Observational Study

Is Serum Hypovitaminosis D Associated with Chronic Widespread Pain Including Fibromyalgia? A Meta-analysis of Observational Studies

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Background: Chronic widespread pain (CWP) is a global musculoskeletal disorder leading to disability and a reduced quality of life. Low levels of serum vitamin D has long been proposed to be associated with CWP, but previous research remains inconclusive.

Objectives: To determine whether hypovitaminosis D was independently associated with CWP.

Study Design: Meta-analysis of observational study.

Methods: Electronic databases were searched for studies published up to November 2014 comparing the prevalence of hypovitaminosis D and serum vitamin D levels between participants with and without CWP. The crude and adjusted odds ratios (ORs) of hypovitaminosis D with CWP were calculated. Subgroup analysis according to gender, threshold of hypovitaminosis, and definition of patients was performed, as well as meta-regression to test the linear relationship between crude ORs and the latitude of study locations.

Results: Twelve studies were included, comprising 1,854 patients with CWP. The patient group showed a significantly higher risk of hypovitaminosis D than the control group (crude OR, 1.63; 95% CI, 1.20 – 2.23). The association was slightly attenuated after adjusting confounders, with a pooled adjusted OR of 1.41 (95% CI, 1.00 – 2.00). There was an increase in ORs of hypovitaminosis D using a lower diagnostic value of serum vitamin D (8 and 10 ng/mL). The subgroup analysis according to gender and definition of CWP did not reveal significant between-group differences. The meta-regression showed no linear relationship between latitude and the crude ORs.

Conclusions: There was a positive crude association between hypovitaminosis D and CWP, and the association was likely to remain after adjusting confounding factors. Use of a cut-off value of hypovitaminosis D (8 – 10 ng/mL) could better define the population with and without CWP. Further prospective follow-up studies are warranted to clarify the causal relationship between hypovitaminosis D and CWP.

Key words: Vitamin D, fibromyalgia, chronic widespread pain, meta-analysis

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Chronic widespread pain (CWP), including fibromyalgia, is a global musculoskeletal disorder leading to disability and a reduced quality of life, and has a prevalence ranging from 10% to 18% in the general population (1,2). Concomitant somatic symptoms may present as complaints of circulatory, respiratory, and neurological system problems and impose a tremendous burden on psychosocial and medical care resources (3). The exact pathophysiology remains unclear and possible causal mechanisms include central sensitization of pain perception and reduced levels of anti-inflammatory cytokines (4,5). Vitamin D, a hormone precursor essential for maintaining homeostasis of the musculoskeletal system, has long been proposed as an associated factor in CWP. The most severe type of hypovitaminosis D, osteomalacia, features generalized body pain, especially in the shoulder, rib cage, and lumbar and pelvic regions. The biological relationship between CWP and vitamin D deficiency is still under investigation, and may be mediated through vitamin D receptors on muscle tissues and vitamin D's regulatory role in autoimmune responses (6). A number of studies have been conducted to explore the association of low levels of serum vitamin D with diffuse musculoskeletal pain, including fibromyalgia, but the results appear inconclusive. The potential causes of the controversial outcomes were heterogeneity in the study and reference population, different thresholds of defining hypovitaminosis D, and the presence of confounding factors. Therefore, the present meta-analysis aimed to determine whether hypovitaminosis D was associated with CWP syndrome and also investigate whether the association was independent of confounders known to affect vitamin D metabolism.

Methods

Selection Criteria

We searched 2 online databases, PubMed and Scopus, from the earliest record to September 2014. PubMed was used based on its open access and wide coverage of biomedical literature, and Scopus was used to ensure that all the relevant studies were included. We manually scrutinized the Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov, and bibliographies of included trials and related reviews for pertinent references. We included all observational studies comparing the prevalence of hypovitaminosis D or serum vitamin D levels between participants with and without CWP. The key terms used were vitamin D, pain, and fibromyalgia, and they were entered as medical subject headings and key words for searches.

We excluded case reports, case series, and single-arm, longitudinal follow-up studies. Studies investigating localized pain syndrome, such as tension headache and migraine, were not included. Each of the retrieved trials was required to measure the prevalence of hypovitaminosis D or the distribution of serum 25-(OH) vitamin D levels in the patient and reference groups. The definition of CWP was derived from the American College of Rheumatology criteria for fibromyalgia syndrome (6), and was defined as persistent diffuse pain over 2 contra-lateral body quadrants and axial skeletons for at least 2 months. The information regarding pain was ascertained by questionnaires using blank body manikins or interviews with physical examinations.

