Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women[1–4]

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ABSTRACT

Background: Vitamin D may plausibly reduce the occurrence of depression in postmenopausal women; however, epidemiologic evidence is limited, and few prospective studies have been conducted.

Objective: We conducted a cross-sectional and prospective analysis of vitamin D intake from foods and supplements and risk of depressive symptoms.

Design: Study participants were 81,189 members of the Women's Health Initiative (WHI) Observational Study who were aged 50–79 y at baseline. Vitamin D intake at baseline was measured by food-frequency and supplement-use questionnaires. Depressive symptoms at baseline and after 3 y were assessed by using the Burnam scale and current antidepressant medication use.

Results: After age, physical activity, and other factors were controlled for, women who reported a total intake of ≥800 IU vitamin D/d had a prevalence OR for depressive symptoms of 0.79 (95% CI: 0.71, 0.89; *P*-trend < 0.001) compared with women who reported a total intake of <100 IU vitamin D/d. In analyses limited to women without evidence of depression at baseline, an intake of ≥400 compared with <100 IU vitamin D/d from food sources was associated with 20% lower risk of depressive symptoms at year 3 (OR: 0.80; 95% CI: 0.67, 0.95; *P*-trend = 0.001). The results for supplemental vitamin D were less consistent, as were the results from secondary analyses that included as cases women who were currently using antidepressant medications.

Conclusions: Overall, our findings support a potential inverse association of vitamin D, primarily from food sources, and depressive symptoms in postmenopausal women. Additional prospective studies and randomized trials are essential in establishing whether the improvement of vitamin D status holds promise for the prevention of depression, the treatment of depression, or both. *Am J Clin Nutr* 2011;94:1104–12.

INTRODUCTION

A limited body of research supported a role for vitamin D in the reduction of the occurrence of depression (1). Vitamin D receptors are present in neuronal and glial cells in the central nervous system (2). The majority of brain regions that possess vitamin D receptors also showed substantial immunoreactivity for 1,α-hydroxylase enzymes that are capable of metabolizing 25(OH)D[5] to the biologically active metabolite 1,25-dihydroxyvitamin D (3, 4), which suggested that 1,25-dihydroxyvitamin D likely has autocrine and/or paracrine activity in these regions (3).

In animal studies, rat pups deprived of vitamin D in utero developed brains with thinner neocorticies, greater cell proliferation, heavier weight, and decreased amounts of nerve growth factor and glial cell line–derived neurotrophic factor compared with controls (5). Vitamin D may affect the function of dopamine and norepinephrine, which are monoamine neurotransmitters that are likely involved in depression (2). Furthermore, vitamin D may modulate the relation between depression and inflammation (6–8).

Epidemiologic evidence concerning vitamin D and depression is limited (1). Cross-sectional studies (9–17) have been limited in their ability to evaluate the temporal relation between vitamin D status and depression and exclude the possibility of reverse causation. A small number of prospective studies have suggested that vitamin D may be inversely related to risk of depression and/or depression symptoms (18–20), but all of these studies had small sample sizes (<350 cases) and a limited ability to account for important confounders and effect modifiers including race-ethnicity, adiposity, and physical activity. Dietary vitamin D intake and supplement use are easily modifiable and could provide

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[5] Abbreviations used: 25(OH)D, 25-hydroxyvitamin D; OS, observational study; WHI, Women's Health Initiative.

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new avenues for the prevention and treatment of depression. We evaluated these relations in a large prospective study of postmenopausal women.

SUBJECTS AND METHODS

Study population

The WHI OS (n = 93,676) has been described previously (21). Briefly, between 1993 and 1998, women aged 50–79 y were recruited through direct-mailing campaigns and media-awareness programs. Enrollments were made at 40 clinical centers throughout the United States. Major ineligibility criteria included enrollment in a WHI clinical trial, medical conditions likely to result in death within 3 y, a previous history of breast or other cancers (except nonmelanoma skin cancer), and conditions that were likely to interfere with retention in the study. All OS participants had physical measurements made at a clinical center at baseline and after 3 y and provided information on health-related factors by questionnaire at both time points and annually by mail. The study protocol was approved by institutional review boards at each participating institution.

Assessment of vitamin D and other factors

At their baseline clinic visit, we asked participants to complete a semiquantitative food-frequency questionnaire that was designed and validated for use in the WHI (22). Participants were asked to report their usual intakes of 122 foods or food groups in the 3 previous months with response options that ranged from never or $<$1 time/mo to $\geq$2 times/d ($\geq$6 times/d for beverages) and to specify their usual portion size compared with a stated serving. Additional questions were asked about usual cooking method, fats added during cooking, and usual intakes of specific food groups. The vitamin D intake from food sources was calculated by multiplying the nutrient content of the specified portion size of each food (University of Minnesota Nutrient Coding Center nutrient database) by its frequency of consumption and summing the contributions of all foods.

