مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

Delivering the safest,
most effective and compassionate care
to each and every one of our patients

EVIDENCE SYNTHESIS SERVICE

Providing the best available knowledge about effective care

Vitamin D and Depression

RAPID REVIEW OF EVIDENCE

V2.0, 10 May 2015

Contents

Background

Hamad Medical Corporation and Evidence Synthesis

The vision of Hamad Medical Corporation is to provide the safest, most effective and compassionate care to each and every one of our patients. A service to provide evidence syntheses about the effectiveness of healthcare has been established to support local Qatar healthcare providers in applying the best available knowledge to healthcare decisions at organisational, team and individual clinician levels.

Syntheses of existing evidence are also essential to identify the needs for new research and to design research protocols.

The purpose of this evidence synthesis

The purpose of this Rapid Review report was to summarise the best available evidence to answer questions about the prevalence of Vitamin D deficiency; the association between Vitamin D deficiency and depression; and the possible role of Vitamin D deficiency in the prevention and treatment of depression.

Information has also been provided about defining Vitamin D deficiency or status, and about doses of Vitamin D used in clinical trials.

The report may assist in the design of new trials of Vitamin D and depression to be conducted by HMC.

Methods

Defining questions of interest for this report

Four clinical questions about Vitamin D and depression were of interest for this rapid review:

1. What is the prevalence of Vitamin D deficiency in Qatar and other Arabic countries?
2. Is there an association between Vitamin D deficiency and depression?
3. Does Vitamin D supplementation prevent the development of depression?
4. Does Vitamin D supplementation reduce depressive symptoms in patients with depression?

Evidence to answer the first two questions was required as background only to the treatment questions about the use of Vitamin D supplementation to prevent the development of depression and to reduce symptoms in patients with a diagnosis of depression.

The report also provides brief information about clinical trials of Vitamin D and depression that have been registered in various clinical trials registers.

Identifying potentially relevant published reports

To identify published reports that were potentially relevant to answering the clinical questions about the prevalence of Vitamin D deficiency and its possible association with depression, Medline was searched for reviews of studies and for observational studies. To identify published reports to answer the main clinical questions about treatment, ie the use of Vitamin D supplementation, Medline was searched for reviews and for controlled clinical trials. The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) was also searched for relevant reviews and for controlled trials of treatment with Vitamin D.

The detailed search strategy is shown in appendix 1.

CCDANCTR was also searched for records from clinical trials registers to provide information about relevant clinical trials that have been planned and may now be in progress.

Inclusion and exclusion of reviews

Initial examination of published reports identified by the search strategy was limited to review articles. The abstracts for all reviews were read by a single assessor to determine relevance to the questions of interest. Validation of all exclusions will be undertaken by a second assessor[1]. The ROBIS tool[2] was used to guide assessment of relevance, comparing target questions (as described above) with questions addressed by the review being assessed. Disagreements will be resolved by discussion (see footnote [1] and the rationale for all decisions to include or exclude have been documented (see table 1).

Characteristics of studies

The full text of included studies was examined by a single assessor to confirm their relevance to the target questions and ascertain whether or not they represented systematic reviews. For systematic reviews, information was extracted about the number of studies included in the review; the type and number of participants; the interventions and/or observations of interest; and the principal outcomes (see table 2).

Quality assessment of systematic reviews regarded as key resources

All systematic reviews judged to be key resources for this rapid review were assessed for quality by one assessor using the risk of bias assessment tool, ROBIS. A second assessor will evaluate a proportion of the publications to indicate consistency of judgements[3]. Findings for all reviews are presented in table 3.

Data extraction and findings

[1] Validation of excluded studies not undertaken for this draft version of the report.
[2] See: http://www.robis-tool.info/
[3] Evaluations of study quality by a second assessor not undertaken for this draft version of the report.

All data was extracted from key systematic reviews into an 'outcomes/findings' table (table 4). Data extraction was undertaken by a single reviewer. A second assessor will check data extraction for a proportion of studies to reduce the possibility of bias[4].

Information provided in the table is grouped in relation to: prevalence of Vitamin D deficiency; association between Vitamin D deficiency and depression; and Vitamin D supplementation for depression.

Information has been summarised about how studies cited by the included systematic reviews have defined Vitamin D deficiency or status, and what doses of Vitamin D (cholecalciferol) have been used in clinical trials.

Results

Search results

The Medline search identified 482 published articles, including 20 reviews. A further four reviews were identified by a search of CCDANCTR. Given the large number of reviews, 13 of which were published recently (in 2013 or 2014), no attempt was made to examine other types of published study in reviewing evidence about the association of Vitamin D deficiency and depression and the effects of Vitamin D supplementation on depression.

All the reviews were assessed for relevance to the target questions. Thirteen of the 24 reviews were assessed as being relevant to the target questions (see table 1) and were examined in more detail to ascertain their characteristics (see below).

None of the reviews identified specifically addressed the background question about prevalence of Vitamin D deficiency. Table 5 lists publications identified by the Medline search as being potentially relevant to the prevalence of Vitamin D deficiency.

Characteristics of included reviews

All reviews for which characteristics were assessed are cited in the reference list. Four of these were assessed as being narrative reviews and the full text for one systematic review (Lach & Krajewski-Siuda, 2010) was unavailable at the time of writing. The remaining seven systematic reviews were assessed for risk of bias.

Quality of reviews

Seven systematic reviews regarded as key sources for this rapid review were assessed for risk of bias using the ROBIS tool developed by The Cochrane Collaboration (see table 3)[5].

[4] Evaluations of data extraction by a second assessor not undertaken for this version of the report.
[5] Several assessments are to follow in the final version of this report.

Selection of published reports at each stage of assessment

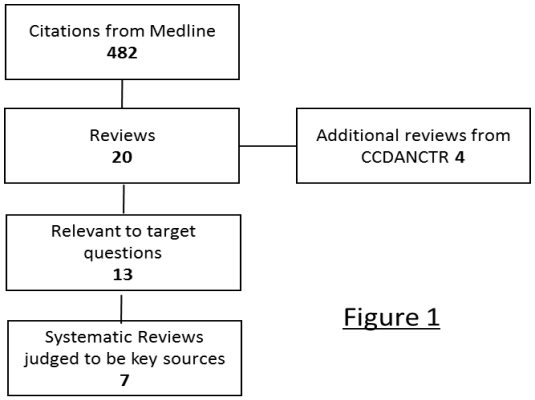

Figure 1

Findings from reviews and other selected sources

Prevalence of Vitamin D deficiency

None of the reviews identified for this report included studies of prevalence of Vitamin D deficiency. A number of other types of study were identified but, because prevalence was a background question only in this report, no attempt was made to undertake a comprehensive review of the evidence in these reports. They are, however, listed in table 5.

Vitamin D deficiency (hypovitaminosis D) is claimed to affect one billion people worldwide (Annweiler, et al., 2013). Qatar, and other countries in the Persian Gulf, are reported to have experienced changes in lifestyles associated with modernisation that result in sedentary activity, lack of sunlight and unhealthy diet, leading to Vitamin D under-nutrition and deficiency (Fields, et al., 2011).

Interestingly, a study of Vitamin D status amongst healthcare professionals working for Hamad Medical Corporation, a group that might be expected to be aware of issues about diet, lifestyle and health, concluded that the prevalence of Vitamin D deficiency within this group was very high (Mahdy, et al., 2010). It is reasonable to assume that, at least at the time of this study, the prevalence of Vitamin D deficiency would have been high amongst the wider Qatar population.

Association of Vitamin D deficiency and depression

Receptors for Vitamin D are present in areas of the brain that have been implicated in the pathophysiology of depression (Eyles, et al., 2005). The suggestion of an association between Vitamin D deficiency and depression therefore has biological plausibility.

Reports of individual studies of the association between Vitamin D deficiency and depression vary in their findings, with some studies reporting an association and others failing to demonstrate a relationship.

Four systematic reviews examining the association between Vitamin D and depression are included in this report.

