Systematic Review

Mapping the Association between Vitamin D and Low Back Pain: A Systematic Review and Meta-Analysis of Observational Studies

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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: 03-28-2017
Revised manuscript received: 05-22-2017
Accepted for publication: 05-30-2017

Free full manuscript: www.painphysicianjournal.com

Background: Low back pain (LBP) is the highest contributor to disability worldwide, with current intervention strategies only providing small to moderate analgesic effects. The use of vitamin D supplementation for LBP has gained interest due to its proposed anti-inflammatory and neuromodulatory properties. However, it is still unclear whether vitamin D levels differ between those with and without LBP or if vitamin D levels are associated with pain intensity.

Objectives: We aim to investigate the association between vitamin D levels and LBP and to determine if vitamin D levels correlate with pain intensity in individuals with LBP.

Study Design: This study was conducted in accordance with the guidelines for performing a Meta-analysis and Systematic Review Of Observational Studies in Epidemiology (MOOSE).

Methods: We performed electronic database searches combined keywords relating to vitamin D and LBP in MEDLINE, CINAHL, EMBASE, AMED, WEB OF SCIENCE, and SCOPUS from the earliest record to March 2017. Studies were included if they reported any quantitative measure of vitamin D, such as serum 25-hydroxyvitamin D [25(OH)D], with adequate data in patients with and without LBP or adequate data on pain intensity in patients with LBP. No restriction on the type or duration of LBP, nor the age and gender of patients was applied. Two reviewers independently performed the selection of studies, extracted data, and assessed the methodological quality of the included studies using a modified 15-item Downs and Black checklist.

Results: After the removal of duplicates and the screening of titles and abstracts, 105 full texts were evaluated. There were 29 articles included in this systemic review (22 entered into a meta-analysis), including 19 cross-sectional studies, 9 case-control studies, and one single-arm surgical trial where the pre-operative data were used in our analyses. The pooled results from 19 studies showed that individuals with LBP were more likely to have vitamin D deficiency (pooled OR = 1.60, 95% CI: 1.20 - 2.12, $P = 0.001$, n = 19), severe deficiency (pooled OR = 2.08, 95% CI: 1.19 - 3.64, $P = 0.010$, n = 7), and lower serum concentrations of 25(OH)D (weighted MD = 3.86, 95% CI: 0.20 - 7.52, $P = 0.039$, n = 12) compared to those without LBP (where "n" is the number of studies). The association between vitamin D deficiency (pooled OR = 1.83, 95% CI: 1.26 - 2.66, $P = 0.002$, n = 9) or serum 25(OH)D (weighted MD = 7.64, 95% CI: 4.02 - 11.26, $P < 0.001$, n = 4) and LBP was stronger for women but failed to be statistically significant for men (pooled OR = 1.06, 95% CI: 0.62 - 1.81, $P = 0.213$, n = 3). In addition, there were strong associations between vitamin D deficiency and LBP in patients < 60 years old (particularly women). We found minimal evidence to support an association between vitamin D levels and pain intensity in patients with LBP.

Limitations: We were unable to investigate whether vitamin D deficiency increases the risk of developing LBP as there were no longitudinal studies included in this review.

Conclusion: Vitamin D deficiency is associated with LBP, with stronger associations observed in younger women and those with severe levels of deficiency. The association between vitamin D levels and pain intensity is inconsistent. These results may guide the implementation of future studies on vitamin D supplementation for LBP.
PROSPERO Registration No: CRD42016046874.

Key words: Vitamin D, low back pain, deficiency, pain intensity, serum 25-hydroxyvitamin D, supplementation, cross-sectional study, case-control study

Pain Physician 2017; 20:611-640

Low back pain (LBP) is a global problem, being the highest contributor of years lived with disability in both developed and developing countries (1). From an economic perspective, the burden of LBP can be seen across many countries (2,3), with the annual cost of LBP in Australia estimated around $5 billion (4). The majority of research on LBP has concerned management strategies; however, given the small effect sizes of current interventions (5), a better understanding of the factors associated with the prevalence and risk of developing LBP is needed to guide future intervention strategies.

A previous history of LBP appears to be the only strong and consistent risk factor for developing LBP (6), with other factors only demonstrating weak associations, including obesity (7), heavy work-related physical activity (8), poor general health (9), educational attainment (10), and symptoms of depression (11). A number of studies have demonstrated an association between vitamin D deficiency and the presence of chronic painful conditions (12-15). However, the evidence surrounding vitamin D levels in people with and without LBP, along with how vitamin D levels influence pain intensity in patients with LBP appears to be conflicting. Some studies show a positive association between vitamin D deficiency and LBP (16,17) and between vitamin D levels and pain intensity (18,19), while others have failed to find an association (20) or have only found a significant association in women (21).

There are numerous mechanisms that provide rationale for the link between vitamin D and the risk of LBP, including: the regulation of anti- and pro-inflammatory cytokines that control pain and inflammation (22) and the modulation of pain through sensory neuron excitability (23,24). Furthermore, there appears to be an inverse relationship between inflammatory markers and serum concentrations of 25-hydroxyvitamin D (25(OH)D) (a common measure of vitamin D levels) (25), with research showing reductions in inflammatory markers following vitamin D supplementation (26,27). Therefore, given the increasing interest in vitamin D supplementation for the management of LBP (28,29), a better understanding of the relationship between vitamin D levels and LBP is needed. The aim of this systematic review is to investigate if vitamin D levels are associated with the prevalence and risk of LBP and if vitamin D levels correlate with pain intensity in patients with LBP.

Methods

Search Strategy

The protocol for this systematic review was registered on PROSPERO (Registration No: CRD42016046874) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (30) and the guidelines for performing a Meta-analysis and Systematic Review Of Observational Studies in Epidemiology (MOOSE) (31). We performed electronic database searches (from the earliest records to March 2017) combing key words relating 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.) in MEDLINE, CINAHL, EMBASE, AMED, WEB OF SCIENCE and SCOPUS databases (Appendix 1). We performed citation tracking and hand-searched the reference lists of included studies to capture articles missed through our database search.

Study Selection

Two reviewers (JZ and AS) independently performed the selection of studies by screening the titles, abstracts, and full texts of articles. Both of the reviewers used a study eligibility form based on items from the inclusion/exclusion criteria and resolved any disagreements by discussion or consultation with a third reviewer (DS). Studies in a language other than English needed to be translated or at least have the abstract in English to be included. We included conference abstracts or the abstracts of articles where the full text was not available.

Studies reporting the association between vitamin D levels [serum concentrations of 25(OH)D or the presence of vitamin D deficiency] and LBP (or pain intensity in people with LBP) or with adequate data to calculate a relevant measure of association [mean difference (MD), odds ratio (OR), Pearson's correlation coefficient (r), or Spearman's rho (ρ)] were included. There was no restriction on the duration or type of LBP assessed (e.g., non-specific LBP or LBP with radicular symptoms), the cut-off for vitamin D deficiency used, the measure of pain intensity, nor the age or gender of the patients. We included longitudinal and cross-sectional studies, case-control studies, and case-series that fit the above inclusion criteria. We excluded studies investigating the effectiveness of vitamin D supplementation for LBP, which includes randomized and non-randomized trials.

Methodological Quality

The methodological quality of the included studies with an accessible full text was independently assessed by 2 reviewers (JZ and AS) using a modified Downs and Black checklist (32). Any disagreement was resolved by discussion or consultation with a third reviewer (DS).

Data Extraction

Two reviewers (JZ and AS) used a standardized data extraction form to independently extract the data from the included studies. The data on the patients' characteristics (age and gender), study geographical location, study setting (e.g., hospital or community), sample size, and features specific to the study design, such as the exposure variables [e.g., serum 25(OH)D], outcome variables (e.g., LBP), pain intensity measures, and confounders, were extracted.

Statistical Analysis

The data on the most relevant statistics to measure the association between vitamin D and LBP (mean difference [MD] or odds ration [OR]) or association between vitamin D and pain intensity in patients with LBP (MD, OR, r, ρ) and their 95% confidence interval (CI) were extracted from the included studies. When studies were considered sufficiently homogenous we attempted to pool the results using the most adjusted models reported in the studies using Comprehensive Meta-Analysis Version 3.0 (BioStat, Englewood, NJ). If more than half of the studies failed to adjust their results for potential confounders, we stratified our meta-analyses by age, gender, and cut-offs for vitamin D deficiency where possible (sensitivity analysis). We attempted to transform data into MD and their 95% CI when studies only reported: i) the mean (standard deviation [SD]) serum 25(OH)D in people with and without LBP, ii) the mean (SD) serum 25(OH)D in people with LBP who had varying levels of pain intensity, or iii) the mean (SD) pain intensity in people with and without vitamin D deficiency. In addition, we attempted to transform data into OR and their 95% CI when studies only reported: i) the number of patients with and without LBP who were vitamin D deficient (or severely deficient) or ii) the number of individuals with severe or mild pain who were vitamin D deficient. The authors of the included studies were contacted when required data was not published. We assessed heterogeneity using the I^2 statistic and considered $I^2 < 25\%$, $I^2 \geq 50\%$, and $I^2 \geq 75\%$ as indications of low, moderate, and high heterogeneity respectively (33). When I^2 was < 50% we used fixed-effects models, and if it was ≥ 50% we used random-effects models.

Results

Description of Studies

We identified 3,534 articles through our database searches with 3 articles (34-36) identified through hand-searching the reference lists of the included studies (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 105 articles. A total of 29 observational studies (with data on 21,764 patients) were eligible for inclusion in this review, including 19 cross-sectional studies (including 4 conference abstracts), 9 case-control studies, and one single-arm surgical trial where we used the pre-operative data in our analyses. The full texts of 2 included case-control studies (37,38) could not be obtained, thus we used the data included in the abstracts for our review. There were no longitudinal studies that met our inclusion criteria. The characteristics of the included studies can be found in Table 1. The duration of LBP symptoms included in the studies varied, with 17 of the 29 studies including patients who reported LBP of any duration (8 studies only included patients with non-specific LBP) and 8 studies including patients with chronic LBP (4 studies only included patients with non-specific chronic LBP). We defined chronic LBP as pain lasting for at least 3 months (39) and operationalized this over all of the studies, regardless of the authors' classification. The remaining 4 studies included patients with lumbar spinal stenosis (n = 1), patients seeking spinal surgery (n = 2), or patients reporting ongoing symptoms following spinal surgery (n = 1). The majority of the included studies were conducted in the Middle-East/Mediterranean region (n = 12), with the remaining studies being conducted in Europe (n = 3), India (n = 3), United Kingdom (n = 3), Korea (n = 2), Thailand (n = 1), Japan (n = 1), Brazil (n = 1), United States (n = 1), Australia (n = 1), or across numerous countries (n = 1) (16) (Table 1). There were differences between the setting for each study with the majority of studies recruiting patients from either health/medical centers or outpatient/rheumatology clinics (n = 16) (Table 1). The sample size of individual studies ranged from 9 to 9,305 patients. In cross-sectional studies investigating vitamin D levels in people with and without LBP, the prevalence of LBP ranged from 3.5% to 74%. The classification of serum 25(OH)D was similar across studies, with 19 studies using serum 25(OH)D < 20 ng/mL as an indicator of deficiency, 9 studies using serum 25(OH)D between 20 – 30 ng/mL as an indicator of insufficiency, and 9 studies considering serum 25(OH)D > 30

