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DOI: 10.17235/reed.2020.6851/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:
OR 6851

Meta-analysis of protein intake on the effect of Crohn’s disease and ulcerative colitis

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Received: 28/1/2020
Accepted: 17/4/2022

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Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Background and purpose: published studies have assessed the effect of protein intake on Crohn’s disease (CD) and ulcerative colitis (UC). However, the results were inconsistent. To provide a more precise estimation, a meta-analysis was performed to evaluate the association of protein intake in Crohn’s disease and ulcerative colitis.

Methods: the PubMed, Chinese National Knowledge Infrastructure databases (CNKI), and Wanfang databases were searched to identify relevant studies. The summarized results of the relative risk (RR) with the corresponding 95 % confidence intervals (CI) were calculated using a random effects model.

Results: the final analysis included a total of nine articles. Nine studies reported on protein intake for the risk of UC and five studies reported on protein intake for the risk of CD. Overall, based on current studies, no significant association was found between protein intake and the risk of UC (RR = 1.13, 95 % CI = 0.82-1.55) or CD (RR
1.18, 95% CI = 0.51-2.74). A significant change was not found in the stratified analysis by study design and geographic location.

**Conclusions:** in conclusion, the present meta-analysis suggested that dietary protein intake did not show a significant effect on the risk of UC or CD.

**Keywords:** Protein. Dietary. Crohn’s disease. Ulcerative colitis. Meta-analysis.

**INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the intestinal tract (1). Crohn’s disease (CD) and ulcerative colitis (UC) are the two major manifestations of IBD (2). The prevalence of CD and UC varies considerably across countries (3,4). It is higher in Europe and North America. However, steady increases have been reported over the last decades in South America, Africa and Asia (5). Unfortunately, the cause of this increase remains unclear, but risk factors including genetic susceptibility (6,7) and environmental factors (changes in lifestyle, diet factors, etc.) (8) may be responsible. Previous meta-analysis of 15 pooled epidemiology studies showed that total dietary carbohydrate intake had a non-significant relationship with IBD risk (9). Liu et al. performed a meta-analysis on dietary fiber intake and IBD risk and suggested that dietary fiber was significantly associated with a decreased risk of IBD (10). Carbohydrates, fiber and proteins are important nutrients for the human body. Recently, evidence from a number of observational studies focused on the effects of protein intake on the risk of UC and CD. However, the results of these studies were inconclusive. To provide a more precise estimation, we performed a meta-analysis to estimate the effect of protein intake on the risk of UC and CD. The potential publication bias and between-study heterogeneity were also assessed.

**MATERIALS AND METHODS**

The current study was performed via the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (11).
Identification and eligibility of relevant studies

Literature searches of the PubMed, Chinese National Knowledge Infrastructure databases (CNKI) and Wanfang databases (up to March 1st, 2020) were performed to identify eligible studies. The structured strategies used the following search terms: “protein” AND (“inflammatory bowel disease” OR “ulcerative colitis” OR “Crohn’s disease”). In addition, the reference lists of identified studies were manually checked to identify other potentially eligible trials.

Inclusion and exclusion criteria

The inclusion criteria of the eligible studies in the meta-analysis were as follows: a) observational studies; b) evaluating the association of protein intake on the risk of ulcerative colitis (UC) or Crohn’s disease (CD); c) available relative risk (RR) for protein intake on the risk of UC or CD; and d) studies reported in humans.

The exclusion criteria were as follows: no usable data, duplicate of an earlier publication, animal studies or reviews.

Data extraction and quality assessment

Data were extracted and independently crosschecked by two authors. The following information was collected for each study: first author’s name, year of publication, study location, sample size (cases and controls), details of the study design, category of RR, age, sex, protein type, disease type and assessment of diet. The Newcastle-Ottawa-Scale (NOS) was used to evaluate the quality of each study (12).

