

# Calcium supplementation in osteoporosis: useful or harmful?

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## Abstract

Osteoporosis and fragility fractures are important social and economic problems worldwide and are due to both the loss of bone mineral density and sarcopenia. Indeed, fragility fractures are associated with increased disability, morbidity and mortality. It is known that a normal calcium balance together with a normal vitamin D status is important for maintaining well-balanced bone metabolism, and for many years, calcium and vitamin D have been considered crucial in the prevention and treatment of osteoporosis. However, recently, the usefulness of calcium supplementation (alone or with concomitant vitamin D) has been questioned, since some studies reported only weak efficacy of these supplementations in reducing fragility fracture risk. On the other hand, besides the gastrointestinal side effects of calcium supplements and the risk of kidney stones related to use of co-administered calcium and vitamin D supplements, other recent data suggested potential adverse cardiovascular effects from calcium supplementation. This debate article is focused on the evidence regarding both the possible usefulness for bone health and the potential harmful effects of calcium and/or calcium with vitamin D supplementation.

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## Introduction

The burden of osteoporotic fractures is an important social and economic problem worldwide and both the loss of bone mineral density (BMD) and the reduction of muscle function are major causes of these health-defining events (1, 2, 3). Fragility fractures are associated with important disability, increased morbidity and a 20% increased mortality (2).

For many years, a normal calcium balance together with normal vitamin D status has been considered crucial for maintaining well-balanced bone metabolism and in the prevention and treatment of osteoporosis (4, 5). However, in recent years, the usefulness of calcium supplementation (alone and with concomitant vitamin D supplementation) has been questioned, since some studies reported only weak efficacy of these supplementations in reducing fragility fracture risk (6, 7, 8). Concomitantly, besides the known gastrointestinal side effects of calcium

supplements and the risk of kidney stones related to use of co-administered calcium and vitamin D supplements, other evidence suggested potential adverse cardiovascular effects from calcium supplementation (9, 10, 11).

The aim of this debate article is to focus on the evidence regarding both the possible usefulness for bone health and the potential harmful effects of calcium and/or calcium with vitamin D supplementation.

## Calcium supplementation in osteoporosis: useful (Iacopo Chiodini)

### Calcium intake

The concept of the usefulness of calcium supplementation for bone health is based on the fact that in humans, as

in other mammals, the bone-parathyroid-kidney-ileum axis is finely tuned for the maintenance of physiological calcium and phosphorous levels and the renewal of bone tissue (12). The fact that at bone level the type 1 collagen matrix is strengthened with the apposition of calcium hydroxyapatite crystals supports the idea that an adequate calcium status is crucial for bone health (13). The dietary calcium intake may be adequate in most individuals, but, there is evidence that in subjects with inadequate calcium and vitamin D intake, the supplementation strategies are useful for preventing osteoporosis-related fragility fractures (14, 15). Indeed, in the presence of inadequate calcium intake and/or vitamin D production, the latter being fundamental for a proper intestinal calcium absorption, the incipient hypocalcemia leads to a secondary hyperparathyroidism, increased bone turnover, bone loss and increased fracture risk (16). Interestingly, in turn, vitamin D levels appear to be dependent on calcium intake at or above recommended levels (17).

Moreover, calcium is fundamental even for the muscle physiology and in the skeletal–muscle interaction. Indeed, within the muscle cells, the contraction and relaxation of myosin fibers and the glycolytic and mitochondrial metabolisms have been suggested to be regulated by calcium levels (18, 19). Therefore, the adequate calcium status is important for both bone and muscle.

