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Calcium Intake and Risk of Cardiovascular Disease: A Review of Prospective Studies and Randomized Clinical Trials

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Introduction

It has been widely accepted that adequate calcium intake is critical for development and maintenance of bone health, particularly in children and elderly adults. In addition to a pivotal role in skeletal metabolism, the potential effects of calcium on non-skeletal health outcomes have received growing attention recently,[1] among which the effect of calcium intake on cardiovascular disease (CVD) is a subject of intense interest. In *vitro* and in *vivo* experimental studies provide evidence for the involvement of calcium in multiple physiologic processes that may modify the function or structure of the cardiovascular system. Some, but not all, epidemiological studies report associations between inadequate calcium intake and both an adverse CVD risk factor profile and increased risk of CVD events. Moreover, several completed randomized clinical trials have evaluated the risks and benefits of calcium supplementation on bone mineral density and/or fracture incidence. These trials offer valuable, though preliminary, data regarding possible effects of calcium supplements on risk of CVD. Since many generally healthy US adults take supplemental calcium for bone health,[2] it is important to better understand the balance of risks and benefits related to calcium supplement use. This review covers experimental, epidemiological, and clinical evidence regarding the role of calcium intake in the development of CVD among adults.

Metabolism and Physiologic Significance of Calcium

Calcium is quantitatively the most abundant mineral in the human body. An average adult's body typically contains about 1.0–1.5 kg calcium, 99% of which resides in bones and teeth. Besides the structural role in skeleton, calcium is a vital electrolyte that is required for many critical biological functions, including muscle contraction, vascular tone, nerve transmission, and many enzyme-mediated processes.[3] Intracellular Ca^{2+} is typically 10^3–10^4 fold lower than the extracellular level. When the cell is stimulated, calcium enters the cell from extracellular compartments to activate the proteins that carry out the proper actions. Upon the completion of response, calcium is pumped outside the cell or into intracellular storage to await the next activation cycle. Calcium homeostasis is tightly controlled by the calciotropic hormones: vitamin D, parathyroid hormone and calcitonin. These hormones regulate calcium absorption from intestine, excretion or re-absorption from kidney, and

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deposition or release from bone. As a result, circulating concentration of calcium is usually maintained constant in the range of 1.0 to 1.2 mmol/L. Unless there is prolonged and severe calcium deficiency, calcium level in blood is rarely compromised. Excessively high levels of calcium in blood - known as hypercalcemia - rarely occurs due to excessive dietary or supplemental calcium intake, but commonly results from primary hyperparathyroidism or malignancy. Hypercalcemia can cause many medical disorders, such as renal insufficiency, vascular and soft tissue calcification, and kidney stone.

Calcium Intake in the US Population

Since calcium cannot be produced in humans and its excretory conservation is weak, sufficient daily intake is required to maintain adequate calcium supply in each individual. The amount of daily calcium need varies by age. The National Institutes of Health (NIH) recommends a daily intake of 1000 mg for men between 25 and 65 years of age. The same amount is also recommended for women between 25 and 50 years, except for pregnant or lactating women or postmenopausal women not on estrogen replacement therapy, for whom 1,500 mg/day is recommended. For all men and women over 65 years old, the NIH recommends daily calcium intake to be 1,500 mg.[4] The US Institute of Medicine (IOM) recently updated the dietary reference intakes for calcium and recommends intake of 1,000 mg/day for all adults aged 19 through 50 and for men until age 70 and of 1,200 mg/day for women starting at age 51 and both men and women aged >70 years.[5] Calcium-rich foods (milk and other dairy products) are the preferred source of calcium intake due to higher absorption efficiency,[6] while calcium supplementation is an alternative means to reach optimal intake for those who cannot obtain adequate calcium through diet alone.

Despite the well-recognized benefits of calcium on bone health, the daily calcium intake in general US population remains below current recommendations, particularly among elderly adults and women. The mean estimated dietary intake of calcium was 952 and 872 mg/d respectively for men aged 51–70 and ≥71 years and 788 and 750 mg/d respectively for women in the same age groups.[5] More than half of American men older than 50 years and American women in all age groups fail to meet the recommended intake of calcium from food sources; less than 25% of women aged >50 years achieved the recommended level.[5] Because a large number of US adults, mostly older women, take high-dose calcium supplements, it is also necessary to consider the health effects of not only dietary calcium but also supplemental calcium intake.

Potential Effect of Calcium on Cardiovascular Disease Risk

Laboratory studies have shown multiple biological mechanisms through which calcium may affect the risk of developing CVD (Table 1). When consumed in large amounts, calcium binds to fatty acids and bile acids in intestine to form insoluble soaps, subsequently decreases fatty acid absorption and lowers blood cholesterol levels.[7, 8] Dietary calcium also down-regulates activity of renin-angiotensin system,[9] improves sodium-potassium balance,[10] and decreases vascular smooth muscle tone,[11] which all contribute beneficially to blood pressure regulation. High calcium intake suppresses the influx of calcium from outside the cells. In adipocytes, reductions in intracellular calcium inhibit fatty acid synthase and activate lipolysis, potentially leading to an anti-obesity effect.[12] In pancreatic β-cells, insulin secretion is a calcium-dependent process that will be compromised when intracellular calcium is either too high or too low.[13] An optimal range of intracellular calcium is also required for insulin-mediated activities in liver, skeletal muscle, and adipose tissues.[14–17] Maintaining relatively low intracellular calcium levels in these target organs has favorable effects on insulin signal transduction[16, 18] and peripheral insulin sensitivity.[17, 18] In addition, low intracellular calcium inhibits platelet

aggregation,[19] attenuates cytokine-induced inflammation,[20] and augments vascular relaxation.[21–23] Lastly, the cardiovascular benefits of greater calcium consumption may also be indirectly mediated through induced activities of the calciotropic hormones.[12] However, excessively high calcium intake may also lead to hypercalcemia and vascular calcification, thereby raising CVD risk.[24]

