

Association study of the serum 25(OH)D concentration and myopia in Chinese children

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Abstract

To analyze the serum 25 hydroxyvitamin D (25[OH]D) concentration in Chinese children with myopia and explore its correlation with myopia.

From July to September in 2019, myopic children were collected from the Myopia Influencing Factors Survey Project. The basic information and vision related behaviors of the subjects were collected by questionnaire. The diopter of the children without dilated pupils was measured by the computerized refractometer. Meanwhile, 5 ml fasting venous blood samples were collected for the determination of serum 25(OH)D concentration.

A total of 186 children were included in this study, including 90 males and 96 females, with an average age of 8 ± 3.26 years. The detection rate of serum 25(OH)D deficiency in myopic children was 65.59% (122/186). There was statistical significance in the detection rate of serum 25(OH)D deficiency in children with different myopic degrees ($\chi^2 = 6.635$, $P = .010$). The average serum 25(OH)D concentration in myopic children was 14.86 (10.67–18.96) ng/ml, and the difference of serum 25(OH)D concentration in children with different myopia degrees was statistically significant ($Z = 20.23$, $P < .001$). Logistic regression analysis showed that after controlling for gender, parental myopia, after-school class, and outdoor activities, the prevalence of developing moderate and high myopia was 2.051 times (95% confidence interval: 1.272–3.724) higher in the serum 25(OH)D deficiency group than in the serum 25(OH)D sufficiency group. There is a positive correlation between serum 25(OH)D concentration and the equivalent spherical degree of myopic children.

The study found that serum 25(OH)D concentration is closely related to the prevalence of myopia in Chinese children. The results further support the conclusion that children with a higher level of serum 25(OH)D have a lower prevalence of moderate to high myopia. The results of this study provide a basis for further research into the relationship between vitamin D and visual development in children and its mechanisms.

Abbreviations: 25(OH)D = 25 hydroxyvitamin D, 95% CI = 95% confidence interval, SE = spherical degree.

Keywords: children, myopia, vitamin D

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Myopia is a common eye condition that causes visual impairment and affects an estimated 1.6 billion people worldwide.^[1] There were an estimated 1.4 billion people with myopia (22.9% of the world population) and 163 million people with high myopia (2.7% of the world population) in 2000. By 2050, it is predicted that there will be 4.758 billion people with high myopia (49.8% of the world population) and 938 million people with high myopia (9.8% of the world population).^[2] The prevalence of myopia varies greatly among different regions and ethnicities. For example, the prevalence of myopia in East Asian population is twice as high as that in white population of the same age.^[3] Nevertheless, the prevalence of myopia in different regions and countries shows an increasing trend, especially among young people in East Asia.^[4–6] Blurred vision caused by mild myopia can be corrected with glasses, contact lenses or laser refractive surgery. However, people with high myopia (greater than -6.0 diopter (D)) is prone to a variety of complications, such as retinal detachment, retinal degenerative changes and choroidoid neovascularization, which can lead to irreversible visual impairment and increase the risk of blindness.^[7,8]

Pathological causes of myopia are complex and varied, and it is generally believed that gene and environmental factors play a crucial role in the occurrence and development of myopia.^[9] In

recent years, more and more epidemiological studies have shown that near work and less time spent in outdoor activities are closely related to the occurrence and progress of myopia, but the specific mechanism has not been fully clarified.^[10-13] Some researchers hypothesize that sunlight exposure in outdoor activities promotes the release of dopamine in the retina, thereby inhibiting axial lengthening.^[14] Another hypothesis is that outdoor ultraviolet exposure leads to increased production of vitamin D, which directly protects the occurrence and development of myopia. This hypothesis has been confirmed by most studies, but the results are not uniform.^[15,16]

It is also possible that the association between vitamin D levels and myopia observed in cross-sectional studies is based on time spent outdoors, with more exposure to sunlight and higher blood vitamin D levels. Therefore, vitamin D may be a confounding factor in the association between time spent in outdoor activities and myopia. Therefore, whether vitamin D is directly involved in myopia development or merely as a biomarker of time spent in outdoor activities urgently needs to be verified. Mutti etc. put forward for the first time in a small study of serum vitamin D levels directly associated with the risk of myopia, after adjustment for age and dietary intake.^[17] The study provides preliminary evidence for a possible direct link between vitamin D and myopia, but due to the small sample size, it is inconclusive. The association between serum vitamin D levels and myopia was then analyzed in a large sample size study. The results of the Korean National Health and Nutrition Survey on the concentration of 25 hydroxyvitamin D (25(OH)D) in serum and myopia of 2 038 Korean adolescents aged 13 to 18 years showed that the diopter of myopia group was correlated with the concentration of 25 (OH)D in serum after adjusting for place of residence, parental income, total energy intake, dietary calcium intake, milk consumption, and smoking experience.^[18] However, the study had some limitations in that it did not consider the effects of time spent outdoors and sun exposure, which have been shown to influence myopia development and changes in 25(OH)D levels.

