Vitamin D Supplementation for Depressive Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objective: The aim of this study was to review the effects of vitamin D supplementation on depressive symptoms in randomized controlled trials. Although low vitamin D levels have been observationally associated with depressive symptoms, the effect of vitamin D supplementation as an antidepressant remains uncertain. Methods: MEDLINE, CINAHL, AMED, PsycINFO, Scopus, The Cochrane Library, and references of included reports (through May 2013) were searched. Two independent reviewers identified and extracted data from randomized trials that compared the effect of vitamin D supplementation on depressive symptoms to a control condition. Two additional reviewers assessed study quality using The Cochrane Risk of Bias Tool. Seven trials (3191 participants) were included. Results: Vitamin D supplementation had no overall effect on depressive symptoms (standardized mean difference [SMD], 0.14; 95% confidence interval [CI], −0.33 to 0.05, p = .16), although considerable heterogeneity was observed. Subgroup analysis showed that vitamin D supplementation for participants with clinically significant depressive symptoms or depressive disorder had a moderate, statistically significant effect (2 studies: SMD, −0.60; 95% CI, −1.19 to −0.01; p = .046), but a small, nonsignificant effect for those without clinically significant depression (5 studies: SMD, −0.04; 95% CI, −0.20 to 0.12; p = .61). Most trials had unclear or high risk of bias. Studies varied in the amount, frequency, duration, and mode of delivery of vitamin D supplementation. Conclusions: Vitamin D supplementation may be effective for reducing depressive symptoms in patients with clinically significant depression; however, further high-quality research is needed. Key words: vitamin D, depression, depressive symptoms, randomized controlled trials, meta-analysis, systematic review.

25(OH)D = 25-hydroxyvitamin D; SD = standard deviation; SMD = standardized mean difference; IU = international units; RCT = randomized controlled trial; MDD = major depressive disorder; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression scale; GDS = Geriatric Depression Scale; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asburg Depression Rating Scale; nM = nanomolar; IM = intramuscular.

INTRODUCTION

Depression is a highly prevalent and debilitating chronic illness that can be difficult to treat (1,2), and both depressive disorders and subthreshold depressive symptoms are associated with significant disability, mortality, and health care costs (3,4). Although the underlying pathophysiology of depression remains unknown and probably involves several mechanisms, a possible role of vitamin D in depression has received considerable attention (5). Indeed, a recent systematic review and meta-analysis (6) of case-control, cross-sectional, and prospective observational cohort studies of depression and vitamin D provided some support for an association of depression with low concentrations of serum 25-hydroxyvitamin D (25(OH)D), the primary circulating form of vitamin D that is used to determine a patient’s vitamin D status (7). Although these findings are compelling, the most important questions concerning the association of vitamin D with depression are as follows: a) Is the association causal? and b) Does vitamin D supplementation affect depressive symptom level?

We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to investigate whether vitamin D supplementation improves—or potentially worsens—depressive disorder or depressive symptoms. On the basis of previous narrative reviews (8,9), we hypothesized that vitamin D supplementation would have a minimal effect on depression in these trials.

METHODS

We followed the Cochrane Handbook for Systematic Reviews to plan and conduct this meta-analysis (10), and we report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (11).

Data Sources and Searches

We systematically identified all RCT that examined the effect of vitamin D supplementation on depressive disorder or depressive symptoms. Although it is difficult to detect treatment effects in those with few, if any, baseline depressive symptoms (12), we nonetheless included studies of both nondepressed and depressed individuals because of our interest in determining whether vitamin D supplementation either worsened or improved depression. Potential relevant articles were identified by searching the biomedical electronic databases Ovid MEDLINE, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Allied and Complimentary Medicine Database, PsycINFO, and Scopus. Dates were searched from inception to the second week of May 2013. Registers of clinical trials were searched for unpublished and ongoing studies. The initial search was conducted on June 1, 2012, and weekly searches were conducted thereafter through May 15, 2013. All relevant subject headings and free-text terms were used to represent vitamin D and depression. Additional records were identified by searching the reference lists of relevant studies and reviews and by using the Related Articles feature in PubMed and the Cited Reference Search in ISI Web of Science. The search did not have any language or year restrictions, and we considered all studies regardless of their publication status. The exact search terms and search strategies for each database are reported in Table S1 in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A118.

