Impact of vitamin D supplementation on C-reactive protein; a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: To evaluate the effect of vitamin D supplementation on C-reactive protein (CRP) through a systematic review and meta-analysis of randomized control trials (RCTs).

Methods: PubMed-Medline, SCOPUS, Google Scholar and Web of Science databases were searched (up until April 2016) to identify RCTs evaluating the impact of vitamin D supplementation on CRP. We used random effects models (using DerSimonian-Laird method) as well as the generic inverse variance methods for quantitative data synthesis. For sensitivity analysis, we applied leave-one-out approach. To examine the heterogeneity we used I2 index. Registration code: CRD42016036932.

Results: Among 1274 search items, 24 studies met the inclusion criteria in the final evaluation. Pooling the data together indicated a non-significant decrease in CRP level following administration of vitamin D (weighted mean difference [WMD] -0.26 (mg/l), (95% CI -0.75 to 0.22, N = 26 arms, heterogeneity p = 0.042; I² 54.2%). The WMDs for IL6 was 0.67 pg/ml, (95% CI 0.29 to 1.06, N = 16 arms, heterogeneity p = 0.234; I² 19.1%), 0.43 pg/ml, (95% CI 0.08 to 1.05, N = 26 arms, heterogeneity p = 0.120; I² 42.1%), for IL10, and −0.11 pg/ml, (95% CI -0.53 to 0.30, N = 12 arms, heterogeneity p = 0.423; I² 9.2%) for TNF-α, 4.03 pg/ml, (95% CI 3.50 to 4.57, N = 3 arms, heterogeneity p = 0.752; I² 8.1%) for adiponectin. Sensitivity analyses confirmed the robustness of the findings.

Conclusions: This study provided evidence that vitamin D supplementation had no impact on serum CRP, IL10, and TNF-α, while significantly increased serum IL6. We recommend RCTs with longer period of follow-up time (12 months) for future studies to provide explicit results.

Keywords: Meta-analysis, Vitamin D supplementation, C-reactive protein

Background

Historically, vitamin D is recognized for its important role for bone health. However, recent studies suggest extraskeletal effects of vitamin D through autocrine and paracrine systems. Low vitamin D concentrations are related with several diseases with inflammatory nature including rheumatoid arthritis, metabolic syndrome, type 2 diabetes, cardiovascular diseases, and some types of cancer [1]. Low vitamin D status is reported to be related to acute phase response in which casue elevated concentrations of C-reactive protein (CRP), several hemostatic factors and different pro-inflammatory cytokines [2–4]. Studies suggest vitamin D supplementation may reduce circulating CRP levels and some other plasma inflammatory cytokines. However, inconsistent results are reported across completed randomized trials [5–7]. Cytokines such as interleukin 6 (IL-6), interleukin 10 (IL-10) and tumor necrosis factor- alpha (TNF-alpha) mediate the inflammatory response in human for therefore they can serve as potential biomarkers of chronic inflammatory diseases [8–10]. The elevated circulating concentrations of pro-inflammatory cytokines, such as IL6, and hepatic...

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acute phase proteins (e.g. CRP) is a common feature of such diseases with chronic inflammation [11, 12].

The potential effect of vitamin D supplementation in decreasing chronic inflammation, if proven, is of public health interest given the disproportionate prevalence of vitamin D deficiency and insufficiency across the globe. A number of recent clinical trials have assessed vitamin D supplementation in different populations for its impact on circulating concentrations of several pro- and anti-inflammatory factors. However, such studies have had limitations such as small sample size, poor research design and subject traits (gender, ethnicity, age, etc.), and underpowered to achieve a comprehensive and reliable conclusion. Therefore there is substantial uncertainty about the net effect of vitamin D supplementation on CRP levels. A systematic study which has addressed this issue dates back to 2014 including only a few studies [13]. Therefore, a comprehensive evaluation of evidence is needed to achieve an evidence-based conclusion. Hence, we aimed to address this uncertainty by systematically reviewing the literature, and meta-analysis of all trials, to explore the effects of vitamin D supplementation on CRP levels.

