Vitamin D Deficiency Is Associated With Low Mood and Worse Cognitive Performance in Older Adults

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Background: Vitamin D deficiency is common in older adults and has been implicated in psychiatric and neurologic disorders. This study examined the relationship among vitamin D status, cognitive performance, mood, and physical performance in older adults. Methods: A cross-sectional group of 80 participants, 40 with mild Alzheimer disease (AD) and 40 nondemented persons, were selected from a longitudinal study of memory and aging. Cognitive function was assessed using the Short Blessed Test (SBT), Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR; a higher Sum of Boxes score indicates greater dementia severity), and a factor score from a neuropsychometric battery; mood was assessed using clinician’s diagnosis and the depression symptoms inventory. The Physical Performance Test (PPT) was used to measure functional status. Serum 25-hydroxyvitamin D levels were measured for all participants. Results: The mean vitamin D level in the total sample was 18.58 ng/mL (standard deviation: 7.59); 58% of the participants had abnormally low vitamin D levels defined as less than 20 ng/mL. After adjusting for age, race, gender, and season of vitamin D determination, vitamin D deficiency was associated with presence of an active mood disorder (odds ratio: 11.69, 95% confidence interval: 2.04 - 66.86; Wald $\chi^2 = 7.66, df = 2, p = 0.022$). Using the same covariates in a linear regression model, vitamin D deficiency was associated with worse performance on the SBT ($F = 5.22, df = [2, 77], p = 0.044$) and higher CDR Sum of Box scores ($F = 3.20, df = [2, 77], p = 0.047$) in the vitamin D-deficient group. There was no difference in performance on the MMSE, PPT, or factor scores between the vitamin D groups. Conclusions: In a cross-section of older adults, vitamin D deficiency was associated with low mood and with impairment on two of four measures of cognitive performance. (Am J Geriatr Psychiatry 2006; 14:1032-1040)

Key Words: Vitamin D, mood disorder, cognitive impairment

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The prevalence of vitamin D deficiency is between 25% and 54% of all adults over age 60 years. Although the prevalence of vitamin D deficiency may vary by geographic regions and ethnicity, it is prevalent throughout the United States. Select populations, including women with Alzheimer disease (AD), have an increased prevalence of vitamin D deficiency (74%). Whether vitamin D deficiency is a cause or consequence of AD is unknown.

Because few persons are screened for vitamin D deficiency, the proportion of individuals with unrecognized vitamin D deficiency potentially is large. The primary source of vitamin D is derived from cutaneous synthesis after ultraviolet exposure so that nutritious diets may not preclude vitamin D deficiency. Multiple steps in the metabolism of vitamin D are adversely affected by aging. The efficiency of skin conversion of 7-dehydrocholesterol to vitamin D, the hepatic hydroxylation of 25-hydroxyvitamin D, and the tissue response to 1,25-dihydroxyvitamin D all decrease with age. Many older adults thus may be vulnerable to vitamin D deficiency.

The effects of vitamin D deficiency on bone density are widely accepted. Until recently, however, the consequences of vitamin D deficiency unrelated to bone have been less studied. Nonclassic vitamin D-responsive tissues (those not dependent on calcium regulation) are the focus of recent research and include the central nervous system. There is a growing body of literature to support a role for vitamin D in brain function and development, including quantification of vitamin D receptors in the brain, neuroprotection by vitamin D in vitro, and downregulation of vitamin D receptors in hippocampal cells in AD. Additionally, treatment with vitamin D for both 8 and 12 months resulted in a higher density of CA1 neurons in the rat hippocampus.

For years, the association between vitamin D and mood disorders has been debated. Because seasonal affective disorder (SAD) has been associated with winter months and sunlight deprivation, vitamin D deficiency has been considered a possible contributor to SAD. Early studies found no association with depression and 1,25-dihydroxyvitamin D, but subsequent studies found correlations between 25-hydroxyvitamin D and SAD and depression. Additionally, vitamin D supplementation was found to be superior to phototherapy in SAD and, in a placebo-controlled trial, vitamin D enhanced positive affect. Little is known about whether older adults with vitamin D deficiency are more likely to have depressed mood.