To determine the studies to be included in the meta-analysis, two trained reviewers (N.E., PL.) independently read the title and/or abstract of every record retrieved. All potentially relevant articles were investigated as full text, and differences in opinion between the two reviewers were resolved by consensus or in consultation with one of the authors (J.A.S.).
Database Extraction and Quality Assessment

Two additional reviewers (L.F., K.H.) worked independently of each other and in consultation with the first author to extract relevant data from each report. These data included study characteristics (setting, design, randomization, masking, intention-to-treat analyses, sample size, trial entry criteria related to depression and vitamin D, and primary depression measure), participant demographic characteristics (age and sex), and clinical characteristics (baseline concentration of 25(OH)D and depression status). Additional data were extracted to characterize the type, amount, frequency, duration, and mode of delivery of vitamin D supplementation; type of control conditions; and trial requirements regarding the use of nonstudy vitamin D supplementation. Study quality was assessed using the Cochrane Risk of Bias Tool (13), which considers the reporting and adequacy of random sequence generation, randomization concealment, masking of participants, research personnel, and outcome assessors, as well as methods for dealing with participants who were lost to follow-up or had missing data for other reasons.

Data on mean (standard deviation [SD]) depressive symptoms were extracted as the primary end point, given that no studies included a diagnosis of depressive disorder as an end point. We used available data to calculate change-from-baseline differences within and between treatments. Change scores were standardized using the SD of change. Two studies (14,15) reported results as mean (SD) preintervention and postintervention depressive symptom scores but did not provide estimates of the pre-post correlation of depression scores that are required to compute effect sizes. We attempted to contact study authors to request these additional data but ultimately estimated the pre-post correlation of depression scores using published data (16,17). Two studies included two intervention groups with different doses of vitamin D supplementation (14,18), and one study included two control groups (15). We pooled means and SDs across the two intervention and control groups in these studies to calculate effect sizes.

Statistical Analysis

Data were entered into an electronic database and analyzed using Comprehensive Meta-Analysis (version 2.0; BioStat Software, Englewood, NJ) (19). We weighted each study’s effect size using the inverse-variance method. To summarize intervention effects across trials, we pooled data in random-effects models, which accounts for the possibility of substantial heterogeneity across studies. We used the Cochrane Q statistic (20) to test for evidence of between-study heterogeneity and the I² statistic (21) to quantify the percentage of the total variability across studies that is due to heterogeneity rather than sampling error. If between-study heterogeneity was significant (I² > 50%), we conducted sensitivity analyses using random-effects models that included fixed-effects models for trials with similar participant characteristics. We conducted subgroup analyses if at least two studies were available to conduct stratified analyses. We also conducted meta-regression analyses to evaluate the impact of study characteristics on effects across trials. We used Mantel-Haenszel tests to pool data across trials using log odds ratios for dichotomous outcomes. We used random-effects models to pool data across studies for continuous outcomes.

RESULTS

Search Results

The search for RCT of vitamin D supplementation for depressive disorder or depressive symptoms identified 2394 reports. Details of the study flow are documented in Figure S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A118. Of the 1829 nonduplicate articles identified by the initial search, 1797 were deemed ineligible or irrelevant based on their titles and abstracts; the remaining 32 articles, in addition to 2 articles (18,26) that were identified after the completion of the initial search through weekly database searches, required full reading. Of these 34 potentially eligible articles, 7 RCT (14–16,26–29) met our criteria for inclusion in our meta-analysis. We conducted sensitivity analyses in which we substituted a range of pre-post correlations (r = 0.1, 0.4, 0.8, and 0.9) in depressive symptoms for the two studies that did not report these data. An additional sensitivity analysis was conducted that excluded an unpublished thesis that qualified for inclusion in our meta-analysis (15).

Although the validity of procedures for detecting publication bias is limited when the number of studies is as small as in the current meta-analysis (24), we planned to inspect funnel plots and compute Rosenthal’s fail-safe N, which provides an estimate of the number of missing studies with nonsignificant effects that would be needed to make a significant p value for the observed aggregate effect nonsignificant (25). Given that we obtain a nonsignificant overall effect, however, we did not conduct these assessments.

