A Review of Calcium Supplements and Cardiovascular Disease Risk[1,2]

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ABSTRACT

A group of academic and industry experts in the fields of nutrition, cardiology, epidemiology, food science, bone health, and integrative medicine examined the data on the relationship between calcium supplement use and risk of cardiovascular events, with an emphasis on 4 of the Bradford Hill criteria for causal inference: strength, consistency, dose-response, and biological plausibility. Results from 2 epidemiological studies and a meta-analysis of randomized, controlled clinical trials, including a subgroup analysis from the Women's Health Initiative, have prompted concern about a potential association between calcium supplement use and a small increase in the risk of adverse cardiovascular events. However, a number of issues with the studies, such as inadequate compliance with the intervention, use of nontrial calcium supplements, potential bias in event ascertainment, and lack of information on and adjustment for known cardiovascular risk determinants, suggest that bias and confounding cannot be excluded as explanations for the reported associations. Findings from other cohort studies also suggest no detrimental effect of calcium from diet or supplements, with or without vitamin D, on cardiovascular disease risk. In addition, little evidence exists for plausible biological mechanisms to link calcium supplement use with adverse cardiovascular outcomes. The authors do not believe that the evidence presented to date regarding the hypothesized relationship between calcium supplement use and increased cardiovascular disease risk is sufficient to warrant a change in the Institute of Medicine recommendations, which advocate use of supplements to promote optimal bone health in individuals who do not obtain recommended intakes of calcium through dietary sources. *Adv. Nutr. 3: 763–771, 2012.*

Introduction

Calcium is the fifth most abundant element in the human body, with >99% residing in the skeleton as a complex calcium phosphate mineral crystal. Although skeletal calcium is a major contributor to the structural strength of bones, it also serves as a reservoir to maintain serum calcium concentrations. Thousands of milligrams of calcium passively diffuse into and out of bone on a daily basis. Hundreds of milligrams are bioactively moved into and out of bone during cell-mediated bone remodeling. The kidneys filter as much as 10,000 mg of calcium each day, with ~98% being reabsorbed (1). When calcium intake is insufficient from dietary and supplemental sources, compensatory loss of calcium from the bone follows, weakening the skeleton and increasing the risk of subsequent fracture (2).

Calcium and vitamin D supplements may be useful in reducing the risk of osteoporosis in populations such as postmenopausal women who have low levels of these nutrients in their diets (3). Beyond its role in maintaining bone health, emerging evidence suggests that calcium supplementation may be associated with favorable nonskeletal outcomes such as reduced risk of the development of adenomatous polyps in the colon (4), cancers (5), and pre-eclampsia (6). The US Institute of Medicine (IOM)[8] Food and Nutrition Board currently designates a tolerable upper intake level of 2500 mg/d for adults 19–50 y of age and 2000 mg/d for adults older than 50 y of age as being free of the risk of adverse health

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[8] Abbreviations used: CVD, cardiovascular disease; IOM, Institute of Medicine; MI, myocardial infarction; PTH, parathyroid hormone; RECORD, Randomized Evaluation of Calcium or Vitamin D; RCT, randomized controlled trial.

effects for nearly all persons in the general population (2). However, extremely high intake levels of calcium (5000–6000 mg/d) have been reported without known adverse effects in Olympic swimmers consuming large amounts of food to meet their energy needs, as well as in nomadic herding tribes from Lapland to Kenya who live mainly off the milk of their herds (7,8).

Although the 2010 NHANES report showed that a much greater percentage of Americans are meeting the recommended daily allowance for calcium than has been the case in recent decades, dietary calcium insufficiency is still prevalent in the United States and worldwide, particularly among elderly persons with an increased risk of osteoporotic fracture. NHANES data suggest that ~43% of the US population and 70% of older women use calcium supplements (9). Recently, a study commissioned by the North American branch of the International Life Sciences Institute aimed to determine total usual nutrient intakes from relative contributions of foods (including both those naturally occurring nutrients and those added via enrichment/fortification) and dietary supplements within a nationally representative sample of the US population 2 y of age and older. The results of this study indicated that 54% of Americans did not meet the estimated average requirement for calcium with diet alone; furthermore, 38% of Americans did not meet the estimated average requirement even when the supplements were considered (10). Net absorption of calcium (intake minus the quantity excreted in feces) decreases with age; therefore, higher levels of calcium intake are recommended for adults older than 50 y of age (6). **Table 1** describes the current dietary reference intake values and supplemental use of calcium by sex and age.

