REVIEW

Dose–Response Association of Dietary Inflammatory Potential with All-Cause and Cause-Specific Mortality

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ABSTRACT

Although the association of dietary inflammatory potential, evaluated by the dietary inflammatory index (DII), with all-cause and cause-specific mortality has been reported, evidence remains equivocal, with no relevant dose–response meta-analysis having been conducted. To examine the dose–response association of dietary inflammatory potential with risk of all-cause, cancer, and cardiovascular disease (CVD) mortality, PubMed, Embase, and Web of Science were systematically searched up to August 9, 2021. Cohort studies were included if DII was reported as ≥3 levels or per incremental increase, and if the associations of DII with all-cause, cancer, and CVD mortality were assessed. Generalized least squares regression was used to estimate study-specific dose–response associations, and the random effect model was used to pool the RRs and 95% CIs of all-cause, cancer, and CVD mortality per 1-unit increase in DII. Restricted cubic splines were used to intuitively display the dose–response association between dietary inflammatory potential and mortality. Of the 1415 studies retrieved, 15 articles (17 cohort studies involving 397,641 participants) were included in this meta-analysis. With per 1-unit increase in DII, the risks were significantly increased for all-cause mortality (RR: 1.04; 95% CI: 1.03, 1.05, $I^2 = 51.8\%$; *P*-heterogeneity = 0.009), cancer mortality (RR: 1.02; 95% CI: 1.00, 1.04, $I^2 = 58.6\%$; *P*-heterogeneity = 0.013), and CVD mortality (RR: 1.04; 95% CI: 1.02, 1.06, $I^2 = 85.7\%$; *P*-heterogeneity <0.001), respectively. Restricted cubic splines showed significant positive linear associations between DII and the above 3 outcomes. Our study indicated that proinflammatory diets can increase the risk of all-cause, cancer, and CVD mortality in a linear manner. *Adv Nutr* 2022;13:1834–1845.

Statement of Significance: Our study is the first meta-analysis to quantify the dose–response association between dietary inflammatory potential and mortality risk. For each 1-unit increase in dietary inflammatory index score, 4%, 2%, and 4% additional risk was associated with all-cause, cancer, and cardiovascular disease mortality, respectively.

Keywords: dietary inflammatory potential, mortality, dose–response, cohort study, meta-analysis

Introduction

Chronic inflammation is a long-term and maladaptive bodily response that has been confirmed as associated with cancer and cardiovascular disease (CVD) incidence and mortality (1–3). Recent epidemiological studies have reported that dietary factors can change the expression of inflammatory genes and the concentration of inflammatory markers in human bodies, both effects being reputedly associated with multiple chronic diseases (4–6). Given that cancer and CVD are the leading causes of death globally, research on the association between dietary inflammatory potential and risk of cancer and CVD mortality is needed (7, 8).

Dietary inflammatory index (DII) is a literature-derived and population-based indicator used to evaluate dietary inflammatory potential (9). Compared with other dietary indicators, DII is most widely used in epidemiological studies to explore the association between dietary inflammatory potential and disease because it is based on dietary nutrient intake rather than the type of food consumed (10–12). Multiple studies have explored the association

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between dietary inflammatory potential (evaluated by DII) and all-cause and cause-specific mortality, but their results have been inconsistent (13, 14). A cohort study based on 150,405 American adults suggested a positive association between DII and the risk of all-cause and cause-specific mortality (13); however, another US cohort study based on 161,808 postmenopausal female participants reported that no significant association was found with either all-cause or cancer mortality (14). Moreover, no dose–response meta-analysis has been performed to comprehensively evaluate the association between DII and risk of all-cause, cancer, and CVD mortality.

It is clearly necessary to provide more convincing evidence to clarify the association of dietary inflammatory potential with all-cause, cancer, and CVD mortality. Accordingly, we conducted a systematic review and dose–response meta-analysis based on cohort studies to explore the association.

Methods

Exposure assessment

Dietary inflammatory potential was evaluated by DII. Calculation of the DII was based on specific foods or nutrients cited in dietary intake data. Means and SDs of 45 food parameters (**Table 1**) representing regional and world databases were provided by Shivappa et al. (9). Briefly, the *z*-score was calculated from the amounts of food reported for individuals based on the mean and SD of each food parameter. To minimize the effect of "right skewing," the *z*-score was converted to a percentile score. To achieve a symmetrical distribution with values centralized on 0, each percentile score was doubled and then 1 subtracted. The centralized percentile value for each food parameter was then multiplied by its respective "overall food parameter-specific inflammatory effect score" to obtain the "food parameter-specific DII score." Finally, all of the "food parameter-specific DII scores" were summed to create the "overall DII score" for each individual. It is worth noting, however, that not all studies quantified the 45 food parameters when calculating DII scores (15, 16).

Literature search strategy

PubMed, Embase, and Web of Science up until August 9, 2021 were systematically searched for cohort studies assessing the association of dietary inflammatory potential with mortality. Other potentially relevant studies were manually searched. MeSH terms and free-text terms were used in the literature search, which was restricted to English-language publications. Details of the search strategy are supplied in **Supplemental Table 1**. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses process was followed (17). The dose–response meta-analysis is registered at PROSPERO as CRD42021275275.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they: *1*) were based on a cohort study; *2*) focused on participants 18 y and older at baseline; *3*) reported dietary inflammatory potential as exposure, and mortality (including all-cause, cancer, and CVD mortality) as outcome; *4*) reported RRs and 95% CIs or other relevant data (such as number of cases and person-years for each category) to enable calculation of them; and *5*) divided exposure into ≥3 categories for dose–response analysis. Studies reporting exposure as continuous estimations were also included. In addition, if several studies were published based on the same cohort, we included the one with the most comprehensive information or the longest follow-up period. The excluded articles and reasons for exclusion are presented in **Figure 1**.

Data extraction and quality assessment

Two authors (JZ and YF) extracted relevant information independently using the same form, including first author, publication year, country, the name of the cohort study, outcomes, sample size, number of food parameters included in DII, number of cases and person-years/number of participants for every DII category, follow-up years, sex, mean or median age of study participants at baseline, measurement method of dietary information, different ranges of DII scores, RRs of outcomes with 95% CIs for each DII category, and variables adjusted for in the analysis. If multiple RRs and 95% CIs were reported based on different models, we extracted those with the strongest controls for potentially confounding variables. Any potential disagreements were resolved by consulting the third author (YZ).

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies with a maximum of 9 points and a minimum of 0 (18). The NOS included 3 categories: 4 points for selection, 2 points for comparability, and 3 points for outcome. We nominated 0–3, 4–6, and 7–9 points as low-, moderate-, and high-quality studies, respectively.