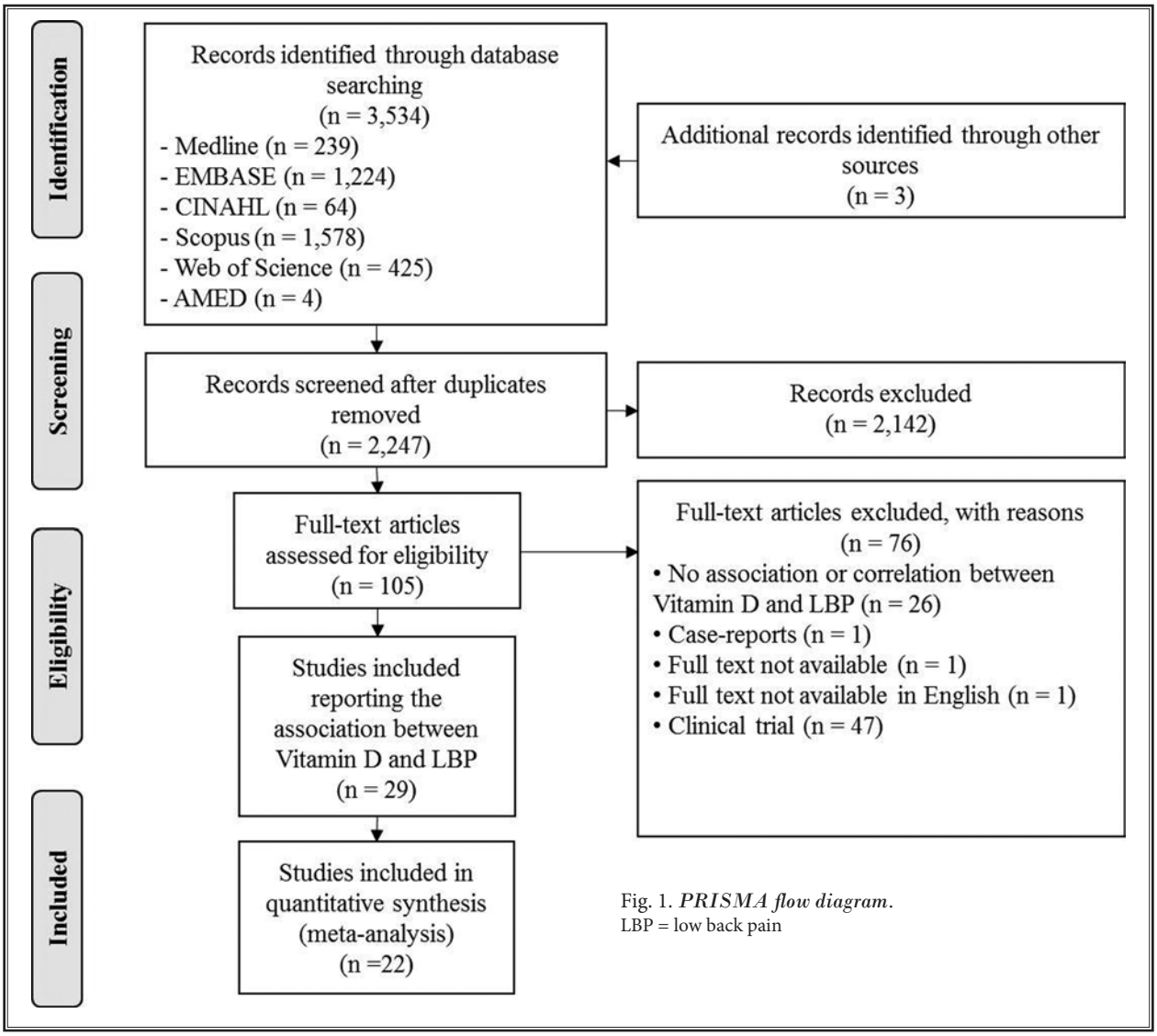


Fig. 1. *PRISMA flow diagram.*
LBP = low back pain

ng/mL as normal. Despite the remaining studies using different cut-off values (Table 1), we decided to base the terminology in our review on the above values, as these cut-offs are most commonly used in the vitamin D literature (40,41). Furthermore, the most common cut-off for severe deficiency was < 10 ng/mL (4 studies) (range: 5 – 15 ng/mL), so we decided to use this value throughout the manuscript.

Methodological Quality

The original Downs and Black checklist contained 27 items (32). However, since our review only included cross-sectional observational studies, we removed checklist items only relevant to longitudinal studies or clinical trials. The remaining 15 items provided an overall score for study quality based on 5 categories: study quality (7 items), external validity (2 items), study bias (3 items), and confounding and selection bias (3 items) (Appendix 2). Individual study scores ranged from 8 – 14 (out of a possible 16) with a mean score of 10.7 (Appendix 2). The main methodological limitations included: failing to describe (n = 14) and adjust for potential confounders (n = 20), failing to report that patients willing to participate were representative of the entire population from which they were recruited (n = 22), and not specifying whether any of the results presented were based on "data-dredging" (n = 23).

Table 1. *Characteristics of all of the included studies.*

Author (yr)	Setting	Population	n	LBP Definition	Prevalence of LBP	Vitamin D Cut-Offs for Serum 25(OH)D used in Each Study*	Baseline Vitamin D Levels in ng/mL [mean (SD) or %]*
Abdulmonem A (2014) CS	School teachers in Saudi Arabia	Women between 20 – 29 yrs	486	Self-reported LBP	66.7%	Self-reported deficiencies	Deficient: 42.4% Not deficient: 14.8% Don't know: 42.8%
Alipour M (2015) CS	Iranian population	Men and women > 60 yrs; Mean age (SD): 69.2 (7.3) yrs	857	Self-reported chronic LBP (> 3 mos duration)	48.6%	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Sufficiency: > 30 ng/mL	29.19 (27.30) Deficient: 41.9% Insufficient: 34.4% Sufficient: 23.7%
Al-Jarallah K (2013) CC	Rheumatology clinic in a university hospital in Kuwait	Men and women; Mean age (SD): Cases: 41.7 (13.9) yrs Controls: 43.7 (7.4) yrs	206	Self-reported non-specific LBP	14.6% of cases (n = 18 with LBP)	Deficiency: < 20 ng/mL	Cases:16.0 (6.5) Deficient: 66.7% Controls: 10.3 (6.0) Deficient: 96.3%
Baykara B (2014) CC	Turkish medical clinic	Male and female health care workers between 20 – 50 yrs	90	Self-reported non-specific LBP (< 12 wks duration)	60 cases	Deficiency: < 10 ng/mL Insufficiency: < 20 ng/mL	Not reported
Ducher G (2011) CS	Vocational ballet dance program in Melbourne, Australia	Men between 10 – 19 yrs	16	Self-reported current or previous LBP	25%	Deficiency: < 10 ng/mL Insufficiency: 10 – 20 ng/mL Sufficiency: >20ng/mL	Cases: 18.4 (11.4) Deficient: 50.0% Controls: 20.8 (8.8) Deficient: 58.3%
e Silva AV (2013) CS	232 sites in 23 countries	Women between 60 – 85 yrs; Mean age: 67 yrs	9305	Self-reported non-specific LBP	67.5%	Deficiency: < 20 ng/mL	Deficient: 24.4%
Ghai B (2015) CS	Outpatient pain clinic in tertiary hospital in North India	Men and women between 36 – 52 yrs; Mean (SD): 43.8 (13.9) yrs	328	Self-reported chronic LBP (> 3 mos duration)	All had LBP	Deficiency: < 20 ng/mL Insufficiency: 21 – 29.99 ng/mL Normal: > 30 ng/mL Deficiency grading Severe: 5 – 8 ng/mL Moderately severe: 9 – 12 ng/mL Moderate: 13 – 16 ng/mL Marginal: 17 – 20 ng/mL	18.4 (11.7)
Hampton M (2016) Abstract CS	Patients undergoing scoliosis correction surgery in a UK hospital	Men and women between 12 – 17 yrs; Mean age: 15 yrs	41	Seeking surgery for adolescent idiopathic scoliosis	All had LBP	Deficiency: < 10 ng/mL Insufficiency: 10 – 20 ng/mL Normal: > 20 ng/mL	Deficient: 22% Insufficient: 34% Normal: 44%
Haroon M (2011) CS	Rheumatology outpatient clinic in Ireland	Men and women between 19 – 91 yrs; Mean (SD): 53 (16) yrs	231	Self-reported non-specific LBP	3.5%	Severe deficiency: < = 12 ng/mL Deficiency: < = 21 ng/mL Normal: > 21 ng/mL	Severe deficiency: 26% Deficient: 70% Normal: 4%
Heidari B (2010) CC	Hospital outpatient clinics in Iran	Men and women; Mean age (SD): Cases: 44.3 (15.0) yrs Controls: 46.4 (14.2) yrs	505	Self-reported non-specific LBP (> 2 mos duration) and tender on palpation	19.6% of cases	Deficiency: < 20 ng/mL	Case: 33.9 (32.9) Control: 33.1 (28.4)

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

Author (yr)	Setting	Population	n	LBP Definition	Prevalence of LBP	Vitamin D Cut-Offs for Serum 25(OH)D used in Each Study*	Baseline Vitamin D Levels in ng/mL [mean (SD) or %]*
Heidari B (Nov 2014) CC	Rheumatology clinic in Babol, Northern Iran	Women; Mean age (SD): Cases: 35.1 (8.2) yrs Controls: 37.4 (7.9) yrs	182	Self-reported non-specific chronic LBP (> 3 mos)	81 cases	Deficiency: < 20 ng/mL	Deficient Cases: 70.4% Controls: 46.5% Median (range) Cases: 14.4 (4-130) Control: 21.0 (3-120)
Heidari B (2014) CC	Rheumatology clinic in Iran	Men (17%) and women (83%)	1473	Self-reported LBP	14.8	Deficiency: < 20 ng/mL	Not reported
Hicks GE (2008) CS	Italian population	Men and women between 65 – 102 yrs	958	Back pain (cervical to lumbar) that occurred quite often or almost every day within the last yr	Unable to determine	Severe deficiency: < 10 ng/mL	Median (IQR): Men: 19.6 (14.2, 29.4) Women: 13.6 (9.4, 20.3)
Hussein K (2013) Abstract CS	Saudi Arabian population	Women; No data on age	223	Self-reported non-specific LBP	61.4%	Deficiency: < 20 ng/mL	Deficient: 77%
Johansen J (2013) CS	Secondary outpatient hospital in Denmark	Men and women between 19 – 64 yrs; Mean age (SD): 44.6 (11.2) yrs	152	Self-reported chronic LBP (> 3 mos duration)	All had LBP	Severe deficiency: < 15 ng/mL Moderate deficiency: 5 – 10 ng/mL Mild deficiency: 10 – 20 ng/mL Normal: > 20 ng/mL,	23.5 (10.5)
Kesiktas N (2011) Abstract CS	Turkish population	Women between 20 – 30 years old	120	Self-reported LBP	All had LBP	Not reported	Not reported
Kim T (2013) CS	Orthopaedic outpatient clinic in Seoul, Korea	Men and women between 50 – 79 yrs; Mean age: 66.1 yrs	350	Self-reported chronic LBP and leg pain, with diagnosed lumbar spinal stenosis	All had LBP	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Normal: > 30 ng/mL	15.9 (7.1)
Kim T (2012) Intervention	Orthopaedic surgical department in Seoul, Korea	Women between 53 – 76 yrs; Mean age: Deficient: 65.8 yrs Insufficient: 66.0 yrs Normal: 68.8 yrs	31	Posterior decompression and posterior-lateral fusion for lumbar spinal stenosis	All had LBP	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Normal: > 30 ng/mL	15.8
Lee KC (2014) Abstract CS	Outpatient clinic in the UK	No data on age or gender	3361	Self-reported LBP	All had LBP	Severe deficiency: < 6 ng/mL Deficiency: 6 – 12 ng/mL	Not reported
Lodh M (2015) CC	Orthopedic department (cases) and department of biochemistry and orthopedics (controls) in India	Men and women between 13 – 75 yrs; Mean age (SD): Cases: 46.19 (15.69) yrs Control: Unknown	400	Self-reported presence of CLBP (didn't define duration)	200 cases	Insufficiency:< 30 ng/mL	Cases: 35.26 (20.98) Controls: No data

