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REVIEW

Supplemental calcium intake in the aging individual: implications on skeletal and cardiovascular health

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Abstract

Adequate calcium intake during childhood is necessary to achieve optimal peak bone mass and this has the potential by increasing bone reserves, to modulate the rate of age-associated bone loss. However, data regarding the efficacy of calcium obtained either through the diet or in the form of medicinal supplementation, for prevention of bone loss and osteoporotic fractures in the elderly is conflicting. Calcium alone is unlikely to be of benefit for this purpose though the co-administration of calcium and vitamin D may have modest fracture risk benefits. Supplemental calcium with or without vitamin D has recently come into the spotlight after the publication of the findings from a controversial randomized controlled trial that associated calcium supplementation with an increased risk of myocardial infarction. Since then, multiple studies have explored this potential link. The data remains conflicting and the potential mechanistic link if any exists, remains elusive. This review examines the relationship between supplemental calcium intake and skeletal and cardiovascular health in the aging individual through an appraisal of studies done on the subject in the last three decades. It also briefly details some of the studies evaluating fractional absorption of calcium in the elderly and the rationale behind the current recommended dietary allowances of calcium.

Keywords Calcium supplementation · Dietary calcium · Fracture · Cardiovascular risk · Myocardial infarction · Fractional absorption

Introduction

The adult human body contains about 1200 g of calcium of which 99% is present in the bones and the teeth. This contributes to the rigidity and structure of these mineralized tissues. The remaining 1% is found in blood, extracellular fluid and muscles, and plays a vital role in mediating vascular function, muscle contraction and nerve transmission. The concentration of calcium in the plasma is kept within a tightly regulated range through the complex interaction of the hormones; parathyroid hormone (PTH) and 1,25 dihydroxycolecalciferol (1,25(OH2) D3) with the kidneys, bones and the intestine. Calcium is required for normal skeletal growth and development. Until early adulthood, calcium accrual in the skeleton occurs at a steady rate. In humans, bone mass is believed to peak in early adulthood (Fig. 1). The timing of the peak is thought to vary by gender at different skeletal sites. By the time adulthood is reached, the skeleton is in calcium equilibrium. Later, as aging sets in; at the time of menopause in women and about age 55 in men, bone balance starts becoming negative with bone loss occurring at all skeletal sites resulting in calcium losses of approximately 15 g per year [1]. Adequate calcium intake during childhood is essential to achieve optimal peak bone mass and this has the potential by increasing bone reserves to modulate the rate of bone loss that is associated inevitably with aging.

The role that supplemental calcium plays in improving bone mass and/or preventing bone loss and reducing fracture risk in older populations is hotly debated and in recent years this role has come under scrutiny because of studies suggesting potential adverse cardiovascular effects

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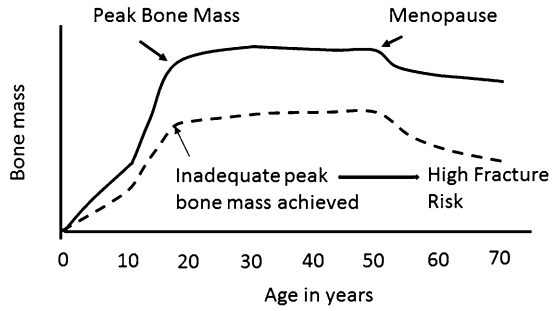

Fig. 1 Diagrammatic representation of the bone mass life-line in individuals who achieve their full genetic potential for skeletal mass and in those who do not

with supplemental calcium use. The purpose of this narrative review is to examine the relationship between supplemental calcium intake and skeletal and cardiovascular health in older individuals (defined arbitrarily as being more than 50 years of age) through an appraisal of studies done on the subject in the last three decades. The review also describes the rationale behind the current recommended dietary allowance of calcium and also provides a short description of the studies evaluating fractional absorption of calcium in the elderly since this has important implications on the efficacy of calcium.

Bioavailability of calcium in the elderly

Calcium retention in the body is determined by the relationship between calcium intake and calcium excretion and absorption. Calcium is absorbed in the small intestine by two general mechanisms: a transcellular active transport process, located largely in the duodenum and upper jejunum; and a paracellular, passive process that functions throughout the length of the intestine [2]. Calcium absorption efficiency influences calcium balance. Calcium absorption decreases with age [3, 4]. An additional decrease is documented in women at the time of menopause [5]. Inefficient absorption or malabsorption of calcium from the gastrointestinal tract can be due to a reduction in renal 1,25-dihydroxyvitamin D synthesis, a decline in intestinal vitamin D receptors or resistance to 1,25 D, 25-hydroxyvitamin D deficiency, or due to a decrease in active calcium transport [3, 4, 6, 7]. Ethnic variations in fractional absorption of calcium exist. White postmenopausal women have been shown to have significantly lower fractional absorption of calcium compared to Hispanic and Black women on dual isotope studies [8]. The average fractional calcium absorption amongst Chinese adults was 33% at an intake of 600 mg/day of calcium [9]. This is approximately 10% higher than Caucasian adults in the United States in whom the average intake of calcium is approximately 800 mg/day [10]. There may thus be a difference in the efficiency of utilization of dietary calcium between races. Fractional absorption of calcium has been shown to remain at a high level with little changes when calcium intake ranges between 300 and 1000 mg/day in Chinese adults [9]. This contrasts with that reported in Caucasians in whom fractional absorption reaches a peak of approximately 35% at a intake of about 400 mg and then falls off as intake increases further to a plateau of 20% with an intake of approximately 1000 mg [10]. Higher fractional absorption and retention of calcium reported in Asian Chinese [11] may thus be a physiological adaptation to low calcium intake that is characteristically seen amongst this population. It is probable the dietary calcium may be more efficiently utilized (with better fractional absorption and less excretion) in Chinese compared to Caucasians.

It is important to note that calcium absorption, metabolism and excretion is a collaborative process which is dependent upon a complex interaction with other nutrients such as dietary protein [12], vitamin D [13] and phosphorous [14]. High dietary protein intakes are well known to increase urinary calcium [15] excretion and some studies have concluded that dietary protein is an even more important regulator of urinary calcium than calcium intake [16]. This hypercalciuria was earlier thought to be exclusively secondary to increased bone resorption. However, recent studies suggest that alterations in dietary protein can profoundly affect intestinal calcium absorption. Increased dietary protein has been shown to be accompanied by a significant increase in intestinal calcium absorption in dual stable isotope studies [15]. Dietary protein intakes at and below 0.8 gm/kg were associated with reductions in intestinal calcium absorption sufficient to cause secondary hyperparathyroidism in the same study [15]. The long-term consequences of these low-protein induced changes in calcium metabolism are not known fully, but it may be detrimental to skeletal health especially in the elderly who are likely to have low protein diets. This needs to be elucidated further.

