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REVIEW PAPER

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Calcium supplementation and cardiovascular risk: A rising concern

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Over the past decade, the number of individuals taking calcium supplementation worldwide has been on the rise, especially with the emergence of new pharmaceutical companies specialized in the marketing of dietary supplements; with calcium supplementation being their main business axis. This is mostly because of the established role of calcium in the prevention and treatment of osteoporosis and, to a lesser extent, its role in the prevention of fractures. Recently, a rising body of evidence on the adverse effect of calcium supplementation on nonskeletal, especially cardiovascular, health has been a cause for concern. In fact, a significant number of studies have reported an association between calcium supplementation and adverse cardiovascular events, even though high dietary calcium intake was shown to have a protective effect. The mechanism by which calcium supplementation could cause a cardiovascular event was still unclear until a recent study published in the *Journal of the American Heart Association*. Combining this recent finding with available data associating calcium supplementation with cardiovascular mortality and all-cause mortality, we call on the need for an evidence-based approach to calcium supplementation, while stressing on the safety of dietary calcium intake over the former on cardiovascular health.

1 | INTRODUCTION

In daily practice, health workers encounter an increasing number of patients currently taking calcium supplements without any proven deficit, especially elderly postmenopausal women. This practice quickly spread in the past decade based on the supposed role of calcium in the prevention of osteoporosis and fractures, especially hip fractures, among the elderly population. In fact, recent studies have reported up to 70% of older women taking calcium supplementation in some developed countries.[1] Few data are available in developing countries on the subject, but the practice is just as commonly encouraged as calcium and vitamin D inadequacies, especially in the elderly, have been a cause for concern.[2] With the emergence of new companies specializing in the selling of dietary supplements that have made calcium supplementation a priority marketing axis, this practice can only escalate.[3] The Institute of Medicine's guideline-recommended daily allowance for calcium intake is 1000 mg/d for men aged 18 to 70 years and women aged 18 to 50 years and 1200 mg/d for men 70 years and older and women 50 years and older.[4] But to date, many people in general population consume high doses calcium-containing multivitamin and mineral supplements.[5] Nevertheless, there is rising concern on the cardiovascular effects of calcium supplementation, especially when it leads to high calcium intake, which is thought to increase the risk of myocardial infarction, stroke and cardiovascular mortality, as well as other noncardiovascular events such as kidney stones.[6,7] The increased cardiovascular risk and overall mortality reported by some cohort studies is far from unanimous, in part because of the scarcity of findings related to the pathophysiological mechanism underlying such an observation.[8] In this sense, a study recently published in the *Journal of the American Heart Association* by Anderson and colleagues,[7] assessing the association between the risk of coronary artery calcification (CAC) and calcium intake, showed that, after 10 years of follow-up, calcium supplement use was associated with increased risk for incident CAC (relative risk [RR], 1.22; 95% confidence interval [CI], 1.07–1.39). This brought light to the issue and relaunched the debate on the necessity of and risk associated with calcium supplementation in the general population as practiced and promoted today.[7]

2 | IMPORTANCE OF CALCIUM ON CARDIOVASCULAR HEALTH

The benefit of calcium intake on blood pressure (BP) has been consistent among several studies, demonstrating an inverse relationship between calcium and BP. In 2006, a Cochrane review including 13 randomized control trials with a sample size of 485 participants demonstrated a small but significant reduction in mean systolic BP by 2.5 mm Hg (95% CI, −4.5 to −0.6) in patients with hypertension, even though they failed to show any benefit on diastolic BP.[9] These findings were attributed to a small sample size and possible bias, as the included studies were mostly of poor quality. A more recent Cochrane review including 16 trials with 3048 normotensive participants showed a mean reduction in systolic and diastolic BP by 1.43 mm Hg (CI, −2.15 to −0.72) and 0.96 mm Hg (CI, −1.46 to −0.50), respectively, with the greatest effect observed among participants younger than 35 years and a daily dose of calcium supplementation >1000 mg.[10] However, the authors cautioned that these results must be interpreted carefully as the mechanism by which calcium causes a reduction in BP is still unclear. They also called for more basic and clinical studies in order to allow a better understanding of the mechanism underlying the association between calcium supplementation and BP reduction. In addition, the authors suggested that more studies should be carried out to evaluate the required dose and best strategy to improve calcium intake, comparing the effect of dietary with supplemental calcium. Evidence on the causal association between calcium supplementation and BP reduction has been demonstrated by other studies.[11] Investigators[11] showed that calcium supplementation has the ability to reduce the risk of pregnancy-related hypertensive disorders, especially preeclampsia.

