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The Role of Vitamin D in the Prevention of Late-life Depression

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Abstract

BACKGROUND—In this article, we review current evidence regarding potential benefits of vitamin D for improving mood and reducing depression risk in older adults. We summarize gaps in knowledge and describe future efforts that may clarify the role of vitamin D in late-life depression prevention.

METHODS—MEDLINE and PsychINFO databases were searched for all articles on vitamin D and mood that had been published up to and including May 2015. Observational studies and randomized trials with 50 or more participants were included. We excluded studies that involved only younger adults and/or exclusively involved persons with current depression.

RESULTS—Twenty observational (cross-sectional and prospective) studies and 10 randomized trials (nine were randomized placebo-controlled trials [RCTs]; one was a randomized blinded comparison trial) were reviewed. Inverse associations of vitamin D blood level or vitamin D intake with depression were found in 13 observational studies; three identified prospective relations. Results from all but one of the RCTs showed no statistically significant differences in depression outcomes between vitamin D and placebo groups.

LIMITATIONS—Observational studies were mostly cross-sectional and frequently lacked adequate control of confounding. RCTs often featured low treatment doses, suboptimal post-intervention changes in biochemical levels of vitamin D, and/or short trial durations.

CONCLUSION—Vitamin D level-mood associations were observed in most, but not all, observational studies; results indicated that vitamin D deficiency may be a risk factor for late-life depression. However, additional data from well-designed RCTs are required to determine the impact of vitamin D in late-life depression prevention.

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Keywords

25-hydroxyvitamin D; cholecalciferol; mood; geriatric; epidemiology

BACKGROUND

PART 1: OVERVIEW

The problem of late-life depression and the need to identify risk factors and prevention strategies—Depression is the leading cause of disease burden in developed regions, responsible for between 5% and 8% of the total disability-adjusted life years (DALYs) in countries considered to be middle- or high-income(WHO, 2008). In the United States, the burden of depression in late-life is expected to increase, as the proportion of the population aged over 65 years continues to rise rapidly(Djernes, 2006; Mathers and Loncar, 2006). It is estimated that major depressive disorder (MDD) currently affects approximately 2% of older adults living in the community and 6.5–9% of elderly patients of primary care clinics(Beekman et al., 1999; Katon et al., 2003; Steffens et al., 2009). Clinically relevant depressive symptoms are even more common among older adults than MDD *per se:* between 8–20% of older adults in the community, and it has been estimated that over 30% of those seen in primary care settings, suffer from clinically relevant depressive symptoms (i.e., this may include minor depression, major depression or dysthymia)(Steinman et al., 2007). Despite its high prevalence, however, depression among older adults tends to be under-recognized and under-treated(Mulsant and Ganguli, 1999; Steinman et al., 2007; Unützer J et al., 2000). Importantly, although the incidence of depression and/or clinically relevant depressive symptoms is lower in older adults than in young and middle-aged persons, these observed rates (about 20–25 cases/1,000 person-years)(Luijendijk HJ et al., 2008; Norton MC et al., 2006; Pa!sson SP et al., 2001) are comparable to those of other major illnesses among older adults – such as cardiovascular disease(Ridker PM et al., 2005) and breast cancer(Cook NR et al., 2005).

Costs of depression include both direct medical costs and indirect costs resulting from reduced productivity(Greenberg et al., 2003). Depressive symptoms have been linked to impaired daily functioning(Beekman et al., 2002), an outcome that can translate into diminished work productivity among younger adults and still-working older adults alike. However, there are important ways in which costs of depression can become exaggerated among older compared to younger adults. First, adult caregivers of older adults with depression often experience high levels of caregiver burden and psychological distress(Martire LM et al., 2010; Scazufca et al., 2002), which may result in lost productivity among stressed carers – potentially further contributing to workplace-related costs. Second, as a large proportion of older adults are retired from work, healthcare costs make up much of the economic burden of late-life depression(Greenberg et al., 2003; Romeo et al., 2011). In addition to having a role in increasing disability and reducing overall well-being and quality of life, depression is associated with considerable costs among older adults(Beekman et al., 2002; Katon et al., 2003). In a study(Katon et al., 2003) of approximately 9,000 elderly patients recruited from primary care clinics, outpatient costs were 43% to 52% higher among depressed versus non-depressed elderly patients, even after adjustment for medical

comorbidities; the increased cost burden was observed broadly across health care, and only a small proportion of increased costs was specifically due to mental health or depression treatment. Notably, the authors did not find that there were costs differences among elderly patients with subthreshold depressive syndromes compared with those with DSM-IV-based depressive disorders – highlighting the importance for older persons of preventing occurrence of even milder depressive syndromes.

The development of strategies to prevent late-life depression is necessary to reduce its impact on disease burden and associated costs. If investigators are able to identify key risk factors for depression in older persons – especially those that are modifiable – then interventions can be targeted at high-risk groups, and a substantial amount of morbidity may be prevented(Okereke et al., 2013). Indeed, the combination of low recognition/under-treatment, high morbidity and disability burden, and high cost speaks strongly to an imperative for prevention of late-life depression(Reynolds, 2008).

Concepts of dietary/nutritional factors in depression risk—Given the strong need for late-life depression prevention, increasing attention has turned to readily addressable risk factors. Dietary modification may be a highly feasible means of intervention for reducing depression risk among older adults. The potential influence of diet on mood has emerged as a major research interest in recent years(Freeman MP, 2010; Soh N et al., 2009). A number of potential diet-related risk factors for late-life depression have been identified: examples range from micronutrient intakes and/or deficiencies to adherence to certain dietary patterns(Bertone-Johnson et al., 2011; Rienks et al., 2013; Skarupski KA et al., 2010; Skarupski et al., 2010; Skarupski et al., 2013; Vashum et al., 2014). The use of nutritional supplements has been gaining popularity in recent years as a possible method of improving mood outcomes, although intervention studies that have involved vitamin supplementation to prevent and/or treat depression have had inconsistent results(Lavretsky, 2009). As few randomized placebo-controlled trials (RCTs) that examine the relationship between vitamin D treatment and depressive symptoms in older adults have been carried out to date, the impact of vitamin D on late-life depression prevention remains unclear. Thus, as described in this review, while biologic evidence and observational data are compelling, further clinical trial evidence is needed to confirm whether or not this link exists in older populations. We conclude this review by discussing key attributes that future clinical trials should possess in order to provide a highly informative picture of the role of vitamin D in late-life depression prevention.

PART 2: BASICS OF VITAMIN D

Key concepts in vitamin D biology and relevance to late-life depression—Vitamin D refers to a group of closely related secosteroid hormones(Holick, 2007; Norman, 2008). Vitamin D is obtained as vitamin D2 or D3 from diet or supplements, or as D3 (cholecalciferol) from conversion of 7-dehydrocholesterol in the skin by ultraviolet B radiation(Holick, 2007; Norman, 2008), and is synthesized in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite(Dawson-Hughes et al., 2005; Giovannucci, 2005). 25(OH)D is hydroxylated to 1,25-dihydroxyvitamin D [1,25(OH)2D3]. 1,25(OH)2D3 is the metabolically active form of vitamin D(Holick, 2007; Norman, 2008).

1,25(OH)2D3 binds to vitamin D receptors (VDR), which can be found in more than 30 cell types throughout the body, including neurons(Holick, 2007). Although vitamin D is well known for its role in calcium homeostasis and bone metabolism, accumulating evidence suggests broader effects on health, including mood and depression(Giovannucci, 2009; Holick, 2007; Hoogendijk et al., 2008; Jorde et al., 2008; Norman, 2008; Norman et al., 1980; Palomer et al., 2008).

