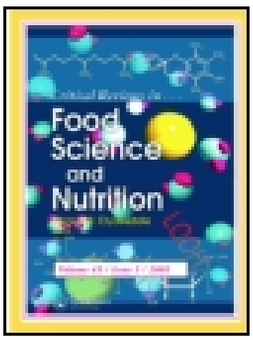

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The effect of calcium supplement intake on lipid profile: a systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Despite the potential role of dietary calcium in fat excretion, the favorable effects of calcium supplements on lipid profile remains inconclusive. The current study aimed to review the effect of calcium supplement intake on lipid profile in randomized controlled clinical trials (RCTs). This systematic review and meta-analysis was conducted in PubMed, Scopus, Embase, and Central. RCTs which assessed the effects of calcium supplementation on lipid profile were included. All outcomes were recorded as continuous variables, and the effect size was measured. We classified studies according to dose of supplement, study duration, and dyslipidemia. Calcium supplement intake was associated with a significant reduction in low density lipoprotein cholesterol (LDL-C) level (WMD:-0.08; 95%CI:-0.16,-0.01)(mmol/l), especially with intakes of at least 1000 mg/day (WMD:-0.13; 95%CI:-0.23,-0.03)(mmol/l), with intakes of at least 12 weeks (WMD:-0.08; 95%CI: −0.16,-0.00)(mmol/l), and in individuals without dyslipidemia (WMD:-0.15; 95%CI:-0.26,-0.04)(mmol/l). Also, in another subgroup analysis, consumption of less than 1000 mg/day calcium supplement caused a significant increase in Total Cholesterol (TC) level (WMD: 0.24; 95%CI: 0.05,0.42) (mmol/l). In other blood lipids or study subgroups we observed no significant effect. We concluded that calcium supplements had a favorable effect on LDL-C level, especially in individuals without dyslipidemia, higher calcium intakes, and longer period of consumption.

KEYWORDS

Calcium; total cholesterol; triacylglycerol; high density lipoprotein cholesterol; low density lipoprotein cholesterol

Introduction

Calcium supplementation is widespread especially among older adults for bone health (Bailey et al. 2010). However, beyond the role of preventing and treating bone disorders, it has some non-skeletal benefits such as: cardiovascular health by modulating blood pressure or lipid profile (Reid, Bolland, and Gray 2012). Although previous interventional/observational studies demonstrated the protective role of dietary calcium on cardiovascular disease (CVD) (Cappuccio et al. 1995; Reid et al. 2002), randomized controlled trials showed conflicting results on calcium supplements (Bolland et al. 2010, 2011).

In fact, it is suggested that calcium may reduce the risk of CVD via its effects on blood lipids (Chai et al. 2013; Grey et al. 2006; Reid et al. 2010). It is reported that calcium could increase fecal saturated fat excretion and decrease serum TC and LDL-C (Denke, Fox, and Schulte 1993). According to a meta-analysis in 2009, calcium intake has the potential to prevent metabolic abnormalities related to weight (re-)gain by increasing fecal fat excretion. (Christensen et al. 2009). Moreover, another meta-analysis of randomized controlled trials demonstrated that chronic high calcium intake increases fat oxidation significantly to approximately 11 percent. Also, the results of acute high calcium consumption were the same. It has been demonstrated that high calcium intake could increase fat oxidation rate and prevent fat accumulation in the body. (Gonzalez, Rumbold, and Stevenson 2012).

Despite mentioned suggested mechanisms, some clinical trials resulted in no significant benefits of calcium supplement intake on lipid and/or lipoprotein concentrations (Celik and Inanc 2016; Raziani et al. 2016). Since there is no meta-analysis on this topic, and given the contradictory findings about the impacts of calcium supplements on blood lipids and CVD risk, we decided to do a systematic review and meta-analysis to evaluate the effects of calcium supplement intake on lipid profile in adults and to answer the question "whether calcium supplement influence blood lipids or not".

Methods

Search strategy

To find relevant papers, we searched PubMed, Central, Scopus, and Embase. The following Medical Subjects and Headings (MeSH) terms and keywords were used: 1)

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"calcium supplement"; 2)"cholesterol" or "triglycerides" or "Cholesterol, HDL" or "Cholesterol, LDL" or "Triacylglycerol" or "Hypercholesterolemia" or "LDL Cholesterol" or "Low Density Lipoprotein Cholesterol" or "beta-Lipoprotein Cholesterol" or "High Density Lipoprotein Cholesterol" or "alpha-Lipoprotein Cholesterol" or "HDL Cholesterol" or "alpha Lipoprotein Cholesterol" or "lipid profile"; 3) 1 & 2. To find more relevant papers, a hand search was performed on the references of related papers. All studies published at any time till December 2019 were included with no language restriction.

Study eligibility

This systematic review and meta-analysis was conducted in accordance with 2009 PRISMA checklist (Liberati et al. 2009). Two different authors (MA, SF) assessed the title, abstract and full text of the articles. Eligibility criteria was based on the PICOS format, where "population" were adults, "intervention" involved calcium supplements consumption, "Comparator" was a control group, "outcomes" included serum lipid profiles, and "study design" included randomized controlled trial studies. However, these papers were excluded: 1) animal studies, editorial/letters to editor, review articles, 2) studies which were not published in peer-reviewed journals such as abstracts from conference proceedings, dissertations, and master's thesis, 3)studies with any designs other than RCT 4) trials with insufficient data 5) studies that did not evaluate the pure effects of calcium supplements on lipid profiles.

