

## Review Article

# A systematic review of the effects of calcium supplementation on body weight

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Animal studies and epidemiological studies have suggested that Ca supplementation (with Ca supplements or dairy products) may be associated with weight loss in human adults. We aimed to assess whether any association was present by reviewing relevant randomized controlled trials in human subjects. The study was a systematic review and subsequent meta-analysis of randomized controlled trials that used Ca supplementation as an intervention in persons 18 or more years of age, and that reported body weight as a final outcome. A total of thirteen randomized controlled trials were included in the meta-analysis. There was no association between the increased consumption of either Ca supplements or dairy products and weight loss after adjusting for differences in baseline weights between the control and intervention groups ( $P=0.19$  and  $0.85$ , respectively). We therefore concluded that Ca supplementation has no statistically significant association with a reduction in body weight.

### Calcium supplementation: Systematic review: Weight loss

Obesity is a worldwide public health issue. In the UK, the incidence of obesity has tripled in the past 20 years, and this trend is set to continue. According to the National Audit Office (2001), a fifth of the UK population were obese and therefore at increased risk of several diseases, including heart disease and stroke. It is suggested that obesity was responsible for over 30 000 deaths in 1998 and is estimated to cost the UK National Health Service £0.5 billion directly and £2 billion indirectly each year. As weight loss is known to reduce the risk of disease, any reduction in the trend of obesity and help towards weight reduction in this country and worldwide is worthwhile.

Although energy balance is the most critical factor in weight regulation, studies have suggested that Ca supplementation, either as a supplement tablet or powder or in the form of dairy products, could aid weight loss. A potential relationship between weight loss and Ca supplementation has been noted in animal studies (Metz *et al.* 1988; Bursey *et al.* 1989) and several large epidemiological studies (McCarron, 1983; Davis *et al.* 2000; Heaney, 2003; Parikh & Yanovski, 2003) have shown an inverse relationship between Ca intake and body weight or BMI in man. Furthermore, possible biochemical mechanisms by which Ca promotes weight loss have been suggested (Zemel, 2003). However, a previous (non-systematic) review has suggested that there is no relationship between Ca intake and a reduction in body weight (Barr, 2003). To further assess whether

Ca supplementation using supplements or dairy products is associated with weight loss in adults, we undertook a systematic review.

### Experimental method

We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) that used Ca supplements or dairy products as interventions and that reported weight as a final outcome measure.

### Search procedure

A search for relevant RCT was undertaken using the Complete Cochrane Library Database of Controlled Trials from its earliest record (1800) up to May 2004. The search strategy consisted of 'calcium' or 'dairy supplement', which encompassed terms such as 'calcium supplement(s)' and 'calcium supplementation'. This term was then added to 'weight' and 'administering' terms to form the search strategy. Using the same search strategy, Medline, Embase and Cinahl were searched from 2002 onwards. The bibliographies of any relevant papers were also screened for potentially eligible studies.

### Inclusion criteria

Studies included in the review were RCT of Ca supplements or an increased provision of dairy products that were conducted

**Abbreviations:** RCT, randomized controlled trial.

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for 12 or more weeks in non-pregnant, non-lactating individuals over the age of 18 years, and in which body weight was measured at the end of the follow-up period. Additionally, to ensure that participants were receiving at least their minimum requirement of Ca per day, only studies with a Ca level of 300 mg or more per day were included (this figure being based on the minimum level cited in UK Department of Health guidelines for recommended daily amounts of Ca; Department of Health, 1991). There was no upper limit for the level of Ca administered during the trials.

Calcium in the form of Ca-fortified foodstuffs or as milk powder supplements were included in the review, both being considered in the same category as Ca supplements (e.g. calcium carbonate and calcium citrate) as they do not contain the bioactive products present in dairy products. RCT that fitted the inclusion criteria but which had study populations with severe co-morbidities, for example renal problems or cancer, were excluded as the underlying hypothesis may not be applied to such patients.