Even though the mechanism by which calcium influences BP is poorly understood, it has been hypothesized that low calcium intake would result in changes in vitamin D and parathyroid hormones. These changes in vitamin D and parathyroid hormones result in an increase in intracellular calcium and hence increased reactivity of the vascular smooth muscles. Increased reactivity of vascular smooth muscles would lead to raised peripheral resistance and consequently increased BP.[10,12,13] According to this hypothesis, a raised BP is an indirect effect of a compensatory release of the vitamin D and parathyroid hormones in response to low calcium levels in the organism.[14]

3 | STRENGTHS AND LIMITATIONS OF AVAILABLE EVIDENCE ON THE BENEFITS OF CALCIUM SUPPLEMENTATION ON BONE HEALTH

The widespread use of calcium supplementation is mainly based on the effect of calcium in the prevention of osteoporosis and related fractures. Although a very large number of studies has investigated this issue, there is still weak evidence that calcium supplementation in elderly individuals within the general population improves bone health. In the early 2000s, the National Institutes of Health reached a consensus on the supplementation of calcium and vitamin D in individuals with inadequate dietary intake for the prevention of osteoporosis.[15] This assertion was later the subject of much debate and further meta-analyses assessing the true effect of calcium supplementation provided no evidence on the benefits of calcium supplementation on bone health in the general population.[7,8] Even though there is an established role of calcium supplementation in the prevention of osteoporosis, available evidence supporting its role in the prevention of fractures is weak and inconsistent among studies.[16] While some findings, mostly drawn from institutionalized and vitamin D–deficient patients, showed a small or marginal effect of calcium supplementation on bone loss and risk of total fracture, others reported no reduction in hip fracture risk with calcium supplementation and a neutral effect for nonvertebral fractures.[7,8] For instance, in a recently published systematic review and meta-analysis by Chung and colleagues,[17] including studies where calcium supplementation dose was provided, calcium supplementation was found to be neither harmful nor beneficial. There was a lack of dose-response benefit for calcium supplementation, challenging the thinking that "more is better." Given that, Bolland and colleagues[6] suggested that widespread prescription of calcium supplements to prevent fractures should be abandoned since there is no strong evidence on the benefits of calcium supplementation in the general population and universal supplementation without proven deficit in the elderly was thought unnecessary. So, there is a need for stronger evidence in order to incorporate this suggestion into daily clinical practice.

4 | CALCIUM SUPPLEMENTATION AND CARDIOVASCULAR RISK

Recently, there has been an increasing interest on the nonskeletal outcomes, including cardiovascular health of calcium intake, especially calcium supplementation and consequently its relation with cardiovascular mortality or morbidity.[1,6,18] Most studies agree on the fact that adequate calcium intake is important for bone health and several major physiologic functions. But the effects of calcium supplementation on other health outcomes are still controversial. At the root of this debate is the meaning of the term "adequate" since the problem is not only the quantity but also the quality and source of calcium intake. In this context, many cohort studies have shown an increase in cardiovascular risk and mortality associated with calcium supplementation but not dietary calcium intake. Thus, it is generally admitted that dietary calcium intake is safe compared with calcium supplementation.[1,6] For instance, in a large prospective cohort of 388 229 men and women aged 50 to 71 years, Xiao and colleagues[1] found that men with >1000 mg/d intake of supplemental calcium had significantly higher risk of total CVD death (multivariate RR=1.20, [95% CI, 1.05, 1.36]) after an average follow-up of 12 years. Another prospective study conducted by Yang and colleagues,[19] which involved 132 823 participants followed during 17.5 years, reported

