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Serum 25-Hydroxyvitamin D and the Onset of Late-Life Depressive Mood in Older Men and Women: The Pro.V.A. Study

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Introduction. Biological evidence suggests that vitamin D might be involved in regulating mood. The relationship between 25-hydroxyvitamin D (25OHD) and the onset of depressive symptoms was examined over a 4.4-year follow-up in a sample of older adults.

Methods. This research was part of the *Progetto Veneto Anziani* (Pro.V.A.), an Italian population-based cohort study on a total of 1,039 women and 636 men aged 65 and older. Serum 25OHD levels were measured at baseline. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS) at the baseline and during the follow-up. Analyses were adjusted for relevant confounders, including health and performance status.

Results. 25OHD levels correlated inversely with baseline GDS scores, but only in women. After controlling for confounders, women deficient in vitamin D (25OHD < 50 nmol/L) had higher GDS scores than those who were replete (25OHD > 75 nmol/L), with mean [*SE*] GDS scores: 9.57 [0.37] vs 8.31 [0.31], respectively, $p = .02$. In men, the relationship between 25OHD levels and baseline GDS scores was no longer significant after controlling for covariates. Adjusted hazard ratios and 95% confidence intervals for incident depression in participants who were vitamin D deficient vs replete were not statistically significant (hazard ratio: 0.74, 95% confidence interval [0.47–1.16] in women; hazard ratio: 0.96 95% confidence interval [0.45–2.06] in men).

Conclusion. Although an independent inverse association between 25OHD levels and GDS scores emerged for women on cross-sectional analysis, vitamin D deficiency showed no direct effect on the onset of late-life depressive symptoms in our prospectively studied population. Further studies are warranted to clarify the potential influence of vitamin D on psychological health.

Key Words: 25-Hydroxyvitamin D—Depression—Elderly—Community-dwelling adults.

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DEPRESSION is a debilitating chronic condition, and its diagnosis and treatment in elderly people are often challenging. Because depressive mood seems to follow a seasonal pattern, peaking in summer and winter (1), it has recently been suggested that, through its action on the hypothalamus (which is involved in mood regulation), vitamin D might account for the link between seasonal changes in photoperiod and seasonal mood swings (2). Acting as a neurosteroid hormone, vitamin D may regulate human and animal neurotransmission, neuroprotection, and neuroimmunomodulation (3), and nuclear vitamin D receptors have been located in the human cortex and hippocampus (4). Although an association between vitamin D deficiency and depressive disorders is biologically feasible, results from clinical and epidemiological studies are still *contradictory*.

Findings from several cross-sectional studies consistently point to hypovitaminosis D being related to mood disorders in elderly people, and serum 25-hydroxyvitamin D (25OHD) concentrations have been found lower in the depressed than in healthy controls (5–8). Very few longitudinal studies have prospectively explored the relationship between hypovitaminosis and late-life depression, however,

and with conflicting results. In the InChianti population-based study, 25OHD levels less than 50 nmol/L seemed to raise the risk of developing depressive mood (9). On the other hand, Chan and coworkers (10) found no evidence of any association between 25OHD levels and incident depression in elderly people in their large Chinese prospective population-based study. Intervention studies on the effect of vitamin D supplementation on mood have been contradictory too, partly because they involved only small samples of participants and short periods of treatment, with no placebo control, and they failed to control for initial vitamin D status (11,12).

Hypovitaminosis D and depression might share the same matrix because the two conditions commonly coexist in unhealthy older people. Despite this association between hypovitaminosis D and mood disorders in the elderly people, we hypothesized that low serum 25OHD concentrations might no longer be significant in predicting late-life depression after controlling for health, functional status, and physical performance.

The aim of this study was thus to examine the longitudinal relationship between 25OHD levels and the onset of clinically relevant depressive symptoms over a lengthy follow-up (4.4 years) in a representative group of older men and women, controlling for functional status, physical performance, and a number of common later-life comorbidities.

