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Sugar-sweetened beverages, artificially sweetened beverages and natural juices and risk of inflammatory bowel disease: a cohort study of 121,490 participants

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Summary

Background: Inflammatory bowel diseases (IBD) have been related to high-sugar dietary patterns, but the associations of different types of beverages with IBD risk are largely unknown.

Aims: To examine the associations of intake of sugar-sweetened beverages, artificially sweetened beverages and natural juices with IBD risk.

Methods: This cohort study included 121,490 participants in the UK Biobank who were free of IBD at recruitment. Intake of beverages was obtained from repeated 24-h diet recalls in 2009–2012. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of beverage intake with IBD risk.

Results: During a mean (standard deviation) follow-up of 10.2 (1.5) years, we documented 510 incident IBD cases, (143 Crohn's disease (CD) and 367 ulcerative colitis (UC)). Compared to non-consumers, participants consuming >1 unit per day of sugar-sweetened beverages were at significantly higher risk of IBD (HR 1.51, 95% CI 1.11–2.05), but the trend was non-significant (p-trend = 0.170). This association was significant for CD (HR 2.05, 95% CI 1.22–3.46), but not for UC (HR 1.31, 95% CI 0.89–1.92). We did not observe significant associations for the consumption of artificially sweetened beverages or natural juices.

Conclusions: Our findings suggest an association between consumption of sugar-sweetened beverages, rather than artificially sweetened beverages or natural juices, and IBD risk.

Tian Fu, Hui Chen and Xuejie Chen contributed equally.

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1 | INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic gastrointestinal diseases with unknown aetiology.[1] Accumulating evidence has linked its rising incidence to dietary changes, including higher intake of fat, sugar, food additives and lower fibre intake.[2] As one of the major sources of free sugar, beverages have been related to inflammation-related health outcomes[3–9] but received less attention in the field of IBD.

In vitro and in vivo researches linked beverages to IBD through dysbiosis of gut microbiota and enhanced colitis susceptibility,[10,11] but population-based evidence was inconclusive. Two meta-analyses based on cross-sectional and cohort studies showed positive associations between soft drinks and sugar-sweetened beverages and IBD risk,[12,13] in line with another large prospective study.[14] On the contrary, another recent prospective study and a meta-analysis found null associations.[15,16] The disparities might result from the differences in definitions of beverages and heterogeneity of populations. For example, a study conducted in two Swedish cohorts treated both sugar-sweetened beverages and artificially sweetened beverages as sugary beverages,[16] without considering the different sweetener components in these two beverages. As for artificial sweetener, epidemiological and animal studies have suggested its effect on gut bacteria and immunity,[17] while whether they were associated with gastrointestinal inflammation was controversial. Also, the relations of natural juices with IBD risk have not been studied and deserve more exploration for the different forms of sugar they contain.

Therefore, we aim to explore the associations of sugar-sweetened beverages, artificially sweetened beverages and natural juices with IBD risk in the UK Biobank, a large population-based cohort.

2 | METHODS

2.1 | Study population

This study was based on the UK Biobank, a large population-based cohort, with over 500,000 participants being recruited in England, Wales and Scotland from 2006 to 2010. More details about the UK Biobank are described elsewhere.[18] The UK Biobank received ethical approval from the North West-Haydock Research Ethics Committee (REC reference: 16/NW/0274). All participants in this study provided informed consent when they were recruited.

For the present study, participants who completed 24-hour questionnaires at least twice with typical diet and credible energy (defined as >0–20 MJ for males, >0–18 MJ for females)[19,20] were included in the analysis. We further excluded participants with IBD at recruitment (n = 1465), unclear IBD diagnostic information during follow-up (n = 1). The final analysis included 121,490 participants (Figure 1).

2.2 | Assessment of exposure

Dietary intake was measured using a web-based 24-h diet recall questionnaire (Oxford Web-Q). The questionnaires were sent out in April 2009–September 2010, February 2011–April 2011, June 2011–August 2011, October 2011–December 2011 and April 2012–June 2012. Participants were asked how many units (glasses/cans/250 ml/cartons) of beverages they drank yesterday, and the options included 0, 0.5, 1, 2, 3, 4, 5 and more than 6 units. In the current study, sugar-sweetened beverages included fizzy drink and squash, artificially sweetened beverage referred to low-calorie drinks, and natural juices included pure orange juice, grapefruit juice and other pure fruit or vegetable juice.[21] We


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┌─────────────────────────────┐
│ Participants recruited from │
│ 2007 to 2010 and had at     │
│ least two valid 24-h dietary│
│ questionnaire in the UK     │
│ Biobank (N=122 956)         │
└─────────────────────────────┘
              │          ┌──────────────────────────────┐
              │─────────▶│ Excluded participants        │
              │          │ 1 with IBD at baseline       │
              │          │   (N=1465)                   │
              │          │ 2 with unclear diagnosis     │
              │          │   during follow-up (N=1)     │
              ▼          └──────────────────────────────┘
┌─────────────────────────────┐
│ Participants in analyse     │
│ (N=121 490)                 │
└─────────────────────────────┘

Primary analyses:
 Association between three beverages intake and risk of IBD, CD, UC
Secondary analyses:
1) Total sugar intake and risk of IBD, CD, UC
2) Subgroup analyses for beverage intake and IBD risk
Sensitivity and additional analyses:
1) Further adjusted for total sugar/comorbidities
2) Used Mediterranean diet score in place of AHEI
3) Dealt with missing covariates using multiple imputation
4) Ascertained incident IBD as at least twice IBD diagnosis
5) Lag 4-year analysis and latency analyses
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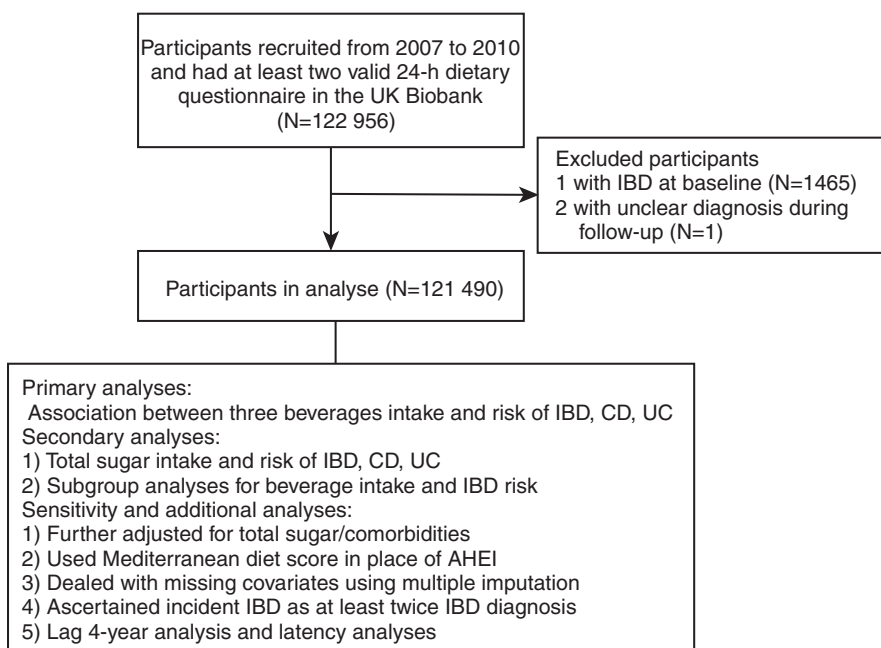
FIGURE 1 Participant inclusion. AHEI, alternative healthy eating index; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