Statistical analysis

Data were calculated as RR with 95 % CI to determine the effect of protein intake on the risk of UC and CD (13). A random-effect model was used for the analyses because results in the random-effect model had a wider CI than a fixed-effect model and could obtain more cautious results (14). The $I^2$ statistic test was performed to assess the heterogeneity between studies (14). A significant $X^2$ test (p < 0.05) and an $I^2$ statistic of > 50 % indicated heterogeneity in effect sizes among the studies (15). A subgroup analysis was also performed by study design and geographic location.
Sensitivity analyses were performed to evaluate the stability of the results. Publication bias was investigated by funnel plot (16) and estimated Egger’s tests (17). Data analysis was performed using the software STATA (version 12.0).

RESULTS
Identification of eligible studies
Based on the current search strategy, a total of 24,251 articles were retrieved from the initial database search in PubMed, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases. One article was also identified from the reference list of an article. Among them, the full-text of 41 articles was reviewed. Finally, nine articles (18-26) that included 1,095 cases were finally identified as eligible studies. All of the nine studies had a relatively high quality (over 6 stars), with an average NOS score of 7.33. The detailed process of selecting and excluding studies is presented in figure 1.

Characteristics of published studies
Persson et al. (22) reported on protein intake for UC and CD risk in males and females, respectively. Therefore, we regard this article as two independent studies. Nine studies reported on protein intake for the risk of UC and five studies on protein intake for the risk of CD. Three articles reported both UC and CD with protein intake. Five articles were from Europe, three from Asia and one from South America. Six studies had a case-control design, two a prospective cohort design and one a cross-sectional design. The detailed characteristics of these studies are listed in table 1.

Protein intake and UC risk
Nine studies were performed to assess the association between protein intake and UC risk. Eight studies reported a non-significant association for UC risk with a high protein intake, while only one study concluded an increased risk of UC with a high protein intake. The summarized RR for the highest category of dietary protein intake versus the lowest intake was 1.13 (95% CI = 0.82-1.55). No significant heterogeneity was found (I² = 39.5 %, p = 0.104) (Fig. 2).
In the stratified analysis by study design, no significant association was found in case-control studies (summarized RR = 1.19, 95 % CI = 0.69-2.05; I² = 30.1 %, p = 0.209) or cohort studies (summarized RR = 1.47, 95 % CI = 0.37-5.82; I² = 79.4 %, p = 0.027).

With regard to the subgroup analysis by geographic location, there were consistent results in European populations (summarized RR = 1.03, 95 % CI = 0.47-2.26; I² = 61.6 %, p = 0.034) and Asian populations (summarized RR = 1.54, 95 % CI = 0.92-2.60; I² = 0.0 %, p = 0.924). The Begg’s funnel plot (Fig. 3) and Egger’s linear regression test (p = 0.523) did not detect any publication bias.

The sensitivity analysis was also used to detect the influence of the individual study on the pooled results, by omitting one single study each time from the pooled analysis. The pooled RR and 95 % CI did not change significantly when any part of the study was omitted (Fig. 4), which indicated that any single study had little impact on the overall RR.

**Protein intake and CD risk**

Five studies assessed the association between protein intake and CD risk. The summarized RR for the highest category of dietary protein intake versus the lowest intake was 1.18 (95 % CI = 0.51-2.74). Significant heterogeneity was found (I² = 69.0 %, p = 0.012) (Fig. 2).

Four of the included studies were from Europe and there was no significant association found in European populations (summarized RR = 1.00, 95 % CI = 0.35-2.82; I² = 68.9 %, p = 0.022). According to the subgroup analysis by study design, the association did not change in case-control studies (summarized RR = 0.95, 95 % CI = 0.38-2.40; I² = 70.9 %, p = 0.016). The RR were not combined for the cohort studies, as only one study had a cohort design.

No single study had an essential impact on the overall RR according to the sensitivity analysis (Fig. 5). Egger’s linear regression test (p = 0.891) did not detect any publication bias.

