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Ocular Perfusion Pressure in 7- and 12-Year-Old Chinese Children: The Anyang Childhood Eye Study

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Purpose: The purpose of this study was to report the distribution of mean ocular perfusion pressure (MOPP) and its associated factors in Chinese children.

Methods: We enrolled 3048 grade 1 students and 2258 grade 7 students of the Anyang Childhood Eye Study in central China. Systolic and diastolic blood pressure (SBP and DBP) were recorded with a digital automatic sphygmomanometer. Intraocular pressure (IOP) was assessed by a non-contact tonometer. MOPP was calculated as 2/3 × (DBP + 1/3[SBP − DBP]) - IOP. Risk factors for myopia were obtained through a questionnaire survey.

Results: The MOPP was 33.83 ± 6.37 mm Hg (mean ± SD) in grade 1, which was lower than 36.99 ± 6.80 mm Hg in grade 7 ($P < 0.001$). Compared with myopic eyes, non-myopic eyes had higher MOPP in grade 7 (37.72 ± 6.72 mm Hg versus 36.58 ± 6.57 mm Hg, $P < 0.001$) and in grade 1 (33.88 ± 6.29 mm Hg versus 33.12 ± 7.03 mm Hg, $P = 0.12$). Multivariable analysis showed that higher MOPP was associated with less myopia ($P < 0.001$), higher body mass index (BMI; $P < 0.001$), thinner central corneal thickness ($P < 0.001$), less time on near work ($P < 0.001$), and more time on sleeping ($P = 0.04$).

Conclusions: MOPP was higher in children of older age, with higher BMI, less time on near work, and more time on sleeping, and was higher in eyes with less myopia.

Translational Relevance: We found that MOPP might be an indicator for the detection of myopia development.

Introduction

Myopia causes a considerable personal and societal burden due to its inconvenience in life and increased risk of many sight-threatening complications, including myopic retinal degeneration, retinal detachment, glaucoma, and blindness.[1,2] However, the pathogenesis of myopia is still unclear. Decreased choroidal blood perfusion can cause scleral hypoxia and scleral extracellular matrix (ECM) remodeling, one mechanism of which may be mediated by hypoxia-inducible factor 1 alpha (HIF-1α), leading to the development and progression of myopia.[3–6]

With increased intraocular pressure (IOP), blood flow and perfusion of the choroid and retina reduced.[7–9] As mentioned above, an elevation of IOP might induce myopia development. However, studies have inconsistencies in the results. Some studies showed IOP was not associated with refractive error.[10,11]

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In contrast, others showed an inverse association between IOP and myopia.[12,13] We speculate that the inconsistencies in the results occur from the fact that IOP is an influencing factor of ocular perfusion pressure but cannot represent ocular tissue perfusion.[9]

Mean ocular perfusion pressure (MOPP), calculated as 2/3 × (diastolic blood pressure [DBP] + 1/3 × [systolic blood pressure [SBP] - DBP) - IOP, was proposed as an indicator for assessing human ocular blood circulation after using topical timolol initially.[14] Later, large diurnal fluctuations in MOPP have been shown to produce faster paracentral visual field defect progression in normal IOP glaucoma.[15–18] Some researchers suggested that higher MOPP may offer relative protection from glaucomatous damage.[19] Jaewan and colleagues proposed that MOPP could represent ocular perfusion status appropriately, as MOPP integrated IOP, SBP, and DBP.[18] Perfusion pressure determines the blood flow of an organ. Reduced ocular perfusion pressure may result in ischemia of ocular structures.[20,21]

The principal objective of this project was to determine whether MOPP is associated with myopia. Some work has been undertaken on the association between MOPP and refractive error. In myopic populations, the MOPP decreased by 0.385 mm Hg/D with the increasing myopic refraction.[22] Research found that the MOPP acrophase (the time where the fitted cosine reaches its peak) of emmetropia (22.6 hours) was later than that of myopia (21.44 hours).[23] However, the actual association between MOPP and myopia in school-age children of all refractive states is unknown.