Methods
We conducted his systematic review based on the international referred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [13, 14]. We registred our study in the International Prospective Register of Systematic Reviews, PROSPERO (registration no: CRD42016036932).

Literature search strategy
In literature search we considered the effect of vitamin D supplementation on plasma CRP concentration as the primary exposure of interest. The secondary exposure was the effect of vitamin D supplementation on inflammatory and anti-inflammatory markers and cytokines. We considered multiple databases including PUBMED/ Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science and Google Scholar, until April 2016 for literature search. We applied relevant search terms to find a published and unpublished studies for our interested outcome (Additional file 1: Table S1). We considered no limitation on language.

Selection criteria
We selected published randomized control trials (RCTs) assessing the impact of vitamin D administration on the inflammatory parameters. Criteria for selecting studies: (i) clinical trial with single-arm, parallel or cross-over designs; (ii) RCTs of participants received vitamin D supplement compared to control group (either no vitamin D or placebo); and (iii) studies with information on primary outcome at the baseline and the endpoint in each group or the net change values. Exclusion criteria were: (i) non-clinical trials including those with case–control, cross-sectional or cohort designs; and (ii) studies missing to report mean (or median) plasma concentrations of our measures of interest at the baseline and/or at the endpoint. We carried out the selection by removing the of duplicates followed by titles and abstracts screening by two reviewers. The agreement between the reviewers was considerable (Kappa index: 0.87; p < 0.001). We resolved the disagreements at a meeting between reviewers prior to selected articles being retrieved.

Data extraction and management:
Two reviewers (MM, PR) retrieved the full text of studies the met the inclusion criteria, and screened to determine the eligibility. After assessment of methodological quality, the two reviewers extracted data onto a purpose-designed data extraction form. The same reviewers independently summarised the most significant results of each study. We compared the summaries and any variations of ideas resolved through a discussion with the third reviewer (HV). Details information from selected RCTs is summarized in Table 1. An independent reviewer confirmed all data entries.

Quality assessment
We used the Cochrane criteria to assess potential bias [14].

Data preparation for meta-analysis:
According to Cochrane Handbook recommendations, the mean change from baseline in the level of variables of interest and standard deviation (SD) for both groups were collected and used to compute the effect size [15]. The following formula was used: \( SD = SEM \times \sqrt{n} \), where \( n \) is the number of subjects. We sued the GetData Graph Digitizer 2.24 [16] to extract the required data when there were presented in graphs.

We applied random effects model (using the DerSimonian– Laird method) and the generic inverse variance method to take to account the heterogeneity of studies in terms of demographic characteristics of populations [17]. A quantitaved assessment of Heterogeneity was conducted using \( I^2 \) index, where values of 25%, 50%, and 75% reflect low, medium and high heterogeneity, respectively. We expressed the effect sizes as the weighted mean differences (WMD) and 95% confidence interval (CI). Sensitivity analysis was applied to assess the effect of each RCT on the overall effect size [18–20].

