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Plasma Vitamin D and Intermediate Age-Related Macular Degeneration: Insights from the Longitudinal ALIENOR Study

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Objective: Age-related macular degeneration (AMD) is a leading cause of vision loss in older adults, with limited options to prevent disease progression. Vitamin D may influence AMD pathogenesis through anti-inflammatory, antioxidative, and antiangiogenic effects. This study aims to investigate the association between deseasonalized plasma 25-hydroxyvitamin D [25(OH)D] levels and the risk of incident AMD, as well as longitudinal changes in macular layer thickness in an elderly population.

Design: Population-based cohort study.

Participants: Seven hundred eyes from 429 participants aged ≥65 years from the ALIENOR Study, followed up over 18 years.

Methods: Baseline deseasonalized plasma 25(OH)D levels were measured and categorized as sufficient (≥50 nmol/l), insufficient (25–49 nmol/l), or deficient (<25 nmol/l). Cox proportional hazards models adjusted for demographic, lifestyle, and clinical covariates were used to estimate the risk of incident AMD. Longitudinal linear mixed-effects models assessed changes in outer retinal layer thicknesses derived from OCT imaging.

Main Outcome Measures: Incident intermediate and advanced AMD based on fundus color photographs and OCT.

Results: The mean baseline deseasonalized plasma 25(OH)D level was 37.9 ± 14.9 nmol/l. Vitamin D deficiency (<25 nmol/l) was significantly associated with increased risk of incident intermediate AMD compared to sufficient levels (≥50 nmol/l, hazard ratio [HR] = 2.34; 95% confidence interval [CI]: 1.19–4.61; $P = 0.01$), while insufficiency (25–49 nmol/l) showed a borderline increased risk (HR = 1.74; 95% CI: 0.98–3.08; $P = 0.06$). No significant associations were observed with advanced AMD. Vitamin D–deficient participants also experienced a significant increase in retinal pigment epithelium–Bruch membrane (RPE–BM) complex thickness over time (β = 0.07 μm/year; 95% CI: 0.01–0.13; $P = 0.02$), while other outer retinal layers showed no significant change.

Conclusions: Low deseasonalized plasma 25(OH)D levels were associated with a higher risk of developing intermediate AMD and progressive thickening of the RPE–BM complex, a key retinal structure implicated in AMD pathogenesis. These findings support an association hypothesis and highlight vitamin D status as a candidate modifiable factor worthy of further investigation.

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Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is a progressive and multifactorial retinal disease, recognized as one of the leading causes of legal blindness in developed countries.[1,2] It affects approximately 8.7% of people between the ages of 45 and 85 years worldwide.[3] Although extensive research is ongoing, there is currently no available therapy that can cure the disease or stop its progression.

Early AMD is typically asymptomatic and marked by medium-sized drusen. As the disease advances, drusen enlarge, and pigmentary changes in the retinal pigment epithelium (RPE) emerge, indicating intermediate AMD. Further progression can lead to advanced AMD, including geographic atrophy (loss of photoreceptors and RPE) and neovascular AMD (choroidal neovascularization with exudation), both causing significant central vision loss.[4]

Advances in multimodal imaging, notably OCT and fundus autofluorescence, have enabled detailed characterization of AMD-related changes.[5] Automated OCT layer segmentation has further enhanced the study of individual macular layers.[6,7] Importantly, increased photoreceptor segment layer and thickening of the RPE–Bruch

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membrane (BM) complex have been linked to disease progression.[8–12]

While imaging has improved diagnosis and monitoring, the underlying molecular mechanisms remain incompletely understood. Oxidative stress, chronic inflammation, and immune dysregulation are thought to play central roles in AMD pathogenesis, disrupting the structure and function of the RPE, BM, and the underlying choriocapillaris.[13,14]

Vitamin D, traditionally recognized for its central role in calcium and phosphate homeostasis and bone mineralization, has increasingly drawn scientific interest for its involvement in immune modulation, inflammation, and cellular homeostasis.[15,16] Vitamin D exists in two primary forms—vitamin D2 (ergocalciferol), derived from plant sources, and vitamin D3 (cholecalciferol), synthesized in the skin upon exposure to ultraviolet B radiation.[17] Once produced or ingested, vitamin D undergoes a two-step hydroxylation process in the liver and kidneys to become biologically active. The resulting metabolite, 1,25-dihydroxyvitamin D [25(OH)D], exerts its effects mediated by the vitamin D receptor, which is widely expressed across human tissues, including the retina and RPE.[18]

Epidemiological studies have identified an association between osteoporosis and AMD, suggesting a shared systemic background potentially mediated by vitamin D–dependent pathways.[19–22] Low bone mineral density and osteoporosis have been linked to an increased prevalence and incidence of AMD, with pronounced sex-specific differences. These disease-specific associations support the hypothesis that dysregulated mineral metabolism, inflammation, and vitamin D deficiency may represent common mechanisms underlying both impaired bone health and AMD.

