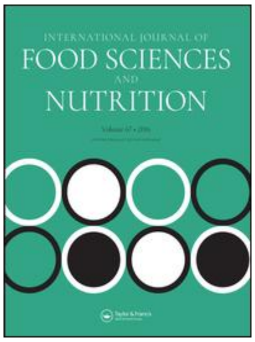

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COMPREHENSIVE REVIEW

Meta-analysis of randomized controlled trials on calcium supplements and dairy products for changes in body weight and obesity indices

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ABSTRACT

This meta-analysis was performed to investigate whether calcium supplements and dairy products change obesity indices including fat mass. Original articles published in English between July 2009 and August 2019 were identified. Ten and 14 randomised controlled trials (RCTs) with $\geq$ 12 weeks interventions of calcium supplements and dairy products among overweight or obese adults aged $\geq$18 were critically reviewed. Mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval (CI) were obtained using a random effect meta-analysis. Dairy products significantly changed fat mass (SMD, 95% CI; −0.40 [−0.77, −0.02]) and BMI (MD, 95% CI: −0.46 kg/m2 [−0.67, −0.26]), and calcium supplements also showed changes in fat mass (SMD, 95% CI; −0.15[−0.28, −0.02]). However, in the analysis of RCTs with low risk of bias scores, the significant changes remained only in the dairy-products intervention. Our findings suggest that dairy products without distinction of fat percentage may help reduce fat mass and BMI, but calcium supplements may not.

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Meta-analysis; obesity; dietary factor; calcium intake; body mass index; fat mass

Introduction

Obesity is a major public health problem worldwide and one of the leading risk factors for chronic diseases such as cancer, cerebrovascular disease, heart disease, and diabetes, which are major causes of death (WHO 2020). Researchers have suggested that dietary calcium might facilitate weight control by inhibiting fat absorption (Jacobsen et al. 2005; Christensen et al. 2009). Therefore, since the first report on the subject in 1984 (McCarron et al. 1984), calcium supplements and calcium food sources have been studied, particularly in the context of body weight (Davies et al. 2000; Heaney et al. 2002; Heaney 2003; Varenna et al. 2007; Newberry et al. 2014). The results of previous meta-analyses of studies about body weight reduction through calcium supplementation are inconsistent. One meta-analysis reported small but significant weight loss in overweight and obese individuals (Onakpoya et al. 2011), but the others found no significant associations (Trowman et al. 2006; Booth et al. 2015; Li et al. 2016).

Obesity is not simply an increase in weight. It is a medical condition in which excess adipocytes have accumulated (WHO 2020). Low calcium intake is known to induce high blood 1,25(OH)2D level to increase Ca(2+), which leads to increased calcium content in tissues such as adipocytes, which in turn stimulates fatty acid synthase activity and decreases lipolysis (Zemel et al. 2000). Accordingly, dietary calcium could play a role in the fat mass metabolism of adipocytes. In previous studies, fat mass, waist circumference (WC), and body mass index (BMI) have commonly been used as both obesity indices and outcome variables. Dairy products such as milk, cheese, and yogurt, which are rich in calcium, have been studied relatively more than calcium supplements with respect to obesity indices, and in previous studies of calcium supplementation and dairy products, BMI and WC did not show consistent findings (Onakpoya et al. 2011; Abargouei et al. 2012). Dairy products intake also has been reported that there is probable or possible evidence of a decrease in metabolic syndrome, hypertension, and CVD (Godos et al. 2020) of which an important risk factor is obesity. However, a

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few meta-analyses (Abargouei et al. 2012; Chen et al. 2012; Booth et al. 2015; Stonehouse et al. 2016) have examined changes in body fat after dairy product interventions and found benefits or conditional benefits with energy restriction. Only a small amount of inconsistent evidence is available on the effect of calcium supplementation on fat mass (Onakpoya et al. 2011; Booth et al. 2015).

Among those previous meta-analyses of obesity indices, there were only two meta-analyses demonstrating the effects of both calcium supplements and dairy products (Trowman et al. 2006; Booth et al. 2015) intervened during at least 12 weeks to ensure minimum quality (European Medicines Evaluation Agency (EMEA) 2008; US Department of Health and Human Services 2008). Even those two studies analysed only body weight and fat mass, not including BMI and WC, common obesity indices. Furthermore, data extracting methods, especially how to extract standard deviation (SD) of the change in obesity indices or how to handle control group in the studies using more than one intervention group, were not described (Trowman et al. 2006; Onakpoya et al. 2011; Li et al. 2016; Stonehouse et al. 2016) or not in detail (Abargouei et al. 2012; Chen et al. 2012; Booth et al. 2015).

Therefore, we conducted a new meta-analysis of RCTs that used at least 12 weeks of supplementation and were published to examine whether calcium and dairy products supplementation affect BMI, WC, fat mass, and body weight in overweight or obese adults (18 years or older).

Materials and methods

Data search sources and strategy

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines provided by the PRISMA Group (Liberati et al. 2009). Because the differences in ubiquitous risk factors for obesity between the particular points in time may make a difference in the effect of a specific factor on obesity (Pearce 2011), ignoring changes over time and analysing together articles published over time may make an unexpected finding. Therefore, relevant original articles published were screened using a comprehensive search in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Ovid-EMBASE (http://ovidsp.tx.ovid.com) for articles published during the past 10 years (July 2009 and August 2019). The search terms included ("Calcium" or "Ca2+") for calcium supplements and ("Dairy" or "Dairy Products") for dairy products, along with ("Body Weight" or "Obesity" or "Obese" or "Body Fat" or "Overweight" or "Body Composition" or "Body Mass Index" or "Weight" or "Adiposity") as outcome variables (Supplemental Table 1-1 and 1-2). Search filters provided by *British Medical* Journal TBM (BMJ Best Practice 2019) were used as terms for the study design. Four studies using 'calcium-rich foods' instead of 'dairy' were found when searching with calcium supplement terms and selected as articles with dairy-product interventions.

Inclusion criteria and study selection

We included all RCTs that tested calcium supplements or dairy products in general populations with a parallel design that lasted at least 12 weeks. The exclusion criteria were literature reviews, including systematic reviews and meta-analyses; studies among participants younger than 1 year, pregnant or lactating women, or patients with wasting diseases such as cancer; interventions that combined calcium supplementation or dairy products (whole dairy foods or dairy supplements) with other nutrients (except vitamin D) or other foods; and studies without an appropriate comparison group. Age was not a criterion for excluding articles, but because of a lack of studies with subjects younger than 18 years, we eventually restricted our selections to articles about adults aged 18 years or older. RCTs using milk, yogurt, and cheese or calcium supplements were selected, and one article using a dairy substitute (powdered milk) (Angeles-Agdeppa et al. 2010) was included with the dairy-product studies. All selected studies were original, full-length, and published in English.

The first and second screening steps, the title and abstract reviews and the full-text review step, were conducted independently by two reviewers (Supplemental Figure 1). If they could not reach a consensus about the eligibility of an article, it was resolved with the help of a third investigator.

Data extraction and study quality

We extracted the following data from each study: title; authors; country; year of publication; journal in which it was published; objective; funding source and conflicts of interest; study design (duration, randomisation sequence, blinding, treatment allocation, concealment); basic information about the subjects (age range, sex distribution, sample size (numbers enrolled and completed), health status); intervention and control regimes (calcium intake of each group, method of intervention (type of supplement or food), calorie restriction); exercise protocol (when available); measurements to assess outcomes; outcome results; and conclusions.