Although these findings all support the protective effect of 25 (OH)D on myopia, the current evidence on the association between myopia and 25(OH)D is observational, and it is not clear whether 25(OH)D acts directly on the development of myopia or merely acts as an intermediate product of outdoor activities. In addition, the biological mechanism of 25(OH)D on the occurrence and development of myopia is still in the theoretical hypothesis stage, lack of animal experimental support. In this study, a visual acuity survey was conducted in children and serum 25(OH)D concentration was detected to analyze the correlation between serum 25(OH)D concentration and myopia. To explore whether high serum 25(OH)D concentration is a protective factor for myopia in children, and to provide evidence for the etiology of myopia and the formulation of preventive and control measures. If higher serum 25(OH)D levels are effective in reducing the prevalence of myopia, it may provide a basis for myopia intervention based on dietary intake.

2. Materials and methods

2.1. Study design and subjects

We compared the factors of the myopia prevalence in a cross-sectional study of children with myopia stratified according to different myopia degrees. Children with myopia who collected

from the Myopia Influencing Factors Survey Project from July to September 2019. Inclusion criteria for subjects were:

- (1) Equivalent spherical degree (SE) $\leq -0.5D$;
- (2) Children attending primary school or below;
- (3) No other eye diseases;
- (4) According to informed consent, children or their parents are willing to participate in this study.

Relevant social demographic characteristics and vision related behaviors of the subjects were collected through questionnaire survey. Visual examination was performed by using computerized optometry. Total of 5 ml serum samples of the subjects were collected for determination of serum 25(OH)D concentration. Written informed consent was obtained from every participant.

2.2. Ethics

Our study was conducted according to the tenets of the Declaration of Helsinki. Ethics approval was received from the committee of the Zhoushan center for disease control and prevention (ZSCDC2020001).

2.3. Questionnaire and Vision detection

Questionnaires were used to collect general demographic information and behavioral factors related to vision of the subjects, including gender, age, myopia of parents, tutorial class, outdoor activities. The undilated diopter of the students' eyes was measured by a professional optometrist using a computerized optometrist. Calculate the equivalent spherical degree (SE) from the diopter measurement, which is the number of spherical degree plus half of the column degree. According to the national uniform standard of refractive status in flexion optics group, myopia was defined as naked visual acuity < 5.0 in any eye and SE of computerized optometry $< -0.50D$ in without dilated pupils. The myopia standard was set as SE $\leq -0.5D$, in which $-3.0D < SE \leq -0.5D$ was considered mild myopia, $-0.6D < SE \leq -3.0D$ was considered moderate myopia, and SE $\leq -6.0D$ was considered high myopia.

2.4. Determination of serum 25(OH)D concentration

Before the blood sample collection, the subjects were required to fast for 12 to 14 hours, and 5 ml of fasting peripheral venous blood was collected from the elbow vein of the subjects by the examiner at 7 to 9. am in the morning of the next day using non-anticoagulant vacuum sampling vessel. On the day of blood collection, the blood sample was centrifuged at a speed of 3500 RPM for 15 minutes, and the upper serum was absorbed and put into a 300 microliter cryopreserved tube. In this study, the concentration of serum 25(OH)D was determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), which is currently the internationally recognized gold standard for the determination of serum 25(OH)D. Serum 25(OH)D concentration $> 20ng/ml$ was defined as vitamin D sufficient.

2.5. The Universe and power

Since only one hospital was included in the study, we should be cautious when extrapolating the results to the whole population. Statistical power was calculated using the Power and Sample Size

Calculation Software (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>), with 2 independent proportions.

