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Gender Differences in Vitamin D and Depressive Symptoms: A Systematic Review

Day CMJ[1]*, Kripalani M[1], Rees K[2], Weich S[2], Clarke A[2] and Stranges S[3]

[1]South London and Maudsley NHS Trust, University Hospital Lewisham, UK

[2]Division of Health Sciences, University of Warwick Medical School, UK

[3]Department of Population Health, Luxembourg Institute of Health, Luxembourg

***Corresponding author:** Day CMJ, Lady well Unit, South London and Maudsley NHS Trust, University Hospital Lewisham, London, UK

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Abstract

Background: Both vitamin D insufficiency and depression are major public health concerns particularly in women. Recent animal and cross-sectional studies have suggested an association between low vitamin D levels and increased depressive symptoms with some evidence that vitamin D supplementation may be more beneficial in women.

Objective: (i) To examine the gender differences in the observational prospective association between vitamin D status (using serum levels) and depressive symptoms; (ii) to determine if vitamin D supplementation is more effective in women than in men.

Methods: MEDLINE, EMBASE, Web of Science & Knowledge, PsychInfo, the Cochrane Library and trial registers were searched with no language restrictions from inception to December 2015.

Results: 22 separate studies met the inclusion criteria, 5 observational prospective studies and 17 RCTs. The most robust cohort study found a significant association only in women. Only seven out of seventeen RCTs found a significant effect of vitamin D on depressive symptoms. Six of these were mixed-sex studies and one was a female only study that had the greatest effect size. The females included in these seven trials were mostly of childbearing age.

Conclusion: There is suggestive evidence of potential benefits of vitamin D supplementation in women of childbearing age with depressive symptoms. Further large randomized placebo-controlled secondary prevention trials in both men and women of childbearing age, with low vitamin D levels, are needed to investigate the relative efficacy of vitamin D supplementation in depression in men and women.

Keywords: Systematic review; Vitamin D; Depression; Gender differences; Randomized control studies; Observational studies; Prevention; Vitamin D; Gender differences; Female

Abbreviations

RCT: Randomized Control Trial; BDI: Beck Depression Inventory; CES-D: Centre for Epidemiologic Studies –Depression Scale; SCID: Structured Clinical Interview for DSM Disorders; CIDI: Composite International Diagnostic Interview; NOS: Newcastle-Ottawa Quality Assessment Scale; ADL: Activities of Daily Living; SPPB: Short Physical Performance Battery; PTH: Parathyroid Hormone; HDRS: Hamilton Depression Rating Scale; POMS: Profile of Mood States; ANCOVA: Analysis of Covariance; SF-12 MCS: Mental Component of the Short Form 12 Health Survey; HADS: Hospital Anxiety and Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; GDS: Geriatric Depression Scale.

Introduction

Depression is the third most common cause of disease burden in the world for both men and women and is the leading cause of disease burden for women in the world [1]. Epidemiological data show that women are twice as likely as men, to develop depression during their childbearing years [2-4]. Furthermore, it is estimated that 1 billion people worldwide have either deficient or insufficient vitamin D levels [5], and some epidemiological data show that women may be more at risk of this than men [6-13] women. Vitamin D fortification of milk was mainstream in Europe in the early twentieth century; however this was banned in the 1950's due to case reports of hypercalcaemia in children [5].

For both sexes, there is now epidemiological evidence of association of hypovitaminosis D with many non-skeletal health conditions [5,14] and more recently, cross-sectional and cohort studies have shown an association between low vitamin D levels and depression [15-17]. These epidemiological findings are corroborated by biological experimental evidence supporting a potential role of vitamin D in the pathogenesis of depression [18-20].

Given that women are at increased risk of depression and hypovitamonis D, there has already been some interest in the role of vitamin D in depression in women [21]. Some cross-sectional data show that the association between low vitamin D levels and depressive symptoms is stronger in women than in men [22,23]. It is not clear whether this is because women are, a priori, more at risk of hypovitaminosis D or whether there is a specific gender-based interaction between vitamin D and depression. Like the sex

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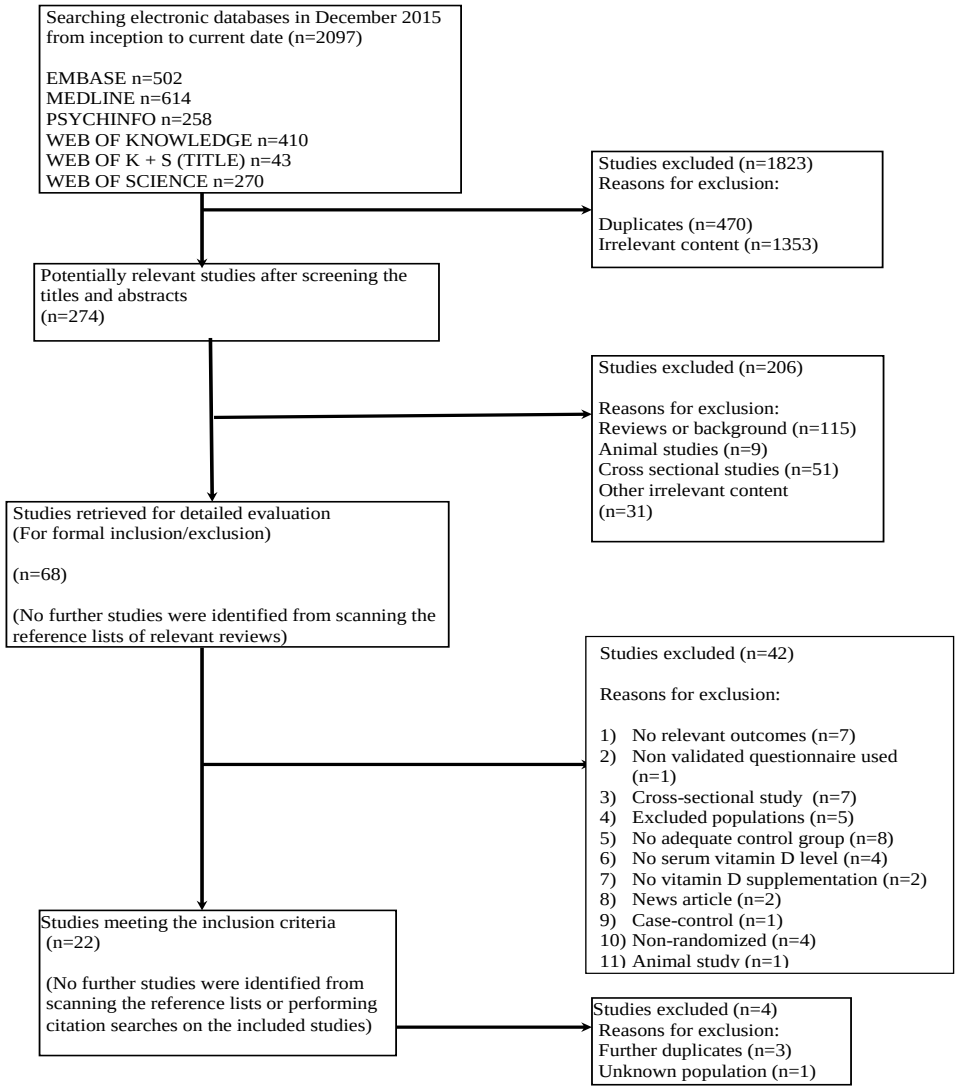