#### Study selection

All abstracts were screened according to the inclusion criteria. Those abstracts that were thought to be eligible or whose eligibility was unclear were obtained as full publications. At this stage, all previously screened studies were again double-checked against the eligibility form. If necessary, authors were contacted to obtain relevant information that may have been collected but which was not presented in the final publication.

At each stage of the screening process, the primary reviewer (R. T.) provided a random sample (of about 10%) of abstracts or studies to an independent second reviewer (J. D.). The agreement of inclusion of trials between the two reviewers was assessed using the kappa statistic, any disputes being settled by a third, independent party.

#### Data extraction

Trials eligible for meta-analysis had data extracted on general trial information, study design, interventions assigned, study population and outcome data. All weight outcome data were converted to kilograms where required. When trials reported change scores as percentage changes in weight, the percentages were calculated and added (or subtracted) from the baseline weights to produce values for the mean final weights; the standard deviation was assumed to be the same as for the baseline. When trials did not report the number of patients allocated to each intervention group, it was assumed that there would be an equal allocation in the trial. If trials only reported data separately for men and women, these data were pooled. When there were more than two arms in a trial, the intervention arm with the greatest Ca supplementation level was used.

#### Statistical analysis

**Meta-analysis.** All meta-analyses were conducted on Rev Man (version 4.2.3; Nordic Cochrane Collaboration, Rigshospitalet, Denmark) with final body weight (kg) as the outcome. The meta-analyses were performed using the weighted mean differences between the control and intervention groups, separately for the Ca supplementation groups and the dairy product

groups. All treatment effects were presented with 95% CI, and the null hypothesis of no treatment effect was rejected at  $P \leq 0.05$ .

In order to assess whether or not there was any statistical heterogeneity between the trials, consistency between treatment effects was assessed using the  $\chi^2$  test statistic, namely  $Q$ . We rejected the null hypothesis of homogeneity if  $P < 0.1$  (as the power of this test is low). In cases where statistical heterogeneity was evident, the use of a random effect model was planned; otherwise, a fixed effect model was used. The possibility of publication bias was investigated using a funnel plot.

**ANCOVA.** As there were concerns about differences in baseline body weight within individual trials, ANCOVA was carried out using STATA (Statacorp, TX, USA) to provide an estimated treatment effect when differences between the treatment groups at baseline were accounted for. A regression was performed of final mean weights (dependent variable) *v.* treatment group (independent variable), adjusting for mean baseline weights (covariate), weighted by the sample size of each treatment group.

## Results

#### Study inclusion

A total of 919 abstracts were obtained from the database searches. After screening, a total of ninety-nine full study papers were obtained. At this stage, all supplementation studies were included, even those among people younger than 18 years old. The kappa score of agreement between the two reviewers as to whether full papers should be obtained was 0.936. Of these ninety-nine papers, fifteen were duplicates, fifty were excluded, seventeen were included as relevant RCT, and seventeen required the authors to be contacted for further information. For this stage of the screening, the kappa score was 0.843. Subsequently, four further studies that fitted the inclusion criteria were identified: one as a result of contacting authors, one from cross-referencing and two from sourcing from an expert. Thus, a total of twenty-one papers published from 1990 to 2004, reporting a total of twenty-three studies, were potentially available for the meta-analysis. Of these, eleven papers reporting a total of thirteen trials had a study population 18 or more years of age (Baran *et al.* 1990; Summerbell *et al.* 1998; Heaney *et al.* 1999; Jensen *et al.* 2001; Lau *et al.* 2001; Reid *et al.* 2002; Chee *et al.* 2003; Bowen *et al.* 2004; Shapses *et al.* 2004; Winters-Stone & Snow, 2004; Zemel *et al.* 2004).