Most dairy-product RCTs discussed their intervention doses as amount of calcium per day. In one study (Tanaka et al. 2014), calcium amount was estimated using the calcium content of each dairy food according to the Korean national food composition table (Rural Development Administration NRRDI 2006). The differences between experimental and control groups in amount of calcium consumed per day were estimated. We extracted the mean and standard deviation (SD) of changes in body weight, BMI, WC, and fat mass (total body fat, trunk fat, or visceral fat) between baseline and endpoint, and we also extracted the mean and SD at baseline and endpoint. If measurements were performed at multiple time points, the values at the last time point were selected as the endpoint values. Most of the articles reported data for completers and did not contain an intention-to-treat (ITT) analysis (Yanovski et al. 2009; Reid et al. 2010; Josse et al. 2011; Rosado et al. 2011; Tanaka et al. 2014). Sometimes, even when the article noted that the study was ITT, it still reported data only for completers. Therefore, data for completers were extracted unless only ITT data were available. When the article did not specify an SD value, one of three methods was used to calculate it. First, when the p-value, standard error, and confidence interval (CI) were given, the SD was calculated using the method described in the Cochrane Handbook (Higgins et al. 2019a). Second, if data were presented only in figures (mean value was usually given in the text), we used WebPlotDigitizer 4.2ver (Rohatgi 2017) to extract the SD. Third, when an article gave the mean and SD of only the baseline and final measurements, the SDs were estimated using the method described in chapter 6 of the Cochrane Handbook (Higgins et al. 2019a): the correlation coefficients of baseline and final values were calculated from the studies presented their data in considerable detail, and the SDs were estimated from those correlations. In this study, we decided to impute SDs from a study that provided only the duration, measurement scale, outcome values, and correlation coefficients for the test and control groups.

The quality of each study was evaluated using the Cochrane Collaboration's Risk of Bias (RoB) tool for RCTs (Higgins et al. 2011; Higgins and Thomas 2019c). Critical assessments were performed individually by two investigators, and any disagreements were resolved by consensus with a third investigator.

Statistical analysis

We used mean difference (MD) to analyse the same outcome variables across studies (changes of body weight, BMI, and WC) and standardised mean difference (SMD) to analyse different but similar outcome variables (body fat, visceral fat, and trunk fat in fat mass change) (Higgins and Thomas 2019a). MD and SMD are presented with 95% CI.

A meta-analysis to consider errors caused by duplicate use of studies was performed because using multiple arms from a single study previously used without considering multiple weighting can cause bias (Moeyaert et al. 2017; Rucker et al. 2017). If a study had several intervention groups (differences in type or dosage of the intervention) and only one control group (Reid et al. 2010; Zhou et al. 2010; Josse et al. 2011; Stancliffe et al. 2011; Subih et al. 2018), the control group was subdivided until it equalled the number of intervention groups (Stonehouse et al. 2016). In the case of fat mass, when data for two types of fat mass were extracted from a single article, the number of subjects in both the intervention group and control group was divided in half and allocated separately in the meta-analysis.

A random effect model (DerSimonian and Laird 1986; Fleiss and Gross 1991; Ades et al. 2005) and the inverse variance method were used to perform the meta-analysis in Review Manager (RevMan, version 5.3, The Cochrane Collaboration, London, England, 2014) (Centre 2014), and the pooled effect across studies is provided. To eliminate potential biases in our findings, we performed additional analysis of only RCTs with low RoB scores. We also provide Cochran's Q and I^2 statistics (Higgins and Thompson 2002) to detect differences between observed effect sizes (Huedo-Medina et al. 2006) at a significance level of $p < 0.1$ (Fleiss 1986). A funnel plot analysis was generated to assess potential publication bias through a visual analysis of the plot, and Egger's regression asymmetry test was conducted at the significance level of 0.05 using STATA, version 15.1 (Stata Corp., College Station, TX, USA).

Results

Literature search results

Totals of 2,388 articles about calcium supplements (881 from PubMed and 1,507 from EMBASE with 723 duplicate records) and 1,013 about dairy products (430 from PubMed and 583 from EMBASE with 325 duplicate records) initially met the inclusion criteria. After screening the titles and abstracts, 50 and 69 articles, respectively, remained for the full text evaluation (Supplemental Figure 1(A,B)). In the end, after excluding studies at 1 to 17 years old due to the small number of articles (≤ 2 articles for each obesity index), 13 study arms from 10 articles about calcium supplements (Yanovski et al. 2009; Reid et al. 2010; Shalileh et al. 2010; Zhou et al. 2010; Palacios et al. 2011; Smilowitz et al. 2011; Jones et al. 2013; Torres and Sanjuliani 2013; Zhu et al. 2013; Subih et al. 2018) and 16 study arms from 14 articles about dairy products (Kukuljan et al. 2009; Wennersberg et al. 2009; Angeles-Agdeppa et al. 2010; Thomas et al. 2010; Gilbert et al. 2011; Josse et al. 2011; Palacios et al. 2011; Rosado et al. 2011; Smilowitz et al. 2011; Stancliffe et al. 2011; Van Loan et al. 2011; Jones et al. 2013; Tanaka et al. 2014; Bendtsen et al. 2018) were included in the meta-analysis.

Study characteristics

Study participants

Tables 1 and 2 present the study characteristics of the 10 (13 arms) calcium-supplement and 14 (16 arms) dairy-product RCTs. Seven of the 10 studies about calcium supplements and all 14 studies about dairy products were performed with overweight and obese participants. Most RCTs had a large proportion of women. Two RCTs about calcium supplements and one about dairy products included only men.

Interventions

Among the 10 RCTs about calcium supplements, seven used placebo control groups, and two provided a certain amount of dairy products. The estimated calcium dose difference ranged from 600 mg to 1500 mg (1200 mg or more in most studies). Four studies did not restrict caloric intake during intervention. All studies with caloric restriction and three studies without caloric restriction reported that their interventions were iso-caloric between intervention and control groups. None of those studies regulated exercise. In the 14 RCTs about dairy products, the intervention methods varied: 1) mixing milk powder with water (n = 1); 2) using milk only (n = 4); 3) using both milk and other dairy products (n = 8); and 4) using both dairy products and a calcium supplement (n = 1). The first and second methods were considered to use only milk (substitute). The interventions were mostly done by comparing low-dairy diets as a control group with adequate-dairy diets as the experimental group. The criteria for low-dairy varied from none to habitual intake; none (Rosado et al. 2011), lower than 0.5 serving per day (serving/d) (Stancliffe et al. 2011), about 1 serving/d (Josse et al. 2011; Smilowitz et al. 2011; Van Loan et al. 2011; Jones et al. 2013; Bendtsen et al. 2018), 2 serving/d (Angeles-Agdeppa et al. 2010; Gilbert et al. 2011), and habitual intake (Kukuljan et al. 2009; Wennersberg et al. 2009; Thomas et al. 2010; Palacios et al. 2011; Tanaka et al. 2014). It was based on one serving amount for each dairy product (200–250 ml for milk, 170–180 g for yogurt, and 30–60 g for cheese). And in RCTs included in the meta-analysis, the adequate-dairy diet was designed to be taken mostly at 3–4 servings per day, up to 5–6 servings per day, or 2 more servings than low-dairy diets. The estimated calcium differences between experimental and control groups in the dairy-product intervention studies varied from 336 mg to 1500 mg per day. Ten dairy-product studies restricted calories, and one study was not iso-caloric. Two studies restricted exercise during the intervention. The number of participants in the intervention group varied from 20 to 733 in the calcium-supplement studies and from 20 to 113 for the dairy-product studies.

