The Association of Calcium Supplementation and Incident Cardiovascular Events in the Multi-Ethnic Study of Atherosclerosis (MESA)

L.M. Raffield[#,†,a], **S. Agarwal**[#,b], **F.C. Hsu**[c], **I.H. de Boer**[d], **J.H. Ix**[e], **D. Siscovick**[f], **M. Szklo**[g], **G.L. Burke**[h], **A.C. Frazier-Wood**[i], and **D.M. Herrington**[j]

[a]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC

[b]Department of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, IL

[c]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC

[d]Division of Nephrology and Kidney Research Institute, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA

[e]Nephrology Section, Veterans Affairs San Diego Healthcare System, Division of Nephrology and Hypertension, University of California School of Medicine, San Diego, CA

[f]New York Academy of Medicine, New York, NY

[g]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[h]Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC

[i]Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX

[j]Section on Cardiology, Wake Forest School of Medicine, Winston-Salem, NC

[#] These authors contributed equally to this work.

Abstract

Background and Aims—Many US adults use calcium supplements to address inadequate dietary intake and improve bone health. However, recent reports have suggested that use of calcium supplements may elevate cardiovascular disease (CVD) risk. In this study, we examined associations between baseline calcium supplement use and incident myocardial infarction (MI) (n=208 events) and CVD events (n=641 events) over 10.3 years in men and women from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (n=6,236), with dietary calcium intake at baseline also examined as a supplementary objective.

Methods and Results—Using Cox proportional hazards models, no compelling associations between calcium intake from supplements or diet and incident CVD events were observed upon

[†] Corresponding author Dr. Laura M. Raffield, Department of Genetics, University of North Carolina, 5100 Genetic Medicine Building, 120 Mason Farm Road, Chapel Hill, NC, 27517, raffield@email.unc.edu.

multivariate adjustment for potential confounders. An association with lower MI risk was observed comparing those with low levels of calcium supplement use (1-499 mg) to those using no calcium supplements (hazard ratio 0.69, 95% CI 0.48, 0.98, p=0.039). Relationships were homogeneous by gender, race/ethnicity, or chronic kidney disease. Results were also similar when the analysis was limited to postmenopausal women only.

Conclusion—Analysis of incident MI and CVD events in the MESA cohort does not support a substantial association of calcium supplement use with negative cardiovascular outcomes.

Keywords

calcium; supplements; myocardial infarction; cardiovascular disease; Multi-Ethnic Study of Atherosclerosis

Introduction

Calcium is essential for bone health, but most US adults have calcium intakes considered inadequate by Institute of Medicine recommendations [1-3]. To address this, large portions of the population use calcium supplements, with >50% of men and >60% of women over 60 years old reporting calcium supplement use in the 2003-2006 National Health and Nutrition Examination survey [1,3]. Calcium supplementation has been linked to increases in bone mineral density [4] and reduced risk of fractures [5], though evidence is mixed [6].

Concern that calcium supplementation may increase cardiovascular disease (CVD) risk was originally raised by the Auckland calcium clinical trial, which included 1,471 healthy postmenopausal women. In this trial, there was a significant increase in adjudicated self-reported myocardial infarction (MI) (relative risk (RR) 2.12, 95% confidence interval (CI) 1.01 to 4.47, p=0.047) in women randomized to calcium supplementation (1000 mg/day) [7]. Comparing calcium supplementation to placebo, a similar increase in MI risk was also observed in a subsequent meta-analysis of five randomized trials with patient level data and eleven additional randomized trials with trial level data [8]. The results of the large Women's Health Initiative (WHI) calcium-vitamin D trial have been disputed. A modest elevation in MI risk was observed by Bolland et al. in participants not taking personal calcium supplements at baseline (hazard ratio (HR) 1.22, 95% CI 1.00 to 1.50, p=0.05, n=16,718) [9], but the WHI clinical trial investigators reported no adverse effect of calcium and vitamin D on any cardiovascular end point (HR 1.04; 95% CI, 0.92 to 1.18, p=0.50, n=36,282) [10,11], with no adverse effect observed when analyses included only those with no personal calcium supplement use at baseline [11]. A recent meta-analysis of both published and unpublished randomized trials using verified events also found no associations of calcium supplements with coronary heart disease (CHD) events (n=48,460) or all-cause mortality (n=62,383) [12]. Results of observational cohort studies have also been mixed [13,11,14,15]. Based on this conflicting literature on the CVD impacts of calcium supplementation, we examined the association of calcium supplementation and incident cardiovascular events in the Multi-Ethnic Study of Atherosclerosis (MESA).

