Food Processing and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Neeraj Narula[1]
Nicole H. Chang[1]
Danah Mohammad[1]
Emily C.L. Wong[1]
Ashwin N Ananthakrishnan[2]
Simon S M Chan[3]
Franck Carbonnel[4]
Antoine Meyer[4]

[1] Department of Medicine (Division of Gastroenterology) and Farncombe Family Digestive Health Research Institute; McMaster University, Hamilton ON, Canada
[2] Division of Gastroenterology, Massachusetts General Hospital, and Harvard Medical School
[3] Department of Gastroenterology, Norfolk and Norwich University Hospital and Norwich Medical School, University of East Anglia, Norwich, UK
[4] Department of Gastroenterology, University Hospital of Bicêtre, Assistance Publique-Hôpitaux de Paris and Université Paris-Saclay, Le Kremlin Bicêtre, France

Version: October 2022

Word Count: 2436

KEYWORDS: Ulcerative Colitis; Inflammatory Bowel Disease; Crohn's Disease; Ultra-Processed Food;

Guarantor of the article: Neeraj Narula

Corresponding author: Neeraj Narula
Email: Neeraj.narula@medportal.ca
Address: McMaster University Medical Centre, 1280 Main St West, Unit 3V67, Hamilton, ON, L8S 4K1
Phone: 905-521-2100 x76782
Fax: 905-523-6048

Specific author contributions:

Neeraj Narula - study concept and design; acquisition and compilation of data; statistical analysis; data interpretation; drafting of the manuscript;
Nicole H Chang – acquisition and compilation of data; statistical analysis; drafting of the manuscript;
Danah Mohammad - acquisition and compilation of data; statistical analysis; drafting of the manuscript;
Emily CL Wong – study concept and design; acquisition and compilation of data; statistical analysis; data interpretation; drafting of the manuscript;
Ashwin Ananthakrishnan – study concept and design; data interpretation; drafting of the manuscript;
Simon Chan – study concept and design; data interpretation; drafting of the manuscript;
Franck Carbonnel – study concept and design; data interpretation; drafting of the manuscript;
Antoine Meyer - study concept and design; data interpretation; drafting of the manuscript;

Conflicts of interest:

Neeraj Narula has received honoraria from Janssen, Abbvie, Takeda, Pfizer, Merck, Sandoz, Fresenius Kabi, Innomar, Iterative Scopes and Ferring.

Antoine Meyer: no competing interest

Franck Carbonnel has received honoraria from Abbvie, Amgen, Arena, Biogen, Celltrion, Enterome, Ferring, Janssen, MaaT pharma, Medtronic, MSD, Nordic, Pfizer, Pharmacosmos, Pileje, Roche, Takeda, and Tillotts

Simon Chan has received travel grants from Abbvie and Takeda

No other authors have any relevant conflicts of interest.

No authors have received support for the submitted manuscript.

All authors approved the final version of the manuscript.

Figure 1 – Flow chart for literature search

Figure 2 – Forest plot with studies reporting association between food processing and risks of Crohn's disease. *Results are presents highest quantile compared to lowest quantile. aHR: adjusted hazard ratio; CD: Crohn's disease; CI: confidence interval.*

Figure 3 – Forest plot with studies reporting association between food processing and risks of ulcerative colitis. *Results are presents highest quantile compared to lowest quantile. aHR: adjusted hazard ratio; CI: confidence interval; UC: ulcerative colitis.*

Table 1 – Characteristics of included studies

Table 2 – Summary of evidence (GRADE assessment)

Supplementary Table 1 – Quality of evidence assessment (performed using Newcastle-Ottawa scale for cohort studies)

Supplementary Figure 1 – Funnel plot of studies reporting on ultra-processed foods intake and risk of Crohn's disease

Supplementary Figure 2 – Funnel plot of studies reporting on ultra-processed foods intake and risk of ulcerative colitis

Supplementary Appendix 1 – Literature search keywords used

Abstract

Introduction: Several studies have been published on the association between food processing and risks of Crohn's disease (CD) and ulcerative colitis (UC) with some variability in results. We performed a systematic literature review and meta-analysis to study this association.

Methods: From Pubmed, Medline and Embase until October 2022, we identified cohort studies that studied the association between food processing and the risk of CD or UC. Risk of bias of the included studies was assessed by the Newcastle-Ottawa scale. We computed pooled hazard ratios (HR) and 95% confidence intervals (CI) using random effects meta-analysis based on estimates and standard errors.

Results: A total of 1,068,425 participants were included (13,594,422 person-years) among five cohort studies published between 2020 and 2022. Four of the five included studies were scored as high quality. The average age of participants ranged from 43 to 56 years; 55 to 83% were female. During follow-up, 916 participants developed CD and 1934 developed UC. There was an increased risk for development of CD for participants with higher consumption of ultra-processed foods compared to those with lower consumption (HR: 1.71, 95%CI: 1.37-2.14, I2=0%) and a lower risk of CD for participants with higher consumption of unprocessed/minimally processed foods compared to those with lower consumption (HR: 0.71, 95%CI: 0.53-0.94, I2=11%). There was no association between risk of UC and ultra-processed foods (HR: 1.17, 95%CI: 0.86-1.61, I2=74%) or unprocessed/minimally processed foods (HR: 0.84, 95%CI: 0.68-1.02, I2=0%).

