Systematic Review

Effect of Vitamin D Supplementation on Pain: A Systematic Review and Meta-analysis

Zhenqiang Wu, MSc, Zarintaj Malihi, MSc, Alistair W Stewart, BSc, Carlene M. M. Lawes, MD, PhD, and Robert Scragg, MD, PhD

From: University of Auckland Epidemiology and Biostatistics New Zealand

Address Correspondence: Robert Scragg, MD, PhD University of Auckland Epidemiology and Biostatistics Private Bag 92019 Auckland, New Zealand 1142 E-mail: r.scragg@auckland.ac.nz

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 12-02-2015 Revised manuscript received: 03-10-2016 Accepted for publication: 04-28-2016

Free full manuscript: www.painphysicianjournal.com

Background: There is conflicting evidence from previous qualitative reviews on the effect of vitamin D supplementation on pain.

Objective: To determine with quantitative methods if vitamin D supplementation lowers pain levels.

Study Design: Quantitative meta-analysis of published randomized controlled trials (RCTs).

Setting: This meta-analysis examined all studies involving the effect of vitamin D supplementation on pain score.

Method: Electronic sources (Medline, Embase, Cochrane Central Register of Controlled Trials, clinical trials website, and Google scholar) were systematically searched for RCTs of vitamin D supplementation and pain from inception of each database to October 2015.

Results: Nineteen RCTs with 3,436 participants (1,780 on vitamin D supplementation and 1,656 on placebo) were included in the meta-analysis. For the primary outcome (mean change in pain score from baseline to final follow-up), 8 trials with 1,222 participants on vitamin D and 1,235 on placebo reported a significantly greater mean decrease in pain score for the vitamin D group compared to placebo (mean difference -0.57, 95% CI: -1.00 to -0.15, $P = 0.007$). The effect from vitamin D was greater in patients recruited with pre-existing pain (P-value for interaction = 0.03). Fourteen studies (1,548 on vitamin D, 1,430 on placebo) reported the mean pain score at final follow-up outcome, and no statistical difference was observed (mean difference -0.06, 95%CI: -0.44 to 0.33, $P = 0.78$). In 4 studies which reported pain improvement (209 on vitamin D, 146 on placebo), the effect size although not significant, shows participants in the vitamin D supplementation group were more likely to report pain improvement compared with the placebo group (relative risk 1.38, 95%CI: 0.93 to 2.05, $P = 0.11$).

Limitations: Only a few studies reported the mean score change from baseline to final follow-up, and we do not have enough data to determine any modifying effect of baseline vitamin D status and different doses of vitamin D supplementation on pain.

Conclusion: A significantly greater mean decrease in pain score (primary outcome) was observed with vitamin D supplementation compared with placebo in people with chronic pain. These results suggest that vitamin D supplementation could have a role in the management of chronic pain.

Key words: Meta-analysis, pain, randomized controlled trials, vitamin D supplementation

Pain Physician 2016; 19:415-427

Musculoskeletal disease is a growing health issue (1) which results in a major burden on individuals, and health and social care systems (2), requiring health expenditures of hundreds of billion dollars every year (3). Pain is one of the consequences from musculoskeletal disease and has major effects on physical health by limiting mobility and quality of life (4), and leading to numerous health problems, such as stress and depression (5,6).

Although the pathophysiology of pain remains unclear, observational studies suggest that vitamin D deficiency may contribute to the development of pain. A recent meta-analysis of observational studies showed lower blood levels of 25-hydroxyvitamin D (25(OH)D) in patients with statin related myalgia than those without (7).

Moreover, a number of randomized controlled trials (RCTs) have been conducted to determine if there is a benefit from vitamin D supplementation on different kinds of pain. Three previous review articles used qualitative methods to summarize RCTs of vitamin D supplementation and pain, and came to conflicting conclusions (8-10). To our knowledge, no review article has used quantitative meta-analytic techniques to clarify if there are benefits from vitamin D supplementation on pain.

The aim of this article is to undertake a systematic review and meta-analysis of RCTs to determine whether vitamin D supplementation can reduce pain score when compared with placebo.

Method

Search Strategy

We systematically searched Medline, Embase, Cochrane Central Register of Controlled Trials, and the clinical trials website (http://www.clinicaltrials.com) from inception of each database to October 2015, and also reference lists of included studies and related review articles for relevant literature. In addition, Google Scholar was used for grey literature. Search terms included vitamin D and pain related keywords, specifically: Vitamin D, Vitamin D2, Vitamin D3, Cholecalciferol, Ergocalciferol, 25-hydroxyvitamin D, 25-hydroxycholecalciferol, Pain, Myalgia, Myopathy, Myalgic, Headache, Migraine, and Arthritis.

Outcome

Primary and secondary outcomes were defined at the start of the study. Primary outcome was the mean change in pain score from baseline to final follow-up for each intervention/placebo group. Secondary outcomes were mean pain score at final follow-up for each intervention/placebo group, and the number of participants with improvement in pain. The continuous outcome mainly was based on the visual analog scale (VAS) score. If the included studies did not report a VAS score, similar pain scores which assess for pain intensity were used and transformed to a score which ranged over 0 – 10 (described below). In addition, subgroup analyses were performed between participants recruited with pain-related medical conditions (such as chronic low back pain, myalgia, chronic musculoskeletal pain, arthritis, etc.) from hospitals and those who used non-pain criteria to recruit (e.g., though community clinics, population surveys, or recruitment based on vitamin D status).

Eligibility Criteria

We included RCTs in the systematic review and meta-analysis if the study: randomly assigned participants to vitamin D (vitamin D2, vitamin D3) or placebo group; reported pain related outcomes; enrolled adult participants ≥ 18 years; and with follow-up time of ≥ 4 weeks. For studies with more than one vitamin D treatment group, the data from the higher vitamin D supplementation group, or combined data, were used in this study. If a study reported more than one pain outcome, the pain data for the primary outcome was selected from the largest sample size. Studies with co-interventions (aside from calcium) only in the treatment group were excluded.

Data Collection

Two reviewers (ZW, RS) independently selected the related publications by reading the title, abstract, and full article, and all selected articles were based on the inclusion criteria. Any disagreements were resolved by discussion.

Risk of Bias Assessment

Each included study was assessed for risk of bias using the Cochrane Collaboration's tool (11). We assessed all the 7 domains: random sequence generation, allocation concealment, blinding of participants and researcher, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The key information was extracted by 2 researchers independently (ZW, ZM) for appraisal of the risk of bias of each study. Funnel plots and Egger's test were used to examine potential publication bias (12).

Data Processing and Analysis

For continuous outcomes, articles used a variety of pain assessment tools, which included the VAS score, The Western Ontario and McMaster Universities Arthritis Index (WOMAC), Pain severity score, Pain mobility score, Pain assessment in advanced dementia (PAINAD) score, and Brief Pain Inventory (BPI) severity score. Where different pain scales had different ranges, and assessed a similar component, such as intensity of pain,

data were extracted and transformed to a standard range of 0 – 10 (13).

