Dietary inflammatory indices are not associated with inflammatory bowel disease incidence and progression

Title Page: Brief Report

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Short Title:

Dietary inflammation indices and IBD

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Brief Summary:

EDIP and DII are dietary inflammation indices, both previously associated with risk of IBD. We show in the UK Biobank a null association between these indices and incident IBD; we challenge the current ways in which these dietary indices are derived and interpreted. The need to account for the effects of food processing as well as the raw ingredients is emphasized as a confounding variable.

Key words:

EDIP, DII, diet, IBD

Key Messages:

- What is already known?

Diet is a key environmental factor in IBD that might influence disease onset and course, and therefore may become a strategy to mitigate inflammation and symptoms.

EDIP and DII are dietary inflammation indices that have been associated with risk of IBD.

- What is new here?

In this large prospective UK cohort, we show no associations between neither EDIP and DII and IBD onset or IBD-related outcomes.

- How can this study help patient care?

Dietary inflammation indices are potentially important to better understand the role of nutrition on IBD onset and course of disease. Current systems are suboptimal and require re-consideration including the degree of food processing.

Conflicts of interest

There were no financial conflicts of interest among any of the authors.

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1. Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are thought to arise from inappropriate and maladaptive stimulation of the immune system. Emerging evidence demonstrates that environmental factors, including the diet, may play an important role in disease pathogenesis. [1] Patients are in need of guidance regarding which foods to eat and to avoid in order to prevent or control IBD. Dietary inflammation indices, including the empirical dietary inflammatory pattern (EDIP) based on food groups and dietary inflammatory index (DII) based on nutrients, were previously established to assess the overall inflammatory property of a diet. [2,3] The EDIP was based on the Nurses' Health Study (NHS) cohort study, with 18 selected food groups to represent dietary inflammatory potential. [3] Briefly, 39 food groups were regressed with plasma inflammatory biomarker levels by reduced-rank regressions and stepwise linear regressions. The DII score, in contrast, was constructed by using data from peer-reviewed research publications through 2010 and leverages 45 dietary factors to predict concentrations of six inflammatory markers. [2] For both indices, higher scores indicate pro-inflammatory diets. Both scores were shown, using data from the NHS-II and the Health Professionals Follow-up Study (HPFS), to reliably predict concentrations of plasma inflammatory markers. [4] Later, using the same three US cohorts, higher EDIP scores were associated with an increased risk of CD. [5] However, another study based on the Prospective Urban Rural Epidemiology

(PURE) cohort that included seven countries (Argentina, Brazil, Canada, Chile, Poland, South Africa, and Sweden), observed a null association for both UC and CD. [6] Lastly, the DII has been associated with an increased risk of UC in an Iranian case-control study of only 62 patients. [7] All scores rely on food composition, with no account for the method of preparation nor degree of food processing.

In view of these discrepancies, we conducted a prospective cohort study using the UK Biobank cohort to validate these dietary inflammation indices and their relationship with IBD incidence and IBD-related clinical outcomes.

2. Methods

In this study, 121,472 participants from the UK Biobank with two to five valid 24-hour dietary recall questionnaires were included. Participants were asked about their food intake of the previous day, including 206 foods and 32 drinks. The nutrient calculation was based on the food composition table used in the UK Nutrient Databank. [8] Consumption of each food and nutrient was the mean intake of all valid questionnaires and consumption of each food group was the sum of all included food. Sixteen components (eight nutrients and eight foods) of the DII were unavailable in the UK Biobank, leaving 29 of the 45 dietary components for calculation of the score. The design of the UK biobank has been detailed elsewhere. [9]

Participants free of IBD at baseline (N=121,472) were followed up for IBD

incidence, and participants with prevalent IBD (N=1408) were followed up for IBD-related clinical outcomes (colorectal cancer, IBD-related surgery, and all-cause mortality). Covariates for adjustment included age, sex, ethnicity, Townsend's deprivation index (TDI), education level, smoking status, drinking status, physical activity, body mass index, and total energy intake. The primary outcome was the incidence of IBD, CD and UC, ascertained by health records linked to national hospital inpatient, primary care and death registries (ICD 9 and 10 codes). Secondary outcomes included the development of colorectal cancer, the need for IBD-related surgery and all-cause mortality among IBD patients.

