Calcium supplementation for improving bone density in lactating women: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Clinical trials evaluating the effect of calcium supplementation on bone loss in lactating women have been small, with inconsistent results.

Objectives: We aimed to determine the effect of calcium supplementation on bone mineral density (BMD) in lactating women.

Methods: An electronic search of databases was conducted from inception to January 2020. Two authors screened studies, extracted data, and assessed the risk of bias of eligible studies. Percentage change in BMD was pooled using random-effects models and reported as weighted mean differences (WMDs) with 95% CIs. Risk of bias was assessed using the Cochrane risk of bias tool.

Results: Five randomized controlled trials including 567 lactating women were included. All had a high risk of bias. Mean baseline calcium intake ranged from 562 to 1333 mg/d. Compared with control groups (placebo/no intervention), calcium supplementation (600/1000 mg/d) had no significant effect on BMD at the lumbar spine (WMD: 0.74%; 95% CI: −0.10%, 1.59%; $I^2 = 47\%$; 95% CI: 0%, 81%; $n = 527$ from 5 trials) or the forearm (WMD: 0.53%; 95% CI: −0.35%, 1.42%; $I^2 = 55\%$; 95% CI: 0%, 85%; $n = 415$ from 4 trials). BMD at other sites was assessed in single trials: calcium supplementation had a small to moderate effect on total-hip BMD (WMD: 3.3%; 95% CI: 1.5%, 5.1%) but no effect on total body or femoral neck BMD.

Conclusions: Overall, the meta-analysis indicates that calcium supplementation does not provide clinically important benefits for BMD in lactating women. However, there was adequate dietary intake before supplementation in some studies, and others did not measure baseline calcium intake. Advising lactating women to meet the current recommended calcium intakes (with supplementation if dietary intake is low) is warranted unless new high-certainty evidence to the contrary from robust clinical trials becomes available. More research needs to be done in larger samples of women from diverse ethnic and racial groups. This systematic review was registered at www.crd.york.ac.uk/prospero as CRD42015022092. *Am J Clin Nutr* 2020;112:48–56.

Keywords: bone mineral density, calcium supplementation, lactating women, risk of bias, systematic review

Introduction

Low bone mineral density (BMD) is a major risk factor for osteoporotic fracture in the elderly (1, 2). BMD in later life is determined by both peak bone mass and the rate of subsequent bone loss (3). The higher the peak bone mass that is achieved by the early 20s, the greater the likelihood of withstanding the impacts of age-related bone loss (4). Therefore, optimizing BMD in young adulthood is critically important for preventing fractures in later life.

Numerous studies have demonstrated a remarkable bone loss in lactating women (5–8), which is likely due to increased bone resorption to meet the high calcium requirement of their infants. Moreover, there is some evidence that a longer duration of lactation could be associated with a reduction of BMD after 6 mo postweaning (9, 10), although this is not seen in all studies (11–13). Nevertheless, strategies for preventing bone loss or even improving bone density in lactating women are scarce.

Calcium supplementation has potential value for BMD by reducing bone turnover, particularly in those with marginal and low dietary calcium intake (14, 15). In particular, because approximately 200 mg Ca/d are secreted by breastfeeding secretes (16), this period could provide a window of opportunity for younger women to benefit more from calcium supplementation.

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Supplemental Methods and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BMC, bone mineral content; BMD, bone mineral density; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial; WMD, weighted mean difference.

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However, the RDAs for calcium intake for lactating women (17) (1000 or 1300 mg/d depending on age) are the same as those for nonlactating women. The main argument for this is that maternal skeletal resorption is hormonally programmed during lactation to supply the necessary calcium for breastfeeding and there is no evidence from randomized controlled trials (RCTs) and observational studies to show that increased calcium intake could prevent bone loss during lactation (18). However, RCTs examining the effect of calcium supplementation on BMD in lactating women are generally of small sample size and the results are conflicting (19–23). To our knowledge, no systematic review and meta-analysis has been done to quantitively determine the effect of calcium supplementation on BMD in lactating women. Thus, this study aimed to address this evidence gap by determining the effect of calcium supplementation on BMD in lactating women and whether any such effect varies by baseline calcium intake, dose of calcium supplementation, co-intervention of vitamin D, duration of supplementation or breast-feeding, age, or ethnicity.

Methods

Protocol registration

The protocol for the systematic review and meta-analysis was registered with PROSPERO (CRD42015022092) (24). This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (25).

Literature search

We searched EMBASE (via Ovid), MEDLINE (via PubMed), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL, via The Cochrane Library) from inception (that is, from the date the database was established) to June 2015, and updated our search in January 2020, for RCTs of calcium supplementations in lactating women with BMD, total-body bone mineral content (BMC), fracture, quality of life, or adverse events as an endpoint. See the **Supplemental Methods** for a detailed search strategy for MEDLINE. We checked bibliographies of original studies and recent review articles for additional relevant studies. We also searched clinicaltrials.gov and the WHO trials portal (www.who.int/ictrp/en/) for clinical trials that have not been published.