Figure 1: Flow diagram of study selection.

hormones, active vitamin D is a steroid hormone and there is evidence that oestrogen promotes the potency of vitamin D protective effects in animals and humans [24, 25].

One existing systematic review and meta-analysis [26] reported a modest significant effect of vitamin D supplementation on depressive symptoms in adults with depressive symptoms. Another meta-analysis [27] after eliminating studies with biological flaws also found benefit of vitamin D supplementation. In this systematic review, however we aim to investigate any sex-interaction in the association between vitamin D levels and depressive symptoms and in the effect of vitamin D supplementation on depressive symptoms, which has not been explored yet. From current evidence of micronutrient supplementation trials, where, supplementation is more effective in high-risk individuals [28], we hypothesise that the effect of vitamin D supplementation will be most clearly seen in (a) those with depressive symptoms at baseline of both sexes and (b) those who are vitamin D deficient. Furthermore, given the oestrogen promoted differences in local vitamin D metabolism, we hypothesize that both effects (a) and (b) will be greater in women than in men.

Materials and Methods

Search strategy and study selection

The following electronic databases were systematically searched with no language restrictions from their inception to December 2015; In MEDLINE; EMBASE; Web of Science; Web of knowledge; Web of Knowledge and Science (title); Psych Info; Cochrane Library and Meta RCT trial registers. Existing reviews and articles retrieved from the search terms were scanned for further studies and hand searching of various relevant journals was also performed. Due to the diverse nomenclature of vitamin D, extensive search strategies were created and tailored to individual databases. The search strategy for the various databases is shown in the appendix.

Studies met the inclusion criteria if they fulfilled the following criteria:

1. Study design - observational prospective studies (cohort/

Table 1: Cohort Studies investigating association between vitamin D levels and subsequent depressive symptoms.

Study, Year	Country	Participants	No	% Female	Age, y	Vitamin D level Exposure definition (nmol/L)	Follow up	Outcome measure	Association between vitamin D levels and depression (adjusted odds and hazard ratios)
Yue et al. 2014 [34]	China	Acute ischaemic stroke patients	184	35.3	62.8 (8.1)	1)<28 2)>28	6 months	Prevalent depression diagnosed according to DSM-III-R criteria using algorithms based on psychiatric interview.	Adjusted Odds ratio <28nmol/L *vs*..>28nmol/L: OR 10.32, 95% CI 4.97-28.63; p<0.001
Milan-eschi et al. 2010 [33]	Italy	Healthy adults 74.6% females and 50.4% males had vitamin D < 50nmol/L.	535	55.7	>65 Mean: 73.6	1) <31.7 2) 31.7-53.9 3) >53.9 And 1) <50 2) >50	3 years 6 years	Incident depression diagnosed by Center for Epidemiological Studies Depression Scale (CES-D) (score>16 = depression).	43.6% of females & 20.5% of males developed depressed mood. Hazard Ratios categorized by tertiles *Women*: Tertile 1 (<31.7nmol/l) *vs.* Tertile 3 (>53.9nmol/l): HR=2.90(1.53-5.50) p=0.001 *Men:* Tertile 1 (<31.7nmol/l) *vs.* Tertile 3 (>53.9nmol/l): HR=1.67 (0.76-3.68) p=0.21 Hazard Ratios categorized by conventional cut-offs *Women*: (<50nmol/l) *vs.* (>50nmol/l) HR=2.09(1.25-3.49) p=0.005 *Men*: (<50nmol/l) *vs.* (>50nmol/l) HR=1.46 (0.81-2.65) p=0.21 Fully adjusted Cox regression model did not find statistically significant vitamin D status-by-sex interaction.
Williams et al. 2011 [31]	USA	Well- functioning community dwelling adults.	2240	52%	70-79	1) <50 2) >75	3 years	Incident depression as defined by CES-D score (short) >10 or current treatment with antidepressant medication.	Hazard Ratios (95% CI) Sufficient vitamin D levels (>75nmol/L) HR: 1 'Deficient' vitamin D levels (<50nmol/L) HR: 1.54 (1.19-1.99)
May et al. 2010 [32]	USA	Patients with previous cardio-vascular diagnosis	7358	58.8%	>50 Mean: 73	1) <37.5 2) 40-75 3) 77.5-125 4) >125	1 year	Incident depression defined as having received a clinical diagnosis of depression (ICD-9 codes 296.2-296.36 and 311).	Hazard Ratios (95% CI): Optimal (>50ng/ml) or (>125nmol/l); HR = 1 Normal (31-50ng/ml); HR = 1.95 (0.99-3.87) p = 0.06 Low (16-30ng/ml); HR = 2.15 (1.1-4.21) p = 0.03 VL (<15ng/ml); HR = 2.7 (1.35-5.4) p = 0.005 Males only (n=3034): (<<37.5nmol/l) *vs.* >125nmol/L) HR 6.68, p=0.07 Females only (n=4324): (<37.5nmol/l) *vs.* >125nmol/L) HR 2.13, p=0.05 No significant interaction between sex and vitamin D (p interaction =0.75).
Chan et al. 2011 [35]	Hong Kong	Chinese community-dwelling male volunteers	801	0%	>65	1) <50 2) 50-74 3) 75-99 4) >100	4 years	Depression diagnosed by face-to-face interviews using a validated Chinese version of Geriatric Depression Scale. (GDS>=8 = diagnosis of depression)	Cases/controls at 4years + Odds Ratios (95% CI) (<50nmol/L[1])= 1/32 OR = 1 (50-74nmol/L) = 10/251 OR 95% CI = 1.5(0.16-14.56) (75-99nmol/L) = 9/234 OR 95% CI = 1.27 (0.13-12.89)

nested case control studies) or Randomized Control Trials (RCTs).