Data extraction

Three authors (SF, SG, SMDR) were responsible for extracting the data. The following data were extracted from each

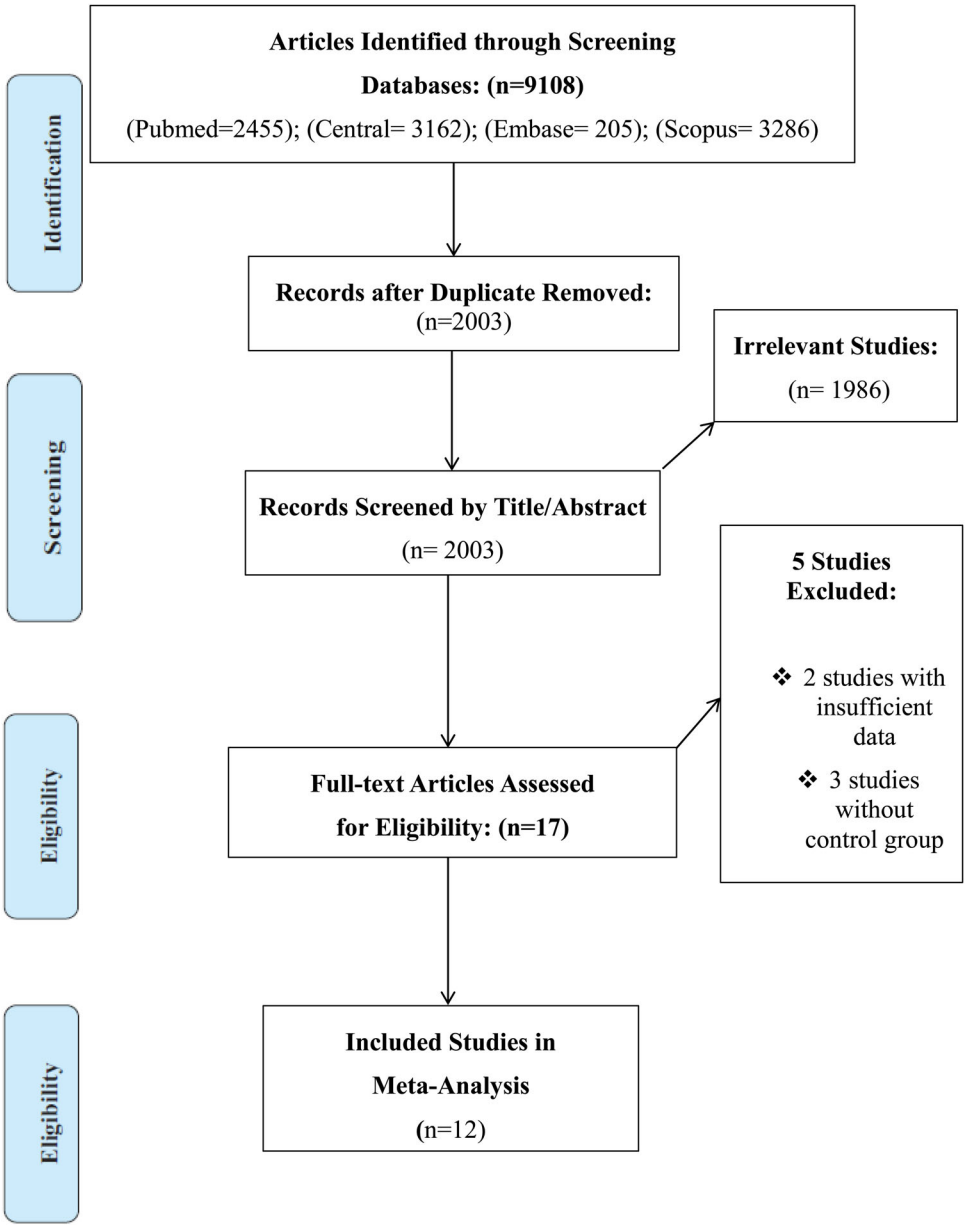

Figure 1. Flow diagram of database searches and study selection.

Table 1. Characteristics and main outcome of the RCTs.

Author (Country/ Year)	Number of Participants (int/con)	Age (mean ± SD)	Sex	RCT (Design)	Intervention (Dosage)	Duration (day)	Health status	Adverse Effect	Results
Asemi et al. (Iran, 2015)	26:26	25 ± 0.5	Female	PA	Supplement (1000 mg/d)	56	PCO	No AE	NS
Chai et al. (USA, 2013)	21:21	60 ± 8	Both	PA	Supplement (2ooo mg/d)	180	Colorectal adenoma	NO AE	TG decreased significantly, NS change in TC.
Grey et al. (Newzealand, 2006)	59:57	72 ± 4	Female	PA	Supplement (1000 mg/d)	365	Healthy	No AE	NS
Karandish et al. (Iran, 2009)	24:20	25 ± 6	Female	PA	Supplement (1000 mg/d)	20	Obese	No AE	NS
Karanja et al. (USA, 1994)	49:55	50 ± 10	Males	PA	Supplement (1000 mg/d)	84	Hypertensive/ normotensive	No AE	NS
	60:56	50 ± 10	Female	PA	Supplement (1000 mg/d)	84	Hypertensive/ normotensive	No AE	NS
Li et al. (China, 2013)	179:180	46 ± 9	Female	PA	Supplement (800 mg/d)	730	Dyslipidemia	No AE	TC increased significantly, NS changes in TG, LDL-C, and HDL-C.
Masse et al. (Canada, 2008)	20:20	47 ± 6	Female	PA	Supplement (500 mg/d)	365	Healthy	No AE	NS
Menon et al. (Brazil, 2009)	8:7		Female	PA	Supplement (800 mg/d)	90	Stone former	No AE	NS
Palacios (Portorico, 2011) 9:8	8:8	37 ± 2	Both	PA	Supplement (1300 mg/d)	147	Obese	No AE	NS
Reid et al. (Newzealan, 2002)	81:77	72 ± 4	Female	PA	Supplement (1000 mg/d)	365	Post-menopause	No AE	HDL-C increased; NS change in LDL-C, and TG.
Subih et al. (Jordan, 2018)	10:10	18-48	Female	PA	Supplement (1200 mg/d)	84	Obese	No AE	NS change in TG; significant increases in cholesterol level.
Zemel et al. (USA, 2004)	11:10	49 ± 6	Both	PA	Supplement (800 mg/d)	168	Healthy	No AE	NS

