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Effect of vitamin D supplementation on serum C-reactive protein level: a meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Vitamin D may have anti-inflammatory actions; however, there is no consensus on the effects of vitamin D supplementation on C-reactive protein (CRP) level in randomized clinical trials (RCTs). In a systematic review and meta-analysis, we investigated the effect of vitamin D supplementation on serum CRP levels.

Methods: A systematic search for RCTs was conducted on PubMed, and Scopus, and completed by a manual review of the literature from January 2000 to May 2015. The pooled effect was estimated using a random-effects model and the statistical heterogeneity was assessed by Cochran's Q and I2 statistics.

Results: Of 157 potentially relevant studies retrieved, 20 clinical trials met the inclusion criteria. Mean baseline CRP levels in the intervention and the control groups were 3.5 ± 2.6 and 3.3 ± 2.3 mg/L, respectively. The mean duration of the studies was 29.0 ± 30.2.0 weeks (8 to 144 weeks). The dose of vitamin D3 supplementation varied between 200 and 57142 IU/day. Pooled analysis showed a nonsignificant increase of 0.04 mg/L (95% CI, −0.12 to 0.21; p = 0.61), with no evidence of heterogeneity (I2 = 17.8%, p = 0.17).

Conclusion: Vitamin D supplementation may not be effective in reducing CRP. However, a more accurate estimate of the effect requires further large and well-designed clinical trials.

Introduction

Hypovitaminosis D is one of the most prevalent micronutrient deficiencies and has become a universal health issue [1, 2]. Vitamin D is mainly involved in calcium homeostasis and bone metabolism, but it has many other physiologic functions in the body [3]. Recently, vitamin D has gained growing interest for its novel anti-inflammatory properties [4, 5]. Inflammation presumably plays critical roles in chronic diseases, and C-reactive protein (CRP) is a reliable and well-established biomarker of systemic inflammation among a broad range of inflammatory biomarkers [6]. There are several ways in which vitamin D affects the immune system. For instance, $1,25(OH)_2$ D3 regulates cytokine expression directly, through influencing gene transcription, and indirectly, through interfering with signaling pathways [7].

In recent years, a growing number of observational and interventional studies have investigated the effect of vitamin D supplementation on circulating CRP level and yielded inconsistent results [8-13].

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These discrepancies could mostly be attributed to small sample size, the dose of vitamin D administered, short trial duration, variation in study design, and the baseline plasma levels of 25(OH)D and CRP.

Therefore, given the increased statistical power afforded by meta-analysis, we conducted this meta-analysis of randomized controlled trials (RCTs) to evaluate whether vitamin D supplementation could improve circulating CRP level.

Methods

Data sources, search strategy, and eligibility criteria

This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. A comprehensive search and systematic assessment of studies and data extraction were conducted in a stepwise process in accordance with our specific question: What is the effect of vitamin D3 supplementation on CRP? The PICOS (population, intervention, comparator, outcome, study design) framework is shown in Table 1. The literature search was conducted by two independent authors for studies published from January 2000 to May 2015 in MEDLINE and EMBASE databases using the following keywords: ((“Cholecalciferol”[Mesh] OR vitamin d3 supplementation [title/abstract]) OR (vitamin d3[title/abstract] AND supplementation [title/abstract])) AND “C-Reactive Protein” OR “CRP” OR “high-sensitivity C-reactive protein” OR “high-sensitive C-reactive protein” OR “hs-CRP”). The search was limited to studies published in English. We also checked the reference lists of the published papers for relevant studies. Any discrepancies were resolved with discussion. First, we perused the title and abstract of each of these citations and then retrieved potentially eligible articles for perusal in full text. Studies were eligible for inclusion if they fulfilled the following criteria: (a) the study design was an RCT, (b) the intervention was oral vitamin D3 supplementation, (c) the outcome of interest was CRP, and (d) the population of interest was adults (aged > 18 years). Trials which compared vitamin D3 supplementation with a placebo, or compared calcium + vitamin D3 supplementation with calcium were included. Studies were excluded if they were animal studies, observational studies, uncontrolled trials, without a placebo group, or involved vitamin D in forms other than cholecalciferol or in the form of vitamin D3-fortified products. Studies were also excluded if they involved pregnant/lactating women or patients with renal disease, hypercalcemia, hyperparathyroidism, malabsorption, or hyperthyroidism. Studies which did not report CRP at baseline and its changes after intervention were also excluded.

