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Calcium supplements: benefits and risks

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Abstract. Reid IR, Bristow SM, Bolland MJ (University of Auckland, Auckland; and Auckland District Health Board; Auckland, New Zealand). Calcium supplements: benefits and risks. (Review). *J Intern Med* 2015; doi: 10.1111/joim.12394.

Calcium is an essential element in the diet, but there is continuing controversy regarding its optimal intake, and its role in the pathogenesis of osteoporosis. Most studies show little evidence of a relationship between calcium intake and bone density, or the rate of bone loss. Re-analysis of data from the placebo group from the Auckland Calcium Study demonstrates no relationship between dietary calcium intake and rate of bone loss over 5 years in healthy older women with intakes varying from <400 to >1500 mg day^{-1}. Thus, supplements are not needed within this range of intakes to compensate for a demonstrable dietary deficiency, but might be acting as weak anti-resorptive agents via effects on parathyroid hormone and calcitonin. Consistent with this, supplements do acutely reduce bone resorption and produce small short-term effects on bone density, without evidence of a cumulative density benefit. As a result, anti-fracture efficacy remains unproven, with no evidence to support hip fracture prevention (other than in a cohort with severe vitamin D deficiency) and total fracture numbers are reduced by 0–10%, depending on which meta-analysis is considered. Five recent large studies have failed to demonstrate fracture prevention in their primary analyses. This must be balanced against an increase in gastrointestinal side effects (including a doubling of hospital admissions for these problems), a 17% increase in renal calculi and a 20–40% increase in risk of myocardial infarction. Each of these adverse events alone neutralizes any possible benefit in fracture prevention. Thus, calcium supplements appear to have a negative risk–benefit effect, and so should not be used routinely in the prevention or treatment of osteoporosis.

Keywords: bone density, calcium balance, calcium intake, fracture, osteoporosis.

Introduction

Calcium is an essential element in the human diet; however, there has long been controversy regarding its optimal intake, and the significance of calcium deficiency in the pathogenesis of osteoporosis. In the 1940s, Albright proposed that, while calcium and vitamin D deficiency would result in osteomalacia, postmenopausal osteoporosis was a result of sex hormone deficiency, and unrelated to calcium nutriture [1]. Consistent with this, populations in which levels of calcium intake were very low did not appear to suffer poorer bone health or greater rates of fracture [2–5]. In 1953, the recommended intake of calcium in the USA and Canada was lowered from 1000 to 800 mg day^{-1} [6, 7]. In a report in 1962, the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) [8] concluded that '*Most apparently healthy people – throughout the world – develop and live satisfactorily on a dietary intake of calcium which lies between 300 mg and over 1000 mg a day. There is so far no convincing evidence that, in the absence of nutritional disorders and especially when the vitamin D status is adequate, an intake of calcium even below 300 mg or above 1000 mg a day is harmful*'. Based on this report, in 1974, the FAO and WHO recommended even lower intakes of calcium for adults of 400–500 mg day^{-1} [9].

In the decades following this report, opinions shifted, and an inadequate intake of calcium became regarded, particularly in North America, as having an important role in the pathogenesis of osteoporosis. The results of an influential series of calcium balance studies indicated that intakes below 1000–1500 mg day^{-1} were inadequate to replace obligatory calcium losses in women [10, 11]. These studies were followed by trials demonstrating beneficial effects of calcium supplements on bone density [12, 13], and of calcium plus vitamin D on fractures [14, 15]. As a result, in the USA and Canada, the recommended adequate

intake of calcium for adults aged >50 years was raised to 1200 mg day^{-1} in 1997 [16], and in 2002, the FAO and WHO recommended intakes of calcium for postmenopausal women and men over 65 years of 1300 mg day^{-1} [17]. However, in the UK, recommended intakes remained at 700 mg day^{-1} for all adults [18]. These recommended levels of intake were above what most older adults were able to consume in their diets, so resulted in the widespread promotion of calcium supplements. With recent questions relating to the safety of calcium supplements, the focus has returned to the diet as the preferred source of this element [19, 20]. Therefore, achieving an optimal *dietary* calcium intake is again a central issue when advising patients at risk of osteoporotic fractures. Here, we will review the evidence relating to dietary calcium requirement, before considering the advantages and disadvantages of supplement use.

What is the optimal calcium intake?

In recent years, many government and professional organizations with an interest in bone health have made further recommendations for optimal calcium intakes, most of which have been based primarily on the results of calcium balance studies [21]. The most prominent recent such recommendations are from the Institute of Medicine in 2010 [22], which again rely heavily on balance data.

Calcium balance studies

The balance studies of Heaney and colleagues have been particularly influential [10, 11]. Among 168 perimenopausal nuns, they found that calcium balance was closely related to calcium intake, which is not surprising as balance is directly derived by subtracting intake from output. When the participants were grouped according to menopausal status and use of oestrogen, the intake associated with zero balance was 990 and 1504 mg day^{-1} in premenopausal and untreated postmenopausal women, respectively. The latter figure, derived from studies of early postmenopausal women, became a generalized recommendation to all postmenopausal women.

More recently, Hunt and Johnson examined data from a series of balance studies, which together included 73 women aged 20–75 years (mean 47 years) and 82 men aged 19–64 years (mean 28 years) [23]. The calcium intake predicted to produce a neutral calcium balance was 741 mg day^{-1}, regardless of age or sex. Even though about half the women were over 50 years, this value is very different from the 1500 mg day^{-1} suggested for postmenopausal women in the earlier balance studies [11]. Hunt and Johnson concluded:

> ... that calcium balance was highly resistant to a change in calcium intake across a broad range of typical dietary calcium intakes (415-1740 mg/d; between the ~25th and >99th percentiles of typical calcium intake for all female children and adults aged ≥9 year). In other words, homeostatic mechanisms for calcium metabolism seem to be functional across a broad range of typical dietary calcium intakes to minimize calcium losses and accumulations.