Methods

Study Population

The data for this analysis were drawn from the *Progetto Veneto Anziani* (Pro.V.A), an observational cohort study on an Italian population aged 65 and older living in two areas in the Northeast of Italy (in and around the towns of Camposampiero and Rovigo), which was designed to identify risk factors for all-cause mortality and disability in older men and women. The sampling procedure, study design and data collection method have been extensively described elsewhere (13). Briefly, the baseline Pro.V.A study population consisted of 3,099 age- and sex-stratified, community-dwelling Caucasian participants (1,245 men and 1,854 women), randomly selected between 1995 and 1997 using a multistage-stratified method designed to keep the male-to-female ratio at 2:3 and to oversample the oldest age group.

Individuals who lacked baseline serum 25OHD values (n = 295) or baseline Geriatric Depression Scale (GDS) scores (n = 313) were excluded. Among the remaining 2,491 participants, another 582 were excluded because they were lost to follow-up and 234 because longitudinal data on any depressive symptoms were lacking. Compared with the sample as a whole, the participants lost to follow-up were more likely to be women (53.5 vs 46.1%; chi-square test $p < .0001$) and older (mean [*SD*] age, 80.6 [6.4] vs 73.1 [6.2] years). They had higher scores on the GDS (mean [*SD*], 10.2 [6.6] vs 8.2 [6.1]) and lower serum 25OHD levels (mean [*SD*], 59.2 [20.2] vs 77.5 [43.7] nmol/L; one-way ANOVA, $p < .0001$ for all comparisons). They were also more likely to have been diagnosed with depression (42.5% vs 29.5%), dementia (56.3.7% vs 25.0%), and disability in activities of daily living (32.7% vs 10.2%), and they had a twofold higher prevalence of cardiovascular diseases (36.4.4% vs 15.7%; chi-square test, $p < .0001$ for all comparisons).

The ethical committees of Padua University and the Local Public Health Units (USSL n. 15 and 18) of the Veneto Region approved the study protocol, and participants gave their written informed consent. Individuals unable to give their informed consent were not enrolled.

Clinical and Laboratory Data

At baseline and follow-up, participants were examined at city hospitals by trained physicians and nurses. Information was collected on their formal education, physical activity, and smoking habits during a face-to-face interview. Educational level (years of school attendance) was categorized as less than or equal to 5 vs greater than 5 years of schooling. Regular physical activity was defined as at least moderate physical activity (brisk walking, cycling, gardening, dancing, or exercising at the gym) for 4 or more hours a week during the previous month. Smoking was categorized as "never/former" (including those who had given up smoking at least a year earlier) vs "current" smokers. Body weight and height were measured by trained physicians, and participants' body mass index (kg/m^2) was calculated. Any diseases existing at the baseline were ascertained by board-certified physicians involved in the study, who examined all the clinical information collected on each participant, including their medical history, self-reported symptoms recorded using standardized questionnaires, medical and hospital records, blood tests, and a physical examination. A history of major diagnosed disease included any of the following: cardiovascular diseases (ie, congestive heart failure, angina and myocardial infarction, stroke, and peripheral artery disease), diabetes, chronic obstructive pulmonary diseases, cancer, dementia, osteoporosis, and osteoarticular diseases (including osteoarthritis and osteoarthrosis of hand/knee/hip, and hip fracture). Participants' glomerular filtration rate was also included in the analysis. Cognitive function was assessed by administering the 30-item Mini-Mental State Examination, and scores lower than 24 indicated a cognitive impairment (14). Physical performances were assessed using the Short Physical Performance Battery (SPPB), a standardized measure of lower extremity physical performance that includes 4-m self-paced walking speed, a balance test, and a chair stand test (15). Each task in the SPPB scores from 0 (unable to complete the task) to 4, and the sum of the scores ranges from 0 to 12, with higher scores indicating a better performance (15). Disability was

defined as the inability to perform, or need for assistance in performing one or more activities of daily living, ie, bathing, dressing, eating, using the toilet, or transferring.