Data synthesis and analysis

Studies from the NHANES database were identified as separate studies if they were based on different baseline participants. Where results independently reported males and females, they were treated as 2 separate reports. If the participants or person-years were not reported, we assumed the size was equal in each category (19). If the number of cases was not reported, we calculated them by using RRs and number of total cases (19). The median or mean DII in each category was considered as exposure dose. If the median or mean DII dose was not reported, the midpoint of lower and upper boundaries was considered as exposure

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Supplemental Tables 1–3 and Supplemental Figures 1 and 2 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/advances/.
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Abbreviations used: CVD, cardiovascular disease; DII, dietary inflammatory index; NOS, Newcastle–Ottawa Scale.

Table 1 The 45 food parameters for DII calculation (9)[1]

Food parameter	Mean	SD	e	Food parameter	Mean	SD	e
Alcohol, g	13.98	3.72	−0.278	Riboflavin, mg	1.70	0.79	−0.068
Vitamin B-12, μg	5.15	2.70	0.106	Saffron, g	0.37	1.78	−0.140
Vitamin B-6, mg	1.47	0.74	−0.365	Saturated fat, g	28.6	8.0	0.373
β-Carotene, μg	3718	1720	−0.584	Selenium, μg	67.0	25.1	−0.191
Caffeine, g	8.05	6.67	−0.110	Thiamin, mg	1.70	0.66	−0.098
Carbohydrate, g	272.2	40.0	0.097	*Trans* fat, g	3.15	3.75	0.229
Cholesterol, mg	279.4	51.2	0.110	Turmeric, mg	533.6	754.3	−0.785
Energy, kcal	2056	338	0.180	Vitamin A, RE	983.9	518.6	−0.401
Eugenol, mg	0.01	0.08	−0.140	Vitamin C, mg	118.2	43.46	−0.424
Total fat, g	71.4	19.4	0.298	Vitamin D, μg	6.26	2.21	−0.446
Fiber, g	18.8	4.9	−0.663	Vitamin E, mg	8.73	1.49	−0.419
Folic acid, μg	273.0	70.7	−0.190	Zinc, mg	9.84	2.19	−0.313
Garlic, g	4.35	2.90	−0.412	Green/black tea, g	1.69	1.53	−0.536
Ginger, g	59.0	63.2	−0.453	Flavan-3-ol, mg	95.8	85.9	−0.415
Iron, mg	13.35	3.71	0.032	Flavones, mg	1.55	0.07	−0.616
Magnesium, mg	310.1	139.4	−0.484	Flavonols, mg	17.70	6.79	−0.467
MUFA, g	27.0	6.1	−0.009	Flavonones, mg	11.70	3.82	−0.250
Niacin, mg	25.90	11.77	−0.246	Anthocyanidins, mg	18.05	21.14	−0.131
n–3 Fatty acids, g	1.06	1.06	−0.436	Isoflavones, mg	1.20	0.20	−0.593
n–6 Fatty acids, g	10.80	7.50	−0.159	Pepper, g	10.00	7.07	−0.131
Onion, g	35.9	18.4	−0.301	Thyme/oregano, mg	0.33	0.99	−0.102
Protein, g	79.4	13.9	0.021	Rosemary, mg	1.00	15.00	−0.013
PUFA, g	13.88	3.76	−0.337				

[1] e = overall inflammatory effect score. DII, dietary inflammatory index; RE, retinol equivalents.

dose (19). If studies reported RRs and 95% CIs by taking a higher category as reference, we recalculated them by setting the lowest DII category as reference. For those reporting DII as continuous estimations, we converted them per 1-unit increase.

First, we performed dose–response analyses to evaluate the association of dietary inflammatory potential with all-cause, cancer, and CVD mortality. Generalized least squares regression was used to estimate study-specific RRs and 95% CIs for all-cause, cancer, and CVD mortality per 1-unit increase in DII, then pooled RRs and 95% CIs of all-cause, cancer, and CVD mortality were estimated by the random effect model for the highest compared with lowest DII categories and per 1-unit increase in DII, taking both within- and between-study variations into consideration (20). Moreover, we estimated possible associations by modeling DII exposure using a restricted cubic spline with 3 knots located at the 25th, 50th, and 75th percentiles of the distribution. The *P* value for nonlinearity (*P*-nonlinearity) was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0 (21).

Heterogeneity between studies was tested by Cochran *Q* and I^2 statistics. $P < 0.05$ was considered statistically significant for *Q* statistic, whereas 25%, 50%, and 75% for I^2 values were considered low, moderate, and high heterogeneity between studies, respectively (22). Subgroup analyses were stratified by age (mean or median ≥60 compared with <60 y), sex (male compared with female compared with both), region (US compared with non-US), exposure assessment method (FFQ compared with 24-h recall compared with weighting), number of food parameters included in DII (≤27 compared with >27 compared with not reported), follow-up years (mean or median >15 compared with ≤15), sample size (≤10,000 compared with >10,000), and adjustments (such as BMI, physical activity, and energy). Sensitivity analysis was conducted by excluding 1 study at a time to assess the stability of results and potential sources of heterogeneity. Publication bias was estimated by asymmetric funnel plots and Egger linear regression test (23). The trim-and-fill method was used to correct if publication bias was detected.

All analyses were conducted with Stata 14.2 (Stata Corp). $P < 0.05$ with 2 sides was considered statistically significant.

Results

Literature search and study characteristics

Of the 1415 studies retrieved, 46 records were screened for full text after excluding 609 for duplication and 760 for irrelevant title and abstract. After full-text review, records of 31 were excluded as conference presentations or comment ($n = 8$), reviews or meta-analyses ($n = 4$), failure to access full text ($n = 3$), non–cohort study ($n = 11$), irrelevant exposure ($n = 4$), and outcome ($n = 1$). Finally, 15 articles representing 17 cohort studies with 397,641 participants were included in the meta-analysis. Details of those are shown in Figure 1.