As fracture incidence is the clinical endpoint that may or may not be influenced by calcium intake, calcium balance is only a valid surrogate measure if it can be shown to be related to fracture risk. There is little direct evidence to suggest that this is the case, although it has been assumed that positive or negative calcium balance reflects gain or loss of bone density, respectively. This assumption might not be valid. The introduction of bone densitometry in the 1980s has permitted the accurate measurement of bone density, which does indeed predict fracture risk [24]. Bone densitometry demonstrates that there is ongoing loss of bone in postmenopausal women with high calcium intakes [25]. By contrast, calcium balance studies suggest that calcium intakes >1500 mg in postmenopausal women are associated with positive calcium balance [11] and that an intake of 2000 mg day^{-1} achieves a balance of +460 mg day^{-1} [26]; if correct, this would result in a doubling of total body calcium over a period of several years. Thus, calcium balance does not appear to reflect bone balance, possibly because of inaccuracies in the calculation of balance, or because calcium can accumulate outside the skeleton, particularly in elderly individuals and in those with renal failure [26]. The deficiencies of the balance technique have been reviewed previously [27].

Calcium intake and bone density

Because defining optimal dietary calcium intake is increasingly important with regard to public health

policy for osteoporosis prevention, techniques other than calcium balance are needed. From cross-sectional studies, there is little evidence of a relationship between bone density and calcium intake [28–32]. A more sophisticated use of bone densitometry is the sequential measurement of bone density over time, which permits the direct assessment of *bone* balance, obviating the problems associated with calcium balance as a surrogate. Relating bone balance to calcium intake provides a sounder basis for determining optimal calcium intake. A number of studies have investigated the relationship between bone loss and dietary calcium intake in adults (see Table 1).

In most studies, no relationship was found between calcium intake and bone loss at any site [33–39]. One study showed a null relationship at the femoral neck, but a weak *negative* relationship at the lumbar spine in women only [40]. Of those that demonstrated a beneficial effect of higher calcium intakes, none produced consistent results across the principal measurement sites (lumbar spine and femoral neck) in the primary analyses. A trend towards lower rates of bone loss with higher calcium intakes at the femoral neck in men but not in women was found in one study [41], while another showed some effects in premenopausal but not postmenopausal women [42]. Sirola *et al.* reported an association at the lumbar spine in women who had never smoked (and at the femoral neck after adjustment for several covariates), but not in women who had ever smoked, or in the groups combined [43]. Finally, one small, 6-month study demonstrated a greater rate of bone loss only among women with very low calcium intakes (<406 mg day^{-1}) compared with those with the highest levels of intake (>776 mg day^{-1}) [44].

Auckland calcium study

We have reinvestigated the question of whether calcium intake influences bone balance, using data from the placebo group of a 5-year clinical trial, the Auckland Calcium Study. A total of 570 healthy postmenopausal women aged >55 years (>5 years postmenopausal), who were not receiving therapy for osteoporosis or taking calcium supplements, were included in this analysis. Bone mineral density (BMD) and content of the spine, hip and total body were measured three times over 5 years. Mean calcium intake (based on a validated food frequency questionnaire) of the whole group was 840 mg day^{-1}; the means for the first and fifth quintiles were 425 and 1344 mg day^{-1}, respectively. Baseline BMD was not related to quintile of calcium intake at any site, before or after adjustment for covariables. There was no relationship between bone loss and quintile of calcium intake at any site, with or without adjustment for covariables (Fig. 1). The change in total body bone mineral content was also unrelated to an individual's calcium intake ($P = 0.53$; Fig. 2). For comparison, Fig. 2 also shows the changes in total body bone mineral content that would be predicted from the calcium balance results of Heaney *et al.* [11]. The calcium balance data were converted to changes in bone mineral content based on calcium constituting 40% of hydroxyapatite [45]. The slope of this calcium balance line lies outside the confidence intervals for the regression line for total body bone mineral content. These marked differences suggest that calculated calcium balance does not reflect actual bone mineral balance. A total of 109 fractures occurred during follow-up, but fracture incidence was also unrelated to quintile of calcium intake.

It is interesting to note that calcium intake using this questionnaire was inversely correlated with circulating parathyroid hormone level in postmenopausal women ($P < 0.01$) [46] and in a cohort of older men (Bolland, unpublished observations). The fact that calcium intake is related to parathyroid hormone levels but not to rates of bone loss reflects the efficiency of the homeostatic mechanisms involved. Parathyroid hormone regulates intestinal calcium absorption (via vitamin D hydroxylation) causing high fractional calcium absorption in individuals with low intakes, and vice versa. This conclusion is very similar to that reached by Hunt and Johnson, as discussed above, that homeostatic mechanisms insulate bone health from the effects of varying dietary calcium intakes [23]. Thus, from an international perspective, populations in Asia and Africa maintain good bone health on calcium intakes of about 300 mg day^{-1}, and European populations with high intakes of dairy products are protected from the sequelae of calcium overload (soft tissue calcification and renal calculi) despite having 4- to 5-fold higher intakes.

The present analysis differs from previously published studies in that it involves over 500 women who were not using calcium supplements or other bone-active medications, followed over a 5-year period with multiple bone density measurements at multiple sites, including the total body. Further,

Table 1 *Calcium intake and bone loss in prospective cohort studies*

Study	*t* (years)	*n*	Mean age (years)	Mean calcium intake (mg day^{-1})	Site	Effect
Riggs 1987 [33]	4	45 pre-w	41	991	Radius	None
					Lumbar spine	None
		61 post-w	64	871	Radius	None
					Lumbar spine	None
Dawson-Hughes 1987 [44]	0.6	76 post-w	60	198–1416[a]	Lumbar spine	Positive
van Beresteijn 1990 [34]	8	154 peri-w	53	750 and 1520[b]	Radius[c]	None
Hansen 1991 [35]	12	121 post-w	51	1184	Forearm[c]	None
Reid 1994 [36]	2	122 post-w	58	762	Total body	None
					Lumbar spine	None
					Femoral neck	None
					Trochanter	None
					Ward's	None
Hosking 1998 [37]	2	394 post-w	53	876	Lumbar spine	None
					Total hip	None
					Total body	None
					Total forearm	None
Burger 1998 [41]	2	1856 men	67	1156	Femoral neck	Positive
		2452 post-w	67	1116	Femoral neck	None
Dennison 1999 [40]	4	173 men	66	719	Lumbar spine	None
					Femoral neck	None
					Intertrochanter	None
					Trochanter	None
					Ward's	None
		143 post-w	66	642	Lumbar spine	Negative
					Femoral neck	None
					Intertrochanter	None
					Trochanter	None
					Ward's	None
Hannan 2000 [38]	4	278 men[d]	74	810	Femoral neck	None
					Trochanter	None
					Radius	None
					Lumbar spine	None
		486 post-w[d]			Femoral neck	None
					Trochanter	None
					Radius	None
					Lumbar spine	None
Sirola 2003 [43]	6	182 peri-w ever smokers	54	778	Lumbar spine	None
					Femoral neck	None

