Dietary Antioxidants, Circulating Antioxidant Concentrations, Total Antioxidant Capacity, and Risk of All-Cause Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Observational Studies

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ABSTRACT

The associations of various dietary or circulating antioxidants with the risk of all-cause mortality in the general population have not been established yet. A systematic search was performed in PubMed and Scopus, from their inception up to October 2017. Prospective observational studies reporting risk estimates of all-cause mortality in relation to dietary intake and/or circulating concentrations of antioxidants were included. Random-effects meta-analyses were conducted. Forty-one prospective observational studies (total $n = 507,251$) involving 73,965 cases of all-cause mortality were included. The RRs of all-cause mortality for the highest compared with the lowest category of circulating antioxidant concentrations were as follows: total carotenes, 0.60 (95% CI: 0.46, 0.74); vitamin C, 0.61 (95% CI: 0.53, 0.69); selenium, 0.62 (95% CI: 0.45, 0.79); β-carotene, 0.63 (95% CI: 0.57, 0.70); α-carotene, 0.68 (95% CI: 0.58, 0.78); total carotenoids, 0.68 (95% CI: 0.56, 0.80); lycopene, 0.75 (95% CI: 0.54, 0.97); and α-tocopherol, 0.84 (95% CI: 0.77, 0.91). The RRs for dietary intakes were: total carotenoids, 0.76 (95% CI: 0.66, 0.85); total antioxidant capacity, 0.77 (95% CI: 0.73, 0.81); selenium, 0.79 (95% CI: 0.73, 0.85); α-carotene, 0.79 (95% CI: 0.63, 0.94); β-carotene, 0.82 (95% CI: 0.77, 0.86); vitamin C, 0.88 (95% CI: 0.83, 0.94); and total carotenes, 0.89 (95% CI: 0.81, 0.97). A nonsignificant inverse association was found for dietary zinc, zeaxanthin, lutein, and vitamin E. The nonlinear dose-response meta-analyses demonstrated a linear inverse association in the analyses of dietary β-carotene and total antioxidant capacity, as well as in the analyses of circulating α-carotene, β-carotene, selenium, vitamin C, and total carotenoids. The association appeared to be U-shaped in the analyses of serum lycopene and dietary vitamin C. The present study indicates that adherence to a diet with high antioxidant properties may reduce the risk of all-cause mortality. Our results confirm current recommendations that promote higher intake of antioxidant-rich foods such as fruit and vegetables.   *Adv Nutr* 2018;9:701–716.

Keywords: antioxidants, ascorbic acid, carotenoids, meta-analysis, mortality, prospective studies

Introduction

Noncommunicable diseases (NCDs) are the leading causes of death in the world (1). It has been estimated that ∼68% of all global deaths in 2012 were attributable to NCDs (2). Oxidative stress is defined as an imbalance between the production and detoxification of oxidants (3). It is considered to be one of the most important underlying causes of current major public health concerns including type 2 diabetes (4), cardiovascular disease (CVD) (5), and different types of cancers (6–8), and may possibly contribute to the aging process and its related disorders (9). In addition, it has recently been hypothesized that oxidative stress plays an important role in the development and progression of systemic inflammation (10), which is an important underlying cause of chronic diseases.

Adv Nutr 2018;9:701–716; doi: https://doi.org/10.1093/advances/nmy040.

Considering the evidence, it would appear that dietary antioxidants would be important in the prevention of NCDs. Extensive studies have indicated that adequate intakes of different dietary antioxidants such as vitamin C, vitamin E, carotenoids, and selenium are associated with a lower risk of chronic diseases (11–14). However, interventional studies have presented inconsistent evidence. Two recent meta-analyses of randomized controlled trials (RCTs) failed to show that supplementation with vitamin C or selenium can decrease the risk of CVD (15, 16), whereas 2 other meta-analyses showed that groups that received a supplement of antioxidants had an increased risk of all-cause mortality (17, 18). Another recent meta-regression analysis of 53 RCTs with low risk of bias suggested that high-dose supplementations with vitamin E (in a dose >15 mg/d), β-carotene (in a dose >9.6 mg/d), and possibly vitamin A (in a dose >800 µg/d) were associated with an increased risk of all-cause mortality (19).

To our knowledge, no systematic review and meta-analysis has summarized data for the relation between different dietary and/or circulating antioxidants such as vitamin C, vitamin E, total and individual carotenoids, selenium, and zinc and risk of all-cause mortality in the general population. Thus, the extent to which these antioxidants are associated with risk of all-cause mortality is still unclear. To our knowledge, only 1 meta-analysis of 13 prospective cohort studies indicated that a high dietary intake of β-carotene was associated with a 17% lower risk of all-cause mortality, and a high circulating concentration of β-carotene was associated with a 31% lower risk (20). However, the shape of the dose-response relation was not determined. In addition, there is no summarized evidence regarding other dietary and circulating antioxidants. Considering the fact that high-dose supplementations with some antioxidants have been associated with a higher risk of all-cause mortality (19), it may be useful to determine the shape of the dose-response relation within the usual dietary intakes or circulating concentrations.

In the present study, we used prospective observational studies to quantify the degree of the association of dietary intake and circulating concentration of various antioxidants and the total antioxidant capacity (TAC) with risk of all-cause mortality in the general population. Whenever possible, we also determined the shape of the dose-response relation.

Methods
We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to write the present systematic review and report the results (21).

Search strategy
We systematically searched the PubMed and Scopus search engines, with studies published from 1966 up to October 2017. The systematic search included combinations of keywords relevant to dietary antioxidant intake, circulating antioxidant concentration, mortality, and study design (**Supplemental Table 1**). The reference lists of all related articles

and reviews were also manually searched. The search was restricted to articles published in English.

Eligibility and study selection
Two independent authors (AJ and MSZ) reviewed the titles and abstracts of all studies identified. Prospective cohort, nested case-control, case-cohort, or prospective reports within RCT studies were obtained and included in this review if they: *1*) were conducted among adults aged ≥18 y; *2*) measured and reported baseline dietary intakes or circulating (either serum or plasma) concentrations of ≥1 of the following antioxidants: vitamin C, vitamin E, α-tocopherol, γ-tocopherol, vitamin A, selenium, zinc, retinol, and total and individual carotenoids including α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin, as well as indexes of TAC including ferric ion–reducing antioxidant power (FRAP), total radical-trapping antioxidant parameter (TRAP), and oxygen radical absorbance capacity and in ≥2 categories; *3*) reported the outcome of interest as all-cause mortality at follow-up; *4*) reported risk estimates (RR, HR, or OR) and the corresponding 95% CIs of all-cause mortality for each category of the aforementioned dietary/circulating antioxidants; and *5*) reported the number of cases and participants/noncases or person-years in each category of the aforementioned exposures, or reported sufficient information to allow estimation of those numbers. Studies that reported results per unit increment in any of the dietary/circulating antioxidants or per SD increment were also included. If several publications from the same study were identified, the study which defined exposures as categoric was selected for inclusion in both the linear and nonlinear dose-response meta-analyses. We did not include magnesium and flavonoids in the present meta-analysis because 2 recent dose-response meta-analyses completely evaluated the association between these 2 antioxidants and risk of all-cause mortality in the general population (22, 23). We excluded studies that were: *1*) conducted in children and adolescents; and *2*) conducted among patients with specific diseases such as hypertension, type 2 diabetes, or institutionalized elders.

Data extraction and assessment for study quality
Two independent authors (AJ and MP) reviewed the full text of selected eligible studies, and extracted the following information: first author's name, publication year, location, follow-up duration, number of participants/cases, mean age and/or age range, gender, exposures, exposure assessment method, covariates adjusted in the multivariate analyses, exposure levels, and reported risk estimates and the 95% CIs of all-cause mortality across categories of each dietary/circulating antioxidant. We included effect estimates based on models with the most comprehensive covariate adjustment. The Newcastle-Ottawa scale was used to assess the quality of the studies included, and those with ≥7 stars were considered high quality (24). Any discrepancies were resolved through discussion under supervision of a senior author (SS-B).