These considerations explain the high number of studies investigating both the calcium intake in the different populations and the usefulness of calcium and vitamin D supplementation strategies for preventing fragility fractures. However, it is important to note that the dietary calcium intake is very different among the various populations around the world, and, therefore, the calcium supplements may be of importance for bone health in some countries but much less in others (20). For example, in a study in the United States, less than one-third of women aged 9–71 years had an adequate intake of calcium from their diet alone and even among supplement users (75% of cases) less than 50% of subjects achieved the recommended calcium intake (21). In a study on about 370 Italian postmenopausal women, the mean daily calcium intake was about 600mg/day and the 20% of subjects were taking less than 300mg/day of calcium from dairy products (22). In keeping, in a more recent study in a population of Italian patients with type 1 diabetes, the 50% of men and 27% of women showed a calcium intake below the threshold recommended for the Italian general population (23). At variance, for example, in two studies on non-osteoporotic men in New Zealand conducted by the group of the coauthor of the present

article, the mean calcium intake was about 800mg/day (24, 25). Further complicating matters, the national recommendations on calcium intake for different ages and genders vary worldwide (20), being for example between 1000 and 1300mg/day in those from the US National Institutes of Health (26) and between 700 and 1000mg/day in those from the National Osteoporosis Society (27). In general, even if these latter recommendations defines 400mg/day as the lowest amount of calcium required to maintain a healthy skeleton (28), the adequate calcium supplementation for bone health is still a matter of debate, and it is influenced by several factors, such as age and vitamin D levels (17). It is clear, therefore, that the different calcium intake among the different populations may be an important confounding factor in interpreting the results of the studies on the effect of calcium supplements on bone, since data from randomized controlled trials were not able to be adjusted for baseline personal calcium intake without making subgroups analyses with the consequent loss of the randomized design (6).

Other important confounding factors in the interpretation of these studies are that the different lifestyle and social habits may have influenced the outcomes. For example, it is possible that calcium and other supplements are used by patients with very poor health, with the hope of improving daily activities and quality of life. On the other hand, the use of calcium supplements may be frequent among the very healthy subjects with lifestyle and other dietary habits associated with low morbidity and mortality (6). It is possible, therefore, that the small effect of calcium supplements that can be appreciated at the population level, is, in fact, derived from an important effect in a small number of subjects.

### Calcium supplements and bone mineral density (BMD)

The importance of the calcium intake during adolescence has been evidenced by a recent double-blind randomized controlled trial on 220 Chinese teens showing that, after two years of low, medium or high calcium intake levels, the BMD increases in female adolescents who ingested more calcium (28, 29). In keeping, some data suggest that BMD is reduced and the fracture is increased in adult women who drunk less milk during childhood and adolescence (30).

Even in adults, BMD has been suggested to be possibly influenced by calcium intake. Indeed, in the Women's Health Initiative (WHI) study on more than 36 000

postmenopausal women BMD at hip was slightly higher in the calcium plus vitamin D group than in the placebo group (31). In a more recent study on about 7000 subjects older than 50 years of age, a calcium intake below 400 mg/day was associated with lower BMD and femoral cortical thickness, while a calcium intake above 1200 mg/day was positively correlated with BMD (32). In keeping, the meta-analysis from Shea and coauthors found that calcium was more effective than placebo in reducing the rates of bone loss after at least two years of treatment, with a difference in percentage change from baseline of 1.7% and 1.6% for spinal and hip BMD, respectively (33). Another five-year randomized controlled trial on about 1450 elderly women reported an improvement in ultrasonographic parameters related to bone density in women with an adequate (>80%) compliance to the supplements, suggesting that adherence to treatment is crucial for the therapy to be effective (34). Similarly, a recent meta-analysis of nine studies showed that supplementation with calcium plus vitamin D, has a small-to-moderate effect on spinal and femoral BMD in healthy males (35). Partially in discordance, in the meta-analysis of Tai and coauthors (including 59 studies) increasing calcium intake from dietary sources increased femoral BMD by 0.6–1.0 and femoral and spinal BMD by 0.7–1.8% at two years, but the increase in BMD at later time points was similar to the increase at one year (36).

Overall, these data suggest that calcium supplement have positive effects on BMD, which is probably more important in subjects with adequate compliance to the supplements and with baseline lower dietary calcium intake (8).

