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Review article

The effect of vitamin D-calcium co-supplementation on inflammatory biomarkers: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Data on the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers, compared to placebo or intake of calcium and vitamin D supplements alone, are conflicting. The current systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to summarize available findings on the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers in adults. Online databases including PubMed, Scopus, ISI Web of Science and Google Scholar were searched using relevant keywords up to June 2019. We included RCTs investigating the effect of vitamin D-calcium co-supplementation, compared to placebo or intake of calcium and vitamin D supplements alone, on inflammatory biomarkers. In total, 8 RCTs that enrolled 706 participants, aged ≥18 years, were included. Pooling 9 effect sizes from 8 RCTs on C-reactive protein (CRP) levels revealed a significant reducing effect of vitamin D-calcium co-supplementation on serum CRP concentrations compared to placebo intake (WMD: −0.82, 95% CI: −1.56, −0.07 mg/L, P = 0.03). However, this beneficial effect became non-significant when compared to the intake of calcium and vitamin D supplements alone. Also, we found that the associations of vitamin D-calcium dosages and duration of intervention with the reduction in CRP concentrations were in a non-linear fashion. Combining 5 effect sizes for IL-6 and 3 effect sizes for TNF-α, we found no significant effect of joint calcium and vitamin D supplementation on serum concentrations of IL-6 (WMD: −1.45, 95% CI: −5.31, 2.41 pg/mL, P = 0.46) and TNF-α (WMD: −0.79, 95% CI: −2.19, 0.61 pg/mL, P = 0.26). We found a beneficial effect of vitamin D-calcium co-supplementation on serum CRP concentrations. However, such a beneficial effect was not seen for IL-6 and TNF-α concentrations.

1. Introduction

It has been shown that dietary intakes of vitamin D and calcium are inversely associated with the risk of non-communicable diseases including obesity, diabetes mellitus, cardiovascular diseases, metabolic syndrome, and some cancers [1–7]. The reducing effects of vitamin D and calcium intakes on the risk of these conditions might be mediated through their effects on inflammation. Vitamin D may obstruct inflammatory processes through direct interaction with the promoter region of cytokine genes, inhibition of NF-κB dependent signaling pathways, and increment in the expression of calcium-binding proteins [8,9]. Also, it has been claimed that calcium intake might reduce inflammation through a reduction in circulating levels of Parathyroid hormone (PTH) which is positively associated with IL-6 and TNF-α

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concentrations [10,11]. In confirmation of these mechanisms, earlier randomized controlled trials (RCTs) have shown a beneficial effect of vitamin D supplementation on serum concentrations of pro-inflammatory cytokines [12–14]. A meta-analysis of clinical trials revealed a lowering effect of vitamin D supplementation on C-reactive protein (CRP) concentrations [15]. In spite of the favorable effects of vitamin D supplementation on inflammation, it is not clear whether the combined intake of calcium and vitamin D supplements is more effective than individual administration of these nutrients. Some clinical trials revealed a significant lowering effect of vitamin D-calcium co-supplementation on serum levels of pro-inflammatory cytokines compared to placebo or calcium and vitamin D supplementation alone [16–18] while others failed to reach such a significant effect [19–22]. Also, in a clinical trial, vitamin D-calcium co-supplementation resulted in a non-significant increase in CRP concentrations compared to placebo [23].

Overall, findings on the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers are conflicting and we believe that a meta-analysis examining this issue through summarizing all available clinical trials is lacking. Therefore, current systematic review and meta-analysis of published randomized clinical trials was done to summarize available findings on the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers in adults.

2. Methods

This study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol for reporting systematic reviews and meta-analyses [24].

2.1. Search strategy

We performed a systematic search for RCTs that assessed the effects of vitamin D-calcium co-supplementation on inflammatory biomarkers. We searched for relevant articles through all available online databases including PubMed, Scopus, ISI Web of Science, and Google Scholar that cover both Western and Eastern Hemisphere studies. Of note, we did not apply any filter for geographical regions. We also performed a hand-searching to avoid missing any relevant article. Databases were searched up to June 2019, using the following search terms: ("vitamin D" OR "cholecalciferol" OR "ergocalciferol" OR "vitamin D2″ OR "vitamin D3″ OR "calcium" OR "Ca") AND ("Inflammation" OR "inflammatory" OR "cytokines" OR "cytokine" OR "adipokine" OR "interleukin-1B" OR "IL-1B" OR "interleukins" OR "interleukin" OR "systemic inflammation" OR "tumor necrosis factor" OR "TNF-α" OR "TNF" OR "C-Reactive protein" OR "C reactive protein" OR "high-sensitivity CRP" OR "CRP" OR "hsCRP" OR "hs-CRP" OR "IL-6″) AND ("intervention" OR "random" OR "placebo" OR "clinical trial" OR "trial" OR "RCT"). No restriction was considered for the time of publication and language. In addition, the reference lists of the relevant articles were screened to avoid missing any publication. Duplicate citations were removed after the search was completed.

2.2. Inclusion criteria

Publications with the following criteria were included in the current meta-analysis: (1) randomized controlled trials (either parallel or cross-over) investigating the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers; (2) studies that were done on adults (≥18 years); (3) studies that reported means and standard deviations (SDs) for inflammatory biomarkers or any other effect sizes, by which the calculation of means ± SDs is possible; and (3) studies that were placebo-controlled or had a control group that received calcium or vitamin D alone. However, in the meta-analysis, placebo-controlled clinical trials and those that prescribed calcium and vitamin D alone for the control group were analyzed separately. If > 1 article was found for the same population, we included the more complete one.

2.3. Exclusion criteria

In the current meta-analysis, we did not include letters, comments, short communications, reviews, meta-analyses, ecologic studies, and animal studies. Moreover, studies performed on children and those with the intervention of foods or diets rich in calcium and vitamin D were excluded. Studies that investigated the effect of joint calcium and vitamin D along with other nutrients were excluded as well. Unpublished documents and grey literature such as conference papers, dissertations, and patents were not included.

