Systematic Review

Is Vitamin D Supplementation Effective for Low Back Pain? A Systematic Review and Meta-Analysis

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Background: Low back pain (LBP) is the leading cause of years lived with disability worldwide. Current intervention strategies are failing to reduce the enormous global burden of LBP and are prompting researchers to investigate alternative management strategies, such as vitamin D supplementation. Vitamin D supplementation appears to down regulate pro-inflammatory cytokines which lead to pain and up regulate anti-inflammatory cytokines that reduce inflammation. These mechanisms might explain the increasing interest in the use of vitamin D supplementation for LBP.

Objectives: To determine whether vitamin D supplementation improves pain more than a control intervention for individuals with LBP.

Study Design: This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Methods: We performed searches in numerous electronic databases combining key words relating to "vitamin D" and "LBP" until March 2017. Studies were included if they investigated vitamin D supplementation in participants with LBP, provided there was a comparison intervention. There was no restriction on the type of LBP, the intervention parameters investigated, or the type of clinical trial (e.g., randomized, non-randomized). Two reviewers independently performed the selection of studies, extracted data, rated the methodological quality of the included studies, and evaluated the overall quality of the evidence using the Grading of Recommendations Assessment, Delevopment, and Evaulation (GRADE) approach.

Results: After screening 3,534 articles, 8 clinical trials were included in this systematic review. There is very low quality evidence (based on the GRADE approach) that vitamin D supplementation is not more effective than any intervention (including placebo, no intervention, and other conservative/pharmacological interventions) (continuous pain measures [0–100]: mean difference [MD] = -2.65, 95% confidence interval [CI]: -10.42 to 5.12, $P = 0.504$, n = 5; self-reported reduction in pain: pooled odds ratio [OR] = 1.07, 95% CI: 0.35 to 3.26, $P = 0.906$, n = 5) or placebo/no intervention for individuals with LBP (continuous pain measures: MD = 1.29, 95% CI: -3.81 to 6.39, $P = 0.620$, n = 4; self-reported reduction in pain: pooled OR = 1.53, 95% CI: 0.38 to 6.20, $P = 0.550$, n = 4), where 'n' is the number of studies included in the meta-analysis. These results did not change when we stratified the meta-analyses by the type of vitamin supplementation (vitamin D3 vs. alfacalcidol) or the type of LBP (non-specific vs. LBP resulting from osteoporosis or vertebral fractures).

Limitations: The overall quality of evidence was "very low" due to the poor methodological quality and small sample sizes of the included studies.

Conclusions: Vitamin D supplementation is not more effective than placebo, no intervention, or other conservative/pharmacological interventions for LBP (based on very low quality evidence). These results are consistent, regardless of the type of LBP or vitamin D supplementation. Until well-designed and adequately powered clinical trials suggest otherwise, the prescription of vitamin D for LBP cannot be recommended.

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Low back pain (LBP) is the leading cause of years lived with disability worldwide (1), with the total yearly costs of LBP estimated at $9 billion in Australia (2) and €300 billion for the whole of Europe (3). The majority of LBP cases presenting to primary care are classified as 'non-specific' (~85%) (4), as there is a poor correlation between symptoms and structural abnormalities identified by medical imaging (5,6). A small percentage of individuals may present with LBP that can be attributed to a structural pathology (<5%) (7,8), such as osteoporosis or vertebral fractures, and can experience significant pain and disability (9). Numerous intervention strategies have been investigated for non-specific LBP and are recommended in most evidence-based clinical practice guidelines (10), such as structured exercise programs (11) and advice to remain active (12). In addition, numerous conservative (13,14), pharmacological (15,16), and surgical interventions (17) have been investigated for the management of LBP resulting from osteoporosis or vertebral fractures. However, despite an abundance of research investigating different types and doses of these interventions (18-22), the analgesic effects are modest at best (23), and are failing to reduce the enormous global burden of LBP (1). With this in mind, it may be time to consider alternative interventions, rather than investigating procedural adjustments of those already established. One of the current and popular alternative treatments for painful conditions (24), including LBP (25,26), is vitamin D supplementation.

Vitamin D is an essential hormone for optimal bone, neuromuscular, and immune function. Skin exposure to sunlight is the main pathway by which vitamin D is synthesized, although supplementation and some foods may provide an additional source (27). Vitamin D is commonly recommended by medical professionals for individuals with osteoporosis (28), as it can increase bone mineral density through calcium absorption and bone mineralization (29). Nevertheless, there is conflicting evidence regarding the effect vitamin D has on pain. For participants with LBP resulting from osteoporosis or vertebral fractures, increases in bone mineral density may provide analgesic effects (29). However, other proposed mechanisms by which vitamin D supplementation could reduce pain include: a down-regulation of pro-inflammatory cytokines which lead to pain or an up-regulation of anti-inflammatory cytokines that reduce inflammation (30). Two recent systematic reviews investigated the effectiveness of vitamin D supplementation compared to placebo for chronic painful conditions (e.g., knee osteoarthritis, rheumatoid arthritis, fibromyalgia, and LBP) (31,32). One review found no consistent effect of vitamin D compared to placebo but did not perform a meta-analysis due to substantial heterogeneity between studies in regards to the methodological quality, chronic painful condition investigated, and vitamin D dosage (32). In contrast, another systematic review performed a meta-analysis despite between-study heterogeneity and found that vitamin D supplementation was slightly more effective than placebo when considering changes in pain from baseline (mean difference [MD] = -0.57, 95% confidence interval [CI]: -1.00 to -0.15, P = 0.007). However, vitamin D supplementation was not more effective than placebo when considering post-intervention pain scores (MD = -0.06, 95% CI: -0.44 to 0.33, P = 0.780) or self-reported reductions in pain (relative risk = 1.38, 95% CI: 0.93 to 2.05, P = 0.110). A significant limitation of these reviews is a general focus on chronic painful conditions, as this can introduce significant heterogeneity between study findings and neglect different disease presentations (e.g., acute vs. chronic). This highlights the need to investigate the effects of vitamin D supplementation in specific conditions, such as LBP. Vitamin D supplementation is easily accessible, cheap, and has minimal side effects, which may explain why its use for the management of LBP is gaining increasing attention (25,26). Therefore, to better understand whether vitamin D supplementation is effective for LBP, it is important to consider all presentations of the condition (e.g., non-specific LBP, LBP resulting from osteoporosis or vertebral fractures). The aim of this systematic review is to investigate the effectiveness of vitamin D supplementation for LBP.

Methods

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (33), and the protocol was registered on PROSPERO (Registration No: CRD42016046874). MEDLINE, CINAHL, EMBASE, AMED, WEB OF SCIENCE, and SCOPUS databases were searched to identify eligible studies from the earliest record to March 2017. Our search combined key words related to vitamin D (e.g., "alfacalcidol" OR "ergocalciferol" OR "1-alpha hydroxyvitamin D3," etc.) and LBP (e.g., "back ache" OR "back pain" OR "spinal pain," etc.) and remained sensitive to the study design to capture all types of clinical trials (e.g., randomized

controlled trials, non-randomized trials) (Appendix 1). Citation tracking was performed for all studies found by electronic searches, and the reference lists of the included studies were hand-searched to identify studies missed by the above processes.

Study Selection

Two reviewers (JZ and AS) independently screened the titles, abstracts, and selected full text articles for inclusion using a study eligibility form based on items from the inclusion/exclusion criteria. Disagreements were resolved by discussion and consultation with a third reviewer (DS). There was no restriction on the language or geographic setting of the study, although studies not published in English were excluded when an appropriate translation was not available. There was no restriction on the age or gender of participants or the type of publication (e.g., conference abstract or dissertation).

Studies were included if they assessed any measure of pain (e.g., visual analog scale [VAS], Face Scale, numeric rating scale [NRS]), function (e.g., Roland Morris Disability Questionnaire, Patient-Specific Functional Scale), or subjective measure of improvement in people with LBP following vitamin D supplementation. We included studies investigating participants with non-specific LBP and LBP resulting from osteoporosis (including studies which enrolled participants with vertebral compression fractures) but excluded studies investigating participants with evidence of nerve root compression or a diagnosis of serious spinal pathology, such as metastatic disease or cauda equina syndrome. There was no restriction on the intervention parameters (e.g., type of supplement, dosage, duration, and administration route). Studies with no comparison intervention or where vitamin D was used in conjunction with another active therapy (e.g., calcium supplementation, nonsteriodal anti-inflammatory drugs) were excluded, unless the additional active therapy was identical for both the intervention and control group (e.g., vitamin D and calcium supplementation vs. calcium supplementation alone). We included both randomized and non-randomized trials to get a broader overview of the efficacy of vitamin D supplementation for LBP. We excluded single-arm trials (no comparison), case series, and case reports.

