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Review article

Vitamin D deficiency and depression in adults: systematic review and meta-analysis

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Background
There is conflicting evidence about the relationship between vitamin D deficiency and depression, and a systematic assessment of the literature has not been available.

Aims
To determine the relationship, if any, between vitamin D deficiency and depression.

Method
A systematic review and meta-analysis of observational studies and randomised controlled trials was conducted.

Results
One case–control study, ten cross-sectional studies and three cohort studies with a total of 31 424 participants were analysed. Lower vitamin D levels were found in people with depression compared with controls (SMD = 0.60, 95% CI 0.23–0.97) and there was an increased odds ratio of depression for the lowest *v.* highest vitamin D categories in the cross-sectional studies (OR = 1.31, 95% CI 1.0–1.71). The cohort studies showed a significantly increased hazard ratio of depression for the lowest *v.* highest vitamin D categories (HR = 2.21, 95% CI 1.40–3.49).

Conclusions
Our analyses are consistent with the hypothesis that low vitamin D concentration is associated with depression, and highlight the need for randomised controlled trials of vitamin D for the prevention and treatment of depression to determine whether this association is causal.

Declaration of interest
None.

Depression is associated with significant disability, mortality and healthcare costs. It is the third leading cause of disability in high-income countries,[1] and affects approximately 840 million people worldwide.[2] Although biological, psychological and environmental theories have been advanced,[3] the underlying pathophysiology of depression remains unknown and it is probable that several different mechanisms are involved. Vitamin D is a unique neurosteroid hormone that may have an important role in the development of depression. Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been implicated in the pathophysiology of depression.[4] Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development,[5] making it biologically plausible that this vitamin might be associated with depression and that its supplementation might play an important part in the treatment of depression. Over two-thirds of the populations of the USA and Canada have suboptimal levels of vitamin D.[6,7]

Some studies have demonstrated a strong relationship between vitamin D and depression,[8,9] whereas others have shown no relationship.[10,11] To date there have been eight narrative reviews on this topic,[12–19] with the majority of reviews reporting that there is insufficient evidence for an association between vitamin D and depression. None of these reviews used a comprehensive search strategy, provided inclusion or exclusion criteria, assessed risk of bias or combined study findings. In addition, several recent studies were not included in these reviews.[9,10,20,21] Therefore, we undertook a systematic review and meta-analysis to investigate whether vitamin D deficiency is associated with depression in adults in case–control and cross-sectional studies; whether vitamin D deficiency increases the risk of developing depression in cohort studies in adults; and whether vitamin D supplementation improves depressive symptoms in adults with depression compared with placebo, or prevents depression compared with placebo, in healthy adults in randomised controlled trials (RCTs).

Method

Search strategy

We searched the databases MEDLINE, EMBASE, PsycINFO, CINAHL, AMED and Cochrane CENTRAL (up to 2 February 2011) using separate comprehensive strategies developed in consultation with an experienced research librarian (see online supplement DS1). A separate search of PubMed identified articles published electronically prior to print publication within 6 months of our search and therefore not available through MEDLINE. The clinical trials registries clinicaltrials.gov and Current Controlled Trials (controlled-trials.com) were searched for unpublished data. The reference lists of identified articles were reviewed for additional studies.

Eligibility criteria

The following study designs were included: RCTs, case–control studies, cross-sectional studies and cohort studies. All studies enrolled adults (age 18 years) and reported depression as the outcome of interest and vitamin D measurements as a risk factor or intervention. Cross-sectional and cohort studies were required to report depression outcomes for participants with vitamin D deficiency (as defined by each study, see Tables 1 and 2) compared with those with normal vitamin D levels. There was no language restriction. Eligibility criteria are detailed in online supplement DS2.

Outcome

Our primary outcome for all studies was depression diagnosed using one of the following:

(a) a standardised psychiatric interview for the DSM diagnoses of depressive disorders (e.g. the Structured Clinical Interview for DSM Disorders) or ICD diagnoses of a depressive episode or

depression (e.g. the Composite International Diagnostic Interview);[22,23]

(b) a clinical diagnosis of a depressive disorder, depressive episode or depression not otherwise specified;

(c) a diagnosis of depression using an established cut-off point on a validated rating scale, such as a score of $\geqslant 16$ on the Center for Epidemiological Studies – Depression scale or $\geqslant 8$ on the Geriatric Depression Scale.[24,25]

For RCTs that enrolled patients with depression our secondary outcome was change in depressive symptoms using a validated rating scale. This secondary outcome was not used for RCTs that enrolled non-depressed participants or other study designs because it was not meaningful in those contexts.

Study selection and data abstraction

Two authors (R.A. and Z.S.) independently reviewed all titles and abstracts identified by the search. Articles were selected for full-text review if inclusion criteria were met or if either reviewer considered them potentially relevant. Disagreements were resolved by discussion between the two reviewers, and a third author (S.M.) was available to determine eligibility if consensus could not be reached. Initial agreement was assessed using an unweighted κ value. Data were extracted by two authors (R.A. and Z.S.) independently using a form developed for this review, with disagreements resolved as above. We attempted to contact study authors for additional or missing information when needed.

Assessment of risk of bias

Two reviewers (R.A. and Z.S.) independently assessed the risk of bias using a modified Newcastle–Ottawa Scale (see online supplement DS3).[26] In observational studies one of the main sources of bias is confounding. Known confounders can be statistically adjusted, but unknown confounders may still result in bias. It was decided *a priori* that studies that adjusted for factors shown elsewhere to affect vitamin D levels (chronic disease, body mass index, geographical location, season and physical activity)[27,28] would be considered to have a low risk of bias, studies that adjusted only for other potential confounders would have an unclear risk of bias, and any studies that did not adjust for any confounders would have a high risk of bias. Publication bias was assessed using funnel plots.

Statistical analysis

Search results were compiled using citation management software (RefWorks version 2.0; ProQuest, http://www.refworks.com). Statistical analysis was performed using Review Manager software (Revman version 5.1; Cochrane Collaboration, Oxford, UK), Epi Info version 6.0 (CDC, Atlanta, Georgia, USA) and PASW Statistics version 18.0 (SPSS, Chicago, Illinois, USA) for Mac.

Case–control studies

The standardised mean difference (SMD) of vitamin D levels between the participants with depression and the healthy controls was calculated. An SMD below 0.4 was considered small, 0.4–0.7 moderate and over 0.7 large.[29] Our protocol proposed pooling SMDs for meta-analysis using a random effects model.