There is strong biologic plausibility for importance of vitamin D in mood health. Indeed, several mechanisms have been proposed linking vitamin D to mood(Berk et al., 2007; Bertone-Johnson, 2009; Cherniack et al., 2009). While a detailed review of the subject is outside the scope of the current work, and reviews of potential relevance of vitamin D to the brain and disorders of the nervous system have been provided by others(Fernandes de Abreu DA et al., 2009; Garcion et al., 2002; McCann JC and Ames BN, 2008), several key points merit mention. First, vitamin D receptors are widely distributed throughout the human brain(Eyles et al., 2005; Garcion et al., 2002), including limbic structures, such as the hippocampus, as well as prefrontal cortex regions that are likely involved in regulation of mood and affect(Langub, Herman et al. 2001). Second, consequences of vitamin D deficiency for brain health have been observed in animal models, and vitamin D deprivation has been shown to alter the brain function and/or behavior of rodents(McCann JC and Ames BN, 2008). Overall, findings from animal studies suggest that vitamin D may have influences on behavior(Burne et al., 2006; Kalueff et al., 2006; Kalueff et al., 2004; McCann JC and Ames BN, 2008). Finally, data from human studies offer possible biologic links between vitamin D and depression. A report from Kuningas and colleagues(Kuningas et al., 2009) suggested that VDR genetic variation may directly influence susceptibility to late-life depression. Among 563 participants of the Leiden 85-plus cohort, VDR genetic variation was associated with depressive symptoms; all participants were genotyped for the Cdx-2, FokI, BsmI, ApaI and TaqI polymorphisms, and carriers of ApaI variant-allele and of haplotype 1 (baT) had lower depressive symptoms. In another analysis, Timms et al.(Timms PM et al., 2002) found that low levels of vitamin D and VDR genetic variation were significantly associated with levels of inflammatory markers (MMP9, TIMP-1, CRP), and that reductions in these biomarkers followed vitamin D supplementation. Notably, inflammation is a well-known hypothesized mechanism for depression.(Maes M, 1999; Maes M et al., 1993; Maes M and Smith RS, 1998)

Of note, vitamin D deficiency is a common public health problem nationwide(Holick, 2004), and it has been associated with many adverse health outcomes(Dawson-Hughes et al., 2005; Giovannucci, 2005; Holick, 2004; Pittas et al., 2007). Vitamin D insufficiency and deficiency are on the rise in the U.S.: comparing data collected from 1988–94 with those from 2001–04, a recent study from the National Health and Nutrition Examination Survey (NHANES) demonstrated a marked decrease in mean serum 25(OH)D levels (from 75 nmol/L to 60 nmol/L), with a corresponding increase in the prevalence of 25(OH)D levels of less than 25 nmol/L (from 2% to 6%)(Ginde et al., 2009). However, because of differences in assay methods and population characteristics, there is no consensus on the cutoff values defining vitamin D insufficiency, deficiency or frank deficiency by 25(OH)D level. Nevertheless, vitamin D insufficiency has been previously reported to range from levels of 40 to 75 nmol/L (16 to 30 ng/mL); vitamin D deficiency is generally defined as levels <50

nmol/L (20 ng/mL)(Bischoff-Ferrari et al., 2006; Holick, 2007; Malabanan et al., 1998), and frank deficiency is considered as levels <25 nmol/L (10 ng/mL)(Cherniack et al., 2008).

Vitamin D deficiency is likely determined by many factors, including age, gender and race/skin pigmentation, as well as lifestyle, cultural and genetic factors(Holick, 2007). Notably, older adults may have heightened vulnerability to vitamin D deficiency though inadequate for a variety of reasons(Holick, 2007): 1) aging may decrease the ability of skin to produce the necessary precursors for vitamin D synthesis (reduction of 7-dehydrocholesterol in the skin can reduce vitamin D_3 synthesis by ~75% in a 70-year-old(Holick, 2007)); 2) older adults may have lower sun exposure (e.g., by spending more time indoors); 3) malabsorption of vitamin D may occur in older adults due to changes in adiposity (reduced fat absorption), digestive conditions or use of certain medications; 4) increased prevalence of renal function impairment in older persons may lead to reduced synthesis of 1,25-dihydroxyvitamin D; 5) older adults may consume diets that are poorer in vitamin D(Cherniack et al., 2008; Gloth et al., 1995; Holick, 2007).

In summary, there is emerging evidence from animal and human studies of direct relevance of vitamin D to brain health and functioning, including mood. The presence of vitamin D receptors widely throughout the brain, including in regions relevant to the neural circuitry of depression, suggests importance of this hormone. Overall, low levels of vitamin D may be predisposing factors for abnormal brain function and behavior, and older adults have higher susceptibility to low vitamin D levels.

PART 3: REVIEW OF EVIDENCE ON VITAMIN D AND LATE-LIFE DEPRESSION

METHODS—We conducted a systematic review of observational studies and randomized controlled trials in order to evaluate the relation of vitamin D to depression and associated mood outcomes in late-life. A search of the existing literature (up to May 2015) was performed using the MEDLINE and PsychINFO databases. Several MeSH and search terms related to vitamin D and the outcomes of interest were used, including “vitamin D,” “cholecalciferol,” 25-hydroxyvitamin D,” “depression,” “depressive disorder,” “mental health,” “mood,” “well-being,” “quality of life,” “aged,” and “elderly.” Because the focus of this review was on prevention, treatment clinical trials of depressed participants were not included. Studies that focused exclusively on young adults were not included in this review; thus, we excluded 2 trials that focused exclusively on college and university students (participant age range=18–30 years). We also excluded 3 randomized trials of vitamin D that all had fewer than 50 participants; these studies would not otherwise have met criteria for our review, as they included one treatment trial of 15 participants with seasonal affective disorder, a trial (n=44) that did not include any participants over age 43 years, and another trial (n=43), restricted to participants aged 18–65 years, that included very few older persons. To generate the summary of current/pending clinical trials of vitamin D and mood outcomes, we queried the ClinicalTrials.gov and ISRCTN trial registry databases.

RESULTS

Observational evidence regarding vitamin D and late-life depression: We identified 20 observational studies that met our inclusion criteria; 6 of these were prospectively designed,

and the remaining 14 were cross-sectional (Table 1). Three of the six prospective studies also reported the results of cross-sectional analyses from the baseline data; details of those analyses are presented further below under "*Prospective studies*". Thus, the results from a total of 17 cross-sectional and 6 prospective analyses are presented in the tables. The majority of the studies involved only older participants: these included 5 prospective cohort and 9 cross-sectional studies.

Cross-sectional studies

Clinical depression or mood disorder as outcomes: We identified three cross-sectional studies that focused on outcomes of depression or mood disorder diagnosis. First, in an analysis by Wilkins and colleagues(Wilkins et al., 2006) serum 25(OH)D concentrations were significantly related to mood disorder in a group of 80 adults aged 60 and older: participants with serum levels <10 ng/mL were over 11 times more likely to have a current mood disorder than those considered to be vitamin D-sufficient (≥20 ng/mL) (OR=11.69; 95% CI=2.04, 66.86). Second, in a study conducted by Lapid et al.(Lapid et al., 2013a), a similar association between serum vitamin D status and likelihood of depression was observed. In this sample of 1,618 older primary care patients, incrementally higher serum 25(OH)D levels were significantly related to decreased odds of depression diagnosis in multivariable-adjusted models (OR=0.990; 95% CI=0.983, 0.998). By contrast, a third study, also by Lapid and colleagues(Lapid et al., 2013b), examined serum vitamin D levels and various mood disorders among 141 psychiatric inpatients aged 65 and older and did not observe an association between 25(OH)D level and psychiatric disorders, including major depression. However, is it possible that this small, specialized sample of inpatients with high prevalence of major psychiatric and medical comorbidities may not have been adequately representative for estimation of the association between vitamin D level and late-life depression.