Table 1: Characteristics of included studies

Author	Year	Country	Total No.	Mean age (y)	Participants	Sex	Treatment	Trial duration (month)	Daily Dose (Ca(mg)/Vitamin D(IU))	Final MD of serum 25(OH)D[a] (nmol/ml)
Pittas, A. G.	2007	USA	222	71	Caucasian adults without diabetes and with normal fasting glucose	3	Ca+Vit D3	36	500 /700	111
Pittas, A. G.	2007	USA	92	71	Caucasian adults without diabetes but with impaired fasting glucose	3	Ca+Vit D3	36	500 /700	111
Bjorkman, M. P.	2009	Finland	77	84.5	Bedridden patients >65 y	3	Vit D3	6	400	NA
Bjorkman, M. P.	2009	Finland	73	84.5	Bedridden patients >65 y	3	Vit D3	6	1200	NA
Von Hurst, P. R.	2010	New Zealand	42	41.4	South Asian women with insulin resistnce and hypovitaminosis D	2	Vit D3	6	4000	80
Barnes, M. S.	2011	Ireland	47	30.5	Healthy younger (20-40y)	3	Vit D3	22 week	200	50.4
Barnes, M. S.	2011	Ireland	55	30.6	Healthy younger (20-40y)	3	Vit D3	22 week	400	59.6
Barnes, M. S.	2011	Ireland	53	29.2	Healthy younger (20-40y)	3	Vit D3	22 week	600	69
Barnes, M. S.	2011	Ireland	48	70.7	older adults (>64y)	3	Vit D3	22 week	200	53.2
Barnes, M. S.	2011	Ireland	52	70.6	older adults (>64y)	3	Vit D3	22 week	400	70.3
Barnes, M. S.	2011	Ireland	48	71.2	older adults (>64y)	3	Vit D3	22 week	600	73.9