Table 1 (*Continued*)

Study	*t* (years)	*n*	Mean age (years)	Mean calcium intake (mg day^{-1})	Site	Effect
		772 peri-w never smokers	54	796	Lumbar spine	Positive
					Femoral neck	Positive
Macdonald 2004 [94]	6	891 peri-w	47	1055	Femoral neck	Positive
					Lumbar spine	None
Ho 2004 [95]	1.5	398 post-w	55	536	Total body	Positive
					Lumbar spine	None
					Femoral neck	None
					Trochanter	None
					Intertrochanter	None
					Ward's	Positive
Uusi-Rasi 2008 [42]	10	133 pre-w	28	1370 and 650[e]	Femoral neck[c]	None
					Trochanter[c]	Positive
		134 post-w	63	1520 and 660[e]	Femoral neck[c]	None
					Trochanter[c]	None
Nakamura 2012 [39]	6	389 post-w	73	619	Forearm	None

T, study duration; BMD, bone mineral density; pre-w, post-w and peri-w, premenopausal, postmenopausal and perimenopausal women, respectively.
[a]Range of dietary calcium intakes (mg day^{-1}); [b]mean dietary calcium intake in the first and third tertiles (mg day^{-1}); [c]bone mineral content site; [d]dietary calcium intake assessed in a subset of 671 men and women; [e]approximate mean intakes in 'high' (>1200 mg day^{-1}) and 'low' (<800 mg day^{-1}) dietary calcium groups.

calcium intake was assessed at the beginning and end of the study, rather than only at the outset. Together with the already published data, this provides a body of evidence indicating that calcium intakes of between 400 and 1500 mg day^{-1} do not influence rates of postmenopausal bone loss. Consistent with these findings, calcium intake has not generally been found to be predictive of fracture risk [47–51]; this is reflected in its absence from the fracture risk calculators in routine clinical use (FRAX and the Garvan Fracture Risk Calculator).

Benefits of calcium supplements

Bone density

Ingestion of a calcium bolus, in the form of a supplement, acutely increases circulating calcium concentrations and reduces parathyroid hormone levels and markers of bone resorption, with a decline in bone formation markers 2–3 months later (Fig. 3). This produces a benefit to bone density of about 0.5–1% in the hip and spine, mostly in the first year of treatment [52]. In most trials, no relationship was found between individuals' baseline dietary calcium intake and their bone density response [25, 53]. In general, calcium doses ≥1000 mg day^{-1} have been used in supplement studies [54]. Doses of 250–600 mg day^{-1} have been found to produce no or minimal effects on BMD [55, 56], except in individuals with very low calcium intakes [12, 57]. Collectively, these findings suggest that calcium supplements act as weak anti-resorptive agents, reducing bone turnover whatever the baseline calcium intake, and producing a one-off gain in bone density as a result of filling-in of some of the osteoclastic resorption sites. This, however, does not produce cumulative benefits in terms of bone mass.

Fractures

In the early 1990s, Chapuy *et al.* conducted the first study designed to test the anti-fracture efficacy of calcium (with vitamin D in this case) [14]. At 18 months, there was a 43% decrease in hip fractures in a completers' analysis, which equated

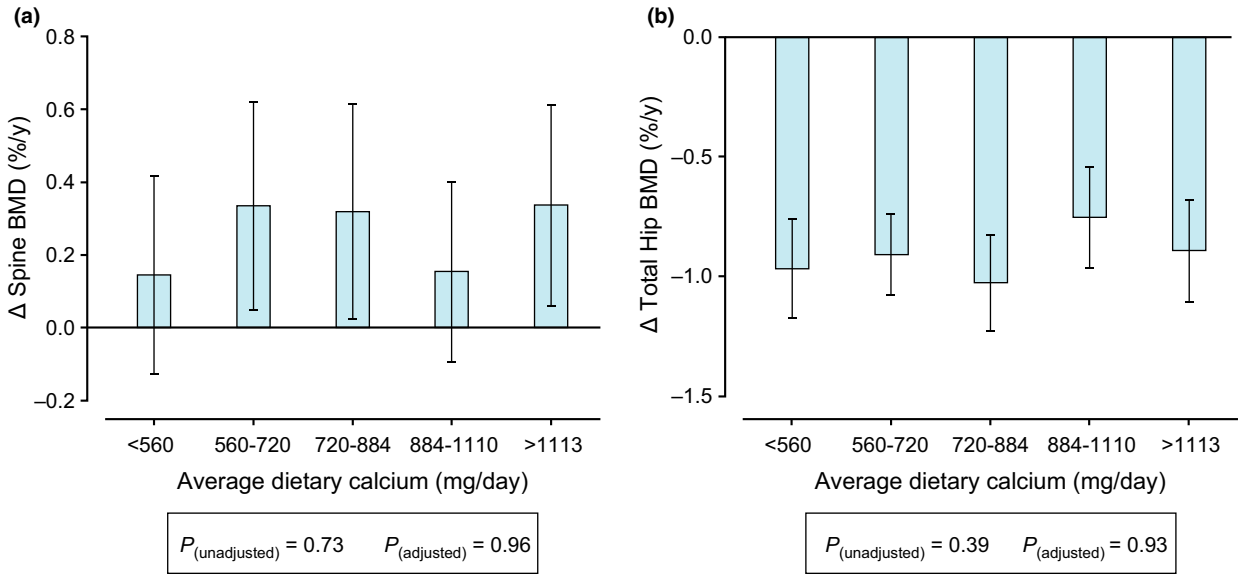

Fig. 1 *Mean annual change (Δ) in spine and hip bone mineral density (BMD) over 5 years (calculated from individual regression lines) in normal postmenopausal women, as a function of quintile of average calcium intake assessed at baseline and year 5 by a validated food frequency questionnaire [91]. There were no significant effects of quintile of calcium intake on bone loss before or after adjustment for height, weight, age, current smoking status and serum 25-hydroxyvitamin D (all assessed at baseline). Data are mean ± 95% confidence intervals.*

