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Association of Circulating Vitamin D in Midlife With Increased Tau-PET Burden in Dementia-Free Adults

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Abstract

Background and Objectives

Low circulating vitamin D in later life has been associated with increased risk of cognitive impairment and clinical dementia. However, whether serum vitamin D in early midlife is associated with neuroimaging markers of preclinical dementia is unknown. We aimed to determine the association between early midlife serum vitamin D and subsequent tau and amyloid burden on brain-PET, in a cohort of dementia-free adults.

Methods

This was a prospective cohort study of Framingham Heart Study Generation 3 cohort participants who were dementia-free at the time of PET, had serum 25-hydroxyvitamin D [25(OH)D] measured at examination cycle 1 (2002–2005), and had available 11C-Pittsburgh Compound-B (PiB)-PET and/or 18F-Flortaucipir (FTP)-PET completed between 2016 and 2019. Outcomes included global tau-PET deposition (across all 34 FreeSurfer defined cortical regions), composite tau (those regions most susceptible to early tau involvement in AD dementia, namely, entorhinal cortex, parahippocampal gyrus, fusiform gyrus, amygdala, and inferior and middle temporal cortices), and amyloid-PET deposition (composite region including the frontal, lateral temporal, parietal, and retrosplenial cortices). Data were analyzed using multivariable linear regression models adjusted for age, sex, time from blood sampling to PET, PET camera type, depression, season, current smoking, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, cardiovascular disease, and body mass index.

Results

In our sample (n = 793, 53% women, mean age 39 ± 8 years) with available serum 25(OH)D and amyloid (n = 424) and/or tau-PET (n = 369), the mean time between blood sampling and PET was 16 ± 2 years. On multivariable linear regression analysis, higher serum 25(OH)D was associated with lower global (β = −0.022; 95% CI −0.040 to −0.004; $p = 0.010$]) and composite tau-PET deposition (β = −0.023; 95% CI −0.043 to −0.003; $p = 0.016$]) but was not associated with amyloid-PET burden.

Discussion

In a group of dementia-free individuals, higher serum 25(OH)D at early midlife was associated with lower tau deposition on brain-PET a mean of 16 years later. Low vitamin D in midlife may represent a potentially modifiable target to mitigate the risk of neuroimaging signs of preclinical dementia.

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Glossary

***APOE* ε4** = apolipoprotein E ε4; **BMI** = body mass index; **FLR** = frontal, lateral, and retrosplenial regions; **MCI** = mild cognitive impairment; **SBP** = systolic blood pressure.

Introduction

Dementia is a major contributor to global morbidity, affecting an estimated 57 million people worldwide.[1] Low circulating vitamin D, measured in later life, has been associated with an increased risk of cognitive impairment and clinical dementia. Although there is no agreed-upon definition for low serum levels of 25-hydroxyvitamin D [25(OH)D], some experts define vitamin D deficiency as 25(OH)D levels <20 ng/mL (50 nmol/L).[2-5] In a meta-analysis of studies of low 25(OH)D levels (defined as <20 ng/mL), serum vitamin D demonstrated a dose-response relationship with AD dementia, with stronger associations (50% increased risk) noted with more profound vitamin D deficiency (<10 ng/mL) compared with moderate vitamin D deficiency (10–20 ng/mL, 36% increased risk).[6] Similarly, in another meta-analysis using the same 25(OH)D reference level of 20 ng/mL (50 nmol/L), 25(OH)D of 10–20 ng/mL was associated with an 18% increased risk of dementia, while <10 ng/mL was associated with a 58% increased risk of dementia.[7] In the Healthy Aging in Neighborhoods of Diversity across the Life Span study (age range 30–64 years), higher 25(OH)D status was associated with a slower decline in verbal fluency (overall sample), verbal memory (younger women), and visuospatial skills (white individuals), over a mean of 4.6 years of follow-up.[8]

In addition, a number of randomized controlled trials have evaluated the effect of vitamin D supplementation on cognition. In a clinical trial of individuals 65 years or older with mild cognitive impairment (MCI) (n = 183), compared with placebo, vitamin D supplementation (800 IU/dy) over 12 months significantly improved cognitive function.[9] In a small clinical trial of 82 cognitively healthy adults, high-dose (4000 IU/d) compared with low-dose (400 IU/d) vitamin D3 supplementation over 18 weeks resulted in greater improvements in nonverbal (visual) memory tasks; this effect was particularly notable in the subgroup with low baseline 25(OH)D levels [<30 ng/mL (<75 nmol/L).][10] In a clinical trial of patients with Alzheimer disease (n = 210), compared with placebo, vitamin D supplementation (800 IU/d) over 12 months significantly improved cognitive function (arithmetic, digit span, vocabulary, block design, picture arrange score, IQ) and decreased plasma Aβ-related biomarkers (plasma Aβ42, APP, BACE1, APPmRNA, BACE1mRNA levels).[11] In a meta-analysis of 24 randomized controlled trials, involving 7,557 participants with a mean age of 65 years, vitamin D supplementation resulted in a small but significant positive effect on global cognition, with stronger effects observed in those with baseline vitamin D deficiency.[12]

