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**Anderson JJ, Kruszka B, Delaney JA, He K, Burke GL, Alonso A, Bild DE, Budoff M, Michos ED. 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 Oct 11;5(10):e003815.**

## What We Know, Think We Know, or Are Starting to Know

Calcium is one of the most important minerals in the human body, and up to 99% of calcium in the body is deposited in the skeletal system [i.e., bones and teeth]. The remaining extracellular calcium in the blood is very tightly regulated within narrow ranges, and although this compartment only comprises ~1% of total body calcium, plasma calcium plays vital roles in muscle contraction [including the heart], neurotransmitter release, and vascular functions [(1)].

Much of the emphasis on calcium has been by reference to bone health, specifically the potential for reduced risk of osteoporosis [(2)]. And there does appear to be widespread public awareness of calcium, for example there are estimates that over 50% and 70% of elderly men and women, respectively, regularly supplement with calcium [(3)].

However, supplementation with calcium may not be entirely without risk; there is evidence suggesting that calcium supplementation may in fact increase risk for cardiovascular disease [CVD] [(4,5)]. This is a controversial association, with evidence of lower risk from dietary calcium, but higher risk with calcium supplements [(4,5)].

As you can infer, there is a lot to unpack with this research question. At the broadest level, it appears that we can make one distinction; that dietary calcium intakes do not appear to increase CVD risk, but supplemental calcium intakes may increase CVD risk [(3–6)].

By what mechanism could calcium supplementation potentially increase CVD risk? The simplest description is that calcium supplementation may lead to surges in plasma calcium levels that disturb calcium balance, leading to calcification of tissues, but specifically coronary artery calcification [CAC; see ***Geek Box** below for more detail] [(3,6)].

The present study investigated the associations between calcium intakes and CAC in a U.S. cohort.

## *Geek Box: Coronary Artery Calcification

*Calcification of tissues is a process that can occur in response to injury. In the process of atherosclerosis development – which occurs over decades, often from the second decade of life – the arteries are exposed to repeated injury from trapped cholesterol, and the resulting immune responses and inflammatory responses that occur. The lesions that occur in the artery as a result become calcified. The extent of coronary artery calcification is strongly correlated with the extent of atherosclerosis, and is highly predictive of cardiovascular disease mortality. Coronary artery calcification [CAC] results in impaired vascular function, and blood flow to the heart. However, unless identified by an angiography, CAC is asymptomatic, and does not have any specific clinical manifestation [unlike, for example, high blood cholesterol levels]. The two primary risk factors for CAC are age and biological sex, with evidence of CAC in >90% of men over the age of 70yrs, and in >67% of women over the same age. CAC is defined by the "Agatston score": 0 = no calcification; 100-300 = moderate calcification; >300 = severe calcification. To date, there is no established intervention to treat CAC, either pharmacologically, surgically, or nutritionally. In addition, the exact pathophysiology of CAC remains to be fully elucidated. Nonetheless, CAC is very important for prognosis of cardiovascular disease risk in both primary and secondary prevention.*

## The Study

The Multi-Ethnic Study of Atherosclerosis [MESA] cohort is a prospective study conducted across six states in the U.S. [Maryland, Illinois, New York, North Carolina, California, and Minnesota]. The cohort was characterised by four ethnicities; non-Hispanic White, non-Hispanic Black, Hispanic, and Chinese.

At baseline [~2000-2002], participants underwent CAC scans to assess the presence of arterial calcification, dietary assessment, and medical examination. Diet was assessed using a food-frequency questionnaire, which was validated in the ethnic groups included in the cohort. The dietary assessment at baseline included assessment of calcium supplement intake. Blood samples were also taken to measure levels of cardio-metabolic risk factors, including cholesterol, inflammation [CRP], and homocysteine.

At 10yrs follow-up [~2010-2012], a subgroup of participants underwent a second CAC scan. This allowed for changes in CAC from the baseline to the second scan to be analysed.

The primary exposure of interest was calcium intake, including total calcium intake and the source of calcium, i.e., dietary calcium or supplemental calcium. The primary outcome was CAC at baseline and follow-up.

The present study consisted of two analyses:

1. A cross-sectional analysis of the association between calcium intake and risk of prevalent CAC at baseline [i.e., a CAC score of >0]. The findings from this analysis were reported as prevalence ratios [PR] and 95% confidence intervals [95% CI].

