

Letter from the editor

Does vitamin D prevent heart disease? A comparison of two trials.

Context: Dietary guidelines on vitamin D intake are currently based on the need to maintain optimum bone strength rather than to prevent heart disease (see the *BMJ Clinical Evidence* review on fracture prevention for more information). A recent observational study has suggested an association between low vitamin D levels and cardiovascular disease, prompting a reassessment of the current thinking on recommended vitamin D intake.[1] However, just months earlier, another study was published with contrasting results,[2] making it difficult for clinicians to advise on optimal vitamin D intake. These conflicting results must be correctly interpreted so that practitioners can offer sound advice based on good evidence.

In the observational study, David Martins and colleagues reported a significant association between risk factors for cardiovascular disease, diabetes mellitus, and low serum vitamin D levels.[1] Although a single observational study is unlikely to prove causation, these results imply that giving vitamin D supplements might reduce cardiovascular disease risk factors, and therefore might reduce the risk of adverse cardiovascular events. By contrast, the earlier paper by Judith Hsia and colleagues reported that, in a randomised controlled trial (RCT), calcium plus vitamin D supplementation had no effect on the risk of coronary heart disease or stroke in postmenopausal women over a 7 year period.[2]

Summary and results: Martins and colleagues looked at data from a national survey, which estimated the prevalence of risk factors for cardiovascular disease and diabetes for 15,088 adults across the United States. The risk factors of interest included hypertension, triglyceride and cholesterol levels, blood glucose levels, history of hypertension and diabetes mellitus, body mass index, sex, race and age. Serum levels of vitamin D were measured for each person in the study and the mean vitamin D levels were compared against the prevalence of cardiovascular disease risk factors across the population.

The study reported the prevalence of each cardiovascular disease risk factor for both the lowest quartile (<21 ng/mL) and the highest quartile (≥37 ng/mL) of serum vitamin D levels in the study population. Women, African-American people and older people were most likely to have low vitamin D levels. The prevalence of all of the cardiovascular disease risk factors of interest was higher in the lowest quartile serum vitamin D level group than the highest quartile group. Specifically, hypertension was 5% more prevalent (P=0.001); diabetes was 4% more prevalent (P<0.001); and obesity (defined as BMI ≥30) was 13% more prevalent (P<0.001) in the group with the lowest vitamin D levels compared with the group with the highest vitamin D levels.

The association of low vitamin D levels with several cardiovascular disease risk factors raises an important question: does vitamin D supplementation protect people against cardiovascular disease?

Hsia and colleagues tackled this question by randomising 36,282 women aged 50 to 79 years to receive either combined calcium carbonate 500 mg plus vitamin D 200 IU twice daily, or placebo. They reported the occurrence of adverse cardiovascular events in each group, which included myocardial infarction, death from heart disease, bypass grafting, angina, heart failure, stroke, and transient ischaemic attack.

After 7 years follow up, the RCT found no significant difference in the risk of cardiovascular events between the treatment and placebo groups. Myocardial infarction or death from coronary heart disease occurred in 499 women given calcium plus vitamin D and 475 women given placebo. The hazard ratio for the two groups was 1.04 (95% CI 0.92 to 1.18), which indicates hardly any risk difference between the groups (a hazard ratio of 1 implies no difference in risk, whereas a hazard ratio of 2 implies double the risk). Similarly, stroke occurred in 362 women given calcium plus vitamin D and 377 women given placebo, with a hazard ratio of 0.97 (95% CI 0.79 to 1.20).

From this analysis, Hsia and colleagues have answered the question raised by the Martins observational study: vitamin D supplementation is unlikely to be beneficial for preventing heart disease.

Appraisal: Although these two studies seem to report conflicting conclusions, in fact, they are designed to assess quite different issues.

The Martins study found an association between low vitamin D levels and increased cardiovascular disease risk factors for a group of people at one point in time. Because this is an observational study, nothing else can be deduced about this association. The results could mean that coronary heart disease causes depletion of serum vitamin D, or that low amounts of serum vitamin D cause cardiovascular disease. Alternatively, the observed association could be a random, chance finding.

There may be dozens of other factors that affect cardiovascular disease risk factors in the study population. As the whole of the United States' population was included in the study, there may be large variances among people in the amount of exposure to sunlight, which is one of the primary sources of vitamin D — the study was not designed to account for these geographical differences. Similarly, the study was not designed to examine the effect of differences in diet in the population.

But, despite these fundamental limitations, this observational study does what it is designed to do — it provides an interesting analysis of the general characteristics of people who are most likely to have vitamin D insufficiency. Martins and colleagues rightly report that further prospective studies are warranted to assess a direct benefit of vitamin D supplementation on cardiovascular risk factors, although a more clinically relevant study would aim to establish a link, if any, between vitamin D insufficiency and cardiovascular *events* (rather than just *risk factors*).

This clinically important question was addressed by Hsia and colleagues' RCT, which also does what it was designed to do — determine the effects of a treatment on a predetermined outcome. If the Hsia study showed that vitamin D supplementation reduced cardiovascular events, this would provide a robust platform on which to base further studies to establish a causal relationship between vitamin D insufficiency and cardiovascular disease, if it exists.

That the study failed to show such benefit makes it unlikely that there is such a causal relationship. However, it does not rule out such a relationship entirely — all an RCT can show is whether two interventions lead to a statistically significant difference in outcomes. Failure to detect a difference in adverse cardiovascular events between the intervention and control groups may be caused by various factors, including the possibility that most of the women in the RCT had adequate vitamin D levels (baseline levels were not reported), or that there were not enough cardiovascular events in the study population to be able to detect a small benefit from supplementation.

These two papers are a good example of how two different types of study can complement each other. The suspicion of an association between low vitamin D levels and increased cardiovascular risk was

raised in the observational study, but the RCT provided robust evidence that vitamin D supplementation does not prevent heart disease over 7 years.

Mark Stuart

Clinical and Commissioning Editor, *BMJ Clinical Evidence*

mstuart@bmjgroup.com

References

1. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States. *Arch Intern Med* 2007; 167:1159–1165.
2. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115: 846–854.