Depressive symptoms or scores as outcomes: We identified four cross-sectional studies that reported statistically significant associations between vitamin D and depressive symptoms. First, in a sample of 286 adults with Parkinson's disease(Peterson et al., 2013), serum 25(OH)D concentrations were significantly inversely associated with Geriatric Depression Scale (GDS) scores; when the analysis was restricted to participants without dementia, this association was still statistically significant. Second, Armstrong and colleagues(Armstrong et al., 2007) observed that in a sample of 75 adults with fibromyalgia, patients with serum 25(OH)D levels under 25 nmol/L had significantly higher Hospital Anxiety and Depression Scores (HADS) than those with concentrations of 25–50 nmol/L or 50+ nmol/L. Furthermore, results from two additional, larger studies that included data on several potential confounders also illustrated inverse associations between 25(OH)D and depressive symptoms. In the sixth Tromsø study(Kjaergaard et al., 2011) (N=10,086), Kjaergaard and colleagues found that those in the top quartile of 25(OH)D were significantly less likely to report depressive symptoms compared to those in the bottom quartile. Similarly, Hoang et al. reported that higher 25(OH)D measurements corresponded to a significantly lower odds of having CES-D scores ≥ 10 (OR for 10 ng/mL increase=0.92, 95% CI=0.87–0.97) in the Cooper Center Longitudinal Study(Hoang et al., 2011) (N=12,594). Although none of these

studies focused exclusively on older adults, the study populations were made up of mostly mid-life and older persons.

In contrast with the above findings of statistically significant associations, we identified three investigations(Brouwer-Brolsma et al., 2013a; Pan et al., 2009; Zhao et al., 2010) that reported initial inverse relations between vitamin D levels and depressive symptoms in crude analyses, but found that the associations were no longer significant after adjustment for key covariates. First, in a population-based sample of US adults (N=3,916), serum 25(OH)D was not related to moderate-to-severe depression (PHQ-9 score ≥ 10), after multiple demographic and lifestyle variables were taken into consideration in the models(Zhao et al., 2010). Similarly, in an adjusted analysis from the Survey in Europe on Nutrition and the Elderly (SENECA) study(Brouwer-Brolsma et al., 2013a) (N=593), which accounted for education level, body mass index, physical activity and other covariates, GDS-15 scores were not significantly lower in older individuals who were categorized in the middle or highest tertiles vs. the lowest tertile of 25(OH)D concentration (RR=0.73; 95% CI=0.51, 1.04 and RR=0.76; 95% CI=0.52, 1.11, respectively). Third, (Pan et al., 2009), Pan and colleagues did not find that adults aged 50–70 years (N=3,262) with plasma 25(OH)D levels in the highest tertile had a significantly reduced odds of prevalent depressive symptoms compared to those with concentrations in the bottom tertile (OR=0.75, 95% CI=0.53–1.06) – after potential confounders such as physical activity, income, and number of chronic diseases were included in the analysis.

Four additional studies examined cross-sectional relations of vitamin D levels to mental health-related quality of life (QOL) scores. First, vitamin D status was strongly associated with self-rated health, but not mental health-related QOL, in an analysis involving participants of the Longitudinal Aging Study Amsterdam (N=1,248)(Rafiq et al., 2014). While individuals in the low serum 25(OH)D (<25 nmol/L) group were 45% less likely to report good self-rated health than those in the >50 nmol/L group (OR= 0.55; 95% CI=0.35, 0.85), a difference in Short-Form Health Survey (SF-12) mental component scores was not observed in the multivariable-adjusted models. Similarly, Verhoeven and colleagues(Verhoeven et al., 2012) did not observe a link between vitamin D levels and overall mental health-related QOL in a cross-sectional analysis of 589 nursing home residents; however, it is worth noting that over 75% of the elderly patients enrolled were classified as vitamin D-deficient in this study. When more extreme contrasts of 25(OH)D levels were examined, however, differences in mental health-related quality of life variables were apparent in secondary analyses: participants with serum vitamin D levels in the lowest decile had a significantly greater odds of noting that they felt "down in the dumps" on the SF-36 than those with 25(OH)D concentrations in the highest decile (OR=3.10; 95% CI=1.21, 7.96); they were also more likely to report antidepressant use (OR=4.59; 95% CI=1.34, 15.79). Third, Brouwer-Brolsma and colleagues(Brouwer-Brolsma et al., 2013b) assessed both dietary intakes and serum levels of vitamin D in 127 frail and prefrail community-dwelling adults aged 65 and older enrolled in the ProMuscle Study. Neither measurement of vitamin D exposure was associated with depression in an adjusted analysis; however, this finding may have been related to the narrow range of vitamin D intake and relatively low levels of depressive symptoms that characterized this study population. Lastly, in a fourth study of mental QOL, a statistically significant association was observed between

dietary vitamin D and mental health-related QOL in the Iowa Women's Health Study (N=15,954)(Motsinger et al., 2012): middle-aged and older women whose daily intake was less than 400 IU had significantly lower mental health-related QOL scores on the SF-36 than women who consumed at least 400 IU of vitamin D per day. When physical activity was included as a covariate in the regression model, this association was attenuated, but a statistically significant inverse relation of vitamin D intake to mental health scale score remained. This last investigation stands can be contrasted with all the above-mentioned cross-sectional studies in that the vitamin D exposure variable was dietary intake; the other studies included measurement of 25(OH)D.

Finally, there were three cross-sectional analyses that featured the baseline results from prospective studies(Bertone-Johnson et al., 2011; Chan et al., 2011; Toffanello et al., 2014), detailed later in this review. All three of these analyses identified significant cross-sectional associations between vitamin D and depressive symptoms.

Summary: Although the majority of the aforementioned analyses suggest that a connection between vitamin D status and mood exists, the cross-sectional nature of these investigations prevents them from being highly informative regarding the possibility of protective temporal associations. Another limitation was lack of adjustment for important potential confounders. Physical activity is a major potential confounder of the relation between vitamin D exposure and depression; yet, it was a covariate in only seven(Brouwer-Brolsma et al., 2013a; Brouwer-Brolsma et al., 2013b; Hoang et al., 2011; Kjaergaard et al., 2011; Motsinger et al., 2012; Pan et al., 2009; Zhao et al., 2010) of the studies summarized above. An equal number(Hoang et al., 2011; Kjaergaard et al., 2011; Lapid et al., 2013a; Motsinger et al., 2012; Pan et al., 2009; Rafiq et al., 2014; Zhao et al., 2010) of the analyses adjusted for the presence of medical comorbidities. Notably, the studies that included information on at least one of these major potential confounders more often had null results than those that considered only gender, age, and/or season as covariates. Thus, it possible that significant reported associations in cross-sectional analyses may have arisen due to inadequate control confounding.