Data also support a role for vitamin D in neuromuscular function. Recent observations have demonstrated an association between vitamin D deficiency, postural instability, and falls. There is a significant correlation between 25-hydroxyvitamin D concentration and the occurrence of falls in the elderly. Supplementation with vitamin D in one group of elderly women with vitamin D deficiency resulted in a significant decrease in body sway and fewer falls per subject over one year. In a study of shorter duration, a 49% decrease in falls was observed after three months of vitamin D treatment without change in independent measures of muscle strength. The reduction in falls without improved muscle strength suggests that other mechanisms such as effects on the central nervous system may explain the results.

Because vitamin D deficiency occurs in a large number of older adults and is a treatable condition, it is important to determine if it is associated with cognitive impairment or mood disorders in nonfrail elderly. To explore this association, we assessed the frequency of vitamin D deficiency in community-dwelling, ambulatory older adults with and without mild AD and examined the relationship between vitamin D status, cognition, and mood.

**METHODS**

**Participants**

This is a cross-sectional study of older adults participating in studies of cognitive and functional aging at the Alzheimer’s Disease Research Center (ADRC) at Washington University. The ADRC recruits cognitively healthy and demented older adult participants from the greater metropolitan St. Louis, MO, area (population: 2.5 million). Participant recruitment occurs through public service announcements (radio, TV, and print media), requests to private physicians and organizations (e.g., the St. Louis, MO, chapter of the Alzheimer Association), and word of mouth. Inclusion criteria for this study were age over 60, ambulatory, able to complete all assess-
ments, and willingness to provide serum. Persons with moderate or severe dementia, history of stroke, renal failure, Parkinson disease, and use of prescription vitamin D supplements or nonprescription vitamin D greater than 800 IU daily were excluded.

Participants who were assessed in the ADRC between September 1999 and October 2001 (N=271) and who met the inclusion/exclusion criteria for this study were consecutively included until 80 subjects (40 persons with mild AD and 40 nondemented persons) with available serum were obtained. The AD group included 20 persons with a Clinical Dementia Rating (CDR) of 0.5 and 20 with CDR 1. None of the participants were involved in interventional or treatment studies of cognition or mood.

Clinical and Cognitive Assessments

The clinical evaluation included obtaining medical, social, and family history from a reliable informant, usually a spouse or adult child. Information regarding possible cognitive change in comparison with previously obtained levels that was sufficient to interfere with accustomed activities was obtained by a clinician from semistructured interviews with the informant and separately with the participant. Included in the clinical assessment protocol were the items from the Mini-Mental State Examination (MMSE)35 and the Short Blessed Test (SBT),36 although the items were dispersed so the clinician was unaware of the test score. Also included in the assessment protocol is an aphasia battery, a medication inventory, and a depressive features battery.

The clinician used the depressive symptoms inventory, a nine-item administered survey, which has been previously used for diagnosis of depression37 to determine the presence or absence of an active mood disorder. This inventory uses questions based on the nine Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition symptoms for major depression.38 The participant was asked if the following depressive features had occurred for 2 weeks or more in the past year: depressed mood, diminished interest, change in weight or appetite, sleep disturbance, fatigue, psychomotor disturbance, feelings of worthlessness, indecisiveness, and suicidal ideation. The depressive features score was the sum of the endorsed features. A similar score was obtained from the informant who was also asked if these features had occurred in the participant. Prior studies have found a reliable informant to be important to the diagnosis of depression in demented individuals.38,39 Additionally, the clinician determined the presence or absence of a mood disorder and whether it was active or remote based on the clinical interview with the participant and the informant.

Using all information from the clinical assessment protocol but without reference to the participant’s psychometric performance (see subsequently), the clinician determined the Clinical Dementia Rating (CDR) for the participant. The CDR determines the presence or absence of dementia and, when present, rates its severity.40 The CDR rates cognitive performance in each of six categories: memory, orientation, judgment and problem-solving, community affairs, home management and hobbies, and personal care. A global CDR of zero indicates no dementia; a global CDR of 0.5 indicates very mild dementia; and global CDR of 1, 2, and 3 indicate mild, moderate, and severe dementia. The CDR Sum of the Boxes score is the summation of the individual scores in each of the six CDR categories (i.e., boxes) and provides a more quantitative measure of cognitive impairment.41 Possible Sum of Boxes scores range from zero (i.e., the individual scores are zero in all six CDR categories) to 18 (i.e., the individual scores are three in all six CDR categories). A higher global CDR or larger Sum of Boxes score indicates greater dementia severity. Validity and interrater reliability for the CDR have been established.42,43