The systematic review conducted by Anglin et al (Anglin, et al., 2013) included one case-control, 10 cross-sectional, and three cohort studies. The single case-control study showed a moderate difference in Vitamin D levels between women with depression and healthy controls. Meta-analysis of the 10 cross sectional studies demonstrated an increased but non-significant odds of depression for the lowest compared with the highest Vitamin D categories. The three cohort studies used very different

categories of Vitamin D and Anglin et al therefore conducted several meta-analyses, concluding that, overall, summary estimates suggested a relationship between Vitamin D and depression and that all but one of these were close to being statistically significant.

Anglin et al describe the limitations of their review that are due to the lower quality evidence provided by observational studies compared to RCTs. In particular, reverse causality cannot be ruled out, whereby hypovitaminosis D could result from depression, perhaps as a result of reduced exposure to sunlight and a poor dietary intake, deficient in Vitamin D-rich foods.

Annweiler et al (Annweiler, et al., 2013) undertook a re-analysis (a new random-effects MA) of five of the studies included in Anglin's review (one case-control, three cross-sectional and one cohort study), concluding that there is 'compelling evidence that depressed adults have lower Vitamin D concentrations than non-depressed adults' and suggesting that hypovitaminosis D should be treated. Annweiler et al also emphasise the possibility of reverse causality explaining the association and the need for new RCTs to establish a causal relationship between Vitamin D deficiency and depression.

The systematic review by Christensen (Christesen, et al., 2012) examined studies of the effect of Vitamin D status and supplementation on a range of pregnancy outcomes. Their review included only one observational study relating to Vitamin D and depression. This study concluded that postpartum depression was associated with 25(OH)D levels of <80 nmol/l. Interestingly, the report asserts that 25(OH)D levels associate directly with pregnancy associated breast cancer.

The systematic review by Ju et al (Ju, et al., 2013) included 11 case-control and five cohort studies. Meta-analysis showed that 25(OH)D levels were inversely associated with depression in five of 11 case control studies and two of five cohort studies. The authors reported that a 10ng/l increase in 25(OH)D was associated with an 8% decrease in incidence of depression in cohort studies and a 4% decrease in cross-sectional studies.

Vitamin D supplementation to prevent or treat depression

Reports of an association between Vitamin D deficiency and depression has led naturally to an interest in a possible role for Vitamin D supplementation as an intervention to prevent and to treat depression.

This report includes three systematic reviews that provide information about the effects of Vitamin D supplementation on preventing or treating depression, all published in 2014.

The systematic review reported by Li et al (Li, et al., 2014) included six RCTs with a total of 1203 participants. Only one of these studies recruited patients with established depression; the other five enrolled patients at risk of depression. Meta-analysis showed no significant effect of Vitamin D supplementation on post-intervention depression scores. Li et al reported that RCTs were low quality because of unexplained heterogeneity and the risk of selective outcome reporting.

Shaffer et al (Shaffer, et al., 2014) included seven RCTs with a total of 3,191 participants in a systematic review of the effects of Vitamin D supplementation on depressive symptoms. The authors report substantial heterogeneity of the included trials. Across all seven RCTs, meta-analysis demonstrated that Vitamin D supplementation neither worsened nor improved depressive symptoms. Sub-group analyses showed that Vitamin D supplementation was associated with a statistically significant moderate reduction in depressive symptoms in patients with clinically significant depressive symptoms and/or major depressive disorder (MDD). In participants with non-clinically significant depression, Vitamin D supplementation was associated with a small, but non-statistically significant effect.

The RCTs included by Shaffer et al varied substantially in dose, duration and route of administration of Vitamin D. There were two trials of patients with clinically significant depressive symptoms. The trial showing the largest effect of Vitamin D on depressive symptoms enrolled patients with MDD and used Vitamin D as an adjunct to pharmacotherapy with the SSRI, fluoxetine. The other trial that enrolled patients with significant depressive symptoms used substantially higher doses of Vitamin D than used in the other trials.

Spedding (Spedding, 2014) suggests that previous meta-analyses of studies of Vitamin D and depression may have failed to demonstrate efficacy because 'biological flaws' in some primary studies preclude them from testing the research hypothesis. Spedding's report sets out the 'biological flaws' regarded as relevant to studies of Vitamin D and depression, including ineffective interventions that failed to significantly change serum 25(OH)D levels and inclusion of participants whose baseline 25(OH)D levels were not measured or did not indicate Vitamin D deficiency[6].

Spedding's review includes a meta-analysis of two RCTs 'without biological flaws' selected because they used the same depression outcome measure (the Beck Depression Inventory). The participants of one study had a diagnosis of depression and the other study was of obese individuals. Meta-analysis of the two studies demonstrated a statistically significant positive effect of Vitamin D supplementation on depression scores.

Definitions of Vitamin D deficiency and doses of Vitamin D used in clinical trials

Further information about how Vitamin D deficiency or status has been defined, and the doses of Vitamin D used in clinical trials is provided in appendix 2.

Conclusions

Vitamin D deficiency and depression are both highly prevalent and Vitamin D supplementation, if shown to be effective in preventing or treating depression, could have significant public health benefits. Vitamin D supplementation may be relatively harm free, but note should be taken of the apparent finding of an association between Vitamin D and pregnancy associated breast cancer (Agborsangaya, et al., 2010) that was noted in the review by Christesen et al (Christesen, et al., 2012).

<u>The target questions for this rapid review</u>

Systematic reviews suggest an association between Vitamin D deficiency and depression. This finding is based on observational studies and establishing that the relationship is causal, ie that Vitamin D deficiency causes depression, requires RCTs of supplemental Vitamin D in individuals with and without depression.

Systematic reviews of studies of Vitamin D supplementation and depression suffer from a relatively small number of RCTs that show considerable heterogeneity. The overall quality of the published RCT evidence has been assessed in systematic reviews as poor. Two of the systematic reviews (Shaffer, et al., 2014) (Spedding, 2014) report statistically significant beneficial effects of Vitamin D supplementation on depressive symptoms. Li et al (Li, et al., 2014) assert that there is currently

[6] Spedding's research hypothesis is presumed to relate only to the possibility of Vitamin D supplementation being beneficial for depression in individuals with Vitamin D deficiency.

insufficient evidence to support the efficacy of Vitamin D supplementation to improve depressive symptoms, but suggest that individuals with depression and those at risk of depression *who have Vitamin D deficiency* should take Vitamin D supplements.

The need for further research

Reviews of Vitamin D and depression show that uncertainties remain about the possible benefits of Vitamin D supplementation in depression, and good quality RCTs are therefore urgently required that address a range of issues.

New trials need to consider the potential role of Vitamin D in preventing the onset of depression in those at higher risk of depressive symptoms and in those with different severities of established clinically significant depression. Trials in patients with clinically significant depression need to consider baseline Vitamin D status, and to distinguish between those with and without hypovitaminosis D at baseline.

RCTs will need to consider dose and mode of administration of Vitamin D (Shaffer, et al., 2014). Annweiler et al (Annweiler, et al., 2013) suggest important different mechanisms may account for a causal link between hypovitaminosis D and depression. Hypovitaminosis D could actively trigger the onset of depression, or alternatively may act as a risk factor that passively removes protection of the CNS against depression. If the causal mechanism is active triggering, it might be expected that higher doses of Vitamin D administration would be beneficial, whereas if hypovitaminosis D simply removes protection of the CNS, the level of supplementation required might be only that needed to correct the deficiency[7].

Clinical trial protocols identified from CCDANCTR are shown in table 6. No attempt has been made to determine the progress or status of these trials.

Reference list

Agborsangaya, C. et al., 2010. Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study.. *Eur J Cancer,* Volume 46, p. 467–70.

Anglin, R., Samaan, Z., Walter, S. & McDonald, S., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *British Journal of Psychiatry,* Volume 202, pp. 100-107.

Annweiler, C., Rastmanesh, R., Richard-Devantoy, S. & Beauchet, O., 2011. *Geriatr Psychol Neuropsychiatr Vieil,* 9(3), pp. 259-267.

Barnard, K. & Colon-Emeric, C., 2010. Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition. *American Journal of Geriatric Pharmacotherapy,* 8(1).

[7] Spedding describes the very wide range of doses of Vitamin D used in some of the trials to date.

Bertone-Johnson, E., 2009. Vitamin D and the occurrence of depression: causal association or circumstantial evidence?. *Nutrition Reviews,* 67(8), pp. 481-492.

