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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

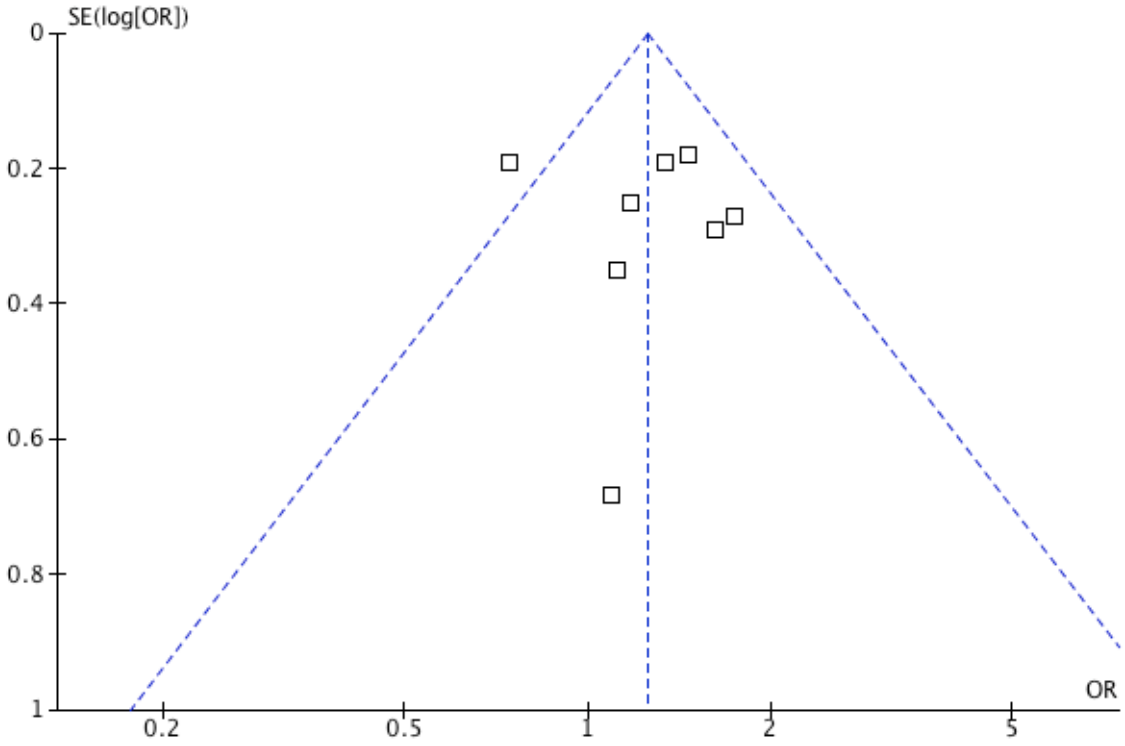
Supplement DS5 Risk of bias assessments

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

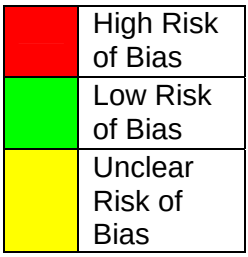
	High Risk of Bias
	Low Risk of Bias
	Unclear Risk of Bias

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]

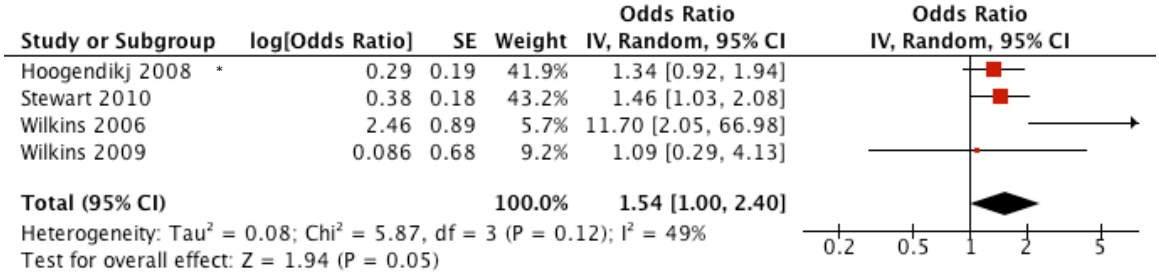
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts on basis of design or analysis (2 pts)	Assessment of outcome	Length of follow-up	Adequacy of follow-up	TOTAL POINTS / 9
Chan et al, 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