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

Author (yr)	Setting	Population	n	LBP Definition	Prevalence of LBP	Vitamin D Cut-Offs for Serum 25(OH)D used in Each Study*	Baseline Vitamin D Levels in ng/mL [mean (SD) or %]*
Lotfi A (2007) CC	Rheumatology and rehabilitation outpatient clinic in Egypt	Women in child-bearing period between 20 – 50 yrs; Mean age (SD): Cases: 32.8 (7.1) yrs. Controls: 33.6 (8.6) yrs	80	Self-reported non-specific chronic LBP (> 3 mos duration)	60 cases	Deficiency: < 40 ng/mL Sufficiency: > 40 ng/mL	Cases: 36.2 (6.2) Control: 39.8 (6.9)
Madani M (2014) CS	Nurses working in a hospital in Iran	Women between 22 – 48 yrs; Mean age (SD): 32.1(5.2) yrs	200	Self-reported LBP	74%	Severe deficiency: < 10 ng/mL Deficiency: 10 – 30 ng/mL	17.0 (21.1)
Prakash S (2013) CS	Neurology department in India	Men and women diagnosed with chronic tension type headache between 18 – 68 yrs; Mean age (SD): 38 (13) yrs	71	Self-reported LBP	49%	Deficiency: < 20 ng/mL	Not reported
Rkain H (2013) CC	Rheumatology clinic in Morocco	Postmenopausal women and healthy controls	150	Self-reported non-specific chronic LBP	105 cases	Deficiency: <20ng/mL	Deficient Cases: 79% Controls: 61.4%
Santos F (2015) CS	Brazilian population	Men and women between 80 – 100 yrs; Mean age (SD): 86.6 yrs	330	Self-reported LBP	6.1%	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Sufficiency: > 30 ng/mL Above normal: > 100 ng/mL	Cases: 21.7 (9.9). Deficient: 35%. Insufficient: 45% Normal: 20%. Controls: 20.0 (9.6). Deficient: 56.9%, Insufficient: 28.7%. Normal: 13.9%. Above normal: 0.5%
Tanaka S (2013) CS	Japanese hospital	Postmenopausal women with osteoporosis over 40 yrs; Mean age (SD): < 20 ng/mL: 63.9 (11.5) yrs 20 – 24 ng/mL: 63.5 (10.5) yrs > = 25 ng/mL: 63.6 (9.2) yrs	1470	Self-reported LBP	< 20 ng/mL: 29.6% 20 – 24 ng/mL: 30.6% ≥ 25 ng/mL: 31.9%	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Sufficiency: > 30 ng/mL	Not reported
Thörneby A (2016) CC	Swedish population	Men and women; Mean age (SD): Cases: 55 (16) yrs Control: 55 (15) yrs	88	Self-reported non-specific chronic LBP (> 3 mos duration)	44 cases	Severe deficiency: < 10 ng/mL Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Sufficiency:> 30 ng/mL	Cases: 32.4 (10.8) Controls: 32.0 (10.0)
Waltman N (2009) CS	Post-menopausal breast cancer survivors in the US	Women; Mean age (SD): 60.1 (8.3) yrs	29	Self-reported presence of combined back and neck pain	All had LBP	Deficiency: < 20 ng/mL Insufficiency: 20 – 29.99 ng/mL Normal: > 30 ng/mL	25.6 (9.2)
Waikakul S (2012) CS	Patients with ongoing symptoms following lumbar surgery in Thailand	Men and women between 25 – 54 yrs old; Mean age (SD): 39.2 (9.8) yrs	9	Ongoing chronic LBP following surgery	All had LBP	Deficiency: < 20 ng/mL Low: 20 – 30 ng/mL Normal: > 30 ng/mL	17.0 (6.0)

n = sample size; LBP = low back pain; SD = standard deviation; CS = cross-sectional study; CC = case-control study; 25(OH)D = 25-hydroxyvitamin D . * 10 ng/mL = 25 nm/L

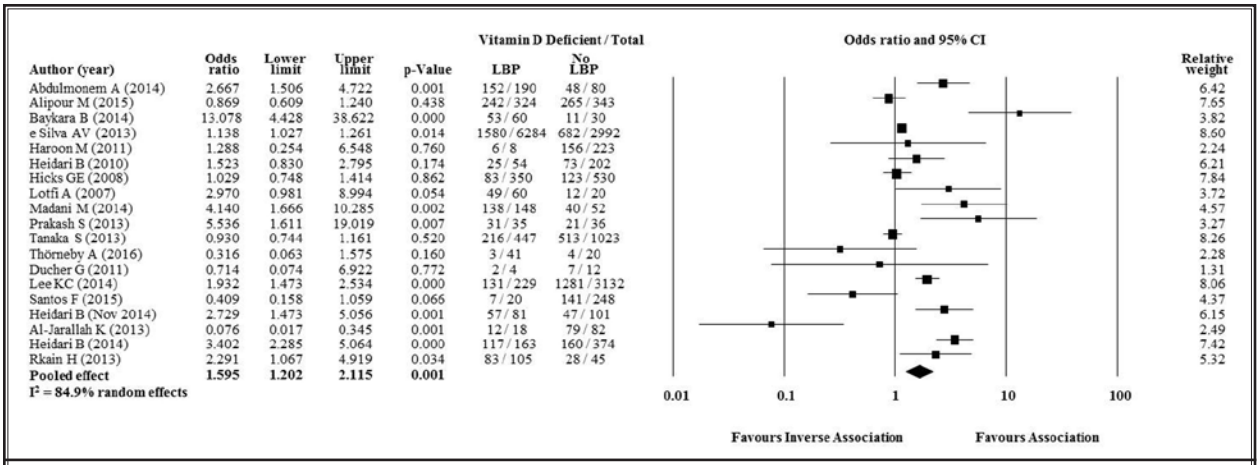


Fig. 2. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP for all of the included studies.*
LBP = low back pain; CI = confidence interval

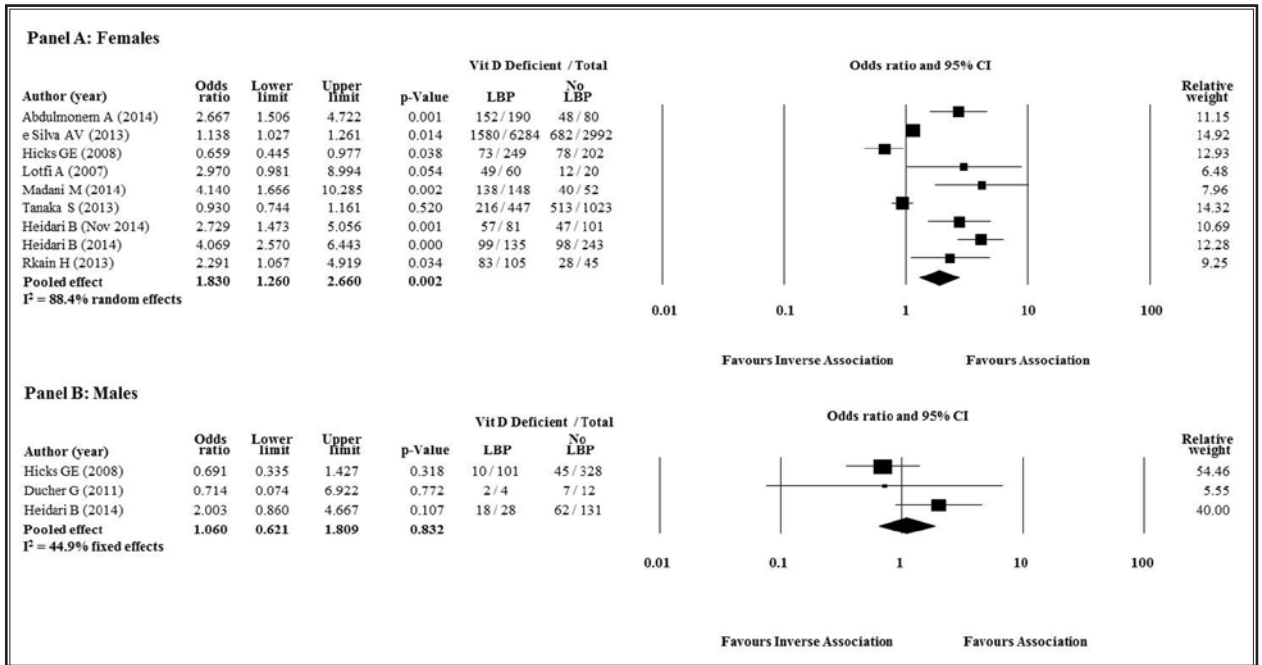


Fig. 3. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP for women (A) and men (B).*
LBP = low back pain; CI= confidence interval

Association between Vitamin D Deficiency and LBP

The pooled results from 19 studies (11 cross-sectional studies and 8 case-control studies) demonstrated a significant association between vitamin D deficiency and LBP (pooled OR = 1.60, 95% CI: 1.20 – 2.12, P = 0.001, n = 19) (Fig. 2), where 'n' is the number of studies and an OR > 1 indicates patients with LBP are more likely to have vitamin D deficiency compared to those without LBP. This association was stronger for women (pooled OR = 1.83, 95% CI: 1.26 – 2.66, P = 0.002, n = 9), but failed to be statistically significant for men (pooled OR = 1.06, 95% CI: 0.62 – 1.81, P = 0.832, n = 3) (Fig. 3). We further stratified our meta-analyses by age and cut-offs for vitamin D deficiency.

The age of the patients varied substantially between

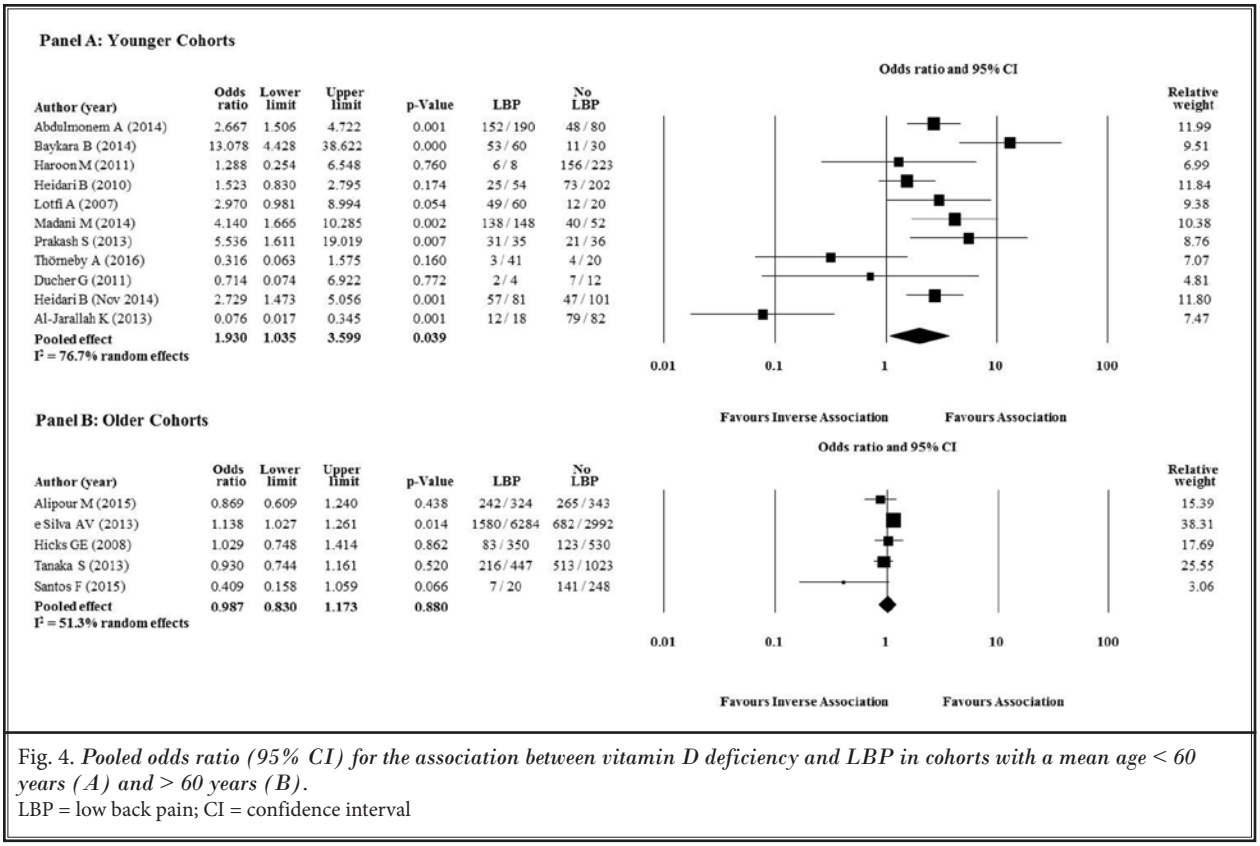


Fig. 4. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP in cohorts with a mean age < 60 years (A) and > 60 years (B).*
LBP = low back pain; CI = confidence interval

studies so we stratified our meta-analyses by samples with a mean age < 60 or > 60 years old to ensure the majority of postmenopausal women were included in the same category. There was a significant association between vitamin D deficiency and LBP in studies with a mean age < 60 years old (pooled OR = 1.93, 95% CI: 1.04 – 3.60, *P* = 0.039, n = 11), but no association in the samples with a mean age > 60 years old (pooled OR = 0.99, 95% CI: 0.83 – 1.17, *P* = 0.880, n = 5) (Fig. 4). There was a strong association between vitamin D deficiency and LBP in women < 60 years old (pooled OR = 2.91, 95% CI: 2.03 – 4.17, *P* < 0.001, n = 4), but no association in women > 60 years old (pooled OR = 0.94, 95% CI: 0.72 – 1.22, *P* = 0.631, n = 3) (Fig. 5). The association between vitamin D deficiency and LBP was investigated in men between 65 – 102 years old in one study (OR = 0.69, 95% CI: 0.34 – 1.43, *P* = 0.318) (21) and in men between 10 – 19 years old in another study (OR = 3.67, 95% CI: 0.17 – 77.56, *P* = 0.404) (Table 2) (42). Neither of these studies showed statistically significant results.