Conclusions: Higher ultra-processed food and lower unprocessed/minimally processed food intakes are associated with higher risk of CD but not UC.

Introduction

Inflammatory bowel diseases (IBD) are a heterogenous group of disorders consisting of Crohn's disease (CD) and ulcerative colitis (UC), which are characterized by inflammation of the gastro-intestinal tract that is thought to be caused by an interplay of genes, gut microbiome and environmental factors, including diet [1]. Several studies, based on large prospective cohorts of healthy participants, have found associations between nutrients or foods and the risk of IBD [2-6]. Dietary pattern analyses provide a more holistic approach. They describe not only the foods, food groups, and nutrients but also their combination and variety. Studies have found associations between a non-Mediterranean diet and CD [7] and others have found an association with a high inflammatory diet and risk of CD, but not UC [8, 9]. There has recently been interest in whether the processing of foods may increase the risk of IBD. Ultra-processed foods have been implicated in non-communicable chronic diseases such as cardiovascular diseases, diabetes, obesity and cancers [10-12]. Determining whether the rise in IBD is due to dietary processing of foods is crucial into understanding its pathogenesis. Thus, this systematic review and meta-analysis aimed to evaluate the association of food processing and development of CD and UC.

Methods

This study was conducted according to the guidelines detailed in the Cochrane Handbook[13] and the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) and assigned the designation CRD42022361061.

STUDY SELECTION

A systematic literature search was conducted to identify studies that investigated dietary consumption according to food processing and subsequent development of CD or UC. We identified sources from the MEDLINE®, Embase, and PubMed databases from the years 1950 to October 30, 2022. There were no language restrictions with Google translate used to translate for articles in languages other than English [15]. Supplementary Appendix 1 provides detail of the literature search keywords used. Both free-text words and subject headings were searched. Variations of root words were searched alone or in combination. The reference lists of any

studies meeting inclusion criteria were reviewed manually to identify additional relevant publications.

INCLUSION/EXCLUSION CRITERIA

For inclusion in the meta-analysis, studies were required to meet the following criteria: (i) cohort design; (ii) assessment of food processing by NOVA classification; (iii) enrolled adult subjects without any known diagnosis of CD or UC at baseline; (iv) followed for at least one year; (v) assessment for CD or UC during follow-up; and (vi) comparison of risks of CD or UC according to ultra-processed foods or unprocessed/minimally processed foods intake. Where studies did not provide sufficient information, authors were contacted to obtain additional data. We excluded review articles.

EXPOSURE

The exposures of interest were ultra-processed foods (NOVA classification 4) and unprocessed/minimally processed foods (NOVA classification 1). The NOVA classification system classifies food groups according to the degree of processing that has gone into producing a food [16]. Group 1 includes foods that underwent minimal or no processing, such as legumes, fruits, vegetables, chicken, milk and eggs [16]. Group 2 includes processed culinary ingredients such as sugar, salt, butter and vegetable oils [16]. Group 3 includes processed foods such as canned fruits and vegetables, salted or cured meats, cheeses or freshly made bread [16]. Group 4 includes ultra-processed foods, which involve extractions and chemical modifications with addition of artificial flavourings, colours and other non-natural ingredients to formulate products with very little group 1 foods remaining. Examples include processed meat (e.g. chicken nuggets and hot dogs), cold breakfast cereal, various types of sauces, sodas, refined sweetened foods (e.g. energy bars, pre-packaged cakes, candy, chocolate, jam, jelly, brownies, pudding), chips, ice cream, commercially prepared breads, biscuits, and fruit drinks [16].

Methods of data collection on food consumption vary. FFQs (food frequency questionnaires) and semi-quantitative FFQs have widely been used to assess and evaluate dietary intake in populations [17]. They involve a list of foods and beverages with responses categorizing frequency of consumption over a given time period, such as three months or one year [18]. They have been well validated, and can be country-specific to reflect the dietary

patterns of the region [18]. 24-hour dietary recall questionnaires also can be used to provide comprehensive, quantitative information about a person's diet during the preceding 24 hours [19].

OUTCOMES OF INTEREST

The primary outcomes of interest were diagnoses of CD or UC over the period of follow-up.

DATA EXTRACTION AND QUALITY ASSESSMENT

Study selection and data extraction was carried out independently by two investigators (NN, DM) with discrepancies resolved by consensus in consultation with the senior authors (FC and AM). The quality of non-randomized studies was assessed using the Newcastle-Ottawa scale (NOS), a tool which allows for quality appraisal of nonrandomized studies in meta-analyses [20]. The highest score is 9. Studies with a score of 7 of higher were deemed as high quality, consistent with several other meta-analyses [21, 22]. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the quality of evidence. GRADE uses several domains, including design, consistency, precision, directness, and publication bias, to rate the quality of evidence as high, moderate, low or very low. These ratings represent an assessment of the likelihood that further research would lead to changes in the estimate of effect [23].

