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Please cite this article as:
Jin Zhong-Qin , Lu Hui-Gang , Wu Qing-Bin , Ge Hai-Xia , Zhou Ting-Ting, Zhang Xiao-Qing, Xu Li-Xiao . A meta-analysis of dietary carbohydrate intake and inflammatory bowel disease risk: evidence from 15 epidemiology studies . Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5490/2018.

A meta-analysis of dietary carbohydrate intake and inflammatory bowel disease risk: evidence from 15 epidemiology studies

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ABSTRACT

Background and purpose: epidemiological studies that assess the association of dietary total carbohydrate intake and inflammatory bowel disease risk (IBD) have yielded controversial results. Therefore, this study of various epidemiological studies was conducted in order to explore this relationship.

Methods: a systematic literature search of the PubMed, Embase, Web of Science and Medline databases was performed up to September 2017. Cohort, case-control or cross-sectional design studies were included that reported the association of dietary carbohydrate intake and IBD risk. Summary odds ratio (OR) and the corresponding 95% CI were calculated using the random effects model.

Results: a total of eight articles with 15 individual studies that included 1,361 cases were eligible according to the inclusion criteria. Dietary carbohydrate intake had a

non-significant relationship with the risk of IBD (OR = 1.091, 95% CI = 0.817-1.455, I^2 = 31.6%, $p_{for\ heterogeneity}$ = 0.116). The pooled OR and 95% CI for ulcerative colitis (UC) and Crohn's disease (CD) with regard to dietary carbohydrate intake was 1.167 (0.777-1.752) and 1.010 (0.630-1.618), respectively. These associations were also non-significant in both European and Asia populations.

Conclusions: a higher dietary total carbohydrate intake had a non-significant relationship with IBD risk. Further studies with large populations are needed to verify this relationship.

Key words: Carbohydrates. Inflammatory bowel disease. Meta-analysis.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic relapsing inflammatory diseases of the intestinal tract (1). There are two major phenotypes, ulcerative colitis (UC) and Crohn's disease (CD). These diseases affect individuals and their families, with a significant impact on their quality of life (2). Some risky situations such as hospitalization, surgery, complications and death could be caused by the disease. The burden on society is related to the disability caused by disease activity and complications (3,4).

Some reports have indicated that environmental factors may play an increased role in the development of IBD (5,6). Such environmental factors include early appendectomy and smoking (7). However, neither of these two risk factors can fully explain all variations in IBD incidence and prevalence. Up to now, differences in diet may be the most relevant and likely factors that account for this variability (8). Accordingly, diets containing differing amounts of carbohydrates may play a role in IBD etiology (9). The various studies conducted to assess the relationship between dietary carbohydrates intake and IBD risk have produced inconsistent results. Thus, the objective of this article was to systemically explore the relationship between dietary carbohydrate intake and IBD risk, including UC and/or CD risk.

METHODS

Literature search strategy and inclusion criteria

PubMed, Embase, Web of Science and Medline (up to September 30th, 2017) were independently searched by two authors to find suitable articles. The following terms were applied "inflammatory bowel disease" OR "ulcerative colitis" OR "Crohn's disease" AND "carbohydrates" OR "nutrition" for study selection. The first search was based on the titles and abstracts and then potential eligible full papers were reviewed. Different search results from the two investigators were judged with a discussion and then an agreement was reached. This study was conducted according to PRISMA and MOOSE statements (10).

Articles were included with the following criteria: a) the study assessed the relationship of dietary total carbohydrate intake and IBD or UC or CD risk; b) odds ratio (OR) estimates and their 95% confidence intervals (95% CI) were given or could be calculated; and c) articles written in the English language were retrieved.

Data extraction and quality assessment

Two investigators screened the potentially relevant studies and extracted the following crucial data: name of the first author, publication year, country, study design, sex, mean age or age range, number of cases and participants, OR in each study with 95% CI as well as the adjustments or number of patients/total for the independent and dependent variable. Different data from these two investigators were reviewed by a third author. Newcastle-Ottawa-Scale (NOS) (11) was used to assess each study's quality by two independent authors.

