



## Review

## Calcium and bone

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## ARTICLE INFO

## Article history:

Received 23 December 2011  
 Received in revised form 4 May 2012  
 Accepted 8 May 2012  
 Available online 17 May 2012

## Keywords:

Calcium intake  
 Calcium supplementation  
 Bone mineral density  
 Peak bone mass  
 Fracture  
 Children  
 Adolescents  
 Older people

## ABSTRACT

**Objective:** Evaluate the role of calcium on bone health.

**Methods:** Review of literatures on calcium and bone development during childhood and bone health in adulthood and older age.

**Results:** Calcium intake influences skeletal calcium retention during growth and thus affects peak bone mass achieved in early adulthood. Increased calcium intake is associated with increased bone mineral accretion rate up to a threshold level in all ethnic groups. The minimum intake to achieve maximal retention is 1140 mg/day for white boys and 1300 mg/day for white girls. Calcium also plays a role in preventing bone loss and osteoporotic fractures in later life. Meta-analyses report that calcium supplementation reduce bone loss by 0.5–1.2% and the risk of fracture of all types by at least 10% in older people. Low calcium intake is a widespread problem across countries and age groups.

**Conclusion:** Adequate calcium intake throughout lifetime is important for bone health and the prevention of osteoporosis and related fractures.

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## Introduction

The adult human body contains around 1 kg calcium on average, more than 99% of which exists in bone and teeth. In bone, calcium exists in mineral form as hydroxyapatite  $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ . Calcium influences bone strength through its effect on bone mass. Calcium intake is one of the important modifiable environmental factors for the normal development of the skeleton during growth and the maintenance of bone mass in later life.

## Calcium and bone development during childhood and adolescence

### *Calcium and dairy intake and bone mineral accretion*

Bone mineral accretion during growth is a major determinant of peak bone mass, which is associated with the risk of developing osteoporosis in older age. The peri-pubertal and pubertal years are a critical period for bone mineral accretion, with around 39% of young adult total body bone mineral gained in the 4 years surrounding peak height velocity [1]. Many factors, including genetics, gender, endocrine and nutritional factors influence the attainment of peak bone mass. Most epidemiologic and randomised studies of calcium intake have been undertaken in subjects with diets adequate in other nutrients such as protein, carbohydrate and fat.

Calcium intake influences skeletal calcium retention during bone growth and thus plays a role in peak bone mass achieved in early adulthood. Longitudinal studies in Canadian boys [2] and Chinese girls [3] have shown that calcium intake was a minor but significant predictor of total body bone mass. Inadequate calcium intake during growing period could compromise peak bone mass attained at skeletal maturity and thus predispose individuals to increased risk of osteoporotic fracture in later life. A study of 3251 Caucasian women from the third American National Health and Nutrition Examination survey showed that women with low milk intake during childhood and adolescence had low bone density in adulthood and greater risk of fracture [4]. In addition, low bone mass may also contribute to childhood fracture. A report in New Zealand children showed that those who avoided cow's milk had 1.7 times higher risk for pre-pubertal fracture [5].

The majority of intervention studies with dairy foods or calcium supplement in children and adolescents from different ethnic backgrounds have shown positive effects on bone mineral accretion at one or more of the sites measured [6–12]. Two meta-analyses evaluated the effects of calcium supplementation on bone mass in children. The first meta-analysis which included 19 studies ( $n = 2859$ ) showed that calcium supplementation had a significant effect on total body bone mineral content (BMC) (standardised mean difference 0.14, 95% CI 0.01–0.27) and forearm bone mineral density (BMD) (0.14, 95% CI 0.04–0.24), but no effect on BMD at the femoral neck or lumbar spine [13]. The other meta-analysis included 12 randomized controlled trials of calcium or dairy intervention ( $n = 2460$ ) and showed that there was no significant effect on total body BMC in the overall analysis [14]. However, as the data demonstrated statistical heterogeneity, further analysis by pooling the 3 studies in subjects with low calcium intakes of 450–750 mg/day demonstrated that calcium or dairy intervention led to a 50 g (95% CI 24–77 g) (1–3%) higher total body bone mineral accretion [14]. A few studies also followed up the study participants for a further 1–3.5 years to investigate whether the effects of short-term intervention could be maintained after the withdrawal of the supplement. While some studies showed that the effect was maintained [15–17], others did not [18–20]. The reason for the differences in findings could be due to study participants' habitual calcium intake, pubertal status and the form of intervention.