The previous studies evaluating the association between 25(OH)D and dementia and cognitive function typically have measured circulating vitamin D in later life (age range 58–73 years),[13-17] and there are currently a lack of studies evaluating vitamin D in early midlife specifically, and its association with adverse cognitive outcomes. In particular, it remains unknown if low 25(OH)D in early midlife is associated with early, preclinical signs of dementia in later midlife (age 55 years), such as deposition of amyloid and tau on brain-PET. A greater understanding of this relationship could inform population-level approaches to dementia prevention at a preclinical stage, when there is greater opportunity for disease modification, for example, guidance regarding optimizing vitamin D monitoring and treatment in young middle-aged adults.

In this study, we aimed to determine the association between serum 25(OH)D in early midlife and neuroimaging markers of preclinical dementia (tau-PET and amyloid-PET burden) among a sample of individuals confirmed to be dementia-free at baseline.

Methods

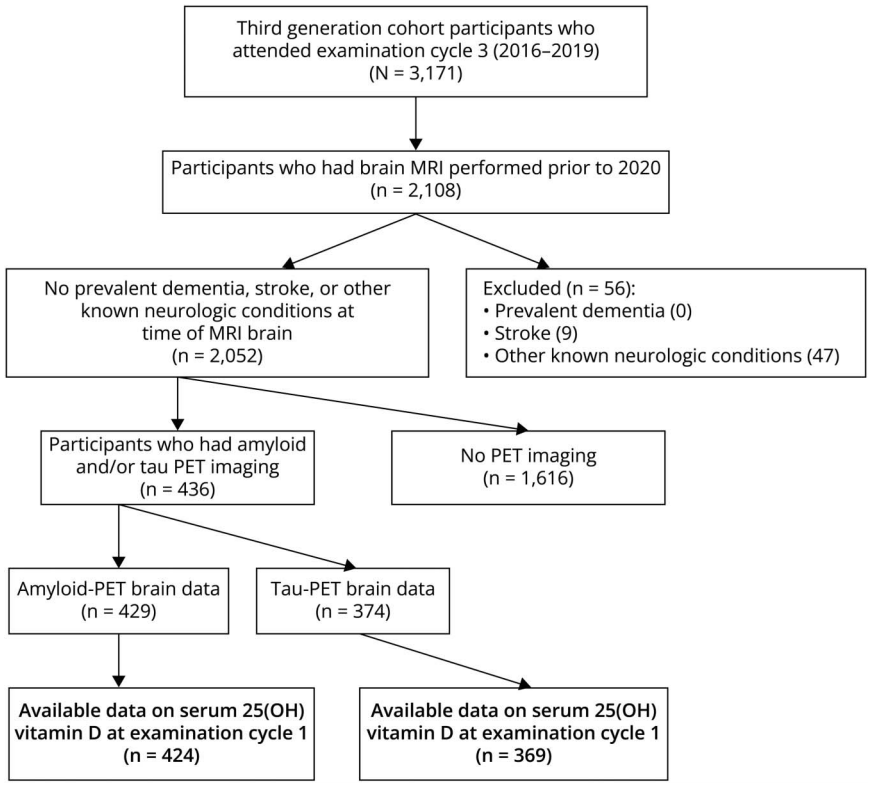
Study Sample

The Framingham Heart Study is a comprehensive, community-based, multigenerational cohort study that has been continuously monitored for the development of cardiovascular risk factors, vascular outcomes, and dementia. The Framingham Heart Study Generation 3 (Gen. 3) cohort commended in 2002 and includes 4,095 participants.[18] In this study, we included third-generation cohort participants who attended examination cycle 3 (2016–2019; n = 3,171); had an MRI brain completed (before 2020; n = 2,108); did not have prevalent dementia, stroke, or other known neurologic conditions at the time of MRI brain (n = 2052); underwent amyloid and/or tau-PET imaging (2015–2023; n = 436); and had available data on serum 25(OH) vitamin D at examination cycle 1 (2002–2005; n = 435). Of these individuals, n = 424 participants had amyloid-PET brain imaging, n = 369 participants had tau-PET imaging, and n = 360 had both amyloid and tau-PET imaging; a flowchart of this process is shown in Figure. The study protocols and consent forms were approved by the Institutional Review Board at Boston University Medical Center, and written informed consent was obtained from all participants.