Author	Year	Country	Total No.	Mean age (y)	Participants	Sex	Treatment	Trial duration (month)	Daily Dose (Ca(mg)/Vitamin D(IU))	Final MD of serum 25(OH)D[a] (nmol/ml)
Carrrilo	2012	USA	10	26.2	overweight and obese adults participating in a progressive resistance exercise	3	Vit D3	3	4000	33.4
Beilfuss, J.	2012	Norway	110??	50	Healthy overweight and obese adults	3	Vit D3	12	40000/ week	138l
Beilfuss, J.	2012	Norway	110??	50	Healthy overweight and obese adults	3	Vit D3	12	20000/ week	97
Genpner A.D	2012	USA	57	64.1	post-menopausal women	3	Vit D3	4	2500	NA
Muldowney, S.	2012	Ireland	202	29.9	Healthy younger (20-40y)	3	Vit D3	22 week	200	NA
Muldowney, S.	2012	Ireland	202	29.9	Healthy younger (20-40y)	3	Vit D3	22 week	400	59.6
Muldowney, S.	2012	Ireland	202	29.9	Healthy younger (20-40y)	3	Vit D3	22 week	600	69.8
Muldowney, S.	2012	Ireland	192	70.8	older adults (>64y)	3	Vit D3	22 week	200	NA
Muldowney, S.	2012	Ireland	192	70.8	older adults (>64y)	3	Vit D3	22 week	400	68.9
Muldowney, S.	2012	Ireland	192	70.8	older adults (>64y)	3	Vit D3	22 week	600	70.9
Wood A.D	2012	United Kingdom	102	63.5	postmenopausal women	2	Vit D3	12	400	64.86
Wood A.D	2012	United Kingdom	101	64.1	postmenopausal women	2	Vit D3	12	1000	75.66
Breslavsky, A.	2013	Israel	24	66.8	diabetic patients	3	Vit D3	12	1000	17.6
Rahimi-Ardabili, H.	2013	Iran	24	26.8	PCOD women with hypovitaminosis D	2	Vit D3	2	50000/ 20 days	22.9
Wamberge L	2013	Denmark	26	41.2	Obese adults	3	Vit D3	26 weeks	7000	NA
Witham, M. D.	2013	United Kingdom	39	64.3	Patients with a history of myocardial infarction	3	Vit D3	2	100000	NA
Witham, M. D.	2013	United Kingdom	39	64.3	Patients with a history of myocardial infarction	3	Vit D3	6	100000	NA
Yiu, Y. F.	2013	Japan	50	65.8	diabetic patients	3	Vit D3	3	5000	58.6
Chandler, P. D.	2014	USA	81	51.1	Healthy African Americans Adults	3	Vit D3	3	1000	29.7
Chandler, P. D.	2014	USA	83	50.3	Healthy African Americans Adults	3	Vit D3	3	2000	34.7
Chandler, P. D.	2014	USA	83	51.3	Healthy African Americans Adults	3	Vit D3	3	4000	45.9
Gagnon, C.	2014	Canada	35	53.8	Adults at risk of type 2 diabetes	3	Ca+Vit D3	6	1200/2000	95
Mason, C.	2014	USA	109	60.3	overweight/ obese women	2	Vit D3	12	2000	35
Sadiya, A.	2014	UAE	45	49	obese type 2 diabetic subjects	3	Vit D3	3	6000	77.2
Sadiya, A.	2014	UAE	45	49	obese type 2 diabetic subjects	3	Vit D3	3	3000	61.4
Sharifi, N.	2014	Iran	27	40.33	adult patients with non-alcoholic fatty liver disease	3	Vit D3	4	50000 (twice per month)	30
Sinha-Hikim, I.	2014	USA	40	51.6	Latino and African-American Subjects with Pre-Diabetes and Hypovitaminosis D	3	Vit D3	6	85 300 IU ± 16 000 per week	NA
Sinha-Hikim, I.	2014	USA	40	51.6	Latino and African-American Subjects with Pre-Diabetes	3	Vit D3	12	85 300 IU ± 16 000 per week	70
Sollid, S. T.	2014	Norway	242	62.3	and Hypovitaminosis D Adults with IFG or IGT	3	Vit D3	12	20000/week	105.7

Data extraction

We used a predesigned data abstraction form to extract relevant information. The extracted information included sample size, study design, location, participants' age, trial duration, number of participants in control and intervention groups, type and dose of daily vitamin D, and mean baseline and postintervention serum CRP levels. Authors were contacted if extra data were required. If a study used two or more doses of vitamin D3 versus placebo, we considered each dose of vitamin D3 as a single study, and these were included separately in the analysis. Moreover, if a study measured CRP at various intervals over a protracted follow-up period, we included each interval as a separate study in analysis. Additionally, in the case of multiple publications, we included the most up-to-date or comprehensive information.

Assessing the risk of bias

Two reviewers independently assessed each trial's risk of bias, taking into account factors such as randomization, allocation concealment, blinding, completeness of outcome assessment, and selective reporting. Quality of studies was assessed using the Jadad scale for reporting randomized controlled trials [15]. The Jadad score is based on the description of randomization, blinding, and dropouts. The studies were considered as low-quality if their Jadad score was < 3, and the rest were considered as high-quality studies.

Data synthesis

Weighted mean differences (MD) and 95% confidence intervals (95% CI) were pooled using a random-effects model. Cochran's Q and I^2 were used to assess statistical heterogeneity (I^2 > 50% was deemed significant). Publication bias was measured by visual inspection of funnel plots. Statistical analysis was performed with STATA version 8.0 (StataCorp, College Station, TX, USA). Level of significance was set at 0.05.