Epidemiologic Studies of Dietary Calcium Intake and Cardiovascular Disease Risk

As reviewed before,[3] ecologic studies and cross-sectional studies found both positive and inverse correlations between higher calcium intake and CVD risk factors, including high blood pressure, dyslipidemia, diabetes, and obesity. Reverse causation is a concern in these studies, and thus prospective cohort studies provide more valuable information in assessing the potential effects of long-term dietary and supplemental calcium intake on subsequent development of CVD (Table 2). Among 34,486 US postmenopausal women in the Iowa Women's Health Study, reduction in coronary heart disease (CHD) mortality was observed with high calcium intake: the relative risk (RR) of CHD mortality in the highest versus the lowest quartile of calcium intake was 0.67 (95% CI: 0.47–0.94) for total calcium and 0.63 (95% CI: 0.40–0.98) for dietary calcium without supplements.[25] Among 23,366 participants in a population-based cohort of Swedish men, higher dietary calcium was associated with a borderline significant lower rate of CVD mortality during 10 years of follow-up (RR in the highest compared with the lowest tertile of intake: 0.77, 95% CI: 0.58–1.01).[26] However, no such associations between dietary calcium intake and CHD mortality was found in cohorts of Dutch civil servants,[27] US male health professionals,[28] and Japanese men and women.[29] There was also no association between dietary calcium intake and subsequent incidence of total CHD (including nonfatal myocardial infarction (MI) and CHD death) in US,[28] Finnish,[30] and Japanese cohorts.[31]

For stroke, in the Honolulu Heart Program, the multivariable RR of thromboembolic stroke in the lowest quartile of dietary calcium intake compared with the highest quartile was 1.8 [95% CI: 1.1–2.9].[32] In the Nurses' Health Study, women in the highest quintile of dietary calcium had a multivariable RR of incident ischemic stroke of 0.73 [95% CI: 0.53–1.01] compared to those in the lowest quintile (p for trend=0.04).[33] Similar inverse associations between dietary calcium intake and incident stroke were also observed in two Japanese cohorts[29, 31] but not in the Health Professionals Follow-up Study[34] or the Alpha-Tocopherol, Beta-carotene Cancer Prevention Study.[35] When we conducted meta-analyses to combine these data, the pooled RR of CVD comparing the highest to the lowest level of dietary calcium intake was 0.92 [95% CI: 0.80–1.07] for any CHD and 0.86 [95% CI: 0.69–1.06] for any stroke (Figure 1).

Epidemiologic Studies of Calcium Supplement Use and Cardiovascular Disease Risk

We are aware of five prospective studies that have specifically examined calcium supplement use and risk of CVD, of which four studies found no significant associations (Table 3). In the Health Professionals Follow-up Study, comparing men who took the highest dose of calcium supplement (median of 1000 mg/d) with nonusers, the RRs were 0.87 (95% CI: 0.64–1.19) for total CHD, 1.02 (95% CI: 0.71–1.46) for nonfatal MI, and 0.61 (95% CI: 0.34–1.10) for CHD death;[28] comparing men who took ≥400 mg/d of calcium supplements with nonusers, the RR of stroke was 0.88 [95% CI: 0.60–1.27].[34] In the Iowa Women's Health Study, the RR of CHD mortality comparing women taking ≥500 mg/d of calcium supplements versus nonusers was 0.88 [95% CI: 0.64–1.23].[25] In the

Nurses' Health Study, the RR of stroke for women taking ≥400 mg/d of calcium supplements versus nonusers was 0.75 [95% CI: 0.56–1.01].[33] One recent study of 10,555 Finnish women, aged 52–62 years old, from the Kuopio Osteoporosis Risk Factor and Prevention Study found an increased risk of CHD with the use of calcium supplements or calcium plus vitamin D supplements. During an average of 6.6 years of follow-up, the multivariable RR of CHD comparing women who used calcium or calcium+vitamin D supplements to nonusers was 1.24 (95% CI: 1.02–1.52).[36] Combining these data, the pooled RR of CVD in the highest versus the lowest dose of calcium supplement use was 1.01 (95% CI: 0.78–1.30) for CHD and 0.80 (95% CI: 0.63–1.01) for stroke (Figure 2). These pooled data show no significant benefits of calcium supplements use in reducing the risk of CHD or stroke.

Epidemiologic Studies of Blood Calcium level and Cardiovascular Disease Risk

Since blood concentration of calcium is controlled by calciotropic hormones, calcium intake only modestly changes blood calcium levels. We found only few studies that examined the association between circulating calcium levels and CVD. In a cohort of 2183 middle-aged Swedish men, serum calcium was an independent risk factor for MI during 18-year follow-up. The estimated risk of MI varied from 0.06 to 0.15 over the range of mean ±2 SDs of serum calcium levels. The odds ratio of MI corresponding to the difference was 2.33 (95% CI: 1.21–4.51).[37] In the ARIC study, by contrast, serum calcium was not associated with risk of CHD but was positively associated with risk of stroke over 12.6 years follow-up. The hazard ratio per 0.4 mg/dL increase in serum calcium was 1.01 (95% CI: 0.96–1.06) for CHD and 1.16 (95% CI: 1.07–1.26) for stroke.[38] These data seem to suggest a possible adverse effect of serum calcium on risk of CVD, but the evidence is limited and weak. In a Finnish cohort study of elderly men and women with follow-up for up to 10 years, higher serum concentrations of calcium was not significantly associated with increased risk of acute MI or stroke.[30]

