BMC Ophthalmology

RESEARCH Open Access

Correlation between longitudinal serum vitamin D levels and myopia in children: a prospective birth cohort analysis

Ju-Hsien Li[1], Ho-Min Chen[1], Kuan-Wen Su[2,3], Yu-Kai Kuo[1], Cheng-Hsiu Wu[1], Nan-Ni Chen[4], Pei-Wei Huang[1] and Chi-Chin Sun[1,3*]

Abstract

Background Myopia is an increasingly prevalent visual impairment associated with severe ocular complications. Risk factors for childhood myopia include genetics, East Asian ethnicity, age, parental myopia, and various environmental factors. The relationship between vitamin D levels, outdoor activity, and myopia remains inconclusive. This study aims to investigate the correlation between longitudinal serum vitamin D levels and myopia in Taiwanese children.

Methods The study measured serum 25-hydroxyvitamin D (25(OH)D) concentrations in children from the Prediction of Allergies in Taiwanese Children (PATCH) study at multiple time points, including umbilical cord blood and ages 1, 3, and 5 years. Refractive error under cycloplegic conditions and axial length were assessed from January 2021 to April 2022. Myopia was defined as a mean spherical equivalent in both eyes ≤ -0.5 diopter. Independent sample t-tests, partial correlation analyses, and generalized estimating equation (GEE) analyses were conducted to examine the relationship between serum vitamin D concentrations and myopia.

Results A total of 126 eyes from 63 children (mean age: 8.90 ± 2.24 years) were analyzed. The lowest serum vitamin D level (19.11 ± 9.10 ng/mL) was observed in umbilical cord blood, while the highest level (37.01 ± 12.61 ng/mL) occurred at 1 year of age. No significant differences in serum vitamin D concentrations were found between children with and without myopia during gestation, at birth, or at ages 1, 3, and 5 years (all $P > 0.05$). Additionally, GEE analysis revealed that serum vitamin D levels were not significantly associated with cycloplegic spherical equivalent or axial length after adjusting for age and sex.

Conclusions This prospective birth cohort study found no association between serum vitamin D concentrations at birth, 1, 3, or 5 years of age and the development of myopia in Taiwanese children. These findings suggest that other factors, such as ethnicity, near work activities, or lighting conditions, may play more significant roles in myopia development, particularly among East Asian populations.

Keywords Serum vitamin D, 25(OH)D, Myopia, Longitudinal birth cohort

*Correspondence:
Chi-Chin Sun
chichinsun@gmail.com
[1]Department of Ophthalmology, Chang Gung Memorial Hospital, 222 Mai Chin Road, An Leh District, Keelung, Taiwan
[2]Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[3]School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[4]Department of Ophthalmology, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan

Introduction

Myopia is a refractive error related to excessive axial elongation. As a primary cause of visual impairment, myopia has become an global public health problem due to its rapidly increasing prevalence and various ocular complications [1, 2]. Commonly associated complications include myopic macular degeneration, retinal detachment, open-angle glaucoma, and cataract [3]. Childhood myopia has multiple risk factors, such as ethnicity (particularly occurring in those of East Asian descent), age, genetics, parental myopia, and environmental factors [4–6]. Other potential etiologies include up-close activities, school achievement, and urbanization [5, 7, 8].

Vitamin D, an endogenous hormone synthesized through sunlight exposure, is a biomarker of time spent outdoors [9, 10]. The relationship between vitamin D and myopia remains undetermined, although some studies have demonstrated that low serum vitamin D concentration was related to myopia prevalence [11–13]. However, other studies have demonstrated that vitamin D was not an indicator of future myopia, and they argued that the association was an erroneous link possibly resulting from the confounding effect of outdoor activities [9, 14]. Most studies supporting the association between low vitamin D levels and myopia have been cross-sectional studies based on single measurements of vitamin D concentration, not longitudinal birth cohort studies [9, 11–13].

The present prospective birth cohort study longitudinally measured serum vitamin D concentrations from birth to childhood [15–17] to explore the correlation between longitudinal vitamin D concentrations and myopia in children.

Materials and methods

Study population

This study utilized participants from the Prediction of Allergies in Taiwanese Children (PATCH) study, a prospective, population-based birth cohort established at Keelung Chang Gung Memorial Hospital between October 2007 and September 2010. The PATCH study recruited healthy newborns with a gestational age greater than 34 weeks, after obtaining informed consent from pregnant mothers at 32 weeks of gestation. Detailed prenatal information was collected, and cord blood samples were obtained at birth. The study protocol, including inclusion and exclusion criteria, has been described in detail in previous publications. The PATCH study was approved by the Human Research Ethics Committee of Chang Gung Memorial Hospital (No. 100–0201B) [15–17].