that dietary calcium was not associated with all-cause mortality in either sex. However, men who were taking ≥1000 mg/d supplemental calcium had a higher risk of all-cause mortality (RR, 1.17; 95% CI, 1.03–1.33) and cardiovascular disease–specific mortality (RR, 1.22; 95% CI, 0.99–1.51). For women, they found that supplemental calcium was inversely associated with mortality from all causes (RR, 0.90 [95% CI, 0.87–0.94], 0.84 [95% CI, 0.80–0.88], and 0.93 [95% CI, 0.87–0.99] for intakes of 0.1 to <500, 500 to <1000, and ≥1000 mg/d, respectively; *P* trend <.01). Overall, total calcium intake was inversely associated with mortality in women (*P* trend <.01) but not in men.[19] There is a growing concern on the increase in cardiovascular and all-cause mortality related to supplemental calcium intake; however, despite this rising evidence, many gray areas persist regarding the mechanism by which calcium supplementation may increase the risk of myocardial infarction and overall cardiovascular mortality (Tables 1 and 2).

5 | CALCIUM SUPPLEMENTATION AND CORONARY ARTERY CALCIFICATION (CAC)

Until now, scant evidence existed for biological mechanisms linking calcium supplementation to atherosclerotic heart disease.[5] A previous substudy of the Women's Health Initiative Calcium/Vitamin D Supplemental Trial found no difference in coronary artery calcium scores after 7 years of follow-up in women receiving supplements (1000 mg of elemental calcium and 400 IU of vitamin D3 daily) and those receiving placebo.[21] More recently, the National Osteoporosis Foundation and the American Society for Preventive Cardiology convened an expert panel to evaluate the effects of dietary and supplemental calcium on cardiovascular disease based on the existing peer-reviewed scientific literature. According to this panel, there was currently moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has a relationship (beneficial or harmful) with the risk for cardiovascular and cerebrovascular disease mortality, or all-cause mortality in generally healthy adults. In light of available evidence, their conclusion was that calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000–2500 mg/d) should be considered safe from a cardiovascular standpoint.[22] However, the paper published by Anderson and collaborators[7] suggests the opposite. Indeed, they provided evidence of the association between the risk of CAC and calcium intake, both dietary and supplementary, in a large cohort of patients involving 2742 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) without cardiovascular disease. In this cohort, baseline total calcium intake was assessed from diet (using a food frequency questionnaire) and calcium supplements (by a medication inventory) and categorized into quintiles: 313.3 mg/d, 540.3 mg/d, 783.0 mg/d, 1168.9 mg/d, and 2157.4 mg/d. Baseline CAC was also measured by computed tomography, and CAC measurements were repeated after 10 years.[7] They found that after adjusting for confounders, the RR of incident CAC by quintile 1 through 5 of calcium intake were 1 (reference), 0.95 (0.79–1.14), 1.02 (0.85–1.23), 0.86 (0.69–1.05), and 0.73 (0.57–0.93), respectively. This indicates that high total calcium intake may be associated with a decreased risk of incident atherosclerosis over long-term follow-up. On the contrary, they found that calcium supplement use was associated with a 22% increase in risk of incident CAC (RR, 1.22; 95% CI, 1.07–1.39). In addition, Li and colleagues[42] prospectively evaluated the association of dietary calcium intake and calcium supplementation with MI, stroke risk, and overall cardiovascular disease mortality. They showed that after an average follow-up of 11 years, in comparison with nonusers of any supplements, users of calcium supplements had a statistically significantly increased MI risk (HR, 1.86; 95% CI, 1.17–2.96), which was more pronounced for users of calcium supplements only (HR, 2.39; 95% CI, 1.12–5.12). It is noteworthy that among previous studies that did not demonstrate a relationship between the consumption of calcium supplements and coronary arterial calcifications, were not primarily designed to evaluate the effect of calcium supplements on cardiovascular or coronary heart disease outcomes; increasing the potential for false-positive findings.[5] Therefore, the recent findings by Anderson and colleagues[7] offer additional information on the possible mechanism by which calcium supplements may raise the risk of myocardial infarction. This may be through an increase in incident atherosclerosis since the CAC score is a well-established surrogate marker for burden of atherosclerosis and its prognosis.[7] These studies suggest that long-term consumption of calcium supplements might increase the risk of atherosclerosis. On the contrary, there might be a protective effect of total calcium intake on incident coronary atherosclerosis, particularly among nonsupplement users. Indeed, patients achieving high calcium intake with lower dietary proportion and higher supplement use present the greatest risk of coronary subclinical atherosclerosis. This is of paramount importance because more patients with high calcium needs such as the elderly, encouraged by advertisements of companies specializing in the manufacturing and selling of calcium supplements, rely on regular consumption of high doses of calcium supplements to fill their daily needs. These findings clearly show that increasing calcium intake should ideally be done by increasing dietary intake, not a supplement that has a harmful effect on cardiovascular health. Thus, the widespread use of calcium supplements, largely prevalent in older individuals, is not a beneficial way to meet the growing needs of calcium with age and should indeed be abandoned.