### Calcium, vitamin D and risk of falling

An important issue that might support the usefulness of calcium supplementation (with or without vitamin D), at least in patients with low calcium intake, is the possible positive role of these supplements on muscle function. This hypothesis has been tested in several randomized clinical trials and several meta-analyses that tried to summarize these results. Overall, the majority of these studies showed that a steady vitamin D supplementation reduced the risk of falling in particular in patients with vitamin D deficiency and who reach adequate vitamin D levels (37, 38, 39, 40, 41, 42), even though some authors were not able to find the same conclusions (43).

The possible adjunctive effect of calcium to vitamin D on the risk of falling, however, is still not clear, probably due to the fact that these effects may be concealed in patients with normal calcium intake, which has not been

estimated in the majority of studies. This idea is reinforced by the finding that alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily (44). In general, the available studies failed to demonstrate an adjunctive effect of calcium (41, 42, 43, 45, 46), even though two studies found that the vitamin D effect in reducing the risk of falls was stronger when calcium supplements were co-administered (38, 46).

However, some evidences suggest a relation between low calcium intake and low muscle mass (47), since a decreased calcium absorption and an altered calcium homeostasis are associated with muscle weakness in the aged individuals (48, 49). Therefore, although we have low evidence for an effect of calcium supplementation in addition to vitamin D for reducing the risk of falling, in patients with osteoporosis estimating the calcium intake is mandatory, since, besides secondary hyperparathyroidism, an incipient hypocalcemia leads muscle-related symptoms, than can ameliorate with calcium supplementation. Overall, it is reasonable to consider calcium supplements in the prevention and treatment of sarcopenia in older adults with a low calcium intake (3).

### Calcium supplements and risk of fracture

Since the vitamin D status is crucial for calcium absorption, the efficacy of calcium supplement alone may be different from that of calcium with concomitant vitamin D supplements. In the meta-analysis of Tang and coauthors, which included more than 52 000 patients, a statistically significant reduction of fragility hip fracture risk was demonstrated for calcium with vitamin D supplements (relative risk, RR 0.87) but not with calcium alone supplements (50). In keeping, a subsequent meta-analysis, having the risk of hip fracture as outcome, was not able to find any protective effect of calcium alone supplements, which were even associated with an increased number of events (51). At variance, in a more recent meta-analysis including 13 studies, the coauthor of the present article found that the calcium supplementation alone was associated with a 15% reduction in risk of any fracture but not of hip, vertebral or forearm fractures (52).

Data on the fracture risk reduction related to the use of calcium with vitamin D supplements are more consistent. In 2010, the Group DVDIPAoRT published an individual data meta-analysis including 68 500 patients from 7 randomized controlled trials (with a follow-up between 18 and 85 months, 2 studies being performed in

institutionalized subjects) showing a statistically significant reduction in all fractures (hazard ratio, HR 0.92) and hip fractures (HR 0.83) for the calcium with concomitant vitamin D supplements (53). Interestingly, since patients enrolled in the trials assessing the efficacy of calcium with vitamin D were all community dwelling, this study suggests that this type of supplementation is efficacious even in the free-living setting. Similarly, in the trial data, meta-analysis performed by the US National Osteoporosis Foundation (NOF), which included 8 studies (about 31 000 subjects), a 15% reduction of overall fracture risk and a 30% reduction of hip fracture risk was found (7). These data are similar to those previously published in the meta-analysis of Tang and coauthors, who found a statistically significant reduction of all fractures (RR 0.99) and hip fractures (0.87) in participants taking calcium with concomitant vitamin D supplements (50).