TABLE 1 Baseline characteristics of overall participants according to consumption of sugar-sweetened beverages (n = 121,490)

Variables	Overall (n = 121,490)	Sugar-sweetened beverages		
		0 unit per day (n = 80,547)	>0–1 unit per day (n = 26,485)	>1 units per day (n = 14,458)
Sex (%)				
Female	67,726 (55.7)	46,517 (57.8)	14,379 (54.3)	6830 (47.2)
Male	53,764 (44.3)	34,030 (42.2)	12,106 (45.7)	7628 (52.8)
Age (mean, SD) (years)	56.2 (7.8)	56.5 (7.7)	56.4 (7.9)	54.2 (8.2)
Ethnicity (%)				
White	117,716 (96.9)	78,352 (97.3)	25,575 (96.6)	13,789 (95.4)
Others	3774 (3.1)	2195 (2.7)	910 (3.4)	669 (4.6)
TDI tertiles (%)				
Low	40,522 (33.4)	26,973 (33.5)	8970 (33.9)	4579 (31.7)
Moderate	40,515 (33.3)	26,755 (33.2)	9006 (34.0)	4754 (32.9)
High	40,453 (33.3)	26,819 (33.3)	8509 (32.1)	5125 (35.4)
Education (%)				
High school and below	64,656 (53.2)	41,352 (51.3)	14,881 (56.2)	8423 (58.3)
College and above	56,834 (46.8)	39,195 (48.7)	11,604 (43.8)	6035 (41.7)
Smoking status (%)				
Current	8377 (6.9)	5507 (6.8)	1738 (6.6)	1132 (7.8)
Never	69,804 (57.5)	45,556 (56.6)	15,711 (59.3)	8537 (59.0)
Previous	43,309 (35.6)	29,484 (36.6)	9036 (34.1)	4789 (33.1)
Alcohol drinking status (%)				
Current	114,433 (94.2)	76,423 (94.9)	24,760 (93.5)	13,250 (91.6)
Never	3520 (2.9)	1991 (2.5)	917 (3.5)	612 (4.2)
Previous	3537 (2.9)	2133 (2.6)	808 (3.1)	596 (4.1)
Physical activity levels (median [IQR]) (MET-minutes/week)	2085.0 (939.0, 2868.0)	2078.0 (942.0, 2848.3)	2106.0 (956.0, 2904.0)	2106.0 (924.0, 3024.0)
BMI (mean, SD) (kg/m^2)	26.7 (4.6)	26.5 (4.5)	26.8 (4.6)	27.5 (4.8)
Total energy intake (mean, SD) (KJ/day)	8663.9 (2229.4)	8467.9 (2200.1)	8850.1 (2103.4)	9415.2 (2419.2)
Total sugar intake (mean, SD) (g/day)	119.8 (44.4)	112.8 (42.4)	125.3 (40.8)	148.3 (48.8)
Number of 24-h questionnaire				
2	44,870 (36.9)	31,884 (39.6)	6620 (25.0)	6366 (44.0)
3	41,084 (33.8)	26,952 (33.5)	9381 (35.4)	4751 (32.9)
≥4	35,536 (29.3)	21,711 (27.2)	10,484 (39.6)	3341 (23.1)

Notes: Continues variables are displayed as means (SDs) or median (IQR) and categorical variables are displayed as numbers (%).

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; TDI, townsend deprivation index.

calculated the mean intake of the beverage intake in multiple 24-h recalls as the exposure variables.

The Oxford Web-Q has been widely used and validated in large-scale prospective studies.[22,23] In the UK Biobank, this dietary assessment tool has been validated and showed moderate validity (correlation coefficients=0.3–0.5 for macronutrients).[24]

2.3 | Ascertainment of outcome

In the current study, the outcome was the incidence of IBD during follow-up, obtained through hospital inpatient data (International Classification of Disease ninth and tenth editions [ICD-9 and ICD-10]), death registry data (ICD-10) and coded primary care data. Incident IBD cases were defined as CD (ICD-9 codes 555, ICD-10 codes K50) or UC (ICD-9 codes 556, ICD-10 codes K51). The health data of participants was updated until 30 September 2021 for England, 31 July 2021 for Scotland and 28 February 2018 for Wales.

2.4 | Assessment of covariates

Covariates were selected for adjustments based on a priori knowledge and a previous study,[21] including age (continuous in years), sex

TABLE 2 Associations between consumption of three types of beverages and risk of inflammatory bowel disease

	Incident cases/person-year	Minimally adjusted model[a] HR 95% CI	p-value	Fully adjusted model[b] HR 95% CI	p-value
Sugar-sweetened beverages					
0 unit per day	331/819469	Ref		Ref	
>0–1 unit per day	130/343335	0.94 [0.76, 1.15]	0.526	0.91 [0.74, 1.12]	0.355
>1 units per day	49/75718	**1.62 [1.19, 2.19]**	**0.002**	**1.51 [1.11, 2.05]**	**0.009**
p for trend			0.074		0.170
Artificially sweetened beverages					
0 unit per day	392 /971678	Ref		Ref	
>0–1 unit per day	93/201529	1.17 [0.93, 1.46]	0.181	1.09 [0.87, 1.38]	0.457
>1 units per day	25/65314	0.98 [0.66, 1.48]	0.937	0.85 [0.56, 1.28]	0.436
p for trend			0.461		0.818
Natural juices					
0 unit/day	220/553581	Ref		Ref	
>0–1 unit per day	252/591603	1.05 [0.88, 1.26]	0.587	1.14 [0.95, 1.37]	0.173
>1 units per day	38/933 37	1.00 [0.71, 1.41]	0.990	1.08 [0.76, 1.53]	0.664
p for trend			0.742		0.320

Notes: Tests reaching a significance level of 0.05 were marked bold.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Fully adjusted model, further adjusted for education, Townsend deprivation index, physical activities, smoking status, alcohol drinking status, BMI, total energy, AHEI and mutually adjusted for another two beverages.

[b]Minimally adjusted model, Cox proportional hazard model-adjusted age, gender and ethnicity.
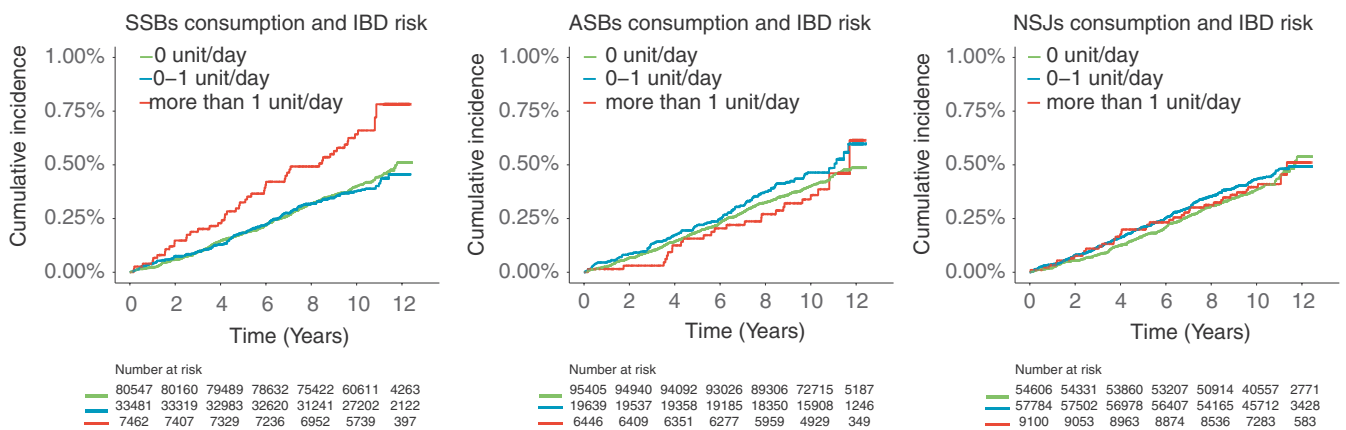

FIGURE 2 Cumulative incidence of inflammatory bowel disease, Crohn's disease and ulcerative colitis according to consumptions of sugar-sweetened beverages, artificially sweetened beverages and natural juices unit/day.