In this study, we aimed to report the distribution of MOPP and its associated factors in a sample of grade 1 and grade 7 students in China.

Methods

Study Population

The Anyang Childhood Eye Study (ACES) is a population-based cohort study designed to report the prevalence, incidence, and progression of myopia among Chinese students in urban Anyang City, Henan Province, Central China. Details of the methodology have been reported.[24] In this study, a total of 3048 grade 1 students (response rate 97.94%) and 2258 grade 7 students (response rate 95.56%) completed ophthalmologic examinations. The ACES complied with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University. Oral consent was obtained from each student and informed written consent was obtained from at least one parent. During or after data collection, we obtained the information identifying individual participants.

Procedures

Height and weight were measured using an automatic and professional integrated set.[24] From these objectively assessed values, body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared (kg/m^2). SBP and DBP were measured with a digital automatic sphygmomanometer (HEM-907; Omron, Kyoto, Japan). The IOP of each subject was measured using a non-contact tonometer (Havitz, HNT-7000). MOPP was calculated as 2/3 × (DBP + 1/3[SBP − DBP]) - IOP.[25] Ocular biometric parameters were measured with IOL Master (Carl Zeiss, Meditec AG Jena, Germany) and averaged with five measurements. Cycloplegia was performed with 2 drops of 1% cyclopentolate (Alcon) and one drop of tropicamide (Mydrin P; Santen, Osaka, Japan) at 5-minute intervals. Thirty minutes after the last drop, the third drop of cyclopentolate was administered if the pupillary light reflex was still present or pupil size was <6.0 mm. An autorefractor (HRK-7000A; HUVITZ, South Korea) was used to measure the children's refractive error after cycloplegia. Autorefraction was performed three times and the average was used for analyses. Refraction was defined as the spherical equivalent refractive error (sphere power + cylinder power/2). According to the cycloplegic spherical equivalent (SE), children were categorized into two groups, the myopic group (SE ≤ -0.5 diopters [D]) and the non-myopic group (SE > -0.5 D).

Data on the number of myopic parents, time spent on near work (hours per week), outdoors (hours per week), sleeping, and whether headache during near work was obtained using questionnaires that have been published elsewhere.[24]

Statistical Analysis

Due to the high correlation of MOPP between left and right eyes (Pearson correlation coefficient $r = 0.92$ in grade 1, and $r = 0.94$ in grade 7), only right eyes were included for data analyses. All analyses were performed using SAS software (version 9.1.3; SAS Institute, Inc., Cary, NC, USA). Data were presented as mean ± SD or percentages. Independent *t*-test was used to compare normally continuous data, and the chi-square test was used for the categorized data.

Table 1. Baseline Characteristics of Grade 1 and Grade 7 Children

	Grade 1 ($n = 3048$)	Grade 7 ($n = 2258$)	*P* Value
Age, y	7.16 ± 0.40	12.69 ± 0.48	<0.01
Gender, girls (%)	1335 (43.80)	1148 (50.84)	<0.01
Body mass index, kg/m^2	16.06 ± 2.40	21.60 ± 56.79	<0.01
Systolic blood pressure, mm Hg	97.14 ± 10.20	105.59 ± 11.63	<0.01
Diastolic blood pressure, mm Hg	58.02 ± 9.25	66.02 ± 9.71	<0.01
Intraocular pressure, mm Hg	13.54 ± 3.07	15.85 ± 3.47	<0.01
Mean arterial pressure, mm Hg	71.06 ± 8.93	79.21 ± 9.37	<0.01
Mean ocular perfusion pressure, mm Hg	33.83 ± 6.37	36.99 ± 6.80	<0.01
Boys	33.39 ± 6.40	37.61 ± 7.03	<0.01
Girls	34.15 ± 6.28	36.35 ± 6.50	<0.01
Central corneal thickness, µm	540.30 ± 30.97	549.26 ± 33.13	<0.01
Anterior chamber depth, mm	2.89 ± 0.24	3.64 ± 0.27	<0.01
Axial length, mm	22.72 ± 0.76	24.41 ± 1.13	<0.01
Cycloplegic spherical equivalent, D	0.94 ± 1.05	−1.55 ± 2.06	<0.01
Time spent on near work, h/wk	12.85 ± 7.43	25.74 ± 14.01	<0.01
Time spent outdoors, h/wk	6.80 ± 6.04	15.45 ± 12.94	<0.01

