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Associations of sugar-sweetened beverages, artificially sweetened beverages, and natural juices with cardiovascular disease and all-cause mortality in individuals with inflammatory bowel disease in a prospective cohort study

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Abstract

Background: Beverage consumption was found to be associated with cardiovascular disease and mortality in the general population. However, it is unclear whether this association still exists in individuals with inflammatory bowel disease (IBD).

Objectives: To investigate the associations of sugar-sweetened beverages, artificially sweetened beverages, and natural juices with cardiovascular disease and all-cause mortality among individuals with IBD.

Design: Prospective cohort study.

Methods: We included 1981 participants with IBD in the UK Biobank. Consumption of beverages was measured using a validated 24-h diet recall. Outcomes of interest were overall cardiovascular disease and all-cause mortality. Cox proportional hazard models were used to estimate the hazard ratios and 95% confidence intervals (CIs).

Results: During a mean (SD) follow-up of 10.1 (1.7) years, we documented 205 cardiovascular events and 133 deaths. Compared to non-consumers, those consuming sugar-sweetened beverages more than 1 unit/day (reported in glasses/cans/250 ml/cartons) were associated with 64% (95% CI: 5–155, $p = 0.030$) and 97% (95% CI: 16–233, $p = 0.012$) increased risk of cardiovascular disease and all-cause mortality, respectively. We also observed a 78% (95% CI: 3–205, $p = 0.038$) increased risk of cardiovascular disease in participants who consumed artificially sweetened beverages more than 1 unit/day when compared with non-consumers. We did not observe significant associations between natural juice consumption and the two outcomes in IBD.

Conclusion: Higher sugar- and artificially sweetened beverage consumption were associated with adverse cardiovascular and mortality outcomes in IBD. These exploratory results were consistent with the evidence in the general population and highlighted the importance of diet management in individuals with IBD.

Keywords: cardiovascular disease, cohort study, inflammatory bowel disease, mortality, nutrition, sugar

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Introduction

The global prevalence of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is increasing.[1] Accumulating epidemiological evidence is deepening the understanding between a high-sugar, high-fat, low-fiber diet, and the development of IBD.[2] As a major source of free sugar intake, sugar-sweetened beverage consumption has been linked to the risk of IBD in previous large cohort studies, suggesting the potentially harmful influence of beverages on individuals with IBD.[3]

Currently, there is little evidence of the association between beverage consumption and the prognosis of patients with IBD. A cohort study followed 1133 patients with IBD for 3 years, finding that high sugar-sweetened beverage consumption was associated with higher healthcare utilization.[4] However, the association of beverage consumption with the intermediate- and long-term outcomes of IBD remains unknown. Furthermore, it is also unknown whether the consumption of artificially sweetened beverages, which are conventionally considered safer alternatives to sugary beverages, is safe for patients with IBD. In the general population, higher sugar-sweetened beverage consumption has been linked to an increased risk of mortality,[5] while recent studies have reported adverse evidence about the cardiovascular risks of artificial sweeteners.[6,7] Therefore, there is a need to clarify the cardiovascular and mortality risks associated with beverage consumption in people with IBD, a group that is more vulnerable than the general population.

Hence, we conducted a prospective cohort study to investigate the associations of sugar-sweetened beverages, artificially sweetened beverages, and natural juice consumption with the risk of cardiovascular disease (CVD) and all-cause mortality among individuals with IBD.

Methods

Study population

This study leveraged data from the UK Biobank, which is an ongoing national prospective cohort project that enrolled over 500,000 volunteers from 22 assessment centers in the United Kingdom between 2006 and 2010. All participants have signed an electronic consent and received a series of data collection that were described in detail elsewhere.[8,9]

The follow-up of health-related outcomes relied on the external linkage to the national medical data of participants including inpatient data [recorded in International Classification of Diseases (ICD) codes], primary care data (mapped read codes into ICD-10), and mortality data (ICD-10). Individuals with IBD were identified based on ICD-10 codes K50 (CD) and K51 (UC), and ICD-9 codes 555 (CD) and 556 (UC). Self-reported information was also included, which was confirmed in a verbal interview by trained staff at the recruitment centers and recorded according to a coding tree with specific mappings to ICD-10 codes. In the present study, we excluded the following: (1) participants reporting incredible energy intake (defined as <800 or >4200 kcal/day for males, <600 or >3500 kcal/day for females)[10] or non-typical diet ($n=239$) and (2) participants with a diagnosis of CVD before baseline ($n=312$). Finally, 1981 individuals with IBD were included in our study (Supplemental Figure S1). This article followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11] The checklist was presented in the Supplemental Method.