2.6. Statistical analysis

EpiData 3.0 software was used to establish the database, and the questionnaire and visual acuity data were recorded. Serum 25(OH)D concentration was non-normally distributed, expressed as P50 (P25~P75). The Mann-Whitney U rank sum test was used to compare the difference of serum 25(OH)D concentration among different genders, different myopia degree and whether there were extracurricular tutoring classes. Kruskal-Wallis test with k independent samples was used to compare serum 25(OH)D concentrations between different time outdoors, different Parental myopia status. Enumeration data were expressed as percentage, and the chi-square test was used for comparison between groups. The odd ratio value and 95% confidence interval (95% CI) of the group with serum 25(OH)D deficiency were evaluated by multivariate Logistic regression model. Since there was a high correlation between the right eye SE and the left eye SE ($r=0.94$, $P<.01$), we randomly select one visual data between the left and the right eye, and finally the visual acuity data of the right eye was used in the analysis of this study. The correlation between serum 25(OH)D concentration and SE was evaluated by multiple linear regression. Statistical analysis was performed using SPSS 25.0 statistical analysis software package. P -values $<.05$ were considered to be significant.

3. Results

3.1. General information about the subjects

A total of 186 children who met the criteria were included in this study, including 90 males and 96 females. The age range was 6 to 12 years old, with an average age of 8 ± 3.26 years old. There were 92 patients (49.46%) with mild myopia, 87 patients (46.77%) with moderate myopia, and 7 patients (3.76%) with high myopia.

3.2. Serum 25(OH)D concentration in myopic children

In this study, group sample sizes of 92 in group of mild myopia and 94 in group of moderate and high myopia achieve 84.12%

power to detect a difference between the group proportions assuming an alpha value of 0.15. The serum 25(OH)D deficiency rate was 65.59% (122/186) in children with myopia, 56.52% (52/92) in children with mild myopia, and 74.47% (70/94) in children with moderate and high myopia. The difference of serum 25(OH)D deficiency rate in children with different myopia levels was statistically significant ($\chi^2=6.635$, $P=.010$). The mean serum 25(OH)D concentration was 14.86 (10.67–16.96) ng/ml in myopic children, 14.72 (11.30–17.23) ng/ml in mild myopic children, and 11.44 (9.76–14.76) ng/ml in moderate and high myopic children. The difference of serum 25(OH)D concentration in children with different myopic degrees was statistically significant ($z=20.233$, $P<.001$). The comparisons of serum 25(OH)D concentration in children with different demographic characteristics are shown in Table 1.

3.3. Correlation between serum 25(OH)D and myopia in children

In different degree of myopia as dependent variables (0=mild myopia, 1=moderate and high myopia), serum 25(OH)D group as the independent variable (as reference by normal group), adjustment of gender, parental myopia, extracurricular classes, outdoor activities, using Logistic regression model to evaluate the serum 25(OH)D different group produces myopia odd ratio value and 95% CI. Logistic regression analysis showed that after controlling for relevant factors, the prevalence of moderate and high myopia in children with serum 25(OH)D deficiency was 2.051 times (95% CI: 1.272–3.724) higher than that in children with serum 25(OH)D sufficiency. The details are shown in Table 2.

3.4. Correlation between serum 25(OH)D and SE in myopic children

The association between serum 25(OH)D concentration and equivalent spherical degree was analyzed using multiple linear regression. After adjusting for age and sex, the equivalent spherical degree was positively correlated with serum 25(OH)D concentration ($\beta=0.14$, $P<.05$) in myopic children. After adjusting for age, gender, parental myopia, extracurricular classes, and outdoor activity time, the equivalent spherical degree

Table 1
Comparison of serum 25(OH)D concentrations in myopic children with different demographic characteristics.

Characteristics	Samples	25(OH)D	Z/ χ^2	P-value	
Myopia degree	Mild	92	14.72 (11.30-17.23)	20.233 ^a	<.001
	Medium and high	94	11.44 (9.76-14.76)		
Gender	Male	90	15.06 (11.76-18.76)	28.451 ^a	<.001
	Female	96	12.13 (10.87-14.95)		
Parental myopia	No myopic parents	140	14.25 (10.35–17.49)	3.282 ^b	.194
	One myopic parent	34	14.20 (10.30–16.68)		
	Both parents myopic	12	13.56 (11.65–16.54)		
Tutorial class	No	134	14.52 (11.76–17.90)	3.383 ^a	.185
	Yes	52	14.13 (11.13–17.54)		
Time outdoors*	Low	34	14.12 (11.01–17.07)	9.05 ^b	.011
	Moderate	92	14.28 (11.24–18.06)		
	High	60	15.46 (12.23–18.10)		

* Tertile ranges of 90r time spent outdoors per day are as follows: low (0–2 hours), moderate (2–4 hours), and high (>4 hours).

^a Mann-Whitney U rank sum test with Z-value.