Abbreviations: Int: Intervention; Con: Control; NS: Non-Significant; AE: Adverse Effect; PA: parallel; PCO: Poly Cystic Ovarian

Table 2. Results of subgroup analysis in each lipid variable.

Serum Lipids			Effect Size	95%CI	I^2 (%)	P for Heterogeneity
TG	Dosage	<1000 mg/d	0.02	(-010, 0.13)	0.0	0.97
		≥1000 mg/d	0.02	(-0.04, 0.09)	4.1	0.40
	Duration	<12 Weeks	−0.12	(-0.45, 0.21)	64.9	0.09
		≥12 weeks	0.03	(-0.02, 0.09)	0.0	0.91
	Dyslipidemia	Without Dyslipidemia	0.04	(-0.05, 0.13)	0.0	0.94
		With Dyslipidemia	0.02	(-0.05, 0.08)	0.9	0.42
TC	Dosage	<1000 mg/d	0.24	(0.05, 0.42)	9.7	0.33
		≥1000 mg/d	−0.04	(-0.11, 0.03)	0.0	0.93
	Duration	<12 Weeks	−0.19	(-0.54, 0.17)	0.0	0.50
		≥12 weeks	0.02	(-0.10, 0.15)	54.6	0.01
	Dyslipidemia	Without Dyslipidemia	−0.02	(-0.11, 0.06)	0.0	0.59
		With Dyslipidemia	0.02	(-0.15, 0.19)	53.7	0.02
LDL-C	Dosage	<1000 mg/d	−0.01	(-0.14, 0.12)	0.0	0.93
		≥1000 mg/d	−0.13	(-0.23, -0.03)	0.0	0.70
	Duration	<12 Weeks	−0.14	(-0.46, 0.19)	0.0	0.97
		≥12 weeks	−0.08	(-0.16, -0.00)	0.0	0.74
	Dyslipidemia	Without Dyslipidemia	−0.15	(-0.26, -0.04)	0.0	0.81
		With Dyslipidemia	−0.03	(-0.13, 0.08)	0.0	0.92
HDL-C	Dosage	<1000 mg/d	−0.02	(-0.05, 0.01)	0.0	0.81
		≥1000 mg/d	0.01	(-0.05, 0.07)	28.1	0.21
	Duration	<12 Weeks	−0.03	(-0.15, 0.09)	0.0	1.0
		≥12 weeks	−0.00	(-0.05, 0.04)	20.8	0.25
	Dyslipidemia	Without Dyslipidemia	0.04	(-0.05, 0.14)	29.9	0.23
		With Dyslipidemia	−0.02	(-0.05, 0.00)	0.0	0.81