The vitamin D intake from supplemental sources was assessed by trained interviewers by using a standard questionnaire that measured dose, frequency (pills per week), and duration (months and years) of use of multivitamins, multivitamin-mineral, and single supplements. Participants were asked to bring to their clinic interview bottles for all supplements they were currently taking, which allowed staff members to transcribe ingredients. Only supplements used once per week or more were included. The supplement dose assessed with this procedure has been shown to correlate well with data from photocopied supplement bottle labels (range of r = 0.8–1.0) (23, 24). In a validation study conducted within the WHI, the vitamin D intake measured by a food-frequency questionnaire correlated well with the intake measured with 4 d of diet recalls plus 4 d of food records (deattenuated r for vitamin D from foods = 0.70; deattenuated r for total vitamin D = 0.73) (23).

At the baseline and follow-up clinic visits, women completed questionnaires that assessed demographic, behavioral, and health-related factors including age, race-ethnicity, education, previous use of hormone therapy and oral contraceptives, alcohol intake, history of smoking, and participation in physical activity. We measured weight and height directly and calculated BMI (weight in kilograms divided by height in square meters). We used the RAND-36 Physical Function Scale to assess the current level of physical function that related to muscle weakness and walking speed; lower scores on this scale (range: 0–100) indicated that health impaired physical function (25, 26). The annual amount of solar irradiance was estimated by using methods previously described (27). Briefly, Garland and Garland (28) used measurements from the US Weather Bureau to estimate the annual mean amount of sunlight that reached the ground over large areas of the United States. Estimates of Langleys of total solar irradiance at each of the WHI clinical centers were adapted from this publication and ranged from 300–500 g-calorie/cm^2.

Assessment of depressive symptoms

We assessed the prevalence of depressive symptoms at baseline and follow-up with the Burnam 8-item scale for depressive disorders (29). This scale included 6 items from the Center for Epidemiologic Studies–Depression Scale and 2 items from the Diagnostic Interview Schedule and has been validated for use in the WHI (30). Questions from the Center for Epidemiologic Studies–Depression Scale asked women to report how often in the past week they felt depressed (blue or down), their sleep was restless, they enjoyed life, they had crying spells, they felt sad, and they felt that people disliked them. Response options were rarely or none of the time ($<$1 d), some or a little of the time (1–2 d), occasionally or a moderate amount of time (3–4 d), or most or all of the time (5–7 d). Responses were assigned scores of 0–3, respectively (the question on enjoying life was reverse scored). Questions from the Diagnostic Interview Schedule were as follows: In the past year, have you had $\geq$2 wk during which you felt sad, blue, or depressed or lost pleasure in things that you usually cared about or enjoyed?; Have you had $\geq$2 y in your life when you felt depressed or sad most days, even if you felt okay sometimes?; and if yes, Have you felt depressed or sad much of the time in the past year? Responses to these 3 questions received scores of 0 (no) and 1 (yes).

We calculated the Burnam score by using questionnaire responses and a logistic regression-based algorithm (29). Values for this scale ranges from 0 to 0.99, and higher scores indicated greater depressive symptomology. We dichotomized the continuous Burnam score by using a cutoff of 0.06 to identify women who met criteria for depressive symptoms (31, 32). As previously discussed (33), this screening tool identifies women who experience symptoms that are consistent with depressive disorders, including major depression and dysthymia, but is not, itself, a measure of clinical depression. An ancillary study that evaluated the reliability of the Burnam algorithm compared with a standard of clinical diagnosis for depression screening showed a sensitivity of 74% and specificity of 87% (30). Depressive symptoms assessed with the Burnam scale have been predictive of other outcomes in the WHI including cardiovascular disease and heart-rate variability (31, 33).

We measured the use of antidepressant medications at baseline and year 3. Participants were asked to bring all current medications to their clinic visits, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, modified cyclics, tricyclic agents, and other medications classified as antidepressants. Medications used regularly (ie, for $\geq$2 wk) were recorded along with information on the dose and duration of use.

Statistical analysis

We limited our analyses to women with complete baseline information on diet, depression, and covariates. Participants with an implausible calorie intake (<600 and >5000 kcal/d) were excluded, which resulted in a final study population of 81,189 women. We compared the age-adjusted baseline mean total vitamin D intake, vitamin D intake from supplements, and the prevalence of depressive symptoms across categories of participant characteristics by using *F* tests. We divided the study population into categories of total vitamin D intake (ie, vitamin D from foods and supplements combined), intake of vitamin D from food sources only, and intake from supplemental sources only. Category cutoffs were based on available supplement doses and established Dietary Reference Intakes for vitamin D (34).

We evaluated depression status at baseline in 2 ways. First, we included women who currently experienced depression symptoms (assessed as a Burnam score ≥0.06) as cases and compared them with women who did not currently experience depression symptoms (Burnam score <0.06). In addition, to include women who had been clinically diagnosed with depression but whose symptoms had remitted after antidepressant therapy as cases, we created a secondary case definition that included women who either currently experienced symptoms (Burnam score ≥0.06) or who currently used antidepressant medications and compared them to women with neither indicator of depression. We assessed the relation of both of these outcomes with the vitamin D intake by calculating the OR by using logistic regression and calculated 95% CIs. In multivariable analyses, we adjusted for factors that were significantly associated with vitamin D intake and/or depressive symptoms and factors that have been identified as confounders in previous studies. These factors included age, race-ethnicity, BMI, waist-to-hip ratio, education, smoking status, alcohol intake, past hormone therapy use, total energy intake, marine omega-3 fatty acid intake, marital status, physical activity, physical function score, history of cardiovascular disease, and solar irradiance. In making these adjustments, continuous versions of each variable were used when possible. In addition, we adjusted analyses of vitamin D from food sources for the intake from vitamin D supplements to allow us to independently evaluate the effect of vitamin D from foods. Similarly, we adjusted the vitamin D intake from supplements for the vitamin D intake from food sources.

