

## COMMENTS AND RESPONSES

## High-Dosage Vitamin E Supplementation and All-Cause Mortality

**TO THE EDITOR:** Miller and colleagues (1) concluded that high-dosage vitamin E supplements may increase all-cause mortality. However, we question some of the methods of this meta-analysis. Supplements labeled vitamin E contain either RRR- $\alpha$ -tocopherol (the only naturally occurring stereoisomer of  $\alpha$ -tocopherol) or synthetic all-rac- $\alpha$ -tocopherol (a mixture of RRR- $\alpha$ -tocopherol with 7 non-natural stereoisomers). Miller and colleagues combined data from clinical trials that administered either RRR- $\alpha$ -tocopherol or all-rac- $\alpha$ -tocopherol. This is not appropriate, even though there are no known differences in the symptomatic effects of RRR- $\alpha$ -tocopherol and all-rac- $\alpha$ -tocopherols. By definition, products that are different mixtures of stereoisomers are not bioequivalent and are not therapeutic equivalents (that is, generic substitutes) for each other because most biological processes occur in a highly stereospecific manner (2, 3). Both RRR- $\alpha$ -tocopherol and all-rac- $\alpha$ -tocopherol are similarly potent antioxidants in vitro (4), but probably differ in their antioxidant effects in vivo because of variations in bioavailability (5). RRR- $\alpha$ -tocopherol and all-rac- $\alpha$ -tocopherol will markedly differ in their many nonantioxidant effects that involve specific interactions with chiral molecules in the cytoplasm and nuclei of most cells (6–8).

Miller and colleagues expressed the dose of vitamin E supplements in international units (IU) of vitamin E activity, but by definition, IU of vitamin E activity refers only to the potency of RRR- $\alpha$ -tocopherol and all-rac- $\alpha$ -tocopherol for preventing or treating symptoms of vitamin E deficiency (9, 10). The units for dose should be milligrams in studies that assess the risk for adverse effects of RRR- $\alpha$ -tocopherol or all-rac- $\alpha$ -tocopherol (10).

The meta-analysis by Miller and colleagues excluded 12 clinical trials that reported fewer than 10 deaths each. However, Collins and colleagues (11) stated that a meta-analysis minimizes the risk for bias only if it is “a systematic overview of the totality of the evidence from all relevant unconfounded randomized trials.” In a meta-analysis intended to assess the relative risk for death, Miller and colleagues created the appearance of bias by excluding clinical trials that show a low rate of death.

Miller and colleagues assessed the association between death and random assignment to the vitamin E group but did not assess the adherence of study participants. One method of assuring adherence in clinical trials of vitamin E supplementation is to measure the plasma concentration of  $\alpha$ -tocopherol in every participant in both the vitamin E group and the placebo group. As far as we know, the Cambridge Heart Antioxidant Study (CHAOS) (12) is the only vitamin E trial that administered only RRR- $\alpha$ -tocopherol or placebo, measured plasma RRR- $\alpha$ -tocopherol concentrations in every participant, and attempted to assess whether adverse outcomes correlated with regular intake of vitamin E supplements or failure to regularly take vitamin E supplements. In CHAOS, only 6 of 38 cardiovascular deaths in the  $\alpha$ -tocopherol group were of patients known to have adhered to the study protocol. Twenty-one of the patients who died were known to be nonadherent, and in 11 of the patients who died, adherence was unknown (13).

However, CHAOS is the only trial of vitamin E supplementation that administered more than 1 dose of RRR- $\alpha$ -tocopherol, and

some observations of CHAOS are consistent with Miller and colleagues' conclusion that risk for death increases with dosages greater than 400 IU/d. In CHAOS, cardiovascular deaths were observed in 2.0% of patients taking 400 IU of RRR- $\alpha$ -tocopherol per day, 2.4% of patients taking placebo, and 3.1% of patients taking 800 IU of RRR- $\alpha$ -tocopherol per day. Similarly, nonfatal myocardial infarction occurred in 0.20% of patients taking 400 IU of RRR- $\alpha$ -tocopherol per day versus 2.0% of patients taking 800 IU of RRR- $\alpha$ -tocopherol per day. We agree with Miller and colleagues that it is necessary to determine dose–effect relationships for vitamin E, and we recommend that future clinical trials of vitamin E use only natural RRR- $\alpha$ -tocopherol.

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**TO THE EDITOR:** There are several flaws in the meta-analysis by Miller and colleagues (1), including erroneous interpretation of the pooled trials of  $\alpha$ -tocopherol and lack of clarity in vitamin E nomenclature. The analysis includes trials from many time periods, with different trial designs, doses and combinations, and end points that make comparisons difficult and fallacious. Participants in several of the trials had significant medical conditions, such as coronary artery disease, end-stage renal disease, diabetes mellitus, Parkinson disease, and Alzheimer disease. Given this heterogeneity in the participant pool, we would consider it presumptuous to draw solid conclusions of the magnitude of Miller and colleagues', even with complex statistical tools such as meta-analysis, and to extend the observations to normal, healthy people. In addition to clinical heterogeneity, this analysis also suffered from heterogeneity in test nutrients. In many of the trials, vitamin E was used alone and in combination with another nutrient, such as  $\beta$ -carotene. In these cases, the authors combined the data for vitamin E alone with the data for vitamin E plus another nutrient even when the data for the other nutrient indicated that it was statistically significantly associated with increased mortality. Moreover, those studies in which fewer than 10 deaths occurred were excluded from the meta-analyses, giving an artificial weight to studies in which more patients died—that is, those in which patients had serious illness compared with studies of healthy individuals. A close look at the odds ratios in Miller and colleagues' Figure 2 does not suggest harmful effects at a dose of 400 IU of  $\alpha$ -tocopherol, and yet the authors concluded that harmful effects begin at a dose of 150 IU.

