Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies

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ABSTRACT

Background: High dietary intake or blood concentrations (as biomarkers of dietary intake) of vitamin C, carotenoids, and vitamin E have been associated with reduced risk of cardiovascular disease, cancer, and mortality, but these associations have not been systematically assessed.

Objective: We conducted a systematic review and meta-analysis of prospective studies of dietary intake and blood concentrations of vitamin C, carotenoids, and vitamin E in relation to these outcomes.

Design: We searched PubMed and Embase up to 14 February 2018. Summary RRs and 95% CIs were calculated with the use of random-effects models.

Results: Sixty-nine prospective studies (99 publications) were included. The summary RR per 100-mg/d increment of dietary vitamin C intake was 0.88 (95% CI: 0.79, 0.98, $I^2 = 65\%$, $n = 11$) for coronary heart disease, 0.92 (95% CI: 0.87, 0.98, $I^2 = 68\%$, $n = 12$) for stroke, 0.89 (95% CI: 0.85, 0.94, $I^2 = 27\%$, $n = 10$) for cardiovascular disease, 0.93 (95% CI: 0.87, 0.99, $I^2 = 46\%$, $n = 8$) for total cancer, and 0.89 (95% CI: 0.85, 0.94, $I^2 = 80\%$, $n = 14$) for all-cause mortality. Corresponding RRs per 50-μmol/L increase in blood concentrations of vitamin C were 0.74 (95% CI: 0.65, 0.83, $I^2 = 0\%$, $n = 4$), 0.70 (95% CI: 0.61, 0.81, $I^2 = 0\%$, $n = 4$), 0.76 (95% CI: 0.65, 0.87, $I^2 = 56\%$, $n = 6$), 0.74 (95% CI: 0.66, 0.82, $I^2 = 0\%$, $n = 5$), and 0.72 (95% CI: 0.66, 0.79, $I^2 = 0\%$, $n = 8$). Dietary intake and/or blood concentrations of carotenoids (total, β-carotene, α-carotene, β-cryptoxanthin, lycopene) and α-tocopherol, but not dietary vitamin E, were similarly inversely associated with coronary heart disease, stroke, cardiovascular disease, cancer, and/or all-cause mortality.

Conclusions: Higher dietary intake and/or blood concentrations of vitamin C, carotenoids, and α-tocopherol (as markers of fruit and vegetable intake) were associated with reduced risk of cardiovascular disease, total cancer, and all-cause mortality. These results support recommendations to increase fruit and vegetable intake, but not antioxidant supplement use, for chronic disease prevention. *Am J Clin Nutr* 2018;108:1069–1091.

Keywords: vitamin C, carotenoids, beta-carotene, vitamin E, coronary heart disease, stroke, cardiovascular disease, cancer, mortality, meta-analysis

INTRODUCTION

Worldwide cardiovascular disease and cancer accounted for 25.5 million deaths in 2013 (1). A high intake of fruits, vegetables, and nuts has been associated with reduced risk of cardiovascular disease, cancer, and mortality (2–11) and these findings provide a basis for dietary recommendations to prevent chronic diseases and premature mortality (9).

Fruit, vegetables, berries, herbs, nuts, and legumes contain a number of nutrients that have been hypothesized to contribute to their purported beneficial effects including fiber, vitamin C, vitamin E, carotenoids, flavonoids, potassium, and a large number of other components (12). Dietary intake as well as blood concentrations of some of these nutrients including vitamin C, vitamin E, and carotenoids have been related to risk of cardiovascular disease, cancer, and all-cause mortality (13–28). Blood concentrations of vitamin C and carotenoids are considered biomarkers of fruit and vegetable intake (29–31) and studies that use biomarkers of fruit and vegetable intake complement questionnaire-based studies by providing an integrated measure of both intake and absorption (32). Many prospective studies have investigated the association between dietary antioxidants including vitamin C, vitamin E, and carotenoids and coronary heart disease (13, 14, 33–43), stroke (13, 41, 44–52), cardiovascular disease overall (41, 53–56), total cancer (14, 20, 36, 53, 56, 57), and all-cause mortality (14, 19, 36, 38, 53, 54, 56, 58–60), but studies are not entirely consistent with some showing an inverse association (14, 36, 38, 39, 41, 43, 47, 48, 54, 55, 57, 58) and others reporting no significant association (19, 33–35, 37, 40, 42, 44–46, 49–53, 56, 59–61). Some of the previous studies may have been too small and therefore underpowered to find a significant association (20, 33, 35, 44, 49, 50, 52, 53, 59). In addition, some degree of measurement error and regression dilution bias is inevitable in dietary studies and may at least to some degree have attenuated some findings in previous studies. Aune et al. (62) recently reported stronger inverse associations between blood concentrations of carotenoids when compared with dietary intake as measured by food frequency questionnaires in relation to breast cancer risk. There was only a 5–6% reduction in the RR for the highest compared with the lowest dietary intake of carotenoids; however, when blood concentrations of carotenoids were analyzed there was a 25–30% reduction in the RR for those with the highest compared with the lowest concentrations (62) and similar results have been found in pooled analyses (63, 64). One meta-analysis also suggested an inverse association between dietary intake and blood concentrations of vitamin C and risk of stroke (65). However, whether or not blood concentrations of different types of antioxidants are associated with risk of cardiovascular disease, total cancer, and mortality is not clear (13–25, 28) and has not previously been comprehensively evaluated across multiple exposures and outcomes in a meta-analysis. For these reasons we conducted a meta-analysis of dietary intake and blood concentrations of vitamin C (ascorbic acid), vitamin E (tocopherol), and carotenoids (total carotenoids, α-carotene, β-carotene, lycopene, β-cryptoxanthin) and the risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause mortality, and specifically aimed to clarify the strength and the shape of the dose-response relation.

METHODS

Search strategy

We searched the PubMed and Embase databases from their inception to 31 May 2014 using a comprehensive list of search terms shown in **Supplemental Table 1** and the searches were later updated to 14 February 2018. There was no protocol for the current review. We included prospective cohort studies and nested case-control studies that reported adjusted RR estimates (ORs, HRs, incidence rate ratios, or risk ratios) of the association between vitamin C, vitamin E, and carotenoids in the diet or measured in blood and the risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause mortality. Studies that only assessed supplemental intake of these antioxidants were excluded. For the dose-response analysis a quantitative measure of intake or the blood concentrations for $\geq$3 categories had to be available. A list of the excluded studies and reasons for exclusion is found in **Supplemental Table 2**. Standard criteria for reporting meta-analyses were followed (66).

Data extraction

We extracted the following data from each study: first author's last name, publication year, country where the study was conducted, study name, follow-up period, sample size, sex, age, number of cases or deaths, dietary assessment method (type, number of items, and whether it was validated), laboratory method for analysis of antioxidants in blood, exposure, exposure dose, RRs and 95% CIs, and variables adjusted for in the analysis. DA conducted the data extraction and NK and LTF checked the extractions for accuracy.

Statistical methods

To take into account heterogeneity between studies, we used a random-effects model to calculate summary RRs and 95% CIs for the highest compared with the lowest level of antioxidant exposure and for the dose-response analysis (67). The average of the natural logarithm of the RRs was estimated, and the RR from each study was weighted with the use of random-effects weighting. A 2-tailed $P < 0.05$ was considered statistically significant.

Details of the methods for the dose-response analysis have been published elsewhere (62). Briefly, we used the method described by Greenland and Longnecker (68) to compute linear trends and 95% CIs from the natural logs of the RRs and CIs across categories of antioxidant exposure. We used mean or median values when provided in the papers, but used the midpoint of the upper and lower boundaries when the exposure was provided as a range. When the highest and lowest categories were open-ended or had extreme upper or lower values we used the width of the adjacent interval to estimate the upper and lower boundaries for the category. For studies that did not report the distribution of cases and person-years or noncases we estimated the distribution by dividing the total number of cases or person-years by the number of categories. For studies that reported plasma or serum concentrations of carotenoids, α-carotene, β-carotene, or lycopene in µmol/L we converted the data to µg/dL by dividing the concentration in µmol/L by 0.01863 (69), whereas

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Supplemental Tables 1–34 and Supplemental Figures 1–125 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn.

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for studies of β-cryptoxanthin we divided the concentration in µmol/L by 0.01809. For studies of vitamin E, data in µmol/L were divided by 232.2 to convert the data to µg/dL (70). For the linear dose-response analysis we used an increment with the size of the approximate mean difference between the highest and lowest level of exposure across studies.

A potential nonlinear dose-response relation between antioxidant exposures and cardiovascular disease, cancer, and mortality was examined with the use of restricted cubic splines with 3 knots at 10th, 50th, and 90th percentiles of the distribution, which was combined with the use of multivariate meta-analysis (71, 72). A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (73).

Heterogeneity between studies was assessed through the use of Q and I^2 statistics (74). We conducted subgroup analyses by study characteristics including duration of follow-up, sex, geographic location, number of cases, study quality, exclusion of prevalent cases of diseases at baseline, and adjustment for confounders, as well as influence analyses to investigate the robustness of the results when there were $\geq$6 studies in the dose-response analysis. Study quality was assessed with the use of the Newcastle-Ottawa Scale, which awards 0–9 stars based on the selection, comparability, and outcome assessment (75). Small-study effects, such as publication bias, were assessed with the use of a funnel plot and Egger's test, with results considered to indicate potential small-study bias when $P < 0.10$ (76). Stata version 13.0 software (StataCorp) was used for the statistical analyses.

RESULTS

A total of 69 prospective studies (99 publications) (13–28, 33–61, 70, 77–127) were included in the analyses of dietary (includes total intake and dietary intake only) antioxidant intake and blood concentrations of antioxidants and coronary heart disease, stroke, cardiovascular disease, cancer, and mortality (**Supplemental Tables 3–12**, **Figure 1**). Thirty-six of the studies were from Europe, 24 from America, and 9 studies were from Asia (Supplemental Tables 3–12). One publication included combined results from two studies (53) and another publication included results from two studies (81). Because some studies only reported a high against low comparison or a continuous estimate, the number of studies included for each exposure and outcome comparison in the high against low and dose-response analyses may differ slightly from the total number of studies included in the analysis of each exposure and outcome. The number of studies, cases or deaths, and participants and references for studies included in each analysis are provided in **Table 1**. Supplemental Tables 3–12 show a summary of the study characteristics of the included studies. **Supplemental Tables 13–24** show the results of the nonlinear dose-response analyses and **Supplemental Tables 25–34** show the results of the subgroup analyses. Figure 1 shows a flow chart of the study selection. **Figures 2–14** show the results for the dose-response analyses of vitamin C and β-carotene in relation to all outcomes and carotenoids and vitamin E in relation to all-cause mortality. **Supplemental Figures 1–95** show the results of the high against low analysis as well as dose-response results for the remaining antioxidant exposures and outcomes. **Supplemental Figures 96–107** show the funnel plots from the tests for publication bias and **Supplementary Figures 108–125** shows the results from the influence analyses excluding one study at a time.

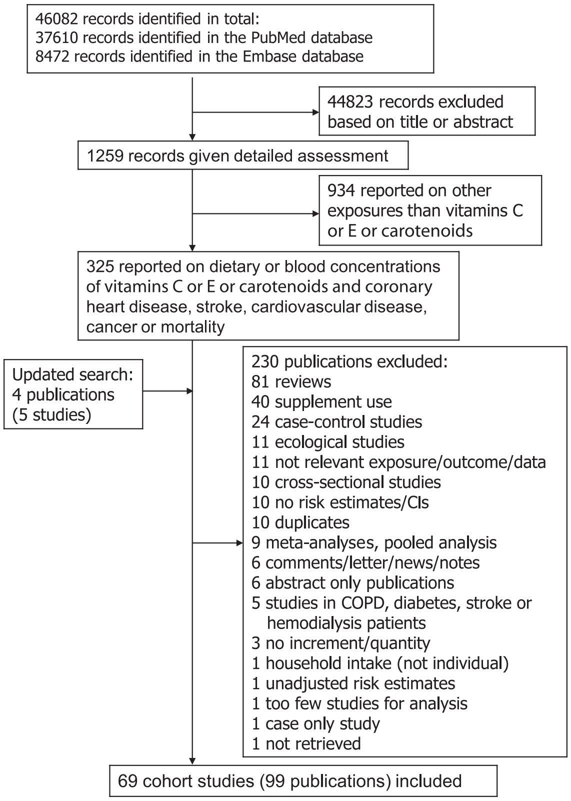

FIGURE 1 Flow chart of study selection. COPD, chronic obstructive pulmonary disease.

Dietary vitamin C intake

Twelve (13, 14, 33–41, 49), thirteen (41, 44–52, 58, 61, 123), eleven (9 publications) (19, 26, 41, 53–56, 80, 81), nine (7 publications) (14, 20, 36, 53, 56, 57, 81), and seventeen (16 publications) (14, 19, 20, 36, 38, 53, 54, 56, 58–60, 81–84, 127) studies were included in the analysis of dietary vitamin C intake and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause mortality, respectively. A statistically significant 12%, 8%, 11%, 7%, and 11% reduction in the RR was observed for coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality (Figures 2A–6A, Table 1, Supplemental Figures 1–5), respectively. There was evidence of nonlinearity for coronary heart disease ($P_{\text{nonlinearity}} < 0.0001$), stroke ($P_{\text{nonlinearity}} < 0.0001$), cardiovascular disease ($P_{\text{nonlinearity}} < 0.0001$), total cancer ($P_{\text{nonlinearity}} = 0.006$), and mortality ($P_{\text{nonlinearity}} < 0.0001$) with stronger reductions in risk at lower amounts of intake in all analyses (Figures 2C–6C, Supplemental Table 13).