**DISCUSSION**

This study reported the relationship between dietary protein intake and UC and CD
risk, using a comprehensive meta-analysis. A total of nine articles were included in the study. Findings from this study suggested that there was no significant association of protein intake on the risk of UC or CD. Significant changes were not found in the stratified analysis by study design and geographic location. The publication bias was evaluated by the Egger’s test and Begg’s funnel plot and there was no significant association for the whole or subgroup analyses. Thus, allowing a much greater possibility of reaching reasonable conclusions about dietary protein intake on UC and CD risk.

The etiology of UC and CD is unclear, but previous studies have shown potential genetic and environment factors (6,7). Diet is one of the most modifiable environmental factors involved in IBD pathogenesis, although limited information is available (27,28). Proteins contain variable proportions of heme and amino acids. They are not absorbed by the small bowel and reach the colonic lumen, where they are metabolized by the micro flora (29). This results in a number of end products, which include hydrogen sulfide, phenolic compounds, amines and ammonia, some of which are potentially toxic to the colon (29).

In the studies included here, only one study (Geerling et al., 2000) reported an association between vegetable protein and the risk of UC and two studies (Geerling et al. 2000; Jantchou et al. 2010) reported an association between animal protein and the risk of UC. Therefore, a subgroup analysis of animal or vegetable proteins was not performed. Considering the different sources of proteins, further studies with detailed information of animal or vegetable proteins are warranted to explore the association between animal protein and vegetable protein and UC risk.

However, there are some limitations in this meta-analysis that should be noted. Firstly, due to the limited data, we did not perform a subgroup analysis for other factors, such as age, gender, etc. Secondly, the dose-response analysis about protein intake on UC and CD risk was not performed due to the limited data in each individual study. Thirdly, only five independent studies reported the relationship between protein and CD risk. Thus, more convincing conclusions cannot be drawn due to the small number of studies and sample size. Fourth, the searches in our study were limited to the English and Chinese literature, which might bias the
results. Fifth, significant heterogeneity was found between protein intake and CD risk ($I^2 = 69.0\%$, $p = 0.012$). In order to explore the significant between-study heterogeneity found in the overall analysis, univariate meta-regression with the covariates of publication year, geographic location and study design was performed. There were no significant findings in the above-mentioned covariates. In conclusion, our findings should be cautiously interpreted on account of the above mentioned limitations.

CONCLUSIONS
The present meta-analysis suggested that dietary protein intake did not show a significant effect on the risk of UC or CD.