Univariable analysis was performed to assess the associated factors for MOPP. Multivariable analysis was then performed using variables with *P* values less than 0.2 in univariable analysis or biological rationality. Any $P < 0.05$ was considered statistically significant. Because MOPP was significantly associated with gender in all children ($P < 0.01$), analyses were stratified by gender. SBP, DBP, and IOP measurements were not individually analyzed further because the MOPP was derived from these three variables.

Results

Data were available for 2740 grade 1 students (88.05%) and 1993 grade 7 students (84.34%) examined. The mean age of grade 1 and 7 students was 7.16 and 12.69 years. Compared with grade 1, grade 7 students had a higher BMI, SBP, DBP, mean arterial pressure, thicker central cornea thickness (CCT), deeper anterior chamber, longer axial length, more myopia, and more time spent on near work (Table 1).

MOPP was 33.83 ± 6.37 mm Hg in grade 1, and lower than 36.99 ± 6.80 mm Hg in grade 7 ($P < 0.01$) (Table 1). In grade 1 (Fig. 1A), the MOPP of non-myopic eyes (33.88 ± 6.29 mm Hg) was higher than myopic eyes (33.12 ± 7.03 mm Hg), whereas the difference was not significant ($P = 0.12$). In grade 7 (Fig. 1B), non-myopic eyes were shown to have higher MOPP than myopic eyes (37.72 ± 6.72 mm Hg versus 36.58 ± 6.57 mm Hg, $P < 0.001$), as well as in boys (38.09 ± 6.71 mm Hg versus 37.17 ± 6.77 mm Hg, $P = 0.04$) and girls (37.22 ± 6.70 mm Hg versus 36.08 ± 6.36 mm Hg, $P = 0.02$).

In grade 1, girls had higher MOPP than boys (34.15 ± 6.28 mm Hg versus 33.39 ± 6.40 mm Hg, $P = 0.002$). On the contrary, boys had significantly higher MOPP than girls in grade 7 (37.61 ± 7.03 mm Hg versus 36.35 ± 6.50 mm Hg, $P < 0.001$; Fig. 2). Changes in BMI were consistent with MOPP. In grade 1, girls had significantly higher BMI than boys (16.26 ± 2.47 kg/m^2 vs. 15.81 ± 2.28 kg/m^2, $P < 0.001$), reversed in grade 7 (19.35 ± 3.32 kg/m^2 vs. 20.26 ± 5.16 kg/m^2, $P < 0.001$; Fig. 3).

Table 2 shows the results of univariable and multivariable analyses of two grades. In multivariable analysis in grade 1, MOPP was higher with female gender ($\beta = 0.08$, $P < 0.001$), less time spent on near work ($\beta = -0.05$, $P = 0.02$), and thinner CCT ($\beta = -0.19$, $P < 0.001$). In grade 7, MOPP was higher with male gender ($\beta = -0.06$, $P = 0.04$), less time spent on near work ($\beta = -0.10$, $P < 0.001$), and dominant eye ($\beta = 0.08$, $P = 0.01$). Table 3 shows the results of multivariable analysis combining the 2 groups of children and stratifying them by gender. In all children, MOPP was higher with less time spent on near work ($\beta = -0.08$, $P < 0.001$), more time spent on sleeping ($\beta = 0.03$, $P = 0.04$), less myopia ($\beta = 0.08$, $P < 0.001$), thinner CCT ($\beta = -0.11$, $P < 0.001$), and higher BMI ($\beta = 1.73$, $P < 0.001$).