The MESA cohort presents a unique opportunity to examine this question in a race/ethnic diverse population with well-documented and adjudicated measures of MI and other CVD

events, measures of cardiovascular risk factors, and food questionnaires. Most previous studies examining associations of calcium supplementation with negative CVD outcomes have focused on predominantly European populations. Moreover, associations of calcium supplementation and CVD risk have been largely studied in postmenopausal women, while MESA provides an opportunity to assess the association of calcium and CVD events in younger women and men.

Methods

Study Population

MESA is a community-based cohort study designed to determine the prevalence, determinants, and progression of subclinical CVD which recruited men and women aged 45-84 from four major race/ethnicity groups from 6 different locations in the United States (2000-2002). All participants were free of clinical CVD at baseline [16]. All subjects with calcium supplementation data (n=6,236) were included in our analyses. This included participants from all 6 recruitment sites, including Wake Forest University (15.6%), Columbia University (14.6%), Johns Hopkins University (15.3%), University of Minnesota (16.1%), Northwestern University (17.9%), and University of California, Los Angeles (20.4%); calcium supplement use category was associated with recruitment site (p<0.0001), and site was included as a covariate in all adjusted models. Data for clinical and demographic factors included in this study were collected in Exam 1, with a standard questionnaire used to determine participant's basic demographic data, smoking status, medication use, and medical history. Physical activity was assessed using a semiquantitative questionnaire, and usual diet was assessed using a previously validated food frequency questionnaire (FFQ) [16]. The FFQ is a modified version of the Block FFQ, which was based on the FFQ used in the Insulin Resistance Atherosclerosis Study and modified to account for race/ethnic differences in usual diet [17,18]. The FFQ was used to determine if participants used calcium supplements once a week or more and, if so, the number of pills consumed per week and dose of calcium in each pill.

Data on total dietary energy intake (kcal) and total dietary calcium intake (mg) was also drawn from this FFQ. For approximately 1/3 of the participants in MESA, data were unavailable on the intake of 14 foods (fruit juice, dark / whole grains, fruit, salty snacks, other vegetables, leafy green vegetables, yoghurt, potato, red meat, high-fat & processed meat, high-fat dairy, desserts, cottage cheese and legumes). As the majority of these participants were from one of two MESA field centers, these data may not be missing at random. For these 14 intakes for this portion of the MESA population, imputation was conducted using sequential chained regression [19] implemented in Stata 12, accounting for basic demographic factors.

Basic clinical measures, including blood pressure, lipid levels, and estimated glomerular filtration rate using the CKD-EPI equation [20], were also assessed at the baseline exam [16]. The blood pressure measures were the average of the first two of three seated readings using the Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) [16]. Diabetes was defined as serum glucose levels of 126 mg/dL or use of

medications. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2.

Average follow-up time was 10.3 (standard deviation 2.7) years. A standard protocol was used by MESA to adjudicate events, as has been previously described [16]. Briefly, participants were contacted every 9-12 months by telephone interview and asked about interim hospital admissions, CVD related outpatient diagnoses and procedures, and deaths. These reports were confirmed using death certificates and medical records. Two physicians adjudicate each endpoint, with the full committee adjudicating in case of disagreement. In some studies, calcium supplement use significantly increased MI risk but not risk of stroke and other CVD outcomes [7,8], so MI events were the main focus for our analyses. However, we also considered all CVD events, defined as MI, resuscitated cardiac arrest, definite angina, probable angina that was followed by revascularization, stroke, and stroke, CHD, atherosclerotic, or other CVD death. In total, there were 208 incident myocardial infarctions and 641 CVD events; these 641 events included 169 CVD related deaths, 183 strokes, 26 resuscitated cardiac arrests, and 187 cases of definite angina, with a number of individuals having multiple CVD events.

Statistical Analysis

Associations of calcium supplementation categories, as well as dietary calcium quartiles, with incident MI and CVD events were analyzed using Cox proportional hazards models. Daily supplemental calcium intake was divided into four categories: no calcium supplements, 1-499 mg, 500-999 mg, and 1000 mg. Dietary calcium, which included calcium from food intake only, not supplements, was adjusted for total energy intake using a residual method before dietary calcium intake quartiles were derived [21], with the cohort then divided into 4 equal quartiles based on total energy intake-adjusted dietary calcium measures. Results are shown both for our main analysis of all men and women in MESA with calcium supplementation data and an exploratory analysis in postmenopausal women only, the group in which the negative CVD impacts of calcium supplementation were initially reported [7]. We also analyzed use of any calcium supplements as a dichotomous variable. We analyzed each supplement use category as compared to no supplement use, any supplement use as compared to no supplement use, and a test for trend across supplement use categories, in order to increase our ability to detect an association of incident events with calcium supplement use whether or not this relationship was dependent on supplementation dose. Total energy intake-adjusted dietary calcium quartiles were also analyzed with respect to the lowest quartile and with a test for trend across quartiles.

