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# Serum 25-Hydroxyvitamin D Levels and Depression in Older Adults: A Dose–Response Meta-Analysis of Prospective Cohort Studies

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**ABSTRACT**

***Objective:*** *The association between serum vitamin D and risk of depression in older adults is controversial. We performed a dose–response meta-analysis of prospective cohort studies to examine the association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and the risk of depression in older population.* ***Methods:*** *Studies published before February 2018 in the PubMed, Cochrane Library, Web of Science, PsycINFO, and EMBASE databases were systematically searched. Prospective cohort studies that examined the association between serum 25(OH)D levels and the risk of depression in older adults were included. A random-effects model was used to calculate the pooled hazard ratio and the corresponding 95% confidence intervals. A nonlinear dose–response association was examined using restricted cubic spline functions.* ***Results:*** *Six prospective studies covering 16,287 older adults with 1,157 cases of depression were included and analyzed. The pooled hazard ratio of depression for per 10-ng/mL increment in serum 25(OH)D was 0.88 (95% confidence intervals: 0.78–0.99, $I^2$ = 79.0%, p <0.001 for heterogeneity). A linear dose–response association between serum 25(OH)D concentrations and incident depression was observed (p = 0.96 for nonlinearity).* ***Conclusion:*** *Serum 25(OH)D concentration*

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*is negatively associated with the risk of depression in older adults. This meta-analysis suggests that increasing 25(OH)D levels may be a useful approach to reduce the risk of depression in older adults and highlights the need for further large-scale clinical studies.* (Am J Geriatr Psychiatry 2019; ■■:■■−■■)

## INTRODUCTION

Depression is a common psychiatric disorder that affects more than 200 million people globally.[1] The aging population has been increasing steadily worldwide, with the proportion of those aged 60 years and older projected to increase from 10.0% in 2000 to 21.8% in 2050 and to 32.2% in 2100.[2] Due to a host of biological and psychosocial factors, depression is highly prevalent in older adults and is associated with lower quality of life.[3]

Vitamin D deficiency is common in older people, mainly due to poor nutrition and the lack of outdoor activity and sun exposure, which reduces vitamin D synthesis.[4] Apart from the role of vitamin D in maintaining calcium homeostasis and bone health, vitamin D receptors in the brain have been implicated in the pathophysiology of depression.[5]

The past few years have seen the topic of vitamin D in depression prevention rush into the forefront of academia. Several cross-sectional and cohort studies have found a strong association between serum 25 (OH)D concentrations and the risk of depression,[6−8] which, however, has not been confirmed in other studies.[9,10] A few randomized clinical trials (RCTs) also showed mixed findings.[11,12] Moreover, the completed RCTs generally suffered from some limitations[13] and few focused on depression of older adults. Although meta-analyses[14,15] have examined the dose−response association between serum 25 (OH)D concentration and depression, the results in older adults were not reported. This was the rationale to conduct a dose−response meta-analysis of prospective studies to examine the association between serum 25(OH)D concentrations and the risk of depression in older adults.

## METHODS

This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42018108965) and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for observational studies.[16]

### Search Strategy

Articles that reported the association between serum 25(OH)D concentration and risk of depression were independently searched by two investigators (HL and DS) in PubMed, the Cochrane Library, Web of Science, PsycINFO, and EMBASE from their inception date to February 2018. The following search terms were used: "vitamin D," "1,25-dihydroxyvitamin d," "25-hydroxyvitamin d," "25(oh)d," "25(oh)-vitamin d," "calcidiol," or "calcitriol"; "mental disease," "emotional disorder," "mood disorder," "mental health," "depression," "major affective disorder," "minor affective disorder," "depressive," or "depressed," and "nest case control," "prospective study," or "cohort study," There was no language restriction in the literature search the details of which are shown in Supplemental Table 1.

### Selection Criteria

Titles and abstracts of relevant records were screened independently by two investigators (HL and DS) and then the full texts were read for eligibility. Studies were included in the meta-analysis if they fulfilled the following criteria: 1) prospective cohort study design targeting only older adults (aged ≥50 years); 2) examining the association between serum 25(OH)D concentrations and incident depression. Following previous meta-analyses,[14,17] the diagnosis of depression was established according to study-defined criteria, such as standardized psychiatric interview, clinical diagnosis, or using an established cutoff point on a validated rating scale; 3) reporting a hazard ratio (HR) and corresponding 95% confidence interval (CI) of depression across different serum 25(OH)D concentration categories or providing information that could generate HR and 95% CI; 4) having at least three serum-25(OH)D levels to show a dose−response relationship; and 5)