Data Extraction and Quality Assessment

All eligible reports were independently reviewed by 2 authors. The data extracted from the selected studies included demographics of the patient and reference groups, countries or cities where the research was conducted, criteria for diagnosing CWP syndrome, methods for measuring vitamin D levels, and definition of hypovitaminosis D. The Newcastle-Ottawa scale, a risk of bias assessment tool for observational studies, was used to evaluate the quality of participant selection, comparability between the patient and reference groups and the ascertainment of exposure and outcome (7-10). The maximum scores given were 9 points and articles with 4 points or less were considered low in quality. Discrepancies in evaluations between the 2 reviewers were resolved through discussion or the judgment of the corresponding author; the quality assessment results are listed in Table 1.

Data Synthesis and Analysis

The primary outcome was expressed by the odds ratio (OR): the odds of patients with serum vitamin D less than a defined level in the patient group divided by the odds of hypovitaminosis D in the reference group. Values exceeding one indicated a positive association of hypovitaminosis D with CWP. Besides crude ORs, we also synthesized the ORs adjusted for confounding factors. The adjusted covariates varied across studies and comprised gender, sunlight exposure, social status, cigarette smoking, alcohol consumption, physical activities, and dietary supplement. The mean values of serum

Table 1.*Summary of included studies*

Author, Year	Study Design	Area/ Country Latitude	Season of Measurement	Age of Patients (years)	Age of Controls (years)	Gender (M, F, Mixed)	Definition of CWP	Patient Characteristics	Control Characteristics	Patient Number	Control Number	Threshold of Hypo-Vitamin D (ng/ml)	Newcastle-Ottawa Scale
Al-Allaf, A. W., 2003	Cross section, observational	Dundee, UK 56, N	Not mentioned	42.5 ± 3.6	42.5 ± 4.3	F	ACR 1990 criteria	FM, premenopausal	Healthy subjects; age and sex matched	40	37	8	7
Macfarlane, G. J., 2005	Cross section, observational	Greater Manchester, UK 53.5, N	Not mentioned	18-36	18-36	F	CWP in ACR 1990 criteria	CWP, in screening survey of South Asians(India, Pakistan, Bangladeshi) and white Europeans	Screening survey of South Asians(India, Pakistan, Bangladeshi) and white Europeans	8	101	10	7
Warner, A. E., 2008	Cross section, observational[a]	Kansas, USA 39.6, N	May-Aug	54.4 ± 11.7	66.4 ± 10.5	Mixed	ACR 1990 criteria, tenderness not systemically evaluated	FM	Osteoarthritis (< = 3 peripheral joints); age and sex not matched	184	104	20	5
Tandeter, H., 2009	Cross section, observational	Beer Sheva, Israel 31.15, N	Not mentioned	43.83 ± 7.57	40.37 ± 9.85	F	ACR 1990 criteria	FM, premenopausal	Subjects attended for regular blood test in the same clinic; age and sex matched	68	82	20	6
Atherton, K., 2009	Cross section, observational	Scotland and Wales, UK 52~56, N	Sep-Mar	45	45	Mixed	CWP in ACR 1990 criteria	CWP, in biomedical survey of the nationwide 1958 British birth cohort	Subjects in the same biomedical survey of the nationwide 1958 British birth cohort	743	5593	20	7
de Rezende Pena, C., 2010	Cross section, observational	Santa Catarina, Brazil 26.0, S	Nov-Jan	18-60, 44.87 ± 8.57	18-60, 32.03 ± 10.52	Mixed	ACR 1990 criteria	FM	Subjects from the same source with no chronic musculoskeletal pain	87	92	15	5
McBeth, J., 2010	Cross section, observational	Italy, Belgium, Poland, Sweden, UK, Spain, Hungary, Estonia	Not mentioned	40-79	40-79	M	CWP in ACR 1990 criteria	CWP, in population-based sampling questionnaire	No pain in population-based sampling questionnaire	263	1262	20	7

