Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

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Background: Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non–statistically significant increases in total mortality.

Purpose: To perform a meta-analysis of the dose–response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials.

Patients: 135 967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d).

Data Sources: PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Clinical Trials Database and review of citations of published reviews and meta-analyses. No language restrictions were applied.

Data Extraction: 3 investigators independently abstracted study reports. The investigators of the original publications were contacted if required information was not available.

Data Synthesis: 9 of 11 trials testing high-dosage vitamin E (≥400 IU/d) showed increased risk (risk difference > 0) for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10 000 persons (95% CI, 3 to 74 per 10 000 persons; $P = 0.035$). For low-dosage vitamin E trials, the risk difference was −16 per 10 000 persons (CI, −41 to 10 per 10 000 persons; $P > 0.2$). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.

Limitations: High-dosage (≥400 IU/d) trials were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult.

Conclusion: High-dosage (≥400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

Ⓞn the basis of the premise that vitamin E reduces oxidative stress, many clinical trials have tested vitamin E supplementation as a therapy to prevent various chronic diseases. The results of these trials have been largely disappointing (1–3). Three recent meta-analyses, which did not consider dose–response relationships, reported no overall effect of vitamin E on survival (4–6). However, several trials of high-dosage vitamin E supplementation have reported non–statistically significant increases in total mortality. Because individual trials typically tested only 1 dosage of vitamin E and large-scale trials with several dosages are not feasible, we performed this dose–response meta-analysis to evaluate a potential dose-dependent effect of vitamin E supplementation. We focused on all-cause mortality because this end point has unambiguous clinical relevance and, in contrast to cause-specific events such as cardiovascular morbidity or death, is resistant to miscoding.

METHODS

Search Strategy and Inclusion Criteria

We searched for all reports of clinical trials (with no language restrictions) that tested the effect of vitamin E supplementation in humans. We performed a MEDLINE search by using the Medical Subject Heading (MeSH) terms *vitamin E*, *antioxidant vitamins*, *alpha tocopherol*, *tocopherol*, and *clinical trials*. The search period was 1966 through August 2004. We complemented the MEDLINE search by searching the Cochrane database of randomized, controlled trials; reviewing the reference lists from original research, review articles, and previous meta-analyses; and reviewing the files of the investigators.

Our prespecified inclusion criteria were 1) random allocation of participants, 2) use of vitamin E supplementation alone or combined with other vitamins or minerals, 3) presence of a control or placebo group, 4) study sample limited to men or nonpregnant women, 5) duration of vitamin E supplementation and follow-up longer than 1 year, and 6) occurrence of at least 10 deaths in the trial. The restriction to include studies with follow-up longer than 1 year and at least 10 deaths was determined a priori because we anticipated that many small trials did not collect mortality data. We contacted the investigators of the original studies if information required to establish inclu-

Context

Does vitamin E supplementation increase mortality in adults?

Contribution

This meta-analysis of 19 randomized, controlled trials involving more than 135 000 participants found that high-dosage vitamin E supplementation (≥400 IU/d for at least 1 year) increased all-cause mortality. Benefits or harms of lower-dosage supplementation were unclear.

Cautions

Trials that tested high dosages involved adults with chronic diseases, and these findings may not be generalizable to healthy adults. Some trials evaluated multivitamin combinations. The findings don't clearly establish that the lowest dosage of supplementation is associated with increased mortality risk.

Implications

Avoid high-dosage vitamin E supplementation.

–The Editors

sion criteria or information on trial design or mortality results was not available in the published reports. Three investigators independently abstracted the articles. They resolved disagreements by consensus. We converted the dosage of vitamin E in each trial to international units per day (IU/d) (7). Only 1 trial (8) used 2 vitamin E dosage groups (400 and 800 IU/d); however, all-cause mortality data were available for both vitamin E groups combined (9), not for the separate dosages. For this trial, we assigned all deaths in the 2 vitamin E groups to the average dosage of 600 IU/d.

Statistical Analysis

We conducted all analyses according to the intention-to-treat principle. For trials with a factorial design, we based main results on 2-way analyses, that is, all trial participants receiving vitamin E were compared with all participants not receiving it. We used a 2-level hierarchical logistic regression model (10, 11) to evaluate the association between vitamin E supplementation and all-cause mortality. In the first within-study level, we specified a logistic model for the probability of death as a function of randomized assignment to vitamin E treatment in each trial. In the second between-study level, we first introduced an indicator variable for high-dosage vitamin E trials (≥400 IU/d) to evaluate the differences in effect of high- and low-dosage vitamin E supplementation. For dose–response analyses, we replaced the above indicator variable with a quadratic-linear spline model (12) for log-dose of vitamin E. The quadratic-linear spline assumed a quadratic trend below the median vitamin E dosage across studies (400 IU/d) and a linear trend more than this dosage. We selected the lower quadratic term to allow for nonlinear

responses, while ensuring a null effect for 0 dose level. We restricted the upper term to be linear to avoid implausible shapes at high dosages of vitamin E. Thus, this quadratic-linear spline model is more flexible, less influenced by extreme values, and more plausible than the usual linear or quadratic polynomial models (12–14).