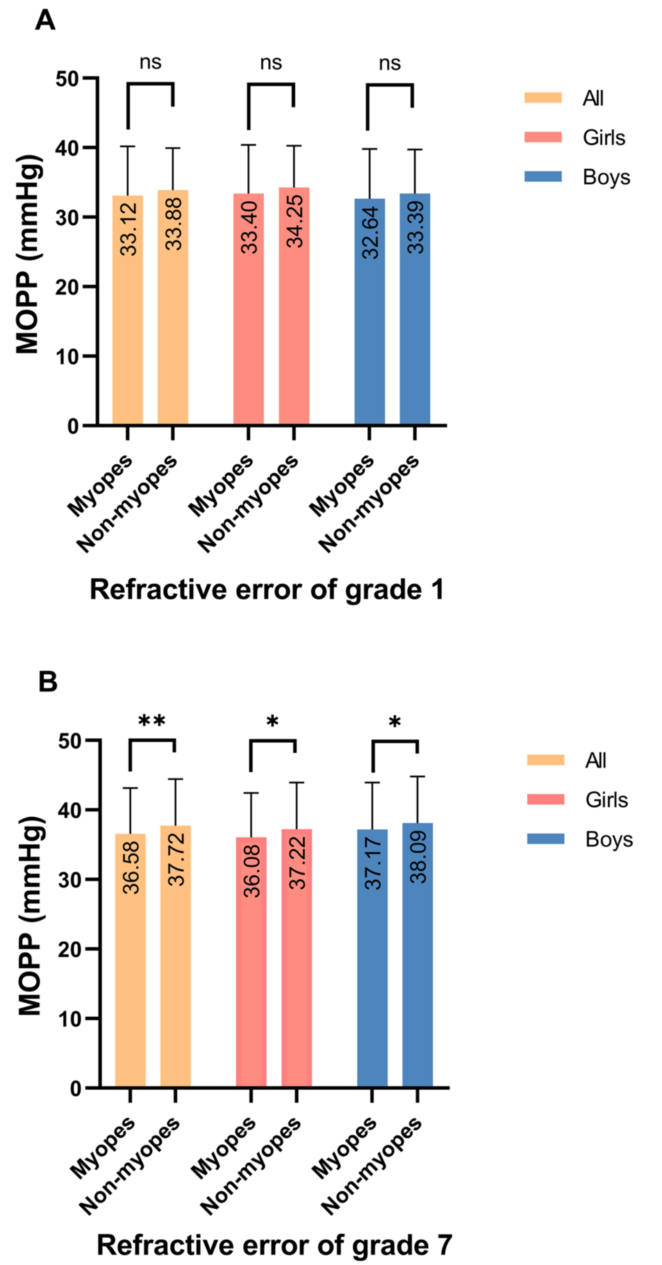

Figure 1. Mean Ocular Perfusion Pressure (MOPP) Stratified by Gender and Refractive Error in Grade 1 (A) and Grade 7 (B) Children. There was no significant difference in MOPP between myopic and non-myopic eyes in grade 1 (**A**). In grade 7 (**B**), non-myopic eyes had significantly higher MOPP than myopic eyes, consistent with the results in grade 7 boys and girls. $^{*}P < 0.05$, $^{**}P < 0.001$.