For continuous outcomes, the sample size, mean, and standard deviation (SD) of the pain score for each comparison group were extracted from eligible studies. Where studies reported the pain score using median and range, or by showing it only in a graph, Hozo's method (14) and Digitizer software (GetData Graph Digitizer 2.26, http://www.getdata-graph-digitizer.com/) were used to estimate the mean and SD of the pain score. For dichotomous outcomes, the total sample size of each intervention group and the numbers of participants with pain improvement were collected.

We calculated mean differences (MD) and 95% confidence intervals (CIs) for continuous outcomes, and risk ratios (RR) and 95% CIs for dichotomous outcomes. Statistical heterogeneity among individual studies was assessed using Cochran's Q statistic and I^2 index (I^2 > 50%, large heterogeneity) (15). A random effects model was used to estimate the overall effect (16). Interactions were formally tested using standard methods (17). We performed a sensitivity analysis by excluding studies individually from the summary calculation. All results were based on the 2 tailed test and a *P*-value ≤ 0.05 was considered statistically significant in the meta-analysis. All the analyses were performed in Review Manager software (Revman version 5.2) and Stata statistical software (version 13.1).

Results

Study Characteristics

We identified 872 related articles, after duplicates were removed, by searching all 4 electronic databases and Google Scholar. After review of the titles, 110 articles were selected for abstract review, of which 39 articles were excluded because they were not relevant, not an RCT, or were review articles. Of the 71 articles selected for full text review, 19 studies met the inclusion criteria of the review. The details of study selection are shown in the flow diagram (Fig. 1).

The 19 RCTs published between 1973 and 2015 included 3,436 participants (1,780 with vitamin D supplementation and 1,656 with placebo) with a median age of 55.1 years (median SD: 8.6), median female percentage of 76% (range: 40% – 100%), and median follow-up time of 3 months (range: 1 – 24). Eight trials (18-25), which included 1,222 participants with vitamin D and 1,235 with placebo, reported the primary outcome (mean change in pain score from baseline to final follow-up). Fourteen studies (19,21-24,26-34) reported the final follow-up pain score information among 2,978 participants (one study [28] reported oral and parenteral vitamin D supplementation separately, which are reported as 2 studies in this meta-analysis), and 4 studies (29,32,35,36) with 355 patients reported the number of participants with improvement in pain. The baseline characteristics of all 19 included clinical trials (16 hospital based and 3 community based) appear in Table 1.

Risk of Bias Assessment

Results of the risk of bias assessment are shown in Fig. 2 and Fig. 3. One study shows high risk of bias in blinding of participants and researcher, and in blinding of the outcome assessment domain because of insufficient information in the published article. This study is based on the abstract, which did not have enough information for assessing if it was double-blind (25).

Quantitative Data Synthesis

Primary Outcome

The studies that reported mean change in pain score from baseline to final follow-up are described in Table 2. There was a significantly greater mean decrease in pain score for the vitamin D supplementation group compared to placebo (mean difference -0.57, 95% CI: -1.00 to -0.15, $P = 0.007$) (Fig. 4). There was heterogeneity in the primary outcome ($P < 0.00001$, $I^2 = 88\%$). A sensitivity analysis, by removing each study one by one, revealed similar results (data not shown). In a subgroup analysis, the mean decrease in pain from vitamin D supplementation was observed in hospitalized patients with pain-related medical conditions (mean difference -0.70, 95% CI: -1.26 to -0.14, $P = 0.01$), but not in surveys which recruited from the community or based on vitamin D status (mean difference -0.03, 95% CI: -0.27 to 0.21, $P = 0.81$). There was a significant interaction between the 2 subgroups from the effect of vitamin D supplementation on change in pain score ($Z = -2.16$, $P = 0.03$). However, there was no difference ($P = 0.29$) in the effect of vitamin D supplementation on pain between studies of widespread non-specific pain (pain, diffuse pain, musculoskeletal pain, fibromyalgia) and studies of localized pain (low back pain, dysmenorrhea, arthritis, migraine). Further, a subgroup analysis between short-term (< 6 months) and long-term (≥ 6 months) supplementation did not show any difference in effect between these 2 groups ($P = 0.47$). Subgroup analyses between vitamin D2 or D3 and between high

