Antioxidant Supplements and Mortality

To the Editor: Based on their meta-analysis of antioxidant supplementation trials, Dr Bjelakovic and colleagues[1] conclude that some of the intervention nutrients appeared to be associated with increased mortality. Particular aspects of their approach, analysis, and reported findings may have led to incomplete or biased determinations of the real effect of such nutrients in various populations.

Although vitamin A is related to beta carotene (and other provitamin A carotenoids) by virtue of its in vivo formation through oxidative cleavage of the latter, it is not considered an antioxidant nutrient.[2] Its primary inclusion in the meta-analysis, except as an eligible trial cosupplement, is therefore surprising, with specific implications for the 2 trials that tested vitamin A only. Controlled trials of several other nonantioxidant vitamins could have been similarly included in the analysis along with those testing vitamin A.

Nearly half of the studies originally identified from the literature (405 of 815) were excluded because no deaths occurred, and most of the 68 trials that were analyzed were small, with few deaths (12 trials had only 1 death). This would yield findings heavily weighted by a few large studies. Also, it would be useful to know what hypotheses formed the basis for the "preconceived" subgroup analyses that excluded selenium and high-bias risk trials, which showed essentially protective effects and whose exclusion would certainly shift the risk estimates higher.

The findings from this analysis have implications primarily for supplementation in high-risk populations. Sixty-nine percent of the studies involved secondary prevention and tested efficacy for recurrence or advancement of preexisting cardiovascular, neoplastic, neurological, ocular, and other diseases. Even of the 21 primary prevention trials, many encompassed elevated baseline population risks from smoking,[3] asbestos exposure,[4] or multinutritional deficiencies,[5] for example. The population risk-antioxidant-mortality interaction might be more clearly elucidated if the respective summary relative risk (RR) estimates for the primary and secondary prevention trials were provided. Also, is it possible that primary vs secondary prevention trials did not significantly differ with respect to mortality in the models, as stated on page 847, when according to the article's Figures 2 and 3 and Tables 1 and 2, these studies had median crude mortality rates of 2.1 and 6.0 deaths per 100 participants (or median crude annual rates of 0.9 and 3.3 deaths per 100 person-years), respectively?

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To the Editor: We have several concerns about the meta-analysis of randomized trials of antioxidant supplements by Dr Bjelakovic and colleagues.[1] First, establishing causality requires considering temporal relationship, dose-response relationship, evidence of supplement use, effects that disappear after discontinuation of supplementation, lack of alternative explanations, and recurrence after restarting supplement use. It is difficult to establish a causal relationship between supplement use and risk of death when 2 of the criteria (response to rechallenge and response to discontinuation of use) cannot be applied to the outcome of death. Hence, greater reliance must be placed on plausible biological mechanisms and evidence that nutrients affect specific disorders. As the authors pointed out, it is likely that increased cancer and cardiovascular mortality are the main reasons for the increased all-cause mortality. The review would have been more convincing if it had also addressed cause-specific mortality.

Second, the exclusion of 405 studies with no deaths might have biased the results toward finding a difference in total mortality. We question the legitimacy of the exploratory analysis in which an arbitrary mortality was added to each comparison group, and we wonder why multiple imputation techniques were not used instead.

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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 colleagues[1] 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 outside 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 colleagues[1] 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

visited monthly to assess adherence and ascertain end points (no performance or detection bias); and follow-up and endpoint ascertainment were essentially complete, with only 0.2% lost to follow-up (no attrition bias). Indeed, the methods used in this trial were identical to those used in the concurrent Linxian Dysplasia NIT,[3] which the authors classified as a "trial with low risk of bias."

Misclassification of the General Population NIT was important because it probably changed the main conclusion of the meta-analysis. Inclusion of this trial's 2127 deaths in the analysis of low-bias risk trials (as shown in the article's Figure 2) would reduce the overall antioxidant relative risk from the reported 1.05, likely rendering it nonsignificant.

Second, the authors based their final conclusions about antioxidant-specific effects on models that excluded selenium trials (in the article's Table 5). Exclusion of these trials, which showed mortality protection, biased results for the other 4 nutrients toward a harmful effect. A much stronger a priori assumption is the harmful effect of high-dose beta carotene in smokers,[4,5] which the authors did not address; in the current article, 2 large beta carotene trials involving smokers provided more than half the deaths in the low-bias risk trials analysis, likely driving the meta-analysis results and the article's final conclusions.

The best models for evaluating antioxidant-specific effects are those that include all low-bias risk trials (including the General Population NIT) without single agent exclusions. The closest approximations to such models in the article are the ones including all trials (as shown in the article's Table 5). These models found statistically insignificant summary RRs for beta carotene (RR, 1.01), vitamin A (RR, 1.05), vitamin E (RR, 1.01), and vitamin C (RR, 0.97), but a significant benefit for selenium (RR, 0.91; 95% CI, 0.84-0.99). These results suggest a very different interpretation of this meta-analysis.