#### Study characteristics

Details of the trials are summarised in Table 1. Thirteen trials were included in the meta-analysis of weight. Of the included trials, four used dairy products (Baran *et al.* 1990; Summerbell *et al.* 1998; Heaney *et al.* 1999; Bowen *et al.* 2004). The comparators for these trials were either usual diets (Baran *et al.* 1990; Heaney *et al.* 1999) or energy-restricted diets (Summerbell *et al.* 1998; Bowen *et al.* 2004). Eight trials used Ca supplements (including powdered milk products) as their intervention. Five of these supplement trials were placebo-controlled (Reid *et al.* 2002; Shapses *et al.* 2004; Winters-Stone & Snow, 2004), two used usual diet controls

Table 1. Study characteristics

Study	Number of participants	Age*	Sex	Intervention (Ca concentration)	Length of follow-up	Country
Baran <i>et al.</i> (1990)	37	36-4	Female	Dairy product (610 mg/d)	36 months	USA
Bowen <i>et al.</i> (2004)	50	47-6	Mixed (obese)	Dairy product (2400 mg/d)	12 weeks	Australia
Chee <i>et al.</i> (2003)	173	58-9	Female (postmenopausal)	Ca supplement (1200 mg/d)	24 months	Malaysia
Heaney <i>et al.</i> (1999)	204	65-2	Female (postmenopausal)	Dairy product (729 mg/d)	12 weeks	USA
Jensen <i>et al.</i> (2001)	52	NA	Female (obese postmenopausal)	Ca supplement (1000 mg/d)	6 months	Denmark
Lau <i>et al.</i> (2001)	185	57-0	Female (postmenopausal)	Ca supplement (800 mg/d)	24 months	China
Reid <i>et al.</i> (2002)	223	72-0	Female (postmenopausal)	Ca supplement (1000 mg/d)	24 months	New Zealand
Summerbell <i>et al.</i> (1998)	31	41-8	Mixed (obese)	Dairy product (NA)	16 weeks	UK
Shapses <i>et al.</i> (2004)	36	59-3	Female (obese postmenopausal)	Ca supplement (1000 mg/d)	25 weeks	USA
Shapses <i>et al.</i> (2004)	30	56-0	Female (obese postmenopausal)	Ca supplement (1000 mg/d)	25 weeks	USA
Shapses <i>et al.</i> (2004)	42	41-0	Female (obese postmenopausal)	Ca supplement (1000 mg/d)	25 weeks	USA
Winters-Stone & Snow (2004)	23	24-8	Female (athletes)	Ca supplement (1000 mg/d)	12 months	USA
Zemel <i>et al.</i> (2004)	41	46	Mixed (obese)	Dairy product (1200-1300 mg/d) Calcium supplement (800 mg/d)	24 weeks	USA

NA, not available.

\*Mean age. When age was reported separately by subgroups, the mean between the groups was calculated.

(Lau *et al.* 2001; Chee *et al.* 2003), and one involved an energy-restricted diet (Jensen *et al.* 2001). The final trial had three arms; subjects in all arms were undergoing a weight-loss programme. One arm also had a Ca supplement with placebo, and one arm high dairy supplementation with a placebo. The control arm was a weight-loss diet and placebo.

Nine of the trials were conducted only on women (Baran *et al.* 1990; Jensen *et al.* 2001; Lau *et al.* 2001; Reid *et al.* 2002; Chee *et al.* 2003; Shapses *et al.* 2004; Winters-Stone & Snow, 2004), seven on postmenopausal women (Jensen *et al.* 2001; Lau *et al.* 2001; Reid *et al.* 2002; Chee *et al.* 2003; Shapses *et al.* 2004) and two on younger women (Baran *et al.* 1990; Winters-Stone & Snow, 2004). One mixed-sex trial also included only postmenopausal women (Heaney *et al.* 1999). Seven trials were conducted with obese participants (Summerbell *et al.* 1998; Jensen *et al.* 2001; Bowen *et al.* 2004; Shapses *et al.* 2004; Zemel *et al.* 2004), with four including postmenopausal obese women (Jensen *et al.* 2001; Shapses *et al.* 2004). The mean ages of the adults in all the trials included ranged from 23.7 to 72 years. Eleven studies were performed in the Western world, in countries classed as 'dairy societies', such as the UK and the USA, and two involved Chinese women living in Asia (Lau *et al.* 2001; Chee *et al.* 2003).