We performed several sensitivity analyses to evaluate the robustness of the results. First, we replicated the analyses assuming different knot values (100, 200, 300, 400, or 500 IU of vitamin E per day) for the quadratic-linear, dose–response model. The results were virtually insensitive to the selected knot for the quadratic-linear model, and the shape of the dose–response curve remained essentially unchanged (not shown). Then, we repeated the analyses on the basis of 4-way analysis of factorial trials. In this analysis, we restricted data from factorial trials to participants who were not exposed to the second factorial intervention. In addition, we included other study-specific explanatory variables as second-level covariates in the categorical and dose–response hierarchical models. Because of the limited number of trials, we separately evaluated the effect of adding the following variables: sex distribution, mean age, use of other vitamins or minerals combined with vitamin E, and average duration of follow-up. Finally, we evaluated the influence of each trial on the results by removing each individual study from the analysis.

In all analyses, we estimated and inferred vitamin E effects by using population-average models with robust standard errors (11, 15). Population-average models esti-

Figure 1. **Flow diagram of the trial selection process.**
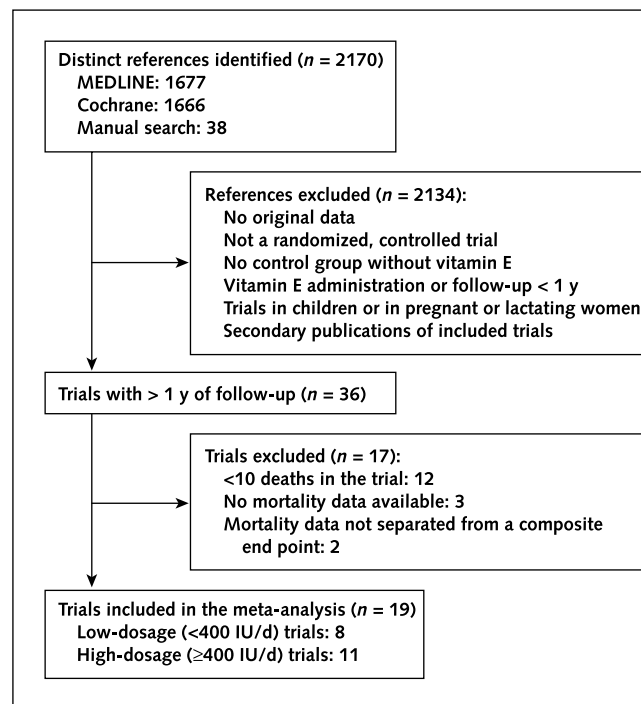
mate the effects at different vitamin E dosages averaged across all trials, whereas robust standard errors are relatively insensitive to model misspecification. We transformed the logistic model results into risk differences and risk ratios of the effect of vitamin E supplementation compared with control for easier clinical interpretability. We obtained CIs for risk differences and risk ratios by using the delta method. We performed analyses by using S-PLUS 2000 (Mathsoft, Inc., Seattle, Washington) (16) and HLM 5 (Scientific Software International, Lincolnwood, Illinois) (17).

Role of the Funding Sources

The funding sources had no role in the collection, analysis, and interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Study Description

Figure 1 summarizes the trial selection process. We identified 36 randomized, controlled trials with follow-up longer than 1 year. We excluded 12 trials with fewer than 10 deaths (18–29), 3 trials with unavailable mortality data (30–32), and 2 trials in which mortality data were not separated from a composite end point (33, 34). Nineteen trials (8, 35–53) met our inclusion criteria (**Table 1**). The selected trials were reported between 1993 and 2004, and their sample sizes varied between 196 and 29 584 participants. The total number of participants was 135 967, with 12 504 all-cause deaths. The reported mean age ranged from 47 to 84 years. Seventeen trials included men and women, 1 trial included only men, and 1 trial included only women. Most trials targeted populations at high risk for a chronic disease, most often coronary heart disease. Nine of 19 trials used vitamin E alone, while the other 10 trials combined vitamin E with other vitamins or minerals. All but 3 trials (42, 43, 51) were placebo-controlled and double-blind. Average follow-up ranged from 1.4 to 8.2 years. Vitamin E dosage varied between 16.5 and 2000 IU/d, with a median dosage of 400 IU/d. High-dosage (≥400 IU/d) trials, however, were smaller on average, and only 40 950 patients (30.1% of all randomly assigned patients) participated in high-dosage trials.

Combined Effect of Vitamin E on All-Cause Mortality

The average death risk across trials in the control groups was 1022 per 10 000 persons. Overall, vitamin E supplementation did not affect all-cause mortality. The pooled risk difference comparing vitamin E with control was 10 per 10 000 persons (95% CI, −18 to 38 per 10 000 persons) and the risk ratio was 1.01 (CI, 0.98 to 1.04; $P > 0.2$) (**Figure 2**). However, there was significant heterogeneity of study results ($P = 0.020$) that was explained by differences in results between low-dosage (<400 IU/d) and high-dosage (≥400 IU/d) vitamin E trials ($P = 0.18$ for residual heterogeneity). In 8 trials testing

low-dosage vitamin E supplementation, the pooled risk difference comparing vitamin E with control was −16 per 10 000 persons (CI, −41 to 10 per 10 000 persons) and the risk ratio was 0.98 (CI, 0.96 to 1.01; $P > 0.2$). In 11 trials testing high-dosage vitamin E, the pooled risk difference was 39 per 10 000 persons (CI, 3 to 74 per 10 000 persons) and the risk ratio was 1.04 (CI, 1.01 to 1.07; $P = 0.035$) (**Figure 2**).