Results

Study selection

A total of 157 articles were found in our initial search, 82 of which were excluded by screening the titles and abstracts (Figure 1). A further 40 articles were excluded either because they did not detail randomized controlled trials or they were review articles. Ten more trials were excluded because they did not meet the inclusion criteria. Thus, 20 randomized trials were included in the final analysis.

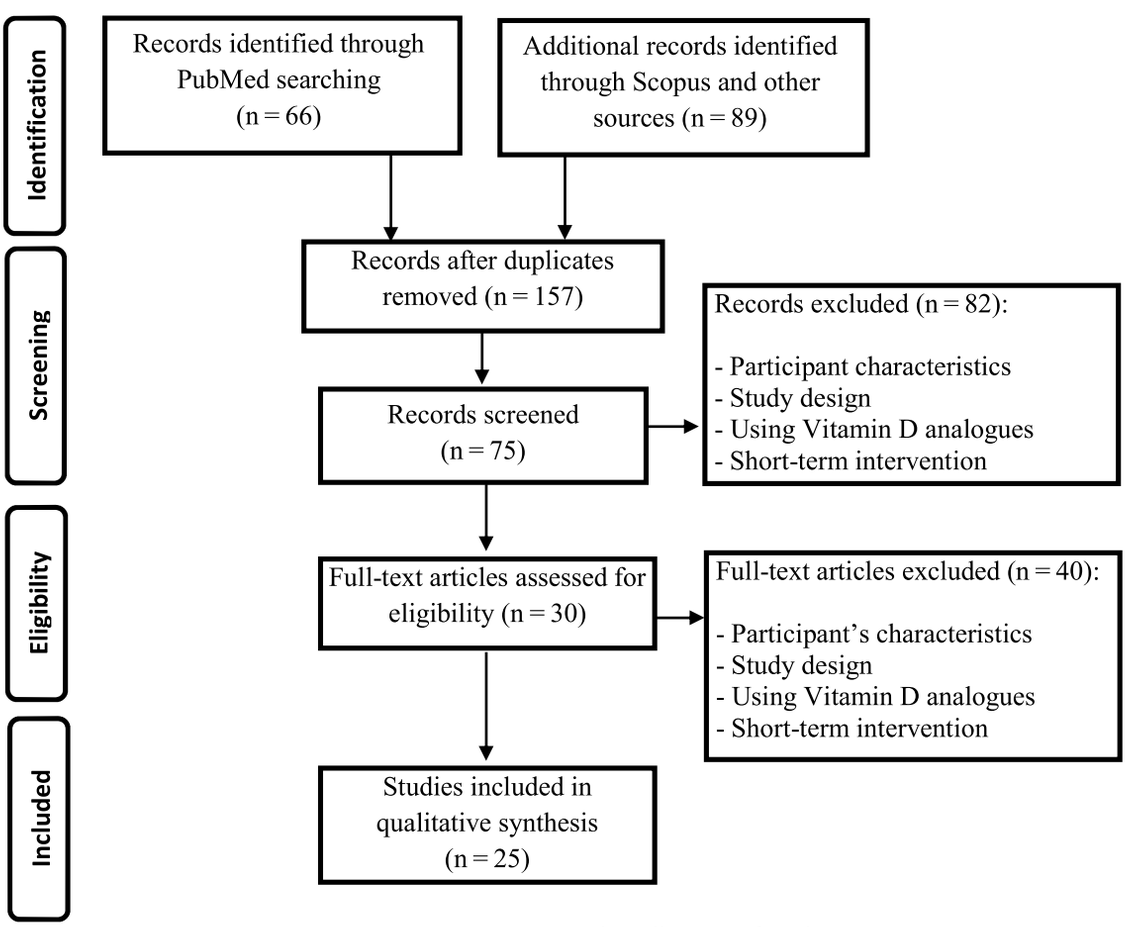

Figure 1. Flow diagram of study

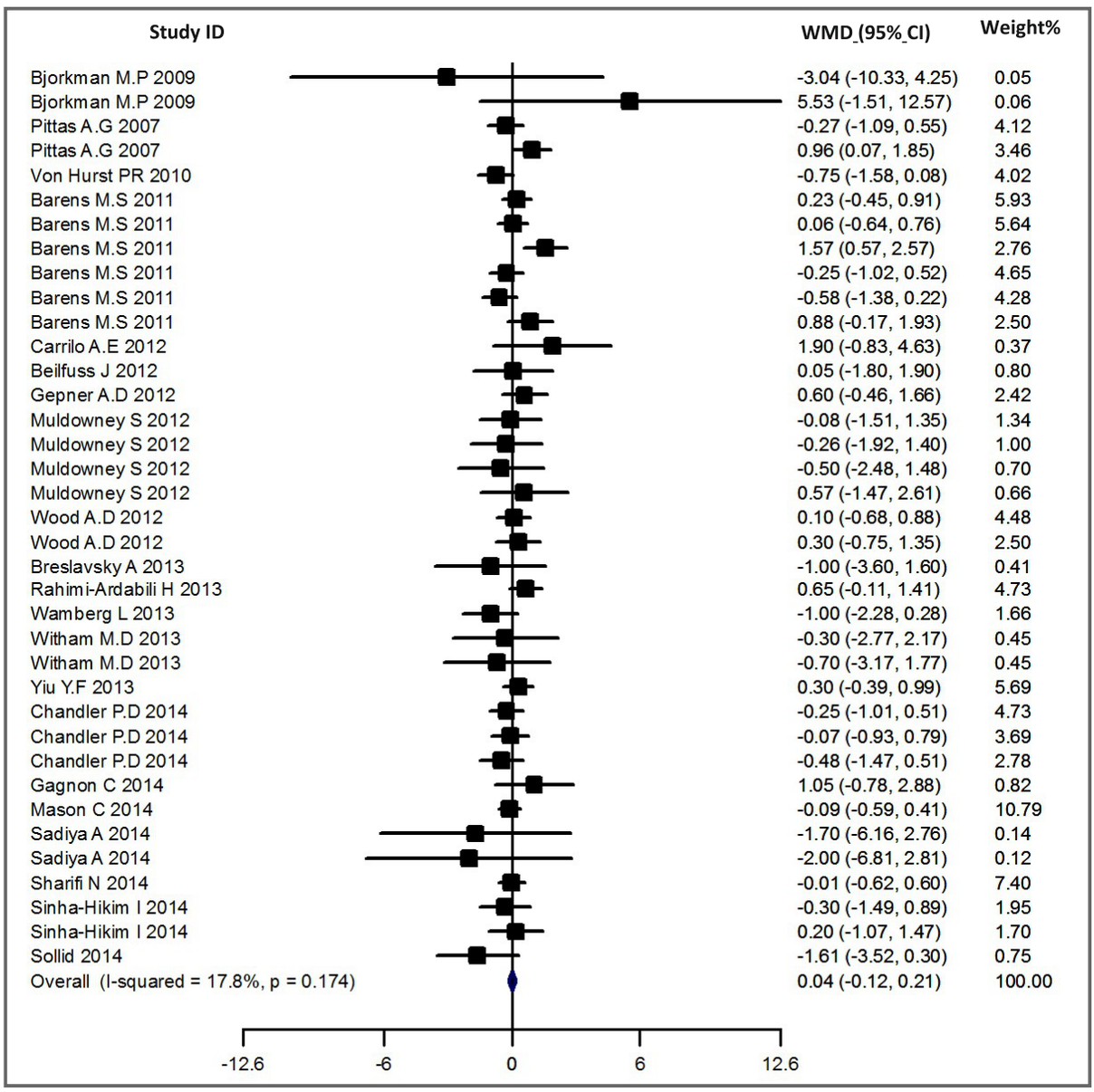

Figure 2. Characteristics of the studies on the effects of vitamin D supplementation on serum CRP levels

Study characteristics

Characteristics of the included studies are shown in Table 2. The mean (±SD) age of participants was 54.7 ± 16.4 year. Baseline CRP levels were 3.5 ± 2.6 and 3.3 ± 2.3 mg/L in the intervention and the placebo group, respectively. The mean duration of the studies was 29.0 ± 30.2.0 weeks (8 to 144 weeks). Doses of vitamin D3 supplementation varied between 200 and 57142 IU/day. Studies were generally of low or unclear risk of bias. Only one of the studies had low quality (Jadad score < 3) [16].