Experimental studies suggest that vitamin D may protect against AMD by mitigating oxidative damage, dampening inflammatory responses, and inhibiting pathological angiogenesis.[23–25] Epidemiological data on serum vitamin D levels are relatively inconsistent,[26] particularly for early AMD; however, two meta-analyses based on population studies suggest an increased risk of late-stage AMD among individuals with circulating 25(OH)D levels below 50 nmol/l.[27,28] With regard to dietary vitamin D intake, several cohort studies have reported that individuals with higher dietary vitamin D intake have a lower risk of developing AMD.[29–32]

To our knowledge, no previous study has examined whether plasma 25(OH)D levels are associated with AMD-related changes in the macular layers; therefore, we undertook the present study to address this question.

Methods

Study Cohort

The ALIENOR Study is an ancillary study of the prospective, population-based Three-City Study, which began in 1999 and enrolled adults aged ≥ 65 years from electoral rolls in Montpellier, Dijon, and Bordeaux, France. In 2006, participants from the Bordeaux cohort were invited for detailed ophthalmologic examination, marking the launch of the ALIENOR Study. A total of 963 participants were included at baseline (2006 − 2008). Both the Three-City and ALIENOR studies have been described in detail previously.[33,34]

Briefly, the ALIENOR Study involved biennial eye examinations conducted at the Department of Ophthalmology, University Hospital of Bordeaux, from 2006 through 2024 (http://www.alienor-study.com/langue-english-1.html, accessed on 16 November 2025). All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III, approval code 2006/10), in accordance with the Declaration of Helsinki.

Ophthalmic Examination, Retinal Imaging, and Macular Layer Segmentation

Comprehensive ophthalmologic examinations included visual acuity, refraction, intraocular pressure, and 45° color fundus photography. From the first follow-up visit onward (2009–2011), spectral-domain OCT (Spectralis, Heidelberg Engineering) was added.[8] Automated macular layer segmentation was performed using Heidelberg Eye Explorer 2, yielding thickness measurements for individual outer retinal layers (Figure S1, available at www.ophthalmologyscience.org) across the ETDRS grid. Analyses focused on the inner ETDRS ring (1–3 mm), where early AMD-related structural changes are most prominent,[12] with thickness calculated as the mean of the four inner sectors. All OCT scans from participants with missing data, coexisting retinal diseases, or signal strength below 15 dB were reviewed by an ophthalmologist to assess segmentation quality. Images exhibiting motion artefacts, segmentation errors, or other technical limitations were excluded from the analysis (752 scans excluded, representing 21.3% of all available scans, Table S1, available at www.ophthalmologyscience.org). Detailed information on OCT acquisition, layer definitions, segmentation procedures, and quality control is provided in the Supplementary Methods (1).

AMD Classification

Age-related macular degeneration was graded using the International Classification System, adapted from the Multi-Ethnic Study of Atherosclerosis,[35,36] by two independent graders, with a retina specialist resolving discrepancies.[33]

To enhance comparability with routine clinical practice, the present study applied the Beckman AMD classification.[4] Intermediate AMD was defined by the presence of large drusen (>125 μm), pigmentary abnormalities, or both on fundus photographs, in the absence of features of advanced AMD (atrophic or neovascular disease).

Incident intermediate AMD was defined as progression from no or early AMD at baseline to intermediate AMD during follow-up; incident advanced AMD was defined similarly. Onset was estimated as the midpoint between the last visit without and first visit with intermediate and advanced AMD, respectively.

Vitamin D

Plasma 25(OH)D was chosen as the primary measure of vitamin D status as it integrates both cutaneous synthesis and dietary sources and reflects biologically relevant vitamin D exposure more accurately than dietary intake.[37] Plasma 25(OH)D concentrations were assessed from fasting blood samples collected at baseline and stored at −80°C, with a one-step immunoassay (Architect 25-OH Vitamin D Assay; Abbott Diagnostics). Deseasonalization was performed using a sinusoidal regression of 25(OH)D to account for annual variation (for the formula and further details, see Supplemental Methods 2, available at www.ophthalmologyscience.org).

