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Association Between Myopia, Ultraviolet B Radiation Exposure, Serum Vitamin D Concentrations, and Genetic Polymorphisms in Vitamin D Metabolic Pathways in a Multicountry European Study

Katie M. Williams, FRCOphth; Graham C. G. Bentham, MA; Ian S. Young, MD; Ann McGinty, PhD; Gareth J. McKay, PhD; Ruth Hogg, PhD; Christopher J. Hammond, MD; Usha Chakravarthy, PhD; Mati Rahu, PhD; Johan Seland, PhD; Gisele Soubrane, MD; Laura Tomazzoli, MD; Fotis Topouzis, MD; Astrid E. Fletcher, PhD

IMPORTANCE Myopia is becoming increasingly common globally and is associated with potentially sight-threatening complications. Spending time outdoors is protective, but the mechanism underlying this association is poorly understood.

OBJECTIVE To examine the association of myopia with ultraviolet B radiation (UVB; directly associated with time outdoors and sunlight exposure), serum vitamin D concentrations, and vitamin D pathway genetic variants, adjusting for years in education.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional, population-based random sample of participants 65 years and older was chosen from 6 study centers from the European Eye Study between November 6, 2000, to November 15, 2002. Of 4187 participants, 4166 attended an eye examination including refraction, gave a blood sample, and were interviewed by trained fieldworkers using a structured questionnaire. Myopia was defined as a mean spherical equivalent of −0.75 diopters or less. Exclusion criteria included aphakia, pseudophakia, late age-related macular degeneration, and vision impairment due to cataract, resulting in 371 participants with myopia and 2797 without.

EXPOSURES Exposure to UVB estimated by combining meteorological and questionnaire data at different ages, single-nucleotide polymorphisms in vitamin D metabolic pathway genes, serum vitamin D_3 concentrations, and years of education.

MAIN OUTCOMES AND MEASURES Odds ratios (ORs) of UVB, serum vitamin D_3 concentrations, vitamin D single-nucleotide polymorphisms, and myopia estimated from logistic regression.

RESULT Of the included 3168 participants, the mean (SD) age was 72.4 (5) years, and 1456 (46.0%) were male. An SD increase in UVB exposure at age 14 to 19 years (OR, 0.81; 95% CI, 0.71-0.92) and 20 to 39 years (OR, 0.7; 95% CI, 0.62-0.93) was associated with a reduced adjusted OR of myopia; those in the highest tertile of years of education had twice the OR of myopia (OR, 2.08; 95% CI, 1.41-3.06). No independent associations between myopia and serum vitamin D_3 concentrations nor variants in genes associated with vitamin D metabolism were found. An unexpected finding was that the highest quintile of plasma lutein concentrations was associated with a reduced OR of myopia (OR, 0.57; 95% CI, 0.46-0.72).

CONCLUSIONS AND RELEVANCE Increased UVB exposure was associated with reduced myopia, particularly in adolescence and young adulthood. The association was not altered by adjusting for education. We found no convincing evidence for a direct role of vitamin D in myopia risk. The relationship between high plasma lutein concentrations and a lower risk of myopia requires replication.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Astrid E. Fletcher, PhD, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom (astrid.fletcher@lshtm.ac.uk).

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Myopia, or short-sightedness, is a complex trait influenced by numerous environmental and genetic factors. Myopia is becoming more common worldwide, most dramatically in urban Asia, but rises in prevalence have also been identified in the United States and Europe.[1,2] This has major implications, both visually and financially, for the global burden from this potentially sight-threatening condition.

An increased risk of myopia has been associated with urbanization, higher socioeconomic status, prenatal factors, near work, and education.[2-5] The protective effect of time outdoors on myopia has been identified in studies of school-aged children and young adults, with replication in different climates.[6-10] A meta-analysis of 7 cross-sectional studies[11] concluded that there was a 2% reduced odds of myopia per additional hour of time spent outdoors per week. The recommendation for children to spend time outdoors provides an attractive option, and intervention studies are in progress.[12] However, it remains unclear which of the numerous elements associated with time spent outdoors, such as light intensity, ultraviolet radiation (UVR), or distant focus, confers the reduced risk of myopia. Vitamin D concentrations have been inversely associated with myopia in some but not all studies,[13-17] while genetic polymorphisms in vitamin D pathway genes have been associated in 1 study but not in another.[13,17]

We exploited the availability of relevant existing information (ie, refractive status, UVR, education, serum vitamin D concentrations, and genetic polymorphisms in vitamin D pathway genes) in the European Eye Study with the objective of investigating their association with myopia.