Although the RoB of most studies was not high, some calcium-supplementation studies needed some consideration in the randomisation process, and those on dairy products needed consideration in processing missing outcome data.

Meta-Analysis

In the RCTs about calcium supplements and dairy products, body weight (n = 9 and 13 studies, respectively), BMI (n = 7 and 9 studies), WC (n = 5 and 10 studies), and fat mass (n = 6 and 10 studies) were used as outcomes. Among the studies that used fat mass, body fat (n = 5 and 10 calcium-supplement and dairy-product studies, respectively), trunk fat (n = 1 and 3 studies, respectively), and visceral fat (n = 1 calcium-supplement study) were used. We observed moderate to high heterogeneity up to 93%.

Effects of calcium supplementation on body weight and obesity indices

Eleven study arms from 9 individual articles used in the meta-analysis considered body weight, 9 arms from 7 articles considered BMI, 6 arms from 5 articles considered WC, and 9 arms from 6 articles considered fat mass (Figure 1–4). Only fat mass changed

Table 1. Characteristics of randomised controlled trials included in the systematic review and meta-analysis of how calcium supplements affect obesity indices.

Reference (Country)	Quality Score[a]	Duration (Weeks)	Outcomes Assessed	N[b]	Age (Years)	Description	Female (%)	Control	Calcium	Estimated Dose Difference of Calcium	Caloric Restriction[c]	Iso-Caloric	Exercise Restriction
Jones et al. 2013 (Canada)	Low	12	Weight, BMI, WC, BF	20 (18)	20-60	Low dairy and calcium consumers (<700 mg/d) with metabolic syndrome BMI: 27-37	63.16	1 serving/d of dairy (non-fat or 1% milk or yogurt)	3–4 servings/d of dairy (non-fat or 1% milk or yogurt) and 350 mg calcium supplement	700 mg/d	− 2090 kJ/d	Yes[d]	No
Palacios et al. 2011 (Puerto Rico)	Low	21	Weight	9 (8)	21-50	Sedentary obese adults who were low calcium consumers (≤700 mg/d) BMI: ≥30	80	Usual diet + a placebo tablet	1200-1300 mg/d of calcium (≈700 mg/d from diet and 600 mg/d from a supplement)	600 mg/d	No	Yes	No
Reid et al. 2010a (New Zealand)	Low	96	Weight, BF	108 (54)	> 40	Generally healthy men	0	Placebo	600 mg calcium twice daily	1200 mg/d	No	Yes[e]	No
Reid et al. 2010b (New Zealand)	Low	96	Weight, BF	108 (53)	> 40	Generally healthy men	0	Placebo	Placebo before breakfast and 600 mg elemental calcium in the evening	600 mg/d	No	Yes[e]	No
Shalileh et al. 2010 (Iran)	Low	24	Weight	20 (20)	20-60	Overweight or obese adults BMI: >25	85	Placebo	1000 mg/d of calcium carbonate	1000 mg/d	− 2090 kJ/d	Yes[d]	No
Smilowitz et al. 2011 (USA)	Some concerns	12	Weight, BMI, WC	16 (23)	18-35	Overweight or mildly obese adults who were low calcium consumers (<800 mg/d) BMI: 25-34.9	80	0-1 serving of dairy products/d and 500 mg/d of calcium and a daily placebo supplement	0-1 serving of dairy products/d and 500 mg/d of calcium and 900 mg/d of calcium carbonate	900 mg/d	− 2093 kJ/d	Yes[d]	No
Subih et al. 2018a (Jordan)	Low	12	Weight, BMI, WC	10 (5)	18-48	Obese women with vitamin D deficiency (≤20 ng/dL of serum vitamin D3) BMI: ≥30	100	No prescribed supplements	1200 mg/d of calcium	1200 mg/d	− 3135 kJ/d	Yes[d]	No
Subih et al. 2018b (Jordan)	Low	12	Weight, BMI, WC	12 (5)	18-48	Obese women with vitamin D deficiency (≤20 ng/dL of serum vitamin D3) BMI: ≥30	100	No prescribed supplements	1200 mg/d of calcium and 50,000 IU/week of cholecalciferol	1200 mg/d	− 3135 kJ/d	Yes[d]	No

(*continued*)

Table 1. Continued.

Reference (Country)	Quality Score[a]	Duration (Weeks)	Outcomes Assessed	N[b]	Age (Years)	Description	Female (%)	Control	Calcium	Estimated Dose Difference of Calcium	Caloric Restriction[c]	Iso-Caloric	Exercise Restriction
Torres and Sanjuliani 2013 (Portugal)	Some concerns	16	Weight, BMI. WC, BF	18 (17)	20-60	Obese adults with low calcium BMI: 30-34.9	91.43	<500 mg/d of calcium	1200–1300 mg/d of calcium supplemented with non-fat powdered milk (60 g/d)	700 ~ 800 mg/d	− 3344 kJ/d	Yes[d]	No
Yanovski 2009 (USA)	Some concerns	96	Weight, BMI, BF	168 (167)	18-71	Overweight or obese adults who were low calcium consumers (<600 mg/d or <1200 mg/d) BMI: ≥25	72.06	Placebo	1500 mg/d of calcium carbonate	1500 mg/d	No	Yes[e]	No
Zhou et al. 2010a (USA)	Some concerns	192	BMI, TF	274 (89)	>55	Generally healthy postmenopausal women	100	Placebo	1400 mg/d of calcium citrate or 1500 mg/d of calcium carbonate	1400 ~ 1500 mg/d	No	NI	No
Zhou et al. 2010b (USA)	Some concerns	192	BMI, TF	297 (89)	>55	Generally healthy postmenopausal women	100	Placebo	1400 mg/d of calcium citrate or 1500 mg/d of calcium carbonate plus supplemental vitamin D3 (1100 IU/d)	1400 ~ 1500 mg/d	No	NI	No
Zhu et al. 2013 (China)	Low	12	Weight, BMI, WC, BF, VF	22 (21)	18-25	Generally healthy overweight or obese adults who were low calcium consumers (<600 mg/d) BMI: ≥24	90.7	Placebo	600 mg/d of calcium carbonate	600 mg/d	− 2090 kJ/d	Yes[d]	No

BMI: body mass index; WC: waist circumference; BF: body fat; TF: trunk fat; VF: visceral fat; NI: no information.
Reid et al. 2010a: the intervention group received 1200 mg of calcium; Reid et al. 2010b: the intervention group received 600 mg of calcium; Subih et al. 2018a: the intervention group received calcium supplement only; Subih et al. 2018b: the intervention group received calcium and vitamin D supplements; Zhou et al. 2010a: the intervention group received calcium supplement only; Zhou et al. 2010b: the intervention group received calcium and vitamin D supplements

[a]Quality score derived from the Risk of Bias tool in the Cochrane Library.
[b]The numbers of subjects in the calcium-intervention and control groups are shown outside and inside parentheses, respectively.
[c]1 kcal = 4.18 kJ
[d]Estimated using the nutrient composition ratio, as stated in the text.
[e]Estimated using p-diff < 0.05 shown in the table.

Table 2. Characteristics of randomised controlled trials included in the systematic review and meta-analysis of how dairy products affect obesity indices.