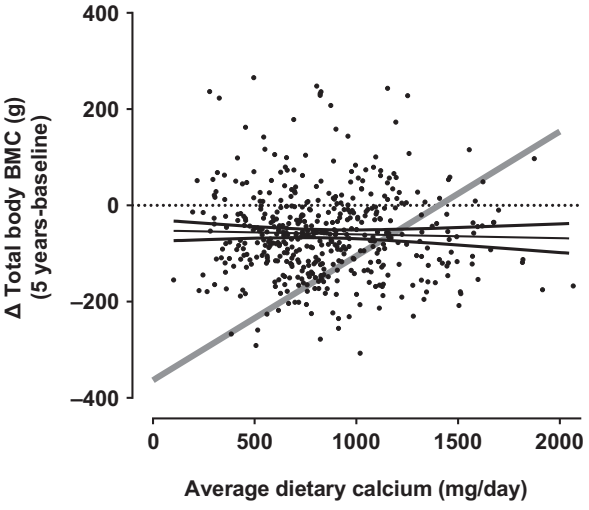

Fig. 2 *Absolute change (Δ) in total body bone mineral content (BMC) over 5 years in normal postmenopausal women, as a function of each woman's average calcium intake assessed at baseline and year 5. The black lines show the regression (with 95% confidence intervals) for this relationship (P = 0.53). The grey line shows the changes in total body bone mineral that would be predicted from the calcium balance results of Heaney* et al. *[11] assuming that calcium constitutes 40% of bone mineral.*

to a 26% decline in fracture rate on an intention-to-treat basis. The effect was similar at 36 months [58]. Non-vertebral fracture numbers were decreased by 25% and 17%, at 18 and 36 months, respectively (intention-to-treat analysis). This led to the conclusion that calcium and vitamin D were an essential part of osteoporosis management, because of their demonstrable anti-fracture efficacy and their presumed safety. Several features of this study by Chapuy and colleagues should be mentioned. First, it was carried out in frail elderly women living in institutions. Secondly, calcium intakes were ~500 mg day^{-1} and mean serum 25-hydroxyvitamin D concentration was 25 nmol L^{-1} in placebo subjects 12 months into the study, equating to 13.7 nmol L^{-1} after correction for inaccuracies in assay calibration [59]. Finally, calcium plus vitamin D produced a between-group difference in total hip bone density of 7.3%, a response larger than reported with any anti-osteoporotic medication. Such a large effect can only be explained as a response to the treatment of osteomalacia, which is highly likely to have affected many of these women, considering their marked vitamin D deficiency.

In the last 10 years, the results of five large trials of calcium supplements have been reported; none

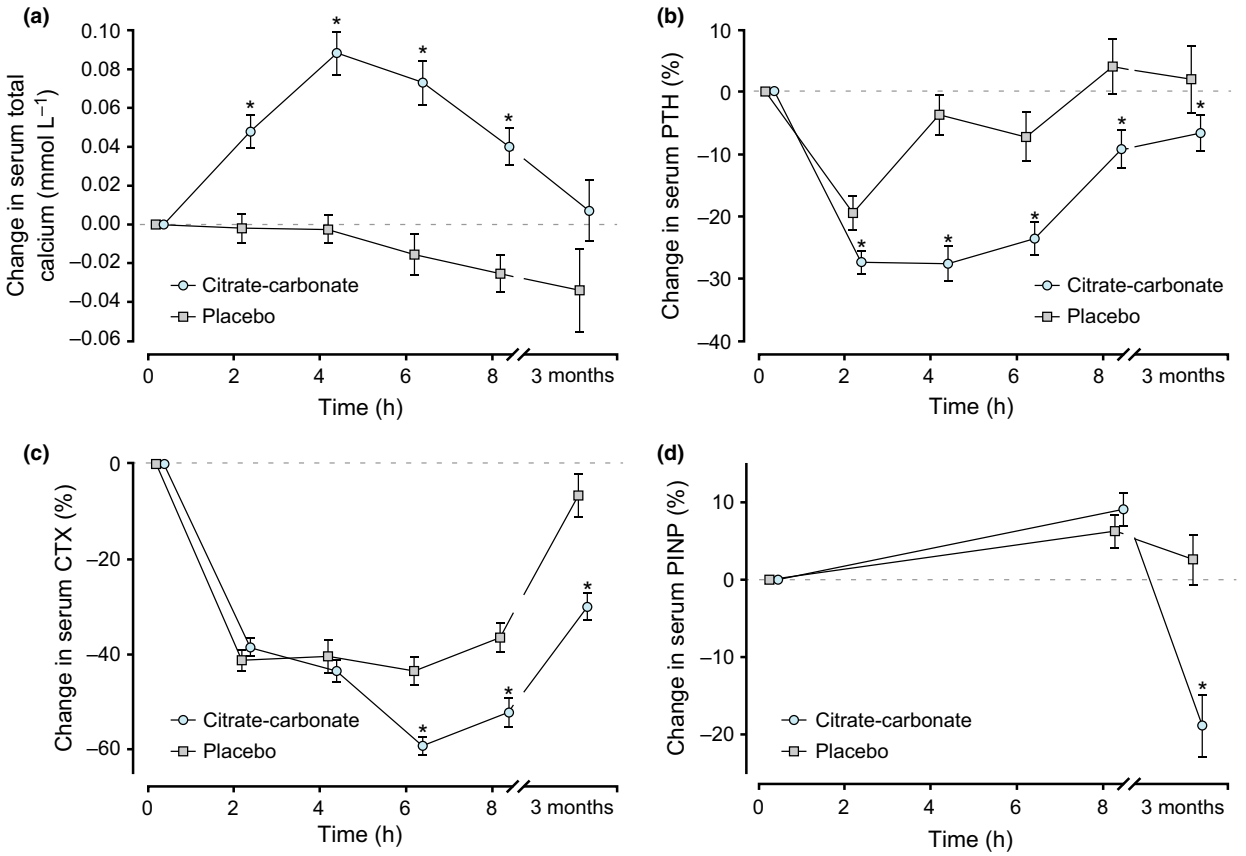

Fig. 3 *Changes in total calcium (a), parathyroid hormone (PTH) (b), serum C-telopeptide (CTX) (c) and serum procollagen type-I N-terminal propeptide (PINP) (d) over 8 h in postmenopausal women after the ingestion of 1 g calcium as citrate or carbonate (citrate-carbonate;* n = *38) or a placebo containing no calcium (*n = *20), and after 3 months of continuous supplementation. Participants were given a light breakfast after the ingestion of the trial medication on day 1. *Significantly different from placebo,* P < *0.05. Values are mean ± SEM. Adapted from Bristow* et al. *[92].*

