Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials

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Abstract

Objectives To assess the effectiveness of calcium supplementation for improving bone mineral density in healthy children and to determine if any effect is modified by other factors and persists after supplementation stops.
Design Meta-analysis.
Data sources Electronic bibliographic databases, hand searching of conference proceedings, and contacting authors for unpublished data.
Review methods We included randomised placebo controlled trials of calcium supplementation in healthy children that lasted at least three months and had bone outcomes measured after at least six months of follow-up. Two reviewers independently extracted data and assessed quality. Meta-analyses predominantly used fixed effects models with outcomes given as standardised mean differences.
Results We included 19 studies involving 2859 children. Calcium supplementation had no effect on bone mineral density at the femoral neck or lumbar spine. There was a small effect on total body bone mineral content (standardised mean difference 0.14, 95% confidence interval 0.01 to 0.27) and upper limb bone mineral density (0.14, 0.04 to 0.24). This effect persisted after the end of supplementation only at the upper limb (0.14, 0.01 to 0.28). There was no evidence that sex, baseline calcium intake, pubertal stage, ethnicity, or level of physical activity modified the effect.
Conclusions The small effect of calcium supplementation on bone mineral density in the upper limb is unlikely to reduce the risk of fracture, either in childhood or later life, to a degree of major public health importance.

Introduction

At least 90% of peak bone mass (the maximum bone mass attained by an individual) is obtained by the age of 18.[1] Intervention in childhood to maximise peak bone mass by improving modifiable factors such as diet and physical activity[2] might minimise the impact of bone loss related to age. Intervention might also have a beneficial effect on fracture in childhood.

Clinical trials of calcium supplementation[w1 w12 w15 w17 w19] and dairy products[3] have shown increases in bone mineral density in children, although the increases may not be maintained.[w15] Narrative reviews conclude that overall calcium supplementation seems to have a modestly favourable effect on bone outcomes at the end of the treatment period.[4–6]

We carried out a systematic review to determine the effectiveness of calcium supplementation for improving bone mineral density in healthy children; if any effect varies by sex, baseline calcium intake, pubertal stage, ethnicity, or level of physical activity; and whether any effect persists after calcium supplementation stops.

Methods

Description of the review methods is available elsewhere.[7] We included randomised controlled trials of calcium supplementation (including in food) compared with placebo, with a treatment period of at least three months; participants were children (age < 18) without coexisting medical conditions or treatments affecting bone metabolism; outcome measures included areal or volumetric bone mineral density, bone mineral content, broadband ultrasound attenuation, or speed of sound measured at any site; and bone outcomes were measured after at least six months of follow-up.

We applied the search strategies (see bmj.com) to the following electronic bibliographic databases: CENTRAL, (Cochrane Central Register of Controlled Trials), Medline, Embase, CINAHL, AMED, MANTIS, ISI Web of Science, Food Science and Technology Abstracts, and Human Nutrition. We also hand searched conference abstract books (*Osteoporosis International* 1990-9, *Journal of Bone and Mineral Research* 2002-3). Two reviewers independently assessed articles for inclusion, extracted data, and assessed quality.

We had data for total body bone mineral density and for density at the femoral neck, lumbar spine, distal

A list of references for the included studies (w1-w35) and the search strategy can be found on bmj.com.