Methodological Quality

Two reviewers (JZ and AS) independently assessed the methodological quality of the included studies and the overall quality of evidence and strength of recommendation, resolving any disagreement by consensus. For studies satisfying the eligibility criteria, we used the valid and reliable PEDro scale to score the methodological quality of each study (34). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the overall quality of evidence and the strength of recommendation (35). The quality of evidence was downgraded for each of the following 5 factors encountered: limitations in the design and implementation [>25% of the trial, weighted by their sample size, scored <7 on the PEDro scale (36)], indirectness of evidence (trial design and objective not concordant), unexplained heterogeneity ($I^2 > 50\%$), imprecision of results [comparisons with less than 400 participants were deemed "low quality evidence" (36,37)], and high probability of publication bias [assessed using Egger's funnel plot (38)]. We did not assess publication bias when a meta-analysis was not possible or if less than 10 studies were included in the meta-analysis (38,39). The quality of evidence was downgraded by one level if both reviewers (JZ and AS) judged the limitation was 'serious' or by 2 levels if it was judged as 'very serious.' The following was used to define the quality of evidence for each outcome (40):

- High quality: very confident the true effect lies close to the effect estimate with no known or suspected reporting biases; all domains were fulfilled
- Moderate quality: moderately confident the true effect lies close to the effect estimate with some possibility that it is substantially different; one domain was not fulfilled
- Low quality: limited confidence the true effect lies close to the effect estimate; 2 domains were not fulfilled
- Very low quality: very little confidence the true effect lies close to the effect estimate; 3 domains were not fulfilled.

Data Extraction

Data was independently extracted from the included studies by 2 reviewers (JZ and AS) using a standardized data extraction form to collect relevant information on participant characteristics (age and gender), study setting (e.g., hospital or community), sample size, features specific to the study design, type and duration of LBP, baseline and follow-up measures of pain and function (all time-points), intervention parameters (type of supplementation, dosage, duration, and ad-

ministration route), the comparison intervention, loss to follow-up, and the incidence of adverse events.

Statistical Analysis

We extracted data on the between-group MD (continuous data) or odds ratio (OR) (dichotomous data) and 95% CI at all time-points (including change scores when reported) for measures of pain and function following a course of vitamin D supplementation in individuals with LBP. Scores on pain and function outcomes were transformed to a 0–100 scale, where 0 represents no pain/poor function and 100 represents highest pain/highest level of function. We attempted to calculate a pooled weighted MD or OR (95% CI) when studies were considered sufficiently homogenous using Comprehensive Meta-Analysis Version 3.0 (Biostat, Englewood, NJ). For continuous data, when pre- and post-intervention means and standard deviation (SD) were available, but the MD and 95% CI were not reported, these were calculated in the meta-analysis software. For dichotomous outcomes, when pre- and post-intervention event data (percentages) were available, but the OR and 95% CI were not reported, these were calculated in the meta-analysis software. For outcomes measured on a 0–100 scale (e.g., VAS), a 20-point between-group difference was considered clinically meaningful (41).

Heterogeneity was assessed using the I^2 statistic and was considered low where $I^2 < 25\%$, moderate where $I^2 \geq 50\%$, and high where $I^2 \geq 75\%$ (42). Fixed effects models were used when $I^2 < 50\%$, and random effects models were used when $I^2 \geq 50\%$. If there were enough studies investigating various types of LBP (e.g., chronic LBP, acute LBP, LBP resulting from osteoporosis or vertebral fractures, etc.), doses of vitamin D, types of supplementation (e.g., alfacalcidol/calcitriol vs. vitamin D3), or where there were between study differences in participant demographics (e.g., age, gender, etc.) and the comparison intervention (e.g., placebo, no intervention, conservative/pharmacological interventions), we stratified meta-analyses accordingly (sensitivity analysis).

Results

Description of Studies

We identified 3,534 articles through our database searches with 2 articles identified through hand-searching the reference lists of included studies (43,44) (Fig. 1.). Following the removal of duplicates, 2 reviewers (JZ and AS) independently screened the articles' titles and abstracts and screened the full-text of 102 articles. A total of 8 clinical trials were eligible for inclusion in this review, with available data from 747 participants. The characteristics of the included studies can be found in Table 1. We included 4 published randomized controlled trials (25,44-46), 2 conference abstracts of randomized controlled trials (47,48), one randomized cross-over trial (49), and one non-randomized controlled trial (50). The PEDro scale was used to score the methodological quality of each study and ranged from 4 to 8 (Table 2). The 2 conference abstracts were not scored as per the criteria for including clinical trials in PEDro (51). The most common methodological limitations were lack of therapist (n = 5) and assessor (n = 3) blinding, no intention-to-treat analysis (n = 6), and no attempt to conceal group allocation (n = 4).

The assessment of LBP differed between studies with 4 studies including participants who reported the presence of any LBP (44-47,50), 2 studies including participants reporting chronic LBP (lasting for at least 3 months) (25,49), and one study including participants reporting LBP for at least 2 weeks (48). In addition, 5 of the studies only investigated participants with LBP resulting from osteoporosis or vertebral fractures (44,45,47,48,50), while 3 studies (25,46,49) only investigated participants with non-specific LBP (2 studies investigated chronic non-specific LBP (25,49) and one study did not specify the duration of LBP symptoms at baseline (46)). There were differences between the settings for each study, with 4 studies recruiting participants from hospitals (2 in Japan (45,50), one in Iran (25), and one in Greece (44)), one study recruiting participants from 10 general practices in the Netherlands (49), one study recruiting participants from a local immigrant activity centre in Norway (46), and 2 studies (conference abstracts) not reporting the source of participants (47,48). The intervention parameters differed across studies with 3 studies (25,46,49) prescribing vitamin D3 for individuals with non-specific LBP (dosage ranging from 25–179 ug daily and duration ranging from 6–16 weeks) and 5 studies (44,45,47,48,50) prescribing alfacalcidol (or calcitriol in one study (47)) for individuals with LBP resulting from osteoporosis or vertebral fractures (dosage ranging from 1–1000 ug daily and duration ranging from 1–24 months). Co-interventions included the prescription of oral cyclical etidronate or oral celecoxib and advice to take calcium supplementation, perform home exercises, or seek physiotherapy or additional analgesics if required. Comparison interventions varied according to the presentation of LBP. All