Vitamin C in blood

Four (13–15, 92), five (16, 17, 58, 87, 98), six (18–22, 103), six (14, 18, 20–22, 116), and eight (9 publications) (14, 18–23, 58, 126) studies were included in the analysis of blood concentrations of vitamin C and risk of coronary heart disease, stroke,

TABLE 1

Summary RRs for the high vs. low and dose-response analyses of antioxidants and risk of coronary heart disease, stroke, cardiovascular disease, total cancer and mortality

Outcome	Comparison	No. of studies	Cases, *n*	Participants, *n*	RR (95% CI)	I^2	$P_{\text{heterogeneity}}$	*P* (Egger' test)	References
Dietary vitamin C									
Coronary heart disease	High vs. low	12	4297	241,579	0.83 (0.71, 0.98)	50.7	0.02	0.97	(13, 14, 33–41, 49)
	Per 100 mg/d	11	4167	240,824	0.88 (0.79, 0.98)	65.1	0.001	0.007	(13, 14, 33–41)
Stroke	High vs. low	13	7294	298,066	0.84 (0.77, 0.91)	6.2	0.39	0.93	(41, 44–52, 58, 61, 123)
	Per 100 mg/d	12	7049	296,596	0.92 (0.87, 0.98)	68.0	<0.0001	0.02	(41, 44–52, 58, 123)
Cardiovascular disease	High vs. low	9	7986	246,711	0.84 (0.77, 0.91)	0	0.53	0.71	(19, 26, 41, 53, 55, 56, 80, 81)
	Per 100 mg/d	10	8175	247,765	0.89 (0.85, 0.94)	27.2	0.19	0.81	(19, 20, 26, 41, 53, 55, 56, 80, 81)
Total cancer	High vs. low	7	7068	181,318	0.87 (0.78, 0.95)	17.7	0.30	0.91	(14, 36, 53, 56, 57, 81)
	Per 100 mg/d	8	7208	181,318	0.93 (0.87, 0.99)	45.5	0.08	0.28	(14, 20, 36, 53, 56, 57, 81)
Mortality	High vs. low	16	38,079	315,214	0.86 (0.80, 0.92)	68.5	<0.0001	0.001	(14, 19, 36, 38, 53, 54, 56, 58–60, 81–84, 127)
	Per 100 mg/d	14	36,404	295,152	0.89 (0.85, 0.94)	80.2	<0.0001	<0.0001	(14, 19, 20, 36, 38, 53, 54, 56, 58–60, 81, 84)
Vitamin C in blood									
Coronary heart disease	High vs. low	4	1368	6992	0.71 (0.59, 0.86)	0.4	0.39	0.90	(13, 14, 87, 92)
	Per 50 µmol/L	4	1420	7514	0.74 (0.65, 0.83)	0	0.71	0.49	(13–15, 92)
Stroke	High vs. low	5	957	27,843	0.60 (0.49, 0.73)	0	0.86	0.70	(16, 17, 58, 87, 98)
	Per 50 µmol/L	4	926	24,869	0.70 (0.61, 0.81)	0	0.41	0.36	(16, 17, 58, 98)
Cardiovascular disease	High vs. low	5	2792	45,273	0.61 (0.45, 0.83)	55.6	0.06	0.22	(18, 19, 21, 22, 103)
	Per 50 µmol/L	6	2981	46,327	0.76 (0.65, 0.87)	55.7	0.05	0.31	(18–22, 103)
Total cancer	High vs. low	5	1831	47,678	0.68 (0.57, 0.80)	0	0.51	0.65	(14, 18, 21, 22, 116)
	Per 50 µmol/L	5	1681	45,758	0.74 (0.66, 0.82)	0	0.49	0.82	(14, 18, 20–22)
Mortality	High vs. low	8	7528	47,238	0.68 (0.60, 0.77)	43.1	0.09	0.07	(14, 18, 19, 21–23, 58, 126)
	Per 50 µmol/L	8	8179	48,060	0.72 (0.66, 0.79)	48.2	0.06	0.13	(14, 18–23, 58)
Dietary total carotenoids									
Coronary heart disease	High vs. low	5	1835	91,838	0.78 (0.67, 0.90)	0	0.54	0.59	(14, 34, 35, 37, 42)
	Per 5000 µg/d	5	1835	91,838	0.85 (0.77, 0.93)	37.0	0.18	0.22	(14, 34, 35, 37, 42)
Stroke	High vs. low	0	—	—	—	—	—	—	—
	Per 5000 µg/d	0	—	—	—	—	—	—	—
Cardiovascular disease	High vs. low	2	3198	134,358	0.87 (0.74, 1.01)	0	0.51	—	(81)
	Per 5000 µg/d	4	3584	135,971	0.80 (0.70, 0.90)	0	0.76	0.93	(20, 55, 81)
Total cancer	High vs. low	3	4441	135,038	0.93 (0.82, 1.06)	0	0.59	0.42	(14, 81)
	Per 5000 µg/d	4	4581	136,092	0.93 (0.82, 1.05)	4.4	0.37	0.93	(14, 20, 81)
Mortality	High vs. low	5	11,431	188,025	0.87 (0.80, 0.94)	11.6	0.34	0.45	(14, 42, 54, 81)
	Per 5000 µg/d	6	12,148	189,079	0.88 (0.83, 0.93)	2.2	0.40	0.51	(14, 20, 42, 54, 81)
Carotenoids in blood									
Coronary heart disease	High vs. low	4	634	6014	0.67 (0.53, 0.85)	0	0.88	0.20	(14, 87, 88, 90)
	Per 100 µg/dL	3	502	3040	0.83 (0.72, 0.95)	0	0.56	0.69	(14, 88, 90)
Stroke	High vs. low	1	31	2974	0.48 (0.18, 1.28)	—	—	—	—
	Per 100 µg/dL	0	—	—	—	—	—	—	—
Cardiovascular disease	High vs. low	2	1386	14,324	0.81 (0.64, 1.03)	0	0.34	—	(108, 109)
	Per 100 µg/dL	3	1534	15,492	0.61 (0.33, 1.10)	53.8	0.12	—	(107, 109)
Total cancer	High vs. low	5	1178	20,231	0.74 (0.60, 0.90)	0	0.99	0.39	(14, 108, 110, 116, 118)
	Per 100 µg/dL	3	741	14,976	0.61 (0.36, 1.03)	72.5	0.03	0.49	(14, 107, 108)
Mortality	High vs. low	6	1578	17,391	0.75 (0.64, 0.88)	0	0.80	0.65	(14, 24, 25, 108, 121, 125)
	Per 100 µg/dL	7	1966	18,559	0.74 (0.62, 0.88)	50.9	0.06	0.14	(14, 24, 25, 107, 108, 121, 125)

(*Continued*)

TABLE 1 *(Continued)*

Outcome	Comparison	No. of studies	Cases, *n*	Participants, *n*	RR (95% CI)	I^2	$P_{\text{heterogeneity}}$	*P* (Egger' test)	References
Dietary β-Carotene									
Coronary heart disease	High vs. low	4	2104	99,345	0.73 (0.63, 0.85)	0	0.46	0.29	(36, 38, 39, 43)
	Per 5000 µg/d	4	2104	99,345	0.82 (0.68, 0.98)	45.0	0.14	0.20	(36, 38, 39, 43)
Stroke	High vs. low	7	5468	201,587	0.84 (0.75, 0.94)	21.9	0.26	0.25	(44, 45, 47, 48, 51, 52, 123)
	Per 5000 µg/d	7	5468	201,587	0.81 (0.66, 0.98)	59.4	0.02	0.07	(44, 45, 47, 48, 51, 52, 123)
Cardiovascular disease	High vs. low	4	1767	39,643	0.98 (0.84, 1.15)	10.4	0.34	0.21	(19, 53, 56, 80)
	Per 5000 µg/d	4	1851	38,988	0.91 (0.74, 1.11)	36.6	0.19	0.47	(53, 55, 56, 80)
Total cancer	High vs. low	4	2797	46,280	0.90 (0.81, 1.00)	0	0.55	0.02	(36, 53, 56, 57)
	Per 5000 µg/d	4	2797	46,280	0.96 (0.90, 1.02)	24.9	0.26	0.006	(36, 53, 56, 57)
Mortality	High vs. low	8	11,729	142,798	0.82 (0.78, 0.87)	0	0.51	0.57	(19, 36, 38, 53, 54, 56, 60, 127)
	Per 5000 µg/d	6	11,120	143,140	0.92 (0.85, 0.98)	66.2	0.01	0.008	(36, 38, 53, 54, 56, 60)
β-Carotene in blood									
Coronary heart disease	High vs. low	4	1128	3179	0.73 (0.57, 0.94)	0	0.61	0.11	(89, 91, 93, 95)
	Per 25 µg/dL	3	1005	2933	0.80 (0.66, 0.97)	10.4	0.33	0.90	(91, 93, 95)
Stroke	High vs. low	3	1548	30,144	0.85 (0.71, 1.01)	0	0.66	0.52	(97, 99, 100)
	Per 25 µg/dL	3	1548	30,144	0.85 (0.74, 0.97)	0	0.50	0.27	(97, 99, 100)
Cardiovascular disease	High vs. low	7	3232	34,090	0.71 (0.57, 0.88)	17.7	0.30	0.13	(19, 21, 27, 103, 105, 106, 109)
	Per 25 µg/dL	8	3451	24,428	0.86 (0.78, 0.96)	3.1	0.41	0.38	(19–21, 27, 102, 103, 106, 109)
Total cancer	High vs. low	6	2654	66,892	0.76 (0.65, 0.89)	0	0.80	0.22	(21, 27, 28, 105, 115, 118)
	Per 25 µg/dL	8	2519	56,773	0.76 (0.68, 0.85)	0	0.74	0.17	(20, 21, 27, 28, 102, 115, 117, 120)
Mortality	High vs. low	7	5659	23,141	0.68 (0.55, 0.83)	43.5	0.10	0.15	(19, 21, 27, 117, 121, 122, 124)
	Per 25 µg/dL	7	5659	23,141	0.81 (0.72, 0.90)	46.5	0.08	0.20	(19–21, 27, 102, 117, 121, 124)
α-Carotene in blood									
Coronary heart disease	High vs. low	4	1963	18,251	0.88 (0.71, 1.10)	0	0.63	0.64	(91, 93–95)
	Per 10 µg/dL	4	1963	18,251	0.87 (0.71, 1.07)	0	0.89	0.60	(91, 93–95)
Stroke	High vs. low	3	784	16,943	0.74 (0.48, 1.14)	0	0.73	0.58	(94, 99, 100)
	Per 10 µg/dL	3	784	16,943	0.80 (0.55, 1.18)	0	0.80	0.39	(94, 99, 100)
Cardiovascular disease	High vs. low	4	3556	30,640	0.80 (0.58, 1.09)	68.2	0.02	0.25	(94, 106, 108, 109)
	Per 10 µg/dL	5	3745	31,694	0.83 (0.62, 1.10)	68.2	0.01	0.81	(20, 94, 106, 108, 109)
Total cancer	High vs. low	2	878	17,671	0.62 (0.40, 0.96)	0	0.56	—	(94, 118)
	Per 10 µg/dL	4	1177	19,043	0.58 (0.45, 0.74)	0	0.66	0.95	(20, 94, 117, 120)
Mortality	High vs. low	4	4285	18,928	0.76 (0.59, 0.98)	49.9	0.12	0.08	(24, 94, 117, 121)
	Per 10 µg/dL	5	5002	19,982	0.71 (0.64, 0.79)	0	0.86	0.07	(20, 24, 94, 117, 121)
β-Cryptoxanthin in blood									
Coronary heart disease	High vs. low	2	811	1902	1.01 (0.43, 2.37)	70.8	0.06	—	(91, 93)
	Per 15 µg/dL	2	811	1902	1.12 (0.33, 3.79)	67.3	0.08	—	(91, 93)
Stroke	High vs. low	0	—	—	—	—	—	—	—
	Per 15 µg/dL	0	—	—	—	—	—	—	—
Cardiovascular disease	High vs. low	3	2246	42,636	0.83 (0.67, 1.03)	0	0.77	0.38	(104, 106, 108)
	Per 15 µg/dL	4	2435	43,690	0.90 (0.76, 1.06)	0	0.70	0.79	(20, 104, 106, 108)
Total cancer	High vs. low	2	777	16,421	0.83 (0.60, 1.15)	0	0.56	—	(108, 118)
	Per 15 µg/dL	3	944	14,665	0.74 (0.60, 0.91)	0	0.99	0.16	(20, 108, 120)
Mortality	High vs. low	2	3104	13,931	0.81 (0.64, 1.03)	27.0	0.24	—	(108, 121)
	Per 15 µg/dL	3	3821	14,985	0.84 (0.76, 0.94)	0	0.99	0.84	(20, 108, 121)

(Continued)

TABLE 1 *(Continued)*

Outcome	Comparison	No. of studies	Cases, *n*	Participants, *n*	RR (95% CI)	I^2	$P_{\text{heterogeneity}}$	*P* (Egger' test)	References
Dietary lycopene									
Coronary heart disease	High vs. low	2	1199	111,731	0.88 (0.71, 1.10)	11.1	0.29	—	(43, 78)
	Per 12,000 µg/d	2	1199	111,731	0.91 (0.76, 1.08)	19.9	0.26	—	(43, 78)
Stroke	High vs. low	3	1371	108,776	0.80 (0.63, 1.01)	35.1	0.21	0.36	(45, 47, 78)
	Per 12,000 µg/d	3	1371	108,776	0.72 (0.39, 1.34)	83.7	0.002	0.31	(45, 47, 78)
Cardiovascular disease	High vs. low	1	719	39,876	0.90 (0.69, 1.17)	—	—	—	(78)
	Per 12,000 µg/d	2	916	40,435	0.94 (0.79, 1.12)	0	0.32	—	(55, 78)
Total cancer	High vs. low	0	—	—	—	—	—	—	—
	Per 12,000 µg/d	0	—	—	—	—	—	—	—
Mortality	High vs. low	2	881	48,805	0.74 (0.54, 1.02)	48.1	0.17	—	(54, 127)
	Per 12,000 µg/d	0	—	—	—	—	—	—	—
Lycopene in blood									
Coronary heart disease	High vs. low	4	1128	3179	0.90 (0.62, 1.29)	52.9	0.10	0.47	(89, 91, 93, 95)
	Per 25 µg/dL	3	1005	2933	1.11 (0.32, 3.85)	72.7	0.03	0.15	(91, 93, 95)
Stroke	High vs. low	2	491	1625	0.59 (0.36, 0.96)	0	0.35	—	(99, 100)
	Per 25 µg/dL	2	491	1625	0.49 (0.19, 1.25)	59.7	0.12	—	(99, 100)
Cardiovascular disease	High vs. low	4	1749	43,667	0.88 (0.70, 1.10)	8.0	0.35	0.24	(104, 106, 108, 109)
	Per 25 µg/dL	5	1938	44,721	0.81 (0.63, 1.06)	34.8	0.19	0.15	(20, 104, 106, 108, 109)
Total cancer	High vs. low	3	918	17,418	0.81 (0.54, 1.21)	65.5	0.06	0.13	(108, 118, 119)
	Per 25 µg/dL	5	1129	18,015	0.95 (0.68, 1.33)	65.9	0.02	0.13	(20, 108, 117, 119, 120)
Mortality	High vs. low	4	3233	16,438	0.91 (0.77, 1.07)	0	0.60	0.08	(108, 117, 121, 124)
	Per 25 µg/dL	5	3950	17,492	0.87 (0.74, 1.02)	25.5	0.25	0.07	(20, 108, 117, 121, 124)
Dietary vitamin E									
Coronary heart disease	High vs. low	9	3010	239,610	0.86 (0.65, 1.05)	68.2	0.001	0.81	(14, 34, 35, 37–39, 41, 49, 77)
	Per 5 µg/d	8	2880	238,855	0.94 (0.87, 1.02)	67.6	0.003	0.18	(14, 34, 35, 37–39, 41, 77)
Stroke	High vs. low	10	7003	311,965	0.89 (0.78, 1.02)	34.4	0.13	0.58	(41, 44–49, 51, 61, 123)
	Per 5 µg/d	8	6688	292,966	0.97 (0.93, 1.02)	54.4	0.03	0.18	(41, 44–48, 51, 123)
Cardiovascular disease	High vs. low	8	7852	233,310	0.90 (0.78, 1.03)	55.5	0.03	0.05	(19, 41, 53, 55, 56, 80, 81)
	Per 5 µg/d	8	7928	233,130	0.99 (0.96, 1.01)	41.6	0.10	0.06	(20, 41, 53, 55, 56, 80, 81)
Total cancer	High vs. low	5	5578	168,182	1.01 (0.92, 1.10)	0	0.69	0.72	(14, 53, 56, 81)
	Per 5 µg/d	6	5718	169,236	0.97 (0.93, 1.02)	61.1	0.03	0.07	(14, 20, 53, 56, 81)
Mortality	High vs. low	9	15,321	229,830	0.98 (0.93, 1.04)	2.9	0.41	0.92	(14, 19, 38, 53, 54, 56, 81, 127)
	Per 5 µg/d	8	15,429	222,223	1.00 (0.99, 1.01)	0	0.59	0.07	(14, 20, 38, 53, 54, 56, 81)
α-Tocopherol in blood									
Coronary heart disease	High vs. low	8	1407	47,374	1.22 (0.96, 1.57)	0	0.80	0.18	(14, 85, 86, 89–91, 95, 96)
	Per 500 µg/dL	5	1182	42,882	1.05 (0.95, 1.15)	18.6	0.30	0.51	(14, 90, 91, 95, 96)
Stroke	High vs. low	5	1966	69,569	0.71 (0.58, 0.85)	0	0.70	0.61	(85, 96, 97, 99, 100)
	Per 500 µg/dL	4	1951	69,386	0.90 (0.86, 0.95)	0	0.43	0.61	(96, 97, 99, 100)
Cardiovascular disease	High vs. low	6	8053	47,012	0.79 (0.56, 1.10)	68.8	0.007	0.69	(19, 21, 70, 79, 85, 103)
	Per 500 µg/dL	8	8607	51,283	0.92 (0.82, 1.03)	69.9	0.002	0.97	(19–21, 70, 79, 102, 103, 107)
Total cancer	High vs. low	10	7201	56,258	0.80 (0.74, 0.87)	0	0.73	0.34	(14, 21, 70, 110–114, 116, 118)
	Per 500 µg/dL	10	6919	51,210	0.91 (0.83, 0.99)	70.1	<0.0001	0.77	(14, 20, 21, 70, 102, 107, 111–114)
Mortality	High vs. low	6	18,316	47,853	0.89 (0.72, 1.08)	59.6	0.03	0.79	(14, 19, 21, 70, 121, 124)
	Per 500 µg/dL	9	20,051	52,376	0.94 (0.89,0.99)	56.3	0.02	0.97	(14, 19–21, 70, 102, 107, 121, 124)