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

Author, Year	Study Design	Area/ Country Latitude	Season of Measurement	Age of Patients (years)	Age of Controls (years)	Gender (M, F, Mixed)	Definition of CWP	Patient Characteristics	Control Characteristics	Patient Number	Control Number	Threshold of Hypo-Vitamin D (ng/ml)	Newcastle-Ottawa Scale
Heidari, B., 2010	Cross section, observational	Babol, Iran	May-Jun	44.3 ± 15	46.4 ± 14.2	Mixed	Nonspecific skeletal pain (> = 2 months), persist tenderness at 2 visits 2 weeks apart; FM by ACR 1990 criteria	Nonspecific widespread pain and FM	Subjects attended for laboratory check-up, urinary tract infection or dyspepsia (< = 4 weeks) in the same clinic	42	202	15	6
Al-Jarallah, K., 2013	Cross section, observational	Mubarak Al-Kabeer, Kuwait	May-Jan	41.71 ± 13.86	43.73 ± 7.40	Mixed	ACR 1990 criteria	FM	Healthy subjects	124	82	20	6
Okumus, M., 2013	Cross section, observational	Ankara, Turkey	Nov-Mar	41.23 ± 4.8	39.48 ± 4.08	F	ACR 1990 criteria	FM, premenopausal	Mechanical low back pain, tendonitis; age and sex matched	40	40	NA	5
Olama, S. M., 2013	Cross section, observational	Mansoura, Egypt	May-July	32.3 ± 9.4	33.1 ± 9.7	F	ACR 1990 criteria	FM, premenopausal	Healthy subjects; age and sex matched	50	50	20	7
Mateos, F., 2014	Cross section, observational	Northern Spain	Nov-Dec	51 ± 9.6	51.3 ± 9.9	F	Not mentioned	FM	Subjects from another primary care center; age and time matched	205	205	8	5

Note: Abbreviation: N, north; S, south; M, male; F, female; ACR, The American College of Rheumatology; CWP, chronic widespread pain; FM, fibromyalgia; NA, not applicable.

vitamin D were pooled separately in the patient and reference groups, and the absence of overlaps of their 95% confidence intervals (CIs) was defined as a significant between-group difference.

We used random-effects meta-analyses to estimate pooled ORs and mean serum vitamin D levels along with their 95% CIs. Heterogeneity across studies was assessed with the Cochran Q statistic ($\chi 2$) and I square test, and a P value < 0.1 for chi-squared testing of the Q statistic or a I square > 50% was regarded as significant heterogeneity (11). We performed subgroup analyses based on gender, threshold of hypovitaminosis D, and definition of the patient groups. A meta-regression was used to test whether the pooled OR was correlated to the latitude where the studies were conducted (12). The visual inspection of funnel plots and the Begg-Mazumdar test were used to detect publication bias, defined as the tendency for positive trials to be published and for negative and null trials to remain unpublished (12). All analyses were conducted with STATA software version 10.0 (STATA Corporation, College Station, TX, USA). All P values were 2-sided and $P < 0.05$ was considered statistically significant, except those for testing between-study heterogeneity.

Results

Characteristics of Included Studies

Of the 291 non-duplicate articles identified from the literature search, 37 observational studies were screened for eligibility (Fig. 1). The excluded citations were 13 studies that enrolled only patients, without a reference group, and 7 studies in which the chosen patients failed to meet our selection criteria. The final meta-analysis comprised 12 refer-

ences (13-24), 8 of which enrolled patients with a definite diagnosis of fibromyalgia syndrome (13-20) and 4 of which investigated participants presenting CWP (21-24). Regarding the outcome measurements, crude and adjusted ORs of hypovitaminosis D were extracted from 9 (13,14,16,18-20,22-24) and 3 (21,22,24) included studies, respectively, whereas the mean values of serum vitamin D were reported in 7 studies (13,15,17-20,22).

Participant Characteristics in the Included Studies

The 12 included studies comprised 1,854 patients with CWP and 7,850 control participants. Most studies enrolled people with no symptoms of pain as controls; only one study recruited patients with osteoarthritis (20) and one recruited patients with mechanical low back pain in the reference group (13). Six studies focused on women (13,14,17-19,23), 5 included both genders (15,16,20-22), and only one study investigated men (24). The mean age of the patients ranged from 32.3 to 51.3 years. The threshold for defining hypovitaminosis varied among citations; 20 ng/mL was the most used value. The quality assessment results for the retrieved studies are listed in Table 1.

The Association of Hypovitaminosis D with Fibromyalgia Syndrome and CWP

The crude ORs of hypovitaminosis D in the patient population and those in the reference group were extracted from 9 studies (13,14,16,18-20,22-24), involving a total of 2,735 participants. In the unadjusted analysis, the patient group showed a significantly higher risk of