Reference (Country)	Quality Score[a]	Duration (Weeks)	Outcomes Assessed	N[b]	Age (Years)	Description	Female (%)	Control	Dairy products	Type of Food	Estimated Dose Difference of Calcium[c]	Caloric Restriction[d]	Iso-Caloric	Exercise restriction
Angeles-Agdeppa et al. 2010 (Philippines)	Low	16	Weight, BMI, WC	30 (30)	56-57	Healthy but overweight and obese postmenopausal women	100	2 servings/d of low-calcium placebo drink	2 servings/d of milk (containing 4 scoops or 30 g of milk powder + 200 ml of water)	Milk (powder)	1146 mg/d	No	Yes	No
Bendtsen et al. 2018 (Denmark)	Some concerns	24	Weight, BMI, WC, BF	22 (30)	18-60	Overweight or obese adults who were low calcium consumers (<800 mg/d) BMI: 28–36	86.25	0-1 portions of dairy products	~1200 mg/d from dairy products	Dairy products	600 ~ 1500 mg/d	− 2100 kJ/d	Yes[e]	No
Gilbert et al. 2011 (USA)	Low	24	Weight, BMI, WC, BF	13 (12)	25-50	Healthy overweight women who were low calcium consumers (≤800 mg/d) BMI: 27-42	100	Placebo milk 463 mL/d	Milk 568 mL/d	Milk	1000 mg/d	− 2508 kJ/d	Yes[f]	No
Jones et al. 2013 (Canada)	Low	12	Weight, WC, BF	20 (18)	20-60	Low dairy and calcium consumers (<700 mg/d) with metabolic syndrome BMI: 27-37	63.16	1 serving/d of dairy (non-fat or 1% milk or yogurt)	3–4 servings/d of dairy (non-fat or 1% milk or yogurt) and 350 mg calcium supplement	Dairy products with calcium supplement	700 mg/d	− 2090 kJ/d	Yes[e]	No
Josse et al. 2011a (Canada)	Low	16	BF, TF	12 (30)	19-45	Healthy premenopausal overweight or obese women who were low dairy consumers BMI: 27-40	100	0–1 serving/d of dairy products	3–4 serving/d of dairy products	Milk	≈ 900 mg/d	− 2090 kJ/d	Yes[e]	Yes
Josse et al. 2011b (Canada)	Low	16	BF, TF	12 (27)	19-45	Healthy premenopausal overweight or obese women who were low dairy consumers BMI: 27-40	100	0–1 serving/d of dairy products	5–6 servings/d of dairy products	Milk	≈ 1200 mg/d	− 2090 kJ/d	Yes[e]	Yes
Kukuljan et al. 2009 (Australia)	Some concerns	72	Weight, BF	39 (35)	50-79	Healthy middle-aged and older men BMI: >35	0	No intervention	400 mL/d of reduced-fat (1%) ultrahigh temperature (UHT) milk	Milk	1000 mg/d	No	No[f]	No
Palacios et al. 2011 (Puerto Rico)	Low	21	Weight, BMI, BF	8 (8)	21-50	Sedentary obese adults low calcium consumers (≤700 mg/d) BMI: ≥30	80	Usual diet + a placebo tablet	4 servings/d of dairy products (low-fat milk, low-fat cheese, and low-fat yogurt)	Dairy products	500 ~ 600 mg/d	No	Yes	No
Rosado et al. 2011 (Mexico)	Some concerns	16	Weight, BMI, WC	43 (41)	25-45	Obese women low dairy consumers (<3 servings/d) BMI: ≥30	100	No intake of milk	Low-fat milk 250 mL x 3	Milk	≈ 600 mg/d	− 2090 kJ/d	Yes[e]	No
Smilowitz et al. 2011 (USA)	Low	12	Weight, BMI, WC	22 (23)	18-35	Overweight or mildly obese adults who were low calcium consumers (<800 mg/d) BMI: 25-34.9	80	0-1 serving of dairy products/d and a daily placebo supplement	3 servings/d of dairy products (milk, cheese, and/or yogurt)	Dairy products	900 mg/d	− 2093 kJ/d	Yes[e]	No

(*continued*)

Table 2. Continued.

Reference (Country)	Quality Score[a]	Duration (Weeks)	Outcomes Assessed	N[b]	Age (Years)	Description	Female (%)	Control	Dairy products	Type of Food	Estimated Dose Difference of Calcium[c]	Caloric Restriction[d]	Iso-Caloric	Exercise restriction
Stancliffe et al. 2011a (USA)	Some concerns	12	Weight, BMI, WC, BF, TF	10 (10)	37.0 ± 9.9	Obese adults with metabolic syndrome BMI: 30-39.9	52.5	<0.5 serving/d of dairy	>3.5 servings/d of dairy products	Dairy products	Minimum 600 mg/d	1.2-1.4 times RMR	Yes[e]	No
Stancliffe et al. 2011b (USA)	Some concerns	12	Weight, BMI, WC, BF, TF	10 (10)	37.0 ± 9.9	Overweight adults with metabolic syndrome BMI: 25-30	52.5	<0.5 serving/d of dairy	>3.5 servings/d of dairy products	Dairy products	Minimum 600 mg/d	1.2-1.4 times RMR	Yes[e]	No
Tanaka et al. 2014 (Japan)	Low	24	Weight, WC	102 (98)	20-60	Men with ≥2 components of metabolic syndrome	0	Dietary counselling	Dietary counselling + milk and dairy products (400 g/d)	Dairy products	Averaged 336 mg/d	reference body weight multiplied by 25 to 30 kcal/kg/d,	Yes[f]	No
Thomas et al. 2010 (USA)	Low	16	Weight, WC, BF, TF	14 (15)	29-45	Overweight sedentary women who were low dairy consumers (≤1 serving/d) BMI: 25-30	100	NI	≥3 servings/d of low-fat dairy products	Dairy products	Minimum 700 mg/d	− 1045 kJ/d	Yes[e]	Yes
Van Loan et al. 2011 (USA)	Low	12	Weight, BF	35 (36)	20-45	Overweight or obese adults who were low dairy consumers (≤1 servings/d and total calcium intake ≤600 mg/d) BMI: 28-37	NI	≤1 serving/d of dairy products (milk, yogurt, and cheese)	3-4 servings/d of dairy products (milk, yogurt, and cheese)	Dairy products	Averaged 879 mg/d	− 2090 kJ/d	Yes[e]	No
Wennersberg et al. 2009 (Finland, Norway, Sweden)	Low	24	Weight, BMI, WC, BF	52 (54)	30-65	Healthy men or postmenopausal women with ≥2 components of metabolic syndrome who were low dairy consumers (≤2 portions/d)	67.26	Habitual diet without changing the intake of dairy products	3–5 portions/d of dairy products	Dairy products	Averaged 359 mg/d	No	Yes[f]	No

BMI: body mass index; WC: waist circumference; BF: body fat; TF: trunk fat; NI: no information

Josse et al. 2011a: the intervention group received 3–4 servings/d of dairy products; Josse et al. 2011b: the intervention group received 5–6 servings/d of dairy products; Stancliffe et al. 2011a: the intervention group consisted of obese adults; Stancliffe et al. 2011b: the intervention group consisted of overweight adults

[a]Quality Score derived from the Risk of Bias tool in the Cochrane Library.

[b]The numbers of subjects in the calcium-intervention groups and control groups are shown outside and inside parentheses, respectively.

[c]The amount of calcium described in the paper is reflected; if the amount of calcium is not listed, we estimated using 198 mg of calcium per glass of milk (200 ml).

[d]1 kcal = 4.18 kJ

[e]Estimated using the nutrient composition ratio, as stated in the text.

[f]Estimated using p-diff <0.05 shown in the table.

significantly (SMD, 95% CI; −0.15 [−0.28, −0.02], $p = 0.02$). No significant decreases were found in body weight (MD, 95% CI; −0.23 [−0.83, 0.36], $p = 0.45$), BMI (MD, 95% CI; −0.11 [−0.25, 0.03], $p = 0.14$), or WC (MD, 95% CI; −0.17 [-2.37, 2.03], $p = 0.88$).