^b Kruskal-Wallis test with χ^2 value.

Table 2
Logistic regression analysis of serum 25(OH)D concentration and myopia in Chinese children.

Characteristics		β	S x	Wald χ^2	P-value	OR (95%CI)
25(OH)D	Insufficient	0.745	0.180	17.124	<.001	2.051 (1.272–3.724)
	Sufficient	Ref.				
Parental myopia	Both are myopic	0.531	0.740	0.642	.424	1.300 (0.800–2.521)
	One myopic parent	0.587	0.291	0.290	.589	1.100 (0.823–2.324)
	All are not myopic	Ref.				
Gender	Female	0.459	0.170	7.449	.004	1.611 (1.152–2.260)
	Male	Ref.				
Tutorial classes	Yes	0.189	0.211	0.802	.369	1.221 (0.801–1.749)
	No	Ref.				
Time outdoors*	Low	0.720	0.570	6.619	.023	2.049 (1.680–4.216)
	Moderate	0.250	0.179	3.784	.095	1.279 (0.500–3.039)
	High	Ref.				

OR = odd ratio.

* Tertile ranges for time spent outdoors per day are as follows: low (0–2 hours), moderate (2–4 hours), and high (>4 hours).

in myopic group was still positively correlated with the serum 25(OH)D concentration ($\beta=0.13$, $P<.05$) in myopic children. The results of multiple linear regression analysis of serum 25(OH)D concentration and the equivalent spherical degree in myopic children are shown in Table 3.

4. Discussion

The prevalence of myopia is rising globally, so identifying modifiable risk factors is important to control the development of myopia. In recent years, more and more attention has been paid to the correlation between vitamin D and myopia. Serum 25(OH)D concentration is the most commonly used index to evaluate human vitamin D status. In this study, the correlation between serum concentration of 25(OH)D and myopia was explored among 186 myopic children collected in the outpatient department. It was found that the level of serum 25(OH)D was relatively low and the deficiency rate of serum 25(OH)D was high in myopic children, and there were significant differences in the level of serum 25(OH)D in children with different myopic degrees. We also found that the serum concentration of 25(OH)D in boys was higher than that in girls and children who spend more time outdoors are higher than those who spend less time outdoors.

Evidence suggested that vitamin D deficiency is very common among Chinese children and adolescents. In a survey of adolescent females aged 12 to 14 in Beijing,^[19] the severe vitamin D deficiency was as high as 45.2% in winter. Another

study on 381 children aged 7 to 11 in Beijing showed that the detection rate of vitamin D deficiency in boys was 60.1%, and that in girls was 68.5%.^[20] The main source of vitamin D in the body is known to be endogenous synthesis in the skin (through UV exposure), and vitamin D is found in very low levels in natural foods. Therefore, the lower serum 25(OH)D concentration in female children may be attributed to the fact that female students are more prone to indoor activities after school and have less exposure to sunlight than male students.

We also found that serum vitamin D levels in children were significantly negatively associated with the prevalence of high myopia. After adjusting for potential confounding factors such as gender, parental myopia, tutorial classes, and outdoor activities, the prevalence of myopia in children with serum 25(OH)D deficiency was 2.051 times higher than that in the control group. After adjusting for age and sex, there was a positive correlation between serum 25(OH)D concentration and equivalent spherical degree. This association persisted after adjusting for age, gender, parental myopia, tutorial classes, and outdoor activities.

The results of this study are supported by other studies. Shen et al^[21] detected serum 25(OH)D in 29 clinically collected myopic children, and found that the serum 25(OH)D level of myopic children was lower than that of children with normal vision. The serum 25(OH)D level may be related to the decrease of outdoor activity time, and there was a certain correlation between the serum 25(OH)D level and the ocular axis. Zeng et al found that serum 25(OH)D concentration was closely related to myopia risk of primary and middle school students, and children and

Table 3
Multivariate regression analysis of the association between 25(OH)D and equivalent spherical degree (D) in Chinese children.

Characteristics	Model Ia			Model IIb		
	B	95% CI	P-value	B	95% CI	P-value
25(OH)D	0.14	0.11–0.17	.031	0.13	0.11–0.15	.023
Age	–0.32	–0.64–0.01	.053	–0.29	–0.55–0.03	.036
Gender	–0.23	–0.34–0.12	<.001	–0.34	–0.42–0.26	<.001
Parental myopia				0.19	0.01–0.39	.050
Tutorial classes				–0.05	–0.32–0.21	.684
Time outdoors*				–0.61	–0.83–0.398	<.001

95% CI = 95% confidence interval.