Table 1. Current dietary reference intake values and supplemental use of calcium by sex and age

Life stage group, *y*	Estimated average requirement[1]	RDA[1]	Tolerable upper intake level[1]	Users of calcium supplements[2]
		mg/d		%
Males				
1–3	500	700	2500	18 ± 2
4–8	800	1000	2500	29 ± 2
9–13	1100	1300	3000	20 ± 2
14–18	1100	1300	3000	19 ± 2
19–30	800	1000	2500	34 ± 2
31–50	800	1000	2500	45 ± 2
51–70	800	1000	2000	51 ± 2
	1000	1200	2000	56 ± 3
Females				
1–3	500	700	2500	20 ± 2
4–8	800	1000	2500	26 ± 3
9–13	1100	1300	3000	24 ± 3
14–18	1100	1300	3000	24 ± 2
19–30	800	1000	2500	39 ± 2
31–50	800	1000	2500	52 ± 2
51–70	1000	1200	2000	67 ± 1
	1000	1200	2000	65 ± 2

[1] Data from the Institute of Medicine Food and Nutrition Board 2010 Dietary Reference Intakes for Calcium and Vitamin D (2). RDA, recommended daily allowance.
[2] Data are from (9). Data are presented as % ± SE (n = 5217).

Consumption of calcium and vitamin D–containing supplements has increased in recent years, and data from the 2003–2006 NHANES suggest that middle-aged to elderly educated white women, in particular, use calcium supplements (9). The study showed that women rely on calcium supplements for approximately half of their daily intake, with mean intakes from supplements of 578 and 608 mg/d for women 51–70 y of age and older than 71 y of age, respectively (9).

No suggestions of serious adverse effects from this supplemental calcium intake had been reported until a series of reports from Bolland et al. (11) and Reid et al. (12) raised the issue of a possible increase in risk of adverse cardiovascular events in men and women associated with the use of calcium or calcium plus vitamin D supplements. The initial reports were from 2 clinical trials in which women (11) and men (12) had been randomly assigned to receive a calcium supplement or placebo and were followed for 2 y (men) or 5 y (women). The primary outcome measure was the change in bone mineral density in each of these studies; however, adverse cardiovascular events were prespecified secondary outcomes. Trends were reported toward increased cardiovascular events in the groups receiving calcium supplementation in both studies. The trial conducted in women showed a statistically significant unadjusted HR of 1.43 (P = 0.043; 95% CI: 1.01–2.04) for a composite endpoint of myocardial infarction (MI), stroke, or sudden death, with at least 1 of these events having occurred in 8.2% of participants in the calcium supplement group (n = 732) versus 6.8% of those in the placebo group (n = 739). However, after adjustment for known cardiovascular risk factors in multivariate analysis, statistical significance for this association was lost (P = 0.08) (11).

Bolland et al. (13,14) followed these articles with the publication of a meta-analysis of data from other randomized controlled trial (RCT) of calcium supplementation, as well as an article reporting a subgroup analysis of data from the Women's Health Initiative that included an update of their previous meta-analysis. In this subgroup assessment of the Women's Health Initiative, calcium plus vitamin D trial, Bolland et al. (14) investigated whether calcium (1000 mg) plus vitamin D (400 IU/d) treatment vs. placebo was associated with cardiovascular event risk in subgroups of women who were users (54%) and nonusers (46%) of personal calcium supplements at baseline (personal supplement use was allowed to continue during the trial). They reported significant interactions between treatment and personal calcium use for clinical MI (P = 0.04), stroke (P = 0.02), and the composite of clinical MI or stroke (P = 0.006). The HR for clinical MI or stroke was 1.16 (95% CI:, 1.00–1.35; P = 0.05) in the nonusers of personal calcium supplements, and 0.88 (95% CI: 0.76–1.02; P = 0.09) among users of personal calcium supplements. The update of their previous meta-analysis to include these results produced pooled RR estimates of 1.24 for MI (95% CI: 1.07–1.45; P = 0.004), 1.15 for stroke (95% CI: 1.00–1.32; P = 0.06), and 1.15 for MI or stroke (95% CI: 1.03–1.27; P = 0.009) (14). On the basis of their results, Bolland et al. (14) concluded that use of calcium supplements with

