	1.31 (1.23, 1.40)
Overdue	16.2 (15.9, 16.6)*	6.20 (5.97, 6.43)*	8.29 (8.02, 8.55)**	1.73 (1.61, 1.86)***
Before due date	14.7 (14.4, 14.9)***	5.68 (5.52, 5.84)***	7.45 (7.27, 7.63)***	1.52 (1.43, 1.60)***
Diseases in pregnancy				
Hypertension				
No	15.7 (15.5, 15.9)	6.10 (5.99, 6.21)	8.12 (8.00, 8.25)	1.48 (1.43, 1.54)
Yes	17.5 (16.1, 18.9)**	7.22 (6.26, 8.18)*	8.18 (7.17, 9.19)	2.13 (1.60, 2.67)**
Diabetes				
No	15.8 (15.6, 16.0)	6.13 (6.02, 6.24)	8.17 (8.04, 8.29)	1.49 (1.43, 1.54)
Yes	12.7 (11.6, 13.8)***	5.31 (4.57, 6.05)*	5.82 (5.05, 6.59)***	1.60 (1.19, 2.01)
Intrahepatic cholestasis				
No	15.7 (15.6, 15.9)	6.12 (6.01, 6.23)	8.13 (8.01, 8.25)	1.49 (1.44, 1.55)
Yes	11.9 (8.84, 14.9)*	4.79 (2.79, 6.80)	5.71 (3.54, 7.88)	1.37 (0.28, 2.46)

Hypothyroidism				
No	15.7 (15.6, 15.9)	6.11 (6.01, 6.22)	8.13 (8.00, 8.25)	1.49 (1.44, 1.55)
Yes	14.0 (11.0, 17.0)	5.83 (3.80, 7.85)	6.99 (4.79, 9.19)	1.17 (0.24, 2.09)
Hyperthyroidism				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.50 (1.45, 1.56)
Yes	16.0 (13.3, 18.7)	6.93 (5.06, 8.80)	7.92 (5.93, 9.91)	1.13 (0.35, 1.91)
Anemia				
No	16.0 (15.8, 16.1)	6.15 (6.04, 6.27)	8.28 (8.16, 8.41)	1.53 (1.47, 1.59)
Yes	12.9 (12.3, 13.5)***	5.64 (5.22, 6.06)*	6.16 (5.73, 6.60)***	1.08 (0.89, 1.26)***
Viral hepatitis				
No	15.8 (15.6, 16.0)	6.12 (6.01, 6.23)	8.17 (8.05, 8.29)	1.51 (1.45, 1.56)
Yes	13.2 (11.6, 14.8)**	5.97 (4.85, 7.09)	6.32 (5.17, 7.47)**	0.93 (0.48, 1.38)
Other				
No	15.8 (15.6, 15.9)	6.12 (6.01, 6.23)	8.15 (8.03, 8.28)	1.51 (1.45, 1.56)
Yes	15.2 (13.2, 17.2)	6.47 (5.07, 7.86)	7.89 (6.36, 9.42)	0.84 (0.32, 1.36)
Any disease above				
No	16.0 (15.9, 16.2)	6.15 (6.04, 6.27)	8.36 (8.22, 8.49)	1.52 (1.46, 1.58)
Yes	13.6 (13.1, 14.1)***	5.82 (5.50, 6.15)	6.47 (6.13, 6.81)***	1.31 (1.15, 1.46)*
Children without siblings				
No	13.4 (13.2, 13.6)	5.75 (5.61, 5.89)	6.84 (6.69, 7.00)	0.76 (0.71, 0.081)
Yes	18.5 (18.3, 18.8)***	6.53 (6.37, 6.70)***	9.65 (9.45, 9.85)***	2.36 (2.26, 2.46)***
One or both parents' education				
<=12 years	14.0 (13.7, 14.4)	6.12 (5.91, 6.33)	7.39 (7.15, 7.62)	0.53 (0.47, 0.60)
>12 years	16.3 (16.1, 16.5)***	6.10 (5.98, 6.23)	8.37 (8.22, 8.51)***	1.81 (1.74, 1.88)***
Father smoking				
Never smoked	16.1 (15.9, 16.3)	6.15 (6.01, 6.30)	8.38 (8.21, 8.55)	1.56 (1.48, 1.64)
Quit for >1 year	17.8 (17.2, 18.5)***	6.83 (6.41, 7.25)**	9.23 (8.74, 9.71)***	1.76 (1.54, 1.97)
Quit for <1 year	15.4 (14.3, 16.5)	6.41 (5.65, 7.18)	7.81 (6.97, 8.64)	1.19 (0.85, 1.53)
Current smoking	14.8 (14.5, 15.0)***	5.88 (5.70, 6.05)*	7.52 (7.33, 7.72)***	1.35 (1.26, 1.43)***
Father's refractive error, diopter				
Normal	13.9 (13.7, 14.1)	5.67 (5.55, 5.79)	7.17 (7.03, 7.30)	1.04 (0.99, 1.09)
>-3.00 D	20.4 (19.9, 20.9)***	7.31 (6.99, 7.64)***	10.5 (10.1, 10.9)***	2.66 (2.45, 2.86)***
<= -3.00 D to >= -6.00 D	23.4 (22.8, 24.1)***	7.35 (6.92, 7.77)***	12.5 (12.0, 13.0)***	3.60 (3.30, 3.90)***
<-6.00 D	27.3 (25.5, 29.0)***	8.01 (6.93, 9.08)***	14.1 (12.7, 15.4)***	5.19 (4.31, 6.14)***
Mother's refractive error, in either eye,				