We evaluated whether the vitamin D intake at baseline was associated with our 2 measures of depression status at year 3 in women with no evidence of depression at baseline. Therefore, in this analysis, we excluded women who had either a Burnam score ≥0.06 at baseline or who reported baseline antidepressant use (n = 13,253).

We assessed whether a relation between the baseline total vitamin D intake and depression status at year 3 was modified by factors including age, race-ethnicity, education, BMI, current smoking status, alcohol use, amount of solar irradiance, physical activity, and physical function. Interactions were assessed by using multiplicative interaction terms in multivariable models, with $P < 0.05$ judged to be significant. Finally, we conducted a sensitivity analysis with adjustment for the season of baseline and year-3 depressive-symptom assessments to evaluate potential confounding by the seasonality of depression. All analyses were performed with SAS for Windows software (version 9.2; SAS Institute).

RESULTS

Selected participant characteristics by mean total and supplemental vitamin D intakes are shown in **Table 1**. All differences were significant at $P < 0.001$ because of the large sample size. The mean total vitamin D intake varied most substantially by ethnicity, smoking status, marine omega-3 intake, physical activity, and amount of solar irradiance. The mean supplemental vitamin D intake varied most substantially by ethnicity, smoking status, BMI, and physical activity.

At baseline, 8952 women (11.0%) had a Burnam score ≥0.06 and, thus, met criteria for prevalent depressive symptoms (Table 1). Differences in prevalence across categories of all characteristics evaluated were significant at $P < 0.001$. The prevalence of depressive symptoms varied most substantially by age, antidepressant use, marital status, income, physical activity, and level of physical functioning.

We observed a significantly inverse linear relation between the total vitamin D intake at baseline and prevalent depressive symptoms as assessed by a Burnam score ≥0.06 (P-trend < 0.001) (**Table 2**). Women who consumed ≥800 IU vitamin D/d had a prevalence OR of 0.79 (95% CI: 0.71, 0.89) compared with women who consumed <100 IU vitamin D/d. Similarly, a high intake of vitamin D from food sources was associated with a significant 20% lower prevalence of depression (prevalence OR: 0.80; 95% CI: 0.71, 0.90; P-trend < 0.001). Although a moderate intake of vitamin D from supplements (400 to <800 IU/d) was associated with lower risk of depression, an intake ≥800 IU vitamin D/d was not.

When we assessed depression by using the combined outcome of a Burnam score ≥0.06 or current antidepressant use, relations with vitamin D intakes were inconsistent (Table 2). Although a higher vitamin D intake from food sources was significantly but modestly associated with lower risk (P-trend = 0.002), the total vitamin D intake and vitamin D intake from supplements were not linearly related to risk.

The vitamin D intake from food sources was inversely related to depressive symptoms at year 3 as assessed by a Burnam score ≥0.06 (P-trend = 0.001) (**Table 3**). Women who consumed ≥400 IU vitamin D/d had an RR of 0.80 (95% CI: 0.67, 0.95) compared with women who consumed <100 IU vitamin D/d. The total vitamin D intake was not linearly related to depressive symptoms (P = 0.61), although risk was significantly lower in women who consumed 100 to <200, 200 to <400, and 400 to <800 IU vitamin D/d compared with women who consumed <100 IU vitamin D/d. The intake of vitamin D from supplements was not associated with depressive symptoms. In analyses that used the combined measure of a Burnam score ≥0.06 or current antidepressant use together to indicate depressive symptoms, we did not observe evidence of a linear relation with vitamin D intake.

We did not find evidence that the relation between the total vitamin D intake and depressive symptoms at year 3 as assessed by a Burnam score ≥0.06 compared with <0.06 was modified by other factors including age, BMI, race-ethnicity, or solar irradiance (**Table 4**). Finally, results from our sensitivity analysis that were adjusted for the season of baseline and year-3 symptom assessments were virtually identical to the main analyses (results not shown).

