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Association Between Dietary Inflammation Index and The Risk of Colorectal Cancer: A Meta-Analysis

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ABSTRACT
Objectives: We performed a meta-analysis to assess the association and possible dose–response relationship between dietary inflammation index (DII) and colorectal cancer (CRC). Methods: A literature search was performed in PubMed, Web of Science and Chinese National Knowledge Infrastructure (CNKI) database for all relevant studies. The pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated by random effects model. Results: A total of eight studies were included in this meta-analysis. The pooled RRs of CRC, colon and rectal cancer for the highest versus lowest DII categories were 1.43 (95% CI 1.25–1.63), 1.37 (95% CI 1.16–1.62) and 1.44 (95% CI 1.23–1.69), respectively. A significant positive association was observed both in cohort studies (RR 1.26, 95% CI 1.14–1.38) and case–control studies (RR = 1.81, 95% CI 1.48–2.22). Nonlinear associations between DII scores and the risk of CRC, colon and rectal cancer were found in the dose–response analyses, the results showed that the risks of CRC, colon and rectal cancer increased slowly when the DII score was above 1.30, 2.21, and 1.30, respectively. Conclusion: Higher DII scores might increase CRC risk. Thus, people should adopt more anti-inflammatory diets such as those high in vegetables, fruits, whole grains, herbs, and spices.

Introduction
Colorectal cancer (CRC) is the third most commonly diagnosed cancer among both men and women in the United States (1). Worldwide, CRC is the third and second most commonly diagnosed and the fourth and third most deadly cancers among men and women, respectively (2). It has been found that family history, obesity, physical inactivity, excessive alcohol consumption, and smoking are related to the risk of CRC (3–5). Diets high in meats, added sugar, and protein are also risk factors for CRC (6–8).

Chronic inflammation is known to have an important role in colorectal cancer (9), and certain dietary components such as omega-3 polyunsaturated fatty acid, fruit and vegetables, vitamin D may modulate inflammation (10). Recently, the dietary inflammatory index (DII) was developed as a new tool to evaluate the inflammatory potential of the diet (11). A positive score indicates a more pro-inflammatory diet, while a negative score reflects a diet that is more anti-inflammatory. Advantages of the DII over other dietary indices are as follows:

(i) It was based on a peer-reviewed literature using information from nearly 2000 research studies;
(ii) It was designed to measure dietary inflammatory potential and
(iii) it is standardized to a global database which allows it to be used across populations. It also has the potential to be used for assessing and guiding individuals to set dietary goals and further help decrease levels of inflammation (11). The DII has been shown to be associated with various inflammatory markers, including C-reactive protein (11, 12), Interleukin 6 (12, 13) and homocysteine (13). In addition, higher DII scores (indicated as a pro-inflammatory diet) have been found to be linked to the risks of many diseases, e.g. depression (14, 15), asthma (16), diabetes (12, 17), mortality (18, 19), obesity (20, 21), cancer (22–24), cardiovascular disease (25–27), adverse pregnancy outcomes (28, 29), and mild cognitive impairment/dementia (30), etc. With regard to colorectal and colon cancer, although most studies (31–37) revealed that there was a significant association between DII and the risk of colorectal cancer as well as colon cancer, they did not get the significant cut-off values that

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could increase the risks of both colorectal cancer and colon cancer. In addition, regarding rectal cancer, four studies (32, 33, 36, 37) observed that higher DII scores had a significant effect on the risk of rectal cancer, while the other three studies (34, 35, 38) got the opposite results.

Therefore, we carried out a meta-analysis of observational studies to (i) assess the association between DII and the risk of colorectal cancer; and (ii) assess the possible dose–response relationships between them.

**Materials and Methods**

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta- Analyses guidelines (PRISMA) (39).

**Search Strategy**

To identify all relevant studies that were conducted in humans and published in English or Chinese, we performed a literature search up to 13 March 2017 in the databases of PubMed, Web of Science and Chinese National Knowledge Infrastructure (CNKI). Search terms were as follows: “dietary inflammation index” or “DII” and “cancer” or “tumor” or “neoplasms”. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies. The flow diagram of the literature search is shown in Figure 1.

**Inclusion Criteria**

Two investigators independently searched and reviewed all the identified studies, and studies were included if they met the following criteria: (i) an observational study (cohort or case-control) published in English or Chinese; (ii) the exposure was DII, excluding the DII calculated from the data of food supplements; (iii) the outcome was CRC (studies have to have CRC, but adenomas were not included); and (iv) the odds ratios (ORs) or relative risks (RRs) with 95% confidence intervals (CIs) were provided (we presented all results with RR for simplicity). If data were duplicated which means multiple articles used the same data source, we chose the articles that have the most complete data.