Prospective studies

Clinical depression or mood disorder as outcomes: Only one prospective study(May et al., 2010) specifically addressed the outcome of incident clinical diagnosis (clinical depression, defined by ICD-9 code); however, this is not surprising given the large sample sizes and person-years of observation required to detect associations between an exposure and incident disease(Cuijpers P, 2003). In this analysis involving 7,358 cardiovascular disease patients aged 50 and older(May et al., 2010), low baseline 25(OH)D measurements were related to incident depression diagnosis. Study participants with serum vitamin D levels under 15 ng/mL or between 16 and 30 ng/mL were significantly more likely to develop depression over an average follow-up period of 1.07 years than those classified as having "optimal" vitamin D level (>50 ng/mL): HR=2.70, 95% CI=1.35–5.40, and HR=2.15, 95% CI=1.10–4.21, respectively.

Depressive symptoms or scores as outcomes: The other longitudinal studies addressed the relationship between vitamin D and depression symptoms or scores as the outcomes. The

largest of these was the Women's Health Initiative Observational Study(WHI-OS)(Bertone-Johnson et al., 2011); the study sample was comprised of 81,189 postmenopausal women between the ages of 50 and 79 years. This study also differs from all five other prospective investigations in that the vitamin D exposure variable was dietary intake – not serum 25(OH)D level. At baseline, investigators observed that total vitamin D intake was inversely related to depressive symptoms; the association remained statistically significant after adjustment for multiple covariates. A multivariable-adjusted analysis of longitudinal data showed that women with vitamin D intakes of 400 IU or more per day from food sources alone had a significantly lower likelihood of having depressive symptoms after 3 years of follow-up than those whose daily vitamin D consumption was below 100 IU (OR=0.80; 95% CI=0.67, 0.95). Vitamin D intake from supplements alone was not found to be associated with incident depressive symptoms in the WHI-OS.

The four remaining prospective studies related 25(OH)D blood level as the vitamin D exposure to depressive symptoms. Two of these studies presented data from both the cross-sectional and prospective portions of the investigations. First, Toffanello and colleagues(Toffanello et al., 2014) did not observe a relation of baseline 25(OH)D levels to GDS scores after 4.4 years of follow-up in a multivariable-adjusted analysis of 1,675 adults aged 65 and above (the Progetto Veneto Anziani Study) – despite observing a significant cross-sectional association between low 25(OH)D and higher GDS scores at baseline in the women of this same sample. Second, in another study with an average 4-year follow-up period, a similar result was observed by Chan et al.(Chan et al., 2011): these investigators evaluated the vitamin D status and GDS scores of 629 community-dwelling older men and also included several confounders in the analyses; they found that while serum 25(OH)D level was related to depressive symptoms at baseline, it was not related to the outcome at the end of the 4-year follow-up period. A third study address the relation of 25(OH)D level to incident depressive symptoms over a slightly longer study period of 6 years: in the InCHIANTI cohort (N=954)(Milaneschi et al., 2010), there was an overall association between serum 25(OH)D below 50 nmol/L and greater 6-year risk of developing depression, compared to levels ≥ 50 nmol/L. Finally, Knippenberg and colleagues(Knippenberg et al., 2014) found that participants of the Southern Tasmanian Multiple Sclerosis Longitudinal Study (N=198) with high 25(OH)D concentrations (>80 nmol/L) had lower HADS scores over 2.3 years of follow-up than those with measurements of under 40 nmol/L ($\beta \geq -0.64$; 95% CI= −1.15, −0.13). Once self-reported sun exposure was added to the multivariate model, the effect of vitamin D was no longer statistically significant; however, as sun exposure is likely to be the main factor contributing to serum vitamin D levels, adjustment for this variable could be considered tantamount to self-adjustment and likely masked the association between 25(OH)D and depressive symptoms in the model.

Summary: Available data from prospective studies do not consistently show relations of vitamin D to subsequent risk of depression. Of the 6 prospective cohort studies reviewed, three showed evidence of an association between vitamin D and risk of incident depression or depressive symptoms; three did not, after multivariate adjustments. Of note, two of the prospectively-designed studies had shown that a cross-sectional association existed between low serum vitamin D level and depression, but that low vitamin D was not prospectively

related to development of depression in these cohorts; such findings highlight the importance of longitudinal follow-up in clarifying the role of vitamin D status in development of late-life depression. Finally, only one of the prospective studies specifically addressed relations of dietary intakes of vitamin D to depression (similarly, only 3 of 17 cross-sectional analyses addressed dietary vitamin D); thus, the literature appears inadequate at present for drawing conclusions regarding the relation of dietary vitamin D intake to depression outcomes.

Integration of the observational evidence on vitamin D and late-life depression: Data from 3 of 6 prospective studies and from 8 of 14 cross-sectional studies showed significant inverse associations between vitamin D blood or intake level and depression-related outcomes. The remaining observational studies did not show associations between vitamin D and depression outcomes.

Important limitations from the studies described above should be noted. First, the cross-sectional analyses lacked information on temporality, and cannot directly inform the relationship between vitamin D and subsequent development of late-life depression. Another consideration is that the heterogeneity in outcomes assessed – including major depressive disorder, depressive symptoms, and mental well-being – may explain some of the inconsistencies in the reviewed literature. Clinical diagnosis of major depression was the outcome of interest in four of these studies; in the others, depression screening and symptom instruments were used; the latter may increase opportunities for depression misclassification and also creates challenges for comparing findings across studies: although screening measures, such as the CES-D, GDS, etc., feature validated cutpoints for categorizing depression, it is not clear that these would correspond to the same proportions of individuals categorized as depressed across the different studies. Another issue that surfaced was the lack of variability in exposure or outcome that existed in some of the study populations. In the study by Verhoeven and colleagues(Verhoeven et al., 2012), nearly all participants were either vitamin D-deficient or insufficient, while in other cases(Chan et al., 2011; Toffanello et al., 2014) the number of deficient individuals may have been too low. For example, the investigation by Chan and colleagues(Chan et al., 2011) reported a vitamin D deficiency prevalence of only 6%, and in the cross-sectional analysis by Lapid et al.(Lapid et al., 2013b), there was high homogeneity in the clinical status among participants (all of whom were psychiatric inpatients). Thus, it is possible that these study samples did not have sufficient variation in vitamin D status and/or depression outcome to discern an association between the two variables.

Overall, the observational evidence in the available literature indicates that vitamin D deficiency may be a risk factor for depression. However, the variation in the specific cutpoint (e.g., <25 nmol/L, <50 nmol/L, <30 ng/mL, tertiles or quartiles of the sample distribution, etc.) used across studies to denote deficient or low vitamin D level renders direct comparisons between studies challenging. In all but two(Bertone-Johnson et al., 2011; Motsinger et al., 2012) of the observational studies, vitamin D status of participants in the studies reviewed was determined by serum concentration of 25(OH)D; the serum 25(OH)D level is a more accurate measure of vitamin D status because it incorporates vitamin D attained via both diet and exposure to sunlight(Ginde et al., 2009). However, there is lack of

consensus regarding how precisely a “low” or “deficient” vitamin D level is defined – e.g., at <50 nmol/L, as suggested by some experts(Holick, 2007), vs. at a lower level, as done by several studies in this review. Additional high-quality, large-scale prospective studies of older adults are needed to evaluate whether there are thresholds of vitamin D blood level or nutrient intake that are more consistently related to development of depression. High-quality RCTs must also be conducted in order to inspect the potential protective effects of vitamin D on the mental health of aging individuals.

