Photochemical & Photobiological Sciences

PERSPECTIVE

Time outdoors, blood vitamin D status and myopia: a review

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Background: Myopia is a major public health concern throughout the world and the prevalence has been increasing rapidly in recent years, especially in urban Asia. The "vitamin D hypothesis" has been raised recently because vitamin D may be a link between less time outdoors and increased risk of myopia. *Methods*: We reviewed all studies published in English which examined the association of time outdoors and blood vitamin D status with myopia. *Results*: The protective effect of time spent outdoors on the risk of myopia onset has been well-established with numerous observational studies and three trials published. Five studies reporting the association between the blood vitamin D status and the risk of myopia and two studies examining the variations in the vitamin D receptor as potential risk factors for myopia development were identified. Most of the current evidence was cross-sectional in nature and had not properly controlled important confounders in its analyses. The evidence supporting that vitamin D played a role in myopia development is weak and the mechanisms are unclear. *Conclusions*: At the current stage, it is still unclear whether blood vitamin D status regulates the onset or progression of myopia. Blood vitamin D status may only serve as a biomarker of outdoor exposure, which is the real protective factor for myopia.

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Background

Myopia is a multifactorial visual disorder, in which light rays from a distant object are focused in front of the retina.[1] Myopic individuals present with blurry distance vision and myopic eyes are often characterized by a steeper corneal curvature or a longer axial length (AL) compared with non-myopic eyes.[2] The accuracy and reliability of ophthalmologic examinations are crucial in epidemiologic studies. The "gold standard" for measurement of refractive errors, particularly in children, is cycloplegic refraction.[3] Cycloplegia is the temporary paralysis of the ciliary muscle of the eye, resulting in loss of ability to focus on nearby objects. Myopia is a major public health concern throughout the world[4] and the prevalence has been increasing rapidly in recent years, especially in urban Asia.[5–7] Numerous studies have reported the prevalence of myopia in population-based samples with different ages and ethnicities

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and significant variations were observed.[8] A recent systematic review summarized the prevalence of myopia reported in 145 population-based studies and estimated that myopia prevalence would show a significant increase globally and affect nearly 5 billion people by the year of 2050.[9]

Predictors for myopia have been widely investigated. Recently, the protective effect of time spent outdoors, which could be construed as a proxy for exposure to sunlight, has been of particular interest to global myopia investigators as time spent outdoors is a modifiable lifestyle-related exposure and has important public health implications for disease prevention.[10] Up to now, there has been sufficient evidence supporting that more time spent outdoors could reduce the risk of myopia onset though it is still debatable whether the effect also applies to myopia progression.[11] Sherwin *et al.* summarized the relationship between time spent outdoors and myopia in children and young adults in a systematic review and meta-analysis of observational studies[12] and found that an additional hour spent outdoors per week was associated with a 2% reduction in the prevalence of myopia (pooled odds ratio [OR], 0.98; 95% confidence interval [CI], 0.97, 0.99). Although the protective effect of time outdoors on the risk of myopia has been confirmed, the exact biological plausibility behind the observed effect of time outdoors on myopia development has not been fully elucidated. The "vitamin D hypothesis" has been raised because vitamin D may be a link between less time outdoors and increased risk of myopia and several studies have found that a lower blood level of 25-hydroxyvitamin D (25(OH)D, the usual marker of vitamin D status) is associated with an increased likelihood of myopia. Alternatively, it is possible that the observed cross-sectional associations between the 25(OH)D level and myopia were confounded by time outdoors. It is well known that the blood vitamin D status is a surrogate marker for time outdoors. Children spending more time outdoors are more likely to be exposed to sunlight and subsequently are more likely to have higher blood levels of 25(OH)D. The blood 25(OH)D level may also be a confounder rather than an intermediate between time outdoors and myopia. Thus, there is a pressing need to clarify whether myopia development is driven by vitamin D deficiency or whether vitamin D is just a marker of time outdoors for myopia development. In this paper, we reviewed and summarized literature reports linking time outdoors and blood vitamin D levels to the risk of myopia.