or without vitamin D modestly increases cardiovascular risk and suggested that recommendations for the use of such supplements in older people should be reassessed. However, these conclusions have been questioned by a number of experts who have raised concerns about the methodology used and the potential for bias and confounding that may account for the reported association (1,15–18).

Most recently, Li et al. (19) reported findings similar in some respects to those of Bolland et al. from the European Prospective Investigation into Cancer and Nutrition cohort of 23,980 men and women 35–64 y of age who were free of cardiovascular disease (CVD) at baseline. The group reported that, compared with the lowest quartile, the third quartile of total dietary and dairy calcium intake had a significantly reduced MI risk with an HR of 0.69 (95% CI: 0.50–0.94) and 0.68 (95% CI: 0.50–0.93), respectively. Most of the reported associations were null; however, after adjustment for 15 covariates, and compared with nonusers of any dietary supplements, users of calcium supplements had a statistically significant increased MI risk with an HR of 1.86 (95% CI: 1.17–2.96). This was more pronounced for calcium supplement–only users, with an HR of 2.39 (95% CI: 1.12–5.12).

The above-described articles have received wide publicity and may have resulted in diminished use of calcium supplements. In addition, concerns among some health care professionals prompted changes in the recommendations that they provide regarding the use of calcium supplements by their patients. Given the widespread use of calcium supplements in the population, an examination of the reported association between calcium supplement use and increased CVD risk was warranted. To accomplish this goal, a group of academic and industry experts in the fields of nutrition, cardiology, epidemiology, food science, bone health, and integrative medicine examined the data on the relationship between calcium supplement use and risk of cardiovascular events, with an emphasis on 4 of the Bradford Hill criteria for causal inference: strength, consistency, dose-response, and biological plausibility (20). Data from RCT, meta-analyses, and prospective cohort studies are reviewed here.

Current status of knowledge

The evidence context

The reports and analyses by Bolland et al. (11–14) and Li et al. (19) have not occurred in an evidential vacuum. Calcium supplementation has been used for many years, and dozens of clinical trials have reported varying outcomes, including unexpected events such as mortality and various forms of CVD. To convey some sense of this body of evidence, results from pertinent long-term RCT in this area are summarized in **Table 2** (5, 22–26). In addition, results from pertinent long-term prospective cohort studies other than those published by Bolland et al. (14) and Li et al. (19) are summarized in **Table 3** (26–33). Wang et al. (34), funded by the American Heart Association and National Heart, Lung, and Blood Institute, performed a systematic review and meta-analysis of data from RCT and prospective cohort studies. The aggregate RR for CVD-related events was 1.14 (95% CI: 0.92–1.41) in RCT that used calcium supplements vs. placebo. An additional meta-analysis involving 2 RCT with a total sample size of 36,473 evaluated calcium plus vitamin D supplementation vs. placebo. The aggregate RR for CVD-related events was 1.04 (95% CI: 0.92–1.18). The authors concluded that vitamin D at moderate to high doses may reduce CVD risk, whereas calcium supplements seem to have minimal cardiovascular effects.