STATISTICAL ANALYSIS

Meta-analyses were conducted by combining individual reported hazard ratios (HR) into a pooled HR using a random-effects model. When provided, HRs adjusted for potential confounders were used. Where studies assessed risk based on quantiles of UPF consumption, the highest quantile was compared with the lowest quantile. If studies reported on quantiles based on percentage of energy intake from UPF consumption, this was used for inclusion within the meta-analysis. Where this was not reported, it was requested from the corresponding authors. A secondary analysis was also conducted based on quantiles of unprocessed/minimally processed food consumption, from studies where these data were provided. We tested for heterogeneity using the chi-squared test and the I^2 test. The chi-squared test suggests heterogeneity between studies when the p-value is less than 0.10 [24]. The I^2 test describes the percentage of variability

in effect estimates that is due to heterogeneity rather than chance. For I2 values below 40%, heterogeneity might not be important, between 30% and 60% may represent moderate heterogeneity, between 50% and 90% may represent substantial heterogeneity, and above 75%, heterogeneity is considerable [24]. A random-effects model was used, as this provides a more conservative estimate than a fixed effects model when heterogeneity is present. For assessment of publication bias, we planned to perform funnel plots and calculate Egger's regression intercept if there were ten or more studies that reported our primary outcomes [25]. Analyses were performed with R statistical software (version 3.6.3) and the "meta" R package.

Results

SEARCH RESULTS

The literature search identified 94 citations, of which 41 were removed due to duplicates. Additionally, 48 were excluded on review of the title and abstracts (Figure 1), including one excluded due to case control design [26]. Overall, five studies with 1,068,425 participants were eligible for meta-analysis [27-31].

CHARACTERISTICS OF INCLUDED STUDIES

Characteristics of studies included are outlined in Table 1. All five studies were prospective cohort studies, published between 2020 and 2022 with a total of 1,068,425 participants (13,594,422 person-years). Over the observational period, 2,850 participants developed inflammatory disease including 916 who developed Crohn's disease and 1934 who developed ulcerative colitis. The average age ranged from 43 to 56 years and the percentage of women from 55 to 83%. In the low and high quantile, UPF consumption (% of kcal/day) varied from 13% to 21% and 45% to 51%, respectively. One study provided only the UPF intake and risk of IBD, but not CD and UC separately, and was unable to provide this detail in percentage of energy intake from UPF, so was excluded [27].

FOOD PROCESSING AND RISK OF CROHN'S DISEASE

Those with higher consumption of UPF had increased risk for development of CD than those with lower consumption (pooled HR: 1.71, 95%CI: 1.37-2.14). The heterogeneity of this estimate was low with an $I^2 = 0\%$ and χ^2 p-value 0.74. Those with higher consumption of

unprocessed/minimally processed foods had decreased risk for development of CD than those with lower consumption (pooled HR: 0.71, 95%CI: 0.53-0.94). The heterogeneity of this estimate was low with an I^2 = 11% and χ^2 p-value 0.29 (Figure 2).

FOOD PROCESSING AND RISK OF ULCERATIVE COLITIS

There was no association between UPF intake and risk of UC (pooled HR: 1.17, 95%CI: 0.86-1.61) with substantial heterogeneity (I^2 = 73% and χ^2 p-value of 0.01). There was no association between unprocessed/minimally processed food intake and risk of UC (pooled HR: 0.84, 95%CI: 0.68-1.02) with low heterogeneity (I^2 = 0% and χ^2 p-value of 0.61) (Figure 3).

QUALITY ASSESSMENT AND PUBLICATION BIAS

Table 2 provides a summary of the overall quality of evidence using the GRADE system, along with detailed rationale for the designated scores (Supplementary table 1). Four of the five included studies were scored as high quality using the Newcastle-Ottawa scale (score $\geq$ 7). According to the GRADE system for assessing quality, evidence from observational evidence begins with a “low” rating. We upgraded the overall rating to moderate based on low risk of bias and consistency of effect estimates.

Funnel plots were generated to assess for publication bias of studies that reported on our primary outcomes of interest. The symmetric distribution of these plots (Supplementary Figures 1 and 2) suggests no publication bias. However, caution should be applied in interpretation of the funnel plots given that few studies were included.

Discussion

In this large meta-analysis consisting of over one million participants, we observed that higher intake of ultra-processed foods and lower intake of unprocessed/minimally processed foods were associated with increased incidence of CD but not UC. No heterogeneity was observed when comparing risk estimates for CD. Our findings support the hypothesis that consumption of ultra-processed foods and low consumption of unprocessed/minimally processed foods may increase the risk for CD.

The incidence of IBD has increased in North America and Europe during the latter half of the 20th century, and more recently in newly industrialized areas such as Asia, the Middle East,

and South America. Globalization has brought with it westernization of diet and processing of foods, especially in South and East Asian countries [32]. The results of this meta-analysis are consistent with trends in CD incidence.

Previous epidemiologic studies have highlighted differential associations between diet CD, and UC [29]. CD is linked with non-Mediterranean and pro-inflammatory dietary patterns, as well as low fibre, zinc, and potassium intakes [5, 7, 33-35]. UC is associated with a high intake of linoleic acid, low intake of docosohexaenoic acid, as well as high red meat consumption [36]. These results likely exhibit interplay with previous observations such as lower recurrence of CD with diversion of luminal gut contents, and improved control of gut inflammation with exclusive enteral feeding in CD but not UC [37-39].