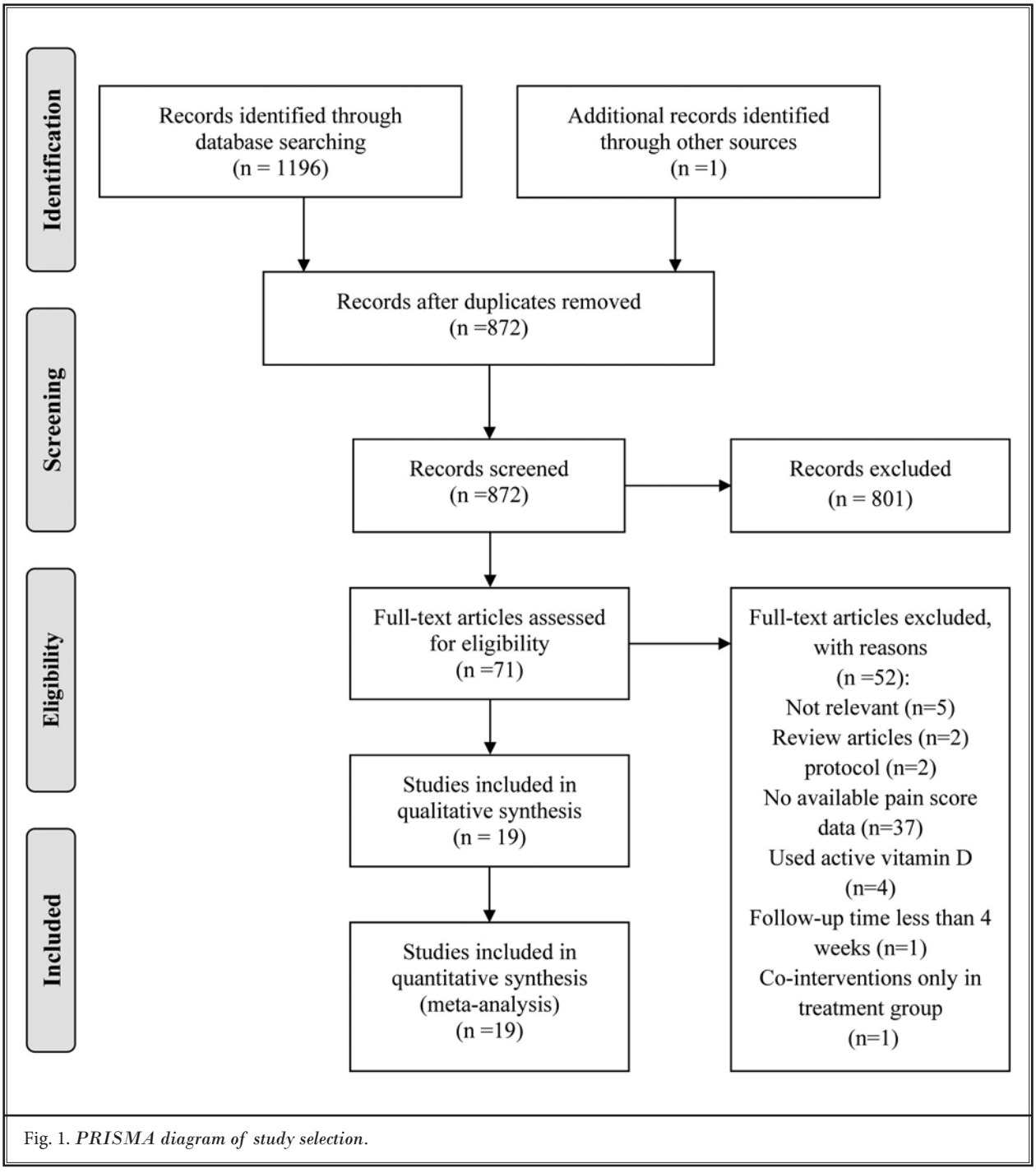

Fig. 1. *PRISMA diagram of study selection.*

dose (≥ 1,000 IU/day) or low dose (< 1,000 IU/day) vitamin D supplementation were not conducted because of too few studies (only one study was in vitamin D2 subgroup, and one study in the low dose subgroup).

Secondary Outcomes

The studies that reported the mean pain score at final follow-up are described in Table 3 and a forest plot of their results shown in Fig. 5. There was no statistical

Table 1. *Characteristics of included double-blind randomized placebo controlled trials.*

Study, year	Population	Country	Mean age, years (SD)	Female (%)	N			Interventions	Daily equivalent (IU)	Duration (month)	Pain Outcomes	Type of study
					Total	TG	PG					
(Brohult, 1973) (36)	Patients with rheumatoid arthritis	Sweden	52 (NA)	34 (68)	49	24	25	100,000 IU calciferol daily or placebo	100,000	12	Joint status improvement	Hospital based
(Bjorkman, 2008) (32)	Patients with pain or pain behaviour	Finland	84.5 (7.5)	164 (80)	170	114	56	400 IU or 1200 IU vitamin D3 daily or placebo	400 or 1200	6	PAINAD at rest; PAINAD during daily nursing; DBS	Hospital based
(Warner, 2008) (19)	Patients with diffuse pain	USA	57.4 (9.3)	42 (100)	42	22	20	50,000IU vitamin D2 weekly or placebo	7,100	3	VAS; FPS	Hospital based
(Arvold , 2009) (24)	Patients with vitamin D deficiency	USA	58.8 (14.8)	36 (40)	90	48	42	50,000 IU vitamin D3 weekly or placebo.	7,100	2	Pain severity; FIQ	Community based
(Rastelli, 2011) (29)	Patients with musculoskeletal pain	USA	61.5 (8.4)	57 (100)	57	28	29	50,000 IU Vitamin D2 weekly for 8 weeks then monthly for 4 months; or 50,000 IU vitamin D2 weekly for 16 weeks then monthly for 2 months.	7,100	6	BPI; FIQ; HAQ-DI; discontinue of pain medication	Hospital based
(Lasco, 2012) (22)	Patients with dysmenorrhea	Italy	26.7 (6.1)	40 (100)	40	20	20	300,000 IU vitamin D3 5 days before the next menstrual cycle or placebo	10,000	2	VAS	Hospital based
(Sakalli , 2012) (28) #	Rheumatology outpatient	Turkey	70.1 (4.3)	57 (47.5)	60	30	30	300,000 IU intramuscular vitamin D once or placebo	10,000	1	VAS	Hospital based
(Sakalli, 2012) (28) #	Rheumatology outpatient	Turkey			60	30	30	300,000 IU oral vitamin D once or placebo	10,000	1	VAS	Hospital based
(Salesi, 2012) (27)	Patients with rheumatology arthritis	Iran	50.0 (12.8)	89 (91)	98	50	48	50,000 IU Vitamin D weekly or placebo	7,100	3	VAS	Hospital based
(Schreuder, 2012) (35)	Patients with nonspecific musculoskeletal pain	Netherlands	41.9 (10.4)	64 (76)	79	43	36	150,000 IU Vitamin D3 at baseline or placebo	3,600	1.5	5 point Likert scale	Hospital based

Abbreviations SD: Standard deviation; TG: Treatment group; PG: Placebo group; NA: Not available; PAINAD: Pain assessment in advanced dementia; DBS: Discomfort behaviour scale; VAS: Visual analog scale; FPS: Function pain score; FIQ: Fibromyalgia impact questionnaire; BPI: Brief pain inventory short form; HAQ-DI: Health assessment questionnaire-disability index; 5 point Likert scale: Much less pain, less pain, equal, more pain, much more pain; Join pain severity score: None=0, Mild=1, Moderate=2, Severe=3; WOMAC: Western Ontario and McMaster Universities Arthritis Index; MPQ: McGill pain questionnaire.

#: Analysed as two studies in this meta-analysis based on oral and parenteral vitamin D supplementation;

##: 1,000 mg elemental calcium daily in treatment group;

*: Not stated double blind in the original abstract.

Table 1 (cont.). *Characteristics of included double-blind randomized placebo controlled trials.*

Study, year	Population	Country	Mean age, years (SD)	Female (%)	N			Interventions	Daily equivalent (IU)	Duration (month)	Pain Outcomes	Type of study
					Total	TG	PG					
(Chlebowski, 2013) (23)	Postmenopausal women	USA	62.0 (NA)	1911 (100)	1911	945	966	400 IU vitamin D3 daily or placebo ##	400	24	Join pain severity score	Community based
(McAlindon, 2013) (18)	Patients with knee osteoarthritis,	USA	62.4 (8.5)	89 (61)	146	73	73	2,000 IU vitamin D3 daily or placebo	2,000	24	WOMAC pain	Hospital based
(Sandoughi, 2013) (21)	Patients with nonspecific chronic low back pain	Iran	33.2 (6.5)	40 (76)	53	26	27	50,000 IU vitamin D3 weekly or Placebo	7,100	2	VAS	Hospital based
(Sanghi, 2013) (20)	Patients with knee osteoarthritis	India	53.1 (8.6)	66 (64)	103	52	51	60,000 IU vitamin D3 daily for 10 days followed by 60,000 IU once a month or placebo	2,000	12	VAS; WOMAC pain	Hospital based
(Abou-Raya, 2014) * (25)	Patients with fibromyalgia	Egypt	NA	NA	72	36	36	2,000 IU vitamin D3 daily or placebo	2,000	6	VAS	Hospital based
(Hansen, 2014) (31)	Patients with rheumatology arthritis	USA	58.0 (12.3)	10 (46)	22	11	11	50,000 IU Vitamin D2 3 times weekly for 4 weeks, then 50,000 IU twice monthly for 11 months	3,300	12	VAS	Hospital based
(Knutsen, 2014) (30)	Healthy population aged 18-50 years	Norway	37.3 (7.8)	182 (73)	215	144	71	1,000 IU or 400 IU vitamin D3 daily or placebo	400 or 1000	4	VAS	Community based
(Wepner, 2014) (26)	Patients with fibromyalgia	Austria	48.4 (5.3)	27 (90)	30	15	15	2,400IU or 1,200IU vitamin D3 daily or placebo	1,200 or 2,400	3	VAS; FIQ	Hospital based
(Gendelman, 2015) (33)	Patients with chronic musculoskeletal pain	Israel	57.1 (13.4)	60 (80)	74	36	38	4,000 IU vitamin D3 Daily or placebo	4,000	3	VAS; MPQ	Hospital based
(Mottaghi et al., 2015) (34)	Patients with migraine	Iran	33.3 (11.0)	47 (72)	65	33	32	50,000 IU Vitamin D weekly or placebo	7,100	2.5	VAS	Hospital based