TABLE 1. Participant and Study Characteristics of Randomized Controlled Trials Investigating the Effect of Vitamin D Supplementation on Depressive Symptoms

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants</th>
<th>Country</th>
<th>Intervention, n</th>
<th>Control, n</th>
<th>Age, y</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorde et al., 2008 (14)</td>
<td>Community members and outpatients with overweight or obesity</td>
<td>Norway</td>
<td>222 (135 F, 87)</td>
<td>112 (71 F, 41 M)</td>
<td>21–70</td>
<td>Three-arm RCT with pre-post assessment</td>
</tr>
<tr>
<td>Dean et al., 2011 (28)</td>
<td>Healthy volunteers</td>
<td>Australia</td>
<td>63 (39 F, 24 M)</td>
<td>65 (34 F, 31 M)</td>
<td>18–30</td>
<td>Two-arm RCT with pre-post assessment</td>
</tr>
<tr>
<td>Bertone-Johnson et al., 2012 (27)</td>
<td>Postmenopausal women</td>
<td>United States</td>
<td>1109 (1010 F, 0 M)</td>
<td>1143 (1143 F, 0 M)</td>
<td>50–79</td>
<td>Two-arm RCT with pre-post assessment</td>
</tr>
<tr>
<td>Kjaergaard et al., 2012 (29)</td>
<td>Community members with low 25(OH)D level</td>
<td>Norway</td>
<td>120 (66 F, 54 M)</td>
<td>110 (63 F, 47 M)</td>
<td>30–75</td>
<td>Two-arm RCT with pre-post assessment</td>
</tr>
<tr>
<td>Khoraminyan et al., 2012 (26)</td>
<td>Psychiatric outpatients with MDD and elevated depressive symptoms</td>
<td>Iran</td>
<td>20 (17 F, 3 M)</td>
<td>20 (17 F, 3 M)</td>
<td>18–65</td>
<td>Two-arm RCT with repeated assessments</td>
</tr>
<tr>
<td>Mozaffari-Khosravi et al., 2013 (18)</td>
<td>Psychiatric outpatients with elevated depressive symptoms and low vitamin D levels</td>
<td>Iran</td>
<td>75 (52 F, 23 M)</td>
<td>34 (26 F, 8 M)</td>
<td>20–60</td>
<td>Three-arm RCT with pre-post assessment</td>
</tr>
</tbody>
</table>

F = female; M = male; RCT = randomized controlled trial; 25(OH)D = 25-dihydroxyvitamin D; MDD = major depressive disorder.

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TABLE 2. Depression and Vitamin D Trial Entry Criteria in Randomized Controlled Trials Investigating the Effect of Vitamin D Supplementation on Depressive Symptoms

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Depression Entry Criteria</th>
<th>Depression Measure</th>
<th>Baseline Depression Score, M (SD)</th>
<th>Vitamin D Entry Criteria</th>
<th>Baseline 25(OH)D Concentration, M (SD), nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogie-Lorenzen, 2003 (15)</td>
<td>None reported</td>
<td>GDS</td>
<td>3.3 (3.0)</td>
<td>None reported</td>
<td>8.2 (3.0)</td>
</tr>
<tr>
<td>Jorde et al., 2008 (14)</td>
<td>Current antidepressant use excluded</td>
<td>BDI</td>
<td>4.8 (4.3)</td>
<td>None reported</td>
<td>53.1 (14.3)</td>
</tr>
<tr>
<td>Dean et al., 2011 (28)</td>
<td>Current mood disorder excluded</td>
<td>BDI</td>
<td>6.5 (6.7)</td>
<td>None reported</td>
<td>76.6 (19.9)</td>
</tr>
<tr>
<td>Bertone-Johnson et al., 2012 (27)</td>
<td>Diagnosed mental disorder excluded</td>
<td>Burnham scale</td>
<td>Not reported</td>
<td>None reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kjaergaard et al., 2012 (29)</td>
<td>Elevated depressive symptoms (BDI &gt;29, MADRS &gt;34) or depression diagnosis excluded</td>
<td>BDI</td>
<td>4.0 (6.8)</td>
<td>25(OH)D &lt;55 nM</td>
<td>47.5 (15.7)</td>
</tr>
<tr>
<td>Khoraminya et al., 2012 (26)</td>
<td>Diagnosis of MDD and a HDRS score ≥15 included; recent, nonstudy antidepressant use excluded</td>
<td>HDRS</td>
<td>32.1 (7.3)</td>
<td>None reported</td>
<td>58.2 (10.7)</td>
</tr>
<tr>
<td>Mozaffari-Khosravi et al., 2013 (18)</td>
<td>BDI-II scores ≥17 included; current antidepressant use excluded</td>
<td>BDI-II</td>
<td>26.9 (7.2)</td>
<td>25(OH)D &lt;40 nM</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

M = mean; SD = standard deviation; 25(OH)D = 25-dihydroxyvitamin D; nM = nanomolar; GDS = Geriatric Depression Scale; BDI = Beck Depression Inventory; MADRS = Montgomery-Ashburg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; MDD = major depressive disorder.

