REVIEW

Cardiovascular safety of calcium, magnesium and strontium: what does the evidence say?

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Abstract

Calcium, magnesium and strontium have all been implicated in both musculoskeletal and cardiovascular health and disease. However, despite these three elements being closely chemically related, there is marked heterogeneity of their characteristics in relation to cardiovascular outcomes. In this narrative review, we describe the relevant evidential landscape, focusing on clinical trials where possible and incorporating findings from observational and causal analyses, to discern the relative roles of these elements in musculoskeletal and cardiovascular health. We conclude that calcium supplementation (for bone health) is most appropriately used in combination with vitamin D supplementation and targeted to those who are deficient in these nutrients, or in combination with antiosteoporosis medications. Whilst calcium supplementation is associated with gastrointestinal side effects and a small increased risk of renal stones, purported links with cardiovascular outcomes remain unconvincing. In normal physiology, no mechanism for an association has been elucidated and other considerations such as dose response and temporal relationships do not support a causal relationship. There is little evidence to support routine magnesium supplementation for musculoskeletal outcomes; greater dietary intake and serum concentrations appear protective against cardiovascular events. Strontium ranelate, which is now available again as a generic medication, has clear anti-fracture efficacy but is associated with an increased risk of thromboembolic disease. Whilst a signal for increased risk of myocardial infarction has been detected in some studies, this is not supported by wider analyses. Strontium ranelate, under its current licence, thus provides a useful therapeutic option for severe osteoporosis in those who do not have cardiovascular risk factors.

Keywords Osteoporosis · Epidemiology · Calcium · Magnesium · Strontium · Cardiovascular

Introduction

That the cardiovascular safety of calcium, magnesium and strontium is under consideration might indicate concerns across this particular section of the periodic table. The reality is that the cardiovascular associations of these three elements are markedly heterogeneous, as is their use in medicine. Calcium is perhaps the most studied, with evidence for modest efficacy in terms of fracture risk reduction when taken with vitamin D supplementation [1]; evidence over the last 5 years has suggested associations between calcium or calcium/vitamin D supplementation and increased cardiovascular risk [1]. However, the links are far from conclusive, with other studies demonstrating no association; key considerations such as a potential mechanism remain to be delineated [1]. Magnesium has little evidential support in terms of fracture prevention, although is often sold as a component of bone health nutritional supplements [2, 3]; greater dietary intake and serum concentrations appear to be protective for cardiovascular outcomes [4–7]. Strontium has been used in the form of strontium ranelate as a therapy for osteoporosis [8]. Whilst it has efficacy for vertebral and non-vertebral fractures, initial trials demonstrated an increased risk of thromboembolic disease [9, 10]. In post-marketing data, a signal for increased risk of myocardial infarction led

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the European Medicines Agency to change to its indication [11], and the drug was subsequently withdrawn from the market by the manufacturer, only to reappear as a generic more recently. In this narrative review, we explore this heterogeneous landscape, focusing principally on the cardiovascular safety of calcium supplementation, together with newer evidence around potential mechanisms, and appraise the evidence for links between magnesium salts or strontium ranelate and cardiovascular disease.

Calcium

Background

Whilst dietary calcium intake and endogenous vitamin D synthesis are sufficient for most individuals in many populations, there is evidence that supplemental approaches [12–16], particularly targeted to individuals with inadequate calcium and vitamin D status, may benefit bone mass and reduce fracture risk. In recent years, the role of calcium, together with that of concomitant vitamin D supplementation, has come under close scrutiny as a result of studies suggesting potential adverse cardiovascular effects from calcium or calcium and vitamin D supplementation [1].

Calcium, bone health and fracture risk

Although several studies, at least in the short term, have indicated positive effects of calcium supplementation on bone mineral density [17–20], the key outcome in terms of effectiveness is fracture reduction. There have been many randomised controlled trials of either calcium alone or calcium in combination with vitamin D for fracture reduction and several subsequent meta-analyses seeking to elucidate the overall effect of this intervention [21–25]. Furthermore, the vast majority of antiosteoporosis treatments have been licensed in the context of calcium and vitamin D repletion, most usually achieved with supplementation [26]. Taken as a whole the evidence base thus supports the use of calcium in combination with vitamin D supplementation rather than as the sole agent for reduction of fracture risk, but with the magnitude of effect being modest. However, efficacy has not been demonstrated for all individual fracture types, or for calcium supplementation alone. Intervention is probably best directed, therefore, at those judged to be at high risk of calcium/ vitamin D deficiency. How this high-risk population may be defined is much debated, and the reader is referred to the guidance from the US Institute of Medicine [27]. The role of routine calcium and vitamin D supplementation as a population health strategy for fracture prevention is not robustly supported.

Calcium supplementation, renal stones and gastrointestinal side effects

Until the BMJ publication by Bolland et al. in 2008 [28], the only potential adverse effects associated with calcium and vitamin D supplementation had been an increased risk of renal calculi and gastrointestinal symptoms. Indeed, a 2014 Cochrane review has confirmed the modest increase in renal stone risk [29], which is mainly informed by data from the Women's Health Initiative, demonstrating that the intervention was associated with a 17% increased risk of renal stones (HR 95% CI: 1.02, 1.34). It is important to note the magnitude of this outcome in the context of the WHI study, given that there was no statistically significant decrease in hip or other fractures. The WHI investigators also examined the risk of renal stones, stratified by use of personal calcium and vitamin D supplements at baseline and adherence to study medication [30]. In the subset who did not use personal supplements, the hazard ratio for renal stones with calcium and vitamin D supplementation was 1.08 (95% CI: 0.88, 1.32); in the subset who did use personal supplements, the hazard ratio was 1.23 (95% CI: 1.01, 1.48), although the interaction term was not statistically significant. Within the personal supplements group, there was no difference in the hazard ratio for renal stones by adherence.

Gastrointestinal side effects have been relatively commonly noted in trials of calcium supplementation. Symptoms include constipation, excessive abdominal cramping, bloating, and, importantly, upper GI symptoms. Lewis et al. [31] reviewed the risk of GI side effects across seven studies included in the Bolland et al. 2010 meta-analysis [32], and in which myocardial infarction was self-reported. Overall, the risk of GI side effects was increased by 43% in the calcium/calcium and vitamin D groups [RR: 1.43 (95% CI: 1.28, 1.59); $p < 0.001$]. The authors did not identify any effect of the formulation or dose of the calcium supplement, but did find evidence of both upper and lower GI events being increased. Using the adjudicated hospital admissions for GI complaints derived from hospital discharge summaries in one Australian study, 6.8% of calcium-treated patients experienced a GI complaint ($n = 50$) compared with 3.6% ($n = 26$) allocated to placebo [RR: 1.92 (95% CI: 1.21, 3.05); $p = 0.006$]. Thus it is clear that gastrointestinal side effects are an important consideration in any strategy predicated on widespread use of calcium supplements. Importantly, the authors hypothesised that self-reported myocardial infarction may, in some cases, represent misclassified gastrointestinal events, an effect

demonstrable in the calcium only trials of Bolland et al. [28], and Prince et al. [33].

## Potential cardiovascular effects of calcium supplementation: initial evidence

In their 2008 BMJ paper Bolland et al. reported the adverse event follow-up from a New Zealand randomised controlled trial of calcium supplementation (without vitamin D) [28]. Amongst 1471 postmenopausal women with a mean age of 74 years, who had been randomised to either 1 g of elemental calcium citrate or placebo, incident cardiovascular events were self-reported, and adjudicated by review of medical records. The authors analysed the events in terms of simple self-report, adjudicated self-report, and then adjudicated events with additional (non-participant reported) events from Health Registry data. A further regression analysis adjusted for covariates. A more detailed examination of the study is presented in [1]. The multiplicity of endpoints provided heterogeneous results [28], and it was notable that the baseline characteristics of the participants appeared to tend towards greater cardiovascular risk in the treatment than placebo group. The message of increased cardiovascular risk from calcium supplementation that was widely taken from this paper rests very much on the analysis of self-reported events, which were not the primary outcomes of the study. Indeed the findings were not supported by the further analysis reported in the manuscript, points which seem to be have been largely ignored in its interpretation.

Cardiovascular outcomes in meta-analyses of calcium/vitamin D supplementation

This initial paper was followed by a meta-analysis of randomised trials of calcium supplementation [32] combining 8151 persons in a patient level analysis, in which the RECORD study provided two-thirds of the cases and two-thirds of the myocardial infarction events (Fig. 1a). Second, the authors undertook a trial level analysis of 11,921 participants, the RECORD study providing 44% of the cases and 55% of the myocardial infarction events. In the patient level analysis, there was weak evidence of an increased risk