Data synthesis and statistical analysis

The RR and 95% CI were considered as the effect size of all studies. The reported ORs and HRs were considered as equal to RR. For the highest compared with the lowest category meta-analysis, the reported risk estimates for the highest compared with the lowest category of dietary/circulating antioxidants were combined with the use of the DerSimonian and Laird random-effects model (25). If studies reported results across sex or other subgroups separately, we combined subgroup-specific risk estimates using a fixed-effects model and included the combined effect size in meta-analysis. If studies reported risk estimates per SD increment in dietary/circulating antioxidants, we used the following method to translate per SD increment risk estimate to the high compared with the low RR: first, we calculated the differences between the median points of the highest and lowest categories of that dietary/circulating antioxidant in other studies included in the relevant analysis. Then, the mean difference between the medians of the highest and lowest categories was calculated. Finally, per-SD increment risk estimate was translated to per "calculated mean difference" and was included in the relevant analysis. If the exact amount of SD was not reported in the primary studies, we assumed the difference between the highest and lowest categories was SD × 2.18 (26). A meta-analysis was conducted separately for each dietary/circulating antioxidant when at least 2 studies reported risk estimate for the same exposure. In the analysis of TAC, we separately conducted the meta-analyses of FRAP and TRAP. However, we conducted in addition an analysis with the inclusion of studies with any definition of TAC including TRAP, FRAP, and other composite indexes. In that analysis, if a given study reported the results for >1 index of TAC, we combined index-specific risk estimates using a fixed-effects model and used the pooled effect size for meta-analysis. Between-studies heterogeneity was explored via Cochrane's Q test of heterogeneity and the I^2 statistic ($P < 0.05$) (27). Publication bias was assessed through the use of funnel plots asymmetry and tested by Egger's asymmetry test (28), and Begg's test ($P < 0.10$) (29), when the number of studies was ≥10. To test the potential effect of each study on pooled effect size, influence analysis was done with the stepwise exclusion of each study at a time. Subgroup analyses were done by some of the study and participant characteristics when there were sufficient studies.

We measured the linear dose-response relation using generalized least squares trend estimation, according to the methods developed by Greenland and colleagues (30, 31). This method needs distribution of cases and participants/noncases or person-years and adjusted risk estimates across different categories of each dietary/circulating antioxidant. Study-specific results were combined with the use of a random-effects model. The median point in each category of dietary/circulating antioxidants was assigned. If medians were not reported, we estimated approximate medians by using the midpoint of the lower and upper bounds. If the highest category was open-ended, we considered it to have the same widths as the closest category. If the lowest category was open-ended, we considered the lower bound as equal to 0. If only the mean of each category was reported, we considered it to be the same as the median (this method was used in 3 studies). If the median point of each category was reported per specific amount of energy intake (for example, per 1000 kcal) or per specific amount of another variable (e.g., serum cholesterol in the analysis of α-tocopherol), we recalculated the median point by dividing it by the reported mean or median energy intake or serum cholesterol of that category. If the number of participants/cases or person-years was not reported in the primary studies, we estimated them by dividing the total number of participants/cases or person-years by the number of categories, if the exposures were defined as quantiles (32). For studies in which the reference category was not the lowest one, we recalculated risk estimates taking the lowest category as reference, if the numbers of participants and cases across categories were reported (33).

A nonlinear dose-response meta-analysis was performed when there were sufficient eligible studies ($n \geq 3$). A potential nonlinear association was examined by modeling dietary/circulating antioxidant levels with the use of restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (34). A P value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to 0. All analyses were conducted with Stata software, version 13 (Stata Corp., College Station, TX). A P value <0.05 was considered statistically significant.

Results

Literature search and study characteristics

The systematic search identified 17,296 articles, plus 6 articles through hand searching (**Figure 1**). Of these, 2161 articles were duplicates and another 14,995 were not relevant and were eliminated on the basis of screening of the title and abstract. Of the remaining 146 articles, another 107 articles were excluded by full-text assessment; respective reasons for study exclusions are detailed in Figure 1. Finally, 39 articles were considered eligible for inclusion in the present meta-analysis (35–73). One article reported the results of the Shanghai Women's Health Study and the Shanghai Men's Health Study on dietary total carotenes, vitamin C, and vitamin E; these were regarded as 2 separate studies (73). Another article reported the results of those 2 cohorts on dietary selenium intake, which also were regarded as 2 separate studies (68). Three articles reported the results of the NHANES III study on different serum antioxidants (45, 59, 65), 2 articles reported the results of the Epidemiology of Vascular Ageing (EVA) study on plasma selenium and total carotenoids (36, 37), and another 2 articles reported the results of the InCHIANTI study on plasma selenium and total carotenoids (56, 57), which separately were included in the relevant analyses. Eventually, 41 prospective cohort studies, with a total of 507,251 participants and 73,965 cases of all-cause mortality, were included in the present meta-analysis.
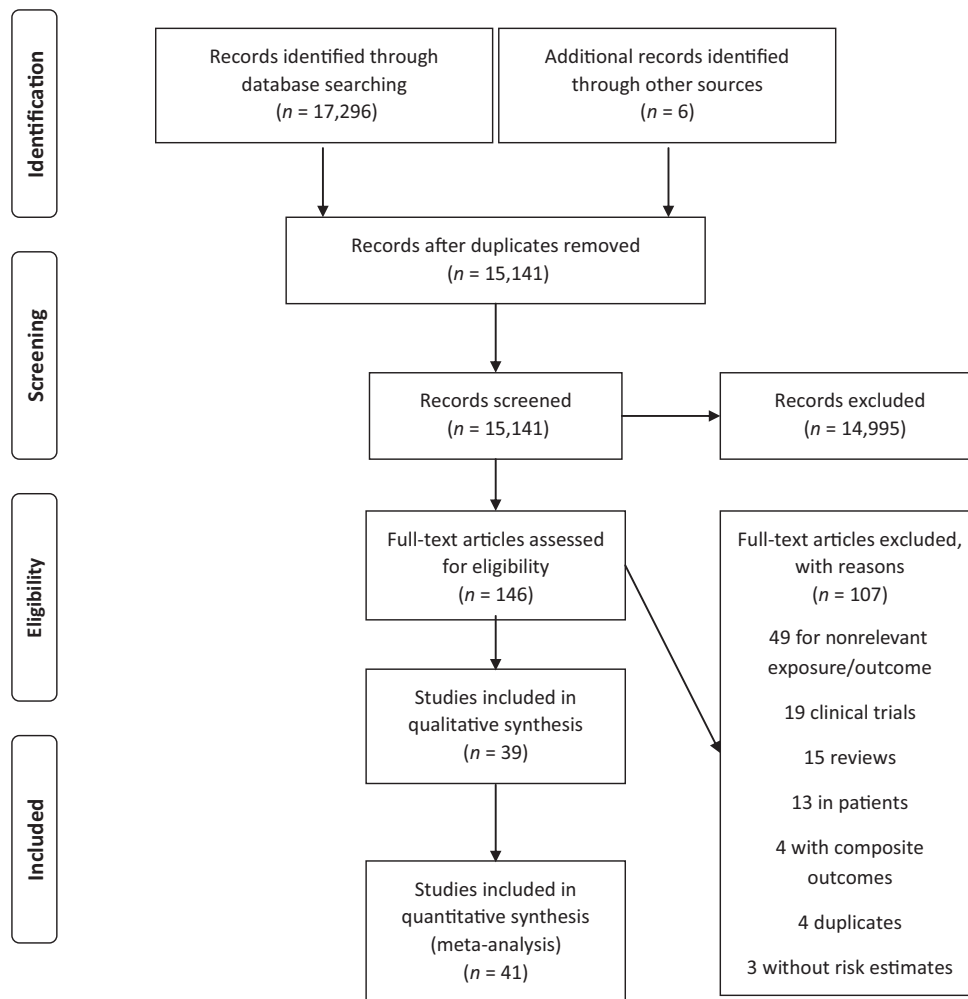
FIGURE 1 Search strategy to find the relevant articles for inclusion in meta-analysis of dietary/circulating antioxidants and risk of all-cause mortality.