Criteria for inclusion. Nearly all studies that were excluded at the full-text stage of review did not feature intervention designs; however, we excluded three intervention studies that did not feature randomization (30), did not include a depression outcome measure (31), or for which no published data could be identified (32).

### Trial Characteristics

Tables 1 and 2 detail the characteristics of the seven RCT identified by our search that examined the effect of vitamin D supplementation on depressive symptoms (total N = 3191; age range, 18–79 years) by participant and study characteristics and depression and vitamin D trial entry criteria, respectively. All trials were published between 2003 and 2013. Two studies required participants have low levels of 25(OH)D at baseline (18,29), and participants in a third study (15) of older adults also had baseline concentrations of 25(OH)D consistent with deficiency (<50 nanomolar [nM]). Five trials either did not specifically recruit participants with depression (15) or excluded those with depressive disorders, elevated depressive symptoms, and/or current antidepressant use (14,27–29). The baseline depressive symptom scores of the participants in these five trials suggest that they had no depressive disorder or minimal, nonclinically significant depressive symptoms (22,23). The primary end point for all seven studies was depressive symptom scores, although the specific instruments used to assess depressive symptoms varied.

Characteristics of the vitamin D supplementation used in each of the seven RCT included in this review are reported in Table 3. All but one study (18) specified vitamin D3 (cholecalciferol) as the type of supplement. Mode of delivery, dosage (range, 600–300,000 IU), frequency (daily versus weekly versus one-time administration), and duration (range, 6 weeks to 2 years) of supplementation varied between studies, as did types of control conditions and requirements regarding the use of nonstudy vitamin D supplementation.

Assessment of study quality with the Cochrane Risk of Bias Tool demonstrated at least one unclear or high risk of bias in all but two trials (Table S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A118) (28,29). The most common types of bias pertaining to randomization concealment (14–16,26,27) and masking of research personnel (14,15,18,26,27), which were rated as posing a high or unclear risk in five of seven trials.

### Effect of Vitamin D Supplementation on Depressive Symptoms

The overall reduction in depressive symptoms associated with vitamin D supplementation was small and nonsignificant (SMD = −0.14, 95% CI = −0.33 to 0.05, p = .16; Fig. 1). Analyses of heterogeneity revealed substantial variation among intervention effects ($Q_6 = 20.2, p = .003, I^2 = 70.3$), and SMDs ranged from $-0.96 (p = .004)$ in favor of vitamin D supplementation to 0.15 ($p = .49$) in favor of control.

Subgroup analyses were conducted to identify potential sources of heterogeneity among intervention effects (Fig. 1). The four studies of participants whose baseline vitamin D status was sufficient (>50 nM) showed a larger reduction in depressive symptoms (SMD = −0.22, 95% CI = −0.53 to 0.08, p = .15) than the three studies of participants whose baseline vitamin D status was insufficient (SMD = −0.05, 95% CI = −0.31 to 0.20, p = .69); however, the difference in intervention effects between these two
subgroups of studies was not significant ($Q_1 = 0.70, p = .40$), and neither subgroup of studies had a statistically significant intervention effect.

A post hoc subgroup analysis was also conducted to compare studies of participants with clinically significant depressive symptoms and/or MDD with those that either explicitly excluded participants with clinically significant depression or included participants with nonclinically significant depressive symptoms at baseline (Fig. 1). These analyses revealed that the effect of vitamin D supplementation on depressive symptoms was moderate and statistically significant in the two studies of participants with clinically significant depressive symptoms and/or MDD (SMD = $-0.60$, $95\%$ CI $= -1.19$ to $-0.01$, $p = .046$). In contrast, the effect of vitamin D supplementation on depressive symptoms among trials of nonclinically depressed participants was small and not statistically significant (SMD = $-0.04$, $95\%$ CI $= -0.20$ to $0.12$, $p = .61$). The difference in intervention effects between these two subgroups approached statistical significance ($Q_1 = 3.22, p = .07$). We planned to investigate further sources of heterogeneity by conducting subgroup analyses of dose; however, the use of different amounts, frequencies, and durations of vitamin D in each trial precluded this analysis.