Venous blood samples were obtained after an overnight fast, centrifuged, and stored at −80°C. 25OHD and parathyroid hormone tests were performed at Padua University laboratories. Serum 25OHD levels were measured by radioimmunoassay (RIA kit, DiaSorin). The intra-assay and interassay coefficients of variation for 25OHD were 8.1% and 10.2%, respectively. Serum intact parathyroid hormone levels were measured using a two-site immunoradiometric assay kit (N-tact PTHSP, DiaSorin); the intra-assay and interassay coefficients of variation for parathyroid hormone were 3.0% and 5.5%, respectively. Serum creatinine was measured using a standard Jaffe method (Roche Diagnostics, Germany) and the glomerular filtration rate was calculated with the modification of diet in renal disease (MDRD) formula.

Depression Assessment

Presence of any depressive symptoms was assessed at the baseline and follow-up using the GDS (16), a 30-item self-reporting tool for identifying depression that has been extensively validated for use in the elderly people. GDS scores range from 0 to 30, and a score of greater than or equal to 11 is indicative of depressive symptoms. The test was administered by personnel expert in psychiatric diseases in the elderly people.

Statistical Analysis

Participants' characteristics were summarized using means (± *SD*s) for continuous variables, and counts and percentages for categorical variables. For continuous variables, normal distributions were tested using the Shapiro–Wilk test. All data analyses were stratified by sex, given the gender differences in 25OHD serum levels and the significant sex by 25OHD level interaction ($p < .0001$). Means and proportions were calculated for conventional serum 25OHD cutoffs, based on previously adopted 25OHD thresholds for improving general health, obtaining three clinical groups with 25OHD deficiency (<50 nmol/L), 25OHD insufficiency (≥50 to <75 nmol/L), and 25OHD sufficiency (≥75 nmol/L) (17). Differences between the means of the covariates were checked by vitamin D group using ANOVA for continuous variables and the chi-square test for categorical variables. General linear models were used to examine the independent association between baseline 25OHD levels (categorized according to conventional cutoffs) and baseline and follow-up GDS scores, and longitudinal variations in GDS scores. The results of testing for any nonlinear (quadratic) effect of 25OHD concentrations were negative, so only the linear associations were modeled. Known factors associated with 25OHD levels and/or depressive symptoms were examined for inclusion in the analysis. The following confounders were added in Model 1: age in years, educational level, smoking habits, season when blood samples were collected (winter, spring, summer, autumn), body mass index, disability in activities of daily living, Mini-Mental State Examination score, glomerular filtration rate, diagnoses of cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, or osteoarticular diseases (including osteoporosis). In the fully adjusted model, the confounders considered were those included in Model 1 plus: regular physical activity and SPPB scores. Parathyroid hormone concentrations were also initially considered for inclusion in the analysis because they might act as intermediate factors of altered 25OHD levels, but they were subsequently removed from the models due to a high collinearity, as quantified by the variance inflation factor. For all analyses, 25OHD status was coded as an indicator variable, considering the highest level (>75 nmol/L) as the reference group.

A Cox proportional hazards model was fitted to correlate vitamin D status with the risk of developing depressed mood during the follow-up. Participants with prevalent depressive symptoms at the baseline (GDS baseline scores ≥11) were excluded (*115 men and 378 women*). Participants who did not become depressed were censored as at the date of their latest follow-up. Hazard ratios and 95% confidence intervals were used to compare the rates of depressed mood across the different 25OHD levels, and they were also calculated for all the previously selected covariates found significantly related to the outcome. All analyses were performed using SAS (rel. 8.2; SAS Institute, Inc., Cary, NC), assuming statistical significance at $p < .05$.