Cross-sectional studies

Our protocol proposed examining adjusted odds ratios (ORs) of depression for those with or without vitamin D deficiency (as defined in each study) and the associated 95% confidence intervals. We planned to pool the adjusted ORs for meta-analysis. Unfortunately the cross-sectional studies used different reference categories of vitamin D concentration (either <50 nmol/l or the lowest and highest category) and presented data using different quartiles, tertiles or categories. After protocol development, but prior to analysing the data, we decided to use the adjusted OR of depression for the lowest *v.* highest vitamin D categories reported. The inverse variance method and random effects model were used for all meta-analyses. A random effects model was chosen because we anticipated heterogeneity among studies. Where ORs were reported for subgroups of patients within a single study, they were combined into a single OR for our analysis.[30]

Cohort studies

As with the analysis of cross-sectional studies, the variability in presentation of results of the cohort studies precluded the calculation of a pooled adjusted OR. We therefore contacted the authors of all three cohort studies to obtain the number of depressed participants and the person-years of follow-up in each category of vitamin D, and requested data using the cut-off point of 50 nmol/l. This allowed us to calculate hazard rates for each category, so that we could then account for losses to follow-up and variable follow-up periods; also, by assuming a constant hazard rate over time, we could pool hazard ratios using a cut-off point of 50 nmol/l. All authors provided some data, but one provided only data using the cut-off points of 37.5 nmol/l and 75 nmol/l.[9] We therefore performed a sensitivity analysis using these two cut-off points in a meta-analysis.

Additionally, we decided to analyse the cohort data using the highest *v.* lowest vitamin D categories in order to use the adjusted results and take confounding into account. For this analysis the adjusted hazard ratios were used; the adjusted OR from one study was converted first to a relative risk and then to a hazard ratio (HR).[10] Finally, we performed a third analysis in which we calculated the increase in the natural logarithm of the hazard rate (ln(HR)) of depression per 20 nmol/l decrease in vitamin D for each study.[31] The mid-point of each category of vitamin D was calculated and half the width of the adjacent category was used to define the corresponding point for open-ended categories. The ln(HR) for each category was then regressed on the vitamin D mid-points (divided by 20) using a linear model, with the data weighted by the inverse variance of the ln(HR), to generate a coefficient that represented the change in ln(HR) per 20 nmol/l decrease in vitamin D and its associated standard error. The coefficients for each study were then pooled for meta-analysis.

Assessment of heterogeneity

Heterogeneity between the studies was measured using Cochran's Q statistic, with a probability value of $P<0.05$ (two-tailed) considered statistically significant. The I^2 statistic was used to quantify the degree of heterogeneity and we considered values below 25% to be low, 25–50% moderate and over 50% high.[32]

Subgroup and sensitivity analyses

We planned the following subgroup analyses *a priori*: gender, age $\geqslant 65$ years, prevalence of vitamin D deficiency, proportion of participants with a disease known to affect vitamin D, and adjustment for different confounders. We planned *a priori* to perform a sensitivity analysis excluding studies with a high risk of bias. For the cohort studies we performed a sensitivity analysis using the cut-off point of 37.5 nmol/l compared with 75 nmol/l for the one study that did not provide data using our standard cut-off

point of 50 nmol/l. We also performed a sensitivity analysis for the cross-sectional studies excluding one study that had recruited participants aged 15–39 years[33] (our inclusion criteria specified adults aged 18 years).

Results

Our primary search identified 6675 citations (Fig. 1). No additional article or abstract was selected from other sources. After duplicates were removed 5484 citations remained for title and abstract screening. Of these, 35 were identified and retrieved for full-text screening; all were in English. After full text review, one case–control study,[34] three cohort studies,[9,10,35] and ten cross-sectional studies,[8,11,20,21,30,33,36–39] met eligibility criteria and were included (unweighted $\kappa = 0.75$). Figure 1 lists the reasons for excluding the other studies.[19,40–58]

Study characteristics

Baseline information on the case–control, cross-sectional and cohort studies is presented in Tables 1 and 2. There were 31 424 participants in total. All studies were published between 2006 and 2011; study locations included the USA, Europe and East Asia. Seven of the ten cross-sectional studies included older adults.

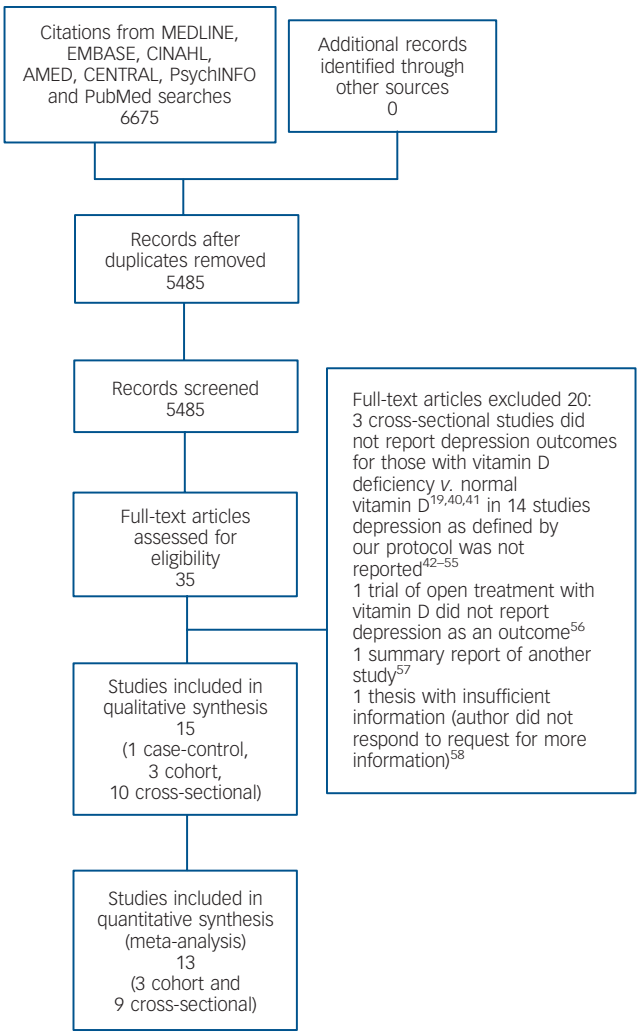

Fig. 1 Study selection process.

Risk of bias in included studies

Case–control study

The agreement between the reviewers in assessing the risk of bias for the case–control study across the nine points of the Newcastle–Ottawa Scale was 100%, with both reviewers assigning the same four points. There was potential for selection bias as participants were recruited through advertisements and were all premenopausal women; also, the study did not control for known confounders.

Cross-sectional studies

Agreement between the reviewers in assessing the risk of bias in cross-sectional studies was 95%, unweighted $\kappa = 0.84$. Four studies were thought to be unrepresentative of the general population: Johnson *et al* included only low-income older adults;[20] Lee *et al* included only elderly men;[37] and the two studies by Wilkins *et al* included only elderly participants, half of whom in the 2006 study were purposely selected to have Alzheimer's disease, and in the 2009 study were purposely selected to include African Americans and European Americans in equal numbers.[8,39] Seven studies received a high risk of bias assignment for assessment of outcome because they used cut-off points on self-reported psychiatric rating scales. Two studies received an unclear risk of bias assignment for using administered surveys, which were felt to have an intermediate risk of bias between a self-report scale and clinician-administered standardised psychiatric interview. All studies adjusted for multiple confounders (online supplement DS4). The funnel plot (online supplement DS5) did not suggest significant publication bias.

