



JAMDA

journal homepage: www.jamda.com

Original Study

Vitamin D Deficiency Is Associated With an Increased Likelihood of Incident Depression in Community-Dwelling Older Adults



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A B S T R A C T

Keywords:

Depression
vitamin D
vitamin D deficiency
longevity
affect

Objective: To examine the prospective relationship between vitamin D status and incident depression in a large cohort of nondepressed community-dwelling older people.

Design: Longitudinal study examining the relationship between vitamin D levels at baseline (wave 1) and incident depression at 2 and 4 years (waves 2 and 3), embedded within the Irish Longitudinal Study on Aging. Participants with depression at wave 1 were excluded. Logistic regression models reporting odds ratios were used to analyze the longitudinal association of vitamin D categories with incident depression. Analysis was weighted for attrition.

Setting and Participants: Almost 4000 community-dwelling people aged ≥ 50 years.

Measures: A score ≥ 9 on the Center for Epidemiologic Studies Depression Scale-8 at wave 2 or 3 was indicative of incident depression. Vitamin D analysis was performed using liquid chromatography-tandem mass spectrometry and deficiency, insufficiency, and sufficiency were defined as <30 , $30\text{--}50$, and >50 nmol/L, respectively.

Results: The incident depression group (400/3965) had a higher likelihood of baseline vitamin D deficiency (proportional estimation 19.4) [95% confidence interval (CI) 15.1–24.7] vs [12.4 (95% CI 11.1–14.0); $Z = 3.93$; $P < .001$]. Logistic regression models demonstrated that participants with vitamin D deficiency had a significantly higher likelihood of incident depression (odds ratio 1.75, 95% CI 1.24–2.46; $t = 3.21$; $P = .001$). This finding remained robust after controlling for relevant covariates including physical activity, chronic disease burden, cardiovascular disease and antidepressant use.

Conclusions/Implications: This study demonstrates that vitamin D deficiency is associated with a significant increase in the likelihood of developing depression in later life. These findings are important, given the high prevalence of vitamin D deficiency among older people, the fact that supplementation has a low risk of toxicity or side effects, as well as the significant adverse effect depression can have on functional status and longevity in later life.

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Vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25(OH)D) ≤ 30 nmol/L,¹ is prevalent in later life. Over 13% of community-dwelling older people within the population-

representative cohort of the Irish Longitudinal Study on Aging (TILDA) were found to be vitamin D deficient,² although rates are higher in specific patient groups, such as those seen in primary care³ or by an orthogeriatric service⁴ and nursing home residents.⁵

This higher prevalence of deficiency in later life and particularly among vulnerable patient groups is likely due to several factors, including reduced capacity of the skin to synthesize vitamin D,⁶ malnutrition,⁷ reduced sun exposure,⁸ and impaired hydroxylation by the liver and kidney.⁹ Inadequate vitamin D has an adverse impact on frailty status, bone health, cardiovascular disease, and mortality,^{10–12} and there is also growing interest in the link between vitamin D and late life mental health.

Financial support was provided by Irish Government, the Atlantic Philanthropies and Irish Life plc. These funders had no involvement in the study design, collection, analysis and interpretation of data, writing of the paper or submission for publication. Any views expressed in this report are not necessarily those of the Department of Health and Children or of the Minister for Health.

The authors declare no conflicts of interest.

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<https://doi.org/10.1016/j.jamda.2018.10.006>

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Several large population studies of older people have shown that vitamin D levels are inversely related to depressive symptom burden across diverse settings.^{13–17} Further studies have suggested that these findings may be due to a direct effect of vitamin D on brain tissue, and vitamin D receptors are widespread throughout the brain,¹⁸ including the frontal lobe.¹⁹ Vitamin D may also protect the brain from inflammatory or vascular insults, both of which are seen as key steps in the pathogenesis of depression in later life.^{20–22}

Most studies examining this association are cross-sectional, however,²³ and have not controlled for important covariates, such as functional status, medication use, and cardiovascular disease. Prospective studies are limited, particularly those involving an exclusively older cohort, and have produced inconsistent results to date.^{23–25}

Understanding the link between vitamin D status and depression in later life is important as vitamin D status is relatively easy and inexpensive to modify through supplementation or fortification. Late life depression significantly reduces quality of life²⁶ and is a potent risk factor for functional decline,²⁷ admission to residential care,²⁸ and early mortality.²⁹ Given the complex nature of the illness, including that the majority of older adults with depression are undiagnosed,³⁰ prevention of cases should be a priority and identification of important risk factors is, therefore, crucial.