Clinical trial evidence regarding vitamin D and late-life depression: Our review identified 10 clinical trials, to date, of vitamin D supplementation as a strategy specifically for depression prevention (Table 2). Six of the 10 existing trials specifically addressed depression or related mental health outcomes among persons aged 50 years and above; however, the remaining four did not focus exclusively on older adults. All of the trials utilized outcomes of depressive symptoms or mental health-related quality of life scores, rather than clinical diagnosis of depression or mood disorder based.

Studies including only older participants: Of RCTs that have focused exclusively on older participants, none has illustrated evidence of an effect of vitamin D treatment on the outcome of interest. First, Bertone-Johnson and colleagues(Bertone-Johnson et al., 2012) investigated the impact of daily vitamin D (400 IU) and elemental calcium (1,000 mg) supplementation on depression scores among 2,263 participants in the Women’s Health Initiative Calcium and Vitamin D (CaD) Trial; postmenopausal women who were given the supplements were no less likely to have depressive symptoms after two years of follow-up than women who received placebo (OR=1.16; 95% CI: 0.86, 1.56). Second, similar findings were observed an another trial that included only postmenopausal women (N=489): participants were given either calcitriol, hormone therapy, both, or placebo daily for 36 months(Yalamanchili and Gallagher, 2012); neither calcitriol (OR=1.15, 95% CI=0.43–3.11) nor combination treatment (OR=1.01; 95% CI=0.36–2.80) affected GDS scores compared with placebo. Third, Dumville and colleagues(Dumville et al., 2006) found no association between vitamin D consumption and mental component score of the SF-12 in a sample of 2,117 female primary care patients aged 70 and older; women who took 800 IU of vitamin D each day for 6 months did not have significantly different scores at the end of the study period than those taking placebo. Fourth, in the Vital D Study(Sanders et al., 2011) (N=2,258), which featured the longest follow-up period for mental health outcomes of trials focused on older women, individuals in the treatment group were given a single dose of 500,000 IU every year for three to five consecutive years. Comparing the vitamin D and placebo groups, there were no differences observed in any of the four questionnaire-based measures of QOL and mental well-being at any point during the 3–5 year follow-up period. Fifth, in another trial – this time, an RCT described by Kenny et al. (N=65)(Kenny et al., 2003) that included only community-dwelling older men – there were again no significant changes in mental health-related QOL among participants assigned to 1,000 IU/d vitamin D for six months vs. control group participants. Finally, a large-sample trial that included both genders (men and women aged 70 and older who had sustained a low-trauma fracture within the previous decade) showed no association between daily supplement treatment and

QOL(Grant et al., 2005); patients in this study (N=5,292) had received either 800 IU of vitamin D, 1,000 mg of calcium, a combination of both, or placebo for at least 24 months.

Studies including younger and older participants: Four RCTs involved study samples that contained both younger and older adults; these studies all utilized moderate to high doses of vitamin D. First, in a study reported by Kjaergaard and colleagues(Kjaergaard et al., 2012), a subset of Tromsø study participants aged 30–75 with low serum 25(OH)D levels (N=230) were administered a weekly high dose (40,000 IU) of vitamin D; the treatment did not affect depression scores after six months of follow-up. In contrast with the other trials that included both older and younger persons, this study was able to stratify by later-life vs. younger ages (categorized as aged ≥ 54 years vs. younger, by the authors); however, analyses showed no differences in the findings among older vs. younger participants. By contrast, a trial described by Jorde et al., which included 441 overweight and obese adults aged between 21 and 70 years, showed a significant effect of supplementation on depressive symptoms(Jorde et al., 2008). Those who received a treatment of either 20,000 IU or 40,000 IU of vitamin D each week for one year experienced a significant reduction in depressive symptoms (greater decrease in Beck Depression Inventory (BDI) 1–13 subscale scores), compared with those given placebo pills; although the study included older persons in the sample, it did not report stratified results for later-life participants. In a third trial(Arvold et al., 2009), 100 primary care patients with 25(OH)D measurements of 10–25 ng/mL were given either 50,000 IU of vitamin D or a placebo weekly for just eight weeks (the investigators treated patients found to have severe vitamin D deficiency (defined as 25[OH]D <10 ng/mL) in an unblinded fashion). Participants assigned to placebo appeared to have a greater increase in depression scores (0.55 points; 95% CI=−0.3, 1.4) over the study period than patients treated with vitamin D (0.12 points; 95% CI=−0.8, 1.1), but this was not statistically significant. However, the very short treatment duration is an important potential limitation of this study. Finally, a trial reported by Vieth and colleagues(Vieth et al., 2004) involved a vitamin D intervention to mostly middle-aged adults (N=64) who had serum 25(OH)D levels of less than 61 nmol/L during the previous summer, as these individuals were expected to be vitamin D deficient by the winter. Subjects received either 4,200 IU of vitamin D per week (600 IU/day) or 28,000 IU of vitamin D per week (4000 IU/day) for six months, with a subset of participants continuing their treatment for a full year. At the time of the first follow-up questionnaire, well-being scores in the high dose group had improved more than those in the lower dose group; after one year of supplementation, however, the high dose treatment was not observed to have a significantly greater impact on well-being. Of note, because the entire study population was vitamin D-deficient, the investigators ensured that all participants were given, at minimum, an adequate weekly dose of vitamin D and there was no placebo condition; therefore, it was not possible to determine how vitamin D supplementation influenced well-being compared to inert placebo.

Integration of the evidence from trials of vitamin D and late-life depression: As with the evidence from observational studies, the existing literature on RCTs involving vitamin D for depression prevention or mood improvement features important limitations. Some of these issues include: relatively small sample sizes (prevention studies for mental disorders tend to require high sample sizes for adequate statistical power(Cuijpers P, 2003)), low doses and/or

short treatment durations – three factors that may have prevented investigators from detecting significant differences between the treatment and control groups. Regarding adequacy and duration of treatment exposure, only two of the 10 trials reviewed featured high vitamin D doses for long durations (i.e., average treatment duration greater than 2 years). Another potential limitation was that various self-report measures on aspects of well-being – rather than specific scales for depression or clinical diagnosis of depression – were often used to assess outcomes. While some of these measures have high sensitivity and specificity and have been validated for detecting depression and clinically relevant depressive symptoms among older adults(Okereke, 2015), others may be less precise for characterizing depression status.

