Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention: Systematic Review and Meta-analysis

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REVIEW

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

Systematic Review and Meta-analysis

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Context Antioxidant supplements are used for prevention of several diseases.

Objective To assess the effect of antioxidant supplements on mortality in randomized primary and secondary prevention trials.

Data Sources and Trial Selection We searched electronic databases and bibliographies published by October 2005. All randomized trials involving adults comparing beta carotene, vitamin A, vitamin C (ascorbic acid), vitamin E, and selenium either singly or combined vs placebo or vs no intervention were included in our analysis. Randomization, blinding, and follow-up were considered markers of bias in the included trials. The effect of antioxidant supplements on all-cause mortality was analyzed with random-effects meta-analyses and reported as relative risk (RR) with 95% confidence intervals (CIs). Meta-regression was used to assess the effect of covariates across the trials.

Data Extraction We included 68 randomized trials with 232 606 participants (385 publications).

Data Synthesis When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, 1.16; 95% CI, 1.05-1.29) and selenium (RR, 0.998; 95% CI, 0.997-0.9995) were significantly associated with mortality. In 47 low-bias trials with 180 938 participants, the antioxidant supplements significantly increased mortality (RR, 1.05; 95% CI, 1.02-1.08). In low-bias risk trials, after exclusion of selenium trials, beta carotene (RR, 1.07; 95% CI, 1.02-1.11), vitamin A (RR, 1.16; 95% CI, 1.10-1.24), and vitamin E (RR, 1.04; 95% CI, 1.01-1.07), singly or combined, significantly increased mortality. Vitamin C and selenium had no significant effect on mortality.

Conclusions Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

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OXIDATIVE STRESS IS IMPLICATED in most human diseases.[1,2] Antioxidants may decrease the oxidative damage and its alleged harmful effects.[3-6] Many people are taking antioxidant supplements, believing to improve their health and prevent diseases.[7-10] Whether antioxidant supplements are beneficial or harmful is uncertain.[11-15] Many primary or secondary prevention trials of antioxidant supplements have been conducted to prevent several diseases.

We found that antioxidant supplements, with the potential exception of selenium, were without significant effects on gastrointestinal cancers and increased all-cause mortality.[14,15] We did not examine the effect of antioxidant supplements on all-cause mortality in all randomized prevention trials.[16] Our aim with the present systematic review was to analyze the effects of antioxidant supplements (beta carotene, vitamins A and E, vitamin C [ascorbic acid], and selenium) on all-cause mortality of adults included in primary and secondary prevention trials.

METHODS

The present review follows the Cochrane Collaboration method[17] and is based on the principles of our peer-reviewed protocol and review on antioxidant supplements for gastrointestinal cancer prevention.[14,15,18,19] We included all primary and secondary prevention trials in adults randomized to receive beta caro-

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tene, vitamin A, vitamin C, vitamin E, or selenium vs placebo or no intervention. Parallel-group randomized trials and the first period of crossover randomized trials were included.[17] Trials including general or healthy populations were classified as primary prevention. Trials including participants with specific disease were classified as secondary prevention. We excluded tertiary prevention (treatment) trials, like trials on acute, infectious, or malignant diseases except nonmelanoma skin cancer.

We included antioxidant supplements at any dose, duration, and route of administration. We analyzed the antioxidants administered singly, in combination with other antioxidants, or with other vitamins or trace elements. Trials with collateral interventions were included if the interventions were used equally in the trial groups. Subgroup analyses without high-bias risk trials and selenium trials were preconceived. Our outcome measure was all-cause mortality at maximum follow-up.

Data Sources

We searched The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 3, 2005), MEDLINE (1966 to October 2005), EMBASE (1985 to October 2005), and the Science Citation Index Expanded (1945 to October 2005).[20] We scanned bibliographies of relevant articles for additional trials.

Data Extraction

Two of the 3 authors (G.B. and D.N., and R.G.S.) independently assessed trial eligibility. Excluded trials were listed with the reasons for exclusion. Disagreement was resolved by discussion or in consultation with a third author (C.G.). We contacted authors of the trials for missing information.

From each trial we recorded first author; country of origin, country income category (low, middle, high)[21]; number of participants; characteristics of participants: age range (mean or median) and sex ratio; participation rate; dropout rate; trial design (parallel, factorial, or crossover); type of antioxidant; dose; duration of supplementation; duration of follow-up (ie, treatment duration plus posttreatment follow-up); and cointerventions. We extracted the date, location, sponsor of the trial, and the publication status.

Due to the risk of overestimating intervention effects, analyses were stratified according to the risk of bias (methodological quality).[14,15,18,19,22-24] Trials with adequate generation of the allocation sequence, adequate allocation concealment, adequate blinding, and adequate follow-up were considered low-bias risk trials (high methodological quality).[24] Trials with one or more unclear or inadequate quality components were classified as high-bias risk trials (low methodological quality).[24] Generation of the allocation sequence was considered adequate if the allocation sequence was generated by a computer or random-number table, or similar; allocation concealment was considered adequate if concealed up to the point of treatment by central randomization, sealed envelopes, or similar; blinding was considered adequate if the trial was described as double-blind and using identical placebo; follow-up was considered adequate if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals. Bias risk was assessed without blinding of 2 authors (G.B. and D.N. or R.G.S.). Consensus was reached through discussion or arbitration by a third author (C.G. or L.L.G.) before data entry. We have found high inter-rater agreement between blinded and unblinded assessments and also between 2 independent assessors.[24]

Statistical Analyses

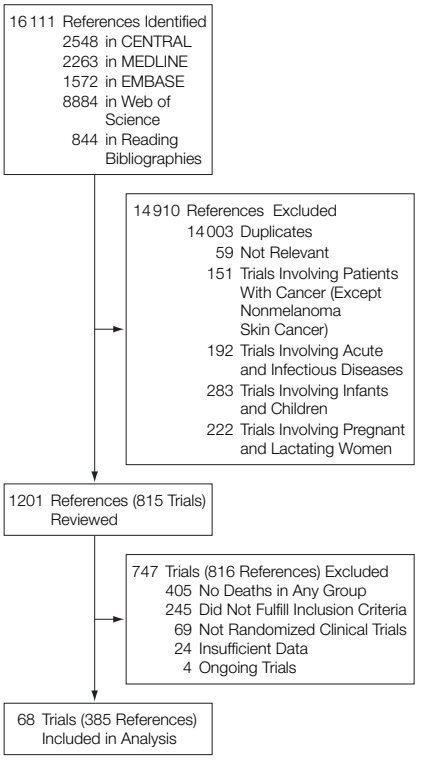
We used The Cochrane Collaboration software (RevMan Analyses 1.0; www.cochrane.org), STATA 8.2 (STATA Corp, College Station, Tex), Sigma Stat 3.0 (SPSS Inc, Chicago, Ill), and StatsDirect (StatsDirect Ltd, Altrincham, England). We analyzed the data with a random-effects model,[25] calculating the relative risk (RR) with 95% confidence intervals (CIs). To account for 0 cells in the 2×2 tables, we calculated the RR with 3 different continuity corrections (0.5; 0.1; 0.01).[26,27] We did not include trials with 0 events in both intervention groups.[27,28] Because the number of such trials was large, we performed exploratory analysis adding an imagined trial with 1 death and 20 000 participants in each group.

We used the STATA metareg command for the random-effects meta-regression to assess which covariates influenced the intervention effect across trials.[29] The included covariates were bias risk, type and dose of supplement, single or combined supplement regimen, duration of supplementation, and primary or secondary prevention. Univariate and multivariate analyses including all covariates were performed. Results are presented with regression coefficients and 95% CI.

All analyses followed the intention-to-treat principle. For trials with factorial design, we based our results on at-margins analysis,[30] comparing all groups that received antioxidant supplements with groups that did not. To determine the effect of a single antioxidant, we performed inside-the-table analysis[30] in which we compared the group taking a single antioxidant with the group taking placebo or receiving no intervention. In trials with more than 2 groups assessing additional therapy, we compared only groups receiving antioxidants, placebo, or no intervention.

We assessed heterogeneity with I^2 that describes the percentage of total variation across trials due to heterogeneity rather than chance.[17,31] I^2 can be calculated as $I^2 = 100\% \times (Qv - df)/Q$, where Q is Cochran's heterogeneity statistics and df the degrees of freedom. Negative values of I^2 are put equal to 0, so I^2 lies between 0% (no heterogeneity) and 100% (maximal heterogeneity).[31] We compared the estimated treatment effects in trials with a low- or high-risk of bias with test of interaction.[32] We performed adjusted-rank

Figure 1. Flow Diagram of Identification of Randomized Trials for Inclusion



correlation[33] and regression-asymmetry tests[34] for detection of bias.