#### Meta-analysis by calcium source

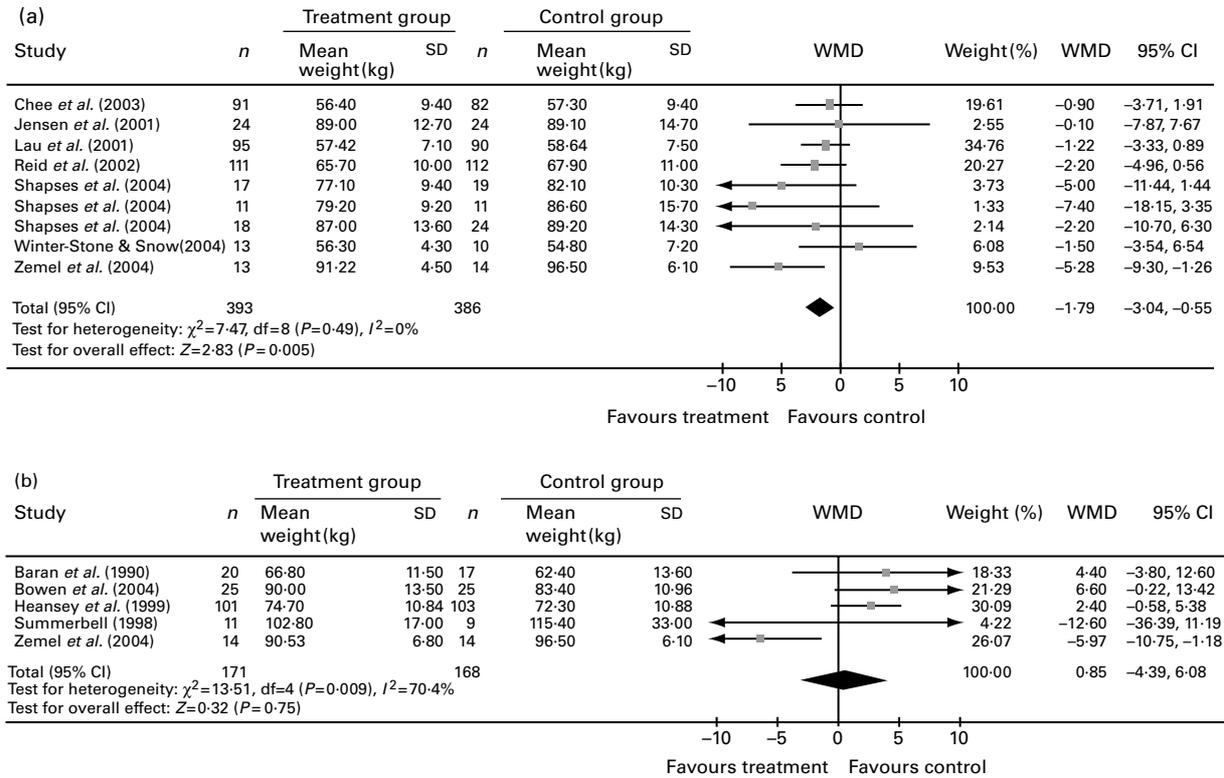
Thirteen trials assessed weight at baseline and final follow-up. When the groups were analysed by Ca supplementation source, the final mean weights for the groups receiving Ca supplements were significantly lower than their control groups, with an overall mean difference of  $-1.79$  kg ( $P=0.005$ ; Fig. 1(a)). There was, however, no significant difference between the groups receiving increased dairy products and their control groups, with an overall mean difference of  $0.85$  kg ( $P=0.75$ ; Fig. 1(b)). As there was heterogeneity in the dairy products analysis, this was analysed using a random effects model. A funnel plot did not indicate any evidence of publication bias (Fig. 2). The Zemel *et al.* (2004) study was excluded from this plot because of its three arms, but a funnel plot of the Ca supplementation only also did not show publication bias (results not shown).

