

Third, dying from a supplement after only a few months of use seems biologically implausible. The finding that supplementation duration had no effect on total mortality diminishes the likelihood that these micronutrients increase the risk of death.

Fourth, the conclusions are based predominantly on findings from the “low-bias risk” subgroup defined by methodological quality assessment. The authors note that methodological details might not have been reported from studies implemented in ways that met the quality assessment criteria so that a lack of reporting might have been mistaken as a lack of high quality. More importantly, the quality of trial implementation may cause even greater bias. For example, a study reporting a 60% dropout rate is more likely to produce biased results than a study with no dropouts that does not report on dropouts. Adherence to study supplement use and self-selection into supplementation can also create bias.²⁻⁴ These issues are particularly relevant to trials conducted in recent years when self-selected supplement use was prevalent, and the low-bias risk trials defined by Bjelakovic et al tended to have been conducted more recently than the high-bias risk trials.

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To the Editor: Dr Bjelakovic and colleagues¹ showed that there is no evidence from randomized trials that antioxidant supplements reduce mortality. However, the authors did not consider that the effects might vary among different population subgroups so that an average for a large group of people could be misleading.

Analyses of the large-scale Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study found substantial divergence in the effect of 50 mg/d of vitamin E on common cold incidence in elderly men. Among participants 72 years or older, who smoked heavily, and lived out-

side cities, use of vitamin E increased common cold incidence by 58% (95% confidence interval [CI], 23%-101%; 0.83 vs 0.53 colds per year), whereas in less-smoking city-dwellers it reduced common cold incidence by 46% (95% CI, -20% to -63%; 0.47 vs 0.86 colds per year).² The effect of vitamin E on the incidence of pneumonia also diverged so that the risk increased or decreased depending on the age of smoking initiation.³ Furthermore, among participants who exercised during leisure, vitamin E reduced the incidence of pneumonia by 50% (95% CI, -16% to -70%; 1.5 vs 3.0 cases of pneumonia per 1000 person-years); however, the number needed to treat was high, so that 667 people would need to take vitamin E for one year to prevent one episode of pneumonia.⁴ Although the practical significance of these findings is uncertain, they indicate that subgroups of people may benefit, or may be harmed from vitamin E supplementation even though the average effect in the population is nil.

The widespread use of vitamin E supplements should be discouraged because there is no evidence that the general population would benefit from such practice. However, the subgroup findings of the ATBC Study warrant further research to characterize the small groups of people for whom vitamin E supplementation may be beneficial.

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To the Editor: We believe that the approach used in the meta-analysis of mortality in randomized trials of antioxidant supplements by Dr Bjelakovic and colleagues¹ erred in several important ways, probably resulting in biased conclusions.

First, the Linxian General Population Nutrition Intervention Trial (NIT)² was misclassified as a “trial with high risk of bias.” This double-blind placebo-controlled trial of 29 584 persons contained all the attributes described by the authors as defining trials with low risk of bias: more than 60% of the target population was enrolled and computer-randomized, and participant characteristics were virtually identical across all supplement groups (no selection bias); all pill bottles were masked throughout the trial (adequate allocation concealment and blinding); all participants were