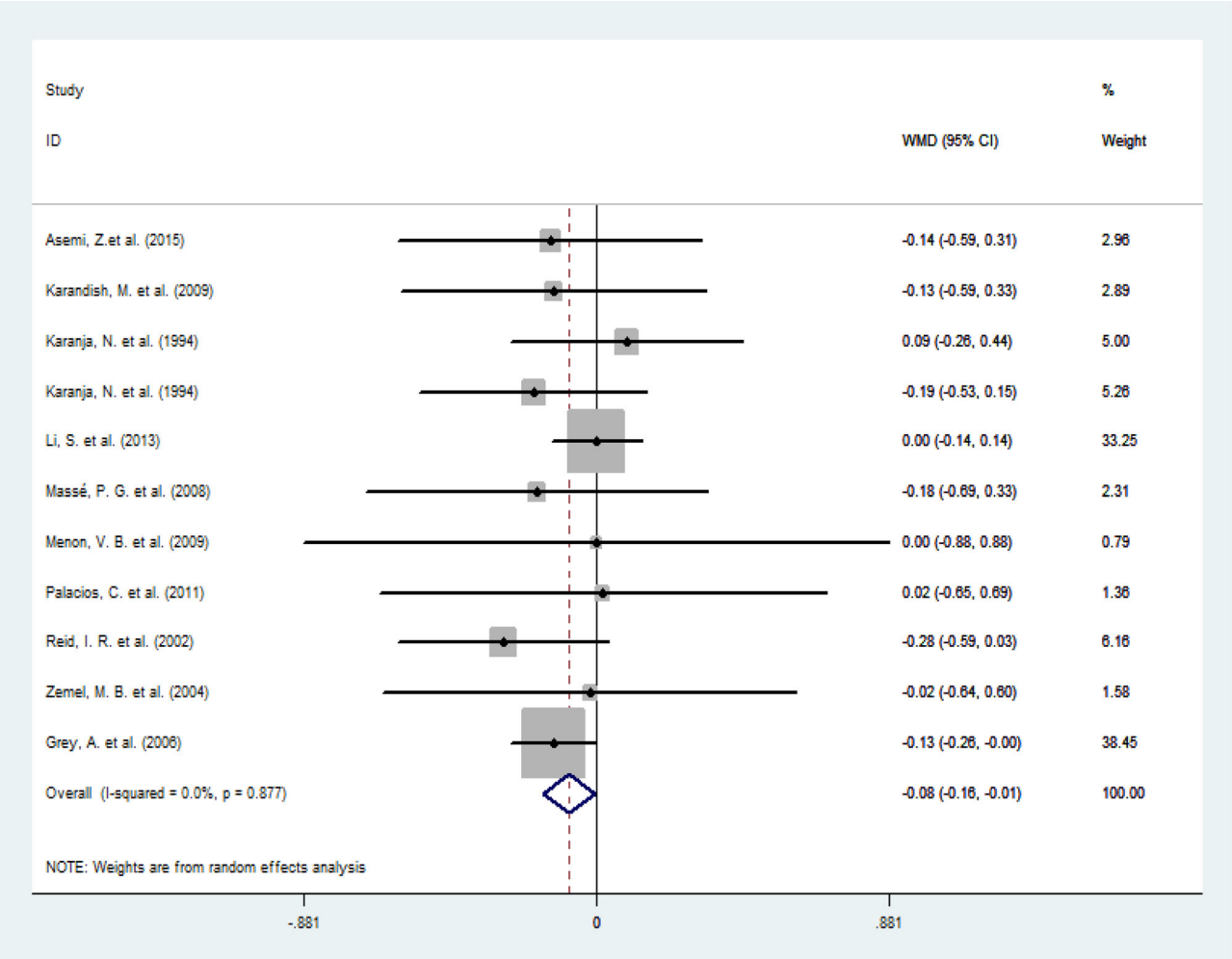

Figure 2. Meta-analysis of the effect of calcium supplements on low density lipoprotein cholesterol (LDL-C) level.

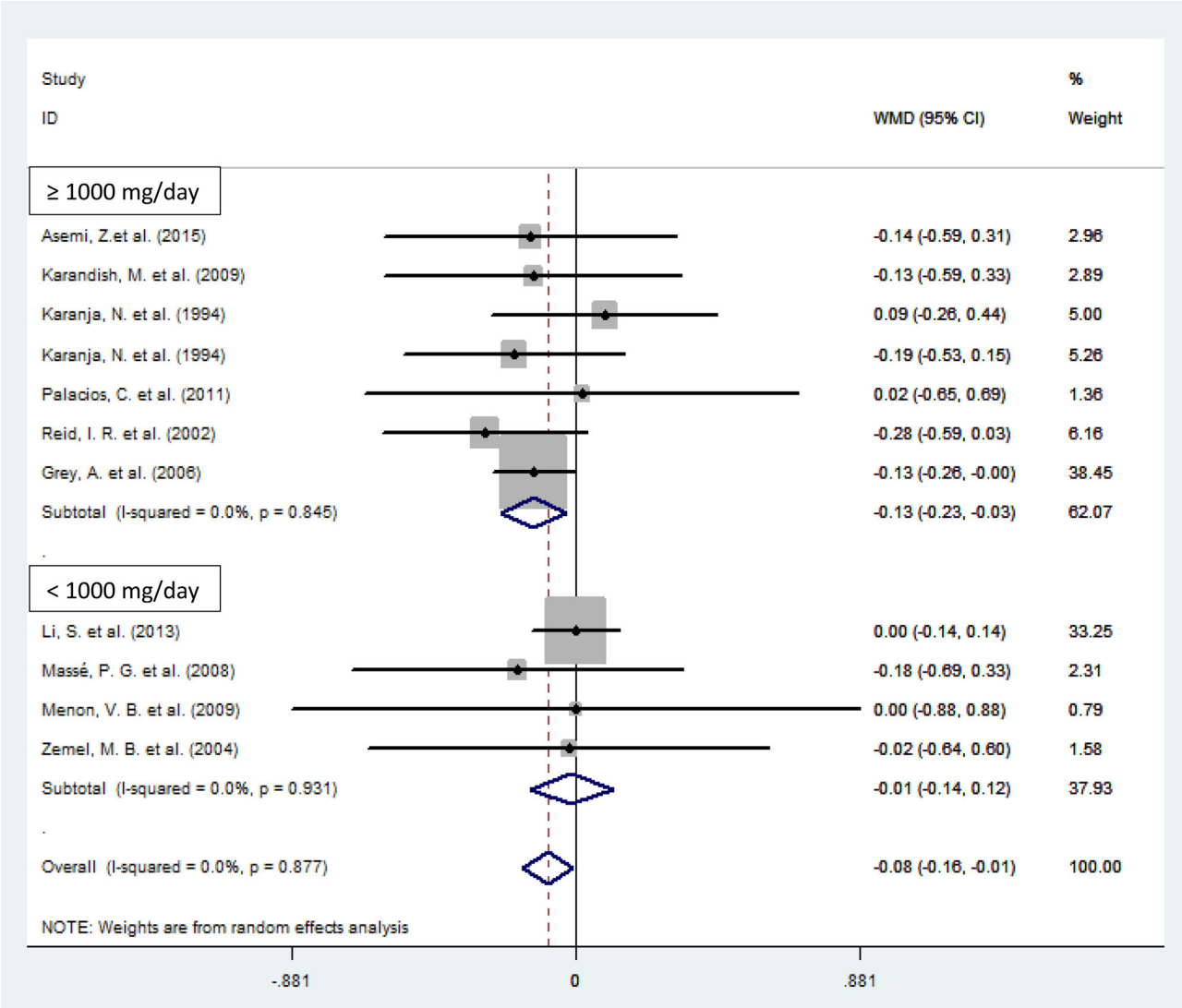

Figure 3. Meta-analysis of the effect of calcium supplements on low density lipoprotein cholesterol (LDL-C), level stratified by dosage.

relevant paper: first author's information, study design, sample size, intervention dosage, study duration, age, sex, health status, adverse effects, and results. Means and standard deviations (SD) or standard errors (SE) of the main outcomes (TC, LDL-C, HDL-C, and TG) were also extracted for the effect size calculation.