Effect of Calcium Supplementation on Cardiovascular Disease Outcomes in Randomized Clinical Trials

To our knowledge, no randomized clinical trial has specifically tested the effect of calcium supplementation on CVD as a primary endpoint. However, several trials have considered CVD outcomes in secondary analyses or as adverse events (Table 4). A trial of 930 US men and women documented number of hospitalized events due to CVD during 4 years intervention, and found that similar proportions of participants in the groups of 1200 mg/d calcium supplementation and placebo had cardiac disease (11% vs. 10%) and stroke (3% vs. 2%).[39] A randomized, double-blind, placebo-controlled trial of 1,460 Australian women reported a RR of 1.12 (95%CI: 0.77–1.64) for clinically diagnosed CHD comparing women taking 1200 mg/d of calcium carbonate (given in 2 divided doses) versus those taking placebo.[40] A more recent report from the same trial extended analyses to examine the combined endpoint of mortality or first-hospitalization due to CVD after 5 years of randomized treatment plus 4.5 years of post-trial follow-up. The multivariable RR was 0.94 (95%: 0.69–1.28) at the conclusion of treatment, and 0.92 (95%: 0.74–1.15) after all 9.5 years of follow-up.[41] In another trial in New Zealand, 1,471 healthy postmenopausal women were randomized to take 1g/day of calcium citrate or placebo. After 5 years treatment and follow-up, women in the calcium group experienced more adjudicated MI events and composite CVD endpoints including MI, stroke, and sudden death than women in the placebo group.[42] However, when unreported events identified from the national database of hospital admissions were added, the increased RR in the calcium group was no

longer significant (RR=1.49, 95% CI: 0.86–2.57 for MI and RR=1.21, 95% CI: 0.84–1.74 for composite CVD). Finally, a trial of 323 healthy men ≥40 years old from New Zealand randomized participants to take 600 mg/d calcium citrate, 1200 mg/d calcium citrate, or placebo. The composite endpoint of vascular events including angina, MI, sudden death, and coronary revascularization were more common in calcium supplement versus placebo group. Because the vascular event rates were low, however, statistical power to detect any difference was small.[43]

Some trials also evaluated the cardiovascular effects of combined calcium and vitamin D supplementation. In a multi-center trial conducted in France, 192 elderly women with vitamin D insufficiency (25-dehydroxyvitamin D ≤12 ng/mL) were randomized to receive either a combination tablet containing 1,000 mg calcium carbonate and 800 IU vitamin D_3 daily, or placebo tablet. Six patients in active supplement group and five patients in placebo group reported occurrence of cardiovascular event during 1 year of follow-up.[44] Among 36,282 postmenopausal women in the Women's Health Initiative (WHI), daily supplementation of 1000 mg calcium and 400 IU vitamin D (as 25-dehydroxyvitamin D_3) did not alter the risk of CVD during 7 years of follow-up (RR=1.05, 95% CI: 0.91–1.20 for non-fatal MI, RR=1.01, 95% CI: 0.79–1.29 for CHD death, and RR=0.95, 95% CI: 0.82–1.10 for stroke).[45] In another trial of 1,179 community-dwelling healthy postmenopausal women, there was no significant difference in MI or other vascular events after 4 years supplementation with either vitamin D (1000 IU/d) plus calcium (as calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) or calcium alone compared with placebo.[46] When the two calcium treatment groups were combined, the vascular event rate was 4.76/1000 person-year in supplement group and 6.94/1000 person-year in placebo group.

When we combined the data from randomized trials, the pooled RRs of CVD were 1.14 [95% CI: 0.92–1.41] for calcium supplements vs. placebo and 0.99 [95% CI: 0.79–1.22] for combined calcium plus vitamin D supplements vs. double placebos (Figure 3).

Comments

Experimental studies have demonstrated that calcium is involved in multiple physiologic processes potentially related to development of CVD. There have also been several epidemiologic studies examining dietary and supplemental calcium intake in relation to CVD risk, with considerable heterogeneity in study design, participant characteristics, and potential for confounding. Randomized trials specifically designed to evaluate the cardiovascular effects of short- and long-term calcium supplementation remain lacking; current available data is primarily derived from secondary analyses of existing trials. In assessing the totality of evidence to date, it appears that calcium intake, either from diet or from supplements, has little or no effect on CVD risk.

Pooled analyses combining data from several large-scale, population-based, prospective cohort studies showed a non-significant inverse association of dietary calcium intake with incident CHD, incident stroke, and total CVD. A seemingly stronger association with risk of stroke might be attributed to an established blood pressure-lowering effect of dietary calcium.[47] Fewer studies have examined the association between calcium supplement use and incident CVD. The generally null findings noted to date suggest that calcium supplementation is unlikely to confer a strong effect on CVD risk. The Kuopio Osteoporosis Risk Factor and Prevention Study[36] was the only study that reported a significantly increased risk of CHD among users of calcium supplements versus nonusers.[36] Of note, in this study the mean dietary calcium intake from liquid milk products and cheese was 773.8 mg/day for calcium supplements users and 818.2 mg/day for nonusers. Although the study did not determine the daily dose of calcium supplements, total calcium intake likely

exceeded the upper limit of 2000 mg/day by NIH[4] and IOM guidelines[5] for participants with both high habitual dietary and supplemental calcium intake, and these individuals might be at risk for hypercalcemia and its complications. In addition, since this study did not separate calcium and calcium plus vitamin D supplement users, it is not clear whether the increased CHD risk is specifically related to calcium or vitamin D.