Assessment of exposures

Dietary information was obtained by a web-based 24-h diet recall questionnaire (Oxford WebQ) that was administered for five rounds in April 2009–September 2010, February 2011–April 2011, June 2011–August 2011, October 2011–December 2011, and April 2012–June 2012. Participants were presented with a list of up to 206 foods and 32 beverages commonly consumed in the United Kingdom and selected the number of portions consumed from each food.[12,13] The exposure was the consumption of sugar-sweetened beverages (fizzy drinks and squash), artificially sweetened beverages (low-calorie drinks), and natural juices (pure orange juice, grapefruit juice, and other pure fruit or vegetable juice), as suggested by the previous studies.[3,14] Participants reported the consumption of these beverages yesterday (in glasses/cans/250 ml/cartons) with options including 0, 0.5, 1, 2, 3, 4, 5, and more than 6 units. We calculated the cumulative mean intake of the beverage consumption from 24-h recalls as the exposure variables and categorized them into three groups (0, >0–1, and

>1 unit/day) according to previous studies investigating associations between beverage intake and incident IBD.[3]

The 24-h WebQ was validated with interviewer-administered 24-h recall completed on the same day, and Spearman correlation coefficients calculated from the 24-WebQ ranged from 0.5 and 0.9 (mean 0.6) for most nutrients.[15] Moreover, a single round of 24-h WebQ recall has also shown good agreement with long-term consumption and frequency of food groups collected by baseline food frequency questionnaires.[16] Comparing dietary measures based on the first 24-h recall questionnaire completed *versus* the mean of all completed questionnaires, the Pearson correlation coefficients between the two measures were as follows: sugar-sweetened beverages, 0.802; artificially sweetened beverages, 0.852; and natural juice, 0.835.[14] Therefore, we included participants with at least one 24-h recall ($n = 1981$) in the primary analysis given the sample size and the incidence of outcomes. The full text of 24-h recall was available online.[17]

Ascertainment of outcomes

The primary outcomes of interest included overall CVDs (including coronary heart disease, cerebrovascular disease, and peripheral artery disease) and all-cause mortality. Overall CVD was identified based on the diagnostic codes from nationwide inpatient data, primary care data, and death registry. We additionally used self-reported information reviewed by nurses to identify prevalent CVD. Diagnostic codes were presented in Supplemental Table S1 in detail. Deaths were ascertained *via* the death registry. The secondary outcome was coronary heart disease. Given the limited incident cases [all <3% (~60 cases) of the population], other endpoints like cerebrovascular disease, peripheral artery disease, and cause-specific mortality were not considered in the secondary analysis but only in quantitative descriptions. The Audit Commission review of 2009–2010 concluded diagnostic coding ICD-10 overall accuracy of 89%.[18]

Participants were followed up from the completed date of the first available 24-h WebQ to the date of incidence of the outcome, death, loss, or the end of follow-up (latest updated time for health data, September 2021 for participants in England, July 2021 for participants in Scottish, and February 2018 for participants in Wales), whichever came first.

Assessment of covariates

We included covariates ascertained *via* touchscreen questionnaire as follows: age, sex (female, male), ethnicity (white, others), education (college, below college), smoking status (never, ever), and physical activity (adequate, inadequate). The physical activity level was measured by a validated international physical activity questionnaire (short form) and was categorized into adequate and inadequate levels according to the American Heart Association.[19] Body mass index was calculated using height and weight measured at recruitment centers. Townsend deprivation index was included as an indicator of socioeconomic deprivation.[20] We calculated the Charlson comorbidity index to represent baseline comorbidities. Charlson comorbidity index was constructed based on 17 comorbidities with different weights identified using inpatient data.[21] Regular use of IBD-related medicine (amino salicylates, corticosteroids, and immunomodulators) was obtained *via* information recorded in a face-to-face interview. Two systematic inflammation indicators, C-reactive protein (CRP), and INFLA-score were included. INFLA-score was an indicator for low-grade inflammation based on white blood cell count, platelet count, and the neutrophil-to-lymphocyte ratio.[22] Dietary information was ascertained from the 24-h WebQ. The calculation of total energy, total sugar, and alcohol was described in detail elsewhere. We defined a heavy consumption of alcohol based on American dietary guidelines (more than 14 g/day for women and 28 g/day for men).[23] A modified Alternative Healthy Eating Index (AHEI) was calculated to represent overall diet quality.[14]

The details for the assessment of covariates are presented in Supplemental Table S2. If covariate information was missing or recorded as 'unknown', we imputed the median values for continuous variables or applied a most frequently used category for categorical variables.