Ultra-processing includes addition of non-natural ingredients including artificial flavours, stabilizers, emulsifiers, sweeteners and preservatives [40]. The use of such additives has effects on a cellular level that potentially play a part in the pathogenesis of CD. For instance, emulsifiers have been shown to increase epithelial permeability, disruption of the intestinal barrier and gut dysbiosis in mice [41]. Carboxymethylcellulose has been shown to facilitate bacterial adherence to gut epithelium, possibly leading to bacterial overgrowth and invasion of bacteria in between the intestinal villi [42]. Furthermore, additives like carrageenan, titanium dioxide and maltodextrin have been shown to promote intestinal inflammation through various mechanisms, including microbiota disruption, mucus depletion and decreased mucosal healing [43-45]. Specific food subgroups such as ultra-processed breads and breakfast foods, frozen or shelf-stable ready to eat/heat meals, and sauces, cheeses, spreads and gravies were shown to have a greater association with CD compared to other subgroups [29]. This may in part be due to the inclusion of emulsifiers and thickeners in these subgroups, including pre-packaged cake, margarine and mayonnaise [29]. In fact, in small human pilot studies, restriction of emulsifying agents in diets was linked with better control of CD [46]. However, it is intriguing that enteral nutrition formulas contain food additives and emulsifiers. Yet, experimental studies have shown a differential effect of different emulsifiers on gut microbiome [47].

This meta-analysis holds out several strengths. Firstly, it includes more than one million participants from different ethnicities and nations and many person-years of follow-up, amounting to high-quality prospective data. Secondly, validated, standardized, and country-

specific questionnaires were used for measurement of dietary intake in each study – this is critical in accurate quantification of UPF intake.

There are limitations to this meta-analysis. First, age group of the populations within the studies tended toward middle to old age groups. Given that IBD tends to occur at younger age groups, prospective cohort studies of younger populations would be worthwhile reviewing food intake particularly in early childhood and teenage years. Second, there were a wide variety of countries included but the majority of participants were Caucasians of North American and European descent, which may limit applicability to other ethnicities and to those from developing countries. Third, while each study included in the meta-analysis provided a comparison of the highest quartile and the lowest quartile, the cut-offs for the quartiles varied between the different studies, so it is not possible to provide concrete guidance on a threshold of UPF intake that is considered too high, or that is associated with an increasing risk of CD. Fourth, there may be a classification bias for UPF exposure as some items do not neatly fall into the NOVA classification, and because over time, the processing of foods has gradually changed. However, since it is a prospective cohort, any measurement error would be non-differential, and thus only would underestimate potential associations. Lastly, the observational studies included may not have accounted for some potential confounders, such as breast-feeding in infancy, antibiotic exposure in childhood, air pollution and socioeconomic status. These unmeasured confounders, along with unknown confounders, may impact the results found at the individual study level and in our meta-analysis.

In conclusion, in this meta-analysis of over 1 million participants, we observed that higher UPF and lower non-processed/minimally processed food intakes were associated with higher risk of CD but not UC. The low heterogeneity among the studies providing estimates for CD increases the confidence of this finding. Advancements in food processing and associated changes in dietary patterns could explain the rise of IBD incidence during the 20th and 21st centuries. Further investigations are needed to identify the specific potential culprits among processed foods which could account for the increased risk of CD observed.

References

1. Maslowski, K.M. and C.R. Mackay, *Diet, gut microbiota and immune responses.* Nat Immunol, 2011. 12(1): p. 5-9.
2. Tjonneland, A., et al., *Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study.* Gut, 2009. 58(12): p. 1606-11.
3. Ananthakrishnan, A.N., et al., *Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease.* Gut, 2014. 63(5): p. 776-84.
4. Ananthakrishnan, A.N., et al., *A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis.* Gastroenterology, 2013. 145(5): p. 970-7.
5. Andersen, V., et al., *Fibre intake and the development of inflammatory bowel disease: A European prospective multi-centre cohort study (EPIC-IBD).* J Crohns Colitis, 2018. 12(2): p. 129-136.
6. Andersen, V., et al., *Diet and risk of inflammatory bowel disease.* Dig Liver Dis, 2012. 44(3): p. 185-94.
7. Khalili, H., et al., *Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies.* Gut, 2020. 69(9): p. 1637-1644.
8. Lo, C.H., et al., *Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis.* Gastroenterology, 2020. 159(3): p. 873-883.e1.
9. Narula, N., et al., *Does a High-inflammatory Diet Increase the Risk of Inflammatory Bowel Disease? Results From the Prospective Urban Rural Epidemiology (PURE) Study: A Prospective Cohort Study.* Gastroenterology, 2021. 161(4): p. 1333-1335.e1.
10. Levy, R.B., et al., *Ultra-processed food consumption and type 2 diabetes incidence: A prospective cohort study.* Clin Nutr, 2021. 40(5): p. 3608-3614.
11. Fiolet, T., et al., *Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort.* Bmj, 2018. 360: p. k322.
12. Srour, B., et al., *Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé).* Bmj, 2019. 365: p. l1451.
13. Higgins, J., S. Green, and C. Cochrane, *Cochrane handbook for systematic reviews of interventions.* 2011.
14. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.* BMJ, 2021. 372: p. n71.
15. Jackson, J., *The Accuracy of Google Translate for Abstracting Data From Non–English-Language Trials for Systematic Reviews.* Annals of Internal Medicine, 2019. 171(9): p. 677-679.
16. Monteiro, C.A., et al., *The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing.* Public Health Nutr, 2018. 21(1): p. 5-17.
17. Liu, L., et al., *Assessing the validity of a self-administered food-frequency questionnaire (FFQ) in the adult population of Newfoundland and Labrador, Canada.* Nutr J, 2013. 12: p. 49.
18. Macedo-Ojeda, G., et al., *Validation of a semi-quantitative food frequency questionnaire to assess food groups and nutrient intake.* Nutr Hosp, 2013. 28(6): p. 2212-20.
19. Foster, E., et al., *Erratum: Validity and reliability of an online self-report 24-hour dietary recall method (Intake24): A doubly-labelled water study and repeated measures analysis - CORRIGENDUM.* J Nutr Sci, 2019. 8: p. e41.
20. Stang, A., *Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.* Eur J Epidemiol, 2010. 25(9): p. 603-5.

