**TO THE EDITOR:** Fortmann and colleagues (1) calculated that vitamin E supplementation does not influence all-cause mortality (95% CI, −2% to 4%). This estimate was based on the pooling of the results of 5 studies. However, conclusions of study-level analyses can differ from those of corresponding individual-level analysis, a difference known as the "ecological fallacy" (2).

Recently, a colleague and I analyzed heterogeneity in the effect of vitamin E on the mortality of participants in the ATBC (Alpha-Tocopherol, Beta-Carotene) study, who were male smokers aged 50 to 69 years at baseline (3). The combination of age and dietary vitamin C intake modified the effect of vitamin E supplementation so that the heterogeneity over 6 subgroups was highly significant ($P < 0.001$).

In 11 448 participants of the ATBC study aged 50 to 62 years who had dietary vitamin C intake greater than the median, vitamin E increased all-cause mortality by 19% (CI, 5% to 35%). In 872 participants aged 66 to 69 years who had vitamin C intake greater than the median, vitamin E decreased mortality by 41% (CI, −56% to −21%). Vitamin E did not influence mortality among men who had vitamin C intake less than the median.

The modifying effect of vitamin C was not explained by other substances in fruit and vegetables (3). At the biochemical level, the interaction between vitamins C and E is well-known and may explain the role of vitamin C as a modifying factor (4). Furthermore, the benefit of vitamin E for men aged 66 years or older implies that survival time might be influenced. In a further exploratory analysis, we found that participants who received vitamin E lived 0.5 year longer at the upper end of the survival curves (5).

Because of the mainly negative findings in the vitamin trials as summarized by Fortmann and colleagues, discouraging the general population from receiving supplements until we have better knowledge of the restricted groups of persons who might benefit seems justified. Nevertheless, the pooled effect of vitamin E that the authors calculated does not seem to apply to all persons or indicate in what direction further investigation should proceed. The individual-level analysis of the ATBC study suggests that trials on vitamins E and C for men older than 70 years are warranted (5).

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**Disclosures:** None. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L14-0083.

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**TO THE EDITOR:** Fortmann and colleagues (1) identified 5 randomized, controlled trials (RCTs) of calcium or vitamin D supplements and cardiovascular disease and cancer. Data were available on all-cause mortality for 3 RCTs of calcium, 1 RCT of vitamin D, and 1 RCT of calcium and vitamin D; cardiovascular disease incidence for 1 RCT of calcium, 2 RCTs of vitamin D, and 1 RCT of calcium and vitamin D; and cancer incidence for 3 RCTs of calcium, 2 RCTs of vitamin D, and 1 RCT of calcium and vitamin D.

In previous systematic reviews of calcium supplementation, we identified 8 RCTs with complete trial-level data available for myocardial infarction, stroke, and all-cause mortality (2) and 7 RCTs with complete trial-level data available for cancer incidence (3). A systematic review by Elamin and associates (4) identified 30 RCTs of vitamin D with data available for mortality, 6 RCTs with data for myocardial infarction, and 6 RCTs with data for stroke. Some of these data were unpublished and provided by the lead authors, but data from other published papers are missing from Fortmann and colleagues' review.

When unpublished data have been obtained and published in previous systematic reviews or meta-analyses, they should be considered "published" and incorporated into subsequent reviews. Fortmann and colleagues' omission of unpublished data is important because the body of unpublished data for adverse events or secondary outcomes can be considerably greater than the body of data available from primary publications (5). Because their review considers only a subset of the available data on the effect of calcium and vitamin D supplements on cardiovascular events, cancer incidence, and mortality, their conclusions may not be representative or reliable.

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