providing the number of depression cases and participants or person-years or nondepression cases across categories of serum 25(OH)D. In case that more than one article was based on the same dataset, only the one with the largest sample size or the longest follow-up was included. The exclusion criteria were as follows: 1) studies that did not measure serum 25(OH)D concentrations at baseline and/or did not evaluate depression at study endpoint; 2) studies that did not provide the mean or median or range of each of at least three 25 (OH)D levels; and 3) studies that referred to depression as a continuous variable, but not a dichotomous outcome. Any discrepancies between the two investigators in the literature search and selection were resolved by consulting with a third investigator (AW).

### Data Extraction

Data were independently extracted, including the first author, publication year, country, duration of follow-up, mean age of participants, proportion of women, depression scales, sample size, number of cases with depression, serum 25(OH)D levels, covariates adjusted for in the multivariable analyses of the included studies, and HR and the 95% CI for depression across different 25(OH)D levels. When more than one multivariate model was reported, the adjusted HRs were extracted from the model adjusted for the largest number of confounding variables in the original studies.

### Quality Assessment

The study quality was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS consists of eight items that address subject selection and comparability and the assessment of the outcome. The NOS scores range from 0 to 9 points; scores of ≥7 were considered to indicate high quality.[18]

### Statistical Analysis

The HR and 95% CI were considered as the effect size. In five included studies, Cox proportional hazard regression was used to examine the association between serum 25(OH)D concentration categories and the risk for depression and the adjusted HR and 95% CI was reported. In one study,[10] logistic regression analysis was used, therefore the odds ratio was transformed into relative risk according to the formula recommended by Zhang and Yu,[19] and then the estimated relative risk was considered as equal to HR following previous meta-analyses.[14,20–23] Additionally, following another study,[20] the number of subjects was multiplied by the average follow-up time to estimate the person-years across serum 25(OH)D concentration categories in the Chan et al's study.[10] The method recommended by Hamling et al.[24] was used to convert risk estimates in the case that the reference concentration (i.e., the reference category) used in analyses was not the lowest concentration of 25(OH)D. Since different units of measurement were used across studies to express serum 25(OH)D levels (nmol/L or ng/mL), the concentrations were converted into a homogeneous measure using the following equivalency: 10 ng/mL = 25 nmol/L. Moreover, the midpoint of each concentration was used for studies that did not present the median or mean doses of serum 25(OH)D levels. If the highest or lowest category was open-ended, that is, there was no highest or lowest boundary, its midpoint concentration was calculated with the lower limit multiplied by 1.5 (for the highest category) or the higher limit divided by 1.5 (for the lowest category). When the number of cases with depression in each serum 25(OH)D category were not available, the number of cases with depression was estimated based on the total number and HR of each serum 25 (OH)D concentration.[25,26]

To examine the association between the specific levels of serum 25(OH)D and the risk of depression, the two-stage generalized least-squares trend estimation method[27] recommended by Greenland and Longnecker was performed. A random-effects model was conducted to examine the linear trend.[28] The dose−response outcomes were presented as per 10 ng/mL (25 nmol/L) increment in serum 25(OH)D in the forest plots. In addition, a potential nonlinear dose−response relationship between serum 25(OH)D and the risk of depression was assessed using restricted cubic spline functions with three knots at fixed percentiles of 10%, 50%, and 90% of the distribution.[29]

Heterogeneity was assessed using Cochran's Q test and $I^2$ statistic, where $I^2$ greater than 50% indicated substantial heterogeneity.[30] Subgroup and meta-regression analyses were conducted using the following variables

in line with a recent meta-analysis:[23] numbers of incident depression cases (≤200; >200), sample size (≤2,000; >2,000); duration of follow-up (≤5 years; > 5years); region (Europe; American; and others), numbers of adjusted covariates (≤8; >8), study quality (<7 points; ≥7 points), and diagnosis of depression by a clinical interview (no; yes). Sensitivity analyses were performed by excluding the Chan et al. study[10] and then comparing the findings with the primary results. Publication bias was assessed by funnel plot. Begg's and Egger's tests were not performed because the number of original studies included in the analysis was less than 10.