Effects of dairy products on body weight and obesity indices

Fourteen study arms from 13 individual articles considering body weight, 9 arms from 8 articles considering BMI, 11 arms from 10 articles considering WC, and 18 arms from 10 articles considering fat mass were included in the meta-analysis for dairy products (Figure 1–4). There were significant decreases in BMI (MD, 95% CI; −0.46 [−0.67, −0.26], $p < 0.00001$) and fat mass (SMD, 95% CI; −0.40 [−0.77, −0.02], $p = 0.04$). Body weight (MD, 95% CI; −0.17 [-1.05, 0.70], $p = 0.70$) and WC (MD, 95% CI; −0.80 [-2.20, 0.61], $p = 0.27$) did not change significantly.

Sensitivity analysis and publication bias

In the sensitivity analysis using only studies with low RoB scores, changes in fat mass and BMI were significant only with supplementation of dairy products (SMD, 95% CI; −0.39 [−0.77, −0.01], p = 0.04 for fat mass;

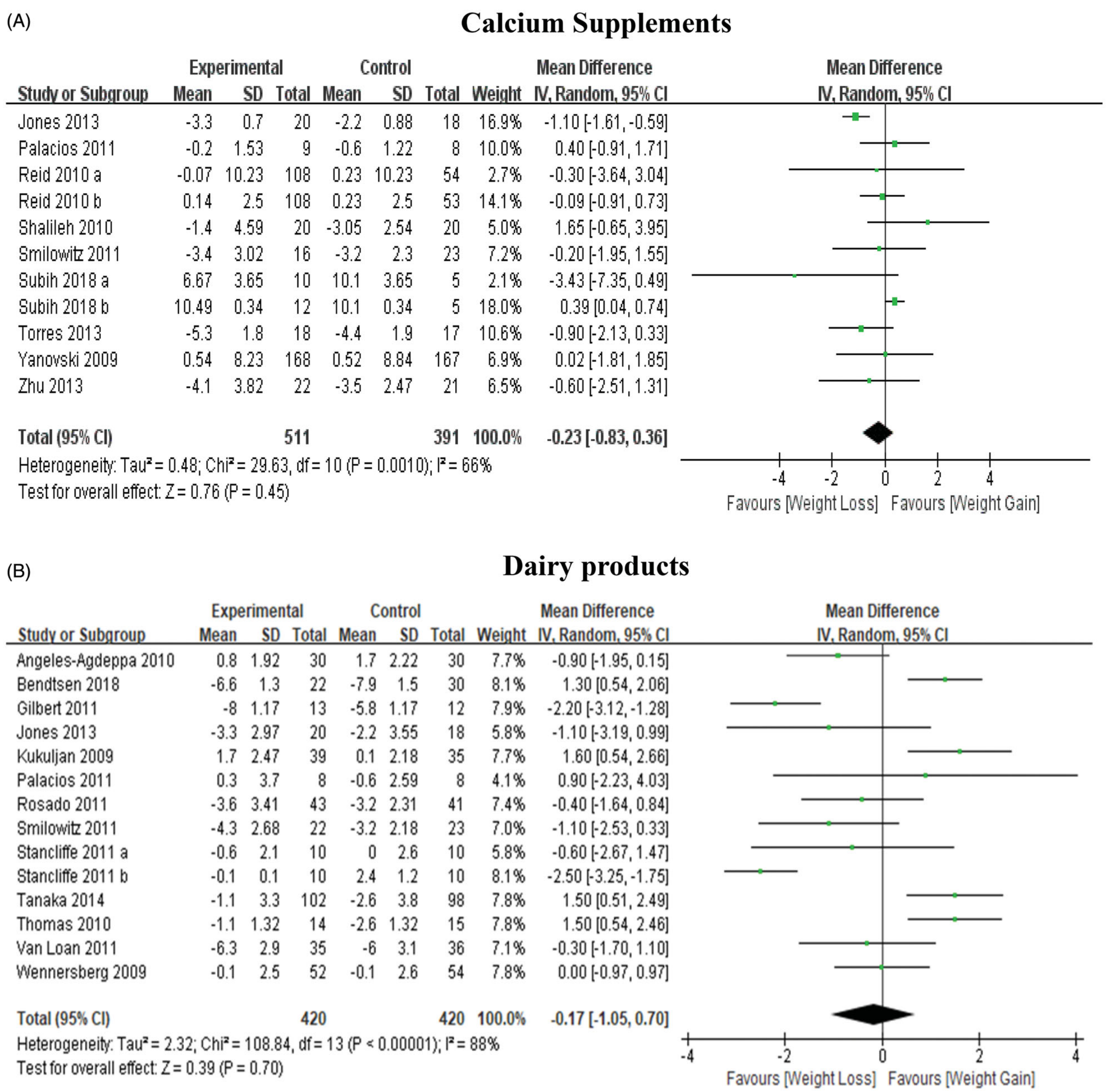

Figure 1. Forest plot detailing the mean difference (MD) and 95% confidence interval (CI) for the effects of calcium supplements (A) and dairy products (B) on body weight. Meta-analysis was performed using a random-effects model.

