Protein intake and inflammatory bowel disease: A meta-analysis for Asian ethnicity

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Running title: Protein intake and IBD risk

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ABSTRACT

Background and Objectives: Although the association between dietary protein intake and inflammatory bowel disease (IBD) risk has been investigated, the results are inconsistent. Therefore, we conducted a meta-analysis to reassess the relationship between dietary protein intake and IBD risk. **Methods and Study Design:** The PubMed, Web of Knowledge, and Wanfang databases were searched for pertinent studies through January 31, 2020. Relative risks (RRs) with 95% confidence intervals (CIs) were derived using a random-effect model. Subgroup analyses according to disease type, geographic location, and sex; sensitivity analysis; and publication bias analysis were performed. **Results:** The current report includes 8 articles consisting of 12 studies with 1069 cases and 330,676 participants. The pooled RR (95% CI) of the highest vs. the lowest categories of dietary protein intake for the IBD risk was 1.561 (0.384-6.347) in cohort studies and 1.060 (0.663-1.694) in case-control studies. Evidence of heterogeneity was found both in cohort studies (I^2=86.4%, p=0.007) and in case-control studies (I^2=49.0%, p=0.039). However, the association was significant among Asian populations (RR=1.675, 95% CI=1.096-2.559) but not in other populations. We did not find any relationship of dietary protein intake with the risk of either Crohn's disease or ulcerative colitis. **Conclusions:** Based on limited information, the highest dietary protein intakes among Asians may increase the risk of IBD, undifferentiated for ulcerative colitis or Crohn's disease. This may reflect dietary patterns for which protein is a marker rather than implicate protein itself.

Key Words: protein, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, meta-analysis

INTRODUCTION

Inflammatory bowel diseases (IBDs) are immune-mediated diseases characterized by chronic relapsing-remitting inflammation involving the small and large intestines.[1,2] IBDs consist of two major manifestations: Crohn's disease (CD) and ulcerative colitis (UC). CD occurs as a discontinuous but transmural (full-thickness) inflammation that may affect any region of the gastrointestinal tract, whereas UC is mostly limited to the colon/rectum and specifically involves the mucosal and submucosal layers.[3] The incidence and prevalence of IBD have greatly increased over the past several decades in many regions worldwide. It affects 1.5 million individuals in the United States, 2.2 million individuals in Europe, and several

thousand individuals in other countries worldwide.[2,4] Thus, IBD is an emerging global health issue.[3,4]

Although the etiology is not well understood, current hypotheses entertain multifactorial disease models with both genetic and nongenetic risk factors.[5,6] Diet is one of the most modifiable environmental factors involved in IBD pathogenesis; however, limited information is available.[7,8] Proteins contain variable proportions of heme and amino acids, which are not absorbed by the small bowel and reach the colonic lumen, where they are metabolized by the microflora.[9] This results in a number of end products, including hydrogen sulfide, phenolic compounds, and amines and ammonia, some of which are potentially toxic to the colon. However, existing studies provide no resolution among these possibilities.[9] The association of dietary protein intake with IBD as a putative risk indicator remains to be determined. We have performed a comprehensive meta-analysis to address this possibility.

MATERIALS AND METHODS

Literature selection

This meta-analysis was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.10 A comprehensive systematic literature search was conducted in the PubMed, Web of Knowledge, and Wanfang databases up to January 31, 2020, with search terms in the following format: ("protein" OR "diet" OR "nutrition") AND ("inflammatory bowel disease" OR "Ulcerative colitis" OR "Crohn's disease" OR "IBD" OR "UC" OR "CD"). We searched the reference lists of all retrieved studies and published reviews to find additional references, and all identified relevant articles were included. However, conference literature, gray literature, and unpublished literature were not retrieved. Two independent authors performed the search, and any discrepancies resolved by a third author.

Studies were included in this meta-analysis if they met the following criteria: (1) prospective cohort, case-control, or cross-sectional design; (2) human population investigation; (3) dietary protein intake as the exposure of interest; (4) IBD or UC or CD risk as the outcome of interest; (5) available data on relative risks (RRs), odds ratios (ORs), and their corresponding 95% confidence intervals (CIs) for dietary protein intake and IBD risk, or sufficient data to compute them; and (6) publication in English and Chinese. If multiple papers involved the same population, we included the most recent and complete study.