Study selection

Two authors (GC and JT) independently screened titles and abstracts for all identified studies and retrieved the full texts of potentially relevant studies for further screening. Full-text reviews were performed according to the a priori selection criteria that are detailed in the registered protocol (24). Briefly, we included studies if they were *1*) online published full-text articles or conference abstracts; *2*) written in any language; *3*) RCTs evaluating the effect of calcium supplementations (including calcium-fortified food) with or without a co-intervention of vitamin D for ≥3 mo in lactating women who decided to breastfeed their infants for ≥3 mo; and *4*) aimed at BMD, total-body BMC, fractures, quality of life, or adverse events as an outcome measure. If the supplementation started during pregnancy, studies were included if the duration of supplementation in the postpartum period was at least double that in pregnancy. Studies eligible for the systematic review were included in the meta-analysis if they provided sufficient data for pooling on any of the aforementioned outcome measures. Given that few placebo-controlled trials ($n = 3$) were available for this review, we amended the protocol to also include trials that used no intervention as a control group rather than only including placebo-controlled trials as originally planned.

Data extraction

Two authors (GC and FW) independently extracted information from each included study using a data collection form. Data extracted were *1*) study characteristics (first author, year of publication, study design, inclusion and exclusion criteria, sample size, and duration of follow-up); *2*) participants' characteristics (age, ethnicity, and baseline calcium intake); *3*) interventions (dose and duration of calcium supplementation); and *4*) outcome measures (techniques, sites, and timing of BMD measurement). Where available, we extracted the percentage of change in BMD in the calcium supplementation group and the control group at the following sites: total hip, femoral neck, lumbar spine, and forearm. Because BMD at the forearm can be measured at different sites (e.g., ultradistal, proximal, distal third of radius), we used BMD at the most commonly reported site (ultradistal radius) or any other radius site if BMD at the ultradistal radius was not available. For BMD that was measured at multiple time points, we extracted data for the time points that were *1*) shared by most studies included and *2*) at the end of supplementation. When the outcomes were shown as graphs only, we converted graphical data to numerical data using Engauge Digitizer software (version 10.11) (26, 27). Data on other prespecified outcomes (i.e., total-body BMC, fractures, quality of life, and adverse events) were not extracted because they were not reported in any study.

Assessment of risk of bias and quality of evidence

Two authors (GC and FW) independently assessed the risk of bias using Cochrane's risk of bias assessment (28), with disagreements discussed with a third author (JT). For each outcome, we assessed quality of evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach, which combines risk of bias, consistency of effect, imprecision, indirectness, and publication bias (29). Quality of evidence was downgraded from high (i.e., RCT) to very low based on the seriousness of each component in the GRADE. The GRADE Summary of Findings table was generated using the GRADEpro Guideline Development Tool on the GRADEpro website (https://gdt.gradepro.org/app/).

Data synthesis

No studies reported fractures, quality of life, adverse events, or withdrawals due to adverse events so these could not be

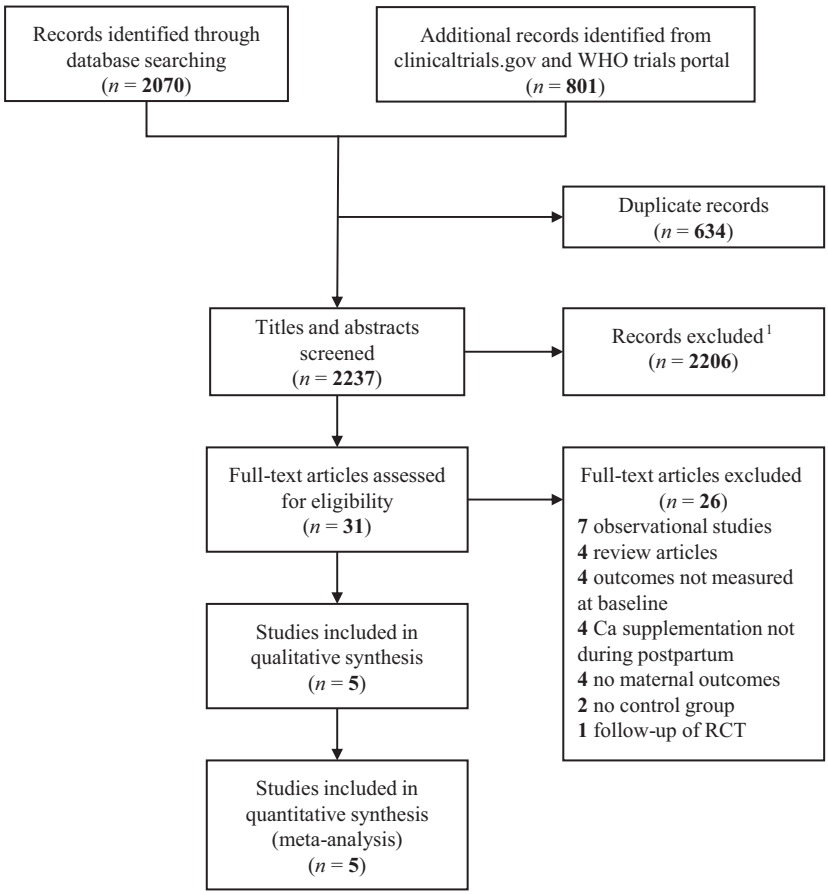

FIGURE 1 Flowchart of the study. All records from clinicaltrials.gov and the WHO trials portal were assessed and excluded.