showed beneficial effects on fractures in their primary analyses [25, 60–63], although some found beneficial and adverse fracture effects in secondary analyses. This is reflected in recent meta-analyses, which showed either no effect of calcium on fracture or small effects [54, 64]. The influential nature of the study by Chapuy and colleagues in the first of these meta-analyses, by Tang *et al.* [54], is noteworthy. In the subgroup analyses, the group in which Chapuy lies usually is found to have the greatest therapeutic effect. Thus, total fractures were only reduced by 6% in community-dwelling subjects. Fracture prevention was reduced with trial duration, reaching no effect at 7 years, and with declining compliance [relative risk 0·96, 95% confidence interval (CI) 0·91–1·01, with <80% compliance] (Fig. 4). Tang *et al.* did not consider hip fracture as a separate endpoint, but at least three meta-analyses have shown upward trends in hip fracture from the use of calcium alone [51, 64, 65]. The effects of calcium plus vitamin D on hip fracture are dominated by the results of Chapuy *et al.*, but analyses of community-dwelling subjects have shown no evidence of fracture prevention. Recently, the investigators from the Women's Health Initiative (WHI) demonstrated a significant interaction between randomization to calcium plus vitamin D and to hormones on risk of hip fracture in their study [66]. When results from the non-hormone-treated WHI subjects were used in the meta-analysis, there was a trend towards an adverse effect on hip fracture risk from the use of calcium plus vitamin D [65] (Fig. 5).

In summary, calcium supplements clearly have small beneficial effects on bone density, but a

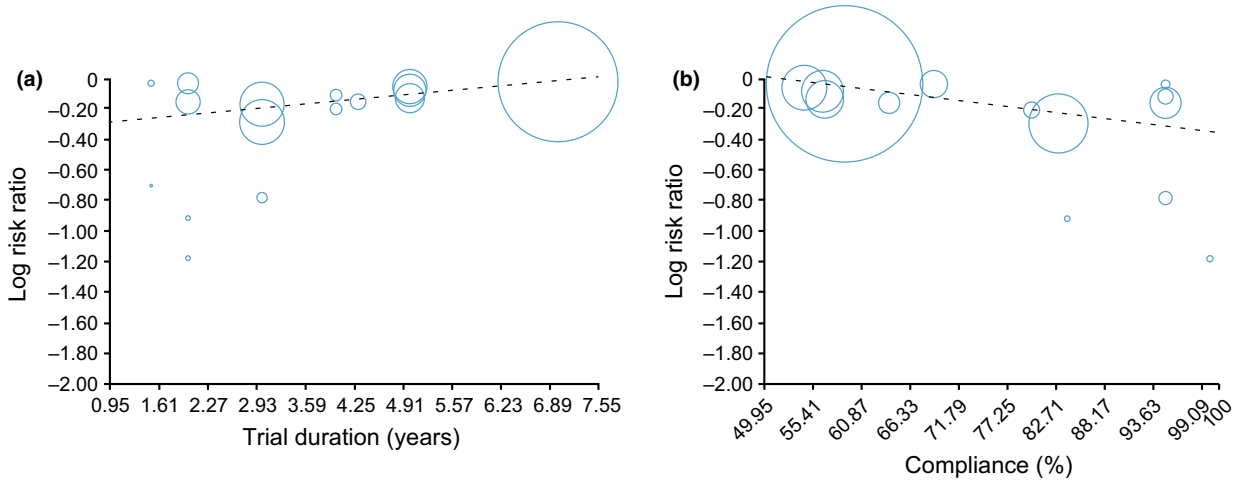

Fig. 4 *Meta-regression analysis of the effects of trial duration (a) and compliance (b) on anti-fracture efficacy of calcium supplements. Size of the circles corresponds to the weight of each study. From Tang* et al. *[54], with permission.*

cumulative density benefit has not been demonstrated in most studies. As a result, the anti-fracture efficacy of calcium supplements remains an open question; there is no evidence to support a role in hip fracture prevention (other than in a cohort with severe vitamin D deficiency) and total fracture numbers are only reduced by 0–10%, depending on which meta-analysis is considered. This has led to the US Preventive Services Task Force not recommending their use [67], a view supported by some journal editorials [68].

Risks of calcium supplements

Over the few decades of calcium supplement use, there was an assumption that a natural element, such as calcium, must intrinsically be safe. Comparison with other minerals and nutrients given in pharmacological doses would suggest that such an assumption is questionable.

Gastrointestinal effects

From their earliest use, there has been an awareness that calcium supplements have gastrointestinal side effects, mainly constipation but also, with the use of calcium carbonate, flatulence. However, it has been assumed that such side effects are only of minor inconvenience. The frequency of minor gastrointestinal symptoms with calcium supplements has been confirmed, and this appears to contribute to low compliance [25]. These adverse effects were summarized in the recent meta-analysis by Lewis *et al.* [69] (Fig. 6). The authors described the symptoms as 'constipation, excessive abdominal cramping, bloating, upper gastrointestinal events, gastrointestinal disease, gastrointestinal symptoms and severe diarrhoea or abdominal pain'. However, of more concern, was the finding by Lewis and colleagues of acute admissions to hospital with acute abdominal symptoms: 6.8% in the placebo group and 3.6% in the calcium-treatment group (over 5 years). In fact, they found that the absolute excess of hospital admissions for acute abdominal problems was numerically greater than the decrease in total fracture numbers. In contrast to the fracture results, the difference in hospital admissions for gastrointestinal emergencies was statistically significant. This suggests that serious gastrointestinal side effects alone abrogate the possible benefit of calcium supplements for fracture prevention.