Two to 4 weeks after the clinical assessment, participants completed a psychometric battery44; psychometricians were not informed of the results of the clinical evaluation. The battery includes the Mental Control, Logical Memory, Digit Span Forward and Backward, and Associate Learning subtests from the Wechsler Memory Scale45; Information, Block Design, and Digit Symbol subtests from the WAIS46; Boston Naming Test47; the Benton Visual Retention test Forms C (10-second delay) and D (copy)48; Trail Making test Part A49; word fluency for S and P50; and Crossing-off.51 As reported previously,52 a principal components analysis of these tests in 81 nondemented individuals produced a single-factor solution that accounted for 34% of the variance. Scores on the 14 measures for the present sample were standardized using the means and standard deviations from the previous report52 weighted by the factor
loadings from that analysis and averaged to form a composite representing overall performance.

Physical Assessment

After the general physical and neurological examination, the Physical Performance Test (PPT) was administered by a trained research nurse. Scores on the original PPT instrument (developed by Reuben and Siu\textsuperscript{53,54}) correlates with degree of disability, loss of independence, and mortality.\textsuperscript{55,56} We modified the PPT by substituting the chair rise and Progressive Romberg test of standing balance\textsuperscript{56} for the stair-climbing tasks. Performance on these two tasks, which have been included in other modifications of the original PPT,\textsuperscript{55,57} has been associated with self-reported disability, nursing home placement, and mortality.\textsuperscript{56} Specific tasks in our modified PPT are: writing a sentence, simulated eating (i.e., spooning beans into a container), lifting a book, simulated dressing (i.e., putting on and taking off a jacket), picking up a penny from the floor, turning in a complete circle (i.e., steadiness and continuity of steps), walking 50 feet., the chair rise (i.e., sitting in and rising from a chair five times), and the Progressive Romberg test of standing balance (i.e., standing with feet in tandem, semitandem, and side-by-side positions). Most of the tasks in our PPT were scored on a five-point scale. The total PPT score, a simple summation of the individual item scores, is a composite measure of frailty. The maximum (i.e., best) total score was 36 with a decreasing score indicating increasing frailty.

Vitamin D Assessment

Serum was collected at the time of the clinical assessment and PPT. The 25-hydroxyvitamin D levels were determined using a competitive radioimmunoassay. Subjects were divided into three subgroups based on vitamin D level as defined by previously reported data\textsuperscript{58,59}: vitamin D-sufficient (serum level of 25-hydroxyvitamin D of greater than or equal to 20 ng/mL), -insufficient (serum 25-hydroxyvitamin D of 10–19.9 ng/mL), and -deficient (serum 25-hydroxyvitamin D of less than 10 ng/mL). No other biochemical assessments were performed and vitamin D was assessed on only one occasion. Serum was collected throughout the year and the season of each participant’s serum collection was recorded.

Statistical Analysis

Sample size calculations based on a pilot study projected that 40 persons per group were needed to detect a 20% difference in vitamin D levels between cognitively impaired and nonimpaired persons with a power of 80% and alpha of .05. Demographic, clinical, cognitive, and physical data represent data collected at the time of serum collection. Unadjusted differences across the three vitamin D groups in demographic characteristics and clinical and neuropsychologic measures were tested using one-way analysis of variance for quantitative variables. When differences were found, pairwise comparisons were performed using Tukey’s honestly significant difference test. Descriptive statistics were expressed as number, percentage, mean, and standard deviation.

Logistic regression models (PROC LOGISTIC, SAS version 9.1 for Windows, Cary, NC) were used to test whether vitamin D status was associated with the likelihood of receiving diagnoses of dementia (CDR 0 versus CDR >0) and of mood disorder, while adjusting for and simultaneously testing the effects of age, race, sex, and season of vitamin D ascertainment. Preliminary models tested the interaction of vitamin D category with each of the other independent variables. Interactions that were significant in preliminary models were included in the final model.

The adjusted effect of vitamin D on the continuous dependent variables (CDR Sum of Boxes, Short Blessed Test, MMSE, the factor score, and total PPT score) was tested using general linear models (PROC GLM, SAS version 9.1 for Windows). The independent variables were the same as those tested in the logistic regression models and similar to those analyses, the interaction of vitamin D group with each of the other independent variables on the dependent variable was tested in preliminary models.