For this study, participants were selected from children who attended follow-up visits at Keelung Chang Gung Memorial Hospital between January 2021 and April 2022. During this period, 201 children were contacted via telephone and invited to participate in an ophthalmologic sub-study. The inclusion criteria for this analysis were children aged 5 to 14 years who had no prior ocular diseases and were able to complete comprehensive ocular examinations. However, the recruitment process coincided with the peak of the COVID-19 pandemic in Taiwan, which significantly limited participation due to widespread concerns about infection and potential isolation measures.

Of the 201 children contacted, many declined participation due to pandemic-related fears. Exclusions included three children with severe hyperopia, one child with a history of previous ocular surgeries, and one child diagnosed with amblyopia. Additionally, three families declined participation due to their children's attention deficit hyperactivity disorder (ADHD), which made compliance with the prolonged ophthalmologic examinations challenging.

After accounting for these exclusions, 67 children agreed to participate in the ophthalmologic examination. Among them, four children were excluded due to incomplete ophthalmologic examinations, resulting in 63 eligible participants for the final analysis. Informed consent was obtained from the parents or legal guardians of all participants. The flowchart for study cohort assembly is presented in Fig. 1.

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.: 201901822A3) and was conducted in accordance with the Declaration of Helsinki.

Ocular examination data collection

All the participants underwent detailed ophthalmologic examinations that included axial length and refractive error under cycloplegic conditions (IOL Master 500, Carl Zeiss Meditec, Jena, Germany). Cycloplegia was induced using 0.5% Tropicamide, administered in three drops at five-minute intervals, followed by a 30-minute waiting period before refraction measurement. The ocular examinations were completed by certificated ophthalmologists. The spherical equivalent (SE) was defined as the sum of the sphere power and half of the cylinder power. Mean SE was the average of the SE in the participants' 2 eyes. This study defined myopia as a mean SE of −0.5 diopter (D) or worse.

Serum vitamin D concentration and questionnaire

Serum vitamin D concentrations were measured in maternal blood during pregnancy, in participants' umbilical cord blood at birth, and at ages 1, 3, and 5 years. Serum vitamin D levels were analyzed using an automated electrochemiluminescence-based assay (Elecsys® Vitamin D Total assay; Roche Diagnostics, Mannheim, Germany) with nonfasting blood samples. The assay has