Statistical analysis

Baseline characteristics were displayed by the consumption of sugar-sweetened beverages and artificially sweetened beverages. Characteristics were summarized in number (percentage) for

categorical variables and in mean [standard deviation (SD)] for continuous variables. The associations between three types of beverages (0, >0–1, and >1 unit/day) and CVD and all-cause mortality were first presented as a cumulative incidence plot. The Cox model treating age as timescale was applied to estimate the hazard ratios (HRs) and 95% confidence interval (CI). Three multivariable models were constructed: the model 1 (minimally adjusted model) adjusted for age, sex, and ethnic background; the model 2 further adjusted for Townsend deprivation index, education, alcohol consumption, smoking status, AHEI score, and total energy based on the minimally adjusted model; and the model 3 (fully adjusted model) further adjusted for body mass index based on the model 2. The consumption of three types of beverages was mutually adjusted in the models. We also reported the HRs of AHEI score in the primary analysis given that overall diet quality included beverage consumption and is also associated with clinical outcomes in IBD.[24] Proportional hazard assumptions were confirmed using a weighted residual method ($p > 0.38$).[25]

In the secondary analysis, we explored the associations in individuals with CD and UC separately. We also investigated the associations between three types of beverages and the risk of coronary heart disease. Subgroup analyses stratified by age (<60, ⩾60 years), sex, and body mass index categories (<25, 25–<30, ⩾30 kg/m^2) were conducted and multiplication interactions were tested. To determine how accurately one or more 24-h dietary recalls represent the average diet intake,[14] we divided the individuals into two subgroups, those who completed 1–2 (61%) and >2 (39%) dietary questionnaires.

Several sensitivity analyses were conducted: based on the fully adjusted model, we further (1) excluded outcomes of interest within the first 4 years of follow-up ($n = 104$) to minimize potential reverse causation; (2) applied multiple imputation method[26] instead of single imputation to explore the potential effect of imputation method; (3) adjusted for Charlson comorbidity index; (4) adjusted for regular use of IBD-related medicine; (5) adjusted for CRP/INFLA-score; (6) adjusted for total sugar; (7) using the date of the return of the last 24-h recall as the baseline date to further address immortal time bias; and (8) applied competing risk model account for death when investigating the associations between beverage consumption and CVD risk.

Results

Characteristics of the study sample

In this study, 1981 individuals with IBD (676 CD and 1305 UC) were included and followed up for a mean (SD) of 10.1 (1.7) years. Baseline characteristics are summarized in Table 1. Of the 1981 participants, the mean (SD) age was 58.7 (7.9) years and 1040 (52.5%) were female. We documented 205 CVD events (107.1 cases per 10,000 person-years) and 133 deaths (66.2 cases per 10,000 person-years) throughout the follow-up. In terms of other endpoints, 153 people developed coronary heart disease, 61 people developed cerebrovascular disease, 14 developed peripheral artery disease, and 22 people developed more than one CVD. During the follow-up, 28 people died from CVD, according to the death registry.

Primary analysis

The intake of more than 1 unit/day of sugar-sweetened beverages was positively associated with CVD and all-cause mortality, whereas the consumption of more than 1 unit/day of artificially sweetened beverages was positively associated with CVD risk (Supplemental Figure S2 and Table 2). Specifically, the risk of CVD and all-cause mortality was 64% (95% CI: 5–155, $p = 0.030$) and 97% (95% CI: 16–233, $p = 0.012$) higher for those who consumed more than 1 unit of sugar-sweetened beverages per day compared to non-consumers. We observed that higher consumption of artificially sweetened beverages (more than 1 unit/day) was associated with an increased risk of CVD (HR: 1.78, 95% CI: 1.03–3.05, $p = 0.038$) when compared with non-consumers while we did not observe significant associations between artificially sweetened beverage consumption and all-cause mortality ($HR_{>1\ versus\ 0\ unit/day}$: 1.25, 95% CI: 0.58–2.72, $p = 0.56$). We did not observe significant associations between natural juice consumption and AHEI score with the risk of CVD and all-cause mortality among individuals with IBD (all $p > 0.05$).