**Data Abstraction**

Data were extracted independently by two investigators who achieved the agreement on all of the items. The following information was extracted: the first author’s name, publication year, country in which the study was conducted, continent, study design, sample size, number of cases, age in case and control groups, DII scores of case and control group, the RRs with corresponding 95% CIs for the highest versus lowest DII categories (the use of categories was not consistent between studies) and continuous DII, and variables adjusted for in the analysis. For dose–response analysis, the number of cases and participants (person-years), and RR (95% CI) for each category of DII were also extracted.

**Statistical Analysis**

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI to assess the strength of association between DII and the risk of CRC. $I^2$ of Higgins and Thompson (40) was used to assess heterogeneity among studies ($I^2$ values of 0, 25, 50, and 75% represent no, low, moderate, and high heterogeneity, respectively). Given that the DerSimonian and Laird random effects model (REM) typically produces more conservative estimates of the significance of the treatment effect (i.e. a wider confidence interval) than fixed effects models, we used a REM as the pooling method (41). Meta-regression with covariates of publication year, continent, study design, sample size and adjusted for smoking status was conducted to explore the potential sources of heterogeneity. Subgroup analysis was performed by study design, continent and sample.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country (continent)</th>
<th>Age range /mean age</th>
<th>Study design</th>
<th>Sample size</th>
<th>Disease type</th>
<th>Cases (person-year)</th>
<th>RR (95%CI)</th>
<th>Adjustment for covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivappa, N. (2014)</td>
<td>America (North America)</td>
<td>55–69</td>
<td>Cohort</td>
<td>34703</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>1636 1329 325</td>
<td>1.12 (0.91–1.38) 1.06 (0.84–1.33) 1.48 (0.94–2.34)</td>
<td>Adjusted for age, the other DII variable, BMI, smoking status, pack-years of smoking, HRT use, education, diabetes, and total energy intake</td>
</tr>
<tr>
<td>Shivappa, N. (2015)</td>
<td>Italy (Europe)</td>
<td>62/58</td>
<td>Case control</td>
<td>6107</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>1953 1225 728</td>
<td>1.55 (1.29–1.85) 1.39 (1.13–1.71) 1.47 (1.14–1.90)</td>
<td>Adjusted for age, sex, study center, education, BMI, alcohol drinking, physical activity, history of colorectal cancer and energy intake</td>
</tr>
<tr>
<td>Tabung, F. K. (2015)</td>
<td>America (North America)</td>
<td>50–79</td>
<td>Cohort</td>
<td>152536</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>1920 1559 361</td>
<td>1.22 (1.05–1.43) 1.23 (1.03–1.46) 1.20 (0.84–1.72)</td>
<td>Adjusted for age, total energy intake, BMI, race/ethnicity, physical activity, educational level, smoking status, family history of colorectal cancer, hypertension, diabetes, arthritis, history of colonoscopy, history of occult blood tests, NSAID use, category and duration of estrogen use, category and duration of progesterone use, diet modification trial arm, hormone therapy trial arm, and calcium and vitamin D arm</td>
</tr>
<tr>
<td>Wirth, M. D. (2015)</td>
<td>America (North America)</td>
<td>62.0 ± 54</td>
<td>Cohort</td>
<td>342870</td>
<td>CRC Rectal cancer</td>
<td>6225 1680</td>
<td>1.40 (1.28–1.53) 1.45 (1.22–1.73)</td>
<td>Adjusted for age, smoking status, BMI, self-reported diabetes, energy intake, physical activity, marital status and education</td>
</tr>
<tr>
<td>Zamora-Ros, R. (2015)</td>
<td>Spain (Europe)</td>
<td>66.2 ± 11.7/ 65.1 ± 12.5</td>
<td>Case control</td>
<td>825</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>424 265 159</td>
<td>1.65 (1.05–2.60) 2.24 (1.33–3.77) 1.12 (0.61–2.06)</td>
<td>Adjusted for age, sex, total energy intake, BMI, tobacco consumption, level of physical activity, regular medications, and first-degree family history of CRC</td>
</tr>
<tr>
<td>Cho, Y. A. (2016)</td>
<td>Korea (Asia)</td>
<td>56.6 ± 9.7/ 56.1 ± 9.1</td>
<td>Case control</td>
<td>2769</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>923 460 444</td>
<td>2.16 (1.71–2.73) 2.05 (1.53–2.74) 2.23 (1.66–3.00)</td>
<td>Adjusted for age, sex, BMI, education, family history of colorectal cancer, physical activity and total caloric intake</td>
</tr>
<tr>
<td>Harmon, B. E. (2017)</td>
<td>America (North America)</td>
<td>45–75</td>
<td>Cohort</td>
<td>190963</td>
<td>CRC Colon cancer Rectal cancer</td>
<td>4388 3372 982</td>
<td>1.21 (1.11–1.32) 1.20 (1.09–1.33) 1.22 (1.02–1.47)</td>
<td>Adjusted for age, sex, race/ethnicity, BMI, self-reported previous diagnosis of diabetes, asthma, heart attack, use of supplements, smoking status, family history of colon cancer, education, hormone use and aspirin use</td>
</tr>
<tr>
<td>Shivappa, N. (2017)</td>
<td>Jordan (Asia)</td>
<td>53.8 ± 11.7/ 51.6 ± 11.1</td>
<td>Case control</td>
<td>355</td>
<td>CRC</td>
<td>153</td>
<td>2.13 (1.23–3.72)</td>
<td>Adjusted for age, sex, education, physical activity, BMI, smoking and family history of colorectal cancer</td>
</tr>
</tbody>
</table>
size. The influence analysis was carried out with the exclusion of one study at a time to assess whether the results could have been affected markedly by a single study (42). Publication bias was evaluated by the funnel plot and Egger’s test (43).