Vitamin E is not a single compound and exists in 8 different isoforms in nature (4 tocopherols and 4 tocotrienols) that have distinct biopotencies, biokinetics, and cancer-preventive properties. Food sources vary in their content of the vitamin E isoforms.  $\gamma$ -Tocopherol, the primary source of dietary vitamin E, is abundant in plant seeds (corn, soybean, and sesame), vegetable oils, and nuts (walnuts, pecans, and peanuts). It is not appropriate to "lump" all the different forms of vitamin E into a single basket and call them "vitamin E." Natural vitamin E forms have different properties than synthetic vitamin E does. Most of the trials cited in Miller and colleagues' analysis used synthetic  $\alpha$ -tocopherol. This should have been emphasized. Dietary and supplemental sources of vitamin E isoforms have unique properties that can influence critical pathways involved in cancer, inflammation, cardiovascular disease (CVD), and neurodegenerative disease. For example, mechanistic differences between the  $\alpha$ - and  $\gamma$ -tocopherols and their metabolites provide a molecular basis for the superiority of  $\gamma$ -tocopherol (2–5). Although  $\alpha$ -tocopherol has a high concentration in supplements, the primary form of vitamin E in the diet is  $\gamma$ -tocopherol, which is present at a concentration 2 to 4 times higher than that in  $\alpha$ -tocopherol. A high intake of synthetic  $\alpha$ -tocopherol can lower plasma and tissue levels of  $\gamma$ -tocopherol. We believe that carefully conducted randomized studies with long follow-up periods and well-defined end points are required to address the potential clinical efficacy of the different isoforms of vitamin E. We also have to be clear on the terminology that is used when we discuss the properties and effects of the different forms of vitamin E.

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**TO THE EDITOR:** In their important meta-analysis focusing on the potentially harmful effects of vitamin E supplementation, Miller and colleagues (1) assumed that there may be a precise threshold level and that larger intakes of the vitamin would progressively increase the risk for harm. However, there may be biological heterogeneity between population groups, meaning that persons' characteristics would determine whether vitamin E supplementation causes net benefit or harm.

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, the effect of vitamin E on the risk for pneumonia was significantly modified by the age of smoking initiation ( $P < 0.001$ ) (2). Vitamin E increased pneumonia risk in those who began smoking at age 20 years or earlier (relative risk, 1.14 [95% CI, 0.98 to 1.32]), but decreased pneumonia risk in participants who began smoking at later ages (relative risk, 0.65 [CI, 0.49 to 0.86]). Furthermore, in the latter subgroup, the benefit was greater among those who smoked less or quit smoking during the trial. Thus, less exposure to cigarette smoking was associated with greater benefit of vitamin E.

In the ATBC Study, the vitamin E dosage was 50 IU/d (50 mg/d of dl- $\alpha$ -tocopheryl acetate), which is substantially less than the threshold of 150 IU/d estimated by Miller and colleagues (1). However, from the subgroup differences described in the ATBC Study, it seems probable that some population groups experience ill effects at this low dosage while other persons benefit. Assuming that there is biological heterogeneity between population groups, further studies should characterize people who benefit from or are harmed by vitamin E rather than just estimating a uniform threshold for harm and presuming it is valid for everyone.

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**TO THE EDITOR:** Miller and colleagues (1) highlighted the danger of assuming the safety of high-dose vitamin E in the absence of definitive long-term safety data. The impact of their study, however, may be mitigated by methodologic concerns.

The first issue is the restrictive inclusion criteria stipulating that a trial have at least 10 deaths, apparently because the authors “anticipated that many small trials did not collect mortality data.” This exclusion contradicts the *raison d’être* of meta-analysis, which involves the statistical pooling of multiple trials that individually have inadequate statistical power. The exclusion of at least 3 reasonably large, well-conducted trials (2–4) of high-dose vitamin E in which fewer than 10 deaths occurred and the inclusion only of trials meeting this arbitrary cutoff would spuriously increase the power of the meta-analysis. We would also be interested in the funnel plot analysis to determine whether publication bias affected the study results.

Although the authors attempted to adjust for average follow-up in their analysis, a more robust statistical treatment of the variance in follow-up periods across included trials would be to express the summary statistic of pooled death risk as the number of deaths per 10 000 person-years (as opposed to per 10 000 persons).

Heterogeneity in the study samples may not have been fully accounted for despite the use of the random-effects model and dosage differentiation. In particular, people with CVD may be a select group at distinct risk from the effects of high-dose vitamin E. Seven of the 8 high-dosage trials showing harmful effects of vitamin E involve participants with vascular risk factors or those who had established CVD. In contrast, the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson’s Disease (DATATOP) study and the Alzheimer’s Disease Cooperative Study (ADCS) used megadoses of vitamin E (2000 IU/d) in individuals with neurodegenerative disorders rather than in those with CVD but did not reveal safety concerns. A separate meta-analysis looking solely at neurodegenerative diseases (including a recent study using 5000 mg of vitamin E per day [5]) may be warranted.

Although Miller and colleagues’ study may have focused on safety, the data ultimately challenge the advocates of high-dose vitamin E to reexamine the evidence for benefit. Efficacy in controlled trials ranges from minimal to modest, in contrast to the more positive results of observational studies. It is time for clinicians to return to the drawing board and review both the safety and efficacy data for vitamin E supplementation.