Cohort studies

Agreement between the reviewers in assessing the risk of bias across cohort studies was 88%, unweighted $\kappa = 0.61$. Two studies[9,10] were considered unrepresentative of the general population, and the study by May *et al* was thought to be at high risk of bias for selection of the non-exposed cohort because vitamin D levels were obtained at the discretion of treating physicians,[9] which may have biased whose vitamin D levels were observed. All studies included in this review adjusted for multiple confounders, but May *et al* did not measure or adjust for physical activity, body mass index or the presence of chronic diseases and therefore received an unclear risk of bias rating. Chan *et al* and Milaneschi *et al* used cut-off points on self-report scales to diagnose depression,[10,35] which is less reliable than a clinical diagnosis, and therefore these studies were rated at high risk of bias. Although May *et al* used a clinical diagnosis of depression using ICD-9 codes, it was not clear whether all participants underwent a clinical assessment or whether record linkage was used; an unclear risk of bias was therefore assigned. May *et al* presented the average duration of follow-up period but did not otherwise describe loss to follow-up, and therefore this received an unclear rating. Because there were only three cohort studies the funnel plot was uninformative.[59] Further information on the risk of bias assessments is included in online supplement DS5.

Outcome evaluation and meta-analysis

A summary of the results from the cross-sectional and cohort meta-analyses including subgroup and sensitivity analyses is presented in Table 3. Three cross-sectional studies did not report ORs, and the authors of these studies were contacted.[20,36,39] One author replied and the OR provided was included in the meta-analysis;[36] an unadjusted OR and 95% CI were calculated

Table 1 Characteristics of included studies: case–control and cross-sectional studies

Study, year	Country	Population	Mean age, years	*n*	Diagnosis of depression	Categories of vitamin D, nmol/l	Measurement of vitamin D
Case–control studies							
Eskandari (2007)[34]	USA	Women aged 21–45 years	35	133	SCID	NA	CPBA
Cross-sectional studies							
Ganji (2010)[33]	USA	Men and women aged 15–39 years	27.5	7970	DIS	<50, 50–75, >75	RIA
Hoogendijk (2008)[36]	The Netherlands	Men and women aged 65–95 years	75.1	1282	Score ⩾16 on CES-D	Cut-off point 50	CPBA
Johnson (2008)[20]	USA	Older adults	77	158	Score ⩾11 on GDS-10	<25, 25–50, >50	RIA
Lee (2011)[37]	Several European countries	Men aged 40–79 years	59.7	3151	Score ⩾14 BDI-II	<25, 25–49.9, 50–74.9, >75	RIA
Nanri (2009)[30]	Japan	Men and women aged 21–67 years	43.4	527	Score ⩾16 on CES-D	Quartiles (medians 53.75, 64.75, 72.5, 82)	CPBA
Pan (2009)[11]	China	Men and women aged 50–70 years	NR	3262	Score ⩾16 on CES-D	Quartiles (means 26.1, 41.1, 65.1)	RIA
Stewart (2010)[38]	UK	Men and women aged ⩾65 years	73.7	2070	Score ⩾3 on GDS-10	<25, <50, <75	RIA
Wilkins (2006)[8]	USA	Men and women aged >60 years	74.5	80	Depression Symptoms Inventory	<25, 25–50, >50	RIA
Wilkins (2009)[39]	USA	Men and women aged >55 years	74.99	60	Depressive Features Inventory	Cut-off point 50	CPBA
Zhao (2010)[21]	USA	Men and women aged ⩾20 years	NR	3916	Score ⩾10 on PHQ-9	<37.5, 37.5–50, 50–65, >65	RIA
Total cross-sectional studies				22 476			

BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies – Depression scale; CPBA, competitive protein binding assay; DIS, Diagnostic Interview Schedule; GDS, Geriatric Depression Scale; NA, not applicable; NR, not reported; PHQ, Patient Health Questionnaire; RIA, radioimmunoassay; SCID, Structured Clinical Interview for DSM-IV.

Table 2 Characteristics of included studies: cohort studies

Study, year	Country	Population	Mean age, years	*n*	Diagnosis of depression	Categories of vitamin D, nmol/l	Measurement of vitamin D	Loss to follow-up, %	Length of follow-up, years
Chan (2011)[10]	China	Men aged >65 years	72.5	801	Score 8 on GDS	Quartiles (<63, 64–76, 77–91, >92) and categories (<50, 50–74, 75–99, >100)	RIA	21	4
May (2010)[9]	USA	Cardiovascular patients aged ⩾50 years	73.1	7358	Clinical diagnosis	Categories (<37.5, 37.5–75, 75–125, >125	CIA	NR[a]	1[b]
Milaneschi (2010)[39]	Italy	Men and women aged ⩾65 years	74.4	656	Score ⩾16 on CES-D	Tertiles (<31.7, 31.7–53.9, >53.9) and cut-off point (<50 or ⩾50)	RIA	3	6
Total cohort studies				8815					

CIA, chemiluminescent immunoassay; CES-D, Center for Epidemiological Studies – Depression scale; GDS, Geriatric Depression Scale; NR, not reported; RIA, radioimmunoassay.
a. Most of cohort (71%) 'not evaluable' at 500 days.
b. Mean follow-up period.

for another study using data provided in the paper and Epi Info version 6.0,[39] but the third study could not be included.[20]

Case–control study

One study compared vitamin D levels in women with depression and healthy controls.[34] The mean difference between the groups was 17.5 nmol/l ($P=0.002$), with an SMD of 0.60 (95% CI 0.23–0.97). This represented a moderate difference,[29] which was also clinically significant. Meta-analysis could not be performed as only one study met our inclusion criteria.

Cross-sectional studies

The cross-sectional studies measured rates of depression and vitamin D in a population at a single point in time to determine whether there was an association between depression and vitamin D levels. Nine studies reported on depression for the lowest *v.* the highest vitamin D categories, with a pooled OR of 1.31, 95% CI 1.00–1.71 (Fig. 2). There was substantial heterogeneity between studies ($I^2=54\%$, $\chi^2=17.24$, $P=0.03$). The only subgroup analysis that could be performed was of studies that had an average sample age of 65 years (online supplement DS5). When these studies were combined there was an increased – although non-significant – odds of depression with low vitamin D (OR = 1.54, 95% CI 1.00–2.40). A sensitivity analysis excluding the study by Ganji *et al* (online supplement DS6) had a minimal effect on our summary estimate (OR = 1.34, 95% CI 0.99–1.83, $I^2=59\%$, $\chi^2=17.16$, $P=0.02$).[33]

Cohort studies

Three studies measured vitamin D levels at baseline in non-depressed individuals and followed them over time to determine whether vitamin D levels were associated with a risk of developing

Table 3 Summary of results from the meta-analysis of cross-sectional and cohort studies of the relationship between vitamin D and depression

	Number of studies	Participants *n*	Vitamin D categories	Pooled OR or HR (95% CI)	I^2, %
Cross-sectional studies					
All studies	9	22 318	Lowest *v.* highest	OR = 1.31 (1.00 to 1.71)	5 ($P = 0.03$)
Older adults	4	3492	Lowest *v.* highest	OR = 1.54 (1.00 to 2.40)	49 ($P = 0.12$)
Cohort studies					
	3	8815	Lowest *v.* highest	HR = 2.21 (1.40 to 3.49)	21 ($P = 0.28$)
	3	8815	Change in HR depression per 20 nmol/l change in vitamin D	β −0.19 (−0.41 to 004)	100 ($P < 0.00001$)
	3	8815	Vitamin D cut-off points of 50 nmol/l and 37.5 nmol/l (May *et al*)	HR = 1.04 (0.59 to 1.86)	98 ($P < 0.00001$)
	3	8815	Vitamin D cut-off points of 50 nmol/l and 75 nmol/l (May *et al*)	HR = 1.31 (0.97 to 1.77)	91 ($P < 0.0001$)

HR, hazard rate; OR, odds ratio.