Calcium and bone health in the elderly

Peak bone mass in adulthood is predictive of subsequent bone density and, therefore, osteoporosis risk in later life [17, 18]. Short-term longitudinal studies appear to suggest that increasing consumption of calcium rich foods or supplementation with calcium in early life is associated with increased peak bone mass [19].Whether it can result in less loss of bone in later life is unclear. In the setting of chronic calcium deficiency due to habitual inadequate intake or poor intestinal absorption of calcium due to vitamin D deficiency,

circulating calcium concentration is likely to be maintained at the expense of skeletal mass in the elderly unlike in the case of adolescents and young adults in whom circulating calcium levels can be maintained by increasing intestinal calcium absorption. The cumulative effect of calcium depletion on the skeleton over several years can contribute to the development of osteoporotic fractures with aging [4, 20]. Theoretically, a high calcium intake can decrease bone loss in the elderly by impacting remodeling. Bone remodeling is a sequential process involving bone resorption by osteoclasts followed by osteoblasts forming new bone. Bone loss occurs when bone resorption exceeds bone formation in each remodeling unit. Calcium by decreasing bone turnover and the number of bone remodeling units, can potentially result in a decrease in bone loss.

While available data to support optimizing this nutrient in growing children for bone accrual has been consistent, its effectiveness in adults and specifically the elderly is fraught with controversy. There have been numerous studies exploring the efficacy or lack thereof of calcium supplementation on bone health in elderly adults (Table 1). The results have been inconsistent and this is not unexpected given that these studies vary in design and the study populations and outcomes have been very heterogenous. There are several reasons why generalizing the results obtained from these studies is difficult. These include baseline differences in the study population's dietary calcium intake, i.e., whether it is sufficient or insufficient and difficulty in separating out the effect of calcium versus vitamin D, since in most cases, they are co-administered. It is difficult to delineate doses that may be harmful or beneficial and, because the type, and doses of calcium and vitamin D vary amongst the trials, it is also difficult to isolate the effect of dietary calcium versus the effects of supplementation. It is also important to consider whether it was bone mineral density gains or fracture reduction that was the end point in the studies and important to consider the hormonal status of the subjects involved since the biological effects of the mineral may vary between pre and post-menopausal women. Lastly, adherence to the supplementation can also affect the outcomes studied.

Effects of dietary calcium and tablet supplementation on bone mineral density in the elderly

Studies of calcium supplementation in post-menopausal women have been mostly of short duration ranging from 1 to 5 years. These studies in general show that the effectiveness of calcium differs by skeletal site, by duration of menopause and that it also is dependent upon the quantity of habitual calcium intake.

Calcium supplementation during the first 5 years after menopause (when typically, bone loss is most rapid) was not shown to be effective in preventing bone loss from trabecular regions of the skeleton though there was a trend towards a slowed loss in cortical bone in one study [21]. Similar results of a lack of effect on slowing of trabecular bone loss, but with effect on slowing of cortical BMD loss with calcium supplementation in post-menopausal women has been shown in other studies also [22, 23]. The significance of this reduction in the rate of cortical bone loss noted in these studies and whether this reduction is sustained remains a topic of debate, however.

Calcium supplementation was found to increase BMD by 0.7–1.8% at all skeletal sites assessed at one, two and over two and a half years but the size of the increase in BMD at later time points was similar to the increase at 1 year in a random effects meta-analysis of 59 randomized controlled trials which included both studies exploring dietary sources of calcium as well as those that studied calcium supplements [24]. In a meta-analysis conducted to assess whether the assumption that the effects of calcium supplementation is the same year after year, it was found that the reduction in bone loss with calcium supplementation was significant only in the first year of supplementation [25].

The influence of gender on the efficacy of calcium on bone health is not well studied. A large cross-sectional study in Korea exploring associations between calcium intake with metabolic syndrome and bone mineral density in 14,705 men and women found that in men and in post-menopausal women, dietary calcium intake between 400 to $\leq$ 800 mg daily was associated with significantly increased BMD at both the femoral neck and lumbar spine [26].

Calcium supplementation appears to be more effective in maintaining bone density or retarding its loss in women who are more than 5 years postmenopausal [22, 27–30] and in women who have lower intakes of calcium at baseline [22]. The investigators of this latter randomized double-blind placebo-controlled trial surmised that healthy older women who had their menopause 6 years or longer before and had a daily calcium intake of less than 400 mg /day can significantly reduce bone loss by increasing their calcium intake to 800 mg /day [22].

The relative contributions of calcium and vitamin D to bone mineral density in the elderly have been explored in large cross-sectional studies such as the National Health and Nutrition Examination Survey (NHANES) III [31]. In NHANES III, it was found that the BMD of men and women increased with increasing serum 25(OH)D concentration independent of calcium intake. In the women, calcium intake was significantly and positively associated with femoral neck BMD in those with serum 25(OH)D concentrations below 50 nmol/L, but not in those with higher 25(OH)D concentrations. The investigators concluded that in both men and

Table 1 Supplemental calcium and its effect on BMD and fracture risk

Authors/study	Number of participants	Characteristics of study	Type of calcium supplementation	Results
Riis et al. [21]	43 early post-menopausal women	Randomized controlled trial Follow up: 2-years Outcome: BMD	Calcium tablet supplements (2000 mg daily) versus 17 beta-estradiol versus placebo	Calcium supplementation had minor effect on slowing cortical bone loss. No effect on trabecular bone loss
Dawson-Hughes et al. [22]	301 healthy postmenopausal women	Randomized controlled trial Follow up: 2 years Outcome: BMD	Calcium carbonate or citrate (500 mg daily) tablet supplements versus placebo	In older (> 6 years post-menopause) women and in those with low calcium intake;(< 400 mg/day), Calcium Citrate prevented bone loss at the femoral neck, radius and spine and Calcium carbonate prevented bone loss at the femoral neck and radius
Elders et al. [23]	248 perimenopausal women	Randomized controlled trial Follow up: 3 years Outcome: BMD	Calcium tablet supplements (1000 or 2000 mg daily) versus no supplementation	Calcium supplementation reduces cortical and trabecular bone loss pre/peri- menopause. In postmenopausal women, cortical bone loss is reduced but not lumbar spine bone loss
Tai et al. [24]	13,790 subjects > 50 years old	Meta-analysis of 59 Randomized controlled trials Outcome: BMD	5 studied dietary sources of calcium ($n = 1533$) and 51 studied calcium tablet supplements ($n = 12,257$)	Increasing calcium intake from dietary sources increased BMD by 0.6-1.0% at the total hip and total body at one year and by 0.7–1.8% at total hip and total body and the lumbar spine and femoral neck at two years Calcium supplements increased BMD by 0.7–1.8% at all five skeletal sites at one, two, and over two and a half years, but the size of the increase in BMD at later time points was similar to the increase at one year (i.e., non-progressive)
Mackerras et al. [25]	957 post-menopausal women	Meta-analysis of 9 randomized controlled trials Outcome: BMD	Heterogenous studies: both diet and tablet supplementation	The rate of bone loss at spine, femoral neck, trochanter, intertrochanter, mid-tibia and ultra-tibia was significantly less in the first year after randomization than in the second year
Shea et al. [41]	1806 post-menopausal women	Meta-analysis of 15 Randomized controlled trials Outcome: BMD vertebral and non-vertebral fractures	Calcium tablets supplementation or usual calcium intake in the diet	Calcium tablet supplementation is associated with a 1.7–2.1% increase in total body, spine, hip or forearm BMD and a trend towards reduction in vertebral fractures
Kim et al. [26]	14,705 participants (5953 men, 4258 premenopausal women, and 4494 postmenopausal women)	Cross-sectional Outcome: BMD	Dietary Calcium based on a 24-h dietary recall	Calcium intake > 400 mg and ≤ 800 mg daily significantly increased BMD in both femoral neck and lumbar spine in both men and postmenopausal women