2.4. Data extraction

Two independent investigators conducted the study selection and data extraction. The following information was extracted from each eligible study: first author's name, year of publication, mean age (SD) of participants in each group, health status of study subjects, number and sex of participants in each group, length of the intervention (week or month), study design (parallel, crossover), dosage of prescribed calcium and vitamin D, mean and SD of serum levels of inflammatory biomarkers at baseline and the end of intervention or changes in these biomarkers from baseline to the end-of-trial and variables adjusted in the statistical analysis. If a study provided multiple data at different time points, only the latest were considered. When data for an inflammatory biomarker were reported in different units, we converted them to the most frequently used one.

2.5. Risk of bias assessment

We applied the Cochrane Risk of Bias Assessment tool to assess the risk of bias for each study [22]. This tool contains seven domains including random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias and other sources of bias. Each domain was scored as "high risk" if it contained methodological flaws that may have affected the results, "low risk" if the flaw was deemed inconsequential, and "unclear risk" if the information was insufficient to determine. If a study was "low risk" based on all domains, it was considered a high-quality study with total low risk of bias. Conversely, a study was supposed as low quality if that study was scored as "high risk" for at least one domain of Cochrane Risk of Bias Assessment Tool.

2.6. Statistical analysis

Mean change and standard deviation (SD) of cytokine concentrations were used to calculate the overall effect size. When mean changes were not reported, we calculated them by considering changes in each inflammatory cytokine throughout the study. We converted reported standard errors (SEs), 95% confidence intervals, and interquartile ranges to standard deviations (SDs) using relevant formulas. The overall effect size was obtained using a random-effects model (using DerSimonian and Laird method), which takes between-study variation into account [25]. Cochran's Q test and I^2 values were used to assess between-study heterogeneity [26–28]. To detect probable sources of heterogeneity, we did subgroup analysis by the use of a fixed-effects model. Subgroup analyses were conducted based on sex (both vs. females), duration of intervention (≥12 vs. < 12 weeks), dosage of joint calcium and vitamin D supplement (≥1000 IU/d vitamin D plus ≥1000 mg/d calcium vs. < 1000 IU/d vitamin D plus < 1000 mg/d calcium) and adjustment for baseline values of inflammatory cytokines (adjusted vs. unadjusted). Sensitivity analysis was used to explore the dependence of overall estimates on a particular study. We used fractional polynomials modeling to examine the effects of vitamin D-calcium dosages (IU-mg/d) and treatment duration (weeks) on serum

concentrations of inflammatory biomarkers. Publication bias was examined by visual inspection of funnel plots and the application of Begg's test. All statistical analyses were conducted using Stata, version 11.2 (StataCorp). *P* values < 0.05 were considered as statistically significant.

3. Results

We found 1497 publications in our initial search, of them 376 were duplicate and thus removed. Out of the remaining 1121 articles, 1101 were identified as unrelated after reviewing for titles and abstracts. When investigating full texts of articles, additional 12 papers were excluded due to the following reasons: (1) studies that administered only calcium or vitamin D without any intervention group taking combined calcium and vitamin D supplements (n = 9) [12,13,29–35], (2) studies in which subjects received combined calcium and vitamin D along with other ingredients such as magnesium and zinc (n = 1) [36] and (3) studies done on animal models (n = 2) [37,38]. Finally, 8 studies remained for inclusion in the current systematic review and meta-analysis [16–23]: 8 studies had provided data for CRP [16–23], 4 trials reported data for IL-6 [16,19,20,23] and 3 studies were on TNF-α [16,20,23]. Data on other inflammatory biomarkers were not sufficient to do a meta-analysis. A Flow diagram of study selection is shown in Fig. 1.

3.1. Findings from the systematic review

Overall, 8 RCTs, published between 2007 and 2016, were included in our systematic review [16–23]. The characteristics of the included studies are presented in Table 1. These studies included a total of 706 participants aged ≥18 years. Out of 8 studies, 4 trials were performed on both sexes [16,19,20,23] and 4 studies were conducted on females only [17,18,21,22]. Two studies were performed in the United States [19,23], one in Australia [20] and the remaining five studies in Asia [16–18,21,22]. Of 2 studies from the USA, one RCT included only white persons [19] and the other trial was performed mostly on white persons (71% were white) [23]. In the Australian RCT [20], 69% of participants had a European background, 23% were Asian, and 9% were from other ethnic groups. All studies had a parallel design. The intervention period in the included RCTs varied from 6 weeks to 3 years.

Out of eight included RCTs, two studies enrolled apparently healthy individuals [20,23] and 3 studies recruited pregnant women [17,21,22]. Three trials included patients with specific medical conditions including diabetes [16], PCOS [18], and colorectal adenoma [23]. In all included RCTs, vitamin D-calcium co-supplementation was compared with the placebo. In addition to comparison to placebo, in 3 studies, vitamin D-calcium co-supplementation was compared with the intake of calcium and vitamin D alone [16,18,23]. The prescribed dosage for vitamin D ranged from 700 IU/d to 50000 IU/2wk and for calcium varied from 500 to 2000 mg/d. In 6 out of 8 studies, statistical analysis was controlled for baseline values of inflammatory cytokines [16,18–22]. Only one trial had a low risk of bias in all domains of Cochrane Risk of Bias Assessment Tool [16] while others were judged as high risk of bias at least in one domain of this tool [17–23] (Supplemental Table 1).

Among 8 studies on serum CRP concentrations, 3 studies concluded a significant reduction in CRP concentrations after co-supplementation with calcium and vitamin D compared to the placebo [16–18] whereas others reported no significant effect [19–23]. In regard to IL-6 concentrations, only one study had reported a significant lowering effect of vitamin D-calcium co-supplementation compared to the placebo [16]. Three studies had examined the effect of vitamin D-calcium co-supplementation on serum TNF-α concentrations compared to the placebo; of them, only one revealed a beneficial effect and others did not find any significant effect [16]. Among studies in which vitamin D-calcium co-supplementation was compared to intake of calcium and vitamin D supplements alone, none had shown a beneficial effect on CRP, IL-6, and TNF-α concentrations.