Statistical analysis

The random effects model mentioned by DerSimonian and Laird was used to pool the study-specific OR and 95% CI for the association between carbohydrate intake and IBD risk (12). Between-study heterogeneity was explored using the Chi-square test and I^2 test; I^2 values were divided into no ($I^2 = 0\%$), low ($I^2 = 25\%$), moderate ($I^2 = 50\%$) and high heterogeneity ($I^2 = 75\%$) (13). Subgroup analysis was performed to further explore the high between-study heterogeneity. A sensitivity analysis was performed to evaluate if the result could have been markedly affected, by removing

each one single study at a time (14). Publication bias was assessed using the Egger's test and funnel plot (15). The Stata software version 12.0 was used in this study. p ≤ 0.05 (two-tailed) was accepted as statistically significant.

RESULTS

Study selection

The PubMed, Embase, Web of Science and Medline databases were searched and a total of 461 articles were identified after removing duplicate articles. After reading the titles or abstracts, 432 unsatisfactory articles were excluded directly. The full texts of the remaining 31 relevant articles were thoroughly reviewed and the following articles were excluded: duplicate publications (n = 3), unreported OR (n = 8), review articles (n = 4), animal studies (n = 6) and letters to the editors (n = 2). Finally, eight articles (9,16-22) of 15 studies that involved 1,361 cases were included in the analysis. The flow chart in figure 1 describes this process more clearly. All of the included studies were of a relatively high quality (over six stars). The characteristics of the included studies are shown in table 1.

Dietary carbohydrates intake and risk of IBD

The 15 studies included ten case-control studies and five cohort studies with 1,361 patients and 332,202 participants. Overall, the highest dietary total carbohydrate intake levels *vs* low levels had no significant association with an increased risk of IBD (OR = 1.091, 95% CI = 0.817-1.455, I^2 = 31.6%, $p_{heterogeneity}$ = 0.116) (Fig. 2). With regard to dietary total carbohydrate intake and IBD risk, the pooled OR for UC and CD were 1.167 (0.777-1.752) and 1.010 (0.630-1.618), respectively. According to the stratified analysis by geographic locations, the association was also non-significant, for both European (OR = 1.171, 95% CI = 0.848-1.617) and Asian populations (OR = 0.982, 95% CI = 0.455-2.117). A subgroup analysis of study design was performed and the highest dietary total carbohydrate intake level had no significant relationship with IBD risk, either in cohort or in case-control design studies. The findings are shown in table 2.

Between-study heterogeneity

Overall, there was a low heterogeneity of the relationship between carbohydrate intake and IBD risk. Therefore, a univariate meta-regression analysis was performed using covariates of publication, disease type, number of cases, study design and geographic locations to investigate the reason. However, none of these factors contributed significantly to the heterogeneity.

Sensitivity analysis

There was no individual study with an excessive impact on the pooled effect between dietary total carbohydrate intake and IBD risk according to the sensitivity analysis (Fig. 3).

Publication bias

There was no significant publication bias according to the Begg's funnel plot (Fig. 4) and Egger's test (p = 0.439).

DISCUSSION

Findings from the current report suggest that there is no significant relationship between IBD risk and a higher dietary total carbohydrate intake. The associations with dietary carbohydrates were also non-significant in the UC and the CD group intake. A negative association was also found for the subgroup analysis by geographic locations for both European and Asian populations.

There was a low heterogeneity according to the pooled analysis of all results (I^2 = 31.6%, $p_{heterogeneity}$ = 0.116). However, between-study heterogeneity is common in the meta-analysis (23). Therefore, a meta-regression analysis was used to evaluate this heterogeneity. Each covariate of publication year, disease type, cases number, study type and geographic locations had no impact on the heterogeneity. Although subgroup analyses were performed, there was between-study heterogeneity according to the subgroup analysis. Therefore, there may be some other genetic and environment variables that cause the heterogeneity observed.