A total of 15 articles representing 17 cohort studies (12, 13, 24–36) were included for all-cause mortality with 101,181 cases and 397,641 participants; 8 articles representing 9 cohort studies (12, 13, 24, 25, 31, 33–35) were included for cancer mortality with 26,165 cases and 294,681 participants; and 9 articles representing 10 cohort studies (12, 13, 24, 25, 29, 31, 33–35) were included for CVD mortality with

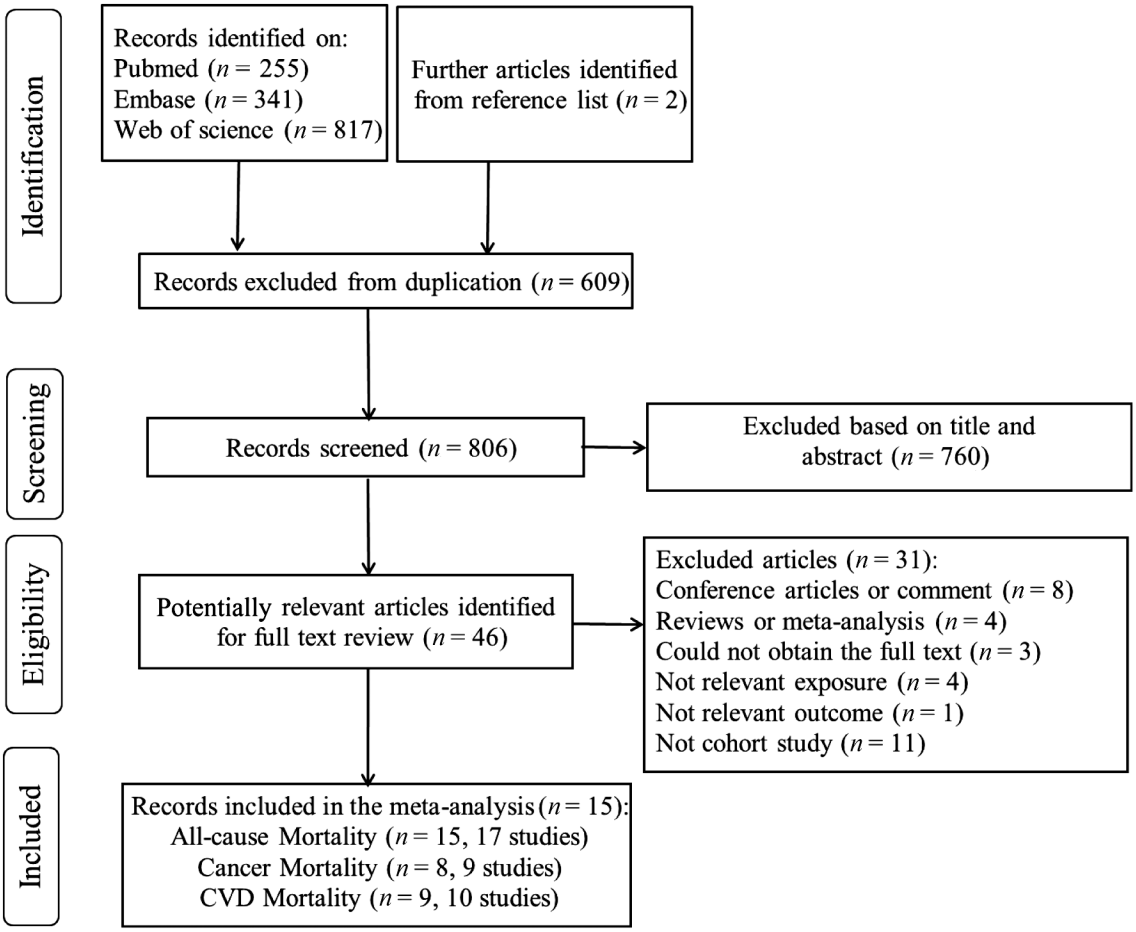

Figure 1 Flowchart of study selection. CVD, cardiovascular disease.

35,550 cases and 334,213 participants. Nine cohort studies were conducted in North America, 4 in Europe, 1 in Oceania, and 1 in Asia. The mean follow-up was 14.8 y. The mean NOS score for quality assessment was 8.4. Details of the study characteristics are shown in **Supplemental Table 2.** Exposure and the main outcomes are shown in **Supplemental Table 3.**

Dietary inflammatory potential and all-cause mortality

For the association of the highest compared with lowest DII category, the pooled RR of all-cause mortality was 1.17 (95% CI: 1.12, 1.21) in the meta-analysis of the 12 included articles, with moderate heterogeneity ($I^2 = 40.1\%$; P-heterogeneity = 0.060; **Figure 2**) (13, 24–29, 31–35). Sensitivity analysis produced similar results. Publication bias was not found by funnel plot (**Supplemental Figure 1**A) or Egger test ($P = 0.05$).

Fourteen articles were included in the meta-analysis for the dose–response association. The pooled RR of all-cause mortality per 1-unit DII increase was 1.04 (95% CI: 1.03, 1.05), with moderate heterogeneity ($I^2 = 51.8\%$; P-heterogeneity = 0.009; **Figure 3**) (12, 13, 24, 25, 27–36). The sensitivity analysis conducted by excluding 1 study at a time did not change the results. Publication bias was detected by asymmetric funnel plot (**Supplemental Figure 2**A) and Egger test ($P = 0.001$). With adjustment by the trim-and-fill method, the summary RR slightly decreased (RR: 1.03; 95% CI: 1.02, 1.04). There was no evidence of a nonlinear dose–response association of DII with all-cause mortality (P-nonlinearity = 0.604; **Figure 4**A). All results were robust among subgroups (**Table 2**).

Dietary inflammatory potential and cancer mortality

For the association of the highest compared with lowest DII category, the pooled RR of cancer mortality was 1.07 (95% CI: 1.01–1.14) in the meta-analysis of the 7 included articles with low heterogeneity ($I^2 = 13.9\%$; P-heterogeneity = 0.321; Figure 2) (13, 24, 25, 31, 33–35). The results did not change with sensitivity analysis. We found no evidence of publication bias by funnel plot (Supplemental Figure 1B) or Egger test ($P = 0.888$).

Eight articles were included in the meta-analysis for the dose–response association. A borderline significant association of cancer mortality per 1-unit DII increase was found (RR: 1.02; 95% CI: 1.00, 1.04), with moderate heterogeneity ($I^2 = 58.6\%$; P-heterogeneity = 0.013; Figure 3) (12, 13, 24, 25, 31, 33–35). The significant association remained with sensitivity analysis. No evidence of publication bias was detected by funnel plot (Supplemental Figure 2B) or Egger