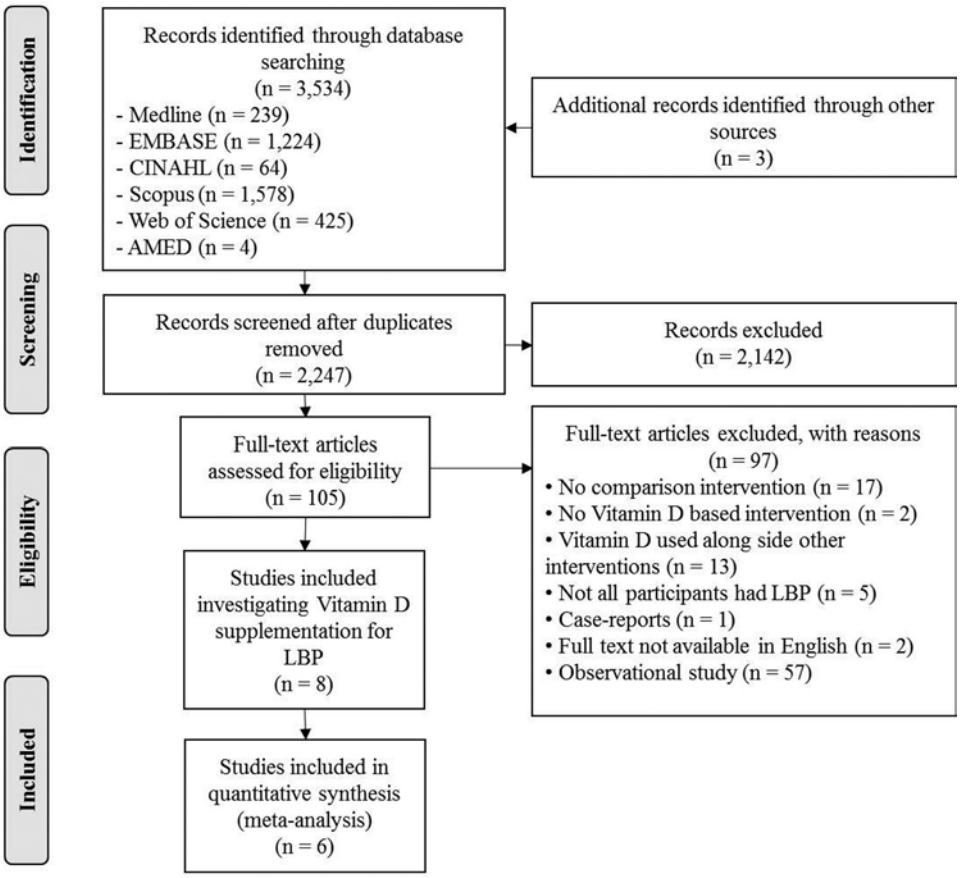

Fig. 1. *PRISMA flow diagram. LBP = low back pain*

studies investigating participants with non-specific LBP used a placebo as the comparison intervention (with the same packaging, appearance, and taste). For studies investigating participants with LBP resulting from osteoporosis or vertebral fractures, the comparison interventions included: placebo, no intervention, and other conservative/pharmacological interventions (oral risedronate, oral raloxifene, intramuscular injections of eel calcitonin, or intramuscular injections of nandrolone decanoate). All of the included studies assessed pain, with some using multiple outcome measures (e.g., VAS and percentage of participants reporting clinical improvements). Five studies assessed pain using the VAS (0–100) (25,46,48-50), one study using the Face Scale (45), one study using a 5-point scale (where '0' = no pain and '5' = very severe pain) (44), 4 studies using the percentage of participants that improved from baseline (25,44,47,49), and one study reporting the proportion of participants still in pain at follow-up (46). Function was not assessed in any study. One conference abstract (48) failed to report sufficient data to be included in the meta-analysis, while the results from the other conference abstract (47) were only included in the meta-analyses of dichotomous outcomes since their outcome was the presence of a reduction in pain from baseline. We did not include the non-randomized controlled trial in any meta-analysis (50).

Overall Effectiveness of Vitamin D Supplementation

The overall pooling showed that vitamin D supplementation had no effect on pain levels for LBP when compared to any intervention (including placebo, no intervention, and other conservative/pharmacological interventions) (MD = -2.65, 95% CI: -10.42 to 5.12, P = 0.504, n = 5) (Fig. 2) or when only compared to pla-

Table 1. *Characteristics of included studies.*

Author (yr)	Study Design	Setting	Population	n	LBP Definition	Intervention (a)	Comparison	Co-Interventions Common to Intervention and Comparison Groups
Iwamoto et al (2003) (45)	RCT	Japanese hospital	Postmenopausal women between the ages of 60–86 years old with OP and no lumbar vertebral fractures	40	Back pain	1 ug daily alfacalcidol for 12 mos	Control	200 mg oral cyclical etidronate daily for 2 weeks every 3 months; Instructed to take 800 mg calcium through food
Knutsen et al (2014) (46)	RCT	Local immigrant activity centers in Norway	Healthy population of men and women aged between 18–50 yrs old	251	Presence of LBP based on the Standard Nordic Questionnaire	25 ug vitamin D3 (one tablet) daily for 16 wks OR 10 ug vitamin D3 daily	Placebo	N/A
Sandoughi et al (2015) (25)	RCT	Rheumatology clinic in an Iranian hospital	Healthy population of men and women aged between 18–40 yrs old	53	Chronic NSLBP (> 3 mos)	50000 IU oral vitamin D3 once per wk for 8 wks (1,250 ug weekly = 178.57 ug daily)	Placebo	Advised to exercise at home and given up to 200 mg oral celecoxib daily if required
Wandless et al (1980) (47)	Abstract of a RCT	Unclear	Men and women with a mean age (SD) of 69.9 (9.8) with OP (some had vertebral compression fractures)	25	Back pain	0.5–1.0 mg of either alfacalcidol or calcitriol daily for 6 mos	Placebo	N/A
Ota & Ito (2007) (48)	Abstract of a RCT	Unclear	Postmenopausal women with BMD below the young adult mean and without recent vertebral fractures	140	LBP (> 2 wks)	1 ug oral alfacalcidol daily for 4 mos	5 mg oral risedronate daily OR 60 mg oral raloxifene daily OR 20 IU intramuscular eel calcitonin once a wk	N/A
Majima et al (2009) (50)	Non-randomized controlled trial	Japanese hospital	Men recently diagnosed with OP with mean age (SD) of 63.62 (9.4) in the vitamin D group and 63.98 (8.7) in the risedronate group	66	Back pain	1 ug oral alfacalcidol daily for 2 yrs	2.5 mg oral risedronate daily	At least every 3 mos all participants were instructed to take at least 800 mg calcium (but less than 2500 mg) in their food, exercise, and take care not to fall.

Table 1 (cont.). *Characteristics of included studies.*

Author (yr)	Study Design	Setting	Population	n	LBP Definition	Intervention (a)	Comparison	Co-Interventions Common to Intervention and Comparison Groups
Schreuder et al (2012) (49)	Randomized cross-over trial	Non-western immigrants in 10 general practices throughout the Netherlands	Men and women aged between 18–60 yrs with vitamin D deficiency (<20 ng/mL) and vising their GP for recurrent MS pain lasting > 3 mos	84	Chronic LBP (> 3 mos)	150,000 IU single dose of oral vitamin D3 with 6–12 wks follow-up* (~90 ug daily)	Placebo	Physiotherapy and analgesics as required.
Lyritis et al (1994) (44)	RCT	Greek hospital	Postmenopausal women with established OP (>10 yrs) and at least one non-traumatic vertebral collapse; mean age (SD) of 66.3 (8.5) in the intervention group and 67.5 (9.1) in the comparison group	88	Back pain	1 ug oral alfacalcidol daily for 12 mos plus placebo intramuscular injections	50 mg intramuscular injections of nandrolone decanoate every 3 wks	N/A

n = number of participants included in the study; LBP = low back pain; RCT = randomized controlled trial; SD = standard deviation; BMD = bone mineral density; MS = musculoskeletal; GP = general practitioner; OP = osteoporosis; IU = international units; ug = micrograms; mg = milligrams; nm = nanomole

*Dependent on whether participants crossed-over to the placebo group or stayed in the intervention group.

(a) = 1 IU of vitamin D3 = 0.025ug = 0.000025mg

cebo/no intervention (MD = 1.29, 95% CI: -3.81 to 6.39, *P* = 0.620, n = 4) (Fig. 3), where 'n' is the total number of studies and a positive MD favors the intervention group. When improvement was based on a self-reported reduction in pain from baseline, there was no difference between vitamin D supplementation and any intervention (including placebo and other conservative/pharmacological interventions) (pooled OR = 1.07, 95% CI: 0.35 to 3.26, *P* = 0.906, n = 5) (Fig. 4) or placebo only (pooled OR = 1.53, 95% CI: 0.38 to 6.20, *P* = 0.550, n = 4) (Fig. 5), where an OR > 1 indicates a higher likelihood of improvement for individuals receiving vitamin D supplementation. The follow-up time-points varied between studies included in the meta-analyses, ranging from 6 weeks to 24 months (Table 1). The quality of the evidence for all meta-analyses was downgraded to "very low" due to imprecision of the results (all comparisons had a sample size less than 400) and limitations in study design and implementation (>25% of the studies, weighted by their sample size, scored <7 on the PEDro scale). As outlined previously, the types of LBP and vitamin D supplementation varied across studies, and we performed a number of sensitivity analyses accordingly. Across all included studies, individuals with non-specific LBP were prescribed vitamin D3, while individuals with LBP resulting from osteoporosis/vertebral fractures were prescribed alfacalcidol (or calcitriol in one study (47)).

