

Randomized trials assessing calcium supplementation in healthy children: relationship between industry sponsorship and study outcomes

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Abstract

Objective: To explore the relationship between industry sponsorship of Ca supplementation studies in healthy children and study outcomes.

Design: An electronic search for published randomized controlled trials (RCT) was conducted. We collected data on study design features aimed at reducing bias, statistical significance of results, authors' conclusions and financial sponsorship of study. We used Fischer's exact test to examine associations between sponsorship and study results and conclusions.

Subjects: Healthy children between the ages of 9 and 18 years.

Results: Nineteen trials met our inclusion criteria. Seventeen out of nineteen studies reported a statistically significant improvement of supplementation on bone mineral density. Subjects in eight of the seventeen studies had a baseline daily Ca intake of 800–1300 mg. There was no significant association between study design features and the results or conclusions of the studies. Three studies received government funding, two of which (66.7%) concluded in favour of additional supplementation. Sixteen studies were either industry-funded or had mixed industry funding, thirteen (81.3%) of which had a conclusion supporting Ca supplementation in children. There was no significant association between study sponsorship and authors' conclusions.

Conclusions: The majority of RCT assessing the effects of Ca supplementation in healthy children are industry-funded and support Ca supplementation. The clinical significance of the outcomes measured in Ca supplementation studies should be considered when examining associations between study design and results. Further non-industry funded research is needed to thoroughly assess the impact of funding on authors' conclusions in nutrition research.

Keywords
Calcium
Nutrition
Industry sponsorship
Children

The importance of adequate Ca intake has been supported on both global (e.g. FAO) and national levels. Guidelines have been published by multiple organizations outlining nutritional recommendations regarding Ca intake. The Finnish Nutrition Recommendations recommend daily Ca intake of 900 mg for adolescents⁽¹⁾. The Australian National Health and Medical Research Council recommends a range of 800–1200 mg/d (age-dependent) for Australian adolescents⁽²⁾. Other organizations, such as the US Institute of Medicine/National Academy of Sciences and the UN FAO, recommend daily intake as high as 1300 mg^(3–5). Depending on location, the average daily baseline consumption of Ca in adolescents ranges from 340–460 mg (in geographic locations where inadequate nutrition is common)^(6,7) to 750–1000 mg (in geographic locations with better access to adequate nutrition)^(8–10). With such variation in daily Ca consumption, the question

of the effectiveness of Ca supplementation in healthy children has been studied.

Multiple studies have been published evaluating the effectiveness of Ca supplementation on bone mineral density (BMD) and dental health in pre-teen and adolescent children⁽¹¹⁾. These studies have yielded conflicting results. A recent Cochrane Collaboration systematic review evaluated the effect of Ca supplementation on BMD and concluded that such supplementation has little effect on BMD. The only site with a significant increase in BMD was the upper limb. This effect translated into a 1.7% greater increase in BMD in the supplemented groups compared with non-supplemented groups. The review does not support the use of Ca supplementation in healthy children as a public health intervention⁽¹²⁾.

Industry sponsorship of research is associated with outcomes that favour the sponsor^(13–17). This trend has

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held true for studies published recently in the nutrition literature^(14,18,19). To date, no studies have examined the association of study characteristics, such as sponsorship, with clinical outcomes of studies evaluating the effectiveness of Ca supplementation in healthy children between the ages of 9 and 18 years. Thus the present study explores the relationship between industry sponsorship of Ca supplementation studies conducted in healthy children and study results and conclusions.

Experimental methods

Identification of studies for inclusion

We searched MEDLINE and the Cochrane database for randomized controlled trials (RCT) evaluating Ca supplementation in children published between January 1966 and June 2006. Ca supplementation was defined as use of any type of Ca supplement in addition to baseline Ca intake from the diet. Search terms included: calcium, calcium supplementation, milk, dairy products, bone density, bone mineral density, osteoporosis, fracture, dental, teeth, caries, tooth, and lactose intolerance. We also reviewed the contents of selected peer-reviewed nutrition and paediatric journals (*Journal of the American College of Nutrition*, *American Journal of Clinical Nutrition*, *Pediatrics*, *Osteoporosis International*, *Journal of Bone and Mineral Research*, *Bone*, *European Journal of Clinical Nutrition*, *Journal of the American Dietetic Association* and *British Journal of Nutrition*). References of articles selected from these searches were also reviewed for inclusion.

Articles identified from the initial search were selected by reviewing the abstract and/or the study for the following inclusion criteria: (i) studies reporting a randomized controlled (RCT) design; (ii) those including healthy children between the mean ages of 9 and 18 years in the study population; (iii) children with no co-morbid disease states; (iv) study duration of at least 6 months; and (v) those evaluating Ca effectiveness on BMD. Studies published in any language were included.