Secondary analysis

We found several associations of beverage consumption with risk of CVD and mortality were no

Table 1. Baseline characteristics of the study sample at baseline visit according to sugar-sweetened beverages and artificially sweetened beverages consumption.*

Chracteristics	Total (n = 1981)	Sugar-sweetened beverages (unit/day)			Artificially sweetened beverages (unit/day)		
		0 (n = 1332, median intake 0 unit/day)	>0–1 (n = 492, median intake 0.50 units/day)	>1 (n = 157, median intake 2.0 units/day)	0 (n = 1854, median intake 0 unit/day)	>0–1 (n = 316, median intake 0.67 units/day)	>1 (n = 123, median intake 2.0 units/day)
Age at baseline [mean (SD)]	58.69 (7.93)	58.91 (7.87)	58.55 (8.05)	57.24 (7.92)	59.42 (7.88)	58.18 (8.00)	57.54 (8.08)
Sex (%)							
Female	1040 (52.5)	741 (55.6)	248 (50.4)	51 (32.5)	920 (49.6)	173 (54.7)	73 (59.3)
Male	941 (47.5)	591 (44.4)	244 (49.6)	106 (67.5)	934 (50.4)	143 (45.3)	50 (40.7)
Townsend deprivation index [mean (SD)]	−1.59 (2.83)	−1.63 (2.80)	−1.62 (2.85)	−1.15 (3.03)	−1.54 (2.85)	−1.70 (2.80)	−1.50 (2.97)
Education (%)							
Below college degree	1227 (62.3)	810 (61.3)	307 (62.4)	110 (70.1)	1147 (62.2)	206 (66.2)	83 (67.5)
College degree	743 (37.7)	511 (38.7)	185 (37.6)	47 (29.9)	698 (37.8)	105 (33.8)	40 (32.5)
Ethnicity (%)							
White	1909 (96.8)	1286 (97.1)	475 (96.7)	148 (94.9)	1787 (96.8)	307 (97.8)	118 (95.9)
Others	63 (3.2)	39 (2.9)	16 (3.3)	8 (5.1)	59 (3.2)	7 (2.2)	5 (4.1)
Physical activity (%)							
Inadequate	981 (49.6)	648 (48.8)	260 (52.8)	73 (46.5)	907 (49.0)	141 (44.6)	59 (48.4)
Adequate	995 (50.4)	679 (51.2)	232 (47.2)	84 (53.5)	943 (51.0)	175 (55.4)	63 (51.6)
Smoking status (%)							
Never smoked	619 (31.2)	414 (31.1)	151 (30.7)	54 (34.4)	600 (32.4)	99 (31.3)	41 (33.3)
Previous or current smokers	1362 (68.8)	918 (68.9)	341 (69.3)	103 (65.6)	1254 (67.6)	217 (68.7)	82 (66.7)
Alcohol consumption (%)							
None to moderate consumption	340 (17.2)	240 (18.1)	82 (16.7)	18 (11.5)	322 (17.4)	55 (17.4)	23 (18.7)
Heavy consumption	1638 (82.8)	1089 (81.9)	410 (83.3)	139 (88.5)	1529 (82.6)	261 (82.6)	100 (81.3)

(Continued)

Table 1. (Continued)