Seventeen studies reported dietary antioxidant intakes (35, 38, 41, 42, 44, 48, 55, 61–63, 66–69, 73), 8 studies measured plasma concentrations (36, 37, 40, 46, 52, 53, 56, 57), 13 studies measured serum concentrations (45, 47, 49–51, 54, 58–60, 65, 70–72), and another 3 studies measured and reported both plasma concentrations and dietary intakes (39, 43, 64). Two studies conducted dietary history interview to assess dietary intakes (35, 62), 3 studies used food records (39, 64, 66), 2 studies used a 24-h dietary recall (42, 55), 1 study used a lifestyle questionnaire (41), and another 10 studies used a validated FFQ (38, 43, 44, 48, 61, 63, 67–69, 73). Four studies were prospective reports within the RCT studies (43, 46, 48, 72), 1 study was a case-cohort evaluation within a RCT study (71), and the remainder were prospective cohort studies. Follow-up duration ranged from 2 to 32 y. Eighteen studies were from Europe (35–40, 43, 48, 52–54, 56–58, 63, 67, 69, 72), 15 studies were from the United States (41, 42, 44–47, 49, 55, 59–62, 64, 65, 70), and 8 studies (6 articles) were from Asia (50, 51, 66, 68, 71, 73). All of the studies controlled for age. Most studies controlled for

BMI ($n = 32$), smoking ($n = 33$), and alcohol consumption ($n = 27$); and some of the studies adjusted for physical activity ($n = 19$) and energy intake ($n = 16$). However, only a few studies controlled for other dietary components (38, 42, 45, 61, 62, 64, 66, 68, 73) or vitamin/mineral supplementation (43, 45, 49, 53, 65, 68, 73). The general characteristics of the studies are presented in **Supplemental Table 2** and the number of participants/cases and reported risk estimates of all-cause mortality across categories of each dietary/circulating antioxidant in the primary studies are provided in **Supplemental Table 3**.

α-Carotene

Five studies (total $n = 21{,}522$) with 4796 cases of all-cause mortality were included in the analysis of circulating α-carotene (39, 50, 51, 59, 70). A significant inverse association was found for the highest compared with the lowest category of circulating α-carotene (RR: 0.68, 95% CI: 0.58, 0.78; $I^2 = 7.4\%$) (**Supplemental Figure 1**, Table 1), and for a 0.10-μmol/L increment in circulating concentration

TABLE 1 Dietary and circulating antioxidants and risk of all-cause mortality[1]

	Highest vs. lowest category meta-analysis				Dose-response meta-analysis				
	Studies, n	RR (95% CI)	I^2, %	$P_{heterogeneity}$	Dose, unit	Studies, n	RR (95% CI)	I^2, %	$P_{heterogeneity}$
Circulating biomarkers									
α-Carotene	5	0.68 (0.58, 0.78)	7	0.36	0.1 μmol/L	4	0.82 (0.75, 0.88)	21	0.28
β-Carotene	9	0.63 (0.57, 0.70)	0	0.47	0.1 μmol/L	6	0.96 (0.94, 0.98)	61	0.02
Lycopene	4	0.75 (0.54, 0.97)	67	0.03	0.1 μmol/L	3	0.97 (0.94, 1.00)	38	0.20
Total carotenoids	6	0.68 (0.56, 0.80)	21	0.27	0.5 μmol/L	5	0.93 (0.90, 0.95)	0	0.46
Vitamin C	7	0.61 (0.53, 0.69)	27	0.23	20.0 μmol/L	7	0.87 (0.83, 0.90)	55	0.04
α-Tocopherol	6	0.84 (0.77, 0.91)	18	0.30	10.0 μmol/L	4	0.94 (0.91, 0.98)	19	0.30
Selenium	7	0.62 (0.45, 0.79)	85	<0.001	0.2 μmol/L	6	0.89 (0.84, 0.95)	89	<0.001
Total carotenes	2	0.60 (0.46, 0.74)	0	0.95	—	—	—	—	—
Zeaxanthin/lutein	3	0.85 (0.74, 0.97)	0	0.42	—	—	—	—	—
Zinc	2	0.86 (0.77, 0.95)	0	0.61	2.0 μmol/L	2	0.88 (0.81, 0.95)	0	0.78
β-Cryptoxanthin	3	0.88 (0.79, 0.97)	0	0.98	0.1 μmol/L	2	0.94 (0.89, 0.99)	0	1.00
Vitamin E	2	0.92 (0.71, 1.12)	0	0.37	10.0 μmol/L	2	0.96 (0.89, 1.04)	36	0.21
Vitamin A	2	0.93 (0.78, 1.08)	0	0.67	0.5 μmol/L	2	0.97 (0.94, 1.00)	0	1.00
Retinol	2	1.14 (0.77, 1.51)	0	0.32	—	—	—	—	—
Dietary intakes									
β-Carotene	8	0.82 (0.77, 0.86)	0	0.61	1 mg/d	6	0.95 (0.92, 0.99)	64	0.01
Vitamin C	15	0.88 (0.83, 0.94)	66	<0.001	50 mg/d	11	0.96 (0.93, 0.98)	80	<0.001
Vitamin E	11	0.95 (0.90, 1.01)	49	0.03	5 mg/d	9	0.99 (0.98, 1.01)	3	0.41
Selenium	3	0.79 (0.73, 0.85)	0	0.95	10 μg/d	2	0.95 (0.93, 0.97)	0	1.00
Zinc	3	0.90 (0.63, 1.16)	48	0.14	—	—	—	—	—
FRAP	3	0.76 (0.69, 0.83)	0	0.73	5 mmol/d	3	0.84 (0.71, 0.97)	89	<0.001
TRAP	2	0.78 (0.71, 0.84)	0	0.92	5 mmol/d	2	0.73 (0.59, 0.88)	50.2	0.16
TAC	5	0.77 (0.73, 0.81)	0	0.80	—	—	—	—	—
Lycopene	2	0.72 (0.49, 0.95)	34	0.22	—	—	—	—	—
β-Cryptoxanthin	2	0.73 (0.58, 0.88)	0	0.76	—	—	—	—	—
Total carotenoids	3	0.76 (0.66, 0.85)	0	0.62	—	—	—	—	—
α-Carotene	2	0.79 (0.63, 0.94)	0	0.51	—	—	—	—	—
Lutein	2	0.83 (0.66, 1.00)	0	0.96	—	—	—	—	—
Total carotenes	2	0.89 (0.81, 0.97)	0	1.00	1 mg/d	2	0.97 (0.94, 0.99)	0	0.64
Zeaxanthin	2	0.94 (0.75, 1.13)	0	0.59	—	—	—	—	—

[1] FRAP, ferric ion–reducing antioxidant power; TAC, total antioxidant capacity; TRAP, total radical-trapping antioxidant parameter.

(RR: 0.82; 95% CI: 0.75, 0.88; $I^2 = 21.2\%$, $n = 4$ studies) (**Supplemental Figure 2**, Table 1). In the sensitivity analyses, removing each study at a time did not change the pooled RRs materially. However, when the NHANES III study was excluded (59), because the weight of this study was much bigger than other studies, the association changed to 0.77 (95% CI: 0.63, 0.91) in the high compared with low analysis, and to 0.87 (95% CI: 0.78, 0.97) in the linear dose-response meta-analysis. There was evidence of a nonlinear dose-response association (P for nonlinearity = 0.05, $n = 4$ studies) (**Figure 2**A).

Two studies (total $n = 48,805$) with 881 cases were included in the analysis of dietary α-carotene (35, 48), and the result showed that higher dietary α-carotene intake was significantly and inversely associated with risk of all-cause mortality (RR: 0.79; 95% CI: 0.63, 0.94; $I^2 = 0\%$) (Table 1).