TABLE 1
Baseline demographic and behavioral characteristics of participants by mean total vitamin D intake, supplemental vitamin D intake, and depression status at baseline in the WHI Observational Study[1]

Characteristic	*n*	Total vitamin D intake	Supplemental vitamin D intake (IU/d)	Burnam score <0.06	Burnam score ≥0.06
		IU/d	*IU/d*	*n (%)*	*n (%)*
Age					
50–59 y	26,153	367 ± 1.8[2]	200 ± 1.6	22,475 (85.9)	3678 (14.1)
60–69 y	35,851	401 ± 1.5	223 ± 1.4	32,260 (90.0)	3591 (10.0)
70–79 y	19,185	412 ± 2.1	229 ± 1.9	17,502 (91.2)	1683 (8.8)
Ethnicity					
White	69,193	408 ± 1.1	227 ± 1.0	62,005 (89.6)	7188 (10.4)
Black	5661	279 ± 3.8	137 ± 3.4	4829 (85.3)	832 (14.7)
Hispanic	2636	303 ± 5.6	154 ± 5.0	2066 (78.4)	570 (21.6)
Other or unknown	3699	345 ± 4.7	187 ± 4.2	3337 (90.2)	362 (9.8)
School after high school					
No	16,577	350 ± 2.2	189 ± 2.0	14,185 (85.6)	2392 (14.4)
Yes	64,612	403 ± 1.1	224 ± 1.0	58,052 (89.8)	6560 (10.2)
Marital status					
Divorced or separated	12,478	385 ± 2.6	214 ± 2.3	10,488 (84.1)	1990 (15.9)
Never married	3808	388 ± 4.7	203 ± 4.2	3381 (88.8)	427 (11.2)
Married or living as married	51,197	397 ± 1.3	220 ± 1.1	46,497 (90.8)	4700 (9.2)
Widowed	13,706	385 ± 2.6	211 ± 2.3	11,871 (86.6)	1835 (13.4)
Smoking status					
Never	41,028	395 ± 1.4	215 ± 1.3	36,817 (89.7)	4211 (10.3)
Former	35,203	397 ± 1.5	224 ± 1.4	31,381 (89.1)	3822 (10.9)
Current	4958	337 ± 4.1	176 ± 3.6	4039 (81.5)	919 (18.5)
BMI					
<25 kg/m^2	33,537	408 ± 1.6	237 ± 1.4	30,477 (90.9)	3060 (9.1)
25 to <30 kg/m^2	27,636	389 ± 1.7	213 ± 1.5	24,719 (89.4)	2917 (10.6)
≥30 kg/m^2	20,016	371 ± 2.0	187 ± 1.8	17,041 (85.1)	2975 (14.9)
Alcohol intake					
0 drinks/d	23,491	372 ± 1.9	200 ± 1.7	20,308 (86.5)	3183 (13.5)
>0 to <1 drink/d	47,115	402 ± 1.3	222 ± 1.2	42,242 (89.7)	4873 (10.3)
≥1 drink/d	10,583	397 ± 2.8	228 ± 2.5	9687 (91.5)	896 (8.5)
Antidepressant use					
No	75,115	390 ± 1.0	215 ± 0.9	67,936 (90.4)	7179 (9.6)
Yes	6074	416 ± 3.7	232 ± 3.3	4301 (70.8)	1773 (29.2)
Marine omega-3 intake					
<0.048 g	20,121	341 ± 2.0	206 ± 1.8	17,716 (88.0)	2405 (12.0)
0.048–0.092 g	20,434	370 ± 2.0	213 ± 1.8	18,119 (88.7)	2315 (11.3)
0.093–0.163 g	20,263	400 ± 2.0	220 ± 1.8	18,092 (89.3)	2171 (10.7)
≥0.164 g	20,371	459 ± 2.0	227 ± 1.8	18,310 (89.9)	2061 (10.1)
Physical activity					
<3.00 MET-h/wk	19,282	351 ± 2.06	184 ± 1.8	16,306 (84.6)	2976 (15.4)
3.00–9.99 MET-h/wk	20,538	383 ± 1.99	208 ± 1.8	18,109 (88.2)	2429 (11.8)
10.00–19.99 MET-h/wk	20,875	409 ± 1.98	230 ± 1.8	18,932 (90.7)	1943 (9.3)
≥20.00 MET-h/wk	20,494	424 ± 2.00	243 ± 1.8	18,890 (92.2)	1604 (7.8)
Physical function construct (RAND score)					
≤50	8399	371 ± 3.2	193 ± 2.8	6477 (77.1)	1922 (22.9)
51–90	41,477	394 ± 1.4	217 ± 1.3	36,766 (88.6)	4711 (11.4)
>90	31,313	396 ± 1.7	222 ± 1.5	28,994 (92.6)	2319 (7.4)
History of CVD[3]					
No	75,366	394 ± 1.1	218 ± 0.9	67,360 (89.4)	8006 (10.6)
Yes	5823	366 ± 3.8	193 ± 3.4	4877 (83.8)	946 (16.2)
Solar irradiance					
300–325 Langleys	23,131	406 ± 1.9	217 ± 1.7	20,821 (89.0)	2310 (10.0)
350 Langleys	17,446	406 ± 2.2	224 ± 1.9	15,459 (88.6)	1987 (11.4)
375–380 Langleys	9295	359 ± 3.0	191 ± 2.7	8254 (88.8)	1041 (11.2)
400–430 Langleys	13,825	392 ± 2.4	227 ± 2.2	12,191 (88.2)	1634 (11.8)
475–500 Langleys	17,492	378 ± 2.2	215 ± 1.9	15,512 (88.7)	1980 (11.3)

[1] *P* values for all comparisons were significant at <0.001; distributions of variables were compared with *F* tests. CVD, cardiovascular disease; MET-h, metabolic equivalent task hours; RAND, RAND-36 Physical Function Scale; WHI, Women's Health Initiative.

