

Carbohydrate Intake in the Etiology of Crohn's disease and ulcerative colitis

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Abstract

Background. Diet may have a role in the etiology of inflammatory bowel disease (IBD). In prior studies, the associations between increased intakes of carbohydrates, sugar, starch and IBD are inconsistent. However, few prospective studies have investigated the associations between these macronutrients and incident Crohn's disease (CD) or ulcerative colitis (UC).

Methods. A total of 401 326 men and women were recruited between 1991-1998. At recruitment, dietary intakes of carbohydrate, sugar and starch were measured using validated food frequency questionnaires. The cohort was monitored identifying participants who developed incident CD or UC. Cases were matched with 4 controls, and odds ratios (ORs) were calculated for quintiles of total carbohydrate, sugar and starch intakes adjusted for total energy intake, body mass index and smoking.

Results. 110 participants developed CD and 244 participants developed UC during follow up. The adjusted OR for the highest versus the lowest quintiles of total carbohydrate intake for CD was 0.87, 95% CI=0.24-3.12 and for UC 1.46, 95% CI=0.62-3.46, with no significant trends across quintiles for either (CD, $P_{\text{trend}}=0.70$; UC, $P_{\text{trend}}=0.41$). Similarly, no associations were observed with intakes of total sugar (CD, $P_{\text{trend}}=0.50$; UC, $P_{\text{trend}}=0.71$) or starch (CD, $P_{\text{trend}}=0.69$; UC, $P_{\text{trend}}=0.17$).

Conclusion. The lack of associations with these nutrients is in agreement with many case-control studies that have not identified associations with CD or UC. As there is biological plausibility for how specific carbohydrates could have an aetiological role in IBD, future epidemiological work should assess individual carbohydrates although there does not appear to be a macronutrient effect.

Key words. Crohn's disease, ulcerative colitis, etiology, sugar, carbohydrate, starch

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases that are believed to arise as a consequence of a dysfunctional immune response to the gut microbiota on a background of susceptible genetics(1). However, the precise etiology of these diseases remains unknown. To date, genome wide association studies (GWAS) have successfully identified over 160 genetic risk loci in association with IBD(2), yet despite these successes it has been estimated that the risk contribution of these genetic loci is less than 25%(3). This implies that other non-genetic variables may have a role in the etiology of IBD as evident by the increasing incidence of IBD in previously low incidence areas that have adopted a more Westernised lifestyle including changes to habitual dietary intakes(4, 5). Importantly, changes in diet significantly alter the composition of the gut microbiota(6). This subsequently leads to changes in the gut microbiota metabolites that are produced, which may have diverse effects on host immune and inflammatory responses(7, 8). Accordingly, diets containing differing amounts of carbohydrates may shape the composition of the gut microbiota to one that predisposes to the development of IBD. Alternatively, excess intakes of carbohydrate can lead to obesity which is associated with increased markers of bowel inflammation(9) and intestinal permeability(10), both hallmarks of IBD.

The previous epidemiological studies investigating the associations between total dietary carbohydrates, sugar and starch intakes with the risk of developing IBD have almost exclusively been retrospective case-control studies(11-16) and have reported conflicting findings(4, 17). These inconsistencies may have resulted from methodological errors in such work including selection and recall biases. In the latter, patients often have difficulties reporting their pre-illness diet, which is reflective of disease etiology, particularly if IBD was

diagnosed many years previous. Only one cohort study has reported on all these macronutrients in UC(18) and none for starch or sugar intake in CD. To help confirm if there are associations between these nutrients and IBD, and to overcome previous methodological limitations, we utilised the multi-center European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. This investigation is the first to report the effects of these macronutrients in the EPIC study for CD and expands on the previous smaller dataset on UC that reported on countries predominantly from northern Europe(18).