The aim of this study, therefore, is to examine the longitudinal relationship between vitamin D status and incident depression in the large Irish Longitudinal Study on Aging (TILDA) cohort of nondepressed, community-dwelling older people.

Methods

Ethics

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki. All assessments were carried out by trained research nurses.

Study Design

This study is embedded within TILDA, a large population-based study of a nationally representative sample of community dwelling older adults aged ≥ 50 years. The study was designed to investigate how the health, social, and economic circumstances of the older Irish population interact in the determination of “healthy” aging. The TILDA study design has been outlined previously³¹ but in short, the first wave of data collection (wave 1, 2009–2011) was conducted using a stratified clustered procedure to randomly sample postal addresses from the Irish Geo-Directory (a listing of all residential addresses in the Republic of Ireland). All postal addresses in Ireland were assigned to one of 3155 geographic clusters; using RANSAM (a random sampling design for Ireland), a sample of 640 of these clusters was selected stratified by socioeconomic group and geography, where all household residents aged ≥ 50 years were eligible to participate; wave 2 was conducted in 2011–2012 and wave 3 was conducted in 2014–2015.

This is a longitudinal study examining the relationship between vitamin D levels at baseline (wave 1) and incident depression at 2- and 4-year follow-up. Therefore, participants with depression at wave 1 were excluded. The remaining participants were screened for depression at waves 2 and 3.

We analyzed data from the first, second, and third waves. Participants were included in this study if they were aged 50 years or more, and underwent assessment at wave 1 including measurement of serum 25-hydroxyvitamin D and screening for depression. Participants were excluded if they did not complete 4-year follow-up, including assessment of depressive symptoms at both wave 2 and wave 3.

Vitamin D

Vitamin D analysis was performed on frozen nonfasting total plasma.

A nonfasting blood sample was collected by venepuncture and two 10 mL ethylenediaminetetraacetic acid tubes were taken for long-term storage by a trained phlebotomist. Samples were kept chilled and centrifuged (3000 rpm for 15 minutes), and plasma aliquots were labeled and stored at -80°C until required for analysis.

Vitamin D analysis included total plasma 25(OH) D (D2 and D3) concentrations, which were quantified by a fully validated method (MassChrom 25-OH-Vitamin D3/D2; Chromsystems Instruments and Chemicals GmbH) using liquid chromatography-tandem mass spectrometry (API 4000; AB SCIEX, Grafelfing, Germany) and batch analyzed in the Biochemistry Department of St James's Hospital [which is accredited (ISO 15189)]. The quality of the method was monitored by the use of internal quality controls, the use of the National Institute of Standards and Technology 972 vitamin D standard reference material and with participation in the vitamin D External Quality Assessment Scheme. The respective inter- and intra-assay coefficients of variation were 5.7% and 4.5%.

Low and high vitamin D synthesis periods were defined as winter-spring and summer-autumn, respectively.³² As per Health and Medicine Division (formerly Institute of Medicine) guidelines,¹ vitamin D deficiency, insufficiency, and sufficiency were defined as <30 , $30\text{--}50$, and >50 nmol/L, respectively.

Depression

Depressive symptoms were assessed at wave 1 using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D)-20. A score of ≥ 16 was used to define cases of depression.³³ Participants with depression at wave 1 were excluded from the study.