Fig. 1 **a** Calcium supplementation and risk of myocardial infarction, with outcomes from self-report and/or verified sources. Reproduced with permission from Bolland et al., 2010 [32]. **b** Calcium and vitamin D supplementation and risk of myocardial infarction, with the outcome ascertained from self-report and/or verified sources. Reproduced with permission from Bolland et al., 2011 [121]
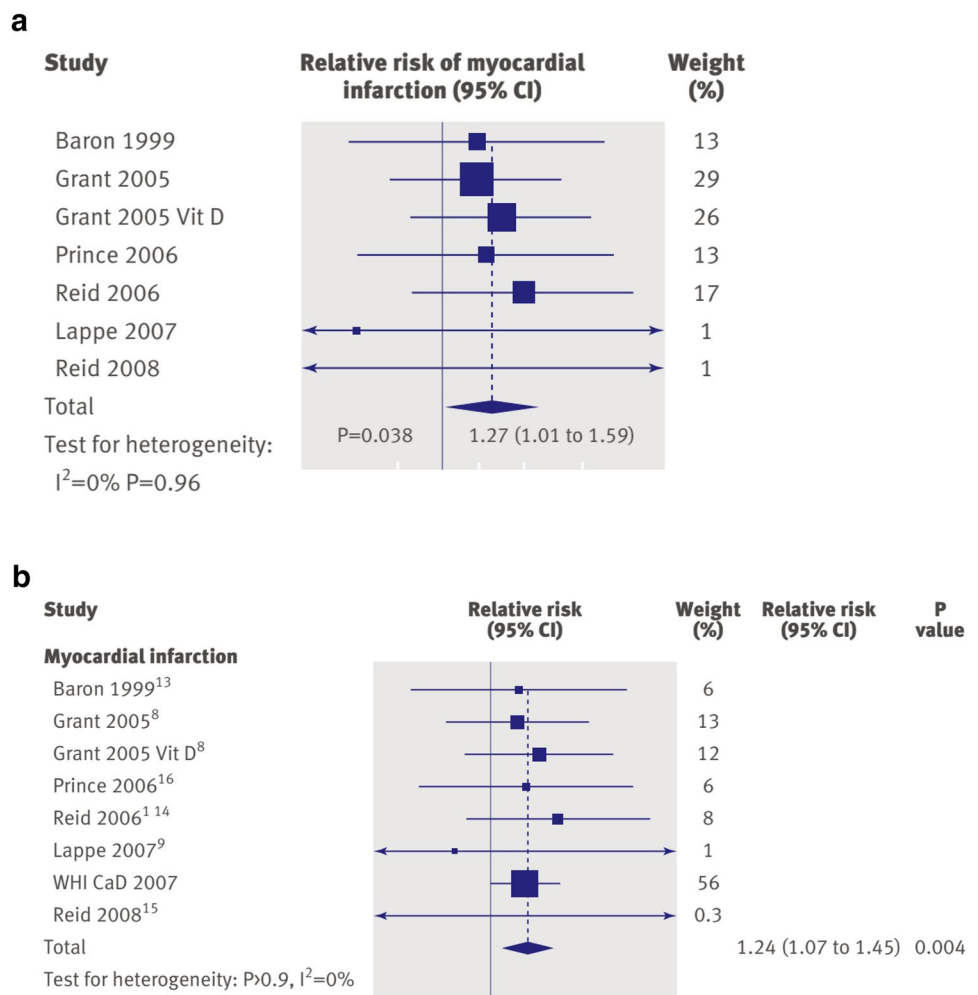
of myocardial infarction [HR: 1.31 (95% CI: 1.02, 1.67); $p = 0.035$] but not of stroke or death, or of the composite outcome including all three [HR: 1.18 (95% CI: 1.00, 1.39); $p = 0.057$]. There was evidence of an interaction between treatment and baseline dietary calcium intake, which was only observed for the outcome of myocardial infarction. Thus the treatment myocardial infarction association appeared to be stronger above than below the median calcium intake of 825 mg per day, but there was no similar interaction for the other outcomes; there was no consistent increase in the hazard ratio for myocardial infarction associated with calcium supplementation by fifths of dietary calcium intake. In the trial level analysis, differences were similar but even smaller [myocardial infarction, HR: 1.27 (95% CI: 1.01, 1.59); $p = 0.038$; and composite end point, HR: 1.12 (95% CI: 0.97, 1.30); $p = 0.13$]. Although all events were adjudicated blind by the investigators, the included studies recorded cardiovascular outcomes in different ways with some using self-report (including RECORD), some hospital records and some death certificates.

The suggestion of an interaction between treatment and baseline calcium intake is intriguing given findings from a re-analysis of the WHI study, undertaken by the same group, Bolland et al., in 2011. They also included the WHI study in their second meta-analysis, investigating both calcium and vitamin D supplementation [34]. In this paper the authors used the WHI calcium and vitamin D study public access dataset to investigate the effect of calcium and vitamin D supplementation versus placebo in 36,282 community dwelling postmenopausal women. The WHI allowed women to take personal calcium and vitamin D supplementation in addition to the study medication, and the authors reasonably hypothesised that this might modify the effect of the trial medication. They, therefore, stratified their analysis by personal calcium and vitamin D supplementation and found that there was evidence of an interaction between personal use of supplements and allocation to calcium and vitamin D or placebo for cardiovascular events. However, the importance of this interaction is uncertain, given the lack of any clear associations in either stratum, and no real evidence of a differential pattern of relationships. There was weak evidence of an association between supplementation and clinical myocardial infarction or re-vascularisation in the group who did not use personal calcium supplementation, but there was no difference in death from all causes. Amongst those who were using personal calcium supplementation, death from all causes was actually greater in the placebo group, and both stroke and the composite outcome of clinical myocardial infarction or stroke appeared, if anything, less frequent in those allocated to calcium and vitamin D who were taking personal supplements [calcium and vitamin D group 4.8% versus placebo 5.5%, HR 0.88 (95% CI: 0.76, 1.02); $p = 0.006$]. Critically, in terms of the requirements to
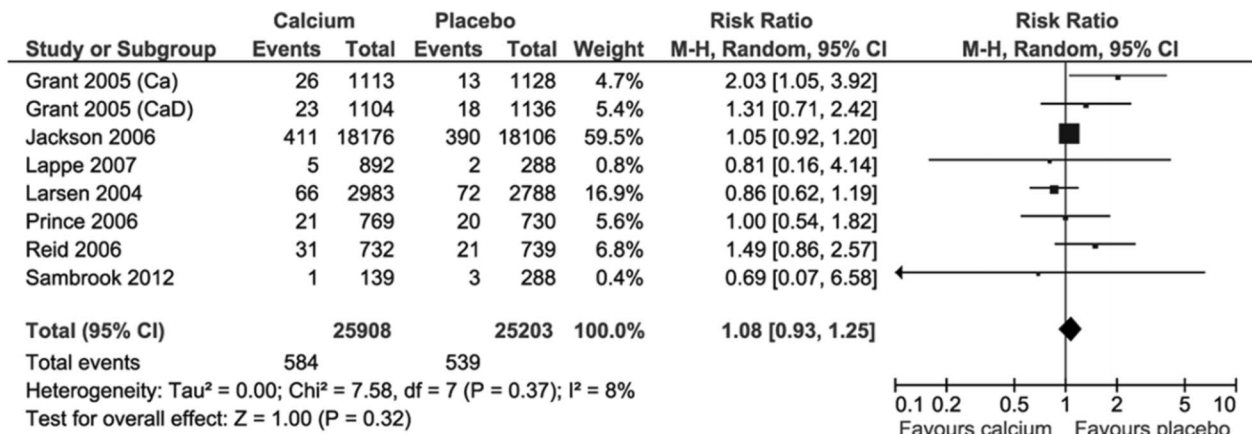
establish a casual relationship, there was no evidence of a dose effect according to personal calcium supplementation ranging from 0 to above 1000 mg per day.

The addition of the WHI data into a trial level meta-analysis with two other studies of calcium and vitamin D demonstrated a 21% increased risk of myocardial infarction (Fig. 1b) with calcium and vitamin D supplementation (RR 95% CI: 1.01, 1.44; $p = 0.04$) with a similar but borderline difference in stroke ($p = 0.05$) and a statistically significant increase for the combination of the two outcomes [RR: 1.16 (95% CI: 1.02, 1.32); $p = 0.02$]. Findings from a patient level data meta-analysis including 24,869 participants from five trials of calcium/ vitamin D supplementation, and the WHI calcium and vitamin D study participants who were not taking personal supplements at baseline, demonstrated an increased risk of myocardial infarction [HR: 1.26 (95% CI: 1.07, 1.47); $p = 0.005$] and stroke [HR: 1.19 (95% CI: 1.02, 1.39); $p = 0.03$] and the combined outcome, but not for death from any cause ($p = 0.5$) [34].

These two meta-analyses and the original study come with a number of concerns, including the heterogeneity of event reporting, that cardiovascular events were not the primary outcome of any included study, that the majority of findings demonstrate weak associations at best, that potentially beneficial effects of similar magnitude have not been emphasised, and that the issue of correction for multiple testing in the secondary analyses has also not been adequately addressed. The lack of dose–response in relation to baseline intake in the WHI study, and the suggestion of opposing effects of baseline dietary intake in the first meta-analysis and personal supplementary intake in WHI are also troubling, as it is difficult to envisage a biological mechanism whereby such a difference could occur.

Lewis et al. recently undertook a similar meta-analysis to those of Bolland et al., combining trial level data on 63,563 female participants, obtained from published and unpublished results [35], summarised in Fig. 2. The authors focused on women as there are insufficient men in the original trials to form valid conclusions, and the greater rates of cardiovascular events in men than women may lead to erroneous conclusions if randomisation to calcium/placebo is not balanced by sex. The authors also used only trials in which coronary heart disease endpoints were validated and used ICD-based definitions which are globally recognised and encompass different components of coronary heart disease. Given the risk of gastrointestinal side effects with calcium supplements, and that these may be misclassified as cardiovascular events (see above) [31], such adjudication is essential. Furthermore, previous assessments of the validity of self-reported cardiovascular events have demonstrated that confirmation may only be achieved in 60–70% of cases [36, 37]. Bolland et al. also undertook an analysis excluding self-reported outcomes (i.e. limiting the analysis to validated

a myocardial infarction

Study or Subgroup	Calcium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	26	1113	13	1128	4.7%	2.03 [1.05, 3.92]
Grant 2005 (CaD)	23	1104	18	1136	5.4%	1.31 [0.71, 2.42]
Jackson 2006	411	18176	390	18106	59.5%	1.05 [0.92, 1.20]
Lappe 2007	5	892	2	288	0.8%	0.81 [0.16, 4.14]
Larsen 2004	66	2983	72	2788	16.9%	0.86 [0.62, 1.19]
Prince 2006	21	769	20	730	5.6%	1.00 [0.54, 1.82]
Reid 2006	31	732	21	739	6.8%	1.49 [0.86, 2.57]
Sambrook 2012	1	139	3	288	0.4%	0.69 [0.07, 6.58]
Total (95% CI)		25908		25203	100.0%	1.08 [0.93, 1.25]
Total events	584		539			

