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Review

Adverse health outcomes in vitamin D supplementation trials for depression: A systematic review

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ABSTRACT

Background: Vitamin D deficiency is a universal risk factor for adverse health outcomes. Since depression is consistently associated with low vitamin D levels as well as several adverse health outcomes, vitamin D supplementation may be especially relevant for depressed persons. This review examines the potential benefits of vitamin D for (somatic) health outcomes in randomised controlled supplementation trials for depression.
Method: Systematic literature search to assess whether adverse health outcomes, such as frailty, falls, or cognitive functioning, were included in vitamin D supplementation trials for depression, and whether these outcomes were affected by supplementation. The revised Cochrane tool for assessing risk of bias in randomised trials was used.
Results: Thirty-one trials were included. Adverse health outcomes were considered in five studies. Two studies reported some beneficial effect on an adverse health outcome.
Conclusions and implications: While depressed persons are at increased risk of vitamin D deficiency, supplementation trials hardly addressed the common negative health consequences of low vitamin D levels as secondary outcome measures. Well-designed trials of the effects of vitamin D supplementation in late-life depression should explore whether adverse health outcomes can be prevented or stabilised, and whether depression benefits from this improvement.

1. Introduction

A poor vitamin D status is considered a universal risk factor for adverse health outcomes. Depending on the presence of other risk factors, vitamin D deficiency may lead to the onset of several diseases (De Borst et al., 2011). Importantly, almost half of the persons older than 65 years have a vitamin D deficiency (Oosterwerff et al., 2011), which has led to many prevention guidelines on vitamin D supplementation (Pludowski et al., 2018).

Vitamin D supplementation may be particularly relevant for depressed persons. Vitamin D deficiency and depression often occur together, as consistently reported in observational studies (Anglin et al., 2013). Vitamin D deficiency in depression is at least partly a consequence of negative lifestyle effects of depression, such as limited sun exposure and inadequate diet (Jovanova et al., 2017). A causal role is also hypothesised, based on a dose-response relationship between lower vitamin D levels and the incidence of late-life depression (Li et al., 2019), and plausible mechanisms such as the neurotrophic effects of vitamin D and its role in the synthesis of neurotransmitters (Eyles et al., 2013; Garcion et al., 2002; Humble, 2010). Nonetheless, results of randomised controlled trials (RCTs) evaluating vitamin D supplementation for depression are inconsistent, partly due to heterogeneity of the present studies regarding the assessment of depression, vitamin D status, and vitamin D supplementation regime. One overall meta-analysis of RCTs on vitamin D supplementation in depression demonstrated no effect (Gowda et al., 2015). Nevertheless, a beneficial effect of vitamin D on depression was observed in two smaller meta-analyses of four studies limited to clinically depressed persons (Vellekkatt and Menon, 2019) and seven studies without 'biological flaws' (such as inclusion of participants without vitamin D deficiency, or inadequate vitamin D supplementation strategies) among persons with depressive symptoms (Spedding, 2014).

Depressive disorder is associated with the onset of a poor health status and several chronic diseases (Penninx et al., 2013). Therefore, vitamin D supplementation may be particularly relevant for the prevention of these adverse health outcomes. Adverse health outcomes in

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depression that have also been associated with low vitamin D levels are frailty, poor cognitive functioning, falling, and physical disability (Alexopoulos, 2005; Autier et al., 2014; Iaboni and Flint, 2013; Marcos-Pérez et al., 2020). Recently, we found that among depressed older persons, a decrease in vitamin D levels over a two-year follow-up was not associated with a change in depressive symptom severity whereas it was associated with frailty and exhaustion (Van den Berg et al., 2021). Vitamin D supplementation may thus be relevant to improving the somatic health status among depressed persons (selective prevention).

Therefore, the aim of the present systematic review is to explore whether vitamin D supplementation trials in depression have evaluated adverse health outcomes secondary to depression, and whether vitamin D supplementation improves adverse health outcomes related to vitamin D deficiency and depression.

2. Methods

2.1. Search strategy

A systematic search was conducted in the electronic databases of PubMed, EMBASE, and PsycInfo, last on 23 November 2020. For each database, a comprehensive search strategy was developed in consultation with a librarian. We combined search terms on depression, vitamin D, study design (randomised controlled trials/reviews), and their derivatives and synonyms (see supplemental information for the complete search strategy). Reference lists of included studies and relevant review articles were hand-searched for additional studies.

This systematic review was performed according to the PRISMA guidelines (Moher et al., 2015). The protocol was registered at PROSPERO (www.crd.york.ac.uk/prospero; registration number CRD42020215912).

2.2. Eligibility

Eligible studies were peer-reviewed and published randomised clinical trials of vitamin D supplementation with the main focus on depression or depressive symptoms. Studies in English or Dutch were eligible. No restrictions regarding the year of publication were applied.

Studies in adult populations in different settings (community samples or clinical populations, i.e. in hospitals, mental health care institutions and nursing homes) were included. Given the low prevalence of adverse health outcomes in younger age groups, studies performed in children/adolescent populations or exclusively in adults under 40 years were non-eligible. Studies among participants with primary diagnoses other than depression, i.e. schizophrenia or dementia, or with a focus on anxiety, well-being or quality of life were excluded.

Studies evaluating supplementation of vitamin D in a clear dosing schedule, regardless of administration form (oral/intramuscular), were included, as well as studies giving an additional supplement besides vitamin D, i.e. calcium or fish oil. If dosages were unclear, i.e. if vitamin D was supplemented in the form of a multinutrient (preparations composed of multiple vitamins or nutrients) or a vitamin D-fortified food instead of as a singular vitamin D preparation, these studies were excluded.

2.3. Outcome measures

We assessed whether adverse health outcomes that may be related to vitamin D deficiency as well as depression, such as frailty, falls, somatic chronic diseases, physical disability, or poor cognitive functioning (Alexopoulos, 2005; Autier et al., 2014; Halfon et al., 2015; Iaboni and Flint, 2013), were included in vitamin D supplementation trials for depression. We also assessed whether these outcomes were affected by vitamin D supplementation. Since different assessment methods are available for the adverse health outcomes under study, we did not apply any restrictions on the specific instruments. Regarding frailty, we also considered the five components of the frailty phenotype (slowness, physical activity, muscle weakness, exhaustion, and unwanted weight loss) (Fried et al., 2001).

Due to our focus on health outcomes and not on intermediate factors, we did not assess the effects of vitamin D supplementation on laboratory values, anthropometric measures, psychiatric outcomes other than depression, or other factors related to mental health.

2.4. Data extraction

After a first screening on title and abstract by one of the authors (KvdB), full text versions of all possible eligible papers were evaluated independently for inclusion in the systematic review by two authors (KvdB and JH). Differences in judgement were discussed and resolved.

A standardised, piloted form was used for data-synthesis. We determined for each study whether adverse health outcomes were an inclusion or exclusion criterion, stratification variable, covariate, or outcome measure, and recorded the definition and method of assessment used. We also assessed the impact of vitamin D supplementation relative to the control condition on these outcomes.