Abbreviations SD: Standard deviation; TG: Treatment group; PG: Placebo group; NA: Not available; PAINAD: Pain assessment in advanced dementia; DBS: Discomfort behaviour scale; VAS: Visual analog scale; FPS: Function pain score; FIQ: Fibromyalgia impact questionnaire; BPI: Brief pain inventory short form; HAQ-DI: Health assessment questionnaire-disability index; 5 point Likert scale: Much less pain, less pain, equal, more pain, much more pain; Join pain severity score: None=0, Mild=1, Moderate=2, Severe=3; WOMAC: Western Ontario and McMaster Universities Arthritis Index; MPQ: McGill pain questionnaire.

#: Analysed as two studies in this meta-analysis based on oral and parenteral vitamin D supplementation;

##: 1,000 mg elemental calcium daily in treatment group;

*: Not stated double blind in the original abstract.

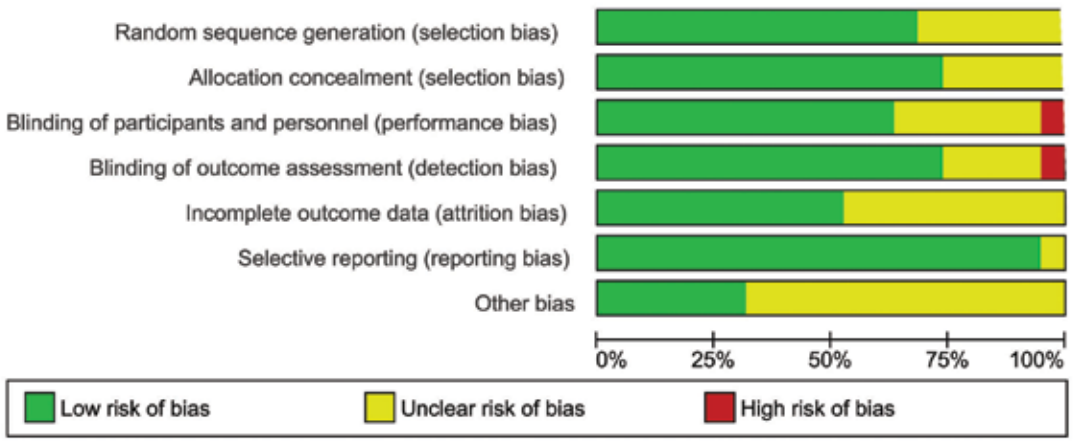

Fig. 2. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.*

Table 2. *Transformed information for the primary outcome: mean change in pain score from baseline to final follow-up.*

Study, year	Pain scale information	Sample size (N)		Original Score change from baseline Mean (SD)		Transformed score change from baseline (0-10) Mean (SD)	
		TG	PG	TG	PG	TG	PG
(Warner, 2008) (19) *	VAS (range: 0-100, 0=no pain, 100=severe pain)	22	20	-7.1 (19.1)	-9.7 (28.4)	-0.71 (1.91)	-0.97 (2.84)
(Arvold, 2009) (24) *	Pain severity (range: 0-10, 0=none, 10=severe)	48	42	-0.33(1.96)	0.21 (2.92)	-0.33(1.96)	0.21 (2.92)
(Lasco, 2012) (22)	VAS (range:0-10, 0=no pain, 10=severe pain)	20	20	-2.30 (1.30)	0.05 (0.75)	-2.30 (1.30)	0.05 (0.75)
(Chlebowski, 2013) (23)	Pain severity (range: 0-3, 0=none, 3= severe)	945	966	0.06 (0.84)	0.06 (0.82)	0.2 (2.80)	0.3 (2.73)
(McAlindon, 2013) (18)	WOMAC pain scale (range: 0-20, 0=no pain, 20=extreme pain)	73	73	-2.31 (3.98)	-1.46 (3.72)	-1.16 (1.99)	-0.73 (1.86)
(Sandoughi, 2013) (21)	VAS (range:0-10, 0=no pain, 10=severe pain)	26	27	-2.38 (2.62)	-3.33 (3.67)	-2.38 (2.62)	-3.33 (3.67)
(Sanghi, 2013) (20) *#	WOMAC pain (range: 0-20,0: 0=no pain, 20=extreme pain)	52	51	-0.55 (1.68)	1.16 (1.22)	-0.28 (0.84)	0.58 (0.61)
(Abou-Raya, 2014) (25)	VAS (range: 0-100, 0=no pain, 100=severe pain)	36	36	-6.6 (2.5)	-2.9 (2.7)	-0.66 (0.25)	-0.29 (0.27)

Abbreviations SD: Standard deviation; TG: Treatment group; PG: Placebo group; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.
*: Studies that provided more than 1 pain related outcomes, others similar pain outcomes were used for sensitively analysis;
#: VAS data were inconsistent in this study, so WOMAC pain data were used.

difference between the vitamin D supplementation group and placebo group in their final mean pain score (mean difference – 0.06, 95%CI: -0.44 to 0.33, $P = 0.78$). There was heterogeneity in this secondary outcome ($P < 0.0001$, I2 = 69%). A sensitivity analysis (removing individual studies) did not change this result, and subgroup analyses found the same pattern of no difference in pain between vitamin D and placebo groups for hospital or community samples (Fig. 5), for wide-spread or localized pain, long-term or short-term supplementation, vitamin D2 or D3, and low dose or high dose (data not shown).