Sensitivity analyses, in which a range of pre-post correlations among depressive symptom scores were substituted for the published estimates used in the primary analyses, did not change the statistical significance of the overall intervention effect or the analyses of between-study heterogeneity among effects. Removal of the unpublished thesis from our analyses also did not change the primary results.

**DISCUSSION**

This systematic review and meta-analysis report is the first to examine the effect of vitamin D supplementation on depressive symptoms. We found that vitamin D supplementation neither worsened nor improved depressive symptoms across seven RCT but considerable heterogeneity of study characteristics and intervention effects among studies was observed. Although baseline vitamin D status did not explain the between-study heterogeneity in intervention effects, baseline depression status may have. Although vitamin D supplementation was associated with a statistically significant, moderate reduction in depressive symptoms across two trials that recruited patients with clinically significant depressive symptoms and/or MDD, its effect in trials of participants with nonclinically significant depression was small and nonsignificant.

Notwithstanding the biological plausibility of a causal role for vitamin D deficiency in depression (33), the results of this review suggest that the use of vitamin D supplementation to reduce depressive symptoms for individuals without clinically significant depression may not be warranted. Although trials of nonclinically depressed individuals differed considerably in the type of participants they included, their study locations and designs, and characteristics of their intervention and control conditions, four of these five trials had nonsignificant intervention effects (15,27–29). These null findings are not entirely surprising given that the association of vitamin D with depressive symptoms has not clearly been established in nondepressed individuals. Although a recently conducted meta-analysis of observational studies of vitamin D deficiency and depression in older adults found a moderate and statistically significant association of lower vitamin D levels with clinically meaningful depression in cross-sectional studies, the studies included in that review had several methodological biases (6). In particular, cross-sectional studies cannot rule out the possibility of reverse causation in which patients with subthreshold depressive symptoms or depressive disorders have less exposure to sunlight and thus lower vitamin D levels (9). Interestingly, the same meta-analysis included three prospective cohort studies (34–36) that found a statistically significant, two-fold increased risk of developing clinically significant depression or depressive symptoms among those with low vitamin D levels. To date,
however, no study has examined whether vitamin D supplementation offsets the risk of incident depressive disorder or depressive episodes, and future RCT may thus need to do so.

Of note, not all trials of nonclinically depressed participants in this review featured null intervention effects. A trial conducted by Jorde and colleagues (14), which included participants with overweight and obesity, found a small but statistically significant reduction in depressive symptoms with vitamin D supplementation. This trial had an unclear risk of bias in three of the six domains of the Cochrane Risk of Bias Tool; however, its findings suggest a possible need for additional studies that examine mechanistic aspects of the association of vitamin D with depressive symptoms and vitamin D intervention effects in this distinct population. These findings also hint that overweight and obesity may contribute to some of the observed heterogeneity of effects among the studies included in this meta-analysis, although we could not test this hypothesis given a lack of reported data on overweight and obesity across trials.

Although our subgroup analysis of trials with versus without participants with clinically significant depressive symptoms and/or MDD suggests a possible explanation for the heterogeneity of intervention effects observed in overall analyses, several characteristics other than participants’ baseline depression status differed between the former trials and the latter ones. In particular, characteristics of the vitamin D interventions used in all seven trials varied, and no two studies featured the same dose or duration of vitamin D supplementation. In addition, the trial in which we observed the largest effect of vitamin D supplementation on depressive symptoms not only included participants with MDD and elevated depressive symptoms (26) but also used vitamin D...
supplementation as an adjunctive intervention to pharmacotherapy with fluoxetine. The other trial of participants with clinically significant depression used a dose of vitamin D that far exceeded the single, but not necessarily cumulative, doses featured in other studies (18). Vitamin D supplementation was also administered via intramuscular injection in that trial, whereas other trials included in this review administered supplementation via capsule or food. The interaction between vitamin D supplementation and selective serotonin reuptake inhibitors such as fluoxetine, the comparative efficacy of different vitamin D dose amounts, and the implications of using alternate modes of administration of vitamin D supplementation thus remain unknown and require investigation in future trials.

