Vitamin D and Risk of Cognitive Decline in Elderly Persons

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Background: To our knowledge, no prospective study has examined the association between vitamin D and cognitive decline or dementia.

Methods: We determined whether low levels of serum 25-hydroxyvitamin D (25(OH)D) were associated with an increased risk of substantial cognitive decline in the InCHIANTI population-based study conducted in Italy between 1998 and 2006 with follow-up assessments every 3 years. A total of 858 adults 65 years or older completed interviews, cognitive assessments, and medical examinations and provided blood samples. Cognitive decline was assessed using the Mini-Mental State Examination (MMSE), and substantial decline was defined as 3 or more points. The Trail-Making Tests A and B were also used, and substantial decline was defined as the worst 10% of the distribution of decline or as discontinued testing.

Results: The multivariate adjusted relative risk (95% confidence interval [CI]) of substantial cognitive decline on the MMSE in participants who were severely serum 25(OH)D deficient (levels <25 nmol/L) in comparison with those with sufficient levels of 25(OH)D (≥75 nmol/L) was 1.60 (95% CI, 1.19-2.00). Multivariate adjusted random-effects models demonstrated that the scores of participants who were severely 25(OH)D deficient declined by an additional 0.3 MMSE points per year more than those with sufficient levels of 25(OH)D. The relative risk for substantial decline on Trail-Making Test B was 1.31 (95% CI, 1.03-1.51) among those who were severely 25(OH)D deficient compared with those with sufficient levels of 25(OH)D. No significant association was observed for Trail-Making Test A.

Conclusion: Low levels of vitamin D were associated with substantial cognitive decline in the elderly population studied over a 6-year period, which raises important new possibilities for treatment and prevention.

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istered to measure visuospatial scanning, sequential process-

A and B (hereinafter referred to as Trails A and B) were admin-

scores reflecting worse cognitive function. Trail-Making Tests of cognitive function were administered at baseline, after

3 years, and after 6 years. The 30-item MMSE28 is the most widely

used neuropsychological measure of cognitive function and is
effective screening instrument for dementia in the general

population. Scores for the MMSE range from 0 to 30, with lower

an effective surrogate consent.

Blood samples obtained after the patient had fasted for 12 hours and

rested for at least 15 minutes were centrifuged and stored at

80°C until analyzed.29 Serum levels of 25(OH)D were mea-
sured by radioimmunoassay (RIA kit; DiaSorin, Stillwater, Min-

nesota): intraassay and interassay coefficients of variation were

8.1% and 10.2%, respectively.

Tests of cognitive function were administered at baseline, after

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used neuropsychological measure of cognitive function and is
an effective screening instrument for dementia in the general

population. Scores for the MMSE range from 0 to 30, with lower

scores reflecting worse cognitive function. Trail-Making Tests A

and B (hereinafter referred to as Trails A and B) were admin-

istered to measure visuospatial scanning, sequential process-

ning, motor speed, attention, and executive function. Follow-up

data for Trails A was available for 680 participants, and 487 par-

icipants also completed at least 1 follow-up assessment on Trails B. Trails A involves connecting a series of consecutively num-

bered circles and focuses particularly on attention, whereas Trails B incorporates an alternating sequence of numbered and let-
tered circles and places greater emphasis on executive function. Worse performance is indicated by longer times to complete the Trails A and B.

Multivariate logistic regression models were used to determine the relationship of serum 25(OH)D levels to substantial cogni-
tive decline, which we defined as (1) a decline in MMSE score of 3 or more points at any stage of follow-up (n=290); and (2) as

scoring in the worst 10% of cognitive decline or having the testing discontinued owing to multiple mistakes in Trails A (n=165)

and Trails B (n=275). We divided levels of serum 25(OH)D into clinical groups to aid interpretation: severely 25(OH)D deficient
(<25 nmol/L); 25(OH)D deficient (≥25 to <50 nmol/L); 25

(OH)D insufficient (≥50 to <75 nmol/L); and 25(OH)D suffi-
cient (≥75 nmol/L).1 In unadjusted models, we controlled for base-

line cognitive score only. In fully adjusted models, we adjusted for variables that have been identified as potential confounders in studies of cognition or 25(OH)D levels: age in years, sex, edu-
cation (whether they completed elementary school), season dur-

ing which blood samples were obtained, current smoking sta-
tus, depressive symptoms (score ≥16 on the Italian Center for

