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Serum 25-hydroxyvitamin D level is associated with myopia in the Korea national health and nutrition examination survey

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Abstract

The aim of this article was to assess the associations of serum 25-hydroxyvitamin D [25(OH)D] and daily sun exposure time with myopia in Korean adults.

This study is based on the Korea National Health and Nutrition Examination Survey (KNHANES) of Korean adults in 2010–2012; multiple logistic regression analyses were performed to examine the associations of serum 25(OH)D levels and daily sun exposure time with myopia, defined as spherical equivalent \leq -0.5D, after adjustment for age, sex, household income, body mass index (BMI), exercise, intraocular pressure (IOP), and education level. Also, multiple linear regression analyses were performed to examine the relationship between serum 25(OH)D levels with spherical equivalent after adjustment for daily sun exposure time in addition to the confounding factors above.

Between the nonmyopic and myopic groups, spherical equivalent, age, IOP, BMI, waist circumference, education level, household income, and area of residence differed significantly (all P < 0.05). Compared with subjects with daily sun exposure time ≥ 2 hour, subjects with sun exposure time ≥ 2 to <5 hour, and those with sun exposure time ≥ 5 hour had significantly less myopia (P < 0.001). In addition, compared with subjects were categorized into quartiles of serum 25(OH)D, the higher quartiles had gradually lower prevalences of myopia after adjustment for confounding factors (P < 0.001). In multiple linear regression analyses, spherical equivalent was significantly associated with serum 25(OH)D concentration after adjustment for confounding factors (P = 0.002).

Low serum 25(OH)D levels and shorter daily sun exposure time may be independently associated with a high prevalence of myopia in Korean adults. These data suggest a direct role for vitamin D in the development of myopia.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, BP = blood pressure, D = diopter, h = hour, IQR = interquartile range, KNHANES = Korea National Health and Nutrition Examination Survey (KNHANES), OR = odds ratio, Q = quartile, SE = standard error, Sph. E = spherical equivalent.

Keywords: KNHANES, myopia, outdoor acitivity, vitamin D

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1. Introduction

Myopia is one of the most common ocular disorders worldwide,^[1] and the myopic population in Southeast Asia has grown significantly in recent years.^[2–6] The costs of examinations and surgical correction of myopia are significant, and this disorder has been associated with other pathological eye conditions, such as macular and retinal degeneration, foveoschisis, and rhegmatogenous retinal detachment.^[7–9] Although the cause of myopia is as yet unclear, genetic and environmental factors may contribute to its development.^[10–15] Some recent studies suggested that increasing time spent outdoors may prevent the development of myopia,^[14–17] although the results of some epidemiological studies oppose this theory.^[18,19]

One possible risk factor for myopia that has received attention is vitamin D, which is cutaneously synthesized during exposure to sunlight. The 25-hydroxyvitamin D [25(OH)D] is an essential hormone that controls calcium and bone metabolism.^[20,21] It is now clear that 25(OH)D has diverse effects on the immune system, cardiovascular system, obesity, diabetes, and oncogenesis.^[22–28] The relationship between 25(OH)D and several ocular diseases, such as myopia, age-related macular degeneration, diabetic retinopathy, uveitis, and glaucoma, is also under investigation.^[29–38] Regarding myopia, several previous studies have found that low hydroxyvitamin D is associated with a high

prevalence of myopia in young populations.^[36,37,39] However, there is controversy as to whether 25(OH)D is an independent factor for progression of myopia.^[38–40] To date, the possible independent associations of serum vitamin D levels and sunlight exposure time with myopia have not been sufficiently evaluated.

Compared with the United States and Canada, Korea has a lower mean 25(OH)D level and a higher prevalence of vitamin D insufficiency. A population study revealed that 25(OH)D deficiency (<20 ng/mL) was present in 69.5% of male and 83.1% of female workers aged 20 to 65 years.^[41] This may be related to the high latitude (34° - $38^\circ N$) of Korea, and reduced levels of time spent outdoors (owing to high educational pressure and indoor working conditions).^[41–43] Considering the high prevalence of myopia and deficiency of vitamin D in the Korean population, it would be useful to understand the associations of vitamin D deficiency and daily sun exposure time with myopia in this population. Thus, in this cross sectional study, we investigated the relationship between serum 25(OH)D and daily sun exposure time and the prevalence of myopia in Korean adults.