***Note***: A 'prevalence ratio' [PR] is similar to odds ratio [OR] for cross-sectional analyses, but may avoid overestimating associations that is common with OR when there is a high prevalence of the outcome in the study cohort.

2. A prospective analysis of the associations between calcium intake and change in CAC from baseline to follow-up. The findings from this analysis were reported as relative risk [RR] and 95% CI.

Both analyses were adjusted for lifestyle factors [e.g., total energy intake, smoking, exercise, age, race/ethnicity, education, sex, etc.] and cardiovascular disease [CVD] risk factors [e.g., blood pressure, blood cholesterol, family history of heart disease, etc.].

**Results:** A total of 5,448 participants were included in the study at baseline and in the cross-sectional analysis; 2,742 participants had a second CAC at 10yrs follow-up and were included in the prospective analysis. 51% of participants were female, and the average age at baseline was 59.7yrs. 45.8% of participants were calcium supplement users. 42.9% of participants had a baseline CAC score of >0.

For calcium intake, the overall cohort ranged from the lowest of 313mg/d to highest of 2,157mg/d. In women, average total, dietary, and supplemental calcium intake was 1,080mg/d, 704mg/d, and 712mg/d, respectively. In men, average total, dietary, and supplemental calcium intake was 907mg/d, 756mg/d, and 415mg/d, respectively.

In women, supplemental calcium intake ranged from 94mg/d to 1,212mg/d; in men supplemental calcium ranged from 97mg/d to 966mg/d. Among the quintiles [fifths] of total calcium intake, Q.4 averaged 1,168mg/d calcium, which is closest to U.S. recommendations of ~1,200mg/d; the average in Q.5 of 2,157mg was almost twice the recommended intake.

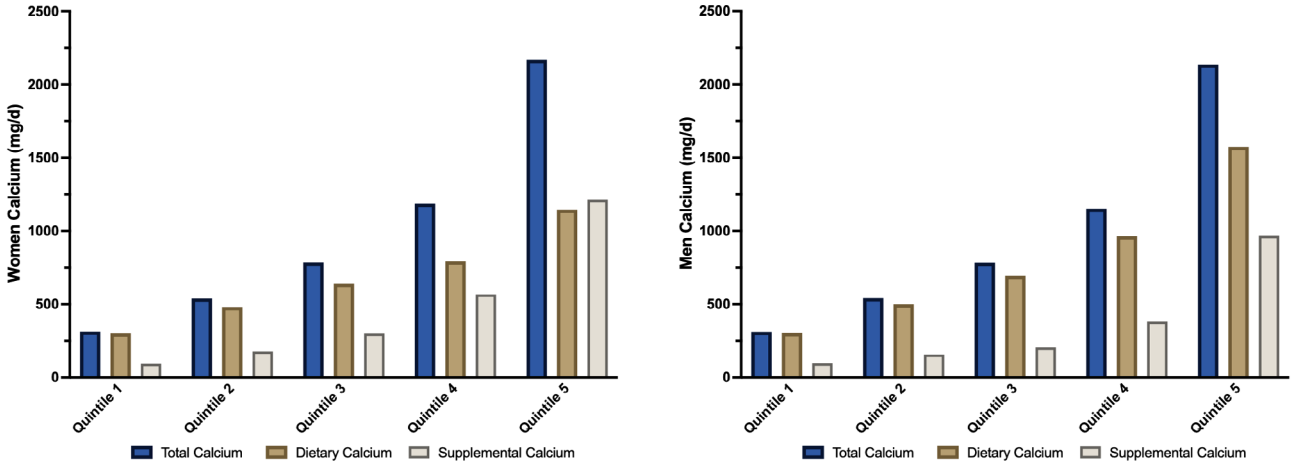
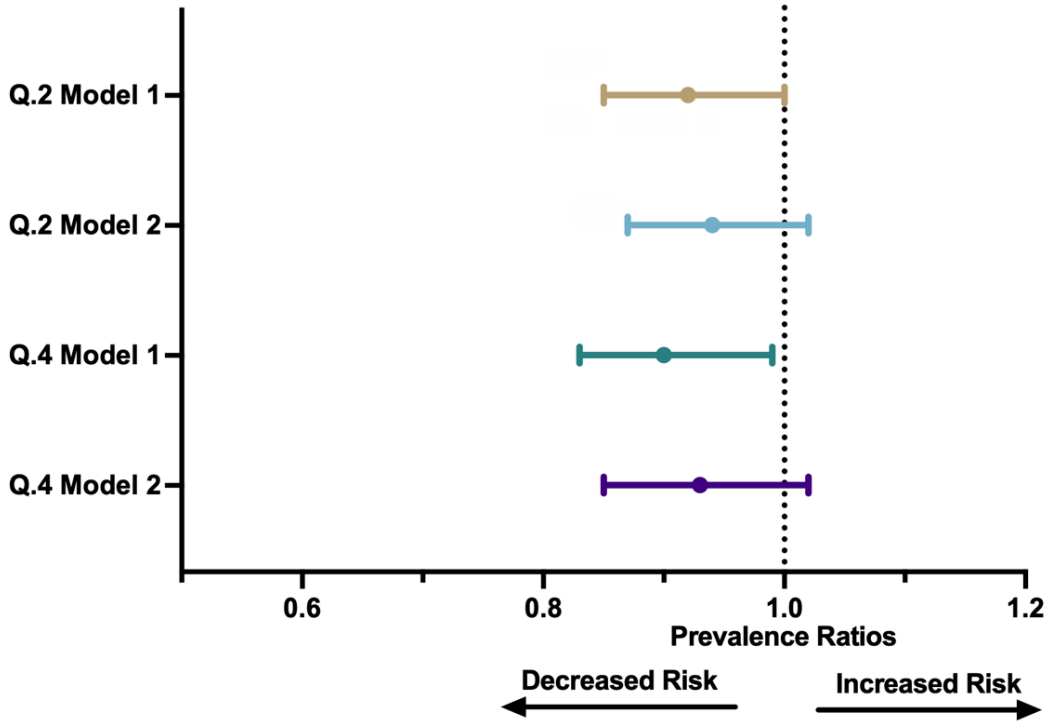