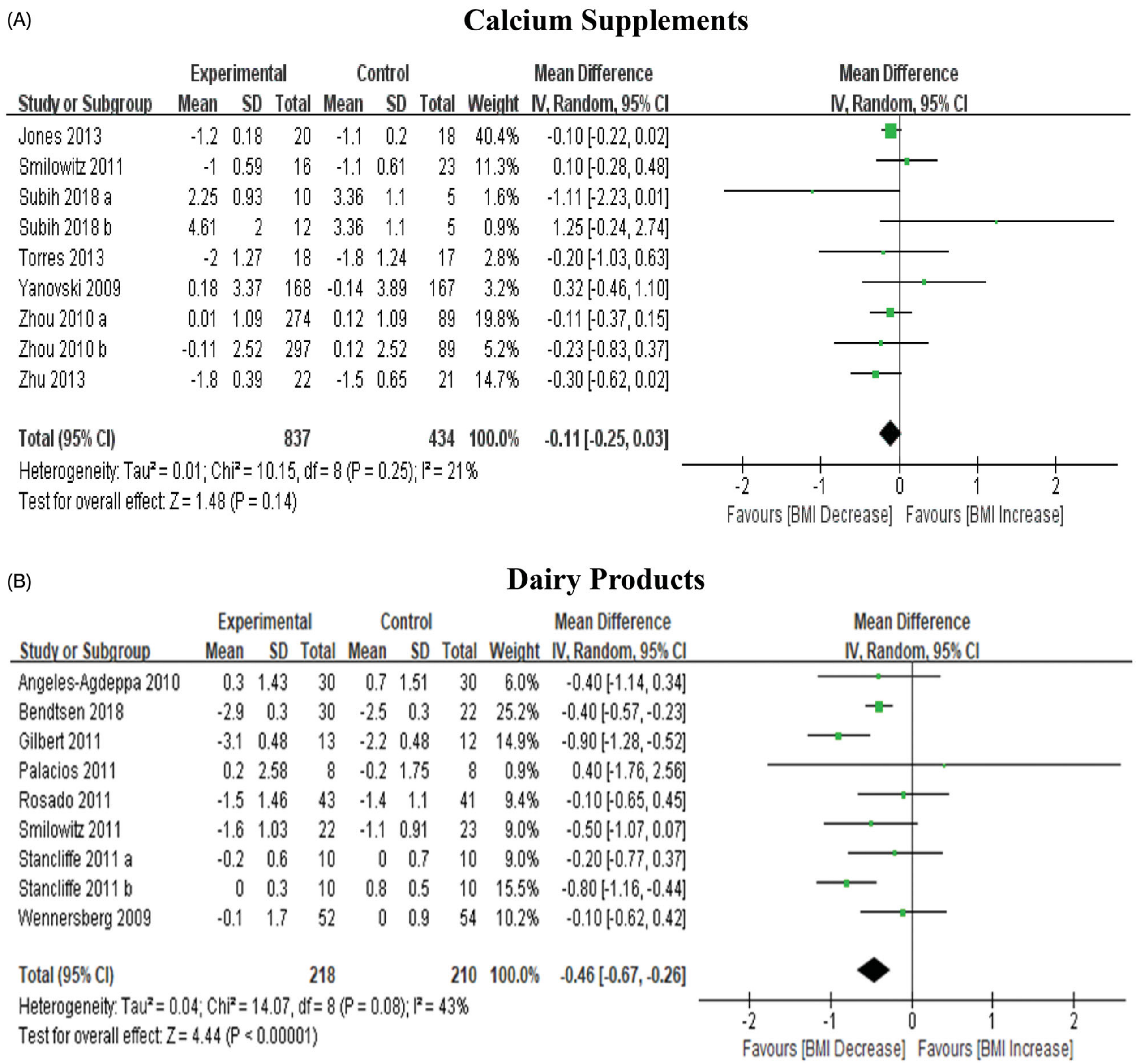

Figure 2. Forest plot detailing the mean difference (MD) and 95% confidence interval (CI) for the effects of calcium supplements (A) and dairy products (B) on body mass index (BMI). Meta-analysis was performed using a random-effects model.

MD, 95% CI; −0.49 [−0.86, −0.12], p = 0.01 for BMI), not with calcium supplements (Figure 5).

The funnel plot and Egger's test are presented to identify the potential for publication bias (Supplemental Figure 2). We found no evidence of publication bias among the calcium-supplement studies (Egger's test: $p = 0.59$ for body weight, $p = 0.85$ for BMI, $p = 0.26$ for WC, and $p = 0.12$ for fat mass) or the dairy-product studies ($p = 0.89$ for body weight, $p = 0.54$ for BMI, $p = 0.57$ for WC, and $p = 0.74$ for fat mass).

Discussion

This meta-analysis was conducted to determine how supplementation of calcium and dairy products affects obesity indicators. Our main findings are that calcium supplementation is inversely associated with fat mass during an intervention of more than 12 weeks among overweight or obese adults. Dairy products were beneficial for reducing fat mass and BMI. Neither calcium supplements nor dairy products produced significant changes to body weight or WC. In the meta-analysis using only RCTs with low RoB, the beneficial effects on fat mass and BMI only remained for dairy products.

In the present study, calcium supplements were beneficial for fat mass reduction but not for changes in body weight, WC, or BMI. Previous meta-analyses on the association between calcium supplements and obesity indices reported inconsistent findings (Trowman

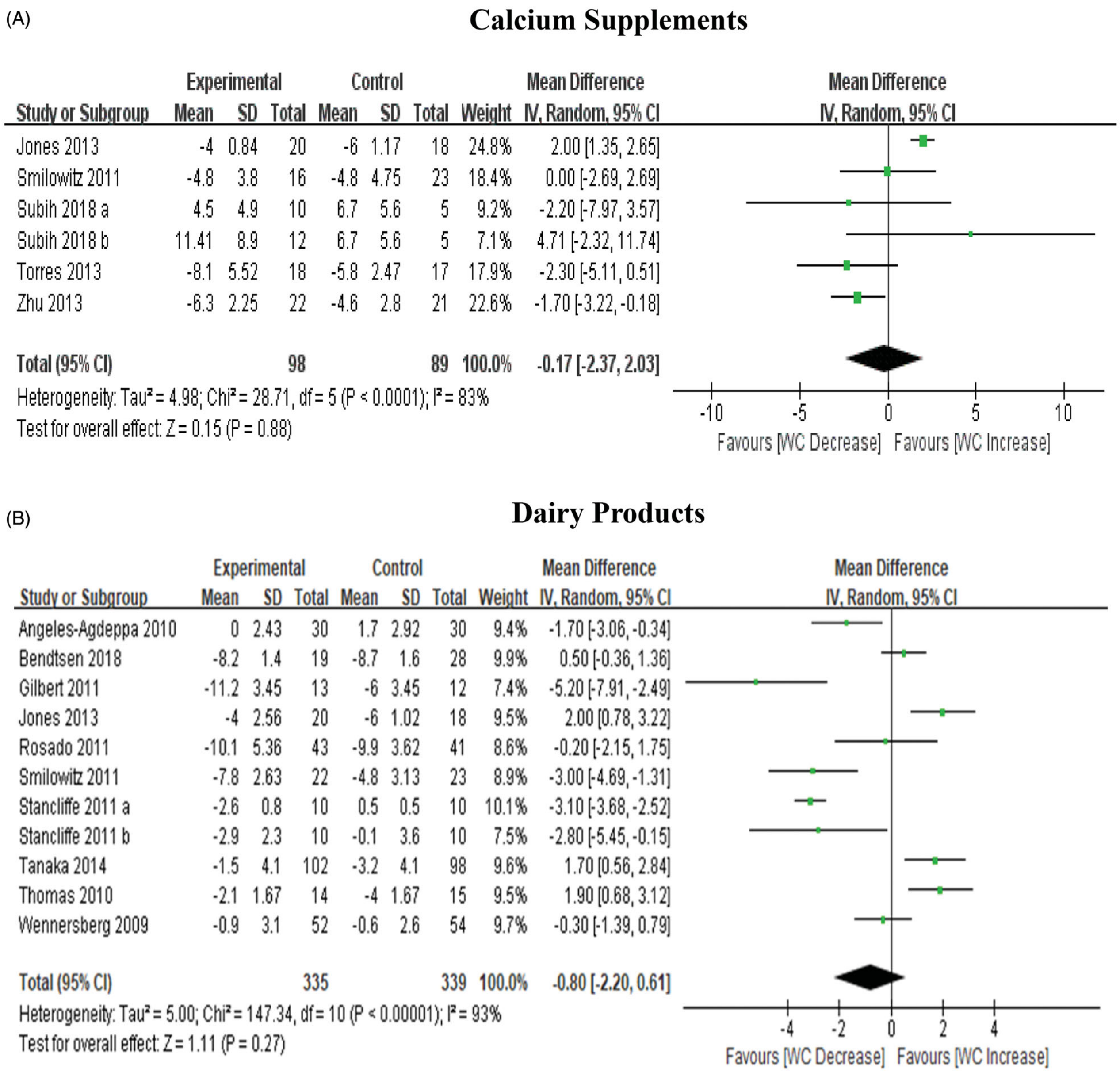

Figure 3. Forest plot detailing the mean difference (MD) and 95% confidence interval (CI) for the effects of calcium supplements (A) and dairy products (B) on waist circumference. Meta-analysis was performed using a random-effects model.

et al. 2006; Onakpoya et al. 2011; Booth et al. 2015; Li et al. 2016). Two meta-analyses about changes in fat mass with calcium supplements produced inconsistent findings (Onakpoya et al. 2011; Booth et al. 2015). In the case of body weight and BMI, various findings have been reported. Two meta-analyses reported a significant decrease in body weight (Trowman et al. 2006; Onakpoya et al. 2011). However, one meta-analysis among them simply compared the final value of the body weight between the control and intervention group, not using changes in body weight (Trowman et al. 2006) and the other meta-analysis used only a small number of articles and a fixed-effect model (Onakpoya et al. 2011). For BMI, one meta-analysis reported a non-significant but increasing tendency in BMI upon calcium supplementation (Onakpoya et al. 2011).