As no consensus for optimal 25(OH)D levels in blood exists[38], we applied, in line with several existing classification systems, the following simplified categorization of vitamin D status:[39–43] plasma 25(OH)D levels below 25 nmol/L (corresponding to 10 ng/mL; to convert from nmol/L to ng/mL, divide by 2.496) are considered indicative of deficiency. Levels between 25 and 49 nmol/L (10–19 ng/mL) are typically classified as insufficient. Concentrations of 50 nmol/L or higher (20 ng/mL or more) are regarded as sufficient.

Covariates

Covariates for the multivariable models were selected a priori based on prior literature, biological plausibility, and a directed acyclic graph, a graphical framework used to identify potential confounding relationships between variables.[44] The models were adjusted for demographic factors (age, sex), lifestyle and clinical characteristics (body mass index, smoking, hypertension, diabetes, physical activity, and Mediterranean diet score), lipid profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), civil status, vitamin D supplementation, and baseline AMD stage to account for potential confounders while avoiding overadjustment.

All sociodemographic, lifestyle, and medical data were collected at the baseline visit of the Three-City Study.[34] Medical conditions such as diabetes (defined as fasting blood glucose $\geq$7 mmol/L and/or the use of antidiabetic medication) and hypertension (blood pressure >140/90 mmHg and/or use of antihypertensive treatment) were also assessed during this baseline examination.

Plasma biomarkers were analyzed from blood samples collected at baseline (1999–2001), ensuring consistent and standardized measurement conditions across participants.

Adherence to the Mediterranean diet was assessed using the MEDI-LITE (Mediterranean diet based on the literature) score, a validated dietary index developed by Sofi et al.[45] This score ranges from 0 to 18, with higher values indicating greater adherence to the Mediterranean dietary pattern.

Statistical Analyses

Cox Proportional Hazards Model. Cox proportional hazards models with age as the time scale and clustering by eye were used to assess associations between deseasonalized 25(OH)D and incident AMD. Using age as the time scale adjusts automatically for the confounding effect of age and thus allows for a more appropriate adjustment of age in the elderly than the classical Cox models based on the time from entry into the study.[46] Models were performed separately for incident intermediate and advanced AMD. Given the limited number of events and nonsignificant findings for advanced AMD, the main analysis and descriptive statistics in this manuscript focus on intermediate AMD. Results related to advanced AMD are presented in the Supplementary Material.

All conditions for the application of the Cox model were verified. Linearity was checked using penalized splines with four degrees of freedom (pspline function in the Coxph function of R). The proportional hazards assumption was checked using Schoenfeld residuals.

Linear Mixed Model

To analyze the outer macular layer thicknesses in relation to deseasonalized plasma 25(OH)D levels, we applied longitudinal linear mixed-effects models, using the eye as the unit of analysis, consistent with previously established methods.[47,48] Two separate models were constructed for each retinal layer, with the outcome variable defined as the layer thickness measured in the inner ETDRS circle and random intercepts for the eye nested within the subject. Model 1 was adjusted for sex, age, and follow-up time, while model 2 was adjusted for age at inclusion, sex, follow-up time, hypertension, diabetes, total energy intake, axial length, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, oral vitamin D supplementation, and AMD stage at baseline. Each model included fixed effects for age at baseline, sex, and follow-up time, allowing us to characterize how layer thickness evolved over time. Interaction terms between age and time, and between sex and time, were tested but ultimately excluded, as model selection criteria (Akaike Information Criterion and Bayesian Information Criterion) favored simpler models without these interactions.

All assumptions required for valid application of linear mixed-effects models were assessed.

Imputation was performed using multiple imputation by chained equations, which assumes that missing data were Missing At Random. The missing values were imputed based on the observed values for a given individual and the relations observed in the data for other participants.[49] For the fraction of missing/imputed data, see Table S2 and S3, available at www.ophthalmologyscience.org.

Statistical significance was defined as a P value < 0.05. All analyses were conducted using R software (version 4.3.3; R Foundation for Statistical Computing).