Person-years were calculated from the date of the first available 24-hour questionnaire to the date of IBD diagnosis (among general participants) or IBD-related clinical outcome (among IBD patients), death, loss, or the end of follow-up, whichever occurred first. Participants were grouped into quintiles of EDIP and DII scores. The lowest quintile was used as the reference group. Cox proportional hazard regression models were performed to examine the associations of EDIP and DII with the risk of IBD incidence and IBD-related clinical outcomes. A series of sensitivity analyses, including further adjusting for baseline comorbidities represented by Charlson comorbidity Index, medication use (antibiotics, proton pump inhibitors and non-steroidal anti-inflammatory drugs) and lag-1 year analysis were conducted to test the robustness of primary findings. Analyses were performed by R 4.2.1. All tests were two-sided, with a

P-value<0.05 indicating statistical significance.

3. Results

Among 121,472 eligible participants (mean age of 56.2 years, 55.8% female, 96.9% white ethnicity), we documented 511 incident IBD cases (143 CD and 368 UC) during a mean follow-up of 10.3 years. We did not observe any significant associations between per SD increment of EDIP or DII and IBD incidence. When examining associations by quintiles, neither EDIP (HR in quintile 5 vs 1: 1.06, 95% CI 0.80-1.40, P trend=0.287) nor DII (HR in quintile 5 vs 1: 1.01, 95% CI 0.74-1.36, trend=0.893) were associated with IBD risk in any model (**Table 1**). When considering CD and UC separately, a null association was observed for both CD (HR for EDIP in quintile 5 vs 1: 1.14, 95% CI 0.65-1.99, P trend=0.696; HR for DII in quintile 5 vs 1: 1.20, 95% CI 0.70-2.06, P trend=0.454) and UC (HR for EDIP in quintile 5 vs 1=1.03, 95% CI 0.75-1.42, P trend=0.315; HR for DII in quintile 5 vs 1=0.94, 95% CI 0.65-1.35, P trend=0.532) (**Table 1**). Similarly, neither EDIP nor DII was associated with the development of colorectal cancer, the need for IBD-related surgery or all-cause mortality among IBD patients (**Table 2**). The null findings remained consistent in all sensitivity analyses.

4. Discussion

In this large and independent cohort study involving 121,472 participants, we

computed two dietary inflammation indices based on food groups and nutrients to assess their associations with IBD risk. We found no associations between EDIP, DII and the risk of IBD incidence and progression.

This contrasts the findings from the North American prospective study, showing a positive association between EDIP scores and CD incidence. The PURE cohort on the other hand found only a similar trend. Compared to the first study that was partly based on the same cohort used for the development of the score, the PURE cohort included a global population with different ethnicities. Compared with these studies, we considered more confounding factors and additionally investigated the associations with the progression of IBD. Despite multiple sensitivity analyses, our results remained negative. Given our current results, the validity of the EDIP score as a tool for the assessment of the inflammatory potential of dietary patterns in IBD could be called into question. Of note, there are differences in incidence of IBD in our study (11.5 and 29.5/100,000 person-years for CD and UC) and the previous study (6.6 and 8.6/100,000 person-years for CD and UC in the NHS, NHS II and HPFS) [5]. Similarly, start time and follow-up periods differ in cohort studies exploring for this topic. The period for the current analysis was 2006 to 2021, while it was 1984-2014, 1991-2015 and 1986-2012 for NHS, NHS II and HPFS, respectively [5]. Regrettably, the different measurements for follow-up time limited the normalization. In addition, populations in different regions, ethnicities (eg. US and UK), age (eg. middle age in the NHS, NHS II and HPFS and older age in

the UK Biobank) were reported with the dietary discrepancy, thus resulting in different diet-related health outcomes [10,11]. Overall, confounding factors (including age, ethnicity, follow-up time, nutrient intake and response, genetics, family history, antibiotic use, etc.) differ between this and previous studies, limiting the comparison and extrapolation of results, although we have taken confounders into account as much as possible in the analytic models.

First, it needs to be considered that of the 18 selected food groups, fish, tomatoes and 'other vegetables' are said to have pro-inflammatory properties, whereas pizza, snacks and fruit juice are mentioned to be anti-inflammatory. [3] However, critically, cooking methods are not captured and one might propose, for example that fried fish could have a different inflammatory potential than steamed fish due to the formation of advanced glycation end products and contaminants such as trans-fatty acids and acrylamide. [1]

It is especially noteworthy that we recently reported a positive association between the intake of ultra-processed foods (UPFs) and CD incidence using data from the same UK biobank cohort, although no associations were observed in UC. The association between CD incidence (not UC) and intake of UPF intake has now been confirmed by a recent meta-analysis including four other studies. [12] Thus in addition to cooking methods, degree of processing before products are bought for consumption may also be of great importance. To illustrate this point, when we consider the same food group 'tomatoes', this category included fresh tomatoes, tomato juice and tomato sauce. Using the