Data extraction and quality assessment

Two investigators independently extracted relevant data. From each eligible study, we abstracted data on IBD type (CD or UC), first author's name, year of publication, study location, study design, number of cases and controls, and age of exposure. We used the maximally adjusted OR or RR estimates from each study when provided. If they were not available, univariate RRs and 95% CIs were calculated according to the frequency of exposure among cases and controls or participants. We extracted data as separate studies if the article reported on UC and CD, or on men and women. Any discrepancies in the data abstracted by the two independent authors were resolved by a third author. The 9-star system of the Newcastle-Ottawa Scale was used to assess the quality of the studies.[11]

Statistical analysis

Stata version 12.0 (Stata Corporation, College Station, TX) was used to calculate the pooled RRs and 95% CIs. A random-effect model was used to perform the analysis.[12] Heterogeneity between studies was assessed using the Q-test and I^2-test.[13] I^2 is the total variation explained by between-study variations. If I^2 <50%, then heterogeneity was absent; however, if I^2 >50%, then heterogeneity was considered present. We defined statistically significant heterogeneity as p<0.10[14] or I^2 >50%. Meta-regression[15] was performed to assess the influence of covariates on the strength of the association between exposures and outcomes. To investigate the potential sources of heterogeneity, we performed sensitivity and subgroup analyses. First, we reran the meta-analysis with removal of one study at a time to investigate whether the results could have been markedly influenced by a particular study. Second, subgroup analyses were performed according to disease type, geographical region of the study, and sex of the study participants. Publication bias was assessed using Egger's test[16] and Begg's funnel plot.[17] A two-sided p-value of <0.05 indicated independent statistical significance.

RESULTS

Study selection and study characteristics

Figure 1 provides a flowchart of the literature search and the studies included for further analysis. A total of 3608 articles were identified through the database search (1782 articles from PubMed, 1532 articles from Web of Knowledge, and 294 articles from Wanfang). After the exclusion of 895 duplicated studies and 2687 obviously irrelevant articles, 28 articles remained and were reviewed in full text. However, 20 articles were further excluded for the following reasons: 3 articles were reviews; 1 article had duplicated data; 12 articles did not

provide data of RRs and their corresponding 95% CIs; and 4 articles were animal studies. Finally, 8 articles[18-25] consisting of 12 studies with 1069 cases and 330,676 participants were included in this meta-analysis. Among these studies, 10 had a case-control design and the other 2 studies had a prospective design. Ten studies were performed in Europe, and four in Asia. All of the included studies had a relatively high quality (>6 stars), with an average NOS score of 6.88. The characteristics of the included studies are summarized in Table 1.

Overall and subgroup analyses for case-control studies

The pooled RR indicated no significant association between the IBD risk and the highest category of dietary protein intake (RR=1.060, 95% CI=0.663-1.694) in case-control studies, with significant heterogeneity among studies (I^2=49.0%, p=0.039) (Figure 2).

In the subsequent subgroup analysis, we did not find any significant association between dietary protein intake and UC risk (RR=1.172, 95% CI=0.684-2.009) or CD risk (RR=0.952, 95% CI=0.378-2.398). Considering the geographical location, studies conducted in Asia (RR=1.675, 95% CI=1.096-2.559) showed statistically significant results with respect to increased risk of IBD with the highest category of dietary protein intake (Figure 2). However, the association was not significant in European populations (RR=0.719, 95% CI=0.353-1.467). Furthermore, we also conducted subgroup analysis according to sex, and the results are consistent with the overall results. The detailed results are presented in Table 2.

Overall analysis for cohort studies

The pooled RR indicated no significant association between IBD risk and the highest category of dietary protein intake (RR=1.561, 95% CI=0.384-6.347) in cohort studies, with significant heterogeneity among studies (I^2=86.4%, p=0.007) (Figure 2). We did not perform any subgroup analysis because only two cohort studies were included.

Publication bias

The statistical significance of publication bias was assessed using Begg's funnel plot (Figure 3). Egger's test (p=0.327) found no publication bias in the meta-analysis of studies on dietary protein intake and IBD risk.

Sensitivity analysis

The sensitivity analysis (Figure 4) removing one study at a time showed that no individual study had an excessive influence on the association between dietary protein intake and IBD risk.