Christesen, H., Falkenberg, T., Lamont, R. & Jorgensen, J., 2012. The impact of vitamin D on pregnancy: a systematic review. *Acta Obstetricia et Gynecologica Scandinavica,* 91(12), pp. 1357-1367.

Eyles, D. et al., 2005. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in the human brain. *J Chem Neuroanat,* Volume 29, pp. 21-30.

Fields, J., Trivedi, N., Horton, E. & Mechanick, J., 2011. Vitamin D in the Persian Gulf: integrative physiology and socioeconomic factors. *Current Osteoporosis Reports,* 9(4), pp. 243-250.

Ju, S., Lee, Y. & Jeong, S., 2013. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. *Journal of Nutrition, Health & Aging,* 17(5), pp. 447-455.

Lach, K. & Krajewski-Siuda, K., 2010. Vitamin D3 in prevention of diseases in adults--a systematic review. *Wiadomosci Lekarskie,* 63(4), pp. 316-330.

Li, G. et al., 2014. Efficacy of vitamin D supplementation in depression in adults: a systematic review. *Journal of Clinical Endocrinology & Metabolism,* 99(3), pp. 757-767.

Mahdy, S. et al., 2010. Vitamin D status in health care professionals in Qatar. *Saudi Medical Journal,* 31(1), pp. 74-77.

Miller, B. et al., 2013. Dietary supplements for preventing postnatal depression. *Cochrane Database of Systematic Reviews,* Volume 10, p. CD009104.

Murphy, P. & Wagner, C., 2008. Vitamin D and mood disorders among women: an integrative review. *Journal of Midwifery & Women's Health,* 53(5), pp. 440-446.

Shaffer, J. et al., 2014. Vitamin D Supplementation for Depressive Symptoms: A Systematic Review. *Psychosomatic Medicine,* Volume 76, pp. 190-196.

Spedding, S., 2014. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients,* 6(4), pp. 1501-1508.

Thacher, T. & Clarke, B., 2011. Vitamin D insufficiency. *Mayo Clinic Proceedings,* 86(1), pp. 50-60.

Table 1: Published reviews included and excluded from this report based on relevance

The table shows all reviews identified by searches of Medline and CCDANCTR. Each review was assessed for **relevance** of questions addressed by the review to the target questions. Studies were included or excluded from this report accordingly. The table shows the rationale for decisions to include or exclude reviews.

(a) Reviews identified from Medline search

Author(s)	Title	Year	Relevance to target questions[8]			Include/ exclude
			Prevalence (Qu 1)	Association (Qu 2)	Treatment (Qus 3 and 4)	
Abba, K, Sudarsanam, TD, Grobler, L and Volmink, J	Nutritional supplements for people being treated for active tuberculosis	2008	Not relevant - deals with tuberculosis only.			E
Albert, PJ, Proal, AD and Marshall, TG	Vitamin D: the alternative hypothesis	2009	Not relevant - deals with autoimmune disease only.			E
Anglin, RE, Samaan, Z, Walter, SD and McDonald, SD	Vitamin D deficiency and depression in adults: systematic review and meta-analysis	2013		SR and MA of case-control and cross-sectional studies to determine association of Vit D defy and depression in adults	SR and MA of cohort studies to determine whether Vit D deficiency increases risk of developing depression in adults.	I

[8] Target questions: 1. What is the **prevalence** of **Vitamin D deficiency** in Qatar and other Arabic countries? 2. Is there an **association** between **Vitamin D deficiency** and **depression**? 3. Does **Vitamin D supplementation prevent** the development of **depression**? 4. Does **Vitamin D supplementation reduce depressive symptoms** in patients with **depression**?

Author(s)	Title	Year	Relevance to target questions[8]			Include/ exclude
			Prevalence (Qu 1)	Association (Qu 2)	Treatment (Qus 3 and 4)	
					SR and MA of RCTs to determine whether Vit D supplementation improves depressive symptoms in adults with depression or prevents depression compared to placebo in healthy adults.	
Annweiler, C, Rastmanesh, R, Richard-Devantoy, S and Beauchet, O	The role of vitamin D in depression: from a curious idea to a therapeutic option	2013		MA of serum Vit D in cases with depression compared to non-depressed controls.		I
Barnard, K and Colon-Emeric, C	Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition	2010		Deals with association of Vit D and mood. (Full text not available at time of writing)		?I
Belvederi Murri, M, Respino, M, Masotti, M, Innamorati, M, Mondelli, V, Pariante, C and Amore, M	Vitamin D and psychosis: mini meta-analysis	2013	Deals with association of Vit D and psychosis			E
Bertone-Johnson, ER	Vitamin D and the occurrence of depression: causal association or circumstantial evidence?	2009		Deals with association of	Refers to single RCT of Vit D	I

Author(s)	Title	Year	Relevance to target questions[8]			Include/ exclude
			Prevalence (Qu 1)	Association (Qu 2)	Treatment (Qus 3 and 4)	
				Vit D and depression	supplementation for depression	
Christesen, HT, Falkenberg, T, Lamont, RF and Jorgensen, JS	The impact of vitamin D on pregnancy: a systematic review	2012		Includes one study of association of low serum 25(OH)D and post partum depression		I
Ju, SY, Lee, YJ and Jeong, SN	Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis	2013		SR of studies of association of vit D defy and depression		I
Lach, K and Krajewski-Siuda, K	Vitamin D3 in prevention of diseases in adults - a systematic review	2010		Deals with Vit D and prevention of depression		I
Li, G, Mbuagbaw, L, Samaan, Z, Falavigna, M, Zhang, S, Adachi, JD, Cheng, J, Papaioannou, A and Thabane, L	Efficacy of vitamin D supplementation in depression in adults: a systematic review	2014			SR of Vit D supplemetation and depression	I
Miller, BJ, Murray, L, Beckmann, MM, Kent, T and Macfarlane, B	Dietary supplements for preventing postnatal depression	2013			SR of dietary supplements and effect on post-natal depression.	I
Murphy, PK and Wagner, CL	Vitamin D and mood disorders among women: an integrative review	2008		SR of studies of association of Vit D defy and mood disorders, including depression, in women.		I

Author(s)	Title	Year	Relevance to target questions[8]			Include/ exclude
			Prevalence (Qu 1)	Association (Qu 2)	Treatment (Qus 3 and 4)	
Perez-Lopez, FR, Chedraui, P, Gilbert, JJ and Perez-Roncero, G	Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-Women's Health Initiative era	2009	Not relevant - deals with factors affecting risk of cardiovascular disease, including depression.			E
Rubovszky, G and Horvath, Z	Menopausal symptoms emerging during hormonal therapy of breast cancer, and their treatment	2011	Not relevant - deals with treatments for menopausal symptoms.			E
Shaffer, JA, Edmondson, D, Wasson, LT, Falzon, L, Homma, K, Ezeokoli, N, Li, P and Davidson, KW	Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials	2014			SR and MA of RCTs of Vit D supplementation and depressive symptoms	I
Sinclair, D, Abba, K, Grobler, L and Sudarsanam, TD	Nutritional supplements for people being treated for active tuberculosis	2011	Not relevant - deals with treatments for TB.			E
Spedding, S	Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws	2014			SR and MA of studies of Vit D supplements and depression.	I
Thacher, TD and Clarke, BL	Vitamin D insufficiency	2011	Probably not SR - may provide some background information. Deals with Vit D deficiency/insufficiency and non-skeletal outcomes.		Narrative review – reference to Vit D supplementation in participants with overweight and obesity.	I
Veling, W	Ethnic minority position and risk for psychotic disorders	2013	Not relevant – deals with low Vit D as risk factor for psychosis.			E

(b) Additional reviews identified from CCDANCTR

Author(s)	Title	Year	Relevance to target questions			Include/ exclude
			Prevalence (Qu 1)	Association (Qu 2)	Treatment (Qus 3 and 4)	
Autier P, Boniol M, Pizot C, Mullie P	Vitamin D status and ill health: A systematic review	2014	Probably not SR - may provide some background information. Unlikely to add information.			E
Hogberg G, Bech P, Hallstrom T, Petersson M	Does vitamin D play a role in depression? A review of clinical, epidemiological and biological	2014	Probably not SR - may provide some background information. Unlikely to add information.			E
Qureshi NA // Al-Bedah Abdullah Mohammed	Mood disorders and complementary and alternative medicine: A literature review	2013	Probably not SR - may provide some background information. Unlikely to add information.			E
van Orten-Luiten AC, Janse A, Dhonukshe-Rutten RA, Witkamp RF	The association between drugs frequently used by the elderly and vitamin D blood levels: a review of observational and experimental studies.	2014	Not relevant - Deals with drug use and Vitamin D status in elderly patients.			E