NOVA classification to assess the processing of these products, the first would be considered NOVA, whereas juice and sauce are at least NOVA, [2] or processed, if not ultra-processed. [13] If we presume that the average American consumer is not preparing tomato juice and sauce from scratch, this would make these products NOVA, or ultra-processed. As well as variable degrees of processing and cooking, UPFs also typically have lower nutritional values, contain food additives and other industrial components, as well as contaminants of packaging. [14] These elements might additionally impact on development of disease on top of the raw ingredients. Unfortunately, this type of granularity cannot be assessed using food frequency questionnaires, which potentially limits the validity of the EDIP score. Taken together, we propose that total UPF intake is a better-validated tool to assess healthier dietary patterns in IBD than the '*pro-inflammatory*' scores.

Regarding the DII, we acknowledge that we were only able to capture 29 out of the 45 dietary components, which might negatively affect our results. However, the previously mentioned Iranian case-control study was only able to capture 27 items. [7] In addition, for a Belgian prospective study in healthy volunteers, the yield was as low as 17 dietary components, which calls into question the practicality and usability of this scoring system [15]. Finally, residual bias and confounding cannot be fully avoided in observational studies as well as in our analysis.

Finally, we would like to point out that interindividual differences in response to

nutrients and food handling might exist, as was previously illustrated by Armstrong et al. who showed that dietary fibers might have a counterintuitive pro-inflammatory effect in individuals with active IBD who lack fermentative microbial enzymatic activities. [16] Both human and microbial handling of foods are relevant. A better understanding of these inter-individual differences may be key to the development of personalized dietary strategies. [17]

In summary, we examined the role of both food group and nutrient-derived inflammatory indices in the development and progression of IBD in the UK biobank cohort and found null associations. Given the increasing awareness of the importance of diet on intestinal inflammation, this highlights the complexity and variability of dietary patterns, and the emerging need is for well-validated dietary scoring systems that take into account the degree of food processing and cooking techniques as well as the raw ingredients.

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Conflicts of interest

There were no financial conflicts of interest among any of the authors.

Author contributions to the manuscript

Author Contributions: JC: Conceptualization (equal), Methodology (equal), Formal analysis (lead), Writing-original draft (lead); TF: Methodology (equal), Formal analysis (lead), Writing-original draft (equal); JW: Methodology (supporting), Formal analysis (equal), Writing-review and editing (lead), Writin-original draft (lead); YZ: Methodology (supporting), Formal analysis (equal), Writing-original draft (supporting); KR: Methodology (supporting), Formal analysis (supporting), Writing-review and editing (supporting); JS: Conceptualization (lead), Formal analysis (supporting), Methodology (equal), Project administration (lead), Writing-review and editing (equal); ET: Conceptualization (lead), Formal analysis (supporting), Methodology (equal), Project administration (lead), Writing-review and editing (equal); XL: Conceptualization (lead), Formal analysis (supporting), Methodology (equal),

Project administration (lead), Writing-review and editing (lead). All authors contributed to data acquisition and interpretation, approved the final version of the manuscript.

Data availability

Data can be requested from the UK Biobank (www.ukbiobank.ac.uk/).

Abbreviations

IBD, inflammatory bowel disease; CD, Crohn's disease; UC ulcerative colitis; EDIP, empirical dietary inflammatory pattern; DII, dietary inflammatory index; PURE, Prospective Urban Rural Epidemiology; TDI, Townsend's deprivation index; ICD, International Classification of Diseases; HR, hazard ration; CI, confidence interval; SD, standard deviation.

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Table 1. Associations of dietary inflammation indices and risk of IBD, CD and UC