21. Narula, N., D. Charleton, and J.K. Marshall, *Meta-analysis: peri-operative anti-TNFalpha treatment and post-operative complications in patients with inflammatory bowel disease.* Aliment Pharmacol Ther, 2013. 37(11): p. 1057-64.
22. Eom, C.S., et al., *Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies.* Ann Fam Med, 2011. 9(3): p. 257-67.
23. Guyatt, G.H., et al., *GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology.* J Clin Epidemiol, 2011. 64(4): p. 380-2.
24. Cumpston, M., et al., *Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions.* Cochrane Database Syst Rev, 2019. 10: p. Ed000142.
25. Simmonds, M., *Quantifying the risk of error when interpreting funnel plots.* Systematic Reviews, 2015. 4(1): p. 24.
26. Trakman, G.L., et al., *Processed Food as a Risk Factor for the Development and Perpetuation of Crohn's Disease-The ENIGMA Study.* Nutrients, 2022. 14(17).
27. Vasseur, P., et al., *Dietary Patterns, Ultra-processed Food, and the Risk of Inflammatory Bowel Diseases in the NutriNet-Santé Cohort.* Inflamm Bowel Dis, 2020.
28. Narula, N., et al., *Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study.* BMJ, 2021. 374: p. n1554.
29. Lo, C.H., et al., *Ultra-processed Foods and Risk of Crohn's Disease and Ulcerative Colitis: A Prospective Cohort Study.* Clin Gastroenterol Hepatol, 2022. 20(6): p. e1323-e1337.
30. Chen, J., et al., *Intake of ultra-processed foods is associated with an increased risk of Crohn's disease: a cross-sectional and prospective analysis of 187,154 participants in the UK Biobank.* J Crohns Colitis, 2022.
31. Meyer, A., et al., *Food processing and risk of Crohn's disease and ulcerative colitis: A European Prospective Cohort Study.* Clin Gastroenterol Hepatol, 2022.
32. Hu, F.B., *Globalization of food patterns and cardiovascular disease risk.* Circulation, 2008. 118(19): p. 1913-4.
33. Lo, C.H., et al., *Dietary Inflammatory Potential and Risk of Crohn's Disease and Ulcerative Colitis.* Gastroenterology, 2020. 159(3): p. 873-883 e1.
34. Ananthakrishnan, A.N., et al., *Zinc intake and risk of Crohn's disease and ulcerative colitis: a prospective cohort study.* Int J Epidemiol, 2015. 44(6): p. 1995-2005.
35. Khalili, H., et al., *Identification and Characterization of a Novel Association between Dietary Potassium and Risk of Crohn's Disease and Ulcerative Colitis.* Front Immunol, 2016. 7: p. 554.
36. Dong, C., et al., *Meat Intake Is Associated with a Higher Risk of Ulcerative Colitis in a Large European Prospective Cohort Studyø.* J Crohns Colitis, 2022. 16(8): p. 1187-1196.
37. Rutgeerts, P., et al., *Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum.* Lancet, 1991. 338(8770): p. 771-4.
38. Dziechciarz, P., et al., *Meta-analysis: enteral nutrition in active Crohn's disease in children.* Aliment Pharmacol Ther, 2007. 26(6): p. 795-806.
39. Narula, N., et al., *Enteral nutritional therapy for induction of remission in Crohn's disease.* Cochrane Database Syst Rev, 2018. 4(4): p. Cd000542.
40. Monteiro, C.A. and A. Astrup, *Does the concept of "ultra-processed foods" help inform dietary guidelines, beyond conventional classification systems? YES.* Am J Clin Nutr, 2022.
41. Chassaing, B., et al., *Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome.* Nature, 2015. 519(7541): p. 92-6.
42. Swidsinski, A., et al., *Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice.* Inflamm Bowel Dis, 2009. 15(3): p. 359-64.

43. Shang, Q., et al., *Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, Akkermansia muciniphila, in the gut microbiota of C57BL/6J mice.* Toxicol Lett, 2017. 279: p. 87-95.
44. Laudisi, F., et al., *The Food Additive Maltodextrin Promotes Endoplasmic Reticulum Stress-Driven Mucus Depletion and Exacerbates Intestinal Inflammation.* Cell Mol Gastroenterol Hepatol, 2019. 7(2): p. 457-473.
45. Ruiz, P.A., et al., *Titanium dioxide nanoparticles exacerbate DSS-induced colitis: role of the NLRP3 inflammasome.* Gut, 2017. 66(7): p. 1216-1224.
46. Sandall, A.M., et al., *Emulsifiers Impact Colonic Length in Mice and Emulsifier Restriction is Feasible in People with Crohn's Disease.* Nutrients, 2020. 12(9).
47. Naimi, S., et al., *Direct impact of commonly used dietary emulsifiers on human gut microbiota.* Microbiome, 2021. 9(1): p. 66.