In dose–response analysis, all-cause mortality progressively increased as vitamin E dosage increased by more than 150 IU/d, and the pointwise 95% CIs for the risk difference did not include 0 for dosages greater than 900 IU/d (**Figure 3**). **Table 2** displays risk differences estimated from the model at different vitamin E dosage levels. For dosages less than 150 IU/d, all-cause mortality slightly but nonsignificantly decreased. Both the linear and the quadratic components of the dose–response model were statistically significant ($P = 0.027$ and 0.037, respectively), indicating that this quadratic-linear model had increased explanatory ability compared with a simple linear model. In the dose–response analyses, no residual heterogeneity in vitamin E effects was observed after consideration of the different dosages ($P = 0.15$).

Sensitivity Analyses

In 4-way analysis, the overall pooled risk difference between vitamin E and control was 8 per 10 000 persons (CI, −23 to 39 per 10 000 persons; $P > 0.2$). As in 2-way analyses, there was significant heterogeneity ($P = 0.039$) that was explained after disaggregation of low- and high-dosage vitamin E trials ($P > 0.2$ for residual heterogeneity). The pooled risk difference for low-dosage vitamin E trials was −33 per 10 000 persons (CI, −60 to −5 per 10 000 persons; $P = 0.021$), and the pooled risk difference for high-dosage vitamin E trials was 34 per 10 000 persons (CI, 5 to 63 per 10 000 persons; $P = 0.022$) (**Figure 4**). The dose–response relationship for 4-way analyses was very similar to that for 2-way analyses (data not shown), with significant linear and quadratic components ($P = 0.027$ and 0.030, respectively) and no residual heterogeneity ($P > 0.2$).

The effect of vitamin E supplementation did not change appreciably after adjustment for differences in sex distribution, mean age, or average follow-up across trials (**Table 3**). However, when we controlled for the concomitant use of other vitamins or minerals, the reduction in all-cause mortality for low-dosage vitamin E trials was slightly attenuated (pooled risk difference, −6 per 10 000 persons [CI, −38 to 26 per 10 000 persons]) and the increase in risk of high-dosage vitamin E trials was more marked (pooled risk difference, 63 per 10 000 persons [CI, 6 to 119 per 10 000 persons]). Similar increases in all-cause mortality at high vitamin E dosages were observed in dose–response analyses after adjustment for use of other vitamins or minerals (**Table 2**).

The influence of each trial was approximately propor-

Table 1. **Clinical Trials of Vitamin E Supplementation and Risk for All-Cause Mortality, Ordered by Dosage of Vitamin E***

Study, Year (Reference)	Country	Population	Men, %	Mean Age, y	Vitamin E Dosage, IU/d
MIN.VIT.AOX, 1999 (35)	France	Institutionalized elderly	26	84	16.5
Linxian Study A, 1993 (36)	China	General population	45	Range, 40–69	33
SU.VI.MAX, 2004 (37)	France	Healthy adults	40	48	33
ATBC, 1994 (38, 39)	Finland	Smokers	100	57	50
Linxian Study B, 1993 (40)	China	Esophageal dysplasia	44	54	60
Linqu Study, 2001 (41)	China	General population	51	47	200
GISSI-Prevenzione, 1999 (42)	Italy	Recent myocardial infarction	85	59	330
PPP, 2001 (43)	Italy	At least 1 CVD risk factor	42	64	330
HOPE, 2000 (44)	19 countries	High risk for CVD events	73	66	400
AREDS, 2001 (45)	United States	Well-nourished older adults	44	68	400
PPS, 1994 (46)	United States	Recent history of large-bowel adenoma	78	61	440
VECAT, 2004 (47)	Australia	Healthy older adults	44	66	500
CHAOS, 1996 (8, 9)	United Kingdom	Angiographic evidence of CAD	84	62	400 or 800
REACT, 2002 (48)	United States, United Kingdom	Early age-related cataracts	41	66	660
MRC/BHF HPS, 2002 (49)	United Kingdom	High risk for CVD events	75	Range, 40–80	660
SPACE, 2000 (50)	Israel	Dialysis patients with CVD	69	65	800
WAVE, 2002 (51)	United States, Canada	Postmenopausal women with CAD	0	65	800
ADCS, 1997 (52)	United States	Alzheimer disease	35	73	2000
DATATOP, 1998 (53)	United States, Canada	Early Parkinson disease	66	62	2000

* ADCS = Alzheimer's Disease Cooperative Study; AREDS = Age-Related Eye Diseases Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; CAD = coronary artery disease; CHAOS = Cambridge Heart Antioxidant Study; CVD = cardiovascular disease; DATATOP = Deprenyl and Tocopherol Anti-oxidative Therapy of Parkinsonism; GISSI-Prevenzione = Gruppo Italiano per lo Studio della Sopravvvivenza nell'Infarcto Miocardio Prevenzione; HOPE = Heart Outcomes Prevention Evaluation; MIN.VIT.AOX = The Geriatrie/MINéraux, VITamines, et AntiOXydants Network; MRC/BHF HPS = Medical Research Council/British Heart Foundation Heart Protection Study; PPP = Primary Prevention Project; PPS = Polyp Prevention Study; REACT = Roche European American Cataract Trial; SPACE = Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntioXydants; VECAT = Vitamin E, Cataracts, and Age-Related Maculopathy; WAVE = Women's Angiographic Vitamin and Estrogen.

tional to the number of deaths, and none seemed to be driving the results. The increased risk at high vitamin E dosages remained statistically significant after exclusion of each of the 11 high-dosage trials, with pooled all-cause mortality risk differences ranging from 28 to 55 per 10 000 persons.