Even in the meta-analysis performed by the coauthor of this article including 26 trials (more than 69 000 subjects) a risk reduction for all and hip fractures (RR 0.92 and 0.84, respectively) with combined calcium and vitamin D administration was found. However, when the analysis was confined to the four trials at low risk of bias, as defined by the authors using the Cochrane guidance, the effect on the risk of fracture at any site was no longer present (42). However, even though these studies were a low risk of bias, they might be intrinsically biased. Indeed, since these studies have been designed on the intention-to-treat principle, the optimal adherence to the medicaments prescribed was not certain, potentially leading to confounding results (31, 34, 54, 55). For example, in the study by Prince and coauthors, even though in the intention-to-treat analysis calcium supplementation did not significantly reduced the fracture risk, among the 830 patients (56.8%) who took 80% or more of their tablets (calcium or placebo) per year, patients taking calcium had a statistical significant reduction of the fracture incidence (HR 0.66) compared with subjects taking placebo (34). In the RECORD study, performed on 5292 already fractured elderly people (85% women), who were randomly assigned to oral vitamin D or calcium with vitamin D or calcium alone or placebo, the authors did not find difference in the risk fracture in any site, but it must be observed that in this study, there was about 10% reduced compliance in patients taking tablets containing calcium as compared with those taking vitamin D or placebo, partly because of gastrointestinal symptoms (54). Finally, in the WHI study, the intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a not statistically significant HR of 0.88 for hip fracture, which, however

was reduced to 0.71 and became statistically significant after censoring data from women not adherent to the study medication (31). The deviation from an intention-to-treat analysis may be an exceptionable approach, but it might be justified for establishing the efficacy (a biological effect) of these supplements, considering the often poor compliance with calcium supplementation. Interestingly, the several adjustment analyses performed in the NOF meta-analysis for adjusting for the possible unbalanced randomization derived from deviating from the intention-to-treat analysis confirmed the protective effect of calcium and concomitant vitamin D supplementation on fracture risk (7, 56, 57).

Some other considerations should be done about the issue of the correct intake of the prescribed supplements during the study protocols. For example, a possible confounding factor in the interpretation of these studies is the possibility that participants personally used calcium and vitamin D supplements. Indeed, a reanalysis of the WHI trial, in which study subjects were permitted personal use of calcium and vitamin D (31), showed that after stratifying by personal use of these supplements, the fracture reduction with calcium and vitamin D supplementation was no longer evident (58). However, again, as the randomization procedure was not designed to ensure balancing of patients according to this criterion, this stratification transformed this randomized controlled trial in an observational study, thus reducing its strength (6). Anyway, the explanation of these results is quite intuitive, as the efficacy of interventions for threshold nutrients cannot be established in individuals who are already sufficient (59). At the opposite, the persistence of low calcium intake even in patients included in the treatment-arm of the randomized controlled trials, due to low or sub-optimal adherence to the supplements prescribed, is an important issue, since treatments cannot work if they are not taken. This problem may be less important in studies performed in institutions, since in these latter, the administration of supplements may be more controlled. Therefore, the institution-settled studies may give more information about the efficacy of these supplements and some evidence seems to support this theory. First of all, one of the most clear fracture risk reduction with calcium and vitamin D supplements was found in the milestone study by Chapuy and coauthors, which has been performed in nursing and/or residential homes (60), while the fact that the RECORD study has been performed in a community setting may account for the completely negative results (54). Secondly, in the meta-analysis performed by the coauthor of this article,

the hip fracture reduction with calcium and vitamin D supplementation was statistically significant when considering the trials performed on institutionalized patients but not when considering those including community-dwelling participants (52). Furthermore, even in the meta-analysis by Tang and coauthors, the calcium and vitamin D supplementation reduced the overall risk of fractures more in institutionalized patients than in community-dwelling ones, even if the important difference in the sample size of the two groups (49 233 vs 3392 individuals) may have introduced an important selection bias (50). In general, the community-based clinical trials, in which compliance was moderate or less, have often been negative, whereas studies in institutionalized patients, in whom medication administration was supervised, often demonstrated significant benefits (61).

Finally, a very recent meta-analysis of 33 randomized trials involving more than 51 000 community-dwelling older adult participants found no significant association of combined calcium and vitamin D with hip, non-vertebral or total fractures compared with placebo (62). Even though the authors performed subgroup analyses showing that these results were generally consistent regardless of serum 25-hydroxyvitamin D concentration, dietary calcium and other confounders, again the community-dwelling setting may have concealed the effectiveness of the supplements. In fact, the data showed a trend (even if not statistically significant) for a reduction of hip, non-vertebral, vertebral and total fracture in individuals taking calcium with concomitant vitamin supplements. Moreover, the risk of hip and non-vertebral fractures tended to be lower in the individuals with vitamin D levels above 20 ng/mL. Therefore, considering that the threshold of 20 ng/mL for vitamin D levels may be too low to ensure an adequate vitamin D status (63), it is not possible to exclude that the lack of effectiveness found in this meta-analysis may be due also to the lack of a normal vitamin D status in a significant part of the included individuals.