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Initial evidence linking time outdoors to myopia in observational studies

The protective association between time outdoors and myopia was initially detected in several cross-sectional analyses among children of different ethnicities. Jones and colleagues first reported that myopic children participated in significantly less time outdoors as well as in sports activities compared with children who did not become myopic.[13] In predictive models, children who spent less time outdoors and on sports had significantly a greater likelihood of becoming myopic. A subsequent report by the same study group[14] reported that children who became myopic spent significantly less time outdoors and in sports than children who did not become myopic, both before and after the onset of myopia, which provided strong evidence supporting that less time spent outdoors was a potentially causal factor for myopia. The Sydney Myopia Study, a landmark epidemiologic study of myopia in Australia, indicated that children who spent greater amounts of time outdoors had a lower prevalence of myopia than children who spent little time outdoors.[10] Besides this main finding, this study also separately analyzed the effects of sports performed outdoors as well as outdoor leisure activities such as family picnics, playing outdoors and bushwalking, and indoor sports, and showed that the most important factor was the total time outdoors while indoor sports were not protective for myopia. In Asian communities where myopia was prevalent, a similar protective effect was reported in Chinese children living in Singapore.[15] In addition, greater time spent outdoors was associated with a significantly shorter AL.

Longitudinal follow-up analyses have replicated the findings observed in cross-sectional designs. For example, the Sydney Myopia Follow-up Study[16] showed that children who eventually became myopic spent less time outdoors at baseline compared with those who remained non-myopic, irrespective of the time spent on near work. The effect size of the time spent outdoors was strongest in younger children compared with the older ones, indicating that the amount of time outdoors when young is of particular importance in terms of refractive development.

Causal relationship – trials on time outdoors and myopia prevention

There have been quite a few observational studies reporting that increased time outdoors could reduce the risk of myopia

in children and adolescents. These studies provided relatively low levels of evidence and have been summarized in a systematic review published previously.[12] In epidemiology, well-designed randomized controlled trials (RCTs) provided the best evidence and there have been several RCTs published regarding the protective association of time outdoors and myopia.

The first trial[17] was carried out in Taiwan which involved 333 students in the interventional program and 238 students were in a control school. The intervention involved performing a recess outside the classroom program which encouraged school students to go outside for outdoor activities during recess, allowing potentially an additional 80 minutes of time outdoors per day. The authors found that the intervention program produced a 53% reduction in one-year incidence of myopia, but no effects on progression.

Another trial[18] was performed in northern China over one year with more than 3000 primary school students aged 6 to 14 years enrolled. The intervention group (n = 1735) unlike the control group (n = 1316) was allowed two additional 20 min recess programs outside the classroom (totally 40 minutes). A significant reduction in the development of uncorrected visual acuity (presumably myopia) was observed, suggesting a 60% reduction in myopia incidence. Changes in AL were also significantly lower in the intervention group (0.16 ± 0.30 mm per year *vs.* 0.21 ± 0.21 mm per year, P = 0.034). Similarly, no significant effect on progression of myopia was detected.

The third trial supporting the protective effect of time outdoors on myopia came from Guangzhou located in southern China, which involved about 900 school children in each group.[19] The intervention was an additional 40 minutes of time outdoors, added to the end of the school day. This intervention produced a 23% reduction in incident myopia over three years.

Possible biological mechanisms

Although the protective effect of time outdoors on myopia has been well established, the biological mechanism underlying this has been explored for years and has not been confirmed. The most dominant hypothesis is that bright light outdoors stimulated the release of dopamine from the retina, which could inhibit axial elongation of the eyeball, resulting in a lower risk of myopia. Experimental evidence has supported that light stimulated dopamine release from the retina and dopamine agonists could reduce axial elongation.[20] This hypothesis has received strong experimental support, because increasing light intensity completely prevented the development of form-deprivation myopia, at light intensities well within those often encountered in human environments.[21] However, there is still debate on the "light–dopamine" hypothesis since light does not protect from experimental lens-induced (defocus-induced) myopia,[22] which many believe to be the best model for human refractive development. Thus, other hypothesis on the protective effect of time outdoors was raised and should be tested.