Excluded articles included non-RCT designs (e.g. reviews, commentaries, editorials or letters), those less than 6 months in duration, those including non-healthy subjects (e.g. children with coexisting gastrointestinal disease states, co-morbid disease states such as diabetes and juvenile arthritis, or drug-induced disease states) and studies focused on follow-up after the withdrawal of Ca supplementation.

Study evaluation

Articles meeting inclusion criteria were examined individually by three reviewers (study investigators: H.I., T.N. and N.N.) and subsequently coded using a standard instrument. The following categories were coded: (i) study type (placebo-controlled trial, comparative trial, cross-over trial);

(ii) study design characteristics aimed to reduce bias (randomization, intention-to-treat, follow-up, blinding); (iii) sample size; (iv) mean age; (v) study population characteristics (nationality, economic status, co-morbid disease states, history of lactose intolerance, patients on treatments that effect bone metabolism); (vi) type of oral supplementation (milk, tablets, powder, dairy foods, non-dairy foods); (vii) whether supplementation met current FAO recommendations of 1300 mg/d⁽⁵⁾; (viii) whether baseline Ca intake was less than the 1300 mg/d recommendation of the FAO⁽⁵⁾; (ix) whether baseline Ca intake was less than the 800–1300 mg/d recommended by US, Chinese, Australian, Finnish and FAO recommendations^(1,2,4,5,20); (x) institutional affiliation of all authors; (xi) country where study was conducted; (xii) outcome measures; (xiii) results; (xiv) adverse events (if reported); (xv) funding source(s); (xvi) role of sponsor; (xvii) disclosed financial ties of authors; and (xviii) authors' conclusion (whether the authors recommended Ca supplementation, did not recommend Ca supplementation or had a neutral conclusion). Standards on how to code each element were defined prior to the coding process. Each reviewer extracted details from the articles independently. After independent review, all three reviewers met to reconcile the results of the coding, and discrepancies were resolved by reviewing the original article and establishing consensus.

Study design characteristics aimed at reducing bias

Each study was coded for randomization, use of intention-to-treat analysis, subject follow-up of greater than 75% and blinding of investigators, statisticians and/or subjects. Coding of such variables is standard in Cochrane systematic reviews as a means to minimize bias and to guide study interpretation⁽²¹⁾.

Results and conclusions of studies

Results for each study were coded based on whether the study reported a statistically significant effect (in either primary or secondary outcomes). If a study found a statistically significant result in a bony region (e.g. hip, spine, forearm), the study was coded as having a statistically significant effect. Studies with measurements from multiple regions were coded as having a statistically significant result if the study found at least one bony region to have a statistically significant change. Results were nominally coded as statistically significant or not.

The study conclusion was evaluated on whether the authors recommended Ca supplementation (in addition to baseline Ca intake), did not recommend Ca supplementation or had a neutral conclusion on Ca supplementation for children. Authors' study conclusion was coded independent of the statistical significance of the results and was determined by reading and interpreting the tone of the conclusions.

Financial sponsorship of study/financial ties of authors

Financial sponsorship of studies and financial ties of authors were evaluated based on statements in acknowledgements, potential conflict of interest statements and/or footnotes. Financial sponsorship was characterized as: (i) industry-funded, defined as including dairy, nutritional supplement and/or pharmaceutical industry; (ii) non-industry funded, defined as including governmental agencies with no industry association (e.g. US National Institutes of Health, universities, non-profit organizations); (iii) mixed funding, including a combination of both industry and non-industry funding; and (iv) none disclosed. If the study received no industry sponsorship but stated that Ca supplements (e.g. milk, Ca tablets) were provided by industry, the study was coded as not receiving industry funding. However, if the paper noted that the industry sponsor provided financial funding in addition to supplements, then the study was coded as receiving industry funding. Explicit statements regarding potential financial ties of all authors were evaluated as well.

Statistical analysis

All elements of the study were coded, entered into a spreadsheet and analysed by a statistician who was blinded to the variable labels and study hypothesis. Potential subgroup analyses (geographic location (e.g. cultural/custom/nutritional differences), stratification based on age (twens: 9–12 years *v.* teens: 13–18 years), type of Ca supplementation) and sensitivity analyses (assessing heterogeneity of studies) were identified a priori; these were to be conducted depending on the variability in study results.

