Original Article

Association between serum 25-hydroxyvitamin D level and myopia in children and adolescents: a cross-sectional study

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Background: Prior reports have indicated an inconsistent relationship between vitamin D levels and myopia in children and adolescents with limited sample size. This study was undertaken to further clarify this relationship with a repeated cross-section study.

Methods: The National Health and Nutrition Examination Survey (NHANES) database with samples <19 years old was utilized. Data on rates of myopia (spherical equivalent less than or equal to −1.0 D), serum 25-hydroxyvitamin D [25(OH)D] level (high performance liquid chromatography), and other key variables were extracted and analyzed. Three models were utilized to evaluate the dose response of vitamin D levels using stepwise logistic regression. Logistic regressions for sex subgroups and other covariates were also performed, and Forest plots were drawn.

Results: Data were available from 6,814 children (49.5% girls; mean age: 14.9±1.85 years). The myopia and non-myopia differed in serum 25(OH)D level, gender, race, poverty income ratio (PIR), and body mass index (BMI). Serum 25(OH)D levels were negatively correlated with myopia [odds ratio (OR) =0.98, 95% confidence interval (CI): 0.77–0.99, P<0.05] regardless of sex. Although the relationship did not appear to be linear, there was a dose effect with higher serum 25(OH)D levels linked with lower rates of myopia. In addition, rates of myopia were increased in females compared with males (OR =1.12, 95% CI: 1.01–1.24, P=0.03), those with a high PIR (OR =1.08, 95% CI: 1.04–1.11, P<0.001), and those with high BMI (OR =1.19, 95% CI: 1.11–1.27, P<0.001). White ethnicity (OR =0.78, 95% CI: 0.68–0.90, P<0.001) and leisure-time exercise (OR =0.94, 95% CI: 0.92–0.97, P=0.02) were associated with lower rates of myopia.

Conclusions: These findings indicate that higher serum 25(OH)D levels and increased amounts of leisure-time exercise are associated with lower rates of myopia in this group of children and adolescents. Meanwhile, female gender, high PIR level, and high BMI were associated with greater rates of myopia. The findings indicated that children and adolescents needed leisure-time exercise to lower the risk of myopia.

Keywords: Vitamin D; 25-hydroxyvitamin D [25(OH)D]; myopia; National Health and Nutrition Examination Survey (NHANES)

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Introduction

Myopia is a multifactorial disease of vision that causes light rays from distant objects to concentrate in front of the retina (1,2). Myopia leads to impaired distant vision and is frequently linked with a steeper corneal curvature or a longer axial length. A recent systematic study of the reported incidence of myopia, that included 145 articles, indicated that by 2050, the global prevalence of myopia will have grown considerably, impacting over 5 billion individuals (3,4). Myopia negatively impacts quality of life, and a dependency on medical devices such as specs or contact lenses, can lead to major public health issues and has considerable economic consequences. High myopia exceeding −6.0 diopters (D) increase with vision-threatening eye illnesses such as glaucoma, macular degeneration, and retinal detachment (5,6).

Outdoor activities are linked to homeostasis in the body, particularly blood vitamin D levels. Vitamin D3 and vitamin D2 can be measured on serum samples (6). Vitamin D3 is the primary source of vitamin D in the body and is produced in the skin as a result of sun exposure (7). Blood levels of 25-hydroxyvitamin D [25(OH)D] is the standard marker of vitamin D status. Vitamin D not only regulates calcium levels but also possesses antioxidant and anti-inflammatory properties (8). Several human studies have reported that low vitamin D levels are associated with chronic inflammation (7-9). Vitamin D deficiency has also been linked to a number of eye illnesses, raising the possibility that it may be employed in therapy. Although time outside has been shown to reduce myopia risk (8), the exact biological mechanism underpinning the reported benefit of time outside on the development of myopia has not been thoroughly explored. Vitamin D is proposed to be a link between decreased outdoor time and an increased risk of myopia, and several studies have found that lower blood levels of 25(OH)D are associated with an increased risk of myopia (9). The association between 25(OH)D and myopia is still controversial, the aim of the current study was to further elucidate the relationship between serum 25(OH)D level and myopia in a large group of children and adolescents. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-617/rc).