* Tertile ranges for time spent outdoors per day are as follows: low (0–2 hours), moderate (2–4 hours), and high (>4 hours).

Adjustment of age and gender.

Adjustment of age, gender, parental myopia, tutorial classes, and time outdoors.

adolescents with higher serum 25(OH)D concentration had a lower risk of myopia.^[22] An Australian pregnancy cohort study also showed that people with vitamin D deficiency had a significantly higher incidence of myopia compared to those with adequate vitamin D.^[23] In South Korea,^[24] South Korea's adult health and nutrition survey analysis results, based on a 2010 to 2012, show that the prevalence of myopia gradually decreased in subjects with higher quartiles compared with subjects with lower serum 25(OH)D quartiles after adjustment for confounders. These data suggest that vitamin D plays a direct role in the development of myopia.

However, most of the current studies on the association between serum vitamin D and myopia are cross-sectional studies, and the evidence is relatively weak, and the mechanism of action remains unclear. There are 2 hypotheses about the mechanism of serum 25(OH)D in myopia in children. One hypothesis is that low 25(OH)D levels cause intracellular calcium changes that lead to impaired ciliary muscle contraction and relaxation, leading to the development of myopia.^[25] Another hypothesis is that 25(OH)D may be involved in the retinal scleral signaling pathway. Retinoic acid is thought to be 1 of the factors in retinal sclerosis signaling leading to eyeball lengthening, and retinoic acid may act on retinoic acid X receptor after heterodimerization of retinoic acid receptor and 25(OH)D receptor.^[26] In addition, gene-level studies have shown that the vitamin D receptor gene FOK1 (VDR, An intracellular hormone receptor) polymorphism is significantly associated with myopia in Asian populations.^[27] Case-control studies have shown that VDR at 12q13.11 and GC SNPs at 4q12–13 are closely associated with myopia in Caucasians.^[28]

The present study investigated the correlation between serum 25(OH)D concentration and myopia in children treated in the ophthalmology clinic of a hospital in Zhoushan. This study provides some hints for future research on serum 25(OH)D concentration and myopia in children, and also provides a basis for enriching related research. In addition, the confounding factors (such as gender, parental myopia, tutorial class and time outdoors) affecting myopia in children were collected comprehensively and accurately in this study, and the influence of various confounding factors on myopia in children was well controlled.

There are still the following limitations in this study. Firstly, this is a clinical-based study and the non-myopic children did not be included for analysis. Secondly, the subjects are all from the same hospital, so the population representation may be insufficient. Third, serum 25(OH)D concentration > 20ng/ml was defined as vitamin D sufficient, but some others think 20–30 is an insufficient level for 25(OH)D. Finally, the study did not measure variables that further supported vitamin D outcomes, such as serum parathyroid hormone levels or bone parameters. These limitations should be addressed in future studies.

5. Conclusions

In conclusion, the present study provides evidence for the correlation between serum 25(OH)D level and myopia in children, and there is a significant negative correlation between serum 25(OH)D level and myopia in children. In addition, the present study found a positive correlation between serum 25(OH)D concentration and the equivalent spherical degree of children, suggesting that high levels of serum vitamin D may be a protective factor for the vision of children. However, taking into

account inadequate adjustment for other potential confounders, the evidence for vitamin D as a causal factor is limited, and the study design was cross-sectional and further experimental studies on the therapeutic potential of vitamin D, such as randomized clinical trials, are needed in the future. If vitamin D supplementation can effectively reduce the prevalence of myopia, it will provide a basis for myopia intervention based on dietary intake. Adding vitamin D to the diet is simpler and more feasible than lifestyle-changing interventions such as increasing time spent outdoors. In addition, functional studies, polymorphism of vitamin D receptor genes, and intervention studies on the mechanism of low serum 25(OH)D concentration on scleral growth should also be conducted to explore how vitamin D plays a role in the development of myopia.