For dose–response analysis, a two-stage random-effects dose–response meta-analysis (44) was performed to compute the trend from the correlated log RR estimates across the score of DII. In the first stage, a restricted cubic spline model with four knots at the 5th, 35th, 65th and 95th percentiles of the score of DII was estimated using generalized least square regression considering the correlation within each set of published RRs (45). Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (46). A $P$-value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. If the results begin to be significant ($CI$ not including 1) from a certain point, the point would be regarded as the cut-off value. All statistical analyses were carried out using STATA Version 10 (StataCorp, College Station, Texas, USA). All reported $P$-values were two-sided with $P \leq 0.05$ considered statistically significant.

Results

Literature Search and Study Characteristics

The search strategy identified 848 articles from PubMed, 1337 articles from Web of Science and 2 articles from CNKI. Six additional articles were found in reference lists. Among these articles, 410 duplicates were excluded (Figure 1). After reviewing the title or abstract, 31 articles were retrieved. Twenty-three articles were subsequently excluded for various reasons after reviewing the full text. As a result, 8 articles with 731128 participants were included in this meta-analysis (31–38). Of these 8 articles, 4 were cohort studies (33, 34, 36, 38) and 4 were case-control studies (32, 35–37). With regard to study continent, 2 were conducted in Asia (31, 37), 4 in North America (33, 34, 36, 38), and 2 in Europe (32, 35). The baseline characteristics of the studies are shown in Table 1 and Supplementary Table 1.

Quantitative Synthesis

The detailed results are summarized in Table 2.

DII and the Risk of CRC

Eight articles (31–38) investigated the association between DII and the risk of colorectal cancer. The pooled RR of CRC for the highest versus the lowest DII categories was 1.43 (95% CI 1.25–1.63, $I^2 = 78.5\%$, $P_{\text{heterogeneity}} < 0.05$) (Figure 2). When analysis was carried out using continuous DII, a 1-unit increment in DII showed a significant positive association with risk of CRC (RR = 1.08, 95% CI 1.03–1.13). In subgroup analysis stratified by study design, the pooled RR for the highest versus the lowest DII categories was 1.26 (95% CI 1.14–1.38) in cohort studies and 1.81 (95% CI 1.48–2.22) in case-control studies (Table 2; Supplementary Figure 1a). In subgroup analysis stratified by continent, the pooled RR for the highest versus the lowest DII categories was 2.16 (95% CI 1.74–2.67) in Asia, 1.26 (95% CI 1.14–1.38) in North America, and 1.56 (95% CI 1.32–1.85) in Europe (Table 2; Supplementary Figure 1b). Regarding the subgroup of sample size, the pooled RR for the highest versus the lowest DII categories in sample size less than 10000 and sample size more than 10000 was 1.81 (95% CI 1.48–2.22) and 1.26 (95% CI 1.14–1.38), respectively (Table 2; Supplementary Figure 1c).