Outcome Measures

Outcome measures included amyloid and tau deposition in the brain as measured by PiB-PET and FTP-PET, respectively. PET scans were performed near the time of examination

Figure Selection of Study Participants



3 (2015–2023). PET imaging was performed using 2 different scanners during the study period: a 5-Ring GE Discovery MI and a Siemens ECAT HR+. To harmonize the data, PiB and FTP scans acquired with the GE system were smoothed using a 6-mm Gaussian filter. PiB-PET imaging was acquired using a 10–15 mCi bolus injection over a 60-minute dynamic acquisition period, while FTP-PET imaging was obtained following a 9–11 mCi bolus injection over 80–100 minutes. The images were coregistered to T1-weighted MRI brain sequences using SPM8, and regions of interest (ROIs) were identified using FreeSurfer software v6.0.[19]

PiB-PET retention was reported as distribution volume ratios for each ROI[20,21] and expressed relative to the cerebellar cortex, which has negligible PiB binding.

The tau outcome measures, calculated by a weighted average of the number of voxels per region, included global tau (a measure of FTP uptake in all 34 cortical regions defined by the FreeSurfer Desikan-Killany atlas)[19] and composite tau (a measure of uptake in those regions most susceptible to early tau involvement in AD dementia, namely, the entorhinal cortex, parahippocampal gyrus, fusiform gyrus, amygdala and the inferior and middle temporal cortices).[22-25] FTP-PET retention was expressed as standardized uptake value ratios, using mean cerebellar grey matter retention as the reference. For each ROI, the average value was calculated from the right and left hemispheres. Both tau outcomes measures were measured using the same scale. The PET protocols have been previously validated against autopsy findings.[26] The amyloid outcome included a global composite measure of PiB retention in the frontal, lateral, and retrosplenial regions (FLR). FLR uptake is derived from the mean PiB uptake in the superior frontal, inferior frontal, rostral middle frontal, rostral anterior cingulate, medial orbitofrontal, inferior temporal, middle temporal, inferior parietal, and precuneus regions.[27]

Laboratory Measurement of Blood Biomarkers

25(OH)D was measured in serum samples, which were collected during the baseline visit (examination cycle 1, 2002–2005). Participants provided early morning serum samples in ethylenediaminetetraacetic acid vials after resting for 10 minutes. Vitamin D levels were measured using a radioimmunoassay (RIA) with the 25-Hydroxyvitamin D ^{125}I RIA Kit from DiaSorin. Serum samples, stored at −80°C, were analyzed in duplicate using the Cobra II Auto-Gamma counter (Packard Instrument Co).

Covariates

Baseline characteristics measured included age, sex, systolic blood pressure (SBP), use of blood pressure lowering medication, history of diabetes mellitus (defined as a fasting blood glucose ≥7 mmol/L, random blood glucose ≥11.1 mmol/L, or use of insulin or oral hypoglycemic medications), history of cardiovascular disease (including peripheral vascular disease, coronary heart disease [including coronary insufficiency,

angina, heart attack], heart failure, cerebrovascular disease [including transient ischemic attack]), body mass index (BMI, kg/m^2), current smoking status (defined as self-reported smoking within the previous 12 months), presence of depressive symptoms (Center for Epidemiologic Studies Depression Scale [CES-D] score ≥16),[28] season at the time of 25(OH)D measurement (Spring [March-May], Summer [June-August], Autumn [September-November] vs Winter [December-February; reference level]), self-reported vitamin D use (obtained through a food frequency questionnaire), and apolipoprotein E ε4 (*APOE* ε4) carrier status.

Statistical Analysis

Vitamin D levels were natural log-transformed to achieve a normalized distribution.

Multivariable linear regression models were used to investigate the relationship between 25(OH)D and amyloid and tau-PET outcomes. Two outliers with high leverage were excluded from tau-PET models as both values were 4 SD above the mean. We evaluated 25(OH)D both as a continuous variable and as a dichotomized variable, using cutoffs consistent with previous RCT findings and current guidelines (that is, <30 ng/mL [reference] vs ≥30 ng/ml.[7,10,29-31] We elected to use a cutoff of <30 ng/mL instead of 20 ng/mL, which has been used in previous studies of older populations,[6,7] due to the small number of middle-aged adults with serum 25(OH)D < 20 ng/mL in our sample (n = 37, 9.3%). In model 1, we adjusted for age, sex, time from blood sampling to PET, and PET camera type (5-Ring GE Discovery MI or Siemens ECAT HR+). In model 2, we additionally adjusted for depressive symptoms (CES-D score ≥16) and season. In model 3 (primary model), we additionally adjusted for current smoking, SBP, use of blood pressure lowering medication, diabetes mellitus, CVD, and BMI.