The cut-offs for vitamin D deficiency varied across studies and we stratified our meta-analyses accordingly. The pooled results from 13 studies that defined deficiency as having serum concentrations of 25(OH)D < 20 ng/mL (one study used < 21 ng/mL) demonstrated no association between vitamin D deficiency and LBP (pooled OR = 1.25, 95% CI: 0.90 – 1.76, *P* = 0.191, n = 13), while the 7 studies that used < 10 ng/mL as a cut-off (2 studies used < 12 ng/mL (43,44)) showed a significant association (pooled OR = 2.08, 95% CI: 1.19 – 3.64, *P* = 0.010, n = 7) (Fig. 6).

Association between Serum 25(OH)D and LBP

There were 12 studies (4 cross-sectional and 8 case-control studies) that investigated the association between serum concentrations of 25(OH)D (continuous measure) and LBP. The pooled results from all of the studies (Fig. 7) and studies investigating women (Fig. 7) and patients < 60 years old (Fig. 8) were similar to the findings for the association between vitamin D deficiency and LBP. There were not enough data to pool the results for men or individuals > 60 years old.

Association between Vitamin D Deficiency and Pain Intensity

There was a significant association between vita-

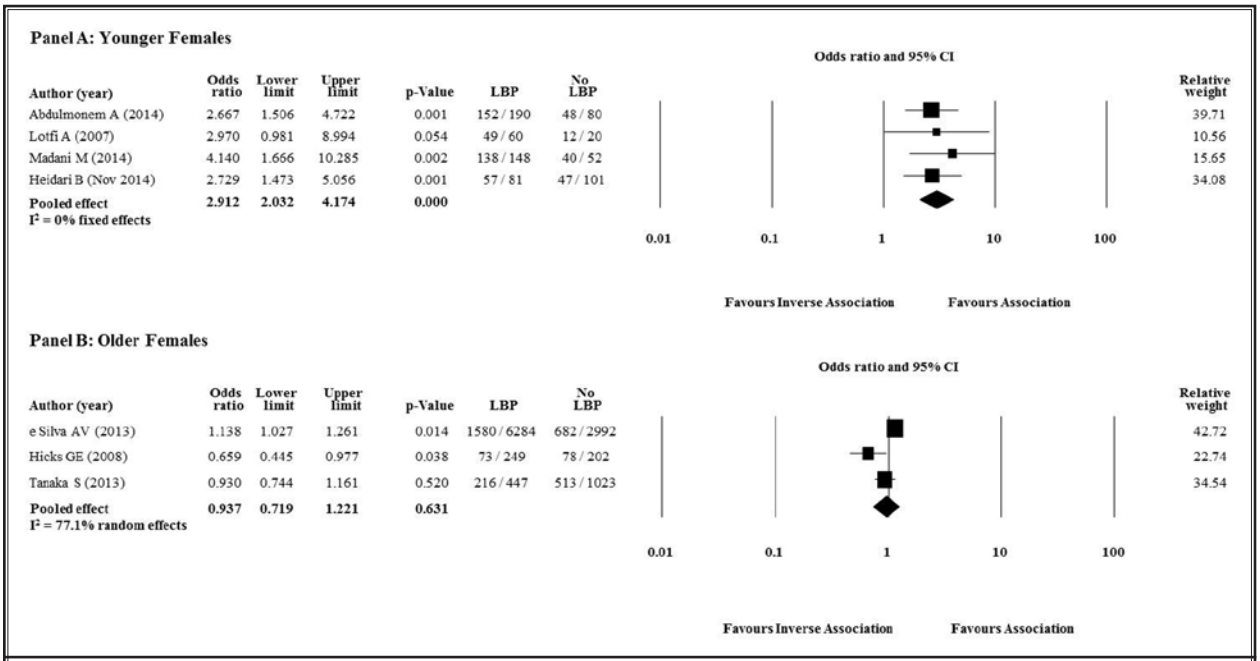


Fig. 5. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP in female cohorts with a mean age < 60 years (A) and > 60 years (B).*
LBP = low back pain; CI = confidence interval

min D deficiency and severe pain (compared to mild pain) (pooled OR = 1.98, 95% CI: 1.05 – 3.75, *P* = 0.036, n = 3) (Fig. 9) but no association between pain intensity (continuous measure: 0 – 100 scale) and vitamin D deficiency (weighted MD = 0.29, 95% CI: -0.35 – 0.94, *P* = 0.373, n = 4) (Fig. 10). In addition, one conference abstract reported similar pain scores in people with deficient, insufficient, and normal vitamin D levels, although no objective data was presented (45) (Table 2).

Association between Serum 25(OH)D and Pain Intensity

Our pooled results showed no association between serum 25(OH)D and pain intensity (0 – 10 scale) (pooled r = -0.02, 95% CI: -0.21 – 0.17, *P* = 0.812, n = 2) (Fig. 11). In addition, one study failed to find a significant association between serum 25(OH)D and pain intensity (46), while another study found a significant association (35) (Table 2). Unfortunately, these studies failed to report objective data and were not included in the above meta-analysis. One cross-sectional study failed to find an association between serum 25(OH)D and severe pain (47), while another study reported a significant negative correlation between serum 25(OH)D and LBP (48) (Table 2). However, it was not clear how the latter study assessed pain intensity or the presence of LBP.

Discussion

This is the first systematic review to investigate the association between vitamin D and LBP and the association between vitamin D and pain intensity in patients with LBP, which is particularly important given the increasing interest in vitamin D supplementation for the management of LBP (28, 29). Our results showed that patients with LBP are more likely to have vitamin D deficiency (particularly severe deficiency) and lower serum concentrations of 25(OH)D, compared to those without LBP. The relationship between vitamin D deficiency and LBP is stronger in women and in those < 60 years old. On the other hand, there is conflicting evidence that vitamin D deficiency influences pain intensity in patients with LBP.

Association between Vitamin D and LBP

The results of this review suggest the association between vitamin D deficiency and LBP is influenced by age and gender, with stronger associations observed in younger women (< 60 years old). However, the geographical location of the included studies may partially explain these results; therefore, we conducted a number of sensitivity analyses to explore this issue. There was a strong association between vitamin D deficiency

Table 2. *Results from all of the included studies.*

Studies Investigating the Association between Vitamin D and LBP						
Author (yr)	**Population**	**n**	**LBP Definition**	**Predictor(s) and Outcome(s)**	**Results**	**Vitamin D cut offs for Serum 25(OH)D***
Abdulmonem A (2014) CS	Women between 20 – 29 yrs	486	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (none vs. mild-moderate-severe)	i) Vitamin D deficiency OR = 2.67 (1.51 – 4.72), P = 0.001	Self-reported deficiencies
Alipour M (2015) CS	Men and women > 60 yrs; Mean age (SD): 69.2 (7.3) yrs	857	Self-reported chronic LBP (> 3 mos duration)	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 0.87 (0.61 – 1.24), P = 0.438	Deficiency: < 20 ng/mL
Al-Jarallah K (2013) CC	Men and women; Mean age (SD): Cases: 41.71 (13.9) rs Controls: 43.7 (7.4) yrs	206	Self-reported non-specific LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 0.08 (0.02 – 0.35), P = 0.001 ii) Mean serum 25(OH)D MD = -5.63 (-8.74 - 2.52), P < 0.001	Deficiency: < 20 ng/mL
Baykara B (2014) CC	Men and women between 20 – 50 yrs	90	Self-reported non-specific LBP (< 12 wks duration)	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Mean serum 25(OH)D Outcome(s): i) Presence of pain	i) Vitamin D deficiency OR = 13.08 (4.4 – 38.62), P < 0.001 ii) Mean serum 25(OH)D Men and women: MD = 13.10 (9.15 – 17.06), P < 0.001 Women: MD = 12.92 (6.89 – 18.95), P < 0.001 Men: MD = 14.30 (7.99 – 20.61), P < 0.001	Severe deficiency: < 10 ng/mL
Ducher G (2011) CS	Men between 10 – 19 yrs	16	Self-reported current or previous LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Severe vitamin D deficiency (Y/N) iii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 3.67 (0.17 – 77.56), P = 0.404 ii) Severe vitamin D deficiency OR = 0.71 (0.07 – 6.92), P = 0.772 iii) Mean serum 25(OH)D MD = 2.32 (-8.34 – 12.98), P = 0.670	Severe deficiency: < 10 ng/mL Deficiency: 10 – 20 ng/mL
e Silva AV, (2013) CS	Women between 60 – 85 yrs; Mean age: 67 yrs	9305	Self-reported non-specific LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Pain in past 6 mos (Y/N) ii) Daily restriction in past 6 mos (Y/N)	i) Vitamin D deficiency (pain) OR = 1.14 (1.03 – 1.26), P = 0.014 ii) Vitamin D deficiency (daily restriction) OR = 1.28 (1.12 – 1.45), P < 0.001	Deficiency: < 20 ng/mL
Haroon M (2011) CS	Men and women between 19 – 91 yrs; Mean age (SD): 53 (16) yrs	231	Self-reported non-specific LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Severe vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 1.29 (0.25 – 6.55), P = 0.760 ii) Severe vitamin D deficiency OR = 1.71 (0.40 – 7.37), P = 0.474	Severe deficiency: ≤ 12 ng/mL Deficiency: ≤ 21 ng/mL
Heidari B (2010) CC	Men and women; Mean age (SD): Cases: 44.3 (15.0) yrs Controls: 46.4 (14.2) yrs	505	Self-reported non-specific LBP (> 2 mos duration) and tender on palpation	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 1.52 (0.83 – 2.80), P = 0.174 ii) Mean serum 25(OH)D MD = -0.80 (-9.63 – 8.03), P = 0.859	Deficiency: < 20 ng/mL

Table 2 (cont.). *Results from all of the included studies.*

Studies Investigating the Association between Vitamin D and LBP						
Author (yr)	**Population**	**n**	**LBP Definition**	**Predictor(s) and Outcome(s)**	**Results**	**Vitamin D cut offs for Serum 25(OH)D***
Heidari B (2014) CC	Women; Mean age (SD): Cases: 35.1 (8.1) yrs Controls: 37.4 (7.9) yrs	182	Self-reported non-specific chronic LBP (> 3 mos)	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Median serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 2.73 (1.47 – 5.06), P = 0.001 ii) Mean serum 25(OH)D MD = 0.60 (-6.59 – 7.79), P = 0.870	Deficiency: < 20 ng/mL
Heidari B (2014) CC	Men (17%) and women (83%); No data on age	1473	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency Men and women OR = 3.40 (2.29 – 5.06), P < 0.001 Men : OR = 2.00 (0.80 – 3.90), P = 0.159 Women : OR = 4.07 (2.57 – 6.44), P < 0.001 ii) Mean serum 25(OH)D Men and women MD = 8.50 (3.47 – 13.54), P = 0.001	Deficiency: < 20 ng/mL
Hicks GE (2008) CS	Men and women between 65 – 102 yrs	958	Back pain (cervical to lumbar) that occurred quite often or almost every day within the last yr	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (No/ mild vs. moderate-severe)	i) Vitamin D deficiency Men and women OR = 1.03 (0.75 – 1.41), P = 0.862 Men: OR = 0.69 (0.34 – 1.43), P = 0.318 Women: OR = 0.66 (0.45 – 0.98), P = 0.038	Severe deficiency: < 10 ng/mL
Hussein K (2013) Abstract CS	Women; No data on age	223	Self-reported LBP	Predictor(s): i) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Mean serum 25(OH)D MD = 7.64 (4.72 – 10.56), P < 0.001	Deficiency: < 20 ng/mL
Lee KC (2014) Abstract CS	No data on age or gender	3361	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Severe vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 1.93 (1.47 – 2.53), P < 0.001 ii) Severe vitamin D deficiency OR = 9.21 (6.22 – 13.66), P < 0.001	Severe deficiency: < 6 ng/mL Deficiency: 6 – 12 ng/mL
Lodh M (2015) CC	Men and women between 13 – 75 yrs; Mean age (SD): Cases: 46.2 (15.7) yrs Control: Not reported	400	Self-reported CLBP (didn't define duration)	Predictor(s): i) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Mean serum 25(OH)D MD = 8.63 (4.33 – 12.93), P < 0.001	Insufficient: < 30 ng/mL
Lotfi A (2007) CC	Women between 20 – 50 yrs; Mean age (SD): Cases: 32.8 (7.1) yrs Controls: 33.6 (8.6) yrs	80	Self-reported non-specific chronic LBP (> 3 mos duration)	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 2.97 (0.98 – 8.99), P = 0.054 ii) Mean serum 25(OH)D MD = 3.60 (0.37 – 6.83), P = 0.029	Insufficient: < 40 ng/mL
Madani M (2014) CS	Women between 22 – 48 yrs; Mean age (SD): 32.1 (5.2) yrs	200	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Severe vitamin D deficiency (Y/N) iii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 4.14 (1.67 – 10.29), P = 0.002 ii) Severe vitamin D deficiency OR = 2.60 (1.32 – 5.15), P = 0.006 iii) Mean serum 25(OH)D MD = 9.00 (2.42 – 15.58), P = 0.007	Severe deficiency: < 10 ng/mL Deficiency: < 30 ng/mL