A recent cohort study (24) with 401,326 participants showed that dietary fiber intake

is not involved in the etiology of UC. However, future work should investigate whether there may be a protective effect of specific types of fiber according to smoking status in CD. The results from the above cohort study are consistent with our results. A review (25) of diet and the association with IBD risk explained the relationship between total dietary carbohydrate intake and IBD risk. The article indicated that a reasonable approach for patients with IBD was to propose a well-balanced, healthy (low-fat, low-sugar) diet prepared from fresh ingredients. The role of diet and IBD is complex and this field of study is continuing to grow and advance. Therefore, more studies related on this topic are needed to assess this relationship.

Despite the lack of associations found in our study, there is a biological plausibility to support a role of carbohydrate intake in the etiology of IBD. However, studies in murine models of IBD report that Western diets, high in carbohydrate and fat, lead to gut microbiota dysbiosis. This facilitates the colonization of the gut by adherent invasive *Escherichia coli* and subsequent release of the proinflammatory cytokine tumor necrosis factor alpha, which promotes bowel inflammation (26). Furthermore, Western diets high in carbohydrates, including refined sugars, are associated with obesity, which is directly associated with a proinflammatory state that increases bowel permeability (27,28).

The current meta-analysis had some advantages. First, a lot of published studies with large numbers of IBD patients and participants were included. This may allow a more comprehensive conclusion between dietary carbohydrate intake and IBD risk. Second, subgroup analyses by disease type, study design and geographic locations were performed to further explore the potential association between dietary carbohydrates intake and IBD risk. Third, no publication bias was found and no individual study had an excessive impact on the pooled effect, indicating that our results were stable.

However, some limitations in this meta-analysis should be highlighted. First, the present study included studies only from Europe and Asia. Thus, additional studies conducted in other countries are required in future studies. Second, ten studies were case-control studies and only five studies were of a cohort design. Therefore, more studies with a cohort design and other designs are required in further studies. Third,

low heterogeneity was found in the whole and subgroup analyses in this study and the between-study heterogeneity was not successfully explored by meta-regression and subgroup analyses. Obviously, other genetic or environment variables and their possible interaction may potentially contribute to this heterogeneity.

In conclusion, this meta-analysis indicated that higher dietary total carbohydrate intake had a non-significant relationship with IBD risk.

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Table 1. Characteristics of studies of dietary carbohydrates intake and inflammatory bowel disease risk

First author, year	Country	Study design	Age	Score quality	Subgroup analysis	Participants, cases	RR (95% CI) for highest *versus* lowest category
Persson et al. 1992	Sweden	Case-control	15-79	6	Sex, UC, CD	907, 297	Males 2.1 (0.5-8.1) for UC 4.0 (0.9-16.7) for CD Females 3.7 (0.5-24.9) for UC 1.0 (0.2-4.3) for CD
Reif et al. 1997	Israel	Case-control	29.6	7	UC, CD	163, 87	3.98 (1.02-15.52) for UC 1.37 (0.37-5.09) for CD
Geerling et al. 2000	Netherlands	Case-control	37.8	7	UC	86, 43	2.2 (0.4-11.8) for UC
Sakamoto et al. 2005	Japan	Case-control	15-34	6	UC, CD	677, 239	0.66 (0.31-1.41) for UC 0.53 (0.27-1.03) for CD
Amre et al. 2007	Canada	Case-control	14.2	7	CD	332, 130	1.12 (0.39-3.28) for CD

Jantchou et al. 2010	France	Cohort	40-65	8	Females, UC, CD	67,581, 73	0.51 (0.24-1.08) for UC 1.31 (0.42-4.14) for CD
Hart et al. 2008	European	Cohort	28-80.8	8	UC	260,686, 138	1.12 (0.92-1.33) for UC
Chan et al. 2014	European	Cohort	20-80	8	UC CD	1,770, 354	1.46 (0.62-3.46) for UC 0.87 (0.24-3.12) for CD

RR: relative risk; CI: confidence intervals; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease.