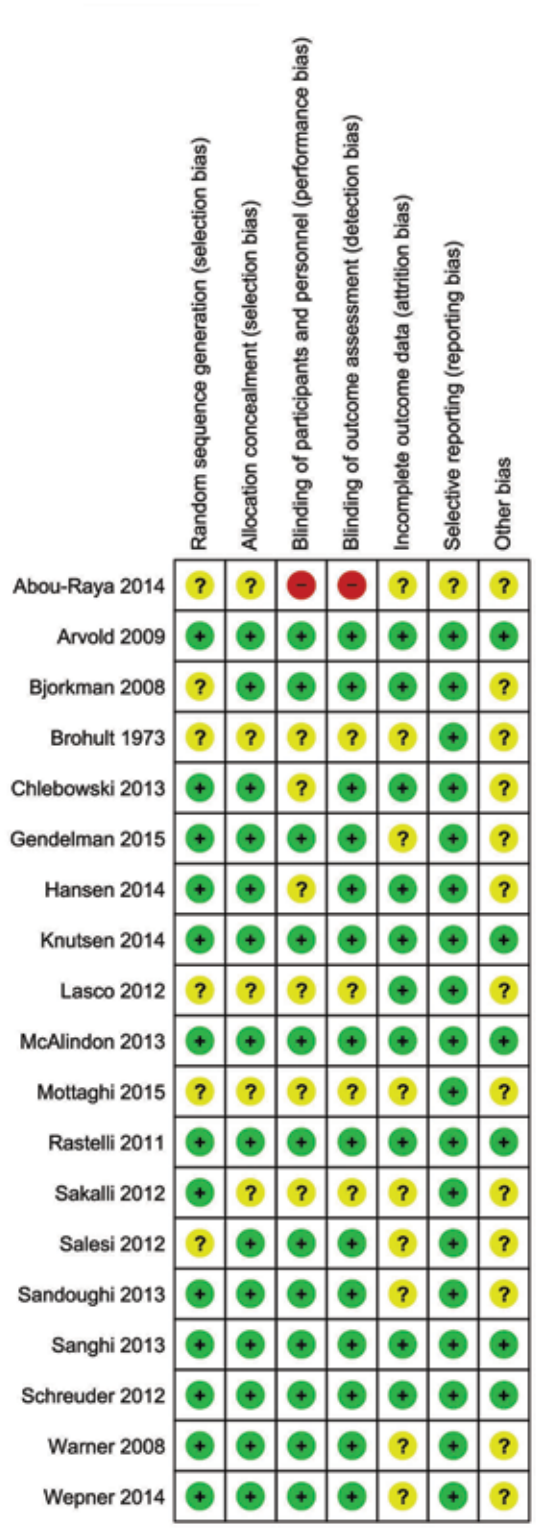

Fig. 3. *Risk of bias summary: review authors' judgements about each risk of bias item for each included study.*

The studies that reported the number of participants with improvement in pain, from baseline to final follow-up, are described in Table 4 and a forest plot of their results is shown in Fig. 6. The pooled results showed a non-significant effect in the vitamin D supplementation group compared with the placebo group (RR: 1.38, 95%CI: 0.93 to 2.05, $P = 0.11$), with no heterogeneity ($P = 0.30$, I2 = 19%) (Fig. 6). Subgroup analysis was not carried out as all participants in these studies reported pain at baseline. A sensitivity analysis, which excluded each study one by one, revealed a similar effect size to that above.

Publication Bias

Egger's tests and funnel plots were conducted on all studies for each outcome. No evidence of publication bias was found in the Egger's test (primary outcome: mean change in pain score from baseline to final follow-up, $P = 0.64$; secondary outcome: mean pain score at final follow-up, $P = 1.00$; secondary outcome: the number of participants with improvement in pain, $P = 0.64$) nor in the funnel plots (Fig. 7).

Discussion

We have found in a quantitative meta-analysis of 8 studies that vitamin D supplementation resulted in a greater decrease in pain than placebo (our primary outcome). In 4 separate studies which reported pain improvement (secondary outcome), although no significant result was observed, the point effect size suggests participants in the vitamin D supplementation group maybe more likely to report pain improvement compared with the placebo group. In addition, vitamin D had no effect on the final mean pain score recorded at follow-up (secondary outcome).

Further, in our subgroup analysis of the primary outcome, we found that there was a greater decrease in mean pain score from baseline to final follow-up in studies which recruited participants with painful medical conditions from hospital clinics compared to studies which recruited from the community or with vitamin D deficiency (Z = -2.16, $P = 0.03$). This interaction could be due to the very low dose of vitamin D (400 IU/day) used in one of the community based studies (23); and another possible reason is that too few studies (only 2) were included in the community based subgroup, where more research is needed.

To our knowledge, this is the first reported quantitative meta-analysis of vitamin D supplementation and pain. Qualitative methods have been used in

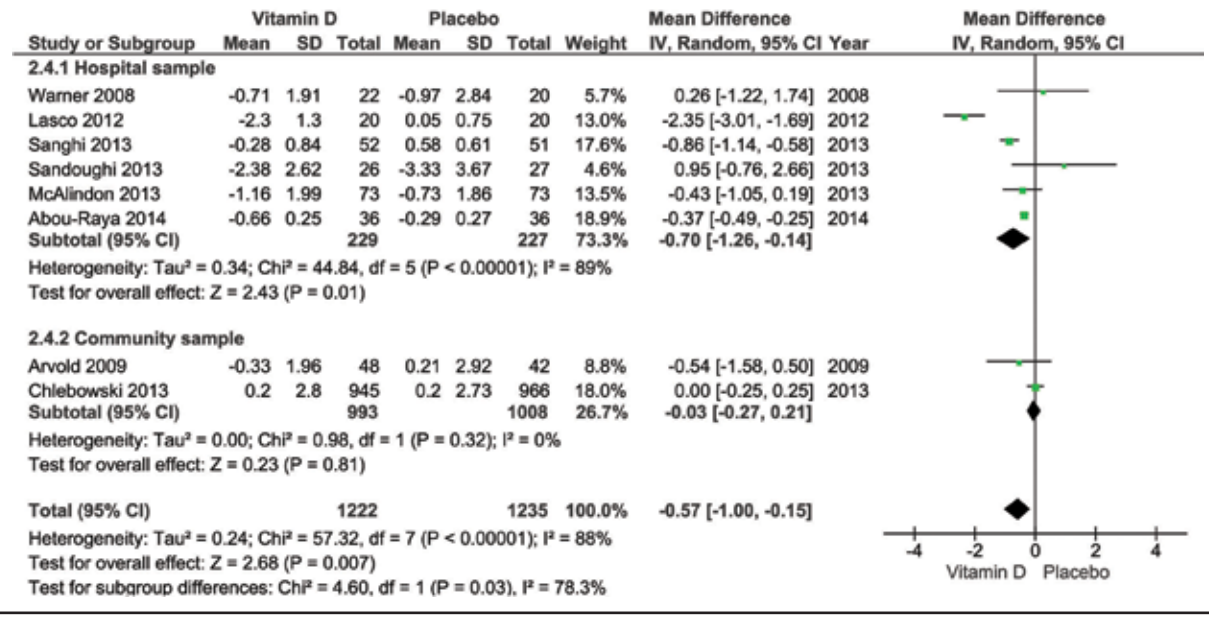

Fig. 4. *Forest plot of the effects of vitamin D supplementation on mean change pain score from baseline to final follow-up outcome.*

Table 3. *Transformed information for the secondary outcome: mean pain score at final follow-up.*