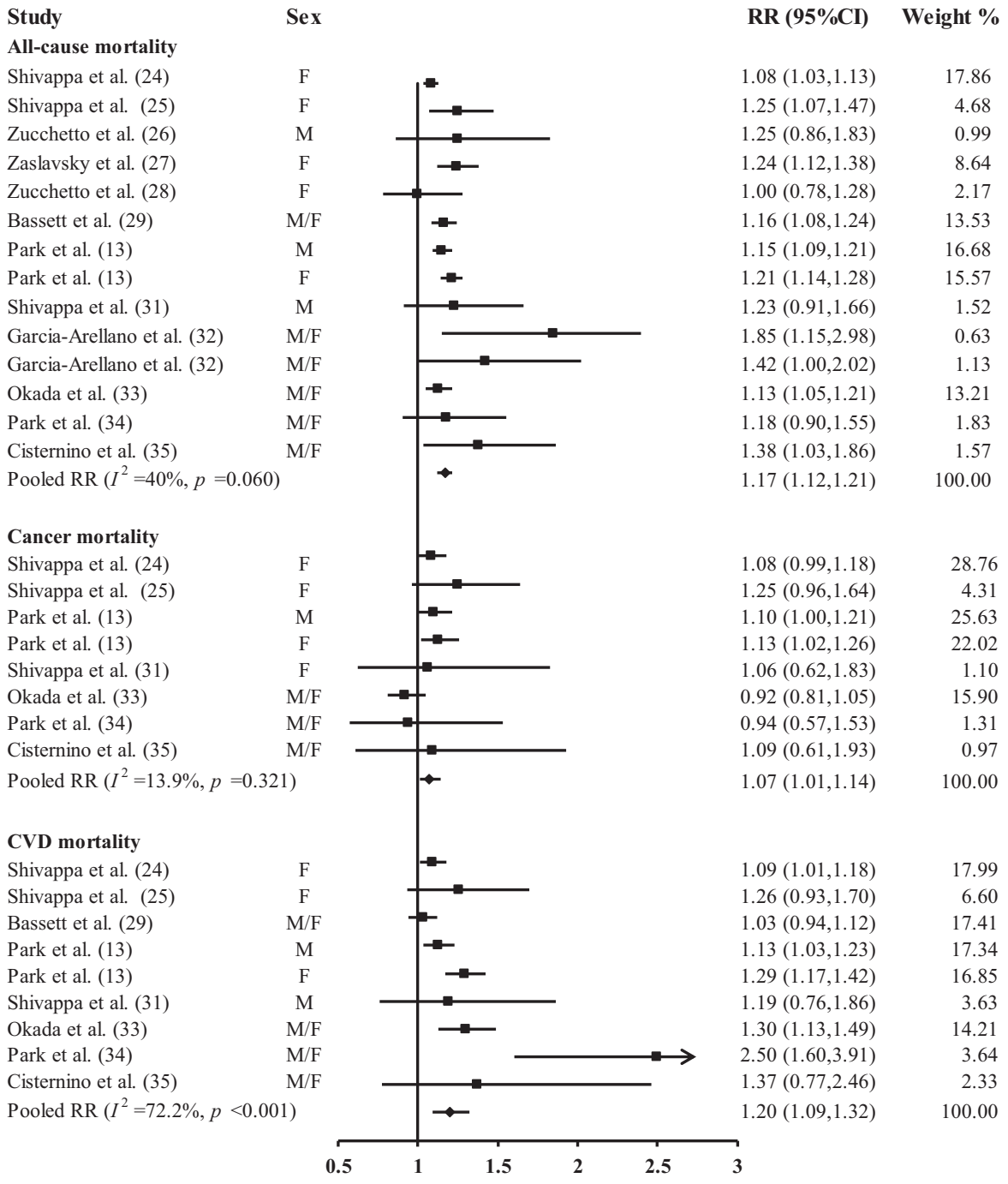

Figure 2 Forest plot of study-specific RR statistics for the highest compared with lowest dietary inflammatory index range. CVD, cardiovascular disease; F, female; M, male.

test ($P = 0.298$). We found no evidence of a nonlinear dose–response association between DII and cancer mortality (*P*-nonlinearity = 0.307; Figure 4B). The source of heterogeneity was found by region, stratified according to subgroup analysis (**Table 3**).

Dietary inflammatory potential and CVD mortality

For the association of the highest compared with lowest DII category, the pooled RR of CVD mortality was 1.20 (95% CI: 1.09, 1.32) in the meta-analysis of the 8 included articles, with high heterogeneity ($I^2 = 72.2\%$; *P*-heterogeneity <0.001; Figure 2) (13, 24, 25, 29, 31, 33–35). Sensitivity analysis found that the results were robust. Publication bias was not detected by funnel plot (Supplemental Figure 1C) or Egger test ($P = 0.111$).

Nine articles were included in the meta-analysis for the dose–response association, The pooled RR of CVD mortality per 1-unit DII increase was 1.04 (95% CI: 1.02, 1.06), with