Key Points

Question What is the association between myopia and ultraviolet B radiation, serum vitamin D concentrations, and polymorphisms in vitamin D metabolism genes in a cross-sectional, population-based random sample of participants 65 years and older from north and south Europe?

Findings In this secondary analysis of the European Eye Study, only ultraviolet B radiation exposure was associated with a reduced odds ratio for myopia, especially in adolescence and early adulthood, despite adjustment for years in education.

Meaning This study, while not designed to determine cause and effect relationships, suggests that increased ultraviolet B exposure, a marker of sunlight exposure, is associated with reduced myopia.

Methods

Study Population

The European Eye Study was designed to maximize heterogeneity of UVR exposure and diet by selection of study centers from northern to southern Europe. Participants were recruited from November 6, 2000, to November 15, 2002, from random sampling of the population 65 years and older in the following centers: Bergen, Norway; Tallinn, Estonia; Belfast, United Kingdom; Paris-Creteil, France; Verona, Italy; Thessaloniki, Greece; and Alicante, Spain.[18] More than 11 000 people were invited, of whom 5040 participated (45.8% response rate). Written informed consent was obtained from all study participants. Ethical approval was obtained for each center from the local ethics committee, and the research adhered to the tenets of the Declaration of Helsinki.

Details of study design are described elsewhere.[19] Participants attended the examination center where they were interviewed by trained fieldworkers, underwent an ophthalmological examination, and gave a blood sample for blood measurements and genotyping. Information collected by the interviewers included years of education, smoking, alcohol use, a brief medical history, a semiquantitative food frequency questionnaire, and a detailed questionnaire on outdoor exposure.

Measurement of UV Exposure

Full details of the methods have been published previously.[20] Participants were sent a residence and employment history survey to complete in advance to facilitate recall at the interview. We used a questionnaire that asked about time spent outdoors between the hours of 9 AM and 5 PM and between 11 AM and 3 PM daily (from the age of 14 years) for different occupational and leisure periods (including homecare) and in retirement up to current age. Information from the questionnaire and residence calendar and geographical coordinates for residence were sent to the University of East Anglia in the United Kingdom to generate estimates of individual years of all-day (9 AM to 5 PM) or middle-of-the-day (11 AM and 3 PM) exposure for different wavelengths of light (ultraviolet A, ultraviolet B [UVB], and blue light). For all residences of 1 year or more, ambient UVB (minimal erythema dose[21]) and ultraviolet A (J/cm^2) were estimated from published sources that take into account time of day, month, and latitudinal variations.[22] We used published coefficients to adjust ambient clear-sky UV for cloud cover[23] and terrain.[24] For each wavelength of light, maximum potential lifetime dose was calculated as the sum of the time-weighted levels at each of the places of residence of the individual. Personal adult lifetime (ie, from age 14 years) UV exposure was estimated for each of the 3 wavelengths and summed for a mean annual lifetime dose at different ages for all-day and middle-of-the-day exposure.

Visual Acuity and Refraction

The protocol for testing visual acuity (VA) was different in 1 of the European Eye Study centers (Alicante, Spain); data from this center was not included in the present analysis. All other centers followed the procedures described below. Presenting distance VA (ie, with spectacles if worn) was tested separately in each eye using the 4-meter ETDRS logMAR chart. Any participant who was unable to achieve 0.3 logMAR (ie, a 20/40 Snellen acuity) in either eye underwent automated refraction or manual retinoscopy, and their best-corrected VA was recorded. For persons who achieved 0.3 logMAR or better, the spectacle correction (if any) worn by the participant for each eye was measured by neutralization using a focimeter or by handheld lenses. The spherical equivalent was obtained by

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adding half of the cylindrical value to the spherical value and the mean of the 2 eyes was calculated, commonly used in epidemiological studies. Myopia was defined as a spherical equivalent of −0.75 diopters (D) or less (low myopia, ≤−0.75 to >−3 D; moderate myopia, ≤−3 to >−6 D; severe myopia, ≤−6 D). Those with a spherical equivalent greater than −0.75 D were not considered to have myopia, nor were those with an unaided VA higher than 0.3 logMAR when refraction was not measured. Participants with late age-related macular degeneration (AMD), aphakia or pseudophakia in either eye, or visual impairment (ie, less than 0.5 logMAR or 20/60 Snellen acuity or less) due to cataract were excluded.