Figure 1 – Flow chart for literature search

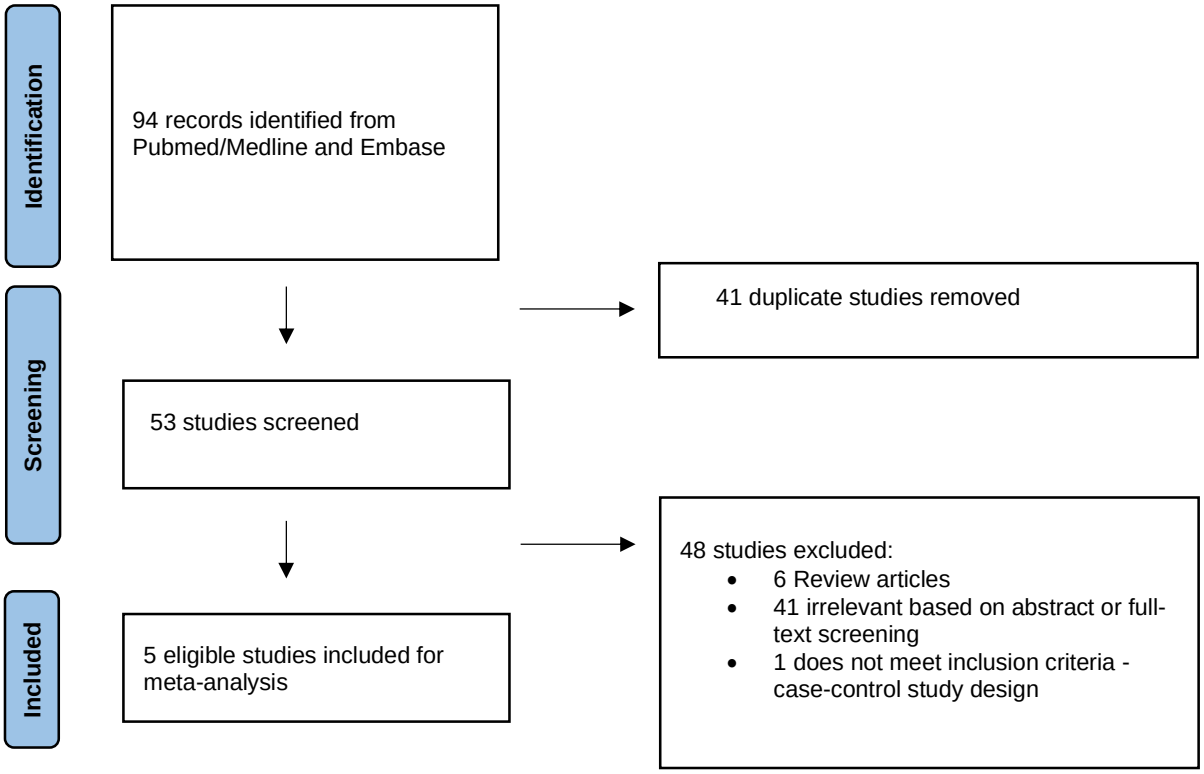


Figure 2- Forest plot with studies reporting association between food processing and risks of Crohn's disease. Results are presents highest quantile compared to lowest quantile. aHR: adjusted hazard ratio; CD: Crohn's disease; CI: confidence interval.

See PDF

			Quartile 1		Quartile 4			
Study	**CD**	**Total**	**CD**	**Total**	**CD**	**Total**	**Weight**	**aHR [95%CI]**
Ultra−processed foods								
Lo, 2021	369	245,112	69	61,278	122	61,278	29.6%	1.70 [1.23; 2.35]
Narula, 2021	90	116,087	15	29,022	47	29,022	20.2%	1.31 [0.63; 2.73]
Chen, 2022	251	185,849	34	37,170	71	37,170	27.6%	2.00 [1.32; 3.03]
Meyer, 2022	179	413,590	37	103,397	52	103,398	22.6%	1.48 [0.79; 2.77]
Total (95% CI)				**230,867**		**230,868**	**100.0%**	**1.71 [1.36; 2.14]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 4.67 (P < 0.01)

Unprocessed/minimally processed foods								
Lo, 2021	369	245,112	110	61,278	77	61,278	53.6%	0.78 [0.57; 1.06]
Meyer, 2022	179	413,590	57	103,397	34	103,398	46.4%	0.57 [0.35; 0.93]
Total (95% CI)				**164,675**		**164,676**	**100.0%**	**0.71 [0.53; 0.94]**

Heterogeneity: $Tau^2 = 0.0056$; $Chi^2 = 1.13$, df = 1 (P = 0.29); $I^2 = 11\%$

Test for overall effect: Z = −2.38 (P = 0.02)

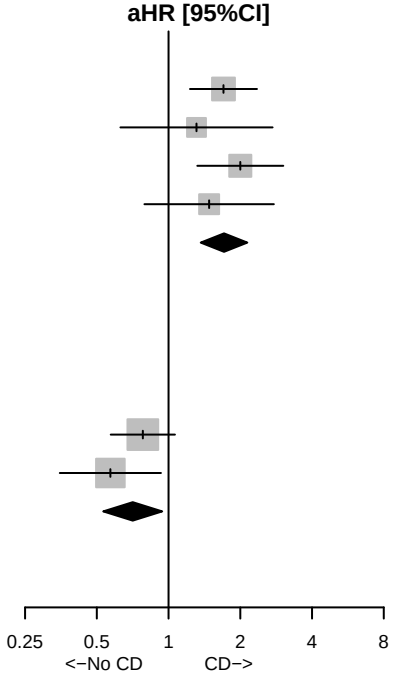


Figure 3- Forest plot with studies reporting association between food processing and risks of ulcerative colitis. Results are presents highest quantile compared to lowest quantile. aHR: adjusted hazard ratio; CI: confidence interval; UC: ulcerative colitis.