β-Carotene

Nine studies (total $n = 30,334$) comprising 7500 cases were analyzed for the association between circulating β-carotene concentration and risk of all-cause mortality (39, 43, 45–47, 49–51, 54). The highest compared with the lowest category of circulating β-carotene concentration was

associated with a 37% lower risk (RR: 0.63; 95% CI: 0.57, 0.70; $I^2 = 0\%$) (**Supplemental Figure 3**, Table 1). In the sensitivity analysis, excluding each study did not substantially change the summary result (RR range: 0.60–0.65). A significant inverse association persisted across all subgroups but not among women, and appeared stronger in the subgroups with lower numbers of cases (<500 compared with ≥500 cases: RRs: 0.58 and 0.65, respectively), shorter follow-up durations (<10 compared with ≥10 y: RRs: 0.58 and 0.65, respectively), lower median circulating β-carotene concentrations (<350 compared with ≥350 nmol/L: RRs: 0.56 and 0.67, respectively), Asian studies, studies without adjustment for vitamin supplementation and main confounders, and among studies that measured serum concentration of β-carotene as compared with plasma concentration (RRs: 0.62 and 0.68, respectively) (**Supplemental Table 4**). All of the studies were of high quality (≥7 scores).

Eight studies used HPLC for measurement of circulating β-carotene, but 1 study (the asbestos-exposed insulators cohort study) did not report the method of assessment (47). The linear trend estimation indicated that a 0.10-μmol/L increment in circulating β-carotene concentration was associated with a 4% lower risk (RR: 0.96; 95% CI: 0.94, 0.98;
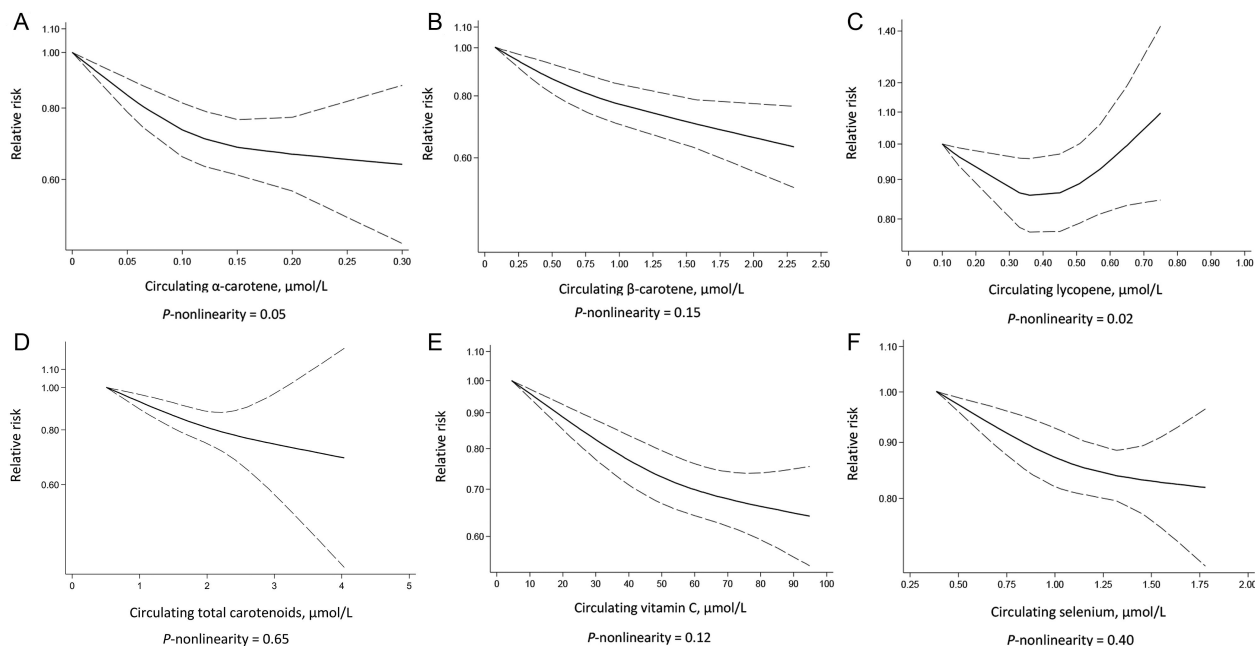
FIGURE 2 Dose-response associations of circulating antioxidant concentrations and risk of all-cause mortality. (A) α-Carotene, (B) β-carotene, (C) lycopene, (D) total carotenoids, (E) vitamin C, (F) selenium.

$I^2 = 61.4\%$, $P_{\text{heterogeneity}} = 0.02$; $n = 6$ studies) (**Supplemental Figure 4**, Table 1). In the sensitivity analysis removing each study in turn, the asbestos-exposed insulators cohort study (47) accounted for all of the observed heterogeneity (RR: 0.95; 95% CI: 0.94, 0.97; $I^2 = 0\%$), but none of the excluded studies changed the summary result materially (RR range: 0.95–0.98). There was a linear association between circulating β-carotene concentration and risk of all-cause mortality (P for nonlinearity $= 0.15$, $n = 5$ studies) (Figure 2B).

Eight studies (total $n = 151,723$) involving 12,305 cases assessed the association of dietary β-carotene and risk of all-cause mortality (35, 43, 44, 48, 62, 63, 67, 69). Those in the highest category of dietary β-carotene experienced a 18% lower risk of all-cause mortality as compared with the lowest intake (RR: 0.82; 95% CI: 0.77, 0.86; $I^2 = 0\%$) (**Supplemental Figure 5**, Table 1). Omitting each study in turn did not alter the summary result materially (RR range: 0.78–0.84). A significant inverse association persisted even after adjustment for energy intake, main confounders, multivitamin supplementation, and among high-quality studies; and appeared stronger among studies that used dietary history interview to assess dietary intakes as compared with FFQ (RRs: 0.78 and 0.82, respectively) (**Supplemental Table 5**). The RR of all-cause mortality for a 1-mg/d increment in dietary β-carotene intake was 0.95 (95% CI: 0.92, 0.99; $I^2 = 64.4\%$, $P_{\text{heterogeneity}} = 0.01$; $n = 6$ studies) (**Supplemental Figure 6**, Table 1). Sequential exclusion of each study did not change the pooled effect size (RR range: 0.94–0.96). However, when the Western Electric Study was excluded (62), the

heterogeneity disappeared and the association changed to 0.94 (95% CI: 0.91, 0.97; $I^2 = 0\%$). A subgroup analysis by dietary assessment method suggested a significant inverse association only among studies that conducted a dietary history interview (RR: 0.92; 95% CI: 0.87, 0.96; $n = 2$ studies, $I^2 = 0\%$), but not among studies that used an FFQ (RR: 0.98; 95% CI: 0.96, 1.00; $n = 4$ studies, $I^2 = 20.7\%$). The risk of all-cause mortality decreased linearly with increasing dietary β-carotene intake (P for nonlinearity $= 0.07$, $n = 5$ studies) (**Figure 3**A).

Lycopene
Four studies (total $n = 18,187$) with 3713 cases reported sufficient information for the association between circulating lycopene concentration and risk of all-cause mortality (39, 50, 51, 65). The RRs for the highest compared with the lowest category and for a 0.10-µmol/L increment in circulating lycopene concentration were 0.75 (95% CI: 0.54, 0.97; $I^2 = 67.3\%$, $P_{\text{heterogeneity}} = 0.03$) (**Supplemental Figure 7**, Table 1) and 0.97 (95% CI: 0.94, 1.00; $I^2 = 37.5\%$; $n = 3$ studies) (**Supplemental Figure 8**, Table 1), respectively. A dose-response meta-analysis suggested a U-shaped association between circulating lycopene concentration and risk of all-cause mortality (P for nonlinearity $= 0.02$, $n = 3$ studies) (Figure 2C).