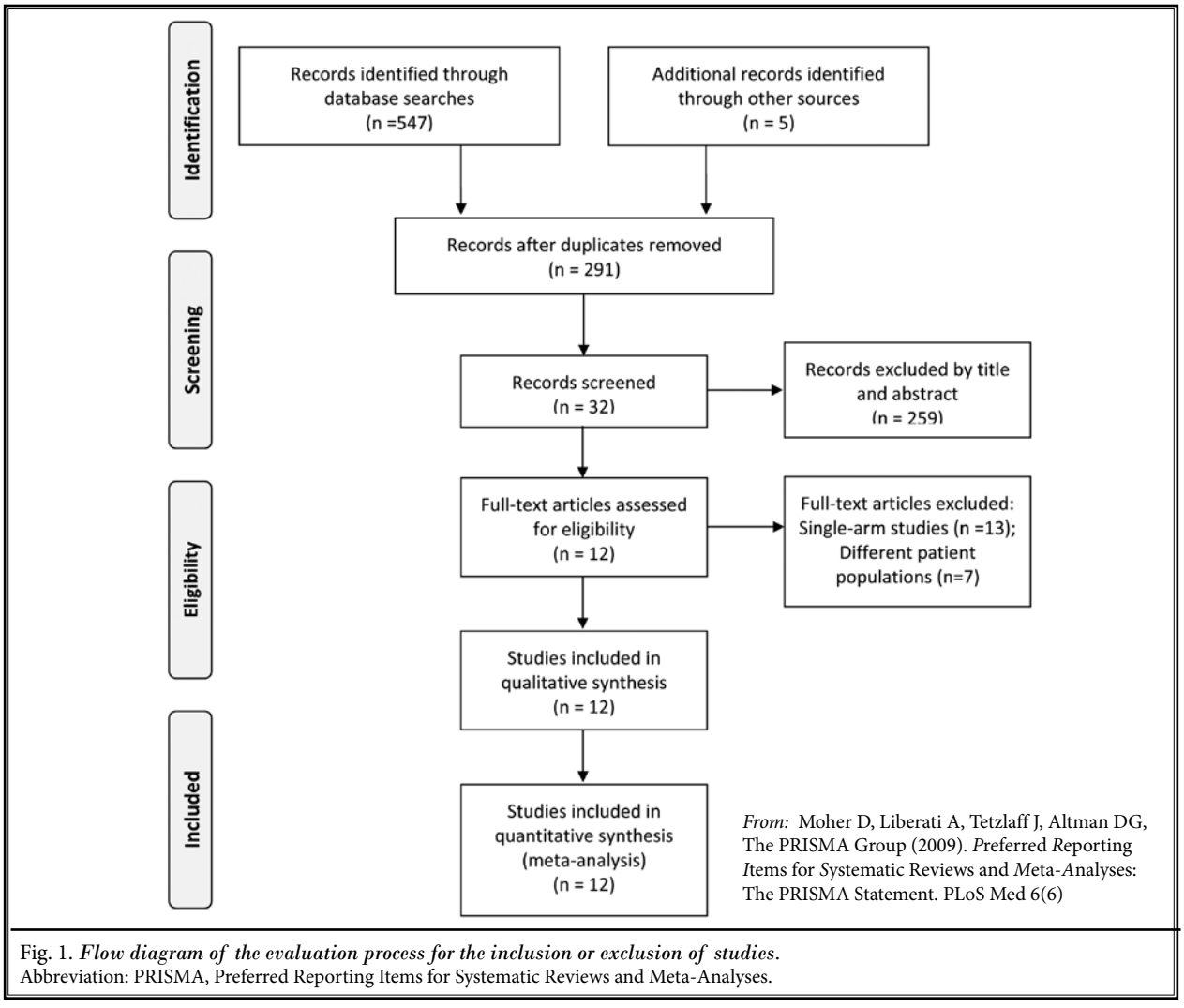

Fig. 1. *Flow diagram of the evaluation process for the inclusion or exclusion of studies.*
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

hypovitaminosis D (OR, 1.63; 95% CI, 1.20 – 2.23 [*P* = 0.117, I2 = 37.8%]) (Fig. 2). The subgroup analysis based on different genders and the populations with or without defined fibromyagia did not reveal significant between-group differences in ORs (Table 2). However, in terms of the diagnostic threshold, a lower value of serum vitamin D (8 and 10 ng/mL) {was likely to be associated with increased ORs of hypovitaminosis D compared to a higher value of serum vitamin D (15 and 20 ng/mL) (Table 2). Three studies provided adjusted ORs (21,22,24), one of which reported its results in men and women, respectively (21). The association of hypovitaminosis D with CWP was slightly attenuated after adjustment for confounders, with a pooled OR of 1.41 (95% CI, 1.00 – 2.00 [*P* = 0.059, I2 = 59.7%]) (Fig. 3). The meta-regression failed to identify potential influences of latitude on the unadjusted ORs of hypovitaminosis D (Fig. 4). We did not conduct the meta-regression for the adjusted OR due to the small amount of data available for analysis. Regarding the mean serum vitamin D level, which was reported in 7 studies, the pooled value in the patient population (15.48 ng/mL; 95% CI, 9.81 – 21.16) was similar to that in the controls (16.50 ng/mL; 95% CI, 11.08 – 21.93), due to a substantial overlap of their 95% CIs (Fig. 5). Neither significant publication bias (*P* > 0.05 determined by Begg's test) nor funnel plot asymmetry was detected in terms of unadjusted and adjusted ORs (Fig. 6). However, funnel plot asymmetry and significant publication bias existed in the reporting of mean serum vitamin D levels in both the patient and control groups (Fig. 6).