Results

Characteristics of the Studied Sample

Nine hundred sixty-three participants were included in the ALIENOR Study at baseline. For the analysis of incident intermediate AMD, we excluded 420 eyes of 294 participants with prevalent intermediate or advanced AMD, 533 eyes of 390 participants due to missing or low-quality baseline or follow-up imaging, 204 eyes of 127 participants with missing deseasonalized 25(OH)D data, and 69 eyes of 44 participants with missing covariates (Table S2), yielding a final sample of 700 eyes from 429 participants

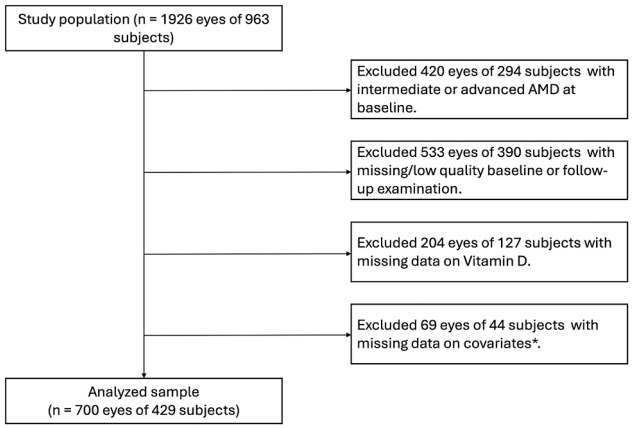


Figure 2. Flow chart showing selection of participants for analyses of incident intermediate AMD. *Covariates include age, sex, smoking status, hypertension, diabetes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, body mass index, civil status, and vitamin D supplementation. AMD = age-related macular degeneration.

(Fig 2). For the analysis of incident advanced AMD, exclusions included 70 eyes of 43 participants with advanced AMD at baseline, 575 eyes of 408 participants with missing or poor-quality imaging, 280 eyes of 160 participants with missing vitamin D data, and 92 eyes of 52 participants with missing covariates (Table S3), resulting in a final analytical sample of 909 eyes from 510 participants (Figure S3, available at www.ophthalmologyscience.org).

Participants included in the analysis (n = 429) were slightly younger on average (mean age: 79.2 ± 4.2 years) than those not included (mean age: 81.0 ± 4.5 years). The gender distribution was comparable between groups. The prevalence of diabetes was lower in the included group (6.1%) compared to the nonincluded group (9.4%). Similarly, the proportion of individuals with hypertension was slightly lower among the included participants (73.0%) than among those not included (77.9%). Cardiovascular disease prevalence, Mediterranean diet score, plasma lipid levels, and smoking status were comparable between the two groups (Table 4). Dietary vitamin D intake was not correlated with circulating 25(OH)D concentrations (Spearman $\rho = 0.01$, $P = 0.78$). In contrast, participants reporting vitamin D supplementation had significantly higher circulating 25(OH)D concentrations than nonusers (mean ± standard deviation [SD]: 24.6 ± 13.5 vs. 14.8 ± 5.7, respectively; $P < 0.001$). The cumulative incidence of intermediate AMD was 29.4%, representing 206 eyes from 166 participants. Of these, 45.1% (93 eyes) had both large drusen and pigmentary abnormalities, 43.7% (90 eyes) had large drusen only, and 11.2% (23 eyes) had pigmentary abnormalities only (Table S5, available at www.ophthalmologyscience.org). Of those 23 with pigmentary abnormalities only, 13 had medium sized drusen. The cumulative incidence of advanced AMD was 8.5%, representing 77 eyes from 55 participants. Of these, 42.8% (33 eyes) had geographic atrophy, 40.3% (31 eyes) had neovascular AMD, and 16.9% (13 eyes) had mixed forms presenting both features. The mean follow-up time was 5.86 ± 3.90 years (range: 0.43−13.61) for incident intermediate AMD and 6.97 ± 3.81 years (range: 0.43−13.68) for incident advanced AMD.

Associations between Deseasonalized Plasma 25(OH)D and Risk of Intermediate AMD

In Cox proportional hazards models adjusted for age, sex, smoking status, hypertension, diabetes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, body mass index, civil status, vitamin D supplementation, participants with deseasonalized plasma 25(OH)D deficiency had a significantly higher risk of developing intermediate AMD compared to those with sufficient levels (hazard ratio = 2.34; 95% confidence interval [CI]: 1.19−4.61; $P = 0.01$). Those with insufficient deseasonalized plasma 25(OH)D levels showed a borderline significant increase in risk (hazard ratio = 1.74; 95% CI: 0.98−3.08; $P = 0.06$) (Table 6). Results from the analysis of advanced AMD were not statistically significant and are provided in in the supplement (Table S7, available at www.ophthalmologyscience.org). A sensitivity analysis using multiple imputation by chained equations to account for missing covariates was performed and did neither change the results on intermediate nor on advanced AMD.

The association was nonlog-linear; therefore, a penalized spline model with 4 degrees of freedom was used. The hazard of intermediate AMD gradually declined with increasing vitamin D levels, stabilizing between 60−75 nmol/l, with a slight additional decrease beyond 75 ng/mL (Fig 4).