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**TO THE EDITOR:** In a meta-analysis of selected randomized trials, Miller and colleagues (1) found an increase in all-cause mortality associated with high-dosage vitamin E supplementation for at least 1 year (1). Their analysis included the DATATOP study, a randomized, placebo-controlled trial of selegiline and vitamin E in 800 patients with early Parkinson disease (2). In the DATATOP trial, 399 of 800 participants were randomly assigned to receive 2000 IU of vitamin E per day, the highest dosage studied in Miller and colleagues’ meta-analysis. Median duration of vitamin E exposure during the randomized phase was 2.6 years. We have now accrued 13 years of follow-up and have documented 296 deaths compared with the 137 DATATOP deaths incorporated into Miller and colleagues’ meta-analysis (3).

A slightly but not significantly higher proportion of patients randomly assigned to vitamin E had died by 13 years after enrollment (154 of 399 in the vitamin E group [39%] vs. 142 of 401 in the placebo group [35%];  $P = 0.35$ ). However, after adjustment for age and sex in a logistic regression, there was no excess mortality in the group assigned to vitamin E (odds ratio, 0.996 [95% CI, 0.72 to 1.38];  $P = 0.98$ ).

We also constructed a Cox model to make full use of survival information, incorporating duration of blinded exposure to vitamin E as a time-dependent covariate. We did not observe increased mortality for each additional year of exposure to vitamin E (hazard ratio, 1.05 [CI, 0.95 to 1.16];  $P = 0.31$ ). Similar results were obtained when both blinded and subsequent open-label tocopherol supplementation were considered.

We found no evidence of increased mortality in DATATOP related to 2.6 years of high-dosage vitamin E exposure through 13 years of observation. The DATATOP cohort was selected for absence of serious comorbid illness and was more highly educated than the general population. These and other differences in selection may

account for the discrepancy between our findings and those of Miller and colleagues.

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**TO THE EDITOR:** Miller and colleagues (1) reported that supplemental intake of vitamin E at dosages greater than 150 IU/d progressively increases all-cause mortality. There are several problems with their analysis and interpretation of the data. The harmful effect above 150 IU/d is an artifact of the model they chose to fit. When researchers fit a quadratic-linear spline, the result must be a quadratic-linear spline regardless of whether the data behave that way. In another reasonable model, the favorable response to vitamin E is constant until a certain dose, above which the change in all-cause mortality risk difference is linear. The constant response to vitamin E persists up to a dosage of 330 IU/d, and the risk difference favors vitamin E until the dosage is 400 IU/d. The sum of weighted squared differences between observed and predicted all-cause mortality risk differences shows that this model fits the data better than does the quadratic-linear spline.

The modeling issue is further supported by the following reanalyses of the data presented in Miller and colleagues' Figure 2. When we grouped the data into several intermediate dose ranges of vitamin E and performed meta-analyses using a random-effects model, we obtained the following results. In 7 studies involving 35 595 patients taking 200 to 500 IU of vitamin E per day, the relative risk was 0.98 (95% CI, 0.88 to 1.09); in 6 studies involving 32 184 patients taking 330 to 500 IU of vitamin E per day, the relative risk was 0.99 (CI,

0.88 to 1.11); and in 4 studies involving 16 355 patients taking 400 to 500 IU of vitamin E per day, the relative risk was 1.00 (CI, 0.80 to 1.25). None of the subgroups that included studies with vitamin E dosages of 500 IU/d or below suggest any harmful effects. Thus, it doesn't seem plausible that increased risk occurs until at least the daily dose of 400 to 500 IU has been exceeded.

We also question the applicability of the data to the general population, since participants in most of the studies with higher doses included in Miller and colleagues' meta-analysis had CVD. Furthermore, we are surprised at the lack of emphasis on the benefits of reduction in all-cause mortality by doses of vitamin E below 400 IU, an effect that reached statistical significance if vitamin E alone was considered. Related to this, in a double-blind, placebo-controlled trial of vitamin E supplementation (200 IU/d for 1 year) in patients in nursing homes, we observed no statistically significant difference in all-cause mortality between placebo and vitamin E groups (14.4% vs. 12.5%). However, significantly fewer patients in the vitamin E group acquired respiratory tract infections, an important public health problem in this age group (2).

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**TO THE EDITOR:** Although we read Miller and colleagues' article (1) with interest, we question their conclusions regarding high-dose vitamin E. First, it is not clear why the authors chose hierarchical logistic regression rather than traditional meta-analytic approaches. We reanalyzed their data from the 11 high-dose trials in their Figure 2 using 2 standard methods (Wolfe inverse variance and Mantel-Haenszel). Both yielded the same point estimates as the ones the authors reported, but with nonsignificant results (relative risk, 1.04 [95% CI, 0.99 to 1.10]). Second, we are concerned that these results are heterogeneous. Both are borderline statistically heterogeneous ( $Q = 16.1$ ;  $P = 0.097$ ), and there is visual evidence of heterogeneity on our Galbraith plots. Better examination of the sources of this heterogeneity is needed.

In addition, we found a suggestion of publication bias among the 11 high-dose trials by using the Begg test ( $P = 0.073$ ) (2), which we confirmed with the trim-and-fill method (3). As the authors noted, studies showing benefit from vitamin E are unlikely to be missing from the literature. However, small studies that demonstrate no effect could well be unpublished. It is also possible that the authors did not include these small trials because they did not search EMBASE and therefore may have excluded European trials. They also excluded trials with fewer than 10 deaths (which seems arbitrary).

trary), and this, in particular, would tend to bias the results toward a finding of harm.