RESULTS

Database searches yielded 16 111 references. Exclusion of duplicates and irrelevant references left 1201 references describing 815 trials. To obtain additional information we wrote to authors of eligible trials. Seventy authors responded. We excluded 816 references (747 trials) due to the following: mortality was 0 in both study groups (n=405 trials, including about 40 000 participants [http://ctu.rh.dk]); did not fulfill inclusion criteria (n=245); was not a randomized trial (n=69); insufficient data (n=24); or still ongoing trial (n=4). We included 385 references describing 68 randomized trials fulfilling our inclusion criteria and able to provide data for our analyses[35-102] (FIGURE 1 [http://ctu.rh.dk]). This corresponds to a median of 6 references per included trial (range, 1-44). Forty trials used parallel-group design, 26 factorial design (23 trials 2 × 2; 2 trials 2 × 2 × 2; 1 trial half replicate of 2 × 2 × 2 × 2), and 2 crossover design.

A total of 232 606 participants were randomly assigned in the 68 trials. The number of participants in each trial ranged from 24 to 39 876 (TABLE 1 and TABLE 2). The mean age was 62 years (range, 18-103 years). The mean proportion of women was 44.5% in the 63 trials reporting sex.

Twenty-one trials were primary prevention trials including 164 439 healthy participants; 47 trials were secondary prevention trials including 68 167 participants with gastrointestinal (n=11), cardiovascular (n=9), neurological (n=6), ocular (n=5), dermatological (n=5), rheumatoid (n=2), renal and cardiovascular (n=1), endocrinological (n=1), or unspecified (n=7) diseases. Main outcome measures in the primary prevention trials were cancer and mortality (cause specific and all cause), and in the secondary prevention trials they were progression of disease and mortality (cause specific and all cause; TABLE 3 and TABLE 4).

All antioxidant supplements were administered orally. The dose and regimen of the antioxidant supplements were: beta carotene 1.2 to 50.0 mg (mean, 17.8 mg) , vitamin A 1333 to 200 000 IU (mean, 20 219 IU), vitamin C 60 to 2000 mg (mean, 488 mg), vitamin E 10 to 5000 IU (mean, 569 IU), and selenium 20 to 200 µg (mean 99 µg) daily or on alternate days for 28 days to 12 years (mean 2.7 years). In one trial[40] antioxidants were applied in a single dose and participants were followed up for 3 months thereafter. The mean duration of follow-up in all trials was 3.3 years (range, 28 days-14.1 years).

Beta carotene was tested in 25 trials, vitamin A in 16, vitamin C in 34, vitamin E in 55, and selenium in 21. Beta carotene was tested singly in 6 trials, vitamin A in 2, vitamin E in 24, and vitamin C and selenium in 3 trials each. The antioxidant supplements were given in the following combinations: beta carotene and vitamin A; beta carotene and vitamin E; beta carotene and vitamin C; vitamin A and vitamin C; vitamin C and vitamin E; vitamin E and selenium; selenium and zinc; beta carotene, vitamin C, and vitamin E; beta carotene, vitamin C, vitamin E, and selenium; beta carotene, vitamin C, vitamin E, selenium, and zinc; vitamin A, vitamin C, vitamin E, selenium, and zinc; vitamin A, vitamin C, vitamin E, selenium, methionine, and ubiquinone. In 11 trials, participants were supplemented with different mixtures of antioxidants as well as with vitamins and minerals without antioxidant properties.*

Sixty-three trials used placebo and 5 trials[43,48,58,69,82] used no intervention in the control group. In 9 trials† the active and placebo (control) groups were supplemented with vitamins and minerals (with or without antioxidant properties). In 6 of the trials, the supplementation was with vitamin E 4 IU,[46,89] vitamin A 1000 IU[40]; vitamin C 20 and 50 mg[48,81]; riboflavin 10 mg[35]; or niacin 100 mg.[65] In the trials with factorial or parallel-group design, the additional interventions tested were multivitamins and minerals (zinc, copper, chromium); ubiquinone; L-methionine; omega-3 polyunsaturated fatty acids; citrus bioflavonoid complex; quercetin, bilberry extract, rutin (bioflavonoids); taurine; *N*-acetyl cysteine; L-glutathione; aged garlic; deprenyl–selegiline (selective monoamine oxidase B inhibitor); donepezil (acetylcholinesterase inhibitor); riluzole (modulator of glutamatergic neurotransmission); amoxicillin, metronidazole (antibiotics); bismuth subsalicylate; omeprazole (proton-pump inhibitor); aspirin; simvastatin (cholesterol-lowering drug); celecoxib (inhibitor of cyclooxygenase), and ramipril (angiotensin-converting enzyme inhibitor).

In 54 trials (79.4%), the antioxidants were provided at no cost from pharmaceutical companies. In the rest

*References 39, 41, 42, 45, 51, 52, 72, 84, 91, 92, 101.
†References 35, 40, 46, 48, 65, 81, 89, 97, 99.

of the trials funding was not reported. The trials were conducted in Europe, North and South America, Asia, and Australia. Six trials came from lower-middle-income countries[41,42,47,62,67,68] and 62 trials from high-income countries.

Methodological Quality of Included Trials

Forty-seven of the 68 trials (69.1%) had low-bias risk, ie, had adequate generation of the allocation sequence, adequate allocation concealment, blinding, and follow-up.[24] The remaining trials had one or more inadequate components.

All Randomized Trials

The pooled effect of all supplements vs placebo or no intervention in all randomized trials was not significant (RR, 1.02; 95% CI, 0.98-1.06). Heterogeneity was not significant (I^2=18.6%, P=.10). Adjusted-rank correlation test (P=.08), but not the regression asymmetry test (P=.26), suggested bias among the trials. Exploratory analysis adding an imagined trial with one death and 20 000 participants in each study group had no noticeable effect on the result.

Univariate meta-regression analyses revealed significant influences of dose of beta carotene (RR, 1.004; 95% CI, 1.001-1.007; P=.012), dose of vitamin A (RR, 1.000006; 95% CI,

Table 1. Characteristics of Included Trials With High Risk of Bias

							Antioxidant Supplement				
Source	Design	No. of Participants	Women, %	Mean Age, y	Duration of Supplement Treatment, y	Follow-up, y	Beta Carotene, mg	Vitamin A, IU	Vitamin C, mg	Vitamin E, IU	Selenium, µg
Gillilan et al,[35] 1977	Crossover	52	NA	57	0.5	0.5				1600	
McKeown-Eyssen et al,[36] 1988	Parallel	185	32	58	2	2			400	400	
Penn et al,[38] 1991	Parallel	30	80	84	0.077	0.077		8000	100	50	
Chandra,[39] 1992	Parallel	96	55	74	1	1	16	1333	80	44	20
Blot et al,[41] 1993	½ (2 × 2 × 2 × 2)	29 584	55	NA	5.25	5.25	15	5000	120	33	50
Wenzel et al,[43] 1993	Parallel	56	20	48	0.082	0.082	12		180	894	200
Takamatsu et al,[46] 1995	Parallel	147	60	47	6	6				136	
de la Maza et al,[47] 1995	Parallel	74	15	50	1	1				500	
ter Riet et al,[48] 1995	2 × 2	88	NA	NA	0.23	0.23			1000		
Hogarth et al,[51] 1996	2 × 2	106	56	83	0.083	0.083		8000	500		
Girodon et al,[54] 1997	2 × 2	81	75	84	2	2	6		120	15	100
Sano et al,[56] 1997	2 × 2	341	65	73	2	2				2000	
Bonelli et al,[57] 1998	Parallel	304	NA	NA	5	5		6000	180	30	200
GISSI,[58] 1999	2 × 2	11 324	15	59	3.5	3.5				330	
Stevic et al,[67] 2001	Parallel	28	25	57	1	1				1200	31.5
You et al,[68] 2001	2 × 2 × 2	3411	49	NA	3.25	3.25	15		500	200	75
de Gaetano,[69] 2001	2 × 2	4495	57	64	3.6	3.6				330	
de Waart et al,[70] 2001	Parallel	218	0	60	1.8	1.8				400	
Sasazuki et al,[81] 2003	2 × 2	439	65	57	5	5	15		500		
Takagi et al,[82] 2003	Parallel	93	55	63	5	5				600	
Petersen et al,[99] 2005	Parallel	516	46	73	3	3				2000	

Abbreviation: NA, not available. Blank cells indicate that the supplement was not part of the study.