Finally, a substantive issue to consider is the incorporation of treatment-related biomarkers into the clinical trial designs. The mean attained post-intervention vitamin D blood level is a critical factor in assessing the likelihood of a given trial to be able to detect benefits of vitamin D. The dose-response curve for 25(OH)D blood level with vitamin D intake appears non-linear: the rise in blood levels is tapered at higher levels of intake(Aloia et al., 2008). Extrapolation of the data from Aloia et al.(Aloia et al., 2008) indicates that it would require a supplement dose equivalent to 2000 IU/d to achieve a mean 25(OH)D of ~80–90 nmol/L in older adults(Aloia et al., 2008; Bischoff-Ferrari et al., 2006). Yet, a value of 75 nmol/L is the reported threshold for health benefits in a recent meta-analysis(Bischoff-Ferrari et al., 2006). Thus, RCT designs that did not provide older adults with doses near 2000 IU/d, or that failed to illustrate post-intervention attained blood 25(OH)D levels that are plausible for inducing health benefits, may not be sufficient to test a hypothesis of late-life depression prevention. Three of the 10 trials reviewed did not report 25(OH)D at baseline vs. at the completion of the study among the participants(Bertone-Johnson et al., 2012; Dumville et al., 2006; Yalamanchili and Gallagher, 2012); although a cross-sectional substudy of 448 women in the WHI-CaD showed that 25(OH)D levels in the treatment group were 28% higher than those in the control group, such a difference is clearly not consistent with an increase in 25(OH)D that would approach the levels describe above – a finding that is somewhat expected, given the low treatment dose of 400 IU/d. The seven other trials reported pre- and post-treatment 25(OH)D measures. Four of these studies(Arvold et al., 2009; Jorde et al., 2008; Kjaergaard et al., 2012; Vieth et al., 2004) were able to demonstrate changes in post-intervention 25(OH)D such that levels were substantially higher with vitamin D treatment and were in the range of plausible health effects; interestingly, of these four, the trial that featured the longest duration (12 months) and used an established depression measure (Beck Depression Inventory) illustrated significant benefit of vitamin D. Three of the trials(Grant et al., 2005; Kenny et al., 2003; Sanders et al., 2011) with pre-/post biomarkers showed statistically significant increases in hydroxyvitamin D levels, but the changes associated with treatment were not large. For example, in the report by Sanders et al.(Sanders et al., 2011), despite short-term (1- and 3-month) increases in levels, the 12-month post-dose levels were ~70 nmol/L in the active treatment group – below the likely threshold for health effects. Similarly, while Grant et al.(Grant et al., 2005) found that vitamin D levels had increased by 9.7 ng/mL vs. 3.1 ng/mL in the vitamin D vs. placebo groups, the baseline 25(OH)D was only 15.2 ng/mL among the subset of 60 participants with these biomarkers; thus, it does not

appear that supplementation achieved increases that would have placed most participants within optimal 25(OH)D ranges.

PART 4: SUMMARY AND FUTURE DIRECTIONS

Observational data generally suggest that vitamin D deficiency is a risk factor for late-life depression. However, there is lack of consensus regarding the precise definition of a deficient vitamin D level, and further study is needed to determine the thresholds of vitamin D blood level or nutrient intake that are related to depression risk. Moreover, the role of vitamin D supplementation – among those with or without biochemical deficiency – for the prevention of depression or maintenance of positive mood in older adults has not been settled. Although the available data from randomized trials does not appear to support the use of vitamin D for prevention of late-life depression, further evidence from well-designed, adequately-powered trials is required before any conclusions can be made. Fortunately, several ongoing randomized controlled trials may help to inform the question of whether vitamin D supplementation can actually reduce the risk of depression or improve mood in late-life. These trials are summarized in Table 3. While not all of these studies were specifically designed to detect effects of vitamin D on mood outcomes, they all include relevant measures of depression. Of note, the two trials with the largest sample sizes (Brigham and Women's Hospital; University of Zurich) both utilize a high dose of vitamin D (2000 IU daily), have long mean treatment durations (3 years and 5 years) and incorporate measurement of 25(OH)D levels at baseline/follow-up. Thus, future results from these RCTs, as well as potential meta-analyzed estimates from all of the trials, are poised to provide more definitive evidence regarding the role of vitamin D in late-life depression prevention and mood enhancement.

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Highlights

- Preventing late-life depression is a priority, and diet may be a useful strategy.
- Low vitamin D is related to adverse brain and behavior outcomes in animal models.
- Observational data suggested vitamin D-mood links but were mostly cross-sectional.
- Vitamin D supplementation was related to better later-life mood in only one RCT.
- RCT limitations: low doses, suboptimal change in vitamin D levels, short durations.

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Table 1

Observational Studies – Vitamin D and Late-life Depression

Cross-sectional Analyses						
Author	**Study Population**	**N**	**Exposure of Interest**	**Duration**	**Outcome measure**	**Results**
Armstrong et al. 2006	Adults with fibromyalgia aged 21–75 y	75	Serum 25(OH)D concentration	N/A	HADS[1]	Participants that were considered to be vitamin D deficient (25(OH)D < 25 nmol/L) had significantly higher HADS scores than those with serum vitamin D levels of 25–50 nmol/L or 50+ nmol/L (p<0.05).
Wilkins et al. 2006	Adults aged ≥ 60 y, either nondemented or with mild AD[2]	80	Serum 25(OH)D concentration	N/A	Depressive symptoms inventory	Vitamin D status was observed to be significantly associated with mood: mood disorders were more prevalent in the vitamin D deficient group (<10 ng/mL) than in the highest serum 25(OH)D group (≥ 20 ng/mL) (OR=11.69, 95% CI=2.04–66.86, p=0.022).
Pan et al. 2009	Community-dwelling adults aged 50–70 y	3262	Plasma 25(OH)D concentration	N/A	CES-D[3]	Prevalence of depressive symptoms was lower in the top vs. bottom tertile of 25(OH)D concentrations (7.2% vs. 11.1%. However, there was no significant association between 25(OH)D and depressive symptoms after physical activity, BMI, geographic location, and number of chronic diseases were included in the regression model (OR=1.35, 95% CI=0.94–1.96, p for trend=0.075).
Zhao et al. 2010	Population-based sample of US adults ≥ 20 y	3916	Serum 25(OH)D concentration	N/A	PHQ-9[4]	After the analysis was adjusted for multiple demographic and lifestyle variables, serum 25(OH)D was not found to be significantly related to moderate-to-severe depression (PHQ-9 score ≥ 10) in this sample (OR Q4 vs. Q1=0.89, 95% CI=0.45-1.79, p for trend=0.62).
Bertone-Johnson et al. 2011	Postmenopausal women (aged 50–79 y) in the Women's Health Initiative cohort	81189	Daily vitamin D intake via FFQ[5] and/or vitamin D supplements	N/A	Burnam scale	Women with a vitamin D intake of ≥ 800 IU/day had a lower odds of prevalent depressive symptoms than women who reported intake of under 100 IU vitamin D/day (OR=0.79, 95% CI=0.71–0.89, p for trend<0.001).
Chan et al. 2011	Community-dwelling men aged ≥ 65 y	629	Serum 25(OH)D concentration	N/A	GDS-15[6]	Men who had serum 25(OH)D levels in the highest quartile were significantly less likely to have depression (GDS-15 ≥ 8) than those in the lowest quartile of vitamin D status (OR=0.46, 95% CI=0.22–0.98, p for trend=0.004).
Hoang et al. 2011	Patients of the Cooper Clinic aged 20–90 y	12594	Serum 25(OH)D concentration	N/A	CES-D	Logistic regression analyses revealed that higher 25(OH)D levels corresponded to a significantly lower likelihood of current

