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LETTER

Uncertain effects of calcium and vitamin D supplementation on fracture risk reduction

S. A. Frost[1,2] · **T. V. Nguyen**[1,3]

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Dear Editors,

In a recent meta-analysis of 8 randomized controlled trials involving 30,970 individuals, Weaver and colleagues concluded that supplements of calcium and vitamin D (CaD) reduced the risk of fracture in both community dwelling and institutionalized individuals [1]. However, we consider that the effect size is more modest and more uncertain than reported for several reasons.

The authors found that *overall*, CaD supplementation was associated with a 15 % reduction in fracture risk (RR 0.85; 95 % confidence interval, 0.73 to 0.98). However, there were differences in calcium and vitamin D dosages and sample sizes between studies. The compliance among studies is also known to be vastly different. The presence of such a heterogeneity tends to reduce the effect size of large studies in the traditional random effects model [2].

The Bayesian approach offers a better way to synthesize the data, because it allows formal inference to be drawn on the plausibility of effect size. We have conducted a Bayesian analysis with uniform prior distribution, and found that the overall relative risk was 0.87, with 95 % credible interval includes unity (0.68 to 1.02). There was a 44 % probability that CaD supplementation reduces fracture risk by at least 15 %. When the analysis was stratified by subpopulation, we found that the effect size was greater among institutionalized individuals (RR 0.70; 95 % credible interval, 0.39 to 1.23) than among community dwelling individuals (RR 0.90; 95 % credible interval, 0.65 to 1.07). In either population, the effect of CaD supplementation on fracture risk is not certain.

In the authors' analysis, the index of heterogeneity was ~50 %, indicating a substantial variation in effect sizes between studies, but it was not clear which factors account for the variation. We have found that this variation could be partially explained by background risk. Figure 1 shows that the effect of CaD supplementation (as measured by the relative risk of fracture) was inversely related to the annual incidence of fracture in the placebo group (i.e., background risk). We estimated that approximately 36 % of the variance in (log) relative risk was attributable to difference in background risk.

Using a Bayesian approach [3], we expanded the analysis to include estimates of the efficacy for various populations with varying background risk. Table 1 shows that the fracture prevention of CaD diminishes in relative terms and in absolute terms as the background risk decreases. For instance, among individuals with low annual risk of fracture, say 5 per 1000 older adults, only about 1 or 2 fractures among 10,000 individuals would be prevented with the use of CaD (numbers needed to treat (NNT) = 6667). Among individuals with a risk, say 50 per 1000, only 84 individuals are needed to treat with CaD supplements to reduce 1 fracture case.

✉ S. A. Frost
s.frost@uws.edu.au

✉ T. V. Nguyen
t.nguyen@garvan.org.au

[1] Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia

[2] University of Western Sydney, Penrith, Australia

[3] University of Technology, Sydney, Australia

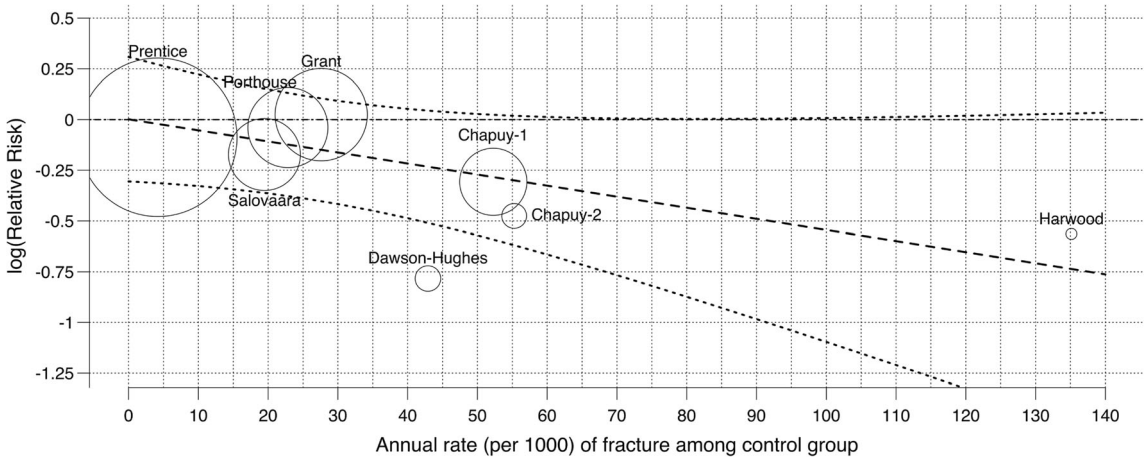

Fig. 1 Relationship between effect size (log relative risk) and background risk of fracture

In conclusion, our analysis of the data suggests that the effect of CaD supplementation on fracture risk reduction is inconclusive, and that the effect size is dependent on patients' baseline risk. This dependency implies that there exists no constant and population-wide overall effect of CaD supplementation.

Table 1 Estimated relative risk, expected number of fractures with treatment, absolute risk reduction, and number needed to treat, based on various annual risks of low-trauma fracture

Annual risk of fracture (per 1000 persons)	Estimated relative risk of fracture with CaD	Absolute risk reduction (per 1000)	Number needed to treat
5	0.97	0.15	6667
10	0.95	0.50	2000
20	0.90	2.0	500
30	0.85	4.5	223
40	0.81	7.6	132
50	0.76	12.0	84
60	0.72	16.8	60

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