Heterogeneity: Tau² = 0.00; Chi² = 7.58, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.00 (P = 0.32)

b coronary heart disease

Study or Subgroup	Calcium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	39	1113	31	1128	2.0%	1.28 [0.80, 2.03]
Grant 2005 (CaD)	39	1104	39	1136	2.2%	1.03 [0.67, 1.59]
Jackson 2006	1405	18176	1363	18106	82.0%	1.03 [0.96, 1.10]
Larsen 2004	166	2983	169	2788	9.7%	0.92 [0.75, 1.13]
Prince 2006	64	769	60	730	3.7%	1.01 [0.72, 1.42]
Sambrook 2012	7	139	8	288	0.4%	1.81 [0.67, 4.90]
Total (95% CI)		24284		24176	100.0%	1.02 [0.96, 1.09]
Total events	1720		1670			

Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 5 (P = 0.67); I² = 0%
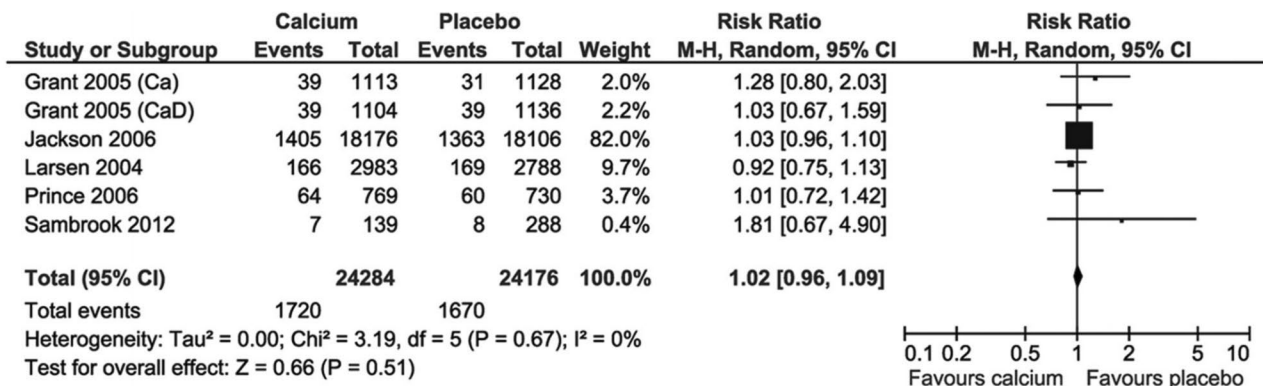Test for overall effect: Z = 0.66 (P = 0.51)

Fig. 2 Calcium supplementation with or without vitamin D supplementation and risk of (**a**) myocardial infarction and (**b**) coronary heart disease: random-effects meta-analysis of validated outcomes in women. Reproduced with permission from Lewis et al., 2015 [35]. (**a**) myocardial infarction (**b**) coronary heart disease

myocardial infarction [38]. Although these results were similar to those from the 2010 meta-analysis (in which 23% of events were ascertained by self-report) [32], it is unclear in this secondary analysis, published in a review article, as to exactly which trials were included in which analysis. In the Lewis study, overall there was no effect of calcium/calcium and vitamin D supplementation on myocardial infarction [RR: 1.08 (95% CI: 0.93, 1.25)], angina pectoris/acute coronary syndrome [RR: 1.09 (95% CI: 0.95, 1.24)] or chronic coronary heart disease [RR: 0.92 (95% CI: 0.73, 1.15)]. In sensitivity analyses, the investigators observed no relationship between supplementation with calcium/ calcium and vitamin D and coronary heart disease or all-cause mortality. However, supplementation with calcium alone was weakly positively associated with myocardial infarction [RR: 1.37 (95% CI: 0.98, 1.92), $p = 0.07$], but it should be noted that

the analysis was based on 139 myocardial infarctions in 6333 participants compared with estimates of the effect of calcium with vitamin D based on 1006 events in 45,796 participants. This meta-analysis, unlike the Bolland meta-analyses, included a cluster randomised trial by Larsen et al. [39] However, further sensitivity analyses demonstrated no difference in the findings when cluster randomised trials were excluded. Whilst the authors did not specifically test for an interaction with personal calcium and vitamin D supplement use in the WHI study, a sensitivity analysis in which the WHI participants using personal supplementation at baseline were excluded yielded very similar results overall. This meta-analysis, therefore, does not support the finding from Bolland et al. of a specific effect within those not taking personal calcium and vitamin D supplementation. Whilst the findings of the Lewis et al. meta-analysis are

largely reassuring, the weak association for calcium supplementation alone for myocardial infarction should be noted, albeit based on a subgroup with a relatively small number of events, and no consistent effect on coronary heart disease or mortality. Furthermore, none of the meta-analyses have been able to address the associations in men, due to the small number of males in the constituent trials.

The WHI study has been analysed by its own investigators who, in an initial follow-up 8 years from randomisation found no increased risk of myocardial infarction/coronary death or stroke with hazard ratios near one [40]. A comprehensive subgroup analysis demonstrated no increases in cardiovascular events with supplementation [30]. Importantly in this study by Prentice et al., the analysis was stratified by use of personal supplementation. There was no increased risk of myocardial infarction with calcium and vitamin D supplementation in either the whole trial population [HR: 1.03 (95% CI: 0.90, 1.19)], in those who took personal supplements [HR: 0.97 (95% CI: 0.80, 1.17)] or in those who took no personal supplementation [HR: 1.11 (95% CI: 0.90, 1.37)], and no statistically significant difference in the hazard ratios between the strata. Interestingly, the risk of myocardial infarction, coronary heart disease and other outcomes was analysed by time from randomisation, with no evidence of any statistically significant change in the hazard ratio with increasing follow-up time. Although the hazard ratios for myocardial infarction within the first 2 years after randomisation were greater than unity within all participants [HR: 1.19 (95% CI: 0.89, 1.59)] and amongst those who did not take personal supplements [HR: 1.30 (95% CI: 0.86, 1.97)], these were not statistically significant, and

over years 2–5, the hazard ratios were close to unity [all participants HR: 0.97 (95% CI: 0.78, 1.21); no personal supplements, HR 1.04 (95% CI: 0.74, 1.47)], with a similar null relationships at > 5 years follow-up. Although clearly limited by variable adherence to medication over the study period, this absence of any time relationship (if anything, there was a decreasing risk with time) with myocardial infarction or other coronary outcomes seems incompatible with any biological mechanism which requires increase in coronary atherosclerosis related to raised calcium concentrations. A further follow-up at up to 5 years after cessation of trial medication again provided reassuring results, finding no difference in coronary heart disease endpoints over 15 years of follow-up in 29,862 women [41], although this was not stratified by use of personal supplements.

Several other meta-analyses have been undertaken, but since the underlying evidence base is essentially very similar in all such studies, they remain very much variations upon a theme [42–45]. A limitation of the randomised trial evidence is the low number of men contributing to the trial populations. However, the largest observational study to date comprising over 500,000 men and women in the UK Biobank cohort (Fig. 3), again demonstrated no association between either calcium supplementation, vitamin D supplementation or both with incident ischaemic heart disease, cardiovascular disease myocardial infarction or cardiovascular death [46].
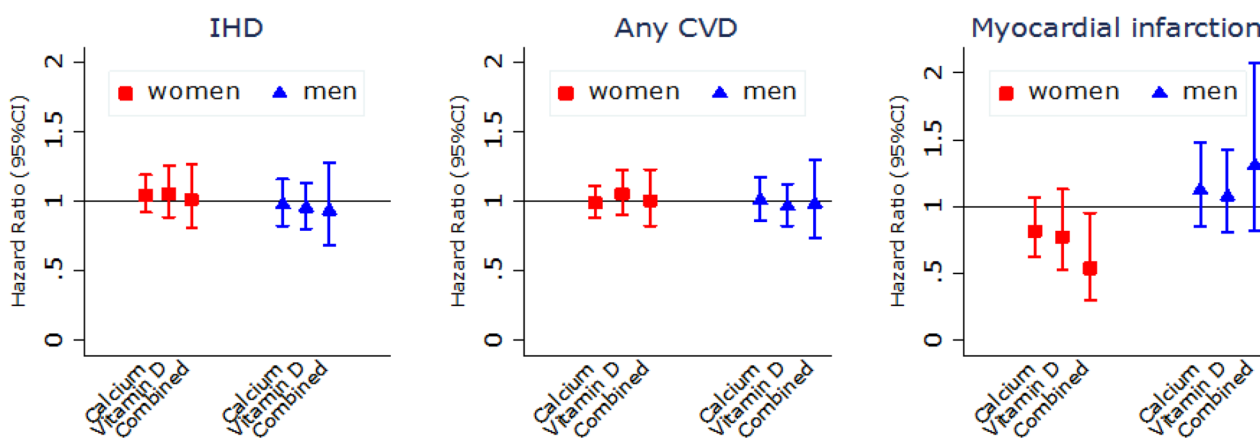
IHD=ischaemic heart disease; CVD=cardiovascular disease

Fig. 3 Calcium and/or vitamin D supplementation and cardiovascular outcomes in UK Biobank. Reproduced with permission from Harvey et al., 2018 [46]. *IHD* ischaemic heart disease, *CVD* cardiovascular disease