Cross-sectional Analyses						
Author	**Study Population**	**N**	**Exposure of Interest**	**Duration**	**Outcome measure**	**Results**
						depressive symptoms (OR for 10 ng/mL increase=0.92, 95% CI=0.87–0.97, p=0.02).
Kjærgaard et al. 2011	Participants of the sixth Tromsø study aged 30–87 y	10086	Serum 25(OH)D concentration	N/A	Hopkins Symptoms Checklist 10	Data for smokers and nonsmokers were analyzed separately. Smokers (OR=0.59, 95% CI=0.39–0.89, p trend=0.003) and nonsmokers (OR=0.74, 95% CI=0.58– 0.95, p for trend=0.01) with 25(OH)D levels in the top quartile were significantly less likely to report depressive symptoms than those in the lowest quartile.
Motsinger et al. 2012	Women aged ≥ 55 y in the Iowa Women's Health Study	15954	Vitamin D intake, determined by FFQ	N/A	SF–36[7]	A significant positive association was found between vitamin D intake and mental health quality of life score (p<0.001). Women whose daily vitamin D intake was less than 400 IU had significantly lower mental health QOL[8] scores than women with intakes of 400–799 IU/day or ≥ 800 IU/day.
Verhoeven et al. 2012	Nursing home residents aged ≥ 65 y	589	Serum 25(OH)D concentration	N/A	SF-36	Individuals with serum vitamin D concentrations in the lowest decile were significantly more likely to report feeling "down in the dumps" on the SF-36 than those with concentrations in the highest decile (OR=3.10, 95% CI=1.21–7.96, p=0.019). They were also more likely to be using antidepressants (OR=4.59, 95% CI=1.34–15.79, p=0.016).
Brouwer-Brolsma et al. 2013	Frail or prefrail participants of the ProMuscle Study aged ≥ 65 y	127	Serum 25(OH)D concentration, vitamin D intake	N/A	CES-D	No association was observed between serum 25(OH)D and depression score. Vitamin D intake was also not found to be related to depression.
Brouwer-Brolsma et al. 2013	Adults aged 70–75 participating in the SENECA[9] study	593	Serum 25(OH)D concentration	N/A	GDS-15	Participants with serum 25(OH)D concentrations in the highest tertile had lower depression scores than those in the lowest tertile (RR=0.76, 95% CI=0.52–1.11), but the difference was not significant (p for trend=0.16).
Lapid et al. 2013	Primary care patients aged ≥ 60 y	1618	Serum 25(OH)D concentration	N/A	Depression diagnosis	Logistic regression analyses showed that serum 25(OH)D levels were inversely associated with depression (OR=0.990, 95% CI=0.983–0.998, p = 0.012). 25(OH)D levels were significantly lower in participants who had been diagnosed with depression than in those in the non- depressed group (p=0.002).
Lapid et al. 2013	Psychiatric inpatients aged ≥ 65 y	141	Serum 25(OH)D concentration	N/A	Depression diagnosis	Serum 25(OH)D concentrations were not found to be associated with major depressive disorder (OR=0.989, 95% CI=0.96–1.02, p=0.44). There were also no associations

Cross-sectional Analyses						
Author	**Study Population**	**N**	**Exposure of Interest**	**Duration**	**Outcome measure**	**Results**
						found between vitamin D concentrations and other psychiatric diagnoses, such as anxiety or bipolar disorder.
Peterson et al. 2013	Adults (mean age=68) with Parkinson's Disease	286	Serum 25(OH)D concentration	N/A	GDS	Serum 25(OH)D concentrations were inversely related to depression scores in the sample ($\beta \geq -0.170$, p=0.015). When including only participants without dementia in the analysis, the association between vitamin D levels and depression was still significant ($\beta \geq -0.205$, $p \geq 0.0083$).
Rafiq et al. 2014	Adults aged ≥ 65 y in the Longitudinal Aging Study Amsterdam	1248	Serum 25(OH)D concentration	N/A	SF-12, self-rated health question	Participants with the lowest levels of serum 25(OH)D (<25 nmol/L) had significantly lower SF-12 physical component scores than those who had serum 25(OH)D concentrations of 50 nmol/L or greater (−2.6, 95% CI≥ −5.1 to −0.2, p≥ 0.035); however, there were no significant differences in SF-12 mental component scores according to 25(OH)D level. Individuals in the <25 nmol/L group were less likely to have good self-rated health than those in the >50 nmol/L group (OR=0.55, 95% CI=0.35–0.85, p=0.008).
Toffanello et al. 2014	Adults aged ≥ 65 y in the Progetto Veneto Anziani	1675	Serum 25(OH)D concentration	N/A	GDS	Women with lower levels (<50 nmol/L) of serum 25(OH)D had higher GDS scores than those with concentrations of > 75 nmol/L (p for trend=0.02), but there was no significant association between vitamin D status and depression scores in men.
Prospective Analyses						
Author	**Study Population**	**N**	**Exposure of Interest**	**Duration**	**Outcome measure**	**Results**
May et al. 2010	Adults aged ≥ 50 y with cardiovascular disease	7358	Serum 25(OH)D concentration	1.07 years (average)	Depression diagnosis	Baseline 25(OH)D levels were characterized as very low (≥ 15 ng/mL), low (16–30 ng/mL), normal (31–50 ng/mL) or optimal (>50 ng/mL). Individuals with very low or low 25(OH)D levels were significantly more likely to have developed depression than participants with optimal levels (HR=2.70, 95% CI=1.35–5.40, p=0.005, and HR=2.15, 95% CI=1.10–4.21, p=0.03, respectively).
Milaneschi et al. 2010	Adults aged ≥ 65 y in the InCHIANTI study	954	Serum 25(OH)D concentration	6 years	CES-D	The two depression outcomes that were assessed were: 1) increase in continuous CES-D score and 2) risk of developing depressive mood, defined as CES-D ≥ 16. Compared with those who had 25(OH)D ≥ 50 nmol/L, women with lower 25(OH)D levels had greater increases in CES-D scores at 3-year (2.1 pts, p=0.02) and 6-year (2.2 pts, p=0.04) follow-up

Cross-sectional Analyses						
Author	**Study Population**	**N**	**Exposure of Interest**	**Duration**	**Outcome measure**	**Results**
						assessments. These women were also significantly more likely to experience incident depressive symptoms over 6 years (HR=2.0, 95% CI=1.2– 3.2, p=0.005) than women who were not vitamin D deficient. While a significantly greater increase in CES-D scores was observed among men in the low vitamin D group vs. those in the 25(OH)D ≥ 50 nmol/L group after 3 years (1.9 pts, p = 0.01), this difference was not significant at 6-year follow-up (1.1 pts, p=0.20). The association between vitamin D group and 6-year risk of depressive symptoms in men also did not reach significance (HR=1.6, 95% CI= 0.9–2.8, p=0.1).
Bertone-Johnson et al. 2011	Postmenopausal women (aged 50–79 y) in the Women's Health Initiative cohort	81189	Daily vitamin D intake via FFQ and/or vitamin D supplements	3 years	Burnam scale	Women who had a vitamin D intake of ≥ 400 IU/day from food sources alone were 20% less likely to develop depressive symptoms than those with an intake of <100 IU/day from food sources (OR=0.80, 95% CI=0.67–0.95, p for trend <0.001). No association was found between vitamin D supplementation and depressive symptoms.
Chan et al. 2011	Community-dwelling men aged ≥ 65 y	629	Serum 25(OH)D concentration	4 years	GDS-15	No association was found between baseline serum 25(OH)D levels and incident depression (p for trend=0.816).
Knippenberg et al. 2014	Adults aged 21–77 y with multiple sclerosis participating in the Southern Tasmanian Multiple Sclerosis Longitudinal Study	198	Serum 25(OH)D concentration, sun exposure	2.3 years	HADS	Participants with serum 25(OH)D of >80 nmol/L had lower depression scores than those with concentrations of < 40 nmol/L (β≥ −0.64, 95% CI= −1.15 to −0.13, p for trend=0.03). The association was no longer significant after reported sun exposure was included in the analysis (p=0.11).
Toffanello et al. 2014	Adults aged ≥ 65 y in the Progetto Veneto Anziani	1675	Serum 25(OH)D concentration	4.4 years	GDS	No association between baseline serum 25(OH)D concentrations and incident depressive symptoms was found in women or men.