In the study of Karanja et al. two different subgroups of calcium supplements were extracted for each gender (Karanja et al. 1994). Thus, we extracted 13 effect sizes for the final meta-analysis.

Statistical analysis

We used mmol/l as unit scale for all values of lipid profile. We used changes in mean and standard deviation (SD) to estimate the effect size. If they were not reported directly, mean differences were computed by subtracting the mean of before- and after- values for intervention and control groups. Then SDs of mean differences were calculated by the following equation: $SD = \sqrt{SD_{before}^2 + SD_{after}^2 - 2*r*SD_{before}*SD_{after}}$, where "r" refers to the correlation between the before and after scores. We used $r = 0.5$ to measure SDs. Mean was calculated by $\times = \frac{a+2m+b}{4}$ where "m" was median and "a" and "b" were low and high end of the range, respectively. The variance was calculated by the following formula: $s^2 = \frac{1}{12}\left\{\frac{(a-2m+b)^2}{4} + (b-a)^2\right\}$ (Follmann et al. 1992).

For heterogeneity assessment both I-squared and chi-squared tests were used. In chi-squared test, alpha value of less than 0.1 declared significant heterogeneity. In I-squared test, values <25% were considered as low heterogeneity, 25% to 50% as moderate heterogeneity, and ≥50% as large amounts of heterogeneity. For calculating pooled effect size the random-effect model (I-V heterogeneity, no standard) was applied. 95% confidence intervals were calculated for the weighted mean difference (WMD), and 0.05 or less were considered as significant level. For assessing small-study

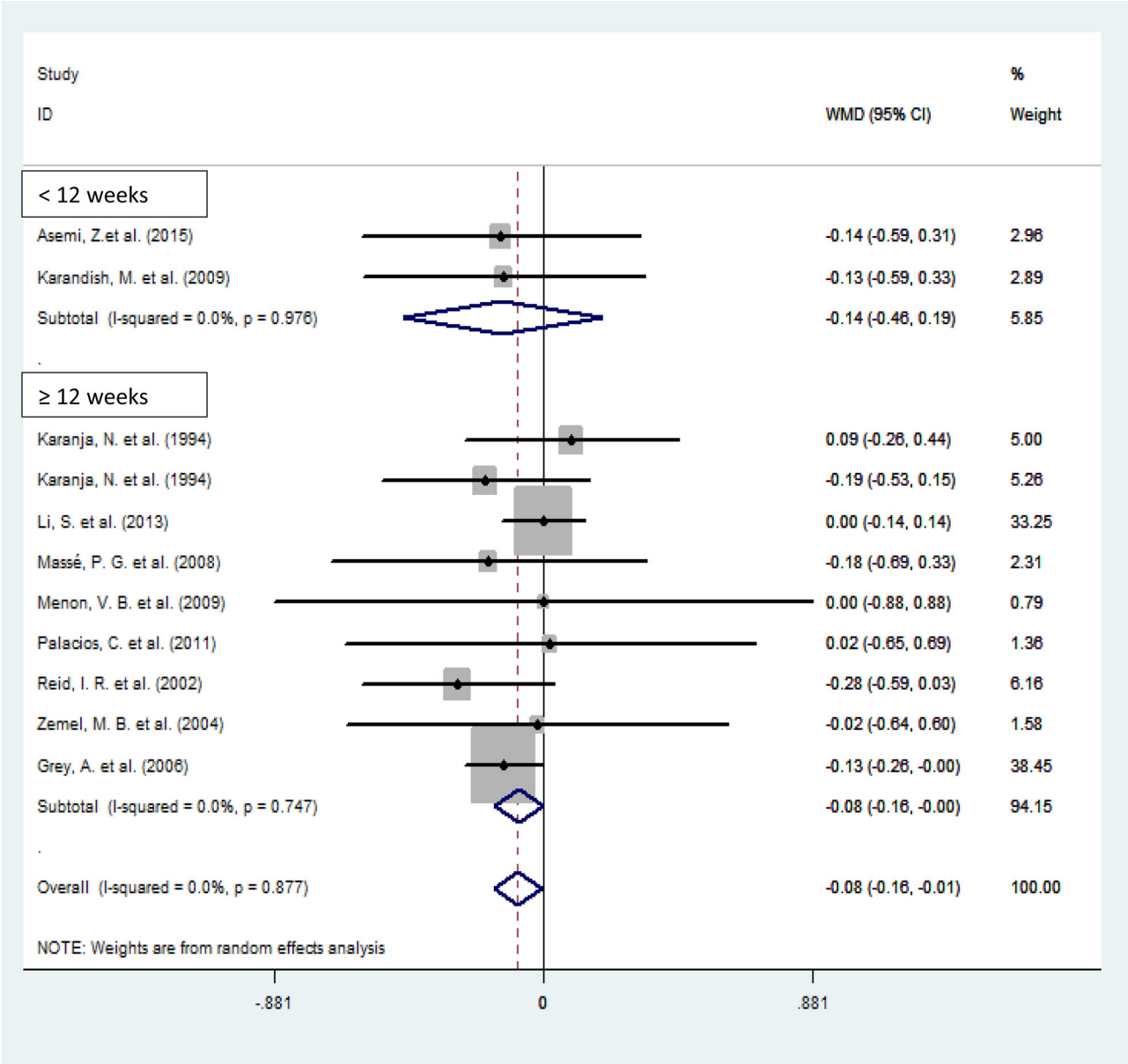

Figure 4. Meta-analysis of the effect of calcium supplements on low density lipoprotein cholesterol (LDL-C), level stratified by duration.

effects, Egger's test and funnel plot were used. All statistical analyses were done with Stata version 11.0 software (Stata Corporation).