Analyses were adjusted for potential confounders including age, gender, race/ethnicity, recruitment site, education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate, physical activity (moderate and vigorous physical activity total, met-min/wk msu), cigarette use (never, former, or current), calcium supplementation category, and total energy intake-adjusted dietary calcium quartile. We considered but did not adjust for total cholesterol and hypertension medication use, as there was no significant trend for these variables across calcium supplement categories. In sensitivity analyses, additional

adjustment for these variables did not substantively change results, nor did additional adjustment for total energy intake in Model 3. Higher calcium supplementation category was also associated with higher seated pulse pressure; adjusting for pulse pressure instead of systolic and diastolic blood pressure in Model 3 also did not substantively change the results. Multiplicative interactions between gender, race/ethnicity, and CKD and calcium supplementation categories and energy-adjusted calcium intake quartiles were also assessed. Additive interaction, as measured by relative risk due to interaction (RERI), was also assessed using the method developed by Li and Chambless [22]. For determining trends in clinical and demographic variables across calcium supplementation categories, linear regression models for continuous measures and logistic regression models for binary measures were used, with differences in discrete variables such as smoking status, income, and education assessed using multinomial logistic regression, with the likelihood ratio test p-value used to assess significance. All analyses were implemented in SAS 9.3, and p-values < 0.05 were considered statistically significant for all analyses, including interaction terms.

Results

Clinical and demographic characteristics of participants stratified by supplemental calcium intake categories are displayed in Table 1. Individuals using high levels of calcium supplements had lower diabetes prevalence, less current smoking, higher HDL cholesterol, and lower BMI, emphasizing the importance of adjusting for these risk factors. By contrast, individuals not taking supplements performed more moderate and vigorous physical activity, had higher estimated glomerular filtration rate, and had lower prevalence of chronic kidney disease. Individuals taking calcium supplements were more likely to be white and female and have higher levels of educational attainment and income.

We found no evidence that calcium supplement use was associated with elevated risk of MI or CVD events (Table 2). Individuals using a low dose of calcium supplements (1-499 mg) had a lower risk of MI than individuals taking no calcium supplements (HR 0.69, 95% CI 0.48, 0.98, p=0.039 in Model 3). A trend towards lower MI risk with increasing calcium supplement use was also observed in unadjusted Model 1 (HR 0.84, 95% CI 0.73, 0.97, p=0.020), but this was attenuated upon adjustment for further confounders (Model 3), including education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate, physical activity, cigarette use, and energy-adjusted dietary calcium quartile. Similar results were observed for calcium supplement use as a dichotomous variable, with an association with lower MI risk in unadjusted models (HR 0.68, 95% CI 0.51, 0.90, p=0.007) attenuated upon confounder adjustment in Model 3. No significant multiplicative or additive interactions between gender, race/ethnicity, or CKD and calcium supplementation categories were observed (p 0.34) for either MI or all CVD events.

No statistical significant p-values were seen for any of the models assessing the association of energy-adjusted dietary calcium intake quartiles with MI and CVD events (Table 3) or for multiplicative or additive interactions with gender, race/ethnicity, or CKD (p 0.12). Dietary intake of calcium was adjusted for total energy intake using a residual method before quartiles were derived.

In analyses limited to postmenopausal women only, results were similar. No associations of calcium supplement use categories and energy-adjusted dietary calcium intake quartiles with MI or all CVD events were observed (Tables 4 and 5).

Discussion

In a large multi-ethnic population of 6,236 individuals from the MESA cohort free of clinical CVD at baseline, no associations of calcium supplement use with risk of incident CVD events were observed. Additionally, no association was observed between dietary calcium intake and incident CVD events. When analyses were restricted to postmenopausal women, the group in which potential negative impacts of calcium supplementation were first reported [7], the results were similar. As supplementary analyses (results not shown), we also analyzed associations of quartiles of the sum of calcium intake from supplements and total energy intake-adjusted dietary calcium. No significant associations were observed, either in the entire cohort or postmenopausal women only, for fully adjusted models. To increase the sample size for the calcium supplement use group, we also performed an analysis where all individuals using 500 mg calcium supplements were analyzed as a single category; no associations with increased risk of incident CVD were observed. These findings suggest that calcium intake has either no impact or a small effect on CVD event risk in this diverse cohort.