analyzed. The most commonly shared time points at which BMD was measured were 3 (19, 21, 22) and 6 (19, 20, 22) mo in 3 studies. Given the limited number of studies, in the main analysis we pooled the data of BMD outcomes at the end of supplementation from all 5 studies [i.e., 6 mo for 2 studies (20, 22) and 9 (23), 10 (21), and 18 (19) mo for each of the remaining 3 studies], and we also pooled the data at the most commonly shared time points (i.e., 3 and 6 mo). We calculated the weighted mean difference (WMD) with 95% CIs between calcium supplementation and control groups in the percentage changes of BMD using DerSimonian and Laird random-effects models (30). The pooled results were presented in forest plots. All data syntheses were carried out with Review Manager software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration).

Assessment of heterogeneity

Statistical heterogeneity was assessed using the I^2 statistic and chi-square test. $I^2 > 50\%$ was considered substantial heterogeneity and a P value ≤ 0.10 in the chi-square test indicated statistical significance. The 95% CIs of the I^2 estimate were calculated based on Higgins and Thompson (31).

Assessment of publication bias

Because only a limited number of studies were included in this systematic review and meta-analysis, we used funnel plots only to visually assess publication bias.

Subgroup analysis

The planned a priori subgroup analyses were not undertaken owing to the small number of included studies. Those planned were by *1*) baseline calcium intake (< or ≥1000 mg/d); *2*) dose of calcium supplementation (< or ≥1000 mg/d); *3*) co-intervention of vitamin D (yes or no); *4*) duration of supplementation (< or ≥12 mo); *5*) duration of breastfeeding (< or ≥6 mo); *6*) age (< or ≥30 y); and *7*) ethnicity.

Sensitivity analysis

A priori sensitivity analyses were performed by omitting studies with inappropriate or unclear allocation concealment and omitting studies that used no intervention as a control group. Given our inability to explore heterogeneity using subgroup analyses owing to the small numbers of studies, we opted to address heterogeneity instead by performing a

post hoc sensitivity analysis excluding a single study (23) which was markedly different from the remaining studies for a number of our prespecified subgroup characteristics (32) and using 6-mo lactation data only of an 18-mo study (19). In addition, another post hoc sensitivity analysis was conducted by excluding a study that was published as a conference abstract (20).

Results

Study selection

Figure 1 details the flowchart of the study selection process. Our electronic search identified 2871 potentially relevant records. Of these, 634 were excluded as duplicates and 2206 excluded after screening for titles and abstracts. We performed full-text screening of the remaining 31 references, and 5 RCTs involving 567 participants (293 in the calcium supplementation group and 274 in the control group) were included in this review.

Table 1 presents the characteristics of the included studies (19–23). Four studies were performed in Caucasians or predominantly Caucasians (19–22) and 1 in Asians (Chinese) (23). The mean age of lactating women ranged from 27.5 to 31 y. The duration of breastfeeding ranged from 3 to 7.6 mo. Of note, 1 study by Yu et al. (23) started calcium supplementation when most participants had ceased lactating. In another, supplementation occurred both during lactation (~6 mo) and for 12-mo postlactation (19). Mean calcium intake at baseline was reported in 4 studies and ranged from 562 to 1333 mg/d (20–23). The dose of calcium supplementation was 1000 mg/d in 4 trials (19–22) and 600 mg/d in 1 trial (23). Two studies provided 400 IU vitamin D/d to both the calcium supplementation and control groups (21, 22). BMD was measured by DXA in all studies. The longest follow-up times ranged from 6 to 18 mo with calcium supplementation provided during the entire follow-up. All studies compared the percentage change of BMD (%) from baseline to the end of follow-up between the calcium supplementation group and control group. All studies measured BMD at the lumbar spine and 4 at the forearm (19–22) and single studies only reported BMD for the whole body (21), total hip (23), and proximal femur (20). No studies reported total-body BMC, fracture, quality of life, or adverse events as outcomes. Two studies reported the mean ± SD BMD at baseline by treatment group. In the Polatti et al. study (19), baseline lumbar spine BMD was 1.239 ± 0.018 g/cm^2 in the calcium supplementation group and 1.220 ± 0.014 g/cm^2 in the control group, and forearm BMD was 0.469 ± 0.009 g/cm^2 and 0.489 ± 0.008 g/cm^2 in the treatment and control groups, respectively. In the Yu et al. study (23), lumbar spine BMD was 0.977 ± 0.099 g/cm^2 and 0.977 ± 0.115 g/cm^2 and total-hip BMD was 0.836 ± 0.118 g/cm^2 and 0.849 ± 0.117 g/cm^2 in the calcium treatment and control groups, respectively. One study had loss to follow-up of <5% (21), 2 between 5% and 20% (19, 22), 1 of 30% (23), and loss to follow-up was unclear in the remaining 1 study (20). None of the studies addressed missing data, and all of them conducted complete data analysis.