An alternative hypothesis is that it is ultraviolet rather than visible light exposure that has caused the protective effect. However, at the current stage, this hypothesis is less supported by experimental studies compared with the light–dopamine hypothesis at the current stage. Bright lights used in experimental studies of protection were generally free of ultraviolet and bright ultraviolet light does not affect the process of emmetropization. Difference in ultraviolet light exposures may lead to a lower vitamin D levels in myopes than non-myopes. Quite a few efforts have been made in examining the possible relationship between blood vitamin D levels and the risk of myopia.

Blood 25(OH)D levels and myopia in epidemiologic studies

Five studies have addressed the issue of the association between blood levels of vitamin D and the risk of myopia and the major characteristics of these studies are summarized in Table 1.

A direct link between blood levels of vitamin D and the risk of myopia was first raised in a small survey of 22 subjects aged 13 to 25 years.[23] Fourteen myopes (≤−0.75 dioptre [D]) and 8 non-myopes (≥+0.25 D) were included in the analysis. The hypothesis that time outdoors might create differences in 25(OH)D could not be evaluated fully because time outdoors was not significantly related to myopia in this small sample. However, after adjusting for differences in the intake of dietary variables, myopes had lower levels of blood 25(OH)D than non-myopes by 3.4 ng ml^{-1}. Although this study provided preliminary evidence on the possible association between vitamin D and myopia, the findings were far from conclusive due to the small sample size.

Following the pilot study by Mutti *et al.*, several large population-based studies have examined the association between blood vitamin D levels and myopia. Considering that both myopia and vitamin D deficiency are common heath concerns in Asians, it is of utmost importance to examine their relationship in Asian cohort. The Korea National Health and Nutrition Examination Survey examined the association between the serum 25(OH)D concentration and the prevalence of myopia in 2038 Koreans aged 13 to 18 years.[24] Refractive errors were measured without cycloplegia and overnight fasting blood samples were collected. Serum 25(OH)D levels were measured by radioimmunoassay using a gamma counter. The authors found that every 1 ng ml^{-1} increase in the blood 25(OH)D level was associated with a 0.03 diopter change (95% CI 0.00–0.06; P = 0.047) towards hyperopia (less myopia) in multivariate analysis. In addition, an increased serum 25(OH)D concentration was also significantly associated with a decreased prevalence of high myopia (OR = 0.55, 95% CI 0.34–0.90; P = 0.017; comparing the highest *vs.* lowest tertile) among myopic individuals after adjusting for confounding factors such as the socio-economic level, rural *versus* urban residence, daily milk and calcium intakes, and smoking history. However, several

Table 1 Epidemiologic studies on the associations between blood 25(OH)D level and myopia

