

High Supplemental Calcium Intake and CVD Mortality Risk **CME**

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CLINICAL CONTEXT

Calcium is purported to benefit bone health, especially in the elderly population. For the prevention and treatment of osteoporosis, the role of calcium is well established, and calcium supplementation is in widespread use.

However, concerns remain regarding the effects of calcium on cardiovascular health and other nonskeletal outcomes. The goal of this prospective study by Xiao and colleagues was to examine whether dietary and supplemental calcium intakes are associated with mortality from total cardiovascular disease (CVD), heart disease, and cerebrovascular diseases in middle-aged and elderly men and women.

STUDY SYNOPSIS AND PERSPECTIVE

The debate over the safety of calcium supplements has been muddied with the publication of a new analysis showing that a high intake of supplemental calcium increases the risk of CVD death in men but not in women [1]. Compared with individuals who took no calcium, men who consumed 1000 mg or more of supplemental calcium per day had a significant 20% increased risk of CVD death, a risk that was driven by a significant 19% increased risk of heart-disease death.

For women, however, there was no association between calcium intake and the risk of death.

"We found a significant interaction by sex," write **Dr Qian Xiao** (National Cancer Institute, Bethesda, MD) and colleagues in their paper, published online February 4, 2013 in *JAMA: Internal Medicine*. "Elevated CVD mortality with increasing supplemental calcium intake was observed only in men; however, we cannot rule out the possibility that supplemental calcium intake may be associated with cardiovascular mortality in women." The group calls the difference in risk between men and women "intriguing," adding that further studies are needed to determine whether such differential risks are real.

In an editorial [2], **Dr Susanna Larsson** (Karolinska Institute, Stockholm, Sweden) said the lack of association between calcium supplementation in women is "perplexing," especially given the results of a reanalysis of the Women's Health Initiative (WHI) conducted by **Dr Mark Bolland** (University of Auckland, New Zealand) and colleagues. In the original WHI analysis on the risks associated with calcium use, investigators found no adverse cardiovascular effects in women taking calcium and vitamin D when compared with those not taking the supplements. However, Bolland et al reexamined the WHI data because 54% of women were already taking calcium and vitamin D by personal choice at the start of the WHI study and were not told to stop if they were randomized to placebo. When the data were reanalyzed, the researchers observed a significant association between calcium intake, as well as vitamin D, with the risk of myocardial infarction.

New Report From NIH Data

The latest report is taken from an analysis of the [National Institutes of Health--AARP Diet and Health Study](#), a study that included 388 229 men and women 50 to 71 years of age from six US states. Individuals self-reported frequency of food intake and portion size during a one-year period and answered questions about the frequency in which they consumed multivitamins, calcium-containing antacids, or calcium supplements alone.

During a mean follow-up of 12 years, there were 7904 and 3874 CVD deaths in men and women, respectively. Dietary intake of calcium was initially associated with total CVD and heart-disease death in men and women, but the association was no longer significant after adjustment for CVD risk factors. Supplemental calcium intake (1000 mg/day vs no calcium supplementation), on the other hand, increased the risk of CVD death and heart-disease death by 20% and 19%, respectively, in men, but there was no association in women. In an analysis that looked only at those taking calcium supplements and not multivitamins, the risk of CVD death and heart-disease death was 24% and 37% higher in men who took 1000 mg/day of calcium compared with those who took no supplements. Again, no association was observed in women who took calcium supplements alone.

There is currently a debate surrounding the benefits and risks of supplemental calcium in men and women. In 2010, researchers published a meta-analysis in *BMJ* showing that the use of calcium supplements without coadministered vitamin D is associated with an increased risk of myocardial infarction. This increased risk was later confirmed in an analysis of the patients participating in the European Prospective Investigation into Cancer and Nutrition Study.

In the editorial, Larsson concludes that the available evidence is suggestive of an adverse cardiovascular effect with excessive use of calcium supplements. Published as part of *JAMA: Internal Medicine's* series on "less is more" in medicine, the editorial states that more calcium, which is promoted because of its proposed benefits on bone health, does translate into health benefits. The best source of calcium, says Larsson, remains diet and the consumption of calcium-rich foods such as low-fat dairy, beans, and green leafy vegetables.

References

1. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality. *JAMA Intern Med* 2013; DOI:10.1001/jamainternmed.2013.3283. Available at: <http://archinte.jamanetwork.com/journal.aspx>.
2. Larsson SC. Are cardiovascular supplements harmful to cardiovascular disease? *JAMA Intern Med* 2013; DOI:10.1001/jamainternmed.2013.3769. Available at: <http://archinte.jamanetwork.com/journal.aspx>.

STUDY HIGHLIGHTS

- Study participants were 388,229 men and women 50 to 71 years old who were enrolled in the National Institutes of Health–AARP Diet and Health Study from 1995 through 1996.
- Participants resided in California, Florida, Louisiana, New Jersey, North Carolina, or Pennsylvania; or in the metropolitan areas of Atlanta, Georgia, or Detroit, Michigan.

- At baseline (1995-1996), participants provided information regarding dietary and supplemental calcium intake, including calcium from multivitamins and individual calcium supplements.
- Using the National Death Index, the investigators determined CVD deaths.
- Relative risks (RRs) and 95% confidence intervals (CIs) were determined by use of multivariate Cox proportional hazards regression models adjusted for demographic, lifestyle, and dietary variables.
- During follow-up (mean duration, 12 years), there were 7904 CVD deaths in men and 3874 CVD deaths in women.
- Approximately half (51%) of men and 70% of women used calcium-containing supplements.
- Supplemental calcium intake in men was associated with an increased risk for CVD death (RR for > 1000 vs 0 mg/day, 1.20; 95% CI, 1.05 - 1.36).
- Supplemental calcium intake in men was associated with heart disease death (RR, 1.19; 95% CI, 1.03 - 1.37) but not significantly with cerebrovascular disease death (RR, 1.14; 95% CI, 0.81 - 1.61).
- Subgroup analyses showed that the adverse effect of supplemental calcium was only seen in smokers, but further study is needed to examine the interplay between calcium and smoking.
- Supplemental calcium intake in women was not associated with death from CVD (RR, 1.06; 95% CI, 0.96 - 1.18), from heart disease (RR, 1.05; 0.93 - 1.18), or from cerebrovascular disease (RR, 1.08; 0.87 - 1.33).
- In both men and women, dietary calcium intake was not related to CVD death.
- On the basis of their findings, the study authors concluded that high intake of supplemental calcium is associated with an excess risk for CVD death in men but not in women, and that additional studies are needed to investigate the effect of supplemental calcium use beyond bone health.
- An accompanying commentary recommends additional large studies to further evaluate the potential health risks or benefits of calcium supplement use on CVD morbidity and mortality.
- The commentator also suggests that a safe alternative to calcium supplements is consumption of calcium-rich foods, including low-fat dairy foods, beans, and green leafy vegetables, which contain calcium as well as many other essential minerals and vitamins.
- Limitations of this study include lack of information on duration of supplement use at baseline and on intake of individual vitamin D supplements, possible unknown confounding factors, reliance on self-reported intake, and measurement of calcium intake only at baseline.

CLINICAL IMPLICATIONS

- A large prospective study showed that high intake of supplemental calcium is associated with an excess risk for CVD death in men. Additional studies are needed to determine the effect of supplemental calcium use beyond bone health.
- In this study, high intake of supplemental calcium was not associated with an excess risk for CVD death in women. In both men and women, dietary calcium intake was not related to CVD death.