Table 2 (cont.). *Results from all of the included studies.*

Studies Investigating the Association between Vitamin D and LBP						
Author (yr)	**Population**	**n**	**LBP Definition**	**Predictor(s) and Outcome(s)**	**Results**	**Vitamin D cut offs for Serum 25(OH)D***
Prakash S (2013) CS	Men and women between 18 – 68 yrs; Mean age (SD): 38 (13) yrs	71	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 5.54 (1.61 – 19.02), P = 0.007	Deficiency: < 20 ng/mL
Rkain H (2013) CC	Women	150	Self-reported non-specific chronic LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 2.29 (1.07 – 4.92), P = 0.034	Deficiency: < 20 ng/mL
Santos F (2015) CS	Men and women between 80 – 100 yrs; Mean age: 86.6 yrs	330	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Severe vitamin D deficiency (Y/N) iii) Mean serum 25(OH)D Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 0.41 (0.16 – 1.06), P = 0.066 ii) Severe vitamin D deficiency OR = 0.70 (0.16 – 3.15), P = 0.641 iii) Mean serum 25(OH)D MD = -1.71 (-6.07 – 2.65), P = 0.442	Severe deficiency: < 10 ng/mL Deficiency: < 20 ng/mL
Tanaka S (2013) CS	Women over 40 yrs; Mean age (SD): < 20 ng/mL: 63.9 (11.5) yrs 20 – 24 ng/mL: 63.5 (10.5) yrs > = 25 ng/mL: 63.6 (9.2) yrs	1470	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Presence of pain (Y/N)	i) Vitamin D deficiency OR = 0.93 (0.74 – 1.16), P = 0.520	Deficiency: < 20 ng/mL
Thörneby A (2016) CC	Men and women; Mean age (SD): Cases: 55 (16) yrs Control: 55 (15) yrs	88	Self-reported non-specific chronic LBP (> 3 mos duration)	Predictor(s): i) Vitamin D deficiency (Y/N) ii) Mean serum 25(OH)D Outcome(s): i) Presence of pain	i) Vitamin D deficiency OR = 0.32 (0.06 – 1.58), P = 0.160 ii) Mean serum 25(OH)D MD = -0.40 (-4.75 – 3.95), P = 0.857	Deficiency: < 20 ng/mL
Baykara B (2014) CC	Men and women between 20 – 50 yrs; Mean age (SD): Case: 30.6 (7.8) yrs Control: 31.0 (6.7) yrs	90	Self-reported non-specific LBP (< 12 wks duration)	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) VAS rest 0 – 10 (mean) ii) VAS activity 0 – 10 (mean)	i) VAS rest MD = 0.67 (-2.41 – 3.75), P = 0.670 ii) VAS activity MD = 0.18 (-1.25 – 1.61), P = 0.805	Severe deficiency: < 10 ng/mL
Ghai B (2015) CS	Men and women between 36 – 52 yrs; Mean age (SD): 43.8 (13.9) yrs	328	Self-reported chronic LBP (> 3 mos duration)	Predictor(s): i) Severe pain VAS ≥ 70 (Y/N) Outcome(s): i) Mean serum 25(OH)D	i) Severe pain OR = 0.93 (0.54 – 1.61), P = 0.795	Deficiency: < 20 ng/mL
Hampton M (2016) Abstract CS	Men and women between 12 – 17 yrs; Mean age: 15 yrs	41	Seeking surgery	Predictor(s): i) Vitamin D status (severe deficiency vs. deficiency vs. insufficiency) Outcome(s): ii) Pain (no measure specified)	Similar pain levels in all groups (no objective data reported)	Severe deficiency: < 10 ng/mL Deficiency: < 20 ng/mL Sufficiency: > 20 ng/mL
Hussein K (2013) CS Abstract	Women; No data on age	223	Self-reported LBP (137 patients)	Predictor(s): i) Pain severity (none-severe) Outcome(s): i) Mean serum 25(OH)D	i) Pain severity r = -0.19, P = 0.006	Deficiency: < 20 ng/mL

Table 2 (cont.). *Results from all of the included studies.*

Studies Investigating the Association between Vitamin D and LBP						
Author (yr)	**Population**	**n**	**LBP Definition**	**Predictor(s) and Outcome(s)**	**Results**	**Vitamin D cut offs for Serum 25(OH)D***
Johansen J (2013) CS	Men and women between 19 – 64 yrs; Mean age (SD): 44.6 (11.2) yrs	152	Self-reported chronic LBP (> 3 mos duration)	Predictor(s): i) Mean serum 25(OH)D Outcome(s): i) NRS 0 – 10 (mean)	No association between serum 25(OH)D and NRS scores (no objective data reported)	Severe deficiency: < 15 ng/mL Moderate deficiency: 5 – 10 ng/mL Mild deficiency: 10 – 20 ng/mL Normal: > 20 ng/mL
Kesiktas N (2011) Abstract CS	Women between 20 – 30 yrs	120	Self-reported LBP	Predictor(s): i) Mean serum 25(OH)D Outcome(s): i) VAS (mean). Scale not reported	Significant association between serum 25(OH)D and VAS scores (no objective data reported)	Not reported
Kim T (2013) CS	Men and women between 50 – 79 yrs; Mean age: 66.1 yrs	350	Self-reported chronic LBP and leg pain, with diagnosed lumbar spinal stenosis	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) Mild-moderate pain (1 – 6 NRS) vs. severe (> 6 NRS)	i) Pain OR = 2.26, 95% CI: 1.13-4.52, P = 0.021	Deficiency: < 20 ng/mL
Kim T (2012) Intervention	Women between 53 – 76 yrs; Mean age: Deficient: 65.8 yrs Insufficient: 66.0 yrs Normal: 68.8 yrs	31	Posterior decompression and posterior-lateral fusion for lumbar spinal stenosis	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) VAS 0 – 100 (EQ-5D) (mean)	Pre-op i) VAS MD = 0.30 (-0.35 – 0.95), P = 0.365	Deficiency: < 20 ng/mL
Lotfi A (2007) CC	Women between 20 – 50 yrs; Mean age (SD): Cases: 32.8 (7.1) yrs Controls: 33.6 (8.6) yrs	80	Self-reported non-specific chronic LBP (> 3 mos duration)	Predictor(s): i) Mean serum 25(OH)D Outcome(s): i) NRS 0 – 10 (mean) ii) Disease duration (mean)	i) NRS r = 0.12, P = 0.290 ii) Disease duration r = -0.24, P = 0.032	Insufficiency: < 40ng/mL
Santos F (2015) CS	Men and women between 80 – 100 yrs; Mean age: 86.6 yrs	330	Self-reported LBP	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) NRS 0 – 10 (mean) ii) Mild-moderate pain (1 – 7 NRS) vs. severe (> 7 NRS)	i) MD = -0.75 (-2.80 – 1.30), P = 0.472 ii) Mild-moderate vs. severe pain OR = 1.00 (0.14 – 3.75), P = 1.000	
Waltman N (2009) CS US	Women; Mean age (SD): 60.1 (8.3) yrs	29	Self-reported combined back and neck pain	Predictor(s): i) Mean serum 25(OH)D Outcome(s): ii) Pain intensity (0 - 10) (mean)	i) Pain r = -0.422, P = 0.022	Deficiency: < 20 ng/mL
Waikakul S (2012) Intervention	Men and women between 25 – 54 yrs; Mean (SD): 39.2 (9.8) yrs	9	Need for surgery due to failed conservative management (7 controls who responded to conservative care)	Predictor(s): i) Vitamin D deficiency (Y/N) Outcome(s): i) VAS 0 – 10 (mean) ii) Mild-moderate pain (1 – 7 NRS) vs. severe (> 7 NRS)	i) VAS MD = 0.00 (-1.00 – 1.00), P = 1.000 ii) Mild-moderate vs. severe pain OR = 0.75 (0.03 – 17.51), P = 0.858	Deficiency: < 20 ng/mL

n = sample size; LBP = low back pain; VAS = visual analog scale; NRS = numeric rating scale; VAS (EQ-5D) = pain dimension of EuroQoL questionnaire; OR = odds ration; CI = confidence interval; MD = mean difference; r = Pearson's correlation; SD = standard deviation; CS = cross-sectional study; CC = case-control study; 25(OH)D = 25-hydroxyvitamin D. * 10 ng/mL = 25 nm/L

and LBP when we pooled the 10 studies conducted in the Middle-East/Mediterranean region, particularly in female-only samples (Appendix 3). The one study conducted in this region investigating a male-only sample found no association (Table 2) (37). In addition, there was no association between vitamin D deficiency and LBP when pooling the 9 studies conducted outside of the Middle-East/Mediterranean region (Appendix 4). Since all of the studies investigating the association between vitamin D deficiency and LBP in younger women were conducted in the Middle-East/Mediterranean region, this may partially account for the strong associations found in this population given the climatic and cultural factors (e.g., sun exposure, cultural veiling, physical activity levels, obesity) likely to confound the relationship between vitamin D deficiency and LBP. Furthermore, all of the studies investigating the association between vitamin D deficiency and LBP in women > 60 years old were conducted outside of the Middle-East/Mediterranean region, which might explain the lack of association found in this population. A high prevalence of vitamin D deficiency in this age group may also explain the lack of association (49), as differences in vitamin D status between those with and without LBP would be negligible (40). However, we did not observe a trend suggesting lower baseline vitamin D levels in studies with older samples (Table 1).

Another explanation for the significant association between vitamin D and LBP in women could be related to a higher number of studies including women (women: n = 13; men: n = 4). This may be the result of a higher prevalence of LBP (49) and vitamin D deficiency (50) in this population, although additional hypotheses deserve attention. It is well-established that vitamin D can facilitate the uptake of calcium and lead to bone mineralisation (51), which is particularly important for women where age and hormonal-related bone density loss (52) can increase the risk of osteoporosis (53), potentially resulting in pain. Therefore, investigating the associations between vitamin D deficiency and health

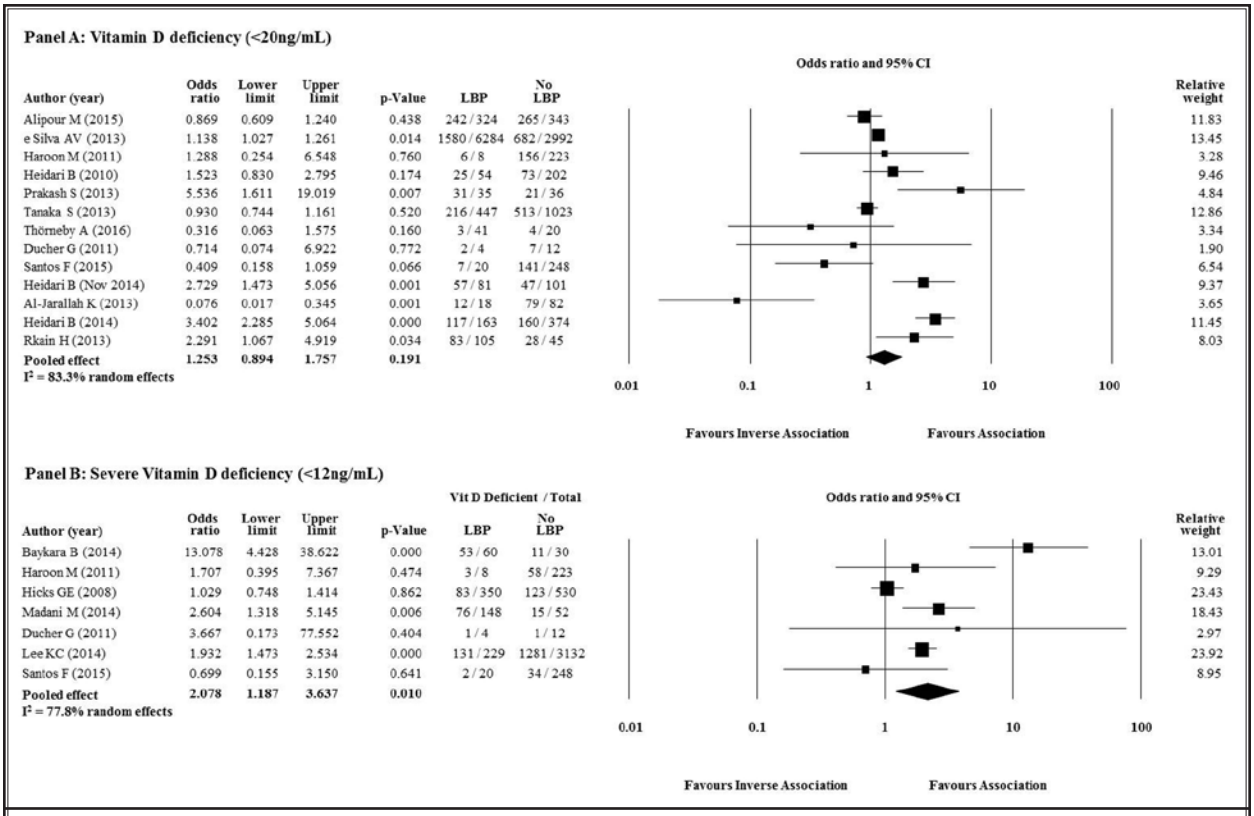


Fig. 6. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP in studies that used a cut-off for deficiency at < 20 ng/mL (A) and < 12 ng/mL (B).*
LBP = low back pain; CI = confidence interval