Highlight box

Key findings

- Improving serum 25-hydroxyvitamin D [25(OH)D] and leisure-time exercise may reduce the risk of myopia in children and adolescents.

What is known and what is new?

- Previous research on the relationship between vitamin D and myopia in children and adolescents has yielded inconsistent findings.
- The results of measurement of vitamin D levels and survey data from a large population were utilized to further explore the association between vitamin D and myopia in children and adolescents.

What is the implication, and what should change now?

- High serum 25(OH)D and greater leisure-time exercise was associated with a lower risk of myopia in this group of children and adolescents. Meanwhile, female gender, high poverty income ratio level, and high body mass index were associated with increased risk of myopia.

Methods

The National Health and Nutrition Examination Survey (NHANES)

The NHANES is a research program in the United States aimed at measuring the nutritional status and health of adults and children (10-14). The NHANES database page on the Centers for Disease Control and Prevention (CDC)'s official website (www.CDC.gov/nchs/NHANES/) was accessed to extract the relevant datasets on 25(OH)D and myopia. The inclusion criteria were as below: (I) samples less than 19 years old, which is based on World Health Organization (WHO) definition; (II) samples with myopia screening; (III) samples with serum 25(OH)D detection; (IV) samples with eligible demographic, health status, social economic and lifestyle data. The exclusion criteria included: (I) participants who were not children or adolescents; (II) participants without myopia or serum 25(OH)D data; (III) participants without other eligible covariates. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Definition of myopia

Myopia was defined as a spherical equivalent (SE) less than or equal to −1.0 D in earlier NHANES refractive error investigations (9). The spherical + 1/2 column was used to determine the SE refractive error. After regularly used corrective lenses were removed, an Autorefractor ARK-

760 (Nidek Co. Ltd., Gamagori, Japan) was used to assess refractive error and the median of three objective measures (spherical, cylindrical, and ocular axis) in both eyes among participants.

Definition of serum 25(OH)D

The CDC quantifies 25-hydroxyvitamin D3 (25OHD3), 3-epi-25-hydroxyvitamin D3 (epi-25OHD3), and 25-hydroxyvitamin D2 (25OHD2) in human serum using high performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS). Typically, analytes are separated chromatographically on one of three pentafluorophenyl (PFP) columns among participants. The mobile phase composition varies somewhat between the three columns, but the methanol in water ranges from 69% to 72%. The solution given to the serum prior to extraction, the solution used for reconstitution, and the needle wash are required to all have the same composition as the mobile phase. Data on 25(OH)D were reported only for the 2001–2010 period, with the unit of measurement for 25(OH)D level being chosen to be nanograms per milliliter (ng/mL).

Covariates

To analyze the association between serum 25(OH)D and myopia in children and adolescents, data on a number of covariates was downloaded from the NHANES database between 2001 and 2008, including age, sex, race, education, body mass index (BMI), poverty income ratio (PIR), and leisure-time exercise.

Because NHANES sampling is weight-based and laboratory quality assurance and monitoring are assessed in mobile testing centers (MECs), 'wtmec4yr' was chosen as the analytic weight.

Statistical analysis

To analyze whether there was a dose-response relationship between serum 25(OH)D and myopia with different covariates, stepwise logistic regression was used. Three models were employed: model 1 = no adjustment; model 2 = model 1 plus sex, age (years, continuous), education (less than high school, high school graduate, more than high school), and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other); and model 3 = model 2 plus leisure-time exercise (minutes/week).

Based on this, the effects of each covariate on myopia levels were further analyzed by multifactor logistic regression, and a corresponding forest plot was produced. All the analysis above was conducted in R software 4.1.2 (The R Foundation for Statistical Computing, USA). Two-sided $P<0.05$ was considered statistically significant.

Results

Baseline difference analysis

Baseline data were analyzed in a subgroup control analysis of the selected population based on the presence or absence of myopia. The two groups differed in serum 25(OH)D level, gender, race, PIR, BMI, and leisure-time exercise but did not differ in terms of age or education (*Table 1*).

