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Original Article

Dietary fat and risk of inflammatory bowel disease: a meta-analysis

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Abstract: *Background:* The association between dietary fat intake and risk of inflammatory bowel disease (IBD) [ulcerative colitis (UC) and Crohn's disease (CD)] has yielded controversial results. Therefore, we conduct a meta-analysis of existing observational published studies assessing the relationship between them. *Methods:* We conducted a comprehensive research on PubMed and Web of Science for the related studies up to October 2015. Summary relative risk (RR) with 95% CI was calculated with the random effects model. *Results:* Eight published articles with 13 studies comprising 1084 cases were included in this meta-analysis. Our results suggested highest dietary fat intake levels vs. low levels were significantly associated with increased risk of IBD (RR = 1.52, 95% CI = 1.16-1.99, I^2 = 0.0%, $P_{heterogeneity}$ = 0.527). The pooled RR with 95% CI of UC and CD for the highest versus lowest category of dietary fat intake was 1.46 (1.02-2.09) and 1.57 (0.90-2.74), respectively. And the associations were also significant among Asia populations and in the subgroup of case-control studies. *Conclusions:* This meta-analysis indicates that higher dietary fat intake could increase the risk of IBD. The association was also significant in the UC, but not in the CD with dietary fat intake.

Keywords: Fat, inflammatory bowel disease, ulcerative colitis, Crohn's disease, meta-analysis

Introduction

Inflammatory bowel diseases (IBD) are chronic relapsing inflammatory diseases of the intestinal tract [1, 2]. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major phenotypes. The diseases have great impact on the quality of life of the affected persons and their families. They can lead to hospitalizations, surgery, complications and death. The burden on the society is related to disability from disease activity and complications [3, 4].

The changing epidemiology of IBD worldwide indicated that environmental factors may play an increased role in the development of this disease [5]. Potential environmental factors including early appendectomy and smoking have been affirmed. However, neither of the two risk factors can fully explain all variations in IBD incidence and prevalence. Up to now, differences in diet may be the most topical and likely factors accounting for the variability [6]. Accordingly, diets containing differing amounts of fat may have role in the etiology of IBD [7]. A number of epidemiologic studies have been published to explore the relationship between dietary fat intake and IBD risk, with inconsistent results. In this study, we conducted a meta-analysis to (1) first assess the association between dietary fat intake and IBD risk; (2) assess the associations between dietary fat intake and UC and/or CD risk; (3) assess the heterogeneity among studies and publication bias.

Methods

Literature search strategy and inclusion criteria

We conducted a literature search to identify relevant available articles published in English from PubMed and Web of Science up to October 2015. Search terms included 'inflammatory bowel disease' OR 'Ulcerative colitis' OR 'Crohn's disease' AND 'fat' OR 'nutrition'. We also reviewed the reference lists of the included studies for undetected relevant studies.

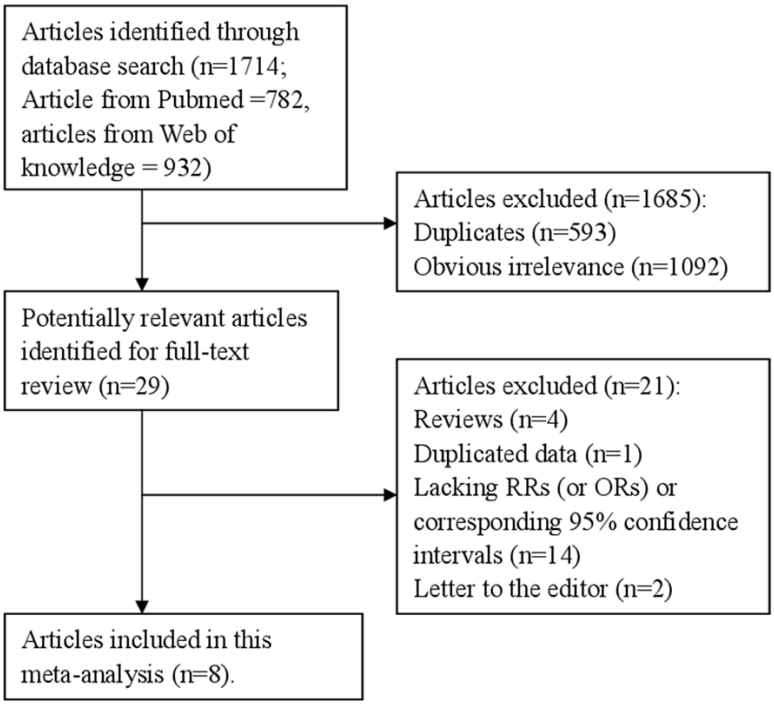

Figure 1. Flowchart of meta-analysis for exclusion/inclusion of studies.