TABLE 1 Characteristics of included studies[1]

Study	Ca/control, *n*	Age, y (mean ± SD)	Ethnicity	Baseline Ca intake, mg/d (mean ± SD)	Duration of lactating, mo	Ca dose, mg/d	Concomitant vitamin D	Intervention[2]			Outcome measures			Techniques of BMD measure	Sites measured
								Start	Duration, mo	Baseline	Endpoints	Time interval, mo		
Cross et al. (21)	7/8	28.2 ± 1.3	White	1333 ± 86	7.6	1000	400 IU/d	<2 wk postpartum	10	<2 wk postpartum	3 mo lactation; 3 mo postweaning	10		DXA	Whole body, lumbar spine, radius (proximal third, mid-, and ultradistal)
Kent et al. (20)	44/35	31 (NS)	White	1056 ± 284[3]	6	1000	No	36 weeks of gestation	7	1 wk postpartum	24 wk lactation	6		DXA	Lumbar spine, proximal femur (neck, trochanteric, and intertrochanteric), radius, and lower limb (shaft and ultradistal)
Kalkwarf et al. (22)	45/42	30 ± 3	84% white	614 [472–753][4]	6	1000	400 IU/d	16 ± 2 d postpartum	6	16 ± 2 d postpartum	3 and 6 mo after enrolment	6		DXA	Lumbar spine, radius (shaft and ultradistal)
Polatti et al. (19)	139/135	29.5 ± 3.0	White	NS	6	1000	No	5–10 d postpartum	18	5–10 d postpartum	3, 6, 7, 12, and 18 mo postpartum	18		DXA	Lumbar spine, radius (distance to ulna < 8 mm)
Yu et al. (23)	58/54	27.5 ± 4.1	Chinese	562 ± 197	3–4[5]	600	No	3 mo postpartum	9	3 mo postpartum	12 mo postpartum	9		DXA	Lumbar spine, total hip

[1] BMD, bone mineral density; NS, not stated.
[2] Polatti et al. (19) and Yu et al. (23) did not have a placebo group and used no intervention as their control groups.
[3] Calcium intake in the placebo group at 12 wk lactation; baseline calcium intake was unavailable.
[4] Median [IQR].
[5] Lactation occurred for ≤1 mo of the supplementation period.

Assessment of risk of bias

Overall, assessment of the risk of bias suggested a high risk of bias in all included studies (**Supplemental Figure 1**). Adequate description of randomization was given in 1 study (19), and the remaining 4 reported randomized allocation but without describing randomization procedures. Allocation concealment was not clearly stated in 3 placebo-controlled studies (20–22) and was inadequate in the remaining 2 studies with no-intervention groups as controls (19, 23). Of the 3 placebo-controlled trials, 2 used a double-blinding design (21, 22) whereas the other 1 did not state the blinding strategy (20). How missing data were handled in 2 studies (20, 23) was not well described, indicating a potential attrition bias. No trials were registered online or provided a study protocol (4 were completed before 2000 and 1 in 2011), suggesting the potential for reporting bias.

Effects of calcium supplementation on BMD

For change in BMD from baseline to the end of calcium supplementation in each study, the pooled results for lumbar spine (5 studies: 275 participants in calcium and 252 in control arms) and forearm (4 studies: 217 participants in calcium and 198 in control arms) BMD are shown in **Figure 2** and **Table 2**. Compared with placebo, calcium supplementation did not significantly reduce the loss of BMD at the lumbar spine (WMD: 0.74%; 95% CI: −0.10%, 1.59%; $P = 0.09$, $I^2 = 47\%$; 95% CI: 0%, 81%) or the forearm (WMD: 0.53%; 95% CI: −0.35%, 1.42%; $P = 0.24$, $I^2 = 55\%$; 95% CI: 0%, 85%). Table 2 also provides the effect estimates from single studies for BMD of the total body (21), total hip (23), and femoral neck (20). Compared with placebo, calcium supplementation increased BMD of the total hip (WMD: 3.30%; 95% CI: 1.53%, 5.07%; $P < 0.001$) but not the total body or femoral neck. However, the single study reporting total-hip BMD (23) had a substantially different design compared with the remaining 4 studies, because it provided calcium supplementation mostly after the cessation of lactating (see also "Sensitivity analysis" below).

Changes in BMD at 3 and 6 mo were reported in 3 studies for lumbar spine and 2 studies for forearm (**Figure 3**). Overall, calcium supplementation reduced the loss of BMD at the lumbar spine over 3 and 6 mo and the forearm over 6 mo, although these findings were primarily driven by 1 large, heavily weighted study (19).