There are some discrepancies in our findings on dietary versus supplemental calcium intake with CVD risk. It has been postulated that these discrepancies may be explained in part by their differential impact on circulating calcium.[48] For calcium supplements, usually taken on their own and without food, there would be an immediate and sizable increase in blood calcium concentrations within a couple of hours, and the calciotropic hormone secretion and bone resorption may be affected.[49] In contrast, calcium from foods, typically during a mixed meal, will be absorbed slowly over several hours. This absorption process is less likely to cause detectable change in blood calcium concentration, and the metabolic response will vary according to simultaneous ingestion of other nutrients.[50] Since available studies on blood calcium in association with risk of CVD are very limited and inconclusive, more studies are needed to provide further insight into a complex relation between intake, metabolism, and biologic effect of calcium on pathogenesis of CVD.

Clinical trial data on the effect of calcium supplementation on CVD risk are limited to secondary analyses. Following the first original study that raised concerns about a possible adverse cardiovascular effect of calcium supplementation,[42] a recently published meta-analysis combined data from a total of 15 eligible clinical trials and investigated whether calcium supplements increase the risk of CVD events.[51] In the analysis of 5 trials with patient level data, RR of MI for participants allocated to calcium supplementation compared with those allocated to placebo was 1.31 (95% CI: 1.02–1.67). The corresponding RRs for stroke, composite endpoint of MI, stroke, or sudden death, and all-cause mortality were 1.20 (95% CI: 0.96–1.50), 1.18 (95% CI: 1.00–1.39), and 1.09 (95% CI: 0.96–1.23) respectively. The analysis of trial level data showed similar results, with a pooled RR for MI of 1.27 (95% CI: 1.01–1.59). The authors concluded that calcium supplements (without coadministered vitamin D) are associated with an increased risk of MI and suggested a reassessment of calcium supplement use.

Although the randomized, controlled trial design provides the strongest support for potential causality, *post-hoc* analyses of secondary endpoints as presented in this meta-analysis should be interpreted with caution. First, none of the included trials was specifically designed to test the effect of calcium supplementation on risk of CVD, and the numbers of CVD events in many trials were too small to draw clinically meaningful conclusions. Second, CVD events were not pre-specified endpoints in most trials and therefore were not systematically ascertained. Only 2 of the 15 trials had CVD events adjudicated by blinded investigators. Third, not a single trial included in this meta-analysis reported a significant difference in CVD events between calcium and placebo groups, but only the pooled RR showed a statistically significant effect. Conclusion of this meta-analysis also heavily depends on unpublished data, which can not be evaluated rigorously. Fourth, the combined trial data seem to suggest that calcium supplements increase the risk of MI, but not the risk of stroke or all-cause mortality. The biological mechanisms explaining this specific effect remain uncertain. Taken these limitations together, currently available evidence from clinical trials does not definitively indicate an adverse effect of calcium supplementation on risk of CVD.

The new report recently released by IOM[5] on dietary reference intakes for calcium and vitamin D cited vast evidence for a role of calcium in promoting skeletal growth and maintenance. However, the evidence for any benefits of calcium beyond bone health

remains insufficient. Though the report noted that once intake of calcium surpasses 2000 mg per day for both men and women aged ≥51 years, the risk for harm may increase, it is premature to make definitive statements about the cardiovascular effects associated with high intake of calcium. Our review of epidemiologic studies and clinical trials support the IOM report. Future studies need to include not only more prospective cohorts but also randomized trials specifically designed to evaluate the risks or benefits of calcium supplementation on CVD endpoints as the primary pre-specified outcome.

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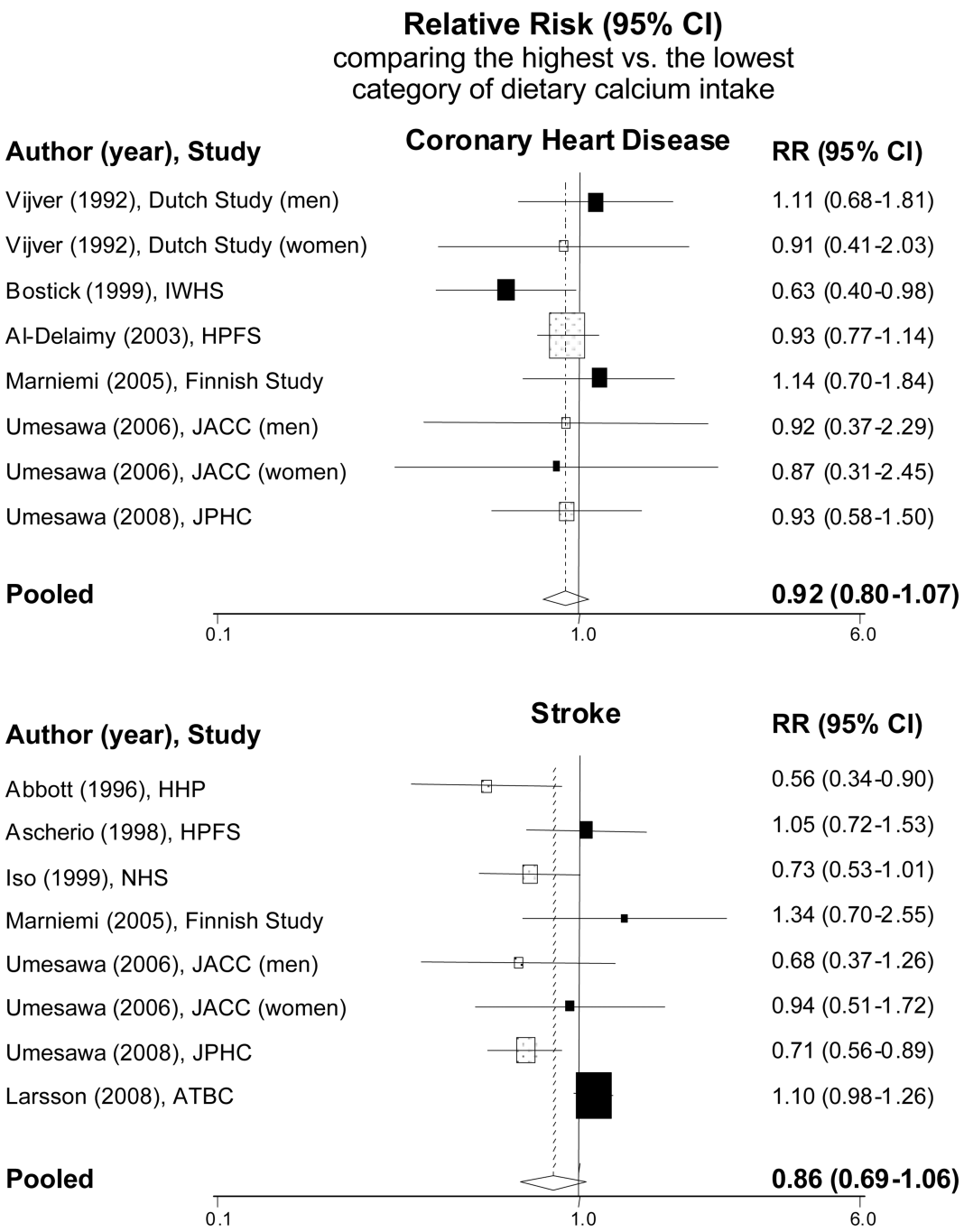