Association analysis between 25(OH)D and myopia

Using the quartile 1 (Q1) group as a reference, stepwise logistic regression was performed to analyze whether the risk of myopia changed with increasing 25(OH)D level in the Q2–Q4 groups (*Table 2*). In model 1, when only 25(OH)D level was used as the independent variable, there was a negatively correlated dose-response relationship between 25(OH)D and level myopia ($P<0.05$), and the odds ratio (OR) for Q4 was much lower than 1 [OR =0.78, 95% confidence interval (CI): 0.65–0.95], which implies that the higher the level of 25(OH)D, the lower the probability of developing myopia.

Model 2 was constructed after incorporating demographic data as covariates, and a negatively correlated dose-response relationship remained. Finally, model 3 demonstrated a negative correlation (OR =0.98, 95% CI: 0.77–0.99) between a high dose of 25(OH)D and myopia after leisure-time exercise was incorporated into the model, but there was no dose-response relationship (*Table 2*).

To further clarify the relationship between myopia and 25(OH)D, a gender subgroup analysis was undertaken. This showed that high serum 25(OH)D remained negatively correlated with the risk of myopia in males (OR =0.88, 95% CI: 0.6–0.99) and in females (OR =0.97, 95% CI: 0.68–0.99) (*Table 3*).

Forest plot of association between covariates and myopia

In addition to analyzing serum 25(OH)D level and the risk of myopia, the relationship between the included covariates and myopia was also analyzed (*Figure 1*). Females may

Table 1 Characteristics of included participants

Characteristics	No myopia (N=3,909)	Myopia (N=2,905)	P value
Vitamin D, ng/mL, mean ± SD	56.0±21.1	54.1±20.5	<0.001*
Age, years, mean ± SD	15.0±1.99	15.1±2.01	0.28
Gender, n (%)			0.043*
Male	2,017 (51.6)	1,426 (49.1)	
Female	1,892 (48.4)	1,479 (50.9)	
Ethnicity, n (%)			0.011*
Mexican American	1,146 (29.3)	910 (31.3)	
Other Hispanic	195 (4.99)	146 (5.03)	
Non-Hispanic white	1,177 (30.1)	774 (26.6)	
Non-Hispanic black	1,248 (31.9)	941 (32.4)	
Other race	143 (3.66)	134 (4.61)	
Education, n (%)			0.11
< High school graduate	3,630 (92.9)	2,659 (91.5)	
High school graduate	201 (5.14)	172 (5.9)	
> High school graduate	78 (2.00)	74 (2.5)	
PIR, mean ± SD	2.13±1.55	2.24±1.55	0.006*
BMI, kg/m^2, mean ± SD	23.3±5.65	24.3±6.36	<0.001*
LTPA, mins/week, mean ± SD	98.9±384	78.4±322	0.017*

*, statistically significant. SD, standard deviation; PIR, poverty income ratio; BMI, body mass index; LTPA, leisure time physical activity.

Table 2 Association between serum 25-hydroxyvitamin D level and myopia using stepwise logistic regression

Overall	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Q1	Reference	Reference	Reference
Q2	0.92 (0.71, 1.18)	1.00 (0.77, 1.31)	1.00 (0.77, 1.3)
Q3	0.86 (0.69, 0.97)*	0.98 (0.76, 0.99)*	0.99 (0.77, 1.28)
Q4	0.78 (0.65, 0.95)*	0.97 (0.75, 0.99)*	0.98 (0.77, 0.99)*
P for trend	0.02*	0.03*	0.14

*, statistically significant. OR, odds ratio; CI, confidence interval.

have a higher risk of myopia than males in childhood and adolescence (OR =1.12, 95% CI: 1.01–1.24), and those with a high PIR level (OR =1.08, 95% CI: 1.04–1.11) or a high BMI (OR =1.19, 95% CI: 1.11–1.27) may also be at a high risk of myopia. In contrast, white ethnicity was associated with a lower risk of myopia than was Mexican American ethnicity (OR =0.78, 95% CI: 0.68–0.90), and more leisure-time exercise was associated with a lower risk of myopia (OR =0.94, 95% CI: 0.92–0.97) (*Figure 1*).