Most of the calcium or dairy intervention studies were for 2 years or less. The only long-term study evaluated the effects of 7-year calcium supplementation in American girls aged 10.9 years at baseline. This study showed that calcium supplementation had a significant

positive influence on bone mineral accretion during the pubertal growth spurt, but the effects were diminished in late adolescence. This suggested that BMD could catch up during the bone consolidation phase to compensate for the compromised bone mineral accretion during the growth spurt because of inadequate calcium intake. However, this study also demonstrated that subjects with low calcium intake may not have complete catch up and thus may not achieve their target peak bone mass [21].

In summary, epidemiological studies showed that milk and calcium intake are related to bone mineral accretion during growth, childhood fracture and bone density at adulthood. Intervention studies showed positive effects of calcium and dairy on bone mineral accretion, particularly in populations with low habitual calcium consumption. However, whether these effects could reduce childhood fracture is uncertain, and whether the effects could be translated into high bone density in adulthood seems related to subjects' characteristics (habitual calcium intake, pubertal stage).

### *Calcium retention in children and adolescents in cross-cultural studies*

The calcium retention efficiency during growth varies among ethnic groups. One study comparing American black and white girls showed that the skeletal calcium retention of black girls was 185 mg/d higher compared to white girls, and that black children had significantly greater net calcium absorption and lower urinary calcium excretion [22]. Chinese children with low habitual calcium intake also have higher calcium retention efficiency compared to Caucasian children. In a longitudinal study of Chinese girls, the calculated apparent calcium retention efficiency was 41% with average calcium intake of 444 mg/day [3], which is greater than the apparent retention efficiency of 30% at peak bone mineral accretion in white Canadian girls with average calcium intake of 1000 mg/day [23]. A calcium balance study in Chinese adolescents aged 12–17 years old with calcium intakes ranging from 352 to 1260 mg/day (diet + supplementation) showed that the apparent calcium absorption rate was 68.7% in boys and 46.4% in girls [24].

Although black children had higher skeletal calcium retention, for each unit of increase in calcium intake black and white children absorb and retain the same amount of calcium (29). Similarly, a calcium balance study in Chinese adolescents showed that in girls, calcium retention increased from 80 mg to 355 mg per day when calcium intake increased from 352 mg to 1260 mg per day, and in boys calcium retention increased from 243 mg to 646 mg per day when calcium intake increased from 427 mg to 1323 mg per day [24]. These data together indicate that despite the differences in habitual calcium intake and calcium retention efficiency, within each ethnic group increased calcium intake is associated with increased bone mineral accretion up to a threshold level.

Calcium requirement during growth can be defined as the intake needed to attain the individual's genetically programmed optimal bone mass. Balance studies of calcium retention in white boys and girls at different levels of calcium intake (700–2100 mg/day) showed that calcium retention plateaus at a certain level of intake. The minimum intake to achieve maximal retention has been reported to be 1140 and 1300 mg/day in white boys and girls, respectively [25,26]. Compared to their white counterparts, the calcium intake needed for achieving maximal calcium retention is significantly lower in Chinese American girls (970 mg/day) and slightly lower in Chinese boys (1100 mg/day) [27]. This could be related to the higher retention efficiency of Chinese children.

### **Calcium and bone in young adults**

A longitudinal study of Canadian boys and girls followed up to 30 years of age showed that total body BMC reached a plateau at 18 years of age in girls and 20 years in boys [1], indicating that peak bone mass is achieved around the age of 20. Once peak bone mass

is achieved, it is maintained without much change for 10 to 20 years. Few studies have evaluated the association between calcium intake and bone density in young adults. One study with young Japanese women and another with 125 young female cross-country runners showed a positive association between calcium intake and bone density [28,29]. Calcium requirement in this period is 20–30% lower compared to the fast growing period, as bone development has completed.