2. Subjects, materials, and methods

2.1. Study population

This study was performed with data from the Korea National Health and Nutrition Examination Survey (KNHANES) V 2010–2012. KNHANES is a cross-sectional, nationally representative sample of the Korean non-institutionalized civilian population aged 1 year or older that uses a rolling sampling design incorporating a complex, stratified, multistage probability sample method. KNHANES is organized regularly by the Korean Ministry of Health and Welfare to monitor the health and nutritional status of the South Korean population. KNHANES is comprised of a health interview survey, a health examination survey-including ophthalmic examination-and a nutrition survey. In this study, individuals aged 20 years or older who participated in the ophthalmologic survey were selected. In total, 25,534 subjects were included in KNHANES from 2010 to 2012, among whom a total of 23,239 completed the ophthalmologic survey. Of these 23,239 subjects, those who had a history of ocular surgery, were younger than 20 years, or had missing values were excluded.

In total, 15,126 subjects were finally selected as the study population. KNHANES V was conducted according to the Declaration of Helsinki, and was carried out by specially trained interviewers or examiners who were not provided with any previous information about the participants. All participants signed an informed consent form. This study was approved by the Institutional Review Board of the Catholic University of Korea.

2.2. Measurements

In the health interview survey, trained interviewers recorded information on demographic status and health-related characteristics, including age, education, residence, and household income. Information about lifestyle characteristics, including smoking, alcohol consumption, and exercise, were recorded using selfreported questionnaires. Residence was categorized as urban (8 major cities in South Korea: Seoul, Gyeonggi, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan) or rural (8 other provinces in South Korea). Household income was divided into quartiles, after family income was adjusted for the number of family members. Participants were grouped in the low-income group if their household income was in the lowest quartile. Subjects' education level was categorized into 4 groups by highest education achieved: elementary school, middle school, high school, and university. Subjects were categorized in the high education group if their highest education level was high school or university. Smoking status was categorized into 3 groups: nonsmokers, current smokers, and exsmokers. Alcohol consumption status was also classified into 3 groups: nondrinker, mild-to-moderate drinker (<30.0 g/day of alcohol) and heavy drinker (\geq 30.0 g/day of alcohol). Regular exercise was categorized as "yes" when participants were engaged in moderate-intensity physical activity (eg, carrying light loads, cycling at a regular pace, playing tennis) for at least 20 minutes at a time on at least 3 occasions per week. Data on current sunlight exposure time were categorized according to sun exposure time, as <2 hours; \geq 2 hours to <5 hours; or \geq 5 hours.

Body measurements of all participants were recorded during the health examination. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 225; SECA Deutschland, Hamburg, Germany) while the participants were standing barefoot. Weight was measured to the nearest 0.1 kg using an electronic scale (GL-6000-20; CAS KOREA, Seoul, Korea) while the participants wore a lightweight gown. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Waist circumference (WC) was measured after normal expiration to the nearest 0.1 cm using a measuring tape (SECA 200; SECA Deutschland), at the mid-level between the lower margin of the ribcage and the iliac crest at the mid-axillary line. Obesity was defined as a BMI $\geq 25 \text{ kg/m}^2$.^[44] Blood pressure (BP) was measured from the right arm using a standard mercury sphygmomanometer (Baumanometer; WA Baum Co, Copiague, NY) after 5 minutes of rest in a sitting position. Systolic and diastolic BPs were measured 3 times at 30-second intervals, and the average of the last 2 values was used for analysis. Hypertension was defined as a systolic BP \geq 140 mmHg, a diastolic BP \geq 90 mmHg, or taking antihypertensive medications.

Serum 25(OH)D levels were assayed according to an agreed protocol. Overnight fasting blood samples were collected from each participant during the survey, and the level of serum 25(OH) D was measured by radioimmunoassay (DiaSorin, Stillwater, MN) using a gamma counter (1470 Wizard; Perkin Elmer, Turku, Finland). The KNHANES study participants were evaluated by the serum 25(OH)D Standardization Program, so the measurement of serum 25(OH)D was standardized to the recently developed National Institute of Standards and Technology-Ghent University reference procedure.^[45] Subjects were categorized into quartiles (Q) of the vitamin D and with cutoff values.