Authors (Year)	Location (Study)	Participants	Type	Cycloplegic refraction	Measurements of exposure	Definition of myopia	Adjusted variables in multivariate regressions	Summary of main findings
Mutti *et al.* (2012)[14]	Worthington (Ohio) city	22 volunteers ranged in age from 13 to 25 years	Cross-sectional study	Yes	25(OH)D	SE ≤ −0.75 D	Age and dietary intakes	In a multiple regression model, myopes had lower levels of blood 25(OH)D than non-myopes by 3.4 ng ml^{-1}.
Yazar *et al.* (2014)[25]	Western Australian Pregnancy Cohort (Raine) Study	A total of 946 young adults aged 20 years	Cross-sectional study	Yes	25(OH)D	SE ≤ −0.5 D	Age, sex, ethnicity, parental myopia, education status, and ocular sun-exposure biomarker score	In multiple analysis, lower serum 25(OH)D concentration was associated with a higher risk of having myopia (OR = 2.07; 95%CI, 1.29–3.32; P < 0.001; <50 *vs.* ≥50 nmol L^{-1}).
Choi *et al.* (2014)[24]	Korea National Health and Nutrition Examination Survey (KNHANES)	A total of 2038 Korean adolescents aged 13 to 18 years	Nationwide, population-based, and cross-sectional survey	No	25(OH)D	SE ≤ −0.5 D	Age, sex, area of residence, parental income, total energy intake, milk consumption, daily calcium intake, and smoking	Every 1 ng ml^{-1} increase in the blood 25(OH)D level was associated with a 0.03 diopter change (95% CI 0.00–0.06; P = 0.047) towards hyperopia (less myopia). An increased serum 25(OH)D concentration was also significantly associated with a decreased prevalence of high myopia (OR = 0.55, 95% CI 0.34–0.90; P = 0.017; comparing the highest *vs.* lowest tertile) among myopic individuals.
Guggenheim *et al.* (2014)[26]	Avon Longitudinal Study of Parents and Children (ALSPAC)	3677 children at age 7 to 15 years	Population-based, prospective cohort study	No	25(OH)D	SE ≤ −1.0 D	Number of myopic parents, time spent reading, and sex	In multiple analysis, there was no independent association between 25(OH)D (per nmol L^{-1} increase) and incident myopia (total, HR = 0.83 [0.66–1.04], P = 0.11; D3, HR = 0.89 [0.72–1.10], P = 0.30).
Tideman *et al.* (2016)[28]	Rotterdam, Netherlands (Generation R Study)	A total of 2666 children aged 6 years	Birth-cohort study	Yes	25(OH)D	SE ≤ −0.5 D	Age, sex, BMI, season of blood withdrawal, ethnicity, television watching, family income, education status of the mother and time spent outdoors	Higher 25(OH)D levels were associated with reduced risk of myopia (OR = 0.65, 95%CI 0.46–0.92, per 25 nmol L^{-1} increase in 25(OH)D level)

OR = odds ratio; HR = hazard risk; 95% CI = 95 percent confidence interval; SE = spherical equivalent; D = diopter; BMI = body mass index.

limitations of this study may have weakened the evidence in this study. First, noncycloplegic refraction is a major concern as it could misclassify refractive groups, making the risk factor analysis inaccurate. In addition, the effects of time spent outdoors and sunlight exposure were not taken into account, which have been shown to affect myopia development and 25(OH)D levels and therefore could have influenced the results of this study. Furthermore, most of the study participants are vitamin D deficient on the usual cut-offs. Given the low prevalence of vitamin D sufficiency in this population, the power of the study to find a significant result might have been reduced. However, although the magnitude of association is small, this study was important in providing evidence that vitamin D could be a potential therapeutic option to control the increasing rates of myopia.

Besides Asians, the association between 25(OH)D concentrations and myopia was also examined in a western population. In the Western Australian Pregnancy Cohort (Raine) Study, Yazar *et al.* analyzed the data of 946 participants aged 20 years.[25] Postcycloplegic autorefraction was performed using an autorefractor and serum 25(OH)D concentrations were determined using mass spectrometry. The results indicated that participants with vitamin D deficiency (<50 nmol L^{-1}) were twice as likely to be myopic as those who were not vitamin D deficient (≥50 nmol L^{-1}) (OR = 2.07; 95% CI 1.29–3.32; $P < 0.001$), which was consistent with the finding in Asians.[24] In addition, this study used a camera system to derive a score for a biomarker of ocular sun exposure by measuring conjunctival UV autofluorescence. The analysis demonstrated that the likelihood of being myopic decreased with increasing 25(OH)D levels in multivariable regression models adjusting for time spent outdoors or conjunctival UV autofluorescence as well as the fully adjusted model. It is important to note that the serum 25(OH)D concentrations increased with increasing CUVAF.