Table 2. Characteristics of Included Trials With Low Risk of Bias

Source	Design	No. of Participants	Women, %	Mean Age, y	Duration of Supplement Treatment, y	Follow-up, y	Antioxidant Supplement				
							Beta Carotene, mg	Vitamin A, IU	Vitamin C, mg	Vitamin E, IU	Selenium, µg
Greenberg et al,[37] 1990	Parallel	1805	30	NA	5	5	50				
Murphy et al,[40] 1992	Parallel	109	NA	NA	0.003	0.25		200 000			
Li et al,[42] 1993	Parallel	3318	56	54	6	6	15	10 000	180	60	50
Greenberg et al,[44] 1994	2 × 2	864	21	61	4	4	25		1000	440	
Pike and Chandra,[45] 1995	Parallel	47	72	69	1	1		2666	90	45	
Clark et al,[49] 1996	Parallel	1312	25	63	4.5	7.4					200
Hennekens et al,[50] 1996	2 × 2	22 071	0	53	12	12.9	25				
Richer,[52] 1996	Parallel	71	7	72	1.5	1.5		20 000	750	200	50
Stephens et al,[53] 1996	Parallel	2002	16	62	1.4	1.4				600	
Moon et al,[55] 1997	Parallel	2297	30	63	3.8	3.8		25 000			
Girodon et al,[59] 1999	2 × 2	725	74	84	2	2	6		120	16.5	100
Green et al,[60] 1999	2 × 2	1621	56	49	4.5	4.5	30				
Boaz et al,[61] 2000	Parallel	196	31	65	1.42	1.42				800	
Correa et al,[62] 2000	2 × 2 × 2	976	54	51	6	6	30		2000		
Jacobson et al,[63] 2000	Parallel	112	42	42	0.5	0.5	12		500	400	
AREDS,[64] 2001	2 × 2	4757	56	68	6.3	6.3	15		500	400	
Brown et al,[65] 2001	2 × 2	160	13	53	3	3	25		1000	800	100
Desnuelle et al,[66] 2001	Parallel	288	45	64	1	1				500	
Chylack et al,[71] 2002	Parallel	297	59	68	3	3	18		750	660	
Graat et al,[72] 2002	2 × 2	652	50	NA	1	1	1.2	2000	60	272	25
Heart Protection Study,[73] 2002	2 × 2	20 536	25	NA	5	5	20		250	660	
Hodis et al,[74] 2002	Parallel	353	52	56	3	3				400	
Waters et al,[75] 2002	2 × 2	423	100	65	3	3			1000	800	
White et al,[76] 2002	Parallel	100	42	63	0.23	0.23			1000	223	
Wluka et al,[77] 2002	Parallel	136	45	64	2	2				500	
Collins et al,[78] 2003	2 × 2	52	2	67	0.5	2.5				400	
Prince et al,[79] 2003	Crossover	61	92	58	0.25	0.25	3		150	74.5	75
Salonen et al,[80] 2003	2 × 2	520	51	NA	6	6			250	272	
Virtamo et al[83] 2003	2 × 2	29 133	0	57	6.1	14.1	20			50	

(continued)

Table 2. Characteristics of Included Trials With Low Risk of Bias (cont)

Source	Design	No. of Participants	Women, %	Mean Age, y	Duration of Supplement Treatment, y	Follow-up, y	Antioxidant Supplement				
							Beta Carotene, mg	Vitamin A, IU	Vitamin C, mg	Vitamin E, IU	Selenium, µg
Allsup et al,[84] 2004	Parallel	164	63	83	0.15	0.5		2666	120	60	60
Goodman et al,[85] 2004	Parallel	18 314	34	58	4	10	30	25 000			
Hercberg et al,[86] 2004	Parallel	13 017	61	49	7.54	7.54	6		120	33	100
Manuel-y-Keenoy et al,[87] 2004	Parallel	24	14	51	0.5	4.5				750	
McNeil et al,[88] 2004	Parallel	1193	56	66	4	4				500	
Meydani et al,[89] 2004	Parallel	617	73	84	1	1				200	100
Mezey et al,[90] 2004	Parallel	51	33	48	0.25	1				1000	
Richer et al,[91] 2004	Parallel	61	4	75	1	1	10	2500	1500	500	200
Avenell et al,[92] 2005	Parallel	910	47	72	1	1		2666	60	10	
Graf et al,[93] 2005	Parallel	160	35	58	1.5	1.5				5000	
Lee et al,[94] 2005	2 × 2	39 876	100	55	10.1	10.1	25			300	
Limburg et al,[95] 2005	2 × 2	360	58	47	0.83	0.83					200
Lonn et al,[96] 2005	2 × 2	9541	27	66	4.5	7				400	
Marras et al,[97] 2005	2 × 2	800	34	61	2.6	13				2000	
Mooney et al,[98] 2005	Parallel	284	45	37	1.25	1.25			500	400	
Tam et al,[100] 2005	Parallel	39	100	46	0.23	2.67			500	800	
Witte et al,[101] 2005	Parallel	32	NA	NA	0.75	0.75		2666	500	400	50
Rayman et al,[102] 2006	Parallel	501	47	67	0.5	0.5					200

Abbreviation: NA, not available. Blank cells indicate that the supplement was not part of the study.

1.000002-1.000009; $P=.003$), dose of selenium (RR, 0.998; 95% CI, 0.997-0.999; $P=.002$), and bias-risk (RR, 1.16; 95% CI, 1.05-1.29; $P=.004$) on mortality. None of the other covariates (dose of vitamin C; dose of vitamin E; single or combined antioxidant regimen; duration of supplementation; and primary or secondary prevention) were significantly associated with mortality.

In multivariate meta-regression analysis including all covariates, dose of selenium was associated with significantly lower mortality (RR, 0.998; 95% CI, 0.997-0.999; $P=.005$) and low-bias risk trials with significantly higher mortality (RR, 1.16; 1.05-1.29; $P=.005$). None of the other covariates was significantly associated with mortality.

Bias Risk of Trials

In trials with low-bias risk mortality was significantly increased in the supplemented group (RR, 1.05; 95% CI, 1.02-1.08) without significant heterogeneity ($I^2=7.0\%$). Exploratory analysis adding an imagined trial with 1 death and 20 000 participants in each study group had no noticeable effect on the result.

In high-bias risk trials (low-methodological quality in ≥1 of the 4 components) mortality was significantly decreased in the supplemented group (RR, 0.91; 95% CI, 0.83-1.00) without significant heterogeneity ($I^2=4.5\%$). The difference between the estimate of antioxidants on mortality in low- and high-bias risk trials was statistically significant by test of interaction ($z=2.88$, $P=.004$; FIGURE 2 and FIGURE 3).

Antioxidant Supplements Given Singly or in Combination

Beta carotene used singly significantly increased mortality (TABLE 5). This effect was not significant when combined with other supplements. After exclusion of

high-bias risk and selenium trials, beta carotene singly or combined significantly increased mortality (Table 5).

Vitamin A given singly or in combination with the other supplements did not significantly affect mortality. After exclusion of high-bias risk and selenium trials, vitamin A singly or combined significantly increased mortality (Table 5).

Vitamin E given singly or in combination with the other supplements did not significantly affect mortality (Table 5). Vitamin E given singly in high (≥1000 IU) or low dose (<1000 IU) did not significantly affect mortality (RR, 1.07; 95% CI, 0.91-1.25; I^2=0% and RR, 1.00; 95% CI, 0.94-1.07; I^2=13.0%, respectively). After exclusion of high-bias risk and selenium trials, vitamin E given singly or combined significantly increased mortality (Table 5).

Vitamin C given singly or in combination with the other supplements was without significant influence on mortality, even after the exclusion of high-bias risk trials and selenium trials (Table 5).

Selenium given singly or in combination with other antioxidant supplements had no significant influence on mortality when analyzed separately (Table 5). Selenium given singly or combined significantly decreased mortality when analyzed together. After exclusion of high-bias risk trials, selenium given singly or with other antioxidants had no significant influence on mortality (Table 5).