Figure 1.
Meta-analysis of prospective observational studies that examined dietary calcium intake in association with risk of cardiovascular disease.

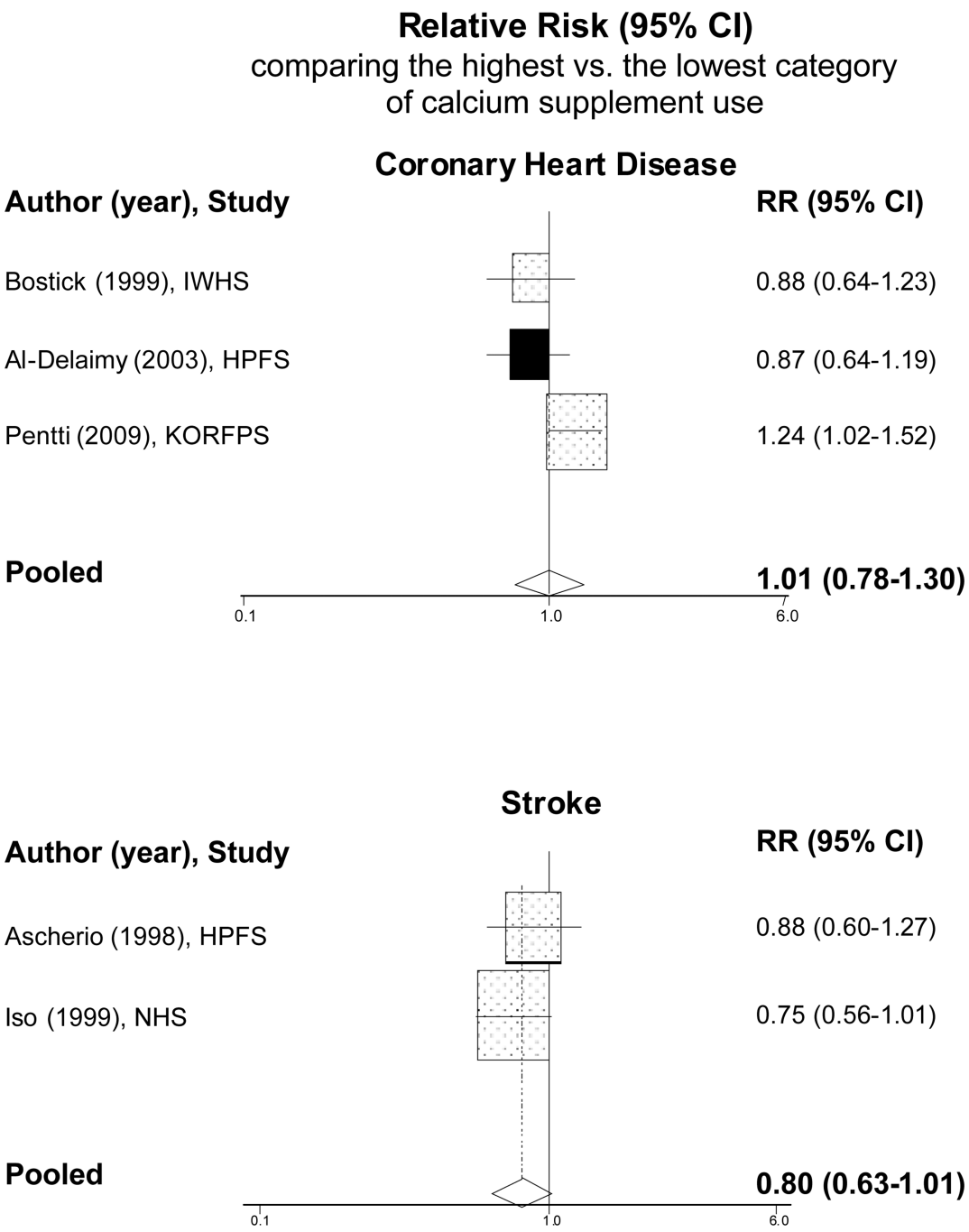

Figure 2.
Meta-analysis of prospective observational studies that examined calcium supplement use in association with risk of cardiovascular disease.