(male and female), ethnicity (white and others), Townsend deprivation index (TDI; low, moderate and high), education (high school and below, college and above), smoking status (never, previous and current), alcohol drinking status (never, previous and current), physical activity levels (continuous in MET-min/week), body mass index (continuous in kg/m²), total sugar (continuous in g), and energy intake (continuous in KJ), diet quality score including Alternative Healthy Eating Index (AHEI) or Mediterranean diet score, and baseline comorbidities[25,26] including diabetes, hypertension, coronary heart disease (CHD), stroke and cancers from multiple sources (hospital, primary care, self-report and cancer registry), ascertained by ICD-10 code.

Townsend deprivation index was an area-based socioeconomic status.[27,28] Physical activity was measured as metabolic equivalents (MET-minute), summed by walking, moderate and vigorous activity from the touchscreen questionnaire. Total sugar and energy were calculated using McCance and Widdowson's The Composition of Foods and provided by the UK Biobank.[29] Diet quality score was calculated using food components and scoring criteria described previously. Briefly, the modified AHEI[21,30] included five items, including red meat, processed meat, fruit, vegetables and fat.[21] Each dietary item scored 0 (unhealthiest), 5 and 10 (healthiest), respectively. Mediterranean diet score was

TABLE 3 Associations between consumption of three types of beverages and risk of Crohn's disease and ulcerative colitis[a]

	Crohn's disease			Ulcerative colitis		
	Incident cases/ person-year	HR 95% CI	p-value	Incident cases/ person-year	HR 95% CI	p-value
Sugar-sweetened beverages						
0 unit per day	94/818141	Ref		237/818951	Ref	
>0–1 unit per day	31/342812	0.79 [0.53, 1.20]	0.274	99/343175	0.95 [0.75, 1.20]	0.665
>1 units per day	18/75550	**2.05 [1.22, 3.46]**	**0.007**	31/75627	1.31 [0.89, 1.92]	0.172
p trend			0.181			0.432
Artificially sweetened beverages						
0 unit per day	120/970197	Ref		272/971033	Ref	
>0–1 unit per day	19/201124	0.72 [0.44, 1.18]	0.197	74/201430	1.26 [0.96, 1.63]	0.090
>1 units per day	4/65182	0.42 [0.15, 1.15]	0.091	21/65290	1.05 [0.67, 1.65]	0.832
p trend			**0.032**			0.281
Natural juices						
0 unit per day	60/552635	Ref		160/553260	Ref	
>0–1 unit per day	70/590663	1.11 [0.78, 1.57]	0.564	182/591225	1.15 [0.92, 1.42]	0.212
>1 units per day	13/93204	1.24 [0.67, 2.28]	0.489	25/93268	1.01 [0.66, 1.55]	0.954
p trend			0.507			0.448

Notes: Tests reaching a significance level of 0.05 were marked bold.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]HR was calculated based on fully adjusted model, which was Cox-proportional hazards model adjusted for age, gender, ethnicity, education, Townsend deprivation index, physical activities, smoking status, alcohol drinking status, BMI, total energy, AHEI and mutually adjusted for another two beverages.

constructed according to nine food items, with total score ranging from 0 to 9. Missing values of continuous and categorical variables were assigned to the mean and the most populated category, respectively.[31]

2.5 | Statistical analyses

Participants were categorised into three groups according to the consumption of each beverage: 0 unit per day (reference group), >0 to 1 unit per day and >1 units per day. Baseline characteristics of participants were described according to the consumption of sugar-sweetened beverages. We calculated person-years from the date of the first available 24-h questionnaire to the date of incidence of outcome, death, loss to follow-up or the end of follow-up (latest updated time for health data), whichever came first.

Associations of sugar-sweetened beverages, artificially sweetened beverages, natural juices with IBD risk were estimated using Cox proportional hazard models. The minimally adjusted model was adjusted for age, the square of age, sex, ethnicity and the fully adjusted model was additionally adjusted for TDI, educational levels,

physical activity levels, smoking status, alcohol drinking status, BMI, total energy, AHEI and the other two beverages. Proportional hazard assumption was tested and verified using Schoenfeld residual methods ($p = 0.460$ for sugar-sweetened beverages, 0.370 for artificially sweetened beverages, 0.098 for natural juices and 0.350 for total sugar in the fully adjusted models). We also separately examined the associations between the three beverages and risk of CD or UC. Cumulative incidence of IBD, CD and UC were also presented according to the consumption of the three types of beverages. In order to understand the relationship between beverage consumption and IBD risk better, we used restricted cubic splines to flexibly model and visualise the associations. In addition, we examined the associations between quintiles of total sugar intake and IBD, CD and UC risk.

