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LETTERS

VITAMIN D AND RISK OF CAUSE SPECIFIC DEATH

Authors' reply to Grant and Garland and to Bolland and colleagues

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We agree with Grant and Garland that, although existing ecological studies support the findings of our meta-analysis of observational studies, further work—especially that involving well powered randomised intervention studies—is needed.[1 2] However, the respective pooled risk ratios that we reported by combining the primary and secondary prevention cohorts are based on indirect comparisons (only a subset of studies provided mortality risk data on people with pre-existing disease).

As Bolland and colleagues note, the overall estimates from the vitamin D_3 randomised controlled trials were indeed presented as a combination of both active and inactive vitamin D_3 supplements, given a lack of power in each component in isolation.[3] We also included a study that evaluated the effects of vitamin D_3 alone without concurrent administration of other pharmacological interventions (which was similarly kept as a vitamin D alone study in the earlier Cochrane report).[1 4] Nonetheless, when this study and the other three calcitriol trials were removed from the analyses,[5-7] there was no significant effect of "any vitamin D supplementation" on mortality (which remains consistent with our original results). The pooled effect estimate for the 10 vitamin D_3 trials became slightly attenuated (0.91, 95% CI 0.82 to 1.00) in our calculation; however, this apparent inverse effect differed significantly from the corresponding pooled estimate of vitamin D_2 (P from meta-regression analysis=0.03, for a comparison between vitamin D_3 and vitamin D_2 trials). That said, we agree with Bolland and colleagues that the selection criteria (such as randomised *v* non-randomised, with calcium supplementation *v* without) and decisions on subgroup analyses vary across reviews on this topic, and this may explain the different findings across these reports. However, as was discussed in our paper (and the accompanying editorial), all these reviews (including ours) are based on largely overlapping trials of mostly high risk, elderly populations (with an average age >75 years in all trials combined). Therefore, before any policy formulation, further large scale and sufficiently prolonged trials with large samples derived from the general population will be required.

Competing interests: None declared.

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