The authors searched for the influence of each trial and determined that “none seemed to be driving the results.” In our reanalysis, exclusion of the largest trial (the Medical Research Council/British Heart Foundation Heart Protection Study) resulted in a wider confidence interval (CI, 0.96 to 1.13). We would like to know if the results became nonsignificant when the authors excluded this or other trials.

Finally, the authors did not account for study quality as a possible explanation of the results. Study quality has been previously shown to affect the results of randomized, controlled trials (4), and accounting for study quality is recommended by the QUOROM statement (5).

In summary, we have trouble accepting Miller and colleagues' conclusions regarding high-dose vitamin E because of the statistical methods used and the lack of controlling for study quality and publication or selection bias. We contend that correction of any one of these factors could negate the marginally significant results. With these problems and with multiple other studies suggesting that vitamin E has no effect on mortality, telling our patients that vitamin E may be harmful seems premature.

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**TO THE EDITOR:** Given the results of the dose–response analysis summarized in Miller and colleagues' Figure 3 (1), the authors observed that the 95% confidence band for the risk difference does not include 0 for dosages greater than 900 IU/d. They go on (in their Table 2) to derive pooled risk differences and ratios therefrom that suggest a statistically significant relationship between dosage of vita-

min E supplementation and all-cause mortality. The authors are to be commended for listing the data they used, thereby facilitating the exploration of alternative analyses. The ability to do this is especially important here because the statistical significance of the observed risk differences is not overwhelming.

If alternative analyses are similarly appropriate for the data at hand and are generally as reasonable as those that the authors have adopted, then one might well expect that they should produce conclusions that are consistent with the authors'. This, unfortunately, is not the case for the dose–response analysis, as the following steps illustrate.

First, instead of focusing on risk difference, I based the dose–response analysis on relative risk, measured by the logarithm of the odds ratio for all-cause mortality. For example,  $\log[(100 \times 258)/(106 \times 261)] = -0.0698$  for The Geriatric/MINéreaux, VITamines, et AntiOXydants Network (MIN.VIT.AOX) in Miller and colleagues' Figure 2. This calculation rests on ample precedent and solid rationale (2).

Second, instead of the authors' spline, I employed a nonparametric, locally quadratic, weighted regression (3) to model the relationship between relative risk and the logarithm of dosage. In these circumstances, the 95% confidence band for this relationship straddles the value 0 (which corresponds to no difference in relative risk) throughout the whole range of dosages represented in the data. This indicates that from this viewpoint, and despite a suggestive trend, there is as yet insufficient evidence to establish incontrovertibly a statistically significant difference in relative risk between the different groups that received vitamin E supplementation in different dosages. Details of the aforementioned computations, performed by using the data in the authors' Figure 2 (and also their Figure 4, with the same conclusion) and the “locfit” package for R (4), as well as the alternative to Figure 3 that summarizes the local regression analysis, will be produced upon request since this letter cannot accommodate them.

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**Disclaimer:** The analyses and the opinions described in this letter are solely those of the author, were developed by him on his personal time, are unrelated to the work he performs for his employer, and do not purport to represent any views or positions held by his employer (General Electric).

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**TO THE EDITOR:** We read with interest the statistically questionable and selective meta-analysis by Miller and colleagues (1). Because of their arbitrary exclusion criteria, they omitted 2 studies that clearly showed the benefit of combined RRR- $\alpha$ -tocopherol and vitamin C supplementation on the primary end point: the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study, which involved 440 hypercholesterolemic patients followed up for 6 years (2), and the Transplant-Associated Arteriosclerosis Study (3).

Also, of the 11 studies that Miller and colleagues suggested show harm from high-dose vitamin E supplementation, 5 used vitamin E along with other antioxidants, including  $\beta$ -carotene, which has previously been shown to be harmful (2). In Miller and colleagues' Figure 2, there does not appear to be a dose response between high-dose vitamin E and mortality; in fact, there was a trend toward benefit in ADCS (2000 IU of vitamin E per day). Furthermore, in 3 of these 11 studies that used vitamin E alone (Cambridge Heart Antioxidant Study [CHAOS], Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease [SPACE] Study, and ADCS), there was a significant benefit on the primary end point without a significant increase in mortality (2, 3).

Since Miller and colleagues do not show the data for the pooled analyses of high-dose vitamin E studies after exclusion of the Women's Angiographic Vitamin and Estrogen (WAVE) study, it is hard to determine whether the questionable statistical significance could be ascribed to this chance finding, as suggested by the WAVE investigators (3). Also, it should be pointed out that only 64% of the patients taking antioxidants in the WAVE trial had exit angiography. This point raises the validity of the meta-analysis with respect to the heterogeneity of the different studies, which had differences in populations, sample sizes, dose and duration of vitamin E, antioxidant cocktails, form of vitamin E (RRR- $\alpha$ -tocopherol vs. all-rac- $\alpha$ -tocopherol), omission of use of biomarkers of oxidative stress, and inflammation. Furthermore, it should be pointed out that RRR- $\alpha$ -tocopherol at dosages greater than 400 IU/d in human volunteers clearly demonstrates antioxidant activity (decrease in low-density lipoprotein oxidizability and  $F_2$ -isoprostanes, a measure of in vivo lipid peroxidation) and displays anti-inflammatory activity, as evidenced by a decrease in proinflammatory cytokines and hs-C-reactive protein levels (an accepted risk marker of cardiovascular disease) (4).

