Dietary inflammatory index and cardiovascular risk and mortality
A meta-analysis of cohort studies

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Abstract
Background: The role of dietary inflammatory index (DII) in cardiovascular disease (CVD) risk and mortality is still controversial. This systematic review and meta-analysis of cohort studies aimed to evaluate the effect of DII, indicating a pro-inflammatory diet, on the incidence and mortality of CVD.

Methods: A comprehensive literature search of articles published through August 2019 was performed in Medline, EMBASE, and Web of Science. The pooled relative risks (RRs) and 95% confidence intervals (CIs) for highest vs lowest DII in relation to CVD risk or mortality were estimated using a DerSimonian and Laird random effects model. The heterogeneity among studies was tested using Cochran’s Q test and I² statistic.

Results: A total of 15 cohort studies were finally included in this meta-analysis. The highest DII score was significantly associated with a higher risk of CVD incidence (RR = 1.41, 95% CI 1.12–1.78) or mortality (RR = 1.31, 95% CI 1.19–1.44), compared with the lowest DII score. There was statistically significant heterogeneity among the studies on the association between DII and CVD mortality (P < .001; I² = 70.8%). No obvious heterogeneity was observed among the studies on the association between DII and CVD risk (P = .160; I² = 37.0%). In the sensitivity analysis, exclusion of any single study did not materially alter the pooled RRs.

Conclusion: The present systematic review and meta-analysis indicates that a higher DII score is related to a higher risk of CVD. Further well-designed prospective cohort or trials are warranted to validate our preliminary findings.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DII = dietary inflammatory index, RR = relative risk.

Keywords: cardiovascular disease, dietary inflammatory index, dietary pattern, mortality, risk

1. Introduction
Various studies have been conducted exploring the effect of specific food items, such as red meat and vegetables, on cardiovascular disease (CVD) risk and mortality.[1] A limitation of these studies is that the dietary inter-correlations between nutrients among foods may distort the actual effects.[2] Therefore, there has recently been a shift in the focus from 1 nutrient or food group studies to dietary pattern studies (e.g., Mediterranean Diet, Healthy Eating Index and Alternative Healthy Eating Index).

The dietary inflammatory index (DII) developed and validated by researchers from the University of South Carolina is a novel scoring system to determine dietary inflammatory effect.[3] About 2000 primary research articles published through December 2010 on the association between diet and 6 inflammatory markers, including IL-1β, IL-4, IL-6, IL-10, TNF-a, and C-reactive protein, were screened and reviewed. A total of 45 food parameters have been assigned an inflammatory weight, which reflects the association of each food parameter with at least 1 of the 6 markers.[4] The DII has been validated in various studies worldwide with different measures of inflammatory biomarkers.[5–6] Previous studies have indicated that higher DII scores are positively associated with various health outcomes, including breast cancer,[7] colorectal cancer,[8] diabetes,[9] and cardiovascular diseases.[10]

Many epidemiological studies have investigated the association between the DII and CVD risk and mortality with inconsistent results,[11–14] highlighting the recent interest in investigating this issue. Therefore, the aim of the present study was to systematically evaluate the association between DII and CVD using a meta-analysis approach based on a total of 15 eligible cohort studies.
2. Materials and methods

2.1. Publication search

A comprehensive literature search of articles published through August 2019 was performed in Medline, EMBASE, and Web of Science with the following search algorithm: ("cardiovascular disease" OR "coronary heart disease" OR "ischemic heart disease" OR "myocardial infarction" OR "stroke" OR "heart attack" OR "hypertension") and ("pro-inflammatory diet" OR "dietary inflammatory index" OR "anti-inflammatory diet" OR "inflammatory potential intake"). The cited references from retrieved articles and reviews/meta-analyses were also examined to identify any additional eligible studies. No publication type and language restrictions were imposed. This systematic review and meta-analysis was planned, performed, and reported according to the standards of quality for reporting meta-analyses.\(^{15}\) This is a systematic review and meta-analysis, which was based on previous published studies and did not have original data. Therefore, no ethical approval and patient consent are required.

2.2. Inclusion criteria

The included studies must meet all the following criteria:
1. the exposure of interest was DII;
2. the outcome of interest was CVD risk or mortality;
3. the study design was cohort or nested case-control; and
4. the relative risks (RRs) with their corresponding 95% confidence intervals (CIs) were reported (or enough data were provided to calculate these values).

We excluded reviews/meta-analyses, case reports, and studies performed in animals or cells. Studies of other dietary patterns and diseases were also excluded.

2.3. Data extraction

Data extraction was performed independently by 2 reviewers with a predefined extraction form. Discrepancies between these 2 reviewers were resolved by consulting a third reviewer. The following information were extracted from each included study: the first authors surname, country, publication year, study design, study name or source, sample size (number of total participants and cases), age of participants, methods of diet assessment, fully-adjusted risk estimates, and adjusted covariates in the design or data analysis.