In addition, the following general study data were collected: authors, journal, year of publication, setting (general, psychiatric or somatic population), geographical location, study design, in- and exclusion criteria, diagnostic procedure for depression (clinical diagnosis or symptom score), duration of supplementation and follow-up, age of participants (range, mean, standard deviation), stratification variables, covariates, and other outcome measures.

Since both depression and adverse health outcomes pose a risk of drop out from a study, the following data on recruitment and attrition were extracted: the number of patients 1) screened, 2) included, 3) randomised, 4) analysed with intention to treat analysis, 5) completed the study, 6) dropped out, plus reasons for attrition.

Details about vitamin D assessment (timing and method; levels of vitamin D at baseline and follow up (mean, range)), method of adjustment for season, vitamin D supplementation (dosage, method of administration, combination with calcium supplementation or other preparations), and control conditions were assessed.

An estimation of the increment of vitamin D with the given vitamin D dosage was calculated, assuming that vitamin D levels would increase with 0.70 nmol/l for each μg (= 40 I.U.) of vitamin D supplementation per day (Heaney et al., 2003). In this way, we assessed whether a sufficient concentration of vitamin D (between 75 and 250 nmol/l) could be achieved, based on the baseline values and the estimated increment, or (if available) on the actual follow-up vitamin D levels.

2.5. Quality assessment

Two authors (KvdB and JH) independently evaluated the quality of the included studies using the revised Cochrane tool for assessing risk of bias in randomised trials (RoB 2; Sterne et al., 2019). The following forms of bias for the depression outcome were assessed: bias arising from the randomisation process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome, and in selection of the reported result. Each study was assigned an overall score for risk of bias (low risk, some concerns, or high risk of bias) as indicated by the RoB 2. Discrepancies were identified and resolved through discussion by the two assessors (KvdB and JH), and if necessary within the complete study group.

Furthermore, physical vulnerability was scored for each study population as high, medium or relatively low, based on the mean age of the population, the presence of somatic comorbidity in the population, and the application of exclusion criteria related to frailty and somatic comorbidity.

2.6. Subgroups

We chose in advance to stratify studies according to diagnostic procedure for depression into 1) a clinical diagnosis of a depressive disorder by a psychiatrist / psychologist or a diagnosis based on a (semi-)

structured interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), or 2) the presence of depressive symptoms based on a screening questionnaire score for depressive symptomatology. It is important to make this distinction, since the use of symptom questionnaires may lead to overestimation of depression due to misclassification of somatic symptoms as depressive features, particularly in populations with frailty or somatic comorbidity (Hegeman et al., 2015).

3. Results

3.1. Study selection and characteristics

A total of 2378 records were retrieved by database searching; one additional record was identified through the reference lists. After deleting duplicates, the title and abstract of 1861 records were screened for eligibility. Full-text versions of 65 papers were assessed, and ultimately, 31 vitamin D supplementation trials with depression as primary outcome could be included in the review (see Fig. A1).

In 13 studies, inclusion was restricted to persons with a depressive disorder (see Table A1). Among the other 18 studies focussed on depressive symptom severity, two studies exclusively included persons with a symptom score above a cut-off value (De Koning et al., 2019; Yosaee et al., 2020).

Nineteen studies were performed in populations with vitamin D deficiency (mean vitamin D levels <50 nmol/l) at baseline. Baseline vitamin D levels were not reported in one study, and three studies were conducted in populations with sufficient vitamin D levels (>75 nmol/l). In seven studies actual follow-up vitamin D levels did not reach 75 nmol/l, and in another four studies the estimated increment of vitamin D levels was not enough to reach sufficiency. In one study no estimation could be made (see Table A1).

Five studies were performed among physically vulnerable populations (Alavi et al., 2019; De Koning et al., 2019; Raygan et al., 2018; Wang et al., 2016; Zheng et al., 2019). Overall risk of bias was low in four studies (see Table A1 and supplementary Table S.1), of which only one was performed in a physically vulnerable population (De Koning et al., 2019).

3.2. Studies including adverse health outcomes

Five studies included adverse health outcomes. Although frailty was not an outcome measure in any of the studies, three studies assessed one or more frailty components: physical activity was an outcome measure in all of these (De Koning et al., 2019; Jorde et al., 2008; Mousa et al., 2018); one additionally assessed muscle strength (De Koning et al., 2019). No effect of vitamin D supplementation was demonstrated in any of these studies. De Koning et al. also included the number of functional limitations, severity of functional limitations, functional mobility, and cognitive functioning (De Koning et al., 2019). Other studies included a comorbidity index (Wang et al., 2016), and fatigue (Rolf et al., 2017). De Koning et al. reported fewer functional limitations after supplementation, but only for participants with baseline vitamin D levels above 50 nmol/l (which does not qualify as vitamin D deficiency). No effect on severity of functional limitations, functional mobility, or cognitive functioning was observed in this study (De Koning et al., 2019). Wang et al. found a sharper decrease of the comorbidity index in the group with vitamin D supplementation compared to the placebo group. Rolf et al. found no effect of supplementation on fatigue.

In four of these studies (De Koning et al., 2019; Jorde et al., 2008; Rolf et al., 2017; Wang et al., 2016) actual follow-up vitamin D levels reached sufficiency (>75 nmol/l). Only in the study by Mousa et al., mean vitamin D levels were still insufficient (56.4 nmol/l) after supplementation.

Of the above five studies including adverse health outcomes, two were conducted in physically vulnerable populations (De Koning et al., 2019; Wang et al., 2016), two in populations with medium vulnerability (Jorde et al., 2008; Rolf et al., 2017) and one with relatively low vulnerability (Mousa et al., 2018). Only one of these five studies had low risk of bias (De Koning et al., 2019). Some concerns arose in two studies (Jorde et al., 2008; Wang et al., 2016), and risk of bias was high in the two other studies (Mousa et al., 2018; Rolf et al., 2017). Thus, the study by De Koning et al. (2019) was the only study in a physically vulnerable population with low risk of bias.

3.3. Meta-analysis

Due to the low number and heterogeneity of studies, we could not perform a meta-analysis.

4. Discussion

This is the first systematic review focussing on adverse health outcomes related to vitamin D deficiency in vitamin D supplementation trials for depression. While depressed persons can be considered a high-risk group for adverse health outcomes, only five of the 31 trials considered adverse health outcomes as a secondary outcome measure (De Koning et al., 2019; Jorde et al., 2008; Mousa et al., 2018; Rolf et al., 2017; Wang et al., 2016). The only high-quality study in a physically vulnerable population reported a beneficial effect on the number of functional limitations (De Koning et al., 2019). This is in line with our hypothesis that vitamin D supplementation in depression may improve adverse health outcomes. Nevertheless, there are currently too few studies in physically vulnerable populations with depression that have examined the effects of vitamin D supplementation on adverse health outcomes to determine whether depressed persons benefit from supplementation effects on adverse health outcomes.