Vitamin D for Non-Specific LBP

In studies investigating individuals with non-specific LBP, vitamin D supplementation had no effect on pain (compared to placebo), regardless of symptom duration, when pain was measured on a continuous scale (all non-specific LBP: MD = 1.90, 95% CI: -7.06 to 10.86, *P* = 0.678, n = 3; chronic non-specific LBP only: MD = 0.59, 95% CI: -12.67 to 13.84, *P* = 0.931, n = 2) (Fig. 6), or when improvement was based on a self-reported reduction in pain from baseline (all non-specific LBP: pooled OR = 0.85, 95% CI: 0.28 to 2.60, *P* = 0.775, n = 3; chronic non-specific LBP only: pooled OR = 1.02, 95% CI: 0.14 to 7.76, *P* = 0.982, n = 2) (Fig. 7).

Vitamin D for LBP Resulting from Osteoporosis or Vertebral Fractures

Similarly, vitamin D (alfacalcidol/calcitriol) had no effect on pain in studies investigating individuals with LBP resulting from osteoporosis or vertebral fractures when compared to any intervention (including no intervention and other conservative/pharmacological

Table 2. *Methodological quality of the included studies**.

Author (yr)	PEDro Scale Checklist											Total Score	n
	1	2	3	4	5	6	7	8	9	10	11		
Iwamoto et al (2003) (45)	+	+	-	+	-	-	-	-	-	+	+	4	40
Knutsen et al (2014) (46)	+	+	+	+	+	-	+	+	-	+	+	8	76
Sandoughi et al (2015) (25)	+	+	+	-	+	-	+	+	-	-	+	6	53
Majima et al (2009) (50)	+	-	-	+	-	-	-	+	-	+	+	4	62
Schreuder et al (2012) (49)	+	+	-	-	+	+	-	+**	-	-	+	5	50
Lyritis et al (1994) (44)	-	+	-	+	+	-	+	-	-	-	+	5	69
% of Studies Fulfilling Each Item*	83.3%	83.3%	33.3%	66.7%	66.7%	16.7%	50%	66.7%	0%	50.0%	100%		

n = number of participants who entered the meta-analyses.
*Wandless et al (47) (1980) and Ota & Ito (48) (2007) were conference abstracts and were not included in this table due to insufficient data.
**Data from the first 6 weeks (before the cross-over) where the drop-out was 3.8% for individuals with LBP.

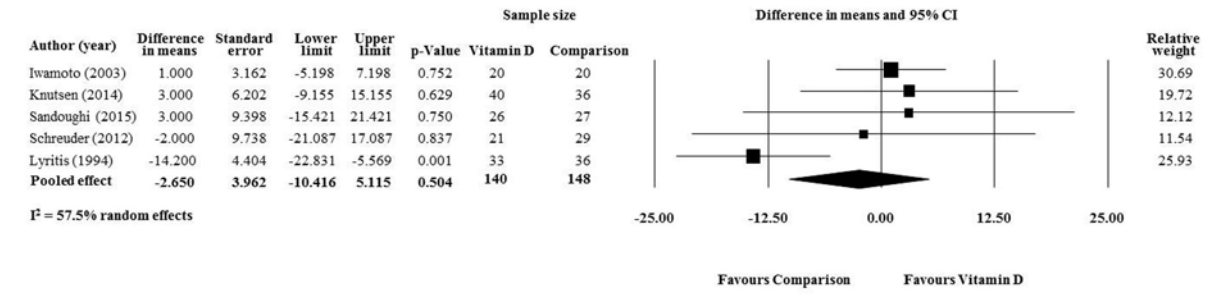

Fig. 2. *Weighted MD (95% CI) for the effectiveness of vitamin D supplementation compared to any intervention on pain.*
CI = confidence interval; MD = mean difference

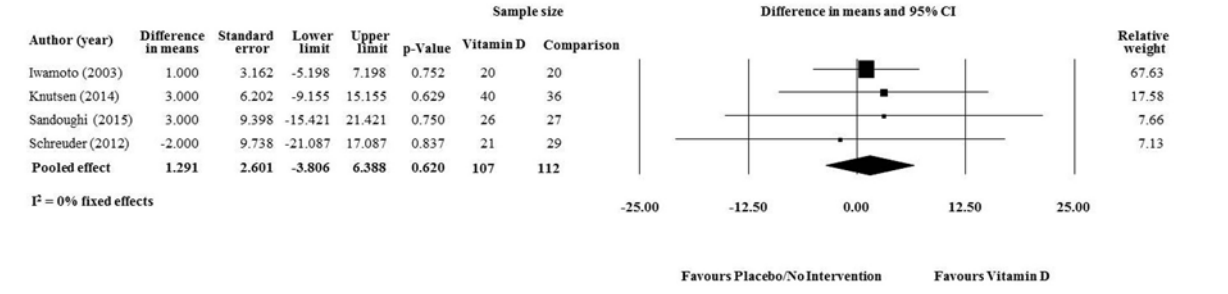

Fig. 3. *Weighted MD (95% CI) for the effectiveness of vitamin D supplementation compared to placebo/control on pain.*
CI = confidence interval; MD = mean difference

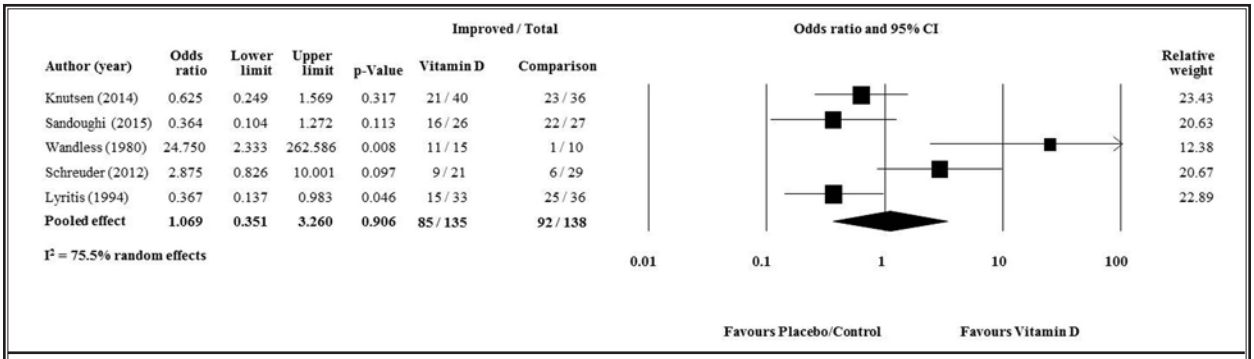

Fig. 4. *Pooled OR (95% CI) on the number of participants reporting improvements in pain (or the absence of pain) at follow-up for the effectiveness of vitamin D supplementation compared to any intervention.*
CI = confidence interval; MD = mean difference

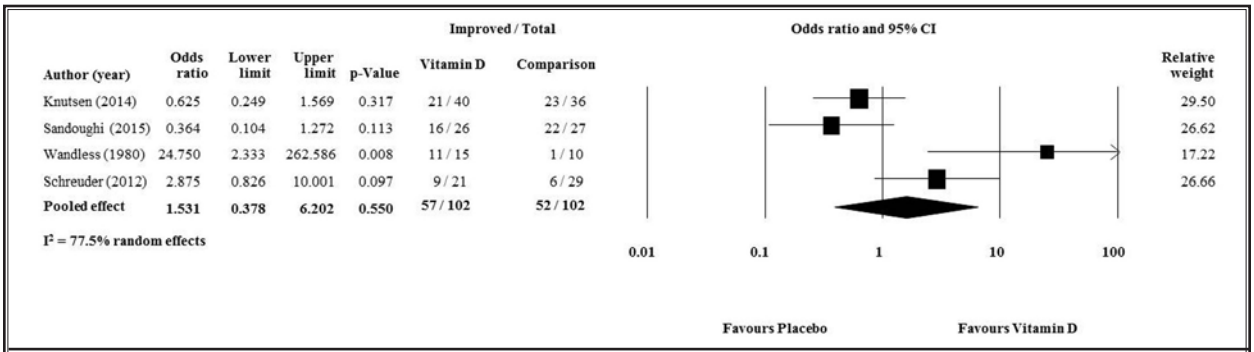

Fig. 5. *Pooled OR (95% CI) on the number of participants reporting improvements in pain (or the absence of pain) at follow-up for the effectiveness of vitamin D supplementation compared to placebo/control.*
CI = confidence interval; MD = mean difference