DISCUSSION

In our meta-analysis, we identified a dose-dependent relationship between vitamin E supplementation and all-cause mortality. Specifically, all-cause mortality progressively increased for dosages approximately greater than 150 IU/d. This dosage is substantially lower than the tolerable upper intake level for vitamin E, which is currently designated at 1000 mg of any form of supplementary α-tocopherol per day (corresponding to 1100 IU of synthetic vitamin E per day or 1500 IU of natural vitamin E per day) (1). The increase in all-cause mortality has obvious public health importance and represents a qualitative departure from previous findings. Three previous meta-analyses (4–6) that did not consider the dose-dependent effect of vitamin E concluded that vitamin E was neither beneficial

nor harmful. A recent meta-analysis that examined the effects of antioxidants, not specifically vitamin E, in preventing cancer noted a possible increase in all-cause mortality (54). However, in an accompanying comment, Forman and Altman (55) cautioned that these mortality analyses were exploratory and incomplete. A strength of our paper is the systematic search for trials that presented mortality data.

Although vitamin E is considered relatively safe compared to other fat-soluble vitamins (56), an increase in mortality at high dosages of vitamin E is biologically plausible. In fact, some researchers warned against the long-term administration of mega-dosages of vitamin E because it could be associated with many adverse effects (57). In vitro studies have shown that vitamin E may have pro-oxidant effects at high doses (58, 59). In in vitro models, the pro-oxidant effect of vitamin E on low-density lipoproteins is related to the production of the α-tocopheroxyl radical, which can be inhibited by co-antioxidants such as vitamin C (60). However, the trials that combined high-dosage vitamin E with vitamin C (48, 49, 51) showed increased mortality in the vitamin E groups, with the exception of the small Polyp Prevention Study (PPS) (46).

Table 1—**Continued**

Vitamin E Combined with Other Vitamins or Minerals	Factorial Design (Factorial Intervention)	Placebo-Controlled	Double-Blind	Follow-up, *y*
Yes (vitamin C, 120 mg; β-carotene, 6 mg)	Yes (selenium, 100 μg; zinc, 20 mg)	Yes	Yes	2.0
Yes (β-carotene, 15 mg; selenium, 50 μg)	Fractional factorial design	Yes	Yes	5.3
Yes (vitamin C, 120 mg; β-carotene, 6 mg; selenium, 100 μg; zinc, 20 mg)	No	Yes	Yes	7.2
No	Yes (β-carotene, 20 mg)	Yes	Yes	6.1
Yes (multivitamin and mineral tablets)	No	Yes	Yes	6.0
Yes (vitamin C, 500 mg; β-carotene, 15 mg; selenium, 75 μg)	Yes (garlic extract, 800 mg; garlic oil, 4 mg)	Yes	Yes	3.3
No	Yes (fish oils, 1 g)	No	No	3.5
No	Yes (aspirin, 100 mg)	No	No	3.6
No	Yes (ramipril, 10 mg)	Yes	Yes	4.5
Yes (vitamin C, 500 mg; β-carotene, 15 mg)	Yes (zinc, 20 mg; copper, 2 mg)	Yes	Yes	6.3
Yes (vitamin C, 1000 mg)	Yes (β-carotene, 25 mg)	Yes	Yes	4
No	No	Yes	Yes	4
No	No	Yes	Yes	1.4
Yes (vitamin C, 750 mg; β-carotene, 18 mg)	No	Yes	Yes	3–5
Yes (vitamin C, 250 mg; β-carotene, 20 mg)	Yes (simvastatin, 40 mg)	Yes	Yes	5
No	No	Yes	Yes	1.4
Yes (vitamin C, 1000 mg)	Yes (hormone replacement therapy)	Yes	No (single-blind)	2.8
No	Yes (selegiline, 10 mg)	Yes	Yes	2
No	Yes (deprenyl, 10 mg)	Yes	Yes	8.2

High dosages of vitamin E may displace other fat-soluble antioxidants (for example, γ-tocopherol) (61), disrupting the natural balance of antioxidant systems and increasing vulnerability to oxidative damage. Vitamin E may also inhibit human cytosolic glutathione *S*-transferases, which help detoxify drugs and endogenous toxins (62).

Vitamin E also has anticoagulant properties, possibly by interfering with vitamin K–dependent clotting mechanisms (63). In fact, the Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study (38) showed a statistically significant increased risk for hemorrhagic stroke among participants assigned to vitamin E. The early literature also suggested that vitamin E might affect the conversion of β-carotene to vitamin A and the tissue distribution of vitamin A in animal studies, but the relevance of this mechanism in humans has never been established (57, 64). Several of the high-dosage studies in our meta-analysis that showed increased mortality were performed in Europe (8, 48, 49), where over-the-counter use of high-dosage supplements of β-carotene or vitamin A is uncommon. It is thus unlikely that vitamin E's adverse effects are mediated through β-carotene or vitamin A.

Irregular use of high-dosage vitamin E may lead to withdrawal effects. Indeed, after reports that anginal symptoms returned after tapering of large dosages of vitamin E, Anderson and Reid (65) recruited 15 patients with stable angina for a placebo-controlled discontinuation trial.

These patients had been taking 400 to 2400 IU of vitamin E per day for long periods. Eight of these patients were randomly assigned to a dosage of vitamin E that was equal to or greater than what they were taking; symptoms in these patients did not change for the duration of the trial (9 weeks). In 4 of the 7 patients randomly assigned to placebo, anginal symptoms worsened ($P = 0.03$); 3 of these patients had to discontinue the trial prematurely. This small study has not been replicated, and the effects of discontinuing high dosages of vitamin E are unknown.