Table 3. Participants and Outcome Measures of Included Trials With High Risk of Bias

Source	Participants and Inclusion Criteria	Outcome Measures	Type of Prevention
Gillilan et al,[35] 1977	Coronary artery disease	Improvement of angina pectoris	Secondary
McKeown-Eyssen et al,[36] 1988	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary
Penn et al,[38] 1991	Elderly long-stay patients	Cell-mediated immune function	Secondary
Chandra,[39] 1992	Elderly individuals	Infectious morbidity	Primary
Blot et al,[41] 1993	General population	Cancer incidence, cancer mortality, all-cause mortality	Primary
Wenzel et al,[43] 1993	Alcoholic hepatitis	Duration of hospitalization, mortality	Secondary
Takamatsu et al,[46] 1995	General population	Any illness	Primary
de la Maza et al,[47] 1995	Alcoholic cirrhosis	Liver function, mortality, hospitalization rates	Secondary
ter Riet et al,[48] 1995	Nursing home patients with pressure ulcers	Wound status and clinometric changes	Secondary
Hogarth et al,[51] 1996	Elderly medical in-patients	Weight, serum albumin levels, activities of daily living, cognitive functioning, length of stay	Secondary
Girodon et al,[54] 1997	Elderly individuals	Infectious morbidity	Primary
Sano et al,[56] 1997	Probable Alzheimer disease	Death, institutionalization, loss of ability to perform 2 of 3 basic activities of daily living	Secondary
Bonelli et al,[57] 1998	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary
GISSI,[58] 1999	Recent myocardial infarction	All-cause mortality, nonfatal myocardial infarction, nonfatal stroke, cardiovascular death	Secondary
Stevic et al,[67] 2001	Probable or definitive amyotrophic lateral sclerosis	Survival and rate of disease progression	Secondary
You et al,[68] 2001	General population	Prevalence of dysplasia, gastric cancer, chronic atrophic gastritis, intestinal metaplasia	Primary
de Gaetano,[69] 2001	Elderly with at least 1 of the major cardiovascular risk factors	Cardiovascular death, nonfatal myocardial infarction and stroke, all-cause mortality, total cardiovascular events, angina pectoris, transient ischemic attacks, peripheral artery disease, revascularization procedures	Primary
de Waart et al,[70] 2001	Male cigarette smokers	Progression of atherosclerosis	Primary
Sasazuki et al,[81] 2003	Chronic atrophic gastritis	Blood pressure	Secondary
Takagi et al,[82] 2003	Liver cirrhosis	Tumor-free survival and cumulative survival rate	Secondary
Petersen et al,[99] 2005	Amnestic mild cognitive impairment	Alzheimer disease	Secondary

Abbreviations: BCC, basal cell carcinoma; CVD, cardiovascular disease; SCC, squamous cell carcinoma of the skin.

COMMENT

Our systematic review contains a number of findings. Beta carotene, vitamin A, and vitamin E given singly or combined with other antioxidant supplements significantly increase mortality. There is no evidence that vitamin C may increase longevity. We lack evidence to refute a potential negative effect of vitamin C on survival. Selenium tended to reduce mortality, but we need more research on this question. We confirm that trials with inadequate bias control overestimate intervention effects.[14,15,19,22-24] Our findings support and extend our previous findings regarding antioxidant supplements and increased mortality.[14,15]

Our review offers a number of strengths. It follows a published, peer-reviewed Cochrane protocol,[18] taking into consideration our previous findings in a systematic review on antioxidant supplements for preventing gastrointestinal cancers.[14,15] Our review represents a comprehensive review of the topic, including 68 randomized trials with almost a quarter of a million participants. This increases the precision

Table 4. Participants and Outcome Measures of Included Trials With Low Risk of Bias

Source	Participants and Inclusion Criteria	Outcome Measures	Type of Prevention
Greenberg et al,[37] 1990	History of BCC or SCC	Newly diagnosed BCC or SCC	Secondary
Murphy et al,[40] 1992	Elderly nursing home residents	Bacterial infections	Secondary
Li et al,[42] 1993	Esophageal dysplasia	Cancer incidence, cancer mortality, all-cause mortality	Secondary
Greenberg et al,[44] 1994	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary
Pike and Chandra,[45] 1995	Elderly individuals	Immune indices	Primary
Clark et al,[49] 1996	History of BCC or SCC	Incidence of SCC and BCC, cancer incidence, cancer mortality, all-cause mortality	Secondary
Hennekens et al,[50] 1996	Male physicians	Incidence of cancer and CVD and all-cause mortality	Primary
Richer,[52] 1996	Age-related macular degeneration	Age-related macular degeneration	Secondary
Stephens et al,[53] 1996	Coronary artery disease	Nonfatal myocardial infarction and cardiovascular death	Secondary
Moon et al,[55] 1997	History of BCC or SCC	Newly diagnosed SCC and BCC	Secondary
Girodon et al,[59] 1999	Institutionalized elderly patients	Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality	Secondary
Green et al,[60] 1999	History of BCC or SCC	Newly diagnosed SCC and BCC	Secondary
Boaz et al,[61] 2000	Stable hemodialysis patients with a documented medical history of CVD	Acute myocardial infarction (fatal and nonfatal), ischemic stroke, peripheral vascular disease, unstable angina, CVD mortality, all-cause mortality	Secondary
Correa et al,[62] 2000	Multifocal atrophic gastritis with or without intestinal metaplasia and dysplasia	Change of gastric precancerous lesions	Secondary
Jacobson et al,[63] 2000			Primary
AREDS,[64] 2001	Aged-related macular degeneration	Increase in nuclear, cortical or posterior subcapsular opacity grades, cataract surgery, loss of visual acuity	Secondary
Brown et al,[65] 2001	Coronary artery disease	Change in coronary stenosis, first cardiovascular event (death, myocardial infarction, stroke, or revascularization)	Secondary
Desnuelle et al,[66] 2001	Probable or definitive amyotrophic lateral sclerosis	Change in functional status, survival, bulbar function	Secondary
Chylack et al,[71] 2002	Cataract	Cataract progression	Secondary
Graat et al,[72] 2002	Elderly individuals	Acute respiratory tract infections	Primary
Heart Protection Study,[73] 2002	Coronary and other occlusive arterial disease or diabetes	Major coronary events, fatal and nonfatal vascular events, cancer, other morbidity	Secondary
Hodis et al,[74] 2002	Healthy individuals (serum LDL cholesterol >3.37 mmol/L)	Rate of change in the right distal common carotid artery intima-media thickness	Primary
Waters et al,[75] 2002	Coronary artery disease	Progression of coronary artery disease	Secondary
White et al,[76] 2002	Patients with Barrett esophagus on long-term acid suppression therapy	Prevention of potentially premalignant modifications to DNA in the human stomach	Secondary
Wluka et al,[77] 2002	Knee osteoarthritis	Change in cartilage volume	Secondary
Collins et al,[78] 2003	Patients with peripheral arterial disease	Walking ability and perceived quality of life	Secondary
Prince et al,[79] 2003	Primary biliary cirrhosis	Change in patient fatigue	Secondary
Salonen et al,[80] 2003	Healthy individuals (serum cholesterol >5 mmol/L)	Progression of carotid atherosclerosis	Primary
Virtamo et al[83] 2003	Male cigarette smokers	Lung cancer and other major cancers, all-cause and cause-specific mortality, incidence of other disease	Primary
Allsup et al,[84] 2004	Older institutionalized people	Response to influenza vaccine	Secondary
Goodman et al,[85] 2004	Cigarette smokers, former smokers, and workers exposed to asbestos	Lung cancer, other cancers, mortality	Primary
Hercberg et al,[86] 2004	General population	Incidence of cancer and CVD and all-cause mortality	Primary
Manuel-y-Keenoy et al,[87] 2004	Type 1 diabetic patients	Impact on lipids and peroxidation during statin treatment	Secondary
McNeil et al,[88] 2004	Early or no cataract	Age-related cataract	Secondary

(continued)

Table 4. Participants and Outcome Measures of Included Trials With Low Risk of Bias (cont)

Source	Participants and Inclusion Criteria	Outcome Measures	Type of Prevention
Meydani et al,[89] 2004	Elderly individuals	Respiratory tract infections, emergency department visits, hospitalization, and death	Primary
Mezey et al,[90] 2004	Alcoholic hepatitis	Clinical and laboratory parameters of liver function and markers of fibrogenesis	Secondary
Richer et al,[91] 2004	Age-related macular degeneration	Visual function	Secondary
Avenell et al,[92] 2005	Elderly individuals irrespective of chronic illness	Self-reported days of infection, use of health services, quality of life	Primary
Graf et al,[93] 2005	Probable or definitive amyotrophic lateral sclerosis	Survival	Secondary
Lee et al,[94] 2005	Female health professionals	Invasive cancer, fatal and nonfatal myocardial infarction, stroke, mortality	Primary
Limburg et al,[95] 2005	Patients with esophageal dysplasia	Change in histological grade of esophageal dysplasia	Secondary
Lonn et al,[96] 2005	History of CVD or diabetes in the presence of at least one additional cardiovascular risk factor	Cancer incidence, cancer deaths, major cardiovascular events, unstable angina, congestive heart failure, revascularization or amputation, all-cause mortality	Secondary
Marras et al,[97] 2005	Early Parkinson disease not requiring levodopa	Level of functional disability for initiation of levodopa therapy	Secondary
Mooney et al,[98] 2005	Cigarette smokers	Level of an intermediate cancer risk marker	Primary
Tam et al,[100] 2005	Systemic lupus erythematosus	Effects on markers of oxidative stress, antioxidant defense, and endothelial function	Secondary
Witte et al,[101] 2005	Stable chronic heart failure due to ischemic heart disease	Left ventricular function, levels of proinflammatory cytokines, quality of life	Secondary
Rayman et al,[102] 2006	General population	Mood, quality of life, plasma selenium levels	Primary

Abbreviations: BCC, basal cell carcinoma; CVD, cardiovascular disease; SCC, squamous cell carcinoma of the skin.
SI conversion: To convert cholesterol values to mg/dL, divide by 0.0259.

and power of our analyses.[17] Previous meta-analyses of preventive trials of antioxidant supplements have included less information (lung cancer, 4 trials with 109 394 participants[103]; cardiovascular diseases, 8 trials with 138 113 participants[104]; gastrointestinal cancers, 14 trials with 170 525 participants[14,15]; colorectal adenoma, 8 trials with 17 620 participants[19]; cancer or preinvasive lesions, 7 trials with 5112 participants[105]; and mortality, 19 trials with 135 967 participants[106]).