[2] Age-adjusted least-squares mean ± SE (all such values).

[3] CVD was defined as myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, or angina.

TABLE 2
Depressive symptoms according to baseline total vitamin D intake, intake of vitamin D from foods, and intake of vitamin D from supplements in the WHI Observational Study[1]

	Burnam ≥0.06 compared with <0.06			Burnam ≥0.06 or current antidepressant use compared with neither outcome	
Vitamin D intake	*n* (yes/no)	Unadjusted POR (95% CI)	Multivariable-adjusted POR (95% CI)[2]	*n* (yes/no)	Multivariable-adjusted POR (95% CI)[2]
Total vitamin D intake					
<100 IU/d	1529/10,482	1.00	1.00	2066/9945	1.00
100 to <200 IU/d	1920/14,371	0.92 (0.85, 0.98)	0.91 (0.84, 0.98)	2751/13,540	0.95 (0.89, 1.02)
200 to <400 IU/d	1596/12,675	0.86 (0.80, 0.93)	0.87 (0.80, 0.95)	2295/11,976	0.90 (0.84, 0.97)
400 to <800 IU/d	3308/29,347	0.77 (0.72, 0.82)	0.83 (0.77, 0.89)	5152/27,503	0.93 (0.87, 0.99)
≥800 IU/d	599/5362	0.77 (0.69, 0.85)	0.79 (0.71, 0.89)	989/4972	0.96 (0.88, 1.05)
P-trend[3]	—	<0.001	<0.001	—	0.36
Vitamin D from food sources					
<100 IU/d	2791/20,946	1.00	1.00	3921/19,816	1.00
100 to <200 IU/d	3534/28,889	0.92 (0.87, 0.97)	0.90 (0.85, 0.95)	5273/27,150	0.95 (0.90, 1.00)
200 to <400	2132/18,555	0.86 (0.81, 0.92)	0.80 (0.75, 0.86)	3306/17,381	0.89 (0.84, 0.95)
≥400 IU/d	495/3847	0.97 (0.87, 1.07)	0.80 (0.71, 0.90)	753/3589	0.89 (0.81, 0.99)
P-trend	—	0.006	<0.001	—	0.002
Vitamin D from supplements					
None	4722/34,022	1.00	1.00	6607/32,137	1.00
<400 IU/d	838/7799	0.77 (0.72, 0.84)	0.86 (0.80, 0.93)	1263/7374	0.90 (0.84, 0.96)
400 to <800 IU/d	3122/28,215	0.80 (0.76, 0.84)	0.89 (0.84, 0.93)	4963/26,374	0.99 (0.95, 1.03)
≥800 IU/d	270/2201	0.88 (0.78, 1.01)	0.99 (0.86, 1.13)	420/2051	1.07 (0.96, 1.20)
P-trend	—	<0.001	<0.001	—	0.71

[1] POR, prevalence OR; WHI, Women's Health Initiative.
[2] Adjusted for age (continuous), race-ethnicity (black, Hispanic, white not of Hispanic origin, and other or unknown), BMI (continuous), waist-to-hip ratio (continuous), education (school after high school, yes or no), smoking status (never, former, or current), alcohol intake (0, >0 to <1, or ≥1 drink/d), past hormone therapy use (never, past, or current use), total energy intake (continuous), marine omega-3 fatty acid intake (quartiles), marital status (divorced or separated, never married, currently married or living as married, or widowed), physical activity (continuous metabolic equivalent task hours per week), physical function score (continuous), history of cardiovascular disease (yes or no), and solar irradiance (300–325, 350, 375–380, 400–430, or 475–500 Langleys). Vitamin D from food sources was additionally adjusted for vitamin D intake from supplements. Vitamin D intake from supplements was additionally adjusted for vitamin D intake from food sources.
[3] Calculated by using the median of each vitamin D category as a continuous variable in the multivariable regression model.

DISCUSSION

In our diverse population of postmenopausal women, we observed some evidence of an inverse relation between intake of vitamin D and depressive symptoms. In cross-sectional analyses that used baseline data, women with the highest intakes of total vitamin D and vitamin D from food sources had a significantly lower prevalence of depressive symptoms as assessed with the Burnam scale compared with women who reported intakes of <100 IU vitamin D/d. In women without evidence of depression at baseline, a higher vitamin D intake from food sources was associated with a lower risk of depressive symptoms at year 3. Results from secondary analyses that included women who used antidepressant medications as well as women who met Burnam score criteria were inconsistent. We did not find supplemental vitamin D intakes to be consistently related to measures of depressive symptoms.

There were several potential explanations for the difference in findings we observed for vitamin D from food sources compared with from supplements. First, vitamin D from dietary sources may be more strongly related to 25(OH)D concentrations than vitamin D from supplements. In the WHI calcium and vitamin D supplementation trial, the correlation of 25(OH)D concentrations and the total vitamin D intake was modestly but significantly higher in women who did not use supplements (ie, vitamin D was from food sources only) compared with women who used both diet and supplemental sources ($r = 0.21$ compared with $r = 0.19$; *P*-difference = 0.03) (35).

