Mapping the association between Vitamin D and low back pain: a systematic review and meta-analysis of observational studies.

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ABSTRACT

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 neuro-modulatory 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: 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 people with and without LBP, or adequate data on pain intensity in people with LBP. No restriction on the type or duration of LBP, nor the age and gender of participants 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, nine 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 females but failed to be statistically significant for males (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 people <60 years old (particularly females). We found minimal evidence to support an association between Vitamin D levels and pain intensity in people 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(s): Vitamin D deficiency is associated with LBP, with stronger associations observed in younger females 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.

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

Introduction

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 prevalence and risk of developing LBP is needed to guide future intervention strategies.

A previous history of LBP appears to be 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 people 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 females (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 individuals 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 earliest record 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 (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 reviewers used a study eligibility form based on items from the inclusion/exclusion criteria, and resolved 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 participants. 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 randomised and non-randomised trials.

Methodological Quality

The methodological quality of the included studies with an accessible full text was independently assessed by two 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 standardised data extraction form to independently extract the data from included studies. Data on participants' 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

Data on the most relevant statistics to measure the association between Vitamin D and LBP (MD or OR), or association between Vitamin D and pain intensity in people with LBP (MD, OR, r, ρ), and their 95% 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. 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 (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 individuals 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. Authors 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 three articles (34-36) identified through hand-searching the reference lists of included studies (Fig 1). Following the removal of duplicates, two 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 participants) were eligible for inclusion in this review, including 19 cross-sectional studies (including four conference abstracts), nine case-control studies, and one single arm surgical trial where we used the pre-operative data in our analyses. The full texts of two included case-control studies (37, 38) could not be obtained so we used the data included in the abstracts for our review. There were no longitudinal studies that met our inclusion criteria. 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 participants who reported LBP of any duration (eight studies only included participants with non-specific LBP), and eight studies including participants with chronic LBP (four studies only included participants with non-specific chronic LBP). We defined chronic LBP as pain lasting for at least 3 months (39) and operationalized this over all studies, regardless of the authors' classification. The remaining four studies included participants with lumbar spinal stenosis (n=1), participants seeking spinal surgery (n=2), or

participants 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 participants from either Health/Medical Centres, or outpatient/Rheumatology clinics (n=16) (Table 1). The sample size of individual studies ranged from 9 to 9305 participants. 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 <20ng/mL as an indicator of deficiency, nine studies using serum 25(OH)D between 20-30ng/mL as an indicator of insufficiency, and nine studies considering serum 25(OH)D >30ng/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 <10ng/mL (four studies) (range: 5-15ng/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 five categories: study quality (seven items), external validity (two items), study

bias (three items), and confounding and selection bias (three 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 studies) and adjust for potential confounders (n=20), failing to report that subjects 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).

Association between Vitamin D deficiency and low back pain

The pooled results from 19 studies (11 cross-sectional and eight 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 individuals with LBP are more likely to have Vitamin D deficiency compared to those without LBP. This association was stronger for females (pooled OR=1.83, 95%CI: 1.26-2.66, p=0.002, n=9), but failed to be statistically significant for males (pooled OR=1.06, 95%CI: 0.62-1.81, p=0.213, n=3) (Fig 3). We further stratified our meta-analyses by age and cut-offs for Vitamin D deficiency.

The age of participants varied substantially between 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 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 females <60 years old (pooled OR=2.91, 95%CI: 2.03-4.17, p<0.001, n=4), but no association in females >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 males between 65-102 years old in one study (OR=0.69, 95%CI: 0.34-1.43, p=0.318) (21), and in males between 10-19 years old in another study (OR=3.67, 95%CI: 0.17-77.56, p=0.404) (Table 2) (42). Neither 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 <20ng/mL (one study used <21ng/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 seven studies that used <10ng/mL as a cut-off (two studies used <12ng/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 low back pain

There were 12 studies (four cross-sectional and eight case-control studies) that investigated the association between serum concentrations of 25(OH)D (continuous measure) and LBP. The pooled results from all studies (Fig 7), and studies investigating females (Fig 7) and individuals <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 results for males, or individuals >60 years old.

Association between Vitamin D deficiency and pain intensity

There was a significant association between Vitamin 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 people 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 individuals 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 females, and in those <60 years old. On the other hand, there is conflicting evidence that Vitamin D deficiency influences pain intensity in people with LBP.

Association between Vitamin D and low back pain

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 females (<60 years old). However, the geographical location of included studies may partially explain these results so we conducted a number of sensitivity analyses to explore this issue. There was a strong association between Vitamin D deficiency 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 nine studies conducted outside the Middle-East/Mediterranean region (Appendix 4). Since all of the studies investigating the association between Vitamin D deficiency and LBP in younger females 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 the studies investigating the association between Vitamin D deficiency and LBP in females >60 years old were conducted outside of 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 females could be related to a higher number of studies including females (females: n=13; males: 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 females where age and hormonal-related bone density loss (52) can increase the risk of osteoporosis (53), potentially resulting in pain. Therefore, investigating associations between Vitamin D deficiency and health conditions (such as LBP) in females may be considered a research priority and explain the higher number of studies in females. A limited number of studies in males 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 females 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 available studies. However, there was a strong association between Vitamin D deficiency and chronic LBP in females (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 <10-12ng/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 management 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 people already suffering from LBP. We were only able to pool results from four studies and the findings

appear to be dictated by how the variables were analysed. There was a significant association between mean Vitamin D levels (continuous) and severe pain (dichotomous), but 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 randomised 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 differences in their intervention dosage (10-179ug per day) and duration (6-16 weeks), and despite the Vitamin D3 groups achieving normal 25(OH)D concentrations post-intervention (>20ng/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 people 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 five 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 minimising 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 strategy 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 females 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 individuals with LBP, clinicians should certainly consider this course of action for populations at increased risk of Vitamin D deficiency (i.e. younger females and individuals 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.

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Figure legends

Fig. 1 PRISMA flow diagram

LBP: low back pain

Fig. 2 Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP for all included studies

LBP: low back pain; CI: confidence interval

Fig. 3 Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP for females (A) and males (B)

LBP: low back pain; CI: confidence interval

Fig. 4 Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP in cohorts with a mean age <60 years olds (A) and > 60 years old (B)

LBP: low back pain; CI: confidence interval

Fig. 5 Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP in female cohorts with a mean age <60 years olds (A) and > 60 years old (B)

LBP: low back pain; CI: confidence interval

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

LBP: low back pain; CI: confidence interval

Fig. 7 Pooled odds ratio (95% confidence interval) for the association between association between serum concentrations of 25(OH)D and LBP for all included studies (A) and for females (B)

LBP: low back pain; CI: confidence interval

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

LBP: low back pain; CI: confidence interval

Fig. 9 Weighted mean difference (95% confidence interval) 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% confidence interval) for the association between mean pain intensity and Vitamin D deficiency

CI: confidence interval

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

CI: confidence interval

Appendices

Appendix 1. Search strategy

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

Appendix 3. Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP in studies conducted in the Middle-East for females and males (A) and for females (B)

LBP: low back pain; CI: confidence interval

Appendix 4. Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and LBP in studies conducted outside the Middle-East for females and males (A), females (B), and males (C)

LBP: low back pain; CI: confidence interval

Appendix 5. Pooled odds ratio (95% confidence interval) for the association between Vitamin D deficiency and chronic LBP for all included studies (A) and for females (B)

LBP: low back pain; CI: confidence interval

Appendix 6. Pooled odds ratio (95% confidence interval) 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