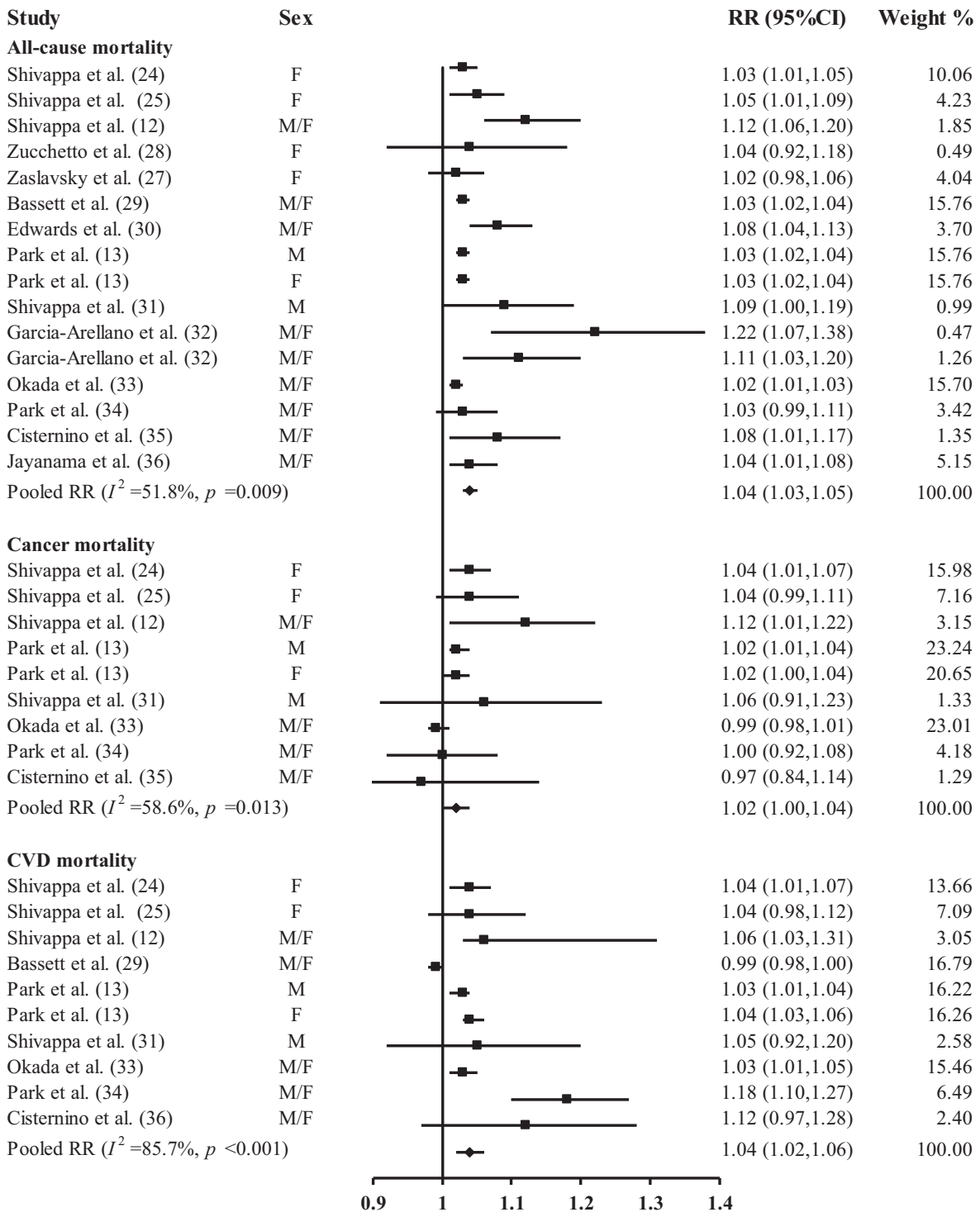

Figure 3 Forest plot of study-specific RR statistics per 1-unit dietary inflammatory index increase. CVD, cardiovascular disease; F, female; M, male.

high heterogeneity (I^2 = 85.7%; *P*-heterogeneity <0.001; Figure 3) (12, 13, 24, 25, 29, 31, 33–35). The results were not altered with sensitivity analysis. We found no evidence of publication bias by funnel plot (Supplemental Figure 2C) or Egger test (P = 0.078). No evidence of a nonlinear dose–response association was detected between DII and CVD mortality (*P*-nonlinearity = 0.858; Figure 4C). All results were robust among most subgroups (**Table 4**).

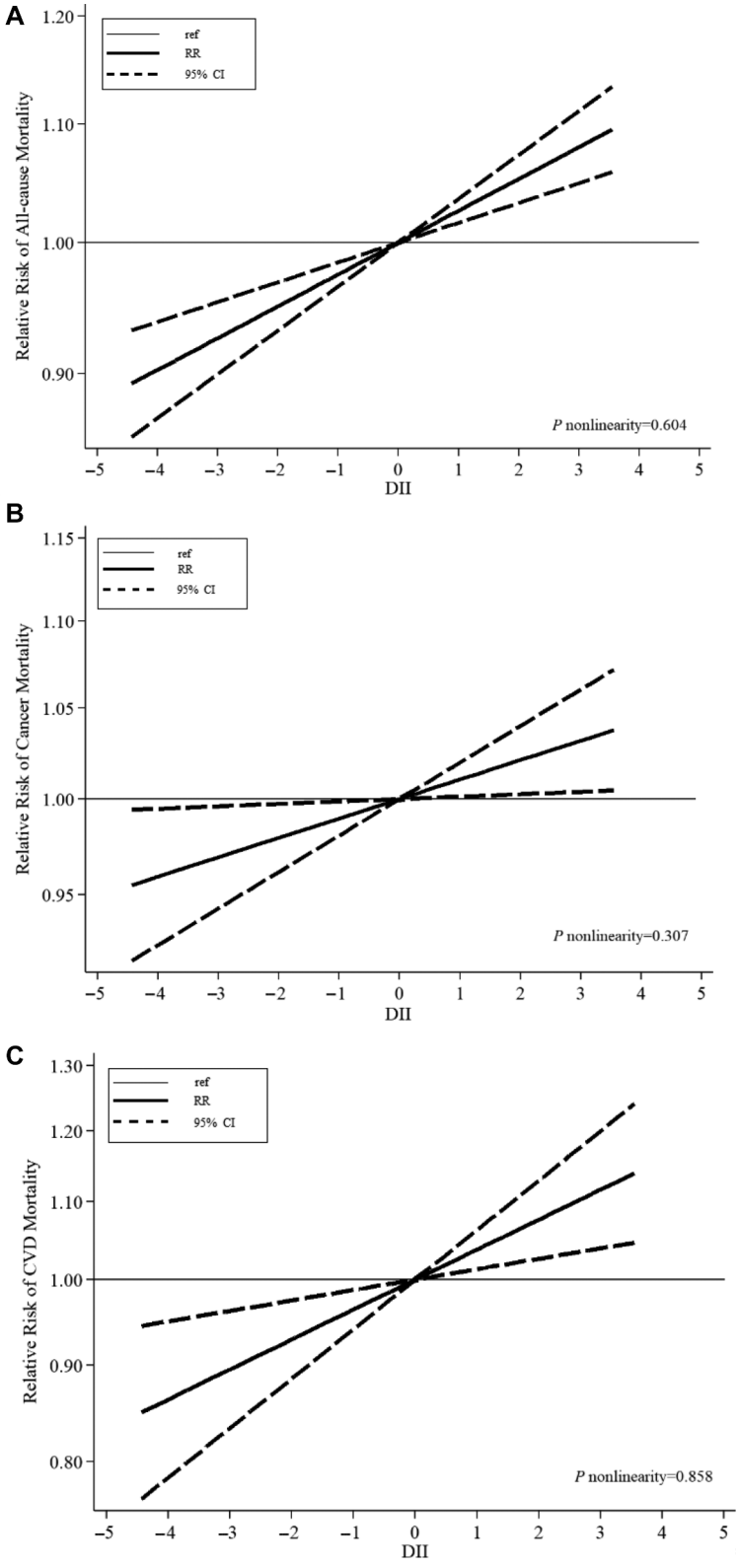

Figure 4 Dose–response association of DII with the risk of (A) all-cause mortality, (B) cancer mortality, and (C) CVD mortality. CVD, cardiovascular disease; DII, dietary inflammatory index; ref, reference line.