We also evaluated whether the associations between beverages and IBD risk were modified by age (≤60 and >60 years), sex (male and female), smoking status (current, previous and never), alcohol drinking status (current, previous and never) and BMI (<30 and ≥30 kg/m^2) by testing the interactions of each beverage and covariate and conducting subgroup analyses. Moreover, we conducted a series of sensitivity analyses: (1) we further adjusted the models for total sugar
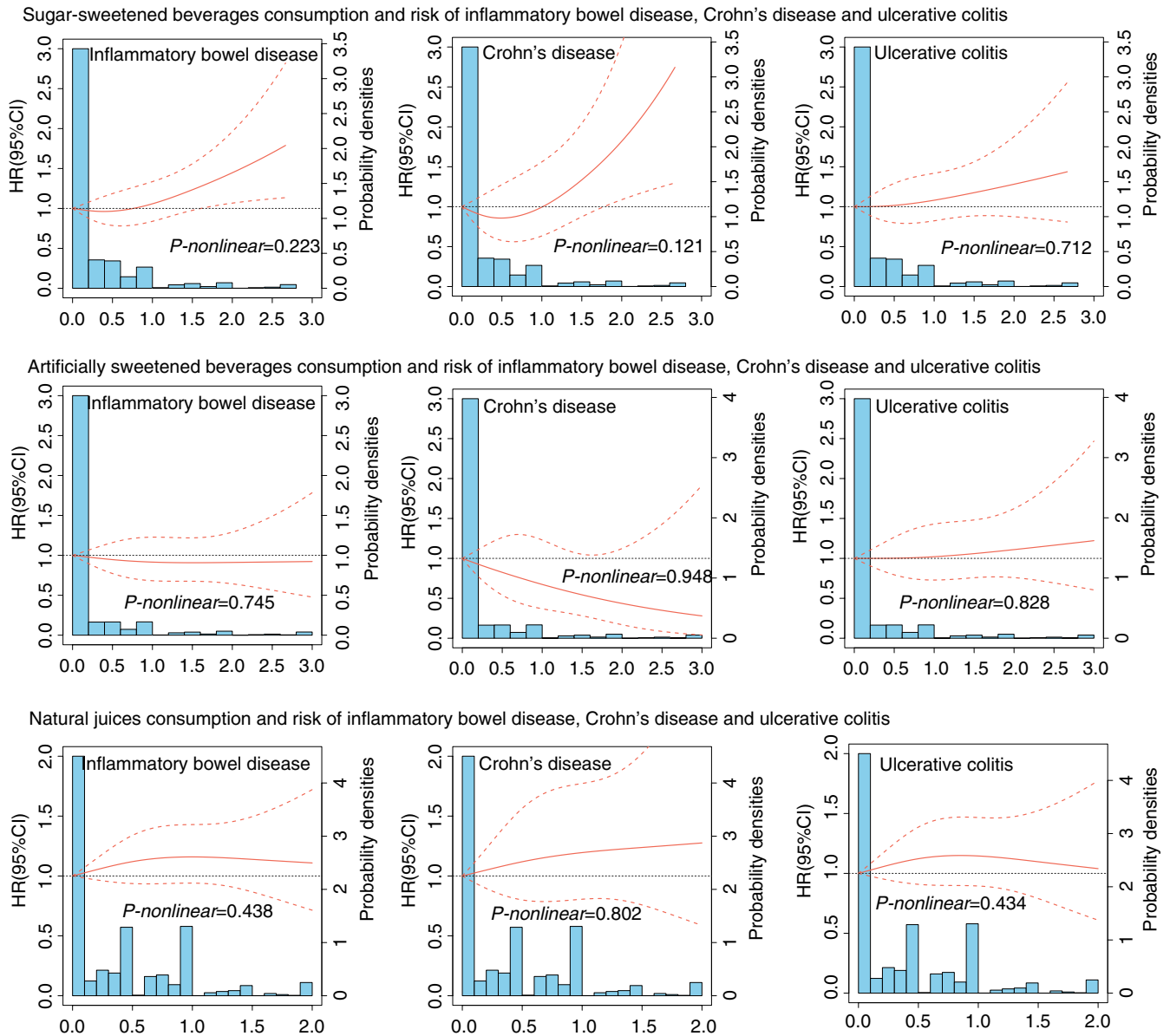
FIGURE 3 Associations between beverage intake and risk of inflammatory bowel disease, Crohn's disease and ulcerative colitis.

intake to check if the associations were independent of total sugar; (2) we used the Mediterranean diet score in place of AHEI to represent the overall diet quality; (3) we further adjusted the models for baseline comorbidities given possible confounding effects of these diseases; (4) we reprocessed missing values of covariates with multiple imputation; (5) we excluded participants who developed IBD within the first 4 years after baseline to reduce the influence of potential reverse causality and (6) we ascertained incident IBD as at least twice IBD diagnosis. We also conducted additional latency analyses stratified by follow-up from the time of exposure ascertainment (<2 years, 2–4 years, 4–8 years and >8 years) to identify the critical window for associations of beverage consumption with IBD risk.

Statistical analyses were performed using R, version 4.1.0. In this study, all statistical tests were two-tailed, and $p < 0.05$ indicated statistical significance.

3 | RESULTS

Baseline characteristics of the study population according to consumption of sugar-sweetened beverages were shown in Table 1. Of the 121,490 participants included, the mean (standard deviation, SD) age was 56.2 (7.8), and 96.9% of them were of white ethnicity. Most participants did not consume any sugar-sweetened beverages (66.3%), and participants consuming sugar-sweetened beverage >1 unit per day were more likely to have a higher BMI, higher intake of total energy and sugar. During an average (SD) follow-up of 10.2 (1.5) years, we documented 510 incident IBD cases (41 cases/100,000 person-years), including 143 CD cases (12 cases/100,000 person-years) and 367 UC cases (30 cases/100,000 person-years).

We observed positive associations between consumption of more than 1 unit per day of sugar-sweetened beverages and IBD
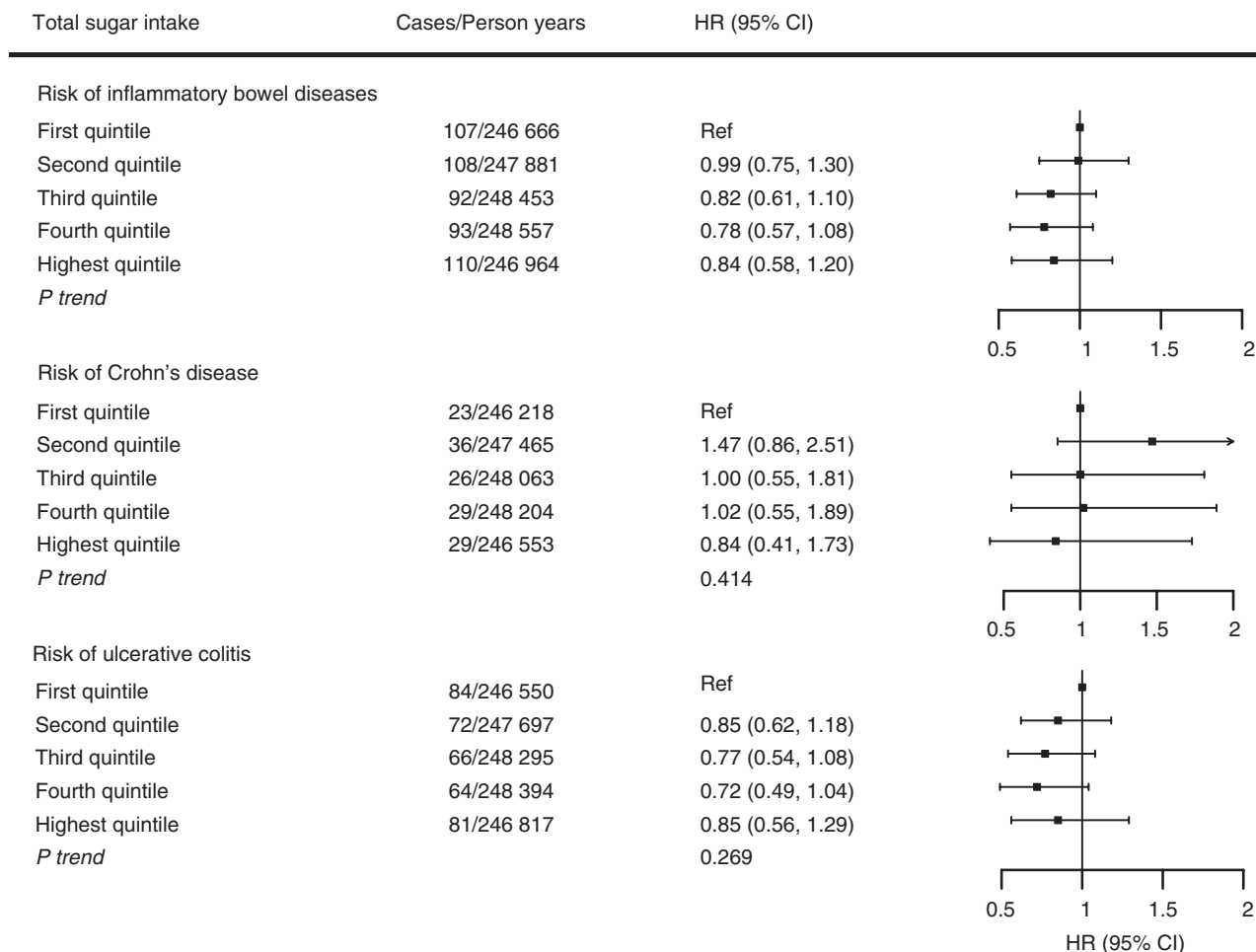
Total sugar intake	Cases/Person years	HR (95% CI)	
Risk of inflammatory bowel diseases			
First quintile	107/246 666	Ref	
Second quintile	108/247 881	0.99 (0.75, 1.30)	
Third quintile	92/248 453	0.82 (0.61, 1.10)	
Fourth quintile	93/248 557	0.78 (0.57, 1.08)	
Highest quintile	110/246 964	0.84 (0.58, 1.20)	
P trend			
Risk of Crohn's disease			
First quintile	23/246 218	Ref	
Second quintile	36/247 465	1.47 (0.86, 2.51)	
Third quintile	26/248 063	1.00 (0.55, 1.81)	
Fourth quintile	29/248 204	1.02 (0.55, 1.89)	
Highest quintile	29/246 553	0.84 (0.41, 1.73)	
P trend		0.414	
Risk of ulcerative colitis			
First quintile	84/246 550	Ref	
Second quintile	72/247 697	0.85 (0.62, 1.18)	
Third quintile	66/248 295	0.77 (0.54, 1.08)	
Fourth quintile	64/248 394	0.72 (0.49, 1.04)	
Highest quintile	81/246 817	0.85 (0.56, 1.29)	
P trend		0.269	