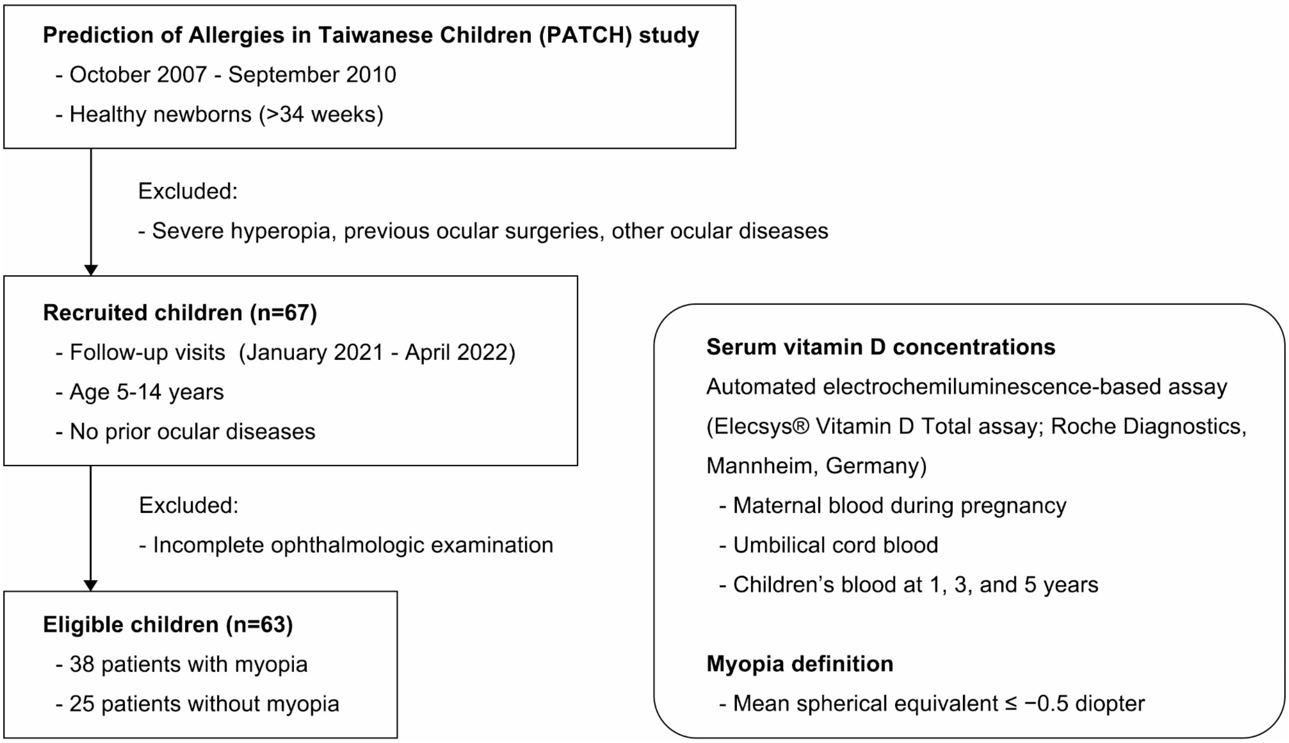

Fig. 1 Algorithm of study population selection

been validated for precision and reliability in clinical and research settings. Additionally, parents completed a questionnaire during their children's ocular examinations, which included information on the participants' time spent outdoors and sun exposure duration. These details were incorporated into the analysis to account for potential confounding factors related to vitamin D status.

Statistical analysis

The collected data were analyzed using SPSS Version 26.0 (IBM, Armonk, NY, USA). Statistical significance was indicated at a two-tailed P value < 0.05. The differences between the patients with and without myopia were analyzed using independent samples t tests. Partial correlation analysis was also conducted to assess the relationship between serum vitamin D concentration and ocular parameters (i.e., cycloplegic SE and axial length), controlling for age and sex, at each time point (i.e., umbilical cord blood, 1 year, 3 years and 5 years). Moreover, generalized estimating equation (GEE) analysis was applied to investigate the associations between longitudinal serum vitamin D levels and ocular parameters, incorporating the data of multiple timepoints.

Results

The present study recruited a total of 134 eyes from 67 children. Eight eyes from 4 children were excluded due to incomplete ocular examinations. The final analysis included 38 patients with myopia and 25 patients without myopia (Fig. 1). The mean age of the 63 participants was 8.90 ± 2.24 years (range: 5–14).

Table 1 Demographic characteristics and clinical data

	All patients (n = 63)
Age (years)	8.90 ± 2.24
Sex (male: female)	29: 34
Axial length (mm)	23.44 ± 1.10
Spherical equivalent (D)	-0.99 ± 1.92
Serum vitamin D concentration	
Mother (ng/mL)	19.9 ± 8.56
Umbilical cord blood (ng/mL)	19.11 ± 9.10
1 year old (ng/mL)	37.01 ± 12.61
3 years old (ng/mL)	31.49 ± 8.39
5 years old (ng/mL)	29.80 ± 8.64

Continuous data are presented as mean ± standard deviation

Axial length and spherical equivalent are mean values of bilateral eyes

Spherical equivalent = cylinder/2 + sphere

Table 1 presents the demographic characteristics and clinical data of the participants. The sample comprised 29 (46%) male patients and 34 (54%) female patients. Vitamin D concentrations were measured in the blood of the participants' mothers during pregnancy, in the participants' umbilical cord blood, and at years 1, 3, and 5. The serum vitamin D level was lowest in the umbilical cord blood. The highest serum vitamin D level occurred at 1 year (37.01 ± 12.61 ng/mL) and gradually decreased

Table 2 Generalized estimating equation analysis of the longitudinal serum vitamin D concentration and cycloplegic SE and axial length

Outcome / Variable	Estimate, β (95% CI)	*P* value
Cycloplegic SE (D)		
Male vs. Female	0.496 (-0.309 to 1.301)	0.227
Age (years)	-0.511 (-0.815 to -0.208)	0.001
Serum vitamin D concentration (ng/mL)	-0.0000004 (-0.0000019 to 0.0000011)	0.606
Axial length (mm)		
Male vs. Female	0.490 (0.016 to 0.964)	0.043
Age (years)	0.240 (0.085 to 0.396)	0.002
Serum vitamin D concentration (ng/mL)	0.0000008 (0.00000028 to 0.0000019)	0.146