The inclusion criteria were as follows: (1) published as case-control studies, cohort studies or cross-sectional studies; (2) the study of interest was fat intake; (3) the outcome of interest was IBD and/or UC and/or CD; (4) relative risk (RR) estimates with their 95% confidence intervals (CI) were available or could be calculated; (5) written in English.

Two investigators searched and reviewed all identified studies independently. If the two investigators cannot reach a consensus about the eligibility of an article, it was resolved by disputing with a third reviewer.

Data extraction

The following data were extracted from each study by two investigators independently: the first author's name, publication year, country where the study was performed, study design, age range or mean age, RR with 95% CI for the highest versus lowest categories of fat exposure and variables adjusted for in the analysis. We extracted RRs adjusted for the most confounders in the original studies.

Statistical analysis

Pooled estimates were calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI to assess the strength of association between fat intake and IBD risk. The DerSimonian and Laird random effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [8]. I^2 of Higgins and Thompson was adopted to assess heterogeneity among studies (I^2 values of 0%, 25%, 50% and 75% represent no, low, moderate and high heterogeneity, respectively) [9]. Subgroup analysis was performed by the disease type, study design and geographic locations. Sensitivity analysis was performed with one study removed at a time to assess whether the results could have been affected markedly by a single study. Small study effect was assessed with visual inspection of the Egger's test [10]. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX, United States). All reported probabilities (*P*-values) were two-sided with $P < 0.05$ considered statistically significant.

Results

Characteristics of studies

We identified 1714 articles by our literature search, of which 1685 were excluded after review of titles and abstracts (**Figure 1**). Five additional articles were found through the reference lists of relevant articles. One article with duplicate data, 4 review articles, 2 letters to the editor and 14 articles without RR about the association between fat intake and the risk of IBD risk were excluded. Finally, 8 published articles [11-18] with 13 studies comprising 1084 cases were included in this meta-analysis. Ten studies were come from Europe and 3 studies from Asia. The baseline characteristics of the studies were shown in **Table 1**.

Dietary fat intake and risk of IBD

Two original studies reported an increased risk for IBD with dietary fat intake, while no signifi-

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

First author, year	Country	Study design	Age	Participants, Cases	RR (95% CI) for highest versus lowest category
Amre et al. 2007	Canada	Case-control	14.2	332, 130	2.30 (0.67-7.96) for CD
Andersen et al. 2012	France	Cohort	40-65	67581, 77	1.24 (0.57-2.72) for IBD
Geerling et al. 2000	Netherlands	Case-control	37.8	86, 43	4.1 (0.6-28.4) for UC
Hart et al. 2008	European	Cohort	20-80	260686, 138	1.13 (0.65-1.99) for UC
Jantchou et al. 2010	France	Cohort	40-65	67581, 73	1.47 (0.56-3.84) for UC
					0.98 (0.25-3.88) for CD
Persson et al. 1992	Sweden	Case-control	15-79	907, 297	Men
					1.3 (0.4-4.4) for UC
					0.9 (0.2-3.1) for CD
					Women
					1.0 (0.2-4.7) for UC
					0.7 (0.2-2.9) for CD
Reif et al. 1997	Israel	Case-control	29.6	231, 87	5.31 (1.35-20.81) for IBD
					3.94 (0.92-16.89) for UC
Sakamoto et al. 2005	Japan	Case-control	15-34	677, 239	1.76 (0.82-3.77) for UC
					2.64 (1.29-5.39) for CD

Abbreviation: RR: relative risk; CI: Confidence Intervals; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: crohn's disease.