### Calcium and bone in older age

From middle age, the age related bone loss in both male and female is approximately 0.5–1.0% per year [30]. For 5–10 years during and after menopause, women lose bone more rapidly than men, at a rate of 2–3% per year. This is mostly due to the deficiency of estrogen at menopause which leads to decreased intestinal calcium absorption and renal calcium re-absorption and increased parathyroid hormone (PTH) secretion and bone resorption [31–37].

### The effect of calcium in preventing bone loss

A number of randomized controlled trials (RCTs) have examined the effects of increased calcium intake on bone mineral density as assessed by dual energy X-ray absorptiometry (DXA). These trials have shown that in older people with a baseline calcium intake of 500–1000 mg/day, increasing the intake by a further 500–1200 mg/day with or without vitamin D can prevent bone loss, possibly due to the effect of calcium in suppressing PTH secretion [36,38–41]. In a meta-analysis that included 23 trials of 41,419 subjects, calcium or calcium and vitamin D supplementation was associated with 0.5% reduction in hip bone loss and 1.2% reduction in spine bone loss [42]. Most of the studies on calcium and bone density were conducted in older women or both women and men. The few studies in men alone showed similar effects of calcium supplementation in maintaining bone mass. In a 2-year RCT in healthy men aged over 40 years, the group that received 1200 mg calcium per day had 1–1.5% greater increase in spine and hip BMD compared to the placebo group [43].

Vitamin D may add extra beneficial effects to calcium supplementation in slowing bone loss. In a 5-year study of older Australian women, who were randomized to receive either 1200 mg/day calcium alone, 1200 mg/day calcium and 1000 IU/day vitamin D or placebo, bone loss was prevented in both treatment groups but not the placebo group at year one. However, the effect was only maintained in the group that received both calcium and vitamin D at 3 and 5 years [44].

### The effects of calcium in preventing fracture

The majority of randomized controlled trials that investigated the effects of either calcium supplementation alone or combined calcium and vitamin D supplementation in older people have shown a reduction in fracture risk, as long as sufficient patient compliance (75–80%) was achieved [38,45,46]. In a study of 1460 western Australian women aged 70–85 years at baseline, where study participants received either 1200 mg/day calcium or placebo for 5 years, there was no overall effect in the intention to treat analysis [45]. However, a 30% reduction in any fracture risk was observed in the per protocol analysis in those taking more than 80% of the tablets (Fig. 1) [45]. The trials that failed to show benefit of calcium supplementation on fracture risk reduction mostly had methodological problems, such as confounding from hormone replacement therapy administered at the time of study [47], lack of evaluation of patient compliance [48] or under-powering of the study [47,48]. A meta-analysis that included 52,625 subjects from 17 trials with fracture as outcome showed that calcium treatment was associated with a 10% reduction and calcium in combination with vitamin D was associated with a 13% reduction in risk of fractures of all types [42]. This meta-analysis also found that the fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high and the treatment effect was better when the calcium dose  $\geq$  1200 mg, and the vitamin D dose  $\geq$  800 IU [42].

Eleven of the 17 trials were in women only, and the other 6 recruited both men and women. A subgroup study showed that the treatment effect was similar in trials of women alone and trials that included both men and women, with a risk reduction of 12% for both [42]. Thus calcium is equally important for fracture prevention in men and women.