Ophthalmic examination procedures were stratified according to age group, and autorefraction and visual acuity testing of participants aged 5 years and older were performed. Participants over 19 years of age underwent full ophthalmological examinations. All ophthalmologic examinations were performed using a slit-lamp (Haag-Streit model BQ-900; Haag-Streit AG, Köniz, Switzerland) by ophthalmologists. The participants underwent ophthalmologic interviews, visual acuity measurements, slit-lamp examinations of the anterior segment, refraction checks, and intraocular pressure (IOP) measurements. Refraction was measured 3 times without cycloplegia using an autorefractorkeratometer (KR-8800, Topcon, Tokyo, Japan) by ophthalmology residents or ophthalmologists. Refraction measurements were converted into spherical equivalents, calculated as the spherical value plus half of the astigmatic value. Myopia was defined by spherical equivalent of -0.50 diopters (D) or more. Mild myopia was defined as >-3.0 D, moderate myopia was defined as \leq -3.0 D, and high myopia was defined as \leq -6.0 D.

IOP was measured once per eye with Goldmann applanation tonometry during the slit-lamp examination. A digital nonmydriatic retinal camera and a Nikon D–80 digital camera (Nikon Inc., Tokyo, Japan) were used to obtain fundus images from all participants without dilating the pupil. Refractive error was defined based on the right eye.

2.3. Statistical analysis

Statistical analyses were conducted with the survey procedure of the SAS software package (ver. 9.3; SAS Institute Inc, Cary, NC), using sampling weights of KNHANES, to acquire nationally representative prevalence estimates. All the analyses performed in this study were adjusted for survey year to minimize the variation among survey years. Data are presented as means ± SE for continuous variables or as proportions (SE) for categorical variables. General and clinical characteristics of subjects were compared according to the presence of myopia. Variables with skewed distributions were analyzed after logarithmic transformation. Simple and multiple linear regression analyses were used to examine the associations of serum 25(OH)D concentrations and daily sun exposure time with spherical equivalent. Multiple logistic regression analysis was used to estimate the magnitude of the association of serum 25(OH)D level and average daily sun exposure time with myopia (spherical equivalent \leq -0.5 D). The odds ratio (OR) was calculated after adjusting for surveyed year, age, and sex in Model 1. Model 2 adjusted for age, sex, household income, BMI, life habitat factors, and education level, and additionally adjusting for serum 25(OH)D levels (for the association between sun exposure and myopia) and average time of daily sun exposure (for the association between serum 25 [OH]D level and myopia), respectively. Adjusted ORs for serum 25(OH)D level and average time of daily sun exposure in subjects with myopia were calculated. A P value <0.05 was considered statistically significant.

3. Results

Among the study participants, 61.2% had myopia (-0.5 D or more myopic). Table 1 shows the general and clinical characteristics of the subjects according to the presence of myopia. The spherical equivalent of refractive error of the myopic group $(-2.81\pm0.04 \text{ D})$ was significantly different from that of nonmyopic group $(0.61\pm0.02 \text{ D}; P<0.001)$. Age, IOP, BMI, WC, education level, household income, and area of residence were significantly different between the nonmyopic and myopic groups (all P<0.05).

In the multiple linear regression analysis for the association between serum 25(OH)D concentration and refractive error (Table 2), refractive error was significantly associated with serum 25(OH)D concentration after adjusting for age and sex (P < 0.001), which was maintained after additional adjustment for BMI, smoking, drinking, education, income, exercise, IOP, and daily sun exposure time (P=0.002).

Figure 1 shows the distribution of daily sun exposure time and serum 25(OH)D concentration according to the severity of myopia. The more myopic subjects had less sun exposure. In contrast, subjects with emmetropia or lower myopia had a tendency to receive more sun exposure (Fig. 1A). Likewise, the higher myopia subjects had lower levels of serum 25(OH)D. Emmetropia or less myopic subjects tended to have higher levels of serum 25(OH)D (Fig. 1B).

Results of the multiple logistic regression analyses for the association of serum 25(OH)D concentration and daily sun exposure time with myopia are shown in Table 3. Compared with subjects were categorized into lowest quartile of serum 25(OH)D, subjects with the higher quartiles had gradually lower prevalence of myopia after adjusting for age and sex (P = 0.003), which was maintained after additional adjustment for household income, BMI, exercise, education level, IOP, and daily sun exposure time (P < 0.001, Model 2). In addition, compared with subjects with daily sun exposure time <2 hours, subjects with sun exposure times of ≥ 2 to <5 hours, and those with sun exposure times of ≥ 5 hours, had a significantly lower prevalence of myopia after adjusting for age and sex (P < 0.001), which was maintained after adjusting for household income, BMI, exercise, education level, IOP, and serum 25(OH)D level (P < 0.001, Model 2).