Epidemiologic Studies Depression Scale35), body mass index (BMI; calculated as weight in kilograms divided by height in meters

squared), alcohol consumption (g/d), total energy intake (kcal/d)

estimated by food frequency questionnaire,31 serum vitamin E level

(alpha-tocopherol [µmol/L]),32 impaired mobility (mean gait speed,

≤0.4 m/s during 2 timed 4-m walks at normal pace34 or self-

reported difficulty walking 100 m without stopping), and length of follow-up in years. There was no evidence of overfitting or co-

linearity. Linear trends across clinical 25(OH)D groups were tested by introducing 25(OH)D groups into separate logistic regres-
sion models as a continuous variable (rather than as a categori-

cal variable). We corrected for possible overestimation of odds ratios using the ZLan and Yu34 method of deriving risk ratios.

We used random-effects models to examine the associa-
tion between serum 25(OH)D level and MMSE scores mod-
eled as a continuous variable at baseline and the 3- and 6-year follow-up waves. Random-effects models were valuable in this context because they allowed us to take into account both varia-
tion between subjects and autocorrelation between repeated mea-

surements of the same participants over time.33 Random-
effects terms included both the intercept and slope of cognitive scores over time. Candidate fixed-effects terms included all base-

line covariates and their interaction with time (years of follow-

up). The Bayesian Information Criterion was used to decide which fixed effects to include.36

Possible 2-way interactions between 25(OH)D level and base-

line cognitive function were tested by including product terms in fully adjusted logistic regression models. In a series of pre-
planned secondary analyses, we excluded those participants with dementia at baseline (n=29) as diagnosed by geriatricians and a psychologist with expertise in cognitive impairment according to criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).37 We investigated whether any observed association was mediated by medical conditions thought to be associated with both vitamin D status and cogni-
tive function: stroke (neurologic signs indicating stroke or medical history); diabetes (using an antidiabetic agent, medi-
cal history, or having a fasting plasma glucose level ≥126 mg/

Dl); and hypertension (using antihypertensive agents, medi-
cal history, or having a systolic blood pressure ≥140 mm Hg

diastolic blood pressure ≥90 mm Hg). (To convert glucose to millimoles per liter, multiply by 0.0555.)

Levels of 25(OH)D were also analyzed as a log-transformed con-

tinuous variable in a series of further random-effects models. Because differential loss to follow-up has the potential to bias re-
sults, we performed weighted logistic regression analyses. We de-

rived weights for each cognitive test using the inverse probability of having completed at least 1 repeated cognitive assessment using a logistic regression model with key variables as predic-
tors (log-transformed 25(OH)D level, baseline cognitive perfor-
mance, age in years, sex, education, and season of serum collect-

ion). Since no difference in the pattern of results was observed whether weighting was used or not, we report only the results of the unweighted analyses.

P values were 2 sided throughout, and the type I error rate for statistical significance was preset at .05. Because this was a post hoc analysis of a previously assessed cohort, statistical power

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The characteristics of the study population are listed in Table 1. Unadjusted baseline MMSE, Trails A, and Trails B scores were significantly lower in those subjects who were 25(OH)D deficient or severely deficient than in those who were 25(OH)D sufficient, and just over half of participants with dementia were severely 25(OH)D deficient. Participants who were 25(OH)D deficient or severely deficient were also more likely than those who were 25(OH)D sufficient to be older and female; to have been tested between December and May; to have significant depressive symptoms, impaired mobility, and lower total energy intake; to have had a stroke; to have no educational qualifications; and to consume no alcohol.

In logistic regression models adjusted only for baseline cognitive function, participants who were severely 25(OH)D deficient were more likely than those who were 25(OH)D sufficient to have substantial cognitive decline on the MMSE and Trails B test scores (Table 2). Significant linear trends between groups suggested a monotonic relationship. These associations were attenuated slightly but remained significant after full adjustment. Those who were severely 25(OH)D deficient were approximately 60% more likely than those who were 25(OH)D sufficient to experience substantial cognitive decline on the MMSE score and 31% more likely to have substantial decline on the Trails B score. There were no significant associations between 25(OH)D levels and performance on Trails A. The same pattern of associations was observed when we restricted the sample to participants who were nondemented at baseline (Table 3).