Thus, we believe that while the benefits of high-dose RRR- $\alpha$ -tocopherol remain to be proven, it should be pointed out that the American Heart Association, in a recent advisory (5), reviewed antioxidant vitamin supplements and CVD in detail and did not conclude that  $\alpha$ -tocopherol increased mortality.

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**Potential Financial Conflicts of Interest:** None disclosed.

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**TO THE EDITOR:** I read with great interest the very useful paper by Miller and colleagues (1), as well as the rapid responses. I checked the type of vitamin E used in the studies reviewed by referencing the fine review by Jialal and Devaraj (2) and by checking the information available on MEDLINE. The use of synthetic vitamin E was not a confounder, except possibly to an extremely small extent.

Use of  $\beta$ -carotene was.

Adjustment for the concurrent use of  $\beta$ -carotene and vitamin E in people who smoked eliminates the excess mortality entirely, even with additional adjustment for the positive effect of fish oil in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI).

Analysis of the relationship between mortality and the ratio of vitamin C to vitamin E given in the studies shows a strong significant trend toward less mortality, with no effect or a small detrimental effect possible at a ratio of less than unity. This analysis culminates in the significant 47% reduction of mortality seen at the dosages of 440 IU/d for vitamin E and 1 g/d for vitamin C in the Polyp Prevention Study. This relationship is consistent with in vitro and epidemiologic literature and the very corroborative HDL Atherosclerosis Treatment Study (HATS), which showed a near-complete stop to progression of plaque in coronary arteries with supplementation of vitamin C and vitamin E at a ratio of more than 2 (3).

By the way, the mortality values listed for CHAOS in Miller and colleagues' Figure 2 seem to be incorrect. The original CHAOS reported 36 and 27 deaths for the vitamin E and placebo groups, respectively (4).

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**Potential Financial Conflicts of Interest:** None disclosed.

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**TO THE EDITOR:** Before the public embraces Miller and colleagues' conclusions (1), several problems with their study should be addressed. First, factorial design data should not have been presented in Figure 3. The plot is much less convincing when data from Figure 4 are used. The SPACE study (2) is incorrectly listed as nonfactorial in Miller and colleagues' Table 1; 42% to 57% of the vitamin E and

placebo groups were prescribed varying doses of vitamins (including 100 to 500 mg/d of ascorbic acid).

Second, the vitamin E group was overweighted for diseases and mortality risk factors in the high-dose Vitamin E, Cataracts, and Age-Related Maculopathy (VECAT) study (3) and CHAOS (4). In the VECAT study, patients in the vitamin E group were more likely to have diagnoses of ischemic heart disease (11.3% vs. 9.0%), diabetes (4.9% vs. 3.5%), and hypertension (38% vs. 33%) compared with patients in the placebo group.

Current cigarette use and high body mass index were also overweighted in the vitamin E group compared with placebo (2.4% vs. 1.7% and 42% vs. 37%, respectively). The authors of CHAOS stated that the distribution of “five conventional coronary risk factors” favored lower mortality in the placebo group (4). As expected, these studies showed higher mortality in the vitamin E group.

Third, a plot of mortality versus supplemental vitamin C dosage for 9 studies (including the Linxian B study [5] at 180 mg/d) is remarkably similar to that in Miller and colleagues’ Figure 3. Similarly, there is no chance that the menopausal status is the same in the low- and high-dose vitamin E studies; the high-dose studies involved a disproportionately higher fraction of postmenopausal women. When all of these factors are considered, this meta-analysis may have uncovered mobilization of iron by high-dose vitamin C and the resultant iron toxicity. These are only 2 of many factors that could act synergistically.

If data from pooled results (uncorrected factorial design data), misclassified results (the SPACE study), and biased results (the VECAT study and CHAOS) are removed, and only data from Figure 4 are used, there is no increased mortality risk for high-dose vitamin E.

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**IN RESPONSE:** Since the publication of our vitamin E dose–response meta-analysis, we have received hundreds of e-mails, letters, and phone calls as well as more than 40 Letters to the Editor submitted

electronically. *Annals* has asked us to prepare a written response to 11 selected letters.

Blatt and Pryor and Krishnan and associates hypothesize that natural vitamin E supplements have greater benefit than synthetic vitamin E supplements, even though no trial has directly compared them on mortality outcomes. In response, we have performed a subgroup analysis comparing the 4 trials using natural supplements, all high-dosage (400 IU/d), with high-dosage trials using the synthetic form. The relative risks for all-cause mortality in the 4 trials that provided natural vitamin E were 1.00 (95% CI, 0.89 to 1.12) in the Heart Outcomes Prevention Evaluation (HOPE) (1), 1.83 (CI, 0.88 to 3.78) in the VECAT study (2), 1.22 (CI, 0.86 to 1.73) in CHAOS (3, 4), and 1.09 (CI, 0.72 to 1.66) in the SPACE study (5). The pooled relative risk comparing vitamin E with control was 1.04 (CI, 1.00 to 1.07) in the high-dosage trials of synthetic vitamin E and 1.05 (CI, 0.97 to 1.13) in the high-dosage trials of natural vitamin E. There was no evidence for a differential effect of synthetic versus natural sources of vitamin E ( $P > 0.2$  for heterogeneity).