Serum 25(OH)D levels according to the severity of myopia are shown in Figure 2. The serum 25(OH) levels decreased significantly according to the severity of myopia after adjustment for survey year, age, sex, household income, BMI, exercise, education level, and daily sun exposure time (*P* for trend <0.001).

Table 1

Clinical characteristics of study	subjects according to the presence	of myopia in Korean adults (n = 15,126).

	Nonmyopia Sph. E \leq $-0.5D$ (95% Cl)	Myopia Sph. E $>-$ 0.5D (95% Cl)	Р
Demographics			
Number	9262	5864	
Sex (male)	49.59 (48.46-50.73)	51.33 (49.79–52.87)	0.106
Age (year)	51.83 (51.27–52.39)	38.13 (37.67–38.6)	< 0.001
Ocular examination			
Refractive error (D)	0.61 (0.57-0.65)	-2.81 (-2.89-2.73)	< 0.001
IOP, mmHg	13.94 (13.82–14.07)	14.18 (14.05–14.31)	< 0.001
Systemic evaluation			
BMI, kg/m ²	23.86 (23.77-23.96)	23.68 (23.54-23.81)	0.027
Waist circumference, cm	82.16 (81.85-82.47)	80.35 (79.96-80.74)	< 0.001
Life habit factors			
Regular physical activity (≥mod intensity, %)	19.78 (18.5–21.07)	20.26 (18.9-21.61)	0.588
Socioeconomic state			
Education level (≥9 years, %)	56.37 (54.62-58.12)	87.36 (86.19–88.53)	< 0.001
Area of residence (Urban, %)	75.52 (71.59–79.44)	84.78 (81.79-87.77)	< 0.001
Low income (Lowest quartile, %)	20.31 (18.96–21.66)	10.69 (9.4–11.97)	< 0.001

BMI=body mass index, D=diopter, IOP=intraocular pressure, Sph.E=spherical equivalent.

Table 2

Multiple linear regression analysis for the association between serum 25(OH)D concentrations and refractive error (D) in Korean adults.

	Model 1		Model 2	
	Beta \pm SE	Р	Beta \pm SE	Р
Serum 25(OH)D concentration	0.017 ± 0.004	< 0.001	0.013 ± 0.004	0.002
Age	0.069 ± 0.002	< 0.001	0.061 ± 0.002	< 0.001
Sex	-0.054 ± 0.046	0.238	0.005 ± 0.052	0.923
Sun exposure time			0.119 ± 0.034	< 0.001
Body mass index			-0.013 ± 0.008	0.088
Current smoker			0.206 ± 0.063	0.001
Heavy drinker			0.144 ± 0.078	0.064
Education			-0.570 ± 0.055	< 0.001
Household income			-0.131 ± 0.073	0.071
Exercise			0.112 ± 0.056	0.047
IOP			-0.051 ± 0.010	< 0.0001

25(OH)D = 25-hydroxyvitamin D, IOP = intraocular pressure, Model 1 = adjusted for sex and age, Model 2 = adjusted for sex, age, body mass index, smoking, drinking, education, low income, exercise, IOP, and daily sun exposure time, SE = standard error.

4. Discussion

In this study, we found that serum vitamin D levels and daily sun exposure time had independent associations with myopia after adjusting for confounding factors (Tables 2 and 3).

At present, recommended methods for preventing myopia that are supported by strong evidence are time outdoors, bifocal lenses, and a drop of atropine.^[17,46–49] Bifocal lenses may slow the progression of myopia by reducing accommodative efforts,