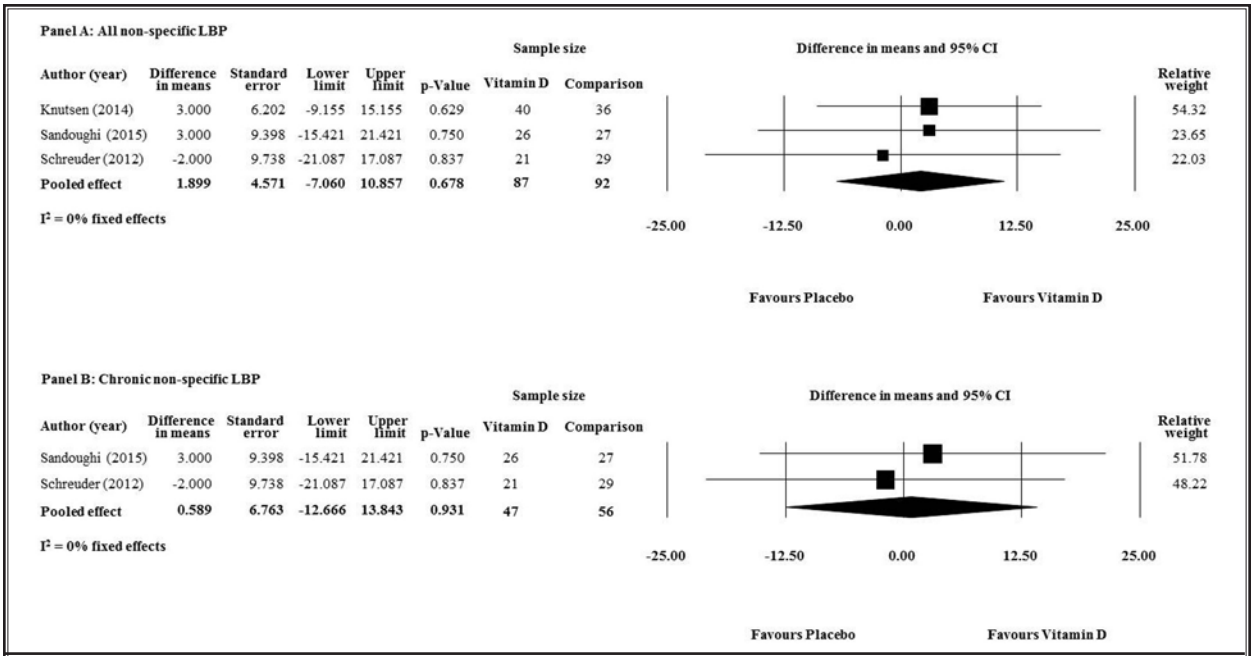

Fig. 6. *Weighted MD (95% CI) for the effectiveness of vitamin D supplementation compared to placebo for non-specific LBP (A: all non-specific LBP; B: chronic non-specific LBP) on pain.*
LBP = low back pain; CI = confidence interval; MD = mean difference

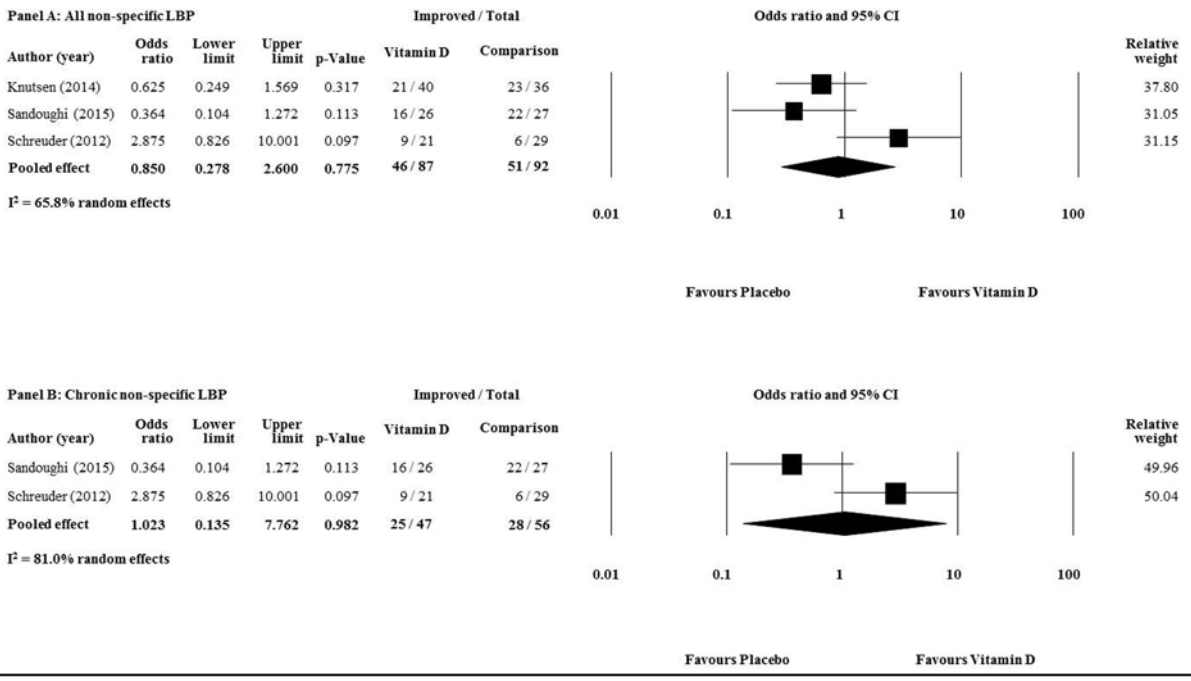

Fig. 7. Pooled OR (95% CI) on the number of participants reporting improvements in pain (or the absence of pain) at follow-up for the effectiveness of vitamin D supplementation compared to placebo for non-specific LBP (A: all non-specific LBP; B: chronic non-specific LBP).
LBP = low back pain; CI = confidence interval; OR = odds ratio

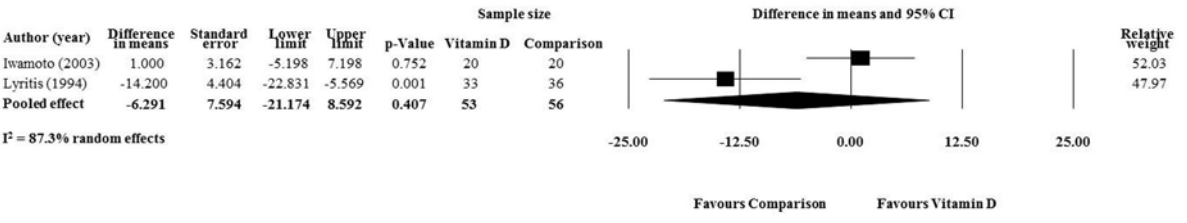

Fig. 8. *Weighted MD (95% CI) on pain for the effectiveness of vitamin D supplementation compared to any intervention for LBP resulting from osteoporosis or vertebral fracture.*
LBP = low back pain; CI = confidence interval; MD = mean difference

interventions) (MD = -6.29, 95% CI: -21.17 to 8.59, *P* = 0.407, n = 2) (Fig. 8) or in one study which compared alfacalcidol to a control group (6 months [0–10 scale]: MD = -0.10, 95% CI: -0.66 to 0.46, *P* = 0.725, 12 months: MD = 0.10, 95% CI: -0.52 to 0.72, *P* = 0.752) (45). When effectiveness was based on the number of participants reporting improvements in pain from baseline, there was no difference between alfacalcidol/calcitriol and any intervention (including placebo and other conservative/pharmacological interventions) (pooled OR = 2.61, 95% CI: 0.04–160.59, *P* = 0.648, n = 2) (Fig. 9). One conference abstract showed that alfacalcidol was less effective than risedronate and eel calcitonin when pain was assessed by a VAS at 4 months (*P* = 0.0091 and 0.0434, respectively). However, the effect sizes were not reported and there was not sufficient data for inclusion in the meta-analyses (48). The only study which demonstrated that vitamin D supplementation was