Calcium (and vitamin D) supplementation and risk of death

It would seem intuitively reasonable that if an intervention leads to an increased risk of a potentially fatal event such as myocardial infarction, then over a reasonable period of time in a large cohort, it would also be associated with an increased risk of death from that cause. Interestingly, to our knowledge, no study has yet demonstrated such an association. Whilst the first meta-analysis by Bolland et al. [32] suggested a possible 7% increase in mortality with calcium supplementation (RR 95% CI: 0.95, 1.19), in their WHI analysis [34], the RR amongst the population not using personal calcium/ vitamin D supplements was very close to unity [RR: 0.99 (95% CI: 0.86, 1.14)]. Amongst those using personal calcium supplements, calcium and vitamin D supplementation were associated with a reduced risk of death [RR: 0.84 (95% CI: 0.73, 0.97)]. In their meta-analysis using verified outcomes, Lewis et al. demonstrated no effect of calcium supplementation on mortality (Fig. 4) [35], a finding similar to that of the DIPART investigators [47], who demonstrated no difference in mortality in an individual patient data meta-analysis of eight studies including RECORD and WHI, and a trial level analysis including a further 16 studies. Again, data from the Women's Health Initiative demonstrated reassuring findings with mortality somewhat lower in the calcium and vitamin D group compared with placebo [HR: 0.91 (95% CI: 0.83, 1.01)] and this result was similar when examined in those below or above 70 years old. Follow-up of the RECORD study of 5292 participants over 70 years old, who had previously experienced a low trauma fracture [48], demonstrated no effect of calcium supplementation on mortality in an intention-to-treat analysis [all-cause mortality HR: 1.03 (95% CI: 0.94, 1.13); vascular disease mortality HR: 1.07 (95% CI: 0.92, 1.24)]. In a secondary analysis adjusting for treatment received (thus with a reduced number of participants), calcium supplementation again was not statistically significantly associated with all-cause mortality or vascular death, although the hazard ratios were greater than in the ITT analysis [all-cause mortality HR: 1.21 (95% CI: 0.83, 2.05); vascular death HR: 1.43 (95% CI: 0.75, 7.61)]. The trial, therefore, does not provide support either way [48]. Given that the increased risk of myocardial infarction associated with calcium supplementation in the Bolland meta-analyses is relatively modest, and that not all myocardial infarctions result in death, it is possible that existing studies are simply not large enough to detect an effect on mortality [38].
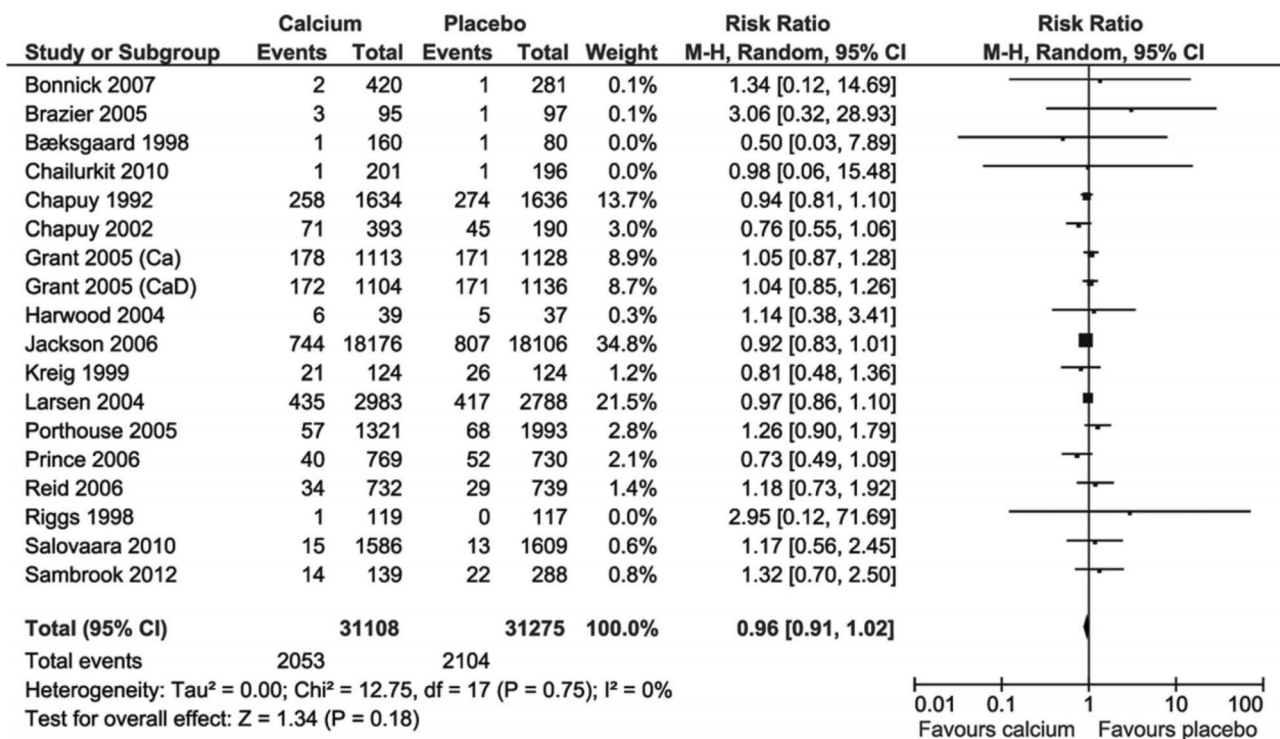
Study or Subgroup	Calcium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bonnick 2007	2	420	1	281	0.1%	1.34 [0.12, 14.69]
Brazier 2005	3	95	1	97	0.1%	3.06 [0.32, 28.93]
Bæksgaard 1998	1	160	1	80	0.0%	0.50 [0.03, 7.89]
Chailurkit 2010	1	201	1	196	0.0%	0.98 [0.06, 15.48]
Chapuy 1992	258	1634	274	1636	13.7%	0.94 [0.81, 1.10]
Chapuy 2002	71	393	45	190	3.0%	0.76 [0.55, 1.06]
Grant 2005 (Ca)	178	1113	171	1128	8.9%	1.05 [0.87, 1.28]
Grant 2005 (CaD)	172	1104	171	1136	8.7%	1.04 [0.85, 1.26]
Harwood 2004	6	39	5	37	0.3%	1.14 [0.38, 3.41]
Jackson 2006	744	18176	807	18106	34.8%	0.92 [0.83, 1.01]
Kreig 1999	21	124	26	124	1.2%	0.81 [0.48, 1.36]
Larsen 2004	435	2983	417	2788	21.5%	0.97 [0.86, 1.10]
Porthouse 2005	57	1321	68	1993	2.8%	1.26 [0.90, 1.79]
Prince 2006	40	769	52	730	2.1%	0.73 [0.49, 1.09]
Reid 2006	34	732	29	739	1.4%	1.18 [0.73, 1.92]
Riggs 1998	1	119	0	117	0.0%	2.95 [0.12, 71.69]
Salovaara 2010	15	1586	13	1609	0.6%	1.17 [0.56, 2.45]
Sambrook 2012	14	139	22	288	0.8%	1.32 [0.70, 2.50]
Total (95% CI)		31108		31275	100.0%	0.96 [0.91, 1.02]
Total events	2053		2104			

Heterogeneity: Tau² = 0.00; Chi² = 12.75, df = 17 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

Fig. 4 Calcium/vitamin D is supplementation and all-cause mortality compared with no supplementation. Reproduced with permission from Lewis et al., 2015 [35]

Mechanistic considerations

Calcium, phosphate and coronary artery calcification

The mechanisms by which calcium supplementation might increase cardiovascular risk have been much debated. It is notable that in the meta-analyses discussed above, there was no evidence for a dose effect or a convincing temporal relationship between calcium supplementation and cardiovascular disease, both key considerations in establishing a causal relationship [49]. A key argument proposed in favour of a mechanistic link is that the transient rise in serum calcium concentrations consequent to ingestion of a calcium supplement might lead to increased calcium deposition within already damaged coronary artery walls [50]. Indeed, calcification is a recognised component of atherosclerotic disease. However, the increase in serum calcium resulting from supplement ingestion is transient and of modest magnitude, and well below concentrations which would lead to $CaHPO_4$ precipitation; at physiological pH and pCO_2 the serum is only half saturated [51]. Whilst there is, to our knowledge, no direct evidence that such transient increases in calcium concentration cause greater coronary calcification or ischaemic cardiac events, there is evidence from observational studies that, at the population level, serum calcium and/or phosphorus concentrations are positively related to risk of ischaemic cardiac events [52–59]. These studies clearly differ markedly in predictor (calcium × phosphate product, total calcium, corrected calcium, serum phosphorus), outcome (coronary artery calcification, clinical event) and study design (cross-sectional, prospective database); the possibility of confounding and/ or reverse causation remain important considerations in these as in earlier investigations. Furthermore, daily recombinant parathyroid hormone injection, as therapy for osteoporosis, leads to a transient rise in serum calcium concentrations with each dose [60], but the randomised trial evidence, observational studies and post-marketing surveillance data have not demonstrated any concerning signals related to myocardial infarction or other ischaemic cardiac events [61, 62]. Patients with mild hyperparathyroidism (who have a much higher serum calcium concentration than would result from taking calcium supplements) do not have an increased risk of soft tissue calcification, and their risk of MI has not been shown to be increased after adjustment for known CVD risk factors [63]. Finally, in a subset of the WHI participants who underwent computed tomography examination of coronary artery calcification at a mean of 7 years follow-up (754 women aged 50–59 years at baseline), there was no difference in coronary artery calcification score according to calcium and vitamin D treatment versus placebo [64].