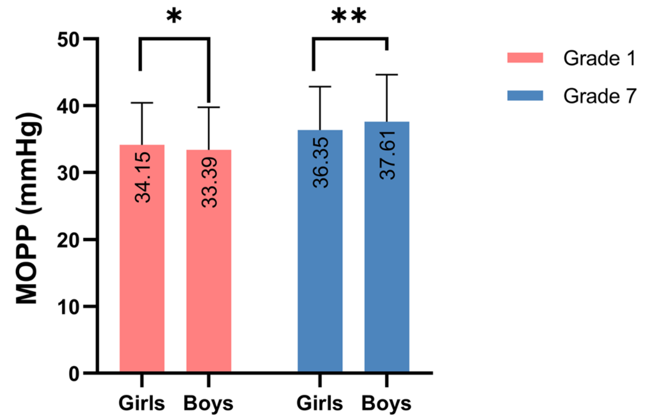

Figure 2. Mean Ocular Perfusion Pressure (MOPP) Stratified by Gender in Grade 1 and Grade 7 Children. In grade 1, girls had significantly higher MOPP than boys. Contrary to the findings of grade 1, in grade 7, boys had significantly higher MOPP than girls. $^{*}P < 0.05$, $^{**}P < 0.001$.

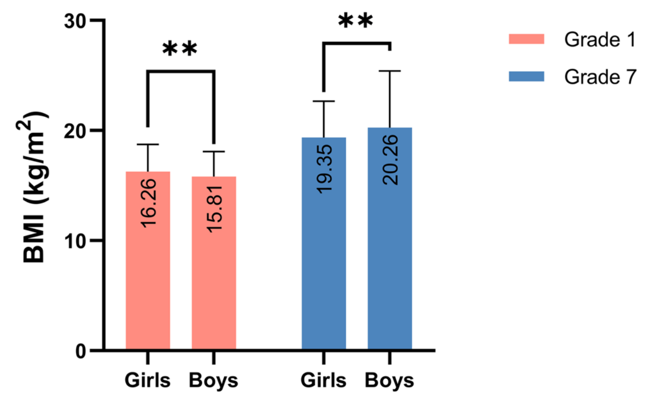

Figure 3. Body Mass Index (BMI) Stratified by Gender in Grade 1 and Grade 7 Children. In grade 1, girls had significantly higher BMI than boys. Contrary to grade 1, in grade 7, boys had significantly higher BMI than girls. $^{**}P < 0.001$.

Discussion

In our study, we found that non-myopic eyes had higher MOPP compared with myopic eyes in grade 7. Multivariable analysis revealed that higher MOPP was associated with less myopia, higher BMI, thinner CCT, less time on near work, and more time on sleeping.

As our study showed, non-myopic eyes had higher MOPP in both grade 7 ($P < 0.001$) and grade 1 ($P = 0.12$), but this difference was not statistically significant in grade 1. On the one hand, the sample size of the myopic group (184 children) was smaller than that of the non-myopic group (2556 children) in grade 1. We deduce that the imbalance of the sample size between the myopic group and the non-myopic group in grade 1 partially contributed to the insignificant difference in MOPP. On the other hand, with growth and development, the biological characteristics of individuals differ gradually. Some studies showed that IOP decreased with age, and blood pressure has been shown to increase with age.[26–28] We speculate that due to the discussion above, the difference in MOPP

Table 2. Association of Mean Ocular Perfusion Pressure on Univariable and Multivariable Analyses in Grade 1 and Grade 7 Children

	Grade 1				Grade 7			
	Univariable		Multivariable		Univariable		Multivariable	
Parameters	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
General parameters								
Age	0.03	0.11	−0.01	0.61	0.05	0.04	0.03	0.23
Gender*	0.06	0.002	0.08	<0.001	−0.09	<0.001	−0.06	0.04
Body mass index	0.29	0.001	−0.10	0.62	0.02	0.29	0.17	0.80
Number of myopic parents†	−0.01	0.58			−0.04	0.07	−0.03	0.23
Time spent on near work	−0.03	0.13	−0.05	0.02	−0.06	0.01	−0.10	<0.001
Time spent outdoors	−0.01	0.73			0.02	0.38		
Time spent sleeping	0.04	0.07	0.03	0.16	0.04	0.09	0.04	0.18
Headache during near work‡	0.01	0.61			−0.02	0.48		
Ocular parameters								
Central corneal thickness	−0.16	<0.001	−0.19	<0.001	−0.02	0.31		
Spherical equivalent	0.03	0.09	0.03	0.19	0.07	0.004	0.07	0.02
Axial length	0.01	0.81			−0.02	0.49		
Anterior chamber depth	0.02	0.31			−0.01	0.69		
Anterior corneal curvature	−0.003	0.89			0.04	0.08	−0.03	0.31
Posterior corneal curvature	−0.01	0.53			0.03	0.22		
Dominant eye	−0.01	0.63			0.05	0.04	0.08	0.01