Study elements for which no variability was noted are reported using descriptive statistics. Fischer's exact test, assuming $\alpha = 0.05$ and 80% power to detect an existent difference, was used to analyse variability found between study sponsorship and outcomes. Computations were performed using the SAS statistical software package version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 7442 publications were retrieved. Of these, 7310 did not meet inclusion criteria based on initial review of study abstracts. The full-text versions of the remaining 132 publications were assessed for final review, of which nineteen met all inclusion criteria (see Fig. 1). Publications included were published between 1992 and 2006. A total of 3469 children participated in the studies, and the mean age was 11.1 years. All included studies evaluated bone health (BMD, bone mineral content or fracture rate); no studies that met the inclusion criteria evaluated dental health (development of caries, tooth decay, etc). In addition, during the coding process, all trials reporting and evaluating lactose intolerance were excluded due to the extensive

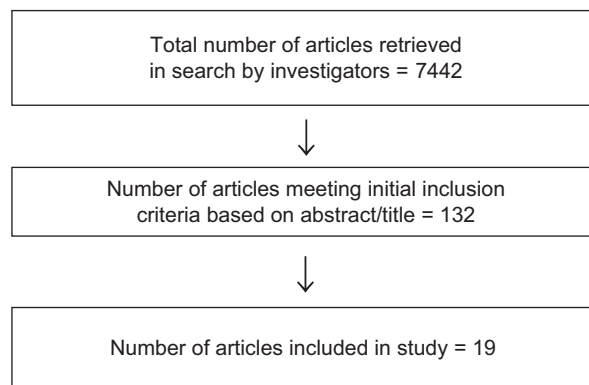


Fig. 1 Flow diagram for inclusion of articles in the study

heterogeneity observed in study design and because the duration of these studies was less than 6 months.

Table 1 shows the characteristics of each included study^(6–10,22–35). Seven studies included children from low income countries. Fourteen out of nineteen studies (73.7%) were placebo-controlled clinical trials. All studies stated they were randomized. However, only six of them (31.6%) included a description of randomization. Ten out of nineteen studies (52.6%) were double-blinded and fifteen studies (78.9%) reported follow-up of greater than 75% after initiation of treatment. Four out of the nineteen studies (21.1%) utilized an intention-to-treat analysis. There was no association between study design characteristics and the results or conclusions of the studies.

As shown in Table 2, seventeen of the nineteen studies (89.5%) reported a statistically significant effect of Ca supplementation on BMD. Of the seventeen studies showing a statistically significant effect, all studies reported a baseline daily Ca intake of less than the FAO recommendation of 1300 mg. Eight of the seventeen (47.1%) studies reported a baseline daily Ca intake between 800 and 1300 mg. The two studies that reported a statistically insignificant effect were sponsored by the dairy industry. There was not enough variability in study results to test for an association between study sponsorship and results.

As shown in Table 3, of the nineteen studies, fifteen (78.9%) had conclusions that suggested support of Ca supplementation, one (5.3%) deemed supplementation as unnecessary and three (15.8%) had a neutral conclusion on whether supplementation was necessary. Of the three non-industry funded studies, two (66.7%) had authors that concluded in favour of additional supplementation. Sixteen studies were either industry-funded or received mixed funding, thirteen (81.3%) of which had a favourable author conclusion for Ca supplementation in children. There was no significant association between type of study sponsorship and authors' conclusion ($P = 0.53$).

Table 1 Characteristics of included studies (*n* 19): randomized controlled trials assessing Ca supplementation in healthy children aged 9–18 years, published between 1992 and 2006 and meeting inclusion criteria