Determining potential publication bias
To determine potential publication bias we used Begg’s rank correlation, and Egger’s weighted regression tests
| Author, year of publication | Country | Study design | Status | Sample size | Sex (% of women) | Mean age | Intervention | Supplemented the dose of vitamin D (IU/day) | Follow-up duration |
|-----------------------------|---------|--------------|--------|-------------|------------------|----------|-------------|------------------------------------------|-------------------|
| A Sadiya (47), 2015          | UAE     | randomized double-blind clinical trial | vitamin D-deficient obese, type 2 diabetic | 87           | Male and Female (70%) | 49 ± 8   | cholecalciferol (vitamin D3) | phase 1: 6000 phase 2: 3000 | 6 month |
| A. Breslavsky (48), 2013     | Israel  | randomized, placebo-controlled | type 2 diabetes mellitus | 47           | Male and Female (53.1%) | 66.8 ± 9.2 | cholecalciferol (vitamin D3) | 1000                      | 12 month |
| Claudia Gagnon [34], 2014    | Australia | randomized, placebo-controlled trial | vitamin D-deficient and at risk of type 2 diabetes | 95           | Male and Female (71%) | 54 years | cholecalciferol (vitamin D3) | 2000-6000                   | 6 month |
| Edgar Turner Overton [33], 2015 | USA     | randomized, double-blind, placebo-controlled | HIV-infected | 167          | Male and Female (9%) | 36 years | cholecalciferol (vitamin D3) | 4000                        | 48-week |
| Gavin Dreyer [30], 2014      | UK      | randomised controlled trial | non-diabetic chronic kidney disease stage 3-4 and concomitant vitamin D deficiency | 38           | Male and Female (39.1%) | 45.8 (10.0) | ergocalciferol | 50,000                      | 6 month |
| Indrani Sinha-Hikim [25], 2015 | USA     | randomized | pre-diabetes and hypovitaminosis D | 80           | Male and Female (70%) | 520 years | cholecalciferol (vitamin D3) | 85,300 IU ± 16,000 | 12 month |
| Isa Gabriela de Medeiros CavaCante [29], 2015 | Brazil   | double blind, randomized, placebo-controlled trial | With vitamin D insufficiency | 40           | Female (100%) | 68 ± 6 | cholecalciferol (vitamin D3) | 200,000                     | 4 week |
| Julia Åivo (49), 2015        | Finland | double-blind, randomized, parallel | With chronic fatigue syndrome | 59           | Male and Female (62.7%) | 38 (22-53) | cholecalciferol (vitamin D3) | 20,000 | 12 month |
| L. Wamberg (50), 2013        | Denmark | double-blind design | chronically impaired mobility | 52           | Male and Female (71%) | 18 to 50 years | cholecalciferol (vitamin D3) | 7000                      | 6 month |
| M.D. Witham (51), 2015       | UK      | Parallel-group, double-blind, randomised placebo-controlled trial | with chronic fatigue syndrome | 50           | Male and Female (52%) | 49 ± 13 | cholecalciferol (vitamin D3) | 100,000                     | 6 month |
| M.P. Bjorkman [28], 2009     | Finland | randomised double-blind placebo controlled trial | chronically impaired mobility | 218          | Male and Female | 845 ± 7.5 | cholecalciferol (vitamin D3) | 0-400/1200                  | 6 month |
| Nafiseh Toghianifar (52), 2015 | Iran    | double blind randomized clinical trial | with a diagnosis of relapsing remitting multiple sclerosis (RRMS) | 94           | Male and Female (84.2%) | 31.50 ± 7.60 | cholecalciferol (vitamin D3) | 50,000                      | 12 week |
| Nasrin Sharifi (53), 2014    | Iran    | parallel double-blind, placebo-controlled | non-alcoholic fatty liver disease (NAFLD) | 53           | Male and Female (51%) | 40.33 ± 8.65 | cholecalciferol (vitamin D3) | 50,000                     | 4 month |
| Ohk-Hyun Ryu [32], 2014      | Korea   | prospective, randomized, double-blind, placebo-controlled trial | type 2 diabetic patients | 62           | Male and Female | 54.5 ± 7.4 | cholecalciferol (vitamin D3) | 2000                        | 24 week |
| Pamela R. von Hurst (54), 2010 | New Zealand | randomised, placebo-controlled trial | | 81           | Female (100%) | 45.5 | cholecalciferol (vitamin D3) | 4000                      | 6 month |
| Paulette D. Chandler (55), 2014 | USA     | Randomized, Placebo-Controlled Trial | | 328          | Male and Female (67.7%) | 51 | cholecalciferol (vitamin D3) | 1000-2000-4000 | 3 month |
| Rahaimi (56), 2013           | Iran    | randomised, placebo-controlled, double-blinded trial | With vitamin D deficiency | 50           | Female (100%) | 30 | cholecalciferol (vitamin D3) | 50,000                      | 2 month |
| Author, year of publication | Country | Study design | Status | Sample size | Sex (% of women) | Mean age | Intervention | Supplemented the dose of vitamin D (IU/day) | Follow-up duration |
|-----------------------------|---------|--------------|--------|-------------|------------------|---------|-------------|----------------------------------|------------------|
| Rolf Jorde (57), 2010       | Norway  | Randomized   | overweight and obese | 437 | Male and Female (64.3%) | 47 | cholecalciferol (vitamin D3) | 40,000 | 12 month |
| Seth I Sokol [31], 2012     | USA     | double-blind, placebo wait-list control design | with CAD and vitamin D deficiency | 90 | Male and Female (26.5%) | 55 ± 9.6 | ergocalciferol | 50,000 | 12 week |
| Tina K. Thethi, 2015        | USA     | double blind, randomized, placebo-controlled trial | with type 2 diabetes and chronic kidney disease | 55 | Male and Female (32.7%) | 63 | Paricalcitol | 1 mcg | 3 month |
| Tyler Barker (58), 2015     | USA     | randomized, double blind, placebo-controlled | | 56 | Male and Female (32.7%) | 32(7) | cholecalciferol (vitamin D3) | 4000 | 5 week |
| Ulla Kampmann (59), 2014    | Denmark | double-blind, randomized, placebo-controlled trial | with type 2 diabetes and hypovitaminosis D | 15 | Male and Female (46.4%) | 59.3 ± 4.4 | cholecalciferol (vitamin D3) | 5600 | 12 week |
| Zatollah Asemi (60), 2013   | Iran    | randomized, double-blind, placebo-controlled clinical | healthy pregnant women | 48 | Female (100%) | 29 | cholecalciferol (vitamin D3) | 400 | 25 week |
The fill’ and ‘fail-safe N’ and Duval & Tweedie ‘trim
methods were applied to adjust for the potential effects
of publication bias [21, 22]. The meta-analysis was pre-
formed using Comprehensive Meta-Analysis (CMA) V3
software (Biostat, NJ) [23, 24].