We evaluated for effect modification by (1) ApoE E4 carrier status and (2) sex, based on previous reports of stronger protective associations of higher circulating 25(OH)D on dementia risk in women and ApoE E4 noncarriers.[32] We also completed sensitivity analyses, (1) including only those individuals who were not receiving vitamin D supplements (n = 413 [95%]) and (2) adjusting for amyloid-PET burden in the global tau analysis, based on previous studies indicating a potentially synergistic role of Aβ on hyperphosphorylated tau burden in dementia pathogenesis.[33] Finally, we completed a post-hoc, exploratory analyses using tertiles, quartiles, quintiles, and deciles of 25(OH)D as well as an exploratory analysis to identify potential clinical cutoffs indicating a threshold effect. A p value < 0.05 was considered statistically significant for the main analyses, and p < 0.01 was considered significant for interaction analyses. Analyses were completed using SAS statistical software, version 9.4.

Standard Protocol Approvals, Registrations, and Patient Consents

All study protocols and standardized consent forms received approval from the Institutional Review Board at Boston University Medical Center (IRB no. H-33395). Written informed consent was obtained from each participant.

Data Availability

The authors were granted complete access to the data and assume full accountability for its analysis, interpretation, and the overall execution of the research.

Results

Baseline Characteristics

The mean (±SD) age of our sample was 39 ± 8 years at the baseline examination, and 54% were women. The mean (±SD) serum 25(OH)D level was 38 ± 15 ng/ml. A total of 146 participants (34%) had a baseline 25(OH)D level below 30 ng/mL and 5% (n = 22) were taking 25(OH)D supplements. Additional baseline characteristics are presented in Table 1.

Vitamin D and Tau-PET Burden

The mean (±SD) time between baseline serum 25(OH)D measurement and PET scan was 16.2 (±2.4). In multivariable analysis adjusting for age, sex, and time between blood draw and PET scan, higher serum 25(OH)D was associated with lower global tau-PET burden (model 1, β = −0.020 ± 0.008, p = 0.011). After additionally adjusting for depressive symptoms and season at the time of 25(OH)D measurement (model 2, β = −0.023 ± 0.008, p = 0.008) as well as vascular risk factors (model 3, β = −0.022 ± 0.009, p = 0.010), the association remained significant. Higher 25(OH)D was also associated with reduced tau deposition in the earliest affected regions in AD dementia (composite tau region) (model 3, β = −0.023 ± 0.010, p = 0.016). In analyses of serum 25(OH)D according to a clinical cutoff of ≥30 vs <30 ng/mL, 25(OH)D was not associated with either global or composite tau-PET burden in fully adjusted models (Table 2).

Vitamin D and Amyloid-PET Burden

On multivariable analysis, serum 25(OH)D was not associated with amyloid deposition in the FLR region in any model (model 1: β = −0.003 ± 0.010, p = 0.745; model 2: β = 0.001 ± 0.011, p = 0.985; model 3: β = 0.001 ± 0.012, p = 0.987). Similarly, in analyses of serum 25(OH)D according to a clinical cutoff of ≥30 vs <30 ng/mL (reference), 25(OH)D was not associated with amyloid-FLR in any model (Table 2).

Sensitivity Analysis

In a sensitivity analysis confined to only those not receiving vitamin D supplementation at baseline (n = 413 [95%]), the results were not materially altered (global tau, [model 1, β = −0.020 ± 0.008, p = 0.013]; composite tau [model 1, β = −0.020 ± 0.009, p = 0.027]; and amyloid-FLR [model 1, β = −0.002 ± 0.011, p = 0.829] (Table 3). In dichotomized analysis, 25(OH)D ≥ 30 vs <30 ng/mL was associated with lower global tau (model 1, β = −0.013 ± 0.006, p = 0.047) but was not associated with any other outcome (Table 3). After adjustment for amyloid-FLR, higher serum 25(OH)D was