[1] Hospital Anxiety and Depression Scale

[2] Alzheimer's disease

[3] Center for Epidemiologic Studies Depression Scale

[4] Patient Health Questionnaire

[5] Food Frequency Questionnaire

[6] Geriatric Depression Scale

[7] Short Form Health Survey

[8] Quality of life

[9] Survey in Europe on Nutrition and the Elderly

Table 2

Published Clinical Trials – Vitamin D and Late-life Depression

Author	Study Population	N	Intervention	Duration	Outcome measure	Results
Kenny et al. 2003	Community-dwelling men aged 65–87 y	65	1000 IU vitamin D/day	6 months	Medical Outcome Survey Short-form 8	Although there was a significant correlation found between 25(OH)D levels and mental health scores at baseline (r=0.30, p=0.025), there was no significant difference in the 6-month change in mental component scores in the vitamin D vs. placebo groups.
Vieth et al. 2004	Middle-aged adults with serum 25(OH)D < 61 nmol/L during summer	64	Either 4000 IU or 600 IU vitamin D/day	6 months – 1 year	Well-being questionnaire	This was a randomized, blinded comparison study of active treatment groups; there was no inert placebo group. In the first part of this two-step study, participants in the higher dose vitamin D group had a greater improvement in well-being scores than participants who were receiving the low dose, though this difference was not significant (p=0.072). After one year of supplementation, however, the higher dose was not observed to have greater effect on well-being scores compared with the low dose.
Grant et al. 2005	Adults aged ≥ 70 y who had had a low-trauma fracture during the past 10 years	5292	800 IU vitamin D/ day, 1000 mg calcium/day, or both	24–62 months (24 months for QOL outcomes)	SF-12, EQ-5D[1]	At 4-month and 24-month follow-up assessments, there were no significant differences in the quality of life outcomes in any of the treatment groups.
Dumville et al. 2006	Female primary care patients aged ≥ 70 y	2117	800 IU vitamin D/day	6 months	Mental Component Summary (MCS) score of SF-12	The average MCS scores of the supplement and placebo groups were not significantly different after 6 months of follow-up, adjusting for baseline scores (p=0.262).
Jorde et al. 2008	Overweight and obese adults aged 21–70 y	441	40,000 IU or 20,000 IU vitamin D per week	12 months	BDI[2]	The two vitamin D groups combined had a significantly greater decrease in average BDI 1–13 subscale scores over the one-year period than the placebo group (p<0.05). BDI scores in the placebo group did not change significantly during the study period.
Arvold et al. 2009	Adult patients (mean age=59 y) with mild to moderate vitamin D deficiency (25(OH)D of 10–25 ng/mL)	100	50,000 IU vitamin D per week	8 weeks	Self-reported depressive symptoms (scale of 0–10) SF-12, General Health	The placebo group experienced a greater increase in depressive symptoms than the vitamin D group (0.55 vs. 0.12 points); however, this difference was not statistically significant.
Sanders et al. 2011	Women aged ≥ 70 y in the Vital D study	2258	500,000 IU vitamin D once a year	3–5 years	Questionnaire, WHO Well-Being Index, Patient Global Impression- Improvement scale	No significant differences in GHQ-12, SF-12, Patient Global Impression-Improvement scale or WHO Well- Being questionnaire scores were found between the vitamin D and placebo groups at any point during the follow-up period.
Bertone- Johnson et al. 2012	Postmenopausal women (aged 50–79) in the Women's Health Initiative Calcium and Vitamin D (CaD) Trial	2263	1000 mg elemental calcium and 400 IU vitamin D/day	2 years	Burnam scale, antidepressant use	The mean change in Burnam scale score in the treatment group was not significantly different than that of the placebo group. Women receiving the supplements were not significantly less or more likely to have depressive symptoms at follow-up than women who received placebo (OR=1.16, 95% CI: 0.86–1.56).
Kjærgaard et al. 2012	Participants of the sixth Tromsø study aged 30– 75 y	230	40,000 IU vitamin D per week	6 months	BDI, HADS, MADRS[3]	The 6-month change in depression scores in the high-dose vitamin D group was not significantly different than that of

Author	Study Population	N	Intervention	Duration	Outcome measure	Results
	with low (<55 nmol/L) serum 25(OH)D levels					the placebo group; the scores in both groups decreased over the study period.
Yalamanchili et al. 2012	Postmenopausal women aged 65–77 y	489	0.625 mg equine estrogens/day, 0.25 g calcitriol 2x/day, or both	36 months	GDS	There were no significant differences in changes in GDS scores among the active treatment groups compared to the placebo group. There was no difference in depression outcome for calcitriol active treatment vs. placebo (OR=1.15, 95% CI=0.43–3.11, p=0.772).

[1] European Quality of Life

[2] Beck Depression Inventory

[3] Montgomery–Asberg Depression Rating Scale

Table 3

Ongoing Randomized Controlled Trials – Vitamin D and Late-life Depression

Trial Name/Sponsor Institution/ ClinicalTrials.gov ID	Years	Age range	Enrollment (N)	Treatment(s)	Duration	Depression outcome measure(s)	Primary outcome(s) of trial
VITAL-DEP: Depression Endpoint Prevention in the VITamin D and OmegA-3 TriaL/Brigham and Women's Hospital/NCT01696435	2010–2017	≥ 50	25875	2000 IU vitamin D3/day, 840 mg omega-3 fatty acids/day, or both (factorial design)	5 years	Depression diagnosis, PHQ	Depression, change in mood scores
Vitamin D Supplementation in Polymorphic Light Eruption (VitD-PLE_2012)/Medical University of Graz/NCT01595893	2012–2015	18–75	36	40000 IU vitamin D3 per 70 kg body weight, administered twice 2 weeks apart	8 months	HADS	Polymorphic Light Eruption test score
DO-HEALTH: Vitamin D3 - Omega3 - Home Exercise - Healthy Ageing and Longevity Trial/ University of Zurich/ NCT01745263	2012–2017	≥ 70	2152	2000 IU vitamin D3/day, 1 g omega-3 fatty acids/day, home exercise programs, or combination (factorial design)	3 years	GDS	Non-vertebral fractures, functional decline, blood pressure, cognitive decline, rate of infections
Sunshine 2 Study for Women with Diabetes/Loyola University/ NCT01904032	2013–2017	≥ 21	180	50000 IU vitamin D3/ week or 5000 IU vitamin D3/week (no inert placebo)	6 months	CES-D	Depressive symptoms
Dose-dependent Effects of Vitamin D on Bone Health/University of Calgary/NCT01900860	2013–2018	55–70	300	400, 4000, or 10000 IU vitamin D/day (no inert placebo)	3 years	Depression symptom measure (BDI or PHQ), SF-36	Bone strength
Vitamin D's Effect on Physical Performance in the Elderly/ University of Miami/ NCT02066441	2014–2015	≥ 55	130	4000 IU vitamin D/day	6 months	BDI	Serum 25(OH)D, parathyroid hormone, osteocalcin, CTX (carboxy-terminal collagen crosslinks), C-reactive protein
Vitamin D Supplementation in Patients With COPD (PRECOVID)/VU University Medical Center/NCT02122627	2014–2017	≥ 40	240	16800 IU vitamin D/week	1 year	CES-D, SF-12	Exacerbation rate of COPD