2.4. Study quality assessment

The methodological quality of each study was evaluated by 2 independent reviewers using the Newcastle–Ottawa Scale (NOS).\(^ {16}\) Discrepancies between these 2 reviewers were resolved by consulting a third reviewer. NOS awards a maximum of 9 scores to each study. High quality was defined as scores ≥7.

2.5. Statistical analysis

The combined RRs and 95% CIs for highest vs lowest DII in relation to CVD risk or mortality were estimated using a DerSimonian and Laird random effects model.\(^ {17}\) The heterogeneity among studies was tested using Cochran’s Q test and the I\(^2\) statistic.\(^ {18}\) The Q statistic was used to examine the existence of heterogeneity among studies.

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Figure 1. Flow of publication search and selection.
heterogeneity with a significance level set at $P \leq .10$. The value of $I^2$ was used to determine the proportion of variation ($I^2 < 25\%$ low heterogeneity; $I^2 = 25\%–50\%$ moderate heterogeneity; $I^2 > 50\%$ large heterogeneity). Meta-regression analysis was further carried out to explore the potential sources of heterogeneity. Stratified analyses were performed according to study region, study quality, and number of cases. Sensitivity analysis was performed by re-calculating the pooled risk estimates after the omission of each study in turn. Potential publication bias was assessed by a visual funnel, Beggs test \(^{[19]}\) and Eggers test \(^{[20]}\). All statistical analyses were performed with STATA 11.0 (StataCorp, College Station, TX), using two-sided $P$ values.

3. Results

3.1. Study search and characteristics

The detailed process of study search and selection is shown in Figure 1. A total of 15 cohort studies\(^{[11-14,21-31]}\) met the inclusion criteria. Nine studies\(^{[11-14,21]}\) reported CVD risk as outcome of interest, respectively. One study\(^{[30]}\) reported both CVD risk and mortality. These studies were performed in the following geographical regions: Americas ($n = 3$), Europe ($n = 7$), Australia ($n = 4$), and Asia ($n = 1$). All of the included studies were published from 2015 to 2019. Dietary information was mainly collected by food-frequency questionnaires (FFQ). All of the included studies utilized the same methodology to assess the dietary inflammatory potential.\(^{[3]}\) The study quality scores assessed by the NOS ranged from 7 to 9. The other study characteristics are presented in Tables 1 and 2.

3.2. Overall analysis and subgroup analysis

The multivariable-adjusted RRs of the highest vs lowest DII scores, for each study and for the combination of all of the studies, are shown in Figures 2 and 3. The highest DII score was significantly associated with a higher risk of CVD (RR = 1.41, 95% CI 1.12–1.78) and CVD mortality (RR = 1.31, 95% CI 1.19–1.44), compared with the lowest DII score. In subgroup analyses, except for number of cases ($P$ for interaction = .015), none of the other factors modified the association between DII and the risk of CVD incidence and mortality (Tables 3 and 4).

3.3. Evaluation of heterogeneity

In this meta-analysis, we used the $Q$ statistic and the $I^2$ index to evaluate the heterogeneity across studies. There was statistically significant heterogeneity among the studies on the association between DII and CVD mortality ($P < .001$; $I^2 = 70.8\%$). No obvious heterogeneity was observed among the studies on the association between DII and CVD risk ($P = .160$; $I^2 = 37.0\%$).

3.4. Sensitivity analysis and publication bias

In the sensitivity analysis, the impact of each study on the pooled RR was examined by repeating the meta-analysis after removing 1 study at a time. Exclusion of any single study did not materially alter the pooled RRs (Fig. 4). There was some evidence of publication bias with Eggers test ($P = .021$) but not with Beggs test ($P = .276$). A certain degree of asymmetry was observed with a funnel plot (Fig. 5).
4. Discussion
The present meta-analysis, which utilized existing evidence from 15 cohort studies, showed strong positive associations between DII score and CVD risk and mortality. Individuals with the highest DII scores had 41.0% and 31.0% elevated risk of CVD incidence and mortality when compared with those with the lowest DII scores.

Previous studies have been performed to examine various dietary patterns and indices in relation to CVD risk and mortality. A systematic review and meta-analysis by Rosato et al.[32] reported that that Mediterranean diet exerted a protective effect on the risk of CVD based on 29 observational studies. Onvani et al.[33] found that high adherence to the Healthy Eating Index (HEI) and Alternative Healthy Eating Index (AHEI) was...
significantly associated with a reduced risk of cardiovascular mortality. The DII is a novel dietary index that is grounded in peer reviewed articles focusing specifically on dietary inflammation. Many studies have reported a significant association between DII and various health outcomes\cite{34,35} since the DII was firstly proposed by Shivappa et al in 2014.\cite{3}

The mechanism underlying the association between a pro-inflammatory diet (high DII score) and a high risk of CVD is still not clear. One possible explanation is that a pro-inflammatory diet is able to increase the levels of cytokines like TNF-α, IL-1, and IFN-γ,\cite{36,37} which may cause attraction and migration of inflammatory cells into vascular tissue. Camargo-Ramos et al\cite{38} reported that an increased inflammatory potential of diet was negatively associated with improved cardiometabolic risk parameters. Correa-Rodriguez et al \cite{39} found that DII was significantly associated with cardiovascular risk factors in Spanish children and adolescents. Finally, Garcia-Calzon et al\cite{40} observed a potential association between the inflammatory potential of the diet and telomere shortening in subjects with a high cardiovascular disease risk. All of these studies indicated that the dietary inflammatory potential would contribute to the CVD risk and mortality.