A large population-based birth cohort study was conducted to determine if the protective effect of time spent outdoors on myopia was mediated by the blood vitamin D status. The Avon Longitudinal Study of Parents and Children[26] performed noncycloplegic autorefraction on 3677 study subjects aged 7 to 15 years. Maternal reports of time outdoors at age 8 years and serum 25(OH)D at age 10 years were treated as exposure variables. A survival analysis was performed and a hazard ratio (HR) for incident myopia was calculated for children spending a high- *versus* low-time outdoors, before and after controlling the blood 25(OH)D level. The authors found that time spent outdoors was associated with increased 25(OH)D levels and reduced incidence of myopia, which was consistent with other studies. However, the protective effect of time spent outdoors was not attenuated when the blood 25(OH)D level was added to the model. One unit change in the natural logarithm of the 25(OH)D concentration (nmol L^{-1}) was not related with incident myopia (hazards ratio = 0.83, 95% CI 0.66–1.04; $P = 0.11$). This study suggests that vitamin D is not the protective factor in time spent outdoors in regards to myopia development. However, several important limitations of this study, such as determination of time spent outdoors using a single questionnaire and refractive error without cycloplegia, should be taken into account when interpreting the results.

Most previous studies have focused on the association between the blood 25(OH)D level and myopia but few have taken AL into consideration. AL is the primary determinant of non-syndromic myopia. It is a parameter representing the combination of the anterior chamber depth, lens thickness and vitreous chamber depth of the eye. AL can also be treated as an endophenotype of myopia and may provide extra advantages in the investigation of its genetic basis.[27] The study of AL will not only identify the determinants of eye elongation, but also provide aetiological evidence for myopia. A recently published study including 2666 children aged 6 years participating in the birth cohort study Generation R has shown measured automated cycloplegic refraction and ocular biometry including AL.[28] The serum 25(OH)D concentration was measured with the use of isotope dilution online solid phase extraction liquid chromatography–tandem mass spectrometry. Outdoor exposure was assessed by using a questionnaire. The study found that the lower serum levels of 25(OH)D were associated with longer ALs and higher risks of myopia after adjusting the covariates (OR = 0.65, 95% CI, 0.46–0.92). The association between the serum 25(OH)D level and AL remained significant after exclusion of myopic children and was similar among the children of European and non-European descent. In addition, both time spent outdoors and the serum 25(OH)D level were risk factors for AL. Time spent outdoors was not a significant risk factor for myopia (OR 0.81; 95% CI 0.61–1.07) when the effect of the serum 25(OH)D level was controlled, possibly due to the small number of myopes in this study. This important study indicated that the effect of the blood 25(OH)D level on myopia appeared independent of outdoor exposure and may suggest a more direct role for the blood 25(OH)D level in myopia pathogenesis.

In the above five major epidemiologic studies which directly assessed the association between the blood 25(OH)D concentrations and myopia, the assays used to measure 25(OH)D concentrations were different among different studies, which made it difficult to compare the effect estimates among different studies. In epidemiology, inaccurate and imprecise measurements of the exposures are likely to distort the effect estimates for the association with the outcome, especially when the sample size is small and/or the effect size is likely to be small.

Genetic polymorphisms in vitamin D in relation to myopia

Understanding the association between genetic polymorphisms in the vitamin D pathway genes and myopia could provide further insights into the role of vitamin D in myopia formation. Two studies have directly examined the variations in the vitamin D receptor (VDR) as potential risk factors for myopia development. In a case-control study conducted by

Annamaneni *et al.*,[29] a total of 206 high myopia, 98 low myopia and 250 control samples were analyzed for VDR gene Fok1 polymorphism using the polymerase chain reaction–restriction fragment length polymorphism technique. The frequency of ff homozygotes (8.3%) was found to be decreased in the high myopia group than the control group (14.0%) while the frequency of FF homozygotes was increased in the high myopic group (68.9% in high myopia *vs.* 62.8% in controls). An increased frequency of the f allele was found only in early ages at onset cases of high myopia and in later ages at onset cases of low myopia as well as in low myopia cases with parental consanguinity. This study suggested that the VDR gene might not be playing a direct role in the development of myopia, but might contribute indirectly to the risk conferred by mechanical stress factors or growth/development related factors through its role in calcium homeostasis and regulation of ciliary muscle function.