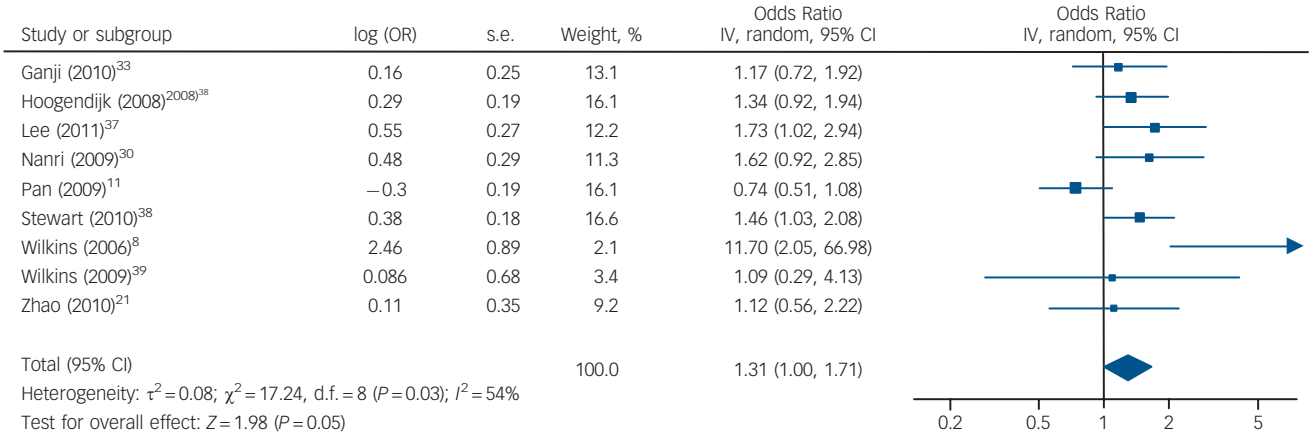

Fig. 2 Cross-sectional studies: forest plot of the odds ratio (OR) of depression for the lowest *v.* highest vitamin D categories. Squares to the right of the vertical line indicate that low vitamin D was associated with increased odds of depression, squares to the left of the vertical line indicate that low vitamin D was associated with decreased odds of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall OR of depression with low vitamin D from the meta-analysis and the corresponding 95% confidence interval (*OR provided by Dr B. Penninx, personal communication, 25 July 2011).

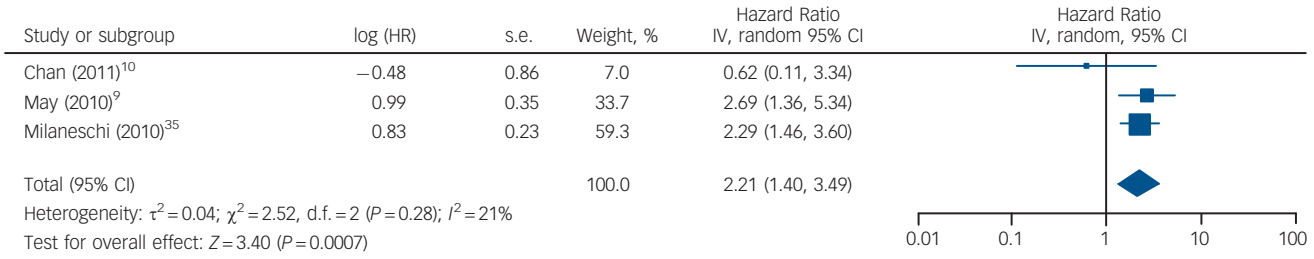

Fig. 3 Cohort studies: forest plot of the hazard ratio (HR) of depression for the lowest *v.* highest vitamin D categories. Squares to the right of the vertical line indicate that vitamin D deficiency was associated with an increased risk of depression, whereas squares to the left of the vertical line indicate that vitamin D deficiency was associated with a decreased risk of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall HR of depression with vitamin D deficiency from the meta-analysis and the corresponding 95% confidence interval.

depression. There was a statistically significant increased risk of depression with low vitamin D (HR = 2.21, 95% CI 1.40–3.49) with non-significant heterogeneity ($I^2 = 21\%$, $\chi^2 = 2.52$, $P = 0.28$) when the HRs for depression for the lowest *v.* highest vitamin D categories in the three cohort studies were pooled (Fig. 3). The change in the ln(HR) of depression per 20 nmol/l change in vitamin D level was calculated for each study and pooled. There was a non-significant decreased ln(HR) of depression for each 20 nmol/l increase in vitamin D (β = −0.19, 95% CI −0.41 to 0.04; Fig. 4).

The HRs of depression for those with and without vitamin D levels below 50 nmol/l from the studies by Chan *et al* and

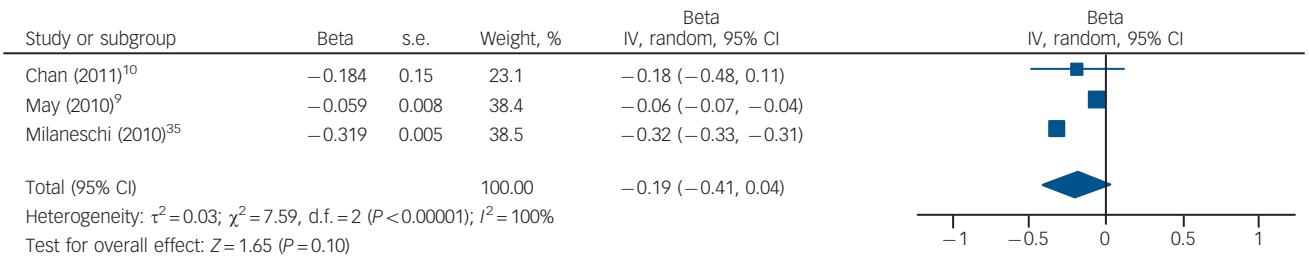

Fig. 4 Cohort studies: forest plot of the change in the natural logarithm of the hazard rate ln(HR) of depression per 20 nmol/l change in vitamin D using trend estimation. Squares to the right of the vertical line indicate a positive slope or increased risk of depression with increased vitamin D levels, whereas squares to the left indicate a negative slope or decreased risk of depression with increased vitamin D levels. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall change in ln(HR) of depression per 20 nmol/l change in vitamin D from the meta-analysis and the corresponding 95% confidence interval.