In keeping with this latter consideration, it must be observed that all available bone-active drugs are licensed in the context of an adequate calcium and vitamin D status, since the registration trials have been performed on patients always supplemented with calcium and vitamin D (64, 65). It is important to remind that the effect of the bone-active drugs in the absence of a concomitant calcium and vitamin D is substantially unknown. On the other hand, in the 'real life', the incidence of fractures during treatment with antiresorptive agents is considerably higher than that observed in randomized clinical trials and the inadequate compliance to antiresorptives or to

supplementation of calcium and vitamin D are similarly important in determining this poor response (66). Again, since the dietary calcium intake is difficult to be estimated (67) and the vitamin D deficiency is extremely frequent (68) but not easily predictable without measuring vitamin D levels (69), in the clinical routine of the 'real life' the administration of supplements may be a simple way to ensure an adequate intake of calcium and vitamin D (7).

## Conclusions

In our opinion, the present evidence suggests that calcium with concomitant vitamin D supplementation, but not calcium alone, leads to an increase in BMD and to a reduction of the risk of total by 15% and of hip fractures by 30%. The entity of the hip fracture risk reduction obtained using calcium plus vitamin D supplements appears to be similar to that of the myocardial infarction risk obtained using statins, drugs that are widely considered to be effective (70). However, this does not justify a population-level intervention with statins, which are prescribed on the basis of the cardiovascular risk profile of the individual patient. Similarly, **calcium supplements should not be suggested in patients with a normal calcium intake.** On the other hand, in patients with an estimated low calcium intake and in those treated with bone-active drugs we should strongly suggest to increase the dietary calcium intake. **In the impossibility to obtain a correct calcium intake through diet, calcium with concomitant vitamin D supplements should be given as, in this setting, they have to be considered an effective therapy for reducing the fragility fracture risk (71).** This idea is also reinforced by the fact that the reported cardiovascular risk due to calcium supplementation is yet to be demonstrated and that studies that have evaluated the influence of dietary calcium intake did not show increase in the cardiovascular risk (28).

Therefore, the debated issue of the use of calcium supplements is perhaps more simple to resolve than expected. **As any other dietary integration, the calcium supplements should be given in patients with insufficient calcium intake, particularly if osteoporotic and taking bone-active drugs.**

## Calcium supplementation in osteoporosis: not useful (Mark Bolland)

For the last few decades many experts, committees and specialist societies have recommended calcium intake

targets for older women and men well above the average population dietary intakes. The most practical way of achieving these targets is to take a calcium supplement. In many western countries, these recommendations have been widely followed, so that the majority of older people take calcium supplements (21, 72, 73, 74). However, in the last 15 years, evidence has emerged that the risk–benefit profile of calcium supplements is not favorable for most people. In this review, I will make the case that widespread calcium supplementation is unnecessary because any small benefits in preventing fractures are outweighed by the common occurrence of mild side effects that lead to stopping the supplements and the less common occurrence of more serious side effects. I will begin by briefly reviewing the history of calcium intake recommendations then discuss the current evidence for benefits and harms of calcium supplements.

### Brief history of calcium intake recommendations

Since Albright introduced the term postmenopausal osteoporosis in 1940, the role of calcium intake in the pathogenesis and treatment of osteoporosis has been investigated and debated. Albright and colleagues reported that estrogen reduced urine calcium excretion in postmenopausal women, creating a positive calcium balance (75, 76). However, they concluded that this was only secondary to the mechanism of action of estrogen and proposed that calcium and vitamin D deficiency could cause osteomalacia, but postmenopausal osteoporosis is caused by estrogen deficiency and not related to calcium intake (75, 76). Contemporaneous studies of populations with low calcium intakes did not report poor bone health, supporting this view (77, 78, 79, 80). Subsequently, many international and national bodies made recommendations about calcium intake for adults, with recommendations lowering from 1000 to 800mg/day in 1953 (81) to 400–500mg/day by 1974 (82).