diopter				
Normal	14.1 (13.9, 14.3)	5.70 (5.57, 5.82)	7.31 (7.16, 7.45)	1.07 (1.02, 1.13)
>-3.00 D	18.9 (18.5, 19.3)***	6.82 (6.53, 7.11)***	9.79 (9.45, 10.1)***	2.29 (2.12, 2.46)***
<= -3.00 D to >= -6.00 D	20.9 (20.3, 21.5)***	7.09 (6.70, 7.47)***	10.6 (10.2, 11.1)***	3.14 (2.88, 3.40)***
<-6.00 D	25.8 (24.2, 27.4)***	8.06 (7.07, 9.05)***	13.2 (12.0, 14.5)***	4.49 (3.74, 5.25)***
Parental myopia				
Two of them were normal	13.1 (12.9, 13.3)	5.44 (5.30, 5.57)	6.77 (6.62, 6.92)	0.86 (0.80, 0.91)
Only father having myopia	19.3 (18.8, 19.8)***	7.02 (6.67, 7.36)***	10.1 (9.69, 10.5)***	2.19 (1.99, 2.39)***
Only mother having myopia	16.8 (16.4, 17.2)***	6.46 (6.18, 6.75)***	8.58 (8.25, 8.90)***	1.75 (1.60, 1.90)***
Two of them having myopia	23.1 (22.6, 23.7)***	7.64 (7.31, 7.97)***	11.9 (11.5, 12.3)***	3.55 (3.32, 3.78)***
Average time for homework per day, hour				
<=1	15.1 (14.8, 15.4)	6.13 (5.92, 6.34)	7.93 (7.70, 8.17)	1.00 (0.91, 1.08)
1-2	12.4 (12.1, 12.6)***	5.42 (5.25, 5.59)***	6.16 (5.97, 6.34)***	0.81 (0.75, 0.88)***
2-3	17.0 (16.7, 17.3)***	6.38 (6.17, 6.60)	8.87 (8.62, 9.12)***	1.76 (1.64, 1.87)***
>3	24.1 (23.5, 24.6)***	7.49 (7.15, 7.83)***	12.6 (12.2, 13.1)***	3.96 (3.70, 4.21)***
Average time for outdoor activities per day, hour				
<1	16.5 (16.3, 16.8)	6.18 (6.02, 6.34)	8.62 (8.44, 8.81)	1.73 (1.65, 1.82)
1-2	15.0 (14.8, 15.3)***	5.99 (5.82, 6.16)	7.66 (7.47, 7.85)***	1.38 (1.30, 1.47)***
2-4	15.0 (14.5, 15.4)***	6.18 (5.85, 6.51)	7.74 (7.38, 8.10)***	1.04 (0.90, 1.17)***
>4	15.2 (14.4, 16.1)**	6.29 (5.74, 6.83)	7.94 (7.33, 8.54)*	1.02 (0.79, 1.24)***

#: VIUCwas defined by uncorrected visual acuity in better-seeing eye (UCVA).LightVIUC: UCVA>=6/18 to <6/12, mild VIUC: UCVA>=6/60 to <6/18, severe VIUC: UCVA<6/60.

†: Logistic regression was used for comparisons between categories. CI: Confidence Interval. Prevalence (95% CI) was presented, * *P*<0.05, ** *P*<0.01, *** *P*<0.001 indicating the significance of the difference from the reference group.