Among 16 studies reviewed in this article involving >358,000 individuals, there was no indication of a connection between calcium intake and atherosclerotic heart disease or stroke. Although a few of the cited studies showed weak but statistically significant positive associations, a similar number showed associations in the opposite direction. This symmetry of trial results is about what would be expected for an agent without effect on the specified outcome. Accordingly, the authors of this review suggest that the evidence presented to date regarding the hypothesized relationship between calcium supplement use and increased CVD risk is insufficient to warrant a change in the IOM recommendations, which advocate use of supplements to promote optimal bone health in individuals who do not obtain recommended intakes of calcium through dietary sources.

A critical evaluation of the analyses reporting an increased risk of MI

The point estimates from the meta-analyses conducted by Bolland et al. (13,14) are heavily influenced by results from the following 2 studies: the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial and the subgroup of participants in the Women's Health Initiative calcium–vitamin D trial who were not taking personal calcium supplements at baseline. This raises concerns about their conclusions. The cardiovascular outcomes data from the RECORD trial were based entirely on self-report (i.e., not adjudicated). The article published by the RECORD trial group (21) was cited in the meta-analyses by Bolland et al. (13,14) but does not contain information regarding the instance of MI or other CVD-related events. Notably, Wang et al. (34) did not include these results in their meta-analysis because they were unpublished. Lewis et al. (35), using data from RCT of calcium supplements, suggest an excess of incorrectly classified cardiovascular events in the calcium groups compared with the placebo groups, resulting in an attenuation of the RR for MI from 1.69 (95% CI: 1.09–2.61) by self-report to 1.45 (95% CI: 0.88–2.45) after adjudication, suggesting ascertainment bias for cardiovascular events in calcium supplement studies that rely on self-report.

Results from the post hoc subgroup analysis of data from the Women's Health Initiative, according to the presence or absence of personal calcium supplement use at the time of randomization, should be interpreted with caution. The pitfalls of overinterpretation of subgroup analyses in clinical trials have been exhaustively documented, and such analyses are best used for generation of hypotheses that require prospective verification (36–38).

Table 2. RCT of calcium supplementation and CVD[1]

Study, year (ref.)	Study design	Participants	Supplement	Primary endpoint(s)	Follow-up, *y*	RR and 95% CI
Baron et al., 1999 (5)	RCT	672 men and 258 women, ages 40–75 y	Oral calcium carbonate supplement: 0 mg/d, 1200 mg/d	Colorectal adenoma	4 y	Hospitalized cardiac event rate of 11% (n = 50) in the calcium treatment group and 10% (n = 46) in the placebo group
Grant et al., 2005 (21)	RCT	5292 men and women 70 y of age and older	Oral calcium carbonate and/or vitamin D supplement: 0 mg/d plus 0 IU/d, 1000 mg/d plus 800 IU/d, 1000 mg/d, 800 IU/d	Low-energy trauma fracture incidence	2 y to 62 mo	No significant differences among death rates in the 4 groups: calcium plus calciferol (16.9%), calciferol (16.2%), calcium (18.5%), placebo (16.3%). No significant differences among death rates in the combined calcium vs. noncalcium groups (17.7% vs. 16.2%)
Brazier et al., 2005 (22)	RCT	192 women older than 65 y of age	Oral calcium carbonate and vitamin D supplement: 0 mg/d plus 0 IU/d, 1000 mg/d plus 800 IU/d	Bone mineral density	1 y	No significant differences among self-reported adverse cardiovascular events in the calcium treatment group (6.3%; n = 6) compared with the placebo group (5.2%; n = 5)
Prince et al., 2006 (23)	RCT	1460 women older than 70 y of age	Oral calcium carbonate supplement: 0 mg/d, 1200 mg/d	Clinical fracture and vertebral deformity	5 y	No significant differences among self-reported diagnosis of CHD in the calcium treatment group (7.7%; n = 56) vs. the placebo group (7.0%; n = 51). RR of 1.12 (95% CI: 0.77–1.64) was observed for the diagnosis of CHD
Jackson et al., 2006 (24)	RCT	36,282 women 51–82 y of age in the Women's Health Initiative study	Oral calcium carbonate and vitamin D supplement: 0 mg/d, 1000 mg/d calcium plus 400 IU vitamin D	CHD and CVD mortality	7 y	RR for total mortality in the calcium plus vitamin D supplement users vs. nonusers, 0.91 (95% CI: 0.83–1.01)
Lappe et al., 2007 (5)	RCT	1179 postmenopausal women older than 55 y of age	Oral calcium carbonate and/or vitamin D supplement: 0 mg/d plus 0 IU/d, 1400–1500 mg/d, 1400–1500 mg/d plus 1100 IU/d	Fracture incidence	4 y	Adjudicated cardiovascular event rates in the calcium treatment group of 4.76/1000 person-years compared with 6.94/1000 person-years in the placebo group
Hsia et al., 2007 (25)	RCT	36,282 women 51–82 y of age in the fracture incidence portion of the Women's Health Initiative study	Oral calcium carbonate and vitamin D supplement: 0 mg/d, 1000 mg/d calcium plus 400 IU vitamin D	Fracture incidence	7 y	RR in those receiving calcium and vitamin D supplements vs. nonrecipients: 0.92 (95% CI: 0.69–1.28)
Lewis et al., 2011 (26)	RCT with follow-up	1460 women with a mean age of 75.1 ± 2.7 y	Oral calcium carbonate supplement: 0 mg/d, 1200 mg/d	Fracture incidence	5 y	5-y RCT death and/or hospitalization multivariate-adjusted HR: 0.938 (95% CI: 0.69–1.275)