Table 2: Characteristics of included studies of Vitamin D and depression

Review reference	Country	Review Type	Number of included studies	Participants	Intervention/ Observations	Outcomes
(Anglin, et al., 2013)	Canada	Systematic review and meta-analysis	14 studies: 1 case-control 10 cross-sectional 3 cohort	Adults with depression and healthy adults. 31,424 participants	Observation studies included in review: Vitamin D levels as risk factor for depression. No RCTs of treatment included in review.	Primary outcome = depression. Secondary outcome (in patients with depression) = change in depressive symptoms.
(Annweiler, et al., 2013)	France	New MA using data from Anglin et al (above)	As for Anglin, RE	As for Anglin, RE	As for Anglin, RE	As for Anglin, RE
(Barnard & Colon-Emeric, 2010)		Narrative review[9]				
(Bertone-Johnson, 2009)	USA	Narrative review				
(Christesen, et al., 2012)	Denmark	Systematic review of Vit D-dependent outcomes of preganancy	Only one observational study relating to Vit D included[10]			
(Ju, et al., 2013)	Korea	Systematic review and meta-analysis	16 studies (reported in 12 articles)	Over 50,000 participants	Observational studies only: Serum 25(OH)D levels	Depression
(Lach & Krajewski-Siuda, 2010)		Full txt not available at time of writing.				

[9] Narrative reviews not assessed in this preliminary version of the report.

[10] For postpartum depression, this single study reported that a 1–7 months' postpartum depression score was associated with 25(OH)D levels≤80 nmol/L. Authors state "The odds ratio of aggressive pregnancy-associated breast cancer was in 111 cases compared with 111 matched controls surprisingly 2.7 times higher when 25(OH)D in pregnancy was >25.8 nmol/L" (Agborsangaya, et al., 2010).

Review reference	Country	Review Type	Number of included studies	Participants	Intervention/ Observations	Outcomes
(Li, et al., 2014)	Canada	Systematic review and meta-analysis	6 RCTs	1203 adult participants incl. 71 depressed patients.	Oral Vitamin D supplementation compared to placebo	Depression scores
(Miller, et al., 2013)	Australia	Cochrane systematic review and meta-analysis	No studies of Vitamin D supplementation included in review.			
(Murphy & Wagner, 2008)	USA	Narrative review				
(Shaffer, et al., 2014)	USA	Systematic review and meta-analysis	7 randomised controlled trials	Non-depressed individuals Depressed individuals. 3191 participants.	Vitamin D supplementation	Depressive symptoms
(Spedding, 2014)	Australia	Systematic review and meta-analysis	15 randomised controlled trials	Diverse populations	Vitamin D supplementation	Depression scores or questionnaires including depression measures
(Thacher & Clarke, 2011)	USA	Narrative review				

Only systematic reviews and meta-analyses shaded green in the table were regarded as key sources of information for the rapid review and were selected for quality assessment.

Table 3: Quality assessment of systematic reviews regarded as key resources

Quality assessment of reviews was undertaken using the ROBIS tool[11], which is designed to assess risk of bias in systematic reviews. The table below summarises assessments for the four domains of the ROBIS tool and gives an overall judgement about risk of bias for each included systematic review judged to be a key resource for this rapid review.

Review reference	Domain 1 Study eligibility	Domain 2 Identification and selection of studies	Domain 3 Data collection and study appraisal	Domain 4 Synthesis and findings	Risk of bias	Comments
(Anglin, et al., 2013)	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low	No RCTs met inclusion criteria and the review therefore provided no evidence about Vitamin D supplementation to prevent or treat depression.
(Annweiler, et al., 2013)	-	-	-	-	-	Not formally assessed – article not a full SR but a new MA using data from Anglin's review (above)
(Christesen, et al., 2012)	Low concern of risk of bias	Low concern of risk of bias	Unclear risk of bias	High concern of risk of bias	High	Specific questions not set for review (depression only one of many 'pregnancy outcomes' investigated). Search may have missed some studies. Assessment of study quality not described. No quantitative synthesis provided and no discussion of limitations of RCTs.
(Ju, et al., 2013)	Low concern of risk of bias	Low concern of risk of bias	Unclear risk of bias	Low concern of risk of bias	Unclear	Actual search strategy not stated. Restricted to English language. Methodological quality of included studies not reported but used in sensitivity analysis ('high vs low quality studies').

[11] See: http://www.robis-tool.info/

Review reference	Domain 1 Study eligibility	Domain 2 Identification and selection of studies	Domain 3 Data collection and study appraisal	Domain 4 Synthesis and findings	Risk of bias	Comments
(Li, et al., 2014)	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low	
(Shaffer, et al., 2014)	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low concern of risk of bias	Low	
(Spedding, 2014)	Low concern of risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	High	Decisions to exclude studies not assessed by 2nd reviewer. Little information provided about data collection and study appraisal. Uncertain validity of approach to synthesis – based on author's views about biological flaws, including lack of measurement of serum 25(OH)D.

Table 4: Outcomes/findings of selected reviews

Review	Main results			Comments
	Prevalence	Association	Treatment	
(Anglin, et al., 2013)	No studies of prevalence included in review.	Demonstrated an overall stat sig association between Vit D deficiency and depression.	No studies of treatment/supplementation with Vit D to prevent or treat depression were included in review.	Overall quality of included studies (case-control, cross-sectional and cohort designs) was low and uncertainty remains about association. Authors note the need for RCTs to determine whether association is causal.
(Annweiler, et al., 2013)	No studies of prevalence included in review.	Demonstrated an overall stat sig association between Vit D deficiency and depression.	No studies of treatment/supplementation with Vit D to prevent or treat depression were included in review.	New MA using data from Anglin et al (above).
(Christesen, et al., 2012)		Concluded that postpartum depression was associated with 25(OH)D levels of <80 nmol/	No studies of treatment/supplementation with Vit D to prevent or treat depression were included in review.	
(Ju, et al., 2013)	No studies of prevalence included in review.	Demonstrated inverse relationship between serum 25(OH)D and risk of depression.	No studies of treatment/supplementation with Vit D to prevent or treat depression were included in review.	Authors report: 10ng/l increase in 25(OH)D associated with 8% decrease in incidence of depression in cohort studies and 4% decrease in cross-sectional studies.
(Li, et al., 2014)	No studies of prevalence included in review.	No studies of association included in review.	No significant effect of Vit D supplementation	Authors state that quality of evidence from RCTs is low.

Review	Main results			Comments
	Prevalence	Association	Treatment	
			on post-intervention depression scores	
(Shaffer, et al., 2014)	No studies of prevalence included in review.		Vit D supplementation was associated with stat sig moderate reduction in depressive symptoms in patients with clin sig depressive symptoms and/or MDD[12]. Vit D supplementation was associated with small, non sig effect in participants with non-clinically significant depression.	Considerable heterogeneity of included studies. Authors note the need for further RCTs.
(Spedding, 2014)	No studies of prevalence included in review.	No studies of association included in review.	MA of studies "without biological flaws" demonstrated a statistically sig improvement in depression with Vit D supplements.	