DISCUSSION

Our study indicated that the highest category of dietary protein intake had a nonsignificant statistical association with the risk of IBD. The included case-control and cohort studies were judged to be of high quality. Moreover, the association was not significant either in case-control studies or in cohort studies. However, we found a positive relationship between dietary protein intake and IBD risk among Asian populations but not among European populations and other populations elsewhere. The RR for the IBD risk of the highest vs. the lowest categories of dietary protein intake was 1.675 (1.096-2.559) among Asian populations.

Notably, significant heterogeneity was found in the whole pooled result (cohort studies: I^2=86.4%, p=0.007; case-control studies: I^2=49.0%, p=0.039). To investigate the significant between-study heterogeneity found in the overall analysis, univariate meta-regression was conducted with publication year, disease type, sex, and study location as covariates. No significant findings were found in the above-mentioned analysis except for the geographic location of the studies. When we divided the study population according to geographic location (Asia or Europe), no between-study heterogeneity (I^2=0.0%, p=0.872) was found among Asian populations.

A previous study that included six articles with seven studies (five case-control studies and two cohort studies) assessed the association between dietary protein intake and UC risk.[26] The authors concluded that there was no significant association between the UC risk (RR=1.010, 95% CI=0.975-1.047) and every 10-g increment/day of protein intake. In our report, we analyzed six case-control studies to assess the association between protein intake and UC risk, and we obtained the same result as that of Wang et al.[26] However, the previous authors assessed the relationship between protein intake and UC risk among Asian populations using only one study with a nonsignificant association. We analyzed four studies to evaluate the association between dietary protein intake and IBD risk among Asian populations, and found that dietary protein intake increases the risk of IBD. Given the different conclusions between the studies, larger Asian population studies are warranted.

In the case-control studies, we found a positive association between protein intake and IBD risk among women (RR=0.439, 95% CI=0.215-0.896), but not among men. In a previous meta-analysis, Wang et al[26] did not perform subgroup analysis for sex, with few studies

available. However, in our analysis of cohort studies, a high protein intake was associated with a 3.3-fold increased risk of IBD.[21] These findings may have reflected different protein intakes. Thus, stratification for sex and protein intake in IBD risk assessment appear important.

The present study considers dietary protein intake and IBD risk through the meta-analysis of large samples of cases and participants. The publication bias evaluated using Egger's test and Begg's funnel plot showed no significance for the overall or subgroup analyses, allowing reasonable conclusions about the potential association between dietary protein intake and IBD risk. However, it has limitations. First, most eligible studies were of case-control design, with the inherent recall and selection bias of retrospective studies. Although different kinds of studies were included, we performed subgroup analysis to reduce bias. Only two prospective cohort studies involving 211 cases were included, and more cohort design is required. Second, found a positive association only for Asian populations, but not European and other populations. More studies by geographic location and ethnicity are required. Third, two different diseases, Ulcerative Colitis and Crohn's Disease, although both chronic inflammatory of the bowel, have been pooled in the current meta-analyses; they are almost certain to have different dietary pattern risks. Fourth, different protein food sources and dietary pattern may be crucial since protein itself may not be the mediator of the associations found. This is likely given the differences in association found between Asian and non-Asian populations where the former traditionally derive their protein more from plant than animal sources than do their non-Asian counterparts. It is conceivable that those Asians more susceptible to IBD have higher protein intakes by consuming it from relatively non-traditional animal sources. Perhaps, more likely is that our finding for protein intake is a surrogate for a more ultraprocessed food intake trend among Asians.[27,28] This would correspond to the findings in the Swedish study by Persson et al[22] where 'fast foods' were the best dietary predictor of both ulcerative colitis and Crohn's disease.

Conclusions

The highest category of dietary protein intake is associated with an increased risk of IBD in Asian populations, not evident in their non-Asian counterparts. This may represent a shift away from traditional plant-based dietary patterns among susceptible individuals. Cohort, intervention and therapeutic studies where dietary patterns are documented and defined in diverse populations at risk of either Ulcerative Colitis or Crohn's disease will be necessary to resolve the uncertainties in the present findings.

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AUTHOR DISCLOSURE

The authors completed the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest, and report no conflicts of interest.