### Calcium and hip fracture risk

A meta-analysis of pooled cohort studies did not show an association between total calcium intake and hip fracture risk in either women or men [49]. In contrast, two meta-analyses of randomized controlled trials of calcium monotherapy, {one including four trials ( $n=6504$ ) [49] and the other including three trials ( $n=5500$  women) [50]}, suggested that calcium supplementation was associated with a higher risk of hip fracture. The authors of the second meta-

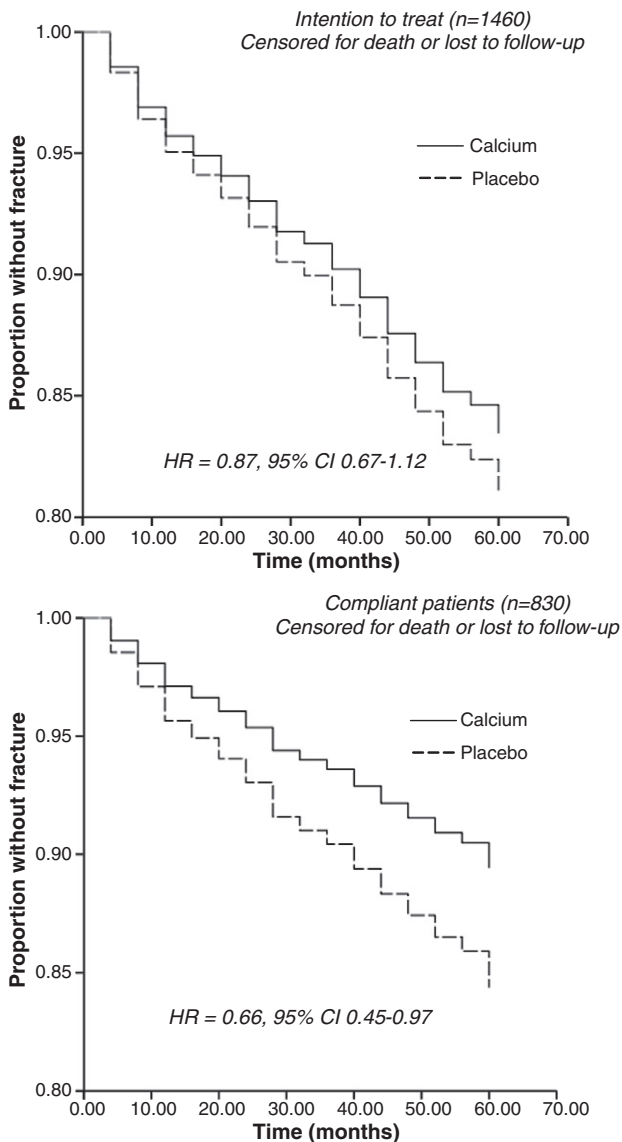


Fig. 1. Cox's proportional hazard analysis of the time to first incident fracture in 1460 older Australian women who received 1,200 mg calcium or identical placebo per day (reproduced from Arch Intern Med 2006;166:873 [45] with permission of the American Medical Association. Copyright © (2006) American Medical Association. All rights reserved.).

**Table 1**  
Recommended calcium intakes in USA, Australia and China.

USA		Australia		China	
Age group (years)	Recommended intake (mg/day)	Age group (yrs)	Recommended intake (mg/day)	Age group (years)	Recommended intake (mg/day)
<b>1–3</b>	EAR 500 RDA 700	<b>1–3</b>	EAR 360 RDI 500	<b>1–3</b>	AI 600
<b>4–8</b>	EAR 800 RDA 1,000	<b>4–8</b>	EAR 520 RDI 700	<b>4–10</b>	AI 800
<b>9–13</b>	EAR 1,100 RDA 1,300	<b>9–11</b>	EAR 800 RDI 1,000	<b>11–14</b>	AI 1,000
<b>14–18</b>	EAR 1,100 RDA 1,300	<b>12–18</b>	EAR 1,050 RDI 1,300	<b>11–17</b>	AI 1,000
<b>Men 19–70 and Women 19–50</b>	EAR 800 RDA 1,000	<b>Men 19–70 and Women 19–50</b>	EAR 840 RDI 1,000	<b>18–49</b>	AI 800
<b>Men &gt; 70 and Women &gt; 50</b>	EAR 1,000 RDA 1,200	<b>Men &gt; 70 and Women &gt; 50</b>	EAR 1,100 RDI 1,300	<b>&gt; 50</b>	AI 1,000