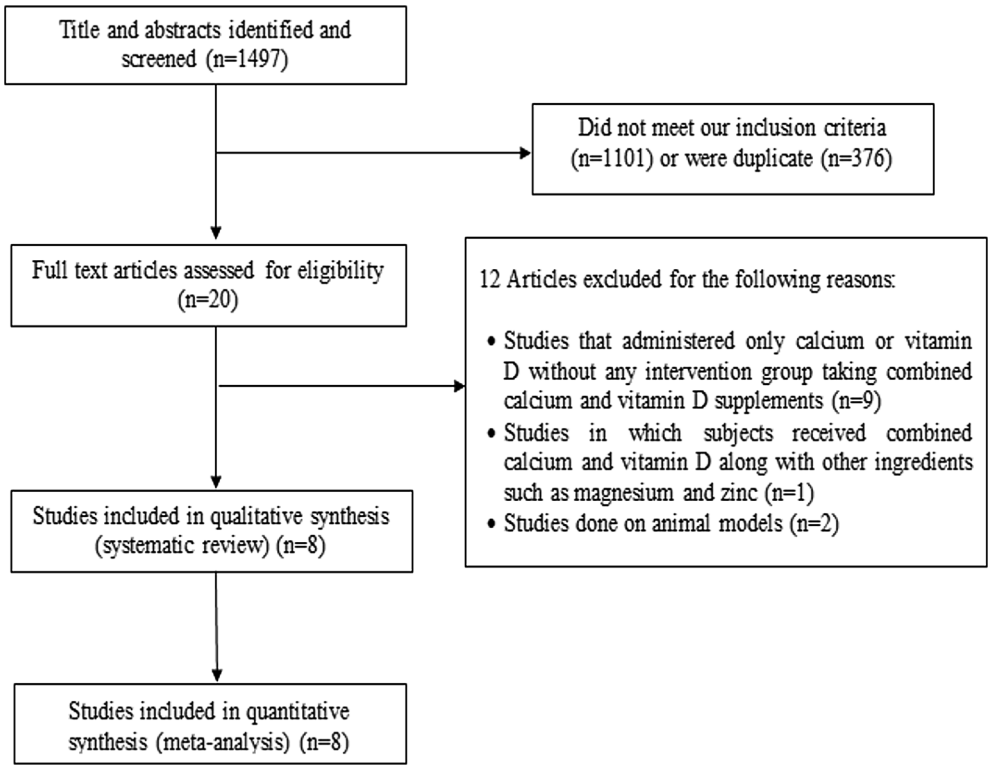

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of randomized clinical trials included in the current meta-analysis

Author (Ref)	n (Int/ cont)	Sex	Ethnicity	Age mean or range, year (Int/ cont)[a]	Health condition	Study design	Supplementation		Intervention period	Outcomes[a]		Adjust/matching
							Intervention group	Control group		Intervention	Control	
Pittas et al. 2007 [19]	108/ 114	M/F	69% European background, 23% Asian, 9% others	70.6 ± 0.4 /71.7 ± 0.4	Healthy	RA/ DB/PC	500 mg/d Ca citrate + 700 IU/d vit D	Placebo (cellulose)	3 years	CRP; change: 0.5 ± 3.32 IL-6; change: 0.14 ± 4.05	CRP; change: 0.79 ± 7.47 IL-6; change: 0.48 ± 6.29	Adjusted for baseline measurements Matched for sex and age
	45/47	M/F		71.1 ± 0.7 /71.3 ± 0.8	IFG	RA/ DB/PC	500 mg/d Ca citrate + 700 IU/d vit D	Placebo (cellulose)	3 years	CRP; change: 1.46 ± 10.46 IL-6; change: 0.78 ± 5.63	CRP; change: 1.19 ± 3.83 IL-6; change: 0.48 ± 4.38	
Hopkins et al. 2011 [23]	21/21	M/F	71% white American	61.7 ± 7.4 /58.5 ± 7.9	Colorectal adenoma	RA/ DB/PC	2000 mg/d elemental Ca + 800 IU/d vit D	Placebo (NR)	6 months	CRP; before: 1.93 ± 2.94, after: 2.21 ± 3.06 IL-6; before: 1.39 ± 4.5, after: 1.62 ± 3.25 TNF-α; before: 3.62 ± 1.75, after: 4 ± 1.62	CRP; before: 1.77 ± 3.8, after: 1.88 ± 4.16 IL-6; before: 1.13 ± 4.54, after: 1.41 ± 2.67 TNF-α; before: 4.13 ± 1.92, after: 4.57 ± 2.05	Matched for sex and anti-inflammatory drugs
Asemi et al. 2014 [21]	28/28	F	Asian	28.7 ± 6.0 /30.8 ± 6.6	Pregnancy with GDM	RA/ DB/PC	1000 mg/d Ca carbonate + 50000 IU/3wk vit D	Placebo (NR)	6 weeks	CRP; change: −0.02 ± 0.68	CRP; change: −0.19 ± 0.68	Adjusted for baseline measurements, age and BMI Matched for BMI and week of gestation
Gagnon et al. 2014 [20]	35/45	M/F	White American	53.8 ± 11.9 /55.3 ± 11.1	Healthy	RA/ DB/PC	1200 mg/day Ca carbonate + 2000 IU/day vit D	Placebo (NR)	6 months	CRP; change: −1.90 ± 9.63 IL-6; change: 0.00 ± 0.74 TNF-α; change: 0.29 ± 1.71	CRP; change: 0.13 ± 1.50 IL-6; change: 0.00 ± 1.54 TNF-α; change: 0.40 ± 1.95	Adjusted for baseline measurements Matched for age, sex and BMI
Tabesh et al. 2014 [16]	29/30	M/F	Asian	49.8 ± 6.1 /51.0 ± 6.1	Type 2 diabetes mellitus	RA/ DB/PC	1000 mg/day Ca carbonate + 50000 IU/wk vit D	Placebo (NR)	8 weeks	CRP; change: −1.19 ± 0.25 IL-6; change: −4.00 ± 1.00 TNF-α; change: −3.20 ± 1.30	CRP; change: 0.08 ± 0.24 IL-6; change: 3.00 ± 1.00 TNF-α; change: −1.00 ± 1.30	Adjusted for baseline measurements, age, sex and physical activity Matched for age, sex, BMI, diabetes duration, type and dose of drugs
Foroozanfard et al. 2015 [18]	26/26	F	Asian	18–40 /18–40	polycystic ovary syndrome	RA/ DB/PC	1000 mg/day Ca carbonate + 50000 IU vit D/wk	Placebo (NR)	8 weeks	CRP; change: −1.00 ± 2.53	CRP; change: 0.52 ± 2.53	Adjusted for baseline measurements, age and BMI Matched for age and BMI
Samimi et al. 2015 [22]	30/30	F	Asian	27.3 ± 3.7 /27.1 ± 5.2	Pregnancy	RA/ DB/PC	1000 mg/day Ca carbonate + 50000 IU /2wk vit D	Placebo (NR)	12 weeks	CRP; change: −1.51 ± 2.73	CRP; change: −0.35 ± 2.73	Adjusted for baseline measurements, age and BMI Matched for age and BMI
Asemi et al. 2016 [17]	21/21	F	Asian	25.7 ± 4.2 /24.3 ± 3.4	Pregnancy	RA/ DB/PC	500 mg/day Ca carbonate + 200 IU/day vit D	Placebo (cellulose)	9 weeks	CRP; change: −1.86 ± 2.65	CRP; change: 0.73 ± 3.13	