Our study had some strength. First, compared with previous studies on the same topic, this updated meta-analysis has the largest sample size and thus may enhance the statistical power. Second, our study only included cohort studies, which avoided the recall and selective bias. Third, sensitivity analysis indicated that the pooled risk estimates were stable and not dominated by any single study, which suggested that findings of our study were steady. Finally, the method used to calculate the DII score in each study was generally consistent,\cite{3} which made these studies highly comparable.

This meta-analysis also had some limitations that should be acknowledged. First, the DII was mainly derived from self-administered FFQ in most included studies and the food parameters used for calculation of DII were not completely consistent across studies, which may cause exposure misclassification and heterogeneity. Second, only 6 cohorts were eligible for the analysis of CVD risk, which was relatively small. Third, substantial heterogeneity was detected with Q and I² score, which may be attributed to the different demographic characteristics across studies. The meta-regression analysis indicated that the number of cases was the potential source of heterogeneity. Finally, although we have performed a comprehensive literature search, a certain degree of publication bias was observed with a visual funnel and Eggers test.

### Table 3

| Subgroup       | N  | Summary RR (95% CI) | \(P_{\text{interaction}}\) | \(Q\) | \(I^2\) (%) | \(P\) |
|----------------|----|---------------------|----------------------------|-------|-------------|-------|
| Total          | 6  | 1.41 (1.12–1.78)    |                           | 7.94  | 37.0        | .160  |
| Region         |    |                     |                            |       |             |       |
| Europe         | 4  | 1.49 (1.18–1.88)    | .453                       | 3.06  | 2.1         | .382  |
| Australia      | 2  | 1.34 (0.71–2.52)    |                           | 3.00  | 66.6        | .083  |
| Follow-up (y)  |    |                     |                            |       |             |       |
| ≥10            | 3  | 1.15 (0.93–1.43)    | .071                       | 1.73  | 0.0         | .421  |
| <10            | 3  | 1.85 (1.36–2.51)    |                           | 0.23  | 0.0         | .890  |
| No. of cases   |    |                     |                            |       |             |       |
| ≥200           | 4  | 1.29 (1.01–1.65)    | .167                       | 4.68  | 35.9        | .197  |
| <200           | 2  | 2.02 (1.26–3.23)    |                           | 0.00  | 0.0         | .975  |

CI = confidence interval, DII = dietary inflammatory index, N = number, RR = relative risk, y = year.

### Table 4

| Subgroup       | N  | Summary RR (95% CI) | \(P_{\text{interaction}}\) | \(Q\) | \(I^2\) (%) | \(P\) |
|----------------|----|---------------------|----------------------------|-------|-------------|-------|
| Total          | 10 | 1.31 (1.19–1.44)    | 0.420                      | 34.26 | 70.8        | <.001 |
| Region         |    |                     |                            |       |             |       |
| Europe         | 4  | 1.47 (1.17–1.85)    |                           | 5.80  | 48.3        | .122  |
| Australia      | 2  | 1.52 (0.95–2.43)    |                           | 3.95  | 74.7        | .047  |
| USA            | 3  | 1.20 (1.08–1.33)    |                           | 11.79 | 74.6        | .008  |
| Asia           | 1  | 1.30 (1.13–1.49)    |                           | -     | -           | -     |
| Follow-up (y)  |    |                     |                            |       |             |       |
| > 15           | 7  | 1.27 (1.14–1.40)    | 0.276                      | 25.75 | 72.8        | .001  |
| ≤ 15           | 3  | 1.48 (1.20–1.83)    |                           | 3.01  | 33.6        | .222  |
| No. of cases   |    |                     |                            |       |             |       |
| ≥ 1000         | 6  | 1.22 (1.13–1.32)    | 0.015                      | 14.23 | 57.8        | .027  |
| < 1000         | 4  | 1.66 (1.33–2.06)    |                           | 4.39  | 31.7        | .222  |

CI = confidence interval, DII = dietary inflammatory index, N = number, RR = relative risk, y = year.
5. Conclusion

In summary, the present systematic review and meta-analysis indicates that a higher DII score is related to a higher risk of CVD. However, due to the large heterogeneity and other limitations as discussed above, further well-designed prospective cohort or trials are warranted to validate our findings.

Author contributions

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