Results

The sample consisted of 1,675 community-dwelling elderly participants (1039 F and 636 M) who completed the follow-up depression assessment. At the baseline, the prevalence of depressive symptoms among the participants was 40.6% in women and 23.8% in men (chi-square test, $p < .0001$). At the follow-up assessment, depressive symptoms were found in another 146 women (incident rate 14%) and 74 men (11.6%). The mean baseline serum 25OHD levels were 71.7 nmol/L (±42.3) in women, and 101.0 nmol/L (±62.7) in men. Vitamin D deficiency (25OHD < 50 nmol/L) was more common in women (34.2%) than in men (11%; chi-square test, $p < .0001$), and was severe (25OHD <25 nmol/L) in 13% of women and only 5% of men (chi-square test, $p < .0001$).

The age-adjusted characteristics of the participants, grouped according to the conventional 25OHD cutoffs, are shown in Tables 1 and 2 for women and men, respectively. Participants with a 25OHD deficiency were significantly older and less active than those with sufficient 25OHD levels (25OHD < 75nmol/L; p for trend < .0001). After adjusting for age, both male and female vitamin-deficient participants had higher GDS scores, higher rates

Table 1. Female Pro.V.A Study Participants' Baseline Characteristics by 25-Hydroxyvitamin D (25OHD) Serum Levels

	25-Hydroxyvitamin D (25OHD) Serum Levels (nmol/L)			
	≤50 (n = 356)	>50 and ≤75 (n = 266)	>75 (n = 417)	Age-adjusted p for Trend
Age (y)	74.7 (6.4)	72.9 (6.0)	71.5 (5.1)	<.0001 (unadjusted)
Educational level (<5 y of schooling), %	62.5	19.7	15.3	.01
Current smokers, %	6.2	8.6	6.0	.27
Regular physical activity, %	63.2	76.9	81.7	<.0001
Gardening, %	31.7	46.2	51.8	<.0001
Season of blood collection				
Winter	23.6	25.5	29.3	.65*
Spring	24.1	35.7	34.3	
Summer	30.6	21.8	24.0	
Autumn	21.6	17.0	12.5	
BMI (kg/m^2)	28.7 (5.2)	28.3 (4.5)	28.0 (4.7)	.02
MMSE score	25.0 (3.6)	24.9 (3.6)	25.4 (3.7)	.50
GDS score	10.3 (6.8)	9.0 (6.1)	8.6 (6.3)	.002
Disability in ADLs, %	19.9	11.6	6.0	<.0001
Dementia, %	31.8	28.0	23.7	.56
Depression symptoms, %	41.3	34.2	33.8	.009
Cardiovascular diseases, %	17.5	9.6	10.6	.07
Osteoporosis, %	56.5	56.0	47.0	.30
Osteoarticular diseases, %	36.5	38.6	32.7	.43
Diabetes, %	8.4	6.4	8.6	.80
COPD, %	5.6	5.6	2.2	.03
Gait speed, m/s	0.62 (0.19)	0.68 (0.16)	0.72 (0.17)	<.0001
SPPB, (0–12 range)	9.5 (1.9)	9.9 (1.7)	10.1 (1.5)	.005
Serum levels				
Parathyroid hormone (ng/L)	46.7 (29.6)	40.0 (18.5)	36.6 (30.9)	<.0001
25OHD (nmol/L)	32.9 (11.1)	61.6 (7.5)	111.2 (37.0)	<.0001

Notes: Numbers are means (and *SD*s) or percentages (%), as appropriate. BMI = body mass index; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; ADLs = activities of daily livings; COPD = chronic obstructive pulmonary dseases; SPPB = Short Physical Performance Battery. Unless specified otherwise, p values are based on the age-adjusted general linear model or logistic regression, as appropriate.

*chi-square test.

of disability in activities of daily living, and lower rates of regular exercise and outdoor activity, such as gardening. The physical performance levels emerging from the SPPB scores differed significantly in relation to vitamin D status, in both genders, even after controlling for age (p for trend < .0001). Our analysis did not confirm the expected seasonal differences in serum 25OHD levels (Tables 1 and 2). Differences in the distribution of hypovitaminosis D were also tested by dichotomizing the seasons as "low-vitamin D seasons" (conventionally considered as winter and spring) and "high-vitamin D seasons" (summer and autumn), but no significant differences emerged after controlling for age (p = .61 in women and p = .45 in men). Because a seasonal pattern peaking in summer and winter has been suggested for depressive mood, the effect of season—categorized as autumn/spring(=0) vs summer/winter (=1)—was tested, but no significant association emerged on logistic regression analysis between season and depression (odds ratio 1.31; 95% confidence interval 0.65–1.97, details not shown).