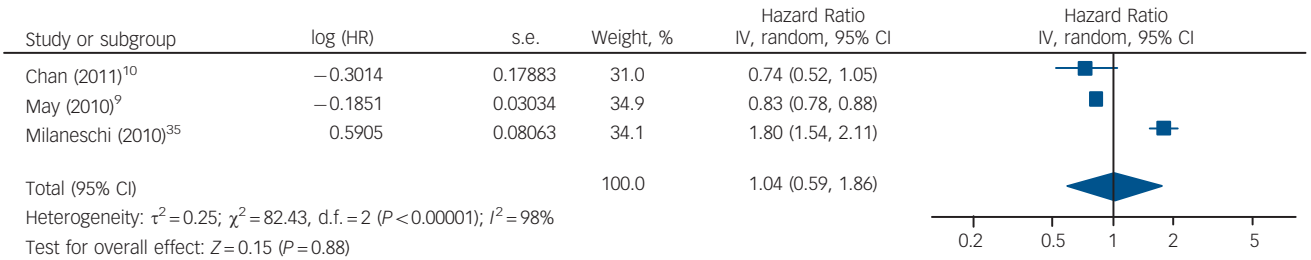

Fig. 5 Cohort studies: forest plot of the hazard ratios (HR) of depression with vitamin D deficiency using cut-off points of 50 nmol/l and 37.5 nmol/l (see caption to Fig. 3 for explanation of symbols).

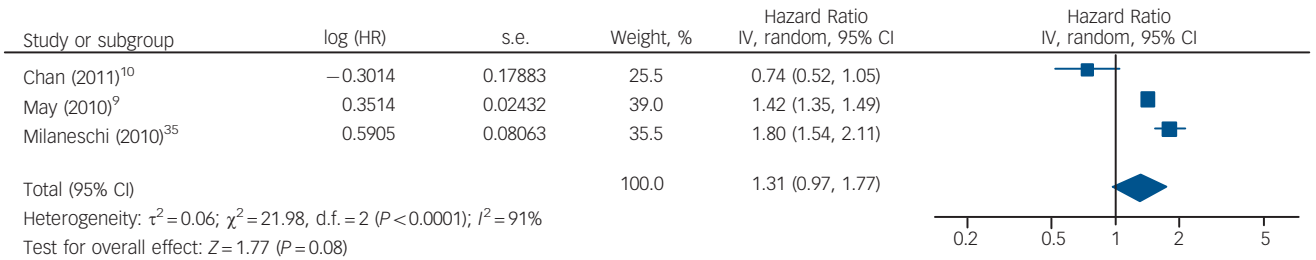

Fig. 6 Cohort studies: forest plot of the hazard ratios (HR) of depression with vitamin D deficiency using cut-off points of 50 nmol/l and 75 nmol/l (see caption to Fig. 3 for explanation of symbols).

Milaneschi *et al* were pooled with the HR of depression for vitamin D below *v.* above 37.5 nmol/l from the study by May *et al* (Fig. 5). The overall HR in this analysis was not significant (HR = 1.04, 95% CI 0.59–1.86). In the second analysis using cut-off points, the HR of depression for vitamin D below *v.* above 75 nmol/l from the May *et al* study was pooled with the other results (Fig. 6). This also gave a non-significant HR of 1.31 (95% CI 0.97–1.77). Interestingly, using the cut-off point of 75 nmol/l compared with 37.5 nmol/l changed the direction of the effect in this study. This appears to result from the highest hazard rate, and largest number of participants, being in the 37.5–75 nmol/l category. Therefore, if this group is included in the vitamin D deficient group (cut-off point 75 nmol/l), the HR suggests an increased risk of depression with vitamin D deficiency. However, if this group is included in the normal vitamin D group (cut-off point 37.5 nmol/l), the HR suggests a decreased risk of depression with vitamin D deficiency. Therefore, the effect of vitamin D deficiency at levels below 50 nmol/l cannot be reliably determined from this study.

No planned subgroup or sensitivity analysis could be performed because of insufficiently reported data and inability to obtain such data from authors.

Discussion

Our systematic review identified one case–control study, ten cross-sectional studies and three cohort studies investigating the association between depression and vitamin D deficiency, but no randomised controlled trial. The single case–control study showed a moderate difference in vitamin D levels between women with depression and healthy controls. Meta-analysis of the cross-sectional studies demonstrated an increased but non-significant odds of depression for the lowest compared with the highest vitamin D categories (OR = 1.31, 95% CI 1.00–1.71, $P = 0.05$). Limiting the analysis to studies with an average participant age of 65 years or over did not substantially change the overall

estimate or statistical significance. There was considerable variability in the vitamin D categories used in the cohort studies, and therefore three different meta-analyses were performed. Our pooled HR of the lowest compared with the highest vitamin D categories in the three cohort studies showed a significantly increased HR of depression with low vitamin D levels (HR = 2.21, 95% CI 1.40–3.49, $P < 0.001$). The pooled change in ln(HR) of depression per 20 nmol/l change in vitamin D level across the three cohort studies also showed an increased hazard of depression with decreasing vitamin D concentration, although this was not significant (β −0.19, 95% CI −0.41 to 0.04, $P = 0.1$). Finally, we analysed the data using different cut-off points as provided in the studies, which yielded different but non-significant pooled HR: 1.04 (95% CI 0.59–1.86) *v.* 1.31 (95% CI 0.97–1.77). Overall, the summary estimates of all analyses suggest a relationship between vitamin D and depression, and all but one were close to being statistically significant.

Strengths and limitations

To the best of our knowledge this is the first systematic review or meta-analysis that has analysed the relationship between vitamin D deficiency and depression. We performed a transparent and methodologically rigorous systematic review of the literature. We developed a comprehensive search to identify articles and assessed their eligibility, extracted data and assessed risk of bias in each study in duplicate with a good level of agreement. Our protocol was developed *a priori* and any *post hoc* analyses were clearly identified. A particular strength was the method used and extensive analyses performed in an attempt to present the data in a uniform and consistent manner to allow for comparison and combination. We were also successful in obtaining supplemental information from several authors, which allowed us to include the majority of studies.

There are several limitations to our systematic review. As, at the time of our review, there was no RCT of vitamin D for depression our review was restricted to observational studies, which usually yield lower-quality evidence than RCTs. Reverse causality, in which patients with depression have less exposure to the sun and therefore lower vitamin D levels, cannot be ruled out in the cross-sectional studies. In addition there were potential biases across all study designs. Several cross-sectional studies had unrepresentative samples, used self-reports of depression and had small sample sizes. The study results were generally consistent, with the exception of those from Pan *et al* who reported a decreased odds of depression with low vitamin D.[11] This was the only cross-sectional study conducted in China, and geographical differences in the nature and prevalence of vitamin D deficiency and depression might explain their discrepant findings. One small study could not be included in the quantitative analysis as insufficient information was available; it found an increased prevalence of depression with vitamin D deficiency[20] and therefore it is unlikely that it would have significantly affected our findings. Most studies adjusted for multiple confounders; however, unadjusted data were used to generate an odds ratio for one study where an adjusted OR was not provided.[39] All the cohort studies had problems with bias and the largest one had a high risk of bias. Publication bias could not be ruled out, and it is possible that additional cohort studies have measured vitamin D and depression but not reported negative results. The majority of the meta-analyses of the cross-sectional studies and cohort studies had significant heterogeneity and lacked precision. Studies used variable definitions of vitamin D deficiency, and therefore we performed analyses using the lowest *v.* highest vitamin D categories and different cut-off points rather than adhering to a strict definition of deficiency. As a result of these limitations the overall quality of the evidence from each study is low and therefore some uncertainty remains about the true association between vitamin D deficiency and depression.