Meta-analysis

The forest plot for the effect of vitamin D3 supplementation on CRP is presented in Figure 2. Vitamin D did not significantly change mean CRP (MD: −0.043 mg/L; 95% CI, −0.12 to 0.21; p = 0.61) compared with no vitamin D3 group. There was no heterogeneity among studies for the effect of vitamin D3 supplementation on CRP (I2 = 17.8%, p = 0.17).

Our findings indicate that the program for the fortification of wheat flour with iron and folic acid was relatively successful in Zanjan province.

Influence and cumulative analysis

Influence analysis also showed that none of the trials had a significant effect on pooled effect size (Figure 3). Cumulative analysis indicated consistency from the year 2009 (Figure 4).

Publication bias

Egger's regression analysis (p = 0.56) showed that there was no publication bias (Figure 5).

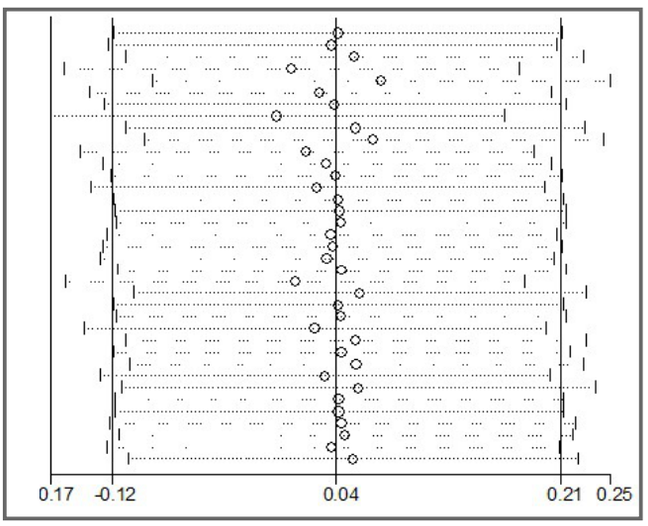

Figure3. Influence analysis

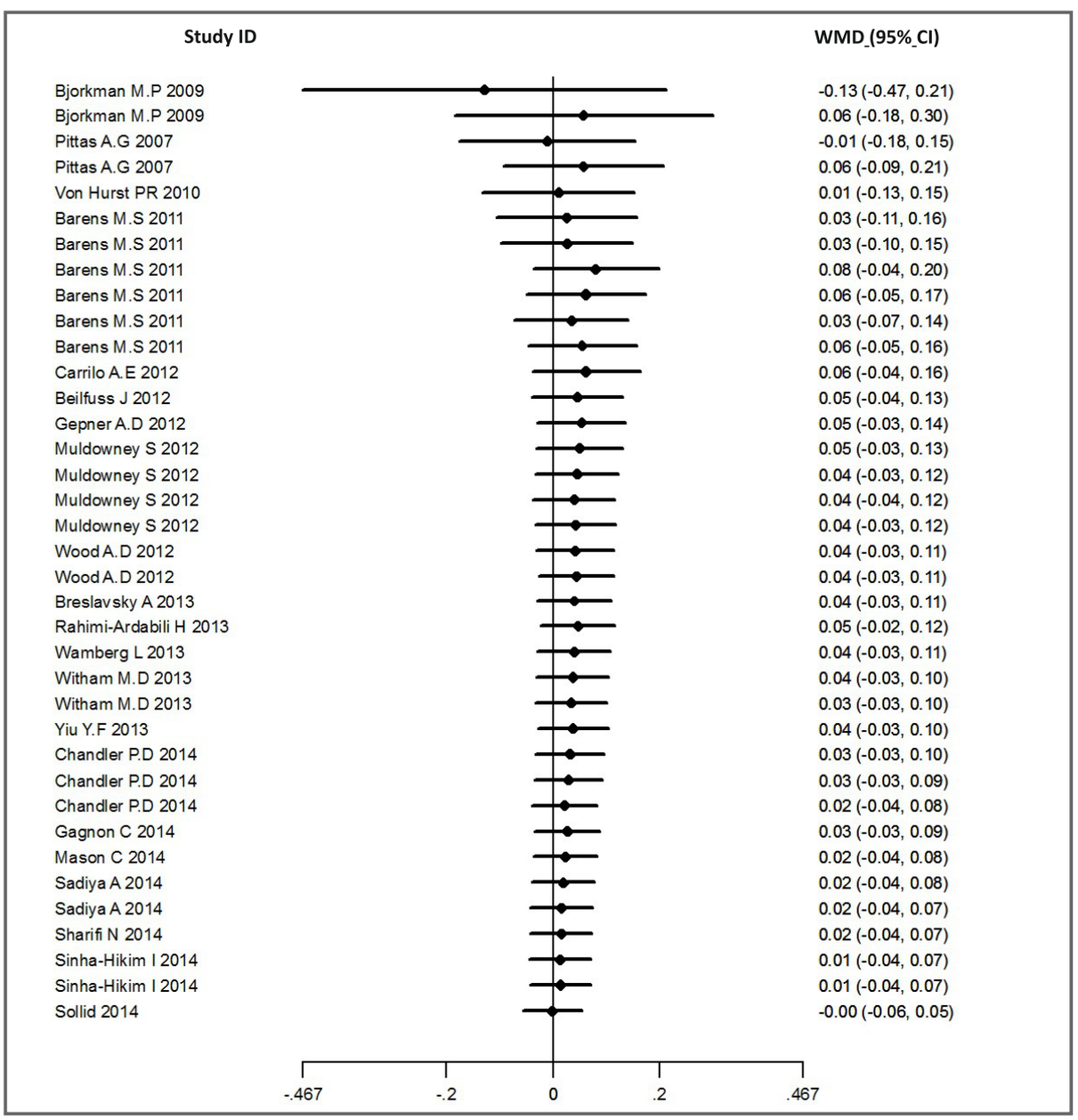

Figure 4. Cumulative analysis

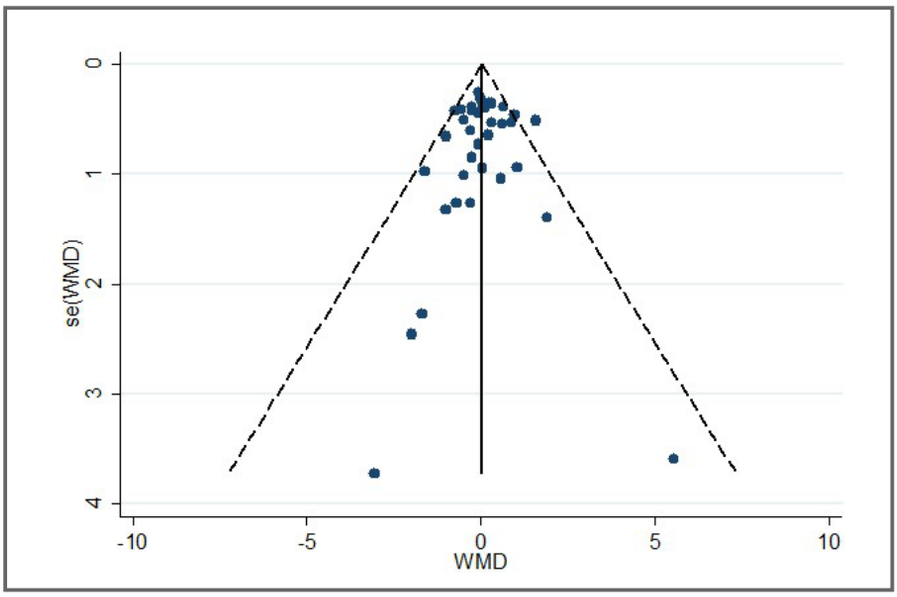

Figure 5. Funnel plot to assess publication bias

Discussion

The current meta-analysis considered previous findings from relevant studies in an attempt to determine the possible effect of vitamin D supplementation on serum levels of CRP. Meta-analysis of twenty clinical trials yielded null results. This means that either the effect of the intervention (in terms of duration or the dose of supplementation) was insignificant or the sample sizes were too small to allow the detection of a small but potentially significant effect.

Although optimal serum concentration of 25(OH)D has not been defined, it has been proposed that concentrations as high as 32 to 40 ng/ml may be required for optimal immune function and other health outcomes [17, 18]—a concentration that was not achieved in most of the included RCTs [19-22]. In addition, it is reasonable to speculate that the effects of vitamin D supplementation are influenced by the baseline levels of vitamin D and CRP and the increment of vitamin D level in blood. Some studies reported a relationship between vitamin D deficiency and increased CRP levels, with no significant effect of vitamin D supplementation on CRP [23, 24].