We classified studies according to 1) interventional dosage (<1000 mg/d vs. ≥1000 mg/d); 2) study duration (<12 weeks vs. ≥12 weeks); and 3) dyslipidemia (with dyslipidemia vs. without dyslipidemia).

Results

Among 9108 papers, 17 full-text articles were assessed for inclusion and exclusion criteria (Figure 1). Five articles were excluded after full-text screening: 2 studies with insufficient data, and 3 studies with no control group. The PICOS criteria of eligible studies are described in Table 1. All studies had a parallel design. The study duration varied from 20 to 730 days. The mean age of the participants ranged from 25 to 72 years. Eight studies were performed on women, and 4 studies on both genders. Dosage of intervention ranged from 800 to 2000 mg/day. Among the eligible studies 4 studies were performed on healthy participants, while 8 studies were done on individuals with dyslipidemia. Finally, 12 studies (Kashkooli et al., 2019) with 1119 participants had sufficient data to be enrolled in the meta-analysis.

The results of studies were stratified according to duration, dosage, and dyslipidemia, for each blood lipid as shown in Table 2.

Calcium supplements and high-density lipoprotein cholesterol (HDL-C)

The overall effect of calcium supplements on HDL-C level was −0.01 mmol/L (95% CI: −0.04, 0.01) with low heterogeneity (I^2 =1.7%, and P = 0.426). None of the subgroups demonstrated a significant effect.

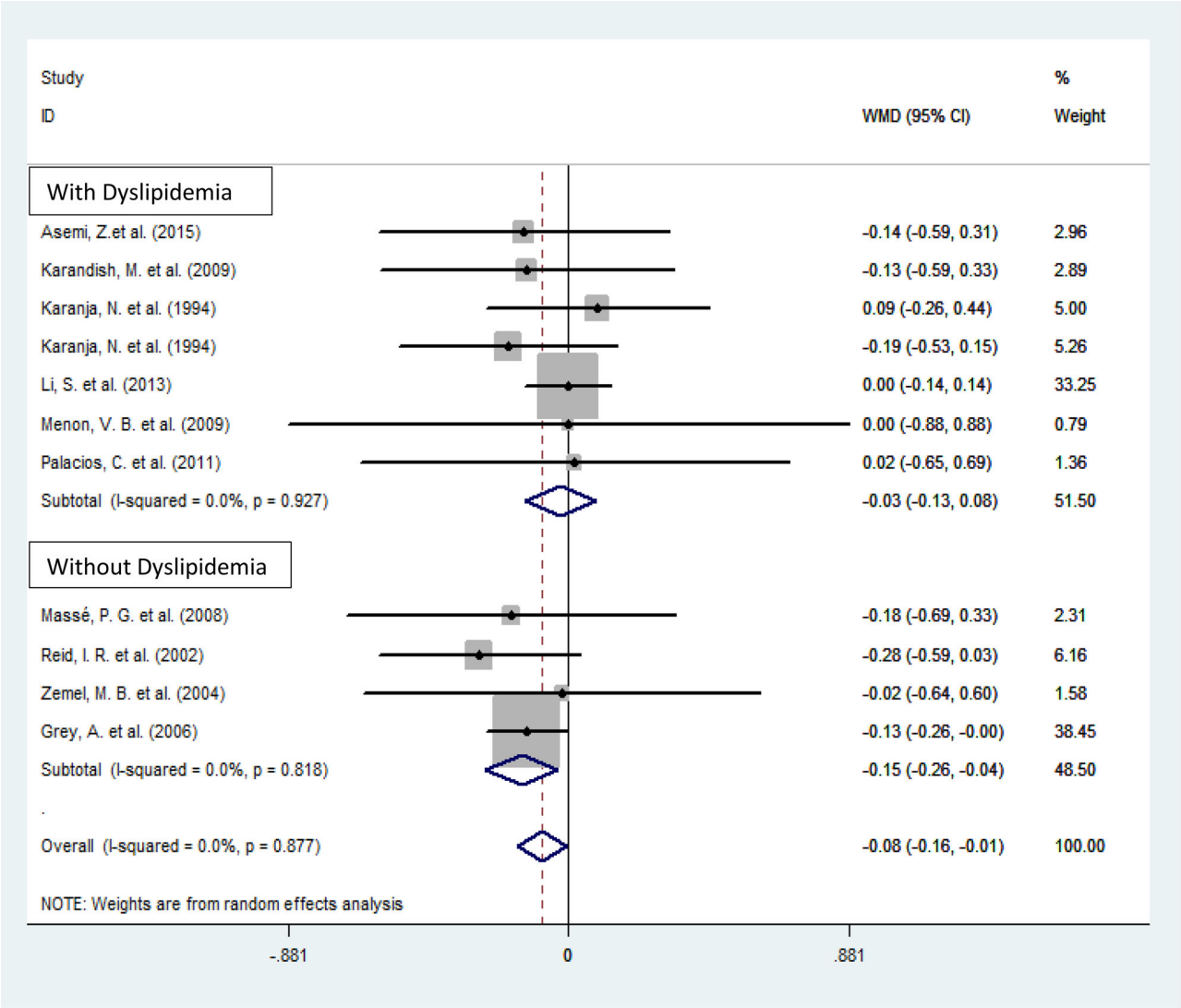

Figure 5. Meta-analysis of the effect of calcium supplements on low density lipoprotein cholesterol (LDL-C), level stratified by dyslipidemia.