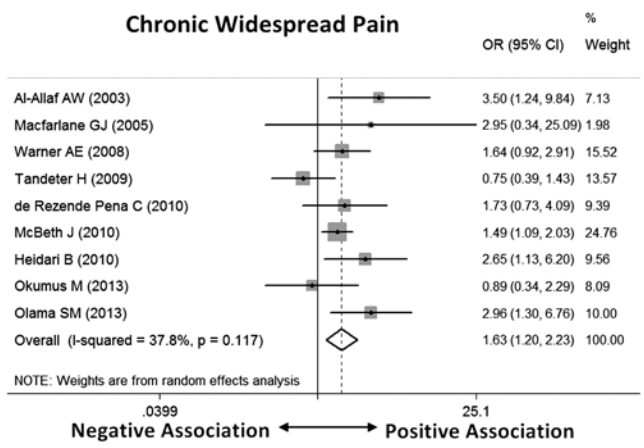

Fig. 2. *Forest plot of crude ORs of CWP with hypovitaminosis D.*

Table 2. *Subgroup analysis of the crude odds ratios (ORs) of hypovitaminosis D with chronic widespread pain (CWP) stratified by gender, threshold of hypovitaminosis D and definition of patient and reference groups.*

Subgroup	Crude odds ratio
Gender	
Male	1.49 (1.09, 2.03)
Female	1.64 (0.79, 3.41)
Mixed	1.86 (1.23, 2.83)
Threshold of hypovitaminosis D (ng/mL)	
8	3.5 (1.24, 9.86)
10	2.95 (0.34, 25.34)
15	1.41 (1.04, 1.92)
20	1.68 (1.03, 2.74)
Definition of patient group	
With defined fibromyalgia	1.61 (1.03, 2.52)
Without defined fibromyalgia	1.72 (1.06, 2.82)
Definition of reference group	
Asymptomatic	1.78 (1.19, 2.66)
Localized pain	1.37 (0.79, 2.36)

Note: The values were expressed by their point estimates with a 95% confidence interval.

Discussion

Our meta-analysis, employing data from 12 studies involving 1,854 patients and 7,850 controls, found that participants with CWP were associated with serum hypovitaminosis D and the association was likely to exist after adjusting potential confounding factors. The differences in gender and geographical latitude in which the research was conducted did not pose a significant influence on the association, whereas the studies using a lower serum vitamin D level as the diagnostic threshold of hypovitaminosis D tended to have a higher magnitude of associations.

For decades, there have been debates about whether hypovitaminosis D was related to CWP. A brief review by Heath and Elovic (25) had noted a correlation between vitamin D deficiency and musculoskeletal pain but the evidence was based on several case series and single-arm observational studies. Two systematic reviews in 2009 and 2011 addressed this issue and their results were inconclusive (26,27). The main