Renal calculi

Calcium balance is maintained within tight limits to ensure that circulating levels are adequate to facilitate skeletal mineralization, yet not elevated to levels that would cause mineralization of soft tissues. Accordingly, the use of calcium supplements is associated with increases in urine calcium excretion [55]. This has caused concern that calcium supplements would increase the risk of renal calculi, as was confirmed in the WHI (hazard ratio for renal calculi 1.17, 95% CI 1.02–1.34). As for adverse gastrointestinal symptoms, the absolute increase in renal stone events in the active

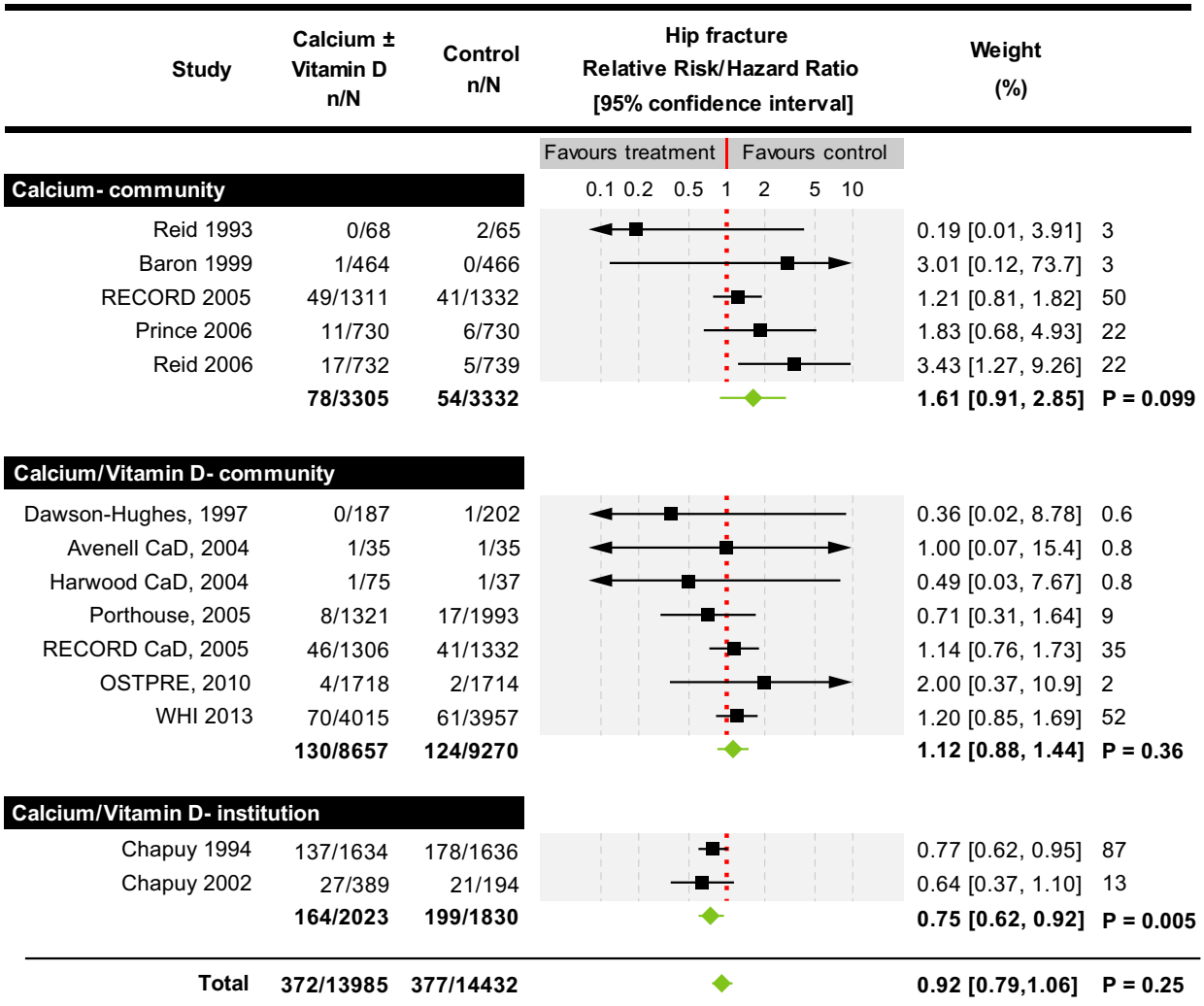

Fig. 5 *Meta-analysis of the effects of calcium alone or with vitamin D on hip fracture risk in randomized controlled trials. Studies have been divided according to the participants' place of residence (community vs. institution). The classification of the Harwood CaD study is questionable as subjects were hospitalized following fractures at trial entry, but most had previously been living in the community. Copyright MJ Bolland 2013; used with permission.*

treatment group in the WHI was statistically significant and numerically greater than the decrease in fractures, whereas there was no statistically significant difference in fracture rates between groups in the primary analyses. Again, the increase in incidence of renal calculi alone counter-balances any possible fracture benefit from the use of calcium supplements.

Cardiovascular effects

We have recently reviewed the cardiovascular side effects of calcium supplements in detail elsewhere [70]. Deposition of calcium into arterial walls is an integral part of the atherosclerotic process, so there has been concern for some decades that calcium supplementation might increase the risk of cardiovascular disease. However, this concern has principally been expressed by vascular biologists [71] and often not considered seriously by those involved in the therapeutic management of osteoporosis. By contrast, there has been long-standing concern about the use of calcium in patients with chronic renal failure. In pre-dialysis patients, calcium supplements increase coronary artery calcification [72] and adversely impact on survival [73].