[12] MDD – major depressive disorder

Table 5: Non review articles relating to prevalence of Vitamin D deficiency

Publications identified by Medline search for studies of prevalence of Vitamin D deficiency

Author(s)	Title	Journal	Year	Vol	Issue	Pages
Abdullah, MA	Epidemiology of type I diabetes mellitus among Arab children [Comment in: Saudi Med J. 2006 Jun;27(6):916; PMID: 16758073]	Saudi Medical Journal	2005	26	6	911-7
Bener, A and El Ayoubi, HR	The role of vitamin D deficiency and osteoporosis in breast cancer	International Journal of Rheumatic Diseases	2012	15	6	554-61
Bener, A and Kamal, M	Predict attention deficit hyperactivity disorder? Evidence -based medicine	Global Journal of Health Science	2014	6	2	47-57
Bener, A, Al-Ali, M and Hoffmann, GF	Vitamin D deficiency in healthy children in a sunny country: associated factors	International Journal of Food Sciences & Nutrition	2009	60 Suppl 5		60-70
Bener, A, Al-Ali, M and Hoffmann, GF	High prevalence of vitamin D deficiency in young children in a highly sunny humid country: a global health problem	Minerva Pediatrica	2009	61	1	15-22
Bener, A, Alsaied, A, Al-Ali, M, Al-Kubaisi, A, Basha, B, Abraham, A, Guiter, G and Mian, M	High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children	Acta Diabetologica	2009	46	3	183-9
Bener, A, Alsaied, A, Al-Ali, M, Hassan, AS, Basha, B, Al-Kubaisi, A, Abraham, A, Mian, M, Guiter, G and Tewfik, I	Impact of lifestyle and dietary habits on hypovitaminosis D in type 1 diabetes mellitus and healthy children from Qatar, a sun-rich country	Annals of Nutrition & Metabolism	2008	53	03-Apr	215-22
Bener, A, Ehlayel, MS, Tulic, MK and Hamid, Q	Vitamin D deficiency as a strong predictor of asthma in children	International Archives of Allergy & Immunology	2012	157	2	168-75

Author(s)	Title	Journal	Year	Vol	Issue	Pages
Ehlayel, MS, Bener, A and Sabbah, A	Is high prevalence of vitamin D deficiency evidence for asthma and allergy risks?	European Annals of Allergy & Clinical Immunology	2011	43	3	81-8
Fields, J, Trivedi, NJ, Horton, E and Mechanick, JI	Vitamin D in the Persian Gulf: integrative physiology and socioeconomic factors	Current Osteoporosis Reports	2011	9	4	243-50
Hamilton, B, Grantham, J, Racinais, S and Chalabi, H	Vitamin D deficiency is endemic in Middle Eastern sportsmen	Public Health Nutrition	2010	13	10	1528-34
Hamilton, B, Whiteley, R, Farooq, A and Chalabi, H	Vitamin D concentration in 342 professional football players and association with lower limb isokinetic function	Journal of Science & Medicine in Sport	2014	17	1	139-43
Mahdy, S, Al-Emadi, SA, Khanjar, IA, Hammoudeh, MM, Sarakbi, HA, Siam, AM and Abdelrahman, MO	Vitamin D status in health care professionals in Qatar	Saudi Medical Journal	2010	31	1	74-7
Racinais, S, Hamilton, B, Li, CK and Grantham, J	Vitamin D and physical fitness in Qatari girls	Archives of Disease in Childhood	2010	95	10	854-5
Sharif, EA and Rizk, NM	The prevalence of vitamin D deficiency among female college students at Qatar University	Saudi Medical Journal	2011	32	9	964-5
Soliman, AT, Adel, A, Wagdy, M, Alali, M and Aziz Bedair, EM	Manifestations of severe vitamin D deficiency in adolescents: effects of intramuscular injection of a megadose of cholecalciferol	Journal of Tropical Pediatrics	2011	57	4	303-6
Soliman, AT, Al Khalaf, F, Alhemaidi, N, Al Ali, M, Al Zyoud, M and Yakoot, K	Linear growth in relation to the circulating concentrations of insulin-like growth factor I, parathyroid hormone, and 25-hydroxy vitamin D in children with nutritional rickets before and after treatment: endocrine adaptation to vitamin D deficiency	Metabolism: Clinical & Experimental	2008	57	1	95-102
Soliman, AT, El-Dabbagh, M, Adel, A, Al Ali, M, Aziz Bedair, EM and Elalaily, RK	Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets	Journal of Tropical Pediatrics	2010	56	1	19-26
Teaema, FH and Al Ansari, K	Nineteen cases of symptomatic neonatal hypocalcemia secondary to vitamin D deficiency: a 2-year study	Journal of Tropical Pediatrics	2010	56	2	108-10

Table 6: Registered clinical trials of Vitamin D and depression

Trial register reference	Author(s)	Title of protocol	Trial register	Year of regn.
IRCT201412065623N29	Asemi Z	Effects of vitamin D supplementation on insulin resistance and inflammatory factor in patients with depression [IRCT201412065623N29]	Iranian Registry of Clinical Trials [http://www.irct.ir/searchresult.php?id=5623&number=29]	2014
NCT02272387	Bimson B	Is Vitamin D Insufficiency and Deficiency Associated With Antepartum and Postpartum Depression?	http://clinicaltrials.gov/show/NCT02272387	2014
IRCT2014080315276N2	Effatpanah M	Evaluating the effect of vitamine D in improvement rate of 18-65 years old patients with treatment resistant depression in ziaeian hospital in 2014 [IRCT2014080315276N2]	Iranian Registry of Clinical Trials [http://www.irct.ir/searchresult.php?id=15276&number=2]	2014
NCT01932931	Eriksen SA // Linde JS // Vestergaard P	Depression - Can Vitamin D Alleviate Symptoms of Depression Not Cured by Antidepressants as Well as Alleviate Negative Skeletal Effects Caused by Antidepressants?	http://clinicaltrials.gov/show/NCT01932931	2013
NCT00472823	Gallagher JC	Determination of RDA for Vitamin D in Caucasian and African American Women [VIDOS]	http://clinicaltrials.gov/show/NCT00472823	2007
NCT01630720	Hoffer J	Vitamin Therapy in JGH Patients	http://clinicaltrials.gov/show/NCT01630720	2011
ACTRN12613000540718	Houghton L	Effect of vitamin D supplementation on wellbeing in young adults – a randomised controlled trial	http://www.anzctr.org.au/ACTRN12613000540718.aspx	2013
IRCT201201072394N6	Jazayeri S // Khoraminya N	Effect of vitamin D supplementation on depression severity, inflammatory and oxidative markers in major depressive disorder disorder [IRCT201201072394N6]	Iranian Registry of Clinical Trials [http://www.irct.ir/searchresult.php?id=2394&number=6]	2012

Trial register reference	Author(s)	Title of protocol	Trial register	Year of regn.
ACTRN12613001051730	Kaplan B	In people suffering depression or anxiety following the Southern Alberta flood, what are the mental health effects of three different micronutrient formulas?	http://www.anzctr.org.au/ACTRN12613001051730.aspx	2013
NCT02072187	Katzman MA	Adjunctive Vitamin D in the Treatment of Non-remitted Depression	http://clinicaltrials.gov/show/NCT02072187	2013
IRCT201105306641N1	Khosravi HM // Ardekani MY	Comparison between efficiency of two different doses of vitamin D injection in depressed patients with vitamin D deficiency on depressive symptoms [IRCT201105306641N1]	Iranian Registry of Clinical Trials [http://www.irct.ir/searchresult.php?id=6641&number=1]	2011
NCT01884844	Marsh W	Randomized Double-Blind Placebo-Controlled Pilot Study of Vitamin D Supplementation for the Treatment of Bipolar Depression	http://clinicaltrials.gov/show/NCT01884844	2013
NCT00960232	NCT00960232	Vitamin D, Blood Pressure, Lipids, Infection and Depression	ClinicalTrials.gov [www.clinicaltrials.gov]	2009
NCT01904032	NCT01904032	Vitamin D Supplement to Women With Type 2 Diabetes	http://clinicaltrials.gov/show/NCT01904032	2013
NCT01462058	Nielsen CT	The Role of Vitamin D Supplementation on Well Being and Symptoms of Depression During the Winter Season in Health Service Staff (D3-vit-SAD)	http://clinicaltrials.gov/show/NCT01462058	2011
eudract -2011-002585-20	Nielsen CT	The role of vitamin D supplementation on well-being and symptoms of depression during the Winter season in health service staff [eudract_number:2011-002585-20]	https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-002585-20/DK/	2011
NCT01390662 // EUCTR2010-023531-42-DK	Nielsen CT // Dahl E // Toft T	Phase 4 Study of Vitamin D3 Supplementation for Outcomes in Patients With Unipolar Depression	http://clinicaltrials.gov/show/NCT01390662	March 2011
NCT01696435	Okereke OI	VITAL-DEP: Depression Endpoint Prevention in the VITamin D and OmegA-3 TriaL	http://clinicaltrials.gov/show/NCT01696435	2012
NTR3845 // EUCTR2012-005332-29-NL	Schoor NM	Prevention of depression and poor physical function in older persons with vitamin D supplementation. - D-Vitaal	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3845	2013