[1] CHD, coronary heart disease; CVD, cardiovascular disease; RCT, randomized, controlled trial.

Table 3. Observational studies with calcium supplementation and CVD as primary endpoints[1]

Study, year (ref.)	Study design	Participants	Supplement	Primary endpoint(s)	Follow-up, *y*	RR and 95% CI
Ascherio et al., 1998 (27)	Cohort	43,738 men 40–75 y of age in the Health Professionals Follow-Up Study	Oral calcium supplement: 0 mg/d, ≥400 mg/d	Incident stroke	8 y	RR observed for total stroke in participants who received ≥400 mg/d vs. nonrecipients: 0.88 (95% CI: 0.60–1.27). RR observed for ischemic stroke in participants who received ≥400 mg/d vs. nonrecipients: 0.83 (95% CI,0.52–1.34)
Bostick et al., 1999 (28)	Cohort	34,486 postmenopausal women 55–69 y of age in the Iowa Women's Health Study	127-item FFQ covering usual food intake and vitamin/ mineral supplement use	Ischemic heart disease mortality	8 y	Multivariate-adjusted RR for the highest vs. lowest quartiles of calcium intake: 0.67 (95% CI: 0.47–0.94). Multivariate-adjusted RR for high supplemental calcium vs. low dietary calcium intake: 0.66 (95% CI: 0.36–1.23)
Iso et al., 1999 (29)	Cohort	85,764 women 34–59 y of age in the Nurses' Health Study	Oral calcium supplement: 0 mg/d, <400 mg/d, ≥400 mg/d	Incident stroke	14 y	RR for stroke in recipients of ≥400 mg/d vs. nonrecipients: 0.88 (95% CI: 0.66–1.18)
Al-Delaimy et al., 2003 (30)	Cohort	39,800 men 40–75 y of age in the Health Professional's Follow-Up Study	Quintiles of calcium supplement use: medians of 0, 57, 200, 325, 500, 1000 mg/d	Incident CHD	12	RR for the highest vs. lowest quintiles of total calcium intake: 0.97 (95% CI: 0.81–1.16). RR for the highest quintile of calcium supplement users vs. nonusers: 0.87 (95% CI: 0.64–1.19).
Pentti et al., 2009 (31)	Cohort	10,555 elderly women 52–62 y of age in the Kuopio Osteoporosis Risk Factor and Prevention Study	Postal inquiry of calcium or calcium plus vitamin D supplement use	CHD		RR for calcium supplement users vs. nonusers: 0.87 (95% CI: 0.64–1.19)
LaCroix et al., 2009 (32)	Cohort	36,282 women 51–82 y of age in the Women's Health Initiative Study	Oral calcium carbonate and vitamin D supplement: 0 mg/d, 1000 mg/d calcium plus 400 IU vitamin D.	CHD and CVD mortality	7 y	RR for CHD in the calcium plus vitamin D supplement users vs. nonusers: 1.01 (95% CI: 0.79–1.29). RR for CVD mortality in the calcium plus vitamin D supplement users vs. nonusers: 0.92 (95% CI: 0.77–1.10).
Lewis et al., 2011 (26)	RCT with follow-up	1460 women with a mean age of 75.1 ± 2.7 y	Oral calcium carbonate supplement: 0 mg/d, 1200 mg/d	Atherosclerotic vascular disease	9.5 y (4.5 y of observation)	9.5-y observational study death and/or hospitalization multivariate-adjusted HR: 0.919 (95% CI: 0.737–1.146)
Wolfe et al., 2011 (33)	Cohort	23,228 patients with rheumatic diseases in the National Data Bank for Rheumatic Disease	Oral calcium plus vitamin D supplement use	Myocardial infarction	8 y	RR in those receiving calcium (with or without vitamin D) but no other bone-active agents: 0.57 (95% CI: 0.42–0.77). RR in those receiving calcium (with or without vitamin D) and taking other bone-active agents: 0.38 (95% CI: 0.22–0.66)