*Boys as reference.
†0 as reference.
‡Answer "no" as reference.

between the myopic group and the non-myopic group was not statistically significant in grade 1.

Previous studies have shown possible links between MOPP and refractive error. Yang et al. found that in myopic Chinese adults, with the increasing myopic refraction, the MOPP decreased by 0.385 mm Hg/D.[22] Burfield et al. reported that the MOPP acrophase of subjects with emmetropia (22.6 hours) was later than those with myopia (21.44 hours).[23] We found that non-myopic eyes had higher MOPP than myopic eyes in grade 7 and MOPP was associated with less myopia, the findings reported here contribute to the current understanding of the involvement of the MOPP in myopia progression. The role of MOPP on myopia development may be related to the effect of MOPP on choroidal blood circulation. Studies have shown that hypoxia caused by the reduced choroidal blood flow triggered the activation of the HIF-1α signaling pathway.[29] The procedure led to the transdifferentiation of fibroblasts into myofibroblasts expressing low levels of type I collagen. As the mammalian sclera's elasticity increased, the posterior segment of the eye grew.[29,30] Increasing the choroidal blood perfusion would reduce scleral hypoxia and slow down ECM remodeling.[31] During recovery from form deprivation myopia, an increase of choroidal blood perfusion triggered the thickening of the choroid and conduced the retina to shift toward the new focal plane.[32] This suggested that the choroid thickened through increasing blood perfusion, which may help in regulating eye growth and the recovery of myopia. Considering the highly vascular nature of the choroid, MOPP may be a significant factor associated with choroidal blood flow and choroid thickness. Therefore, MOPP may potentially be an indicator of myopia development. The association between MOPP and myopia development still needs further study.

Interestingly, we found that lower MOPP was associated with more time on near work. The result matched those observed in earlier studies that near work significantly reduced the choroidal blood perfusion and choroidal thickness.[6,33] Given the fact that the choroid is primarily a vascular structure, variations in choroidal thickness might be mainly caused by changes in choroidal blood flow.[34] In our previous study, the close reading distance was significantly associated with

Table 3. Association of Mean Ocular Perfusion Pressure on Multivariable Analysis Combining Grade 1 and Grade 7 Children and Separating by Gender

	Overall		Boys		Girls	
Parameters	β	*P* Value	β	*P* Value	β	*P* Value
Age	−0.004	0.97	−0.18	0.29	−0.07	0.62
Grade*	−0.11	0.32	0.20	0.23	−0.28	0.05
Gender†	0.02	0.26				
Time spent on near work	−0.08	<0.001	−0.07	0.02	−0.10	<0.001
Time spent on sleeping	0.03	0.04	0.07	0.002	−0.002	0.93
Spherical equivalent	0.08	<0.001	0.09	0.01	0.06	0.03
Dominant eye	0.03	0.10	0.03	0.23	0.02	0.28
Central corneal thickness	−0.11	<0.001	−0.13	<0.001	−0.10	<0.001
Body mass index	1.73	<0.001	1.70	0.001	0.84	<0.001
Headache‡	−0.02	0.25	−0.03	0.29	−0.02	0.39

*Boys as reference.
†Grade 1 as reference.
‡Answer "no" as reference.

myopia in 12-year-old Chinese children.[35] The progression of myopia might be due to the decrease of choroidal blood flow led by lower MOPP. Thus, visual stimuli, such as near work, might lead to the hypoxia of the scleral microenvironment by regulating choroid blood flow and then lead to the occurrence of ECM remodeling and myopia.[3,6,36,37]

In the present study, we found that higher MOPP was associated with a longer time on sleeping. It is possible that the higher educational intensity would result in more near work and consequently lead to shorter sleep duration.[38] Such association between MOPP and sleep duration could be confounded by more time on near work. Some studies also found that decreased sleep duration and quality were associated with more myopia.[38–40] Whether sleep duration affects MOPP and, in turn, affects myopia needs to be further explored.