Previous studies either found no beneficial or harmful effect of the supplements[19,103-105,107] or reported a significantly increased mortality.[14,15,103,104,106] We conducted a thorough assessment of trial methodology following the recommendations of the Cochrane Collaboration[17] and findings of methodological studies.[22-24] More than two thirds of the included trials with more than 180 000 participants fall in the group of low-bias risk trials. This highlights the validity of our results.[22-24] Antioxidant supplements not only seem to be one of the most researched topics in the world, they also seem to be one of the most adequately researched clinical questions. Only a small proportion of trials use adequate methodologies.[108,109] Our meta-analyses had little trial heterogeneity. This increases the trustworthiness of our findings. Our analyses were robust to sensitivity analyses involving different imputations of mortality in the 0-event study groups. We gave full account of all 405 identified trials assessing the supplements having 0 events in both study groups. These trials were mostly assessing short-term supplement administration and surrogate outcome measures. Our results were robust to exploratory analyses adding an imagined trial with 20 000 participants and one death in each intervention group. Accordingly, the increased mortality does not seem to be an artifact created by exclusion of trials with 0 events in both study groups.[27,28] Furthermore, all-cause mortality should generally be connected with unbiased estimates.

A large number of unpublished trials on supplements may exist. Their results are more likely to have been either neutral or negative than to have shown beneficial effects.[110] Accordingly, our estimates of increased mortality of about 5% is likely to be conservative.

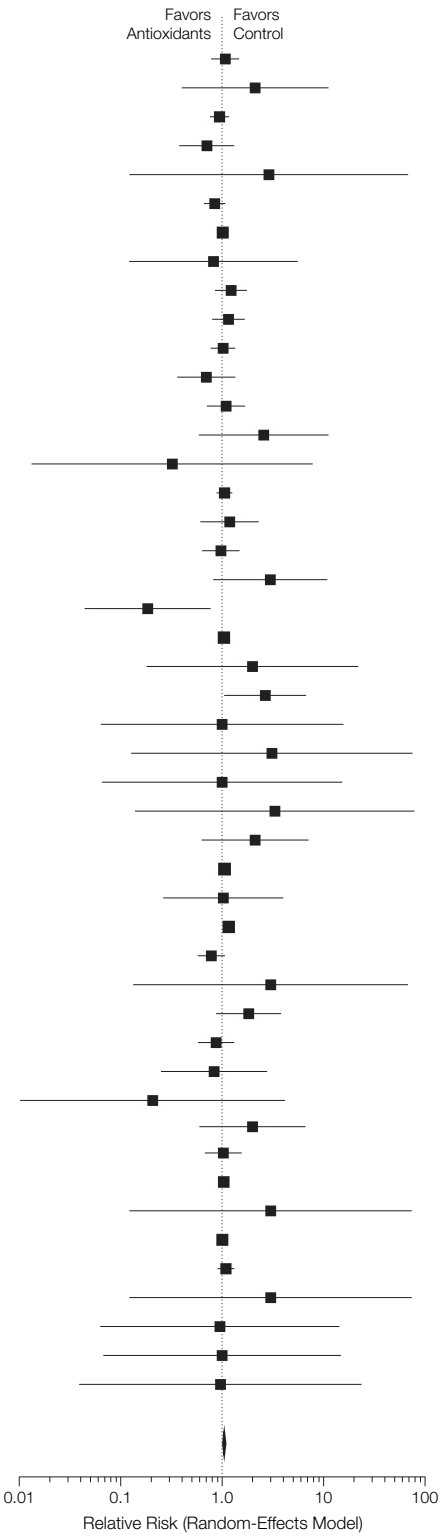
The choice of statistical model for performing meta-analysis of sparse data are important.[27,28] Because many methods are based on large sample approximations, they may be unsuitable when events are rare. Bradburn et al[28] found that no method gives completely unbiased estimates. At event rates below 1%, the Peto odds-ratio method appears to be the least biased and most powerful method when there is no substantial imbalance in treatment and control group sizes within trials, and treatment effects are not exceptionally large. Bradburn et al[28] also demonstrated that the Peto odds ratio works well up to event rates around 10%. The calculation

Figure 2. Intervention Effect of Antioxidant Supplements vs Placebo on Mortality in Trials With Low Risk of Bias

Source	Mortality: Antioxidants, No./Total	Mortality: Control, No./Total	Relative Risk (Random-Effects Model) (95% CI)
Greenberg et al,[37] 1990	79/913	72/892	1.07 (0.79-1.46)
Murphy et al,[40] 1992	4/53	2/56	2.11 (0.40-11.06)
Li et al,[42] 1993	157/1657	167/1661	0.94 (0.77-1.16)
Greenberg et al,[44] 1994	30/650	14/214	0.71 (0.38-1.31)
Pike et al,[45] 1995	1/24	0/23	2.88 (0.12-67.29)
Clark et al,[49] 1996	108/653	129/659	0.84 (0.67-1.07)
Hennekens et al,[50] 1996	979/11 036	968/11 035	1.01 (0.93-1.10)
Richer,[52] 1996	2/39	2/32	0.82 (0.12-5.50)
Stephens et al,[53] 1996	68/1035	52/967	1.22 (0.86-1.73)
Moon et al,[55] 1997	62/1157	53/1140	1.15 (0.81-1.65)
Girodon et al,[59] 1999	155/543	51/182	1.02 (0.78-1.33)
Green et al,[60] 1999	15/801	22/820	0.70 (0.36-1.34)
Boaz et al,[61] 2000	31/97	29/99	1.09 (0.72-1.66)
Correa et al,[62] 2000	16/739	2/237	2.57 (0.59-11.08)
Jacobson et al,[63] 2000	0/57	1/55	0.32 (0.01-7.74)
AREDS,[64] 2001	251/2370	240/2387	1.05 (0.89-1.25)
Brown et al,[65] 2001	17/84	13/76	1.18 (0.62-2.27)
Desnuelle et al,[66] 2001	34/144	35/144	0.97 (0.64-1.47)
Chylack et al,[71] 2002	9/149	3/148	2.98 (0.82-10.79)
Graat et al,[72] 2002	3/499	5/153	0.18 (0.04-0.76)
Heart Protection Study,[73] 2002	1446/10 269	1389/10 267	1.04 (0.97-1.11)
Hodis et al,[74] 2002	2/177	1/176	1.99 (0.18-21.73)
Waters et al,[75] 2002	16/212	6/211	2.65 (1.06-6.65)
White et al,[76] 2002	1/50	1/50	1.00 (0.06-15.55)
Wluka et al,[77] 2002	1/67	0/69	3.09 (0.13-74.50)
Collins et al,[78] 2003	1/26	1/26	1.00 (0.07-15.15)
Prince et al,[79] 2003	1/29	0/32	3.30 (0.14-77.95)
Salonen et al,[80] 2003	19/390	3/130	2.11 (0.63-7.02)
Virtamo et al,[83] 2003	8226/21 846	2605/7287	1.05 (1.02-1.09)
Allsup et al,[84] 2004	4/81	4/83	1.02 (0.27-3.96)
Goodman et al,[85] 2004	1855/9420	1509/8894	1.16 (1.09-1.23)
Hercberg et al,[86] 2004	76/6481	98/6536	0.78 (0.58-1.05)
Manuel-y-Keenoy et al,[87] 2004	1/12	0/12	3.00 (0.13-67.06)
McNeil et al,[88] 2004	20/595	11/598	1.83 (0.88-3.78)
Meydani et al,[89] 2004	39/311	44/306	0.87 (0.58-1.30)
Mezey et al,[90] 2004	4/25	5/26	0.83 (0.25-2.75)
Richer et al,[91] 2004	0/30	2/31	0.21 (0.01-4.13)
Avenell et al,[92] 2005	8/456	4/454	1.99 (0.60-6.57)
Graf et al,[93] 2005	31/83	28/77	1.03 (0.68-1.54)
Lee et al,[94] 2005	636/19 937	615/19 939	1.03 (0.93-1.15)
Limburg et al,[95] 2005	1/180	0/180	3.00 (0.12-73.16)
Lonn et al,[96] 2005	799/4761	801/4780	1.00 (0.92-1.10)
Marras et al,[97] 2005	154/399	142/401	1.09 (0.91-1.31)
Mooney et al,[98] 2005	1/142	0/142	3.00 (0.12-73.03)
Tam et al,[100] 2005	1/20	1/19	0.95 (0.06-14.13)
Witte et al,[101] 2005	1/16	1/16	1.00 (0.07-14.64)
Rayman et al,[102] 2006	1/380	0/121	0.96 (0.04-23.43)
Overall	15 366/99 095	9131/81 843	1.05 (1.02-1.08)