	EDIP				DII			
	Case	**Person years**	**Crude model HR (95% CI)**	**Multivariable model HR (95% CI)**	**Case**	**Person years**	**Crude model HR (95% CI)**	**Multivariable model HR (95% CI)**
IBD								
Per SD			1.01 (0.93, 1.11)	1.02 (0.93, 1.11)			1.01 (0.92, 1.10)	1.01 (0.91, 1.11)
Q1	102	250,347	Ref	Ref	112	250,840	Ref	Ref
Q2	88	250,749	0.86 (0.65, 1.15)	0.90 (0.68, 1.20)	101	250,757	0.90 (0.69, 1.18)	0.92 (0.70, 1.20)
Q3	104	249,962	1.02 (0.78, 1.34)	1.08 (0.82, 1.43)	89	250,387	0.80 (0.60, 1.05)	0.81 (0.61, 1.08)
Q4	111	249,915	1.09 (0.83, 1.43)	1.15 (0.87, 1.51)	98	249,466	0.88 (0.67, 1.15)	0.89 (0.66, 1.18)
Q5	106	248,397	1.05 (0.80, 1.38)	1.06 (0.80, 1.40)	111	247,920	1.00 (0.77, 1.31)	1.01 (0.74, 1.36)
P trend			0.297	0.287			0.957	0.893
CD								
Per SD			1.04 (0.88, 1.24)	1.05 (0.88, 1.24)			1.06 (0.90, 1.24)	1.11 (0.91, 1.35)
Q1	24	249,930	Ref	Ref	36	250,418	Ref	Ref
Q2	29	250,230	1.21 (0.70, 2.07)	1.28 (0.74, 2.20)	22	250,406	0.61 (0.36, 1.04)	0.63 (0.37, 1.08)
Q3	34	249,528	1.42 (0.84, 2.39)	1.52 (0.90, 2.58)	22	249,933	0.61 (0.36, 1.04)	0.65 (0.38, 1.12)
Q4	29	249,611	1.21 (0.70, 2.08)	1.28 (0.74, 2.22)	26	249,010	0.73 (0.44, 1.20)	0.79 (0.46, 1.35)
Q5	27	248,019	1.13 (0.65, 1.97)	1.14 (0.65, 1.99)	37	247,552	1.04 (0.66, 1.65)	1.20 (0.70, 2.06)
P trend			0.699	0.696			0.686	0.454
UC								
SD			1.00 (0.91, 1.11)	1.01 (0.91, 1.12)			0.99 (0.89, 1.09)	0.97 (0.86, 1.09)
Q1	78	250,159	Ref	Ref	76	250,708	Ref	Ref
Q2	59	250,597	0.76 (0.54, 1.06)	0.79 (0.56, 1.10)	79	250,566	1.04 (0.76, 1.43)	1.05 (0.77, 1.45)
Q3	70	249,830	0.90 (0.65, 1.24)	0.95 (0.68, 1.31)	67	250,217	0.88 (0.64, 1.23)	0.88 (0.63, 1.24)
Q4	82	249,775	1.05 (0.77, 1.44)	1.10 (0.80, 1.51)	72	249,294	0.95 (0.69, 1.32)	0.93 (0.66, 1.31)
Q5	79	248,230	1.02 (0.75, 1.40)	1.03 (0.75, 1.42)	74	247,804	0.99 (0.72, 1.36)	0.94 (0.65, 1.35)

P trend	0.325	0.315	0.752	0.532

Cut-off of EDIP was -0.53, -0.28, -0.10, 0.12, and DII was -3.32, -2.75, -2.25, -1.69. Multivariable model: Cox model adjusted for age, sex, ethnicity, TDI, education, smoking, drinking, physical activity, body mass index and total energy. EDIP, empirical dietary inflammatory pattern; DII, dietary inflammatory index; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

Table 2. The associations of dietary inflammation indices with the risk of the progression among IBD patients

	Case	Person years	Crude model		Minimally adjusted model		Fully adjusted model	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Colorectal cancer								
EDIP								
Per SD			0.84 (0.60, 1.16)	0.279	0.82 (0.58, 1.16)	0.272	0.84 (0.59, 1.18)	0.312
Q1	8	2776	Ref		Ref		Ref	
Q2	6	2798	0.75 (0.26, 2.16)	0.595	0.75 (0.26, 2.20)	0.604	0.79 (0.27, 2.34)	0.673
Q3	4	2793	0.50 (0.15, 1.65)	0.253	0.45 (0.13, 1.52)	0.198	0.47 (0.14, 1.60)	0.227
Q4	6	2822	0.74 (0.26, 2.15)	0.585	0.70 (0.24, 2.05)	0.513	0.72 (0.25, 2.13)	0.557
Q5	2	2805	0.25 (0.05, 1.17)	0.079	0.25 (0.05, 1.20)	0.084	0.25 (0.05, 1.22)	0.087
P trend				0.098		0.096		0.101
DII								
Per SD			0.82 (0.56, 1.20)	0.309	0.85 (0.57, 1.25)	0.410	0.87 (0.56, 1.37)	0.555
Q1	6	2818	Ref		Ref		Ref	
Q2	6	2785	1.03 (0.33, 3.18)	0.964	1.04 (0.33, 3.27)	0.940	1.06 (0.33, 3.36)	0.920
Q3	6	2784	1.03 (0.33, 3.19)	0.962	1.12 (0.36, 3.51)	0.842	1.15 (0.36, 3.71)	0.812
Q4	6	2821	1.01 (0.32, 3.12)	0.993	1.05 (0.34, 3.31)	0.928	1.10 (0.32, 3.77)	0.878
Q5	2	2785	0.34 (0.07, 1.70)	0.189	0.39 (0.08, 1.97)	0.254	0.42 (0.07, 2.38)	0.324
P trend				0.281		0.397		0.536
IBD-related surgery								
EDIP								
Per SD			0.99 (0.80, 1.21)	0.889	0.98 (0.79, 1.22)	0.881	1.01 (0.82, 1.24)	0.961
Q1	20	2741	Ref		Ref		Ref	
Q2	12	2784	0.59 (0.29, 1.21)	0.151	0.56 (0.27, 1.16)	0.117	0.61 (0.30, 1.26)	0.183
Q3	17	2759	0.84 (0.44, 1.61)	0.607	0.83 (0.43, 1.60)	0.575	0.92 (0.47, 1.79)	0.805
Q4	25	2760	1.24 (0.69, 2.24)	0.469	1.27 (0.70, 2.31)	0.429	1.35 (0.74, 2.46)	0.327
Q5	17	2743	0.85 (0.45, 1.62)	0.622	0.85 (0.43, 1.65)	0.623	0.87 (0.45, 1.70)	0.686
P trend				0.596		0.547		0.517