Results
Selection RCTs
From searches in different search engines overall 1273
single citations recognized, of these, 126 were duplicates.
From 1147 items, 35 left after assessment based on titles
and abstracts, of which, 11 were not selected due to fact
that: genetic, non-human studies, or molecular studies
\( n = 4 \); editorial or review articles \( n = 3 \); incomplete
data \( n = 2 \); Fig. 1. Consequently, 23 RCTs were used for
pooling the data.

Risk of bias assessment
Results of assessment of bias revealed that some of the
selected items recognized by the absence of information
about the random sequence generation, blinding of out-
come assessment and blinding of participants and study
personnel, and allocation concealment. Though, nearly
all of the assessed RCTs had a low risk of bias accord-
ing to selective outcome reporting, with the exemption
of two, which did not have sufficient material [25]. De-
tails of the quality of bias assessment are presented in
Additional file 1: Table S2.

Characteristics of the studies
A summary of the characteristics of the studies is
presented in Table 1. The included studies have been
published between 2009 and 2015 from 12 countries in-
cluding the United States of America (six studies), Iran
(four studies), Finland, Denmark, UK (two studies) and
Norway, Australia, Korea, UAE, New Zealand, Israel,
Brazil (one study), respectively. The number of study
participants ranged from 15 to 437 among studies. Four
studies included only women; while the proportion of
women in other studies ranged from 9% to 84.1%. The
age of participants ranged from 18 to 92 years. The fol-
low up duration from the baseline to endpoint across
studies was from 4 weeks to one year. Various supple-
ment regimens were assessed. Range of study popula-
tion was from 15 [26] to 328 participants [27]. Twenty
one studies used cholecalciferol in a dosage range from
0 IU/d [28] to 200,000 IU/d [29]. In two of the studies,
participants were supplemented with ergocalciferol
at a dose of 50,000 IU at baseline for 26 [30] or 12 [31]
weeks. In three studies, calcium supplements had also
been administered in doses of 200 [32], 1000 [33], 1200
[34] mg/d, respectively.