Two studies (total $n = 48,085$) with 881 cases were included in the analysis of dietary lycopene (35, 48). The highest compared with the lowest category of dietary lycopene intake was associated with a 28% lower risk (RR: 0.72; 95% CI: 0.49, 0.95; $I^2 = 34.0\%$) (Table 1).
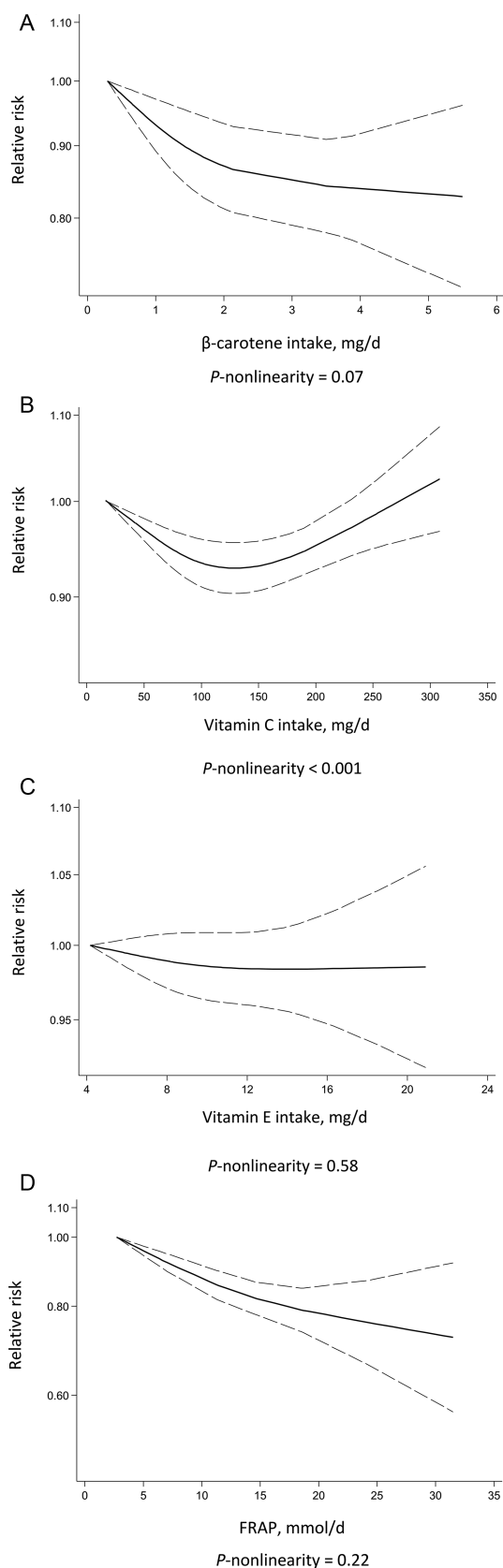
FIGURE 3 Dose-response associations of dietary antioxidants and risk of all-cause mortality. (A) *β*-Carotene, (B) vitamin C, (C) vitamin E, (D) FRAP. FRAP; ferric ion–reducing antioxidant power.

Total carotenes

Total carotenes generally are defined as the sum of *α*-carotene, *β*-carotene, and lycopene. Two studies (total *n* = 3632) with 534 cases were included in the analysis of circulating total carotenes (40, 50), and another 2 Chinese cohort studies (total *n* = 134,358) with 10,079 cases were included in the analysis of dietary total carotenes (73). The RRs for the higher circulating concentration, higher dietary intake, and for a 1-mg/d increment in dietary total intake of carotenes were 0.60 (95% CI: 0.46, 0.74; $I^2 = 0\%$), 0.89 (95% CI: 0.81, 0.97; $I^2 = 0\%$), and 0.97 (95% CI: 0.94, 0.99; $I^2 = 0\%$), respectively (Table 1).

Xanthophylls

Xanthophylls generally consist of lutein, *β*-cryptoxanthin, and zeaxanthin. Three cohorts were included in the analysis of circulating *β*-cryptoxanthin (39, 50, 65) and 2 studies evaluated the association of dietary *β*-cryptoxanthin and risk of all-cause mortality (35, 48). The results showed that the highest compared with the lowest categories of circulating and dietary *β*-cryptoxanthin were associated with a 12% and a 27% significant lower risk of all-cause mortality, respectively (Table 1). Also, a 0.10-μmol/L increment in circulating *β*-cryptoxanthin concentration was associated with a 6% lower risk (RR: 0.94; 95% CI: 0.89, 0.98; $I^2 = 0\%$). Summary results for the other dietary and circulating xanthophylls are presented in Table 1.

Total carotenoids

Total carotenoids are considered as the sum of total carotenes and xanthophylls. Six studies (total *n* = 19,215) with 3908 cases reported data for the relation of circulating total carotenoids and all-cause mortality risk (37, 50, 57, 64, 65, 70). A significant inverse association was found for the highest compared with the lowest category of circulating total carotenoids (RR: 0.68; 95% CI: 0.56, 0.80; $I^2 = 21.1\%$) (**Supplemental Figure 9**, Table 1), and for a 0.50-μmol/L increment in circulating concentration (RR: 0.93; 95% CI: 0.90, 0.95; $I^2 = 0\%$) (**Supplemental Figure 10**, Table 1). The risk of all-cause mortality decreased linearly along with the increase in circulating total carotenoid concentration (*P* for nonlinearity = 0.65, *n* = 5 studies) (Figure 2D). In the analysis of dietary total carotenoids (35, 39, 64), summary results suggested that the risk of all-cause mortality decreased by 24% when the highest and lowest categories of dietary total carotenoids were compared (RR: 0.76; 95% CI: 0.66, 0.85; $I^2 = 0\%$) (**Supplemental Figure 11**, Table 1).

Vitamin C

Seven studies (total *n* = 45,868) with 7398 cases were included in the analysis of circulating vitamin C (39, 43, 45, 52, 53, 60, 64). The RR of all-cause mortality for the highest compared with the lowest category of circulating vitamin C concentration was 0.61 (95% CI: 0.53, 0.69; $I^2 = 26.5\%$) (**Supplemental Figure 12**, Table 1). In the sensitivity analysis, sequential exclusion of each study did not alter the result materially (RR range: 0.58–0.64). In the subgroup analyses, a

significant inverse association persisted across all subgroups and appeared stronger among European studies than among US ones (RRs: 0.54 and 0.70, respectively), studies with lower-quality scores (<7 compared with ≥7 scores: RRs: 0.50 and 0.65, respectively), higher median vitamin C concentrations (≥50 compared with <50 μmol/L: RRs: 0.58 and 0.63, respectively), shorter follow-up durations (<10 compared with ≥10 y: RRs: 0.54 and 0.72, respectively), lower numbers of cases (<1000 compared with ≥1000 cases: RRs: 0.51 and 0.66, respectively), studies which measured serum vitamin C concentration as compared with plasma concentration (RRs: 0.54 and 0.72, respectively), studies that used methods other than HPLC to assess circulatory concentrations (RRs: 0.58 and 0.63, respectively), those with older participants (≥60 compared with <60 y: RRs: 0.56 and 0.64, respectively), and among studies without adjustment for main confounders (**Supplemental Table 6**).

A dose-response meta-analysis indicated that a 20-μmol/L increment in circulating vitamin C concentration was associated a 13% lower risk (RR: 0.87; 95% CI: 0.83, 0.90; $I^2 = 55.2\%$, $P_{\text{heterogeneity}} = 0.04$) (**Supplemental Figure 13**, Table 1). Omitting each study at a time did not change the summary result (RR range: 0.86–0.88). The subgroup analyses suggested that study quality, baseline mean age, and adjustment for main confounders were potential sources of the heterogeneity (**Supplemental Table 7**). There was a linear association between increasing circulating vitamin C concentration and decreasing risk of all-cause mortality (P for nonlinearity = 0.12, n = 6 studies) (Figure 2E).