Implications of the study

The importance of vitamin D to many brain processes including neuroimmunomodulation and neuroplasticity suggests that it might have a role in psychiatric illness such as depression. The biological plausibility of the association between vitamin D and depressive illness has been strengthened by the identification of vitamin D receptors in areas of the brain implicated in depression,[4] the detection of vitamin D response elements in the promoter regions of serotonin genes,[60] and demonstration of interactions between vitamin D receptors and glucocorticoid receptors in the hippocampus.[61] Given the high prevalence of both vitamin D deficiency and depression, an association between these two conditions would have significant public health implications, particularly as supplementation with vitamin D is cost-effective and without significant adverse effects. The observational studies to date provide some evidence for a relationship between vitamin D deficiency and depression, but RCTs are urgently needed to determine whether vitamin D can prevent and treat depression.

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EXTRA CONTENT ONLINE

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Vitamin D deficiency and depression in adults: systematic review and meta-analysis

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Supplement DS1 Search strategy

EMBASE Search Strategy

1 exp DEPRESSION/
2 exp major depression/
3 exp mood disorder/
4 exp MOOD/
5 exp AFFECT/
6 (depression or depressive disorder* or mood disorder* or mental disorder* or affect or affective symptom* or affective disorder* or major depress* or unipolar depress* or psychiatric symptom* or mood).mp
7 1 or 2 or 3 or 4 or 5 or 6
8 exp vitamin D/
9 exp vitamin D deficiency/
10 exp vitamin blood level/
11 exp cholecalciferol/
12 exp ergocalciferol/
13 (vitamin D or vitamin D deficien* or hydroxycholecalciferol* or 25-hydroxyvitamin D or cholecalciferol* or ergocalciferol* or calcifediol* or calcitriol* or hydroxyvitamin*).mp
14 8 or 9 or 10 or 11 or 12 or 13
15 7 and 14
16 Nonhuman/ not human/
17 15 not 16

MEDLINE and Pubmed Search Strategy

1 exp Depression/
2 exp Mood Disorders/
3 exp Depressive Disorder/
4 exp Affect/
5 exp Affective Symptoms/
6 (depression or depressive disorder* or mood disorder* or mental disorder* or affect or affective symptom* or affective disorder* or major depress* or unipolar depress* or psychiatric symptom* or mood).mp
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Vitamin D/
9 exp Vitamin D Deficiency/
10 exp cholecalciferol/
11 exp ergocalciferol/
12 exp Hydroxycholecalciferols/
13 (vitamin D or vitamin D deficien* or hydroxycholecalciferol* or 25-hydroxyvitamin D or cholecalciferol* or ergocalciferol* or calcifediol* or calcitriol* or hydroxyvitamin*).mp
14 8 or 9 or 10 or 11 or 12 or 13
15 7 and 14
16 Animals/ not humans/
17 15 not 16

PsycINFO Search Strategy

1 exp Major Depression/
2 exp Psychiatric Symptoms/
3 exp Emotional States/
4 exp Mental Disorders/
5 exp Affective Disorders/
6 (depression or depressive disorder* or mood disorder* or mental disorder* or affect or affective symptom* or affective disorder* or major depress* or unipolar depress* or psychiatric symptom* or mood).mp
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Vitamins/
9 exp Vitamin Deficiency Disorders/
10 (vitamin D or vitamin D deficien* or hydroxycholecalciferol* or 25-hydroxyvitamin D or cholecalciferol* or ergocalciferol* or calcifediol* or calcitriol* or hydroxyvitamin*).mp
11 8 or 9 or 10
13 7 and 11

AMED Search Strategy

1 exp Depression/
2 exp Depressive Disorder/
3 exp Affective disorders/
4 (depression or depressive disorder* or mood disorder* or mental disorder* or affect or affective symptom* or affective disorder* or major depress* or unipolar depress* or psychiatric symptom* or mood).mp
5 1 or 2 or 3 or 4
6 exp Vitamin D/
7 exp cholecalciferol/
8 exp Vitamins/
9 exp Dietary supplements/
10 (vitamin D or vitamin D deficien* or hydroxycholecalciferol* or 25-hydroxyvitamin D or cholecalciferol* or ergocalciferol* or calcifediol* or calcitriol* or hydroxyvitamin*).mp
11 6 or 7 or 8 or 9 or 10
12 5 and 11

CINAHL Search Strategy

S1 Depression +
S2 Affective Disorders +
S3 Mental Disorders + OR Mental Disorders, Chronic
S4 depression or depressive disorder* or mood disorder* or mental disorder* or affect or affective symptom* or affective disorder* or major depress* or unipolar depress* or psychiatric symptom* or mood
S5 Vitamin D + OR Vitamin D Deficiency + OR Cholecalciferol OR Ergocalciferols
S6 vitamin D or vitamin D deficien* or hydroxycholecalciferol* or 25-hydroxyvitamin D or cholecalciferol* or ergocalciferol* or calcifediol* or calcitriol* or hydroxyvitamin*
S7 S1 or S2 or S3 or S4
S8 S5 or S6
S9 S7 and S8

Supplement DS2 Detailed eligibility criteria

The following study designs were eligible for inclusion:
(1) (RCTs) that enrolled adults (age ≥ 18) with depression (major depressive disorder, depressive episode or depression NOS) and reported depression as the outcome of interest as defined below or depressive symptoms measured using a validated scale.
(2) RCTs that enrolled any adults and reported depression outcomes of interest.
(3) case- control studies that compared adults with depression to healthy controls and reported vitamin D measurements.
(4) cross-sectional studies that measured vitamin D levels in adults and reported depression outcomes of interest associated with vitamin D deficiency (as defined by each study, Tables 1 & 2) compared to those with normal vitamin D.
(5) cohort studies that measured serum vitamin D levels in adults and reported the rates of depression as the outcome of interest at follow-up for those with vitamin D deficiency compared to those with normal vitamin D.