Table 1 Baseline Characteristics

	Overall	Baseline vitamin D < 30 ng/mL	Baseline vitamin D ≥ 30 ng/mL
	435	**146**	**289**
Age, y, mean (SD)	39.2 (8.2)	39.5 (8.4)	39.1 (8.1)
Women	234 (53.8)	70 (48.0)	164 (56.8)
BMI, mean (SD)	26.7 (4.8)	28.4 (5.6)	25.8 (4.2)
Current smoker	45 (10.0)	14 (9.6)	31 (10.1)
Time to PET, mean (SD)	16.2 (2.4)	15.9 (2.3)	16.4 (2.4)
Systolic blood pressure mm Hg, mean (SD)	115.9 (14.5)	118.7 (4.9)	114.5 (13.5)
Antihypertensive treatment	36 (8.3)	15 (10.3)	21 (7.3)
Cardiovascular disease	4 (0.9)	1 (1.0)	3 (1.0)
Diabetes mellitus	8 (1.8)	4 (2.7)	4 (1.4)
Serum vitamin D, ng/mL, mean (SD)	38.1 (14.8)	23.4 (4.9)	45.5 (12.4)
Serum vitamin D ≥ 30 ng/mL	289 (66.4)	—	289 (100.0)
Serum vitamin D 12 to <30 ng/mL	143 (32.9)	143 (98.0)	—
Serum vitamin D < 12 ng/mL	3 (0.7)	3 (2.1)	—
***APOE* ε4 carrier**	98 (23.3)	40 (28.8)	58 (20.1)
Depression (CES-D score ≥16)	7.0 (7.2)	22 (15.1)	24 (8.3)
Season of vitamin D measurement			
Spring (March-May)	132 (30.3)	55 (37.7)	77 (26.6)
Summer (June-August)	111 (25.5)	16 (11.0)	95 (32.9)
Autumn (September-November)	104 (23.9)	25 (17.1)	79 (27.3)
Winter (December-February), reference	88 (20.2)	50 (34.3)	38 (13.2)
Use of vitamin D supplements	22 (5.1)	2 (1.4)	20 (6.9)

Results are presented as n (%), except where indicated.

Table 2 Vitamin D and Amyloid and Tau-PET

	Global tau			Composite tau			Amyloid-FLR		
	β	**95% CI**	***p* Value**	**β**	**95% CI**	***p* Value**	**β**	**95% CI**	***p* Value**
Vitamin D (continuous)									
Model 1	**−0.020**	**−0.036 to −0.004**	**0.011**	**−0.020**	**−0.038 to −0.002**	**0.018**	−0.003	−0.023 to 0.017	0.745
Model 2	**−0.023**	**−0.039 to −0.007**	**0.008**	**−0.024**	**−0.042 to −0.006**	**0.010**	<0.001	−0.021 to 0.021	0.985
Model 3	**−0.022**	**−0.039 to −0.005**	**0.010**	**−0.023**	**−0.043 to −0.003**	**0.016**	<0.001	−0.024 to 0.024	0.987
Vitamin D (<30 ng/mL vs ≥ 30 ng/mL)									
Model 1	−0.012	**−0.024 to 0.000**	0.052	−0.012	−0.026 to 0.002	0.087	−0.001	−0.019 to 0.017	0.898
Model 2	**−0.015**	**−0.029 to −0.001**	**0.029**	−0.015	−0.031 to 0.001	0.052	0.001	−0.017 to 0.019	0.913
Model 3	−0.013	**−0.027 to 0.001**	0.061	−0.013	−0.029 to 0.003	0.100	0.002	−0.018 to 0.022	0.845

Model 1: adjusted for age, sex, time from blood sampling to PET, and PET camera type. Model 2: additionally adjusted for depressive symptoms (CES-D score ≥16) and season. Model 3 (primary model): additionally adjusted for current smoking, SBP, use of blood pressure lowering medication, diabetes mellitus, CVD, and BMI. Tau-PET models: n_1 = 369, n_2 = 348, n_3 = 346; Amyloid-PET models: n_1 = 424, n_2 = 399, n_3 = 397. β: beta. Significant associations (p<0.05) are highlighted in bold.

Table 3 Sensitivity Analysis (Only in Those Not Taking Vitamin D Supplements)

	Global tau			Composite tau			Amyloid-FLR		
	β	95% CI	*p* Value	β	95% CI	*p* Value	β	95% CI	*p* Value
Vitamin D (continuous)									
Model 1	**−0.020**	**−0.036 to −0.004**	**0.013**	**−0.020**	**−0.038 to −0.002**	**0.027**	−0.002	−0.024 to 0.020	0.829
Vitamin D (<30 ng/mL vs ≥ 30 ng/mL)									
	−0.013	**−0.025 to 0.000**	**0.047**	−0.012	−0.026 to 0.002	0.089	−0.001	−0.019 to 0.017	0.895

Model 1 adjusted for age, sex, time from blood sampling to PET, and PET camera type. β: beta.
Tau-PET models: n = 352; Amyloid-PET models: n = 402. Significant associations (p<0.05) are highlighted in bold.

associated with lower global tau (β = −0.019; 95% CI, −0.035 to −0.004; $p = 0.013$) and lower composite tau (β = −0.020; 95% CI, −0.036 to −0.003; $p = 0.021$) (Table 4).

Interaction and Subgroup Analyses

There was no significant interaction between 25(OH)D and APOE ε4 genotype on tau or amyloid-FLR PET deposition (Table 5). There was also no significant interaction between 25(OH)D and sex on tau or amyloid-FLR PET deposition (Table 6).