At Waves 2 and 3 the 8-item CES-D-8 was used to screen for depression. The CES-D-8 was introduced in the TILDA study at waves 2 and 3 to reduce the time taken to conduct participant assessments, as well as to reduce respondent burden and fatigue. A score of ≥ 9 on this scale was used to define cases of depression and participants with a CES-D-8 score ≥ 9 at either wave 2 or 3 were defined as having incident depression.³⁴

Other Measures

Detailed social and biological data were collected at wave 1. Functional impairment was defined as impairment in 1 or more instrumental activities of daily living, which includes cleaning and maintaining the house, managing money, moving within the community, and preparing meals. Alcohol excess was assessed using the Cut Down, Annoyed, Guilty, Eye Opener (CAGE) Alcohol Scale. Cardiac disease was defined as self-report of prior myocardial infarct, cardiac failure, angina, hypertension, or cardiac arrhythmia. Self-report was also elicited for chronic disease burden, with respondents asked specifically about a history of lung disease, osteoporosis, cancer, liver disease, age-related macular degeneration, cataracts, glaucoma, arthritis, urinary incontinence, Parkinson disease, and diabetes. Participants were asked about physical activity within the last week, and those who were inactive for the full 7 days were defined as having low physical activity, compared with moderate (active 1–3 days) and high (active 4 or more days) physical activity levels. Cognitive impairment was defined as a Mini-Mental State Examination score of ≤ 24 .

Statistical Analysis

Data were analyzed using Stata (StataCorp, College Station, TX). Analysis was weighted for attrition. These weights corrected for the systematic difference in attrition rates over subgroups and reduced

the bias caused by this difference in attrition rates and were calculated based on the reciprocal of the probability of a wave 1 respondent taking part in wave 2 and wave 3. This probability was calculated using a logistic regression model. Factors in the model, which were shown to affect attrition, included measures of cognitive and behavioral health, marital status, and several health measures

Normally distributed continuous variables were compared across groups using Student *t*-test with adjusted Wald test used post-estimation. Proportional estimation was used for categorical variables with *z* score calculated postestimation.

Logistic regression models reporting odds ratios were used to analyze the longitudinal association of vitamin D categories (ie, deficiency, insufficiency, and sufficiency, with incident depression). Variables were chosen a priori based on their likely probability of modifying the index relationship between vitamin D and depression status. Three models were tested: the first model was unadjusted; the second model adjusted for age, sex, body mass index, smoking status, and alcohol excess; and the third model adjusted for clinical covariates such as cardiac disease, cognitive impairment, chronic disease burden, and antidepressant use.

To confirm that results were not related to antidepressant use or vitamin D supplementation, analyses were rerun excluding participants prescribed either of these medications/supplements.

A *P* value of $\leq .05$ was considered statistically significant.

Results

Over 10% (400/3965) of the study sample met criteria for incident depression during the 4-year follow-up. Participants with incident depression were more likely to be female, current smokers, and have burden of chronic disease and impairment in instrumental activities of daily living. Participants with incident depression were significantly more likely to be taking antidepressant medication at wave 1 compared with those who did not meet criteria for depression (Table 1).

The prevalence of vitamin D deficiency, insufficiency and sufficiency were 12% (466/3965), 29% (1150/3965), and 59% (2349/3965), respectively. As shown in Table 2, there was no significant difference between study groups in terms of mean vitamin D levels at wave 1, but the incident depression group had a higher likelihood of vitamin D deficiency [proportional estimation 19.4 (95% confidence interval, CI 15.1–24.7) vs 12.4 (95% CI 11.1–14.0); $Z = 3.93$; $P < .001$] and lower likelihood of vitamin D sufficiency [proportional estimation 50.8 (95% CI: 45.3–56.4) vs. 57.1 (95% CI 55.1–59.1), $Z = -2.41$; $P = .016$].

Figure 1 shows incidence of depression during follow-up by vitamin D category, with those in the vitamin D deficiency category having a significantly higher incidence than those with sufficient levels [proportional estimation 16.3 (95% CI 12.6–20.8) vs 10.0 (95% CI 8.7–11.6); $Z = 3.96$, $P < .001$].