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	N	Treatment mean (SD)	N	Control mean (SD)	Weight (%)	SMD (fixed) (95% CI)
At end of supplementation (all data)						
Johnston 1992	45	317.09 (69.40)	45	311.51 (69.67)	5.81	0.08 (-0.33 to 0.49)
Lee 1994	77	487.00 (41.00)	82	480.00 (43.00)	10.22	0.17 (-0.15 to 0.48)
Bonjour 1995	55	312.00 (29.66)	53	308.00 (29.12)	6.96	0.14 (-0.24 to 0.51)
Lee 1995	44	492.00 (39.00)	40	491.00 (51.00)	5.41	0.02 (-0.41 to 0.45)
Wang 1996	79	486.00 (37.00)	83	479.00 (31.00)	10.40	0.20 (-0.10 to 0.51)
Dibba 2000	80	253.00 (50.00)	80	231.00 (50.00)	10.09	0.44 (0.12 to 0.75)
Stear 2003	65	427.00 (38.00)	66	418.00 (43.00)	8.41	0.22 (-0.12 to 0.56)
Cameron 2004	24	418.00 (43.00)	24	414.00 (42.00)	3.10	0.09 (-0.47 to 0.66)
Matkovic 2004	79	450.00 (53.00)	98	438.00 (50.00)	11.22	0.23 (-0.06 to 0.53)
Chevalley 2005	114	309.60 (28.00)	118	308.20 (32.00)	14.97	0.05 (-0.21 to 0.30)
Courteix 2005	22	336.18 (43.19)	63	351.00 (69.75)	4.19	-0.23 (-0.72 to 0.26)
Prentice 2005	73	479.00 (61.00)	70	482.00 (51.00)	9.23	-0.05 (-0.38 to 0.27)
Total (95% CI)	757		822		100.00	0.14 (0.04 to 0.24)
Test for heterogeneity: χ^2=8.69, df=11, P=0.65, I^2=0%						
Test for overall effect: z=2.71, P=0.007						
At longest point after end of supplementation (all data)						
Johnston 1992	43	365.23 (77.08)	43	361.31 (74.84)	10.30	0.05 (-0.37 to 0.47)
Lee 1994	77	505.00 (45.00)	82	505.00 (40.00)	19.04	0.00 (-0.31 to 0.31)
Bonjour 1995	67	429.00 (26.32)	58	418.00 (32.74)	14.64	0.37 (0.02 to 0.73)
Lee 1995	44	516.00 (44.00)	40	517.00 (49.00)	10.04	-0.02 (-0.45 to 0.41)
Dibba 2000	80	256.00 (43.00)	80	242.00 (48.00)	18.95	0.31 (-0.01 to 0.62)
Chevalley 2005	110	319.70 (28.00)	116	316.40 (32.00)	27.02	0.11 (-0.15 to 0.37)
Total (95% CI)	421		419		100.00	0.14 (0.01 to 0.28)
Test for heterogeneity: χ^2=4.26, df=5, P=0.51, I^2=0%						
Test for overall effect: z=2.09, P=0.04						

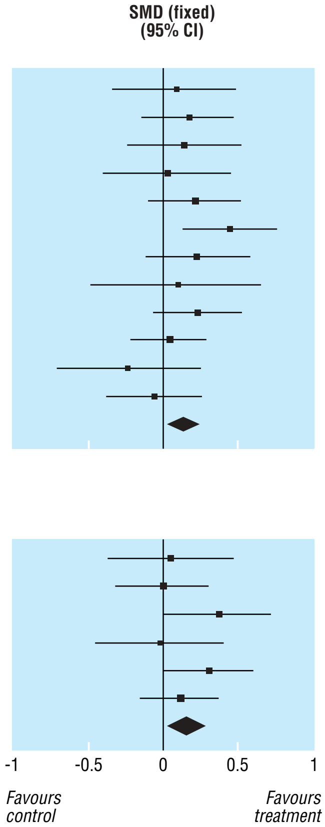

Fig 1 Effect of calcium supplementation on bone mineral density at the upper limb at the end of trial and at the longest point after supplementation stopped (SMD=standardised mean difference)

radius, and upper limb (defined as the distal radius or the upper limb site closest to that point). We used endpoint data rather than change data to maximise data availability. We converted outcome measures to standardised mean differences. We assessed heterogeneity of the data and conducted a meta-analysis according to a fixed effects model for the main effect outcomes. Where there was heterogeneity in subgroup analyses we used random effects models.

Subgroup analyses were performed for sex, baseline calcium intake, pubertal stage, ethnicity, physical activity, type of supplementation (milk extract compared with other calcium supplement forms), and duration of supplementation. The median mean baseline calcium intake for each study (794 mg/day) was used as the cut-off for calcium intake subgroups. We chose a cut-off point of 18 months for the study duration subgroups. We also performed a subgroup analysis by whether the calcium intake in the intervention group in the trial exceeded the probable threshold (1400 mg/day) below which skeletal accumulation varies with intake and above which skeletal accumulation seems constant regardless of intake.

We used intention to treat data from trials wherever possible (see bmj.com). We performed a sensitivity analysis for the main effects omitting studies for which data was imputed,[w1 w7 w11 w19 w33 w35] and a sensitivity analysis omitting the study[w1] that reported results only from analysis of treatment received.

We used the standardised mean difference to estimate an absolute benefit in mg/cm[2][8] and estimated the relative difference in the change from baseline expressed as a percentage (see bmj.com) and used funnel plots to assess publication bias.

