Problems with epidemiological approach and conclusions-the response

The Authors' reply We are not surprised by the controversy caused by our recently published paper in *Heart*,[1] showing that taking calcium supplements might roughly double the risk of myocardial infarction (MI) among middle-aged and elderly adults. Our paper contributes to the ongoing debate evoked by previous meta-analyses of clinical trials,[2 3] in particular, which alarmed the public that calcium supplements might also provide unfavourable health effects.

We would like to rectify a few of the criticisms by Prince.[2] First, we confirm that, contrary to Dr Prince's reading of our manuscript, we did, in fact, verify systematically all self-reported disease outcomes, that is, MI, stroke and cardiovascular deaths, against medical records, and that was also stated in our manuscript. It has been well documented by other observational studies that self-reporting has very high sensitivity for the ascertainment of occurrences of MI,[4–6] and our subsequent verification against medical records additionally ensures high specificity. Second, our analysis focussed on incident MI, stroke, as well as cardiovascular mortality since we are sure that these data are valid. By contrast, other possible cardiovascular endpoints, including transient ischaemic attacks or unstable angina pectoris, are much more difficult to assess, and therefore, were not ascertained systematically. The results of the statistical analysis show no association of calcium supplementation with the risk of stroke or early cardiovascular disease death. The reasons for these results are certainly intriguing. However, the discrepancy between our findings for MI and the other endpoints cannot be taken as an argument of 'lack of quality' of study results. Indeed, our findings regarding stroke and cardiovascular mortality are comparable with those of the meta-analysis of clinical trials with Ca supplementation.[2 3]

Third, as reported in our manuscript, the statistical model did include several adjustment variables which were carefully selected by a data-driven approach. Hypertension, as well as use of antihypertensive drugs and lipid-lowering drugs, were examined as potential adjustment factors, but not finally included, since this variable did not cause substantial change in results (with adjustment for hypertension: HR=1.88; 95% CI 1.18 to 2.98; without adjustment for hypertension: HR=1.86; 95% CI 1.17 to 2.96).

As with every study, our study too has strengths and limitations which we mentioned in the discussion. One important issue is sample size. Our analysis is based on 354 cases of MI, 260 cases of stroke and 267 CVD deaths which occurred during a mean follow-up of our cohort of 11 years. The number of MI cases in calcium supplement users was limited (n=20); nevertheless, the association with MI was strong enough to be statistically significant.

In summary, while we reject some of the methodological criticisms raised by Dr Prince and colleagues, we do have concern that observational studies alone may not provide an ultimate proof that calcium supplements do increase the risk of heart attack. However, the concordance of our study findings with those from a number of randomised trials, as reviewed by Bolland *et al*,[2 3] makes us believe that use of calcium supplements should be considered with care.

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