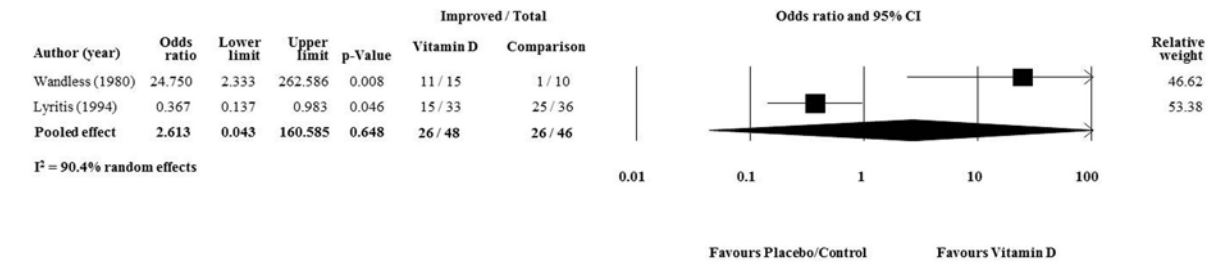

Fig. 9. *Pooled OR (95% CI) on the number of participants reporting improvements in pain (or the absence of pain) at follow-up for the effectiveness of vitamin D supplementation compared to placebo/control for LBP resulting from osteoporosis or vertebral fracture.*
LBP = low back pain; CI = confidence interval; OR = odds ratio

Table 3. *Results from individual studies.*

Author (yr)	Study Design	Population	n	Intervention vs. Comparison	Results
Iwamoto et al (2003) (45)	RCT	Postmenopausal women between the ages of 60–86 yrs old with O*P* and no lumbar vertebral fractures	40	1 ug daily alfacalcidol for vs. control	Face scale (0–10) 6 mos *Alfacalcidol (n = 20) vs. control (n = 20): MD = -0.10, 95% CI: -0.66 to 0.46, *P* = 0.725 12 mos Alfacalcidol (n = 20) vs. control (n = 20): MD = 0.10, 95% CI: -0.52 to 0.72, *P* = 0.752
Knutsen et al (2014) (46)	RCT	Healthy population of men and women aged between 18–50 yrs old	76	25 ug OR 10 ug vitamin D3 daily vs. placebo	16 wks VAS (0–100) *25 ug vitamin D3 (n = 40) vs. placebo (n = 36): MD = 3.00, 95% CI: -9.16 to 15.16, *P* = 0.629 10 ug vitamin D3 (n = 41) vs. placebo (n = 36): MD = 6.00, 95% CI: -19.15 to 7.15, *P* = 0.367 Number not in pain (%) *25 ug vitamin D3 (n = 40): 21 (52.5%) Placebo (n = 36): 23 (50.0%) OR = 0.63, 95% CI: 0.25 to 1.57, *P* = 0.317 10 ug vitamin D3 (n = 41): 18 (43.9%) Placebo (n = 36): 23 (50.0%) OR = 0.44, 95% CI: 0.18 to 1.11, *P* = 0.082
Sandoughi et al (2015) (25)	RCT	Healthy population of men and women aged between 18–40 yrs old	53	50000 IU oral vitamin D once per wk vs. placebo	8 wks VAS (0–10) *Vitamin D3 (n = 26) vs. placebo (n = 27): MD = 0.30, 95% CI: -1.54 to 2.14, *P* = 0.750 Improved from baseline (%) *Vitamin D3 (n = 26): 16 (61.5%) Placebo (n = 27): 22 (81.5%) OR = 0.36, 95% CI: 0.10 to 1.27, *P* = 0.113
Wandless et al (1980) (47)	Abstract of an RCT	Men and women with a mean age (SD) of 69.9 (9.8) yrs with O*P* (some had vertebral compression fractures)	25	0.5–1.0 mg of either alfacalcidol or calcitriol daily vs. placebo	Improved from baseline (%) 6 mos *Alfacalcidol (n = 15): 11 (73.3%) Placebo (n = 10): 1 (10.0%) OR = 24.75, 95% CI: 2.33 to 262.59, *P* = 0.008

Table 3 (cont.). *Results from individual studies*.

Author (yr)	Study Design	Population	n	Intervention vs. Comparison	Results
Ota & Ito (2007) (48)	Abstract of an RCT	Postmenopausal women with BMD below the young adult mean and without recent vertebral fractures	140	1 ug oral alfacalcidol daily vs. 5 mg oral risedronate daily OR 60 mg oral raloxifene daily OR 20 IU intramuscular eel calcitonin once a wk	VAS (0–100) 1 mo Risedronate (n = 35) more effective than alfacalcidol (n = 35) (*P* = 0.0035) 4 mos Risedronate (n = 35) more effective than alfacalcidol (n = 35) (*P* = 0.0091) Eel calcitonin (n = 35) more effective than alfacalcidol (n = 35) (*P* = 0.0434)
Majima et al (2009) (50)	Non-randomized controlled trial	Men recently diagnosed with O*P* with mean age (SD) of 63.62 (9.4) yrs in the vitamin D group and 63.98 (8.7) yrs in the risedronate group	62	1 ug oral alfacalcidol daily vs. 2.5 mg oral risedronate daily	VAS (0–100) 3 mos *Alfacalcidol (n = 21) vs. risedronate (n = 41): MD = -3.73, 95% CI: -14.82 to 7.36, *P* = 0.510 12 mos Alfacalcidol (n = 21) vs. risedronate (n = 41): MD = -5.86, 95% CI: -17.51 to 5.79, *P* = 0.324 2 yrs Alfacalcidol (n = 21) vs. risedronate (n = 41): MD = -6.84, 95% CI: -17.66 to 3.98, *P* = 0.215
Schreuder et al (2012) (49)	Randomized cross-over trial	Men and women aged between 18–60 yrs with vitamin D deficiency (<50 nm/L) and vising their G*P* for recurrent MS pain lasting > 3 mos	50	150,000 IU single dose of oral vitamin D vs. placebo	6 wks VAS (0–100) *Vitamin D (n = 21) vs. placebo (n = 29): MD = -2.00, 95% CI: -21.09 to 17.09, *P* = 0.837 Improved from baseline (%) *Vitamin D3 (n = 21): 9 (42.9%) Placebo (n = 29): 6 (20.7%) OR = 2.88, 95% CI: 0.83 to 10.00, *P* = 0.097
Lyritis et al (1994) (44)	RCT	Postmenopausal women with established O*P* (>10 yrs) and at least one non-traumatic vertebral collapse; mean age (SD) of 66.3 (8.5) yrs in the intervention group and 67.5 (9.1) yrs in the comparison group	88	1 ug oral alfacalcidol daily (plus placebo intramuscular injections) vs. 50 mg intramuscular injections of nandrolone decanoate every 3 wks	6 mos 5-point pain scale *Alfacalcidol (n = 37) vs. nandrolone decanoate (n = 40): MD = -0.21, 95% CI: -0.57 to 0.15, *P* = 0.252 12 mos 5-point pain scale Alfacalcidol (n = 33) vs. nandrolone decanoate (n = 36): MD = -0.71, 95% CI: -1.14 to -0.28, *P* = 0.001 Improved from baseline (%) at *Alfacalcidol (n = 33): 15 (45.5%) nandrolone decanoate (n = 36): 25 (69.4%) OR = 0.37, 95% CI: 0.45 to 1.31, *P* = 0.327

n = number of participants that entered the analyses; LBP = low back pain; VAS = visual analog scale; RCT = randomized controlled trial; SD = standard deviation; BMD = bone mineral density; MS = musculoskeletal; GP = general practitioner; OP = osteoporosis; IU = international units; ug = micrograms; mg = milligrams; nm = nanomole
(a) = 1 IU of vitamin D3 = 0.025 ug = 0.000025 mg
*Results included in meta-analysis

effective for LBP was reported in a conference abstract and included 25 participants with a mean age (SD) of 69.9 (9.8) years old, diagnosed with osteoporosis (self-reported reduction in pain at 6 months: OR = 24.75, 95% CI: 2.33 to 262.59, *P* = 0.008) (47) (Table 3).

Adverse Events

Only 4 of the 8 included trials reported on the incidence of adverse events (45,46,48,49), although no study presented objective data. Three of these studies stated there were no adverse effects of vitamin D

supplementation (48,49), including issues related to the following areas: gastrointestinal, skin, nervous system, musculoskeletal, or urinary-tract (45). One study stated that adverse events were few, mild, and equally distributed between vitamin D and placebo groups at all time-points (46).