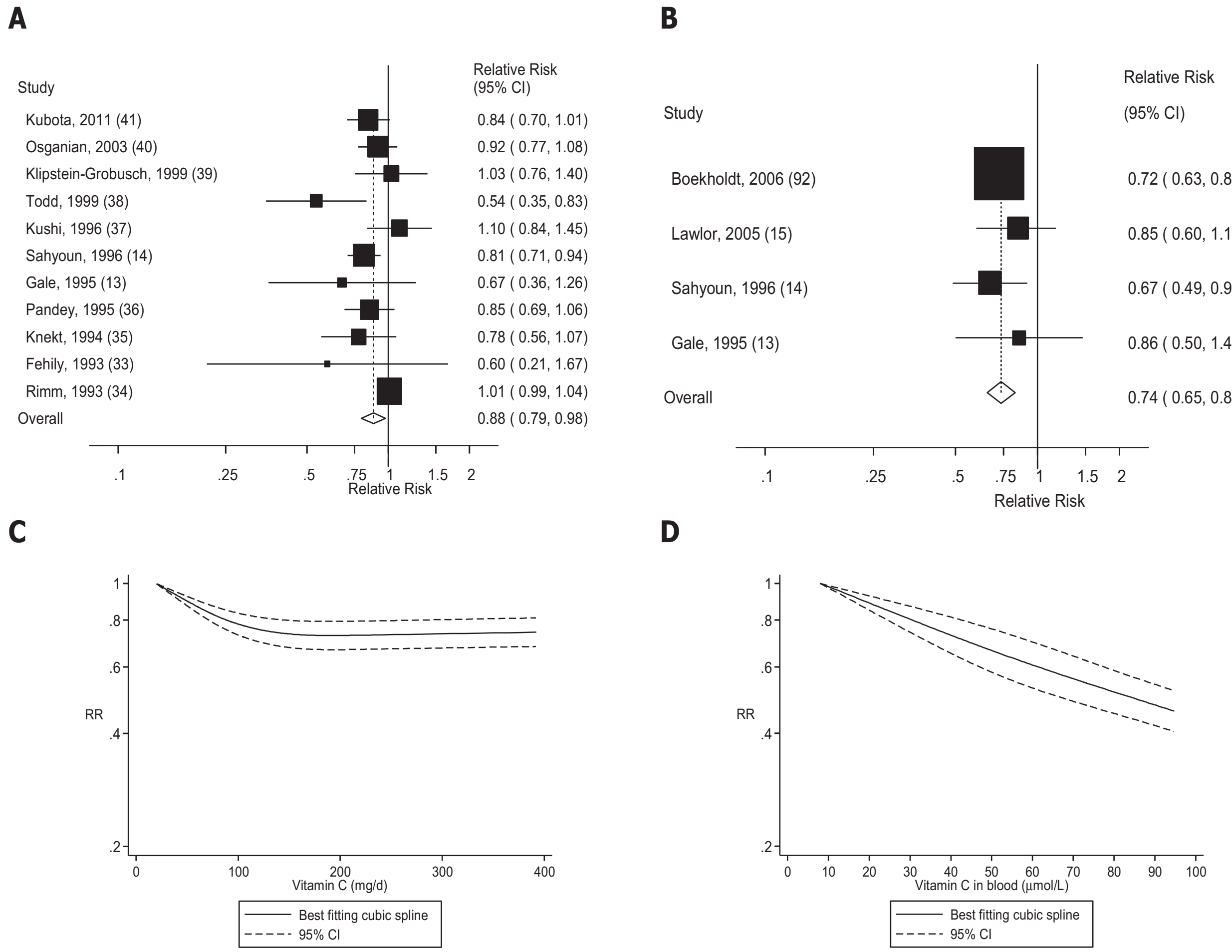

FIGURE 2 Dietary intake and blood concentrations of vitamin C and coronary heart disease: dose-response analyses. (A) Dietary vitamin C and coronary heart disease: linear dose-response analysis. The summary RR per 100 mg/d was 0.88 (95% CI: 0.79, 0.98, $I^2 = 65\%$, $P_{\text{heterogeneity}} = 0.001$, $n = 11$). (B) Vitamin C in blood and coronary heart disease: linear dose-response analysis. The summary RR per 50 μmol/L was 0.74 (95% CI: 0.65, 0.83, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.71$, $n = 4$). (C) Dietary vitamin C and coronary heart disease: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin C and coronary heart disease ($P_{\text{nonlinearity}} < 0.0001$). (D) Vitamin C in blood and coronary heart disease: nonlinear dose-response analysis. There was no evidence of nonlinearity for vitamin C in blood and coronary heart disease ($P_{\text{nonlinearity}} = 0.49$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

cardiovascular disease, total cancer, and mortality, respectively. Inverse associations were observed for all outcomes, with 24–30% reductions in the RR (Figures 2B–6B, Supplemental Figures 6–10). There was evidence of a nonlinear association between vitamin C in blood and total cancer ($P_{\text{nonlinearity}} = 0.006$), with stronger inverse associations at lower vitamin C concentrations but not for coronary heart disease ($P = 0.49$), stroke ($P_{\text{nonlinearity}} = 0.16$), cardiovascular disease ($P_{\text{nonlinearity}} = 0.26$), or mortality ($P_{\text{nonlinearity}} = 0.90$) (Figures 2D–6D, Supplemental Table 14).

Total dietary carotenoid intake

Five (14, 34, 35, 37, 42), four (3 publications) (20, 55, 81), four (3 publications) (14, 20, 81), and six (5 publications) (14, 20, 42, 54, 81) studies were included in the analysis of total dietary carotenoid intake and risk of coronary heart disease, cardiovascular disease, total cancer, and mortality, respectively. A statistically significant 15%, 20%, and 12% reduction in the RR was observed for coronary heart disease, cardiovascular disease, and mortality (Figure 7A, Table 1, Supplemental Figures 11A, 12, 13, 14A, and 17), respectively, but no association was observed for total cancer (Table 1, Supplemental Figures 15 and 16A). There was evidence for a nonlinear association between total carotenoid intake and cardiovascular disease ($P_{\text{nonlinearity}} = 0.002$), total cancer ($P_{\text{nonlinearity}} = 0.01$), and mortality ($P_{\text{nonlinearity}} < 0.0001$), but not for coronary heart disease ($P_{\text{nonlinearity}} = 0.95$) (Figure 7B, Supplemental Table 15, Supplemental Figures 11B, 14B, and 16B), with most of the reduction in risk observed up to an intake of between 4000 and 6000 μg/d.

Total carotenoids in blood

Four (14, 87, 88, 90), two (108, 109), three (14, 108, 110), and seven (14, 24, 25, 107, 108, 121, 125) studies were included in the analyses of blood concentrations of total carotenoids and risk of coronary heart disease, cardiovascular disease, total cancer, and mortality, respectively. A statistically significant 17% and 31% reduction in RR was observed for coronary heart

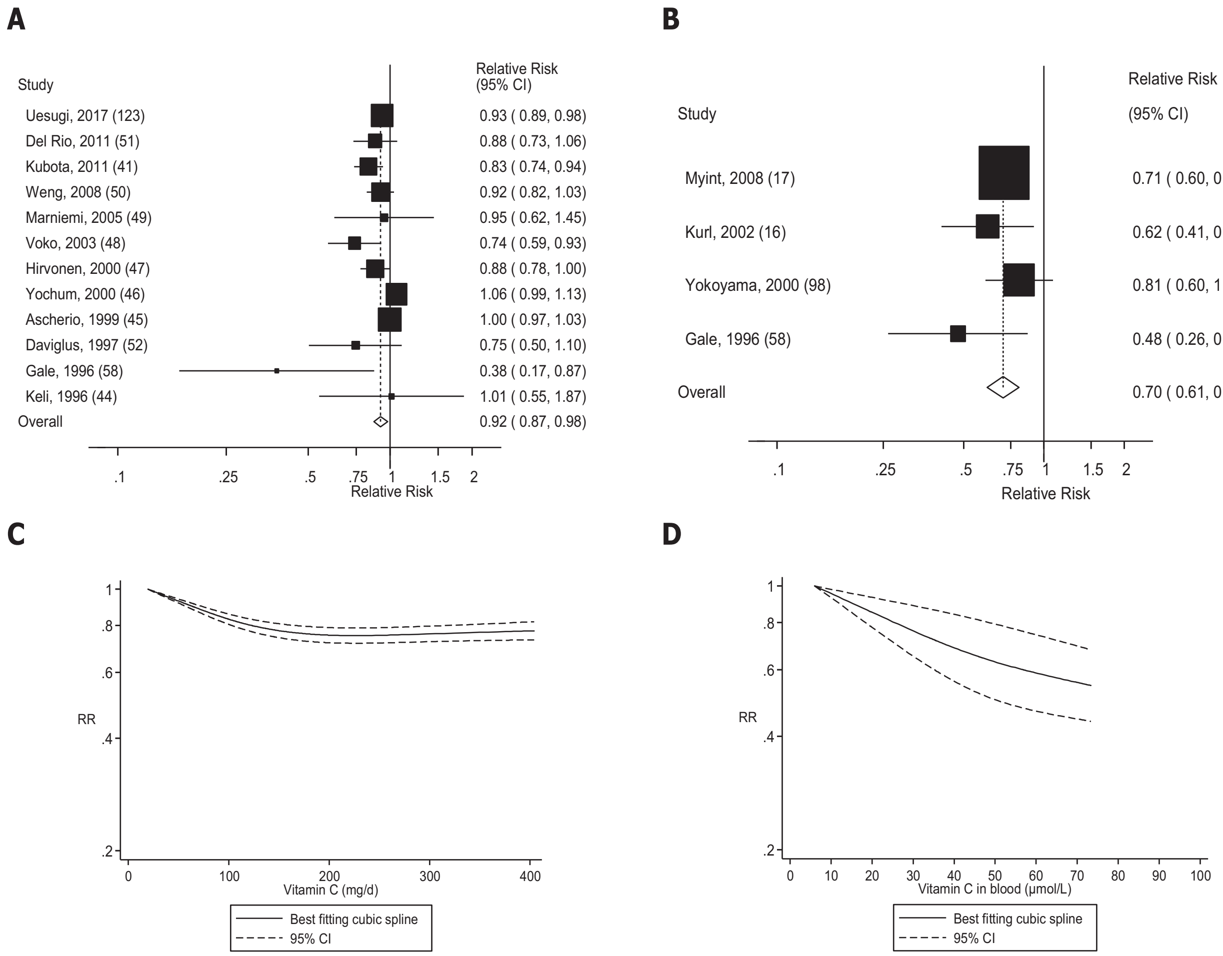

FIGURE 3 Dietary intake and blood concentrations of vitamin C and stroke: dose-response analyses. (A) Dietary vitamin C and stroke: linear dose-response analysis. The summary RR per 100 mg/d was 0.92 (95% CI: 0.87, 0.98, $I^2 = 68\%$, $P_{\text{heterogeneity}} < 0.0001$, $n = 12$). (B) Vitamin C in blood and stroke: linear dose-response analysis. The summary RR per 50 µmol/L was 0.70 (95% CI: 0.61, 0.81, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.41$, $n = 4$). (C) Dietary vitamin C and stroke: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin C and stroke ($P_{\text{nonlinearity}} < 0.0001$). (D) Vitamin C in blood and stroke: nonlinear dose-response analysis. There was no evidence of nonlinearity for vitamin C in blood and stroke ($P_{\text{nonlinearity}} = 0.16$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

disease and mortality, respectively, and a significant association was observed for total cancer only in the high compared with low analysis and the nonlinear dose-response analysis (Table 1, Figure 7B, Supplemental Figures 18A, 19, and 22A–24), whereas the association for cardiovascular disease only was significant in the nonlinear analysis (Table 1, Supplemental Figures 20 and 21, Supplemental Table 16). There was evidence of a nonlinear association for coronary heart disease ($P_{\text{nonlinearity}} = 0.008$) and cardiovascular disease ($P_{\text{nonlinearity}} = 0.004$), but not for total cancer ($P_{\text{nonlinearity}} = 0.33$) or mortality ($P_{\text{nonlinearity}} = 0.73$) (Figure 7, Supplemental Figures 18D, 20D, and 22D, Supplemental Table 16).