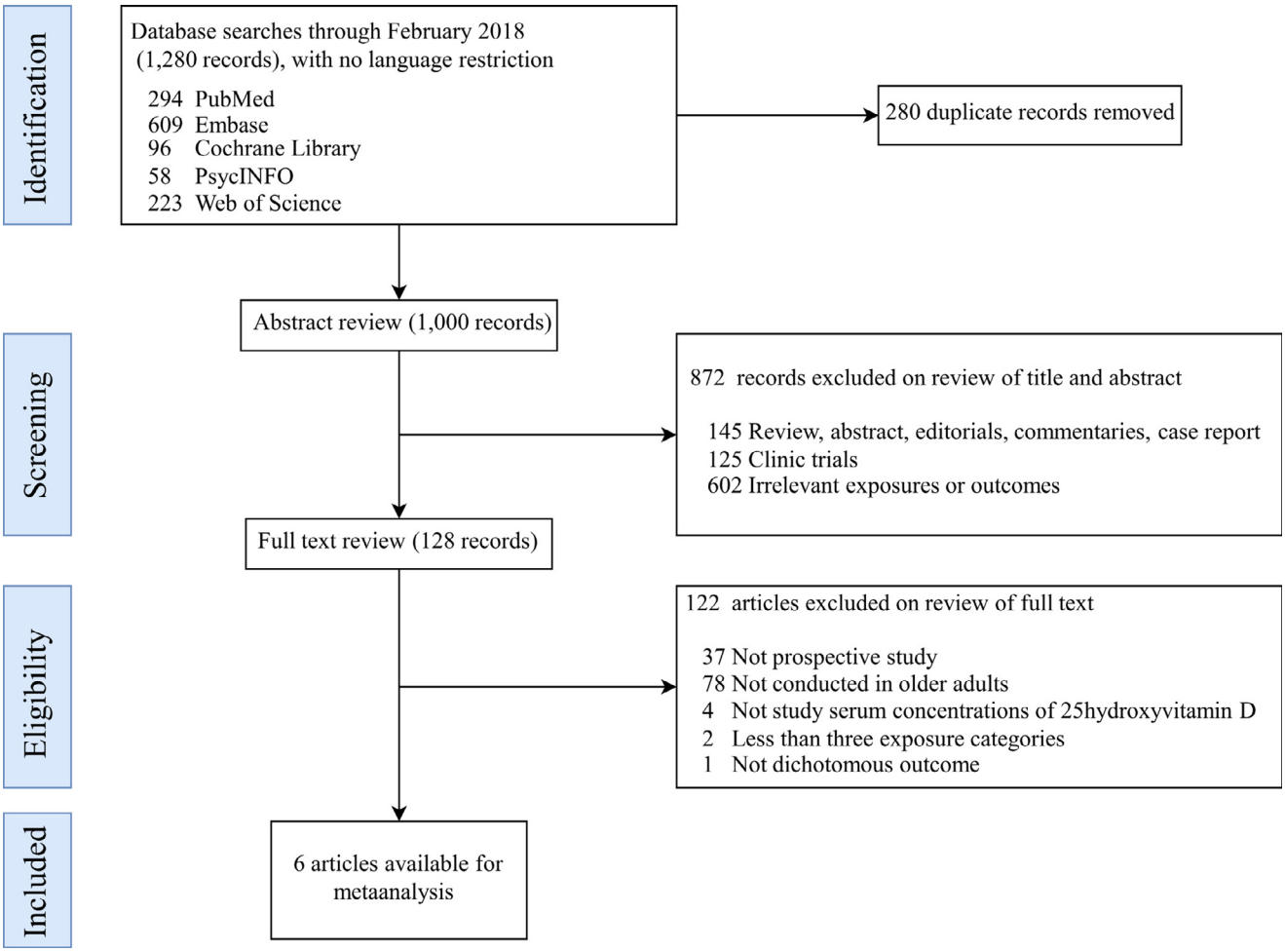
Statistical analyses were performed using Stata software (Version 14.0; StataCorp). The significance level was set as 0.05 (two-sided).

## RESULTS

### Study Selection

One hundred and twenty-eight of the 1,280 studies identified in the initial search were selected for full-text review; and 119 were excluded, leaving 9 studies (Fig. 1). One study only described depressive symptoms as continuous and not a dichotomous variable, using a cutoff value,[31] while two studies[32,33] only reported two levels of serum 25(OH)D. Finally, six cohort studies[6,10,34–37] were included in the meta-analysis. One study[35] reported outcomes separately for men and women, and they were handled as separate arms.