6 | CONCLUSIONS

Recently published data suggest a significant increase in incident CAC with calcium supplementation. Along with previous data associating calcium supplementation with cardiovascular mortality and all-cause mortality, this new evidence stresses the need for an evidence-based approach to calcium supplementation. Moreover, it is urgent to educate health care providers on the possible risk of excessive and unnecessary calcium supplementation. From a cardiovascular perspective, dietary calcium intake by eating foods high in calcium appears safer than calcium loading with supplements.

TABLE 1 Randomized Controlled Trials Examining the Effects of Calcium With or Without Vitamin D Supplementation on CVD Outcomes

Name of First Author, Publication Year	Sample Size	Intervention	Primary CVD Outcome	Follow-Up Duration, y	Relevant Findings
Avenell, 2012[23]	5 292	Calcium and vitamin D supplementation	All-cause mortality, vascular disease mortality and cancer mortality	3	Supplemental calcium showed no effect on vascular disease mortality
Bolland, 2011[24]	36 282	Calcium and vitamin D supplementation	Incidence of MI, coronary revascularization, death from coronary heart disease, and stroke	7	Increased risk of MI (HR, 1.21; 95% CI, 1.01–1.44) and stroke (HR, 1.2; 95% CI, 1.00–1.43)
Bolland, 2015[25]	36 282	Calcium and vitamin D supplementation	Incidence of cardiovascular events and death	7	Increased risk of MI (HR, 1.2; CI, 0.97–1.48) and stroke (HR, 1.15; CI, 0.93–1.43)
Cauley, 2013[26]	36 282	Calcium and vitamin D supplementation	Incidence and mortality of CVD	11.9	No effect on CVD incidence (HR, 1.03; CI, 0.94–1.13) or mortality (HR, 0.99; 95% CI, 0.84–1.18)
Donneyong, 2015[27]	35 983	Calcium and vitamin D supplementation	Occurrence of heart failure in postmenopausal women	7.1	No significant reduction in incidence of heart failure However, calcium and vitamin D supplementation showed a beneficial effect on incidence of heart failure in high-risk groups, ie, patients with prior coronary heart disease, diabetes mellitus, or hypertension (HR, 0.63; 95% CI, 0.46–0.87)
Hsia, 2007[28]	36 282	Calcium and vitamin D supplementation	Incidence of MI or CHD and stroke	7	No effect on coronary or cerebrovascular risk
LaCroix, 2009[29]	36 282	Calcium and vitamin D supplementation	Incidence of CHD, stroke, and total mortality	7	No significant effect on coronary or cerebrovascular risk or total mortality
Prentice, 2013[30]	36 282	Calcium and vitamin D supplementation	Incidence of total heart disease, CHD, MI, and stroke	7	No significant effect on the risk of total heart disease, CHD, MI, and stroke
Lewis, 2011[31]	1 460	Calcium supplementation daily	Incidence of first-time hospitalization or mortality from atherosclerotic vascular disease	9.5	No significant effect on the mortality (HR, 0.938; 95% CI, 0.690–1.275) or incidence of first-time hospitalization (HR, 0.919; 95% CI, 0.737–1.146) from atherosclerotic vascular disease

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction.