Trial register reference	Author(s)	Title of protocol	Trial register	Year of regn.
ISRCTN70909899 // EudraCT 2013-002928-16	Schreuder F	Vitamin D and non-specific musculoskeletal complaints in non-Western immigrants: a randomized controlled trial	http://isrctn.com/ISRCTN70909899	2013
ACTRN12605000164695	Singh MF	Hip Fracture Intervention Trial (HIPFIT): A randomized controlled trial of a targeted multifactorial intervention to improve long term disability after hip fracture	http://www.anzctr.org.au/ACTRN12605000164695.aspx	2005

Appendix 1: Search strategy

Vitamin D and depression

OVID MEDLINE search (2014-01-25)

1. vitamin d/ or cholecalciferol/ or hydroxycholecalciferols/ or calcifediol/ or dihydroxycholecalciferols/ or calcitriol/ or 24,25-dihydroxyvitamin d 3/
2. Vitamin D Deficiency/
3. (vitamin d or cholecalciferol* or hydroxycholecalciferol* or calciferol* or calcitriol).mp.
4. or/1-3
5. (prevalen* or deficien* or insuff*).mp.
6. (Qatar or Quatar or Katar).mp.
7. 4 and 5 and 6 *[PREVALENCE]*
8. Depression/
9. Depressive Disorder/
10. (depress* or unipolar or MDD).mp.
11. or/8-10
12. (relation* or associat* or correlat* or causal*).mp.
13. exp epidemiologic studies/
14. or/12-13
15. 4 and 11 and 14 *[ASSOCIATION - observational studies]*
16. (((systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update$ or summary).ti. or review.pt.)) or (meta analysis.pt. or meta analysis/ or "0266-4623".is.) or (reviewed systematically or systematically reviewed).tw. or (1469-493X or 1366-5278 or 1530-440X).is.) not ((animals/ not humans/) or letter.pt.)
17. ("review" or "review academic" or "review tutorial").pt.
18. (medline or medlars or embase or pubmed).tw,sh.
19. (scisearch or psychinfo or psycinfo).tw,sh.
20. (psychlit or psyclit).tw,sh.
21. cinahl.tw,sh.
22. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
23. (electronic database$ or bibliographic database$ or computeri#ed database$ or online database$).tw,sh.
24. (pooling or pooled or mantel haenszel).tw,sh.
25. (retraction of publication or retracted publication).pt.
26. (peto or dersimonian or der simonian or fixed effect).tw,sh.
27. or/18-26
28. 17 and 27
29. meta-analysis.pt.
30. meta-analysis.sh.
31. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
32. (systematic$ adj5 review$).tw,sh.
33. (systematic$ adj5 overview$).tw,sh.
34. (quantitativ$ adj5 review$).tw,sh.
35. (quantitativ$ adj5 overview$).tw,sh.

36. (quantitativ$ adj5 synthesis$).tw,sh.
37. (methodologic$ adj5 review$).tw,sh.
38. (methodologic$ adj5 overview$).tw,sh.
39. (integrative research review$ or research integration).tw.
40. or/29-39
41. 16 or 28 or 40
42. 4 and 11 and 41 *[SYSTEMATIC REVIEWS – any type of study]*
43. randomized controlled trial.pt.
44. controlled clinical trial.pt.
45. randomi?ed.ab.
46. placebo$.ab.
47. trial.ti.
48. (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab.
49. drug therapy.fs.
50. (animals not (humans and animals)).sh.
51. or/43-49
52. 51 not 50
53. 4 and 11 and 52 [CLINICAL TRIALS – RCTs]
54. 15 and 41 *[SYSTEMATIC REVIEWS: observational studies]*

Appendix 2: Definitions of Vitamin D deficiency and doses of Vitamin D used in clinical trials

Further data extraction

This appendix provides further information from systematic reviews included in the rapid review and from relevant prospective clinical trials identified in clinical trials registers, about:

(a) how Vitamin D deficiency has been defined, or how Vitamin D status has been categorised, in studies of Vitamin D and depression; and
(b) the Vitamin D doses used in clinical trials of Vitamin D supplementation for depression.

For each study cited by the systematic reviews (table A), and for each record of a prospective clinical trial (table B), the attached tables summarise information about:

- Participants
- Vitamin D trial entry criteria (where appropriate)
- Vitamin D categories (for observational studies) or baseline status (for treatment trials) (table A only)
- Actual (table A) or proposed (table B) dosage(s) of Vitamin D and route of administration
- Equivalent dose of Vitamin D per week (IU)
- Length of course of treatment

Vitamin D levels are expressed as serum levels of 25(OH)D in nmol/l. Vitamin D supplementation doses are expressed as IU of cholecalciferol and, where available, route of administration is indicated.

How studies included in the systematic reviews have defined Vitamin D deficiency or described Vitamin D status

The review by Anglin (Anglin, et al., 2013) included 10 observational studies for which information about categories of Vitamin D status were described. The studies assessed the association of depression with these various categories of serum Vitamin D. Although the Vitamin D categories cannot be regarded as definitions of Vitamin D deficiency, they provide information about the levels of Vitamin D considered to be important by those conducting these studies.

In the other reviews of observational studies, the review by Annweiler (Annweiler, et al., 2013) did not provide information about Vitamin D levels for individual studies. The review by Christensen (Christesen, et al., 2012) included only one relevant study (in pregnant women) and Vitamin D categories used in this study are shown in table A. The review by Ju (Ju, et al., 2013) includes a table that provides information about Vitamin D levels but these cannot be equated to values for defining Vitamin D deficiency.

In one of the reviews of treatment studies (Shaffer, et al., 2014), details were given of serum Vitamin D levels required for entry into two trials. In one trial (Kjaergaard et al, 2012) the entry requirement was a serum 25(OH)D level below 55 nmol/l; in the second trial (Mozaffari-Khosravi et al, 2013) the requirement was a level below 40 nmol/l.

Other than in one case, we have not examined the publications of individual primary studies. Some of these publications may include more information about Vitamin D levels used as patient entry requirements. However, it is clear that some, if not most, of the trials cited by reviews have selected patients only on the basis of measures of depression, and Vitamin D status or deficiency has not been a requirement of trial entry. This was confirmed to be the case for one trial where we had cause to examine the trial publication (Khoraminya et al, 2012).

Doses of Vitamin D (cholecalciferol) used in trials included in the reviews

Further data about doses of Vitamin D used in clinical trials has been extracted from the three systematic reviews of Vitamin D supplementation for depression. These reviews cited 19 individual treatment trials and, where available from the review publications, data about dose(s) of Vitamin D (as IU of cholecalciferol) are shown in table A. To allow comparison, we have shown the equivalent doses of Vitamin D per week for each trial, and also shown duration of treatment.

Most trials have used doses of Vitamin D between 20,000 IU and 50,000 IU per week, though the range is wide.

The review by Spedding (Spedding, 2014) only provided doses in the form of a diagram. We therefore approximated the actual values and expressed these as weekly doses. Spedding suggested that the dose used in one trial (Khoraminya, 2013) was between 14,000 and 15,000 IU per day (equivalent to about 100,000 IU per week) but this is an error in Spedding's publication. The two other reviews quoted the daily dose as 1,500 IU (equivalent to 10,400 IU per week) and we have confirmed this value by reference to the trial publication.

Information about proposed trials identified from clinical trial registers

Table B provides information about 20 proposed trials of Vitamin D and depression identified from clinical trials registers (see main report). For each record of a proposed clinical trial, the same categories of information have been extracted.

Seven of the 20 proposed trials indicated a serum Vitamin D level as a trial entry requirement, with values ranging from <40 to <100 nmol/l of 25(OH)D.

Planned weekly doses of Vitamin D supplementation in proposed trials varied considerably. In about half of the trials, intended doses were between about 20,000 and 50,000 IU of cholecalciferol per week.