Hemilä, Krishnan and associates, Lim and coworkers, Marras and colleagues, and Meydani and associates were concerned about the generalizability of our findings to healthy populations, since many of the high-dosage vitamin E trials enrolled participants with chronic diseases. In general, trials enroll high-risk individuals to increase study power. When interventions are shown to be effective in high-risk populations, subsequent trials are conducted in low-risk populations, and the same relative effects are often observed (as in statin trials in primary prevention). As for vitamin E, the findings of the Women’s Health Study, a large primary prevention trial presented after the publication of our meta-analysis (6), suggest that the mortality increase that we observed is likely to apply to healthier groups. In this study, 39 876 healthy women were randomly assigned to receive 600 IU of vitamin E on alternate days or placebo for 10 years. At the end of follow-up, there were 636 deaths in the vitamin E group and 615 in the placebo group. This increase in mortality (relative risk, 1.04 [CI, 0.93 to 1.16]), although nonsignificant in this individual trial, is consistent with the findings of our meta-analysis.

Meydani and associates argue that we should have used a model with a constant effect of vitamin E up to a certain change-point dose and a linear effect above it. This model is problematic for a variety of reasons. First, it forces the effect of vitamin E to be constant over a wide range of low doses, an implausible assumption from a biological standpoint. Second, it forces a sharp change in effect at the chosen change-point dose, which is implausible in population studies even if there were sharp change-point effects in individual patients (7). Finally, the conclusions from this model largely depend on the chosen change-point, but this choice is difficult from a statistical perspective, and the sequential evaluation of change-points with selection of the best-fitting model underestimates the uncertainty in the final model (8). Our quadratic linear-spline model overcomes these difficulties and, contrary to the implications of Meydani and associates, it does not force a harmful effect above 150 IU of vitamin E per day. Meydani and associates argue that higher risk for death is not evident until the dosage exceeds 400 IU/d, instead of 150 IU/d as we describe. We indicated in our paper that establishing the precise dose of vitamin E at which the relative risk for death increases above 1 is very difficult. However, as also shown by the findings of the large Wom-

en's Health Study, it is highly likely that this threshold is below 400 IU/d.

DeZee and coworkers question our use of a hierarchical logistic regression model as opposed to traditional meta-regression. We believe that our model is more appropriate because it produces the same results that would be obtained if we had individual patient data on randomized treatment assignment, trial dose, and survival status. In fact, the results of their reanalysis of our data using traditional meta-analytic techniques are very similar to ours, and it is hard to believe that different conclusions can be obtained from their analysis and from ours. As argued in our paper, the dose of vitamin E is likely to be the explanation for the heterogeneity of the study results identified by DeZee and coworkers in their letter.

Possolo reanalyzed our data using a nonparametric, locally quadratic weighted regression model and also found a positive but statistically nonsignificant association between vitamin E dose and increased mortality. It is difficult to evaluate this analysis on the basis of the information provided in the letter, but we note that weighted regression routines available in general statistical packages are inadequate for meta-analysis, and specialized meta-regression programs are needed to obtain correct standard errors and confidence intervals (9).

DeZee and coworkers, Jialal and Devaraj, and Lim and coworkers criticize our decision to exclude trials with fewer than 10 deaths. We decided a priori to exclude studies with less than 1 year of follow-up or fewer than 10 deaths because we suspected that a variety of small or short-term trials designed primarily to evaluate the effect of vitamin E on physiologic intermediate outcomes would not collect or report mortality data systematically. On the other hand, it is hard to imagine trials designed to evaluate the effect of vitamin E supplements on clinical outcomes or mortality, the objective of our meta-analysis, with fewer than 10 deaths. In addition, there is no a priori reason to believe that trials with fewer than 10 deaths would quantitatively differ from larger trials or that excluding such trials would result in biased estimates of effect. Furthermore, when we compiled data from 11 trials with fewer than 10 deaths, the number of deaths among participants assigned to vitamin E exceeded the number of deaths among participants assigned to placebo (22 vs. 18 deaths, respectively; reference list available upon request).

Baggott suggests that some cardiovascular disease risk factors in some of the trials were higher among participants assigned to vitamin E, which would create a bias against vitamin E. However, it is unlikely that randomized experiments involving more than 135 000 participants would have imbalances in risk that systematically favor one randomization group.

Jialal and Devaraj mention 2 trials of vitamin E supplementation showing a beneficial effect on surrogate markers of atherosclerosis. The Transplant-Associated Atherosclerosis Study, a small trial ( $n = 40$ ) that reported no deaths, showed ultrasonographic evidence for benefit among heart transplant recipients (10). The ASAP study, which used a  $2 \times 2$  factorial design and examined the use of vitamin E (272 IU/d) and vitamin C (1000 mg/d) in hypercholesterolemic smokers, reported that vitamin E supplementation reduced progression of carotid artery disease (11, 12). However, the mortality data from the ASAP trial were consistent with our findings, since there were 4 deaths in the vitamin E groups and 2 deaths in the nonvitamin E groups after 3 years of follow-up. At year 3, all participants in the vitamin groups were given an open-label combination of vitamins C and E, while the placebo group continued without supple-

mentation. At 6 years, the relative risk for death was higher in those assigned to the combination of vitamins compared with those assigned to placebo (19 deaths in 390 participants taking supplements vs. 3 deaths in 130 participants taking no supplements). On a final note, other trials have shown greater progression of atherosclerosis among those assigned to vitamin E (13–15).

Carter suggests that HATS, which we excluded because it had only 2 deaths, demonstrated that antioxidant vitamin supplementation (including 800 IU of vitamin E per day) provided angiographic evidence of slowed progression of coronary artery disease (16). On the contrary, HATS showed that antioxidant supplementation alone did not slow the progression of coronary plaque and that, surprisingly, antioxidants diminished the protective effect of simvastatin–niacin at slowing the progression of coronary disease.