Study	Pain scale information	Sample size		Original Score at Follow-up Mean (SD)		Transformed score at Follow-up (0-10), Mean (SD)	
		TG	PG	TG	PG	TG	PG
(Bjorkman, 2008) (32)	PAINAD (at rest) (range: 0-10, 0=none, 10=severe)	114	56	1.2 (1.8)	1.4 (1.7)	1.2 (1.8)	1.4 (1.7)
(Warner, 2008) (19)	VAS improvement (Range: 0-100, 0=no pain, 100=severe pain)	22	20	64.7 (18.0)	53.6 (26.8)	6.47 (1.80)	5.36 (2.68)
(Arvold, 2009) (24)	Pain severity (range: 0-10, 0=none, 10=severe)	48	42	3.2 (2.6)	3.4 (2.5)	3.2 (2.6)	3.4 (2.5)
(Rastelli, 2011) (29)	BPI pain severity at 2 month (range 0-10, 0=none, 10=severe)	28	29	2.7 (1.9)	3.5 (1.5)	2.7 (1.9)	3.5 (1.5)
(Lasco, 2012) (22)	VAS (range: 0-10,0=no pain, 10=severe pain)	20	20	3.50 (1.27)	5.70 (1.59)	3.50 (1.27)	5.70 (1.59)
(Sakalli, 2012) (28) #	VAS (intramuscular vitamin D) (range:0-10, 0=no pain, 10=severe pain))	30	30	5.4 (2.2)	4.2 (3.1)	5.4 (2.2)	4.2 (3.1)
(Sakalli, 2012) (28) #	VAS (oral vitamin D) (range:0-10, 0=no pain, 10=severe pain)	30	30	5.1 (2.3)	5.5 (2.8)	5.1 (2.3)	5.5 (2.8)
(Salesi, 2012) (27)	VAS (range:0-100, 0=no pain, 100=severe pain)	50	48	45.7 (19.9)	38.7 (20.4)	4.57 (1.99)	3.87 (2.04)
(Chlebowski, 2013) (23)	Pain severity (range: 0-3, none=0, severe=3)	941	961	1.10 (0.85)	1.10 (0.85)	3.67 (2.83)	3.67 (2.83)
(Sandoughi, 2013) (21)	VAS (range: 0-10, ,0=no pain, 10=severe pain)	26	27	3.03 (3.14)	3.11 (3.08)	3.03 (3.14)	3.11 (3.08)
(Hansen, 2014) (31)	0-10 pain scale (range: 0-10,0=no pain, 10=severe pain)	11	11	3.87 (1.91)	2.42 (1.91)	3.87 (1.91)	2.42 (1.91)
(Knutsen, 2014) (30)	VAS Total (Range: 0-1000, 0=no pain, 1000=severe)	144	71	140 (152)	143 (152)	1.4 (1.52)	1.43 (1.52)
(Wepner, 2014) (26)	VAS (Range:0-100,0=no pain, 100=severe pain)	15	15	50.6 (25.01)	61.1 (26.26)	5.06 (2.50)	6.11 (2.63)
(Gendelman, 2015) (33)	VAS (Range:0-100,0=no pain, 100=severe pain)	36	38	48.6 (26.0)	54.6 (28.3)	4.86 (2.60)	5.46 (2.83)
(Mottaghi et al., 2015) (34)	VAS (range: 0-10, ,0=no pain, 10=severe pain)	33	32	5.9 (1.5)	5.0 (2.0)	5.9 (1.5)	5.0 (2.0)

Abbreviations SD: Standard deviation; TG: Treatment group; PG: Placebo group; PAINAD: Pain assessment in advanced dementia; VAS: Visual Analog Scale; BPI: Brief pain inventory short form. #: Analysed as two studies in this meta-analysis based on oral and parenteral vitamin D supplementation.

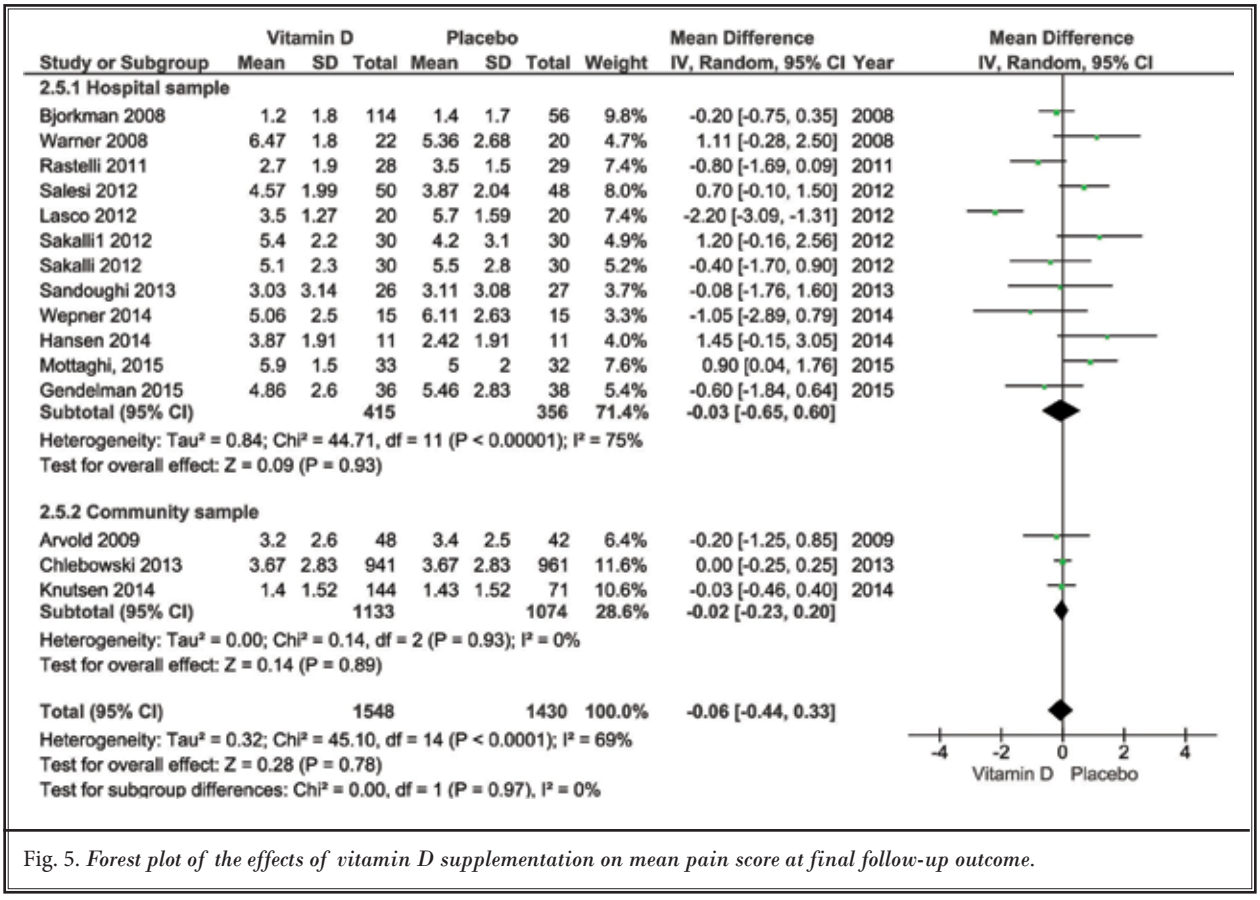

Fig. 5. *Forest plot of the effects of vitamin D supplementation on mean pain score at final follow-up outcome.*

Table 4. *Data information for the secondary outcome: the number of participants with improvement in pain.*