Calcium supplements and low-density lipoprotein cholesterol (LDL-C)

The overall effect of calcium supplements on LDL-C level was −0.08 mmol/L (95% CI: −0.16, −0.01) with low heterogeneity (I^2 =0.0%, and P = 0.877). In the subgroup analysis according to the interventional dosage: at least 1000 mg/d calcium supplement intake showed a significant reduction in LDL-C level (-0.13; 95% CI: −0.23, −0.03). In the subgroup analysis based on duration of the study, calcium supplement intake for at least 12 weeks caused a significant reduction in LDL-C level (-0.08; 95% CI: −0.16, −0.00). Also, in subgroup analysis according to dyslipidemia, in individuals without dyslipidemia calcium supplement consumption caused a significant reduction in LDL-C level (-0.15; 95% CI: −0.26, −0.04). (Figures 2–5, respectively).

Calcium supplements and total cholesterol (TC)

The overall effect of calcium supplements on TC level was 0.00 mmol/L (95% CI: −0.11, 0.12) with moderate heterogeneity (I^2 =49.6%, and P = 0.026). In the subgroup analysis according to the interventional dosage: less than 1000 mg/d calcium supplement intakes showed a significant increase in TC level (0.24; 95% CI: 0.05, 0.42) (Figure 6).

Calcium supplements and triacylglycerol (TG)

The overall effect of calcium supplements on TG level was 0.02 mmol/L (95% CI: −0.03, 0.08) with low heterogeneity (I^2 =0.0%, and P = 0.740). None of the subgroups demonstrated a significant effect.

Discussion

This meta-analysis showed that calcium supplement intake caused a significant reduction in LDL-C level, especially in dosages ≥ 1000 mg/d, for at least 12 weeks, and in individuals without lipid abnormalities. On the other hand, lower doses of calcium supplements caused a significant increase in TC level. No significant effect was found in overall effect or any subgroup analysis on TG or HDL-C level.

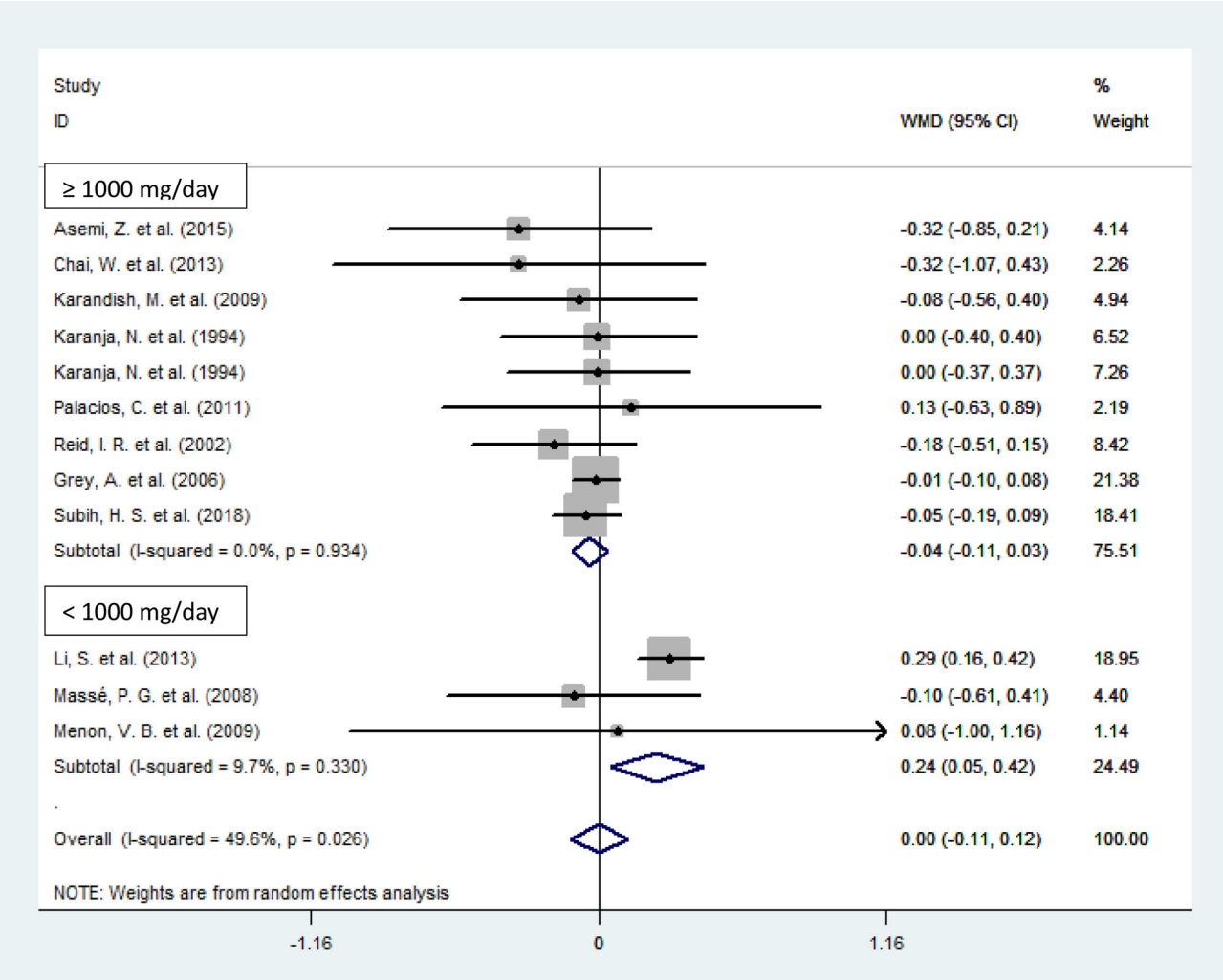

Figure 6. Meta-analysis of the effect of calcium supplements on total cholesterol (TC), level stratified by dosage.