Fifteen studies (total n = 315,534) involving 38,534 cases were included in the analysis of dietary vitamin C (35, 39, 41–44, 48, 61–64, 67, 69, 73). The RR of all-cause mortality associated with the highest compared with the lowest category of dietary vitamin C intake was 0.88 (95% CI: 0.83, 0.94; $I^2 = 66.1\%$, $P_{\text{heterogeneity}} < 0.001$) (**Supplemental Figure 14**, Table 1). Sequential exclusion of each study at a time had minimal effect on the summary result (RR range: 0.86–0.88). A significant inverse association persisted across most of the subgroups, and remained significant even after adjustment for main confounding variables including BMI, physical activity, energy intake, and smoking status (**Supplemental Table 8**). A significant inverse association appeared stronger among studies that used dietary records or dietary history interview as compared with FFQ (RRs: 0.69, 0.73, and 0.93, respectively). The subgroup analyses suggested region, dietary assessment method, and adjustment for BMI as the potential sources of the heterogeneity. A separate analysis yielded a nonsignificant association across either sex (Supplemental Table 8).

A 50-mg/d increment in dietary vitamin C intake was associated with a 4% lower risk (RR: 0.96; 95% CI: 0.93, 0.98; $I^2 = 79.7\%$, $P_{\text{heterogeneity}} < 0.001$; n = 11 studies) (**Supplemental Figure 15**, Table 1). A significant inverse association persisted when each study was sequentially excluded from the pooled analysis (RR range: 0.94–0.96). None of the excluded studies accounted for the heterogeneity in the data. The subgroup analyses suggested region, number

of cases, study quality, follow-up duration, dietary assessment method, and adjustment for BMI and smoking as the potential sources of the heterogeneity (**Supplemental Table 9**). A dose-response meta-analysis suggested a U-shaped association between dietary vitamin C intake and risk of all-cause mortality with a nadir at intake of ~125 mg/d, which remained protective up to an intake of ~225 mg/d (P for nonlinearity <0.001; n = 8 studies) (Figure 3B).

Vitamin E

Six studies (total n = 37,199) with 15,525 cases were included in the analysis of circulating α-tocopherol (39, 40, 43, 50, 54, 72). The meta-analysis suggested a significant inverse association for the highest compared with the lowest category of circulating α-tocopherol concentration (RR: 0.84; 95% CI: 0.77, 0.91; $I^2 = 18.3\%$) (**Supplemental Figure 16**, Table 1), and for a 10-μmol/L increment in circulating concentration (RR: 0.94; 95% CI: 0.91, 0.98; $I^2 = 18.6\%$, n = 4 studies) (**Supplemental Figure 17**, Table 1). However, the weight of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was much bigger than other studies (72), and when this study was excluded from the pooled analyses, the association became nonsignificant in the high compared with low analysis (RR: 0.89; 95% CI: 0.76, 1.02) and in the linear dose-response analysis (RR: 0.99; 95% CI: 0.92, 1.05).

Two studies (total n = 16,755) with 4442 cases reported data on circulating vitamin E (45, 64), but the meta-analysis indicated that there was not a significant inverse association between circulating vitamin E concentration and risk of all-cause mortality (RR: 0.92; 95% CI: 0.71, 1.12; $I^2 = 0\%$) (Table 1).

Eleven studies (total n = 386,854) with 22,823 cases were analyzed for the relation between dietary vitamin E intake and risk of all-cause mortality (35, 39, 43, 44, 48, 63, 64, 67, 69, 73). The highest compared with the lowest category of dietary vitamin E intake was not associated with risk of all-cause mortality (RR: 0.95; 95% CI: 0.90, 1.01; $I^2 = 48.8\%$, $P_{\text{heterogeneity}} = 0.03$) (**Supplemental Figure 18**, Table 1). The association did not reach statistical significance when each study was sequentially excluded from the pooled analysis. A nonsignificant association persisted across all subgroups, as well as among either sex (**Supplemental Table 10**). The subgroup analyses yielded number of cases, region, study quality, follow-up duration, and adjustment for energy intake and vitamin supplementation as the potential sources of the heterogeneity (Supplemental Table 10). A 5-mg/d increment in dietary vitamin E intake was not associated with risk of all-cause mortality (RR: 0.99; 95% CI: 0.98, 1.01; $I^2 = 2.9\%$, n = 9 studies) (**Supplemental Figure 19**, Table 1). A nonsignificant association persisted with the stepwise exclusion of each study at a time. A dose-response meta-analysis demonstrated a little change in the risk with increasing dietary vitamin E intake (P for nonlinearity = 0.58, n = 6 studies) (Figure 3C).

Vitamin A and retinol

Two studies (total n = 17,062) with 4942 cases (39, 45) and 2 studies (total n = 3584) with 410 cases (43, 50) were

included in the analyses of circulating vitamin A and retinol, respectively. The meta-analysis indicated that none of the aforementioned antioxidants were associated with risk of all-cause mortality (Table 1).

Selenium

Seven studies (total $n = 23{,}516$) with 6623 cases were included in the analysis of circulating selenium (36, 39, 45, 54, 56, 70, 71). The RR of all-cause mortality for the highest compared with the lowest category of circulating selenium concentration was 0.62 (95% CI: 0.45, 0.79; $I^2 = 84.4\%$, $P_{\text{heterogeneity}} < 0.001$) (**Supplemental Figure 20**, Table 1). Sequential exclusion of each study minimally altered the association (RR range: 0.58–0.67). None of the excluded studies explained the heterogeneity in the data. In the subgroup analyses, a stronger inverse association was found among European studies as compared with US ones (RRs: 0.59 and 0.72, respectively), studies with lower numbers of cases (<500 compared with ≥500: RRs: 0.50 and 0.70, respectively), shorter follow-up durations (<10 compared with ≥10 y: RRs: 0.50 and 0.70, respectively), those without adjustment for BMI and physical activity, studies with a mean age of >60 compared with <60 y (RRs: 0.46 and 0.79, respectively), those with higher median selenium concentrations (≥1 compared with <1 μmol/L: RRs: 0.52 and 0.76, respectively), and studies that measured plasma concentration of selenium as compared with serum concentration (RRs: 0.41 and 0.76, respectively) (**Supplemental Table 11**). The subgroup analyses suggested that region, number of cases, follow-up duration, and adjustment for main confounders were potential sources of heterogeneity.

A dose-response meta-analysis indicated that the risk of all-cause mortality decreased by 11% for a 0.20-μmol/L increment in circulating selenium concentration (RR: 0.89; 95% CI: 0.84, 0.95; $I^2 = 89.2\%$, $P_{\text{heterogeneity}} < 0.001$; $n = 6$ studies) (**Supplemental Figure 21**, Table 1). A significant inverse association persisted when each study was sequentially excluded from the pooled analysis (RR range: 0.86–0.93). The risk of all-cause mortality decreased in a linear fashion with increasing circulating selenium concentration (P for nonlinearity = 0.40, $n = 5$ studies) (Figure 2F).

Three studies (total $n = 141{,}404$) with 10,285 cases were included in the analysis of dietary selenium (48, 68). Summary results for the highest compared with the lowest category and for a 10-μg/d increment in dietary selenium intake were 0.79 (95% CI: 0.73, 0.85; $I^2 = 0\%$) (**Supplemental Figure 22**, Table 1) and 0.95 (95% CI: 0.93, 0.97; $I^2 = 0\%$) (Table 1), respectively.

Zinc

Three studies (total $n = 11{,}353$) with 1220 cases (39, 48, 66) and 2 studies (total $n = 4664$) with 742 cases (39, 58) were included in the analyses of dietary and circulating zinc, respectively. Higher dietary intake of zinc was not associated with risk of all-cause mortality (RR: 0.90; 95% CI: 0.63, 1.16; $I^2 = 48.5\%$) (**Supplemental Figure 23**, Table 1), whereas the highest compared with the lowest category of circulating zinc concentration and a 2-μmol/L increment in circulating zinc concentration were associated with a 14% and a 12% significant lower risk of all-cause mortality, respectively (Table 1).