Physiology in health and severe chronic kidney disease

Importantly, the primary abnormality in the development of atherosclerosis is thought to be pathological intimal thickening, with atherosclerotic plaques forming at sites of endothelial damage, rather than exposure to circulating calcium. Indeed, calcification of plaques appears to be related to macrophage apoptosis leading to microcalcifications, which may coalesce [65]. If there were a causal link between calcium supplementation and atherosclerosis then it could potential be via other cardiovascular risk factors, but there is little evidence for this. Where there have been associations, such as with blood pressure and lipid profile, these have generally been protective [66–70]. Furthermore, whilst there is evidence that calcium supplementation (in phosphate binders) is associated with increased risk of myocardial infarction and death in end-stage renal failure, it is important to appreciate that chronic renal failure leads to a highly perturbed metabolic milieu, in which endothelial dysfunction is an important component [71]. To illustrate, in a study comparing arterial wall calcification in vessels from healthy and chronic renal failure patients, exposure to raised calcium concentrations had no effect on arterial wall calcification in the healthy tissue, but led to increased calcification in the vessels of chronic renal failure patients [72]. The degree of renal failure at which calcium supplementation might become problematic has not been defined. This is an important question, because of the large number of elderly individuals who have mild to moderate renal impairment. The question of whether cardiovascular risk might be raised by calcium supplements specifically in those with pre-existing ischaemic cardiovascular disease remains unanswered. Further work is clearly needed to investigate these mechanistic aspects, but whilst the evidence to date suggests calcium supplementation in end-stage renal failure increases cardiovascular risk, there is no direct evidence of a causal link in healthy individuals.

Mechanistic inference from causal analyses

Recent investigations have made use of advances in genetic understanding and the widespread availability of genome-wide genotyping in large cohorts, to undertake causal analyses, exploring associations between genetically determined calcium concentrations and cardiovascular outcomes. Among a sample of 184,305 individuals (60,801 coronary artery disease cases [approximately 70% with myocardial infarction] and 123,504 controls), 6 SNPs were estimated to explain about 0.8% of the variation in serum calcium levels [73]. Using an inverse-variance weighted meta-analysis (combining the estimates of the 6 SNPs), the odds ratios per 0.5 mg/dL increase in genetically predicted serum calcium

levels were 1.25 (95% CI: 1.08, 1.45) for coronary artery disease and 1.24 (95% CI: 1.05, 1.46) for myocardial infarction. However, in a study of published genome-wide data, amongst 6504 all-cause heart failure cases and 387,652 non-cases of European ancestry, there was no evidence of an association between genetically determined calcium concentrations (7 SNPs) and heart failure [74]. A similar Mendelian randomisation analysis demonstrated no association between genetically determined calcium concentration and any ischaemic stroke subtype in the MEGASTROKE consortium comprising 34,217 cases and 404,630 controls [75]. Again, no convincing association was demonstrated between genetically determined calcium concentration and atrial fibrillation in a further Mendelian randomisation study [76].

Whilst such causal analyses provide weak evidence for a causal association with myocardial infarction, there are substantial limitations with regard to how they should be incorporated into the interpretation of the evidence base as a whole. There are key assumptions which must be satisfied in a Mendelian randomisation analysis. These may be unprovable, such as that the genetic instrument only acts on the outcome through the exposure of interest. Furthermore, given the very small amount of the variance of the exposure explained by the genetic instrument, large cohorts are required to attain statistical power, and the population structure of the cohort can substantially influence the findings [77]. Finally, such studies demonstrate associations between an outcome and lifelong genetically determined exposures. The relevance of this lifelong exposure to the effect of supplementation, which might lead to regular but very transient modest changes in serum calcium concentration, over a defined period in old age, is completely unknown. The gold standard, therefore, remains evidence from randomised, double-blinded, placebo-controlled interventional studies which have validated cardiovascular outcomes. Recent evidence, presented in abstract form, has suggested no effect of calcium supplementation on aortic calcification (assessed from DXA vertebral fracture assessment images) [78] or high-sensitivity troponin [79] (a sensitive marker of myocardial compromise) in 1460 women aged > 70 years, randomised in a double-blind design to either 1200 mg calcium carbonate per day versus matched placebo and followed for 5 years.

Magnesium

Background

Magnesium is the fourth most abundant mineral found in the body, with 60% stored in the skeleton [5]. However, consumption of magnesium is variable throughout the world. In the United States, the prevalence of inadequate magnesium intake for adults is about 64% among males and 67% among females, with greater rates of insufficiency at older ages [80]. In the UK National Diet and Nutrition Survey, data suggest that the reference nutrient intake for magnesium is attained in 91.7% adults aged 50 years or over [81].

Bone effects

Magnesium deficiency has been linked with adverse skeletal outcomes through several potential mechanisms [82], including altered bone mineralization and parathyroid hormone/1,25(OH)$_2$-vitamin D physiology; increased bone loss by promoting pro-inflammatory cytokines stimulating remodeling and osteopenia; and increased endothelial dysfunction [83]. Experimental animal and human studies suggest that magnesium deficiency is associated with reduced osteoclastic and osteoblastic activity, osteopenia, and skeletal fragility [84, 85]. A severely magnesium deficient diet leads to impaired bone growth and exacerbation of loss of bone mass in rats [86–88] and mice [89]. Interestingly, animal studies and data from human pregnancies where high doses of magnesium salts have been used to treat preeclampsia, have suggested the potential for adverse effects on bone mineralisation at very high intakes of magnesium [90–92].

Magnesium, osteoporosis and fracture risk

Although the findings from animal studies and experimental investigations suggest the importance of magnesium in bone health, the evidence for a substantial role of magnesium in the pathogenesis of osteoporosis or as a predictor of fracture risk is rather mixed. A recent meta-analysis identified 11 eligible studies involving 2776 postmenopausal women in which magnesium concentrations have been measured and bone density assessed [82]. Overall, there was evidence of a lower concentration of serum magnesium in women with osteoporosis compared with normal controls, with similar findings for bone mineral density at both the femoral neck and lumbar spine, and when stratified by age, but which differed by geographic location. Thus, differences were observed in European women but not in those from Asia. The findings from this meta-analysis are consistent with an earlier systematic review and meta-analysis demonstrating more marginal associations between magnesium dietary intake and bone mineral density at the hip. Given that circulating concentrations of magnesium are tightly regulated, and may not reflect intake closely, it is difficult to properly compare studies of dietary intake with those of serum concentrations. There are few studies of magnesium concentrations or intake with fracture outcomes. Given the critical role of magnesium in cardiovascular health, it could be hypothesised that perturbations in magnesium physiology

might lead to fractures through increased propensity to falling through cardiovascular arrhythmias, in addition to any effect on bone mineral density. In the US Women's Health Initiative Observational Study, total daily magnesium intake was estimated from baseline food frequency questionnaires, together with intake from supplements [2]. Amongst the 73,684 postmenopausal women, baseline hip BMD was 3% higher and whole body BMD was 2% higher in women who consumed > 422.5 mg compared with < 206.5 mg magnesium per day. However, the incidence and relative risk of hip and total fractures did not differ across fifths of intake. In contrast, risk of forearm or wrist fractures increased with higher magnesium intake [multivariate-adjusted hazard ratios: 1.15 (95% CI: 1.01, 1.32) and 1.23 (95% CI: 1.07, 1.42) for fifths 4 and 5, respectively, compared with the lowest fifth], with this finding potentially explained by greater physical activity and exposure to falls risk. In a more recent meta-analysis, fracture outcomes were ascertained from two studies for hip fracture and two for all fractures (both including the WHI study) [3]. The findings provided no evidence for an association between magnesium intake and fracture outcomes, but clearly represent a fairly limited evidence base. With the advent of widespread genome-wide genotypic data on large cohorts, Mendelian randomisation analyses have become possible. A recent such study across various cohorts used a genetic instrument for magnesium concentration consisting of 5 single nucleotide polymorphisms in a sample of 15,366 individuals, and then tested the association in a cohort of 508,253 osteoporotic fracture patients and 53,236 participants from the general population (all of European ancestry) with osteoporosis status documented [93]. The finding that an increase in genetically predicted magnesium concentration of 0.16 mmol/L was associated with a 0.10 g/cm^2 greater BMD suggests a causal association between magnesium concentration and BMD. However, as described above, the approach relies on several assumptions, which may not be testable, and importantly represents a lifelong genetic influence, and indeed a very small proportion of the variance in overall magnesium concentrations, so cannot really be extrapolated to any effect of dietary intake or supplementation in old age.

Cardiovascular safety of magnesium

Observational and experimental studies have shown that magnesium can exert beneficial effects on the cardiovascular system by enhancing endothelium-dependent vasodilation, improving lipid metabolism, reducing inflammation, and inhibiting platelet function [4, 94, 95]. Indeed hypomagnesemia (e.g. below 0.65 mmol/L) increases risk of cardiac arrest [96]. In two small randomised, controlled, crossover trials restricted dietary magnesium in healthy postmenopausal women to less than half (101–130 mg) the recommended

dietary allowance. This led to increased risk of non-malignant cardiac arrhythmias, changes which were reversed by magnesium supplementation [4, 97, 98]. Severe reductions in dietary magnesium intake may also lead to alterations in oxidative metabolism, glucose homeostasis, and electrolyte balance [97–99]. Although marked reductions in magnesium concentrations or intakes produce adverse effects, whether cardiovascular disease (CVD) risk differs across the normal physiologic concentration range of circulating magnesium or dietary magnesium intake is unclear [4]. A 2005 pooled analysis of prospective cohorts found no significant association between dietary magnesium and IHD (RR: 0.87; 95% CI: 0.67, 1.10) [100].