The incidence of intermediate AMD during follow-up was 35.6% in the deficient group, 30.3% in the insufficient group, and 21.3% in the sufficient group.

Evolution of Outer Retinal Layers of Participants with Deficient Deseasonalized Plasma 25(OH)D Levels

Using linear mixed-model analyses (for the selection of participants see Table S1 and Figure S5, available at www.ophthalmologyscience.org), significant longitudinal associations were found for the RPE−BM complex. In both adjusted models, deseasonalized plasma 25(OH)D−deficient participants exhibited a significant increase in RPE thickness over time compared to those with higher levels of deseasonalized plasma 25(OH)D (model 1: $\beta = 0.07$ µm/year; 95% CI: 0.01−0.13; $P = 0.02$; model 2: $\beta = 0.07$ µm/year; 95% CI: 0.01−0.13; $P = 0.02$, Table 8). This association is illustrated in Figure 6, showing diverging trajectories in RPE thickness over time based on deseasonalized plasma 25(OH)D status.

In contrast, no significant associations were observed between deseasonalized plasma 25(OH)D status and changes in the outer plexiform layer, outer nuclear layer, or photoreceptor segments (Table 8).

Discussion

In this study, we found an inverse association between deseasonalized plasma 25(OH)D levels and the risk of incident intermediate AMD in an elderly Caucasian population, and a significant increase in RPE−BM complex thickness over time in participants with deficient plasma 25(OH)D levels.

Experimental data support several mechanisms by which vitamin D could exert protective effects on the retina, including regulation of inflammation,[50,51] oxidative stress,[23,24] and angiogenic signaling[52−54], key drivers in AMD pathogenesis. These actions are thought to be mediated through both genomic mechanisms (via activation of the nuclear vitamin D receptor), and nongenomic pathways.[17] Importantly, the vitamin D receptor and vitamin D-activating enzymes are expressed in retinal tissues[18], and in vitro studies have demonstrated that RPE cells can convert 25(OH)D into its active form, suggesting a functional retinal vitamin D signaling system.[55]

However, the existing epidemiological literature presents a mixed picture, likely reflecting heterogeneity in study

Table 4. Baseline Sociodemographic, Lifestyle, and Medical Characteristics of Included vs. Nonincluded Participants (ALIENOR Study, 2006)

Characteristics	*Included (n = 429)*	*Nonincluded (**n** = 534)*
	Mean ± SD or n (%)	
Age (years)	79.2 ± 4.2	81.0 ± 4.5
Sex		
Men	167 (38.9)	200 (37.5)
Women	262 (61.1)	334 (62.5)
Smoking (packyear)	(n = 429)	(n = 522)
Never smoker	272 (63.4)	342 (64.0)
<20 years	84 (19.6)	94 (17.6)
≥20 years	73 (17.0)	86 (16.1)
Plasma 25-hydroxyvitamin D levels (nmol/l)	37.9 ± 14.9	38.7 ± 18.9
Mediterranean diet score	10.6 ± 2.1	10.4 ± 2.2
Plasma lipids (mmol/L)		
LDL	3.7 ± 0.8	3.6 ± 0.9
HDL	1.6 ± 0.4	1.6 ± 0.4
Triglycerides	1.2 ± 0.5	1.3 ± 0.6
Body mass index (BMI) (kg/m^2)	(n = 429)	(n = 526)
(0, 18.5)	0 (0.0)	7 (1.3)
(18.5, 25)	161 (37.5)	198 (37.6)
(25, 30)	198 (46.2)	237 (45.1)
(30, 59)	70 (16.3)	84 (16.0)
Diabetes	26 (6.1)	50 (9.4)
Hypertension	313 (73.0)	416 (77.9)
Cardiovascular diseases	33 (7.7)	47 (8.8)

LDL = low-density lipoprotein; HDL = high-density lipoprotein; SD = standard deviation.

populations, vitamin D assessment methods, and AMD classification criteria.[5,9,18,29,38,56–71] Furthermore, most observational studies to date have measured vitamin D levels after AMD diagnosis, making it difficult to infer causality due to potential reverse causation.