The multivariate-adjusted mean GDS scores recorded at the baseline and follow-up assessments and the mean variation over the intervening period are shown in Table 3, by baseline vitamin D status. In women, a significant linear trend in the GDS scores was only apparent at the baseline, and the association between GDS scores and vitamin D status remained significant even after controlling for confounders (functional, health, and performance status; p = .02). In men, both baseline and follow-up GDS scores were associated with vitamin D status in the unadjusted analysis and after controlling for comorbidities, but the associations were no longer significant after controlling for physical performance (baseline: p = .37; follow-up: p = .56). Longitudinal variations in GDS scores were unassociated with baseline vitamin D status in either gender (p = .15 in women, and p=.80 in men).

Using Cox regression analysis, 25OHD deficiency and insufficiency were not associated with a higher probability of developing depressed mood during the follow-up (Table 4) in either gender. Compared with participants in the reference group (25OHD > 75 nmol/L), the men and women with lower vitamin D levels did not carry a higher risk of developing depressive symptoms (Table 4). Among the covariates possibly associated with depressive symptoms, including health and functional status, the only significant predictor of depressed mood in both genders was their baseline level of physical performance, as assessed by

Table 2. Male Pro.V.A Study Participants' Baseline Characteristics by 25-Hydroxyvitamin D (25OHD) Serum Levels

	25-Hydroxyvitamin D (25OHD) Serum Levels (nmol/L)			
	≤50 (n = 69)	>50 and ≤75 (n = 109)	>75 (n = 458)	Age-adjusted p Values
Age (y)	76.8 (7.7)	73.7 (6.8)	72.7 (6.0)	<.0001 (unadjusted)
Educational level (<5 y of schooling), %	48.1	15.0	12.1	<.0001
Current smokers, %	30.4	22.9	22.5	.03
Regular physical activity, %	80.3	81.0	89.5	.01
Gardening, %	30.8	47.7	55.6	.004
Season of blood collection				
Winter	26.1	25.7	29.5	.41*
Spring	24.6	29.4	28.8	
Summer	36.2	20.2	24.0	
Autumn	13.0	24.7	17.7	
BMI (kg/m^2)	27.4 (4.8)	27.5 (4.1)	27.1 (3.6)	.06
MMSE score, (range 0–30)	25.9 (3.2)	25.9 (3.3)	25.9 (3.3)	.30
GDS score, (range 0–30)	7.9 (5.0)	6.4 (4.8)	6.1 (5.0)	.002
Disability in ADL, %	10.1	8.2	7.4	.85
Dementia, %	21.7	24.7	20.2	.48
Depression symptoms, %	31.8	15.6	16.6	.02
Cardiovascular diseases, %	31.8	20.2	19.5	.27
Osteoporosis, %	21.7	15.6	17.2	.88
Osteoarticular diseases, %	27.9	26.6	27.3	.52
Diabetes, %	10.1	11.0	7.4	.21
COPD, %	20.3	8.3	12.2	.39
Gait Speed, m/s	0.62 (0.19)	0.68 (0.15)	0.72 (0.16)	.002
SPPB, (0–12 range)	9.5 (1.9)	9.9 (1.6)	10.1 (1.5)	.002
Serum levels				
Parathyroid hormone (ng/L)	46.7 (30.3)	40.4 (19.9)	36.3 (19.0)	<.0001
25OHD (nmol/L)	32.7 (11.0)	61.6 (7.5)	111.0 (36.0)	<.0001

Notes: Numbers are means (and *SD*s) or percentages (%), as appropriate. BMI = body mass index; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; ADL = activities of daily living; COPD = chronic obstructive pulmonary diseases; SPPB = Short Physical Performance Battery. Unless specified otherwise, p values are based on the age-adjusted general linear model or logistic regression, as appropriate.