Supplement DS3 Modified Newcastle–Ottawa Scales

Newcastle-Ottawa Scale for case–control studies data abstraction form[26]					
Bias	**Case control**	*** High Quality**			
Selection **(max 4*)**	Is the case definition adequate?	☐ Yes, with independent validation	☐ Yes, eg record linkage or based on self report	☐ No description	
	Representativeness of the cases	☐ Consecutive or obviously representative series of cases	☐ Potential for selection bias or not stated		
	Selection of controls	☐ Community controls	☐ Hospital controls	☐ No description	
	Definition of controls	☐ No history of disease (endpoint)	☐ No description of source		
Comparability **(max 2*)**	Cases and controls on the basis of the design or analysis	☐ Study controls for important factor (chronic diseases, BMI or physical activity)	☐ No control for any important factor		
		☐ Study controls for a 2nd important factor	☐ No control for a 2nd important factor		
Exposure **(max 3*)**	Ascertainment of exposure	☐ Secure record ☐ Structured interview where blind to case/control status	☐ Interview not blinded to case/control status	☐ Written self report or medical record only	No des'n
	same method of ascertainment for cases	☐ Yes	☐ No		
	Non-response rate	☐ Same rate for both groups	☐ Non respondents described	☐ Rate different and no designation	

Newcastle–Ottawa Scale for cohort studies data abstraction form[26]				
Bias	**Cohort**	*** High Quality**		
Selection **(max 4*)**	Representativeness of **exposed** cohort (Vitamin D deficient and insufficient participants)	☐ **Truly representative** of the general population ☐ **Somewhat representative** of general population	☐ **Selected group** eg: particular disease group, particular occupation	☐ **No description** of derivation of cohort
	Selection of **non exposed** cohort (adequate vitamin D levels)	☐ Drawn from the **same community** as the exposed cohort	☐ Drawn from a **different source**	☐ no description of derivation of non exposed cohort
	Ascertainment of **exposure**	☐ Reliable measurement of vitamin D	☐ Reported intake of vitamin D	☐ no description
	Demonstration that outcome of interest was not present at start of study	☐ yes	☐ no	
Comparability **(max 2*)**	Comparability of cohorts on basis of design or analysis	☐ Study controls for important factor (chronic diseases, BMI or physical activity)	☐ Fails to control for an important factor	
		☐ Study controls for any additional factor	☐ Does not control for any factors	
Outcome **(max 3*)**	Assessment of outcome	☐ Independent blind assessment Record linkage	☐ Self report	☐ No description
	Was **follow-up long enough** for outcome to occur	☐ Yes (>=3 months)	☐ No (<3 months)	
	Adequacy of follow up of cohorts	☐ Complete follow up-**all** subjects accounted ☐ Subjects lost to follow up unlikely to introduce bias – small # lost (<20%) or description provided of lost	☐ Follow up rate >80% and no description of the lost	☐ No statement

Newcastle–Ottawa Scale adapted for cross-sectional studies data abstraction form[26]				
Bias	**Cross-Sectional Study**	*** High Quality**		
Selection **(max 3*)**	Representativeness of **exposed** cohort (Vitamin D deficient participants)	☐ **Truly representative** of the general population ☐ **Somewhat representative** of general population	☐ **Selected group** eg: particular disease group, particular occupation	☐ **No description** of derivation of cohort
	Selection of **non exposed** cohort (adequate vitamin D levels)	☐ Drawn from the **same community** as the exposed cohort	☐ Drawn from a **different source**	☐ no description of derivation of non exposed cohort
	Ascertainment of **exposure** (Vitamin D measurement)	☐ **Secure record** (reliable measurement of vitamin D)	☐ Reported intake of vitamin D	☐ no description
	Demonstration that outcome of interest was not present at start of study	☐ N/A		
Comparability **(max 2*)**	Comparability of cohorts on basis of design or analysis	☐ Study controls for chronic diseases or other important factor	☐ No control for any important factors	
		☐ Study controls for any additional factor		
Outcome **(max 1*)**	Assessment of outcome (depression)	☐ Independent blind assessment Record linkage	☐ Self report	☐ No description
	Was **follow-up long enough** for outcome to occur	☐ N/A		
	Adequacy of follow up of cohorts	☐ N/A		

Supplement DS4 Adjustment for potential confounding variables for analyses across included studies

CASE-CONTROL STUDIES	
Study, Year	**Adjusted variables**
Eskandari, 2007	None
CROSS-SECTIONAL STUDIES	
Study, Year	**Adjusted variables**
Ganji, 2010	Age, sex, race/ethnicity, geographical location, urbanization, vitamin/mineral supplement use, prescription medication use, poverty income ratio, BMI, serum creatinine
Hoogendijk, 2008	Age, sex, BMI, smoking, chronic conditions
Johnson, 2008	No OR provided, study adjusted for demographic characteristics, sunlight exposure, supplemental intake of vitamin D, milk intake
Lee, 2010	Age, center, smoking, physical activity, alcohol, BMI, life events, psychotropic drugs and morbidities
Nanri, 2009	Age, sex, BMI, job position, marital status, alcohol, folate intake
Pan, 2009	Age, sex, urban/rural, BMI, physical activity, smoking status, number of chronic diseases, social activity level, marital status, household income, geographical location
Stewart, 2010	Age, sex, social class, season, vitamin D supplementation, smoking, BMI, long-standing illness, subjective general health
Wilkins, 2006	Age, ethnicity, sex, season
Wilkins, 2009	Unadjusted OR calculated, study adjusted for SBT score, PPT score, BMD, age, race
Zhao, 2010	Age, sex, ethnicity, education, marital status, BMI, serum creatinine, physical activity, alcohol, number of chronic diseases
COHORT STUDIES	
Study, Year	**Adjusted variables**
Chan, 2011	Age, BMI, education, PASE, number of ADLs, DQI, smoking status, alcohol use, season of measurement, number of chronic diseases, CSI-D score and serum (ln) PTH concentration
May, 2010	Age, sex, diabetes, season, PTH, hypertension, coronary artery disease, prior MI, heart failure, prior fracture, renal failure
Milaneschi, 2010	Age, baseline CES-D, ADL disabilities, use of antidepressants, number of chronic diseases, SPPB, high PTH, season of data collection

Legend: ADL = activities of daily living, BMD = bone mineral density, BMI = body mass index, CES-D = center for epidemiological studies depression scale, CSI-D = community screening instrument for dementia, MMSE = mini mental state examination, PASE = physical activity scale of the elderly, PPT = physical performance test, PTH = parathyroid hormone, SBT = short blessed test, SPPB = short physical performance battery