Another concern is that concomitant use of other vitamins or minerals, particularly β-carotene, as part of the study intervention may explain the observed increase in mortality associated with vitamin E. However, only 3 of the 11 high-dosage vitamin E studies tested a combination of vitamin E with β-carotene. Furthermore, adjustment for combined use of vitamin E with other vitamins or minerals did not modify our findings.
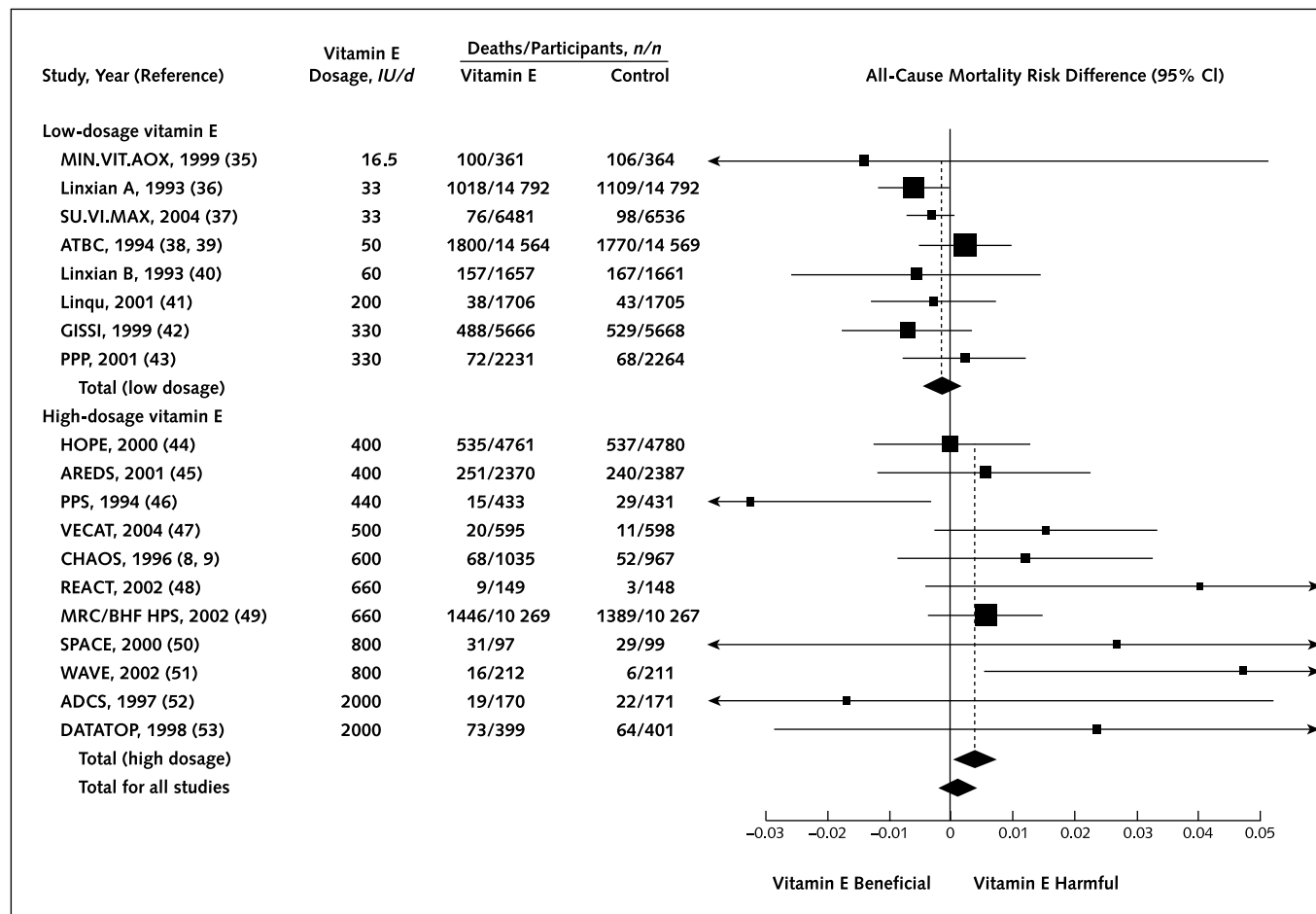
Our analysis may have other limitations. The small size of several of the trials plus inconsistent reporting of events across trials precluded a detailed dose–response analysis of cause-specific end points. However, in the 2 largest high-dosage vitamin E trials reporting cause-specific deaths (Cambridge Heart Antioxidant Study [CHAOS] [8] and Medical Research Council/British Heart Foundation Heart Protection Study [MRC/BHF HPS] [49]), the relative risk

for cardiovascular mortality associated with vitamin E exceeded 1.0. The biological activity of vitamin E compounds also differs among isomer forms (1). Hence, biological activities of vitamin E compounds are reported relative to all-rac-α-tocopherol acetate on the basis of in vivo assays (1). We converted the vitamin E dosages of the studies included in our meta-analysis to IU/d relative to all-rac-α-tocopherol acetate (7) for standardization across studies. Publication bias is also a potential source of bias in meta-analysis. We would expect, however, underreporting of vitamin E studies that failed to show a beneficial effect, which would bias against our findings. In addition, high-dosage vitamin E trials were often performed in patients with various chronic diseases, and we could not evaluate the generalizability of our findings to healthy adult populations. Finally, the ideal study design to assess dose

response is a long-term, large trial with several doses. Such trials are almost impossible to conduct, especially with total mortality as an outcome. Hence, although precisely identifying the threshold at which risk increases is difficult, our meta-analysis probably provides the best estimate of the dose–response effect of vitamin E supplementation on mortality.