Blood Measurement

Blood samples were sent to a single laboratory (Queen's University Belfast in the United Kingdom) for analysis. Serum 25-hydroxy vitamin D_2 (25[OH]D_2) and 25-hydroxy vitamin D_3 (25[OH]D_3) concentrations were measured by liquid chromatography-tandem mass spectrometry.[25] In all analyses, vitamin D levels were adjusted for season of measurement. Plasma lutein concentrations, zeaxanthin concentrations, β-cryptoxanthin concentrations, α-carotene and β-carotene concentrations, α-tocopherol and γ-tocopherol concentrations, lycopene concentrations, and retinol concentrations were measured by reversed-phase high-performance liquid chromatography. Total ascorbate was measured using an enzyme-based assay in plasma stabilized with metaphosphoric acid. All assays were standardized against appropriate National Institute of Standards and Technology standard reference materials. Cholesterol was measured using an enzymatic assay (Randox, Crumlin) on a Cobas FARA centrifugal analyzer (Roche Diagnostics).

Statistical Analysis

Statistical analysis was carried out using Stata version 13 (StataCorp). All analyses took account of the study design of the 6 centers by use of robust errors. All-day (9 AM to 5 PM) adult lifetime UVB exposure and 25(OH)D_3 concentrations were the primary measures of interest, as vitamin D_3 is produced in the skin following exposure to UVB whereas vitamin D_2 is mainly derived from fortified foods and vitamin supplements.[26] Following the exclusion of 67 participants with very high levels, the distribution of 25(OH)D_3 concentrations was normal. We investigated 25(OH)D_3 both as a continuous variable and categorized by quintiles. Dietary vitamin D was estimated using food composition tables[27] and was energy adjusted. Exposure to UVB was normalized using a square root transformation and then z transformed to investigate an increase in exposure of 1 SD. We calculated years of education from the difference between the start and leaving dates and categorized these data into tertiles to reflect the common tiers of education (ie, primary, secondary, and higher) for inclusion as an independent myopia risk factor.

We ran preliminary regression analyses to identify factors associated with changes in 25(OH)D_3 concentrations and with UVB as possible confounders of any association with myopia. A large number of variables were independently associated with 25(OH)D_3 concentrations, including age, sex, season, study center, current smoking, diabetes, obesity, dietary vitamin D intake, fish and fish oil supplement intake, and antioxidants, including vitamin C, lutein (or zeaxanthin), retinol, α-tocopherol, and cholesterol. Lutein and zeaxanthin were highly correlated (r = 0.85), and results were almost identical when separately introduced into the models; we presented lutein only for simplicity. Of these, only lutein was (inversely) associated with myopia and entered the models as a potential confounder. The factors independently associated with UVB were 25(OH)D_3 concentrations, study center, sex, and education; only education was (positively) associated with myopia. Therefore, in our final logistic regression models for myopia, we retained age, sex, study center, and season as well as our primary exposure variables (UVB, 25[OH]D_3, and education) and identified confounders, namely lutein. Our outcome measure was the confounder-adjusted association between myopia and our key exposures expressed as the adjusted odds ratio (OR) in logistic regression.