Post Hoc Exploratory Analyses

In post hoc exploratory analyses according to tertile, quartile, quintile, and decile of 25(OH)D, there was a suggested beneficial association between the highest vs the bottom 4 quintiles of 25(OH)D and composite tau-PET deposition (β = −0.017; 95% CI −0.034 to 0.000; $p = 0.05$), as well as a protective association between the top vs the bottom 9 deciles of 25(OH)D for both global (β = −0.020; 95% CI −0.040 to 0.000; $p = 0.04$) and composite tau-PET burden (β = −0.027; 95% CI −0.049 to −0.005; $p = 0.02$) (eTables 1 and 2). In addition, in an exploratory analysis of clinical cutoffs for 25(OH)D, relative to a reference of <30 ng/mL, levels of 30–54 ng/mL (β = −0.010; 95% CI −0.022 to 0.002; $p = 0.12$) and 55–99 ng/mL (β = −0.023; 95% CI −0.043 to −0.002; $p = 0.02$) were associated with reduced global tau-PET burden (eTable 3). However, given the exploratory nature of these analyses, the results should be interpreted with caution.

Discussion

In a sample of dementia-free individuals, higher serum 25(OH)D in early midlife was associated with lower global tau deposition on brain-PET a mean of 16 years later but was not associated with amyloid-FLR PET deposition.

We found a protective association between higher serum vitamin D levels measured at a mean age of 39 years and a lower burden of tau deposition on brain-PET on average 16 years later. This effect was notable for both global deposition of tau as well as tau burden in a composite region including some of the earliest affected regions in AD dementia (entorhinal cortex, parahippocampal gyrus, fusiform gyrus, amygdala, and the inferior and middle temporal cortices). To the best of our knowledge, there have been no previous studies evaluating an association between serum vitamin D and neuroimaging markers of preclinical dementia. Notably, our study included individuals in early midlife, when there is greater opportunity for risk modification. There are some animal model data in the literature implicating a role of vitamin D on tau burden in the brain. In a preclinical study of APP/PS1 transgenic mice, activation of vitamin D receptors resulted in reduced tau phosphorylation in the brain by inhibiting the GSK3β phosphorylation.[34] Furthermore, in an experimental murine model of traumatic brain injury, vitamin D supplementation, in combination with Omega-3 fatty acids, reduced plasma t-tau levels, hypothesized to be related to attenuation of neuroinflammation

Table 4 Sensitivity Analysis (Adjusting for Amyloid FLR)

	Global tau			Composite tau		
	β	SE	*p* Value	β	SE	*p* Value
Vitamin D (continuous)						
Model 1	**−0.019**	**−0.035 to −0.004**	**0.013**	**−0.020**	**−0.036 to −0.004**	**0.021**
Vitamin D (<30 ng/mL vs ≥ 30 ng/mL)						
Model 1	−0.012	−0.024 to 0.000	0.058	−0.012	−0.026 to 0.002	0.082

Abbreviations: Amyloid FLR = composite PET amyloid burden in the frontal, lateral temporal, parietal, and retrosplenial cortices; SE = standard error.
Model 1 adjusted for age, sex, time from blood sampling to PET, PET camera type, and additionally amyloid FLR. Significant associations (p<0.05) are highlighted in bold.

Table 5 Subgroup Analyses: Vitamin D * APOE ε4 Interactions

	Global tau	Composite tau	Amyloid-FLR
	p Value	*p* Value	*p* Value
Vitamin D (continuous)			
Model 1	0.178	0.412	0.625
Vitamin D (<30 ng/mL vs ≥ 30 ng/mL)			
Model 1	0.474	0.798	0.686

Model 1 adjusted for age, sex, time from blood sampling to PET, and PET camera type.
Tau-PET models: n = 356; Amyloid-PET models: n = 410.

and neuronal damage.[35] One clinical trial evaluated the effect of vitamin D supplementation on plasma tau levels. In this trial of 289 adults aged 70 years or older with self-reported subjective memory complaints, there was no effect of a 1-year nutritional blend intervention (including vitamin D) on plasma p-tau181 levels, with p-tau181 levels noted to increase during follow-up in both the intervention and control groups. Of note, the mean age of the trial population was much older than our sample (mean age 78.1 years), and participants already had subjective memory difficulties at baseline.[36] Supplementation with higher doses of vitamin D, and/or over longer periods of time in younger, cognitively healthy individuals may be beneficial, as the window of opportunity for disease modification is greater. However, this will require formal testing in clinical trials. We did not observe an association between 25(OH)D and tau-PET when analyzed according to clinical cutoffs (<30 ng/mL vs ≥ 30 ng/mL). However, this may be due to the small number of individuals with lower 25(OH)D levels in our sample (n = 146 with baseline 25(OH)D < 30 ng/mL). Alternatively, a lower cutoff of <20 ng/mL may be a more appropriate threshold, as used in some previous studies[2-5]; however, owing to the small number of middle-aged adults with serum 25(OH)D < 20 ng/mL in our sample (n = 37, 9.3%), we were unable to explore this. We completed post hoc exploratory analyses using additional cutoffs for 25(OH)D, with a suggestion of a linear dose response relationship, with the highest quartile of 25(OH)D associated with reduced tau-PET burden. However, these analyses should be interpreted with caution. Further studies in larger samples will be required to assess the relationship using clinical cutoffs.