More recent systematic reviews and meta-analyses, together with causal analyses, have consistently suggested a protective effect of greater magnesium intake and serum concentrations for cardiovascular events within the normal population. It is important to appreciate that these findings should not be extrapolated to disease states such as extremes of serum hypo- or hyper- magnesaemia. An analysis of 532,979 participants from 19 studies (11 studies on dietary magnesium intake, 6 studies on serum magnesium concentrations, and two studies on both) included 19,926 CVD events [5]. The pooled relative risks of total CVD events for the highest versus lowest dietary magnesium intake and serum magnesium concentrations were 0.85 (95% CI: 0.78, 0.92) and 0.77 (95% CI: 0.66, 0.87), respectively. A further very similar meta-analysis that same year (reassuringly) reached the same conclusion, but presented the findings perhaps more usefully [4]. Of 2303 articles, 16 studies met the eligibility criteria; these studies comprised 313,041 individuals and 11,995 CVD, 7534 IHD, and 2686 fatal IHD events. Greater circulating magnesium concentration was associated with a 30% lower risk of CVD [RR: 0.70 (95% CI: 0.56, 0.88) per 0.2 mmol/L)] and possible evidence of a weaker association with lower risks of IHD [0.83 (95% CI: 0.75, 1.05)] and fatal IHD [0.61 (95% CI: 0.37, 1.00)]. Consistent with these findings, there were modest associations between greater dietary magnesium (per 200 mg/d increment) and lower risk of IHD [RR: 0.78 (95% CI: 0.67, 0.92)] and to a lesser extent CVD [(RR: 0.89 (95% CI: 0.75, 1.05)]. The association between dietary magnesium and fatal IHD was found to be non-linear, with an inverse association up to a threshold of 250 mg/d [RR 0.73 (95% CI: 0.62, 0.86)]. Similarly, reassuring protective properties for magnesium intake have been demonstrated with regard to cardiovascular mortality, which, amongst 449,748 individuals (10,313 cardiovascular deaths), cardiovascular mortality was 16% lower in women and 8% lower in men in the remaining population compared with the lowest dietary magnesium intake group [6]. Finally, in a Mendelian randomisation study of 60,801 coronary artery disease cases and 123,504 controls, genetically determined serum magnesium concentration (based

on six SNPs) was inversely associated with coronary artery disease [101]. Thus, the odds ratio for coronary artery disease was 0.88 (95% CI: 0.78, 0.99) per 0.1 mmol/L increase in genetically predicted serum magnesium levels, consistent with a causal relationship between lower magnesium concentrations and coronary artery disease, albeit with the caveats mentioned above. The same group undertook similar analyses for genetically determined magnesium serum concentration with the outcomes of heart failure (no association) [74], stroke (inverse association with cardioembolic stroke) [75] and atrial fibrillation (inverse association) [76].

Overall, the evidence suggests that at the level of the population, higher magnesium intake and serum concentrations are generally associated with better health, both in terms of cardiovascular outcomes and, less robustly, with bone outcomes. However, there is no convincing evidence that supplementation with magnesium is an efficacious or practicable route to improving bone mineral density or reducing fracture risk. Indeed, evidence for altered mineralisation with high intakes of magnesium in animal models suggests that care would be needed with such an approach to not inadvertently impair bone health. Currently, adherence to generally advised nutritional guidelines for the recommended intake of magnesium appears a sensible approach.

Strontium ranelate

Background

Strontium, an element directly below calcium in group 2 of the periodic table, was first discovered in the eighteenth century as a result of lead mining in Scotland [102, 103]. It is present in the human diet in small quantities for example in leafy greens, grains and seafood [104]. Following the observation that strontium was incorporated into the skeleton, it was recognised that strontium, as with calcium and magnesium, could affect myocardial contractility, influence parathyroid hormone secretion and influence uterine contractions [105, 106]. In the normal human diet, 99% of ingested strontium is deposited in bone, which results in replacement by strontium of around 0.035% calcium in the skeleton [104]. Interestingly, excessive strontium substitution may cause defective bone mineralisation, reminiscent of osteomalacia [104, 107, 108]. Isotopes of strontium have been used to treat bone pain patients with metastatic bone cancer and as a tool for imaging bone lesions [109, 110].

Bone effects

Strontium lactate and strontium chloride have both been studied as potential treatments for osteoporosis in human and animal studies [107, 111–113]. In the most recent

incarnation, strontium is combined with ranelic acid as a carrier to form strontium ranelate. It is taken as a single daily oral dose. Its mechanism of action remains a subject of research, but there is evidence that it increases bone strength by altering bone material properties [103]. Administration of strontium ranelate leads to a substantial increase in BMD at the spine and hip, though part of this increase is artefactual, due to incorporation of strontium (which has a greater atomic mass than calcium) into bone. Studies have shown a 36% relative risk reduction in hip fracture over 3 years in osteoporotic patients [10].

Anti-fracture efficacy

The anti-fracture efficacy of strontium ranelate in postmenopausal osteoporosis derived originally from two large pivotal randomized controlled trials, for which the results were reported in 2004 [9] and 2005 [10], and which formed basis of its initial clinical indication. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial included 1442 women aged > 50 years with postmenopausal osteoporosis with at least one prevalent vertebral fracture and a femoral neck T score of -2.8 and a lumbar spine T score of -3.5 [9]. Participants were allocated randomly to either 2 g/day strontium ranelate or matched placebo. Vertebral fractures occurred in 20.9% of women in the strontium ranelate group versus 32.8% in the placebo group over the 3 years' follow-up. In the second trial (Treatment of Peripheral Osteoporosis Trial: TROPOS), 5091 postmenopausal women with osteoporosis were randomised to either 2 g/day strontium ranelate or matched placebo [10]. Here, 11.2% of strontium ranelate patients had at least one osteoporosis-related nonvertebral fracture, and 8.7% at least one major osteoporotic fracture over the 3 years' follow-up, compared with 12.9 and 10.4% (respectively) participants in the placebo group.

Cardiovascular safety of strontium ranelate

In 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) noted concerns over cardiac safety emerging from annual periodic safety update reporting (the mechanism whereby manufacturers submit regular safety data to the EMA) and subsequently recommended a reappraisal of the overall benefit-risk ratio of strontium ranelate [11, 114–116]. The pooled analysis in 7572 postmenopausal women (3803 strontium ranelate and 3769 placebo) indicated an increased risk for myocardial infarction (MI) with strontium ranelate, with estimated annual incidences of 5.7 cases per 1000 patient years versus 3.6 cases per 1000 patient years with placebo [11]. The odds ratio for MI was 1.60 (95% CI: 1.07, 2.38) for strontium ranelate versus placebo (incidences of 1.7 versus 1.1%, respectively).

Interestingly, among the cases of MI, fatal events were less frequent with strontium ranelate (15.6%) than with placebo (22.5%). Post-marketing surveillance data covering > 3.4 million patient years of treatment from September 2004 to February 2013 did not support an increased risk of MI [11, 116]. Subsequent observational studies with very large populations have similarly not indicated any adverse signal. Thus, a prospective observational cohort study of 12,076 patients on strontium ranelate did not demonstrate increased risk of cardiac events over the 32.0 ± 9.7 months of follow-up [11, 116, 117]. In a nested case-control study of 112,445 women with treated postmenopausal osteoporosis, of whom 6487 were receiving strontium ranelate, the annual incidence rates for first definite MI, MI with hospitalisation and cardiovascular death were 3.24, 6.13, and 14.66 per 1000 patient years, respectively. As expected, in this analysis within the UK Clinical Practice Research Datalink (CPRD), obesity, smoking and cardiovascular treatments were associated with greater risk of cardiac events, but current use or past use of strontium ranelate was not associated with increased risk for first definite myocardial infarction (compared with patients who had never taken strontium ranelate) [OR: 1.05 (95% CI: 0.68, 1.61) and 1.12 (95% CI: 0.79, 1.58), respectively], hospitalisation with myocardial infarction [0.84 (95% CI: 0.54, 1.30) and 1.17 (95% CI: 0.83, 1.66)], or cardiovascular death [0.96 (95% CI: 0.76, 1.21) and 1.16 (95% CI: 0.94, 1.43)] [118]. The most recent study combined data from three multinational multi-database sources to undertake case-control studies nested within a cohort of new users of strontium ranelate or bisphosphonates [119]. Cases of acute myocardial infarction, venous thromboembolism or cardiovascular death were matched with up to ten controls by sex, year of birth, index date and country. The results indicated that there was no apparent excess risk of acute myocardial infarction with current strontium ranelate versus current bisphosphonate use [Odds Ratio: 0.89 (95% CI 0.70, 1.12)] nor with current versus past strontium ranelate use [0.71 (95% CI: 0.56, 0.91)]. There was evidence for an increased risk of venous thromboembolism with current strontium ranelate compared with current bisphosphonate use [1.24 (95% CI: 0.96, 1.61)], and current versus past strontium ranelate use [1.30 (95% CI: 1.04, 1.62)]. Cardiovascular death was more common with current strontium ranelate versus current bisphosphonate use [1.35 (95% CI: 1.02, 1.80)]. However, when current use was compared with past strontium ranelate use (which better controls for confounding by indication) a reduced risk of cardiovascular death was apparent [0.68 (95% CI: 0.48, 0.96)] [119]. Importantly, this study was undertaken after the change in label and specification of cardiovascular disease as a contraindication to strontium and late use. Cessation of therapies during end-of-life care and residual confounding

by indication are suggested by the authors to potentially partly explain these apparently discrepant findings [116, 119].

Summary and conclusions

Whilst calcium, magnesium and strontium have chemical similarities, the evidence base surrounding their links with bone and cardiovascular health is heterogeneous. Thus, calcium combined with vitamin D supplementation leads to a modest reduction in fracture risk but calcium supplementation is associated with a small increase risk of renal stones, and a more marked increase in risk of gastrointestinal symptoms. The purported links between calcium/vitamin D and cardiovascular outcomes are not consistently supported across the literature and indeed not convincingly apparent when validated outcomes are used; a mechanistic explanation in the context of normal renal physiology is still lacking; and no dose response or convincing temporal relationship between supplementation and cardiovascular outcomes have been demonstrated.

Dietary intake and serum concentrations of magnesium have been positively associated with bone mineral density but links to fracture risk are, as yet, not well characterised; reassuringly, greater dietary intake and serum concentrations appear to be generally protective from cardiovascular events.