TABLE 2 Prospective Cohorts Examining the Effects of Calcium With or Without Vitamin D Supplementation on CVD Outcomes

Name of First Author, Publication Year	Sample Size	Intervention	Primary CVD Outcome	Follow-Up Duration, y	Relevant Findings
Adebamowo, 2015[32]	42 669	Dietary and supplemental calcium	Incidence of stroke	24	No significant effect of dietary (HR, 0.85; CI, 0.73–1.00 [*P*=.1]) or supplemental (HR, 0.94; CI, 0.80–1.10 [*P*=.43]) calcium on the incidence of stroke
Adebamowo, 2015[32]	180 864:86 149 in Nurses' Health Study and 94 715 in Nurses' Health Study II	Dietary and supplemental calcium	Incidence of stroke	30	A protective effect of dietary calcium on incidence of stroke (HR, 0.85; 95% CI, 0.76–0.94 [*P*=.006]) No significant effect of dietary or supplemental calcium on incidence of stroke (HR, 0.97; 95% CI, 0.87–1.09)
Khan, 2015[33]	41 514	Dietary calcium	Incidence of nonfatal CVD, incidence of stroke events	12	Significant protection against nonfatal CVD (HR, 0.84; 95% CI, 0.70–0.99 [*P*=.04]) and stroke (HR, 0.69; 95% CI, 0.51–0.93 [*P*=.02])
Larsson, 2011[34]	34 670	Supplemental calcium	Incidence of stroke	10.4	Increased risk of stroke with calcium supplementation (RR, 2.04; 95% CI, 1.24–3.35 [*P*=.47])
Block, 2005[35]	129	Supplemental calcium	Effect on CACS	1.5	Progressive increase in patients with CACS >30 (*P*<.05)
Al-Delaimy, 2003[36]	39 800	Dietary and supplemental calcium and vitamin D	Incidence of IHD	12	No association was found between dietary (RR, 0.93; 95% CI, 0.77–1.14 [*P*=.27]) and supplemental (RR, 0.87; 95% CI, 0.64–1.19 [*P*=.31]) calcium and vitamin D
Ascherio, 1998[37]	43 738	Supplemental calcium	Incidence of stroke	8	Nonsignificant decrease in the risk of stroke (RR, 0.88; 95% CI, 0.63–1.23 [*P*=.1])
Chan, 2013[38]	3139	Dietary calcium	Death from CVD	9.1	Nonsignificant decrease in the risk of death from CVD (HR, 0.70; 95% CI, 0.41–1.21 [*P*=.228])
Iso, 1999[39]	85 764	Calcium supplementation	Incidence of stroke	1 164 674 person-years	Protective effect of supplemental calcium (RR, 0.69; 95% CI, 0.50–0.95 [*P*=.02])
Kaluza, 2010[40]	23 366	Dietary calcium intake	CVD mortality	10	No association between dietary calcium and CVD mortality (HR, 0.91; 95% CI, 0.75–1.10 [*P*=.77])
Larsson, 2008[41]	26 556	Dietary calcium intake	Incidence of stroke	13.6	No effect on incidence of stroke (RR, 0.96; 95% CI, 0.84–1.10)
Li, 2012[42]	23 980	Dietary calcium intake	CVD deaths, incidence of MI, and stroke	11	Nonsignificant decrease in risk of MI (RR, 0.67; 95% CI, 0.48–0.94 [*P*=.39]) and a neutral association with the risk of stroke (RR, 1.17; 95% CI, 0.77–1.77) and CVD mortality (RR, 1.22; 95% CI, 0.83–1.81)
Michaelsson, 2013[43]	61 433	Dietary and supplemental calcium	Incidence of MI, stroke, and CVD mortality	11	Dietary calcium intake was associated with increased risk of CVD-related death (HR, 1.49; 95% CI, 1.09–2.02) and IHD (HR, 2.14; 95% CI, 1.48–3.09) but no association with risk of stroke (HR, 0.73; 95% CI, 0.33–1.65) Total calcium intake was associated with increased risk of CVD mortality (RR, 1.51; 95% CI, 1.23–1.84) and IHD (HR, 1.90; 95% CI, 1.45–2.49) but not stroke (HR, 0.96; 95% CI, 0.61–1.50)
Paik, 2014[44]	74 245	Dietary and supplemental calcium and vitamin D	Incidence of CHD and stroke	24	Protective effect against the risk of CHD (RR, 0.71; 95% CI, 0.61–0.83 [*P*<.001]) but neutral effect against the risk of stroke (RR, 1.03; 95% CI, 0.87–1.21 [*P*=.61])