In many RCTs in which participants did not have a specific disease, CRP levels did not significantly change [20, 23-26], and only one trial reported a significant decline in CRP level following high-dose vitamin D supplementation [27]. One study showed that vitamin D supplementation induced a modest, but nonsignificant, decrease in circulating CRP [28], while another trial reported nonsignificantly increased CRP levels in overweight or obese subjects [16]. In spite of the high baseline CRP level in Sadiya et al [22] and Bjorkman et al [12], no significant inverse association was observed between baseline levels vitamin D and serum CRP. Other studies concluded no effect of vitamin D supplementation on CRP.

Our results are supported by observational studies. Shea et al [8] investigated the relation of vitamin D with several inflammatory markers in 1 381 subjects and showed no significant association between vitamin D status and most of the markers, including CRP. Michos et al [9] measured 25(OH)D levels in 650 Amish participants and, similarly, reported no significant association between vitamin D and CRP.

In contrast to our results, a previous meta-analysis of 10 relevant studies, totaling 924 subjects, found that vitamin D had a significant effect on CRP [29]; however, because there was evidence of heterogeneity, the results should be interpreted with caution. The strength of our study is that we pooled information from homogeneous and qualified randomized RCTs, making the results provided here more precise and powerful than the previous meta-analysis.

It has been proposed that vitamin D affects the immune system and reduces inflammation [4, 30, 31]. There are several ways through which vitamin D affects the immune system, although the exact molecular basis of these effects remains to be identified. It has been suggested that vitamin D may reduce inflammation by modulating the expression of several cytokine genes controlled by the vitamin D receptor (VDR) [32, 33]. Vitamin D suppresses inflammation through targeting the NF-kB pathway, which is a major transcription factor in response to inflammatory stimulation [34].

Our review has several limitations. First, we

found few eligible studies, although with high quality. Second, as with any meta-analysis, the potential for publication bias needs to be discussed. However, the visual inspection of the funnel plot suggests that the presence of publication bias in this meta-analysis is less likely. Finally, none of the studies included in our analysis were specifically designed to evaluate the effect of vitamin D on serum CRP. For all of these reasons, the results of this meta-analysis should be treated with considerable caution. Therefore, the inflammation-modulating effects of vitamin D supplementation should be further investigated through large-scale, higher-quality and strictly-randomized trials with adequate doses and with a proper population with a higher level of circulating CRP as an inclusion criterion.

Conclusion

Vitamin D supplementation does not seem to significantly reduce circulating CRP. These findings are generally consistent with individual reports, most of which have reported null effects.

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SE designed the study. SE and ZY performed the literature search, data extraction, and reviewing. SE performed the statistical analyses. ZY wrote the first draft of the manuscript. ZY and SE prepared the final draft.

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Conflict of Interest

None of the authors have any conflict of interest

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