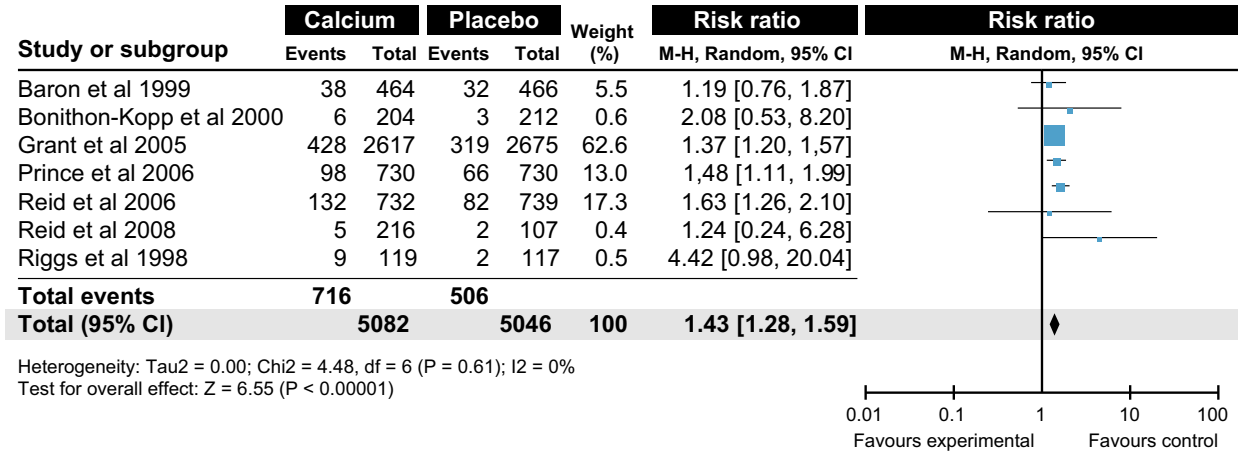

Fig. 6 *Random effects model of calcium supplementation on the risk of gastrointestinal side effects compared with placebo. In the study by Prince* et al.*, acute hospitalizations for gastrointestinal symptoms were increased from 3.6% in the placebo group to 6.8% in those randomly assigned to calcium [relative risk 1.9, 95% confidence interval (CI) 1.2–3.1,* P = *0.006]. From Lewis* et al. *[69], with permission.*

These patients have renal function comparable to that seen in many older individuals at risk of osteoporosis [74]. This concern has resulted in 'the demise of calcium-based phosphate binders' in many centres [75, 76].

More than a decade ago, we and others observed that calcium supplements appeared to produce small benefits in terms of blood pressure [77, 78] and circulating lipid levels [79], although the latter findings have not been consistent. On the basis of these possible beneficial effects, a number of cardiovascular events were pre-specified as secondary endpoints in the Auckland Calcium Study. We were surprised to discover that the incidence of myocardial infarction was significantly increased in this study, and there was an upward trend in stroke incidence [80]. Subsequently, as part of an international consortium, we conducted a meta-analysis of all trials in older adults randomly assigned to calcium or placebo for ≥1 year [81]. This analysis confirmed a 27% increase in the incidence of myocardial infarction and again suggested an adverse effect on the risk of stroke. A quarter of myocardial infarctions in this analysis were self-reported; the hazard ratio was 1.44 (95% CI 1.08–1.91, $P = 0.013$) if these events were excluded [82]. A similar numerical increase in myocardial infarction risk associated with calcium monotherapy has been found in two subsequent meta-analyses [83, 84], although their statistical significance was marginal because of smaller numbers in those analyses.

Our findings with calcium monotherapy appeared to contradict those of the WHI, which concluded that there was no adverse effect of calcium plus vitamin D on cardiovascular health [85]. However, their analyses did demonstrate an interaction between body mass index and cardiovascular disease risk, such that the incidence of myocardial infarction increased by 17% in non-obese subjects. In addition, an almost significant hazard ratio of 1.08 (95% CI 0.99–1.19) was reported for a composite endpoint that included myocardial infarction and coronary artery revascularization, which is not reassuring from a safety perspective.

The WHI differed in several important respects from those studies included in the first meta-analysis led by Bolland [80]. The subjects were, on average, 10 years younger, the active treatment group received vitamin D in addition to calcium, and participants were accepted into the trial even if they were already taking calcium supplements, and were permitted to continue these self-administered calcium supplements throughout the trial. Thus, at randomization, 54% of subjects were self-administering calcium, and this proportion rose to 69% at trial end. We hypothesized that contamination with self-administration of calcium might have obscured an adverse effect of supplements on cardiovascular disease risk and designed a protocol to address this issue. Following approval of the analysis plan by the NIH, we obtained the publicly available WHI data set. We found a significant

interaction between self-administration of calcium supplements and the effect of the calcium/vitamin D intervention on cardiovascular disease risk [86]. There were no adverse effects from the addition of further calcium in those already taking a supplement, but, in calcium-naive subjects, an increase in risk very similar to that found in our first meta-analysis was demonstrated. The adverse trends applied to both myocardial infarction and stroke. As shown in Fig. 7, the time courses of the effects of calcium supplementation on myocardial infarction and stroke are very similar between our meta-analysis of calcium monotherapy and the analysis of the calcium-naive subjects in the WHI. It is also noteworthy that the onset of adverse effect is more rapid for myocardial infarction than for stroke and this difference is consistent between the two separate data sets. Thus, there is no evidence that the addition of vitamin D abrogates the adverse effects of calcium on cardiovascular disease risk, and this is consistent with the much larger body of clinical