Abbreviations: Int: intervention, Cont: control, DB: double-blinded, PC: placebo-controlled, RA: randomized, NR: not reported, F: Female, M: Male, vit: vitamin, Ca: calcium, BMI: Body mass index, GDM: gestational diabetes mellitus, IFG: Impaired fasting glucose, CRP: C-reactive protein, TNF: tumor necrosis factor

[a] Data are presented as mean ± SD.

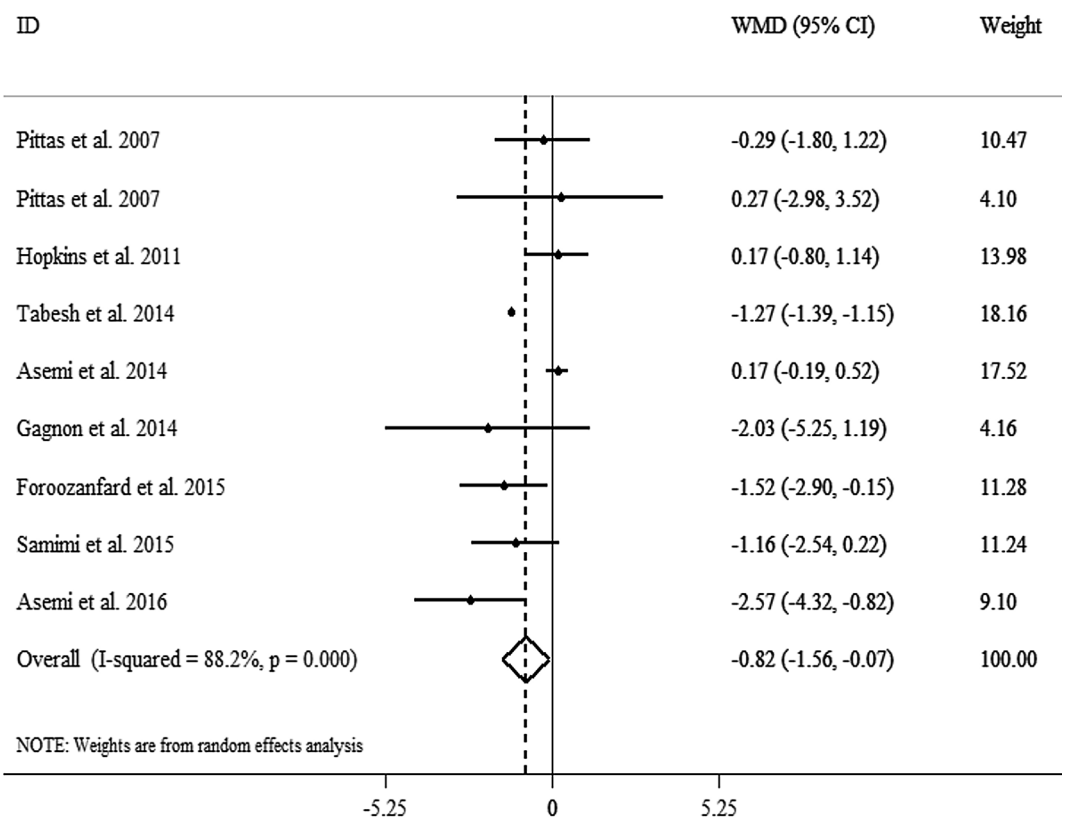

Fig. 2. Forest plot for the effect of vitamin D-calcium co-supplementation on serum CRP concentrations, compared with the placebo. Horizontal lines represent 95% CIs. Diamonds represent pooled estimate from random-effects analysis. CRP: C-reactive protein, WMD: weighted mean difference, CI: confidence interval.

3.2. Findings from the meta-analysis

Overall, 8 RCTs with a total sample size of 706 participants aged ≥18 years were included in the current meta-analysis. In the study by Pittas et al., the effects of vitamin D-calcium co-supplementation on inflammatory cytokines were separately assessed in participants with and without impaired fasting glucose [19]. Therefore, we considered that study as two separate studies. In this section, we compared the effect of vitamin D-calcium co-supplementation with placebo or intake of calcium and vitamin D supplements alone. However, because of the limited number of studies on IL-6 and TNF-α, comparing joint intake of calcium and vitamin D supplements against individual supplementation of these nutrients was not possible.