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Table 1. Characteristics of eligible studies of dietary protein intake and inflammatory bowel disease

First author, year	Country	Study design	Age	Disease type	Participants, Cases	Quality score	Sources of protein	Category
Amre et al. 2007 [18]	Canada	Case-control	14.2	CD	332, 130	7	Vegetable	Q4 vs Q1
Geerlinget al. 2000 [19]	Netherlands	Case-control	37.8	UC	86, 43	6	Vegetable and animal	Highest vs. lowest
Hart et al. 2008 [20]	Europe	Cohort	20-80	UC	260686, 138	8	Vegetable and animal	Q4 vs Q1
Jantchouet al. 2010 [21]	France	Cohort	40-65	IBD, UC, CD	67581, 73	8	Animal	T3 vs. T1
Perssonet al. 1992 [22]	Sweden	Case-control	15-79	UC, CD	907, 297	7	Vegetable and animal	≥75 mg/d vs ≤54 g/d
Rashvand et al. 2015 [23]	Iran	Case-control	20-80	UC	186, 62	7	Animal	T3 vs T1
Reifet al. 1997 [24]	Israel	Case-control	29.6	UC	163, 87	6	Animal	Highest vs lowest
Sakamoto et al. 2005 [25]	Japan	Case-control	15-34	UC, CD	677, 239	6	Vegetable and animal	Q4 vs Q1

First author, year	RR (95%CI) for highest versus lowest category	Adjustment
Amre et al. 2007 [18]	0.45 (0.13-1.50) for CD	Adjusted for total energy intake, age, gender, and body mass index.
Geerlinget al. 2000 [19]	0.20 (0.02-1.50) for UC	Adjusted for energy intake.
Hart et al. 2008 [20]	0.79 (0.44-1.42) for UC	Adjusted for energy intake.
Jantchouet al. 2010 [21]	3.31 (1.41-7.77) for IBD 3.24 (1.07-9.84) for UC 3.34 (0.90-12.4) for CD	Adjusted for alcohol-free energy intake.
Perssonet al. 1992 [22]	Men: 2.2 (0.7-6.9) for UC 2.0 (0.6-6.6) for CD Women: 0.5 (0.2-1.8) for UC 0.4 (0.2-1.3) for CD	Adjusted for age and, when applicable, for total energy intake.
Rashvand et al. 2015 [23]	1.70 (0.75-3.15) for UC	Adjusted for total energy intake, H.pylori infection, history of appendectomy, dietary fat, carbohydrate, and food groups intakes.
Reifet al. 1997 [24]	1.47 (0.28-7.72) for UC	Adjusted for energy intake.
Sakamoto et al. 2005 [25]	1.36 (0.58-3.20) for UC 2.06 (0.99-4.28) for CD	‡Adjusted for age, sex, study area, education, and smoking habits.

RR: relative risk; CI: Confidence Intervals; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; Q4: Quartile 4; Q1: Quartile 1; T3: Tertile 3; T1: Tertile 1.

Table 2. Summary risk estimates of overall and subgroup analyses

Subgroups	No. cases	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*p* value
Case-control studies	825	10	1.060 (0.663-1.694)	49.0	0.039
Disease type					
UC	415	6	1.172 (0.684-2.009)	29.8	0.212
CD	410	4	0.952 (0.378-2.398)	70.9	0.016
Geographic locations					
Europe	470	6	0.719 (0.353-1.467)	51.5	0.067
Asia	355	4	1.675 (1.096-2.559)	0.0	0.872
Sex					
Men	145	2	2.102 (0.919-4.810)	0.0	0.910
Women	152	2	0.439 (0.215-0.896)	0.0	0.762
Cohort studies	181	2	1.561 (0.384-6.347)	86.4	0.007

CI: confidence interval; UC: ulcerative colitis; CD: Crohn's disease.