Table 2 Subgroup analysis of all-cause mortality per 1-unit DII increase[1]

Subgroup	*n*	RR (95% CI)	I^2, %	P^2	P^3
All	16	1.04 (1.03, 1.05)	51.8	0.009	
Mean age, y					0.166
<60	9	1.05 (1.03, 1.06)	67.3	0.002	
≥60	7	1.03 (1.02, 1.04)	5.9	0.383	
Sex					0.188
Male	2	1.04 (1.00, 1.09)	37.8	0.205	
Female	5	1.03 (1.02, 1.04)	0	0.874	
Both	9	1.05 (1.03, 1.07)	71.6	<0.001	
Region					0.967
US	9	1.04 (1.03, 1.05)	44.0	0.075	
Non-US	7	1.04 (1.02, 1.06)	61.6	0.016	
Exposure assessment					0.282
FFQ	12	1.03 (1.02, 1.04)	54.2	0.013	
24-h recall	3	1.05 (1.02, 1.08)	29.2	0.244	
Weighting	1	1.09 (1.00, 1.19)	0	—	
Food parameters,[4] *n*					0.821
≤27	8	1.04 (1.03, 1.06)	62.5	0.009	
>27	6	1.03 (1.02, 1.05)	53.2	0.058	
NR	2	1.04 (1.00, 1.09)	35.5	0.213	
Follow-up period, y					0.100
≤15	7	1.05 (1.03, 1.07)	0	0.485	
>15	9	1.03 (1.02, 1.04)	62.0	0.007	
Sample size, *n*					0.064
≤10,000	5	1.07 (1.03, 1.11)	25.2	0.253	
>10,000	11	1.03 (1.02, 1.04)	51.8	0.023	
BMI					0.559
Adjusted	14	1.04 (1.02, 1.05)	50.0	0.017	
Not adjusted	2	1.05 (1.00, 1.10)	79.0	0.029	
Physical activity					0.997
Adjusted	10	1.04 (1.02, 1.05)	62.4	0.004	
Not adjusted	6	1.04 (1.02, 1.05)	22.1	0.267	
Energy intake					0.015
Adjusted	7	1.03 (1.02, 1.03)	4.2	0.394	
Not adjusted	9	1.06 (1.03, 1.08)	64.4	0.004	

[1] DII, dietary inflammatory index; NR, not reported.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups.
[4] Food parameters: number of food parameters included in the original study; *n* = number of included studies.

Discussion

To the best of our knowledge, this is the first comprehensive dose–response meta-analysis to focus on assessing the association of dietary inflammatory potential with all-cause, cancer, and CVD mortality. In our meta-analysis, compared with the lowest DII category, the risk of all-cause mortality was increased by 17%, cancer mortality by 7%, and CVD mortality by 20% for the highest DII category. Further, linear dose–response associations were found, with the risk increasing by 4%, 2%, and 4% per 1-unit DII increase, respectively.

We found substantial heterogeneity across studies in subgroup analyses, such as in age, sex, and region. The heterogeneity could be due to the variations in study population, sample size, method of data collection, and background or lifestyle characteristics; for instance, we observed different health effects according to age, with a weaker association in those older than 60 compared with those under 60. That could be explained by reverse causation bias, with older people perhaps changing their dietary patterns to more anti-inflammatory ones after developing cancer or other chronic disease conditions related to early mortality. We also observed regional differences in the association of dietary inflammatory potential with cancer mortality. This could be due to the limited number of included studies further causing unstable risk estimates. Future studies should be conducted in non-US regions to provide relevant evidence. In addition, BMI and physical activity could be important confounding factors for the association between dietary inflammatory potential and mortality. By combining studies that controlled for these variables in the subgroup analysis, the associations remained significant for all-cause mortality, but the associations for cancer and CVD mortality disappeared. Due to the limited number of studies with adjustment for other variables, we cannot exclude the possibility that other specific factors might have contributed to these subgroup differences.

Findings of an association between dietary inflammatory potential and mortality from the current study are consistent

Table 3 Subgroup analysis of cancer mortality per 1-unit DII increase[1]

Subgroup	*n*	RR (95% CI)	I^2, %	P^2	P^3
All	9	1.02 (1.00, 1.04)	58.6	0.013	
Mean age, y					0.948
<60	4	1.03 (0.97, 1.08)	57.9	0.068	
≥60	5	1.02 (1.01, 1.03)	0	0.685	
Sex					0.784
Male	2	1.02 (1.01, 1.04)	0	0.618	
Female	3	1.03 (1.01, 1.04)	0	0.501	
Both	4	1.01 (0.96, 1.07)	53.9	0.089	
Region					<0.001
US	7	1.02 (1.01, 1.04)	0	0.445	
Non-US	2	0.99 (0.98, 1.00)	0	0.794	
Exposure assessment					0.784
FFQ	7	1.02 (1.00, 1.04)	68.2	0.004	
24-h recall	1	1.06 (0.91, 1.23)	0	—	
Weighting	1	1.00 (0.92, 1.08)	0	—	
Food parameters,[4] *n*					0.431
≤27	5	1.02 (0.98, 1.06)	54.9	0.065	
>27	2	1.02 (1.01, 1.03)	0	1	
NR	2	1.04 (1.01, 1.07)	0	0.808	
Follow-up period, y					0.581
≤15	3	1.03 (0.98, 1.09)	0	0.665	
>15	6	1.02 (1.00, 1.04)	72.0	0.003	
Sample size, *n*					0.512
≤10,000	4	1.04 (0.97, 1.11)	27.6	0.246	
>10,000	5	1.02 (1.00, 1.04)	71.8	0.007	
BMI					—
Adjusted	9	1.02 (1.00, 1.04)	58.6	0.013	
Not adjusted	0	—	—	—	
Physical activity					0.243
Adjusted	7	1.02 (1.00, 1.04)	61.4	0.017	
Not adjusted	2	1.04 (1.01, 1.07)	0	0.379	
Energy intake					0.098
Adjusted	5	1.01 (0.99, 1.03)	62.7	0.030	
Not adjusted	4	1.04 (1.01, 1.08)	9.7	0.345	

[1] DII, dietary inflammatory index; NR, not reported.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups.
[4] Food parameters: number of food parameters included in the original study; *n* = number of included studies.

with previous studies. For the highest compared with lowest DII category, a pooled analysis based on 6 cohort studies reported that the risk increased by 21%, 28%, and 30% for all-cause, cancer, and CVD mortality, respectively (37). Another analysis reported that for each 1-unit DII increase, the risk of all-cause, cancer, and CVD mortality increased by 4%, 5%, and 5%, respectively (12). In addition, randomized controlled trials suggested that proinflammatory diets were associated with increased risk of all-cause, cancer, and CVD mortality (38, 39).

Although the mechanisms underlying the association of dietary inflammatory potential with premature mortality are not clear, there are a number of possible pathways. First, a higher inflammatory potential in the diet could significantly increase the concentration of inflammatory factors such as IL-1β, IL-6, IL-4, and IL-10 (9). Inflammatory factors are considered an indispensable participant in fostering cancer cell proliferation, survival, and migration, significantly increasing the risk of cancer mortality (40, 41). Atherosclerosis, considered an inflammatory state, is associated with a high risk of CVD mortality (42, 43). Second, greater proinflammatory potential in the diet could significantly accelerate the rate of telomere shortening (44). A previous meta-analysis based on 23 cohort studies suggested the risk of all-cause mortality increased by 26% when comparing the shortest with the longest telomere length (45). Third, proinflammatory diets could significantly increase the concentration of VLDL, LDL, and TNFα, all of which are associated with a higher risk of mortality (46–48). Fourth, proinflammatory diets tend to involve intake of more inflammatory nutrients, particularly saturated fats, which have a proven association with a higher risk of all-cause, cancer, and CVD mortality (49).