We found that dairy products had beneficial effects on fat mass and BMI but not on body weight or WC. The finding of an association between dairy products and obesity indices has been only partially consistent (Trowman et al. 2006; Abargouei et al. 2012; Chen et al. 2012; Booth et al. 2015; Stonehouse et al. 2016). Our fat mass finding was similar to those from all but one (Booth et al. 2015) previous meta-analysis (Onakpoya et al. 2011; Abargouei et al. 2012; Chen et al. 2012; Stonehouse et al. 2016). The BMI reduction associated with dairy products in this study was

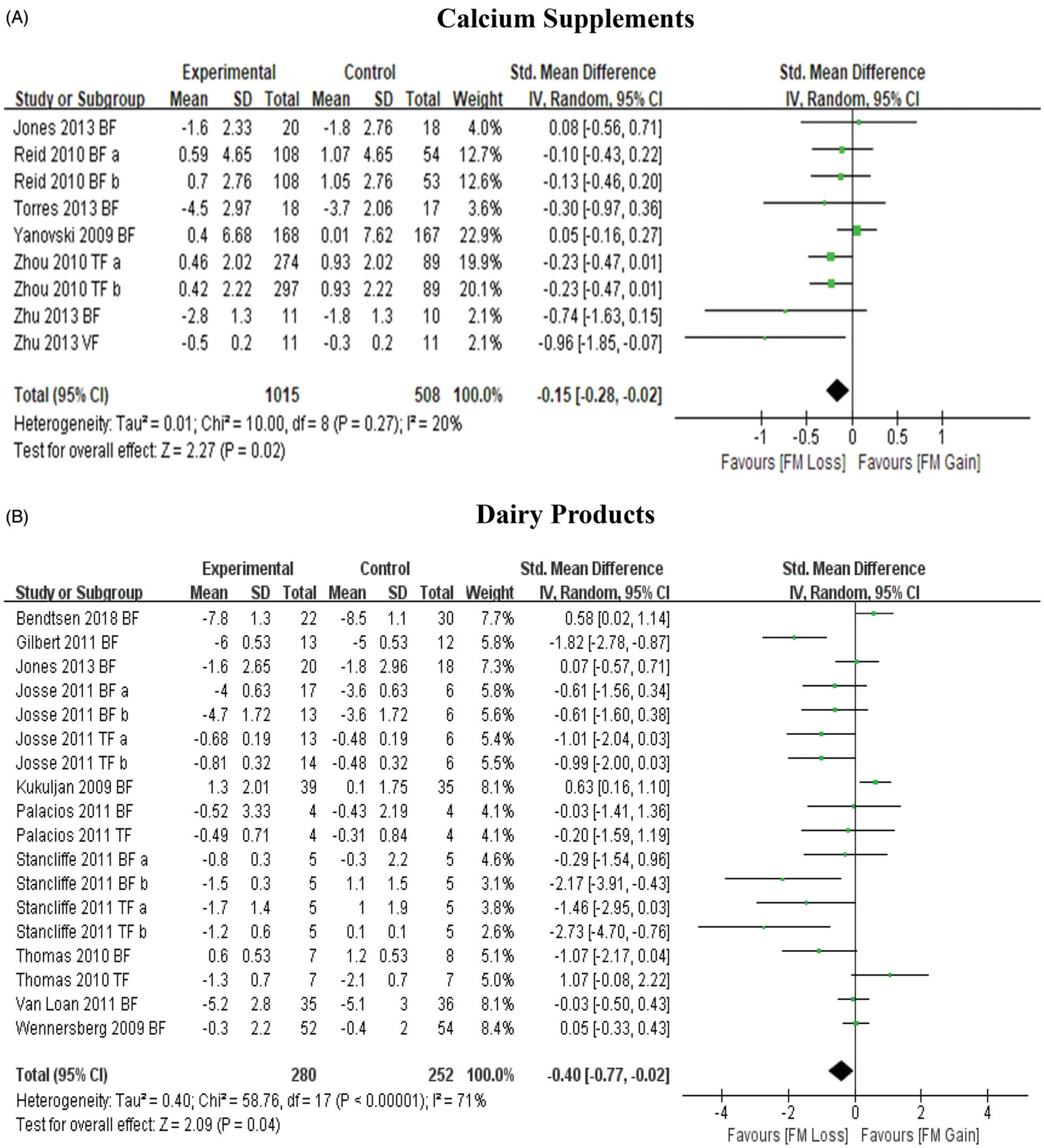

Figure 4. Forest plot detailing the standard mean difference (SMD) and 95% confidence interval (CI) for the effects of calcium supplements (A) and dairy products (B) on fat mass. Meta-analysis was performed using a random-effects model.

also found in previous studies reporting that dairy products were more effective for BMI reduction than regular calcium supplements (Zemel et al. 2000; Shi et al. 2001; Zemel and Geng 2001; Pereira et al. 2002; Zemel et al. 2002). For body weight, our non-significant findings were in accordance with all previous studies (Trowman et al. 2006; Abargouei et al. 2012; Chen et al. 2012; Booth et al. 2015; Stonehouse et al. 2016). For WC, unlike our finding, a previous meta-analysis found a significant decrease (Abargouei et al. 2012), but that study included four articles from one author.

Two possible fat metabolism mechanisms have been suggested in relation to dietary calcium and body weight (Davies et al. 2000; Heaney et al. 2002; Jacobsen et al. 2005; Christensen et al. 2009; Newberry et al. 2014). First, dietary calcium intake could break down fat and suppress fat accumulation