Strontium is a trace element and is considered in the context of the skeleton mainly in terms of treatment for osteoporosis, in the form of strontium ranelate. Here, efficacy for vertebral and non-verbal fractures has been demonstrated, but with convincing evidence of increased risk of thromboembolic disease. However, pooled analysis of randomised trial data suggesting an increased risk of myocardial infarction have not been supported by post-marketing surveillance data or analyses of large real-world population datasets.

In conclusion, we suggest that calcium supplementation is most appropriately used in combination with vitamin D supplementation and targeted at those who are deficient in these nutrients, or in combination with antiosteoporosis medications [120]. There is little evidence to support routine magnesium supplementation for bone health. Strontium ranelate, which is now available again as a generic medication, provides a useful therapeutic option for osteoporosis in those at high fracture risk who do not have cardiovascular risk factors.

Compliance with ethical standards

References

1. Harvey NC, Biver E, Kaufman JM et al (2017) The role of calcium supplementation in healthy musculoskeletal ageing: 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). Osteoporos Int 28:447–462

2. Orchard TS, Larson JC, Alghothani N et al (2014) Magnesium intake, bone mineral density, and fractures: results from the women's health initiative observational study. Am J Clin Nutr 99:926–933

3. Farsinejad-Marj M, Saneei P, Esmaillzadeh A (2016) Dietary magnesium intake, bone mineral density and risk of fracture: a systematic review and meta-analysis. Osteoporos Int 27:1389–1399

4. Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D (2013) Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 98:160–173

5. Qu X, Jin F, Hao Y, Li H, Tang T, Wang H, Yan W, Dai K (2013) Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. PLoS ONE 8:e57720

6. Fang X, Liang C, Li M et al (2016) Dose-response relationship between dietary magnesium intake and cardiovascular mortality: a systematic review and dose-based meta-regression analysis of prospective studies. J Trace Elem Med Biol 38:64–73

7. Zhao L, Hu M, Yang L, Xu H, Song W, Qian Y, Zhao M (2019) Quantitative association between serum/dietary magnesium and cardiovascular disease/coronary heart disease risk: a dose-response meta-analysis of prospective cohort studies. J Cardiovasc Pharmacol 74:516–527

8. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C (2015) Recent advances in the pathogenesis and treatment of osteoporosis. Clini Med 15(Suppl 6):s92-96

9. Meunier PJ, Roux C, Seeman E et al (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350:459–468

10. Reginster JY, Seeman E, Vernejoul MCD et al (2005) Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90:2816–2822

11. Reginster JY (2014) Cardiac concerns associated with strontium ranelate. Expert Opin Drug Saf 13:1209–1213

12. Rozenberg S, Body JJ, Bruyere O et al (2016) Effects of dairy products consumption on health: benefits and beliefs-a commentary from the belgian bone club and the european society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases. Calcif Tissue Int 98:1–17

13. Bruyere O, Cavalier E, Souberbielle JC et al (2014) Effects of vitamin D in the elderly population: current status and perspectives. Arch Public Health 72:32

14. Rizzoli R, Boonen S, Brandi ML et al (2013) Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 29:305–313

15. Ethgen O, Hiligsmann M, Burlet N, Reginster JY (2016) Cost-effectiveness of personalized supplementation with vitamin D-rich dairy products in the prevention of osteoporotic fractures. Osteoporos Int 27:301–308

16. Cianferotti L, Parri S, Gronchi G et al (2015) Changing patterns of prescription in vitamin D supplementation in adults: analysis of a regional dataset. Osteoporos Int 26:2695–2702

17. Silk LN, Greene DA, Baker MK (2015) The effect of calcium or calcium and vitamin D supplementation on bone mineral density in healthy males: a systematic review and meta-analysis. Int J Sport Nutr Exerc Metab 25:510–524

18. Lips P, Bouillon R, van Schoor NM et al (2010) Reducing fracture risk with calcium and vitamin D. Clin Endocrinol (Oxf) 73:277–285

19. Boonen S, Bischoff-Ferrari HA, Cooper C et al (2006) Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. Calcif Tissue Int 78:257–270

20. Tai V, Leung W, Grey A, Reid IR, Bolland MJ (2015) Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ 351:h4183

21. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A (2007) Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 370:657–666

22. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA et al (2007) Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 86:1780–1790

23. DIPART-Group (2010) Patient level pooled analysis of 68500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 340:b5463

24. Bolland MJ, Leung W, Tai V et al (2015) Calcium intake and risk of fracture: systematic review. BMJ 351:h4580

25. Weaver CM, Alexander DD, Boushey CJ et al (2016) Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int 27:367–376

26. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C (2016) Recent advances in the pathogenesis and treatment of osteoporosis. Clin Med 16:360–364

27. Ross AC, Manson JE, Abrams SA et al (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 96:53–58

28. Bolland MJ, Barber PA, Doughty RN et al (2008) Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 336:262–266

29. Bjelakovic G, Gluud LL, Nikolova D et al (2014) Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 1:CD007470

30. Prentice RL, Pettinger MB, Jackson RD et al (2013) Health risks and benefits from calcium and vitamin D supplementation: women's health initiative clinical trial and cohort study. Osteoporos Int 24:567–580

31. Lewis JR, Zhu K, Prince RL (2012) Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. J Bone Miner Res 27:719–722

32. Bolland MJ, Avenell A, Baron JA et al (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341:c3691

33. Prince RL, Devine A, Dhaliwal SS, Dick IM (2006) Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 166:869–875

34. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR (2011) Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's health initiative limited access dataset and meta-analysis. BMJ 342:d2040

35. Lewis JR, Radavelli-Bagatini S, Rejnmark L et al (2015) The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res 30:165–175

36. Rosamond WD, Sprafka JM, McGovern PG, Nelson M, Luepker RV (1995) Validation of self-reported history of acute myocardial infarction: experience of the Minnesota Heart Survey Registry. Epidemiology 6:67–69

37. Colditz GA, Martin P, Stampfer MJ et al (1986) Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol 123:894–900

38. Bolland MJ, Grey A, Reid IR (2013) Calcium supplements and cardiovascular risk: 5 years on. Ther Adv Drug Saf 4:199–210

39. Larsen ER, Mosekilde L, Foldspang A (2004) Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res 19:370–378

40. Hsia J, Heiss G, Ren H et al (2007) Calcium/vitamin D supplementation and cardiovascular events. Circulation 115:846–854

41. Cauley JA, Chlebowski RT, Wactawski-Wende J et al (2002) Manson JE (2013) Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Women's Health 22:915–929

42. Mao PJ, Zhang C, Tang L et al (2013) Effect of calcium or vitamin D supplementation on vascular outcomes: a meta-analysis of randomized controlled trials. Int J Cardiol 169:106–111

43. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ (2016) Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med 165:856–866

44. Khan SU, Khan MU, Riaz H et al (2019) Effects of nutritional supplements and dietary interventions on cardiovascular outcomes: an umbrella review and evidence map. Ann Intern Med 171:190–198

45. Yang C, Shi X, Xia H et al (2020) The evidence and controversy between dietary calcium intake and calcium supplementation and the risk of cardiovascular disease: a systematic review and meta-analysis of cohort studies and randomized controlled trials. J Am Coll Nutr 39:352–370

46. Harvey NC, D'Angelo S, Paccou J et al (2018) Calcium and vitamin D supplementation are not associated with risk of incident ischemic cardiac events or death: findings from the UK Biobank cohort. J Bone Miner Res 33:803–811

47. Rejnmark L, Avenell A, Masud T et al (2012) Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab 97(8):2670–2681

48. Avenell A, MacLennan GS, Jenkinson DJ et al (2012) Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 97:614–622

49. Podrebarac T, Tugwell P, Hébert PC (1996) A reader's guide to the evaluation of causation. Postgrad Med J 72:131–136

50. Reid IR, Bolland MJ (2008) Calcium supplementation and vascular disease. Climacteric 11:280–286

51. Heaney RP, Kopecky S, Maki KC, Hathcock J, Mackay D, Wallace TC (2012) A review of calcium supplements and cardiovascular disease risk. Adv Nutr 3:763–771

52. Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S (1997) Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 50:967–973

53. Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH (1999) Serum calcium and cardiovascular risk factors and diseases: the Tromso study. Hypertension 34:484–490

54. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G (2005) Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation 112:2627–2633

55. Dhingra R, Sullivan LM, Fox CS et al (2007) Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med 167:879–885

56. Foley RN, Collins AJ, Ishani A, Kalra PA (2008) Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 156:556–563

57. Larsson TE, Olauson H, Hagstrom E et al (2010) Conjoint effects of serum calcium and phosphate on risk of total, cardiovascular, and noncardiovascular mortality in the community. Arterioscler Thromb Vasc Biol 30:333–339

58. Slinin Y, Blackwell T, Ishani A, Cummings SR, Ensrud KE (2011) Serum calcium, phosphorus and cardiovascular events in post-menopausal women. Int J Cardiol 149:335–340

59. Rohrmann S, Garmo H, Malmstrom H et al (2016) Association between serum calcium concentration and risk of incident and fatal cardiovascular disease in the prospective AMORIS study. Atherosclerosis 251:85–93

60. Shiraki M, Sugimoto T, Nakamura T (2013) Effects of a single injection of teriparatide on bone turnover markers in postmenopausal women. Osteoporos Int 24:219–226

61. Neer RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441

62. Nardi A, Ventura L, Cozzi L et al (2013) The bone anabolic therapy. Aging Clin Exp Res 25(Suppl 1):S121–124

63. Nordin BE, Lewis JR, Daly RM et al (2011) The calcium scare–what would Austin Bradford Hill have thought? Osteoporos Int 22:3073–3077