Our study adds to the existing body of literature linking 25(OH)D levels with clinical neurocognitive outcomes. In a longitudinal cohort study of 1,927 individuals (mean age 74 years) from the Progetto Veneto Anziani (Pro.V.A.) cohort, low serum 25(OH)D (defined as <30 ng/mL) was associated with an increased risk of cognitive decline over a mean 4.4 years follow-up, with individuals with low 25(OH)D having a 40% higher risk of substantial cognitive decline (≥3-point decrease in Mini-Mental State Examination [MMSE] score).[37] In a prospective cohort of 10,186 Danish individuals followed for 30 years, baseline 25(OH)D (<25 nmol/L) was associated with a 1.28 times higher risk of dementia,[13] while in a prospective cohort study of 1,658 elderly (mean age 73.6 years) dementia-free adults from the US Cardiovascular Health Study, followed for a mean of 5.6 years, low 25(OH)D (defined as <50 nmol/L, i.e., 20 ng/mL) was associated with a significantly increased risk (HR 2.25) of all-cause dementia.[16] In a previous Framingham Heart Study including 1,663 generation 2 cohort participants (mean age 72 years for dementia follow-up and 60 years for cognitive and imaging outcomes), low serum 25(OH)D was associated with poorer executive function, processing speed, and visuoperceptual skills, as well as lower hippocampal volumes, but was not associated with 9-year dementia risk.[38]

In a study involving 1,990 aging adults from the SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) trial and SU.VI.MAX 2 observational study, there was a positive association between midlife self-reported dietary vitamin

Table 6 Subgroup Analyses: Vitamin D by Sex Interactions

	Global tau	Composite tau	Amyloid-FLR
	p Value	*p*	*p* Value
Vitamin D (continuous)			
Model 1	0.20	0.31	0.24
Vitamin D (<30 ng/mL vs ≥ 30 ng/mL)			
Model 1	0.18	0.35	0.35

Model 1 adjusted for age, sex, time from blood sampling to PET, and PET camera type. Tau-PET models: n = 369; Amyloid-PET models: n = 424.

D intake and short-term memory performance (forward digit span task) a mean of 13 years later.[39] Our study builds on these findings, by demonstrating an association between serum 25(OH)D levels in early midlife and preclinical markers of early dementia in a cohort of asymptomatic, dementia-free individuals.

Vitamin D may exert neurocognitive benefits via several possible mechanisms. Vitamin D receptors and 1 alpha-hydroxylase, the enzyme necessary for the synthesis of active vitamin D, are widely distributed in the nervous system, including the hippocampus.[40,41] Immune cells express vitamin D receptors, and vitamin D can alter both innate and adaptive immune responses, reduce inflammatory cytokine generation, and strengthen anti-inflammatory defence.[42] Vitamin D deficiency may result in greater neuroinflammation, impaired antioxidation, and increased tau phosphorylation.[43] Oxidative stress has been closely linked with tau pathology, and vitamin D may protect against tau hyperphosphorylation by enhancing antioxidant effects.[44] Vitamin D deficiency increases tau phosphorylation at key sites (Thr181, Thr205, Ser396) by upregulating the activity of cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3α/β (GSK3α/β). This is associated with reduced antioxidant capacity, specifically through downregulation of superoxide dismutase 1 (SOD1), glutathione peroxidase 4 (GPx4), and the cystine/glutamate exchanger (xCT), leading to enhanced oxidative stress and subsequent tau pathology.[43] In neuronal cell models, 1,25(OH)D (calcitriol) alleviates Aβ-induced tau hyperphosphorylation by restoring glial cell line–derived neurotrophic factor signaling and normalizing PI3K/Akt/GSK-3β pathway activity.[45] 25(OH)D treatment increases LCMT-1 and MTHFR expression, which rescues methylated PP2A levels and suppresses tau accumulation in okadaic acid-induced AD models. This suggests that vitamin D may modulate tau pathology through effects on protein phosphatase 2A (PP2A) methylation and related regulatory pathways.[46] In APP/PS1 (Amyloid Precursor Protein/Presenilin-1) mice treated with a vitamin D–deficient diet for 13 weeks, the mice exhibited increased tau phosphorylation along with greater Aβ aggregates and neuronal loss in the cortex.[47] Furthermore, in APP/PS1 transgenic mice, vitamin D_3 supplementation for 20 weeks (compared with no supplementation) resulted in reduced cortical levels of amyloid-beta, total tau, and phosphorylated tau, and improved cognitive performance.[45] These findings suggest that 25(OH)D may modulate tau pathology through regulation of kinase activity (CDK5, GSK3β), antioxidant defenses, neurotrophic signaling, and phosphatase methylation, providing a multifaceted mechanistic basis for its neuroprotective effects.