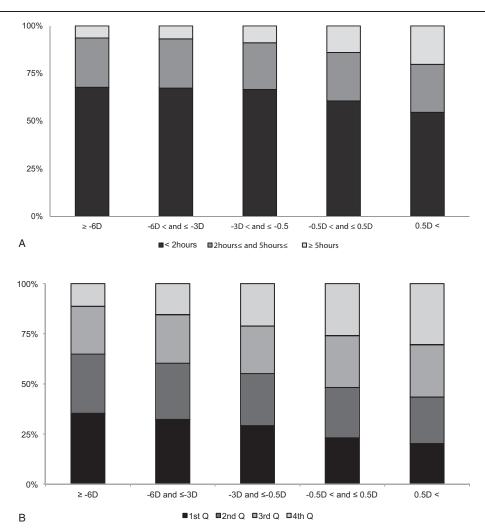


Figure 1. Distribution of daily sun exposure time and serum 25-hydroxyvitamin D [25(OH)D] level according to severity of myopia. (A) The more myopic subjects had less sun exposure time. In contrast, subjects with emmetropia or lower myopia tended to have more sun exposure time. (B) Likewise, the higher myopia subjects had lower levels of serum 25(OH)D. Subjects with emmetropia or lower myopia tended to have higher levels of serum 25(OH)D. The quartile(Q) cutoff values of 25 (OH)D (ng/mL) were 1st Q less than 13.2, 2nd Q 13.2 to <16.72, 3rd Q 16.72 to <20.93, and 4th Q greater \geq 20.93. D, diopter.

Table 3

		Model 1		Model 2		
	OR	95% CI	P for trend	OR	95% CI	P for trend
Serum 25(OH)D concer	ntration					
1 st quartile	1	ref		1#	ref	
2nd quartile	0.870	0.765,0.990		0.849	0.741, 0.973	
3rd quartile	0.832	0.728,0.952		0.822	0.718, 0.942	
4th guartile	0.773	0.670,0.893		0.826	0.714, 0.955	
P for trend			0.003			< 0.001
Sun exposure time						
<2 h	1	ref		1*	ref	
2-<5 h	0.839	0.742,0.950		0.868	0.763, 0.988	
≥5 h	0.622	0.526,0.735		0.692	0.579, 0.828	
P for trend			< 0.001			< 0.001

25(OH)D = 25-hydroxyvitamin D, CI = confidence interval, OR = odds ratio. The odds ratio was calculated after adjusting for surveyed year, age and sex in Model 1. In model 2, the odds ratio was calculated after adjusting for age, sex, household income, BMI (body mass index), life habitat factors, IOP (intraocular pressure) and education level, and additionally adjusting for serum 25-hydroxyvitamin D (25(OH)D) levels (^{*} for the association between serum 25(OH)D level and myopia). The quartile(Q) cutoff values of 25(OH)D (ng/mL) were 1st Q <13.2, 2nd Q 13.2 to <16.72, 3rd Q 16.72 to <20.93, and 4th Q \geq 20.93.

whereas the use of atropine not only inhibits accommodation but also has biochemical effects on the retina and remodeling of the sclera.^[50-54] Studies on outdoor activities are still controversial: some indicate no association between myopia and outdoor activities,^[18,55] but in others reports there is a strong association between myopia and outdoor activities.^[17,56-58]

One theory regarding the protective effect of outdoor activity is that it may be mediated by the effects of light on retinal dopamine: this theory is partly supported by animal experiments.^[57,59,60] Another theory is that 25(OH)D produced by outdoor activities may reduce the progression of myopia.^[39] We designed the present study to assess whether 25(OH)D independently affected the prevalence of myopia and showed that serum 25(OH)D levels can influence myopia prevalence independently, regardless of sun exposure time. Some researchers suggest that a deficiency in 25(OH)D affects myopia develop-

ment. One hypothesis posits that lower 25(OH)D levels induce alterations in intracellular calcium and impaired contraction and relaxation of the ciliary muscles, thereby leading to myopia development.^[61,62] Another hypothesis is that 25(OH)D may be involved in a retinoscleral signaling pathway.^[63] Retinoic acid is known to be a factor in the retinoscleral signal for eyeball lengthening.^[36,64,65] Retinoic acid can act after both retinoic acid receptors and the 25(OH)D receptor heterodimerize with retinoid X receptors.^[66] In the former study, low serum 25 (OH)D levels were significantly associated with myopia, especially high myopia in adolescents in Korea.^[36] The population in the previous study was in their growth period and myopia was progressing; most studies seeking the cause of myopia are targeted at this age group,^[3,10,15,18,40,47] whereas the present study targeted a large adult population in which ocular growth was complete. In this regard, 25(OH)D and sun exposure