[1] CHD, coronary heart disease; CVD, cardiovascular disease; RCT, randomized, controlled trial.

Additional factors that warrant caution in the interpretation of the results of the meta-analyses by Bolland et al. (13,14) include the inability to adjust for established CVD risk factors and/or uncertainty regarding balance between groups for these risk factors in some of the included studies, as well as exclusion of data from smaller studies in which there were few or no adverse cardiovascular events. Some of the studies failed to consider the possible influences of potential confounders or effect modifiers such as dietary calcium intake and prestudy vitamin D status. In addition, because the trials analyzed were often not designed to assess cardiovascular outcomes, variations in the way in which cardiovascular events were ascertained and the potential for bias in reporting must be considered, as discussed above. Some of these concerns are illustrated by an examination of the trial results published by Bolland et al. (11). The allocation of patients into the placebo or calcium treatment groups did not take into consideration risk factors for CVD, resulting in groups that were unbalanced for some potential confounders. The calcium treatment group contained a greater number of individuals who were former smokers (295 vs. 275) or who had a history of hypertension (220 vs. 207), dyslipidemia (67 vs. 56), and stroke or transient ischemic attack (12 vs. 7). In this study, the reported HR for a composite outcome of MI, stroke, or sudden death was 1.43 (95% CI, 1.01–2.04; $P = 0.043$). However, a multivariate Poisson regression model that included cardiovascular risk factors reduced the significance of the treatment group effect to $P = 0.08$. Other expert opinions on these and other concerns may be found in the letters to the editor published in the *British Medical Journal* (16–18).

Similar concerns are present in the observational analysis of Li et al. (19). The administered FFQ asked study participants whether they took "vitamins" but failed to determine which ones and the amounts taken. Incident cardiovascular events during follow-up were reported by participants or their next of kin in follow-up surveys and verified by tracking medical records or official death certificates.

Application of the Bradford Hill criteria for causal inference

Austin Bradford Hill proposed criteria that should be assessed to evaluate the appropriateness of a causal inference regarding an association between an exposure and a disease outcome (20). We reviewed the available data with a focus on 4 of the Bradford Hill criteria: strength of association, consistency, dose-response, and biological plausibility.