Lower levels of serum 25(OH)D were associated with greater year-on-year decline in cognitive function (Table 4). In random-effects models adjusted for baseline cognitive function only, those who were severely 25(OH)D deficient declined by an additional 0.5 MMSE points per year compared with those who were 25(OH)D sufficient. In fully adjusted models, participants who were severely 25(OH)D deficient declined by 0.3 MMSE points per year more than participants who were 25(OH)D sufficient. The increased rate of decline for those who were severely 25(OH)D deficient was statistically significant, as was the linear trend across groups. The Figure shows the estimated mean MMSE decline on the MMSE and Trails B test scores.
Table 2. Logistic Regression Models for Relative Risk of 6-Year Substantial Cognitive Decline in Older Persons by Serum 25(OH)D Level

<table>
<thead>
<tr>
<th>Measure of Substantial Cognitive Declinea</th>
<th>Serum 25(OH)D, nmol/Lb</th>
<th>P Value for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥75</td>
<td>≥50 to &lt;75</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>1.27 (0.93-1.62)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>1.19 (0.84-1.58)</td>
</tr>
<tr>
<td>Trails A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>0.94 (0.56-1.47)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>0.95 (0.55-1.51)</td>
</tr>
<tr>
<td>Trails B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>0.94 (0.69-1.16)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>0.99 (0.74-1.33)</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MMSE, Mini-Mental State Examination29 (range, 0-30; higher score represents better function); Trails, Trail Making Tests (range, 0-300; higher score represents worse function).

a Substantial cognitive decline was defined as 3 or more points on the MMSE and the worst 10% of cognitive decline or test discontinued for the Trails A and B.

b Unless otherwise indicated, data are reported as relative risk (95% confidence interval).

c Adjusted for baseline cognitive score only.

d Adjusted for age, sex, education, baseline cognitive score, season tested, alcohol consumption, current smoking status, depressive symptoms, body mass index, total energy intake, serum vitamin E level (alpha tocopherol), and impaired mobility.

Table 3. Logistic Regression Models for Relative Risk of 6-Year Substantial Cognitive Decline in Nondemented Older Persons by Serum 25(OH)D Level

<table>
<thead>
<tr>
<th>Measure of Substantial Cognitive Declinea</th>
<th>Serum 25(OH)D, nmol/Lb</th>
<th>P Value for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥75</td>
<td>≥50 to &lt;75</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>1.28 (0.94-1.65)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>1.22 (0.86-1.63)</td>
</tr>
<tr>
<td>Trails A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>0.91 (0.54-1.43)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>0.94 (0.54-1.50)</td>
</tr>
<tr>
<td>Trails B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted modelc</td>
<td>1 [Reference]</td>
<td>0.94 (0.69-1.17)</td>
</tr>
<tr>
<td>Fully adjusted modeld</td>
<td>1 [Reference]</td>
<td>0.99 (0.73-1.23)</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MMSE, Mini-Mental State Examination29 (range, 0-30; higher score represents better function); Trails, Trail Making Tests (range, 0-300; higher score represents worse function).

a Substantial cognitive decline was defined as 3 or more points on the MMSE and the worst 10% of cognitive decline or test discontinued for the Trails A and B.

b Unless otherwise indicated, data are reported as relative risk (95% confidence interval).

c Adjusted for baseline cognitive score only.

d Adjusted for age, sex, education, baseline cognitive score, season tested, alcohol consumption, current smoking status, depressive symptoms, body mass index, total energy intake, serum vitamin E level (alpha tocopherol), and impaired mobility.

Table 4. Random-Effects Models Illustrating Change in MMSE-Measured Cognitive Function by Serum 25(OH)D Level

<table>
<thead>
<tr>
<th>Serum 25(OH)D Level, nmol/L</th>
<th>All Participants (n=858)</th>
<th>Non-demented Participants Only (n=829)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted Modelb</td>
<td>Fully Adjusted Modelc</td>
</tr>
<tr>
<td>≥75</td>
<td>0.0 [Reference]</td>
<td>0.0 [Reference]</td>
</tr>
<tr>
<td>≥50 to &lt;75</td>
<td>-0.085 (0.169)</td>
<td>-0.111 (0.115)</td>
</tr>
<tr>
<td>≥25 to &lt;50</td>
<td>-0.139 (0.146)</td>
<td>-0.035 (0.095)</td>
</tr>
<tr>
<td>&lt;25</td>
<td>-0.664 (0.146)</td>
<td>-0.321 (0.109)</td>
</tr>
<tr>
<td>P value for linear trend</td>
<td>&lt;.001</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MMSE, Mini-Mental State Examination29 (range, 0-30; higher score represents better function).

a All data are reported as estimated (SE) b values.

c Adjusted for baseline cognitive score only.

d Adjusted for age, sex, education, baseline cognitive score, season tested, body mass index, impaired mobility, diabetes, and stroke.