**FIGURE 1. Flow-chart of study selection.**



### Study Characteristics

Table 1 shows the characteristics of the included studies. The six studies involved 16,287 older adults with 1,157 cases of depression during follow-up. The mean age of study population was 73.9 years, and the follow-up period ranged from 1.07 to 10 years. Five studies established the diagnosis of depression using screening scales,[10,34,35,37] while one study used the International Classification of Diseases, Ninth Edition diagnostic codes.[6] Two studies each were conducted in Europe,[35,37] and America,[6,34] one each in Australia,[36] and China.[10] Table 2 shows the association between serum 25(OH)D concentration categories and the risk for depression.

### Quality Assessment

Figure 2 shows the study quality assessed by the NOS. Overall, one study was rated as 8,[10] two studies were rated as 7,[36,37] and the remaining three studies were rated as 6.[6,34,35]

### Does–Response Association Between Serum 25 (OH)D and Incident Depression

Figure 3 shows the pooled effect size of the association between serum 25(OH)D and the risk of depression. The pooled HR per 10-ng/mL increment in serum 25 (OH)D using the random-effects dose–response model was 0.88 (95% CI: 0.78–0.99, p = 0.03), which indicates an inverse association between vitamin D levels and the risk of depression although significant heterogeneity was found ($I^2 = 79.0\%$). Figure 4 shows that a linear association between serum 25(OH)D and the risk of depression was found using the restricted cubic splines analysis (p = 0.96 for nonlinearity with Wald test).

The funnel plot was asymmetric and shown in supplementary data (Fig. S1). After excluding Chan et al's study (2011) from the analyses, the results did not change significantly compared to the primary results (pooled HR: 0.86, 95% CI: 0.76–0.97, p = 0.01; $I^2 = 81.6\%$), which indicates that the results were robust (Fig. S2).

### Subgroup and Meta-Regression Analyses

Table 3 shows the results of the subgroup analyses. The association between serum 25(OH)D and the risk of depression was not moderated by the number of incident depression cases, sample size, length of follow-up, region, number of adjusted variables, and the type of assessment of depression. Meta-regression analysis revealed that study quality was a major source of heterogeneity between studies as measured by the $I^2$ between studies (Table 3; Fig. S3).

## DISCUSSION

To the best of our knowledge, this was the first dose–response meta-analysis of prospective cohort studies that examined the relationship between serum 25(OH)D levels and depression in older adults. An

**TABLE 1. Characteristics of Studies Included in the Meta-Analysis**

| First Author, Year | Study Population | Age (SD), Years | No. (% Female) | No. Depression | Follow-Up, Years | Diagnosis of Depression | Country |
|---|---|---|---|---|---|---|---|
| Chan, 2011 | Community-dwelling men aged ≥65 years | 72.5 (4.8) | 629 (0) | 25 | 4 | GDS-15 ≥8 | China |
| Almeida, 2015 | Community-dwelling men aged 71–88 years | 77.0 (3.6) | 2,740 (0) | 81 | 6 | PHQ-9 ≥10 | Australia |
| Williams, 2015 | Community-dwelling adults aged 70–79 years | 74.7 (2.9) | 2,325 (51.5) | 366 | 4 | CES-D-10 ≥10 or antidepressant medication use | America |
| Milaneschi, 2010 | Community-dwelling adults aged ≥65 years | 74.4 (6.9) | 640 (46.6) | 200 | 6 | CES-D-20 ≥16 | Italy |
| May, 2010 | Adults aged ≥50 years with cardiovascular disease | 73.1 (10.2) | 7,358 (58.8) | 335 | 1.07 | Clinical diagnosis (ICD-9) | America |
| Jovanova, 2017 | Community-dwelling adults aged ≥55 years | 71.6 (6.6) | 2,595 (57.4) | 150 | 10 | CES-D-20 ≥16 | Netherlands |

CES-D: Center for Epidemiologic Studies Depression Scale; GDS: Geriatric Depression Scale; ICD: International Classification of Diseases; No: number; PHQ: patient health questionnaire; SD: standard deviation.