Test for Heterogeneity: $\chi^2_{46} = 49.47$; $P = .34$; $I^2 = 7.0\%$

Test for Overall Effect: $Z = 3.06$; $P = .002$



Error bars indicate 95% confidence intervals (CIs).

avoids addition of 0.5-event adjustments (or any other adjustment). When we applied Peto odds ratio, we found even stronger support for detrimental effects of the supplements (for all 68 trials: 1.05; 95% CI, 1.02-1.08; for the 47 low-bias risk trials: 1.07; 95% CI, 1.04-1.10; after exclusion of high-bias risk trials and selenium trials, for beta carotene: 1.09; 95% CI, 1.06-1.13; for vitamin A: 1.20; 95% CI, 1.12-1.29; for vitamin C: 1.06; 95% CI, 0.99-1.14; and for vitamin E: 1.06; 95% CI, 1.02-1.10).

Our systematic review has several limitations. As with all systematic reviews, our findings and interpretations are limited by the quality and quantity of available evidence on the effects of specific supplements on mortality. The examined populations varied. The effects of supplements were assessed in the general population or in patients with gastrointestinal, cardiovascular, neurological, skin, ocular, renal, endocrinological, and rheumatoid diseases. These populations mostly came from countries without overt deficiencies of specific supplements. Accordingly, we are unable to assess how antioxidant supplements affect mortality in populations with specific needs.

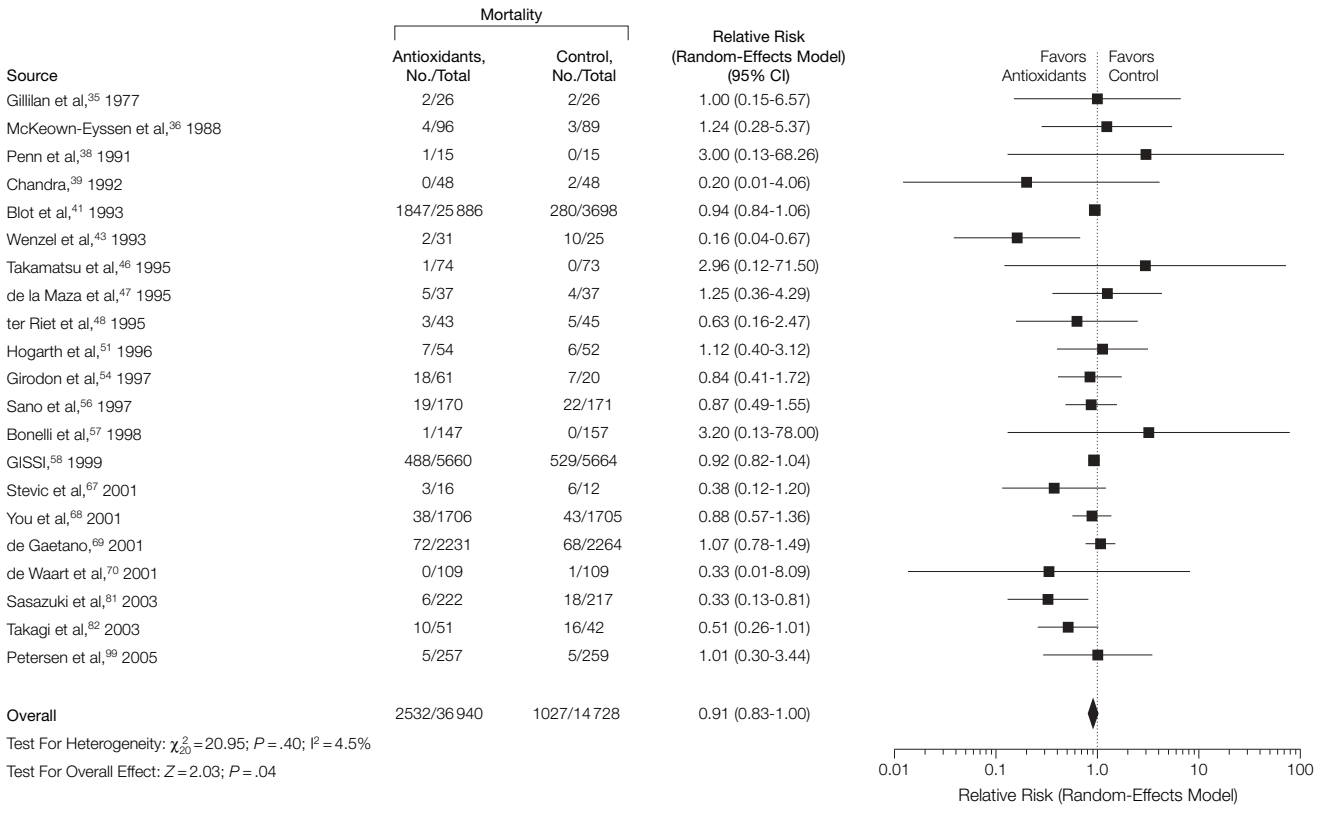
We have compared antioxidants with different properties, given at different doses and duration, singly or combined. We are aware of the potential risks in assessing the effects of different types of antioxidants together with different mechanisms of action, biotransformation, and bioavailability. There are pros[111-113] and cons[114] in the literature about vitamin A being antioxidant. We fully acknowledge this. Most trials assessed combinations of different supplements, which reflects the way supplements are marketed, sold, and taken by people.[7-10]

The methodological quality of some of the trials was assessed using the published reports, which may not reflect the actual design and bias risk of the trials. Some authors responded to our requests for further information.

All available nonenzymatic antioxidants work differently in the human body, and most of them exert effects that are nonantioxidant. We are not able to point to the specific biochemical mechanisms behind the detrimental effects. We found that trials examining the individual supplements singly were rare. It has been suggested that antioxidant supplements may show interdependency and may have effects only if given in combination.[115]

Most trials investigated the effects of supplements administered at higher doses than those commonly found in a balanced diet, and some of the trials used doses well above the recommended daily allowances and even

Figure 3. Intervention Effect of Antioxidant Supplements vs Placebo or No Intervention on Mortality in Trials With High Risk of Bias



Error bars indicate 95% confidence intervals (CIs).

Table 5. Intervention Effects of Different Antioxidant Supplements vs Placebo or No Intervention on Mortality