Table 1 (continued)

Authors/study	Number of participants	Characteristics of study	Type of calcium supplementation	Results
Nelson et al. [27]	36 postmenopausal women	Randomized controlled trial Follow up: 1 year Outcome BMD	Milk supplement, 831 mg/d, vs placebo drink	Femoral-neck BMD increased by 2.0% in women consuming high dietary calcium and decreased by 1.1% in those on moderate calcium intake. No effect on lumbar spine, distal radius, or total body BMD
Reid et al. [28]	122 healthy postmenopausal women	Randomized controlled trialfollow-up: 2 years Outcome: BMD	Calcium tablet supplement (1000 mg per day) or placebo	Calcium supplementation significantly slowed axial and appendicular bone loss in normal post-menopausal women
Chevalley et al. [29]	93 vitamin D replete elderly	Randomized controlled trial Follow up: 18 months Outcome: BMD and vertebral fractures	800 mg/day Calcium tablet supplement	Oral Calcium supplements prevented femoral BMD decrease and lowered vertebral fracture rate in the elderly
Prince et al. [30]	168 postmenopausal women	Randomized controlled trial Follow up: 2 years Outcome: BMD	Placebo versus milk powder containing 1 g of calcium, versus calcium tablets 1 gram daily versus calcium tablets 1 gram daily and an exercise regimen	Calcium tablet and milk powder supplementation resulted in cessation of bone loss at intertrochanteric and trochanteric hip sites. Calcium and exercise group had less bone loss at femoral neck compared to calcium supplementation alone
Bischoff-Ferrari et al. [31]	4958 community-dwelling women and 5003 men ≥ 20 years of age from the U.S. NHANES III population-based survey	Cross-sectional study Outcome: BMD	Diet	Higher calcium intake was significantly associated with higher BMD only for women with low 25(OH)D status (< 50 nmol/L)
Joo et al. [33]	4662 adults (2567 men and 2095 women) ≥ 50 years of age from the 2009–2010 Korea National Health and Nutrition Examination Survey	Cross sectional study Outcome: BMD	Diet	Calcium intake is a significant determinant of serum PTH and femoral neck and lumbar spine BMD at higher as well as lower 25(OH)D levels
Tang et al. [34]	29 RCT in total ($n = 63,897$); adults ≥ 50 years (17 RCT with fracture as an outcome $n = 52\ 625$) (23 RCT with BMD as an outcome, $n = 41,419$)	Meta-analysis Outcome: BMD or fracture	Supplement tablets: Calcium, or calcium in combination with vitamin D	Reduced rate of bone loss at the hip and spine with supplement intake. 12% risk reduction in fractures of all types Fracture risk reduction was significantly greater in trials in which the compliance rate was high Treatment effect was better with calcium doses of ≥ 1200 mg /day and with vitamin D doses of ≥ 800 IU/day

Table 1 (continued)

Authors/study	Number of participants	Characteristics of study	Type of calcium supplementation	Results
Bischoff-Ferrari et al. [35]	170,991 Women (7 prospective cohort studies, 68,606 Men (5 prospective cohort studies) 5666 women and 1074 men (5 randomized controlled trials) and 6504 subjects (randomized controlled trials with separate results for hip fractures)	Systematic review and meta-analysis Outcome: hip and non-vertebral fractures	Diet and calcium tablet supplementation	Neither dietary Calcium intake nor Calcium Supplements significantly associated with hip fracture risk reduction in women or men
Bolland et al. [36]	2 Randomized controlled trials ($n=262$), 44 cohort studies of dietary calcium ($n=37$), milk ($n=14$) or dairy intake ($n=8$) 26 randomized controlled trials ($n=69,107$) with calcium supplements with or without vitamin D	Systematic review Outcome: total, hip, vertebral or forearm fractures	Diet or Calcium tablet supplements with or without vitamin D	No association between dietary calcium intake and risk of any fracture. Calcium supplements reduced risk of total and vertebral fractures but not hip or forearm fractures. In the randomized controlled trials with low risk of bias, no effect of calcium supplements on fracture at any site. Similar results for Calcium alone or calcium plus vitamin D
Weaver et al. [37]	8 Randomized controlled trials (30,970 participants (both community-dwelling and institutionalized middle-aged to older adults)	Meta-analysis Outcome: total and hip fractures	Calcium plus vitamin D tablet supplements	15% reduced risk of total fractures and a 30% reduced risk of hip fractures
Sahni et al. [38]	830 men and women from the Framingham Original Cohort	Prospective cohort study Mean follow-up: 11.6 years Outcome: hip fractures	Diet (Number of servings per week of milk, yogurt, cheese, cream, and milk + yogurt	40% lower risk of incident hip fracture risk in older adults with medium/high milk or milk + yoghurt intake. Effects partially attributed to effect on BMD
Khan et al. [39]	12,097 participants (aged ≥ 50 years) from the Melbourne Collaborative Cohort Study	Prospective cohort study Mean follow-up:12 years Outcome: incident fracture	Diet-Calcium intake from food estimated using a food-frequency questionnaire	Calcium intakes of up to 1348 (316) mg/d from food was associated with decreased risks for incident fracture
Key et al. [40]	26 749 women and 7947 men aged 20–89 years	Prospective cohort study Mean follow-up: 5.2 years Outcome: self-reported fracture	Dietary Calcium intake from food-frequency questionnaire	Women with a low dietary calcium intake had an increased risk of fractures and this association was more marked in younger women below 50 years. No association between dietary calcium intake and fractures in men
Grant et al. [42]	5292 participants aged 70 years or older (4481 [85%] women) with low-trauma fracture	Randomized controlled trial Follow up: 24 to 62 months Outcome: new fracture	Daily oral tablet supplementation of 800 IU vitamin D3 or1000 mg calcium or 800 IU vitamin D3 plus1000 mg or placebo	The incidence of new, low-trauma fractures did not differ significantly between participants allocated the supplements versus those allocated placebo