Discussion

This is the first systematic review to investigate the effect of vitamin D supplementation for numerous presentations of LBP, such as non-specific LBP and LBP resulting from osteoporosis or vertebral fractures, and it may inform whether the benefits of vitamin D supplementation is dependent on an individual's clinical presentation. Vitamin D has the potential to reduce pain and inflammation by modulating sensory neuron excitability (52,53) and the presence of anti- and pro-inflammatory cytokines (30,54-56). In addition, higher vitamin D levels have been linked to increases in muscle strength (57,58), providing rationale for how vitamin D supplementation may improve pain and function in individuals with LBP. However, this review found very low quality evidence that vitamin D supplementation is more effective than placebo, no intervention, or other conservative/pharmacological interventions for LBP, regardless of the type of LBP (non-specific LBP or LBP due to osteoporosis or vertebral fractures) or the type of vitamin D supplementation (vitamin D3 or alfacalcidol/calcitriol).

Comparison to Previous Studies

This review highlights that adequately powered and well-designed clinical trials investigating vitamin D supplementation for LBP are mostly missing from the literature, resulting in very low quality evidence overall. Despite numerous studies reporting the beneficial effects of vitamin D supplementation for LBP, many could not be included in this review as they failed to investigate an appropriate comparison (e.g., no intervention or placebo) (59) or combined vitamin D supplementation with other active therapies (e.g., calcium supplementation) (60) (Fig. 1). Of the 8 clinical trials included in this review, only one scored ≥ 7 on the PEDro scale (25,46), with the most common methodological limitations being a lack of therapist or assessor blinding, no intention-to-treat analysis, or lack of allocation concealment. Despite this, the results from the highest quality study (PEDro score = 8) (46) with the largest sample size (n = 76) (16 weeks [0–100 scale]: MD = 3.00, 95% CI: -9.16 to 15.16, $P = 0.629$) (Table 3) were still in line with the overall results of this study, showing that vitamin D supplementation is no more effective than placebo for reducing pain levels in individuals with LBP (Fig. 3 & 4). Despite these negative findings, the effect of vitamin D supplementation on LBP remains a topic of interest. This is likely driven by a desire to discover an optimal type or dosage of vitamin D supplementation that will elicit the greatest response or a specific sub-group of individuals who will respond favorably to vitamin D supplementation (e.g., individuals with clinical and radiographic evidence of disc herniation (26) or with a particular level of vitamin D deficiency).

There is evidence to support the choice of the type of vitamin D supplementation (e.g., vitamin D3 vs. alfacalcidol) for decreasing mortality in older adults (61) and for reducing the incidence of fractures and rate of falls in individuals with osteoporosis (62), while other studies suggest additional benefits of higher doses of vitamin D supplementation compared to lower doses for various diseases (63,64). Similarly, the results of our review may suggest the type and overall dose of vitamin D supplementation ('daily dose' vs. 'intervention duration') can influence the response to treatment in individuals with LBP. However, the effective dosage of vitamin D for LBP needs to be viewed in light of safety recommendations. The Institute of Medicine recommends 10 ug vitamin D3 daily for both adults and children (20 ug for those over 70 years old), with a tolerable upper intake level at 100 ug daily (65), while the Endocrine Practice Guidelines Committee recommends 37.5–50 ug vitamin D3 daily for people at risk of vitamin D deficiency (< 20 ng/mL), with a tolerable upper intake level at 200 ug daily (66). Furthermore, other guidelines recommend taking 165 ug daily for 8–12 weeks to reach sufficient vitamin D levels, then taking a maintenance dose of 75 ug daily to prevent the recurrence of vitamin D deficiency while avoiding toxicity (67). In contrast, there are no guidelines for the use of vitamin D analogues, such as alfacalcidol or calcitriol, as these medications are usually prescribed by a medical professional. However, a report from the Medicines and Healthcare products Regulatory Agency recommends a safe dosage of 1–3 ug alfacalcidol per day for adults, with higher doses (3–5 ug/day) recommended for the treatment of severe hypocalcaemia (68). The only study (conference abstract) that demonstrated a beneficial effect of vitamin D supplementation compared to placebo prescribed 500–1000 ug alfacalcidol or calcitriol daily for 6 months (7 participants received calcitriol and 8 received alfacalcidol but were included in the same

group) in older individuals (mean age [SD]: 69.9 [9.8]) with LBP due to osteoporosis or vertebral fractures (47) and found a significant between-group difference in the number of individuals who reported reductions in pain from baseline (OR = 24.75, 95% CI: 2.33 to 262.59, *P* = 0.008) (Table 3). However, this dosage is well above the Medicines and Healthcare products Regulatory Agency recommendations (68), which brings into question the safety of this dose and whether the dosage reported in this conference abstract was correct. Nevertheless, a lower overall dosage of alfacalcidol (1 ug daily for 12 months) was not more effective than no intervention (12 months [0–10 pain scale]: MD = 0.10, 95% CI: -0.52 to 0.72, *P* = 0.752) (45) or other conservative/pharmacological interventions for individuals with LBP resulting from osteoporosis or vertebral fractures (44,48,50). These findings may suggest a higher overall dose of alfacalcidol or calcitriol is necessary to provide a beneficial effect in individuals with LBP resulting from osteoporosis or vertebral fractures. However, we cannot rule out the possibility that the prescription of calcitriol for some participants in the study with the highest dosage influenced these results (47). On the other hand, the pooled results from the 3 studies prescribing vitamin D3 for non-specific LBP (dosage ranging from 25–179 ug daily and intervention duration ranging from 6–16 weeks) failed to show a beneficial effect on pain intensity compared to a placebo (weighted MD = 1.90, 95% CI: -7.06 to 10.86, *P* = 0.678, n = 3) (Fig. 6). Since the studies prescribing higher doses of vitamin D3 were generally shorter in duration, it was not possible to investigate the overall impact of vitamin D3 dosage on treatment outcomes. Despite this, one randomized controlled trial included in our review (49) prescribed an overall dosage (179 ug vitamin D3 daily for 6 weeks) close to the tolerable upper intake levels but failed to demonstrate a beneficial effect for people with non-specific LBP. Therefore, if research continues to investigate vitamin D3 supplementation for non-specific LBP, it may be more important to consider the target population rather than the overall dosage to build on these results rather than replicate them.

For over a decade, the search for a particular sub-group of individuals who demonstrate a more favorable response to an intervention has been a popular topic in the field of LBP (69). However, the findings of this review suggest that the effect of vitamin D supplementation is no different for individuals with non-specific LBP or LBP resulting from osteoporosis or vertebral fractures, despite one study suggesting higher doses of alfacalcidol/calcitriol were effective for individuals with LBP resulting from osteoporosis or vertebral fractures (47). Future studies exploring sub-groups of individuals likely to respond to vitamin D supplementation should have a clear rationale, since implementing a well-designed and adequately powered sub-group study requires a large amount of planning and resources (69,70). Although this review failed to clearly identify a sub-group of participants who respond to vitamin D supplementation, evidence from existing observational studies that investigate which populations with LBP have the greatest degree of vitamin D deficiency could help to identify individuals who demonstrate a favorable response to vitamin D supplementation. There are numerous studies providing evidence for a greater degree of vitamin D deficiency in younger women with LBP (<50 years old) (71-74), while evidence for the association between vitamin D levels and LBP in older men and women (>60 years old) appears to be conflicting (75-77). However, these findings may be explained by the geographical location of individual studies, since the studies reporting significant associations were all conducted in the Middle-East or India (71,72,78,79). Nevertheless, these findings may point to a potential benefit of vitamin D supplementation in younger women with LBP. Finally, an additional consideration for future research investigating vitamin D supplementation for LBP is the importance of measuring and reporting serum 25(OH)D before and after supplementation to better understand the mechanism of effect. Only one study included in this review used vitamin D deficiency (<20 ng/mL) as part of their inclusion criteria (49), while 2 studies reported mean serum 25(OH)D concentrations <20 ng/mL at baseline for their sample (25,46). This information is important since the size of the effect may be dependent on the presence of vitamin D deficiency prior to supplementation. In addition, only 2 studies reported serum 25(OH)D concentrations following treatment (25,46) and showed that serum 25(OH)D concentrations reached normal levels following supplementation (> 20 ng/mL). However, these improvements did not correlate with improvements in symptoms of pain.

Strengths and Limitations

Our study has a number of strengths. First, we were able to include 8 clinical trials in this review. This is a substantial improvement on the only other published systematic review on vitamin D and LBP, which only included one clinical trial (80). Second, pooling the results from 5 randomized controlled trials allowed us

to quantify the effect of vitamin D supplementation on LBP, while numerous sub-group analyses explored whether this effect was influenced by the presentation of LBP (e.g., non-specific LBP or LBP due to osteoporosis or vertebral fractures) or type of vitamin D supplementation prescribed (e.g., vitamin D3 or alfacalcidol).