2. Participants - Adults > 18 years free of depressive disorder at baseline for prospective observational studies and primary prevention trials and with a diagnosis of depressive disorder (either clinically or from validated depression/mood scales) for secondary prevention trials. Those with pregnancy, kidney, thyroid or parathyroid disease were excluded.

3. Exposure/intervention – 25-hydroxyvitamin D3 serum levels or any vitamin D supplementation (including multivitamin compound containing vitamin D).

Table 2: Female only randomised control trial characteristics and summary of effect of vitamin D supplementation on depressive symptoms.

Study Year	Country	Participants	Baseline vitamin D levels (nmol/L)	Baseline depressive symptoms	Intervention, n	Control, n	Age, y	Form of Intervention	Dose of Vitamin D	Fre-quency	Duration	Control	Outcome measure	Summary of Effect
Bertone-Johnson et al. 2012 [36]	USA	Postmenopausal	Subset Mean =52.0+/-21.1 (n=898)	9.4% (n=212) clinically depressed based on measure	1109	1143	50-79	D3 + calcium tablet	400IU	Daily	2 years	Placebo tablet	Burnam 8-item scale	No effect
Sanders et al. 2011 [38]	Australia	Risk factor for hip fracture or at high risk for hypovitamonisis D	Subset Mean = 49 (n=118)	14.8% (n=298) on antidepressants	1001	1011	>70	D3 tablet	500,000IU	Yearly	3-5 years	Placebo tablet	SF-12 MCS	Trend effect for those on anti depressants at baseline
Dumville et al. 2006 [39]	UK	Risk factor for hip fracture	Not reported	Not reported	689	941	>70	D3 + calcium tablet	800IU	Daily	6 months	Infor-mation Sheet	SF-12 MCS	No effect
Yalamanchili & Gallagher 2012 [37]	USA	Postmenopausal community-dwelling	Mean = 76.3 +-9.4	Mean GDS score: 4.8 (4.6) Chronic illnesses excluded. 12% (n=57) clinically depressed based GDS	123	123	65-77	Calcitriol tablet	0.5g	Daily	3 years	Placebo tablet	GDS	No effect, including subanalysis in only those depressed.
Harris & Dawson-Hughes 1993 [53]	USA	Postmenopausal	Not reported	7% (n=18)history of depression	125	125	43-72	D3 + calcium tablet	400IU	Daily	1 year	Placebo tablet	POMS	No effect
Haskell et al. 2010 [41]	UK	Healthy with occasional subjective fatigue	Not measured	Baseline POMS score: 72. Any medically significant diagnosis in last 5 yrs excluded.	100 106	107 110	25-50 Mean 36	D3 in multivitamin tablet	200IU	Daily	9 weeks	Placebo tablet	POMS SF-36 MCS	No effect
Brown et al. 2001 [42]	USA	Ethnic Minority	Not measured	Mild-Moderate Depressive Symptoms	53	51	>18	D3 in multivitamin tablet + educational session + daily exercise + coach	400IU	Daily	8 weeks	Placebo tablet + educational session + coach	CES-D POMS	Significant effect

SF-12 MCS: Mental Component Score; GDS: Geriatric Depression Questionnaire; POMS: Profile of Mood States Questionnaire; SF-36 MCS: Mental Component Score; CES-D, Centre for Epidemiology Studies Depression Scale.

4. Outcomes - change in depression/mood scores on a validated, standardized measure, diagnosis or no diagnosis of depressive disorder based on a clinical diagnosis, or a validated, standardized measure (e.g. BDI or CES-D etc.) or interview (e.g. SCID or CIDI).

After database searching, one author independently screened the titles and abstracts for potential relevance. Following this initial screening, full reports of short-listed studies were obtained and two of the study authors (CD & KR) independently assessed the studies for inclusion using the pre-specified inclusion criteria outlined above. If there was any disagreement over study inclusion a third author was consulted (SS).

Methodological quality

CD and KR independently assessed methodological quality by examining the method of randomization, allocation concealment, blinding and losses to follow-up for RCTs and by using the Newcastle-Ottawa Quality Assessment Scale to assess the quality of the cohort studies [29].

Analysis

Cohort studies

We planned to pool the adjusted effect estimate of developing depression for those with vitamin deficiency (<50nmol/L), vitamin D insufficiency (<75nmol/L) and sufficient vitamin D levels (>75nmol/L) in a meta-analysis 30.

Randomized control trials

We planned to pool the standardized mean changes in depression scores of participants who received vitamin D supplementation and of those who received placebo.

Results

Study selection

Searching electronic databases yielded 2097 references. (Figure 1) describes the flow of studies through the review. 1823 references were excluded after removal of duplicates and initial screening for relevance. Of the remaining 274 studies, 206 were excluded as they were reviews, animal studies, or cross-sectional studies or had irrelevant content, and 22 studies met the inclusion criteria. No ongoing trials were identified on the Meta RCT trial register. No further studies were identified by scanning the reference lists of relevant studies or by the performing citation searches of the 22 included studies.

Study characteristics

Details of the included studies are found in (Tables 1-5). Five cohort studies and seventeen RCTs met the inclusion criteria. Given the different populations, interventions, controls and outcomes it was inappropriate to pool the data statistically and so a narrative synthesis was performed.

Table 3: Mixed sex randomized control trial characteristics and summary of effect of vitamin D supplementation on depressive symptoms.