For dose–response analysis, six studies (33–38) including 15516 CRC cases provided the data (Supplementary Table 1). Evidence of a nonlinear association was found ($P$ for nonlinearity = 0.0000) between DII and risk of CRC. The risk of CRC increased slowly when the DII score was above 1.30. The RR (95% CI) of CRC was 0.98 (0.94–1.02), 1.00 (0.93–1.06), 1.10 (1.02–1.20) and 1.26 (1.14–1.39) for $–2.98$, $–1.15$, 1.30 and 4.04 score of DII, respectively.

DII and the Risk of Colon Cancer

Six articles (32, 34–38) investigated the association between DII and the risk of colon cancer. The pooled RR of colon cancer for the highest versus the lowest DII categories was 1.37 (95% CI 1.16–1.62, $I^2 = 74.2\%$, $P_{\text{heterogeneity}} = 0.002$) (Table 2; Supplementary Figure 2). When analysis was carried out using continuous DII, a 1-unit increment in DII showed a significant positive association with risk of colon cancer (RR = 1.07, 95% CI 1.03–1.10). In subgroup analysis stratified by study design, the pooled RR for the highest versus the lowest DII categories was 1.19 (95% CI 1.10–1.29) in cohort studies, and 1.77 (95% CI 1.29–2.44) in case-control studies (Table 2). In subgroup analysis stratified by continent, the pooled RR for the highest versus the lowest DII categories was 2.05 (95% CI 1.53–2.74) in Asia, 1.19 (95% CI 1.10–1.29) in North America, and 1.66 (95% CI 1.06–2.60) in Europe (Table 2). Regarding the subgroup of sample size, the pooled RR for the highest versus the lowest DII categories in sample size less than 10000 and sample size more than 10000 was 1.77 (95% CI 1.29–2.44) and 1.19 (95% CI 1.10–1.29), respectively (Table 2).

For dose–response analysis, three studies (36–38) including 5161 colon cancer cases provided the data...
Evidence of a nonlinear association was found ($P$ for nonlinearity $D_0.0000$) between DII score and risk of colon cancer. The risk of colon cancer increased slowly when the DII score was above 2.21. The RR (95% CI) of colon cancer was 0.96 (0.91–1.02), 1.00 (0.91–1.09), 1.04 (0.94–1.14) and 1.13 (1.00–1.27) for $DII < 2.98$, $DII \geq 0.70$, $DII \geq 0.27$ and $DII \geq 2.21$ score of DII, respectively.

(Supplementary Table 1). Evidence of a nonlinear association was found ($P$ for nonlinearity $D_0.0000$) between DII score and risk of colon cancer. The risk of colon cancer increased slowly when the DII score was above 2.21. The RR (95% CI) of colon cancer was 0.96 (0.91–1.02), 1.00 (0.91–1.09), 1.04 (0.94–1.14) and 1.13 (1.00–1.27) for $DII < 2.98$, $DII \geq 0.70$, $DII \geq 0.27$ and $DII \geq 2.21$ score of DII, respectively.

### Table 2. Pooled relative risks of associations between DII and colorectal cancer.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Number of studies</th>
<th>RR (95% CI)</th>
<th>$I^2$ (%)</th>
<th>$P_{heterogeneity}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>All studies</td>
<td>1.43 (1.25–1.63)</td>
<td>78.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>4.1.26 (1.14–1.38)</td>
<td>59.6</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>4.1.81 (1.48–2.22)</td>
<td>44.3</td>
<td>0.146</td>
</tr>
<tr>
<td></td>
<td>Continent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>2.1.56 (1.32–1.85)</td>
<td>0.0</td>
<td>0.802</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>2.2.16 (1.74–2.67)</td>
<td>0.0</td>
<td>0.964</td>
</tr>
<tr>
<td></td>
<td>North America</td>
<td>4.1.26 (1.14–1.38)</td>
<td>59.6</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>Sample Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10000</td>
<td>4.1.81 (1.48–2.22)</td>
<td>44.3</td>
<td>0.146</td>
</tr>
<tr>
<td></td>
<td>\geq 10000</td>
<td>4.1.26 (1.14–1.38)</td>
<td>59.6</td>
<td>0.059</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>All studies</td>
<td>6.1.37 (1.16–1.62)</td>
<td>74.2</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>3.1.19 (1.10–1.29)</td>
<td>0.0</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>3.1.77 (1.29–2.44)</td>
<td>67.1</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>Continent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>2.1.66 (1.06–2.60)</td>
<td>64.1</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1.2.05 (1.53–2.74)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>North America</td>
<td>3.1.19 (1.10–1.29)</td>
<td>0.0</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10000</td>
<td>3.1.77 (1.29–2.44)</td>
<td>67.1</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>\geq 10000</td>
<td>3.1.19 (1.10–1.29)</td>
<td>0.0</td>
<td>0.566</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>All studies</td>
<td>7.1.44 (1.23–1.69)</td>
<td>54.5</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort</td>
<td>4.1.33 (1.18–1.49)</td>
<td>0.0</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>3.1.63 (1.13–2.34)</td>
<td>68.1</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>Continent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>2.1.41 (1.12–1.79)</td>
<td>0.0</td>
<td>0.419</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1.2.23 (1.66–3.00)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>North America</td>
<td>4.1.33 (1.18–1.49)</td>
<td>0.0</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>Sample Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10000</td>
<td>4.1.55 (1.24–1.93)</td>
<td>64.5</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>\geq 10000</td>
<td>3.1.24 (1.06–1.46)</td>
<td>0.0</td>
<td>0.699</td>
</tr>
</tbody>
</table>