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In Reply: Dr Albanes and Dr Huang and colleagues stress the potential importance of trials with 0 events. In our primary analyses, we calculated RRs and therefore excluded trials with 0 events (405 trials with 40 000 participants). Sensitivity analyses including 1 hypothetical trial with 1 death in each study arm and 40 000 participants reached the same conclusion as the primary analysis (RR, 1.02; 95% CI; 0.98-1.06). Trials with 0 events are likely to have specific characteristics (eg, short duration, low dose). We did not use imputation techniques because they are based on the assumption that any trial can be replaced by a new randomly chosen trial in the same sample.[1]

Albanes argues that vitamin A is not an antioxidant. However, vitamin A has antioxidant activity.[2] In our systematic review, we included 2 trials of vitamin A monotherapy. The trials found no significant effect of vitamin A, and their exclusion had no noticeable effect on the overall or subgroup analyses.

Dr Hemilä is concerned that our review may not have accounted for the beneficial effects of vitamin E seen in certain populations.[3] Although we cannot exclude such an effect, we are unable to analyze the question as only trial-level data were available.

Drs Taylor and Dawsey comment on our subgroup analyses on selenium, which we performed based on previous findings.[4] Selenium had a positive effect in an overall analysis but not when excluding trials with a high-bias risk or separating trials of monotherapy and combination therapy. Additional evidence for selenium is therefore needed.

Albanes emphasizes that 69% of the trials in our review dealt with secondary prevention. These trials included 29% of the participants. Neither the primary prevention trials (RR, 1.03; 95% CI, 0.97-1.09) nor the secondary prevention trials (RR, 1.01; 95% CI, 0.96-1.05) found a significant effect of antioxidants in random-effects models irrespective of bias risk.

Huang et al argue that cause-specific mortality rates provide important information. Although we agree, there was diagnostic heterogeneity across several trials. We focused on overall mortality based on previous findings because antioxidant supplements may increase both cardiovascular and cancer mortality.[4,5] We agree that the effect of antioxidants may be linked with treatment duration, which was included in a metaregression analysis of aggregate trial data. The analysis did not compare participants randomized to long vs short treatment regimens, which may explain why we found no significant influence of treatment duration on treatment effects. To address this question, prospective validation is necessary.

Huang et al stress that trial reports may not reflect what was actually done. However, inadequate reporting may reflect methodological flaws. Previous evidence shows that published trials without adequate randomization, blinding, or follow-up may generate biased estimates of intervention effects.[6] In accordance with this evidence, we found that the

estimated effect of antioxidants was significantly more positive if the reported bias control was low.

We agree with Taylor and Dawsey that there are high-quality aspects of the NIT trial.[7] We classified the NIT trial as having a high-bias risk because the numbers and reasons for dropouts and withdrawals were not clearly reported. Post hoc subgroup analyses of low-bias risk trials found that antioxidants significantly increase mortality irrespective of whether the NIT trial was included (RR, 1.04; 95% CI, 1.01-1.08) or not included (RR, 1.05; 95% CI, 1.02-1.08).

Taylor and Dawsey argue that the inclusion of 2 low-bias risk trials on beta carotene in smokers may drive our results. However, additional analyses show that antioxidants have no significant effect on mortality irrespective of whether these 2 trials were included (RR, 1.02; 95% CI, 0.98-1.06) or not included (RR, 1.00; 95% CI, 0.97-1.04). Our analysis had included a total of 25 beta carotene trials. Because we have no individual patient data, we are unable to analyze the effect of beta carotene in smokers separately. In response to Taylor and Dawsey, we have conducted post hoc analyses that exclude the 25 trials on beta carotene. When these trials were excluded, the subgroup analyses found no significant effect of vitamin A (RR, 1.23; 95% CI, 0.91-1.66) or vitamin E (RR, 1.00; 95% CI, 0.94-1.06) when all trials were included irrespective of bias risk or when only trials with a low risk of bias were included (RR, 1.21; 95% CI, 0.88-1.67; RR, 1.04; 95% CI, 0.97-1.12, respectively). As with all post hoc analyses, they must be interpreted with caution.

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Low Back Pain and the Workplace

To the Editor: We believe that the Commentary on back pain in the workplace by Dr Hadler and colleagues poorly serves clinicians, patients with low back pain, and occupational health and safety professionals seeking to reduce the burden of low back pain among working people.[1] The authors argue that low back pain does not occur as a consequence of occupational physical demands (eg, lifting, twisting of the trunk, whole body vibration) but rather as a result of the "psychosocial context" of work and other phenomena. They claim that "extensive and compelling science" supports their opinions but cite only 2 published reviews and a few additional studies in support of their inference.

We consider it unfortunate that the authors did not cite any of the large international studies in which clinically and statistically significant associations were observed between occupational physical demands and low back pain after adjustment for confounders.[2,3] Also missing were references to experimental studies (including randomized controlled trials) that support such a relationship.[4] A comprehensive review of physical and nonphysical contributors to low back pain is included in the National Research Council and Institute of Medicine report on musculoskeletal disorders of the low back and upper extremity.[5]

The authors further argue that because low back pain is a common predicament inside or outside the workplace, it "cannot be shown to be more specific to the workplace than the viruses that cause upper respiratory infection." We find this kind of analogy a poor substitute for epidemiological evidence. The common occurrence of low back pain outside the workplace proves nothing about low back pain risks that are encountered inside the workplace. Furthermore, evidence of occupational psychosocial exposures as risk factors for low back pain does not negate evidence regarding physical risk factors.[3,5] Contemporary thinking about work-associated low back pain highlights the complex interactions of physical and psychosocial stressors.