Study, Year	Country	Participants	Sex (F:M) % F	Baseline vitamin D levels (nmol/L)	Baseline depressive symptoms	Interven-tion,n	Control, n	Age, y	Form of intervention	Vitamin D dose	Frequency	Duration	Control	Outcome measure	Effect
Wepner et al. 2014 [43]	Austria	Fibro-myalgia	27:3 90%	<80 Median: 52.1 Range: 21.25-72.5	Not stated	15	15	35-55 Mean 48.37	D3 solution	2400IU or 1200IU	Daily	6 months	Placebo solution	HADS	No effect
Mozaffari-Khosravi et al. 2013 [50]	Iran	Depressive disorder + low vitamin D levels	78:31 72%	<40	Mean BDI-II: 26.9 (7.2)	80	40	20-60 Mean 31.5	D3 injection	Either 150,000 or 300,000IU	Once	n/a	No injection	BDI-II	Significant effect
Khoraminya et al. 2013 [51]	Iran	Major depressive disorder (MDD)	34:6 85%	Mean=58.25 95% patients < 75	MDD: 100% (as per DSM-IV criteria and HDRS>15)	20	20	18-65 Mean 39	D3 tablet plus fluoxetine capsule	1500IU	Daily	8 weeks	Placebo tablet + fluoxetine capsule	HDRS BDI	Significant effect
Jorde et al. 2008 [44]	Norway	Overweight & obese adults	282:159 64%	Median=52.6 Range= 11.1-111.5[1]	Mean baseline BDI score = 4.5 (Range 0-18) Antidepressant use excluded.	292	149	21-70 Mean 47.5	D3 capsule + calcium tablet	Either 40,000 IU or 20, 000IU	Weekly	1 year	Placebo + calcium tablet	BDI	Significant effect. In BDI 1-13 effect most clearly seen in females.
Kjaer-gaardeet al. 2012 [52]	Norway	Low vitamin D levels <55nmol/l	129:101 56% F	Mean=47.6 +- 15.7	Those with severe depression excluded. Mean Baseline BDI II scores = 4 Range = 0-49	120	110	30-75 Mean 53.35	D3 capsules	40,000IU	Weekly	6 months	Placebo capsules	BDI II, HADS, MADRS	No overall effect or when stratified to gender. Significant effect seen in those with high BDI, HADS, MADRS score at baseline.
Gariballa & Forster 2007 [45]	UK	Hospitalised patients	83:142 37% F	Not measured	Severe psychiatric history excluded. 37% mild or severe depression (based on GDS).	106	119	>65 Mean 75.6	D3 in multivitamin & nutritional supplement solution	200IU	Daily	6 weeks	Placebo solution	GDS	Significant overall effect after adjustment for baseline GDS, age & gender.
Dean et al. 2011	Australia	Healthy adults	73: 55 57% F	Mean = 76.2 +- 2.6	Current or depressive disorder excluded. Baseline BDI scores = 6.5	63	65	>18 Mean 21.8	D3 capsule	5000 IU	Daily	6 weeks	Placebo capsule	BDI	No effect
Arasteh 2 1994 [47]	USA	Healthy students	Not stated	Not measured	Previous depressive diagnosis excluded. 17% (n=13) 'depressed' at baseline based on BDI>9.	76 in total		Not stated	D3 and calcium tablet	1200IU	Daily	4 weeks	Placebo tablet	BDI	Significant effect. Effect increased significantly in those 'depressed' at baseline.
Arasteh 1 1994 [48]	USA	Healthy students	Not stated	Not measured	Previous depressive diagnosis excluded. 15% (n=7) 'depressed' at baseline based on BDI >9	47 in total		Not stated	D3 and calcium tablet	1200IU	Daily	4 weeks	Placebo tablet	BDI	Significant effect
Lans-downe & Provost 1998 [49]	UK	Healthy students	34:10 77% F	Not measured	Not reported	44 in total.		18-43 Mean 22	D3 and vitamin A capsule	400IU or 800IU	Daily	5 days	Vitamin A capsule	PANAS (Negative affect)	No effect

BDI, Beck Depression Inventory (BDI); BDI II, Beck Depression Inventory II; HADS, Hospital Anxiety & Depression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; GDS, Geriatric Depression Scale; PANAS, Positive and Negative Affect Schedule.

Cohort Studies: Details of the cohort study characteristics are found in Supplementary (Table 1). All five cohort studies involved older adults without a history of depression; four were in both males and females [31-34] and one included only males [35]. For the exposure, the studies used serum 25-hydroxyvitamin D3 levels split into either quartiles [32,35], tertiles [33], 'deficient' (<20ng/ml (50nmol/ml) and 'sufficient' (>20ng/ml) levels [31] or levels<28nmol/L *vs.* >28nmol/L [34]. Three studies measured depression using well-validated depression scales, [31,33,35] one study measured depression by clinical diagnosis [32] and another

Table 4: Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.

Study	Selection	Comparability	Outcome
Yue 2014 [34]	* *	* *	*
Chan 2011 [35]	* * *	* *	
Williams 2011 [31]	* * * *	* *	*
May 2010 [32]	* *	*	
Milaneschi 2010 [33]	* * * *	* *	* *

The Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies - A study can be awarded a maximum of 4 stars for selection (4 questions relate to the representativeness of the cohort, the selection of the unexposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study), a maximum of 2 stars for comparability (exposed and unexposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis) and a maximum of 3 stars for outcome (assessment of outcome, follow-up long enough for outcomes to occur, losses to follow-up).

by clinical diagnosis using a diagnostic algorithm [34]. Follow up periods ranged from 6 months [34], 1 year [32], 3 years [31], 4 years [35] and 6 years [33].

Randomized control trials: The study characteristics of the female-only RCTs and mixed sex RCTs are found in Supplementary (Tables 2,3) respectively. Seven out of fourteen RCTs recruited only female participants [36-42]. Five of these were in postmenopausal women, [36-40]. Mixed sex trials included fibromyalgia patients [43], obese & overweight subjects [44], acutely ill elderly hospitalized patients [45] and healthy students [46-49].

Two mixed sex trials included adults with a depressive disorder [50,51], one of which included only patients with low vitamin D levels [50]. One female-only study included those with mild-moderate depressive symptoms according to a well-validated depression scale at baseline, but who still did not have an existing clinical diagnosis of depression and who were not taking antidepressants [42]. Most other studies published baseline depressive symptom prevalences of 7% to 37% based on a cut-off on a well-validated scale.