*chi-square test.

the SPPB (Table 4): for a 1-point increment in the SPPB score, the risk of developing depressive symptoms over the follow-up decreased by 15% in women and 25% in men (hazard ratio 0.85, 95% confidence interval 0.75–0.96, p = .01 in women; hazard ratio 0.76, 95% confidence interval 0.64–0.92, p = .004 in men).

Discussion

In our large study population, low 25OHD levels were only associated with GDS scores in women on cross-sectional analysis, but there was no evidence of any independent association between hypovitaminosis D and incident depression. The fact that there was no significant association between baseline 25OHD levels and GDS scores in men might be due to the lower prevalence of both vitamin D deficiency and depressive symptoms among our male participants, compared with the women in our sample. This might have reduced the power of our analysis, preventing us from identifying any significant association between depression and vitamin D deficiency in men too, as found in other studies (5,8,18). In another recent cross-sectional population-based study, vitamin D deficiency was associated with a higher risk of depression in elderly men whose mean (±*SD*) 25OHD levels (55.9 ± 22.2 nmol/L) were considerably lower than those found in our study (101.0 ± 62.7 nmol/L) (18). The results of a recent meta-analysis on observational studies seems to confirm that the risk of depressive symptoms drops by 10% for a 10 ng/L increase in 25OHD serum levels, but the marked heterogeneity of the cohort studies considered and the different methods used to diagnose depression might limit the generalizability of these results (19). In contrast, an earlier study on 3262 elderly participants found no association between 25OHD levels and depressive symptoms in either gender (20).

Our cross-sectional analysis failed to confirm the expected seasonal differences in serum 25OHD levels (21,22), and our data do not support any presence of a seasonal effect on late-life mood disorders. Exposure to sunlight has a much less significant effect on 25OHD levels in the elderly people than in younger people (23), partly due to their generally lower exposure and partly to the lower capacity of the skin to synthesize vitamin D on exposure to sunlight.

Our study also failed to identify any independent association between 25OHD and incident depression. Among the

Table 3. Baseline and Follow-up Estimated Mean GDS Scores [mean (*SE*)] by Baseline Serum 25-Hydroxyvitamin D (25OHD) Level in Female and Male Pro.V.A Participants

	25-Hydroxyvitamin D (25OHD) Serum Levels (nmol/L)			
Female Participants	≤50 (n = 356)	>50 and ≤75 (n = 266)	>75 (n = 417)	p for Linear Trend
Baseline GDS scores				
Unadjusted	10.37 (0.34)	9.05 (0.39)	8.66 (0.31)	0.001
Model 1	10.37 (0.34)	8.98 (0.39)	8.73 (0.31)	0.007
Model 2	9.57 (0.37)	8.45 (0.39)	8.31 (0.31)	0.02
Follow-up GDS scores				
Unadjusted	10.64 (0.35)	9.33 (0.39)	9.51 (0.31)	0.01
Model 1	10.35 (0.34)	9.29 (0.39)	9.65 (0.31)	0.11
Model 2	9.81 (0.37)	8.81 (0.39)	9.32 (0.31)	0.18
Delta GDS scores*				
Unadjusted	0.31 (0.28)	0.27 (0.33)	0.85 (0.26)	0.27
Model 1	0.18 (0.29)	0.31 (0.33)	0.91 (0.27)	0.15
Model 2	0.24 (0.33)	0.36 (0.35)	1.01 (0.28)	0.15
Male Participants	≤50 (n = 69)	>50 and ≤75 (n = 109)	>75 (n = 458)	p for Linear Trend
Baseline GDS scores				
Unadjusted	7.92 (0.59)	6.44 (0.47)	6.11 (0.23)	.01
Model 1	7.63 (0.60)	6.58 (0.46)	6.11 (0.22)	.05
Model 2	6.78 (0.50)	6.10 (0.45)	5.89 (0.21)	.37
Follow-up GDS scores				
Unadjusted	9.406 (0.64)	6.92 (0.51)	6.98 (0.25)	.002
Model 1	8.73 (0.64)	6.98 (0.50)	7.07 (0.24)	.05
Model 2	7.57 (0.64)	6.73 (0.50)	6.85 (0.24)	.56
Delta GDS scores*				
Unadjusted	1.47 (0.55)	0.47 (0.44)	0.87 (0.21)	.37
Model 1	1.09 (0.56)	0.40 (0.43)	0.96 (0.31)	.47
Model 2	0.79 (0.59)	0.63 (0.45)	0.95 (0.21)	.80