Although we did not observe an association between serum vitamin D and amyloid burden on brain-PET in our sample, there are some animal data suggesting a role of vitamin D in amyloid pathology in the brain. In a transgenic AβPP mouse model, a vitamin D3–enriched diet correlated with a decrease in both the number of amyloid plaques and Aβ peptide levels in the brain.[48] Similarly, in aged rats, vitamin D supplementation increased Aβ clearance and decreased amyloid burden.[49] However, similar to our findings, some previous human studies have found no relationship between vitamin D and amyloid deposition. In a recent study involving 428 asymptomatic older adults (mean age 71 years), serum vitamin D was not associated with Aβ deposition.[50] However, in a small clinical trial of AD patients (n = 210), vitamin D supplementation (800 IU/d) compared with placebo decreased plasma Aβ-related biomarkers (plasma Aβ42, APP, BACE1, APPmRNA, and BACE1mRNA levels).[11] It is possible that this might reflect enhanced clearance of amyloid from the brain to the periphery rather than a reduction in brain amyloid production.[11] By contrast, in a clinical trial of older adults (mean age 64 years) with vitamin D deficiency (<30 ng/mL), vitamin D supplementation (50,000 IU per week for 8 weeks) compared with placebo resulted in an increase in plasma Aβ40. The authors suggested that 25(OH)D may facilitate clearance of brain amyloid to the periphery, thereby reducing central nervous system amyloid but increasing plasma amyloid.[e1]

Our finding of an association between serum 25(OH)D and tau but not amyloid in younger cohorts may indeed reflect the temporal progression of AD pathology. As suggested by Braak and Braak and confirmed by more recent studies, medial entorhinal cortex tau accumulates earlier than cortical Aβ. Therefore, in younger or preclinical populations, associations with tau may be more readily detectable than those with amyloid, which accumulates significantly later.[e2,e3]

Our results do require validation in other cohorts of younger to middle-aged adults with follow-up data on markers of preclinical dementia. Although our results support a hypothesis that modifying vitamin D levels in early to midlife could reduce the future risk of clinical dementia, this will require formal evaluation in clinical trials.

Strengths of our study include the relatively large sample of individuals (compared with studies to date) with available data on serum 25(OH)D at baseline and follow-up data on gold standard neuroimaging markers of preclinical dementia (i.e., amyloid and tau-PET). In addition, our sample is relatively young (mean age 39 years), enabling us to evaluate the association between 25(OH)D at midlife and future preclinical markers of dementia. In addition, our sample underwent careful surveillance for development of vascular and other risk factors as well as clinical outcomes and were confirmed to be dementia free. Limitations of our study include the predominantly Caucasian sample, which limits generalizability to other ethnicities. In addition, we did not have data available on repeat 25(OH)D over time, precluding an analysis of changes in serum 25(OH)D and cognitive outcomes. Furthermore, measurement of 25(OH)D at a single time point, rather than repeated measures over time, may have resulted in both measurement error and random error resulting in attenuation bias, although this would likely have

biased towards the null. Only 22 participants were taking vitamin D supplements at baseline (likely due to the relatively young age of our sample), limiting our power to complete analysis according to exogenous vitamin D intake. The 10–17-year interval between baseline vitamin 25(OH)D assessment and PET imaging raises the possibility of exposure misclassification due to lifestyle, dietary, or metabolic changes affecting 25(OH)D status. We adjusted for time between blood draw and PET, BMI and season at time of 25(OH)D, and completed sensitivity analyses excluding individuals receiving vitamin D supplementation. However, we did not have detailed information available on lifetime physical activity, dietary habits, or time spent outdoors, which may lead to possible misclassification bias. Further longitudinal studies, including the use of repeated measures of 25(OH)D, will be required to more carefully characterize these effects.

In dementia-free, asymptomatic individuals, higher serum 25(OH)D in early midlife is associated with lower tau deposition on brain-PET a mean of 16 years later. This study suggests that higher vitamin D levels in midlife may offer protection against pathologic tau deposition in the brain, while low vitamin D may represent a potentially modifiable risk factor for healthy middle-aged individuals seeking to reduce dementia risk. However, this requires further testing in clinical trials.

Author Contributions

M.D. Mulligan: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M.R. Scott: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Q. Yang: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Wang: analysis or interpretation of data. S. Ghosh: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K.A. Johnson: major role in the acquisition of data; study concept or design. A.S. Beiser: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. S. Seshadri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. E.R. McGrath: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/OA for full disclosures.

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