Dietary β-carotene

Four (36, 38, 39, 43), seven (44, 45, 47, 48, 51, 52, 123), six (5 publications) (19, 53, 55, 56, 80), five (4 publications) (36, 53, 56, 57), and seven (6 publications) (36, 38, 53, 54, 56, 60) studies were included in the analysis of dietary β-carotene intake and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. Dietary β-carotene was associated with 8–19% reductions in the RRs of coronary heart disease, stroke, and mortality in the dose-response analysis (Table 1, Figures 8A, 9A, and 12A, Supplemental Figures 25, 26, and 29), but there was no association for cardiovascular disease and total cancer (Figures 10A and 11A, Table 1, Supplemental Figures 27 and 28). There was evidence of a nonlinear association between β-carotene intake and coronary heart disease ($P_{\text{nonlinearity}} = 0.006$), stroke ($P_{\text{nonlinearity}} < 0.0001$), total cancer ($P_{\text{nonlinearity}} = 0.003$), and mortality ($P_{\text{nonlinearity}} < 0.0001$), with a stronger reduction in risk at the lower amounts of intake, but there was no evidence of an association or nonlinearity for cardiovascular disease ($P_{\text{nonlinearity}} = 0.51$) (Figures 8C–12C, Supplemental Table 17).

β-Carotene in blood

Four (89, 91, 93, 95), three (97, 99, 100), seven (19–21, 27, 103, 106, 109), seven (20, 21, 27, 28, 115, 117, 120),

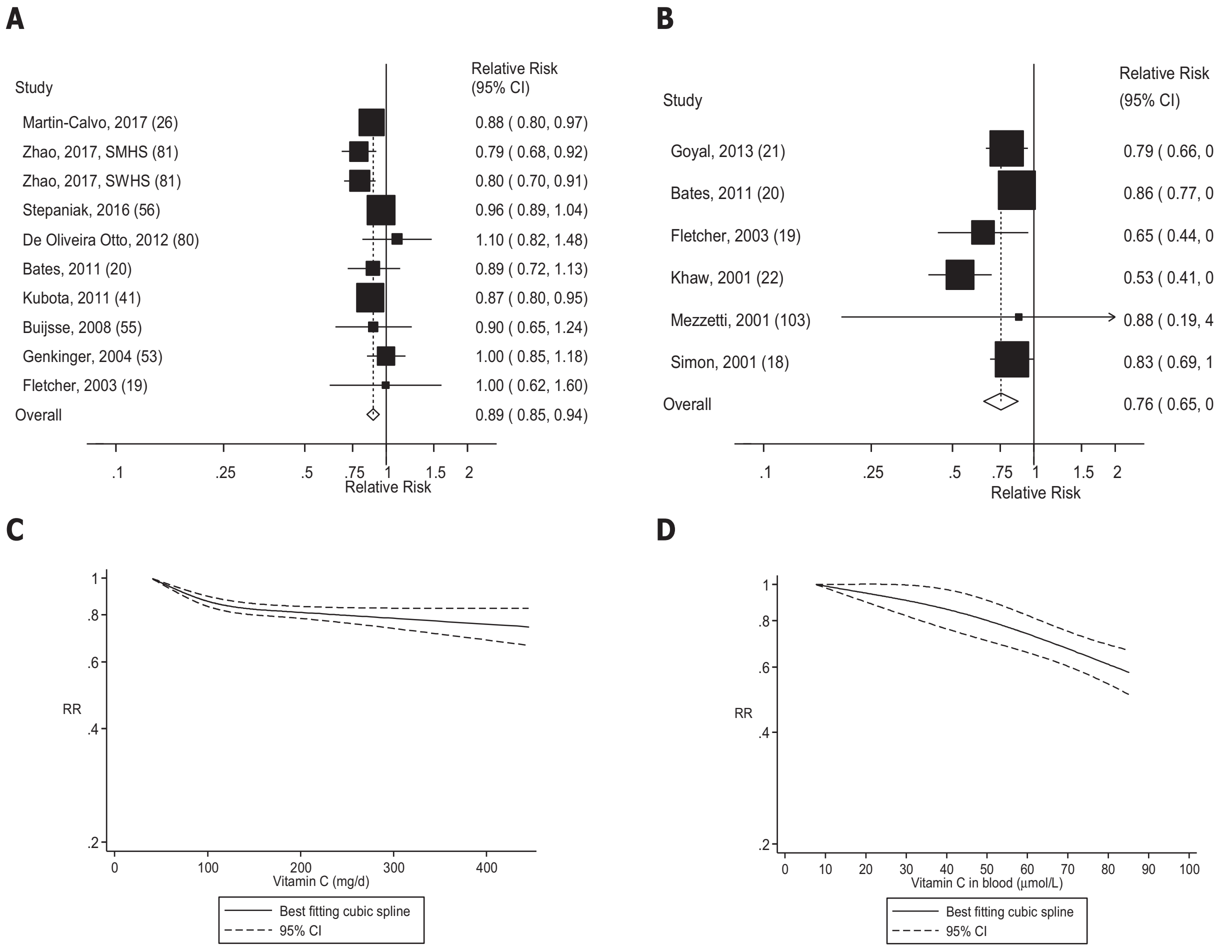

FIGURE 4 Dietary intake and blood concentrations of vitamin C and cardiovascular disease: dose-response analyses. (A) Dietary vitamin C and cardiovascular disease: linear dose-response analysis. The summary RR per 100 mg/d was 0.89 (95% CI: 0.85, 0.94, $I^2 = 27\%$, $P_{\text{heterogeneity}} = 0.19$, $n = 10$). (B) Vitamin C in blood and cardiovascular disease: linear dose-response analysis. The summary RR per 50 μmol/L was 0.76 (95% CI: 0.65, 0.87, $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.05$, $n = 6$). (C) Dietary vitamin C and cardiovascular disease: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin C and cardiovascular disease ($P_{\text{nonlinearity}} < 0.0001$). (D) Vitamin C in blood and cardiovascular disease: nonlinear dose-response analysis. There was no evidence of nonlinearity for vitamin C in blood and cardiovascular disease ($P_{\text{nonlinearity}} = 0.26$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines. SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

and seven (19–21, 27, 117, 121, 124) studies were included in the analysis of blood concentrations of β-carotene and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. A 15–24% reduction in RR was observed for blood concentrations of β-carotene in relation to all outcomes (Table 1, Figures 8B–12B, Supplemental Figures 30–34). There was indication of a nonlinear association for coronary heart disease ($P_{\text{nonlinearity}} = 0.002$), stroke ($P_{\text{nonlinearity}} = 0.07$), cardiovascular disease ($P_{\text{nonlinearity}} = 0.006$), and mortality ($P_{\text{nonlinearity}} = 0.005$), with stronger associations at the lower β-carotene concentrations, but not for total cancer ($P_{\text{nonlinearity}} = 0.60$) (Figures 8D–12D, Supplemental Table 18).

Dietary α-carotene

Two (45, 123) and two (54, 123) studies were included in the analysis of dietary α-carotene and risk of stroke and mortality, respectively. There was a 22% reduction in the RR of mortality for high compared with low intake of α-carotene, but no association was observed for stroke (Supplemental Figures 35–37).

α-Carotene in blood

Four (91, 93–95), three (94, 99, 100), five (20, 94, 106, 108, 109), four (5 publications) (20, 94, 117, 118, 120), and five (20, 24, 94, 117, 121) studies were included in the analysis of blood concentrations of α-carotene and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. A 42% and 29% reduction in RR for total cancer and mortality was observed for α-carotene in blood, but no association was observed for coronary heart disease, stroke, or cardiovascular disease (Figure 13A, Table 1, Supplemental Figures 38–46). There was evidence of nonlinear associations for coronary heart disease ($P_{\text{nonlinearity}} = 0.01$), cardiovascular disease ($P_{\text{nonlinearity}} < 0.0001$), total cancer ($P_{\text{nonlinearity}} < 0.0001$),

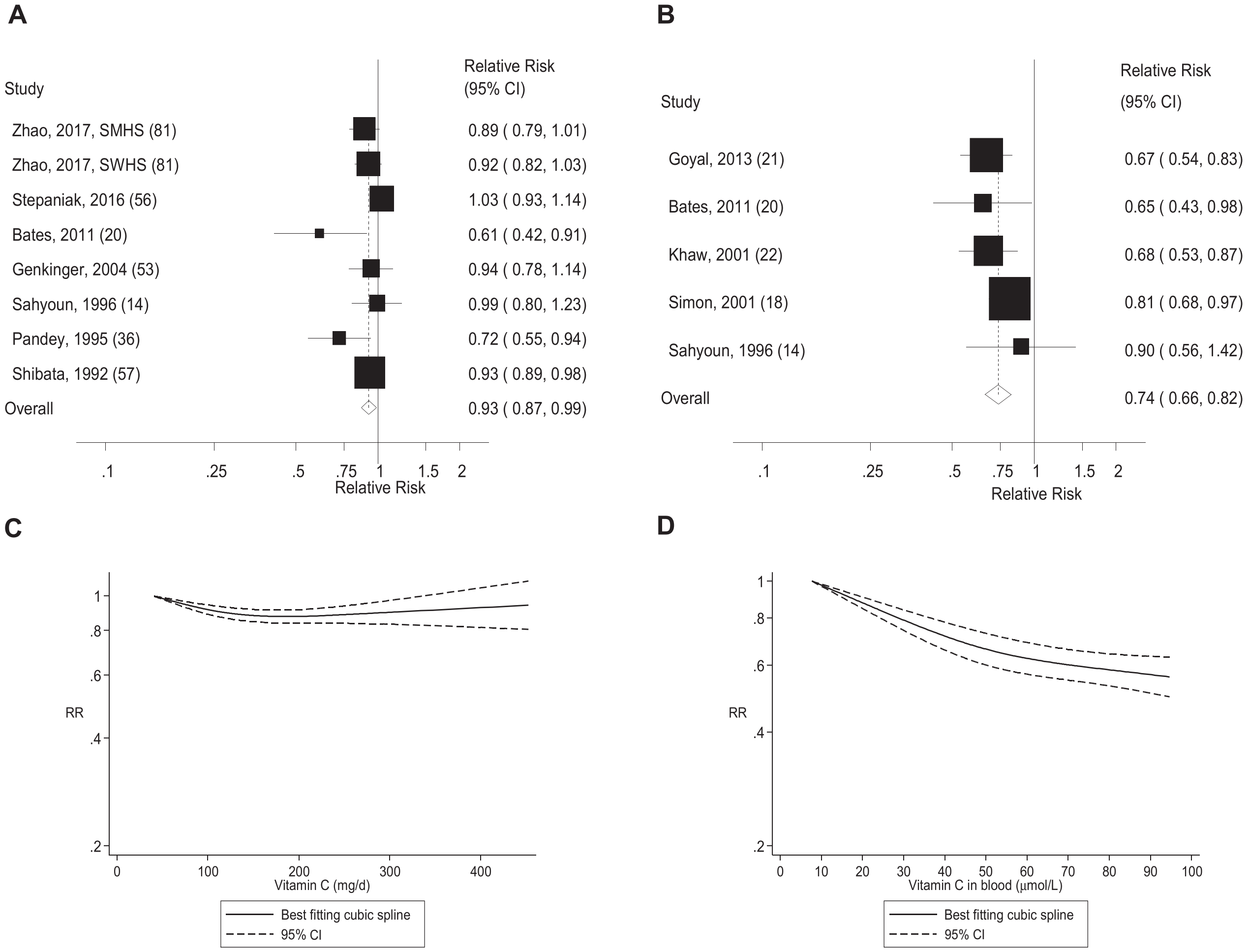

FIGURE 5 Dietary intake and blood concentrations of vitamin C and total cancer: dose-response analyses. (A) Dietary vitamin C and total cancer: linear dose-response analysis. The summary RR per 100 mg/d was 0.93 (95% CI: 0.87, 0.99, $I^2 = 46\%$, $P_{\text{heterogeneity}} = 0.08$, $n = 8$). (B) Vitamin C in blood and total cancer: linear dose-response analysis. The summary RR per 50 µmol/L was 0.74 (95% CI: 0.66, 0.82, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.49$, $n = 5$). (C) Dietary vitamin C and total cancer: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin C and total cancer ($P_{\text{nonlinearity}} = 0.007$). (D) Vitamin C in blood and total cancer: nonlinear dose-response analysis. There was evidence of nonlinearity for vitamin C in blood and total cancer ($P_{\text{nonlinearity}} = 0.006$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines. SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

and mortality ($P_{\text{nonlinearity}} < 0.0001$), with stronger inverse associations at the lower blood concentrations than at higher blood concentrations, but not for stroke ($P_{\text{nonlinearity}} = 0.87$) (Figure 13D, Supplemental Figures 38B, 40B, 42B, and 44B, Supplemental Table 19).

Dietary β-cryptoxanthin

Two studies (54, 123) were included in the high compared with low analysis of dietary β-cryptoxanthin and mortality. There was a 26% reduction in the RR for high compared with low intake (Supplemental Figure 47).

β-Cryptoxanthin in blood

Two (91, 93), four (20, 104, 106, 108), three (20, 108, 120), and three (20, 108, 121) studies were included in the analyses of blood concentrations of β-cryptoxanthin and risk of coronary heart disease, cardiovascular disease, total cancer, and mortality, respectively. A 26% and 16% reduction in the RR of total cancer and mortality was observed, respectively, but no significant association was observed for coronary heart disease and cardiovascular disease (Figure 13B, Table 1, Supplemental Figures 48–54). There was evidence of a nonlinear association between β-cryptoxanthin in blood and coronary heart disease ($P_{\text{nonlinearity}} = 0.01$), but not for cardiovascular disease ($P_{\text{nonlinearity}} = 0.20$) or mortality ($P_{\text{nonlinearity}} = 0.98$) (Figure 13E, Supplemental Figures 48B and 50B, Supplemental Table 20).

Dietary lutein

Two (54, 127) studies were included in the high compared with low analysis of dietary lutein and mortality and there was no significant association (Supplemental Figure 55).