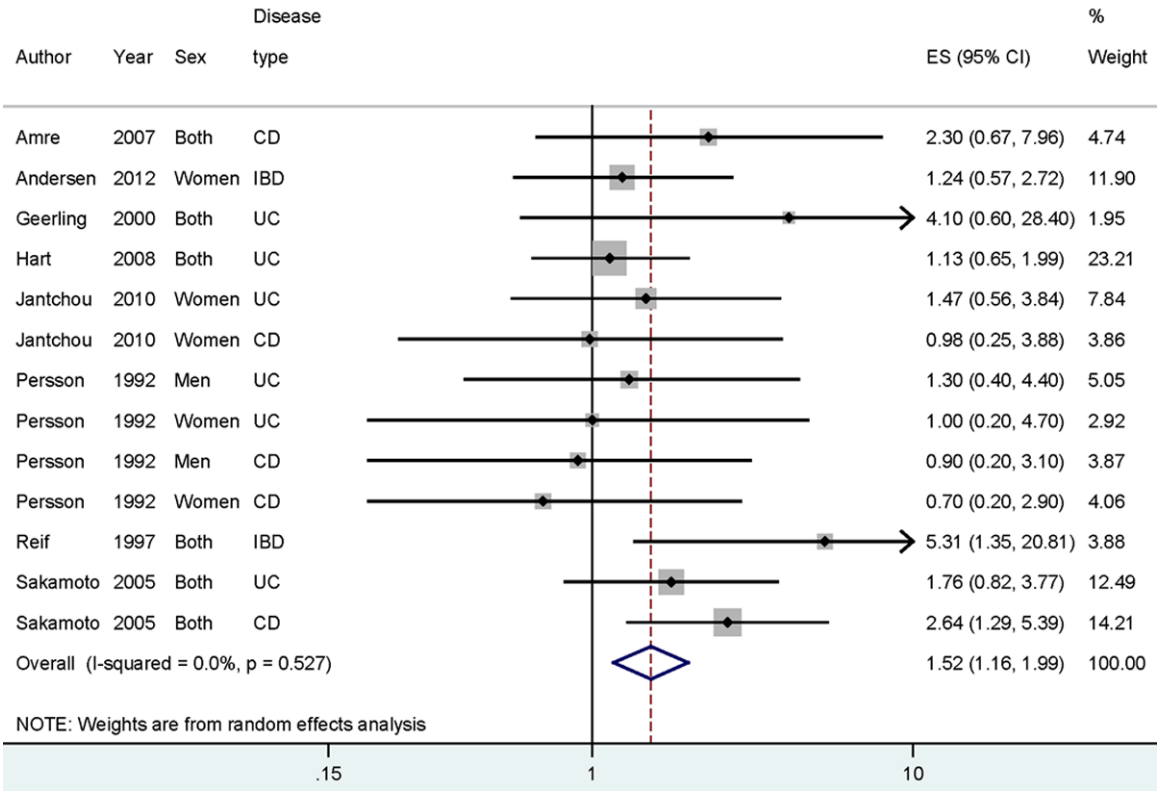

Figure 2. The forest plot of the relationship between dietary fat intake and IBD risk.

cant associations were found in the other 11 studies. Overall, highest dietary fat intake levels vs. low levels were significantly associated with increased risk of IBD (RR = 1.52, 95% CI = 1.16-1.99, I^2 = 0.0%, $P_{heterogeneity}$ = 0.527, **Figure 2**).

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

Subgroups	No. cases	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
Overall	1084	13	1.52 (1.16-1.99)	0.0	0.527
Disease type					
UC	480	6	1.46 (1.02-2.09)	0.0	0.652
CD	440	5	1.57 (0.90-2.74)	17.0	0.306
Study design					
Cohort	288	4	1.19 (0.81-1.77)	0.0	0.959
Case-control	796	9	1.87 (1.29-2.72)	0.3	0.431
Geographic locations					
Europe	758	10	1.23 (0.89-1.70)	0.0	0.926
Asia	326	3	2.44 (1.50-3.98)	0.0	0.369

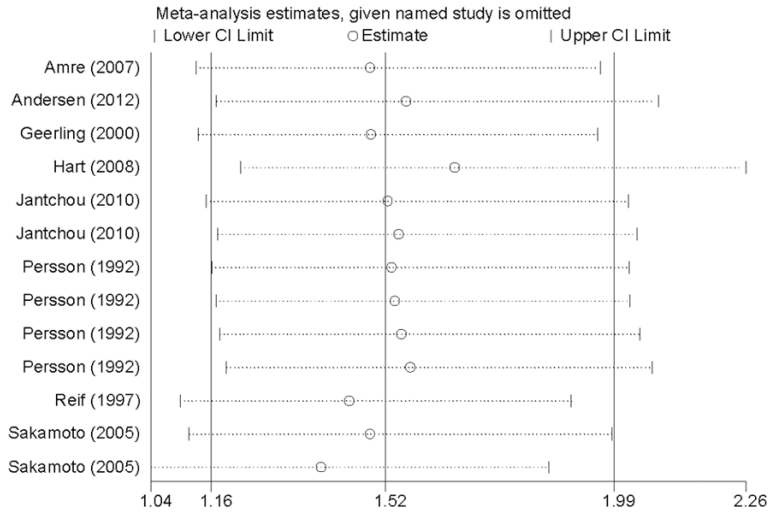

Figure 3. Sensitivity analysis of the association between dietary fat intake and IBD risk.

Sources of heterogeneity and subgroup analysis

As seen in **Figure 2**, no heterogeneity was demonstrated for the associations between dietary fat intake and IBD risk. Therefore, we did not do meta-regression to explore the between-study heterogeneity.