3.2.1. Vitamin D-calcium co-supplementation and serum CRP concentrations

Combining 9 effect sizes from 8 studies [16–23] in which joint vitamin D-calcium supplementation was compared to the placebo revealed a significant reducing effect of vitamin D-calcium co-supplementation on serum CRP concentrations (WMD: −0.82, 95% CI: −1.56, −0.07 mg/L, P = 0.03) (Fig. 2). However, there was a significant between-study heterogeneity (I^2 = 88.2, P < 0.001). When we excluded studies on pregnant women and repeated the analysis, the findings did not change (WMD: −0.81, 95% CI: −1.54, −0.08 mg/L, P = 0.03) (Figure no shown).

To detect probable sources of heterogeneity, we did subgroup analysis based on participants' sex (both vs. females), duration of intervention (≥12 vs. < 12 weeks), dosage of joint calcium and vitamin D supplements (≥1000 IU/d vitamin D plus ≥1000 mg/d calcium vs. < 1000 IU/d vitamin D plus < 1000 mg/d calcium) and adjustment for baseline values of inflammatory cytokines (adjusted vs. unadjusted) (Table 2). Based on this analysis, sex and duration of intervention could explain between-study heterogeneity. Compared with the placebo, vitamin D-calcium co-supplementation resulted in a significant reduction in serum CRP concentrations in studies done on both sexes (WMD: −1.24, 95% CI: −1.36, −1.12 mg/L, P < 0.001), those that had an intervention duration of < 12 weeks (WMD: −1.12, 95% CI: −1.24, −1.01 mg/L, P < 0.001), studies that did intervention with ≥1000 IU/d vitamin D plus ≥1000 mg/d calcium (WMD: −1.10, 95% CI: −1.22, −0.99 mg/L, P < 0.001) and < 1000 IU/d vitamin D plus < 1000 mg/d calcium (WMD: −1.09, 95% CI: −2.17, −0.01 mg/L, P = 0.04), and those that controlled their analysis for baseline levels of CRP (WMD: −1.11, 95% CI: −1.23, −1.00 mg/L, P < 0.001).

In the non-linear dose-response analysis, we found a non-linear association between dosage of vitamin D-calcium co-supplementation and CRP levels (Fig. 3A); such that the reducing effect of vitamin D-calcium on CRP levels was seen at the dosages of ≥700–500 IU-mg/day ($P_{non\text{-}linearity}$ = 0.01). Moreover, the reducing effect was reversed in longer durations (> 12 weeks) ($P_{non\text{-}linearity}$ = 0.01) (Fig. 2B).

Three studies had compared joint calcium and vitamin D supplementation to the intake of these supplements alone [16,18,23]. Combining three effect sizes from these studies, vitamin D-calcium co-supplementation had no significant effect on serum CRP concentrations compared to intake of calcium supplement alone (WMD: −0.83, 95% CI: −1.83, 0.17 mg/L, P = 0.10) (Fig. 4). Such a non-significant effect was also seen when comparing vitamin D-calcium co-supplementation to the intake of vitamin D supplement alone (WMD: −0.35, 95% CI: −1.50, 0.81 mg/L, P = 0.55) (Fig. 4). In both comparisons, between-study heterogeneity was significant (I^2 > 76.0, P < 0.02).

The sensitivity analysis revealed that exclusion of any single study had no significant effect on the overall estimates obtained for the effect of vitamin D-calcium co-supplementation on serum CRP concentrations. Moreover, we found no evidence of substantial publication bias based on visual inspection of the funnel plots (Supplemental Fig. 1) and formal test of Begg (P > 0.10).

Table 2
Subgroup-analysis on the effects of vitamin D-calcium co-supplementation on serum CRP concentrations

	Effect sizes (n)	Mean (95% CI)	P-within[a]	I[b] (%)[b]	Q-test	P-between
Overall	8	−1.10 (-1.22, −0.99)	< 0.001	88.2	< 0.001	
Participants' sex						0.001
Females	4	−0.10 (-0.43, 0.23)	0.54	81.4	0.001	
Both	5	−1.24 (-1.36, −1.12)	< 0.001	63.6	0.02	
Duration of intervention						< 0.001
< 12 weeks	4	−1.12 (-1.24, −1.01)	< 0.001	94.9	< 0.001	
≥12 weeks	5	−0.32 (-1.00, 0.35)	0.34	0	0.46	
Dose of joint Ca and vit D						0.98
< 1000 IU/d vit D plus < 1000 mg/d Ca	3	−1.09 (-2.17, −0.01)	0.04	55.5	0.10	
≥1000 IU/d vit D plus ≥ 1000 mg/d Ca	6	−1.10 (-1.22, −0.99)	< 0.001	92.1	< 0.001	
Adjustment for baseline values						0.13
Non-adjusted	2	−0.47 (-1.31, 0.38)	0.27	86.1	0.007	
Adjusted	7	−1.11 (-1.23, −1.00)	< 0.001	89.7	< 0.001	

Abbreviations: CRP: C-reactive protein; CI: confidence interval, Ca: calcium, vit: vitamin.
[a] Refers to the mean (95% CI).
[b] Inconsistency, percentage of variation across studies due to heterogeneity.

3.2.2. Vitamin D-calcium co-supplementation and serum IL-6 concentrations

When we combined 5 effect sizes from 4 studies [16,19,20,23] evaluated the effect of vitamin D-calcium co-supplementation on serum IL-6 concentrations compared to the placebo, no beneficial effect was found (WMD: −1.45, 95% CI: −5.31, 2.41 pg/mL, P = 0.46) (Fig. 5). Between-study heterogeneity was significant in this regard (I^2 > 99.0, P < 0.001). There was no effect size from studies enrolled pregnant women in this respect. Due to the limited number of studies, we could not conduct a subgroup analysis.