4.1. Strengths and limitations

4.1.1. Current literature

Although we could include 31 studies into the effect of vitamin D supplementation on depression or depressive symptoms in older populations, only one high-quality study (De Koning et al., 2019) remained to draw any conclusions about the effects of vitamin D supplementation on adverse health outcomes related to depression. We encountered a number of shortcomings in the current literature.

First, physical vulnerability is particularly relevant in geriatric populations. However, only eight of the 31 included studies were conducted in older populations (mean age >60 years) (Alavi et al., 2019; Bertone-Johnson et al., 2012; De Koning et al., 2019; Okereke et al., 2020; Raygan et al., 2018; Wang et al., 2016; Yalamanchili and Gallagher, 2018; Zheng et al., 2019). Furthermore, somatic conditions were often reason for exclusion, as well as 'medical conditions likely to result in death within three years' (Bertone-Johnson et al., 2012) or 'substantial comorbidity' and 'physical conditions severe enough to prevent reasonable physical activity' (Yalamanchili and Gallagher, 2018). Thus, besides finding just a limited number of vitamin D supplementation studies in geriatric populations, in at least three of those studies the most physically vulnerable participants appear to have been excluded (Okereke et al., 2020; Bertone-Johnson et al., 2012; Yalamanchili and Gallagher, 2018). Still, the inclusion of adverse health outcomes may be useful in younger age groups, as their prevalence is not limited to older ages, and to compare the effects of vitamin D supplementation on depression and other health outcomes across different age groups.

Second, at least some concerns about the risk of bias exist in all but four of the 31 studies. Of the five studies that included an adverse health outcome, only one (De Koning et al., 2019) had low risk of bias. Thus, the overall quality of the studies most relevant for the current review is questionable.

Moreover, vitamin D dosage should be high enough to reach an adequate blood level. For bone metabolism and the prevention of falls and fractures, 75 nmol/l is considered sufficient (American Geriatrics Society Workgroup on vitamin D supplementation for older adults, 2014; Bischoff-Ferrari, 2007),

although for extra-skeletal effects no clear target vitamin D levels are known. In four of the studies that included adverse health outcomes, vitamin D levels >75 nmol/l were reached (De Koning et al., 2019; Jorde et al., 2008; Rolf et al., 2017; Wang et al., 2016). In one study, vitamin D levels remained insufficient throughout the study (Mousa et al., 2018). Besides, follow-up duration should be long enough for vitamin D to exert its effect on depression or other outcome measures. The maximum biological response (as in maximum vitamin D level and maximum decrease of bone turnover) is seen at three to six months of supplementation (Mazahery and von Hurst, 2015). In contrast, the follow-up duration in 14 of 16 studies reporting a beneficial effect of supplementation on depression was between one and three months, so that these positive findings may be due to chance. However, the studies that included an adverse health outcome had an adequate follow-up duration, varying from 16 weeks (Mousa et al., 2018) to 44 weeks (Rolf et al., 2017) or 1 year (De Koning et al., 2019; Jorde et al., 2008; Wang et al., 2016).

Lastly, to comment on the clinical implications of findings from supplementation studies, results should be applicable to depressed persons in clinical practice. However, generalisability of the current results towards more severely depressed persons (i.e. those treated in mental health care) might be limited as these persons were mostly excluded in the selected studies. In fact, in seven out of thirteen studies in populations with a clinical diagnosis of depression, the presence of severe depression or even the use of an antidepressant was an exclusion criterion. Furthermore, of the 18 studies focussing on depressive symptoms, 16 did not apply a cut-off value and included persons regardless of the severity of depressive symptomatology. Especially in somatically afflicted populations, there is a risk of misattribution of somatic symptoms to depression when symptom questionnaires are used instead of diagnostic interviews (Hegeman et al., 2015). Thus, a beneficial effect on depression, as was reported in seven out of nine somatic populations focussing on depressive symptoms, may rather reflect a decrease of somatic symptoms that were previously misclassified as depressive. Furthermore, generalisability of the results on adverse health outcomes may be reduced since only two out of five studies that included such an outcome were performed in depressed populations. One study included persons with a clinical depression diagnosis and BDI score $>=$ 16 (Wang et al., 2016) and the other only included persons with CES-D scores $>=$ 16 (de Koning et al., 2019). In all of these five studies, major depressive disorder (de Koning et al., 2019), severe depression (Rolf et al., 2017; Wang et al., 2016), clinical depression (Mousa et al., 2018), and/or antidepressant use (Jorde et al., 2008; Wang et al., 2016) were exclusion criteria.

4.1.2. Review level

An important strength of this review is that we are the first to provide a complete overview of adverse health outcomes in vitamin D supplementation trials that target depression or depressive symptoms. We were able to retrieve full text versions of all potentially eligible studies. It is unlikely that we missed any studies in physically vulnerable populations, since we only excluded study populations that were entirely under 40 years of age.

A limitation of our review is that the rules for the inclusion of studies in a systematic review about nutrients (Heaney, 2014) could not all be followed. Dose-response curves for nutrients – unlike drugs – are presumably non-linear, as once the intake of the nutrient is adequate, an increase of the dose produces no additional effect on the outcome. In order to avoid bias towards null, Heaney recommends to only include studies that are similar with respect to baseline values, supplementation dosages, and conutrient status (Heaney, 2014). Although we could not completely avoid heterogeneity of studies, we were able to quantify the change in vitamin D levels in 22 of the 31 studies, and to determine for all but six of the studies whether supplementation had been adequate (see Table A1).

Also, several studies were incorporated into larger vitamin D trials that were not primarily designed to study the effect of supplementation on depression and were often performed in populations with low prevalence of depression. Importantly, in these studies that were not primarily designed to target depression, a probability of publication bias is plausible, since more effort may have been put into reporting positive secondary outcomes rather than negative outcomes. However, our stratification by diagnostic modality for the depression (clinical diagnosis – symptom score above a cut-off value – symptom score regardless of symptom severity) might help to interpret the results.

Since intention-to-treat analyses allow conclusions about supplementation on a population level, those analyses were of primary interest. However, in 17 out of 31 studies no such analyses were performed; accordingly, we report results of the per-protocol analysis for all studies. Where intention-to-treat analyses were available, results were in line with the results of the per-protocol analysis, except in the study by Jorde et al., in which a beneficial effect of vitamin D supplementation on depression was demonstrated in the per-protocol analysis but not in the intention-to-treat analysis (Jorde et al., 2008).

4.2. Supplementation recommendations

Although supplementation of 10−20 μg vitamin D per day (depending on skin colour and sun exposure) is recommended for all older persons (Health Council of the Netherlands, 2012), these guidelines are often not followed (Chel et al., 2013). In the Netherlands, general practitioners are encouraged to follow a pragmatic approach and to actively prescribe vitamin D to persons who will likely benefit from it (Elders, 2015). So far, depressed persons are not one of the risk groups explicitly identified in these guidelines.