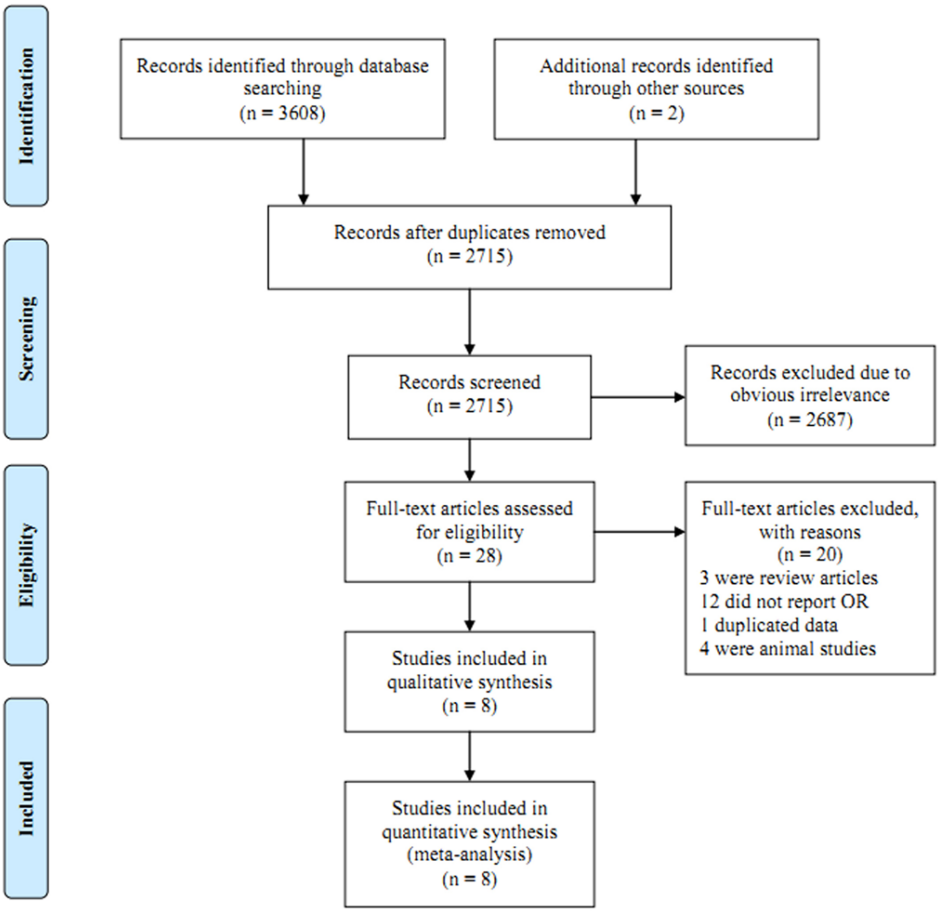

Figure 1. Study selection process for this meta-analysis.