The possibility of a small mortality benefit with low-dosage vitamin E supplementation also deserves comment. The mortality reduction in low-dosage trials was not statistically significant in the primary analysis, although in secondary analyses based on 4-way data, the pooled risk difference for low-dosage vitamin E trials was −33 per 10 000 persons ($P = 0.021$). The effect of vitamin E in low-dosage studies, however, must be interpreted with caution because these studies were often performed in mal-

Figure 2. Risk difference in all-cause mortality for randomized, controlled trials of vitamin E supplementation and pooled results for low-dosage (<400 IU/d) and high-dosage (≥400 IU/d) vitamin E trials.

Study, Year (Reference)	Vitamin E Dosage, IU/d	Deaths/Participants, n/n		All-Cause Mortality Risk Difference (95% CI)
		Vitamin E	Control	
Low-dosage vitamin E				
MIN.VIT.AOX, 1999 (35)	16.5	100/361	106/364	
Linxian A, 1993 (36)	33	1018/14 792	1109/14 792	
SU.VI.MAX, 2004 (37)	33	76/6481	98/6536	
ATBC, 1994 (38, 39)	50	1800/14 564	1770/14 569	
Linxian B, 1993 (40)	60	157/1657	167/1661	
Linqu, 2001 (41)	200	38/1706	43/1705	
GISSI, 1999 (42)	330	488/5666	529/5668	
PPP, 2001 (43)	330	72/2231	68/2264	
Total (low dosage)				
High-dosage vitamin E				
HOPE, 2000 (44)	400	535/4761	537/4780	
AREDS, 2001 (45)	400	251/2370	240/2387	
PPS, 1994 (46)	440	15/433	29/431	
VECAT, 2004 (47)	500	20/595	11/598	
CHAOS, 1996 (8, 9)	600	68/1035	52/967	
REACT, 2002 (48)	660	9/149	3/148	
MRC/BHF HPS, 2002 (49)	660	1446/10 269	1389/10 267	
SPACE, 2000 (50)	800	31/97	29/99	
WAVE, 2002 (51)	800	16/212	6/211	
ADCS, 1997 (52)	2000	19/170	22/171	
DATATOP, 1998 (53)	2000	73/399	64/401	
Total (high dosage)				
Total for all studies				

Area of each square is proportional to inverse of study variance in the analysis. Horizontal lines represent 95% CIs. ADCS = Alzheimer's Disease Cooperative Study; AREDS = Age-Related Eye Diseases Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; CHAOS = Cambridge Heart Antioxidant Study; DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; GISSI-Prevenzione = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio Prevenzione; HOPE = Heart Outcomes Prevention Evaluation; MIN.VIT.AOX = The Geriatrie/MINéraux, VITamines, et AntiOXydants Network; MRC/BHF HPS = Medical Research Council/British Heart Foundation Heart Protection Study; PPP = Primary Prevention Project; PPS = Polyp Prevention Study; REACT = Roche European American Cataract Trial; SPACE = Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntiOXydants; VECAT = Vitamin E, Cataracts, and Age-Related Maculopathy; WAVE = Women's Angiographic Vitamin and Estrogen.

Figure 3. **Dose–response relationship between vitamin E supplementation and all-cause mortality in randomized, controlled trials.**
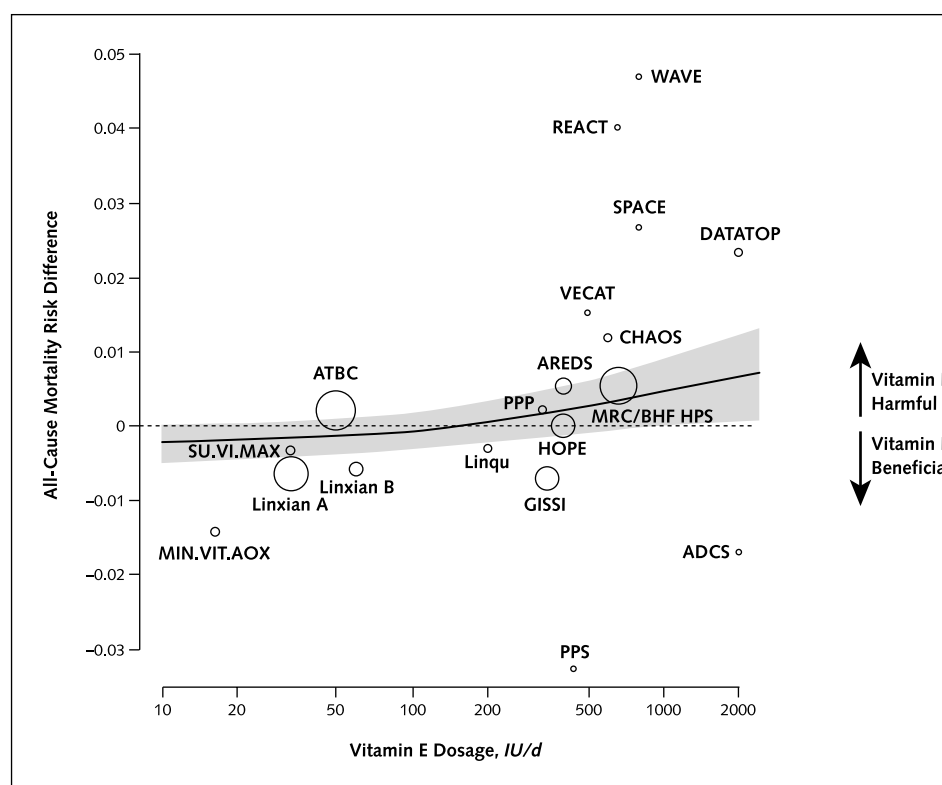
We obtained the risk trend (*solid curve*) and its 95% confidence band (*shaded region*) by using a quadratic-linear spline model. Circled areas are proportional to inverse of study variance in the analysis. ADCS = Alzheimer's Disease Cooperative Study; AREDS = Age-Related Eye Diseases Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; CHAOS = Cambridge Heart Antioxidant Study; DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; GISSI-Prevenzione = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio Prevenzione; HOPE = Heart Outcomes Prevention Evaluation; MIN.VIT.AOX = The Geriatrie/MINéraux, VITamines, et AntiOXydants Network; MRC/BHF HPS = Medical Research Council/British Heart Foundation Heart Protection Study; PPP = Primary Prevention Project; PPS = Polyp Prevention Study; REACT = Roche European American Cataract Trial; SPACE = Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntioXydants; VECAT = Vitamin E, Cataracts, and Age-Related Maculopathy; WAVE = Women's Angiographic Vitamin and Estrogen.