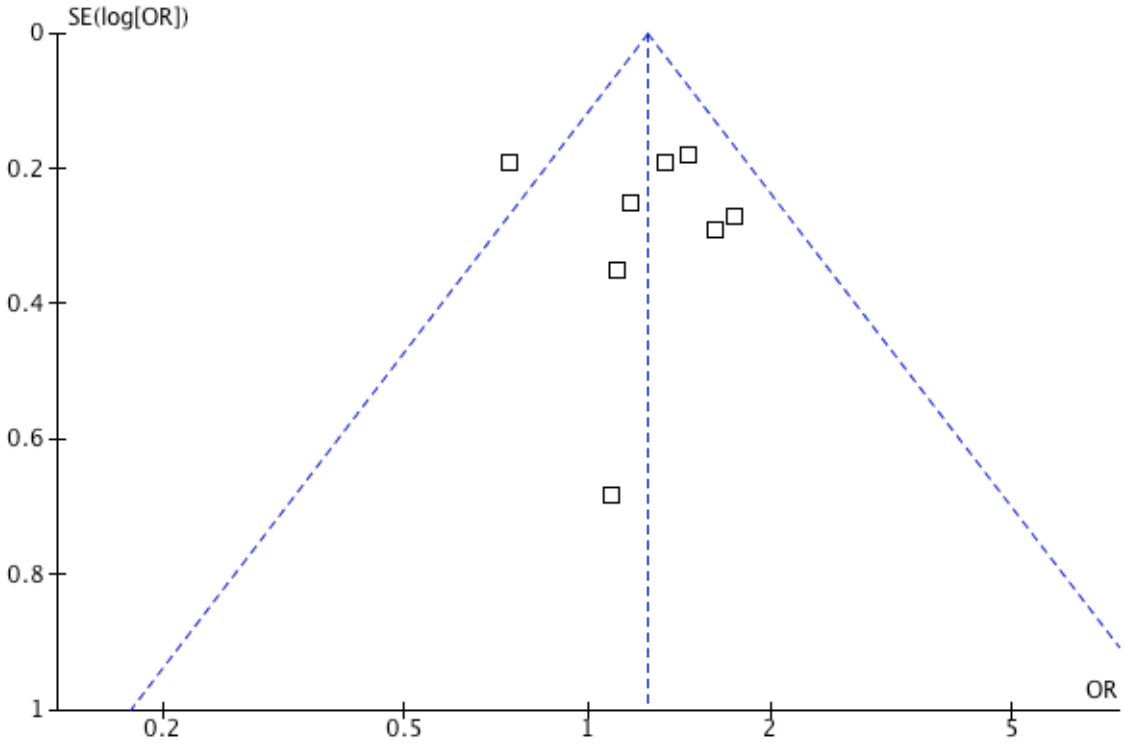
Supplement DS5 Risk of bias assessments

DS5(a) Risk of bias summary for cross-sectional studies: review authors' judgments about each risk of bias item for each included study using the Newcastle-Ottawa Scale[26]

	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Comparability of cohorts on basis of design or analysis (2 pts)	Assessment of outcome	TOTAL POINTS / 6
Ganji, 2010	1	1	1	2	1	6
Hoogendikj, 2008	1	1	1	2	0	5
Johnson, 2008	0	1	1	2	0	4
Lee, 2011	0	1	1	2	0	4
Nanri, 2009	1	1	1	2	0	5
Pan, 2009	1	1	1	2	0	5
Stewart, 2010	1	1	1	2	0	5
Wilkins, 2006	0	1	1	2	0	4
Wilkins, 2009	0	1	1	2	0	4
Zhao, 2010	1	1	1	2	0	5

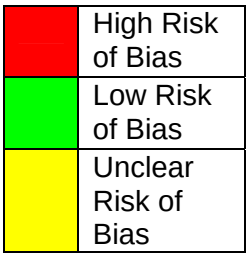
	High Risk of Bias
	Low Risk of Bias
	Unclear Risk of Bias

DS5(b) Funnel plot to look for publication bias for cross-sectional studies of the association between vitamin D and depression



DS5(c) Risk of bias summary for cohort studies: review authors' judgments about each risk of bias item for each included study using the Newcastle-Ottawa Scale[26]

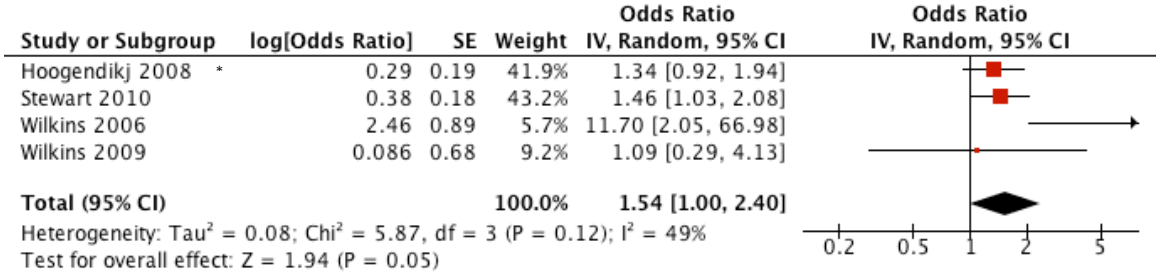
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts on basis of design or analysis (2 pts)	Assessment of outcome	Length of follow-up	Adequacy of follow-up	TOTAL POINTS / 9
Chan et al, 2011[4]	0	1	1	1	2	0	1	1	7
May et al, 2010[3]	0	0	1	1	1	0	1	0	4
Milaneschi et al, 2010[5]	1	1	1	1	2	0	1	1	8



Supplement DS6 Subgroup and sensitivity analyses

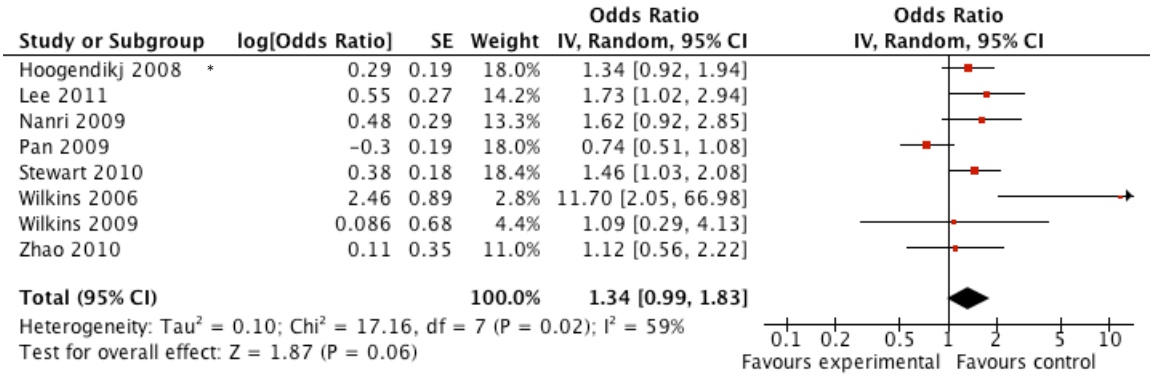
DS6(a) Cross-sectional studies: forest plot of the OR of depression for the lowest versus highest vitamin D categories for studies of older adults (average age ≥ 65)

Squares to the right of the vertical line indicate that low vitamin D was associated with an increased odds of depression, squares to the left of the vertical line indicate that low vitamin D was associated with a decreased odds of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall OR of depression from the meta-analysis and the corresponding 95% confidence interval. * OR provided by Dr.Penninx (personal communication) on July 25, 2011



DS6(b) Cross-sectional studies: forest plot of the OR of depression for the lowest versus highest vitamin D categories excluding Ganji 2010.

Squares to the right of the vertical line indicate that low vitamin D was associated with an increased odds of depression, squares to the left of the vertical line indicate that low vitamin D was associated with a decreased odds of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall OR of depression from the meta-analysis and the corresponding 95% confidence interval. * OR provided by Dr.Penninx (personal communication) on July 25, 2011



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