Study	Study design	Sample size	Mean age (years)	Continent	Baseline Ca consumption (mg/d)	Ca intervention	Result	Author conclusion	Funding source	Role of industry sponsor
Cadogan <i>et al.</i> (1997) ⁽²²⁾	Comparative study	82	12	Europe	740	1 pint milk (~500 mg Ca/d through milk, 1125 mg/d mean)	Sig	Ca favoured	Mixed	Funding, scholarship
Cameron <i>et al.</i> (2004) ⁽²³⁾	Placebo-controlled	128	10	Australia/Oceania	715–786	914 mg/d (taking compliance into account)	Sig	Ca favoured	Non-industry	N/A
Chan <i>et al.</i> (1995) ⁽⁹⁾	Comparative study	48	11	North America	728	Group 1: supplemented with dairy products to at least 1200 mg/d (mean was 1400 mg/d)	Sig	Ca favoured	Mixed	Funding
Cheng <i>et al.</i> (2005) ⁽²⁴⁾	Placebo-controlled	195	11	Europe	<900	4 groups: supplemented daily with 1 g Ca + vit D; 1 g Ca + vit D placebo; 1 g dairy products; or placebo	Sig	Ca favoured	Mixed	SD*
Courteix <i>et al.</i> (2005) ⁽⁸⁾	Placebo-controlled	115	10	Europe	988–1008	800 mg of milk powder product daily	Sig	Neutral	Non-industry	N/A
Dibba <i>et al.</i> (2000) ⁽⁷⁾	Placebo-controlled	162	10	Africa	340	Group 1: 1000 mg Ca (elemental)/d for 5d/week	Sig	Ca favoured	Mixed	Funding; SD
Du <i>et al.</i> (2004) ⁽²⁵⁾	Comparative study	757	10	Asia	415–488	Group 1: 245 mg Ca/d; group 2: 245 mg Ca + vit D/d; group 3: placebo	NS	Ca favoured	Industry	SD, lab analyses, transport, fellowship/ student sponsorship
Gibbons <i>et al.</i> (2004) ⁽²⁶⁾	Placebo-controlled	154	9	Australia/Oceania	934–985	1.2 g/d v. 400 mg/d (food product)	NS	Neutral	Industry	Funding; SD
Iuliano-Burns <i>et al.</i> (2003) ⁽²⁷⁾	Placebo-controlled	75	8	Australia/Oceania	536–700	Food products supplemented with 400 mg Ca (milk-based); total 1000 mg Ca	Sig	Neutral	Industry	Funding
Johnston <i>et al.</i> (1992) ⁽²⁸⁾	Placebo-controlled	140	10	North America	900	Supplementation: 700 mg/d (given 1000 mg Ca citrate)	Sig	Ca favoured	Mixed	Grant funding, manuscript commentary
Lau <i>et al.</i> (2004) ⁽⁶⁾	Comparative study	344	10	Asia	415–460	Group 1: 650 mg Ca (milk powder)/d; group 2: 1300 mg Ca (milk powder)/d	Sig	Ca favoured	Industry	Funding; SD
Lloyd <i>et al.</i> (1993) ⁽¹⁰⁾	Placebo-controlled	112	11	North America	900	Supplementation: 350 mg/d per discussion text (gave 2 tablets of ~250–500 mg)	Sig	Ca favoured	Mixed	Funding; SD
Lloyd <i>et al.</i> (1996) ⁽²⁹⁾	Placebo-controlled	112	11	North America	934	Group 1: 500 mg/d (Ca citrate)	Sig	Ca favoured	Mixed	SD; funding
Matkovic <i>et al.</i> (2005) ⁽³⁰⁾	Placebo-controlled	354	10	North America	~830	1 g/d	Sig	Ca favoured	Mixed	Funding; SD
Merrilees <i>et al.</i> (2000) ⁽³¹⁾	Comparative study	105	15	Australia/Oceania	750	Group 1: supplemented to at least 1000 mg/d (with dairy products), mean 1160 mg/d; after study diet went back to usual diet with ~700 mg Ca/d	Sig	Ca favoured	Industry	No sponsor listed
Melgaard <i>et al.</i> (2004) ⁽³²⁾	Placebo-controlled	113	12	Europe	Group A: 1000–13000; group B: <723	Each group split into two (total four groups); 500 mg/d v. placebo	Sig	Ca not favoured	Mixed	Funding
Nowson <i>et al.</i> (1997) ⁽³³⁾	Placebo-controlled	55	14	Australia/Oceania	700–750	1 g effervescent Ca tablet; placebo	Sig	Ca favoured	Non-industry	N/A
Prentice <i>et al.</i> (2005) ⁽³⁴⁾	Placebo-controlled	150	16	Europe	1203–1286	1 g elemental Ca/d (2.5 g CaCO ₃); placebo	Sig	Ca favoured	Mixed	SD
Shatrugna <i>et al.</i> (2006) ⁽³⁵⁾	Placebo-controlled	268	11	Asia	745	Two groups: placebo (176 mg Ca/d) v. supplement (400 mg Ca/d)	Sig	Ca favoured	Industry	Funding

vit D, vitamin D; Sig, significant; N/A, not applicable; SD, supplement donated. *Study explicitly states that sponsor had no additional role.