A number of other analyses of both randomized clinical trials and observational studies have also found no association between calcium supplementation and CVD outcomes, similar to the results observed in our study. A number of large observational cohort studies have found no association of calcium supplementation with CVD risk [14,11,15]. The investigators for the large WHI calcium-vitamin D trial found no negative CVD impact of calcium supplementation [11,10], and a recent meta-analysis of this and other clinical trials found no association of calcium supplementation with or without vitamin D on CHD or all-cause mortality [12]. Many of the original reports of calcium supplementation increasing risk of CVD events were in the setting of randomized, placebo controlled clinical trials [8,7]. While these controlled trials clearly have some advantages over observational trials such as MESA, the follow-up period for most trials is also generally short, with relatively few events. For our analysis in MESA, we had, on average, over 10 years of follow-up, with 208 MI events and 641 CVD events. We found no evidence favoring an association of calcium supplementation with elevation in MI or CVD events; however, we cannot exclude a small elevation in risk with use of calcium supplements, with a 95% CI for use of any calcium supplementation of 0.56 to 1.02 for MI and 0.80 to 1.12 for all CVD in fully adjusted models. Another limitation of this analysis is that data was not available for use of vitamin D or vitamin K supplements; intake of both vitamins may impact calcium absorption [23,24]. However, through an ancillary study, data was available for annualized serum concentration of 25-hydroxyvitamin D (25(OH)D), adjusted for seasonal variation in measurement; higher levels of calcium supplement use was associated with higher serum vitamin D ($p<0.0001$), likely in part due to concurrent use of calcium and vitamin D supplements in some participants. However, results of fully adjusted models were similar with or without adjustment for serum vitamin D (Supplementary Tables 1 and 2).

Author Manuscript

Our negative results are consistent with the lack of a clear mechanism for why calcium supplementation would increase CVD risk. Vascular calcification, a measure of subclinical CVD risk, has been suggested as a potential mediator of the negative CVD impacts of calcium supplementation [25,9]. However, studies have consistently found no association between calcium supplement use and vascular calcification [26-28]. Other problems with reports of elevated CVD risk with calcium supplementation, including lack of adjustment for baseline CVD risk factors, no correction for multiple endpoints testing, and trials not specifically designed for assessing CVD risk, have been reviewed previously [29].

Our supplemental analysis of dietary calcium intake in MESA also found no associations of dietary calcium and CVD risk. In general, studies have found increased dietary calcium intake to be inversely related to CVD events, but results are mixed [30,31]. A recent meta-analysis of observational cohort studies reported a U-shaped association between dietary intake of calcium and CVD mortality, with lower mortality risk for individuals with intakes around 800 mg/day and higher risk with lower or higher intakes [14]. However, we observed no significant inverse relationships with CVD risk for individuals in quartile 3, who had calcium intakes around 800 mg/day level (642.0 - 876.3 mg). Similar to our results, a number of studies have found no link between dietary calcium intake and CVD [30-32].

In summary, our results do not support the hypothesis that use of calcium supplements or differences in dietary calcium intake increase risk of MI or all CVD events. Results were similar in postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Acronyms

CVD	cardiovascular disease
CKD	chronic kidney disease
CI	confidence interval
FFQ	food frequency questionnaire
HR	hazard ratio
MESA	Multi-Ethnic Study of Atherosclerosis

MI	myocardial infarction
RR	relative risk
RERI	relative risk due to interaction
WHI	Women's Health Initiative

References

1. Mangano KM, Walsh SJ, Insogna KL, Kenny AM, Kerstetter JE. Calcium intake in the United States from dietary and supplemental sources across adult age groups: new estimates from the National Health and Nutrition Examination Survey 2003-2006. J Am Diet Assoc. 2011; 111(5): 687–695. doi:10.1016/j.jada.2011.02.014. [PubMed: 21515114]

2. IOM. Dietary Reference Intakes for Calcium and Vitamin D. 2011

3. Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer JT, Moshfegh AJ, Sempos CT, Picciano MF. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr. 2010; 140(4): 817–822. doi:10.3945/jn.109.118539. [PubMed: 20181782]

4. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006; 354(7):669–683. doi: 10.1056/NEJMoa055218. [PubMed: 16481635]

5. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007; 370(9588):657–666. doi:10.1016/s0140-6736(07)61342-7. [PubMed: 17720017]

6. Seeman E. Evidence that calcium supplements reduce fracture risk is lacking. Clin J Am Soc Nephrol 5 Suppl. 2010; 1:S3–11. doi:10.2215/cjn.06160809.

7. Bolland M, Barber P, Doughty R, Mason B, Horne A, Ames R, Gamble G, Grey A, Reid I. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ (Clinical research ed). 2008; 336(7638):262–266. doi:10.1136/bmj.39440.525752.BE.

8. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010; 341 doi:10.1136/bmj.c3691.

9. Bolland M, Grey A, Avenell A, Gamble G, Reid I. 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 (Clinical research ed). 2011; 342 doi:10.1136/bmj.d2040.

10. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007; 115(7):846–854. doi:10.1161/circulationaha.106.673491. [PubMed: 17309935]

11. Prentice R, Pettinger M, Jackson R, Wactawski-Wende J, Lacroix A, Anderson G, Chlebowski R, Manson J, Van Horn L, Vitolins M, Datta M, LeBlanc E, Cauley J, Rossouw J. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013; 24(2):567–580. doi:10.1007/s00198-012-2224-2.

12. Lewis JR, Radavelli-Bagatini S, Rejnmark L, Chen JS, Simpson JM, Lappe JM, Mosekilde L, Prentice RL, Prince RL. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. 2015; 30(1):165–175. doi:10.1002/jbmr.2311. [PubMed: 25042841]

13. 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 (British Cardiac Society). 2012; 98(12):920–925. doi:10.1136/heartjnl-2011-301345. [PubMed: 22626900]

14. Wang X, Chen H, Ouyang Y, Liu J, Zhao G, Bao W, Yan M. Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. BMC Med. 2014; 12:158. doi:10.1186/s12916-014-0158-6. [PubMed: 25252963]

15. Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int. 2014; 25(8):2047–2056. doi:10.1007/s00198-014-2732-3. [PubMed: 24803331]

16. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr. Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156(9):871–881. [PubMed: 12397006]

17. Burnett-Hartman AN, Fitzpatrick AL, Gao K, Jackson SA, Schreiner PJ. Supplement use contributes to meeting recommended dietary intakes for calcium, magnesium, and vitamin C in four ethnicities of middle-aged and older Americans: the Multi-Ethnic Study of Atherosclerosis. J Am Diet Assoc. 2009; 109(3):422–429. doi:10.1016/j.jada.2008.11.023. [PubMed: 19248857]

18. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, Jacobs DR Jr. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2006; 83(6):1369–1379. [PubMed: 16762949]

19. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011; 30(4):377–399. doi:10.1002/sim.4067. [PubMed: 21225900]

20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006. [PubMed: 19414839]

21. Willett W, Howe G, Kushi L. Adjustment for total energy intake in epidemiologic studies. The American journal of clinical nutrition. 1997; 65(suppl):1220S–1228S. [PubMed: 9094926]

22. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol. 2007; 17(3):227–236. doi:10.1016/j.annepidem.2006.10.009. [PubMed: 17320789]

23. Zittermann A. Effects of vitamin K on calcium and bone metabolism. Curr Opin Clin Nutr Metab Care. 2001; 4(6):483–487. [PubMed: 11706280]

24. Heaney RP. Vitamin D and calcium interactions: functional outcomes. Am J Clin Nutr. 2008; 88(2):541S–544S. [PubMed: 18689398]

25. Thompson B, Towler D. Arterial calcification and bone physiology: role of the bone- vascular axis. Nature reviews Endocrinology. 2012; 8(9):529–543. doi:10.1038/nrendo.2012.36.

26. Samelson E, Booth S, Fox C, Tucker K, Wang T, Hoffmann U, Cupples L, O'Donnell C, Kiel D. Calcium intake is not associated with increased coronary artery calcification: the Framingham Study. The American journal of clinical nutrition. 2012; 96(6):1274–1280. doi:10.3945/ajcn.112.044230. [PubMed: 23134889]

27. Manson J, Allison M, Carr J, Langer R, Cochrane B, Hendrix S, Hsia J, Hunt J, Lewis C, Margolis K, Robinson J, Rodabough R, Thomas A, Women's Health I, Women's Health Initiative-Coronary Artery Calcium Study I. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause (New York, NY). 2010; 17(4):683–691. doi:10.1097/gme.0b013e3181d683b5.

28. Raffield LM, Agarwal S, Cox AJ, Hsu FC, Carr JJ, Freedman BI, Xu J, Bowden DW, Vitolins MZ. Cross-sectional analysis of calcium intake for associations with vascular calcification and mortality in individuals with type 2 diabetes from the Diabetes Heart Study. Am J Clin Nutr. 2014; 100(4):1029–1035. doi:10.3945/ajcn.114.090365. [PubMed: 25099552]

29. Nordin B, Lewis J, Daly R, Horowitz J, Metcalfe A, Lange K, Prince R. The calcium scare--what would Austin Bradford Hill have thought? Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2011; 22(12):3073–3077. doi:10.1007/s00198-011-1680-4.

30. Wang L, Manson JE, Sesso HD. Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. Am J Cardiovasc Drugs. 2012; 12(2):105–116. doi:10.2165/11595400-000000000-00000. [PubMed: 22283597]

31. Rautiainen S, Wang L, Manson JE, Sesso HD. The role of calcium in the prevention of cardiovascular disease--a review of observational studies and randomized clinical trials. Curr Atheroscler Rep. 2013; 15(11):362. doi:10.1007/s11883-013-0362-4. [PubMed: 24022513]

32. Xiao Q, Murphy R, Houston D, Harris T, Chow W-H, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA internal medicine. 2013; 173(8):639–646. doi:10.1001/jamainternmed. 2013.3283. [PubMed: 23381719]

Highlights

Associations of calcium supplement use and cardiovascular disease (CVD) events were examined.