Non-linear dose-response analysis did not show any significant effects of vitamin D-calcium dosages ($P_{non\text{-}linearity}$ = 0.12) and duration of intervention ($P_{non\text{-}linearity}$ = 0.75) on circulating IL-6 (Fig. 2.**C & D**). Findings from the sensitivity analysis revealed that no single study

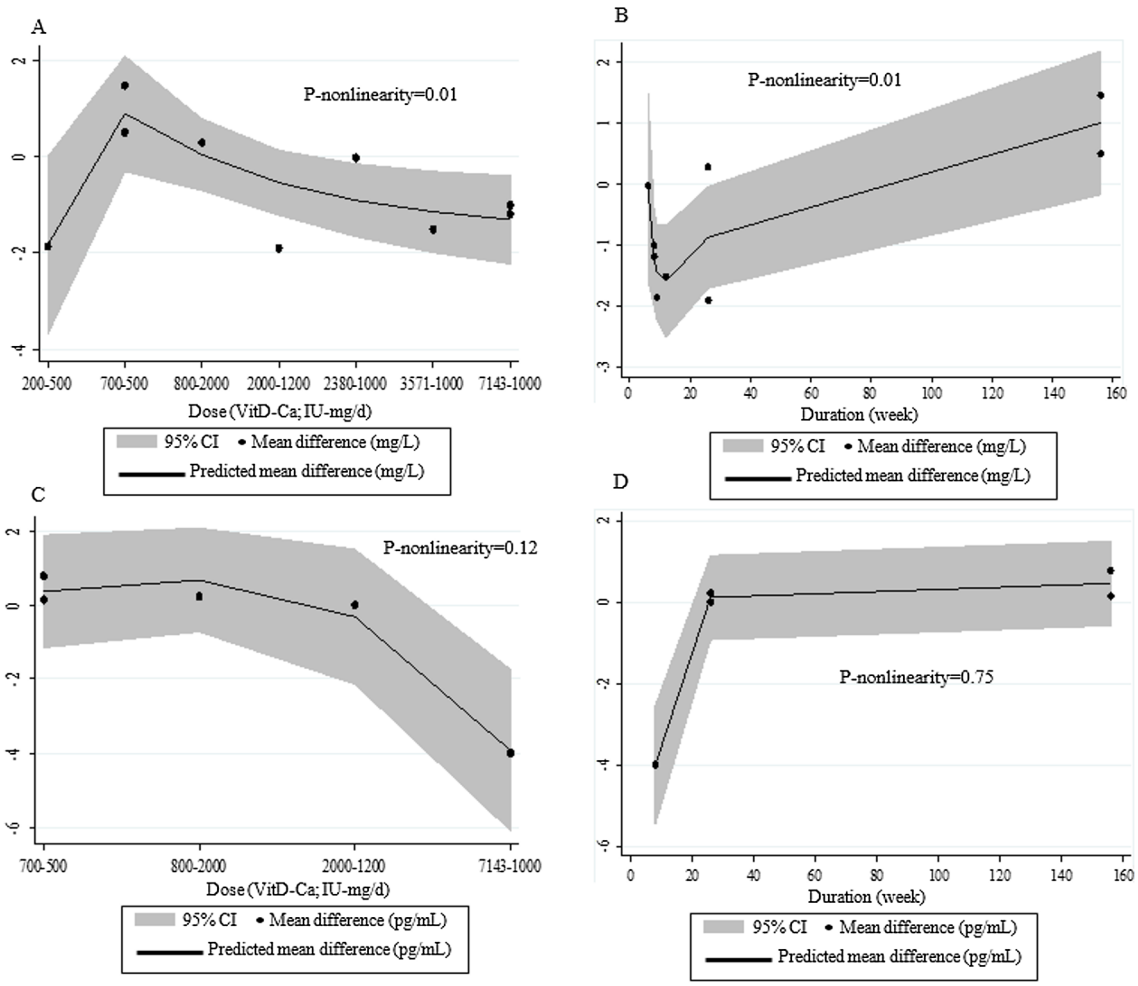

Fig. 3. Non-linear dose-response effects of vitamin D-calcium dosages and intervention duration on serum concentrations of CRP (A & B) and IL-6 (C & D). The 95% CI is demonstrated in the shaded regions. CRP: C-reactive protein, IL-6: interleukin 6, CI: confidence interval.