Experimental Antioxidant Supplements	References	No. of Trials	No. of Participants	Random-Effects Model Meta-analysis: Relative Risk (95% Confidence Interval)	Heterogeneity I^2, %
Beta carotene given singly	37, 44, 50, 60, 62, 83	6	40 977	1.06 (1.01-1.11)	5.4
Beta carotene given in combination with other antioxidant supplements	39, 41-44, 54, 59, 62-65, 68, 71-73, 79, 81, 83, 85, 86, 91, 94	22	139 572	1.01 (0.94-1.08)	55.6
Beta carotene given singly or in combination with other antioxidant supplements	37, 39, 41-44, 50, 54, 59, 60, 62-65, 68, 71-73, 79, 81, 83, 85, 86, 91, 94	25	172 811	1.01 (0.96-1.08)	52.2
Beta carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	37, 44, 50, 60, 62-64, 71, 73, 83, 85, 94	12	132 610	1.07 (1.02-1.11)	36.8
Vitamin A given singly	40, 55	2	2406	1.18 (0.84-1.68)	0
Vitamin A given in combination with other antioxidant supplements	38, 39, 41, 42, 45, 51, 52, 57, 72, 84, 85, 91, 92, 101	14	42 431	1.03 (0.90-1.19)	33.9
Vitamin A given singly or in combination with other antioxidant supplements	38-42, 45, 51, 52, 55, 57, 72, 84, 85, 91, 92, 101	16	44 837	1.05 (0.93-1.19)	26.1
Vitamin A given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	40, 45, 55, 85, 92	5	21 677	1.16 (1.10-1.24)	0
Vitamin E given singly	35, 46, 47, 53, 56, 58, 61, 66, 69, 70, 72, 74, 77, 78, 80, 82, 83, 87, 88, 90, 93, 96, 97, 99	24	47 007	1.02 (0.98-1.05)	0
Vitamin E given in combination with other antioxidant supplements	36, 38, 39, 41-45, 52, 54, 57, 59, 61, 63-65, 67-69, 71-73, 75, 76, 79, 80, 83, 84, 86, 89, 91, 92, 94, 98, 100, 101	36	128 737	1.01 (0.95-1.06)	17.2
Vitamin E given singly or in combination with other antioxidant supplements	35, 36, 38, 39, 41-47, 52-54, 56-59, 61, 63-65, 67-69, 71-73, 75, 76, 79, 80, 83, 84, 86, 89, 91, 92, 94, 98, 100, 101	55	163 510	1.01 (0.98-1.05)	2.8
Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	44, 45, 53, 61, 63, 64, 66, 71, 73-78, 80, 83, 88, 90, 92-98, 100	26	105 065	1.04 (1.01-1.07)	0
Vitamin C given singly	48, 62, 80	3	826	0.88 (0.32-2.42)	0
Vitamin C given in combination with other antioxidant supplements	36, 38, 39, 41-45, 51, 52, 54, 57, 59, 62-65, 68, 71-73, 75, 76, 79-81, 84, 86, 91, 92, 98, 100, 101	33	69 997	0.97 (0.88-1.07)	22.1
Vitamin C given singly or in combination with other antioxidant supplements	36, 38, 39, 41-45, 48, 51, 52, 54, 57, 59, 62-65, 68, 71-73, 75, 76, 79-81, 84, 86, 91, 92, 98, 100, 101	34	70 456	0.97 (0.88-1.06)	19.4
Vitamin C given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	44, 45, 62-64, 71, 73, 75, 76, 80, 92, 98, 100	13	29 275	1.06 (0.94-1.20)	10.3
Selenium given singly	49, 95, 102	3	1993	0.85 (0.68-1.07)	0
Selenium given in combination with other antioxidant supplements	39, 41-43, 52, 54, 57, 59, 65, 67, 68, 72, 79, 84, 86, 89, 91, 101	18	40 980	0.90 (0.81-1.01)	9.5
Selenium given singly or in combination with other antioxidant supplements	39, 41-43, 49, 52, 54, 57, 59, 65, 67, 68, 72, 79, 84, 86, 89, 91, 95, 101, 102	21	54 065	0.91 (0.84-0.99)	0
Selenium given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	42, 49, 52, 59, 65, 72, 79, 84, 86, 89, 91, 95, 101, 102	14	20 525	0.90 (0.80-1.02)	0

above the tolerable upper intake levels.[116,117] Our meta-regression analyses revealed significant effects of dose of beta carotene, vitamin A, and selenium on mortality. The duration of supplementation and follow-up differed among the trials. However, we found no significant effect of treatment duration on our results.

We only assessed all-cause mortality. We are not able to determine the cause of the increased mortality. It is likely that increased cancer and cardiovascular mortality are the main reasons for the increased all-cause mortality.[103,104] Further study of causes of mortality is needed. We fear that its assessment may be difficult due to varying definitions in the included trials. Our results extend previous reviews[14,15,19,103-107] and guidelines,[118-120] suggesting that antioxidant supplements may not be beneficial.

Beta carotene, administered singly or in combination with other antioxidants, significantly increased all-cause mortality. Recent studies have suggested that beta carotene may act as a cocarcinogen.[121,122] Vitamin A combined with other antioxidants significantly increased mortality. We found that vitamin E given singly or combined with 4 other antioxidants did not significantly influence mortality. After exclusion of high-bias risk trials, however, vitamin E given singly or combined significantly increased mortality. This is in agreement with a recent meta-analysis.[106] Dose of vitamin E was without significant effect on mortality in our analysis. The chance that vitamin E may benefit seems low.[123-125]

The trials in which vitamin C was applied singly or in different combinations with beta carotene, vitamin A, vitamin E, and selenium found no significant effect on mortality. According to the CIs, small beneficial or large harmful effects cannot be excluded. We calculated the proportion of participants who died in the trials in which participants took vitamin C alone. In the control group it was 0.019 and in the vitamin C group it was 0.017. With α set to .05 and power to .90, the required sample size would be 186 000 participants. We are still far from having examined a sufficient sample. Studies have demonstrated that vitamin C may act as both a pro-oxidant and as an antioxidant in vivo,[126,127] and trials should be monitored closely for harm.

Selenium given singly or in combination with other supplements seemed to significantly decrease mortality, but after exclusion of high-bias risk trials, the effect disappeared. Results of ongoing randomized trials with selenium will likely increase our understanding of the effects of selenium.[128]

Our findings contradict the findings of observational studies, claiming that antioxidants improve health.[129-132] Considering that 10% to 20% of the adult population (80-160 million people) in North America and Europe may consume the assessed supplements,[7-10] the public health consequences may be substantial. We are exposed to intense marketing with a contrary statement, which is also reflected by the high number of publications per included randomized trial found in the present review.

There are several possible explanations for the negative effect of antioxidant supplements on mortality. Although oxidative stress has a hypothesized role in the pathogenesis of many chronic diseases, it may be the consequence of pathological conditions.[133] By eliminating free radicals from our organism, we interfere with some essential defensive mechanisms like apoptosis, phagocytosis, and detoxification.[134-136] Antioxidant supplements are synthetic and not subjected to the same rigorous toxicity studies as other pharmaceutical agents.[137] Better understanding of mechanisms and actions of antioxidants in relation to a potential disease is needed.[138]

Because we examined only the influence of synthetic antioxidants, our findings should not be translated to potential effects of fruits and vegetables.

CONCLUSION

We did not find convincing evidence that antioxidant supplements have beneficial effects on mortality. Even more, beta carotene, vitamin A, and vitamin E seem to increase the risk of death. Further randomized trials are needed to establish the effects of vitamin C and selenium.

Author Contributions: Dr Bjelakovic had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bjelakovic, Nikolova, L. Gluud, Simonetti, C. Gluud.
Acquisition of data: Bjelakovic, Nikolova, C. Gluud.
Analysis and interpretation of data: Bjelakovic, Nikolova, L. Gluud, Simonetti, C. Gluud.
Drafting of the manuscript: Bjelakovic, Nikolova, L. Gluud, Simonetti, C. Gluud.
Critical revision of the manuscript for important intellectual content: Bjelakovic, Nikolova, L. Gluud, C. Gluud.
Statistical analysis: Bjelakovic, L. Gluud, Simonetti, C. Gluud.
Obtained funding: C. Gluud.
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Study supervision: Bjelakovic, C. Gluud.
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The habit of reading is the only one I know in which there is no alloy. It lasts when all other pleasures fade. It will be there to support you when all other resources are gone. . . . It will make your hours pleasant to you as long as you live.
—Anthony Trollope (1815-1882)

mal details. For measures that lack national standards, such as those developed by individual hospitals, more information is needed to make biases transparent. A framework[1] based on the Users' Guides to the Medical Literature[2] has been developed to help health care organizations evaluate the validity of their quality measures. Rather than provide guidance on a specific measure, the framework provides guidance on estimating and reporting biases in quality and safety measures. Such a framework can initiate discussion of data elements that should be reported for quality measures. It must be coupled with additional research to identify evidence-based quality standards, determine the best strategy for enforcing standardized reporting, and evaluate the costs and benefits of reporting.

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1. Pronovost PJ, Berenholtz SM, Needham DM. A framework for health care organizations to develop and evaluate a safety scorecard. *JAMA*. 2007;298(17):2063-2065.
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Correction: Inaccurate Classification and Information Reported in a Study of Statin Use and Sepsis in Patients With Chronic Kidney Disease

To the Editor: We are writing to inform the readers and editors of *JAMA* about errors in a study of statin use and sepsis in patients with chronic kidney disease published in the April 4, 2007, issue of *JAMA* and for which we were the principal investigators.[1] These errors were detected in the process of reviewing our coding algorithms for health care utilization data from which we identified sepsis events.