Single-Nucleotide Polymorphism Selection, Genotyping, and Genetic Analyses

For reason of costs, genotyping was undertaken in a subsample of the main study. Data on vitamin D pathway single-nucleotide polymorphisms (SNPs) were available for a subset of 109 of 371 participants (29.4%) with myopia and 782 of 2797 participants (28.0%) without myopia. Ninety-three common SNPs located across 7 genes involved in vitamin D metabolism—*GC* (10), *RXRA* (14), *CYP2R1* (7), *DHCR7* (5), *VDR* (29), *CYP27B1* (7), and *CYP24A1* (21)—were selected from Phase III, release 2 HapMap data of Utah residents with ancestry in northern and western Europe using Haploview (http://www.broadinstitute.org/haploview) to determine linkage disequilibrium. Tag SNPs were selected using multimarker tagging with the following criteria: r^2 greater than 0.8, minor allele frequency of 5% or greater, genotype call rate of 95% or greater, and no significant deviation from Hardy Weinberg equilibrium. Genotyping was performed by KBiosciences, and associations between genotypes and myopia status were investigated. Quality filters for exclusion of SNPs included call rates less than 95% and deviation from Hardy Weinberg equilibrium (P < .001). DNA samples were excluded if missing genotypes exceeded 10%. Other quality control measures included duplicates on plates, random sample allocation to plates, independent scoring of problematic genotypes by 2 individuals, and resequencing selected DNAs to validate genotypes. KBiosciences quality control also included validation of all SNP assays on a panel of 44 random white participant-derived samples and 4 nontemplate (negative) controls. Statistical genetic tests were performed using PLINK version 1.07 under an additive genotypic model.[28] Logistic regression adjusted for age, sex, season, and study center to examine association with individual SNPs.

Results

The flow of participants in the study design is illustrated in **Figure 1**. We excluded 515 participants for aphakia or pseudo-

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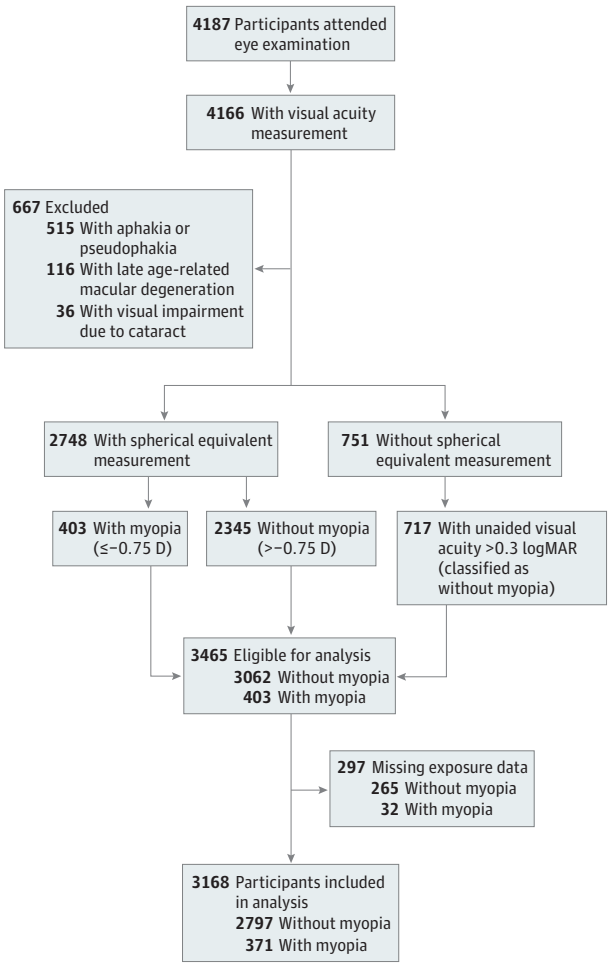
phakia, 116 for late AMD, and 36 for vision impairment due to cataract. Relevant exposure data (mainly serum 25[OH]D_3 concentrations) were missing in 297 participants (32 with myopia and 265 without myopia). Our final analysis was based on 371 participants with myopia, of which 24 (6.5%) had high myopia, and 2797 without myopia with complete data on all relevant exposures. Included participants had a mean (SD) age of 72.4 (5) years, and 1456 (46.0%) were male.

Figure 1. PRISMA Flowchart of Inclusion of Study Participants



In univariate analyses, there were no differences in the age or sex of people with myopia compared with those without, nor in smoking habit, alcohol use, or obesity (**Table 1**). Significant differences were observed between those with and without myopia in years of education, UVB exposure, and serum 25(OH)D_3 concentrations, but there was no difference in dietary vitamin D intake.