Notes: Model 1 adjusted for: age, educational level, season of blood collection, smoking habits, body mass index, baseline Mini-Mental State Examination score, glomerular filtration rate, disability in activities of daily living, cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, osteoarticular diseases (including osteoporosiys). Model 2 adjusted for covariates in Model 1 plus: regular physical activity and SPPB score.

*Delta GDS: variation in Geriatric Depression Score over the follow-up.

various studies focusing on this topic, an association between vitamin D deficiency and the risk of mood disorders in elderly participants was prospectively observed in the InChianti population-based study (9) over a follow-up of 6 years (9). Although our analysis included much the same set of covariables as in the InChianti study(9), these divergent findings might be attributable to methodological differences (for instance, the use of the CES-D questionnaire in the InChianti study to assess depressive symptoms). Another issue might be the higher prevalence of vitamin D deficiency seen in the InChianti sample population: 50% of the men and 74.6% of the women had 25OHD serum levels less than 50 nmol/L, whereas in our study only 11% of the men and 34% of the women were vitamin D deficient. Our results are more similar to those reported by Chan and coworkers (10), who studied a large population of elderly participants and found that vitamin D deficiency was associated with prevalent, but not with incident, depression . The follow-up period, baseline vitamin D levels, and depression rates reported in Chan's study were also all similar to those found in our population.

The absence of any prospectively measurable association between 25OHD levels and depression in our elderly population–based study is supported by several considerations. First, a recent meta-analysis on randomized controlled studies concluded that vitamin D supplementation might have a slight positive effect only on young adults with major depressive disorders, but not on those with minor depressive symptoms (11). Second, although nuclear vitamin D receptors have been identified in numerous areas of the human brain involved in the pathophysiology of depression (24), experimental studies on vitamin D receptor-KO mice identified more symptoms relating to severe anxiety and psychosis, but not relating to depression (25).

Based on our findings, physical performance level (as assessed with the SPPB) seems to be the strongest predictor of incident depression in our elderly population. Recent exercise trials targeting older individuals with and without clinical depression demonstrated that an improvement in performance status coincided with a reduction in GDS scores (26). Our findings confirm that a good performance status can significantly reduce the risk of incident depression, so encouraging the elderly people to engage in regular moderate physical activity—which could improve their SPPB scores (27)—might have a significant antidepressant effect.

Because several observational studies have documented an independent positive association between motor performance and 25OHD levels (28–31), vitamin D might be seen as a biomarker of a good performance status, and an indirect

Table 4. Adjusted Hazards Ratios (95% CI) for Depressed Mood at 4-y Follow-up in the Pro.V.A Participants