### Figure 2. Forest plot of the relative risks (RRs) with corresponding 95% confidence intervals (CIs) of studies on DII and CRC. The size of the grey box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

### NOTE: Weights are from random effects analysis
DII and the Risk of Rectal Cancer

Seven articles (32–38) investigated the association between DII and the risk of rectal cancer. The pooled RR of rectal cancer for the highest versus the lowest DII categories was 1.44 (95% CI 1.23–1.69, $I^2 = 54.5\%$, $P_{\text{heterogeneity}} = 0.040$) (Figure 3). When analysis was carried out using continuous DII, a 1-unit increment in DII showed a significant positive association with risk of colon cancer (RR = 1.07, 95% CI 1.03–1.12). In subgroup analysis stratified by study design, the pooled RR for the highest versus the lowest DII categories was 1.33 (95% CI 1.18–1.49) in cohort studies and 1.63 (95% CI 1.13–2.34) in case–control studies. In subgroup analysis stratified by continent, the pooled RR for the highest versus the lowest DII categories was 2.23 (95% CI 1.66–3.00) in Asia, 1.33 (95% CI 1.18–1.49) in North America, and 1.41 (95% CI 1.12–1.79) in Europe (Table 2). Regarding the subgroup of sample size, the pooled RR for the highest versus the lowest DII categories in sample size less than 10000 and sample size more than 10000 was 1.55 (95% CI 1.24–1.93) and 1.24 (95% CI 1.06–1.46), respectively (Table 2).

For dose–response analysis, four studies (33, 36–38) including 3 105 rectal cancer cases provided the data (Supplementary Table 1). Evidence of a nonlinear association was found ($P$ for nonlinearity = 0.029) between DII score and risk of rectal cancer. The risk of rectal cancer increased slowly when the DII score was above 1.30. The RR (95% CI) of rectal cancer was 1.00 (0.92–1.08), 1.13 (0.95–1.34), 1.21 (1.00–1.46), and 1.38 (1.11–1.72) for −3.24, 0.27, 1.30 and 3.30 score of DII, respectively.

Meta-Regression

To explore the moderate to high between-study heterogeneity in these above-mentioned analyses, meta-regression with the covariates of publication year, continent, study design, sample size and status of adjusting for smoking was performed. In the analysis of DII and the risk of CRC, the results showed that sample size ($P_{\text{heterogeneity}} = 0.017$) and study design ($P_{\text{heterogeneity}} = 0.013$) contributed to heterogeneity. In the analysis of DII and the risk of colon cancer, only sample size ($P_{\text{heterogeneity}} = 0.049$) was found to contributed toward heterogeneity. No significant findings were found in other analyses (Supplementary Table 2).

Influence Analysis and Publication Bias

For both colon and rectal cancer, no individual study had an excessive influence on the pooled RRs. However, for CRC, one study (36) was found to have an impact on the pooled estimate for the highest versus the lowest DII categories. After excluding the study (36), the finding still remained significant (RR = 1.48, 95% CI 1.27–1.73, $I^2 = 75.5\%$, $P_{\text{heterogeneity}} < 0.05$). The funnel plot and Egger’s test showed no evidence of significant publication bias in the analyses between CRC ($P = 0.209$) (Figure 4), colon cancer ($P = 0.134$) and rectal cancer ($P = 0.849$) and DII.