In analyses adjusted for age, sex, and study center, an increase of 1 SD in personal lifetime UVB exposure was associated with reduced odds of myopia (OR, 0.72; 95% CI, 0.56-0.93; P = .001) (**Table 2**). Those in the highest tertile of years of education (median, 14 years) had twice the odds of myopia (OR, 2.08; 95% CI, 1.41-3.06; P = .001) compared with those in the lowest tertile (median, 7 years). In the adjusted analyses, there was no clear evidence for an association of 25(OH)D_3 concentrations (either continuous or by quintiles) with myopia. In contrast, those in the highest quintile of plasma lutein concentrations had nearly half the risk of myopia (adjusted OR, 0.57; 95% CI, 0.46-0.72) compared with the lowest quintile. In a further model adjusted for age, sex, study center, and season and incorporating 25(OH)D_3 concentrations, lutein concentrations, education, and UVB, the estimates for each exposure were virtually unchanged. There was evidence for a stronger inverse association of UVB with increasing myopia severity (low myopia: OR, 0.87; 95% CI, 0.75-1.01; P = .06; moderate myopia: OR, 0.59; 95% CI, 0.36-0.97; P = .04; severe myopia: OR, 0.39; 95% CI, 0.25-0.63; P = .001).

We investigated whether the association with myopia and UVB exposure varied by the personal UVB exposure experienced at different ages. Significant ORs for less myopia with increased UVB exposure were observed in adolescence and early adulthood, between ages 14 to 19 years and 20 to 29 years (**Figure 2**), but not for other age groups.

The subset of 891 patients (28.1%) with genetic data were similar in age (mean [SD] age, 73 [5] years), sex (49% male), and myopia severity (low myopia, 59%; moderate, 34%; and high, 7%) to those without genetic data. Of the 93 genetic variants associated with vitamin D metabolism, 1 SNP in *GC* was excluded for deviation from Hardy Weinberg equilibrium. Of the remaining SNPs, 4 were nominally associated with myo-

Table 1. Characteristics of Participants With and Without Myopia

Characteristic[a]	Myopia (n = 371)	Without Myopia (n = 2797)	*P* Value[b]
Age, mean (SD), y	72.9 (5.5)	72.4 (5.0)	.58
Male, No. (%)	174 (46.9)	1282 (45.8)	.83
Years of education, median (IQR)	11 (7-14)	9 (7-12)	.01
UVB (minimal erythema dose), median (IQR)[c]	314 (140-566)	358 (224-585)	.01
25(OH)D_3, mean (SD), nmol/L	45.3 (20.8)	47.5 (20.9)	.01
Dietary vitamin D, median (IQR), µg/d	1.86 (1.32-2.62)	1.89 (1.35-2.56)	.62
Ever smoked, No. (%)	179 (48.2)	1350 (48.3)	.98
Alcohol at least weekly, No. (%)	134 (36.1)	1106 (39.5)	.49
Obesity (BMI >30), No. (%)	138 (37.2)	1001 (35.8)	.82
Lutein, median (IQR), µmol/L	0.087 (0.04-0.24)	0.130 (0.05-0.39)	<.01

Abbreviations: 25(OH)D_3, serum 25-hydroxy vitamin D_3; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; UVB, ultraviolet B radiation.

[a] Univariate analyses.

[b] Difference in characteristic between those with and without myopia.

[c] Mean annual UVB exposure.

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Table 2. Association of Ultraviolet B Radiation Exposure, Education, Serum Vitamin D_3 Concentrations, and Lutein Concentrations With Myopia

Characteristic	Adjusted OR (95% CI)[a]	*P* Value[b]	Adjusted OR (95% CI)[c]	*P* Value[b]
UVB exposure (1 SD increase)	0.72 (0.56-0.93)	.01	0.75 (0.58-0.97)	.03
Years of education, median		.001		<.001
First tertile (7)	1 [Reference]	NA	1 [Reference]	NA
Second tertile (10)	1.26 (0.99-1.58)	.06	1.22 (0.96-1.57)	.10
Third tertile (14)	2.08 (1.41-3.06)	.001	2.04 (1.40-2.96)	.001
25(OH)D_3 concentrations (continuous)	0.99 (0.98-1.00)	.48	NA	NA
Quintiles of 25(OH)D_3, median, nmol/L		.31		.31
First quintile (19.9)	1 [Reference]	NA	1 [Reference]	NA
Second quintile (33.1)	0.96 (0.79-1.31)	.78	0.95 (0.74-1.22)	.77
Third quintile (45.3)	0.87 (0.64-1.38)	.55	0.89 (0.59-1.36)	.62
Fourth quintile (58.9)	0.75 (0.47-1.20)	.24	0.78 (0.51-1.20)	.28
Fifth quintile (77.0)	0.87 (0.51-1.47)	.60	0.87 (0.56-1.38)	.59
Quintiles of plasma lutein, median, μmol/L		<.001		<.001
First quintile (0.03)	1 [Reference]	NA	1 [Reference]	NA
Second quintile (0.05)	0.93 (0.80-1.08)	.34	0.94 (0.81-1.10)	.48
Third quintile (0.11)	0.82 (0.55-1.20)	.30	0.83 (0.55-1.25)	.39
Fourth quintile (0.22)	0.89 (0.62-1.27)	.51	0.87 (0.63-1.19)	.41
Fifth quintile (0.48)	0.57 (0.46-0.72)	.001	0.59 (0.48-0.73)	<.001