Pooled estimate of the impact of vitamin D supplemen-
tation on C-reactive protein
The pooled estimate (weighted mean difference) of the
effect of vitamin D supplementation on C-reactive protein
was \( -0.26 \text{ (mg/l), (95% CI -0.75 to 0.22, N = 26 arms, het-
ereogeneity } p = 0.042; I^2 54.2\%) across all studies (Fig. 2).
Further, we splited our data based on studies which
followed their subjects >6 months and \( \leq 6 \) months
accordingly. This sub-analysis changed the results as follows,
\( -0.28 \text{ (mg/l), (95% CI -0.44 to 0.12, I^2 22.1\%) and}
\( -0.22 \text{ (mg/l), (95% CI -0.33 to 0.11, I^2 20.9\%) in more than}
6 months and \( \leq 6 \) months accordingly. We have divided
our data based on mean age of the participants (>50 and
50), pooled estimate for >50 group was \( -0.75 \text{ (mg/l), (95% CI -1.29 to -0.21, I^2 32.9\%) and 50 \leq -0.22 \text{(mg/l),}
(95% CI -0.36 to -0.07, I^2 25.9\%). In terms of the sex, we}
ran the analysis for studies which included just females
\( -0.34 \text{ (mg/l), (95% CI -0.66 to 0.23, I^2 10.9\%).}

Pooled estimate of the effect of vitamin D supplemen-
tation on IL-6
The pooled estimate (weighted mean difference) of the
impact of vitamin D supplementation on IL-6 was
0.67 pg/ml, (95% CI 0.29 to 1.06, \( n = 16 \) arms, hetero-
geneity \( p = 0.234; I^2 19.1\%) across all studies (Fig. 3).

Pooled estimate of the effect of vitamin D supplemen-
tation on IL-10
The pooled estimate (weighted mean difference) of the
impact of vitamin D supplementation on IL-10 was
0.43 pg/ml, (95% CI -0.56 to 1.44, \( N = 9 \) arms, hetero-
genity \( p = 0.120; I^2 42.1\%) across all studies.
The pooled estimate (weighted mean difference) of the impact of vitamin D supplementation on TNF-α was −0.11 pg/ml, (95% CI -0.53 to 0.30, N = 12 arms, heterogeneity p = 0.423; I² 9.2%) across all studies.

The pooled estimate (weighted mean difference) of the impact of vitamin D supplementation on adiponectin was 4.03 pg/ml, (95% CI 3.50 to 4.57, N = 3 arms, heterogeneity p = 0.752; I² 8.1%) across all studies.

The pooled estimate (weighted mean difference) of the impact of vitamin D supplementation on ICAM-1 was −0.79 pg/ml, (95% CI 1.33 to 0.26, N = 4 arms, heterogeneity p < 0.001; I² 62.1%) across all studies.

The pooled estimate (weighted mean difference) of the impact of vitamin D supplementation on IL-7 was −2.32 pg/ml, (95% CI -4.32 to −0.31, N = 4 arms, heterogeneity p = 0.635; I² 7.9%) across all studies.

Fig. 2 Weighted mean difference of the effect of vitamin D supplementation on C-reactive protein

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**Pooled estimate of the effect of vitamin D supplementation on IL-13**

The pooled estimate (weighted mean difference) of the impact of vitamin D supplementation on IL-13 was $-0.15 \text{ pg/ml}$, (95% CI -0.78 to 0.48, N = 5 arms, heterogeneity $p = 0.826$; $I^2 = 3.7\%$) across all studies.

**Sensitivity analysis**

The pooled effect estimates remained similar across all studies in leave-one-out sensitivity analyses (Table 2).

**Publication bias**

The visual inspection of funnel plot asymmetry declared no potential publication bias for the comparison of CRP levels between vitamin D supplementation and placebo groups (Fig. 4). Moreover, the presence of publication bias was not suggested by Egger’s linear regression (intercept = 2.12, standard error = 2.68; 95% CI = -3.41, 7.66, $t = 0.79$, df = 24.00, two-tailed $P = 0.435$) and Begg’s rank correlation test (Kendall’s Tau with continuity correction =0.04, $z = 0.28$, two-tailed $P$ value =0.774). After adjustment of effect size for potential publication bias using the ‘trim and fill’ correction, no potentially missing studies were imputed in funnel plots. Hence no difference in effect size than the initial estimate (WMD $-0.26(\text{mg/l})$, 95% CI -0.75 to 0.22) (Fig. 5). The ‘fail-safe N’ test showed that 271 studies would be needed to bring the WMD down to a non-significant ($P > 0.05$) value.