In our article, we had identified sepsis events by using validated *International Classification of Diseases, Ninth Revision (ICD-9)* billing codes (038.0-038.9, septicemia; 790.7, bacteremia) in United States Renal Data System administrative files. However, we inaccurately identified the source administrative files as hospitalization billing files only. The files we received actually included billing data from other treatment settings as well, including outpatient and skilled nursing facilities. Thus, the original 303 sepsis-related "hospitalizations" were incorrectly reported and are more accurately described by the broader term *sepsis events*, which include events in a hospital setting (146 events) and events in other settings (157 events).

With correction of the title and text of the article (see Correction in this issue) by changing "hospitalizations for sepsis" to "sepsis events," the results in the original manuscript are accurately described by this broader definition. The original analyses were correct for this definition of sepsis events, and the results of the published article remain unchanged, as does the conclusion that statin use was associated with a reduced risk of sepsis in this cohort.

On behalf of our coauthors, we apologize to the *JAMA* readers and editors for these errors in our study and for any confusion or inconvenience caused by publication of this incorrect information.

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1. Gupta R, Plantinga LC, Fink NE, et al. Statin use and hospitalization for sepsis in patients with chronic kidney disease. *JAMA*. 2007;297(13):1455-1464.

CORRECTIONS

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"22" and number of 2 × 2 × 2 trials, should have been "3." Accordingly, in Table 2 on page 847, the study design for "Lee et al,[94] 2005" should read "2 × 2 × 2."

On page 845 in the first paragraph of the "All Randomized Trials" subsection, the sentence that read "Heterogeneity was not significant (I^2=18.6%, *P*=.10)" should have read "Heterogeneity was significant (I^2=18.9%, *P*=.10)." In the following sentence that begins "Adjusted-rank correlation test (*P*=.08), but not the regression asymmetry test (*P*=.26), suggested the bias among trials," the respective *P* values should have read "(*P*=.09)" and "(*P*=.24)." In the second paragraph of the same subsection, the portion of the sentence that begins on page 845: "Univariate meta-regression analyses revealed significant influences of dose of beta carotene (RR, 1.004; 95% CI, 1.001-1.007; *P*=.012)," the *P* value should have been equal to ".014." In the latter part of the same sentence that falls on page 847, the *P* value for the dose of selenium that read "*P*=.002" should have read "*P*=.001." In the following part of the sentence, the upper confidence limit that read "1.29" should have read "1.30." In the third paragraph of the same subsection, on page 847, the *P* value for the "multivariate meta-regression" for dose of selenium that read "*P*=.005" should have read "*P*=.004," the lower confidence limit for low-bias risk trials that read "1.05" should have read "1.04," and the *P* value for the low-bias risk trials in the same sentence that read "*P*=.005" should have read "*P*=.006."

In the first paragraph of the "Bias Risk of Trials" subsection on page 847, the I^2 value that read "(I^2=7.0%)" should have read "(I^2=7.5%)." On the same page, in the first and second sentence of the subsection "Antioxidant Supplements Given Singly or in Combination" that read "Beta carotene used singly significantly increased mortality (Table 5). This effect was not significant when combined with other supplements" should have read "Beta carotene used singly or in combination with other antioxidant supplements did not significantly affect mortality."

In the first sentence of the last paragraph of the same subsection that falls in the third column on page 848 that read "Selenium given singly or in combination with other antioxidant supplements had no significant influence on mortality when analyzed separately (Table 5)" should have been divided into 2 sentences that should have read "Selenium given singly had no significant influence on mortality. Selenium given in combination with other antioxidant supplements significantly decreased mortality (Table 5)."

In Figure 2 on page 851, the denominators for the participant mortality ratios in the "Antioxidants" and "Control" columns were reversed for the "Green et al,[60] 1999" study. They should have read "15/820" and "22/801," respectively. The corresponding relative risk (RR) and 95% confidence interval (CI) that read "0.70 (0.36-1.34)" should have read "0.67 (0.35-1.27)." Also in Figure 2, for the "Brown et al,[65] 2001" study, the mortality ratio that read "17/84" for the "Antioxidant" and "13/76" for the "Control" columns, should have read "1/84" and "1/76," respectively. The corresponding RR and 95% CI that read "1.18 (0.62-2.27)" should have read "0.90 (0.06-14.2)." Accordingly, the numerators and denominators for total events that read "15 366/99 095" and "9131/81843" should have read "15 350/99 114" and "9119/81 824," respectively. Tests for heterogeneity that read "χ^2_{46}=49.47; *P*=.34; I^2=7.0%" should have read "χ^2_{46}=49.73; *P*=.33; I^2=7.5%." The test for overall effect that read "*Z*=3.06; *P*=.002" should have read "*Z*=2.98; *P*=.003."

In Table 5 on page 853, the RR (95% CI) in the "Beta carotene given singly" row that read "1.06 (1.01-1.11)" should have read "1.05 (1.00-1.11)" and the I^2 value that read "5.4" should have read "11.8." In the "Beta carotene given in combination with other antioxidant supplements" row, the I^2 value that read "55.6" should have read "55.5." In the "Beta carotene given singly or in combination with other antioxidant supplements" row, the CI range that read "(0.96-1.08)" should have read "(0.95-1.07)" and the I^2 value that read "52.2" should have read "52.5." In the "Beta carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials" row, the I^2 value that read 36.8" should have read "34.4" In the "Vitamin E given singly" row, the number of study participants that read "47 007" should have read "41 341." In the "Vitamin E given in combination with other antioxidant supplements" row, the RR that read "1.01" should have read "1.00" and the I^2 value that read "17.2" should have read "16.9." In the "Vitamin E given singly or in combination with other antioxidant supplements" row, the I^2 value that read "2.8" should have read "2.4." In the "Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials" row, the list of references should have included reference 87 and excluded 95.

In the "Vitamin C given in combination with other antioxident supplements" row, the lower confidence limit that read "0.88" should have read "0.87" and the I^2 value that read "22.1" should have read "21.7." In the "Vitamin C given singly or in combination with other antioxidant supplements" row, the RR that read "0.97" should have read "0.96" and the I^2 value that read "19.4" should have read "18.9." In the "Selenium given in combination with other antioxidant supplements" row, the upper confidence limit that read "1.01" should have read 1.00" and the I^2 value that read "9.5" should have read "6.3." In the "Selenium given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials" row, the upper confidence limit that read "1.02" should have read "1.01."

None of the data errors altered the overall results of the study.

mal details. For measures that lack national standards, such as those developed by individual hospitals, more information is needed to make biases transparent. A framework[1] based on the Users' Guides to the Medical Literature[2] has been developed to help health care organizations evaluate the validity of their quality measures. Rather than provide guidance on a specific measure, the framework provides guidance on estimating and reporting biases in quality and safety measures. Such a framework can initiate discussion of data elements that should be reported for quality measures. It must be coupled with additional research to identify evidence-based quality standards, determine the best strategy for enforcing standardized reporting, and evaluate the costs and benefits of reporting.

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1. Pronovost PJ, Berenholtz SM, Needham DM. A framework for health care organizations to develop and evaluate a safety scorecard. *JAMA*. 2007;298(17):2063-2065.
2. McAlister FA, Straus SE, Guyatt GH, Haynes RB; Evidence-Based Medicine Working Group. Users' guides to the medical literature, XX: integrating research evidence with the care of the individual patient. *JAMA*. 2000;283(21):2829-2836.

Correction: Inaccurate Classification and Information Reported in a Study of Statin Use and Sepsis in Patients With Chronic Kidney Disease

To the Editor: We are writing to inform the readers and editors of *JAMA* about errors in a study of statin use and sepsis in patients with chronic kidney disease published in the April 4, 2007, issue of *JAMA* and for which we were the principal investigators.[1] These errors were detected in the process of reviewing our coding algorithms for health care utilization data from which we identified sepsis events.

In our article, we had identified sepsis events by using validated *International Classification of Diseases, Ninth Revision (ICD-9)* billing codes (038.0-038.9, septicemia; 790.7, bacteremia) in United States Renal Data System administrative files. However, we inaccurately identified the source administrative files as hospitalization billing files only. The files we received actually included billing data from other treatment settings as well, including outpatient and skilled nursing facilities. Thus, the original 303 sepsis-related "hospitalizations" were incorrectly reported and are more accurately described by the broader term *sepsis events*, which include events in a hospital setting (146 events) and events in other settings (157 events).

With correction of the title and text of the article (see Correction in this issue) by changing "hospitalizations for sepsis" to "sepsis events," the results in the original manuscript are accurately described by this broader definition. The original analyses were correct for this definition of sepsis events, and the results of the published article remain unchanged, as does the conclusion that statin use was associated with a reduced risk of sepsis in this cohort.

On behalf of our coauthors, we apologize to the *JAMA* readers and editors for these errors in our study and for any confusion or inconvenience caused by publication of this incorrect information.

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