Results

We identified 233 references to potential studies. We included 35 references to 19 randomised controlled trials involving 2859 participants, aged 3-18 years, in the systematic review [w1-w35] (see bmj.com for details). See elsewhere for methodological quality.[7] Of the 2859

Main effects of calcium supplementation on bone mineral density at different sites

Site	No of studies	No of participants	Effect size* at end of trial	No of studies	No of participants	Effect size* after supplement ceased
Femoral neck (g/cm^2)	10	1073	0.07 (−0.05 to 0.19)	5	617	0.10 (−0.06 to 0.26)
Lumbar spine (g/cm^2)	11	1164	0.08 (−0.04 to 0.20)	5	617	−0.01 (−0.16 to 0.17)
Total body (g)	9	953	0.14 (0.01 to 0.27)†	1	96	0.00 (−0.40 to 0.40)‡
Upper limb (g/cm^2)	12	1579	0.14 (0.04 to 0.24)†	6	840	0.14 (0.01 to 0.28)†

*Standardised mean difference (95% confidence interval); a standardised mean difference of 0.3 is regarded as small.[9]
†P<0.05.
‡Single study only.

	N	Treatment mean (SD)	N	Control mean (SD)	Weight (%)	SMD (fixed) (95% CI)
At end of supplementation (all data)						
Lloyd 1993	44	1783.00 (238.00)	47	1714.00 (302.00)	9.71	0.25 (-0.16 to 0.66)
Iuliano-Burns 2003	30	1179.57 (209.01)	36	1151.25 (195.57)	7.03	0.14 (-0.35 to 0.62)
Rozen 2003	49	860.29 (134.19)	51	860.34 (138.69)	10.77	0.00 (-0.39 to 0.39)
Specker 2003	88	685.55 (88.00)	90	681.50 (80.55)	19.17	0.05 (-0.25 to 0.34)
Stear 2003	65	2143.00 (265.00)	66	2088.00 (235.00)	14.03	0.22 (-0.13 to 0.56)
Cameron 2004	24	1583.00 (504.00)	24	1512.00 (372.00)	5.15	0.16 (-0.41 to 0.72)
Molgaard 2004	54	1932.11 (292.33)	57	1907.53 (328.77)	11.94	0.08 (-0.29 to 0.45)
Courteix 2005	22	1340.90 (216.37)	63	1186.10 (285.32)	6.81	0.57 (0.08 to 1.06)
Prentice 2005	73	2796.00 (415.00)	70	2770.00 (407.00)	15.39	0.06 (-0.27 to 0.39)
Total (95% CI)	449		504		100.00	0.14 (0.01 to 0.27)

Test for heterogeneity: χ^2=4.58, df=8, P=0.80, I^2=0%

Test for overall effect: z=2.13, P=0.03

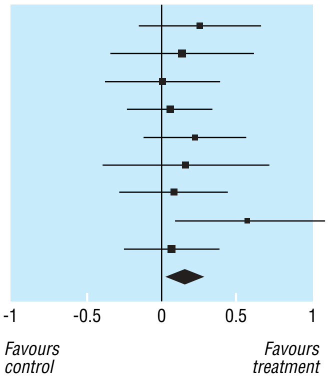

Fig 2 Effect of calcium supplementation on total body bone mineral content at the end of trial (SMD=standardised mean difference)

participants, 1367 were randomised to receive calcium supplementation and 1426 to placebo. Sixty six participants withdrew from studies without their treatment allocation being reported.

Calcium supplementation was with a calcium dose of 300-1200 mg per day from calcium citrate malate, calcium carbonate, calcium phosphate, calcium lactate gluconate, calcium phosphate milk extract, or milk minerals. No studies that used dairy foods as a supplement met the inclusion criteria.

The table gives the treatment effects at each site at the end of supplementation and after the longest period of follow-up available after supplementation stopped for each trial. Results for the distal radius are not reported separately as they were similar to those for the upper limb. There was no effect of calcium supplementation on bone mineral density at the femoral neck or at the lumbar spine at end of trial. The small increase in upper limb density at end of trial persisted after supplementation stopped (fig 1). This effect is about the same as an increase in bone mineral density of 6.38 mg/cm^2 or about 1.7 percentage point greater increase in supplemented groups over the course of supplementation and a 6.30 mg/cm^2 or 1.7 percentage point greater increase after supplementation ceased. There was a small effect on total body bone mineral density at end of trial (fig 2). The single study that reported total body density after supplementation stopped[w31] showed no persistent effect. There was no significant heterogeneity of these results at any site ($P = 0.29$ to $P > 0.99$).

Point estimates of treatment effects during supplementation were greater at all sites in females than males, though the sex difference was not significant (see bmj.com). Subgroup analyses did not significantly modify the effects at any site.