Strength of association. The pooled point estimates for RR of calcium (or calcium plus vitamin D) supplement use for MI (1.21 and 1.27) and stroke (1.20 and 1.12) in the 2 meta-analyses published by Bolland et al. (11,12) are modest and of marginal statistical significance (0.038 and 0.04 for MI and 0.05 and 0.25 for stroke, respectively). Notably, studies in which no events occurred were excluded from both meta-analyses (13,14). The effect is to inflate risk ratio estimates because their inclusion increases the denominator of the ratio without changing the numerator. Five of the 11 trials identified for the first meta-analysis (13) were excluded on these grounds. Nordin et al. (15) calculated that these 5 studies contribute 2400 person-years on calcium supplementation. Inclusion of these studies and a subsequent trial published by Lewis et al., in which no increase in cardiovascular event risk was observed, would lower the point estimates toward the null value (35). These data can hardly be regarded as indicating a "strong" association in light of the exclusion of RCT that show no association (15).

Associations with RR <2.0 are generally considered weak and in a range in which chance (false positives), bias, and/or confounding cannot be ruled out as potential alternative explanations (39). In such cases, consistency of findings from different studies assumes greater importance when evaluating a possible causal inference (39).

Consistency. As discussed earlier, results from prospective, observational studies have generally not favored a positive association between calcium or calcium plus vitamin D supplement use and adverse cardiovascular outcomes (36). The study of Li et al. (19) found only 7 cases of MI among those individuals who took calcium only ($\sim$3.6% of the cohort population supplemented with calcium only). Results from RCT have been mixed, with a large proportion of events for the meta-analyses by Bolland et al. (13,14) contributed by 2 studies (the RECORD trial and a subgroup analysis from the Women's Health Initiative).

Dose-response. The subset analysis of the Women's Health Initiative data by Bolland et al. (14) showed that only women not taking nonprotocol calcium in addition to prescribed calcium were at increased risk of adverse cardiovascular events. In contrast, the women assigned to take calcium plus vitamin D supplements who were already taking personal calcium supplements at baseline showed no increase in risk of MI or stroke. Furthermore, no association was observed between the daily dose of personal supplemental calcium at randomization and subsequent risk of MI or stroke.

Biological plausibility. Calcific deposits in the body occur mainly in areas of previous tissue damage. They consist principally of calcium phosphates. The initial precipitate is typically $CaHPO_4$, and for that crystal form, the serum (at physiological pH and pCO_2) is only half saturated (i.e., for this salt, there is no solubility issue or "physical-chemical pressure" to form calcium deposits). Currently, there is no established mechanism or biological plausibility to support a linkage of calcium supplements to an increased risk of MI or any other CVD-related adverse event.

Briefly, the tissues do not directly sense the source (i.e., food vs. supplement). Instead, the tissues sense only diet-induced changes in serum nutrient concentrations or in hormonal factors altered by the diet and/or supplements. Absorptive calcemia evokes a decrease in parathyroid hormone (PTH) within 30 min of ingestion, amounting to as

much as a 30%–40% decrease in PTH concentration. Both the calcemia and the decrease in PTH are normal, and although this has been well documented mainly through clinical trials involving calcium supplements, it certainly occurs after consumption of other calcium-rich food sources (e.g., dairy) as well. Neither serum change is known to be associated with adverse effects. If anything, the decrease in PTH would result in a lowering of systolic and diastolic blood pressure, thus reducing the risk of MI (15). There is an absorptive increase in extracellular fluid calcium (Ca^{2+}) amounting, at C_{max}, to ~0.025 mmol/L for each 100 mg of calcium in an ingested load. That is a *maximum* figure, and most extracellular fluid concentrations will be less. The small increase in serum calcium concentrations experienced after supplementation is unlikely to be large enough to influence calcification of damaged tissue anywhere in the body. Patients with mild hyperparathyroidism do not have an increased risk of soft-tissue calcification, and their risk of MI has not consistently been shown to be increased after adjustment for known CVD risk factors (in this case, there is a much higher serum calcium concentration than would result from taking calcium supplements) (15).

MI occurs because of occlusion of a coronary artery. Atherosclerotic lesions often calcify. However, that calcification is a result of local tissue factors and not circulating calcium concentrations. Scar tissues calcify as the body's natural reaction to damage. Lipid-rich plaque in which macrophages are active (inflamed) seem to be most susceptible to fissure or rupture, triggering clot formation and a clinical event. There is no known relationship between coronary calcification and instability of calcified plaques; in fact, calcified plaque seems to be less likely to rupture compared with noncalcified plaque (40).