TAC

Three studies (total $n = 121{,}317$) with 5500 cases (35, 38, 48) and 2 studies (total $n = 113{,}870$) with 5181 cases (35, 38) were included in the analyses of FRAP and TRAP, respectively. The highest compared with the lowest categories of FRAP and TRAP were associated with a 24% and a 22% significant lower risk of all-cause mortality, respectively (**Supplemental Figure 24**, Table 1). The RRs for a 5-mmol/d increment in FRAP and TRAP were 0.84 (95% CI: 0.71, 0.97; $I^2 = 88.7\%$, $P_{\text{heterogeneity}} < 0.001$) and 0.73 (95% CI: 0.59, 0.88; $I^2 = 50.2\%$), respectively (**Supplemental Figure 25**, Table 1). The risk of all-cause mortality decreased linearly along with the increase in FRAP (P for nonlinearity = 0.22, $n = 3$ studies) (Figure 3D).

We also conducted an additional analysis by using the studies that defined any composite index as TAC. Five studies (total $n = 146{,}468$) with 13,179 cases were considered eligible for inclusion in this analysis (35, 38, 48, 55, 62). The highest compared with the lowest category of TAC was associated with a 23% lower risk of all-cause mortality (RR: 0.77; 95% CI: 0.73, 0.81; $I^2 = 0\%$) (**Supplemental Figure 26**, Table 1).

Publication bias

We tested the potential small-study effects when there were sufficient studies ($n > 10$). In the analysis of dietary vitamin C ($n = 15$ studies), there was evidence of publication bias with Egger's test ($P = 0.001$) but not with Begg's test ($P = 0.30$) (**Supplemental Figure 27**). In the analysis of dietary vitamin E ($n = 11$ studies), no evidence of bias was found with both Begg's test ($P = 0.88$) and Egger's test ($P = 0.46$) (**Supplemental Figure 28**).

Discussion

This study presents a relatively comprehensive review of the existing evidence on the association of various dietary and circulating antioxidants with risk of all-cause mortality, and indicates that higher circulating concentrations of most antioxidants, except retinol, vitamin A, and vitamin E, are significantly and inversely associated with risk of all-cause mortality. All dietary antioxidants except lutein, zeaxanthin, zinc, and vitamin E were significantly and inversely associated with risk of all-cause mortality. The nonlinear dose-response meta-analyses demonstrated that the risk of all-cause mortality decreased linearly with increasing β-carotene intake and FRAP, as well as with increasing circulating concentrations of α-carotene, β-carotene, total carotenoids, vitamin C, and selenium. The analyses of circulating lycopene and dietary vitamin C demonstrated that the dose-response association appeared to be U-shaped.

In the present study, we comprehensively evaluated the benefits of different dietary/circulating carotenoids such as α-carotene, β-carotene, lycopene, xanthophylls, total

carotenes, and total carotenoids in relation to the risk of all-cause mortality. A recent meta-regression analysis of 53 RCTs indicated that a high-dose supplementation with β-carotene was associated with a higher risk of all-cause mortality (19). In the present review, we tested the association across almost all major dietary and circulating carotenoids. The analyses of dietary β-carotene, and circulating α-carotene, β-carotene, and total carotenoids clearly indicated that the risk of all-cause mortality decreased linearly within the usual dietary intake or circulating concentration of carotenoids.

The antioxidant properties of dietary carotenoids, especially β-carotene, have seen a great deal of interest in the past. β-Carotene has strong antioxidant activity (74), and therefore, by decreasing the oxidation of LDL and subsequent risk of developing and progression of atherosclerosis (75), may be associated with a lower risk of CVD (76, 77). It is a provitamin A carotenoid, and therefore, contributes indirectly in the vital functions of vitamin A in the body including normal organogenesis, tissue differentiation, and immune function (78). Also, by enhancing cell-mediated immune responses (79), it has protective effects against carcinogenesis. In addition, β-carotene and other dietary carotenoids, through their functions against oxidative stress, are associated with a lower risk of chronic diseases (80).

α-Carotene, a provitamin A carotenoid and one of the most abundant dietary carotenoids, is mainly found in green and yellow vegetables and has been shown to have substantial anticarcinogenesis properties (81–83). An in vivo study suggested that the properties of α-carotene in inhibiting the proliferation of human neuroblastoma cells were 10 times more effective than β-carotene (82). It has antimetastatic activities (84, 85), is associated with lung function (86), and is inversely associated with inflammation and oxidative stress (87). It has also been suggested that α-carotene–rich foods have greater bioavailability than β-carotene–rich foods in Western diets and, therefore, may more effectively contribute in formation of vitamin A (88).

The nonlinear dose-response meta-analysis of lycopene suggested that there was a U-shaped association between circulating lycopene concentration and all-cause mortality risk. Lycopene is a nonprovitamin A carotenoid that has strong antioxidant, antiproliferative, and prodifferentiation activities (89), as well as direct anti-inflammatory properties (90, 91). Lycopene availability is high from tomato sauce and cooked and processed tomato as compared with raw tomato. A cross-sectional evaluation of 3089 adults within the European Prospective Investigation into Nutrition and Cancer (EPIC) study in 10 European countries indicated that plasma lycopene concentration was strongly correlated with an intake of tomato sauce and with the sum of all cooked and processed tomato products compared with raw tomato (92). Thus, it is possible that a high circulating lycopene concentration may reflect high intakes of tomato sauce, ketchup, and other processed tomato products, which may indicate a high intake of unhealthy foods such as fast foods. This hypothesis, at least in part, might explain the observed U-shaped association in the analysis of circulating lycopene.

In agreement with this hypothesis, a large prospective cohort study in Spain, where tomatoes were mainly consumed in their raw state (92), found that the risk of all-cause mortality decreased linearly with an increase in dietary lycopene intake (35). However, the number of studies in the analysis of circulating lycopene is too low ($n = 3$ studies) to obtain a definitive conclusion. In addition, foods containing cooked and processed tomato products are not always unhealthy foods; therefore, this hypothesis must be treated with caution. More observational studies may be needed to examine the association between different types of dietary tomatoes and the risk of diseases.

We observed an unexpected U-shaped association in the analysis of dietary vitamin C, with a nadir at an intake of ~125 mg/d. This is lower than the cutoff level of 200 mg/d, which is the dose at which plasma is relatively saturated with vitamin C (~60 µmol/L) (93, 94); however, this level is higher than the current dietary recommendations for men (90 mg/d) and women (75 mg/d). The protective effects remained significant until an intake of ~225 mg/d. Vitamin C has powerful antioxidant properties; can inhibit the oxidation of lipids, proteins, and DNA; and has protective effects against endothelial dysfunction (94). It also has some immunomodulatory properties, and plays a vital role in the retrieval and regeneration of other antioxidants in the body (95). Of the 8 studies (7 articles) that were included in the nonlinear dose-response meta-analysis (35, 44, 61, 62, 67, 69, 73), 6 studies demonstrated evidence of a U-shaped or a reverse J-shaped association (35, 44, 67, 69, 73), and only 1 study showed a linear decrement in risk (62). It has been suggested that vitamin C in high doses, especially in the presence of free transition metals such as high levels of iron, may serve as a pro-oxidant (96–98). However, there is inconsistent evidence (99). In addition, the analysis of circulating vitamin C, which is a more reliable indicator of the status of vitamin C in the body, suggested that there was an inverse linear association. It should be noted that the circulating concentration of vitamin C does not necessarily reflect the dietary intake, because it can be affected by several factors such as storage and preparing of foods, age, comorbidities, smoking, socioeconomic status, and physical activity (100–102). In fact, the dietary intake and the circulating concentration of vitamin C do not represent the same thing (100). A high circulating concentration of vitamin C may be a consequence of several dietary and nondietary factors such as high dietary intake, reduced smoking, increased physical activity, low presence of comorbidities, and better health status (102), which in turn are associated with a lower risk of mortality. This could partially explain the inconsistent findings in the analyses of dietary and circulating vitamin C. Consequently, because dietary vitamin C recommendations differ substantially across countries (40–110 mg/d) (103), it would seem that increasing the dietary intake of vitamin C up to ~125 mg/d for low-intake populations may confer considerable protection against premature death.