Methods and materials

The methods of the main EPIC cohort study (European Prospective Investigation into Cancer and Nutrition) have previously been described(19). Briefly, 519 978 men and women were recruited in 23 collaborating centers in 10 European countries to investigate the effect of diet on the risk of common malignant diseases in a general population. The *EPIC-IBD study* is a sub-cohort of EPIC involving a total of 401 326 initially healthy men and women without Crohn's disease (CD) or ulcerative colitis (UC), in the age range 20-80 years, from 12 centers in 8 European countries (table 1). Participants were recruited between the years 1991 and 1998 and provided information on age, gender, and lifestyle factors including smoking and physical activity via the self-completion of baseline questionnaires. Anthropometric measurements of weight and height were taken at recruitment to calculate body mass index (BMI). Participants' habitual diet over the previous year was measured using validated country-specific food frequency questionnaires (FFQs) that were designed to capture local dietary habits and give high compliance when self-completed. These consisted of approximately 200 food items and nine frequency categories for when these foods were consumed, which varied from never to several times per day. Using national databases of food composition that were standardised(20), total energy and individual nutrient intakes including total carbohydrate (excluding dietary fiber), sugars (mono- and di-saccharides) and starch (including dextrins and glycogen) were calculated from these questionnaires. Participants within the extreme 1% percentiles of energy intake were excluded to reduce the effects of implausible extreme values of energy intake. In the centers for France, Germany, Greece, Italy and The Netherlands, the dietary intakes from the FFQs were compared with the mean intake of 24 hour recall questionnaires repeated monthly over a 1 year period(21, 22). The centers from Denmark, UK and Sweden compared their intakes

from dietary FFQs with 7, 16, and 18 day weighed food records, respectively(23-25). Most centers also compared their FFQ data with plasma and urinary biomarkers for specific nutrients such as vitamins, electrolytes and nitrogen. Overall, there were moderate to good correlations for nutrients between the FFQs, with mean 24 hour recall questionnaires over a 1 year period and weighed food records for carbohydrates, sugar and starch (appendix 1, supplementary digital content 1)(21, 23-30). The research protocols were approved by ethics committees in each center and all participants gave their written informed consent for the study.

The cohort was followed up in all centers until at least May 2004 and in some centers until December 2010 with incident cases of CD and UC that developed in participants identified by several methods. These were: disease registries of inflammatory bowel disease in Italy, Sweden, The Netherlands and Denmark, follow-up questionnaires in Germany, Greece, France and the Oxford cohort, and by a combination of follow-up questionnaires and hospital in-patient and pathology databases for the Norfolk cohort. For each case, physicians were asked to confirm the diagnoses of CD or UC according to information from radiological, endoscopic and histological reports. Information on the extent of intestinal inflammation according to the Montreal classification(31), and the confirmatory diagnostic investigations were recorded. Prevalent cases of CD and UC at recruitment were excluded, as well as participants who were diagnosed with IBD less than 18 months after recruitment. This helped to ensure that the dietary data reflected participants' dietary intake prior to the development of symptoms. Current estimates regarding efficacy of follow-up until 2007 suggests that <2% of the total population is lost to follow-up.

The analysis was a nested case-control one, within the prospective EPIC cohort, with each case matched with four randomly selected unique controls. The matching criteria were: age at recruitment (± 6 months), gender, center and recruitment date (± 3 months). Also controls had to be alive on the date of diagnosis of their matched case, to ensure that the periods of follow up for both cases and controls were similar. None of the controls had CD, UC, microscopic or indeterminate colitis at the time of matching or at the end of each center's follow up period. The dietary intakes of total carbohydrate, sugar, starch and total energy intake were divided into quintiles according to the distribution across the matched controls. Given the size of the cohort and duration of follow up a nested case-control design helped ensure that all cases had a physician confirmed diagnosis of CD or UC and that matched controls were free of CD and UC. Moreover, compared with a full cohort approach using a survival analysis with time dependent variables, the nested case-control analysis is computationally more efficient and produces odds ratios that are similar to hazard ratios when the outcomes (development of CD and UC) are uncommon(32).