#### Randomization issues

A meta-analysis showed that, within the Ca supplementation subgroup, there was a significant difference in baseline weight between the treatment groups (Fig. 3). In trials using Ca supplements, the intervention groups tended to be lighter than the controls at the start of the trial ( $P=0.005$ ). No single trial showed a statistically significant difference between the treatment groups at baseline, but, pooled by supplementation source, the overall differences were profound. This implies that the 'randomization' procedures used in these Ca supplementation trials, rather than the interventions being tested, could be the main reason for the apparent treatment effect.

#### Adjusted analysis

We adjusted for the impact of the imbalance in baseline weight using ANCOVA. This showed us that Ca supplement-



**Fig. 1.** (a) Association between calcium supplementation and final weight. (b) Association between dairy supplementation and final weight. WMD, weighted mean difference; df, degrees of freedom;  $I^2$ , proportion of total variability explained by heterogeneity; Z, z score.

tation from neither a Ca supplement source nor a dairy product source had a significant effect on body weight. The estimated effect was slightly negative for Ca supplements, at  $-0.41$  kg ( $P=0.19$ , 95 % CI  $-1.07$ ,  $0.25$ ), and slightly positive for dairy product supplementation, at  $+0.23$  kg ( $P=0.85$ , 95 % CI  $-2.88$ ,  $3.34$ ), but as the 95 % CI for these coefficients included zero, we could not rule out the null hypothesis of a lack of treatment effect.

**Discussion**

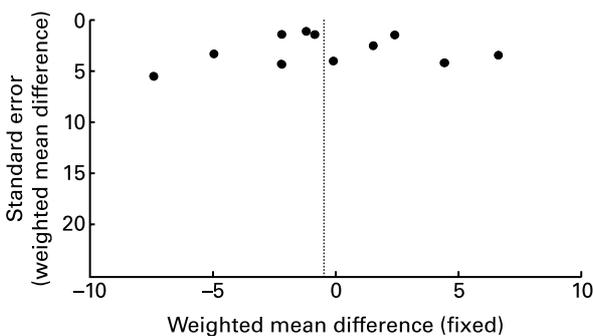
It has been suggested that an increase in Ca intake may aid weight loss in man. To investigate whether there was any evidence to support this suggestion, we undertook a systematic

review of RCT, assessing whether Ca supplementation using Ca supplements or dairy products could promote weight loss. We aimed to extend a previous systematic review on this topic which, although methodologically sound, used only one database (Medline) to search for trials and that crucially did not perform a meta-analysis (Barr, 2003).

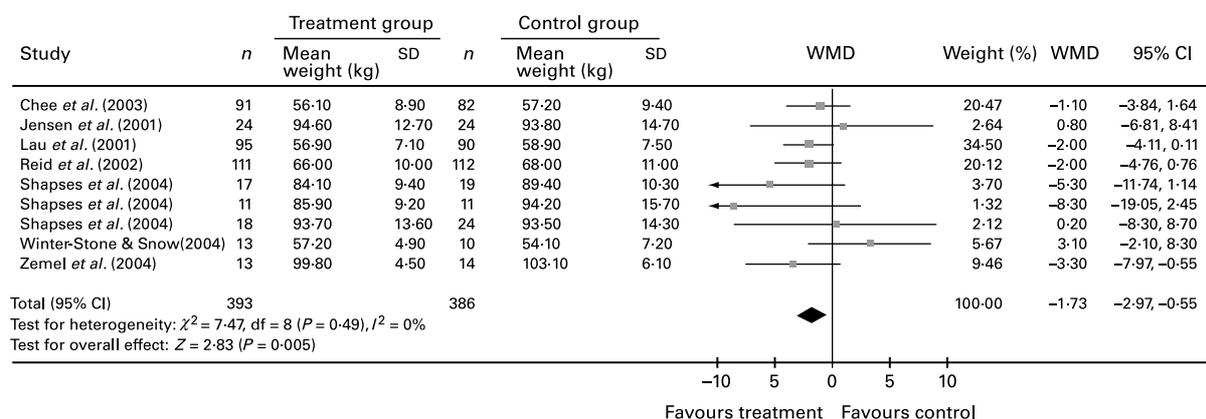
*Calcium supplementation and weight loss*