Chracteristics	Total (n = 1981)	Sugar-sweetened beverages (unit/day)			Artificially sweetened beverages (unit/day)		
		0 (n = 1332, median intake 0 unit/day)	>0–1 (n = 492, median intake 0.50 units/day)	>1 (n = 157, median intake 2.0 units/day)	0 (n = 1854, median intake 0 unit/day)	>0–1 (n = 316, median intake 0.67 units/day)	>1 (n = 123, median intake 2.0 units/day)
BMI, kg/m^2 (%)							
<25	826 (41.8)	562 (42.4)	203 (41.3)	61 (38.9)	779 (42.1)	108 (34.3)	16 (13.1)
25 to <30	789 (39.9)	533 (40.2)	190 (38.7)	66 (42.0)	753 (40.7)	121 (38.4)	50 (41.0)
⩾30	360 (18.2)	232 (17.5)	98 (20.0)	30 (19.1)	318 (17.2)	86 (27.3)	56 (45.9)
Total energy intake [mean (SD)] (kJ/day)	8696.15 (2297.46)	8471.46 (2282.77)	8942.84 (2153.46)	9829.30 (2454.06)	8706.96 (2312.62)	8708.00 (2102.98)	8533.13 (2619.42)
Total sugar intake [mean (SD)] (g/day)	74.36 (27.52)	72.68 (28.21)	76.85 (24.70)	80.85 (28.61)	74.25 (27.82)	73.84 (24.11)	73.16 (32.33)
Number of 24-h recall							
1 round	760 (38.4)	589 (44.2)	115 (23.4)	56 (35.7)	749 (40.4)	74 (23.4)	53 (43.1)
2 rounds	453 (22.9)	295 (22.1)	118 (24.0)	40 (25.5)	425 (22.9)	78 (24.7)	23 (18.7)
3 rounds	415 (20.9)	256 (19.2)	120 (24.4)	39 (24.8)	380 (20.5)	80 (25.3)	26 (21.1)
4 rounds	294 (14.8)	157 (11.8)	118 (24.0)	19 (12.1)	253 (13.6)	70 (22.2)	17 (13.8)
5 rounds	59 (3.0)	35 (2.6)	21 (4.3)	3 (1.9)	47 (2.5)	14 (4.4)	4 (3.3)
Charlson comorbidity index [mean (SD)]	0.30 (0.92)	0.31 (0.95)	0.27 (0.83)	0.41 (0.93)	0.37 (1.03)	0.39 (0.82)	0.57 (1.39)
Aminosalicylate use (%)	698 (35.2)	461 (34.6)	181 (36.8)	56 (35.7)	657 (35.4)	106 (33.5)	36 (29.3)
Corticosteroid use (%)	119 (6.0)	74 (5.6)	28 (5.7)	17 (10.8)	120 (6.5)	14 (4.4)	12 (9.8)
Immunomodulators use (%)	221 (11.2)	138 (10.4)	57 (11.6)	26 (16.6)	208 (11.2)	37 (11.7)	6 (4.9)

*Mean (SD) values and percentages are reported for continuous and categorical variables, respectively.
BMI, body mass index.

Table 2. Associations of consumption of three types of beverages with risk of overall cardiovascular disease and all-cause mortality among individuals with IBD.

Beverage consumption	Cases/person-years	Model 1 (minimally adjusted)		Model 2		Model 3 (fully adjusted)	
		HR (95% CI)*	*p*	HR (95% CI)$	*p*	HR (95% CI)‡	*p*
Overall cardiovascular disease							
Sugar-sweetened beverages							
0 unit/day	133/12,932	Ref		Ref		Ref	
>0–1 unit/day	47/4759	0.98 (0.70, 1.37)	0.920	0.96 (0.69, 1.35)	0.834	0.97 (0.70, 1.36)	0.878
>1 unit/day	25/1453	1.66 (1.07, 2.56)	0.023	1.62 (1.04, 2.52)	0.033	1.64 (1.05, 2.55)	0.030
P-trend			0.124		0.155		0.148
Artificially sweetened beverages							
0 unit/day	170/15,647	Ref		Ref		Ref	
>0–1 unit/day	20/2602	0.84 (0.52, 1.34)	0.456	0.79 (0.50, 1.27)	0.336	0.81 (0.50, 1.29)	0.370
>1 unit/day	15/895	1.82 (1.07, 3.09)	0.028	1.86 (1.09, 3.17)	0.023	1.78 (1.03, 3.05)	0.038
P-trend			0.208		0.238		0.281
Natural juices							
0 unit/day	102/10,184	Ref		Ref		Ref	
>0–1 unit/day	82/7513	0.99 (0.74, 1.33)	0.941	1.00 (0.74, 1.34)	0.977	0.99 (0.74, 1.33)	0.964
>1 unit/day	21/1447	1.32 (0.82, 2.12)	0.249	1.37 (0.85, 2.21)	0.192	1.34 (0.83, 2.15)	0.232
P-trend			0.461		0.389		0.433
AHEI score§		0.93 (0.81, 1.08)	0.352	0.93 (0.80, 1.08)	0.325	0.93 (0.80, 1.08)	0.323
All-cause mortality							
Sugar-sweetened beverages							
0 unit/day	85/13,500	Ref		Ref		Ref	
>0–1 unit/day	30/5045	0.97 (0.64, 1.47)	0.884	0.95 (0.62, 1.45)	0.823	0.97 (0.63, 1.48)	0.883
>1 unit/day	18/1547	1.92 (1.15, 3.22)	0.013	1.94 (1.15, 3.29)	0.013	1.97 (1.16, 3.33)	0.012
P-trend			0.090		0.095		0.086