Abbreviations: SE: spherical equivalent

Table 3 Partial correlation analysis between cycloplegic SE, axial length, and serum vitamin D concentration by age

	Cycloplegic SE		Axial Length	
	*r**	*P* value	*r**	*P* value
Serum vitamin D concentration				
Mother (ng/mL)	-0.16	0.61	0.08	0.80
Umbilical cord blood (ng/mL)	0.04	0.89	-0.16	0.96
1 year old (ng/mL)	0.16	0.61	-0.47	0.89
3 years old (ng/mL)	-0.42	0.17	0.51	0.09
5 years old (ng/mL)	0.24	0.45	-0.42	0.18

r, Pearson's coefficient

*adjusted for age and sex

Abbreviations: SE: spherical equivalent

Table 4 Comparison of time spent outdoors and sun exposure time in myopia and nonmyopia groups

	Myopia (SD)	Nonmyopia (SD)	Mean difference (95% CI)	*P* value
Outdoor activity time (h/week)	4.67 (4.35)	6.72 (5.25)	-2.05 (-4.48 to 0.38)	0.10
Sun exposure time (h/week)	5.51 (5.13)	6.80 (5.36)	-1.29 (-3.97 to 1.40)	0.34

Myopia: Spherical equivalent ≤ – 0.5D; Nonmyopia: spherical equivalent > – 0.5D

Abbreviations: SD: standard deviation

as the patients aged. This result accords with the pattern observed in the rest of the cohort population [18].

Table 2 presents the results of the GEE analysis examining the longitudinal relationships between serum vitamin D levels and two ocular parameters: SE and axial length. The analysis included sex (male vs. female) and age as covariates. For cycloplegic SE, age was significantly negatively associated (β = -0.511, $P = 0.001$), indicating that SE decreases with increasing age. Sex and serum vitamin D concentration were not significantly associated with SE. In contrast, axial length was positively associated with both sex and age; males had longer axial lengths than females (β = 0.490, $P = 0.043$), and axial length increased with age (β = 0.240, $P = 0.002$). Serum vitamin D concentration did not show a significant association with axial length.

Table 3 presents the partial correlation analysis between cycloplegic SE, axial length, and serum vitamin D concentration by age (at each time point). After adjustments for age and sex, the results indicated no significant correlation between cycloplegic SE or axial length and serum vitamin D concentration.

Table 5 Partial correlation analysis between cycloplegic SE, axial length, time spent outdoors, and sun exposure time

	Cycloplegic SE		Axial Length	
	r	*P* value	*r*	*P* value
Time spent outdoors (h/week)	0.084	0.52	-0.172	0.19
Sun exposure time (h/week)	0.092	0.48	-0.099	0.45

P values adjusted for age and sex

Abbreviations: SE: spherical equivalent

This study also investigated the effects of time spent outdoors and sun exposure time on myopia. The differences in time spent outdoors and sun exposure time between the myopia and nonmyopia groups did not achieve statistical significance (Table 4). The results did not reveal a significant difference in time spent outdoors or sun exposure time with respect to cycloplegic SE or axial length after adjusting for age and sex (Table 5).

Discussion

The relationship between vitamin D and myopia remains controversial. To address this, we utilized longitudinally measured vitamin D levels from the PATCH study, a prospective birth cohort, to explore the potential long-term effect of vitamin D on myopia. Our findings demonstrated no significant difference in serum vitamin D concentrations between children with and without myopia at birth or at ages 1, 3, and 5. Additionally, the GEE analysis showed that serum vitamin D levels were not significantly associated with cycloplegic SE or axial length.

This study is unique in collecting longitudinal data from a well-designed cohort, measuring vitamin D from maternal blood during pregnancy and from the participants' blood across early childhood. Unlike many previous studies [9, 11, 12], which employed cross-sectional designs, this study benefits from multiple vitamin D measurements over time. For instance, Choi et al. reported a significant association between low vitamin D concentrations and myopia in Korean adolescents [11], and Tideman et al. found similar associations in a large cohort of young children [12]. However, these studies relied on single measurements of vitamin D and noncycloplegic refractive assessments, both of which may introduce biases.