nourished populations or used other vitamins or minerals in combination with vitamin E. Further research is needed to determine whether low-dosage vitamin E supplementation is beneficial in western populations.

Vitamin E supplements are regularly consumed in the United States (66), particularly by patients with established cardiovascular diseases and cancer (67). Furthermore, vitamin E supplements are often taken at high dosages (for instance, 64% of vitamin E users in the Physicians' Health Study [68] took ≥400 IU/d), far exceeding intake derived from dietary sources (9.3 mg of α-tocopherol equivalents on average per day [approximately 14 IU/d]) (1). On the basis of our study, high-dosage vitamin E supplementation is clearly unjustified. Policymaking bodies, which currently do not recommend antioxidant vitamin supplement use to the general population (1–3), should also caution the public against the use of high-dosage vitamin E supplementation. Current practice guidelines, however, recommend the

Table 2. **Pooled All-Cause Mortality Risk Differences and Risk Ratios for Selected Vitamin E Dosages***

Vitamin E Dosage, IU/d	Unadjusted		Adjusted for Other Vitamins or Minerals	
	Risk Difference (95% CI)	Risk Ratio (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
20	−22 (−48 to 5)	0.98 (0.95 to 1.01)	−16 (−45 to 14)	0.98 (0.95 to 1.02)
50	−15 (−41 to 11)	0.99 (0.96 to 1.01)	−8 (−42 to 25)	0.99 (0.96 to 1.03)
100	−6 (−31 to 19)	0.99 (0.97 to 1.02)	2 (−35 to 38)	1.00 (0.97 to 1.04)
200	6 (−19 to 32)	1.01 (0.98 to 1.03)	15 (−26 to 56)	1.01 (0.98 to 1.05)
500	29 (−6 to 63)	1.03 (1.00 to 1.06)	38 (−11 to 87)	1.04 (0.99 to 1.08)
1000	47 (1 to 94)	1.05 (1.01 to 1.09)	57 (−1 to 115)	1.06 (1.00 to 1.11)
2000	66 (6 to 127)	1.07 (1.01 to 1.12)	76 (8 to 145)	1.08 (1.01 to 1.14)

* Effect estimates were derived from quadratic-linear dose–response models (see text for details). Risk differences are shown as deaths per 10 000 persons.