We downgraded the quality of evidence by 3 levels for high risk of bias, inconsistency, imprecision, indirectness, and/or publication bias for all BMD outcomes, resulting in a GRADE assessment of very low certainty of the evidence for all BMD outcomes.

Sensitivity analysis

All included studies did not perform or state allocation concealment adequately. Therefore, no sensitivity analysis was performed by omitting studies with inappropriate or unclear allocation concealment. After excluding 2 studies that used no intervention as their control group, calcium supplementation showed no or small effect on lumbar spine BMD (WMD: 0.91%; 95% CI: −0.06%, 1.87%; $P = 0.07$, $I^2 = 0\%$; 95% CI: 0%, 85%) or forearm BMD (WMD: 1.01%; 95% CI: −0.003%, 2.03%; $P = 0.05$, $I^2 = 10\%$; 95% CI: 0%, 86%)—$n = 181$ from 3 studies (20–22).

One study (23) was markedly different from the remaining studies in that breastfeeding was of short duration (and in fact the bulk of supplementation was given after breastfeeding ceased), the calcium supplement dose was low, supplementation commenced late (3 mo postpartum rather than ≤2 wk), and the participants were Chinese rather than all or predominantly white. Furthermore, this study was the only study in which lumbar spine BMD increased over the study period in both calcium and control groups. Therefore, this study was excluded in a post hoc sensitivity analysis. In addition, change in BMD over 6 mo from 1 study was used in this post hoc sensitivity analysis because, in this study, that was the point at which breastfeeding ceased (19). In this sensitivity analysis, the effect of calcium supplementation and statistical heterogeneity were both markedly reduced for lumbar spine BMD (4 studies, 455 participants, WMD: 0.40%; 95% CI: 0.32%, 0.49%; $P < 0.001$, $I^2 = 0\%$; 95% CI: 0%, 79%) and were not materially changed for forearm BMD (4 studies, 455 participants, WMD: 0.54%; 95% CI: −0.18%, 1.26%; $P = 0.14$, $I^2 = 41\%$; 95% CI: 0%, 80%). Another sensitivity analysis excluding a study that was published only as a conference abstract (20) did not materially affect the results [BMD of the lumbar spine (4 studies, 448 participants, WMD: 0.67%; 95% CI: −0.37%, 1.72%; $P = 0.21$, $I^2 = 46\%$; 95% CI: 0%, 82%) and forearm (3 studies, 336 participants, WMD: 0.59%; 95% CI: −0.73%, 1.90%; $P = 0.38$, $I^2 = 61\%$; 95% CI: 0%, 89%)].

Publication bias

Visual inspection of the funnel plots for lumbar spine BMD did not suggest publication bias, but there was possible asymmetry for forearm BMD such that publication bias could not be ruled out (**Supplemental Figure 2**).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the effect of calcium supplementation on BMD in lactating women. At best, supplementation of 600–1000 mg Ca/d in lactating women resulted in only a small and statistically nonsignificant benefit for BMD of the lumbar spine (WMD: 0.74%; 95% CI: −0.10%, 1.59%) and the forearm (WMD: 0.53%; 95% CI: −0.35%, 1.42%) that was unlikely to be clinically important. Notably, all included studies had a high risk of bias and the certainty of the evidence was assessed as very low. The effect of calcium supplementation on change in BMD over 3 and 6 mo was primarily driven by the Polatti et al. study (19) because of its larger sample size and greater precision of BMD measurement, but this study did not report baseline calcium intake. Nonetheless, the pooled results were not materially changed after excluding the Polatti et al. study (19) and another study (23) with no intervention as its control group. Evidence for effects at other sites was sparse. BMD at each of total body, total hip, and femoral neck was only assessed in single studies. These reported no effects at those sites except for a 3.30% difference in change in total-hip BMD in a single study (23), but it is important to note that this study (23) had a different design that mainly focused on the effect of calcium supplementation during the postweaning