Table 2. Summary risk estimates of the association between dietary carbohydrates intake and the risk of inflammatory bowel disease

| Subgroups	No. cases	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	p-value
Overall	1,361	15	1.091 (0.817-1.455)	31.6	0.116
Disease type					
UC	778	8	1.167 (0.777-1.752)	44.4	0.083
CD	583	7	1.010 (0.630-1.618)	18.4	0.289
Study design					
Cohort	565	5	0.972 (0.667-1.418)	5.1	0.378
Case-control	796	10	1.331 (0.803-2.207)	43.0	0.071
Geographic locations					
Europe	1,035	11	1.171 (0.848-1.617)	4.9	0.397
Asia	326	4	0.982 (0.455-2.117)	60.9	0.053
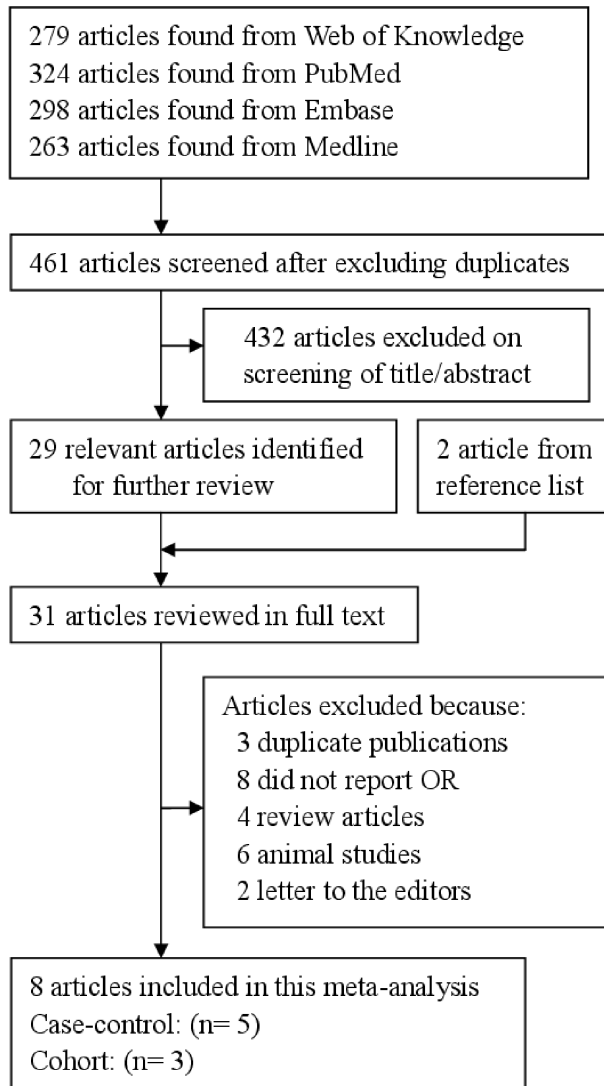
Fig. 1. Flowchart of the meta-analysis for the exclusion/inclusion of studies.
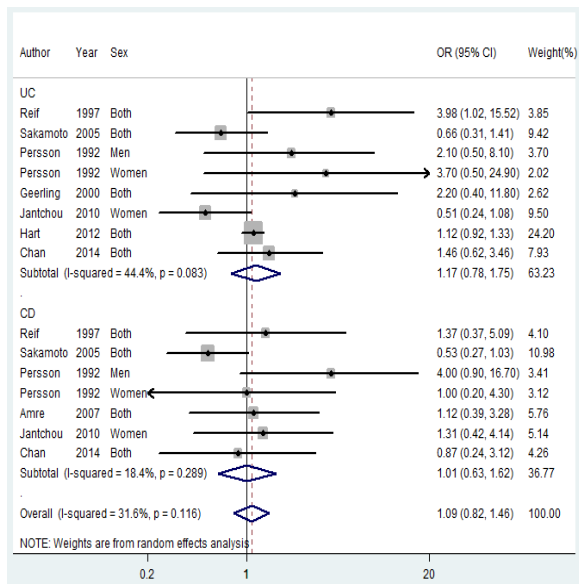
Fig. 2. Forest plot of the relationship between dietary carbohydrate intake and IBD risk.
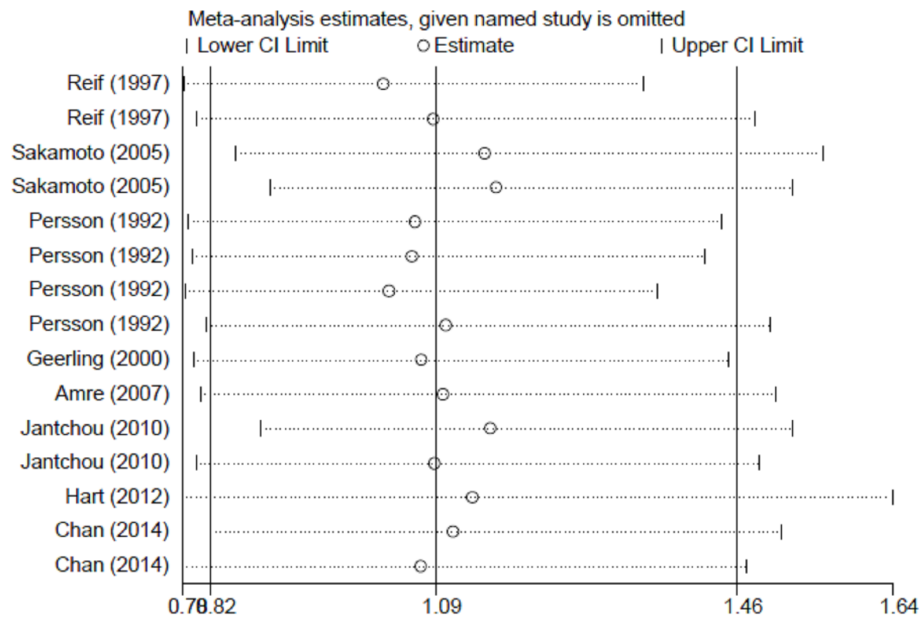
Fig. 3. Sensitivity analysis of the association between dietary carbohydrate intake and IBD risk.
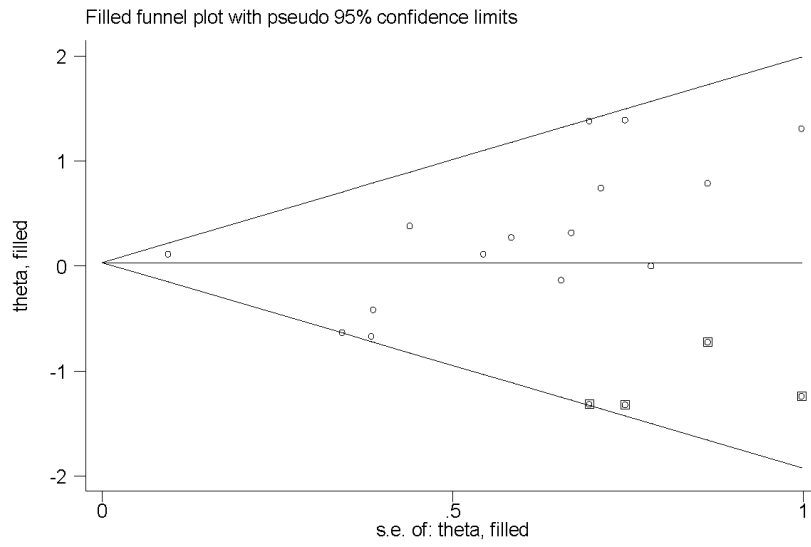
Fig. 4. Funnel plot for the analysis of publication bias between dietary carbohydrate intake and IBD risk.