Informed consent was obtained from all participants and the study was approved by the Human Studies Committee at Washington University.
RESULTS

The sample characteristics at the time of serum collection used for vitamin D determination are shown in Table 1. When the participants are divided into groups by vitamin D status (sufficient, insufficient, and deficient), differences were found in CDR Sum of Boxes, presence of active mood disorder, SBT scores, PPT scores, and age using analysis of variance (Table 2). No difference was found in MMSE, depressive features scores, or factor scores.

In the adjusted analyses (Table 3), vitamin D deficiency was significantly associated with the presence of a mood disorder (Wald $\chi^2 = 7.66, df = 2, p = 0.022$) such that participants who were vitamin D-deficient (odds ratio [OR]: 11.69; 95% confidence interval [CI]: 2.04–66.86) and insufficient (OR: 2.54; 95% CI: 0.63–10.51) were more likely to have a mood disorder compared with those with sufficient vitamin D when the effects of age, sex, race, and season were held constant.

Vitamin D category was not predictive of AD when treated as a categorical variable in the logistic regression analyses (Wald $\chi^2 = 2.16, df = 2, p = 0.339$); however, it was significantly associated with two continuous measures of cognition (Table 4). The main effect of vitamin D category (F = 3.20, df = 2,77, p = 0.047), as well as the interaction of vitamin D category and race (F = 5.21, df = 1,78, p = 0.008), were found to be related to CDR Sum of Boxes scores in the linear regression model. Overall, adjusted mean Sum of Boxes scores were lower for participants who had sufficient and insufficient vitamin D levels compared with those with sufficient levels (F = 2.17, df = 1,78, p = 0.033). There was no significant difference between CDR Sum of Boxes scores for the sufficient and insufficient groups (F = 0.23, df = 1,78, p = 0.820). The interaction effect was such that CDR Sum of Boxes was higher for the vitamin D-deficient group (adjusted mean: 5.7) compared with the insufficient (adjusted mean: 1.0; F = 3.22, df = 1,78, p = 0.002) and sufficient (adjusted mean: 2.1; F = 2.57, df = 1,78, p = 0.012) groups among blacks, but the only significant difference in adjusted means among whites was found for the insufficient and sufficient groups (2.7 versus 1.2; F = 2.24, df = 1,78, p = 0.028).

Likewise, the overall effect of vitamin D category (F = 5.22, df = 2,77, p = 0.008) along with the interaction of vitamin D and race (F = 3.31, df = 2,77, p = 0.0425), significantly predicted scores on the SBT in the final general linear models. Overall, adjusted mean SBT scores were 11.4, 6.7, and 4.0 for the deficient, insufficient, and sufficient groups, respectively, and differences were found between the deficient and insufficient (F = 2.06, df = 1,78, p = 0.0436) and between the deficient and sufficient (F = 3.23, df = 1,78, p = 0.002) groups. For blacks, significant differences occurred between the deficient and insufficient groups (adjusted means: 15.9 versus 5.2, F = 2.76, df = 1,78, p = 0.007) and between the deficient and sufficient groups (adjusted means: 15.9 versus 4.4, F = 3.10, df = 1,78, p = 0.003), whereas significant differences occurred between the insufficient and sufficient groups (adjusted means: 8.2 versus 3.6, F = 2.64, df = 1,78, p = 0.0104) for whites.

As a result of concerns that the homogeneity of variances assumption may have been violated as a result of differences in the number of participants in

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (total N = 80)</th>
<th>Percent</th>
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<tbody>
<tr>
<td>White</td>
<td>62</td>
<td>87.5</td>
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<tr>
<td>Black</td>
<td>18</td>
<td>22.5</td>
</tr>
<tr>
<td>Females</td>
<td>50</td>
<td>62.5</td>
</tr>
<tr>
<td>Vitamin D deficiency or insufficiency</td>
<td>46</td>
<td>57.5</td>
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<tr>
<td>Active mood disorder</td>
<td>18</td>
<td>22.5</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>74.79 years</td>
<td>7.69</td>
</tr>
<tr>
<td>Education</td>
<td>14.44 years</td>
<td>2.99</td>
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<tr>
<td>25-hydroxyvitamin D</td>
<td>18.58 ng/mL</td>
<td>7.59</td>
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<td>Mini-Mental State Examination</td>
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<td>Depressive symptoms score</td>
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<table>
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<tr>
<th>Standard Deviation</th>
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<tbody>
<tr>
<td>Age</td>
<td>60–92</td>
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<tr>
<td>Education</td>
<td>7–20</td>
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<tr>
<td>25-hydroxyvitamin D</td>
<td>3.6–58.5</td>
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<td>Short Blessed Test</td>
<td>0–28</td>
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<tr>
<td>Mini-Mental State Examination</td>
<td>17–30</td>
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<tr>
<td>Depressive symptoms score</td>
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each vitamin D category, a six-level variable reflecting vitamin D category (three levels) and race (two levels) was calculated and the association of this variable with Sum of Boxes and SBT scores was also tested using a nonparametric method. The Kruskal-Wallis test showed that the vitamin D/race variable...
was associated with Sum of Boxes at \( p = 0.041 \) and with SBT at \( p = 0.058 \).