Table 2 Study funding source by statistical significance of bone mineral density results: randomized controlled trials (*n* 19) assessing Ca supplementation in healthy children aged 9–18 years, published between 1992 and 2006 and meeting inclusion criteria

Study	Industry funding/mixed funding	Non-industry funding
With no statistically significant result	2	0
With statistically significant results	14	3

Table 3 Study funding source by authors' conclusion: randomized controlled trials (*n* 19) assessing Ca supplementation in healthy children aged 9–18 years, published between 1992 and 2006 and meeting inclusion criteria

Conclusion	Industry funding/mixed funding	Non-industry funding
Not recommending Ca supplementation	3	1
Recommending Ca supplementation	13	2

Discussion

We were unable to draw conclusions regarding the association of study characteristics and the results of Ca supplementation studies conducted in healthy children because almost all of the included studies were favourable towards Ca supplementation. Eight of the seventeen (47.1%) studies showing statistically significant effects of Ca supplementation were conducted in healthy children with daily Ca intake over 800 mg. Thus, these studies concluded that Ca supplementation was efficient even if baseline Ca intake was adequate. Furthermore, almost all (84.2%) of the studies were industry-sponsored. Thus, there was little variability in study results or sponsorship.

The effect of sponsorship on study outcome has been well documented in the literature. Recipients of industry-supported grants tend to publish research and give advice that favours the sponsor⁽¹³⁾. A recent article by Lesser *et al.*⁽¹⁸⁾ evaluated a wide range of studies examining the health effects of three commonly consumed beverages (soft drinks, juice and milk) and concluded that industry funding may bias conclusions in favour of sponsors' products in the area of nutrition research. Although no statistically significant association between funding source and outcomes was identified in the present study, 81.3% of industry-funded studies and 66.7% of government-funded studies reported favourable conclusions that supported Ca supplementation.

Our study has several limitations. First, there is wide variability in how study design and methodology is reported. Only in the past 5–10 years has improved reporting of study characteristics become standard practice in the scientific literature, particularly financial disclosure statements from authors⁽³⁶⁾. Industry sponsorship was not explicitly defined and the extent of industry involvement in study design and analysis was not reported in most of the trials analysed. It is not known if industry representatives were involved in study data collection and analysis, or only provided the Ca supplements/dairy products with no additional involvement. More detailed disclosure of study design and methodology may have helped tease out certain

study characteristics that may have been associated with study conclusions.

Our study did not evaluate the clinical significance of the reported results in each study. If the authors found a statistically significant improvement in BMD in only one bony region and concluded that Ca supplementation had a positive effect, this was documented as a favourable result. For example, in one of the included studies, Shatrugna *et al.* found after 6 months of Ca supplementation that there was a statistically significant increase in BMD at the neck of the femur but nowhere else⁽³⁵⁾. Although we coded this as a statistically significant result, we did not assess the clinical significance. In addition, when coding whether authors' conclusions were in favour or not in favour of Ca supplementation, we assumed that the authors' conclusion referred to the type of Ca supplementation used in their study.

Adequate Ca intake is important, but the effects of Ca supplementation are less clear. Although the studies we included were conducted in healthy children, seven of the seventeen (41.2%) studies with statistically significant results were conducted in children with baseline daily Ca intake below 800 mg. Winzenberg *et al.* recently published a Cochrane systematic review evaluating the literature on Ca supplementation in children, concluding that Ca supplementation has little effect on BMD and is not recommended in healthy children⁽¹²⁾. Winzenberg *et al.*'s review differs from the present study in that it evaluated the clinical significance of the reviewed studies' results. When combining the data from the included studies, Winzenberg *et al.* found only a small increase in BMD at the upper limb; this result was deemed to be clinically insignificant in terms of fracture rate reduction. Winzenberg *et al.*'s study included eleven out of the nineteen studies included herein. It is not possible to objectively assess whether reported authors' conclusions would be altered if clinical significance were taken into account.

There are a limited number of published RCT, especially non-industry funded studies, in healthy children aged 9–18 years evaluating the effect of Ca supplementation on BMD. With the small sample size (*n* 19),

sixteen of which had some form of industry funding while three had no industry involvement, most studies concluded in favour of Ca supplementation regardless of funding type. Given recent concern over conflict of interest in academic research, it would be beneficial to have a larger sample of non-industry funded studies in this area. An additional study with a larger sample size, including a similar proportion of industry and non-industry funded studies, could be conducted to validate our findings.

From a policy perspective, it is difficult to conclude if dairy industry funding is associated with study results in the area of Ca supplementation in healthy children and nutrition research. Further studies in this area will contribute to our understanding of validity in nutrition research.

Conclusion

No conclusion can be drawn about the association between study characteristics and outcomes among RCT assessing Ca supplementation in healthy children aged 9–18 years. The clinical significance of the outcomes measured in studies of Ca supplementation should be considered when examining associations between study design and results. Further non-industry funded research is needed to thoroughly assess the impact of funding on authors' conclusions in the area of nutritional research.

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