Subsequently, views shifted based on new research and higher calcium intakes again were recommended.

Heaney and colleagues published a series of influential calcium balance studies, concluding that premenopausal women required 1000–1200mg/day and postmenopausal women 1500mg/day to maintain neutral calcium balance (83, 84). Small increases in bone density were reported in randomized controlled trials (RCTs) of calcium supplements with or without vitamin D (85, 86). Chapuy and colleagues reported that calcium and vitamin D reduced hip and total fractures by about 30–40% over 18 months in a very influential large placebo-controlled RCT conducted in frail elderly women living in residential care in France (60). Based on these results, the case for calcium supplementation seemed compelling, at least for older postmenopausal women. Therefore, many major guidelines recommended calcium supplements in doses  $\geq 1000$ mg/day for the treatment and prevention of osteoporosis, and the majority of older people in many western countries took calcium supplements (21, 72, 73, 74). Despite the apparent consensus, important questions remained about the existing research (87, 88) and other issues related to calcium supplement use (Table 1). Many of these questions were addressed in later clinical studies.

### Later research

In a large series of calcium balance studies, Hunt and Johnson reported that neutral calcium balance occurred at a much lower calcium intake (741 mg/day) than reported by Heaney and colleagues, and also was not altered by age or sex (89). Although longer than previous studies (each balance study had a minimum duration of 16 days); nevertheless, these studies still may not be long enough for adaptation to a change in calcium intake. 50 years earlier, Malm reported that after an abrupt decrease in calcium intake, positive calcium balance was eventually restored, but it took many weeks to months before adaptation was complete (87).

Numerous RCTs studying the effect of calcium supplements or increasing calcium intake on bone density have now been reported. In 2015, we performed

**Table 1** Outstanding questions about calcium supplements following publication of the 1993 trial by Chapuy and colleagues (60).

1. Do the results from the calcium balance studies conducted by Heaney and colleagues (83, 84) apply universally, particularly in countries with lower or higher long-term calcium intake?
2. Calcium supplements slowed down but did not prevent bone loss, and results from randomised controlled trials are inconsistent. Would these findings have long-term treatment implications?
3. Are the results of the Chapuy trial that was carried out in frail elderly women living in residential care in France generalizable beyond that population group?
4. Does calcium and vitamin D co-administration produce better results than either agent alone?
5. Calcium supplements are not very palatable and often cause gastrointestinal side effects. What implications would side effects have for long-term compliance and the risk–benefit profile?

a systematic review identifying 59 such RCTs (36). Meta-analyses of these RCTs showed a number of important findings. Firstly, calcium supplements had similar effects on bone density to dietary sources of calcium. Secondly, increases in bone density were only small (<2%) and one-off, that is the increases in bone density were present at one year, and thereafter did not increase. Thirdly, the addition of vitamin D to calcium did not lead to additional benefits, and effects were also similar regardless of calcium dose or baseline calcium intake (36). An early RCT had specifically addressed the issue of effects of calcium supplementation on bone density by baseline calcium intake (90). In 103 postmenopausal women, the effects of 500mg/day of calcium supplements for two years on forearm bone mineral content and urinary calcium excretion were very similar in women with baseline calcium intakes of <550, 550–1150 and >1150mg/day (90). Thus, later trials have not confirmed the reports of sustained important effects on bone density from early RCTs of calcium supplements or the view that there is a state of ‘calcium deficiency’ that can be rectified by supplementation.