We found only one trial that was specifically designed and powered to examine whether or not Ca supplementation with Ca supplements or dairy products led to a change in body weight at follow-up (Zemel *et al.* 2004). Most of the relevant trials in the literature were investigating bone mass during Ca treatment. Nevertheless, a considerable number of trials also monitored body weight during the study and were available for the review. For the trials we found, our meta-analysis showed no statistically significant benefit of Ca supplementation after adjusting for baseline imbalances in weight. This agrees with the conclusions of the previous review carried out in this area (Barr, 2003).

There are potential factors that may influence the impact of Ca on body weight or fat mass. We identified one major potential factor as the source of Ca (supplement or dairy product) and thus performed subgroup analysis for each source. Other factors could include age, baseline weight, energy intake and gender. As this information was not sufficiently detailed in most papers, we did not extensively attempt to explore the potential effect of those factors but summarised the individual study characteristics (Table 1).



**Fig. 2.** Funnel plot of randomized controlled trials of calcium supplementation reporting weight as a final outcome, where ..... indicates the overall effect size from the meta-analysis. The symmetrical shape of the funnel plot suggests that there is no publication bias.



**Fig. 3.** Association between calcium supplements and baseline weight. WMD, weighted mean difference; df, degrees of freedom;  $I^2$ , proportion of total variability explained by heterogeneity; Z, z score.

There might be concerns that some clinical heterogeneity between studies included in the meta-analysis might affect the results of the analysis. An investigation of the statistical heterogeneity of the treatment effect showed that the effect was homogeneous within an allowable extent, except for the original dairy product subgroup analysis. It is interesting to note that the two trials showing weight loss for those receiving Ca supplements were the trials with the heaviest participants. A subgroup analysis of baseline weight (obese and non-obese) was carried out but this did not change the results. Further analysis taking differences in the study populations' calorie intake into account would only be possible when the original individual patient data were available. Additionally, as no trials were performed on men alone, no subgroup analysis exploring gender as a possible source of heterogeneity could be performed.

#### Flawed randomization

An unexpected finding in our review was that there were significant baseline imbalances in terms of body weight in the trials identified. Although it is possible for a single trial to be unbalanced by chance, it is very unlikely that a series of trials would be so unbalanced as to produce a statistically significant difference in baseline body weight. This suggests that some of the randomization may have been flawed, with some trials allocating participants in a way other than through random allocation. Therefore, our finding of no difference in body weight using Ca supplementation should be treated with caution as a benefit might have been obscured by other unidentified biases that might have been introduced by flawed allocation methods.

In summary, we found no evidence of a benefit on body weight through Ca supplementation using Ca supplements or dairy products.

#### Acknowledgements

We thank Professor Martin Bland for his help in the analysis of covariance. D. T. provided the original idea for the study. All authors contributed to the study design. R. T. carried out the systematic review. J. D. wrote the first draft of the

paper, and all authors contributed to subsequent drafts. D. T. has previously received funding to carry out a randomized controlled trial of Ca supplementation in women at risk of fracture. No other authors have conflicts of interest. R. T. was funded by a Medical Research Council studentship.

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