The study included men and women from the Multi-Ethnic Study of Atherosclerosis.

Calcium supplements were not associated with elevated CVD risk.

Dietary calcium intake was also not associated with incident CVD events.

Table 1

Demographic and clinical characteristics of the MESA cohort at Exam 1 (2000-2002), stratified by calcium supplement intake categories. The reported p-value is for the trend across calcium supplement categories using linear regression for continuous variables and logistic regression for dichotomous variables. For discrete variables such as smoking status and site, the likelihood ratio test p-value from multinomial logistic regression is reported.

	Mean (Standard Deviation) or %				
	Calcium Supplement Category 1 (0 mg, n=3370)	Calcium Supplement Category 2 (1-499 mg, n=1550)	Calcium Supplement Category 3 (500-999 mg, n=620)	Calcium Supplement Category 4 (1000 mg, n=696)	p-value
Age (years)	62 (10)	63 (10)	63 (10)	64 (10)	<0.0001
Male Gender (%)	55	51	25	20	<0.0001
Body Mass Index (kg/m^2)	29 (5.4)	28 (5.2)	27 (5.6)	27 (5.2)	<0.0001
HDL Cholesterol (mg/dL)	49 (14)	51 (14)	55 (16)	58 (17)	<0.0001
Total Cholesterol (mg/dL)	194 (36)	194 (35)	194 (34)	196 (34)	0.151
Lipid-lowering Medication Use (%)	15	18	18	17	0.045
Systolic Blood Pressure (mmHg)	127 (22)	126 (21)	125 (22)	126 (22)	0.042
Diastolic Blood Pressure (mmHg)	73 (10)	72 (10)	69 (10)	69 (10)	<0.0001
Hypertension Medication Use (%)	37	39	34	37	0.991
Estimated Glomerular Filtration Rate (CKD-EPI Equation) (ml/min/1.73 m^2)	79 (17)	77 (16)	78 (16)	75 (15)	<0.0001
Chronic Kidney Disease (%)	12	13	14	16	0.006
Moderate and Vigorous Physical Activity Total (met-min/wk m-su)	5821 (6187)	5806 (5703)	5370 (4999)	5248 (5441)	0.009
Diabetes Status (%)	14	12	8.4	7.6	<0.0001
Former Cigarette Smoking (%)	36	39	32	37	<0.0001
Current Cigarette Smoking (%)	15	12	7.1	6.1	
Race/Ethnicity: White, Caucasian (%)	33	45	42	56	<0.0001
Race/Ethnicity: Chinese American (%)	12	13	19	12	
Race/Ethnicity: Black, African-American (%)	29	25	20	18	
Race/Ethnicity: Hispanic (%)	26	17	20	14	
Education Category 1 to 3: Less than High School (%)	23	12	16	9.8	<0.0001
Education Category 4: Completed High School/GED (%)	18	16	19	22	
Education Category 5 to 7: Some College, Technical School Certificate, or Associate Degree (%)	28	28	28	28	
Education Category 8 to 9: Bachelor's Degree or Greater (%)	32	43	37	40	
Income Category 1 to 5: <$20,000 (%)	26	22	20	18	<0.0001
Income Category 6 to 9: $20,000-39,999 (%)	27	24	31	27	

	Mean (Standard Deviation) or %				
	Calcium Supplement Category 1 (0 mg, n=3370)	Calcium Supplement Category 2 (1-499 mg, n=1550)	Calcium Supplement Category 3 (500-999 mg, n=620)	Calcium Supplement Category 4 (1000 mg, n=696)	p-value
Income Category 10 to 13: $40,000 (%)	47	55	49	55	
Annualized Serum Concentration of 25-Hydroxyvitamin D (25(OH)D) (ng/mL)	23 (10)	29 (11)	30 (9.1)	33 (11)	<0.0001

Table 2

Associations between calcium intake categories for supplemental calcium and myocardial infarction and cardiovascular disease events. Hazard ratios reported are for each individual category compared to the group with 0 mg supplemental calcium intake, or, for the "test for trend" row, a one category increase. Hazard ratios comparing use of any calcium supplements to no calcium supplement use are also reported.