Table 1
Baseline Characteristics by Incident Depression

	Nondepressed n = 3565	Incident Depression n = 400	
Age: mean (95% CI), y	63.1 (62.7–63.6)	62.6 (61.4–63.8)	$F = 0.60$; $P = .4397$
Female: prop. (95% CI)	49.3 (47.7–50.8)	58.0 (52.4–63.4)	$Z = 3.41$; $P = .0006$
Educational attainment, prop. (95% CI)			
Primary	27.5 (25.6–29.4)	39.2 (34.0–44.7)	$Z = 4.59$; $P < .001$
Secondary	48.0 (46.1–50.0)	40.8 (35.8–46.0)	$Z = -2.66$; $P = .007$
Tertiary	24.4 (22.8–26.2)	20.0 (16.5–24.0)	$Z = -1.79$; $P = .073$
BMI, prop. (95% CI)			
BMI <24.9 kg/m ²	22.0 (20.4–23.7)	20.6 (16.8–25.0)	$Z = -0.64$; $P = .522$
BMI 25.0–29.9 kg/m ²	46.0 (44.2–47.9)	40.6 (35.4–46.1)	$Z = -2.06$; $P = .039$
BMI ≥ 30.0 kg/m ²	31.9 (30.2–33.7)	38.7 (33.4–44.3)	$Z = 2.75$; $P = .006$
Current smoker, prop. (95% CI)	16.0 (14.6–17.7)	21.6 (17.2–26.9)	$Z = 2.86$; $P = .004$
CAGE alcohol scale, prop. (95% CI)			
CAGE <2	80.7 (79.2–82.1)	73.9 (68.7–78.5)	$Z = -3.22$; $P = .001$
CAGE ≥ 2	10.9 (9.8–12.2)	13.8 (10.5–17.8)	$Z = 1.74$; $P = .082$
Did not complete	8.3 (7.3–9.5)	12.3 (9.0–16.6)	$Z = 2.69$; $P = .007$
Number of d active in last wk, prop. (95% CI)			
0 d active in last wk	70.6 (68.7–72.4)	76.5 (71.5–80.9)	$Z = 2.47$; $P = .013$
1–3 d	16.1 (14.7–17.5)	12.6 (9.5–16.4)	$Z = -1.82$; $P = .069$
≥ 4 d	13.3 (12.0–14.7)	10.9 (7.8–14.9)	$Z = -1.35$; $P = .177$
I-ADL impairment, prop. (95% CI)*	4.4 (3.6–5.5)	7.0 (4.6–10.6)	$Z = 2.34$; $P = .019$
No. of chronic diseases, prop. (95% CI)†			
0 chronic diseases	50.0 (48.0–51.9)	39.3 (33.8–45.0)	$Z = -4.06$; $P < .001$
1 chronic disease	28.4 (26.8–30.1)	25.6 (21.0–30.9)	$Z = -1.18$; $P = .238$
2–3 chronic diseases	19.3 (17.8–20.9)	28.6 (23.7–34.0)	$Z = 4.39$; $P < .001$
≥ 4 chronic diseases	2.3 (1.8–3.0)	6.5 (4.1–10.2)	$Z = 4.89$; $P < .001$
Cardiovascular disease, prop. (95% CI)‡	40.3 (38.5–42.2)	45.9 (40.6–51.3)	$Z = 2.16$; $P = .030$
Cognitive impairment, prop. (95% CI)§	5.4 (4.5–6.5)	8.6 (5.8–12.6)	$Z = 2.61$; $P = .009$
Antidepressant use, prop. (95% CI)	4.3 (3.6–5.2)	11.7 (8.6–15.8)	$Z = 6.41$; $P < .001$

Note. The *Z* score is the number of standard deviations from the mean a data point is; the *F* ratio is the variance of the group means (Mean Square Between) / mean of the within group variances (Mean Squared Error).

BMI, body mass index; CAGE, Cut Down, Annoyed, Guilty, Eye Opener Alcohol Scale; I-ADL, instrumental activities of daily living; prop., proportional estimation; SD, standard deviation.

Baseline characteristics of study sample by depression diagnosis.

Incident depression is 8-item CES-D score ≥ 9 at either wave 2 or wave 3 (ie, 2- or 4-year follow-up).