No significant 2-way interactions between 25(OH)D level and baseline cognitive function were observed for the MMSE (P = .76), Trails A (P = .40), or
Additional adjustment for stroke, diabetes, and hypertension did not change the pattern of results observed (Table 5), suggesting that these conditions are not likely to mediate the observed associations. Random-effects models incorporating log-transformed levels of 25(OH)D rather than pre-defined categories also indicated that baseline levels of 25(OH)D were associated with subsequent cognitive decline. In fully adjusted models, the association between log-transformed 25(OH)D level and performance on the MMSE test was significant for all participants ($\beta=0.143$, SE=0.051, and $P=.005$) and for participants who were nondemented at baseline ($\beta=0.134$, SE=0.050, and $P=.008$).

In this population-based prospective study, we found that elderly people with low levels of 25(OH)D were at increased risk of cognitive decline over 6 years, and there was evidence of a monotonic relationship. The association remained significant after adjustment for a wide range of potential confounders and when analyses were restricted to elderly subjects who were nondemented at baseline. To our knowledge, this is the first prospective study to show that low levels of 25(OH)D are associated with elevated risk of cognitive decline.

The strengths of this study include that we were able to adjust statistically for a wide range of potentially confounding variables such as sociodemographic characteristics, clinical status, health behaviors, and dietary factors. Response rates at each wave of the InCHIANTI study were high, and minimal bias is likely due to attrition. Low levels of 25(OH)D at baseline may reflect the limited physical or outdoor activity of participants who already had dementia and were thus susceptible to further cognitive decline. However, we were able to conduct analyses excluding those with dementia at baseline, and no 2-way interactions were observed between 25(OH)D levels and baseline cognitive function. Taken together with the prospective study design, this fact allows us to be more confident that the association observed was not due to reverse causation. We also adjusted for impaired mobility, which did not greatly attenuate the association. Assessment of cognitive performance included the MMSE, the most widely used measure of cognitive function, and Trails A and B, which are also commonly used.

Our study had some limitations that should be considered when interpreting the results. While the InCHIANTI study is population based, it incorporates participants from a geographically confined area, and further research is needed to examine whether our findings generalize to other regions. Similarly, participants were all of white European origin, and we were not able to assess whether the association was similar in other ethnic groups. While attrition was minimal for a study of this kind, it is still possible that attrition biased our results. However, we conducted weighted analyses to allow for nonrandom attrition, and these gave highly similar results. Finally, the underlying cause of the cognitive changes observed was not assessed, and we were unable to evaluate which of the possible pathophysiologic mechanisms are important on a population level.

It has long been known that calcitriol (1,25-dihydroxycholecalciferol), the bioactive form of 25(OH)D, plays a crucial role in phosphate homeostasis, bone mineralization and regulating levels of calcium. How-

![Figure](https://example.com/figure.png)

**Figure.** Change in cognitive function for 858 older persons by serum 25-hydroxyvitamin D (25(OH)D) concentration. Results are based on a random-effects model with multivariate adjustment for age, sex, education, baseline cognitive score, season tested, body mass index, impaired mobility, diabetes, and stroke.