***Figure*** *illustrating calcium intakes in women [**right**] and men [**left**] in the study, stratified by quintiles [fifths] of intake according to total calcium [**blue bars**], dietary calcium [**brown bars**], and supplemental calcium [**grey bars**]. Of note is that supplemental calcium was higher in women compared to men.*

***Cross-Sectional Analysis – Risk of Prevalent CAC at Baseline by Total Calcium*:** The risk of a CAC score >0 at baseline was 8% [PR 0.92, 95% CI 0.85 to 1.00] and 10% [PR 0.90, 95% CI 0.83 to 0.99] lower in quintile 2 [~541mg calcium] and quintile 4 [~1,160mg calcium], respectively, after adjusting for lifestyle factors. However, after further adjusting for CVD risk factors the association was weakened, to a 6% [PR 0.94, 95% CI 0.87 to 1.02] and 7% [PR 0.93, 95% CI 0.85 to 1.02] lower risk in quintiles 2 and 4, respectively.



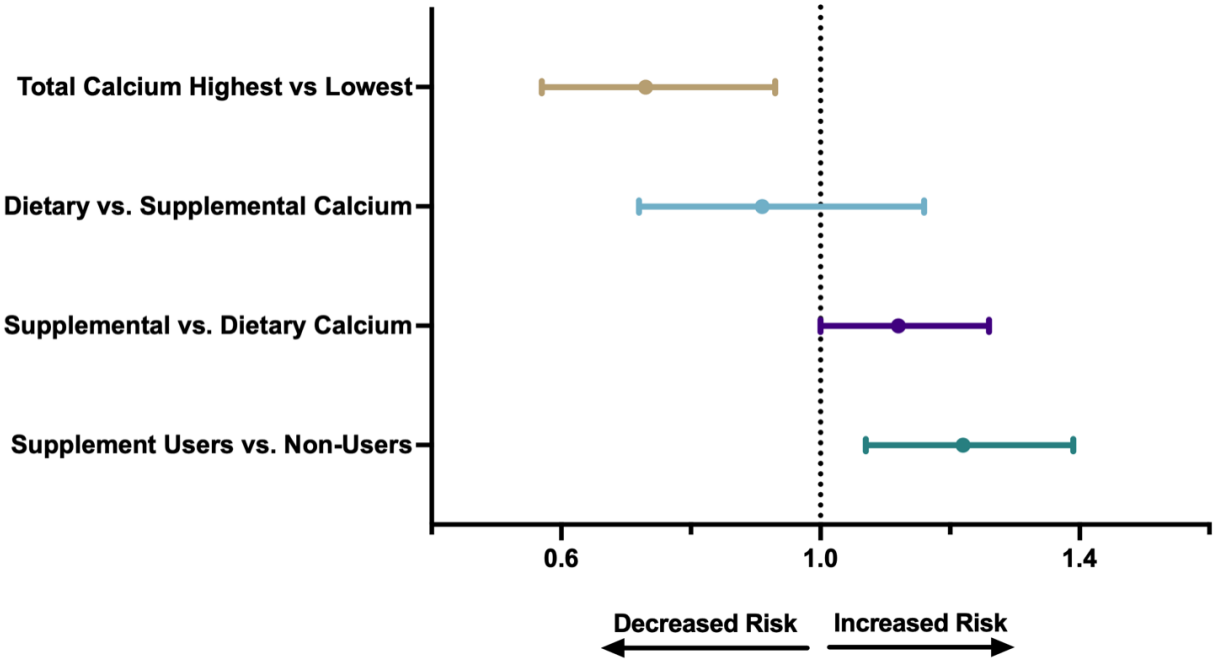

***Forest plot** illustrating the associations between quintile 2 [**Q.2**] and quintile 4 [**Q.4**] and CAC scores >0 at baseline. "Model 1" refers to the analysis that adjusted only for lifestyle factors such as age, education, ethnicity, smoking, energy intake, etc. "Model 2" refers to the additional adjustment of the analysis for CVD risk factors. This is also known as the "fully adjusted model" because it includes everything adjusted for in Model 1. Note that while the fully adjusted model is no longer "statistically significant" as the upper arm of the confidence interval crosses the dotted 'null' line, the direction of effect remains clear.*

***Prospective Analysis 1 – Risk of Developing CAC During Follow-up by Total Calcium*:** Among participants with no baseline CAC evident [CAC score 0], compared to the lowest total calcium intake, the highest total calcium intake was associated with a 27% [RR 0.73, 95% CI 0.57 to 0.93] lower risk of developing CAC at 10yrs follow-up.

***Prospective Analysis 2 – Risk of Developing CAC During Follow-up by Supplemental Calcium*:** Among participants with no baseline CAC evident [CAC score 0], compared to participants not taking supplements, calcium supplementation was associated with a 22% [RR 1.22, 95% CI 1.07 to 1.39] higher risk of CAC at 10yrs follow-up.

***Prospective Analysis 3 – Risk of Developing CAC During Follow-up Comparing Dietary to Supplemental Calcium*:** In this analysis, dietary calcium was not significantly associated with risk of CAC at follow up [RR 0.91, 95% CI 0.72 to 1.16], however, supplemental calcium was associated with a 12% [RR 1.12, 95% CI 1.00 to 1.26] higher risk of CAC.

***Prospective Analysis 4 – Risk of Developing CAC According to Level of Supplement vs. Non-Supplement Use*:** In participants with the lowest total calcium intake, calcium supplements were associated with a 41% [RR 1.41, 95% CI 1.02 to 1.97] higher risk of developing CAC. Participants with the highest calcium intake that did not use supplements showed a 26% [RR 0.74, 95% CI 0.51 to 1.07] lower risk, however, those with the highest intakes who did supplement showed a 9% [RR 0.91, 95% CI 0.72 to 1.15] lower risk.




