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Making too much of a weak case

The paper by Bolland and colleagues is seriously flawed in many respects, the first being its misleading title.\(^1\) It is not a meta-analysis in the usually accepted sense—that is, a review of published trials. Most of the data are unpublished, were obtained by direct request from the relevant authors, and are impossible to investigate independently.

The review provides some data from 15 trials but only five have patient level data. These five comprise a mixture of men and women and are dominated by one trial (which has been split into two parts) accounting for 66% of all the subjects ($292 out of 8033$).\(^2\) None of these five trials shows a significant difference between calcium and placebo, but when they are combined the relative risk of myocardial infarction is $1.31$ ($1.02$ to $1.67$) ($P=0.035$), as shown in their figure 2. The forest plot (figure 3), constructed from trial level data, includes two further trials with cardiovascular events: Prince et al based on self reported events\(^3\) (which the Auckland group should know from their own experience are of little value\(^4\)) and Lappe and Heaney.\(^5\)

Of equal importance is the lack of any plausible explanation for their results. No known physiological pathway could lead from a transient 5% rise in serum calcium to cardiovascular damage. A higher level of proof is required for implausible than plausible outcomes, so $P$ values on the edge of significance must not be allowed to change current public health policy.

More evidence is needed. In a recently accepted paper in which $1460$ women were followed up for five years, $60$ cases of myocardial infarction or ischaemic heart disease occurred in the $730$ women randomised to calcium and $62$ in those randomised to placebo.\(^6\)