Six RCTs of calcium supplements (with or without vitamin D) with fracture as a primary outcome reported their results between 2005 and 2010 (31, 34, 54, 55, 91, 92). All were carried out in community-dwelling individuals, and none reported a statistically significant reduction in fractures. When meta-analyzed together with all other available RCTs, there is only weak and inconsistent beneficial effects of calcium supplements on fracture, with no effect seen in the large double-blind placebo-controlled RCTs at lowest risk of bias (52). Numerous meta-analyses of RCTs of calcium with or without vitamin D with fracture as the outcome have been conducted, and their conclusions often differ even though they review largely the same group of studies. The differing conclusions seem mainly due to differences in trial selection, definition of the fracture outcomes and methods used in the meta-analysis (93). However, recent meta-analyses do consistently conclude that calcium supplements with or without vitamin D in community-dwelling individuals do not prevent hip or total fractures (5, 52, 62, 94). Likewise, in 44 cohort studies, the overwhelming majority reported no relationship between baseline intake of calcium, milk or dairy and fracture outcomes at any site (52). Taken together, there is no evidence currently of an association between calcium intake and fracture risk or that increasing calcium intake alters fracture risk in a meaningful way.

The clear exception is the RCT by Chapuy and colleagues (60), which demonstrated unequivocal benefits from co-administered calcium and vitamin D supplements

and which the same investigators largely replicated in a smaller RCT in a similar population 10 years later (95). The results of these two trials are clear outliers from the results of RCTs of calcium and vitamin D in community-dwelling individuals and also from the results of RCTs of vitamin D in individuals in residential care (42, 94). The reason for these differences is not clear. One possible explanation is a high background rate of untreated osteomalacia in the populations studied by Chapuy and colleagues, which had a mean baseline 25-hydroxyvitamin D level of about 20nmol/L in both RCTs, suggesting that a substantial proportion of participants had severe vitamin D deficiency. A reanalysis of the Chapuy trials by baseline 25-hydroxyvitamin D level might prove instructive. Another important issue is that these two RCTs are extremely influential in any meta-analysis. Whatever subgroup these two RCTs are placed in has reductions in fracture risk that are not consistent with results from subgroups without these trials (52). It seems clear that the results from these studies conducted in a very frail population with marked vitamin D deficiency are so influential in any meta-analysis that they should not be pooled with studies conducted in different patient groups. Recommending widespread use of calcium and vitamin D supplements for otherwise healthy community-dwelling older adults based upon meta-analyses heavily influenced by these RCTs in a unique population group is therefore inappropriate.

If taking calcium supplements did prevent a small number of fractures, there may be large benefits for a population if they were widely used, even though there would be no meaningful benefit for each individual user. In this situation, safety becomes an important consideration, because the small risk of a side-effect can translate into a large number of adverse events when there is widespread use of an agent in a population. The completion of the large RCTs of calcium supplements has clarified their side-effect profile. Calcium supplements are unpalatable to many and commonly cause minor gastrointestinal side effects such as constipation and dyspepsia (55). Frequently, these side effects cause the individual to stop the supplements, and their occurrence is sufficient to explain the poor long-term compliance of 40–60% reported in the large RCTs (31, 34, 54, 55). More significant side effects have been reported from 3 RCTs. In the Women’s Health Initiative, there was a 17% increased relative risk of kidney stones with calcium and vitamin D supplements (31). Prince and colleagues reported that calcium supplements increased the relative risk of acute gastrointestinal symptoms causing hospitalization by

92% (96). In our trial, calcium supplements increased the rate of the composite endpoint of myocardial infarction, stroke and sudden death (97), and the relative risk of hip fracture (55). Subsequent meta-analyses of RCTs of calcium monotherapy confirmed increases of hip fracture of about 50% (51, 98), increases of myocardial infarction of about 30% and reported a possible increase in stroke of about 15–20% (9, 10). Hypercalcemia has also been reported from the use of co-administered calcium and vitamin D supplements (99, 100). The table shows a comparison between the reduction in numbers of participants with fractures and the numbers of participants experiencing adverse events in the large RCTs (101). When adverse event data have been reported from large RCTs, in most cases, there are numerically more serious adverse events than fractures prevented (Table 2). For example, the number needed to harm to cause one vascular event (i.e. 178) is less than the number needed to treat to prevent one fracture (i.e. 302) in community-dwelling individuals (9).