*__Forest plot__ illustrating the findings from analyses 1 to 3 above. High overall calcium intake was associated with lower risk [__brown line graph; top__]; when dietary calcium was analysed without considering total calcium, the result was not significant [__blue line graph; second from top__]; when supplemental calcium compared to added to dietary calcium, there was an increase in risk of CAC [__purple line graph; second from bottom__]; when supplemental calcium users were compared to non-users was a significant increase in risk of CAC [__green line graph; bottom__].*

## The Critical Breakdown

**Pros:** The study had clearly stated aims and hypotheses. The cohort demographics was mixed ethnicity by design, resulting in a very well represented cohort relative to the U.S. general population. CAC was measured using accurate techniques [computed tomography], and each participant was scanned twice with the average of both scans used for the analysis. The dietary assessment method was validated and included ethnicity-specific validation for the population subgroups included in the cohort. The analysis included both cross-sectional and prospective design elements, providing insights into risk of prevalent CAC at baseline and risk of developing CAC over time. The follow-up period was adequate for detecting changes in CAC. Only participants with complete data were included in the primary analysis. The statistical analysis was methodical and thorough for teasing out the respective contributions of calcium source to CAC risk. The analysis was adjusted for lifestyle and CVD covariates.

**Cons:** The overall sample size was modest for a cohort, reflecting the nature of the measures [i.e., computed tomography measures requiring resources, participant attendance, etc.]. Although ~5,000 participants were included in the cross-sectional analysis, the prospective analysis of associations between calcium and CAC included 2,742 participants overall, and the analysis confined to participants with a CAC score of 0 at baseline included 1,567 participants. These are small sample sizes for a cohort. This means that in the quintile analyses there were often ~500 participants per quintile, with low prevalence of supplement use in the lowest total calcium intake quintile. This opens the possibility for bias, and indeed the suggested 41% higher risk from calcium supplements in the lowest quintile of total calcium intake was accompanied by confidence intervals ranging from 2% to 97%; these are so wide as to be practically meaningless. The statistical analysis, although thorough, involved multiple models and testing, so the findings should be read carefully and, as the authors note, the risk from multiple testing is the potential for false positives/negatives.

## Key Characteristic

The key characteristic of the present study is the statistical approach to teasing out independent effects of total calcium, calcium supplements, and dietary calcium intake. The results section may seem slightly dizzying and confusing, so let us work through it in more simple terms.

The first thing to grasp is what is meant by "adjusted for supplemental calcium" or "adjusted for total calcium". We then interpret the findings to be the effect of equal amounts of calcium from other sources.

For example, the first analysis compared highest vs. lowest levels of total calcium, adjusting for calcium supplements. This means that we interpret this finding as the levels of calcium alone; higher is preferable to lower for CAC risk, associated with a 27% lower risk.

Then, the second analysis compared calcium supplement users vs. non-users, adjusting for total calcium. We interpret this as a comparison between equal levels of total calcium, differing only on supplement use. And this analysis showed that, compared to an equal level of calcium, supplements were associated with a 22% higher risk.

The third analysis included dietary calcium and supplemental calcium *without* adjusting for total calcium intake. This means we interpret this as meaning the associations for dietary calcium and calcium supplements, respectively, without the conditional influence of total calcium intake. In this analysis, without the influence of total calcium, there was no significant association for dietary calcium alone, and the associations for supplemental calcium were attenuated [12% higher risk vs. 22% comparing supplement users to non-users].

From the second and third analysis, we can see that the effects of supplemental calcium were conditional on total calcium intake. Thus, the final analysis compared calcium supplement users vs. non-users in each quintile of total calcium intake. And for this, we shall move into our ***Interesting Finding***...