While vitamin D levels of 75 nmol/l are considered sufficient for bone metabolism and the prevention of falls and fractures (American Geriatrics Society Workgroup on vitamin D supplementation for older adults, 2014; Bischoff-Ferrari, 2007), target levels for extra-skeletal effects are unknown. Moreover, while dose-reponse curves are often non-linear (see Heaney, 2014), a recent dose-response meta-analysis that specifically looked for non-linear dose-response associations between vitamin D levels and depression, only found a linear association (Li et al., 2019). Therefore, future supplementation trials should not only address what the optimal vitamin D level should be, but also whether the dose-response curve for these effects is linear or non-linear. Interestingly, the beneficial effect of vitamin D supplementation on the number of functional limitations in the high-quality D-Vitaal study (De Koning et al., 2019) was only seen in the subgroup with baseline vitamin D levels >50 nmol/l. This post-hoc analysis could be a chance finding, but if not, several explanations may apply. First, in case of severe vitamin D deficiency irreversible effects may have occurred, or secondly, higher target values and/or a longer follow-up duration are needed to improve functional limitations. This latter explanation also challenges the idea of fixed target levels for specific outcomes, as target levels may differ conditional on duration and severity of vitamin D deficiency. Finally, the target level of vitamin D to improve functional limitations in depression might be much higher than previously thought and may only be reached by this supplementation strategy among patients who had >50 nmol/l vitamin D levels at baseline. Regarding the uncertainty of optimal vitamin D levels in depression, we advocate considering depressed persons as at risk for vitamin D deficiency and the associated adverse health outcomes.

5. Conclusions and implications

While depressed persons are at increased risk of adverse health effects as well as vitamin D deficiency, supplementation trials in depression have not addressed the common negative health consequences of low vitamin D levels. The findings of the only high-quality study in a physically vulnerable population are in line with our hypothesis that vitamin D supplementation in depression may have beneficial effects on adverse health outcomes. Well-designed trials of the effects of vitamin D supplementation for late-life depression should explore whether vitamin D-related adverse health outcomes can be prevented or stabilised in this vulnerable population. In the meantime, depression should be added to the risk factors for vitamin D deficiency in practical supplementation guidelines.

CRediT authorship contribution statement

Karen S. van den Berg: Conceptualization, Methodology, Investigation, Writing - original draft. **Radboud M. Marijnissen:** Conceptualization, Methodology, Writing - review & editing. **Rob H.S. van den Brink:** Writing - review & editing. **Richard C. Oude Voshaar:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Johanna M. Hegeman:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A

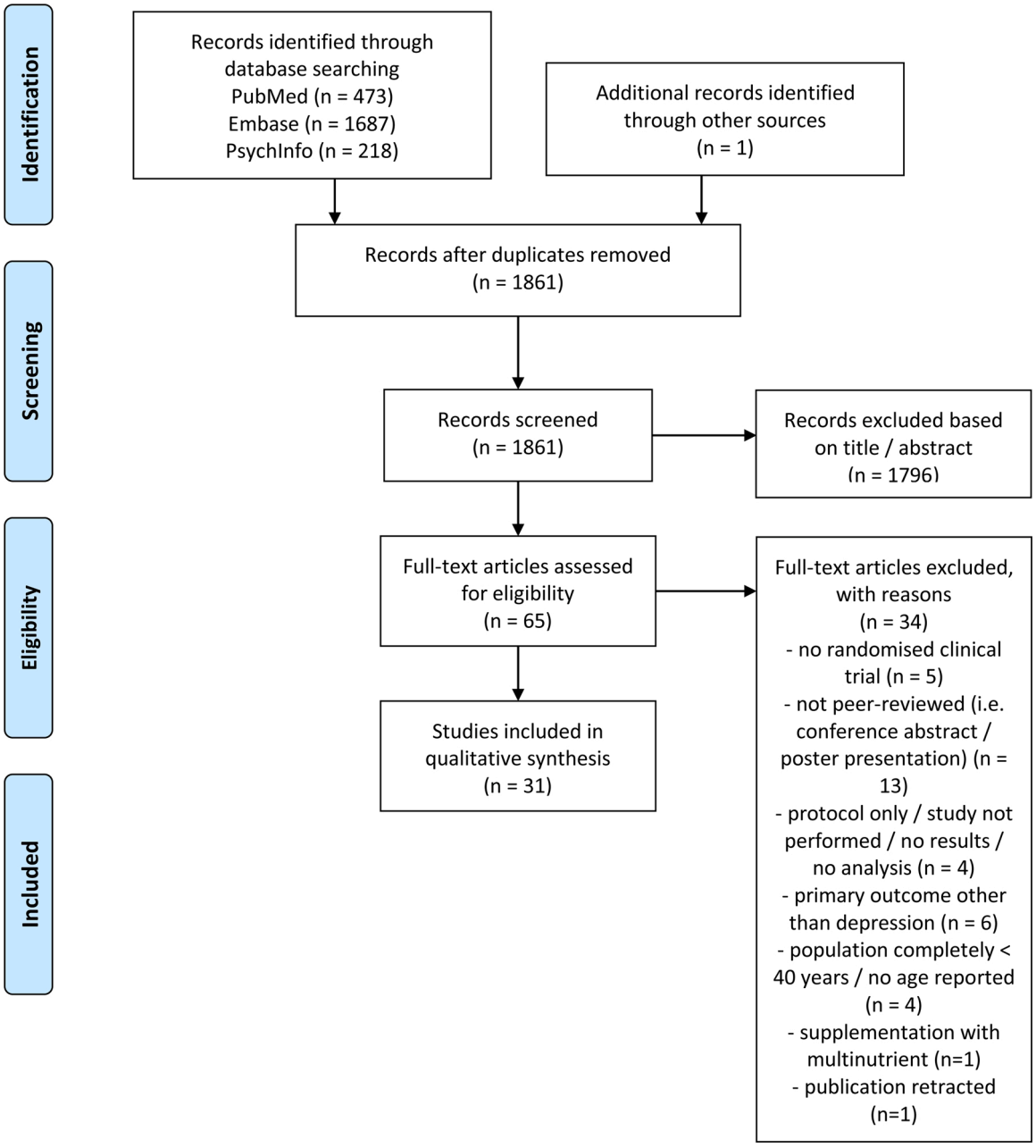

Fig. A1. Flow diagram of the selection process of randomised clinical trials.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta- *A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.
For more information, visit www.prisma-statement.org.

Table A1
Vitamin D supplementation trials for depression, stratified by the presence of depressive disorder and sorted by physical vulnerability and overall risk of bias.