Trait	Number of Events	Model 1				Model 2				Model 3			
		Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
Myocardial infarction													
0 mg (n=3370)	130	1.00			ref.	1.00			ref.	1.00			ref.
1-499 mg (n=1550)	43	0.70	0.50	0.99	0.044	0.66	0.46	0.93	0.018	0.69	0.48	0.98	0.039
500-999 mg (n=620)	16	0.64	0.38	1.07	0.090	0.76	0.45	1.29	0.311	0.88	0.51	1.50	0.633
1000 mg (n=696)	19	0.67	0.42	1.09	0.108	0.75	0.45	1.24	0.258	0.87	0.52	1.44	0.585
Test for Trend		0.84	0.73	0.97	0.020	0.87	0.75	1.02	0.080	0.92	0.79	1.08	0.315
Any Calcium Supplements		0.68	0.51	0.90	0.007	0.69	0.52	0.93	0.014	0.75	0.56	1.02	0.065
CVD (all events)													
0 mg (n=3370)	364	1.00			ref.	1.00			ref.	1.00			ref.
1-499 mg (n=1550)	149	0.87	0.72	1.05	0.156	0.81	0.67	0.99	0.036	0.87	0.71	1.06	0.160
500-999 mg (n=620)	55	0.78	0.59	1.04	0.085	0.87	0.65	1.17	0.352	1.02	0.75	1.37	0.920
1000 mg (n=696)	73	0.93	0.72	1.20	0.568	0.97	0.75	1.27	0.847	1.16	0.88	1.53	0.281
Test for Trend		0.95	0.88	1.02	0.175	0.97	0.89	1.05	0.411	1.03	0.95	1.12	0.501
Any Calcium Supplements		0.87	0.74	1.01	0.069	0.86	0.73	1.01	0.064	0.95	0.80	1.12	0.551

Model 1: Unadjusted

Model 2: Adjusted for age, gender, race/ethnicity, recruitment site

Model 3: Adjusted for age, gender, race/ethnicity, recruitment site, education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate (CKD-EPI equation), physical activity (moderate and vigorous physical activity total, met-min/wk m-su), cigarette use (never, former, or current), total energy intake-adjusted dietary calcium quartile

Table 3

Associations between calcium intake quartiles for total energy intake-adjusted dietary calcium and myocardial infarction and cardiovascular disease events. Hazard ratios reported are for each individual quartile, or, for the "test for trend" row, a one quartile increase.

Trait	Number of Events	Model 1			Model 2			Model 3		
		Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Myocardial infarction										
Quartile 1 (48.8–515.6 mg, n=1559)	51	1.0		ref.	1.0		ref.	1.0		ref.
Quartile 2 (515.6–711.1 mg, n=1559)	50	0.96	0.65 1.41	0.825	0.81	0.54 1.20	0.289	0.87	0.58 1.30	0.486
Quartile 3 (711.1–960.8 mg, n=1559)	50	0.97	0.65 1.43	0.864	0.76	0.50 1.13	0.175	0.80	0.53 1.22	0.298
Quartile 4 (960.9–3328.2 mg, n=1559)	57	1.12	0.77 1.64	0.554	0.85	0.57 1.28	0.443	0.91	0.60 1.37	0.636
Test for Trend		1.04	0.92 1.17	0.555	0.95	0.83 1.09	0.461	0.97	0.84 1.11	0.617
CVD (all events)										
Quartile 1 (48.8–515.6 mg, n=1559)	154	1.00		ref.	1.00		ref.	1.00		ref.
Quartile 2 (515.6–711.1 mg, n=1559)	166	1.07	0.86 1.33	0.567	0.96	0.77 1.20	0.742	1.00	0.79 1.26	0.981
Quartile 3 (711.1–960.8 mg, n=1559)	165	1.07	0.86 1.33	0.568	0.95	0.76 1.19	0.661	1.02	0.81 1.30	0.846
Quartile 4 (960.9–3328.2 mg, n=1559)	156	1.02	0.82 1.27	0.875	0.92	0.72 1.16	0.469	0.94	0.74 1.21	0.641
Test for Trend		1.01	0.94 1.08	0.880	0.97	0.90 1.05	0.473	0.99	0.91 1.06	0.695

Model 1: Unadjusted

Model 2: Adjusted for age, gender, race/ethnicity, recruitment site

Model 3: Adjusted for age, gender, race/ethnicity, recruitment site, education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate (CKD-EPI equation), physical activity (moderate and vigorous physical activity total, met-min/wk m-su), cigarette use (never, former, or current), supplemental calcium category

Table 4

Associations between calcium intake categories for supplemental calcium and myocardial infarction and cardiovascular disease events in postmenopausal women. Hazard ratios reported are for each individual category compared to the group with 0 mg supplemental calcium intake, or, for the "test for trend" row, a one category increase. Hazard ratios comparing use of any calcium supplements to no calcium supplement use are also reported.