Univariate analysis was performed calculating the odds ratios (OR) for developing CD or UC separately, according to dietary variables, using conditional logistic regression (STATA version 12 software; STATA Corporation, College Station, TX). A second analysis was performed that was identical to the first, but was also adjusted for total energy intake, body mass index and smoking. BMI was divided into four categories: ($<20\text{kg}/\text{m}^2$, $20\text{-}24.9\text{kg}/\text{m}^2$, $25\text{-}29.9\text{kg}/\text{m}^2$, $\geq 30\text{kg}/\text{m}^2$) and smoking was categorised into smoker, non-smoker or ex-smoker. Smoking was included due to the observed positive association with the risk of CD and inverse association with UC(33). Energy adjustment helped to account for variables that affect dietary intake such as metabolic rate and physical activity, and also helped to correct

for either under or over-reporting of diet. Adjustment for BMI was included as some epidemiological studies report that this is a risk factor for IBD(34). Sensitivity analyses were repeated for the above, excluding cases diagnosed within 3 years of recruitment, to assess if diet maybe involved nearer to the development of symptoms and diagnosis. The quoted p-values for levels of statistical significance were two sided. OR trends were calculated using the median value for each quintile as a continuous variable.

Results

A total of 110 incident cases of CD (mean age at diagnosis 55.4 years, 72.7% female) and 244 incident cases of UC (mean age at diagnosis 57.5 years, 57.3% female) were identified during follow up. The median interval between recruitment and diagnosis for CD was 5.1 years (range 1.5-14.3 years) and for UC 4.8 years (range 1.5-15.7 years) (data 100% complete). Table 2 shows the baseline characteristics of the participants in this nested case control analysis and the distribution of their subsequent disease. The extent of disease was known for 87% and 79% of those who developed CD or UC respectively. For CD, the distribution of disease was predominantly colonic (32.7%), and for UC mainly left-sided disease (35.2%). Smoking was positively associated with CD (OR=1.95, 95% CI=1.13-3.33) and UC (OR=2.24, 95% CI=1.53-3.29). The FFQ data was 99.6% complete for the CD analysis (cases 100%, controls 99.5%) and 99.1% for the UC analysis (cases 97.9%, controls 99.4%).

In the univariate analysis, we did not observe any significant associations between total carbohydrate, sugar or starch intakes and the odds of developing CD or UC, either according to individual quintiles or trends (table 3). Similarly, there were no significant associations between these macronutrients and CD or UC, in the multivariate analysis adjusted for

smoking, total energy and BMI (table 3). Including only those diagnosed with CD or UC 3 years after recruitment demonstrated no associations with carbohydrates (CD $P_{\text{trend}}=0.81$, UC $P_{\text{trend}}=0.83$), sugar (CD $P_{\text{trend}}=0.95$, UC $P_{\text{trend}}=0.98$) or starch (CD $P_{\text{trend}}=0.76$, UC $P_{\text{trend}}=0.71$). This process excluded 25 cases of CD and 45 cases of UC. In post-hoc analyses, as all the higher quintiles of total carbohydrates and starch intake had positive, but non-significant associations with UC, these macronutrients were analysed further for threshold effects, but none were found (data not shown). Similarly, given the effects of smoking on IBD, and that smoking is positively associated with sugar consumption(35), associations between total sugar intake in non-smokers for CD (n=69) and UC (n=156) were analysed separately. However, despite adjusting for total energy and BMI no associations were observed with CD ($P_{\text{trend}}=0.81$) or UC ($P_{\text{trend}}=0.69$). The findings were similar in smokers for CD ($P_{\text{trend}}=0.85$) and UC ($P_{\text{trend}}=0.67$) although the numbers were small (CD, n=38; UC, n=82). Analysis by the disease site of CD and UC did not affect any of the associations with macronutrients (data not shown). Whilst higher SES has been positively associated with IBD and decreased intake of carbohydrates(36, 37) the associations were further unaffected when adjusted for social economic status (SES) using education (none, primary school, technical/professional school, secondary school and higher education including university) as a proxy of SES (carbohydrates - CD $P_{\text{trend}}=0.75$, UC $P_{\text{trend}}=0.61$; sugar - CD $P_{\text{trend}}=0.98$, UC $P_{\text{trend}}=0.63$; starch CD $P_{\text{trend}}=0.92$, UC $P_{\text{trend}}=0.37$). Similarly adjusting for protein and fat in the multivariate analysis did not affect the associations either (carbohydrates - CD $P_{\text{trend}}=0.95$, UC $P_{\text{trend}}=0.39$; sugar - CD $P_{\text{trend}}=0.90$, UC $P_{\text{trend}}=0.91$; starch CD $P_{\text{trend}}=0.72$, UC $P_{\text{trend}}=0.13$). In order to account for over or under reporting of macronutrients, nutrient density (macronutrient/total energy) was used in sensitivity analyses although again, no associations were seen with either CD or UC (carbohydrates - CD $P_{\text{trend}}=0.69$, UC $P_{\text{trend}}=0.42$;