Author, year of publication	Study population	Estimated physical vulnerability of population	Mean baseline vitamin D level (intervention group)	Vitamin D dosing schedule	Mean increment of vitamin D (intervention group)		Adequate supplementation? **	Adverse physical health outcomes, and other included outcome measures	RoB†
					Estimated*	Observed			
Studies in populations with depressive disorder									
Alavi et al., 2019	Psychiatric population, Iran; persons over 60 yrs under treatment for depression, GDS-15 > 5	High	56.3 nmol/l	50,000 I.U./week for 8 weeks vs. placebo	125 nmol	52.3 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** GDS-15	S
Wang et al., 2016	Somatic population, Iran; persons > = 18 yrs with end-stage renal failure, BDI > = 16 and clinical depression diagnosis	High	54.6 nmol/l	50,000 I.U./week for 52 weeks vs. placebo	125 nmol	46 nmol/l	Yes	***Adverse physical health outcomes:*** *Comorbidity index:* significant decrease in vitamin D group compared to control group. ***Other outcomes:*** BDI-II, markers of bone metabolism, nutrient indices, BMI, hs-CRP	S
Zhang et al., 2018	Somatic population, China; persons > = 18 yrs with pulmonary tuberculosis and depression (DSM-IV)	Medium	57.3 nmol/l	100,000 I.U./week for 8 weeks vs placebo	250 nmol/l	10.5 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, markers of bone metabolism, nutrient indices, inflammatory biomarkers	S
Khoraminya et al., 2013	Psychiatric population, Iran; persons 18–65 yrs with MDD (DSM-IV) and HDRS-17 > = 15	Relatively low	57.6 nmol/l	1500 I.U. + 20 mg fluoxetine/day for 8 weeks vs. placebo + fluoxetine	26.3 nmol/l	Unknown	Probably	***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, BDI	S
Vellekkatt et al., 2020	Psychiatric population, India; persons 18–65 yrs with MDD (DSM 5)	Relatively low	Unknown (<50 nmol/l)	300,000 I.U. once vs. placebo, follow-up 12 weeks	62.5 nmol/l	Unknown	Probably	***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, QLES, CGI-SI	S
Alghamdi et al., 2020	Psychiatric population, Saudi Arabia; persons 18–65 yrs with MDD (DSM 5)	Relatively low	Unknown (30–50 nmol/l)	50,000 I.U./week for 3 months vs. standard of care	125 nmol/l	Around 50 nmol/l (extrapolated from graph)	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, serotonin level	H
Amini et al., 2020	Psychiatric population, Iran; women 18–45 yrs with postpartum depression and EPDS >12	Relatively low	36.6 nmol/l (vit D + calcium group), 39.8 nmol/l (vit D + placebo group)	50,000 I.U./2 weeks +/- calcium 500 mg/ day for 8 weeks vs. placebo	62.5 nmol/l	14.4 nmol/l and 18.2 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes***: EPDS, calcium, estradiol, inflammatory markers	H
Gloth et al., 1999	Psychiatric population, United States; persons 15-61 yrs with SAD (DSM-IV)	Relatively low	27.5 nmol/l	100,000 I.U. once vs. phototherapy, follow-up 1 month	58.3 nmol/l	20.3 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS, SIGH-SAD, SAD-8	H
Hansen et al., 2019	Psychiatric population, Denmark; patients (18–65 yrs) admitted to mood disorder clinic	Relatively low	43.2 nmol/l	2800 I.U./day for 12 weeks vs. placebo, follow-up 6 months	49 nmol/l	54.7 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, major depression inventory; WHO-5 well-being index	H
Kaviani et al., 2020	Psychiatric population, Iran; outpatients (18–60 yrs) with clinical diagnosis of mild to moderate depression	Relatively low	87.1 nmol/l	50,000 I.U./2 weeks for 8 weeks vs. placebo	62.5 nmol/l	40.8 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, oxytocin, serotonin, PTH, weight, BMI, waist circumference, hip circumference, waist-hip ratio, blood pressure	H

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Table A1 (*continued*)

Author, year of publication	Study population	Estimated physical vulnerability of population	Mean baseline vitamin D level (intervention group)	Vitamin D dosing schedule	Mean increment of vitamin D (intervention group)		Adequate supplementation? **	Adverse physical health outcomes, and other included outcome measures	RoB†
					Estimated*	Observed			
Marsh et al., 2017	Psychiatric population, United States; persons 18–70 yrs with clinical diagnosis of bipolar depression	Relatively low	48 nmol/l	5000 I.U./day for 12 weeks vs. placebo	87.5 nmol/l	22 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes:*** MADRS, YMRS, HAM-A	H
Mozaffari-Khosravi et al., 2013	Psychiatric population, Iran; 20–60 yrs with clinical diagnosis of depression	Relatively low	Unknown; most between 12.5 and 25 nmol/l	300,000 or 150,000 I.U. once vs. no treatment, follow-up 3 months	58.3 nmol/l / 29.2 nmol/l	Unknown	Probably / No	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, PTH, calcium, phosphate	H
Zhu et al., 2020	Psychiatric population, China; persons 18–60 yrs with clinical diagnosis of MDD	Relatively low	39.1 nmol/l	1600 mg/day vs. placebo for 6 months	N/A‡	Unknown	Probably not	***Adverse physical health outcomes:*** None ***Other outcomes:*** HDRS-17, HAM-A-14, RSAS, RPAS	H
Studies in populations with a depressive symptom score above a cut-off value									
De Koning et al., 2019	General population, the Netherlands; persons 60–80 yrs with CES-D > = 16, and > = 1 functional limitation	High	46 nmol/l	1200 I.U./day for 12 months vs. placebo	21 nmol/l	40 nmol/l	Yes	***Adverse physical health outcomes:*** *Number of functional limitations:* Fewer limitations in vitamin D group compared to placebo (if baseline vitamin D levels >50 nmol/l). *Severity of functional limitations, physical performance, muscle strength, functional mobility, and cognitive functioning:* no differences between intervention groups. ***Other outcomes:*** CES-D, BAI, health-related quality of life	L
Yosaee et al., 2020	Somatic population, Iran; persons >20 yrs with obesity and BDI > = 10	Relatively low	65.2 nmol/l (vitamin D group) / 26.1 nmol/l (vitamin D + zinc group)	2000 I.U./day or placebo + zinc or placebo for 12 weeks	35 nmol/l	25.6 nmol/l (vitamin D group) / 18.7 nmol/l (vitamin D + zinc group)	Yes / No	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, Brain-derived neurotrophic factor, cortisol, blood pressure, weight, BMI, waist circumference	H
Studies in populations with depressive symptoms regardless of symptom severity									
Raygan et al., 2018	Somatic population, Iran; persons 45–85 yrs with coronary heart disease	High	36.8 nmol/l	50,000 I.U./2 weeks + probiotic for 12 weeks vs. placebo	62.5 nmol/l	29.5 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, glycemic control, hs-CRP, biomarkers of oxidative stress, blood pressure, BAI, GHQ-28	S
Zheng et al., 2019	Somatic population, Australia; persons with knee osteoarthritis	High	43.7 nmol/l	50,000 I.U./month for 24 months vs. placebo	29.2 nmol/l	40.8 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** PHQ	H
Ghaderi et al., 2017	Somatic population, Iran; persons 25–70 yrs on methadone maintenance treatment	Medium	34.8 nmol/l	50,000 I.U./2 weeks for 12 weeks vs. placebo	62.5 nmol/l	20.3 nmol/l	No	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, metabolic status, biomarkers of oxidative stress, PSQI, BAI	L
Kjærgaard et al., 2012	General population, Norway; persons 30–75 yrs	Medium	47.4 nmol/l	20,000 I.U./week for 6 months vs. placebo	50 nmol/l	100.3 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, HADS, SPAQ, MADRS, BMI, serum calcium, PTH	L