Trait	Number of Events	Model 1 Hazard Ratio	Model 1 95% CI		Model 1 p-value	Model 2 Hazard Ratio	Model 2 95% CI		Model 2 p-value	Model 3 Hazard Ratio	Model 3 95% CI		Model 3 p-value
Myocardial infarction													
0 mg (n=1187)	34	1.00			ref.	1.00			ref.	1.00			ref.
1-499 mg (n=621)	17	0.93	0.52	1.66	0.793	0.90	0.50	1.62	0.728	0.98	0.54	1.77	0.935
500-999 mg (n=393)	8	0.68	0.31	1.46	0.322	0.72	0.33	1.56	0.401	0.86	0.39	1.90	0.707
1000 mg (n=501)	9	0.59	0.28	1.23	0.156	0.53	0.25	1.12	0.094	0.62	0.29	1.34	0.224
Test for Trend		0.84	0.67	1.04	0.112	0.82	0.65	1.02	0.080	0.87	0.69	1.10	0.239
Any Calcium Supplements		0.75	0.46	1.20	0.230	0.73	0.45	1.18	0.197	0.83	0.50	1.37	0.470
CVD (all events)													
0 mg (n=1187)	111	1.00			ref.	1.00			ref.	1.00			ref.
1-499 mg (n=621)	52	0.87	0.62	1.20	0.392	0.85	0.61	1.19	0.352	0.89	0.63	1.26	0.505
500-999 mg (n=393)	38	0.99	0.68	1.43	0.943	1.01	0.69	1.47	0.962	1.19	0.80	1.76	0.386
1000 mg (n=501)	45	0.91	0.64	1.28	0.586	0.85	0.60	1.21	0.366	1.07	0.74	1.56	0.723
Test for Trend		0.98	0.87	1.09	0.651	0.96	0.86	1.07	0.471	1.04	0.92	1.17	0.535
Any Calcium Supplements		0.91	0.71	1.17	0.467	0.89	0.69	1.15	0.378	1.01	0.77	1.33	0.925

Model 1: Unadjusted

Model 2: Adjusted for age, race/ethnicity, recruitment site

Model 3: Adjusted for age, race/ethnicity, recruitment site, education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate (CKD-EPI equation), physical activity (moderate and vigorous physical activity total, met-min/wk m-su), cigarette use (never, former, or current), total energy intake-adjusted dietary calcium quartile

Table 5

Associations between calcium intake quartiles for total energy intake-adjusted dietary calcium and myocardial infarction and cardiovascular disease events in postmenopausal women. Hazard ratios reported are for each individual quartile, or, for the "test for trend" row, a one quartile increase.

Trait	Number of Events	Model 1				Model 2				Model 3			
		Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value	Hazard Ratio	95% CI		p-value
Myocardial infarction													
Quartile 1 (48.8-515.6 mg, n=880)	21	1.00			ref.	1.00			ref.	1.00			ref.
Quartile 2 (515.6-711.1 mg, n=768)	21	1.11	0.61	2.03	0.738	1.00	0.54	1.86	0.996	1.03	0.54	1.95	0.933
Quartile 3 (711.1-960.8 mg, n=605)	15	1.01	0.52	1.96	0.974	1.02	0.51	2.03	0.959	1.09	0.53	2.21	0.821
Quartile 4 (960.9-3328.2 mg, n=449)	11	1.03	0.50	2.14	0.936	1.07	0.50	2.30	0.854	1.08	0.50	2.36	0.845
Test for Trend		1.00	0.80	1.25	0.980	1.02	0.81	1.30	0.860	1.03	0.81	1.31	0.807
CVD (all events)													
Quartile 1 (48.8-515.6 mg, n=880)	82	1.00			ref.	1.00			ref.	1.00			ref.
Quartile 2 (515.6-711.1 mg, n=768)	77	1.06	0.78	1.45	0.721	1.01	0.74	1.39	0.939	1.05	0.75	1.47	0.776
Quartile 3 (711.1-960.8 mg, n=605)	52	0.91	0.64	1.29	0.598	0.96	0.67	1.38	0.834	1.06	0.73	1.55	0.748
Quartile 4 (960.9-3328.2 mg, n=449)	35	0.84	0.56	1.24	0.379	0.90	0.60	1.35	0.603	0.92	0.61	1.41	0.714
Test for Trend		0.94	0.84	1.06	0.315	0.97	0.86	1.10	0.597	0.99	0.87	1.12	0.825

Model 1: Unadjusted

Model 2: Adjusted for age, race/ethnicity, recruitment site

Model 3: Adjusted for age, race/ethnicity, recruitment site, education, income, HDL, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, diabetes status, body mass index, estimated glomerular filtration rate (CKD-EPI equation), physical activity (moderate and vigorous physical activity total, met-min/wk m-su), cigarette use (never, former, or current), supplemental calcium category