There are some strengths in the current study. First, because our meta-analysis was based on cohort studies, it could provide stronger evidence to support the hypothesis compared with cross-sectional and case-control studies. Second, the current analysis was based on 17 cohort studies (including 397,641 participants) that could provide

Table 4 Subgroup analysis of CVD mortality per 1-unit DII increase[1]

Subgroup	*n*	RR (95% CI)	I^2, %	P^2	P^3
All	10	1.04 (1.02, 1.06)	85.7	<0.001	
Mean age, y					0.657
<60	5	1.05 (1.00, 1.10)	88.4	<0.001	
≥60	5	1.04 (1.03, 1.05)	0	0.703	
Sex					0.496
Male	2	1.03 (1.02, 1.05)	0	0.778	
Female	3	1.04 (1.03, 1.05)	0	1	
Both	5	1.05 (1.01, 1.10)	89.0	<0.001	
Region					0.202
US	7	1.05 (1.03, 1.07)	55.7	0.035	
Non-US	3	1.02 (0.98, 1.06)	86.8	<0.001	
Exposure assessment					0.002
FFQ	8	1.03 (1.01, 1.05)	84.8	<0.001	
24-h recall	1	1.18 (1.10, 1.27)	0	—	
Weighting	1	1.05 (0.92, 1.20)	0	—	
Food parameters,[4] *n*					0.765
≤27	6	1.05 (1.01, 1.10)	86.7	<0.001	
>27	2	1.04 (1.02, 1.05)	0	0.356	
NR	2	1.04 (1.01, 1.07)	0	0.890	
Follow-up period, y					0.605
≤15	3	1.05 (1.00, 1.11)	0	0.639	
>15	7	1.04 (1.01, 1.06)	90.1	<0.001	
Sample size, *n*					0.007
≤10,000	4	1.12 (1.06, 1.19)	18.2	0.300	
>10,000	6	1.03 (1.00, 1.05)	88.6	<0.001	
BMI					< 0.001
Adjusted	9	1.04 (1.03, 1.06)	47.6	0.054	
Not adjusted	1	0.99 (0.98, 1.00)	0	—	
Physical activity					0.481
Adjusted	7	1.04 (1.02, 1.06)	57.2	0.029	
Not adjusted	3	1.02 (0.97, 1.07)	84.3	0.002	
Energy intake					0.500
Adjusted	5	1.03 (1.03, 1.04)	0	0.673	
Not adjusted	5	1.05 (1.00, 1.12)	87.7	<0.001	

[1] CVD, cardiovascular disease; DII, dietary inflammatory index; NR, not reported.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups.
[4] Food parameters: number of food parameters included in the original study; *n* = number of included studies.

sufficient statistical power for exploring the association of dietary inflammatory potential with mortality. Third, we used various types of analyses (including the highest compared with lowest DII scores analysis and linear or nonlinear dose–response analysis) to assess the association of dietary inflammatory potential with mortality from different perspectives.

Some limitations also deserve attention. First, dietary habit information was collected by self-report in most original studies, possibly involving recall bias and misclassification of DII exposure. Second, although the RRs were extracted with the largest adjustment for confounding factors, residual confounding factors might still exist. Third, there was possible publication bias in the meta-analysis assessing the association of dietary inflammatory potential with all-cause mortality, although the result was not altered with the trim-and-fill application. Fourth, most included studies were in the Euro-American region. Given that dietary habits vary between geographical areas, ethnic populations, and other specific populations, this factor could have affected the results for highest compared with lowest categories of DII.

In conclusion, our meta-analysis provides further evidence that proinflammatory diets are associated with increased risk of all-cause, cancer, and CVD mortality. The results support clinical interventions seeking to reduce consumption of proinflammatory dietary nutrients to reduce the risk of cancer and CVD mortality. To achieve early prevention of chronic diseases, further prospective cohort studies should be conducted to explore the association of proinflammatory diets with the risk of obesity, stroke, and diabetes mellitus.

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Data Availability

The data are available upon reasonable request.