Student *t*-test used for continuous variables with adjusted Wald test postestimation. Proportional estimation used for categorical variables with *z* score calculated postestimation.

*Self-reported difficulty in at least 1 instrumental ADL (ie, shopping, housekeeping, accounting, food preparation, and telephone/transportation).

†Self-report of lung disease, osteoporosis, cancer, liver disease, eye disease (age-related macular degeneration, glaucoma or cataracts), arthritis, urinary incontinence, Parkinson disease, and diabetes.

‡Self-report of myocardial infarction, arrhythmia, hypertension, angina, or cardiac failure.

§Mini-Mental State Examination score of ≤ 24 .

Table 2
Baseline Vitamin D by Incident Depression

	Not Depressed n = 3565	Incident Depression n = 400	
25-hydroxyvitamin D: mean (95% CI), nmol/L	56.4 (55.4–57.3)	53.8 (50.7–56.8)	$P = .1023$
Vitamin D category, prop. (95% CI):			
Deficient (< 30 nmol/L); n = 466	12.4 (11.1–14.0)	19.4 (15.1–24.7)	$Z = 3.93; P < .001$
Insufficient (30–50 nmol/L); n = 1150	30.4 (28.7–32.2)	29.7 (25.3–34.7)	$Z = -0.29; P = .772$
Sufficient (> 50 nmol/L); n = 2349	57.1 (55.1–59.1)	50.8 (45.3–56.4)	$Z = -2.41; P = .016$

Vitamin D level and category by depression diagnosis.

Incident depression is 8-item CES-D score ≥ 9 at either wave 2 or wave 3 (ie, 2- or 4-year follow-up).

Student *t*-test used for continuous variables with adjusted Wald test postestimation. Proportional estimation used for categorical variable with *z* score calculated postestimation.

Logistic regression models demonstrated that participants with vitamin D deficiency had a significantly higher likelihood of incident depression during 4-year follow-up [odds ratio, OR 1.75 (95% CI 1.24–2.46); $t = 3.21$; $P = .001$]. This finding remained significant and was only marginally attenuated after controlling for relevant covariates. Vitamin D insufficiency was not associated with incident depression.

Higher educational attainment was significantly associated with a reduced likelihood of depression. Greater number of chronic disease, subthreshold depressive symptoms, and antidepressant use at baseline were significant predictors of incident depression (Table 3).

When those who reported taking antidepressant medications or using vitamin D supplements were excluded from the analysis, the results from logistic regression models did not change significantly (Table 4).

Discussion

This study demonstrates that vitamin D deficiency was associated with a 75% increase in the likelihood of developing depression by 4 years in a large sample of community-dwelling older people. Importantly, this finding remained robust after controlling for a wide range of relevant covariates, including baseline subthreshold depressive symptoms, chronic disease burden, physical activity, and cardiovascular disease. Furthermore, exclusion of participants taking

antidepressant medication and vitamin D supplementation did not significantly alter our findings.

Although there is an established cross-sectional association between vitamin D status and depression, longitudinal studies to date are less consistent.²³ Analysis involving over 2000 older adults from the Longitudinal Aging Study Amsterdam found that women aged ≥ 65 years with vitamin D levels less than 75 nmol/L had a higher burden of depressive symptoms at 6-year follow-up but showed no significant association for older men.²⁴ Prospective work from the Rotterdam Study involving over 3000 older participants with over 32,000 person-years follow-up demonstrated that low vitamin D status was not associated with change in depressive symptoms or incident depression.²⁵ Conversely, a study of almost 1000 older people from the Invecchiare in Chianti (InCHIANTI) population-based cohort identified vitamin D levels less than 50 nmol/L as a risk factor for increasing depressive symptoms and incident depression, with a stronger association in women.³⁵ There are several methodological differences and limitations between longitudinal studies that may explain these discordant findings, including length of follow-up, different vitamin D cut-offs used, different vitamin D methods of measurement, and number and types of and covariates added to longitudinal models.