Discussion

The results of this study showed a negative dose-response relationship between serum 25(OH)D level and myopia in children and adolescents, although this relationship may not be linear. Serum 25(OH)D level was negatively correlated

Table 3 Subgroup analysis of 25-hydroxyvitamin D level and myopia using stepwise logistic regression

Gender	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Male			
Q1	Reference	Reference	Reference
Q2	0.82 (0.58, 1.15)	0.88 (0.61, 1.26)	0.88 (0.61, 1.27)
Q3	0.91 (0.71, 0.97)*	1.00 (0.73, 1.37)	1.02 (0.74, 1.4)
Q4	0.73 (0.55, 0.98)*	0.86 (0.59, 0.96)*	0.88 (0.6, 0.99)*
P for trend	0.03*	0.09	0.19
Female			
Q1	Reference	Reference	Reference
Q2	1.03 (0.68, 1.56)	0.97 (0.67, 1.4)	1.04 (0.69, 1.56)
Q3	0.8 (0.54, 1.18)	0.71 (0.51, 1)	0.8 (0.54, 1.18)
Q4	0.98 (0.68, 0.99)*	0.87 (0.61, 0.95)*	0.97 (0.68, 0.99)*
P for trend	0.23	0.27	0.21

*, statistically significant. OR, odds ratio; CI, confidence interval.

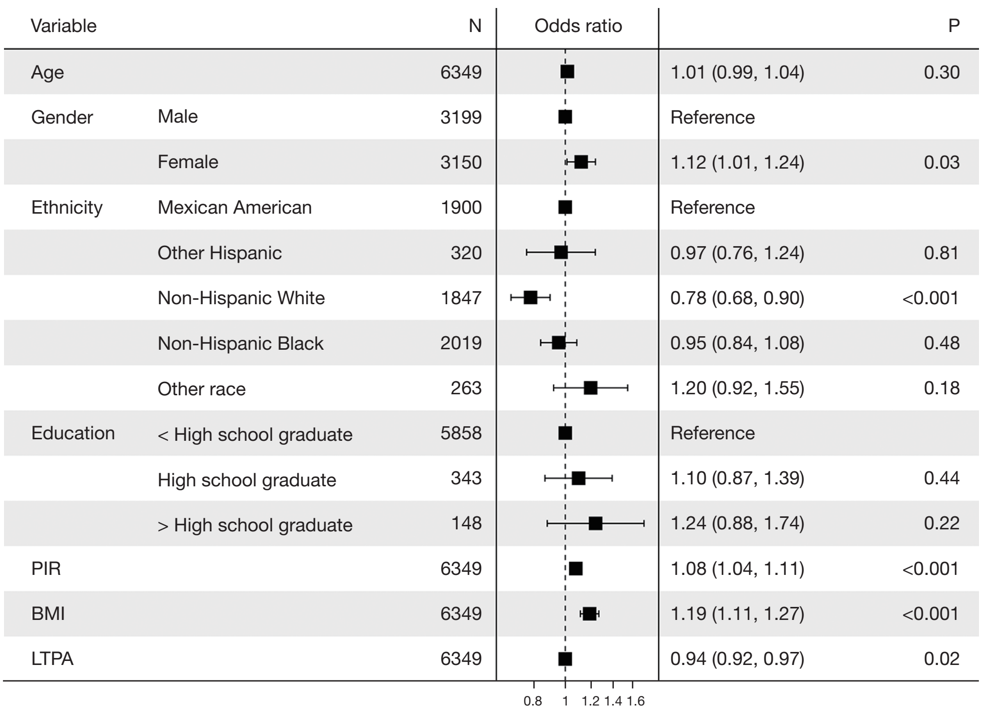

Figure 1 Forest plot of the association between the covariates and myopia. PIR, poverty income ratio; BMI, body mass index; LTPA, leisure time physical activity.

with myopia in children and adolescents in both the male and female groups, with the effect of serum 25(OH)D was more pronounced in the male group. In addition to this, the findings suggest that females may have a higher risk of myopia than males in childhood and adolescence, and those with a high PIR or a high BMI may be at high risk of myopia.