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Table A1 (*continued*)

Author, year of publication	Study population	Estimated physical vulnerability of population	Mean baseline vitamin D level (intervention group)	Vitamin D dosing schedule	Mean increment of vitamin D (intervention group)		Adequate supplementation? **	Adverse physical health outcomes, and other included outcome measures	RoB†
					Estimated*	Observed			
Okereke et al., 2020	General population, United States; men >50 yrs, women >55 yrs	Medium	77 nmol/l (total group)	2000 I.U./day + fish oil for 5.3 years (average) vs. placebo	35 nmol/l	Unknown	Probably	***Adverse physical health outcomes:*** None ***Other outcomes:*** PHQ-8, risk of incident or recurrent depression	L
Bertone-Johnson et al., 2012	General population, United States; postmenopausal women (50–79 yrs)	Medium	52.0 nmol/l	400 I.U./day + calcium 1000 mg vs. placebo, average follow-up 7.0 years	7 nmol/l	Unknown	Probably not	***Adverse physical health outcomes:*** None ***Other outcomes:*** Burnam score, antidepressant use at year 3	S
Jorde et al., 2008	Somatic population, Norway; persons 21–70 yrs with BMI between 28 and 47 kg/m^2	Medium	52.5 nmol/l (total group)	40,000 I.U./week + or 20,000 I.U./week + 500 mg calcium/day vs. placebo for 1 year	100 nmol/l / 50 nmol/l	56.9 nmol/l and 35.6 nmol/l	Yes	***Adverse physical health outcomes:*** *Physical activity:* no difference in IPAQ scores between intervention groups. ***Other outcomes:*** BDI, BMI, calcium, PTH	S
Jorde and Kubiak, 2018	General population, Norway; persons 40–80 yrs	Medium	33.8 nmol/l (total group)	100,000 I.U. once + 20,000 I.U. /week for 4 months vs. placebo	64.6 nmol/l	56 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, calcium and PTH	S
Mirzavandi et al., 2020	Somatic population, Iran; persons 30–60 yrs with diabetes mellitus type II	Medium	39.5 nmol/l	200,000 I.U./4 weeks twice vs. no treatment	125 nmol/l	51.8 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, weight, body fat mass, waist-to-hip ratio	S
Omidian et al., 2019	Somatic population, Iran; persons 30–60 yrs with diabetes mellitus type II	Medium	38.8 nmol/l	4000 I.U./day for 3 months vs. placebo	70 nmol/l	42.3 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, blood pressure, metabolic profile	S
Rolf et al., 2017	Somatic population, the Netherlands; persons 18–55 yrs with multiple sclerosis	Medium	58 nmol/l	7000 I.U./day for 4 weeks, then 14.000 i.u./day up to 44 weeks vs. placebo	245 nmol/l	168 nmol/l	Yes	***Adverse physical health outcomes:*** *Fatigue:* no difference in Fatigue Severity Scale scores between groups ***Other outcomes:*** HADS-D, inflammatory markers	H
Yalamanchili and Gallagher, 2018	General population, United States; women 57–90 yrs with vit D level =<50 nmol/l	Medium	38.3 nmol/l	400–4,800 I.U./day for 12 months vs. placebo	7 – 84 nmol/l	Unknown	Depends on dosage	***Adverse physical health outcomes:*** None ***Other outcomes:*** GDS	H
Sharifi et al., 2019	Somatic population, Iran; persons 18–50 yrs with mild to moderate ulcerative colitis	Relatively low	83.3 nmol/l	300,000 I.U. once vs. placebo, follow-up 90 days	58.3 nmol/l	18.8 nmol/l	Yes	***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI-II, PTH, calcium	S
Frandsen et al., 2014	General population, Denmark; health care professionals 18–65 yrs with SAD symptoms and > = 8 **on** question 2 of SPAQ	Relatively low	68.3 nmol/l	2800 I.U./day for 12 weeks vs. placebo	49 nmol/l	Unknown	Probably	***Adverse physical health outcomes:*** None ***Other outcomes:*** SIGH-SAD, weight, waist circumference, blood pressure, WHO-5 well-being index, absenteeism from work	H
Mousa et al., 2018	General population, Australia; persons 20–60 yrs with BMI >25	Relatively low	33.3 nmol/l	100,000 I.U. once and 4000 I.U./day for 16 weeks vs. placebo	85.6 nmol/l	23.1 nmol/l	No	***Adverse physical health outcomes:*** *Physical activity:* no difference in change in IPAQ-MET between intervention groups.	H

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Table A1 (*continued*)

Author, year of publication	Study population	Estimated physical vulnerability of population	Mean baseline vitamin D level (intervention group)	Vitamin D dosing schedule	Mean increment of vitamin D (intervention group)		Adequate supplementation? **	Adverse physical health outcomes, and other included outcome measures	RoB†
					Estimated*	Observed			
Vafa et al., 2019	Somatic population, Iran; women 18–45 yrs with anemia and vitamin D < 75 nmol/l	Relatively low	42.6 nmol/l	1000 I.U./day + 27 mg iron/day vs. 1000 I.U./day + placebo for 12 weeks	17.5 nmol/l	54.6 nmol/l (vitamin D + iron), 51.4 nmol/l (vitamin D + placebo)	Yes	***Other outcomes:*** BDI-II, BMI, waist-to-hip ratio, % body fat ***Adverse physical health outcomes:*** None ***Other outcomes:*** BDI, BMI, BAI	H

Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BMI: Body Mass Index; CES-D: Centre of Epidemiologic Studies Depression scale; CGI-SI: Clinical Global Impression – Severity of Illness; DSM: Diagnostic and Statistical Manual of Mental Disorders; EPDS: Edinburgh Postpartum Depression Scale; GDS-15: Geriatric Depression Scale, 15 items; GHQ-28: General Health Questionnaire, 28 items; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HDRS-17: Hamilton Depression Rating Scale, 17 items; hsCRP = high sensitivity C-reactive protein; I.U.= international units; IPAQ-MET: International Physical Activity Questionnaire – Metabolic Equivalent of Time; MDD: major depressive disorder; PHQ: Patient Health Questionnaire; PTH: parathyroid hormone; PSQI: Pittsburgh Sleep Quality Index; QLES: Quality of Life Enjoyment and Satisfaction; RPAS: Revised Physical Anhedonia Scale; RSAS: Revised Social Anhedonia Scale; SAD: Seasonal Affective Disorder; SIGH-SAD: Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version; SPAQ-SAD: Seasonal Pattern Assessment Questionnaire; YMRS: Young Mania Rating Scale.

* Estimated increment of vitamin D level (nmol/l): 0.70 nmol/l for each μg (= 40 i.u.) per day (Heaney et al., 2003). If weekly / monthly doses are stated, estimations are based on a calculated daily dose.