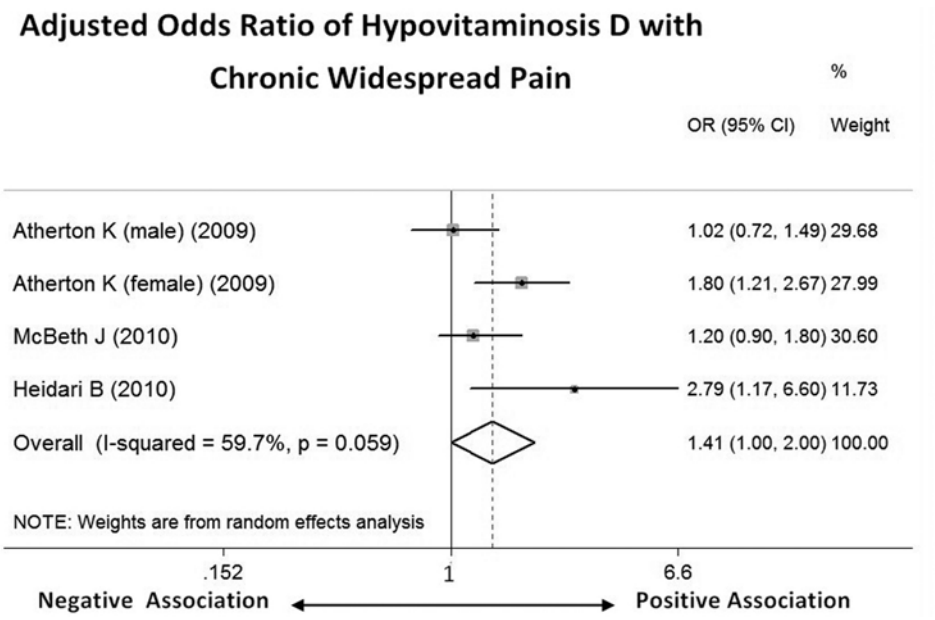

Fig. 3. *Forest plot of adjusted ORs of CWP with hypovitaminosis D.*

reasons included heterogeneity in study designs and limited numbers of enrolled trials. In addition, both reviews included participants with rheumatologic conditions like rheumatoid arthritis or localized musculoskeletal pain syndrome along with CWP. None of them proceeded to quantitative analysis. To our knowledge, this is the first meta-analysis providing integrated data regarding the comparison of serum hypovitaminosis D between participants with and without CWP.

Our meta-analysis found a positive crude association between CWP and hypovitaminosis D. The results came from observational studies, which could not infer any causal relationship. Among the 9 studies in which crude ORs were available (13,14,16,18-20,22-24), the point estimates of the ORs were found positive in 7 studies (14,16,18,20,22-24), only 4 of which claimed a significant association between CWP and hypovitaminosis D (14,18,22,24). Possible reasons for the lack of statistical significance in the remaining 5 studies (13,16,19,20,23) included small numbers of participants, various definitions of the patient population, heterogeneity of the control participants, and lack of a standardized cut-off value for hypovitaminosis D. Besides, numerous factors are known to affect the serum vitamin D level, including age, gender, and latitudes of study location (28,29).

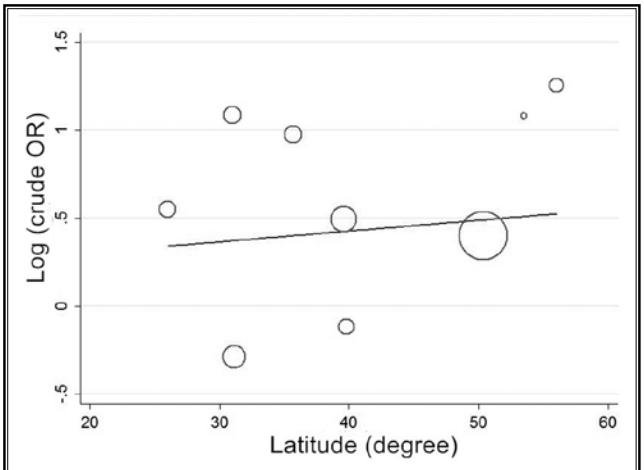

Fig. 4. *Meta-regression plot of the crude ORs with latitudes.*

Our results indicated no significant differences in the crude ORs between the patient populations using patients with defined fibromyalgia syndrome and those without, as well as between the reference groups recruiting asymptomatic participants and patients with localized pain (Table 2). Furthermore, female gender is well recognized for having a higher prevalence of fibromyalgia syndrome (30), but our study did not identify a difference in crude