In a case-control study of Caucasians, Mutti *et al.*[30] found that one single-nucleotide polymorphism within VDR (rs2853559) was significantly associated with the presence of myopia in multivariate analysis. In a subgroup analysis of myopic subjects between −0.75 and −4.00 D, three SNPs within VDR (rs2239182; rs3819545; rs2853559) were significantly associated with the severity of myopia, accounting for 12% of model variance over age alone. The authors suggested that polymorphisms within VDR appear to be associated with low to moderate myopia.

Summary and future directions

In this article, studies which had addressed the relationship between time outdoors (a possible proxy measure for sunlight exposures), blood 25(OH)D level and the risk of myopia were reviewed. Research so far has found that people with lower levels of blood 25(OH)D concentration are more likely to be affected by myopia. However, current evidence linking vitamin D status to myopia was all observational in nature and could not answer the question whether myopia is driven by blood 25(OH)D or is blood 25(OH)D merely a confounder for the association between time outdoors and myopia. Considering that the levels of evidence are relatively weak and the mechanisms are unclear, the effect of vitamin D status on myopia development is far from conclusive and we cannot determine any causal relationship regarding the "vitamin D hypothesis". On the other hand, the protective effect of time outdoors, a possible proxy measure for sunlight exposure, has been well established in several RCTs. At the current stage, more evidence supports that the protective effect of time outdoors on myopia may be explained by the "light-dopamine" hypothesis rather than the "vitamin D" hypothesis.

Up to now, it is still unclear whether blood 25(OH)D regulates the onset or progression of myopia. One major study[26] had reported negative results, but may have limitations associated with the measurement of myopia. In this study, refractive error was assessed without cycloplegia. The necessity of cycloplegia has been emphasized during refractive measurement in children and adolescents, especially when risk factor analysis is the major purpose of the study.[31,32] Misclassification of the outcome measures in epidemiologic studies is likely to lead to biases. Other studies were all cross-sectional in nature and may be susceptible to selection bias and residual confounding.

In addition, no progress has been made in defining the biological mechanism of how vitamin D could prevent myopia onset and halt its progression. There may be several potential pathways. For example, as a powerful regulator of cellular differentiation, vitamin D has strong anticancer and antiproliferative effects.[33] Vitamin D may have antiproliferative effects directly on scleral remodeling that has been shown to play a major role in myopia development. Retinoic acid is a bi-directional regulator of eye growth in animal myopia models and may also be involved.[34,35] Retinoic acid and vitamin D may engage together in some crosstalk in signaling and cell-cycle regulation through overlapping binding specificities.[36] In addition, a recent finding suggested that the ciliary smooth muscle of the eye is larger in myopic children.[37] Enlargement in the ciliary muscle may have functional and structural impacts on the eye.[38] Vitamin D may be beneficial to the function of the smooth muscle. Longitudinal epidemiologic results have shown that a greater dietary intake of vitamin D is associated with a reduced risk of an overactive bladder, a condition characterized by poorly functioning hypertrophic smooth muscle.[39] Clearly more work in needed in this area as well.

Results from school-based trials of increasing the amount of time that children spend outdoors have provided promising results, but vitamin D supplementation trials have not been carried out. To determine whether the protective effect of time outdoors on myopia is driven by vitamin D, observational studies could not help and well-designed vitamin D supplementation RCTs must be conducted. If vitamin D supplementation could effectively reduce the incidence of myopia and halt its progression, it would provide proof of principle for myopia interventions based on dietary intake. Adding vitamin D into daily meals would be a more feasible and effective intervention compared with changing lifestyles such as increasing time outdoors in Asian communities that are currently characterized by high prevalence rates of myopia such as China.[40] If successful, this will provide an excellent example of how integrating human epidemiology can be translated into public health approaches which can provide real health benefits.

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