(Continued)

Table 2. (Continued)

Beverage consumption	Cases/person-years	Model 1 (minimally adjusted)		Model 2		Model 3 (fully adjusted)	
		HR (95% CI)*	*p*	HR (95% CI)$	*p*	HR (95% CI)‡	*p*
Artificially sweetened beverages							
0 unit/day	115/16,414	Ref		Ref		Ref	
>0–1 unit/day	11/2706	0.65 (0.35, 1.21)	0.176	0.66 (0.35, 1.23)	0.192	0.66 (0.35, 1.24)	0.196
>1 unit/day	7/973	1.18 (0.55, 2.54)	0.668	1.27 (0.59, 2.75)	0.538	1.25 (0.58, 2.72)	0.566
P-trend			0.608		0.748		0.727
Natural juices							
0 unit/day	67/10,664	Ref		Ref		Ref	
>0–1 unit/day	54/7890	1.02 (0.71, 1.46)	0.911	1.03 (0.71, 1.47)	0.894	1.02 (0.71, 1.46)	0.924
>1 unit/day	12/1539	1.19 (0.64, 2.20)	0.584	1.21 (0.65, 2.25)	0.554	1.20 (0.65, 2.24)	0.559
P-trend			0.684		0.682		0.706
AHEI score§		0.96 (0.81, 1.15)	0.674	0.99 (0.82, 1.19)	0.919	0.99 (0.82, 1.19)	0.924

*Based on the minimally adjusted model adjusted for age, sex, and ethnic background, and mutually adjusted for the other two beverages.
$Based on model 2 adjusted for age, sex, ethnic background, Townsend deprivation index, education, alcohol consumption, smoking status, AHEI score, total energy, and mutually adjusted for the other two beverages.
‡Based on the fully adjusted model adjusted for age, sex, ethnic background, Townsend deprivation index, education, body mass index, alcohol consumption, smoking status, AHEI score, and total energy, and mutually adjusted for the other two beverages.
§In the present study, we used a modified AHEI score ranging from 0 to 50. We reported the HRs of per 10 scores increment in AHEI score.
AHEI, Alternative Healthy Eating Index; CI, confidence interval; HR, hazard ratio.

longer significant but remained consistent direction among individuals with CD and UC. We only observed significant associations of artificially sweetened beverages with CVD (HR>$_{1\ versus\ 0\ unit/day}$: 3.61, 95% CI: 1.55–8.41, $p=0.003$) and associations of sugar-sweetened beverage with all-cause mortality (HR>$_{1\ versus\ 0\ unit/day}$: 2.53, 95% CI: 1.14–5.61, $p=0.023$) among individuals with CD (Supplemental Table S3).

For associations between beverage consumption and risk of coronary heart disease, we observed that the risk of coronary heart disease was 113% (95% CI: 18–284, $p=0.012$) higher for those who consumed more than 1 unit of artificially sweetened beverages per day compared to non-consumers (Supplemental Table S4).

Subgroup and sensitivity analysis

The associations between beverage consumption and CVD and all-cause mortality were consistent when stratified by age, body mass index, and the number of completed 24-h recalls (Supplemental Tables S5 and S6, all P-interaction >0.05). Statistical differences were detected in all associations of beverage consumption with CVD and all-cause mortality in males and females (all P-interaction <0.05). Specifically, higher HRs for CVD (1.75 *versus* 1.13 for males *versus* females) and all-cause mortality (2.04 *versus* 1.30 for males *versus* females) were observed for males who consumed more than 1 unit of sugar-sweetened beverages per day compared with non-consumers. For consumption of artificially sweetened beverages and natural juices, higher HRs for CVD (males *versus* females: artificially sweetened beverages, 1.70 *versus* 1.81; natural fruit juices, 1.08 *versus* 2.15) and all-cause mortality (males *versus* females: artificially sweetened beverages, 1.29 *versus* 1.35; natural fruit juices, 1.08 *versus* 2.15) were observed for females who consumed more than 1 unit/day compared to non-consumers.