Second, if women who experienced depressive symptoms used fish oil, multivitamins, or other supplements that contained vitamin D as a means of treating their symptoms (36), results for supplement use may have been attenuated. Reverse causation may have biased results from our cross-sectional analysis because we were unable to evaluate the timing of the onset of vitamin D supplement use compared with the onset of depression. However, reverse causation was less likely to have affected results from our prospective analysis, which we limited to women who did not experience depression at baseline when vitamin D intake was assessed.

Third, results that suggested a beneficial effect of vitamin D from food sources could plausibly have reflected confounding by other nutrients shown in vitamin D–rich foods or by an overall healthy dietary pattern. For example, in our population, fatty fish were predominant sources of both vitamin D and omega-3 fatty acids, and marine fatty acids have been inversely associated with depression in many studies (37). For this reason, we adjusted all analyses for the intake of marine omega-3 fatty acids. Although relatively few other nutrients have been consistently associated with depression, we cannot exclude the possibility that other nutrients in fish, dairy foods, and fortified cereals may have contribute to the observed effects.

The range of vitamin D intake in our study population was comparable to ranges in other studies of postmenopausal women

TABLE 3
Incident depressive symptoms after 3 y of follow-up by total vitamin D intake, intake of vitamin D from foods, and intake of vitamin D from supplements: WHI Observational Study[1]

	Burnam score ≥0.06 compared with <0.06			Burnam score ≥0.06 or current antidepressant use compared with neither outcome	
Vitamin D intake	Depression (yes/no)	Unadjusted OR (95% CI)	Multivariable-adjusted OR (95% CI)[2]	Depression (yes/no)	Multivariable-adjusted OR (95% CI)[2]
	n			*n*	
Total vitamin D intake					
<100 IU/d	560/7884	1.00	1.00	834/7197	1.00
100 to <200 IU/d	696/11,109	0.88 (0.79, 0.99)	0.85 (0.76, 0.96)	1087/10,159	0.90 (0.81, 0.99)
200 to <400 IU/d	580/9969	0.81 (0.73, 0.92)	0.79 (0.70, 0.90)	915/9193	0.84 (0.76, 0.94)
400 to <800 IU/d	1427/23,204	0.87 (0.78, 0.96)	0.88 (0.79, 0.97)	2352/21,257	0.95 (0.87, 1.04)
≥800 IU/d	261/4200	0.88 (0.75, 1.02)	0.87 (0.74, 1.02)	444/3850	0.99 (0.87, 1.12)
P-trend[3]	—	0.15	0.61	—	0.14
Vitamin D from food sources					
<100 IU/d	1087/16,080	1.00	1.00	1685/14,691	1.00
100 to <200 IU/d	1383/22,696	0.90 (0.83, 0.98)	0.86 (0.79, 0.94)	2224/20,800	0.90 (0.84, 0.97)
200 to <400	860/14,595	0.87 (0.80, 0.96)	0.79 (0.71, 0.88)	1400/13,409	0.86 (0.79, 0.94)
≥400 IU/d	194/2995	0.96 (0.82, 1.12)	0.80 (0.67, 0.95)	323/2756	0.93 (0.80, 1.07)
P-trend	—	0.11	0.001	—	0.08
Vitamin D from supplements					
None	1684/26,114	1.00	1.00	2609/23,920	1.00
<400 IU/d	361/6278	0.89 (0.79, 1.00)	0.95 (0.84, 1.06)	566/5785	0.93 (0.84, 1.02)
400 to <800 IU/d	1372/22,250	0.96 (0.89, 1.03)	1.02 (0.95, 1.10)	2275/20,381	1.06 (1.00, 1.12)
≥800 IU/d	107/1724	0.96 (0.79, 1.18)	1.02 (0.83, 1.25)	182/1570	1.09 (0.93, 1.28)
P-trend	—	0.30	0.57	—	0.04

[1] WHI, Women's Health Initiative.
[2] Adjusted for age, race-ethnicity, BMI, waist-to-hip ratio, education, smoking, alcohol, hormone use, total energy intake, marine omega-3 fatty acid intake, marital status, physical activity, physical function, history of cardiovascular disease, solar irradiance, and antidepressant medication use. *See* footnote 2 of Table 2 for variable categorization. Vitamin D from food sources was additionally adjusted for vitamin D intake from supplements. Vitamin D intake from supplements was additionally adjusted for vitamin D intake from food sources.
[3] Calculated by using the median of each vitamin D category as a continuous variable in the multivariable regression model.

(38–40). However, we assessed vitamin D from food and supplemental sources alone and at baseline only and were not able to directly evaluate 25(OH)D levels, which are substantially influenced by endogenous vitamin D production after UVB sun exposure as well as by diet. Although previous studies suggested that a dietary intake of vitamin D may not be strongly correlated with 25(OH)D levels (41), recent evidence suggested that only ~30% of circulating 25(OH)D is the product of sunlight exposure (42). Although we were unable to control for individual amounts of sunlight exposure, we adjusted our analyses for the mean amount of solar irradiance at each participant's WHI clinical center and other nondietary predictors of 25(OH)D levels including physical activity, race-ethnicity, and BMI (43). In addition, results in women with lower amounts of solar irradiance did not differ from those in women who lived in sunnier locations.