Study	Sample size		Pain related outcome	Number of participants with improvement in pain (N)	
	TG	PG		TG	PG
(Brohult, 1973) (36)	24	25	Objective and subjective improvement	16	9
(Bjorkman, 2008) (32)	114	56	PAINAD (at rest, 0-10)	33	15
(Rastelli, 2011) (29)	28	29	Discontinuation of pain medication	2	4
(Schreuder, 2012) (35)	43	36	5 point Likert scale	15	7

Abbreviations TG: Treatment group; PG: Placebo group; PAINAD: Pain assessment in advanced dementia; 5 point Likert scale: Much less pain, less pain, equal, more pain, much more pain.

previous reviews (8-10). For example, Straube et al (9,10) conducted a review of vitamin D supplementation and chronic pain, based on 10 RCTs which enrolled participants with chronic pain. They did a qualitative review and concluded there was no concordant effect of vitamin D supplementation on any pain condition. Another review used similar qualitative methods, and from the 8 RCTs analyzed, concluded that the relationship between vitamin D deficiency and chronic pain is inconclusive (8). In comparison to these reviews, the current study extended the inclusion criteria to include also participants recruited from the community, not all of whom will have pain, in addition to those with conditions likely to cause pain. Therefore, our study included more studies than reviewed previously, and we also conducted a quantitative analysis to assess the

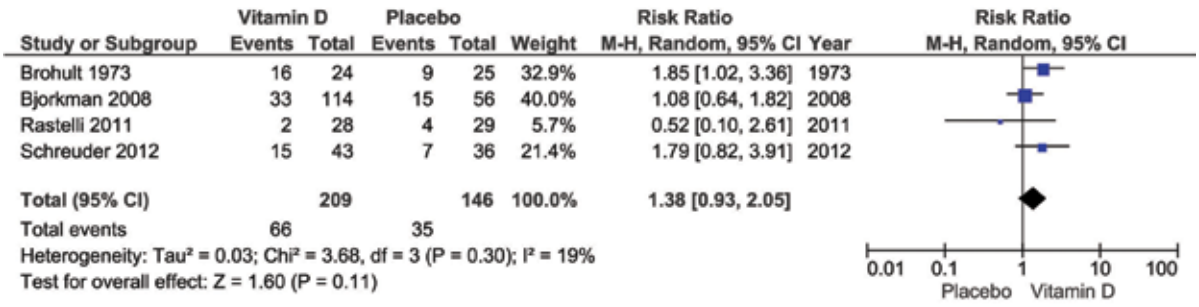

Fig. 6. *Forest plot of the effects of vitamin D supplementation on the number of participants with improvement in pain outcome.*

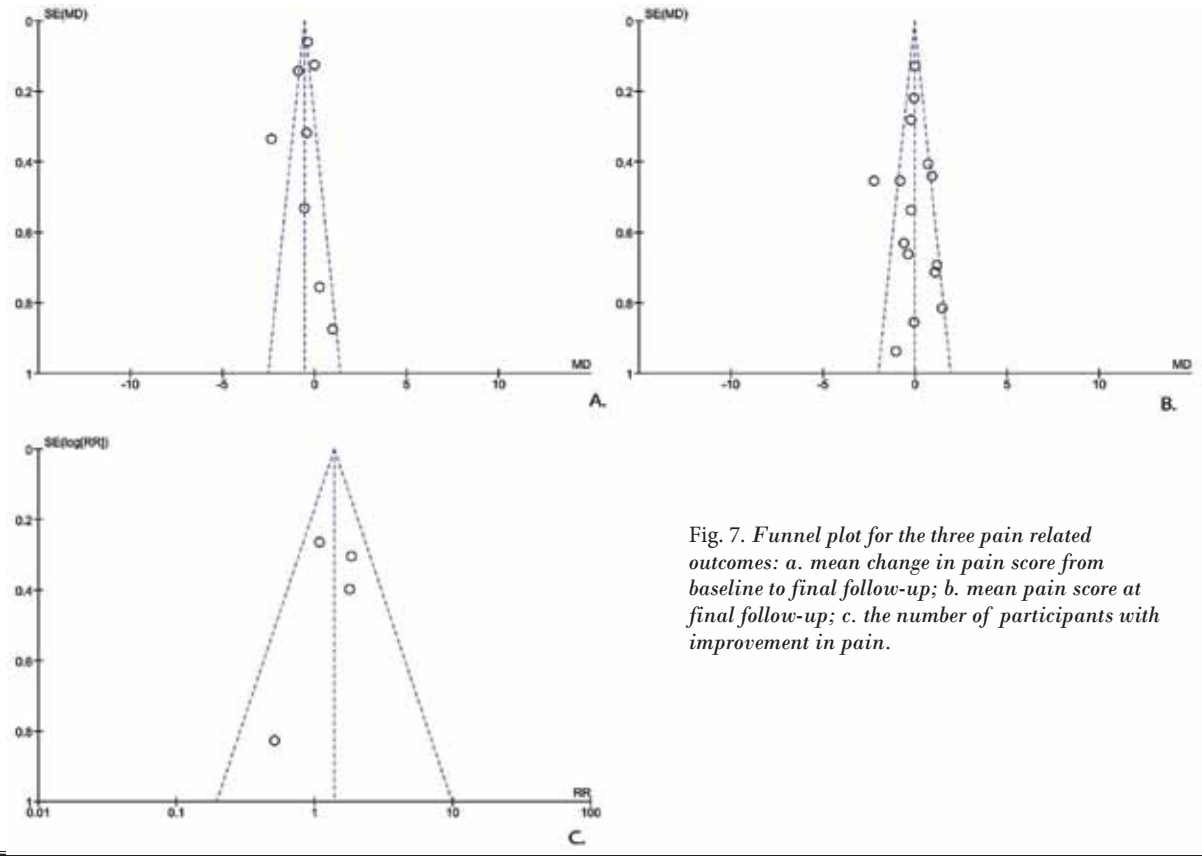

Fig. 7. *Funnel plot for the three pain related outcomes: a. mean change in pain score from baseline to final follow-up; b. mean pain score at final follow-up; c. the number of participants with improvement in pain.*

effect of vitamin D supplementation on pain score.

This meta-analysis has a number of strengths. We defined primary and secondary outcomes before extracting the original data, to minimize bias in our analytical approach. Our primary outcome – mean change in pain score from baseline to final follow-up – could reduce the influence of between-person variability in the data, which could explain the lack of effect from vitamin D seen for the secondary outcome of mean pain score at final follow-up. We used statistical methods to transform the pain scores to a range of 0 – 10, so that data from a greater number of studies could be included in the meta-analysis. The Cochrane Collaboration's tool was used to assess the risk of bias for included stud-

ies, which provided information about the quality of included studies. Finally, we used quantitative analyses to evaluate the effects of vitamin D supplementation, which is more objective than the methods used in previous reviews.