FIGURE 4 Associations between total sugar intake and risk of inflammatory bowel disease, Crohn's disease and ulcerative colitis. HRs were calculated by Cox proportional hazard regression models adjusted for age, gender, ethnicity, education, Townsend deprivation index, physical activities, smoking status, alcohol drinking status, BMI and total energy, alternative healthy eating index and beverages. CI, confidence interval; BMI, body mass index; HR, hazard ratio.

risk (Table 2 and Figure 2). Compared to zero consumption, consuming sugar-sweetened beverages >1 unit per day was associated with increased risk of IBD (HR 1.51, 95% CI 1.11–2.05, *p* trend = 0.170), which was stronger for CD (HR 2.05, 95% CI 1.22–3.46, *p* trend = 0.181), but was non-significant for UC (HR 1.31, 95% CI 0.89–1.92, *p* trend = 0.432) (Table 3). The trend for the associations of sugar-sweetened beverages with risk of IBD, CD or UC was non-significant. In contrast, artificially sweetened beverages (HR 0.85, 95% CI 0.56–1.28, *p* trend = 0.818) or natural juices (HR 1.08, 95% CI 0.76–1.53, *p* trend = 0.320) were not associated with the risk of IBD, CD or UC. In the restricted cubic splines, we did not found non-linear relationship between beverage intake and risk of IBD, CD or UC, but we can observe an elevated risk of IBD and CD with excessive intake of sugar-sweetened beverages, which was consistent with results in the primary analyses (Figure 3). Moreover, no association was observed for total sugar intake with risk of IBD, and HR of comparing extreme quintiles was 0.84 (95% CI 0.58–1.20, *p* trend = 0.173) for IBD risk, 0.84 (95% CI 0.41–1.73, *p* trend = 0.414) for CD risk, and 0.85 (95% CI 0.56–1.29, *p* trend = 0.269) for UC risk (Figure 4).

In subgroup analyses, the main findings did not differ substantially by sex, age, smoking status, alcohol drinking status or BMI (*p*-interactions >0.10, Table 4). The results remained stable in the sensitivity analyses (Tables 5 and 6). Specifically, compared to non-consumers, participants consuming sugar-sweetened beverages >1 unit per day were at increased IBD risk when further adjusted for total sugar intake (HR 1.56, 95% CI 1.13–2.15), baseline comorbidities (HR 1.49, 95% CI 1.10–2.04). Similar results were also observed when we used multiple imputations to deal with the missing values of covariates (HR 1.57, 95% CI 1.12–2.19), used Mediterranean diet score instead of AHEI (HR 1.50, 95% CI 1.10–2.04), used at least twice IBD diagnosis as outcome (HR 1.61, 95% CI 1.06–2.45) or excluded participants with IBD that occurred in the first 4 years after baseline (HR 1.56, 95% CI 1.07–2.29). In the latency analysis, we found the highest risk of IBD occurred within the first 2 years of follow-up (HR 2.47, 95% CI 1.25–4.87), but not significant when the follow-up time exceeded 2 years (Table 6). And no significant associations were found of artificially sweetened beverages and natural juices with IBD risk in the above sensitivity analyses, in line with the primary analyses (Tables 5 and 6).

TABLE 4 Subgroup analyses for the associations between consumption of three types of beverages and the risk of inflammatory bowel diseases

Stratification	Sugar-sweetened beverages unit/day			Artificially sweetened beverages unit/day			Natural juices unit/day		
	0	>0-1	>1	0	>0-1	>1	0	>0-1	>1
Gender									
Female HR 95% CI	Ref	1.01 [0.76, 1.34]	1.31 [0.79, 2.18]	Ref	1.03 [0.75, 1.42]	0.71 [0.39, 1.28]	Ref	1.03 [0.80, 1.33]	0.99 [0.58, 1.67]
Male HR 95% CI	Ref	0.82 [0.61, 1.11]	**1.66 [1.12, 2.46]**	Ref	1.18 [0.84, 1.65]	1.05 [0.59, 1.86]	Ref	1.26 [0.97, 1.65]	1.20 [0.75, 1.92]
p for interaction	0.484			0.787			0.522		
Age (years)									
≤60 HR 95% CI	Ref	0.83 [0.63, 1.09]	1.30 [0.87, 1.92]	Ref	0.92 [0.68, 1.24]	0.77 [0.47, 1.27]	Ref	1.23 [0.97, 1.55]	1.24 [0.80, 1.92]
>60 HR 95% CI	Ref	1.02 [0.74, 1.41]	**1.98 [1.21, 3.24]**	Ref	1.41 [0.99, 2.02]	1.00 [0.49, 2.06]	Ref	1.02 [0.76, 1.36]	0.86 [0.48, 1.56]
p for interaction	0.167			0.116			0.577		
Smoking status									
Current HR 95% CI	Ref	1.66 [0.90, 3.06]	1.56 [0.58, 4.15]	Ref	1.19 [0.58, 2.44]	1.22 [0.42, 3.50]	Ref	0.86 [0.47, 1.58]	1.37 [0.52, 3.63]
Never HR 95% CI	Ref	0.92 [0.68, 1.24]	**1.55 [1.00, 2.40]**	Ref	1.08 [0.76, 1.52]	1.01 [0.57, 1.80]	Ref	1.16 [0.88, 1.52]	1.16 [0.71, 1.87]
Previous HR 95% CI	Ref	0.79 [0.57, 1.09]	1.46 [0.90, 2.38]	Ref	1.08 [0.76, 1.53]	0.60 [0.29, 1.24]	Ref	1.18 [0.90, 1.56]	0.90 [0.49, 1.65]
p for interaction	0.307			0.720			0.767		
Drinking status									
Current HR 95% CI	Ref	0.95 [0.77, 1.17]	**1.61 [1.17, 2.21]**	Ref	1.11 [0.87, 1.40]	0.79 [0.50, 1.24]	Ref	1.14 [0.94, 1.38]	1.08 [0.75, 1.55]
Never HR 95% CI	Ref	0.79 [0.27, 2.33]	1.09 [0.23, 5.21]	Ref	1.02 [0.28, 3.74]	2.34 [0.61, 8.90]	Ref	1.48 [0.56, 3.93]	0.80 [0.10, 6.63]
Previous HR 95% CI	Ref	0.15 [0.02, 1.22]	0.42 [0.05, 3.47]	Ref	0.81 [0.17, 3.87]	0.66 [0.08, 5.52]	Ref	0.74 [0.22, 2.51]	1.71 [0.34, 8.46]
p for interaction	0.180			0.618			0.827		
BMI (kg/m²)									
<30 HR 95% CI	Ref	0.91 [0.72, 1.16]	1.30 [0.88, 1.93]	Ref	1.07 [0.80, 1.42]	1.11 [0.68, 1.82]	Ref	1.23 [0.99, 1.52]	1.22 [0.82, 1.81]
≥30 HR 95% CI	Ref	0.91 [0.60, 1.36]	**2.00 [1.20, 3.34]**	Ref	1.11 [0.74, 1.65]	0.54 [0.26, 1.13]	Ref	0.94 [0.66, 1.35]	0.75 [0.34, 1.64]
p for interaction	0.309			0.278			0.140		