Table 3. Multiple Logistic regression model for detecting the potential risk factors forVIUC*

Variable	UCVA[#]<6/12(n=148,672)†		UCVA<6/18 (n=148,672)†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, Year	1.52 (1.51, 1.53)	<0.001	1.56 (1.55, 1.57)	<0.001
Male	0.77 (0.75, 0.80)	<0.001	0.78 (0.75, 0.81)	<0.001
Birth weight, kg	1.00 (0.96, 1.04)	0.974	1.11 (1.05, 1.17)	<0.001
Neonatal feeding				
Breast feeding	Reference		Reference	
Breast+ formula feeding	0.96 (0.93, 1.00)	0.039	/	/
Formula feeding	1.14 (1.09, 1.20)	<0.001	/	/
Delivery date				
Due date	Reference		Reference	
Overdue	0.93 (0.89, 0.97)	0.002	0.93 (0.88, 0.98)	0.005
Before due date	0.91 (0.87, 0.94)	<0.001	0.93 (0.89, 0.98)	0.003
Child without siblings	1.09 (1.06, 1.13)	<0.001	1.18 (1.13, 1.23)	<0.001
One or both Parents' education >12 years	1.03 (0.99, 1.07)	0.185	1.10 (1.04, 1.16)	<0.001
Father smoking				
Never smoked	Reference		Reference	
Quit for >1 year	1.00 (0.94, 1.07)	0.893	0.94 (0.88, 1.02)	0.117
Quit for <1 year	0.97 (0.87, 1.09)	0.644	0.93 (0.81, 1.07)	0.302
Current smoking	0.97 (0.93, 1.00)	0.049	0.94 (0.90, 0.99)	0.010
Parental myopia, n (%)				
Two of them were normal	Reference		Reference	
Only father having myopia	1.97 (1.87, 2.07)	<0.001	1.98 (1.87, 2.11)	<0.001
Only mother having myopia	1.80 (1.72, 1.89)	<0.001	1.83 (1.73, 1.94)	<0.001
Two of them having myopia	2.96 (2.82, 3.10)	<0.001	3.09 (2.92, 3.27)	<0.001
Average time for homework per day, hour				
<=1	Reference		Reference	
1-2	1.00 (0.95, 1.05)	0.891	0.97 (0.91, 1.03)	0.287
2-3	1.05 (1.00, 1.10)	0.059	1.07 (1.01, 1.13)	0.026
>3	1.05 (0.99, 1.11)	0.092	1.10 (1.03, 1.17)	0.004
Average time for outdoor activities per day, hour				
<1	Reference		Reference	

1-2	0.95 (0.92, 0.99)	0.006	0.92 (0.88, 0.96)	<0.001
2-4	0.94 (0.89, 0.99)	0.017	0.90 (0.84, 0.96)	0.002
>4	0.88 (0.81, 0.96)	0.003	0.80 (0.72, 0.88)	<0.001

*: Variables with $P<0.05$ in simple regression analysis were included in the multiple regression model. The results of simple regression analysis were not listed in the table. OR: Odds Ratio, CI: Confidence Interval.

#: VIUC was defined by uncorrected visual acuity in better-seeing eye (UCVA). Analysis of UCVA<6/12 (>=6/12 as reference) and UCVA<6/18 (>=6/18 as reference) among participants who were singletons with normal birth weight (2.5-4kg) and whose mother had no pregnancy disorder during pregnancy.

†: There were 6,882 (4.42%) to 6,884 (4.43%) observations excluded due to missing values for the response or explanatory variables.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1, Line 1-3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2, Line 1-26**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3, Line 1-32**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3, Line 34-36**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, Line 27-36**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4, Line 11-26**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 4, Line 14-20**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4, Line 27-36**
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 5, Line 2-16**
Bias	9	Describe any efforts to address potential sources of bias **Page 12, Line 12-14**
Study size	10	Explain how the study size was arrived at **Page 4, Line 21-26**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5, Line 19-35**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5, Line 19-35**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5, Line 19-35**
		(*c*) Explain how missing data were addressed **Page 4, Line 21-26**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **N/A**
		(*e*) Describe any sensitivity analyses **N/A**

Results

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 4, Line 21-26**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram **Figure 1**
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4, Line 21-26**
		(b) Indicate number of participants with missing data for each variable of interest **Table 1, Column 2**
Outcome data	15	Report numbers of outcome events or summary measures **Page 6-8, Results Section**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 6-8, Results Section**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 8-12, Discussion Section**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 12, Line 12-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 8-12, Discussion Section**
Generalisability	21	Discuss the generalisability (external validity) of the study results **N/A**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 12, Line 26-31**