Despite growing interest, there is currently no consensus or clinical guideline recommending vitamin D screening or supplementation specifically for AMD prevention. Interventional trials examining the efficacy of vitamin D supplementation on AMD outcomes are still lacking. Nevertheless, given the safety profile of vitamin D and its known benefits in bone and immune health, ensuring adequate vitamin D status in older adults remains a reasonable public health goal.[43,72–74]

Our observation of an association with incident intermediate, but not advanced, AMD reflects the broader literature, which remains inconclusive and presents mixed evidence across AMD stages. This stage-specific association may be explained by several factors. Biologically, vitamin D may exert its protective effects primarily during the earlier stages of AMD, when inflammation, oxidative stress, and extracellular matrix remodeling in the RPE–BM complex are predominant. In contrast, advanced AMD may involve more complex or irreversible pathological processes. Temporally, our assessment of vitamin D status was based on a single baseline blood draw, which may have occurred too far in advance of the onset of advanced AMD to capture biologically relevant changes in vitamin D levels

Table 6. Associations between Deseasonalized Plasma 25-Hydroxyvitamin D and Incident Intermediate AMD (ALIENOR Study, 2006–2020)

	Incident Intermediate AMD		**Nonincident Intermediate AMD**			
	n (eye)	*Mean ± SD or (%)*	*n (eye)*	*Mean ± SD or (%)*	**HR (95% CI)**	***P* Values**
Vitamin D (nmol/l)	206	36.44 ± 15.34	494	38.57 ± 14.91	Not log-linear	
Sufficient ≥ 50 nmol/l	26	(12.6)	96	(19.4)	Reference	
Insufficient 25 − 49 nmol/l	148	(71.8)	340	(68.8)	1.74 (0.98–3.08)	0.06
Deficient < 25 nmol/l	32	(15.5)	58	(11.7)	2.34 (1.19–4.61)	0.01

AMD = age-related macular degeneration; CI = confidence interval; SD = standard deviation; HR = hazard ratio.
Hazard ratios were estimated using the Cox proportional hazards model adjusted for age, sex, smoking status, hypertension, diabetes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, body mass index, civil status, oral vitamin D supplementation, and AMD stage at baseline. Data from the ALIENOR Study.

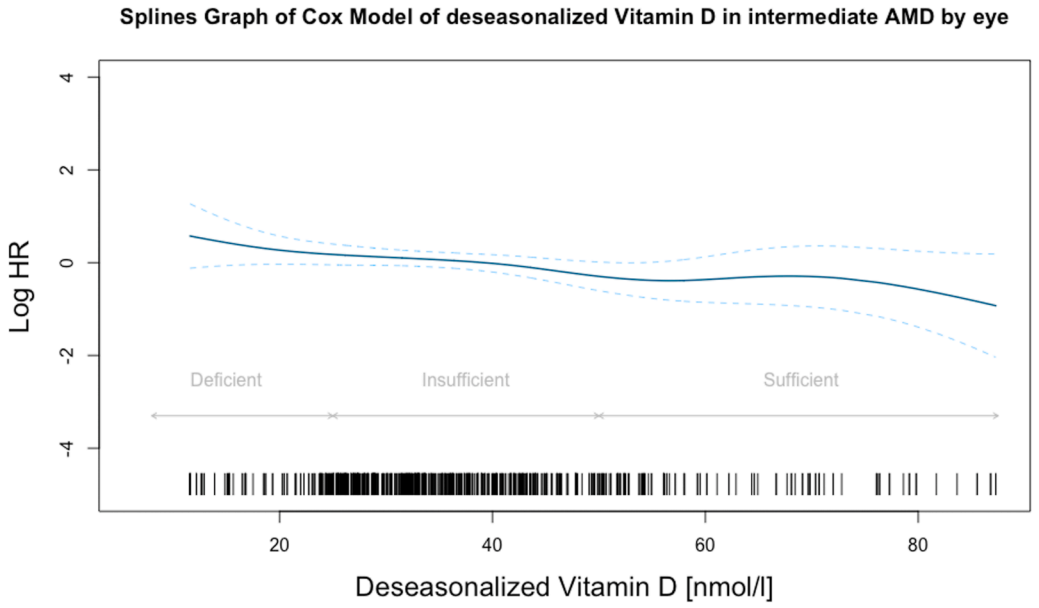


Figure 4. Association between deseasonalized plasma vitamin D and incidence of intermediate AMD adjusted for age, sex, smoking status, hypertension, diabetes, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, body mass index, civil status, vitamin D supplementation, and AMD stage at baseline. Data from the ALIENOR Study, 2006–2020 (n = 700 eyes). Deseasonalized plasma vitamin D was modeled using p-spline with 4 degrees of freedom in the Cox model. AMD = age-related macular degeneration; HR = hazard ratio.

closer to disease progression. Methodologically, the relatively small number of incident advanced AMD cases in our population likely reduced statistical power to detect associations at this stage.