Figure 4. Risk difference in all-cause mortality for randomized, controlled trials of vitamin E supplementation and pooled results for low-dosage (<400 IU/d) and high-dosage (≥400 IU/d) vitamin E trials based on 4-way analyses of trials that used a factorial design.
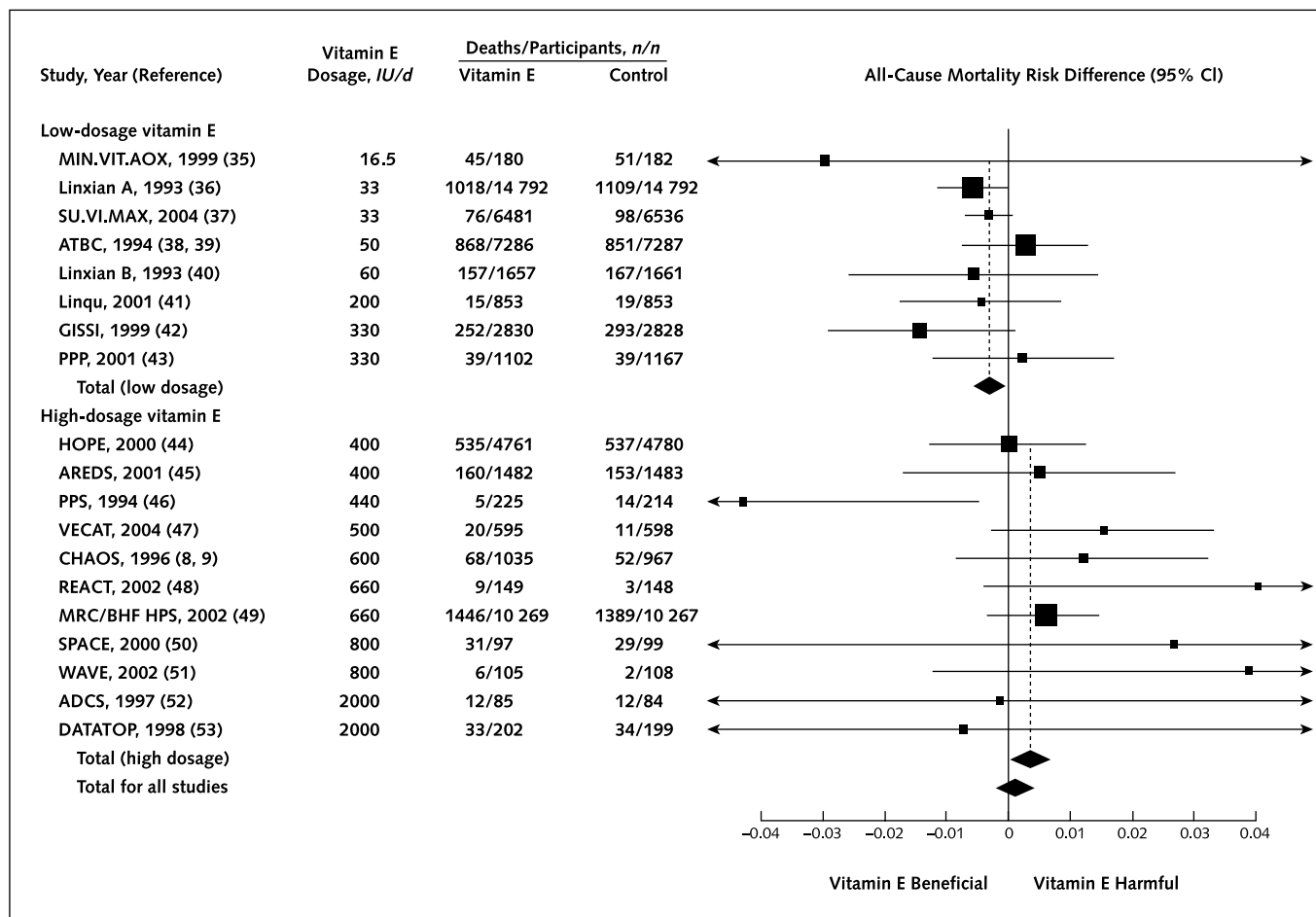
Area of each square is proportional to inverse of study variance in the analysis. Horizontal lines represent 95% CIs. We restricted data from factorial trials to participants who were not exposed to the second factorial intervention, except for the Heart Outcomes Prevention Evaluation (*HOPE*) study (44) and the Medical Research Council/British Heart Foundation Heart Protection Study (*MRC/BHF HPS*) (49) (in which no disaggregated data were available) and for the Linxian A (36) trial (which used a fractional factorial design). For these trials and the trials that did not use a factorial design, we kept the results from 2-way analyses. ADCS = Alzheimer's Disease Cooperative Study; AREDS = Age-Related Eye Diseases Study; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group; CHAOS = Cambridge Heart Antioxidant Study; DATATOP = Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; GISSI-Prevenzione = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardio Prevenzione; MIN-.VIT.AOX = The Geriatrie/MINéraux, VITamines, et AntiOXydants Network; PPP = Primary Prevention Project; PPS = Polyp Prevention Study; REACT = Roche European American Cataract Trial; SPACE = Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; SU.VI.MAX = SUpplementation en VItamines et Minéraux AntiOXydants; VECAT = Vitamin E, Cataracts, and Age-Related Maculopathy; WAVE = Women's Angiographic Vitamin and Estrogen.

use of vitamin E supplementation to delay the progression of Alzheimer disease (69, 70). This recommendation may be premature until larger randomized, controlled clinical

trials evaluate the efficacy and safety of high-dosage vitamin E supplementation in patients with Alzheimer disease. High-dosage vitamin supplementation is often as-

Table 3. Pooled All-Cause Mortality Risk Differences (per 10 000 persons) and Risk Ratios for Low-Dosage (<400 IU/d) and High-Dosage (≥400 IU/d) Vitamin E Trials Adjusted for Study-Specific Variables

Adjustment Variable	Vitamin E Dosage < 400 IU/d		Vitamin E Dosage ≥ 400 IU/d	
	Risk Difference (95% CI)	Risk Ratio (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Men	−24 (−50 to 3)	0.98 (0.95 to 1.00)	45 (10 to 81)	1.04 (1.01 to 1.08)
Mean age	−38 (−75 to −1)	0.96 (0.92 to 1.00)	36 (4 to 68)	1.04 (1.01 to 1.07)
Combined with vitamins or minerals	−6 (−38 to 26)	0.99 (0.96 to 1.03)	63 (6 to 119)	1.06 (1.01 to 1.11)
Average follow-up	−21 (−46 to 5)	0.98 (0.95 to 1.01)	35 (1 to 69)	1.03 (1.00 to 1.07)

sumed to be at worst innocuous. In view of the increased mortality associated with high dosages of β-carotene (4) and now vitamin E, use of any high-dosage vitamin supplements should be discouraged until evidence of efficacy is documented from appropriately designed clinical trials.

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