Evidence from observational studies suggests that time spent outdoors may prevent the development of myopia. A school-based randomized controlled trial found that an additional 40 minutes of outdoor activity reduced the 3-year cumulative prevalence of myopia from 39.5% to 30.4% (15).

Although the mechanism by which spending time outdoors protects against myopia is unknown, it may be explained by (I) the vitamin D hypothesis which suggests that increased ultraviolet (UV) light leads to increased vitamin D production, or (II) the photodopamine hypothesis, which suggests that an increase in light intensity prevents myopia by increasing the release of dopamine (16,17). The vitamin D hypothesis has been supported by a number of studies, and the current findings similarly support this hypothesis. In epidemiologic studies, it is difficult to separately measure exposure to high-intensity visible light outdoors and exposure to UV radiation that induces vitamin D synthesis. Measurements of time spent outdoors do not distinguish between exposure to visible light and UV radiation, and blood 25(OH)D concentrations provide a measure of vitamin D status but are also a marker of recent sun exposure or time spent outdoors (18,19).

According to the photodopamine hypothesis, increasing time spent outdoors increases exposure to bright light, which can have a protective effect against myopia (20). However, at the same time, children's skin may be exposed to more UVB radiation, resulting in higher 25(OH)D concentrations (21).

A deeper understanding of the causal role of vitamin D in the development of myopia can be gained by examining the relationship between vitamin D pathway gene polymorphisms and myopia. To date, seven genes in the vitamin D pathway associated with myopia risk have been investigated: *CYP27B1*, *CYP2R1*, *GC*, *VDR*, *CYP24A1*, *RXRA*, and *DHCR7* (22,23).

A recent article supports the conclusion arising from the current work that female participants have faster rates of myopia progression and axial extension (17). Another study concluded that older age at menarche significantly reduces the risk of myopia and that menarche earlier than 15 years of age is a risk factor for myopia (24). According to previous studies, obesity in school children increases the risk of myopia by 2.7 times. In addition, a Dutch study of 6-year-old children showed an association between myopia and high BMI (25). Obesity often leads to a variety of complications, and one factor associated with myopia is insulin resistance (25,26). Insulin resistance is one of the most common biochemical phenomena associated with obesity, and the suppression of insulin secretion in hyperglycemic states leads to lens thickening, anterior pole shift, and worsening myopia (27).

Unlike with diseases of poverty, a significant risk factor for myopia is the use of electronics, and families with a high PIR tend to have more ability to purchase electronics (the higher the PIR, the wealthier the family) (28,29). Differences in myopia risk between ethnic groups may stem from polymorphisms at genetic loci. Finally, the idea that exercise reduces the risk of myopia, which shares many mechanisms with outdoor myopia risk reduction, has been supported by systematic reviews (30-33).

Overall, this research had several strengths. At first, the included data had high quality and a long collection period, which had a strong evidence quality for an association analysis. Secondly, our research method is mainly based on stepwise logistic regression, which can analyze the association and dose-response relationship. Furthermore, the research topic is practical and meaningful the public health of children and adolescents.

However, some limitations to this study should be mentioned. First, an epidemiologic survey of the 2001–2008 period was utilized rather than a cohort study, which allows for correlation analysis but not causal inference. Second, because the data spanned eight years, serum 25(OH)D level was monitored annually by a laboratory, which does not reflect the continuous exposure of participants to 25(OH)D. Finally, the limited number of covariates examined cannot guarantee that other undetected covariates did not affect the results, and some samples that lacked the required information were excluded, resulting in a small sample size.

Conclusions

This study indicated that higher serum 25(OH)D levels were associated with lower risk of myopia in children and adolescents and that outdoor exercise also reduced the risk of myopia. Meanwhile, females, those with high BMI, and those with high PIR may have an increased risk of myopia.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-617/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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