Nevertheless, there are also several limitations of the included studies and the research methods. First, not all of the included studies used a similar pain assessment tool, and not all of them reported the pain score change from baseline. Although we used statistical methods to transform and standardize the range for pain scores, which allowed us to increase the number of studies summarized, this could have introduced heterogeneity as the included pain scores may have other differences that could not be controlled for. Second, one included study did not state that it was a double-blind RCT (25), which could be another source of heterogeneity, although excluding this study showed similar results in the sensitivity analysis. Third, the participants included hospital-based and community-based participants, which could be a source of statistical and clinical heterogeneity. Fourth, a low dose of vitamin D was supplied in 2 included studies (≤ 1,000 IU daily) (23,30), which may not have increased body vitamin D levels sufficiently enough to see benefit. Fifth, we do not have enough data to determine the effect of baseline vitamin D status and different doses of vitamin D supplementation on pain. In addition, although we limited the follow-up time in the inclusion criteria, the included studies had a wide range of follow-up time, from 2 to 24 months, and it may take time for vitamin D to show a beneficial effect. The publication of further RCTs will offer greater scope in the future for sub-group analyses with greater statistical power which may identify potential causes of the heterogeneity in our results.

Conclusion

In conclusion, the results of this meta-analysis support the conclusion that vitamin D supplementation may reduce pain scores in the patients with pain conditions. This suggests that vitamin D supplementation could have a role in the management of chronic pain. Further well-designed placebo controlled long-term trials should be conducted to confirm these findings.

Acknowledgments

ZW was awarded a State Scholarship Fund of China Scholarship Council.

References

1. Brooks PM. The burden of musculoskeletal disease -- a global perspective. *Clinical Rheumatology* 2006; 25:778-781.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization* 2003; 81:646-656.
3. Yelin E. Cost of musculoskeletal diseases: Impact of work disability and functional decline. *The Journal of Rheumatology Supplement* 2003; 68:8-11.
4. Krocker D, Ullrich H, Buttgereit F, Perka C. Influence of adjuvant pain medication on quality of life in the treatment of postmenopausal osteoporosis. *Der Orthopade* 2008; 37:435-439.
5. Bushnell MC, Case LK, Ceko M, Cotton VA, Gracely JL, Low LA, Pitcher MH, Villemure C. Effect of environment on the long-term consequences of chronic pain. *Pain* 2015; 156:S42-S49.
6. Greenberg EN. The consequences of chronic pain. *Journal of Pain & Palliative Care Pharmacotherapy* 2012; 26:64-67.
7. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Hovingh GK, Farnier M, Moriarty PM, Bittner VA, Lip GYH, Banach M; Lipid and Blood Pressure Meta-analysis Collaboration Group. Analysis of vitamin D levels in patients with and without statin-associated myalgia - A systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol* 2015; 178:111-116.
8. Shipton EE, Shipton EA. Vitamin D deficiency and pain: Clinical evidence of low levels of vitamin D and supplementation in chronic pain states. *Pain and Therapy* 2015; 4:67-87.
9. Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain* 2009; 141:10-13.
10. Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. *The Cochrane Database of Systematic Reviews* 2015; 5:CD007771.
11. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-634.
13. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH, Morton SC. *Handling Continuous Outcomes in Quantitative Synthesis, Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Methods for Effective Health Care, Rockville, MD, 2008.
14. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005; 5:13.

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-560.
16. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; 1:97-111.
17. Altman DG, Bland JM. Statistics notes - Interaction revisited: The difference between two estimates. *Brit Med J* 2003; 326:219-219.
18. McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, Lo G, Dawson-Hughes B. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: A randomized controlled trial. *JAMA* 2013; 309:155-162.
19. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *Journal of Clinical Rheumatology* 2008; 14:12-16.
20. Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, Srivastava RN. Does vitamin D improve osteoarthritis of the knee: A randomized controlled pilot trial. *Clinical Orthopaedics and Related Research* 2013; 471:3556-3562.
21. Sandoughi M, Zakeri Z, Mirhosainee Z, Mohammadi M, Shahbakhsh S. The effect of vitamin D on nonspecific low back pain. *Int J Rheum Dis* 2013.
22. Lasco A, Catalano A, Benvenga S. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: Results of a randomized, double-blind, placebo-controlled study. *Archives of Internal Medicine* 2012; 172:366-367.
23. Chlebowski RT, Pettinger M, Johnson KC, Wallace R, Womack C, Mossavar-Rahmani Y, Stefanick M, Wactawski-Wende J, Carbone L, Lu B, Eaton C, Walitt B, Kooperberg CL. Calcium plus vitamin D supplementation and joint symptoms in postmenopausal women in the women's health initiative randomized trial. *Journal of the Academy of Nutrition and Dietetics* 2013; 113:1302-1310.
24. Arvold DS, Odean MJ, Dornfeld MP, Regal RR, Arvold JG, Karwoski GC, Mast DJ, Sanford PB, Sjoberg RJ. Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: A randomized controlled trial. *Endocr Pract* 2009; 15:203-212.
25. Abou-Raya S, Abou-Raya A, Helmii M. Efficacy of vitamin D supplementation in the treatment of fibromyalgia: Randomized controlled trial. *Ann Rheum Dis* 2014; 73:295-295.
26. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, Hahne J, Friedrich M. Effects of vitamin D on patients with fibromyalgia syndrome: A randomized placebo-controlled trial. *Pain* 2014; 155:261-268.
27. Salesi M, Farajzadegan Z. Efficacy of vitamin D in patients with active rheumatoid arthritis receiving methotrexate therapy. *Rheumatology International* 2012; 32:2129-2133.
28. Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: A prospective, double-blinded, randomized, placebo-controlled study. *Rheumatology International* 2012; 32:2279-2283.
29. Rastelli AL, Taylor ME, Gao F, Armamento-Villareal R, Jamalabadi-Majidi S, Napoli N, Ellis MJ. Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): A phase II, double-blind, placebo-controlled, randomized trial. *Breast Cancer Research and Treatment* 2011; 129:107-116.
30. Knutsen KV, Madar AA, Brekke M, Meyer HE, Natvig B, Mdala I, Lagerlov P. Effect of vitamin D on musculoskeletal pain and headache: A randomized, double-blind, placebo-controlled trial among adult ethnic minorities in Norway. *Pain* 2014; 155:2591-2598.
31. Hansen KE, Bartels CM, Gangnon RE, Jones AN, Gogineni J. An evaluation of high-dose vitamin D for rheumatoid arthritis. *Journal of Clinical Rheumatology* 2014; 20:112-114.
32. Bjorkman M, Sorva A, Tilvis R. Vitamin D supplementation has no major effect on pain or pain behavior in bedridden geriatric patients with advanced dementia. *Aging Clin Exp Res* 2008; 20:316-321.
33. Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. *Lupus* 2015; 24:483-489.
34. Mottaghi T, Askari G, Khorvash F, Maracy MR. Effect of vitamin D supplementation on symptoms and C-reactive protein in migraine patients. *Journal of Research in Medical Sciences* 2015; 20:477-482.
35. Schreuder F, Bernsen RM, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in non-Western immigrants: A randomized controlled trial. *Annals of Family Medicine* 2012; 10:547-555.
36. Brohult J, Jonson B. Effects of large doses of calciferol on patients with rheumatoid arthritis. A double-blind clinical trial. *Scandinavian Journal of Rheumatology* 1973; 2:173-176.