Our results showed that higher MOPP was associated with higher BMI. Cakmak et al. found that MOPP increased significantly with BMI in healthy adults ≥ 40 years of age.[25] Rajalakshmi et al. also found that the MOPP was higher in both men and women in the obese group than in the non-obese group (18 to 19-year-old healthy young adults).[41] A growing body of evidence demonstrated that persons with higher BMI were less myopic.[42,43] Therefore, BMI might affect the refractive error by MOPP.

In addition, girls in grade 1 had higher MOPP than boys, which was reversed in grade 7. Researchers reported that the MOPP value of diabetic retinopathy in male patients was higher than that in female patients.[44,45] However, in a study based on the Indian population, Raman et al. reported that women with type 2 diabetes mellitus had higher MOPP than men.[44] As mentioned above, the association between BMI and MOPP could explain those findings.

In line with previous studies, we showed that the MOPP of grade 7 subjects was higher than that of grade 1 subjects in our study. Kida et al. compared the older (50 to 80 years) and younger groups (20 to 25 years) and found that the nocturnal MOPP was statistically higher in the older group ($P = 0.031$).[46] In the Singapore Malay Eye Study, which enrolled subjects aged 40 to 80 years, they found that MOPP increased with age, which was consistent with our study.[47] Because MOPP is a derived measurement, the age-related changes in IOP and blood pressure may contribute to the relationship between age and MOPP. IOP was found to correlate negatively with age in Chinese university students and European women.[26,27] The Beijing Eye Study reported that the IOP increased up to age 60 to 64 years and decreased thereafter to age 75 years,[48] although there was no identifiable relationship between IOP and age in the EPIC-Norfolk Eye Study.[49] As for blood pressure, both SBP and DBP increase with age.[28] Because conclusions on the relationship of IOP with age are still inconsistent, it seems that we cannot simply explain the difference of MOPP in the two age stages from age-related changes in IOP and blood pressure. In addition, there was no significant relationship between MOPP and age in our multivariable regression analysis, and we speculated that it was caused by the fact that we enrolled students of two grades with two discontinuous age stages.

The strengths of this study are its large sample size, cycloplegic autorefraction, and high participation rate. However, it also suffers from some limitations. First, the two groups of students covered two different age ranges, limiting the extrapolation of the effect of age on MOPP. Second, considering the non-contact tonometer is quick and convenient to use on children, we used a non-contact tonometer rather than the Goldmann tonometer to measure IOP, which may lead to a higher reading of IOP. Whereas the higher reading of IOP existed in both of the myopic group and the non-myopic group, it may have little effect on the difference of MOPP between the myopic group and the non-myopic group. In addition, studies have shown that the IOP measured by noncontact tonometer and Goldmann applanation tonometer among Chinese participants showed no statistical difference.[50] Third, MOPP in the supine position could not be obtained because IOP, SBP, and DBP were not measured in the supine position. It prevented us from further exploring the effect of postural changes on MOPP. Improvements to these deficiencies should be considered in subsequent studies.

In summary, our study revealed that non-myopic eyes had higher MOPP than myopic eyes in children in grade 7. In addition, the multivariable analysis showed that higher MOPP was associated with less myopia, thinner CCT, higher BMI, less time on near work, and more time on sleeping. More extensive studies with longer follow-up may help validate the causal associations of MOPP with myopia in children.

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