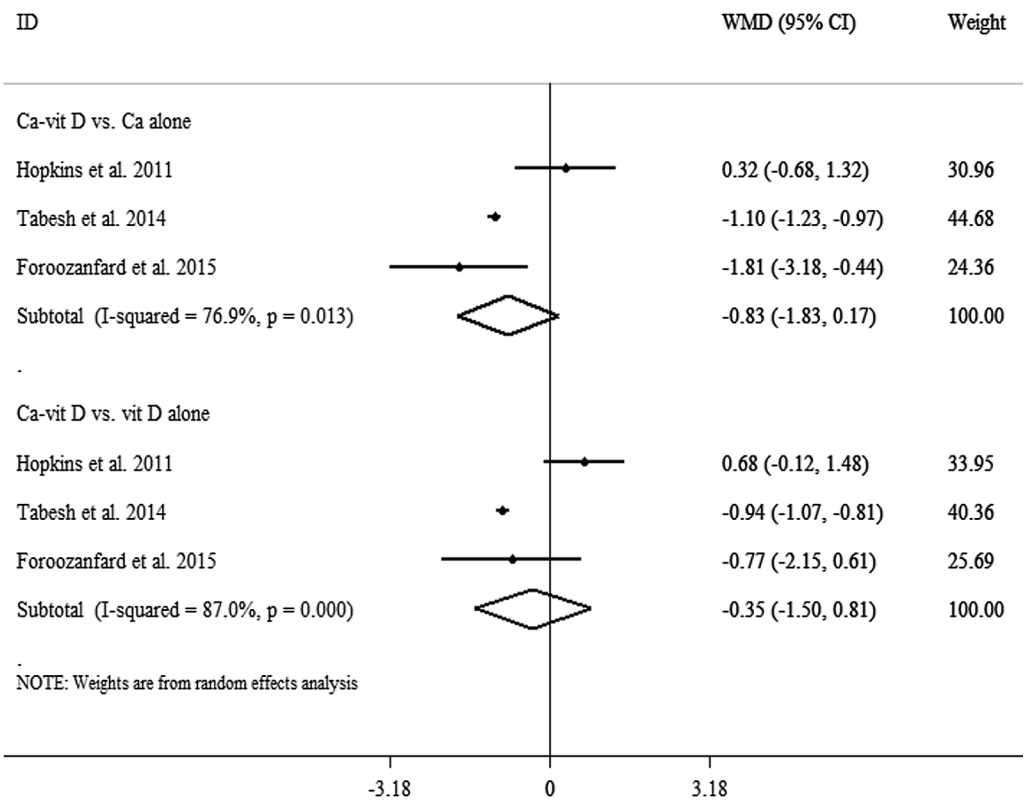

Fig. 4. Forest plot for the effect of vitamin D-calcium co-supplementation on serum CRP concentrations, compared with intake of calcium or vitamin D alone. Horizontal lines represent 95% CIs. Diamonds represent pooled estimate from random-effects analysis. CRP: C-reactive protein, Ca: calcium, vit: vitamin, WMD: weighted mean difference, CI: confidence interval.

influenced the final findings on the effect of vitamin D-calcium co-supplementation on serum IL-6 concentrations. Based on visual inspection of the funnel plot, we observed a moderate asymmetry (Supplemental Fig. 2A). however, Begg's regression test rejected our hypothesis on the presence of substantial publication bias (P = 0.62).

3.2.3. Vitamin D-calcium co-supplementation and serum TNF-α concentrations

In total, combining 3 effect sizes from 3 RCTs [16,20,23] revealed no significant effect of vitamin D-calcium co-supplementation on serum TNF-α concentrations compared with the placebo (WMD: −0.79, 95%

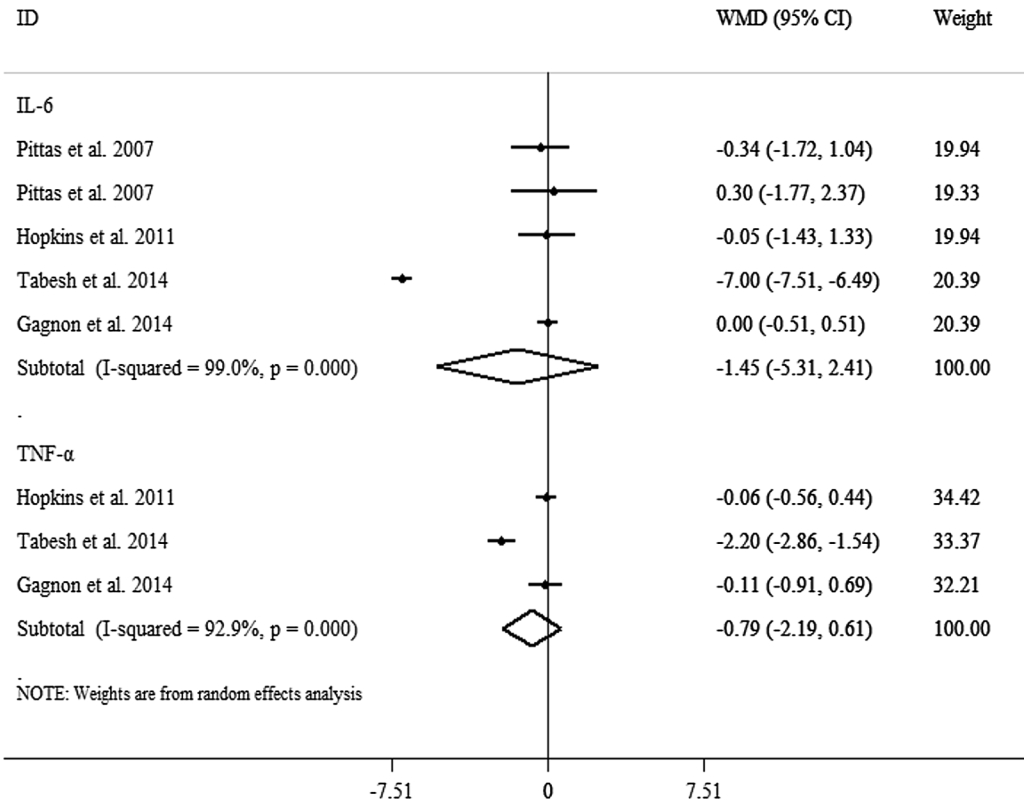

Fig. 5. Forest plot for the effect of vitamin D-calcium co-supplementation on serum IL-6 and TNF-α concentrations, compared with the placebo. Horizontal lines represent 95% CIs. Diamonds represent pooled estimate from random-effects analysis. TNF: tumor necrosis factor, IL-6: interleukin-6, WMD: weighted mean difference, CI: confidence interval.

CI: −2.19, 0.61 pg/mL, P = 0.26) (Fig. 5). There was evidence of between-study heterogeneity (I^2 = 92.9, P < 0.001). This overall estimate contained no effect size from studies performed on pregnant women. We could not conduct a subgroup analysis as well as dose-response analysis because of an insufficient number of RCTs in terms of TNF-α levels. Based on findings from the sensitivity analysis, the overall estimate obtained for TNF-α did not depend on a particular study. No evidence of publication bias was seen based on the funnel plot (Supplemental Fig. 2.B) and Begg test (P = 0.60).

4. Discussion

In the current study, we found that vitamin D-calcium co-supplementation had a significant reducing effect on serum CRP concentrations when compared to the placebo but not against calcium and vitamin D alone. Also, the greatest lowering effect of vitamin D-calcium co-supplementation on CRP concentrations was seen at the dosages of ≥700–500 IU-mg/day. In regard to IL-6 and TNF-α concentrations, joint intake of calcium and vitamin D supplements had no beneficial effect. To the best of our knowledge, this study is the first meta-analysis that summarizes prior publications on the effects of vitamin D-calcium co-supplementation on systematic inflammation.