(Continues)

TABLE 2 (Continued)

Name of First Author, Publication Year	Sample Size	Intervention	Primary CVD Outcome	Follow-Up Duration, y	Relevant Findings
Sluijs, 2014[45]	36 094	Dietary and supplemental calcium	Incidence of stroke	12	Neutral effect of dietary (RR, 0.90; 95% CI, 0.68–1.19) supplemental (RR, 0.98; 95% CI, 0.75–1.29) calcium on stroke
Umesawa, 2008[46]	41 526	Dietary calcium	Incidence of CHD and stroke	533 692 person-years	Protective effect against the risk of stroke (HR, 0.70; 95% CI, 0.56–0.88 [*P*=.007]) but neutral effect against CHD (HR, 0.94; 95% CI, 0.59–1.51 [*P*=.17])
Weng, 2008[47]	1772	Dietary calcium	Incidence of ischemic stroke	10.6	Increased risk of ischemic stroke (RR, 1.66; 95% CI, 1.08–2.53 [*P*=.017])
Yang, 2016[19]	132 823	Dietary and supplemental calcium	All-cause mortality and CVD-specific death	17.5	For men: nonsignificant increased risk of all-cause mortality with supplemental calcium (RR, 1.17; 95% CI, 1.03–1.33), specifically CVD-specific mortality (RR, 1.22; 95% CI, 0.99–1.51) For women: protective effect against all-cause mortality (RR, 0.93; 95% CI, 0.87–0.99 [*P*<.01]) Dietary calcium was not associated with all-cause mortality in both sexes
Xiao, 2013[1]	388 229	Dietary and supplemental calcium intake	All CVD death		Increased risk of CVD mortality with supplemental calcium in men (RR, 1.20; 95% CI, 1.05–1.36), specifically death from cardiac disease (RR, 1.19; 95% CI, 1.03–1.37) No associated mortality or benefit found in women taking supplemental calcium (RR, 1.06; 95% CI, 0.96–1.18) Dietary calcium intake was unrelated to CVD death in men (RR, 1.04; 95% CI, 0.97–1.12) and women (RR, 1.04; 95% CI, 0.94–1.15)

Abbreviations: CACS, coronary artery calcification score; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; RR, relative risk.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. *JAMA Intern Med*. 2013;173:639-646.
2. Tucker KL, Buranapin S. Nutrition and aging in developing countries. *J Nutr*. 2001;131:2417S-2423S.
3. Grey A, Bolland M. Web of industry, advocacy, and academia in the management of osteoporosis. *BMJ*. 2015;21:h3170.
4. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D* [Internet]. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011 [cited 2017 Apr 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK56070/
5. Margolis KL, Manson JE. Calcium supplements and cardiovascular disease risk: what do clinicians and patients need to know? *Ann Intern Med*. 2016;165:884-885.
6. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. *Ther Adv Drug Saf*. 2013;4:199-210.
7. Anderson JJ, Kruszka B, Delaney JA, et al. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc*. 2016;10:5(10).
8. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336:262-266.
9. Dickinson HO, Nicolson DJ, Cook JV, et al. Calcium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev*. 2006;2:CD004639.
10. Cormick G, Ciapponi A, Cafferata ML, Belizán JM. Calcium supplementation for prevention of primary hypertension. *Cochrane Database Syst Rev*. 2015;6:CD010037.
11. The Cochrane Collaboration. *Cochrane Database of Systematic Reviews: Protocols* [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 1996. http://doi.wiley.com/10.1002/14651858.
12. Webb RC. Smooth muscle contraction and relaxation. *Adv Physiol Educ*. 2003;27:201-206.
13. Paziana K, Pazianas M. Calcium supplements controversy in osteoporosis: a physiological mechanism supporting cardiovascular adverse effects. *Endocrine*. 2015;48:776-778.
14. Heaney RP. Calcium intake and disease prevention. *Arq Bras Endocrinol Metabol*. 2006;50:685-693.
15. NIH consensus development panel on osteoporosis prevention diagnosis, and therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285:785-795.
16. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. 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*. 2007;86:1780-1790.
17. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. *Ann Intern Med*. 2016;165:856-866.
18. Asemi Z, Saneei P, Sabihi SS, Feizi A, Esmaillzadeh A. Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: a meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis*. 2015;25:623-634.
19. Yang B, Campbell PT, Gapstur SM, et al. Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the