Data source: USA [52], Australia [53] and China [54]. EAR: Estimated average requirement; RDA: Recommended dietary allowances; RDI: Recommended dietary intake; AI: Adequate intake.

analysis hypothesized that the increased risk of hip fracture could have resulted from suppressed periosteal expansion at the femoral neck with calcium intervention, as periosteal expansion normally provides mechanical compensation for bone mineral decline with ageing [50]. Nevertheless, intervention studies using both calcium and vitamin D have demonstrated significant reduction in hip fracture risk in older women [46,51]. As older people at high risk of hip fracture tend to have both low calcium intake and vitamin D deficiency, it is now widely agreed that calcium should be used in combination with vitamin D to prevent bone loss and fracture.

### Meeting calcium requirement

The recommended calcium intakes for USA [52], Australia [53] and China [54] are summarized in Table 1. The variation in values may be due to cross-cultural differences, disparities in expert opinions, and uncertainty of data in some populations. Generally higher calcium intake is required during the growing period for the achievement of maximal peak bone mass, and in women after menopause (over 50 years old) and in men over 70 years old to prevent menopause and age-related bone loss.

#### Calcium intake in children and older adults

Low calcium intake is a widespread problem across countries and age groups.

#### Children and adolescents

A population-based survey showed that the mean calcium intake of adolescent American boys and girls are 1000 mg/day and 900 mg/day, respectively [55]. However, black children tend to have lower intakes. A longitudinal study of white and black American girls aged 9 to 18 years old using 3-day food record showed that the mean calcium intake was 825 and 644 mg/day for white and black girls, respectively, with the 50th percentile at 793 mg/day for white and 611 mg/day for black girls [56]. Calcium intake is even lower in Asian countries. The 2002 China National Nutrition and Health Survey (CNNHS) found that the daily calcium intakes were 376 mg for boys and 343 mg for girls aged 14–17 of years [57]. In addition, 70%–80% Chinese boys and girls of this age group had calcium intake <50% of the recommended intake (1000 mg/day) and only 3–4% met the recommended intake [57].

#### Older people

In America, less than 10% women aged <70 years and less than 1% women aged >70 years meet the calcium requirement through their diet. In men, only one in four have adequate calcium intake from diet.

In a longitudinal study of free-living older Australian women aged 70–85 years, the mean calcium intake ranged from 900 to 980 mg/day and more than 70% of the population did not achieve the Estimated Average Requirement of 1,100 mg/day [58]. Calcium intake is even lower in countries where dairy is not a staple food. In China, the 2002 China National Nutrition and Health Survey (CNNHS) showed that the average calcium intake was 439 mg/day for adults living in urban areas and 372 for those in rural areas [57]; these represent only about half of the recommended intake of 800–1000 mg/day [54].

#### Intestinal factors affecting intestinal calcium absorption

Milk and dairy products are good sources of calcium. Bony fish, legumes, certain nuts and fortified soy milk and breakfast cereals also contain smaller amounts of calcium. Calcium bioavailability depends on absorbability and the incorporation of absorbed calcium into bone. Therefore, both dietary factors influencing intestinal absorption and the excretion of calcium in urine play a role in calcium bioavailability [59]. Some food components, such as phytate in bran, most cereals, seeds and nuts, oxalate in spinach, rhubarb, walnuts and sorrel, and tannins in tea can form insoluble complexes with calcium, and thus reduce calcium intestinal absorption. A diet high in sodium could increase urinary calcium loss and lead to decreased calcium retention [59].

#### Lactose

In normal subjects, lactose increases calcium absorption from 22% to 36% [60]. However, in patients with lactose intolerance, lactose induces a reduction in calcium absorption by about 5% [60]. This may be due to the osmotic effects of lactose reducing the effective concentration of calcium within the bowel [61]. The connection between lactose intolerance and osteoporotic fracture would appear to be due to reduced calcium intake associated with avoidance of milk products [62,63].