sugar - CD $P_{\text{trend}}=0.50$, UC $P_{\text{trend}}=0.72$; starch CD $P_{\text{trend}}=0.69$, UC $P_{\text{trend}}=0.18$). Finally, stratification by BMI did not show any significant associations for the odds of developing CD or UC in multivariate analyses for those of normal weight (BMI 20-24.9 kg/m²) (carbohydrates - CD $P_{\text{trend}}=0.08$, UC $P_{\text{trend}}=0.30$; sugar - CD $P_{\text{trend}}=0.42$, UC $P_{\text{trend}}=0.53$; starch CD $P_{\text{trend}}=0.22$, UC $P_{\text{trend}}=0.26$) or those defined as overweight or obese (BMI ≥ 25 kg/m²) (carbohydrates - CD $P_{\text{trend}}=0.09$, UC $P_{\text{trend}}=0.91$; sugar - CD $P_{\text{trend}}=0.16$, UC $P_{\text{trend}}=0.63$; starch - CD $P_{\text{trend}}=0.13$, UC $P_{\text{trend}}=0.56$).

Discussion

In this large multi-center, prospective study using dietary data from a validated FFQ, we did not find any associations between: total dietary carbohydrate, sugar (mono- and disaccharides) or starch intakes (a digestible polysaccharide) and the odds of developing CD or UC. There was no evidence of dose-responses or threshold effects, and none according to disease site or time since recruitment. Despite the lack of associations there is biological plausibility to support a role for these nutrients in the etiology of CD and UC. This is based on studies reporting that diet has a dominant role in shaping the gut microbiota with one murine study estimating that diet could account for 57% of the total structural variation in the gut microbiota, whilst genetic changes accounted for up to 12%(38). Potentially diet-induced dysbiosis of the gut microbiota may disrupt immune regulatory mechanisms leading to IBD susceptibility(39, 40), although the exact mechanism by which dysbiosis contributes to IBD has yet to be fully defined. However, studies in murine models of IBD report that western diets, high in sugar and fat leads to gut microbiota dysbiosis that facilitates colonisation of the gut by adherent invasive *E. coli* and subsequent release of the pro-inflammatory cytokine TNF α , promoting bowel inflammation(41). A second mechanism for

how nutrients may influence etiology is that Western diets high in carbohydrates, including refined sugars, are associated with obesity, which is directly associated with a pro-inflammatory state that increases bowel permeability(9, 10). However, two epidemiological studies reporting the role of BMI in IBD have conflicting results(34, 42).

Our study design had several strengths. Firstly, biases were reduced; recall bias for dietary intakes, and selection biases, i.e. inherent differences between cases and controls. Secondly, assessment of diet was through the use of validated questionnaires designed to capture local dietary habits and standardised nutrient databases. Thirdly, our cases of CD and UC were reviewed by physicians to confirm the diagnoses and the number of cases expected during follow-up was similar to that expected using incidence data from The European Collaborative study on Inflammatory Bowel Disease (EC-IBD)(43). Therefore, follow-up bias is probably minimal. Fourthly, we adjusted for covariates including total energy intake, smoking and BMI. Last, our study investigated both genders to help ensure generalizability of our findings. There were some limitations of our study as we were unable to adjust for covariates such as family history of CD or UC and appendectomy. In particular, cases with a positive family history of IBD may consume less carbohydrate based on previous literature. However, we think that this is unlikely to significantly affect our findings as only a minority of cases will have first degree relatives with CD or UC(44, 45).