Notes: HR was calculated based on fully adjusted model, adjusted for age, gender, ethnicity, education, Townsend deprivation index, physical activities levels, smoking status, alcohol drinking status, BMI and total energy. When the subgroup analyses were conducted stratified by the covariate, the covariate will not be adjusted in the model.

Tests reaching a significance level of 0.05 were marked bold.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

TABLE 5 Sensitivity analyses for the associations between consumptions of three types of beverages and risk of inflammatory bowel disease

		Further adjusted for total sugar HR 95% CI	Changed AHEI to Mediterranean diet HR 95% CI	Further adjusted for comorbidities[a] HR 95% CI	Dealt with missing covariates using multiple imputation HR 95% CI	Used at least twice IBD diagnosis as outcome HR 95% CI	Excluded incident of IBD that occurred in the first 4 years HR 95% CI
Sugar-sweetened beverages	0 unit per day	Ref	Ref	Ref	Ref	Ref	Ref
	>0–1 unit per day	0.92 [0.74, 1.13]	0.90 [0.73, 1.11]	0.90 [0.73, 1.11]	0.95 [0.76, 1.19]	0.92 [0.69, 1.23]	0.95 [0.74, 1.23]
	>1 units per day	**1.56 [1.13, 2.15]**	**1.50 [1.10, 2.04]**	**1.49 [1.10, 2.04]**	**1.57 [1.12, 2.19]**	**1.61 [1.06, 2.45]**	**1.56 [1.07, 2.29]**
Artificially sweetened beverages	0 unit per day	Ref	Ref	Ref	Ref	Ref	Ref
	>0–1 unit per day	1.09 [0.87, 1.38]	1.09 [0.87, 1.38]	1.09 [0.86, 1.37]	1.06 [0.82, 1.37]	1.06 [0.76, 1.47]	1.06 [0.80, 1.42]
	>1 units per day	0.85 [0.56, 1.28]	0.85 [0.56, 1.28]	0.84 [0.55, 1.27]	0.94 [0.61, 1.45]	0.98 [0.57, 1.68]	0.89 [0.54, 1.48]
Natural juices	0 unit per day	Ref	Ref	Ref	Ref	Ref	Ref
	>0–1 unit per day	1.15 [0.95, 1.38]	1.14 [0.95, 1.38]	1.14 [0.95, 1.37]	1.10 [0.90, 1.34]	1.17 [0.90, 1.51]	1.04 [0.83, 1.30]
	>1 units per day	1.11 [0.77, 1.59]	1.10 [0.77, 1.57]	1.08 [0.76, 1.54]	1.00 [0.68, 1.47]	1.18 [0.73, 1.89]	0.92 [0.59, 1.45]

Notes: Tests reaching a significance level of 0.05 were marked bold.

Abbreviations: AHEI, Alternative Healthy Eating Index; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel diseases.

[a]The comorbidities included diabetes coronary-heart-disease, hypertension and cancers.

4 | DISCUSSION

In this large population-based study of 121,490 participants in the UK Biobank, we found that compared to non-consumers, sugar-sweetened beverage consumption >1 unit per day was associated with increased IBD risk. A similar association was also observed between sugar-sweetened beverages consumption and risk of CD but not UC. However, we found no significant trend for the associations between sugar-sweetened beverages and the risk of IBD, CD or UC. In contrast, no associations were detected between artificially sweetened beverages, natural juices or total sugar intake with IBD risk. The above findings were robust in a series of sensitivity analyses.

4.1 | Compared with previous studies

A previous cohort study based on European Prospective Investigation into Cancer and Nutrition (EPIC)[32] found that a dietary pattern characterised by high intake of sugar and confectionery foods, and lower intake of vegetables and non-processed seafood is associated with higher UC risk (RR comparing extreme quintiles = 1.68, 95% CI 1.00–2.82). Another study[14] based on 116,087 adults from the Prospective Urban Rural Epidemiology (PURE) cohort found a positive association between soft drinks and IBD risk (HR for ≥3 servings per week vs <0.5 serving per week = 1.94, 95% CI 1.42–2.66), which, to some extent, was confirmed by our findings. On the contrary, a recent cohort study[16] conducted in 83,042 participants from Swedish Men or the Swedish Mammography cohort found no association between sweetened beverages and risk of CD (HR 1.02, 95% CI 0.60–1.73) or UC (HR 1.14, 95% CI, 0.83–1.57). Most of these studies considered both sugar-sweetened beverages and artificially sweetened beverages as soft drinks. Conclusions from meta-analyses were also inconsistent. Three meta-analyses based on cross-sectional and cohort studies showed a positive association between soft drinks and risk of UC[12] and CD,[13,33] while another recent meta-analysis revealed no association.[15] Given the differences in definitions of beverages and cultural background across cohorts, our findings not only added to current literature in a UK context but also provided further evidence in the relation of the types of beverages to IBD. Notably, we did not find a significant trend for the relation between sugar-sweetened beverages and IBD risk, which may be explained by the limited sample size and IBD cases of participants consuming sugar-sweetened beverages >1 unit per day and the trend test was driven by the null association in lower consumption groups. In addition, the categories for beverage consumption (0, >0–1 and >1 units/day) (which was based on the questionnaire) might not be totally biologically plausible, and we attempted to use restricted cubic splines to better understand the relatioship between beverage consumption and IBD risk. Therefore, caution is needed in interpreting the current finding and more large-scaled cohort studies were required to explore the dose–response relationship and effects of other categories of beverages. In general, our findings pointed out that excessive consumption of sugar-sweetened beverages, but not artificially sweetened beverages or natural juices,