**TABLE 2. Association Between Serum 25(OH)D Concentration Categories and the Risk for Depression Across Included Studies in the Original Study**

| First Author, Year | Categories of Serum 25(OH)D, ng/mL | Most Adjusted HR by Category (95% CI) in the Original Study | Most Adjusted HR by Category (95% CI) After Transformation | Covariates in the Most Adjusted Model |
|---|---|---|---|---|
| Chan, 2011[a] | 1: <20<br>2: 20−29<br>3: 30−39<br>4: ≥40 | 1: 1 (reference)<br>2: 1.50 (0.16−14.56)<br>3: 1.27 (0.13−12.89)<br>4: 2.27 (0.18−28.10) | 1: 1 (reference)<br>2: 1.48 (0.17−12.96)<br>3: 1.26 (0.14−11.60)<br>4: 2.19 (0.20−24.31) | Age, BMI, education, PASE, number of ADLs, DQI, smoking status, alcohol use, season of measurement, number of chronic diseases, baseline GDS score, CSI-D score and serum (ln) PTH concentration |
| Almeida, 2015 | 1: <12<br>2: 12−20<br>3: ≥20 | 1: 1.38 (0.43−4.45)<br>2: 0.97 (0.53−1.78)<br>3: 1 (reference) | 1: 1 (reference)<br>2: 0.70 (0.22−2.22)<br>3: 0.72 (0.23−2.33) | Age, living arrangements, season, coronary heart disease and stroke |
| Williams, 2015 | 1: <20<br>2: 20−30<br>3: ≥30 | HR (95 % CI)<br>1: 1.65 (1.23−2.22)<br>2: 1.31 (0.99−1.74)<br>3: 1 (reference) | HR (95 % CI)<br>1: 1 (reference)<br>2: 0.79 (0.60−1.04)<br>3: 0.61 (0.45−0.81) | Age, sex, race, site, season, and education, diabetes, cardiovascular disease, BMI, 3MS score, kidney disease, smoking, alcohol consumption, marital status, physical activity, and history of depression |
| Milaneschi, 2010 | Women:<br>1: <12.68<br>2: 12.68−21.56<br>3: ≥21.56<br>Men:<br>1: <12.68<br>2: 12.68−21.56<br>3: ≥21.56 | Women:<br>1: 2.56 (1.40−4.64)<br>2: 1.72 (0.98−3.00)<br>3: 1 (reference)<br>Men:<br>1: 1.96 (0.96−4.00)<br>2: 1.03 (0.55−1.90)<br>3: 1 (reference) | Women:<br>1: 1 (reference)<br>2: 0.67 (0.41−1.11)<br>3: 0.39 (0.22−0.71)<br>Men:<br>1: 1 (reference)<br>2: 0.53 (0.26−1.05)<br>3: 0.51 (0.25−1.04) | Age, baseline CES-D, ADL disabilities, use of antidepressants, number of chronic diseases, SPPB, high PTH and season |
| May, 2010 | 1: ≤15<br>2: 16−30<br>3: 31−50<br>4: ≥50 | 1: 2.70 (1.35−5.40)<br>2: 2.15 (1.10−4.21)<br>3: 1.95 (0.99−3.87)<br>4: 1 (reference) | 1: 1 (reference)<br>2: 0.80 (0.31−2.02)<br>3: 0.72 (0.28−1.85)<br>4: 0.37 (0.19−0.74) | Age, sex, diabetes, hypertension, coronary artery disease, myocardial infarction, heart failure, fracture, renal failure, parathyroid hormone levels |
| Jovanova, 2017 | 1: <11.43<br>2: 11.43−17.52<br>3: 17.52−25.28<br>4: ≥25.28 | 1: 0.82 (0.67−1.02)<br>2: 1.12 (0.79−1.61)<br>3: 1.24 (0.87−1.78)<br>4: 1 (reference) | 1: 1 (reference)<br>2: 1.38 (0.99−1.91)<br>3: 1.51 (1.09−2.10)<br>4: 1.22 (0.99−1.50) | Gender, age, and baseline depressive symptoms, BMI, alcohol consumption, smoking status, marital status, and ADLs score. |

ADLs: activities of daily living; BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; CI: confidence interval; CSI-D: community screening instrument for dementia; DQI: diet quality index; GDS: Geriatric Depression Scale; HR: hazard ratio; OR: odd ratio; PASE: Physical Activity Scale of the Elderly; PTH: parathyroid hormone; SPPB: short physical performance battery; 3MS: the Modified Mini-Mental State Examination.

[a] For this study, OR and corresponding 95% CI were reported in the original study. OR first converted to RR (relative risk) according to the following formula: $RR = OR/(1 - P_{ref} + P_{ref} \times OR)$, where $P_{ref}$ is the incidence of depression in the reference group of serum 25(OH)D.

inverse association was observed between serum 25 (OH)D levels and the risk of depression in older adults. Every 10-ng/mL increase in serum 25(OH)D was associated with a 12% decrease in the risk of depression. The heterogeneity between studies could be partly due to study quality, measurement of depression, and unmeasured variables that were not controlled for in the included studies. In addition, the different rates of depression across studies could also be associated with heterogeneity.