Only two RCTs were specifically conducted among adults with low vitamin D levels [50,52]. Eight studies didn't measure or report vitamin D levels [39,41,42,45,47-49,53]. Other baseline mean and median vitamin D levels ranged from 49nmol/L to 76.3nml/L [36-38,44,46,50,51], which is regarded as adequate vitamin D status [54].

As with the participants, the intervention also differed widely between studies. The vitamin D3 dosage differed from low doses such as 200IU daily [41] to high doses of 5700IU daily [44]. The duration of intervention period varied from 2 years [36] to a one off injection [50]. Five RCTS used high dose vitamin D3 supplementation alone [38,43, 46,50,52] whereas three RCTs used low dose vitamin D as part of a multivitamin supplementation [41,42,45]. Six RCTs used vitamin D3 plus calcium as their intervention [36,39,44,47,48,53] and one RCT used vitamin D3 plus vitamin A [49] and one RCT used vitamin D3 plus fluoxetine [51].

Fifteen RCTs [36,37,39,41-48,50-53] measured changes in depression score before and after supplementation on validated scales. Two studies only measured depression scores after supplementation [38,49].

Methodological quality

Cohort studies: The methodological quality of the cohort studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) [29] and see (Table 4) for their star ratings. Milaneschi et al. 2010 [33] had the lowest risk of bias. May et al. 2010 [32] had the high risk of bias with an unclear selection protocol, no adjustment for multiple confounders (other than parathyroid hormone) and unreported loss to follow up. This study and Yue et al. 2014 [34] involved patients with a cardiovascular and cerebrovascular disease, respectively, and so have poor generalizability. Only one study used standardized interviews plus diagnostic algorithm to diagnose depression [34] whereas the rest used less reliable self-report measures [31,33,35] or a clinical diagnosis [32] to diagnose depression. Chan et al. 2011 [35] did not include those with extreme vitamin D levels, had a high loss to follow up of 21% and an inadequate assessment of outcome as they measured prevalent depression at one time point 4 years after exposure rather than a more useful outcome such as incidence over 4 years.

Randomized control trials

The methodological quality of the seventeen included trials was assessed by means of the method of randomization and allocation concealment, blinding and losses to follow-up. Please see (Table 5). Most studies used a computer generated randomization and stated that they used a 'double blind' procedure however not all studies explicitly described how they did this.

Other possible biases: Five studies were secondary analyses of trials looking at bone health [36-39,53]. Jorde et al. 2008 [44] was a secondary analysis of a previous study whose primary outcome was weight loss [55]. Gariballa & Forster 2007 [45] was a secondary analysis of a study whose primary outcomes were disability, length of stay and morbidity and mortality [56]. The primary outcomes for Dean et al. 2011 [46] were working memory, response inhibition & cognitive flexibility whereas the depression outcome was one of many secondary outcomes. This was similar for Wepner et al. 2014 [43] whose primary outcomes were fibromyalgia scores.

Association between vitamin D levels and depression

Cohort studies: See Supplementary (Table 1) for the hazard and odds ratios of the five studies. Four out of the five cohort studies found that older adults with 'deficient' or 'insufficient' vitamin D levels and with no known history of depression have a higher likelihood of developing depression in the following few years than older adults with 'sufficient' or 'optimal' vitamin D levels [31-34]. The overall adjusted hazard ratios ranged from 1.54 (1.19-1.99) 31 to 2.7 (1.35-5.4) p = 0.00532 to 10.32 (4.97-28.63) p<0.00134 for both men and women. Milaneschi et al. 2010 [33] stratified their results by sex and found that 130 women (43.6%) and 70 men (20.5%) developed depressed mood. After adjustment for age, baseline CES-D, ADL disabilities, use of antidepressants, number of chronic diseases, SPPB, high PTH, and season of collection, both men and women with low vitamin D levels compared to those with sufficient levels showed an increased risk of developing depression over 6 years but this was only statistically significant in women (Women: (<50nmol/l) *vs.* (>50nmol/l) HR=1.97(1.22-3.17) p=0.005; Men: (<50nmol/l) *vs.* (>50nmol/l) HR=1.61 (0.92-2.82) p=0.1;). May et al. 2010 [32] also stratified their results by sex and found large but

Table 5: Methodological quality of randomized control trials.