Table 1 (continued)

Authors/study	Number of participants	Characteristics of study	Type of calcium supplementation	Results
Zhao et al 2017 [43] DIPART [44]	33 randomized trials involving 51,145 community-dwelling adults > 50 years 68,500 subjects from 7 randomized controlled trials; 14.7% men	Systematic review and meta-analysis Outcome: hip Fracture (Primary Outcome) Non-vertebral, vertebral and total fractures (secondary outcome) Individual patient data analysis using pooled data Outcome: any fracture, clinical vertebral fracture and hip fracture	Calcium, vitamin D, or combined calcium and vitamin D tablet supplements with a placebo or no treatment Vitamin D /vitamin D plus Calcium tablet supplements	Use of supplements that included calcium, vitamin D, or both compared with placebo or no treatment was not associated with a lower risk of hip, non-vertebral, vertebral or total fractures among community-dwelling older adults For the combined use of calcium and vitamin D, reduction in all fractures and hip fractures. No significant effects with vitamin D alone
Prince et al. [46]	1460 elderly women >70 years	Randomized controlled trial Follow-up: 5 years Outcome: clinical incident osteoporotic fracture and vertebral deformity BMD by dual-Xray absorptiometry (DXA) of hip and whole body, quantitative ultrasound (QUS) of heel and peripheral quantitative computed tomography (pQCT) of distal radius	Calcium carbonate, tablet supplements 600 mg twice per day, or identical placebo	Calcium supplements did not significantly reduce incident fracture risk except in those who were compliant > 80% of the time. DXA BMD of femoral neck and whole-body and QUS heel was improved with calcium supplements
Jackson et al. [45]	36,282 post-menopausal women, 50 to 79 years of age (from the WHI Dietary Modification trial, WHI Hormone Therapy trials, or both); 2431 women had DXA scans	Randomized controlled trial Follow up:7 years Outcome: BMD, hip fracture, clinical spine fracture, total fracture	1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 tablet supplements daily or placebo	Calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density and in the intention to treat analysis, nonsignificant, (12%) lower risk of hip fracture compared to placebo. No significant reductions in clinical vertebral fracture, fracture of the lower arm or wrist, or total fractures

women, 25(OH)D status appeared to be the dominant predictor of BMD and that higher calcium intake was beneficial only in those women with 25(OH)D concentrations less than 50 nmol/L [31]. In men, there was no association of calcium intake with femoral neck BMD at any serum 25(OH)D concentrations. However, the mean calcium intake in the NHANES III cohort was over 700 mg/d in women and over 800 mg/d in men. These intakes are considerably higher than calcium intakes in many parts of the world, including Asian countries such as China, India, Japan, and Korea [32]. Whether the impact of calcium as shown above to be confined to those with low serum 25(OH)D concentrations, would be similarly restricted in populations with lower mean calcium intakes was explored in a study amongst South Korean adults aged 50 years and older with a mean calcium intake of only 485 mg/day in the Korean National Health and Examination Survey (KNHANES) [33]. In this study when associations of quintiles of calcium intake with bone mineral density (BMD) within three categories of serum 25(OH)D levels: < 50, 50–75, and > 75 nmol/L were explored, within each category of serum 25(OH)D, higher calcium intake was significantly positively associated with BMD of the femoral neck [33]. Within the lower two 25(OH)D categories, calcium intake was positively associated with BMD of the spine. In this low-intake population, calcium intake was found to be a significant determinant of BMD at higher as well as lower 25(OH)D levels. This finding indicates that low calcium intake cannot be compensated for with higher 25(OH)D levels alone. The investigators concluded that a calcium intake of at least 668 mg/d and a serum 25(OH)D level of at least 50 nmol/L may be needed to maintain bone mass in this calcium deficient population.

Effects of dietary calcium and tablet supplementation on fracture risk in the elderly

Though there have been several randomized control trials, systematic reviews and meta-analyses evaluating the benefit of calcium and vitamin D supplementation on osteoporotic fracture risk [34–37] the effectiveness of isolated calcium supplementation in the prevention of these fractures remains controversial. To study the association between dietary intake of calcium and fractures is even more challenging.

Dietary supplementation of calcium and its effect on fracture risk

The optimal amount of calcium needed (if at all there is such) to prevent fractures is not clear. Elderly subjects with higher milk or milk and yoghurt intakes were found to be at lower risk of hip fractures when assessed 10 years later in a subset of men and women from the Framingham Cohort study [38]. In this study, participants with medium (> 1 and < 7 servings/week) or higher (≥ 7 servings/week) milk intake tended to have lower hip fracture risk than those with low (≤ 1 serving/week) intake [38]. It was postulated that this effect was partially mediated by the effect of these dairy products on bone mineral density. A 30% reduced risk of fractures was reported in subjects with the highest quartile of calcium intake when compared to those in the lowest quartile in another study in which participants were drawn from the Melbourne Collaborative Cohort Study [39]. Increased fracture risk has been reported in women with daily calcium intakes less than 525 mg/day [40]. However, this association was more marked in younger women below the age of 50 than in older women and was not noted in men [40] and in a comprehensive systematic review and meta-analysis of studies that explored associations between calcium intake (from diet and/or supplementation) and risk of fracture in participants 50 years of age and older, most reported no associations between milk and dairy intake and fractures [36].

Non-dietary calcium supplementation and its effect on osteoporotic fracture risk

The efficacy of calcium supplementation in the form of tablets in the prevention of osteoporotic fractures remains controversial. In a large meta-analysis of pooled cohort studies and randomized controlled trials that included 170,991 women and 68,606 men, calcium intake was not significantly associated with any reduction in hip fracture risk and in fact, a potentially increased risk of hip fracture with calcium supplementation alone albeit in a relatively low number of participants was seen [35]. In the randomized trials that were included in the analysis there was a neutral effect of calcium supplementation on any non-vertebral fractures [35]. In another meta-analysis of controlled trials that randomized post-menopausal women to calcium supplementation or usual calcium intake and included 1806 participants who were followed for at least 1 year, there was no meaningful reduction in the incidence of non-vertebral fractures despite a notable increase in BMD [41]. The RECORD (Randomised Evaluation of Calcium Or Vitamin D) study which was a secondary prevention trial that evaluated the efficacies of supplementation with calcium, vitamin D or both in the elderly concluded that none of these methods were effective in reducing the risk of secondary low impact fractures [42]. The authors concluded that the findings did not support routine oral supplementation with calcium and vitamin D3, either alone or in combination, for the prevention of further fractures in previously mobile elderly people. Similar findings were noted in a recent meta-analysis in