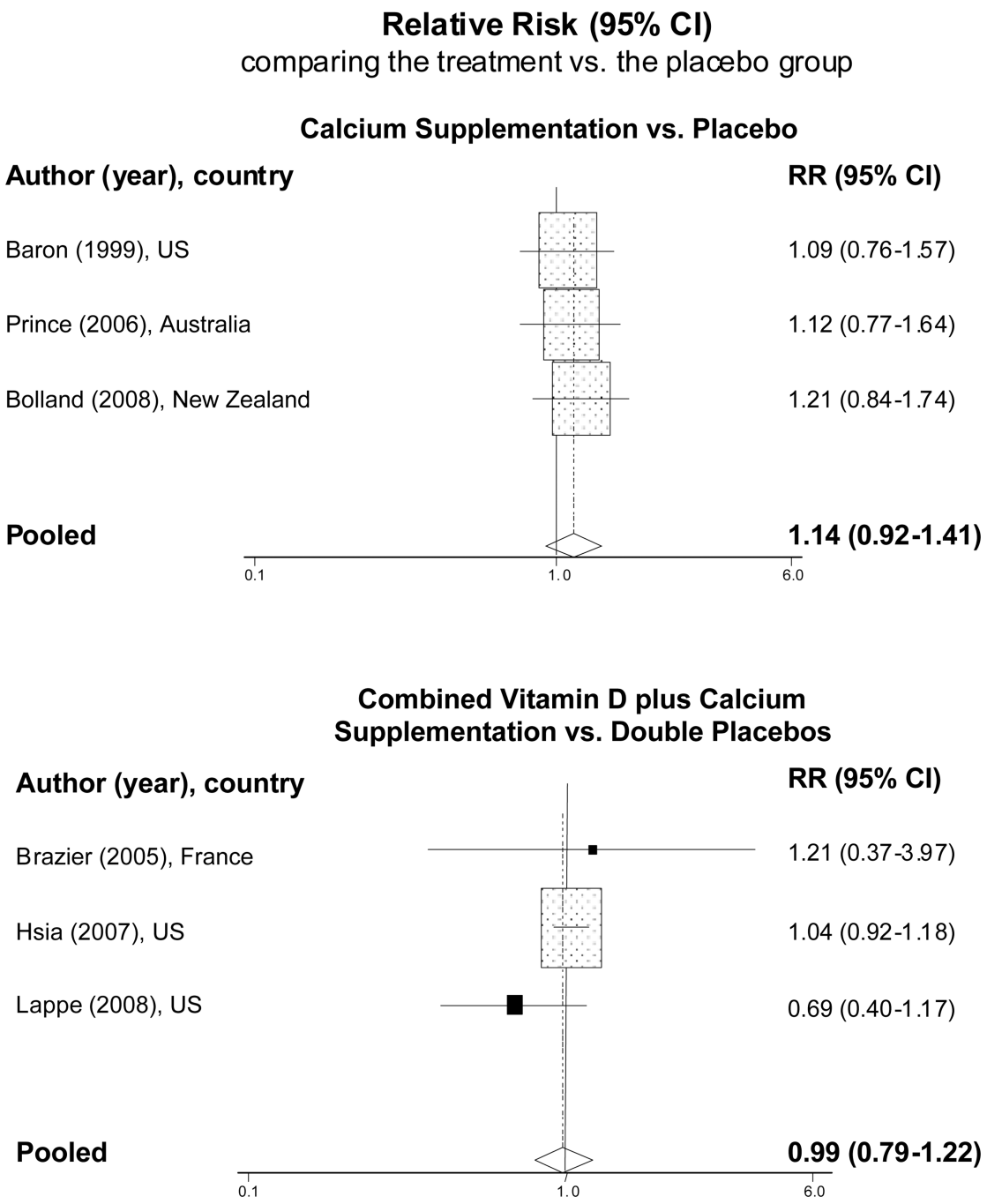

Figure 3.
Meta-analysis of randomized controlled trials of calcium supplementation (with and without vitamin D) that reported the cardiovascular events in the treatment group versus respective placebos.

Table 1

Potential effects and mechanisms of calcium in pathogenesis of cardiovascular disease

Effect	Biological Mechanisms
Favorable cholesterol changes	Binds to fatty acids and bile acids in intestine to form insoluble soaps, increases lipid excretion, and decreases amount of lipids entering enterohepatic circulation.
Blood pressure lowering	Down-regulates activity of renin-angiotensin system, improves sodium-potassium balance, and suppresses vascular smooth muscle tone.
Anti-obesity effect	Reduces adipocyte intracellular calcium, inhibits fatty acid synthase, and activates lipolysis.
Improvement of insulin secretion	Maintains the balance between extracellular and intracellular calcium pools of pancreatic β cell.
Enhancement of insulin sensitivity	Improves insulin signal transduction in primary insulin target tissues, and enhances peripheral insulin sensitivity.
Improvement in inflammatory profile	Inhibits cytokine-induced apoptosis.
Anti-thrombotic property	Reduces platelet intracellular free calcium load and inhibits platelet aggregation.
Augmentation of vasorelaxation	Enhances hyperpolarization by opening of calcium-activated potassium channels, increases sensitivity to nitric oxide, and decreases production of superoxide and vasoconstrictor prostanoids.
Vascular calcification	Calcium deposition in atherosclerotic lesions.