#### Fiber

High fiber diets have been recommended for various benefits on the bowel and the cardiovascular system. Studies that have examined the effects of these diets on calcium consumption have not found any significant deleterious effects at moderate consumption of fibre containing foods [64]. However, calcium retention is reduced from 25% to 19% with high fibre intake [65].

#### Protein

In the past, excessive protein intake had been thought to lead to chronic metabolic acidosis which causes hypercalciuria and increased

mineral dissolution [66]. However, some recent data suggest the effect of protein on calcium balance could be neutral as it increases gut calcium absorption [67]. Furthermore, it has been suggested that adequate protein intake may benefit the skeleton of older people by providing amino acids and increasing circulating insulin-like growth factor I (IGF-I) [68,69]. The only long term dietary protein intervention study was a 2-year randomized controlled trial with 219 healthy ambulant women aged 70–80 years. Participants were randomized to either a high protein drink containing 30 g of whey protein or an isocaloric placebo drink containing 2.1 g protein ( $n = 110$ ). At 2 years, the high-protein group had a marginally higher urinary calcium excretion and significantly higher IGF-I levels compared to the placebo group, but there was no significant difference between the two groups in change in bone mass or strength. This study showed that in protein-replete healthy ambulant women, 30 g of extra protein did not have beneficial or deleterious effects on bone mass or strength [70].

### Achlorhydria

It has been shown that in achlorhydric individuals the absorption of calcium when administered as calcium carbonate is less than when administered as calcium citrate. This differential absorption is abolished if the calcium is taken with food [71]. In terms of preventing bone loss, calcium lactate gluconate has identical effects to milk powder that contains the same amount of calcium [36,72].

### Calcium supplementation

Although obtaining sufficient calcium from diet is preferred, supplementation is needed when adequate calcium intake cannot be achieved with diet. A recent expert panel report has suggested that supplementation with calcium and vitamin D should be recommended in women

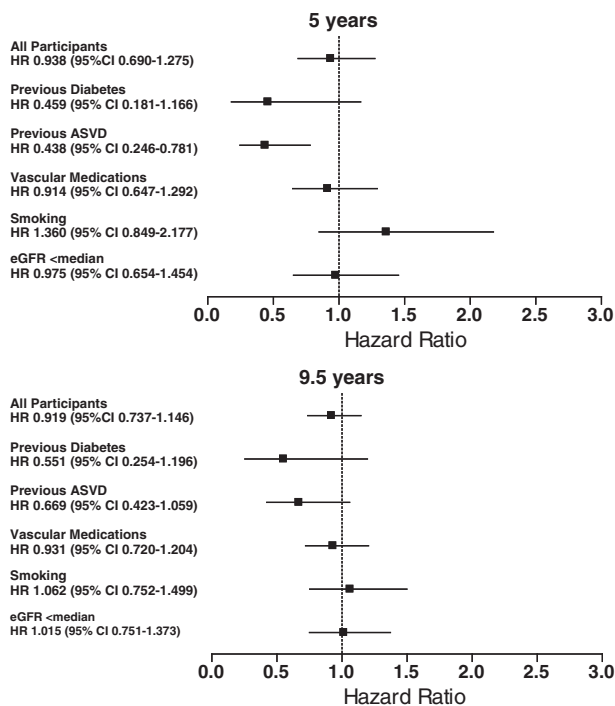
with osteoporosis, or at increased risk of osteoporosis i.e. aged over 65 years, BMD T-score less than  $-1$ , or proven calcium and/or vitamin D insufficiency [73]. The expert panel recommended that women at increased fracture risk should receive both calcium and vitamin D supplements, including 1000–1200 mg calcium (depending on dietary calcium intake) and 800 IU vitamin D daily [73]. It is recommended by the Institute of Medicine that the total calcium intake from diet and supplementation should not exceed the tolerable upper intake limit (UL) of 3,000 mg/day for children and adolescents aged 9–18 years, 2,500 mg/day for 19–50 year olds and 2,000 mg/day for those aged > 50 years [52].