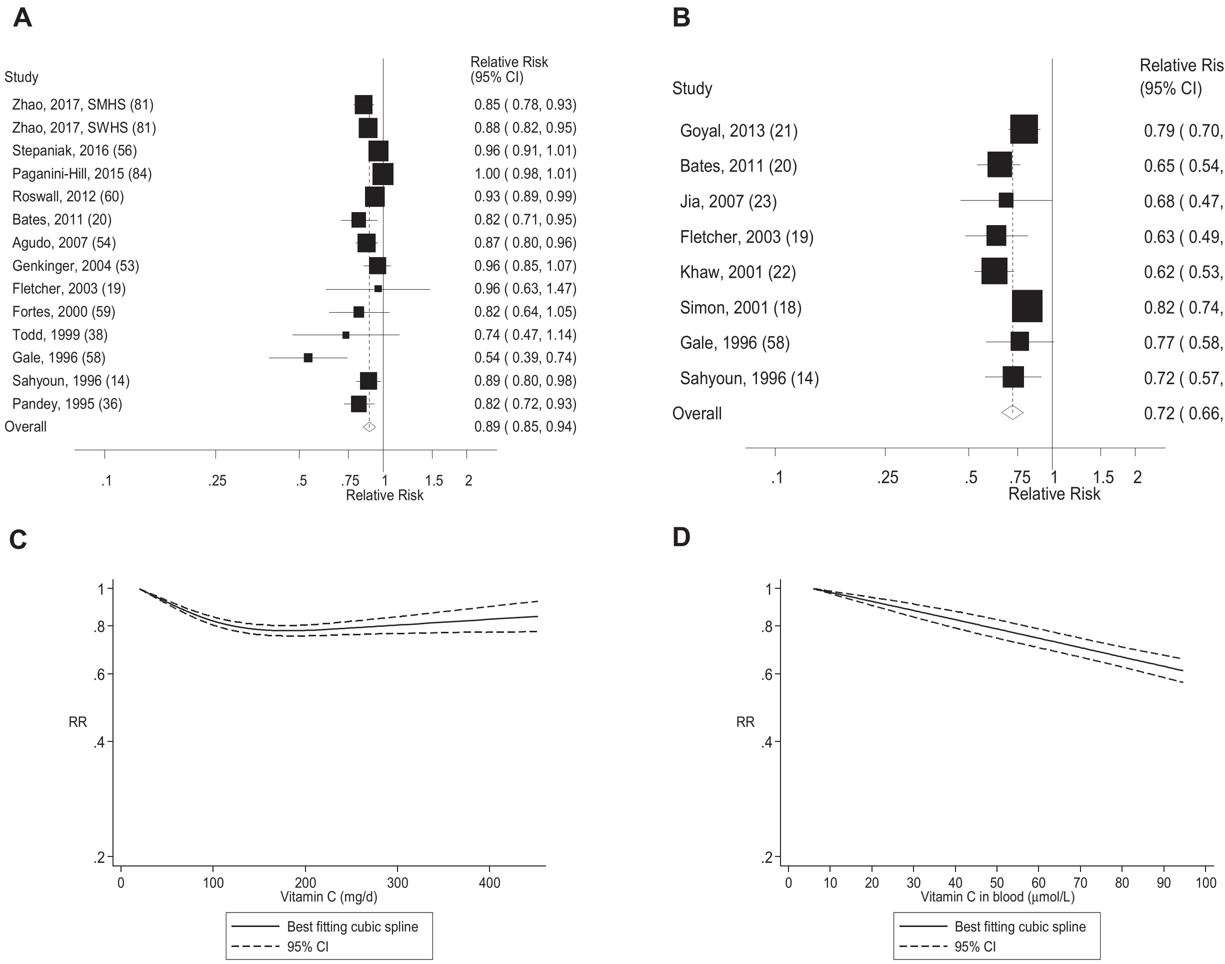

FIGURE 6 Dietary intake and blood concentrations of vitamin C and mortality: dose-response analyses. (A) Dietary vitamin C and mortality: linear dose-response analysis. The summary RR per 100 mg/d was 0.89 (95% CI: 0.85, 0.94, $I^2 = 80\%$, $P_{\text{heterogeneity}} < 0.0001$, $n = 14$). (B) Vitamin C in blood and mortality: linear dose-response analysis. The summary RR per 50 μmol/L was 0.72 (95% CI: 0.66, 0.79, $I^2 = 48\%$, $P_{\text{heterogeneity}} = 0.06$, $n = 8$). (C) Dietary vitamin C and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin C and mortality ($P_{\text{nonlinearity}} < 0.0001$). (D) Vitamin C in blood and mortality: nonlinear dose-response analysis. There was no evidence of nonlinearity for vitamin C in blood and mortality ($P_{\text{nonlinearity}} = 0.90$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines. SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

Lutein in blood

Three (89, 91, 93) studies were included in the high compared with low analysis of lutein in blood and risk of coronary heart disease and there was no significant association (Supplemental Figure 56).

Dietary zeaxanthin

Two (89, 93) and two (54, 127) studies were included in the high compared with low analysis of dietary zeaxanthin and risk of coronary heart disease and mortality, respectively, and there was no significant association in both analyses (Supplemental Figures 57 and 58).

Lutein and zeaxanthin in blood

Four (20, 104, 106, 108), three (20, 108, 118), and two (20, 108) studies were included in the analyses of lutein and zeaxanthin in blood and risk of cardiovascular disease, total cancer, and mortality, respectively. No significant association was observed in all analyses (Supplemental Figures 59–62).

Dietary lycopene

Two (43, 78), three (45, 47, 78), and two (55, 78) studies were included in the analysis of dietary lycopene and risk of coronary heart disease, stroke, and cardiovascular disease. No studies were identified for total cancer, and only 2 were identified for mortality (54, 127), but dose-response analyses were not possible. There was no association between dietary lycopene and coronary heart disease, stroke, cardiovascular disease, or all-cause mortality (Table 1, Supplemental Figures 63–68). There was no evidence of a nonlinear association between lycopene intake and coronary heart disease ($P_{\text{nonlinearity}} = 0.97$) or stroke ($P_{\text{nonlinearity}} = 0.81$) (Supplemental Figures 63B and 65B, Supplemental Table 21).

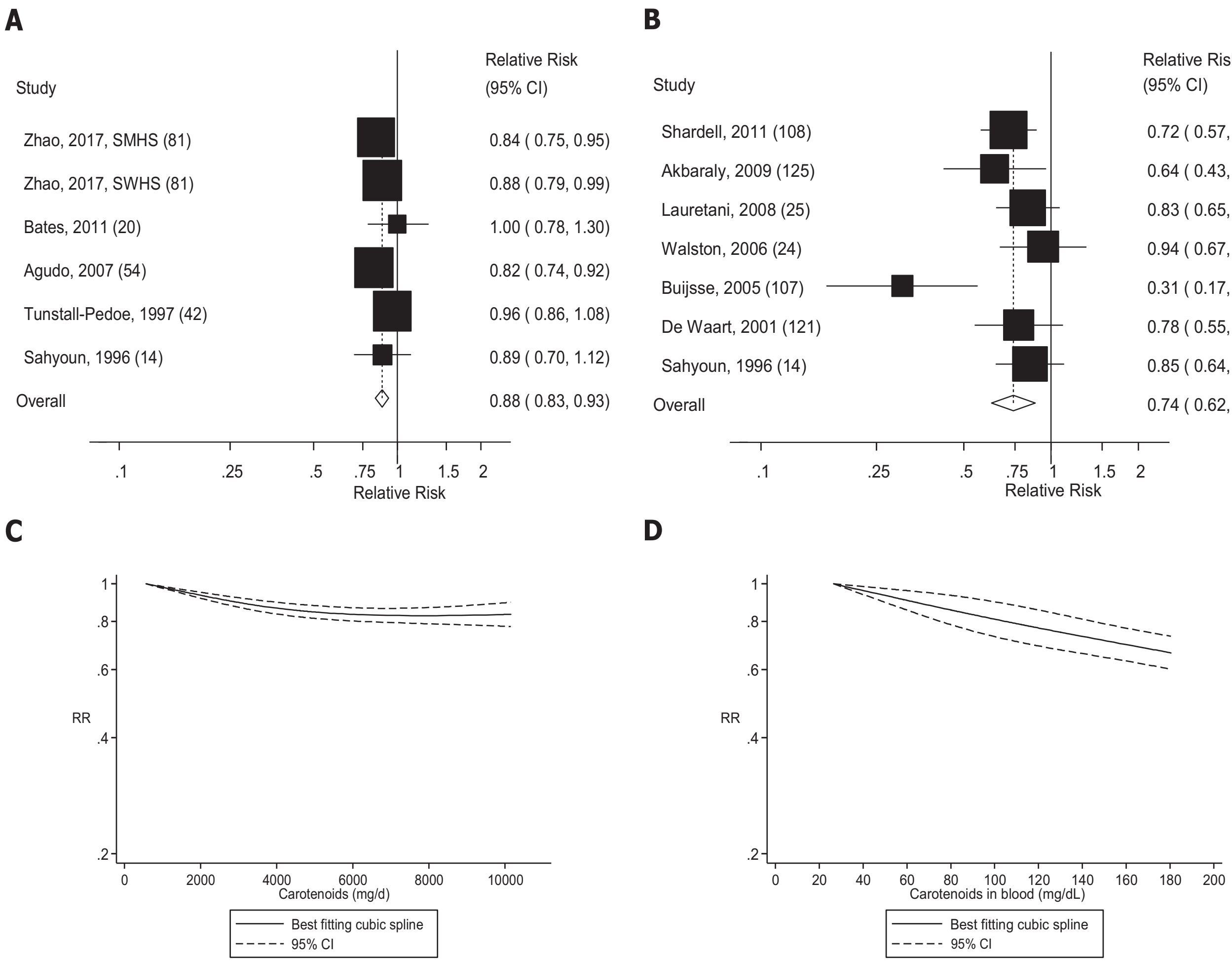

FIGURE 7 Dietary intake and blood concentrations of carotenoids and mortality: dose-response analyses. (A) Dietary carotenoids and mortality: linear dose-response analysis. The summary RR per 5000 µg/d was 0.88 (95% CI: 0.83, 0.93, $I^2 = 2\%$, $P_{\text{heterogeneity}} = 0.40$, $n = 6$). (B) Carotenoids in blood and mortality: linear dose-response analysis. The summary RR per 50 µg/dL was 0.69 (95% CI: 0.59, 0.81, $I^2 = 50\%$, $P_{\text{heterogeneity}} = 0.04$, $n = 10$). (C) Dietary carotenoids and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary carotenoids and mortality ($P_{\text{nonlinearity}} = 0.01$). (D) Carotenoids in blood and mortality: nonlinear dose-response analysis. There was no evidence of nonlinearity for vitamin C in blood and mortality ($P_{\text{nonlinearity}} = 0.73$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines. SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

Lycopene in blood

Three (91, 93, 95), two (93, 95), five (20, 95, 104, 106, 108), five (20, 108, 117, 119, 120), and five (20, 108, 117, 121, 124) studies were included in the analysis of blood concentrations of lycopene and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. There was no significant association between lycopene in blood and any of the outcomes in the linear dose-response analyses or high and low analyses (Figure 13C, Table 1, Supplemental Figures 69–77). Although the test for nonlinearity was not significant for coronary heart disease ($P_{\text{nonlinearity}} = 0.30$), there was indication of a nonlinear association between lycopene in blood and stroke ($P_{\text{nonlinearity}} < 0.0001$), cardiovascular disease ($P_{\text{nonlinearity}} = 0.005$), total cancer ($P_{\text{nonlinearity}} < 0.0001$), and mortality ($P_{\text{nonlinearity}} = 0.001$), and most of the reduction in risk was observed at the lower range of lycopene concentrations (Figure 13F, Supplemental Figures 69B, 71B, 73B, and 75B, Supplemental Table 22).

Dietary vitamin E

Nine (14, 34, 35, 37–39, 41, 49, 77), ten (41, 44–48, 49, 51, 61, 123), nine (7 publications) (20, 41, 53, 55, 56, 80, 81), seven (5 publications) (14, 20, 53, 56, 81), and eleven (9 publications) (14, 19, 20, 38, 53, 54, 56, 81, 127) studies were included in the analysis of dietary vitamin E (including both diet and total vitamin E) and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. Dietary vitamin E was not significantly associated with any of the outcomes in the linear dose-response analysis (Table 1, Figure 14A, Supplemental Figures 78–86). However, there was indication of nonlinearity between vitamin E and coronary heart disease ($P_{\text{nonlinearity}} < 0.0001$), stroke ($P_{\text{nonlinearity}} < 0.0001$), cardiovascular disease ($P_{\text{nonlinearity}} < 0.0001$), total cancer ($P_{\text{nonlinearity}} = 0.003$), and mortality ($P_{\text{nonlinearity}} < 0.0001$) (Figure 14, Supplemental Figures 78C, 80C, 82C, and 84C, Supplemental Table 23), with stronger reductions in risk at lower amounts of intake.