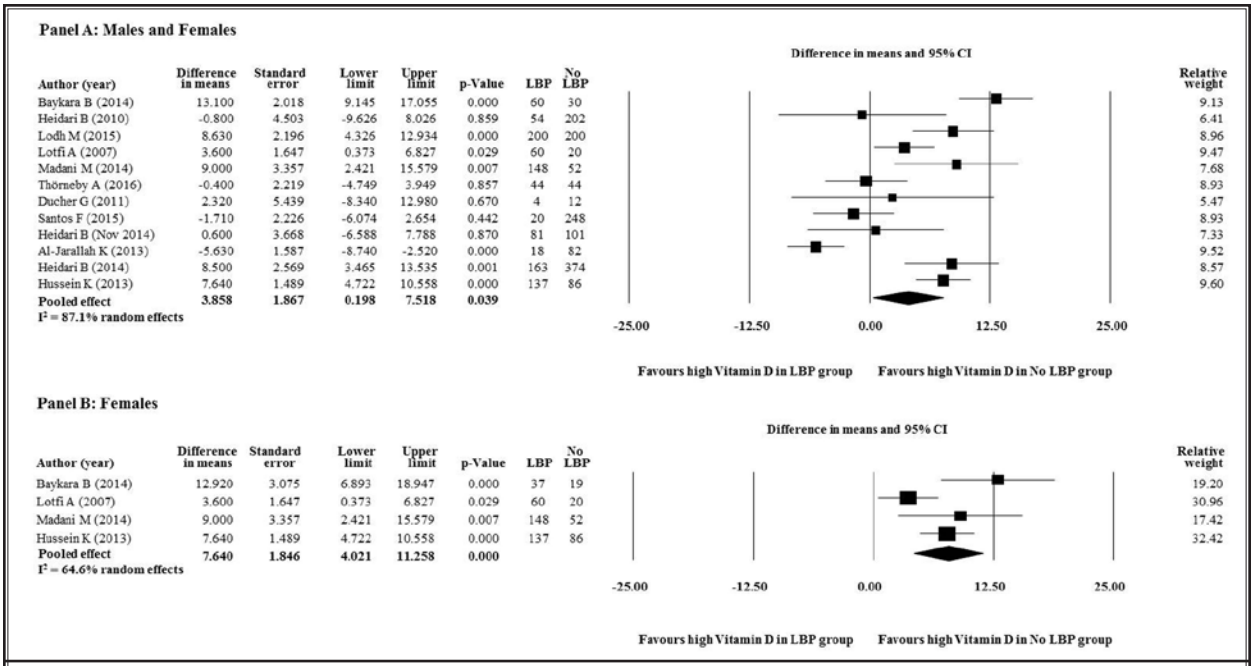


Fig. 7. Pooled odds ratio (95% CI) for the association between association between serum concentrations of 25(OH)D and LBP for all of the included studies (A) and for women (B).
LBP = low back pain; CI = confidence interval

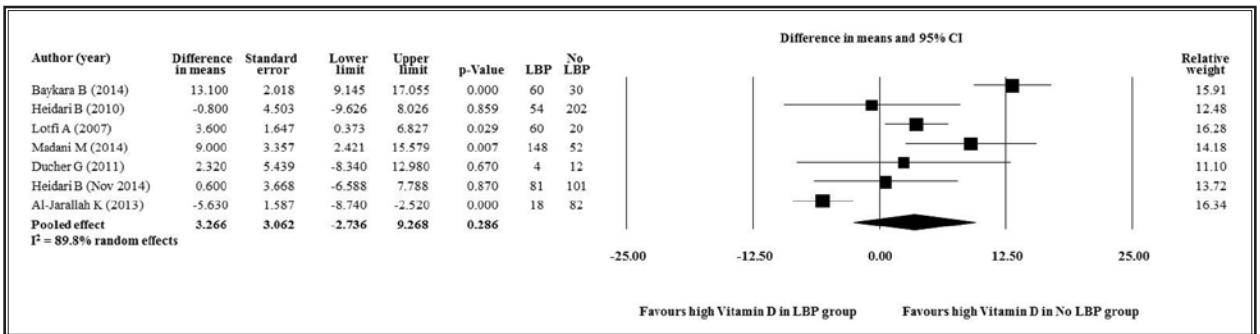


Fig. 8. *Pooled odds ratio (95% CI) for the association between serum concentrations of 25(OH)D and LBP in cohorts with a mean age < 60 years.*
LBP = low back pain; CI = confidence interval

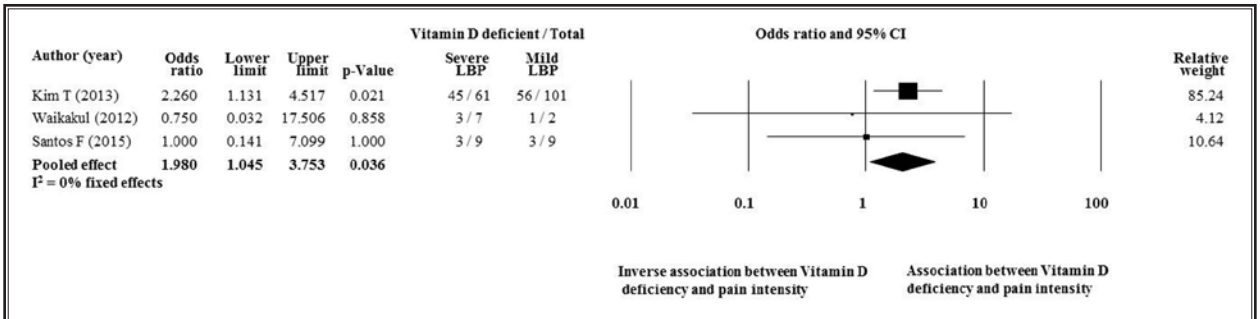


Fig. 9. *Weighted mean difference (95% CI) for the association between vitamin D deficiency and pain intensity (mild vs. severe).*
LBP = low back pain; CI = confidence interval

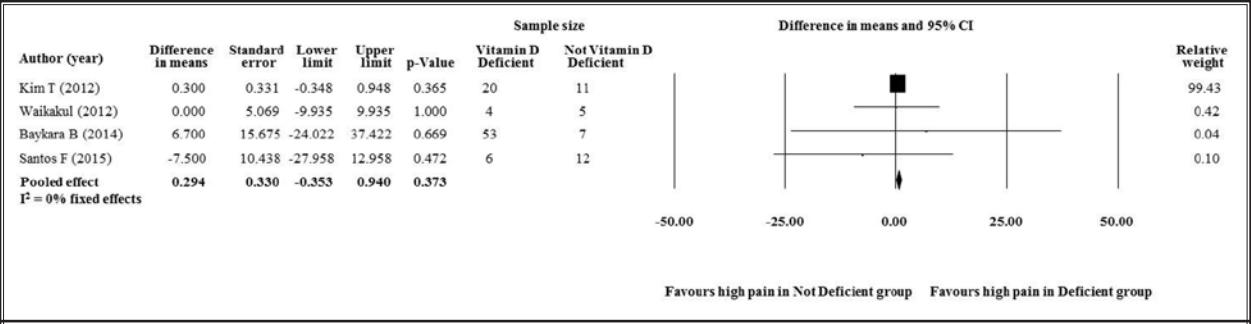


Fig. 10. *Weighted mean difference (95% CI) for the association between mean pain intensity and vitamin D deficiency.*
CI = confidence interval

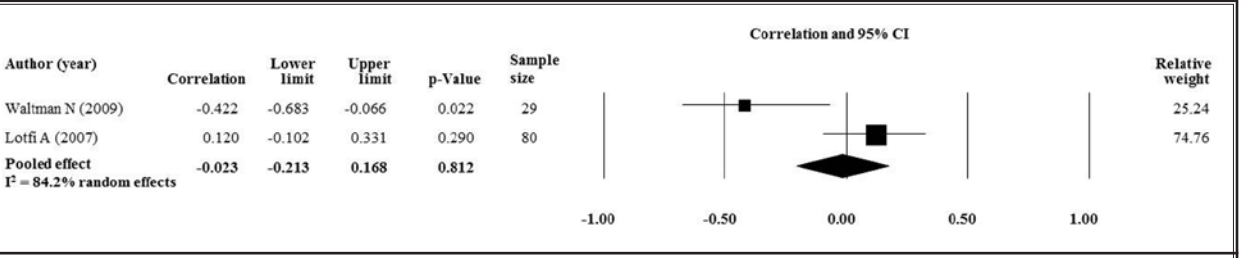


Fig. 11. *Pooled correlation (95% CI) between serum concentrations of 25(OH)D and pain.*
CI = confidence interval

conditions (such as LBP) in women may be considered a research priority and explain the higher number of studies in women. A limited number of studies in men have resulted in imprecise pooled estimates of association. Therefore, a positive association between vitamin D and LBP in men should not be ruled out and needs confirmation in larger samples. Nevertheless, the findings of our study demonstrate an increased prevalence of vitamin D deficiency in younger women with LBP. This may provide a rationale for targeting vitamin D supplementation for the management of LBP in this population or considering vitamin D supplementation to reduce the risk of developing LBP.

The presentation or chronicity of LBP may also be important to consider when determining which populations with LBP are at greatest risk of vitamin D deficiency. To explore this we conducted a number of sensitivity analyses. We found no association between vitamin D deficiency and chronic LBP (Appendix 5) or between vitamin D deficiency and LBP resulting from osteoporosis or low bone mass (Appendix 6) when pooling all of the available studies. However, there was a strong association between vitamin D deficiency and chronic LBP in women (Appendix 5), although the strength of this association may be explained by the studies' geographical location, as all the studies were conducted in the Middle-East/Mediterranean region. Furthermore, the lack of association between vitamin D deficiency and LBP resulting from osteoporosis or low bone mass may have been due to a small number of studies investigating this population (n = 2).

Our results point towards the importance of considering the degree of vitamin D deficiency in people with LBP since this association strengthened when we only considered studies that used a cut-off of < 10 - 12 ng/mL 25(OH)D. This highlights a stronger association between LBP and severe vitamin D deficiency and is consistent with the findings of another review that showed severe deficiencies were more common in individuals with chronic widespread pain compared to individuals without these symptoms (15). This may highlight the importance of screening for severe vitamin D deficiencies in these populations to potentially reduce the risk of serious disease (54-56).

Association between Vitamin D and Pain Intensity

Understanding how vitamin D deficiency influences pain intensity may provide insight into the potential role of vitamin D supplementation for the man-

agement of LBP. However, substantial heterogeneity between studies investigating the association between vitamin D and pain intensity makes it hard to draw firm conclusions about the role vitamin D plays in patients already suffering from LBP. We were only able to pool results from 4 studies, and the findings appear to be dictated by how the variables were analyzed. There was a significant association between mean vitamin D levels (continuous) and severe pain (dichotomous), but there was no association between vitamin D deficiency (dichotomous) and pain intensity (continuous). To add to these conflicting findings, some individual studies failed to find an association between serum 25(OH)D and pain intensity (46,47), while others found a significant association between serum 25(OH)D and duration of pain (17). Given the small number of studies investigating the association between vitamin D and pain intensity, we could not identify a trend between positive findings and study characteristics (e.g., gender, age, geographical location).