Cancer Prevention Study II Nutrition Cohort. *Am J Clin Nutr*. 2016;103:886-894.
20. Wang X, Chen H, Ouyang Y, et al. Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. *BMC Med*. 2014;25:158.
21. Manson JE, Allison MA, Carr JJ, et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause*. 2010;17;683–691.
22. Kopecky SL, Bauer DC, Gulati M, et al. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive Cardiology. *Ann Intern Med*. 2016;165:867.
23. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2009;2:CD000227.
24. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. 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*. 2011;19:d2040.
25. Bolland MJ, Grey A, Gamble GD, Reid IR. Concordance of results from randomized and observational analyses within the same study: a re-analysis of the women's health initiative limited-access dataset. *PLoS One*. 2015;10:e0139975.
26. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health 2002*. 2013;22:915-929.
27. Donneyong MM, Hornung CA, Taylor KC, et al. Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the women's health initiative. *Circ Heart Fail*. 2015;8:49-56.
28. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115:846-854.
29. LaCroix AZ, Kotchen J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2009;64A:559-567.
30. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: women's health initiative clinical trial and cohort study. *Osteoporos Int*. 2013;24: 567-580.
31. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. *J Bone Miner Res*. 2011;26:35-41.
32. Adebamowo SN, Spiegelman D, Flint AJ, Willett WC, Rexrode KM. Intakes of magnesium, potassium, and calcium and the risk of stroke among men. *Int J Stroke*. 2015;10:1093-1100.
33. Khan B, Nowson CA, Daly RM, et al. Higher dietary calcium intakes are associated with reduced risks of fractures, cardiovascular events, and mortality: a prospective cohort study of older men and women. *J Bone Miner Res*. 2015;30:1758-1766.
34. Larsson SC, Virtamo J, Wolk A. Potassium, calcium, and magnesium intakes and risk of stroke in women. *Am J Epidemiol*. 2011;174:35-43.
35. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*. 2005;68:1815-1824.
36. Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. *Am J Clin Nutr*. 2003;77:814-818.
37. Ascherio A, Rimm EB, Hernán MA, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation*. 1998;98:1198-1204.
38. Chan R, Leung J, Woo J. A prospective cohort study examining the associations of dietary calcium intake with all-cause and cardiovascular mortality in older Chinese community-dwelling people. *PLoS One*. 2013;8:e80895.
39. Iso H, Stampfer MJ, Manson JE, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke*. 1999;30:1772-1779.
40. Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, Wolk A. Dietary calcium and magnesium intake and mortality: a prospective study of men. *Am J Epidemiol*. 2010;171:801-807.
41. Larsson SC, Virtanen MJ, Mars M, et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Arch Intern Med*. 2008;168:459-465.
42. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart Br Card Soc*. 2012;98:920-925.
43. Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *BMJ*. 2013;12:346.
44. Paik JM, Curhan GC, Sun Q, et al. Calcium supplement intake and risk of cardiovascular disease in women. *Osteoporos Int*. 2014;25:2047-2056.
45. Sluijs I, Czernichow S, Beulens JW, et al. Intakes of potassium, magnesium, and calcium and risk of stroke. *Stroke*. 2014;45:1148-1150.
46. Umesawa M, Iso H, Ishihara J, et al. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. *Stroke*. 2008;39:2449-2456.
47. Weng LC, Yeh WT, Bai CH, et al. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? *Stroke*. 2008;39:3152-3158.

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