Regarding the RPE–BM thickness finding, the observed rate of 0.07 μm/year (95% CI: 0.01–0.13) is biologically plausible, consistent with histopathological evidence of progressive BM thickening with aging and early AMD.[75,76] Although single-measurement within-subject SD for automated RPE segmentation on Spectralis has been reported in the range of 1.14–2.39 μm[77], the slope was estimated from a linear mixed-effects model across 700 eyes with up to five biannual visits over a mean follow-up of 5.86 years, substantially reducing the standard error relative to any pairwise comparison. Importantly, this OCT finding provides complementary evidence: whereas the incidence analysis captures clinical disease emergence based on fundus grading, progressive RPE–BM thickening has been associated with future risk of advanced AMD and with AMD polygenic risk scores[8], and thus may reflect a biological response to insufficient vitamin D.

This study has also several notable strengths. First, it leverages longitudinal data from a well-characterized, population-based cohort with up to 18 years of follow-up, use of deseasonalized plasma 25(OH)D levels to reduce

Table 8. Longitudinal Change in Outer Retinal Layers in Participants with Deficient Vitamin D Status

	Model	β Coefficient (95% Confidence Interval)	*P* Value
Outer plexiform layer (OPL)	1*	−0.02 (−0.16; 0.13)	0.82
	2†	−0.04 (−0.18; 0.11)	0.62
Outer nuclear layer (ONL)	1	0.10 (−0.09; 0.29)	0.30
	2	0.15 (−0.05; 3.38)	0.14
Photoreceptor segment (PS) layer	1	0.02 (−0.05; 0.08)	0.66
	2	0.00 (−0.07; 0.07)	0.94
Retinal pigment epithelium (RPE)–Bruch's membrane (BM) complex	1	0.07 (0.01; 0.13)	0.02
	2	0.07 (0.01; 0.13)	0.02

Data are from the Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires (ALIENOR) study, 2009-2020 (for model 1: n = 2213 examinations of 501 participants; for model 2: n = 1988 examinations of 443 participants).
*Model 1 was adjusted for sex and age and follow-up time.
†Model 2 was adjusted for age at inclusion, sex, follow-up time, hypertension, diabetes, total energy intake, axial length, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, oral vitamin D supplementation, and AMD stage at baseline.