Several authors have also expressed concerns over our choice of total mortality as an end point in view of the beneficial effects of vitamin E supplementation on physiologic variables related to oxidative stress. Although these surrogate markers can provide mechanistic insights, their clinical relevance is uncertain. In contrast, all-cause mortality, the outcome used in our meta-analysis, has unambiguous clinical relevance.

In conclusion, 19 randomized trials that together enrolled more than 135 000 participants have failed to document a survival benefit with vitamin E supplementation. In contrast, we have provided evidence that high-dosage vitamin E supplementation may increase total mortality. While future trials will refine the estimates of the effect of vitamin E supplementation and the dose at which the relative risk for death exceeds 1, we stand by our conclusions that use of high-dosage vitamin E supplementation should be avoided.

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## Report of Specific Cardiovascular Outcomes of the ADVANTAGE Trial

**TO THE EDITOR:** In light of the attention that the article on the ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) study (1) has received, we thought it would be useful to provide additional information clarifying the specific vascular events that contributed to the aggregate end points reported and the process by which individual cases were assigned to those end points.

Lisse and colleagues (1) reported cardiovascular events in the ADVANTAGE study using 2 aggregate end points: confirmed thrombotic cardiovascular serious adverse experiences and the Antiplatelet Trialists' Collaboration (APTC) combined end point. The former included reports of myocardial infarction, unstable angina, sudden cardiac death, ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism that were confirmed by adjudication according to a prespecified program-wide standard operating procedure. This procedure was initiated in 1998 before the start of the ADVANTAGE

**Table 1. Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in the ADVANTAGE Trial\***

Thrombotic Serious Cardiovascular Term	Rofecoxib Group (n = 2785), n (%)	Naproxen Group (n = 2772), n (%)
Patients with adverse event	9 (0.32)	12 (0.43)
Cardiac events	8 (0.29)	3 (0.11)
Acute myocardial infarction	5 (0.18)	1 (0.04)
Sudden cardiac death†	2 (0.07)	0 (0.00)
Unstable angina pectoris	1 (0.04)	2 (0.07)
Cerebrovascular events	1 (0.04)	7 (0.25)
Ischemic cerebrovascular stroke	0 (0.00)	6 (0.22)
Transient ischemic attack	1 (0.04)	1 (0.04)
Peripheral venous events	0 (0.00)	2 (0.07)
Peripheral venous thrombosis	0 (0.00)	2 (0.07)

\* Patients may be counted in more than one row but are counted only once within a row. ADVANTAGE = Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness.

† Sudden cardiac deaths were reported together with fatal myocardial infarctions in the study by Konstam and associates (4).

trial (2). The APTC combined end point included cardiovascular and hemorrhagic deaths and deaths of unknown cause, nonfatal myocardial ischemia, and nonfatal stroke (3) and was the prespecified end point in the pooled analyses of cardiovascular events with rofecoxib (4, 5).

All investigator reports of potential cardiac, cerebrovascular, or peripheral arterial or venous thrombotic events that used one of a set of prespecified adverse experience terms were prospectively adjudicated by external blinded panels of medical specialists for inclusion in the confirmed thrombotic and APTC end points. In addition, all deaths that did not meet criteria for this external adjudication were prospectively reviewed by a Merck cardiologist blinded to treatment assignment to determine whether the death met the broader APTC end point criteria. Tables 1 and 2 show the confirmed thrombotic cardiovascular serious adverse experiences and APTC combined end point events, respectively, from the ADVANTAGE trial as reported by Lisse and colleagues (1).

**Table 2. Summary of the Antiplatelet Trialists' Collaboration Combined End Point in the ADVANTAGE Trial\***

APTC Term	Rofecoxib Group (n = 2785), n (%)	Naproxen Group (n = 2772), n (%)
Patients with adverse event	10 (0.36)	7 (0.25)
Cardiac events	7 (0.25)	1 (0.04)
Acute myocardial infarction	5 (0.18)	1 (0.04)
Sudden cardiac death†	2 (0.07)	0 (0.00)
Cerebrovascular events	0 (0.00)	6 (0.22)
Ischemic cerebrovascular stroke	0 (0.00)	6 (0.22)
Other events	3 (0.11)	0 (0.00)
Arterial rupture	1 (0.04)	0 (0.00)
Hemorrhagic stroke	1 (0.04)	0 (0.00)
Unknown cause of death‡	1 (0.04)	0 (0.00)

\* Patients may be counted in more than one row but are counted only once within a row. ADVANTAGE = Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness; APTC = Antiplatelet Trialists' Collaboration.

† Sudden cardiac deaths were reported together with fatal myocardial infarctions in the trial by Konstam and associates (4).

‡ The investigator-reported cause of death was hypertensive heart disease, based on autopsy findings. The U.S. Food and Drug Administration retrospectively reclassified the cause of death as sudden cardiac death.