DII								
Per SD			1.06 (0.86, 1.30)	0.574	1.07 (0.86, 1.32)	0.556	**1.29 (1.00, 1.65)**	**0.048**
Q1	15	2807	Ref		Ref		Ref	
Q2	22	2732	1.50 (0.78, 2.90)	0.223	1.44 (0.74, 2.78)	0.283	1.64 (0.84, 3.20)	0.146
Q3	16	2758	1.09 (0.54, 2.20)	0.818	1.12 (0.55, 2.27)	0.763	1.40 (0.67, 2.89)	0.369
Q4	18	2773	1.22 (0.61, 2.41)	0.576	1.18 (0.59, 2.35)	0.642	1.70 (0.81, 3.55)	0.161
Q5	20	2716	1.37 (0.70, 2.68)	0.352	1.39 (0.70, 2.76)	0.343	**2.26 (1.06, 4.85)**	**0.035**
P trend				0.610		0.587		0.065
All-cause mortality								
EDIP								
Per SD			0.89 (0.74, 1.07)	0.214	0.89 (0.73, 1.07)	0.210	0.88 (0.73, 1.07)	0.196
Q1	26	2753	Ref		Ref		Ref	
Q2	16	2768	0.61 (0.33, 1.14)	0.123	0.62 (0.33, 1.16)	0.136	0.61 (0.32, 1.14)	0.123
Q3	19	2787	0.72 (0.40, 1.30)	0.279	0.75 (0.41, 1.38)	0.362	0.73 (0.39, 1.35)	0.313
Q4	17	2764	0.65 (0.35, 1.20)	0.170	0.65 (0.35, 1.21)	0.176	0.64 (0.34, 1.19)	0.161
Q5	22	2754	0.85 (0.48, 1.51)	0.584	0.89 (0.49, 1.62)	0.707	0.89 (0.49, 1.62)	0.706
P trend				0.638		0.706		0.706
DII								
Per SD			1.04 (0.85, 1.26)	0.727	1.08 (0.88, 1.32)	0.462	1.07 (0.85, 1.35)	0.539
Q1	21	2797	Ref		Ref		Ref	
Q2	18	2751	0.87 (0.46, 1.63)	0.666	0.99 (0.52, 1.86)	0.969	0.98 (0.52, 1.86)	0.952
Q3	22	2772	1.06 (0.58, 1.92)	0.855	1.17 (0.64, 2.13)	0.618	1.15 (0.63, 2.13)	0.648
Q4	17	2776	0.82 (0.43, 1.55)	0.541	0.94 (0.49, 1.79)	0.848	0.92 (0.47, 1.82)	0.814
Q5	22	2731	1.09 (0.60, 1.99)	0.773	1.24 (0.67, 2.29)	0.495	1.21 (0.60, 2.40)	0.596
P trend				0.855		0.590		0.694

Crude model: Cox models without adjustment; Minimally adjusted model: Cox model adjusted for age, sex, ethnicity; Fully adjusted model: Cox model adjusted for age, sex, ethnicity, TDI, education, smoking, drinking, physical activity, body mass index and total energy. IBD, inflammatory bowel disease; EDIP, empirical dietary inflammatory pattern; DII, dietary inflammatory index; TDI, Townsend's deprivation index; HR, hazard ration; CI, confidence interval; SD, standard deviation.