A limitation of our study was our reliance on self-reported questionnaires and antidepressant use to assess depressive symptoms instead of the use of psychiatric interviews or a report of clinical diagnoses. The Burnam scale primarily measures depressive symptoms experienced in the previous week and thus would identify women currently experiencing depressive symptoms at the time of the questionnaire completion. However, in prospective analyses, women who developed depression before year 3 but whose symptoms remitted either naturally or after treatment would not be classified as cases. For these reasons, in secondary analyses we also considered antidepressant use as a proxy for depression. However, women may be prescribed antidepressant medications for reasons other than depression, such as fibromyalgia, migraine headache, or panic disorder; these women would be inaccurately identified as depression cases in our analysis. The misclassification of depression status could have attenuated our findings to some extent.

Furthermore, depressed women who use antidepressant medications may differ from depressed women who do not use antidepressant medications in terms of diet, healthy behaviors, and supplement use. In a secondary analysis, we showed high total and supplemental vitamin D intakes to be modestly associated with a higher likelihood of antidepressant use in all women, whereas vitamin D from food sources was unrelated (data not shown). Multivitamin use was somewhat more common in depressed women who used antidepressant medications (40.6%) compared with depressed women who did not use antidepressant medications (37.8%; $P = 0.03$). Alternatively, because serotonin reuptake inhibitors use has been shown to lower C-reactive protein and cytokine concentrations in depressed patients (44, 45), a potentially anti-inflammatory effect of vitamin D on depression may be attenuated by antidepressant use. Furthermore, participants may have experienced depression before baseline. Because women with severe depression may have been unlikely to participate in the WHI OS, our population may have experienced milder symptoms than did patients in studies of clinic populations.

Our study had several notable strengths, including its prospective design. The diversity of our population allowed us to

TABLE 4
Depressive symptoms at year 3 (Burnam score ≥0.06 compared with <0.06) by baseline total vitamin D intake across categories of participant characteristics in the WHI Observational Study[1]