Recent media reports have focused on the U.S. Food and Drug Administration's (FDA's) medical review of unblinded data from this study, in which the FDA reviewer commented that the death of 1 patient in the rofecoxib group, which the investigator had listed as from "hypertensive heart disease" on the basis of autopsy findings, was, in the FDA reviewer's opinion, a case of sudden death. Although the term retrospectively proposed by the FDA reviewer would have met criteria as a potential thrombotic event eligible for adjudication if used by the investigator, the term *hypertensive heart disease* did not trigger adjudication in the existing standard operating procedure. Therefore, this case was not prospectively adjudicated and is not included as a confirmed thrombotic event in Table 1. However, on the basis of internal blinded review, it was determined prospectively that this patient's death met the criteria of the APTC combined end point, and as shown in Table 2, this patient's death *was* included in the combined APTC end point in the article by Lisse and colleagues (1). It was also included in the pooled analyses of cardiovascular events with rofecoxib published by Konstam and associates (4) and Weir and coworkers (5).

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**Potential Financial Conflicts of Interest:** Dr. Braunstein and Mr. Polis are employed by Merck & Co., Inc. and own shares of Merck & Co., Inc., stock.

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## CLINICAL OBSERVATION

### Myocarditis from the Chinese Sumac Tree

**TO THE EDITOR:** *Background:* Myocarditis is commonly assumed to be infectious in origin in many patients who present to the emergency department with chest pain, depressed ejection fraction, and a history compatible with a viral syndrome. Certain naturally occurring products, such as quassinoids in tree sap, may also cause myocarditis.

*Objective:* To describe a case of myocarditis likely due to exposure to sap from the Chinese sumac tree (*Ailanthus altissima*).

*Case Report:* A previously robust, healthy 24-year-old man presented to the emergency department reporting 3 days of fever and chills associated with epigastric pain, substernal chest pressure that radiated to both arms, and shortness of breath. Up to the day of admission, he had been working as a tree surgeon on a team responsible for clearing heavy areas of Chinese sumac, also known as tree-of-heaven. Physical examination showed a blood pressure of 93/59 mm Hg, a heart rate of 60 beats/min, a temperature of 38.5 °C, and no other significant findings. Laboratory tests revealed a troponin T level of 1.8 µg/L and a creatine kinase level of 523 U/L, which had 11% MB; the remainder of the laboratory tests, including blood cultures, yielded normal results. An electrocardiogram showed diffuse 1-mm ST-segment elevation. Emergency department evaluation with computed tomography ruled out aortic dissection and pulmonary embolism, and the patient was treated with morphine and non-steroidal anti-inflammatory drugs for presumed pericarditis or myocarditis. Initial echocardiography showed an ejection fraction of 0.42, and results of subsequent coronary angiography were normal.

The patient's pain intensified substantially over the next 48 hours, but then rapidly abated. He was taking only low-dose ibuprofen when discharged, and his discharge echocardiogram showed an ejection fraction of 0.5. On a return clinic visit, the patient reported that all of his coworkers had also been ill at the time of his hospitalization, many with gastrointestinal symptoms and some with chest pain. He expressed concern that they may not have exercised proper caution while clearing Chinese sumac, since, he said, "the sap on that tree will make you sick." One year later, the patient's cardiac function remains normal, he is taking no medications, and he has resumed his normal active lifestyle.

*Discussion:* Review of the literature shows that the sap of the Chinese sumac may contain proteins, called quassinoids, that can explain our patient's cardiac findings, the illness of his coworkers, and the perceived need among arborists for caution while handling the Chinese sumac (1). The tree-of-heaven, as it is commonly known, is a tree of the sumac family that is native to China. Initially brought to the United States because of its ease of rapid growth and its medicinal implications, this tree has become very common in all areas of the country, particularly the northeastern states. The bark of the tree-of-heaven has been used as an herbal remedy for dysentery and, more recently, for malaria (2). Among its many implications derived from folk medicine, the *Ailanthus altissima* is thought to be a cardiac depressant and has been used to slow heart rate. Researchers have proposed that quassinoids may have a role in treating Epstein-Barr virus infection (3), HIV infection (4), and neoplasms, possibly by depolarization of mitochondrial membranes (5).

*Conclusion:* Because Chinese sumacs spread rapidly and continuously, they often need to be eliminated, posing a health concern for the professionals who remove them. Our patient was exposed to sumac sap through ruptured blisters due to rope burn, which resulted in loss of the protective epithelium. Recent literature indicates that this toxin may have mitochondrial mechanisms of action consistent with the pathophysiologic characteristics of transient myocarditis. This case describes an unusual cause of myocarditis in a previously healthy person and illustrates the importance of taking a thorough occupational history from patients who work in the tree removal industry.

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#### CORRECTION

##### Correction: A New Concept of Unopposed $\beta$ -Adrenergic Overstimulation in a Patient with Pheochromocytoma

A recent letter on a new concept of unopposed  $\beta$ -adrenergic overstimulation (1) contained errors. In the Background section, the first sentence should have read, "The concept of unopposed  $\alpha$ -adrenergic overstimulation during selective  $\beta$ -adrenergic blockade in patients with pheochromocytoma is well recognized." In the Discussion section, the second and third sentences should have read as follows: "In cases of catecholamine excess, selective  $\alpha$ -adrenergic blockade will shift all available amounts of catecholamines to the  $\beta$ -adrenergic receptor compartment, enabling selective  $\beta$ -adrenergic overstimulation concurrently with  $\alpha$ -adrenergic blockade. In contrast to unopposed  $\alpha$ -adrenergic stimulation (as in the case of selective  $\beta$ -blockade), where the main clinical picture is one of severe peripheral vasoconstriction, unopposed  $\beta$ -adrenergic blockade will show opposite features."

#### Reference

1. Kantorovich V, Pacak K. A new concept of unopposed  $\beta$ -adrenergic overstimulation in a patient with pheochromocytoma. *Ann Intern Med*. 2005;143:1026-8.