Author contributions

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References

- [1] Pan CW, Dirani M, Cheng CY, Wong TY, Saw SM. The age-specific prevalence of myopia in Asia: a meta-analysis. *Optom Vis Sci* 2015;92:258–66.
- [2] Holden BA, Frick TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123:1036–42.
- [3] Parssinen O, Lyyra AL. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Invest Ophthalmol Vis Sci* 1993;34:2794–802.
- [4] Lee JH, Jee D, Kwon JW, Lee WK. Prevalence and risk factors for myopia in a rural Korean population. *Invest Ophthalmol Vis Sci* 2013;54:5466–71.
- [5] Dong YH, Liu HB, Wang ZH, Xu RB, Yang ZG, Ma J. Prevalence of myopia and increase trend in children and adolescents aged 7–18 years in Han ethnic group in China, 2005–2014. *Zhonghua Liu Xing Bing Xue Za Zhi* 2017;38:583–7.
- [6] Lv L, Zhang Z. Pattern of myopia progression in Chinese medical students: a two-year follow-up study. *Graefes Arch Clin Exp Ophthalmol* 2013;251:163–8.
- [7] Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt* 2005;25:381–91.
- [8] Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology* 1999;106:2010–5.
- [9] Lyhne N, Sjolie AK, Kyvik KO, Green A. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20–45 year old twins. *Br J Ophthalmol* 2001;85:1470–6.
- [10] Goss DA. Nearwork and myopia. *Lancet* 2000;356:1456–7.
- [11] Hepser IF, Evereklioglu C, Bayramlar H. The effect of reading and nearwork on the development of myopia in emmetropic boys: a prospective, controlled, three-year follow-up study. *Vision Res* 2001;41:2511–20.
- [12] Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia. *Invest Ophthalmol Vis Sci* 2002;43:332–9.
- [13] Bayramlar H, Cekiç O, Hepser I. Does convergence, not accommodation, cause axial-length elongation at near? A biometric study in teens. *Ophthalmic Res* 1999;31:304–8.
- [14] Zhou X, Pardue MT, Iuvone PM, Qu J. Dopamine signaling and myopia development: what are the key challenges. *Prog Retin Eye Res* 2017;61:60–71.
- [15] Choi JA, Han K, Park Y-M, La TY. Low serum 25-hydroxyvitamin D is associated with myopia in Korean adolescents. *Invest Ophthalmol Vis Sci* 2014;55:2041–7.

- [16] Tideman JW, Polling JR, Voortman T, et al. Low serum vitamin D is associated with axial length and risk of myopia in young children. *Eur J Epidemiol* 2016;31:491–9.
- [17] Mutti DO. Blood levels of vitamin D in teens and young adults with myopia. *Optom Vis Sci* 2011;88:377–82.
- [18] Choi JA, Han K, Park YM, La TY. Low serum 25hydroxyvitamin D is associated with myopia in Korean adolescents. *Invest Ophthalmol Vis Sci* 2014;55:2041–7.
- [19] Fraser DR, Vitamin . Vitamin D deficiency and associated factors in adolescent girls in Beijing. *Am J Clin Nutr* 2001;74:494–500.
- [20] Zhao J, Zhang Q, Zhang HM, et al. Body vitamin D content and its relationship with body composition of children in Huairou district of Beijing. *Zhonghua Liu Xing Bing Xue Za Zhi* 2010;31:34–8.
- [21] Shen L, Yang CH. Study on serum vitamin D level in children with myopia. *Chin J Ophthalmol Otolaryngol* 2015;15:94–7.
- [22] Zeng HJ, Xu SJ, Tao FB. Research progress on the association between vitamin D and myopia. *Chinese Journal of School Health* 2018;39: 952–4.
- [23] Burriss HH, Van Marter LJ, McElrath TF, et al. Vitamin D status among preterm and fullterm infants at birth. *Pediatr Res* 2014;75:75–80.
- [24] Kwon JW. Serum 25-hydroxyvitamin D level is associated with myopia in the Korea national health and nutrition examination survey. *Medicine (Baltimore)* 2016;95:e5012.
- [25] Lepple-Wienhues A, Stahl F, Willner U, Schäfer R, Wiederholt M. Endothelin-evoked contractions in bovine ciliary muscle and trabecular meshwork: interaction with calcium, nifedipine and nickel. *Curr Eye Res* 1991;10:983–9.
- [26] Tavera-Mendoza L, Wang TT, Lallemand B, et al. Convergence of vitamin D and retinoic acid signalling at a common hormone response element. *EMBO Rep* 2006;7:180–5.
- [27] Annamaneni S, Bindu CH, Reddy KP, Vishnupriya S. Association of vitamin D receptor gene start codon (Fok1) polymorphism with high myopia. *Oman J Ophthalmol* 2011;4:57–62.
- [28] Mutti DO, Cooper ME, Dragan E, et al. Vitamin D receptor (VDR) and group-specific component (GC, vitamin D-binding protein) polymorphisms in myopia. *Invest Ophthalmol Vis Sci* 2011;52:3818–24.