** Supplementation is considered adequate if actual follow-up vitamin D levels or baseline vitamin D levels plus the estimated increment are between 75 and 250 nmol/l.

† Overall Risk of Bias for the depression outcome: L = low, S = some concerns, H = high.

§ Based on the reported dosage of 1600 mg estimated vitamin D levels would be extremely high. The authors were contacted to verify whether the reported dosage is correct, but did not respond.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101442.

References

Alavi, N.M., Khademalhoseini, S., Vakili, Z., Assarian, F., 2019. Effect of vitamin D supplementation on depression in elderly patients: a randomized clinical trial. Clin. Nutr. 38 (5), 2065–2070.

Alexopoulos, G.S., 2005. Depression in the elderly. Lancet 365 (9475), 1961–1970.

Alghamdi, S., Alsulami, N., Khoja, S., Alsufiani, H., Tayeb, H.O., Tarazi, F.I., 2020. Vitamin D supplementation ameliorates severity of major depressive disorder. J. Mol. Neurosci. 70 (2), 230–235.

American Geriatrics Society Workgroup on vitamin D supplementation for older adults, 2014. Recommendations abstracted from the American Geriatrics Society consensus statement on vitamin D for prevention of falls and their consequences. J. Am. Geriatr. Soc. 62, 147–152.

Amini, S., Amani, R., Jafarirad, S., Cheraghian, B., Sayyah, M., Hemmati, A.A., 2020. The effect of vitamin D and calcium supplementation on inflammatory biomarkers, estradiol levels and severity of symptoms in women with postpartum depression: a randomized double-blind clinical trial. Nutr. Neurosci. 2020.

Anglin, R.E., Samaan, Z., Walter, S.D., McDonald, S.D., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br. J. Psychiatry 202, 100–107.

Autier, P., Boniol, M., Pizot, C., Mullie, P., 2014. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2 (1), 76–89.

Bertone-Johnson, E.R., Powers, S.I., Spangler, L., Larson, J., Michael, Y.L., Millen, A.E., et al., 2012. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. Am. J. Epidemiol. 176 (1), 1–13.

Bischoff-Ferrari, H.A., 2007. The 25-hydroxyvitamin D threshold for better health. J. Steroid Biochem. Mol. Biol. 103 (3-5), 614–619.

Chel, V.G., Elders, P.J., Tuijp, M.L., van den Berg, H.H., van Drongelen, K.I., Siedenburg, R.C., et al., 2013. Vitamin D supplementation in the elderly: guidelines and practice. Ned Tijdschr Geneeskd. 157 (33), A5779.

De Borst, M.H., De Boer, R.A., Stolk, R.P., Slaets, J.P., Wolffenbuttel, B.H., Navis, G., 2011. Vitamin D deficiency: universal risk factor for multifactorial diseases? Curr. Drug Targets 12 (1), 97–106.

De Koning, E.J., Lips, P., BWJH, Penninx, Elders, P.J.M., Heijboer, A.C., Den Heijer, M., et al., 2019. Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am. J. Clin. Nutr. 110 (5), 1119–1130.

Elders, P.J.M., 2015. Vitamine-D suppletie. Huisarts Wet. 58 (3), 156–159 (In Dutch).

Eyles, D.W., Burne, T.H., McGrath, J.J., 2013. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Front. Neuroendocrinol. 34 (1), 47–64.

Frandsen, T.B., Pareek, M., Hansen, J.P., Nielsen, C.T., 2014. Vitamin D supplementation for treatment of seasonal affective symptoms in healthcare professionals: a double-blind randomised placebo-controlled trial. BMC Res. Notes 7 (528), 0500-7-528.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., et al., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56 (3), M146–M156.

Garcion, E., Wion-Barbot, N., Montero-Menei, C.N., Berger, F., Wion, D., 2002. New clues about vitamin D functions in the nervous system. Trends Endocrinol. Metab. 13 (3), 100–105.

Ghaderi, A., Banafshe, H.R., Motmaen, M., Rasouli-Azad, M., Bahmani, F., Asemi, Z., 2017. Clinical trial of the effects of vitamin D supplementation on psychological symptoms and metabolic profiles in maintenance methadone treatment patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 79 (Pt B), 84–89.

Gloth 3rd, F.M., Alam, W., Hollis, B., 1999. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J. Nutr. Health Aging 3 (1), 5–7.

Gowda, U., Mutowo, M.P., Smith, B.J., Wluka, A.E., Renzaho, A.M., 2015. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition 31 (3), 421–429.

Halfon, M., Phan, O., Teta, D., 2015. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res. Int. 2015, 953241.

Hansen, J.P., Pareek, M., Hvolby, A., Schmedes, A., Toft, T., Dahl, E., et al., 2019. Vitamin D3 supplementation and treatment outcomes in patients with depression (D3-vit-dep). BMC Res. Notes 12 (1), 203,019-4218-z.

Health Council of the Netherlands, 2012. Evaluation of the Dietary References Values for Vitamin D. Health Council of the Netherlands, The Hague publication no. 2012/15.

Heaney, R.P., 2014. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr. Rev. 72 (1), 48–54.

Heaney, R.P., Davies, K.M., Chen, T.C., Holick, M.F., Barger-Lux, M.J., 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am. J. Clin. Nutr. 77 (1), 204–210.

Hegeman, J.M., de Waal, M.W., Comijs, H.C., Kok, R.M., van der Mast, R.C., 2015. Depression in later life: a more somatic presentation? J. Affect. Disord. 170, 196–202.

Humble, M.B., 2010. Vitamin D, light and mental health. J. Photochem. Photobiol. B 101 (2), 142–149.

Iaboni, A., Flint, A.J., 2013. The complex interplay of depression and falls in older adults: a clinical review. Am. J. Geriatr. Psychiatry 21 (5), 484–492.