	Total vitamin D intake						
Subgroup	<100 IU/d	100 to <200 IU/d	200 to <400 IU/d	400 to <800 IU/d	≥800 IU/d	*P*-trend[2]	*P*-interaction[3]
Age							0.30
50–59 y	1.00	0.82 (0.68, 0.99)	0.81 (0.66, 0.98)	0.94 (0.80, 1.11)	0.86 (0.66, 1.13)	0.61	
60–69 y	1.00	0.81 (0.68, 0.97)	0.79 (0.65, 0.96)	0.77 (0.65, 0.90)	0.80 (0.63, 1.02)	0.09	
70–79 y	1.00	0.98 (0.75, 1.28)	0.75 (0.56, 0.99)	0.96 (0.76, 1.22)	0.98 (0.70, 1.36)	0.65	
Post-HS education							0.51
No	1.00	0.98 (0.78, 1.23)	0.89 (0.70, 1.14)	0.94 (0.76, 1.15)	0.82 (0.57, 1.17)	0.39	
Yes	1.00	0.81 (0.70, 0.93)	0.76 (0.66, 0.88)	0.85 (0.75, 0.96)	0.87 (0.72, 1.03)	0.87	
BMI							0.74
<25 kg/m^2	1.00	0.90 (0.74, 1.10)	0.74 (0.60, 0.91)	0.89 (0.75, 1.06)	0.84 (0.65, 1.08)	0.60	
25 to <30 kg/m^2	1.00	0.86 (0.71, 1.04)	0.80 (0.65, 0.98)	0.83 (0.70, 0.99)	0.88 (0.67, 1.14)	0.42	
≥30 kg/m^2	1.00	0.79 (0.63, 0.98)	0.85 (0.68, 1.07)	0.90 (0.74, 1.10)	0.90 (0.67, 1.22)	0.60	
Ethnicity							0.49
White	1.00	0.83 (0.73, 0.95)	0.79 (0.69, 0.91)	0.87 (0.77, 0.98)	0.85 (0.71, 1.01)	0.69	
Black	1.00	0.90 (0.63, 1.29)	1.03 (0.69, 1.55)	0.83 (0.59, 1.19)	1.16 (0.58, 2.33)	0.74	
Hispanic	1.00	0.71 (0.43, 1.17)	0.46 (0.25, 0.85)	0.91 (0.58, 1.41)	0.96 (0.44, 2.10)	0.61	
Other or unknown	1.00	1.26 (0.75, 2.11)	0.84 (0.46, 1.52)	0.84 (0.51, 1.39)	0.93 (0.39, 2.18)	0.30	
Current smoking							0.97
No	1.00	0.85 (0.75, 0.97)	0.79 (0.69, 0.91)	0.87 (0.78, 0.98)	0.86 (0.73, 1.01)	0.56	
Yes	1.00	0.81 (0.56, 1.17)	0.73 (0.48, 1.11)	0.84 (0.60, 1.19)	0.99 (0.54, 1.82)	0.98	
Alcohol intake							0.97
0 drinks/d	1.00	0.82 (0.67, 1.00)	0.79 (0.64, 0.98)	0.83 (0.69, 0.99)	0.78 (0.59, 1.03)	0.22	
>0 to <1 drink/d	1.00	0.84 (0.72, 0.99)	0.77 (0.65, 0.91)	0.88 (0.76, 1.01)	0.88 (0.72, 1.09)	0.98	
≥1 drinks/d	1.00	1.01 (0.71, 1.43)	0.92 (0.63, 1.32)	0.99 (0.72, 1.36)	1.05 (0.67, 1.64)	0.77	
Physical activity							0.43
<3.00 MET-h/wk	1.00	0.84 (0.68, 1.03)	0.71 (0.57, 0.90)	0.86 (0.72, 1.04)	0.82 (0.60, 1.13)	0.59	
3.00–9.99 MET-h/wk	1.00	0.92 (0.73, 1.16)	0.92 (0.72, 1.17)	0.96 (0.77, 1.18)	1.26 (0.94, 1.70)	0.12	
10.00–19.99 MET-h/wk	1.00	0.82 (0.63, 1.05)	0.84 (0.65, 1.08)	0.89 (0.72, 1.11)	0.76 (0.55, 1.05)	0.60	
≥20.0 MET-h/wk	1.00	0.84 (0.66, 1.09)	0.72 (0.55, 0.94)	0.80 (0.64, 1.00)	0.72 (0.53, 0.99)	0.14	
Physical function (RAND score)							0.83
≤50	1.00	0.89 (0.64, 1.23)	0.83 (0.58, 1.18)	0.97 (0.73, 1.31)	0.91 (0.58, 1.42)	0.71	
51–90	1.00	0.84 (0.72, 0.99)	0.73 (0.62, 0.86)	0.83 (0.72, 0.96)	0.82 (0.66, 1.01)	0.29	
>90	1.00	0.84 (0.68, 1.04)	0.89 (0.72, 1.11)	0.91 (0.76, 1.09)	0.94 (0.72, 1.23)	0.84	
CVD at baseline							0.62
No	1.00	0.83 (0.74, 0.94)	0.77 (0.67, 0.88)	0.86 (0.77, 0.96)	0.87 (0.73, 1.02)	0.67	
Yes	1.00	1.02 (0.68, 1.52)	1.01 (0.67, 1.54)	1.06 (0.74, 1.52)	0.80 (0.43, 1.47)	0.87	
Solar irradiance							0.33
<350 Langleys	1.00	0.89 (0.70, 1.12)	0.81 (0.64, 1.02)	0.84 (0.69, 1.04)	0.90 (0.67, 1.21)	0.60	
350 to <400 Langleys	1.00	0.87 (0.70, 1.07)	0.89 (0.71, 1.10)	1.01 (0.84, 1.23)	1.08 (0.82, 1.41)	0.06	
≥400 Langleys	1.00	0.83 (0.69, 0.99)	0.72 (0.60, 0.88)	0.81 (0.69, 0.95)	0.71 (0.55, 0.92)	0.04	

[1] All values are multivariable adjusted ORs; 95% CIs in parentheses. Values were adjusted for age, ethnicity, BMI, education, smoking, alcohol, hormone use, antidepressant use, total energy intake, marital status, physical activity, physical function, history of CVD, and solar irradiance. CVD, cardiovascular disease; HS, high school; MET-h, metabolic equivalent task hours; RAND, RAND-36 Physical Function Scale; WHI, Women's Health Initiative.
[2] Calculated by using the median of each vitamin D category as a continuous variable in the multivariable regression model.
[3] Calculated by using multiplicative interaction terms in the multivariable regression model.

assess whether the association of vitamin D and depression may have varied by race-ethnicity and other factors. Our results suggested that vitamin D intakes were not inversely related to the prevalence of depression in black women, who are more likely to experience vitamin D deficiency than are white women (46), but our power for this analysis was relatively low. Additional studies are needed to further evaluate potential differences in this relation between populations.

In conclusion, our results support an inverse association of vitamin D intake from foods and the occurrence of depressive symptoms in older women. Additional prospective studies using plasma 25(OH)D or other vitamin D measurements and studies that further evaluate the effects of vitamin D supplementation are essential for establishing whether improving vitamin D status holds promise for the prevention of depression, the treatment of depression, or both.

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The authors' responsibilities were as follows—ERB-J, LS, and JEM: designed the research; RLB, MNB, SL, JKO, IO, and JEM: conducted the research; ERB-J and JCL: analyzed data and performed statistical analyses; ERBJ: wrote the manuscript; ERBJ and JEM: had primary responsibility for the final content of the manuscript; and SIP, LS, RLB, YLM, JCL, AEM, MNB, ESB, SL, SW-S, JKO, IO, and JEM: critically revised manuscript for important intellectual content. JEM and colleagues at Brigham and Women's Hospital, Harvard Medical School, were recipients of funding from the NIH to conduct the Vitamin D and Omega-3 Trial (VITAL), which is a large-scale randomized trial of vitamin D and omega-3s in the prevention of cancer and cardiovascular disease. No additional conflicts of interest were reported.

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