Conversely, some recent studies align with our findings that vitamin D levels are not directly associated with myopia. Guggenheim et al., in a longitudinal study, suggested that vitamin D levels at age 10 reflect time spent outdoors rather than predicting future myopia [9]. Similarly, Cuellar-Partida et al., using Mendelian randomization analysis, examined single nucleotide polymorphisms in genes influencing vitamin D concentration, including DHCR7, CYP2R1, GC, and CYP24A1. After adjusting for the confounding effect of outdoor activity, they concluded that vitamin D played only a minimal role in myopia development [14, 19]. These findings suggest that vitamin D is better understood as a surrogate marker for time spent outdoors rather than as an independent risk factor for myopia.

Myopia is a multifactorial condition influenced by both genetic and environmental factors. It is well-established that less time spent outdoors is a significant risk factor [5, 20, 21]. In a Taiwanese study, Wu et al. observed that even low sunlight exposure during outdoor activities could reduce myopia progression, suggesting that sunlight is not the sole protective factor [22]. Ethnicity may be a potential factor in the development of axial elongation, particularly in those of Asian descent [23, 24]. Further, various environmental risk factors also affect myopia progression, such as dim light conditions, higher education level, close reading distance, and urbanization [5, 7]. These complexities warrant further investigation into additional potential myopia etiologies in the PATCH cohort.

A notable finding in this study is the longitudinal trend in vitamin D levels, with the lowest levels at birth and the highest at age 1. This pattern is consistent with our previous findings [18], supporting the representativeness of the study sample and minimizing concerns of selection bias. Additionally, the participants in this study maintained adequate vitamin D levels (> 30 ng/mL) [25], unlike those in studies such as Choi et al., which reported deficient vitamin D concentrations in participants with varying refractive statuses [11]. This discrepancy may partly explain the differing conclusions between our study and others.

While our study provides valuable insights, it is important to acknowledge certain limitations. The COVID-19 pandemic impacted our sample size, which may have constrained the statistical power to detect subtle associations between vitamin D levels and myopia. Consequently, some genuine relationships might not have reached statistical significance within our cohort. Nonetheless, the comprehensive longitudinal data collected offer a robust foundation for understanding vitamin D trends over time.

Additionally, the absence of longitudinal SE follow-up data limits our ability to observe changes and developments in myopia throughout the study period. Future research aims to incorporate longitudinal SE assessments to provide a more dynamic understanding of myopia progression. Despite this limitation, the single SE assessment still offers meaningful baseline information and contributes to the overall findings of the study.

Environmental factors such as near work and time spent outdoors were evaluated using a single parental questionnaire rather than objective measurements. This approach may have limited our ability to capture nuanced differences between the myopia and non-myopia groups. However, the study compensates for this by incorporating detailed ocular examinations under cycloplegic conditions and comprehensive longitudinal serum vitamin D measurements, thereby enhancing the reliability and validity of our findings.

Despite these limitations, the study's strengths, including its longitudinal design, multiple vitamin D measurements, and thorough ocular assessments, underscore its significant contribution to the understanding of the relationship between vitamin D and myopia. Future research involving larger-scale studies with long-term SE follow-ups and more precise measurements of outdoor activities is warranted to further elucidate the relationship between vitamin D and myopia.

Conclusions

This prospective birth cohort study found no significant differences in serum vitamin D concentrations between children with and without myopia from birth to 5 years of age. Our findings highlight the multifactorial nature of myopia, influenced by genetic, environmental, and behavioral factors. Future research should explore these potential etiologies in greater depth to better understand and prevent myopia, particularly in populations with a high prevalence, such as East Asian children.

Acknowledgements
We thank Hsing-Fen Lin, Yu-Lin Chou, and the Center for Data Science and Biostatistics at Keelung Chang Gung Memorial Hospital for their invaluable assistance with statistics consultation.

Author contributions
Conception and design of the study (CCS, KWS, JHL); analysis, and interpretation of the data (JHL, HMC, PWH); writing of the article (JHL, HMC, KWS); critical revision (CCS, KWS, NNC); final approval (JHL, KWS, CCS); data collection, (JHL, HMC); provision of materials, patients, or resources (YKK, CHW); obtaining funding (CCS); literature search (YKK, CHW, NNC); administrative, technical, or logistic support (YKK, CHW, NNC, PWH).

Funding
This study was supported by Dr. Chi-Chin Sun of the Chang Gung Medical Research Foundation (CMRPG2K0341, CMRPG2K0342, CMRPG2K0331-2, and CMRPG3K1361-2). The funder had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.: 201901822A3) and conducted in accordance with the principles outlined in the Declaration of Helsinki. As all participants were under the age of 16, informed consent was obtained from their parents or legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 6 October 2024 / Accepted: 4 March 2025
Published online: 18 March 2025

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