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Table 2

Summary of prospective observational studies that examined the association between dietary calcium intake and risk of cardiovascular disease

Source	Country	Study Design	Study Subjects	Dietary Calcium Intake (mg/day)	Endpoints	Follow-up	Main Findings
Van der Vijver *et al.*, 1992 [27]	Netherlands	Cohort study	Civil servants, 1583 M & 1508 W, 40–65 y	M: ≤585, 585–1245, >1245 F: ≤445, 445–850, >850	CVD & CHD mortality	28 y	OR for CVD mortality in the lowest vs. highest quintile: M: 1.3 (0.8–1.9), W: 1.1 (0.6–2.0) OR for CHD mortality in the lowest vs. highest quintile: M: 0.9 (0.6–1.6), W: 1.1 (0.5–2.5)
Abbott *et al.*, 1996 [32]	United States	Cohort study	Honolulu Heart Program, 3,150 M, 55–68 y	<275, 276–406, 407–605, 606–3109	Incident stroke	22 y	RR for thromboembolic stroke in the lowest vs. highest quartile: 1.8 (1.1–2.9)
Ascherio *et al.*, 1998 [34]	United States	Cohort study	HPFS, 43,738 M, 40–75 y	500, 700, 800, 1000, 1400 (medians)	Incident stroke	8 y	RR for total stroke in the highest vs. lowest quintile: 1.05 (0.72–1.53).
Bostick *et al.*, 1999 [25]	United States	Cohort study	IWHS, 34,486 W, 55–69 y	<543, 543–742, 743–1110, >1110	CHD mortality	8 y	RR for CHD mortality in the highest vs. lowest quartile: 0.63 (0.40–0.98).
Iso *et al.*, 1999 [33]	United States	Cohort study	NHS, 85,764 W, 34–59 y	393, 543, 670, 829, 1128 (medians)	Incident stroke	14 y	RR for ischemic stroke excluding nonatherogenic embolic infarction in the highest vs. lowest quintile: 0.73 (0.53–1.01); P trend=0.04.
Al-Delaimy *et al.*, 2003 [28]	United States	Cohort study	HPFS, 39,800 M, 40–75 y	497, 625, 738, 880, 1190 (medians)	Incident CHD	12 y	RR for total CHD in the highest vs. lowest quintile: 0.93 (0.77–1.14); p trend=0.27. RR for nonfatal MI in the highest vs. lowest quintile: 0.82 (0.65–1.05); p trend=0.09. RR for CHD mortality in the highest vs. lowest quintile: 1.21 (0.85–1.71); p trend=0.53.
Marniemi *et al.*, 2005 [30]	Finland	Cohort study	361M & 394W, 65–99 y,	1420 (overall mean), tertiles	Incident MI & stroke	10 y	RR for MI in the highest vs. lowest tertile: 1.14 (0.70–1.84). RR for stroke in the highest vs. lowest tertile: 1.34 (0.70–2.55).
Umesawa *et al.*, 2006 [29]	Japan	Cohort study	JACC, 21,068 M & 32,319 W, 40–79 y	M: 250, 363, 449, 536, 665 (medians)	CVD, CHD, and stroke mortality	9.6 y	RR for CVD mortality in the highest vs. lowest quintile: M: 0.97 (0.64–1.48); p trend=0.95. W: 1.14 (0.74–1.74); p trend=0.14. RR for CHD mortality in the highest vs. lowest quintile: M: 0.92 (0.37–2.29); p trend=0.43. W: 0.87 (0.31–2.45); p trend=0.50. RR for stroke mortality in the highest vs. lowest quintile: M: 0.68 (0.37–1.26); p trend=0.13.

Source	Country	Study Design	Study Subjects	Dietary Calcium Intake (mg/day)	Endpoints	Follow-up	Main Findings
				F: 266, 379, 462, 545, 667 (medians)			W: 0.94 (0.51–1.72); p trend=0.01.
Larsson *et al.*, 2008 [35]	Finland	Cohort study	ATBC Study, 26,556 M, 50–69 y	876, 1178, 1379, 1581, 1916 (medians)	Incident stroke	13.6 y	RR for cerebral infarction stroke in the highest vs. lowest quintile: 1.10 (0.98–1.26); p trend=0.09. RR for intracerebral hemorrhagic stroke in the highest vs. lowest quintile: 1.20 (0.87–1.64); p trend=0.23. RR for subarachnoid hemorrhagic stroke in the highest vs. lowest quintile: 1.56 (0.98–2.47); p trend=0.10.
Umesawa *et al.*, 2008 [31]	Japan	Cohort study	JPHC Study, 19,947 M & 21,579 W, 40–59 y	233, 344, 439, 603, 753 (medians)	Incident stroke and CHD	13 y	RR for total stroke in the highest vs. lowest quintile: 0.71 (0.56–0.89). RR for CHD in the highest vs. lowest quintile: 0.93 (0.58–1.50).
Kaluza *et al.*, 2010 [26]	Sweden	Cohort study	Cohort of Swedish Men, 23,366 M, 45–79 years	<1,230, 1,230–1,598, ≥1,599	CVD mortality	10 y	HR for CVD mortality in the highest vs. lowest tertile: 0.77 (0.58–1.01), p trend=0.064

Abbreviation: M: men; W: women; CVD: cardiovascular disease; CHD: coronary heart disease; MI: myocardial infarction; OR: odds ratio; RR: relative risk; HR: hazard ratio; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women Health Study; NHS: Nurses' Health Study; JACC: Japan Collaborative Cohort Study; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; JPHC: Japan Public Health Center Study.