Given these conflicting findings, it is important to carefully consider the rationale and current evidence on vitamin D supplementation for LBP before additional studies are implemented. Research suggests that vitamin D levels influence the presence of inflammatory markers (22,25-27) and can modulate sensory neuron excitability (23,24). In addition, the influence of vitamin D levels on muscle strength has been highlighted (57,58) and may provide an explanation for the association between vitamin D deficiency and LBP and a rationale for using vitamin D supplementation for treatment. However, evidence supporting the relationship between vitamin D deficiency and reduced muscle strength is conflicting (59-62), and even if vitamin D deficiency could be regarded as a predictor of muscle weakness, muscle weakness is not consistently associated with the prevalence or risk of developing LBP (63-65), nor do improvements in muscle strength correlate with treatment outcomes (66). There has already been a number of studies conducted investigating vitamin D supplementation for the management of non-specific LBP or LBP resulting from osteoporosis or vertebral fractures, however, the results are far from promising. Three randomized controlled trials (28,67,68) failed to show that vitamin D3 was superior to a placebo for reducing pain intensity in individuals with non-specific LBP. This is despite the differences in their intervention dosage (10 – 179 ug per day) and duration (6 – 16 weeks) and despite the vitamin D3 groups achieving normal 25(OH)D concentrations post-intervention (> 20 ng/mL) (28,67). Similarly, vitamin D supplementation for the management of LBP resulting from osteoporosis or vertebral fractures has yielded disappointing results (69). Therefore, given the poor association between vitamin D and pain intensity in patients with LBP and the findings from existing clinical trials, further research is needed before vitamin D supplementation is recommended for the management of LBP.

Strengths and Limitations

This systematic review has numerous strengths. First, to get a comprehensive understanding of the relationship between vitamin D and LBP it was necessary to include different study designs in our review (cross-sectional, case-control, and case-series). In addition, although a number of studies (including abstracts) failed to publish adequate data for initial inclusion in our meta-analyses (n = 10), we contacted these authors and were able to obtain raw data from 5 studies which significantly strengthened the results of this review. Second, including conference abstracts and the abstracts of articles where the full text was not accessible reduced the risk of neglecting important data, while minimizing the risk of publication bias (70). Although the quality of these data is unknown, we conducted a number of sensitivity analyses, and the exclusion of studies where the full text was not accessible (including conference abstracts) did not influence the main findings of this review (Appendix 7).

This review has a number of limitations. First, most of the studies investigating the association between vitamin D and pain intensity in people with LBP used different statistical analyses and investigated different outcomes. This precluded the inclusion of all the data into one meta-analysis. Second, the majority of studies (n = 20) failed to adjust their findings for potential confounding variables (e.g., age, gender, sun exposure, skin type, use of supplementation, muscle strength), so we decided to use the unadjusted values in our meta-analyses for consistency and stratify our meta-analyses by age, gender, and cut-offs of vitamin D deficiency to investigate how these factors influence the relationship between vitamin D and LBP. Furthermore, we conducted a number of sensitivity analyses to investigate the influence of study geographical location and the presentation of LBP. Finally, there were no longitudinal studies investigating whether vitamin D deficiency increases the risk of developing LBP. Information from longitudinal studies is extremely valuable if vitamin D supplementation is to be considered a prevention strat-

egy for LBP in the future since cross-sectional studies cannot infer the temporal relationship between vitamin D levels and LBP (causation).

Conclusion

Vitamin D deficiency is associated with LBP, with stronger associations observed in younger women and those with severe levels of deficiency. The association between vitamin D levels and pain intensity is inconsistent. The findings from existing clinical trials do not support the use of vitamin D supplementation for the management of LBP. However, the results of this review have furthered our understanding on which populations demonstrate the greatest degree of vitamin D deficiency and may guide the implementation of future studies on vitamin D supplementation for LBP. In addition, although current evidence does not support the widespread screening of vitamin D levels in patients with LBP, clinicians should certainly consider this course of action for populations at increased risk of vitamin D deficiency (i.e., younger women and patients with chronic symptoms), as it is inexpensive, safe, and might improve symptoms. Further research evaluating the assessment and treatment of vitamin D deficiency will clarify their role in this difficult therapeutic area. Finally, longitudinal studies investigating whether vitamin D deficiency increases the risk of developing LBP are needed to determine the potential role of vitamin D in the prevention of LBP.

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 "alfacalcidol".mp "calcidiol".mp "calcitriol".mp "calcifediol".mp "calciferol".mp "ergocalciferol".mp exp Ergocalciferols/ "cholecalciferol".mp exp 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
Low back pain	exp Back Pain/ "back pain".mp "backpain".mp exp Low Back Pain/ "low back pain".mp "backache".mp "back ache".mp (lumbar adj5 pain).ti,ab "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

Appendix 1 (cont.). ***Search strategy.***

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
	21 and 35
EMBASE	Searches
Vitamin D	exp vitamin D/ "vitamin D".mp "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 "25 hydroxycholecalciferol".mp "25 hydroxyvitamin D".mp "alfacalcidol".mp "calcidiol".mp "calcitriol".mp "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

Appendix 1 (cont.). ***Search strategy.***

AMED	Searches
Vitamin D	exp Vitamin D/ "vitamin D".mp "vitamin D2".mp "vitamin D3".mp "1,25 dihydroxyvitamin D3".mp "25 hydroxycholecalciferol".mp "25 hydroxyvitamin D".mp "alfacalcidol".mp "calcidiol".mp "calcitriol".mp "calcifediol".mp "calciferol".mp "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 (lumbar adj5 pain).ti,ab "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") TITLE-ABS-KEY("1,25 dihydroxycholecalciferol") TITLE-ABS-KEY("1,25-dihydroxycholecalciferol") TITLE-ABS-KEY(25-hydroxycholecalciferol) TITLE-ABS-KEY("25 hydroxycholecalciferol") TITLE-ABS-KEY("25 hydroxyvitamin D") TITLE-ABS-KEY("25-hydroxy-vitamin D") TITLE-ABS-KEY(25-hydroxycholecalciferol) TITLE-ABS-KEY(alfacalcidol) TITLE-ABS-KEY(calcidiol) 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

Appendix 1 (cont.). ***Search strategy.***

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") TS=("1-alpha-hydroxy-calciferol") TS=("1,25 dihydroxyvitamin D3") TS=("1,25-dihydroxy-vitamin D3") TS=("1,25 dihydroxycholecalciferol") TS=("1,25-dihydroxycholecalciferol") TS=(25-hydroxycholecalciferol) TS=("25 hydroxycholecalciferol") TS=("25 hydroxyvitamin D") TS=("25-hydroxy-vitamin D") TS=(25-hydroxycholecalciferol) TS=(alfacalcidol) TS=(calcidiol) TS=(calcitriol) 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

Appendix 2. *Modified Downs and Black checklist and individual study scores.*

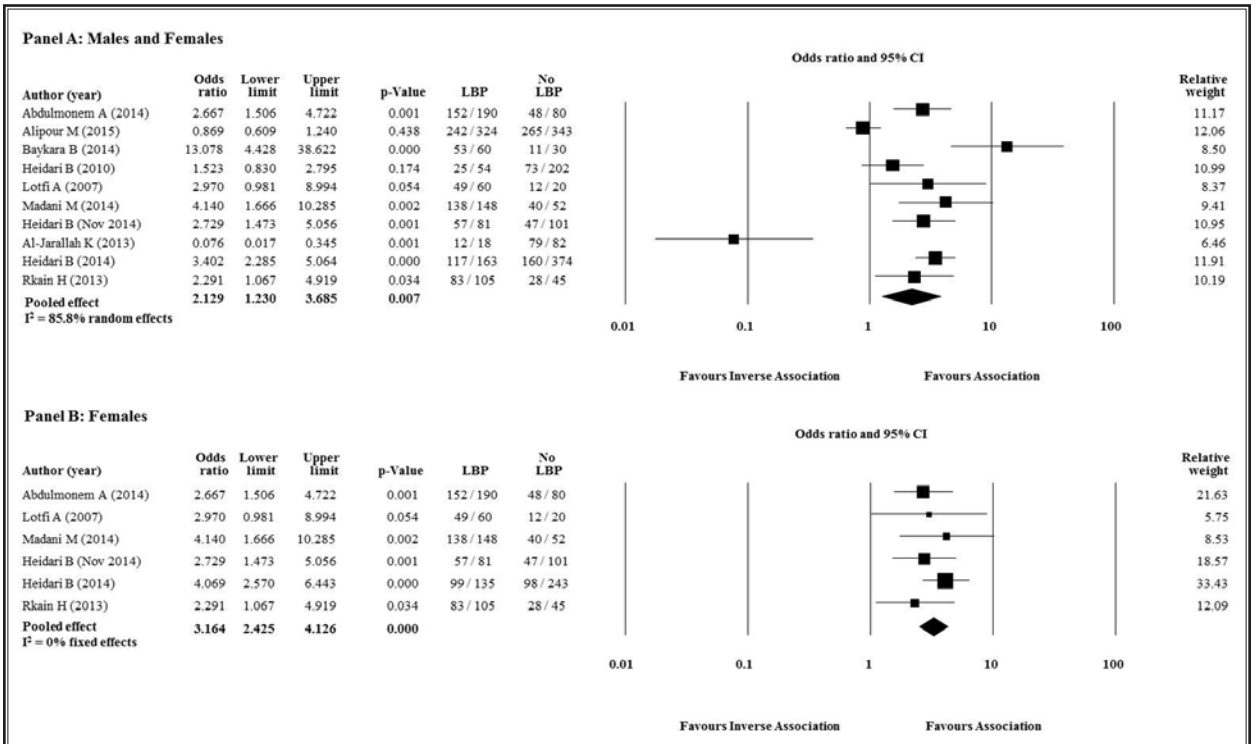
Downs and black checklist items (modified for the purpose of our review)	Scoring system
1. Is the hypothesis/aim/objective of the study clearly described?	Yes or no (1,0)
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes or no (1,0)
3. Are the characteristics of the patients included in the study clearly described?	Yes or no (1,0)
4. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes (2) Partially (1) No (0)
5. Are the main findings of the study clearly described?	Yes or no (1,0)
6. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes or no (1,0)
7. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	Yes or no (1,0)
8. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes or no (1,0). 0 if unable to determine
9. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes or no (1,0). 0 if unable to determine
10. If any of the results of the study were based on "data dredging", was this made clear?	Yes or no (1,0). 0 if unable to determine
11. Were the statistical tests used to assess the main outcomes appropriate? (assume appropriate if unable to determine)	Yes or no (1,0). 0 if unable to determine
12. Were the main outcome measures used accurate (valid and reliable)?	Yes or no (1,0). 0 if unable to determine
13. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes or no (1,0). 0 if unable to determine
14. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes or no (1,0). 0 if unable to determine
15. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes or no (1,0). 0 if unable to determine

Table 1. 'Downs and Black' checklist scores for included studies with an accessible full text.