For dietary fat intake and IBD risk, the pooled RRs for UC and CD were 1.46 (1.02-2.09) and 1.57 (0.90-2.74), respectively. In the subgroup analysis by study design, the association was only significant in the case-control studies (RR = 1.87, 95% CI = 1.29-2.72), but not in the cohort studies. Ten studies were come from Europe and 3 studies come from Asia. However, we only found a significant association in Asian populations (RR = 2.44, 95% CI = 1.50-3.98), but not in the European populations (RR = 1.23, 95% CI = 0.89-1.70). Pooled analysis and subgroup analyses were conducted, and the findings were shown in **Table 2**.

Sensitive analysis and publication bias

In a sensitivity analysis (**Figure 3**) excluding one study at a time, no individual study had excessive influence on the pooled effect between dietary fat intake and IBD risk.

The visual inspection of the funnel plots (**Figure 4**) and Egger's test (*P* = 0.728) showed no evidence of significant small-study effect for dietary fat intake and IBD risk.

Discussion

The findings from this meta-analysis of epidemiologic studies indicated that highest category of dietary fat could increase the risk of IBD. The association was also significant in the UC, but not in the CD with dietary fat intake. Inverse associations were also found in the case-control studies and in the Asian populations.

Previous study had indicated that between-study heterogeneity is common in the meta-analysis [19], and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis. In our meta-analysis, we did not find any significant between-study heterogeneity, in whole or in part. The results from the test of between-study heterogeneity suggested that our results are stable.

As a meta-analysis of published studies, our findings showed some advantages. First, this is

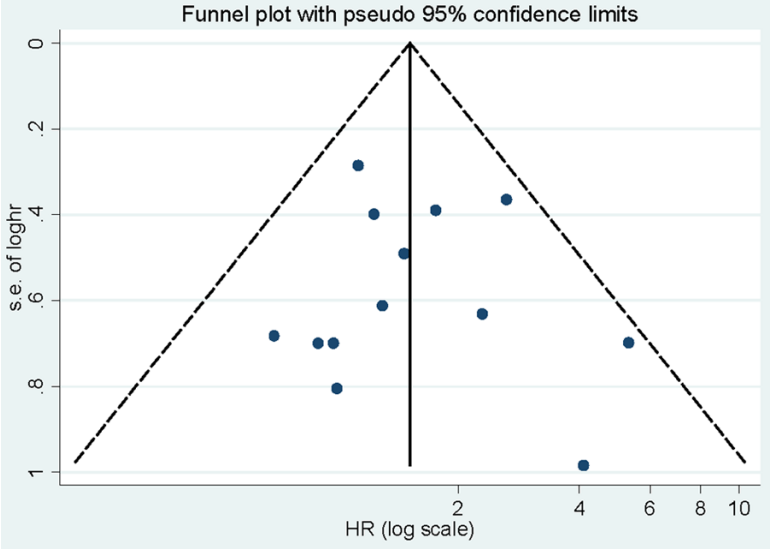

Figure 4. Funnel plot for the analysis of publication bias between dietary fat intake and IBD risk.

the first comprehensive meta-analysis of dietary fat intake and the risk of IBD. Second, large number of cases and participants were included, allowing a much greater possibility of reaching reasonable conclusions between dietary fat intake and IBD risk. Third, no significant publication bias and no between-study heterogeneity were found. However, there were some limitations in this meta-analysis. First, as a meta-analysis of observational studies, it was prone to biases (eg. recall and selection bias) inherent in the original studies. Cohort studies are less susceptible to bias than case-control studies because, in the prospective design, information on exposures is collected before the diagnosis of the disease. Although the results of the meta-regression showed no evidence of significant heterogeneity between subgroups, summary association estimates was different in subgroup analyses by study design. In our meta-analysis, the significant association was only found in case-control studies, but not in the cohort studies, while only 4 studies comprising 288 cases included were prospective design. More studies with prospective design are wanted in the future studies. Second, individual studies may have failed to control for potential confounders, which may have introduce bias in an unpredictable direction. Many, but not all, of the studies adjusted for potential confounding factors. However, no publication bias was found in the current study. Third, we found a significant association between dietary fat intake and IBD risk in the Asian population, but not in the Europe. Due to this limitation, the results are applicable to the Asia, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between dietary fat intake and IBD risk.

In summary, results from this meta-analysis suggested that dietary fat intake was significantly associated with increased risk of IBD, especially among Asian populations. The association was also significant in the UC, but not in the CD with dietary fat intake.

Disclosure of conflict of interest

None.

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