TABLE 6 Association of three types of beverage consumptions with inflammatory bowel disease risk for latency of <2 years, 2–4 years, 4–8 years and >8 years

		Cases	Person-years	HR 95% CI	Cases	Person-years	HR 95% CI
		<2 years[a]			2–4 years[a]		
Sugar-sweetened beverages	0 unit per day	48	160,786	Ref	70	319,984	Ref
	>0–1 unit per day	25	66,836	1.21 [0.74, 1.98]	18	132,961	**0.57 [0.34, 0.96]**
	>1 units per day	11	14,879	**2.47 [1.25, 4.87]**	6	29,557	0.77 [0.33, 1.81]
Artificially sweetened beverages	0 unit per day	65	190,448	Ref	71	378,941	Ref
	>0–1 unit per day	17	39,189	1.15 [0.67, 1.99]	17	779 79	1.14 [0.66, 1.96]
	>1 units per day	2	12,863	0.39 [0.09, 1.60]	6	25,582	1.14 [0.48, 2.68]
Natural juices	0 unit per day	30	108,991	Ref	39	216,875	Ref
	>0–1 unit per day	47	115,347	1.52 [0.96, 2.42]	46	229,498	1.22 [0.79, 1.88]
	>1 units per day	7	18,162	1.38 [0.60, 3.19]	9	36,129	1.45 [0.69, 3.04]
		4–8 years[a]			>8 years[a]		
Sugar-sweetened beverages	0 unit per day	134	629,417	Ref	79	790,933	Ref
	>0–1 unit per day	62	261,068	1.10 [0.81, 1.49]	25	330,968	0.72 [0.45, 1.13]
	>1 units per day	19	58,020	1.48 [0.90, 2.42]	13	73,008	1.71 [0.93, 3.14]
Artificially sweetened beverages	0 unit per day	168	744,967	Ref	88	938,018	Ref
	>0–1 unit/day	38	153,336	0.99 [0.69, 1.42]	21	194,331	1.21 [0.74, 1.97]
	>1 units per day	9	50,202	0.68 [0.34, 1.35]	8	62,561	1.37 [0.65, 2.89]
Natural juices	0 unit per day	96	426,113	Ref	55	533,017	Ref
	>0–1 unit per day	107	451,363	1.14 [0.86, 1.51]	52	571,630	0.87 [0.59, 1.28]
	>1 units per day	12	71,029	0.83 [0.45, 1.53]	10	90,263	1.04 [0.53, 2.07]

Notes: HR was calculated based on fully adjusted model, adjusted for age, gender, ethnicity, education, Townsend deprivation index, physical activities levels, smoking status, alcohol drinking status, BMI and total energy.

Tests reaching a significance level of 0.05 were marked bold.

[a]Follow-up time from the time of exposure ascertainment.

might be a potential risk factor for IBD, but more studies are needed to verify this relation and explore the underlying mechanisms.

4.2 | Possible interpretations

Although the underlying mechanism remained unclear, several pathways could be possible explanations for the observed findings. Animal studies have emphasised the effect of dietary sugar on colitis with multiple mechanisms,[34] including increased mucosal inflammation, decreased gut microbiome diversity,[35] compromised mucus barrier and immunity,[11] and sugar-sweetened beverages were found to be associated with increased risk of systemic inflammation,[36,37] obesity,[38] metabolic syndrome, and diabetes[9]; in parallel, there has been evidence for the critical roles of these diseases in IBD.[39,40] It is noteworthy that we did not observe a positive association between artificially sweetened beverages, natural juices or total sugar intake and IBD risk. The inflammatory role of artificial sweeteners is still on a debate and the effect of natural sugar in natural juices may be counteracted by dietary fibres and bioactive compounds.[41,42] For total sugar, it included many forms of sugar derived from different food, and evidence showed that ingestion of sugar-sweetened beverages increases the risk of chronic diseases more than isocaloric amounts of complex carbohydrates.[43] Finally, we

also observed a positive association between sugar-sweetened beverages and risk of CD instead of UC, in line with previous most studies that diet was more associated with CD risk, which may be partly explained by the different lesion location and imbalanced intestinal microbiota in patients with CD or UC.[44] The current study demonstrated that the associations between sugar-sweetened beverages and IBD risk were in general consistent in latency analysis although not all significant, and the greatest risk occurred in the first 2 years after exposure ascertainment. The latency analyses between beverages consumption and IBD risk have not been investigated before and deserve more exploration.

4.3 | Strengths and limitations

To our knowledge, this is one of the few studies to explore the association of sugar-sweetened beverages, artificially sweetened beverages and natural juices with IBD risk simultaneously in a large cohort. We took advantage of the large prospective cohort study[18,45] with detailed assessments and updated health data linkage. However, there were several limitations in this study. First, at baseline, all participants in the UK Biobank were over 40 years, and we are thus unable to examine the association of beverages with younger-onset IBD. Second, self-reported exposures assessed by the 24-h diet recall questionnaires

were subject to inevitable measurement error and recall bias, although the questionnaire has been validated[22,23] and we tried to address this issue by including participants with at least two assessments. Third, diagnosis for IBD, CD and UC was ascertained by ICD code, as in previous studies,[46,47] which may have limited specificity. In the current study, we further ascertained IBD patients as more than twice diagnosis in the sensitivity analysis. Finally, residual confounding and reverse causation cannot be avoided considering the observational nature of this study, although we have controlled for various potential confounders such as lifestyles, overall diet quality and comorbidities and excluded participants with IBD occurred in the first 4 years in a sensitivity analysis. More studies are needed to confirm the associations observed in the current study and explore the underlying mechanisms.

5 | CONCLUSIONS

In conclusion, our study suggested an association between excessive intake of sugar-sweetened beverages, rather than artificially sweetened beverages or natural juices, and IBD risk, while the trend was non-significant. Our findings, if proven causal, suggested reduced consumption of sugar-sweetened beverages as a strategy for prevention of IBD, especially CD, but further studies are needed to confirm these findings and explore the underlying mechanism before public health policy could be carried out.

AUTHORSHIP

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AUTHOR CONTRIBUTIONS
Tian Fu: Conceptualization (equal); formal analysis (equal); methodology (equal); writing – original draft (lead). **Hui Chen:** Conceptualization (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Xuejie Chen:** Conceptualization (equal); formal analysis (supporting); project administration (equal); writing – review and editing (supporting). **Yuhao Sun:** Formal analysis (equal); methodology (equal); writing – original draft (supporting). **Ying Xie:** Methodology (supporting); writing – original draft (supporting). **Minzi Deng:** Investigation (supporting); writing – review and editing (supporting). **Therese Hesketh:** Methodology (supporting); writing – original draft (supporting). **Xiaoyan Wang:** Conceptualization (equal); methodology (supporting); supervision (lead); writing – review and editing (lead). **Jie Chen:** Conceptualization (lead); formal analysis (supporting); investigation (lead); methodology (equal); project administration (lead); writing – review and editing (lead).

DATA AVAILABILITY STATEMENT
Researchers can request the data we used and approval from the UK Biobank (www.ukbiobank.ac.uk).