Calcium from supplements is absorbed more efficiently when taken in doses less than 500 mg [74]. In the fasting state, calcium is better absorbed from calcium citrate than calcium carbonate, and calcium as carbonate is better absorbed when taken with food. Nevertheless, the Institute of Medicine has recommended taking calcium supplementation with foods to reduce the risk of developing kidney stone [52]. In addition, 500 mg calcium as citrate has been reported to have the equivalent effects of 1000 mg calcium as carbonate in suppressing parathyroid hormone and bone resorption; thus using calcium citrate supplement may be associated with fewer adverse effects and better long-term compliance [75].

### Controversies on calcium supplementation and vascular disease risk

Recently, a secondary analysis of a calcium supplementation study in older New Zealand women [76] and a meta-analysis included 8016 men and women from five prospective calcium intervention studies [77] have raised the concern that calcium supplementation may increase the risk of myocardial infarction. A further meta-analysis included trial level data from 28,072 participants from nine studies using either calcium supplement alone or both calcium and vitamin D [78]. This meta-analysis concluded that supplementation with calcium alone or both calcium and vitamin D increased the risk of myocardial infarction by 24% and the composite of myocardial infarction or stroke by 15% [78]. However, carefully reviewing these three reports, we could see that the conclusions are dependent on studies which have compared multiple endpoints, conducted in heterogeneous populations, and most of the time used less than ideal methods of ascertainment for vascular diseases. A recent report showed that in seven RCTs of calcium intervention, self-reported gastrointestinal adverse event rates were more common in participants receiving calcium and there was a higher error rate in the self-report of myocardial infarction in the calcium group [79]. The authors suggested that the higher error rate in the self-report of myocardial infarction in the calcium group could be due to increased functional gastrointestinal disorders associated with calcium supplementation mistaken for myocardial infarction [79]. It is also interesting to note that in the Women's Health Initiative (WHI), participants who were taking personal calcium supplements at randomisation, addition of calcium and vitamin D did not increase cardiovascular disease risk [78].

In contrast, in a study that used a more accurate method of vascular disease ascertainment, no association of calcium intervention and atherosclerotic vascular disease risk was found [45]. In this trial 1460 women aged  $75.1 \pm 2.7$  years at baseline participated in a 5-year, randomised, double-blind, placebo-controlled trial of calcium carbonate (1200 mg/day calcium or placebo) and were further followed up for an additional 4.5 years [45]. Complete verified atherosclerotic vascular hospitalization and mortality data were obtained using the Western Australia Data Linkage System hospitalization and mortality record. The calcium group did not have a higher risk of death or first-time hospitalisation from atherosclerotic vascular disease in either the 5-year RCT (multivariate-adjusted HR 0.938 95% CI 0.690–1.275) or during the 9.5 years of observational study (multivariate-adjusted HR 0.919 95% CI 0.737–1.146) (Fig. 2) [80]. Thus, this trial using a more accurate method of vascular disease ascertainment provides



**Fig. 2.** The effect of calcium treatment compared with placebo on all atherosclerotic vascular disease hospitalisations and mortality outcomes over 5 and 9.5 years. The analyses utilized groups with the named baseline risk factor. Analyses adjusted for baseline age, calcium intake, compliance, cardiovascular disease, eGFR, diabetes, previous or current smoking and baseline cardiovascular medications unless that covariate was the subject of the analysis. eGFR refers to estimated glomerular function rate while ASVD refers to atherosclerotic vascular disease. (Reproduced from J Bone Miner Res. 2011;26: Page 39 [80] with permission of the American Society for Bone and Mineral Research).

compelling evidence that calcium supplementation of 1200 mg daily does not significantly increase the risk of atherosclerotic vascular disease in elderly women.

## Conclusions

Osteoporosis and related fractures are important public health problems world-wide. Calcium intake influences peak bone mass achieved in early adulthood by influencing skeletal calcium retention during bone growth and plays a role in preventing bone loss and osteoporotic fractures in later life. Low calcium intake is a widespread problem across countries and age groups. Therefore, ensuring adequate calcium intake throughout lifetime is important for bone health and the prevention osteoporosis and related fractures.

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