We found that calcium supplementation was associated with a significant reduction in LDL-C level. The favorable effects of calcium supplements on LDL-C were observed with dosage of at least 1000 mg/d, for intakes of at least 12 weeks, and in non-dyslipidemia individuals. Similarly, Zemel et al. claimed that consumption of 800 mg/d calcium supplements for 2 years had no effect on serum TG, LDL-C, and HDL-C levels in healthy volunteers (Zemel et al. 2004). Another study in Canada showed that 500 mg/d calcium supplement consumption for 1 year caused no significant change in LDL-C level (Massé et al. 2008). Conversely, a parallel-arm clinical trial study in Portorico reported that 1300 mg/d calcium supplementation for 21 weeks led to no significant change in lipid profile (Palacios et al. 2011). Although we found that a significant reduction in LDL-C level via calcium supplementation needs at least 12 weeks, a recent systematic review and meta-analysis showed that up to 8 weeks co-supplementation of vitamin D and calcium could significantly reduce LDL-C level (Kashkooli et al. 2019). It is proposed that the synergic effects of calcium and vitamin D, could reduce intestinal absorption of fats and lipogenesis, also increase lipolysis which leads to LDL reduction in a faster way compared with calcium supplementation alone (Asemi et al. 2015; Challoumas 2014; Major et al. 2007).

In the present meta-analysis, we observed that low intake of calcium supplements (less than 1000 mg/d) increased TC level. However, this is based on just 3 studies, one of which contributes 86% of the weight of the 3 studies, which could distort the results (Menon et al. 2009). Consistently, Li et al. showed that, after calcium supplementation (800 mg/d) for 2 years in post-menopausal women with dyslipidemia, serum cholesterol concentrations and carotid intima-media thickness (CIMT) were significantly augmented ($P = 0.01$); also a mild reduction were observed in HDL-C concentration (Li et al. 2013). However, the results of the present study are in contrast with three other studies on calcium supplements (Zemel et al. 2004; Massé et al. 2008; Menon et al. 2009). Accordingly, two studies performed in Canada and Brazil in 2008 and 2009, respectively, demonstrated that with low dose calcium supplementation (500-800 mg/d) for 3 month to 1 year in women, no significant changes were found in lipid profiles of the participants (Massé et al. 2008; Menon et al. 2009). Also, Torres et al. assessed the effect of a high-calcium low-calorie diet on waist circumference and cardiometabolic risk factors in Brazilians with obesity. After

16 weeks, all anthropometric and metabolic parameters (except for HDL-C) reduced significantly which pointed out that high calcium consumption may reinforce the advantages of energy restriction on abdominal obesity, and metabolic variables (Torres et al. 2010).

The effects of calcium supplements on lipid profile can be explained by two different mechanisms. First, calcium attaches to either fatty acids or bile acids in the gut, thus inhibits lipid absorption. The second occurs through regulation of adipocyte activity by parathyroid hormone and 1,25-dihydroxyvitamin D. In vitro studies showed that high level of parathyroid hormone may decrease lipolysis, which lead to overweight and adiposity in secondary hyperparathyroidism (Grey et al. 1994; Kelly and Gimble 1998; Zemel et al. 2000). Calcium consumption suppresses circulating level of parathyroid hormone and 1, 25-dihydroxyvitamin D, thus developing lipolysis. According to an experimental study in transgenic mice, supplementation with calcium reinforces lipolysis and increases body temperature, while suppresses lipogenesis and decreases body weight, indicating the thermogenesis effect of calcium intake (Zemel et al. 2000). These effects lead to the changes of blood cholesterol or related fractions.

This review has some strengths. It included available RCTs regarding the impact of calcium supplement intake on lipid profile, and it is the latest systematic review and meta-analysis in this topic. Other strengths include uncovering the biases like small-study effects, or defaults in the study design, conduct, analysis, and interpretation. Nevertheless, the present review has some limitations, too. First, since this was an aggregate data meta-analysis, the potential of ecological fallacy, specifically Simpson's paradox, is possible. Second, considering the small sample size of some of the relevant RCTs, significant metabolic changes associated with supplemental calcium might not have been detected. Third, the 'significant' effect of <1000 mg/d on TC is based on just 3 studies, one of which contributed 86% of the weight of the 3 studies. So, this can bias the outcome and should be interpreted with great caution.

In humans, no adverse effects (AEs) were reported with calcium supplements intake. However, more randomized controlled trials with large sample sizes, or longer periods are needed to assess the exact effect of calcium supplements on TC level, or to detect the exact dosage of calcium supplements that could modulate serum lipid concentrations without any significant adverse effects.

Conclusion

In general, these findings showed that calcium supplement consumption had favorable effect on serum LDL-C level. Moreover, the favorable effects of calcium supplements on LDL-C were observed for dosage of at least 1000 mg/d, for intakes of at least 12 weeks, and in individuals without dyslipidemia. However, less than 1000 mg/day calcium supplement consumption caused a significant increase in TC level. Calcium supplementation had no significant effect on other lipid variables.

Acknowledgements

None.

Conflict of interest

None.

Authorship

S.F., S.G., and M.A. designed research; S.F. and S.G. conducted research; S.M.D.R. analyzed data and wrote the paper. S.F., S.G., and M.A edited the paper. S.F. had primary responsibility for final content. All authors read and approved the final manuscript.

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