This study had a number of limitations which need to be considered. First, including any clinical trial that provided a comparison between individuals receiving some form of vitamin D supplementation and a comparison treatment, including no intervention, might introduce substantial between-study heterogeneity. In addition, including studies reported in the form of conference abstracts makes it hard to judge the overall quality of evidence, as information about study design and implementation is limited. However, due to a small number of eligible studies (n = 8), keeping a broad inclusion criteria and including conference abstracts gives a better overall picture of the evidence and reduces the risk of publication bias (81). Furthermore, only 2 studies included in this review were conference abstracts, and our main findings were derived from meta-analyses where conference abstracts were excluded (Fig. 2 & 3). Second, one of the conference abstracts included 140 participants but failed to report effect sizes. This meant a comparison between participant characteristics (e.g., age, gender, type of LBP, etc.) and effect sizes was not possible, and we could not include this study in any meta-analysis. Third, 2 studies allowed participants in the vitamin D and placebo groups to take analgesics as required (25,49). This could mask the true effect of vitamin D supplementation if the utilization of analgesics was significantly different between groups. However, both studies outlined that there were no significant between-group differences in self-reported analgesic use, with one study reporting objective data (25). Finally, the overall quality of evidence was "very low." This was predominately due to the low methodological quality of the included studies (with 78.3% of the trials, weighted by their sample size, scoring <7 on the PEDro scale), and small sample sizes. Despite this, the results of our review provide an overall picture of the effect of vitamin D supplementation for LBP. Researchers interested in continuing to explore this topic should consider the current quality of the evidence and ensure they implement well-designed and adequately powered clinical trials to build on the evidence in this field.

Conclusion

This review found very low quality evidence that vitamin D supplementation is more effective than placebo, no intervention, or other conservative/pharmacological interventions for LBP, regardless of the type of LBP (non-specific or LBP due to osteoporosis or vertebral fractures) or vitamin D supplementation (vitamin D3 or alfacalcidol). Until well-designed and adequately powered clinical trials suggest otherwise, the prescription of vitamin D for LBP cannot be recommended.

Appendix 1. *Search strategy.*

MEDLINE

Searches	
Vitamin D	exp Vitamin D/
	"vitamin D".mp
	"vitamin D2".mp
	"vitamin D3".mp
	"1-alpha hydroxyvitamin D3".mp
	"1-alpha hydroxycalciferol".mp
	"1,25 dihydroxyvitamin D3".mp
	"1,25 dihydroxycholecalciferol".mp
	"25 hydroxycholecalciferol".mp
	"25 hydroxyvitamin D".mp
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	"calcidiol".mp
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	"calcifediol".mp
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	"backpain".mp
	exp Low Back Pain/
	"low back pain".mp
	"backache".mp
	"back ache".mp
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	"lumbar pain".mp
	"spinal pain".mp
	"lumbago".mp.
	"lower back pain".mp
	"dorsalgia".mp
	"vertebral pain".mp
	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
	20 and 35
	Limit 36 to humans

CINHAL

Searches	
Vitamin D	MH "Vitamin D+"
	MH "Vitamin D Deficiency+"
	MH "Ergocalciferols"
	MH "Cholecalciferol"
	"vitamin D"
	"vitamin D2"
	"vitamin D3"
	"1-alpha hydroxyvitamin D3"
	"1,25 dihydroxyvitamin D3"
	"1,25 dihydroxycholecalciferol"
	"25-hydroxycholecalciferol"
	"25 hydroxycholecalciferol"
	"25 hydroxyvitamin D"
	"25-hydroxy-vitamin D"
	"alfacalcidol"
	"calcidiol"
	"calcitriol"
	MH "Calcitriol"
	"calcifediol"
	"calciferol"
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
Low back pain	(MH "Back Pain+")
	"back pain"
	(MH "Low Back Pain")
	"low back pain"
	"lumbago"
	"backache"
	"back ache"
	"lumbar pain"
	"spinal pain"
	"backpain"
	"lower back pain"
	"dorsalgia"
	"vertebral pain"
	22 or 23 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

EMBASE

Searches	
Vitamin D	exp vitamin D/
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	"vitamin D2".mp
	"vitamin D3".mp
	"1-alpha hydroxyvitamin D3".mp
	"1-alpha-hydroxy-calciferol".mp
	"1,25 dihydroxyvitamin D3".mp
	"1,25 dihydroxycholecalciferol".mp
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	"calcifediol".mp
	"calciferol".mp
	"ergocalciferol".mp
	"cholecalciferol".mp
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
Low back pain	exp Backache/
	"backache".mp
	"back ache".mp
	exp Low back pain/
	"low back pain".mp
	exp Spinal pain/
	"spinal pain".mp
	"back pain".mp
	"lumbago".mp
	"lumbar pain".mp
	"lower back pain".mp
	"vertebral pain".mp
	"dorsalgia".mp
	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	18 and 32
	Limit 33 to humans

AMED

Searches	
Vitamin D	exp Vitamin d/
	"vitamin D".mp
	"vitamin D2".mp
	"vitamin D3".mp
	"1,25 dihydroxyvitamin D3".mp
	"25 hydroxycholecalciferol".mp
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	"ergocalciferol".mp
	"cholecalciferol".mp
	exp Cholecalciferols/
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
Low back pain	exp Low Back Pain/
	exp Backache/
	"low back pain".mp
	"back pain".mp
	"backpain".mp
	"backache".mp
	"back ache".mp
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	"lumbar pain".mp
	"spinal pain".mp
	lumbago.mp
	"lower back pain".mp
	dorsalgia.mp
	"vertebral pain".mp
	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
	16 and 31

Scopus

Searches	
Vitamin D	TITLE-ABS-KEY("vitamin D")
	TITLE-ABS-KEY("vitamin D2")
	TITLE-ABS-KEY("vitamin D3")
	TITLE-ABS-KEY("1-alpha hydroxyvitamin D3")
	TITLE-ABS-KEY("1-alpha-hydroxy-vitamin D3")
	TITLE-ABS-KEY("1-alpha hydroxycalciferol")
	TITLE-ABS-KEY("1-alpha-hydroxy-calciferol")
	TITLE-ABS-KEY("1,25 dihydroxyvitamin D3")
	TITLE-ABS-KEY("1,25-dihydroxy-vitamin D3")
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	TITLE-ABS-KEY(calcitriol)
	TITLE-ABS-KEY(calcifediol)
	TITLE-ABS-KEY(calciferol)
	TITLE-ABS-KEY(ergocalciferol)
	TITLE-ABS-KEY(cholecalciferol)
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Low back pain	ALL("back pain)
	TITLE-ABS-KEY(backpain)
	ALL("low back pain")
	TITLE-ABS-KEY(backache)
	TITLE-ABS-KEY("back ache")
	TITLE-ABS-KEY("lumbar pain")
	TITLE-ABS-KEY("spinal pain")
	TITLE-ABS-KEY(lumbago)
	TITLE-ABS-KEY("lower back pain")
	TITLE-ABS-KEY(dorsalgia)
	TITLE-ABS-KEY("vertebral pain")
	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
	24 and 36
	Exclude: "animals" and "animal"

Web of Science

Searches	
Vitamin D	TS = ("vitamin D")
	TS = ("vitamin D2")
	TS = ("vitamin D3")
	TS = ("1-alpha hydroxyvitamin D3")
	TS = ("1-alpha-hydroxy-vitamin D3")
	TS = ("1-alpha hydroxycalciferol")
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	TS = ("1,25 dihydroxycholecalciferol")
	TS = ("1,25-dihydroxycholecalciferol")
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	TS = ("25-hydroxy-vitamin D")
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	TS = (alfacalcidol)
	TS = (calcidiol)
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	TS = (calcifediol)
	TS = (calciferol)
	TS = (ergocalciferol)
	TS = (cholecalciferol)
	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Low back pain	TS = ("back pain")
	TS = (backpain)
	TS = ("low back pain)
	TS = (lumbago)
	TS = (backache)
	TS = ("lumbar pain")
	TS = ("spinal pain")
	TS = ("lower back pain")
	TS = (dorsalgia)
	TS = ("vertebral pain")
	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
	24 and 35
	TS = (animals) NOT TS = (humans)
	36 NOT 37

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