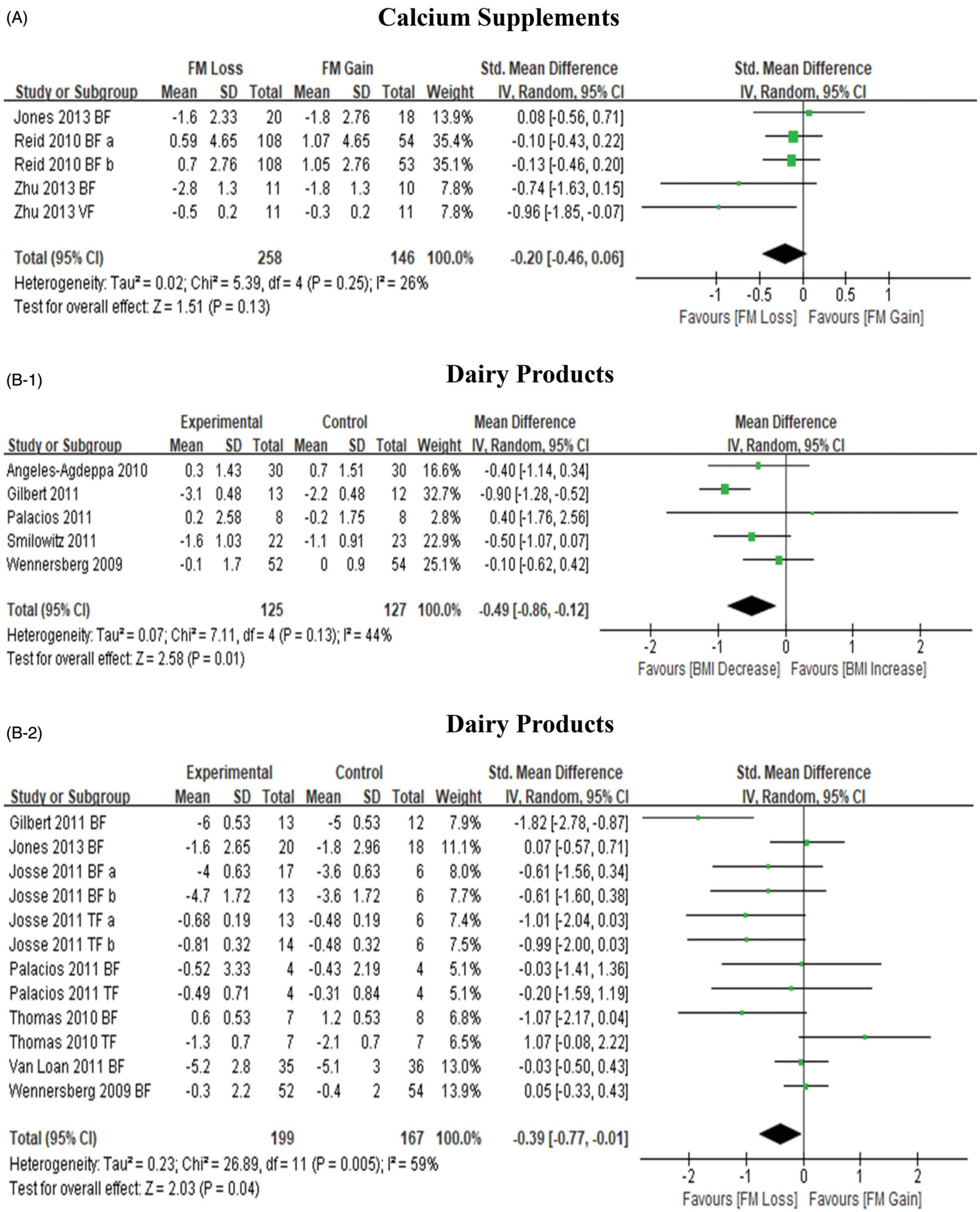

Figure 5. Forest plot detailing the standard mean difference (SMD) and 95% confidence interval (CI) for the effects of calcium supplements (A) and dairy products (B-2) on fat mass and the mean difference (MD) and 95% confidence interval (CI) for the effects of dairy products (B-1) on BMI. Meta-analysis was performed using a random-effects model.

by preventing production of parathyroid hormones and 1,25-(OH)(2)-D (Xue et al. 1998; Zemel 1998; Xue et al. 2001; Parikh and Yanovski 2003). Second, calcium increases faecal fat excretion, thereby reducing weight by preventing fat absorption in the colon (Bhattacharyya et al. 1969; Denke et al. 1993; Welberg et al. 1994; Shahkhalili et al. 2001; Buchowski et al. 2010). Because the overall effects in this study were obtained from studies with various RoB scores, we conducted an additional analysis of only studies with low RoB scores. We found that significant beneficial findings remained for BMI and fat mass only with dairy products, not with calcium supplements. Two possible explanations were suggested in a previous meta-analysis that examined the effects of increasing calcium intake by means of supplements or dairy products (Li et al. 2016). That meta-analysis showed a beneficial effect of calcium supplementation in a normal weight group, and they pointed out that calcium intake is an important nutrient involving energy metabolism as well as body fat accumulation, which might explain why calcium supplementation was beneficial for prevention of obesity in normal weight subjects (Li et al. 2016). However, many metabolic processes are greatly altered in overweight and obese people (Zemel et al. 2000), so that explanation might not be appropriate for our study. Second, the stronger effect of dairy products on fat mass and BMI compared with calcium supplements could be due to other bioactive components of dairy products, especially branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine, that could attenuate adiposity with calcium (Sun and Zemel 2004; Zemel et al. 2005). However, BCAAs were recently reported as risk factors for insulin resistance, diabetes, and cardiovascular disease (Newgard 2012; Ruiz-Canela et al. 2016), which suggests that they could increase susceptibility to overweight or obese (Li et al. 2016). Therefore, it remains unclear which components of dairy products and which mechanisms cause the changes in fat mass and BMI with dairy-product supplementation in overweight and obese subjects. Further studies on this issue are needed.

Although we did not have enough articles for stratification analysis by covariates, we did analyse differences in effect estimates among subgroups of study characteristics: study participants, study design, and quality of data or study; and sex, region, race, obesity status, metabolic syndrome status, energy restriction, method of intervention (calcium supplement: supplement only; dairy product: type of intervention), baseline calcium intake status, calcium difference, with or without vitamin D (calcium supplement), and duration (data not shown). Most subgroup analyses demonstrated still moderate to high heterogeneity up to 93%. When applying the Bonferroni correction to consider multiplicity (Naggara et al. 2011; Jakobsen et al. 2014) and the significance level of 0.1 suggested by the Cochrane Library (Higgins and Thomas 2019b) (the significance level was $0.1/100 = 0.001$ for interactions between subgroups and $0.1/244 = 0.0004$ for the overall estimate within each subgroup), we found no significant differences among those study characteristics.

This meta-analysis had some limitations that affect the interpretation of our findings. During the last 10 years, there were not many RCTs of calcium supplements and dairy products in relation to obesity indices after carefully checking inclusion and exclusion criteria and thus the number of studies in the final meta-analysis is still small, which caused several constraints; as we mentioned above, there might not enough power for stratification analysis by covariates. Even though men and women might have very different biological and behavioural characteristics, we could not test for sex differences because of a lack of RCTs that presented their findings by sex. It is noteworthy that heterogeneity in our meta-analysis was remarkably high, still even in the subgroups of covariates. Although we restricted the duration to the past 10 years, it is possible due to that many different ubiquitous environmental risk factors for obesity between study populations could not be take accounted (Pearce 2011). Additionally, the fat percentage of dairy products may affect health conditions including obesity status, especially fat mass (Kratz et al. 2013). However, in the present study, we could not analyse considering whether dairy products used were low-fat or not, because most studies did not specify fat percentage. Moreover, we could not analyse whether the effects of dairy products differed between types of fat mass, such as visceral fat or trunk fat. Next, there could be unmeasured and unconsidered factors of participants that influenced the effects of calcium and dairy-product supplementation on obesity indices, such as the initial states of obesity indices themselves, serum calcium, and active vitamin D level. Finally, we combined and analysed various types of fat mass in using SMD and furthermore imputed or calculated some estimated mean SD from other studies or graphs. Therefore, we need further studies with more precise values to confirm the present study findings. Despite these limitations, from a public health point of view, it is worthwhile to note that dairy products may help to reduce fat mass in the overweight and obese population because obesity is abnormal or excessive accumulation of adiposity not just an increase in body weight.

Conclusion

This study demonstrated that dairy products may be related to reductions in fat mass and BMI among overweight or obese adults aged 18 years or older when the intervention is 12 weeks or longer. Additional studies are needed to make appropriate public health recommendations for specific populations.

Disclosure statement

The authors declare that they have no conflicts of interest.

Author contributions

JY Hong was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analysing data, interpreting results, updating reference lists, and creating tables. MK Kim was responsible for designing the review protocol and screening potentially eligible studies and contributed to writing the report, interpreting results, creating tables, and providing feedback on the report. HY Woo contributed to writing the report, arbitrating potentially eligible studies, extracting and analysing data, interpreting results, and providing feedback on the report. JS Lee contributed to screening potentially eligible studies and data extraction. AS Om and CK Kwock provided feedback on the report.

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