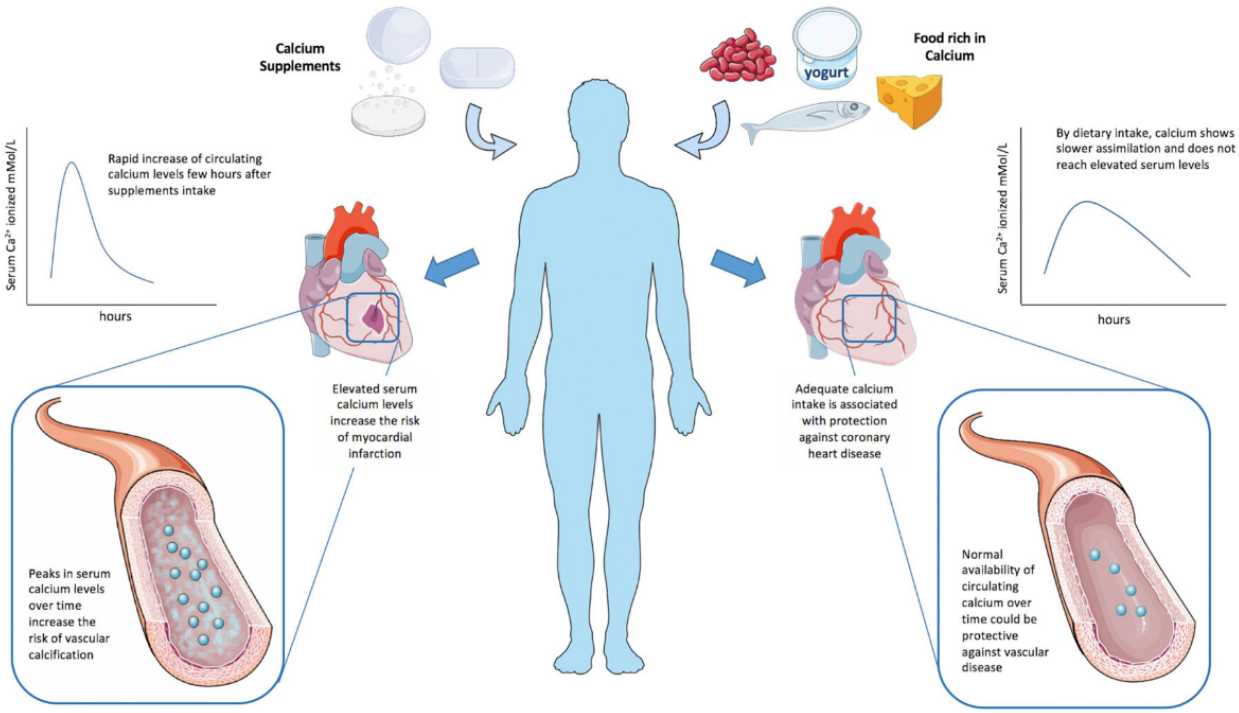
## Interesting Finding

As the associations for supplemental calcium appeared to be conditional on total calcium intake, the final model compared calcium supplement users vs. non-users in each quintile of total calcium intake. In this analysis, the reference group was the lowest calcium intake with no calcium supplement use. Thus, we interpret the relative risks for each other quintile of calcium supplement user vs. non-user as compared to that group.

Thus, in this analysis participants with the highest calcium intakes of 1,280mg/d, but with no calcium supplement use, showed a 26% [RR 0.74, 95% CI 0.51 to 1.07] lower risk of developing CAC. Now, as you can see the upper bound of the confidence interval was 1.07, i.e., crossing 1.0 and not statistically significant. However, there is a direction of effect that is evident. This finding is also consistent with the main primary outcome of a statistically significant 27% [RR 0.73, 95% CI 0.57 to 0.93] lower risk of CAC comparing the highest vs. lowest *total* calcium intakes, as this analysis was adjusted for calcium supplementation.

Conversely, the addition of calcium supplementation was overall associated with a direction of higher risk [albeit only significant in those with the lowest total calcium intake]. Overall, this analysis corroborated the study findings that the addition of calcium supplementation may increase risk for CAC.

Why? The most plausible theory at this point is the difference in calcium metabolism between diet and supplements. Dietary calcium shows a slower assimilation into the circulation, and does not lead to elevated blood levels of free calcium; as a result, calcium balance is maintained and calcium may exert protective effects. Conversely, supplemental calcium in different forms has been shown, as evident in the **figure** below [from [3]], to lead to rapid increases in circulating calcium, disturbing calcium balance and increasing risk of vascular calcification [3,6].