In sensitivity analysis, the results were similar to the primary analysis when excluding incident outcome events in the first 4 years, using multiple imputation methods, using the date of the return of the last 24-h recall as the baseline date, additionally adjusted for Charlson comorbidity index/total sugar intake/IBD-related medication (Supplemental Table S7). When additionally adjusted for CRP/INFLA-score, significant associations were observed between sugar-sweetened beverages and CVD and all-cause mortality, whereas significant associations were not observed between artificially sweetened beverages and CVD risk in the two analyses (Supplemental Table S8). Consistent associations of sugar-sweetened beverages (HR>$_{1\ versus\ 0\ unit/day}$: 1.60, 95% CI: 1.03–2.48, $p=0.037$) and artificially sweetened beverages (HR>$_{1\ versus\ 0\ unit/day}$: 1.79, 95% CI: 1.03–3.11, $p=0.040$) with CVD risk were observed after accounting for death as a competing risk (Supplemental Table S8).

Discussion

In this study of 1981 individuals with IBD, we found that compared to non-consumers, those consuming sugar-sweetened beverages more than 1 unit per day were associated with 64% and 97% increased risk of CVD and all-cause mortality, respectively. We also observed a 78% increased risk of CVD in participants with artificially sweetened beverages consumption of more than 1 unit/day when compared with non-consumers. We did not observe significant associations between natural juice consumption and the two outcomes in IBD. Effect modification of sex was detected in the associations of beverage consumption with CVD and all-cause mortality. Sensitivity analyses demonstrated consistent results with the primary analysis.

A study included 1133 American IBD patients recruited in a clinic found high sugar-sweetened beverage consumption (≥1 unit/day) was positively associated with hospitalization (HR: 1.55, 95% CI: 1.06–2.27) and emergency department visits (HR: 1.53, 95% CI: 1.10–2.13) when compared with low consumption (≤2 units/week).[4] This study suggested the potentially detrimental effect of sugar-sweetened beverages on the short-term outcomes of IBD, but there is no direct evidence linking sugar- and artificially sweetened beverage consumption with medium- and long-term outcomes in individuals with IBD. For cardiovascular risk, a meta-analysis of 10 prospective cohort studies suggested that consumption of both sugar- and artificially sweetened beverages in the highest category increased the risk of CVD by 17% compared to the lowest category.[5] For all-cause mortality, the meta-analysis found that sugar-sweetened beverage consumption in the highest category was associated with a 14% increased risk of all-cause mortality.[5] Our study was consistent with the results of the meta-analysis, but the HRs

for CVD and all-cause mortality were numerically higher. One possible assumption was that the IBD population is more susceptible to the potential adverse health effects of sugar- and artificially sweetened beverages. However, given the relatively wide CIs reported in our study, future larger prospective studies are needed to minimize the influence of random variation. Moreover, we did not observe a significant association between artificially sweetened beverages and all-cause mortality among individuals with IBD, which is not consistent with the meta-analysis.[5] Considering the consistency of the direction of the association, this nonsignificant result may be due to the inadequate sample size in our IBD cohort.

Many studies have reported and discussed plausible mechanisms by which sugary and artificially sweetened beverages contribute to cardiovascular events and deaths.[5–7] Consumption of both beverages is associated with an increased risk of metabolic syndrome.[27,28] This can impair cardiometabolic health and lead to CVD and death. For IBD, high sugar intake exacerbated the symptoms of the dextran sodium sulfate-induced colitis model in mice, reduced intestinal microbial diversity, and depleted short-chain fatty acids with anti-inflammatory properties.[29,30] And, similar to sugar-sweetened drinks, artificially sweetened beverages can also contribute to a high glycemic burden and exacerbate inflammation by affecting the glucagon-like peptide 1 level.[31] Previous studies have demonstrated that hyperglycemic load is associated with elevated plasma CRP.[32] Each of these pathways may exacerbate the susceptibility of IBD patients to sugar- and artificially sweetened beverages and may explain the higher HRs we observed compared to the general population. Furthermore, in sensitivity analyses, the association between artificially sweetened beverages and CVD was no longer significant after adjusting for two different indicators of inflammation. Inflammation is a risk factor for CVD, and previous literature reviews have suggested that artificial sweeteners cause inflammation in multiple ways and harm individuals with chronic inflammatory diseases.[33]