Table 1: Vitamin D and Depression: Data extracted from systematic reviews relating to diagnostic criteria for Vitamin D deficiency and doses of Vitamin D used in clinical trials included in systematic reviews

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
(Anglin, et al., 2013)	Ganji (2010)	Men and women aged 15–39 years	These were all observational studies of the association between depression or depressive symptoms and categories of Vitamin D levels.	Categories: <50, 50–75, >75	Not applicable	Not applicable	Not applicable
	Hoogendijk (2008)	Men and women aged 65–95 years		Cut-off point 50			
	Johnson (2008)	Older adults		<25, 25–50, >50			
	Lee (2011)	Men aged 40–79 years		<25, 25–49.9, 50–74.9, >75			
	Nanri (2009)	Men and women aged 21–67 years		Quartiles (medians 53.75, 64.75, 72.5, 82)			
	Pan (2009)	Men and women aged 50–70 years		Quartiles (means 26.1, 41.1, 65.1)			
	Stewart (2010)	Men and women aged =/>65 years		<25, <50, <75			
	Wilkins (2006)	Men and women aged >60 years		<25, 25–50, >50			
	Wilkins (2009)	Men and women aged >55 years		Cut-off point 50			
	Zhao (2010)	Men and women aged =/>20 years		<37.5, 37.5–50, 50–65, >65			
(Annweiler, et al., 2013)	Information not provided for individual studies						
(Christesen, et al., 2012)	Murphy et al., 2010	Pregnant women	Single observational study examined Vit D and depression	=/<80 vs. >80	Not applicable	Not applicable	Not applicable

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
(Ju, et al., 2013)	Table 1 of the review includes information about 25(OH)D levels – single values for some studies and ranges for others. Please refer to review article for an explanation of how these levels were calculated and presented. They are not directly related to Vit D categories or baseline status as for studies listed above.						
(Li, et al., 2014)	Jorde, 2008	Obese adults with BMI between 28.0 and 47.0 kg/m2, no use of antidepressant or weight-reducing drugs	Vit D level for eligibility not stated in review	DD group, 55.2 (16.8 –97.0); placebo group, 52.4 (18.5–99.4); DP group, 52.2 (15.4 –111.5)	DD group: 2 capsules Vit D/wk (20 000 IU cholecalciferol per capsule); DP group, 1 capsule Vit D and one placebo capsule per week	DD Group: 40,000 IU DP Group: 20,000 IU	12 months
	Arvold, 2009	Patients with mild to moderate Vit D deficiency identified by Vit D screening	Vit D level for eligibility not stated in review	Vit D group, 56.92 (11.13); placebo group, 57.56 (12.72)	One capsule containing 50 000 IU cholecalciferol weekly	50,000 IU	8 weeks
	Sanders, 2011	Females > 70 y old at risk of fracture, and/or at risk of low Vit D and osteoporosis, not taking Vit D supplement >400 IU/d	Vit D level for eligibility not stated in review	Vit D group, pre-dose, 70 (22.2). Placebo group, pre-dose, 49.6 (14.8)	10 tablets containing total of 500 000 IU Vit D3 taken one day annually during autumn/winter	500,000 **once annually** See comments by Spedding about side effects of this dose.	3-5 years
	Kjærgaard, 2012	Participant with low serum 25(OH)D level and without clinical depression, and no use of antidepressant or Vit D	Vit D level for eligibility not stated in review (but see under Shaffer, below)	Vit D group, 47.4 (15.8); placebo group, 47.7 (15.5)	2 Vit D3 capsules (20 000 IU cholecalciferol) per week	20,000	6 months

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
		supplement					
	Yalamanchili & Gallagher, 2012	Older postmenopausal women with normal range of femoral neck density	Vit D level for eligibility not stated in review	Vit D group, 97.31 (28.89); placebo group, 100.81 (34.98)	One pill containing calcitriol 0.25 _g, twice a day	Dose assumed to be reported incorrectly by Spedding	3 years
	Khoraminya, 2013	Adults with a diagnosis of major depressive disorder without psychotic features, no use of any antidepressant or dietary supplements during the previous 2 mo	Vit D level for eligibility not stated in review	Vit D group, 74.89 (12.82); placebo group, 73.30 (14.06)	Daily either 1.5 tablets (1500 IU) of Vit D3 plus one capsule (20 mg) fluoxetine or placebo plus 20 mg fluoxetine	10,500	8 weeks
(Shaffer, et al., 2014)	Hogie-Lorenzen, 2003	Community members	Vit D level for eligibility not stated in review	8.2 (3.0)	600 (in fortified cheese)	4,200	8 weeks
	Jorde et al., 2008	Community members and outpatients with overweight or obesity	Vit D level for eligibility not stated in review	53.1 (14.3)	20,000 or 40,000 weekly (capsule)	20,000 or 40,000	1 year
	Dean et al., 2011	Healthy volunteers	Vit D level for eligibility not stated in review	76.6 (19.9)	5000 daily (capsule)	35,000	6 weeks
	Bertone-Johnson et al., 2012	Postmenopausal women	Vit D level for eligibility not stated in review	Not reported	400 daily (not reported)	2,800	2 years
	Kjaergaard et al., 2012	Community members with low 25(OH)D level	Entry requirement <55 nM	47.5 nM (15.7)	20,000 weekly (capsule)	20,000	6 months

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
	Khoraminya et al., 2013	Psychiatric outpatients with MDD and elevated depressive symptoms	Vit D level for eligibility not stated in review	58.2 (10.7)	1,500 daily (capsule)	10,500	8 weeks
	Mozaffari-Khosravi et al., 2013	Psychiatric outpatients with elevated depressive symptoms and low vitamin D levels	Entry requirement <40 nM	Not stated	150,000 or 300,000 (single dose) (IM injection)	N/A	N/A
(Spedding, 2014)	Arvold et al., 2009	Individuals with Vit D deficiency (10–25 ng/mL) seen for medical care at a primary healthcare clinic	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	50,000[13]	Not stated in review
	Belcaro et al., 2010	Menopausal women with signs of depression and mood disorder	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	Spedding regards stated dose as misprint but shown in diagram as 1,300,000	Not stated in review
	Bertone-Johnson et al., 2012	Postmenopausal Women with depressive symptoms	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	2,800	Not stated in review
	Dean et al., 2011	Young healthy adults (University students)	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	35,000	Not stated in review

[13] Spedding recalculates doses per day and presents only in a graph to illustrate the wide range of doses used. Actual values shown in this table for Spedding are therefore approximate, having been taken from the graph and expressed as weekly doses.

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
	Dumville et al., 2006	Older women with seasonal affective disorder	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	5,600	Not stated in review
	Gloth et al., 1999	Adults with Season Affective Disorder	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	25,000	Not stated in review
	Harris & Dawson-Hughes, 1993	Women with seasonal affective Disorder	Vit D level for eligibility not stated in review		Not stated	2,800	Not stated in review
	Jorde et al., 2008	Overweight and obese adults	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	Two groups: 40,000 and 20,000	Not stated in review
	Khajehei et al., 2009	University female students with premenstrual syndrome	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	Not indicated	Not stated in review
	Khoraminya et al., 2013	Adults with major depressive disorder based on DSM-IV criteria, without psychosis	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	(100,000) NB: This figure is an error in the review by Spedding.	Not stated in review
	Landsdowne & Provost, 1998	Adults with seasonal affective Disorder	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	Two groups: 65,000 and 5,600	Not stated in review
	Sanders et al., 2011	Community dwelling older women with seasonal mood disorders	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	10,000	Not stated in review

Systematic review citing reference	Study reference	Participants	Vit D trial entry criteria (as reported in SR)	Vit D categories or baseline status (nmol/l)	Actual dose (IU) and route of Vit D administered	Equivalent Vit D dose per week (IU)	Length of course of treatment
	Veith et al., 2004	Adults with serum 25(OH)D <61 nmol/L in summer, expected to develop 25(OH)D concentrations <40 nmol/L by winter	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	30,000	Not stated in review
	Yalamanchilli & Gallagher, 2012	Older post-menopausal women with Depression	Vit D level for eligibility not stated in review	Review suggests baseline Vit D level stated in study reference	Not stated	Spedding regards stated dose as misprint	Not stated in review
	Zhang et al., 2011	Hospitalized patients	Vit D level for eligibility not stated in review	Review claims not stated in study reference	Not stated	15,000	Not stated in review