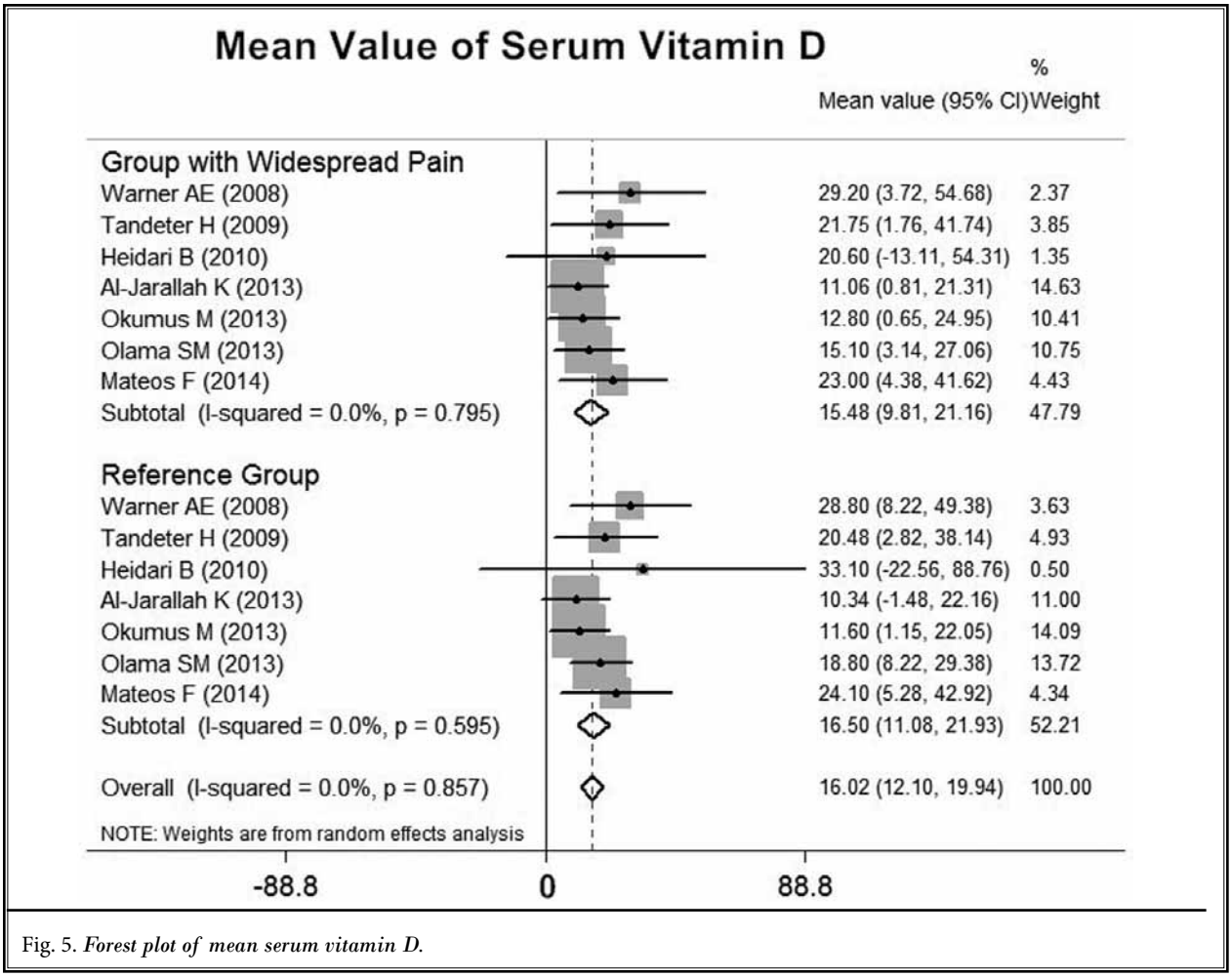

Fig. 5. *Forest plot of mean serum vitamin D.*

ORs between distinct gender groups. Although vitamin D is produced from sunlight substantially dependent on the latitude of study locations, our meta-regression failed to show a linear relationship between the crude ORs and latitudes.

Another important finding was that lower values (8 – 10 ng/mL) of serum vitamin D as the hypovitaminosis threshold tended to have higher crude ORs. This was consistent with the research conducted by Atherton et al (21), in which participants were stratified according to different hypovitaminosis thresholds ranging from 10 to 40ng/mL, and demonstrated higher adjusted ORs in the subgroups with a lower range of serum vitamin D. Of note, our data revealed that the pooled mean serum vitamin D levels in the patient and reference groups were 15.48 and 16.02ng/mL, respectively, both lower than the commonly used diagnostic threshold of 20ng/mL. Several reports indicated that 20ng/mL of serum vitamin D was the minimal level to achieve a normal serum parathyroid hormone concentration (31,32). Our analysis revealed that even in the asymptomatic population, physiological vitamin D insufficiency was also prevalent, and a value less than 10ng/mL might be a better diagnostic threshold of hypovitaminosis D to discriminate between participants with and without CWP.

Three of our retrieved citations reported adjusted ORs (21,22,24), the pooled value of which was slightly lower than the crude OR, but borderline statistical significance remained. Multiple known causes such as age, gender, body composition, sun exposure, skin pigmentation, smoking and alcohol consumption, medications, and cultural factors such as veiling can affect the intake or skin production of vitamin D. Of the 3 studies, Heidari et al (22) adjusted the influence of gender difference, and McBeth et al (24) and Atherton et al (21)

dealt with seasonal variations, body mass index, physical activity, smoking, and alcohol consumption. If the associations between hypovitaminosis D and CWP all resulted from the above-mentioned confounders, the adjusted OR would be shifted toward the value of one and become insignificant. Therefore, our results implied hypovitaminosis D in patients with CWP might be partly mediated through certain pathways other than well-known confounders, and future cohort studies are warranted to investigate potential causal factors leading to hypovitaminosis in patients with CWP.