To date, several observational studies have shown that vitamin D deficiency is associated with increased risk of late-life depression.[38] However, most published RCTs failed to find evidence supporting benefit of vitamin D supplements in depression.[13] Meanwhile, it should be noted that the completed RCTs generally suffered from some limitations. A systematic review and meta-analysis found that RCTs without biological flaws were more inclined to show benefits of vitamin D compared to those featured certain limitations.[39] It warranted well-designed and large-scale randomized trials to give more definitive evidence. Given the inverse relationship between vitamin D and multiple health outcomes, screening for vitamin D deficiency might yield considerable benefits. Actually, it has become one of the most talked about topic owing to insufficient evidence.[40] Recently, the U.S. Preventive Services Task Forces published a research plan to

**FIGURE 2. Study quality assessed using the NOS (Newcastle-Ottawa Quality Assessment Scale).**

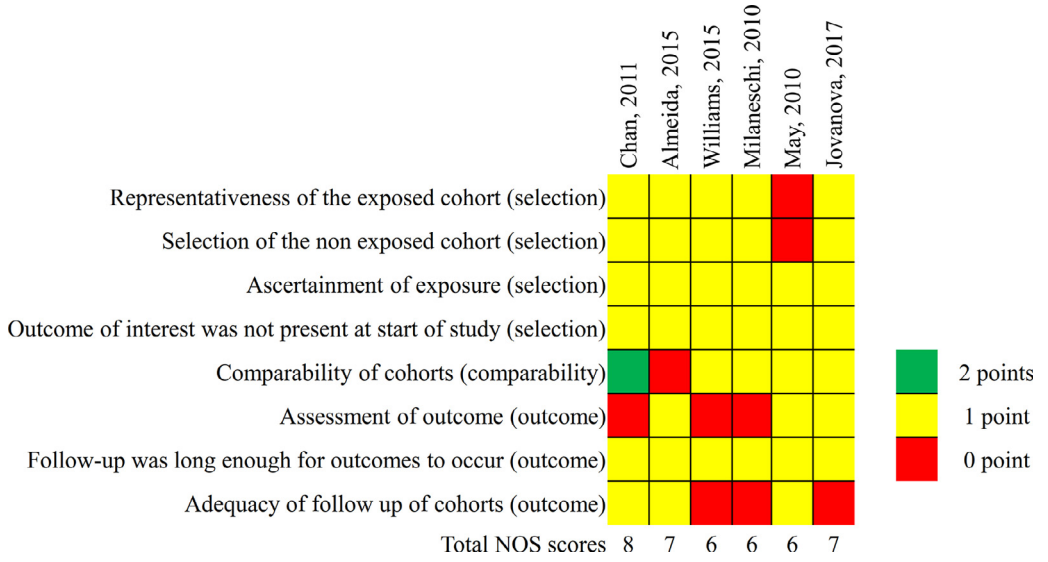



**FIGURE 3. Forest plot showing the pooled effect size of the association between serum 25(OH)D and risk of depression using random-effects model (pooled HR: 0.88; 95% CI: 0.78−0.99). The pooled effect sizes are shown for 10-ng/mL increments in serum 25 (OH)D levels. Solid circles and horizontal lines represent HR (95% CI); the gray boxes reflect the statistical weight of the study; and the red dashed vertical line indicates the line of no effect. p for heterogeneity was calculated by Cochran's Q test with 6 degrees of freedom.**