which it was noted that calcium with or without vitamin D supplementation did not decrease fractures in community dwelling older adults. Neither the incidence of hip, non-vertebral or vertebral or total fractures were lower with calcium supplementation when compared to placebo in this meta-analysis [43]. It has to be noted, however, that in the RECORD study, compliance with the supplements was only moderate with only 63% of study subjects taking the supplements at 2 years [42] and this thus raises questions on the generalizability of the findings noted. The findings from the RECORD study and the meta-analysis mentioned above are contrary to that reported in another meta-analysis in which combined supplementation with calcium and vitamin D resulted in a reduction in the risk of fractures in patients 50 years and older [34]. In this analysis which identified 17 trials reporting fracture as the outcome and included 52,625 subjects, studies of calcium, or calcium and vitamin D, were analysed separately. The majority of patients considered were included in trials of calcium and vitamin D supplementation ($n=46,108$), with only 6517 subjects included in trials of calcium supplementation alone. The relative risk (RR) of any fracture with calcium and vitamin D supplementation was 0.87 (95% CI: 0.77, 0.97), and with calcium alone it was 0.90 (95% CI: 0.80, 1.00), i.e., it was of borderline statistical significance only. In a comprehensive systematic review and meta-analysis of associations between calcium intake (from diet and/or supplementation) and risk of fracture in which 26 trials ($n=69,107$) of calcium supplementation, calcium and vitamin D supplementation or factorial designs using both approaches were identified, calcium supplements reduced the risk of total fracture [RR: 0.89, (95% CI: 0.81,0.96)] and vertebral fracture [RR: 0.86 (95% CI: 0.74, 1.00)], but not hip [RR: 0.95 (95% CI: 0.6,1.18)] or forearm fracture [RR: 0.96 (95% CI: 0.85, 1.09)] [36]. In the 4 randomized controlled trials included in the meta-analysis that had the lowest risk of bias, however, there was no effect of calcium supplementation alone on risk of fracture at any site. The authors concluded that the evidence that calcium supplements prevent fractures is weak and inconsistent [36].

Putting all the evidence together, majority of the randomized controlled trials and cohort studies suggest that the use of calcium in combination with vitamin D supplementation rather than its use as a sole agent may be more efficacious in reducing fracture risk. In an individual patient data (IPD) meta-analysis of seven individual randomized controlled trials with 68,500 subjects drawn from both residential/nursing homes and from the community and with duration of follow-up varying from 18 to 85 months, a modest reduction in all fractures [HR: 0.92 (95% CI: 0.86, 0.99)] and hip fractures [HR: 0.83 (95% CI: 0.69, 0.99) was noted for the combined use of calcium and vitamin D [44].Combined calcium and vitamin D administration was associated with a risk reduction for all fractures [RR: 0.92 (95% CI: 0.86, 0.99)] as well as hip fractures [RR: 0.84 (95% CI: 0.74, 0.96)] in the pooled random effects meta-analysis study described earlier [36]. More than 75% of the participants in the 4 trials that had the least risk of bias included in the above meta-analysis were contributed by the WHI trial where participants were allowed personal consumption of calcium and vitamin D supplements.

Fracture risk reduction with calcium and /or calcium with vitamin D supplementation has been noted to be significantly greater in those trials included in the meta-analysis in which the compliance rate was high. Treatment effect has also been noted to be better with calcium doses of 1200 mg or more than with doses less than 1200 mg and with vitamin D doses of 800 IU or more than with doses less than 800 IU [34]. In the Women's Health Initiative calcium and vitamin D trial, where the adherence was only 59% at the end of the 7 year follow-up, calcium supplementation did not reduce hip fracture rates [45]. However, censoring data from women in the study when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95% CI: 0.52, 0.97) [45]. Reduced risk of osteoporotic fractures and improvements in parameters related to bone density such as quantitative ultrasonography findings of the heel, femoral neck and whole-body dual X-ray absorptiometry data, and bone strength were observed in women who consumed more than 80% of their calcium supplements per year over 5 years compared with placebo-treated patients in a double-blind placebo-controlled trial of elderly women over the age of 70 years [46]. Adherence to the supplements thus appear to play a critical role in the efficacy of calcium supplements with or without vitamin D to reduce osteoporotic fracture risk. It is likely that calcium like vitamin D is a threshold nutrient. Patients who are deficient in the nutrient are at risk and may benefit from supplementation. Nutritional status and supplementation with nutrients including calcium and vitamin D have been shown to be related to outcomes and mortality in older adults with hip fracture who are likely to be deficient in these nutrients [47]. However, patients who have adequate intake of calcium would not benefit from taking calcium supplementation and the efficacy of calcium with or without vitamin D supplementation in healthy postmenopausal women at low risk of fractures is equivocal [45].

An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) concluded that though calcium and vitamin D supplementation leads to a modest reduction in fracture risk, supplementation with calcium alone for fracture reduction is not supported by the literature and that routine supplementation of calcium and vitamin D as a population-level intervention strategy is not recommended [48]. They have, however, opined that it appears reasonable to recommend calcium with concomitant

vitamin D supplementation, for patients at high risk of calcium and vitamin D insufficiency, and in those who are receiving treatment for osteoporosis. This is supported by consensus guidelines as in the European guidance for the diagnosis and management of osteoporosis in postmenopausal women [49].

Calcium supplementation and cardiovascular risk in the elderly

The safety profile of calcium supplementation and its potential effects on especially the cardiovascular system have been of significant concern recently. The link between calcium supplementation and cardiovascular risk is controversial. The controversy started with the publication of a randomized controlled trial in 2008 in which an increased risk of self-reported myocardial infarction that was subsequently adjudicated by review of medical records was noted [RR: 2.24 (95% CI: 1.20, 4.17)] in patients who received calcium citrate supplementation [50]. The composite endpoint of myocardial infarction, stroke or sudden death was also statistically higher in the calcium supplemented group [RR: 1.66 (95% CI: 1.15,2.40)]. It is worth noting that calcium was not administered with vitamin D in this study and that the studied group received high calcium doses (1000 mg/day). This exceeded the RDA when the subjects' average dietary calcium intakes (860 mg/day) was included. The same group of researchers then performed a meta-analysis of 16 studies that evaluated cardiovascular outcomes of patients who received ≥ 500 mg of calcium/day and that had included cardiovascular events obtained from self-reports, hospital admissions, and death certificates. What was found was a statistically significant difference in the incidence of myocardial infarction in the calcium treated group as compared to placebo in both the analysis of patient level data [HR: 1.31(95% CI: 1.02, 1.67, $P = 0.035$)] and in the analysis of trial level data [pooled RR 1.27 (95% CI: 1.01, 1.59, $P = 0.038$)]. There was a statistically significant interaction between treatment and baseline dietary calcium intake [51] with the association between supplemental calcium intake and myocardial infarction stronger when the median calcium intake was more than 825 mg per day. This interaction was observed only for the outcome of myocardial infarction. To counter the criticism that these meta-analyses only evaluated studies with isolated calcium supplementation and to explore further the interaction between treatment and baseline calcium intake, the same investigators extended their original analysis by including a re-analyses of the WHI calcium and vitamin D (WHI CaD) study public access dataset into the meta-analysis with eight other studies [52]. When the analysis was stratified according to personal use of calcium and vitamin D supplements, in those subjects not taking personal supplements at baseline it was found that there was an increased risk of myocardial infarction [RR:1.24 (95% CI: 1.07, 1.45), $p = 0.004$] and the composite of myocardial infarction or stroke [RR: 1.15 (95% CI: 1.03, 1.27, $p = 0.009$]. It must be noted that in the initial meta-analysis by this group, the increased risk of myocardial infarction was seen in those subjects with higher median baseline calcium (though dietary) intake as mentioned earlier whilst in this latter meta-analysis, it was in those who were not taking personal calcium supplements at baseline.