There are several limitations in our meta-analysis. First, all retrieved citations employed a cross-sectional observational design and none of them were able to elucidate the causal relationship between hypovitaminosis D and CWP. Although some claimed theirs as prospective cohort studies, their patient and control groups were defined at the same time as serum vitamin D levels were obtained. Second, the literature search also identified some randomized control trials which mainly explored the effect of vitamin D supplement on pain reduction in patients with CWP or fibromyalgia, and therefore were not included in the present meta-analysis. Third, limited numbers of included studies provided adjusted ORs, and substantial differences existed in the items constituting measured confounders. Finally, we noticed significant publication bias in the reporting of mean serum vitamin D levels in both patient and control groups. This could be due to heterogeneity in the observed population, the season and location at which the study was conducted, and the methods of vitamin D measurement. However, we speculated that the publication bias had limited influence on the interpretation of our results since the ORs in the patient and reference groups were similarly distributed in the funnel plot.

In conclusion, our meta-analysis indicated a positive crude association between hypovitaminosis D and CWP, and the association was likely to remain after the adjustment of potential confounding factors. Using a lower value of serum vitamin D (8 – 10 ng/mL) as the diagnostic threshold appeared to be better than the physiological cut-off level (20 ng/mL) in differentiating the population with and without CWP. Further prospective longitudinal follow-up studies are warranted to clarify the causal relationship between CWP and serum hypovitaminosis D.

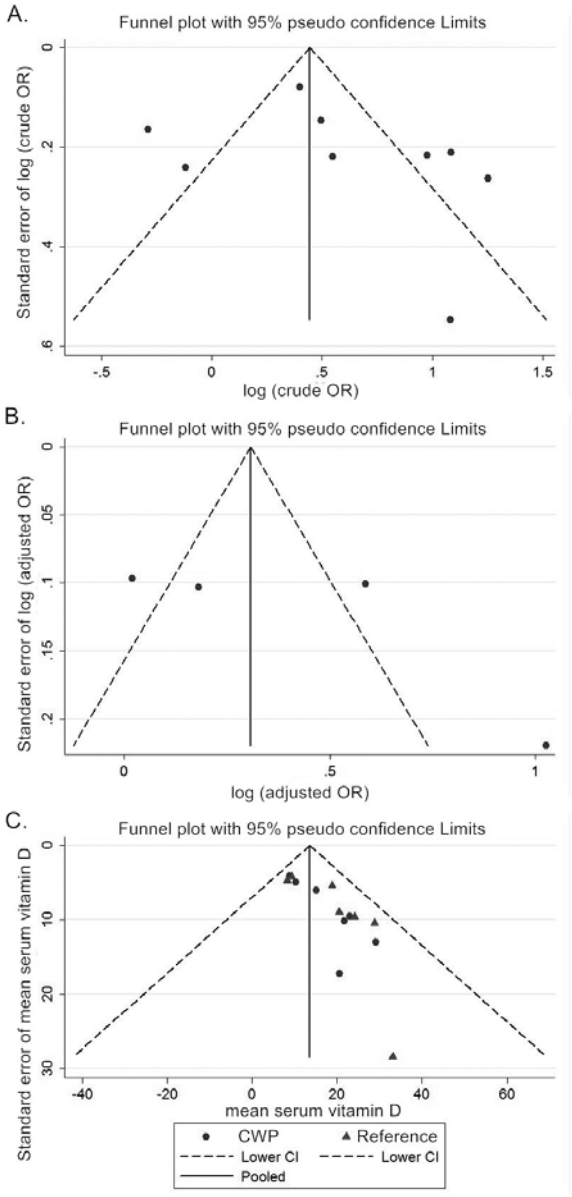

Fig. 6. *Funnel plots of (A) crude ORs (B) adjusted ORs and (C) mean serum vitamin D in the CWP group and reference group.*

Conflict of interest statement

The authors, their immediate family, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

Author contributions:

Conceived and designed the experiments: KVC, MYH. Performed the experiments: KVC, MYH, CYH. Analyzed the data: KVC, MYH, CYH. Wrote the manuscript: MYH, KVC. Data interpretation: KVC, MYH, DSH. Revision of manuscript content: DSH, TGW, KVC. Approving final version of manuscript: MYH, CYH, KVC, DSH, TGW.

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