## Relevance

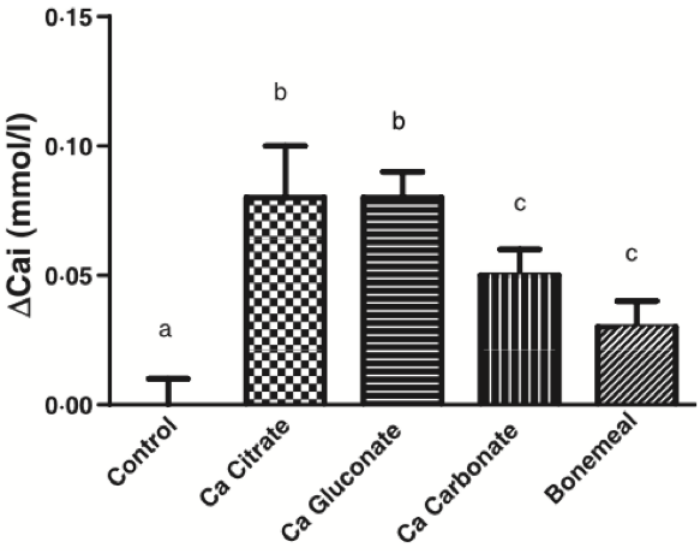
After much controversy, is this research question any closer to being resolved? Several recent meta-analyses of intervention trials have attempted to make sense of this evidence. In a 2021 meta-analysis of RCTs, calcium supplementation increased risk for CVD and coronary heart disease [CHD] by 15% and 16%, respectively [(4)]. However, the study provided confusing risk estimates for supplemental calcium form [i.e., citrate vs. carbonate], dose, and for background dietary calcium intake [(4)].

A comprehensive 2019 meta-analysis by Yang *et al*. [(5)] included both cohort studies and RCTs, and considered source of calcium; in the analysis of RCTs of calcium supplements, there was no association between supplementation and CVD risk, but there was an 8% increase in risk for CHD, but not at supplemental doses <1,000mg/d. There was, however, a 22% increase in risk for myocardial infarction from calcium supplements alone [i.e., not in combination with vitamin D] [(5)].

Thus, the two most recent meta-analyses of RCTs contain some contradictory findings, and it seems the more recent 2021 paper did not include or discuss the Yang *et al*. 2019 paper, which is a glaring omission by the authors. Nevertheless, overall we are left with the reality that there is a signal in the noise of this area, and it points to a higher risk for CVD outcomes from calcium supplements, but not dietary calcium.

The present study adds to this evidence by showing that in individuals with no present CAC at baseline, compared to non-supplement users those taking calcium supplements have a higher risk of developing CAC. There is some plausibility to the theory that surges in blood calcium levels result from rapidly assimilated supplemental forms of calcium; in the **figure** below, you can see the serum calcium responses to different forms of calcium supplements, all at the same dose of 1,000mg [(6)].

What is striking is that these substantial increases are in the form of *free calcium*, which is maintained as part of total serum calcium within very narrow ranges [(1)]; supplemental calcium drives levels of free calcium into the upper end of the reference range for serum calcium within 3hrs of ingestion [(7)]. Such surges would not be observed with food-form calcium; the increase in free calcium after consuming the same calcium dose from dairy would only be 1/6$^{th}$ that of a calcium supplement [(6)].



Open questions remain, however; what is the amount of background dietary calcium on top of which supplemental calcium may increase risk?

Does absolute amount of calcium supplementation matter in any context, or does the form of calcium supplement relate to the dose [i.e., in the example of calcium citrate, where ~1,000mg will lead to greater increases in free calcium compared to other forms]?

Is the effect of calcium supplementation primarily driven by surges in free calcium in the circulation, increasing risk for vascular calcification?

Pending resolution of these questions, the available evidence to date suggests that high-dose calcium supplementation – possibly over ~1,000mg/d – poses risk for cardiovascular health, and that such effects are not observed with dietary intakes of calcium.

## Application to Practice

Although this remains a messy area with the open questions as outlined above, there are some conclusions we can make that emerge from this overall body of evidence. The first is that a high calcium intake seems preferable to a low calcium intake, and this is true for bone-related outcomes [see this previous October 2021 Deepdive on the topic] as it is for CVD outcomes.

However, the second is that while a high calcium intake may be preferable to low, how that intake is achieved appears to matter. The body of evidence for CVD risk specifically demonstrates that dietary calcium intake is not a concern, and appears to be beneficial for cardiovascular health.

The third is that calcium supplementation needs to be carefully considered, and calcium status needs to be assessed to establish average daily intake in an individual before considering supplementation. The present study suggests that calcium supplementation was associated with CAC progression independent of total calcium intakes. RCTs provide us with little additional clarity, however, the Yang *et al*. [5] paper suggests doses of <1,000mg/d show no clear increased risk.

If calcium supplementation is to be considered [i.e., osteoporosis risk], then it seems prudent to keep the dose to a range of 500-600mg/d, and aim to obtain the remainder of total calcium intake from dietary sources up to a level of ~1,000 to 1,200mg/d.

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