Table 2: Vitamin D and Depression: Data extracted from clinical trials registers about proposed diagnostic criteria for Vitamin D deficiency and doses of Vitamin D to be used in clinical trials

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
IRCT201412065623N29	Asemi Z 2014	Effects of vitamin D supplementation on insulin resistance and inflammatory factor in patients with depression [IRCT201412065623N29]	Iranian Registry of Clinical Trials http://www.irct.ir/searchresult.php?id=5623&number=29	Adults, M&F, 20-50 yrs	No requirement	50,000 weekly	50,000	8 weeks
NCT02272387	Bimson B 2014	Is Vitamin D Insufficiency and Deficiency Associated With Antepartum and Postpartum Depression?	http://clinicaltrials.gov/show/NCT02272387	Pregnancy – post partum with Vit D defy	Vit D defy not defined	50,000 IU tablet weekly x 8 weeks plus prenatal vitamin (400 IU vitamin D)	50,000	8 weeks
IRCT2014080315276N2	Effatpanah M 2014	Evaluating the effect of vitamine D in improvement rate of 18-65 years old patients with treatment resistant depression in	Iranian Registry of Clinical Trials http://www.irct.ir/searchresult.php?id=15276&number=2	18-65 year old patients with treatment resistant depression	<50 nmol/l	one Pearl per week up to 8 weeks and then one perl per month up to 4 month[14]	50,000	8 weeks, followed by lower dose for up to 4 months.

[14] In Iran, the oral pharmacologic form of vitamin D is 50,000 IU Pearl vitamin D3.

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		ziaeian hospital in 2014 [IRCT201408031527 6N2]						
NCT01932931	Eriksen SA // Linde JS // Vestergaa rd P 2013	Depression - Can Vitamin D Alleviate Symptoms of Depression Not Cured by Antidepressants as Well as Alleviate Negative Skeletal Effects Caused by Antidepressants?	http://clinicaltrials.gov/show/NCT01932931	Femlaes, 50-90 yrs Current Citalopram or Mirtazapine users < 6 months, or individuals who are going to initiate treatment of either Citalopram or Mirtazapine within the following two months	Not stated	50 ug daily[15] (2,000 IU)	14,000	3 years
NCT00472823	Gallagher JC 2007	Determination of RDA for Vitamin D in Caucasian and	http://clinicaltrials.gov/show/NCT00472823	Female, =/>57 yrs	5-20 ng/ml[16] (12.5 – 50 nmol/l)	Daily 400 800	Weekly 2,800 5,600	One year

[15] ug to IU = ug/0.025
[16] ng/ml x 2.496 = nmol/l

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		African American Women [VIDOS]				1600 2400 3200 4000 4800	11,200 16,800 22,400 28,000 33,600	
NCT01630720	Hoffer J 2011	Vitamin Therapy in JGH Patients	http://clinicaltrials.gov/show/NCT01630720	Mentally competent patients fluent in English or French admitted to the surgical or medical units	Not required	5,000 daily	35,000	7-10 days
ACTRN12613000540718	Houghton L 2013	Effect of vitamin D supplementation on wellbeing in young adults – a randomised controlled trial	http://www.anzctr.org.au/ACTRN12613000540718.aspx	Females aged 18-40 years	Not required	50,000 IU capsule x monthly	12,500	6 months
IRCT201201072394N6	Jazayeri S // Khoraminya N 2012	Effect of vitamin D supplementation on depression severity, inflammatory and oxidative markers in major depressive disorder disorder	Iranian Registry of Clinical Trials http://www.irct.ir/searchresult.php?id=2394&number=6	M&F 18-65 yrs	Not required	1,500/day	10,500	8 weeks

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		[IRCT201201072394N6]						
ACTRN12613001051730	Kaplan B 2013	In people suffering depression or anxiety following the Southern Alberta flood, what are the mental health effects of three different micronutrient formulas?	http://www.anzctr.org.au/ACTRN12613001051730.aspx	>18y with depression, anxiety or stress scores above thresholds	Not required	1,000/day	7,000	6 weeks
NCT02072187	Katzman MA 2013	Adjunctive Vitamin D in the Treatment of Non-remitted Depression	http://clinicaltrials.gov/show/NCT02072187	18-65 yrs with MDD and failure to respond to pharmacological Rx	Not required	28,000 weekly (oral drops)	28,000 reduced to 14,000 if serum D3>100 nmol/L	8 weeks
IRCT201105306641N1	Khosravi HM // Ardekani MY 2011	Comparison between efficiency of two different doses of vitamin D injection in depressed patients with vitamin D deficiency on depressive symptoms	Iranian Registry of Clinical Trials http://www.irct.ir/searchresult.php?id=6641&number=1	20-70 yrs, depression	<40 nmol/l	Gp1: 300,000 Gp2: 150,000 By injection	Single doses	Single doses

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		[IRCT201105306641N1]						
NCT01884844	Marsh W 2013	Randomized Double-Blind Placebo-Controlled Pilot Study of Vitamin D Supplementation for the Treatment of Bipolar Depression	http://clinicaltrials.gov/show/NCT01884844	18-75 yrs Bipolar depression	<30 ng/ml (<75 nmol/l)	5,000/day	35,000	12 weeks
NCT00960232	NCT00960232 2009	Vitamin D, Blood Pressure, Lipids, Infection and Depression	ClinicalTrials.gov www.clinicaltrials.gov	30-75 yrs with low Vit D	Not stated	40,000/week	40,000	6 months
NCT01904032	NCT01904032 2013	Vitamin D Supplement to Women With Type 2 Diabetes	http://clinicaltrials.gov/show/NCT01904032	Female, =/>21 yrs Type 2 DM and depression and low Vit D	<32 ng/dl (<80 nmol/l)	50,000/week (comparison = 5,000/week)	50,000 (5,000)	6 months
NCT01462058	Nielsen CT 2011	The Role of Vitamin D Supplementation on Well Being and Symptoms of Depression During the Winter Season	http://clinicaltrials.gov/show/NCT01462058	18-65 yrs, health workers	Not required	70ug/day (tablet) (2,800 IU)	19,600	12 weeks

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		in Health Service Staff (D3-vit-SAD)						
NCT01390662 // EUCTR2010-023531-42-DK	Nielsen CT // Dahl E // Toft T 2011	Phase 4 Study of Vitamin D3 Supplementation for Outcomes in Patients With Unipolar Depression	http://clinicaltrials.gov/show/NCT01390662	18-65 yrs, unipolar depression	Not required	70 ug/day (tablet) (2,800 IU)	19,600	24 weeks
NCT01696435	Okereke OI 2012	VITAL-DEP: Depression Endpoint Prevention in the VITamin D and OmegA-3 TriaL	http://clinicaltrials.gov/show/NCT01696435	=/>50 yrs	Not required	2,000/day	14,000	Not stated
NTR3845 // EUCTR2012-005332-29-NL	Schoor NM 2013	Prevention of depression and poor physical function in older persons with vitamin D supplementation. - D-Vitaal	http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3845	60-80 yrs	≥ 15 nmol/l and < 50 nmol/l in winter or < 70 nmol/l in summer	1,200/day	8,400	One year
ISRCTN70909899 // EudraCT 2013-002928-16	Schreuder F 2013	Vitamin D and non-specific musculoskeletal complaints in non-Western immigrants: a	http://isrctn.com/ISRCTN70909899	Non-Western immigrants, aged 16-60 years, with lasting muscle pain	<50 nmol/l	200,000 at days 0 and 42	-	-

Trial register reference	Author(s) Year of regn	Title of protocol	Trial register	Participants	Vit D trial entry criteria (as reported in SR)	Planned dose (IU) and route of Vit D administration	Equivalent Vit D dose per week (IU)	Length of course of treatment
		randomized controlled trial		without any known cause and with low vitamin D levels in blood				
ACTRN12605000164695	Singh MF 2005	Hip Fracture Intervention Trial (HIPFIT): A randomized controlled trial of a targeted multifactorial intervention to improve long term disability after hip fracture	http://www.anzctr.org.au/ACTRN12605000164695.aspx	=/>55 yrs, hip facture	<40ng/ml (<100 nmol/l)	1,000/day	7,000	One year