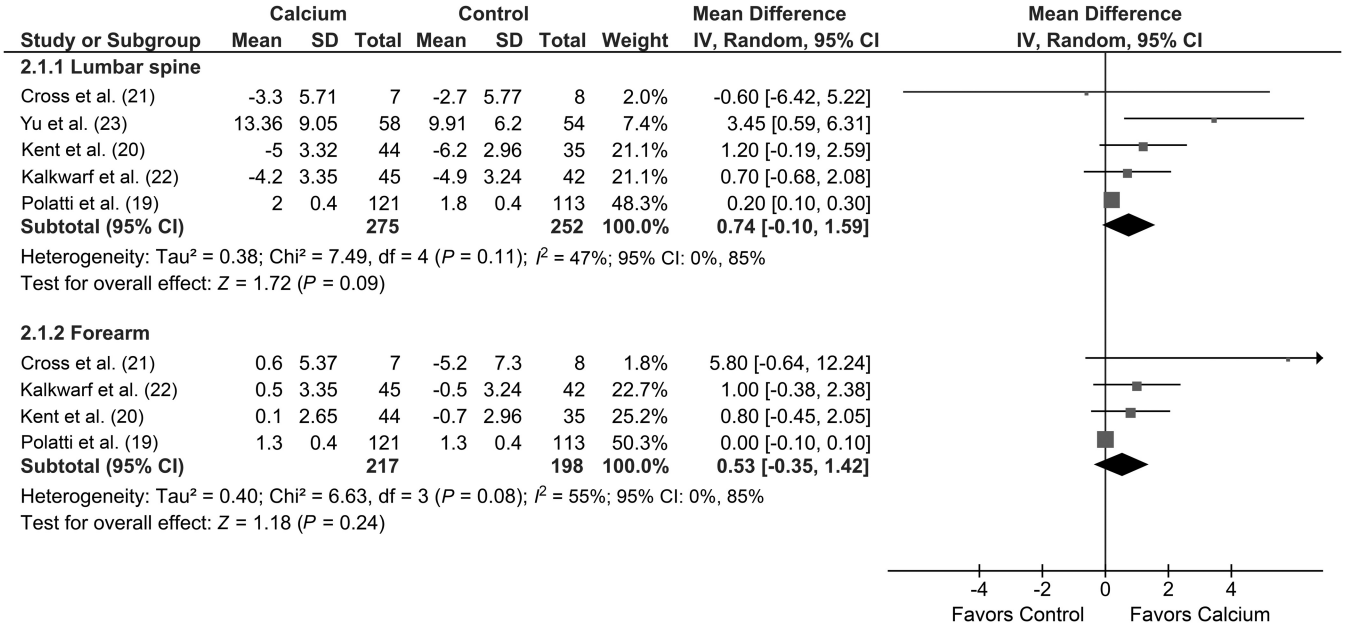

FIGURE 2 Random-effects meta-analysis of effect of calcium supplementation on percentage change in bone mineral density of the lumbar spine and forearm from baseline to the end of supplementation. IV, inverse variance.

period, making the results less comparable with those in other studies. Nevertheless, this study would suggest that calcium supplementation may improve BMD recovery after lactation, and this type of design may be important to consider in future studies.

Irrespective of the poor quality of the evidence, the effect sizes for BMD at the lumbar spine, forearm, total body, and femoral neck (0.33%–1.10%) are too small to be clinically meaningful. In older people, a 10% higher BMD of the lumbar spine and femoral neck is associated with ~50% reduction in long-term fracture risk (33), and the effect sizes of our study are therefore unlikely to be translated into a noteworthy reduction in fracture risk. Moreover, there is no evidence that a history of lactation is associated with increased fracture risk in later life (34), so the likelihood of reducing fractures in later life through this strategy would seem low. Postpartum osteoporosis and fractures are rare and have only been described in a few case reports (35). Although bone loss during lactation may cause an increased risk of osteoporosis and fractures, Kovacs (36) has proposed this may only be a coincidental condition caused by pre-existing low bone density for the majority of women and our review suggests that it is unlikely that calcium supplementation during lactation would have sufficient benefits for BMD to prevent such fractures.

Although calcium supplementation showed a moderate effect on total-hip BMD, this was based on a single study with high risk of bias and in which calcium supplementation began 3 mo after birth and presumably the establishment of breastfeeding, and given that the mean duration of breastfeeding ranged from 80 to 120 d, supplementation was primarily administered after breastfeeding ceased and recovery of bone mass commenced (23). This is consistent with the fact that in this study BMD increased rather than decreased in both intervention groups. The effect on the total hip in this study of 3.3% over 9 mo is closer to being clinically important and this raises the question of whether calcium supplementation upon cessation of rather than during breastfeeding could be beneficial. However, more evidence from high-quality RCTs is needed to address this question.

There were insufficient studies in this review to allow for a meaningful subgroup analysis by baseline calcium intake. In only 2 trials (22, 23) was the mean baseline calcium intake lower than the recommended intake of 1000 mg/d for lactating women aged 18 or older (being 562 and 614 mg/d, respectively). The possibility of a BMD effect occurring in women with very low calcium intake cannot be ruled out and such women could be the target population in any future clinical trials. RCTs in women with low calcium intake may also provide additional evidence to support the setting of recommended dietary calcium intakes in lactating adults. Of note, a higher intake is recommended for lactating women aged 18 y or younger (1300 mg/d) (17), but no trials have examined the effect of calcium supplementation in this age group. Therefore, this recommendation may also be warranted unless new evidence becomes available.

Strengths and limitations of the study

This systematic review was conducted following a pre-specified, registered protocol using Cochrane methodology. We performed a comprehensive search of multiple databases and clinical trial registries without restricting the language or publication status of the trials. It is therefore unlikely that we have missed any relevant trials.