An interesting potential mechanism underpinning the relationship between vitamin D and depression is a direct effect of vitamin D on the brain. This is supported by murine studies which have shown

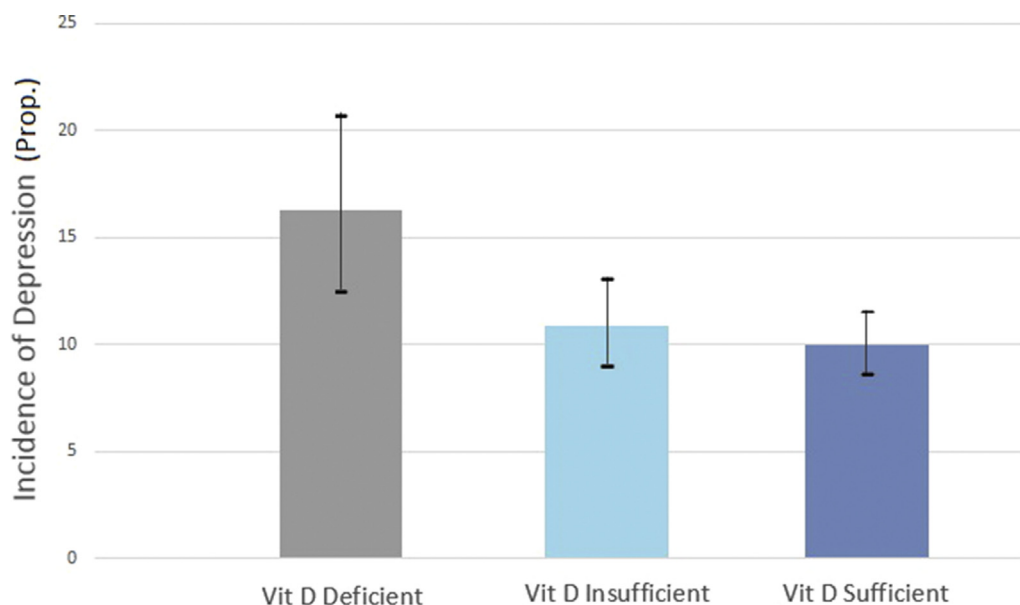


Fig. 1. Incidence of depression by vitamin D status. Prop, proportional estimation; Vit D, vitamin D. n = 3965 (incident depression, n = 400); vitamin D deficient = 25-hydroxyvitamin D < 30 nmol/L, n = 466; vitamin D insufficient = 25-hydroxyvitamin D 30–50 nmol/L, n = 1,150; vitamin D sufficient = 25-hydroxyvitamin D > 50 nmol/L, n = 2,349. Incident depression is 8-item CES-D score ≥ 9 at either wave 2 or wave 3 (ie, 2- or 4-year follow-up).