**Discussion**

In the current meta-analysis of randomized trials, we investigated the impact of high-dose vitamin D supplementation on circulating inflammatory and anti-inflammatory indexes. We detected no effect of vitamin D supplementation on circulating CRP. However our analysis revealed that vitamin D supplementation significantly increased IL-6 level by 0.67(pg/dl), while no significant effect was found on serum IL10 and TNF-α.

From a theoretical point of view, there are several possible mechanisms that may explain vitamin D may affect serum CRP and IL-6. The physiological impact of vitamin D is not limited to the homeostasis of calcium and phosphate. For instance, vitamin D receptors (VDR) play role in the decreased activation of the pro-inflammatory transcription factor nuclear factor kappa B (NF-κB). This suggests that VDR has an intrinsic inhibitory role in inflammation [35, 36]. One important target of vitamin D is NF-κB, which is inhibited by vitamin D, and via NF-κB downstream release of the pro-inflammatory cytokines. NF-κB activation participates in the endogenous induction of CRP. Accordingly, the activated NF-κB may increase the effects of an activator of transcription-3 (STAT3) [37]. Studies have shown the active form of vitamin D (1,25-dihydroxyvitamin D3 [1,25(OH)2D] inhibits NF-κB activation. This inhibitory effect is done by upregulating the inhibitor of NF-κB (IκB-α) and reducing IκB-α phosphorylation in lipopolysaccharide-stimulated murine macrophage cells as well as submissively sensitized human airway smooth muscle cells [38, 39]. Thus, it may be
hypothesised that vitamin D supplementation may suppress CRP via NF-xB and STAT3 signaling. Decreased parathyroid hormone (PTH) production with vitamin D supplementation may also explain the effects of vitamin D on hs-CRP. Low PTH may lead to decreased production of inflammatory factors [40].

According to our results, existing studies report mixed results regarding the impact of vitamin D supplementation on CRP. The Framingham Offspring Study cohort reported no significant association was found between vitamin D and CRP (n = 1381) [41]. While, in a meta-analysis of 10 randomized controlled trials (Chen et al. 2014), investigating the effect of vitamin D supplementation on CRP [13], vitamin D supplementation significantly decreased the circulating CRP level by 1.08 mg/L [13]. In addition, a recent meta-analysis of randomized controlled trials indicated a favourable impact on markers inflammation with vitamin D treatment [40]. It has been stated that heterogeneity across the findings of the studies may be due to supplemental dose of vitamin D, intervention duration and baseline hs-CRP level.

In the study by Forman et al.(2008) in a 1484 young women (aged 32 to 52 years) found that although vitamin D supplementation did not lower CRP specifically, it did lead to improvements in other inflammatory markers, for example IL-10 and TNF-α [42]. In addition, Ngo et al. studied 253 adults (aged 51 to 77 years) with mean CRP level of 3.6 ± 4.0 mg/mL and reported serum vitamin D have significant converse association with CRP level [43]. This association was seen in 147 morbidly obese subjects with CRP levels ranged from 1.88 to 4.01 mg/L [44]. In one study impact of vitamin D supplementation on CRP and IL-6 was different [45]. The one-year vitamin D supplementation in overweight and obese participants resulted in reduced serum IL-6 concentrations, while serum CRP concentrations were significantly increased. The contradictory findings in these studies may be attributed to the length of the study, seasonal change or geographical location [45]. In a randomized control trial in patients with acute myocardial infarction, a short duration of treatment with vitamin D has significant impact on weakening the rise of CRP and IL-6 (but not TNF-α) [46].