If the use of calcium supplements was associated with an increased risk of MI or other CVD-related adverse events, one might anticipate increases in common CVD risk factors. Although several RCT have assessed the effect of calcium supplementation on lipid profiles, glucose tolerance, platelet aggregation, and blood pressure, the authors are not aware of any studies that report adverse effects on these risk markers for CVD. The findings from a number of clinical trials have shown that calcium supplementation was associated with improvements in serum lipid concentrations, particularly in women (41,42), although this finding has not been universal (43). This effect is hypothesized to be due to the binding of calcium to fatty acids and bile acids in the intestine, thus leading to reduced absorption/reabsorption (40,44).

The authors are aware of emerging but limited data to suggest that calcium plus vitamin D supplementation may influence glucose intolerance, mainly among individuals with type 2 diabetes, in a potentially favorable direction (45). Calcium from supplements seems to be inversely related to platelet aggregation, an effect that would be expected to be reduced risk rather than the opposite (46).

Results from several meta-analyses support a conclusion that calcium supplementation has minor but significant beneficial effects on CVD risk factors, such as reducing both systolic and diastolic blood pressure, with the greatest effects shown in those individuals with the lowest baseline calcium intakes before supplementation and/or those who were hypertensive (47–49). This may be due in part to the lowering of PTH, as discussed previously.

Calcium supplements are typically salts, with calcium constituting less than half the mass of the ingested salt. The principal salts used today are carbonate and citrate, with phosphate, hydroxide, and other anions representing a minor fraction of supplements purchased. Bolland et al. (11–14) reported increased CVD risk in studies using both of the 2 principal salts (carbonate and citrate). Currently, there are no recognized mechanisms by which the anion could contribute to MI risk, and it is particularly challenging to propose a mechanism that would be common to both carbonate and citrate. Thus, there is no plausible, clear biological link that would explain the relationship between calcium supplement use and increased risk of adverse cardiovascular events.

Given the relatively modest size of the point estimates reported by Bolland et al. (11–14), the general inconsistency of these results with those from prospective observational studies, and the lack of a clear biological mechanism to explain the association, the authors judge that bias and confounding cannot be ruled out as potential explanations for the associations between calcium supplement use and increased risk of adverse cardiovascular events reported by Bolland et al. (11–14).

Conclusions

After reviewing the available evidence, the authors conclude that a causal inference is not currently warranted between consumption of calcium from diet or supplements and increased risk of adverse cardiovascular events. Other experts in the field who previously expressed similar opinions in the form of letters to the editor in response to the published articles expressed concerns and viewpoints similar to those communicated in this statement (1,15–18). The authors support the recommendations of the IOM Food and Nutrition Board's 2010 report on calcium and vitamin D with regard to the early RCT and first meta-analysis by Bolland et al. (13), which states the following: "The studies included are small, the event frequency is low, and most outcomes have confidence intervals (CIs) that overlap. Moreover, cardiovascular events were not a primary outcome, the events may not have been well adjudicated, and renal function was not considered as a covariate" (2). (Note that this was published before the analysis of the Women's Health Initiative data set, which, albeit large, represents a post hoc subgroup analysis.)

The authors of this article, the IOM Food and Nutrition Board, and other cited experts in the field judge that these studies are not an appropriate basis on which to change current recommendations and that individuals who do not obtain sufficient intakes of calcium from diet should not be advised to avoid using calcium supplements because of concerns about a potential increase in cardiovascular risk.

The authors of this statement judge that the position of Bolland et al. (11–14) and Li et al. (19) should be viewed as a hypothesis for which it is premature to conclude causality. It is recommended that future studies intended to evaluate risks and benefits of calcium or calcium and vitamin D supplementation be designed in a manner that allows reliable evaluation of cardiovascular outcomes, including proper ascertainment of events and comprehensive documentation of known cardiovascular risk determinants.

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