Study	Randomization	Allocation concealment	Blinding	Losses to follow-up
Khoraminya et al. 2013 [51]	'Randomly assigned'	Unclear	Study states double blind, placebo-controlled but not explicitly described.	Intervention: 4.8% Control: 4.8%
Wepner et al. 2014 [43]	Random sampling performed by statistician using STATISTICA 7 software (uniform random number generator) was used b.	Unclear	Double blind stated – although patients and doctors in charge of treatment were aware of what vitamin D dose they were taking.	Intervention: 37.5% Control: 17%
Mozaffari-Khosravi et al. 2013 [50]	Random numbers table	Poor	No blinding – control group received no injection.	Control: 15% Low dose vit D group: 10% High dose vit D group: 2.5%
Kjaergaard et al. 2012 [52]	Performed by a central randomization unit. Participants with low vitamin D were randomized en block, stratified by gender and smoking status, into vitamin D group and a placebo group.	Central randomization unit personnel did not have contact with study participants. Personnel were informed of participants' vitamin D status by the doctor who had access to the serum 25(OH)D levels measured in the sixth Troms Ø study but who did not have access to participants. Even participants with high vitamin D status who were not to continue in intervention study went through randomization process to ensure study nurses remained masked.	Participants were blinded: Independent pharmacists dispensed either active or placebo capsules, which were pre-packed in boxes and consecutively numbered according to a computer generated randomization list. Each participant was assigned an order number and received the capsules in the corresponding pre-packed box. Study nurses were blinded. No mention of assessors: although BDI is self report.	Placebo group = 9% Vitamin D group = 2%
Dean et al. 2011 [46]	Randomization sequence was generated by external clinical trials site. A varying-block randomization protocol was used.	Two researchers not involved in generating the randomization sequence assigned participants to the next consecutive participant number.	All investigators, outcome assessors & participants were blinded to treatment allocation procedures and treatment group throughout the study.	Intervention=0% Placebo = 1.5%
Dumville et al. 2006 [39]	'Randomization' by computer	Randomization carried out by independent researchers	No placebo - information sheet given on increasing calcium	Intervention = 25% Control = 22%
Jorde et al. 2008 [44]	Participants were randomized (not stated how) and stratified by gender and smoking status.	Double blind but allocation concealment not mentioned.	Double blind. Placebo capsules had identical appearance to vitamin D capsules. Authors do not state how investigators were blinded.	High dose intervention = 23% Low dose intervention = 25% Control = 25%
Lansdowne & Provost 1998 (n<100) [49]	Authors state the dispensation procedure was random and double blind.	Authors state the dispensation procedure was random and double blind. Nil else reported.	'Double blind'. No description.	None reported
Haskell et al. 2010 [41]	Computer generated randomization schedule provided by manufacture	Study product dispensed according to corresponding designated randomization number.	Participants and investigators both blinded.	SF-36 MCS = 4.4% POMS = 8.4%
Bertone-Johnson et al. 2012 [36]	'Randomized by a permuted block algorithm' 36,282 randomized but only 2263 were asked to complete depression questionnaires at year 3 but authors did not report how they were chosen. Personal use of vitamin D supplements allowed up to 1000IU/day.	Double blind – nil else reported.	Double blind – nil else reported.	0% due to the nature of the study. While all participants were invited to complete the Burnam scale at year 1, only a subset (n=2263) were invited to complete the Burnam scale at year 3.
Yalamanchili & Gallagher 2012 [37]	Participants were randomly assigned to one of the four groups through a computer-generated randomization list.	Double blind – authors do not state method of allocation concealment.	Authors state 'double-blind'. Participants blinded: placebo pills appeared identical to treatment pills. Authors do not state how study staff were blinded.	15%.
Sanders et al. 2011 [38]	Computer randomization of participants' study identification number (Minitab)	An independent statistician performed allocation of treatment arm.	Double blind – participants and study staff were masked to treatment allocation until completion of study	Reported as 1% however 10% withdrew from study after randomization (these were not counted as losses to follow up).
Arasteh 1 1994 (n<100) [48]	Randomized by random number table	Scales, questionnaires and tablet vial of each individual were identified by ID numbers only.	'Double blind'. No description.	None reported
Arasteh 2 1994 (n<100) [47]	Randomized by random number table	Scales, questionnaires and tablet vial of each individual were identified by ID numbers only.	'Double blind'. No description.	None reported
Harris & Dawson-Hughes 1993 [53]	Women were randomly assigned after being stratified by dietary calcium intake, treatment group in previous trial, and previous category of years since menopause	'Double blind' – does not state how treatment allocation was concealed.	Authors state 'double blind, placebo-controlled' trial.	Intervention = 5.4% Control = 4.3%

Gariballa & Forster 2007 [45]	'Randomized' – not stated how. Unable to obtain previous paper (2006) in which trial details are published.	All administration of treatment and assessment were done blind to treatment assignment,	Investigator and patient blinded to ongoing results of study. All patients had nutritional supplements or placebo prescribed in their drug charts, but coded as to preserve the double-blind nature of the trial.	6 weeks Placebo group = 14% Supplement group = 16% 6 months Placebo group = 4% Supplement group = 6%
Brown et al. 2001 [42]	'Randomized' – not state how.	A consulting statistician who was not a member of the research team designed and implemented the allocation procedures.	The investigators were purposefully vague about the number and nature of the groups. The placebo and active vitamins were identical in appearance and the bottles labeled only with a code number.	Intervention group = 5.6% Placebo group = 9.8%

statistically insignificant hazard ratios in males compared to females (males (<<37.5nmol/l) *vs.* >125nmol/L) HR 6.68, p=0.07; females (<37.5nmol/l) *vs.* >125nmol/L) HR 2.13, p=0.05). Both Milaneschi et al. 2010 and May et al. 2010 [33,32] did not find any statistically significant vitamin D status-sex interactions. Chan et al. 2011 [35], whose cohort consisted only of older men, did not find any statistically significant association between low vitamin D levels and increased incidence of depression.

Effects of vitamin D supplementation

Randomized control trials: Seven out of the seventeen RCTs found a statistically significant overall effect of vitamin D compared to placebo on depressive symptoms; six mixed sex trials [44,45,47,48,50,51] and one female only trial [42]. The effect sizes were as follows; -5.55 (BDI), -4.7 (HDRS) [51]; -9.3 (BDI II) [50]; -1.5 (BDI) [44]; -5.35 (BDI) [47]; -3.05 (BDI) [48]; -0.58 [45]; female only trial -8.6 (CES-D) and -24.2 (POMS) [42]. The other ten RCTs did not find any statistically significant overall effect of vitamin D compared to placebo on depressive symptoms [36-39,41,43,46,49,52,53].

Effects of vitamin D supplementation in those with depressive symptoms at baseline: Khoraminya et al. 2013 [51] and Mozaffari-Khosravi et al. 2013 [50] found a significant effect of vitamin D supplementation compared to control in improving depressive symptoms in adults with a depressive disorder. (Khoraminya et al. 2013 [51]: BDI mean change at 8 weeks: vitamin D + fluoxetine group = -17.7, fluoxetine group: -13; repeated measure analysis of variance of time and group interaction; F8.54, p=0.006. HDRS mean change at 8 weeks; vitamin D + fluoxetine group = -19.25, fluoxetine group: -13.7; repeated measure analysis of variance of time and group interaction; F6.72, p=0.013. Mozaffari-Khosravi et al. 2013 [50]: BDI-II mean change (+- SD): control group: -2.1 (+-3.8); low dose group; -6.8 (+-7.9); high dose group: -9.3 (+-8.7), analysis of variance p<0.001.)

Brown et al. 2001 [42] found a very large statistically significant effect of vitamin D supplementation in women with mild to moderate depressive symptoms (CES-D mean change: intervention group = -8.6, control group = -5.5; ANCOVA p=0.004) POMS mean change: intervention group = -24.2, control group = -18.8; ANCOVA p=0.015). In a per protocol sub analysis Jorde et al. 2008 [44] found that the improvement in BDI 1-13 in the DD (high dose vitamin D (40,000IU per week) and DP (low dose vitamin D: 20,000IU per week) groups was most clearly seen in females (Female Delta scores: DD = -2.0 (p<0.01), DP = -1.8 (p<0.05), PP (placebo) = -0.5 (p>0.05) Male delta scores: DD=-1 (p>0.05), DP= 0 (p>0.05), PP = 0 (p>0.05) who were significantly more depressed at baseline than males (Females: BDI total score: 5 (0-28), Male BDI total score: 3.5 (0-24.5) Mann-Whitney test p<0.001). Sanders et al. 2011 [38], a female only study, found a trend for those taking anxiety/antidepressant medication to score higher (i.e. better) on the SF-12 MCS if they were randomized to receive vitamin D rather than placebo, although this did not reach a statistically significant interaction (p=0.11).