<p>| Table 5. Fully Adjusted Logistic Regression Models for Relative Risk of 6-Year Substantial Cognitive Decline in Older Persons by Serum 25(OH)D Level, Including Adjustment for Potential Mediatorsa |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Measure of Substantial Cognitive Declineb</th>
<th>Serum 25(OH)D Level, nmol/L</th>
<th>Serum 25(OH)D Level, nmol/L</th>
<th>Serum 25(OH)D Level, nmol/L</th>
<th>$P$ Value for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSEc</td>
<td>$\geq 75$</td>
<td>$\geq 50$ to $&lt; 75$</td>
<td>$\geq 25$ to $&lt; 50$</td>
<td>$&lt; 25$</td>
</tr>
<tr>
<td>Trails A</td>
<td>1 [Reference]</td>
<td>$1.24$ (0.88-1.63)</td>
<td>$1.09$ (0.78-1.44)</td>
<td>$1.61$ (1.19-2.01)</td>
</tr>
<tr>
<td>Trails B</td>
<td>1 [Reference]</td>
<td>$0.98$ (0.57-1.55)</td>
<td>$1.18$ (0.75-1.72)</td>
<td>$1.16$ (0.65-1.72)</td>
</tr>
<tr>
<td>Trails C</td>
<td>1 [Reference]</td>
<td>$1.00$ (0.74-1.24)</td>
<td>$1.11$ (0.87-1.31)</td>
<td>$1.32$ (1.03-1.51)</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CES-D, Center for Epidemiologic Studies Depression Scale; MMSE, Mini-Mental State Examination (range, 0-30; higher score represents better function); Trails, Trail Making Tests (range, 0-330; higher score represents worse function).

a Unless otherwise indicated, data are reported as relative risk (95% confidence interval). All analyses have been adjusted for age, sex, education, baseline cognitive score, season tested, alcohol consumption, current smoking status, depressive symptoms, body mass index, total energy intake, serum vitamin E level (alpha tocopherol), and impaired mobility plus potential mediators (stroke, hypertension, and diabetes).

b Substantial cognitive decline was defined as 3 or more points on the MMSE and the worst 10% of cognitive decline or test discontinued for Trails A and B.
ever, accumulating evidence suggests previously unsuspected roles for vitamin D in brain development and neuroprotection. Low levels of serum 25(OH)D may be associated with an increased risk of neurologic diseases such as multiple sclerosis, and Parkinson disease. Vitamin D receptors are present in a wide variety of cells, including neurons and glial cells, and genes encoding the enzymes involved in the metabolism of vitamin D are also expressed in the brain. In a recent review, Buell and Dawson-Hughes emphasize that vitamin D may be neuroprotective through antioxidative mechanisms, immunomodulation, neuronal calcium regulation, detoxification mechanisms, and enhanced nerve conduction. Vitamin D may play a role in brain detoxification pathways by reducing cellular calcium, inhibiting the synthesis of inducible nitric oxide synthase, and increasing levels of the antioxidant glutathione. Vitamin D stimulates neurogenesis and regulates the synthesis of neurotrophic factors, which are important for cell differentiation and survival. Vitamin D is also an immunosuppressor and may inhibit autoimmune damage to the nervous system. Calciotrol stimulates β-amyloid phagocytosis and clearance while protecting against apoptosis. Results from small clinical studies assessing the relationship between vitamin D and cognitive function that incorporate highly selected samples and limited adjustment for potential confounders have been equivocal. Four large population-based cross-sectional studies have examined the association between levels of serum 25(OH)D and cognitive dysfunction. The first of these, by McGrath and colleagues, found no association with a brief measure of verbal memory. However, Llewellyn and colleagues observed a significant association between low levels of 25(OH)D and increased odds of cognitive impairment. Similarly, Buell and colleagues observed a positive association between 25(OH)D levels and tests of executive function and processing speed, but not memory. Finally, Lee and colleagues observed a significant positive association between 25(OH)D levels and a test of sustained attention, but not with a significant positive association between 25(OH)D levels and cognitive dysfunction. The first of these, by McGrath and colleagues, found no association with a brief measure of verbal memory. However, Llewellyn and colleagues observed a significant association between low levels of 25(OH)D and increased odds of cognitive impairment. Similarly, Buell and colleagues observed a positive association between 25(OH)D levels and tests of executive function and processing speed, but not memory. Finally, Lee and colleagues observed a significant positive association between 25(OH)D levels and a test of sustained attention, but not with a significant positive association with cognitive dysfunction. Low levels of 25(OH)D may be particularly detrimental to executive functions, whereas other cognitive domains such memory may be relatively preserved, as previously hypothesized. Future trials of vitamin D supplementation in the elderly population could usefully include tests of cognitive function.

We found that elderly subjects with low levels of 25(OH)D had a higher relative risk of substantial cognitive decline over a 6-year period and that this association remained after adjusting for potential confounders. If future prospective studies and randomized controlled trials confirm that vitamin D deficiency is causally related to cognitive decline, then this would open up important new possibilities for treatment and prevention.