Table 3
Logistic Regression Models reporting ORs for Incident Depression

	OR (95% CI)	t	P
Model 1			
Vitamin D category (ref: sufficient (>50 nmol/L))			
Insufficient (30–50 nmol/L)	1.10 (0.85–1.42)	0.74	.457
Deficient (<30 nmol/L)	1.75 (1.24–2.46)	3.21	.001
Model 2			
Vitamin D category (ref: sufficient (> 50 nmol/L))			
Insufficient (30–50 nmol/L)	1.03 (0.80–1.34)	0.25	.803
Deficient (<30 nmol/L)	1.55 (1.09–2.22)	2.44	.015
Age (Ref: 50–64 y)			
Age 65–74 y	0.74 (0.55–1.01)	–1.93	.054
Age ≥75 y	0.84 (0.57–1.24)	–0.86	.388
Female sex	1.61 (1.25–2.06)	3.74	<.001
Educational attainment (ref: primary)			
Secondary	0.57 (0.43–0.74)	–4.12	<.001
Tertiary	0.56 (0.41–0.77)	–3.60	<.001
BMI (ref: BMI <24.9 kg/m ²)			
BMI 25.0–29.9 kg/m ²	1.02 (0.75–1.39)	0.16	.876
BMI ≥ 30.0 kg/m ²	1.38 (1.00–1.91)	1.97	.050
Current smoker	1.14 (0.97–1.35)	1.57	.117
CAGE alcohol status (ref: CAGE 0–1)			
CAGE 2–4	1.47 (1.03–2.09)	2.13	.033
Did not complete	1.46 (0.99–2.15)	1.92	.055
Model 3			
Vitamin D category (ref: sufficient (>50 nmol/L))			
Insufficient (30–50 nmol/L)	1.04 (0.80–1.36)	0.30	.761
Deficient (<30 nmol/L)	1.56 (1.07–2.26)	2.32	.020
Age (ref: 50–64 y)			
Age 65–74 y	0.69 (0.50–0.94)	–2.33	.020
Age ≥75 y	0.67 (0.43–1.05)	–1.74	.083
Female sex	1.25 (0.96–1.62)	1.63	.104
Educational attainment (ref: primary):			
Secondary	0.63 (0.47–0.84)	–3.09	.002
Tertiary	0.66 (0.48–0.93)	–2.41	.016
BMI (ref: BMI <24.9 kg/m ²)			
BMI 25.0–29.9 kg/m ²	1.07 (0.77–1.48)	0.39	.696
BMI ≥30.0 kg/m ²	1.48 (1.04–2.09)	2.20	.028
Current smoker	1.04 (0.87–1.24)	0.43	.669
CAGE alcohol status (ref: CAGE 0–1)			
CAGE 2–4	1.31 (0.91–1.90)	1.44	.149
Did not complete	1.45 (0.96–2.19)	1.79	.074
Number of d active in last wk (ref: 0 d)			
1–3 d	0.89 (0.64–1.22)	–0.73	.441
≥4 d	0.99 (0.48–1.60)	–0.07	.943
I-ADL impairment*	0.88 (0.48–1.60)	–0.42	.671
CES-D wave 1 (ref: CES-D = 0–5)			
CES-D 6–10	2.30 (1.72–3.09)	5.58	<.001
CES-D 11–15	5.50 (3.88–7.80)	9.59	<.001
No. of chronic diseases (ref: 0 chronic diseases) [†]			
1 chronic disease	1.07 (0.79–1.46)	0.44	.658
2–3 chronic diseases	1.54 (1.11–2.15)	2.58	.010
≥4 chronic diseases	2.60 (1.36–4.95)	2.91	.004
Cardiovascular disease [‡]	1.03 (0.80–1.33)	0.21	.835
Cognitive impairment [§]	1.24 (0.71–2.17)	0.77	.441
Antidepressant use	2.07 (1.32–3.23)	3.20	.001
Season of vitamin D analysis	1.18 (0.91–1.52)	1.26	.208

BMI, body mass index; I-ADL, instrumental activities of daily living; ref, reference value.

Logistic regression models with incident depression as dependent variable.

N = 3965.

*Self-reported difficulty in at least 1 I-ADL (ie, shopping, housekeeping, accounting, food preparation, and telephone/transportation).

[†]Self-report of lung disease, osteoporosis, cancer, liver disease, eye disease (age-related macular degeneration, glaucoma or cataracts), arthritis, urinary incontinence, Parkinson disease, and diabetes.[‡]Self-report of myocardial infarction, arrhythmia, hypertension, angina, or cardiac failure.[§]Mini-Mental State Examination score of ≤24.

increased behavioral symptoms in vitamin D receptor knock-out mice.³⁶ In humans, vitamin D metabolites are found in cerebrospinal fluid and vitamin D receptors are widespread within the central nervous system.³⁷ Given the structural and functional brain changes seen in late life depression, vitamin D may have a protective effect via these receptors by regulating neuronal excitotoxicity, reducing oxidative stress and contributing to the formation of essential proteins and

neurotransmitters.³⁸ Similarly, vitamin D status has also been linked with neurodegenerative conditions such as dementia,³⁹ Parkinson disease, and multiple sclerosis.⁴⁰