One reason sometimes given for recommending the use of calcium and vitamin D is that all major trials of osteoporosis agents have used calcium and vitamin D supplements; therefore, their use is necessary when osteoporosis agents are prescribed (and is safe). However, this view does not withstand scrutiny. RCTs comparing co-administration of an antiresorptive plus calcium and vitamin D with placebo plus calcium and vitamin D do not allow conclusions to be drawn about either the necessity

of calcium and vitamin D or its safety. No large trial with fracture outcomes has compared an effective osteoporosis treatment (e.g. a bisphosphonate) co-prescribed with calcium and vitamin D to the osteoporosis treatment alone. However, trials of osteoporosis treatments without calcium and vitamin D have produced similar outcomes for fracture (102, 103, 104) and bone density (105, 106, 107, 108) to trials where these supplements were co-administered. Thus, the use of calcium with or without vitamin D by patients taking osteoporosis treatments is probably unnecessary. An important caveat is that administration of potent antiresorptive agents to frail elderly patients with marked vitamin D deficiency can provoke significant hypocalcemia, which can be prevented through a short course of vitamin D supplements.

### Current recommendations

Numerous authoritative groups have made recent recommendations about the use of calcium with or without vitamin D. These recommendations range from recommendations against their use in primary fracture prevention (US Preventative Services Task Force) (109) through to daily intake of calcium of 1000–1200 mg and vitamin D of up to 2000 IU (see Table in 110). The reasons for the persistence of strong recommendations for the use of calcium and vitamin D when the available evidence does not support such recommendations are not clear. We hypothesized that strong links between industry

**Table 2** Risk–benefit profile of calcium supplements in large ( $N > 1000$ ) randomized placebo-controlled trials.

Trial	Treatment	Number of participants	Benefit–risk profile	
			Benefit <sup>a</sup>	Harm <sup>a</sup>
(60)	CaD	3270	–55 All fracture –30 Hip fracture	+12 GI symptoms +1 Hypercalcaemia
(54)	Ca or CaD	5292	–36 All fracture	+7 Hip fracture +109 GI symptoms +16 Myocardial infarction
(31)	CaD	36,282	–54 All fracture –14 Hip fracture	+261 Constipation +68 Kidney stone +177 Hypercalcaemia
(34)	Ca	1460	–16 All fracture	+21 Myocardial infarction <sup>b</sup> +5 Hip fracture +32 Constipation
(55)	Ca	1471	–13 All fracture –2 Kidney stone	+24 GI hospitalization +12 Hip fracture +50 Constipation +10 Myocardial infarction

<sup>a</sup>Number of cases in treatment group less number of cases in control group. Benefit: fewer cases in the treatment group; Harm more cases in treatment group. <sup>b</sup>Data for entire cohort. There was an interaction between risk of myocardial infarction, CaD treatment and use of personal calcium supplements (41, 54). In women not taking personal calcium supplements, there were +41 myocardial infarctions in the CaD group; in women taking personal calcium, there were –16 myocardial infarctions in the CaD group.  
Ca, calcium; CaD, calcium and vitamin D; GI, gastrointestinal.



and academics, specialist societies and advocacy groups involved in osteoporosis management might be a possible contributing factor (111).

## Conclusion

Based on the results of the large RCTs of calcium with or without vitamin D with fracture as a primary outcome, it is reasonable to conclude that any benefit in preventing fractures is at best very small, if there is any at all, and that any such benefit is outweighed by the small risk of serious adverse events. This unfavorable risk–benefit profile is further weakened by the issues of poor long-term compliance, which is often related to mild but common gastrointestinal side effects. Faced with this information, taking these supplements is unlikely to be attractive to individuals. Furthermore, there is currently no consistent evidence of a relationship between dietary calcium intake and risk of fracture. This suggests that clinicians, advocacy organizations and health policymakers should not recommend an increase in dietary calcium or the use of calcium with or without vitamin D supplements for fracture prevention or when osteoporosis treatments are prescribed. Individuals at high risk of fracture should be offered treatments proven to prevent fracture that have a favorable risk-benefit profile.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this debate.

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