The trace element selenium has a key role in the function of selenoproteins such as glutathione peroxidase,

thioredoxine reductase, and selenoprotein P, which are vital components of the enzymatic antioxidant defense system (104). Selenium metabolites have anti-inflammatory properties (105), are involved in gene expression and immune function, and can reduce platelet aggregation (106). A nonlinear dose–response meta-analysis indicated that the risk of all-cause mortality decreased linearly to a circulating selenium concentration of ~1.75 µmol/L. This level is higher than the cutoff levels of 1.25 µmol/L and 1.50 µmol/L, which are the optimal plasma selenium concentrations for glutathione peroxidase activity and cancer prevention, respectively (107, 108). However, because 4 of 5 studies in the nonlinear dose–response meta-analysis were from Western countries, generalization of the result to Asian populations should be made with caution. A subgroup analysis by age suggested a very strong inverse association in older populations (RRs: 0.46 and 0.79 in participants with a mean age of >60 y compared with <60 y, respectively). The circulating selenium concentration decreases along with the increase in age (109, 110), and a key role for selenium has been suggested in the age-related proinflammatory state (111). Another possible explanation is the role of deiodinase, another selenoprotein, in the activation of triiodothyronine (112), which is highly affected in older populations.

For circulating β-carotene, vitamin C, and selenium, a subgroup analysis by age indicated that the inverse association was more evident in participants who were >60 y old, which suggested that higher circulating antioxidant concentrations may be more beneficial in older populations compared with younger individuals (<60 y old). Previous prospective investigations also showed that the benefits of dietary antioxidants were more evident in individuals who had some risk factors at baseline (113).

Our results agreed with previous investigations that indicated that the circulating biomarkers of antioxidants were more strongly associated with risk of different cancer types than the dietary intakes (114–117). However, because the circulating biomarkers may be affected by other possible dietary and nondietary factors such as food preparation, absorption process, pathophysiologic processes, genetic factors, comorbidities, alcohol consumption, and cigarette smoking (114), they do not necessarily reflect the dietary intakes. As mentioned, higher circulating concentrations of antioxidants may be a consequence of higher dietary intakes, healthier lifestyle-related behaviors, and better health status, which are also associated with a lower risk of all-cause mortality. Thus, our results regarding the lower risk of mortality in the analyses of circulating antioxidants as compared with dietary intakes may have been overestimated, and as a result, may have been biased toward a greater effect size.

It has previously been suggested that the favorable effects of antioxidant intake are more evident in societies with poor nutritional status (73, 118, 119). However, of the 41 studies examined in the present meta-analysis, 32 studies were from the United States and Western Europe. Thus, our findings in the present meta-analysis regarding the significant inverse

association between almost all antioxidants and all-cause mortality risk may imply again the benefits of an antioxidant-rich diet, even among relatively well-nourished populations with adequate intakes. In the final step, the analyses of TAC, TRAP, and FRAP, especially the nonlinear dose–response meta-analysis of FRAP, indicated that the risk of all-cause mortality decreased significantly and linearly along with the increase in total dietary/circulating antioxidant properties. The TAC is an indicator of the overall and cumulative antioxidant capacity of the whole diet, as well as an appropriate indicator of dietary antioxidant properties (120). However, it should be noted that the antioxidant molecules in polyphenol-rich foods have a wide range of functions, some of which are unrelated to the ability to absorb free radicals (121). Therefore, the benefits of the antioxidant components in foods are not completely related to their antioxidant activities.

The present study was accompanied by several advantages. As mentioned earlier, this is the first attempt, to our knowledge, to examine the association between different dietary/circulating antioxidants and risk of all-cause mortality. We included both dietary and circulating antioxidants because the self-reported assessment of the dietary intakes may have been accompanied by measurement errors, and the circulating concentrations of antioxidants may have been affected by several nondietary factors. Thus, the inclusion of both dietary and circulating antioxidants allowed us to present a relatively comprehensive review of the association with all-cause mortality. We also tested the association across indexes of TAC, which presented a more detailed picture from the association between total dietary/circulating antioxidant properties and risk of all-cause mortality. Finally, we selected all-cause mortality as the outcome of interest instead of an individual outcome, such as different cancer types or CVD, because it gave a more comprehensive indication of the health benefits of the antioxidants.

We also were faced with some important limitations. First, we performed a meta-analysis of observational studies; thus, our findings cannot be interpreted as a causal relation. In general, higher antioxidant intakes are related to higher diet quality and better compliance with dietary guidelines, which lead to higher intakes of components without known antioxidant functions such as potassium and some dietary fibers, and lower intakes of unhealthy foods. In the present meta-analysis, only 2 studies controlled for dietary fats (42, 62), 1 study controlled for dietary fiber (38), and 1 study controlled for intake of fruit and vegetables (45). Thus, owing to the inadequate adjustments for these dietary variables in the primary studies, we may have reached a biased conclusion. Second, the primary studies generally used an FFQ to assess dietary intake, which overestimates the intake of fruits, vegetables, and, as a result, water-soluble antioxidants; and underestimates the intake of fats, oils, and, as a result, fat-soluble antioxidants (67). Third, only a few studies measured vitamin supplements in their dietary assessments or controlled for vitamin supplementations in their

multivariate analyses; this could have biased our conclusions. However, with the inclusion of the circulating biomarkers in our analyses, we could partially overcome these limitations. Fourth, we were faced with some evidence of heterogeneity in the analyses of circulating selenium, vitamin C, lycopene, and β-carotene, as well as in the analyses of dietary β-carotene, vitamin C, vitamin E, and FRAP. However, most of the observed between-study inconsistencies could be explained by the baseline age, geographic location, study quality, follow-up durations, dietary assessment methods, and adjustment for main confounders. Finally, owing to the low number of studies ($n < 10$), publication bias tests were performed only in the analyses of dietary vitamin C and vitamin E, which in turn were accompanied by some evidence of bias. Thus, our results may have been affected by publication bias and, as a result, may have been biased toward greater effect sizes.

In the present meta-analysis of prospective observational studies, we found that adherence to a diet with a high antioxidant property was associated with a lower risk of all-cause mortality. We also found that high circulating concentrations of all major antioxidants were significantly and inversely associated with risk of all-cause mortality. Although the circulating biomarkers of antioxidants may not directly reflect the dietary intakes and may be affected by several nondietary factors, nevertheless several observational (122–126) and interventional studies (127–130) have presented convincing evidence that increasing the consumption of fruits, vegetables, and other antioxidant-rich foods increases the circulating concentrations of different antioxidants. Therefore, increasing the consumption of fruits and vegetables, which are the main dietary sources of antioxidants (131, 132), may help prevent premature deaths. Currently, the WHO guidelines suggest a minimum daily intake of 5 servings of fruits and/or vegetables (133, 134). However, despite all efforts to increase the consumption of fruit and vegetables, the current worldwide consumption is below the minimum recommended daily intake. The World Health Survey (2002–2003) of 52 mainly low- and middle-income countries reported that the prevalence of low fruit and vegetable consumption, which was defined as <5 servings of fruits and/or vegetables/d, was ∼78% (135), with higher prevalence among older individuals. This prevalence is similar with those of developed countries: 75% in the United States (136) and 76% in England (137). Although fruits and vegetables contain several nonantioxidant components that have health benefits, the favorable biological functions of the antioxidants should not be ignored. In recent years, increasing evidence has shown that high dietary and/or circulating TAC is inversely associated with risk of different chronic diseases such as CVD (138–143), metabolic syndrome (144, 145), and different cancer types (44, 146–148). Therefore, increasing the consumption of fruits and vegetables to reach the minimum dietary recommendation of 5 servings of fruits and vegetables/d, especially among older individuals, should be considered to be one of the most important worldwide health priorities.

Conclusion

The present study evaluated the association of different dietary and circulating antioxidants with risk of all-cause mortality. We found that higher dietary intake and circulating concentration of almost all of the antioxidants studied were significantly and inversely associated with risk of all-cause mortality. Our findings could be used to develop more detailed dietary recommendations to reduce the risk of premature death. Further well-designed prospective observational studies are needed to evaluate the association between dietary antioxidants and health outcomes along with considering other dietary components and dietary features. This information would provide more reliable data concerning the health benefits of dietary antioxidants.

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