Arasteh 2 1994 [47], a mixed-sex trial, split participants into 'depressed' and 'non-depressed' before randomization ('depressed' = baseline BDI >9, 'non-depressed; = baseline BDI < 9). The mean BDI score of the 'depressed' subjects in the intervention group decreased (improved) by 11.43 points, while that of the 'depressed' subjects in the placebo group decreased (improved) by 4 points. This interaction between group (intervention *vs.* control) and mood ('depressed' *vs.* 'non-depressed') produced a significant effect in BDI scores (F (1,47) = 4.76, p<0.05). Kjaergaard et al. 2012 [52], a large mixed-sex trial carried out post hoc analyses by stratifying groups according to baseline depression score. Participants with higher BDI scores at baseline (using the median value 4 as a cut-off) were found to have a significant positive effect (less depressed) of vitamin D compared with placebo on total HADS score (p=0.032). Participants with high HADS and MADRS scores at baseline (using 75 percentile as cut-off) had a significant positive effect of vitamin D compared with placebo on HADS score (p=0.01 and p=0.031) respectively. In a subgroup analysis, Yalamanchili et al. 2012 [37], a female only study, found that all women who were depressed at baseline showed a significant improvement, when compared to non-depressed people at baseline, in both placebo and intervention groups (One-way ANOVA, F=68.82, p<0.0001).

Effect of vitamin D supplementation in those with low vitamin D levels: Mozaffari-Khosravi et al. 2013 [50] found a significant of vitamin D supplementation in improving depressive symptoms in adults who not only were depressed, as stated above, but also vitamin D deficient. Although Khoraminya et al. 2013 [51] did not only include those with vitamin D deficiency, 95% of their patients had insufficient vitamin D levels at baseline (<75nmol/L) and as stated above, they also found a significant effect of vitamin D supplementation on depressive symptoms. Kjaergaard et al. 2012 [52] only included participants with low serum vitamin D levels (<55nmol/L) and they did not find any significant differences in delta scores (change in BDI, HADS-D & MADRS scores before and after supplementation) between intervention and control groups, even after stratifying by baseline vitamin D level and gender. Dean et al. 2011 [46] in their secondary analysis examined the effect of change in vitamin D concentrations in only participants with low vitamin D concentrations at baseline (<75.00 nmol/L) but did not find any significant treatment effects. Jorde et al. 2008 [44] carried out a

sub analysis in those with baseline vitamin D levels <40nmol/l and >40nmol/l but did not find a distinct pattern. Although four other studies [36-38,43] measured vitamin D levels at baseline and after supplementation, the majority of participants were not deficient and they did not investigate response to treatment according to baseline vitamin D levels.

Adverse Events

Randomized control trials

Ten studies reported no adverse events [36,37,39,41,45,47-50,53]. Khoraminya et al. 2013 [51] excluded one patient from the fluoxetine + vitamin D group because of severe anxiety at week 2. Wepner et al. 2014 [43] reported one case of mild hypercalcaemia (2.71 nmol/L) and a serum calcifediol level of 63.6 ng/mL in the intervention group. Sanders et al. 2011 [38] reported an increased number of serious adverse events in the supplementation group that nearly reached statistical significance (244 vitamin D *vs.* 207 placebo (p=0.06) but these events were not considered related to study medication. Jorde et al. 2008 [44] reported sustained hypercalcaemia in one participant in low dose vitamin D group who was removed from the trial. Brown et al. [42] found that seven participants (14%) in the control group and sixteen (30%) in the intervention groups (30%) reported a single minor side effects from the vitamins, such as bright yellow urine, gastrointestinal symptoms, sleep disturbances and skin reactions.

Discussion

Our systematic review included seventeen randomized control trials and five cohort studies. Our findings from cohort studies corroborate the association between low vitamin D levels and increased risk of depressive symptoms in both sexes, and demonstrate that female gender may indirectly strengthen this association. Milaneschi et al. 2010 [33], the most methodologically robust cohort study, found that only women, and not men, with low vitamin D levels had a significantly higher hazard of developing depressed mood during 6 years of follow up compared to women with sufficient vitamin D levels. Given that 74.6% of women and 50.4% of men in this study had vitamin D levels less than 50nmol/L at baseline; these findings are possibly secondary to the increased prevalence of vitamin D deficiency in the female sample. May et al. 2010 [32] found a larger, (but non-statistically significant) hazard ratio in men compared to women with low vitamin D levels, however this study was deemed to have a high risk of bias. Both Milaneschi et al. 2010 [33] and May et al. 2010 [32] did not find a significant interaction by sex in the association between vitamin D and depressive symptoms. Furthermore, Yue et al. 2014 [34] who found the largest increased risk of depression in men and women with severe deficiency (<28nmol/L) unfortunately did not stratify by sex. Interestingly, the only cohort study involving men only did not find any association between vitamin D levels and development of depression [35].

Regarding randomized control trials, seven out of the seventeen RCTs found that vitamin D supplementation was significantly more effective than control, in improving depressive symptoms. Six of these were mixed-sex studies and one was female only. Interestingly, the females included in these trials were mostly of childbearing age [42,44, 47,48,50,51]. Furthermore, Brown et al. 2001 [42], which showed the largest effect size of all included trials (Effect size: -8.6 using CES-D and -24.2 using POMS) was carried out purely in females (>18 years) with mild to moderate depressive symptoms. Jorde et al. 2008 [44], a mixed sex study, found their improvement in BDI 1-13 scores was most clearly seen in females, although females had significantly more depressive symptoms at baseline than men. Sanders et al. 2011 [38], a female only study, found a non-significant trend in females taking anxiety/antidepressant medication to score higher (i.e. better) on the SF-12 MCS if they were randomized to receive vitamin D rather than placebo. The two largest RCTs [36,39] that were both in postmenopausal females, did not find a significant effect of vitamin D supplementation on depressive symptoms, but this is not surprising, as the majority of these females were not depressed at baseline. Furthermore both these studies were secondary analyses and had a high degree of confounding and bias.