References

1. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107(3):499–511.
2. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019;51(1):27–41.
3. Pusceddu I, Herrmann W, Kleber ME, Scharnagl H, Hoffmann MM, Winklhofer-Roob BM, et al. Subclinical inflammation, telomere shortening, homocysteine, vitamin B6, and mortality: the Ludwigshafen Risk and Cardiovascular Health Study. Eur J Nutr 2020;59(4):1399–411.
4. Naghshi S, Aune D, Beyene J, Mobarak S, Asadi M, Sadeghi O. Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of cohort studies. BMJ 2021;375:n2213.
5. Pan MH, Lai CS, Dushenkov S, Ho CT. Modulation of inflammatory genes by natural dietary bioactive compounds. J Agric Food Chem 2009;57(11):4467–77.
6. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505–22.
7. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76(25):2982–3021.
8. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5(12):1749–68.
9. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 2014;17(8):1689–96.
10. Bailey MA, Holscher HD. Microbiome-mediated effects of the Mediterranean diet on inflammation. Adv Nutr 2018;9(3):193–206.
11. Mahdavi A, Mohammadi H, Bagherniya M, Foshati S, Clark CCT, Moafi A, et al. The effect of the Dietary Approaches to Stop Hypertension (DASH) diet on body composition, complete blood count, prothrombin time, inflammation, and liver function in hemophilic adolescents. Br J Nutr [Internet] 2021. doi: 10.1017/S0007114521004839.
12. Shivappa N, Hebert JR, Kivimaki M, Akbaraly T. Alternative Healthy Eating Index 2010, dietary inflammatory index and risk of mortality: results from the Whitehall II cohort study and meta-analysis of previous dietary inflammatory index and mortality studies. Br J Nutr 2017;118(3):210–21.
13. Park SY, Kang M, Wilkens LR, Shvetsov YB, Harmon BE, Shivappa N, et al. The dietary inflammatory index and all-cause, cardiovascular disease, and cancer mortality in the multiethnic cohort study. Nutrients 2018;10(12):1844.
14. Zheng J, Zhang J, Liese AD, Tabung FK, Steck SE, Shivappa N, et al. Association between post-cancer diagnosis dietary inflammatory potential and mortality among invasive breast cancer survivors in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev 2018;27(4):454–63.
15. Denova-Gutiérrez E, Muñoz-Aguirre P, Shivappa N, Hébert JR, Tolentino-Mayo L, Batis C, et al. Dietary inflammatory index and type 2 diabetes mellitus in adults: the diabetes mellitus survey of Mexico City. Nutrients 2018;10(4):385.
16. Wang YB, Shivappa N, Hébert JR, Page AJ, Gill TK, Melaku YA. Association between dietary inflammatory index, dietary patterns, plant-based dietary index and the risk of obesity. Nutrients 2021;13(5):1536.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
19. Bekkering GE, Harris RJ, Thomas S, Mayer AM, Beynon R, Ness AR, et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008;167(9):1017–26.
20. DerSimonian RLN. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
21. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175(1): 66–73.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088–101.
24. Shivappa N, Blair CK, Prizment AE, Jacobs DR, Jr, Steck SE, Hébert JR. Association between inflammatory potential of diet and mortality in the Iowa Women's Health Study. Eur J Nutr 2016;55(4):1491–502.
25. Shivappa N, Harris H, Wolk A, Hebert JR. Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. Eur J Nutr 2016;55(5):1891–900.
26. Zucchetto A, Gini A, Dal Maso L, Birri S, Serraino D, Polesel J, et al. Dietary inflammatory index and prostate cancer survival. Int J Cancer 2016;139(11):2398–404.
27. Zaslavsky O, Zelber-Sagi S, Hebert JR, Steck SE, Shivappa N, Tabung FK, et al. Biomarker-calibrated nutrient intake and healthy diet index associations with mortality risks among older and frail women from the Women's Health Initiative. Am J Clin Nutr 2017;105(6):1399–407.
28. Zucchetto A, Serraino D, Panato C, Dal Maso L, Polesel J, Shivappa N, et al. Dietary inflammatory index before diagnosis and survival in an Italian cohort of women with breast cancer. Br J Nutr 2017;117(10):1456–62.
29. Bassett JK, Hodge AM, Dugue PA, Milne RL, English DR, Giles GG, et al. Dietary inflammatory index or Mediterranean diet score as risk factors for total and cardiovascular mortality. Nutr Metab Cardiovasc Dis 2018;28(5):461–9.
30. Edwards MK, Loprinzi PD, Shivappa N, Hebert JR, Wirth MD, Mann JR. The association between physical activity and dietary inflammatory index on mortality risk in U.S. adults. Phys Sportsmed 2018;46(2):249–54.
31. Shivappa N, Hebert JR, Schneider A, Thorand B, Koenig W, Peters A. Association between dietary inflammatory index, and cause-specific mortality in the MONICA/KORA Augsburg Cohort Study. Eur J Public Health 2018;28(1):167–72.
32. Garcia-Arellano A, Martinez-Gonzalez MA, Ramallal R, Salas-Salvado J, Hebert JR, Corella D, et al. Dietary inflammatory index and all-cause mortality in large cohorts: the SUN and PREDIMED studies. Clin Nutr 2019;38(3):1221–31.
33. Okada E, Shirakawa T, Iso H, Shivappa N, Hebert JR, Wakai K, et al. Dietary inflammatory index is associated with risk of all-cause and cardiovascular disease mortality but not with cancer mortality in middle-aged and older Japanese adults. J Nutr 2019;149(8):1451–9.
34. Park YM, Choi MK, Lee SS, Shivappa N, Han K, Steck SE, et al. Dietary inflammatory potential and risk of mortality in metabolically healthy and unhealthy phenotypes among overweight and obese adults. Clin Nutr 2019;38(2):682–8.
35. Cisternino AM, Reddavide R, Inguaggiato R, Rotolo O, Veronese N, Notarnicola M, et al. Dietary inflammatory index and mortality: a

cohort longitudinal study in a Mediterranean area. J Hum Nutr Diet 2020;33(1):138–46.
36. Jayanama K, Godin J, Theou O, Rockwood K, Cahill L, Shivappa N, et al. Relationship between diet quality scores and the risk of frailty and mortality in adults across a wide age spectrum. BMC Med 2021;19(1):64.
37. Namazi N, Larijani B, Azadbakht L. Dietary inflammatory index and its association with the risk of cardiovascular diseases, metabolic syndrome, and mortality: a systematic review and meta-analysis. Horm Metab Res 2018;50(5):345–58.
38. Graffouillère L, Deschasaux M, Mariotti F, Neufcourt L, Shivappa N, Hébert JR, et al. Prospective association between the dietary inflammatory index and mortality: modulation by antioxidant supplementation in the SU.VI.MAX randomized controlled trial. Am J Clin Nutr 2016;103(3):878–85.
39. Bondonno NP, Lewis JR, Blekkenhorst LC, Shivappa N, Woodman RJ, Bondonno CP, et al. Dietary inflammatory index in relation to subclinical atherosclerosis and atherosclerotic vascular disease mortality in older women. Br J Nutr 2017;117(11):1577–86.
40. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420(6917):860–7.
41. Dibaba DT, Judd SE, Gilchrist SC, Cushman M, Pisu M, Safford M, et al. Association between obesity and biomarkers of inflammation and metabolism with cancer mortality in a prospective cohort study. Metabolism 2019;94:69–76.
42. Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med 1999;340(2):115–26.
43. Diehm N, Diehm C. Subclinical atherosclerosis of lower limb arteries: a strong predictor for cardiovascular mortality. Eur Heart J 2006;27(21):2495–6.
44. García-Calzón S, Zalba G, Ruiz-Canela M, Shivappa N, Hébert JR, Martínez JA, et al. Dietary inflammatory index and telomere length in subjects with a high cardiovascular disease risk from the PREDIMED-NAVARRA study: cross-sectional and longitudinal analyses over 5 y. Am J Clin Nutr 2015;102(4):897–904.
45. Wang Q, Zhan Y, Pedersen NL, Fang F, Hägg S. Telomere length and all-cause mortality: a meta-analysis. Ageing Res Rev 2018;48:11–20.
46. Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary inflammatory index and biomarkers of lipoprotein metabolism, inflammation and glucose homeostasis in adults. Nutrients 2018;10(8):1033.
47. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. Eur Heart J 2019;40(33):2760–70.
48. Stoll JR, Vaidya TS, Mori S, Dusza SW, Lacouture ME, Markova A. Association of interleukin-6 and tumor necrosis factor-α with mortality in hospitalized patients with cancer. J Am Acad Dermatol 2021;84(2):273–82.
49. O'Sullivan TA, Hafekost K, Mitrou F, Lawrence D. Food sources of saturated fat and the association with mortality: a meta-analysis. Am J Public Health 2013;103(9):e31–42.