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LETTER

Calcium supplements and cardiovascular risk in the Women's Health Initiative

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Dear Editor,

In their detailed re-analyses of the effects of personal, non-protocol calcium and vitamin D supplementation in the Women's Health Initiative calcium and vitamin D (WHI CaD) study [1], the WHI investigators reported overall results that are generally similar to those from our previous re-analysis of WHI CaD [2, 3]. However, the WHI investigators conclude that the data "provide little support for an influence of calcium and vitamin D supplementation on coronary heart disease risk or cardiovascular disease risk." It is important to highlight several methodological differences between the WHI investigators' analyses and our previous re-analysis of WHI CaD for myocardial infarction (MI) and stroke [3]. Our analyses were pre-specified in a protocol approved by the NHLBI *before* we were provided with the database. We used the publicly available database whereas the WHI investigators used the main database. Because we hypothesized that non-protocol use of calcium supplements might obscure an adverse effect of CaD on vascular endpoints, we classified participants based on whether they were using personal calcium supplements at time of randomisation; the WHI investigators classified participants by whether they were using personal calcium *or* vitamin D supplements at time of entry to the WHI clinical trials program, usually one year before randomisation. This will have led to classification differences, for example, women taking only personal vitamin D will be classified as non-users of personal calcium in our analysis, but users of personal supplements in the WHI analysis. Likewise, women who started personal calcium supplements between WHI program entry and randomisation will be classified differently in the two analyses.

Notwithstanding these methodological differences, the current results [1] are consistent both with our findings and with an increased cardiovascular risk from calcium supplements. The background to our re-analysis of WHI CaD was a meta-analysis of 11 trials of calcium supplements (without vitamin D) that showed a 27–31% increased risk of MI with calcium and suggested a possible 12–20% increased risk of stroke [4]. Our re-analysis of WHI CaD reported a hazard ratio (HR) of 1.20 for total MI with CaD and 1.17 for stroke [3], consistent with the meta-analysis findings [4]. The current analysis by the WHI investigators reported a HR of 1.11 for MI with CaD and 1.12 for stroke [1]. The risk for MI was greater early in the study (HR 1.30), and the risks for MI (HR 1.18) and stroke (HR 1.18) were greater in adherent participants. Thus, their conclusion that there is no evidence to support concern regarding the cardiovascular safety of calcium supplements is not in accord with the data they present, which are consistent both with pre-existing data and with modest increases in MI and stroke from calcium supplements with or without vitamin D. Indeed, when their data are substituted into our previously published meta-analysis, there is still evidence of an increased risk of myocardial infarction (RR 1.20, 95% CI 1.03–1.40, P=0.018).

The paper by Prentice and colleagues has other important implications. It highlights that widespread non-protocol use of a study intervention might obscure important effects of that intervention. This has implications for the interpretation of other studies with similar designs [5, 6]. Additionally, it again highlights the occurrence of major differences in findings between observational studies and randomized controlled trials. With the growing availability of large

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electronic datasets, reports from observational studies will become more common, and these results will increasingly conflict with those of existing randomized trials.

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