As a parallel to the present study, it is worth examining studies evaluating the efficacy of omega-3 supplements for depression, which resemble studies of vitamin D supplementation for depression in several ways. As with studies of vitamin D supplementation for depression, a large proportion of omega-3 trials involve healthy participants or those with subclinical depression (37). Meta-analyses of omega-3 for depression have pooled across these studies and those of participants with clinical depression (37) and concluded that the efficacy of omega-3 for depression is stronger in clinical samples than in nonclinical ones. Similar to the results of one of the studies (26) included in this review, the effect of omega-3 on depression may also be stronger when used to supplement traditional antidepressants rather than as monotherapy (38). Most importantly, meta-analyses of studies of omega-3 for depression have helped to guide subsequent research, as we hope the current meta-analysis will likewise do.

Several limitations of the current review warrant attention. First, we identified few trials overall, the design characteristics of each of these studies differed considerably, and all but two of these trials (28,29) had at least one unclear or high risk of bias. Although the heterogeneity among studies is indeed striking, it is not unlike the heterogeneity observed among studies of vitamin D supplementation for other conditions (39). The overall quality of the evidence from each trial is thus low and poses uncertainty regarding the true effect of vitamin D supplementation on depressive symptoms. Although it is unlikely that poor methodological quality biased the results of trials of nondepressed participants toward the null hypothesis of no intervention effect, it may have inflated the treatment effect observed in the two trials of participants with clinically significant depression. Second, some of the decisions that we made while conducting our review may limit the validity of our findings. Although we drafted a protocol and planned extensively before conducting our review and analyses, we did not register the protocol or anticipate in advance all of the analyses that we conducted. In particular, we performed two post hoc subgroup analyses given that we could not conduct an a priori analysis of whether differences in vitamin D dose contributed to potential heterogeneity among intervention effects. Nonetheless, these post hoc analyses were informed by reasoned clinical and empirical considerations, and we did not conduct an excessive number of these analyses. A third limitation is that we did not consider whether vitamin D supplementation increased levels of 25(OH)D in each trial, and it is possible that the null effects seen in some trials reflect a failure of the intervention to improve vitamin D status.

The small number of studies included in this review, the considerable heterogeneity among these studies, and the unlikely possibility of detecting intervention effects among nonclinical samples (12) may lead one to wonder whether a systematic review and meta-analysis of vitamin D supplementation for depressive symptoms at this time is premature. Given the recently published meta-analysis of observational studies of vitamin D deficiency and depression (6), we believe that now is precisely the time to highlight the dearth of evidence for a causal role of vitamin D in relation to depression and point to the necessary next steps to determine whether any clinical benefit is likely to be gained by vitamin D supplementation.

Notwithstanding these limitations and considerations, this systematic review and meta-analysis report represents a timely contribution to the emerging literature on vitamin D and depression that may inform the development of future clinical trials. Although we found a nonsignificant effect on depressive symptoms associated with vitamin D supplementation, the intervention effects across the seven RCT included in this review varied significantly and considerably. We observed suggestive evidence that vitamin D supplementation may be effective for participants with MDD or subthreshold, clinically significant depressive symptoms but not for those without; however, other potential sources of the between-study heterogeneity of intervention effects such as obesity exist.

We still have limited data to conclusively address whether vitamin D supplementation is effective as either a unique drug or an adjuvant to pharmacotherapy for the treatment of depression. Future trials are needed that not only target depressed patients but also consider baseline levels of vitamin D (40) and how vitamin D dosing and mode of delivery may contribute to its effects on depressive symptoms. We found no evidence of prior dosing studies for vitamin D supplementation in patients with depression, and it may be time to determine the optimal dose and then test this dose against placebo in a double-blind trial. Adding vitamin D supplementation to the armamentarium of remedies for depression, although tempting, seems premature based on the evidence that has accumulated on this topic thus far.

Source of Funding and Conflicts of Interest: Dr. Shaffer received salary support and additional funding from the National Institutes of Health (Grant No. K23-HL112850, HL117832, HL084034, HL114924, HL088117) and the American Heart Association (Grant No. 12CRP8870004). The authors have no conflicts of interest to report.

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