We also only used one measure of diet namely that recorded at baseline which introduces error if diet changes over time. This measurement error would result in underestimates of any potential associations, making it possible that small associations with these macronutrients do occur, which we did not have the sensitivity to detect. However, studies

of repeated measures of longitudinal diet suggest that absolute dietary changes in adults are small(46). Our division of carbohydrates into broad categories meant we could not detect associations with specific individual carbohydrates, which could influence intestinal inflammation. This may be important as murine studies report that the milk oligosaccharide sialyl(α 2,3)lactose increases susceptibility to IBD via Toll-like receptor 4 signalling(47), whilst a short chain oligosaccharide, isomaltooligosaccharide delays the development of an experimental colitis(48). Therefore, although there were no associations with the macronutrient groups studied in this work, it is possible that specific individual components that make up each macronutrient group could have had an effect. Also our population had a mean age of 55-58 years at diagnosis, which is reflected in the clinical distribution of CD and UC, reported as predominantly colonic and distal disease respectively in this age group(49, 50). Accordingly, in terms of generalizability our study is applicable mainly to IBD of later onset.

To the best of our knowledge, our study is the first to prospectively investigate associations between all these macronutrients and the development of CD. This study also expands our previous work, following the recruitment of four additional centers in 4 different countries, and confirms our findings of no associations between these macronutrients and UC(18). This development led to the identification of over one hundred additional cases of incident UC following case ascertainment. With exception to our earlier work in mainly northern European countries on total carbohydrates, sugars and starch in UC(18) and that of the French E3N study, a part of the EPIC-IBD study, who reported no associations between total carbohydrates in CD and UC(51), all other pre-existing studies were retrospective case-control investigations. These had the methodological limitations of recall and selection

biases(4, 17). In aetiological work, it is the accurate reporting of patients' pre-illness diet, rather than their diet following symptoms and diagnosis, which is relevant to aetiological work and minimises recall bias. Recall bias in case-control studies occurs where patients diagnosed with CD or UC, some many years before recruitment, are asked to recall their dietary intake prior to the development of symptoms and diagnosis. However, many patients have difficulties accurately recollecting their pre-illness diet, particularly if CD or UC was diagnosed many years previously. In practice they report their current food intake, which the disease process may have altered. In prospective studies recall bias is minimal as all participants at recruitment are asymptomatic and report their current diet. Moreover, as cases and controls are drawn from the same baseline population, then there are no comparative differences hence reducing selection biases.

Previous studies investigating the associations between total dietary intake of carbohydrate (excluding fiber) with the risk of developing CD or UC report conflicting results(16, 51-54). This is perhaps not surprising as carbohydrates are a heterogeneous group of nutrients consisting of mono- and di-saccharides, oligosaccharides and polysaccharides. A larger number of studies have examined the associations between total dietary sugars (monosaccharides and disaccharides) and the risk of CD and UC. One study reported a statistically significant positive association with sugar and CD(16) and two studies reported similar findings for sugar and UC(16, 55). However, most investigations did not find any significant associations for either CD(14, 56, 57) or UC(14, 53, 58, 59). Notably, earlier studies that reported significantly positive associations for CD and sugar only investigated associations with a limited number of saccharides, predominantly the disaccharide sucrose, or suggested that their results were secondary to recall bias rather than a causal

relationship(12, 13, 15). Interestingly, the only investigation to find a positive association between total dietary sugars and both CD and UC also found a statistically significant association between increased risk of CD and UC, and starch(16). However, crude relative risk ratios were calculated without adjusting for energy intake and cigarette smoking.

In summary, the lack of associations in our study, and the ambiguity of associations in prior retrospective studies suggest there are no consistent links between these macronutrients and the development of CD or UC. Future epidemiological work should specifically assess individual mono- and disaccharides, oligosaccharides and polysaccharides to determine if these influence the risk of CD or UC, although our prospective work suggests measuring the broad nutrient groups is now not probably required. Ideally, other cohort studies should clarify if our findings are consistent, in addition to experimental studies to explore the potential mechanisms of specific carbohydrates. Such work is important to ultimately lead to measures to prevent the development of IBD.

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Conflicts of interest

None

Author statement of contribution

SSMC and ARH designed the study, recruited the centers, analysed the data and wrote the paper. RL generated the master dataset, performed data entry, provided support on statistical analysis and contributed to writing the paper. The remaining co-authors FvS, BO, BB, GH, PK, SL, OG, TK, FLC, MMB, HB, KO, DP, GM, KK, AR, FC, MB, AO, AT, RK, RT, and AT are principal investigators in their respective centers who contributed to the local design, development and recruitment of participants into their cohorts. These authors generated the local IBD databases, and contributed to the analysis and writing of the manuscript.

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