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29. Hughes R, Magee EA, Bingham S. Protein degradation in the large intestine:
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Age</th>
<th>Quality score</th>
<th>Cases</th>
<th>Controls</th>
<th>Disease type</th>
<th>Categories</th>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Persson et al.</td>
<td>1992</td>
<td>Sweden</td>
<td>Case-control</td>
<td>15-79</td>
<td>6</td>
<td>145</td>
<td>305</td>
<td>UC</td>
<td>Men: ( \geq 75 \text{ mg/d} ) vs ( \leq 54 \text{ mg/d} )</td>
<td>2.2 (0.7-6.9)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women:</td>
<td>0.5 (0.2-1.8)</td>
</tr>
<tr>
<td>Persson et al.</td>
<td>1992</td>
<td>Sweden</td>
<td>Case-control</td>
<td>15-79</td>
<td>6</td>
<td>152</td>
<td>305</td>
<td>CD</td>
<td>Men: ( \geq 75 \text{ mg/d} ) vs ( \leq 54 \text{ mg/d} )</td>
<td>2.0 (0.6-6.6)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women:</td>
<td>0.4 (0.2-1.3)</td>
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<tr>
<td>Reif et al.</td>
<td>1997</td>
<td>Israel</td>
<td>Case-control</td>
<td>29.6</td>
<td>7</td>
<td>54</td>
<td>163</td>
<td>UC</td>
<td>Highest vs lowest</td>
<td>1.47 (0.28-7.72)</td>
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<tr>
<td>Geerling et al.</td>
<td>2000</td>
<td>Netherlands</td>
<td>Case-control</td>
<td>37.8 ± 14.7</td>
<td>7</td>
<td>43</td>
<td>43</td>
<td>UC</td>
<td>Highest vs lowest</td>
<td>0.20 (0.02-1.50)</td>
</tr>
<tr>
<td>Sakamoto et al.</td>
<td>2005</td>
<td>Japan</td>
<td>Case-control</td>
<td>15-34</td>
<td>8</td>
<td>111</td>
<td>219</td>
<td>UC</td>
<td>Q4 vs Q1</td>
<td>1.36 (0.58-3.20)</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Age Range (Mean ± SD or Range)</td>
<td>Cases</td>
<td>Controls</td>
<td>Disease</td>
<td>Quartile/ Tertile Compared</td>
<td>RR (95% CI)</td>
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<tr>
<td>Sakamoto et al.</td>
<td>2005</td>
<td>Japan</td>
<td>Case-control</td>
<td>15-34</td>
<td>8</td>
<td>128</td>
<td>CD</td>
<td>Q4 vs Q1</td>
<td>2.06 (0.99-4.28)</td>
<td></td>
</tr>
<tr>
<td>Amre et al.</td>
<td>2007</td>
<td>Canada</td>
<td>Case-control</td>
<td>14.2 ± 2.7</td>
<td>7</td>
<td>130</td>
<td>CD</td>
<td>Q4 vs Q1</td>
<td>0.45 (0.13-1.50)</td>
<td></td>
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<tr>
<td>Hart et al.</td>
<td>2008</td>
<td>UK, Germany, Italy, Sweden, Denmark</td>
<td>Cohort</td>
<td>20-80</td>
<td>8</td>
<td>138</td>
<td>UC</td>
<td>Q4 vs Q1</td>
<td>0.79 (0.44-1.42)</td>
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<tr>
<td>Jantchou et al.</td>
<td>2010</td>
<td>France</td>
<td>Cohort</td>
<td>40-65</td>
<td>8</td>
<td>43</td>
<td>UC</td>
<td>T3 vs T1</td>
<td>3.24 (1.07-9.84)</td>
<td></td>
</tr>
<tr>
<td>Jantchou et al.</td>
<td>2010</td>
<td>France</td>
<td>Cohort</td>
<td>40-65</td>
<td>8</td>
<td>30</td>
<td>CD</td>
<td>T3 vs T1</td>
<td>3.34 (0.90-12.4)</td>
<td></td>
</tr>
<tr>
<td>Urbano et al.</td>
<td>2013</td>
<td>Brazil</td>
<td>Cross-sectional</td>
<td>37-63</td>
<td>7</td>
<td>59</td>
<td>N/A</td>
<td>Highest vs lowest</td>
<td>1.00 (0.97-1.02)</td>
<td></td>
</tr>
<tr>
<td>Rashvand et al.</td>
<td>2015</td>
<td>Iran</td>
<td>Case-control</td>
<td>20-80</td>
<td>8</td>
<td>62</td>
<td>UC</td>
<td>T3 vs T1</td>
<td>1.70 (0.75-3.15)</td>
<td></td>
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</tbody>
</table>

RR: relative risk; CI: confidence intervals; UC: ulcerative colitis; CD: Crohn’s disease; Q4: quartile 4; Q1: quartile 1; T3: tertile 3; T1: tertile 1.
Fig. 1. Study selection process for this meta-analysis.
Fig. 2. Forest plot for the assessment of the association between dietary protein intake and UC and CD risk.
Fig. 3. Funnel plot for the assessment of publication bias between dietary protein intake and UC risk.
Fig. 4. Sensitivity analyses for dietary protein intake and the risk of UC.
Fig. 5. Sensitivity analyses for dietary protein intake and the risk of CD.