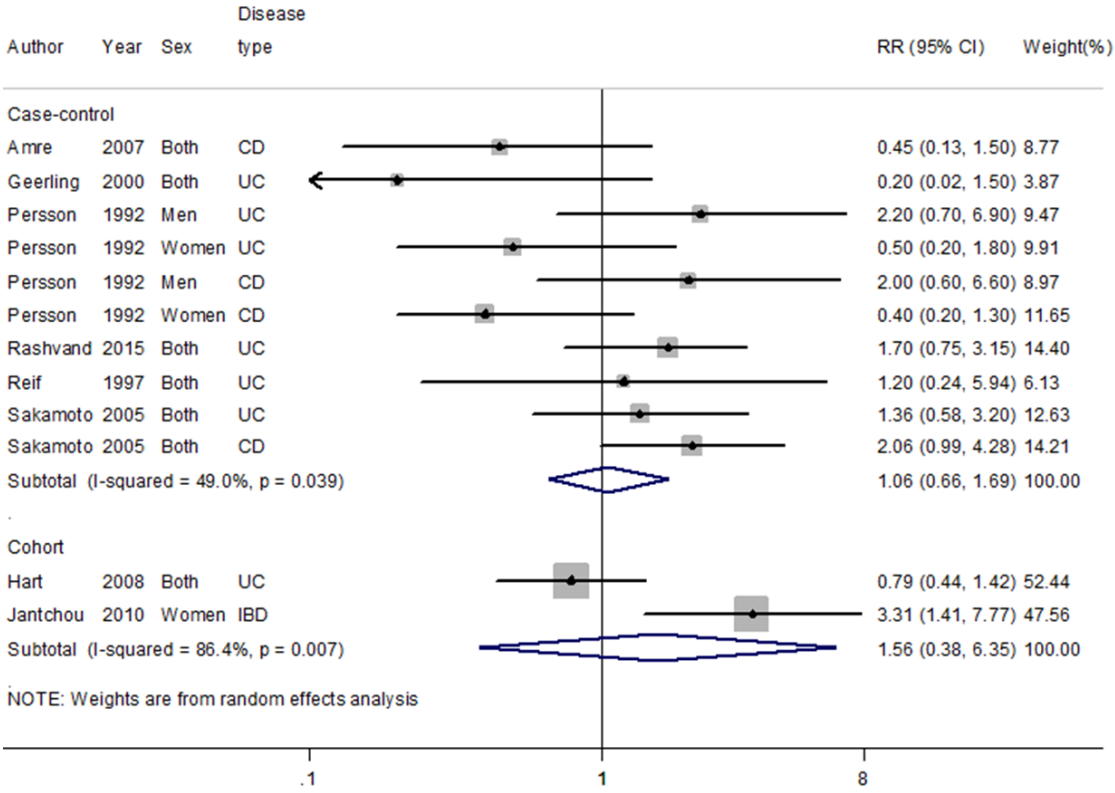

Figure 2. Forest plot for assessing the association between dietary protein intake and IBD risk in subgroups according to geographic locations.

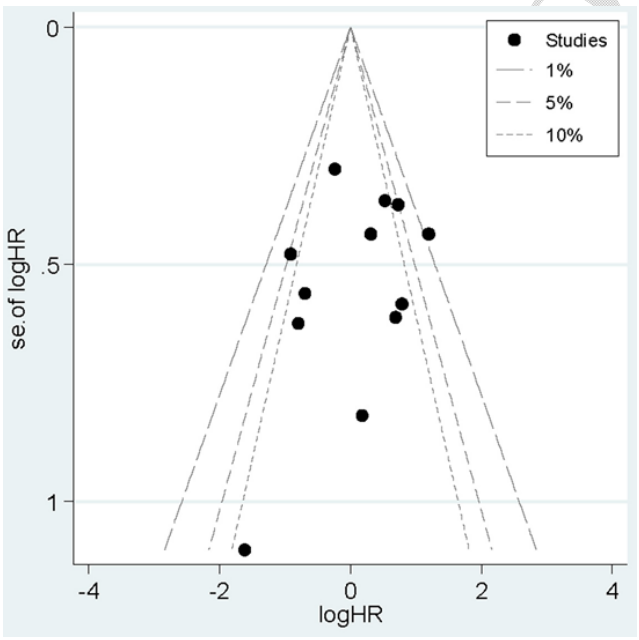

Figure 3. Funnel plot for the assessment of publication bias.

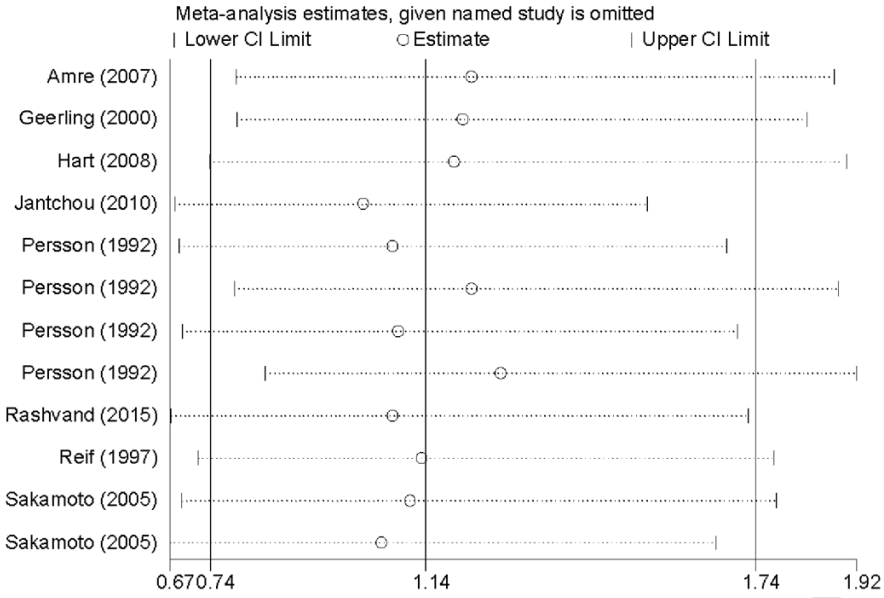

Figure 4. Sensitivity analyses for assessing the association between dietary protein intake and IBD risk.