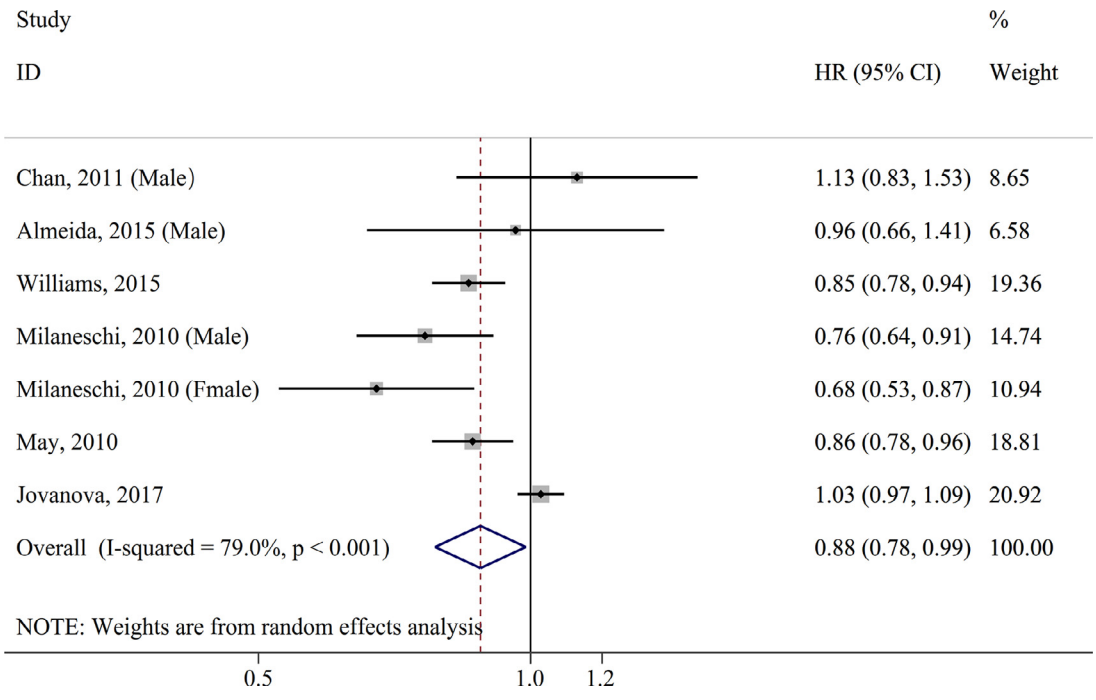


**FIGURE 4. Dose–response analysis between serum 25(OH)D levels and the risk of depression. The solid line represents the pooled HR, and the dashed lines indicate 95% CI.**