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REFERENCES
1. Jairath V, Feagan BG. Global burden of inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2020;5:2–3.
2. Levine A, Sigall Boneh R, Wine E. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. Gut. 2018;67:1726–38.
3. Singh GM, Micha R, Khatibzadeh S, Shi P, Lim S, Andrews KG, et al. Global, regional, and National Consumption of sugar-sweetened beverages, fruit juices, and Milk: a systematic assessment of beverage intake in 187 countries. PLoS One. 2015;10:e0124845.
4. Ng SW, Ni Mhurchu C, Jebb SA, Popkin BM. Patterns and trends of beverage consumption among children and adults in Great Britain, 1986-2009. Br J Nutr. 2012;108:536–51.
5. Bandy LK, Scarborough P, Harrington RA, Rayner M, Jebb SA. Reductions in sugar sales from soft drinks in the UK from 2015 to 2018. BMC Med. 2020;18:20.
6. Greenwood DC, Threapleton DE, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Br J Nutr. 2014;112:725–34.
7. Xi B, Li S, Liu Z, Tian H, Yin X, Huai P, et al. Intake of fruit juice and incidence of type 2 diabetes: a systematic review and meta-analysis. PLoS One. 2014;9:e93471.
8. Gardner C, Wylie-Rosett J, Gidding SS, Steffen LM, Johnson RK, Reader D, et al. Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2012;126:509–19.
9. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation. 2010;121:1356–64.
10. Fajstova A, Galanova N, Coufal S, Malkova J, Kostovcik M, Cermakova M, et al. Diet rich in simple sugars promotes pro-inflammatory response via gut microbiota alteration and TLR4 signaling. Cell. 2020;9(12):2701.
11. Khan S, Waliullah S, Godfrey V, Khan MAW, Ramachandran RA, Cantarel BL, et al. Dietary simple sugars alter microbial ecology in the gut and promote colitis in mice. Sci Transl Med. 2020;12(567):eaay6218.
12. Nie JY, Zhao Q. Beverage consumption and risk of ulcerative colitis: systematic review and meta-analysis of epidemiological studies. Medicine (Baltimore). 2017;96:e9070.
13. Yang Y, Xiang L, He J. Beverage intake and risk of Crohn disease: a meta-analysis of 16 epidemiological studies. Medicine (Baltimore). 2019;98:e15795.

14. Narula N, Wong ECL, Dehghan M, Mente A, Rangarajan S, Lanas F, et al. Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study. BMJ. 2021;374:n1554.

15. Khademi Z, Milajerdi A, Larijani B, Esmaillzadeh A. Dietary intake of total carbohydrates, sugar and sugar-sweetened beverages, and risk of inflammatory bowel disease: a systematic review and meta-analysis of prospective cohort studies. Front Nutr. 2021;8:707795.

16. Khalili H, Hakansson N, Chan SS, Ludvigsson JF, Olen O, Chan AT, et al. No association between consumption of sweetened beverages and risk of later-onset Crohn's disease or ulcerative colitis. Clin Gastroenterol Hepatol. 2019;17:123–9.

17. Basson AR, Rodriguez-Palacios A, Cominelli F. Artificial sweeteners: history and new concepts on inflammation. Front Nutr. 2021;8:746247.

18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.

19. Freedman LS, Commins JM, Moler JE, Arab L, Baer DJ, Kipnis V, et al. Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for energy and protein intake. Am J Epidemiol. 2014;180:172–88.

20. Freedman LS, Commins JM, Moler JE, Willett W, Tinker LF, Subar AF, et al. Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for potassium and sodium intake. Am J Epidemiol. 2015;181:473–87.

21. Anderson JJ, Gray SR, Welsh P, Mackay DF, Celis-Morales CA, Lyall DM, et al. The associations of sugar-sweetened, artificially sweetened and naturally sweet juices with all-cause mortality in 198,285 UK Biobank participants: a prospective cohort study. BMC Med. 2020;18:97.

22. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public Health Nutr. 2011;14:1998–2005.

23. Greenwood DC, Hardie LJ, Frost GS, Alwan NA, Bradbury KE, Carter M, et al. Validation of the Oxford WebQ online 24-hour dietary questionnaire using biomarkers. Am J Epidemiol. 2019;188:1858–67.

24. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. J Nutr Sci. 2018;7:e6.

25. Fan M, Sun D, Zhou T, Heianza Y, Lv J, Li L, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK Biobank participants. Eur Heart J. 2020;41(11):1182–9.

26. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK Biobank study. JAMA Cardiol. 2018;3(8):693–702.

27. Black D. Health and deprivation: inequality and the north. J R Coll Gen Pract. 1988;38:234.

28. Ye J, Wen Y, Sun X, Chu X, Li P, Cheng B, et al. Socioeconomic deprivation index is associated with psychiatric disorders: an observational and genome-wide gene-by-environment interaction analysis in the UK Biobank cohort. Biol Psychiatry. 2021;89:888–95.

29. McCance, R.A.E.M. McCance and Widdowson's the Composition of Foods. 2014: Royal Society of Chemistry.

30. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr. 2012;142:1009–18.

31. Zhang Z. Missing data imputation: focusing on single imputation. Ann Transl Med. 2016;4:9.

32. Racine A, Carbonnel F, Chan SS, Hart AR, Bueno-de-Mesquita HB, Oldenburg B, et al. Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study. Inflamm Bowel Dis. 2016;22:345–54.

33. Yang XY, Chen PF, He JH. High consumption of sweetened beverages might increase the risk of inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019;17:1417–8.

34. Khalili H, Chan SSM, Lochhead P, Ananthakrishnan AN, Hart AR, Chan AT. The role of diet in the aetiopathogenesis of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2018;15:525–35.

35. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016;352:565–9.

36. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. Am J Clin Nutr. 2011;94:479–85.

37. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012;125:1735–41.

38. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr. 2006;84:274–88.

39. Lochhead P, Khalili H, Ananthakrishnan AN, Richter JM, Chan AT. Association between circulating levels of C-reactive protein and Interleukin-6 and risk of inflammatory bowel disease. Clin Gastroenterol Hepatol. 2016;14:818–824.e6.

40. Khalili H, Ananthakrishnan AN, Konijeti GG, Higuchi LM, Fuchs CS, Richter JM, et al. Measures of obesity and risk of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis. 2015;21:361–8.

41. O'Connor L, Imamura F, Brage S, Griffin SJ, Wareham NJ, Forouhi NG. Intakes and sources of dietary sugars and their association with metabolic and inflammatory markers. Clin Nutr. 2018;37:1313–22.

42. Rodriguez-Palacios A, Basson AR, Cominelli F. Artificial sweeteners and whole-food science: could mice help clinicians make diet recommendations for IBD patients? Gastroenterology. 2021;161(1):8–14.

43. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr. 2004;80(2):348–56.

44. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. 2012;13:R79.

45. Ollier W, Sprosen T, Peakman T. UK Biobank: from concept to reality. Pharmacogenomics. 2005;6:639–46.

46. Meyers TJ, Weiner AB, Graff RE, Desai AS, Cooley LF, Catalona WJ, et al. Association between inflammatory bowel disease and prostate cancer: a large-scale, prospective, population-based study. Int J Cancer. 2020;147(10):2735–42.

47. Xia B, Yang M, Nguyen LH, He Q, Zhen J, Yu Y, et al. Regular use of proton pump inhibitor and the risk of inflammatory bowel disease: pooled analysis of 3 prospective cohorts. Gastroenterology. 2021;161(6):1842–52.e10.