Inflammation is involved in the etiology of several chronic diseases [39–41]. The beneficial effects of vitamin D supplementation on inflammatory cytokines have been shown in a recent meta-analysis [42]. Also, earlier studies revealed the anti-inflammatory properties of calcium supplementation [43,44]. However, data on the effects of combined calcium and vitamin D intake on inflammatory cytokines are contradictory. In the current study, we found that vitamin D-calcium co-supplementation resulted in a significant reduction in serum CRP concentrations compared to the placebo. In a review article, Da Silva et al. concluded that consumption of dairy products improved plasma lipids, blood pressure, glucose homeostasis, inflammatory parameters, and oxidative stress profile [45]. Dairy products are known as rich sources of vitamin D and calcium. Anti-inflammatory properties of dairy products were also reported in a systematic review and meta-analysis of RCTs [46]. Moreover, in a study by Neyestani et al., daily consumption of vitamin D-fortified Doogh (a yogurt-based beverage) with and without extra calcium reduced serum CRP concentrations compared to the intake of plain Doogh. However, this effect was more pronounced when participants received vitamin D-fortified Doogh with extra calcium [47].

In opposite to our findings, a prospective cohort study revealed no significant association between dairy product consumption and serum CRP concentrations [48]. In cohort studies, free-living people who consume different amounts of dairy products or food groups rich in calcium and vitamin D are followed for a long time. Therefore, their findings might be comparable to those obtained from RCTs. Nevertheless, summarizing available findings from clinical trials, we observed different findings compared to those obtained from cohort studies. It should be noted that findings from cohort studies are subject to residual bias due to uncontrolled confounders while RCTs are less exposed to this source of bias.

Based on findings from the subgroup analysis, vitamin D-calcium co-supplementation resulted in a significant reduction in serum CRP levels in RCTs with an intervention duration of < 12 weeks but not in those with a duration of ≥12 weeks. This finding was also confirmed by dose-response analysis in which the beneficial effect was only observed in trials with a short duration of intervention. This disparity might be explained by initial levels of serum CRP which is a predictor of response to different interventions including calcium and vitamin D supplementation. For example, in 2 RCTs [19,23] out of 4 studies with ≥12 weeks' duration of intervention [19,20,22,23], baseline values of CRP was less than 3 mg/L while in 3 RCTs [17,18,21] out of 4 studies with < 12 weeks duration of intervention [16–18,21], baseline values of CRP was > 3 mg/L. However, when we confined the analysis to studies that adjusted the analysis for baseline values of serum CRP, a significant reduction was found following vitamin D-calcium co-supplementation.

In the current meta-analysis, we found no significant effect of vitamin D-calcium co-supplementation on serum concentrations of IL-6 and TNF-α. In agreement with our findings, a recent meta-analysis showed that supplementation with vitamin D among patients with psychiatric disorders reduced serum CRP concentration but did not affect other inflammatory cytokines such as IL-6 and TNF-α [15]. The non-significant effect of vitamin D-calcium co-supplementation on these inflammatory cytokines might be due to the limited number of studies with a low risk of bias. For instance, out of 3 included RCTs evaluated the effects of vitamin D-calcium co-supplementation on IL-6 and TNF-α levels [16,20,23], one had low risk of bias in all domains of Cochrane Risk of Bias Assessment Tool and revealed a beneficial effect of this supplementation on IL-6 and TNF-α concentrations [16] whereas the two other studies with high risk of bias in some domains of this tool showed no significant effect [20,23].

Several mechanisms have been proposed for the beneficial effects of joint calcium and vitamin D supplementation on CRP concentrations. It has been suggested that vitamin D regulates the production of macrophages-related inflammatory cytokines through calcium-dependent mechanisms [49]. Vitamin D may reduce inflammation via regulation of serum levels of calcium and suppression of PTH [50]. Circulating levels of PTH are positively associated with serum levels of inflammatory biomarkers [50]. Vitamin D interacts with its response elements in the promoter region of inflammatory cytokine genes to interfere with nuclear transcription factors contributed to cytokine production and action [51]. Moreover, vitamin D can suppress the activation of nuclear factor-kB (NF-kB), as an important regulator of genes encoding inflammatory factors [16,51]. Also, this might have a suppressing effect on cytokines production by up-regulating the expression of calbindin, a cytosolic calcium-binding protein [52].

As for the strengths of the current meta-analysis, it must be noted that we included all RCTs reported the effect of vitamin D-calcium co-supplementation on inflammatory cytokines. However, some limitations should be considered when interpreting our findings. We found significant between-study heterogeneity in our analyses; however, we tried to detect potential sources of this heterogeneity. Clinical trials included in the current meta-analysis were conducted on individuals with different health conditions. Due to the limited number of studies, we could not consider this factor in our subgroup analyses. Other limitations include considering inflammatory biomarkers as the secondary outcome variables in some included RCTs, lack of adjustment for baseline values of cytokines, and disregarding dietary intakes and physical activity of participants throughout the trial in some others. Given that the most studies included in the current meta-analysis were conducted on Caucasians (in the US, Australia, and Asia), it remains possible that our findings apply only to Caucasians and may not generally apply to all peoples with different ethnicity and ancestry. As it is well-known, the prevalence of vitamin D deficiency is different among peoples with different ethnicity [6,53,54]. For instance, Blacks have a higher prevalence of vitamin D deficiency compared with Caucasians [53]. However, we are aware of no study that examined the effect of vitamin D-calcium co-supplementation on inflammatory biomarkers in Blacks. Therefore, the generalizability of our findings should be done with caution.

5. Conclusion

In conclusion, we found a significant reducing effect of vitamin D-calcium co-supplementation on serum CRP concentrations compared to the placebo. However, when compared to the intake of calcium and vitamin D alone, the effect was no longer significant. The beneficial effect of vitamin D-calcium co-supplementation on CRP concentrations was seen at the dosages of ≥700–500 IU-mg/day. Moreover, joint

calcium and vitamin D intake had no significant effect on serum concentrations of IL-6 and TNF-α.

Authors' contributions

OA, MS, AS, HMK, FHS, and OS contributed to the conception, design, statistical analyses, data interpretation, and manuscript drafting. VM and OS contributed to data analysis, data interpretation, and manuscript drafting. OS and MA contributed to manuscript editing. All authors approved the final manuscript for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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