IL-6 is a multi-potential inflammatory cytokine that has a fundamental role in host defence including the immune responses, acute phase reactions and haematoipoiesis [47]. Our analysis presented a positive association between vitamin D supplementation and circulating IL-6 levels. Our results may be influenced by seasonal differences in vitamin D level that cause changes in this increased levels of IL-6, IL-6-related signalling pathways, chronic diseases, congenital diseases, baseline IL-6 level, age, sex of subjects and a supplemental dose of vitamin D. Hence, this finding needs to be reexamined in larger randomized trials specifically designed to investigate the relationship between inflammatory indexes and vitamin D.

Our study has some potential limitations. Internal validity of our results relies on the quality of individual studies as it is seen in all meta-analyses. Several limitations can be named in this regard. Firstly, most studies in this meta-analysis had medium sample sizes. This may lead to overestimation of vitamin D supplementation effects. Smaller trials might be methodologically less robust and more prone to report larger effect sizes [48, 49]. The number of available studies on this topic was rather small. Only four of the studies included in current meta-analyses were with the duration of 12 months. Among them, only one had a relatively large sample. Heterogeneity exist in doses of vitamin and health status of target population at the baseline. Further, most of the studies were conducted in clinical population rather than general healthy population. This may likely affect the baseline levels of vitamin D and the inflammatory markers.

### Table 2 Sensitivity analysis across all studies

| Variables        | Result of the leave-one-out sensitivity analyses |
|------------------|-------------------------------------------------|
| C-reactive protein | -0.26(mg/l), (95% CI -0.75 to 0.22)           |
| Interleukin-6     | 0.67(ng/dl), (95% CI 0.29 to 1.06,)           |
| Interleukin−10    | 0.43(ng/dl), (95% CI -0.56 to 1.44)           |
| TNF-α            | −0.11(ng/dl), (95% CI -0.53 to 0.30)          |
| Adiponectin      | 4.03 (pg/ml), (95% CI 3.50 to 4.57)           |
| ICAM-1           | −0.79 (pg/ml), (95% CI 1.33 to 0.26)          |
| IL-7             | −2.32 (pg/ml), (95% CI -4.32 to −0.31)        |
| IL-2             | −0.111 (pg/ml), (95% CI -1.27 to 1.07)         |
| IL-4             | 0.027 (pg/ml), (95% CI -0.72 to 0.77)          |
| IL-5             | 0.631 (pg/ml), (95% CI -0.05 to 1.32)          |
| IL-12            | 0.045 (pg/ml), (95% CI -0.14 to 0.23)          |
| IL-13            | −0.15 (pg/ml), (95% CI -0.78 to 0.48)          |

N=Number
Fig. 4 Funnel plot of standard error by Std difference in means

Fig. 5 Funnel plot of standard error by Std difference in means
Conclusion
The current study revealed that vitamin D supplementation significantly increase level of IL6, while having no effect on CRP, IL10, and TNF-α concentration. RCTs with larger sample size and longer follow-up period (12 months) should be considered for future investigations to provide an unequivocal answer.

Additional file

Additional file 1: Table S1. Full search terms and strategy for the databases. Table S2. Quality of bias assessment of the included studies according to the Cochrane guidelines. (DOCX 26 kb)

Abbreviations
CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CDSR: randomized control trials; CI: confidence interval; CRP: C-reactive protein; IL-10: Interleukin 10; IL-6: Interleukin 6; Nf-kb: Nuclear factor kappa B; PRISMA: Reporting Items for Systematic Reviews and Meta- Analyses; PROSPERO: International Prospective Register of Systematic Reviews; PTH: parathyroid hormone; SD: standard deviation; SEM: standard error of the mean; TNF-α: Tumour necrosis factor-α; VDR: Vitamin D receptors; WMD: weighted mean differences

Acknowledgements
MM was supported by a TWAS studentship of the Chinese Academy of Sciences, during the preparation of this manuscript.

Funding
None.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
MM and HV designed the study. MM and PR searched databases, performed the selection of studies and wrote the manuscript. MM analyzed the data; HV, Kengne AP, Banach M; Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 supplementation on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2017;103:236–52.

Ethics approval and consent to participate
the selection of studies and wrote the manuscript. MM and HV designed the study. MM and PR searched databases, performed

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 26 November 2016 Accepted: 7 December 2017
Published online: 02 February 2018

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