Discussion

This meta-analysis found that more pro-inflammatory diets, as reflected by higher DII scores, may be related to...
an increased risk of CRC. In addition, increased risks of both colon and rectal cancers were also observed with a more pro-inflammatory diet. In subgroup analysis, significant associations were found both in cohort and case-control studies. Higher DII scores were significantly linked with the increased risk of CRC among studies conducted in Asia, North America as well as in Europe. We found nonlinear associations between DII scores and the risk of CRC, colon and rectal cancer in the dose-response analyses, the results showed that the risk of CRC, colon and rectal cancer increased slowly when the DII score was above 1.30, 2.21, and 1.30, respectively.

Several mechanisms have been proposed to explain the significant association between the DII and the risk of CRC. First, a pro-inflammatory diet has an effect on insulin resistance by increasing systemic inflammation (47, 48). Consumption of food items such as meat, butter and sweets has been shown to affect systemic inflammation by increasing levels of high-sensitivity C-reactive protein, E-selectin and soluble vascular cell adhesion molecule-1 (48), which then are responsible for increasing insulin resistance (47). Increasing insulin resistance may affect colorectal cancer risk by increasing circulating levels of insulin, triglycerides and non-esterified fatty acids (49, 50), which promote excessive proliferation of colonic epithelial cells and expose them to reactive oxygen species, thereby increasing risk of colorectal cancer. Second, activation of the cyclooxygenase 2 (COX-2) pathway may result in focal proliferation, angiogenesis and mutagenesis (50). COX-2 can be upregulated by inflammatory stimuli via inflammatory cytokines (e.g., IL-6), growth factors and certain diet components (e.g., meat, sugar and fat), and it can be downregulated by dietary components (e.g., vitamin D and n-3 fatty acids), physical activity, and medications (51).

Between-study heterogeneity is common in meta-analyses (52), and it is necessary to explore the potential sources of between-study heterogeneity. Our meta-analysis showed relatively high heterogeneity. We used meta-regression to explore the potentially important causes of the between-study heterogeneity. Study design and sample size were found to influence the between-study heterogeneity. In subgroup analyses by study design and sample size, the heterogeneity was decreased. Several possible reasons may lead to heterogeneity. First, both the number and covariates of confounders adjusted in studies are different. For example, half of studies (31, 33, 35, 37) adjusted less than nine confounders, while the other half (32, 34, 36, 38) adjusted more than nine confounders. Moreover, six studies (31, 33–36, 38) adjusted the covariate of smoking compared to the other two studies (32, 37). Second, food components used to calculate the DII are various among the included studies. Third, the range and categories of DII score in each study are different; three studies (33, 35, 36) divided into four categories, two studies (34, 38) divided into five categories and the last one (37) divided into three categories. Fourth, the methods used to validate the food frequency questionnaire (FFQ) vary from study to study; one (32) is 7 d dietary record, three (31, 34, 36) are 24 h dietary recall interviews, and the remaining (33, 35, 37, 38) are FFQ.

To the best of our knowledge, this is the first meta-analysis to explore the association between DII and risk of CRC. Compared to other dietary indices, the DII can be estimated from a variety of diet assessment instruments (e.g., 24-hour recalls, 7-day dietary recalls, and food frequency questionnaires [FFQ]). In addition, it can be used in various populations worldwide. There are some advantages in our study. First, a relatively large number of participants were included, which enabled a much greater possibility of reaching reasonable conclusions. Second, nearly all included studies had adjusted for potential confounders, increasing the credibility of the results. Third, a significant association between DII and the risk of CRC was evaluated from cohort studies in subgroup analysis. Fourth, we conducted dose-response analysis to quantitatively describe the relationship between DII and the risk of CRC, colon cancer and rectal cancer.

However, the limitations of our study should also be considered. First, most studies were based on a single assessment of diet at baseline. So changes in dietary patterns could not be examined; this may have effect on CRC risk. Second, food components included in the DII calculation differed in studies. For studies with use of fewer variables, they may achieve more narrow range of DII score compared to the studies with use of more
variables. Third, confounders adjusted in studies were different; moreover, some unknown factors may have an effect on the association between DII and the risk of CRC. Fourth, the use of DII categories was not consistent, and the dietary reporting methods were not all the same in the included studies.

In conclusion, the results from this meta-analysis suggest that higher DII scores might increase the risks of CRC, colon and rectal cancer. Thus, people should adopt more anti-inflammatory diets such as those high in vegetables, fruits, whole grains, herbs, and spices, which can reduce the risk of CRC as well as other inflammation-related cancers.

Declaration of Interest
All the authors declare that they have no conflict of interest.

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