Sensitivity analysis omitting studies with imputed values reduced the effect at the upper limb after supplementation was stopped from a standardised mean difference of 0.14 (0.01 to 0.28) to 0.10 (−0.07 to 0.28), which was no longer significant, and marginally widened the confidence interval around the treatment effect for total body bone mineral density at the end of supplementation (0.15, −0.01 to 0.31) without changing the point estimate. Sensitivity analyses did not otherwise substantially affect the results. Funnel plots for each outcome did not indicate publication bias.

Discussion

Calcium supplementation has little effect on bone mineral density. The only site where an effect was found was the upper limb and the effect was small, equivalent to about a 1.7 percentage point greater increase in bone mineral density in the supplemented group compared with the control group, which persisted after supplementation stopped. This effect was reduced and did not remain significant when we excluded the studies with imputed outcomes, suggesting this result should be interpreted with caution. This small increase in upper limb bone mineral density is unlikely to result in a clinically important decrease in the risk of fracture. Importantly, we found no effects at other sites where fracture is common—namely, the femoral neck and lumbar spine.

Children with upper limb fractures have been reported to have 1-5% lower bone mineral density compared with controls at sites including the distal radius. Based on the decrease in odds ratio for wrist and forearm fractures observed for each SD increase in bone mineral density,[10] the treatment effect we observed would result in about a 5% decrease in the relative risk of fracture. If this were applied to the peak incidence of all fractures in childhood,[11] the decrease in absolute risk would be at most 0.2% a year in boys and 0.1% in girls. Therefore, the public health impact of calcium supplementation is likely to be small.

Effect in adults

The maximum length of follow-up after supplementation was only seven years,[w1] and we do not know whether increases would persist into later life. In calcium supplement trials in postmenopausal women, the effect of supplementation on risk of fracture is at best small,[12 13] with increases in bone mineral density ranging from 1.13% to 2.05% depending on site. The increases at the lumbar spine and hip in the current review are substantially smaller than this and do not persist once supplementation stops. The upper limb

What is already known on this topic

Narrative reviews of individual clinical trials have shown that bone mineral density in children can be increased by calcium supplementation

What this study adds

Calcium supplementation in healthy children has no effect on bone density at the hip or lumbar spine

Supplementation has a small effect at the upper limb, but the resultant increase in bone density is unlikely to result in a clinically important decrease in risk of fracture

increase we describe is similar but its effect on risk of fracture remains uncertain. Any potential public health benefits of calcium supplementation in later life would probably be small.

A recent review did not support recommendations for consumption of dairy products for bone health end points in children and young adults.[6] They also called into question the public health importance of the modest benefits of high dose calcium supplementation and dairy calcium supplementation on bone health in youth. Our quantitative systematic review confirms this conclusion. Our results also do not support the premise that any type of calcium supplementation is more effective than another.

The consistently greater effects seen in females compared with males, though not significant, suggest a sex difference in the response of bone mineral density and bone mineral content to calcium supplementation. We found no cumulative effect of calcium over longer periods of supplementation.

Calcium supplementation may reduce bone remodelling rather than or as well as increasing bone modelling, accounting for the transient benefit of supplementation seen in some studies.[14] Our data are consistent with this. We would also expect that after supplementation stopped there would be a decrease in treatment effect; we observed this for total body bone mineral content but not upper limb bone mineral density. The reason for inconsistency is not clear.

Our data cannot confirm the level of the threshold below which skeletal accumulation varies with intake, but suggests that it lies below the suggested level of 1400 mg/day.

Limitations

No studies measured fractures as an outcome, adding to the difficulty of interpreting the significance of the results. The results can not be extrapolated to children with medical conditions or taking medications that might affect bone metabolism. Adjustment of bone mineral content for bone area, weight, and height is desirable[15] but we could not include this outcome. Few studies were performed in children with low baseline calcium intakes. The paucity of data in the peripubertal period is an important gap. We also cannot exclude that physical activity might modify the effect.

In conclusion, there is a small effect of calcium supplementation only at the upper limb, but the resultant increase in bone mineral density is unlikely to result in a clinically important decrease in risk of fracture. Our results provide only limited support for the use of calcium supplementation in healthy children as a public health intervention. It may be appropriate to explore possible alternative nutritional interventions, such as increasing vitamin D concentrations and intake of fruit and vegetables.

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Ethical approval: Not required.

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Lots of remedies

When a lot of remedies are suggested for a disease, that means it can't be cured.

Anton Chekov, *The Cherry Orchard*

Submitted by Ruth Green, senior house officer in anaesthetics, Wigan