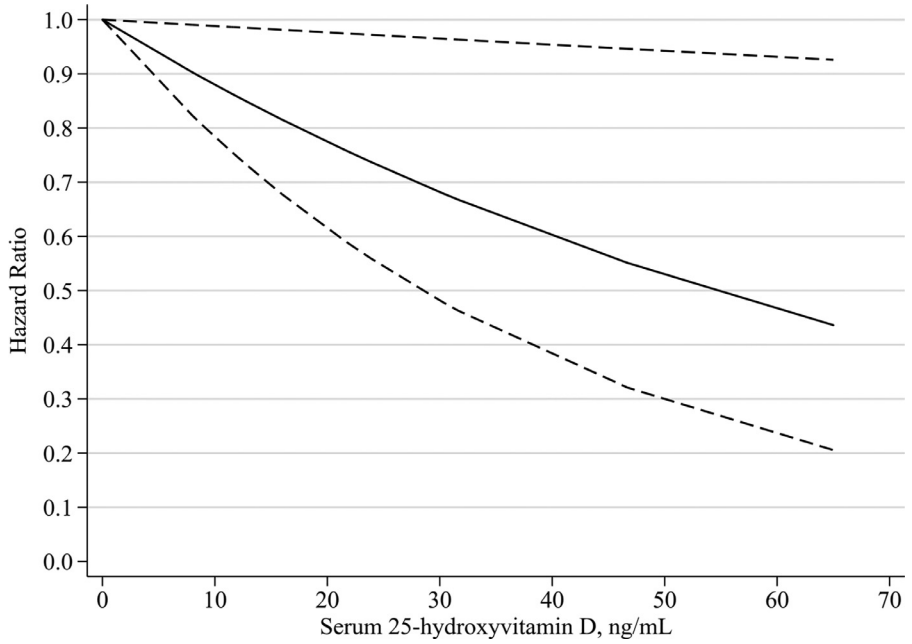



**TABLE 3. Subgroup Analysis of Serum 25(OH)D Levels and the Risk of Depression in Dose–Response Meta-Analysis**

| Subgroup | Number | Hazard Ratio (95% CI) | $I^2$, % | $p_{heterogeneity}$ [a] | $p_{between}$ [b] |
|---|---|---|---|---|---|
| Number of incident depression cases, n | | | | | 0.791 |
| ≤200 | 5 | 0.89 (0.73–1.08) | 79.5 | 0.001 | |
| >200 | 2 | 0.86 (0.80–0.92) | 0.0 | 0.887 | |
| Sample size, n | | | | | 0.349 |
| ≤2,000 | 3 | 0.82 (0.63–1.06) | 70.4 | 0.034 | |
| >2,000 | 4 | 0.92 (0.81–1.04) | 79.9 | 0.002 | |
| Follow-up time, years | | | | | 0.674 |
| ≤5 | 3 | 0.88 (0.80–0.96) | 30.5 | 0.237 | |
| >5 | 4 | 0.85 (0.68–1.07) | 84.0 | <0.001 | |
| Region | | | | | 0.528 |
| Europe | 3 | 0.82 (0.63–1.08) | 89.3 | <0.001 | |
| American | 2 | 0.86 (0.80–0.92) | 0.0 | 0.887 | |
| Others | 2 | 1.06 (0.83–1.34) | 0.0 | 0.529 | |
| Number of adjusted variables | | | | | 0.674 |
| ≤8 | 4 | 0.85 (0.68–1.07) | 84.0 | <0.001 | |
| >8 | 3 | 0.88 (0.80–0.96) | 30.5 | 0.237 | |
| Quality scores, points | | | | | 0.005 |
| <7 | 4 | 0.82 (0.76–0.89) | 31.6 | 0.223 | |
| ≥7 | 3 | 1.03 (0.97–1.09) | 0.0 | 0.797 | |
| Clinical diagnosis of depression | | | | | 0.898 |
| No | 6 | 0.88 (0.77–1.02) | 80.7 | <0.001 | |
| Yes | 1 | 0.86 (0.78–0.96) | - | - | |

[a] $p_{heterogeneity}$ within subgroups calculated by Cochran's Q test with Number (the number of studies) minus 1 degrees of freedom.
[b] $p_{heterogeneity}$ between subgroups calculated by meta-regression analysis with z test.

re-evaluate benefits and harms of screening for vitamin D deficiency in asymptotic adults. However, there is no one-size-fits-all screening strategy, which should vary from country to country, depending on geographic areas and diet habits. Debate on this hot-button topic will go on. Based on this meta-analysis, we suggest that vitamin D deficiency screening should be put in place for older adults, the population group with high risk of both vitamin D deficiency and fracture, depression as well as fall.

Several mechanisms could explain the association between serum 25(OH)D levels and the risk of depression. Vitamin D receptors have been identified in certain brain areas, such as the hippocampus,[5] which are implicated in the pathophysiology of depression. Vitamin D receptor gene polymorphisms are also associated with depression in older adults.[41] Moreover, vitamin D could interact with glucocorticoid receptors in the hippocampus,[42] while high circulating corticosteroid concentrations are thought to be involved in the pathogenesis of depression.[43] Furthermore, vitamin D could influence the expression of serotonin-synthesizing genes tryptophan hydroxylase 1 and tryptophan hydroxylase 2,[44] which are closely linked with the neurobiology of depression. Lastly, vitamin D may indirectly reduce the risk of depression through decreasing inflammatory mediators.[45]

The strengths of this meta-analysis included the relatively large sample size that could enable more sophisticated analyses, such as subgroup and sensitivity analyses. In addition, the inclusion of only prospective cohort studies could have enhanced the homogeneity between studies with respect to the study design. However, there were also limitations in this meta-analysis. First, the association between serum 25(OH)D levels and the risk of depression could be moderated by other variables. Therefore, only the findings of multivariate analyses from the included studies were synthesized. Second, the heterogeneity was relatively large ($I^2 = 79.0\%$). Hence, subgroup analyses were conducted to explore the heterogeneity. Third, similar to another meta-analysis of prospective cohort studies,[46] the number of included studies was relatively small, particularly studies conducted in low- and medium-income countries. Last, both serum 25(OH)D and depression fluctuated over time. Hence, the dynamic association between serum 25(OH)D levels and risk of depression could not be examined.

In conclusion, this meta-analysis demonstrated a negative association between serum 25(OH)D levels and the risk of depression in older adults. Specifically, every 10-ng/mL increase in serum 25(OH)D was associated with a 12% decrease in the risk of depression. However, our work was based on observational studies and could not testify the causal association between vitamin D deficiency and depression. Further findings from high-quality clinical studies are warranted to clarify whether increasing 25(OH)D levels may be a useful approach to reduce the risk of depression in older adults. Fortunately, the ongoing VITAL-DEP study[47] with a large sample size and a long follow-up period should provide more definitive answers to this question.

## AUTHORS' CONTRIBUTION

Conceptualization, YX and XG; methodology, HL, DS, HP, and WF; formal analysis, HL, DS, and AW; writing—original draft preparation, HL, DS, LT, and XL; writing—review and editing, CHN, GSU, and WW, supervision, YX and XG.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2019.05.022.

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