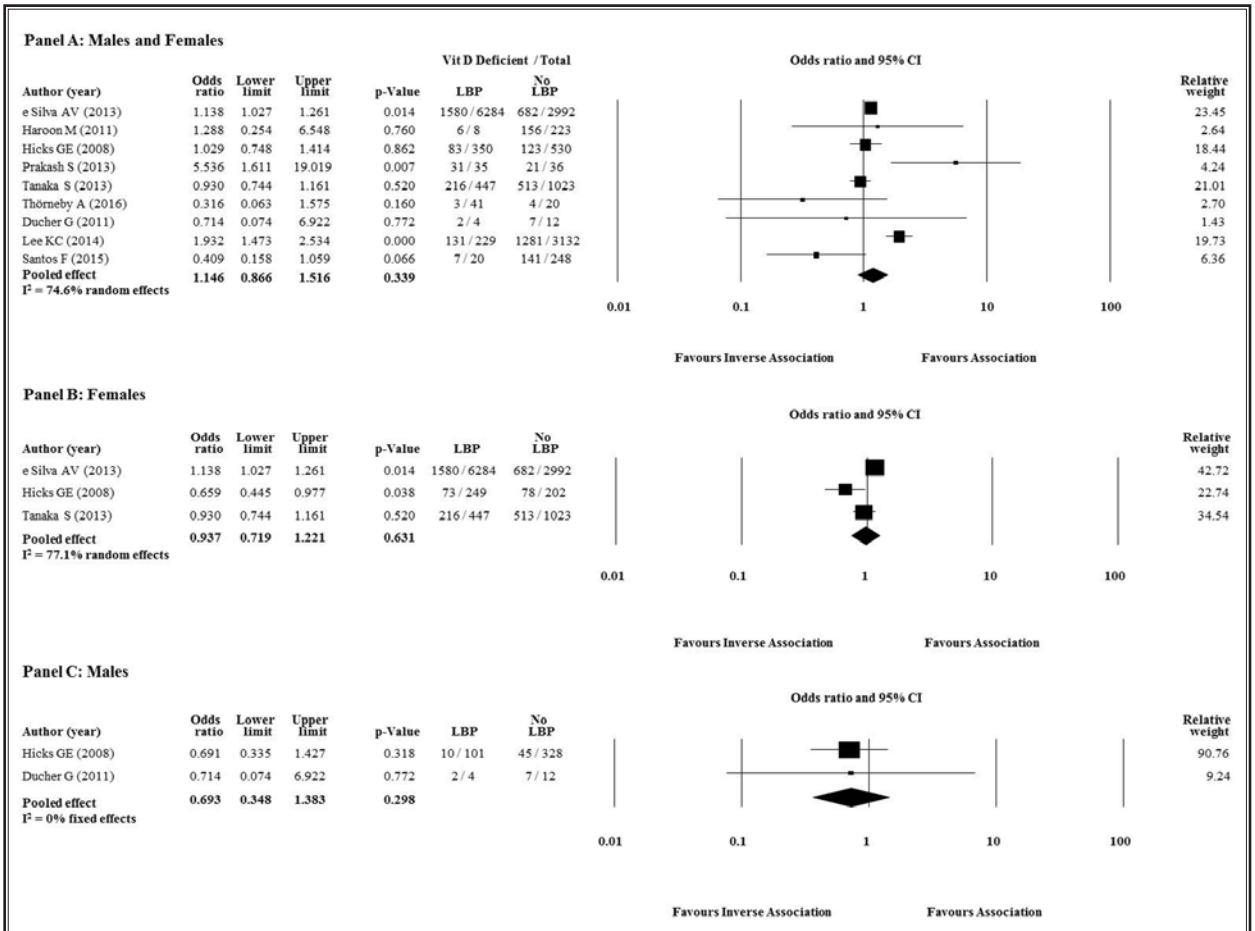
Author (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total (/16)
Abdulmonem A (2014)	1	0	1	0	1	1	1	1	0	0	1	0	1	1	0	9
Alipour M (2015)	1	1	1	1	1	1	1	1	0	0	1	0	1	1	0	11
Al-Jarallah K (2013)	1	1	1	0	1	1	0	1	0	0	1	0	0	1	0	8
Baykara B (2014)	1	1	1	2	1	1	1	0	0	0	1	1	0	1	0	11
Ducher G (2011)	1	1	1	0	1	1	0	1	0	0	1	1	1	1	0	10
e Silva A (2013)	1	0	1	2	1	1	1	1	0	0	1	0	1	1	0	11
Ghai B (2015)	1	1	1	2	1	1	1	1	0	0	1	1	1	1	0	13
Haroon M (2011)	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	11
Heidari B (Nov 2014)	1	1	1	0	1	1	1	1	0	0	1	1	1	1	0	11
Heidari B (2010)	1	1	1	0	1	1	1	1	0	0	1	1	1	1	0	11
Hicks G (2008)	1	1	1	2	1	1	1	1	0	0	1	1	1	1	1	14
Johansen J (2013)	1	1	1	0	1	1	0	1	0	0	1	1	1	1	0	10
Kim T (2013)	1	1	1	2	1	1	1	0	0	0	1	1	1	1	1	13
Kim T (2012)	1	1	1	0	1	1	1	1	0	0	1	1	1	1	0	11
Lodh M (2015)	1	1	1	0	1	1	1	1	0	0	1	0	0	1	0	9
Lotfi A (2007)	1	1	1	0	1	1	1	0	0	0	1	1	0	1	0	9
Madani M (2014)	1	1	1	0	1	1	1	1	0	0	1	1	1	1	0	11

Appendix 2 (cont.). *Modified Downs and Black checklist and individual study scores.*

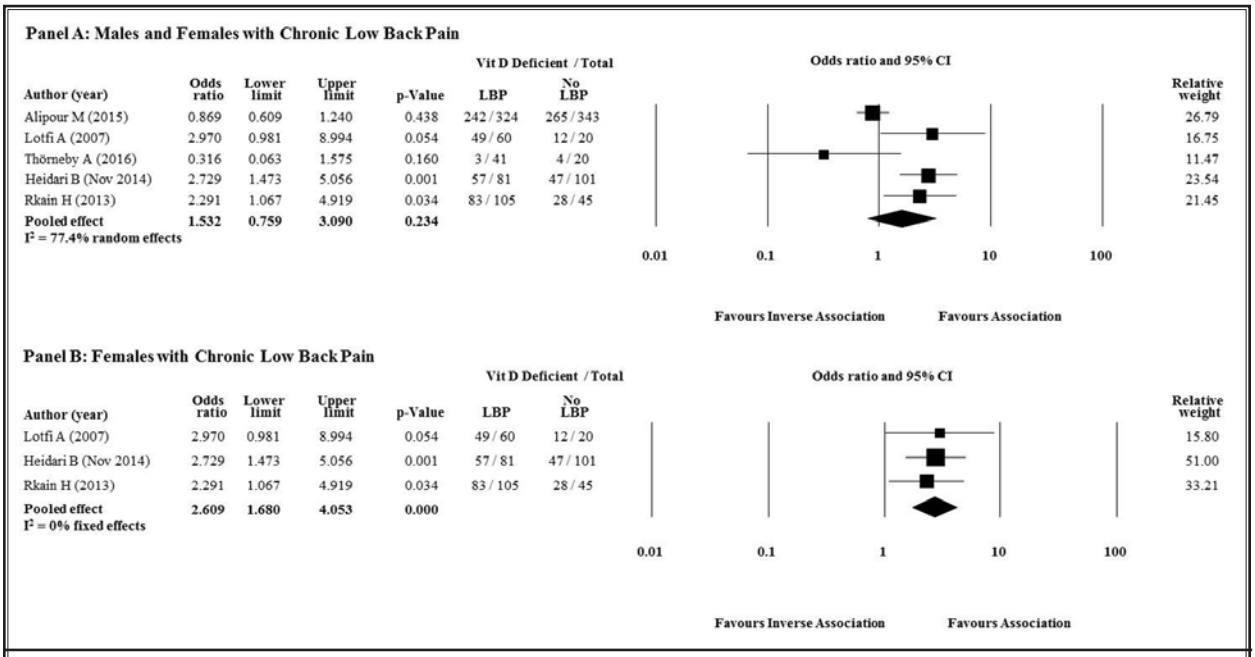
Prakash S (2013)	1	1	1	2	1	1	1	0	0	0	1	0	1	1	0	11
Santos F (2015)	1	1	1	0	1	0	1	1	0	0	1	1	1	1	0	10
Tanaka S (2013)	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	12
Thörneby A (2016)	1	1	1	2	1	1	1	0	0	0	1	1	1	1	1	13
Waltman N (2009)	1	1	1	0	1	0	0	0	0	0	1	1	1	1	0	8
Waikakul S (2012)	1	1	1	0	1	1	0	1	0	0	0	0	1	1	0	8



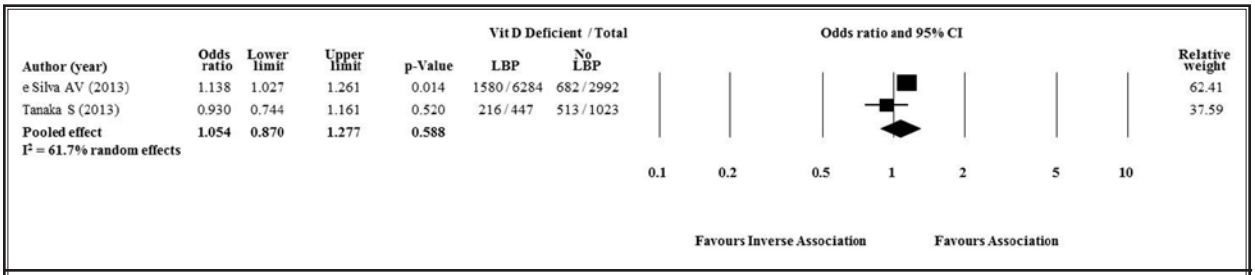
Appendix 3. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP in studies conducted in the Middle-East for women and men (A) and for women (B).*
LBP = low back pain; CI = confidence interval



Appendix 4. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP in studies conducted outside the Middle-East for women and men (A), women (B), and men (C).*
LBP = low back pain; CI = confidence interval



Appendix 5. *Pooled odds ratio (95% CI) for the association between vitamin D deficiency and chronic LBP for all of the included studies (A) and for women (B).*
LBP = low back pain; CI = confidence interval



Appendix 6. Pooled odds ratio (95% CI) for the association between vitamin D deficiency and LBP resulting from osteoporosis or low bone mass.
LBP = low back pain; CI = confidence interval

Appendix 7. *Pooled results excluding studies where the full text was not accessible.*

	ABSTRACTS INCLUDED (Main findings)					ABSTRACTS EXCLUDED*				
	Association between Vitamin D deficiency and LBP: excluding Lee KC (2014), Heidari B (2014) and Rkain H (2013)									
	Pooled OR	**95% CI**	***P***	**n**	**I^2**	**Pooled OR**	**95% CI**	***P***	**n**	**I^2**
All studies	1.60	1.20 - 2.12	0.001	19	84.9	1.42	1.05 - 1.91	0.023	16	80.9
Females	1.83	1.26 - 2.66	0.002	9	88.4	1.45	1.04 - 2.02	0.028	7	83.0
Males	1.06	0.62 - 1.81	0.832	3	44.9	0.69	0.35 - 1.38	0.298	2	0
Cut-off < 20 ng/mL	1.25	0.89 - 1.76	0.191	13	83.3	1.05	0.77 - 1.43	0.774	11	74.3
Cut-off < 10 – 12 ng/mL	2.08	1.19 - 3.64	0.010	7	77.8	2.21	0.92 - 5.28	0.075	6	79.5
	Association between serum 25(OH)D and LBP: excluding Heidari (2014) and Hussein K (2013)									
	Weighted MD	**95% CI**	***P***	**n**	**I^2**	**Weighted MD**	**95% CI**	***P***	**n**	**I^2**
All studies	3.86	0.20 - 7.52	0.039	12	87.1	2.93	-1.36 - 7.21	0.181	10	84.4
Females	7.64	4.02 - 11.26	< 0.001	4	64.6	8.06	2.07 - 14.05	0.008	3	74.9

LBP: low back pain; OR: odds ratio; MD: mean difference; CI: confidence interval; n: number of included studies. *: a number of analyses are missing from this table because the original pooled results didn't include any studies where the full-text was not accessible.

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Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, Charlson F, Davis A, Degenhardt L, Dicker D, Duan L, Erskine H, Feigin VL, Ferrari AJ, Fitzmaurice C, Fleming T, Graetz N, Guinovart C, Haagsma J, Hansen GM, Hanson SW, Heuton KR, Higashi H, Kassebaum N, Kyu H, Laurie E, Liang X, Lofgren K, Lozano R, MacIntyre MF, Moradi-Lakeh M, Naghavi M, Nguyen G, Odell S, Ortblad K, Roberts DA, Roth GA, Sandar L, Serina PT, Stanaway JD, Steiner C, Thomas B, Vollset SE, Whiteford H, Wolock TM, Ye P, Zhou M, Āvila MA, Aasvang GM, Abbafati C, Ozgoren AA, Abd-Allah F, Aziz MIA, Abera SF, Aboyans V, Abraham JP, Abraham B, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NME, Aburto TC, Achoki T, Ackerman IN, Adelekan A, Ademi Z, Adou AK, Adsuar JC, Arnlov J, Agardh EE, Al Khabouri MJ, Alam SS, Alasfoor D, Albittar MI, Alegretti MA, Aleman AV, Alemu ZA, Alfonso-Cristancho R, Alhabib S, Ali R, Alla F, Allebeck P, Allen PJ, AlMazroa MA, Alsharif U, Alvarez E, Alvis-Guzman N, Ameli O, Amini H, Ammar 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