Abbreviations: 25(OH)D_3, serum 25-hydroxy vitamin D_3; NA, not applicable; OR, odds ratio; UVB, ultraviolet B radiation.

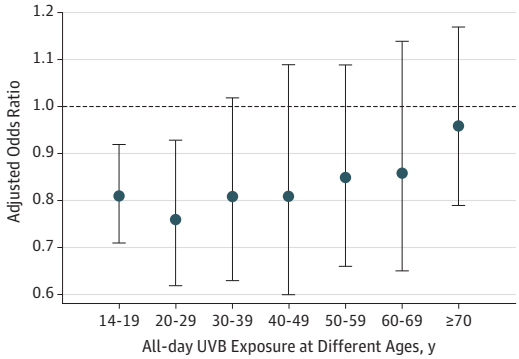
[a] Adjusted for age, sex, study center, and season for 25(OH)D_3 and lutein concentrations.

[b] *P* value for effect of each variable on myopia.

[c] Adjusted for age, sex, study center, season, and all variables in the model (namely, UVB exposure, education, 25(OH)D_3 concentrations, and plasma lutein concentrations).

pia (3 in *CYP2RI* and 1 in *CYP24A1*), but none withstood correction for multiple testing (eTable in the Supplement).

Figure 2. Association of All-Day Ultraviolet B (UVB) Exposure at Different Ages With Myopia



Adjusted for age at time of examination, sex, study center, and years of education. Error bars indicate 95% CIs.

Discussion

We found that higher annual lifetime UVB exposure, directly related to time outdoors and sunlight exposure, was associated with reduced odds of myopia. Exposure to UVB between ages 14 and 29 years was associated with the highest reduction in odds of adult myopia. Myopia was more than twice as common in participants in the highest tertile of education. The association between UVB, education, and myopia remained even after respective adjustment. This suggests that the high rate of myopia associated with educational attainment is not solely mediated by lack of time outdoors.

The protective effect of time outdoors on myopia is well established.[6-9,29] Time outdoors reflects various physiological effects that have been associated with or hypothesized to influence myopia, including brighter light levels,[30,31] a different spectrum of wavelengths compared with artificial lighting with reduced UVR, and an extended focal distance with less hyperopic peripheral defocus.[32] Ultraviolet conjunctival autofluorescence, an indirect marker of ocular sun exposure (in particular, UVR), is inversely associated with myopia[8] and has a stronger effect than time outdoors assessed using questionnaires. One small study[33] measuring UVR using dosimeters found differing exposure between those with emmetropia, those with stable myopia, and those with progressing myopia.

Proposed mediating mechanisms include activation of dopaminergic retinal amacrine cells, which are stimulated by light[31] and influence ocular axial growth,[34] and higher serum vitamin D concentrations induced by sunlight. We, like others, did not find evidence to support the association between myopia and serum vitamin D concentrations[16] or genes involved in vitamin D metabolism. A previous publication[17] examined 12 SNPs from 2 vitamin D pathway genes (*VDR* and *GC*) and reported a significant association between rs2853559 in *VDR* in the overall sample of 289 participants with myopia and 81 controls and a further 3 variants in *VDR* within a subset of participants with low and moderate myopia. In a more recent publication,[13] 33 SNPs across 6 genes associated with vitamin D metabolism were examined in more than 2000 individuals in relation to both refractive error and axial length. Nominal significance was identified for variants in *CYP24A1* and *VDR*,

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but none withstood correction for multiple testing. We investigated the association between myopia and 92 variants in vitamin D metabolism genes, identifying nominal significance in 3 SNPs in *CYP2R1* and 1 SNP in *CYP24A1* (not the same variant as the aforementioned study). None withstood correction for multiple testing. We acknowledge low power for this type of analysis, but notably, we studied more variants as well as previously unexamined genes (ie, *CYP2R1* and *RXRA*) in a substantial cohort.