The most important limitation of this review comes from the 5 included trials themselves. All included trials had a high risk of bias, and we have downgraded the quality of evidence to very low for all findings. The possibility of confounding cannot be ruled out because 4 of the 5 trials included did not

TABLE 2 Summary of findings of eligible RCTs evaluating the effect of calcium supplementation for improving BMD in lactating women[1]

Sites of BMD measures	Absolute effect estimates			Certainty of the evidence (GRADE)	What happens
	Control group	Calcium supplementation	Difference (95% CI)		
Lumbar spine; follow-up: 6–18 mo; participants, *n*: 527 (5 RCTs) (19–23)	Mean 0.79% decreasing	Mean 0.05% decreasing	0.74% (−0.10%, 1.59%; $P = 0.09$)	⊕⊖⊖⊖ VERY LOW (risk of bias, inconsistency, and indirectness)[2]	Calcium supplementation may have no effect for preventing the loss of lumbar spine BMD
Forearm; follow-up: 6–18 mo; participants, *n*: 415 (4 RCTs) (19–22)	Mean 0.27% increasing	Mean 0.80% increasing	0.53% (−0.35%, 1.42%; $P = 0.24$)	⊕⊖⊖⊖ VERY LOW (risk of bias, inconsistency, and publication bias)[3]	Calcium supplementation may have no effect on the loss of forearm BMD
Total-body BMD; follow-up: 10 mo; participants, *n*: 15 (1 RCT) (21)	Mean 1.0% decreasing	Mean 0.03% increasing	1.03% (−0.75%, 2.81%; $P = 0.26$)	⊕⊖⊖⊖ VERY LOW (risk of bias and imprecision)[4]	Calcium supplementation appears to not reduce the loss of whole-body BMD
Total-hip BMD; follow-up: 9 mo; participants, *n*: 112 (1 RCT) (23)	Mean 3.14% increasing	Mean 6.44% increasing	3.30% (1.53%, 5.07%; $P < 0.001$)	⊕⊖⊖⊖ VERY LOW (risk of bias, indirectness, and imprecision)[5]	Calcium supplementation may have a moderate effect for reducing the loss of total-hip BMD
Femoral neck BMD; follow-up: 6 mo; participants, *n*: 79 (1 RCT) (20)	Mean 6.1% decreasing	Mean 5.0% decreasing	1.10% (−0.43%, 2.63%; $P = 0.16$)	⊕⊖⊖⊖ VERY LOW (risk of bias and imprecision)[6]	Calcium supplementation may have little or no effect on the loss of femoral neck BMD

[1] $n = 5$ RCTs. BMD, bone mineral density; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[2] Risk of bias: inadequate random sequence generation, and inadequate or lack of concealment of allocation, resulting in potential selection bias; inadequate or lack of blinding of participants and personnel resulting in potential performance bias; inadequate description of missing data resulting in potential attrition bias. Inconsistency: Yu et al. (23) observed a significantly larger effect of calcium supplementation than other trials and used no intervention as control, and Polatti et al. (19) used no intervention as control and had a remarkably smaller variation of change in BMD than other studies. Indirectness: Yu et al. (23) mainly targeted the effect of calcium supplementation on BMD in postlactating rather than lactating women.

[3] Risk of bias: inadequate random sequence generation and concealment of allocation resulting in potential selection bias; inadequate or lack of blinding of participants and personnel resulting in potential performance bias; inadequate description of missing data resulting in potential attrition bias. Inconsistency: Polatti et al. (19) used no intervention as control and had a remarkably smaller variation of change in BMD than other studies. Publication bias: funnel plot indicates a potential publication bias.

[4] Risk of bias: inadequate random sequence generation and concealment of allocation resulting in potential selection bias; inadequate blinding of participants and personnel resulting in potential performance bias. Imprecision: only 1 study (21) with a very small sample size was available, and the wide CI may influence clinical decision.

[5] Risk of bias: inadequate random sequence generation and concealment of allocation, resulting in potential selection bias; lack of blinding of participants and personnel (no intervention as control) resulting in potential performance bias; inadequate description of a high proportion of missing data (30%) may lead to potential attrition bias. Indirectness: Yu et al. (23) mainly targeted the effect of calcium supplementation on BMD in postlactating rather than lactating women. Imprecision: only 1 study was available, and the wide CI may influence clinical decision.

[6] Risk of bias: inadequate random sequence generation and concealment of allocation, resulting in potential selection bias; inadequate blinding of participants and personnel resulting in potential performance bias; inadequate description of missing data resulting in potential attrition bias; trial was published as a conference abstract with many details of the study unavailable. Imprecision: only 1 study was available (20) and the wide CI may influence clinical decision.

provide detailed information about the randomization process. However, effect sizes in this review were small and of doubtful clinical importance, and given the known tendency of trials with higher risk of bias to overestimate treatment effects (37, 38), it seems likely that the robust clinical trials required to definitively confirm this lack of effect should not be a high research priority. We included 2 trials using no intervention as their control groups owing to the limited number of placebo-controlled trials based on the prespecified protocol, but the main outcome of BMD was measured by DXA which is unlikely to be influenced by knowledge of the grouping. The exclusion of these 2 trials in a sensitivity analysis did not significantly change the pooled results, suggesting no impact of this issue on our conclusions. The limited number of studies precluded using subgroup analyses to explore the moderate statistical heterogeneity observed and assess potential effect modification. Instead, we addressed heterogeneity by excluding a study with markedly different characteristics in terms of study design and population (23). The results of this analysis of the remaining 4 studies showed only a very small effect of calcium supplementation on lumbar spine BMD. Therefore, it may be that the main pooled result overestimates the effect of calcium supplementation in lactating women and should be interpreted with caution.