	Female Participants		Male Participants	
	Hazard Ratio (95% confidence interval)	*p* Value	Hazard Ratio (95% confidence interval)	*p* Value
25OHD levels <50 nmol/L*	0.74 (0.47–1.16)	.19	0.96 (0.45–2.06)	.92
25OHD levels <75 nmol/L*	0.54 (0.54–1.35)	.51	1.08 (0.56–2.07)	.81
Age (y)	1.01 (0.97–1.04)	.63	1.03 (0.99–1.08)	.1
Educational level, (<5 y of schooling)	1.10 (0.95–1.43)	.24	1.07 (0.67–1.94)	.40
Current smokers	1.44 (0.75–2.74)	.26	1.34 (0.73–2.44)	.34
BMI (kg/m^2)	0.99 (0.96–1.03)	.77	0.94 (0.87–1.02)	.14
Disability in ADL	1.38 (0.65–3.02)	.41	0.87 (0.27–2.72)	.81
Dementia	0.88 (0.56–1.38)	.59	1.11 (0.86–1.44)	.10
Cardiovascular diseases	0.90 (0.52–1.55)	.72	1.60 (0.90–2.84)	.99
COPD	0.50 (0.12–2.14)	.35	1.31 (0.54–3.17)	.54
Osteoarticular diseases†	1.31 (0.89–1.94)	.16	1.68 (0.88–3.20)	.11
Diabetes	1.29 (0.70–2.37)	.40	2.15 (0.92–5.02)	.07
Regular physical activity	0.73 (0.42–1.28)	.27	0.75 (0.31–1.79)	.52
SPPB score range 0–12 (for 1-point increment)	0.85 (0.75–0.96)	.01	0.76 (0.64–0.92)	.004

Notes: BMI = body mass index; ADL = activities of daily living; COPD = chronic obstructive pulmonary diseases; SPPB = Short Physical Performance Battery.
*25OHD ≥ 75 nmol/L as the reference category.
†Including osteoporosis.

biomarker of good health too, as extensively supported by recent literature (32). Although serum 25OHD concentrations revealed no direct influence on mood disorders in this study, hypovitaminosis D might have an indirect influence on depressive symptoms due to its direct negative association with performance status (28).

Our study has both strengths and limitations. Its main limitations relate to the fact that the severity of any depressive symptoms could not be assessed using the GDS, and that 25OHD serum levels were not measured during the follow-up. We also had no information on any use of antidepressant medication in our sample, but the baseline data for our study were collected between 1995 and 1997, when the use of antidepressants by the general elderly population was very low, as was the diagnosis of depression. Vitamin D supplementation was also negligible (used by less than 2% of the 3,099 participants initially recruited). Another weakness of our study lies in that its *observational* design might have limited the explanatory power of the results because it is impossible to say whether any relationships observed between 25OHD levels and depression are causal or not. The main strengths of our study lie in the large population with known baseline 25OHD levels (the best indicator of vitamin D status in humans) and in the fact that any presence of depressive symptoms was assessed by personnel expert in psychiatric diseases in the elderly people. Our analyses were also adjusted for a large number of possible confounding factors, including physical activity and particularly the amount of time spent on outdoor activities such as gardening.

In conclusion, we found an inverse association between serum 25OHD and depression on cross-sectional analysis, particularly for female participants in the Pro.V.A study, but our findings do not support any direct effect of serum 25OHD levels on the onset of mood disorders. Physical performance seems to be the strongest predictor of whether people will develop late-life depressive symptoms. Further studies are warranted to see what influence 25OHD serum levels may have on late-life psychological health in elderly populations with a higher prevalence of both vitamin D deficiency and depressive disorders.

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Conflict of Interest

None of the authors have any financial arrangements, organizational affiliations or other relationships that might give rise to any conflict of interest regarding the subject matter of the manuscript submitted.

Authors' Contributions

Study concept and design: Manzato, Perissinotto, Sergi, Toffanello. Data acquisition: Baggio, Corti, Sartori. Data analysis and interpretation: Musacchio, Perissinotto, Toffanello and Zambon. Drafting of the manuscript: Perissinotto, Sergi, Toffanello and Veronese. Critical revision of the manuscript: Coin, Manzato, Perissinotto, Sergi, Toffanello, Veronese and Zambon. Statistical analysis: Toffanello. *Obtaining funding:* Baggio, Crepaldi and Manzato. Administrative and technical support: Baggio, Corti, Crepaldi, Sartori, Zambon. Study supervision: Manzato and Zambon.

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