The other five trials that found a significant effect of vitamin D supplementation on depressive symptoms in men and women unfortunately did not stratify according to gender [45,47,48,50,51]. However the two studies with large effect sizes included 85% [51] and 72% females [50]. These two trials [50,51] were the only two trials whose participants were both depressed and vitamin D deficient, which strengthens the hypothesis that the benefit of vitamin D supplementation will be most clearly seen in those who are depressed and/or vitamin D deficient.

With regard to the biological plausibility of a link between low vitamin D levels and depressive symptoms in both sexes, there is corroborative evidence from animal and laboratory studies. Eyles et al. 2005 [19] identified vitamin D receptors in the prefrontal cortex, hippocampus, cingulated gyrus, thalamus and hypothalamus, areas of the brain that have been associated with depression. Garcion et al. 2002 [57] found that 1,25 hydroxyvitamin D3 appears to increase expression of genes encoding for tyrosine hydroxylase, the precursor of noradrenaline in the adrenal glands, a neurotransmitter implicated in depression. It is also known that vitamin D protects against serotonin-depleting effects of neurotoxic doses of methamphetamine [58]. Furthermore Feron et al. 2005 [59] found that newborn rats deprived of Vitamin D3 in utero showed micro and macro-structural brain changes that persisted into adulthood such as increased cell proliferation, larger lateral ventricles, reduced cortical thickness, reduced expression of nerve growth factor and reduced expression of glial cell line-derived neurotrophic factor. These brain changes are not specific to depression per say and are also found in schizophrenia and neurodegenerative diseases such as Alzheimer's disease. Also, human genetic studies have shown that Vitamin D receptor polymorphisms contribute to age-related changes in depressive symptoms [60].

Women have a higher lifetime prevalence of depression [3] than men and various biological, psychological and social theories have tried to explain this difference [61]. Evidence for an underlying biological process includes the increased risk of depression in women at times of sex steroid level changes; pre-menstrually, during and after pregnancy and peri-menopausally. The female to male ratio of depression at puberty rises from 1:1 to 2:1, pointing to oestrogen and progesterone as culprits [62]. Ovarian steroids have widespread effects throughout the brain; on serotonin pathways, catecholaminergic neurons [63,64]; on the hypothalamic-pituitary-adrenal axis [65] and in fact, animal studies suggest that the amygdala, a structure involved

in emotion, has one of the highest densities of oestrogen receptors in the brain [66]. Furthermore, selective serotonin uptake inhibitors are effective in treating premenstrual dysphoric disorder, a disorder with overlapping symptoms to depression [67].

Whilst obesity, old age, latitude, dark skin, sunscreen use and cultural clothing practices are clear risk factors for vitamin D deficiency, female sex as a risk factor is under dispute. Many studies have found lower levels of vitamin D in women [6-13] although there is also some evidence to the contrary [68-70]. It is thought that external factors related to sunlight exposure as well as hormonal differences underline these sex differences in circulating vitamin D levels [12,54]. However, animal and human studies show that there may be oestrogen-promoted differences in vitamin D metabolism that do not effect circulating levels of vitamin D [24,25,71], hence why vitamin D levels may not necessarily be lower in women.

Strengths and Limitations

This is the first systematic review including randomized control trial data that has investigated the gender differences in the relationship between vitamin D deficiency and depressive symptoms and in the effect of vitamin D supplementation on depressive symptoms. In view of the existence of this data we did not feel it was necessary to include further cross-sectional data given the problem of reverse causality. This review has been subject to a rigorous methodology. Studies were initially found from a systematic search of multiple databases using comprehensive search terms (see supplementary data for search terms) and were then independently assessed using pre-written inclusion criteria forms by two people. Due to the heterogeneity of the studies included in the review in terms of participants, exposures/interventions, and outcome data, meta-analyses were not appropriate and narrative syntheses were performed. We regard this as a strength, as previous systematic reviews in this area have fallen to the temptation of meta-analysis [26, 27], despite the heterogeneity and poor quality of included studies.

There are some limitations to this systematic review that require comment. Generally, we were mostly unable to set the context in which, we hypothesized, vitamin D would have its main effects: a) in those with depressive symptoms at baseline of both sexes, b) in those who are vitamin D deficient. Out of the seventeen randomized control trials included, there were only two studies in those with clinical depression [50,51] and one other study in those with depressive symptoms at baseline [42]. Not surprisingly these three studies displayed the largest significant effect sizes. In the other studies, baseline depression score ranges revealed that a few participants had depressive symptoms indicative of a diagnosis of depression, even though baseline mean scores were low. For example in Jorde et al. 2008 [44], whilst the mean BDI score of all subjects at baseline was 5, the range was 0-28 (score >9 = mild depression, score>18=moderate depression, score>29=severe depression). Therefore the effective sample size in most studies were very small and so the power to detect a difference, low.

Secondly, whilst eight RCTs measured vitamin D levels, only two studies included only those who were vitamin D deficient at baseline [50,52], the second context in which we hypothesized vitamin D supplementation would have a main effect.

It is therefore not possible for us to make conclusive statements on whether gender modifies the effect of vitamin d supplementation and depressive symptoms, as these two contexts, in which we would expect to see a main effect of vitamin D supplementation on depressive symptoms were mostly absent. It is worth noting however that, five of the seven female-only trials [36-39,53] included postmenopausal women. Given the biological hypothesis of oestrogen promoted differences in local vitamin D metabolism, we would not expect vitamin D to have a more dramatic effect in postmenopausal women.

Conclusion

In summary, there is suggestive evidence of potential benefits of vitamin D supplementation in women of childbearing age. However, there is a need for additional large randomized placebo-controlled trials in both men and women of childbearing age, with a diagnosis of depression and vitamin D deficiency or insufficiency with gender-stratified analysis to further explore this. There is no indication that vitamin D supplementation causes hypomania.

Given, the growing body of evidence that vitamin D deficiency is associated with depression as well as multiple other highly prevalent diseases, the re-introduction of regulated and targeted vitamin D fortification in food stuffs should be re-evaluated.

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