Conclusion

Overall, the meta-analysis indicates that calcium supplementation does not provide clinically important benefits for BMD in lactating women. However, the mean dietary intake was adequate before supplementation in some studies, and others did not measure baseline dietary calcium intake. Advising lactating women to meet the current recommended calcium intakes (including with supplements if dietary intake is low and cannot otherwise be increased) is warranted unless new high-certainty evidence to the contrary from robust clinical trials becomes available. More research needs to be done in larger samples of women from diverse ethnic and racial groups and specifically in women with low dietary calcium intakes.

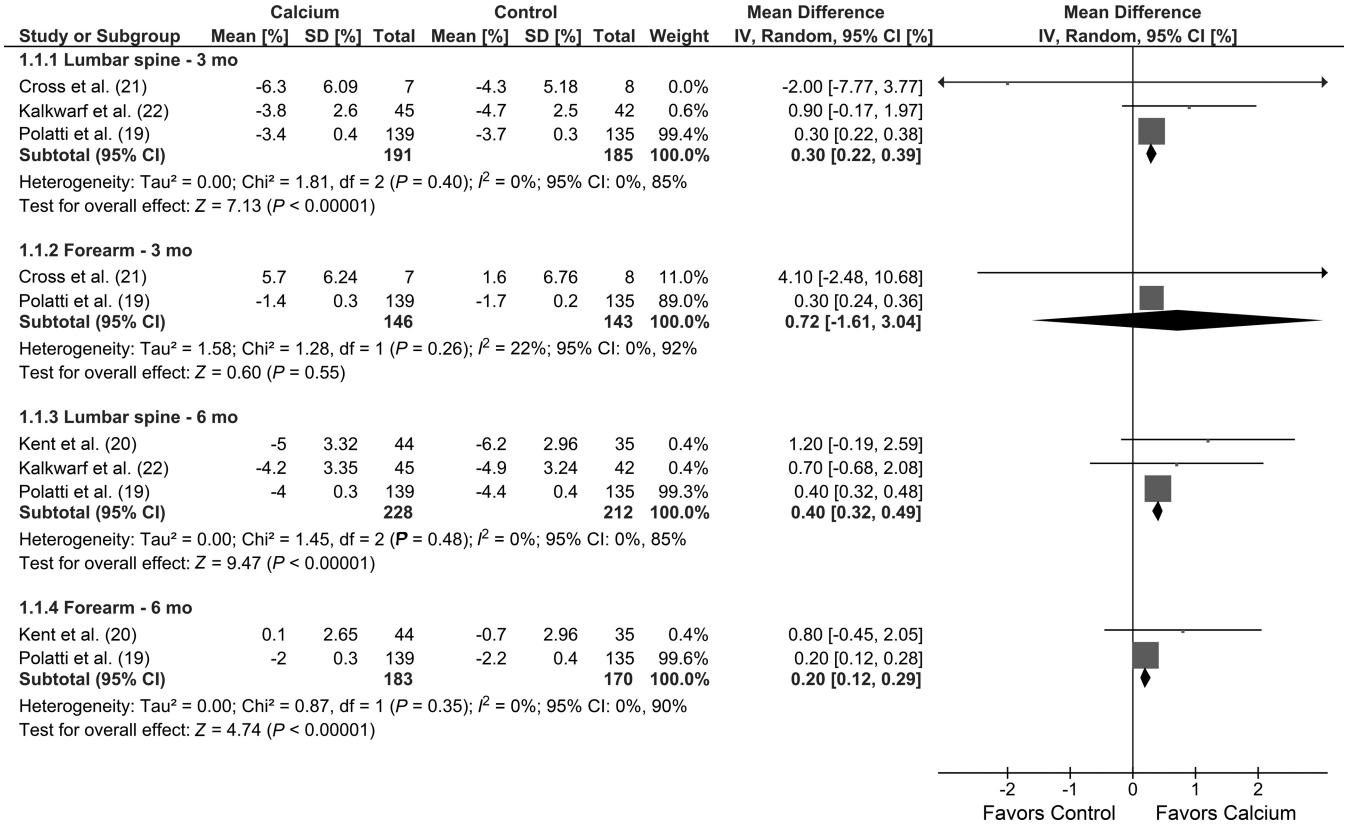

FIGURE 3 Random-effects meta-analysis of effect of calcium supplementation on percentage change in bone mineral density of the lumbar spine and forearm from baseline to 3 or 6 mo. IV, inverse variance.

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