The original randomized controlled trial and the two meta-analysis have come under criticism for several reasons including the heterogeneity of event reporting and multiple end point testing. Other flaws that have been pointed out include the fact that majority of the myocardial infarctions were self-reported, cardiovascular events were not the primary outcome of either the former randomized trial or of the included studies in the meta-analyses, the potentially beneficial effects of supplementation were not emphasized [amongst those who were using personal calcium supplementation in the WHI study, death was actually greater in the placebo group ($p = 0.01$)] and the risk of stroke and the composite outcome of clinical myocardial infarction or stroke were less frequent in those who were taking personal supplements and that in the meta-analyses, studies that did not record myocardial infarction were not included [48, 53, 54]. Notwithstanding the above criticisms, some other studies have also reported an increased MI risk in adult men and women [55] and increased risk of death due to cardiovascular disease in men with calcium supplementation [56, 57].

The relationship between calcium supplementation and CVD risk and the plausible mechanism behind any potential effect of calcium on the cardiovascular system is unclear and tenuous at best. Calcium is not only required for contraction and relaxation of heart muscles, but it also serves as a second messenger in signal transduction pathways of the cardiovascular system. Transient receptor potential vanilloid 2 (TRPV2), a stretch-mediated channel and regulator of calcium homeostasis has been shown to be an important modulator of cardiomyocyte hypertrophy in response to cardiac aging in mice and it may play an important role in humans also [58]. The main hypothesis behind a possible mechanistic link for any deleterious effect of calcium on the cardiovascular system is that an acute elevation in serum calcium levels after supplementation may cause increased vascular resistance, calcification and thrombogenesis [28]. Acute increases in serum calcium have been observed after oral intake of calcium supplements in healthy male volunteers [59]. However, endothelial and myocardial perfusion parameters measured before and 3 h after supplementation with 1000 mg of calcium citrate have shown that arterial constriction decreases and myocardial perfusion increases with elevated serum calcium levels suggesting that it is

unlikely that calcium supplementation is associated with adverse changes in cardiovascular function [60]. Observational studies suggest that serum calcium and/or phosphate concentrations may be related to ischemic cardiac events. However, evidence to suggest a link between serum calcium concentrations and coronary calcification is less clear A sex discordance appears to exist in the association between serum calcium and coronary artery calcification with serum total calcium concentrations positively associated with coronary artery calcification score on CT in men, but not amongst women in one study [61]. However, in another large prospective data base study- the AMORIS Swedish cohort, serum corrected calcium concentrations were associated with increased risk of incident myocardial infarction, non-fatal cardiovascular disease and stroke in women at a greater magnitude than in men [62]. The reason for this apparent conflicting sex discordance is unclear. Serum calcium levels in a multi-ethnic population of older men and women have been found to be associated with carotid plaque thickness; a predictor of clinical coronary and cerebrovascular events [63]. However, reassuringly, no increases in the risk of atherosclerotic plaques or carotid intima-media thickness was seen in elderly women who received calcium supplementation for 3 years in an ancillary study of the CAIFOS randomized controlled trial [64]. Several other studies also confirm this finding with no difference in calcium coronary scores noticed between women who received calcium and vitamin D supplementation for 7 years versus those who did not in the Women's Health Initiative [65] and no increase in calcification noted in the carotid and coronary arteries or abdominal aorta of diabetic patients with either dietary intake or medicinal supplementation of calcium in another study [66]. Though no convincing benefit of either dietary or supplemental calcium intake on blood pressure (another possible ischemic heart disease risk factor) has been observed, there is no evidence of any deleterious effect either [67–71].

In contrast to the studies by Bolland et al. other investigators have failed to find an association between calcium supplementation and myocardial infarction or other cardiovascular complications. Calcium with vitamin D supplementation was shown to neither increase nor decrease coronary or cerebrovascular risk in generally healthy postmenopausal women over a 7-year use period in an initial assessment of the WHI trial in which cardiovascular disease was a prespecified secondary efficacy outcome [72]. It must be noted, however, that subgroup analysis was not performed in this study, and instead subjects who were or were not using personal supplements were analysed together, contrary to Bolland's study that analysed subjects who were not on personal supplementation separately. The WHI study participant data were also re-evaluated with a focus on whether the participants were or were not using calcium supplements at the time of enrolment. No increased risk of myocardial infarction with calcium and vitamin D supplementation in either the entire trial population [HR: 1.03 (95% CI: 0.90, 1.19] or in those who were or were not on personal supplements [HR: 1.11 (95% CI: 0.90, 1.37)] was seen [73]. In an analysis of 20,024 participants of the third National Health and Nutrition Examination Survey (NHANES), no increase in cardiovascular mortality with either dietary or supplemental calcium intake was observed [74]. In a similar meta-analysis to that of Bolland et al. but using only trials in which coronary heart disease end point were validated and used ICD-based definitions, overall there was no effect of calcium or calcium and vitamin D supplementation on myocardial infarction [RR: 1.08 (95% CI: 0.93, 1.25)], angina pectoris [RR: 1.09 (95% CI: 0.95, 1.24)] or chronic heart disease [RR: 0.92 (95% CI: 0.73, 1.15)] was seen [75]. In the UK Biobank; a large prospective cohort comprising 502,637 men and women aged 40–69 years at recruitment, supplementation with calcium/vitamin D was self-reported, and information on incident hospital admission for ischemic heart disease myocardial infarction, and subsequent death was obtained from linkage to national registers. In crude and adjusted analyses, there were no associations between use of calcium supplements and risk of incident hospital admission with either ischemic heart disease or subsequent death. Results were similar for vitamin D and combination supplementation [76].