The overall F value was not significant for the models using MMSE, the factor score, and the PPT score as dependent variables, indicating that vitamin D category and the other independent variables in those models had no statistically significant effect on each of these dependent variables when tested simultaneously (Table 4).

**DISCUSSION**

In this study of older adults without significant functional disability, vitamin D deficiency was associated with low mood and worse performance on two measures of cognitive function. This study also found that 58% of the participants had vitamin D levels below the sufficient range. This finding is similar to prior reports of the prevalence of vitamin D deficiency older adults \(^{1,6}\) but lower than a report by Sato et al. of vitamin D deficiency in persons with AD. \(^{7}\)

Participants in this study with an active mood disorder had significantly lower vitamin D concentrations compared with those without a mood disorder. Prior studies of vitamin D and mood disorders have been conflicting. Depression and seasonal affective disorders have improved with vitamin D supplementation \(^{44}\) and ultraviolet light exposure \(^{60,61}\) but studies have not shown a consistent correlation between vitamin D levels and depression. \(^{27}\) This discrepancy may be in part the result of the use of 1,25-dihydroxyvitamin D concentrations, the active form of the vitamin, as opposed to 25-hydroxyvitamin D concentrations. The latter are more reliable as a result of the longer half-life \(^{62}\) and fewer fluctuations \(^{63}\) in the serum level. Although we found a significant difference between the vitamin D levels of those with and without disordered mood, we cannot conclude that vitamin D is associated with the diagnosis of major depression. There was no structured clinical assessment to determine a diagnosis of depression and most of the clinicians had not been formally trained in psychiatric diagnosis. The presence of depressive symptoms was ascertained by the Depressive Symptoms Inventory, a measure that uses the symptoms of major depression from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Additional studies with a more systematic and comprehensive evaluation of depression are needed to investigate the relationship between depression and vitamin D status in older adults.

Additionally, an association between cognitive performance and vitamin D status was found using the SBT, which has been shown to be an effective screening tool for dementia \(^{66}\) and the CDR Sum of Boxes. The SBT is included in the standard assessments for the Consortium to Establish a Registry for Alzheimer’s Disease \(^{64}\) and may be preferable by some to the MMSE because of its greater sensitivity to detecting impaired recall. \(^{65}\) The finding that the CDR Sum of Boxes scores were higher in persons with vitamin D deficiency is important because the Sum of Boxes has recently been shown to be a strong predictor of progression to AD in persons with questionable AD. \(^{66}\)

Because there was no significant difference in MMSE or factor scores by vitamin D status, the association between worse cognitive performance with lower vitamin D concentrations must be interpreted with caution. Additionally, this was a cross-sectional study so we were unable to determine whether vitamin D levels are fluctuating. An additional limitation of this study is the large number of hypotheses tested given the relatively small sample size. This increases the likelihood of type I error so results should be interpreted with caution. Further studies, including longitudinal evaluations of vitamin D in a larger sample size, are necessary to more fully investigate the possible association between vitamin D status and cognitive function.

This study provides additional support for the hypothesis that vitamin D deficiency is associated with affective and cognitive function in older adults. Vitamin D deficiency is common and often unrecognized and yet may be an important factor contributing to unsuccessful aging. Given that many older adults often have coexisting depression and cognitive impairment, it is important to identify potential contributors that may overlap with these disorders. The association between vitamin D status and mood disorder in this cohort of community-dwelling older adults warrants further study. Additional studies
with larger samples and more systematic assessment of mood are needed. Whether vitamin D supplementation should be considered as additional therapy for this population also needs further investigation.

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