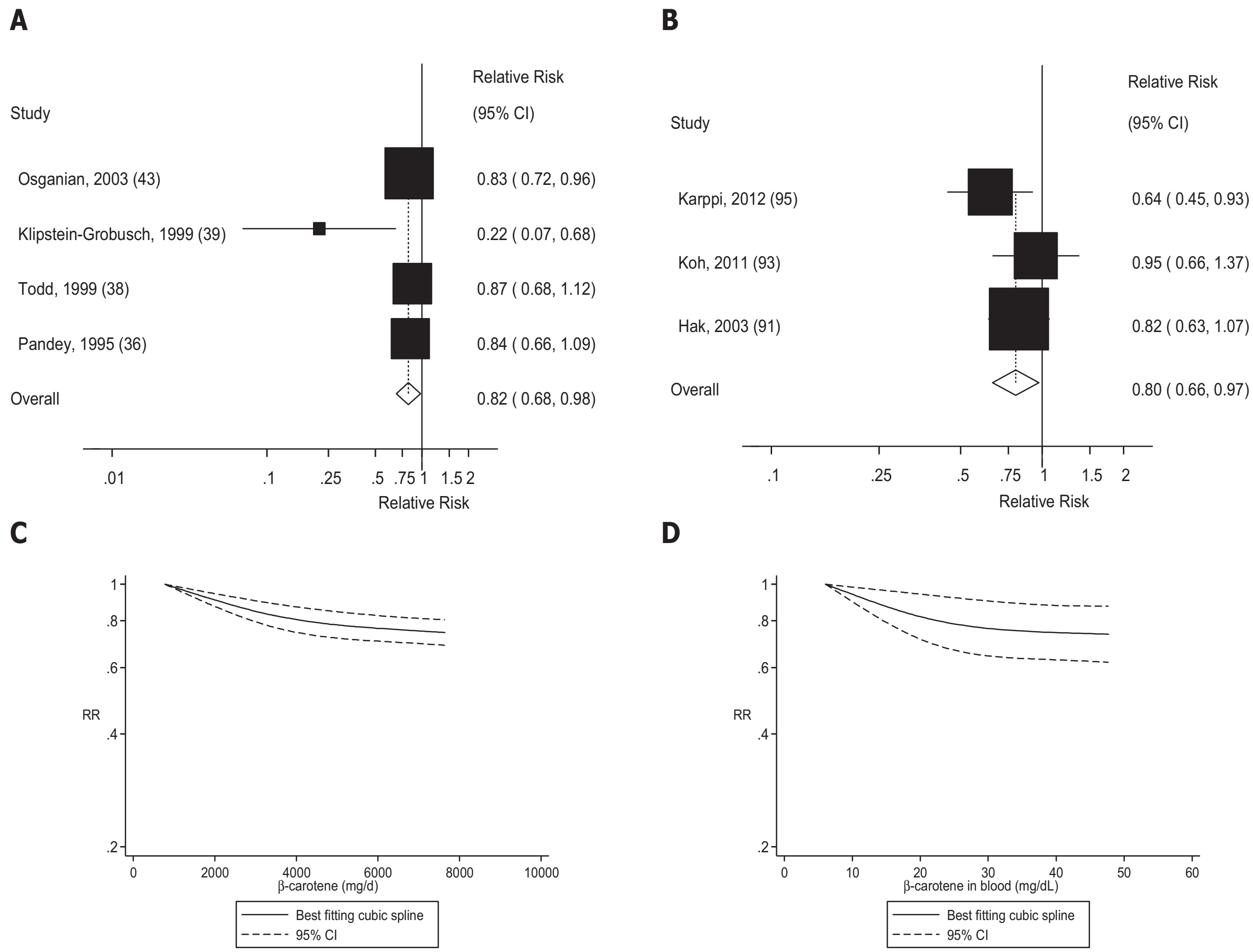

FIGURE 8 Dietary β-carotene and blood concentrations of β-carotene and coronary heart disease: dose-response analyses. (A) Dietary β-carotene and coronary heart disease: linear dose-response analysis. The summary RR per 5000 µg/d was 0.82 (95% CI: 0.68, 0.98, $I^2 = 45\%$, $P_{\text{heterogeneity}} = 0.14$, $n = 4$). (B) β-Carotene in blood and coronary heart disease: linear dose-response analysis. The summary RR per 25 µg/dL was 0.76 (95% CI: 0.62, 0.93, $I^2 = 22\%$, $P_{\text{heterogeneity}} = 0.28$, $n = 4$). (C) Dietary β-carotene and coronary heart disease: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary β-carotene and coronary heart disease ($P_{\text{nonlinearity}} = 0.006$). (D) β-Carotene in blood and coronary heart disease: nonlinear dose-response analysis. There was evidence of nonlinearity for β-carotene in blood and coronary heart disease ($P_{\text{nonlinearity}} = 0.002$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

α-Tocopherol in blood

Five (14, 90, 91, 95, 96), four (96, 97, 99, 100), seven (19–21, 70, 79, 103, 107), eight (9 publications) (14, 20, 21, 70, 107, 110, 112–114), and eight (14, 19–21, 70, 107, 121, 124) studies were included in the analysis of α-tocopherol in blood and risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and mortality, respectively. There was a 10%, 9%, and 6% reduction in the risk of stroke, total cancer, and mortality, respectively, for each 500-μg/dL increase in blood concentrations of α-tocopherol, but no significant association was observed for coronary heart disease or cardiovascular disease overall (Figure 14B, Supplemental Figures 78B, 80B, 82B, 84B, and 87–91). The test for nonlinearity was significant for coronary heart disease ($P_{\text{nonlinearity}} = 0.02$) and mortality ($P_{\text{nonlinearity}} = 0.05$), but not for stroke ($P_{\text{nonlinearity}} = 0.79$), cardiovascular disease ($P_{\text{nonlinearity}} = 0.32$), or total cancer ($P_{\text{nonlinearity}} = 0.59$) (Figure 14, Supplemental Figures 78D, 80D, 82D, and 84D, Supplemental Table 24).

γ-Tocopherol in blood

Three (90, 91, 96) and two (91, 96) studies were included in the analyses of γ-tocopherol in blood and coronary heart disease and stroke, respectively. No significant association was observed in both analyses (Supplemental Figures 92–95).

Publication bias, subgroup and sensitivity analyses, influence analyses, study quality.

There was evidence of publication bias in the following analyses: dietary vitamin C and coronary heart disease, stroke, and all-cause mortality; carotenoids in blood and all-cause mortality; dietary β-carotene and stroke, total cancer, and all-cause mortality; α-carotene in blood and all-cause mortality; lycopene in blood and all-cause mortality; and dietary vitamin E and cardiovascular disease, total cancer, and all-cause mortality (Supplemental Figures 96–107).

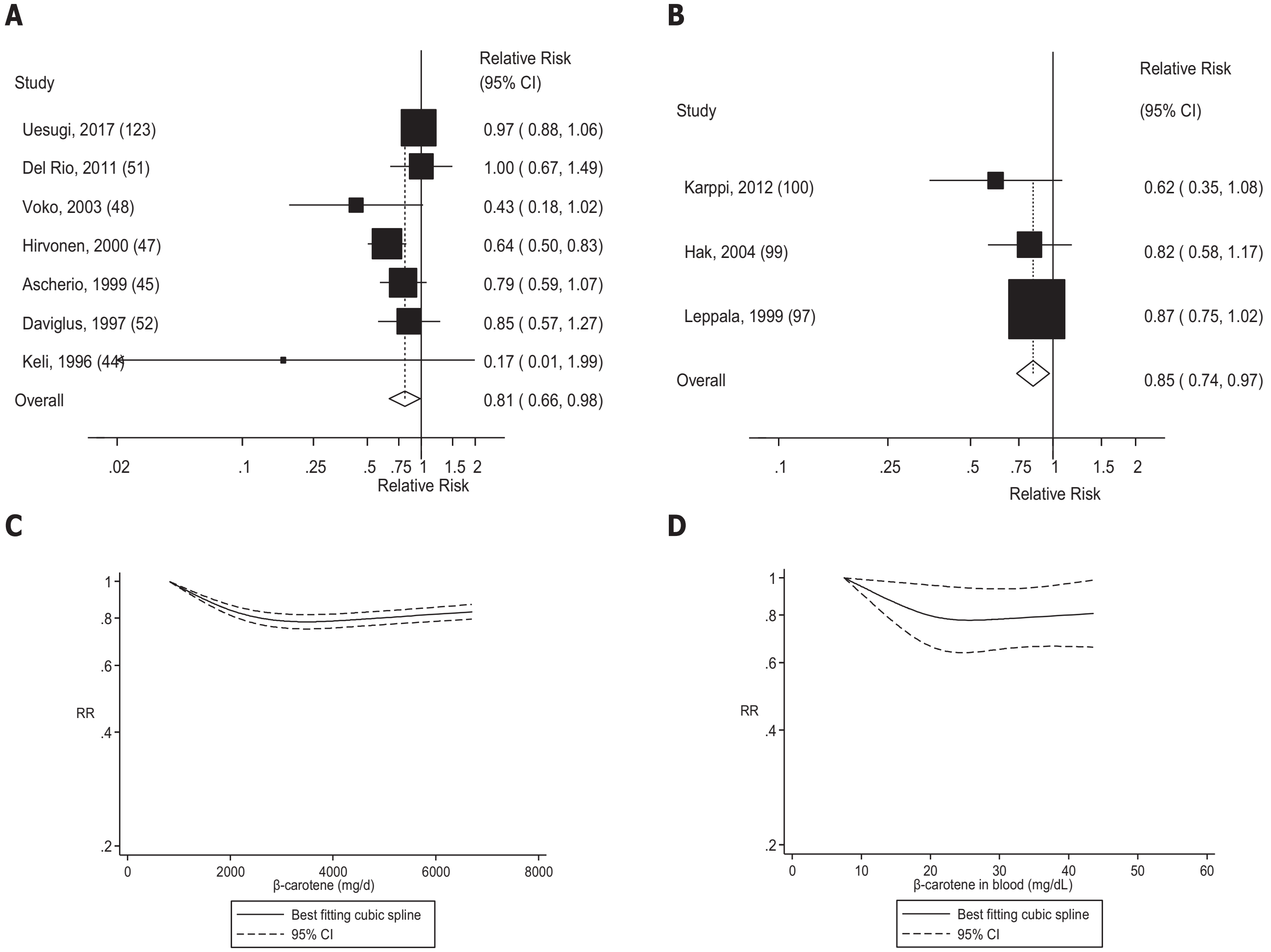

FIGURE 9 (A) Dietary β-carotene and stroke: linear dose-response analyses. The summary RR per 5000 µg/d was 0.81 (95% CI: 0.66, 0.98, $I^2 = 59\%$, $P_{\text{heterogeneity}} = 0.02$, $n = 7$). (B) β-Carotene in blood and stroke: linear dose-response analysis. The summary RR per 25 µg/dL was 0.85 (95% CI: 0.74, 0.97, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.50$, $n = 3$). (C) Dietary β-carotene and stroke: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary β-carotene and stroke ($P_{\text{nonlinearity}} < 0.0001$). (D) β-Carotene in blood and stroke: nonlinear dose-response analysis. There was evidence of nonlinearity for β-carotene in blood and stroke ($P_{\text{nonlinearity}} = 0.07$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

In stratified analyses there was little evidence of heterogeneity between subgroups of studies that investigated vitamin C intake and coronary heart disease, stroke, cardiovascular disease, total cancer, or mortality (Supplemental Tables 25–26). In the analysis of blood concentrations of vitamin C and cardiovascular disease there was evidence of heterogeneity among subgroups of studies that excluded subjects with prevalent disease at baseline ($P = 0.04$), with a stronger association among studies with such exclusions compared with those without (Supplemental Table 27). In the analysis of blood concentrations of vitamin C and mortality, there was heterogeneity by duration of follow-up ($P = 0.02$), with a weaker association among studies with longer follow-up than among studies with shorter follow-up (Supplemental Table 27), and by geographic location ($P = 0.02$), with a stronger association among European studies than among American studies. There was also heterogeneity between subgroups which adjusted for education, smoking, alcohol, BMI, physical activity, hypertension, and serum cholesterol ($P_{\text{heterogeneity}} = 0.02$ or 0.03 for all) (Supplemental Table 27), with weaker associations among studies with such adjustment; however, the inverse associations persisted among studies with such adjustment. There was no between-subgroup heterogeneity for carotenoids in blood and mortality (Supplemental Table 29), dietary β-carotene and stroke (Supplemental Table 30), and β-carotene in blood and cardiovascular disease, total cancer, and mortality (Supplemental Table 31), and little evidence of heterogeneity among studies of vitamin E and coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause mortality (Supplemental Tables 32–33), and among studies of α-tocopherol in blood and cardiovascular disease, total cancer, and mortality (Supplemental Table 34).

In further influence analyses excluding 1 study at a time, most of the associations were robust to the influence of individual studies (Supplemental Figures 108–125).

The study quality of the included studies was, in general, high as the vast majority of the included studies were in the subgroup with 7–9 points (Supplemental Tables 25–34).

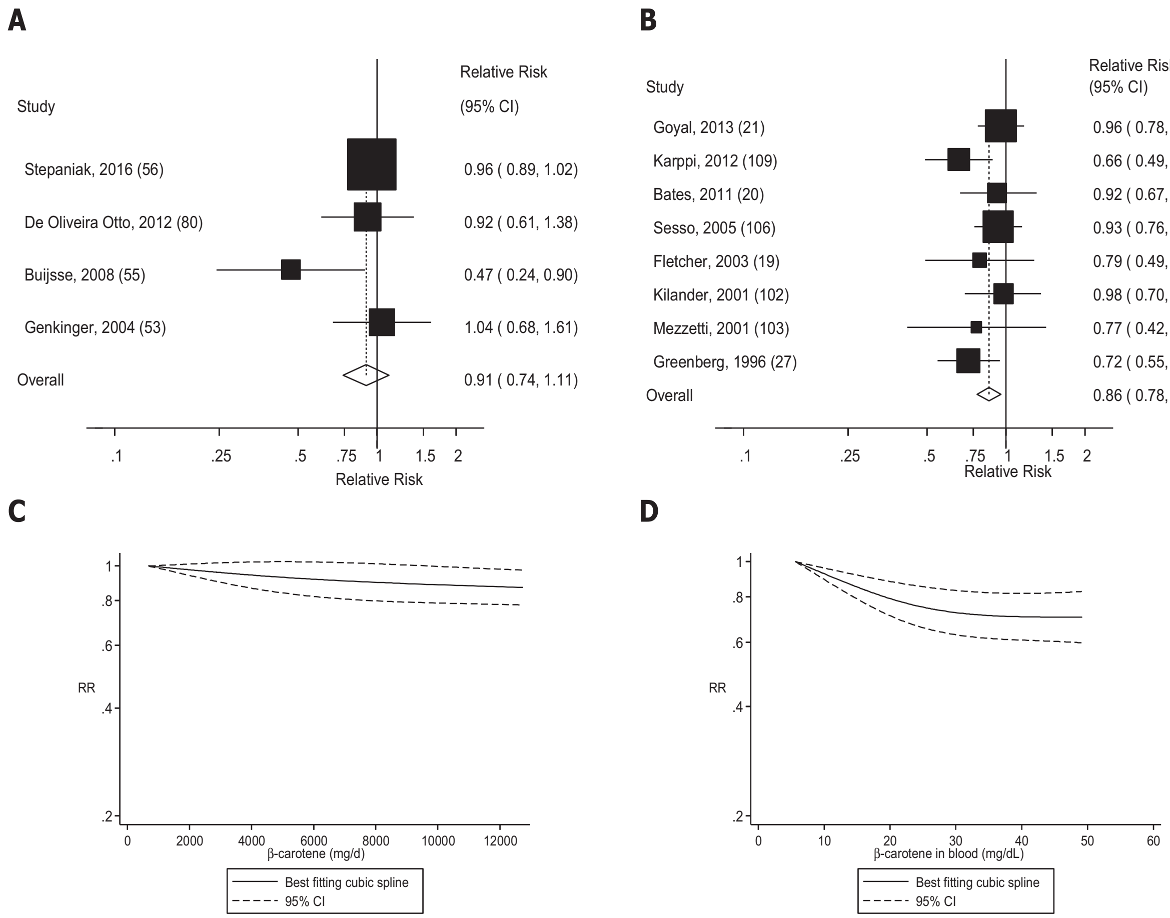

FIGURE 10 Dietary β-carotene and blood concentrations of β-carotene and cardiovascular disease: dose-response analyses. (A) Dietary β-carotene and cardiovascular disease: linear dose-response analysis. The summary RR per 5000 µg/d was 0.87 (95% CI: 0.63, 1.20, $I^2 = 58\%$, $P_{\text{heterogeneity}} = 0.10$, $n = 3$). (B) β-Carotene in blood and cardiovascular disease: linear dose-response analysis. The summary RR per 25 µg/dL was 0.85 (95% CI: 0.76, 0.95, $I^2 = 9\%$, $P_{\text{heterogeneity}} = 0.36$, $n = 7$). (C) Dietary β-carotene and cardiovascular disease: nonlinear dose-response analysis. There was no evidence of nonlinearity between dietary β-carotene and cardiovascular disease ($P_{\text{nonlinearity}} = 0.51$). (D) β-Carotene in blood and cardiovascular disease: nonlinear dose-response analysis. There was evidence of nonlinearity for β-carotene in blood and cardiovascular disease ($P_{\text{nonlinearity}} = 0.006$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

DISCUSSION

This meta-analysis showed an inverse association between dietary intake and blood concentrations of vitamin C and risk of coronary heart disease, stroke, cardiovascular disease overall, total cancer, and all-cause mortality. Vitamin C is found abundantly in fruits, vegetables, especially berries, citrus fruits and juices, kiwi, broccoli, and peppers and some legumes (green beans), as well as dietary supplements. Plasma ascorbic acid correlates with intake of fruit and vegetables (22, 98, 128), especially citrus fruit and citrus fruit juices (14, 129), and epidemiological studies have found a reduced risk of cardiovascular disease, total cancer, and/or all-cause mortality with a high intake of these foods (11).