In summary (Table 2), the evidence for adverse cardiovascular effects with calcium supplementation remains inconclusive. The fact that cardiovascular events were not the primary outcome in any of the studies, were not ascertained and validated homogenously, the interactions between baseline calcium supplement intake and trial medications and the lack of a convincing mechanistic link to explain the adverse outcomes described, all raise doubts on whether truly a detrimental effect of calcium supplementation on the cardiovascular system exists. On the other hand, the signal of an increased risk of myocardial infarction repeatedly seen in several of the studies is not something that can be ignored. A large properly conducted randomized double blinded controlled trial with properly adjudicated and or ascertained cardiovascular end points is needed to convincingly answer this concern though the ethical issues that would surround such a trial would make it problematic to perform it.

Dietary calcium intake and its effect on cardiovascular outcomes in the elderly

There have been several studies that have specifically explored the influence of dietary calcium on cardiovascular outcomes. In the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Heidelberg) where the associations of dietary calcium

Table 2 Relationship between calcium/ calcium and vitamin D supplementation and cardiovascular outcomes

Authors/study	Number of participants	Characteristics of study	Characteristics of participants	Results
Hsia et al. [72]	36,282	Randomized controlled trial Follow-up: 7 years Calcium and vitamin D	50–79 years of age Post-menopausal women from WHI Trial	No association between calcium and vitamin D supplementation and MI risk or stroke
Bolland et al. [50]	1471	Randomized controlled trial Follow-up: 5 years Self-reported events subsequently verified Calcium Only	Post-menopausal women	Positive association between calcium and MI Positive association between calcium and MI + Stroke + Sudden death
Pentti et al. [56]	10,555	Prospective cohort study Mean Follow up: 7 years Calcium or Calcium + vitamin D	52–62 years of age Women without CHD at baseline	Positive correlation between calcium/vitamin D supplementation and CHD
Bolland et al. [51]	8151 individual patient data (IPD) 6116 (trial level)	IPD and trial level meta-analysis Events self- reported/hospital Admissions/death certificate calcium only	Men and women > 40 years of age	IPD: positive association between calcium and MI Trial level: positive association between calcium and MI No association between calcium and MI + stroke + sudden death in either IPD or trial level analysis
Bolland et al. [52]	28,072 (trial level)	Trial level meta-analysis of 9 RCT including participants of the WHI trial not taking personal supplements at baseline Calcium/calcium and vitamin D	Post-menopausal women	Positive association between calcium/calcium and vitamin D and MI and MI + stroke
Lewis et al. [64]	1460	Randomized controlled trial Follow-up: 3 years calcium only	Women 75+/-2.7 years	No association between calcium supplementation and carotid atherosclerosis
Li et al [55]	23,980	Prospective cohort study Mean follow-up: 11 years Dietary calcium and calcium supplementation	35–64 years Women and Men without major CVD events	Positive association between calcium supplements and MI
Prentice et al. [73]	46,892	Combined analysis of the WHI prospective randomized controlled trial and prospective observational study Calcium and vitamin D	Post-menopausal women 50–79 years	No association between calcium and vitamin D and MI, CHD, total heart disease, stroke or overall cardiovascular disease
Van Hemelrijck et al. [74]	18,714	Mortality linkage study Dietary calcium and calcium supplements	NHANES III participants Women and men 17 years of age and older	No association between calcium supplementation and CVD death

Table 2 (continued)

Authors/study	Number of participants	Characteristics of study	Characteristics of participants	Results
Xiao et al. [57]	388,229	Prospective cohort study Mean follow-up 12 years Dietary calcium and calcium supplements	Women and men 50–71 years of age from the National Institutes of Health-AARP Diet and Health Study	Positive association between calcium supplementation and cardiovascular death and heart disease death in men No association between calcium supplementation and cardiovascular/ heart disease or cerebrovascular disease death in women
Lewis et al. [75]	48,460	Trial-level meta-analysis All verified events Calcium/calcium and vitamin D	Women more than 50 years of age	No association between Ca/Ca and Vitamin D and MI, Angina/Acute Coronary Syndrome, chronic CAD or all-cause mortality
Harvey et al. [76]	475,255	Prospective population-based cohort Mean follow-up: 7 years Information on incident hospital admission for ischemic heart disease, myocardial infarction and death obtained from linkage to national registers Calcium/vitamin D/ Calcium + Vitamin D supplements	Men and women (55.8%) 40–69 years of age from the UK Biobank Cohort	No associations between use of calcium / vitamin D/ calcium plus vitamin D supplements and risk of incident hospital admission or with either IHD, or subsequent death

intake and calcium supplementation with MI and stroke risk and overall CVD mortality was assessed, compared with the lowest quartile, the third quartile of total dietary and dairy calcium intake had a significantly reduced MI risk with a HR of 0.69 (95% CI 0.50, 0.94) and 0.68 (95% CI 0.50, 0.93) respectively while only users of calcium supplement had a pronounced increase in MI risk [55]. Associations for stroke risk and CVD mortality were overall null with the dietary intake group. The authors surmised that though increasing calcium intake from the diet may not confer significant cardiovascular benefit, calcium from supplements may raise MI risk. It has to be noted, however, that this was a prospective cohort study and there were only 7 cases of myocardial infarctions in the calcium supplement only group [55]. The highest quartile (median of 1348 mg/day) of dietary calcium intake when compared to the lowest quartile (473 mg/day) was associated with a lower risk of non-fatal CVD [OR: 0.84 (95% CI 0.70, 0.99, $p = 0.04$)] and all-cause mortality [HR: 0.86 (95% ci [CI] 0.76–0.98, $p = 0.01$); in the population-based prospective Melbourne Collaborative Cohort Study [39]. A potential benefit of dietary rather than medicinal supplementation, is the minimization of the transient abrupt increases in serum calcium that has been described in patients taking calcium supplements [60] and what has been hypothesized to be the cause of increased cardiovascular risk in the latter group of patients.

Calcium intake and mortality in the elderly

Reassuringly, no study to date has demonstrated an association between supplemental calcium intake and increased mortality. In the meta-analysis by Bolland et al. that included the WHI CaD study, no effect on mortality was noted amongst the participants not using calcium/vitamin D personal supplementation [RR: 0.99 (95% CI: 0.86, 1.14)] and in those using personal supplementation at baseline, in fact a reduced risk of death [RR:0.84 (95% CI: 0.73, 0.97)] was seen [52]. In another meta-analysis of randomized controlled trials in which seventeen trials contributed all-cause mortality data, the pooled relative risk of mortality was 0.96 (95% CI: 0.91, 1.02; $p = 0.18$) [75] providing reassuring evidence that calcium with or without vitamin D supplementation does not appear to increase mortality risk in elderly individuals. In a study using pooled data from randomized controlled trials to assess mortality amongst participants assigned to vitamin D alone or vitamin D with calcium, when individual patient data (IPD) and trial level meta-analyses were performed, risk of death was reduced if vitamin D was given with calcium (HR: 0.91; 95% CI, 0.84, 0.98) in the IPD analysis while vitamin D alone did not reduce this risk [77]. Trial level meta-analysis (24 trials with 88,097 participants) also showed similar results, i.e.,

mortality was reduced with vitamin D plus calcium (odds ratio, 0.94; 95% CI, 0.88, 0.99), but not with vitamin D alone [OR: 0.98 (95% CI: 0.91, 1.06)] [77].