See PDF

			Quartile 1		Quartile 4			
Study	**UC**	**Total**	**UC**	**Total**	**UC**	**Total**	**Weight**	**aHR [95%CI]**
Ultra−processed foods								
Lo, 2021	488	245,112	108	61,278	136	61,278	27.6%	1.20 [0.91; 1.58]
Narula, 2021	377	116,087	57	29,022	153	29,022	23.5%	1.89 [1.32; 2.71]
Chen, 2022	590	185,849	121	37,170	118	37,170	28.4%	0.91 [0.70; 1.18]
Meyer, 2022	431	413,590	84	103,397	144	103,398	20.6%	0.93 [0.61; 1.42]
Total (95% CI)				**230,867**		**230,868**	**100.0%**	**1.17 [0.86; 1.61]**
Heterogeneity: $Tau^2 = 0.0744$; $Chi^2 = 11.39$, df = 3 (P < 0.01); $I^2 = 74\%$								
Test for overall effect: Z = 0.99 (P = 0.32)								
Unprocessed/minimally processed foods								
Lo, 2021	488	245,112	144	61,278	107	61,278	52.0%	0.80 [0.61; 1.04]
Meyer, 2022	431	413,590	119	103,397	93	103,398	48.0%	0.89 [0.65; 1.21]
Total (95% CI)				**164,675**		**164,676**	**100.0%**	**0.84 [0.68; 1.02]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0\%$								
Test for overall effect: Z = −1.72 (P = 0.08)								

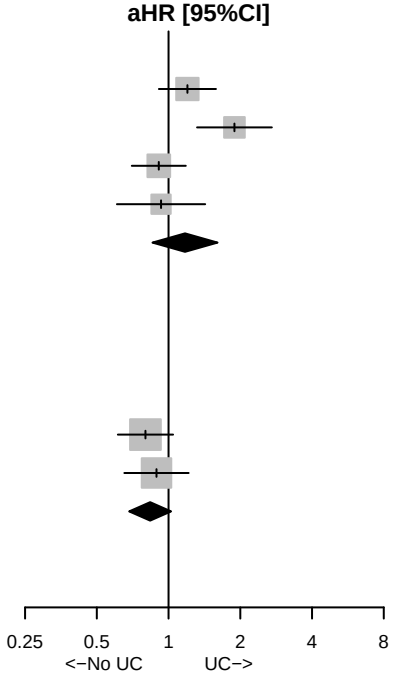


Table 1 – Characteristics of included studies

	Participants (n)	Person-years, n	Mean Age (Years)	Female Gender (%)	Method of food intake assessment	Proportion of UPF in total energy intake (% of kcal/day), mean	Geographic distribution	Mean follow up (years)	IBD cases (n)	CD cases (n)	UC cases (n)
Narula et al (2021)	116,037	1,125,559	50.2	59.2	FFQ	Q1: 19.1% Q4: 44.8%	Europe, North America, South America, Africa, South Asia, Southeast Asia, Middle East, China	9.7	467	90	377
Meyer et al (2022)	413,590	4,920,526	51.7	68.6	FFQ over the past 12 months	Q1: 13.3% Q4: 50.6%	Denmark, France, Germany, Italy, Netherland, Norway, Spain, Sweden, United Kingdom	13.2	510	179	431
Vasseur et al (2021)	105,832	238,924	43.3	78.0	24- hours dietary record	NA	France	2.3	75	27	48
Lo et al (2022)	245,112	5,468,444	56	83.0	semi-quantitative FFQ	Q1: 21.0% Q4: 46.4%	United States	22.3	857	369	488
Chen et al (2022)	187,854	1,840,969	56.2	54.8	24-hours dietary record	41.0% (NA for each quintile)	United Kingdom	9.8	841	251	590

FFQ – food frequency questionnaire; UPF: ultra-processed food; NA – not available

Table 2 – Summary of evidence (GRADE assessment)