Dietary carotenoid intake as well as intake of specific carotenoids (β-carotene, lycopene) were inversely associated with coronary heart disease, stroke, and mortality, whereas blood concentrations of carotenoids (total, β-carotene, α-carotene, lycopene, β-cryptoxanthin) were inversely associated with cardiovascular disease, total cancer, and/or all-cause mortality. Carotenoids are mainly found in green and yellow fruits and vegetables as well as dietary supplements. Intakes of fruits and vegetables, raw vegetables, green or green and yellow vegetables, and carrots are correlated with blood concentrations of total carotenoids, α-carotene, and β-carotene (14, 91, 130, 131), and studies have reported a reduced risk of coronary heart disease, stroke, cardiovascular disease, total cancer, and/or all-cause mortality with a high intake of these food sources of carotenoids (11). Blood concentrations of β-cryptoxanthin correlate well with total fruit and citrus fruit intake (91, 130, 131), whereas blood concentrations of lycopene correlate with tomato and tomato juice intake (91, 131–133). Intake of tomatoes has been inversely associated with coronary heart disease, although associations with other outcomes are less clear (11).

Dietary vitamin E was not significantly associated with any of the outcomes in the linear dose-response analysis; however, inverse associations were observed in the nonlinear dose-response analysis, which might suggest that the nonlinear analysis fit the data better. Blood concentrations of α-tocopherol

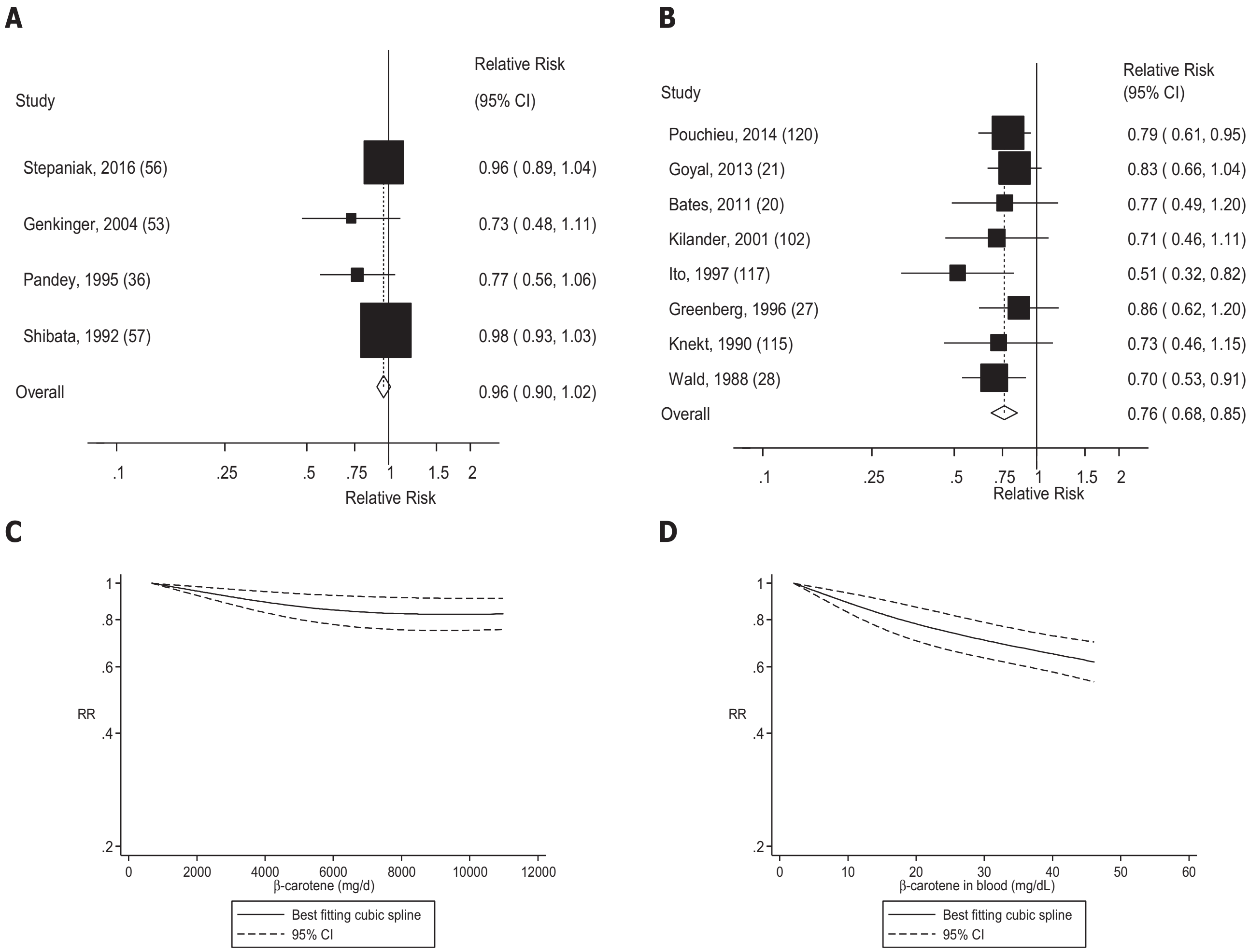

FIGURE 11 Dietary β-carotene and blood concentrations of β-carotene and total cancer: dose-response analyses. (A) Dietary β-carotene and total cancer: linear dose-response analysis. The summary RR per 5000 µg/d was 0.96 (95% CI: 0.90, 1.02, $I^2 = 25\%$, $P_{\text{heterogeneity}} = 0.26$, $n = 4$). (B) β-Carotene in blood and total cancer: linear dose-response analysis. The summary RR per 25 µg/dL was 0.77 (95% CI: 0.68, 0.86, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.64$, $n = 7$). (C) Dietary β-carotene and total cancer: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary β-carotene and total cancer ($P_{\text{nonlinearity}} = 0.003$). (D) β-Carotene in blood and total cancer: nonlinear dose-response analysis. There was evidence of nonlinearity for β-carotene in blood and total cancer ($P_{\text{nonlinearity}} = 0.60$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

were inversely associated with risk of stroke, total cancer, and all-cause mortality. Vitamin E is found mainly in vegetable oils, nuts, seeds, and some fruits and vegetables, as well as dietary supplements, and blood concentrations of α-tocopherol are correlated with intake of fresh fruits and juices and vegetables (134) and vitamin E from diet and supplements (134, 135). Vitamin E intake may be less specific to the intake of fruits and vegetables than vitamin C and carotenoids, possibly accounting for the lack of association between dietary vitamin E and cardiovascular disease, cancer, and mortality, although nut intake has been inversely associated with these outcomes (10).

The inverse associations between blood concentrations of vitamin C, vitamin E, total carotenoids, and β-carotene with disease and mortality endpoints were slightly stronger than for dietary intake. However, the dose-response relation appeared to be more often linear or nearly linear for the blood concentrations of vitamin C, carotenoids, β-carotene, and β-cryptoxanthin and mortality, than for both dietary antioxidant intake in the current analysis and fruit and vegetable intake in our recent meta-analysis (11), where most of the reduction in risk was observed at the lower range of intakes. This could reflect a biological saturation effect, an artifact due to measurement errors with attenuation of the association at higher dietary intakes, or other methodological issues. Vitamin C intake is most strongly associated with plasma vitamin C concentrations at lower intakes, and plasma vitamin C is less responsive at intakes >100–200 mg/d (136), which might explain the nonlinearity in the dietary analyses.

Our results have some limitations. Confounding in both dietary and biomarker studies by physical activity, less obesity, less smoking, and lower intakes of red and processed meat is possible. However, 1 study that used identical covariates for the analysis of dietary intake and plasma concentrations of vitamin C in relation to coronary heart disease risk suggested a stronger association between plasma vitamin C and vitamin C intake estimated from food-records compared with vitamin C intake estimated from food frequency questionnaires (137). Reverse causation

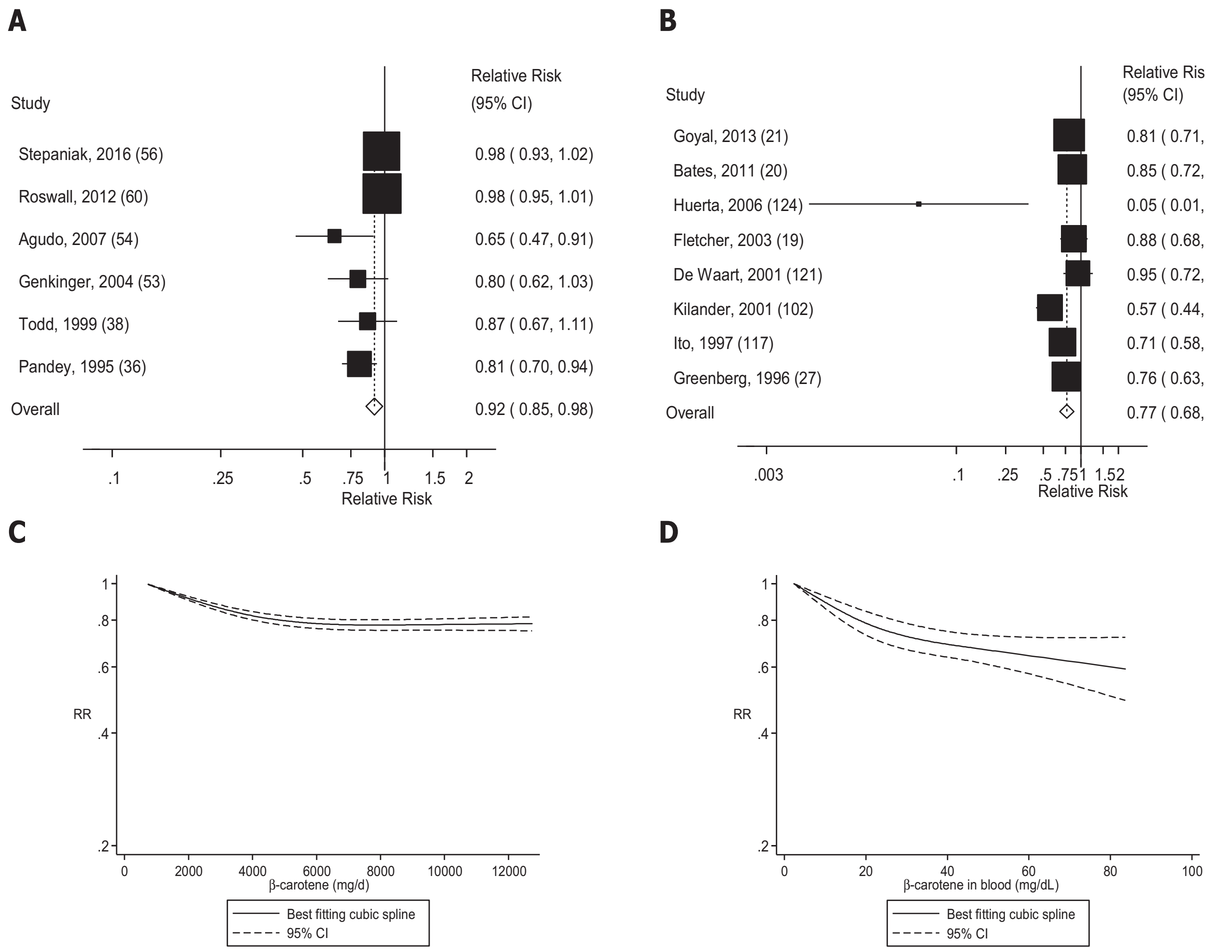

FIGURE 12 Dietary intake and blood concentrations of β-carotene and mortality: dose-response analyses. (A) Dietary β-carotene and mortality: linear dose-response analysis. The summary RR per 5000 µg/d was 0.92 (95% CI: 0.85, 0.98, $I^2 = 66\%$, $P_{\text{heterogeneity}} = 0.01$, $n = 6$). (B) β-Carotene in blood and mortality: linear dose-response analysis. The summary RR per 25 µg/dL was 0.81 (95% CI: 0.72, 0.90, $I^2 = 47\%$, $P_{\text{heterogeneity}} = 0.08$, $n = 7$). (C) Dietary β-carotene and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary β-carotene and mortality ($P_{\text{nonlinearity}} \leq 0.0001$). (D) β-Carotene in blood and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity for β-carotene in blood and mortality ($P_{\text{nonlinearity}} = 0.005$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines.

is also a possibility in studies of biomarkers of antioxidants as antioxidants may be depleted due to oxidative stress or inflammation during the disease process (138). However, this explanation seems less likely as we found that the associations persisted in subgroup analyses of studies that excluded prevalent disease at baseline. In addition, there may have been some inconsistencies between studies in the laboratory methods used for the analyses of blood concentrations of antioxidants, which may have contributed to heterogeneity between studies or could potentially contribute to some of the nonlinear associations observed. There was significant heterogeneity in several of the analyses. Many of the inverse associations persisted in subgroup analyses stratified by sex, location, number of cases, and adjustment for confounding factors, but only in some of the analyses was the heterogeneity explained. Studies of lycopene, α-carotene, β-cryptoxanthin, and dietary carotenoids were small, which limited the statistical power to detect an association and the possibility to conduct subgroup analyses. Evidence of small-study bias or publication bias in some of the analyses suggested that the strength of the associations may have been slightly overestimated in a few analyses, but this is unlikely to substantially alter the overall findings of the study. One last limitation is that there was no protocol for the current review.