Dietary calcium intake and its effect on mortality

A study done in Sweden on two large cohorts, one with 61,433 women (39–74 years at baseline) and one with 45,339 men (45–79 years at baseline) had shown an association between dietary and total calcium intake and mortality from all causes, cardiovascular disease and ischemic heart disease, but not from stoke [adjusted hazard ratio of all-cause mortality 1.15 (95% CI: 1.13, 1.17) in women and 1.03 (95% CI: 1.01, 1.04) in men] [78]. It was cautioned that the observational study designs with the inherent possibility of residual confounding and reverse causation phenomena were likely responsible for this unexpected finding. In another Swedish cohort study, intakes of nonfermented milk and butter were found to be associated with higher all-cause mortality, and fermented milk and cheese intakes associated with lower all-cause mortality [79]. To shed more light on these findings a recent random-effect meta-analyses performed that included 29 cohort studies with 938,465 participants for total dairy (high and low fat), milk, fermented dairy, cheese and yoghurt was performed [80]. No associations were found for total dairy and milk with any of the outcomes of mortality, coronary heart disease or cardiovascular disease. A marginally inverse association of fermented dairy and cheese with mortality and CVD risk was attenuated in sensitivity analysis, and therefore, the investigators surmised that dairy products had no significant association with cardiovascular and all-cause mortality.

Defining recommendations for calcium intake in the elderly

In 2011, the Institute of Medicine (IOM), USA published Dietary Reference Intakes (DRIs) for calcium [81]. The IOM used evidence for skeletal health outcomes for basing the reference values for adequacy for calcium as well as vitamin D. Most of the evidence for the recommendations were derived from single dose studies and hence, a dose–response relationship for calcium was not elucidated. Discriminating the effect of calcium alone was not completely possible with the available data since in most of the studies, calcium and vitamin D were co-administered. There was also not enough data to recommend different calcium requirements for different ethnicities. The basis for the recommendation was derived from data obtained from 19 feeding studies undertaken by the USDA (US Department of Agriculture) in 155 American non-pregnant women and men between the ages of 20–75 years and who had daily calcium intakes of 415–1740 mg [10]. An intake of 741 mg/day was found to be sufficient in this analysis to achieve a neutral calcium balance [10]. This value was approximated to 800 mg /day and adopted as the estimated average requirement (EAR - corresponding to the median need of the population) for males above the age of 50 by the IOM, while the upper limit of the 95% prediction interval (1035 mg/day) was rounded to 1000 mg/day and adopted as the estimated average requirements for women above the age of 50. An additional 200 mg/day as extra allowance was given and the total adopted as the recommended dietary allowance (RDA) in men and women between the ages of 51–70 since this would cover the needs of 97.5% or more of the population (corresponding to two standard deviations above the EAR). Therefore, the RDA for men and women between the ages of 51–70 were set at 1000 mg/day and 1200 mg/day respectively. For adults above 70 years (both men and women), levels of 1000 mg/day were arbitrarily adopted as EAR, and therefore, 1200 mg/day was set as the RDA.

Despite these recommendations, it is well known that the intake of dietary calcium varies widely geographically. Across 74 countries that had data and from which studies were included in a systematic review that drew attention to regions where calcium intake needs to be assessed, it was shown that average national dietary calcium intake ranges from 175 to 1233 mg/day. This review formed the basis for the development of the International Osteoporosis Foundation's Global Calcium Map (https://www.iofbonehealth.org/facts-and-statistics/calcium-map). This map reveals that many countries in Asia have average dietary calcium intake less than 500 mg/day. Countries in Africa and South America mostly have low calcium intake between about 400 and 700 mg/day. Only Northern European countries have national calcium intake averaging greater than 1000 mg/day [32]. This observation could have important implications. Amongst populations such as Caucasians who are at higher risk for osteoporotic fractures, habitual calcium intakes below the UK and EU lower reference value of 400 m/day may be associated with an increased risk of these fractures. In studies from the USA, Italy, UK and Hong Kong, it has been shown that where average dietary intake is low, the risk of hip fracture increases at intakes below the average, but there is no continued risk reduction at intakes higher than the average. In those countries with higher average intakes, there is no evidence of a gradient of fracture risk with calcium intake [82].

Customary dietary calcium intake may also have a bearing on the purported adverse cardiovascular effects of calcium supplementation. As noted previously, in the original randomized controlled trial performed by Bolland et al. [50] the studied group receiving a supplemental intake of

1000 mg of calcium per day had an average dietary calcium intake of 860 mg/day. Whether the same findings would be seen in populations where the customary dietary calcium is much lower is a matter that needs to be elucidated further.

Conclusion

There is no doubt that calcium plays a vital role in human musculoskeletal health. Adequate calcium intake during childhood is essential to achieve optimal peak bone mass and this has the potential by increasing bone reserves to modulate the rate of age-associated bone loss. Although routine supplementation of calcium and vitamin D as a population-level intervention strategy is not recommended based on the evidence, prescribing calcium and vitamin D supplementation only to those individuals who would benefit from such treatment, i.e., those who are at high risk for osteoporosis and fragility fractures and in those who cannot achieve recommended daily requirements appears to be a sensible approach. Dietary intake of calcium has so far not exhibited deleterious cardiovascular effects and intakes as per national guidelines should be followed. The attribution of increased cardiovascular risk to calcium supplement use appears to be restricted to a few studies and they are not convincingly supported by most others. Neither do the plausible mechanisms that are purported to account for the deleterious effects of calcium supplementation on cardiovascular health hold up to rigorous scrutiny. Further studies aimed at assessing the risk–benefit ratios of calcium supplementation in different populations and to delineate the differences in efficiencies in fractional absorption of calcium between different ethnicities and whether this would have a bearing on recommended daily requirements is also essential.

Compliance with ethical standards

Conflict of interest Manju Chandran, Donovan Tay and Ambrish Mithal do not have any Conflicts of interest or disclosures.

Statement of human and animal rights This is a review article and none of the authors have performed any studies with human or animal participants for it.

Informed consent This is a review paper and does not require informed consent.

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