Jorde, R., Kubiak, J., 2018. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J. Nutr. Sci. 7, e30.
Jorde, R., Sneve, M., Figenschau, Y., Svartberg, J., Waterloo, K., 2008. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J. Intern. Med. 264 (6), 599–609.
Jovanova, O., Aarts, N., Noordam, R., Zillikens, M.C., Hofman, A., Tiemeier, H., 2017. Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression. Acta Psychiatr. Scand. 135 (3), 185–194.
Kaviani, M., Nikooyeh, B., Zand, H., Yaghmaei, P., Neyestani, T.R., 2020. Effects of vitamin D supplementation on depression and some involved neurotransmitters. J. Affect. Disord. 269, 28–35.
Khoraminya, N., Tehrani-Doost, M., Jazayeri, S., Hosseini, A., Djazayery, A., 2013. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Aust. N. Z. J. Psychiatry 47 (3), 271–275.
Kjærgaard, M., Waterloo, K., Wang, C.E., Almås, B., Figenschau, Y., Hutchinson, M.S., et al., 2012. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. Br. J. Psychiatry 201 (5), 360–368.
Li, H., Sun, D., Wang, A., Pan, H., Feng, W., Ng, C.H., et al., 2019. Serun 25-hydroxy-vitamin D levels and depression in older adults: a dose-response meta-analysis of prospective cohort studies. Am. J. Geriatr. Psychiatry 27 (11), 1192–1202.
Marcos-Pérez, D., Sánchez-Flores, M., Proietti, S., Bonassi, S., Costa, S., Teixeira, J.P., et al., 2020. Low vitamin D levels and frailty status in older adults: a systematic review and meta-analysis. Nutrients. 12 (8), 2286.
Marsh, W.K., Penny, J.L., Rothschild, A.J., 2017. Vitamin D supplementation in bipolar depression: a double blind placebo controlled trial. J. Psychiatr. Res. 95, 48–53.
Mazahery, H., von Hurst, P.R., 2015. Factors affecting 25-hydroxyvitamin d concentration in response to vitamin D supplementation. Nutrients 7 (7), 5111–5142.
Mirzavandi, F., Babaie, S., Rahimpour, S., Razmpoosh, E., Talenezhad, N., Aghaei Zarch, S.M., et al., 2020. The effect of high dose of intramuscular vitamin D supplement injections on depression in patients with type 2 diabetes and vitamin D deficiency: a randomized controlled clinical trial. Obes Med. 2020/03;17.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4 (1), 1,4053-4-1.
Mousa, A., Naderpoor, N., de Courten, M.P.J., de Courten, B., 2018. Vitamin D and symptoms of depression in overweight or obese adults: a cross-sectional study and randomized placebo-controlled trial. J. Steroid Biochem. Mol. Biol. 177, 200–208.
Mozaffari-Khosravi, H., Nabizade, L., Yassini-Ardakani, S.M., Hadinedoushan, H., Barzegar, K., 2013. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J. Clin. Psychopharmacol. 33 (3), 378–385.
Okereke, O.I., Reynolds 3rd, C.F., Mischoulon, D., Chang, G., Vyas, C.M., Cook, N.R., et al., 2020. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. JAMA 324 (5), 471–480.
Omidian, M., Mahmoudi, M., Abshirini, M., Eshraghian, M.R., Javanbakht, M.H., Zarei, M., et al., 2019. Effects of vitamin D supplementation on depressive symptoms in type 2 diabetes mellitus patients: randomized placebo-controlled double-blind clinical trial. Diabetes Metab. Syndr. 13 (4), 2375–2380.
Oosterwerff, M.M., Eekhoff, E.M., Heymans, M.W., Lips, P., van Schoor, N.M., 2011. Serum 25-hydroxyvitamin D levels and the metabolic syndrome in older persons: a population-based study. Clin. Endocrinol. (Oxf.) 75 (5), 608–613.
Penninx, B.W., Milaneschi, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 11, 129,7015-11-129.
Pludowski, P., Holick, M.F., Grant, W.B., Konstantynowicz, J., Mascarenhas, M.R., Hag, A., 2018. Vitamin D supplementation guidelines. J. Steroid Biochem. Mol. Biol. 175, 125–135.
Raygan, F., Ostadmohammadi, V., Bahmani, F., Asemi, Z., 2018. The effects of vitamin D and probiotic co-supplementation on mental health parameters and metabolic status in type 2 diabetic patients with coronary heart disease: a randomized, double-blind, placebo-controlled trial. Prog. Neuropsychopharmacol. Biol. Psychiatry 84 (Pt A), 50–55.
Rolf, L., Muris, A.H., Bol, Y., Damoiseaux, J., Smolders, J., Hupperts, R., 2017. Vitamin D (3) supplementation in multiple sclerosis: symptoms and biomarkers of depression. J. Neurol. Sci. 378, 30–35.
Sharifi, A., Vahedi, H., Nedjat, S., Mohamadkhani, A., Hosseinzadeh Attar, M.J., 2019. Vitamin d decreases beck depression inventory score in patients with mild to moderate ulcerative colitis: a double-blind randomized placebo-controlled trial. J. Diet. Suppl. 16 (5), 541–549.
Spedding, S., 2014. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients 6 (4), 1501–1518.
Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., et al., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898.
Vafa, M., Azizi-Soleiman, F., Kazemi, S.M., Salehi, M., Zaeri, F., Abiri, B., et al., 2019. Comparing the effectiveness of vitamin D plus iron vs vitamin D on depression scores in anemic females: randomized triple-masked trial. Med. J. Islam. Repub. Iran 33, 64.
van den Berg, K.S., Hegeman, J.M., van den Brink, R.H.S., Rhebergen, D., Oude Voshaar, R.C., Marijnissen, R.M., 2021. A prospective study into change of vitamin D levels, depression and frailty among depressed older persons. Int. J. Geriatr. Psychiatry.
Vellekkatt, F., Menon, V., 2019. Efficacy of vitamin D supplementation in major depression: a meta-analysis of randomized controlled trials. J. Postgrad. Med. 65 (2), 74–80.
Vellekkatt, F., Menon, V., Rajappa, M., Sahoo, J., 2020. Effect of adjunctive single dose parenteral Vitamin D supplementation in major depressive disorder with concurrent vitamin D deficiency: a double-blind randomized placebo-controlled trial. J. Psychiatr. Res. 129, 250–256.
Wang, Y., Liu, Y., Lian, Y., Li, N., Liu, H., Li, G., 2016. Efficacy of high-dose supplementation with oral vitamin D3 on depressive symptoms in dialysis patients with vitamin D3 insufficiency: a prospective, randomized, double-blind study. J. Clin. Psychopharmacol. 36 (3), 229–235.
Yalamanchili, V., Gallagher, J.C., 2018. Dose ranging effects of vitamin D3 on the geriatric depression score: a clinical trial. J. Steroid Biochem. Mol. Biol. 178, 60–64.
Yosaee, S., Soltani, S., Esteghamati, A., Motevalian, S.A., Tehrani-Doost, M., Clark, C.C. T., et al., 2020. Effects of zinc, vitamin D, and their co-supplementation on mood, serum cortisol, and brain-derived neurotrophic factor in patients with obesity and mild to moderate depressive symptoms: a phase II, 12-wk, 2 × 2 factorial design, double-blind, randomized, placebo-controlled trial. Nutrition 71, 110601.
Zhang, L., Wang, S., Zhu, Y., Yang, T., 2018. Vitamin D3 as adjunctive therapy in the treatment of depression in tuberculosis patients: a short-term pilot randomized double-blind controlled study. Neuropsychiatr. Dis. Treat. 14, 3103–3109.
Zheng, S., Tu, L., Cicuttini, F., Han, W., Zhu, Z., Antony, B., et al., 2019. Effect of vitamin d supplementation on depressive symptoms in patients with knee osteoarthritis. J. Am. Med. Dir. Assoc. 20 (12), 1634,1640.e1.
Zhu, C., Zhang, Y., Wang, T., Lin, Y., Yu, J., Xia, Q., et al., 2020. Vitamin D supplementation improves anxiety but not depression symptoms in patients with vitamin D deficiency. Brain Behav. 10 (11), e01760.