Alternatively, it could be argued that one may expect depression and vitamin D deficiency to co-exist as markers of general poor health in later life⁴¹ or that their relationship may be due to reverse causality, in that older people with early or subthreshold depressive symptoms

Table 4
Logistic Regression Models Excluding Antidepressant and Vitamin D Supplement Users

OR (95% CI) for Vitamin D Status Regressed on Incident Depression			
	Model 1	Model 2	Model 3
Excluding antidepressant Users (n = 3777)			
Vitamin D sufficient (>50 nmol/L)	Reference	Reference	Reference
Vitamin D insufficient (30–50 nmol/L)	1.17 (0.89–1.52)	1.10 (0.84–1.44)	1.06 (0.80–1.40)
Vitamin D deficient (<30 nmol/L)	1.73 (1.20–2.50)	1.55 (1.06–2.27)	1.49 (1.00–2.20)
Excluding vitamin D supplement users (n = 3612)			
Vitamin D sufficient (>50 nmol/L)	Reference	Reference	Reference
Vitamin D insufficient (30–50 nmol/L)	1.10 (0.85–1.42)	1.03 (0.80–1.34)	1.04 (0.80–1.36)
Vitamin D deficient (<30 nmol/L)	1.75 (1.24–2.46)	1.55 (1.09–2.22)	1.56 (1.07–2.26)

Logistic regression models excluding antidepressant and vitamin D supplement users.

Logistic regression models, reporting ORs with 95% CIs for vitamin D status regressed on incident depression. Model 1 is unadjusted; model 2 controls for age, sex, educational attainment, body mass index, smoking status, and alcohol excess; model 3 controls for model 2 covariates, as well as subthreshold depressive symptoms, season of vitamin D analysis, functional impairment, physical activity, chronic disease burden, cardiovascular disease, cognitive impairment, and antidepressant use.

are likely to exhibit some behaviors such as poor nutritional intake or physical activity that are associated with lower vitamin D levels.⁴² However, in this current study, we robustly controlled for chronic and cardiovascular disease, functional status, and subthreshold depressive symptoms in our analysis.

An additional important caveat to note with these findings was that vitamin D levels were measured only at baseline, and the trajectory of vitamin D levels during the follow-up period was not available. We attempted to address this by repeating our analysis after removing those taking supplements, as these individuals are most likely to experience significant changes in vitamin D status over time.⁴³ Furthermore, although we have identified a longitudinal association between vitamin D status and depression, this is not sufficient to imply causation and further studies are required to clarify this. There is, however, some evidence that vitamin D supplementation may be beneficial in the context of therapy for established depression, although this is not in a specifically older population.⁴⁴

There are further limitations of this study that should also be noted. Depression diagnosis is based on the CES-D, which has been validated for use in an older population, but structured clinical interview remains the gold standard for depression diagnosis. In addition, self-report was used to define cases of cardiovascular and chronic disease and may, therefore, be subject to response bias. Important strengths of the study include the longitudinal design, the comprehensive TILDA dataset, the use of the established Health and Medicine Division vitamin D reference ranges, as well as the large, well-described study sample. Furthermore, the use of standardized methods performed at a single laboratory to measure 25(OH) D using the gold standard liquid chromatography-mass spectrometry (LC-MS/MS) helped minimize analytical variability and increased reliability.

This study adds significantly to existing literature by analyzing vitamin D by Health and Medicine Division guidelines, using cut-offs that are in use clinically. Furthermore, we control for a wide range of clinical covariates, particularly chronic and cardiovascular disease, and rerun analyses excluding antidepressant and vitamin D supplement users.

Conclusion/Relevance

In conclusion, we have demonstrated that vitamin D deficiency is independently associated with a significantly increased likelihood of depression at 4-year follow-up in a large cohort of nondepressed older people. These findings are important, given the high prevalence of vitamin D deficiency among older people, the fact that supplementation confers an overall health benefit with low risk of toxicity or side effects, as well as the significant adverse effect depression can have on functional status and longevity in later life. Well-designed randomized controlled trials evaluating vitamin D supplementation as a

preventative strategy for late life depression would, therefore, be welcome.

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