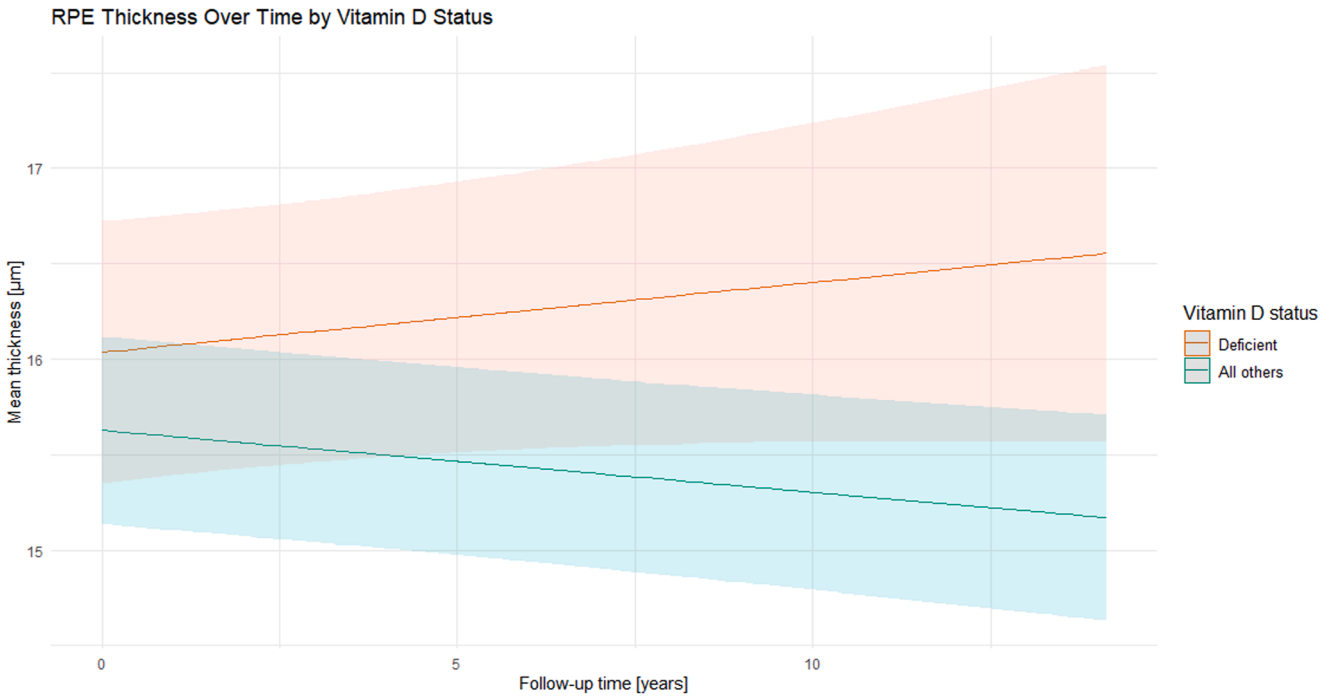


Figure 6. The evolution of the RPE–BM complex in the 1 – 3 mm inner circle of the ETDRS grid over the follow-up time as predicted by linear mixed models (adjusted for age at inclusion, sex, follow-up time, hypertension, diabetes, calorie intake, axial length, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, Mediterranean diet score, physical activity, oral vitamin D supplementation, and AMD stage at baseline) shows significant differences for the longitudinal relationship of participants deficient of deseasonalized plasma 25-hydroxyvitamin D vs. all others. Data from the ALIENOR Study, 2009–2020. AMD = age-related macular degeneration; BM = Bruch's membrane; RPE = retinal pigment epithelium.

seasonal bias, automated OCT layer segmentation for precise structural phenotyping, and rigorous adjustment for a wide range of potential confounders.

Limitations, on the other hand, include the observational design, which precludes causal inference, and the possibility of residual confounding. More than 50% of the original cohort was excluded due to missing imaging or biomarker data. This substantial loss of participants may have reduced representativeness, introduced selection bias, and added to the preliminary nature of the findings. In particular, excluded participants were slightly older and had higher rates of comorbidities, such as hypertension and diabetes. OCT data were only available from the first follow-up visit onward, which may have preferentially excluded participants with more advanced disease or greater frailty at earlier stages. Taken together, these factors may have biased effect estimates towards the null, potentially leading to an underestimation of true associations.

Further, vitamin D status was assessed from a single baseline fasting plasma sample, which may not accurately reflect long-term or time-varying exposure due to supplementation, altered sun exposure, systemic illness, dietary or behavioral changes over follow-up. While dietary vitamin D intake may contribute to circulating vitamin D levels, the association between dietary vitamin D intake and plasma 25(OH)D levels is known to be weak, as cutaneous ultraviolet B synthesis represents the predominant source of vitamin D in most populations.[78,79] In our cohort, dietary vitamin D intake was not associated with circulating 25(OH)D concentrations, consistent with previous literature.[80,81] In contrast, vitamin D supplementation was strongly associated with higher plasma levels. Together with the assessment of dietary intake based on a single 24-hour dietary recall[82,83], these findings suggest that dietary vitamin D intake provides limited information on overall vitamin D status in this population. Therefore, dietary vitamin D intake was not considered in the present analyses.

Finally, generalizability may be limited to similar elderly, predominantly Caucasian populations in developed settings.

In conclusion, our study supports the hypothesis that low deseasonalized plasma 25(OH)D levels may be associated with the development of intermediate AMD. In addition to this increased risk, lower deseasonalized plasma 25(OH)D levels were also associated with progressive structural changes in the RPE–BM complex. Although the observational nature of this single measurement precludes causal inference, the observed association is consistent with the biologically plausible anti-inflammatory and antiangiogenic actions of vitamin D. Given the well-established safety profile of vitamin D and its known benefits beyond skeletal health, ensuring adequate vitamin D intake through dietary sources as well as supplementation at levels recommended for older adults may represent a reasonable component of a comprehensive aging-prevention strategy in older adults. Randomized controlled trials would be needed to establish whether improving vitamin D status can alter the course of AMD.

Footnotes and Disclosures

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This article contains additional online-only material. The following should appear online-only: Tables S1, S2, S3, S5, S7, Figures S1, S3, S5 and Supplementary Methods.

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All authors have completed and submitted the ICMJE disclosures form.

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HUMAN SUBJECTS: Human subjects were included in this study. All participants provided written informed consent and the study protocol was approved by the Ethics Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III, approval code 2006/10), in accordance with the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions:

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Abbreviations and Acronyms:
25(OH)D = 25-hydroxyvitamin D; **AMD** = age-related macular degeneration; **BM** = Bruch membrane; **CI** = confidence interval; **HR** = hazard ratio; **RPE** = retinal pigment epithelium; **SD** = standard deviation.

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