64. Manson JE, Allison MA, Carr JJ et al (2010) Calcium/vitamin D supplementation and coronary artery calcification in the women's health initiative. Menopause 17:683–691

65. Otsuka F, Yasuda S, Noguchi T, Ishibashi-Ueda H (2016) Pathology of coronary atherosclerosis and thrombosis. Cardiovasc Diagn Ther 6:396–408

66. Reid IR, Mason B, Horne A et al (2002) Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. Am J Med 112:343–347

67. Reid IR, Ames R, Mason B et al (2010) Effects of calcium supplementation on lipids, blood pressure, and body composition in healthy older men: a randomized controlled trial. Am J Clin Nutr 91:131–139

68. Denke MA, Fox MM, Schulte MC (1993) Short-term dietary calcium fortification increases fecal saturated fat content and reduces serum lipids in men. J Nutr 123:1047–1053

69. Bell L, Halstenson CE, Halstenson CJ, Macres M, Keane WF (1992) Cholesterol-lowering effects of calcium carbonate in patients with mild to moderate hypercholesterolemia. Arch Intern Med 152:2441–2444

70. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ (1999) The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. Am J Hypertens 12:84–92

71. Floege J (2016) Phosphate binders in chronic kidney disease: a systematic review of recent data. J Nephrol 29:329–340

72. Shroff RC, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, Rees L, Shanahan CM (2010) Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. J Am Soc Nephrol 21:103–112

73. Larsson SC, Burgess S, Michaelsson K (2017) Association of genetic variants related to serum calcium levels with coronary artery disease and myocardial infarction. JAMA 318:371–380

74. Helte E, Åkesson A, Larsson SC (2019) Assessing causality in associations of serum calcium and magnesium levels with heart failure: a two-sample Mendelian randomization study. Front Genet 10:1069

75. Larsson SC, Traylor M, Burgess S et al (2019) Serum magnesium and calcium levels in relation to ischemic stroke: Mendelian randomization study. Neurology 92:e944–e950

76. Larsson SC, Drca N, Michaëlsson K (2019) Serum magnesium and calcium levels and risk of atrial fibrillation. Circ Genom Precis Med 12:e002349

77. Barton N, Hermisson J, Nordborg M (2019) Why structure matters. Elife. https://doi.org/10.7554/eLife.45380

78. Lewis J, Hodgson JM, Lim W et al (2019) Long-term effects of calcium supplementation on abdominal aortic calcification in older women: analysis of a 5-year double-blind randomized controlled trial. American Society for Bone and Mineral Research Annual Scientific Meeting. ASBMR, Orlando, pp LB-1168

79. Lewis J, Hodgson JM, Lim W et al (2019) Long-term effects of calcium supplementation on high-sensitivity cardiac troponin I in older women: analysis of samples from a 5-year doubleblind randomized controlled trial American Society for Bone and Mineral Research Annual Scientific Conference`. ASBMR, Orlando, pp LB SUN-1071

80. Moshfegh A, Goldman J, Cleveland L (2005) What we eat in America, NHANES 2001–2002: usual nutrient intakes from food compared to dietary reference intakes. US Department of Agriculture, Agricultural Research Service pp 1–56

81. Derbyshire E (2018) Micronutrient Intakes of British adults across mid-life: a secondary analysis of the UK national diet and nutrition survey. Front Nutr 5:55

82. Chang J, Yu D, Ji J, Wang N, Yu S, Yu B (2020) The association between the concentration of serum magnesium and postmenopausal osteoporosis. Front Med 7:381

83. Castiglioni S, Cazzaniga A, Albisetti W, Maier JA (2013) Magnesium and osteoporosis: current state of knowledge and future research directions. Nutrients 5:3022–3033

84. Rude RK, Gruber HE, Norton HJ, Wei LY, Frausto A, Kilburn J (2005) Dietary magnesium reduction to 25% of nutrient requirement disrupts bone and mineral metabolism in the rat. Bone 37:211–219

85. Rude RK, Singer FR, Gruber HE (2009) Skeletal and hormonal effects of magnesium deficiency. J Am Coll Nutr 28:131–141

86. Boskey AL, Rimnac CM, Bansal M, Federman M, Lian J, Boyan BD (1992) Effect of short-term hypomagnesemia on the chemical and mechanical properties of rat bone. J Orthop Res 10:774–783

87. Carpenter TO, Mackowiak SJ, Troiano N, Gundberg CM (1992) Osteocalcin and its message: relationship to bone histology in magnesium-deprived rats. Am J Physiol 263:E107-114

88. Kenney MA, McCoy H, Williams L (1994) Effects of magnesium deficiency on strength, mass, and composition of rat femur. Calcif Tissue Int 54:44–49

89. Tu SJ, Wang SP, Cheng FC et al (2017) Attenuating trabecular morphology associated with low magnesium diet evaluated using micro computed tomography. PLoS ONE 12:e0174806

90. Riond JL, Hartmann P, Steiner P et al (2000) Long-term excessive magnesium supplementation is deleterious whereas suboptimal supply is beneficial for bones in rats. Magnes Res 13:249–264

91. Takeda R, Nakamura T (2008) Effects of high magnesium intake on bone mineral status and lipid metabolism in rats. J Nutr Sci Vitaminol 54:66–75

92. Wedig KE, Kogan J, Schorry EK, Whitsett JA (2006) Skeletal demineralization and fractures caused by fetal magnesium toxicity. J Perinatol 26:371–374

93. Cheng WW, Zhu Q, Zhang HY (2019) Mineral nutrition and the risk of chronic diseases: a Mendelian randomization study. Nutrients 11:378

94. Shechter M (2010) Magnesium and cardiovascular system. Magnes Res 23:60–72

95. Mubagwa K, Gwanyanya A, Zakharov S, Macianskiene R (2007) Regulation of cation channels in cardiac and smooth muscle cells by intracellular magnesium. Arch Biochem Biophys 458:73–89

96. Anon (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 8: advanced challenges in resuscitation: section 1: life-threatening electrolyte abnormalities. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:I217–222

97. Klevay LM, Milne DB (2002) Low dietary magnesium increases supraventricular ectopy. Am J Clin Nutr 75:550–554

98. Nielsen FH, Milne DB, Klevay LM, Gallagher S, Johnson L (2007) Dietary magnesium deficiency induces heart rhythm changes, impairs glucose tolerance, and decreases serum cholesterol in post menopausal women. J Am Coll Nutr 26:121–132

99. Nielsen FH, Milne DB, Gallagher S, Johnson L, Hoverson B (2007) Moderate magnesium deprivation results in calcium retention and altered potassium and phosphorus excretion by postmenopausal women. Magnes Res 20:19–31

100. Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S (2005) Dietary magnesium intake and risk of cardiovascular disease among women. Am J Cardiol 96:1135–1141

101. Larsson SC, Burgess S, Michaëlsson K (2018) Serum magnesium levels and risk of coronary artery disease: Mendelian randomisation study. BMC Med 16:68

102. Hope TC (1798) Account of a mineral from strontian, and of a peculiar species of earth which it contains. Trans R Soc Edinb 4:3–39

103. Marx D, Rahimnejad Yazdi A, Papini M, Towler M (2020) A review of the latest insights into the mechanism of action of strontium in bone. Bone Rep 12:100273

104. Watts P, Howe P (2010) Strontium and strontium compounds. World Health Organization, Geneva

105. Papillon MF (1870) Recherches experimentales sur les modifications de la composition immediate des os. C R Acad Sci 71:372

106. Dow EC, Stanbury JB (1960) Strontium and calcium metabolism in metabolic bone diseases. J Clin Invest 39:885–903

107. Morohashi T, Sano T, Yamada S (1994) Effects of strontium on calcium metabolism in rats. I. A distinction between the pharmacological and toxic doses. Jpn J Pharmacol 64:155–162

108. Omdahl JL, DeLuca HF (1971) Strontium induced rickets: metabolic basis. Science 174:949–951

109. Altman GB, Lee CA (1996) Strontium-89 for treatment of painful bone metastasis from prostate cancer. Oncol Nurs Forum 23:523–527

110. Rosenthall L (1965) The role of strontium 85 in the detection of bone disease. Radiology 84:75–82

111. Shorr E, Carter AC (1952) The usefulness of strontium as an adjuvant to calcium in the remineralization of the skeleton in man. Bull Hosp Joint Dis 13:59–66

112. Marie PJ, Garba MT, Hott M, Miravet L (1985) Effect of low doses of stable strontium on bone metabolism in rats. Miner Electrolyte Metab 11:5–13

113. Marie PJ, Hott M (1986) Short-term effects of fluoride and strontium on bone formation and resorption in the mouse. Metabolism 35:547–551

114. Anon (2014) Strontium ranelate. Summary of product characteristics. European Medicines Agency

115. Compston J (2014) Strontium ranelate lives to fight another day. Maturitas 78:75–76

116. Reginster JY, Brandi ML, Cannata-Andia J et al (2015) The position of strontium ranelate in today's management of osteoporosis. Osteoporos Int 26:1667–1671

117. Anon (2013) Assessment report—periodic safety update report (EPAR—Protelos-H-C-560-PSU31). European Medicines Agency

118. Cooper C, Fox KM, Borer JS (2014) Ischaemic cardiac events and use of strontium ranelate in postmenopausal osteoporosis: a nested case-control study in the CPRD. Osteoporos Int 25:737–745

119. Ali MS, Berencsi K, Marinier K et al (2020) Comparative cardiovascular safety of strontium ranelate and bisphosphonates: a multi-database study in 5 EU countries by the EU-ADR Alliance. Osteoporos Int 31:2425–2438

120. Kanis JA, Cooper C, Rizzoli R, Reginster JY (2019) Executive summary of European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Aging Clin Exp Res 31:15–17

121. Bolland MJ, Grey A, Gamble GD, Reid IR (2011) Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. Am J Clin Nutr 94:1144–1149

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