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Table 3

Summary of prospective observational studies that examined the association between calcium supplement use and risk of cardiovascular disease

Source	Country	Study Design	Study Subjects	Calcium Supplement Use	Endpoints	Follow-up	Main Findings
Ascherio *et al.*, 1998 [34]	United States	Cohort study	HPFS, 43,738 M, 40–75 y	Nonuser, < 400 mg/d, ≥400 mg/d	Incident stroke	8 y	RR in user ≥400 mg/d. vs. non-users: 0.88 (0.60–1.27) for total stroke 0.83 (0.52–1.34) for ischemic stroke
Bostick *et al.*, 1999 [25]	United States	Cohort study	IWHS, 34,486 W, 55–69 y	0, 1–500, >500 mg/d	CHD mortality	8 y	RR in users vs. nonusers: 0.76 (0.58–1.00) for 1–500 mg/d, 0.88 (0.64–1.23) for >500 mg/d, P trend=0.46.
Iso *et al.*, 1999 [33]	United States	Cohort study	NHS, 85,764 W, 34–59 y	Nonuser, < 400 mg/d, ≥400 mg/d	Incident Stroke	14 y	RR in user ≥400 mg/d. vs. non-users: 0.75 (0.56–1.01).
Al-Delaimy *et al.*, 2003 [28]	United States	Cohort study	HPFS, 39,800 M, 40–75 y	0, 57, 200, 325, 500, 1000 mg/d (Medians)	Incident CHD	12 y	RR for total CHD in the highest vs. the lowest quintile of users: 0.87 (0.64–1.19); P trend=0.31. RR for nonfatal MI in the highest vs. the lowest quintile of users: 1.02 (0.71–1.46); P trend=0.84. RR for CHD mortality in the highest vs. the lowest quintile of users: 0.61 (0.34–1.10); P trend=0.05.
Pentti *et al.*, 2009 [36]	Finland	Cohort study	Kuopio Osteoporosis Risk Factor and Prevention Study, 10,555 W, 52–62 y	Nonuser, user	Incident CHD	6.55 y	HR in user vs. non-users: 1.24 (1.02–1.52) in entire cohort 1.26 (1.01–1.57) in postmenopausal women

Abbreviation: M: men; W: women; CHD: coronary heart disease; MI: myocardial infarction; RR: relative risk; HR: hazard ratio; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women Health Study; NHS: Nurses' Health Study.

Table 4

Summary of randomized clinical trials of calcium supplementation (with and without vitamin D) that reported the events of cardiovascular disease.

Source	Country	Study Subjects	Intervention	Duration	Primary Endpoints	Main findings on CVD endpoints
			Calcium Supplement only			
Baron *et al*, 1999 [39]	U.S.	672 M&258 W, 61 y (mean)	1200 mg/d as calcium carbonate Placebo	4 years	Recurrence of colorectal adenoma	N of hospitalized cardiac events: 50 (11%) in calcium group 46 (10%) in placebo group N of hospitalized stroke vents: 12 (3%) in calcium group 11 (2%) in placebo group
Prince *et al*, 2006 [40]	Australia	1460 W, >70 y	1200 mg/d (in 2 divided dose) as calcium carbonate Placebo	5 years	Clinical fracture, vertebral deformity	RR of diagnosed CHD in intervention vs. placebo: 1.12 (0.77–1.64)
Bolland *et al*, 2008 [42]	New Zealand	1471 W, postmenopausal, 74 y (mean)	1000 mg/d as calcium citrate Placebo	5 years	Fracture incidence, bone density	RR of CVD events in intervention vs. placebo group: 1.49 (0.86–2.57) for MI 1.37 (0.83–2.28) for stroke 0.51 (0.13–2.01) for sudden death 1.21 (0.84–1.74) for composite CVD
Reid *et al*, 2008 [43]	New Zealand	323 M, ≥40 y	1200 mg/d and 600 mg/d as calcium citrate Placebo	2 years	Bone mineral density	Composite vascular events: N=3 in 1200 mg/d calcium group N=2 in 600 mg/d calcium group N=0 in placebo group P=0.24
			Calcium + Vitamin D Supplement			
Brazier *et al*, 2005 [44]	France	192 W, >65 y	1000 mg/d as calcium carbonate and vitamin D 800 IU/d (in 2 divided dose) Placebo	1 year	Bone mineral density	N of adverse cardiovascular events: 6 (6.3%) in treatment group 5 (5.2%) in placebo group
Hsia *et al*, 2007 [45]	United States	36,282 W, postmenopausal, 50–79 y	1000 mg/d as calcium carbonate and vitamin D_3 400 IU/d (in 2 divided dose) Placebo	7 years	Fracture incidence	RR of CVD events in intervention vs. placebo group: 1.04 (0.92–1.18) for total CHD 1.05 (0.91–1.20) for nonfatal MI 1.01 (0.79–1.29) for CHD death 0.95 (0.82–1.10) for total stroke
Lappe et al, 2008 [46]	United States	1179 healthy W, postmenopausal, >55 y	1400 mg/d as calcium citrate or 1500 mg/d as calcium carbonate and vitamin D placebo Calcium and 1000 IU vitamin D_3/d Double placebos	4 years	Fracture incidence	Total vascular event rate: 4.76/1000 person-year in calcium group (with and without vitamin D), 6.94 /1000 person-year in placebo group RR=0.69 (not statistically significant)

Abbreviation: M: men; W: women; CVD: cardiovascular disease; CHD: coronary heart disease; CABG: coronary artery bypass surgery; PCI: percutaneous coronary interventions; MI: myocardial infarction; RR: relative risk.

Amount of calcium provided in the table is elemental calcium dosage.