In Supplemental Table S3, the associations of beverage consumption with CVD and mortality were significant in CD but not in UC. This may be due to insufficient statistical power by sample size, but the fact that individual with CD is more susceptible to diet is also a possible explanation. Previous studies in UK Biobank had also reported the associations of dietary fiber intake,[34] processed meat intake,[35] and adherence to a healthy diet[24] with long-term outcomes (surgery and death) were stronger in CD than UC. Our result was in line with these studies that showed that diet may be more related to CD. However, the study investigating high sugar-sweetened beverage consumption and healthcare utilization among 1133 IBD patients did not find statistically significant differences by subtypes ($OR_{UC\ versus\ CD\ [ref]}$: 0.79, 95% CI: 0.51–1.23).[4] These pieces of evidence suggest that beverage consumption may be a greater concern for individuals with CD, but studies with larger sample sizes are still needed for confirmation.

We found a significant interaction between gender and the three beverages in the risk of CVD and all-cause mortality. This may be explained as differences in beverage consumption between sexes,[36,37] or it may be due to the effect of sex-related factors on blood glucose and lipid levels, as two previous studies from Asia found that sugary beverage consumption was associated with a more pronounced risk of metabolic syndrome only in females.[38,39] Previous meta-analyses in subgroup analyses only found significant associations of sugar- and artificially sweetened beverages with CVD and all-cause mortality in the female subgroup only, but the study only had up to four studies included in the gender subgroup.[5] Therefore, more research is needed to confirm whether the potential health effects of sugar- and artificially sweetened beverage consumption differ between sexes, both in the IBD and general populations.

To our knowledge, this is the first study to investigate the association of beverage consumption with intermediate and long-term adverse outcomes in the IBD population. The strength of our study is the use of data from the large cohort UK Biobank, with a rich set of variables such as lifestyle, medication information, dietary intake, and a complete follow-up over time. However, our study also has several limitations. First, because our study is observational, potential confounding factors and reverse causation prevent us from proving the causality of our conclusions. However, we adjusted for a range of confounding factors including lifestyle, demographics, comorbidities, and medication use, and obtained similar results after excluding the outcomes occurring in the first

4 years, which demonstrates the robustness of the results. Second, although we used a validated 24-h WebQ, approximately 38% of the study sample had only one questionnaire data. However, subgroup analyses for people with different numbers of completions did not find statistically significant differences. In addition, we minimized the bias seen in self-reported diet information by excluding extreme energy intake and non-typical diets. Third, the relatively small sample size of our study limits the ability to further explore the association between beverage consumption and separate CVD and cause-specific mortality. Finally, the vast majority of participants in our study were over 40 years of age and white, and caution is needed in generalizing our findings to other IBD populations.

Conclusion

We found a 64% and 97% elevated risk of CVD and all-cause mortality for those consuming sugar-sweetened beverages greater than 1 unit/day and a 78% elevated risk of CVD for those consuming artificially sweetened beverages greater than 1 unit/day in the IBD population compared to non-consumers. These results demonstrate the adverse association of sugar- and artificially sweetened beverages with intermediate and long-term outcomes in patients with IBD. Our finding, together with previous studies, calls for a further investigation to confirm whether a restriction to sugar- and artificially sweetened beverages is recommended for IBD.

Declaration

Ethics approval and consent to participate

All participants included have signed electronic consent, and the North West–Haydock Research Ethics Committee granted ethical approval to use the UK Biobank database (REC reference: 21/NW/0157). Our application number is 73595.

Consent for publication

Not applicable.

Author contributions

Lintao Dan: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Tian Fu: Formal analysis; Methodology; Writing – original draft.

Yuhao Sun: Formal analysis; Methodology.

Xixian Ruan: Conceptualization; Writing – original draft; Writing – review & editing.

Shiyuan Lu: Conceptualization; Methodology; Writing – review & editing.

Jie Chen: Conceptualization; Data curation; Methodology; Writing – original draft.

Xiaoyan Wang: Conceptualization; Funding acquisition; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Researchers can require the data and approval from the UK Biobank (https://www.ukbiobank.ac.uk).

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Supplemental material

Supplemental material for this article is available online.

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