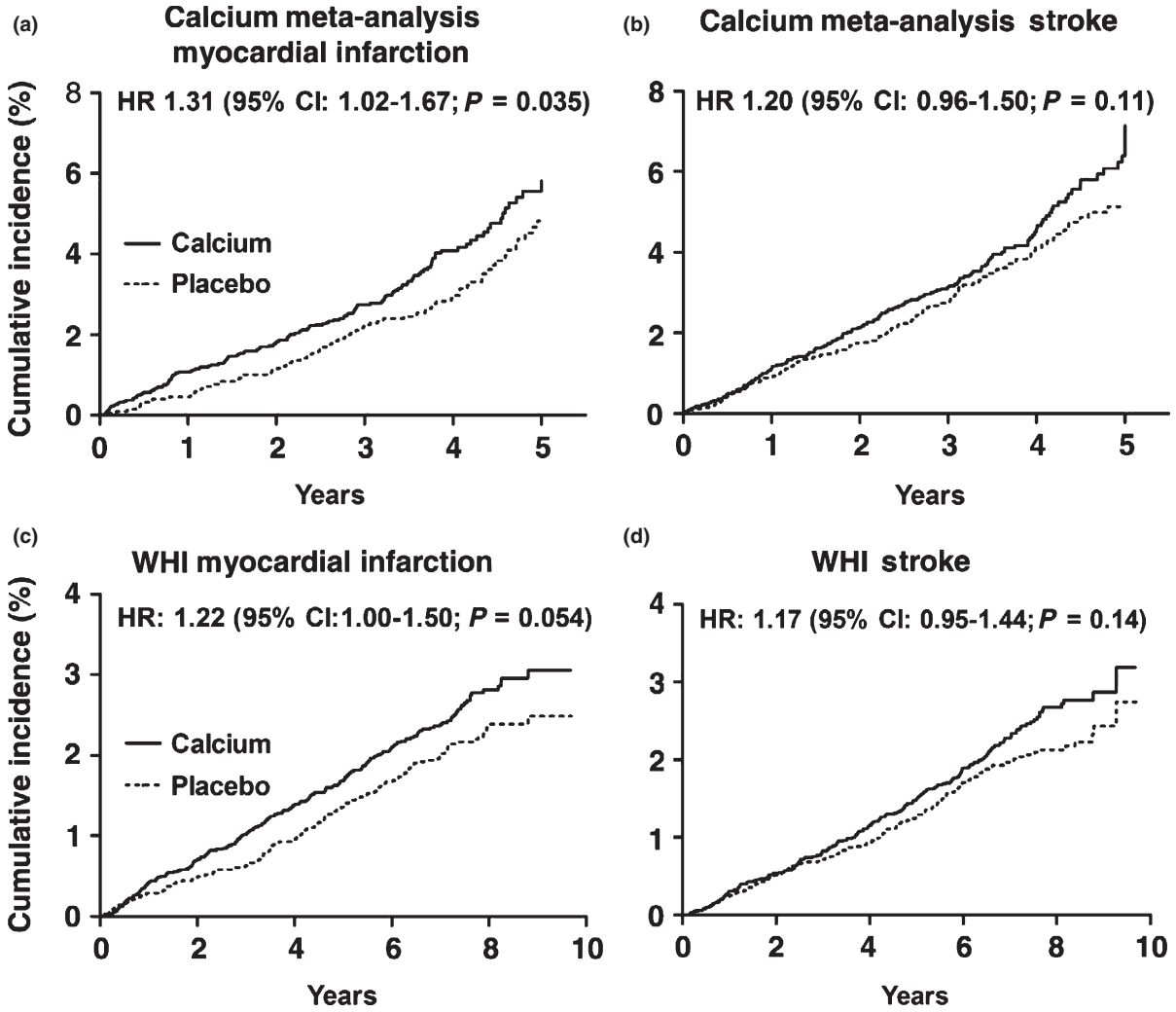

Fig. 7 *Kaplan–Meier survival curves for time to incident myocardial infarction or stroke by treatment allocation in a meta-analysis of patient-level data from five trials of calcium supplements used as monotherapy (*n = *8151) and in women in the Women's Health Initiative (WHI) calcium and vitamin D trial who were not taking calcium supplements at the time of randomization (*n = *16 718). The magnitude and time course of the effects of calcium supplements on the two groups of cardiovascular events were very similar in these independent data sets. From Radford* et al. *[93], with permission. CI, confidence interval; HR, hazard ratio.*

trial evidence suggesting that vitamin D is not cardioprotective [87, 88].

Recently, Lewis *et al.* have performed another meta-analysis of these data, but excluding men and self-reported events [89]. For calcium monotherapy and myocardial infarction, their results were very similar to those of Bolland and colleagues [81] (relative risk 1.37, 95% CI 0.98–1.92); the lack of statistical significance was accounted for by the smaller numbers they included (6333 vs. 10 210). For their analysis of calcium plus vitamin D, Lewis and colleagues added two groups of women not included in the meta-analysis by Bolland *et al.*: 20 000 participants from the WHI who were already taking calcium at the time of randomization, and 6000 women from the study of Larsen *et al.* [90], which was not a randomized, controlled trial. Because we have shown that self-administration of calcium significantly influenced the cardiovascular outcomes of the WHI [86], the first of these additions is not appropriate. In the Larsen study [90], the authors divided the residential area into district 'clusters', with one 'cluster' per intervention. Prospective participants knew what their intervention would be *before* agreeing to participate, and there was a higher participation rate among those offered calcium plus vitamin D. The use of cardiovascular medications, sedatives and analgesics was lower in this group compared with those agreeing to act as controls, suggesting a difference in cardiovascular disease risk and other comorbidities at baseline, which would bias the study against finding an adverse effect of calcium supplements. Thus, this study does not qualify for inclusion in a meta-analysis of randomized, controlled trials. In the analysis by Lewis *et al.*, no effect of calcium plus vitamin D supplements on total coronary heart disease was found, but 82% of the weight in this analysis was from the WHI, so it is essentially a re-publication of those data.

As for gastrointestinal and renal adverse effects, it is instructive to compare the absolute increase in numbers of cardiovascular events with the absolute decrease in number of fractures. For calcium monotherapy, treatment of 1000 persons for 5 years will cause 14 myocardial infarctions, 10 strokes and 13 deaths, while preventing 26 fractures [81]. Thus, consideration of the cardiovascular adverse effects in isolation suggests that calcium supplements produce no net benefit. When these cardiovascular adverse events are considered alongside gastrointestinal events and renal calculi, it is apparent that a negative impact of calcium supplement use is likely.

Conclusions

Concern regarding the safety of calcium supplements has led to recommendations that dietary calcium should be the primary source, and supplements reserved only for those who are unable to achieve an adequate dietary intake. The current recommendations for intakes of 1000–1200 mg day^{-1} are not firmly based on evidence. The longitudinal bone densitometry studies reviewed here, together with the new data included in this review relating to total body calcium, suggest that intakes in women consuming only half these quantities are satisfactory and thus, they do not require additional supplementation. The continuing preoccupation with calcium nutrition has its origin in a period when calcium balance was the only technique available to assess dietary or other therapeutic effects on bone health. We now have persuasive evidence from direct measurements of changes in bone density that calcium balance does not reflect bone balance. Bone balance is determined by the relative activities of bone formation and bone resorption, both of which are cellular processes. The mineralization of newly formed bone utilizes calcium as a substrate, but there is no suggestion that provision of excess substrate has any positive effect on either bone formation or subsequent mineralization.

Based on the evidence reviewed here, it seems sensible to maintain calcium intakes in the region of 500–1000 mg day^{-1} in older individuals at risk of osteoporosis, but there seems to be little need for calcium supplements except in individuals with major malabsorption problems or substantial abnormalities of calcium metabolism. Because of their formulation, costs and probable safety issues, calcium supplements should be regarded as pharmaceutical agents rather than as part of a standard diet. As such, they do not meet the standard cost–benefit criteria for pharmaceutical use and are not cost-effective. If an individual's fracture risk is sufficient to require pharmaceutical intervention, then safer and more effective measures are available which have been subjected to rigorous clinical trials and careful cost–benefit analyses. Calcium supplements have very little role to play in the prevention or treatment of osteoporosis.

Conflict of interest statement

No conflicts of interest to declare.

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