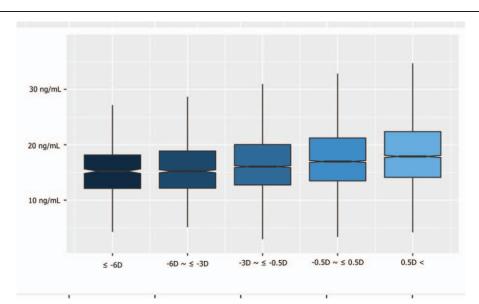


Figure 2. The box and whisker plots of level of serum 25-hydroxyvitamin D [25(OH)D] according to the severity of myopia. The "box" is the interquartile range (IQR, 25th and 75th percentiles) with a notch to show the median. The whiskers show the 10th and 90th percentiles. Serum 25(OH) levels are shown according to the severity of myopia after adjustment for surveyed year, age, sex, household income, body mass index (BMI), exercise, education level, intraocular pressure (IOP), and daily sun exposure time (*P* for trend <0.001). D, diopter.

levels may have different mechanisms in the prevalence of myopia and exert independent effects on myopia.

We also analyzed any association of myopia with sex, age, socioeconomic status, place of living, education level, physical activity, and IOP, because age, education level, income level, place of living, and IOP showed significant differences according to the presence of myopia (Table 1). Concerning the associations of serum 25(OH)D level and sun exposure time with myopia, we adjusted for these confounding factors. First, the age of the myopic population was younger than that of the nonmyopic population, and an analysis by age also showed that the younger population had more myopia (Table 1). This result may be associated with the recent increase in the myopic population in Southeast Asia, a phenomenon that could be explained by genetic factors.^[67-69] However, most epidemiological studies of myopia suggest an interaction of genetic susceptibility and environmental factors that predisposes myopia development.^[70-73] It is thought that, in accordance with the industrialization and urbanization process, younger urban populations tend to spend more time indoors and live nearer to their place of work. The prevalence of myopia also differed significantly according to education level (Table 1). We suggest that those with a higher level of education may spend more time indoors, both during their education and after graduation. Such life habits may result in less sun exposure and more myopia. Additionally, IOP showed significantly higher values in the myopic group (Table 1). There are many recent studies regarding an association between myopia progression and IOP, almost all of which indicate a significant effect of IOP on myopia progression.^[63,74–78]

Most epidemiologic studies have measured the level of 25(OH) D, which is primary circulating form of vitamin D, for investigation of association with myopia.^[36,38–40] But the active form of vitamin D involved in calcium homeostasis is 1,25(OH)D acting on bone, intestine, and kidney.^[79–80] Some studies found in receptor polymorphism of 1,25(OH)D in myopic population.^[61,81] But it is still unclear that how 1,25 (OH)D affects myopic progression.^[82]

The present study had some limitations. First, we used a crosssectional study design to investigate the association of 25(OH)D with myopia in the target population, in which refractive errors become stable. Therefore, the association discovered here may not imply a causal relationship. To investigate the definite causal relationship of serum 25(OH)D level with myopic progression, cohort study designs targeting population in the process of ocular growth seem to be necessary. Second, refractive status was considered as manifest refraction. Because we did not use cycloplegics, there is a possibility of transient accommodative error.^[83] However, we tried to reduce the potential for error by having subjects wear corrective glasses. We did not check axial length, corneal thickness, or family history of myopia. Therefore, there is a possibility that the myopia was of another type than axial myopia. Myopia is associated not only with environmental factors but also with genetic factors. Data adjusting for family history may be helpful in identifying the cause of myopia. And there is potential of bias in that we use self-reported information of life habitat including physical activity. There are some controversies about variation of serum 25(OH)D level by season,[84-86] and the adjustment of seasonal variation is needed for accurate assessment.^[87] But KNHANES does not provide information about the seasons on blood samples examination, so we could not adjust for seasonal variations in serum 25(OH)D level.

In this study, the emmetropia group showed the highest level of 25(OH)D, whereas the hyperopic group showed lower values

than the emmetropia group (Fig. 2). To date, no reported study has examined the association of hyperopia and 25(OH)D level; we suggest that understanding this association is necessary.

In conclusion, this study demonstrated that low serum 25(OH) D levels and shorter daily sun exposure times may be independently associated with a high prevalence of myopia in Korean adults. These data suggest a direct role of vitamin D as a risk factor for myopia.

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