Those in the highest fifth of plasma lutein concentrations had approximately 40% reduced odds of myopia. We excluded those with late AMD because we have previously shown an increased risk of late AMD with blue light exposure in those with low levels of key antioxidants, including lutein.[20] Sensitivity analyses made no appreciable difference; myopia (OR, 0.56; 95% CI, 0.46-0.70) in the highest quintile of lutein was similar when 72 individuals with late AMD were included or excluded (OR, 0.57 vs 0.56). Lutein is a retinal carotenoid, responsible for much of the macular pigment optical density, and has antioxidative, anti-inflammatory, and structural effects in neural tissue.[35] Lutein has been associated with a reduced risk of AMD,[36] with improved contrast sensitivity in healthy individuals,[37] and (inversely) with axial length (and thus axial myopia).[38] Although limited evidence for an association between lutein and myopia is gained from this analysis and, importantly, no causative role can be inferred, it does raise interesting hypotheses for a potential role.

Study Limitations

This study has limitations. We retrospectively calculated UVB exposure data through highly detailed questionnaires over the life course and used this data together with geographically specific, historical data on UVR. Our measure is subject to recall error and lacks the heightened accuracy of UV exposure achieved with light meters. However, we do not have any reason to believe that the UVB association would be biased, as myopia was identified after the interview. A weakness of our study was that we did not collect any data on UVB exposure during childhood, which could be argued to be more relevant in myopia development. However, a significant proportion of refractive error develops in adolescence and early adulthood,[39] and our results showed the greatest effects for these age groups. No myopia was defined either by refraction or good, unaided VA when refraction was unknown. This definition was used in attempt to minimize bias, but to ensure this was appropriate, we performed sensitivity analyses in which those without myopia were only classified on the basis of measured refractive error; analysis using this definition produced very similar results. A limitation was also that vitamin D and lutein concentrations were measured in later life. The association between myopia development and these factors may be more relevant in younger ages. However, there is evidence, albeit limited, that an individual's 25(OH)D concentrations are reproducible over time.[40] Variants in vitamin D pathway genes are not subject to these concerns of temporality and confounding (mendelian randomization); hence, any association with myopia would strengthen a causal relationship with vitamin D. Therefore, we consider it unlikely that vitamin D plays a role in myopia.

Conclusions

This study suggests lifetime exposure of UVB is associated with reduced myopia in adulthood. The protective association is strongest with exposure in adolescence and younger adult life and with increasing severity of myopia. As the protective effect of time spent outdoors is increasingly used in clinical interventions, a greater understanding of the mechanisms and life stages at which benefit is conferred is warranted.

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Author Affiliations: Department of Ophthalmology, King's College London, London, United Kingdom (Williams, Hammond); Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom (Williams); School of Environmental Sciences, University of East Anglia, East Anglia, United Kingdom (Bentham); Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom (Young, McGinty, McKay); Centre for Experimental Medicine, Institute of Clinical Science, Queen's University Belfast, Belfast, United Kingdom (Hogg, Chakravarthy); Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia (Rahu); Eye Department, University of Bergen, Bergen, Norway (Seland); Department of Ophthalmology, Hôtel-Dieu de Paris, Paris Descartes University, Paris, France (Soubrane); Ophthalmology Clinic, University of Verona, Verona, Italy (Tomazzoli); Department of Ophthalmology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece (Topouzis); Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom (Fletcher).

Author Contributions: Dr Fletcher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Williams, McKay, Chakravarthy, Rahu, Tomazzoli, Topouzis, Fletcher.
Acquisition, analysis, or interpretation of data: Williams, Bentham, Young, McKay, Hogg, Hammond, Chakravarthy, Rahu, Seland, Soubrane, Topouzis.
Drafting of the manuscript: Williams, McKay, Tomazzoli, Fletcher.
Critical revision of the manuscript for important intellectual content: Bentham, Young, McKay, Hogg, Hammond, Chakravarthy, Rahu, Seland, Soubrane, Topouzis.
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