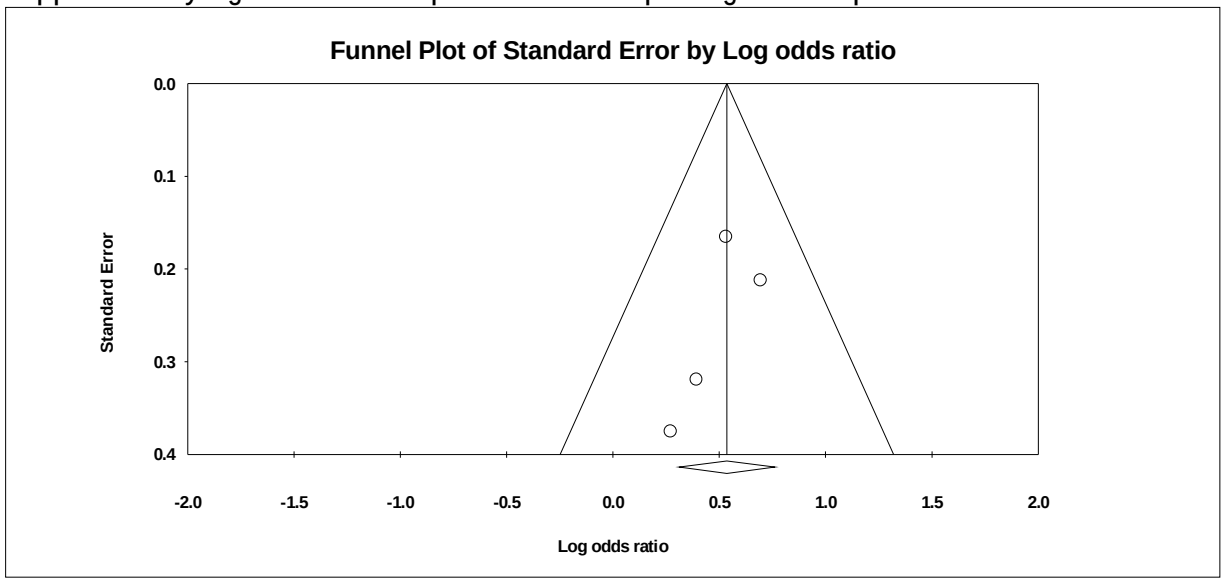
Study	Starting Level of Evidence	Reasons for decreasing the level of evidence					Reasons to increase level of evidence (strong association, plausible confounding and bias adjustment)	Final level of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		
Prospective cohort trials	Low	↔	↔	↔	↔	↔	⬆	Moderate

Supplementary Table 1 – Quality of evidence assessment (performed using Newcastle-Ottawa scale for cohort studies)

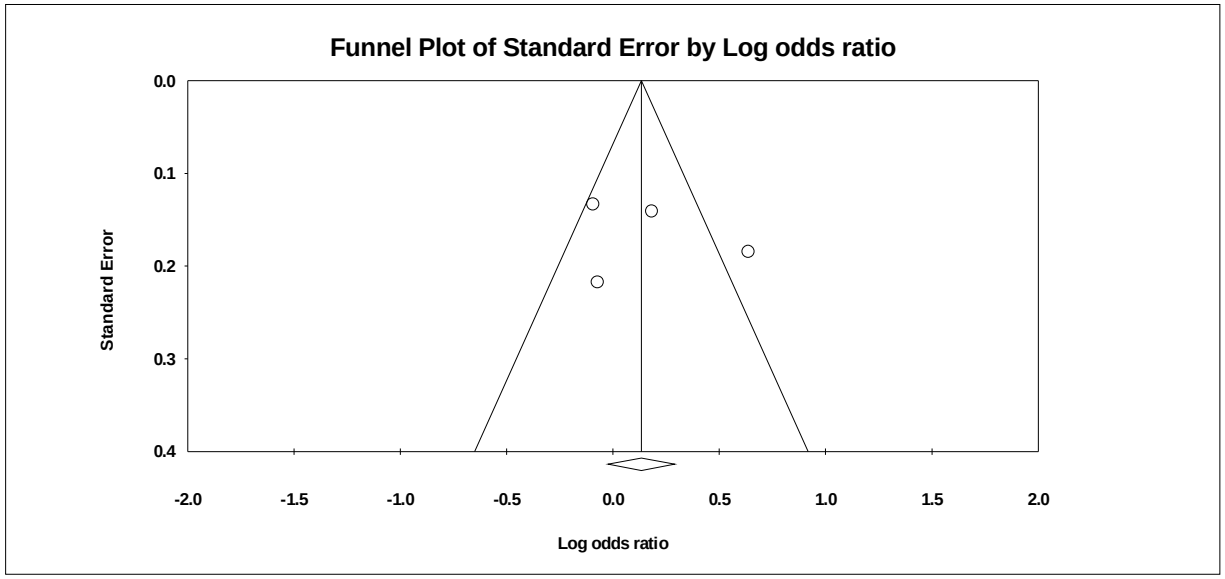
Study	Selection (maximum of 1 point for each item)				Comparability (maximum of 1 point for each item)		Outcome (maximum 1 point)			Score (max 9)
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other factors	Assessment of outcome	Length of follow up	Loss to follow up rate	
Narula et al	1	1	0	1	1	1	0	1	1	7
Vasseur el al	1	1	0	1	1	1	0	0	1	6
Chen et all	1	1	0	1	1	1	1	1	1	8
Meyer at al	1	1	1	1	1	1	1	1	1	9
Lo et al	1	1	0	1	1	1	1	1	1	8

Color coding: a green color meaning that the study fulfilled the point and a high-quality level, and a red color that the study did not meet the point. Studies with a score of 7 of higher were deemed as high quality.

Supplementary Figure 1 – Funnel plot of studies reporting on ultra-processed foods intake and risk of Crohn's disease



Supplementary Figure 2 - Funnel plot of studies reporting on ultra-processed foods intake and risk of ulcerative colitis



Supplementary Appendix 1 - Literature search keywords used

1 Exp Inflammatory bowel diseases /361704
2 Exp crohn's disease /185985
3. Exp colitis, ulcerative /155741
4. 1 or 2 or 3 /362032
5. Ultra-processed food* /5114
6. Processed food* /34737
7. 5 or 6 /34737
8. 4 and 7 /91
9. Remove duplicates from 8 /50