Dietary and biomarker studies have different strengths and limitations. Dietary assessments of antioxidant vitamins and carotenoids are prone to recall mismeasurement and do not reflect bioavailability, but could be more time-integrated than a single biomarker measure. Biomarkers reflect absorption being influenced by the degree of processing or cooking of foods, the lipid content of the diet, the degree of fermentation in the colon, menstrual cycle and hormonal factors, and genetic factors (32, 139). Further, metabolism of antioxidants and vitamins, as well as smoking and high alcohol consumption, may reduce blood concentrations of antioxidants (98, 140), which could induce a bias not inherent in dietary studies, although fruit and vegetable intakes explain more variability in plasma carotenoid concentrations than do smoking and alcohol (141).

Strengths of our analysis include the prospective design and high quality of the included studies, minimizing recall and

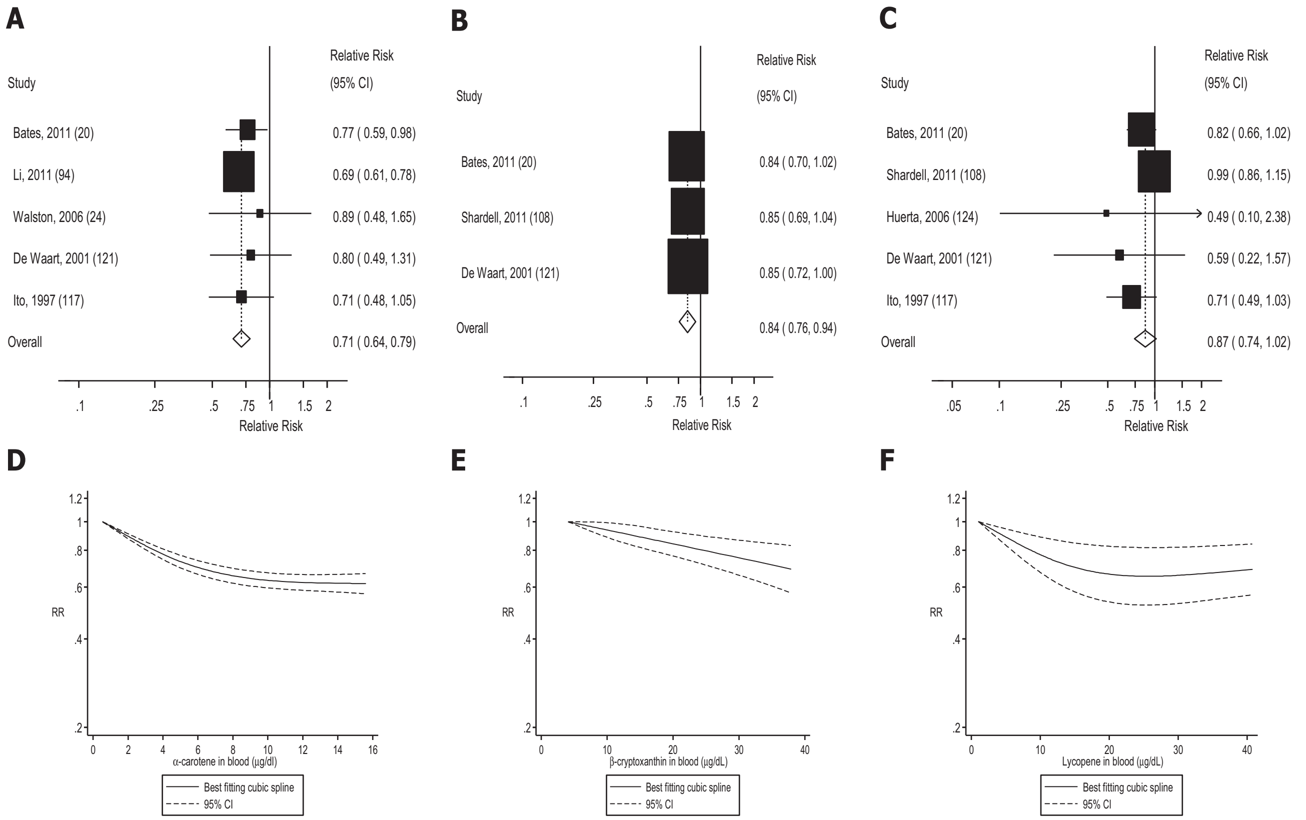

FIGURE 13 Blood concentrations of α-carotene, β-cryptoxanthin, and lycopene and mortality: dose-response analyses. (A) Blood concentrations of α-carotene and mortality: linear dose-response analysis. The summary RR per 10 μg/dL was 0.71 (95% CI: 0.64, 0.79, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.86$, $n = 5$). (B) Blood concentrations of β-cryptoxanthin and mortality: linear dose-response analysis. The summary RR per 15 μg/dL was 0.84 (95% CI: 0.76, 0.94, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.99$, $n = 3$). (C) Blood concentrations of lycopene and mortality: linear dose-response analysis. The summary RR per 25 μg/dL was 0.87 (95% CI: 0.74, 1.02, $I^2 = 26\%$, $P_{\text{heterogeneity}} = 0.25$, $n = 5$). (D) Blood concentrations of α-carotene and mortality, nonlinear dose-response analysis. There was evidence of nonlinearity between α-carotene in blood and mortality ($P_{\text{nonlinearity}} \leq 0.0001$). (E) Blood concentrations of β-cryptoxanthin and mortality: nonlinear dose-response analysis. There was no evidence of nonlinearity for β-cryptoxanthin in blood and mortality ($P_{\text{nonlinearity}} = 0.98$). (F) Blood concentrations of lycopene and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity for lycopene in blood and mortality ($P_{\text{nonlinearity}} = 0.001$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted using restricted cubic splines.

selection bias; the large number of endpoints, which provide great statistical power to detect associations; robustness of results from numerous subgroup and sensitivity analyses; and the detailed dose-response analyses, which clarified the strength and shape of the dose-response relation. Finally, we analyzed both dietary intake and biomarkers of vitamin C, vitamin E, and carotenoids, and with the exception of vitamin E (for which the inverse associations were limited to the nonlinear dose-response analysis), we found that both dietary intake and blood concentrations were inversely associated with risk of cardiovascular disease, cancer, and mortality.

It is likely that the inverse associations between dietary intake and blood concentrations of antioxidants we observed are not due to the effect of single antioxidants but due to multiple antioxidants and food components found in fruit and vegetables. Randomized clinical trials have consistently shown no clear benefit of antioxidant supplements on chronic disease risk and even potential harms of supplementation of vitamin E and β-carotene on mortality and lung cancer risk, respectively (142–144). The randomized trials have used supplements with single or a few antioxidants, whereas the observational studies have assessed these nutrients based on blood concentrations or the dietary intake of foods rich in these nutrients. The dietary sources of these antioxidants (fruits, vegetables, berries, etc.) also contain a myriad of other correlated bioactive compounds that may have synergistic bioactivities. The results from the observational studies could reflect a limited number of bioactive compounds that have not been evaluated in randomized trials or complex, interactive effects of multiple correlated beneficial food components in plant foods. The current meta-analysis therefore addresses a different question than the randomized trials and is therefore not directly comparable with these. In line with synergistic effects of multiple components is a recent randomized intervention study that supplemented diets with kiwi fruit and by using gene expression profiles as proxy outcome, the study indicated that the phytochemicals work in concert rather than individually (145).

Although a combined total antioxidant score may be more strongly correlated with fruit and vegetable intake than individual antioxidants, to date only a few studies have used a total dietary antioxidant score (51, 54, 127, 146, 147) and the results are not substantially different than for individual antioxidants

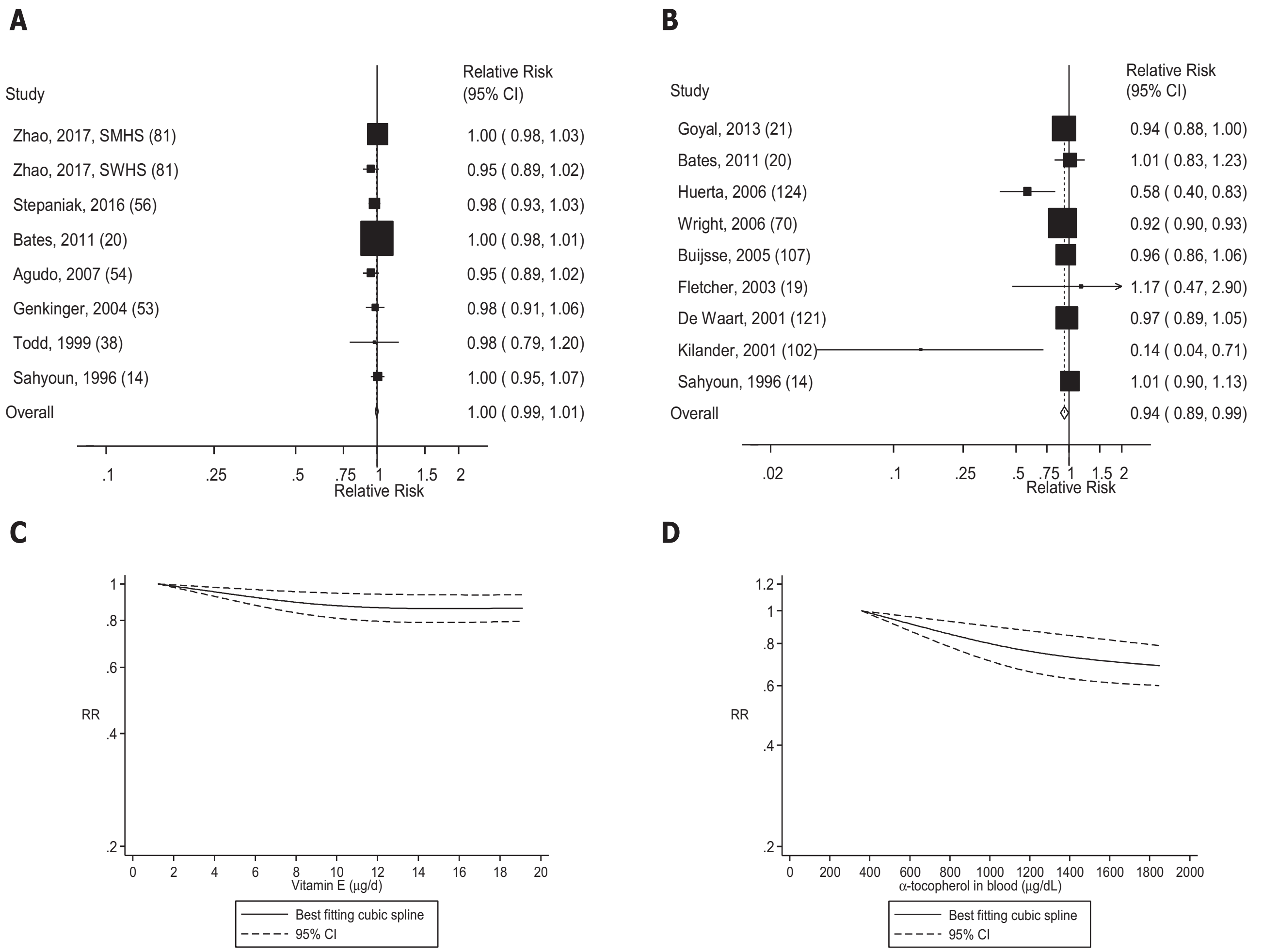

FIGURE 14 (A) Dietary intake of vitamin E and mortality: linear dose-response analysis. The summary RR per 5 µg/d was 0.99 (95% CI: 0.96, 1.01, $I^2 = 42\%$, $P_{\text{heterogeneity}} = 0.10$, $n = 8$). (B) Blood concentrations of α-tocopherol and mortality: linear dose-response analysis. The summary RR per 500 µg/dL was 0.94 (95% CI: 0.90, 0.98, $I^2 = 43\%$, $P_{\text{heterogeneity}} = 0.09$, $n = 8$). (C) Dietary intake of vitamin E and mortality: nonlinear dose-response analysis. There was evidence of nonlinearity between dietary vitamin E and mortality ($P_{\text{nonlinearity}} < 0.0001$). (D) Blood concentrations of α-tocopherol and mortality: nonlinear dose-response analysis. There was indication of nonlinearity for α-tocopherol in blood and mortality ($P_{\text{nonlinearity}} = 0.05$). Summary RRs and 95% CIs were calculated with the use of random-effects models, and the nonlinear dose-response analyses were conducted with the use of restricted cubic splines. SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

(51, 54, 127, 146, 147). We did not identify any studies that used a total antioxidant biomarker. In addition, other, more specific biomarkers (e.g., metabolomics) may enable distinguishing between types of fruits and vegetables in the future (148, 149). Intervention studies have shown increases in serum concentrations of vitamin C and carotenoids with higher intakes of fruits and vegetables (150). However, the size of the increase in blood concentrations was relatively moderate compared with the amount of fruits and vegetables eaten and the range of the blood concentrations of antioxidants observed in the current meta-analysis. Thus, we cannot exclude the possibility that other factors may contribute, at least partly, to the beneficial effect observed of high serum concentrations of antioxidants. The different vitamin C and carotenoid contents of individual fruits and vegetables make it difficult to quantify the amount of fruit and vegetables required to increase the blood concentration of vitamin C or carotenoids by a certain amount.

Together with largely null findings of randomized clinical trials on dietary antioxidant supplements and chronic disease prevention, the current findings have importance for public health because they support dietary recommendations to increase intake of fruit and vegetables (11), but not supplements, to reduce the risk of chronic diseases and premature mortality. Any further studies should investigate associations between less investigated antioxidants or overall antioxidant scores in both diet and blood and these outcomes as well as less common disease outcomes that have been less investigated to date and might benefit from incorporating repeated measures of diet and blood samples.

In conclusion, higher dietary intake and/or blood concentrations of vitamin C, carotenoids, and α-tocopherol (as markers of fruit, vegetable, and nut intake) were associated with reduced risk of cardiovascular disease, total cancer, and all-cause mortality. It is likely that the associations observed are not due to the individual antioxidants themselves, but rather the combination of multiple beneficial components in fruits and vegetables. These results support the notion that a high intake of fruits and vegetables, especially those high in vitamin C and carotenoids, reduces the risk of cardiovascular disease, cancer, and premature mortality.

The authors' responsibilities were as follows—DA and TN: study concept and design; DA, NK, EG, LTF, PB, DCG, ST, ER, LJV, and TN: acquisition, analysis, or interpretation of data; LTF: checking of data extractions for accuracy; DA, NK, EG, PB, LTF, DCG, ER, LJV, ST, and TN: critical revision of the manuscript for important intellectual content: DA and DCG: statistical analysis; DA, LJV, ER, and ST: obtained funding; TN: study supervision; DA: drafted the manuscript and had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis; and all authors: read and approved the final manuscript. None of the authors had any conflicts of interest with regard to this manuscript.

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